Pharmacokinetic models of transdermal drug delivery

Opportunities and pitfalls

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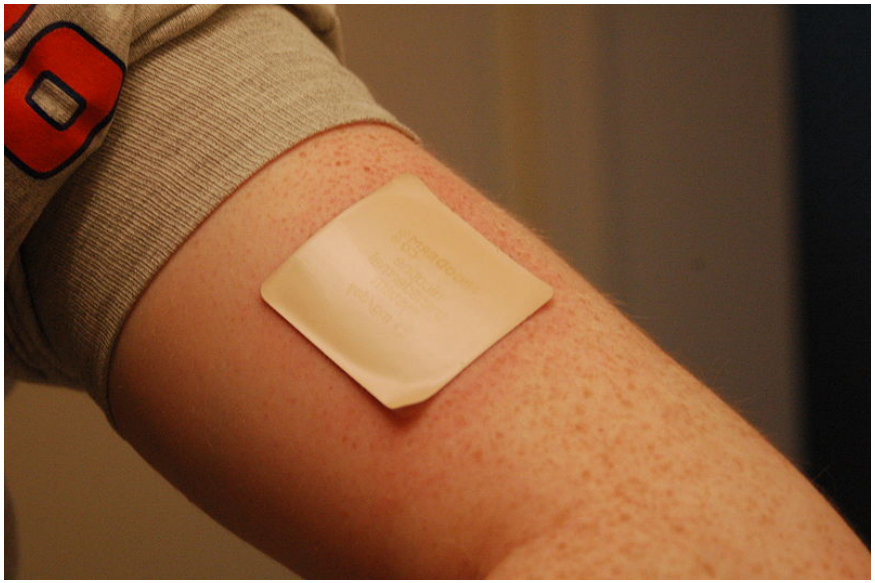
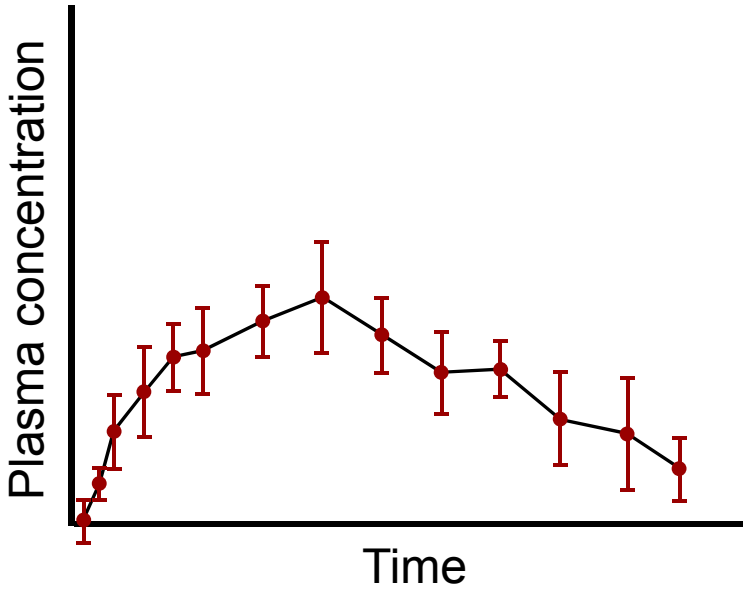
PK models of transdermal drug delivery



http://en.wikipedia.org/wiki/Transdermal_patch

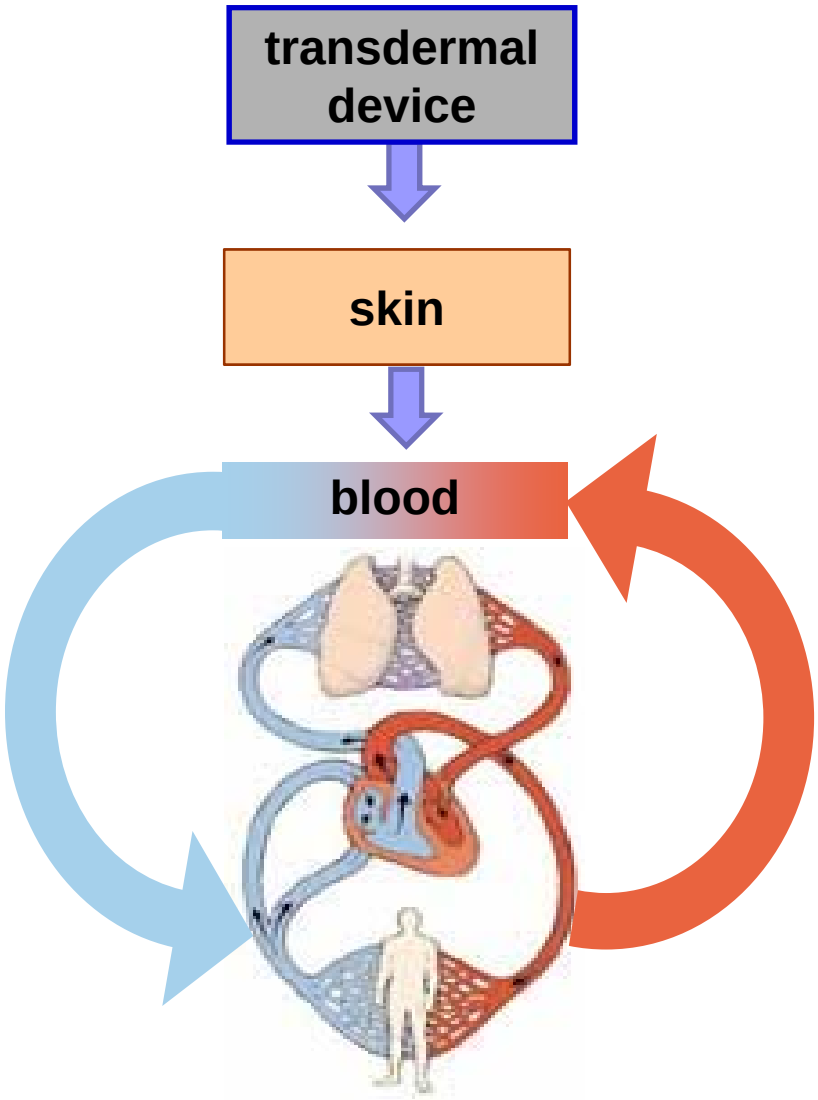


Combine three models

Model 1
Release from device

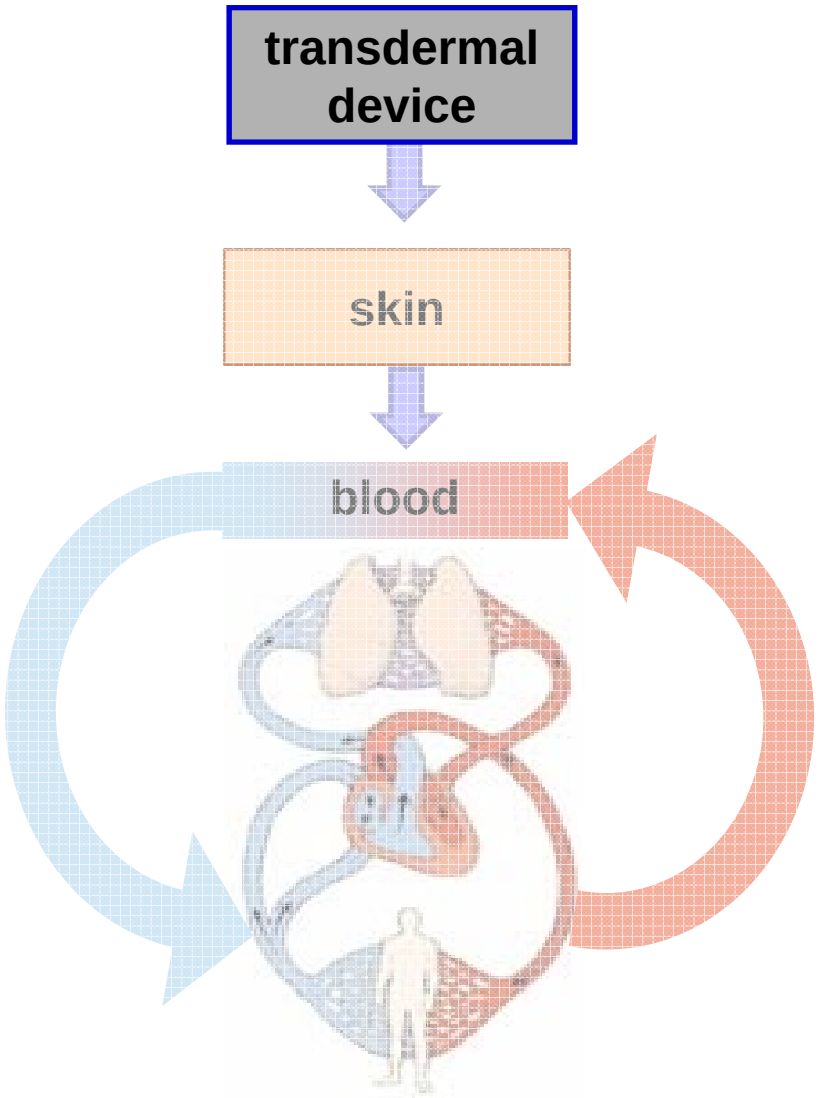
Model 2
Skin permeation

Model 3
Systemic distribution/
metabolism/elimination



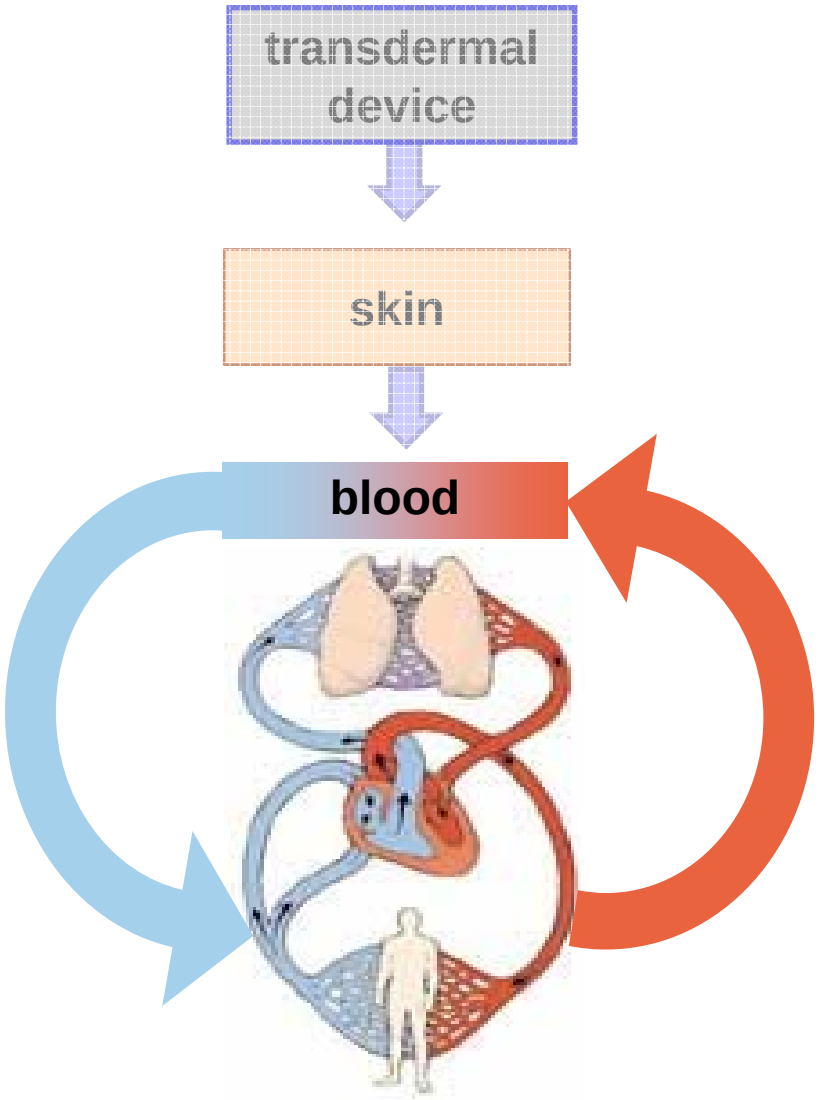
Transdermal device model

- Represent the device design including all diffusion barriers
- Partitioning between all parts of device
- Dissolution of undissolved drug (if present)



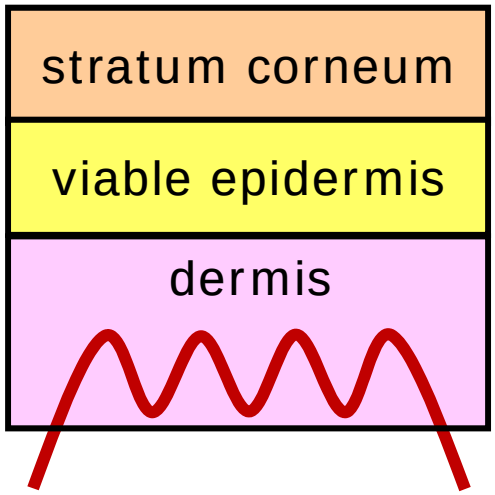
Systemic pharmacokinetic model

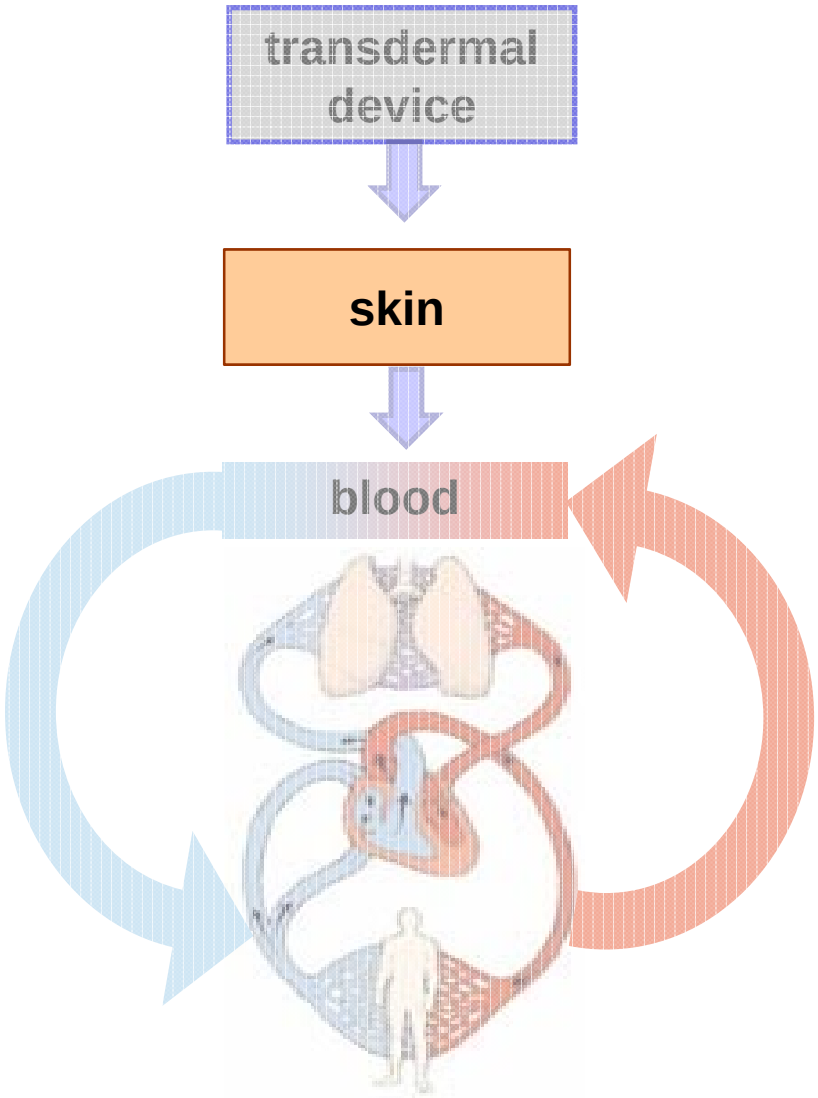
- Could be a 1 or multi-compartment model
- Could be a physically-based PK (PBPK) model
- Model parameters generally derived by separate experiment (e.g., plasma C arising from IV delivery)



Skin model

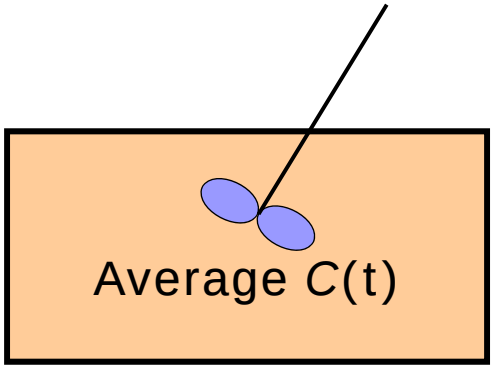
- SC alone or with other layer(s)

