CERTARA
Implementing Translational Science

SIMCYP
simulator | consultancy | education

Mechanistic modelling of dermal drug absorption using *Simcyp MPML MechDermA model*

rationale behind model development, its shape and performance

N, Patel[a], S. Cristea[a], M. Jamei[a], F. Salem[a], S. Polak[a,b]

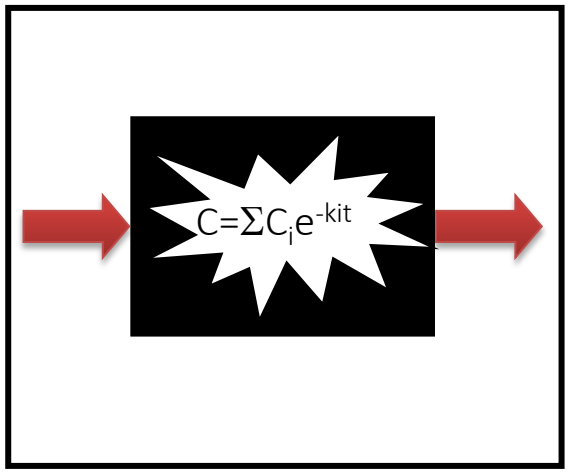
[a]Simcyp Limited (a Certara Company), Sheffield, S2 4SU, U.K.

[b]Faculty of Pharmacy, Jagiellonian University Medical College, Poland

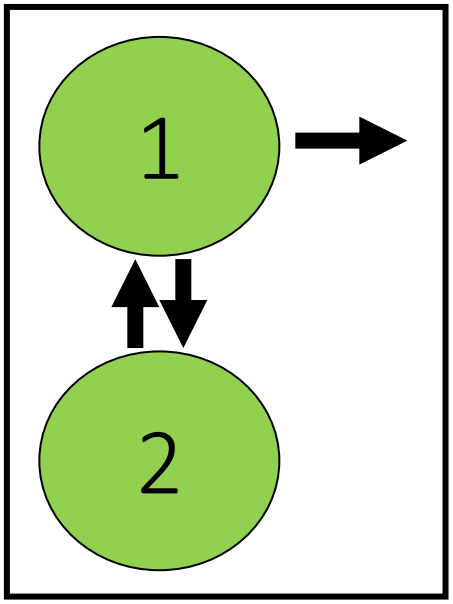
Tripos SIMCYP Pharsight

Typical Models Used to Describe Pharmacokinetics

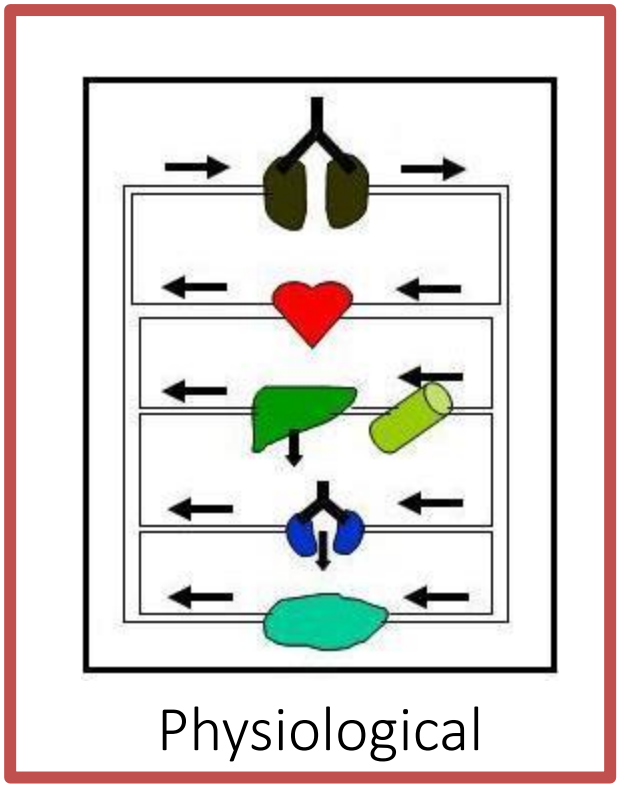
Three type of models can be used to describe concentration time profiles (PK)



Empirical



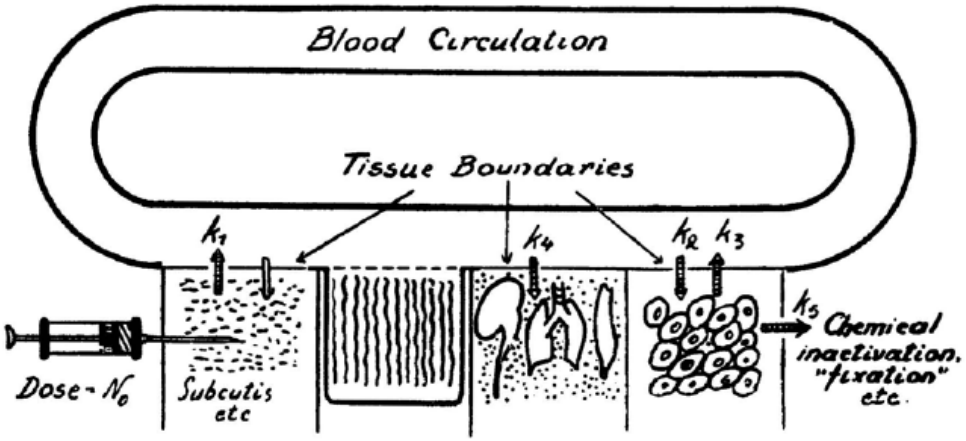
Compartmental



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

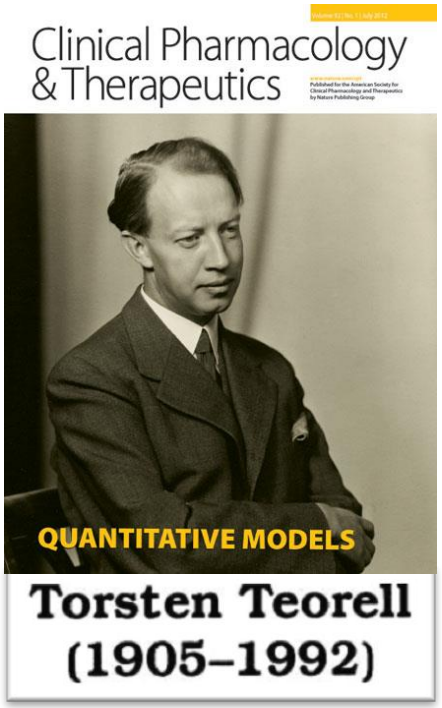
PBPK Modelling is not new



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	—	V_3	—
Concentration	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff	k_1'	—	k_4' .	k_2'	—
Velocity constant out	$k_1 = k_1'/V_1$	—	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	—	not existing	$k_2 = k_2'/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take up -"- output	Inactivation

FIG. 1

Scheme of the Concept of Drug Distribution used in this paper.
Instead the *injection* pictured in the figure, the administration of the drug depot can be made *per os*, *per rectum*, *by inhalation*, etc.



The Father of Pharmacokinetics

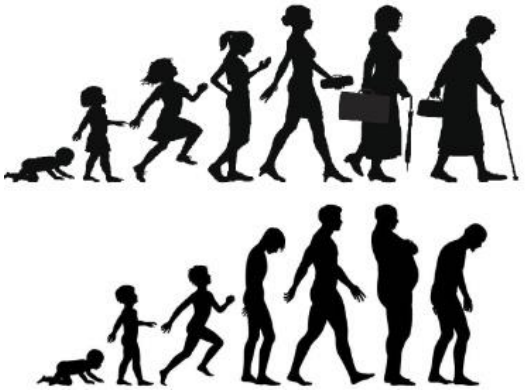
(Teorell, 1937)

Advantage of PBPK: Separating systems & drug information

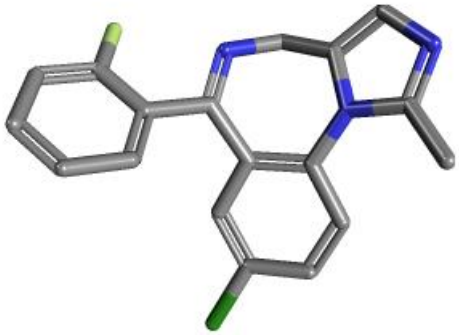
Systems Data

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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Recent Publications on the use of PBPK Modelling

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.33

PERSPECTIVE

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

FDA

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*

Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 00, 00; doi:10.1002/psp4.30

ORIGINAL ARTICLE

Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

EMA

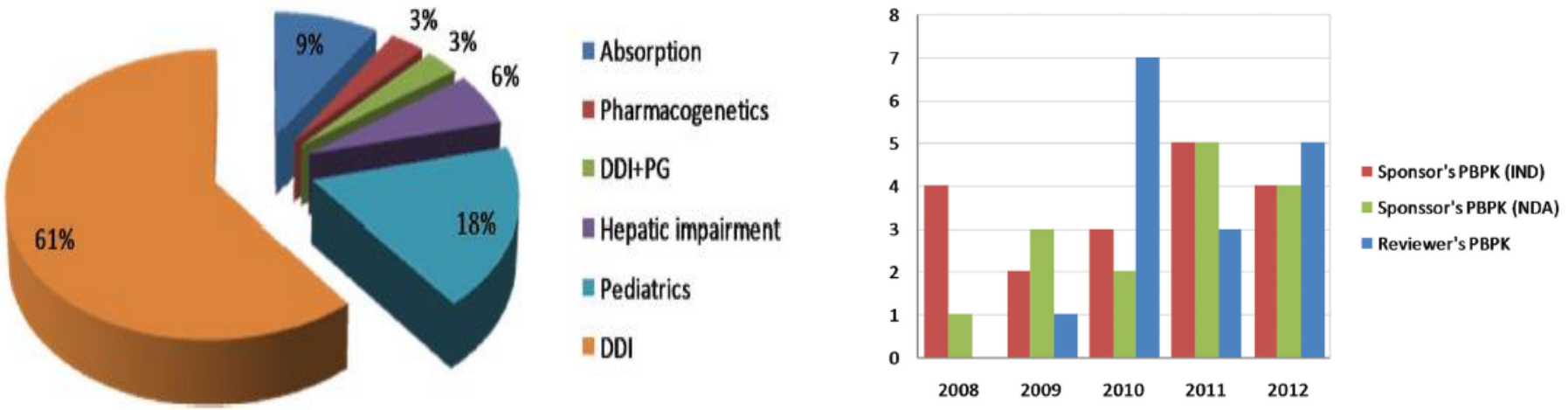
T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development: A Pharmaceutical Industry Perspective

Industry

HM Jones[1], Y Chen[2], C Gibson[3], T Heimbach[4], N Parrott[5], SA Peters[6], J Snoeys[7], VV Upreti[8], M Zheng[9] and SD Hall[10]

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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Further Enhancements as part of the USFDA OGD GDUFA Grant

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)
  - Pediatric (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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Current Progress – On track with many additional features

Milestone	Description	Proposed Duration (month of the project)	Actual Activity in Year 2 Quarter 2
Aim 1	Updating the current healthy volunteer physiology	1-12	Completed
Aim 2	Incorporation of paediatric and geriatric groups and other ethnic and diseased populations	6-36	Ongoing
Aim 3	Addition of deep tissue compartment	1-6	Completed
Aim 4	Incorporation of hydration level of SC as part of the model	1-9	Completed
Aim 5	Collection of skin pH in different anatomical sites of body and its variability	1-9	Completed
Aim 6	Accounting the role of skin appendages on absorption	6-12	Completed
Aim 7	Empirical models to account for effect of formulation excipients on drug absorption	24-36	
Aim 8	Ability to model drug effect on local skin physiology	12-18	Completed Y2Q2
Aim 9	Providing pharmacodynamic models to simulate effect at local or systemic level	24-36	Started Early
Aim 10	Models validation	6-36	Ongoing, four case studies generated
Aim 11	Dissemination of the project outcomes	6-36	3 posters, 2 oral presentations, ms in preparation
	Total	36 months	

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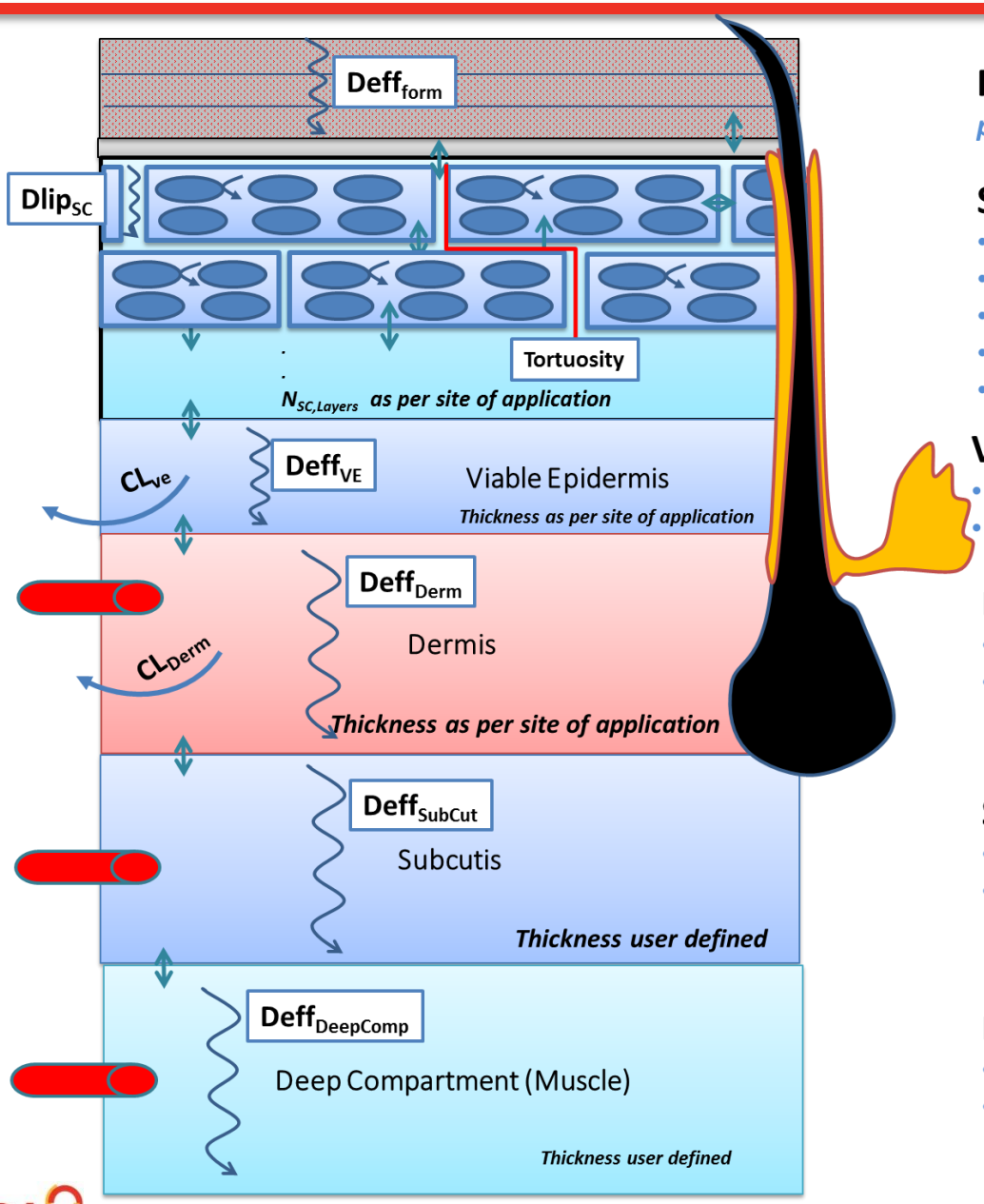
Advantage of PBPK: Separating systems & drug information

