Hansen, S., Lehr, C.-M., Schaefer, U.F.
Modeling the human skin barrier-Towards a better understanding of dermal absorption
(2013) Advanced Drug Delivery Reviews, 65 (2), pp. 149-151.

Preface:
Modeling the human skin barrier - Towards a better understanding of dermal absorption

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A variety of compounds gets into contact with our skin every day. Exposure occurs via the application of pharmaceutical products or cosmetics which are designed for topical or transdermal absorption, unintended at work, or through the use of household chemicals. Some compounds may be absorbed or facilitate the absorption of other potentially harmful substances. Nonetheless, the mechanisms involved in dermal absorption are still not well understood. In contrast to other epithelial or mucosal absorption barriers such as the intestines, the lungs, or the blood-brain-barrier the skin is distinguished by its multi-layered structure and the presence of a cornified epithelium of unique lipid composition and structure.
Computational research tools have contributed a great deal to improve our understanding of skin absorption and to elucidate the fate of absorbed compounds. Advances in computational technology enable us to mimic physiology with finer detail and increasing complexity and thus are proving increasingly powerful for explaining biological complexity. Using mathematical models we can simulate influences computationally that we otherwise would not be able to investigate as we lack the microscopic resolution or analytical possibilities required. Simulation studies, and rigorous experimental validation of predictions are necessary and have already been used to separate essential from negligible variables. Among others new insights from physiology based diffusion models led to a paradigm shift concerning the permeability of the cellular phase of the stratum corneum. It is now widely accepted that the corneocytes are not only inert obstacles towards transport. Instead they participate to a great deal in absorption and hold-up of drugs. In other areas the work is still ongoing. This concerns for example aspects of transport within the tissue itself such as

mechanisms of transport across the stratum corneum lipids; the adsorption of permeants to structural and diffusible proteins; influences of hydration; and clearance mechanisms.

The present issue "Modeling the human skin barrier – towards a better understanding of dermal absorption" aims to give an overview of the state of the art computational research tools that are employed for modeling dermal absorption today. Points that will be addressed include an introduction to modeling techniques and mathematical methods, as well as analytical and approximation methods to deduce input parameters. An important focus of this issue will be on the application of such models. Therefore a series of manuscripts will summarize modeling of special skin absorption scenarios such as the absorption from complex, dynamic vehicles applied as finite dose, co-absorption of permeation enhancers or reducers, the absorption of volatile compounds, and iontophoresis-aided permeation.
Thus a vivid picture is obtained underlining the importance of mathematics and computer science as tools to improve our understanding of skin physiology and as expert systems to predict the outcome of absorption processes.

New computational research tools that are capable of coping with physiological variability tend to become increasingly more complex to the expanse of the computational power required, being easy to operate and the readouts being readily understandable. The first two reviews address how our improved understanding of the physical processes which are involved in solute transport and distribution across the skin has improved and how this knowledge is reflected in different mathematical models which integrate these transport processes to yield computational tools for data analysis and prediction (Jepps et al. *"Modeling the human skin barrier - Towards a better understanding of dermal absorption"*; Anissimov et al. *"Mathematical and pharmacokinetic modeling of epidermal and dermal transport"*).
The following papers give a general overview over the mathematical strategies to solve skin absorption problems. Naegel et al. present one-, two-, and three-dimensional diffusion models focusing on mathematical and numerical techniques to solve partial differential equations which are involved in such models. Homogenization methods are outlined which reduce the complexity of multidimensional models (Naegel et al. "*Detailed modeling of skin penetration – an overview*"). Numerical methods, especially different schemes for discretisation are also the focus of the article by Frasch and Barbero (Frasch and Barbero "*Application of numerical methods for diffusion based modeling of skin permeation*").
Dancik et al. then introduce the implementation of a comprehensive transient model of transdermal absorption in a conventional Excel™ spreadsheet which allows to break down the complex skin absorption process and make a complex mathematical framework available for a variety of users (Dancik et al. "*Design and performance of a spreadsheet-based model for estimating bioavailability of chemicals from dermal exposure*").
Notman and Anwar summarize the use of molecular simulation studies for modeling the molecular motions within the stratum corneum lipid bilayers which are responsible for the main barrier function of the skin. Their model presents a different scale of microscopic resolution of the skin absorption process and allows elucidating for example the action of

penetration enhancers on lipid membranes within the stratum corneum (Notman and Anwar "*Breaching the skin barrier – Insights from molecular simulation of model membranes*").
The last set of papers deals with special application problems of diffusion models. The review by Hansen et al. discusses methods to define input parameters for diffusion models (Hansen et al. "*Improved input parameters for diffusion models of skin absorption*"). High quality sufficiently detailed input parameters are the basis to obtain useful predictions from absorption models.
The absorption from complex vehicles is the topic of the review by Karadzkova et al. (Karadzkova et al. "*Predicting skin permeability from complex vehicles*"). They present an extension of quantitative structure-permeation relationship (QSPR) models which are essentially based on linear free energy relationships to predict dermal absorption from complex multi-component formulations.
Selzer et al discuss technical pitfalls when studying finite doses, elaborating on experiment, data evaluation and mathematical treatment (Selzer et al. "*Finite and infinite dosing: Difficulties in measurements, evaluations and predictions*"). Chen et al summarize recent advances in predicting the absorption of hydrophilic solutes (Chen et al. "*Recent advances in predicting skin permeability of hydrophilic solutes*").
Finally, the contributions by Rauma et al. and Gartieri and Kalia treat special topics of dermal exposure predicting the absorption from chemical vapors - a topic that requires attention especially from occupational safety aspects (Rauma et al. "*Predicting the absorption of chemical vapors*"), and iontophoresis-aided absorption (Gratieri and Kalia "*Mathematical models to describe iontophoretic transport in vitor and in vivo and the effect of current application on the skin barrier*").