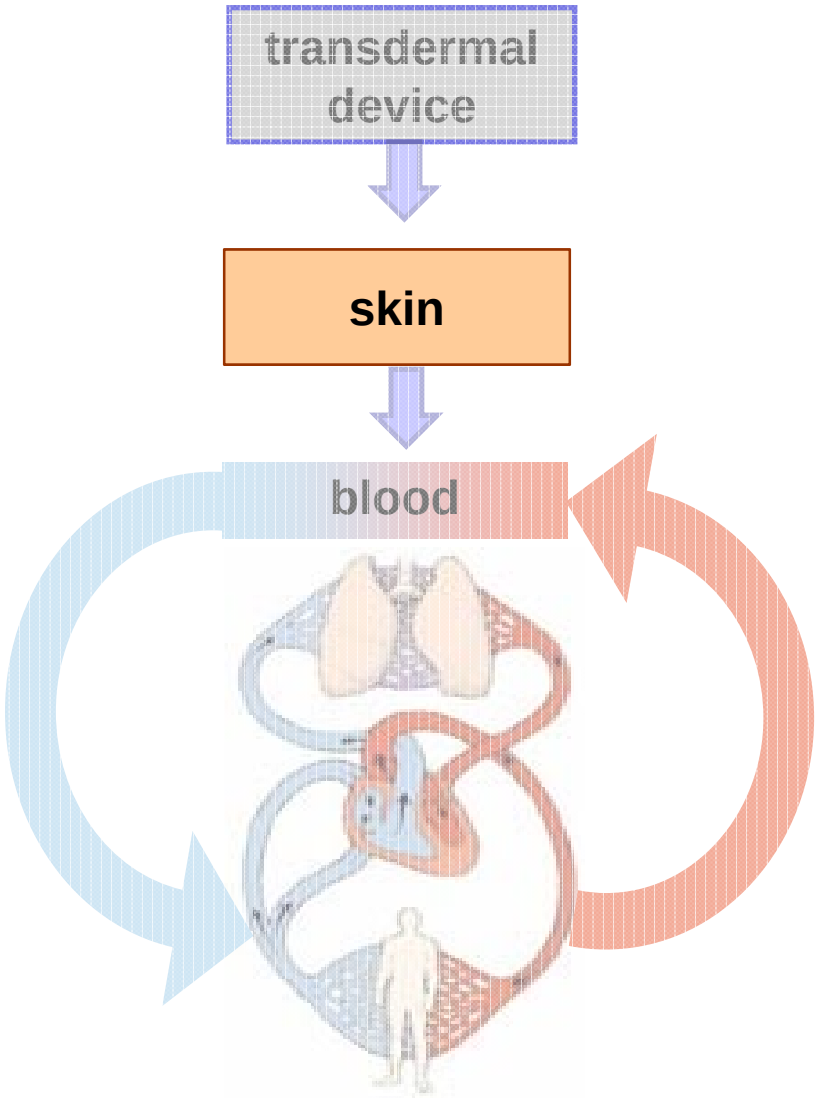




Skin model

- Simple or complex description of each layer
  - “Stirred” compartment

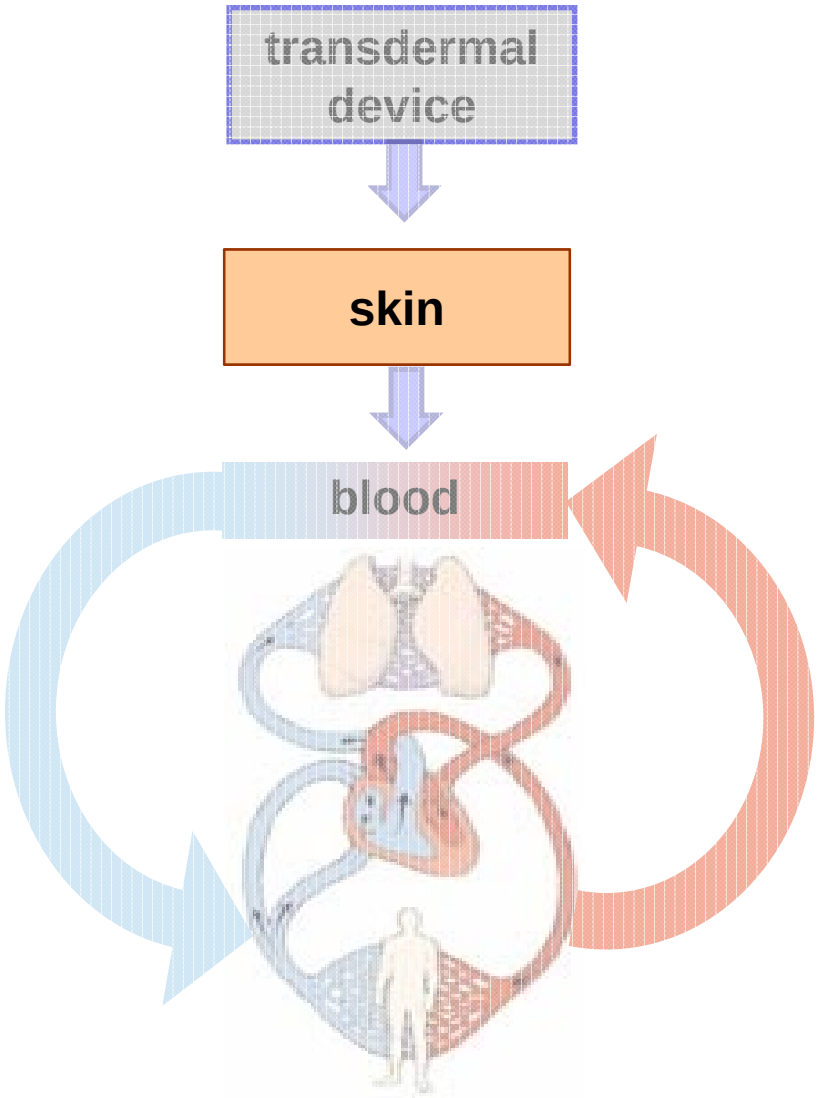




Skin model

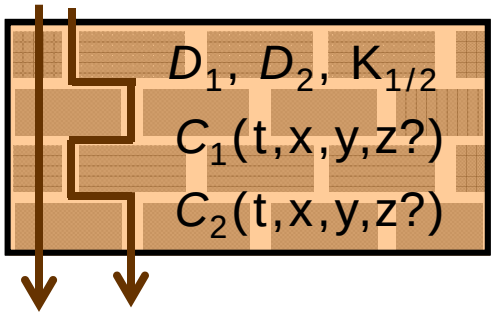
- Simple or complex description of each layer
  - “Stirred” compartment
  - Diffusion barrier

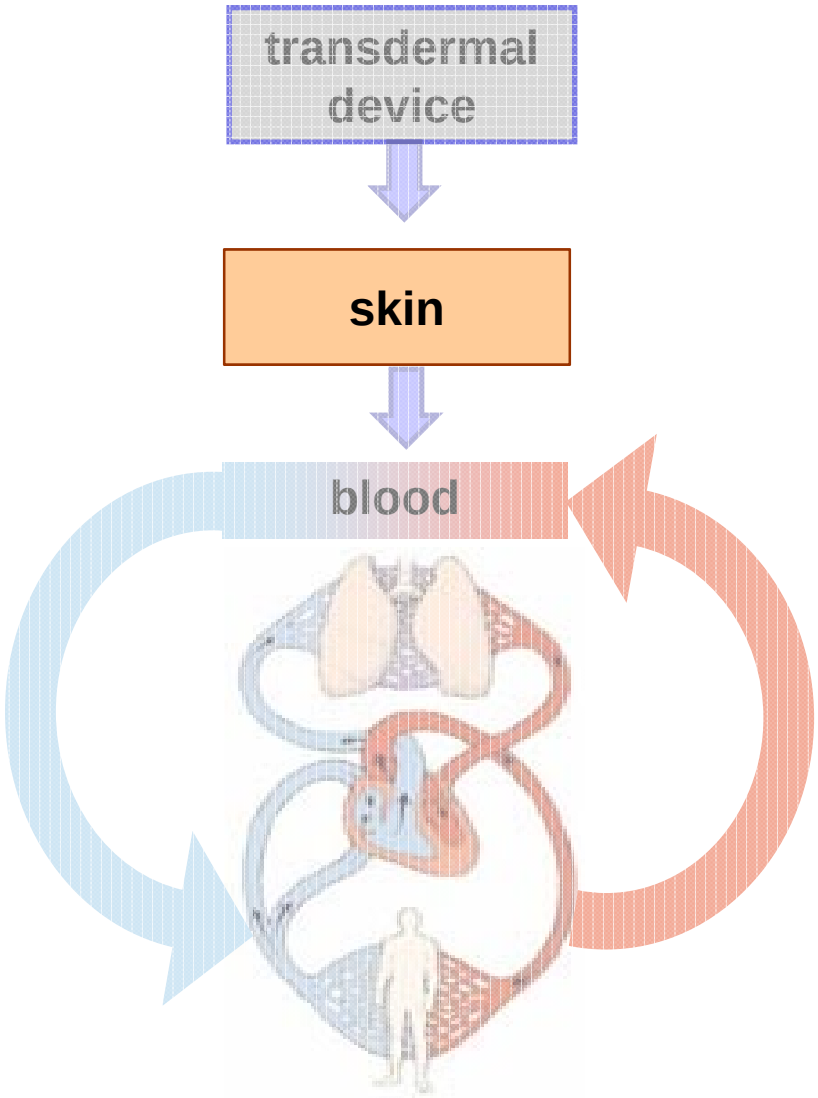
D_{layer}
$C(t,x)$



Skin model

- Simple or complex description of each layer
  - “Stirred” compartment
  - Diffusion barrier
  - Diffusion barrier with multiple, multiphasic pathways





PK modelling opportunities

- Test hypotheses
  - Physically-based models precisely specify mechanisms
  - Identify mechanisms by comparing model predictions with experiments
  - Disagreement with experiment proves that the model is wrong
  - Agreement with experiment does NOT prove that the model is correct (other models might also agree)

PK modelling opportunities (even more)

- Simulate experiments
  - Physicochemical parameters are known precisely
  - Test sensitivity of proposed data analysis; e.g.
    - Does the data analysis give the correct physicochemical parameters?
    - Will the proposed bioequivalence test metric give the correct result?

PK modelling opportunities (still more)

- Answer what-if questions

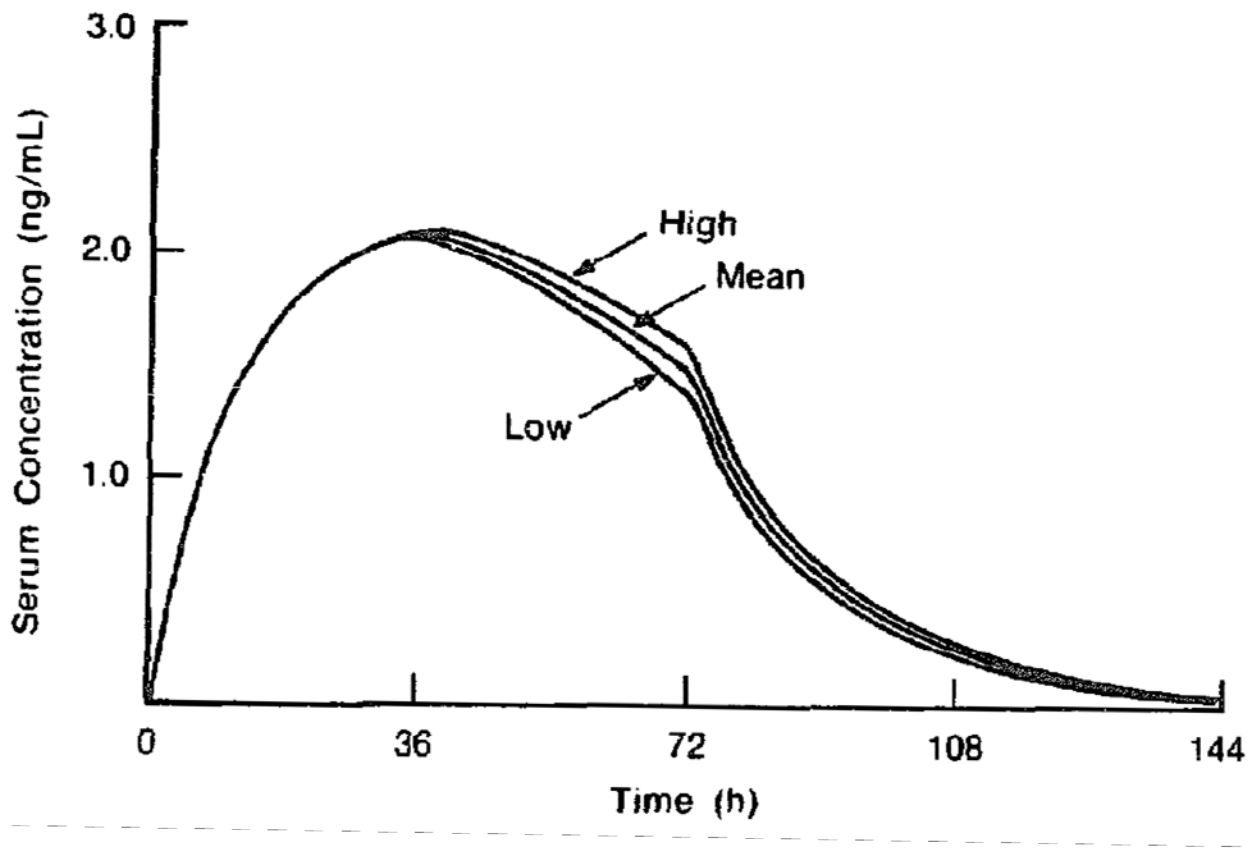
PK modelling opportunities (still more)

- Answer what-if questions; e.g.
  - What happens if the TDD is changed?

Gupta et al., J Pain Symptom Manage, 7:S17-26 (1992)

Effect of membrane thickness

(e.g., manufacturing variation in TDD)



Gupta et al., J Pain Symptom Manage, 7:S17-26 (1992)

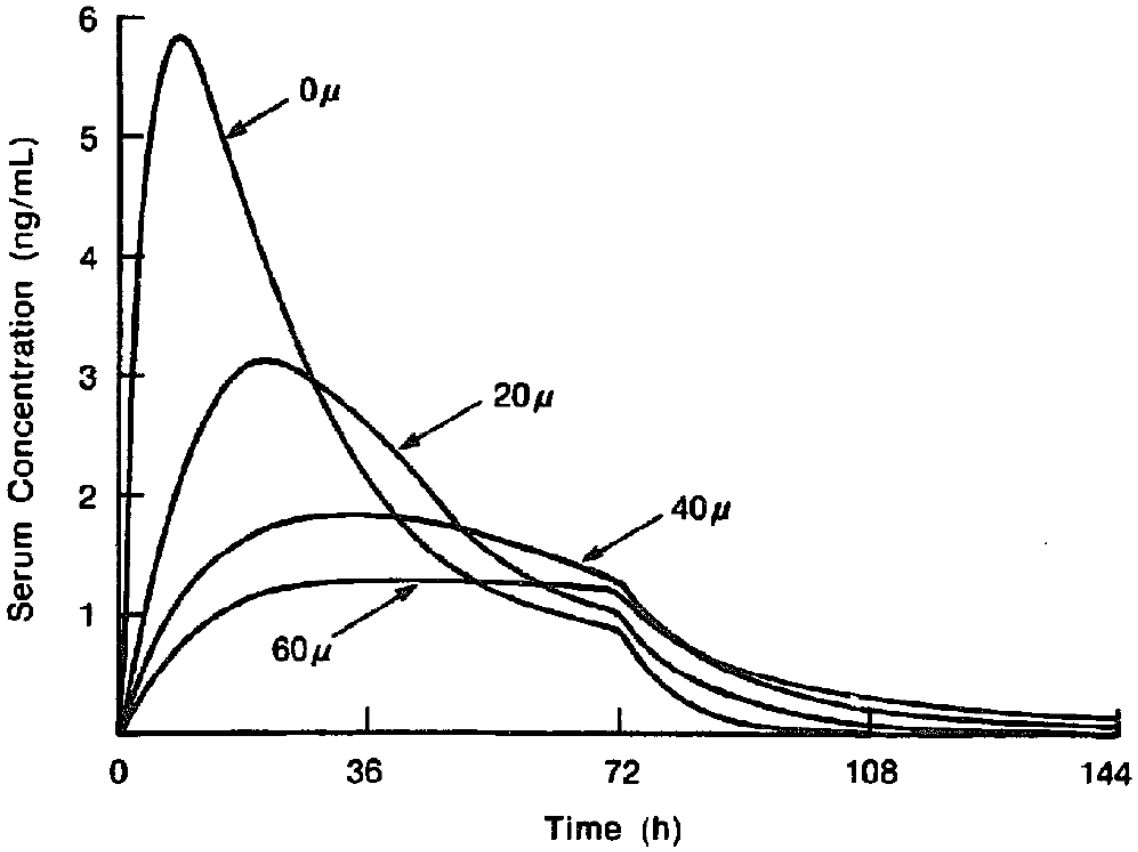
PK modelling opportunities (still more)

- Answer what-if questions; e.g.
  - What happens if the TDD is changed?
  - What if the SC thickness is different?

