GastroPlus®

aaps-VCU Student Chapter
American Association of Pharmaceutical Scientists

GastroPlus applications to various drug delivery routes of administration

John DiBella

Maxime Le Merdy

Webinar: Friday, December 11

7:30 PM CET (Paris) / 10:30 AM PDT (Los Angeles) / 1:30 PM EDT (New York)

https://zoom.us/join
Meeting ID: 986 1112 0237
Passcode: AAPSVCU

SimulationsPlus

Outline

Locally acting drug products

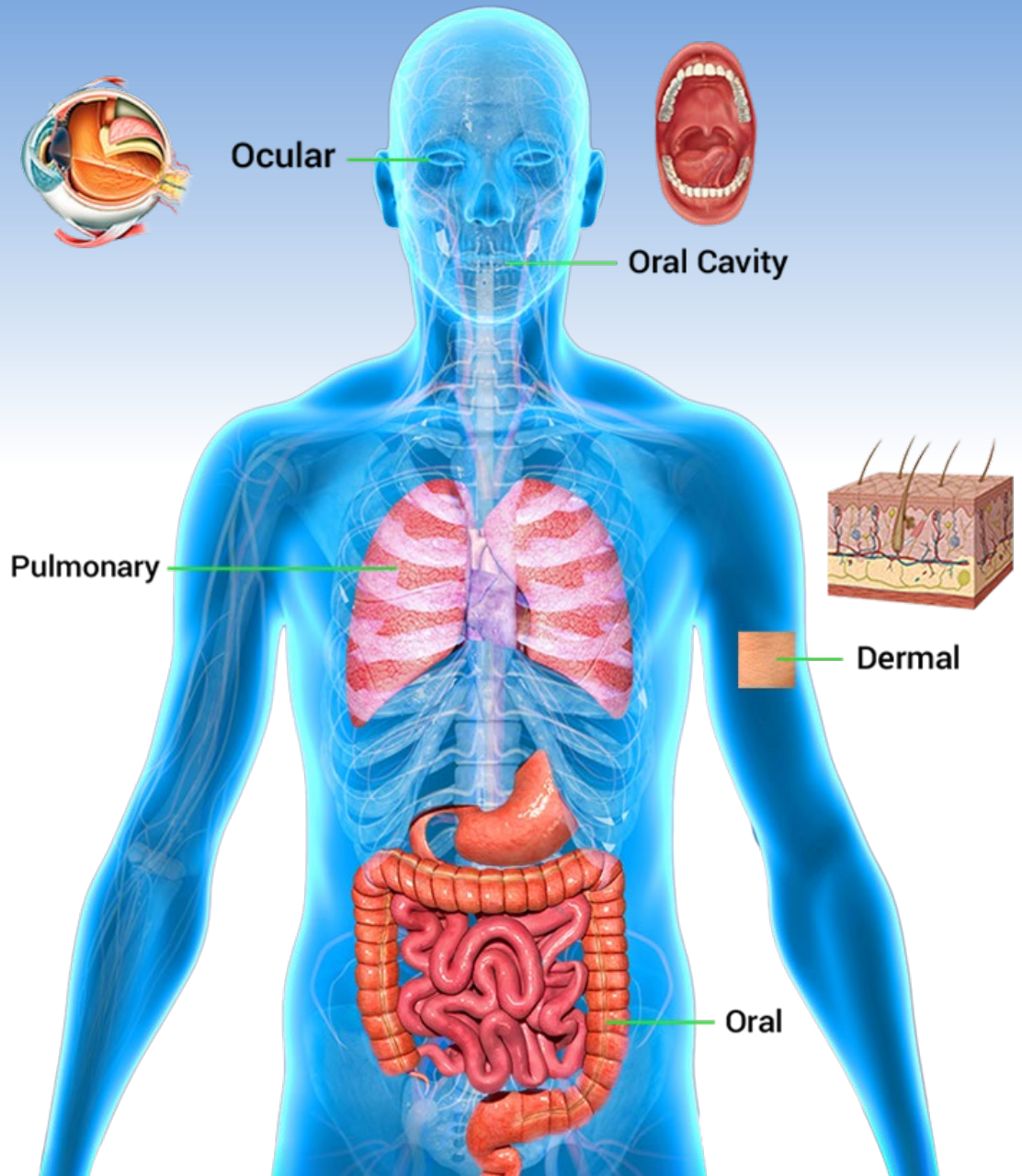
- Ophthalmic route of administration
- Inhalation route of administration

Pharmacodynamic modeling with GastroPlus

Locally acting drug products

Locally-Acting Drugs?

- The main site of action is local, e.g. the skin, the mucosal surface of the nose or lungs, the eyes, the gastrointestinal tract…
- Drug products not intended to be absorbed into the bloodstream
- If the API is detectable in plasma, does the plasma concentration time course reflect local concentrations?
- In the past FDA has relied on clinical endpoint bioequivalence studies when no other alternative was available



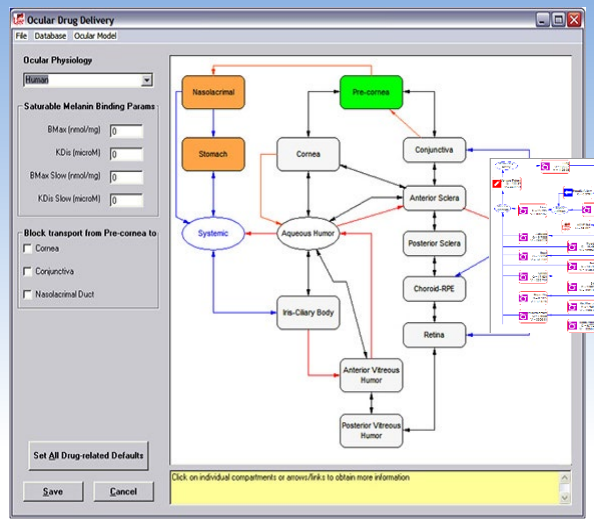
https://www.fda.gov/media/105890/download

Evaluation of BE for Topical Products

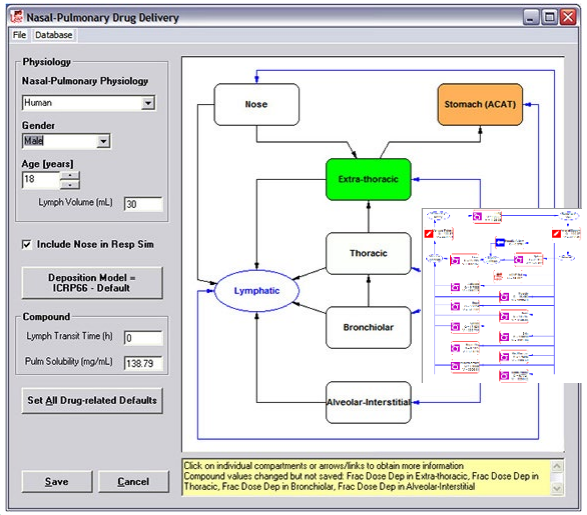
- A Modular Framework for Characterization-Based BE
  - **Qualitative (Q1) and Quantitative (Q2)** Sameness or '***No Difference***'
  - **Physical and Structural (Q3)** Sameness or '***Similarity***'
  - **IVRT** (In Vitro Release Test)
  - **IVPT** (In Vitro Permeation Test)
- Other Types of Evidence to Support a Demonstration of BE
  - **In Vivo Pharmacokinetic** Studies
  - **In Vivo Pharmacodynamic** (e.g., Vasoconstrictor) Studies
  - **In Vivo Comparative Clinical Endpoint BE** Studies
  - **In Silico** Quantitative Methods, Modeling and Simulation

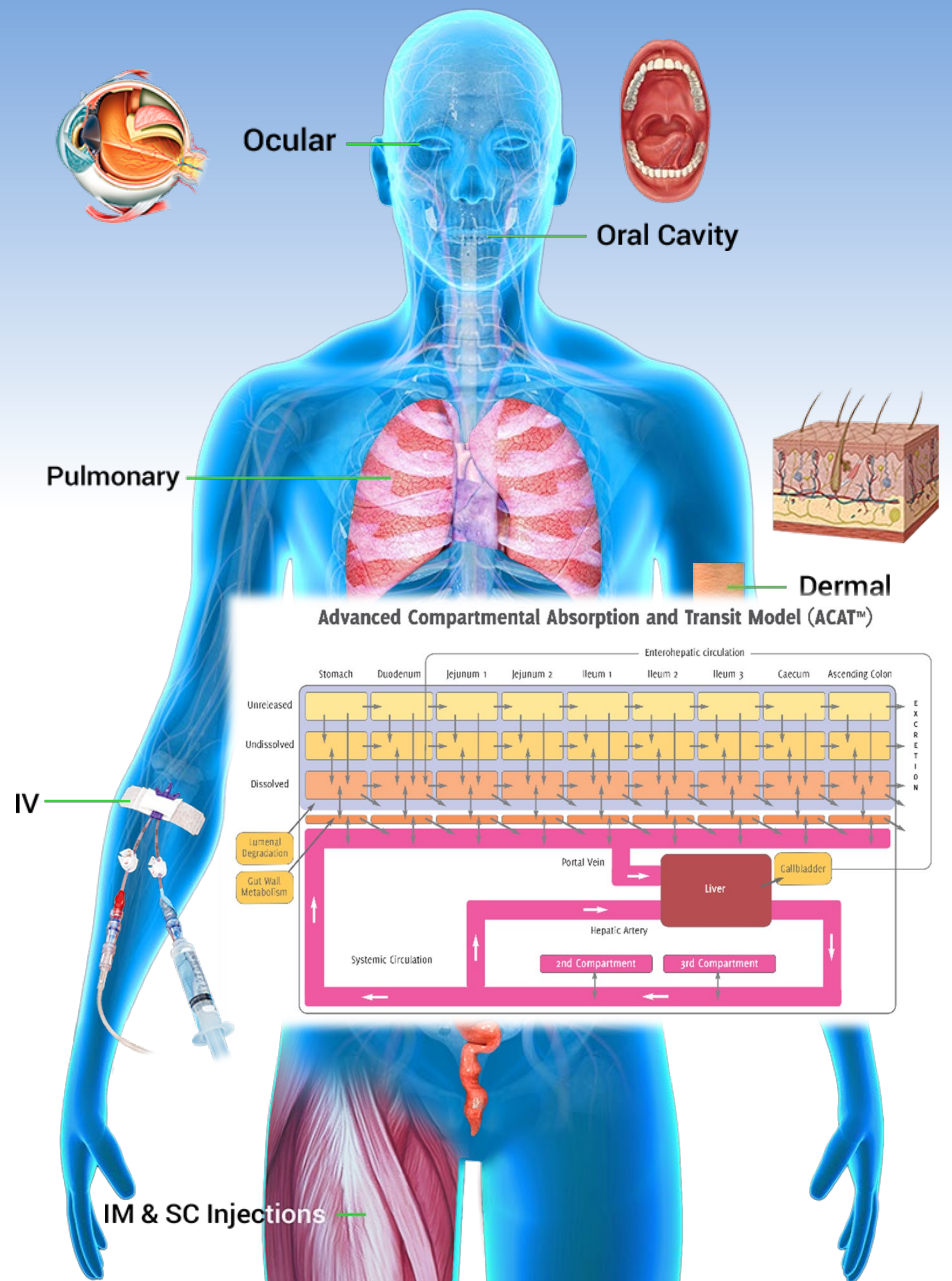
Locally acting PBPK models

Ocular (OCAT™)

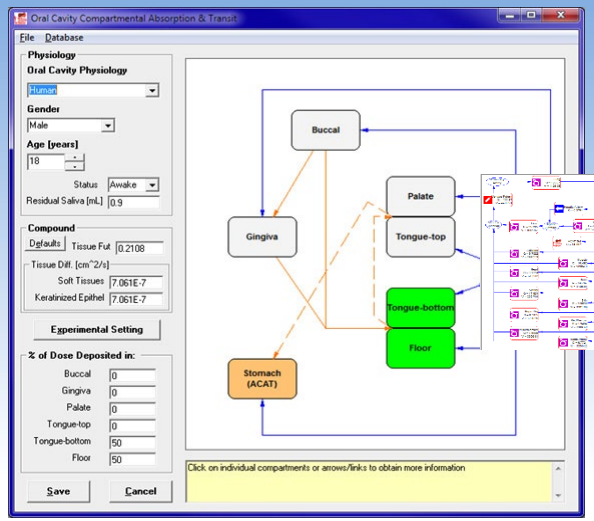


Pulmonary (PCAT™)

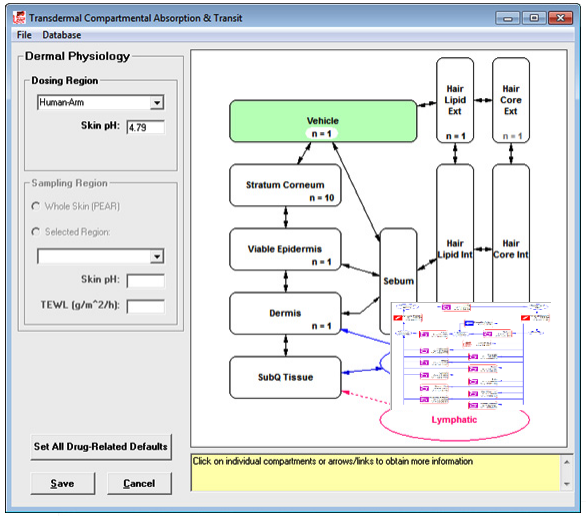




Oral Cavity (OCCAT™)



Dermal (TCAT™)



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Ocular Compartmental Absorption & Transit model

History of the OCAT™ Model

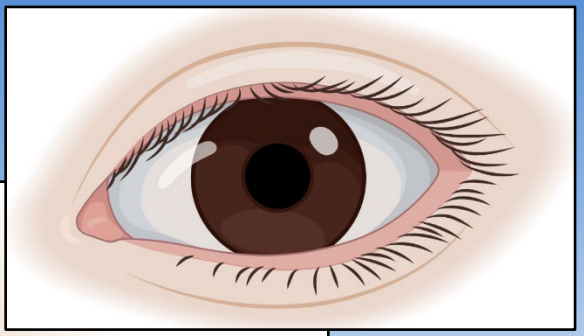
- **2008**: Initial creation of the OCAT V1 model by Simulations Plus scientist in collaboration with Pfizer
- **2014-2017**: Cooperation grant with the FDA → 3-year funded collaborative project with the FDA Office of Generic Drugs on the development of mechanistic models for ocular delivery.

