

# INTRODUCTION TO THE MOBI SKIN PERMEATION MODEL

23<sup>RD</sup> APRIL 2021



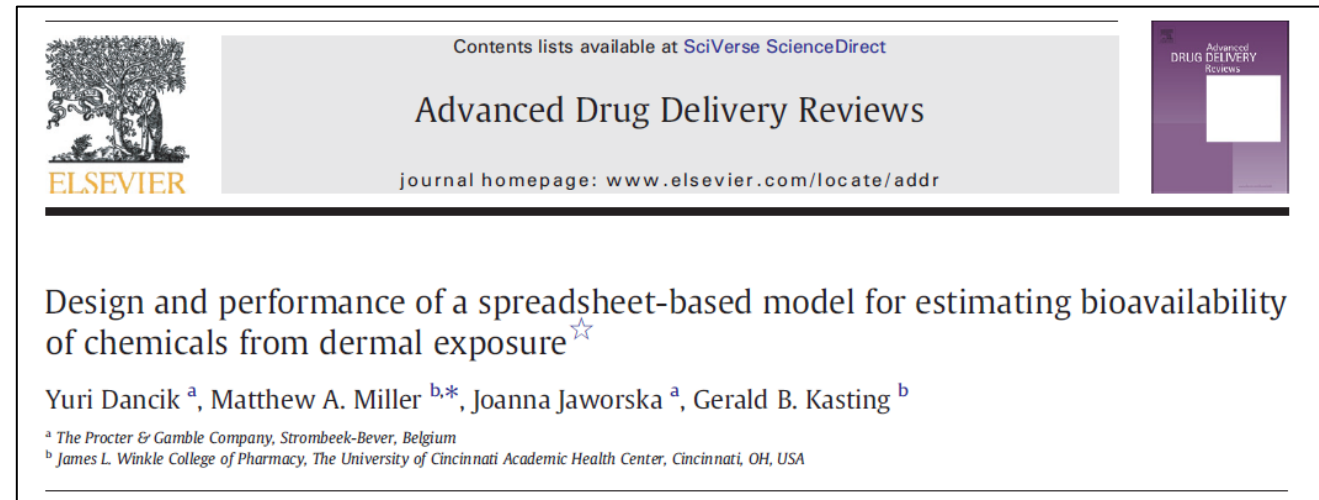
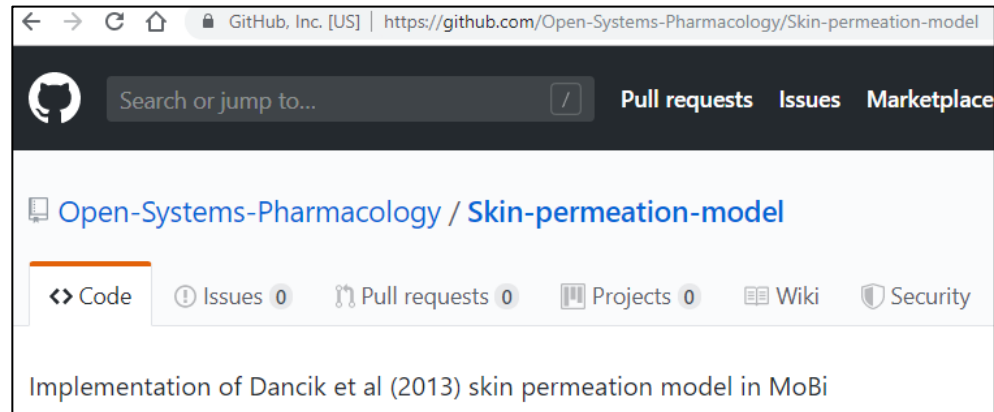
UNIVERSITY OF WATERLOO  
FACULTY OF SCIENCE  
School of Pharmacy

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# WHAT HAVE WE DONE AND WHY?

