Non-Compartmental PK Modelling

"model independent"
Distributed models
Transit/Residence distributions

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Basic Equation

$$\frac{dA_e(t)}{dt} = CL\ C(t) \qquad (1)$$

Rate of drug elimination = Clearance x Plasma concentration

(➡ " model independent " or noncompartmental analysis)

$$\int_0^{\infty} \frac{dA_e(t)}{dt} = A_e(\infty) = CL \int_0^{\infty} C(t)dt$$

$$D_{iv} = CL\ AUC$$

Well-mixed plasma compartment !

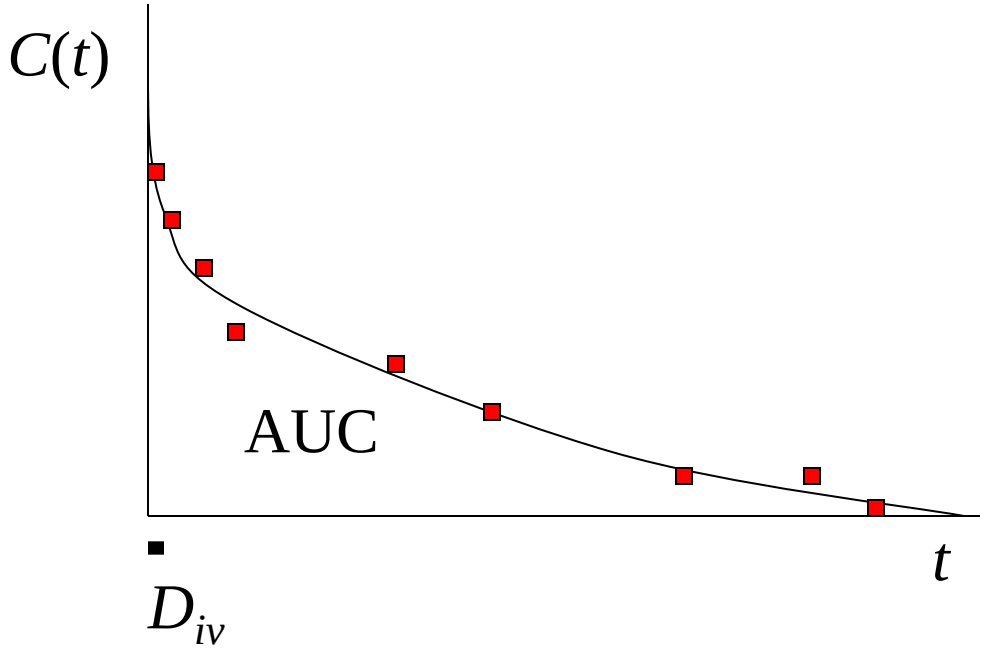
Note: $A_e(\infty) \equiv D_{iv}$ (nothing remains in the body)

Estimation of Clearance (single dose)

$$CL = \frac{D_{iv}}{AUC}$$

Intravenous dose

Area Under the Curve



Single dose

!

$$AUC = \int_0^{\infty} C(t)dt$$

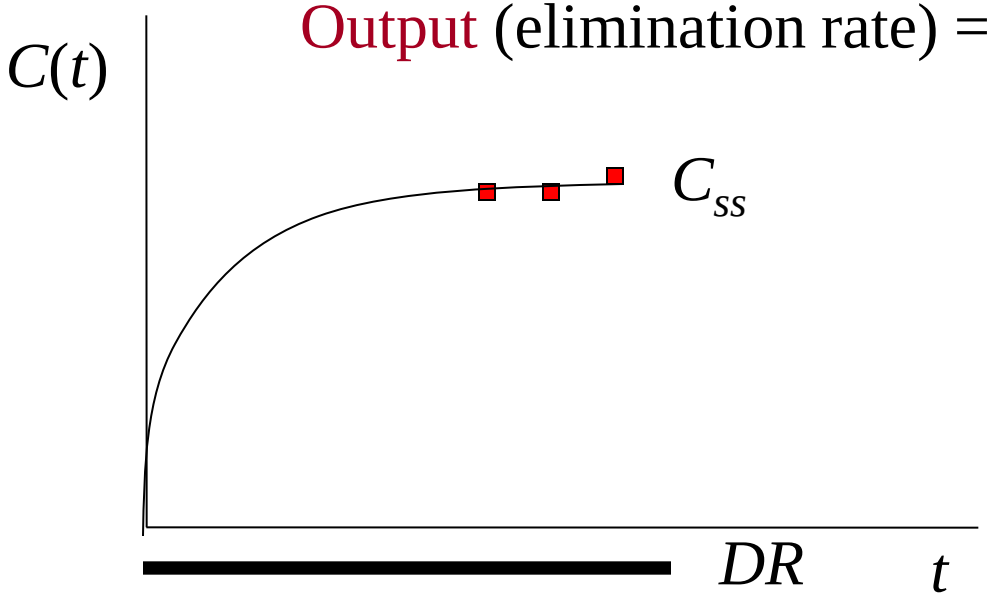
Estimation of Clearance (infusion)

Steady state after continuous i.v. infusion

Elimination rate $= CL\ C_{ss}$

Dose rate $= DR$

Output (elimination rate) = Input (dose rate, infusion rate)



$$CL = \frac{DR}{C_{ss}}$$

Estimation of Bioavailability

$A_e(\infty)$ = *Amount that reaches the systemic circulation*

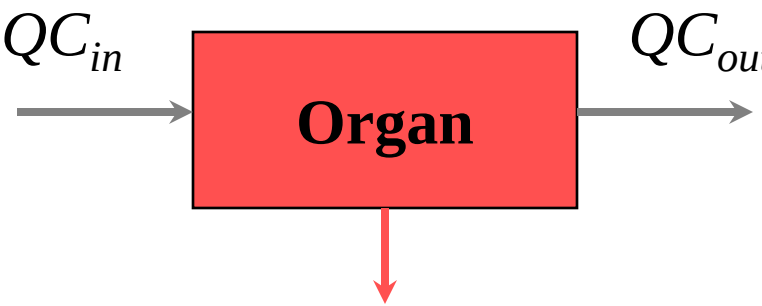
$$A_e(\infty) = CL \int_0^\infty C(t)dt \qquad \text{(cf. Eq. 1)}$$

$$F = \frac{A_{e,or}(\infty)}{A_{e,iv}(\infty)} = \frac{CL \int_0^\infty C_{or}(t)dt}{CL \int_0^\infty C_{iv}(t)dt} = \frac{AUC_{or}}{AUC_{iv}} \qquad (13)$$

Assumption:
CL unchanged !

$$\text{if } D_{or} \neq D_{iv}: \quad F = \frac{D_{iv} AUC_{or}}{D_{or} AUC_{iv}}$$

Determinants of Clearance



$C_{out} = F\, C_{in}$

F (availability)

E = 1-F (extraction)

$$CL_{organ} = Q_{organ} E_{organ} \qquad (4)$$

$$CL = CL_H + CL_R \quad (+CL_{other})$$

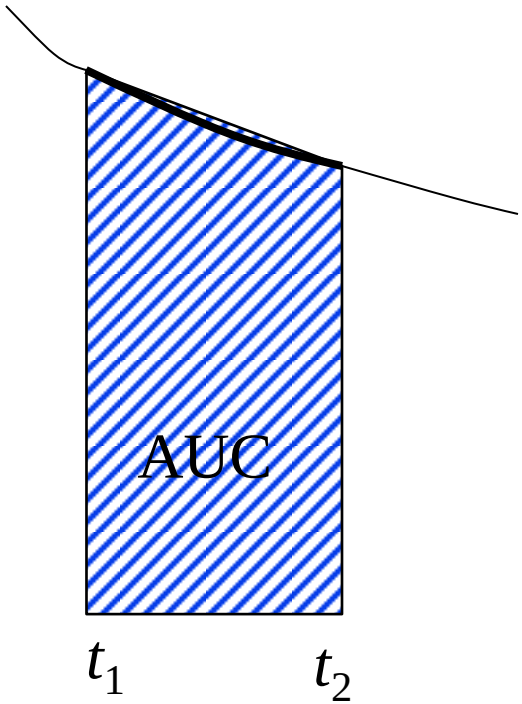
hepatic ***renal***

$$CL = \sum_{i=1}^{N} Q_i E_i$$

Renal Clearance

$$CL_R = \frac{A_{eR,t_1 \to t_2}}{\int_{t_1}^{t_2} C(t)dt} \qquad (5)$$

$$= \frac{amount\,excreted_{t_1 \to t_2}}{AUC_{t_1 \to t_2}}$$



$$CL_H = CL - CL_R$$

Relative Bioavailability

$$\frac{F_{Treat}}{F_{Con}} = \frac{AUC_{or,Treat}}{AUC_{iv,Treat}} \frac{AUC_{iv,Con}}{AUC_{or,Con}}$$

Residence Time Distribution

If an amount of drug molecules (dose Div) is instantaneously injected intravenously, each molecule will spend a random time ***T*** in the body until it is eliminated (the disposition residence time of that molecule).

Residence time distribution, ***F(t)***, is defined by the fraction of molecules which have a residence time less than ***t***:

$$F(t) = \Pr[T < t] = \frac{A_e(t)}{D}$$

$A_e(t)$ is the cumulative amount of drug eliminated up to time t.

$F(0) = 0$ and $F(\infty) = 1$

$$\frac{dA_e(t)}{dt} = CL\,C(t)$$

Density function

$$f(t) = \frac{C(t)}{\int_0^\infty C(t)dt} = \frac{C(t)}{AUC}$$

Mean Residence Time

$$MRT = E[T] = \int_0^\infty t f(t)dt = \int_0^\infty \overline{F}(t)dt = \int_0^\infty [1 - F(t)]dt$$

$$MRT = \frac{\int_0^\infty tC(t)dt}{AUC}$$

$$MRT = \frac{\int_0^\infty [A_{e,R}(\infty) - A_{e,R}(t)]dt}{A_{e,R}(\infty)}$$

$$-\frac{dA_e(t)}{dt} = CLC(t)$$

Weiss, Eur J Clin Pharmacol , 1992

$\bar{F}(t) = P[T > t]$ Probability that residence time *T* of a molecule exceeds *t*.

Continuous infusion: Mass *dA* which entered the body in the time interval [*t*-*dt*,*t*] which remains in the body at time *t* is given by:

$$DR\ \bar{F}(t)dt$$

$$\rightarrow \quad A(t) = DR \int_0^t \bar{F}(t)dt \quad \rightarrow \quad A_{ss} = A(\infty) = DR \int_0^\infty \bar{F}(t)dt$$

