CERTARA
Implementing Translational Science

SIMCYP
simulator | consultancy | education

PBPK Modelling of Dermal Drug Absorption and Population Variability

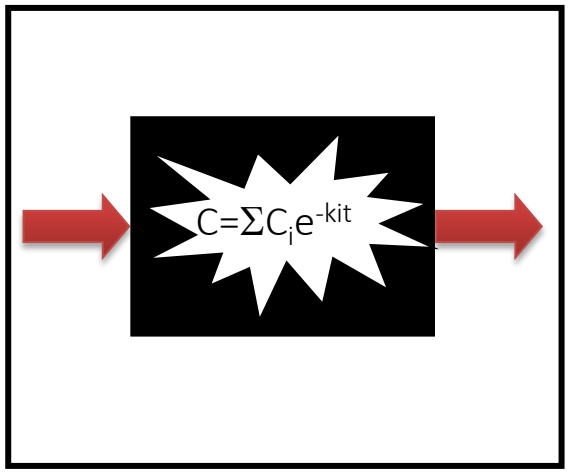
Simcyp MPML MechDermA model

N. Patel, F. Martins, S. Cristea, F. Salem, K. Abduljalil, M. Jamei, S. Polak (PI)

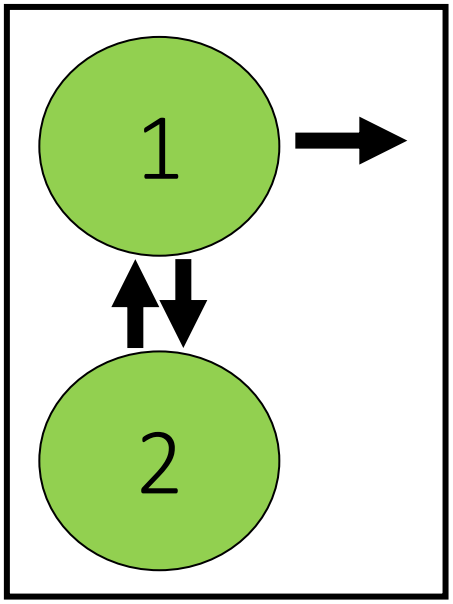
Tripos SIMCYP Pharsight

Typical Models Used to Describe Pharmacokinetics

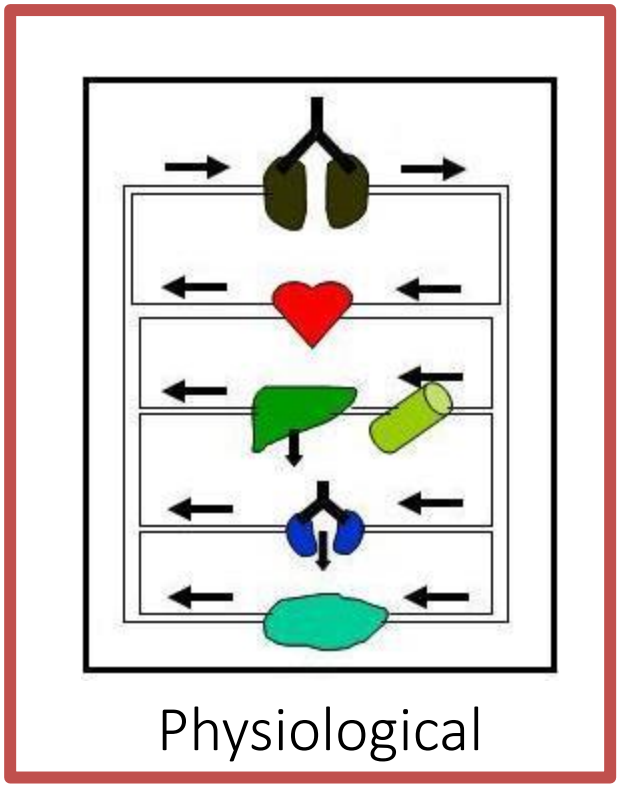
Three type of models can be used to describe concentration time profiles (PK)



Empirical



Compartmental



Physiological

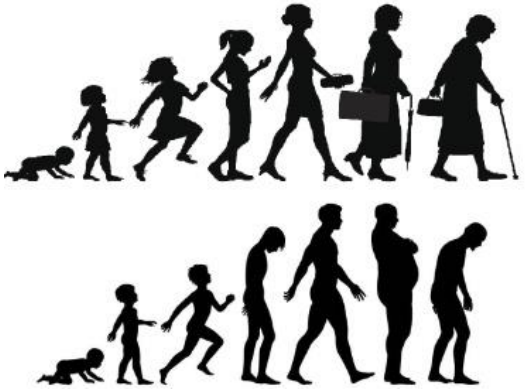
Empirical and compartmental models are fitted to observed data to explain the data whereas physiological models can be used for a priori prediction and then refine as data becomes available

Advantage of PBPK: Separating systems & drug information

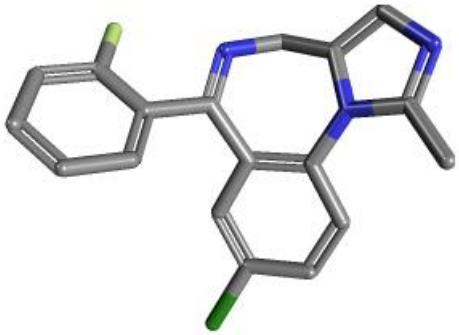
Systems Data

Trial Design

Drug Data



Dose
Administration route
Frequency
Co-administered drugs
Populations



Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

(Jamei *et al.*, DMPK, 2009, Rostami-Hodjegan, CPT, 2012)

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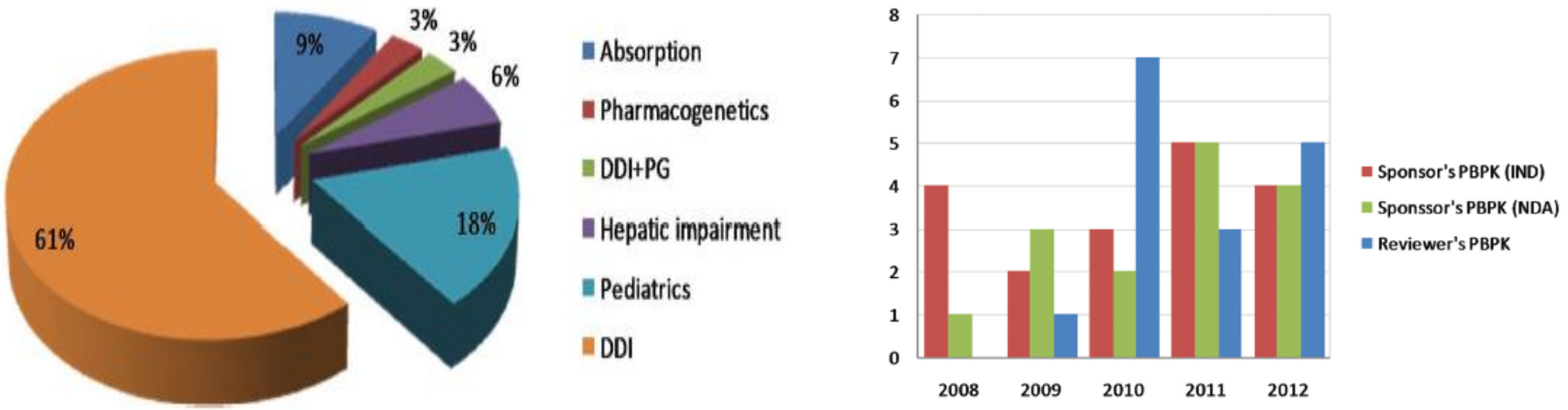
Need for Dermal PBPK Models towards Virtual BE of Generic Products



PBPK Modelling in NDA Submissions

- Low utility in ANDA / Generic Drug Applications
  - PBPK models needed for complex products, topical and locally acting drugs
  - Improvements needed for BA/BE Assessment e.g. WS variability
  - GDUFA – 7 grants for PBPK model development for non-oral drug delivery

(Zhang & Lionberger 2014 CPT; Lionberger 2014, AAPS AM; Huang et al. 2013 J Pharm Sci)

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Mechanistic Dermal Absorption Model

Awarded up to 3 years FDA OGD grant in September 2014

'Development and validation of dermal PBPK modelling platform towards virtual bioequivalence assessment considering population variability'

The project aims to develop a physiologically-based dermal absorption and disposition model along with the supporting database of physiology and its variability for not only the healthy Caucasian volunteers but also special populations such as paediatric, geriatric, other races such as Asian and diseased populations

The new model will also take into account other mechanisms that play an important role in dermal absorption, such as skin surface pH, dermal hydration, skin appendages, binding to keratin, and the effect of permeability-modifying formulation ingredients and drug-physiology interactions

http://www.simcyp.com/News/2014/October/20141023_FDA_Grant.htm?p=1

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Goals

- Develop mechanistic dermal absorption model
- Ability to model and differentiate between formulations
- Support model with human physiology databases
  - Adult Caucasian (male & female)
  - Elderly Caucasian (male & female)
  - Ethnic (Asian or Japanese)
  - Paediatric (physiology changes from birth to teenage years)
  - Disease e.g. psoriasis or acne

- Better ways of *in vitro* to *in vivo* translation
- Translation of product performance from healthy to diseased, elderly or paediatric populations
- Identifications of CQA for product assessment

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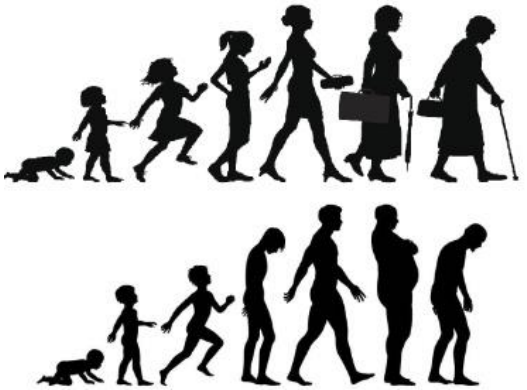
Advantage of PBPK: Separating systems & drug information

Systems Data



Trial Design

Dose
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Drug Data

Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

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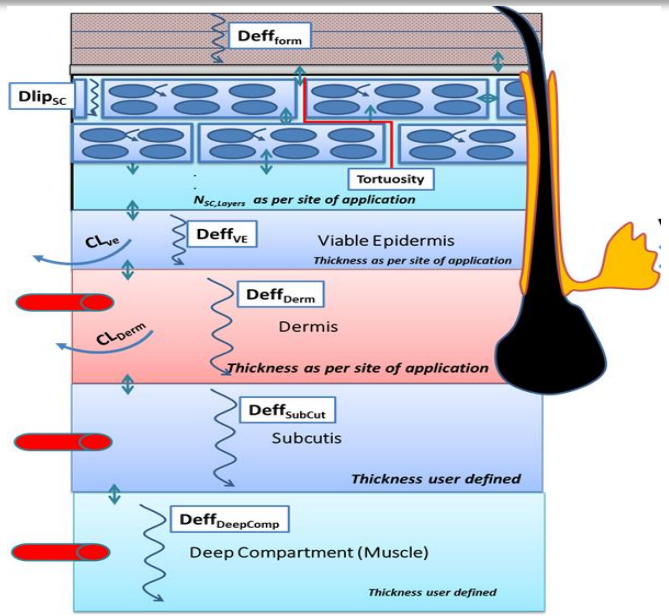
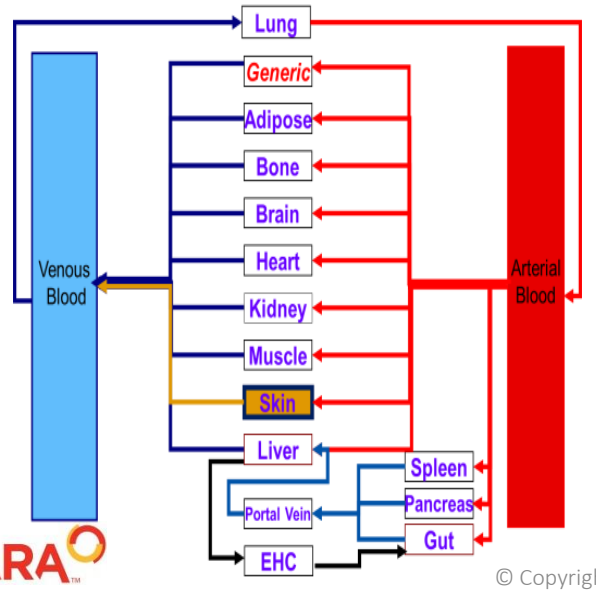
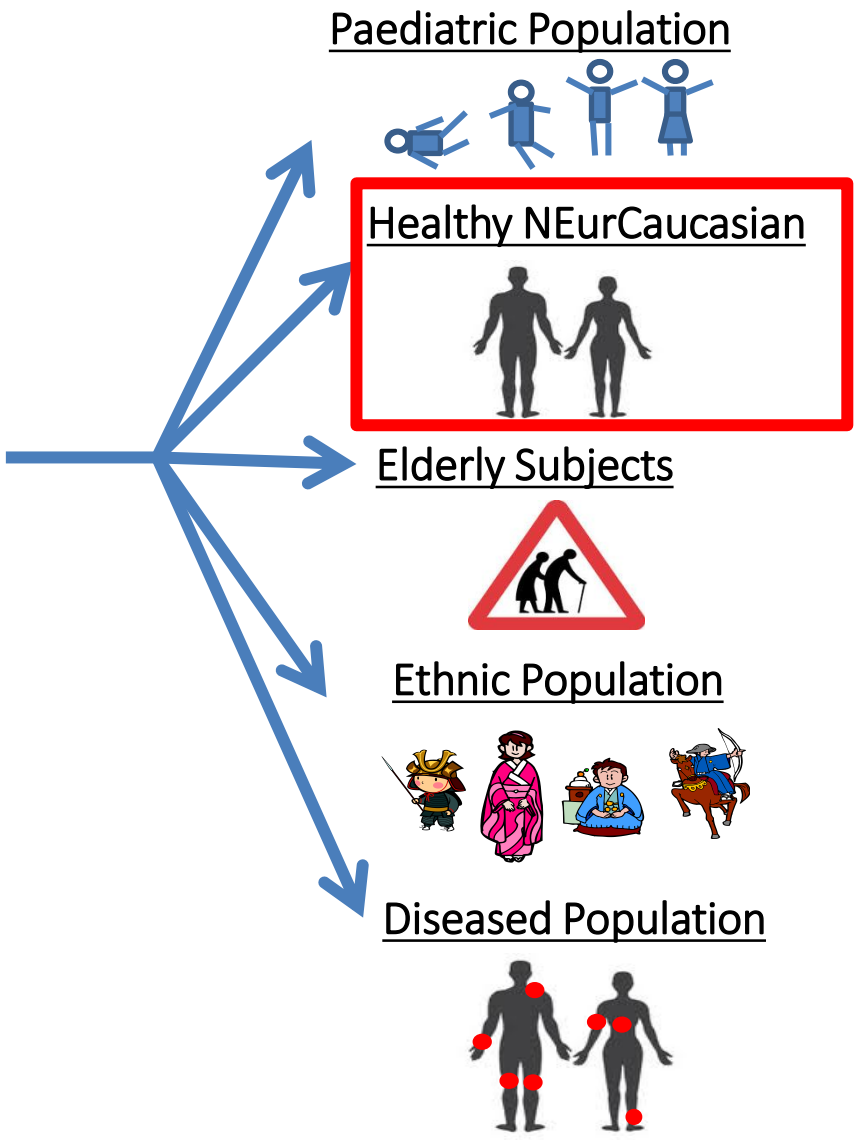
Meta-analysis of Systems Data







