Formal and model driven design for biomedical engineering

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PREFACE

This thesis documents DEng research work at Chiba University which leads towards the formalization of biomedical algorithms for health care systems. The thesis title "formal and model driven design for biomedical engineering" reflects the structure of the research work. The research work was centered on two main areas (a) formal modeling and (b) functional modeling. The formal models describe how a particular system is build. In contrast, the functional models describe what system to build, i.e. the system functionality. For example, an Artificial Neural Network (ANN) algorithm describes the steps necessary to establish a specific decision making functionality. In contrast, formal modeling describes the processes which implement the functionality of the individual steps. Formal methods are used to explore design variations, such as combining multiple functional steps into one process. But the most important reason for introducing formal modeling to biomedical engineering comes from their ability to define system functionality in a clear unambiguous way. Based on the clear description it is possible to proof specific system properties. The remainder of the thesis explains how formal and model driven design leads to safe, reliable and functional biomedical systems.

This work aims to benefit society with a design methodology for reliable biomedical systems. State of the art best practice design fails to deliver the highest possible levels of safety, reliability and functionality. One reason for the failure comes from the fact that biomedical systems are designed with the divide and conquer method. To be specific, divide and conquer can mean one of two things. (1) Creating problem solutions by assembling preexisting smaller systems. This method all too often leads to problem solutions which are looking for a problem. (2) Breaking up complex problems into smaller problems which can be solved with physical problem solutions. There is nothing wrong with dividing a big problem into smaller and manageable parts. However, biomedical systems get more complex and dividing these complex systems into smaller parts usually leads to island solutions. In other words, a lack of overview leads to the kind of incompatible interfaces or inconsistent workflows and piecemeal health information systems we see at the moment. My proposal is to look at systems as a whole and plan the realization of the complete system before the focus shifts to the individual parts.

Every biomedical health care system in existence is a physical realization of an idea or a strategy on how to solve a medical problem. These physical problem solutions must be safe, reliable and functional. The big question is: How do we get safe, reliable and functional systems? The functionality is established through modeling. The reliability is tested by comparing the physical problem solution with the model. For most systems, the comparison takes the form of use and failure case testing. However, for complex physical systems, testing can only confirm the presence of a fault but never proof the absence of system faults. Therefore, it is impossible to

establish safety through testing – the safety critical fault might lurk in an untested system state. Safety is a design property, hence the way we design a system is very important. In general every system design follows some sort of design methodology. In some cases the design methodology exists only in the brain of a single expert, who takes on all the necessary design steps. However, such a design methodology creates dangerous systems, because the safety depends on whether or not the human expert has understood all aspects of the system design. In general, decisions on incomplete data and gut feeling must be avoided for safety critical systems.

With this thesis I propose a formal and model driven design methodology for biomedical systems. The idea is to extend the well-established systems engineering design methodology with formal models. The systems engineering design methodology structures the design efforts. Model driven design means to prove or at least estimate certain aspects of the system, such as safety, reliability and functionality. As part of my drive to improve the functionality of biomedical systems, I demonstrate the efficacy of functional models for diseases, such as diabetes, sleep apnoea, and epilepsy. To improve the safety, I put forward formal models which proof a specific system is deadlock and lifelock free.

The structure of this thesis follows my progression through the research work. To get a feel for the unique challenges of biomedical systems design my work initially focused on biomedical signals and algorithms for Computer-Aided Diagnosis (CAD). Building up a track record in this area allowed me to progress by introducing formal and model driven design methodologies to the process which realizes biomedical systems.

PUBLICATIONS RELATED TO THE THESIS

Published papers for thesis For full text, see Appendix ??:

1. O. Faust, U. R .Acharya, H. Adel, and A. Adeli. Wavelet-based EEG processing for computer-aided seizure detection and epilepsy diagnosis. Seizure, 26, (2015) 56-64. Published Online: January 2015
   Excerpts of this paper appear in the case study III of Chapter 3. The legal right to preprint these excepts was obtained from Elsevier Seizure, see Appendix ??.

2. O. Faust, U. R. Acharya, F. Molinari, S. Chattopadhyay, and T. Tamura. Linear and Non-linear Analysis of Cardiac Health in Diabetic Subjects. Biomedical Signal Processing and Control 7.3 (2012), pp.295–302. Published Online: July 2011
   Excerpts of this paper appear in Chapter 3. The legal right to preprint these excepts was obtained from Elsevier Biomedical Signal Processing and Control, see Appendix ??.

3. O. Faust, R. Shetty, S. Sree, S., U. R. Acharya, E. Ng, C. Poo, and J. Suri. Towards the Systematic Development of Medical Networking Technology. Journal of Medical Systems (2011) 35.6. pp. 1431–1445. Published: December 2011
   A substantial portion of this paper was used in Chapter 4. Reprinted, with permission, from Springer Journal of Medical Systems (JOMS), see Appendix ??.

4. O. Faust, U. R. Acharya, L. C. Min, and B. H. C. Sputh. Automatic Identification of Epileptic and Background EEG Signals Using Frequency Domain Parameters. Int. J. Neural Syst. 20.2 (Apr. 2010), pp. 159–176. Published: April 2010 **A substantial portion of this paper was used in case study III of Chapter 3.**

5. O. Faust, U. R. Acharya, B. H. C. Sputh, and L. C. Min. Systems Engineering Principles for the Design of Biomedical Signal Processing Systems. Computer methods and programs in biomedicine 102.3 (2011), pp. 267–276. Published Online: October, 2010

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First author peer Reviewed Journal Papers:

1. O. Faust, C. W. Yan, M. R. K. Mookiah, U. R. Acharya, E. Y. Ng, and W. Yu. Formal Design and Development of an Anterior Segment Eye Disease Classification System. In: Image Analysis and Modeling in Ophthalmology (2014), CRC Press, pp. 245–263.

2. O. Faust, U. R. Acharya, E. Ng, T. J. Hong, and W. Yu. Application of Infrared Thermography in Computer Aided Diagnosis: A Review. Infrared Physics & Technology 66 (2014), pp. 160–175.

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4. O. Faust, U. R. Acharya, M. Nergui, D. N. Ghista, S. Chattopadhyay, P. Joseph, T. Ahamed, and D. Tay. Effects of Mobile Phone Radiation on Cardiac Health. Journal of Mechanics in Medicine and Biology (2011) 11.05 (2011), pp. 1241–1253.

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Contributing Author Journal Publications:

1. L. H. Shan, O. Faust, and W. Yu. Data Mining Framework for Breast Cancer Detection in Mammograms: A Hybrid Feature Extraction Paradigm. Journal of Medical Imaging and Health Informatics 4.5 (2014), pp.756–765.

2. K. Y. Zhi, O. Faust, and W. Yu. Wavelet Based Machine Learning Techniques for Electrocardiogram Signal Analysis. Journal of Medical Imaging and Health Informatics 4.5 (2014), pp.737-742.

3. N. Z. N. Jenny, O. Faust, and W. Yu. Automated Classification of Normal and Premature Ventricular Contractions in Electrocardiogram Signals. Journal of Medical Imaging and Health Informatics 4.6 (2014), pp. 886–892.

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7. U. R. Acharya, O. Faust, V. S. Sree, D. N. Ghista, S. Dua, P. Joseph, V. I. T. Ahamed, N. Janarthanan, and T. Tamura. An integrated diabetic index using heart rate variability signal features for diagnosis of diabetes. Computer Methods in Biomechanics and Biomedical Engineering 16.2 (2011), pp. 1–13.

CHAPTER 1

INTRODUCTION

1.1 Rationale

The progress made by biomedical science is enormous, because it is fueled by both rapid development of computer systems and more ingenious algorithms for signal analysis. There is a need or social obligation to bring this progress to the people. One of the fundamental problems is that, in order for a biomedical health care system to be useful, it must be complex. This is usually referred to as the enormous complexity of practical systems. We show that the system complexity is coupled with a demand for reliability. We have introduced the term difficulty to express the impact of complexity and reliability on the system requirements. The term refers to either resources needed or cost incurred to meet the requirements. We argue that the difficulty increases exponentially with the complexity under the assumption that the same reliability is required. To cope with the increasing system complexity, it is necessary to move away from evolutionary system design and towards system based development. Evolutionary system designs make only progress, i.e. cope with the complexity problem, from one revision to the next. In contrast, systems based development incorporates feedback loops within the design methodology. Therefore, it can cope with the complexity problem much better.

Unlike mechanical systems, digital processing hardware and functional software do not wear out. Natural errors, such as bit-flip up or down are negligible compared to design faults. Both frequency and severity of design faults are positively correlated with the design complexity. The fundamental problem is that the complexity exceeds the intellectual grasp of a single human being. To cut down the system complexity into manageable parts, i.e. divide and conquer, is not a solution, because design errors are likely to occur when we put together the individual parts. For example, combining a poorly designed software module with slow processing hardware and actuators without safety locks caused the Therac-25 radiation therapy machine to malfunction. These malfunction events were responsible for the death of three patients and radiation poisoning for several others. The only way to reduce design faults, and thereby increase the system safety, is to bring our ability to master complexity in line with the system complexity.

One way to master system complexity in modern design is functional modeling. We establish that this fact also holds for biomedical systems. However, just modeling the system functionality is not sufficient to meet the system requirements. A methodical design approach is needed to create complex systems which are safe, reliable and functional. Systems engineering is such a methodical design approach. It defines a meta-model which has to be adjusted such that it fits a specific application domain. With the necessary meta model adjustments, systems engineering is applicable to a

wide range of biomedical projects. When it is employed, it will guide both technical and management teams to see the bigger picture, i.e. providing a holistic view. This is especially important for the engineering team, because engineers are usually bogged down by a great deal of technical detail and they (sometimes) miss the bigger picture. Therefore, each management decision, which impacts on their work, is seen as an intrusion and usually causes resistance. Systems engineering aims to minimize this resistance by providing adequate support structures for information exchange between different project teams. The well-thought-out support structures make the development process flexible and ultimately they enable the project team to cope with the inherent complexity problem of modern biomedical systems. Hence, systems engineering helps us deliver complex problem solutions on time and within budget.

In the biomedical area, we have high requirements on safety and reliability, because patient wellbeing or indeed patient life depends on the system. Therefore, an informal framework, such as systems engineering, is not sufficient to meet safety and reliability needs for modern biomedical systems. Mathematical rigor, within the design methodology, is required in order to achieve the needed safety and reliability levels. Within the systems engineering meta model, the specification refinement is the best place for mathematical rigor, because the specification defines how we build the system. As a consequence, we propose formal methods to describe the system specification. Such a formal specification can be model checked, i.e. we can proof certain safety properties of the system. By extending the systems engineering meta model with formal methods we have established formal and model driven design for biomedical engineering.

1.2 Objectives

The objective of this work is to benefit society by investigating the formalization of design processes for biomedical health care systems. The benefit of this investigation to society is twofold: the proposed model driven development leads to reliable systems which function according to specification. Reliability is important, because unreliable biomedical systems can cause harm and suffering and ultimately cost lifetime. The second point for model driven design is cost effectiveness. Cost is a big topic for health care systems, because it can be used to measure progress. In other words, progress for health care systems means to achieve more (relive more suffering) with less or equal capital investment. Having done extensive research on the individual fields of biomedical engineering, computer science and mechanical engineering puts us in position to propose the formal and model driven design methodology.

1.3 Importance and novelty of the proposed work

The importance of the proposed work comes from the fact that biomedical systems become more and more complex, at the same time more and more human live depends on these complex systems. The increase in complexity can only be managed with well thought out modeling and design strategies. The design of biomedical systems starts with an initial agreement process. Within the initial agreement process a group of

experts discusses and eventually establishes the need to build new health care systems or to design algorithms for computer aided diagnosis. It is of paramount importance that these health care systems are as safe as possible, within the given cost constraints. The proposed formal and model driven design methodology delivers safe problem solutions with little overhead and with the potential for large cost savings.

Formal methods are the application of logic to the design and analysis of software intensive systems, in our case software intense biomedical systems. They help us to establish specific system properties, such as deadlock, livelock and sequential functionality. Sequential functionality is especially important for biomedical systems, because we have to ensure that a system cannot exhibit a potentially harmful sequence of events. For example, a specific way of entering the Therac-25 radiation therapy machine initiate a radiation overdose to whoever happened to be in the diagnosis room. The fault was not detected with extensive testing, because that particular way of operating the machine was neither in the use nor in the failure case test protocols. Formal methods are one way to spot and subsequently eliminate the dangerous sequence of events.

There is another angle on the importance of the link between safety critical biomedical system failures and the design approach. Namely the surprising lack of recognition from regulation bodies. For example regulatory agencies, like the FDAs Center for Devices and Radiological Health (CDRH), assess device software to ensure that it conforms to standards for safety and reliability. Existing standards, however, concentrate only on quality system development processes, not the integrity of the software itself. Such an approach, though not entirely without its benefits, depends mainly on crafted test case construction and the results of test case executions for validation, with little regard for properties of the actual code. Keeping in mind that safety critical biomedical device failures endanger lives and indeed statistically cause deaths it is of paramount importance to make a clear case for formal and model driven biomedical systems design. That need definition must hold regardless of the particular realization of the design approach.

The novelty of the proposed work comes from the fact that it is located in the fertile ground between medicine, computer science and mechanical engineering. Medicine tells us the need for a particular problem solution and it provides a baseline of what can be achieved. Computer science provides algorithms and formalisms necessary to realize medical processes, such as diagnosis, treatment monitoring and patient administration. Mechanical engineering is the science of building highly complex systems. From mechanical engineering comes our conviction that highly reliable systems can only be achieved with a good design methodology. Formal and model driven design helps us to deliver biomedical systems on time and within budget.

1.4 Related efforts and prerequisites

Introducing formal and model driven design into biomedical engineering requires expertise from a diverse range of fields. A deep knowledge on biomedical systems and formal methods is required. System knowledge comes from detailed study and practical system realizations. To achieve the necessary focus, we dedicated our initial

research to Computer-Aided Diagnosis (CAD) systems. As such, CAD is a very active research field that attracts continued attention and indeed funding from medical as well as engineering bodies. The following sections outline the specific areas upon which the discussion of formal and model driven design for biomedical engineering is based.

1.4.1 Biomedical signals

The analysis of biomedical signals is prerequisite for designing physiological data processing algorithms and for building health care and diagnosis support systems. However, there is such a wide range of different biomedical signals that any work in this area can only focus on a limited number of them. Therefore, we specialized in Electroencephalogrphy (ECG), Heart Rate (HR) and Electroencephalograph (EEG). The following text provides a short introduction for these signals.

1.4.1.1 Electrocardiography (ECG)

Electrocardiography deals with the electrical activity of the heart [1], hence it provides plenty of physiological information [2]. The signal is monitored by placing sensors at the limb extremities of the subject. ECG is a faithful record which indicates both origin and propagation of electric potential through cardiac muscles. It is considered to be a representative signal of cardiac physiology, this makes it useful in diagnosing cardiac disorders. Changes in ECG signals can be related to sleep apnoea and these changes are caused by neuroautonomic and mechanical factors [3]. These changes are cyclic variations in both HR and ECG amplitudes / morphologies.

1.4.1.2 Heart Rate (HR)

The time between two consecutive heart beats, as shown in ECG signals, is used to obtain the HR signal. The time period is strongly dependent on a variety of neural, hormonal, and myocardial factors [4]. Heart Rate Variability (HRV) describes the variation of HR between two consecutive heart beats [5]. Traditionally, HRV is used to diagnose various cardiovascular diseases. More recently, HRV was used to diagnose diabetes.

1.4.1.3 Electroencephalography (EEG)

EEG is a recording of electrical activity along the scalp. Surface electrodes are placed on a number of well defined positions at the hair scalp. The electrodes record the electrical activities that is taking place in the brain. More specifically, EEG measures voltage fluctuations resulting from ionic current flows within the brain neurons. Hence, EEG can be used to diagnose brain diseases, such as epilepsy.

1.4.2 Modeling

Modeling is a significant part of research, education and practice in biomedical and health informatics [6]. To be specific, mathematical dependency modeling aims to produce reliable results which are, in some sense, relevant in the solution of a practical problem [7]. It is essential to have a clear vision of the fundamental principles of modeling [8]. In biomedical engineering, modeling is driven by the understanding of physical phenomena and modeling environment capabilities [9]. Modeling the physical phenomena helps us to establish the system functionality. In contrast, formal models establish system reliability and safety.

1.4.2.1 Formal modeling

Formal methods enable us to perform a special type of modeling where the system design techniques use rigorously specified mathematical models to build software and hardware systems. In contrast to other design systems, formal methods use mathematical proof in addition to system testing in order to ensure correct behavior [10]. However, formal models depend on a set of system level assumptions upon which the logic and ultimately the proofs are based. Therefore, formal models cannot avoid or fix incorrect or incomplete design assumptions. But, they can help to identify errors in the reasoning which would otherwise be left unverified. Usually, identifying errors or indeed proofing the absence of errors is referred to as gaining substantial insight into the system functionality.

Formal modeling, and the associated proofs, add two distinct advantages to the system design. Formal models provide a strong feedback point early in the design process. Without formal methods, the first strong feedback point is system testing. As such, testing the implementation comes late in the design process, therefore any error discovered during testing is very expensive to fix. In contrast, fixing a stable failure, uncovered when a formal proof fails, might be as easy to fix as changing the formal specification. The second benefit comes from the proof itself. Having a proof means we established, beyond reasonable doubt, a specific system property. That is very different from verification testing: A test can only confirm the presence of a fault but never the absence of one or multiple faults in the system.

We understand formal modeling as the process which converts human language requirements into algebraic notation. The algebraic notation constitutes the system specification. The clarity of such a formal specification is a benefit in itself [11]. Even with the aforementioned advantages, formal methods are not a silver bullet which eliminates all design problems. The process which turns the formal specification into an implementation is very important, because an error during the translation might invalidate the proofs. For example, the algebraic proofs are based on axioms and these axioms must hold in the implementation environment as well. Therefore, a great deal of system knowledge is required to judge on whether or not the axioms hold in the implementation environment. The desired situation is that the implementation environment itself ensures the validity of the axioms, because in such a situation the translation from the formal specification to the implementation becomes obvious and

less error prone.

1.4.3 Reliability of biomedical systems

The discussion on reliability for biomedical systems is started by reasoning about the need for this requirement. For the need definition we review the work of domain level experts. For example, Fox and Thomson argue that traditional clinical practices are proving unsustainable (e.g., overuse of drugs and investigations, waiting lists measured in years), and the cost of medical services continues to rise inexorably. In addition, high profile media exposes of clinical errors and increases in litigation, following North American trends, are forcing many European governments and healthcare agencies to acknowledge that their services have structural problems and that the reliability needs to increase [12].

1.4.4 Design methods

Computers are universal machines [13], therefore these devices can assist and empower experts from various domains. In the medical domain, computers help us to improve clinical records, timely prompts and reminders, as well as provide assistance in other care pathways. A number of well-known centers have pioneered such systems, in some cases over decades [14]. Their faith was justified, because objective benefits of computer support, on both clinical improvements and cost effectiveness, are emerging [15]. Therefore, it is only logical to scale these systems up and harvest the rewards on a larger scale. However, scale is a problem, because design methods, which simply scale up existing systems, almost always fail. Especially for complex networked systems which are composed from independent entities. Well thought out design methodologies are required to translate the progress made by biomedical sciences into benefits for people.

1.4.4.1 Systems engineering

Systems engineering is a methodical, disciplined approach for the design, realization, technical management, operations, and retirement of a system [16]. Systems engineering takes into account all steps necessary to create a system. The holistic approach results in safe and reliable systems, because negligence in any of the design steps leads to weaker and therefore less trustworthy systems. Hence, systems engineering has the potential to improve the design of systems where patient safety and process functionality is of paramount importance.

As with all structuring methods, systems engineering does not hold the solution to all problems in the health care domain. Issues that typically arise include the readiness of organizations to embrace a systems engineering approach, the degree of formalization that is appropriate for a given project, uncertainty about the metrics one should use to characterize the human factors that are inherent in a given system and what software tools can be adopted to facilitate the systems engineering processes [17, 18]. Once all these issues are addressed and there is a strong will to adopt

systems engineering, the design methodology opens up a path towards systems which are implemented on time and within budget.

1.5 Link between formal methods and implementation parameters

Formal and model driven design formalizes the practical project realization. In general the creation of a practical problem solution follows a process. The process is either explicit and structured or implicit and unstructured. The unstructured creation process is acceptable in a research setting where the process facilitates a venture into uncharted territories, because the nature of research is that outcomes are not precisely defined and there is some flexibility in the approaches taken. For an industrial setting a more structured approach is necessary, because the outcome, i.e. the product is better specified and most of the time the outcome is just an improvement of an already existing product. The difference between industry and research design approaches explains, to a certain extend the absence of formal methods in academic research design. Furthermore, systems created through the research design approach, are rarely deployed in clinical settings. Hence, system safety is not high on the agenda for such proof of concept systems.

To explain the link between formal methods and implementation parameters it is important to highlight that the majority of faults in electronic components are due to design errors. For all practical problem solutions, it is impossible to test the electronic components in such a way that the absence of faults can be guaranteed. In other words, testing can only confirm the presence of a fault. As a consequence the number of system faults can only be limited with a well thought out design strategy. Systems engineering is such a well-structured design strategy. The systems engineering metamodel structures the design process into need definition, requirements capturing, specification refinement and implementation. The idea of formal and model driven design for biomedical engineering was to extend the specification refinement with formal methods in order to control and limit safety critical design faults.

Having a well-structured design strategy, with formal methods at the heart, has a number of benefits. The most important benefit is clarity. In biomedical engineering and electrical systems design there are numerous terms that relate concepts to the design process. The next sections give a brief description on how the concepts are related to formal and model driven design for biomedical engineering.

1.5.1 Computational complexity

Computational complexity is calculated based on the functional model, because the functional model determines what system we build. It is a serious mistake if the formal model changes the computational complexity, because that means the algorithm, which determines the functionality, is changed. When the algorithm is changed, the properties, such as classification accuracy and sensitivity, evaluated with the functional model are not valid anymore.

1.5.2 Speedup

Speedup describes the benefits of parallel processing. In general, if a task is divided into N equally complex subtasks and these tasks are processed with N processors then the speedup is at most N. Formal models, such as CSP, describe the creation of these subtasks. For example, the direct ANN model, discussed in the presentation used 18 processes to describe the 6 x 3 neuron network. Executing the neuron functionality is a subtask and the computational complexity of the neuron functionality is the same for all 18 neurons. Hence, the maximum speedup is 18, that means the parallel realization of the ANN functionality, described in the direct model, can execute up to 18 times faster compared to a serial (single line of execution) realization. For example, Matlab code, without the use of the parallel processing toolbox, uses only a single line of execution. The speedup definition provides a maximum value which cannot be obtained with practical systems, because of communication overhead. To be specific, splitting a task into multiple subtasks implies that the processors, which process these subtasks must communicate with one another. The time it takes for that communication to happen is referred to as communication overhead. The particular value of communication overhead depends on the processing architecture, i.e. the implementation target.

Another important concept, which is related to parallel processing is state space. The state space opens up when two or more independent entities process the subtasks. The state space increases with the number of processes and with the degree of freedom these processes have. A large state space is a design issue, because design faults, such as deadlocks and livelocks are more likely to happen in large state spaces. The first reason for the increased number of design faults in larger state space comes from the fact that there is more space for them to happen. The second argument which highlights the potential problem created by a large state space are centered on the assumption that the system complexity, expressed in a large state space, easily exceeds the capability of a single human mind. As a consequence a designer abstracts and generalizes the processes. The abstraction and generalization is likely to create design errors when the individual components are integrated to form larger systems.

1.5.3 Processing time

A practical measure of the time it takes to complete a specific task. The processing time is target specific, because the processing time can only be established after the system is implemented. The processing time is used to determine the speedup of different implementations. There are two ways of determining the processing time:

1. Measurement: Most practical way of establishing the processing time.

2. Instruction counting: Error prone method. But if it is executed correctly more accurate than the measurement, because measurements can influence the processing time.

Both, measurement and instruction counting are only valid in hard real-time environments. In hard real-time environment no interrupts are possible, because interrupting

a processing system means to divert the line of execution and hence the processing time for a specific task becomes nondeterministic. The matlab environment takes that non-determinism problem into account by measuring only the processing time. Such a setup allows to compare algorithms, but it is, strictly speaking not a measure of the time it takes for a particular system to execute a specific task. Hence, matlab code, executed by an operating system, is not real-time.

1.5.4 Real time

Real-time means to execute a specific task in a specific time period. Both the time period and the processing task are application specific. However, the time it takes to execute the task is target specific. The processing task is determined by the functional model and the specification determines how the task is processed. The processing target is part of the specification, therefore the specification must ensure that the real time requirement is satisfied.

1.5.5 Discussion

Biomedical systems design is a complex task that involves multiple steps. The way in which we structure these steps will determine not only the system functionality but also the system safety. In the thesis, we proposed to split the design flow into need definition, requirements capturing, specification refinement and implementation. Having such a well thought out design methodology helps us to deal with computational complexity, speedup, processing time and real time.

1.6 Thesis structure

The thesis structure was shaped by the objectives of the work and the chronological buildup of expertise. Chapter 2 outlines the vision for formal methods in biomedical engineering. We put forward that biomedical system designs must follow structured and documented processes. The structure should include the following phases:

- Need definition – In this phase we have to answer: Why do we need a physical problem solution?

- Requirements capturing – In this phase we have to answer: What system do we have to build?
  Functional models help us to establish what a system can do. These models involve sophisticated data analysis and classification algorithms. The functional model results can be compared with the implementation output. Establishing a positive correlation between the model and the implementation output instills trust in the physical problem solution. Furthermore, the model results can be compared with the results of functional models created by other scientists and practitioners working in the field. The resulting competition will improve the functional model and ultimately the physical problem solution.

- Specification refinement – In this phase we have to answer: How do we build the system?
  Formal methods help us to establish the system specification in an unambiguous and logical way. Only for formal specifications, model checking can be used to establish specific system properties, such as functionality deadlock and lifelock. Generally speaking, formal methods force the design team to think deeply about the system functionality early in the design phase. The clarity gained through modeling the system functionality, with formal methods, benefits the implementation step.

- Implementation – In this phase we build the physical problem solution.

- Testing – Failure and use case testing instill trust in the physical problem solution.

To support our ideas on formal and model driven biomedical systems design, the first content chapter presents a survey on the topic and identifies a research gap. To be specific, given the current and predicated importance of formal and model driven design for biomedical engineering, there is not sufficient research on that specific topic. The subsequent chapters provide background and outline case studies that support the point of having formal and model driven design for biomedical engineering.

Chapter 3 discusses the creation of functional models as part of the requirements capturing process. The discussion focuses on the design pattern used to establish such functional models for CAD systems. The design pattern are common for a wide range of functional models. While the algorithms used to establish the needed functionality are distinct for the individual functional models. To support the point about communality and distinctiveness, we put forward two CAD related case studies. The first case study focuses on diagnosing diabetes based on HR signals. The second case study proposes an algorithm structure to support epilepsy diagnosis based on EEG signal. These two distinct case studies were conducted according to a subset of processes defined in the formal and model driven design methodology. To be specific, we describe need definition and the functional model based requirements capturing. Through careful analysis, we learned that the the functional models, for CAD systems, require data analysis and classification. The definition of these processing steps and the associated quality assessment measures are the main results communicated in this chapter.

In Chapter 4 we abstract from individual biomedical systems, that solve specific problems, by discussing health care systems in general. Requirements capturing and specification refinement for health care systems starts with semantics. For example, we define the term hospital network to describe a group of hospitals that work together in order to coordinate and deliver a broad spectrum of services to the community [19, 20]. Once the semantics are established, we use the systems engineering design methodology to structure a discussion on personalized health care. The need definition establishes that the level of personal health care is much higher in urban centers than in rural areas. The resulting health care divide means, people in rural areas suffer more compared to people living in urban centers. That is a powerful

incentive to build physical problem solutions which aim to narrow the health care divide.

Chapter 5 puts the individual ideas together by proposing a formal and model driven design for a biomedical decision making system. We have used the systems engineering meta model to structure the design process which led to the realization of a physical problem solution. We argue that the formal specification refinement gave a deep insight into the system functionality. Furthermore, we could proof safety features, such as the absence of deadlock and livelock. That makes us confident that the physical problem solution is safe, reliable and functional. The document concludes with Chapter 6.

CHAPTER 2

FORMAL METHODS FOR BIOMEDICAL ENGINEERING

2.1 Summary

Physiological signals, medical images, and bio-systems can be used to assess the health of a patient and they can support practitioners by improving both diagnostic and treatment monitoring processes. Biomedical systems in healthcare applications can help by extracting features, automating diagnostic decision and keeping patient records. These systems aim to improving the quality of patient care through safe, reliable and functional physical problem solutions. In the current chapter, we argue that a formal and model driven design methodology can help us to create systems which meet these requirements. During the argument, we observed that modeling is not new to biomedical sciences, but modeling for systems design is less explored. To fill that gap, we review a number of design techniques for biomedical systems and we describe a practicable design example on Computer-Aided Diagnosis (CAD) and automated decision making.

2.2 Introduction

It is well recognized that, as humans get older, they are more likely to depend on biomedical systems for their wellbeing. In recent years the growing dependency has sparked rapid development and wide spread deployment of biomedical systems. These systems have progressed from single purpose island systems to massively networked health care systems with personal health records [21, 22]. Another fact, which documents the rapid progress, is that these networks distribute an ever increasing amount of biomedical data [23, 24]. Therefore, our society is more and more dependent on a technology which gets more and more complex. Biomedical systems help physicians to cope with the complexity by providing computer output based on quantitative analysis of biomedical data [25, 26]. More specifically, CAD has become one of the major research subjects in biomedical engineering [27, 28]. The basic concept of CAD is to provide a computer output which serves as a "second opinion" to assist biomedical data analysis [29]. Hence, for the development of a successful CAD scheme it is necessary to create or select computer algorithms and investigate their usefulness. A prerequisite for determining the usefulness is to answer how helpful the computer output would be for the diagnoses, how to quantify the benefits of the computer output as well as how to maximize the effect of the computer output on the diagnoses [30]. Thus, large-scale observer performance studies, using a reliable methodology, such as Receiver Operating Characteristic (ROC) analysis [31], are as important as the development of computer algorithms in the field of CAD. From these diverse requirements

it is understandable that research and development of CAD has involved a team effort by investigators with different backgrounds, such as physicists, radiologists, computer scientists, engineers, psychologists and statisticians [32].

Even though, CAD is just a subfield of biomedical engineering, it is still very broad, therefore the CAD concept can be applied to both imaging modalities, and bio-signals [33, 34]. However, the majority of CAD schemes developed in the past include the detection of breast lesions on mammograms [35, 36, 37, 38], the detection of lung nodules in chest radiographs [39, 40] and thoracic Computed Tomography (CT) [41, 42, 43], as well as the detection of polyps in CT colonography [44, 45, 46]. However, there is a downside of relying too much on machine based decision making, because human decisions are more reliable when compared to machine generated decisions [47]. In Section 2.3 we show that the need for reliability is clearly recognized on both algorithmic and systemic levels, by reviewing algorithms used in CAD systems. But, there is a gap which opens up during systems design. The gap results from the fact that the demand for reliability impacts on the system requirements, because the reliability requirement is more difficult to achieve for complex systems. In this case, the word difficulty expresses the increase in resources or cost in general to meet the requirement. Over time, the increase in system complexity coupled with similar levels of reliability has caused an exponential rise in the difficulty to meet the system requirements.

In general, high reliability systems need extensive modeling during the design phase. Therefore, it is quite natural for biomedical systems to employ information modeling. Examples for modeling in biomedical system design are given in Section 2.4. Despite the wide spread use of modeling, Kent at al. argue that biomedical information system designers regard modeling as low priority [48]. Designers rush through the design phase and implement hardware and software solutions only after brief assessments of domain requirements. Rushing through the design process results in a rapid development cycle, but the system usually does not or not completely satisfy the user needs and the developers are forced to re-design certain aspects of the system. More fundamentally, projects with a rapid development cycle follow an evolutionary design methodology [49, 50] which makes it difficult to cope with a steep requirement increase. The reason for this slow progress comes from the fact that the evolutionary approach relies on progress which is made from one system generation to another. Unfortunately, even with a rapid development, the product or system lifecycle is still counted in years instead of month or weeks, therefore the evolutionary progress takes time. But, with the exponential rise in difficulty the requirements (or demand) outpaces the rate of progress achievable with evolutionary system design methodologies. Therefore, all solutions to this fundamental problem require a paradigm shift.

Having established the need for a paradigm shift we have to look for solutions from other areas, else there is a danger of reinventing the wheel. Engineers deal with systems all the time, therefore it is likely that there are engineering solutions for this problem. In biomedical engineering the problem is that we have to build highly complex systems which must be very reliable. Aerospace engineers are frequently confronted with similar situations. They have to build flying machines which carry

humans and goods through three dimensional space from point A to point B. In 1961, point A was Cape Canaveral here on earth and point B was the southern Sea of Tranquility on the moon. The Apollo program was setup to build a physical solution for this aerospace problem. The engineers, involved in this project, did not experience an exponential growth in requirements, they saw the requirements jump to another level. This jump was fueled by the same factors which currently drive the requirements for biomedical systems: technical complexity and reliability. Therefore, it is natural to investigate how the engineers, during that time, overcame these massive obstacles. To start with, they had some of the brightest minds working on the project. However, there is a limit of what even the brightest minds can do without appropriate support structures. These support structures came in the form of design methodologies. More specifically, the Apollo program used an engineering method called systems engineering [51]. Many experts believe that the consequent application of systems engineering principals lead to ultimate success. In Section 2.6 we elaborate on design methods for biomedical systems, with a focus on the systems engineering methodology.

In the current chapter, we adopt the position that formal and model driven design approaches can improve the reliability of biomedical systems. We support our decision to advocate systems engineering as a possible solution for the problem of the exponential rise in the difficulty to meet the system requirements by discussing a practical biomedical decision making system. To construct the system, we have extended the systems engineering design methodology with formal modeling. The resulting framework constitutes the backbone of the formal and model driven design methodology.

This chapter is structured such that it helps us to introduce formal methods to systems engineering. In Section 2.7 we sketch out our design approach by establishing the need for a safe and reliable decision making system. Lastly, specification refinement and implementation are described. The chapter is written in the form of an argument, which culminates by showing a formal specification for a biomedical information processing system. Therefore, we close this chapter directly with the conclusion in Section 2.9.

2.3 Reliability of biomedical systems

We start the discussion of reliability for biomedical systems by reasoning about the need for this requirement. Fox and Thomson argue that traditional clinical practices are proving unsustainable (e.g., overuse of drugs and investigations, waiting lists measured in years), and the cost of medical services continue to rise inexorably. In addition, high profile media exposes of clinical errors and increases in litigation following North American trends are forcing many European governments and healthcare agencies to acknowledge that their services have structural problems and that the Quality of Service (QoS) needs to increase [12].

A major aspect of system quality is reliability which means one aspect of improving the QoS is to make biomedical systems, such as CADs, more reliable. This aspect is well understood in the biomedical research community. There is no shortage on

projects which incorporate reliability as one of their goals. In the next sections we review CAD algorithms in terms of their claims on reliability.

2.3.1 Reliability of algorithms used in computer aided diagnosis

An algorithm is a finite list of instructions for calculating a function [52]. Reliability of algorithms is normally related to the function itself and not to the machine executing the instructions. To be specific, algorithm designers require their algorithm to perform the functionality reliable in some statistical sense. In most cases, the reliability assessment is supported by experimental results which yield the required data for statistical analysis. For example, an algorithm for visual positioning of previously defined regions of interest on microscopic slides is assessed in terms of its tolerance to possible variations in visual appearance due to slide rotations, scaling and illumination changes [53]. Other algorithms are assessed based on their ability to perform in well-known scenarios [54, 55]. This leads to statements like: Algorithm accuracy and robustness were demonstrated on two tissue-mimicking phantoms, subjected to controlled amount of angular deviation and the proposed method shows a great reliability in the prediction of these phantoms [56].

Biomedical systems must be reliable, because human wellbeing and even human life directly depends on the correct functionality of these systems. Therefore, researchers constantly thrive to improve the reliability of the algorithms used to construct these systems [57, 58, 59, 60]. Reliability in the communication of data analysis results, from medical personal to patient, is also an important topic. Researchers in biomedical sciences thrive to make the results as accessible as possible [61]. Measures for reliability are sensitivity, specificity and positive predictive value. These reliability measures are of particular importance for classification algorithms. Soda and Iannello worked on the aggregation of classifiers for staining pattern recognition in antinuclear autoantibodies analysis. In terms of reliability, their contribution was a framework, where a novel parameter measures the reliability of the final classification [62]. In their work on detection of multiple sclerosis classification, the experimenters claim that the use of multiple stimulation patterns appears to improve the reliability of the algorithm [63]. Authors have used auditory stimulus optimization with feedback, where optimized algorithms showed a higher reliability [64]. These classification systems can be used in CAD systems.

The reliability of measurements is also an important topic in biomedical science. In general biomedical data is noisy, riddled with artifacts and dependent on the particular measurement setup. Data, such as Magnetic Resonance Imaging (MRI) and physiological signals, can be analyzed and assessed for their reliability with unsupervised clustering methods [65]. Sun et al. present numerical methods and a workstation for the quantitative analysis of real-time myocardial contrast echocardiography. They have illustrated a range of clinical studies to indicate the effectiveness of the system and the reliability of the methods [66]. Even with rather reliable data, one major requirement for algorithms was that the results must be more reliable than the input data [67]. Katouzian et al. have described the challenges in atherosclerotic

plaque characterization with intravascular ultrasound. For this characterization system they have explored the reliability of both the training dataset and the recognition algorithm complexity [68].

A Support Vector Machine (SVM) system for the characterization of clustered microcalcifications using mammograms was proposed [69]. The microcalcifications regions were segmented using edge detection and morphological methods to extract features based on shape, texture, and statistical values. The SVM classifier with Radial Basis Function (RBF) kernel presented 97% accuracy, and the SVM classifier with polynomial kernel gave 95% accuracy. Automatic detection of Clustered Microcalcificationss (MCs) in digitized mammograms was proposed [70]. The pixels of MC were detected and grouped into MC objects using a multilayer feed forward neural network classifier. Seventeen statistical features were extracted from the MC objects and fed to an Adaboost with SVM classifier yielded 89.55% mean true positive detection rate.

Gene expression was used to distinguish benign and malignant thyroid carcinoma. The immunohistochemistry correctly classified 90.6% of fine-needle aspirations and 85% of follicular thyroid adenomas [71]. Fluorescent scanning was used to classify benign and malignant thyroid carcinoma and obtained an accuracy of 90% [72]. Acharya et al. have extracted relevant Discrete Wavelet Transform (DWT) and texture features from the Contrast Enhanced Ultrasound (CEUS) thyroid images [61]. These features, coupled with K-Nearest Neighbour (K-NN) resulted in the classification (benign and malignant) accuracy of 98.9%, a sensitivity of 98%, and a specificity of 99.8%.

