Characterisation of the skin's polar pathway

GB Kasting

The James L. Winkle College of Pharmacy

University of Cincinnati

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Acknowledgements

NIOSH National Institute for Occupational Safety and Health

CDC

THE EUROPEAN COSMETIC TOILETRY AND PERFUMERY ASSOCIATION

In regards to this presentation, the investigators have no conflict of interest to disclose. The conclusions are those of the authors and do not represent the positions of the sponsors of this research.

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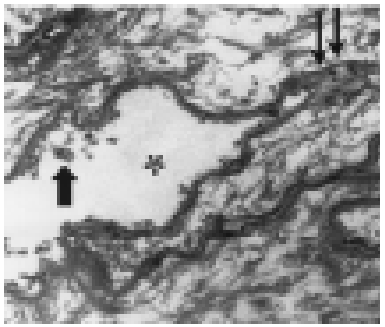
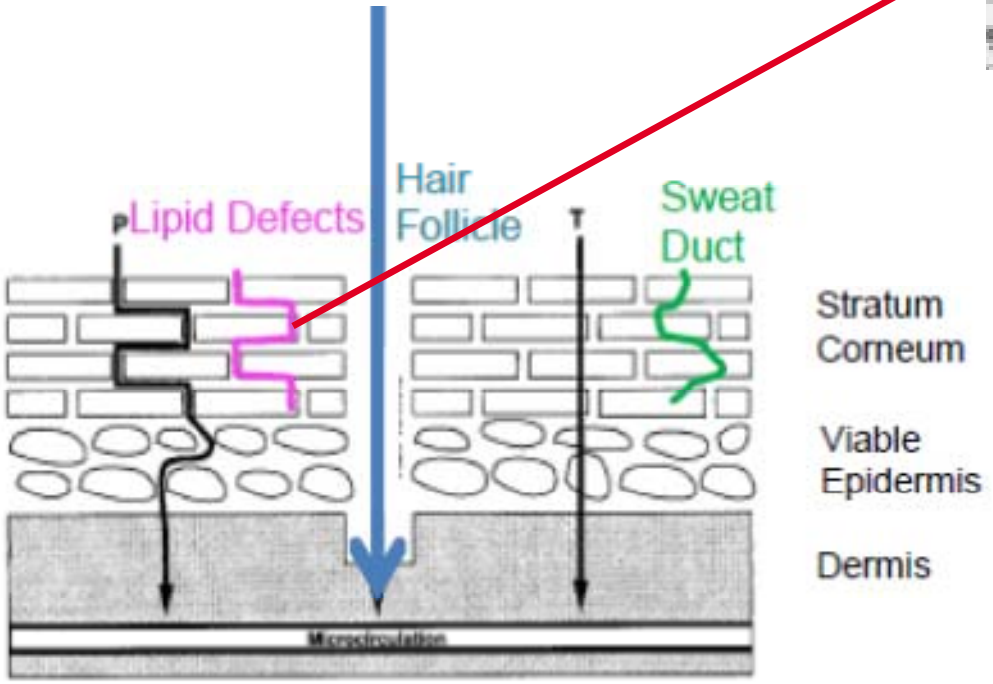
Proposed polar pathways in human stratum corneum





Cullander and Guy, Advanced Drug Delivery Reviews, 1992

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Inset picture: Warner et al., JID, 2003

Why study it?

- Allergic contact dermatitis
  - Metals
  - Hair dyes (cationic)
- Topical and transdermal drug delivery
  - Passive
  - Iontophoresis
  - Sonophoresis

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How this talk is organized

- Polar pathway phenomenology
  - SC electrical properties
  - Temperature dependence of SC permeability
  - Size-selectivity for hydrophilic permeants
  - NMF extraction from the SC
  - Accumulation of charged dyes in the SC
- My concept of what it looks like.
- Alternative hypothesis

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Stratum corneum electrical properties

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Skin resistivity in vivo

5 min exposure in normal saline

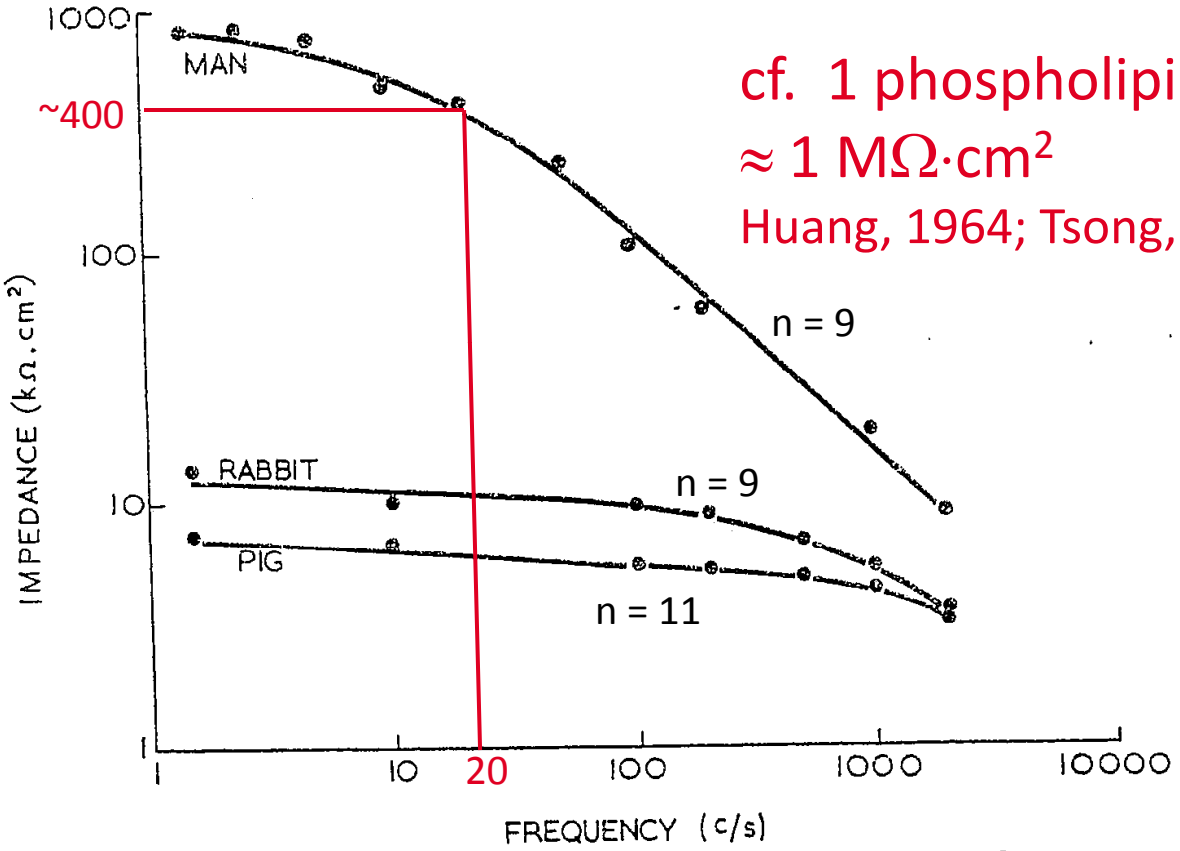


FIG. 24. The impedance of saline-soaked skin related to a.c. frequency.

cf. 1 phospholipid bilayer

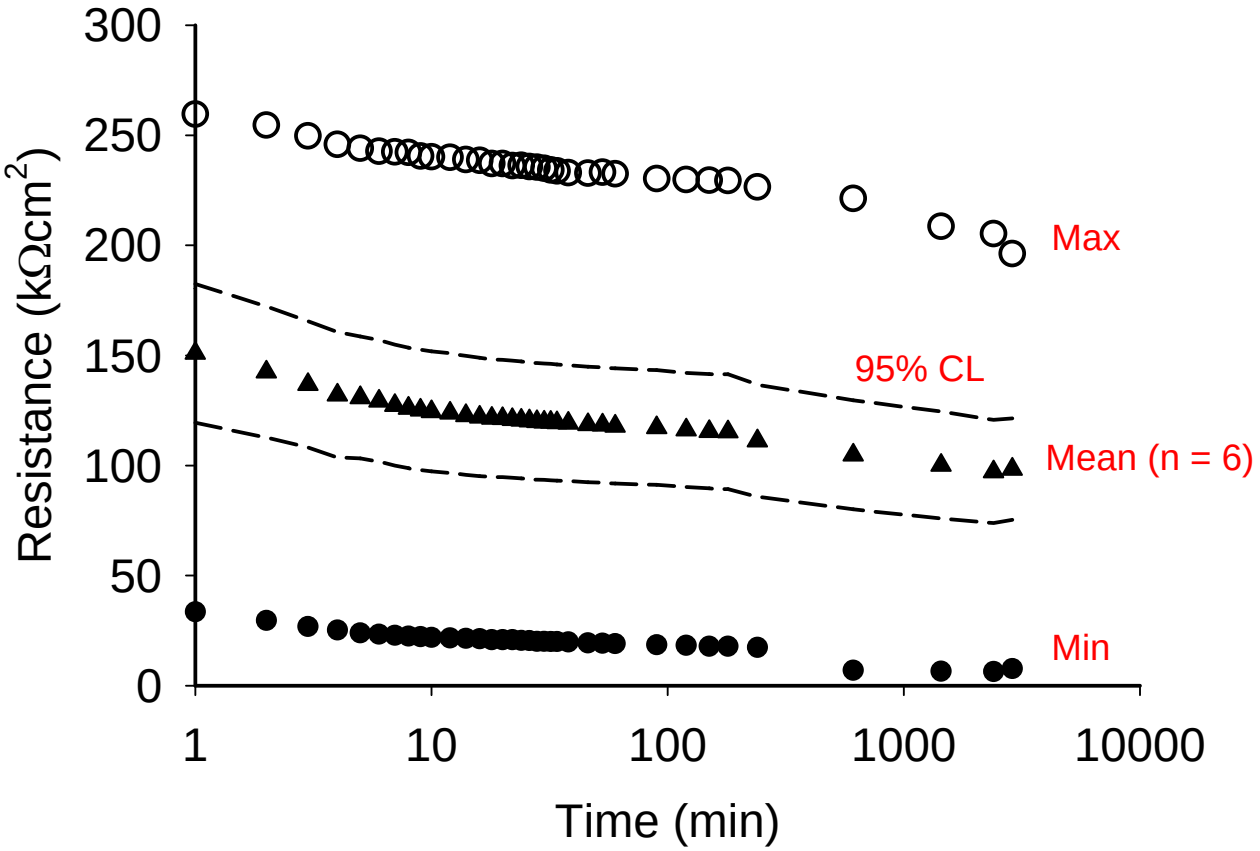
$\approx 1\ M\Omega \cdot cm^2$

Huang, 1964; Tsong, 1991

RT Tregear, *Nature*, 1965

Human skin resistivity in vitro

Time course in normal saline; 20 Hz AC, 7 μA rms

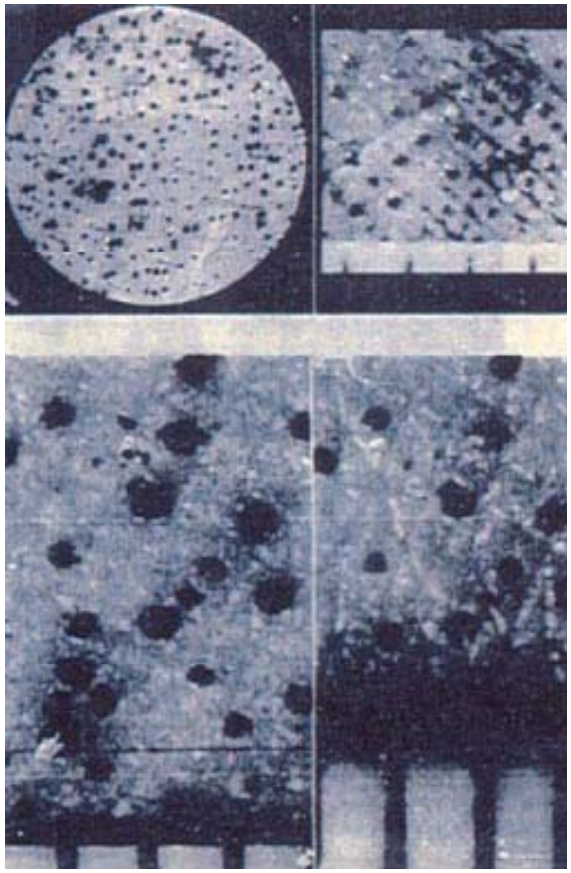


TD LaCount & GB Kasting, *J Pharm Sci*, 2013

Current Pathways in Skin

- Dyes driven electrically into the skin preferentially stain pores and follicles.