Gupta et al., J Pain Symptom Manage, 7:S17-26 (1992)

Effect of SC thickness

(e.g., TDD applied to different sites)



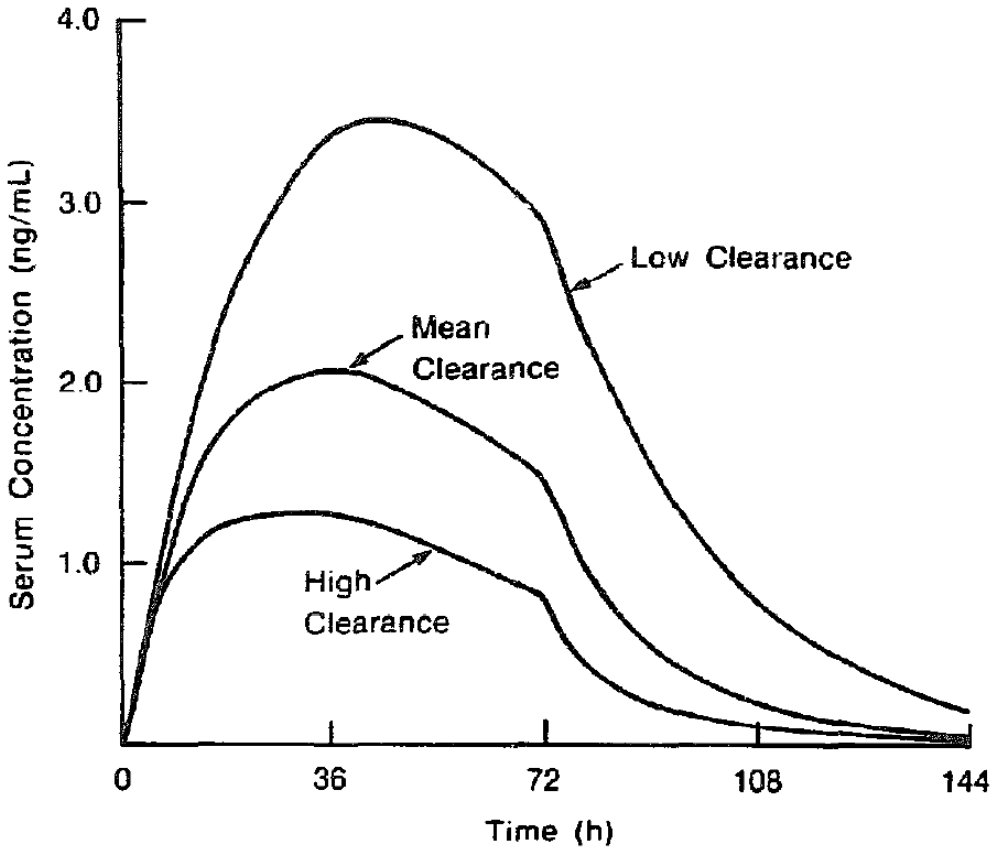
Gupta et al., J Pain Symptom Manage, 7:S17-26 (1992)

PK modelling opportunities (still more)

- Answer what-if questions; e.g.
  - What happens if the TDD is changed?
  - What if the SC thickness is different?
  - What if the clearance rate changes?

Gupta et al., J Pain Symptom Manage, 7:S17-26 (1992)

Effect of clearance rate



Gupta et al., J Pain Symptom Manage, 7:S17-26 (1992)

Pitfalls

- Results are plausible but wrong
- Unreasonable model parameters are used
- Non-unique solutions
- Meaningless extrapolations

Pitfalls: *Results are plausible but wrong*

Just because the calculated results look OK does not mean they are correct

Pitfalls: *Results are plausible but wrong*

- Errors in one (or more) mathematical elements
  - Mass balance in and between compartments
  - Thermodynamic limits
    (partition coefficients at boundaries and equilibrium)
  - Constitutive equations
    (describing how rates of transport and reaction vary with drug concentration)

Example TDD model

An improved diffusion/compartmental model for transdermal drug delivery from a matrix-type device

Achim Göpferich and Geoffrey Lee

Institute for Pharmaceutical Technology and Biopharmaceutics, Heidelberg University, Heidelberg (Germany)

International J of Pharmaceutics, 71:237-243 (1991)

Drug: Clenbuterol

Eliminated slowly from the body; ½ life is ~ 33 h

TDD device: Polymer matrix containing dissolved drug

Example TDD model

Matrix-type TDD

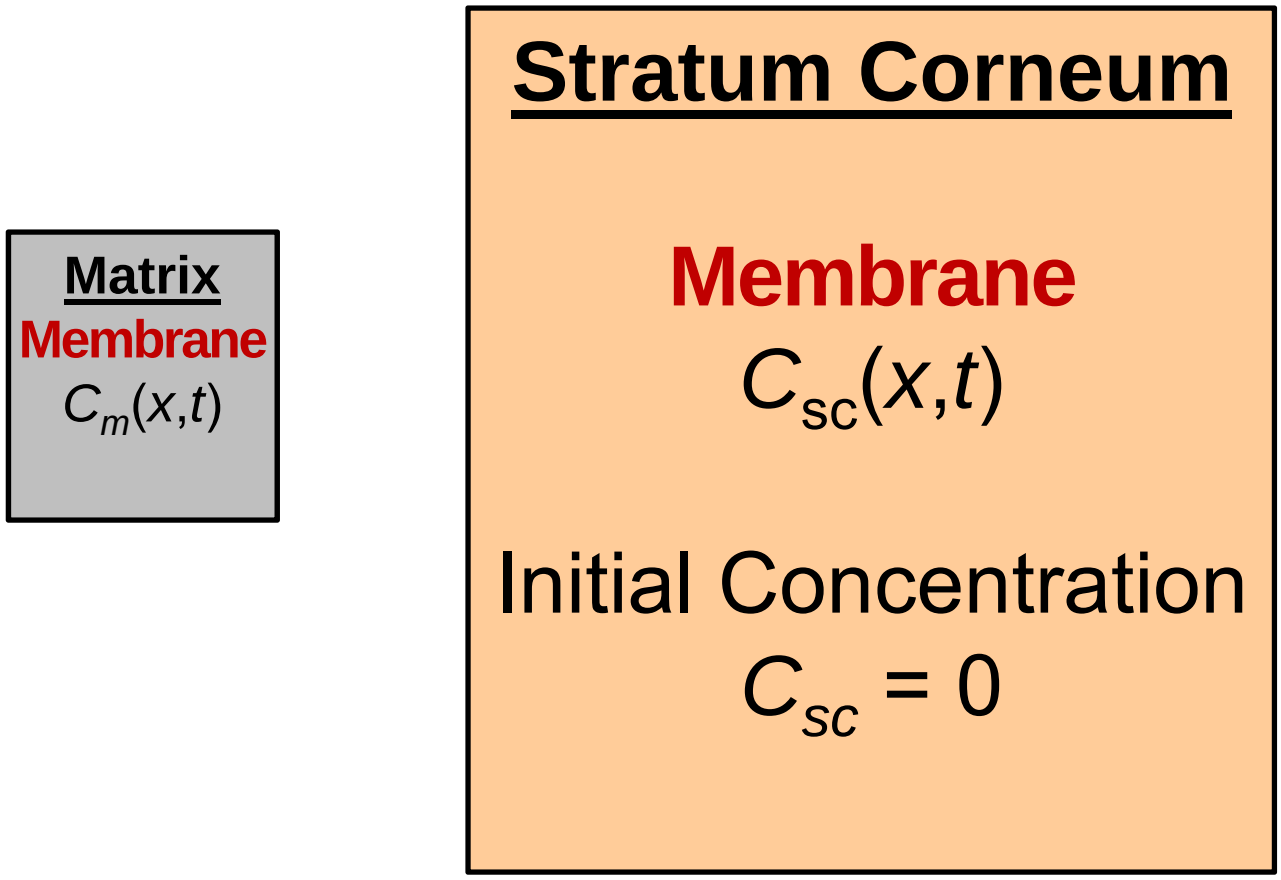
Membrane

$C_m(x,t)$

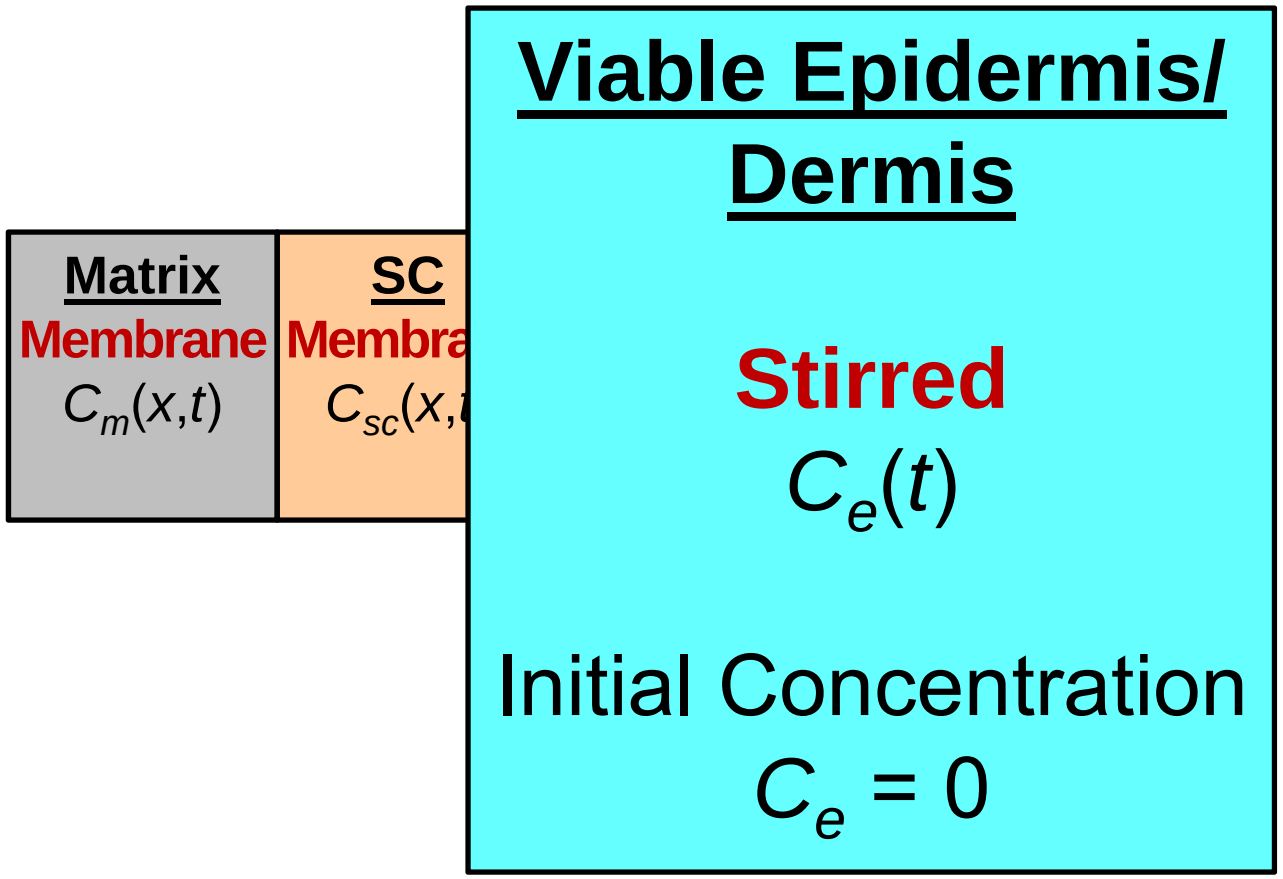
Initial Concentration

$C_{m,o} \leq C_{m,sat}$

Example TDD model



Example TDD model



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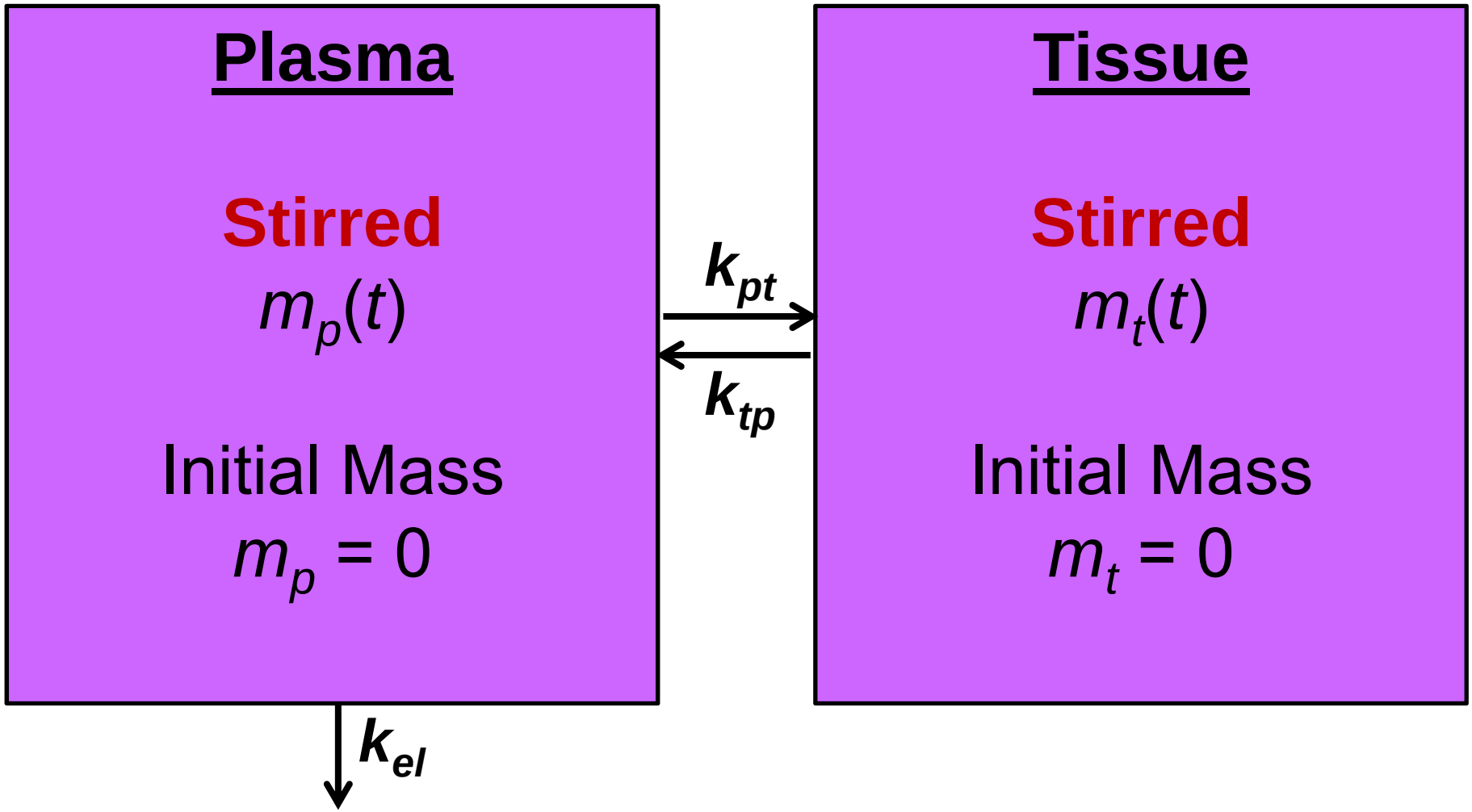
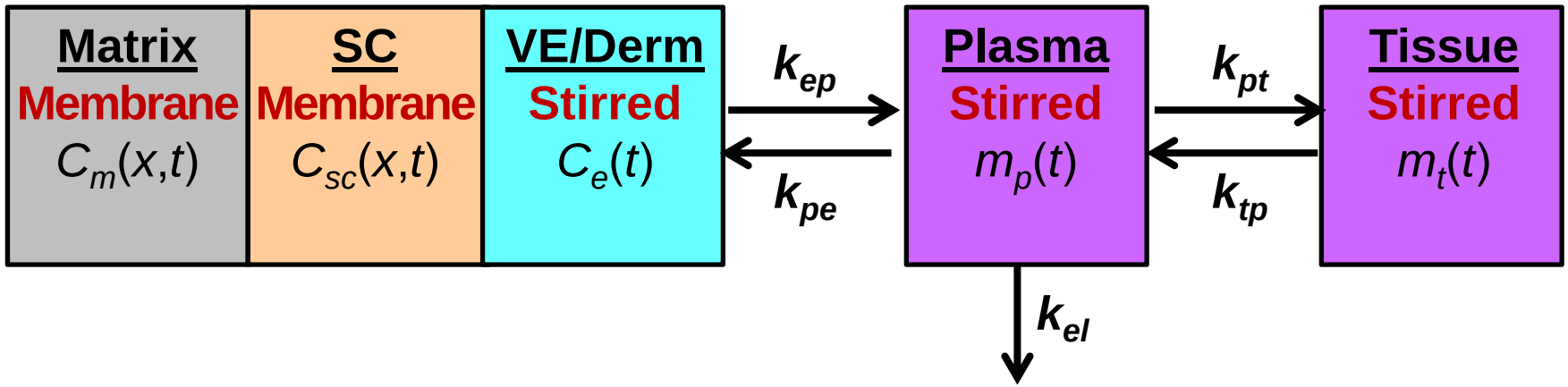
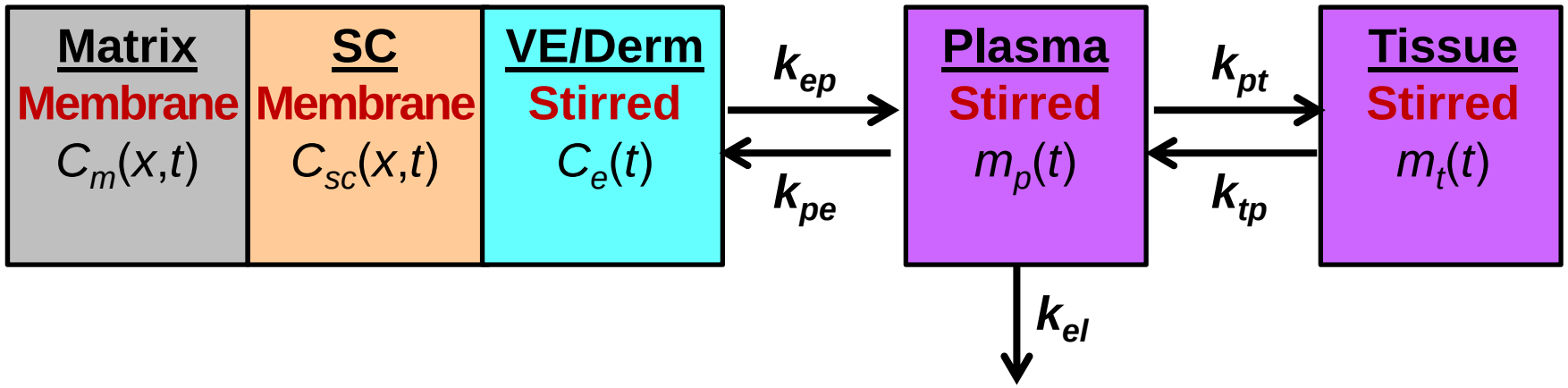


