Mathematical modeling of clearing liquid penetration into the skin

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ABSTRACT

The mathematical model of clearing agent penetration at topical administration of the agent on skin surface has been developed. Two-dimensional plane case has been considered. Skin was presented as multilayer medium with different diffusion coefficients in each layer and boundary conditions between adjacent layers. Analytical solution of the boundary problem has been obtained and approximation for large time interval has been derived.

Keywords: clearing agent, skin penetration, diffusion, mathematical model

1. INTRODUCTION

Over the last decade, non-invasive or minimally invasive spectroscopy and imaging techniques have witnessed widespread exciting applications in biomedical diagnostics.[1] The main limitations of the majority of the imaging techniques, including OCT and near-infrared (NIR) spectroscopy deal with the strong light scattering in superficial tissues, which causes decrease of spatial resolution, low contrast, and small penetration depth. Solution of the problem, i.e. reducing light scattering, and thus improving image quality and precision of spectroscopic information, can be connected with control of tissue optical properties. The tissue scattering properties can be significantly changed due to action of osmotically active immersion liquids, for example, glucose. The aqueous glucose solutions were used for optical clearing of skin, sclera, dura mater, etc.[2] Two techniques are used in the experiments to deliver liquid into the skin: intradermal injection and topical administration on skin surface. In this paper we consider later technique.

After administration of liquid on a skin surface, liquid starts to penetrate into skin. The skin represents as a tissue consisting of many layers, which differ by diffusion coefficients, a porosity, etc. (Fig. 1). Almost each of these layers, in turn, consists of several cell layers. It causes a necessity to construct a diffusion model for modeling of liquid penetration through a tissue with the arbitrary number of layers. At typical experimental conditions the transverse dimensions of the application area are great enough, so it was possible to neglect boundaries influence on processes in the central part, and amount of liquid on skin surface is great enough to consider it as stationary during the long time interval. The layers can penetrate smoothly enough one in other (as, for example, in dermis), or can be separated by thin layers with a small permeability (for example, basal membrane).

2. MATHEMATICAL MODEL

2.1. Preliminary description

The considered problem is completely similar to a problem of thermal conduction in multilayer solids. Let there be a flat multilayer medium, homogeneous in a transverse direction then it is possible to consider a one-dimensional problem. On the upper boundary of the uppermost layer ($j = 1$) there is a liquid layer with a stationary concentration. The boundary conditions of 1-st or 3-rd type (if stratum corneum is considered as "membrane" between liquid and the lower epidermal layers) are possible. Coordinate system we choose is shown in Fig. 2. Here a_j ($j = 1,2, \dots N+1$) – coordinates of the j-th layer upper boundary. Concentration of liquid U as functions of coordinate z and time t is determined as a solution of a diffusion equation in each layer, which is described by diffusion coefficient D_j. On the borders between adjacent layers one of two types (see below) of coupling conditions is satisfied, conforming to presence or lack of “interlaminar membranes”. On the lower boundary of the lowermost layer ($j = N$) some variants of boundary conditions also are

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possible: a) in the following (N+1) layer liquid concentration is constant (mostly equal to zero) – boundary conditions are similar to those at $a_j = a_1$; b) the boundary is impenetrable for liquid – the flux on boundary is equal to zero (a boundary condition of the second type); c) the liquid penetrates in indefinitely thick layer; d) lowermost considered layer is indefinitely thick (see recent paper[3]). In this work the last two cases are not considered.

