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千葉大学審査学位論文（要約）（Summary）

基幹工学 専攻 機械工学 コース
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論文題名（外国語の場合は、その和訳を併記） Thesis Title（foreign language title must be accompanied by Japanese translation）
Mass Transports and Mechanical Properties Parameter Estimation by Integrating of Mass Transport and Poroviscoelastic Model into Electrical Impedance Tomography (EIT) **多孔質粘弾性モデルと電気インピーダンストモグラフィー（EIT）の統合による物質移動と機械的特性パラメータの推定**

Summary:

The estimation of mass transport and mechanical properties by integrating poroviscoelastic-mass transport model into electrical impedance tomography (EIT) has been developed as a new method for lymphedema diagnostic to quantify disease progression and improve the effectiveness of the clinical treatment. The results of this thesis were successfully resolved the three objectives. The whole work of this thesis can be summarized as follows:

- Chapter 1:

This chapter described the background of this research and the current problem in quantifying mass transport and mechanical properties as a parameter for lymphedema diagnostic. The basic idea of lymphedema diagnostic is quantifying the non-normal increasing albumin-rich-fluid level at interstitial space as the Lymphatic vessel does not function normally. The quantification of the increasing albumin-rich fluid is related to how the albumin is transported through the interstitial space. Albumin diffusion, which is quantified as a diffusivity coefficient parameter, represents how far and fast albumin movement might be. Thus, disease progression of early-stage of lymphedema can be detected by measuring the albumin diffusion coefficient.

Moreover, lymphedema is a progressive disease; therefore, as a function of time, the inflammation happens because of fibrosis and lipid deposition (at least in the lymphedema stage II), which then resulted in the change of mechanical structure of subcutaneous adipose tissue [1], [2]. Thus, the albumin (as a dominant solute) diffusivity coefficient is changed because of the physical properties alteration due to albumin-rich-fluid accumulation [3]–[5]. Despite the albumin diffusivity coefficient parameter, which quantifies the albumin movement, the variation in mechanical properties also becomes an opportunity to detect and quantify the pathological development by monitoring and estimating soft tissues' mechanical properties such as hydraulic permeability and viscoelastic properties because its value depends on the tissue structure characteristics [6], [7].

- Chapter 2:

The basic idea of this research is to integrate a poroviscoelastic-mass transport model into EIT. Therefore, the basic knowledge about the general theory of porous medium, poroelastic model (Biot Model), viscous material model, mass transport model, and EIT should be explained. First, the general linear poroviscoelastic model (Biot Model) [8], along with the general boundary conditions, is expressed in the following equations:

$$\nabla \cdot (\boldsymbol{\sigma}_{\boldsymbol{e}}^{s} + \boldsymbol{\sigma}_{\boldsymbol{v}}^{s} - \alpha p\mathbf{I}) = -\mathbf{f} \text{ in } \Omega \tag{2.1}$$

$$\mathbf{q} = -\mathcal{K}(\nabla p + \rho_f \mathbf{g})L \quad \text{in } \Omega \tag{2.2}$$

$$\nabla \cdot \mathbf{q} + \frac{\partial}{\partial t}(\alpha \nabla \cdot \mathbf{u} + S_p p) = s \text{ in } \Omega \tag{2.3}$$

$$\mathbf{u} = \mathbf{u}_D \quad \text{on } \Gamma_D \tag{2.4}$$

$$\mathbf{n} \cdot \boldsymbol{\sigma} = \mathbf{t}_N \quad \text{on } \Gamma_N \tag{2.5}$$

$$p = p_D \quad \text{on } \Gamma_P \tag{2.6}$$

$$\mathbf{n} \cdot \mathbf{q} = q_D \text{ on } \Gamma_F \tag{2.7}$$

$$\mathbf{u}(.,0) = \mathbf{u}^0; \boldsymbol{p}(.,0) = p^0 \quad \text{in } \Omega \tag{2.8}$$