$$\rightarrow \quad A_{ss} = DR\ MDRT$$

$$V_{ss} = \frac{A_{ss}}{C_{ss}} = \frac{DR\ MDRT}{C_{ss}} = MDRT\ CL$$

Weiss, J Pharm Sci , 1991

1. Disposition Curves (Bolus Injection)

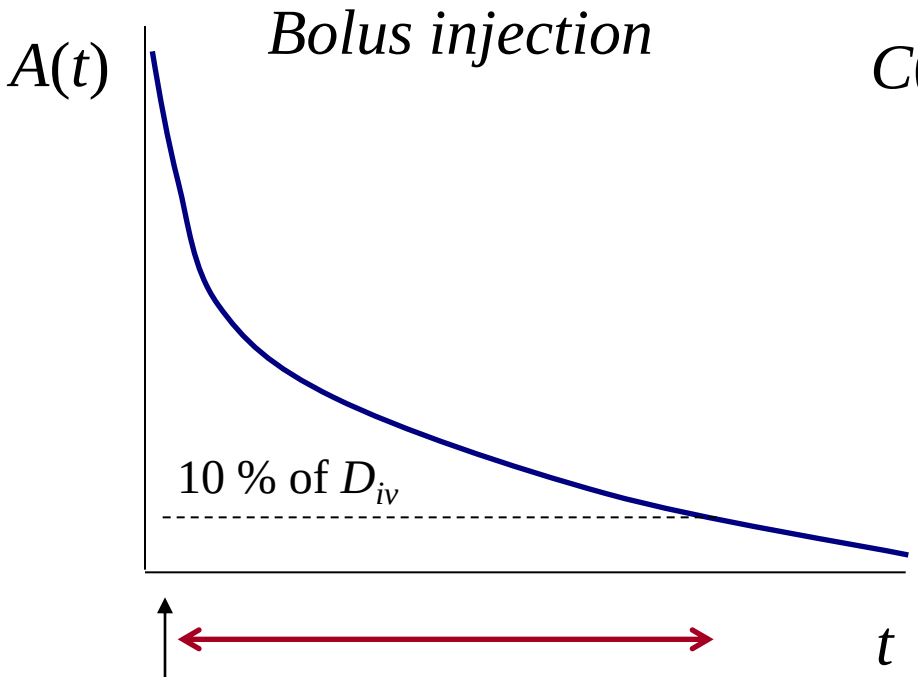
Clearance CL

Volume of distribution at steady state V_{ss}

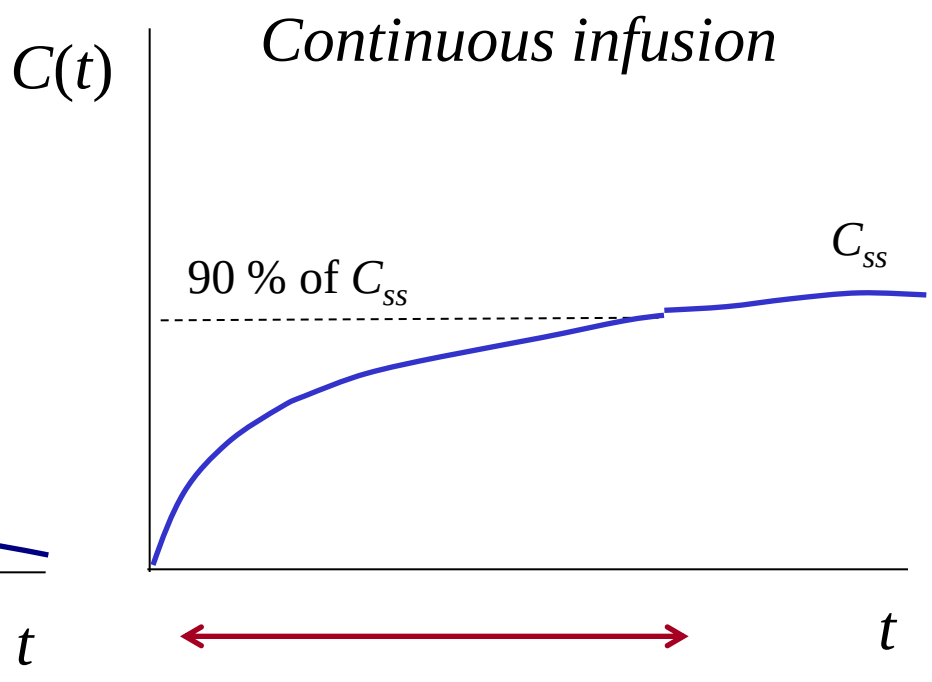
Mean Disposition Residence Time $MDRT$

$$MDRT = \frac{V_{ss}}{CL} \qquad (14)$$

Mean Disposition Residence Time



D_{iv} $t_{90\%}$

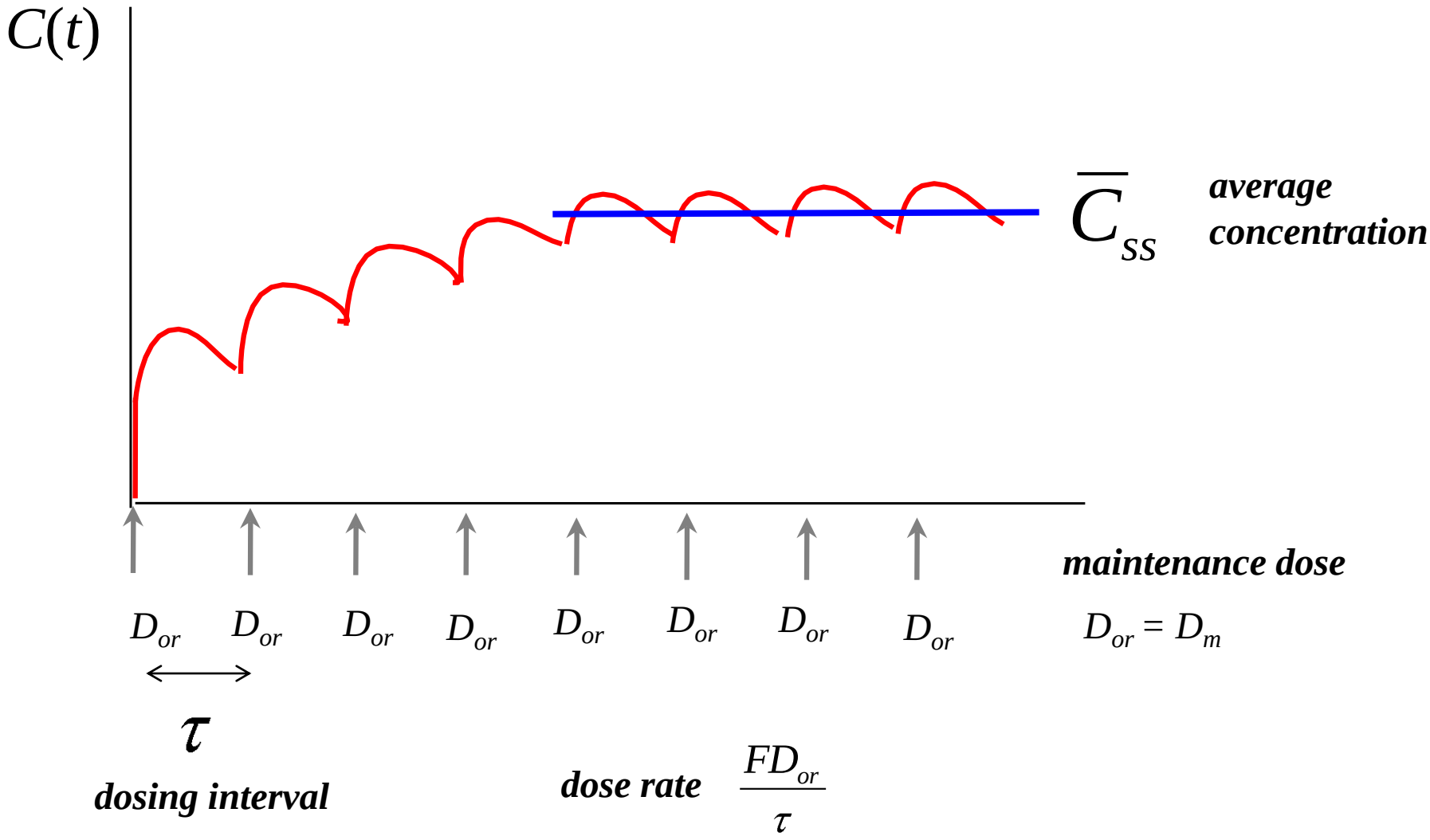


$t_{90\%}$

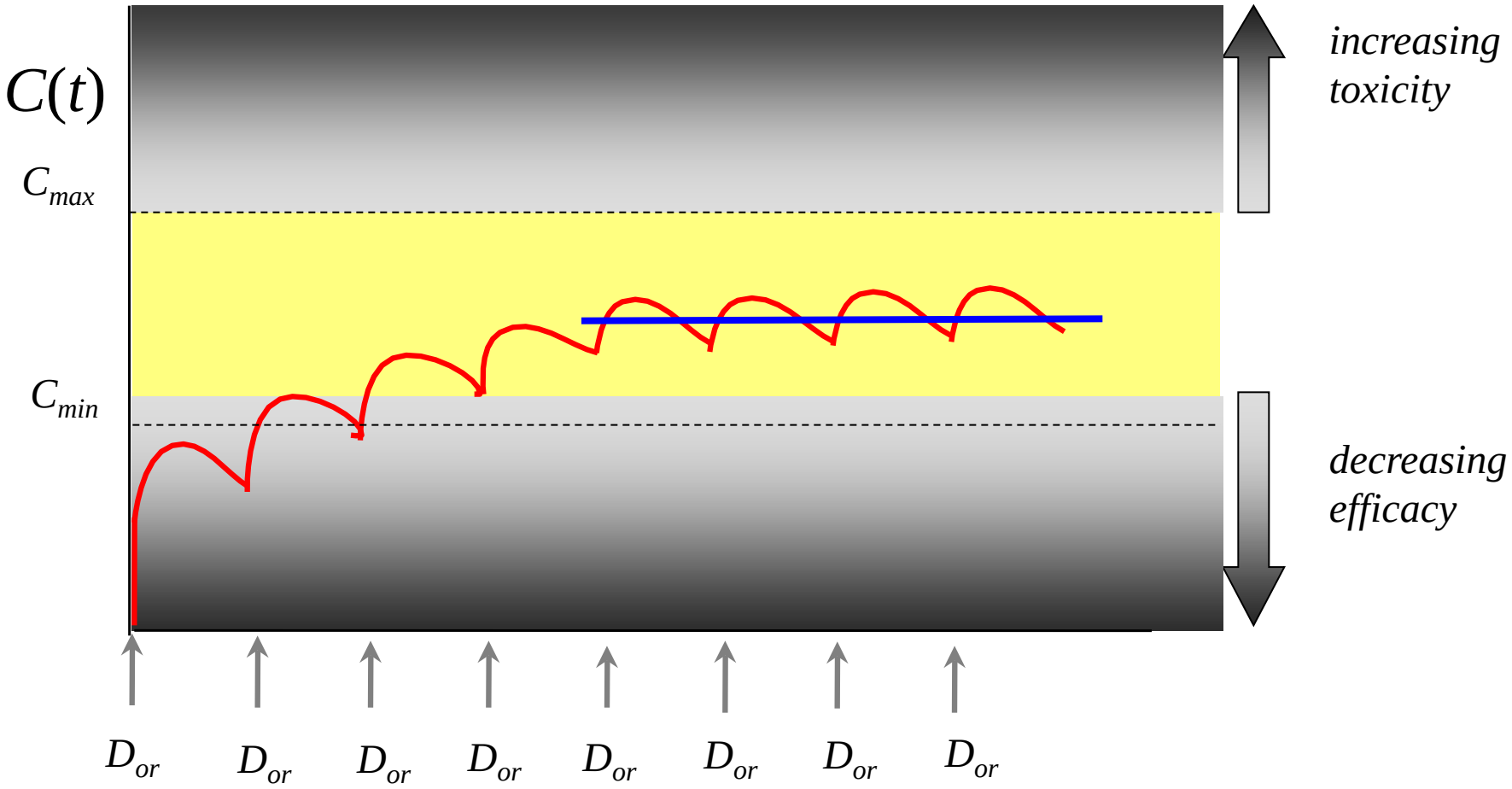
$$t_{90\%} \leq 3.7\, MDRT \qquad (15) \qquad t_{90\%} \approx 4 t_{1/2}$$

Weiss, J Pharmacokin Biopharm, 1986

Multiple Dosing

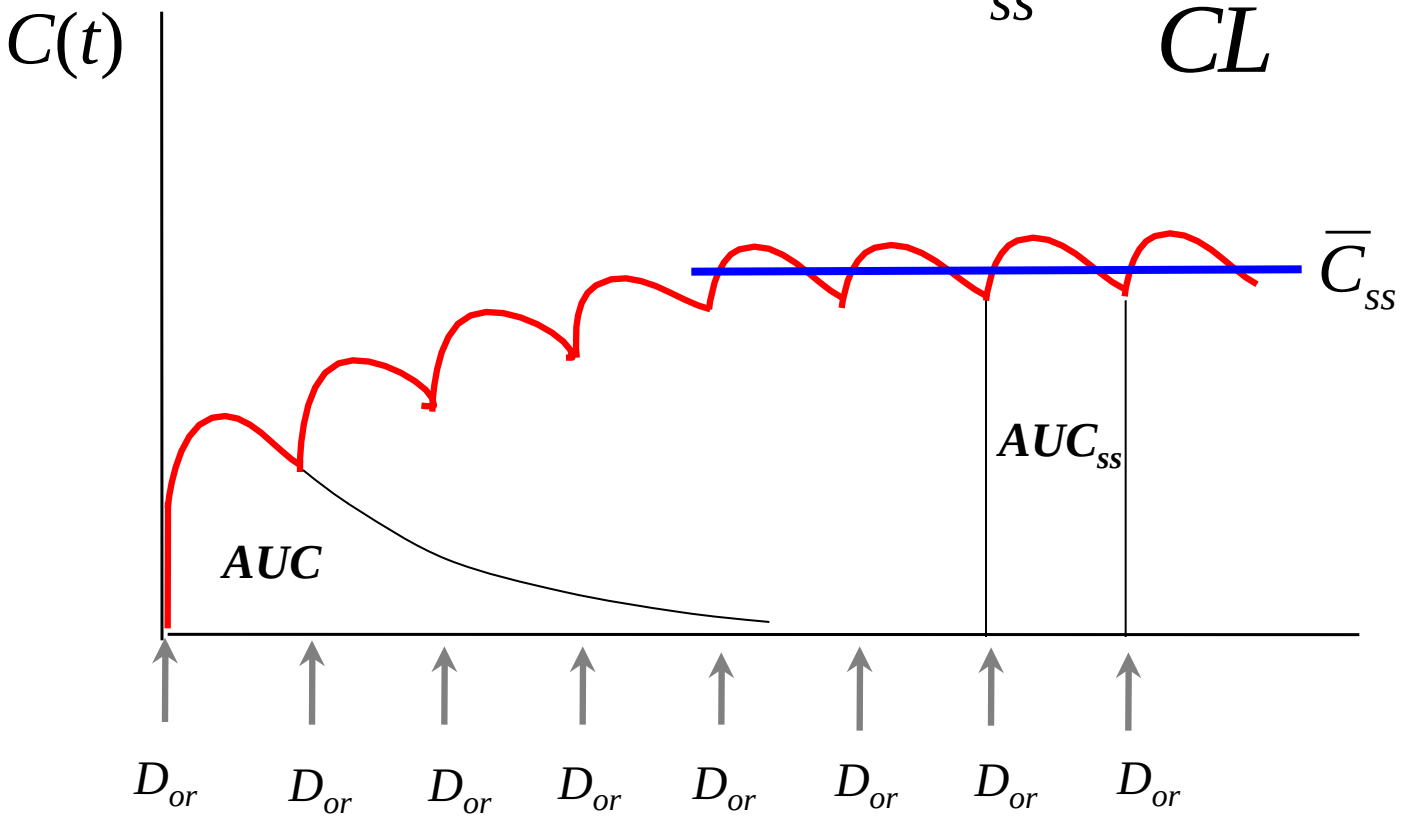


Therapeutic Drug Monitoring (TDM)



$$AUC_{ss} = AUC$$

$$\overline{C}_{ss} = \frac{DR}{CL} = \frac{FD_m}{CL\,\tau}$$



$$\frac{\text{amount in body at steady state}}{\text{maintenance dose}} = \frac{MDRT}{\tau}$$

Basic Pharmacokinetic Parameters

- ***CL*** *determines maintenance dose* D_m
- ***V*** *determines loading dose* D_L
- ***MDRT*** *determines time to steady state* $t_{90\%}$ *and dosing interval* τ