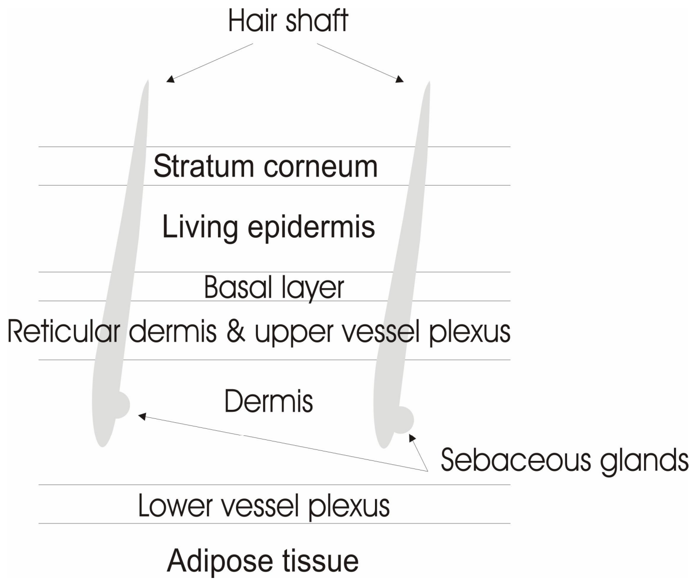

Fig. 1. Scheme of skin layers (from [2]). Thickness of the layers: stratum corneum – 20 μm; living epidermis – 100 μm; basal layer – 15 μm; reticular dermis & upper vessel plexus – 200 μm; dermis – 1500 μm; lower vessel plexus – 100 μm; adipose tissue – 3000 μm.

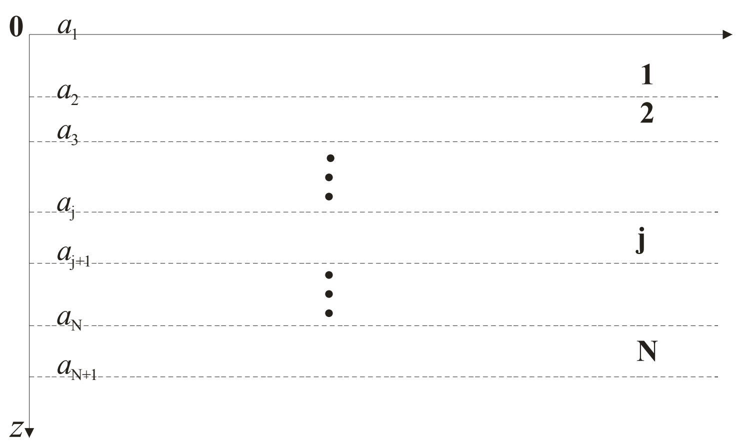

Fig. 2. System of axes and layers positions of model

2.2. Boundary problem

Let

$$U(z,t) = U_j(z,t), \quad \text{if} \quad a_j \le z \le a_{j+1}$$

Then the boundary problem consists of:

Diffusion equation

$$\frac{\partial U_j(z,t)}{\partial t} = \delta_j^2 \frac{\partial^2 U_j(z,t)}{\partial z^2}, \quad \delta_j^2 = D_j, \quad j = 1 \ldots N \tag{2.1}$$

Boundary conditions

$$\begin{aligned} \delta_1^2 \left.\frac{\partial U_1(z,t)}{\partial z}\right|_{z=a_1} &= -\kappa_{1,0}\left(U_0(a_1) - U_1(a_1,t)\right), \\ \delta_N^2 \left.\frac{\partial U_N(z,t)}{\partial z}\right|_{z=a_{N+1}} &= \kappa_{N+1,N}\left(U_0(a_{N+1}) - U_N(a_{N+1},t)\right) \end{aligned} \tag{2.2}$$

Were $U_0(a_1)$, $U_0(a_{N+1})$ – (stationary) concentrations of liquid out of considered layers; $\kappa_{j+1,j}$ – permeability coefficient of boundary between *j*-th and *j*+1-th layers.

Coupling conditions on the borders between adjacent internal layers

$$\begin{aligned} \delta_{j+1}^2 \left.\frac{\partial U_{j+1}(z,t)}{\partial z}\right|_{z=a_{j+1}} &= -\kappa_{j+1,j}\left(U_j(a_{j+1},t) - U_{j+1}(a_{j+1},t)\right), \\ \delta_{j+1}^2 \left.\frac{\partial U_{j+1}(z,t)}{\partial z}\right|_{z=a_{j+1}} &= \delta_j^2 \left.\frac{\partial U_j(z,t)}{\partial z}\right|_{z=a_{j+1}} \end{aligned} \tag{2.3}$$

If $\kappa_{j+1,j} \to \infty$ the first equation from (2.3) transforms into continuity condition of concentration at the boundary of the layers.