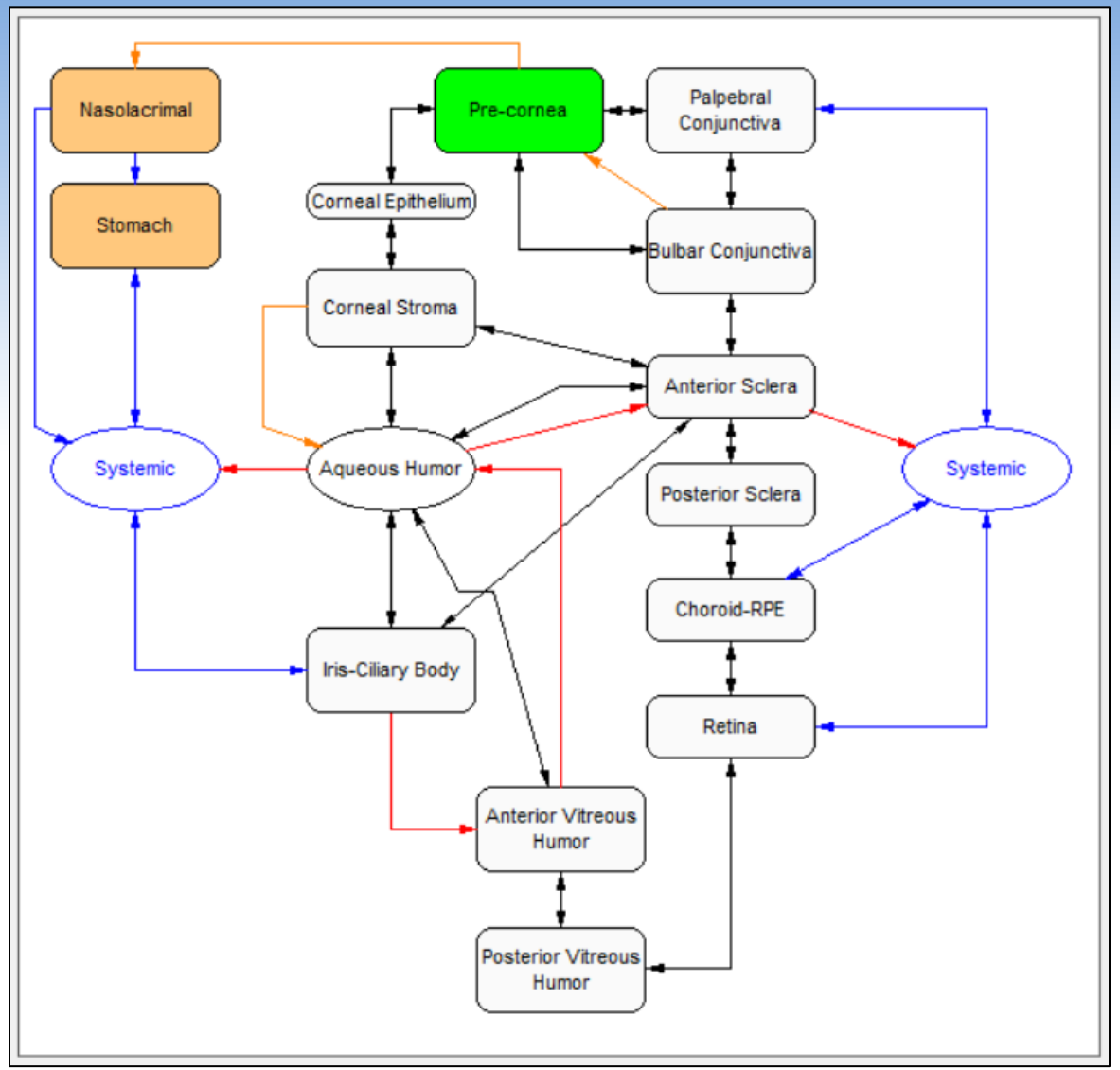
  → Enhancement of the OCAT, creation of V2 and V3
- **2018-2019**: Contract with the FDA Office of Generic Drugs

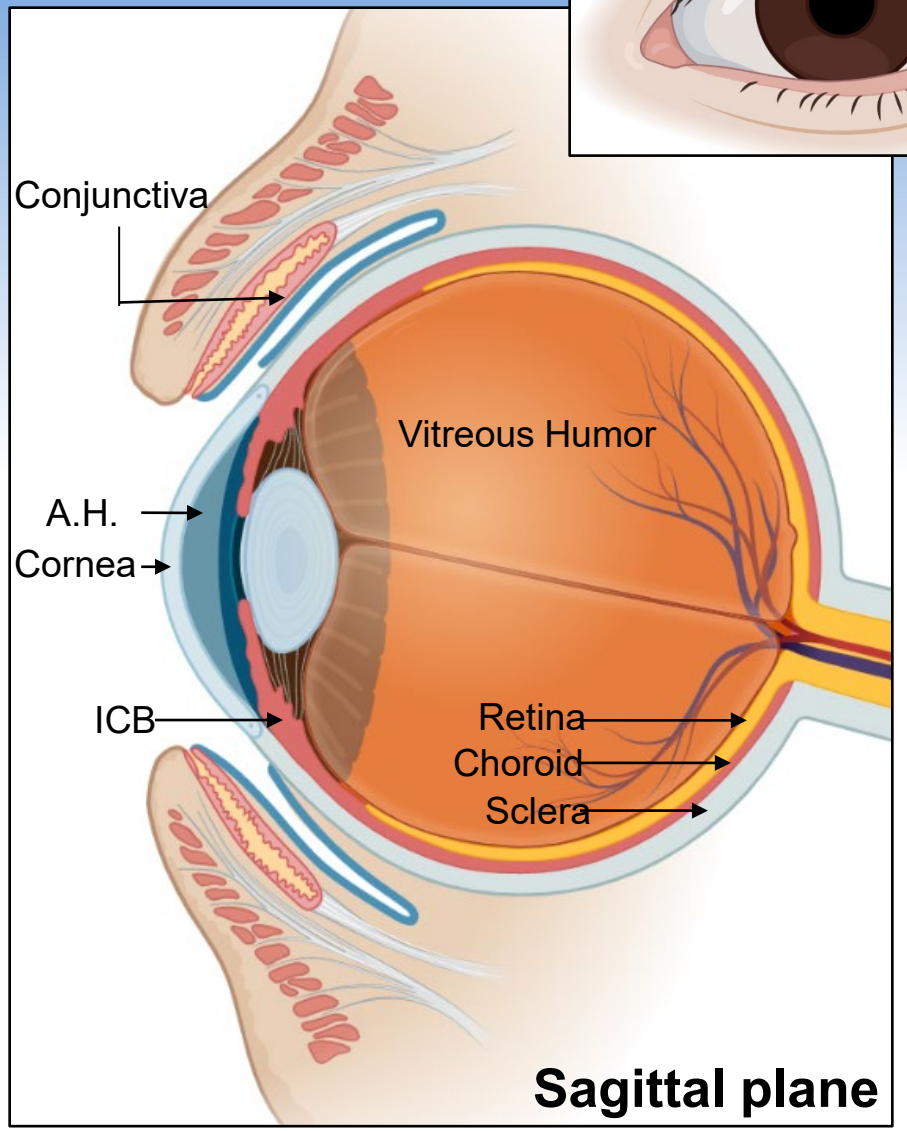
  → Protein binding in ocular tissues, ointment formulation

2020: New Collaboration with the FDA

The Eye and the OCAT™







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Modes of Administration in the Eye

1) Topical

- < 5% reaches anterior segment
- Tiny fraction reaches Retina

2) Systemic

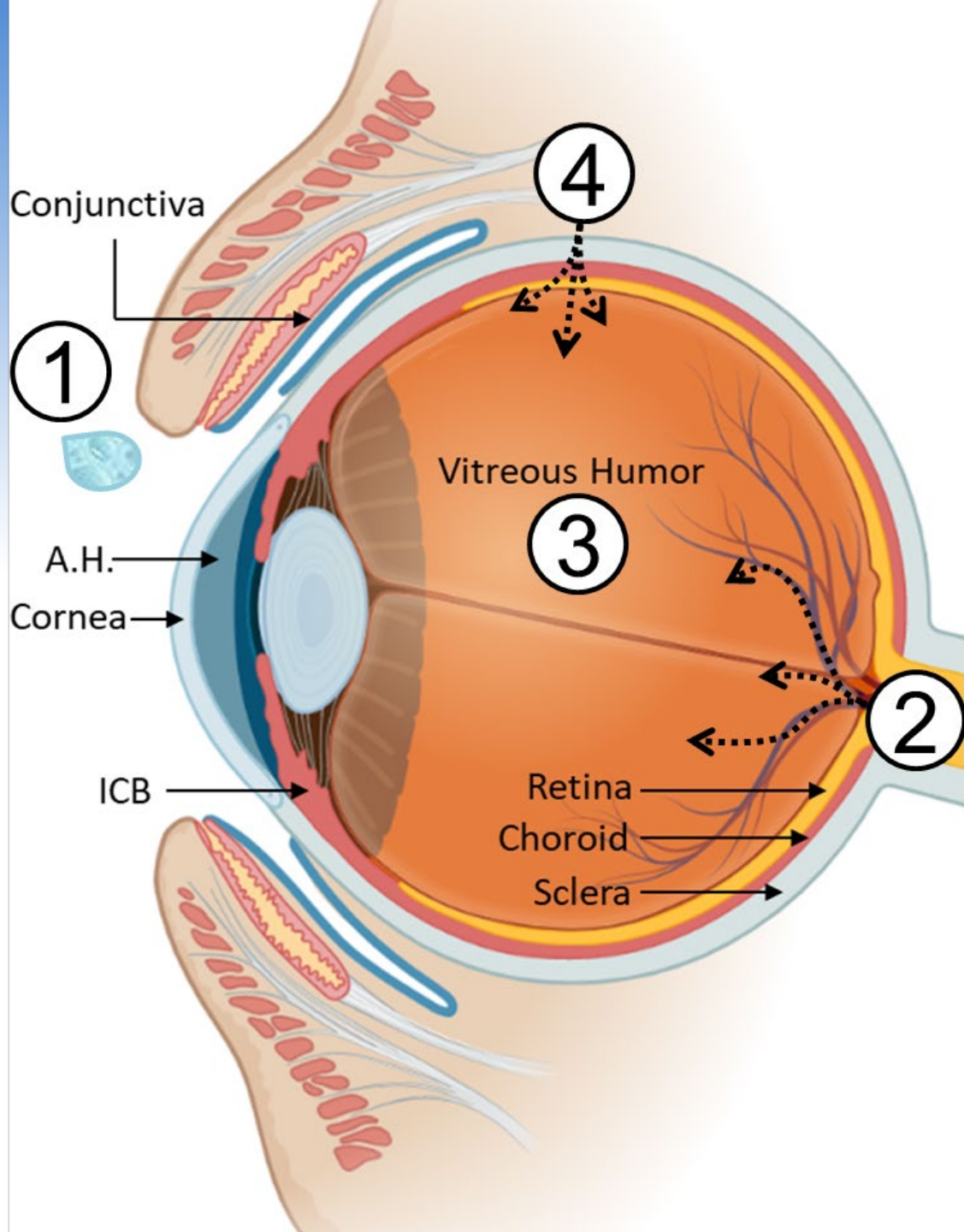
- Penetration is limited by blood aqueous and blood retinal barriers

3) Intravitreal

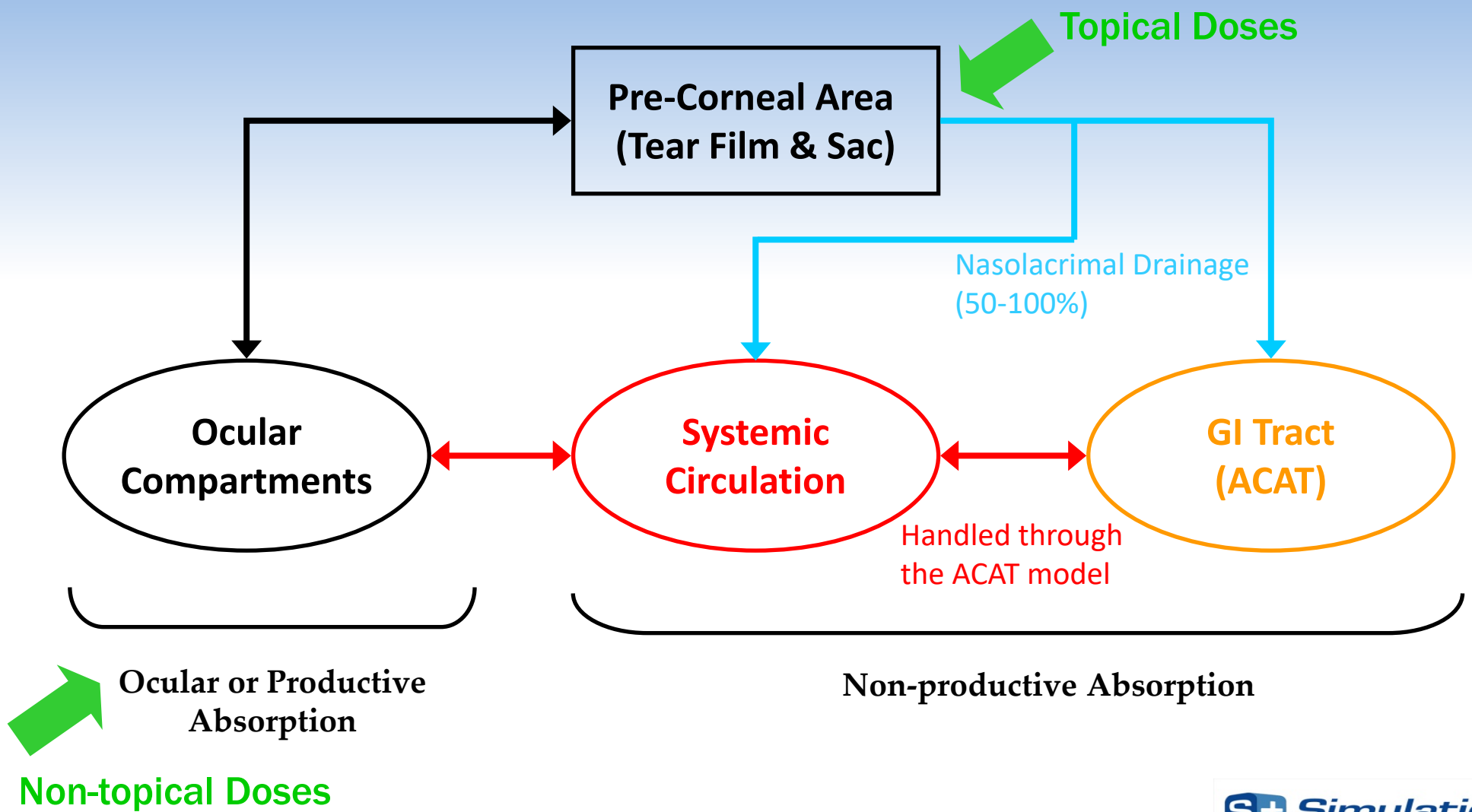
- Effective mode of administration for achieving therapeutic concentrations in retina

4) Transcleral

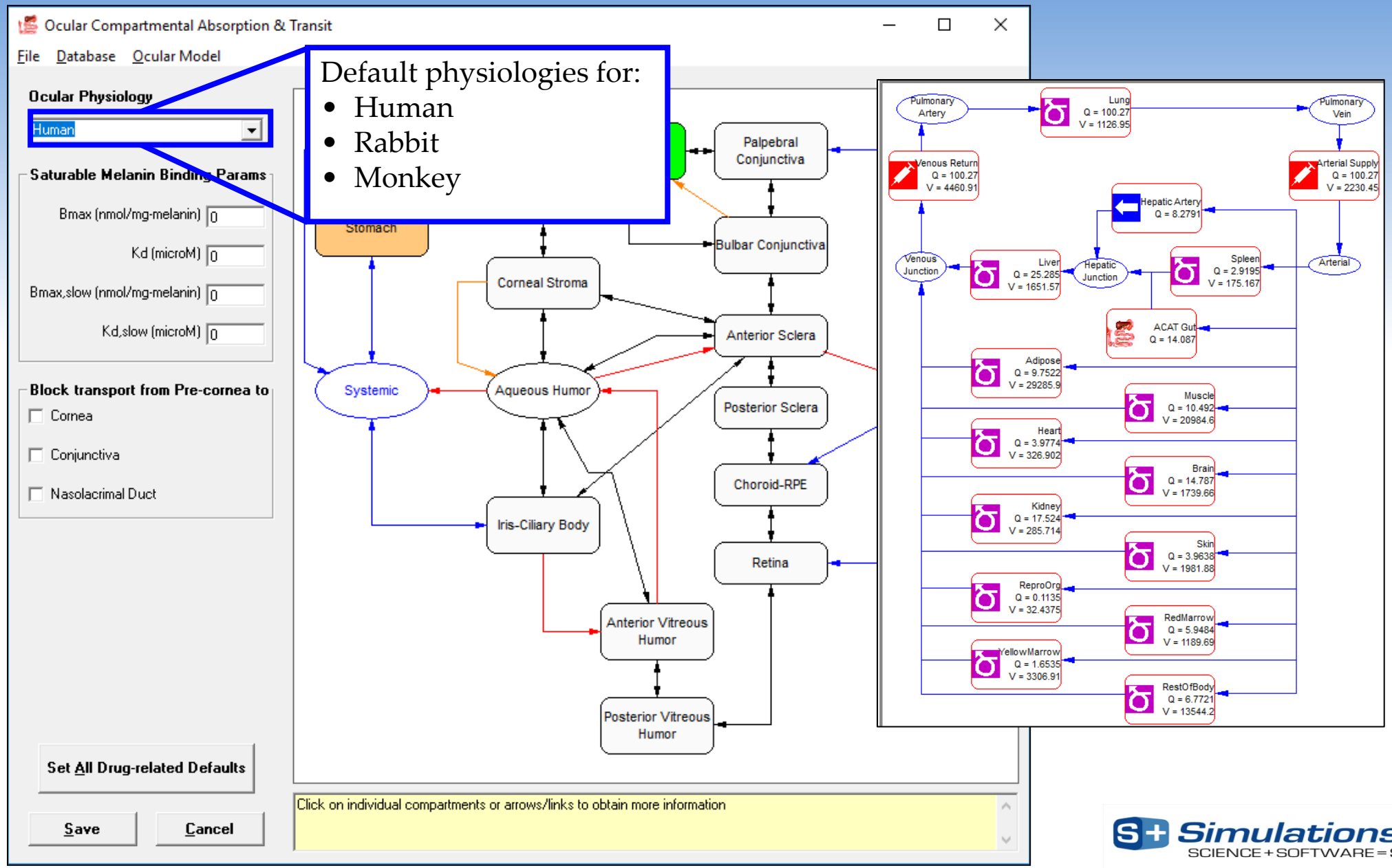
- Noninvasive
- Effectiveness is under investigation



Schematic of Drug Disposition from Ocular Doses (implemented in GastroPlus®)