Intra-individual Variability

- Eight different locations
  1. Forehead
  2. Face (cheek)
  3. Volar Forearm
  4. Dorsal Forearm
  5. Upper Arm
  6. Lower Leg
  7. Thigh
  8. Back

- Various structural elements
  1. Skin surface
  2. Stratum corneum
  3. Viable epidermis
  4. Dermis
  5. Blood Flow

- Various parameters
  1. Skin temperature
  2. Skin surface pH
  3. # hair follicles
  4. Size of follicles

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Physiology data - Tempearture

- Various parameters:
  - Skin surface
    - ✓ Skin temperature – reality (location)

Table 1
The neutral core and skin temperatures, Dubois surface areas, and weights of the body segments (Tanabe et al., 2002)

i	Body segments	Neutral skin temperature (°C)	Neutral core temperature (°C)	Dubois surface area (m^2)	Weight (kg)
1	Left foot	33.9	35.1	0.056	0.480
2	Right foot	33.9	35.1	0.056	0.480
3	Left leg	33.4	35.6	0.112	3.343
4	Right leg	33.4	35.6	0.112	3.343
5	Left thigh	33.8	35.8	0.209	7.013
6	Right thigh	33.8	35.8	0.209	7.013
7	Pelvis	33.4	36.3	0.221	17.57
8	Head	35.6	36.9	0.140	4.020
9	Left hand	35.2	35.4	0.050	0.335
10	Right hand	35.2	35.4	0.050	0.335
11	Left arm	34.6	35.5	0.063	1.373
12	Right arm	34.6	35.5	0.063	1.373
13	Left shoulder	33.4	35.8	0.096	2.163
14	Right shoulder	33.4	35.8	0.096	2.163
15	Chest	33.6	36.5	0.175	12.40
16	Back	33.2	36.5	0.161	11.03
	Whole body			1.87	74

Physiology data –Skin Surface pH

- Various parameters:
  - Skin surface
    - ✓ Skin surface pH – reality (location)

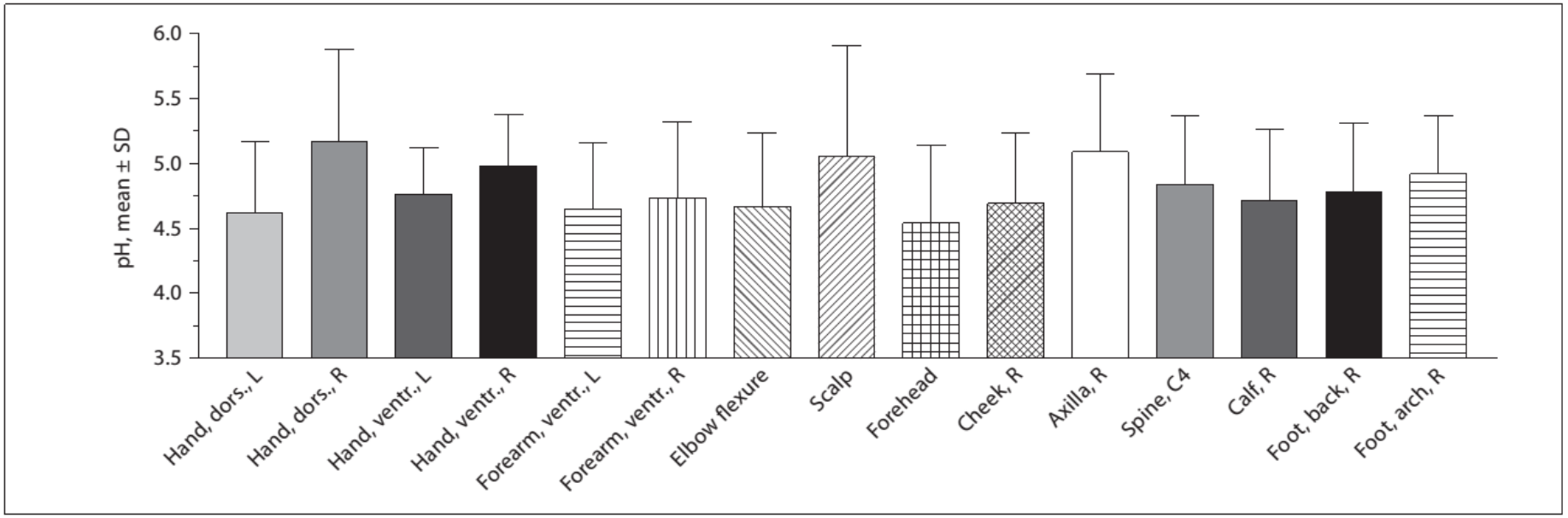

Fig. 4. Skin surface pH values. The skin surface pH was measured with a pH-meter 905 at 15 different anatomical sites in 125 volunteers. The values are expressed in pH units as means ± SD.

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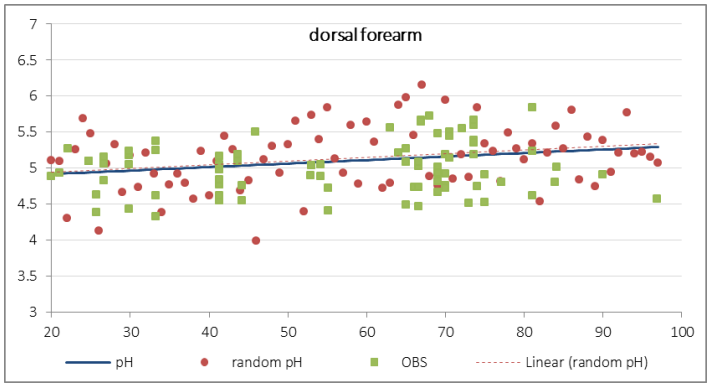
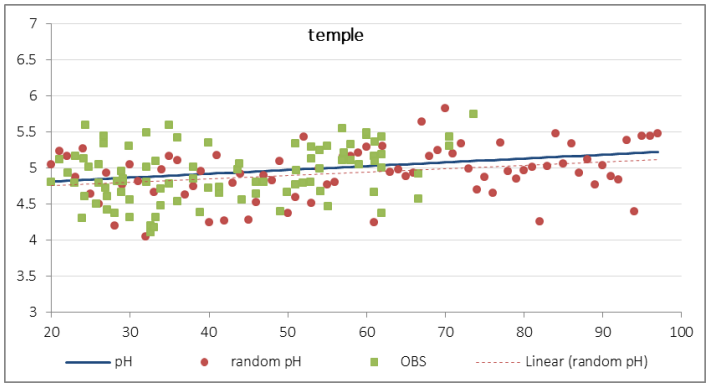
Healthy North-European Caucasians - – influence of ageing on pH (linear regression)