HA Abramson and MH Gorin, *J Phys Chem* **44**:1094-1102 (1940).



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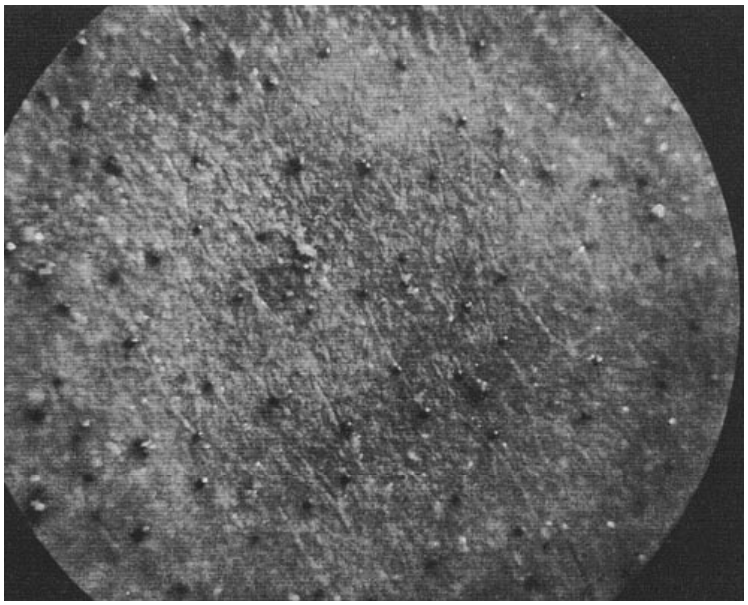
Current pathways, cont.

- Scheuplein (1978) provided an *in vitro* demonstration of this phenomenon.

RJ Scheuplein, in: *The Physiology and Pathophysiology of the Skin, Vol. 5.* Copyright 1978 Academic Press.



$$Fe^{2+} + K_3[Fe(CN)_6] \rightarrow$$

$$2K^+ + KFe_2(CN)_6 \downarrow$$

Prussian blue

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Current pathways, cont.

- Metal foil electrodes placed over the skin can be preferentially etched at the site of ecrine sweat glands.

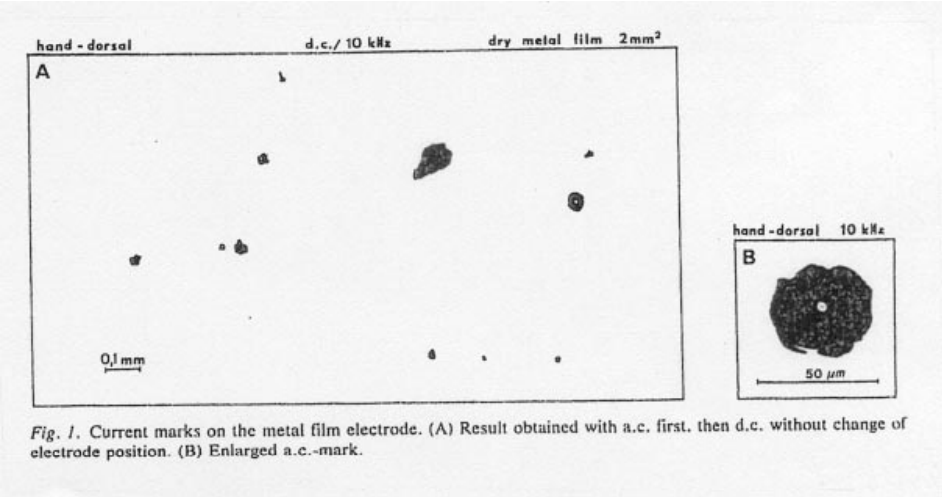

Fig. 1. Current marks on the metal film electrode. (A) Result obtained with a.c. first, then d.c. without change of electrode position. (B) Enlarged a.c.-mark.

S Grimnes, *Acta Derm Venereol* **64**:93-98 (1984).

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Current pathways, cont.

- *In vitro* microelectrode studies have shown high current densities at pores in human skin and hair follicles in rodent skin.

Burnette and Ongpipattanakul, *J Pharm Sci* 77:132-137. See also Cullander and Guy, 1991; Scott et al. 1993.

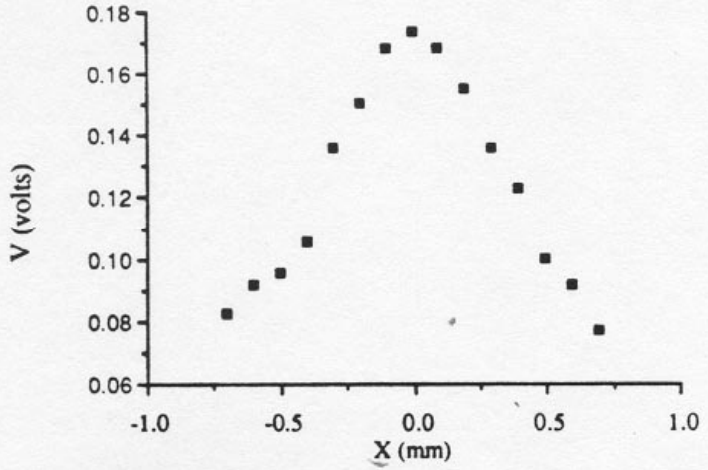

Figure 6—*Plot of voltage difference versus position. Position is relative to the pore with 0 mm representing the center of the pore. The diffusion cell membrane is a piece of parafilm (American Can Company, Greenwich, CT) which has a 0.2-mm hole. The input pulse had an amplitude of 1 V and a duration of 1 s, resulting in a current amplitude of 1.4 μA.*

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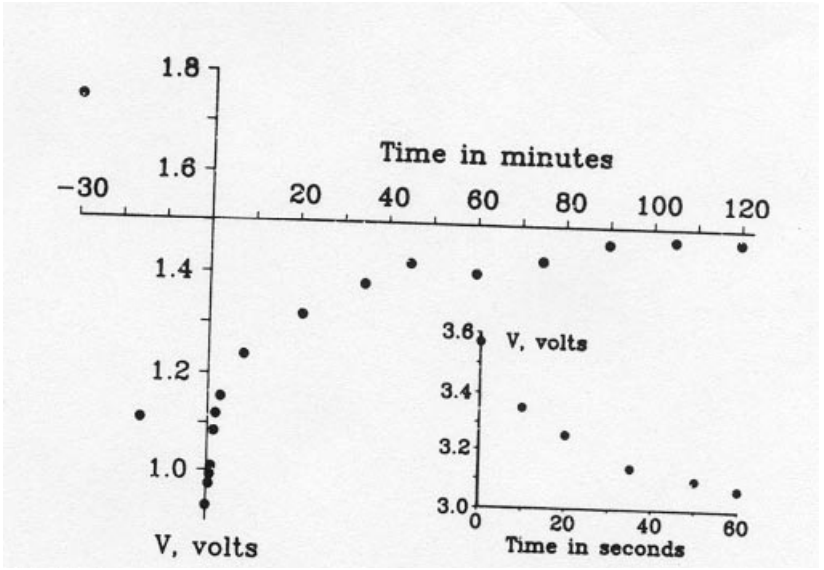
Skin electrical properties

- Electrical resistance of the skin falls rapidly during iontophoretic treatment, then recovers gradually.



GB Kasting and LA Bowman,

Pharm Res **7**:134-143 (1990).

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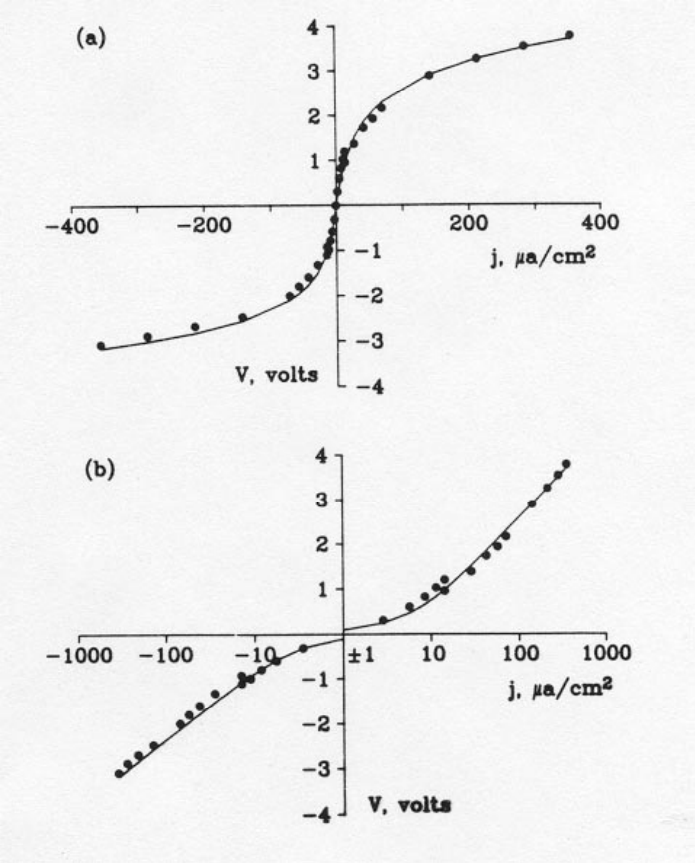
Electrical properties, cont.

- The steady-state current-voltage characteristic is approximately exponential.

GB Kasting and LA Bowman,

Pharm Res **7**:134-143 (1990).



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Temperature dependence of SC permeability

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The Effect of Temperature upon the Permeation of Polar and Ionic Solutes through Human Epidermal Membrane

KENDALL D. PECK[x], ABDEL-HALIM GHANEM, AND WILLIAM I. HIGUCHI

Received December 20, 1994, from the *Department of Pharmaceutics and Pharmaceutical Chemistry, 301 Skaggs Hall, University of Utah, Salt Lake City, UT 84112.* Accepted for publication May 5, 1995[⊗].

