Water and solute active transport through human epidermis: Contribution of electromigration

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ABSTRACT

A triphasic, coarse-grained model of mass transport through the human epidermis is developed, consisting of free extracellular water, live cells (keratinocytes), and inert extracellular matrix. The model accounts for the superposition of active transport of Na^+, K^+ and Cl^- ions across the membrane of keratinocytes, and electromigration driven by an externally imposed electrostatic potential difference. Local cell volume is regulated by the transmembrane fluxes of water and ions according to a time-delay scheme which aims to keep the volume between certain thresholds. Numerical simulations reveal that either weak hyposmotic shocks or negative potential gradients smaller than one millivolt/micrometer across the epidermis can generate travelling waves in extracellular ion concentration. By monitoring the transmembrane (Na^+–K^+–ATPase) pump flux, we have found that maintaining a higher transepidermal potential gradient requires faster active transport through the cells.

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1. Introduction

Skin is the largest organ of the body and it helps maintain homeostasis by establishing a chemical and biological barrier between the external environment and the vulnerable human cells. Understanding mass transfer through the skin is important for the clinician, engineer and scientist. More specifically, this understanding contributes to improving the treatment of wounds, the development of better clothes, the synthesis of benign skin care products, and the improvement of thermal comfort. Emerging applications include the control of transepidermal drug delivery through iontophoresis [1], development of tissue-engineered skin [2], and the formulation of treatments for obesity after elucidating the role of aquaporins [3]. Finally, understanding the permselectivity of skin might contribute to the development of bio-inspired ion exchange membranes for water purification [4].

The barrier function of the skin is related to its ultrastructure and physiology [5,6]. Human skin is a complex, multilayered tissue comprising approximately 2 m^2 of body surface and contributing approximately 16% of the body weight of the average adult. The outermost layer of the viable skin, the epidermis, is a constantly renewed stratifying squamous epithelium, varying in thickness from about 50–800 μm, cf. Fig. 1. The basal cells of the epidermis (stratum basale) proliferate and differentiate as they migrate outwards.

Initially columnar, these epidermal cells (keratinocytes) become rounded, and finally flatten out and die (apoptosis) as they migrate to the outer layer, the stratum corneum. This outmost layer is less permeable than the viable layer and its thickness is sensitive to hydration level variation [6]. Below the epidermis and delineated by the corrugated basal membrane lies the dermis, a highly vascular connective tissue tethered by collagen fibers to the subcutaneous areas of the skin which is cushioned by adipose tissue. The contribution of sweat glands and hair to transepidermal transport is outside the scope of this investigation.

The epidermis forms the primary barrier to mass transfer. Its viability relies on bulk diffusion of water and nutrients since it is devoid of any blood circulation. Prior mass transport studies focused only on the stratum corneum which consists of dead cells, and did not consider the deeper layers of the epidermis. In steady state, the stratum corneum has been modelled as a passive barrier of constant (effective) conductance. For example, Kalia et al. [7] fit the transepidermal transport data obtained after consecutive tape stripping to Fickian diffusion models. Such empirical models fail to reproduce the increase of permeability with hydration. Kasting et al. [8] developed a more sophisticated model employing a concentration-dependent diffusivity for water to reconcile theory with experiments.

Ion migration through the skin is ultimately related to an electrostatic potential across the skin, with the skin surface being more negative than the inner layers. There exist very few investigations of this interplay owing to the difficulty of measuring ion concen-

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Nomenclature

A_c	area of cell membrane
c_i	molar concentration of ion i
$\mathbf{D}^*_{mi}$	effective transport coefficient
$\mathbf{D}^{**}$	effective total transport coefficient
F	Faraday constant
J_i	transmembrane flux of ion i, or net ionic pump flux when $i = p$
j^*_i	molar flux of ion i
m_i	number of moles of ion i
P_i	membrane permeability for ion i
Q^*_K	constant for volume induced transmembrane flux, due to KCl cotransporter
Q^*_{Na}	constant for volume induced transmembrane flux, due to NaCl cotransporter
R	universal gas constant
S_{ij}	source term of ion i in phase j
T	temperature
v^+	upper threshold for cell volume
v^-	lower threshold for cell volume
$\mathbf{v}^*_i$	molar velocity vector of phase i
V_m	cell membrane potential
V_c	cell volume

t	time
x	spatial coordinate normal to epidermis
X^-	membrane-impermeable extracellular species with valence -1
z_i	valence of ion i