Texture and motion pattern features were extracted from carotid atherosclerosis images and fed to a fuzzy C-means classifier for classification into symptomatic and asymptomatic plaques [73]. The experimenters were able to classify 74% of plaques based solely on texture features, 79% of plaques were correctly classified based entirely on motion features and 84% were correctly classified using a combination of motion and texture features. The texture features, coupled with SVM classifiers, were used for the automated identification of symptomatic and asymptomatic plaque images [74]. The classification accuracy was 82.4% for a SVM classifier with RBF kernel.

A clinical trial is under way to examine the impact of metabolic control over time in children with type 1 diabetes, as compared to standard insulin treatments due to the infusion of autologous cord blood stem cells [75]. The results showed that an infusion of cord blood stem cell was safe. Furthermore, this technique may provide some slowing of the loss of insulin production in children with type 1 diabetes.

Biomaterials or new drugs must be biocompatible, only then they can be used in a clinical setting [76]. For example, a defective heart valve which is replaced by a mechanical valve implant. This valve is coated with pyrolytic carbon, and secured to the surrounding tissue with a mesh of woven fabric called Dacron™ (du Pont's trade name for polyethylene terephthalate). The mesh allows for the body's tissue to grow while incorporating the valve [77].

In the past, telemedicine was made possible using telephone and radio. Recently these techniques were supplemented with video telephony, advanced diagnostic methods are supported by distributed client/server applications, and telemedical devices

to aid in-home care [78]. Developments in mobile collaboration technology have been benefited from using hand-held mobile devices which allow healthcare professionals in multiple locations to view, and monitor patient issues as if they were in the same room [79].

Karimi et al. presented a technique which uses wavelet analysis and Artificial Neural Network (ANN) for analyzing heart sounds to detect coronary artery disease [80]. They detected normal classes with 90% accuracy and coronary artery disease classes with 85% accuracy. A combination of uncertainty methods (fuzzy and probabilistic) was used in the diagnosis of coronary artery disease using Electroencephalogrphy (ECG) stress signals, and the experimenters observed an accuracy of around 80% [81]. Binary Particle Swarm Optimization (BPSO) and genetic algorithm techniques were used to extract features from exercise stress testing data. The system obtained 81.46% accuracy in coronary artery disease detection using SVM classifier [82]. Babaoglu et al. also used Principal Component Analysis (PCA) for dimension reduction on the same dataset, with that strategy they obtained an accuracy of 79.71% with the SVM classifier [83].

A wavelet-chaos-neural network methodology was used for classification of healthy, ictal, and interictal Electroencephalograph (EEG) classes [84]. Wavelets were used to decompose the EEG signals into delta, theta, alpha, beta, and gamma sub-bands. Standard deviation, Correlation Dimension (CD), and Largest Lyapunov Exponet (LLE) were extracted from the sub bands. A Spiking Neural Network (SNN) was developed using three training algorithms (SpikeProp, QuickProp, and RProp). With the RProp algorithm, the SNN classifier obtained an accuracy of 92.5%, using the mixed-band feature space consisting of nine parameters (CD and LLE from wavelet coefficients). The researchers obtained an accuracy of 96.7% using the Levenberg-Marquardt back propagation neural network and a mixed-band feature space consisting of nine parameters [85]. Lyapunov features were used in a Recurrent Neural Network (RNN) for classifying the three classes with an efficiency of more than 96% [86]. Higher Order Spectra (HOS) features were found to be significant enough for differentiating normal, interictal and epileptic EEG signals [87]. On using the HOS features in Gaussian Mixture Model (GMM) and SVM classifier, they obtained accuracies of 93.11% and 92.67%, respectively [88].

A Clustering Linear Discriminant analysis Algorithm (CLDA) was used to decode hand movement directions from a small number of training trials for magnetoencephalography-based Brain Computer Interfaces (BCIs) [89]. CLDA starts with a spectral clustering algorithm which automatically partitions the BCI features into several groups where the within-group correlation was maximized and the between-group correlation was minimized. The results show an average accuracy of 87% in decoding of four directions for single movement. The design of spring-loaded crutches was optimized for reliability by choosing an appropriate spring stiffness based on their dynamic characteristics [90].

Acoustic attenuation coefficients, wavelet coefficients and Autoregressive (AR) model coefficients were used as features for a Bayes classifier to classify steatosis and normal livers [91]. The results show very high sensitivity ($\approx$95%), specificity

(≈95%), and accuracy (≈95%). Using only the AR model coefficients, the experimenters obtained accuracy, sensitivity, and specificity dropped to 90%, 87%, and 95%, respectively. Three types of liver images, namely, normal, hepatoma, and cirrhosis, were classified using fractal feature vector based on M-band wavelet transform [92]. The results show that a hierarchical classifier was least 96.7% accurate in classifying normal and abnormal liver images.

Variables, such as age, menopausal status, maximum tumor diameter, tumor volume, locularity, presence of papillary projections, presence of random echogenicity, presence of analyzable blood flow velocity waveforms, peak systolic velocity, time-averaged maximum velocity, pulsatility index, and resistance index were obtained from 52 benign and 15 malignant transvaginal B-mode ultrasonography images [93]. These features coupled with back propagation method, obtained sensitivity and specificity of 100% and 98.1% respectively. Zimmer et al. proposed an automatic analysis of benign and malignant ovarian cancer ultrasound images by quantification of grey-level intensity variations (mean, standard deviation, etc.) [94]. They obtained a low accuracy of 70% for tumors containing solid portions.

Advanced image processing, data mining techniques, and computer simulations were used to improve the diagnostic accuracy in healthcare systems, such as ophthalmology [95]. Glaucoma and Diabetic Retinopathy (DR) are common eye diseases which may cause vision loss, if not diagnosed early enough [96]. Thermography using Infrared (IR) imaging is an effective noninvasive imaging technique that is widely used in the medical field. This technique detects temperature changes in vascular tissues, hence, it provides an instrument with which to study ocular surface temperature and ocular diseases [97].

2.4 Modeling

Modeling is a significant part of research, education and practice in biomedical and health informatics [6]. To be specific, mathematical dependency modeling aims to produce reliable results which are, in some sense, relevant in the solution of a practical problem [7]. Despite widespread applications in biomedical research, the role of models and modeling is often controversial and ill understood. It is usual to find that fundamental definitions, axioms, and postulates used in the modeling process have become implicit assumptions. It is essential to have a clear vision of the fundamental principles of modeling [8]. In biomedical engineering, modeling is driven by the understanding of physical phenomena and the modeling environment capabilities [9]. For example, biomedical phenomena can be modeled in terms of metabolomics [98, 99, 100, 101], genomics [102, 103, 104, 105], and proteomics [106, 107, 108, 109, 110, 111]. In these fields, very complex models have been used to understand the behavior at a decreasing scale: from metabolomics, which is focused on the system, to proteomics, which is focused on the proteins, to genomics, which is focused on genes. In general, the decreasing scale was associated with more model data and modeling algorithms with higher computational complexity [112]. Therefore, the processing requirements for the modeling environment increased [113].

We explore modeling for biomedical system design from three different perspectives: formal modeling, biomedical informatics and processing platforms. Each of these domains has requirements and expectations on the model.

2.4.1 Formal modeling

Computer simulation enables system developers to execute a model of an actual or theoretical system with a computer and analyze the execution output. Peleg et al. have used Petri Net tools to study systems behavior. The systems were represented using three kinds of biomedical models: a biological workflow model used to represent biological processes, and two different computer-interpretable models of health care processes derived from clinical guidelines [114]. A typical example of formal modeling is the mathematical formulation of working-memory capacity limits proposed on the key assumption of mutual interference between items in working memory [115]. Tarakanov and Dasgupta have presented a functional model based on the features of antigen, antibody bindings in the immune system [116]. Hakman and Groth have designed a system which integrates quantitative simulation with symbolic reasoning techniques, under the control of a user interface management system, using a relational database management system for data storage and interprocess communication [117]. Lyons and Arbib have used port automata to model sensor based robotics. This formal model ensured consistency and well-definedness, and it facilitates plan verification as well as automatic plan generation [118]. Bernot et al. have provided a computer science approach to treat temporal properties of biological regulatory networks, expressed in formal computational tree logic [119]. Jetley et al. have used formal methods to model medical device reviews [120]. Arney et al. have based their development of a patient-controlled analgesia infusion pump on formal methods [121].

2.4.2 Biomedical informatics

Biomedical informatics is the science of information, applied to or studied, in the context of biomedicine [122]. While we are still in the process of identifying and defining the underlying principles, educators and practitioners are increasingly acknowledging the growing importance of computer science in medicine. The technology itself is growing at rates that make the future of the field both unbounded and impossible to predict [123]. However, a general problem with all software based systems is the almost limitless state space of such systems. In order to create awareness and to manage this huge state space, biomedical information uses modeling. Maojo et al. have provided an overview of current approaches related to biomedical informatics and genomic medicine, particularly in Europe [124]. Objects play a major role in both database and artificial intelligence research [125]. Hakman and Groth have addressed the issue of modeling objects with a new object-oriented biomedical continuous system modeling language. With the object oriented approach, complex models were structured as multilevel, multi-component model hierarchies [126]. Another application area for biomedical informatics is prediction and reaction of current and future bioterrorist attacks. The challenge is that a comprehensive and timely

response requires data acquisition, threat detection, and response infrastructure with unprecedented scope in time and space [127].

2.4.3 Processing platforms

Telemedicine has emerged as a new health care field. The new field offers health care providers, professionals and patients a plethora of opportunities to respond to social and geographical inequalities in health care provision [128]. A prerequisite for telemedicine is the design and development of safe, reliable and functional processing platforms. Manolokos et al. have proposed a parallel processing system for biomedical signal processing that is optimal in terms of total execution time for multiple pipelined data blocks [129]. Bajaj et al. have implemented a computational environment to produce libraries of executable, combinable and customizable computer models of natural and synthetic biosystems, which provide a supporting framework for the predictive understanding of both structure and behavior. The environment was designed by multi-scale geometric modeling and multi-physics simulations [130]. A Biomedical Sensor Network (BSN) is a small-size sensor network for medical applications, that may contain tens of sensor nodes. A formal model was used to validate and tune the temporal configuration parameters of a BSN in order to meet desired QoS requirements on network connectivity, packet delivery ratio and end-to-end delay [131].

2.5 Traceability in safety critical systems

Traceability is a very important aspect of safety critical systems design [132, 133]. When a fault happened we need to find out what went wrong. There is the issue of responsibility and the level of guilt. From a systems design perspective there is not such a thing like an unavoidable technical defect. A defect, in an active component of a biomedical system, indicates either a design or a maintenance or a manufacturing problem. Traceability means that we can trace back the design steps which led to the particular system setup. Tracing back the design decisions might uncover immoral behavior like criminal negligence.

Another very important aspect of traceability is the ability to improve the design process [134]. Only if we have a documented design process, such as the meta model, can we maximize the improvement by learning from past mistakes. Learning also happens when there are no design documents, but the learning is unstructured and erratic. Hence, without a design methodology improvement through learning comes down to personal effort. These personal efforts yield improvements which are not shared between relevant people and departments. The situation is different with formal and model driven design for biomedical systems. The formal model plays an important role for traceability. Following scientific reasoning, we will put forward the possible shortcomings of formal models. In case a fault happens there are only four things which might have gone wrong. Let's start with the least likely issue first: the formal proof was incorrectly executed. For example, an automated model

checker tool, like FDR[1], had a bug. Highly unlikely, because the tools have been developed with formal methods themselves. The second issue with formal methods is that the context of the proof. A proof is based on specific assumptions, hence the proof is only valid if and only if these assumptions hold. For example, if it is assumed that data is coming in a specific sequence, and the system relies on that sequence, then the formal proof is not valid, in the implemented system, when the data is allowed to come in another sequence. Issue number three is the translation of the formal model into the implementation. That translation is the most error prone, because it is largely done by hand with little or no tool support. The translation is a creative process with some margin of error. Furthermore, the translation process can only be standardized when both the formal method and the implementation target are fixed. However, there is lots of progress on the implementation targets, i.e. changing processor architectures and processing environments. Hence, formalizing the translation process is a challenge, because the implementation target changes. The final point, why a formal and model driven design can go wrong, is the implementation target itself. For example, there might be a fault in the processing chip or there might a bug in the implementation of the programming language used to implement the software part of the biomedical system.

Any fault encountered in the physical system falls within one of the four categories, for systems which were designed with formal and model driven design. Having well defined fault categories and structured design processes means tracing is possible. First, we check whether or not the formal model was translated correctly. Second, we compare the assumptions which led to the formal model creation with the actual scenario encountered with the implementation. Next, we check for bugs and faults in the implementation target framework. Finally we suspect the proof based on the formal model.

Tracing back a fault to any of the four areas leads to stronger system realization in the future, because the lessons learned from the tracing activity will become part of the domain specific meta model. These are very important points in favor of the formal and model driven design methodology.

2.6 Design methods

According to Turing, computers are universal machines [13], therefore these devices can be used to provide various forms of assistance to clinicians, such as better clinical records, timely prompts and reminders, and assistance in following care pathways. A number of well-known centers, particularly in North America, have pioneered such systems, in some cases over decades [14]. Their faith was justified, because objective benefits of computer support on both clinical and cost effectiveness are emerging [15]. It is logical to scale these systems up and harvest the rewards on a larger scale. However, scale is a problem, because design methods which simply scale up existing systems almost always fail. Especially for complex networked systems which are composed from independent entities. Well thought out design methodologies are

[1]Formal Systems (Europe): `http://www.fsel.com/`

required to translate the progress made by biomedical sciences into benefits for people.

There is no shortage in very specifically targeted design methods for biomedical systems. For example, Shah et al. have used an object-oriented design methodology to design and develop a software system in a modular fashion [135]. Fox and Thomson have described both development and application of a unified technology for clinical decision support and disease management. Their work was based on logic engineering, a distinct design and development methodology which combines concepts from knowledge engineering, logic programming, and software engineering [12].

All these projects were done by domain level experts and outstanding researchers. However, all the literature they produced just documents the project design which was executed. This is a problem, because the research papers do not document the thought process which led the authors to adopt a specific way of designing a system. That means, lots of implicit knowledge is required to design biomedical systems successfully and the design process takes a considerate amount of creative energy. Now, domain level expertise is always required, however the energy spend on thinking about the design process can be reduced. The way to achieve this reduction is by following well proven and standardized design methods. The following sections introduce systems engineering as a well proven and successful design methodology.

2.6.1 Systems engineering

Systems engineering is a methodical, disciplined approach for the design, realization, technical management, operations, and retirement of a system [16]. Systems engineering takes into account all steps necessary to create a system. The methodical approach leads to reliable and safe systems, because negligence in any of the design steps results in weaker and therefore less trustworthy systems.

The design and development of safety critical information systems can benefit from adopting the full systems engineering approach. Particularly with regard to bringing a human-centered perspective to the formulation of system requirements and the configuration of effective user interfaces [136]. This helps us to design medical information systems which have to provide a reliable link and good coordination between hospital departments [137].

Despite the many positive properties and striking advantages, structuring methods, such as systems engineering, cannot provide the solution to all health care problems. Issues, that typically arise upon the introduction of systems engineering, include the readiness of organizations to embrace the new approach and specifying the degree of formalization that is appropriate for a given project. More specifically, the question is what metrics one should use to characterize the human factors challenges that are inherent in a given system and what software tools can be adopted to facilitate the systems engineering processes [17, 18]. Nevertheless, systems engineering can be applied to a wide range of engineering problems. For example, Diez et al. used the systems engineering methodology to develop computer-supported learning systems [138]. Palanisamy and Selvan proposed a novel method for identifying relevant subspaces for data mining using fuzzy entropy and perform clustering [139]. Their theories and algorithms were evaluated through experiments which were designed

according to the systems engineering method.

The next section introduces the design of an ANN classification system. We use this design to introduce systems engineering in greater detail and we put forward formal methods as a useful extension in the specification refinement step.

2.7 Formal methods in embedded decision making: an abstract example

The embedded decision making system design illustrates some of the ideas, which were developed above, in a more practical setting. We follow the systems engineering meta model, shown in Figure 1, to design the system. The systems engineering meta model describes an iterative design process where both ideas about and understanding of the problem get more and more concrete. The need definition is still speculative and it is the phase where ideas get thrown around. At the end of speculative stage a group of experts decides whether or not the project progresses to the requirement capturing phase.

Requirements define what the system is expected to achieve and they should be obtained as a result of an informed discussion [140, Chapter 1]. Therefore, field specific research work and the associated functional models constitute some of the system requirements. Analyzing field specific research answers questions about the work context. To be specific, it answers the questions like: "What can be achieved?" and "What are the most promising approaches to solve a problem in practice?". It is not uncommon that a specific need translates into a requirement which is impossible meet. Therefore, the requirements have to be verified against the needs and the needs have to be adjusted if they were overambitious. However, adjusting the need always brings the whole project into question. That means, once the need has been adjusted; there must be a decision on whether or not the project will continue.

Once the requirements have been captured, the project moves into the specification stage. The specification must be expressed as formal as possible, because only a high degree of formalism leads us to an unambiguous system description [141, 142]. Such a system description is important, because the specification is discussed by both engineering and management groups. The systems engineering model is constructive, the ideas of iteration and looping processes hold also for the relationship between specification and requirements. To be specific, the specification has to be validated against the requirements. With the specification, we establish how we build the system and in the implementation phase we actually go about building it. In the best case, the implementation is just an automated or mechanical translation of the specification. However, most of the time the specification just describes the high level architecture and not the detailed processes which make up the system functionality. Therefore, lots of handcrafting is necessary in the translation process. Once the implementation is done, we still don't have a product. The design process is only complete after product verification. This step is particularly important for high reliability and safety critical systems, such as biomedical products, because product verification involves use and failure case testing. In the validation loop we check whether or not we

have built the right system, because this step checks the implementation against the requirements. If and only if the implementation passes all tests, we have a product which can be released.

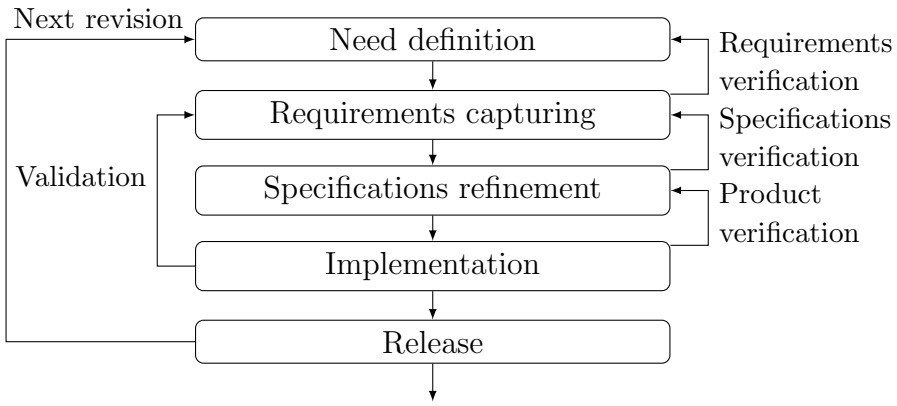


Figure 1: The systems engineering lifecycle model.

The description above focused on need definition, requirements capturing and specification refinement. The example shows that systems engineering, combined with formal models, improves our ability to reason about the design. This reasoning breeds understanding and understanding is what it takes to build reliable systems which are safe, reliable and functional.

2.7.1 Need definition

Empirical science dictates the need for data collection in order to learn about specific physical phenomena. Biomedical science is no exception, more and better sensors acquire an increasing amount of data in medical information systems. In the past, the organization of this data was driven by the data source. The source centric model did not support the cognitive processes of physicians [143]. Therefore, new methods to visualize patient medical records are becoming imperative in order to assist physicians with clinical tasks and medical decision making. This is a crucial result of the need definition process: we have a clearly defined problem. In all subsequent discussions we will not go beyond this problem. The next step in the need definition is to focus on and to reason about the specific application area.

To cope with the sheer data volume, methods like data mining and knowledge representation are needed [144]. However, these techniques don't go far enough, because they just extract relevant information from the data. Nevertheless, this is an important prerequisite for disease diagnosis [145]. The most advanced form to support physicians is CAD. For example, accurate and reliable decision making in oncological prognosis can help in the planning of suitable surgery and therapy, and generally, improve patient management through the different stages of the disease [146]. Böröczky et al. have proposed a feature subset selection method based on genetic algorithms to improve the performance in the area of false positive reduction

in lung nodule CAD [147]. By selecting CAD, we have narrowed down the application area. The next step must focus on state of the art techniques for CAD.

The diagnosis itself can be modeled as a decision making process. Any method of data analysis, intended to support the clinical decision-making process, should meet several criteria: it should capture clinically relevant features, be computationally feasible, and provide easily interpretable results [148].

Movement of health care delivery towards both the primary care sector and the home setting can result in substantial benefits in terms of health outcome, social provision, cost effectiveness and resource utilization. In order to gain maximum benefit from such a distributed approach, it is necessary to ensure that there is a full and proper understanding of the roles of all those involved in health care delivery as well as making available the best possible support for clinical decision making [149]. More specifically, machine learning algorithms can provide predictions complemented with valid confidence measures. In medical diagnosis, such predictions are highly desirable, because medical experts can gain additional information for each machine diagnosis. A risk assessment in each prediction can play an important role for medical decision making, in which the outcome can be critical for the patients [150]. Ji et al. have proposed a novel team-based intelligent agent software system approach for proactively monitoring and detecting potential adverse drug reactions of interest using electronic patient records [151].

Figure 2 shows a typical block diagram of a medical decision making system. Data acquisition, preprocessing and feature extraction steps are data dependent. Classification methods are more general, i.e. classification algorithms can be used for a wide range of feature vectors $\mathbf{v}$. The example, we want to introduce in this section, should be as general as possible, therefore we focus on the classification method.

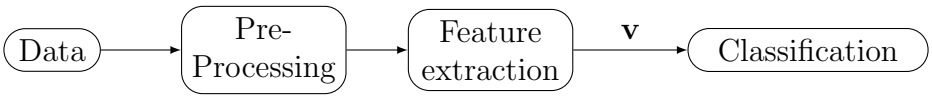


Figure 2: Block diagram of a general decision making system.

There is a wide range of classification algorithms available [152], hence the main task in the need definition step is to select appropriate algorithms. Medical decision making can be regarded as a process, which combines both analytical cognition and intuition. It involves reasoning within complex causal models of multiple concepts, usually described by uncertain, imprecise, and/or incomplete information. Iakovidis and Papageorgiou have proposed a novel approach based on cognitive maps and intuitionistic fuzzy logic [153]. Kusiak and Law have proposed a data mining algorithm to extract robust rules that can be used in clinical practice. The rules improve our understanding of clinical processes and they help to avoid unwanted medical events [154]. Güler and Übeyli have proposed a multiclass SVM with error-correcting output codes for a multiclass EEG signal classification problem. The Probabilistic Neural Network (PNN) and multilayer perceptron neural network were also tested and benchmarked for their performance on the classification of the EEG signals [155]. Bayesian Averaging (BA) over ensembles of decision models allows technologists to evaluate

the uncertainty of decisions, this is of crucial importance for safety critical applications, such as medical diagnostics [156]. Exarchos et al. have used association rules for the automated detection and classification of transient events in EEG recordings [157]. The expanded disability status scale has been the most widely used measure of disability in multiple sclerosis clinical trials. Automatic EDSS (AEDSS) is an expert system designed to overcome this problem. It constrains the neurologist to follow precise reasoning steps, enhancing EDSS reliability [158].

ANN is amongst the oldest machine classification algorithms [159, 160]. It mimics both functionality and structure of a human brain. Therefore, it is widely used in medical decision making [161, 162, 163, 164]. For example, a blood product transfusion is a financial concern for hospitals and patients. In response to that financial need, a study evaluated the efficacy of using Artificial Neural Network (ANN) to predict the transfusion requirements of trauma patients using readily available information [165, 166]. Another research team applied weight-elimination neural networks to coronary surgery mortality prediction. The objective was to assess the effectiveness of the weight-elimination cost function in improving classification performance of ANNs and to observe how changing the a priori distribution of the training set affects the network performance [167]. ANN based techniques have been used for monitoring dangerous infections [168], predicting high-risk preterm birth [169], and epileptic EEG detection [170]. Shin et al. have developed an automatic classification system for cough sounds to symptoms which indicate abnormal health conditions [171]. The ANN model used energy cepstral coefficients obtained by filter banks based on human auditory characteristics as input parameters. A novel neural-network model for deriving standard 12-lead ECGs from serial three-lead ECGs: application to self-care [172]. Tzallas et al. used ANN classification to extract epileptic seizure events from EEG signals [173]. The wide range of applications and the pervasive use of ANN led us to adopt this algorithm as basis for the system design.

In general, and the current example is no exception, need definition is a highly speculative process and a result is reached by a panel of experts. Never the less, the need definition forms the bedrock of the design. All subsequent design steps aim to realize a system which fulfills these needs.

2.7.2 Requirements

In the previous section we established the need for an ANN classification system. Hence, the first requirement is that the system, to be designed, must operate according to the ANN theory. During the need definition phase, we focused on biomedical information processing problems. From the discussion in Section 2.3 it necessarily follows that the system must be safe and reliable, this constitutes the second requirement. In the need definition phase we have fixed the application area to biomedical signal processing, but in the application itself was left open. Hence, the ANN implementation must be as generic as possible. Figure 3 shows the network diagram of a general ANN system [174, Chapter 1]. The system assumes an l dimensional input vector $\mathbf{v}$ which is the result of the feature extraction step, as shown in Figure 2. The process network is modeled as an array of $n+1 \times m+1$ neurons which are arranged

in n layers. The neurons in layer $(1 < y < n-1)$ are fully connected to the neurons the adjacent layer $(y-1 \,\&\, y+1)$. The network structure can be further refined by establishing the functionality of the neurons.

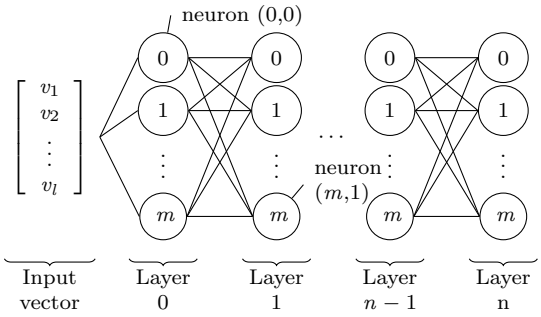


Figure 3: General ANN network diagram which gives a graphical representation of the CSP Equations 7 to 11.

In general, the system requirements are not complete, because a specific processing platform is not defined. However, a discussion on processing platforms and processing requirements, such as real-time, is not within the scope of this chapter. For the purpose of this chapter, the requirements are sufficient to proceed to the specification.

2.7.3 Specification

This section introduces formal methods for biomedical systems design. By using formal methods, we respond to both safety and reliability requirements [175, 176]. We have chosen CSP as modeling language. CSP is a process algebra which was invented by Hoare [177, 178] and which has by now over 30 years of solid research behind it [179, 180]. In a practical setting, CSP has been used to model percolation effects for large scale mesh networks [181]. Sputh et al. used CSP to model hardware and software for In-situ remote monitoring systems [182]. The CSP part of the ANN algorithm model defines the network structure. There is ample of literature which describes the ANN functionality in terms of algebraic equations [183, 184, 185], but these equations do not specify how to construct processing networks which execute the algorithm instructions. Without a formal language it is difficult to reason about the way this network structure is implemented. A discussion about the implementation is important, because it allows engineers to communicate their ideas to the management team and potential architectural problems can be found in an early design stage.

2.7.3.1 Fault classes of software intense systems

The link between design and safety critical system faults comes from the complexity of electronic based software systems. As such, electronic systems create a very safe and reliable environment for information processing. The problem is that electronic based software systems still fail. Fundamentally, there are three error classes: Syntax error: Modern compiler take care of these errors.

- **Functionality related errors:** An algorithm is not implemented correctly. Most of the functional errors can be found through use and failure case testing. For example, a functional model of a CAD system established that a specific signal input is classified as normal, but the implementation classifies the same signal as diseased. Hence, there is a discrepancy between the functional model and the implementation and we have to revisit the implementation to rectify that problem.

- **Design related error:** Such errors occur in complex systems which result from a collaborative effort of many people. Having many people or indeed many different groups of people working on the same project requires to divide the overall system functionality into smaller manageable parts. These parts are taken on by individual work groups and they produce modules. In a final step, these modules are assembled to form the overall system functionality. Adopting that design methodology implies there is no single person who understands the complete system. Assembling the individual modules to form the system functionality can only be understood on an abstract level. However, abstraction leads to nondeterminism [186]. The nondeterminism is a problem, because it describes an unavoidable lack of understanding. For example, the combination of multiple modules might deadlock. Such a deadlock describes a situation where it is impossible for a network of modules to make progress. In a two module scenario, the simplest deadlock case can be described informally as:

  > *Module A waits for a message of module B and module B waits for a message from module A. Clearly, these messages will never come, because both modules are waiting.*

  For complex systems, it is impossible to find design errors, such as deadlocks, through testing, because such errors depend on specific conditions and a test would have to recreate these conditions first before the fault happens. For all practical systems, natural language fails to describe these conditions. Formal language is necessary to establish the rigor necessary to analyze the conditions which lead design problems. These design problems are also called *stable failures*, and the most common stable failures are deadlocks. For example, the formal method of CSP describes a process (module) in terms of state. The process state changes whenever a communication happens. With that formal language, we can describe the simple deadlock scenario, introduced above, as follows:

  $$\textbf{channel}\ c.\{0,1,2\} \tag{1}$$

  where **channel** defines a communication channel c, that can carry the messages 0, 1 and 2.

  $$\begin{aligned} A = &\quad c!0 \rightarrow c!1 \rightarrow c!2 \rightarrow A \\ B = &\quad c?0 \rightarrow c?2 \rightarrow c?1 \rightarrow B \end{aligned} \tag{2}$$

where A and B are processes that engage in blocking[2] communication over the channel c. The $\rightarrow$ operator indicates a state transition. For example, in the initial state process A is able to send a 0 over channel c. Once the message is send a state transition occurs. Similarly, in the initial state, process B is able to receive the message 0 from channel c. Once the message is received, a state transition occurs.

$$MAIN = A \mid \{| \ c \ |\} \mid B \tag{3}$$

MAIN combines processes A and B in parallel. The processes must agree on all messages send over channel c. By combining the individual, deadlock free processes, A and B we have constructed a processes which exhibits the following functionality. The process A communicates message 0 over channel c to process B. Subsequently, both processes transit to a new state. In that new state process B waits for a 2 over channel c. But, process A is willing to send only a 1 over channel c. As a consequence, both processes A and B will wait forever. The process *MAIN* deadlocks after the message 0 was observed. More formally, the trace $\langle c.a \rangle$ leads to a deadlock state. Hence, we have described the system state in terms of a trace, i.e. the messages observed. Figure 4 shows a screen-shot of the formal modeling tool. The main window displays the machine readable CSP (CSPm) code of the simple deadlock model. The window entitled 'Model Check together with the message window, indicate that a deadlock occurred after checking three states.

Correcting the simple deadlock model is a design issue, because removing the deadlock means to change the system specification. For example, if it is not necessary process A to communicate messages 1 and 2 to process B the deadlock is removed by correcting the *MAIN* process:

$$MAIN = A \mid \{c.0\} \mid B \tag{4}$$

In contrast, if the messages $c.1$ and $c.2$ are vitally important for both processes, then the sequence of messages in the process definition must be changed. In any case, having the model checking result is beneficial for the system design, because it forces the designer to consider the system specification more deeply.

The example, in the previous paragraph, was a straight forward adaptation of the simplest deadlock scenario. Such a system is not sufficiently complex to model a meaningful biomedical system. Models of meaningful biomedical systems, such as the formal ANN introduced in the next section, involve choice and more than two processes. The state space grows exponentially with the system complexity they model. Every model is different, therefore the exact state space growth trajectory needs to be evaluated on a case by case basis. In Section 2.8 we discuss the state space growth for the CSP ANN model. However, the idea that the state space growth exponentially with the system complexity explains the difficulties of biomedical systems design. To be specific, the individual modules function according to their specification, but

[2]The message is exchanged if and only if all communication partners are ready to engage in that communication.

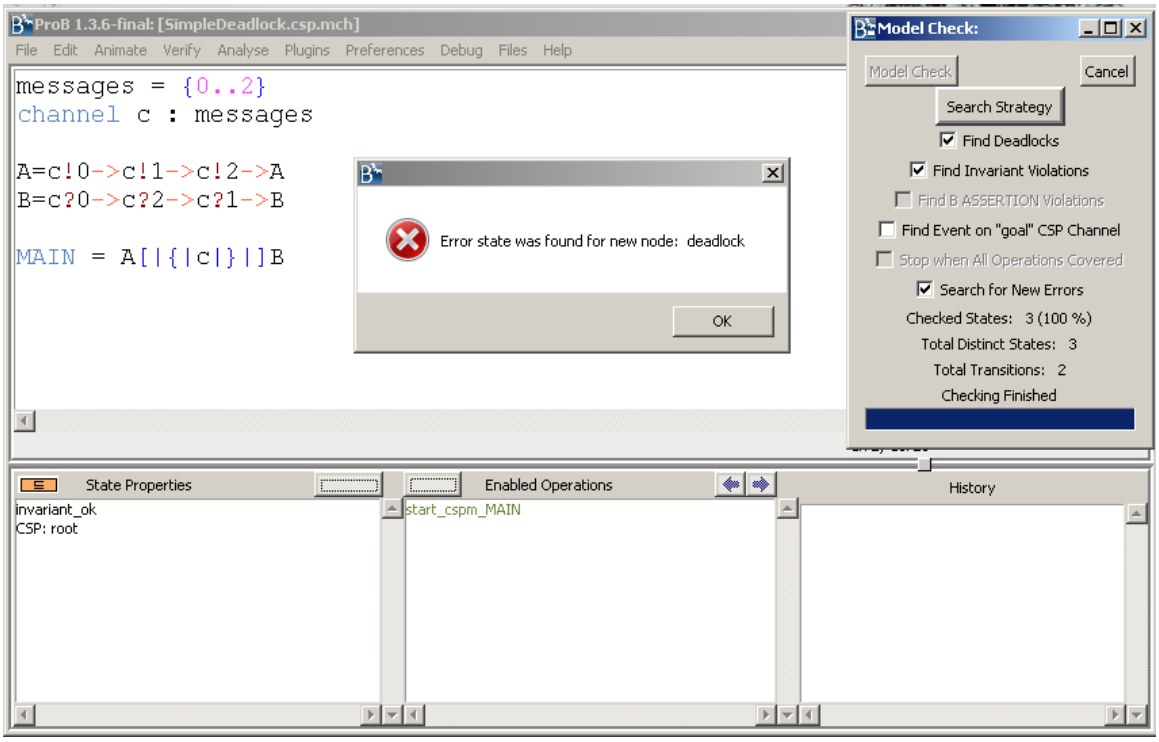


Figure 4: Model checker detects a deadlock, as indicated by the message box. The main model checker window shows the formal CSPm model. The window in the right upper corner indicates that it took three states to find the deadlock.

assembling them the final system can introduce stable failures, because of the exponential growth of the state space. As such, not the huge state space is the problem, it is the lack of understanding which is likely to introduce stable failures.

There is no solution to the problem of state space growth, because it is inherent in complex problem solutions, such as biomedical systems. The only way forward is to limit the safety and reliably implications of the large state space. That limitation has to come in from the specification. A particular module has to be specified according to the needs of the overall network as well as in terms of the individual functionality. As a consequence, the formal and model driven design approach includes formal methods in the specification. The formal methods model the network aspect of a proposed system. The model gives good insight in the state space of a system. Furthermore, it is possible to prove the absence of stable failures, such as deadlock and livelock from the model. Hence, if the formal model is translated correctly into an implementation, then we have reason to believe that the implementation possesses the same beneficial properties. With the carefully planned steps, outlined above, formal methods can help to improve the safety and reliability of biomedical systems.

2.7.3.2 The formal ANN model

To model the system in CSP we follow the process network diagram, shown in Figure 3. First we define a neuron as a process. Figure 5 shows a network diagram which

depicts the inputs and outputs of a neuron process.

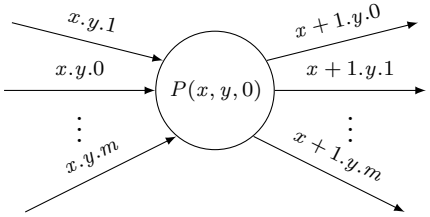


Figure 5: Neuron process model which is defined by Equations 7 and 8 and used in Equation 11 to build the ANN.

Block or network diagrams, such as the ones shown in Figures 3 and 5, fail to communicate the internal functionality of the components they show. Therefore, it is impossible to extract the systemic information from such diagrams. For example, it is impossible to reason about the sequence of events based on a diagram alone. A much stronger method is to define all necessary functionality in a formal but abstract way. Functional descriptions offer the required clarity and logical consistency. Before we proceed with the mathematical description of the process shown in Figure 5, there is some housekeeping necessary. Equation 5 defines three sets which are used in the formal model of the ANN functionality.

$$\begin{aligned} \mathit{from} &= \{0..m\} \\ \mathit{to} &= \{0..m\} \\ \mathit{column} &= \{0..n+1\} \end{aligned} \tag{5}$$

The connections between the neurons are modeled as channels. Equation 6 defines c as an $(m+1) \times (n+1)$ channel array.

$$\textbf{channel}\ c : \mathit{column}.\mathit{from}.\mathit{to} \tag{6}$$

The process $P(x, y, cnt)$ models the communication behavior of the neuron. The parameters x and y indicate the neuron position in terms of row and column. The variable cnt is used internally by the process to keep track of the messages which were received. Equation 7 defines that the neuron consumes a data value from all connected channels before it progresses to $P'(x, y, 0)$.

$$\begin{aligned} &P(x, y, cnt) = \\ &\quad \textbf{if}\ (cnt < m)\ \textbf{then} \\ &\qquad c.x.cnt.y \rightarrow P(x, y, cnt+1) \\ &\quad \textbf{else} \\ &\qquad c.x.cnt.y \rightarrow P'(x, y, 0) \end{aligned} \tag{7}$$

Equation 8 defines the communication functionality of $P'(x, y, cnt)$. To be specific,

$P'(x, y, cnt)$ outputs data on all connected output channels.

$$
\begin{array}{l}
P'(x, y, cnt) = \\
\quad \textbf{if } (cnt < m) \textbf{ then} \\
\quad\quad c.x + 1.y.cnt \rightarrow P'(x, y, cnt + 1) \\
\quad \textbf{else} \\
\quad\quad c.x + 1.y.cnt \rightarrow P(x, y, 0)
\end{array} \tag{8}
$$

After defining the process, which represents the individual neuron, we assemble the process network shown in Figure 3. Equation 9 combines the individual layers with the replicated interleave operator ($|||$) to form the process I.

$$I(x) = ||| \ \ y \ : \ \{0..m\} \ \ @ \ P(x, y, 0) \tag{9}$$

Equation 10 combines the layers I recursively to form the network of neurons.

$$
\begin{array}{l}
PC(x) = \textbf{if } (x < 2) \textbf{ then} \\
\quad I(0)[| \ \{| \ c.1 \ |\} \ |]I(1) \\
\textbf{else} \\
\quad PC(x - 1)[| \ \{| \ c.x \ |\} \ |]I(x)
\end{array} \tag{10}
$$

Having the recursive network definition, allows us to parameterize the *MAIN* process which represents the ANN, as shown below.

$$MAIN = PC(n) \tag{11}$$

That concludes our discussion of the formal ANN model. The next section details the results obtained with the model checker. As part of the results, we discuss the state space explosion inherent to the model defined above.