Initial conditions

$$\left.U(z,t)\right|_{t=0} = 0, \quad \text{при} \quad a_1 \le z \le a_{N+1} \tag{2.4}$$

3. SOLUTION OF THE BOUNDARY PROBLEM

We shall look for solution in the form:

$$\begin{aligned} &U(z,t) = V(z,t) + W(z), \quad U_j(z,t) = V_j(z,t) + W_j(z), \\ &W_j(z) = A_{0j} + A_{1j} z, \end{aligned} \tag{3.1}$$

where $W_j(z)$ – stationary solution of boundary problem, satisfying non-homogeneous boundary conditions; $V_j(z,t)$ – non-stationary solution of boundary problem, satisfying homogeneous boundary conditions.
For $W_j(z)$ we have:

$$\left.\delta_{j+1}^2 \frac{dW_{j+1}(z)}{dz}\right|_{z=a_{j+1}} = -\kappa_{j+1,j}\left(W_j\left(a_{j+1}\right) - W_{j+1}\left(a_{j+1}\right)\right),$$
$$\left.\delta_{j+1}^2 \frac{dW_{j+1}(z)}{dz}\right|_{z=a_{j+1}} = \left.\delta_j^2 \frac{dW_j(z)}{dz}\right|_{z=a_{j+1}},$$

$$\begin{pmatrix} A_{0\,j+1} \\ A_{1\,j+1} \end{pmatrix} = \begin{pmatrix} a_{j+1}\left(1 - \frac{\delta_j^2}{\delta_{j+1}^2} + \frac{\delta_j^2}{\kappa_{j+1,j} a_{j+1}}\right) & 1 \\ \frac{\delta_j^2}{\delta_{j+1}^2} & 0 \end{pmatrix} \begin{pmatrix} A_{0\,j} \\ A_{1\,j} \end{pmatrix}, \tag{3.2}$$

and

$$A_{0N} = \left[C_1 + \sum_{k=2}^{N-1}\left(\frac{\delta_k^2}{\delta_{k+1}^2} C_k\right)\right] A_{11} + A_{01}, \quad A_{1N} = \frac{\delta_1^2}{\delta_N^2} A_{11}$$
$$C_k = a_{k+1}\left(1 - \frac{\delta_k^2}{\delta_{k+1}^2} + \frac{\delta_k^2}{\kappa_{k+1,k} a_{k+1}}\right). \tag{3.3}$$

From boundary conditions

$$\left.\delta_1^2 \frac{dW_1(z)}{dz}\right|_{z=a_1} = -\kappa_{1,0}\left(U_0\left(a_1\right) - W_1\left(a_1, t\right)\right),$$
$$\left.\delta_N^2 \frac{dW_N(z)}{dz}\right|_{z=a_{N+1}} = \kappa_{N+1,N}\left(U_0\left(a_{N+1}\right) - W_N\left(a_{N+1}, t\right)\right),$$

and

$$\begin{pmatrix} A_{01} \\ A_{11} \end{pmatrix} = \frac{1}{\kappa_{N+1,N}\left(\kappa_{1,0} a_1 - \delta_1^2\right) - \kappa_{1,0} Z_1} \begin{pmatrix} \kappa_{N+1,N} U_0\left(a_{N+1}\right)\left(\kappa_{1,0} a_1 - \delta_1^2\right) - \kappa_{1,0} Z_1 U_0\left(a_1\right) \\ \kappa_{N+1,N}\kappa_{1,0}\left(U_0\left(a_1\right) - U_0\left(a_{N+1}\right)\right) \end{pmatrix}$$
$$Z_1 = \delta_1^2 + \kappa_{N+1,N}\left\{\frac{\delta_1^2}{\delta_N^2} a_{N+1} + \left[C_1 + \sum_{k=2}^{N-1}\left(\frac{\delta_k^2}{\delta_{k+1}^2} C_k\right)\right]\right\}, \tag{3.4}$$

For $V_j(z,t)$ we have:

$$\begin{aligned}
&\delta_1^2 \frac{\partial V_1(z,t)}{\partial z}\bigg|_{z=a_1} - \kappa_{1,0} V_1(a_1,t) = 0, \\
&\delta_{j+1}^2 \frac{\partial V_{j+1}(z,t)}{\partial z}\bigg|_{z=a_{j+1}} = -\kappa_{j+1,j}\left(V_j(a_{j+1},t) - V_{j+1}(a_{j+1},t)\right), \\
&\delta_{j+1}^2 \frac{\partial V_{j+1}(z,t)}{\partial z}\bigg|_{z=a_{j+1}} = \delta_j^2 \frac{\partial V_j(z,t)}{\partial z}\bigg|_{z=a_{j+1}} . \\
&\delta_N^2 \frac{\partial V_N(z,t)}{\partial z}\bigg|_{z=a_{N+1}} + \kappa_{N+1,N} V_N(a_{N+1},t) = 0
\end{aligned} \tag{3.5}$$

