Absorption modelling

assessment of the extent and rate of bioavailability

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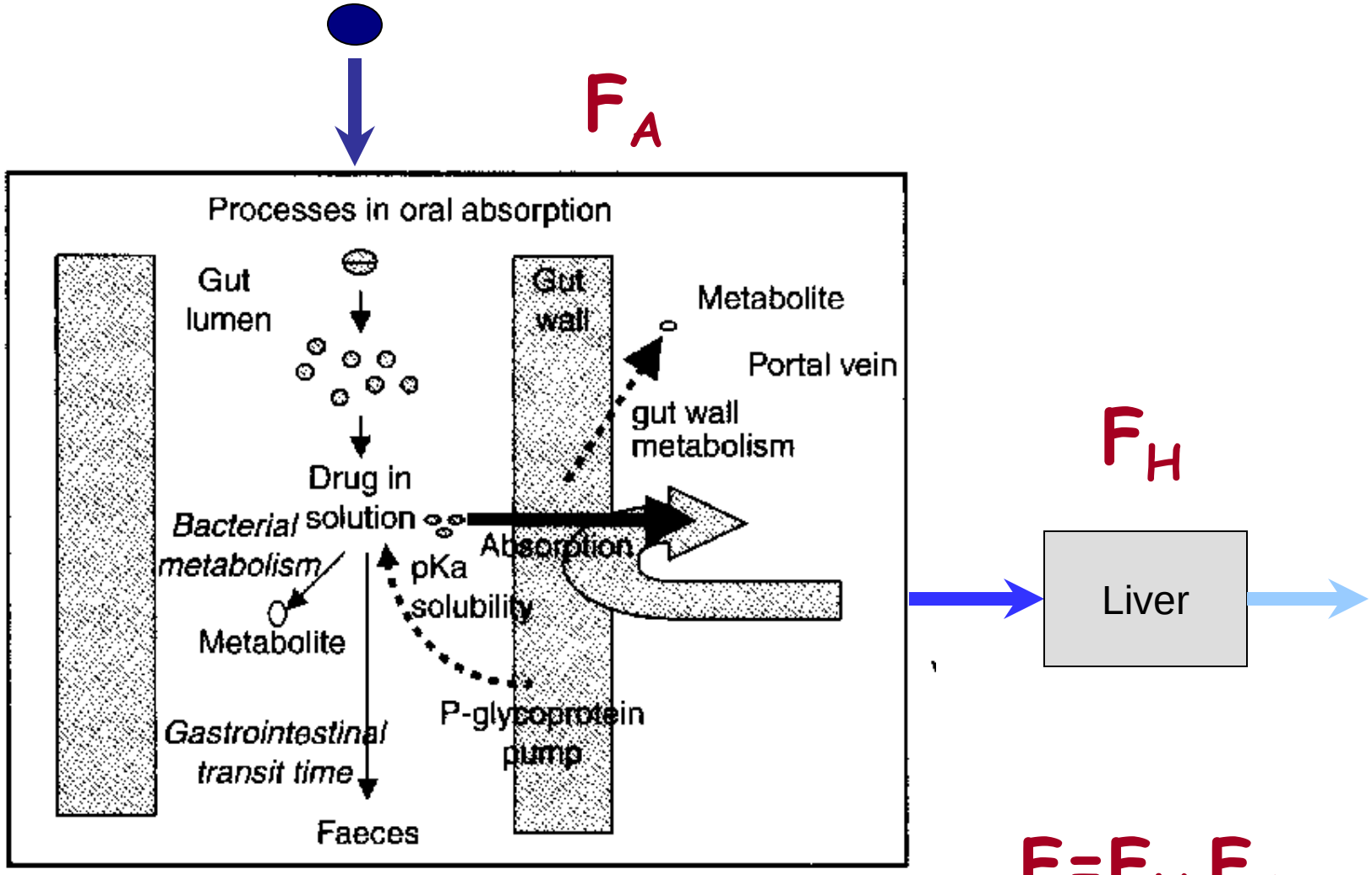
Determinants of Bioavailability