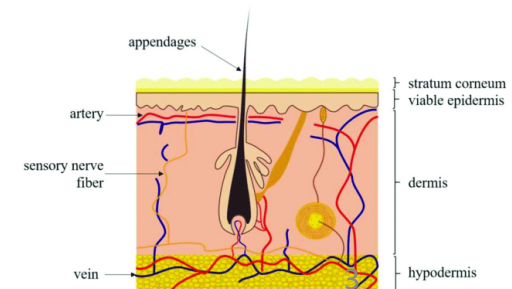
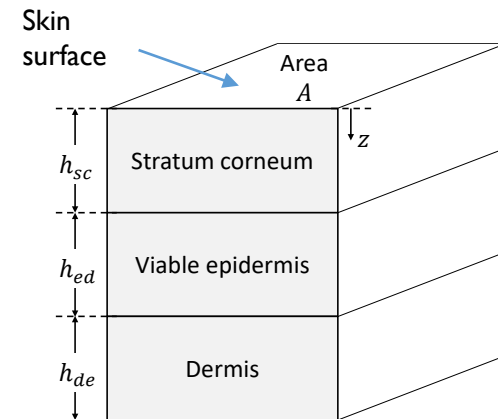
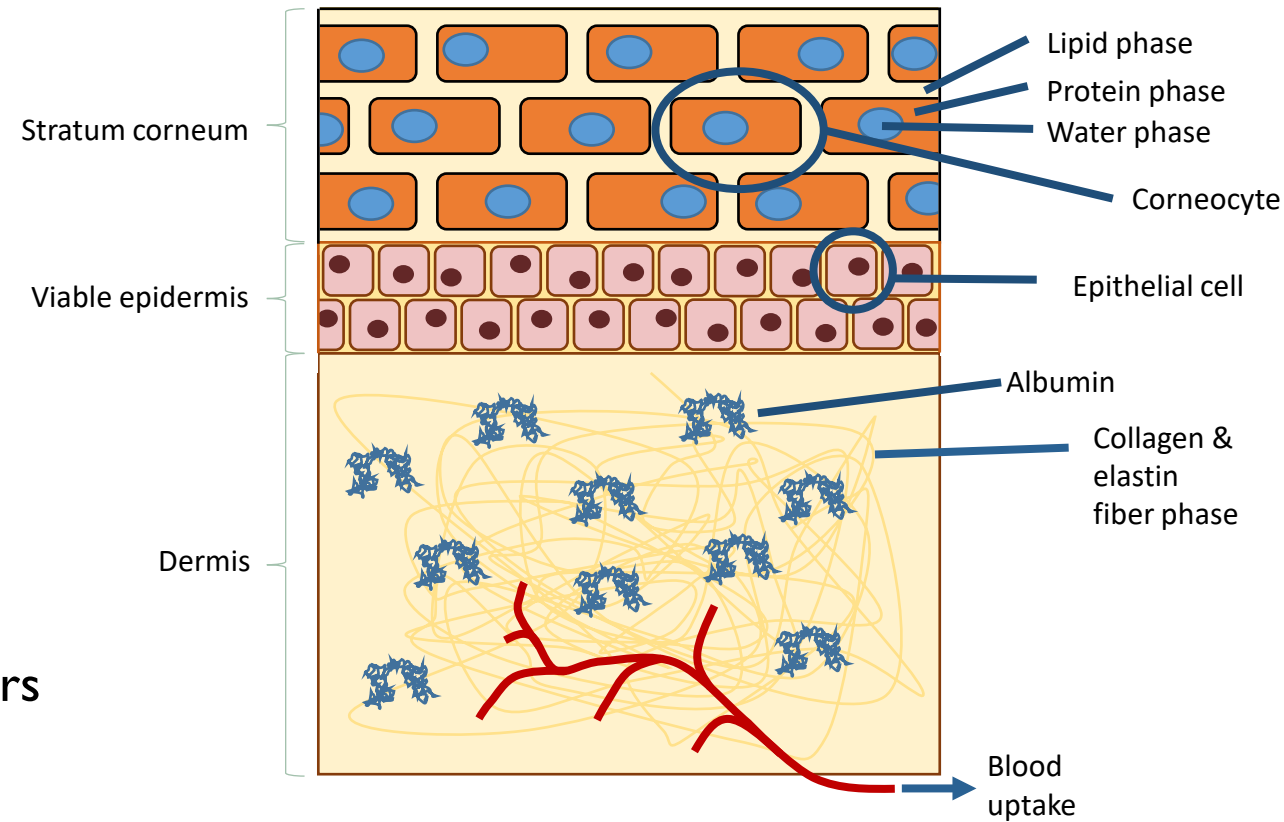
We have built a computational model of dermal absorption based on **Dancik et al. 2013**

- Model implemented in MoBi, available at **<https://github.com/Open-Systems-Pharmacology/Skin-permeation-model>**
- **Aim is to simulate disposition of dermally applied chemicals**
- Integrates many previously published ‘sub-models’