Parametric Curve Model

$$C_{iv}(t) = \sum_{i=1}^{n} B_i e^{-\lambda_i t}$$

fit to data, estimate B_i *and* λ_i $(i = 1..n)$

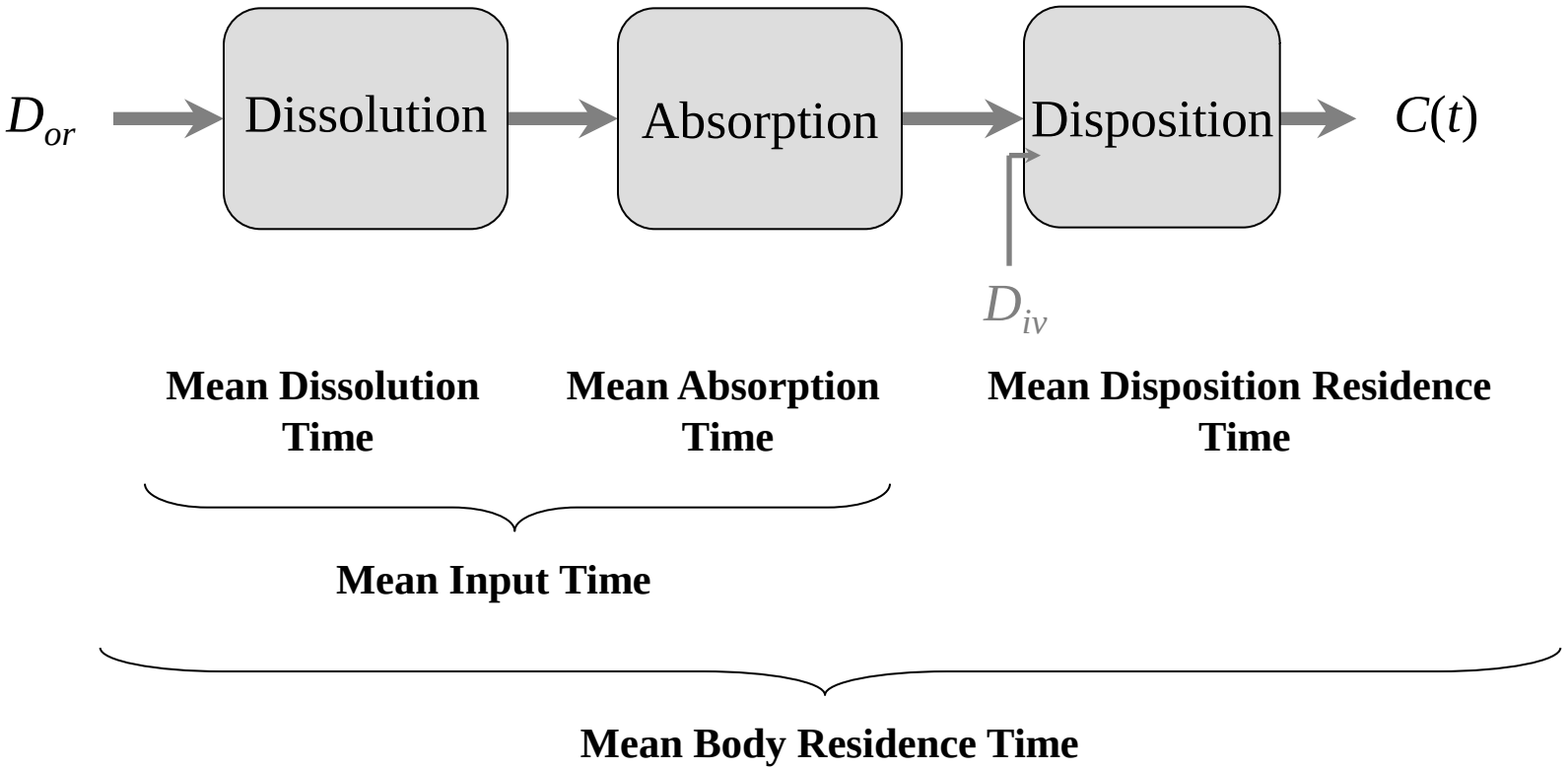
$$CL = \frac{D_{iv}}{\sum_{i=1}^{n} \frac{B_i}{\lambda_i}}$$

$$\int_0^{\infty} C(t)dt = AUC = \sum_{i=1}^{n} \frac{B_i}{\lambda_i}$$

$$MDRT = \frac{\int_0^{\infty} tC_{iv}(t)dt}{\int_0^{\infty} C_{iv}(t)dt} = \frac{AUMC_{iv}}{AUC_{iv}} = \frac{\sum_{i=1}^{n} \frac{B_i}{\lambda_i^2}}{\sum_{i=1}^{n} \frac{B_i}{\lambda_i}}$$

$$V_{ss} = CL\, MDRT$$

Mean Residence Time after Oral and Intravenous Administration



$$MBRT = MDT + MAT + MDRT$$

Mean Disposition Residence Time *MDRT*

$$MDRT = \frac{\int_0^\infty tC_{iv}(t)dt}{\int_0^\infty C_{iv}(t)dt} = \frac{AUMC_{iv}}{AUC_{iv}}$$

Mean Body Residence Time *MBRT*

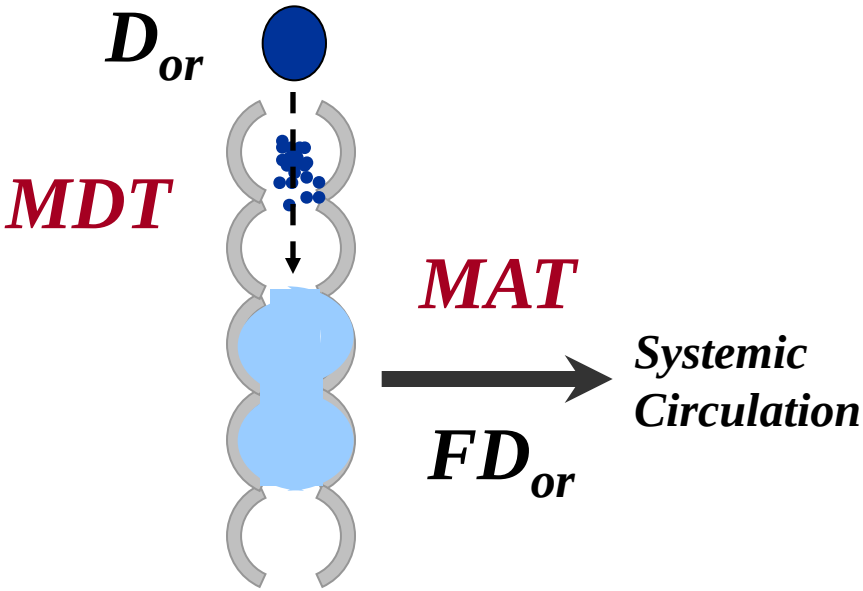
$$MBRT = \frac{\int_0^\infty tC_{or}(t)dt}{\int_0^\infty C_{or}(t)dt} = \frac{AUMC_{or}}{AUC_{or}}$$

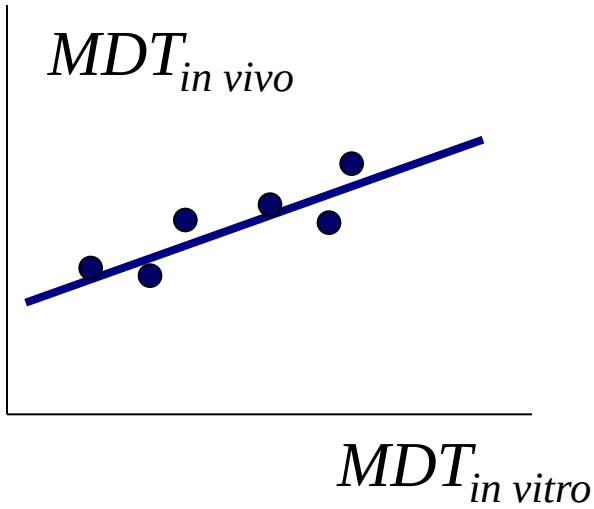
Oral Administration

Mean Input Time $MIT = MDT + MAT$

Dissolution $MDT = MBRT_{Tablet} - MBRT_{Solution}$

Absorption $MAT = MBRT_{Solution} - MDRT$

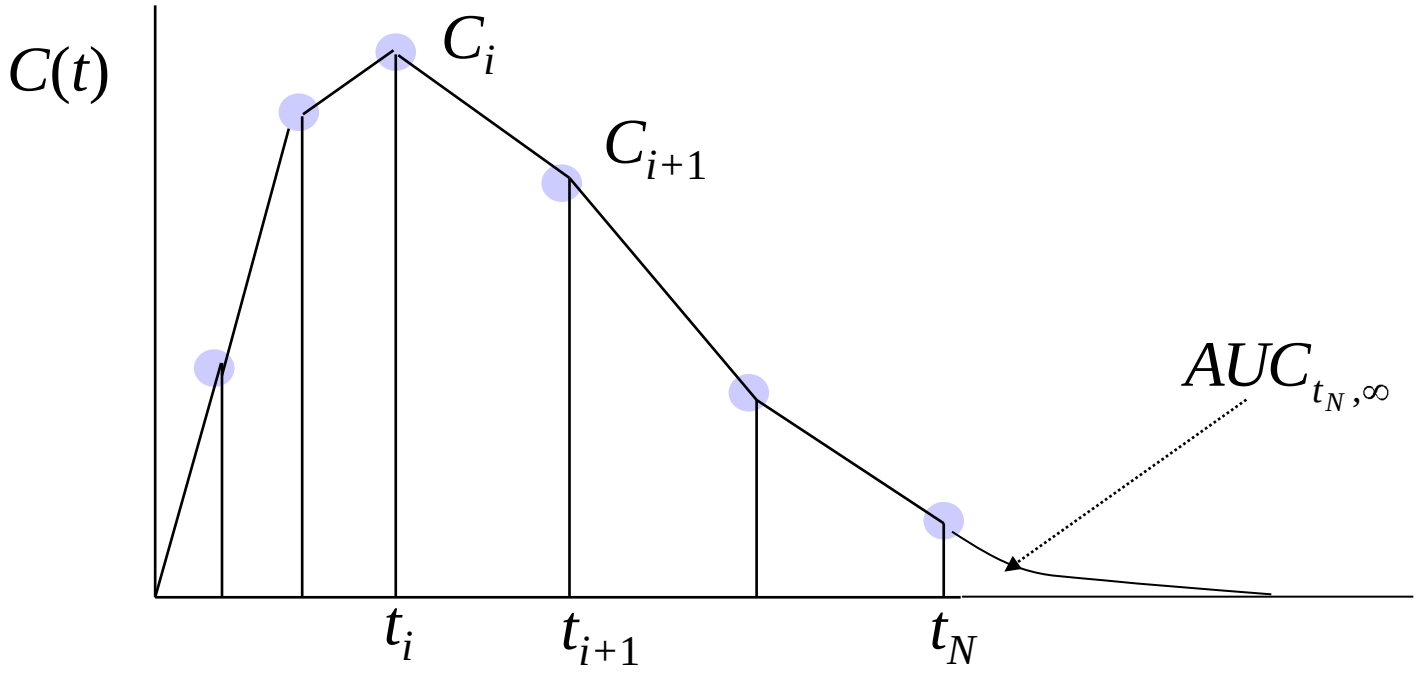




C(t) after extravascular (oral) administration

$$\int_0^\infty C(t)dt = AUC \qquad \text{and} \qquad \int_0^\infty tC(t)dt = AUMC$$

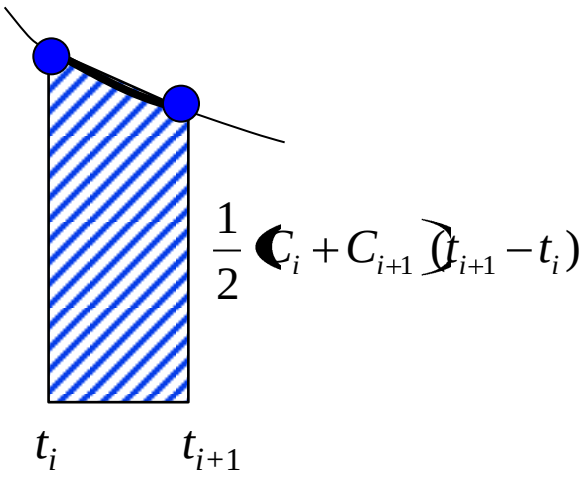
by numerical integration **Trapezoidal rule**



Trapezoidal rule

$$AUC = \sum_{i=1}^{N-1} \frac{1}{2}\left(C_i + C_{i+1}\right)\left(t_{i+1} - t_i\right) + \frac{C_N}{\lambda_z}$$

$$= AUC_{0,t_N} + AUC_{t_N,\infty}$$

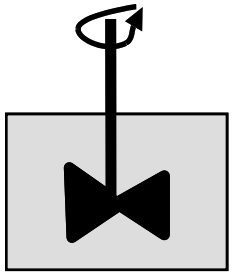


$$AUMC = \sum_{i=1}^{N-1} \frac{1}{2}\left(t_i C_i + t_{i+1} C_{i+1}\right)\left(t_{i+1} - t_i\right) + C_N\left(\frac{t_N}{\lambda_z} + \frac{1}{\lambda_z^2}\right)$$

$$= AUMC_{0,t_N} + AUMC_{t_N,\infty}$$

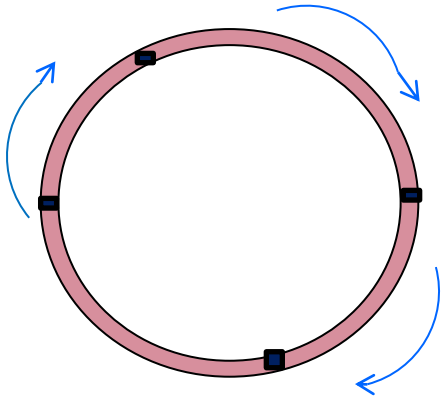
How to describe mixing/distribution kinetics ?

Steady-state → transient state

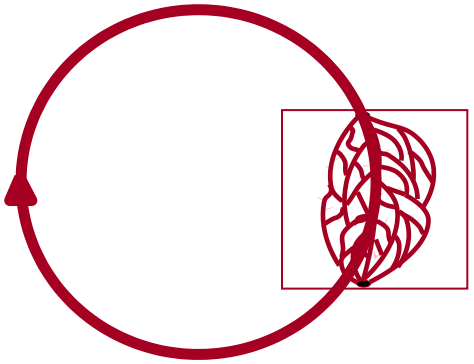


Reactor:

Turbulent mixing

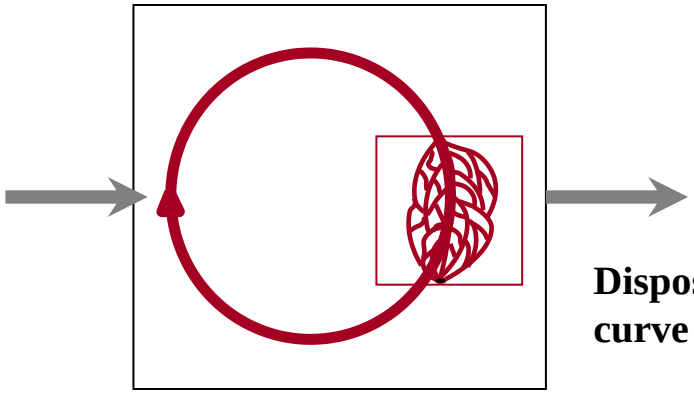


Circulation without dispersion:
no mixing



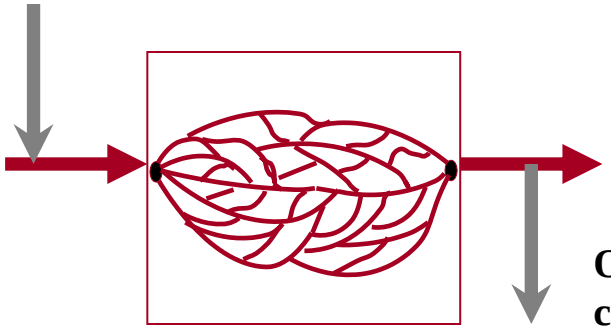
Transit time dispersion
in microcirculatory network:
mixing