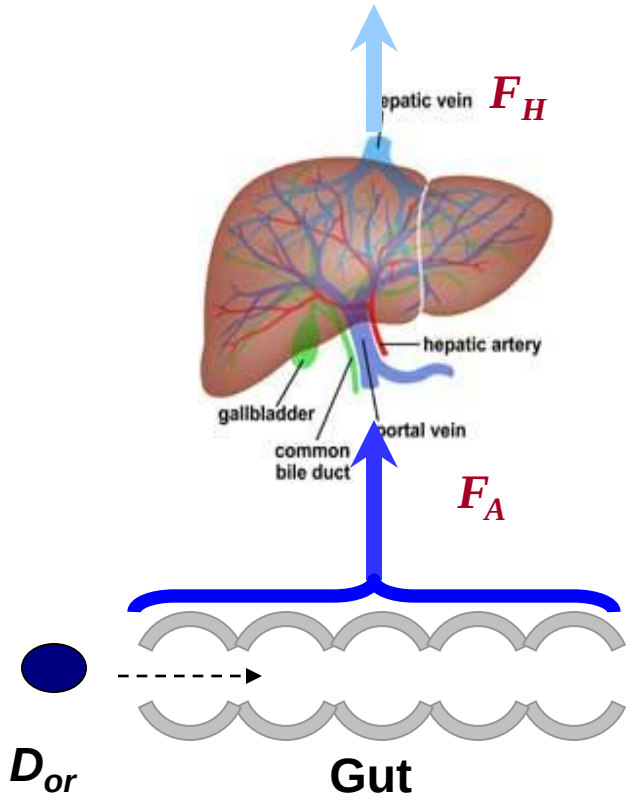


Absorption and Bioavailability

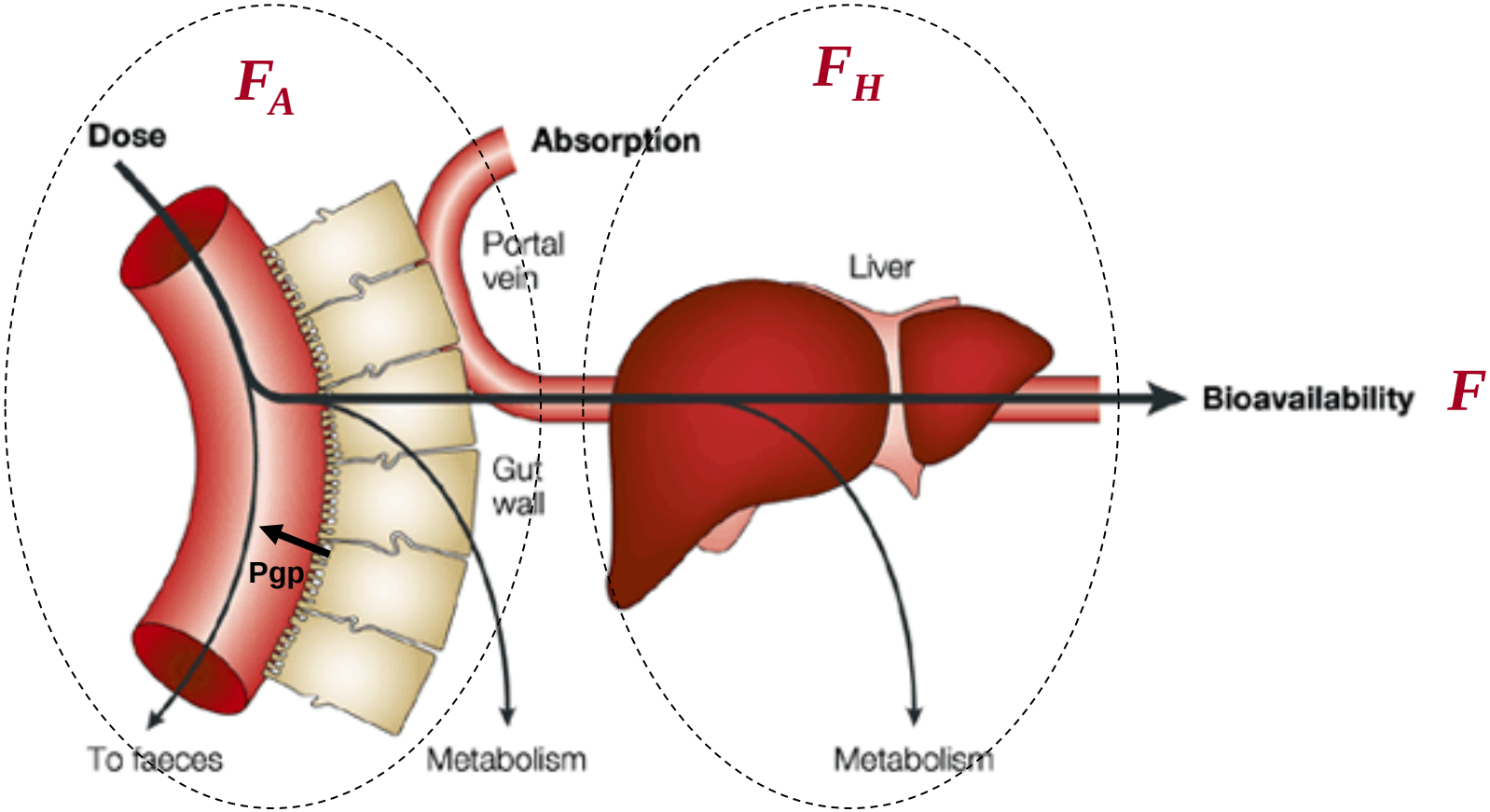
$$F = F_A F_H$$

Bioavailability *F*

= Fraction of D_{or} that reaches the systemic circulation



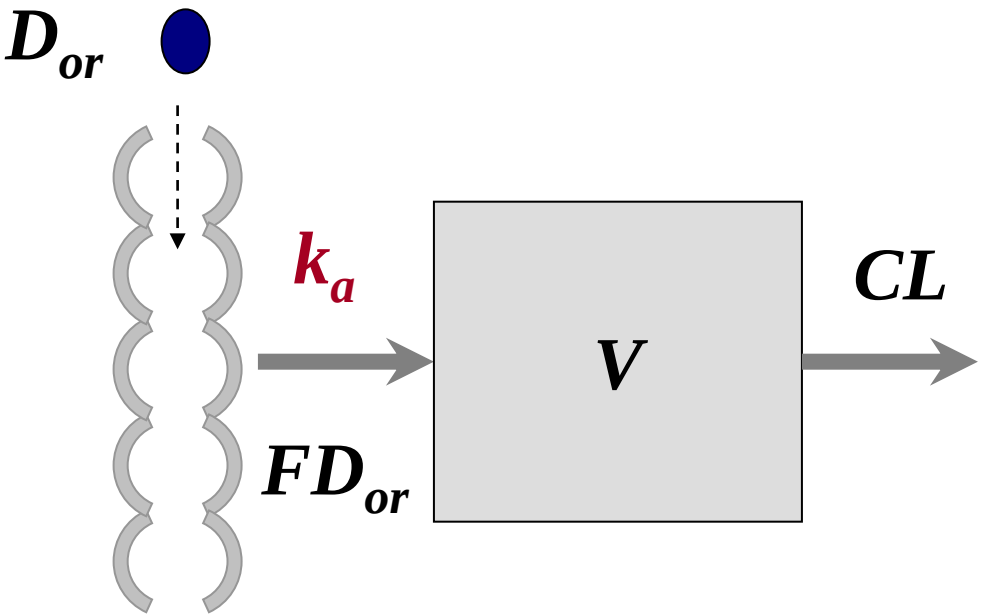
Determinants of Bioavailability

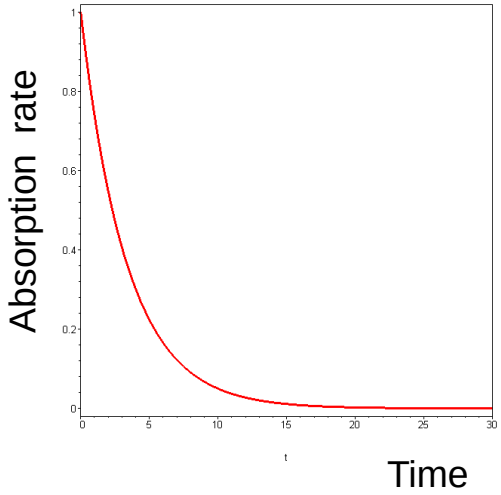


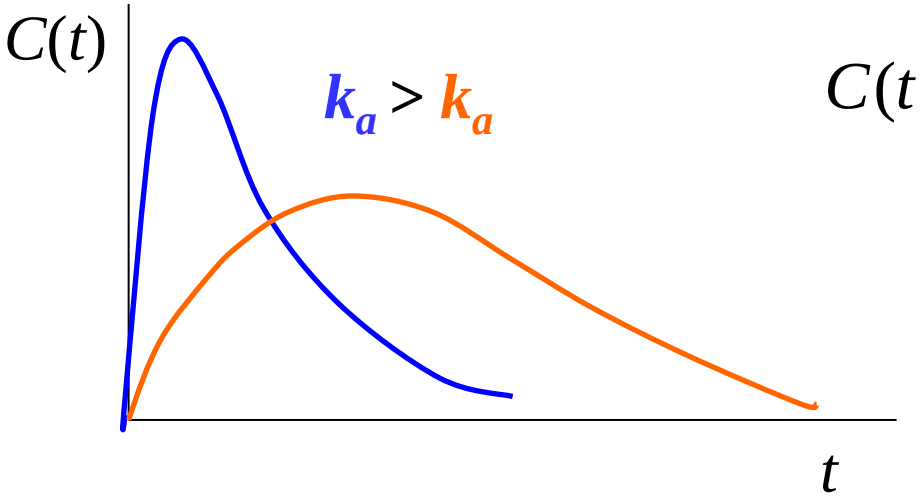
Absorption
Back-transport of Pgp-substrates
Intestinal metabolism

Hepatic metabolism
Biliary excretion

Absorption Rate (1-Compartment)







$$C(t) = \frac{FD_{or}}{V} \frac{k_a}{k_a - k_e} \left(e^{-k_e t} - e^{-k_a t} \right)$$

$$k_e = \frac{CL}{V}$$

Absorption/Disposition Modeling

Rate and Extent of Bioavailability

- Why?

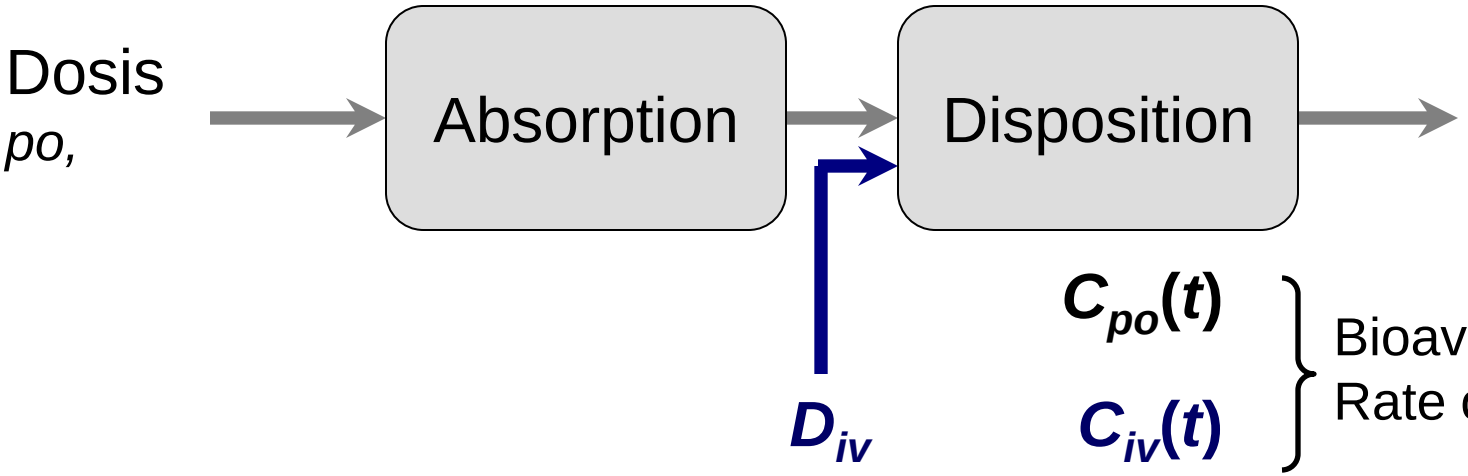
To avoid biased estimates due to model misspecification

when assuming first order absorption

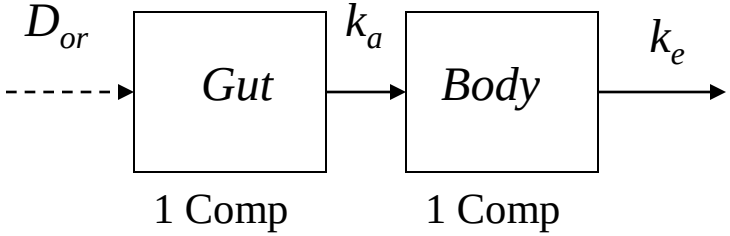
→ Maximum absorption rate is not achieved instantaneously !