OCAT™ Interface



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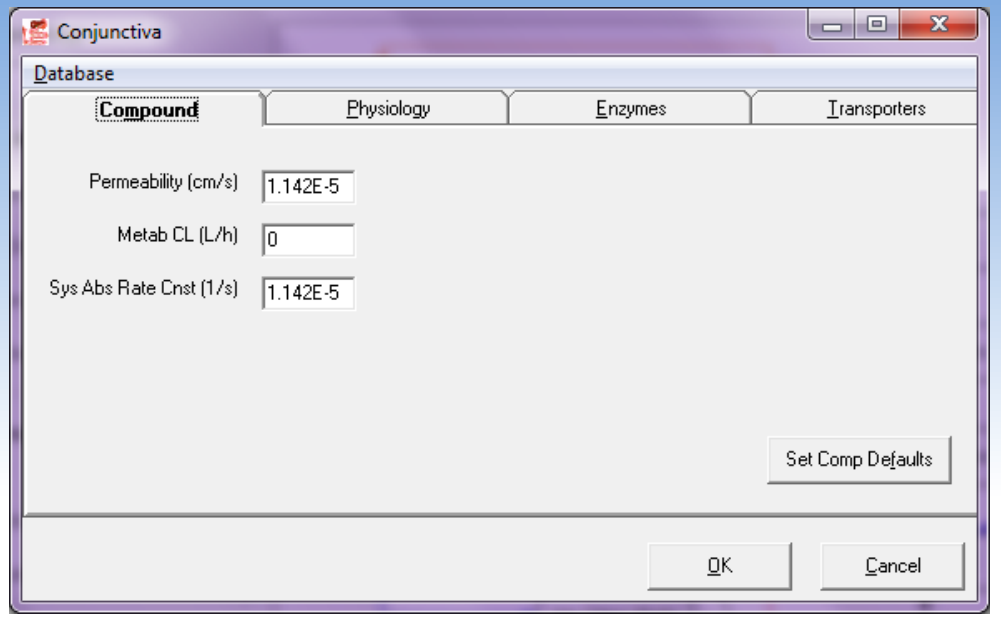
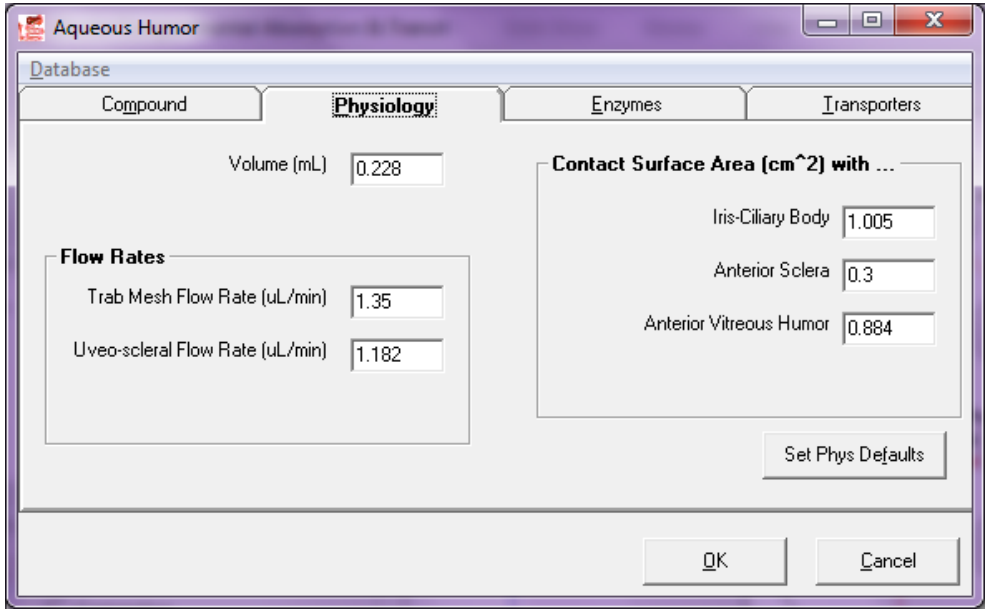
Compound Specific and Physiological Parameters



Compound Specific

- Permeability in each eye tissue
- Systemic absorption rate from vascular eye tissues
- Melanin binding
- Protein binding
- Enzyme and transport parameters



Physiological

- Volume
- Contact Surface Area between tissues/compartments
- Flow Rates (tear flow, aqueous humor flows, etc...)
- Melanin content

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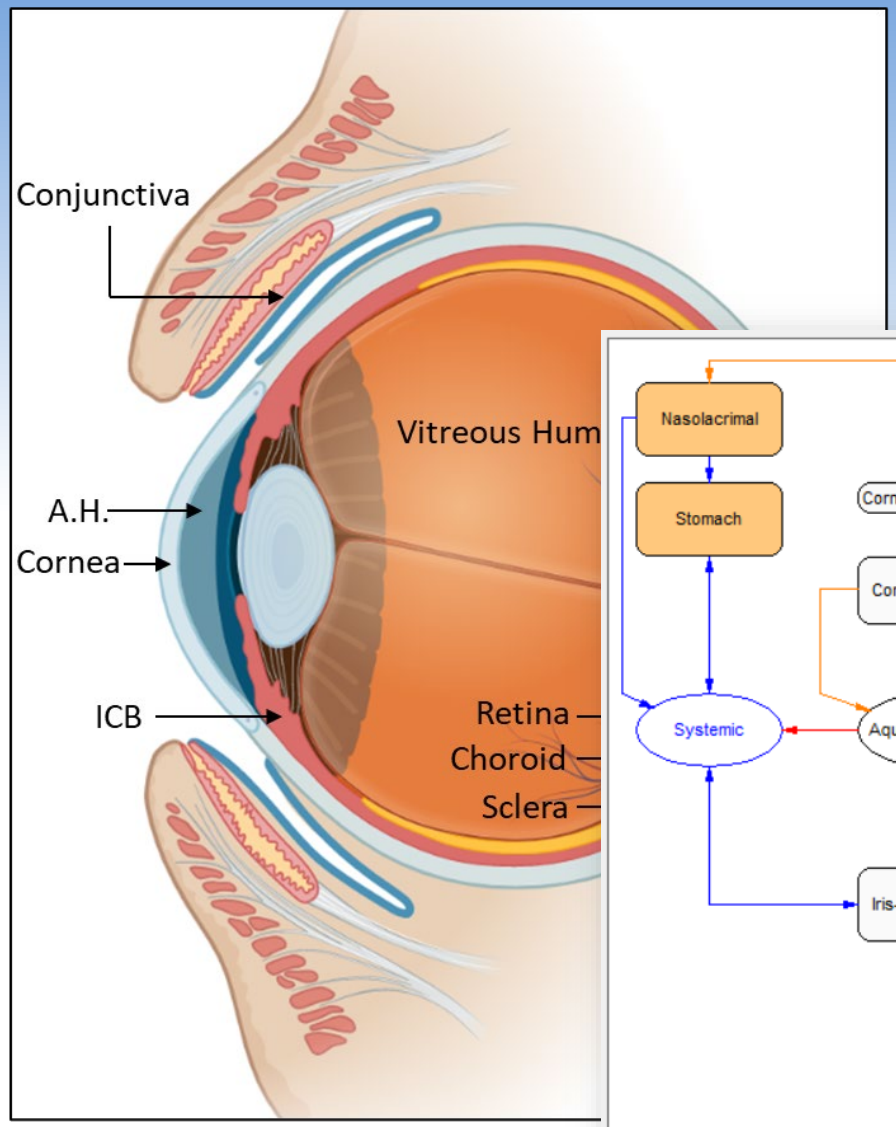
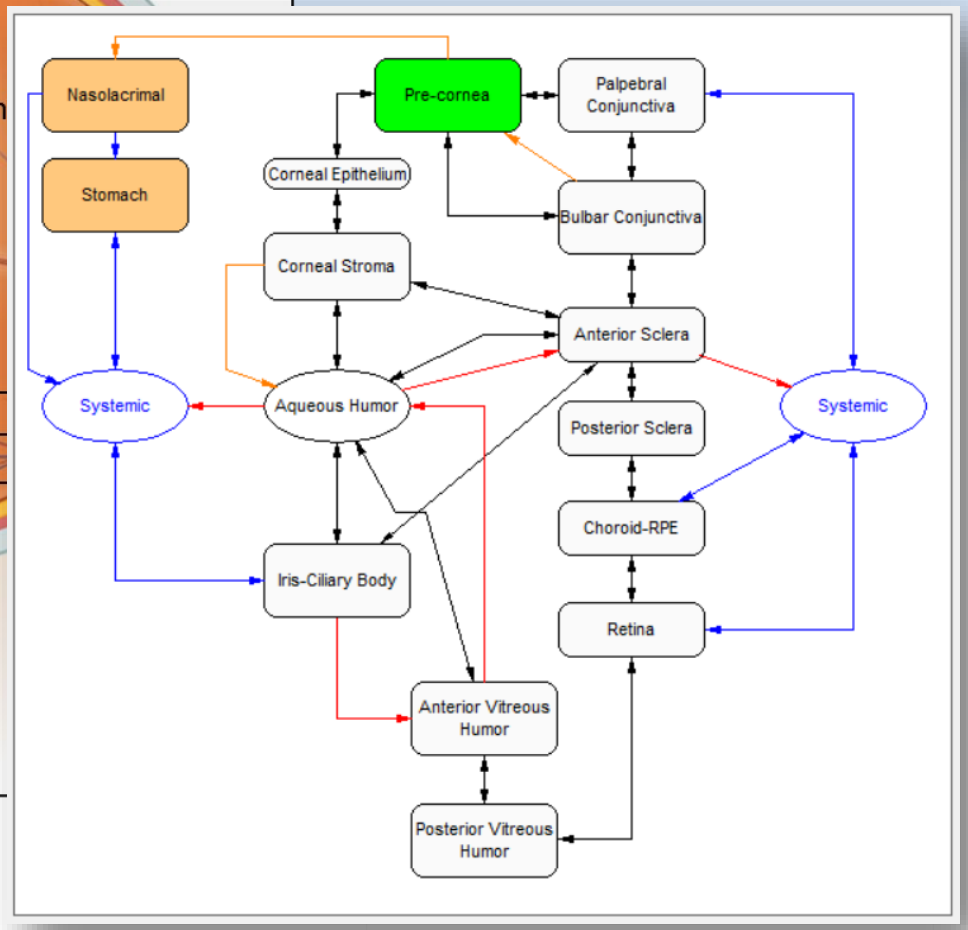
Relevant Mechanisms

- **Absorption & transport**
  - Simple Diffusion (transcellular)
  - Carrier-mediated transport
  - Convective flow
- **Metabolism**
  - Linear
  - Saturable
- **Melanin binding**
  - Linear
  - Saturable





Ocular Dosage Forms

- Topical (delivered to the front of the eye)
  - Immediate-release (eyedrops; both liquid and suspension; ointment)
- Intravitreal
  - Immediate-release (injections; both liquid and suspension)
  - Controlled-release (implants)
- Other
  - Subconjunctival implants

Capabilities of the Program

- Determine the degree of productive and non-productive absorption and loss
- Determine the amount of drug cleared into systemic circulation from the eye
- Physiological parameters can be edited from their default values (to reflect specific conditions or disease states) or complete physiologies for other species can be created by user and saved as custom physiologies
- Integration with GastroPlus® features such as *Parameter Sensitivity Analysis*, *Population Simulations*, *Pharmacodynamic Analysis*, *Drug-Drug Interaction,* etc.
- Optimize ocular parameters against experimental data
- Simulate concentration-time profiles of the drug and plot along with experimental data for compartments/tissues of the body (including eye) and plasma
- Determine Cmax, Tmax and AUCs for all ocular compartments

Ocular Statistics

Ocular Compartmental Simulation Output for Model: v2-Convection

Comp Name	Cmax-Obs	Cmax-Calc	Tmax-Obs	Tmax-Calc	AUC-Obs (0-t)	AUC-Calc (0-t)	AUC-Obs (0-inf)	AUC-Calc (0-inf)
Pre-cornea	927.1	1000.0	0.017	0.0	472.3	151.4	226.8	151.2
Cornea	75.23	83.36	0.030	0.080	41.46	70.15	41.15	70
Conjunctiva	0.0	1.26E-4	0.0	3.000	0	3.21E-4	0.0	0.000321
Aqueous Humor	3.250	4.116	0.250	0.310	4.624	7.612	4.473	7.555
Sclera	9.290	9.119	0.080	0.360	11.43	22.51	10.44	22.35
Anterior Sclera	20.84	31.31	0.080	0.120	22.53	37.80	21.34	37.65
Posterior Sclera	3.515	8.250	0.080	0.450	5.86	20.77	4.989	20.61
Iris-Ciliary Body	9.490	6.997	0.030	0.310	8.343	12.94	8.018	12.84
Retina	0.0	7.977	0.0	0.500	0	20.18	0.0	20.01
Vitreous Humor	0.0	0.190	0.0	0.920	0	0.805	0.0	0.74
Anterior Vitreous Humor	0.0	1.764	0.0	0.880	0	6.589	0.0	6.35
Posterior Vitreous Humor	0.047	0.029	0.250	3.000	0.621	0.116	0.093	0.116
Choroid-RPE	0.0	8.054	0.0	0.450	0	20.30	0.0	20.14

OK

Case Study: Fluorometholone

Background and Aims

- Background
  - Tobradex® 0.1% Dexamethasone
  - Tobradex ST® 0.05% Dexamethasone

Active ingredient	Strength (%)	logP	MW (g/mol)	Water solubility (mg/mL)	Solubilized (%)	Suspended (%)
Dexamethasone	0.1	1.93	392.5	0.089	8.9	91.1
	0.05	1.93	392.5	0.089	17.8	82.2

➔ Aqueous humor exposure is similar despite the strength differences.
Same particle size (PS) but difference in viscosity
(75 cps for Tobradex ST® and 1.5 cps for Tobradex®)

- Aims
  - Verify an OCAT™ model for fluorometholone suspension 0.1%
  - Design a new suspension 0.01% with the same aqueous humor exposure

Modeling Strategy

Model Development → Model Validation → New Formulation

4.10^{-5} M Solution of Flm

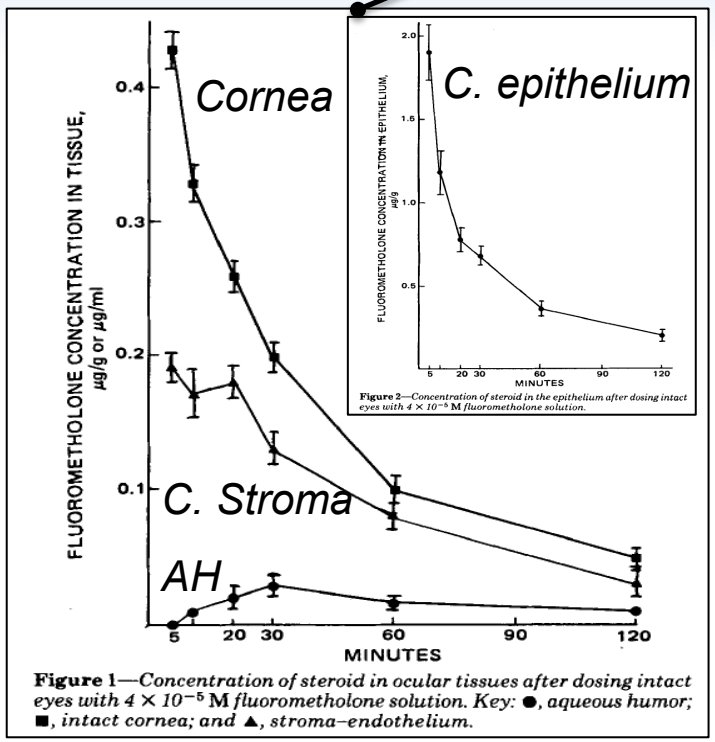


Figure 1—*Concentration of steroid in ocular tissues after dosing intact eyes with 4 × 10^{-5} M fluorometholone solution. Key: ●, aqueous humor; ■, intact cornea; and ▲, stroma–endothelium.*

Figure 2—*Concentration of steroid in the epithelium after dosing intact eyes with 4 × 10^{-5} M fluorometholone solution.*