Example TDD model



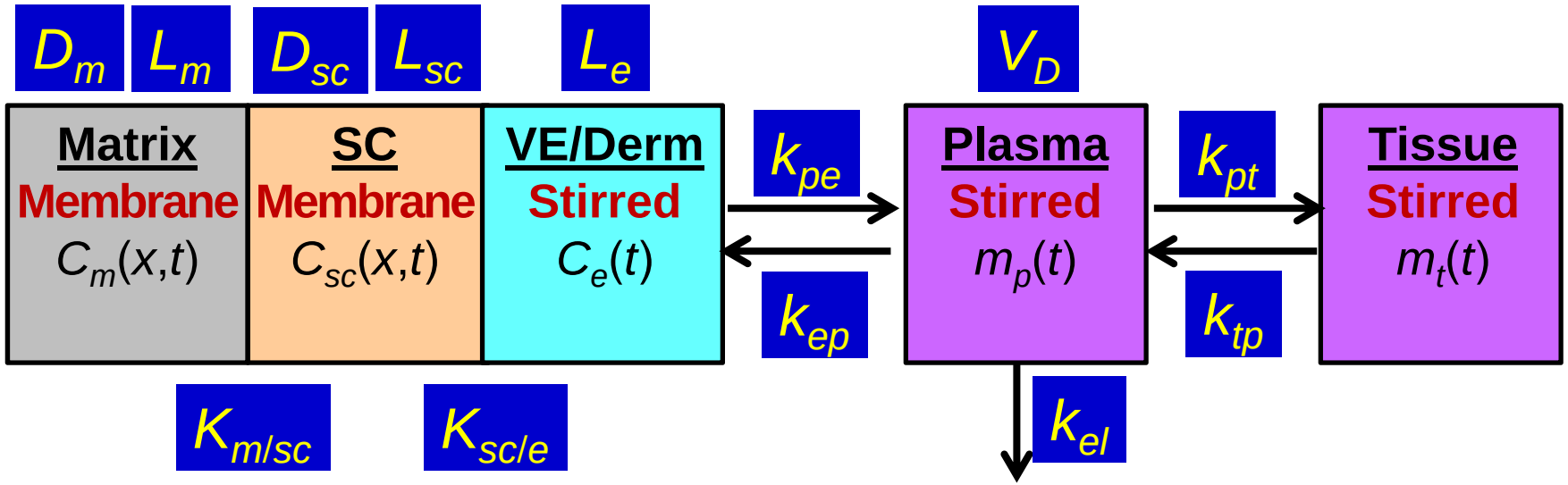
Example TDD model: *Model parameters*

Operational Parameters: *TDD area, initial concentration*



Example TDD model: *Model parameters*

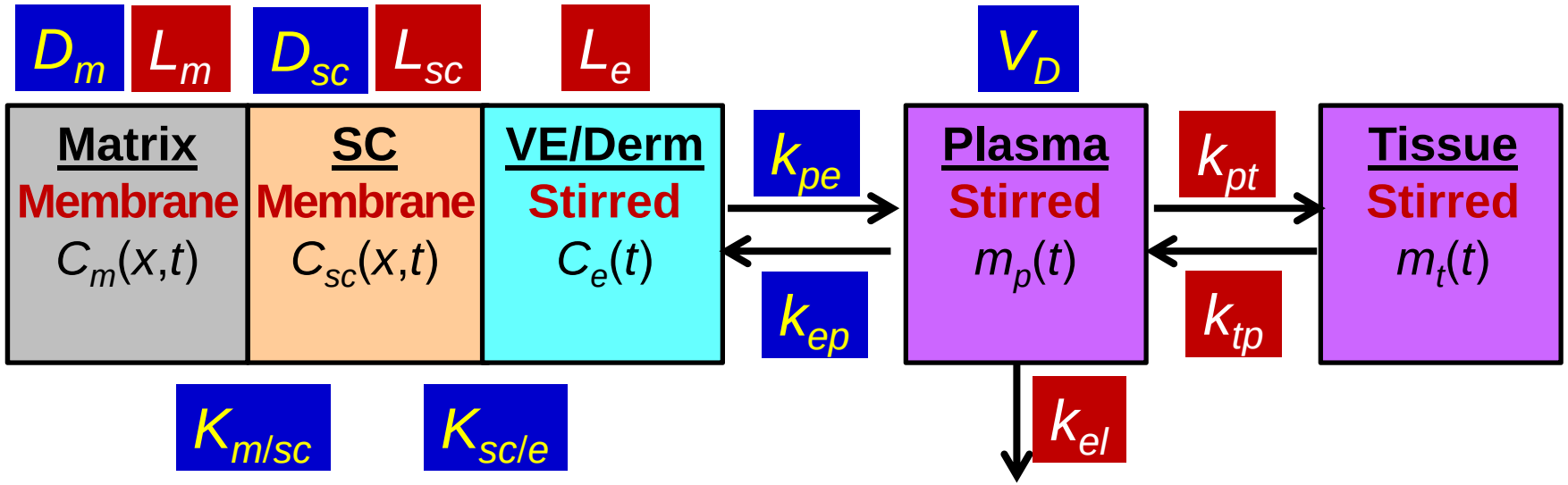
Operational Parameters: *TDD area, initial concentration*



Model parameters: 13

Example TDD model: *Model parameters*

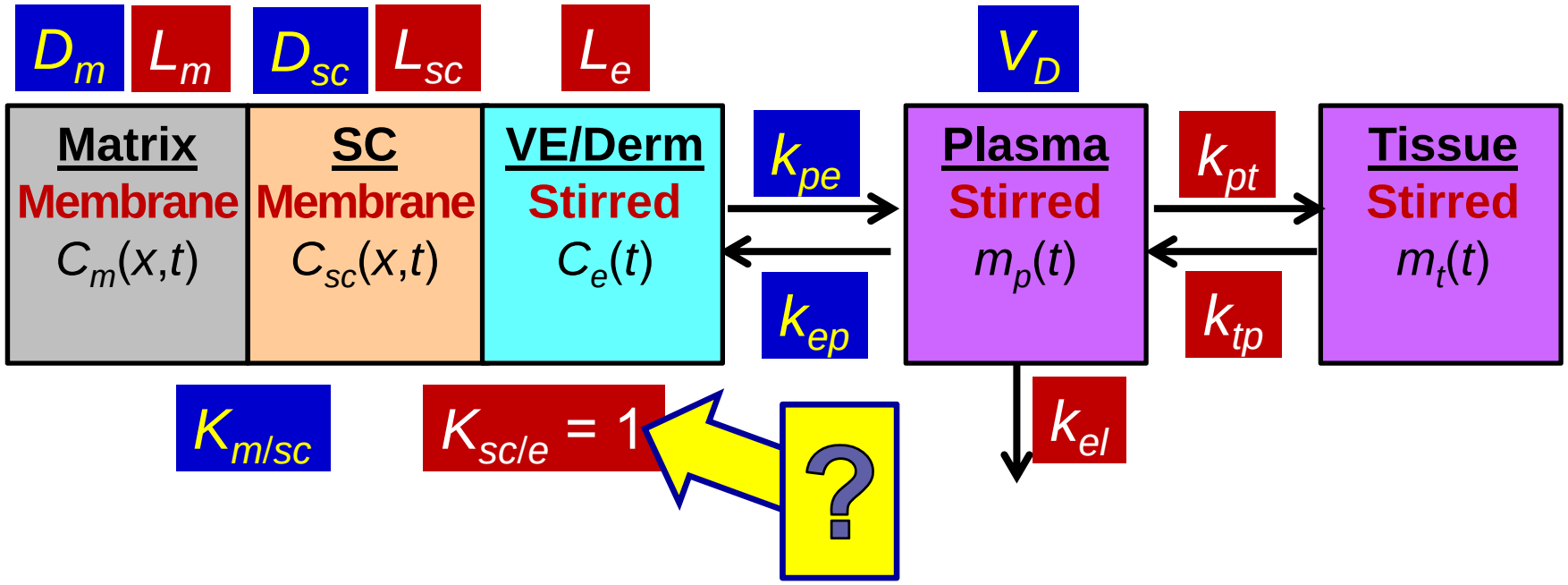
Operational Parameters: *TDD area, initial concentration*



Model parameters: 13
Independent experiment: 6
Regressed to data: 7

Example TDD model: *Model parameters*

Operational Parameters: *TDD area, initial concentration*



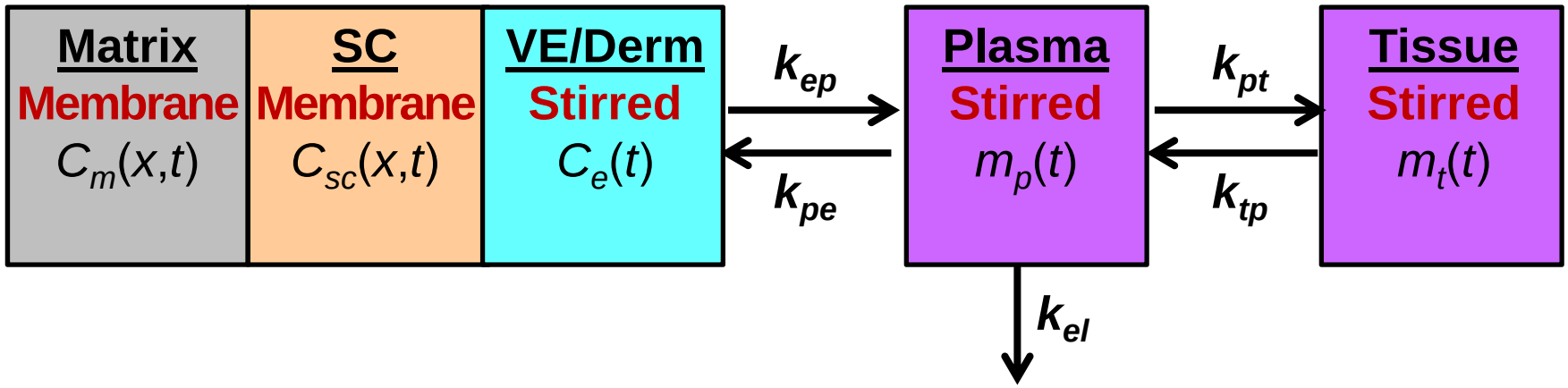
Model parameters: 13

Independent experiment: ~~8~~ 7

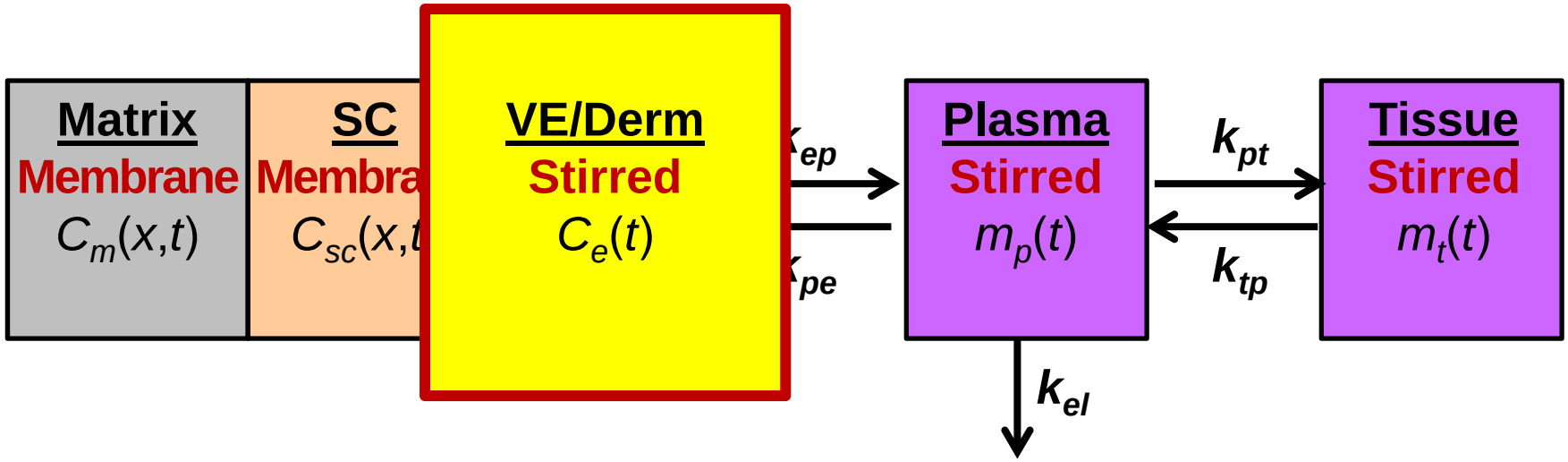
Regressed to data: ~~7~~ 6

- Plasma concentration(t)
- Mass in urine(t)
- Mass in TDD (? at end)

Example TDD model: *Model equations*



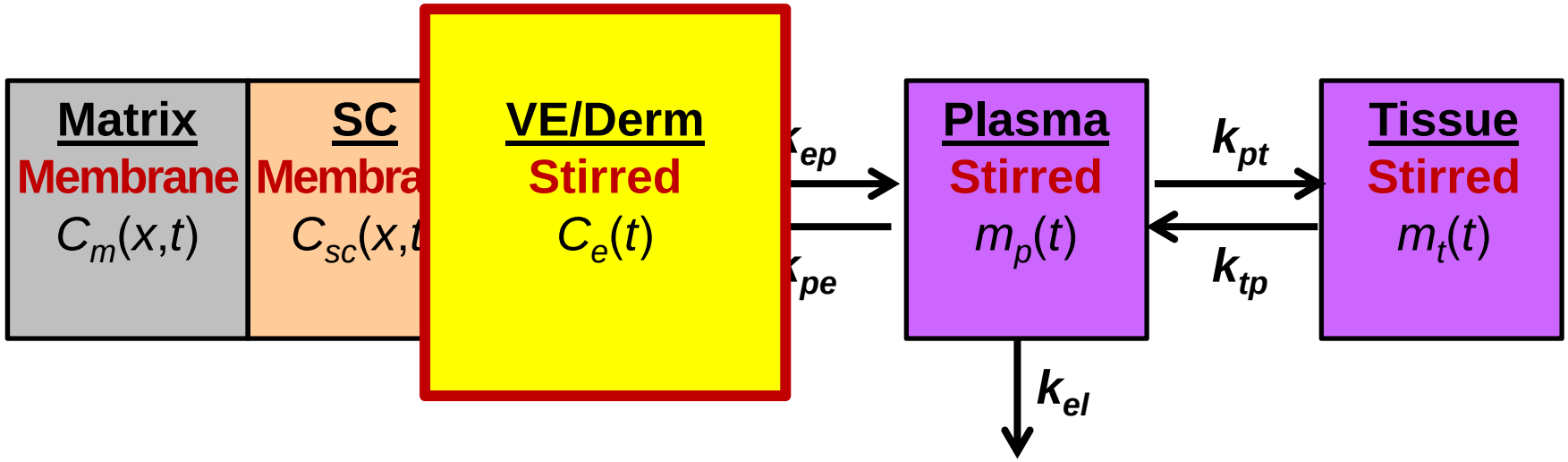
Example TDD model: *Model equations*



$$\frac{dm_e}{dt} = -A_m D_{sc} \left.\frac{\partial C_{sc}}{\partial x}\right|_{x=sc/e \text{ interface}} + k_{pe}\, m_p - k_{ep}\, m_e$$

Change in mass in VE/D with time = Transfer in from SC + Transfer in from plasma − Transfer out to plasma

Example TDD model: *Model equations*



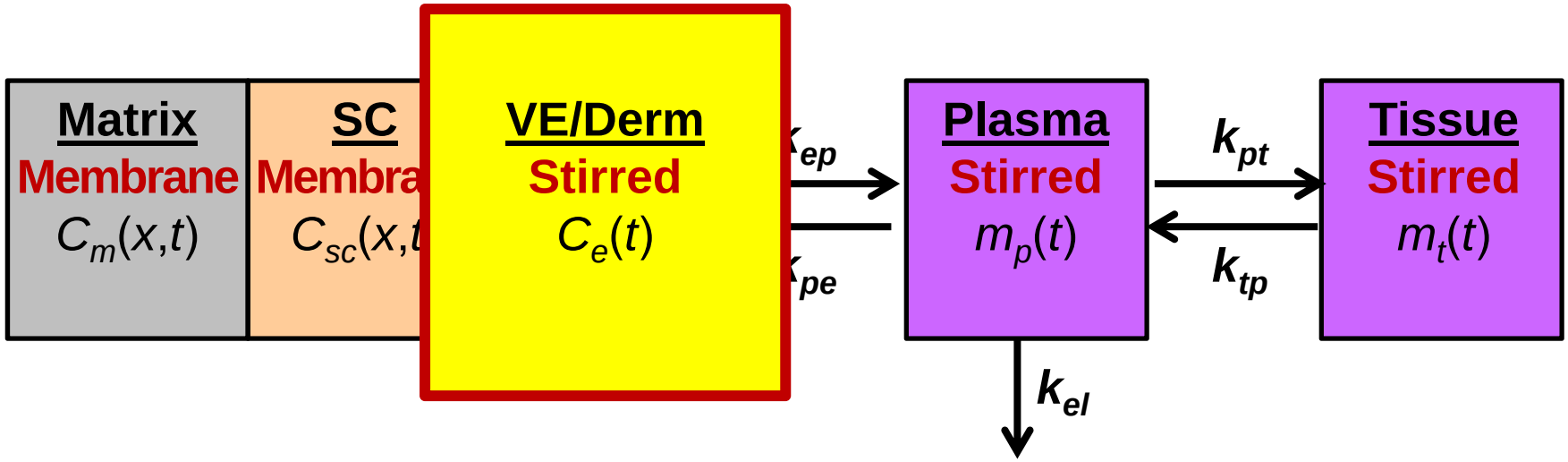
$$\frac{dm_e}{dt} = -A_m D_{sc} \left.\frac{\partial C_{sc}}{\partial x}\right|_{x=sc/e \text{ interface}} + k_{pe} m_p - k_{ep} m_e$$