Here Ω is a bounded domain in $\mathbb{R}^2$ or $\mathbb{R}^3$, with the defined boundary conditions, $\partial\Omega_{elasticity} = \Gamma_D \cup \Gamma_N$ for displacement (Dirichlet) and stress (Neumann) boundary conditions and $\partial\Omega_{flow} = \Gamma_P \cup \Gamma_F$ for pressure (Dirichlet) and flux (Neumann) boundary conditions, with outward-pointing unit normal $\mathbf{n}$. The momentum and mass conservation equations are coupled through the Biot-Willis coefficient $\alpha \in (0,1)$ and the non-negative constrained specific poroelasticity storage $S_p \geq 0$. The S_p is commonly known as the inverse of Biot Modulus M_b ($S_p = \frac{1}{M_b}$). The increment ζ of the fluid volume per unit volume of the porous medium may be written as $\zeta = \alpha \nabla \cdot \mathbf{u} + S_p p$. From this definition, we can observe that $S_p p$ measures the amount of fluid that can be injected into porous material under certain pressure, and $\alpha \nabla \cdot \mathbf{u}$ represents the additional amount of fluid that can be squeezed out due to the local change in volume. Second, the general mass transport model or generally known as the advection-diffusion equation, is described as follows:

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (-D_i \nabla c_i + \mathbf{v} c_i) = S_i + R_i \quad \text{in } \Omega \tag{2.9}$$

$$c_i = c_{D,i} \quad \text{on } \Gamma_D \tag{2.10}$$

$$-\mathbf{n} \cdot (-D_i \nabla c_i) = \mathbf{g}_{N,i} \quad \text{on } \Gamma_N \tag{2.11}$$

$$-\mathbf{n} \cdot (-D_i \nabla c_i + \mathbf{v} c_i) = \mathbf{r}_{R,i} \quad \text{on } \Gamma_R \tag{2.12}$$

$$c_i(.,0) = c_i^0 \quad \text{in } \Omega \tag{2.13}$$

where D is the diffusivity coefficient of substances c_i in the porous medium, $\mathbf{v}$ is velocity field, R_i is a reaction rate expression for substances c_i, and S_i is an arbitrary source term, for example, due to a fluid flow source or sink. $\mathbf{g}_{N,i}$, $\mathbf{r}_{R,i}$, and $c_{D,i}$ are given scalar-valued functions, and $\mathbf{n}$ denotes the outward unit normal on $\partial\Omega$. $R > 0$ means that a chemical reaction creates more substances while $R < 0$ means that a chemical reaction destroys the substances. Third, Electrical impedance tomography (EIT) is a noninvasive type imaging method. The underlying principle is to reconstruct the electrical conductivity inside the object or body to form a tomographic image based on surface electrode measurements. Electrical conductivity $\gamma(\mathbf{r})$ varies considerably among specific characteristics of various biological tissues or the movement of fluids, substances, and gases within tissues where $\mathbf{r} \in \Omega \subset \mathcal{R}^N$ indicate the vector position in *N*-dimension. The main point of EIT is to estimate the $\gamma(\mathbf{r})$ (known as the inverse problem or image reconstruction of EIT) of an object from the Neumann-to-Dirichlet map is. EIT image is obtained via minimization of a regularized objective function $\Phi(\boldsymbol{\gamma})$: $\mathcal{R}^N \to \mathcal{R}$, where *N* is the number of elements:

$$\begin{aligned} \Delta\boldsymbol{\gamma} &= \arg\min \Phi(\boldsymbol{\gamma}) \\ &= \arg\min \frac{1}{2}\left\{ \| A(\boldsymbol{\gamma}) - \Delta\mathbf{U}_{meas} \|^2_{\Sigma_h^{-1}} + \lambda \Psi(\boldsymbol{\gamma}) \right\} \end{aligned} \tag{2.14}$$

where $A(\boldsymbol{\gamma})$ is the forward map, Σ_h^{-1} is the covariance of the measurement noise, $\Psi(\boldsymbol{\gamma})$ is the regularization function, and λ is the regularization parameter. Several optimization methods are used to minimize $\Phi(\boldsymbol{\gamma})$.