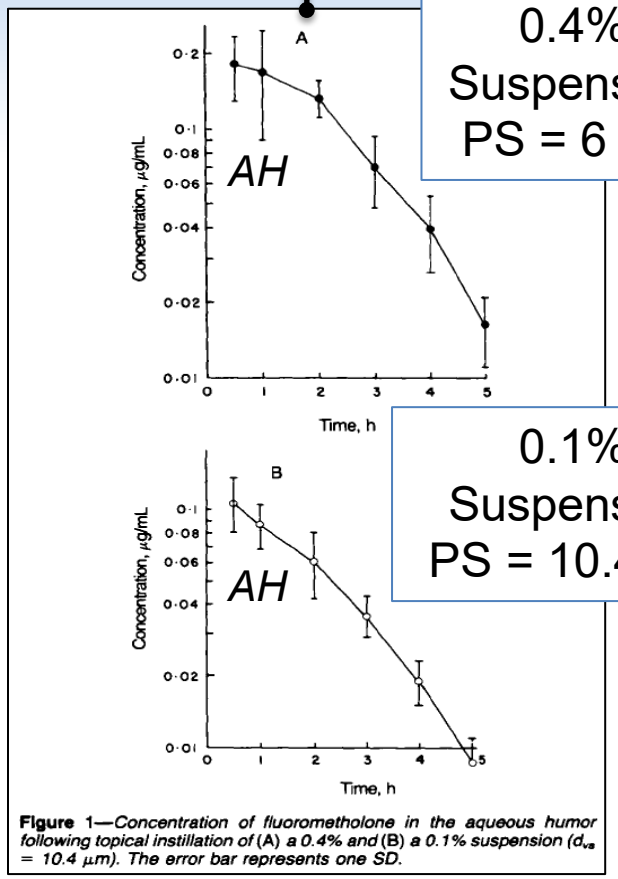


Figure 1—*Concentration of fluorometholone in the aqueous humor following topical instillation of (A) a 0.4% and (B) a 0.1% suspension (d_{vs} = 10.4 μm). The error bar represents one SD.*

0.4% Suspension PS = 6 μm

0.1% Suspension PS = 10.4 μm

Requirements

Safety:

- Dose= 0.01%
- PS < 10 μm

Efficacy:

- AH exposure comparable to the 0.1% Suspension; PS= 10.4 μm

Sieg-J Pharm Sci-Sep-70-9-1026-9-1981

Hui-Robinson-JPharmSci-73-3-280-1986

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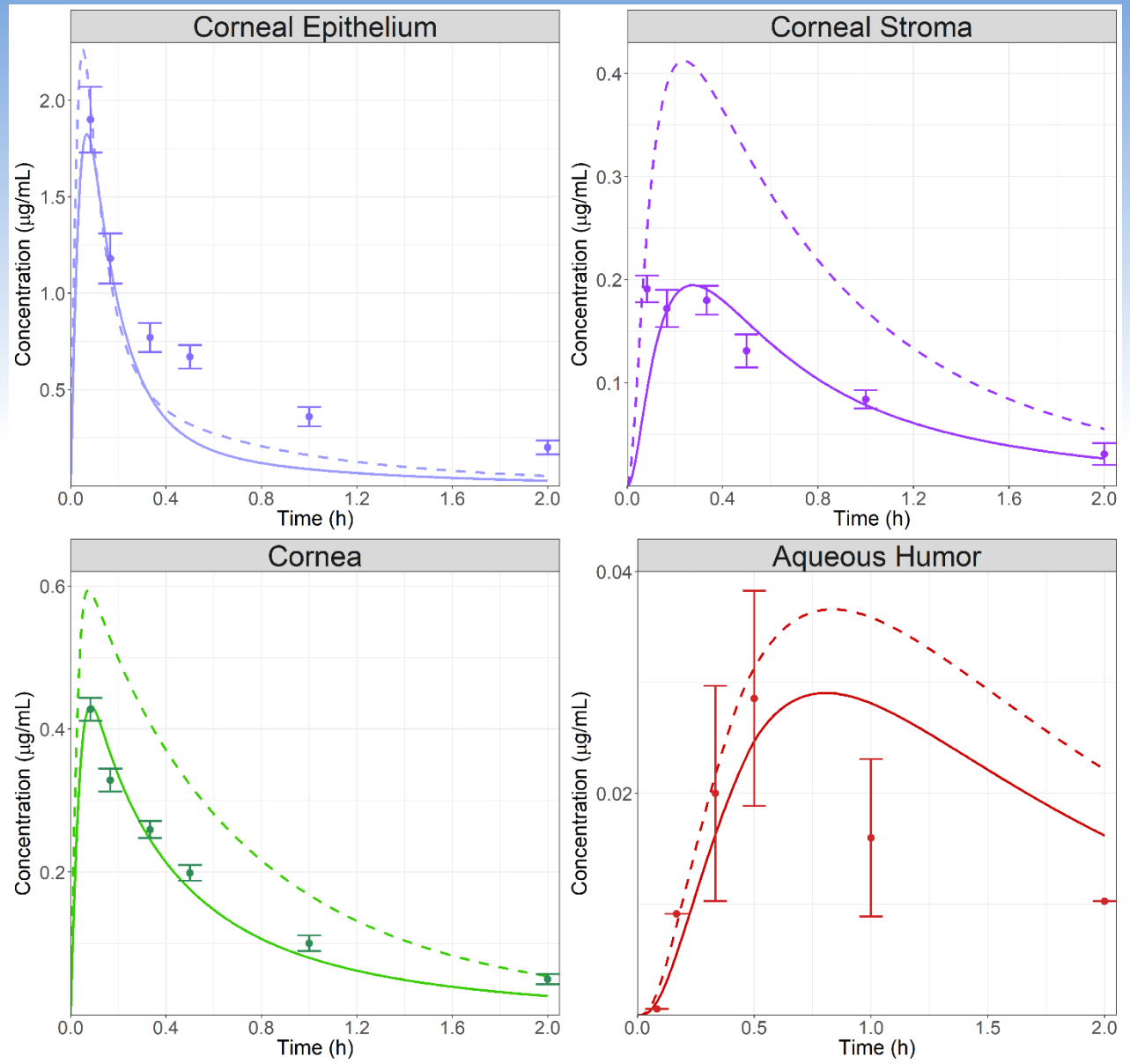
Summary



Model Development

4.10^{-5} M Solution of Flm

Sieg-J Pharm Sci-Sep-70-9-1026-9-1981

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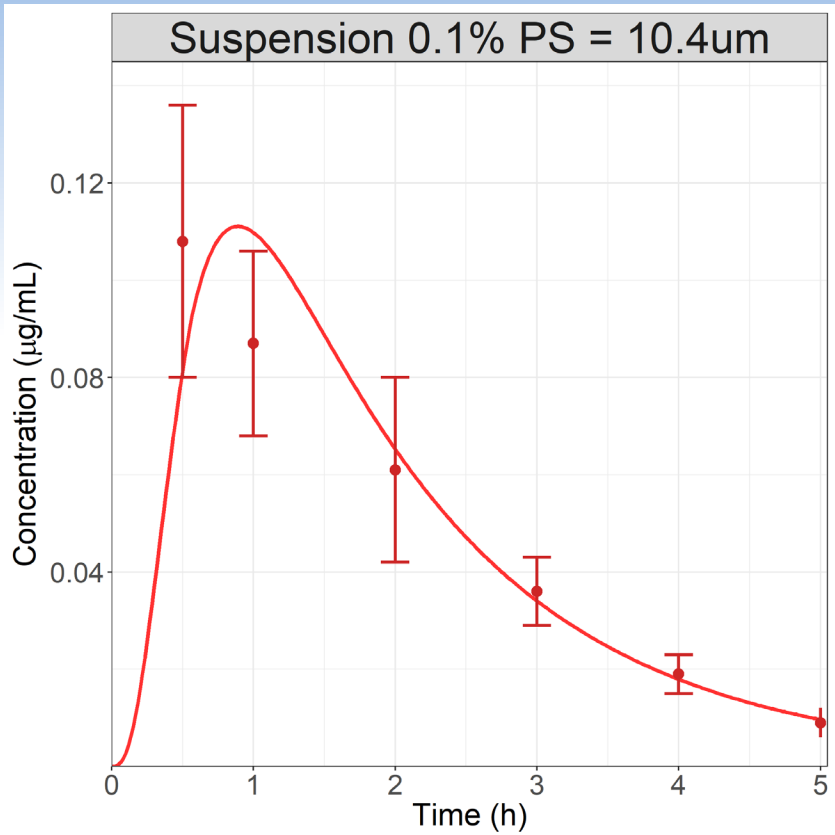
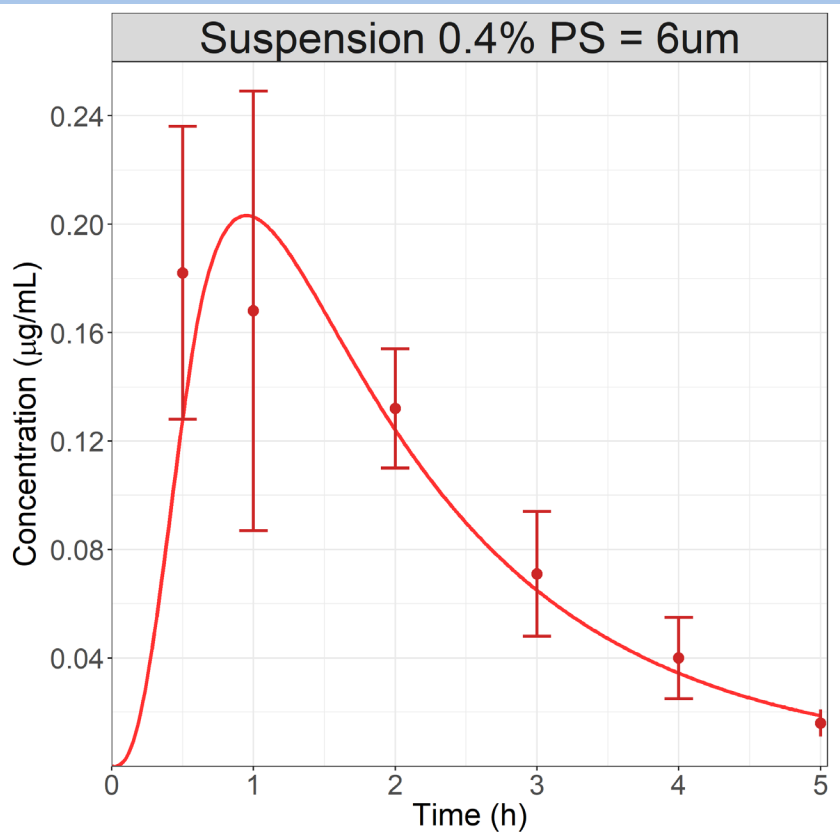
Summary





Model Validation

- 0.1% Suspension PS = 10.4 µm
- 0.4% Suspension PS = 6 µm

Hui-Robinson-JPharmSci-73-3-280-1986

New Formulation

Requirements

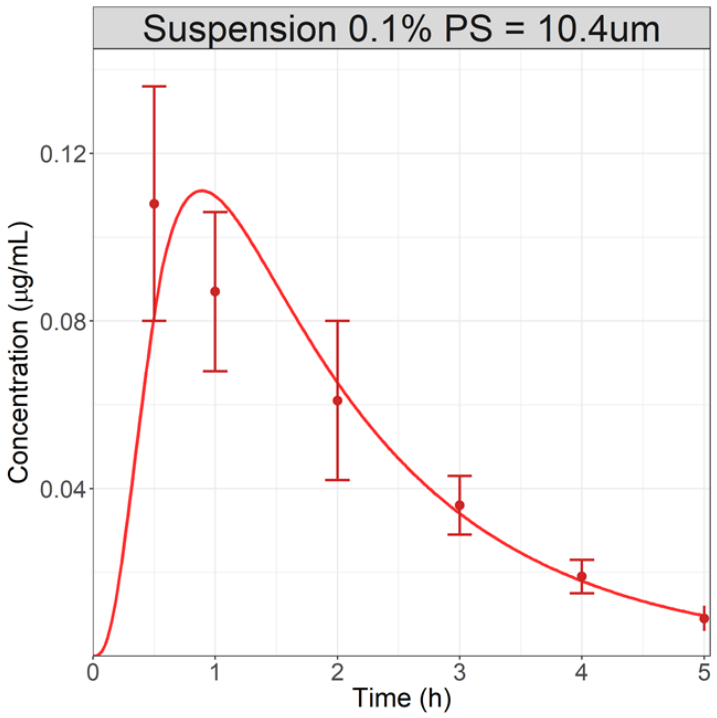
Safety:

- Dose= 0.01%
- PS < 10 m

Efficacy:

- AH exposure comparable to the 0.1% Suspension; PS = 10.4 µm

Suspension 0.1%; PS = 10.4 µm	
AH AUC (µg.h/mL)	0.480
Cmax (µg/mL)	0.108



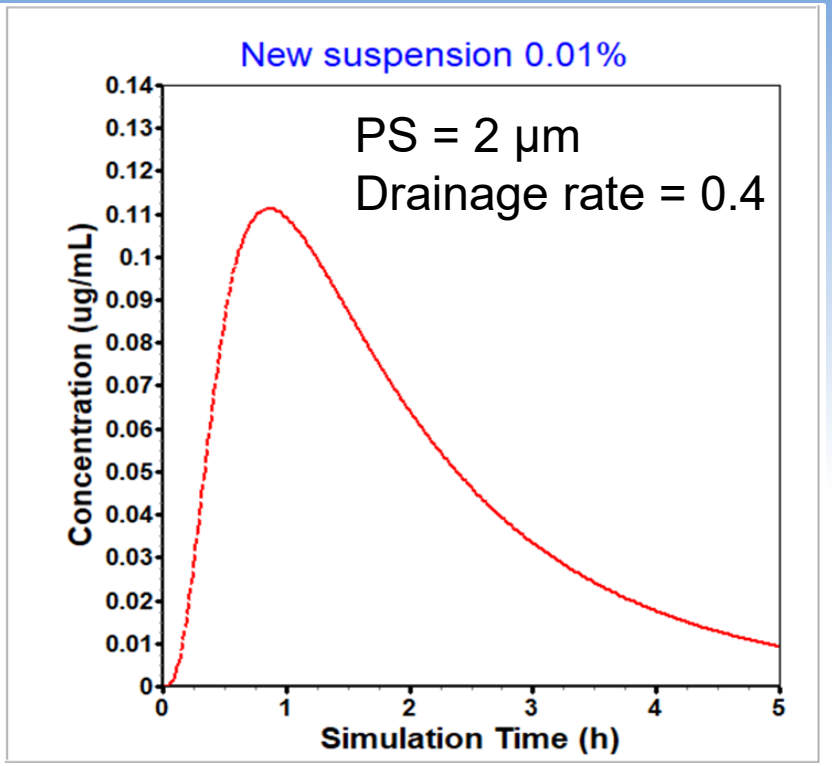


Table I—Drainage Rate Constant of Polyvinyl Alcohol Solutions as a Function of Concentration and Viscosity

Concentration, %	Viscosity, cps	k, min^{-1}	Number of Determinations
0.0[a]	1.0	0.54	3
0.5	3.1	0.32 (0.05)[b]	5
1.1	4.2	0.25 (0.03)	5
1.9	6.1	0.25 (0.03)	10
2.25	7.7	0.31 (0.04)	5
3.5	17.5	0.08 (0.02)	7
5.0[c]	57.8	0.14 (0.02)	9

AH AUC (µg.h/mL)	0.491
Cmax (µg/mL)	0.111

Patton-Robinson-JPharmSci-1975

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To learn More:

Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model

Asho
Jiang
U.S.
Fede

Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: a Case Study Using Dexamethasone Suspension

Maxim
Elefthe
Suresh
Lei Zh

Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

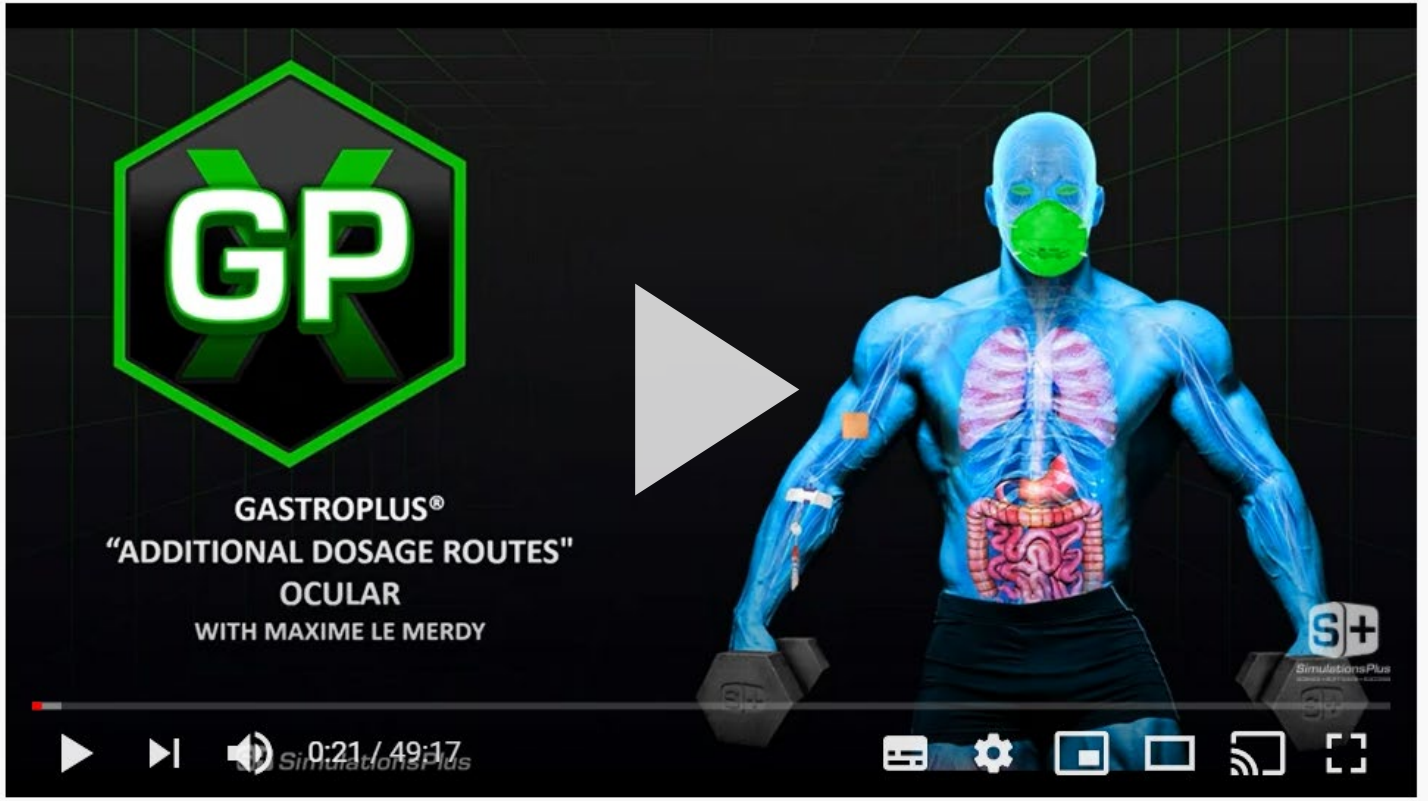
[1] Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA.