In the paper

$$\frac{dm_e}{dt} = -K_{e/sc} = L_e D_{sc} \left.\frac{\partial C_{sc}}{\partial x}\right|_{x=sc/e \text{ interface}} + k_{pe} m_p - k_{ep} m_e$$

Example TDD model: *Model equations*

$$\frac{dm_e}{dt} = -f\,A_m D_{sc}\left.\frac{\partial C_{sc}}{\partial x}\right|_{x=L_m+L_{sc}} + k_{pe}\,m_p - k_{ep}\,m_e$$

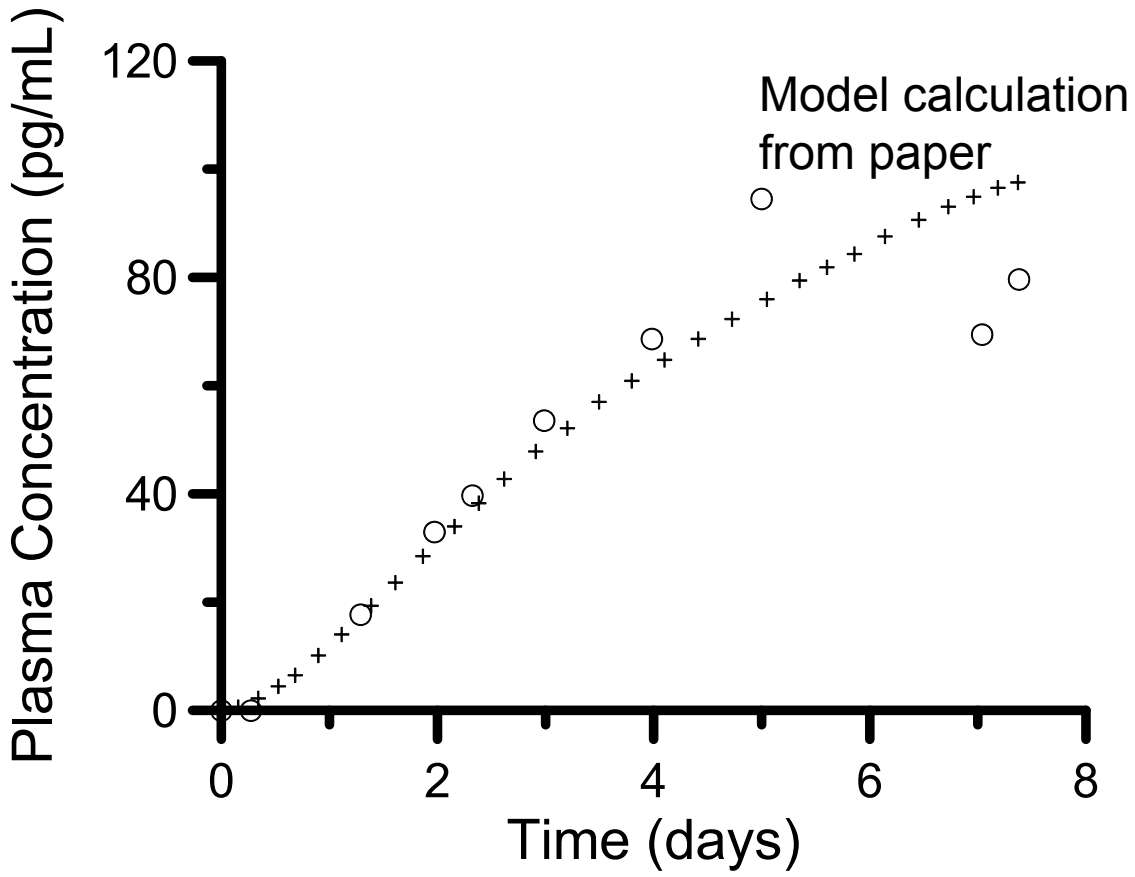


where $f = K_{e/sc}\,L_e / A_m$ = 1/(*length*) in unknown units

This makes the equation dimensionally inconsistent.

Example TDD model: *Model calculations*

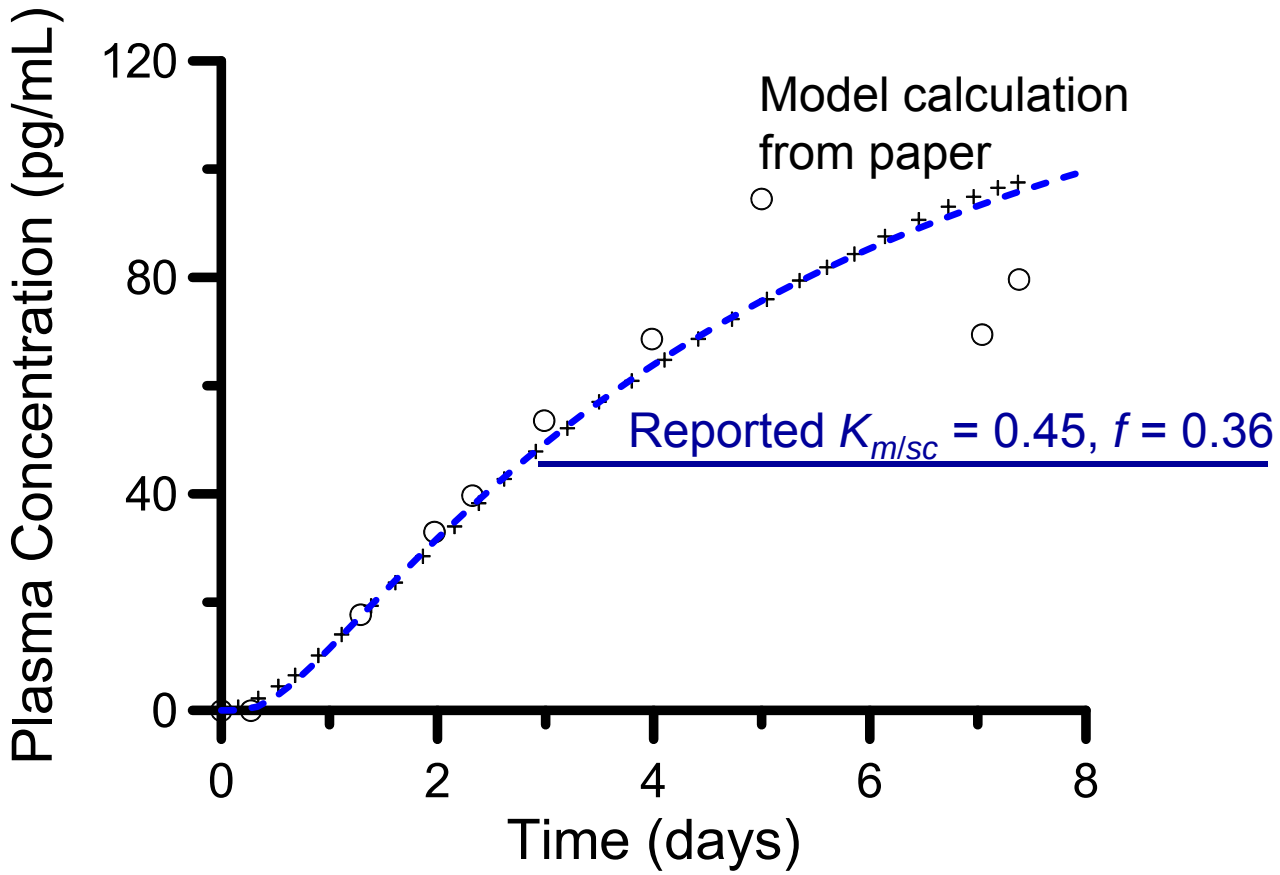
Plasma concentration



Göpferich and Lee, Intl J Pharmaceut, 71:237-43 (1991)

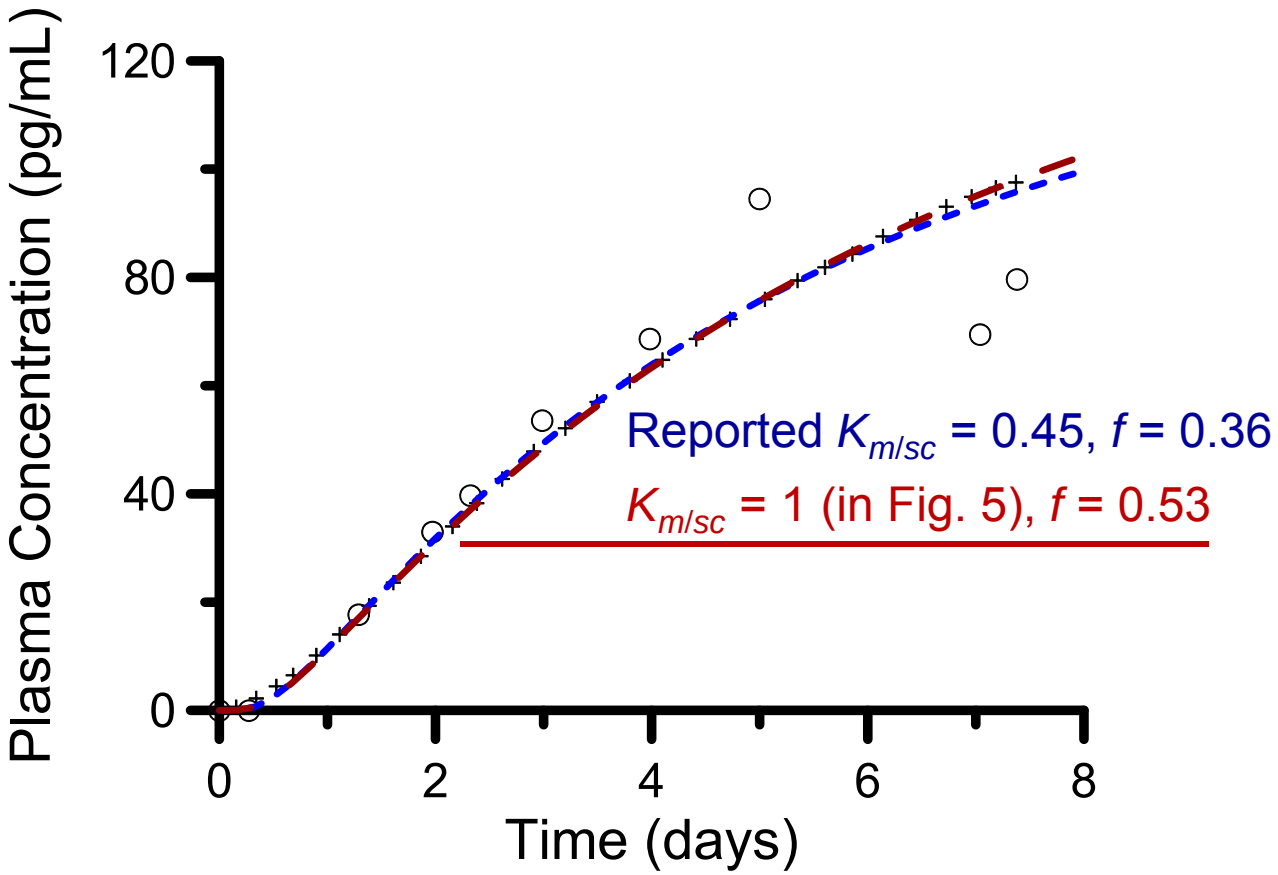
Example TDD model: *Model calculations*

Plasma concentration



Example TDD model: *Model calculations*

Plasma concentration



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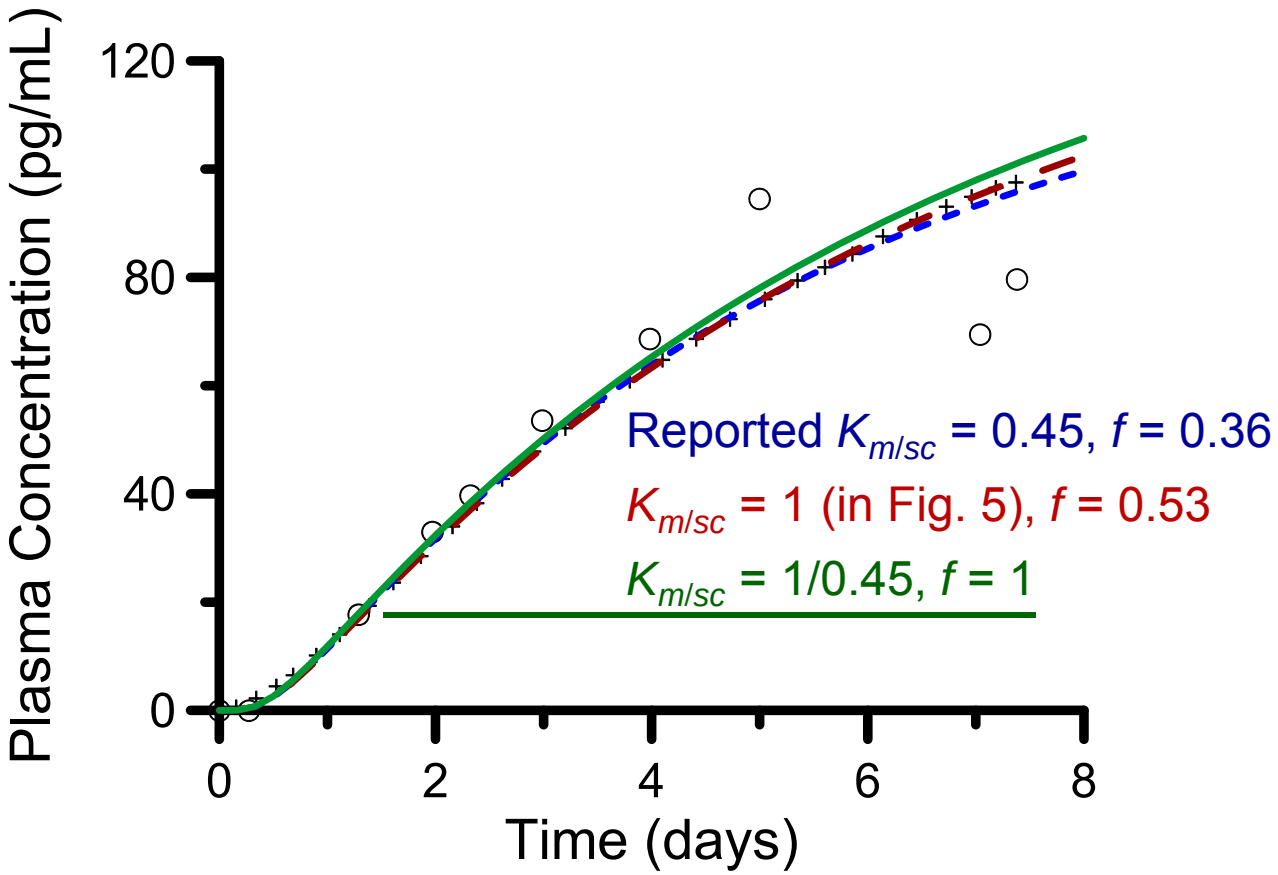
Example TDD model: *Model calculations*