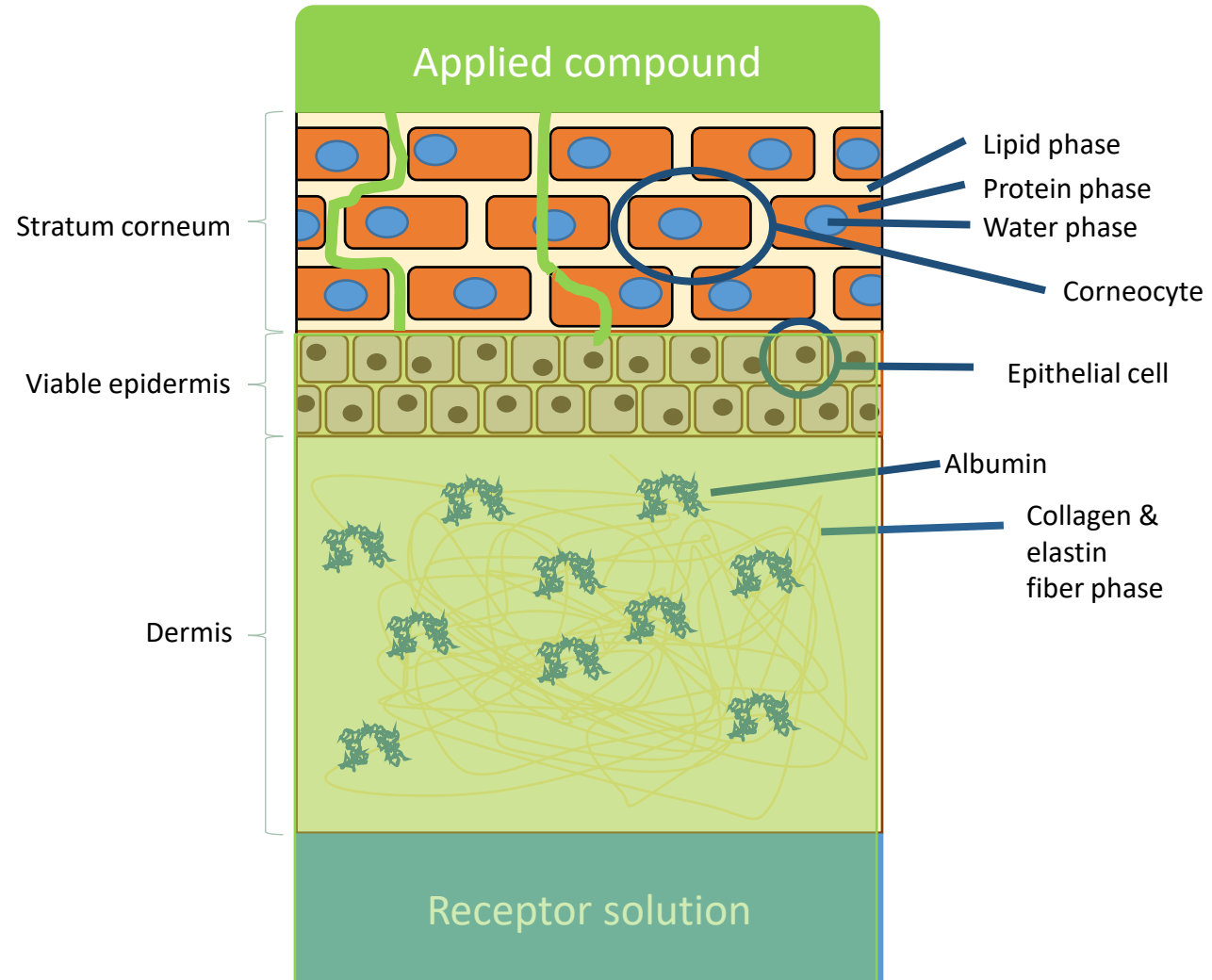


# SKIN ANATOMY

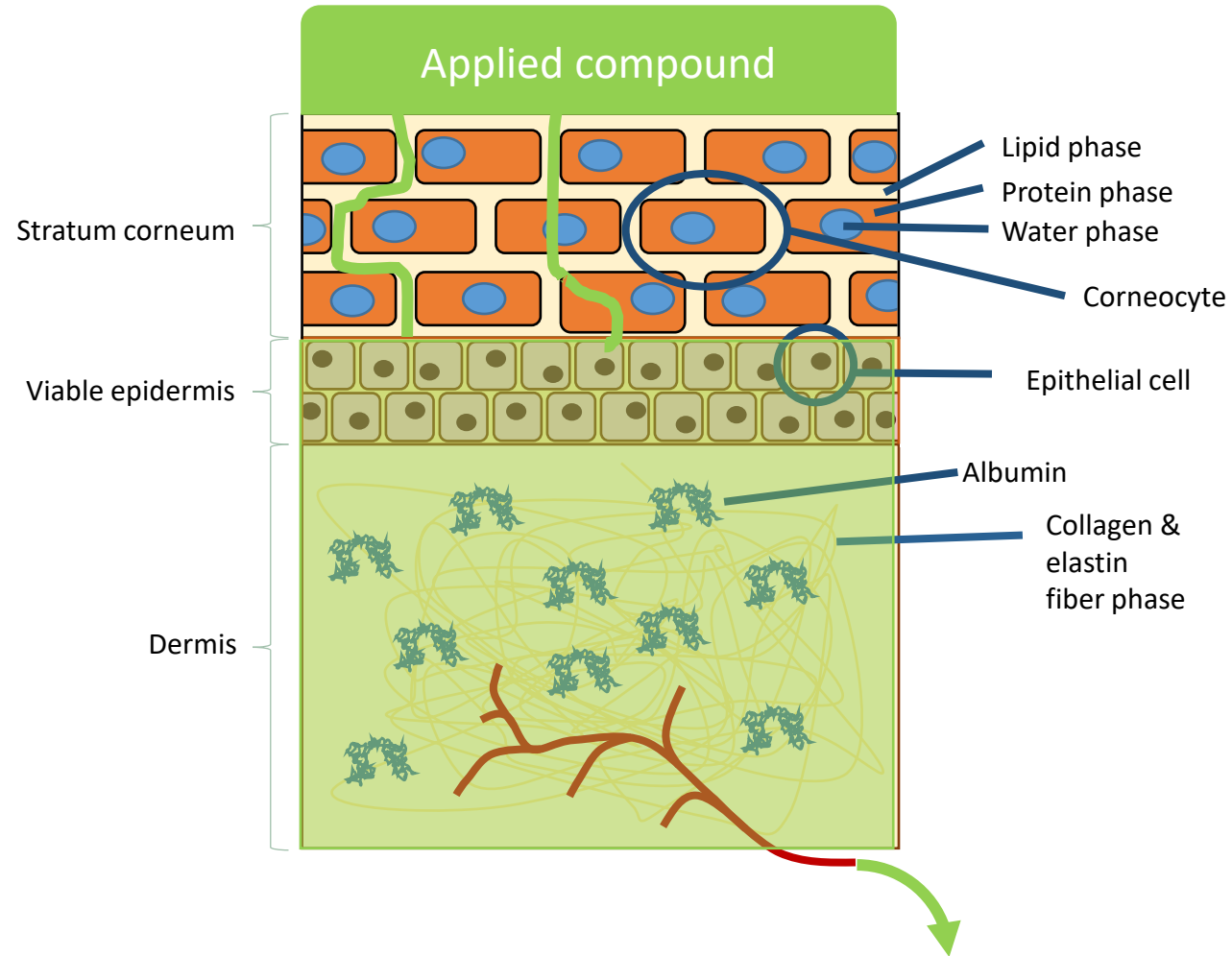
- Skin slab of cross-sectional area  $A$
- Three stacked layers:
  - Stratum corneum (SC):
    - Lipid matrix (lipid phase)
    - Corneocytes (protein and water phases)
  - Viable epidermis (ED)
    - Epithelium
  - Dermis (DE):
    - Collagen & elastin fibers
    - Aqueous phase (partially albumin accessible)
- Permeant applied on top of SC layer, diffuses into layers below
- *In vivo* clearance of the permeant takes place in the DE layer.
- Model allows for permeant evaporation from top layer