Determination of the absorption (input) kinetics

Identifiability



Simplification:



reality

$$C_{iv}(t) = \sum_{i=1}^{3} B_i e^{-\lambda_i t}$$

$$Input(t) = I_0 e^{-k_a t} \qquad C_{iv}(t) = C_0 e^{-\lambda t}$$

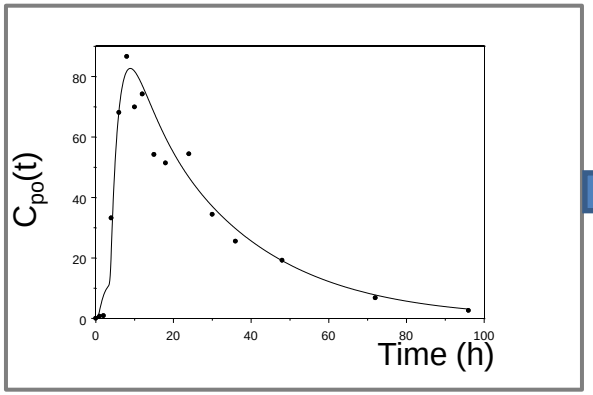
unrealistic

$$C_{or}(t) = B(e^{-\lambda t} - e^{-k_a t})$$

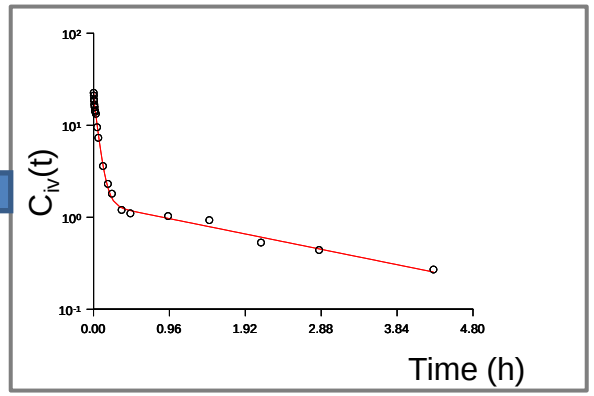
$k_a \neq$ real absorption rate constant!

$\lambda \neq k_e$!

oral data

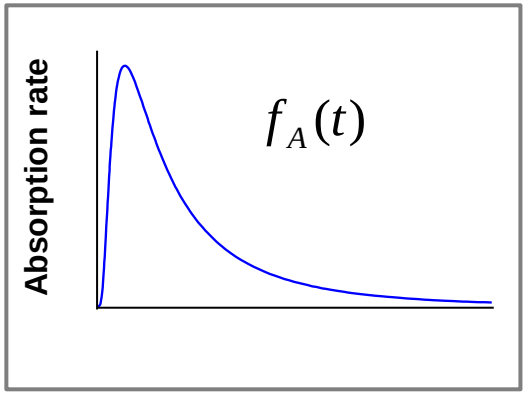


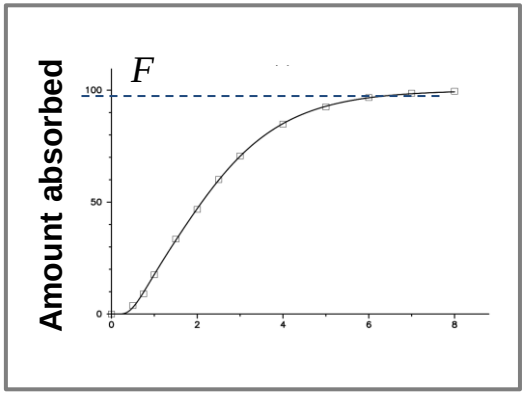
iv data



$$C_{po}(t) = \int_0^t f_A(\tau)\, C_{iv}(\tau) d\tau$$

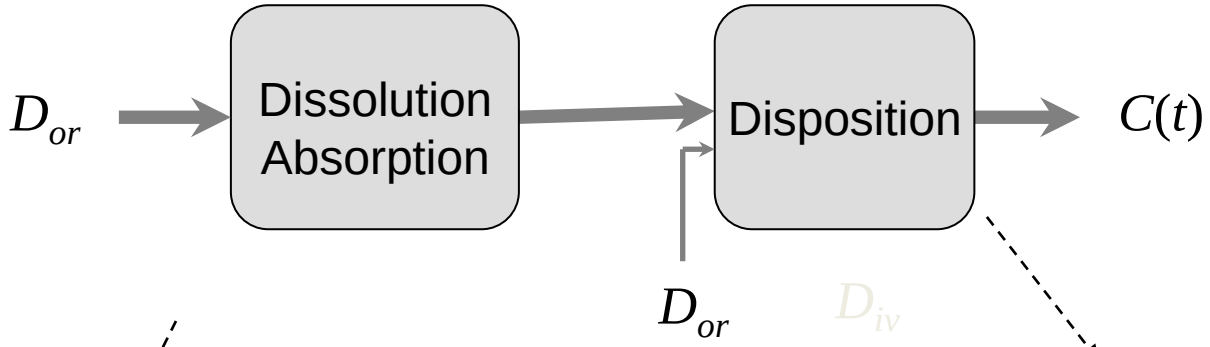
Deconvolution or parametric model

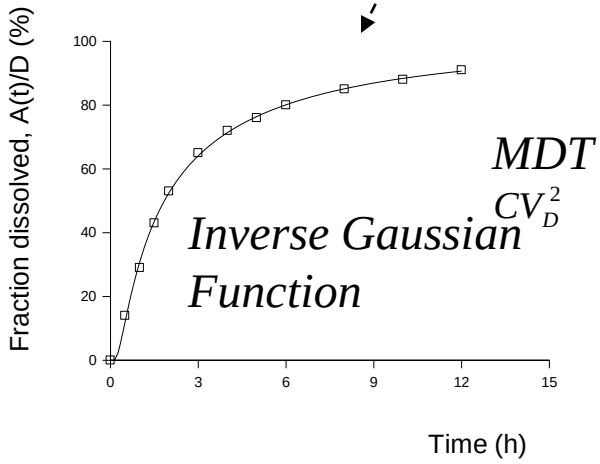




Dissolution as Determinant of Drug Input

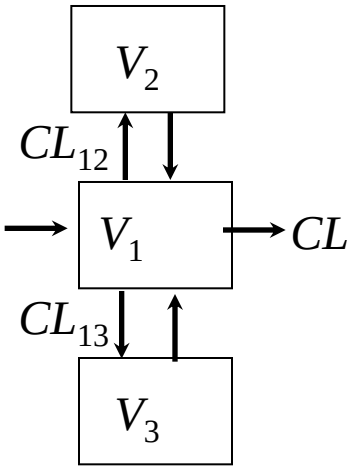
"Extended Release" dosage form





1. Fit of iv data

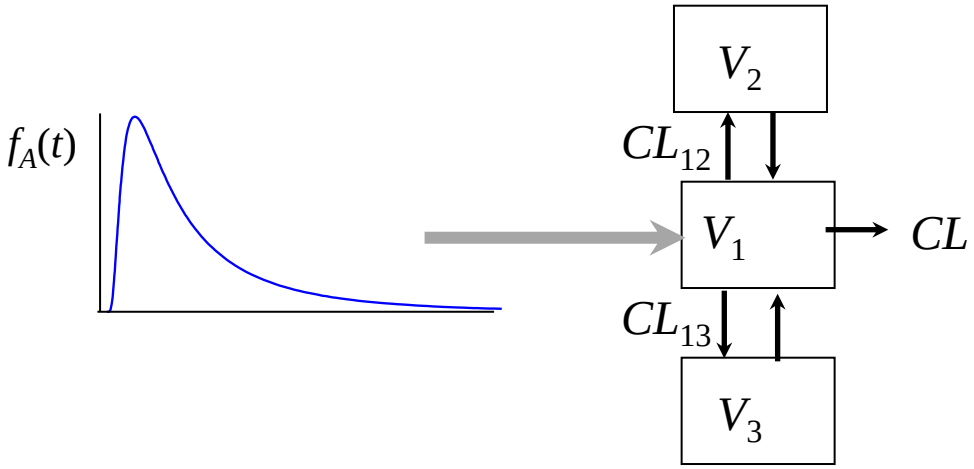
2. Fit of oral data with 3-comp. Parameters fixed