Plasma concentration



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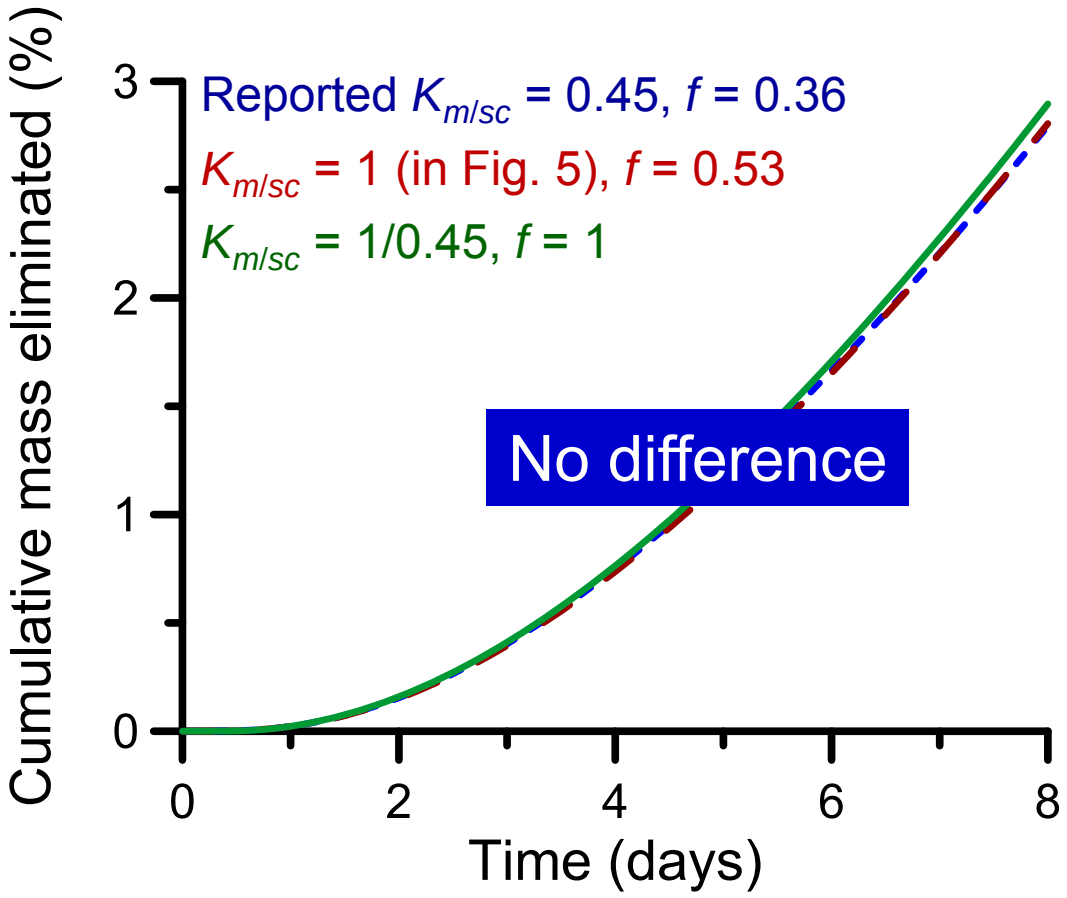
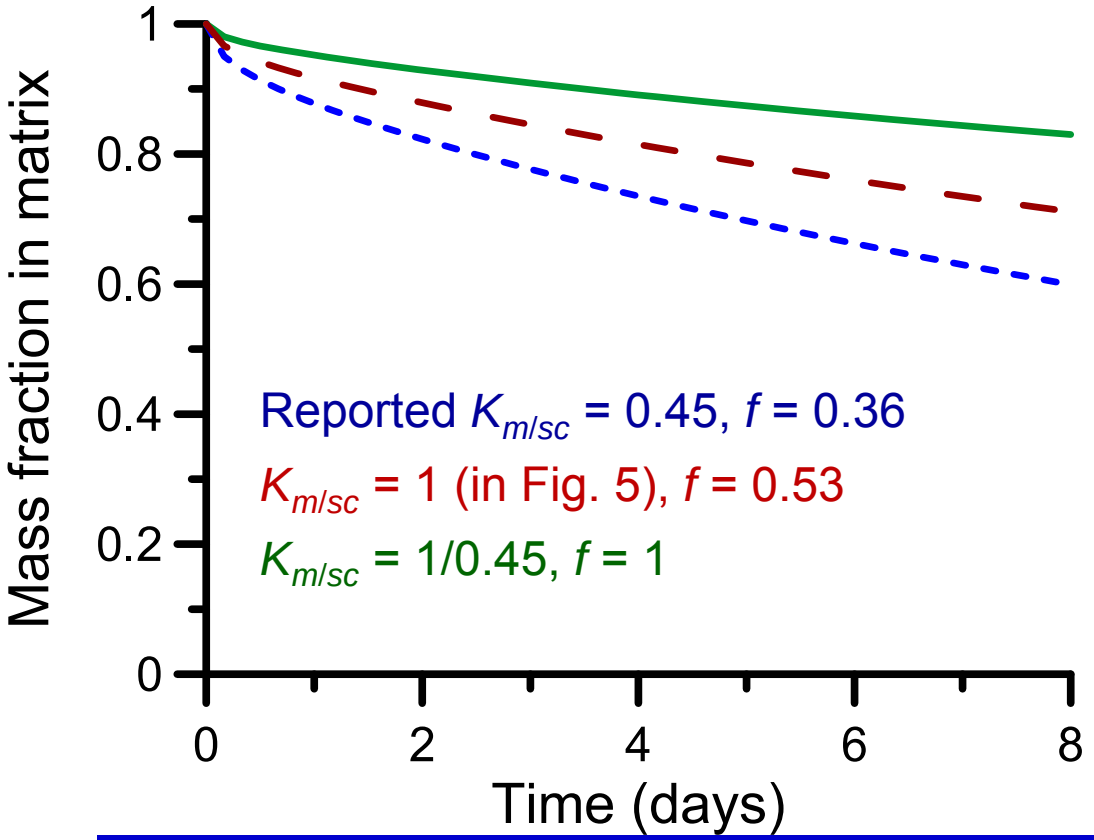
Example TDD model: *Model calculations*

Mass eliminated



Example TDD model: *Model calculations*

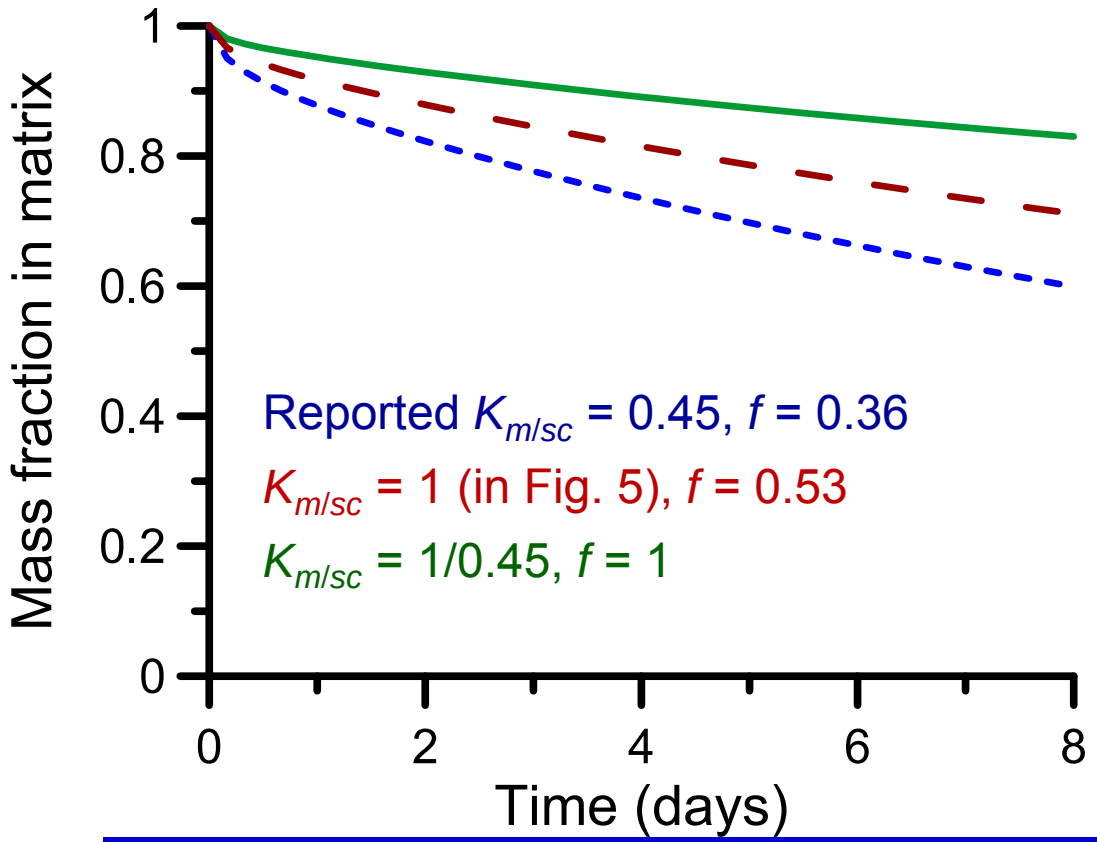
Mass fraction in TDD



Difference might be too small to discriminate between calculations

Example TDD model: *Model calculations*

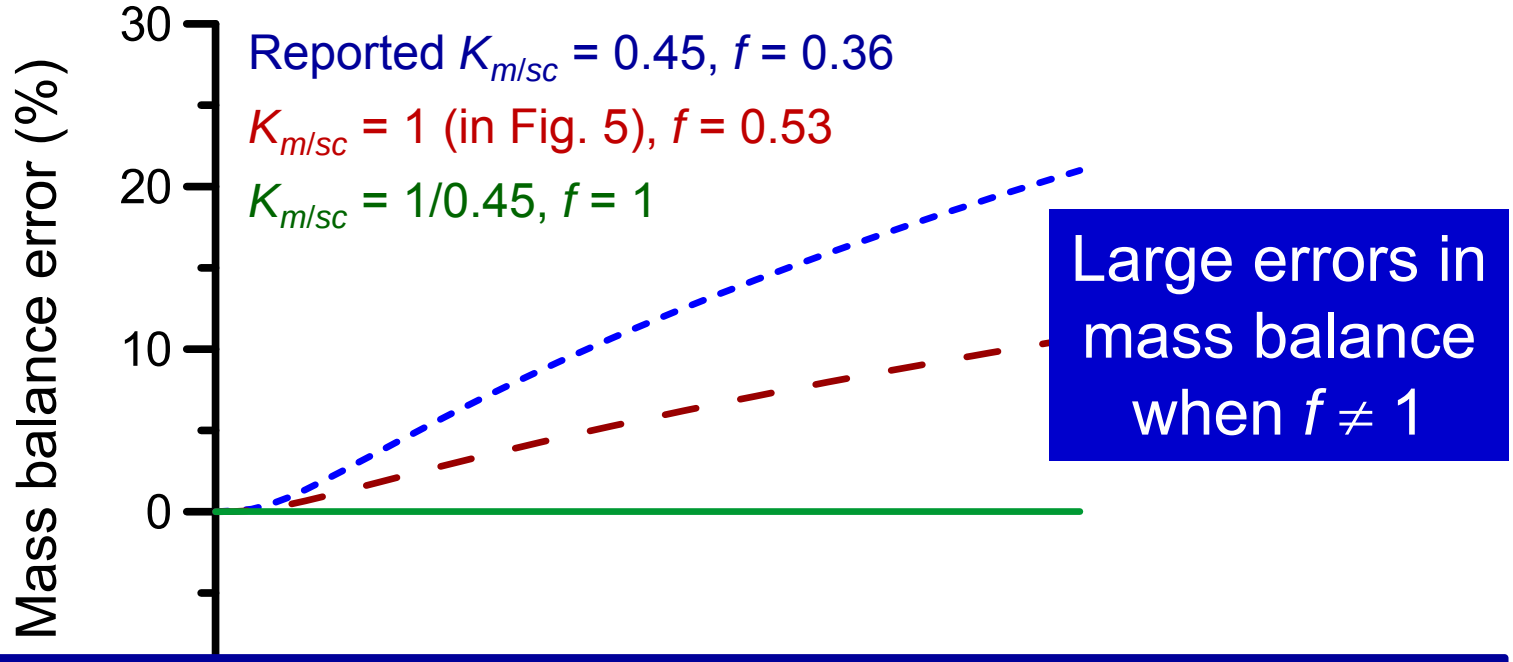
Mass fraction in TDD



All results look reasonable

Example TDD model: *Model calculations*

Mass balance



Mass balance error =

1 –

(Mass in TDD + Mass in all compartments + Mass eliminated)

/ (Initial mass in TDD)

Pitfalls: *Results are plausible but wrong*

- Errors in one (or more) mathematical elements
  - Mass balance in and between compartments
  - Thermodynamic limits
    (partition coefficients at boundaries and equilibrium)
  - Constitutive equations
    (describing how rates of transport and reaction vary with drug concentration)

Errors in mass balance equations are revealed by doing an overall mass balance.

Pitfalls: *Results are plausible but wrong*

- Errors in one (or more) mathematical elements
  - Mass balance in and between compartments
  - Thermodynamic limits
    (partition coefficients at boundaries and equilibrium)
  - Constitutive equations
    (describing how rates of transport and reaction vary with drug concentration)

Mass balances should be done and results reported as “proof” of model correctness.

Pitfalls: *Results are plausible but wrong*

- Errors in one (or more) mathematical elements
  - Mass balance in and between compartments
  - Thermodynamic limits
    (partition coefficients at boundaries and equilibrium)
  - Constitutive equations
    (describing how rates of transport and reaction vary with drug concentration)

Errors in thermodynamic limits or constitutive equations may not produce mass balance errors (and thus, may not be discovered)

Pitfalls: *Results are plausible but wrong*

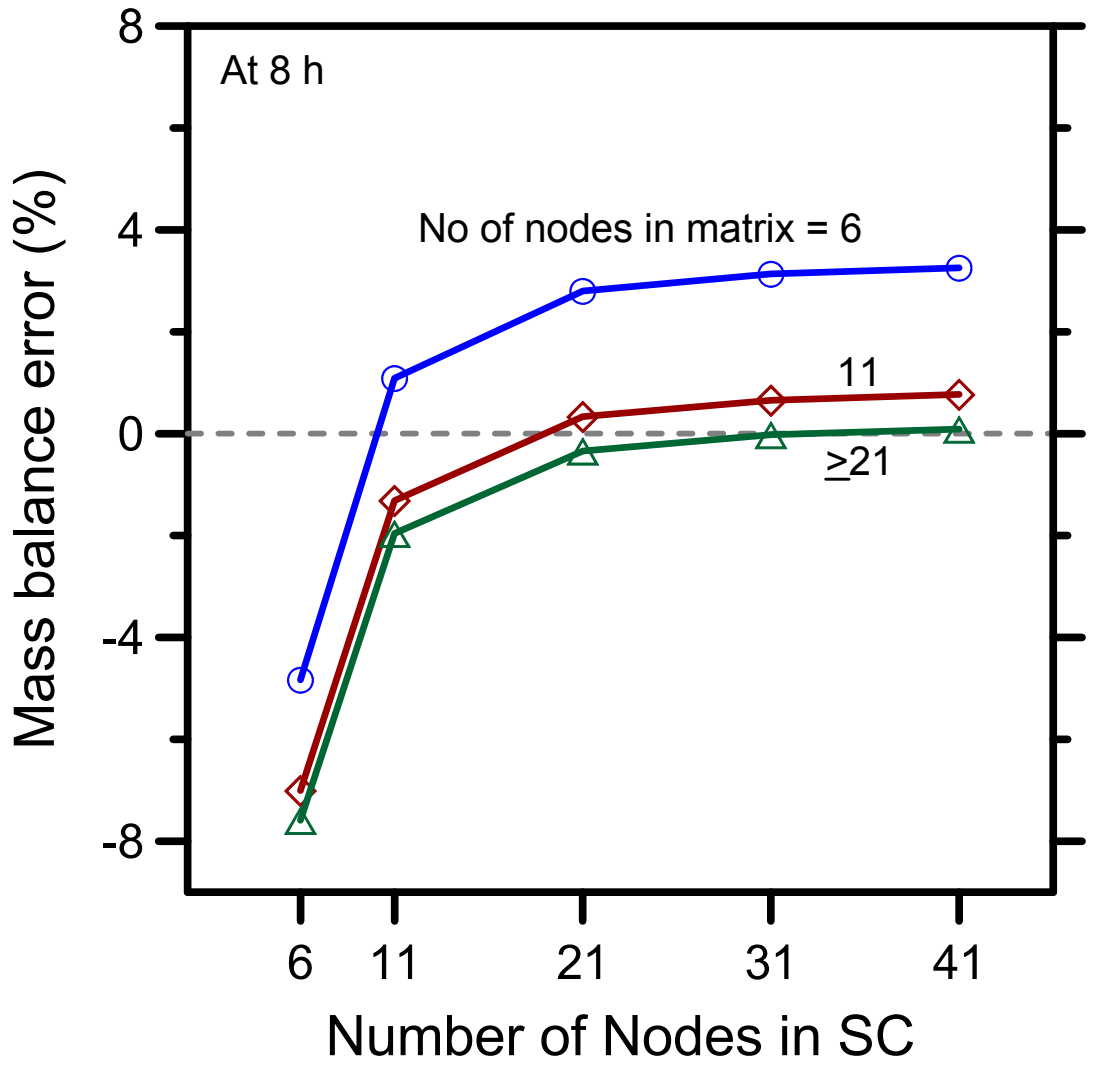
- Errors in one (or more) mathematical elements
  - Mass balance in and between compartments
  - Thermodynamic limits
    (partition coefficients at boundaries and equilibrium)
  - Constitutive equations
    (describing how rates of transport and reaction vary with drug concentration)
- Numerical errors

Example TDD model: *Numerical Errors*

- Numerical solutions approximate derivatives in the model equations
- Derivative approximations may be poor:
  - If spacing between positions (nodes) at which concentration is calculated are spaced too far apart (in finite-difference methods)
  - If size of volume within which concentration is calculated are too large (in finite-element methods)

Numerical errors may be discovered by errors in the mass balance.