Mechanistic IVIVE linked PBPK models

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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Close Collaboration and Transparency with FDA

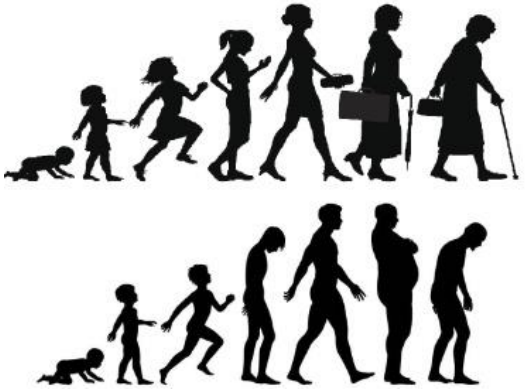
- Shared the R code(s) for critical review and feedback from you

```
#Simcyp Dermal Gel formulation  in vivo minimal PBPK model (multi-layer/multi-phase stratum corneum)
#2016/01/20

#the following section is to define R packages
library(deSolve)
require(lattice)


# ================>>>>>>>   the following section is to define design and dose parameters
VDose = 30*40/10000 # volume of formulation appl ied i n mL (cm3)
dose <- 24  # calculated dose [mg]
A <- 30 # area of application (cm2)

# ================>>>>>>>   the following section is to define system parameters
AbsTemp = 302 # temp in kelvin (equaivalent of body temperature of 37C)
Boltz = 1.38*10^-16 # boltzman constant (g*cm2/s2*K)
visAq = 1 # viscosity of water in centipoise (cP)
visGel = 20000 # 2% aqueous gel of HEC  in cP
vislip = 1000   # viscosity of SC lipid phase in cP (values reported in literature 30-100cP for human
visVE = 3 # viscosity of viable epidermis in  cP (viscosity of intracellular fluid)
vissb = 32 # viscosity of sebum in cP (motwani 2001)
```

- The model with variability will be available in Simcyp V16 for wider use and validation – no coding skills required

Advantage of PBPK: Separating systems & drug information

Systems Data



Trial Design

Dose
Administration route
Frequency
Co-administered drugs
Populations

Drug Data

Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

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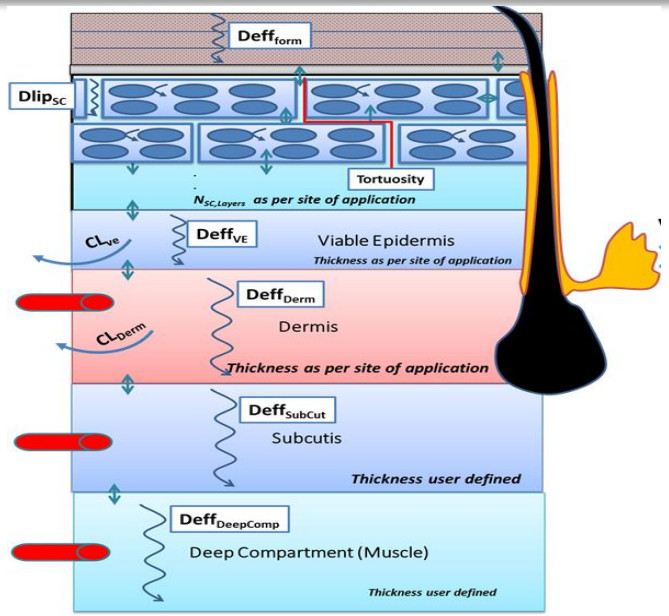
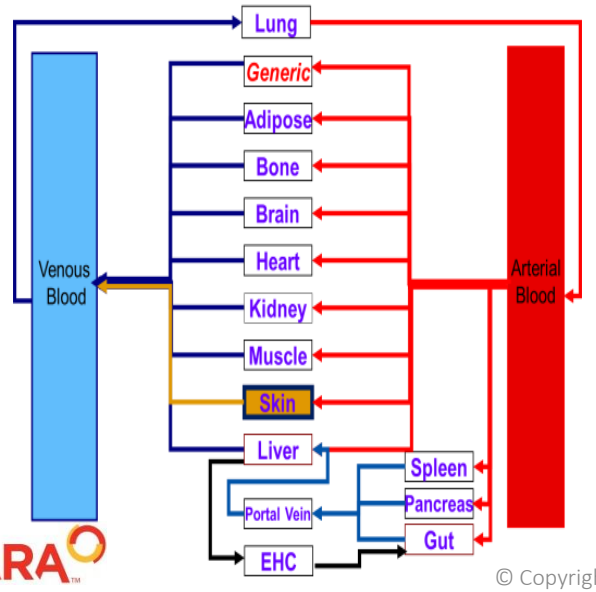
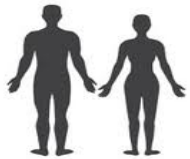
Meta-analysis of Systems Data





Paediatric Population

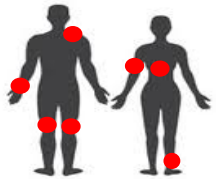
Healthy NEurCaucasian



Elderly Subjects

Ethnic Population

Diseased Population



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. Skin temperature
  2. Skin surface pH

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Physiology data summary

- Various parameters:
  - Skin surface
    - ✓ Skin temperature - model

```
15  AbsTemp = 302 # temp in kelvin (equaivalent of body temperature of 37C)
```

```
34  #Diffusion coefficient
35  MolVol = MW/((Density)*6.023*10^23) # calculated molecular volu
36  MolRad = (3*MolVol/(4*pi))^(1/3) # calculation of molecular rad
37  Dw = (3600*100*AbsTemp*Boltz)/(6*pi*visAq*MolRad) # Diff coeff
38  Dgel = (3600*100*AbsTemp*Boltz)/(6*pi*visGel*MolRad)  #9.36*(10
39  Dlip = (3600*100*AbsTemp*Boltz)/(6*pi*vislip*MolRad) # 1.8*(10^
40  Dve =  (3600*100*AbsTemp*Boltz)/(6*pi*visVE*MolRad) #3600 * 7.1
41  Dsb = (3600*100*AbsTemp*Boltz)/(6*pi*vissb*MolRad) # diffusion
42  Dd = Dve # diffusion coefficient in dermis (assumed to be equal
```

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Physiology data summary

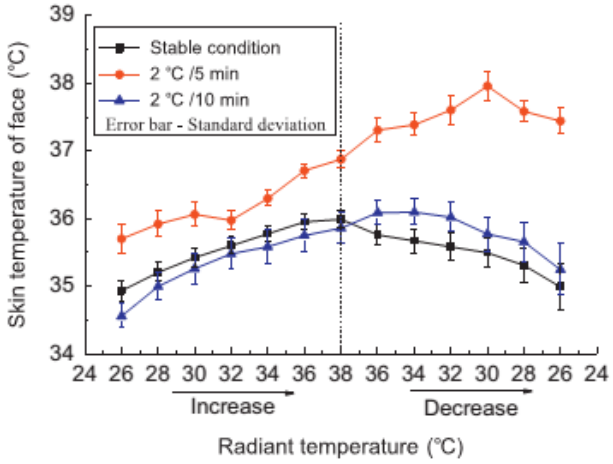
- Various parameters:
  - Skin surface
    - ✓ Skin temperature – reality (location)

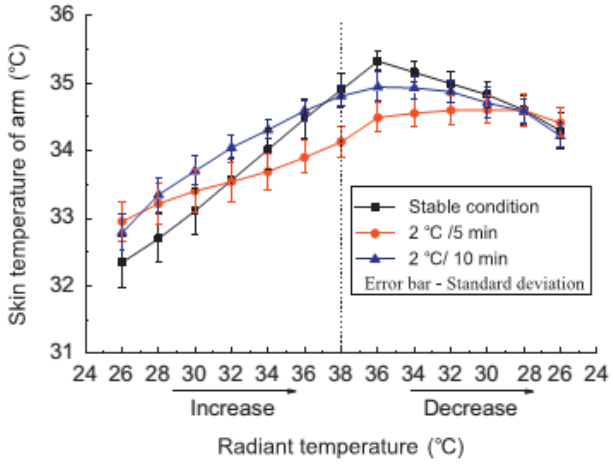
Table 1
The neutral core and skin temperatures, Dubois surface areas, and weights of the body segments (Tanabe et al., 2002)

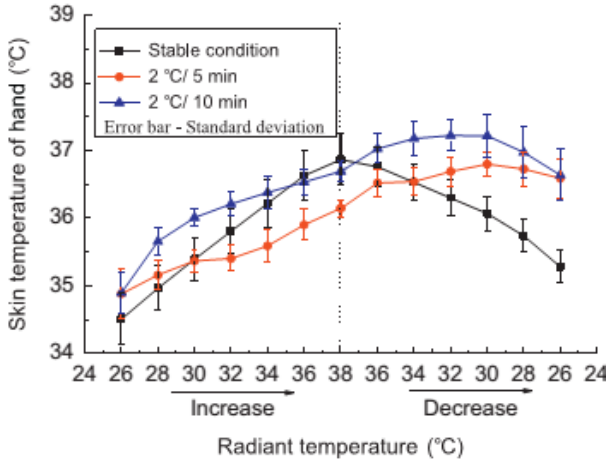
i	Body segments	Neutral skin temperature (°C)	Neutral core temperature (°C)	Dubois surface area (m^2)	Weight (kg)
1	Left foot	33.9	35.1	0.056	0.480
2	Right foot	33.9	35.1	0.056	0.480
3	Left leg	33.4	35.6	0.112	3.343
4	Right leg	33.4	35.6	0.112	3.343
5	Left thigh	33.8	35.8	0.209	7.013
6	Right thigh	33.8	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 summary

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







Physiology data summary

- Various parameters:
  - Skin surface
    - ✓ Skin temperature – final value for the first version
      - user modifiable in GUI
      - average value for all locations (32^{O}C – 305K)
      - possibly expanded in the next version to account for intra- and inter-individual variability

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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. Skin temperature
  2. Skin surface pH

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Physiology data summary

- Various parameters:
  - Skin surface
    - ✓ Skin surface pH - model

```
31    fni <- 0.002 # fraction of drug non-ionised at skin surface pH,
```

Physiology data summary

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

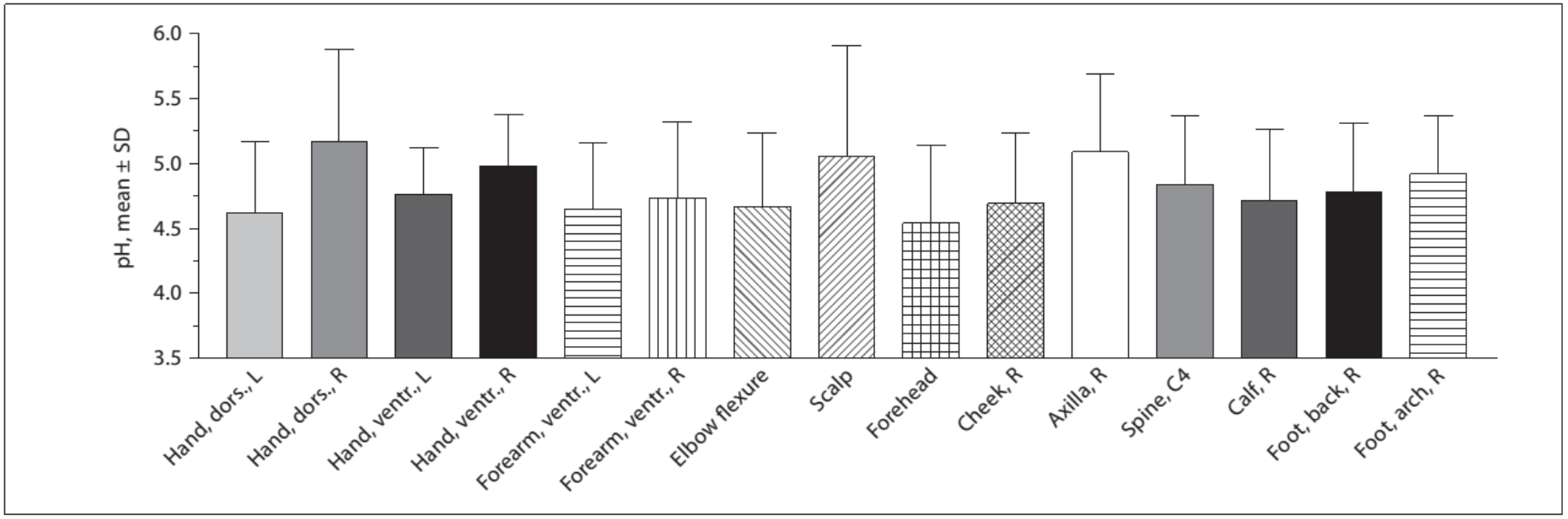

Fig. 4. Skin surface pH values. The skin surface pH was measured with a pH-meter 905 at 15 different anatomical sites in 125 volunteers. The values are expressed in pH units as means ± SD.