Max

Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations

Maxime Le Merdy [1] • Jessica Spires [1] • Viera Lukacova [1] • Ming-Liang Tan [2] • Andrew Babiskin [2] • Xiaoming Xu [3] • Liang Zhao [2] • Michael B. Bolger [1]

To learn More (bis):



The GastroPlus® Additional Dosage Routes Seminar Series Ocular with Maxime Le Merdy

https://www.youtube.com/watch?v=IoNeSlUN-4Q&t=2406s&ab_channel=SimulationsPlus%2CInc.

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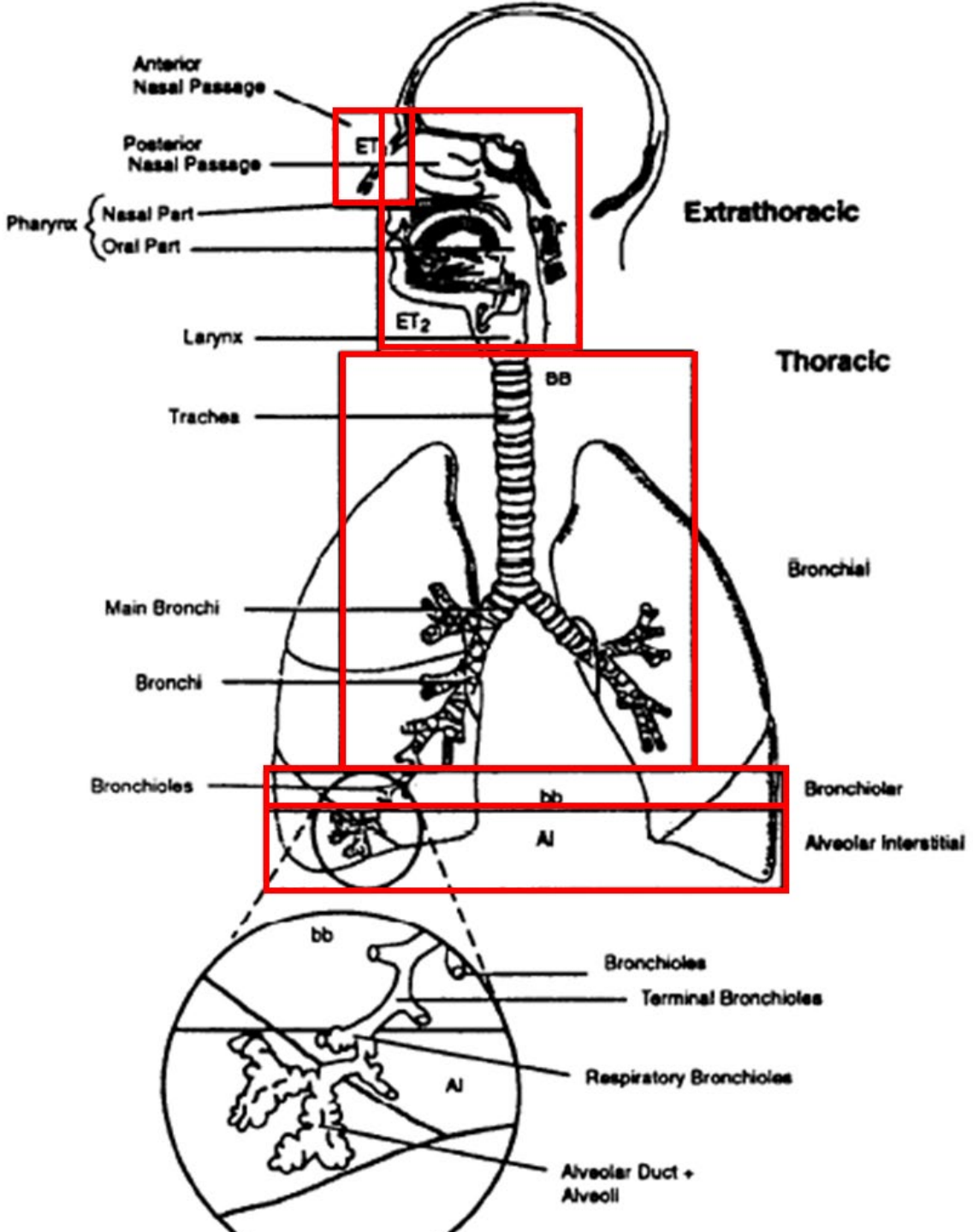
Pulmonary Compartmental Absorption & Transit model

Compartmentalization of the Lung (ICRP66)



- ET1 = Anterior nasal passage
- ET2 = Posterior nasal passage, oral cavity, larynx, pharynx etc.
- BB = Trachea and bronchi
- Bb = Bronchioles (up to terminal)
- AI = Respiratory bronchioles, alveolar duct, alveoli etc.

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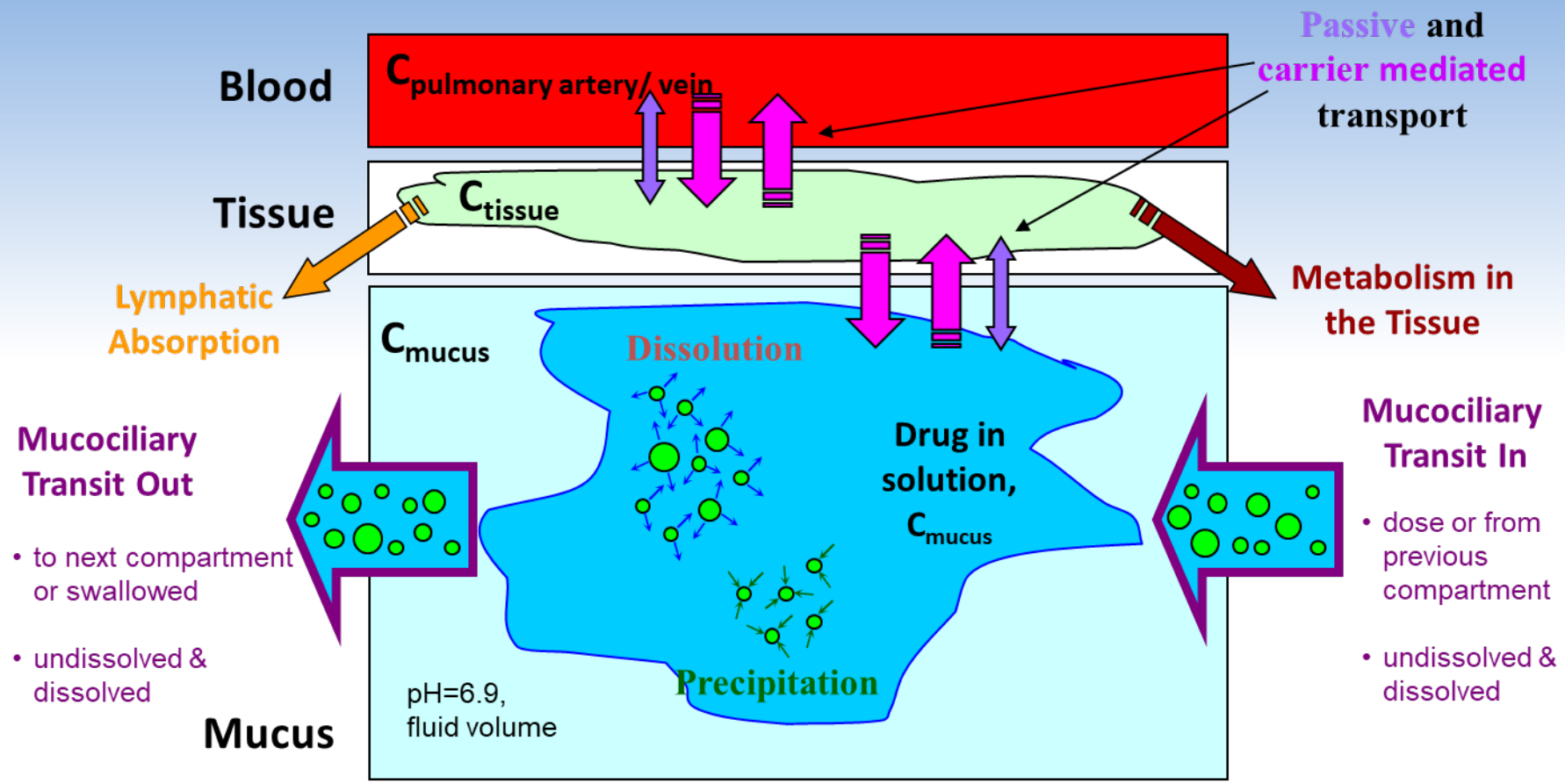
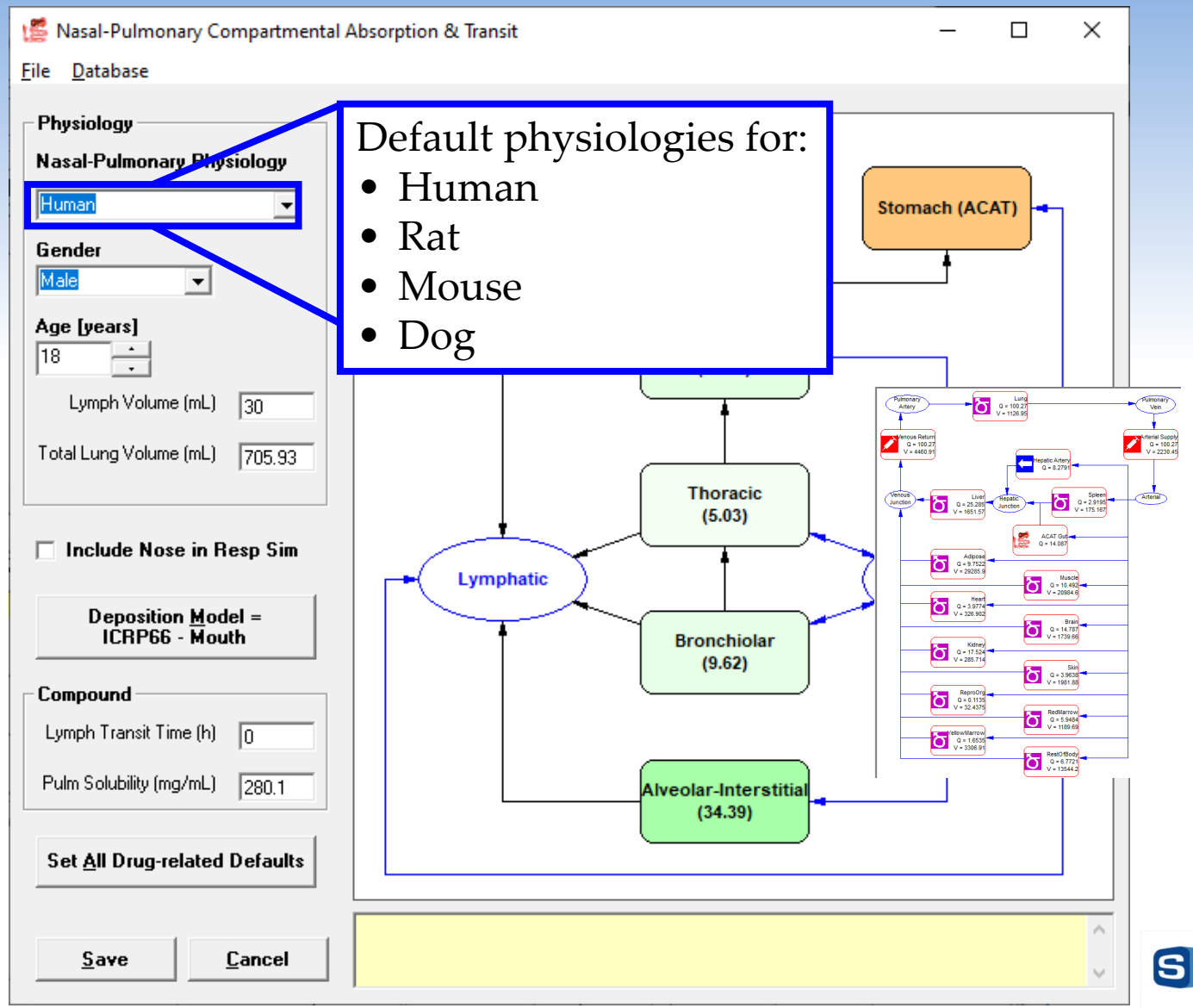
Processes Involved in Nasal-Pulmonary Absorption



These phenomena:

- are happening simultaneously
- are repeated in each of the compartments of the nasal-pulmonary model

Pulmonary Compartmental Absorption and Transit Model



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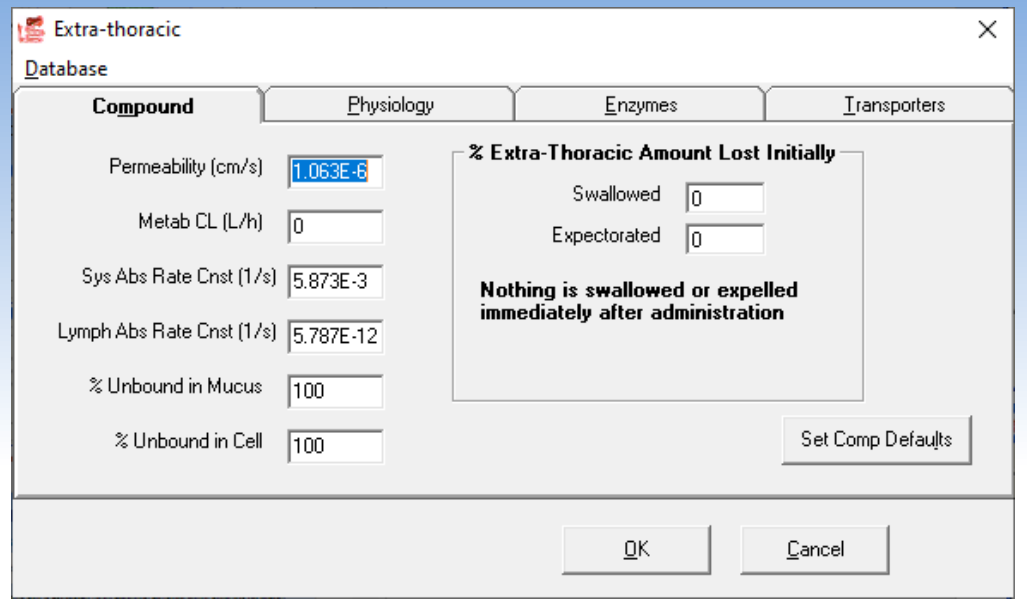
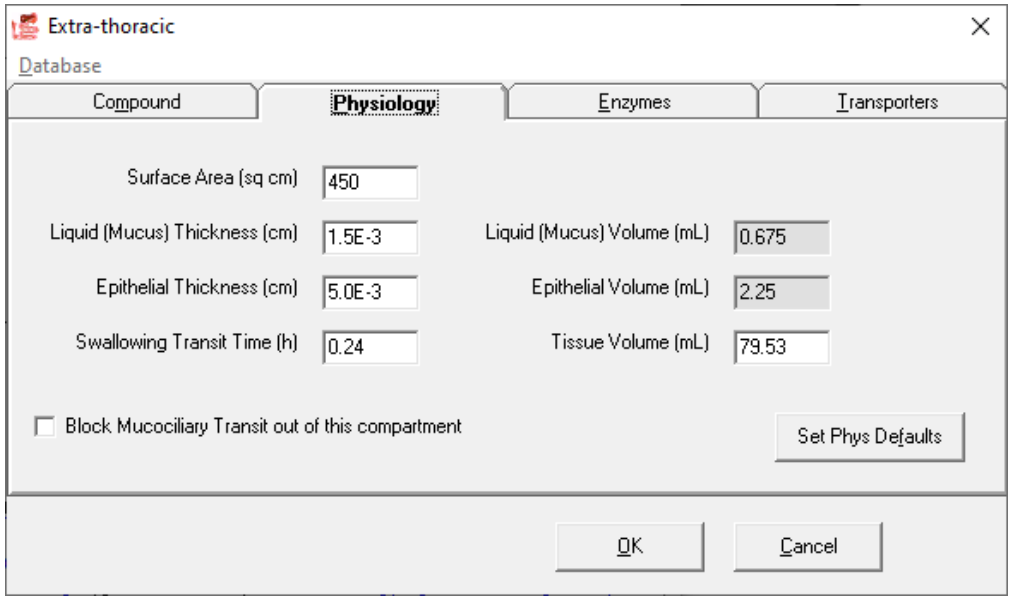
Compound Specific and Physiological Parameters