2.7.4 Specification results

To demonstrate the fitness of the model, Figure 6 shows the CSPm code of the ANN example together with the model checking results. That particular ANN model contained nine neuron processes (P) arranged in three rows and three columns. The state space of the model was 46333 and it took 219028 transitions to check the model.

Table 1 relates the model complexity to the state space. The ANN model complexity depends on the number or neuron processes (P). The least complex model has four neurons arranged in two columns and two rows. The state space contains 137 distinct states. The most complex model had 12 neuron processes (P) and a state space of 320286. The largest state space of all the tested models was found in a configuration with two columns ($n = 1$) and four rows ($m = 3$), i.e. eight neuron processes (P). From that discussion follows that model complexity and state space don't have a linear relationship. The state space depends on the individual model realization. Therefore, speaking purely about model complexity is vague it needs to be backed up with state space measures. Apart from the relationship of neuron configuration and state space, Table 1 indicates also a phenomenon known as *state space*

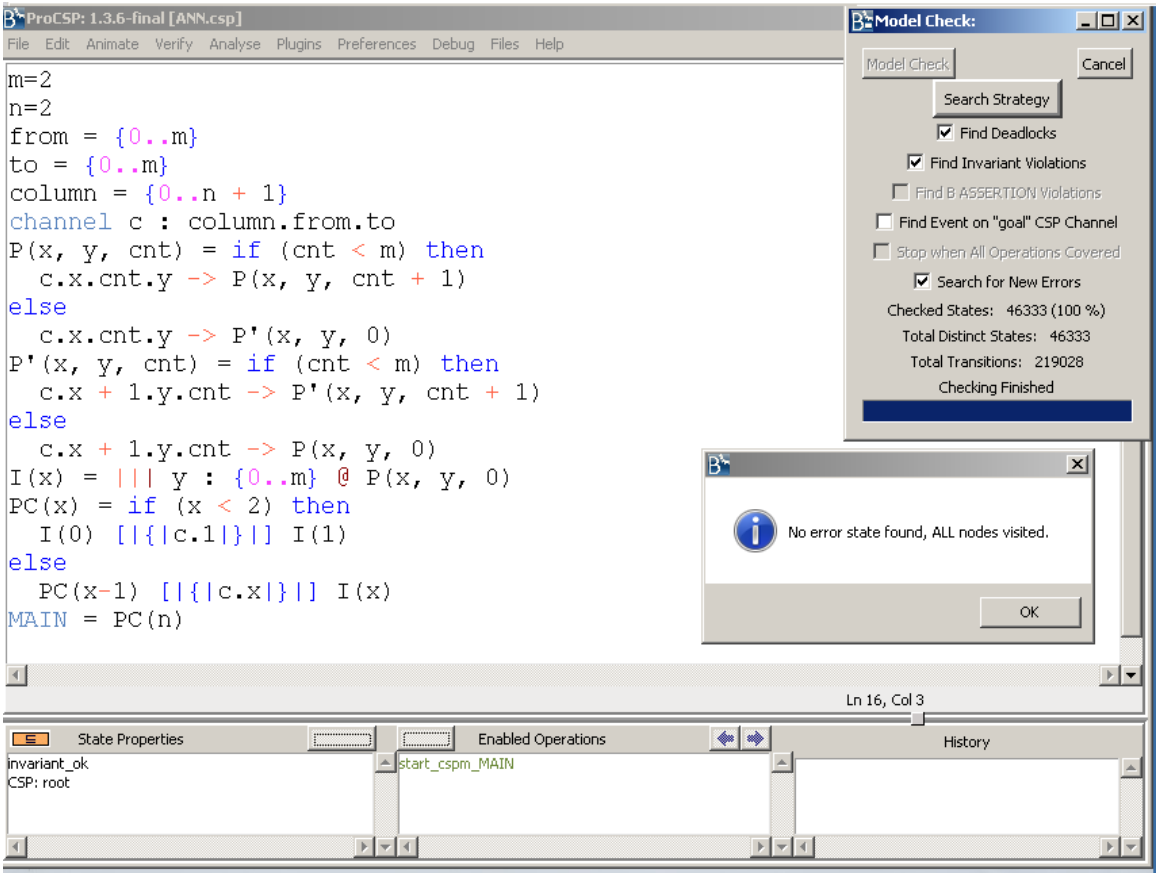


Figure 6: Model checker proofs the absence deadlock, as indicated by the message box. The main model checker window shows the formal CSPm code for the ANN model. The window in the right upper corner indicates that the model opens up a state space with 46333 distinct states.

explosion. The state space increases rapidly even if there is only a modest increase in the number of neuron processes (P). In the table, '–' indicates that 12 GB of Random-Access Memory (RAM), in the PC used for model checking, were insufficient to evaluate the formal ANN model. In general, the fact that the state space resulting from a modest increase in system complexity quickly outstrips state of the art PC and indeed supercomputer technology, is the biggest problem of process algebras and formal methods in general. On the positive side, to experience the state space explosion is educational, because it highlights the importance of good design. Chapter 5 presents a good design for the ANN example. To be specific, by combining CSP with the B-method we could overcome the state space explosion.

Through testing we gained insights in the communication within the ANN process network. Through formal model checking, we established that the model is livelock and deadlock free [187]. These are two important properties for parallel systems. Only rigorous proofs, such as model checking, ensure that the model works reliably. The implementation is just a translation of the formal model into language constructs for the processing platform. With the right tool support, the translation is almost

	$n=1$	$n=2$	$n=3$	$n=4$	$n=5$
$m=1$	137	560	2108	7978	30475
$m=2$	5475	46333	320286	–	–
$m=3$	450671	–	–	–	–

Table 1: State space for the individual ANN model configurations

mechanical, therefore we do not elaborate on the translation process in this chapter. Chapter 5 introduces the translation of a formal model into an implementation.

2.8 Discussion

Biomedical systems need to be safe reliable and functional. Formal and model driven design can help to meet these needs, because safety as well as reliability and to a lesser extend functionality are design issues. Safety means that a system cannot execute a potentially disastrous sequence of actions. Reliability means that a system functions according to specification for long periods of time. Finally, functionality means a system has the potential to function according to specification.

The relevance of formal and model driven design for biomedical systems comes from the fact that biomedical system are complex. Indeed they are so complex that it is impossible for one person to understand the complete system. Furthermore, the biomedical systems are based on electronic components and software processing. These components do not wear out and the likelihood of a natural error, such as bit alterations through radiation, is very remote. Hence, the main source of errors must come from the system design. If an electronic or software component fails, the design is to blame. In general, system complexity is positively correlated with the amount of design errors. In other words, there are more design errors in complex systems when compared to less complex ones. As outlined before, biomedical system designs are very complex, therefore design errors in electronic modules are likely. As a consequence, such systems can fail at any time without prior warning. That is a clear safety issue, because (a) these machine may take disastrous action or (b) they fail to do their job. Both cases can endanger human life. State of the art designs partition the design into individual modules and later in the design these modules are combined to from the complete system functionality. Once the system is realized and the modules are assemble testing begins. However, testing can only establish the presence of a fault, but it cannot conclusively rule out the presence of a fault. Testing does not cover the complete state space of a system, there might be a safety critical fault in the untested state space. Complex biomedical systems have an enormous state space, therefore the untested state space is potentially enormous as well. As a consequence errors in the untested state space are very likely.

Safety critical faults in electronic and software systems are a design issue. Hence, the solution must also be concerned with the system design. Many design issues are a direct result of an insufficient understanding of the system. Formal methods can help to increase the understanding of modern distributed processing systems. These

formal models are created in the specification of the project and automated model checkers can be used to establish certain model properties, such as the absence of deadlock and livelock, beyond reasonable doubt. The implementation is realized by translating the formal model into hardware and software structures. If the translation is done correctly, the implementation will possess the same beneficial properties as the formal model.

2.9 Chapter conclusion

The progress made by biomedical science is enormous, because it is fueled by the rapid development of computer systems and more ingenious algorithms for signal analysis. There is a need or social obligation to bring this progress to the people. One of the fundamental problems is that, in order for a biomedical system to be useful, it must be complex. This is usually referred to as the enormous complexity of practical systems. Computer aided diagnosis systems are no exceptions to this rule. In recent years, novel algorithms in data mining, signal and image processing have been developed to aid clinicians by automating routine diagnostic tasks. In the first section of this chapter we reason that complexity is coupled with a demand for reliability. To express the impact of complexity and reliability on the system requirements we have introduced the term difficulty. The term refers to the resources needed or cost to meet the requirement. We argue that the difficulty increases exponentially with the complexity under the assumption that the same reliability is required. To cope with the increasing system complexity it is necessary to move away from evolutionary system design and towards system based development. Evolutionary systems design makes only progress, i.e. copes with the complexity problem, from one revision to the next. In contrast, systems based development incorporates feedback loops within the (systems engineering) design methodology. Therefore, it can cope with the complexity problem much better.

One of the cornerstones of modern design is modeling. We established that this fact also holds for biomedical systems. However, modeling is most of the time not enough to meet the system requirements. A methodical design approach is needed to create complex biomedical systems which are reliable. A prominent design methodology is systems engineering. Systems engineering defines a meta model which needs to be adopted to the application domain. Systems engineering is applicable to a wide range of biomedical projects. When it is employed, it will guide both technical and management teams to see the bigger picture, i.e. providing the holistic view. Having a holistic perspective is especially important for the engineering team, because engineers are usually bogged down by a great deal of technical detail and they (sometimes) miss the bigger picture. Therefore, each management decision, which impacts on their work, is seen as an intrusion and usually causes resistance. Systems engineering aims to minimize this resistance by providing adequate structures for information exchange between the different teams. Having these communication channels makes the development process flexible and ultimately this enables the project to cope with the inherent complexity problem of modern biomedical systems.

The thesis of this review chapter is that the combination of formal modeling

and systems engineering has the capability to improve the reliability of biomedical systems. By reviewing scientific literature, we have established that reliability is a central requirement for biomedical system, such as CAD, and that reliability can be established through modeling. The main contribution of this review is to work out the relationship between modeling and reliability. We adopt the position that the relationship between modeling and reliability can only be understood from a design perspective. To be more specific, structured design methodologies, such as systems engineering, help us to understand the problems and achieve safety as well as reliability.

Having proposed a formal and model driven design methodology, we move on to discuss functional modeling. The next chapter introduces the design pattern to establish a functional model which governs the requirements capturing for biomedical systems design. The design pattern are common amongst a wide range of designs, but the algorithm structure which establishes the functionality is unique. To highlight that important point, the next chapter introduces three case studies from the area of CAD. We apply the design pattern to each case study, but the functional model becomes unique through the sophisticated algorithms used to establish needed capabilities.

CHAPTER 3

FUNCTIONAL MODEL DESIGN

3.1 Summary

This chapter discusses the creation of functional models as part of the requirements capturing process. The discussion focuses on the design pattern used to establish such functional models for CAD systems. The design pattern are common for a wide range of functional models. While the algorithms used to establish the needed functionality are distinct for the individual functional models. To support the point about communality and distinctiveness, we put forward two CAD related case studies. The first case study focuses on diagnosing diabetes based on Heart Rate (HR) signals. The second case study proposes an algorithm structure to support epilepsy diagnosis based on EEG signal. These two distinct case studies were conducted according to a subset of processes defined in the formal and model driven design methodology. To be specific, we describe need definition and the functional model based requirements capturing. Through careful analysis, we learned that the the functional models, for CAD systems, require data analysis and classification. The definition of these processing steps and the associated quality assessment measures are the main results communicated in this chapter.

3.2 Introduction

The formal and model driven design methodology for biomedical systems defines all steps necessary to create safe, reliable and functional problem solutions [188]. To improve the quality and availability of medical diagnosis is a pressing problem. The task is to find cost effective solutions to the diagnosis problem, because the lack of medical diagnosis affects a large part of the population, especially in developing counties [189, 190, 191, 192]. A promising solution is based on computing technology, because computers are highly flexible and therefore they can be used to model human decision making. However, decision making in general and establishing a medical diagnosis in particular is a largely unstructured process without clear decision boundaries. Hence, computer based medical diagnosis support is a very difficult problem.

From a design perspective, the issue is even worse, because we require that the resulting diagnosis support system is safe, reliable and functional. Even a nonfunctional biomedical system has the potential to endanger human life, hence functionality is also a safety issue. The previous chapter described the safety aspect of biomedical system design. In the current chapter we focus on the functionality aspect of biomedical systems which is captured by the requirements. We use CAD as an example and to introduce our ideas about need definition and requirements capturing. Through critical analysis, we realized that thee CAD system requirements are captured with functional models. As such, the functional model defines an algorithm

structure which automates human decision making. The primary main objective of the functional model is to establish the highest possible QoS to meet the need for safety, reliability and functionality. Establishing the QoS implies that rigid tests are performed and discriminative tools are used to asses the test results. Hence, we included statistical and model checking tests in the functional design. The requirements capturing process concludes with a discussion of the test results in terms of cooperation and competition.

The chapter is structured such such that it highlights the similarities and the differences of functional models for different CAD applications. The next section introduces the design pattern used to establish a functional model which captures the requirements during formal and model driven biomedical systems design. Once a common design pattern is established, we move on to discuss individual case studies. The first case study introduces the design of a formal model for computer aided diabetes diagnosis based on heart rate signals. The second case study focuses on the formal model design for a computerized sleep apnoea detection system. The final case study is concerned with establishing a formal model for EEG based epilepsy detection.

3.3 Design pattern

The formal and model driven design methodology defines requirement capturing as the process which answers the question: What system do we build? For CAD systems design, answering that question comes down to establishing and testing an algorithm structure. The algorithm structure, which includes signal processing and performance evaluation algorithms, is know as the functional model. Once the functional model is established, a discussion is necessary to determine the model quality. The quality is assessed in terms of cooperation and competition. Cooperation highlights the connection between the functional model test results and medical research. At the very least, the functional model results should not contradict medical research. Many advanced functional models for CAD systems clarify and in some cases even refine medical research results. The importance of the cooperative aspect of the discussion is that we gain insights which lead to more functional problem solutions. An equally important aspect is the competitive result analysis where the test results of the functional model are compared with the results from other systems. The discussion establishes the functional model quality when compared to the wider scientific knowledge. Once the quality is established, a decision can be made on whether to progress to the specification refinement or to loop back to the need definition phase. Looping back means the proposed functional model does not have the required qualities to meet the need.

Requirements capturing is part of the systems engineering lifecycle model, shown in Figure 1. The requirements capturing follows after the need definition phase and it is preceded by the specification refinement phase. The requirements capturing process either loops back to the need definition through requirements verification or it progresses to the specification refinement. Figure 7 shows the requirements capturing block diagram for CAD systems. The diagram details the functional model and the decision process which resolves the choice of progressing to the specification refinement

or looping back to the need definition. The functional model for CAD systems is a structure which consists of analysis and automated classification algorithms. These algorithms process specific data and they are evaluated after each processing step. The evaluation takes the form of statistical and classification performance tests. The evaluation results provide the foundation for a cooperative and competitive discussion of the functional model. The discussion result will determine whether or not to progress to the specification refinement.

The design pattern for the functional model are abstract, because they must hold for a large range of CAD system designs. To make these abstract ideas more concrete, we introduce two case studies. The first case study comes from the area of diabetes diagnosis. The second case study focuses on the important task of epilepsy detection. Each case study starts off with the need definition which incorporates medical research to establish why a particular physical problem solution is necessary. The structure of the subsequent requirements capturing phase follows the process sequence outlined in Figure 7. As a consequence, each case study has a section detailing the specific processes necessary to establish the functional model. The case studies conclude with a cooperative and competitive discussion of the mode test results.

3.4 Case study I: Design of a Diabetes Diagnosis System based on Heart Rate Variability

The interpretation of ECG signals is difficult, therefore it takes a long training process to extract relevant information from these heart signals. The statement is especially true for diagnosing diabetes from subtle abnormalities in ECG signals. To overcome that difficulty, we have used the formal and model driven design methodology to specify a system that helps practitioners to diagnose diabetes. As part of the design process, we developed a technique that is based on Heart Rate Variability (HRV) signals, which are extracted from ECG signals. The proposed system automates the process of diagnosing diabetes by detecting subtle changes in HRV signals with digital signal processing.

The main work in this case study was to design the functional model for the diabetes diagnosis system. Through statistical analysis we found that CD, Poincaré geometry properties ($SD2$), Recurrence Plots (RP) properties (Recurrence Rate (REC), Determinism (DET)) are particularly useful features. The significance of these features comes from their ability to differentiate between HR data from diabetes patients and that from normal patients. The feature quality has been further validated by using a variety of classifiers. In our study, among many other classifiers, we found that the AdaBoost classifier, with perceptron as weak learner, yielded the best classification accuracy of 86% for the two-class problem.

3.4.1 Need definition

Following the systems engineering design methodology, we start with the need definition. For the proposed work, the need arises from a discussion about the medical

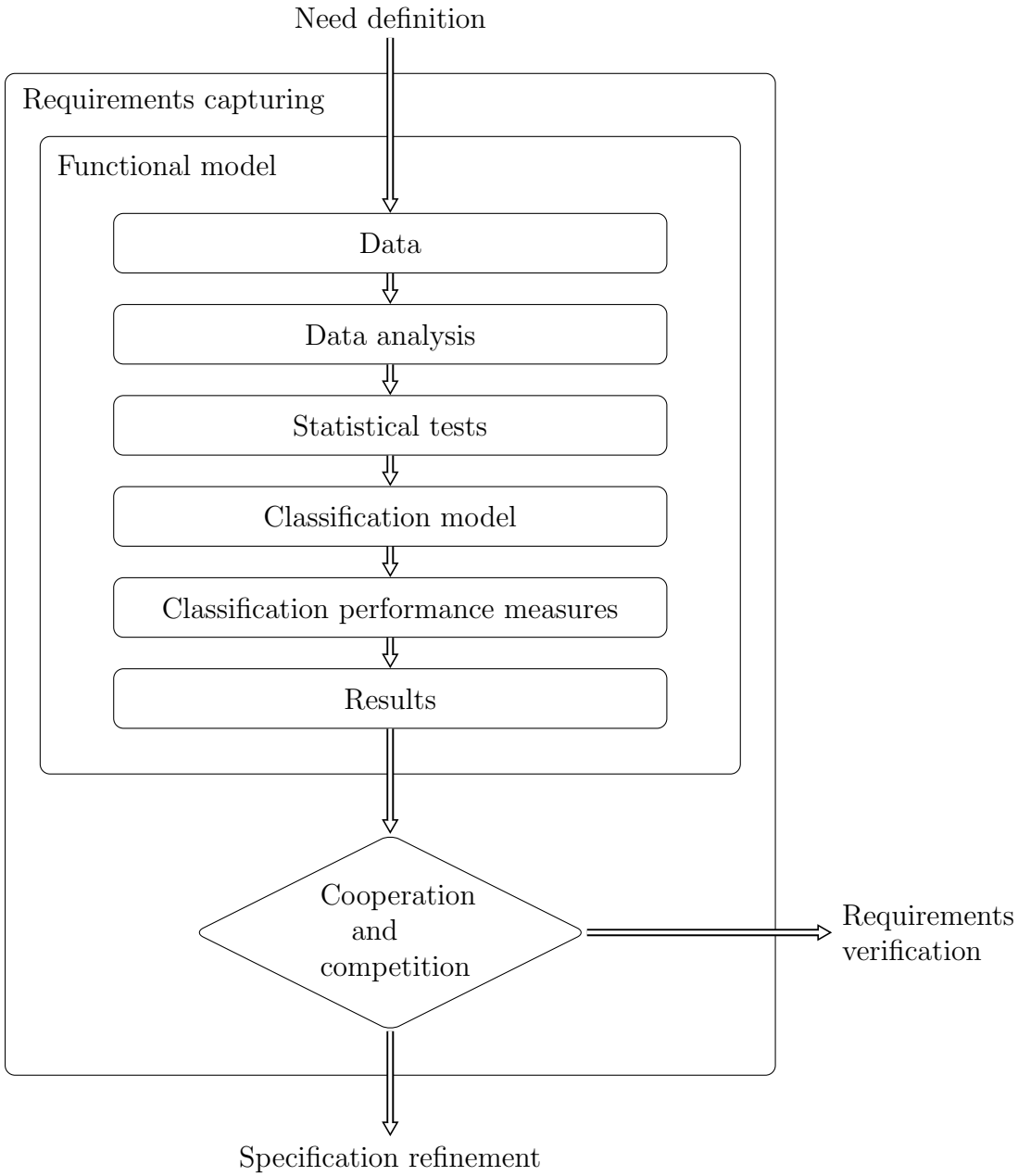


Figure 7: Requirements capturing block diagram for CAD systems.

background of Diabetes Mellitus (DM). In medical terms, DM is defined as a chronic disease, which is characterized by hyperglycaemia. As such, hyperglycaemia is a metabolic disorder, where excess glucose is present in the blood [193]. Hence, the condition leads to an elevated blood glucose level, which leads to serious detrimental consequences affecting eye, heart, kidney and nerves. DM inflicts a huge cost on society, because of the disease prevalence and the severity of the symptoms. According to the World Health Organization (WHO), in 2009 there were more than 220 million confirmed cases of diabetes worldwide. The figure is believed to be an underrepresentation, because people may live for years with diabetes, but their cause of death is usually documented as cardiovascular disease or renal failure. It is estimated that the confirmed number of diabetes cases worldwide will increase to 440 million by the year 2030 [194]. In 2008, the American Diabetes Association (ADA) reported that 23.6 million (approximately 7.8% of the population) children and adults, in the United States, have diabetes [195]. In the same year, the Singaporean Ministry Of Health (MOH) reported that DM is ranked as the 7^{th} leading principal cause of death. Furthermore, about 10% of the Singaporean population (about 300,000 people) were diagnosed with diabetes. That means, 1 out of 11 people is diabetic and they are usually between 18 to 69 years old.

The problem of diabetes is too complex, i.e. the needs are too diverse, for a single physical solution. Therefore, the problem area requires refinement before we can design a physical problem solution. For diagnostic support systems refinement comes from selecting and subsequently using a specific symptom of the disease. For the current case study, we focus on Cardiovascular Autonomic Neuropathy (CAN), which is a common form of diabetic autonomic neuropathy that affects the dynamics of both central and peripheral vascular systems and also causes abnormalities in HR signals. The cumulative incidence of Diabetic Neuropathy (DN) in type 1[1] diabetes is 25–30% [196]. Cardiovascular autonomic neuropathy has been linked to postural hypotension [197], exercise intolerance [198], enhanced intraoperative cardiovascular lability [199], increased incidence of asymptomatic ischemia and myocardial infarction, and decreased likelihood of survival after myocardial infarction [200]. The condition occurs in around 17% of patients with type 1 and 22% of those with type 2 diabetes. An additional nine percent of type 1 patients and 12% of type 2 patients have borderline autonomic dysfunction [201]. In ECG signals, neuropathy can be seen from a prolonged corrected QT interval and QT dispersion (the difference between the longest and shortest QT interval) [202]. This indicates an imbalance between right and left sympathetic innervation. Diabetic patients with a regional sympathetic imbalance and QT interval prolongation may be at greater risk for incurring arrhythmias.

The next step in the need definition is to discuss a specific medical symptom. The idea is to design a system which exploits that symptom to provide diagnostic support for physicians. A symptom of DM is the decreased beat-to-beat variability during deep breathing [203, 204]. In studies, comparing cardiac autonomic function tests with HRV indices (based on both short (5 min) and long (24 h) ECG recordings), show that, in diabetic patients without abnormal function tests, the HRV was lower [205].

[1]Section 3.4.1.1 details the different types of diabetes.

It was concluded that cardiac (parasympathetic) autonomic activity was diminished in diabetic patients before clinical symptoms of neuropathy became evident [206, 207]. Hence, lower HRV is a good indicator for DM and therefore we exploit that symptom for our diagnostic support system.

Modeling is an integral part of the proposed design methodology. Hence, the need definition must include a discussion on modeling techniques. From a systems perspective it is quite clear that the cardiovascular system can never be linear in nature, because of its immense complexity. Therefore, nonlinear models lead to a better understanding of the underlying biological system. Schumacher et al. [208] have explained the use of linear and nonlinear methods in the analysis of HR signals. Efforts have been made to find relevant nonlinear parameters, like CD, for physiological signal analysis and it has been shown that they are useful indicators of pathologies. Methods, based on chaos theory, have been applied in tracking HRV signals and predicting the onset of events, such as Ventricular Tachycardia, in congestive heart failure situations [209].

After the need definition step, we are in a position to propose a biomedical system which provides diagnostic support to practitioners. The novelty of the proposed design comes from the advanced algorithm structure used in the functional modeling phase. The algorithms were used to extract linear and nonlinear features from HR signals. The key step, in the proposed time series analysis method, was to select significant features which extract useful information from HR signals. Good features provide adequate representation of relevant HR signal characteristics. There are many ways to select such good features. In our work, we have used only features which are statistically significant, i.e. whose values are correlated with either presence or absence of diabetes. The level of correlation is proportional to the ability of the feature to discriminate between HR data from diabetic patients and normal controls. To harvest the analytical capability of the selected features, we fed them into supervised learning machines. Based on the classification results, the disease detection accuracies of these classifiers were evaluated. The detection accuracy is another performance indicator for the features, because it measures the ability of the feature to aid a medical diagnosis.

The case study is organized as follows. The materials and methods section characterizes the analyzed data and it gives a brief description of the extracted features. Furthermore, the same section introduces the statistical t-test, which was used to evaluate the selected features. The results section presents the statistical test results for the significant features and the classification performance measures. The result analysis is given in the discussion section. The conclusion section provides closing remarks and an outlook into the future of DN diagnosis.

3.4.1.1 Diabetes

A good understanding of all the relevant medical information is prerequisite to modeling the CAD system functionality. In the current case study, we focus on diabetes and its symptoms. Diabetes develops either because insufficient insulin is produced by the pancreas or because the cells fail to respond to insulin in a normal way. Glucose

is the body's main source of energy. The pancreas, an organ located behind the lower part of the stomach, produces a hormone called insulin. Insulin regulates the blood glucose level. In general, we differentiate between type 1 and type 2 diabetes. Type 1 diabetes results from a failure of the human body to produce insulin. Therefore, people with type 1 diabetes take insulin injections. Type 1 diabetes is less common than type 2 diabetes. Type 2 diabetes is characterized by insulin resistance and relative insulin deficiency. It is estimated that 90–95% of Americans, who are diagnosed with diabetes, have type 2 diabetes [210]. Type 2 diabetes usually develops in adults older than 40 and the disease is most common in patients aged 55 and above. About 80% of people with type 2 diabetes are overweight. It was reported that type 2 diabetes is often part of a metabolic syndrome that includes obesity, elevated blood pressure, and high levels of blood lipids [211].

Uncontrolled diabetes, over a prolonged period of time, causes harm to the body, especially to nerves and blood vessels. Complications of diabetes can be grouped into micro- and macro-vascular categories. Examples of micro-vascular complications, which are due to the damage of small blood vessels, include eye (retinopathy), kidney (nephropathy), nerves (neuropathy) and heart (cardiomyopathy). These complications are discussed below.

DR is the name of a complication which comes from the effect diabetes has on the retinal blood vessels. The retina is the internal layer of the eye which is responsible for receiving, transmitting and interpreting visual images. Right after the onset of diabetes, small blood vessels (capillaries) in the retina die. New blood vessels grow on the surface of both retina and optic nerve, but they are immature, therefore they tend to rupture and start bleeding. The blood accumulates in the eye cavity. Another problem of raptured blood vessels is scar formation. The scared tissue contracts and pulls on the retina, the force of this pull can cause retina detachment. In 2007, it was reported that about 38% of type 2 diabetics patients have some degree of DR [212]. The majority of type 1 diabetes patients develops some degree of retinopathy over time [213]. DR is the main cause of end-stage renal diseases. The disease is usually detected during screening, because no symptoms are felt by the patient. From these facts it is understandable that DR is the leading cause of blindness. Fortunately, with early diagnosis, vision can be preserved, because treatment is available [54].

Diabetic nephropathy is the name of a complication which comes from the effect diabetes has on the kidney blood vessels. When the body digests protein it contaminates the blood with waste products. The kidneys filter out these waste products. A large number of capillaries are an essential component of this filter. After 20 to 30 years of having diabetes, the capillaries start to leak and useful protein is lost to the urine [214]. One-third of type 1 diabetes patients and 10 to 20% of type 2 diabetes patients develop some sort of kidney disease after living with diabetes for 15 years or more [215]. It was stated that an interruption of the renin-angiotensin system slows the progression of renal diseases in patients with type 1 diabetes, but similar data are not available for patients with type 2 [216]. Diabetes is one of the leading factors of kidney failure among Singaporeans. About 500 new cases of renal failure are diagnosed annually, and 40% (200) of these cases are attributed to diabetes.

DN describes nerve damage which is caused by DM. In general, nerve fibers can

be injured throughout the body, but usually the damage is limited to legs and feet. Pain, numbness, burning sensation and problems encountered with the urinary tract or even the heart, are some of the symptoms experienced by patients, depending on which nerves are affected. Numbness in the extremities means that cuts or injuries to the skin can go unnoticed. If medical attention is not given, even small injuries can develop into ulcer or infection and may lead to amputation. As nerve fibers are everywhere throughout the body, nerve injuries can happen to any organ. This implies that problems can arise in the digestive system with symptoms like diarrhea and vomiting. Urinary Tract Infection (UIT) or loss of bladder control can be symptoms which indicate that the urinary tract is affected. In worst case scenarios, impotence is observed. DN results in a gradual loss of nerve function which limits the amount of sensation on the plantar aspects of the feet [217]. This diminished sensation disables individuals because they loose the ability to feel the onset or the actual occurrence of a foot injury. As a result, patients with this disease are more inclined to experience plantar ulceration. People with DM can develop nerve problems at any time, but the longer a person has diabetes, the greater is the risk. Acharya et al. found out that abnormal plantar pressures play a major role in the pathologies of neuropathic ulcers in the diabetic foot [218].

Diabetic cardiomyopathy describes the effects of diabetes on the human cardiovascular system. Cardiovascular Diseases (CVDs) are the number one cause of death globally. The WHO estimated that in 2004 about 29% of deaths were due to CVDs (totaling 17.1 million). The organization projected that about 23.6 million people will succumb to the disease by 2030 [219]. That means, a person is more likely to die from heart disease or stroke compared to any other disease. A person with diabetes is twice as likely to suffer from cardiovascular or heart disease as a person with diabetes.

Macro-vascular complication, as the name implies, describes damage, caused by diabetes, to larger blood vessels (arteries). As such, arteries are the blood vessels that transport nutrients and oxygen from the heart to other parts of the body. Healthy arteries are strong, flexible and elastic. However, high levels of blood sugar can lead to a buildup of fats (cholesterol) on the inner artery walls. The buildup happens over time, as a consequence the vessel narrows and the blood flow slows down, in worst case scenarios the blood flow comes to a hold. Arteriosclerosis, or hardening of arteries as it is commonly known, is a major preceding factor for many cardiovascular diseases. The accumulated fat on the artery walls (known as plaque) can become mobile and when that happens, a blood clot forms. When the blood clot travels to the brain, the patient can get a stroke and if the blood clot travels to the heart, a heart attack is impending. Patients with both diabetes and ischemic heart disease seem to have an enhanced myocardial dysfunction leading to accelerated heart failure, this condition is known as diabetic cardiomyopathy. Thus, patients with diabetes are prone to congestive heart failure [220].

With the review on diabetes, we have addressed the requirement of understanding the disease. Now we can move on to formulate a functional model for diabetes diagnosis based on heart rate variability.

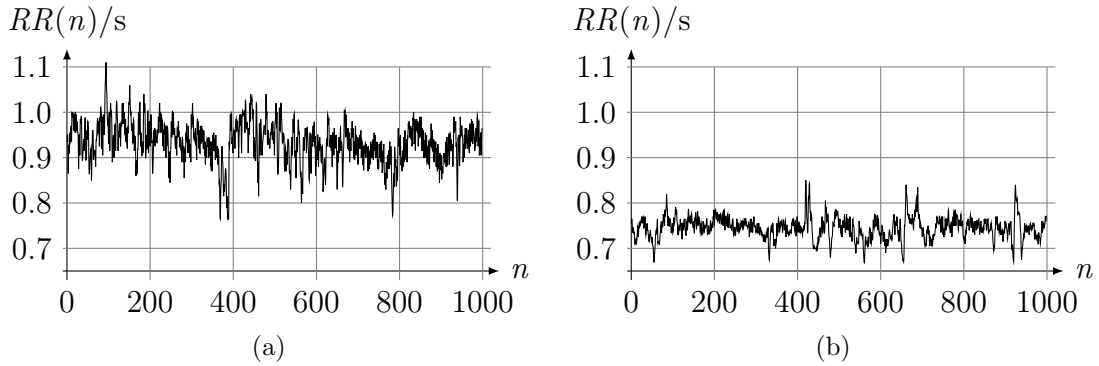


Figure 8: Typical plots of RR-interval duration over the interval number n, (a) normal subject and (b) diabetic subject.

3.4.2 Requirements capturing

The proposed diabetes diagnosis system has to interpret ECG signals. To establish the desired functionality requires a functional model with a sophisticated algorithm structure. Figure 7 shows the block diagram of the required algorithm structure. As such, the algorithms are chained to perform a sequence of operations. The analysis and the classification algorithms provide a decision on whether or not the ECG data was taken from a diabetic. The statistical tests and the classification performance measures assess how reliable the decision was. The next section introduce the individual algorithms in more detail.

3.4.2.1 Data

The functional model of the proposed biomedical system is based on ECG signals which were measured from diabetic as well as healthy individuals. The data was obtained from Manipal University Hospital in India. 15 healthy volunteers (Group A) and 15 patients with diabetes (Group B) consented to have their ECGs recorded in a relaxed supine position for 60 minutes. BIOPACTM equipment, in corporation with the AcqKnowledge software, was used to record and process the ECG signals [221]. Figures 8a and 8b show sample HR signals from normal and diabetic patients, respectively. The ECG sampling rate was 200 Hz.

To ensure accuracy, disturbances, such as noise from electromagnetic induced currents in the equipment, respiration, and muscle movements, were removed. Tompkins's algorithm [222] was used to detect R peaks from the ECG signals. A total of 82 data sets from 15 normal subjects and 80 data sets from 15 diabetic subjects were used in this project. Each data set contained 1,000 samples.

3.4.2.2 Linear data analysis

This section discusses linear algorithms which are used to model the feature extraction from HR data. First, we introduce five time domain parameter, namely

Mean Heart Rate ($\overline{HR}$), $NN50$, $PNN50$, Triangular Interpolation of NN interval histogram ($TINN$) and $HRV\triangle Index$. In the second part, we discuss the Low by High Frequency (LF/HF) domain feature. All these parameters were selected because they are statistically significant.

Mean heart rate ($\overline{HR}$) A specific RR-interval n, within the ECG signal ($T_{RR}(n)$ seconds), is defined as the interval of two successive QRS complexes and the HR (beats per minute) is given as:

$$HR(n) = \frac{60\text{s}}{T_{RR}(n)} \tag{12}$$

The HR mean ($\overline{HR}$) can is calculated as:

$$\overline{HR} = \frac{1}{N}\sum_{n=0}^{N-1} HR(n) \tag{13}$$

where N is the observation interval in samples.

Statistical parameters ($NN50$, $PNN50$) In this study, we have used the two statistical parameters $NN50$ and $PNN50$. $NN50$ is the number of successive RR-interval pairs that differ by more than 50 milliseconds. $PNN50$ is the number of successive difference of intervals which differ by more than 50 milliseconds, expressed as a percentage of the total number of ECG cycles analyzed. In other words, $NN50$ divided by the total number of RR-intervals and expressed as a percentage gives $PNN50$:

$$PNN50 = \frac{NN50}{N-1} \times 100 \tag{14}$$

Histogram parameters ($TINN$, $HRV\triangle Index$) Besides the statistical parameters mentioned above, we used the RR-interval histogram, shown in Figure 9, to calculate the geometric parameters $TINN$ and $HRV\triangle Index$. $TINN$ is defined as the baseline width of the RR histogram, it is calculated by:

$$TINN = M - N \tag{15}$$

Triangular interpolation approximates the RR-interval distribution by a linear function and the baseline width of this approximation is used as a measure of the HRV index [223, 224]. This index possess a high correlation with the standard deviation of all RR-intervals [224]. The $HRV\triangle Index$ is calculated as the RR-interval histogram integral D, which indicates the Area Under Curve (AUC), divided by the height Y of the histogram. It is a measure where the length of the triangle base is used to approximate the main peak of the RR-interval frequency distribution diagram.

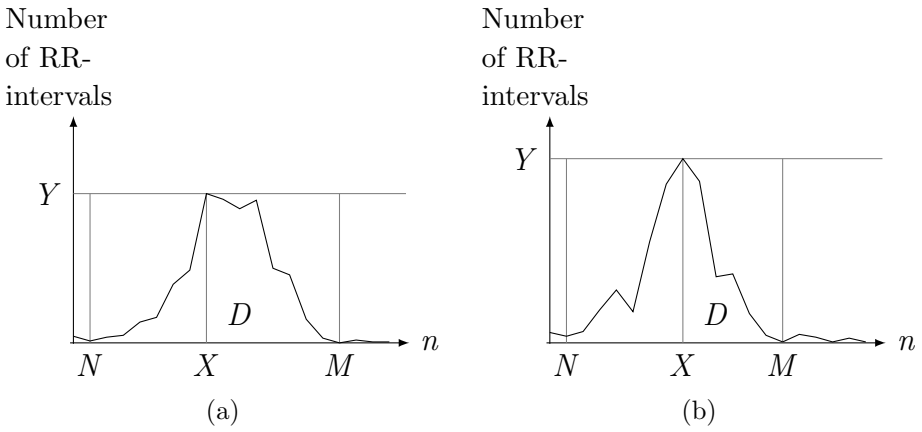


Figure 9: Typical RR-interval duration histograms, (a) normal subject and (b) diabetic subject.

Low by high frequency (LF/HF) Although, time domain methods are straight forward and easy to use, they lack the ability to differentiate HRV signals into either sympathetic or para-sympathetic. To overcome this shortcoming, the Power Spectrum Density (PSD) estimate can be used to analyze HRV signals.

