# Mathematical modeling of clearing liquid drop diffusion after intradermal injection

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## ABSTRACT

The mathematical model of clearing agent diffusion after intradermal injection has been developed. Skin was presented as multilayer medium, but one layer with proper boundary conditions is considered. Analytical solution of the boundary problem for small and large time intervals is obtained.

**Keywords:** clearing agent, 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 first technique.

Let us consider the process of diffusion of glucose in skin dermis, from the moment of the beginning of an injection. It is possible to distinguish four various stages:

- The first one – "inflation" of a drop due to inflow of liquid from a needle (the characteristic time – a few seconds). Following processes take place: a) intercellular liquid is displaced from the volume occupied by a drop; b) the medium enclosing a drop is squeezed due to shift of collagen filaments; c) diffusion of glucose through moving borders of a drop occurred, however it does not play an essential role.
- The second one – interaction of a drop with borders of a dermis and adjacent layers – adipose tissue and basal membrane, since in experiments the maximum diameter of a drop exceeds depth of a derma. At this time drop is deflated slightly in areas near the dermis borders and simultaneously these borders are bulged. In dependence on elastic properties of the next layers and borders between layers, the interrelation of contributions of the indicated effects in the form of a drop varies. As follows from the experimental data, penetration of glucose into the next layers can be neglected. Some qualitative consideration allows assuming that the resulting drop shape will be a full-sphere with a diameter smaller than one of the same-volume-drop in a boundless layering, but larger than initial depth of a dermis. This "dilating" of a dermis, certainly, exists only in a neighbourhood of a drop, but error due to a modification of depth of all layers should not be large. Note, that under indicated requirements the center of a drop "automatically" is disposed precisely in the middle of a layer.
- The third one – a diffusion of glucose from a drop through a layer of a squeezed dermis (the characteristic time – a few minutes). This process can be presented as diffusion through «membrane» with certain permeability. Though this effect can be of great importance, it demands special reviewing and in the given work is not taken into account.
- The fourth one – the free diffusion of a drop in the infinite flat layer (the characteristic time – from dozens of minutes up to a few hours). This stage is a subject of the present paper.

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Saratov Fall Meeting 2006: Optical Technologies in Biophysics and Medicine VIII, edited by
Valery V. Tuchin, Proc. of SPIE Vol. 6535, 65351Z, (2007) · 1605-7422/07/$18 · doi: 10.1117/12.741083

## 2. MATHEMATICAL MODEL

Let us introduce cylindrical coordinate system with origin in drop center at $t = 0$ (beginning with fourth stage, see above), as shown in Fig. 1. Due to axial symmetry, concentration of glucose $U$ has no dependence on angle $\varphi$, hence we well not take into account this variable in mathematical model.

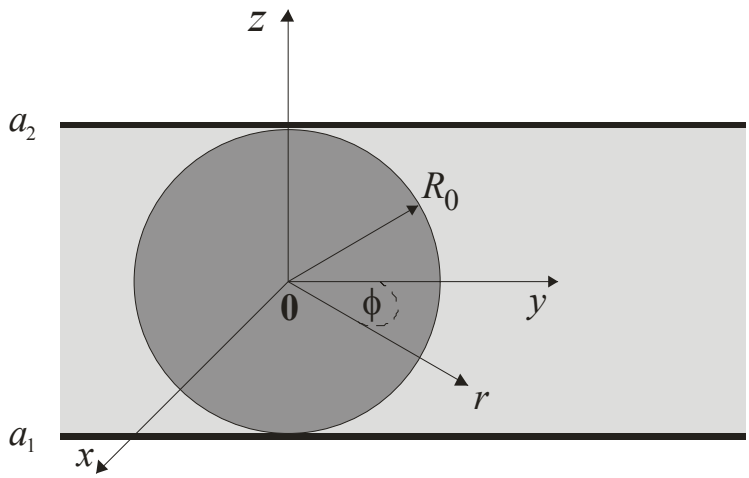


Fig. 1. Coordinate systems and drop position at $t = 0$.
$\{x, y, z\}$ – Cartesian coordinates; $\{r, \varphi, z\}$ – cylindrical coordinates; $R_0$ – initial radius of drop; $a_1 = -a_2$.

Let $U(r,z,t)$ be glucose concentration as function of *r, z* (see Fig. 1) and *t* (time). Then the boundary problem consists of:

**Diffusion equation**

$$\frac{\partial U(r,z,t)}{\partial t} = \delta^2 \left( \frac{\partial^2 U(r,z,t)}{\partial r^2} + \frac{\partial^2 U(r,z,t)}{\partial z^2} \right), \quad \delta^2 = D, \tag{2.1}$$

where $D$ – diffusion coefficient of glucose in dermis;

**Boundary conditions**

$$\left.\frac{\partial U(r,z,t)}{\partial z}\right|_{z=a_1} = 0, \qquad \left.\frac{\partial U(r,z,t)}{\partial z}\right|_{z=a_2} = 0 \qquad 0 \le U(r,z,t)\big|_{r=0} < \infty, \qquad \lim_{r\to\infty} U(r,z,t) = 0 \tag{2.2}$$

**Initial conditions**

$$U(r,z,t)\big|_{t=0} = \begin{cases} U_0, & \text{if} \quad \sqrt{r^2+z^2} \le R_0 \\ 0, & \text{otherwise} \end{cases} \tag{2.3}$$

where $U_0$ – initial (constant) glucose concentration.