# In vitro skin penetration



# In vivo skin penetration



WHOLE-BODY  
DISPOSITION MODEL

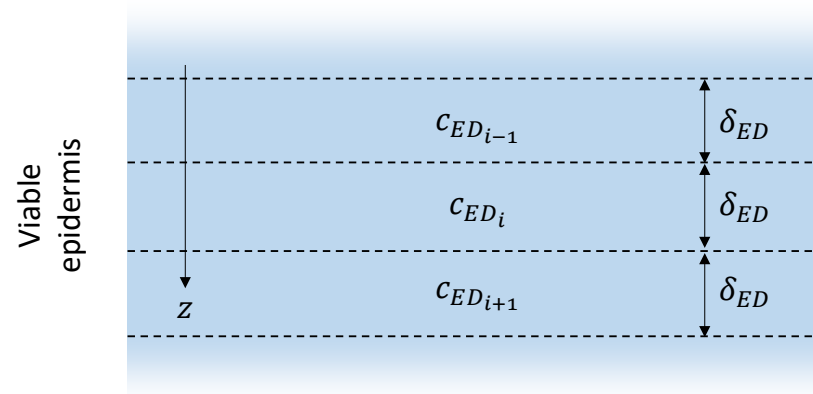


# FLOW OF PERMEANT INTO SKIN GOVERNED BY THE DIFFUSION EQUATION

Diffusion of permeant numerically computed using method of finite differences and Fick's law:

$$J(z, t) = -D \frac{\partial c(z, t)}{\partial z}$$

$J$  = diffusive flux,  $D$  = diffusion coefficient,  $c$  = local concentration of permeant



$$\frac{\partial c_{EDi}}{\partial t} \approx \frac{1}{\delta_{ED}} \left( D_{ED} \cdot \frac{c_{EDi-1} - c_{EDi}}{\delta_{ED}} - D_{ED} \cdot \frac{c_{EDi} - c_{EDi+1}}{\delta_{ED}} \right) - f_m(c_{EDi})$$