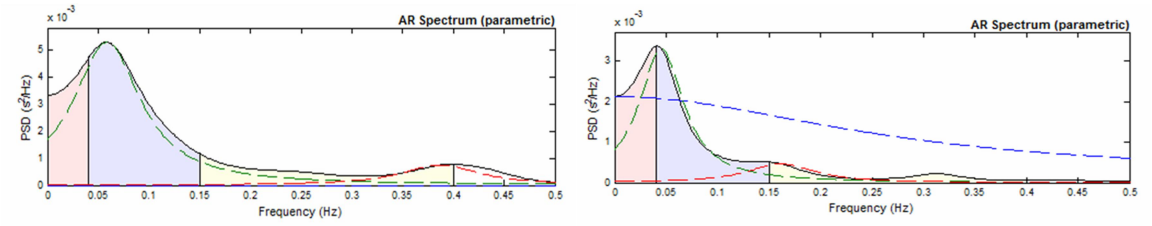
We have used an AR method to estimate the PSD. The necessary AR coefficients ($a(k)$) were calculated using linear equations, hence PSD estimation is a linear method. The data is modeled as the output of a causal all pole discrete filter with white noise as input:

$$x(n) = -\sum_{k=1}^{p} a(k)\, x(n-k) + w(n) \tag{16}$$

where p is the filter order and $w(n)$ is white noise with a variance of σ^2. A specific model is characterized by the parameters: $a(1)$, $a(2)$, ..., $a(p)$, and σ^2.

Akaike and other researchers have stressed the importance of the model order p on the accuracy of the PSD estimation [225, 226]. In this case study we have taken the AR model order: $p = 16$, because that specific order yields the most significant features. Figures 10a and 10b show the frequency domain (AR Spectrum) of HR signals from normal and diabetic subjects, respectively.

In the frequency domain, the ratio of low to high frequency is used to detect cardiomyopathy abnormalities. In the PSD, two major oscillatory components are usually detectable: The first component, which is synchronous with respiration, is described as High Frequency (HF) (about 0.25 Hz and varying with respiration), whereas the other, corresponding to the slow waves of arterial pressure, is described as Low Frequency (LF) (about 0.1 Hz). The LF/HF ratio is considered an index of cardiac sympathetic/parasympathetic tone balance [227].



(a) (b)

Figure 10: Typical AR Spectrum graphs, (a) normal subject and (b) diabetic subject.

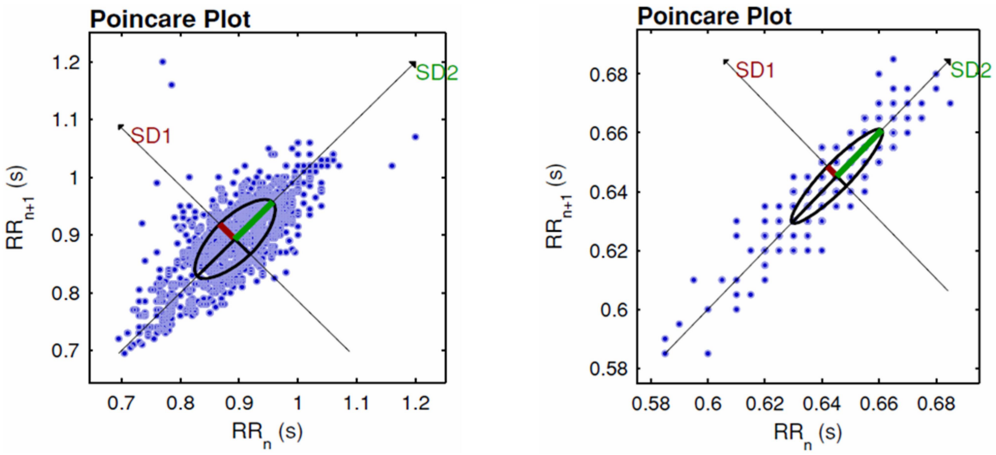
3.4.2.3 Nonlinear analysis

Given the complexity of the cardiovascular system, it is appropriate to assume that nonlinear mechanisms are involved in the generation of HRV [228]. This point is supported by studies which suggest that the heart is a non-periodic oscillator under normal physiological conditions [229, 228, 230]. As a consequence, we included nonlinear analysis in our functional model. The resulting model aims to quantify the dynamics of HR fluctuations, based on the following nonlinear methods: Poincaré plots, RP, CD, Approximate Entropy (ApEn) and Sample Entropy (SampEn).

Poincaré plot geometry (SD1, SD2) The Poincaré plot is a graphical representation where each RR-interval is plotted as a function of the previous RR-interval. In other words, it is a graphical display of the correlation between consecutive intervals. Poincaré plot analysis involves features, such as the shape of the plot being categorized into functional classes that indicate the degree of heart failure in a subject [231]. The plots provide a summary of the HR information content as well as detailed beat-to-beat statistics which reveal the behavior of the heart [232]. The geometry of the Poincaré plot includes fitting an ellipse onto a line-of-identity that appears at 45° to the normal axis in the Poincaré plot.

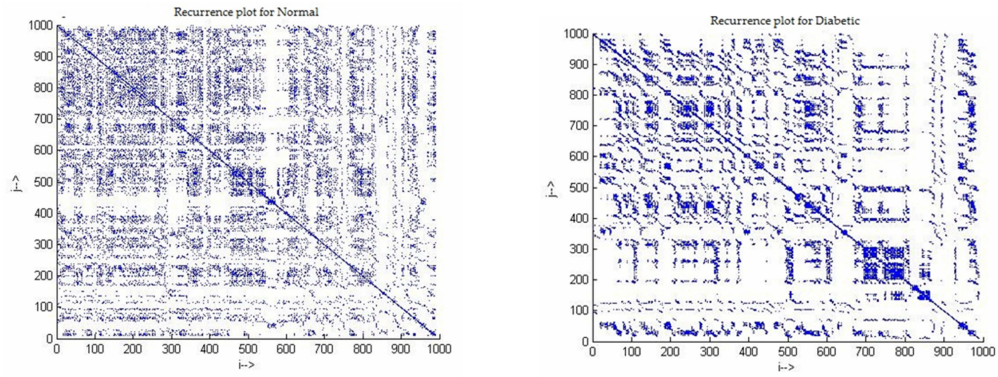
The Poincaré plot, depicting the RR-interval, typically appears as an elongated cloud of points oriented along the line-of-identity. The short term variability of the heart signal is quantified by the Standard Deviation of the points that are perpendicular to the line-of-identity ($SD1$). The long term variability, on the other hand, is quantified by Standard Deviation of the points that are located along the line-of-identity ($SD2$). Quantitative analysis of Poincaré plots is carried out by determining the standard deviations of the distances of the RRn interval to the lines $y = x$ and $y = -x + 2 \times \text{RRm}$, where RRm is the mean of all RRn intervals [233]. Figure 11 shows typical Poincaré plots of the HR for a normal and a diabetic subject.

$SD2$ indicates the long term variability and $SD1$ describes the short range variability due to Respiratory Sinus Arrhythmia (RSA). The Poincaré plot of normal HR (Figure 11 a) appears as an ellipse shaped cloud of points which is aligned at the center and $SD2$ longer than $SD1$, indicating more long term variability than short range variability [234]. But for diabetes subjects (Figure 11 b) the plot is shifted upwards and $SD1$ is reduced as compared to normal subjects (Figure 11 a).



(a) (b)

Figure 11: Poincaré plot of (a) Normal subject (b) Diabetic subject.



(a) (b)

Figure 12: Recurrence Plots (RP) of (a) Normal subject (b) Diabetic subject.

Recurrence plots (REC, DEC) In time series analysis, the dynamic properties of the data under consideration are relevant and valid only if the data is stationary. RPs, first proposed by Eckmann et al. [235], are used to reveal the non-stationary status of time series data.

Figure 12 shows typical RPs of normal and diabetic subjects. For normal cases, the plot has a diagonal line and fewer squares, indicating more variation in the HR. In the case of heart diseases, such as ischemic/dilated cardiomyopathy and complete heart block, the plot shows a higher number of squares. The increased amount of squares indicates an inherent periodicity of the underlying HR signal and a lower variation [234]. Therefore, the RP of a diabetic subject has a more uniform texture than the normal RP.

Appendix B.6 defines *REC* as the ratio of ones and zeros in the *RP* matrix and *DET*, is the percentage or fraction which forms diagonal lines.

Correlation dimension (CD) CD gives information on the minimum number of dynamic variables needed to model the underlying system, i.e. it is a measure of the dimensionality of the space occupied by a set of points. Appendix B.4 provides more information about this nonlinear method.

Entropy analysis (*ApEn*, *SampEn*) ApEn is a technique which allows us to detect changes in the system complexity from data. Therefore, this method can be used to analyze time series data, such as HR. More specifically, the ApEn extracted from HR signals will indicate changes in the Autonomic Nervous System (ANS) complexity. See Appendix B.8 for more details and a mathematical description of ApEn.

SampEn is another useful tool for investigating the dynamics of time series data, such as HR. SampEn is the negative natural logarithm of an estimate which expresses the conditional probability that subseries (epochs) of length m match pointwise, within a tolerance r, also match at the next point. See Appendix B.9 for more details and a mathematical description of SampEn.

3.4.2.4 Statistical tests

The main reason for having models is their testability. One very prominent statistical test for functional models is Student's t-test. It can be used to assess whether or not the means of two groups are statistically different from each other. The result of this test is called p-value [236, 237]. A low p-value indicates that the two groups are statistically different. The ability to assess the difference between data groups is important for this case study, because we want to assess the capability of the extracted features to discriminate between neuropathy and normal data. To assess this capability, we must find features with low p-values. Typically, features with p-values below 0.05 are regarded as clinically significant. This p-value is calculated for each feature. All the values of each feature of both classes are used to evaluate the p-value (Student's t-test).

Surrogate data analysis Surrogate data is used to test for nonlinear dynamics [238]. The test is executed by comparing the feature values from measurement data, in this case HR signals, and surrogate data. The presence of nonlinearity cannot be ruled out if the two feature values are significantly different. For this project, we used a randomized HR signals as surrogate data. The signals were generated such that they had the same mean, variance, and autocorrelation function as the original HR signal. More specifically, the surrogate data was obtained by phase randomizing the original HR signal. The presence of nonlinear dynamics was determined by comparing any of the nonlinear parameters of the original HR signal with the corresponding surrogate data. In this work, we have compared the value of ApEn for original signal and phase-randomized surrogate data. The ApEn in the two cases differ more than 59%, hence the original signal is most likely nonlinear.

3.4.2.5 Classification model

Biomedical systems need to adopt to and indeed work in the human environment. Hence, there is a need for safety, fault tolerance and flexibility. We address the need for safety with formal and model driven design. The next sections focus on models that cater for the needed fault tolerance and flexibility. To be specific, we discuss models for automated classification.

AdaBoost classifier In 1994, Kearns and Valiant [239, 240] discussed the question of whether or not it is possible to boost the prediction quality of a weak learner, even if the prediction accuracy of this learner is just slightly better than a random guess. The answers to this question sparked a number of improvements on boosting algorithms. For example, Freund and Schapire (1997) introduced the AdaBoost algorithm, which solved many of the practical shortcomings of earlier algorithms [241].

AdaBoost is a machine learning algorithm which feeds the input training set to a weak learner algorithm repeatedly. During these repeated calls, the algorithm maintains and updates a set of weights for the training set. Initially, all weights are equal. However, after each call, the weights are updated such that the weights of incorrectly classified examples are increased. This forces the weak learner to focus on the hard examples in the training set.

In this study, we have used three weak learner algorithms for the AdaBoost classifier. The first of these weak learner algorithms is the perceptron [242]. The perceptron algorithm learns the concepts or structure of the data which is repeatedly presented to the algorithm. A characteristic of all ANNs is to update weights and biases during the training phase. In the special case of the perceptron, both weight and bias updates follow the perceptron learning rule. With this training algorithm, the perceptron has the ability to generalize from training vectors and work with randomly distributed connections. This ability makes the perceptron suited for a wide range of classification problems.

The second weak learner algorithm is called *pocket with ratchet* or *pocket* [243]. This algorithm is an extension of perceptron learning. The increased stability of this algorithm is achieved by keeping the best solution seen so far in a pocket, i.e., the pocket algorithm will always deliver a training result even if it was impossible to classify all training data correctly, because the training set is not linearly separable. This ability of the pocket algorithm prevents an infinite training time that can occur for the native perceptron.

The third algorithm is the decision stump. This model consists of a single-level decision tree that uses the value of a single input feature for prediction.

Support Vector Machine (SVM) SVMs were initially designed for two-class problems. But, they have been extended to multi-class problems. The text below briefly explains the two-class SVM approach. The SVM operation searches for a hyperplane which acts as a decision surface that separates positive and negative values from each other with maximum margin [244, 245]. This involves orienting the separating hyperplane perpendicular to the shortest line separating the convex hulls of

the training data for every class, and locating it midway along this line. Let the separating hyperplane be given by $x \cdot w + b = 0$, where w is its normal. For linearly separable data $\{x_i, y_i\}$ where $x_i \in \mathbb{R}^n$ and $y_i = \{-1, 1\}, \quad i = 1, ..., N$, the optimum boundary, chosen with the maximal margin criterion, is found by minimizing the objective function:

$$E = \|w\|^2 \tag{17}$$

Subject to $(x_i \cdot w + b)y_i \geqslant 1 \quad \forall\, i$.

The solution for the optimum boundary w_0 is a linear combination of a subset of the training data, $s \in \{1, ..., N\}$ known as the *support vectors*. This solution can be obtained more easily by translating it into its "dual form". The optimization problem can be solved by quadratic methods giving the optimum decision boundary w_0 as:

$$\mathbf{w}_0 = \sum_{\langle i \rangle} \alpha_i \, \mathbf{y}_i \, \mathbf{x}_i \tag{18}$$

which is a linear combination of the support vectors with $\alpha_i \neq 0$.

Kernel functions can be used to extend the solution to nonlinear boundary problems. The dot product $(\cdot)$ in the feature space is expressed by some functions (i.e., the kernels) of two vectors in input space. Both polynomial and RBF kernels are commonly used. With the use of kernels, an explicit transformation of the data to the feature space is not necessary.

3.4.2.6 Classification performance measures

In terms of formal and model driven design, a model is incomplete without a test method. Therefore, we propose to evaluate the classification model with the following measures: True Positive (TP) indicates the number of diseased patients for whom the test results were positive, True Negative (TN) indicates the number of disease-free patients for whom the test results were negative, False Positive (FP) indicates the number of disease-free patients for whom the test results were positive, and False Negative (FN) indicates the number of diseased patients for whom the test results were negative.

Sensitivity and specificity are widely used performance measures in diagnostic tests. Sensitivity indicates the probability of a positive test among diseased patients and specificity describes the probability of a negative test among disease free patients. Higher sensitivity implies a greater disease detection rate and hence lower FN. Higher specificity indicates a lower FP rate. The Positive Predictive Value (PPV) indicates the probability of a subject with a positive test actually having a disease. Accuracy is the ratio of number of samples correctly classified to the total number of samples used.

The mean average of accuracy, sensitivity, specificity, PPV, and AUC was calculated for all three trials to obtain the overall performance. Mean and variance of the features and the classification results are shown in the following sections.

Features	Norm (Mean ± SD)	Diab (Mean ± SD)	p-Value
$\overline{HR}$	69.1 ± 8.97	84.0 ± 8.17	< 0.0001
$NN50$	118 ± 133	31.8 ± 99.9	< 0.0001
$PNN50$	14.4 ± 15.9	3.46 ± 10.8	< 0.0001
$TINN$	201 ± 62.3	155 ± 127	0.0061
$HRV \triangle Index$	10.5 ± 3.89	4.44 ± 1.66	< 0.0001
LF/HF	2.49 ± 1.52	2.05 ± 1.72	0.11

Table 2: Results of time domain analysis.

3.4.2.7 Results

Model assessment yields results. The current section documents the results of the individual model assessment methods. As such, the results section has the same structure as the materials and methods section. We report on the selected features and the performance measures obtained by using classifiers.

Linear analysis results Table 2 shows the t-test analysis results for the linear parameters. All features, apart from $TINN$ and LF/HF, are statistically significant, because they possess p-values of less than 0.0001. Even though time domain parameters, such as $\overline{HR}$, $NN50$ and $PNN50$, are widely used, it can be shown that the results can be affected by disturbances like artifacts and noise. To effectively measure these parameters, sufficient precautions have to be taken to eliminate them prior to data collection. In our case, the careful measurement is reflected in the low p-value reported in Table 2.

The linear geometric methods $HRV \triangle Index$ and $TINN$ yield also very low p-values. These measures are insensitive to disturbances, artifacts, noises etc. In this report, we found that both parameters measured had a lower mean HR for the diabetes group.

The last row in Table 2 shows the t-test analysis results for the frequency domain feature LF/HF. It can be seen that the p-value is high, which indicates that this feature is insufficient to distinguish the groups.

Nonlinear analysis results Table 3 shows that all nonlinear features, apart from SampEn, gave p-values below 0.0001. Figure 11 shows the Poincaré plot for both normal and diabetes group. The plot for the normal subject is ellipse-shaped and aligned at the center with $SD2$ longer than $SD1$, that means more long term variability than short range variability. The same is true for the diabetic subject, but both $SD1$ and $SD2$ are lower [246]. These differences explain the low p-values reported in Table 3.

Entropy measures and quantifies the regularity of time-series data. A lower entropy value is observed in the diabetes group for ApEn and SampEn.

CD is the quantitative measurement of the nature of trajectory of the phase space plot. It has higher values for normal HR signals and this value falls when the beat to beat variation decreases [5, 247]. The results, shown in Table 3, support these points.

Features	Norm (Mean ± SD)	Diab (Mean ± SD)	p-value
$SD2$	64.9 ± 26.6	30.9 ± 20.6	< 0.0001
REC	36.4 ± 10.0	45.6 ± 13.3	< 0.0001
DET	98.2 ± 1.20	99.1 ± 0.76	< 0.0001
CD	2.44 ± 1.50	0.288 ± 0.324	< 0.0001
ApEn	1.33 ± 0.119	1.18 ± 0.242	< 0.0001
SampEn	1.54 ± 0.307	1.32 ± 0.456	0.0008

Table 3: Results of nonlinear analysis.

Class	Normal	Diabetics	Total
Total no. of datasets	82	80	162
Datasets used for training	57	55	112
Datasets used for testing	25	25	50

Table 4: Amount of data samples used for training and testing.

Classification results We have used classification algorithms to make the feature analysis even more comprehensive. During the training phase both features (input) and corresponding class label (output) are presented to enable the classifier to learn the relationship between input and output. After training, only the features from the test data are presented. In the test scenario the classifier automatically predicts unknown class labels with the help of knowledge which was gained during the training phase.

Table 4 lists the number of datasets used for training and testing. We have used a total of 162 data sets; 112 data sets were used for training and 50 data sets for testing. Table 5 shows the AdaBoost results for with different configurations, and Table 6 shows the SVM results for various kernel functions.

The first column in Table 5 indicates the weak learner algorithm for the AdaBoost, while the first column in Table 6 indicates the different kernel functions used for the SVM. The next four columns indicate the TN, FN, TP and FP. Columns 6, 7, 8, 9, 10 and 11 indicate accuracy of classification, PPV, sensitivity, specificity, number of correctly classified diabetic and normal subjects respectively.

Table 5 shows that the AdaBoost classifier, with perceptron as weak learner, is able to identify diabetes and normal subjects successfully with an accuracy of 86%, sensitivity of 87.5% and specificity of 84.6%. In Table 6, the SVM classifier with RBF and polynomial of order 2 kernel presents a classification accuracy of 82%, as well as sensitivity and specificity of 80.8% and 83.3% respectively.

It can be seen from Table 5 that the AdaBoost meta-classifier, with perceptron as weak learner, achieved a maximum accuracy of 86% which is the best result for all the tested classification algorithms.

Classifier	TN	FN	TP	FP	Accuracy (%)	PPV (%)	Sensitivity (%)	Specificity (%)	Diab Right	Norm Right
Perceptron-AdaBoost	**22**	**3**	**21**	**4**	**86**	**84**	**87.5**	**84.6**	**21**	**22**
Pocket- AdaBoost	22	3	20	5	84	80	87.0	81.5	20	22
Stumps- AdaBoost	22	3	18	7	80	72	85.7	75.9	18	22

Table 5: Performance measures of various classifiers.

SVM	TN	FN	TP	FP	Accuracy (%)	PPV (%)	Sensitivity (%)	Specificity (%)	Diab Right	Norm Right
Linear Kernel	19	6	21	4	80	84	77.8	82.6	21	19
Polynomial Kernel with order 1	19	6	21	4	80	84	77.8	82.6	21	19
Polynomial Kernel with order 2	20	5	21	4	82	84	80.8	83.3	21	20
Polynomial Kernel with order 3	21	4	20	5	82	80	83.3	80.8	20	21
RBF Kernel	20	5	21	4	82	84	80.8	83.3	21	20

Table 6: Performance measures of the SVM classifiers, using various kernel functions.

3.4.2.8 Cooperation and competition

An important part of formal and model driven design is to establish the QoS. One major aspect of QoS is the relative performance of the proposed system. Therefore, we set the linear and nonlinear analysis results into perspective with findings, speculations and conclusions from other researchers. In 1973, Wheeler and Watkins reported a decreased beat-to-beat variability during deep breathing in DN patients [203]. Subsequent studies, which compared cardiac autonomic function tests and HRV (based on both short (5 min) and long (24 h) ECG recordings), show that in diabetic patients without abnormal function tests, the HRV was lower [205]. The authors of these studies concluded that cardiac (parasympathetic) autonomic activity was diminished in diabetic patients, even before clinical symptoms of neuropathy became evident [205, 207].

Mølgarad et al. found that patients with incipient or overt nephropathy had significantly lower vagal activity during both wake and sleep states when compared with healthy control subjects [248]. An increasing degree of nephropathy was clearly associated with an increasing attenuation of 2 h vagal activity. The authors concluded that a covariation of both neuropathy degree and nephropathy may have common pathogenetic mechanisms. Furthermore, they speculated that a reduced 24 h vagal activity, even in the early stages of nephropathy, could be an important risk factor for cardiac death in insulin-dependent diabetic patients.

Meinhold et al. showed that long-term type 1 diabetes, without nephropathy, is not associated with impaired cardiac autonomic function [249]. Nevertheless, the authors discovered that in those patients with nephropathy, a loss of both vagal and sympathetic activity was present, and the severity of CAN correlated positively with more advanced nephropathy.

What all these excellent studies fail to report is a way, or at least a proposal for

a way, to support the diabetes diagnosis process. Therefore, with this study we aim to design such a diagnostic aid. Our main focus was to establish a functional model based on discriminate features (time and frequency domain as well as nonlinear) that are capable of differentiating normal from diabetic patients in a significant way. Owing to the chaotic nature of HR signals, we extracted nonlinear features from these signals.

The functional model was tested and significant features were selected (for lower p-values) using the t-test. The capability of the selected features for good diagnosis was studied using supervised classifiers. The low p-value obtained using t-test and the high accuracy values obtained by using these features in classifiers indicate the usefulness of these features.

The performance of time domain parameters may be affected by artifacts and outliers. Fourier transform techniques are not entirely suitable for analyzing non-stationary signals, because of the way the spectrum is obtained. It converts the time domain signal into complex exponential functions, along with information of their phase shift, measured at a specific reference instant [250]. Therefore, any deviation from the time domain signal will manifest in terms of a frequency spectrum (from $-\infty$ to $+\infty$) and their phase shift. Hence, even finite length signals are expressed as the sum of several frequency components of infinite duration. As a consequence, Fourier transform techniques not provide an exact time localization.

The heart is not a periodic oscillator under normal physiologic conditions [229], and the commonly used statistical analysis tools may not be useful to detect subtle variations in HR signals. Therefore, various nonlinear dynamical methods have been employed to unearth the hidden complexities of HR fluctuations [229, 230, 251]. We argue that HR is a non-rhythmic, nonlinear and non-stationary signal. Hence, it can be effectively analyzed using nonlinear features.

3.5 Case study II: Design of an Epileptic and Background Identification system based on Electroencephalogram Signals

The case study on epileptic and background identification based on EEG data concludes our discussion of functional modeling. We use the formal and model driven design methodology to create the functional model for the epilepsy diagnostic support system. Within the design methodology, the need definition determines the particular structure of the functional model. For the current case study, the need definition centers around the fact that EEG analysis continues to be a problem due to our limited understanding of the signal origin. This limited understanding leads to ill-defined models, which in turn make it hard to design effective evaluation methods. Despite these shortcomings, ECG analysis is a valuable tool in diagnosing neurological disorders and evaluating the overall cerebral activity. For this case study we constructed a functional model which allowed us to compare different PSD estimation methods and different classification methods. Specifically, we used Autoregressive Moving Average (ARMA) as well as from Yule-Walker and Burg's methods, to extract PSDs from

representative signal samples. Local maxima and minima were detected from these spectra. In a subsequent processing step, the locations of these extrema were used as input to the following classifiers: GMM, ANN, and SVM. The classification results are documented with confusion matrices and compared with ROC curves. We found that Burg's method for spectrum estimation together with a SVM classifier yields the best classification results. This combination reaches a classification rate of 93.33%, the sensitivity is 98.33% and the specificy is 96.67%.

3.5.1 Need definition

Formal and model driven design for biomedical engineering starts with a need definition based on medical research. The current case study is no exception, the need definition centers on epilepsy. We start with a definition of the disease. Epilepsy is a chronic neurological disorder of the brain, which is characterized by recurrent unprovoked seizures [252, 253]. These seizures are transient signs of the disorder. The symptoms of epilepsy reach from abnormal to excessive or synchronous neuronal activity in the brain [254]. Worldwide, about 50 million people have epilepsy, with almost 90% of these people living in developing countries [255]. The disease is more likely to develop in young children or in people over the age of 65 years, however, even outside this age group, it can occur at any time [256].

The combination of disease severity and disease prevalence gives us an idea of the social and economic cost. To reduce cost and indeed to reduce suffering we have to diagnose epilepsy early. As part for the need definition, we look at the work of other researchers who have worked in the field of epilepsy diagnosis. Epilepsy can be diagnosed using EEG and brain scan technology, because it affects the normal neuronal activity. Interictal, preictal and ictal are typical stages of epilepsy [257]. The detection of epileptic seizures from EEG data, using nonlinear methods, was proposed by Paivinen et al. [258]. They used short time sliding windows to partition the time series data. From each of these data parts, a set of features were computed. These features were extracted with time domain, frequency domain and nonlinear methods. They employed discriminant analysis to determine the best seizure-detecting features. They found that the best results could be obtained by using a combination of features from both linear and nonlinear methods.

Another core part of the need definition is to draw appropriate conclusions from the gathered medical information. In terms of signal analysis, EEG waveforms are highly complex and nonlinear in nature. The specific signal characteristics depend on both age and mental state of the subject. The symptoms of epilepsy, such as epileptic seizure, occur randomly. Therefore, the frequency of occurrence can only be estimated and stated in a statistical sense. To make an accurate forecast of eminent and future epileptic seizures implies that we understand the precise nature of the brain. This is impossible, at least with the current state of technology. The best we can do is to model the human brain as a cognitive machine which is composed out of billions of interconnected neurons. They form a network which permanently changes its state. Due to this permanent or asynchronous state change and due to the sheer complexity of the network it is impossible to understand and predict the precise state

of the brain. With current technology and understanding, the best we can do is to try to estimate the state with advanced signal processing techniques and its correlation to the physiological mechanisms.

In the research work done with a leading group of experts, Faust et al. explored wavelet based processing for computer-aided epileptic seizure detection [189]. It was found that the linear wavelet method is particularly suited for detecting the subtle changes in EEG signals. Time frequency resolution is particularly important to pinpoint down the exact time when a seizure happens. For the current work, we opted against time frequency methods and focused on frequency methods to establish the discriminative power of that particular feature extraction method.

In this case study we analyze frequency measures for the detection of epileptic activity in EEGs. The study is based on EEG data samples which are classified into three distinct groups: normal, epileptic background and epileptic seizure. We used ARMA, Yule-Walker and Burg's method, to extract the PSD from representative EEG signal samples. Local maxima and minima were detected from these spectra. The locations of these extrema became input vectors to the classifiers. Analysis Of Variance (ANOVA) tests on these input vectors show that the information, conveyed by these input vectors, is statistically significant. The three classifiers used were: GMM, ANN, and SVM. The different classification results are documented with confusion matrices and compared with ROC curves. We found that Burg's method for spectrum estimation together with a SVM yields the best classification results. This combination reaches a classification rate of 93.33%, the sensitivity is 98.33% and the specificity is 96.67%.

The case study is structured in accordance with the formal and model driven design methodology. The introduction highlighted the need for the proposed system. The materials and methods section details the algorithms used to construct the functional model. Subsequently, we improve the understanding of epilepsy detection by putting forward collaborative and competitive statements, based on the model assessment results.

3.5.2 Requirements capturing

This section focuses on the materials and methods used to create the functional model for the epilepsy detection system. The functional model follows the overview diagram shown in Figure 7. The data analysis was based on spectrum estimation. Section 3.5.2.2 discusses the feature extraction. To be specific, it introduces the peak detection algorithm which states value and position of both local maxima and minima of a signal. We use GMM, SVM and ANN as algorithms for the classification model. The next section introduces the data sets which were used to obtain the results.

3.5.2.1 Data

The EEG data for the present study was obtained from a database which is maintained by Bonn University [259]. Gautama et al. discussed the database structure and how the datasets datasets were obtained [260]. From the available data, we

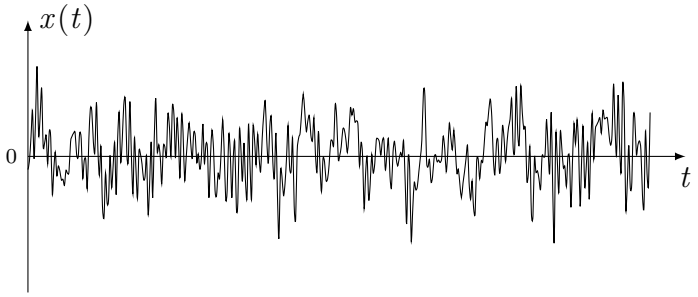


Figure 13: Normal EEG.

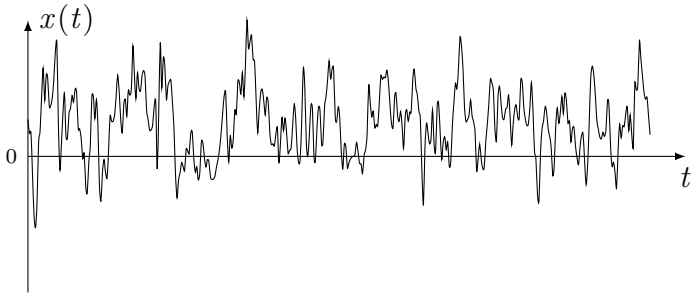


Figure 14: Preictal EEG.

selected three sets, (normal, epileptic background (preictal) and epileptic seizure (ictal)). Each individual dataset was a single channel time series data with a duration of 23.6 seconds. There were 200 data sets in both normal and preictal classes while the ictal class had 100 data sets. The normal EEG data was obtained from five healthy volunteers using a standardized electrode placement scheme, in the relaxed awake state with open eyes. In the present study, we considered only 100 data sets per class, 70 to train the classifiers and 30 to test the classifiers. The ictal EEG data was recorded during epileptic seizures from five epilepsy patients. The preictal EEG data was recorded from the same five epilepsy patients during seizure free periods. All EEG signals were recorded with the same 128 channel amplifier system, digitized with a sampling rate of 173.61 Hz and with a 12 bit A/D resolution. The data was filtered using a band pass filter with settings 0.5340 Hz $\sim$ 12dB/octave. Figures 13 to 15 show 11.8 seconds of sample recordings for normal, preictal and ictal EEG respectively.

3.5.2.2 Data analysis

Parametric (model based) power spectrum estimation methods avoid the problem of spectral leakage and provide a better frequency resolution when compared with non-parametric methods. In general, parametric methods produce smooth PSDs and the frequency bands are easily distinguishable. Furthermore, the post-processing is simpler, this makes the PSD estimation more accurate. The only drawback of parametric methods is that the model order must be chosen such that the PSD estimation method yields good results for each signal class. In this study, we used

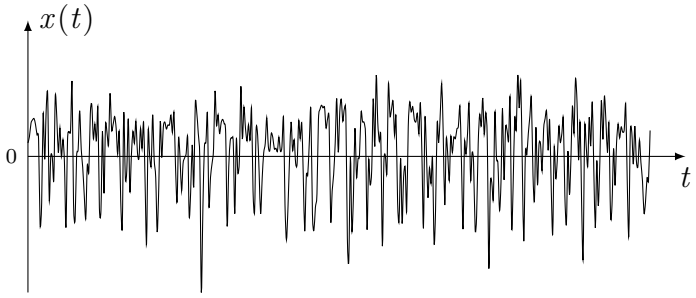


Figure 15: Ictal EEG.

three parametric PSD estimation methods, namely ARMA, Yule-Walker, and Burg. The following sections describe these methods.

Yule-Walker's method The Yule-Walker AR method of spectral estimation computes the so called AR parameters by forming a biased estimate of the signal's autocorrelation function and solving the least squares minimization of the forward prediction error [261]. This results in the Yule-Walker equations:

$$A \times B = C \tag{19}$$

with:

$$A = \begin{bmatrix} r_{xx}(0) & r_{xx}(-1) & \cdots & r_{xx}(-p+1) \\ r_{xx}(1) & r_{xx}(0) & \cdots & r_{xx}(-p+2) \\ \vdots & \vdots & \ddots & \vdots \\ r_{xx}(p-1) & r_{xx}(p-2) & \cdots & r_{xx}(0) \end{bmatrix}$$

and

$$B = \begin{bmatrix} \hat{a}_p(1) \\ \hat{a}_p(2) \\ \vdots \\ \hat{a}_p(p) \end{bmatrix}; \quad C = \begin{bmatrix} r_{xx}(1) \\ r_{xx}(2) \\ \vdots \\ r_{xx}(p) \end{bmatrix}$$

where r_{xx} is a biased form of the autocorrelation function. This form ensures that the autocorrelation matrix, A, is positive definite. The biased form of the autocorrelation estimate is calculated as follows:

$$r_{xx}(m) = \frac{1}{N} \sum_{n=0}^{N-m-1} x^*(n)\, x(n+m) \quad m \geqslant 0 \tag{20}$$

The AR coefficients ($\hat{a}_p$) can be obtained by solving the of $p+1$ linear equations, extracted from Equation 19 (for instance, by using the fast Levinson Durbin algorithm [262, 263]). The corresponding PSD estimate is calculated as follows:

$$\hat{P}_{\mathrm{YW}}(f) = \frac{\sigma^2_{wp}}{\left|1 + \sum_{k=1}^{p} \hat{a}_p(k)\; e^{-j2\pi fk}\right|^2} \tag{21}$$

where $\hat{\sigma}^2_{wp}$ is the estimated minimum mean square error for the p^{th}-order, predictor calculated as follows:

$$\hat{\sigma}^2_{wp} = \hat{E}^f_p = r_{xx}(0) \prod_{k=1}^{p} \left[1 - |\hat{a}_p(k)|^2\right] \tag{22}$$

Burg's method Burg's method is another algorithm to the get AR model parameters. It is computationally efficient and yields a stable AR model [264]. Burg's method is based on minimizing both forward and backward prediction errors as well as estimating the reflection coefficient. The power spectrum of the pth order AR process is defined as:

$$\hat{P}_{\text{Burg}}(f) = \frac{\hat{e}_p}{\left|1 + \sum_{l=1}^{p} \hat{a}_p \; e^{-j2\pi l}\right|^2} \tag{23}$$

Where $\hat{e}_p$ denotes the total least square error. It is the sum of forward and backward prediction errors, $\hat{e}_{f,p}$ and $\hat{e}_{b,p}$ respectively. The prediction errors are calculated as follows:

$$\begin{array}{ll} \hat{e}_{f,p} & = x(n) + \sum_{i=1}^{p} \hat{a}_{p,i} \; x(n-i) \\ \hat{e}_{b,p} & = x(n-p) + \sum_{i=1}^{p} \hat{a}^*_{p,i} \; x(n-p+i) \end{array} \tag{24}$$

where $x(n)$ is a time domain signal with N samples and $n = p+1, ..., N$.

One of the most important aspects to consider when using the AR method is the selection of the model order p. In this work the order of the AR model is taken as: $p = 20$ [265, 266].

ARMA method The ARMA model is a combination of AR and Moving Average (MA) models [267, 268]. The power spectrum of an ARMA process is given by:

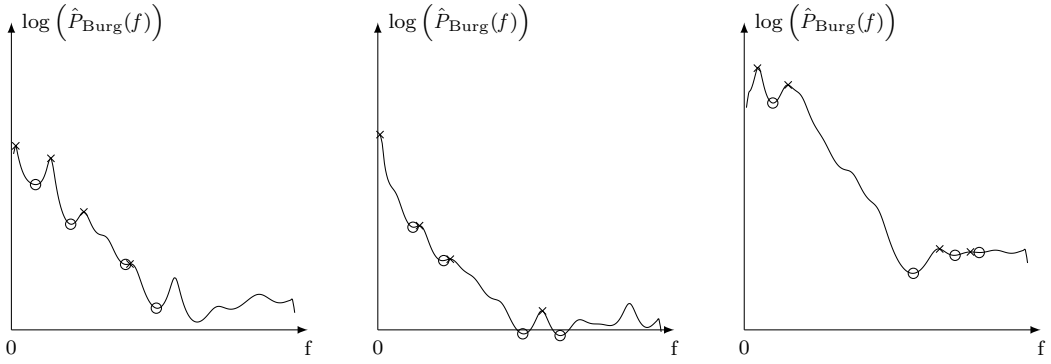
$$\hat{P}_{\text{ARMA}}(f) = \frac{\sigma^2 \; \left|\sum_{l=0}^{q} \hat{b}_p(l) \; e^{-j2\pi l}\right|^2}{\left|1 + \sum_{l=1}^{p} \hat{a}_p(l) \; e^{-j2\pi l}\right|^2} \tag{25}$$

where σ^2 is the prediction error variance. Both AR coefficients ($\hat{a}_p$) and MA coefficients ($\hat{b}_p$) were obtained with the Yule Walker method, as described in the previous section. In general, the ARMA model is generated by filtering a unit variance noise source with a filter having p poles and q zeros. This method is based on the assumption that the output value depends on the previous values of the same signal (AR component) and on the present and previous values of a different input signal (MA component), plus an additional noise factor. The advantage of the ARMA model is that it can incorporate both AR and MA terms.

Peak detection In this work, we have used Billauer's[2] 'Peak detection' algorithm to locate the first 4 local maxima and the first 4 local minima in the two dimensional PSD signals. Figure 16 shows the results of Burg's method of PSD estimation for normal, epileptic background and seizure signals. The local maxima are marked

[2]http://billauer.co.il/peakdet.html

with a cross ($\times$), the coordinates are encoded as an ordered pair. The first element in this ordered pair is the amplitude $aX_{\max}$ and the second element is frequency $fX_{\max}$, where $X \in \{1, ..., 4\}$ is the number of the maxima. For example, the ordered pair $(a1_{\max}, f1_{\max})$ encodes the coordinates of the first maxima. Similarly, the local minima are marked with circles ($\circ$), the coordinates are encoded by the amplitude $aX_{\min}$ and by the frequency $fX_{\min}$, where $X \in \{1, ..., 4\}$ is the number of the minima.