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Physiology data summary

- Various parameters:
  - Skin surface
    - ✓ Skin surface pH – final values for first version

		surface pH
Forehead	av	4.9
	cv	12%
Forearm inner (volar)	av	4.9
	cv	13%
Forearm outer (dorsal)	av	5
	cv	13%
Upper arm	av	5
	cv	11%
Face (cheek)	av	5
	cv	10%
Leg (lower)	av	4.7
	cv	11%
Leg (upper=thigh)	av	5.4
	cv	10%
Back	av	5
	cv	11%

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Physiology data summary

- Various parameters:
  - Skin surface
    - ✓ Skin surface pH – reality (gender, age)

TABLE 1. Mean skin surface pH, SD and CV for each person for left and right arm

Subject	Left arm			Right arm			Total
	Mean pH	SD	CV	Mean pH	SD	CV	
Male							
1	5.30	0.08	1.6	5.09	0.04	0.8	5.80
2	5.86	0.10	1.7	5.91	0.12	2.0	(range 5.01–6.50)
3	5.84	0.07	1.3	5.81	0.07	1.3	
4	6.08	0.18	3.0	6.34	0.09	1.4	
5	6.18	0.09	1.4	6.27	0.11	1.8	
6	5.65	0.19	3.4	5.71	0.14	2.4	
Mean value	5.81	0.32	5.5	5.79	0.39	6.7	
P value[1]							0.140
Female							
1	5.24	0.09	1.6	5.36	0.10	1.9	5.54
2	5.85	0.20	3.4	5.74	0.24	4.2	(range 4.32–6.59)
3	4.49	0.10	2.3	4.58	0.10	2.2	
4	6.19	0.17	2.8	6.27	0.21	3.3	
5	5.88	0.09	1.5	5.78	0.20	3.5	
Mean value	5.53	0.62	11.3	5.55	0.59	10.54	
P value[1]							0.196
P value[2]							<0.001

Physiology data summary

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

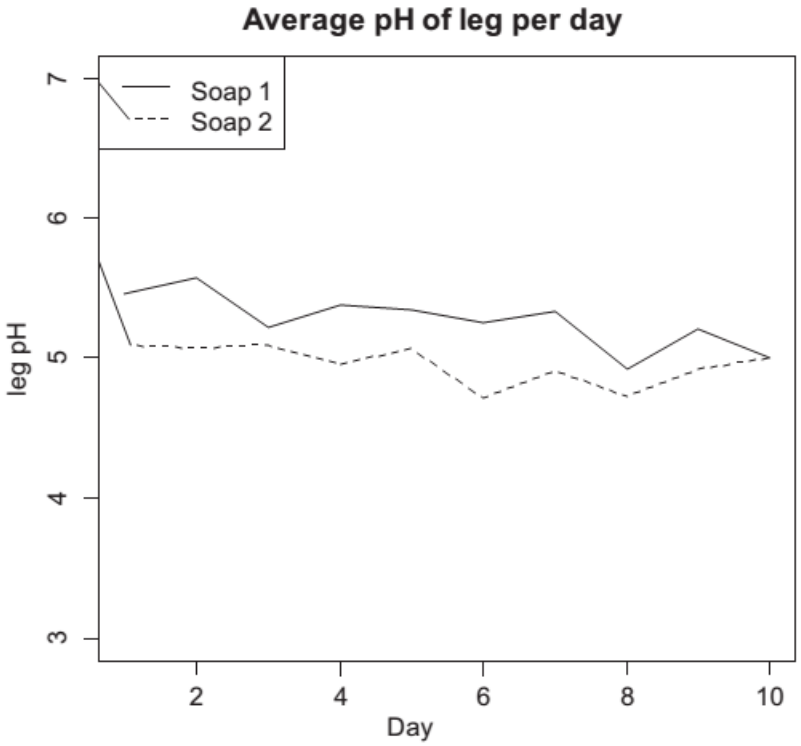
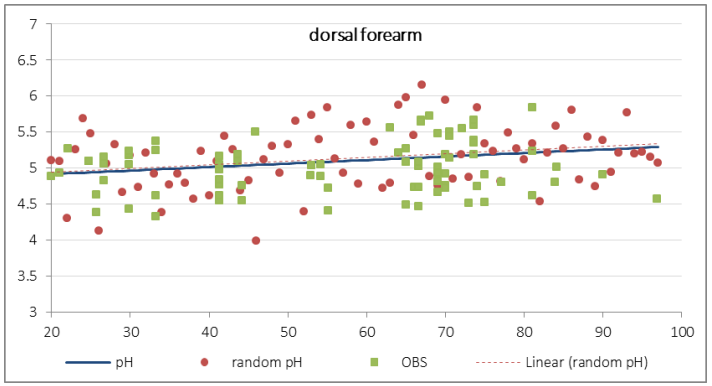
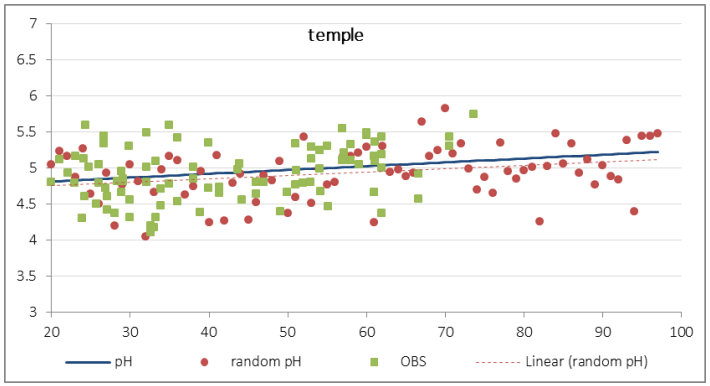


Figure 1 Average leg pH: soap versus pH cleanser.

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

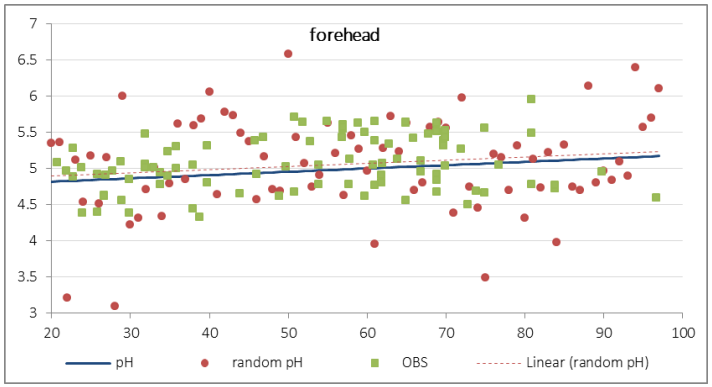
pH = 0.00489 × AGE + 4.818



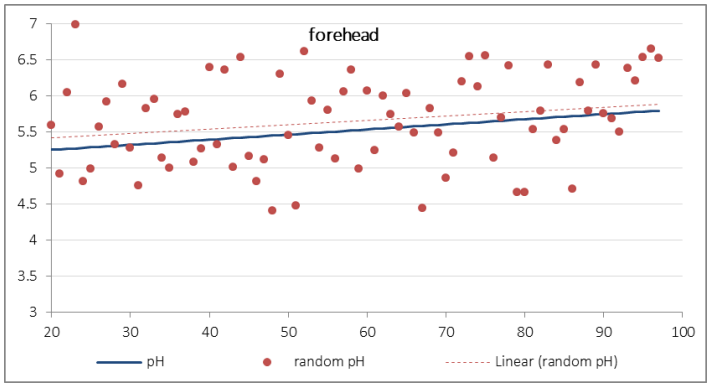


Schreml 2012

pH = 0.00529 × AGE + 4.709



pH = 0.00459 × AGE + 4.725



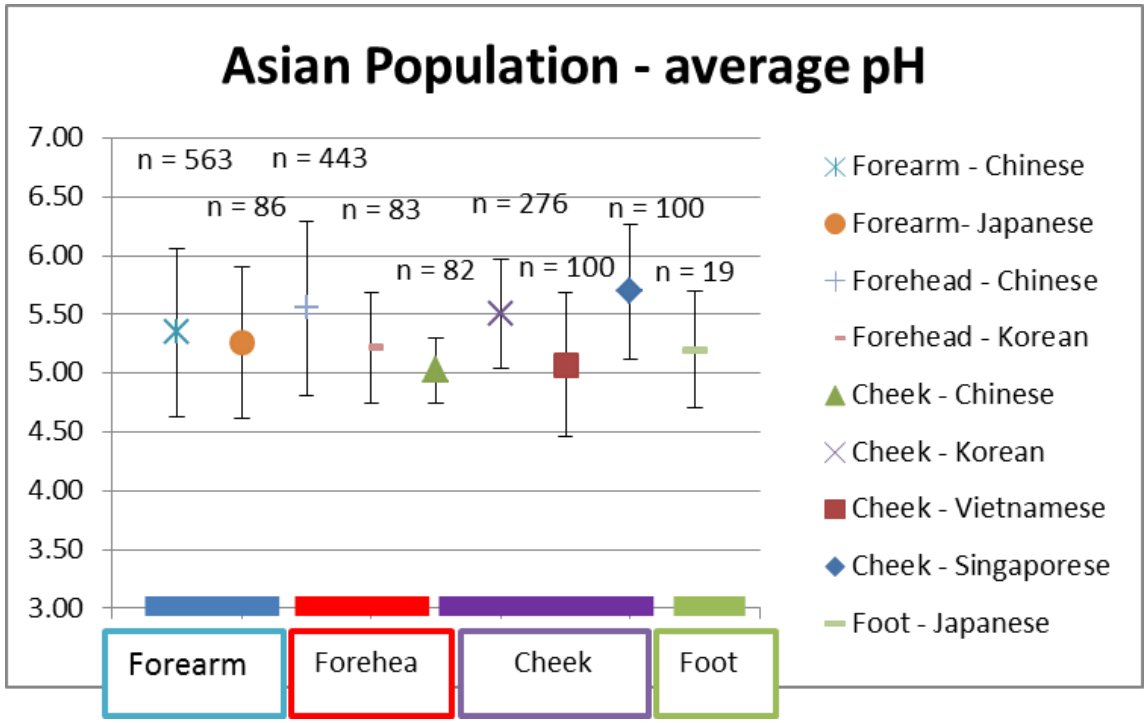
Dikstein 1984

pH = 0.0071 × AGE + 5.11

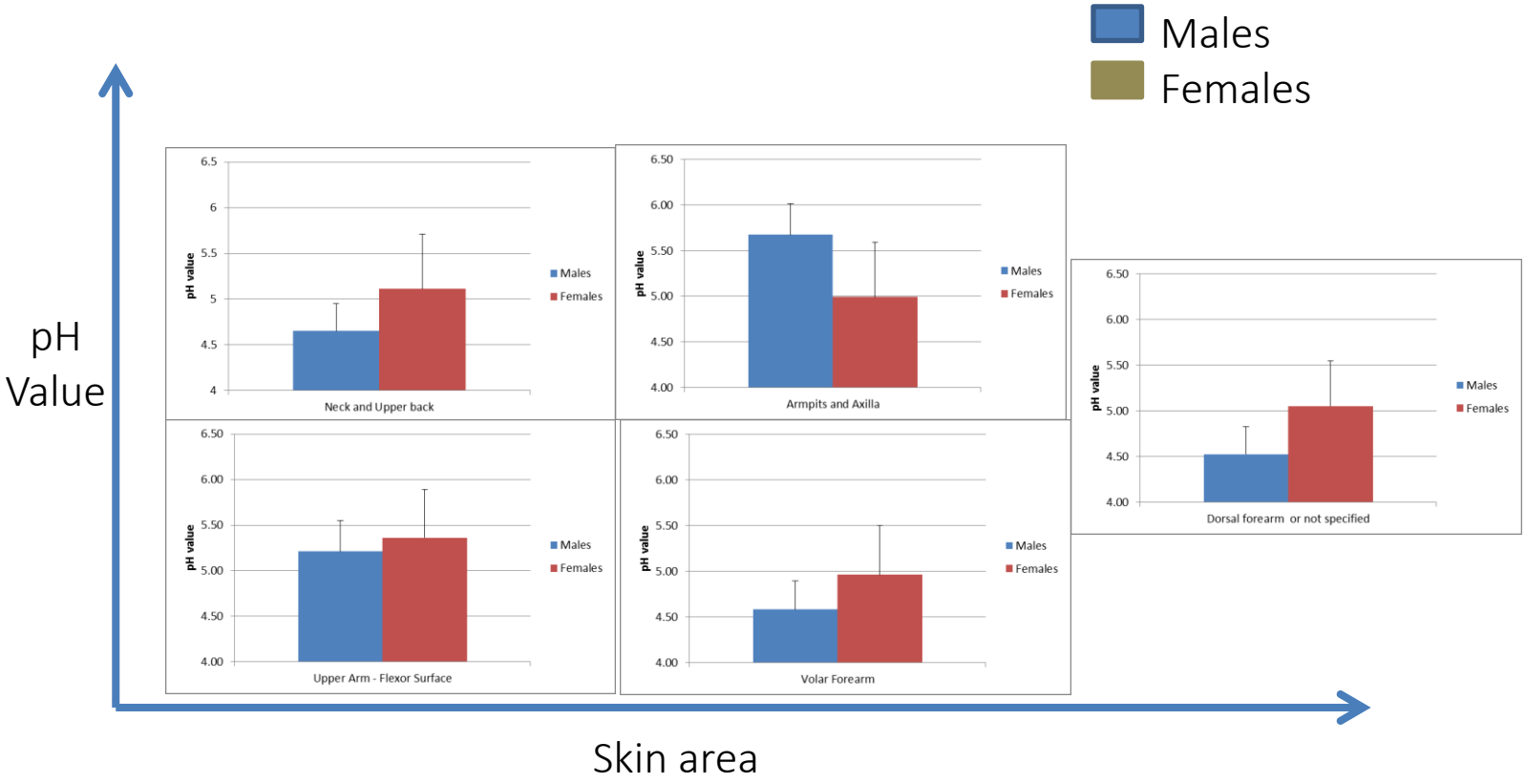
pH units

Age (years)