3-Compartment

Weiss, Pharm Res ,1996

Absorption (Input) Rate



$$f_A(t) = F\sqrt{\frac{MAT}{2\pi CV_A^2 t^3}}\exp\left[-\frac{(t-MAT)^2}{2CV_A^2 MAT\, t}\right]$$

Inverse Gaussian density

Mean absorption time (MAT)

Bioavailability (F)

Dispersion of absorption time CV_A^2

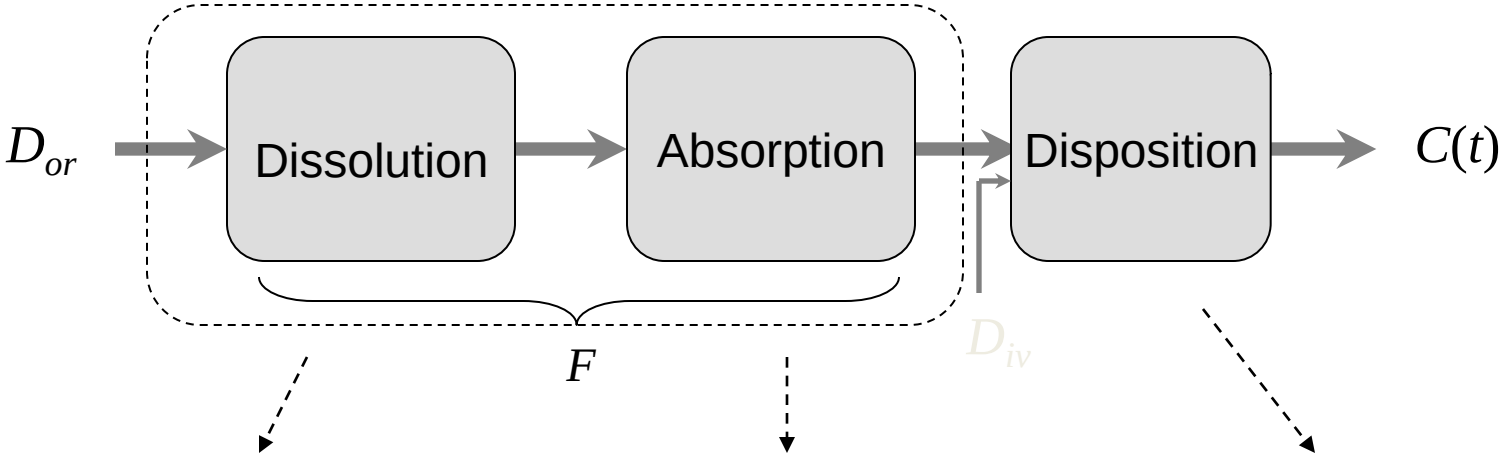
$$F_A(t) = \int_0^t f_A(\tau)d\tau$$

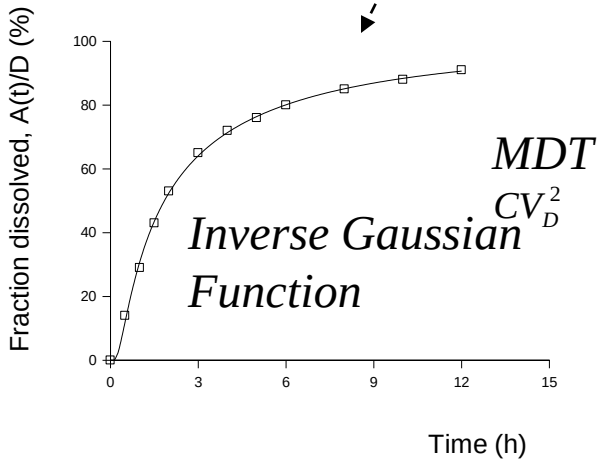
$$t_{A,\max} = MAT\left(\sqrt{1+\frac{9}{4}CV_A^4} - \frac{3}{2}CV_A^2\right)$$