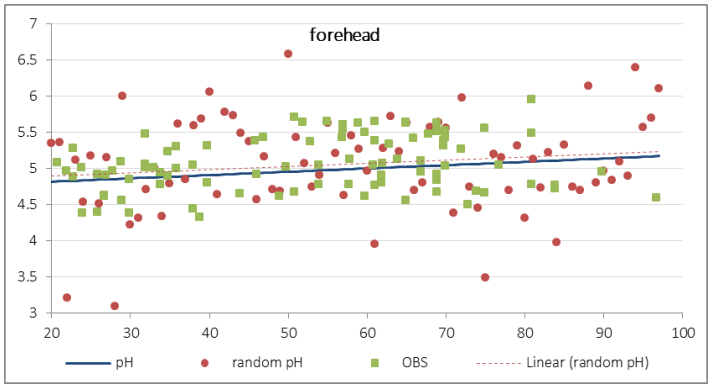
pH = 0.00489 × AGE + 4.818



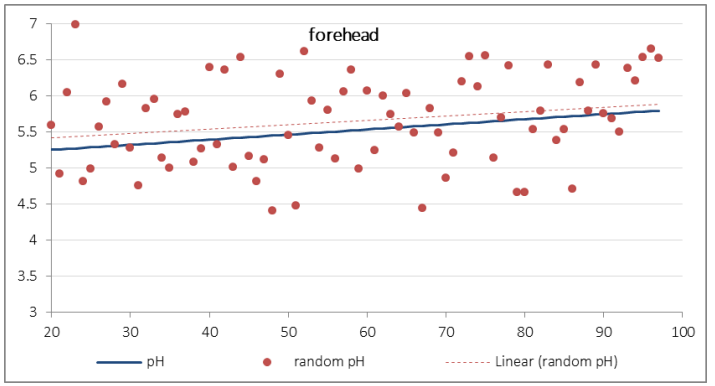


Schreml 2012

pH = 0.00529 × AGE + 4.709



pH = 0.00459 × AGE + 4.725



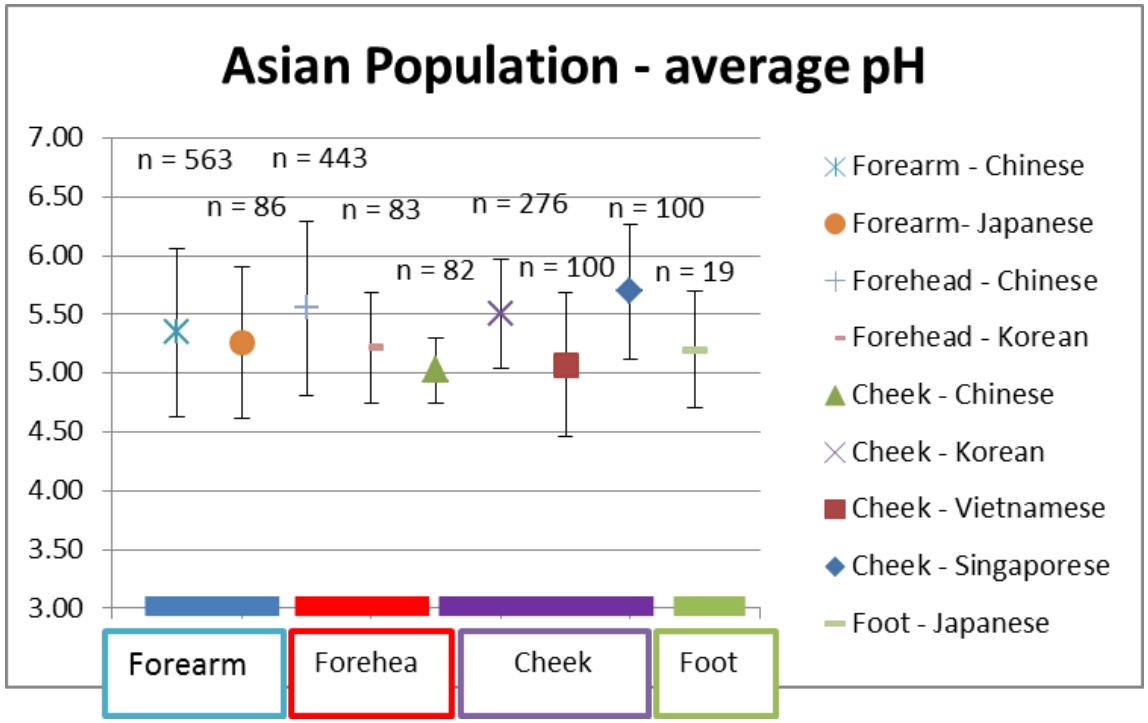
Dikstein 1984

pH = 0.0071 × AGE + 5.11

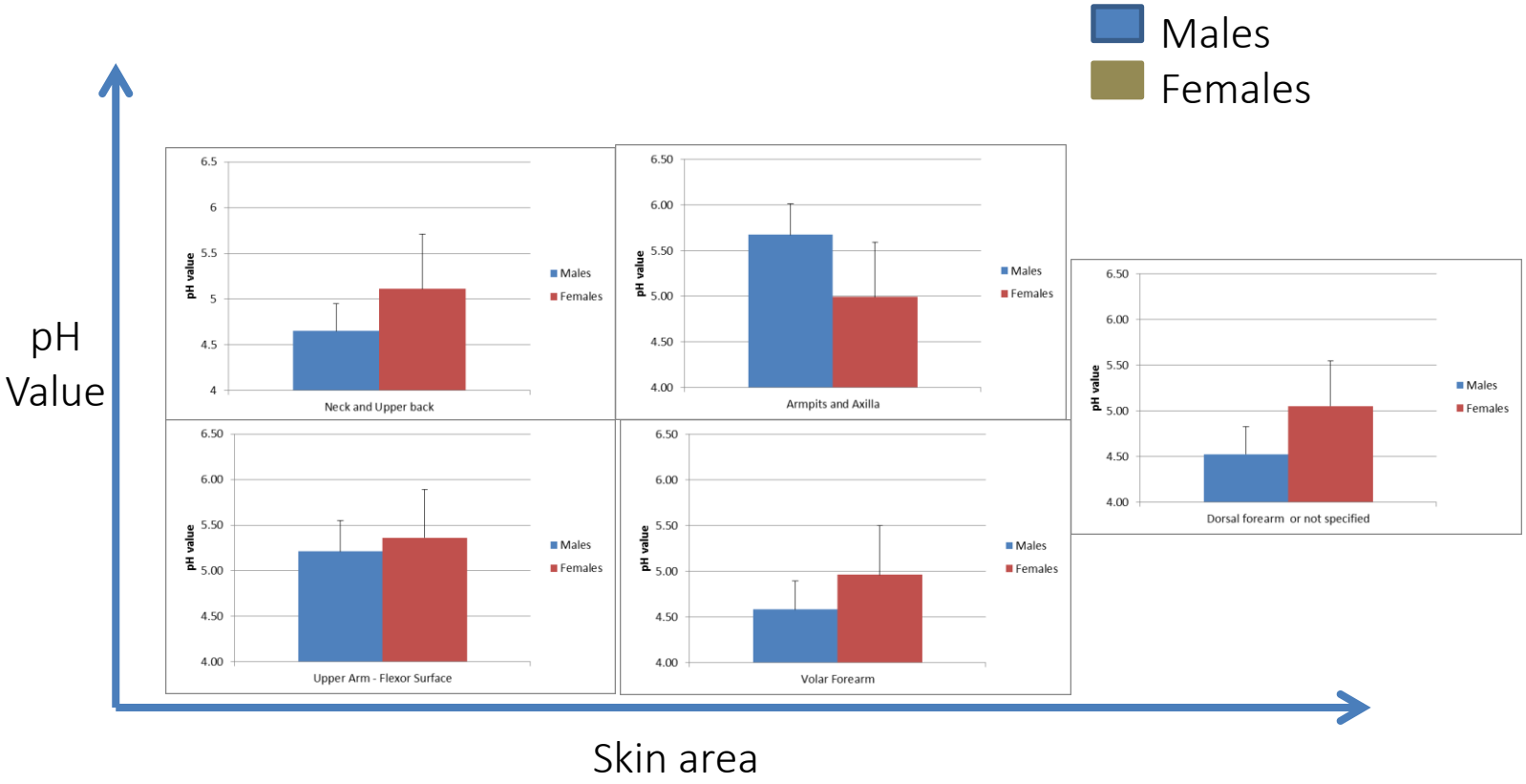
pH units

Age (years)

Asian Population – pH on different body sites

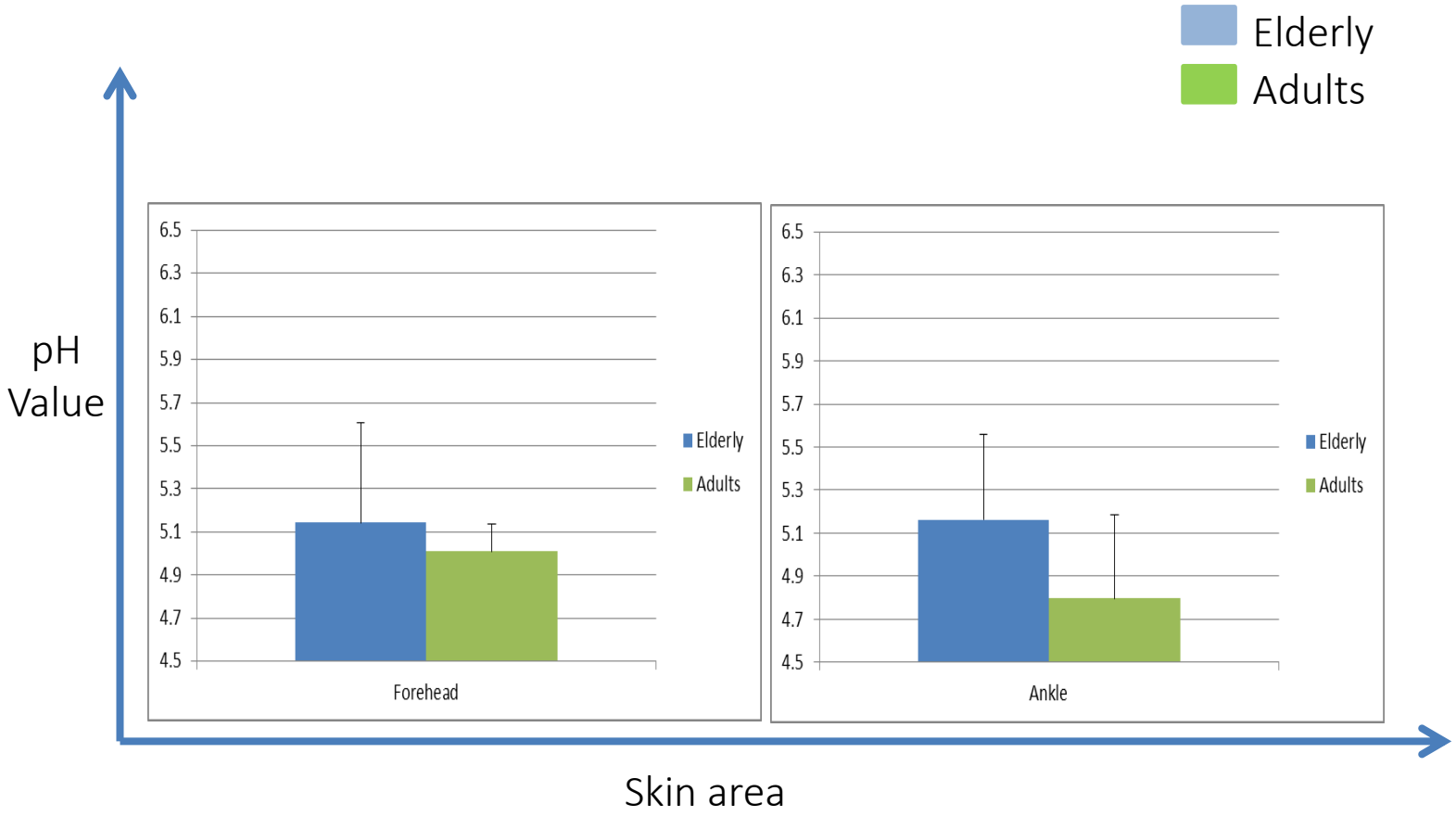


pH differences between males and females



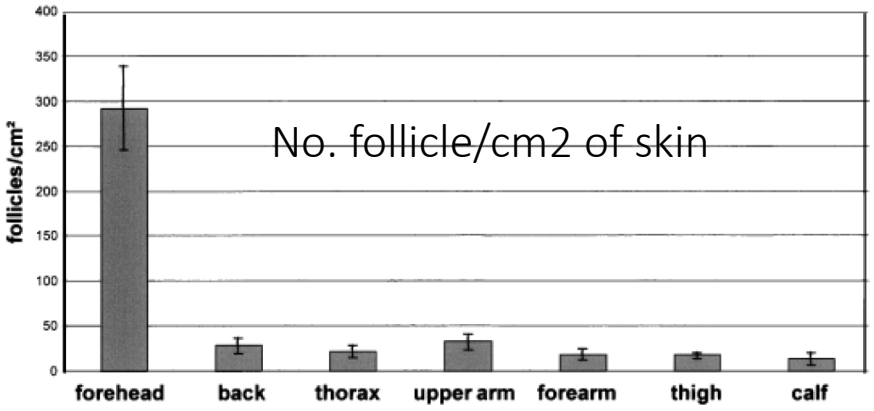
- On average, the pH of females is about 0.5 units higher than in males
- The pH varies between individuals, genders and skin areas

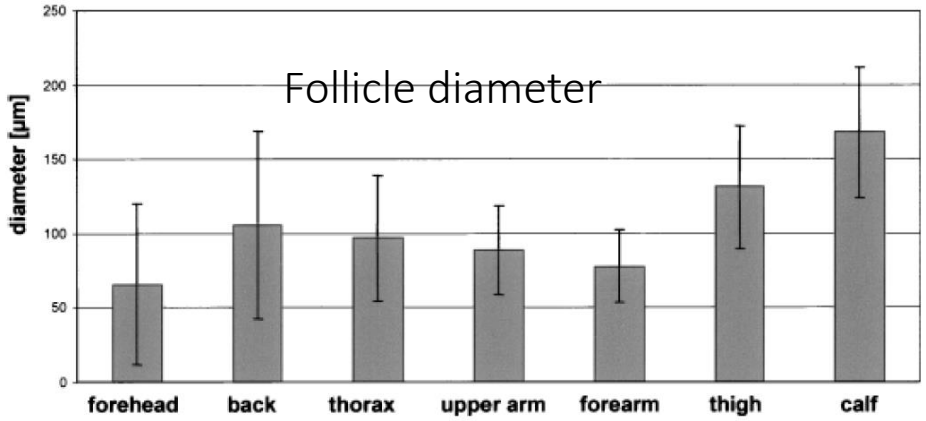
Skin surface pH in elderly vs. adult skin



Wilhelm et al. (1991) found that the pH in the forehead and ankle is higher in the elderly population

Hair follicle/sebum





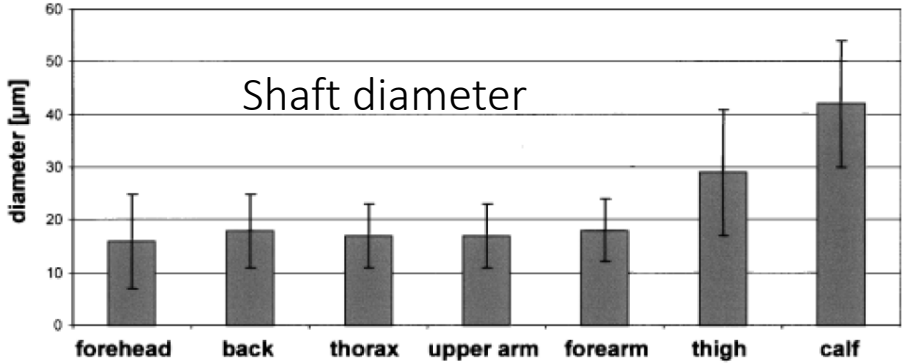


Table I. Percentage mean (± SD) of follicular orifices on the skin surface in seven body sides

Skin area						
Forehead	**Back**	**Thorax**	**Upper arm**	**Forearm**	**Thigh**	**Calf region**
1.28 (± 0.24)	0.33 (± 0.15)	0.19 (± 0.08)	0.21 (± 0.09)	0.09 (± 0.04)	0.23 (± 0.12)	0.35 (± 0.25)

Sebum duct area/volume can be calculated

Otberg 2004

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Intra-individual Variability