Residence time sytem



Disposition curve

Transit time sytem



Outflow curve

Mean transit time ⇨ **Extent of distribution**

Transit time dispersion ⇨ **Rate of distribution**

Relative Dispersion of Disposition Residence Time Distribution

Normalized (dimensionless) variance

$$RD_D^2 = \frac{VDRT}{MDRT^2}$$

$$C_{iv}(t) = \sum_{i=1}^{n} B_i e^{-\lambda_i t}$$

$$m_j = \int_0^{\infty} t^j C(t) dt = j! \sum_{i=1}^{n} \frac{B_i}{\lambda_i^{j+1}}$$

$$VDRT = \frac{m_2}{m_0} - \left(\frac{m_1}{m_0} \right)^2$$

$$MDRT = \frac{m_1}{m_0}$$

Rate of Distribution: Mixing Clearance

Closed (noneliminating) system ($CL = 0$)

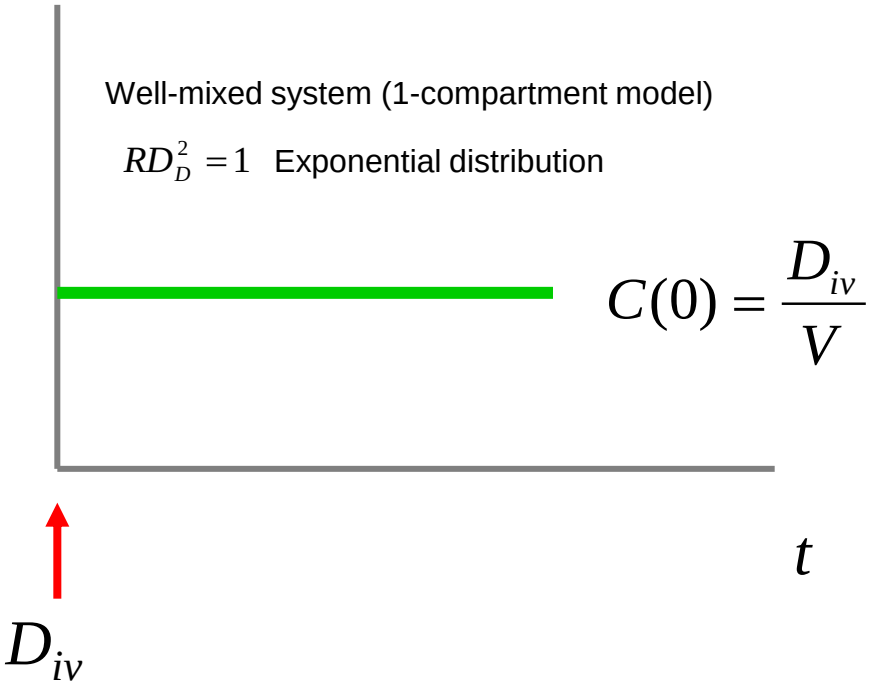
$$V_0 \frac{dC(t)}{dt} = -CL_M \left[C(t) - C(\infty) \right]$$

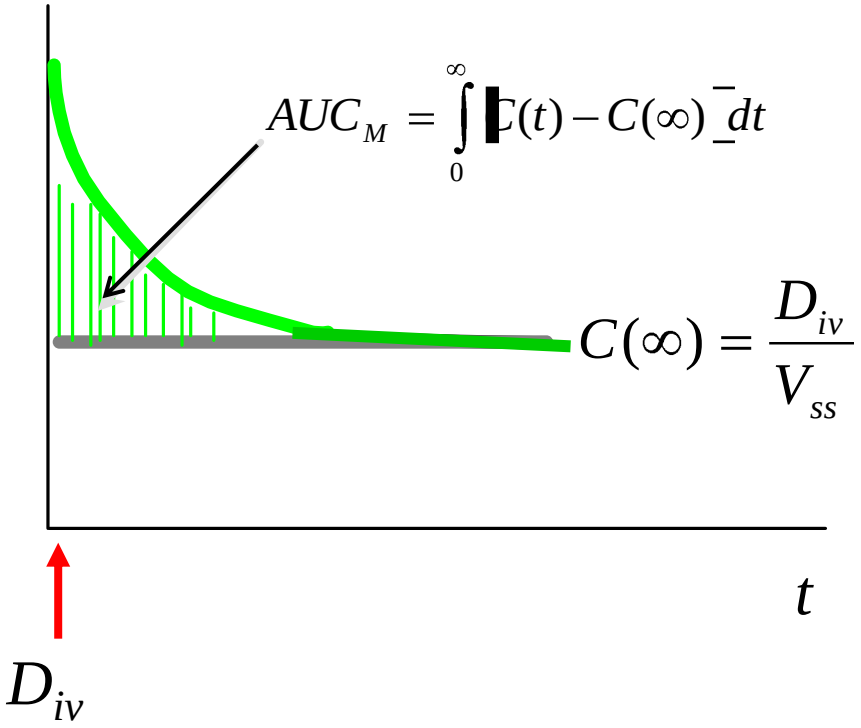
$$\frac{AUC_M}{AUC} = \frac{1}{2}(1 - RD_D^2)$$

$$CL_M = \frac{D_{iv}}{AUC_M} = \frac{2CL}{1 - RD_D^2}$$

Well-mixed system (1-compartment model)

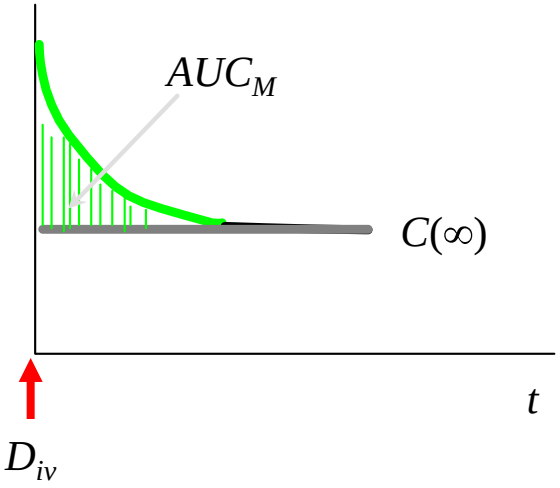
$RD_D^2 = 1$ Exponential distribution

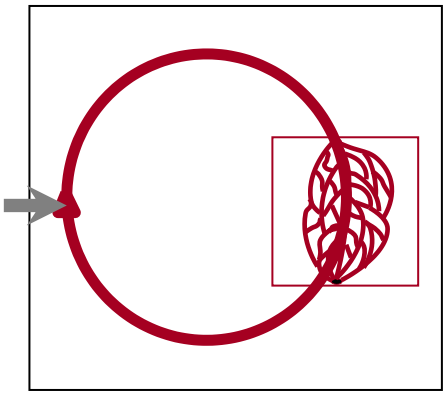




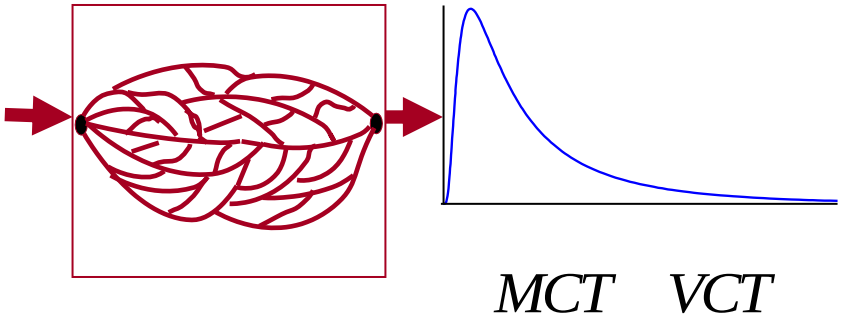
Weiss, Pharm Res , 2007

AUC_M: Circulatory Transit Time





Closed (noneliminating) system ($CL = 0$)



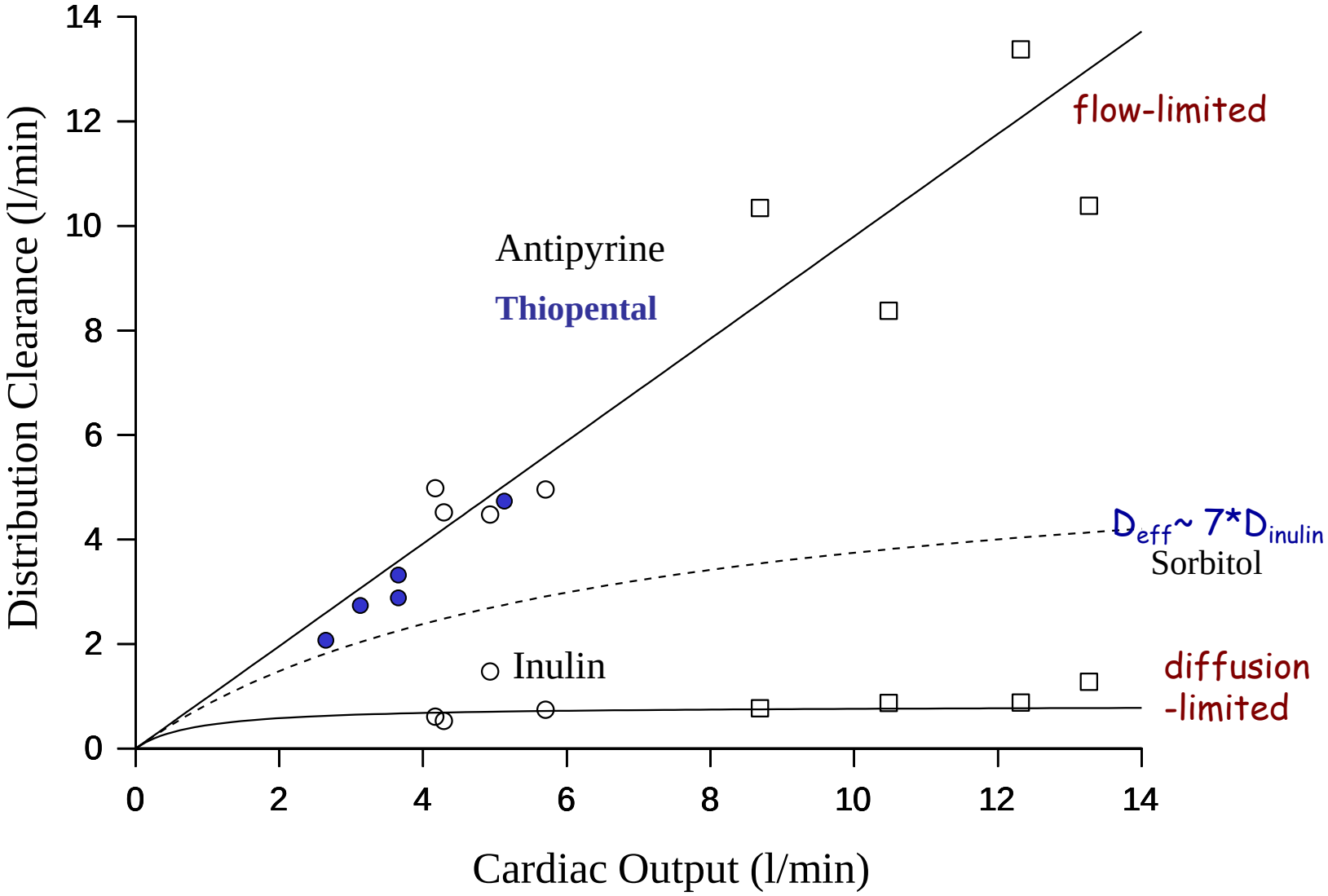
$$AUC_M = \frac{D_{iv}}{Q}\frac{1}{2}(RD_c^2 - 1)$$

$$RD_D^2 - 1 = \frac{CL}{Q}(RD_c^2 - 1)$$

Weiss & Pang, J Pharmacokin Biopharm, 1992

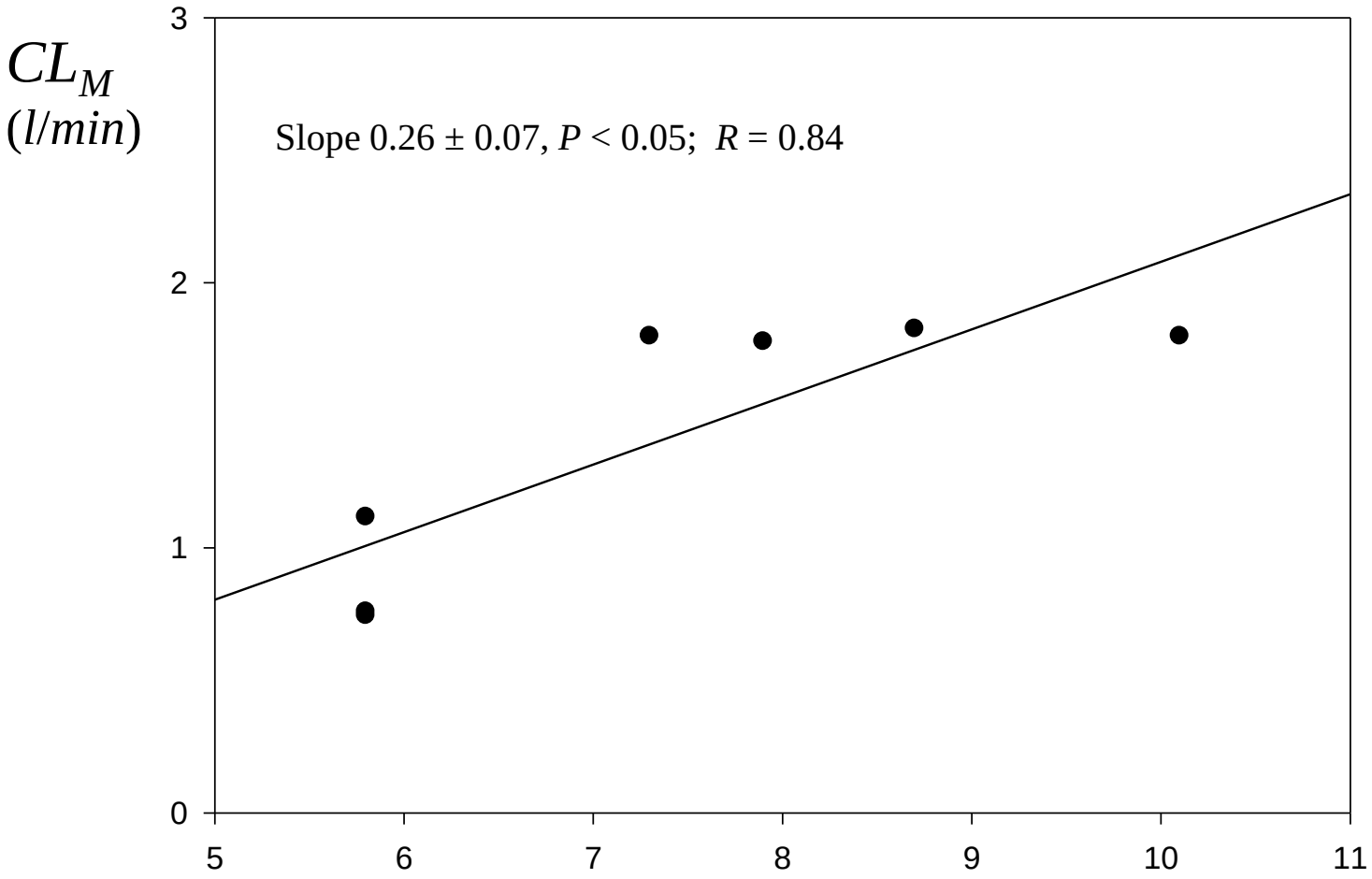
From Flow-to Diffusion-Limited Distribution Kinetics