Journal of Pharmaceutical Sciences / **975**
Vol. 84, No. 8, August 1995

NOTES

Temperature Dependence of Skin Permeability to Hydrophilic and Hydrophobic Solutes

SAMIR MITRAGOTRI

Department of Chemical Engineering, University of California, Santa Barbara, Santa Barbara, California 93106

Received 28 February 2006; revised 10 May 2006; accepted 6 September 2006

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20793

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Arrhenius plot – urea in HEM

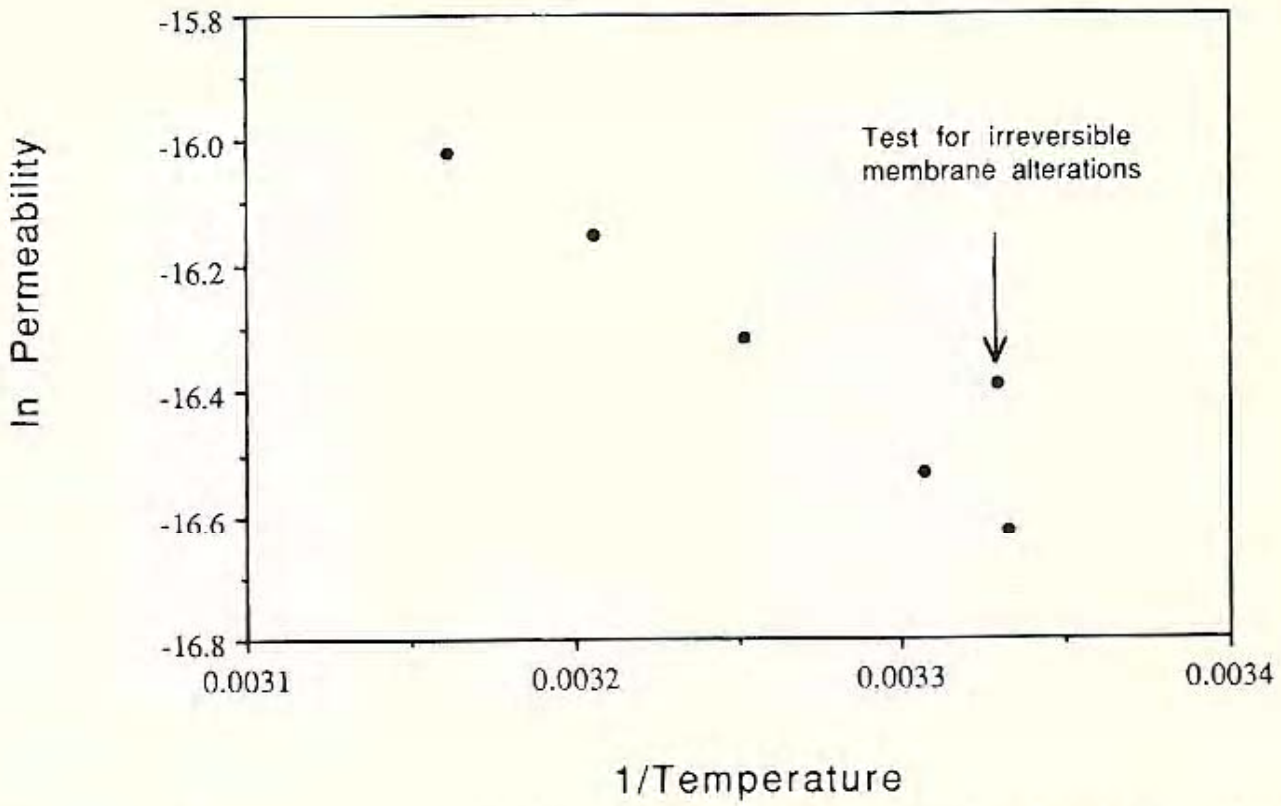

Figure 1—Representative Arrhenius plot of urea data from the five-temperature protocol showing the test for irreversible changes in HEM barrier properties. Units of permeability are cm/s, and the temperature is the absolute temperature.

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Peck et al., 1995

Two-temperature protocol -- urea

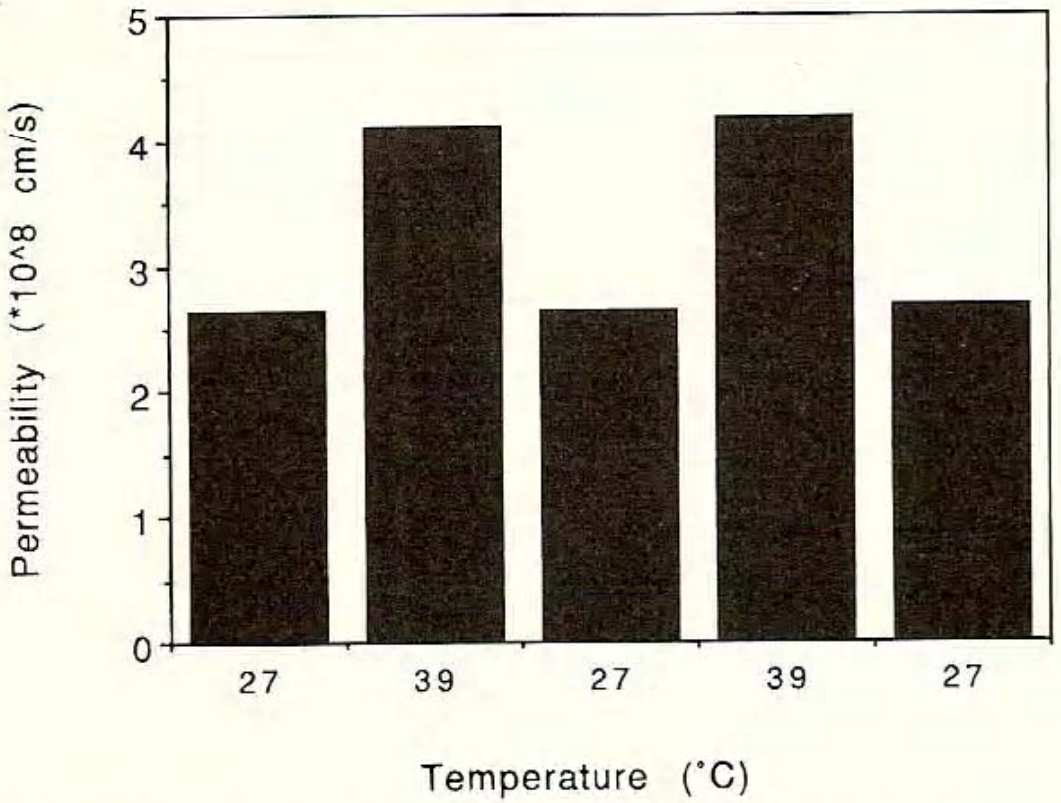

Figure 2—Permeability coefficient results from a representative urea two-temperature experiment. Permeability coefficients were obtained from a single HEM sample and are plotted in the order that they were determined.

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Peck et al., 1995

Two-temperature protocol -- corticosterone

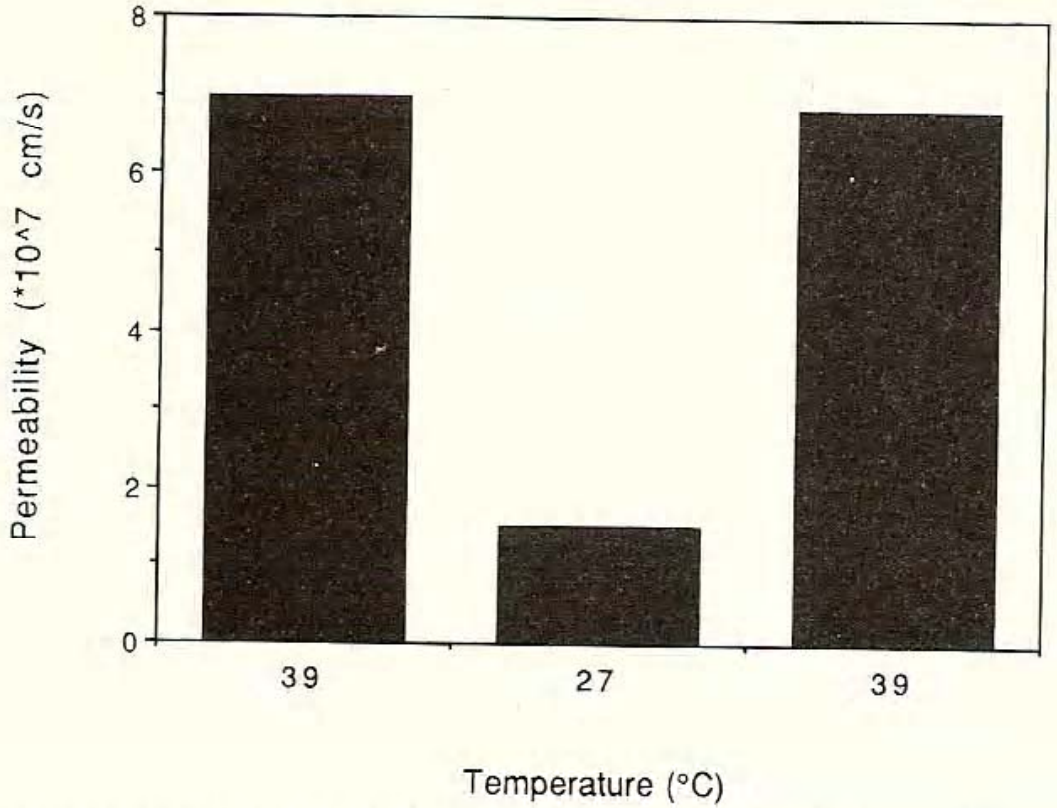

Figure 5—Permeability coefficient results from a representative corticosterone two-temperature experiment. Permeability coefficients were obtained from a single HEM sample and are plotted in the order that they were determined.

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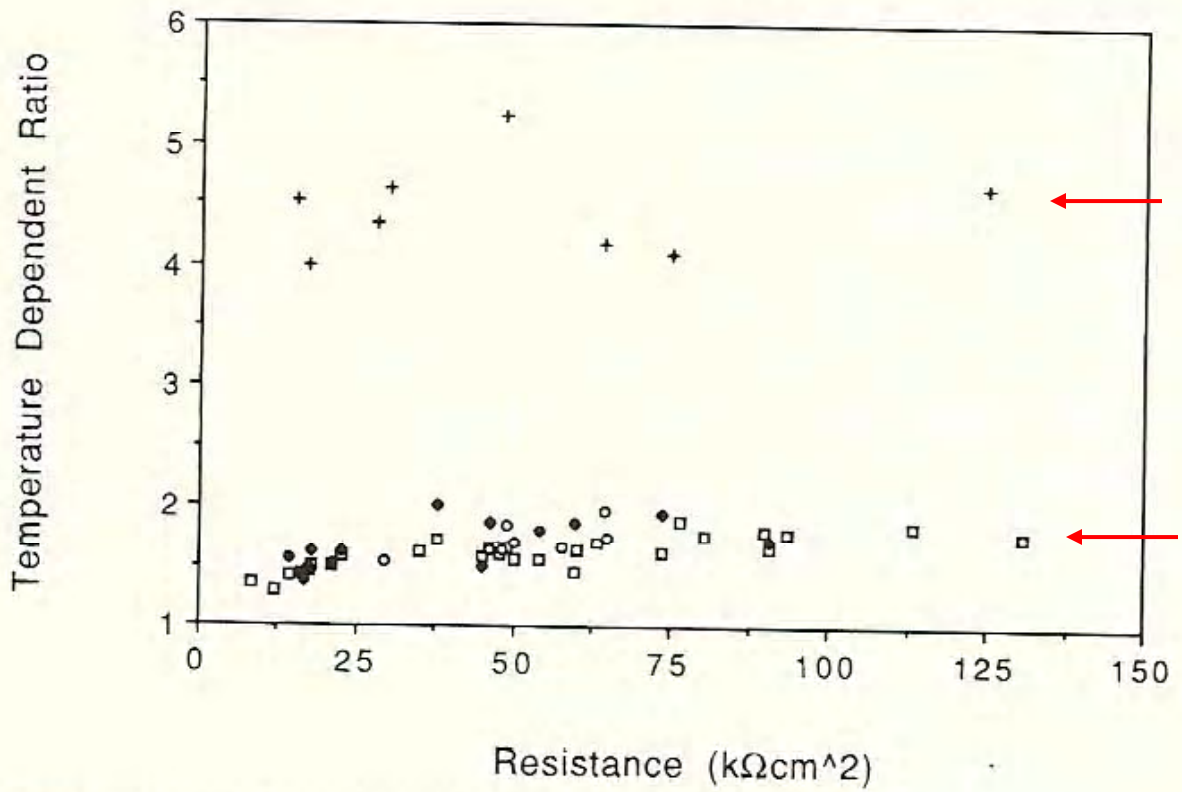
Peck et al., 1995

Permeability ratio vs. skin resistance



corticosterone

urea
mannitol
TEA

Figure 6—Temperature dependent ratios (permeability coefficients measured at 39 °C divided by permeability coefficients measured at 27 °C) from the two-temperature studies for urea (□), mannitol (◆), TEA (○), and corticosterone (+). Each point represents the average of data collected from an individual HEM sample.

