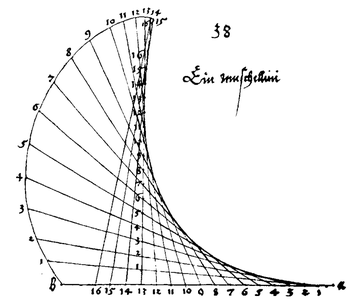
Modelling and Simulation of Corneocyte Swelling: A Theoretical Contribution on the Barrier Properties of the Skin



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Abstract

In transient finite dose experiments, one typically observes not only uptake of substance, but also a considerable swelling of the corneocyte cells. In this study, we present mathematical models describing this. (i) In a first step, we assume a quasi-static configuration. This means that one assumes different time-scales for permeation of water and substance, which allows decoupling these processes. (ii) In a second step, we remove this assumption and describe a transient fully coupled process. For both models we present and discuss results of numerical simulations.

Static Swelling Model

This swelling model is based on a tetrakaidekahedral cell morphology that was suggested for transport in the stratum corneum (SC) earlier [1]. Cells consist of corneocytes C embedded in a matrix of lipid bilayers L. Any cell configuration $(C, L) =: \mathcal{C} = \mathcal{C}(a, h, w, \theta)$ is uniquely defined by a set of four geometric parameters: edge length a, height h, width w, and lipid channel thickness θ:

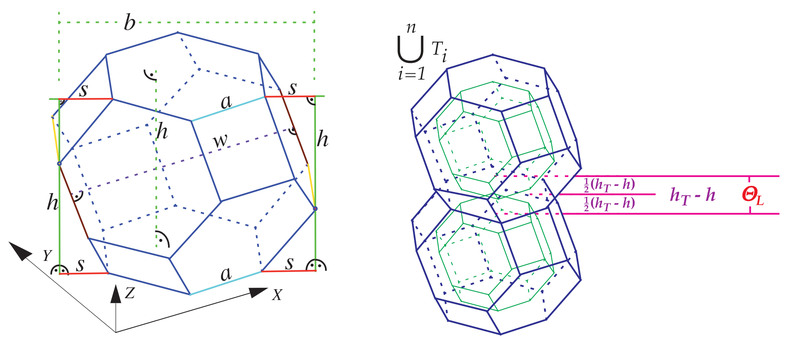

Figure 1: Tetrakaidekahedron representing corneocyte cell $C = C(a, h, w)$ (left). When cells are stacked, they are surrounded by a lipid bilayer $L \equiv L(C, \theta)$ of thickness θ.

Let $\mathcal{C}_0 := (C_0, L_0)$ denote an initial cell configuration. Given that the corneocyte volume changes by a factor $0 \leq \alpha$, we assume that the resulting configuration of the new cell $(C, L) = \mathcal{C} = \mathcal{C}(\alpha)$ is subject to the following contraints:

a) The corneocyte volume decreases/increases by a factor α:

$$V(C) = \alpha V(C_0) \tag{1a}$$

b) The volume of the lipid bilayer remains constant:

$$V(L) = V(L_0) \tag{1b}$$

c) The area of the cornified envelope remains constant:

$$A(\partial L \cap \partial C) = A(\partial L_0 \cap \partial C_0) \tag{1c}$$

Here, $V(X)$ and $A(S)$ denote the *volume* of X and the *surface area* of a surface S respectively.

Suppose, that water uptake can be described explicitly by a differential equation w.r.t. the time variable t:

$$\dot{\alpha}(t) = f(\alpha), \alpha(0) = 1 \tag{2}$$

Then, by means of (1), the cell configuration $\mathcal{C} = (C, L)$ is also a function of time $\mathcal{C} = \mathcal{C}(t, \mathcal{C}_0)$. The barrier properties of such a deformed membrane can be computed as described in [1].