Asian Population – pH on different body sites

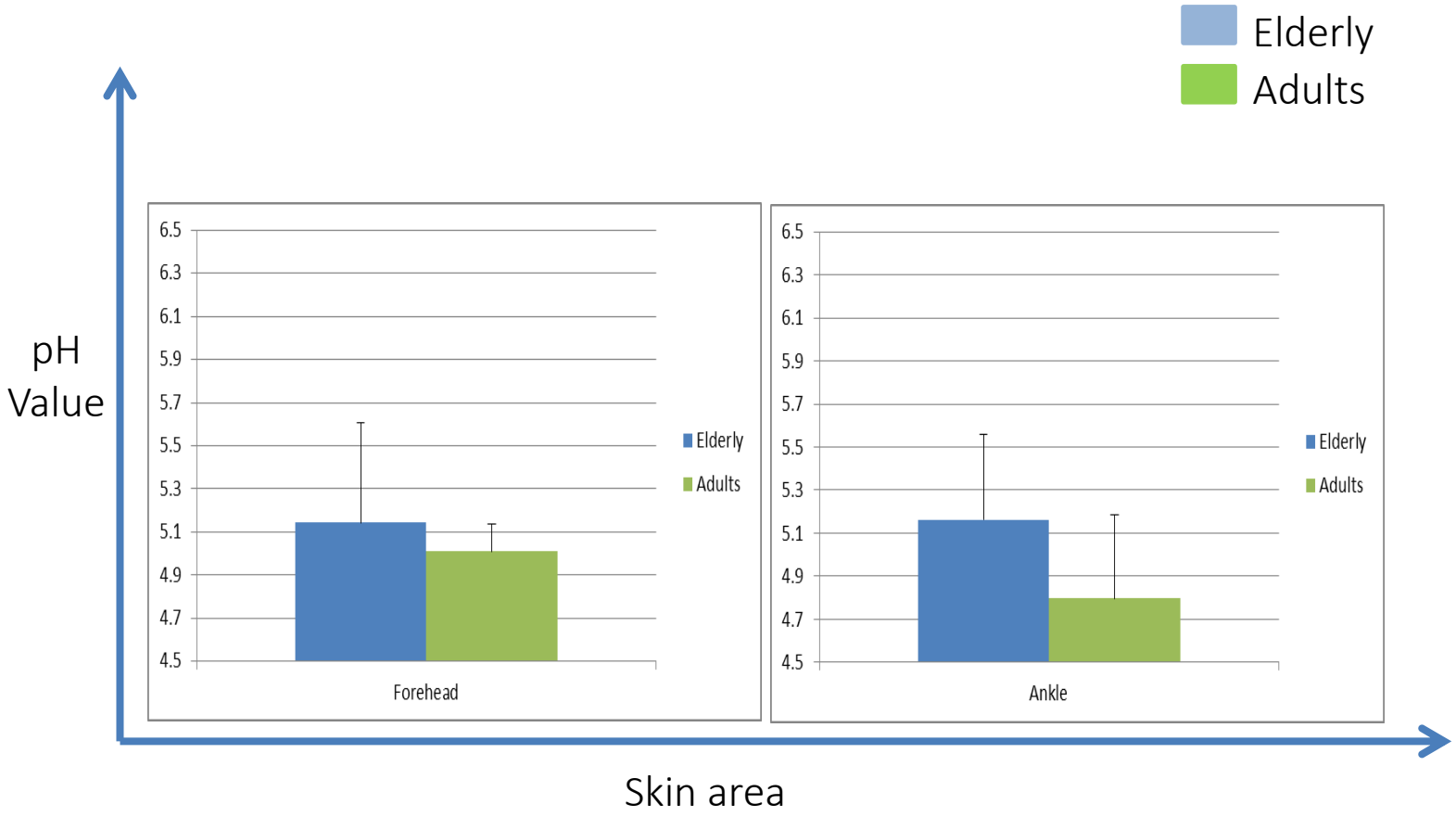


pH differences between males and females



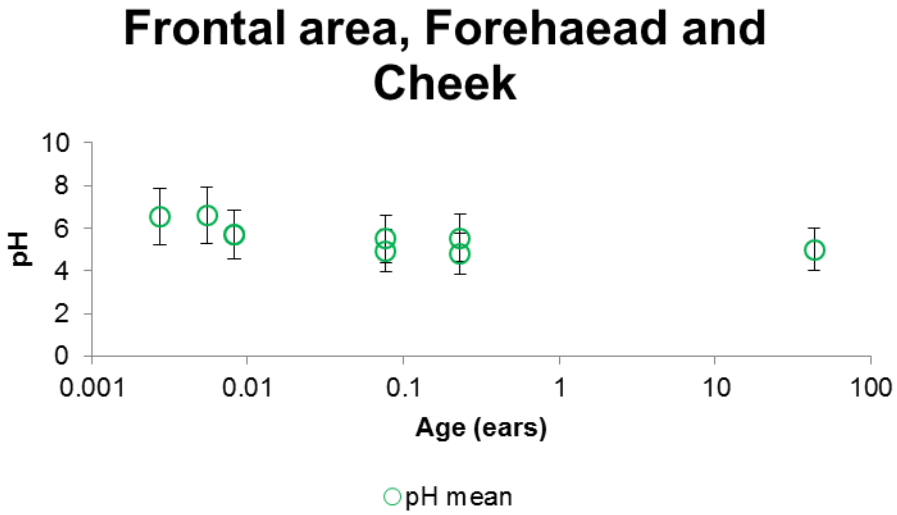
- On average, the pH of females is about 0.5 units higher than in males
- The pH varies between individuals, genders and skin areas

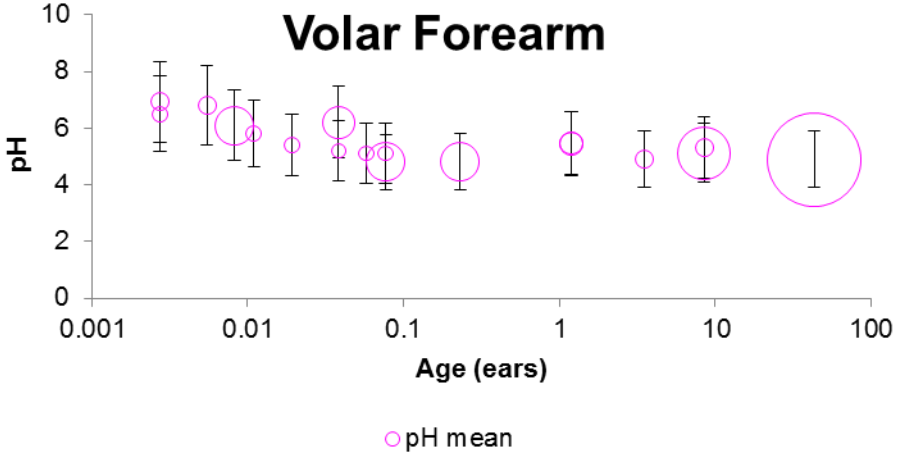
Skin surface pH in elderly vs. adult skin

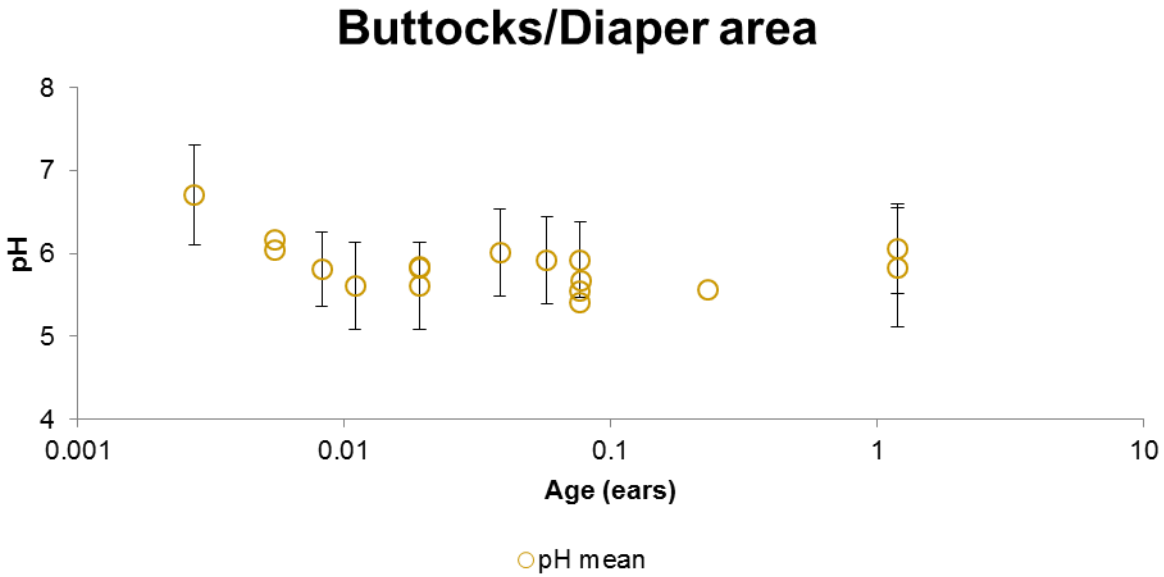


Wilhelm et al.(1991) found that the pH in the forehead and ankle is higher in the elderly population

Pediatric Skin surface pH - ontogeny







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. Fraction of p/w/l
  5. Tortuosity
  6. Lipids fluidity/th

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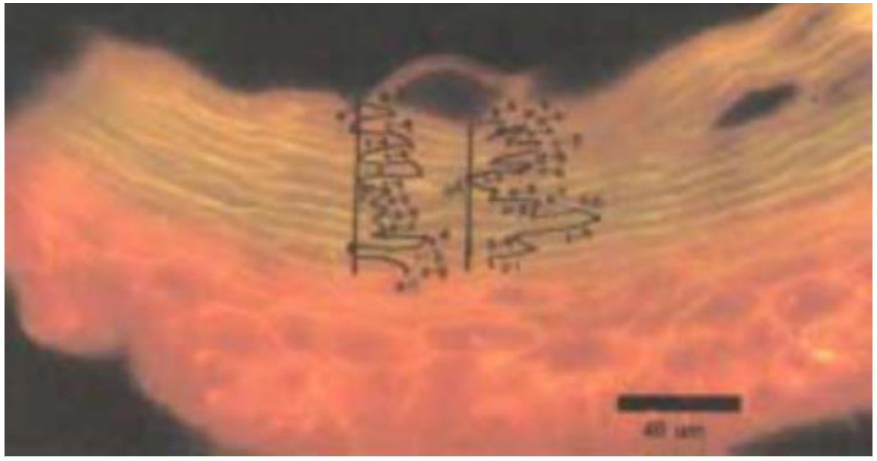
Tortuosity and hydration expansion

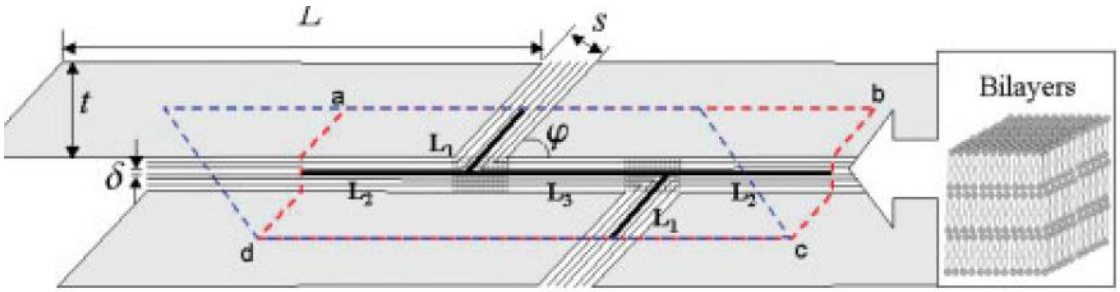


Talreja 2001

Figure	Donor, sex, age, site	τ_{ge} Mean ± SD (no. of determinations/image)
1A	Donor #1, unspecified	3.3 ± 0.1 (4)
1B	Donor #2, male, 72, back	4.0 ± 0.7 (4)
1C	Donor #1, unspecified	3.9 ± 0.6 (4)
1D	Donor #2, male, 72, back	3.0 ± 0.7 (5)
1E	Donor #2, male, 72, back	4.4 ± 0.7 (5)
Mean ± SD		3.7 ± 0.7

Table 2. Geometrical tortuosity, τ_g, of lipid pathway in unexpanded human stratum corneum (SC) for the images in Figure 1, calculated according to Equation 1 using E_l = 1.11.

Figure	τ_{ge}	h_e, μm[a]	h, μm[b]	E	τ_g
1A	3.3	68	11.4	5.9	13.2
1B	4.0	41	11.4	3.6	10.7
1C	3.9	52	8.8	5.9	16.4
1D	3.0	43	7	6.1	12.0
1E	4.4	43	13	3.3	11.1
Mean ± SD					12.7 ± 2.3



(a) Lengths, Thicknesses, Angular Parameter φ, and Tortuosity Parameters

State of SC	L (μm)	t (μm)	s (μm)	φ (°)	τ	ω
Unswollen (partially hydrated)	30.00	0.80	0.091	20	9.66	0.20
Swollen (fully hydrated)	31.20	2.80	0.091	50	3.38	0.19

Wang 2006

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  3. Corneocyte size
  4. Fraction of p/w/l
  5. Tortuosity
  6. Lipids fluidity/th

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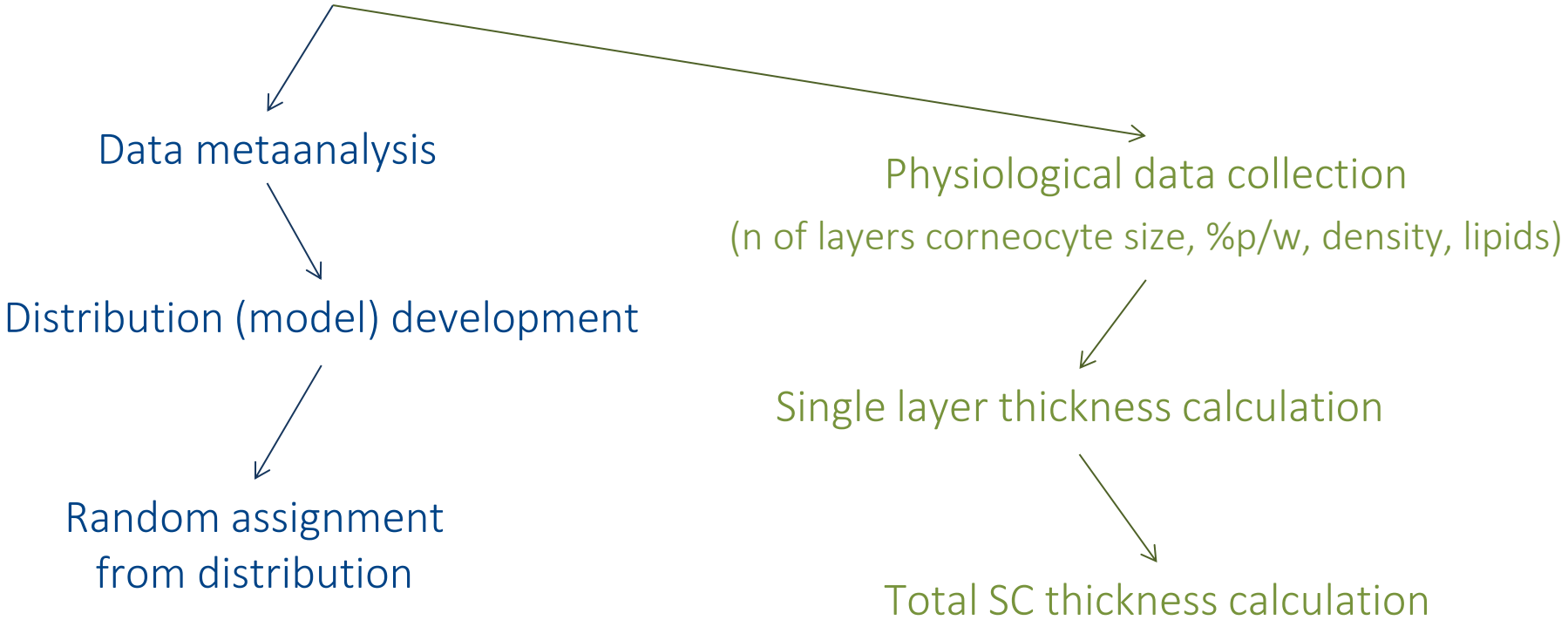
Physiology data summary