$$F_A(\infty) = F.$$

Dissolution as Determinant of Bioavailability

"Extended Release" dosage form





Inverse Gaussian Function

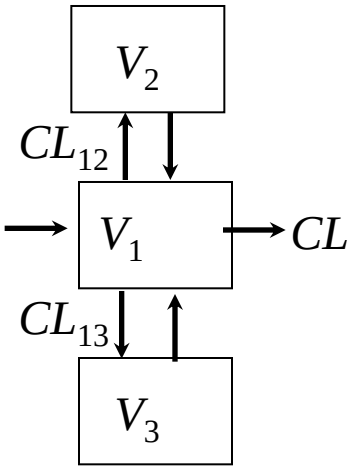
MDT

CV_D^2

First order

MAT= 1/

k_a



3-Compartment

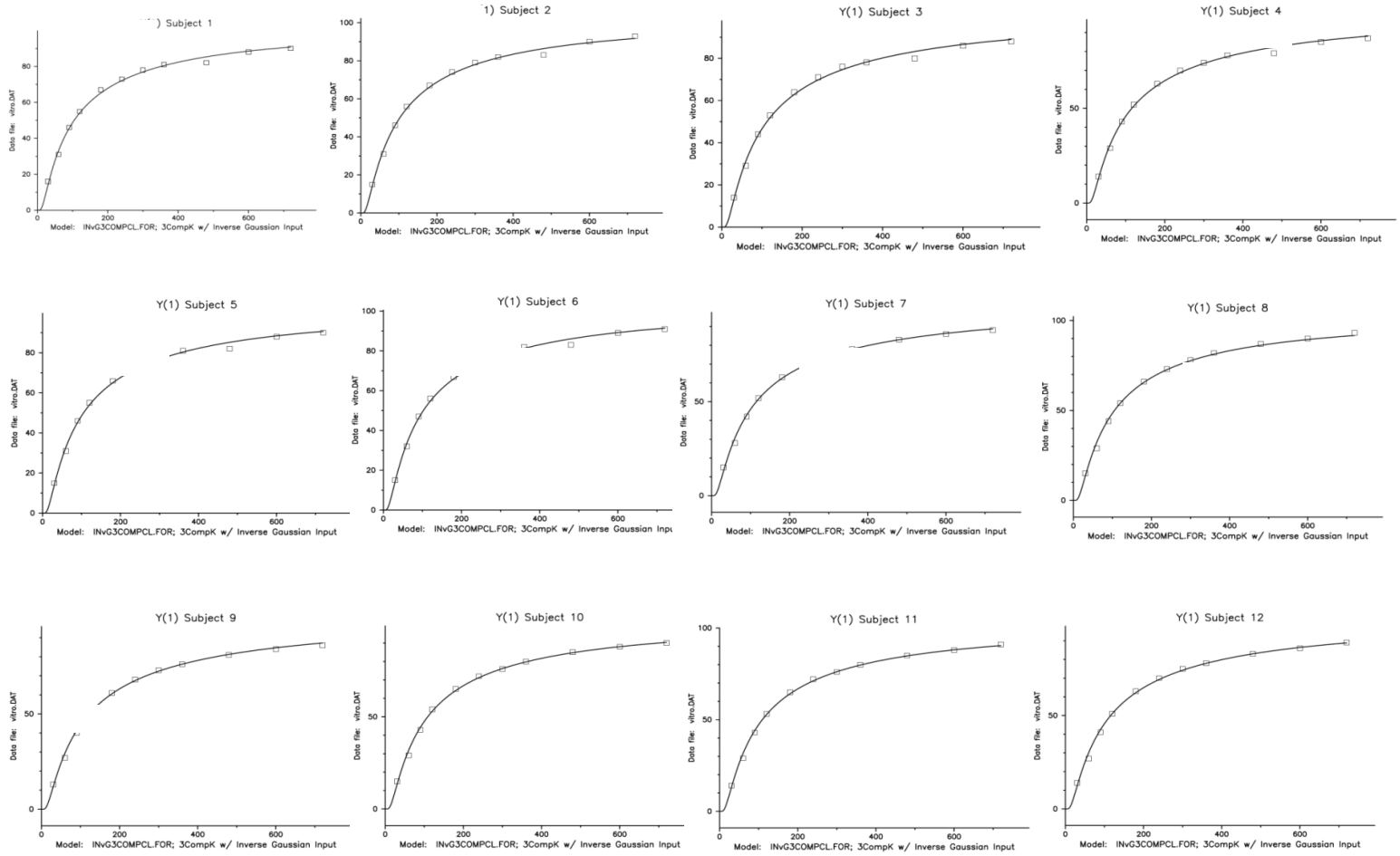
1. Fit of iv data

2. Fit of oral data with 3-comp. Parameters fixed

Wang, Weiss, D'Argenio J Clin Pharmacol , 2008

IG- Fit of Dissolution Data (ADAPT Population Analysis)

Slow Release Formulation

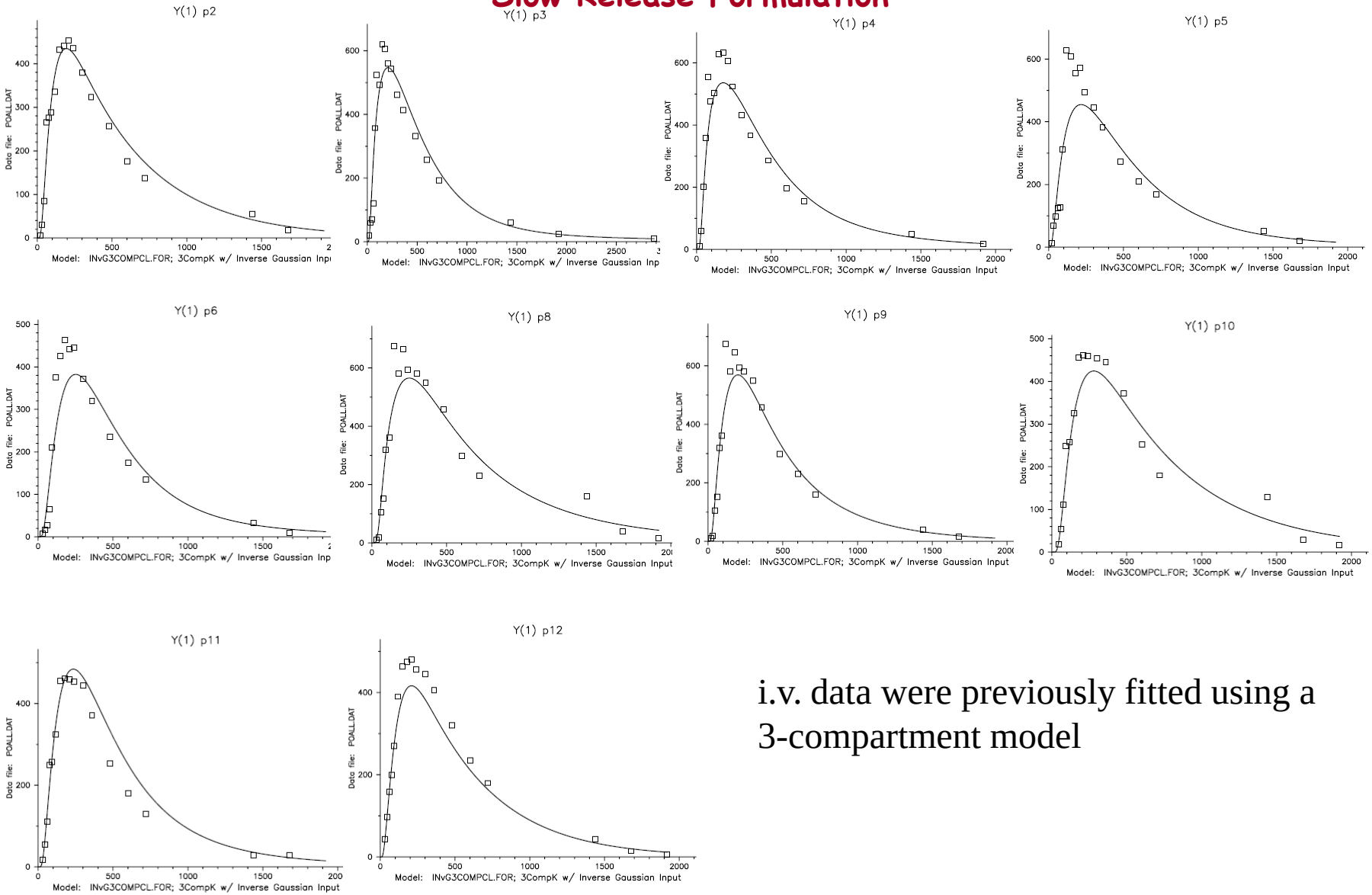


$$MDT = \int_0^{\infty} [1 - F(t)]dt \qquad F(t) = \frac{A_{diss}(t)}{A_{diss}(\infty)}$$

Wang, Weiss D'Argenio J Clin Pharmacol , 2008

IG-Input Model Fit of Oral Data (ADAPT Population Analysis)