Results

1. For the sake of simplicity, let us assume a gradual constant increase in volume ($f = 1$). Solving (1)-(2) for $\mathcal{C}_0$ defined by $a_0 = 14.7\mu m$, $h_0 = 1\mu m$, $w_0 = 30\mu m$, $\theta_0 = 0.1\mu m$ yields the following results:

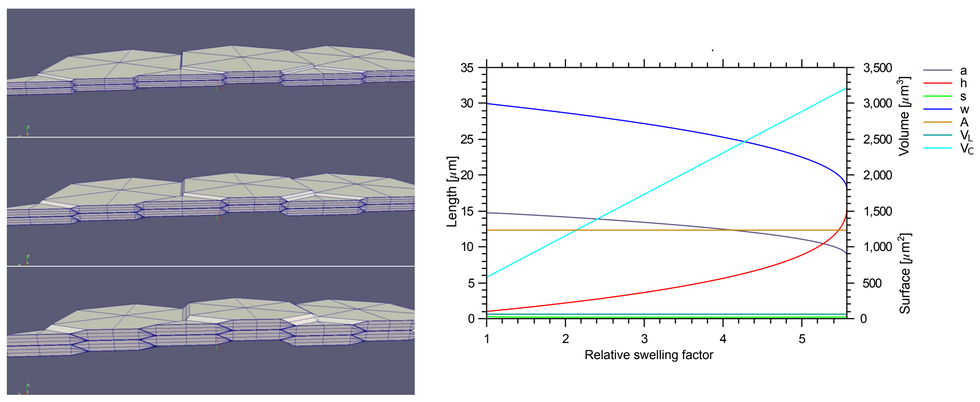

Figure 2: Illustration of a swelling membrane (left), and corresponding analysis of geometric parameters (right). Note: Vertical swelling is predominant in this case.

2. Depending on $\mathcal{C}_0$, the constraints in (1) also restrict the potential deformations:

$$0 \leq \alpha_{\text{min}}(C_0, L_0) \leq \alpha \leq \alpha_{\text{max}}(C_0, L_0).$$

Figure 3 illustrates this for $\mathcal{C}_0 = \mathcal{C}_0(a_0, h_0, w_0, \theta_0)$ with parameters as above, but with variable edge length a_0.

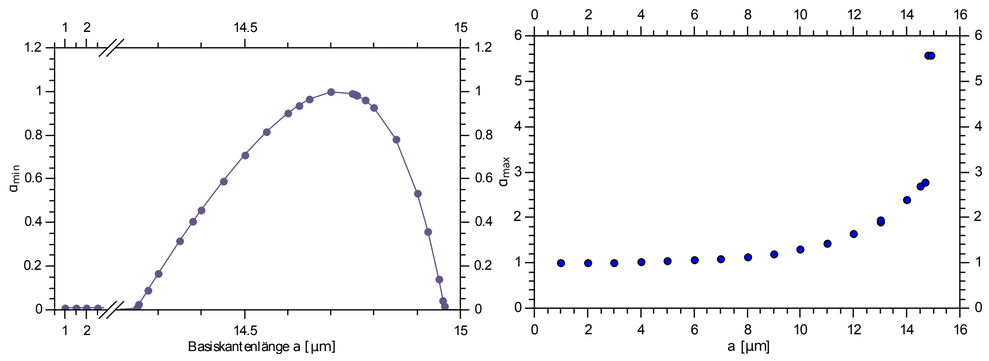

Figure 3: Minimum volume decrease (*shrinking*, left), maximum volume increase (*swelling*, right).

Dynamic Swelling Model

For this model, we assume that the corneocytes (and thus the SC as a whole), behave like a hydrogel. Employing mixture theory, the constituents are a fluid phase f (consisting, e.g., of water in the corneocytes, lipids etc), and a solid phase s (consisting of structural elements such as keratin filaments). Numerous swelling models have been suggested earlier; here, we use an extension of a four-phasic model suggested in [2]. For small strains (small deformations) the model reads as follows:

$$\text{Momentum of mixture}: \quad \nabla[\sigma - pI] - F\Phi_f(z_0c_0 + \sum_i z_i c_i)\nabla\Psi = 0 \tag{3a}$$

$$\text{Mass of mixture}: \quad \partial_t(\nabla \cdot \vec{u}) + \nabla \cdot [-\Phi_f \kappa(\nabla p + \frac{F}{RT}(\sum_i z_i c_i)\nabla\Psi)] = 0 \tag{3b}$$

$$\text{Mass of component } i: \quad \partial_t(\Phi_f c_i) + \nabla \cdot [-\Phi_f D_i(\nabla c_i + c_i \frac{z_i F}{RT}\nabla\Psi)] = 0 \tag{3c}$$

$$\text{Charges}: \quad \nabla \cdot [-\epsilon\epsilon_0\nabla\Psi] = F(z_0c_0 + \sum_i z_i c_i) \tag{3d}$$