Peck et al., 1995

Urea permeability vs. Skin resistance

The slope of this log-log plot is almost –1, supporting that urea traverses a similar pathway to sodium and chloride ions.

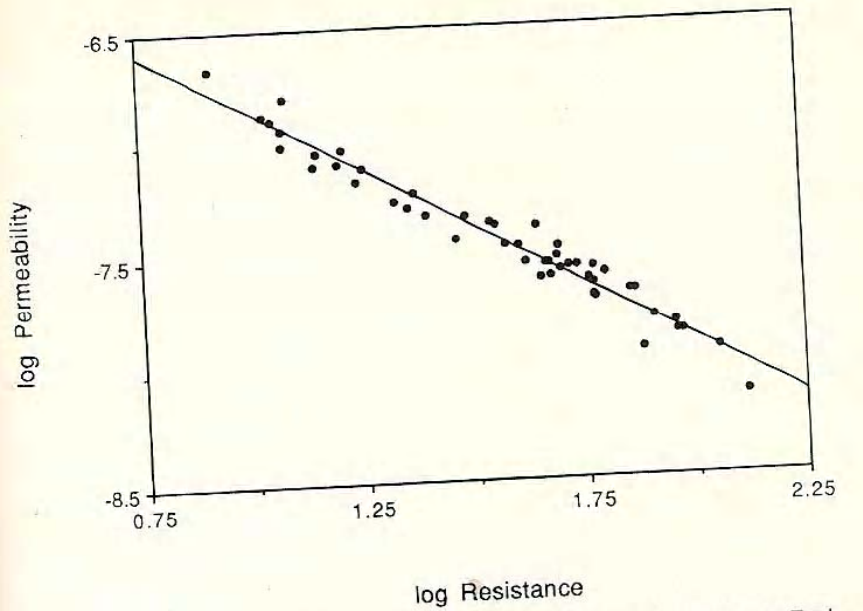


Figure 7—Correlation between urea permeability and electrical resistance. Each point represents the average of data collected at a given temperature for an individual HEM sample. Units of permeability are cm/s, and units of resistance are kΩ cm^2. Slope of the best-fit curve resulting from linear regression is –1.04 ± 0.06 with $r^2 = 0.959$.

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Peck et al., 1995

Size selectivity for hydrophilic permeants

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Pharmaceutical Research, Vol. 11, No. 9, 1994

Hindered Diffusion of Polar Molecules Through and Effective Pore Radii Estimates of Intact and Ethanol Treated Human Epidermal Membrane

Kendall D. Peck,[1,2] Abdel-Halim Ghanem,[1] and William I. Higuchi[1]

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Table I. Permeant Physical Parameters

Permeant	$D * 10^{6}$ [a,b] cm^2/s	r_s(Å)[a]	$D* 10^{6}$ cm^2/s	r_s(Å)
^{14}C-urea	18.5	2.64	17.5 ± 0.4[c]	2.73
^{3}H-mannitol	9.14	4.33	9.03 ± 0.3[c]	4.44
^{14}C-sucrose	6.98	5.55	6.98 ± 0.2[d]	5.55
^{3}H-raffinose	5.81	6.54	5.72 ± 0.1[c]	6.62

[a] Taken from reference 18.
[b] Corrected for temperature and viscosity from 25°C to 37°C.
[c] Average ± standard deviation, n = 5.
[d] Taken from reference 21.

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Peck et al., 1994

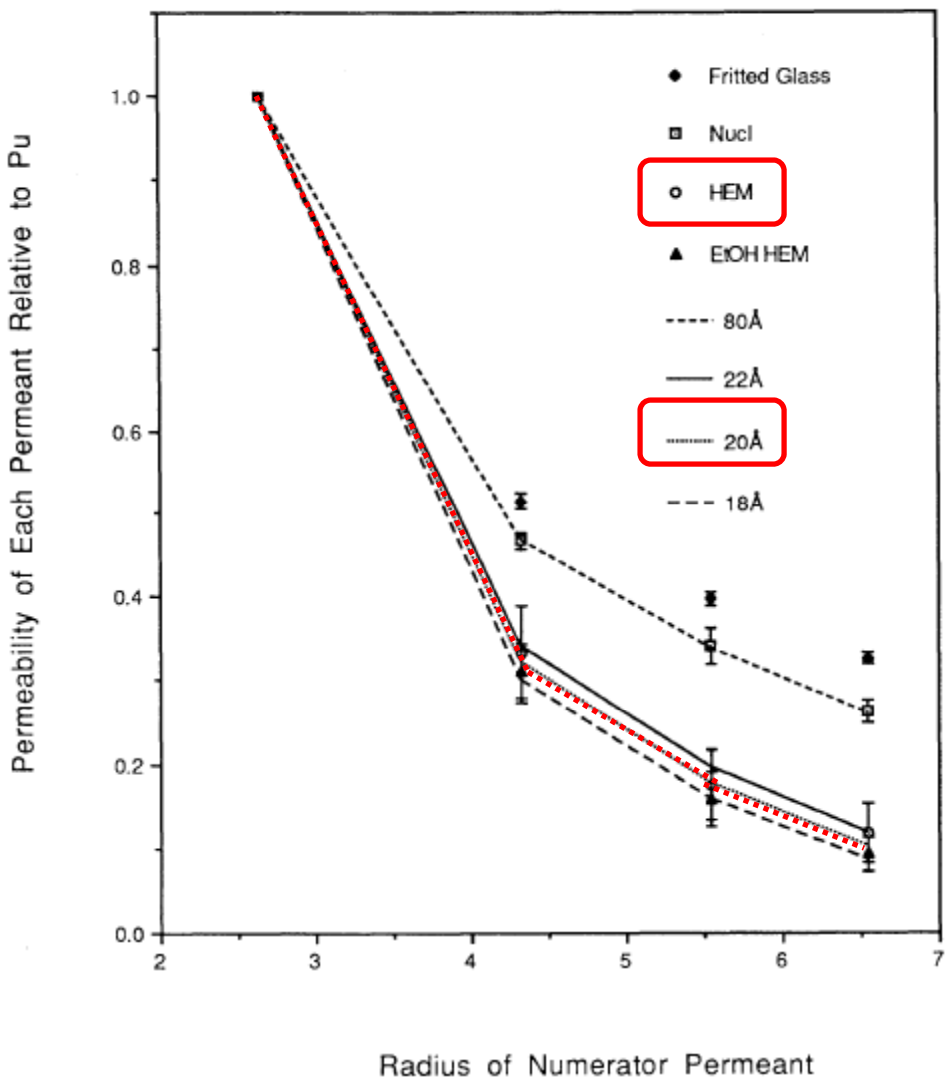

Fig. 6. Relative effect of hindrance for the four membrane systems studied. The superimposed lines correspond to calculated results based upon Eq. (4) and the Rp indicated in the legend.

Peck et al., 1994

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ELSEVIER

Journal of Controlled Release 58 (1999) 323–333

journal of controlled release

An analysis of solute structure–human epidermal transport relationships in epidermal iontophoresis using the ionic mobility: pore model

Pamela M. Lai, Michael S. Roberts*

Department of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane, Queensland 4102, Australia

Received 9 March 1998; accepted 22 September 1998

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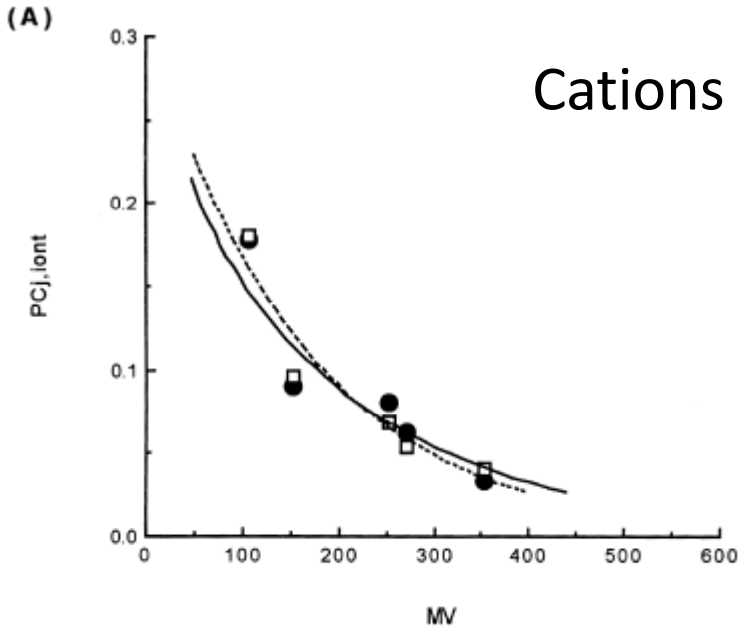
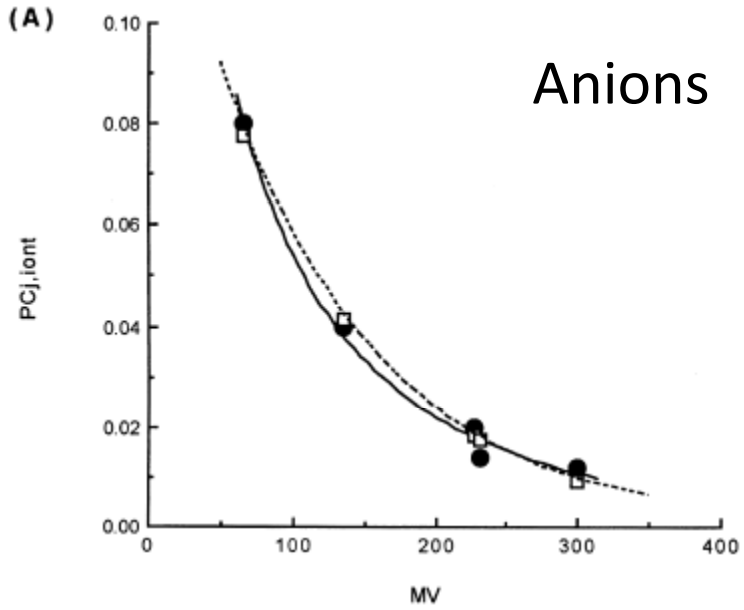
Iontophoretic permeability coefficients versus molecular volume