Example TDD model: *Numerical Errors*

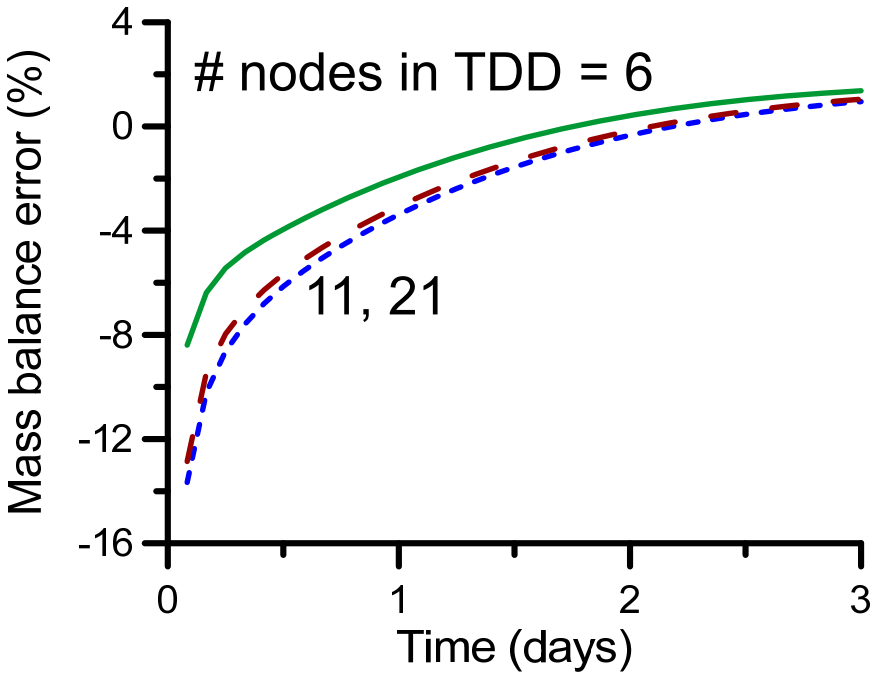


Model Parameters

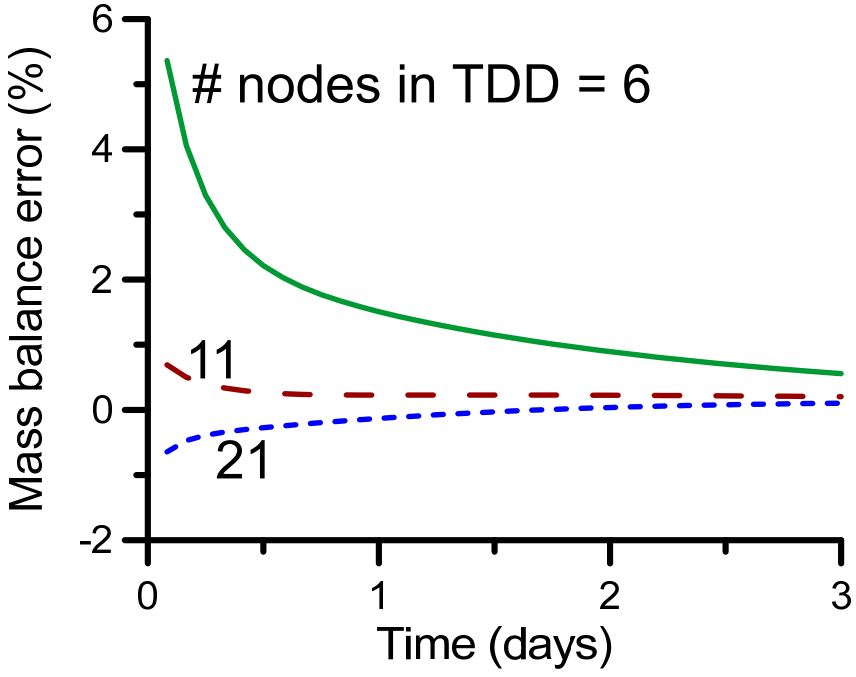
$C_{m,o}$ = 91.9 mg/mL
L_{sc} = 15 μm
L_e = 50 μm
L_m = 13.6 μm
$K_{sc/m}$ = 1000
$K_{sc/e}$ = 25
$K_{e/p}$ = 1
k_{ep} = 15 h^{-1}
k_{pe} = 1.33 x 10^{-4} h^{-1}
k_{pt} = 0.2 h^{-1}
k_{tp} = 0.5 h^{-1}
k_{el} = 2.8 h^{-1}
V_D = 1130 mL
D_m = 2 x 10^{-8} cm^2/h
D_{sc} = 1 x 10^{-8} cm^2/h

Example TDD model: *Numerical Errors*

nodes in SC = 6

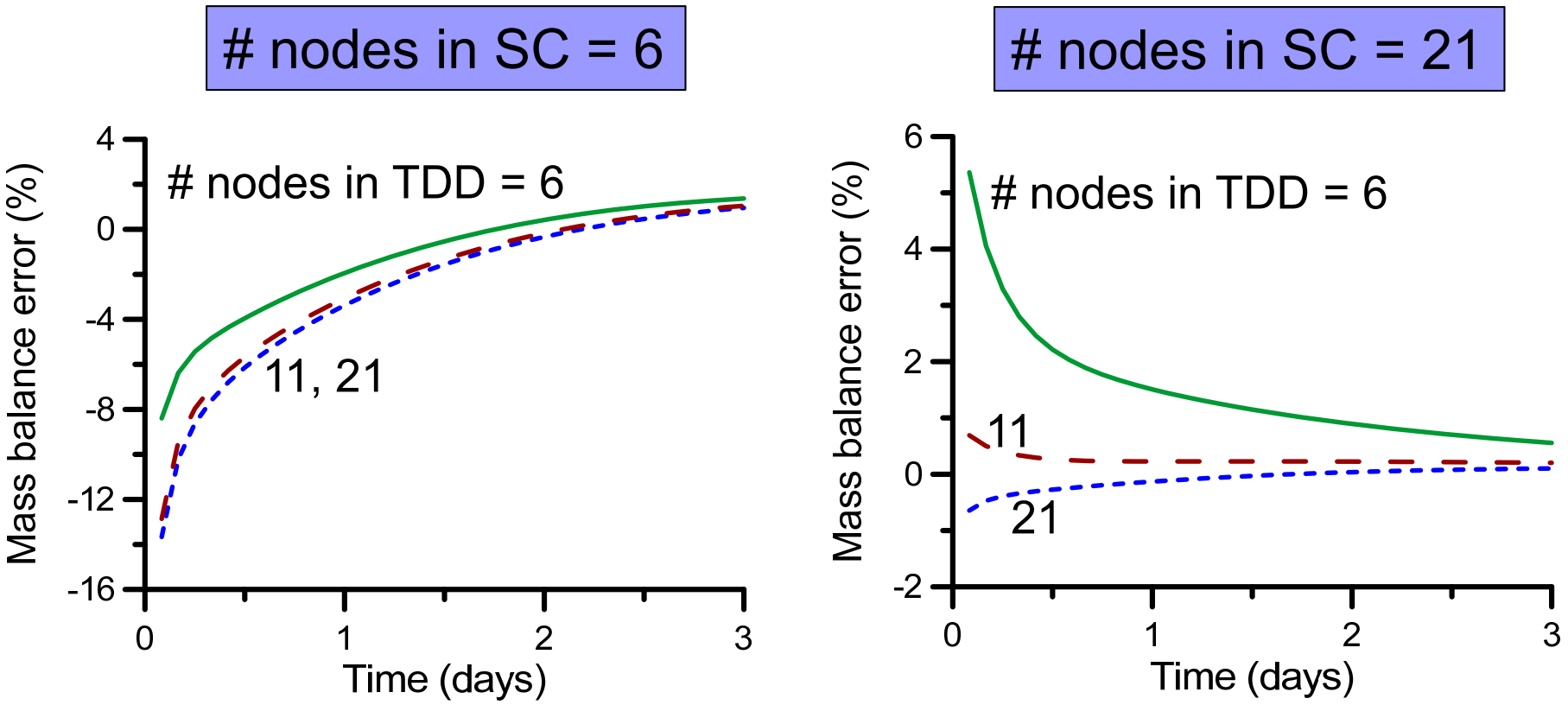


nodes in SC = 21



Optimize # of nodes in all compartments

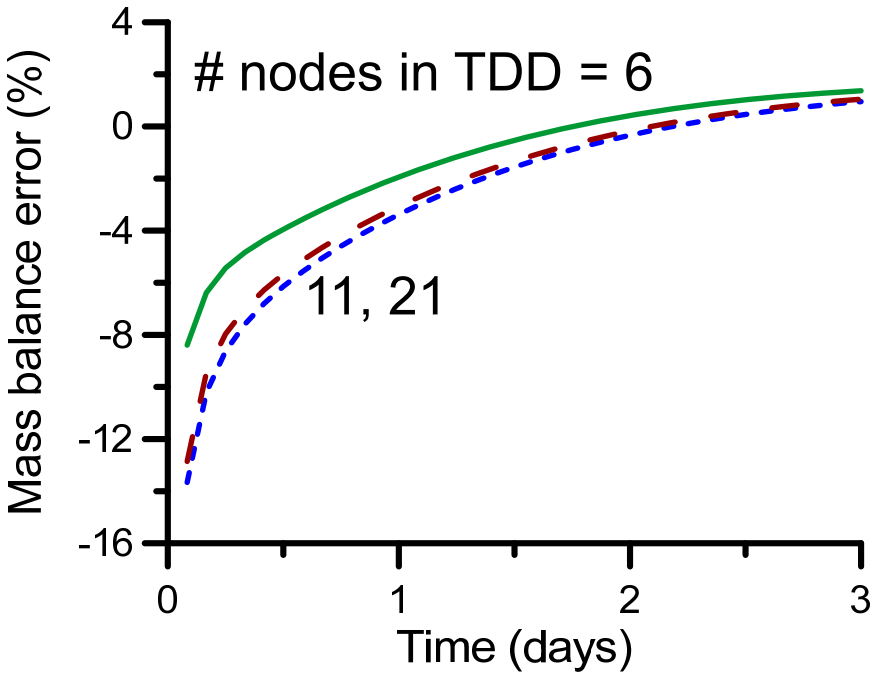
Example TDD model: *Numerical Errors*



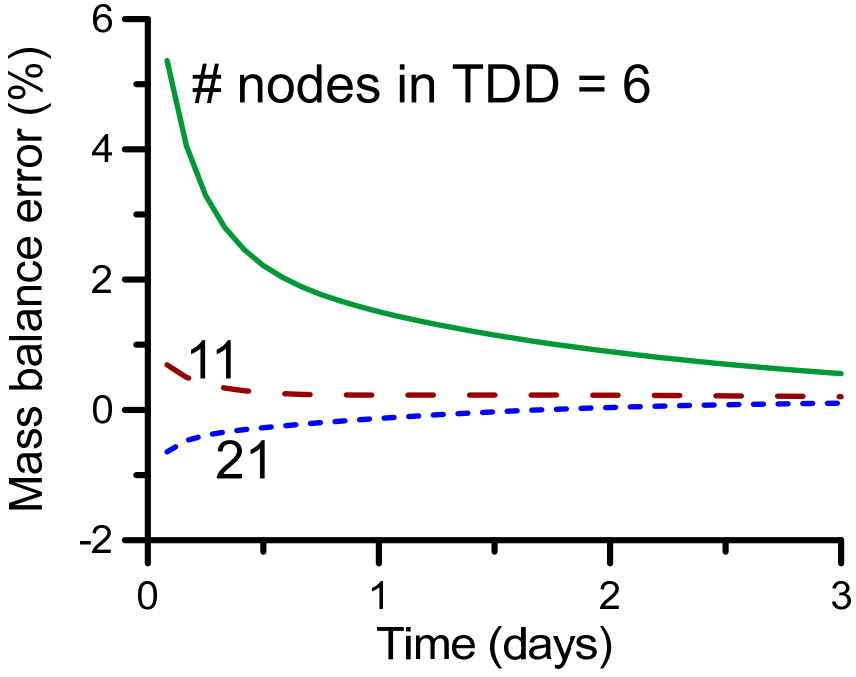
Numerical errors are generally larger at shorter times

Example TDD model: *Numerical Errors*

nodes in SC = 6



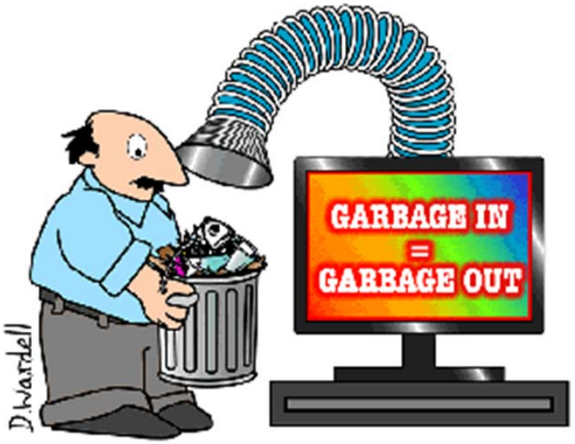
nodes in SC = 21



Errors at shorter times can affect longer time results

Pitfalls: *Unreasonable parameter values*

Results are only as good as the model parameters used in the calculations

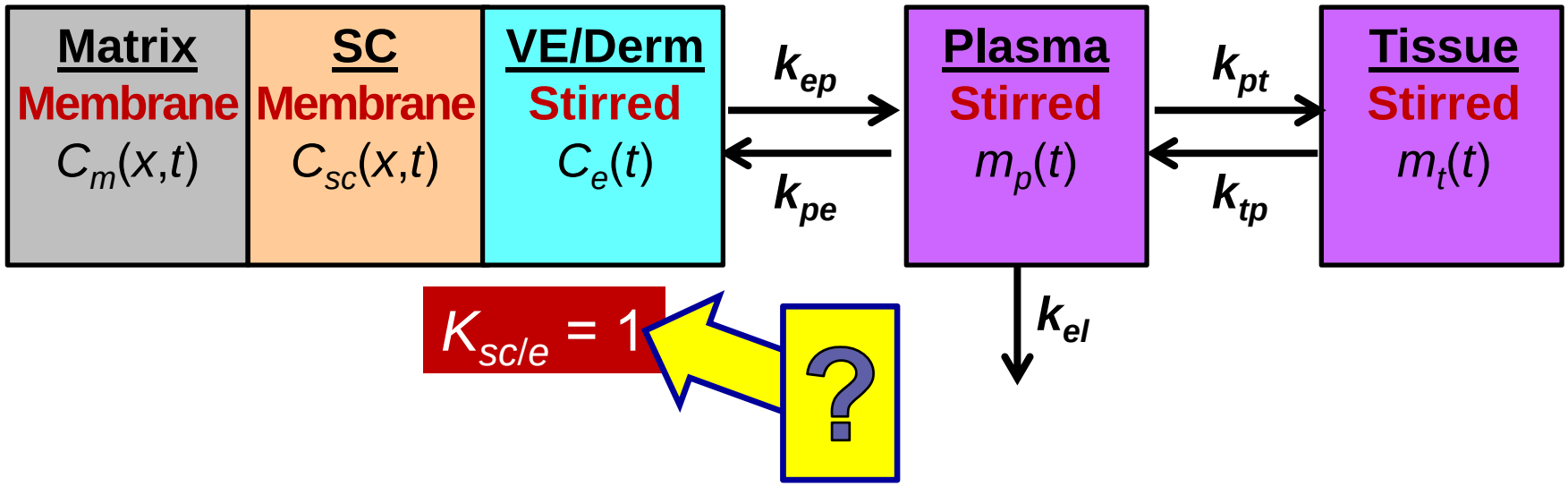


From http://www.donwardell.ca/cartoons.php

Pitfalls: *Unreasonable parameter values*

- Poorly chosen values

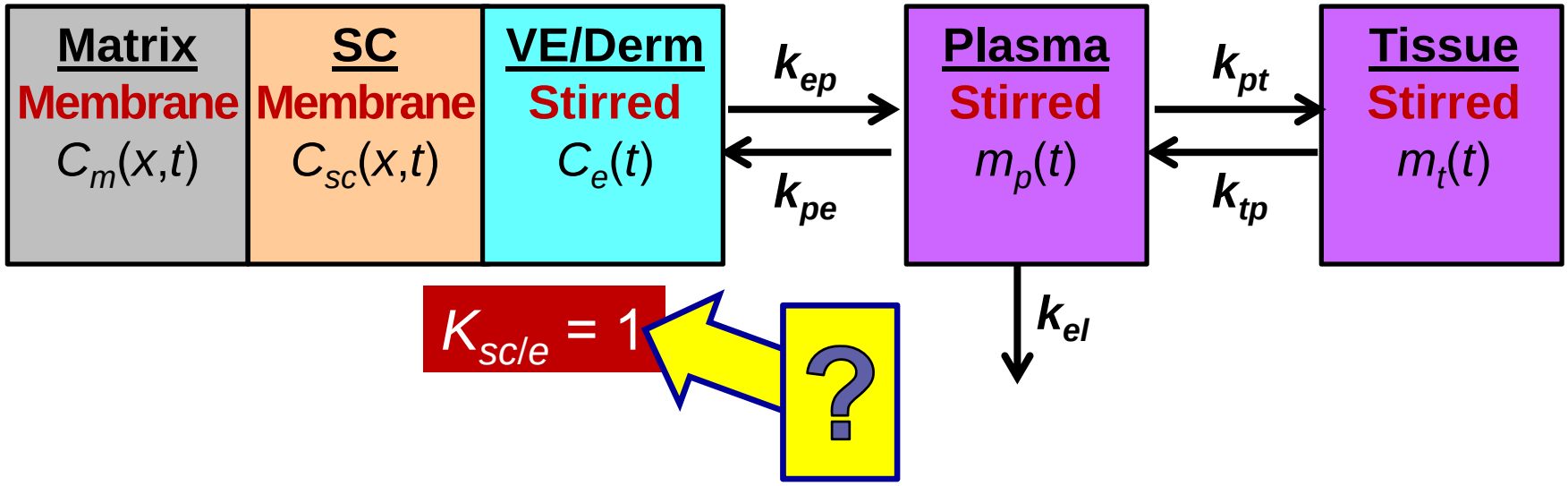
Example TDD model: *Model Parameter*



Example TDD model: *Model Parameter*

Estimated $K_{oct/w}$ = 100

$K_{sc/e}$ = 1 does NOT seem reasonable



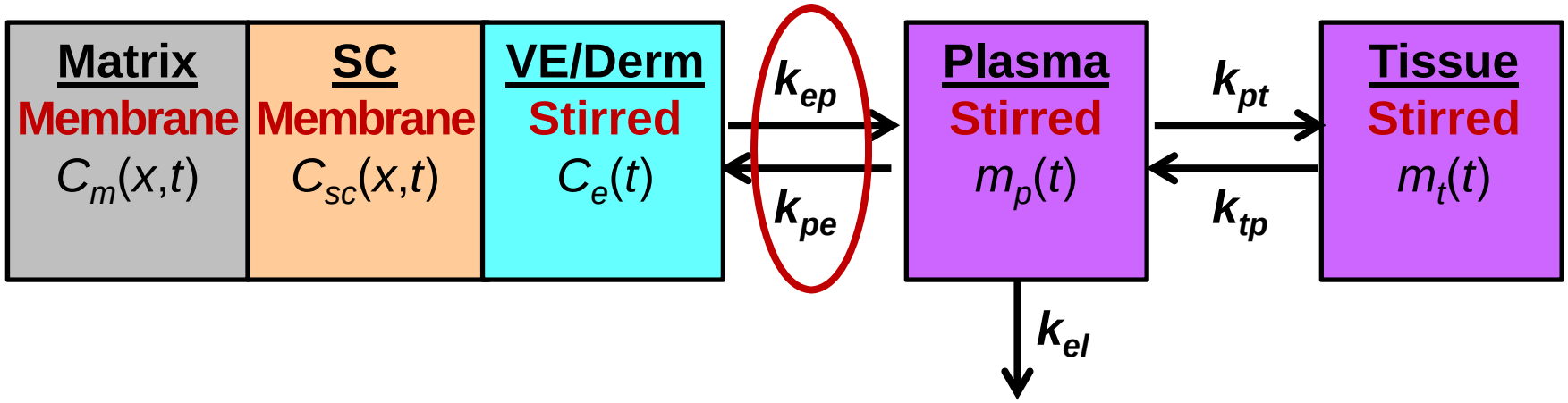
⇨ $\log K_{sc/e} \approx 0.7 \log K_{oct/w}$

$K_{sc/e} \approx 25$

Pitfalls: *Unreasonable parameter values*

- Poorly chosen values
- Parameter regression without consideration of connections or limits in the parameter values

Example TDD model: *Parameter limits*



k_{ep} = 1.47 h^{-1} and k_{pe} = 12.6 h^{-1}

Mass transfer rate from VE to plasma = $k_{ep}\, m_e - k_{pe}\, m_p$

Göpferich and Lee, Intl J Pharmaceut, 71:237-43 (1991)

Example TDD model: *Parameter limits*

Mass transfer rate from VE to plasma = $k_{ep}\, m_e - k_{pe}\, m_p$

Values for k_{ep} and k_{pe} are related by equilibrium limits.