(a) Normal (b) Epileptic Background (c) Seizure

Figure 16: Results of local maxima and minima in the Burg PSD spectra of normal, epileptic background and seizure.

3.5.2.3 Statistical tests

We require a low p-value for the current classification problem. In other words, a low p-value gives some certainty that it is possible to differentiate the individual classes with an automated classifier, such as GMM, ANN and SVM. Therefore, if the observed differences are high, i.e. the p-value is low, then the test result is considered to be statistically significant.

3.5.2.4 Classification models

The following sections introduce the three classification algorithms used in the functional model of the epileptic and background identification system.

Gaussian Mixture Model (GMM) GMMs have been widely used in many areas, such as pattern recognition and classification. Their use has been especially successful in speaker identification and verification [269, 270]. In GMM models, a probability density function is expressed as a linear combination (with weights w_i) of N multi-dimensional Gaussian basis functions. Each of these basis functions is specified by its mean values μ_i and its covariance matrix Σ_i, both can be derived from the input signal. For a single observation, x, the probability density function of a given GMM

model, λ:

$$p(x \mid \lambda) = \sum_{i=1}^{N} w_i \; g\left(s \mid \mu_i, \Sigma_i\right) \tag{26}$$

The probability density function of a single Gaussian component of D dimensions is defined as:

$$g\left(x \mid \mu_i, \Sigma_i\right) = \frac{1}{\sqrt{(2\pi)^D \left|\Sigma_i\right|}} \; e^{\left[-\frac{1}{2}\left(x-\mu_i\right)' \Sigma_i^{-1} \left(x-\mu_i\right)\right]} \tag{27}$$

where ($'$) denotes the vector transpose. The solution, to determine the parameters of the GMM, uses the Maximum Likelihood (ML) parameter estimation criterion. The model parameters are estimated through training, the goal is to maximize the likelihood of the observations using the so called *Expectation-Maximization* (E-M) algorithm [271].

We estimated the initial parameters values from a sample of the training data with the K-means algorithm [272]. The K-means procedure starts with randomly chosen initial means and assumed unit variances for the covariance matrix.

Artificial Neural Network (ANN) We discussed the ANN algorithm in Section 2.7.2. For the current functional model, Figure 17 shows the ANN structure which was used for classification. The nature of the class boundaries was not clearly known. Under these circumstances, there is no theoretical method with which the network structure can be determined. By trial and error we found that a four layer network with sigmoid activation function gives good results. The input layer had 9 neurons, the two hidden layers have 15 neurons each and the output layer had two neurons.

The multilayer perceptron was trained with the Back-Propagation Algorithm (BPA). This is a supervised learning algorithm which aims to reduce the error between actual and desired network outputs. BPA is a so called *steepest decent method*, where weight values are adjusted in an iterative fashion while moving along the error surface to arrive at minimal range of error, when input patterns are presented to the network for learning.

During the initialization phase, the connection weights of the ANN were randomly assigned. During the training phase they are progressively modified to reduce the overall mean square error. The weight update, aimed at maximizing the rate of error reduction, was set to 10^{-9}. There is no definite rule for choosing the weight increment. In this work we increased the weight in small steps. With the trail and error method we arrived at $\eta = 0.9$ (constant that controls the step size).

The ideal training data set is large in size and uniformly spread throughout the class domains. In the absence of an ideal training dataset, the available data was used iteratively until the error function came down below a threshold. For quick and effective training, the data was fed from all classes in a routine sequence, so that the right message about the class boundaries was communicated to the ANN.

Support Vector Machine (SVM) The SVM algorithm for a two class (binary) problem was introduced in Section 3.4.2.5. There are several algorithms that extend

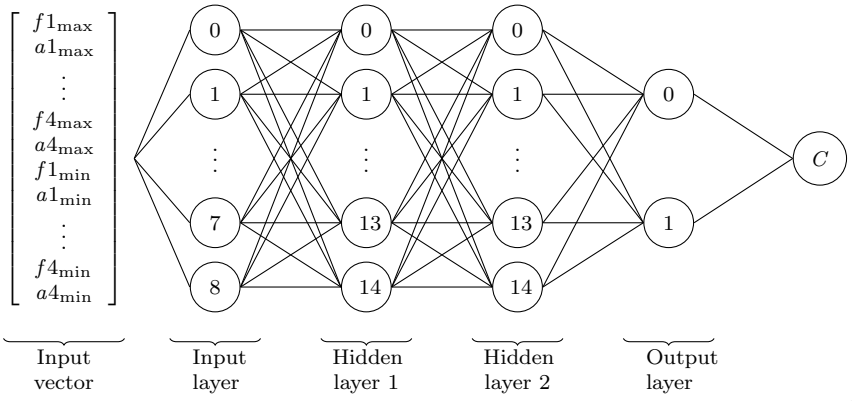


Figure 17: MLPNN with 9 input neurons, 15 neurons in the first and second hidden layer and 2 neurons in the output layer.

the basic binary SVM classifier to be a multi-class classifier. Examples are: the one-against-one SVM, one-against-all SVM, half against half SVM, and Directed Acyclic Graph SVM (DAGSVM). We used the RBF kernel function with a one-against-all algorithm to classify an input EEG segment among the three classes (normal, ictal and preictal). The SVM algorithm performed an initial search for control parameters by using a "grid search" approach, as suggested by Hsu [273].

3.5.2.5 Classification performance measures

The ROC curve is a plot in a two dimensional space. The x-axis is '1 - specificity' and the y-axis is 'sensitivity'. Sensitivity, also known as TP fraction, refers to the probability that a test result is positive when a disease is present, as discussed in Section 3.4.2.6.

The area under the ROC curve indicates the classifier performance across the entire range of cut-off points. Conventionally, the area under the ROC curve must fall in the range between 0.5 and 1 [274]. An area closer to 1 means that the classifier has a better accuracy. The area under the ROC curve is a good indicator for the classifier's performance [275].

For example, Fogarty et al. have used ROCs to analyze the tradeoff between TP and FP for sensor based estimates. Their case studies compare sensor-based estimates with human performance. They have optimized a feature selection process for the area under the ROC curve, and they have examined end-user selection for a desirable tradeoff [276].

In this work, we have used ROC to test the selected classifiers for their ability to differentiate normal from both epileptic background and seizure. Specificity measures the proportion of signals from the normal group which are correctly identified. Similarly, sensitivity measures the proportion of both epileptic background and seizure groups which were correctly identified.

C	$f1_{\max}$	$a1_{\max}$	$f2_{\max}$	$a2_{\max}$	$f3_{\max}$	$a3_{\max}$	$f4_{\max}$	$a4_{\max}$
N	0.0548 ±0.0716	0.4672 ±0.1133	0.1738 ±0.3074	0.0300 ±0.1316	0.1229 ±0.0923	0.3231 ±0.2443	0.0374 ±0.0945	0.0166 ±0.1036
EB	0.2640 ±0.1400	0.3144 ±0.2365	0.1424 ±0.2156	0.1230 ±0.2362	0.2728 ±0.1968	0.1488 ±0.1922	0.0625 ±0.1383	0.0364 ±0.0824
S	0.1200 ±0.0530	0.1200 ±0.1756	0.0978 ±0.2599	0.0290 ±0.1260	0.3167 ±0.1468	0.0858 ±0.1342	0.0177 ±0.0611	0.0057 ±0.0267
p	0	0	0.1248	0.0001	0	0	0.0092	0.0197

Table 7: ARMA max: Mean and variance results calculated from individual elements of the input vector, for one class.

3.5.2.6 Results

Model assessment is an integral part of formal and model driven design. For this case study, the functional model is evaluated with statistical and classification accuracy tests. The current section states the results and the next section discusses the result. The block diagram, shown in Figure 7, gives an overview on how the results were obtained. The first step is to estimate the PSD from individual EEG signals. The PSD is estimated by applying three different methods, namely: ARMA, Yule-Walker and Burg. The local maxima and minima of the PSD curve were extracted with the peak detection algorithm. The location of the first four maxima and the first four minima forms a 16 dimensional feature vector. The feature vectors were used as classifier input. With respect to the local extrema location, 'first' means the extrema being located at the lowest frequency. The next sections report the performance results of the individual classifier. The result presentation is structured such that there is a subsection for each PSD estimation method. The subsection contains a confusion matrix for the classifier under discussion and the classifiers are compared within ROC graphs. Section 3.5.2.6 compares the results across the individual PSD estimation methods.

For all tables, presented in the following sections, C = class, N = normal, EB = epileptic background and S = seizure. 'p' stands for p-value. For all p-values, a 0 indicates a result lower than 0.0001.

ARMA method Despite the fact that the ARMA method uses both AR and MA parameters, the classification results, presented in the following text, are the poorest of all three tested methods. The classification results are based on the parameters, i.e. location of the local extrema. Table 7 indicates the statistical relevance of these parameters. It shows mean and standard deviation of both frequency f and amplitude a values for the first four maxima within each class. The last row shows the p-values from the ANOVA test. Similarly, Table 8 shows these measures for the first four local minima. The only general trend, within the ANOVA results, is that both local maxima and local minima are statistically significant.

The discussion of the classification result starts with the GMM classifier. The classification rate of the GMM classifier was 31.11%, which is below 50%. Table 9 shows the 3×3 confusion matrix for this test. The first row indicates that the GMM

C	$f1_{\min}$	$a1_{\min}$	$f2_{\min}$	$a2_{\min}$	$f3_{\min}$	$a3_{\min}$	$f4_{\min}$	$a4_{\min}$
N	0.2715 ±0.0872	0.1465 ±0.2597	0.0282 ±0.1209	0.0194 0.0996	0.1046 ±0.0446	0.0235 ±0.0481	0.0117 ±0.0513	0.0134 ±0.0750
EB	0.2471 ±0.1833	0.1297 ±0.1950	0.1288 ±0.2470	0.0791 ±0.2022	0.1027 ±0.1427	0.0687 ±0.1708	0.0579 ±0.1496	0.0368 ±0.1251
S	0.0947 ±0.1481	0.0956 ±0.2591	0.0315 ±0.1377	0.0235 ±0.1446	0.0927 ±0.1417	0.0194 ±0.0725	0.0134 ±0.0684	0.0055 ±0.0519
p	0	0.3123	0	0.0103	0.7478	0.0025	0.0011	0.0372

Table 8: ARMA min: Mean and variance results calculated from individual elements of the input vector, for one class.

Classifier	Target	Normal	Seizure	EB
GMM	Normal	3	27	0
	Seizure	6	23	1
	EB	2	26	2
ANN	Normal	24	5	1
	Seizure	1	25	4
	EB	0	8	22
SVM	Normal	26	3	1
	Seizure	1	25	4
	EB	1	3	26

Table 9: Confusion matrix results.

method classified only 3 data sets, taken from normal EEGs, correctly as normal. But, 27 normal subjects were wrongly classified as epileptic seizure and no data sets were classified as epileptic background. Similarly, the second row details that 23 data sets were correctly identified as epileptic seizure. But, six were wrongly classified as normal and one was wrongly classified as epileptic background. Finally, the last row indicates that 26 data sets were correctly identified as epileptic background and four data sets were wrongly classified. The sum of the elements within each row is always 30, i.e. the number of data sets, within each class, used to test the classifier.

The ANN is the second classifier, which was tested on the same data sets. The classifier achieved a classification rate of 78.89%. The confusion matrix, given in Table 9, shows that the classification performance for normal data sets was better than the performance of the GMM classifier for the same data set. However, the classification of epileptic background was not satisfactory, because eight out of 30 epileptic background data sets were wrongly classified as epileptic seizure.

Finally, the SVM classifier was also tested with the same data set. It achieved an even higher classification rate than the ANN classifier. To be specific, the classification rate of the SVM classifier was 85.56%. The confusion matrix, presented in Table 9, shows that SVM achieved acceptable results for all classes.

To compare the classifier performance we used ROC curves. The ROC curves, shown in Figure 18, highlight the poor performance of the GMM classifier.

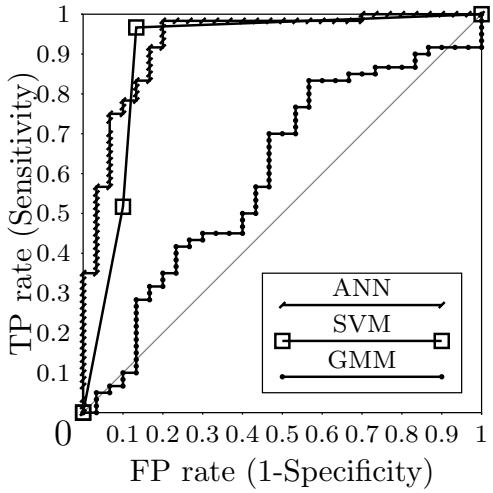


Figure 18: ROC curves of the classifiers based on ARMA method.

Classifier	AUC	S.E. 95%	CI	Sensitivity	Specificity
GMM	0.61556	0.06114	0.49572–0.73539	0.7000	0.5333
ANN	0.93167	0.02576	0.88118–0.98215	0.9167	0.8333
SVM	0.95278	0.02110	0.91142–0.99413	0.9667	0.8667

Table 10: ROC analysis. For all classifier, the area under the ROC is statistically greater than 0.5.

Table 10 presents the statistical analysis of the ROC curves. AUC indicates the area under the curve.. In general, larger AUC values indicate a better classification performance. The area under the curve was further analyzed with the Standard Error (SE) [277] and the Confidence Interval (CI) [278]. Apart from AUC analysis, Table 10 provides sensitivity and specificity of the tests as well. These results reveal that the SVM classifier is the best choice for classifying the parameters obtained from ARMA PSD.

Yule-Walker method The second test sequence was conducted with parameters which were extracted from Yule-Walker PSD. Tables 11 and 12 detail the statistical significance of the parameters. The values in Table 12 support the claim that the positions of local minima are also statistically significant. Overall, the p-values are lower than the ones from the ARMA PSD parameters.

As before, the weakest classification method was the GMM classifier. The classification rate of the GMM classifier was 81.11%. Compared with the ARMA classification rate, this roughly 50% higher. The confusion matrix entries, shown in Table 13, reflects the increase. According to this table, GMM delivered poor results for normal classification, the results for the other two classes were acceptable.

Even though, the GMM classification rate was acceptable, with a classification rate of 85.56% the ANN classifier was better. Especially the performance on the

C	$f1_{\max}$	$a1_{\max}$	$f2_{\max}$	$a2_{\max}$	$f3_{\max}$	$a3_{\max}$	$f4_{\max}$	$a4_{\max}$
N	0.1400 ±0.0391	0.1346 ±0.0209	0.2870 ±0.1210	0.5489 ±0.1365	0.0108 ±0.0241	0.0210 ±0.0272	0.0132 ±0.0213	0.0243 ±0.0494
EB	0.5808 ±0.2463	0.2673 ±0.2501	0.5986 ±0.2787	0.6620 ±0.3380	0.1030 ±0.1449	0.1389 ±0.1948	0.0373 ±0.1185	0.0360 ±0.1333
S	0.1758 ±0.0767	0.3595 ±0.2850	0.5598 ±0.2962	0.4631 ±0.3818	0.0098 ±0.0259	0.0019 ±0.0037	0.0003 ±0.0008	0.0012 ±0.0017
p	0	0	0.1248	0.0001	0	0	0.0092	0.0197

Table 11: Yule-Walker max: Mean and variance results calculated from individual elements of the input vector, for one class.

C	$f1_{\min}$	$a1_{\min}$	$f2_{\min}$	$a2_{\min}$	$f3_{\min}$	$a3_{\min}$	$f4_{\min}$	$a4_{\min}$
N	0.1068 ±0.0231	0.2584 ±0.1215	0.5099 ±0.1266	0.6591 ±0.1631	0.0042 ±0.0019	0.0065 ±0.0090	0.0196 ±0.0554	0.0154 ±0.0475
EB	0.2981 ±0.2834	0.5307 ±0.2443	0.6169 ±0.3205	0.4467 ±0.4348	0.1498 ±0.2012	0.0339 ±0.1161	0.0421 ±0.1414	0.0785 ±0.1724
S	0.4290 ±0.3381	0.4885 ±0.2451	0.4101 ±0.3378	0.2759 ±0.3569	0.0025 ±0.0038	0.0002 ±0.0004	0.0011 ±0.0023	0.0024 ±0.0046
p	0	0	0	0	0	0.001	0.0046	0

Table 12: Yule-Walker min: Mean and variance results calculated from individual elements of the input vector, for one class.

normal class was more accurate, according to the confusion matrix given in Table 13.

Compared to both: GMM and ANN, the SVM classification rate of 87.78% was the best for parameters extracted from Yule-Walker PSDs. The SVM classifier performed good for all three classes, as shown in the confusion matrix of Table 13. This table shows that the SVM classifier yields its weakest result for seizure classification.

The ROC curves, shown in Figure 19, refine the results of the confusion matrices. However, in this case the ROC curves fail to deliver a result which was similar to the confusion matrix results. According to Figure 19 the ANN classifier was better than SVM and GMM. This comes from the fact that ROC curves detail only two class

Classifier	Target	Normal	Seizure	EB
GMM	Normal	18	8	4
	Seizure	0	27	3
	EB	0	2	28
GMM	Normal	25	4	1
	Seizure	0	26	4
	EB	0	4	26
GMM	Normal	26	1	3
	Seizure	2	25	3
	EB	0	2	28

Table 13: Results of the GMM classification.

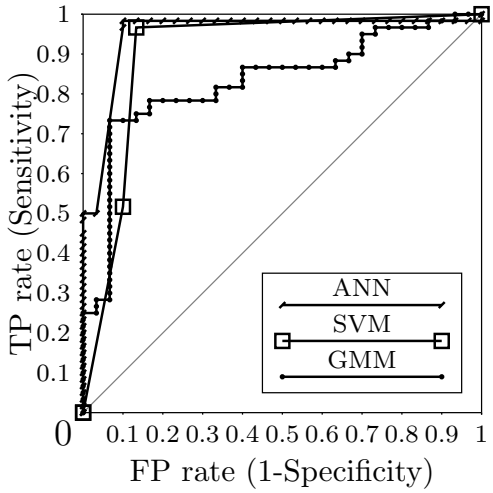


Figure 19: The result of ROC curves of the classification based on Yule-Walker method.

Classifier	AUC	S.E. 95%	CI	Sensitivity	Specificity
GMM	0.83111	0.04206	0.74867–0.91355	0.7833	0.8333
ANN	0.96722	0.01737	0.93318–1.00127	0.9833	0.9000
SVM	0.92167	0.02775	0.86728–0.97605	0.9667	0.8667

Table 14: Result of ROC analysis for GMM, ANN and SVM classifiers. For all classifier, the area under the ROC is statistically greater than 0.5.

problems (disease present or not).

Table 14 provides a detailed ROC analysis. The area under the ROC curve favors the ANN classifier, it has an area of 0.96722 compared to an area of 0.92167 for the SVM classifier. Similarly, both sensitivity and specificy of the ANN classifier were also the best, when compared to the SVM and GMM classifiers.

Burg's method In general, Burg's method of spectrum estimation outperformed the other two PSD estimation techniques. Tables 15 and 16 show the statistics of these parameters. The p-values are slightly better than the ones obtained from Yule-Walker parameters. However, only the classification results provide a strong support for the claim that Burg's method is the best PSD estimation method, among the three methods which were tested for EEG signal classification.

We achieved a classification rate of 82.22% even with the GMM classifier. The confusion matrix for the GMM classifier, provided in Figure 17, shows a perfect classification for epileptic background. However, the classification for normal is poor and therefore the overall performance of GMM is the weakest of the three tested classifiers.

With a classification rate of 90%, the ANN classifier was better than the GMM classifier. The confusion matrix, shown in Table 17, reveals that the ANN performs

C	$f1_{\max}$	$a1_{\max}$	$f2_{\max}$	$a2_{\max}$	$f3_{\max}$	$a3_{\max}$	$f4_{\max}$	$a4_{\max}$
N	0.1400 ±0.0391	0.1345 ±0.0210	0.2838 ±0.1176	0.5390 ±0.1432	0.0112 ±0.0260	0.0211 ±0.0273	0.0124 ±0.0199	0.0248 ±0.0497
EB	0.5725 ±0.2484	0.2623 ±0.2448	0.5925 ±0.2838	0.6566 ±0.3407	0.0981 ±0.1383	0.1434 ±0.1971	0.0388 ±0.1186	0.0337 ±0.1325
S	0.1708 ±0.0743	0.3355 ±0.2672	0.5617 ±0.2869	0.4247 ±0.3661	0.0097 ±0.0255	0.0018 ±0.0037	0.0003 ±0.0007	0.0011 ±0.0015
p	0	0	0	0	0	0.0007	0.0096	0

Table 15: Burg max: Mean and variance results calculated from individual elements of the input vector, for one class.

C	$f1_{\min}$	$a1_{\min}$	$f2_{\min}$	$a2_{\min}$	$f3_{\min}$	$a3_{\min}$	$f4_{\min}$	$a4_{\min}$
N	0.1079 ±0.0238	0.2555 ±0.1178	0.5024 ±0.1318	0.6427 ±0.1764	0.0042 ±0.0019	0.0061 ±0.0084	0.0218 ±0.0564	0.0139 ±0.0462
EB	0.2961 ±0.2814	0.5223 ±0.2457	0.6127 ±0.3247	0.4486 ±0.4296	0.1522 ±0.2022	0.0340 ±0.1140	0.0416 ±0.1514	0.0602 ±0.1573
S	0.4110 ±0.3280	0.4920 ±0.2369	0.3717 ±0.3160	0.3101 ±0.3636	0.0023 ±0.0033	0.0002 ±0.0004	0.0011 ±0.0022	0.0023 ±0.0043
p	0	0.3123	0	0.0103	0.7478	0.0025	0.0011	0.0372

Table 16: Burg min: Mean and variance results calculated from individual elements of the input vector, for one class.

well for all three classes.

The best classifier, for parameters obtained from Burg's PSD, was the SVM with a classification rate of 93.33%. Table 17 shows the confusion matrix. The SVM performed especially well for normal classification.

Figure 20 shows the ROC curves of the three classifiers which took part in this test. The curves show that the performance of ANN and SVM is similar. They are both superior when compared to the GMM classifier.

Table 18 gives a detailed ROC analysis. The table shows that ANN had a slightly larger area under the ROC curve then SVM. However, sensitivity and specificity were the same for ANN and SVM. Both, ANN and SVM outperform the GMM classifier in all measures.

Comparison of the different PSD estimation methods This section compares the results of the SVM classifier, obtained from parameters which were extracted from different PSDs. Tables 19 and 20 summarize the ANOVA test results. These results show two trends: 1) The first extrema are statistically more significant than the following extrema, i.e. the p-value goes up towards the right side of the tables. 2) Both parameter sets, Yule-Walker and Burg, show more statistical significance when compared to parameters obtained from the ARMA PSD.

The discussion of the ANOVA tests (p-vlaues) gives an indication of how well the classification methods may perform. In the previous sections, both classification rate and confusion matrices show that the SVM was the best classifier for the parameters obtained from all the different PSDs. The ROC curves, shown in Figure 21, indicate

Classifier	Target	Normal	Seizure	EB
GMM	Normal	18	8	4
	Seizure	0	26	4
	EB	0	0	30
GMM	Normal	28	0	2
	Seizure	0	27	3
	EB	0	4	26
GMM	Normal	29	0	1
	Seizure	0	27	3
	EB	1	1	28

Table 17: Confusion matrixes for features derived from PSDs according to Burg's method.

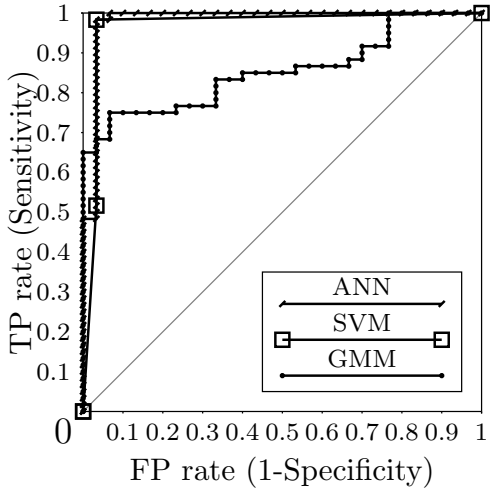


Figure 20: The result of ROC curves of the classification based on Burg's method.

Classifier	AUC	S.E. 95%	CI	Sensitivity	Specificity
GMM	0.85444	0.03886	0.77828–0.93061	0.7500	0.9333
ANN	0.98222	0.01261	0.95750–1.00694	0.9833	0.9667
SVM	0.97583	0.01480	0.94683–1.00484	0.9833	0.9667

Table 18: ROC analysis. For all classifier, the area under the ROC is statistically greater than 0.5.

PSD	$a1_{\max}$	$f1_{\max}$	$a2_{\max}$	$f2_{\max}$	$a3_{\max}$	$f3_{\max}$	$a4_{\max}$	$f4_{\max}$
ARMA	0	0	0.1248	0.0001	0	0	0.0092	0.0197
YW	0	0	0	0	0	0	0.0008	0.0102
Burg	0	0	0	0	0	0	0.0004	0.0149

Table 19: 'p-values' of the parameters obtained from the position, i.e. value v and frequency f, of the first 4 maxima. A 0 indicates a p-value better than 0.0001.

PSD	$a1_{\min}$	$f1_{\min}$	$a2_{\min}$	$f2_{\min}$	$a3_{\min}$	$f3_{\min}$	$a4_{\min}$	$f4_{\min}$
ARMA	0	0.3123	0	0.0103	0.7478	0.0025	0.0011	0.0372
YW	0	0	0	0	0	0.001	0.0046	0
Burg	0	0	0	0	0	0.0007	0.0096	0

Table 20: 'p-values' of the parameters obtained from the position, i.e. value v and frequency f, of the first 4 minima. A 0 indicates a p-value better than 0.0001.

Classifier	ARMA	YW	Burg
GMM	29	0	1
SVM	0	27	3
ANN	1	1	28

Table 21: Area under ROC curves.

that Burg's method yields the best classification result. This does not contradict the ANOVA test results.

The most detailed and therefore most valuable way of comparing the SVM performance is the combined confusion matrix, shown in Table 22. A sequence of three rows describes the SVM results of the three PSDs for the same target. The first group describes the results for normal. With 29 correctly classified data sets, obtained from the Burg PSD, the SVM classifier showed the best result. For the seizure group, the Burg PSD also yielded the best SVM classification results. For epileptic background, there was a tie between the SVM classification results, obtained from Burg and Yule-Walker PSD.

3.5.2.7 Cooperation and competition

Formal and model driven design fosters cooperation and competition. For this case study the cooperation aspect comes from a medical interpretation of the functional model test results. Medical research indicates that during epilepsy, the effected neurons in the cerebral hemispheres may mis-create abnormal electrical activity. The abnormal electrical activity leads to a sudden increase in neural discharge. Furthermore, neurons, affected by epilepsy, are not available for useful information processing. As a consequence, the electrical activity, associated with useful information processing, is reduced [279, 280]. These two effects explain the changes in the PSD.

The competition aspect of formal and model driven design comes from comparing the functional model results with the findings of other researchers. We conduct the competition by stating the related research results and subsequently pointing out the differences to our work. Ghosh-Dastidar et al. have investigated automatic epilepsy and seizure detection using a pattern recognition method [84]. Their proposed spiking neural network model resulted a high classification accuracy of 92.5%. In other research work, by the same leading authors, a novel PCA-enhanced cosine radial basis function neural network classifier was used to detect the epilepsy and seizure [281]. Their method yielded a high classification accuracy (96.6%) and was robust

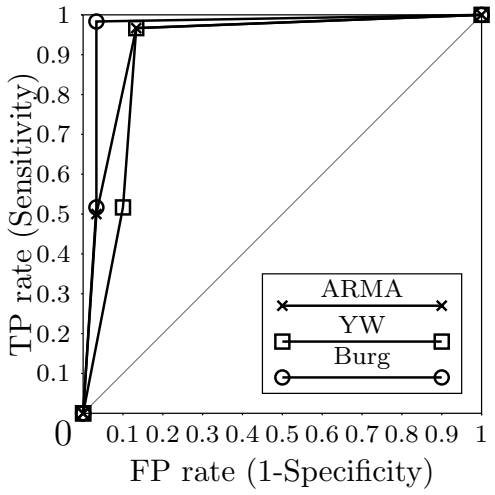


Figure 21: Performance of the SVM classifiers.

Target	PSD method	Result		
		Normal	Seizure	EB
Normal	ARMA	26	3	1
	YW	26	1	3
	Burg	29	0	1
Seizure	ARMA	1	25	4
	YW	2	25	3
	Burg	0	27	3
EB	ARMA	1	3	26
	YW	0	2	28
	Burg	1	1	28

Table 22: Comparison of the SVM confusion matrices from the three different spectrum estimation methods. In all cases, Burg's method outperforms the other two PSD estimation methods.

to changes in the training data with a low standard deviation of 1.4%. For epilepsy diagnosis, when only normal and interictal EEGs were considered, the classification accuracy of the proposed model was 99.3%. In their most recent work, they used a Multi-Spiking Neural Network model together with a new supervised learning algorithm to identify epilepsy and seizure [282]. The classification accuracy of this system was in the range of 90.7% to 94.8%.

Kannathal et al. have used different types of entropies to analyze normal and epileptic EEG signals [283]. They have successfully identified normal and epileptic EEG signals using different entropies as well as neuro-fuzzy classifier with an accuracy of more than 90%.

Partial and generalized epilepsy has been detected using Radial Basis Function Neural Network (RBFNN) and Multilayer Perceptron Neural Networkss (MLPNNs) [284]. The study indicates that, RBFNN (95.2%) performs better than the MLPNN (89.2%).

Recently, Chua et al. have used HOS to differentiate between normal, background (preictal) and epileptic EEG signals [285]. These HOS features were fed as input to GMM and SVM classifiers for automatic identification. The results show that their HOS features, coupled with the selected classifier, were able to achieve 95.78% and 91.70% classification accuracy.

Hamani et al. revealed that there was a significant drop in phase synchronization for the preictal state [286]. In a controlled study, they were able to predict seizures up to an accuracy of 70% cases with no FPs in the control groups.

Chaotic features, like CD, Hurst exponent (H), LLE and ApEn, can be used to characterize EEG signals. The resulting features were used for automatic diagnosis of seizure onsets [287]. These nonlinear features were used to train both GMM and SVM classifiers. Their results show that the GMM classifier performed better with average classification efficiency of 95%, sensitivity and specificity of 92.22% and 100% respectively.

The test results of our functional model show that the linear feature extraction method of PSD estimation can be used for EEG analysis. Burg's method, coupled with an SVM classifier, outperformed all other tested combinations. To be specific, this combination was able to identify the unknown class with a specificity is 98.33% and s sensitivity of 96.67%. These results are comparable with nonlinear methods.

During the last decade, electrical stimulation has been used to treat several neurologic disorders such as epilepsy [288]. Recently, therapeutic stimulation of epileptic foci has attracted interest in the research community [289]. We hope that accurate classification of normal, preictal and ictal mental states will improve integrated epilepsy treatment systems, such as the ones proposed by Shoeb et al. and Osorio / Frei [290, 291].

3.6 Chapter conclusion

In this chapter we investigated the functionality aspects of formal and model driven biomedical systems design. Within the design methodology, the requirements capturing process establishes the system functionality. For CAD systems, the requirements

are captured with a functional model. The design pattern for the functional model are common for all CAD system designs. But, the algorithms used are distinct for individual problem solutions. To support the point about communality and distinctiveness, we conducted two case studies. For each case study, the functional model describes a unique algorithm structure which implements signal analysis and automated decision making methods. The individual case studies define their own algorithms to model the needed functionality. Algorithm selection and creation is the most important intellectual activity when designing a functional model. The output of each processing step is tested with appropriate performance measures. Constant testing helps us to steer the model building procedures by providing feedback to the designer about the quality of their work. Even though, tests are carried out continuously and a conversation about the test results happens as they become available, there is a final discussion and elaboration at the end of the requirements process. The aim of the final discussion is to relate the functional model test results to the wider research community. The relation should be established in terms of cooperation and competition. For cooperation, the functional model test results are related to medical research. In the best case, the functional model test results augment and extend medical knowledge. In the worst case, the test results contradict established medical knowledge. In such a case, it might be necessary to revisit the need definition and come up with another strategy for designing the functional model. The second method of relating the functional model results to other findings and performance measures is through competition. Most CAD systems attempt well known and important problems, such as diabetes diagnosis, sleep apnoea classification and epilepsy detection. There are systems from other researchers in existence which attempt to solve the same problem. Therefore, it is possible to compare the results of the functional model under discussion with previously published results. The outcome of that comparison will determine whether or not it is feasible to specify the system which implements the functional model. If it turns out that the proposed functional model is inferior to state of the art solutions, it is necessary to revisit the need definition.

The current chapter provides a comprehensive review of model driven design for CAD. During the review we found that the systems engineering meta model fits very well to that particular application domain. Furthermore, we show that the functional model creation for CAD systems follows the same template. The formal and model driven design methodology has a strong emphasis on model testing. Therefore, we introduced sophisticated CAD performance measures. These measures govern the research that aims to find the most functional solution for a given biomedical problem. The two case studies on CAD systems focus on creating the functional models which govern the requirement analysis. As such, the requirement analysis is only one part of the formal and model driven design methodology. With the case studies we show that functional improvements for CAD systems are possible. But, having achieved these functional improvements does by no means coincide with the improvement of patient care. An improvement of patient care comes from safe, reliable and functional physical problem solutions. The design of these problem solutions requires us to execute all aspects of the design methodology. The discussion of the functional models falls well short of executing all aspects of formal and model driven design, a more holistic point

of view is needed.

The next chapter introduces the systems aspect of the formal and model driven design methodology. We discuss the application of medical network technology for diabetic and health-care systems. The discussion on networking technology sets the CAD systems into perspective with more inclusive health-care systems. The expansion of focus is necessary to design more effective CAD systems with the formal and model driven design methodology.

CHAPTER 4

CASE STUDY IV: A SYSTEMS ENGINEERING FRAMEWORK FOR HEALTHCARE SYSTEMS

4.1 Summary

Currently, there is a disparity in the availability of doctors between urban and rural areas in developing countries. Most experienced doctors and specialists, as well as advanced diagnostic technologies, are available in urban areas. People living in rural areas have less or sometimes even no access to affordable healthcare facilities. Increasing both number of doctors and charitable medical hospitals or deploying advanced medical technologies in these areas might not be economically feasible, especially in developing countries. Hence, there is health care divide where people living in rural areas receive significantly lower levels of care when compared with people from urban centers. To overcome the divide calls for cost effective strategies to design biomedical health care systems.

We need to mobilize science and technology to master the complex, large scale problem in an objective, logical, and professional way. The solution can only be achieved through a collaborative effort where a team of experts works on both technical and non-technical aspects of this health care divide. In this chapter we use formal and model driven design to discuss hospital networks which might be a solution for the problem. We argue, that with the advancement in communication and networking technologies, economically middle class people and even some rural poor have access to internet and mobile communication systems. Thus, Hospital Digital Networking Technologies (HDNT), such as telemedicine, can be developed to utilize internet, mobile and satellite communication systems to connect primitive rural healthcare centers to advanced urban setups and thereby provide better consultation and diagnostic care to needy people. This chapter describes requirements and limitations of the HDNTs. It also presents the features of telemedicine, the implementation issues and the application of wireless technologies in the field of medical networking.

4.2 Introduction

We start our discussion on the formal and model driven design of health care systems with semantics. The term hospital network describes a group of hospitals that work together in order to coordinate and deliver a broad spectrum of services to the community [19, 20]. A health care system comprises of two or more hospitals owned, sponsored, or contract managed by central organizations. Most of these health care systems follow allopathic or modern medicine (Western medicine) [292]. Furthermore, there is a variety of other healthcare practices available these days [293] and people follow either one, or a combination, of these practices for a healthy living.

Now we turn our attention to personalized health care. We found that there are medical practices [294, 295] in operation that are designed to treat individuals based on their specific genetic code. The specialization was done in order to provide a tailored approach to treating the ailments of patients. These practices use preventive, diagnostic, and therapeutic interventions that are based on genetic tests and family history information. The goal of personalized health care is to improve the overall health of the population.

Based on these observations, we establish that there is a need to deliver health care to people living in both rural and urban areas. The health care delivery should be done appropriately and effectively using at least either western or alternative practices. We found that efficient health care delivery systems require the use of digital networking technologies for connecting urban and rural areas as well as the various hospitals and diagnostic centers around the globe. These networking technologies, which are used in hospital setups, are called *Hospital Digital Networking Technologies (HDNT)*. They can prove to be very efficient in providing healthcare services to even the remotest parts of the world.

Having established the focus on HDNT, we move on with the need definition by looking at the work published by experts in the relevant field. For example, Aanestad and Hanseth introduced new non-desktop technologies for a complex medical work practice (surgery). Using actor-networking technology, they argue that conceptualizing the process as cultivating the hybrid collective of humans and non-humans, technologies and non-technologies is a suitable and useful approach. Following their line of thought, this concept may capture the open ended and emergent nature of the process and indicate the suitability of an environmental approach [296].

Other research work focused on the design of the so called EchoCardiographic Healthcare Online Networking Expertise in Tasmania (ECHONET) system – a telemedicine system developed by CSIRO Australia. It aims to facilitate the sharing of expertise and services between the intensive care units of a major tertiary hospital and a remote hospital in Tasmania, Australia. A baseline study, which was conducted alongside this project, was used to evaluate the ways in which the action research approach influenced the project directions and its success. The study results gave valuable information to the project team; the data provided the base to improve the system such that the clinicians needs are more adequately met [297].

Research and development moves ahead and there is even a perception in modern society that technology is a solution for all problems. However, the conclusion is not quite correct: Technology, which is not properly designed, tested and integrated into an organization or business does not serve its purpose. Therefore, there is an urgent need to ensure that HDNTs are designed according to the needs of the system stake holders [298, Chapter 16].

This chapter shows the formal and model driven design of a health care framework. We give a basic insight into the ways in which computer and communication technologies can be used to connect medical facilities centered in urban areas to the majority of people who still live in rural areas. We tackle the health care divide problem with a systems approach [299]. Thereby, we follow the ideas of Ramo and St.Clair, who asked such provocative questions like: “If we can record the heartbeat of

an astronaut ten thousand miles above the earth, then why can we not readily provide superb medical monitoring for the bed patients of our hospitals?" [300]. Questions like these form the anchor point for their discussion on the systems thought. The argument is that there is no perfect solution for large scale problems; however there are multiple optimal solutions. The multitude of optimal solutions arises from the fact that a multitude of system properties can be measured in different ways. The first step to overcome these difficulties is to gather information about the problem itself, the environment, the system has to operate in, and current technical solutions. The information enables us to state the system goals. A second step outlines concrete properties which enable the system to meet these goals and it proposes measures and measurement guidelines. These measures, which are taken according to the measurement guidelines, indicate to which level the properties were archived. Having such a list of properties and measures enables a group of technologists to implement the system. This implementation must pass various tests. These tests must be designed such that they establish trust in the implemented system.