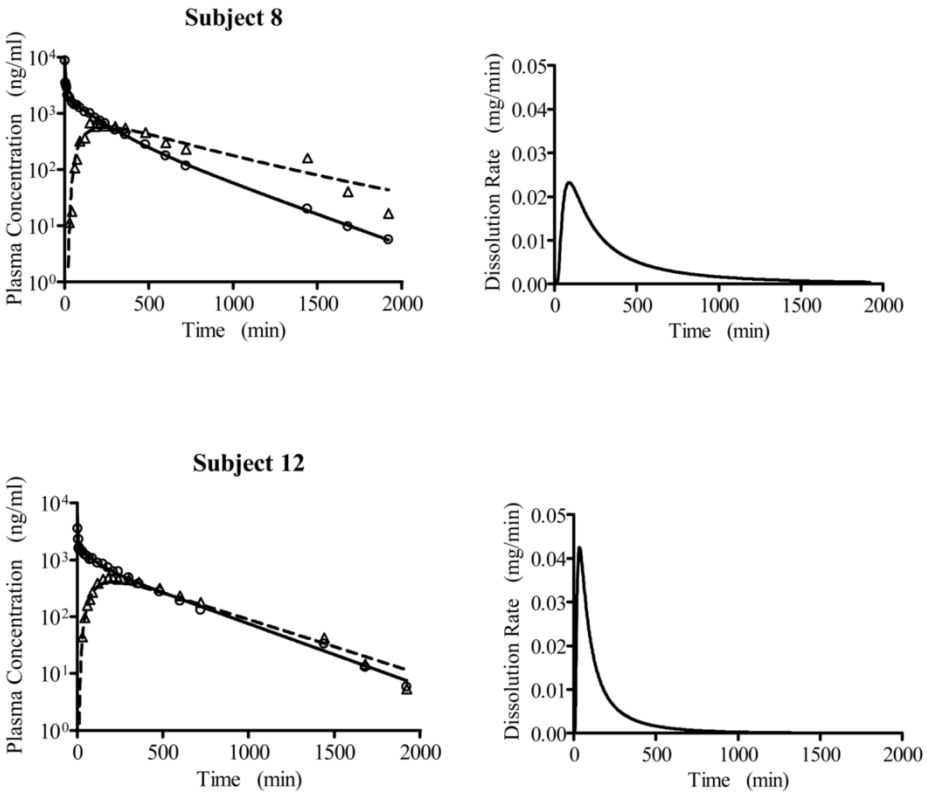
Slow Release Formulation



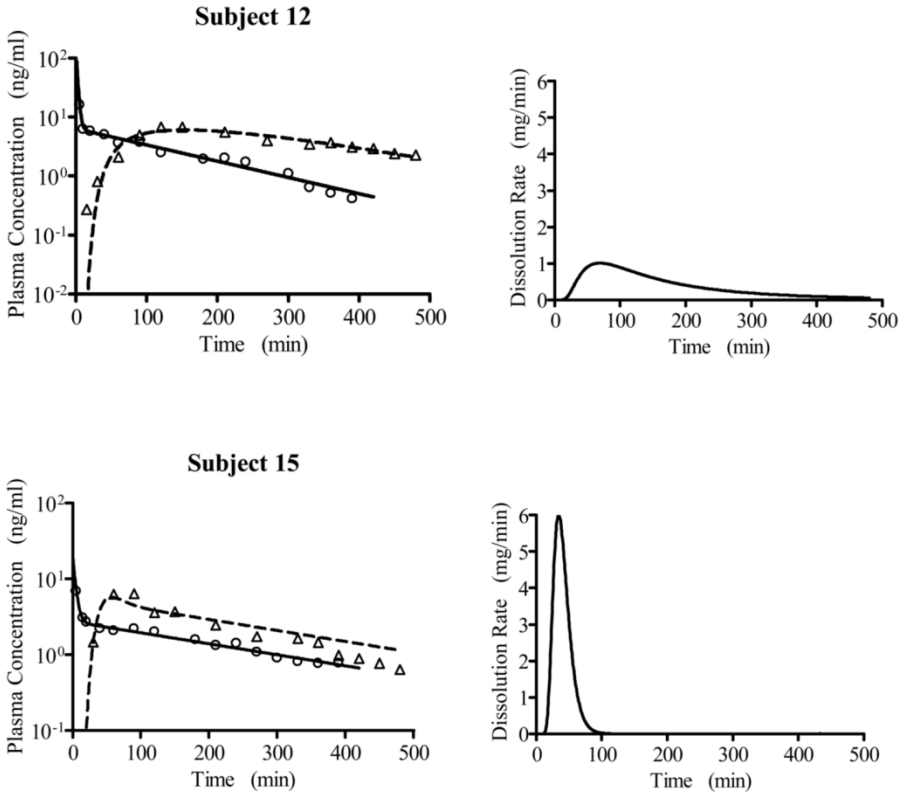
i.v. data were previously fitted using a 3-compartment model

Wang, Weiss D'Argenio J Clin Pharmacol , 2008

Slow release formulation



Immediate release (trapidil)



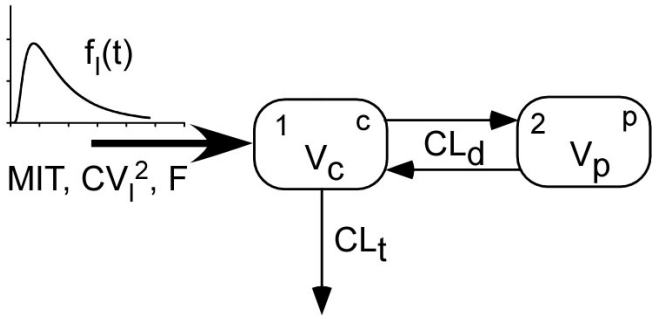
Wang, Weiss D'Argenio J Clin Pharmacol , 2008

Comparison of the Population Analysis of Oral Data for the Extended-Release Dosage Form Using the 2 Different Input Models

	IG/MAT Model			IG Model	
	Population Mean	Population SD		Population Mean	Population SD
F, %	69.9	9.22	F, %	69.8	9.10
MDT, min	318	115	MIT,min	332	77.7
MAT, min	33.9	14.4			
CV^2_D	1.93	0.369	CV^2_I	1.22	0.178
$t_{D,max}$	53.4	19.8	$t_{I,max}$	84.8	19.7
$MDT_{invitro}$, min	302	39			
AIC	1954			1970	

IG, inverse Gaussian; AIC, Akaike information criterion.

IGABS



ADAPT 5

igabs.for *

```
      Subroutine DIFFEQ(T,X,XP)
      Implicit None

      Real*8 fI, MIT, CVI2, F
      MIT=P(5)
      CVI2=P(6)
      F=P(7)

C  Define the Inverse Gaussian Input Funtion fI
      if(t .eq. 0.0) then
       fI = 0.0
      else
       fI = F*B(1)*dsqrt(MIT/(2.0*pi*CVI2*t**3))*
     x           dexp(-(t-MIT)**2/(2.0*CVI2*MIT*t))
      endif

C PK Model with Inv. Gaussian Representing Systemic Drug Delivery
      XP(1) = -(P(1)+P(3))/P(2)*X(1) + P(3)/P(4)*X(2)  + fI
      XP(2) = P(3)/P(2)*X(1) - P(3)/P(4)*X(2)
```