- Various parameters:
  - Stratum corneum
    - ✓ Thickness (h)



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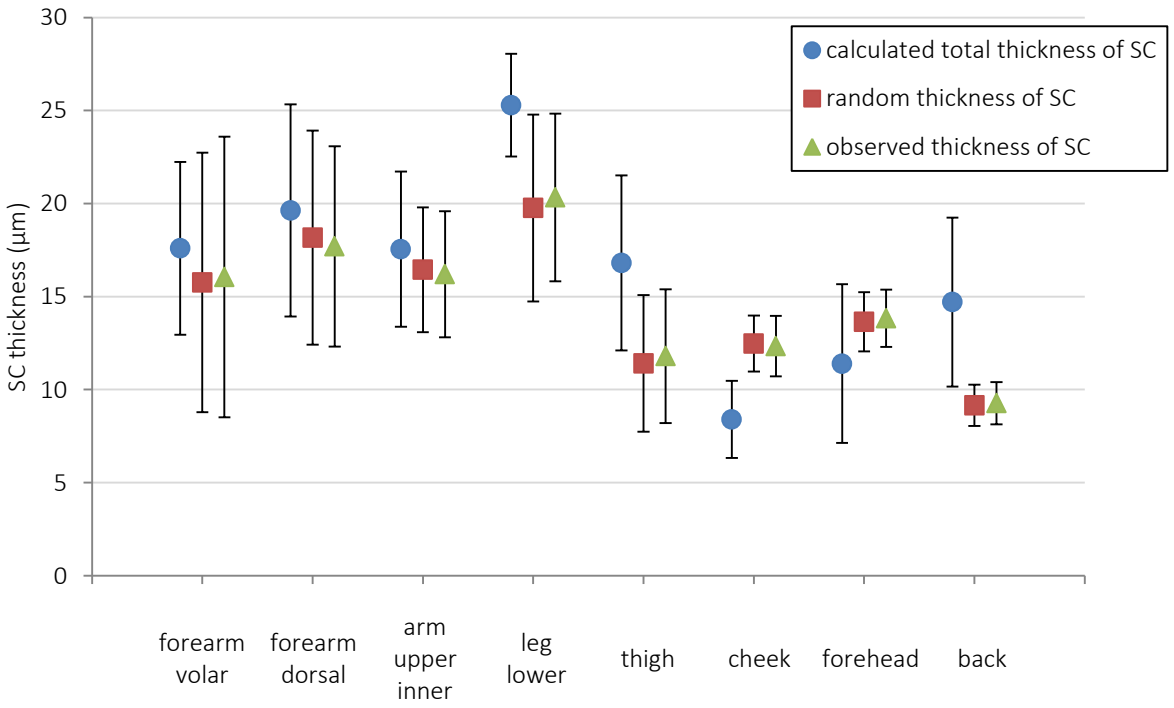
Physiology data summary

- Various parameters:
  - Stratum corneum
    - ✓ Thickness (h)

methods comparison - 100 virtual individuals



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Intra-individual Variability

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  1. Forehead
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  7. Thigh
  8. Back

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

- Various parameters
  1. Hair follicle diameter
  2. Hair shaft diameter
  3. Hair follicle density
  4. Sebum fluidity

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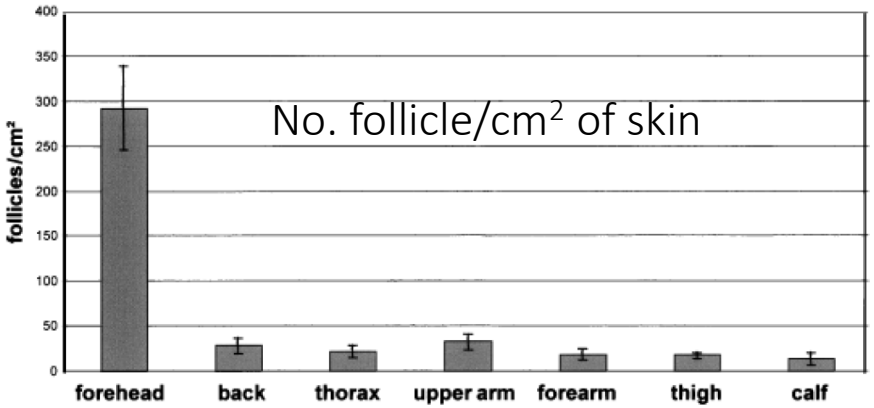
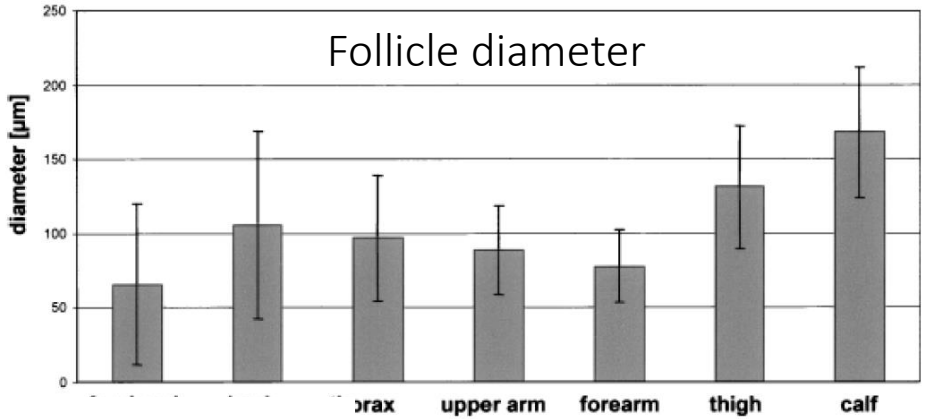
Hair follicle/sebum





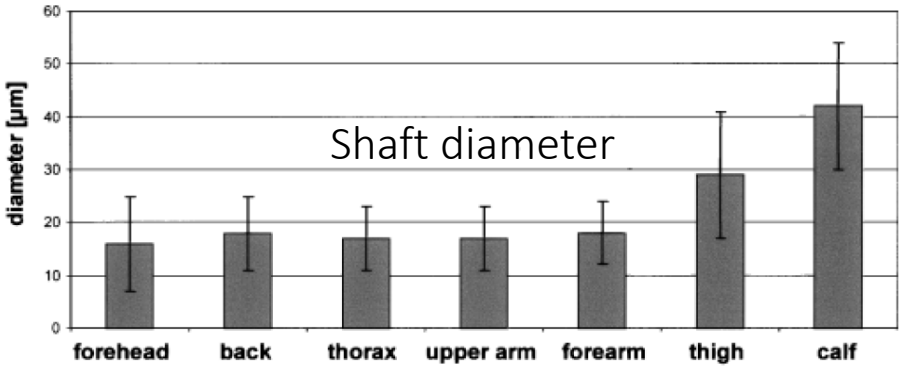


Table I. Percentage mean (± SD) of follicular orifices on the skin surface in seven body sides

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

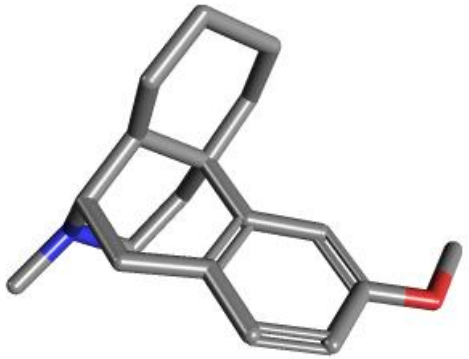
Advantage of PBPK: Separating systems & drug information

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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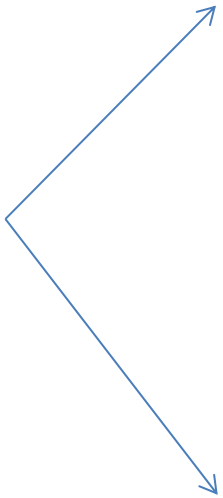
Drug Related Parameters

- 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_w
  2. D_{lip}
  3. D_{ve}
  4. ....

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Sebum D_{sb}/$Peff_{sb}$ bottom up predicted OR QSAR

Table I
Physical Properties of Sebum

Property	Forehead sebum (ref. 4)	Scalp sebum (ref. 5)
Specific gravity	0.91 g/cm^3	0.90 g/cm^3 for three normal samples
Surface tension	24.9 dyne/cm from 26.5 to 31°C	22.9 dyne/cm for six normal samples at 30°C
Viscosity	0.55 poise at 38°C 1.00 poise at 26.5°C Viscosity discontinuous at 30°C due to the separation of a precipitate in the sebum	0.32 poise at 35°C 0.82 poise at 25°C
Freezing point	Sample started to freeze at 30°C and then solidified at 15°–17°C	15°–17°C

Calculate diffusion coefficient, partition coefficient from QSAR and predict permeation process via sebum rather than steady-state Peff from QSAR

Motwani 2001

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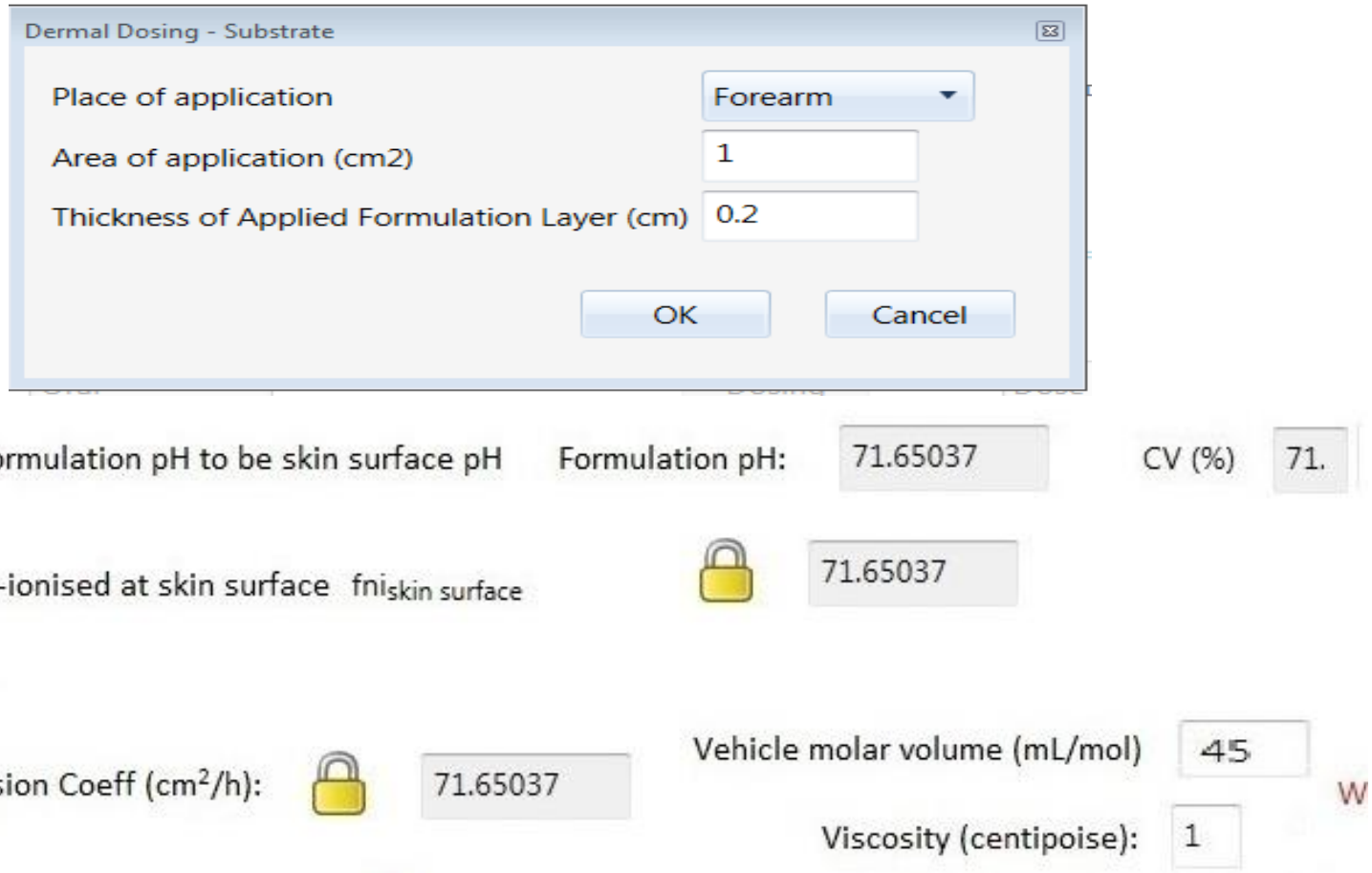
Advantage of PBPK: Separating systems & drug information