The structure of this chapter reflects the formal and model driven design methodology, which lies at the center of this work. Before a technological solution, i.e. a HDNT system can be discussed, it is necessary to understand both the nature of the problem and the environment in which a system, which solves the problem, must operate. Both points are covered in the requirements analysis, presented in Section 4.3. This section states also the goals for the proposed HDNT system. Section 4.4 moves the argument on to implementation aspects of HDNT systems. In this section we make the case for wireless health care networks. Both requirements and implementation are discussed in Section 4.5. The chapter concludes with Section 4.6.

4.3 Requirements and specification

This section documents our efforts to execute the formal and model driven design process. We start the process with the requirements analysis for the HDNT design. The requirements analysis begins with understanding the problem background. Therefore, Section 4.3.1 discusses different health care systems. The data, which shows the health care divide problem, is analyzed in Section 4.3.2. Based on the data analysis results, Section 4.3.3 presents the case for medical networking. The limitations of current HDNT technologies and security issues related to this technology are presented in Sections 4.3.4 and 4.3.5, respectively. Based on both data analysis results and current limitations, we formulate the requirements of a HDNT system in Section 4.3.6. Finally, Section 4.3.7 refines the requirements into a system specification.

4.3.1 Health care systems

Some alternative health care systems are in fact traditional medical systems, which, in the early twentieth century, were considered incomprehensible, cryptic and masked in mysticism. These systems are now gaining acceptability all over the world as alternative lines of treatment. Some of these systems are also being integrated into

mainstream health care systems as complementary systems. The list below sets western medicine alongside a few very popular and widely followed traditional systems of medicine which were practiced before the advent of modern medical practices.

1. Western Medicine: Western medicine stands in the Greek tradition. However, by using modern scientific biomedical research it has risen above its herbalist traditions [301]. Western medicine follows strict clinical practice where doctors personally assess patients in order to diagnose, treat and prevent disease.

2. Ayurveda: Ayurveda or ayurvedic medicine is an ancient Indian system of health care. Its origins can be traced to around 1200 BC. It is native to the Indian subcontinent and it is commonly used in neighboring countries like Nepal and Srilanka. Ayurveda, literally means the science of life, it aims at healing the individual as a whole, instead of merely at the molecular level. Ayurveda is a holistic system of medicine which promotes healthy living along with therapeutic measures that relate to physical, mental, spiritual and social harmony [302, 303].

3. Siddha: It is a form of south Indian traditional medicine and it is one among the trio of Indian medical systems – Ayurveda, Siddha and Unani. It is believed to be the oldest medical system on earth. The human body is considered to be a conglomeration of three humors, seven types of body tissues and waste products. This system is believed to have been invented by 'Siddhars', the ancient supernatural saints of India who in turn received this knowledge from lord Shiva, the Hindu God [304, 305, 306].

4. Unani: Unani medicine (originated in Greece during 460–377 BC) is based on the theory of four bodily fluids or humors, with each humor leading to a specific temperament in a human being. The four humors are phlegm, blood, yellow bile and black bile. The term Unani refers to a Graeco-Arabic medical system which is based on the teachings of Hippocrates, Galen and Avicenna (Hakim Ibn Sina) [306, 307, 308].

5. Naturopathy: It is a system of medicine which emphasizes on the ability of the body to heal and maintain itself. Naturopathic practitioners prefer to avoid invasive surgery or synthetic drugs and prefer natural remedies like herbs and fruits. Thus, it is based on the practice of applying simple laws of nature to cure diseases. Breathing exercises which induce relaxation and wellbeing and meditation are used to promote positive health and wellbeing. These practices are also helpful in assisting the body to overcome certain illnesses [309, 310].

6. Homeopathy: Homeopathy lays emphasis on strengthening the immune system. Homeopathic practitioners contend that an ill person can be treated using a substance that can produce, in a healthy person, symptoms similar to those of the illness. Homeopathy was conceived by Hahnemann in the early years of the nineteenth century. It quickly became popular in Europe and America. Its popularity in these countries has declined with the advent of modern medical

Country	Number of doctors per 1000 Population
USA	2.6
UK	2.31
China	1.1
India	0.61
Bangaladesh	0.28
World average	1.3

Table 23: Approximate availability of doctors per 1000 people in developed and developing countries.

practices based on allopathy. However, it has a large following in India where degrees in homeopathic medicine are on offer [311, 312].

4.3.2 Data analysis

The number of doctors available per one thousand people can serve as a quality measure of national or regional health care services. For example, in the USA this figure is 2.6 doctors for every 1000 people. This figure is a respectable 2.31 in the UK and it drops to 0.28 in a developing country like Bangladesh. The world average is 1.31 doctors for every thousand people. Table 23 details the approximate availability of doctors per 1000 people in developed and developing countries. Migration of trained doctors from developing to developed countries is further lowering the availability of doctors to the general population in the former.

In addition, it is observed that there is disparity in the availability of doctors in urban and rural areas especially in developing countries. For analytical purposes, we consider the situation in India. About 72% of doctors work in urban areas, serving about 30% of the population. The remaining 70% of the population is served by the remaining 28% of doctors. Thus, while world class health care is available to a few wealthy citizens in urban centers, the rural poor are deprived of even elementary health care. Such a situation exists in almost all developing countries.

4.3.3 Medical networking

There are a number of charitable hospitals which provide free medical treatment to patients in developing countries. The Sai Medical Institutions, run by Sri Satya Sai Baba group in Bangalore [313], and the Amrita Institute of Medical Sciences, run by the Mata Amritaanandamayi group in Kochi, are a few examples of such hospitals in India. Though, there are many other similar institutions, they are far too few in number, given size and population of a country like India. While the government must encourage the initial setup up of charitable hospitals, which can make the cost of health care affordable to the common man of modest means, this alone will not solve the problem. A technological solution, which can bridge the gap between people living in remote areas and the specialist doctors practicing in big cities, is needed. To address this issue, the concept of telemedicine was developed. It is a rapidly

evolving technology where patient information is transferred between a network of hospitals and diagnostic centers via communication and networking technologies for the purpose of consultation, treatment decision making, and sometimes even to assist in remote medical procedures or examinations.

4.3.4 Current limitations of HDNT

Currently, there are certain limitations in both availability and implementation of networking technologies in the medical field. Some of these are listed below.

1. Improper network design and implementation.
2. No fool proof protection against misuse of medical records.
3. Use of pirated software.
4. Lack of personnel training. This prevents the tool from being utilized properly.
5. Incompatibility, which results in the need for system upgrades. The history of science and technology shows us that the basic axioms of mathematics have not changed while newer and newer branches of mathematics have opened up. In other sciences like physics, more general and complete theories have replaced earlier ones. For example, the theory of relativity includes Newtonian mechanics as a special case. Similar developments have occurred in medical as well as in computer and communication science. As a result of these developments, new instruments are constantly being developed, data/video formats and hardware specifications are also undergoing constant change. Some of these have to be upgraded / changed every two or three years. Most of the software supplied, regardless of the specific application area, is in operation for just a few years. At the end of the life cycle, there is a need to upgrade to a new version, maybe upgrade to a new operating system which may be designed for a new hardware architecture. In this case, a hospital may have to upgrade the hardware as well.
6. Lack of standardization, which results in incompatibilities. The formulations used in the allopathic system of medicine developed alongside a great deal of study and execution of extensive clinical trials. However, a lack of standardization is seen in medicines prescribed by practitioners of alternative medical systems. The medicines prescribed by their text books should be identified and analyzed. The medicines and treatment protocols should be put through clinical tests before releasing them into the market. A great deal of research work is under way in this field which aims to standardize these medical formulations. However, more work is required before the public can repose the same degree of confidence in these formulations as they do in the case of standard allopathic medicines.

4.3.5 Security in medical networks

When it comes to using modern technologies, such as HDNTs, there are a variety of risks involved. Currently, the biggest risk comes from the fact that it is difficult to ensure information security over the internet. Hence, design and implementation of information security is an important parameter in medical networking systems. Designing secure systems involves the right knowledge of hardware, operating system, communication path, type of information to be transferred and the protocols that handle information transfer. In the United States, any kind of medical data transfer, via a computer network, requires that Health Insurance Portability and Accountability Act (HIPAA) [314, 315] compliance is ensured. Further, the American National Standards Institute (ANSI) X.12 [316] standard must be followed as well. The design of medical networking systems should focus on specific security issues concerning both application and communication security.

Apart from the information security risks, there are also social problems associated with medical networks. Fundamentally, the Internet is an open medium which is accessible by everyone. The availability of online question and answer documents might tempt people to resort to self-medication, which is not a good practice. Hence, proper protocols should be framed to ensure reliability of health-related data that is published on the internet. In general, the public should be well informed about the problems which arise from self-medication.

4.3.6 Requirements of HDNT

The typical hospital is a large complex of people, equipment, material, and information flow. Business, logistics, accounting, and medical test data are moving about. Training and treatment coexist. Patients, interns, doctors, nurses, visitors, accountants, orderlies, medicines, towels, and X-ray machines weave in and out of a busy mountain of activity. Exceedingly sophisticated activity is intermixed with the many specialized and mundane aspects of keeping a facility, which involves many people and things, going smoothly. To aid this activity, a number of technological innovations are taking place in the medical domain. Novel and sophisticated diagnostic instruments are being designed, methods of diagnosis are changing (noninvasive diagnosis tools are gaining popularity), doctors are seeking second opinions from their peers over the internet and online communication between groups of hospitals across the globe is taking place. There is a variety of networking strategies available to design medical networks.

4.3.7 Specification refinement

As highlighted in the previous section, there is a notable discrepancy in health care services which are available for the rural poor and for the urban citizens. The discrepancy is going to remain in place for the foreseeable future and it cannot be set right easily. However, modern computer and communication technologies together with modern management practices can be leveraged to address the problem. Therefore, there is a need for networking these technologies to address the lack of medical

facilities which is a reality in most parts of the developing world. The number of patients, kinds of illnesses to be treated, training, examinations, business and test data, and visitor handling must be estimated and listed. What the hospitals have to do and what equipment and installations they should possess must be set down carefully. Flow diagrams have to be set up to show the movement of people, physicians, nurses, clerical staff, patients, and others and the type and flow of information and of items, like clinical patient records, medicines, X-ray films, food, etc. New technology affecting medical care must be considered. Comparative, economic, and performance analyses would lead to alternative ways of treating patients, location of ambulatory and acute care facilities, layout of the hospital and of modes of operation. The information required and the functions of all the people must be carefully examined.

At an abstract level, a HDNT system should possess the following properties:

1. An efficient method to extract raw data from a hub.
2. The capability to efficiently handle the Structured Query Language (SQL) queries in the database.
3. An efficient and user friendly Graphical User Interface (GUI) implementation.
4. A medical network protocol which specifies the interconnectivity of various modules in the network.

4.4 Implementation

In this section we move on with the formal and model driven design methodology. We progress from the specification refinement to the implementation phase. The implementation process involves a review some of the techniques used in HDNT implementations. Before we embark on the review, we discuss the features of telemedicine. These features are drawn from existing telemedicine systems. These existing systems provide the basis for Section 4.4.2, where we discuss implementation issues. After that, we enter into the area of wireless networking. Section 4.4.3 makes the case for wireless networking technology in the area of telemedicine. Next, we discuss different wireless technologies before we outline the types of wireless networks. The last section reviews some applications of wireless technology in the health care sector.

4.4.1 Features of telemedicine

Since 1991, the popularity of mobile phones in virtually every country has increased many folds. Broad band connectivity, radio and television services are now available to middle class citizens in developing countries. Thus, these wired and wireless technologies can be used to bridge the gap in the provision of medical services to people of all categories. Such a service should have the following minimum features.

1. It should provide basic information about the availability of doctors, nursing homes, tertiary care hospitals, blood banks, diagnostic laboratories and various health care service providers.

2. It should provide secure online counseling to assist people to cope with anxiety and stress. The services of trained HIV / AIDS counselors can also be made available through this service.

3. Virtual physical examination of patient through video-conferencing – a process of patient consultation through broad band network to provide medical data – should be designed. This can involve transmission of video, audio, still or live images between patient and physician. The system should be used in diagnosis and evolution of treatment plans. The service can originate from Primary Health Centers (PHC), Community Health Centers (CHS) or designated area hospitals.

4. Once a remote patient monitoring is facilitated, the medical data can be sent to a central control center for interpretation by medical experts. Both results and diagnosis can then be conveyed back to the patient.

5. An online Frequently Asked Questions (FAQ) section on diseases and the best known methods of prevention must be set up. Because, prevention is better than cure.

6. The telemedicine system should include an online patient database. The database must contain data like date of birth, finger prints (for security purposes) and his or her past medical history. However, security should be provided for database access and usage so that it can be accessed only by authorized personnel. For example, the availability of an online database will be useful in monitoring the progress of pregnancy. The health of children as they grow up can also be remotely monitored.

7. The health of people suffering from chronic diseases can be monitored and they can be regularly called to the central hospital for treatment if necessary. This system will also help the authorities in ensuring that events like birth and death are registered.

Thus, the branch of technology, which employs telecommunication and medical electronics as tools, is becoming increasingly popular in many countries as a platform for bringing affordable and good quality medical care to common people. It bridges the rural-urban health care divide. Developing countries are in the process of adopting this system. The system can be designed such that the charges levied on the patient are affordable.

4.4.2 Implementation issues in telemedicine

The vision of such telemedicine based online collaboration systems, using multiple information technology tools and covering a wide variety of consumer as well as management healthcare topics, is unfolding very rapidly. The key concepts of integration, transparency, and quality should shape these systems. Very soon, patients, physicians and hospital administrators will be sharing information, expectations, challenges and

collaborative solutions using these tools. Some of these systems have already percolated down to the big hospitals. Certain technical and cultural challenges delaying the adoption of telemedicine and Information Technology (IT) in health care services are listed below.

1. Systems integration remains a key concern in underserved areas of healthcare IT. In the absence of a worldwide standard, many piecemeal solutions and standalone systems exist. These different solutions have not been designed to communicate with each other. This can make health care system integration a challenging task. Thus, the lack of standardization in the representation of health care data and the lack of interoperability between different products has damped the adoption of these systems.

2. In general, integration methods vary from best to worst: point-to-point, Application Programming Interface (API), message-level (HL7) and batch interfaces. This challenge will continue as healthcare providers look to share more information within multi-facility healthcare systems as well as with external providers.

3. There is a wide range of products for specific tasks, but there is still a need for integrated solutions with a standardized information exchange (HL7). In dedicated institutions, like rehabilitation hospitals, there is a need for integrated solutions merging documentation, therapy planning, accounting, etc.

4. Interoperability is going to be the key feature which enables us to move forward. Monolithic products, which were extensively used in the past decade, will not survive, because they are too expensive and hard to implement. Healthcare providers will probably go back to a model similar to "best of breed" where they will buy the best ICU tool, emergency department tool, theatre package etc. to meet their needs. These tools will have to be designed to communicate with each other.

5. A few companies have developed software for hospitals that are linked to several diagnostic centers. Often, this software is designed poorly without the aid of a clear design methodology, such as formal and model driven design. For instance, diagnostic centers may send the information to a network hospital over the network, but this information does not reach the respective hospital. Hence, acknowledgement based failsafe medical networking is lacking in most of the existing software which is used in developed or developing nation's hospitals.

6. When a hospital merges with another hospital, then software integration is a big hurdle, mainly because of freelance implementations of software tools by different vendors in different hospitals.

7. The budget, earmarked for adoption of IT networking tools, is usually small and hence upgrading medical networking systems is often difficult.

8. Identity management: healthcare providers and healthcare consumers must be assured that the identity information, which was collected and collated, will be

controlled and it is secured within policy guidelines, like HIPAA. A lot of effort is required to ensure that these safeguards are put into place. This is an area of opportunity to medical networking service providers.

9. In some countries, cultural and legal issues limits technology adoption. In such cases, it is hoped that the passage of time will remove prejudices associated with the adoption of medical networking technology. It is expected that attitudes will change over a period of time and all stake holders in the system will be able to work together for mutual benefit. Thus, it may only be a matter of time before doctors, patients and other health care professionals, located anywhere across the globe, can sit down at a virtual table and talk to each other.

4.4.3 Applications of wireless technology in medical networking

In recent years, the rapid growth of portable electronics and wireless technologies has transformed healthcare policies and it shifted the responsibility for healthcare back to the patient, especially for long term chronic diseases. Wireless communication fascinates the medical community, because of its ability to remove cables, which hinder patient mobility, from health monitoring equipment.

Integrating mobile computing, medical sensors, instrumentations and wireless communication technologies with ultra-low power electronics will further enable the creation of a new generation of highly mobile, personal healthcare devices which can effectively support e-health and m-health applications by providing extremely flexible vital-sign monitoring systems with powerful mobile communicating systems.

Rural areas in developing countries might have very little medical supervision available. In situations, where patients require constant supervision, for example a cardiac condition at mediocre risk level, the patient might find a portable handheld Electroencephalogrphy (ECG) monitor highly cost-effective, because the patient saves on hospital bills and transportation cost. The data, from such a handheld device, could be transferred to the hospital using wireless technology. For such a biomedical health care system, the popular Bluetooth technology can be used to transfer ECG signals from a small device to a PC anywhere in the household, or through a cell phone, which transmits the data through the internet to the hospital network. Other examples of such usages include blood glucose measurement and hormonal level control. The following sections briefly highlight different types of wireless networks, popular wireless technologies and current limitations in using these technologies in the medical field.

4.4.3.1 Wireless Wide Area Network (WWAN)

Wireless Wide Area Network (WWAN) are wireless computer networks that span across very large geographical areas, like cities and countries. WWAN uses standardized mobile telecommunication technologies, such as Worldwide interoperability for Microwave Access (WiMAX) (Universal Mobile Telecommunications System

Organi.	1992	1994	1998	2002	2004	2006	2007	2008	2009
3GPP	GSM			UMTS		HSDPA	HSUPA		LTE
3GPP2	CDMA	IS95A	1X		EVDO	EVDO rev A		EVDO rev B	UMB
IEEE	WiFI		802.11 b/g		802.16 d		802.16e WiMAX		802.16m WiMAX 802.20 MBWA

Table 24: Evolution of WWAN.

(UMTS), General Packet Radio Service (GPRS), CDMA2000, Global System for Mobile communications (GSM), High-Speed Downlink Packet Access (HSDPA) or International Mobile Telecommunications-2000 (3G) and Successor to 3G (4G)) to achieve coverage and data transfer capability. Table 24 details the evolution of WWANs and Table 25 provides a comparison of various WWAN types.

4.4.3.2 Wireless Metropolitan Area Network (WMAN)

Wireless Metropolitan Area Networks (WMANs) are large networks that usually connect a number of buildings within a city. Technologies, like Automated Teller Machine (ATM), Fiber Distributed Data Interface (FDDI), and Switched Multimegabit Data Service (SMDS), are used in WMANs.

4.4.3.3 Wireless Personal Area Network (WPAN)

Wireless Personal Area Networks (WPANs) are personal networks for interconnecting devices centered on an individual workspace. Institute of Electrical and Electronic Engineers (IEEE) 802.15 is the 15^{th} working group of the IEEE 802 standard which specializes in WPAN standards. It includes six task groups numbered from 1 to 6. There are three possible types of topologies for the WPAN networks as shown in Figure 22.

4.4.3.4 Wireless Local Area Network (WLAN)

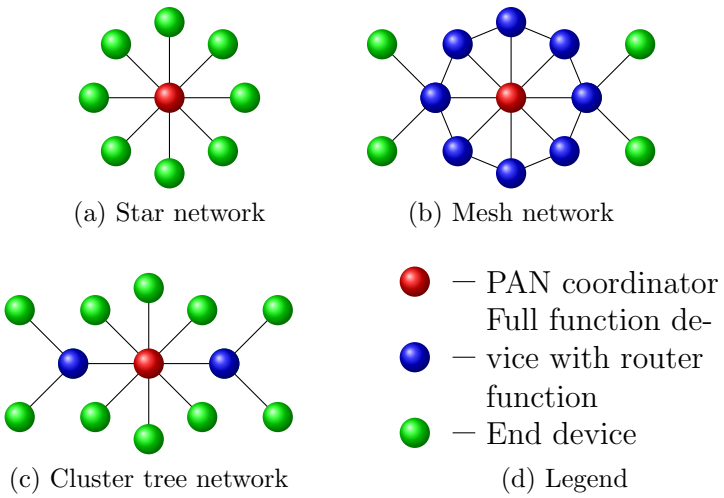
The Wireless Local Area Networks (WLANs) connect devices located within a limited area. The latest WLAN technology uses spread spectrum access methods and Orthogonal Frequency-Division Multiplexing (OFDM) modulation for communication. WLANs can be implemented as peer-to-peer networks where the devices communicate directly with each other or they can be configured as a bridge network wherein a wireless bridge allows the connection of devices on a wired Ethernet network to a wireless network.

4.4.3.5 Wireless Body Area Network (WBAN)

A Wireless Body Area Network (WBAN) links several intercommunicating sensors. These sensors are either worn by or implanted into a patient for continuous monitoring

Standard	Maximum	Average	Medical application
GRPS (GSM)	114 Kbps	35 Kbps	Browser, for text message dispatching and database queries.
CDMA 1X	153 Kbps	60Kbps	
EDGE	384 Kbps	115Kbps	All the above and • Basic video; • Biometric data (constrained); • Reports; • Internet.
UMTS	14 Mbps	256 Kbps	All the above plus: – Images; – Video (buffert); – Remote control.
EV-DO	144 Kbps-2.4 Mbps	400 Kbps	
HSPA (D/U)	14.4 Mbps	1.0 Mbps	
WiMAX	70 Mbps (coverage up to 50km)	4.0 Mbps	All the above plus: – Biometric data; – Full motion video; – Multimedial; – Remote camera viewing; – Remote control.
Long Term Evolution (LTE)	300 Mbps (coverage up to 100 km)	50 Mbps travelling at 110 km/h (Tested)	
802.11g	56Mbps	14.4Mbps	

Table 25: WWAN Comparison.



(a) Star network (b) Mesh network

(c) Cluster tree network (d) Legend

Figure 22: Network architectures.

of vital body signs. These sensors transmit measurement data to a base station which further relays the data to a hospital or a clinic.

4.4.4 Wireless Technologies

A few of the popular wireless technologies, which find application in the medical field, are addressed below.

Bluetooth technology is a WPAN standard. Bluetooth keeps its transmission power extremely low, usually in the order of 1 milliwatt, therefore it is ideal for mobile battery operated devices [317]. Bluetooth devices can automatically detect and communicate with other Bluetooth devices. This is very useful for patients, because with this functionality they can save the hassle from following necessary procedures before sending their physiological information to their doctors. Bluetooth-capable medical devices can transmit data to other medical devices, not within sight of the patient, up to a radius distance of 10 meters. Sophisticated protocols ensure that Bluetooth devices experience the least amount of interference from other Bluetooth capable devices while communicating with each other. The protocols control the amount of data that will be sent, the type of communication between the devices and the radio frequency or frequencies used for communication. However, it is not designed for bulk data transfer, for bulk data applications Wi-Fi would be a better alternative. Furthermore, Bluetooth can connect several devices together to form larger networks called *piconet*, and several piconets could be formed to connect a wide range of medical devices. In such piconets possible interferences are minimal, because the connected devices change their transmission frequencies 1600 times every second [318]. Power efficiency and security are two conflicting requirements. Therefore, Bluetooth technology does not focus on security. For example, prior to Bluetooth 2.1, encryption is not required and can be turned off at any time. Moreover, the encryption key, defined by the standard, is only good for approximately 23.5 hours; using a single encryption key longer than this time allows simple XOR attacks to retrieve the encryption key.

Wireless and ultra-low power technologies continue to evolve very rapidly. The Cambridge Silicon Radio (CSR) has demonstrated a Ultra-Low Power (ULP) Bluetooth silicon targeted at medical applications. ULP Bluetooth consumes 10 times less power than standard Bluetooth when connected and it achieves a packet data rate which is about 50 times faster than that of standard Bluetooth, implying that the devices consume as little as 1/50th of the power.

Another wireless technology standard, which is cheaper and simpler than Bluetooth, is ZigBee. It is a low-cost, low-power, wireless mesh networking standard based on the IEEE 802.15.4 standard for WPANs. The ZigBee technology has been used in a Home Integrated Health Monitor (HIHM) to transmit several vital signs, such as ECG, blood pressure, blood glucose, and ear temperature, to a healthcare center [319]. Compared with Bluetooth, ZigBee security, which is based on a 128-bit Advanced Encryption Standard (AES) algorithm, is always enabled.

Wi-Fi describes wireless devices that conform to the IEEE 802.11 standards [320]. These standards operate fundamentally on radio waves with a range of up to 300

Type	IEEE Standard	Data throughput	♢	♡	♣	Protocol stack size	Network Range	Network join time
Bluetooth	802.15.1, 802.15.2.1	Mbps 2 Mbps (EDR)	N	Y	Y	250 Kbytes	10 meters (Typical)	3 Seconds
UWB	802.15.3, 3a	> 20 Mbps	Y	Y	Y	-	10 meters	-
ZigBee	802.15.4, 5	< 250 Kbps	Y	Y	Y	28 Kbytes	70 meters	30 msec
WBAN	802.15.6	0.01 ≈ 1 Mbps (unconfirmed)	Y	-	-	-	< 2m	-

Table 26: Features of different wireless network modes. In the table there are symbols relating to battery types: ♢ = Button Cell, ♡ = AA Batteries and ♣ = Li-Ion.

meters. The technology is actually an extension of wired Ethernet with almost the same principles as its wired counterpart, aiming to provide users with identical high speed and reliable connections to the internet. IEEE 802.11 comes with a choice between no security, Wired Equivalent Privacy (WEP) and Wi-Fi Protected Access (WPA). For HDNTs no security is not an option. But, the WEP algorithm is not anymore secure [321], therefore WPA is the only sensible choice for HDNTs.

Ultra Wideband (UWB) systems transmit across a much wider frequency range (> 500 MHz) than conventional systems, hence such systems are used for short-range high-bandwidth communications. UWB has many applications in the medical field, especially in the areas of imaging, patient motion monitoring, vital signs monitoring, etc. [322, 323]. UWB systems have an inherited security advantage, because the signal is transmitted within the noise floor. That means, it is extremely difficult to detect the presence of an UWB signal. Apart from this general advantage, the security of UWB signals depend on the particular encryption standard used. The salient features of the different wireless network modes are shown in Table 26.

With the emergence of wireless communication standards, all newly created wireless medical devices are moving away from proprietary wireless solutions by adopting standard wireless communication technology. In general, adopting international wireless communication standards has the following advantages:

- Greater economy of scale, cost savings, smaller in size and higher reliability through high levels of electronic integration.
- More powerful, robust radio systems with higher communication security which are enabled by low cost microprocessor intelligence.
- Reduced interference in protected medical frequency bands.

- High interoperability between devices.

4.4.5 Applications in the healthcare sector

Wireless technology has been successfully deployed in a wide range of areas within the healthcare sector, from supplies and inventory to emergency services. An elaborate discussion of the latest applications of this technology in the healthcare sector can be found in [324]. In the USA, a few ambulance services installed wireless based video systems in their vehicles. These systems capture photo images of the patient and transmit them to hospitals for review ahead of their arrival. Singaporean ambulances have employed wireless devices that communicate with traffic lights, turning red lights to green and vice versa, to free the traffic paths of other vehicles on the road.

In hospitals, mobile workstations utilize wireless technology to allow medical doctors and nurses real time access to patient's electronic monitoring recordings at their bedside. Such workstations are also used in operating theaters where surgeons stay in contact with other specialists located in different rooms, or even in different parts of the world.

Healthcare workers, armed with handheld WLAN enabled devices in hospitals, can access information from patient records, such as lab results, pharmaceutical information, insurance information, medical resources, work schedules, as well as patient arrival details. Furthermore, with these handheld devices, staff has constant access to email within the hospital area. A new area, in which wireless technology is being employed, is wireless health monitoring. The technology uses small wearable devices which are strapped onto the patient. These devices transmit physiologic data to a monitor or workstation using wireless technology.

With the adoption of cellular technologies, WWANs have removed the physical range limits and they have extended the wide area networks into metropolitan area networks with superb mobility and extreme range of coverage. Both WiMAX and LTE have excellent coverage range (LTE – rural up to 400 sq miles) and support moving vehicles traveling at a speed up to 100 km/h, and they are suitable for remote diagnosis, ambulances using audio and video capturing of patient consulting doctor in hospital on-line. These advantages enable quicker and more accurate treatment in shorter time. Ultimately, the technology will save live and it gives back quality time to the patient by shortening recovery time.

The evolution of e-health and m-health systems is driven by both rapid advancement of ULP electronics and low-power wireless communication technologies. These technologies constitute very good platforms for the development of wearable electronics, because standardized mass-produced parts can be used, which provide both minimization of weight and size, ubiquitous connectivity, reliability and seamless system integration. Wearable health-monitoring devices typically consist of a number of inexpensive, lightweight, miniature and intelligent sensor platforms, each monitoring one or more physiological signals, such as ECGs, motion sensors or Electromyographys (EMGs) etc. These sensors could be located on the body as tiny intelligent units, integrated into user's clothing or implanted under the skin or into muscles. In general, these sensors are inter-connected to portable electronic devices using WPAN or

WBAN. Global connectivity is feasible using WWAN, where data can be exchanged with external servers for long term recording and analysis.

Despite the potential benefits wireless technology has to offer in the healthcare area, it is not without problems, namely network performance, battery life of mobile devices, signal reliability and even more worrisomely IT security. Wireless technologies are already known to have serious security flaws. Much work is required for wireless standards to meet privacy laws, such as HIPAA and the Data Protection Act. These issues must be addressed before wireless technology fully penetrates healthcare.

4.5 Discussion

The formal and model driven design methodology incorporates the ideas of cooperation and competition. For this case study, cooperation means to share the shortcomings of the approach and the general findings. One of our findings was that there is a fundamental problem with the planning of modern HDNT. The specification, outlined in Section 4.3.7, is very short, it is just one paragraph and a small number of bullet points. There are several reasons for the shortfall. The most important reason comes from the fact that there is no formal language with which these specifications are formulated. Therefore, a group of experts, which is composed of decision makes, i.e. administrators, health care professionals and technologists is needed. The group must formalize the semantics of the language which is used to write the specification, i.e. they must define the meaning of the words they use. Only with such strict definitions it is possible to limit the misunderstandings between experts from different fields. The specification itself should be formulated as clearly as possible in an unambiguous way. The required mathematical precision can be achieved with formal models.

For formal and model driven design, competition means to compare the results of the design process with published work from other researchers. We found that here is some research going on which applies formal models to health care systems. For example, Goertzen and Stausberg point out that an essential aspect for the utilization of medical data is their quality, thus computer-based medical documentation systems should be reliable and under no circumstances cause data corruption. Therefore, the authors define a grammar for modeling medical documentation systems to increase both integrity and completeness of collected data, focusing attention on integrity constraints. An integrity constraint defines requirements with which the involved entities had to comply. Furthermore, it defines possible implications in case of failure. Their grammar is declared using a schema in extensible markup language-format. The model can be used in both Computer-Aided Diagnosis (CAD) and clinical documentation systems. The authors claim that it minimizes effort and ensures data quality. This was tested by an evaluation based on a specification of a registry for HIV-infected patients [325].

Baksi applies a type of formal software verification technique, known as lightweight model checking, to a domain model in healthcare informatics. The Alloy analyzer verification tool is utilized for model checking. The author claims that such verification work is very effective in either uncovering design flaws or in providing guarantees on

certain desirable system properties early in the development process of any safety critical project [326].

Other research work from Baksi provides formal specification of interactions in typical public health surveillance systems. These systems involve healthcare agencies at local, state and federal levels [327]. The author highlights that the quality of medical care provided is an end result of a well-designed choreography of diverse services provided by different healthcare entities. One of the major challenges in this field appears to be explicit formal specification of such interactions. Such formal specification work is the first step leading to both design and verification of important properties of public healthcare systems. Therefore, he modeled two different configurations of public health surveillance systems using π-calculus [328].

4.6 Chapter conclusion

In this day and age, technology has become so pervasive that we often talk about it as if it was a living creature that will save the day for us despite of our wrong doings. This is not a correct view to adopt. Technology is a mere tool and it can be used to heal as well as harm. We need systems thinking to use science and technology in a sensible and beneficial way.

It is not right to think that computer technology can ever treat and cure a patient without human intervention. Hence, it cannot serve as an alternative to a physician. But, the process of diagnosis and treatment can be made affordable and efficient if competent professional doctors, who make use of well-designed IT tools, serve the vast majority of people in rural areas who do not otherwise have access to them. To assist this development, an international standard for the development of medical networking technology should be created. Such a standard can be tailored / customized according to geographical and cultural needs. Some standardization of diagnostic equipment is also necessary so that seamless transfer of information becomes possible. For example, in the USA, Health 2.0[1] has a very good chance of becoming the world's leading standard in the area of wireless medical e-health services. It aims to provide breakthroughs in medical networking, hopefully it provides an acceptable international standard, which can be used by professionals all around the world to make medical advancements and joint collaborations around the world feasible and possible in the near future.

Experts in IT, computer scientists, doctors and healthcare professionals as well as medical software developers should be involved in analysis, design and implementation of these distributed health information systems and networks. The system administrators in the participating hospitals should be given proper training on the use of these systems. One can only imagine the incredibly tedious procedure of having to decipher data, which is recorded in a different format to the preferred format that one is familiar with. To overcome the problem, an international standard, which allows for the various systems in a medical network to integrate with each other, is needed. Many have suggested that influential multi-national IT companies, such as

[1] `http://www.health2con.com/`

Microsoft and Google should come forth to provide such a standard, along with other companies. In recent years, Microsoft has developed HealthVault, a common health application platform that can be used for storing and sharing health information between a variety of providers' health services and health devices [329]. Google came up with Google Health [330] which is a free online personal health information management application. The benefits of such applications are clear as systems designed on the same platform can be easily merged into a medical network, which may even extend the integration at regional and even global levels someday.

In addition to practitioners of allopathic medicine, physicians representing alternative medicine streams also stand to benefit from medical networking. In developing countries, like India, China and Sri Lanka, alternative therapeutic systems have a definite role to play in alleviating sickness – both chronic and acute. As per the report from the World Health Organization (WHO), the market size for alternative medical systems in India is valued at 12 billion US dollars. As a result of adoption of medical networking technologies, people suffering from chronic diseases, for which allopathic medicine does not have a cure, will benefit. Thus, medical networking technologies, if put in place, have the potential to bring healthcare to millions of people in poor countries who are now excluded from modern healthcare. This will go a long way in reducing the pain and suffering of common people at large who still constitute the vast majority of humanity.

The current chapter covered the systems aspects for the formal and model driven design methodology. We structured the discussion of health care systems with the systems engineering meta model. To be specific, the discussion covered need definition, requirements capturing, specification refinement and implementation. The formal modeling aspect was important, but the techniques were not discussed in detail. The next chapter makes up for that short coming by focusing on a formal model for CAD.

CHAPTER 5

PUTTING IT TOGETHER: REALIZATION OF A FORMAL AND MODEL DRIVEN SYSTEM DESIGN

5.1 Summary

Formal and model driven design aims to produce reliable systems which function according to specification. In this chapter we follow the systems engineering meta model to design a biomedical signal processing system. We discuss requirements capturing, specification refinement, implementation and testing of a classification system. These steps are executed as formal as possible. The requirements, which motivate the system design, are based on diabetes research. The main requirement for the classification system is to be a reliable component of a machine which controls diabetes. Reliability is very important, because uncontrolled diabetes may lead to hyperglycaemia (raised blood sugar) and over a period of time may cause serious damage to many of the body systems, especially the nerves and blood vessels. In a second step, these requirements are refined into a formal CSP‖B model. The formal model expresses the system functionality in a clear and semantically strong way. Subsequently, the proven system model was translated into an implementation. This implementation was tested with use cases and failure cases.

Formal modeling and automated model checking gave us deep insights in the system functionality. Having the systemic knowledge enabled us to create a reliable and trustworthy implementation. With extensive tests we established trust in the reliability of the implementation.

5.2 Introduction

The formal and model driven design methodology for biomedical engineering extends systems engineering with formal modeling. As such, systems engineering is a methodical, disciplined approach for the design, realization, technical management, operations, and retirement of a system [16]. Systems engineering takes into account all steps necessary to create a system. Following the design methodology leads to trustworthy systems, because negligence in any of the design steps leads to weaker and therefore less trustworthy systems. For a large class of systems these design steps are need definition, requirements capturing, specification refinement, implementation and testing, as shown in Figure 1. Progress from one step to another is only made when all predefined conditions are met [140, Chapter 1]. Therefore, the work-groups which are involved in the individual design steps can focus on their task.

We are faithful to the formal and model driven design methodology. Therefore, we review related research as part of the need definition process. Systems engineering can be applied to a wide range of engineering problems. For example, Diez et al.

used the systems engineering methodology to develop computer-supported learning systems [138].

Palanisamy and Selvan propose a novel method for identifying relevant subspaces for data mining using fuzzy entropy and perform clustering [139]. Their presented theories and algorithms are evaluated through experiments on a collection of benchmark data sets. Empirical results have shown its favorable performance in comparison with several other clustering algorithms. Their design strategy follows systems engineering principles.

Qian and Tang argue that with a strengthening buyer's market, retailers have begun to lead product development by introducing their own private label products [331]. The success of such a new product launch relies on transmission of demand information along a supply chain. The authors analyze the phenomenon by modeling vertical information transmission in supply chains. The approach follows the systems thought, where formal modeling leads to a deeper understanding of the system.

In terms of the systems engineering methodology, field specific research work and the associated functional models constitute some of the system requirements. In general, requirements define what the system is expected to achieve and they should be obtained as a result of informed discussion. Analyzing field specific research answers questions about the work context. To be specific, it answers the questions regarding what can be achieved and what are the most promising approaches to solve a problem in practice.

The need, which motivates our research work, is distilled from the paper "Automated Identification of Diabetic Type 2 Subjects with and without Neuropathy Using Wavelet Transform on Pedobarograph" [332]. The study examined the plantar pressure distribution in normal, diabetic type 2 with and without neuropathy subjects. Acharya et al. approach this subject by taking foot scans from patients and healthy subjects. The resulting images were preprocessed to extract relevant parameters. These parameters were used to train and test a four-layer feedforward Artificial Neural Network (ANN) for classification. Acharya et al. demonstrated a sensitivity of 100% and specificity of more than 85% for the classifiers [332]. In this chapter we focus on the feedforward ANN and bring this structure one step closer to implementation by refining the requirements into a specification.