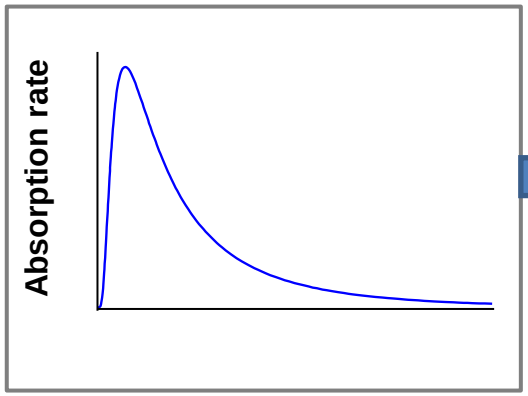
D'Argenio et al, 2009

Parametric model of input/absorption rate

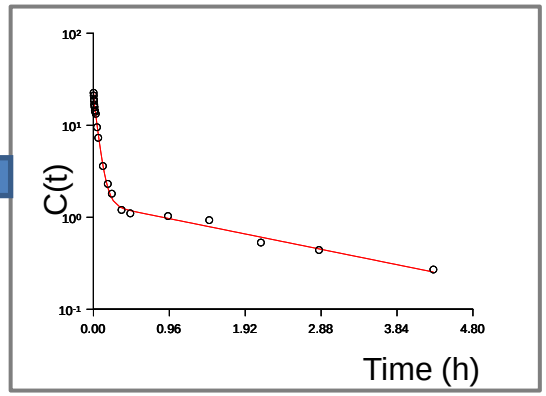
Inverse Gaussian

Sum of inverse Gaussians

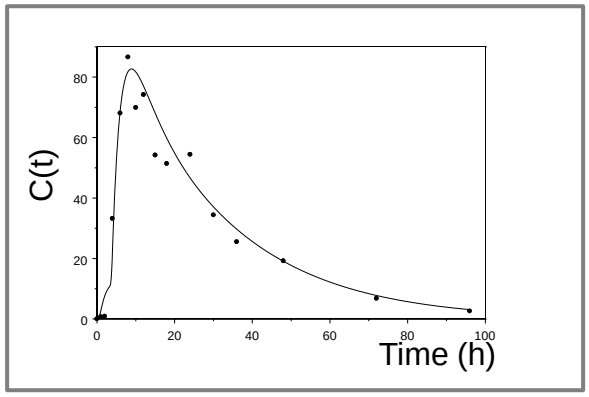
Weibull



iv data

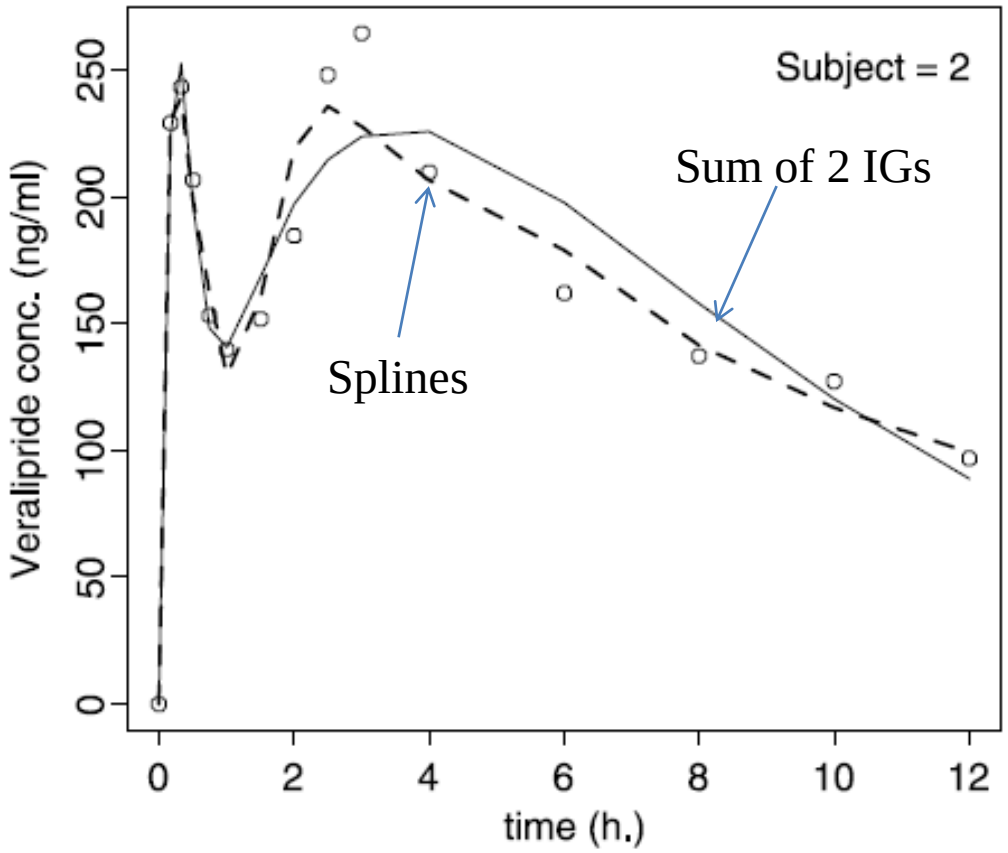


Fit of oral data



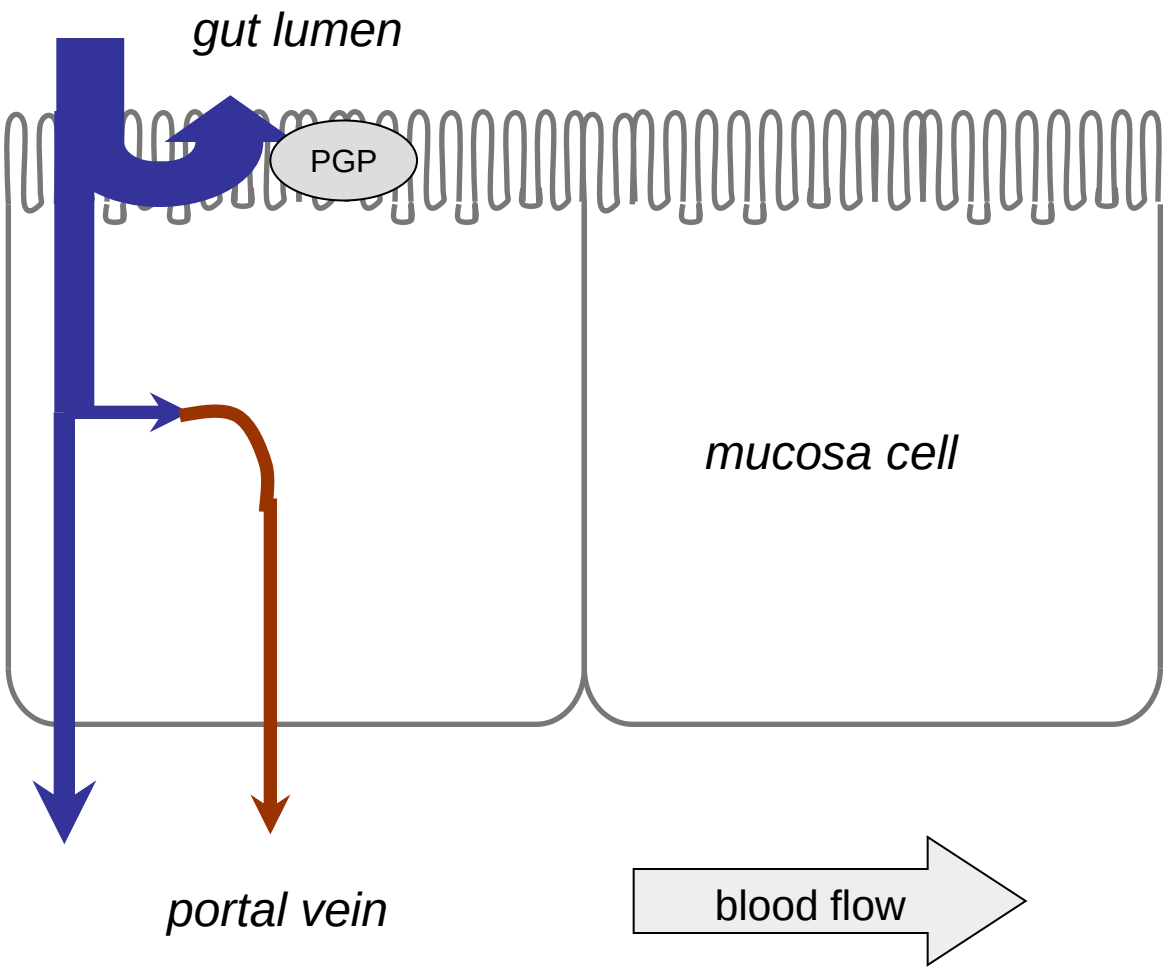
Sum of IG-Functions

Irregular C(t)-Curves

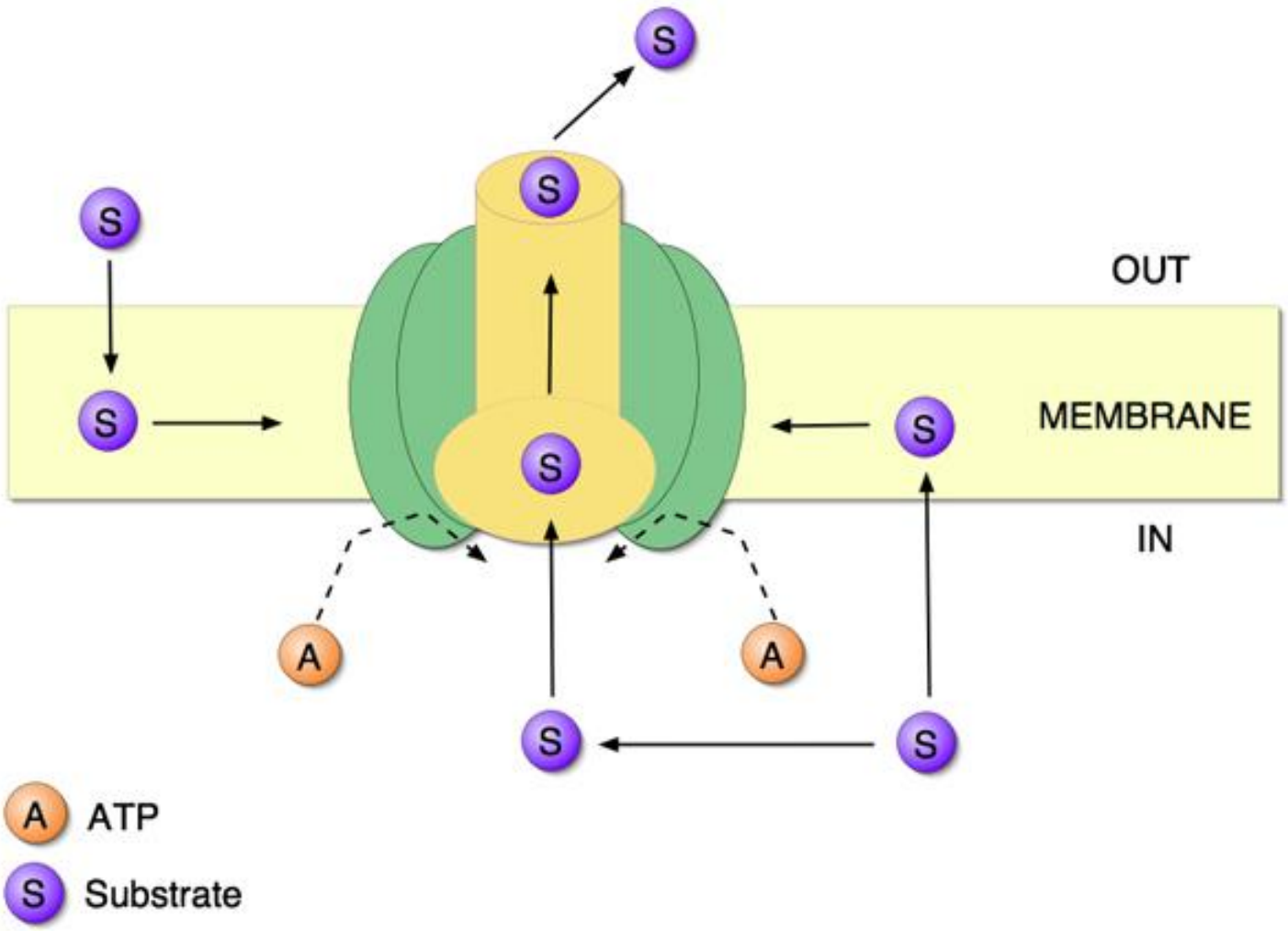


Csajka C, Drover D, Verotta D. The use of a sum of inverse Gaussian functions to describe the absorption profile of drugs exhibiting complex absorption. Pharm Res 2005;22:1227–1235.