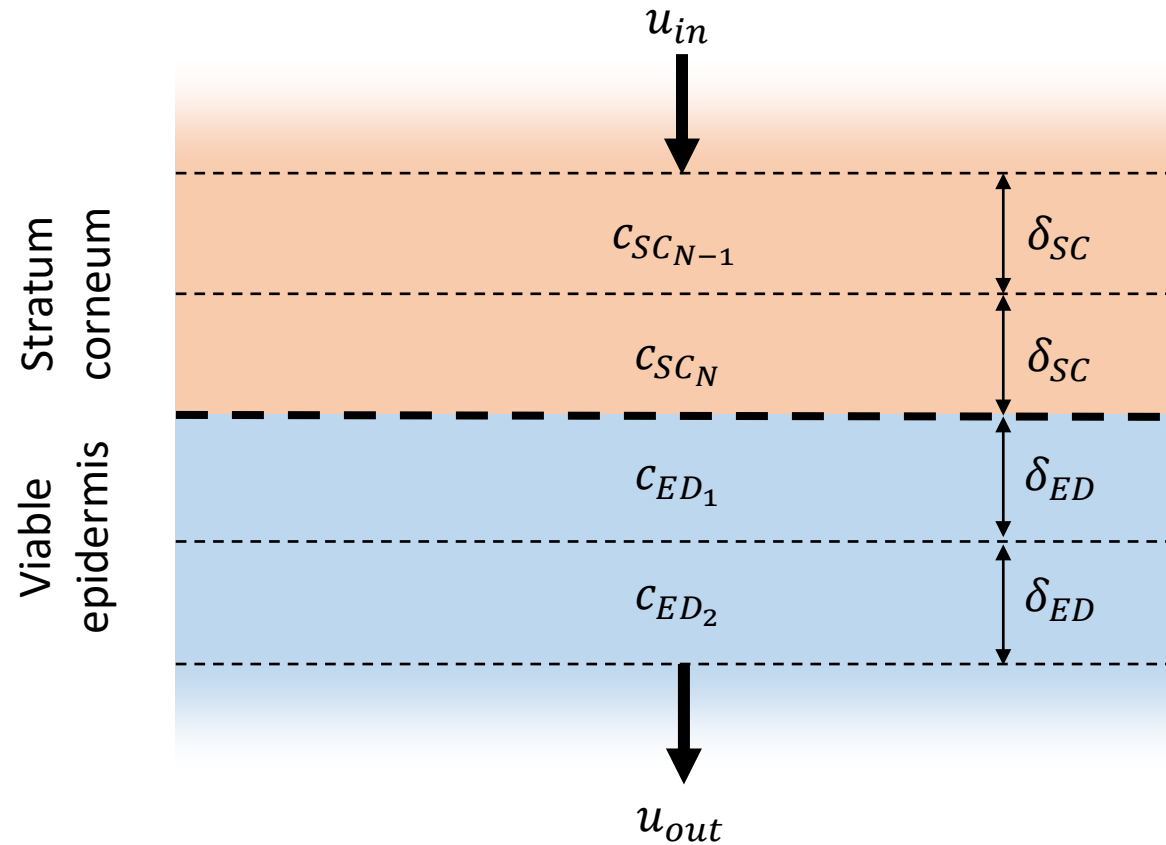
Permeant  
local concentration  
rate of change

Permeant  
flux in

Permeant  
flux out

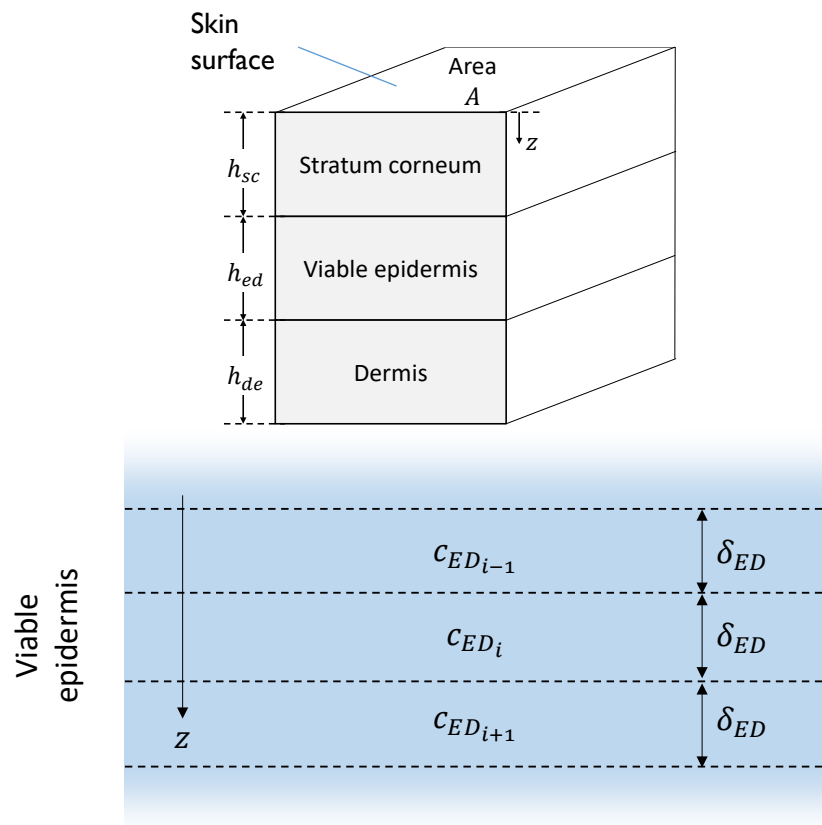
Permeant  
metabolism rate  
per unit volume

$$f_m(c) = V_{max} \frac{c}{c + K_M}$$



- Flow out of stratum corneum = flow into viable epidermis
- Ratio of concentrations at interface governed by partition coefficient between stratum corneum and viable epidermis