- Chapter 3:

In this chapter, the albumin diffusivity coefficient D_I^a is estimated by integrating Albumin Diffusion Model (ADM) into EIT (iADM-EIT). ADM is developed based on Krogh`s tissue cylinder geometry model following the design of the dynamic phantom. Agarose gel was used to mimic the porous structure of interstitial space. ADM predicted the spatio-temporal albumin concentration

$C_I^a(r,t)$ in the surrounding capillary area in *r*-direction. EIT reconstructed the spatio-temporal distribution of conductivity difference $\Delta\gamma(r,t)$ resulted from the increasing experimental albumin concentration ${C_I^a}_{ex}(r,t)$ during albumin diffusion through the interstitial space. To relate between $\Delta\gamma(r,t)$ and ${C_I^a}_{ex}(r,t)$, a constitutive relationship among ${C_I^a}_{ex}(r,t)$, $\Delta\gamma(r,t)$, and porosity $\emptyset$ is derived by combining the specific relationship between albumin concentration and electrical conductivity in a solution and Archie`s Law which describes the electrical conductivity in porous media. D_I^a is estimated by applying curve fitting technique between $C_I^a(r,t)$ and experimental ${C_I^a}_{ex}(r,t)$. The iADM-EIT successfully estimated the albumin diffusivity coefficient in agarose gel as an imitated porous structure of interstitial space for five different porosity (from $\emptyset_1 = 0.922$ to $\emptyset_5 = 0.990$) with relative albumin diffusivity coefficient D_I^a/D_0^a value range from 0.271 to 0.694 and the percent average relative error δ to the literature in the same porous media (agarose gel) was 6.83 ± 2.72 % [9]. This result was found to be in good agreement with the literature in the range of 0.2 – 0.9.

- Chapter 4:

The hydraulic permeability $\mathcal{K}$ of human subcutaneous adipose tissue (SAT) is estimated by integrating the poroelastic-mass transport model (*pe*-MTM) into wearable EIT (*w*-EIT). The *pe*-MTM is developed based on poroelasticity material behavior that induces the ion diffusion and convection inside SAT. The *pe*-MTM was capable of describing the mechanical load-induced fluid flow in SAT under the influence of external compressive pressure $-P$ (with maximum pressure P_{max} = 50 mmHg (6,666.1 Pa); 80 mmHg (10,665.8 Pa); and 120 mmHg (15,998.7 Pa)) and predicting the ion concentration distribution $c_{mod}(r,\mathrm{z},t)$. The *w*-EIT was performed in the *in-vivo* experiment for four different healthy subjects to measure the time-difference conductivity distribution $\Delta\gamma(r,\theta,t)$ resulted from the ion transport in SAT that induced by applying external compressive pressure $-P$ to the human calf boundary. The present *in-vivo* method was proved to be safe for the human body. The $\mathcal{K}$ was estimated by using an iterative curve-fitting between the normalized ion concentration distribution $\hat{c}_{mod}$ predicted from *pe*-MTM and the experimental normalized ion concentration distribution $\hat{c}_{exp}$ derived from *w*-EIT. The present *in-vivo* method successfully estimated hydraulic permeability $\mathcal{K}$ in SAT by applying a curve-fitting technique between $\hat{c}_{mod}(\tilde{r},L,t)$ and the experimental $\langle\hat{c}_{ex}\rangle(\tilde{r},t)$ at $(\theta = \theta_1,\theta_2,\theta_3)$ derived by *w*-EIT for four different healthy subjects with the value of $\mathcal{K}$ range from 1.45-1.63 × 10^{-11} m s^{-1} Pa^{-1}. This result was comparable to most soft tissues published in the literature. The comparison was made between the $\mathcal{K}$ that was estimated from this

method to the $\mathcal{K}$ of the animal's soft tissue (primarily mammals). Most soft tissues $\mathcal{K}$ have a value in the range of 1-10 × 10^{-11} m s^{-1} Pa^{-1}. Moreover, the hard tissues $\mathcal{K}$, such as bone and cartilage, have a value below 1 × 10^{-10} m s^{-1} Pa^{-1} [10]. The estimated $\mathcal{K}$ of human SAT is not so different compared to other tissues in the range of 10^{-11} m s^{-1} Pa^{-1}. Similar tissue can be found in the mice subcutaneous tissue with the value of $\mathcal{K}$ of mice subcutaneous tissue is less than $\mathcal{K}$ of human SAT [11]. The sensitivity of three constant dominant parameters (Young modulus of adipose cells matrix E_c; Poisson`s ratio of adipose cells matrix v_s; and SAT porosity ϕ) with ±20% variations were discussed on the estimated $\mathcal{K}$, showed a minor influence on the estimated value of $\mathcal{K}$ with the variation of $\mathcal{K}$ no larger than 10% for all healthy subjects.