Trial Design

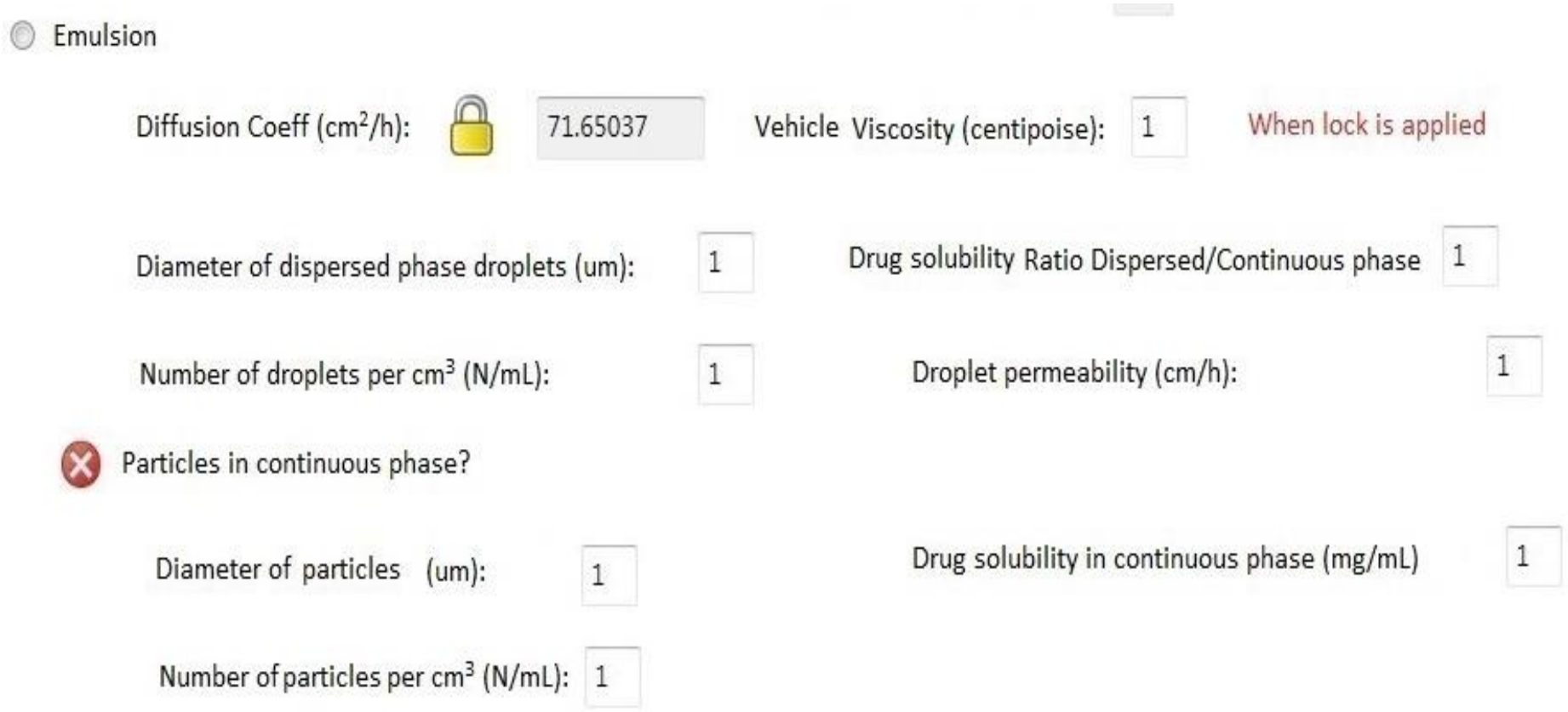
Dose
Administration route
Frequency
Co-administered drugs
Populations

Formulation Data - Solution



- Can be used for clear gels and solutions with appropriate parameterisation of diffusion coefficient

Formulation Data - Emulsion



- Emulsions, emulsion creams and gels with or without particles

Formulation Data – Suspension/Paste/Patch

Suspension / Paste

Vehicle molar volume (mL/mol) 45

When lock is applied

Diffusion Coeff (cm^2/h): 71.65037

Vehicle Viscosity (centipoise): 1

Drug solubility in vehicle (mg/mL): 1

Particle diameter (um): 1

Dermal Patch

Empirical release rate

Zero Order Release Rate (mg/h) 1

First Order Release Rate Constant (1/h) 1

Controlled Release (CR)

Diffusion based release kinetics

Vehicle molar volume (mL/mol) 45

Diffusion Coeff (cm^2/h): 71.65037

Vehicle Viscosity (centipoise): 1

Volume fraction of polymer 45

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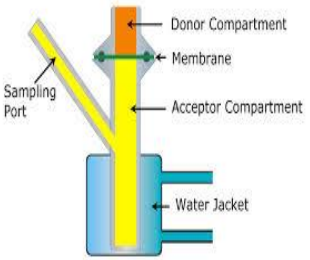
Simcyp IVIVE: Translating in vitro permeability to clinical situations

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

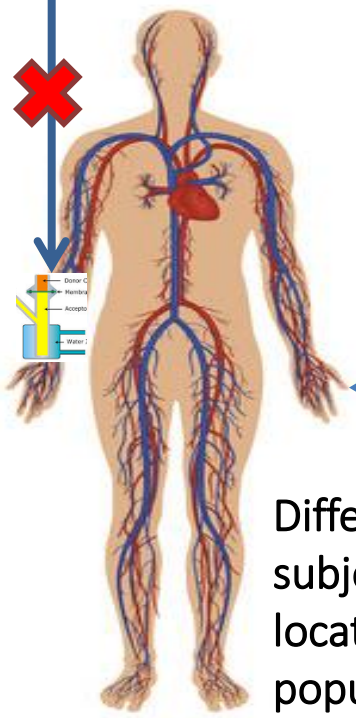
- Diffusion coefficient
- Partitioning
- Keratin binding
- Refine Unknown/uncertain

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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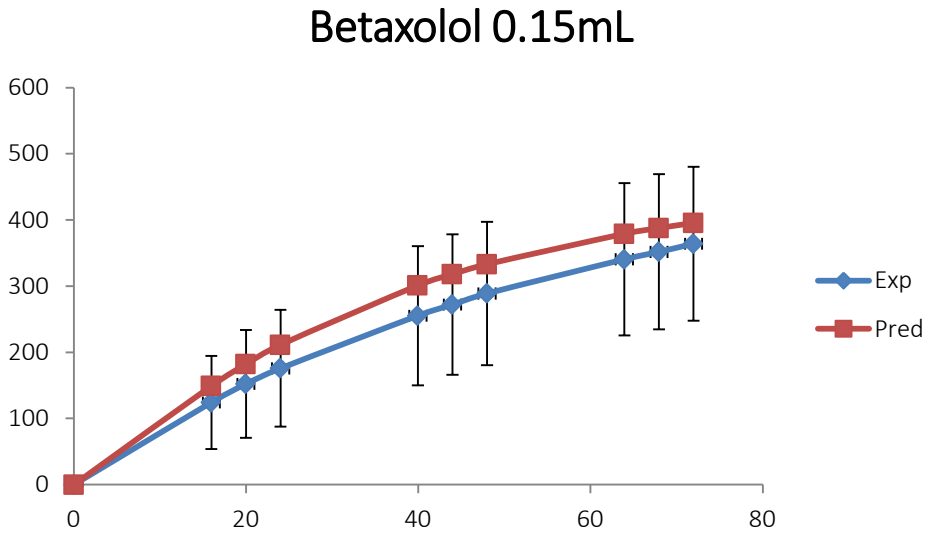
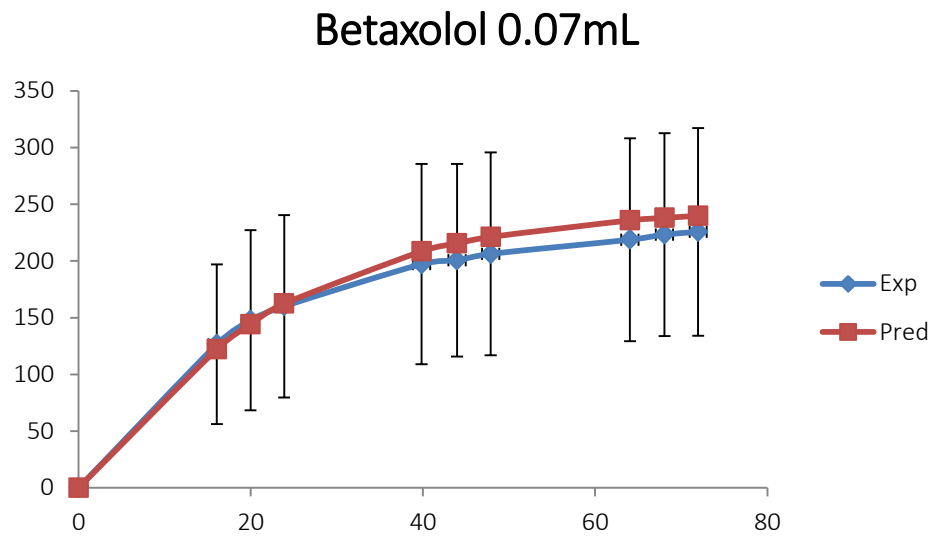
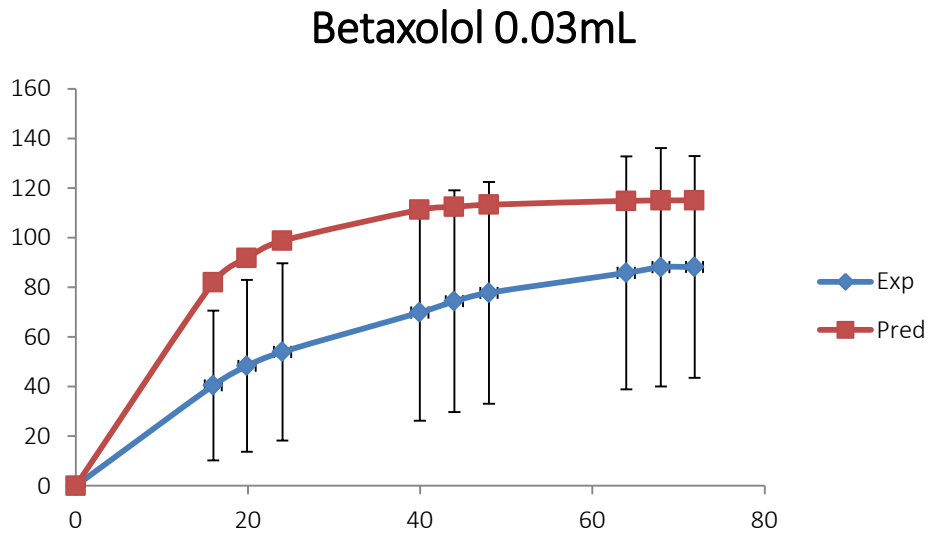
Betaxolol Prediction for three doses







- 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)
- Hydration expansion of SC (2.5-fold)
- **Tortuosity (2.5-fold) –** fitted parameter to match observations (but within the limits of reported value)

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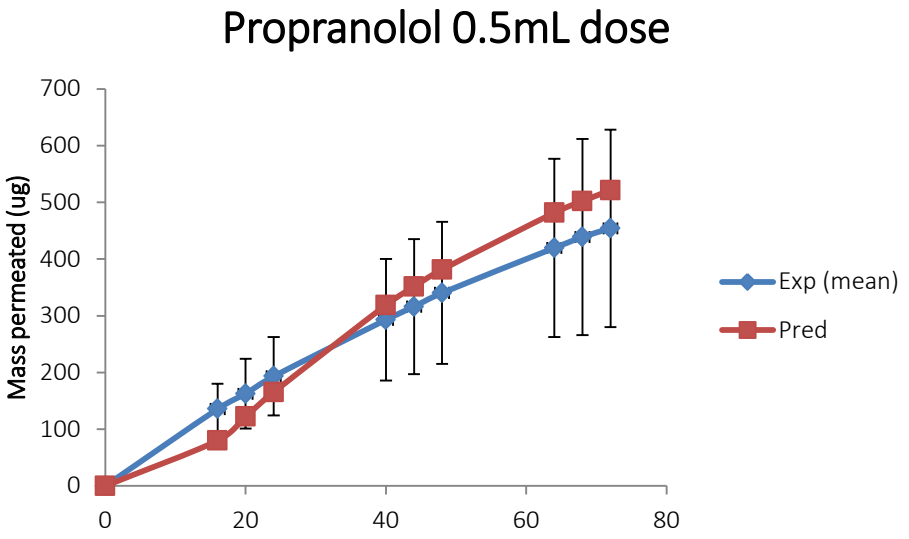
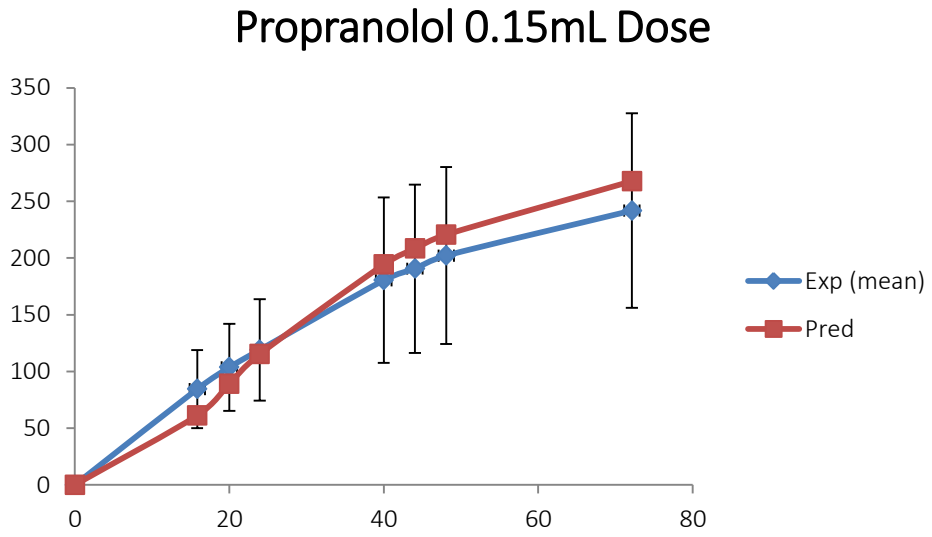
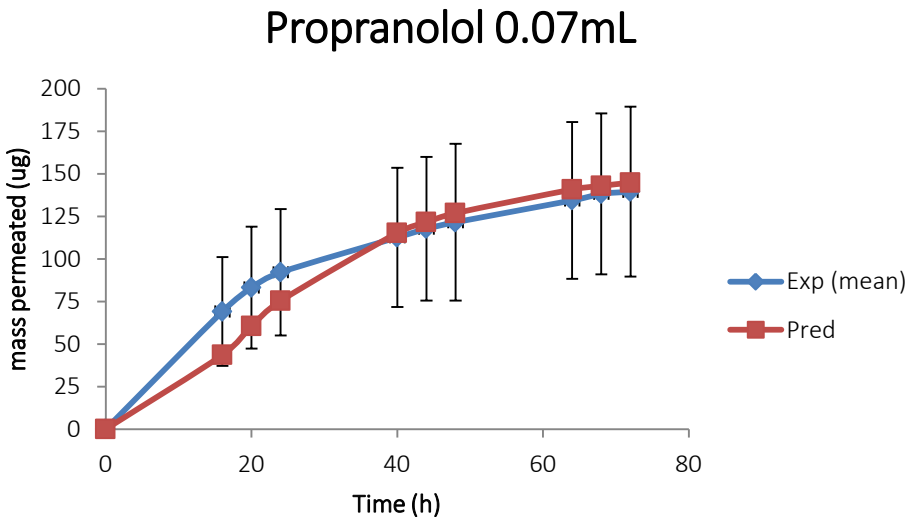
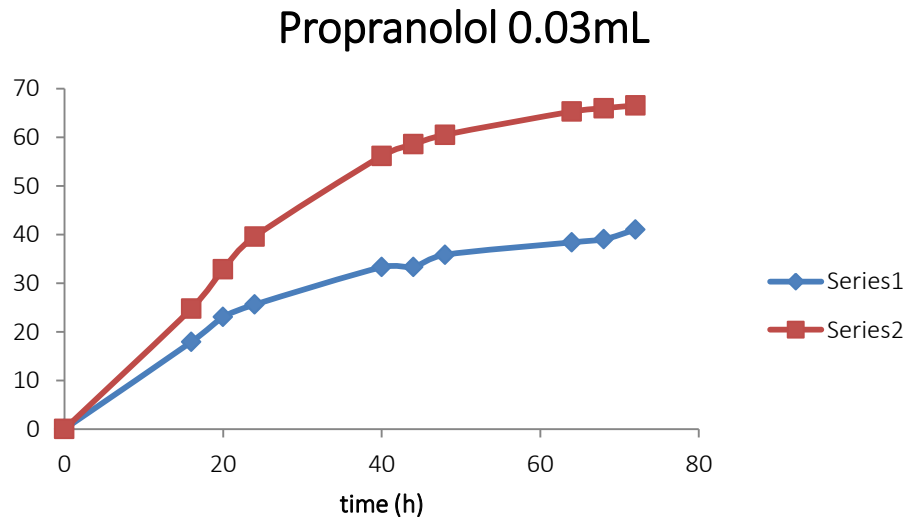
Propranolol Prediction for four doses