Compound Specific

- Permeability in each tissue
- Metabolic clearance
- Systemic absorption rate from nasal-pulmonary tissues
- Mucus/cell binding
- Enzymes & Transporters tabs

Physiological

- Surface Area
- Mucus Layer Thickness
- Epithelial Thickness
- Mucociliary Transit Time

Human physiology can be scaled based on Gender and Age

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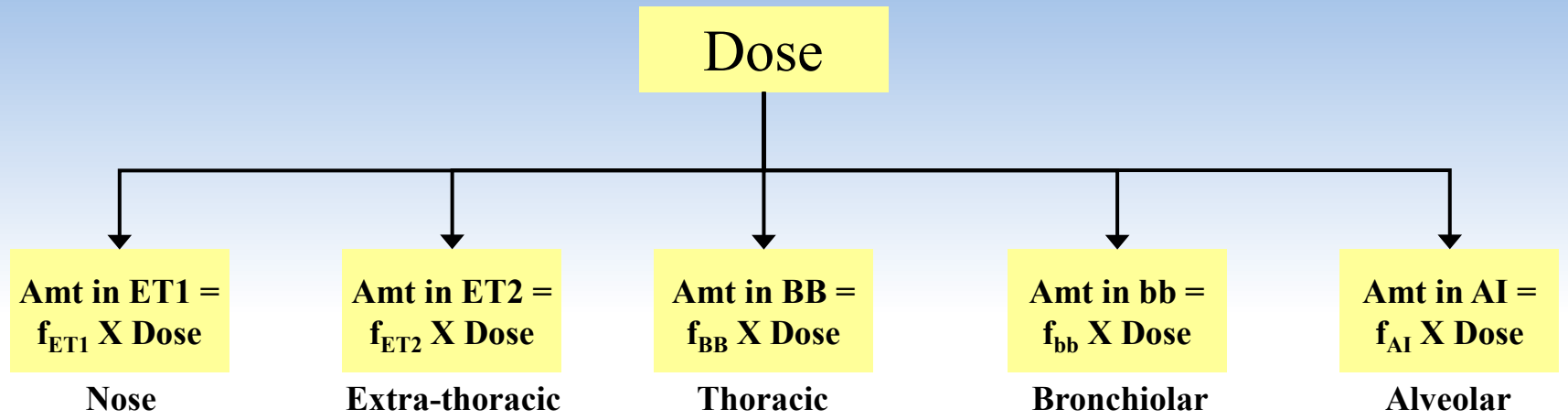
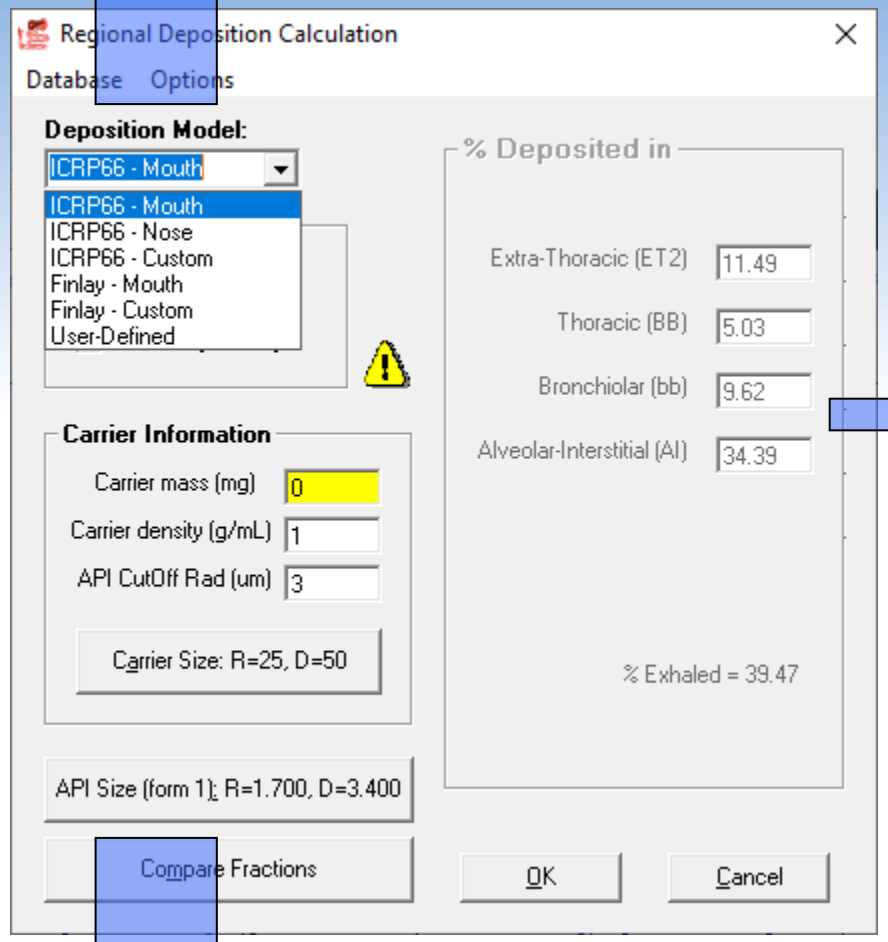
Distribution of Dose into Pulmonary Compartments



- The fractions (f_{ET1} to f_{AI}) can be
  - Calculated (dependent, e.g., on particle radius) – option "ICRP66"

  - Manually specified by the user (independent of radius) – option "User Defined"

Regional Deposition Calculation



Regional lung deposition can be predicted (from particle size distribution, standard deviation, etc. using the ICRP66 or Finlay deposition model) or specified manually by the user

Output (% deposited) that distributes the administered dose into different lung compartments

Size distribution and additional information for drug carrier (excipient) can be incorporated in calculation of regional deposition

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Nasal-Pulmonary Dosage Forms

Dosage Form Name	Dosing Compartment	Dosing Form Type	Physical State
PL: Soln	Distributed	Immediate	Liquid
PL: Powder	Distributed	Immediate	Solid
PL: IT Soln	Thoracic	Immediate	Liquid
PL: IT Powder	Thoracic	Immediate	Solid
PL: Nasal Soln	Nose	Immediate	Liquid
PL: Nasal Powder	Nose	Immediate	Solid
PL: Inf Soln	Distributed	Slow Infusion	Liquid
PL: Inf Powder	Distributed	Slow Infusion	Solid

Specific Nasal-Pulmonary Capabilities

- Evaluation of the independent contribution of pulmonary and gut absorption after inhaled administration
- Evaluation of formulation effects (dosage form, particle size, distribution, density, shape factor, presence of excipient, etc...)
- Additional mechanisms and functionality to be incorporated
  - Phagocytosis, lysosomal trapping
  - New deposition models and physiologies

Selected Pulmonary Example (1)

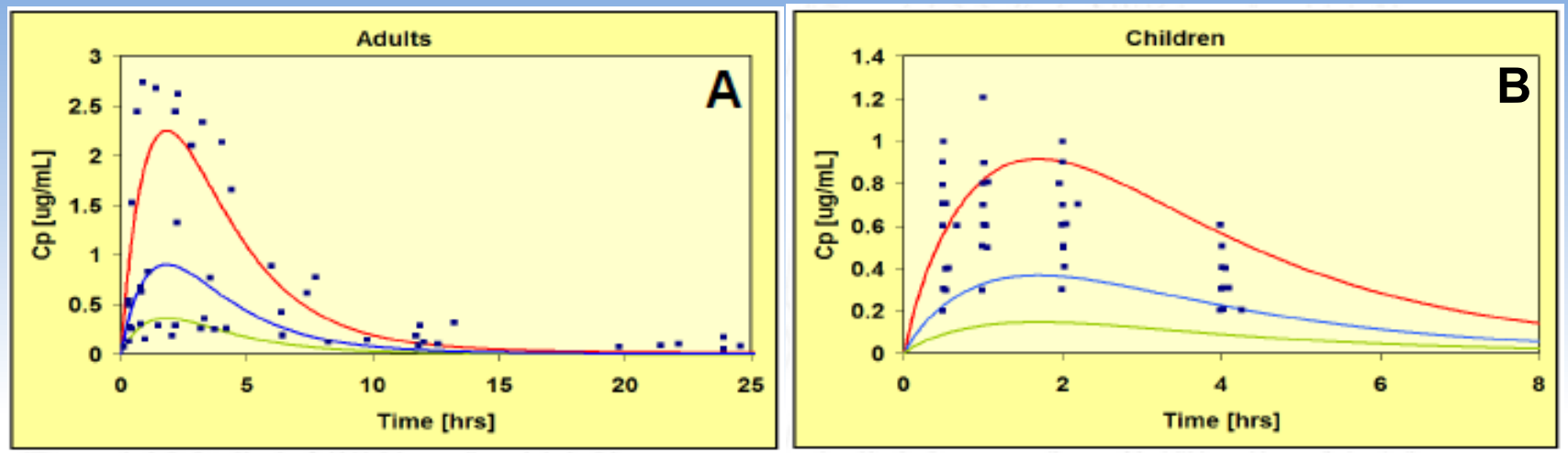
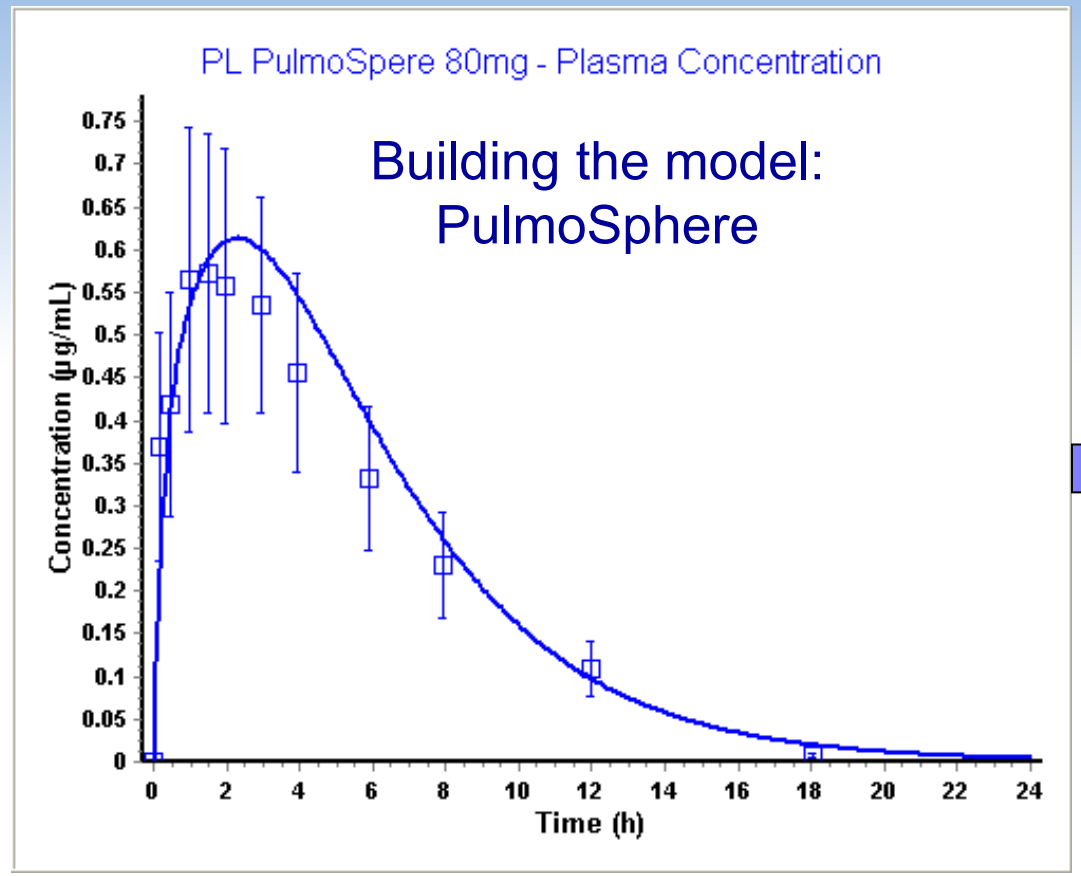


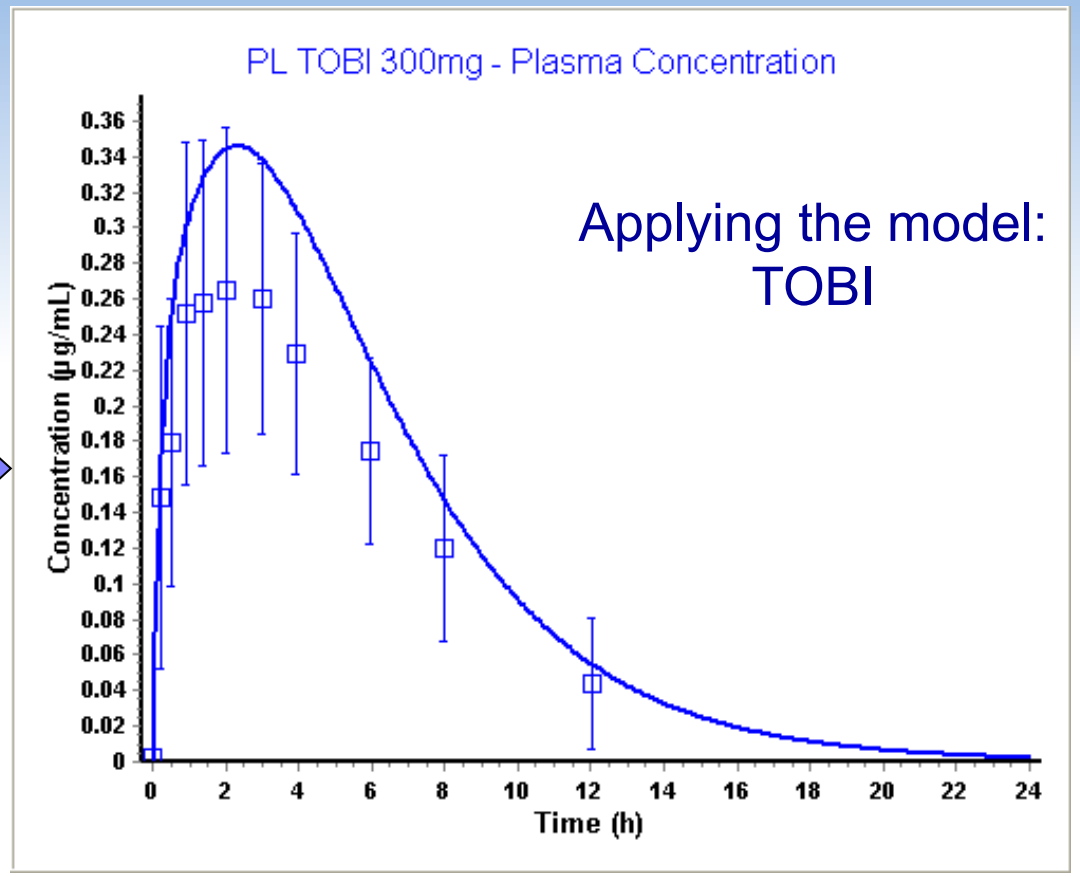
Figure 3. Simulated (lines) and experimental (points) Cp-time profiles of tobramycin after inhaled (nebulizer) administration in adults and children (average age about 4 years): A – 600 mg dose in adults [7], blue - prediction assuming the same deposition fractions as reported for TOBI nebulizer, green and red – prediction assuming 2.5-times lower and higher, respectively, deposition efficiency than reported for TOBI nebulizer; B – prediction for 300 mg dose in children [8] after scaling the respective deposition efficiencies from adults, blue – scaled adult deposition reported for TOBI nebulizer, green and red – scaled the low and high adult deposition efficiency, respectively.