$$V(z,t)\big|_{t=0} = -W(z), \quad V_j(z,t)\big|_{t=0} = -W_j(z)$$

We shall look for solution in Fourie series form:

$$\begin{aligned}
&V(z,t) = \sum_{n=0}^{\infty}\left(S_n v_n(z) e^{-\lambda_n t}\right), \\
&v_n(z) = v_{jn}(z) = \alpha_{jn}\sin(\mu_{jn} z) + \beta_{jn}\cos(\mu_{jn} z), \quad \text{при} \quad a_j \le z \le a_{j+1} \\
&S_n = -\frac{1}{|v_n|^2}\sum_{j=1}^{N}\left(\int_{a_j}^{a_{j+1}} v_{jn}(z) W_j(z)\,dz\right), \quad |v_n|^2 = \sum_{j=1}^{N}\left(\int_{a_j}^{a_{j+1}} v^2{}_{jn}(z)\,dz\right)
\end{aligned} \tag{3.6}$$

From diffusion equation and coupling conditions we have:

$$\mu_{jn} = \frac{\sqrt{\lambda_n}}{\delta_j}, \quad \begin{pmatrix}\alpha_{j+1,n} \\ \beta_{j+1,n}\end{pmatrix} = \hat{M}_j(\mu_{1n})\begin{pmatrix}\alpha_{jn} \\ \beta_{jn}\end{pmatrix} \tag{3.7}$$

$$\hat{M}_j(\mu_{1n}) = \frac{1}{2}\frac{\delta_j}{\delta_1}\begin{pmatrix} D_{jn}^{+}\cos(\varphi_{jn}^{+}) + D_{jn}^{-}\cos(\varphi_{jn}^{-}) & D_{jn}^{+}\sin(\varphi_{jn}^{+}) + D_{jn}^{-}\sin(\varphi_{jn}^{-}) \\ D_{jn}^{+}\sin(\varphi_{jn}^{+}) - D_{jn}^{-}\sin(\varphi_{jn}^{-}) & D_{jn}^{-}\cos(\varphi_{jn}^{-}) - D_{jn}^{+}\cos(\varphi_{jn}^{+}) \end{pmatrix}$$

$$\delta_j^{\pm} = \frac{\delta_1}{\delta_j}\left(1 \pm \frac{\delta_j}{\delta_{j+1}}\right) \qquad D_{jn}^{\pm} = \sqrt{\left(\delta_j^{\mp}\right)^2 + \left(\frac{\delta_1^2\mu_{1n}}{\kappa_{j+1,j}}\right)^2} \qquad \varphi_{jn}^{\pm} = \delta_j^{\pm}\mu_{1n}a_{j+1} + \tan^{-1}\left(\frac{\delta_1^2\mu_{1n}}{\delta_j^{\mp}\kappa_{j+1,j}}\right) \tag{3.8}$$

and

$$\begin{pmatrix}\alpha_{Nn}\\ \beta_{Nn}\end{pmatrix}=\hat{M}_{\Sigma}\left(\mu_{1n}\right)\begin{pmatrix}\alpha_{1n}\\ \beta_{1n}\end{pmatrix}$$

$$\hat{M}_{\Sigma}\left(\mu_{1n}\right)=\prod_{j=1}^{N-1}\hat{M}_{j}\left(\mu_{1n}\right)\equiv\begin{pmatrix}M_{\Sigma}\left(\mu_{1n}\right)_{11} & M_{\Sigma}\left(\mu_{1n}\right)_{12}\\ M_{\Sigma}\left(\mu_{1n}\right)_{21} & M_{\Sigma}\left(\mu_{1n}\right)_{22}\end{pmatrix} \tag{3.9}$$