Greek symbols

Δ	difference operator
ε_o	permittivity of free space
ε	dielectric constant of water
θ_i	volume fraction of phase i
τ	time delay
ϕ_K	transmembrane flux due to KCl cotransporter
ϕ_{Na}	transmembrane flux due to NaCl cotransporter
ψ	electrical potential

Subscripts

i	ionic species
j	phase
α	extracellular fluid phase
β	intracellular fluid phase
γ	extracellular solid phase

tration profiles in the epidermis [9]. In addition to its relevance in iontophoresis, the skin surface electric potential has been widely used for physiological or psychological studies but the mechanism of its generation has not been elucidated. Denda et al. [10] investigated experimentally the interplay between epidermal ion concentration and endogenous skin surface potential in hairless mice skin in organ culture, and suggested that the ion flux through the keratinocyte membrane regulates this potential.

To fill several gaps in the area of physiologically-motivated models of transport through live tissue, the present study focuses on the transport of water and several ionic species across the viable part of the epidermis which is devoid of a *stratum corneum* layer. Water and ion transport through any viable tissue involves transcellular as well as paracellular pathways. Therefore, candidate mass transport models have to account for both local extracellular transport and transmembrane fluxes, the later coupled to cell volume regulation. Fifty years before high resolution images of ion transmembrane channels became available, their role was modeled by the Goldman–Hodgkin–Katz equation, which has been used to correlate intracellular and extracellular concentrations, permeabilities, and membrane potential [11]. Even water transport across cellular membranes is not fully understood. A process of solute–water cotransport is proposed as a possibility, against the so far accepted osmotic transport mechanism [12]. Adding to the multitude of pumps and ion channels, a number of cotransporters coexist in the cell membranes [11]. Animal cell regulation has not been fully described mathematically, since the activation and regulation mechanisms of each independent pathways are not completely known. As a tool to investigate the effects of live cells on mass transport in a tissue, the simplified model proposed by Hernández and Cristina [13] is chosen for the present study. This generic model accounts for the basic components of cell volume regulation, which includes the function of ion channels for sodium, potassium and chloride, the sodium potassium pump, and cotransporters which are activated under stress conditions. As more sophisticated and tissue specific models become available, the various components of the compound model can be simply substituted for the simplified model.

In anticipation of the ultimately integration of water and ion concentration measurements obtained with novel techniques

[14,9] towards explaining the barrier function of the whole epidermis, a realistic model of the tissue as an active, rather than a passive, medium is needed. The emphasis of the present study is to characterize the contribution of electromigration. Specifically, we aim to model the variation of interstitial (extracellular) water and the concentration of three physiologically-relevant solutes (Na^+, K^+ and Cl^- ions) through the viable non-swelling epidermis due to an imposed (exogenous) electric potential difference across the epidermis. We proceed in two steps: first, we develop a polyphasic model including active transport of the three ions through the membrane of the keratinocytes, and second, we use the model to predict of response of the epidermis to osmotic shocks and electrostatic gradient effects.

2. Formulation of polyphasic model for epidermis

The viable epidermis is modeled as a volume-averaged porous medium with three distinct phases: the extracellular fluid phase, denoted by α, the intracellular fluid phase, denoted by β, and the extracellular matrix, denoted by γ. The extracellular fluid phase α contains water, Na^+, K^+ and Cl^- ions, and larger, less mobile molecules which are dissolved in water. The cell membrane is not permeable to these larger molecules, which have a valence of -1 and are collectively referred as component X^- in the model discussed below. The phase β contains water and the same three ions, and all non-water-soluble chemicals are assigned to the γ phase. This decomposition in three phases allows a coarse-grained representation of the tissue. The spatial characteristic scale in the model is larger than the representative elementary volume (REV), which in turn is larger than the scale of a single epidermal cell, as shown in Fig. 2. Given the thickness of the epidermis (x-direction), and in order to maintain separation of spatial scales, the REV is defined as a long prism with its principal axis perpendicular to the x–y plane. The x-coordinate defines the direction normal to the skin and pointing towards the ambient air, while the y-coordinate is tangential to the skin surface. The modeling of each of the three phases is discussed below.