- Eight different locations
  1. Forehead
  2. Face (cheek)
  3. Volar Forearm
  4. Dorsal Forearm
  5. Upper Arm
  6. Lower Leg
  7. Thigh
  8. Back

- Various structural elements
  1. Skin surface
  2. Stratum corneum
  3. Viable epidermis
  4. Dermis
  5. Hair

- Various parameters
  1. Number of layers
  2. Corneocyte pH
  3. Corneocyte size
  4. Hydration level
  5. Tortuosity
  6. Lipids fluidity

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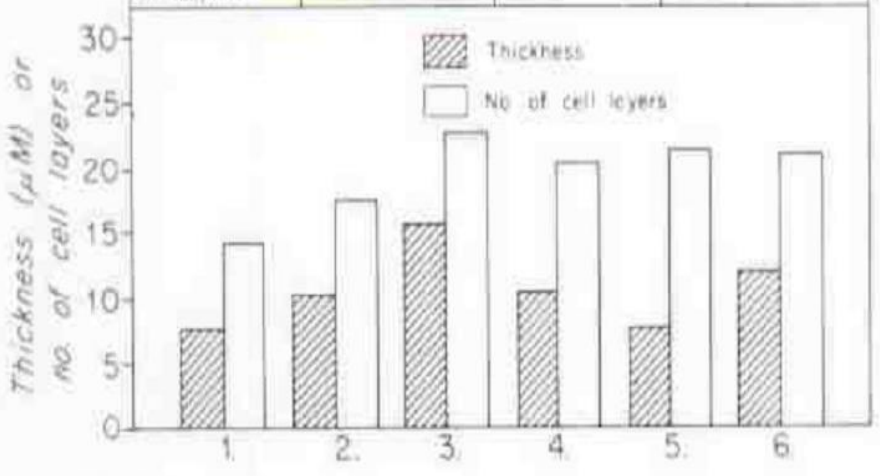
Thicknesses – Top down or Bottom up or User-specified

Mean thickness (μm) and mean number of cell layers of the stratum corneum from the thigh of six human subjects

Subject	Sex	Age	Mean thickness (μM)	Mean no. of cell layers	Calculated mean cell thickness
1.	M	27	7.7 ± 1.4	14.3 ± 2.6	.19
2.	M	25	10.3 ± 1.8	17.5 ± 2.7	.17
3.	M	26	15.3 ± 3.1	22.7 ± 4.0	.15
Mean values - ♂			10.9 ± 3.8	18.0 ± 4.5	.17
4.	F	31	10.1 ± 2.0	20.1 ± 2.5	.20
5.	F	30	7.7 ± 1.4	21.2 ± 3.0	.28
6.	F	30	11.9 ± 1.5	20.7 ± 2.4	.17
Mean values - ♀			11.0 ± 2.0	20.7 ± 2.7	.22
Mean values for all subjects			10.9 ± 3.1	19.3 ± 4.0	.18



Holbrook & Oland 1974

Table 1 Comparison of the number of cell layers of the SC at various anatomical locations

Location	Number of cell layers (mean ± SD)
Face	9 ± 2 (n = 84)
Forehead	9 ± 1 (n = 8)
Eyelid	8 ± 2 (n = 16)
Cheek	10 ± 3 (n = 43)
Nose	10 (n = 2)
Nasolabial fold	7 (n = 2)
Lip	10 (n = 2)
Ear	7 ± 2 (n = 8)
Periauricular region	10 ± 3 (n = 3)
Scalp	12 ± 2 (n = 12)
Neck	10 ± 2 (n = 5)
Trunk	13 ± 4 (n = 94)
Shoulder	13 ± 2 (n = 3)
Chest	13 ± 4 (n = 9)
Back	13 ± 3 (n = 18)
Abdomen	14 ± 4 (n = 44)
Buttock	12 ± 4 (n = 20)
Genital	6 ± 2 (n = 9)
Extremities	15 ± 4 (n = 55)
Extensor surface, upper arm	13 ± 4 (n = 13)
Flexor surface, upper arm	14 (n = 2)
Flexor surface, forearm	16 ± 4 (n = 4)
Thigh	16 ± 4 (n = 31)
Flexor surface, leg	18 ± 5 (n = 5)
Acral region	47 ± 24 (n = 42)
Dorsum of the hand	25 ± 11 (n = 10)
Dorsum of the foot	30 ± 6 (n = 7)
Palm	50 ± 10 (n = 8)
Sole	55 ± 14 (n = 12)
Heel	86 ± 36 (n = 5)

Ya-Xian 1999

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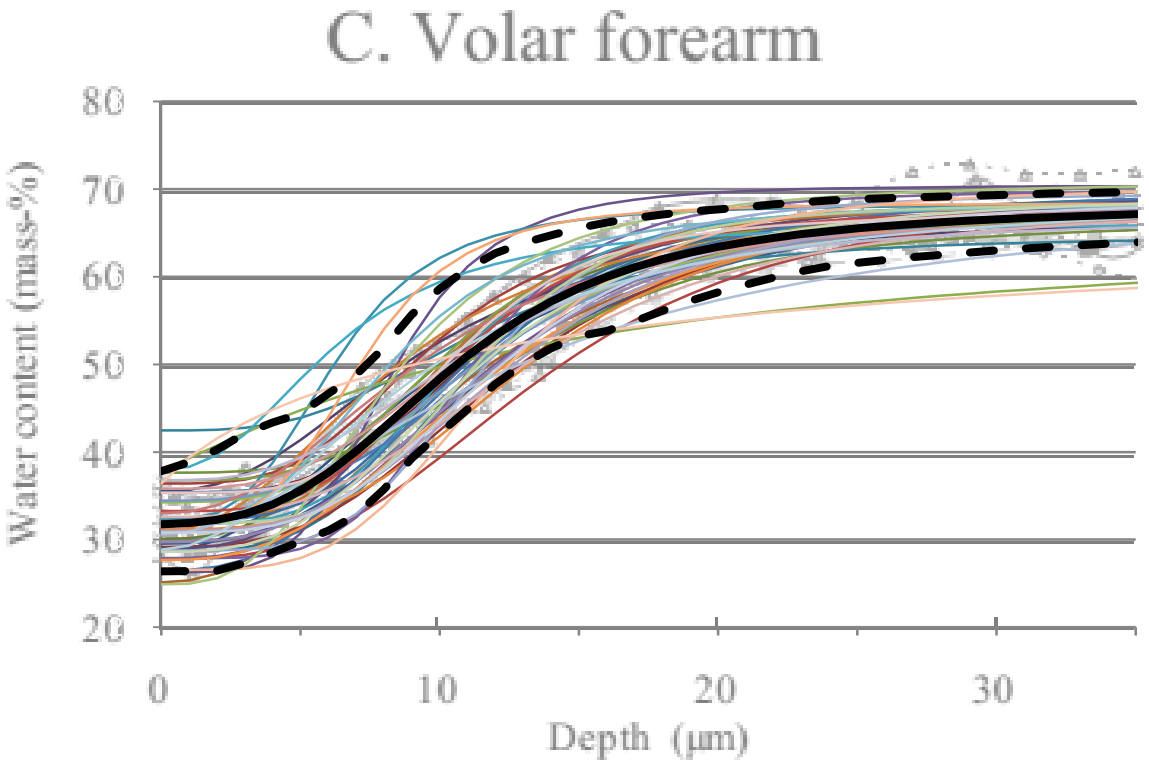
Tortuosity and hydration expansion

Hydration depth profile – implementation to be decided



Locations

- Cheek
- Upper arm
- Volar forearm

$$Response = Baseline \pm \frac{E_{max} \bullet C_R^{\gamma}}{C_{R,50\%}^{\gamma} + C_R^{\gamma}}$$

Egawa 2007

Advantage of PBPK: Separating systems & drug information

Systems Data

Trial Design

Drug Data

Dose
Administration route
Frequency
Co-administered drugs
Populations

Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

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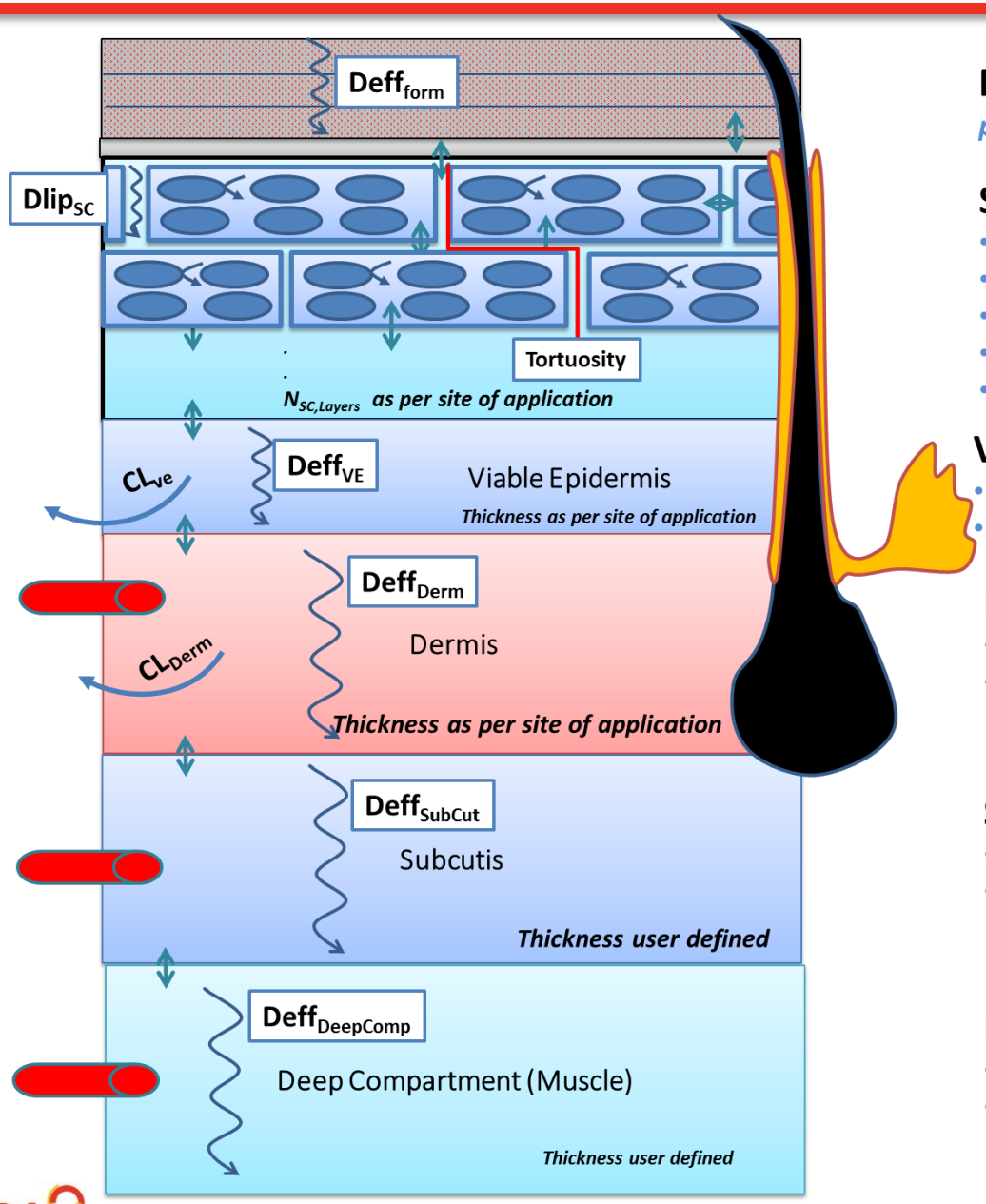
MPML MechDermA Model



Formulation *(Gel, cream, lotions, paste, patch, ointments, etc.)*

Stratum Corneum (SC)

- *Define cell shape and size*
- *Cell membrane permeability*
- *Keratin bonding kinetics*
- *Tortuosity and fluidity*
- *Hair follicle density and size*

Viable Epidermis (VE)

- *Thickness, fluidity*
- *Metabolism*

Dermis

- *Thickness, fluidity*
- *Metabolism, blood flow*

Subcutis

- *Thickness, fluidity*
- *Blood flow*

Deep Tissue

- *Thickness, fluidity*
- *Blood flow*

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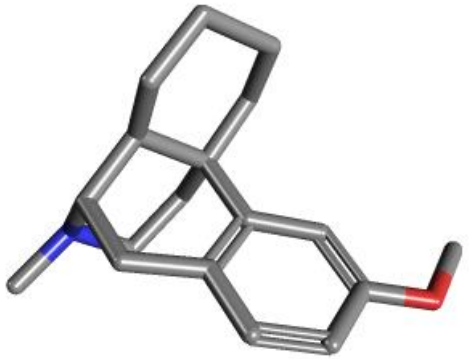

Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

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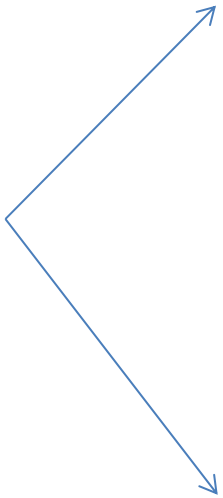
Drug Related Parameters

- Phys-chem
  1. MW
  2. Density
  3. LogP
  4. LogD
  5. pKa

- Protein binding and ionization
  1. fu_{SC}
  2. fni

- ADME parameters
  1. BP
  2. fu
  3. CL
  4. ....