A Continuous Transition



Weiss et al, Pharm Sci, 2007

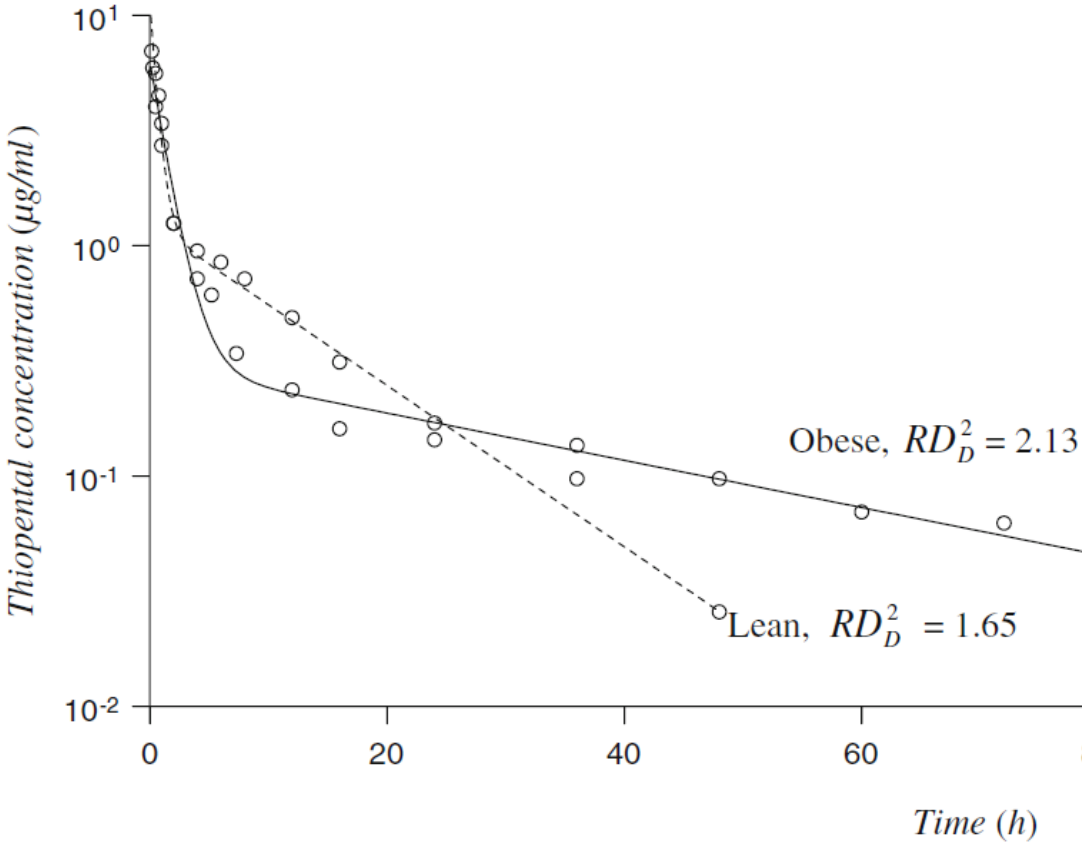
Distribution Kinetics of Alfentanil

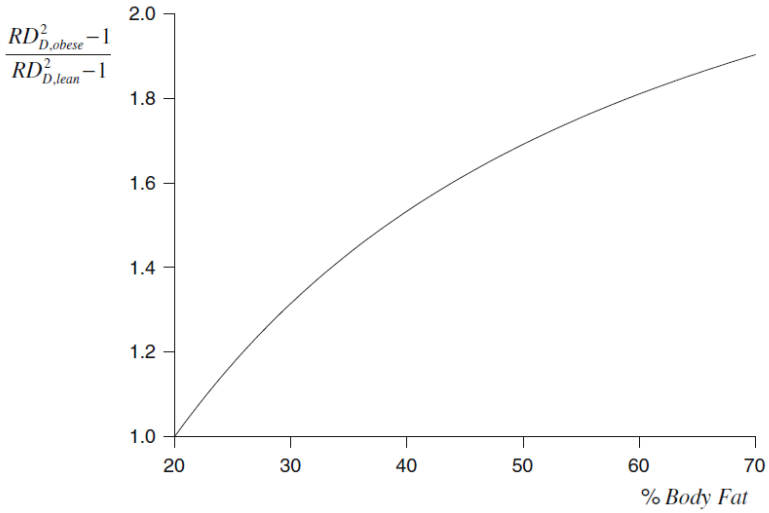


$$C_{iv}(t) = \sum_{i=1}^{4} B_i e^{-\lambda_i t} \qquad m_j = j! \sum_{i=1}^{4} \frac{B_i}{\lambda_i^{j+1}}$$

Data from: Henthorn et al., Clin Pharmacol Ther, 1992

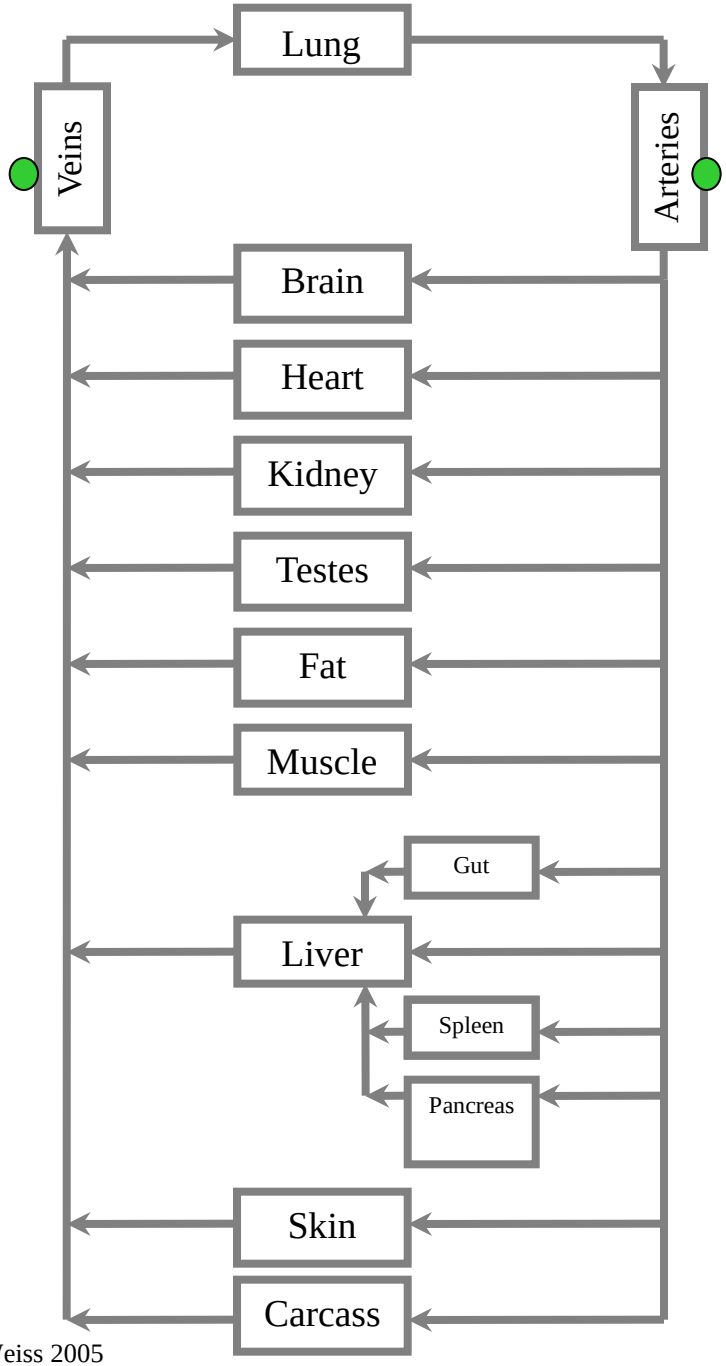
Thiopental: heterogeneity of residence time distribution increases with obesity

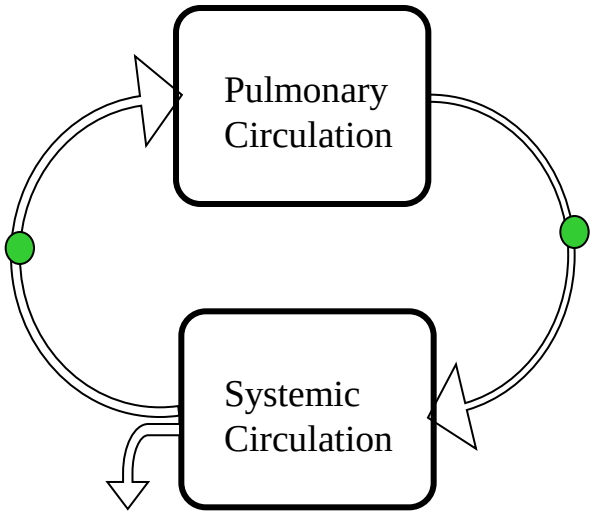




Weiss , Pharmacokin Pharmacodyn, 2008

Minimal Circulatory PK Model





Heterogeneous subsystems
Transit time distributions

Less than 0.1% of PK models used in literature are circulatory models

Why are they relevant?

1) Description of initial mixing kinetics (2 min after bolus injection)

Front-end kinetics of short acting iv anesthetics

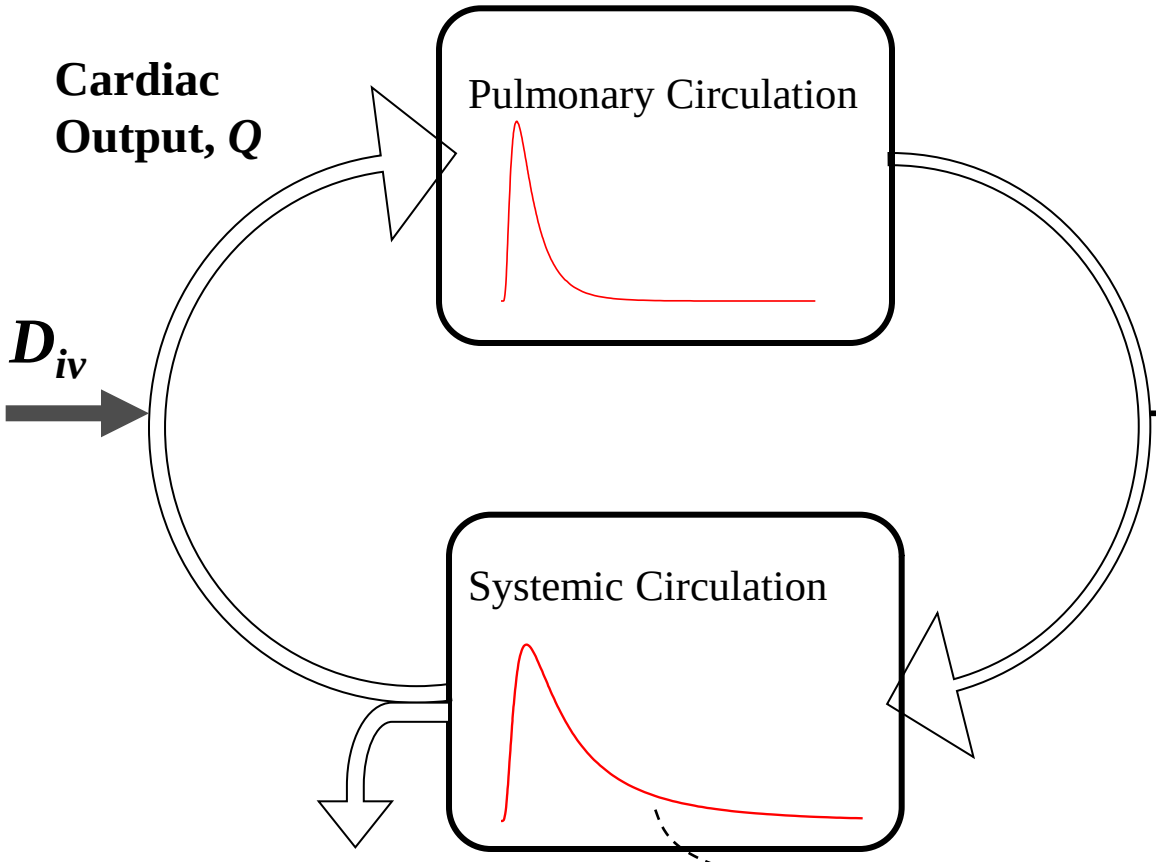
2) First-principles modeling of distribution kinetics

Role of cardiac output, convective dispersion and intratissue diffusion (*ICG*, *inulin*, *antipyrine*, *thiopental*, *rocuronium*)

Modeling of slow tissue binding (*digoxin*)

Use of the multiple indicator approach in parameter estimation

Circulatory minimal model



$$f_{IG}(t) = \sqrt{\frac{MTT}{2\pi RD\, t^3}} \exp\left[-\frac{(t-MTT)^2}{2RD\,MTT\,t}\right]$$

Weiss et al., Br J Clin Pharmacol ,1996

Recirculatory PK Model

$$\hat{f}_{circ}(s) = \frac{\hat{f}_p(s)}{1-(1-E)\,\hat{f}_s(s)\,\hat{f}_p(s)}$$

$$E = \frac{CL}{Q}$$

Extraction (probability of elimination in one passage through systemic circulation)