Fitted pulmonary permeability against *in vivo* adult data and used to predict PK in children

Lukacova V, Poster presentation, Rosenon Meeting 2010, Stockholm, Sweden, Sept 9-11, 2010

Selected Pulmonary Example (2)





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To learn More:

The GastroPlus® Additional Dosage Routes Seminar Series Pulmonary with John DiBella and Jim Mullin

https://www.youtube.com/watch?v=fnkbENLMGuY&ab_channel=SimulationsPlus%2CInc.

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Pharmacodynamie

Entering the era of computationally driven drug development

Neha Maharao[a], Victor Antontsev[a], Matthew Wright[b] and Jyotika Varshney[a]

[a]VeriSIM Life Inc., San Francisco, CA, USA; [b]DMPK, Genentech Inc., San Francisco, CA, USA

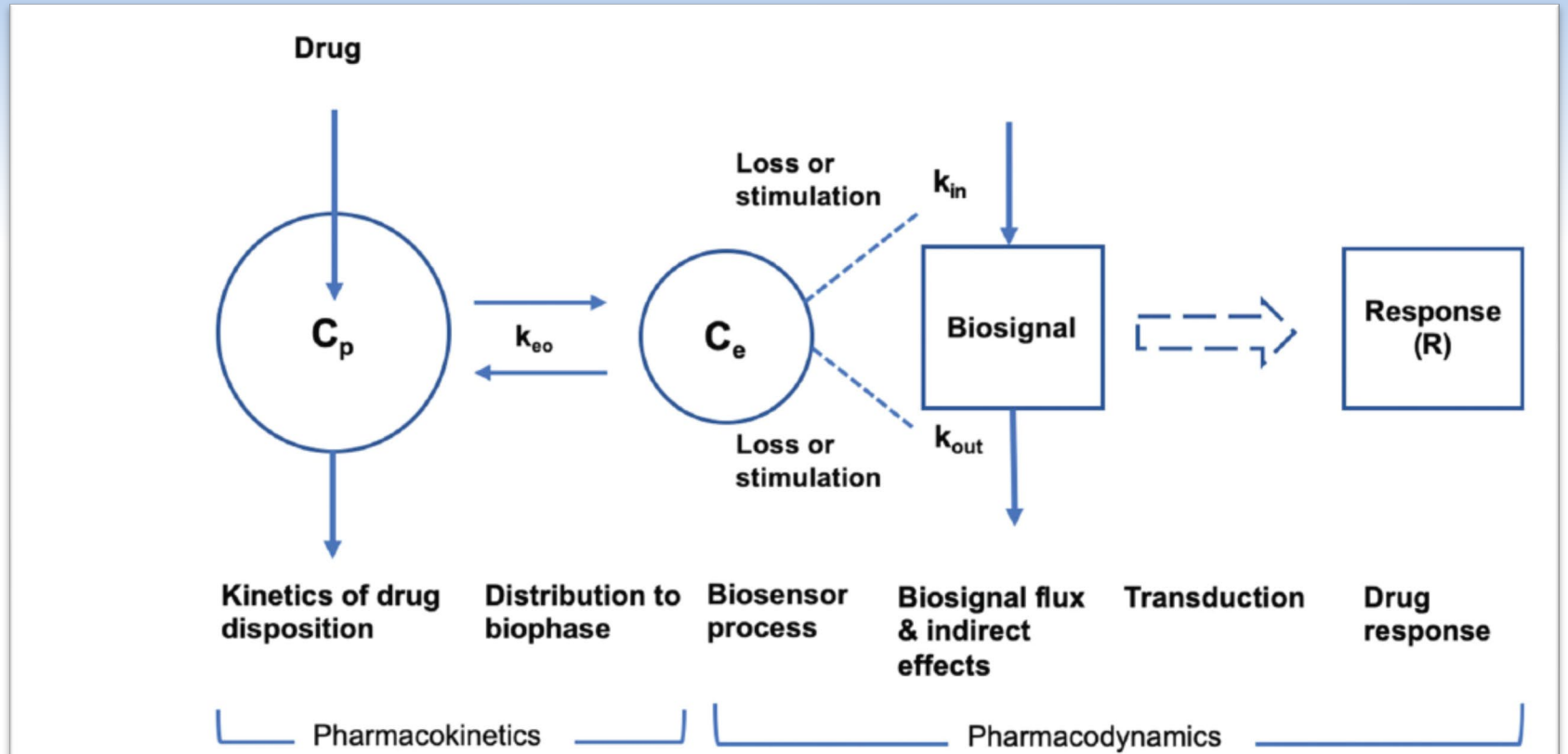
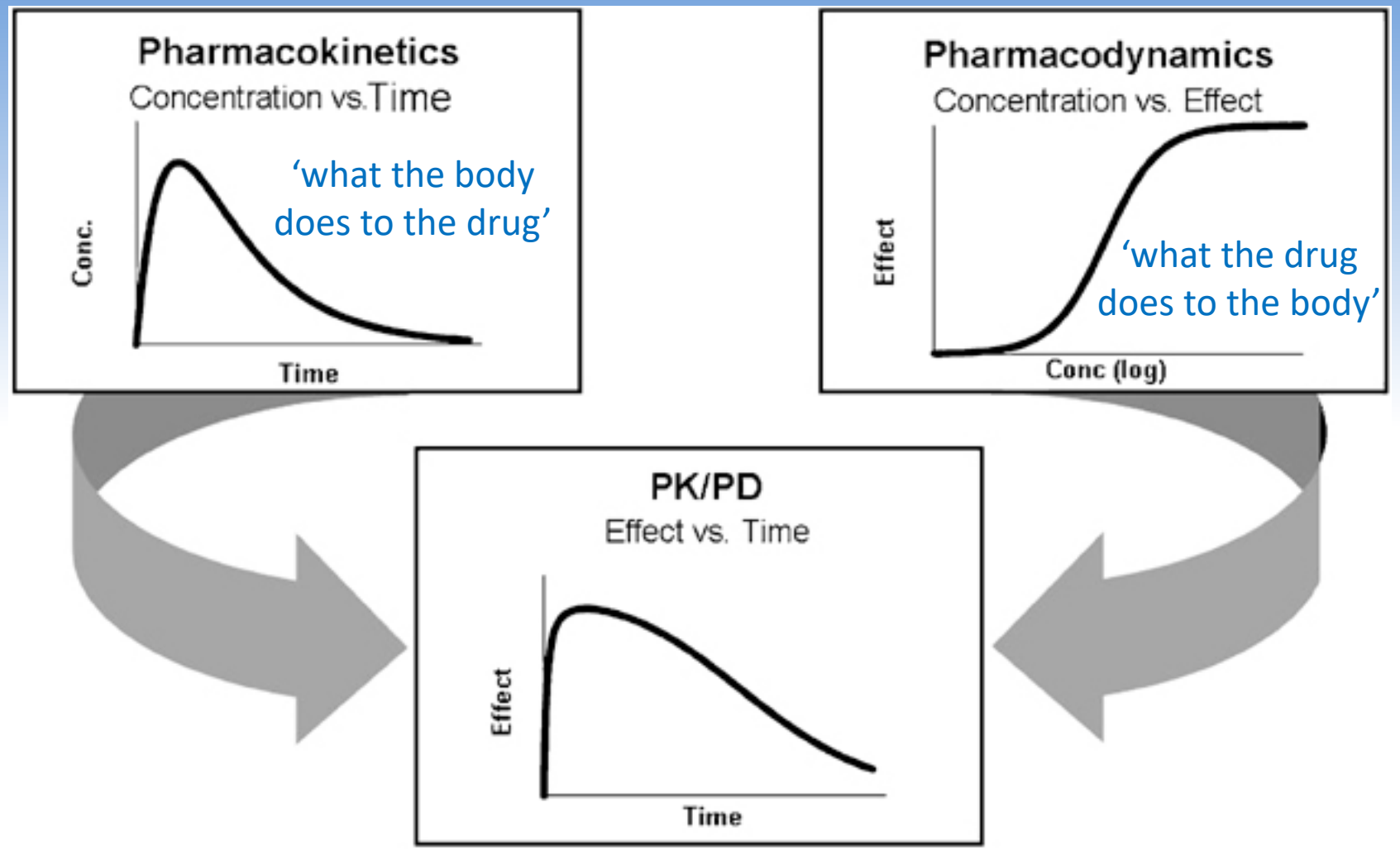


Figure 4. Basic components of PK/PD models adapted with minor modifications from Jusko et al. (1995).

PK/PD



PK/PD: link pharmacokinetics and pharmacodynamics in order to establish a dose-concentration-response relationship and subsequently describe and predict the effect-time course resulting from a drug dose

PDPlus™ Module

Standard Jusko/Derendorf pharmacodynamic models:

- **Direct**
  - Linear
  - Log-linear
  - Emax
  - Sigmoid Emax
- **Indirect**
  - Indirect Link: Effect compartment
  - Class I – IV
  - Cell killing
  - Bacterial kill and growth (power & sigmoidal model)
  - Precursor dependent (indirect models V – VIII)

Direct Response Models

- **Linear**

  $E = E_0 + S*C$

- **Log linear**

  $E = E_0 + S*\log(C)$

- **E_{max}**

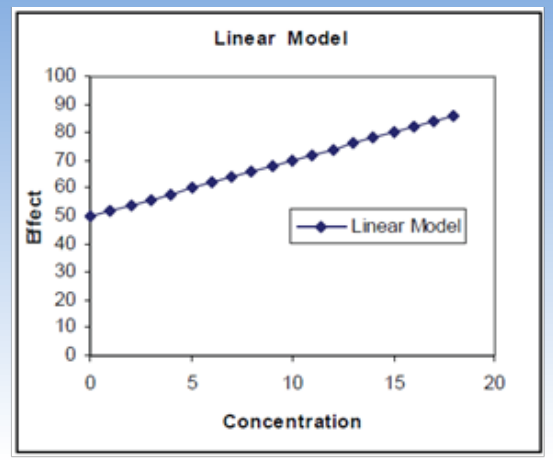
  $E = E_0 + E_{max} * C / (EC_{50} + C)$

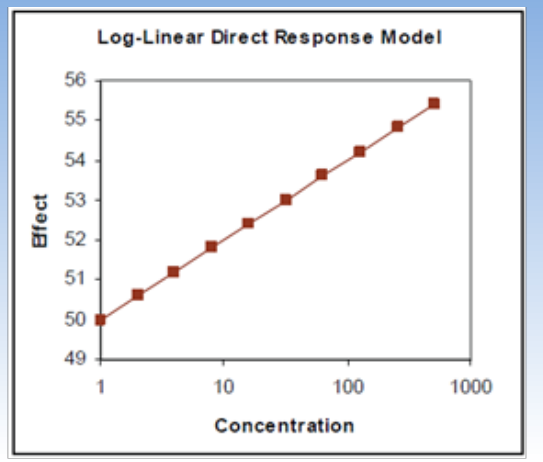
  $E = E_0 - I_{max} * C / (IC_{50} + C)$ [inhibition]

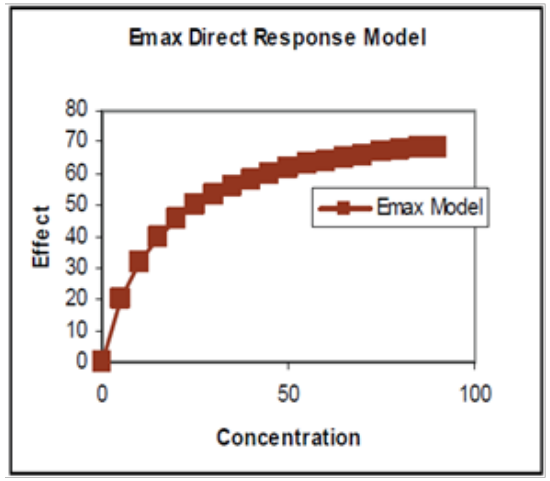
- **Sigmoid E_{max}**

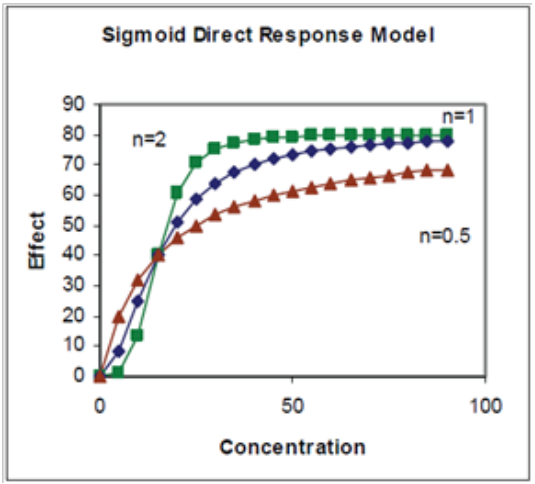
  $E = E_0 + E_{max} * C^{\gamma} / (EC_{50}^{\gamma} + C^{\gamma})$

  $E = E_0 - I_{max} * C^{\gamma} / (IC_{50}^{\gamma} + C^{\gamma})$ [inhibition]



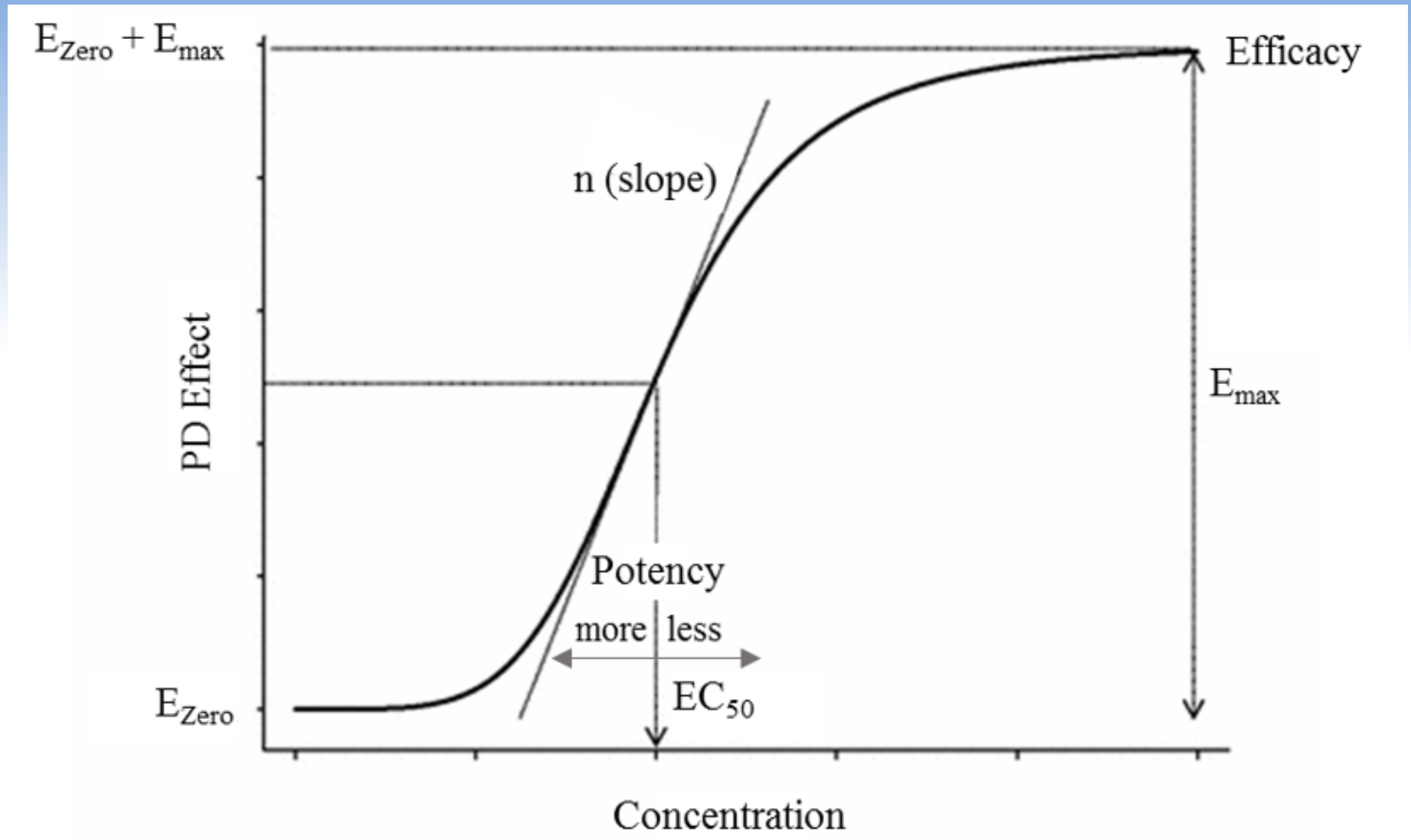






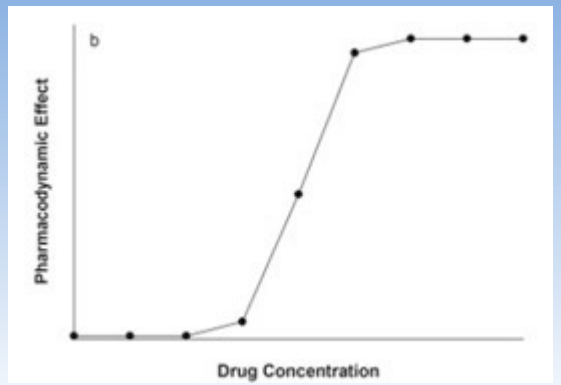
C = *Concentration* *E* = *Effect*
E_0 = *Baseline Effect* *S* = *Slope*
E_{max}/I_{max} = *Maximum Effect/Inhibition*
EC_{50}/IC_{50} = *Concentration at which 50% of the maximum effect/inhibition is observed*
γ = *Hill parameter (describes the steepness of the concentration-effect relationship)*