- Partition coefficients
  1. $K_{lip/w}$
  2. K_{vw}
  3. $K_{SC/VE}$
  4. .....

- Diffusion coefficients
  1. D_{veh}
  2. D_{lip}
  3. D_{ve}
  4. ....

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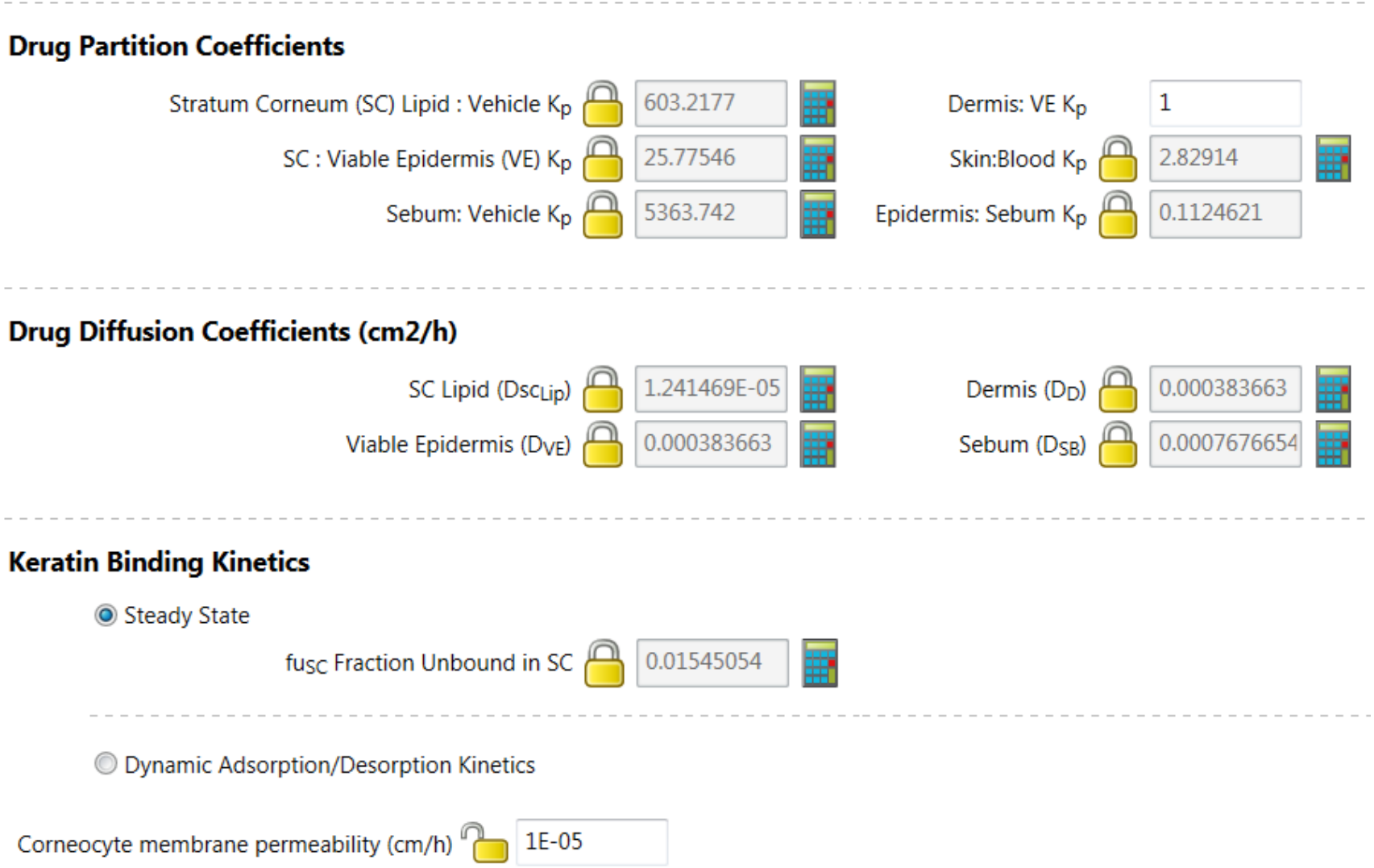
Drug Related Parameters

Obtain from in vitro measurements or predict using QSAR models



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Advantage of PBPK: Separating systems & drug information

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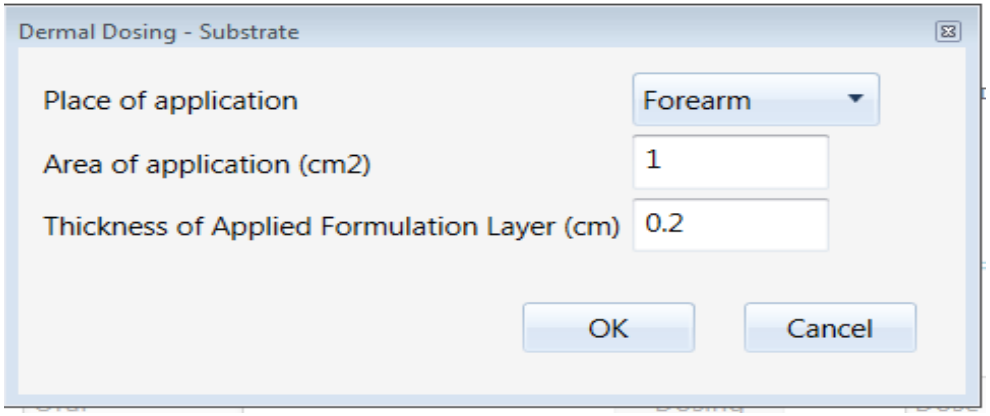
Formulation Data - Solution



Formulation Options and Parameters

Formulation pH is skin surface pH Formulation pH 6.5 CV (%) 30

Fraction non-ionised at skin surface $fni_{skin\ surface}$ 0.02505982

Solution

Formulation Diffusion Coefficients (cm^2/h)

Diffusion Coeff in Vehicle

Method: Scheibel 1954

Vehicle Viscosity (cP): 10000 Predicted Dveh (cm^2/h): 2.134354E

Vehicle Molar Volume (mL/mol): 18

Diffusion Coeff in Polymer (Gel or Patch Formulations)

Method: Mackie and Meares 1955

Volume Fraction of Polymer: 0.5 Predicted D_{poly} (cm^2/h): 2.371504E

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Formulation Data - Emulsion

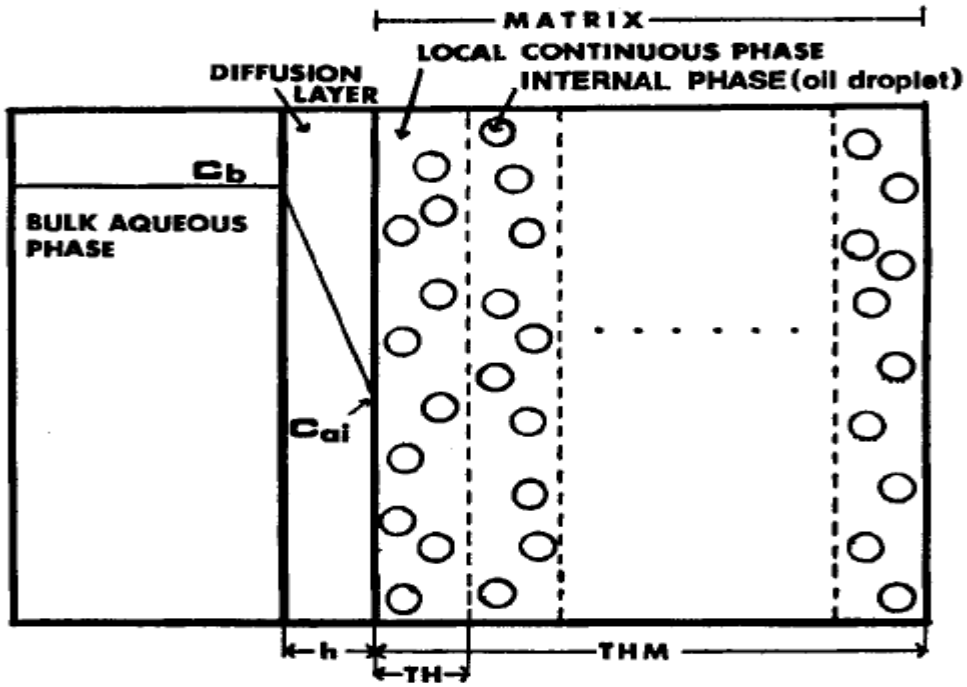
Emulsion

Diffusion Coeff (cm^2/h)	2.134354E-05	Vehicle molar volume (mL/mol)	18
		Viscosity (centipose)	1000
Diameter of dispersed phase droplets (µm)	10	Drug solubility ratio dispersed/continuous phase	9333
Number of droplets per cm^3 (N/mL)	1000	Droplet permeability (cm/h)	1E-05

Particles in continuous phase?

Diameter of particles (µm)	10	Drug solubility in continuous phase (mg/mL)	1
Number of particles per cm^3 (N/mL)	1E+07		

- Diffusion of drug is modelled
- Oil droplets movement neglected
- During storage and application, drug distribution is assumed to be at the thermodynamic equilibrium



Yotsuyangi et al. 1973, JPS, 62(1), 41

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Formulation Data – Suspension/Paste/Patch

Suspension / Paste

Diffusion Coeff (cm^2/h) 0.02134354

Vehicle viscosity (centipose) 1

Vehicle molar volume (mL/mol) 18

Drug solubility in vehicle (mg/mL) 1

Particle diameter (µm) 10

Number of particles per cm^3 (N/mL) 1E+07

Dermal Patch

Empirical release rate

Zero order release rate (mg/h) 1

First order release rate constant (1/h) 0.1

Controlled Release (CR)

Diffusion based release kinetics

Diffusion Coeff (cm^2/h) 2.371504E-06

Vehicle molar volume (mL/mol) 18

Vehicle viscosity (centipose) 1000

Volume fraction of polymer 0.5

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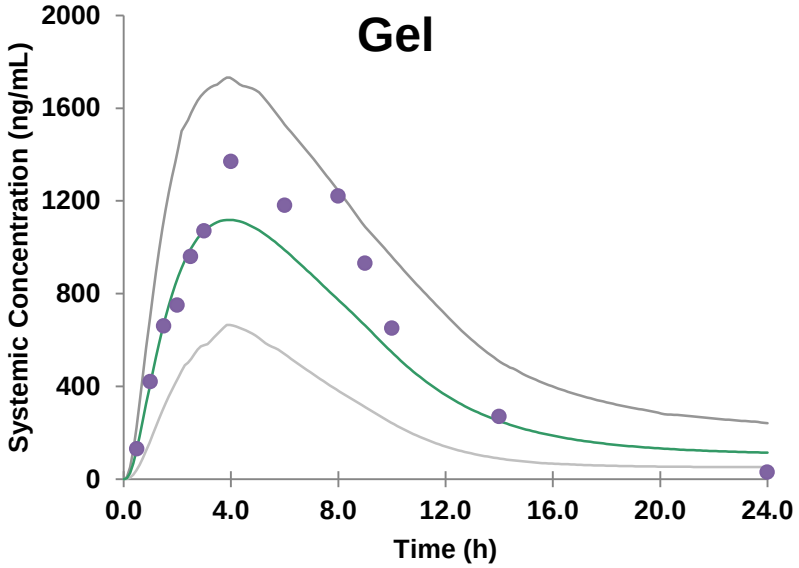
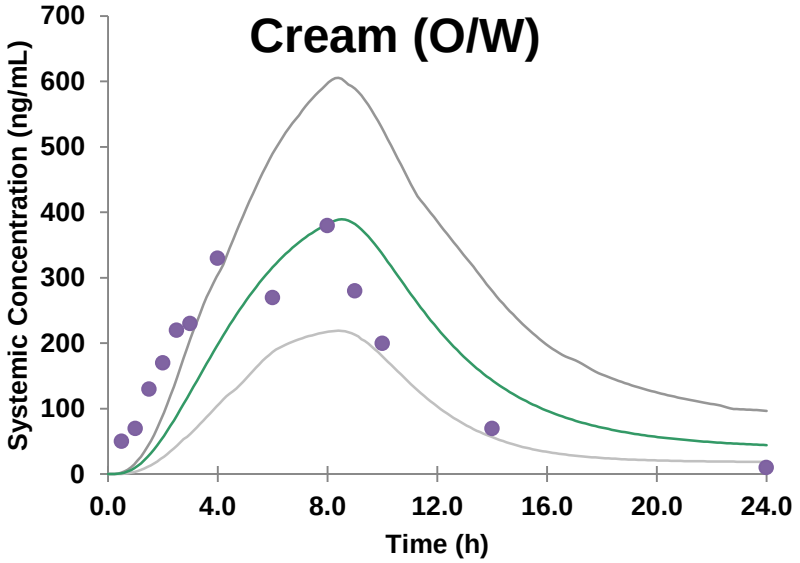
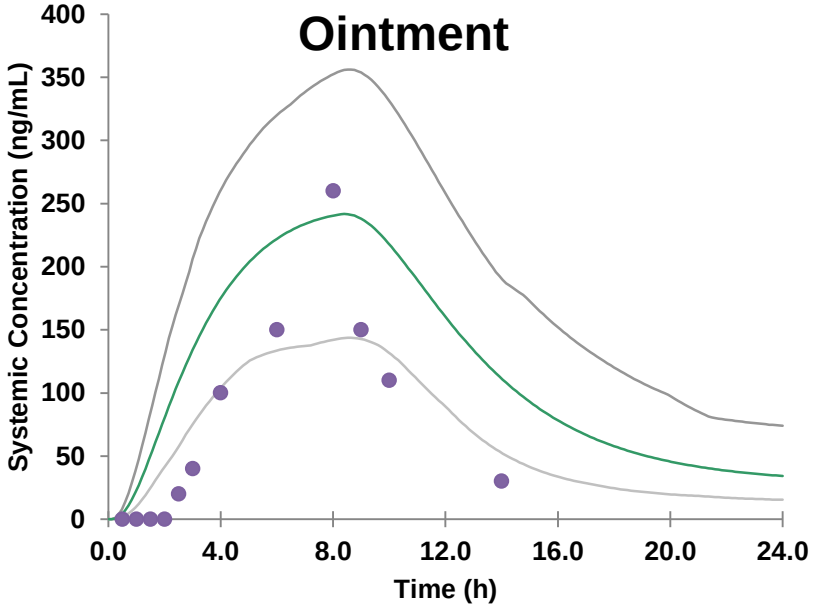
Case Study: Ibuprofen Formulations