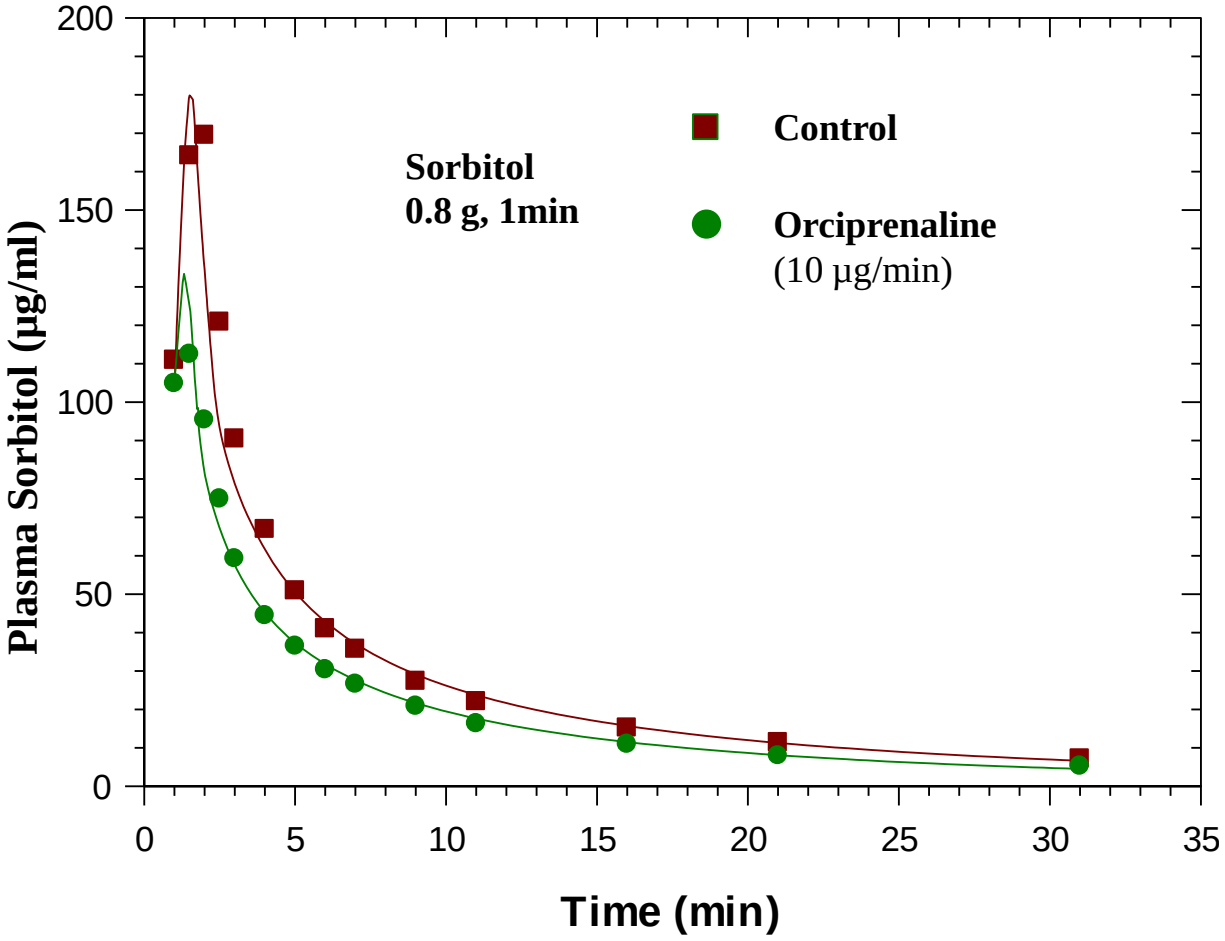
Numerical inverse Laplace Transformation

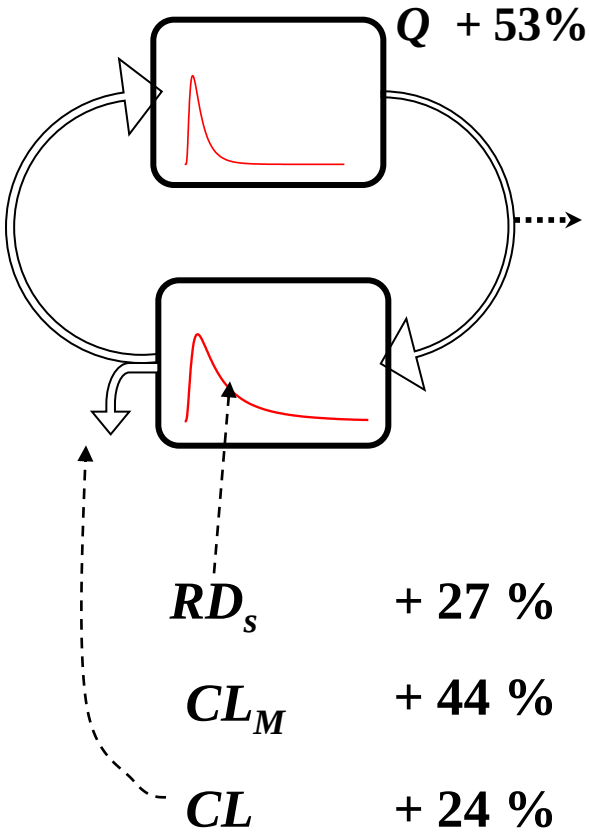
Schalla & Weiss, Eur J Pharm Sci, 1999

$$C(t) = L^{-1}\left\{\frac{D}{Q}\,\hat{f}_{circ}(s)\right\}$$

Hemodynamic Influences on Sorbitol Kinetics in Humans

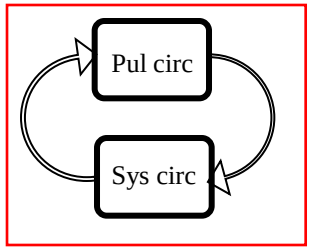
Inverse Gaussian Transit Time Density





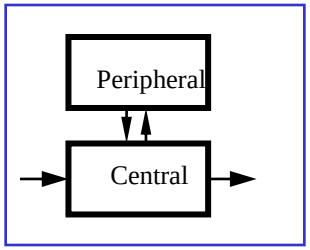
Weiss et al., Br J Clin Pharmacol,1996

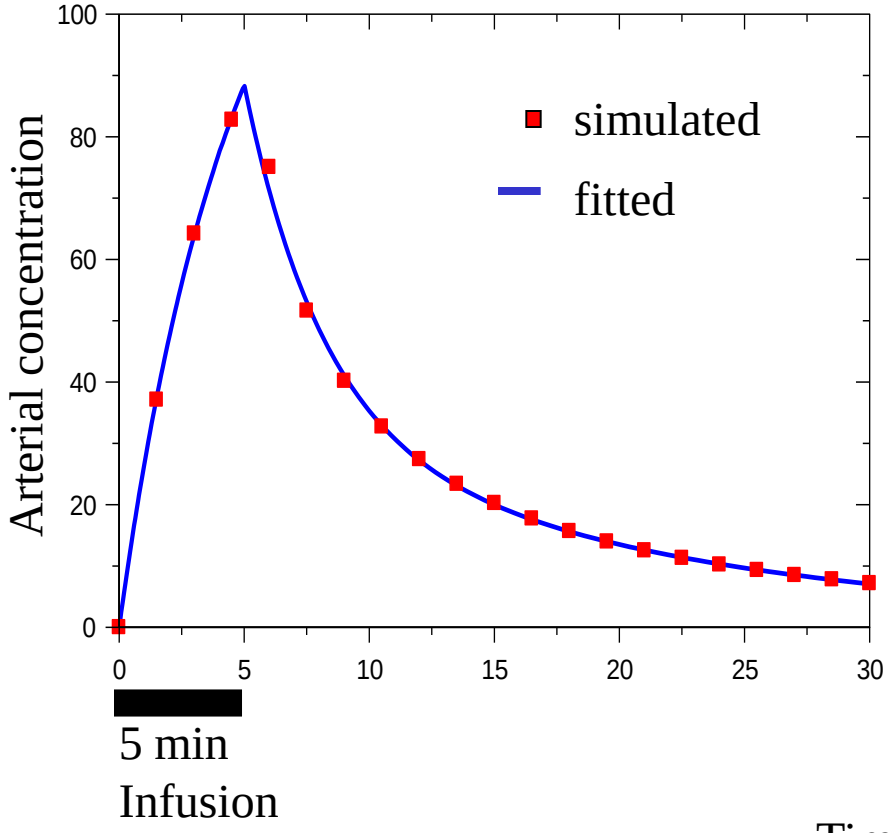
Physiological
(recirculatory)

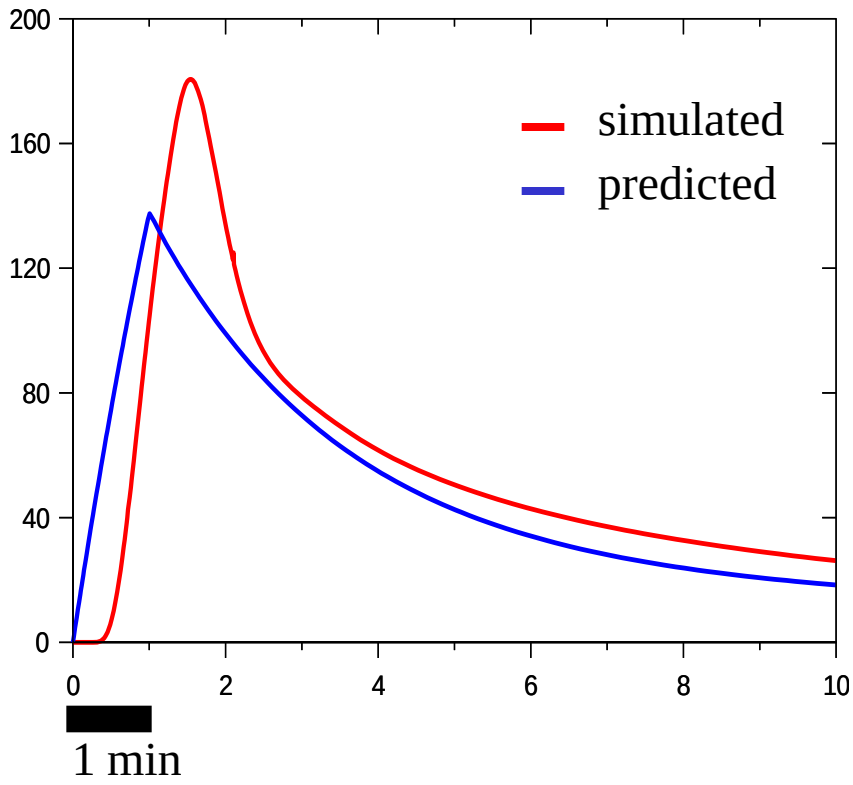


vs.

Compartmental
(biexponential)

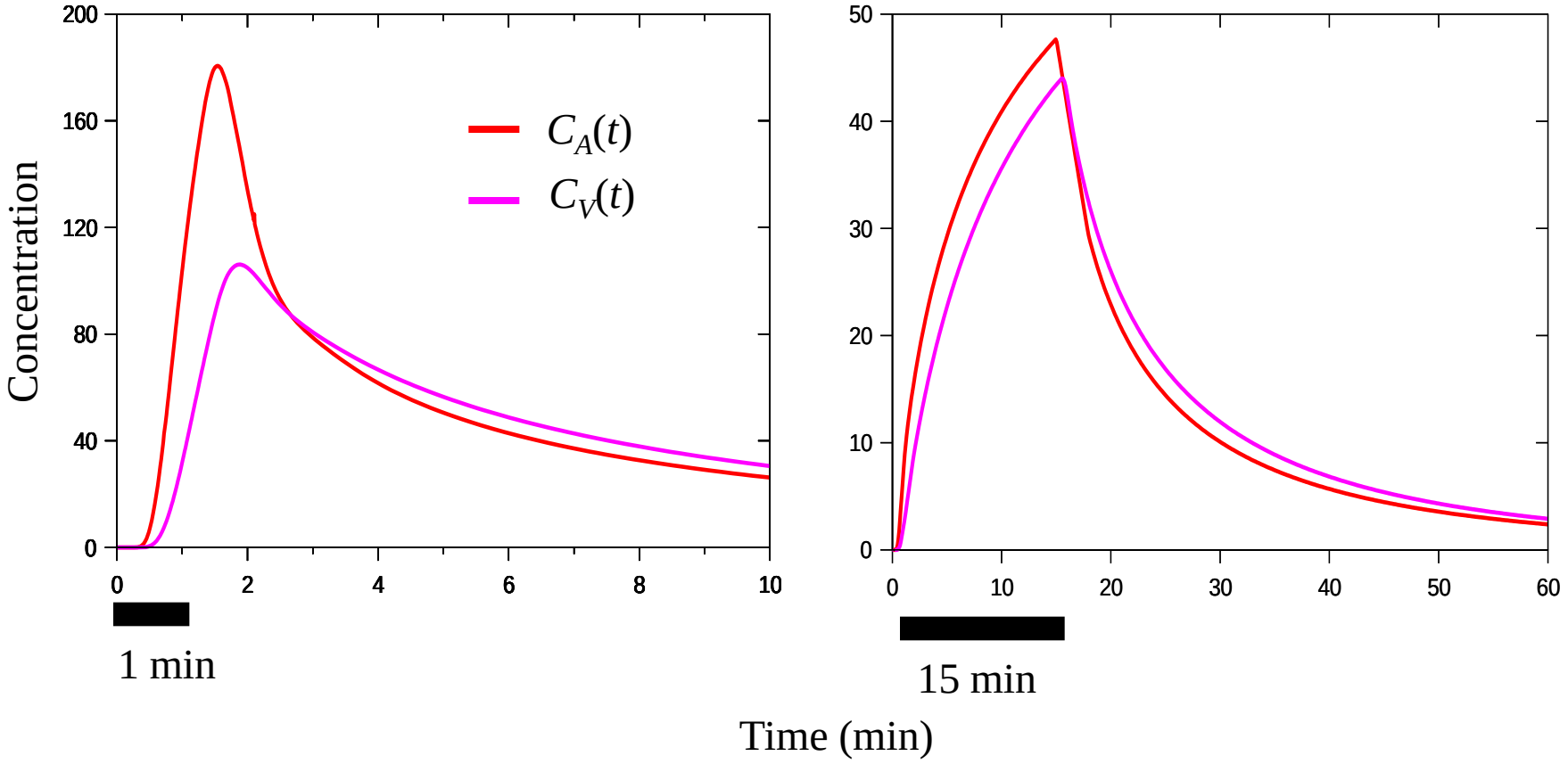




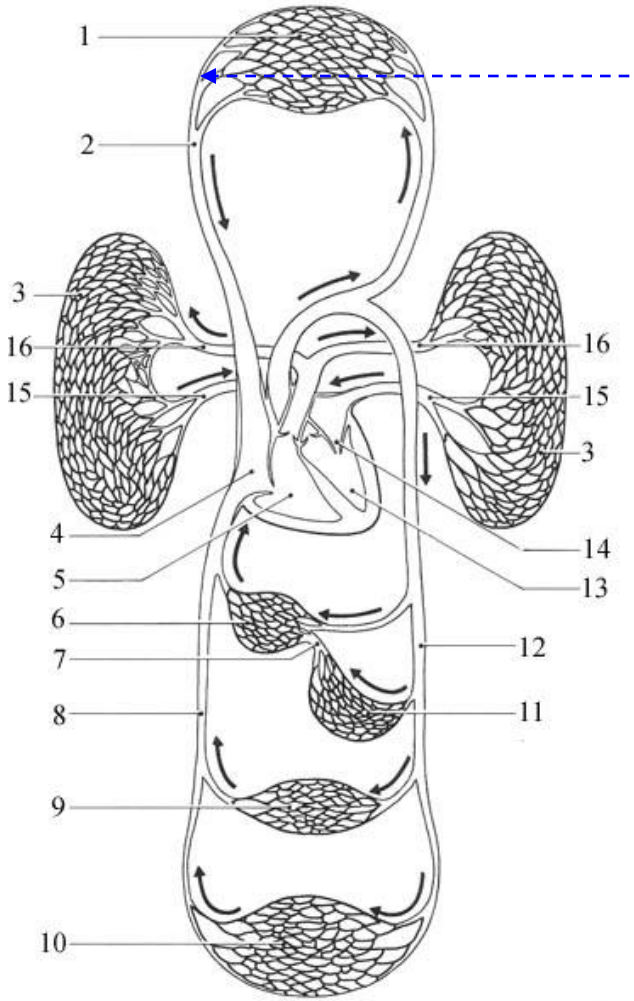


Time (min)