- Chapter 5:

In this chapter, viscoelastic properties of human subcutaneous adipose tissue (SAT), which are shear modulus of SAT G_v and relaxation time of SAT τ_v is estimated by integrating poroviscoelastic-mass transport model (*pve*-MTM) into *w*-EIT under the influence of external compressive pressure $-P$ with maximum pressure P_{max} = 50 mmHg (6,666.1 Pa); 80 mmHg (10,665.8 Pa); and 120 mmHg (15,998.7 Pa). The *w*-EIT was performed in the *in-vivo* experiment for three different healthy subjects (S_1, S_2, and S_3) and to measure the time-difference conductivity distribution $\Delta\gamma(x, y, t)$ resulted from the ion transport in SAT. Based on the integration, G_v and τ_v are estimated by applying an iterative curve-fitting between the normalized average ion concentration distribution $\langle\hat{c}_{mod}\rangle(t)$ predicted from *pve*-MTM and the experimental normalized average ion concentration distribution $\langle\hat{c}_{exp}\rangle(t)$ derived from *w*-EIT. The estimated value of G_v and τ_v are 4.9±0.2 (S_1), 5.2±0.2 (S_2), 6.3±0.3 (S_3) kPa and 38.50±3.70 (S_1), 27.50±2.60 (S_2), 30.50±3.20 (S_3) s, respectively, with the value of average goodness-of-fit curve fitting R^2> 0.76. These value of G_v and τ_v were compared to the human and animal tissue from the literature to verify this method. There is a similarity in mechanical properties between animal and human tissue, even though they are anatomically different [12], [13]. The mechanical properties (elastic and viscous properties) of animal tissue with a similar value to the human tissue can predict the stress or strain distribution as same as conducting a human experiment directly. We observed that G_v values range from 0.21 to 30 kPa which are still in the range of the literature data [14]. Generally, our present study estimates the value of G_v that is acceptable among the literatures. In terms of τ_v, the closest value of SAT is within the range of the rat subcutaneous tissue (τ_v = 3.83-30.15 s) [15] and the rat dorsal skin (τ_v = 6.3 s). The value of τ_v for porcine subdermal fat range from 115 – 564 s which are vary widely as it is highly

dependent on the loading condition in the measurement test. The τ_v of mice subcutaneous tissue [16] and human adipose tissue [17] is not available due to different testing methods and viscoelastic models. Even though the results from the present study is in the range of variation value of the literature, this comparison is only a brief verification since there are so many aspects that should be consider. At least, this present study provides a piece of new knowledge for future research toward establishing an *in-vivo* method to assess human SAT viscoelastic parameters that are still limited in number [14].

The response characteristic of $\hat{c}_{mod}(t)$ to the variation of G_v and τ_v provide evidence that G_v and τ_v plays a role in the numerical solution of *pve*-MTM. When the value of $\hat{\tau}_v$ increase, there is a time delay of the increase of $\langle \hat{c}_{mod} \rangle$. Contrarily, for the lower value of $\hat{\tau}_v$, the time-dependent characteristic of $\langle \hat{c}_{mod} \rangle$ is close to the pressure profile $-P(t)$. For a case that the value of $\hat{\tau}_v$ close to zero, the reduced relaxation function $\Gamma(t)$ only consist of G_d and the time dependant viscous stress tensor $\boldsymbol{\sigma}_v$ disappear [14]. It means that the SAT is reduced only to poroelastic media. The value of $\hat{G}_v$ affect on the viscous stress tensor contribution $\boldsymbol{\sigma}_v$ to the total stress $\boldsymbol{\sigma} = \boldsymbol{\sigma}_v + \boldsymbol{\sigma}_e$. The decrease of $\hat{G}_v$ reduces the value of $\boldsymbol{\sigma}_v$ because the value of $\Gamma(t)$ become smaller .

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