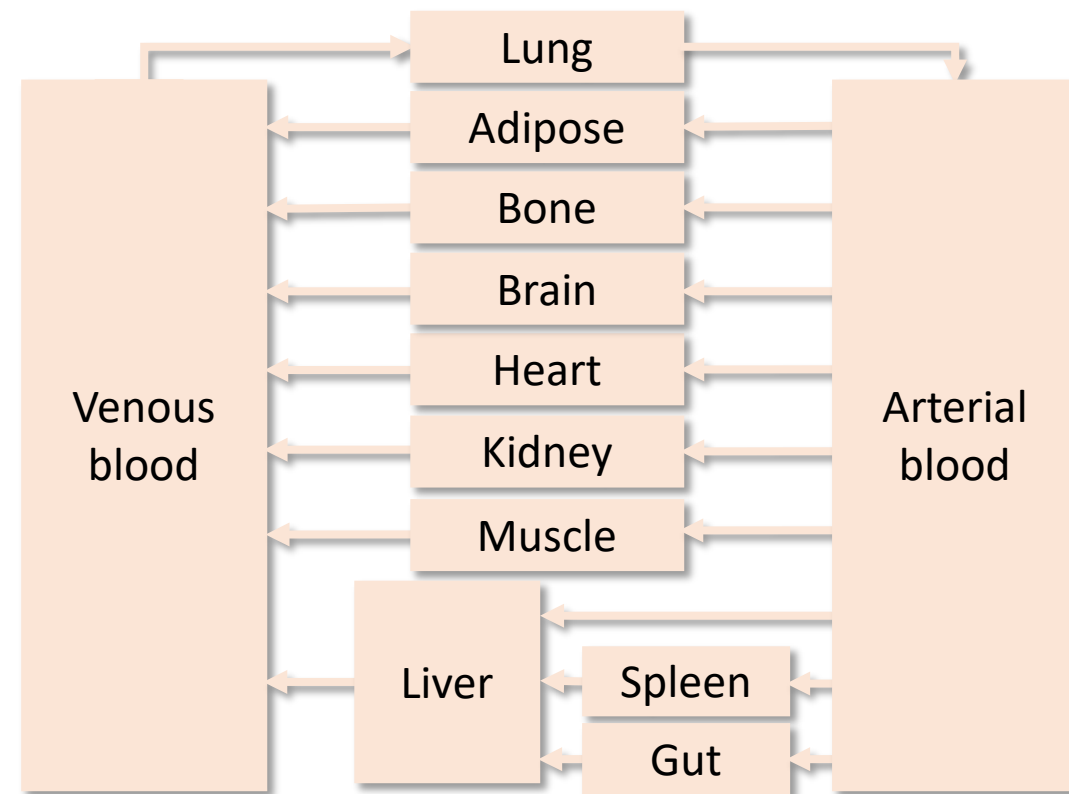
# MODEL PHILOSOPHY: COMPARTMENTALIZE SKIN SUBLAYERS AS IN PBPK MODELS



## Dermal model

SC, epidermis, dermis layers each compartmentalized into forty sublayers

Permeant flows downwards from one layer to the next via diffusion.

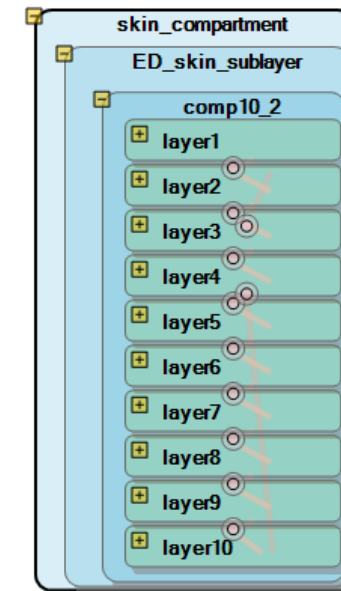
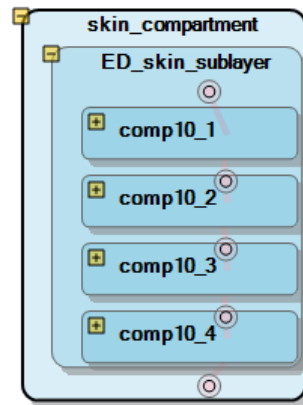
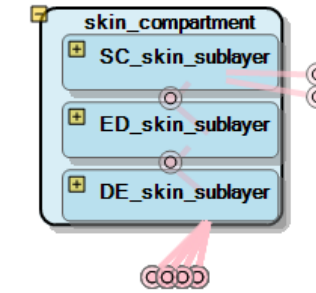
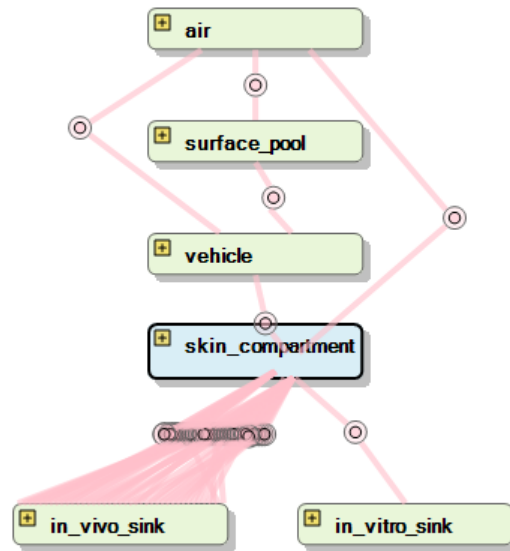