Cations

Lai and Roberts, 1999

Iontophoretic permeability coefficients versus molecular volume



Anions

Lai and Roberts, 1999

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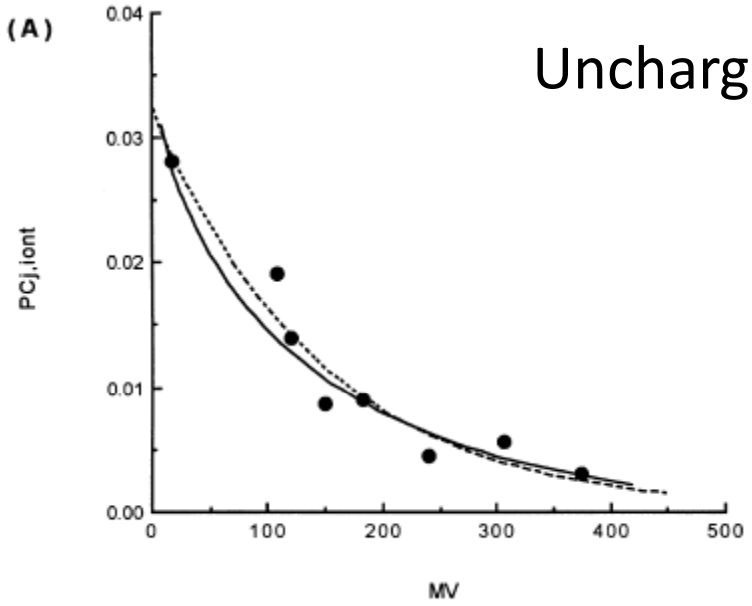
Iontophoretic permeability coefficients versus molecular volume



Uncharged solutes

Lai and Roberts, 1999

RESEARCH ARTICLE

Human Skin is Permselective for the Small, Monovalent Cations Sodium and Potassium but not for Nickel and Chromium

TERRI D. LA COUNT, GERALD B. KASTING

Winkle College of Pharmacy, The University of Cincinnati Academic Health Center, Cincinnati, Ohio

Journal of Pharmaceutical Sciences

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Skin/solution mobility ratio[a]

Salt	$u_{skin}/u_{soln} \times 100$
K^+	2.31
Na^+	2.16
Ni^{2+}	0.99
Cr^{3+}	0.68
Cl^-	1.24
NO_3^-	2.39
SO_4^{2-}	1.52
CrO_4^{2-}	1.04
$Cr_2O_7^{2-}$	1.20

[a]Temperature-adjusted to 32°

LaCount & Kasting, *J Pharm Sci*, 2013

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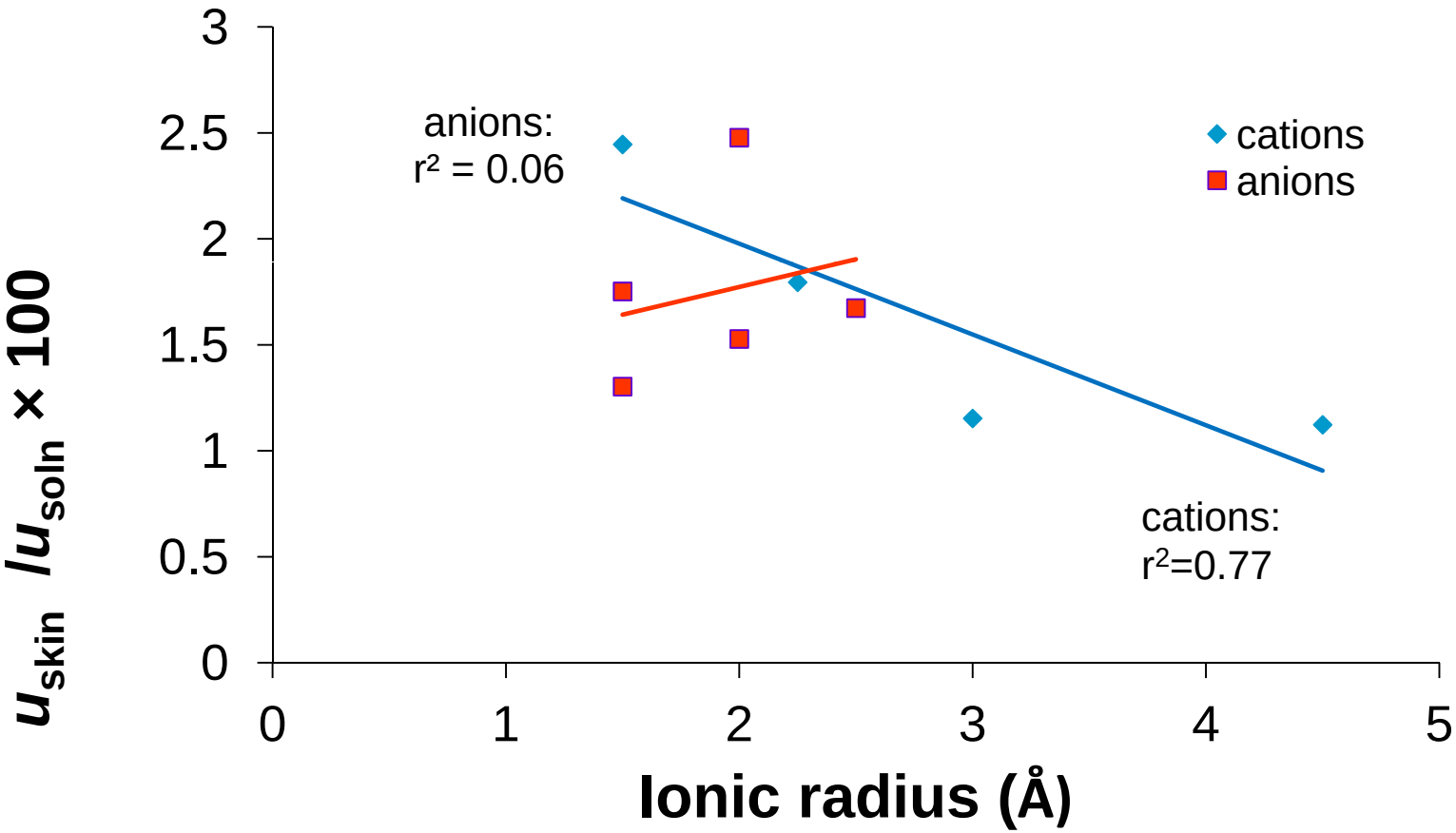
Effect of permeant size on mobilities



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LaCount & Kasting, *J Pharm Sci*, 2013

NMF extraction from the stratum corneum

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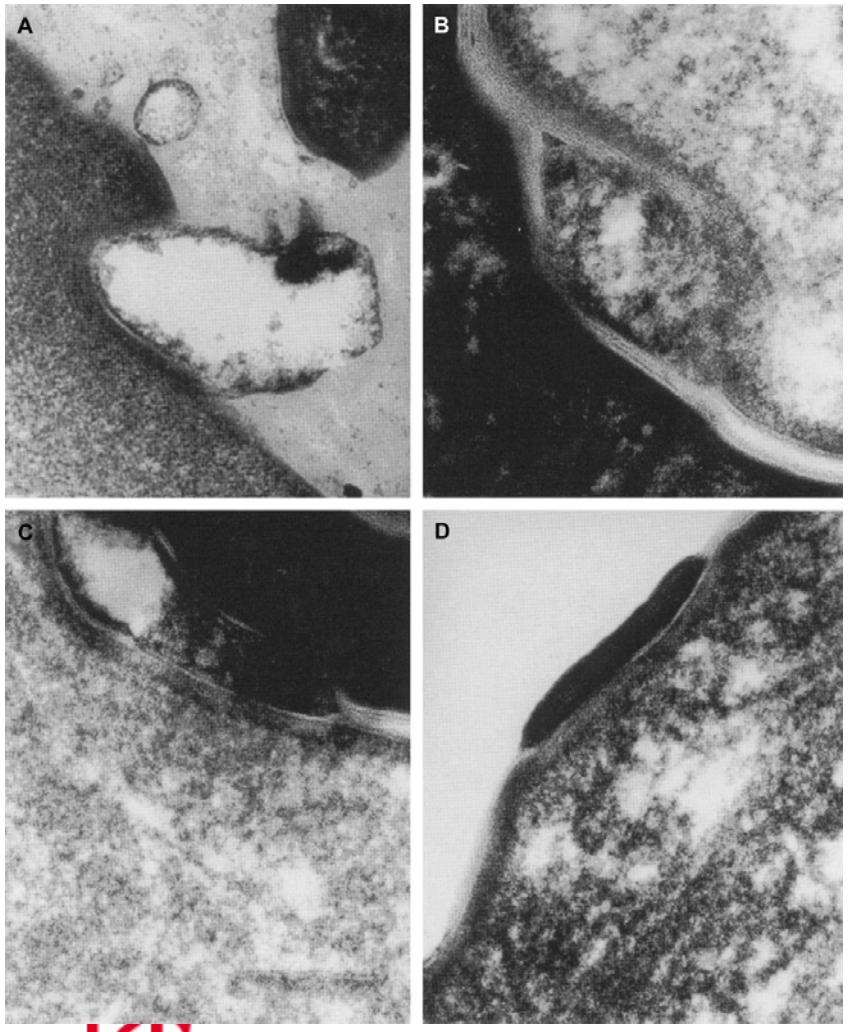
The desmosome degradation process



A. First strip, fully degraded DS
B. Second strip, lipids encapsulating DS
C. Second strip, partially degraded DS
D. Third strip, normal DS

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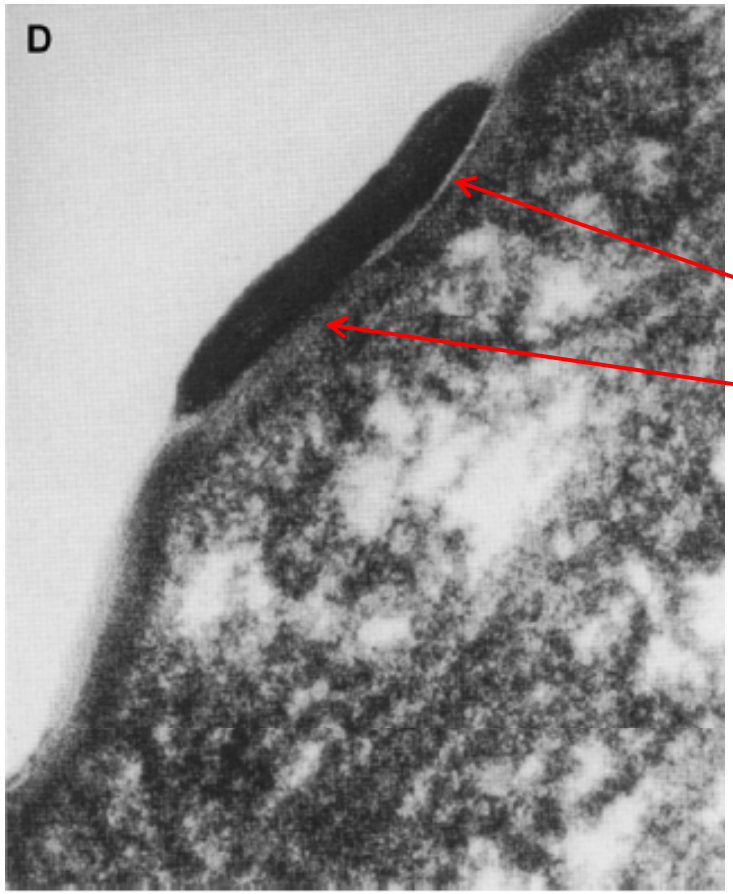
Rawlings et al., *J Soc Cosmet Chem*, 1994

The desmosome degradation process



D. Third strip, normal DS; lipid envelopes in direct contact with DS. Note the boundary between the DS and the corneocyte.