The aim of this chapter is to show how the systems engineering meta model can be applied to biomedical signal processing. The authors strongly believe that applying systems engineering methods to biomedical signal processing systems results in more reliable systems which behave according to their specification. The reason for this strong belief comes from the fact that systems engineering formalizes the design process. This formalization simplifies and therefore improves the design process, because there is no need to invent a project specific design methodology. In this chapter, we focus on extending systems engineering with formal methods to create the formal and model driven design methodology for biomedical systems. The main technical contribution is the formal specification, verification and implementation of ANN functionality in specialized hardware. We do not contemplate on the decision making processes which takes place during the development. Furthermore, the life cycle aspect of systems engineering is also missing.

Types	Control Subjects (CS)	Diabetic type 2 (D)	Neuropathic (N)
Age	14-52	32-79	57-94
Gender	19 Males 9 Females	23 Males 5 Females	20 Males 8 Females
Weight (Kg)	65.64 ± 16.71	67.24 ± 14.18	$71.76 + 12.57$
Height (m)	1.66 ± 0.09	1.60 ± 0.07	$1.62 + 0.13$
BMI (Kg/m^2)	23.52 ± 4.65	26.19 ± 4.77	$26.12 + 4.13$
Sensation Level	N.A	$\leqslant 7$	$\leqslant 6$

Table 27: Range of age, gender, weight, height, body mass index and sensation level value of subjects in each group.

The next section introduces the systems engineering design steps which lead to a reliable implementation of the ANN classifier. The results of both automated model checking and implementation testing are stated in Section 5.4. Section 5.5 relates the formal development of the ANN classifier to other research work in the area of biomedical systems. The last section in this chapter gives conclusions and discusses further work.

5.3 Materials and methods

This section introduces requirements capturing, specifications refinement, implementation and testing of an ANN classification system. In terms of systems engineering requirements capturing and specification refinement are the two most important steps, because errors in either requirements capturing or specification refinement are hard to correct in the implementation phase. Therefore, such errors often increase both project cost and development time. As a consequence, the following text emphasizes on these design steps.

5.3.1 Requirements capturing

The first design step is requirements capturing. We start by describing the background of the theoretical research work. The work was based on foot pressure images for 84 subjects: 62 males (M) and 22 females (F) with age ranging from 14 to 94 years. The data was taken for subjects in the relaxed standing position. Diabetic type 2 and neuropathic subjects were recruited from the medical records available within the Diabetes Centre of Alexandra Hospital, Singapore. The foot pressure data was classified into three groups: normal, diabetic (without neuropathy) and neuropathic subjects based on their foot sensation level. The number and details of subjects in each group, their weight and body mass index is shown in Table 27. The authors have sought the permission from the ethics committee of the hospital for this study.

5.3.1.1 Functional model analysis

The second step is detailed analysis of the methods used to create the functional model. The foot pressure image data was analyzed in the wavelet domain. Discrete

Wavelet Transform (DWT) coefficients in different plantar regions were evaluated using the DWT. Then they were fed to the neural network for classification. The feature extraction methods using DWT are explained below. The DWT is based on sub-band coding and it helps to compute the wavelet transform fast.

It can be computed by successive low pass and high pass filtering of the discrete time signal. The low pass filtered signal indicates the slowly changing component of the signal, and it has half the number of samples in the original signal. The high pass filtered signal is the difference between the signals and indicates information about the sudden changes in the original signal. The DWT on the image yields these possibilities during filtering:

1. Low pass filtering is performed to rows and columns (LL coefficients).

2. Low pass filtering to the rows and high pass filtering to the columns are performed (HL coefficients).

3. High pass filtering to the rows and low pass filtering to the columns are performed (LH coefficients).

4. High pass filtering to the rows and high pass filtering to the columns are performed (HH coefficients).

Decomposition was done at different levels by further decomposing the LL sub band coefficients in order to attain the next coarser scale of wavelet coefficients. In this work, Daubechies (db)8 was used as the mother wavelet.

Three DWT coefficients of region 7 were fed into the four layer feedforward neural network for classification. Each hidden layer had seven neuron. They were able to classify the unknown plantar image correctly up to 90% [332].

5.3.1.2 Functional model distillation

After analyzing the functional model of the theoretical study, we formulate the following concrete goals for the ANN implementation: An implementation must have the same classification results as the functional model. This implies that the system must be reliable, because an unreliable implementation has a negative impact on the classification result. In other words, the theoretical classification results can only be achieved when the ANN classifier implementation is working reliably.

To progress towards these goals, we analyze the functional model of the ANN classifier. This analyzing phase is important, because it gives project stakeholders certainty about what the implemented system can achieve. We start the analysis by describing the network architecture of the ANN. The network architecture, shown in Figure 23, has 7 neurons in the input layer, 7 neurons in the hidden layer and 2 neurons in the output layer. All neurons use the sigmoid activation function to compute the output. Hence, the two output neurons can encode 4 possible classes. However, the ANN was trained to identify only three classes, control subjects, diabetic control and neuropathic, given by the decoded binary output [00, 01, 10]. The training itself was done with the so called *backpropagation* algorithm [333]. It is a supervised learning

algorithm which delivers good results for classification based on parameter vectors [334].

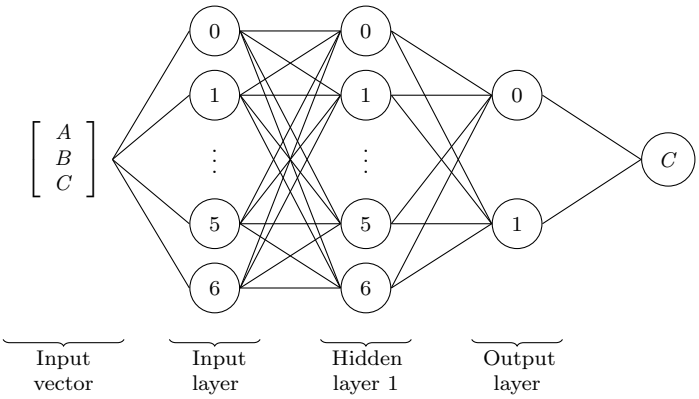


Figure 23: Network architecture with 7 input neurons, 7 neurons in the hidden layer and 2 neurons in the output layer.

The next step in the analysis focuses on the neuron. Equation 28 gives a mathematical model of the neuron functionality. The equation contains the following variables: s is the scalar output, $A(...)$ is the activation function, $input$ is the di dimensional input vector, w is the di dimensional weight vector and b is the bias. Both bias and weight vector were obtained during the training phase [332].

$$s = A\left(\sum_{k=0}^{di-1} w_k \times input_k + b\right) \tag{28}$$

where w_k is the k^{th} element of the weight vector and $input_k$ is the k^{th} element of the input vector.

We analyzed the mathematical model of the feedforward ANN in terms of network structure and neuron functionality. In the next section we refine the analysis results into a specification.

5.3.2 Specification refinement

In systems engineering terms, the requirements are refined into a specification. The specification describes the implementation system. This description must be as formally as possible, in order to avoid ambiguities which might lead to faulty implementations. Therefore, as part of the formal and model driven design methodology we use a formal model to express the specification. In general, these formal models state concrete system properties, which can be measured.

To proceed with the running example, the formal modeling language CSP‖B [335] was used to model the neural network specification. In order to keep this chapter short, the concepts of CSP‖B are not introduced here, the interested reader may consult the standard literature on B, Communicating Sequential Processes (CSP) and CSP‖B [179, 336, 337].

Even though, CSP‖B is a relative new formal method, it was already used in the design of several systems. For example, McEwan et al. outline that the development in CSP‖B is both top-down and piece-wise: refinement is from an abstract sequential specification into a highly concurrent implementation. This gave them fine grain control over the level of concurrency in their system, that control enables effective load balancing [338]. A more practical application came from Schneider et al. who translated CSP‖B models to Handel-C for prototyping [339].

Figure 24 shows an overview diagram of the CSP‖B model setup. The setup incorporates a CSP and a B model. CSP is used to model the network aspect of the ANN and B is used to model the processing aspect of the ANN. The network model governs the processing part, i.e. the network defines which input is fed to the individual machine (neuron). To symbolize the dependency between CSP and B, Figure 24 shows unidirectional arrows from the CSP model to the B machine. To be specific, the B machine is controlled via the events, $il, h1, ol$ and r. These events are exhibited by the CSP process network.

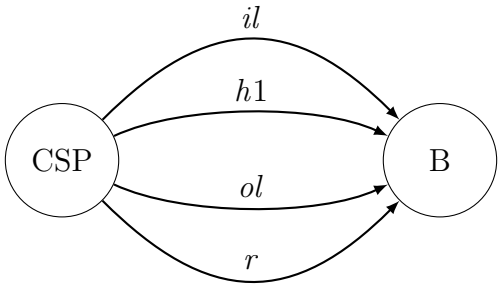


Figure 24: CSP‖B model setup.

The following section introduces the CSP model of the aANN network. The model is less complex than the network setup of the functional model shown in Figure 23. In the formal CSP‖B model the complexity was shifted from the process oriented CSP model towards the abstract machine oriented B model. This shift reduces the complexity of the formal model and subsequently it also reduces the implementation resource requirements. The overall system functionality remains the same.

5.3.2.1 CSP model

CSP is a process algebra which was invented by Hoare and which has by now over 30 years of solid research behind it [177, 178]. The CSP part of the CSP‖B model defines the network structure. Each ANN layer is modeled as a CSP process. The connections between the layers are modeled with CSP channels. Figure 25 shows the process network of the CSP model. The network model incorporates the following processes:

- *IL*: The *IL* process represents the input layer functionality. Input to the *IL* process is the *il* channel and output is the $h1$ channel.

- $H1$: The IL process represents the hidden layer functionality. Input to the $H1$ process is the $h1$ channel and output is the ol channel.
- OL: The OL process represents the output layer functionality. Input to the OL process is the ol channel and output is the r (result) channel.
- $TEST$: The $TEST$ process generates test events.

The ANN process combines the individual layer processes IL, $H1$ and OL. The complete network setup is represented by the $MAIN$ process.

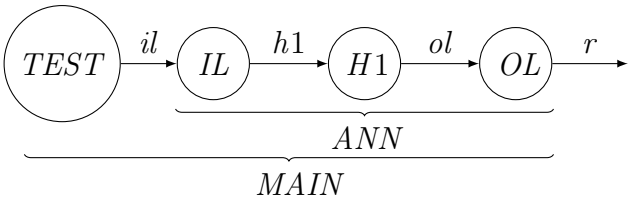


Figure 25: Network setup of the CSP model.

We approach the CSP model bottom-up, i.e. connecting the individual processes with channels, such that they form a process network which models the system functionality. As a consequence, the $MAIN$ process, which represents the network setup, is introduced at the end of this description. The CSP model starts with constant definitions. The definitions in Equation 29 govern the network setup of the model.

$$\begin{aligned} di &= 3 \\ iln &= 7 \\ h1n &= 7 \\ oln &= 2 \end{aligned} \tag{29}$$

where di is the dimensionality of the input vector, iln defines the number of neurons in the input layer, $h1n$ defines the number of neurons in the first hidden layer and oln defines the number of neurons in the output layer.

Next, we define helper structures, such as sets and unions. Equation 30 defines num as being the set of all natural numbers from 0 to 21.

$$num = 0..21 \tag{30}$$

Equation 31 defines the channels which are used in the CSP model. All channels can carry elements of the set num.

$$\begin{aligned} &\textbf{channel} \quad il \quad : \; num \\ &\textbf{channel} \quad h1 \quad : \; num \\ &\textbf{channel} \quad ol \quad : \; num \\ &\textbf{channel} \quad r \quad : \; num \end{aligned} \tag{31}$$

The layer functionality is modeled with two processes. The first of these processes is $LI(ci, di, co, do, x)$ which is defined in Equation 32. In the equation ci defines

the input channel, di defines the dimension of the input vector, co defines the output channel, do is the number of neurons within the layer which is modeled by $LI(...)$, and x is a process intern variable. The $IL(...)$ process inputs a sequence of $\langle ci.j, ..., ci.j \rangle$ where j is a variable and the cardinality of the sequence is equal to di.

$$\begin{aligned} &LI(ci, di, co, do, x) = ci?j \rightarrow \\ &\quad \textbf{if } di - 1 == x \textbf{ then} \\ &\qquad LO(ci, di, co, do, 0) \\ &\quad \textbf{else} \\ &\qquad LI(ci, di, co, do, x + 1) \end{aligned} \tag{32}$$

$LO(ci, di, co, do, x)$, defined in Equation 33, is the second process which takes part in the layer functionality definition. The parameters are the same as for the $LI(...)$ process. The $LO(...)$ process outputs the sequence of $\langle co.0, co.1, ..., co.(do-1) \rangle$ before it behaves like $LI(...)$.

$$\begin{aligned} &LO(ci, di, co, do, x) = co!x \rightarrow \\ &\quad \textbf{if } do - 1 == x \textbf{ then} \\ &\qquad LI(ci, di, co, do, 0) \\ &\quad \textbf{else} \\ &\qquad LO(ci, di, co, do, x + 1) \end{aligned} \tag{33}$$

The $TEST(x)$ process, defined in Equation 34, has only the local variable x as parameter. It outputs the sequence $\langle il.0, il.1, ..., il.(di - 1) \rangle$.

$$\begin{aligned} &TEST(x) = il!x \rightarrow \\ &\quad \textbf{if } di - 1 == x \textbf{ then} \\ &\qquad TEST(0) \\ &\quad \textbf{else} \\ &\qquad TEST(x + 1) \end{aligned} \tag{34}$$

The $IL \| H1$ process, defined in Equation 35, combines the processes which represent the input and the hidden layer in parallel. Both processes synchronize on all events which are send over $h1$.

$$IL \| H1 = \underbrace{LI(il, di, h1, iln, 0)}_{\text{Input layer}} \Big\|_{\{|h1|\}} \underbrace{LI(h1, iln, ol, h1n, 0)}_{\text{Hidden layer}} \tag{35}$$

The ANN process represents the CSP model of the ANN functionality. It is defied in Equation 36 as the parallel combination of $IL \| H1$ and the $LI(...)$ process which represents the output layer. Both processes must synchronize on the events $\{|\ ol\ |\}$.

$$ANN = IL \| H1 \Big\|_{\{|ol|\}} \underbrace{LI(ol, h1n, r, oln, 0)}_{\text{Output layer}} \tag{36}$$

The $MAIN$ process, defined in Equation 37, is the parallel combination of the ANN process and the $TEST(0)$ process. Both processes must synchronize on all events which the $TEST$ process outputs on the il channel.

$$MAIN = TEST(0) \Big\|_{\{|il|\}} ANN \tag{37}$$

5.3.2.2 B machine

The B-method, originally devised by Abrial [340], has by now generated a great deal of interest in the formal community. The main advantage of the B method over process algebras, such as CSP, is the fact that it allows variables and it provides elaborate scoping rules which govern the access to these variables. However, there is no support for floating point variables, because floats are used in data processing and not in abstract machine control.

The B machine, which is described in this section, specifies the abstract machine part of the system. The description contains pieces of information that describe the processing aspects of the ANN functionality. We approach the discussion of the B model by splitting up the machine into three parts and describing each of these parts individually. The individual parts are presented as Abstract Machine Language (AML) descriptions.

The constant part incorporates the MODEL name, CONSTANTS declaration and PROPERTIES definition. The constants di, iln, h1n and oln are the same as in the CSP model. The constants il_b, h1_b and ol_b define the bias vectors for the layers. The constants il_w, h1_w and ol_w define the weight vectors. The constant input defines an example input vector.

MODEL

Ann

CONSTANTS

di, iln, h1n, oln, il_b, h1_b, ol_b, il_w, h1_w, ol_w, input

PROPERTIES

di = 3 $\wedge$ iln = 7 $\wedge$ h1n = 7 $\wedge$ oln = 2 $\wedge$

il_b = {(x $\mapsto$ y) | x:($[\![0, 1000]\!]$) $\wedge$ y:($[\![0, 1000]\!]$) $\wedge$ x < iln $\wedge$ x=y} $\wedge$

h1_b = {(x $\mapsto$ y) | x:($[\![0, 1000]\!]$) $\wedge$ y:($[\![0, 1000]\!]$) $\wedge$ x < h1n $\wedge$ y=x+iln} $\wedge$

ol_b = {(x $\mapsto$ y) | x:($[\![0, 1000]\!]$) $\wedge$ y:($[\![0, 1000]\!]$) $\wedge$ x < oln $\wedge$ y=x+iln+h1n} $\wedge$

il_w = {(x $\mapsto$ y) | x:($[\![0, 1000]\!]$) $\wedge$ y:($[\![0, 1000]\!]$) $\wedge$ x < (di * iln) $\wedge$ x=y} $\wedge$

h1_w = {(x $\mapsto$ y) | x:($[\![0, 1000]\!]$) $\wedge$ y:($[\![0, 1000]\!]$) $\wedge$ x < (iln * h1n) $\wedge$ y=x+di * iln} $\wedge$

ol_w = {(x $\mapsto$ y) | x:($[\![0, 1000]\!]$) $\wedge$ y:($[\![0, 1000]\!]$) $\wedge$ x < (h1n * oln) $\wedge$ y=x+di * iln + iln * h1n} $\wedge$

input = {(x $\mapsto$ y) | x:($[\![0, 1000]\!]$) $\wedge$ y:($[\![0, 1000]\!]$) $\wedge$ x < di $\wedge$ x=y}

The variables part of the B model declare the VARIABLES state their INVARIANT and provide the INITIALIZATION. The variables il_s, h1_s and ol_s declare the output vector which holds the results of all the neurons in the layer. The variable res contains the result of the ANN classification. It is initialized as res(0)=5830027 and res(1)=6384463. Invariant checking ensures that these values never change. The variable x is used as loop count within the operations.

VARIABLES

il_s, h1_s, ol_s, res, x

INVARIANT

il_s $\in$ 0..iln-1 $\rightarrow$ ($[\![0, 1000000000000]\!]$) $\wedge$

```
  h1_s ∈ 0..h1n-1 → (⟦0, 1000000000000⟧) ∧
  ol_s ∈ 0..oln-1 → (⟦0, 1000000000000⟧) ∧
  res(0) = 5830027 ∧ res(1) = 6384463 ∧
  x < 30
INITIALISATION
  il_s := {(x ↦ y)—x:(⟦0, 1000⟧) ∧ y:(⟦0, 1000⟧) ∧ x < iln ∧ y=0} ||
  h1_s := {(x ↦ y)—x:(⟦0, 1000⟧) ∧ y:(⟦0, 1000⟧) ∧ x < h1n ∧ y=0} ||
  ol_s := {(x ↦ y)—x:(⟦0, 1000⟧) ∧ y:(⟦0, 1000⟧) ∧ x < oln ∧ y=0} ||
  res := {0 ↦ 5830027, 1 ↦ 6384463} ||
  x := 0
```

The OPERATIONS of the B machine are defied in the following AML part. The abstract machine can perform four operations. These operations correspond to the four different events the CSP model can exhibit. When the CSP model is combined with the B model to form the CSP‖B model, then each time a CSP event occurs the corresponding B operation is executed. For example, if the CSP model produces an $il.0$ event then the operation num(0) is executed. The execution is atomic, i.e. the CSP model does not make further progress until the B operation has completed. The operations il(num), h1(num) and ol(num) model input, hidden and output layer functionality respectively. The functionality of these three operations is similar. When the parameter num is within the specified range, a while loop is executed. The loop executes until x is greater or equal to the number of neurons in the layer. The loop variable x indicates the neuron within the layer. The first instruction within the loop is to check whether or not the layer name_s value for the particular neuron x must be initialized with the corresponding bias. The second instruction is to update the layer name_s value. This update is a sequential version of the functionality expressed in Equation 28.

```
OPERATIONS
  il(num) = PRE num ∈ 0..di-1 THEN
      x:=0;
      WHILE x < iln DO
        IF 0 = num THEN
          il_s(x) := il_b(x)
        END;
        il_s(x) := il_s(x) + input(num) * il_w(num+x*di);
        x := x+1
        INVARIANT x=x
        VARIANT iln-x
      END
    END;
  h1(num) = PRE num ∈ 0..iln-1 THEN
      x:=0;
      WHILE x < h1n DO
        IF 0 = num THEN
          h1_s(x) := h1_b(x)
```

```
      END;
      h1_s(x) := h1_s(x) + il_s(num) * h1_w(num+x*iln);
      x := x+1
      INVARIANT x=x
      VARIANT h1n-x
    END
  END;
  ol(num) = PRE num ∈ 0..h1n-1 THEN
    x:=0;
    WHILE x < oln DO
      IF 0 = num THEN
        ol_s(x) := ol_b(x)
      END;
      ol_s(x) := ol_s(x) + h1_s(num) * ol_w(num+x*h1n);
      x := x+1
      INVARIANT x=x
      VARIANT oln-x
    END
  END;
  r(num) = PRE num ∈ 0..oln-1 THEN
    res(num) := ol_s(num)
  END
END
```

5.3.3 Implementation

In accordance with the systems engineering methodology, this section describes the translation of the formal CSP‖B model into an implementation. This translation is always target specific. For this study we selected a XS1-G4 processor from XMOS [341] as target architecture. This particular architecture supports two high level languages with which the desired functionality can be implemented. The first language is the XMOS-originated 'xc' language [342] and the second language is the well-known 'c' language [343]. To discuss these two languages in detail is outside the scope of this chapter. However, we discuss the two languages in terms of their ability to implement network structure and abstract machine functionality.

To understand the 'xc' language it is necessary to introduce the processor architecture first. Figure 26 shows a simplified block diagram of the XS1-G4 processor. The architecture incorporates 4 independent processing entities called *XCores*. Internal hardware channels enable the communication between XCores. Each XCore contains a 32-bit processor, memory (RAM), I/O ports for communicating with external components and hardware channels to communicate between individual XCores. Each XCore can execute up to 8 XThreads concurrently. A hardware scheduler assigns processing time to the individual XThreads, this scheduling process is transparent for the programmer. Apart from this scheduling, the XS1-G4 processor supports

also (software) channel communication between different XThreads. The data is exchanged via events which are send over channels. Individual XThreads can wait for events and select from a number of possible events. The architecture follows CSP principals, therefore an event occurs if and only if both sender and receiver are ready to perform it. For XThreads within one XCore channel communication is optional, even though it is encouraged by both ease of use and good tool support. All communication off chip and between cores is done over hardware channels. A switch, located between the 4 XCores, supports low latency and deterministic communication between the XThreads in different XCores.

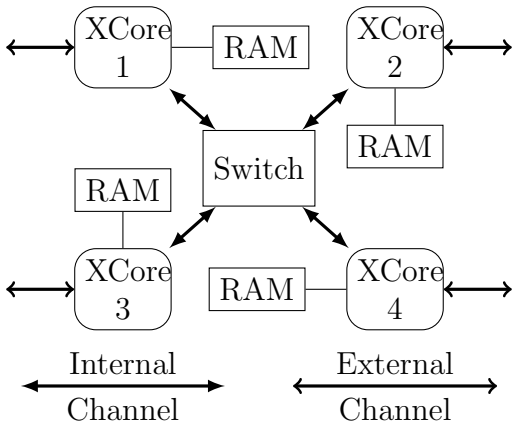


Figure 26: XS1-G4 architecture.

The 'xc' language offers a subset of the 'c' language constructs. This subset does not include support for pointers and floating point variables. On the plus side, the language is strongly typed, i.e. the compiler detects more type errors compared to 'c'. Furthermore, the 'xc' language contains specific constructs to build up process networks. These constructs include the 'parallel' command which opens up two or more XThreads which execute in parallel[1]. The 'xc' language also provides constructs for channel communication. These constructs include commands to send and receive channel data. A receiving XThread can wait on multiple events, the technique is known as alternation [344]. In general the 'xc' language is suitable to implement network structures and to establish channel communication between nodes (processes) of the network.

The 'c' language complements the 'xc' language. That means, the 'c' language incorporates the complete set of C language constructs, including pointer and 32bit floating point support. Therefore, this language is suitable for abstract machine implementations. In this case the 'c' language is even necessary, because the ANN functionality requires floating point variables and this functionality is not supported by the 'xc' language.

[1]These threads execute only in parallel when they are mapped to different XCores. When they sit on the same XCore they are scheduled via a hardware scheduler and therefore they make progress sequentially. But this is transparent for the user and, if there are no timing issues, two or more x-threads can be thought of as executing in parallel.

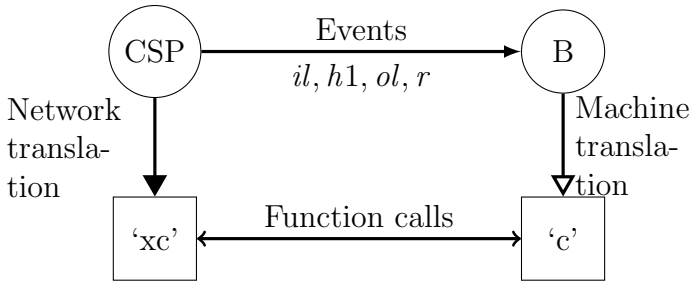


Figure 27: Commutative diagram.

Having established the general capabilities of the two high level programming languages for the XMOS chip, the translation from the CSP‖B implementation model is straight forward. The network centric CSP model is translated into 'xc' code and the data processing centric B machine is translated to 'c' code. Figure 27 shows the 4 elements, which are involved in the translation process. These elements are CSP and B models, for the CSP‖B model, as well as 'xc' and 'c' source code for the implementation. The CSP model communicates with the B model via events which are send over the il, $h1$, ol and r channels. The process network of the implementation, i.e. the XThread setup, is established by translating the CSP model into 'xc' source code. The ANN layer functionality is established by translating the abstract machine description of the B model into a 'c' implementation. The 'xc' language communicates with the 'c' language via function calls, therefore the translation of the events in the CSP‖B model is not straight forward. In the formal model events describe only state (the state of the system) and in the implementation events transfer also data. Events in the implementation describe how data is transferred in the XThread network. The 'xc' part of the XThread takes care of the data transfer. The data itself is passed from the 'xc' part of the XThread to the 'c' part with a function call. The processed data is passed from the 'c' part to the 'xc' part also with a function call. Therefore, Figure 27 shows a double arrow between 'xc' and 'c' implementations.

Figure 28 shows the XThread network of the ANN implementation. Both `IL` and `H1` XThreads are executed by XCore1. The `IL` XThread receives the input data from the external channel `il` and communicates its processing results via the `h1` software channel. The `H1` XThread takes these results in and produces its own output. This output is transferred via the hardware channel `ol` and the data is consumed by `OL`. The `OL` XThread implements the last ANN layer. Therefore, its output is send out via the `r` channel.

The two additional blocks, connected to the external hardware channels, test the ANN implementation. The `test_tx` block sends out test vectors via the external hardware channel `il`. The `test_rx` block consumes the test results and compares these results with prerecorded values. The precise nature of these tests is described in the next section.

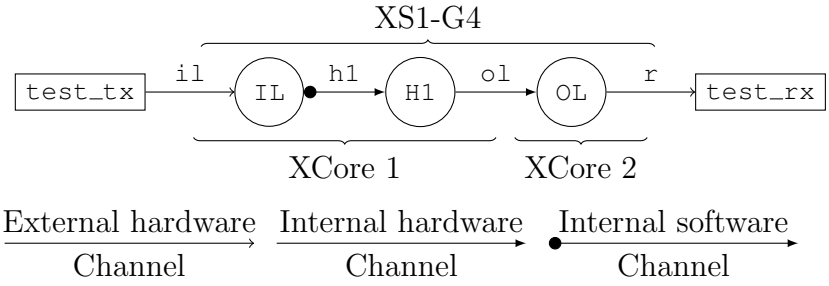


Figure 28: XThread setup of the implementation.

5.3.4 Testing

Testing is one way to establish trust in the system implementation. The following text discusses two types of tests, a) use case testing and b) failure case testing.

5.3.4.1 Use cases

A use case is constructed by providing the system under test with well known input. The test is successful when the system produces the expected output. The use cases for the ANN implementation come from both formal CSP‖B and functional models. From the formal model we obtain an integer test. This test is good for establishing the system functionality, because integer values are easier to handle compared with double values. The test vectors from the functional model establish trust in the implementation system. To be specific, this trust arises from the fact that a successful test shows that the implemented system is equivalent (for the test vector) to the functional model. The results of the tests are discussed in Section 5.4.

5.3.4.2 Failure cases

Failure cases are constructed by providing the system under test with abnormal input and checking whether or not the system produces a correct output. We constructed the following 5 failure cases:

1. The ANN implementation was tested with a maximum input vector. That means, all elements of the input vector were set to the maximum value.
2. The ANN implementation was tested with a minimum input vector. That means, all elements of the input vector were set to the minimum value.
3. The ANN implementation was tested with an input vector having too few entries.
4. The ANN implementation was tested with an input vector having too many entries.
5. No input vector was provided.

The test results are discussed in the next section.

5.4 Results

In this section we present and discuss the automated model checking results which were obtained during specification refinement. Furthermore, we state the results of both use case and stable failure case tests.

5.4.1 Automated model checking

With model checking we prove that the CSP‖B model is deadlock and livelock free as well as functional. To establish deadlock and livelock freedom we use the CSP model checker FDR [345]. To test only the CSP part for deadlock and livelock is sufficient, because only the network part of the CSP‖B model can exhibit this type of failures. The FDR result establishes, beyond reasonable doubt, that the model is deadlock and livelock free.

To test the functionality of the CSP‖B model we created an example and used the ProB [346, 337] model checker to prove the functionality. The example is not based on parameters and results from the functional model, because the B method does not support floating point numbers. The example is entirely based on integer values. Figure 29 shows an overview diagram of the integer example. The diagram shows that all parameters (bias and weight vectors) are initialized with an increasing sequence. The initialization of the specific bias and weight vectors is shown within the blocks which represent the layers. With the input vector defined as the sequence from 0 to 3, the model produces the same result for each run. To be specific, the result for res(0) is 5830027 and the result for res(1) is 6384463[2]. With an IVARIANT clause in the B machine, detailed in Section 5.3.2.2, we ensure that these result values never change during machine execution.

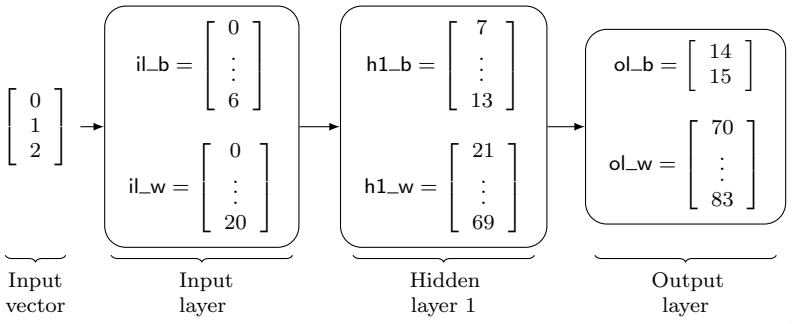


Figure 29: Integer example setup.

ProB confirms that indeed the result values did not change. The tool also establishes that no invariant was violated and all possible network states were tested. Figure 30 shows the model checker screen-shot which documents the model checking results, i.e. the absence of deadlock.

[2]The result values were independently verified with spreadsheet calculations.

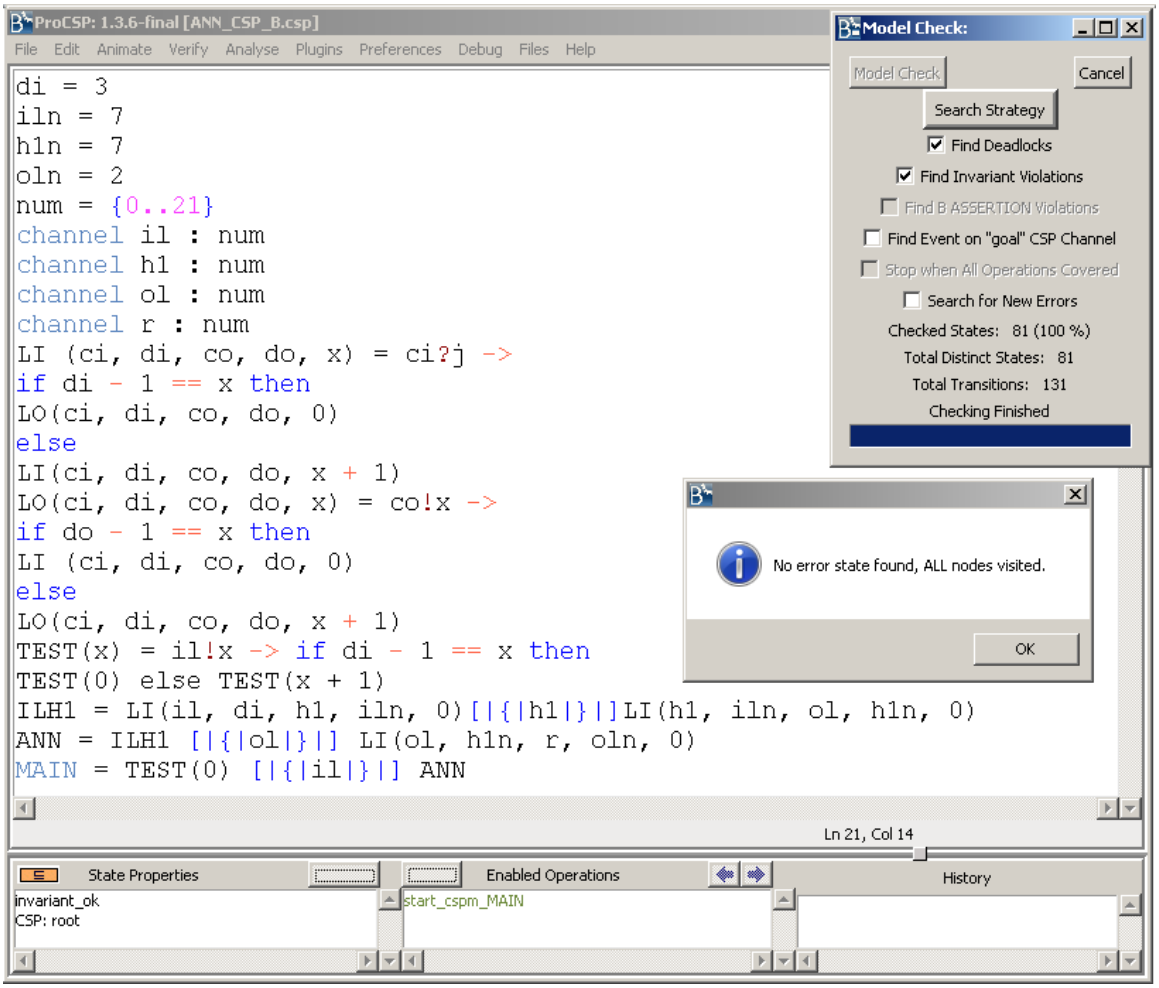


Figure 30: The model checker proofs the absence deadlock, as indicated by the message box. The main model checker window shows the formal CSPm code, which guides the B-model for the ANN model. The window in the right upper corner indicates that the model opens up a state space with 81 distinct states.

5.4.2 Implementation testing

Section 5.3.4.2 describes use case testing. The use cases, to test the XMOS ANN implementation, come from the functional model. The functional model is basically a Matlab implementation which trains and tests the feedforward ANN. Both, training and testing is done with classified data sets (input vectors). The training phase yields the relevant parameters (bias and weights) for both functional (Matlab) model and ANN implementation. To test the implementation, 200 of the classified data sets (input vectors) were selected as use cases. Figure 31 shows the bock diagram of the use case testing. The 200 input vectors were fed to both functional model and XMOS implementation. Their respective outputs are compared. For the 200 input vectors the results of the functional model and the XMOS implementation are the same. Therefore, the use case testing was successful.

Section 5.3.4.2 describes 5 failure cases with which the XMOS implementation

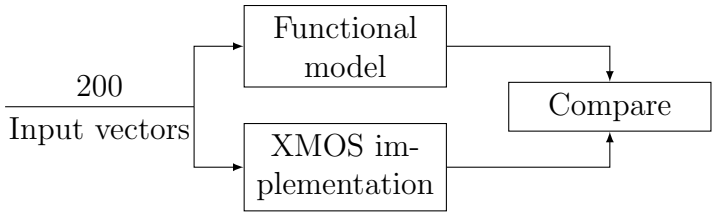


Figure 31: Block diagram use case test setup.

was tested. Failure case 1. results in a wrong answer of the XMOS implementation system. This wrong answer is due to overflow effects. However, there was no deadlock or livelock. Failure case 2. results in a correct answer of the XMOS implementation. There was no deadlock or livelock. For failure cases 3. and 4. the XMOS implementation deadlocks. That means, the system does not make progress until the correct number of input elements, in this case 3, is supplied. Finally, failure case 4. results in a wrong result and a subsequent deadlock. Or if after this failure case correct input vectors are supplied, all subsequent results are wrong. Therefore, the input stage, which sources the XMOS implementation, must make sure that always the correct number of elements is in the input vector.

5.5 Discussion

During implementation testing we encounter three types of errors. Formal methods help to reduce these errors, because they provide insight into the system functionality and they

- Type 1 error: programming error
  Formal methods cannot prevent programming errors unless the formal model is directly translated into an implementation. However, they can improve the code quality and thereby reduce the amount of programming errors, because of the insights gained in the formal specification phase. For example, during the formal modeling phase, we design the process structure of the system to be implemented. As part of the formal model, the process structure is checked for deadlocks, livelocks and functionality. Hence, the formal models help to establish the process structure. Furthermore, the formal method of Communicating Sequential Processes (CSP) requires the processes to behave in a specific way, they engage only in so called blocking communication. If and only if the programmer ensures that the implemented process follows the same rules, as the formal model process, then the formal model proofs hold also for the implementation.

- Type 2 error: input over range
  The B-model checks for invariant violations and the invariant checking checking is done for every function call. Invariant checking means the function parameters are checked against allowed value ranges. The wrong answer in Failure case 1 results from a shortcoming of the formal model. To be specific, the formal

model uses only integer numbers to model the functionality and the implementation uses floating point numbers. Hence, the formal model does not cover that aspect of the implementation. The overflow, experienced in Failure case 1, exposes a clear shortcoming of the selected formal models. The combination of CSP and B-method was selected because the CSP process algebra covers the parallel processing aspects of the model and the B-method covers the machine, i.e. sequential, aspects. With the current state of processing and formal method technology, it is impossible to cover all aspects of an implementation. Hence, we had to carefully select the formal methods based on their merits. The combination of CSP and B extends the CSP functionality with integer variables and invariant checking. With these extensions, it was possible to verify the system functionality, that means given a specific integer input, such as [0; 1; 2], the system will produce a verifiable output (res(0) = 5830027 and res(1) = 6384463). Now, the same input ([0; 1; 2]) was fed to the XMOS implementation and it produced the same output (res(0) = 5830027 and res(1) = 6384463). For formal model driven design, that is an important result, because it shows that the implementation behaves like the formal model.

- Type 3 error: process error, such as, inputs that could cause deadlock
  The model checker checks the range of all input variable, as specified by the formal model. The fact that the model checker did not flag a deadlock means, beyond reasonable doubt, that the formal model is deadlock free. In other words, no specified input values can cause a deadlock.