## Typical PBPK model

Blood flow transports drug



# IMPLEMENTATION IN MOBI – A HIERARCHICAL VIEW OF MODEL STRUCTURE



# USER INPUTS FOR SIMULATION

Spatial Structure: skin\_compart - MoBi 7.3

File Modeling Parameter Identification & Sensitivity Working Journal Import/Export Utilities Views Edit Organism

Buildin... Spatial Structures skin\_compart

Parameters Formulas

Tree Diagram

Favorites

- User Defined
- MoleculeProperties
- skin\_compart
  - MoleculeProperties
    - DE\_skin\_sublayer
    - ED\_skin\_sublayer
    - SC\_skin\_sublayer
  - drain
  - air
  - vehicle
  - surface\_pool
  - Neighborhoods

Name	Value	Description
MW	148.20 g/mol	**Permeant property**
log_K_ow	0.05	**Permeant property**
Solubility S_v	0.95 g/cm³	**Permeant property**
C atoms	7.00	**Permeant property**
Br atoms	0	**Permeant property**
Cl atoms	0	**Permeant property**
H atoms	16.00	**Permeant property**
N atoms	0	**Permeant property**
O atoms	3.00	**Permeant property**
F atoms	0	**Permeant property**
S atoms	0	**Permeant property**
I atoms	0	**Permeant property**
Permeant includes other elements	0	**Permeant property**
Double bonds	0	**Permeant property**
Triple bonds	0	**Permeant property**
Rings	0	**Permeant property**
Compound type	0	**Permeant property**
Use experimental permeant density	1.00	**Permeant property**
Temperature at experimental permeant density	298.00 K	**Permeant property**
Experimental permeant density	0.96 g/cm³	**Permeant property**
Grain class	0	**Permeant property**
Boiling temperature	461.00 K	**Permeant property**
Use experimental permeant water solubility	1.00	**Permeant property**
Temperature at experimental permeant water solu...	298.00 K	**Permeant property**
Experimental permeant water solubility	0.83 g/cm³	**Permeant property**
Melting temperature	193.00 K	**Permeant property**
Use strongest acid pKa	0	**Permeant property**
Strongest acid pKa	0	**Permeant property**
Use strongest base pKa	0	**Permeant property**
Strongest base pKa	0	**Permeant property**
Vapor pressure	0.14 mmHg	**Permeant property**
Dose	933254.00 mg/m²	**Application property**

Building Blocks

- Spatial Structures
- Molecules
- Reactions
- Passive Transports
- Observers
- Events
- Simulation Settings
  - DPGME\_inf\_aq\_dose
  - DPGME\_large\_dose
  - testosterone\_small\_dose
- Molecule Start Values
  - initial\_amounts
- Parameter Start Values
  - DPGME\_inf\_aq\_dose
  - DPGME\_large\_dose
  - testosterone\_small\_dose
- Observed Data

# DIFFUSION COEFFICIENT USED IN IMPLEMENTATION OF FICK'S LAW

Passive Transports: Passive Transports - MoBi 7.3

File Modeling Parameter Identification & Sensitivity Working Journal Import/Export Utilities Views Edit Passive Transport

New Load Load From Template Add

Building Blocks

- Spatial Structures
  - skin\_compartment
- Molecules
- Reactions
- Passive Transports
  - Passive Transports
- Observers
- Events
- Simulation Settings
- Molecule Start Values
- Parameter Start Values

Simulations

- Simulations
- Parameter Identifications
- Sensitivity Analyses

Spatial Structure: skin\_compartment

Passive Transports Formulas

Drag a column header here to group by that colour

Name
SC_layer1_layer2_pt
SC_layer2_layer3_pt
SC_layer3_layer4_pt
SC_layer4_layer5_pt
SC_layer5_layer6_pt
SC_layer6_layer7_pt
SC_layer7_layer8_pt
SC_layer8_layer9_pt
SC_layer9_layer10_pt
ED_layer1_layer2_pt
ED_layer2_layer3_pt
ED_layer3_layer4_pt
ED_layer4_layer5_pt
ED_layer5_layer6_pt
ED_layer6_layer7_pt
ED_layer7_layer8_pt
ED_layer8_layer9_pt
ED_layer9_layer10_pt

Properties Kinetic Parameters

Formula type: Formula (an explicit formula)