The primary unknowns are the (gradient of the) *pressure* p, the *deformation of the solid matrix* $\vec{u}$, the *concentrations* c_i of substances, and the *electric potential* Ψ. Substance i may be charged as indicated by corresponding valence z_i. Charges fixed to the solid phase are regarded as a material property, and are expressed by a concentration c_0 (relative to the volume of the fluid phase), and valence z_0. Additional constants are the ion diffusivities D_i, the Faraday constant $F \approx 96485.33\ C/\text{mol}$, the gas constant $R = 8.3144\ \frac{J}{\text{mol}K}$, and the temperature T.

System (3) will be solved in a simplified form: First, let us assume an electrostatic equilibrium:

$$z_0c_0 + \sum_i z_i c_i \approx 0.$$

Second, if no gradient in the electric potential is applied across the membrane, the system reduces to the quasi-static Biot equation. Third, we assume that the stresses σ are isotropic and given by the linear elastic law:

$$\sigma = \lambda tr(\epsilon)I + 2\mu\epsilon, \ \epsilon_{ij} = \frac{1}{2}\left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i}\right)$$

Results

The simplified problem is a first step and allows studying interactions between pressure p and deformation $\vec{u}$ as illustrated in Figure 4:

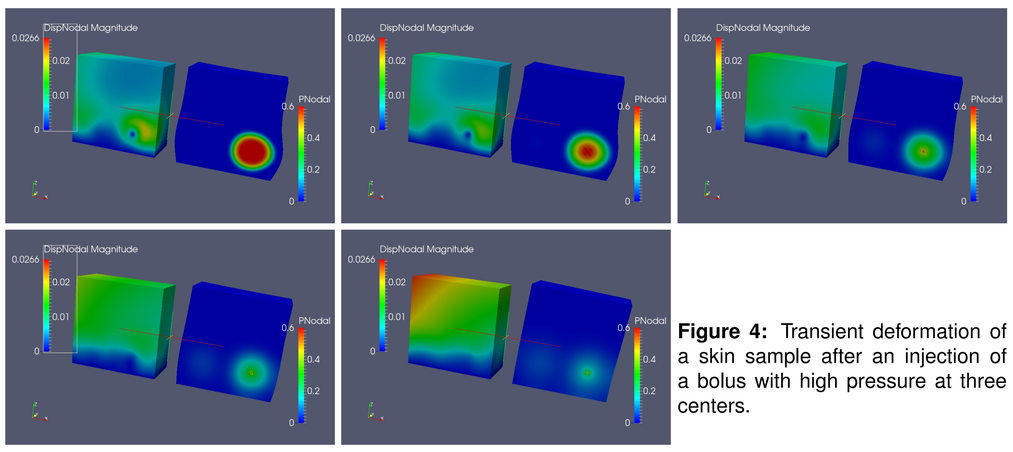

Figure 4: Transient deformation of a skin sample after an injection of a bolus with high pressure at three centers.

Conclusions

- Presented two models for swelling of corneocytes. Substance transport is treated independently (static model) or included implicitly (dynamic model).
- The **static model** is purely based on geometric considerations such conservation of volume and surface. Swelling must be added explicitly, e.g., by (2).
- Depending on the geometric configuration of the cell, the maximum increase in volume observed is 300-600 %. This is consistent with [3, 4]. However, for some configurations, the increase in volume is limited.
- The **dynamic model** is based on mixture theory and models the skin as a hydrogel. This approach yields a description that is consistent with thermodynamics. Although the static model induces a homogeneous swelling, Eqns. (2) and (3b) reveal the similiarity between both models.

Forthcoming Research

- Extend the implementation of (3) to finite strains (large deformations).
- Comparison with experimental data, e.g., for non-trivial potential gradients.
- Include non-isotropic material properties for stresses as well as for diffusion coefficients.

References

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