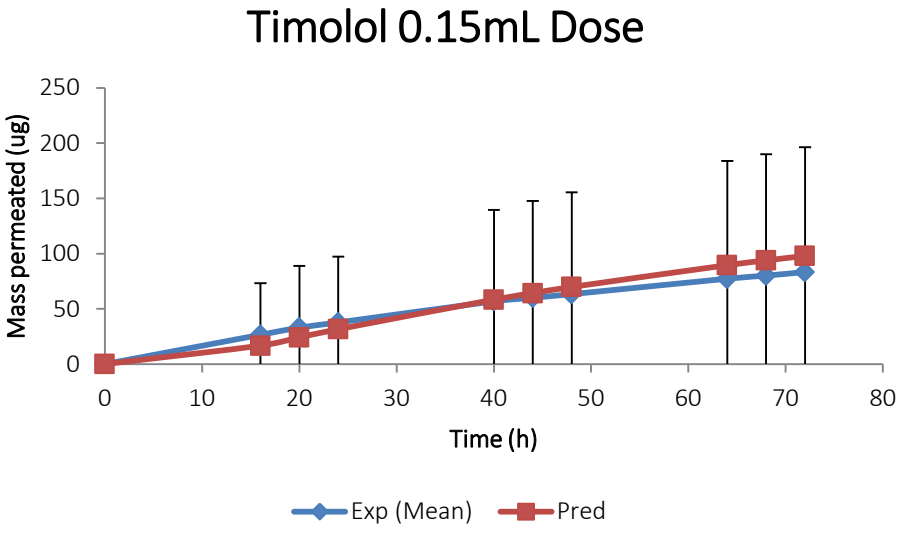


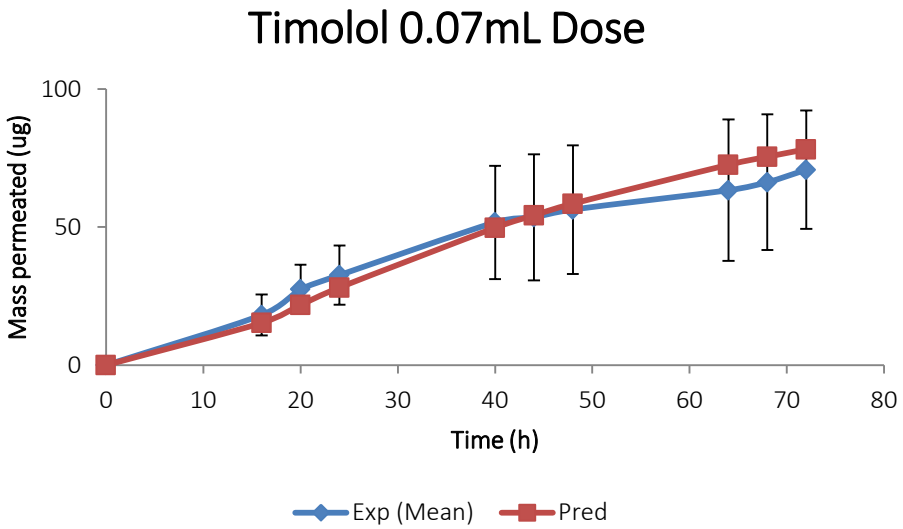


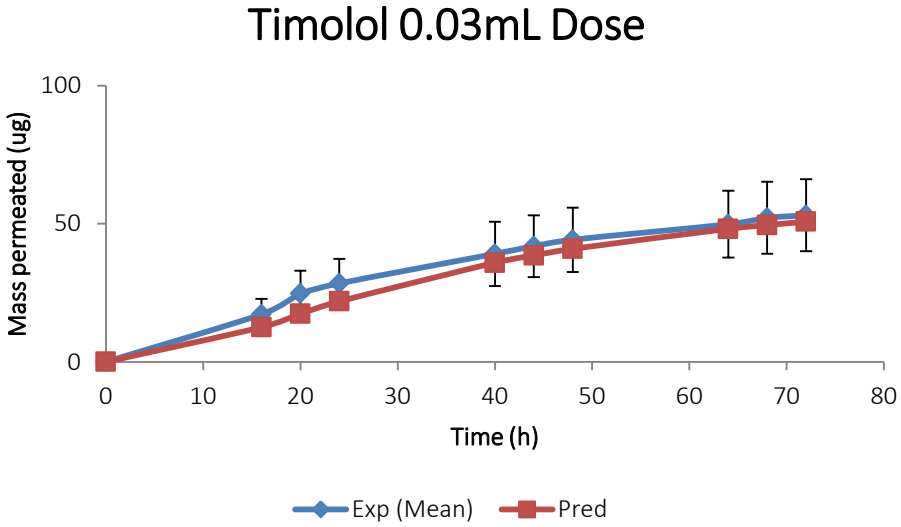


CERTARA

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)
- Hydration expansion of SC (2.5-fold)
- **Tortuosity (1.5-fold) –** fitted parameter to match observations (but within the limits of reported value)

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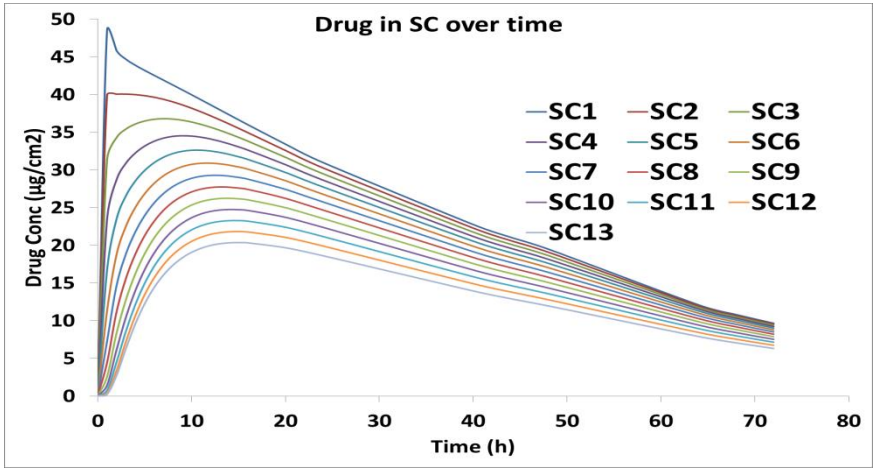
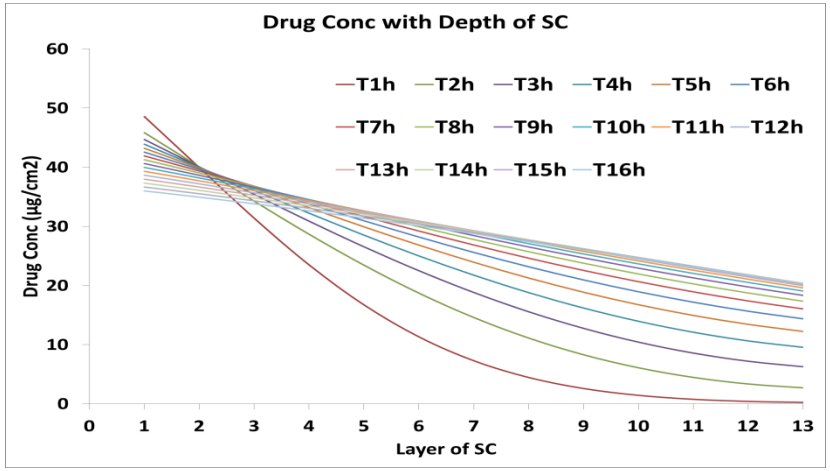
Timolol – Matrix-type Patch formulation

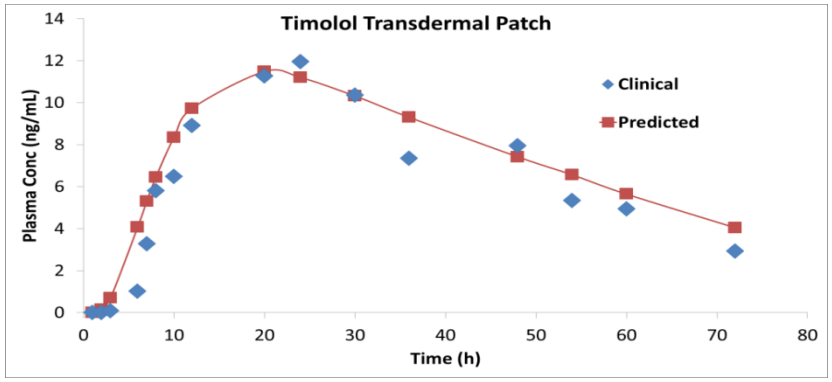


Drug conc. in layers of SC changing with time



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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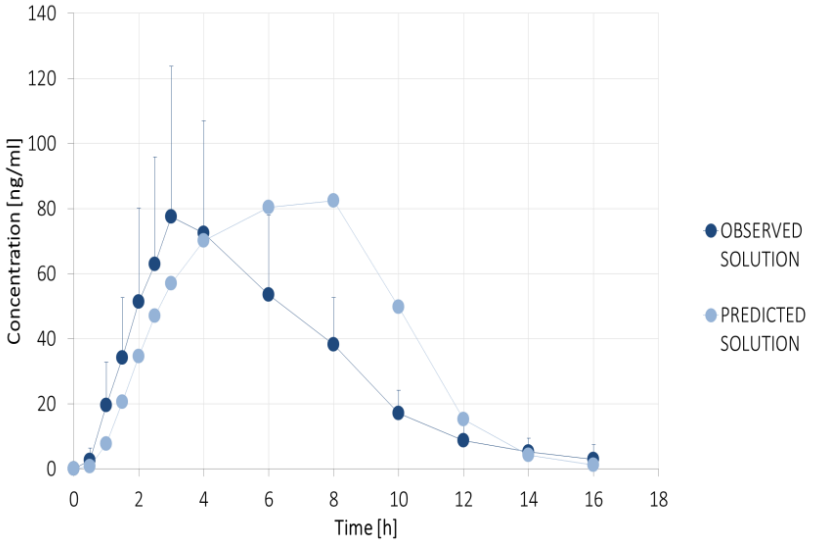
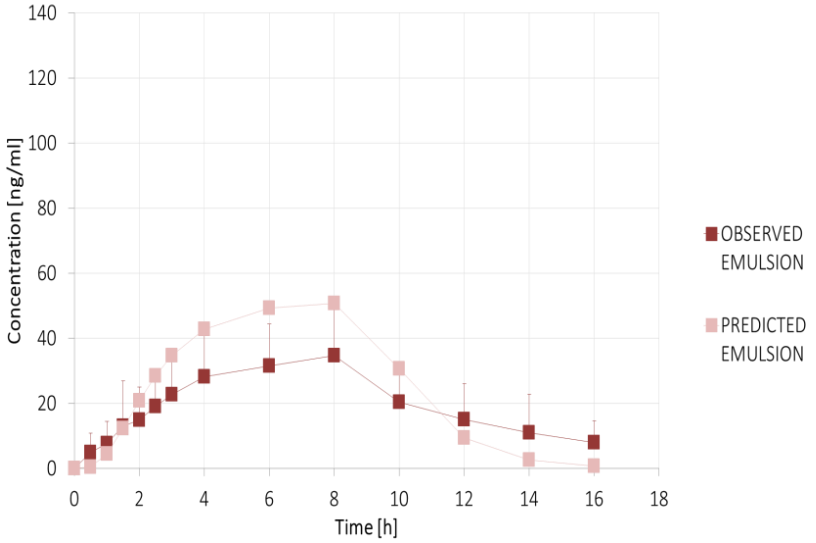
Diclofenac – solution gel vs. emulsion gel



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

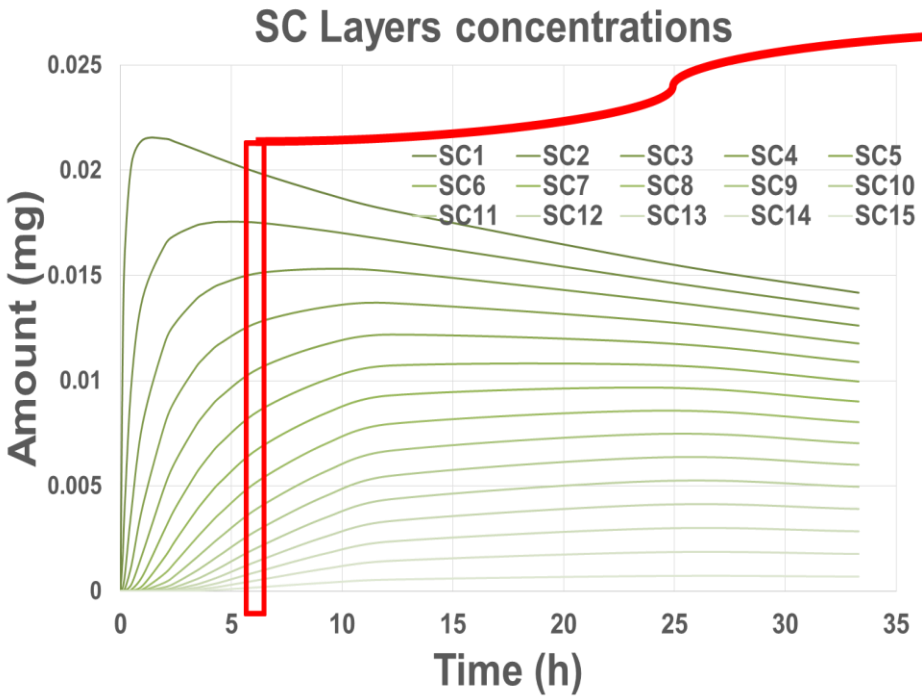


Figure 2. Erythromycin SC individual layers PK profiles.