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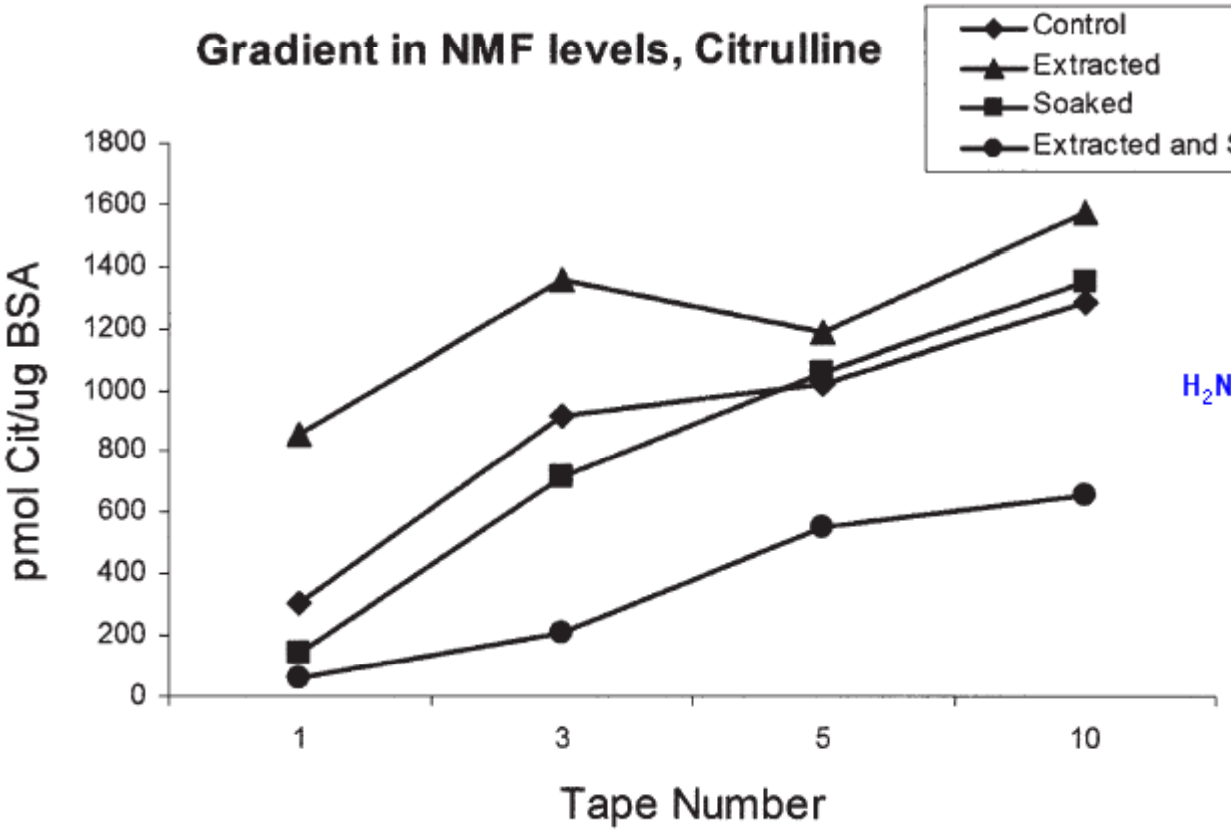
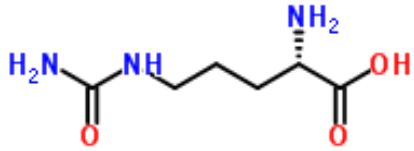
Rawlings et al., *J Soc Cosmet Chem*, 1994

Extraction of NMF components from the SC





Log Kow = –3.19

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Robinson et al., *J Cosmet Sci*, 2010

Accumulation of charged dyes in the stratum corneum

Farahmand S and Kasting GB
COLIPA Investigators Workshop
Brussels, 2009

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Test dataset

- A test set composed of 78 in vitro permeation studies involving 64 chemicals used in rinse-off cosmetic products (primarily hair dyes) was used for model evaluation.
  - 34 direct hair dyes
  - 22 oxidative hair dyes
  - 8 cationic hair dyes
  - 5 products of oxidative hair dye coupling
  - 4 preservatives
  - 2 solubilizers
  - 3 reference compounds (cinnamaldehyde, PPD(2))

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In vitro protocol

- Split-thickness human or pig skin
- Franz diffusion cells
- Compounds applied at various concentrations in fully formulated products (mostly hair dye formulations)
- Skin was washed thoroughly after 30 min.
- Samples collected after 24 hours.
- Most studies involved radiochemicals.

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Available data (24 h samples)

All data expressed as % of applied dose

- Stratum corneum content (from tape strippings)
- Viable epidermis + dermis content
- Receptor fluid content

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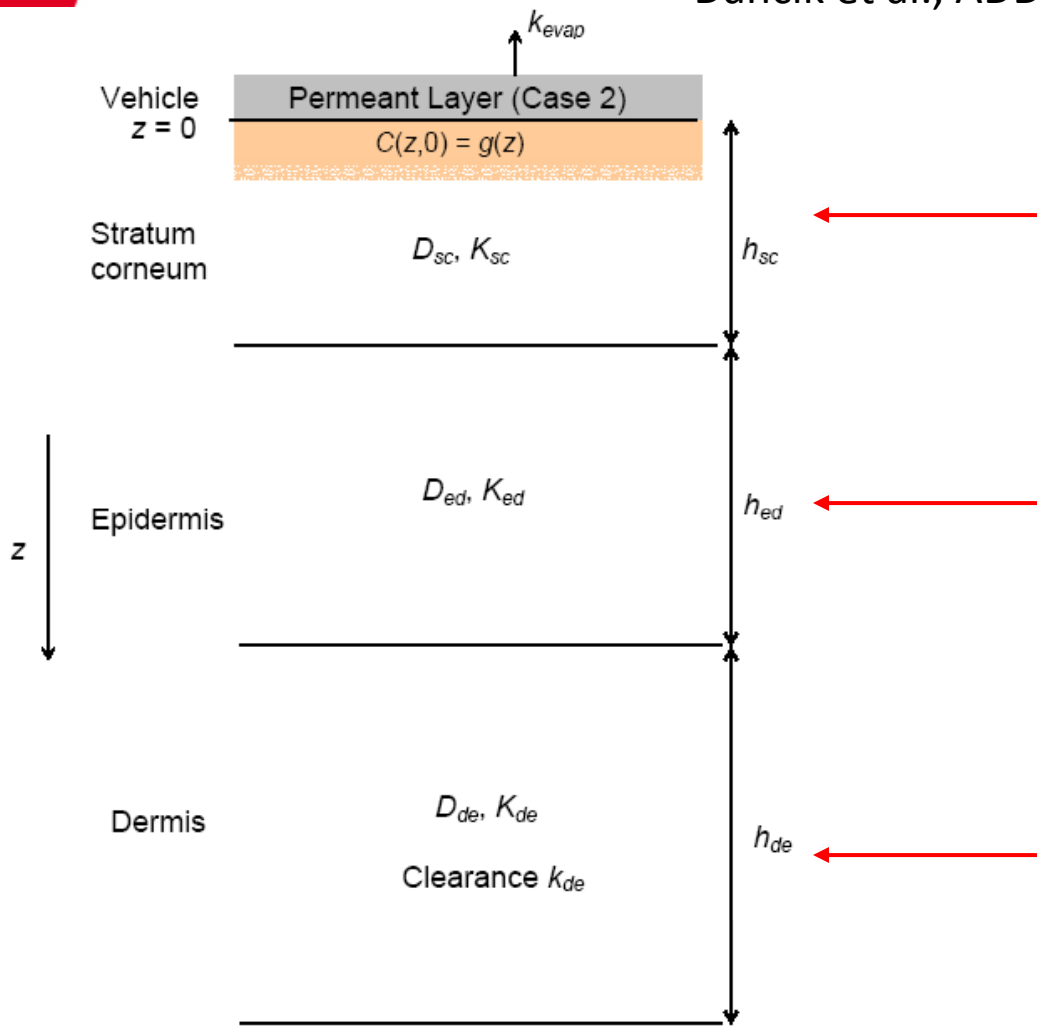
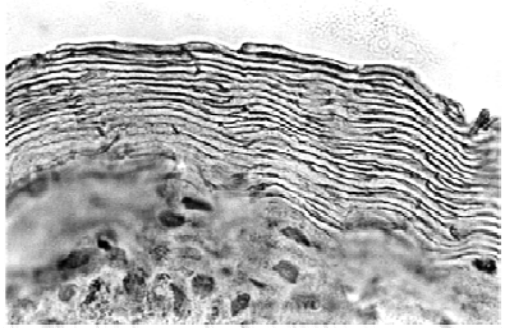
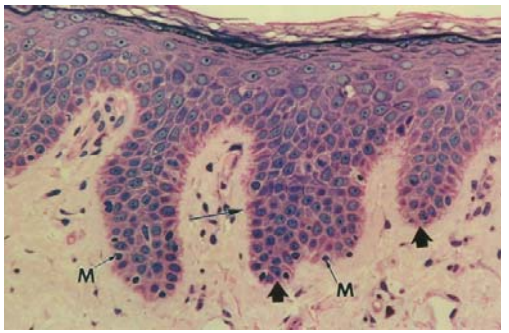
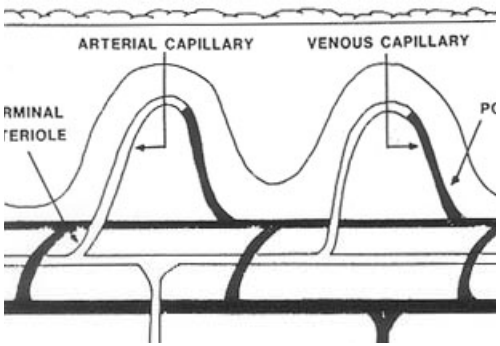
Data were analyzed using a three-layer skin diffusion model

Dancik et al., ADDR, 2012









Model assumptions

- Aqueous vehicles, 20 μL per 0.8 cm^2 diffusion cell
- ½ of vehicle evaporates during 30 minute exposure
- Partially hydrated skin
- Indoor wind velocity (0.17 m/s)

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Results of diffusion model analysis

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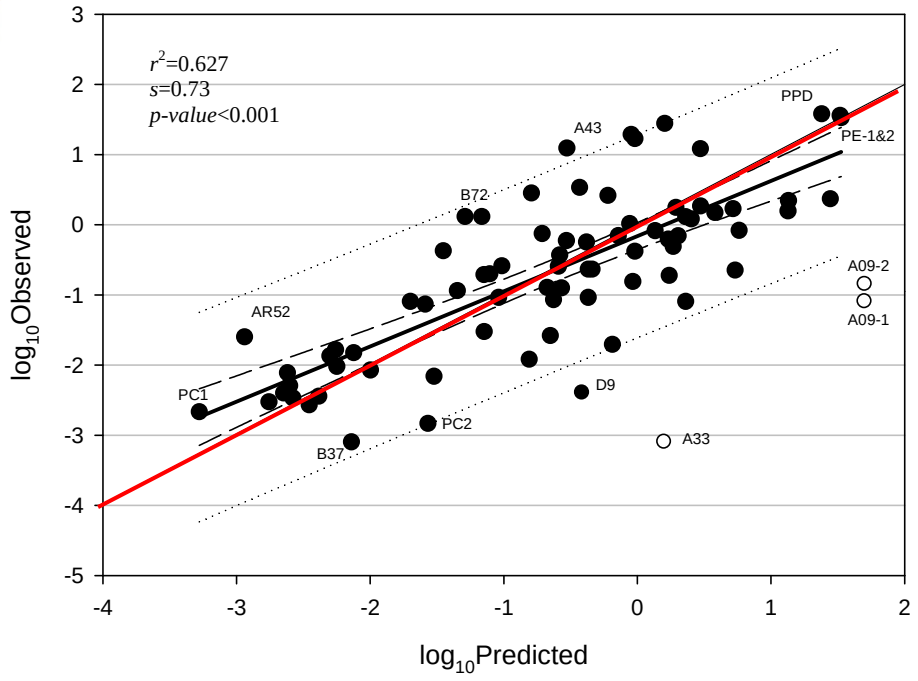
Receptor solution content



Human in vitro skin permeation (receptor level) of uncharged hair dyes and associated compounds was moderately well described.