From this equation and boundary conditions we have for α_{1n}, β_{1n} a homogeneous system of linear algebraic equations, which has the following condition for nontrivial solution existence:

$$\begin{aligned}&\left(T_{Nn}\delta_{N}\delta_{1}\mu_{1n}-\kappa_{N+1,N}\right)\left(\delta_{1}^{2}\mu_{1n}-T_{1n}\kappa_{1,0}\right)M_{\Sigma}\left(\mu_{1n}\right)_{11}\\&+\left(T_{Nn}\delta_{N}\delta_{1}\mu_{1n}-\kappa_{N+1,N}\right)\left(\delta_{1}^{2}\mu_{1n}T_{1n}+\kappa_{1,0}\right)M_{\Sigma}\left(\mu_{1n}\right)_{12}\\&+\left(T_{Nn}\kappa_{N+1,N}+\delta_{N}\delta_{1}\mu_{1n}\right)\left(T_{1n}\kappa_{1,0}-\delta_{1}^{2}\mu_{1n}\right)M_{\Sigma}\left(\mu_{1n}\right)_{21}\\&-\left(T_{Nn}\kappa_{N+1,N}+\delta_{N}\delta_{1}\mu_{1n}\right)\left(T_{1n}\delta_{1}^{2}\mu_{1n}+\kappa_{1,0}\right)M_{\Sigma}\left(\mu_{1n}\right)_{22}=0\end{aligned} \tag{3.10}$$

$$T_{1n}=\tan\left(\mu_{1n}a_{1}\right),\quad T_{Nn}=\tan\left(\frac{\delta_{1}}{\delta_{N}}\mu_{1n}a_{N+1}\right)$$

Roots of this equation determine λ_n, and then we can find β_{1n}/α_{1n}:

$$\frac{\beta_{1n}}{\alpha_{1n}}=\frac{\dfrac{\delta_{1}^{2}\mu_{1n}}{\kappa_{1,0}}-\tan\left(\mu_{1n}a_{1}\right)}{\dfrac{\delta_{1}^{2}\mu_{1n}}{\kappa_{1,0}}\tan\left(\mu_{1n}a_{1}\right)+1}, \tag{3.11}$$

which is simplified at $a_1=0$:

$$\frac{\beta_{1n}}{\alpha_{1n}}=\frac{\delta_{1}^{2}\mu_{1n}}{\kappa_{1,0}} \tag{3.12}$$

Finally, we have:

$$\begin{aligned}&V\left(z,t\right)=\sum_{n=0}^{\infty}\left(\tilde{S}_{n}\tilde{v}_{n}\left(z\right)e^{-\lambda_{n}t}\right),\\&\quad\tilde{v}_{n}\left(z\right)=\tilde{v}_{jn}\left(z\right)=\sin\left(\mu_{jn}z\right)+\left(\beta_{jn}/\alpha_{jn}\right)\cos\left(\mu_{jn}z\right),\quad\text{if}\quad a_{j}\le z\le a_{j+1}\end{aligned} \tag{3.13}$$

$$S_n = 2\frac{\sum_{j=1}^{N}\frac{1}{\mu_{jn}}\left[\tilde{v}'_{jn}\left(a_j\right)W_j\left(a_j\right)-\tilde{v}'_{jn}\left(a_{j+1}\right)W_j\left(a_{j+1}\right)+\frac{A_{1j}}{\mu_{jn}}\left(\tilde{v}_{jn}\left(a_{j+1}\right)-\tilde{v}_{jn}\left(a_j\right)\right)\right]}{\sum_{j=1}^{N}\left\{\left[1+\left(\frac{\beta_{jn}}{\alpha_{jn}}\right)^2\right]\left[\left(a_{j+1}-a_j\right)-\frac{1}{\mu_{jn}}\sin\left(\mu_{jn}\left(a_{j+1}-a_j\right)\right)\cos\left(\mu_{jn}\left(a_{j+1}+a_j\right)+2\arctan\left(\frac{\beta_{jn}}{\alpha_{jn}}\right)\right)\right]\right\}}, \tag{3.14}$$

$$\tilde{v}'_{jn}\left(z\right)=\cos\left(\mu_{jn}z\right)-\left(\beta_{jn}/\alpha_{jn}\right)\sin\left(\mu_{jn}z\right)$$

4. CONCLUSION

Analytical solution of the boundary problem for clearing liquid diffusion obtained in this work could be applied for calculation of optical clearing at sufficiently large time intervals. It should be noted that (3.13) is deviation from stationary solution and therefore vanishes at $t \to \infty$. Hence, if t is large enough, one can use only first term of series.

Approximation for short time intervals also is of special interest and will be subject of following work.

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