- Drug Parameters predicted with QSAR
- Formulation pH assumed 6.5
- Viscosity assumed 10000 cP
- Liberation assumed instantaneous in Ointment
- No excipient effect modelled explicitly

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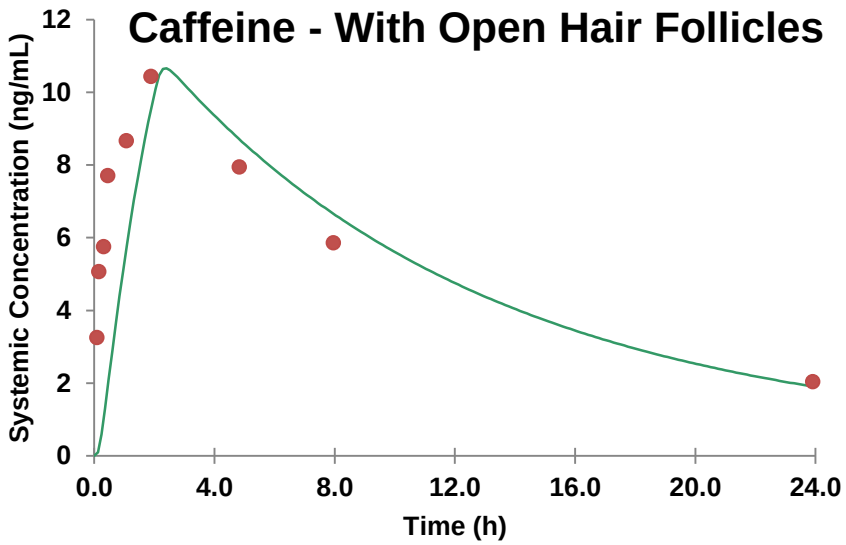
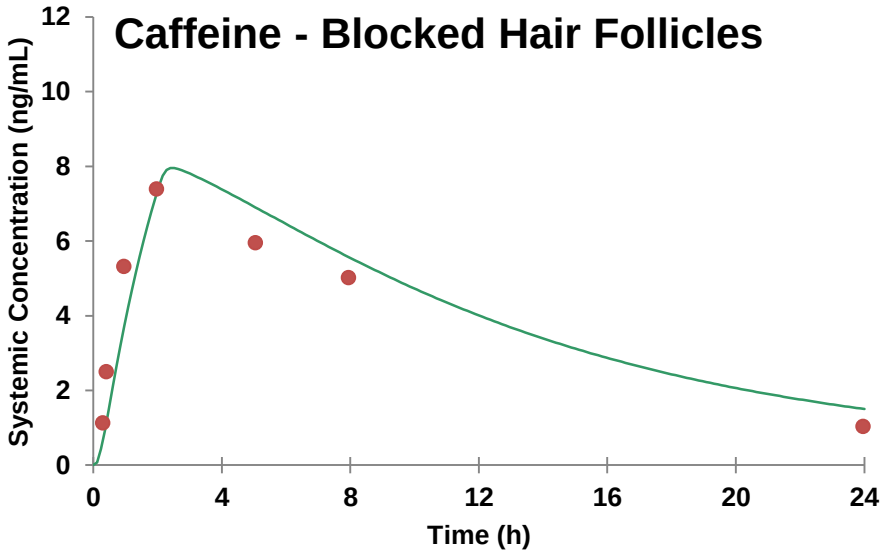
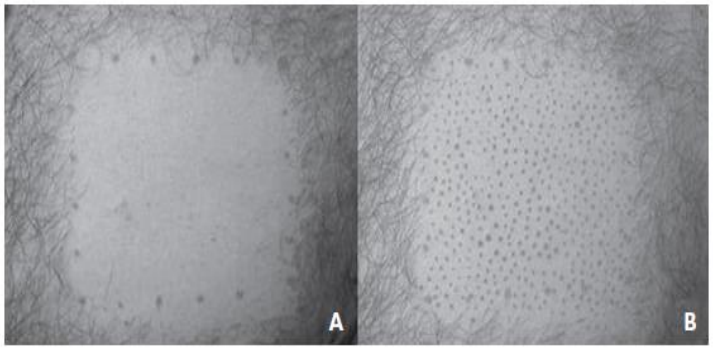
Caffeine Case Study – Predicting Contribution of Hair Follicle





Clinical data and trial design from Liu et al. BJCP, 2011, 72, 768

- When simply hair follicles are closed, predictions were higher than clinical measurement
- With reduction in area of block around the hair follicle, we were able to predict clinical observation



Otberg *et al*. 2007

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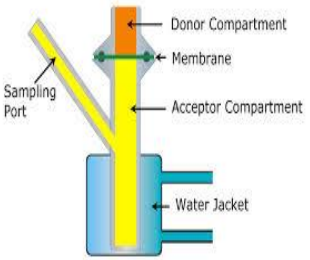
Simcyp IVIVE: Translating in vitro permeability to clinical situations

IVIVE (*In vitro-in vivo* extrapolation)



Simcyp MechDermA Model

In vitro systems data

In vitro Systems parameters

- skin thickness
- pH
- Hydration level
- hair follicle density

API/Formulation parameters

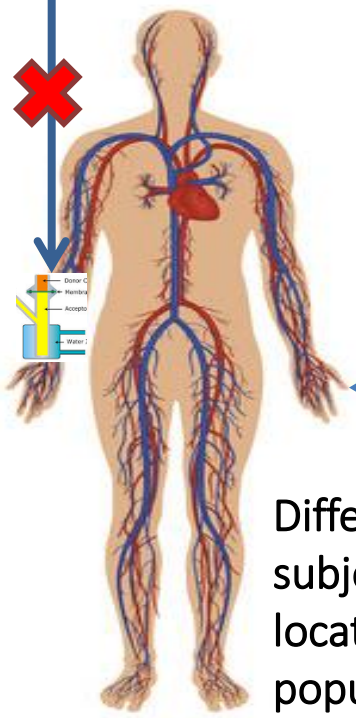
- Diffusion coefficient
- Partitioning
- Keratin binding
- Refine Unknown/uncertain

Simcyp MechDermA Model

Simcyp simulator

In vivo Systems parameters + variability

- skin thickness
- pH
- hydration
- Hair follicle density



Different subjects, locations, populations

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Model Performance Verification in vitro – Three Beta-blockers

Evaluation of β-Blocker Gel and Effect of Dosing Volume for Topical Delivery

Zhang, Chantasart, and Li, JOURNAL OF PHARMACEUTICAL SCIENCES

β-Blocker	log $K_{o/w}$[a]	log $K_{o/w}$[b]	Gel pH	f_{union}
Propranolol	3.3	3.48 ± 0.02	7.4	0.0079
Betaxolol	2.8	2.80 ± 0.02	7.4	0.0108
Timolol	2.1	1.79 ± 0.02	7.4	0.0153

β-Blocker	Molecular Weight (g/mol)	p*K*a	log $K_{o/w}$
Propranolol	259.3	9.5 ± 1.2[a]	3.3[a]
Betaxolol	307.4	9.4[b]	2.8[b]
Timolol	316.4	9.2[c]	2.1[c]

Table 2. Experimental Conditions Used in the Franz Cell Experiments of the β-Blockers

β-Blocker	Donor Concentration	Experimental Condition	Dosing Volume (mL)
Propranolol	4 mg/mL propranolol hydrochloride	Nonocclusive	0.15
		Occlusive	0.03, 0.07, 0.15, 0.5
Betaxolol	5 mg/mL betaxolol hydrochloride	Nonocclusive	0.15
		Occlusive	0.03, 0.07, 0.15
Timolol	5 mg/mL timolol maleate	Nonocclusive	0.15
		Occlusive	0.03, 0.07, 0.15

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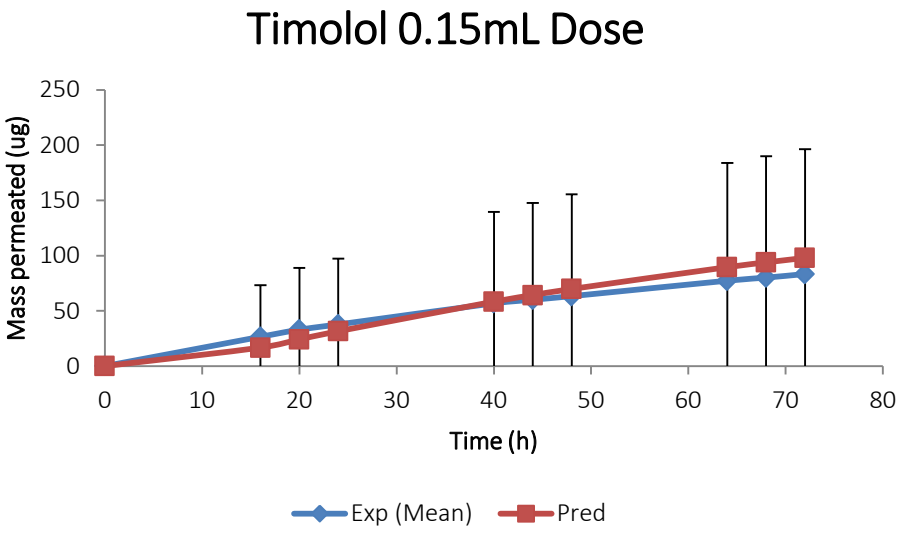
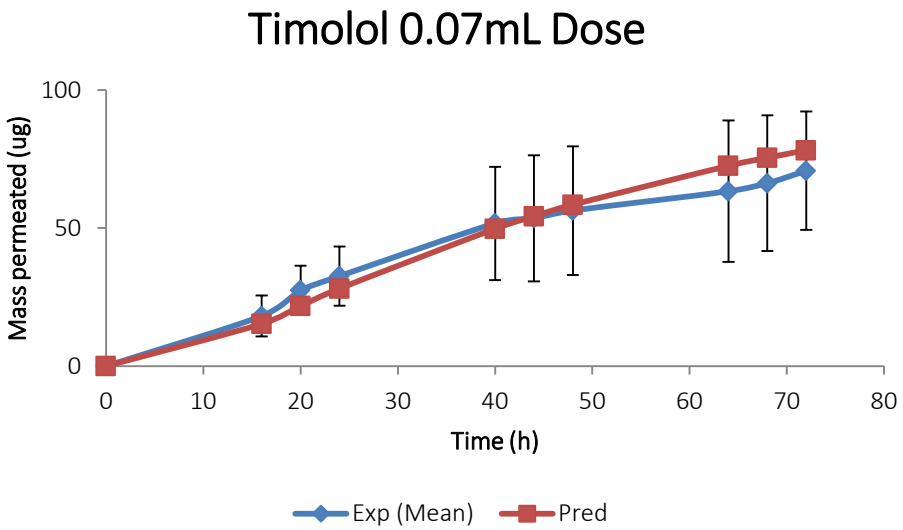
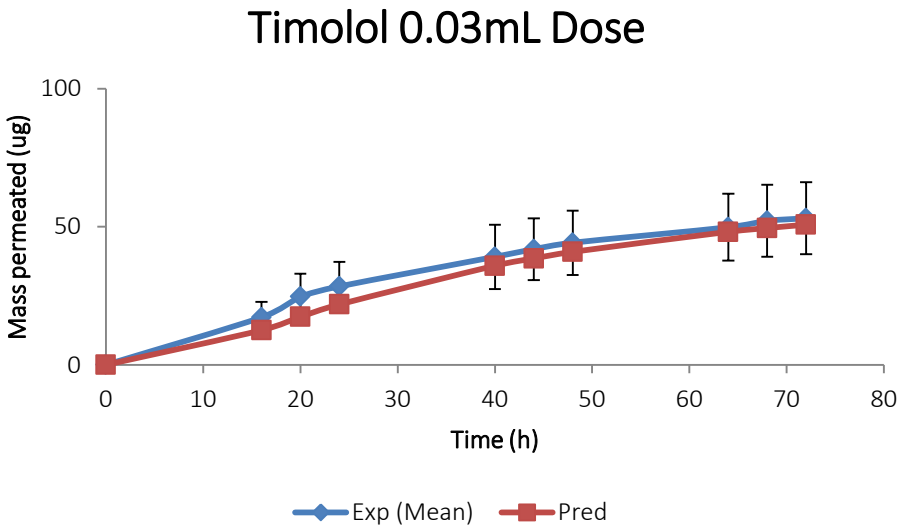
Timolol Prediction for three doses