Farahmand S and Kasting GB
COLIPA Investigators Workshop
Brussels, 2009

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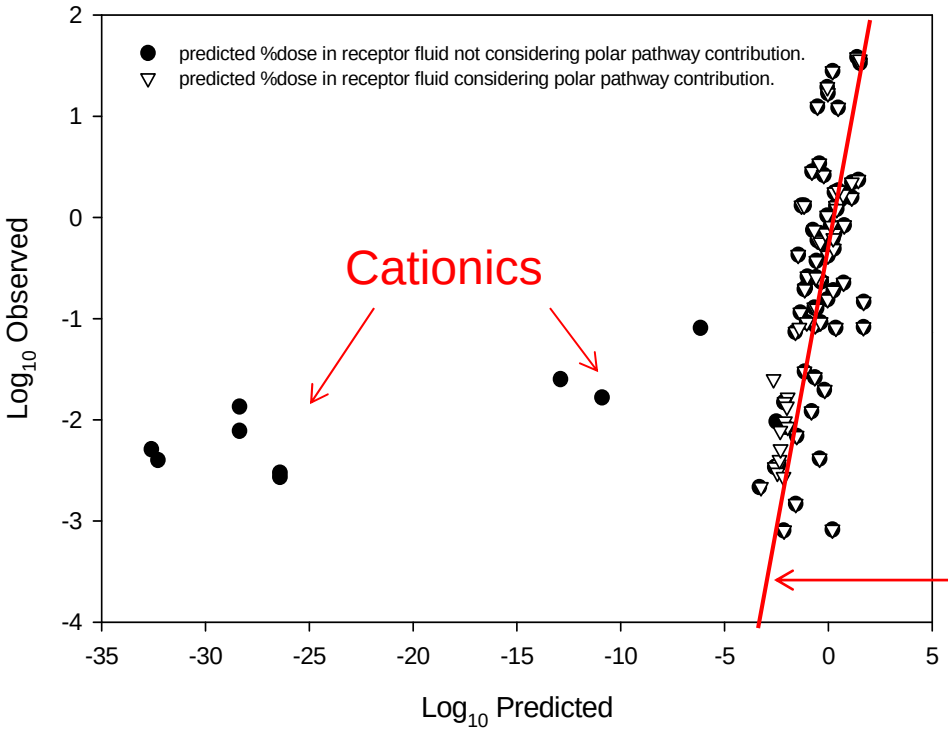
Receptor solution content



However, the permeation of cationic hair dyes was greatly underestimated.

Line of perfect fit

Farahmand S and Kasting GB
COLIPA Investigators Workshop
Brussels, 2009

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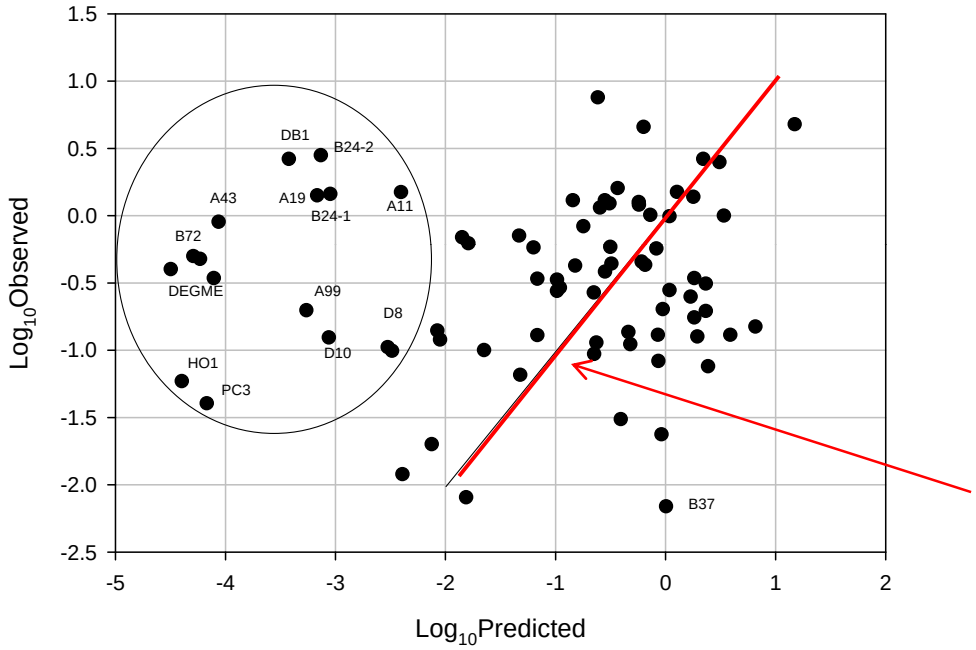
Stratum corneum concentration



SC concentrations of these compounds and a few others was also greatly underestimated.

Line of perfect fit

Farahmand S and Kasting GB
COLIPA Investigators Workshop
Brussels, 2009

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Implications of analysis

Permanently charged hair dyes not only permeated human skin in vitro, but also accumulated in the stratum corneum.

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My picture of the polar pathway…

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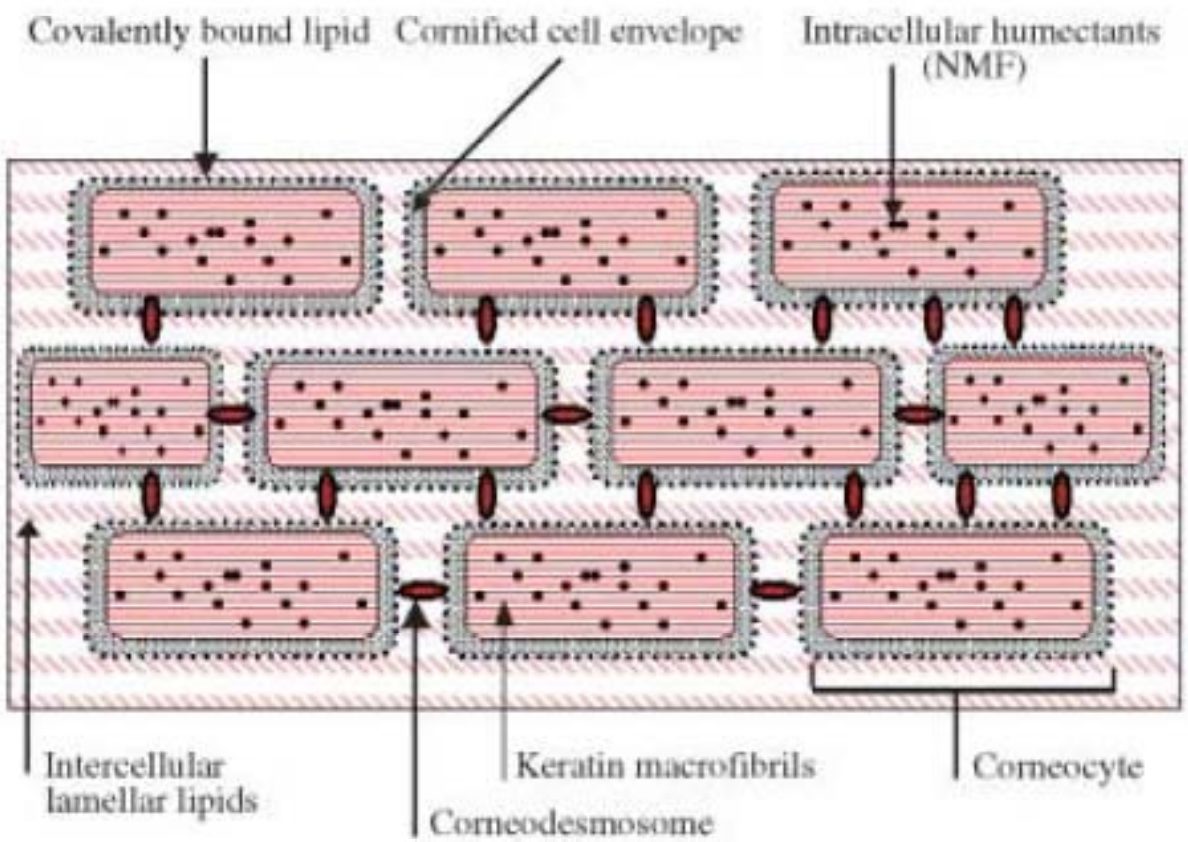
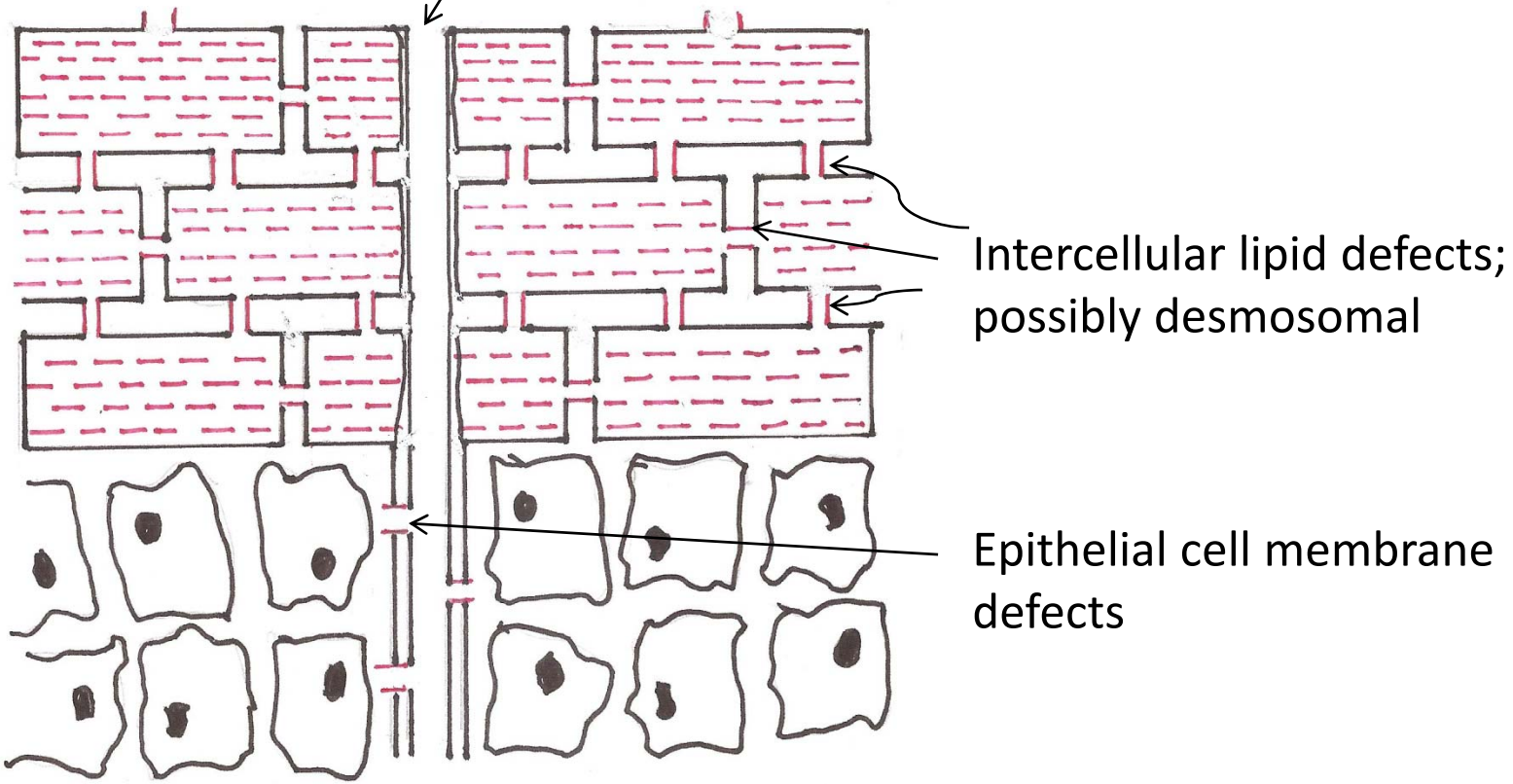
Start with a recent bricks-and-mortar model of the SC