At <u>equilibrium</u> between VE and plasma:

$C_e = K_{e/p}\, C_p$

Mass transfer rate from VE to plasma = 0

$$\Rightarrow \quad k_{pe} = k_{ep}\left(\frac{K_{e/p}\, L_e\, A_m}{V_D}\right)$$

k_{ep} and k_{pe} are <u>NOT</u> independent!

Example TDD model: *Parameter limits*

From Göpferich and Lee, 1991:

k_{ep} = 1.47 h^{-1} and k_{pe} = 12.6 h^{-1}

L_e = 50 μm, V_D = 113 L and A_m = 2 cm^2

If $K_{e/p} \approx 1$

for k_{ep} = 1.47 h^{-1}

k_{pe} = 13 x 10^{-8} h^{-1} (NOT 12.6 h^{-1})

Pitfalls: *Unreasonable parameter values*

- Poorly chosen values
- Parameter regression without consideration of connections or limits in the parameter values
- Poorly chosen or incorrect model parameters for a model compartment:
  - May not matter if that compartment is not rate controlling, but
  - Could matter if conditions change (e.g., longer times, other parameter values change)
  - Might lead to misinterpretation of the physical situation

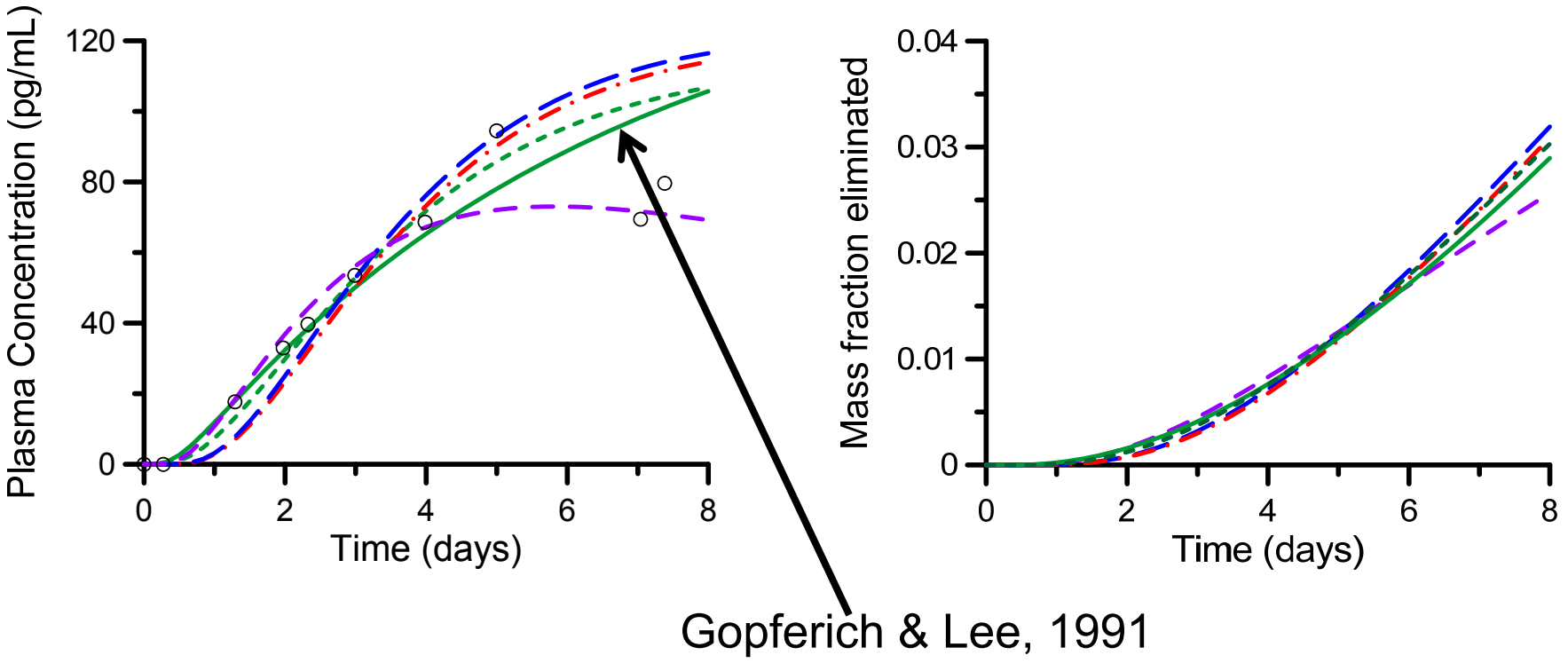
Pitfalls: *Non-unique solutions*

- Even simple PK models of TDD have many model parameters
- Commonly multiple combinations of parameter values provide similar results
- Discriminating between model parameter choices is especially difficult if experimental data are variable

Pitfalls: *Non-unique solutions*

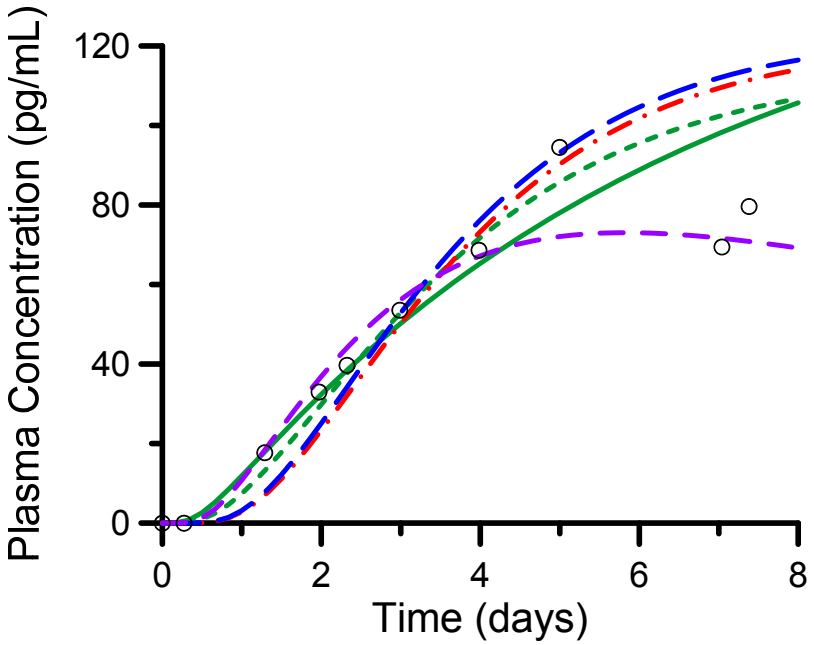
Plasma concentration

Mass fraction eliminated

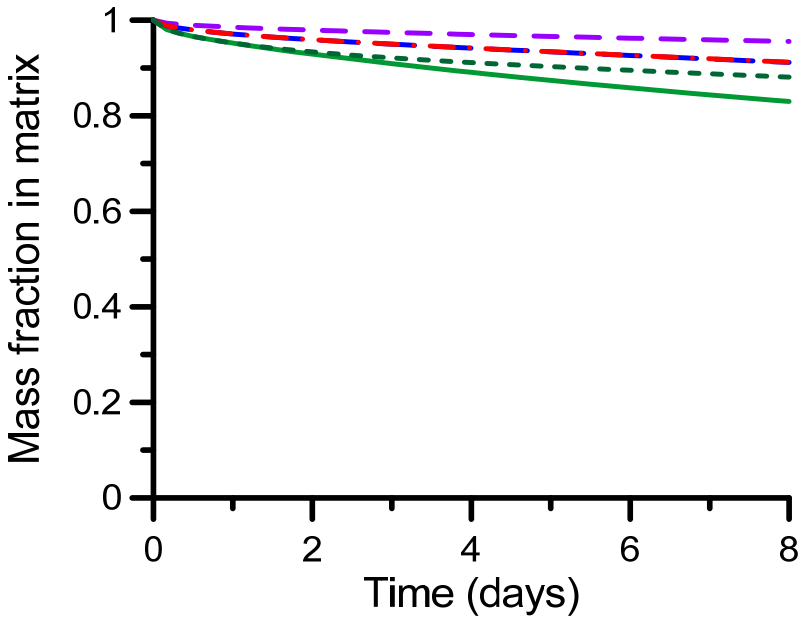


Pitfalls: *Non-unique solutions*

Plasma concentration



Mass fraction in TDD



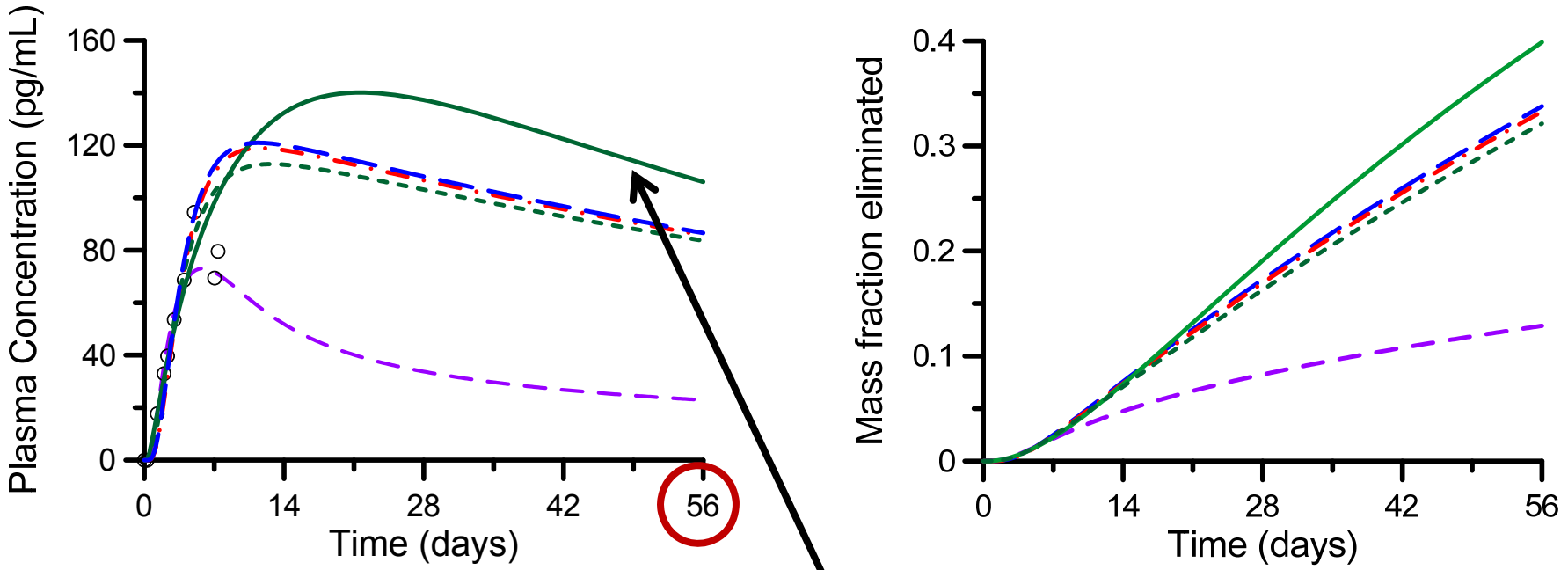
Pitfalls: *Meaningless extrapolations*

- Multiple sets of model parameters may fit the data but extrapolate to different results
- Extrapolation with model parameters determined by regression to data are particularly unreliable
- Extrapolations may be done with more confidence if the model parameters have been determined in separate experiments (and fit the experimental data)

Pitfalls: *Meaningless extrapolations*

Plasma concentration

Mass fraction eliminated

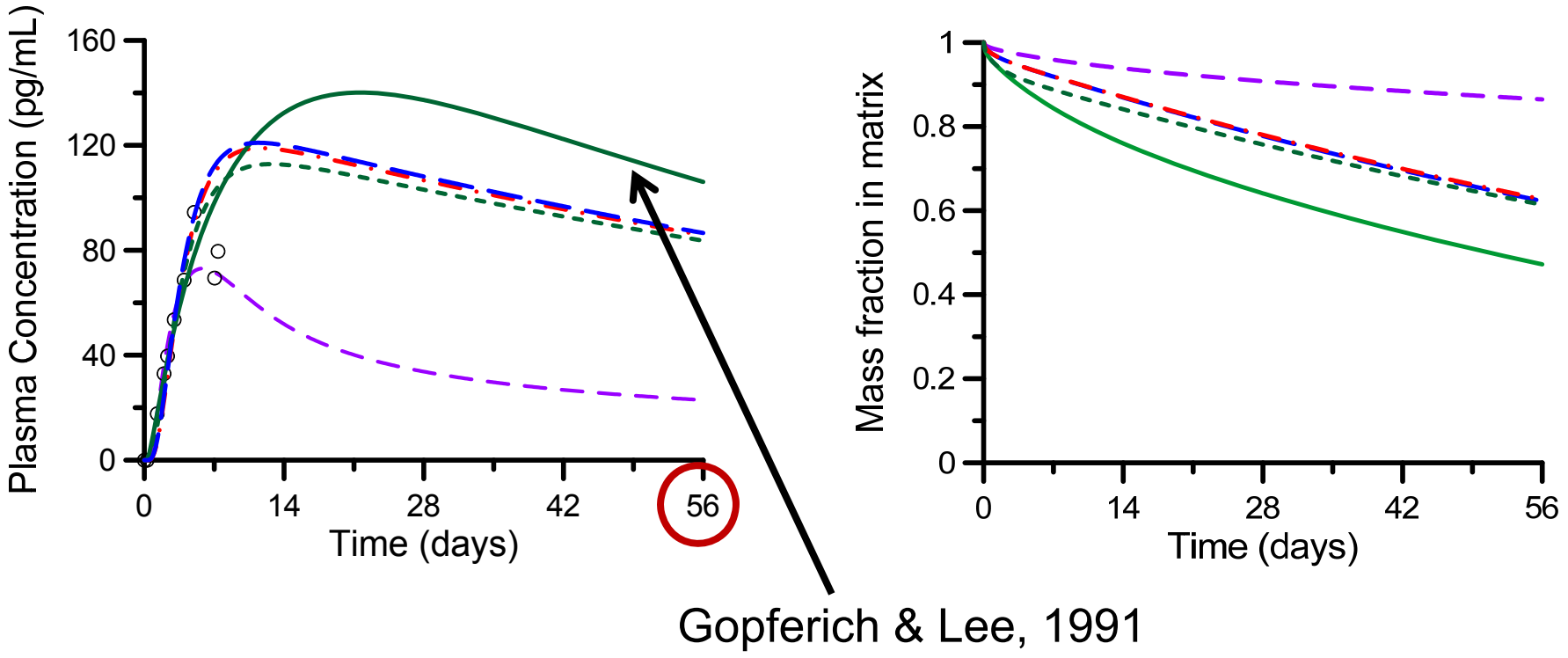


Gopferich & Lee, 1991

Pitfalls: *Meaningless extrapolations*

Plasma concentration

Mass fraction in TDD



Gopferich & Lee, 1991

Recommendations for PK models of TDD

- Write out all equations
  - Word descriptions leave room for interpretation
- Describe derivation of all model parameters
- Recognize physical constraints on model parameter values
  - Not all can be set independently
- Independent experimental sources for model parameters are preferred over regression
- Check the mass balance and report results
- Extrapolate cautiously

The End

Questions?