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Detailed modeling of skin penetration—An overview ☆

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ABSTRACT

In recent years, the combination of computational modeling and experiments has become a useful tool that is proving increasingly powerful for explaining biological complexity. As computational power is increasing, scientists are able to explore ever more complex models in finer detail and to explain very complex real world data. This work provides an overview of one-, two- and three-dimensional diffusion models for penetration into mammalian skin. Besides diffusive transport this includes also binding of substances to skin proteins and metabolism. These models are based on partial differential equations that describe the spatial evolution of the transport process through the biological barrier skin.
Furthermore, the work focuses on analytical and numerical techniques for this type of equations such as discretization schemes or homogenization (upscaling) techniques. Finally, the work compares different geometry models with respect to the permeability.

Contents

Abbreviations: RW, random walk; LT, Laplace transform; FD, finite difference; FE, finite element; FV, finite volume; IE, implicit Euler; RK, Runge–Kutta method; BDF, backward difference formula; TKD, tetrakaidekahedron; DON, donor; SC, stratum corneum; EPI, Epidermis; DER, Dermis; DSL, Deeper skin layers (viable epidermis/dermis); 1D, one-dimensional; 2D, two-dimensional; 3D, three-dimensional; PDE, partial differential equation; ODE, ordinary differential equation; w.r.t., with respect to.

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1. Introduction

Generally speaking, understanding in science is founded on different columns: The classical columns are theory and experiment. Mathematical modeling and simulation have become a third pillar and are decisive for quantitative understanding. Once set up, model parameters can be modified easily. This allows a hypothesis driven approach by checking scenarios. Often, models allow us to get insight into processes, which cannot be investigated by experiments, such as long-term environmental studies, climate research, etc. In other cases, modeling allows a faster, easier and often cheaper way to get a quantitative understanding of processes. In particular, models based on first principles in combination with advanced numerical methods for partial differential equations as used e.g. in engineering are able to compute processes with full resolution in time and space. This greatly promotes understanding form–function relations, since geometry and dynamics become accessible simultaneously by modeling. Up to now, this approach is quite rarely used in modeling bioprocesses, mainly since the level of mathematics needed to understand and deal with the models and to derive and finally implement numerical solution algorithms is quite high, and abstract and the numerical and computational skills necessary to gain results are quite demanding. On the other hand, novel imaging methods allow us to obtain detailed morphology information, so detailed simulations have a substantial basis.

Classical experiments in the laboratory can only address a few parameters and deliver mosaic information about the whole processes. Mathematical modeling is needed to integrate all these different parameters into a complete model. Combined with modeling and simulation, the experiment takes a new role in validating the model and verifying or falsifying the simulation experiments. The comparison of quantitative results from experiments and simulations can directly be used for adjusting the model. This generates the feedback in the loop of modeling, simulation and experiment. This interplay between modeling, simulation and experiment gives a major push in the quantitative understanding of biomedical systems. An example, where spatially resolved models based on partial differential equations together with advanced numerical simulation methods have been used successfully to get insight into a biological process is penetration into human skin.

Over the last 10–15 years, mathematical modeling and numerical simulation have become even more important for biomedical engineering. Because of the tremendous growth in computational algorithms and science, algorithms, hardware and software, in silico tools are nowadays very attractive to model and simulate biological/chemical/physical processes to replace in vitro and in vivo testing of drugs (e.g. replacing human and animal experiments). In-silico methods are also very helpful to assess the risk of chemical exposures. On the other hand, legal authorities increasingly emphasize product responsibility. Thus, a thorough understanding of a product and its often-complex intertwined links to our life and environment are crucial for the long-term commercial success.

Today, various mathematical models are used to describe skin permeability. Mitragotri et al. [1] recently published a review providing an excellent overview of the state of the art. Most models are physiology based in the sense that they comprise a notion of compartments like skin layers and the vehicle. The first major category is high-resolution pharmacokinetic models, [2], which just describe transport dynamics without spatially resolving the compartments using ordinary differential equations (ODE). The second category is diffusion models, which are based on partial differential equations (PDE). Not only do these methods describe the time evolution of solute concentrations, but also resolve their spatial variations. The methods are derived from first principles, such as balance of mass, and additional assumptions such as Fick's laws of diffusion.

In this work we focus on this second approach, as the related tools and techniques are very general and can be employed in larger contexts as well. We do not elaborate, however, on analytical tools, solutions by Laplace-transform (LT), [3] or on random walk (RW) models [4]. Instead, we describe an approach for detailed modeling, using sophisticated numerical methods for the simulation of the models. Moreover, we comment on homogenization techniques which facilitate the transition, e.g., from a (microscopic) sub-cellular scale to a (macroscopic) membrane scale.

Bridging scales is an important task. For the skin, various one-dimensional (1D) models featuring a variety of effects have been developed. These models have been complemented by a variety of two-dimensional (2D) and three-dimensional (3D) models for the stratum corneum (SC). This heterogeneous membrane in the uppermost part of the epidermis is the main barrier of the skin. Models resolving its geometric structure have the great advantage that the parameters, e.g. diffusion and partition coefficients, are frame-independent and allow frame-independent parameter identification. Therefore, the effects of different parameters like corneocyte permeability, corneocyte alignment, diffusion and partition coefficients, protein binding, etc. on transport through the skin can be studied in-silico. Simulation results then show the relevance and sensitivity of the parameters, leading to a deeper insight into the process and helping to design drugs. By means of this approach, the processes can be studied on different morphologies. These are classical brick-and-mortar (2D), and more advanced (3D) cuboid and tetrakaidekahedral geometries.

This work is organized as follows: In Section 2 we give an introduction to diffusion models for the skin barrier. We define various aspects of the problem and provide mathematical descriptions. Further, homogenization and upscaling are presented. In Section 3 we give an overview of macroscopic models. Here, one-dimensional diffusion models and reduced two-dimensional diffusion models are described. Section 4 is dedicated to microscopic models like detailed two-dimensional and three-dimensional diffusion models. In Section 5 numerical aspects like discretization schemes, computational complexity and adaptivity are presented. A comparison of different SC geometry models is given in Section 6. The last section is devoted to conclusions.

2. Preliminaries on diffusion models

In this section we provide a general overview on the class of diffusion models. After a general description of the effects, we provide a mathematical description. Categorizing the different length scales