This compilation of reviews makes clear that while both research and computational power have advanced a great deal within the last decade we have still a long way to go before we can substitute experiments by computations. We realize that under carefully defined conditions (which are often artificial and far away from realistic exposure scenarios) we already hold capable computational solutions in our hands. Thus we can probably predict the absorption of a solute form an aqueous solution applied as an infinite source diffusing across a quasi-homogeneous membrane into a perfect sink with reasonable accuracy today. Moreover, we present herein individual solutions which are adept at solving more specialized problems involved in skin absorption, important features including complex formulations, finite dosing, and physical and chemical enhancement methods among others. A universal model which can take care of all of these problems is still at large.
A topic which has been totally disregarded so far but is nonetheless very relevant is the absorption across diseased skin. The huge variety of skin conditions (form merely a mild irritation or dry skin to severe inflammation, atopic disorders, psoriasis…) which is involved with more or less severe changes in the barrier function, morphology and absorption characteristics is not systematically investigated and will be a big challenge for the future. In the progress it will be important to identify the relevant features of membrane, permeant, and vehicle that have to be integrated ideally into one general theoretical framework.

At the same time we need better and more information on details of the absorption process. Here we are looking forward to upcoming analytical techniques such as chemical fingerprinting coupled with microscopic resolution (fluorescence lifetime imaging, confocal Raman microscopy), and new insights from cryo-electron microscopy on the morphology and architecture of the membrane in their native state to name but a few.
Finally we also need to design user-friendly tools to make them available to a larger group of applicants who are not necessary experts with an extensive mathematical background.

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Cover Figure

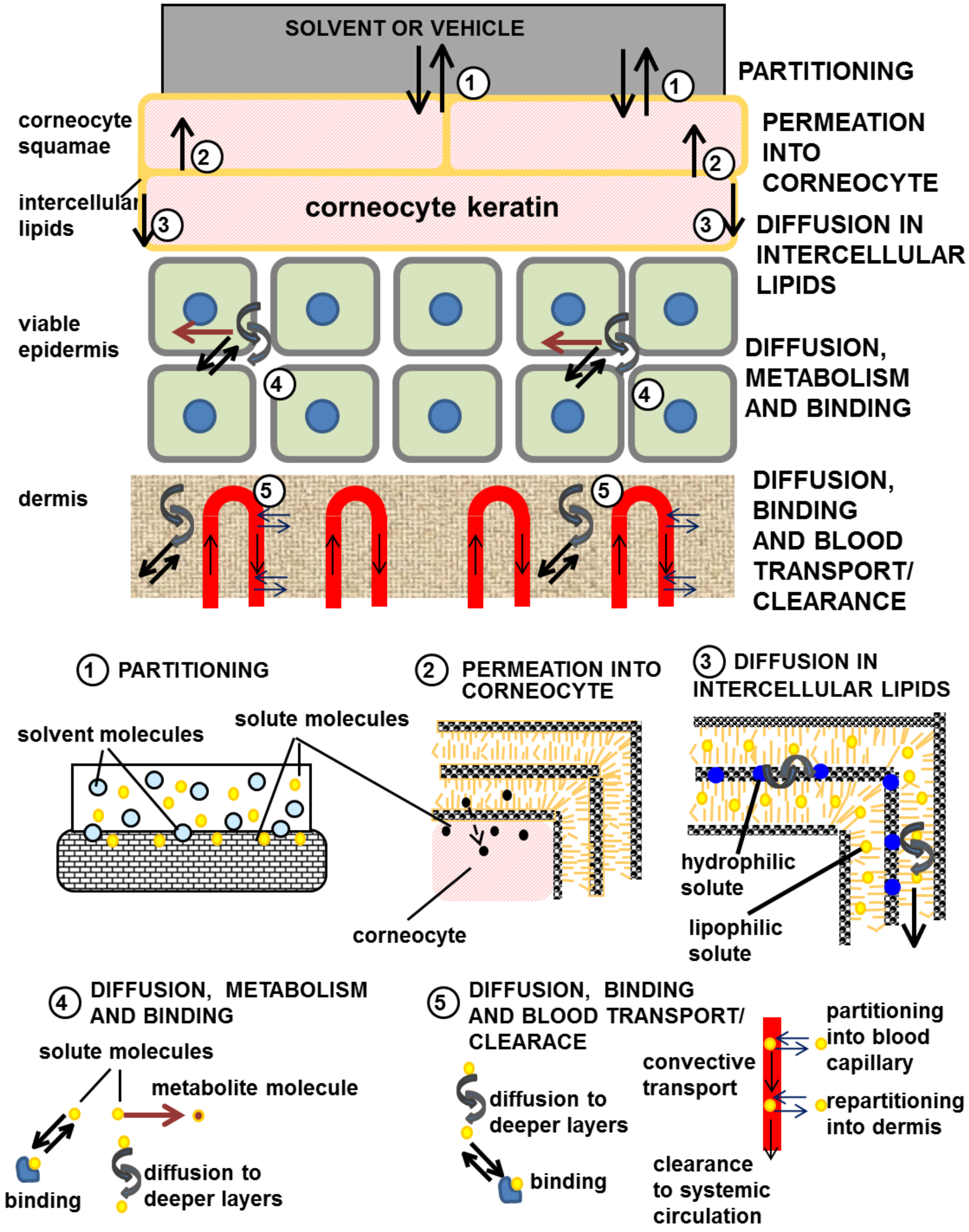

Figure caption: Skin absorption of solutes is a multifactorial process which needs implemented for computational modeling.