Arterial vs. peripheral venous sampling

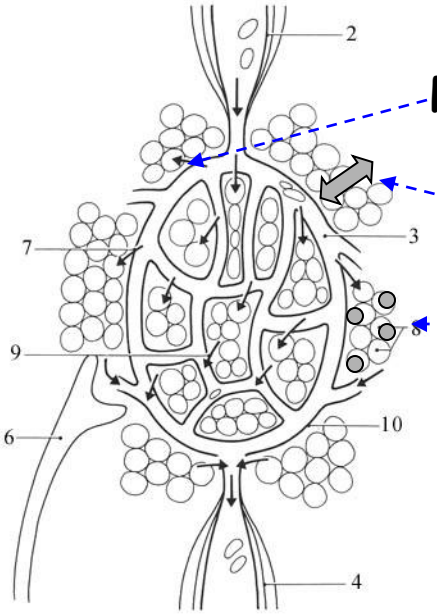


First-principles modeling of distribution kinetics



Advective transport

Advective dispersion → Vascular mixing



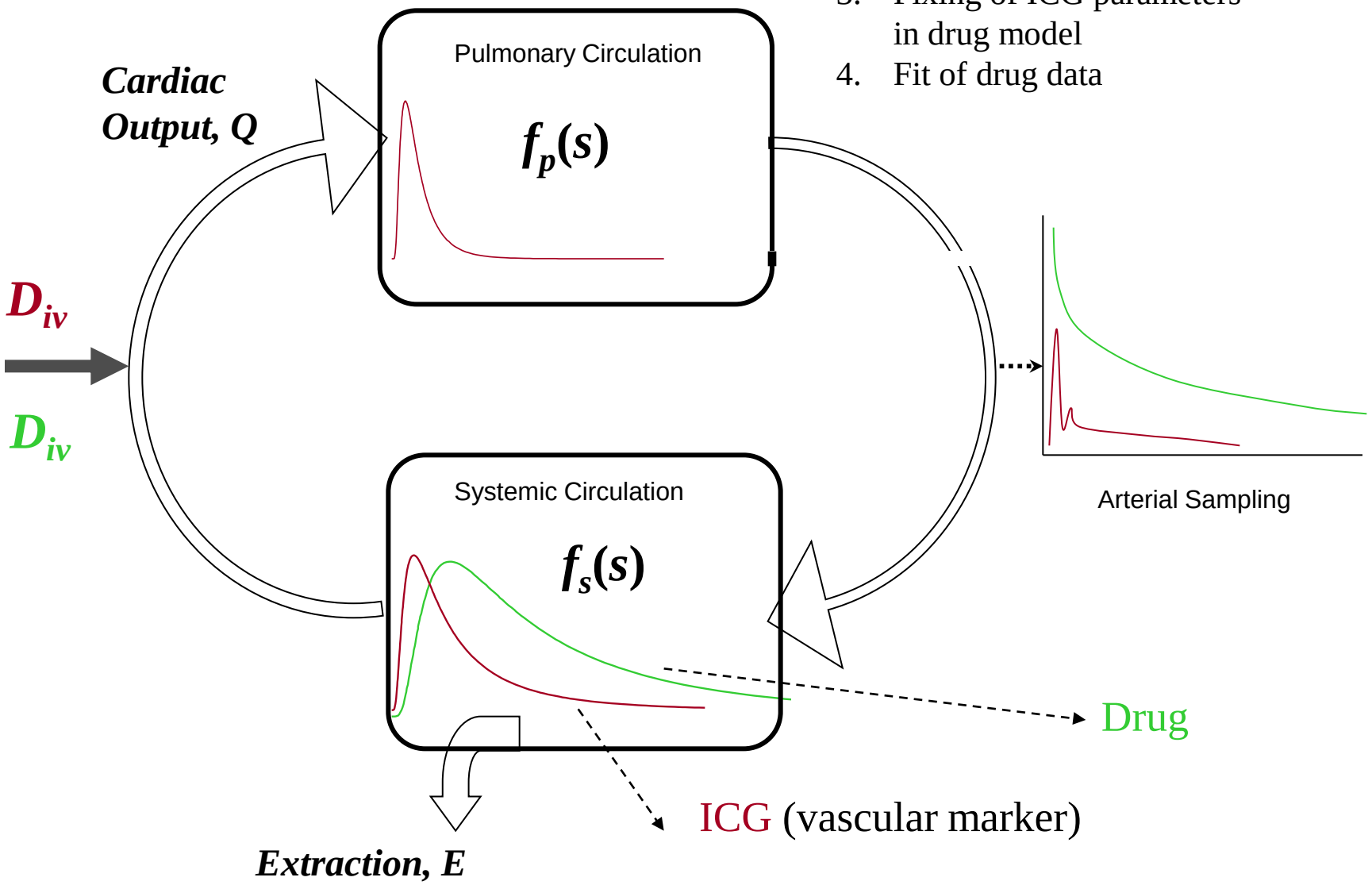
Permeation (Capillary uptake)

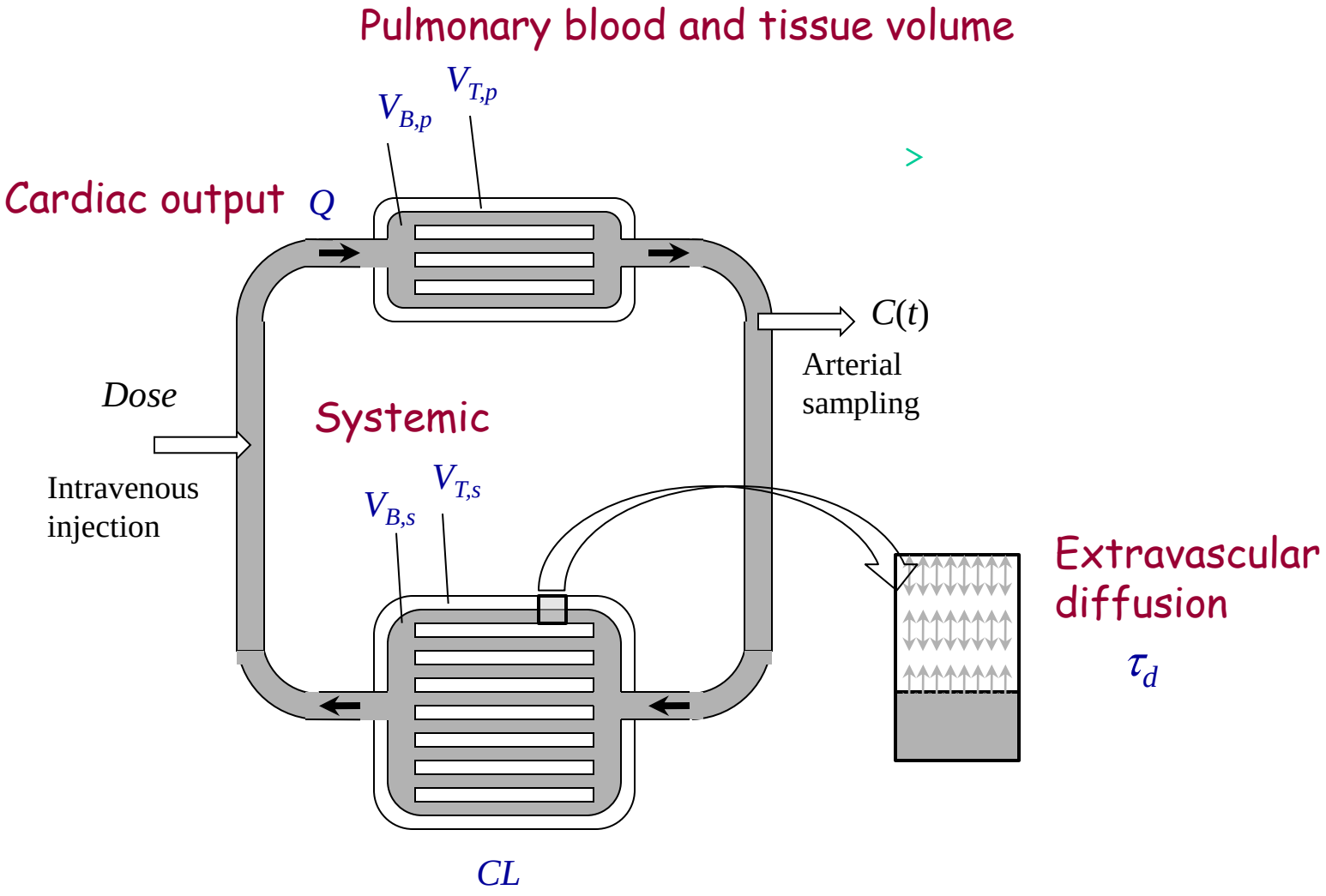
Diffusion (Extravascular)

Tissue Binding

Drug+vascular marker (ICG)

1. Simultaneous injection, ICG+drug
2. Fit of ICG data (IG model)
3. Fixing of ICG parameters in drug model
4. Fit of drug data

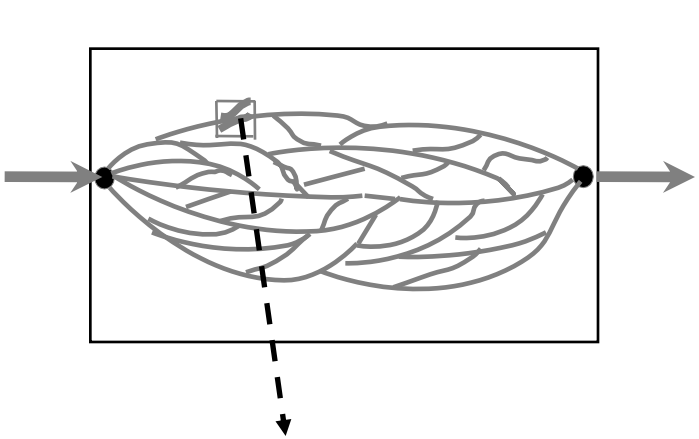



Pulmonary blood and tissue volume
$V_{T,p}$
$V_{B,p}$
Cardiac output Q
$C(t)$
Arterial sampling
Dose
Intravenous injection
Systemic
$V_{T,s}$
$V_{B,s}$
Extravascular diffusion
τ_d
CL

Systemic circulation: Advection-diffusion model

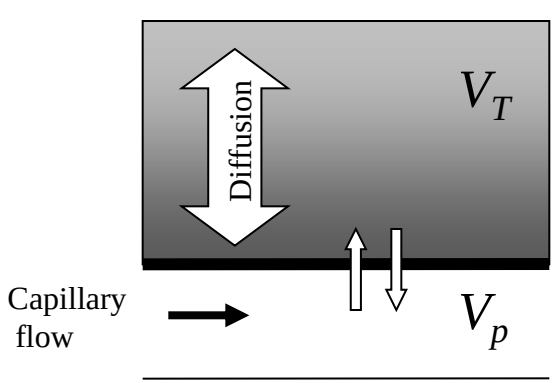
Stochastic model of transit time distribution

Microcirculatory network



Intravascular mixing (vascular marker)