Formula name: SC\_layer\_to\_layer\_pt\_formula

Alias	Path	Dimension		
D_sc	skin_comparm...	Diffusion coeffi...	X	+
Ar	skin_comparm...	Area	X	+
con_source	SOURCE A Co...	Concentration (...)	X	+
con_target	TARGET A Con...	Concentration (...)	X	+
dx	skin_comparm...	Length	X	+

References to add

Local Reference Point

☒ Absolute path ☐ Relative path

Possible Referenced Objects

- SC\_layer7\_layer8\_pt
- TIME
- skin\_compartment

Fick's law 😊

$$dN/dt = D\_sc * (con\_source - con\_target) * Ar / dx$$

Notifications

0 Errors 0 Warnings 0 Messages Save...

Drag a column header here to group by that column

Object Type	Object Name	Building Block Type	Building Block Name	Message	Origin
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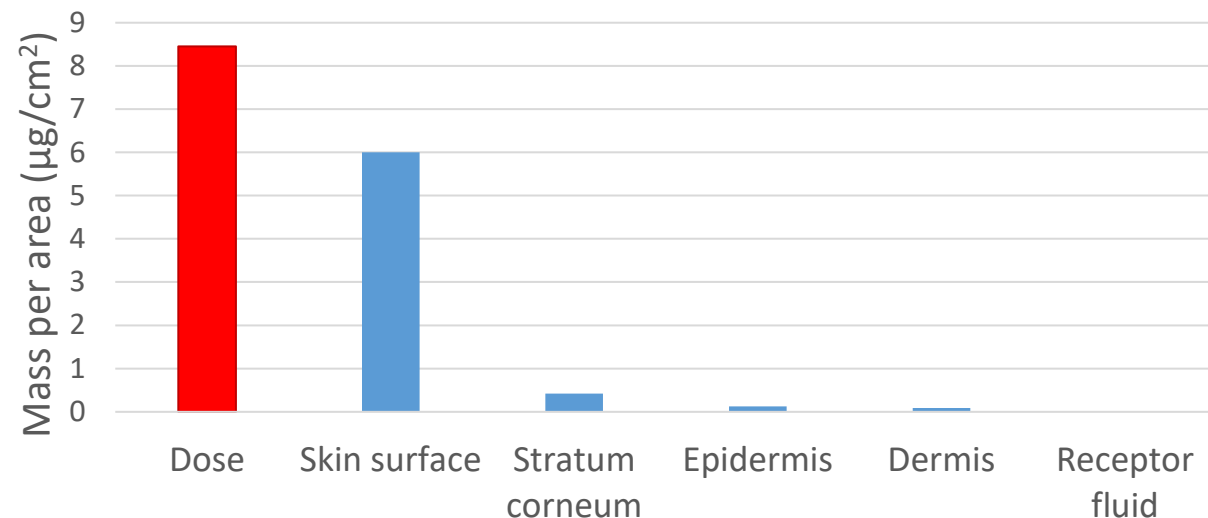
Project: Dancik\_model - Copy C:\Users\ahamadeh\Dropbox\skinproject\Dancik\_model - Copy.mbp3 Amount based reactions 7.3.0 - Build 35

## APPLIED EXAMPLE: IN VITRO-TO-IN VIVO EXTRAPOLATION OF UV FILTER SKIN ABSORPTION

- **In vitro skin penetration experiment:**

- **Avobenzone** in vitro skin penetration data provided by **A. Najjar & D. Lange, Beiersdorf**.
- Measured accumulation of avobenzone in skin layers and receptor fluid over 24 hrs
- Dose:  $8.45\mu\text{g}/\text{cm}^2$
- Solvent: Ethanol

Avobenzone dose (red) and disposition 24 hr after in vitro dermal application (blue)



- **Want to:**

- learn model parameters from data
- estimate in vivo dermal absorption based on learned parameters

- **Sensitivity analysis shows dermal absorption sensitive to some uncertain model parameters (to be optimized):**

- Avobenzone lipophilicity (Range: 4.2-6.1)
- Water solubility (Range:  $10^{-8} - 10^{-6} \text{ g}/\text{cm}^3$ )
- Permeability across stratum corneum lipids (Range:  $10^{-7.5} - 10^{-5} \text{ cm}/\text{s}$ )

## FINAL REMARKS

- Presented a MoBi implementation of the Dancik et al. 2013 dermal absorption model
- MoBi simulates skin penetration by solving diffusion equation
  - anatomical skin layers are divided into thin sub-layers (compartments)
  - Fick's law applied to model diffusive flow between sub-layers
- MoBi model can be appended to a whole-body model in PK-Sim
- Presented an example of dermal model optimization to in vitro data for extrapolation to in vivo scenario
- We have built a **dedicated R package** based on **OSPSuite-R** for MCMC-based **in vitro to in vivo inference of dermal absorption**
- Please send any questions to [ahamadeh@uwaterloo.ca](mailto:ahamadeh@uwaterloo.ca)

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