From C. Harding (2004) *Dermatologic Therapy* **17**:6-15

Add appendageal shunts



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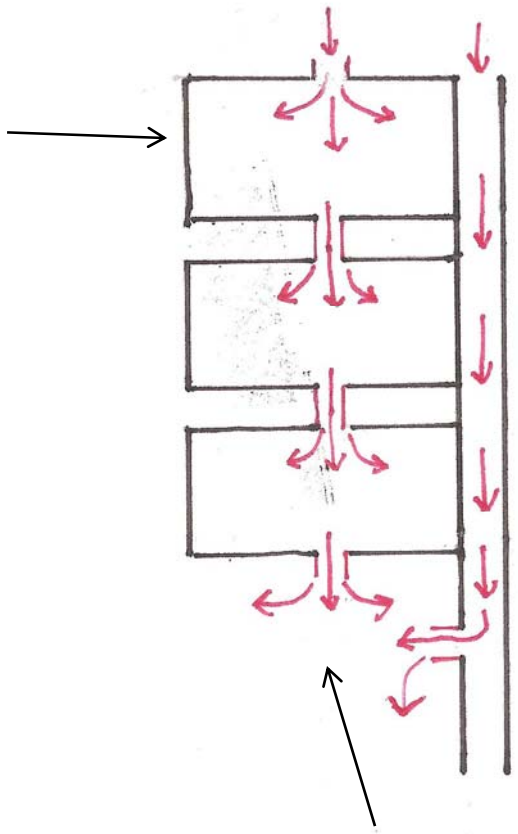
Simplify to essential components

Component 1:
transcellular



Component 2:
transappendageal

Both routes deposit permeants in viable skin tissues, bypassing the intercellular SC lipids.

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An alternative hypothesis*

*Recently advanced by the skin research group from China Agricultural University (includes Dr. Lian from Unilever)

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The CAU group has developed a stratum corneum microscopic model that accommodates polar solutes.

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Recent advances in predicting skin permeability of hydrophilic solutes☆

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See also:
Chen et al., *Ind Eng Chem Res*, 2008
Chen et al., *AIChE J*, 2010
Wang et al., *Int J Pharm*, 2010

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CAU Model

- This model accounts for the steady-state permeation rates of hydrophilic solutes within a brick-and-mortar structure.
- How is this accomplished?

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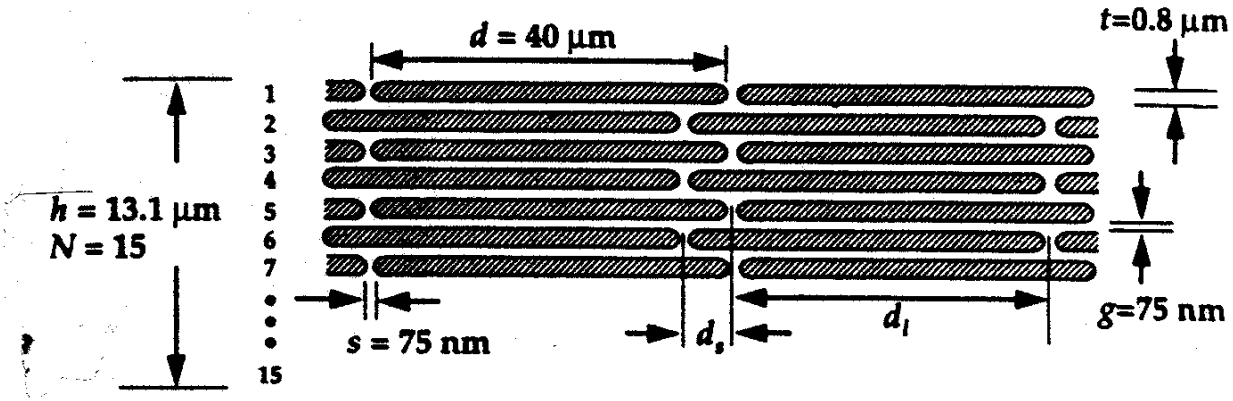
The CAU model employs a geometry very similar to that proposed by the MIT group in 1997.



Effective tortuosity: ($\omega = d_l/d_s$)

$$\tau^* = 1 + \frac{2g}{h}\ln\left(\frac{d}{2s}\right) + \frac{Ndt}{sh} + \left(\frac{d}{1+\omega}\right)^2\left(\frac{\omega}{hg}\right)(N-1)$$

Johnson et al., *J Pharm Sci*, 1997

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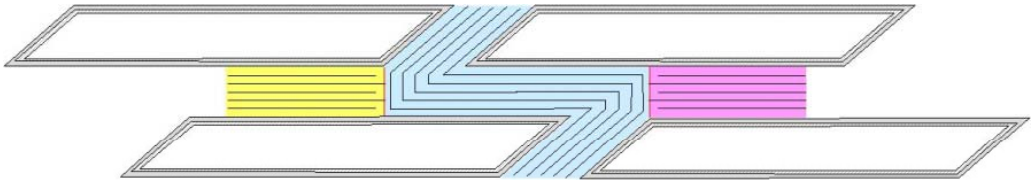
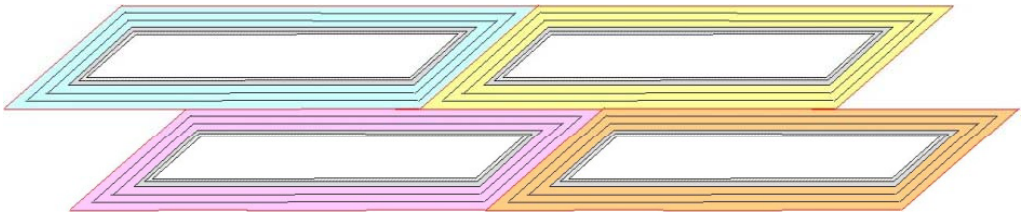
But unlike the MIT analysis (or our own), lipid phase diffusion in the CAU model is isotropic.

Model 1 (MIT)



Model 2 (UB/UC)[a]



[a]Wang et al., *J Pharm Sci*, 2006;
Wang et al., *J Pharm Sci*, 2007

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Corneocytes are permeable in the CAU model, but barely so. The fiber matrix diffusion model for D_{cor} was adapted from another MIT group [1].

Property	MIT	CAU	UB/UC[a] Partial hydration	UB/UC Full hydration
Sucrose				
$D_{cor} \times 10^6$, $cm^2 s^{-1}$	NA	6.13E-06	1.08	4.17
K_{cor}	0	0.808	0.232	0.755

[1]. Biophysical Journal Volume 70 February 1996 1017–1026 1017

Hindered Diffusion in Agarose Gels: Test of Effective Medium Model

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The parameters α and β in the Johnson et al. model were modified in order to match bulk SC permeabilities for 8 selected solutes.

Table 2. Eight Representative Solutes for Deriving Two Parameters (α and β) in Eq 5

Permeants	log K_{ow}	M_W (Da)	Observed log K_p (cm/s)	Predicted log K_p (cm/s)
Mannitol	−3.01	182.2	−8.16	−8.04
Water	−1.38	18	−6.32	−6.48
Methanol	−0.77	32	−6.56	−6.44
Hydrocortisone	1.61	362.5	−7.48	−7.36
Hexanol	2.03	102.2	−5.11	−5.42
Octanoic acid	3.05	144.2	−5.16	−5.13
Ibuprofen	3.97	206.3	−5.00	−5.02
Decanol	4.57	158.3	−4.30	−4.20

Chen et al., *AIChE J, 2010*

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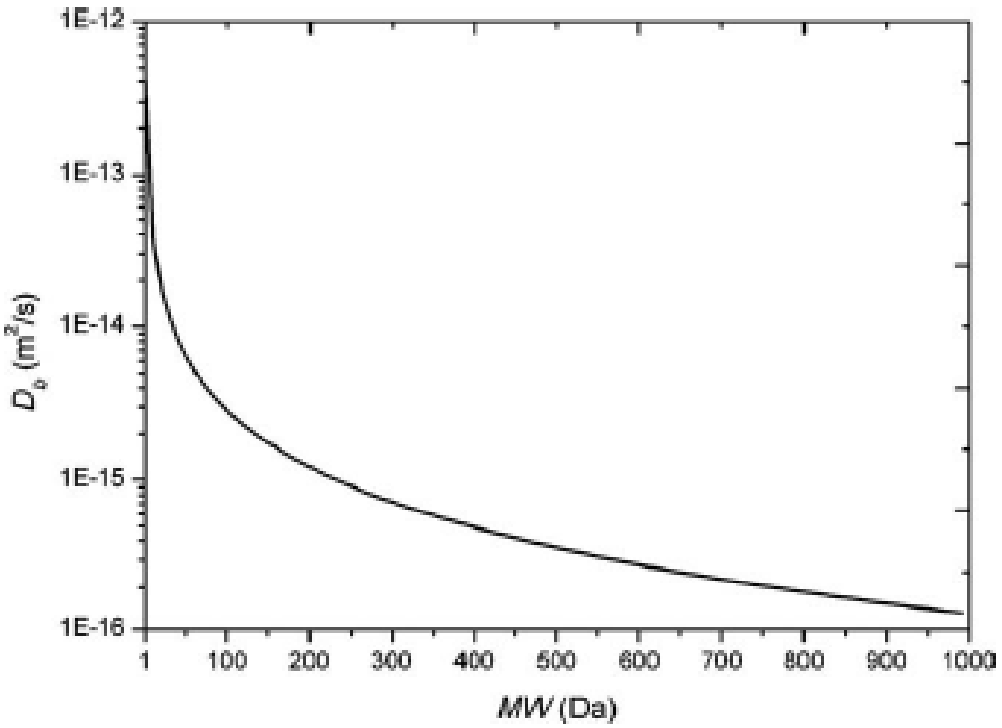
The result was a diffusion model that was much more restrictive to transport than the original version.



Chen et al., *AIChE J, 2010*

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Lipids are much more permeable to ALL solutes in the CAU model than in the UB/UC model. The difference lies in the transverse mass transfer coefficient (effective diffusivity = $k_{trans}\delta$).

Property	MIT	CAU	UB/UC Partial hydration	UB/UC Full hydration
Sucrose				
$D_{lat} \times 10^9$, $cm^2 s^{-1}$	-	5.91	2.86	8.57
$k_{trans}\delta \times 10^9$, $cm^2 s^{-1}$	-	[5.91][b]	0.235E-03	0.706E-03
K_{lip}	15.4E-04	25.7E-04	4.33E-04	4.33E-04

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Consequences of parameter selection

- The CAU and UB/UC models both predict that diffusion through the SC is primarily transcellular. (MIT was strictly intercellular.)
- The limiting resistance in the CAU model is diffusion in the corneocytes; the limiting factor for UB/UC is transbilayer hopping in the lipid phase.
- CAU accommodates the permeation of hydrophilic solutes, whereas MIT and UB/UC do not. But at what cost?

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Issues raised by CAU model

- Long time lags for hydrophilic permeants
- High permeability of delipidized SC
- Temperature dependence
- Electrical conductance of pores and follicles

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Questions?

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