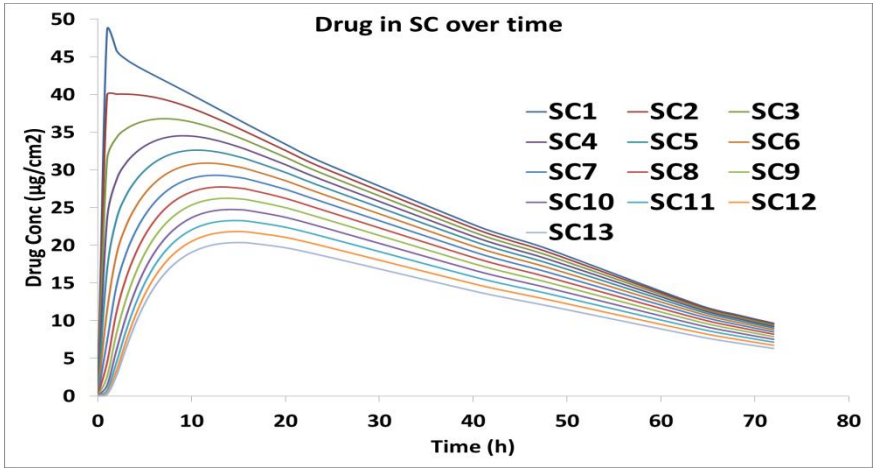




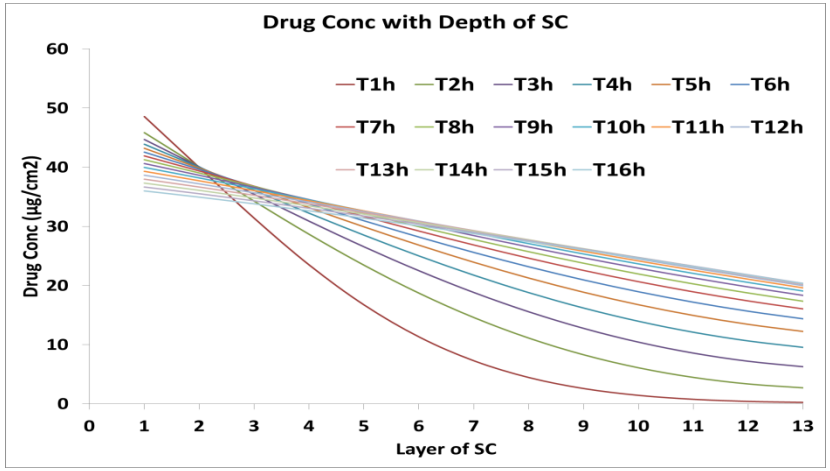


- Thickness of skin layers not reported
  - ✓ Assumed SC thickness 10um (Simcyp value for back is 9um)
  - ✓ Assumed VE thickness 100um (value typical for split-thickness skin)
- **Tortuosity (1.5-fold) –** fitted parameter to match observations (but within the limits of reported value)

Timolol – Matrix-type Patch formulation

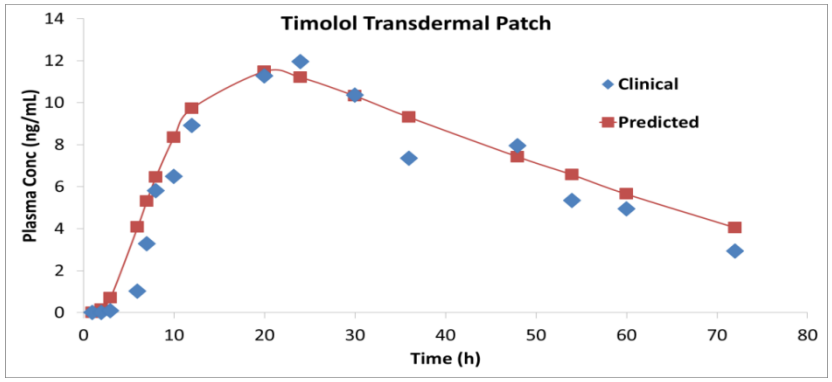


Drug conc. in layers of SC changing with time



Drug conc. changing with depth of SC

- Able to simulate the transient phase and transition to steady-state diffusion
- 12-16 h to achieve steady state diffusion



Simulated plasma drug conc. overlaid with clinically observed data

PK Parameter	Clinical	Simulated	%PE
C_{max} (ng/mL)	12.7	11.48	9.63
T_{max} (h)	22.9	21	8.3
AUC_{inf} (ng/mL.h)	613	633.33	-3.3
F_{AUC}	74.4	74.3	0.13
Lag time (h)	3	2	33.3

Comparison of Observed and Predicted PK parameters and %prediction errors

Patel et al. 2015 GRC Dermal Barrier Conference

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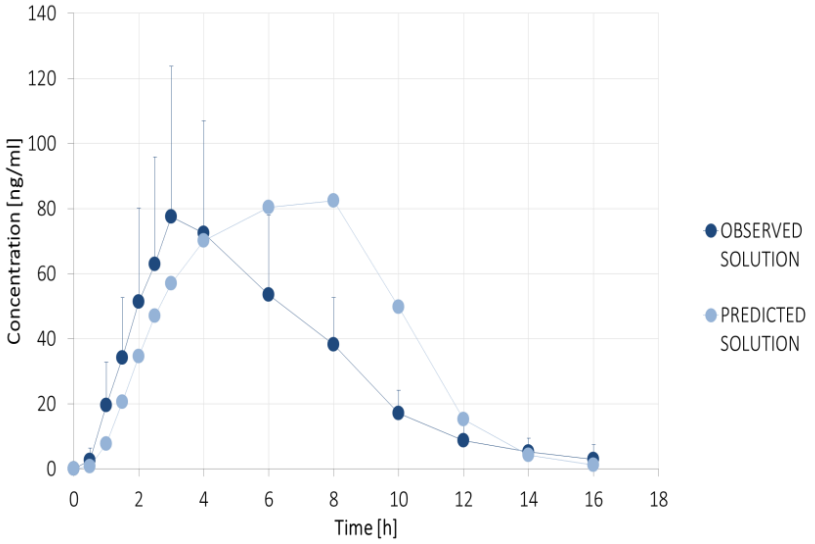
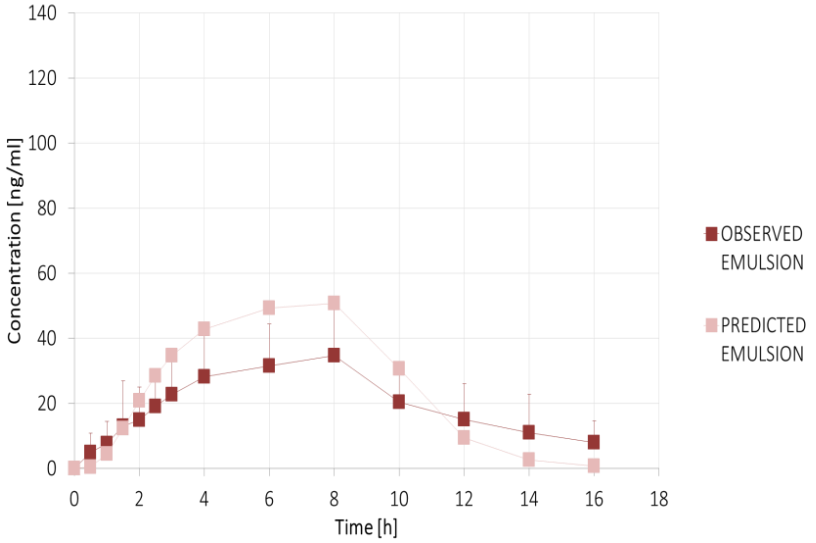
Diclofenac – solution gel vs. emulsion gel



Observed vs. Predicted drug concentration after solution gel application



Observed vs. Predicted drug concentration after emulsion gel application

- Predictions using as input physicochemical properties of the drug and formulation characteristics
- T_{max} over-predicted for the solution gel
- Diffusion coefficients: QSAR predicted / Stokes Einstein equation

Parameter	Observed	Simulated
S/E Cmax ratio	1.54	1.63
S/E AUC ratio	2.07	1.62
F_{AUC}	4.5% (S); 2.8% (E)	3.3% (S); 2.2% (E)

S – solution gel; E – emulsion gel

Polak et al. 2015 GRC Dermal Barrier Conference

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Topical Erythromycin Solution

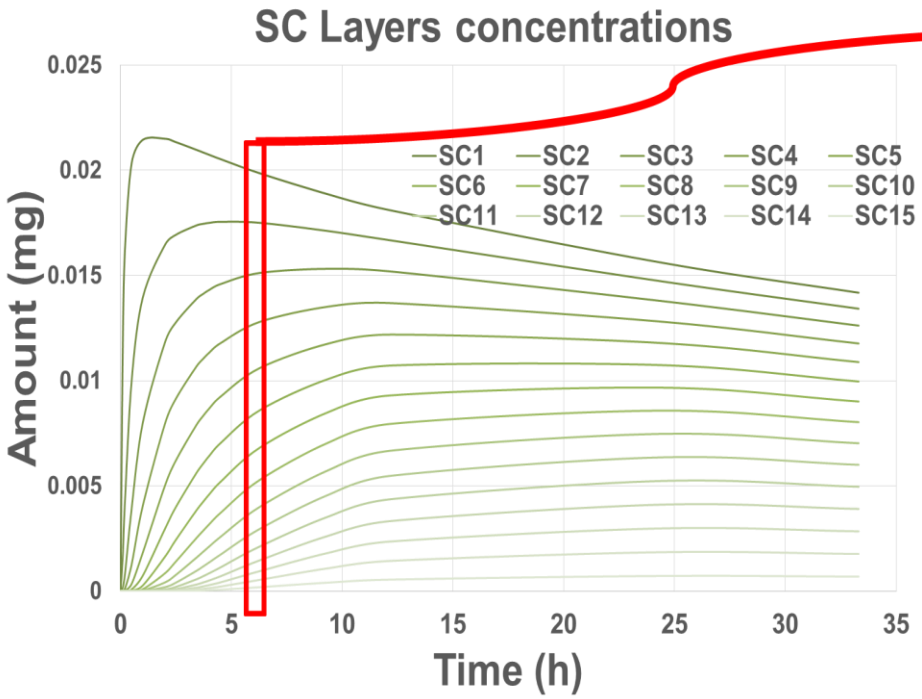

Figure 2. Erythromycin SC individual layers PK profiles.