Sigmoid E_{max} Model

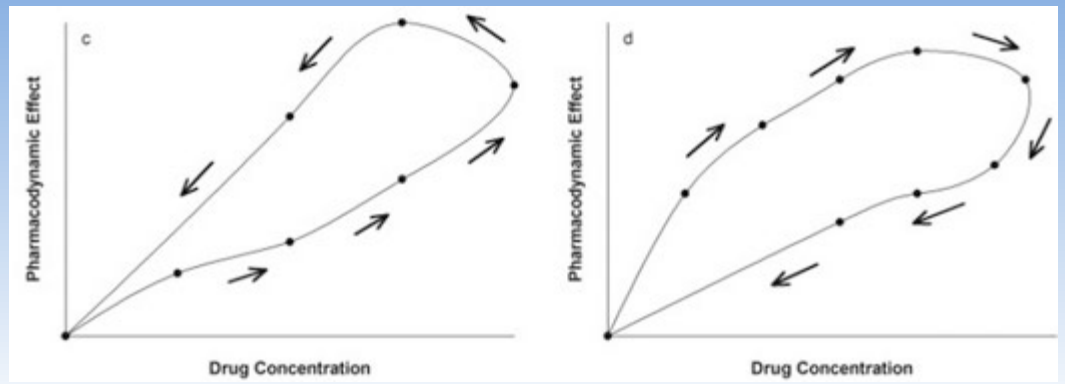


Direct vs. Indirect

Direct



Indirect: Hysteresis



Counter clockwise **Clockwise**

Mechanistic Explanations for Hysteresis	
Counter-clockwise	**Clockwise**
Distribution delay between the plasma and effect site	
Indirect effects: • Stimulation of input • Inhibition of output	Indirect effects: • Inhibition of input • Stimulation of output
Sensitization (receptor upregulation)	Tolerance (receptor downregulation)
Active agonist metabolite	Active antagonistic metabolite

Louizos et al. J Pharm Pharm Sci. 2014; 17(1): 34–91

Indirect Models in PDPlus™

Indirect Link: Effect compartment: Sigmoid E_{max} model, but C_e instead of C_p

Class I - inhibition of buildup: Drug inhibits transfer of drug into effect compartment

Class II - inhibition of dissipation: Drug inhibits transfer of drug out of effect compartment

Class III - stimulation of buildup: Drug stimulates transfer of drug into effect compartment

Class IV – stimulation of dissipation: Drug stimulates transfer of drug out of effect compartment

Cell killing – phase nonspecific: Effect of chemotherapeutic agents – drug causes mitotic arrest of cancer cells

Bacteria kill and growth: Drug causes the death of bacteria in the non-resistant subpopulation

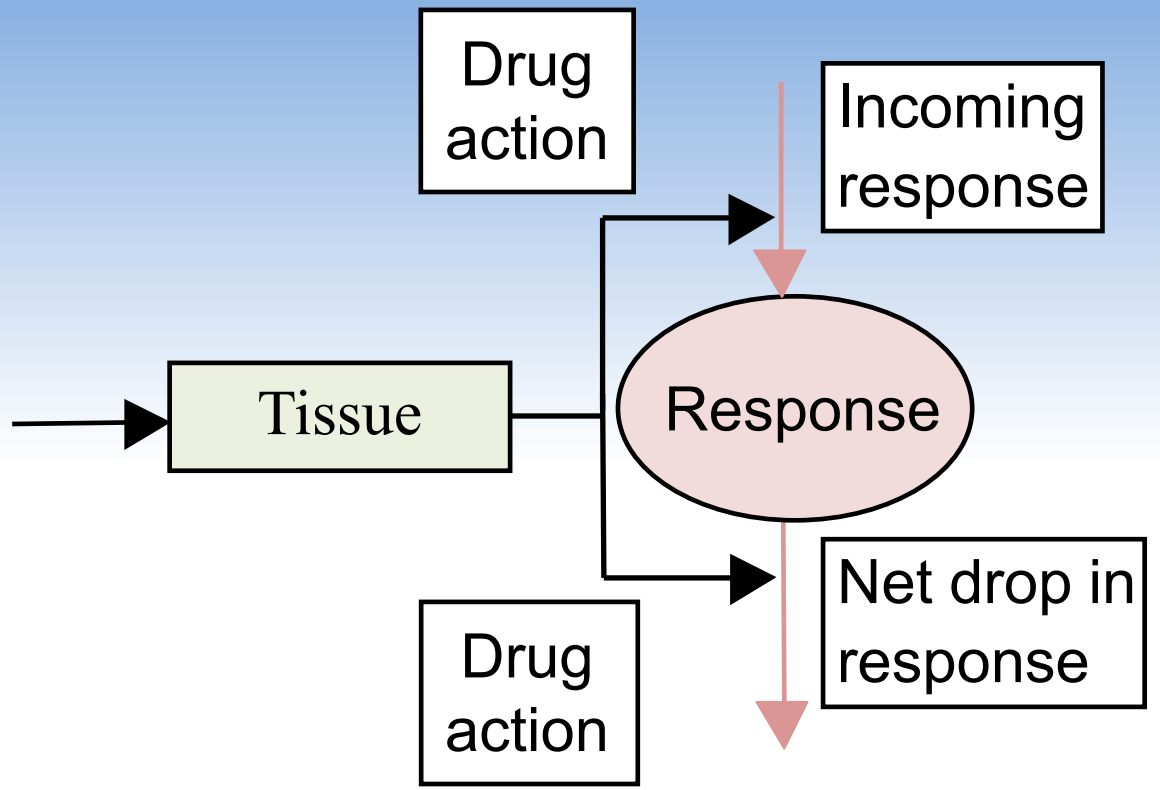
Class V - inhibition of buildup: Drug inhibits response production

Class VI - inhibition of buildup: Drug stimulates response production

Class VII - inhibition of buildup: Drug inhibits precursor production

Class VIII - inhibition of buildup: Drug stimulates precursor production

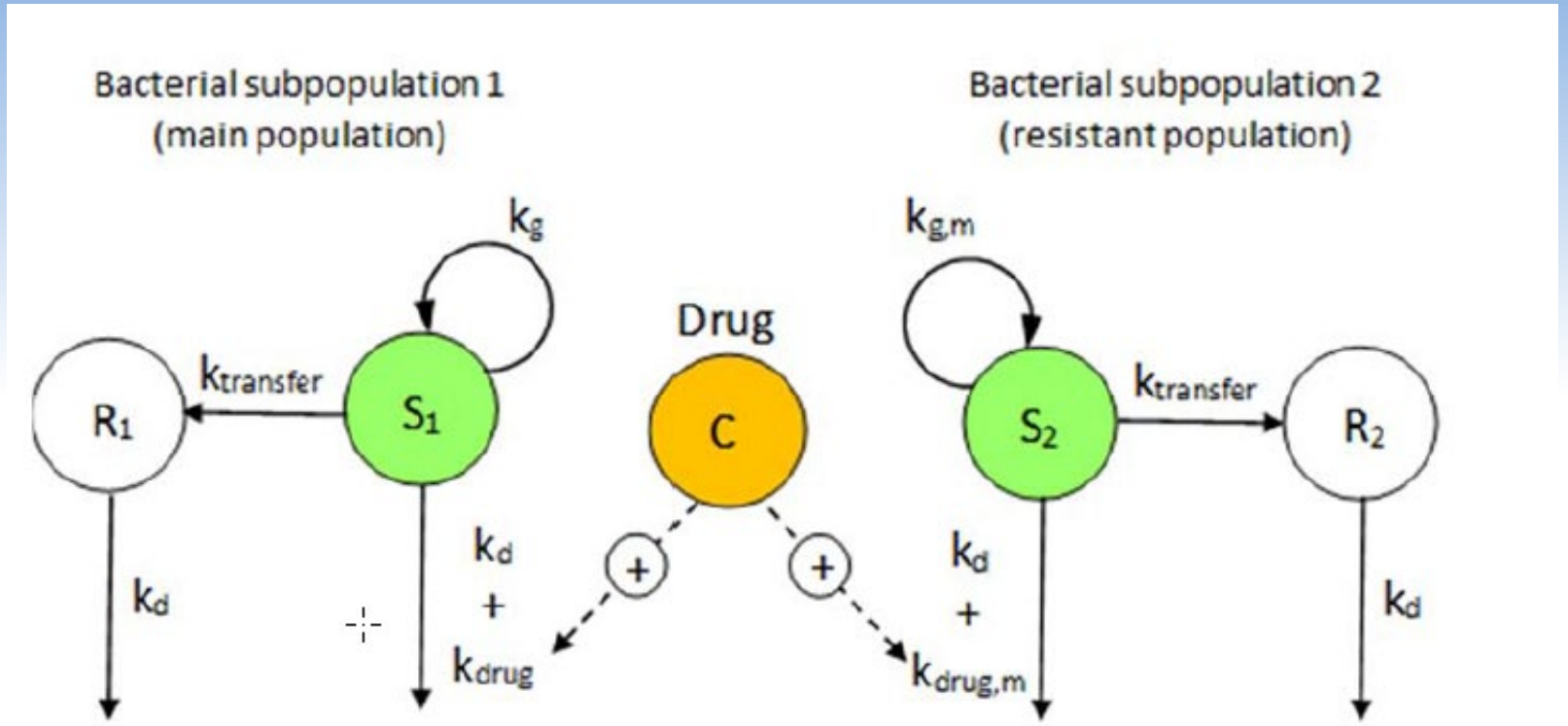
Indirect Link - Class I-IV



$$\frac{dR}{dt} = K_{in}\left(1 - \frac{I_{\max}.C}{IC_{50} + C}\right).\left(1 - \frac{E_{\max}.C}{EC_{50} + C}\right) - K_{out}\left(1 - \frac{I_{\max}.C}{IC_{50} + C}\right).\left(1 - \frac{E_{\max}.C}{EC_{50} + C}\right)R$$

Class I Class II Class III Class IV

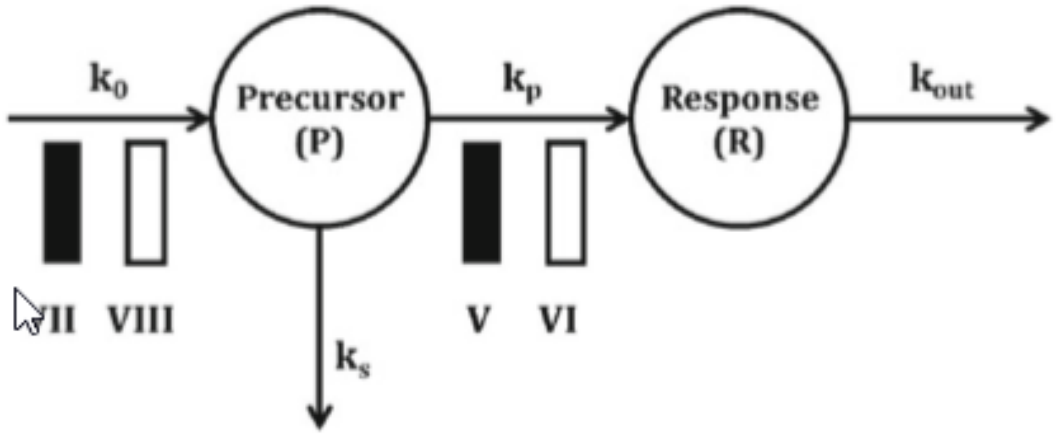
Indirect Link
Bacteria Killing and Growth Model



The model consists of two bacterial population: one susceptible and one pre-existing resistant

From Kristoffersson (Pharm Res. 2016)

Precursor-dependent Indirect Model



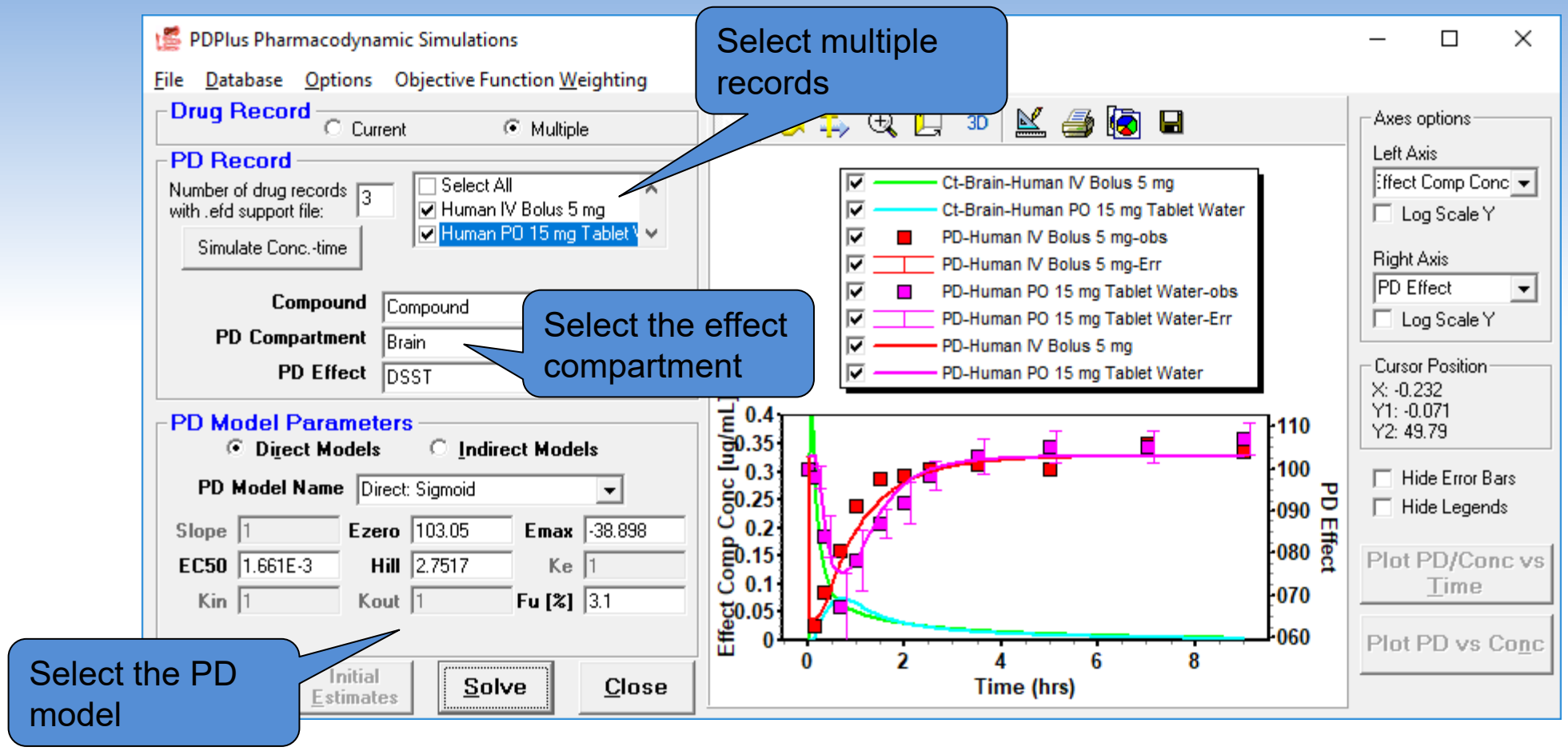
$$\frac{dP}{dt} = k_o\{1 \pm H_1(C_p)\} - (k_s + k_p\{1 \pm H_2(C_p)\})P, \quad (11)$$

$$\frac{dR}{dt} = k_p\{1 \pm H_2(C_p)\} \times P - k_{out} \times R, \quad (12)$$

k_0: the zero-order rate constant for precursor production
k_p: the first-order rate constant for production of the response variable
k_s and k_{out}: first-order rate constants for loss of the precursor or response
H_1: the inhibition or stimulation of precursor production
H_2: the inhibition or stimulation of response production
Stimulation or inhibition of k_p is more commonly observed than alterations in the production of precursor.

From Felmlee (Methods Mol Biol. 2012)

Building PK/PD Models



Thank you!

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Email: maxime@simulations-plus.com

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