The Green function for such type configuration is[3, 4]:

$$G(r,\rho,z,\varsigma,t) = G_r(r,\rho,t)\,G_z(z,\varsigma,t),$$

$$G_r(r,\rho,t) = \rho \exp\left(-\frac{r^2+\rho^2}{4\delta^2 t}\right) I_0\left(\frac{r\rho}{2\delta^2 t}\right)$$

$$G_z(z,\varsigma,t) = \frac{1}{2l\delta^2 t}\left\{1 + 2\sum_{n=1}^{\infty} \cos\left[\frac{\pi n(\varsigma - a_1)}{l}\right] \cos\left[\frac{\pi n(z-a_1)}{l}\right] \exp\left[-\left(\frac{\pi n\delta}{l}\right)^2 t\right]\right\} \tag{2.3}$$

$$l = a_2 - a_1 = 2R_0$$

where $I_0$ – modified Bessel function of zero-order. For small values of $t$ we have another form of $G_z(z,\varsigma,t)$:

$$G_z(z,\varsigma,t) = \frac{1}{4\delta^3\sqrt{\pi t^3}} \sum_{n=-\infty}^{\infty} \left\{\exp\left[-\frac{(z-\varsigma-2nl)^2}{4\delta^2 t}\right] + \exp\left[-\frac{(z+\varsigma-2a_1-2nl)^2}{4\delta^2 t}\right]\right\} \tag{2.4}$$

Thus, one can write solution of boundary problem in following form:

$$U(r,z,t) = U_0 \int_{a_1}^{a_2} G_z(z,\varsigma,t) \left( \int_0^{\sqrt{R_0^2-\varsigma^2}} G_r(r,\rho,t)\,d\rho \right) d\varsigma \tag{2.5}$$

## 3. RESULTS

Let us introduce dimensionless variables and constants:

$$z \to \frac{z}{l}, \quad \varsigma \to \frac{\varsigma}{l}, \quad r \to \frac{r}{l}, \quad \rho \to \frac{\rho}{l}, \quad t \to \left(\frac{\delta}{l}\right)^2 t, \quad U \to \frac{U}{U_0},$$
$$a_1 \to \frac{a_1}{l} = -\frac{1}{2}, \quad a_2 \to \frac{a_2}{l} = \frac{1}{2}, \quad R_0 \to \frac{R_0}{l} = \frac{1}{2} \tag{3.1}$$

These variables were used for our calculations.

Some calculations were made to compare expressions (2.3) and (2.4) for $G_z\left(z,\varsigma,t\right)$. Finally, these expressions give very close values at $0.001 \le t \le 1$.

In Fig. 2 distributions $U\left(r,0,t\right)$ and $U\left(r,0.5,t\right)$ are shown.

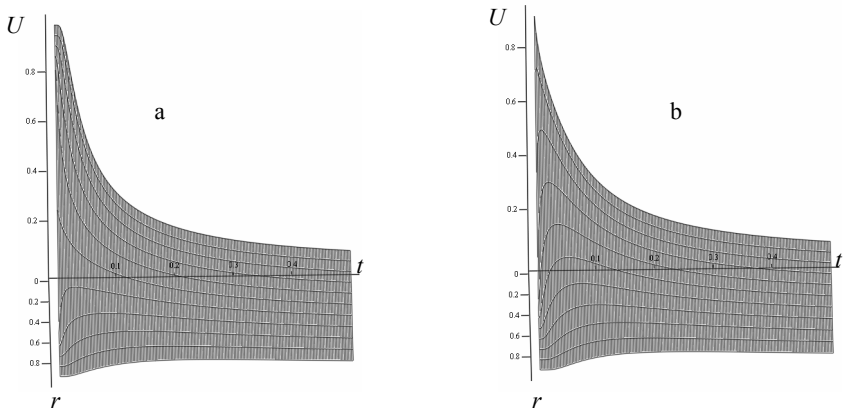


Fig. 2. Dynamics of radial distribution of glucose concentration at fixed $z$.
$0 \le r \le 1$, $0.001 \le t \le 0.5$.
a). $z = 0$; b). $z = 0.5$;

## 4. CONCLUSION

Analytical solution of the 3-dimensional boundary problem for small and large time intervals is obtained. These results can be used for determination of glucose diffusion coefficient in intercellular medium.

## ACKNOWLEDGEMENTS

The research described in this publication has been made possible, in part, by grants PG05-006-2 and REC-006 of U.S. Civilian Research and Development Foundation for the Independent States of the Former Soviet Union (CRDF) and the Russian Ministry of Science and Education, grant of the Russian Federal Agency of Education Russian Federation 1.4.06, and grant of RFBR No. 06-02-16740-a. The authors thank Dr. S.V. Eremina (Department of English and Intercultural Communication of Saratov State University) for the help in manuscript translation to English.

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