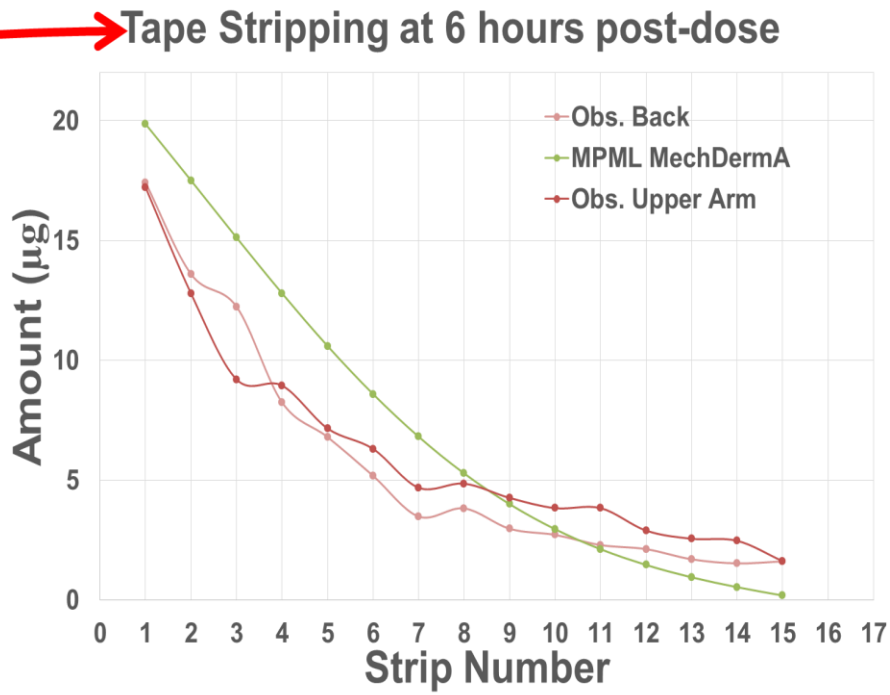

Figure 4. MPML MechDermA skin stripping experiments Predictions vs. Observations

- The model produces outputs that can be compared with tape-stripping or biopsy data

Cristea *et al.* 2015, DMDG Drug Delivery Symposium GSK

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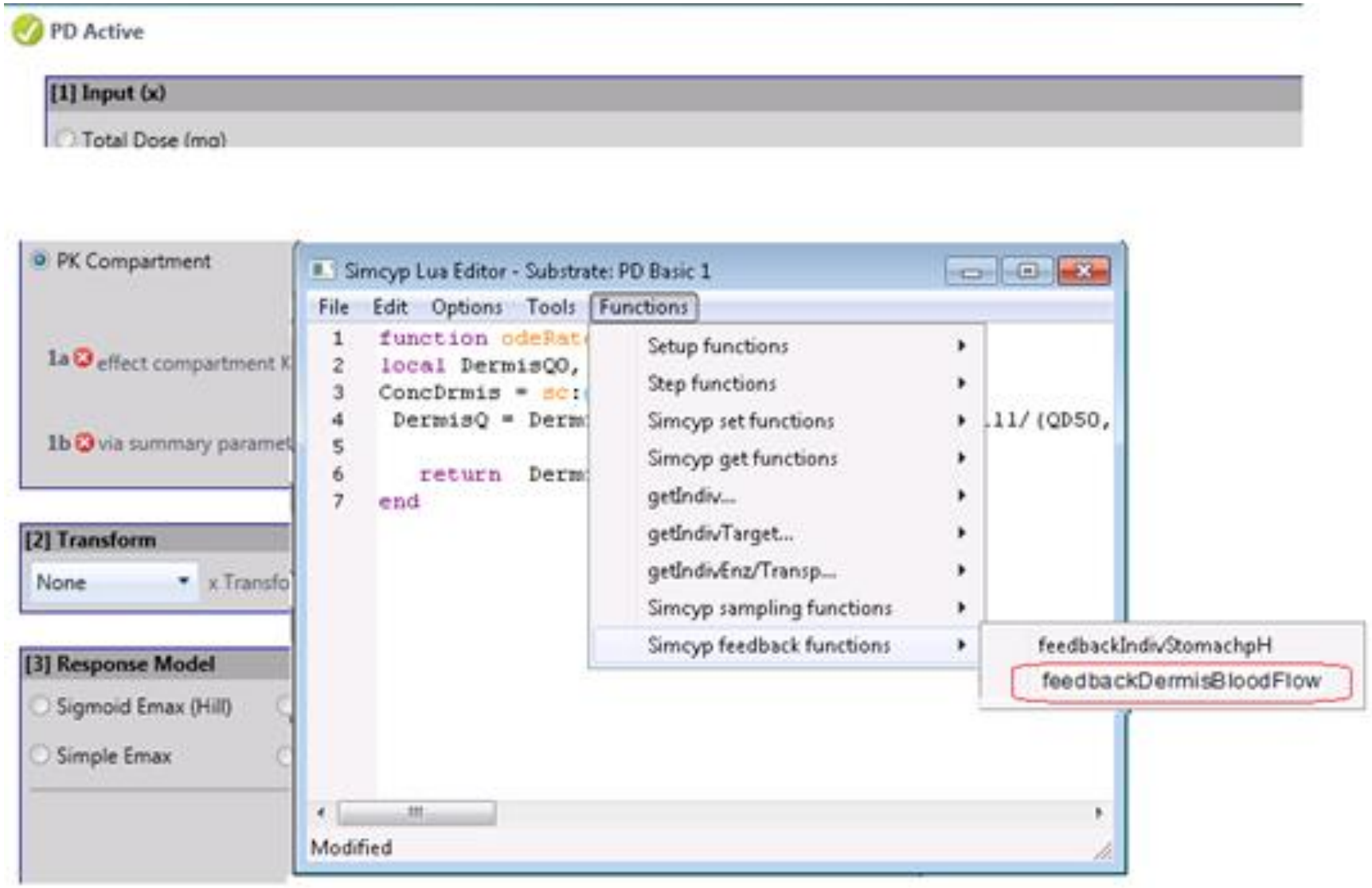
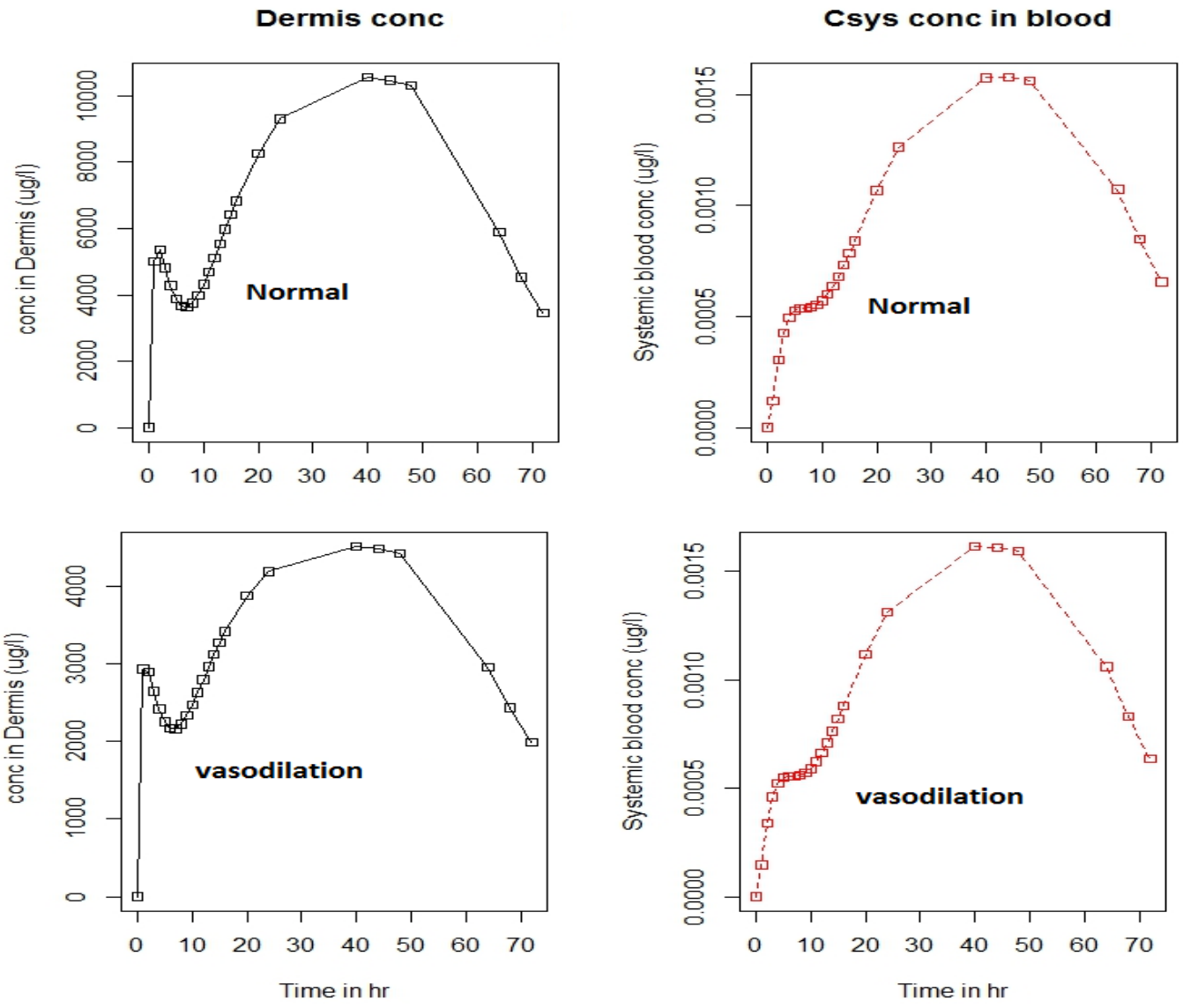
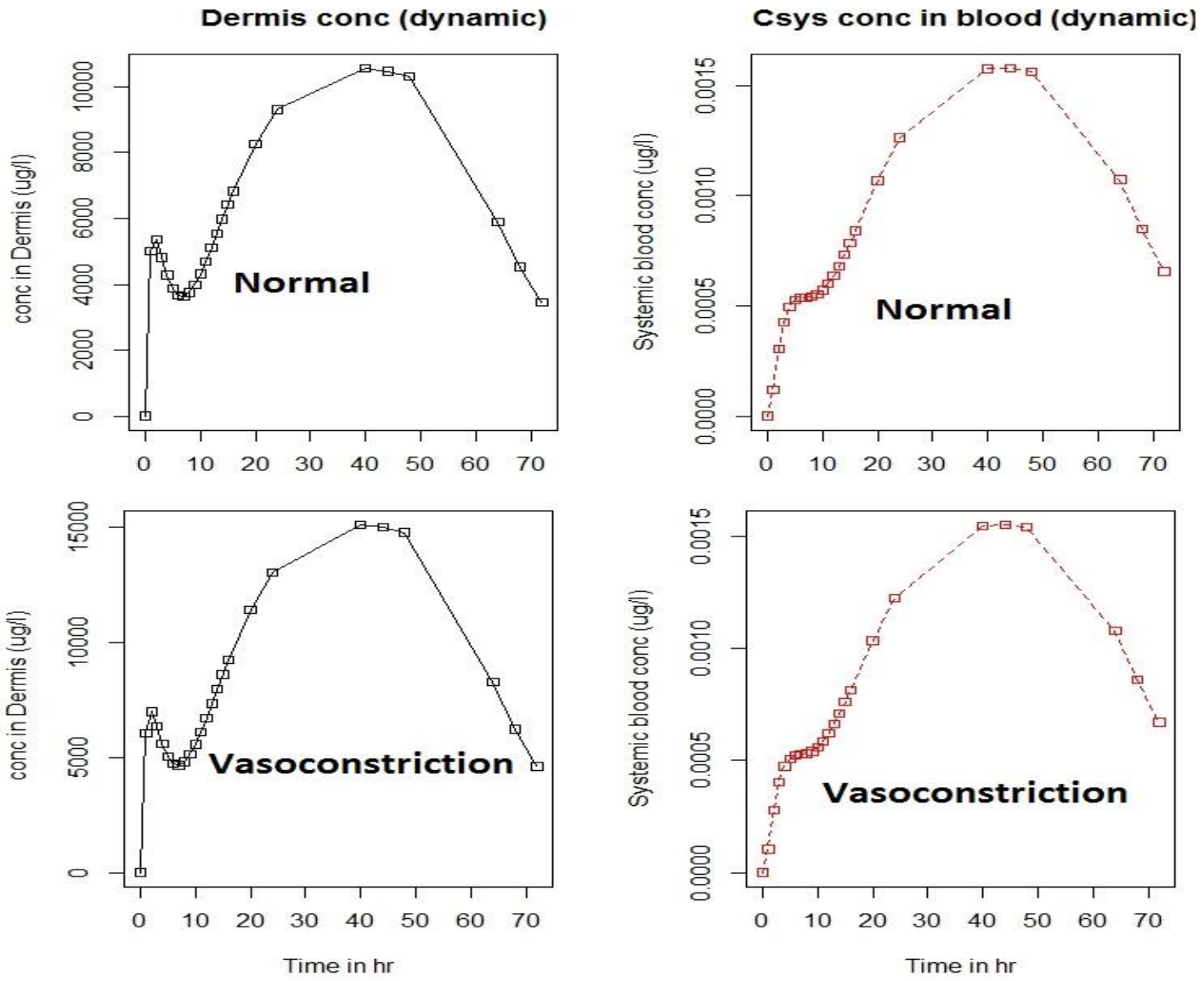
Drug/Excipient effect on local blood flow and absorption



Blood Flow change impact: vasodilation



Blood Flow change impact: vasoconstriction



Future Direction and Your Inputs

- Further validation of the approach for various drugs and different formulations is required to improve confidence in such approach
- Modelling of excipient effects is crucial for BE but very challenging
- Vehicle evaporation and its impact on drug solubility and flux
- Inter-occasion variability for virtual BE – negligible data available in public domain
- Many gaps in understanding of skin physiology and its variability
- Disease (psoriasis) population – many gaps in known physiology

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