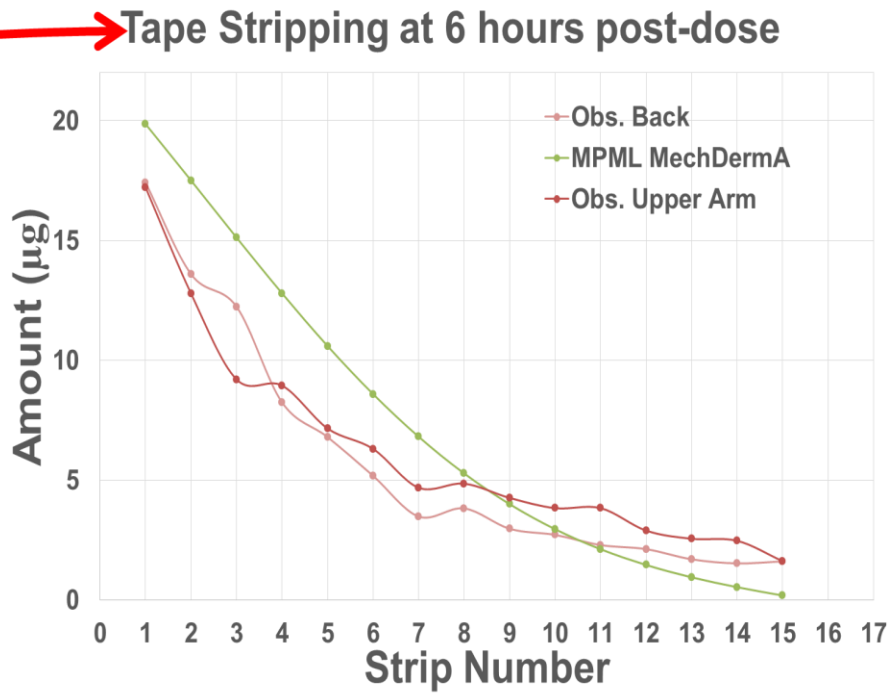
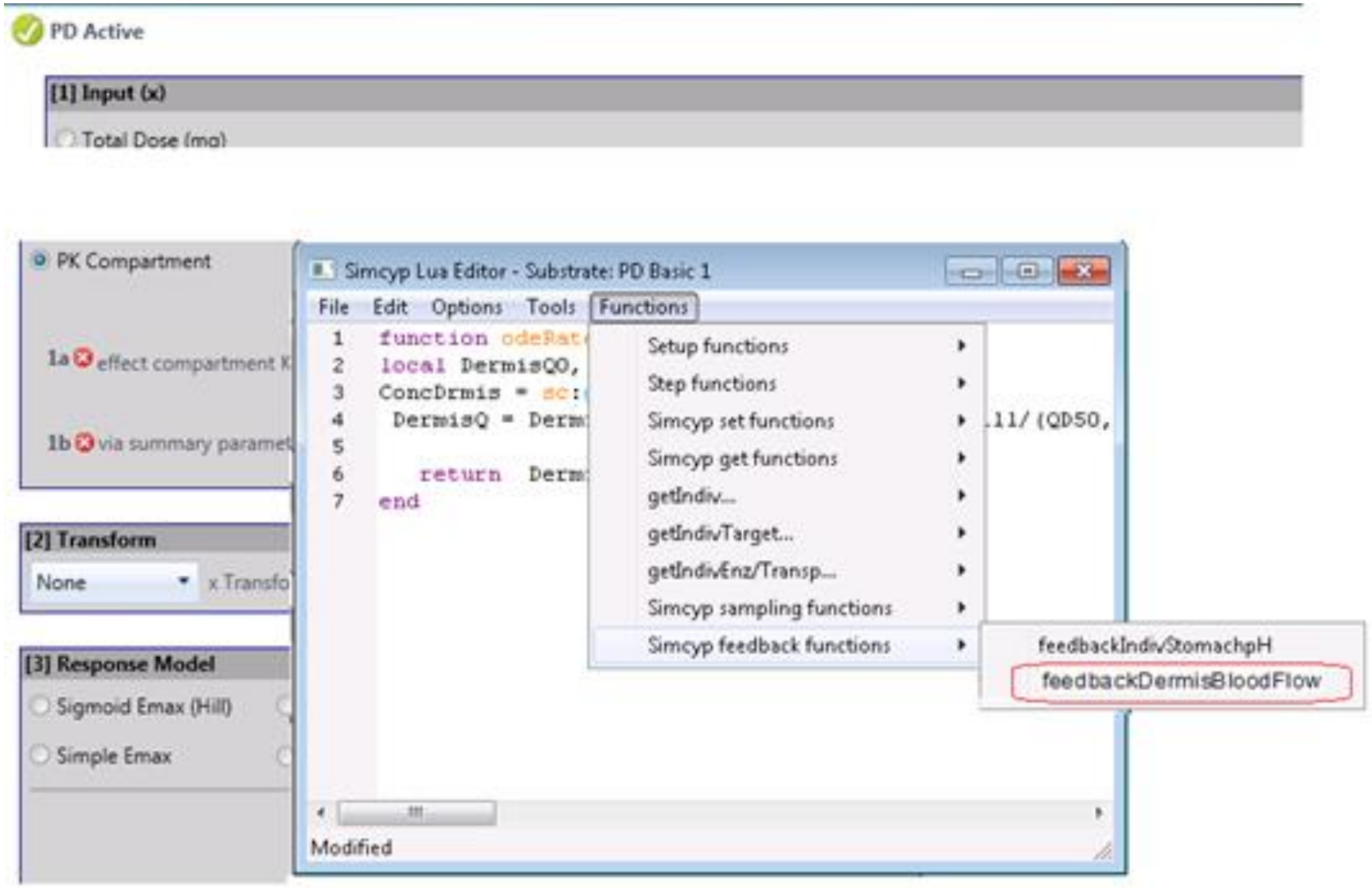


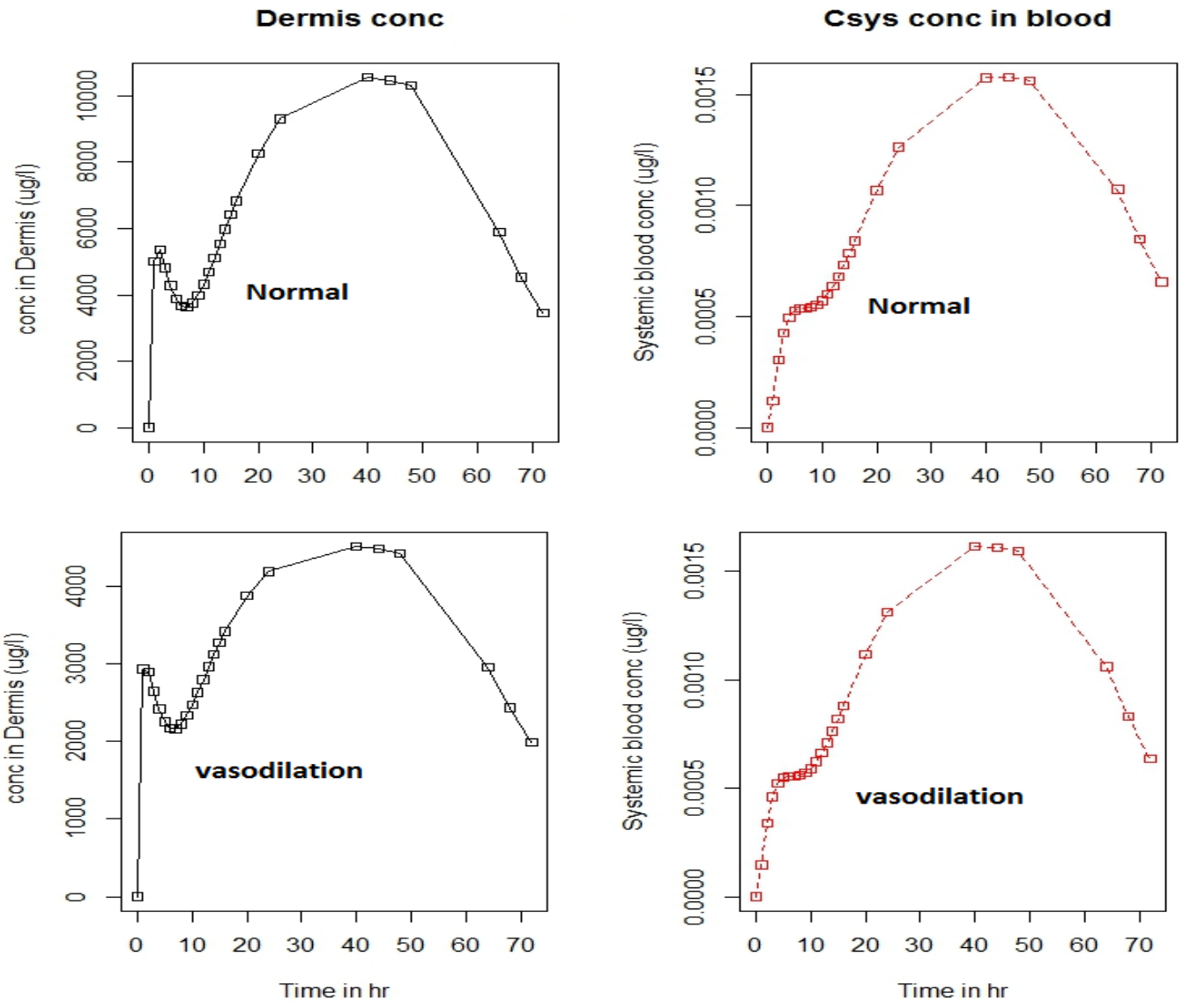
Figure 4. MPML MechDermA skin stripping experiments Predictions vs. Observations

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

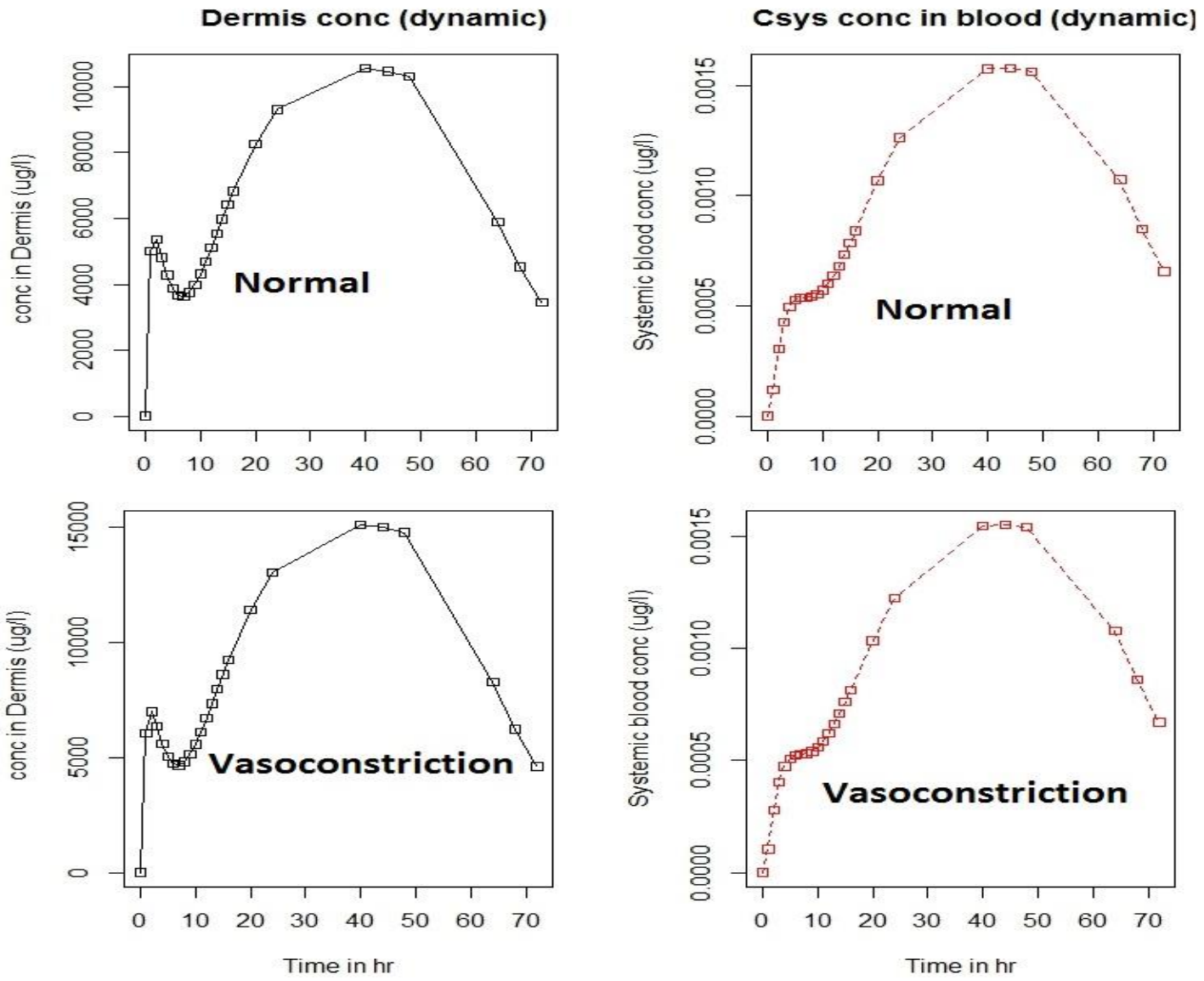
Drug/Excipient effect on local blood flow and absorption



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 – to be studied in year 3
- Vehicle evaporation and its impact on drug solubility and flux – to be studied from next quarter
- Inter-occasion variability for virtual BE – no data available in public domain, any way to get access to hidden data?
- Many gaps in understanding of skin physiology and its variability – new grants and how to apply, what to focus on???
- Disease (psoriasis) population – many gaps in known physiology

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