  Both failure cases 3 and 4 constitute violation of the contract between the ANN implementation and the environment. The domain of the formal model ends at the interface to the outside world. In case of the ANN implementation, the formal model covers the processing which starts with the acceptance of a complete input vector and ends at the result delivery. In Failure case 4, all the ANN implementation does is waiting for a complete input vector. For whatever reasons, the environment fails to provide a complete input vector, hence the ANN implementation waits forever - a classical deadlock. However, the ANN implementation behaves according to the contract with the environment and the environment is in breech of the contract. Therefore, a deadlock can only be avoided when the contract between the ANN implementation and the environment is changed. For example, it is possible to implement a watchdog functionality which discards incomplete input vectors after a specific time period. Strictly speaking, such watchdog timers are not covered by the formal methods used, because for both CSP and B the notion of time is not present in the model. Both formal methods relay on the notion of sequence. CSP relies on the sequence of events and the B-method relies on the sequence of function calls. Currently, there are efforts to model watchdog times with timed-CSP [347].

Good formal model design is the only way to avoid state space explosion. To show the effect of good model design, we compare the formal ANN model outlined

in Chapter 2 with the model in outlined in this chapter. The model in this chapter is based on CSP‖B, where the CSP part is modeled Equations 29 to 37. In contrast, the model in Chapter 2 is purely in CSP. In terms of model complexity, the CSP‖B model has 16 neuron processes, as shown in Figure 23 and the state space was 81. In contrast, Table 1 reports the state space for a 12 node CSP only ANN model ($m = 2$, $n = 3$) as 320286. The CSP‖B model with a higher complexity has a much lower state space than the CSP only model presented in Chapter 2. The stark differences between the state spaces of the two models presented in this thesis highlights the importance of the specification phase and indeed it highlights the importance of formal modeling to describe the specification. Stable failures are much more likely to occur in 320286 than in 81 states. Furthermore, having a large number of freewheeling processes, such as the interleaved layer processes in the CSP only model, results in a high communication overhead.

In general, systems engineering formalizes the process which turns ideas into trustworthy implementations. The ability to build trustworthy and reliable systems is very important for biomedical and health care applications. In these areas, human life depends either directly or indirectly on a machine which must function according to its specification. In the past, formalized engineering approaches have been used to design health care infrastructure systems.

Goertzen and Stausberg point out that an essential aspect for the utilization of medical data is their quality, thus a computer-based medical documentation systems should be reliable and under no circumstances corrupt the data. Therefore, the authors define a grammar for modeling medical documentation systems to increase integrity and completeness of collected data, focusing attention on integrity constraints. An integrity constraint defines requirements with which the involved entities had to comply. Furthermore, it defines possibly implications in case of failure. Their grammar is declared using a schema in extensible markup language-format (XML-schema). The model can be used in computer-aided design and implementation of clinical documentation systems. It achieves both minimizing effort and ensuring data quality. This was tested by an evaluation based on a specification of a registry for HIV-infected patients [325].

Baksi applies a type of formal software verification technique, known as lightweight model checking, to a domain model in healthcare informatics. The Alloy analyzer verification tool is utilized for model checking. The author claims that such verification work is very effective in either uncovering design flaws or in providing guarantees on certain desirable system properties in the earlier phases of the development lifecycle of any critical project [326].

The research work from Baksi further provides formal specification of interactions in typical public health surveillance systems involving healthcare agencies at local, state and federal levels [327]. The author highlights that the quality of medical care provided is an end result of a well-designed choreography of diverse services provided by different healthcare entities. One of the major challenges in this field appears to be explicit formal specification of such interactions. Such formal specification work is the first step leading to both design and verification of important properties of public healthcare systems. Therefore, he modeled two different configurations of public

health surveillance systems using π-calculus [328].

5.6 Chapter conclusion

This chapter provides a practical example which shows how formal and model driven design can be used to create biomedical signal processing systems. The focus was on formalizing requirements capturing and specification refinement. The implementation was a mere translation of the specification to a specific implementation target. For the requirements capturing we focused on the functional (mathematical) model for the feedforward ANN. In the second step, the requirements were refined into specifications. These specifications were captured in a formal CSP‖B model. The model was checked with two different model checkers. The model checking established deadlock as well as livelock freedom and no invariant violations were detected. The last point establishes the functionality of the CSP‖B model for one test case. After having established the desired model properties, the formal model was translated into an implementation for the XMOS processor. This implementation was tested with use and failure cases.

The design steps, outlined in this chapter, follow the systems engineering methodology. The aim is to produce reliable systems at a calculable cost. Reliability can only be achieved with formal development, because formal models provide a higher level of abstraction and therefore they can be reviewed by many stakeholders. Furthermore, it is possible to do automated model checking with the formal models. Model checking establishes certain model properties. Given that the translation from the formal model to the implementation is not too complex, there is a high level of confidence that the implementation will also possess the proven properties.

The current chapter outlined the formal and model driven design methodology as an extension of systems engineering. Mathematical formalisms helped us to specify the Computer-Aided Diagnosis (CAD) system. The formal specification helped us to build a safe system.

CHAPTER 6

CONCLUSION

This thesis documents work done in partial fulfillment of the DEng requirement for Chiba University. Looking back upon the body of work done, it is clear that the formal and model driven design methodology has fractal properties. We found the same structures at different system design scales. As such, all content chapters were written in terms of need definition, requirements capturing, specification refinement, implementation and testing. Chapter 2 highlights the need for formal and model driven design. Traceability is one of the main requirements of safety critical systems. We found that only a well documented design process is traceable. Proofs, associated with formal models, form an important part of the tracing process, because there is no need to look or trace into to the logic of the formal model. In other words, during the tracing process, everything, apart from the formal model is questioned. That is the reason why formal and modeling is so important for safety. In contrast, the functional model ensures that a system is able to fulfill the need. In the biomedical domain, a system needs to help patients by reducing or eliminating suffering.

The first case study starts of very focused on the medical condition of diabetes. We show that diabetes is an important problem, because it is a chronic disease, which leads to serious long-term complications: retinopathy, neuropathy, nephropathy and cardiomyopathy. Hence, there is a need to build diagnosis systems which automate and improve the diagnosis process. In the requirements phase we analyzed Heart Rate Variability (HRV) fluctuations for signals from both normal and diabetic patients using linear and nonlinear techniques. Through statistical analysis we found that nonlinear features are particularly useful to differentiate Heart Rate (HR) data from diabetes patients and that from normal patients. A second analysis step shows that the nonlinear features, combined with an AdaBoost classifier yield a classification accuracy of 86% for this binary disease non-disease problem.

The second case study on Electroencephalograph (EEG) signals we compared different model based power spectral density estimation methods and different classification methods. We found that Burg's method for spectrum estimation together with a support vector machine classifier yields the best classification results. This combination reaches a classification rate of 93.33%, the sensitivity is 98.33% and the specificy is 96.67%.

After the groundwork on the systematic design of biomedical algorithms, we went on to investigate health care systems. Currently, there is a disparity in the availability of doctors between urban and rural areas of developing countries. Most experienced doctors and specialists, as well as advanced diagnostic technologies, are available in urban areas. People living in rural areas have less or sometimes even no access to affordable healthcare facilities. Increasing the number of doctors and charitable medical hospitals or deploying advanced medical technologies in these areas might not be

economically feasible, especially in developing countries. We argue that, with the advancement in communication and networking technologies, economically middle class people and even some rural poor have access to internet and mobile communication systems. Thus, Hospital Digital Networking Technologies (HDNT) can be developed to utilize Internet, mobile and satellite communication systems to connect primitive rural healthcare centers to well advanced modern urban setups and thereby provide better consultation and diagnostic care to the needy people. We present the features of HDNTs, the implementation issues and the application of wireless technologies in the field of medical networking.

The last content chapter puts the individual ideas together. We provide a practical example which shows how formal and model driven design can be used to create biomedical signal processing systems. The focus was on formalizing both requirements capturing and specification refinement. The implementation was a mere translation of the specification to a specific implementation target. For the requirements capturing we focused on the functional (mathematical) model for the feedforward Artificial Neural Network (ANN). In the second step, the requirements were refined into specifications. These specifications were captured in a formal CSP‖B model. The model was checked with two different model checkers. The model checking established deadlock as well as livelock freedom and no invariant violations were detected. The last point establishes the functionality of the CSP‖B model for one test case. After having established the desired model properties, the formal model was translated into an implementation for the XMOS processor. This implementation was tested with use and failure cases.

The formal and model driven design methodology aims to benefits society by formalizing design processes for biomedical health care systems. The benefit of the formal design description is twofold: the proposed model driven development leads to reliable systems which function according to specification. Reliability is important, because unreliable biomedical systems can cause harm and suffering and ultimately cost lifetime. The second point for model driven design is cost effectiveness. Cost is a big topic for health care systems, because it can be used to measure progress. In other words, progress for health care systems means to achieve more (relive more suffering) with less or equal capital investment. Having done extensive research on the individual fields of biomedical engineering, computer science and mechanical engineering puts us in position to propose the formal and model driven design methodology.

We are aware that this thesis is by far not sufficient to achieve an adoption of formal and model driven design in the creation of biomedical systems, it constitutes only a small step towards this goal. More work is needed to address the difficulties that arise from the design of complex systems which must be reliable. To be specific, research on large scale biomedical systems must involve formalizing the design methodology.

6.1 Future direction

Our future direction for computer aided diagnosis algorithms and health care systems design is centered on reliability. In particular, more research has to be done on the

use of sleep Electrooculography (EOG), Electromyography (EMG) or EEG signals to detect sleep apnoea. In this way we hope to support sleep physicians better in their task of sleep apnoea diagnosis.

Systems thinking and design methodologies for algorithms in Computer-Aided Diagnosis (CAD) health care systems will gain importance. Therefore, specialists are needed who can guide the way towards highly complex health care systems which are safe, reliable and functional. More work is needed to establish special design methodologies for biomedical systems. These design methodologies must steer the design process such that the resulting system meets the required reliability.

Chapter 5 lays the ground work for further investigations. Having a formal basis means that there is a high level of certainty that the system is deadlock and livelock free. Furthermore, we established that the system always delivers the correct result. Having such a clear understanding of the system functionality is a prerequisite for extending the system. For example, extending the system can mean to make it even more reliable. There are a number of ways to tackle these increased reliability requirements. One of the most promising techniques is triplication. Due to the process oriented nature of the formal model, such triplication can be realized without fundamental design changes.

Reliability for algorithms in biomedical health care systems is and will continue to be a big if not growing topic. Therefore, methods of risk assessment are necessary to establish what significant levels of system reliability are. In future, both complexity and pervasiveness of health care systems will go up. Hence, the risk that if something goes wrong it goes very wrong is high. As a direct consequence, the demand for reliability goes up. This argument will take center stage in my future work. Assessing risk and determining the level of systematic reliability will be important tasks.

APPENDIX A

ACRONYMS

3G	International Mobile Telecommunications-2000
4G	Successor to 3G
ADA	American Diabetes Association
AES	Advanced Encryption Standard
ApEn	Approximate Entropy
ANS	Autonomic Nervous System
ANN	Artificial Neural Network
ANSI	American National Standards Institute
ANOVA	Analysis Of Variance
API	Application Programming Interface
AR	Autoregressive
ARMA	Autoregressive Moving Average
ATM	Automated Teller Machine
AUC	Area Under Curve
BA	Bayesian Averaging
BCI	Brain Computer Interface
BPA	Back-Propagation Algorithm
BPSO	Binary Particle Swarm Optimization
BSN	Biomedical Sensor Network
CAD	Computer-Aided Diagnosis
CAN	Cardiovascular Autonomic Neuropathy
CD	Correlation Dimension
CEUS	Contrast Enhanced Ultrasound
CI	Confidence Interval
CHS	Community Health Centers
CLDA	Clustering Linear Discriminant analysis Algorithm
CSP	Communicating Sequential Processes
CSPm	machine readable CSP
CT	Computed Tomography
CSR	Cambridge Silicon Radio
CVD	Cardiovascular Disease
DET	Determinism
DM	Diabetes Mellitus
DN	Diabetic Neuropathy
DR	Diabetic Retinopathy
DWT	Discrete Wavelet Transform
E-M	Expectation-Maximization
ECG	Electroencephalogrphy

ECHONET EchoCardiographic Healthcare Online Networking Expertise in Tasmania
EEG Electroencephalograph
EMG Electromyography
EOG Electrooculography
FAQ Frequently Asked Questions
FD Fractal Dimension
FDDI Fiber Distributed Data Interface
FN False Negative
FNN False Nearest Neighbor
FP False Positive
GMM Gaussian Mixture Model
GPRS General Packet Radio Service
GSM Global System for Mobile communications
GUI Graphical User Interface
H Hurst exponent
HDNT Hospital Digital Networking Technologies
HF High Frequency
HIHM Home Integrated Health Monitor
HIPAA Health Insurance Portability and Accountability Act
HOS Higher Order Spectra
HR Heart Rate
HRV Heart Rate Variability
$HRV \triangle Index$ See paragraph 3.4.2.2 on page 46
HSDPA High-Speed Downlink Packet Access
IEEE Institute of Electrical and Electronic Engineers
IR Infrared
IT Information Technology
KS Kolmogorov Sinai
K-NN K-Nearest Neighbour
LLE Largest Lyapunov Exponet
LF Low Frequency
LF/HF Low by High Frequency
LTE Long Term Evolution
MA Moving Average
$\overline{HR}$ Mean Heart Rate
MC Clustered Microcalcifications
ML Maximum Likelihood
MLPNN Multilayer Perceptron Neural Networks
MOH Ministry Of Health
MRI Magnetic Resonance Imaging
$NN50$ Number of successive difference of intervals which differ by more than 50 milliseconds
OFDM Orthogonal Frequency-Division Multiplexing
PCA Principal Component Analysis

PHC	Primary Health Centers
PNN	Probabilistic Neural Network
$PNN50$	NN50 in percent
PSD	Power Spectrum Density
PPV	Positive Predictive Value
QoS	Quality of Service
RAM	Random-Access Memory
RBF	Radial Basis Function
RBFNN	Radial Basis Function Neural Network
REC	Recurrence Rate
RNN	Recurrent Neural Network
ROC	Receiver Operating Characteristic
RP	Recurrence Plots
RSA	Respiratory Sinus Arrhythmia
SampEn	Sample Entropy
$SD1$	Standard Deviation of the points that are perpendicular to the line-of-identity
$SD2$	Standard Deviation of the points that are located along the line-of-identity
SE	Standard Error
ShanEn	Shannon Entropy
SMDS	Switched Multimegabit Data Service
SNN	Spiking Neural Network
SQL	Structured Query Language
SVM	Support Vector Machine
$TINN$	Triangular Interpolation of NN interval histogram
TN	True Negative
TP	True Positive
UIT	Urinary Tract Infection
ULP	Ultra-Low Power
UMTS	Universal Mobile Telecommunications System
UWB	Ultra Wideband
WBAN	Wireless Body Area Network
WEP	Wired Equivalent Privacy
WHO	World Health Organization
WiMAX	Worldwide interoperability for Microwave Access
WLAN	Wireless Local Area Network
WMAN	Wireless Metropolitan Area Network
WPA	Wi-Fi Protected Access
WPAN	Wireless Personal Area Network
WWAN	Wireless Wide Area Network

APPENDIX B

NONLINEAR ALGORITHMS FOR HEALTH CARE SYSTEMS

From the time of the enlightenment onwards, scientists like Galileo and Newton aimed to understand the world in terms of laws and regularities. They observed and captured data from nature and extracted patterns as well as relevant properties which allowed them to classify the phenomena which caused this data. Repeated classification and mounting evidence led them to formulate general laws and theories. These laws and theories are the cornerstones for the success story of modern science, because they can forecast physical phenomena from a set of initial conditions. More specifically, the quality of laws and theories is measured by both accuracy and simplicity with which they are able to forecast physical phenomena. But the simplicity requirement poses a problem, because the idea that the world is governed by simplicity sits in tension with irregularities, asymmetries and diversities which were observed in natural data. The secret to unlock this problem is nonlinear feedback in natural processes. Scientific understanding of such processes is a recent achievement, which was made possible by combining a number of different discoveries made over the last century. At the heart of this new understanding lies the mathematical concept of chaos.

The mathematical concept of chaos is applied to such seemingly diverse systems like weather, earthquakes and biomedical signals. The basic assumption is that complex phenomena, including life, emerge from simple underlying phenomena in a chaotic fashion. This process results in self-organizing systems which maintain themselves far from equilibrium. The systems walk the fine line between an ordered state and chaos. This state is maintained by an influx of external energy, for living animals the energy comes from food and if we view the planet earth itself as a chaotic systems, the energy, which maintains the state on the edge of chaos, comes from the sun. The strong point about the chaos theory is that it explains the emergence of phenomena that are far more complex then the sum of simpler parts which cause them.

The advent of computing systems gave chaos analysis a massive boost. Only with sufficient inexpensive computing power it is possible to model and analyze natural processes from evolution through natural selection to information extraction from biomedical signals. Computing power is necessary because these systems are very sensitive to either changes in the initial parameters or fluctuations in the feedback loop. To be specific, this sensitivity requires chaotic models to be very precise in terms of time and processing accuracy, both requirements increase the computational complexity.

Chaos theory shows that chaos and order are not mutually exclusive, they are symbiotically related. For example a human EEG shows a large number of small variations, but the overall shape of the heart beat signals stays the same. According

to the chaos theory, the overall shape represents a state of delicate equilibrium always close to the verge of collapse. Per Bak was the scientist who first described this phenomenon as self-organizing criticality [348].

This chapter gives an educational overview of the nonlinear analysis methods used in the content chapters of this thesis. The discussion begins by introducing the phase space of a signal. The properties of this phase space are exploited with algorithms, such as Largest Lyapunov Exponet (LLE), Correlation Dimension (CD), Fractal Dimension (FD), Recurrence Plots (RP), Poincaré plot geometry and Hurst exponent (H). Next we introduce entropy as an important measure which discriminates between chaotic and ordered states. The last 3 sections of this chapter are dedicated to this task. They introduce Approximate Entropy (ApEn), Sample Entropy (SampEn) and Kolmogorov Sinai (KS) Entropy.

B.1 State space

State space is defined as an abstract mathematical space which is spanned by the dynamical variables of the system. The number of dynamic variables (n) defines the dimensionality of the state space $\mathbb{R}^n$. Hence, particular variable values represented one point in the state space. Such points are called *system states*. As the variables change over time the corresponding point traces out a path in the state space. This path is continuous for time continuous systems and discrete for time discrete systems [349, Ch. 1, p. 3].

B.1.1 State space reconstruction

The first step in nonlinear time series analysis is state-space reconstruction. One-dimensional data $y(n)$ where $n = 1, 2, ..., N$ is viewed in an m-dimensional Euclidean space, $\mathbb{R}^m$. An attractor is created by a path that joins the vectors in the state-space and this attractor maintains the topological properties of the original unidentified attractor.

The method of delays is a popular way to reconstruct the state-space [350]. According to this method, m-dimensional vectors, x_n in the state-space are produced from the time-delayed samples of the original signal, $y(n)$, as follows:

$$x_n = [y(n), y(n-d), y(n-2d), ..., y(n-(m-1)d)] \tag{38}$$

where d indicates embedding delay, and m indicates the embedding dimension (i.e. number of coordinates).

The minimal sufficient embedding dimension, m can be achieved by using a method called False Nearest Neighbor (FNN) [351].

B.2 Largest Lyapunov Exponet (LLE)

LLE reflects the sensitivity of the system to the initial conditions. The time-domain signal is embedded in the phase space, and examined there in. If the attractor, during

its orbit, passes closely to a state it was previously in and diverges, provides a measure of the rate of this (typically exponent) divergence [352].

It defines the averaged rate of divergence (or convergence) of two neighboring trajectories. For two points in a space X_0 and $X_0 + \Delta x_0$, that are function of time and each of which will generate an orbit in that space using some equation or system of equations, then the separation between the two orbits Δx will also be a function of time. This separation is also a function of the location of the initial value and has the form $\Delta x(X_0, t)$. For chaotic data set, the function $\Delta x(X_0, t)$ will behave erratically. The mean exponential rate of divergence of two initially close orbits is characterized by

$$\lambda = \lim_{t \to \alpha} \frac{1}{t} \times \frac{\mid \Delta x(X_0, t) \mid}{\Delta X_0} \tag{39}$$

This number, called the Lyapunov exponent "λ", is useful for distinguishing among the various types of orbits.

B.3 Fractal Dimension (FD)

In 1983, Mandelbrot used the term "fractal" for the first time [353]. The name refers to a sequence of numbers that, when looked at smaller scales, resembles the sequence at a larger scale. As such, FD originated from fractal geometry. To understand FD, we have to define the topological or Euclidean dimension as the number of directions each differential of the object occupies in space. That particular definition of dimension falls apart for objects whose level of detail, complexity or "space-filling" is not the same. For example, two fractals with the same Euclidean dimension, can have a different level of "space-filling". Hence, the Euclidean dimension fails to provide that information. The FD indicates the amount of space an object occupies between Euclidean dimensions. In biomedical engineering, FD is used for transient detection. The transient detection in Electroencephalogrphy (ECG) and EEG helps with both identification and distinguishing specific states of and underlying physiologic function. We have used Higuchi's algorithm [354] and the algorithm proposed by Katz [355].

B.4 Correlation Dimension (CD)

CD is frequently used to determine whether or not a time series is self-similar. In this study we used an algorithm which was proposed by Grassberger and Procaccia [356]. CD indicates the minimum number of variables required to model the underlying system. That means it estimates the dimensionality of the space occupied by a set of points.

The x-axis of the phase-space plot represents the heart-rate $X[n]$ while the y-axis represents the signal after a *delay* $X[n + delay]$. An appropriate *delay* can be calculated using the minimal mutual information technique [357, 358]. We selected an embedding dimension of 10 and a time *delay* of 1 [251]. CD is calculated using the fundamental definition:

$$\mathrm{CD} = \lim_{r \to 0} \frac{\log[C(r)]}{\log(r)} \tag{40}$$

Where the correlation integral $C(r)$ is given by:

$$C(r) = \frac{1}{N^2} \sum_{x=1}^{N} \sum_{y=1, x \neq y}^{N} \Theta \left(r - \mid X_x - X_y \mid \right) \tag{41}$$

where N is the number of data points in phase space, Θ is the Heaviside step function, r radial distance around each reference point X_i and X_x, X_y refers to points of the trajectory in the phase space.

B.5 Hurst exponent (H)

The H is a measure that has been widely used to evaluate the self-similarity and correlation properties of fractional Brownian noise, the time series produced by a fractional (fractal) Gaussian process. It is used to evaluate the presence or absence of long-range dependence and its degree in a time series. However, local trends (nonstationarities) are often present in physiological data and may compromise the ability of some methods to measure self-similarity. H measures the smoothness of a fractal time series based on the asymptotic behaviour of the rescaled range of the process. It is defined as:

$$\mathrm{H} = \log \left(\frac{R/S)}{\log(T)} \right) \tag{42}$$

where T is the duration of the sample of data, and R/S the corresponding value of rescaled range.

$$\langle \xi \rangle_\tau = \frac{1}{\tau} \sum_{t=1}^{\tau} \xi(t) \tag{43}$$

$$X(t, \tau) = \sum_{u=1}^{t} \xi(t) \langle \xi \rangle_\tau \tag{44}$$

$$R(\tau) = \max \left(X(t, \tau) \right) - \min \left(X(t, \tau) \right) \tag{45}$$

where $1 \leq t \leq \tau$.

Rescaled range definition.

$$R/S = \frac{R(\tau)}{S(\tau)} \tag{46}$$

$$S(\tau) = \sqrt{\frac{1}{\tau} \sum_{t=1}^{\tau} \left[\xi(t) - \langle \xi \rangle_\tau \right]^2} \tag{47}$$

$$E \left[\frac{R(n)}{S(n)} \right] = C \, n^{\mathrm{H}} \qquad \text{as } n \to \infty \tag{48}$$

For a random walk H is equal to 0.5

$$E \left[\frac{R(n)}{S(n)} \right] = C \, n^{0.5} \qquad \text{as } n \to \infty \tag{49}$$

The above expression is obtained from Hurst's generalized equation of time series that is also valid for Brownian motion. It is given by $R/S = k \times T\mathrm{H}$, where k is a constant. If H = 0.5, the behavior of the time-series is similar to a random walk; if H < 0.5, the time-series covers less "distance" than a random walk (i.e., if the time-series increases, it is more probable that then it will decrease, and vice-versa); if H > 0.5, the time-series covers more "distance" than a random walk (if the time-series increases, it is more probable that it will continue to increase). Given a time series $x(n)$, with $n = 1, ..., N$, H can be estimated by taking the slope of (R/S) plotted vs. n in a log-log scale. H is related to the FD by the parameter D: $\mathrm{H} = E + 1 - D$, where E is the Euclidean dimension.

B.6 Recurrence plots

In 1987, Eckmann et al. proposed that RP which reveal non-stationary components of the time series [235]. It is a 2 dimensional plot that can be used in the diagnosis of drift and hidden periodicities. For this study we have extracted both Recurrence Rate (REC) and Determinism (DET) as parameters form RP.

The algorithm which was used to extract REC and DET can be justified as follows: Let $s(i)$ be the i^{th} point on the orbit describing a dynamical system in d_E dimensional space. The RP is an $N \times N$ square, where a dot is placed at (i, j) whenever $s(j)$ is sufficiently close to $s(i)$. To obtain a RP from time series $s(n)$, an embedding dimension d_E, is chosen by method of delays [359]. Next, we choose $r(i)$ such that the ball of radius $r(i)$, centered at $s(i)$, in $\mathcal{R}^{d_E}$ contains reasonable number of other points $s(j)$ of the orbit. Finally, we plot at each point (i, j) for which $s(j)$ is in the ball of radius $r(i)$ centered at $s(j)$. The resulting plot is the RP. For our studies we have extraction both REC and DET as parameters from the RPs.

REC is the ratio of ones and zeros in the RP matrix. The number of 'one' elements in the RP matrix is equal to $N - m + 1$, and the recurrence rate is given as:

$$\mathrm{REC} = \frac{1}{(N - m + 1)^2} \sum_{i,j=1}^{N-m+1} RP(i, j) \tag{50}$$

DET, is the percentage or fraction which forms diagonal lines. It can be obtained using the equation below:

$$DET = \frac{\sum_{l=l_{\min}}^{N} l \times P(l)}{\sum_{i,j}^{N} RP(i, j)} \tag{51}$$

where $P(l)$ is the histogram of length l of the diagonal lines.

B.7 Poincaré plot geometry ($SD2$)

The Poincaré plot is a diagram in which each RR-interval of a tachogram is plotted as a function of the previous RR-interval for a predetermined segment length. The program used in these experiments provides a graphic display of the plots and a

quantitative analysis of the shape of the scattergrams. The markings of the plot are gathered around a line of unitary slope (slope=1) passing through the origin. The center point of the markings is at (RR_{aver}, RR_{aver}), where RR_{aver} is the average RR-interval length for the tachogram.

The Poincaré plot is defined as follows: Given a time series

$$\mathrm{RR} = \{\mathrm{RR}_1, \mathrm{RR}_2, ..., \mathrm{RR}_n, \mathrm{RR}_{n+1}\} \tag{52}$$

the standard Poincaré plot is a scattergram constructed by locating points from the time series on the coordinate plane according to the pairing $(\mathbf{x}_i, \mathbf{y}_i)$ in which,

$$\begin{array}{ll} \mathbf{x} = & \{x_1, x_2, , x_n\} = \{\mathrm{RR}_1, \mathrm{RR}_2, ..., \mathrm{RR}_n\} \\ \mathbf{y} = & \{y_1, y_2, , y_n\} = \{\mathrm{RR}_2, \mathrm{RR}_3, ..., \mathrm{RR}_{n+1}\} \end{array} \tag{53}$$

and $i = 1, 2, 3, ..., n$ where n is the number of points in the Poincaré plot which is one less than the length of the RR time series [360]. As mentioned above, SD1 and SD2 are two standard descriptors of Poincaré plot. SD2 is defined as the standard deviation of the projection of the Poincaré plot on the line of identity ($\mathbf{y} = \mathbf{x}$), and SD1 is the standard deviation of projection of the Poincaré plot on the line perpendicular to the line of identity ($\mathbf{y} = -\mathbf{x}$). So we can define the two parameters as:

$$SD1 = \sqrt{\mathrm{Var}(d1)} \tag{54}$$

$$SD2 = \sqrt{\mathrm{Var}(d2)} \tag{55}$$

where $\mathrm{Var}(d)$ is the variance of d, and

$$d1 = \frac{x - y}{2}, \quad d2 = \sqrt{\frac{x + y}{2}} \tag{56}$$

B.8 Approximate Entropy (ApEn)

ApEn is defined as the logarithmic likelihood that the patterns of the data that are close to each other will remain close for the next comparison with a longer pattern. Thus ApEn provides a generalized measure of regularity. A deterministic signal with high regularity has a higher probability of remaining close for longer vectors of the series and hence has a very small ApEn value. On the other hand, a random signal has a very low regularity and produces a high ApEn value.

ApEn is a measure of complexity and is applied to relatively short and noisy data [230, 361]. Two parameters m and r must be chosen prior to the computation of ApEn where specifies the pattern length and r is the effective filter. Here, one has to compute the correlation integral $C^m(r)$ (with embedding dimension m and time lag of 1. This measure is finally obtained as follows:

$$\begin{array}{ll} \mathrm{ApEn}(m, r, L) = & \frac{1}{L-m} \sum_{i=1}^{L-m} \log \left[C_i^{m+1}(r)\right] \\ & - \left(\frac{1}{L-m+1}\right) \sum_{i=1}^{L-m+1} \log \left[C_i^{m}(r)\right] \end{array} \tag{57}$$

Thus ApEn quantifies the (log) likelihood that sets of patterns that are close on next incremental comparison. Smaller values of ApEn imply a greater likelihood that certain patterns of measurements will be followed by similar measurements. If the time series is highly irregular, the occurrence of similar patterns in the future is less likely.

B.9 Sample Entropy (SampEn)

SampEn was developed to measure both regularity and complexity of clinical and experimental time-series data [362]. SampEn does not count self-matches, because comparisons within itself will indicate that the signals are more regular than they actually are. When estimating conditional probabilities, SampEn adopts a one template approach to find a match of length $m+1$. With the vector comparison removed, we have:

$$C_i^m(r) = \left\{ \text{the number of } j \; ; j \neq i, j \leq Nm+1, \text{ such that } \frac{d[u(i), u(j)] \leq r}{(N \leq m+1)} \right\} \quad (58)$$

we can further determine that:

$$\theta^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} C_i^m(r) \quad (59)$$

Therefore, we have:

$$\text{SampEn}(m, r, N) = -\ln \left\lfloor \frac{\theta^m(r)}{\theta^{m+1}(r)} \right\rfloor \quad (60)$$

Although the measure of signal complexity is similar for both ApEn and SampEn, but their dependence on parameters N and r is different. When r increases, SampEn decreases monotonically. Theoretically, SampEn is not dependent on N. However, it was found that when analyzing time series with less than 200 data points, the confidence interval of the results were so large that it was unacceptable. The same results are obtained for ApEn and SampEn for large N and r.

B.10 Shannon Entropy (ShanEn)

Shannon Entropy (ShanEn) is a simple quantitative measure that indicates the uncertainty in a data set. One can narrow down to certain data sets with low entropy and others with high entropy. In short, ShanEn is a number to measure the amount of uncertainly.

ShanEn is given by the equation below:

$$\text{ShanEn}_n(p_1, p_2, ..., p_n) = -\sum_{i=1}^{n} p_i \log_2(p_i) \quad (61)$$

Let us take (x) to be a discrete random variable.

- Where $x_1, x_2, ..., x_n$ with probabilities $p_1, p_2, ..., p_n$;
- Let ShanEn_n be defined on the interval (0,1);
- $p_i \geq 0,\ i = 1, 2, ..., n$ and $\sum_{i=1}^{n} p_i = 1$.

Low entropy indicates a low variation and conversely high entropy indicates high variation.

B.11 Kolmogorov Sinai (KS) Entropy

The KS algorithm extracts the entropy measure from an embedded time series data. The algorithm finds points on the phase space trajectory, that are space but not time correlated. The pair of points is monitored to see how quickly they separate (increase the distance in phase space). Kolmogorov entropy, expressed in bits per seconds, is defined as the time taken for point pairs to move apart. KS is given by:

$$r_{div}\left(\frac{\text{bits}}{\text{sec}}\right) = 2^{Kt} \tag{62}$$

Where t_{div} is the average time for the pair to move apart. Entropy is a reflection of how well the behavior of each respective part of the trajectory from the other are predicted. Higher entropy means it is less predictable and is a step closer to stochasticity [363].

APPENDIX C

FEATURE ANALYSIS

C.0.1 Gaussian Mixture Model (GMM)

Gaussian Mixture Models (GMMs) have been widely used in many areas, such as pattern recognition and classification. Their use has been especially successful in speaker identification and verification [269, 270]. In GMM models, a probability density function is expressed as a linear combination (with weights w_i) of N multi-dimensional Gaussian basis functions. Each of these basis functions is specified by its mean value μ_i and its covariance matrix Σ_i, both can be derived from the input signal. For a single observation, x, the probability density function of a given GMM model, λ is calculated as:

$$p(x \mid \lambda) = \sum_{i=1}^{N} w_i \; g\left(s \mid \mu_i, \Sigma_i\right) \tag{63}$$

The probability density function of a single Gaussian component of D dimensions is defined as:

$$g\left(x \mid \mu_i, \Sigma_i\right) = \frac{1}{\sqrt{(2\pi)^D \left|\Sigma_i\right|}} \; e^{\left[-\frac{1}{2}\left(x-\mu_i\right)' \Sigma_i^{-1} \left(x-\mu_i\right)\right]} \tag{64}$$

where $(')$ denotes the vector transpose. The solution, to determine the parameters of the GMM, uses the Maximum Likelihood (ML) parameter estimation criterion. The model parameters are estimated through training, the goal is to maximize the likelihood of the observations using the so called *Expectation-Maximization (E-M)* algorithm [271].

Usually, the initial estimates of the parameters are obtained from a sample of the training data using a simpler procedure, such as K-means [272]. The K-means procedure starts with randomly chosen initial means and assumed unit variances for the covariance matrix. This method has been adopted in this work.

C.0.2 Artificial Neural Network (ANN)

ANNs are comprised of densely interconnected adaptive simple processing elements called *neurons*. These neurons are interconnected, but independent entities, therefore they are capable of performing parallel computations for data processing and knowledge representation. The most commonly used neural network is called Multilayer Perceptron Neural Networks (MLPNN). We adopted MLPNNs for this study, because they operate fast and they are easy to implement. The MLPNN has been used widely for a variety of detection and estimation tasks [364, 365].

Figure 32 shows the ANN used for classification in this study. In this work, the nature of the class boundaries was not clearly known. Under these circumstances

there is no theoretical method with which the network setup can be determined. By trial and error we found that a four layer network with sigmoid activation function gives good results. The input layer had 9 neurons, the two hidden layers have 15 neurons each and the output layer has two neurons.

The multilayer perceptron was trained with the back Back-Propagation Algorithm (BPA). This is a supervised learning algorithm which aims to reduce the error between actual and desired network outputs. BPA is a so called *steepest decent method*, where weight values are adjusted in an iterative fashion while moving along the error surface to arrive at minimal range of error, when input patterns are presented to the network for learning.

During the initialization phase, the connection weights of the neural network were randomly assigned. During the training phase they are progressively modified to reduce the overall mean square error. The weight update, aimed at maximizing the rate of error reduction was set to 10^{-9}. With regards to the choice of the weight increment, there is no definite rule for its selection; however the weight increment was done in small steps. In the present case, a learning constant, $\eta = 0.9$ (that controls the step size) was chosen by trial and error.

The ideal training data set is large in size and uniformly spread throughout the class domains. In the absence of an ideal training dataset, the available data was used iteratively until the error function came down below a threshold. For quick and effective training, data was fed from all classes in a routine sequence so that the right message about the class boundaries was communicated to the ANN.

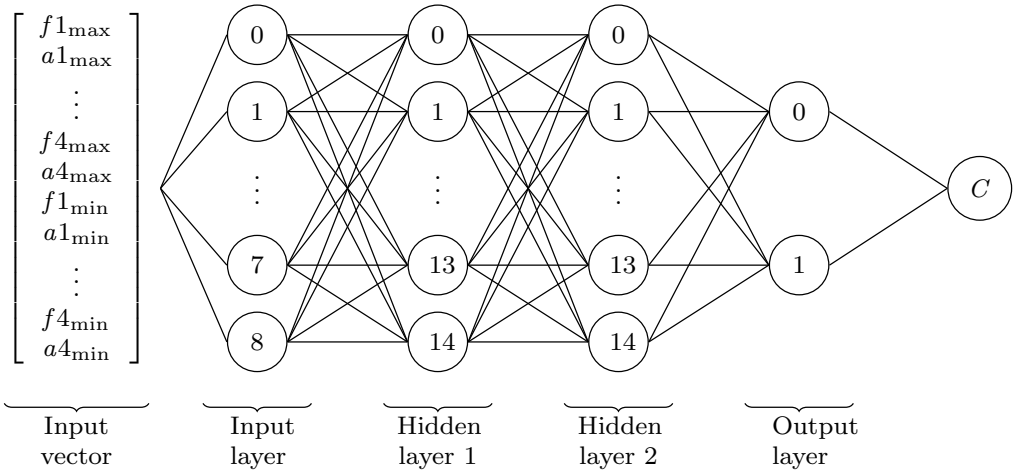


Figure 32: MLPNN with 9 input neurons, 15 neurons in the first and second hidden layer and 2 neurons in the output layer.

In order to train the ANN, we used a supervised learning algorithm called BPA [366]. This algorithm is best suited for feed-forward networks and it is used for automatic detection of unidentified data. BPA uses an iterative gradient which is created to lessen the mean square error between the actual output and the wanted output [366]. The layered neurons between input and output layers are called hidden layers or nodes, as shown in Figure 32. When BPA is in process, weights connected

to the hidden layers are altered constantly, hence enabling the pre-selected neural network to learn.

C.0.3 Receiver Operating Characteristic (ROC)

The Receiver Operating Characteristic (ROC) curve is a plot in a two dimensional space. The x-axis is '1 - specificity' and the y-axis is 'sensitivity'. Sensitivity, also known as True Positive (TP) fraction, refers to the probability that a test result is positive when a disease is present.

The area under the ROC curve indicates the classifier performance across the entire range of cut-off points. Conventionally, the area under the ROC curve must fall in the range between 0.5 and 1 [274]. An area closer to 1 means that the classifier has a better accuracy. The area under the ROC curve is a good indicator for the classifier's performance [275].

For example, Fogarty et al. used ROCs to analyze the tradeoff between TP and False Positive (FP) for sensor based estimates. Their case studies compare sensor-based estimates with human performance. They optimize a feature selection process for the area under the ROC curve, and they examine end-user selection of a desirable tradeoff [276].

In this work we used ROC to test the classifiers in their ability to differentiate normal from both epileptic background and seizure. In this test, specificity measures the proportion of signals from the normal group which are correctly identified. Similarly, sensitivity measures the proportion of both epileptic background and seizure groups which are correctly identified.

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