Microscopic volume element

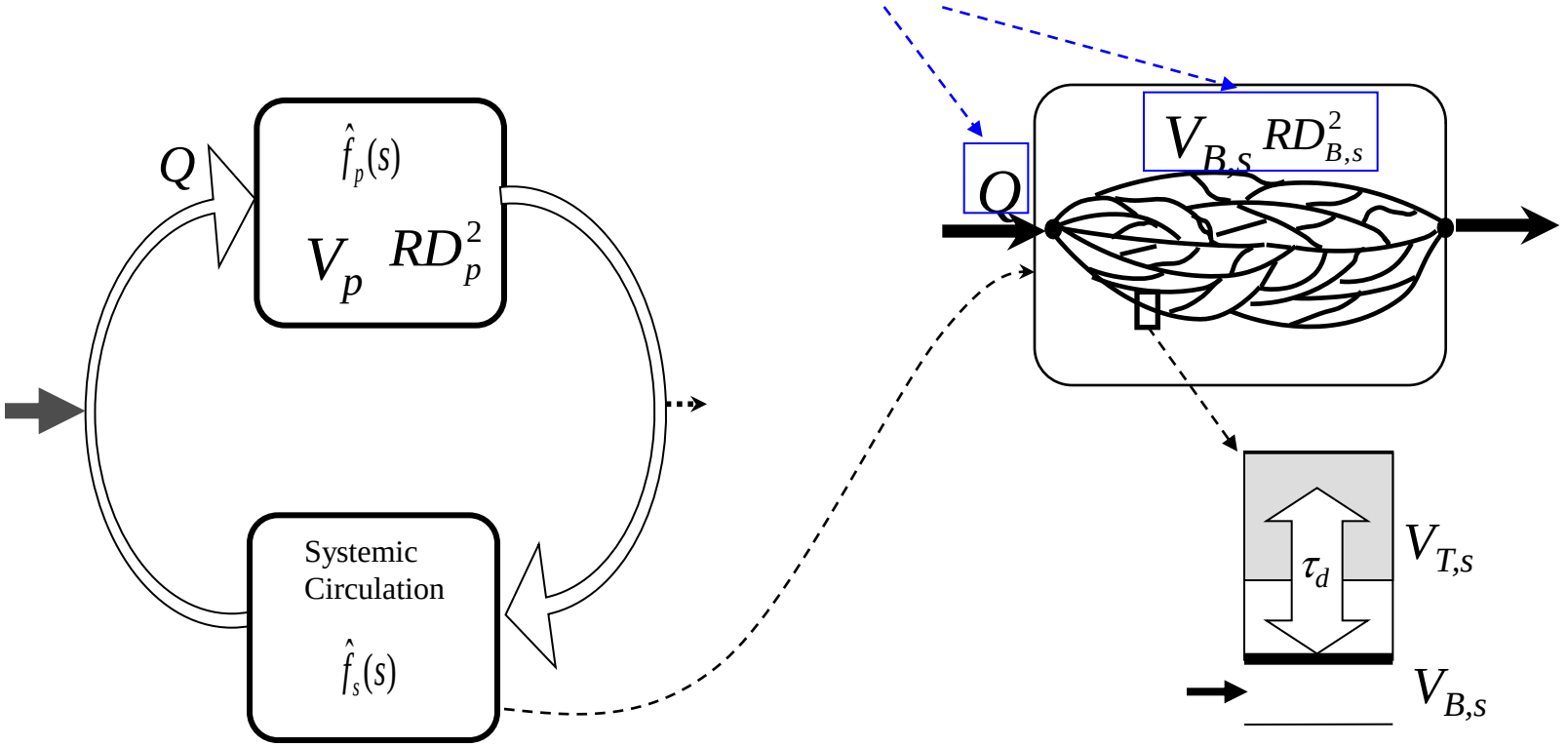


Tissue distribution

Weiss & Roberts, J Pharmacokin Biopharm, 1996

Extravascular Diffusion Kinetics

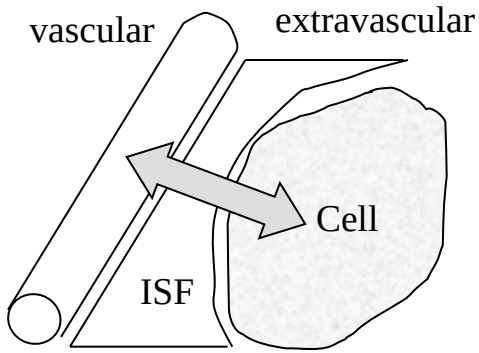
Rocuronium (+ICG as vascular marker)



$$\nu = \frac{V_T}{V_B}$$

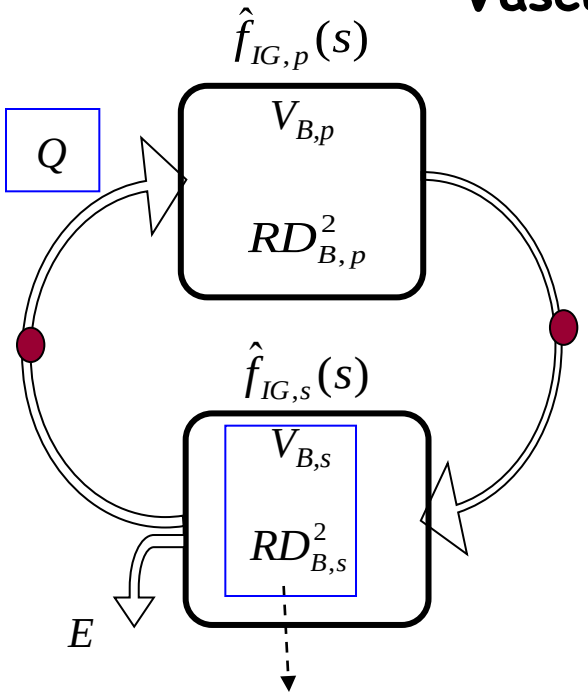
$$\tau_d = \frac{L^2}{D_{eff}}$$

$$\hat{f}_s(s) = \hat{f}_{IG}\left(s + \frac{\nu_s}{\tau_d}\sqrt{\tau_d s}\tanh\sqrt{\tau_d s} \right)$$

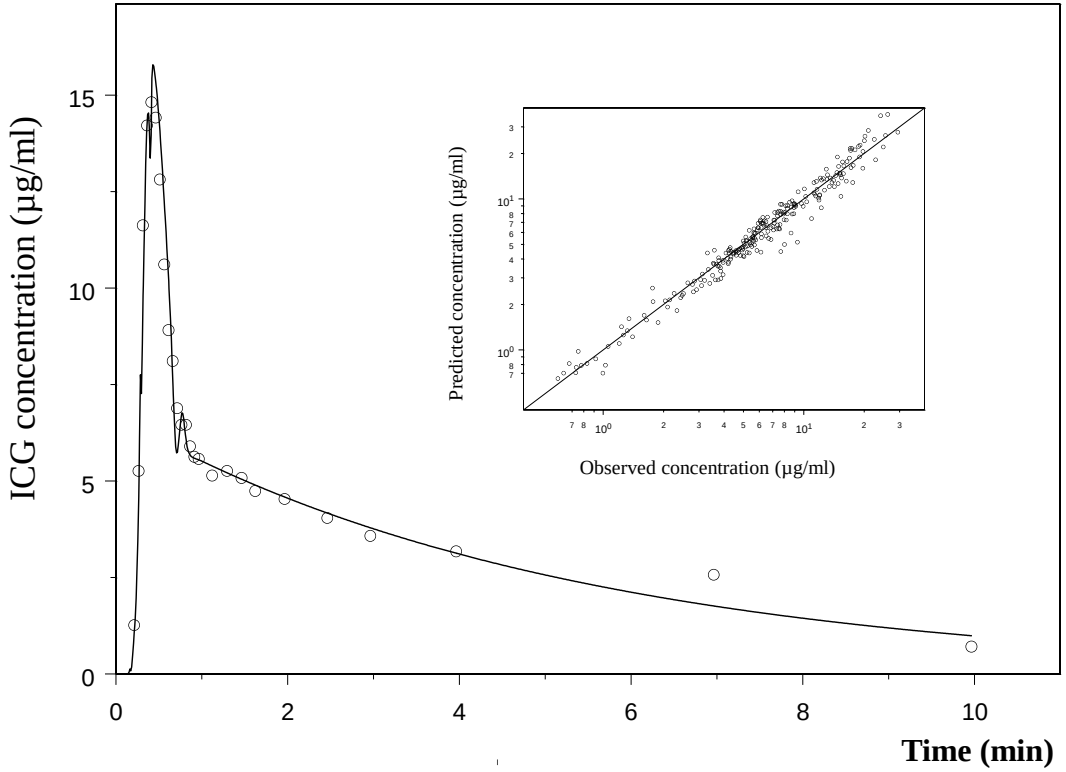


Vascular Mixing Kinetics

Vascular Marker (ICG) in Patient



Relative dispersion
-> Intravascular mixing

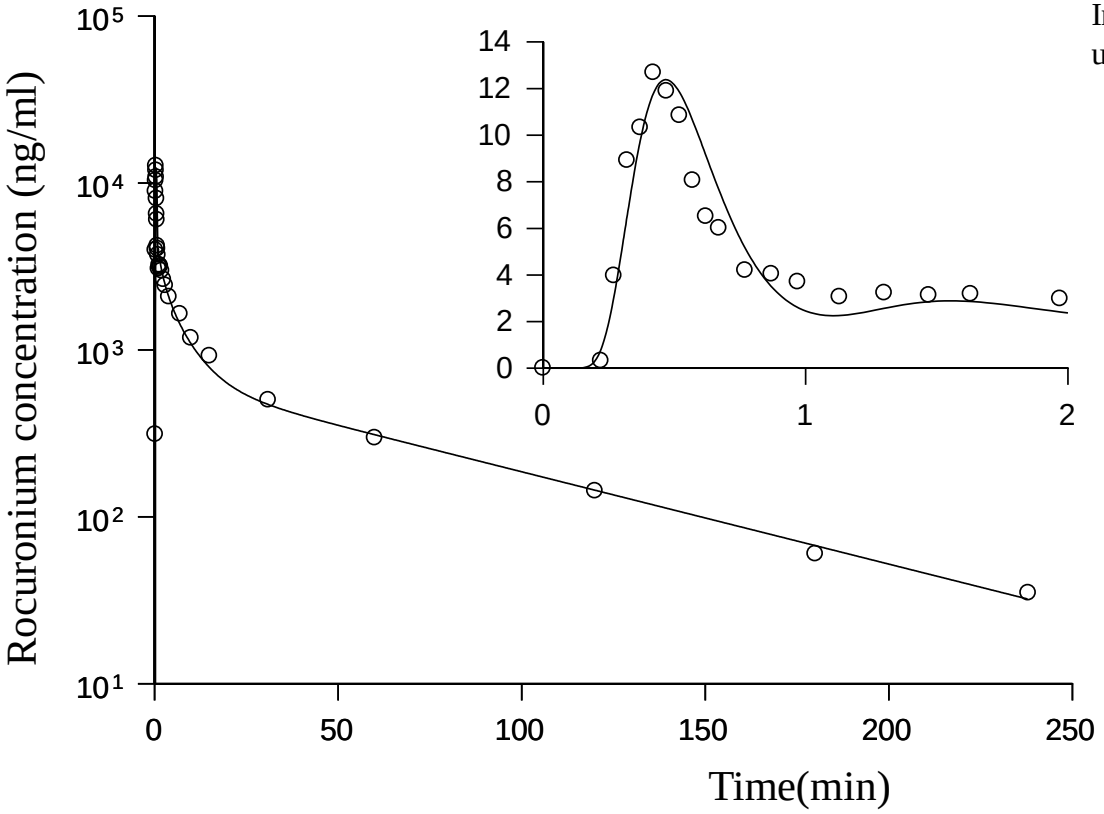


		Population Mean	Interpatient CV(%)
Cardiac output	Q (L/min)	3.52	20
Pulmonary circulation	$RD^2_{B,p}$	0.09	12
Systemic circulation	$RD^2_{B,s}$	0.37	21

TT dispersion

Weiss et al.,
J Pharmacokin
Pharmacodyn, 2011

Rocuronium Kinetcs in Patients

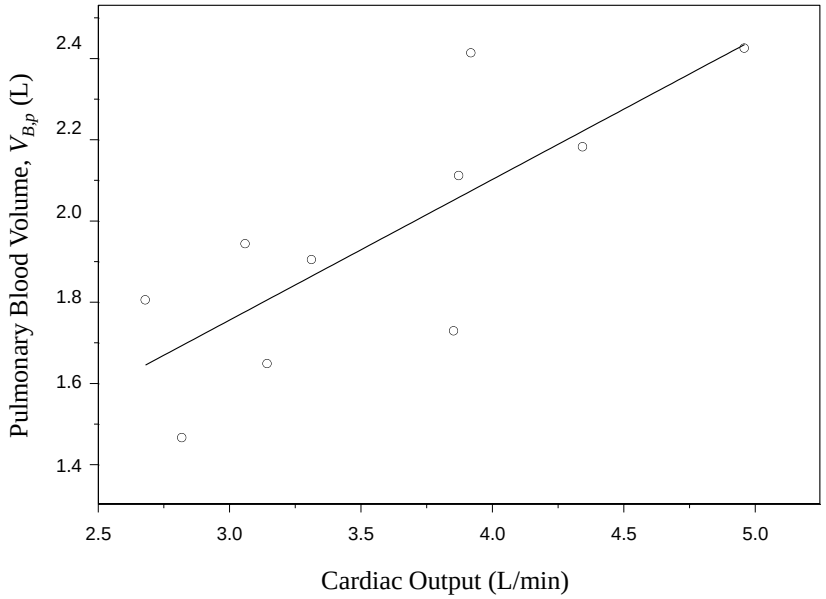


Individual estimates of ICG parameters were used as fixed parameters in fitting rocuronium data.

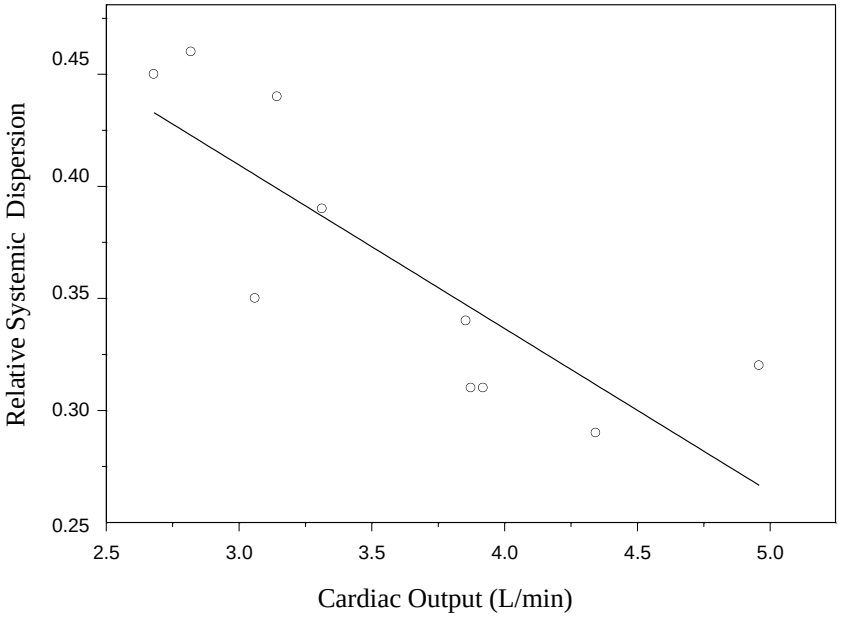
Distribution kinetics of rocuronium

		Population Mean (%RSE)	Interpatient %CV (%RSE)
Interstitial diffusion, time constant	τ_d (min)	89 (37)	50(62)
Interstitial volumes	$V_{T,p}$ (L))	2.66(97)	115 (61)
	$V_{T,s}$ (L)	14.2 (30)	29 (96)

Weiss et al.,J Pharmacokin Pharmacodyn, 2011



Central blood volume increases linearly with cardiac output (P<0.01)



Systemic transit time heterogeneity of ICG decreases linearly with cardiac output (P< 0.005)

Weiss et al.,J Pharmacokin Pharmacodyn, 2011

Conclusions

Minimal PBPK models are relevant for explaining

-Initial intravascular mixing
(blood volumes, TT dispersion, role of the lungs)

-Tissue distribution kinetics (permeation,diffusion,binding)

-Effect of obesity (highly lipid-soluble drugs)

-Effect of cardiac output and hemorrhagic shock

-Hemodynamic drug interactions

-Hepatic function in vivo (ICG)

Model selection and experimental design are strongly interrelated:
Frequent early blood sampling and multiple indicator method

The validity of a model is determined by the modeling objectives

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