Intestinal Absorption (Effect of P-Glycoprotein)



P-Glycoprotein Pump (PGP)



Modeling the Kinetics of Digoxin Absorption: Enhancement by P-glycoprotein Inhibition

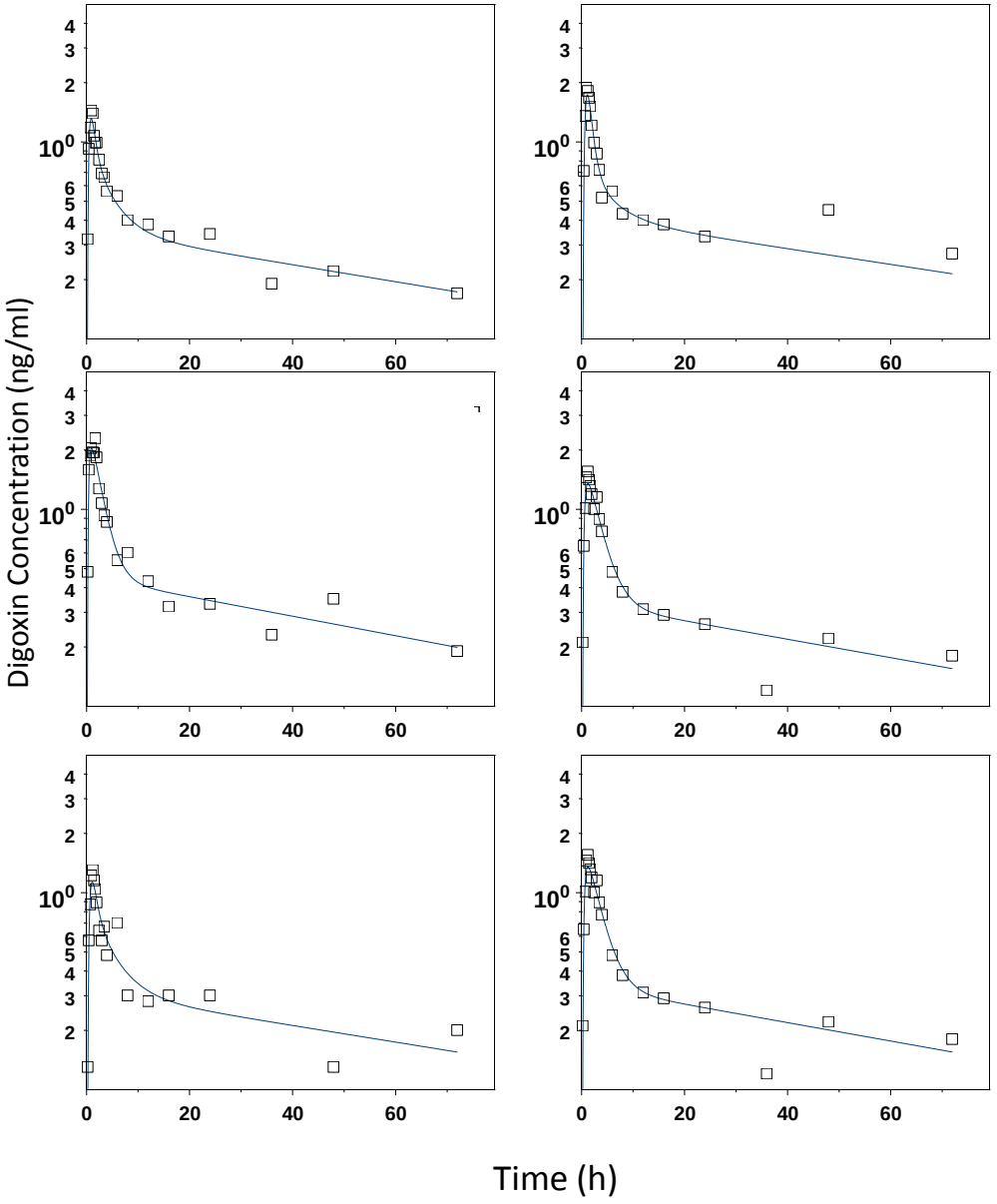
10 healthy volunteers received a single dose 0.5 mg digoxin (2 tablets Lanicor, Boehringer Mannheim, Germany) alone and concomitantly with oral talinolol (100 mg).

Westphal et al., Clin Pharmacol Ther, 2000

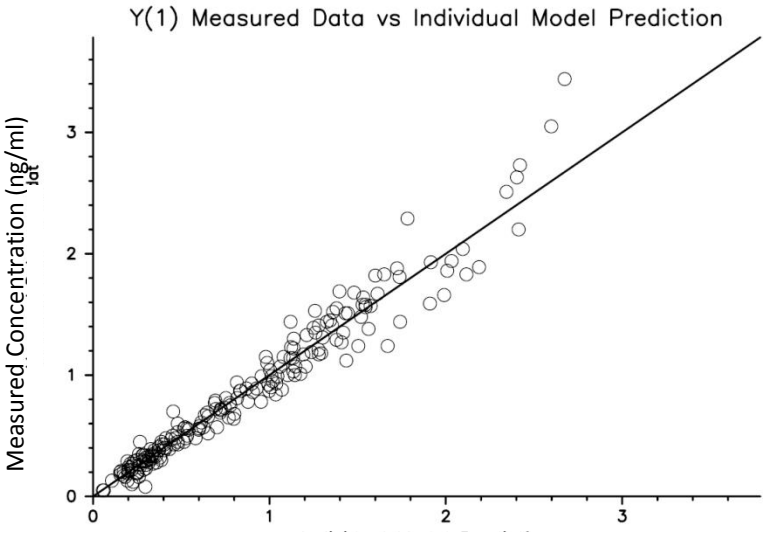
iv data

Kramer et al., J Pharmacokinet Biopharm, 1974

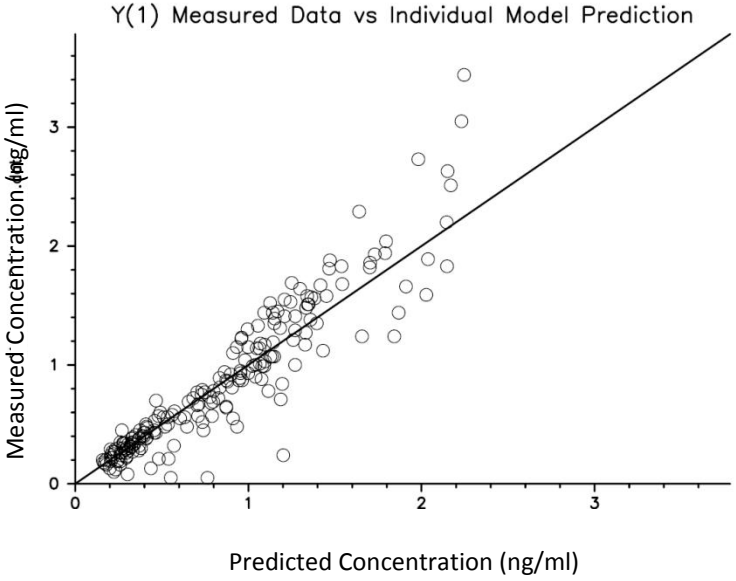
Dioxins Tablets
(0.5 mg Lanicor®)



inverse Gaussian absorption model

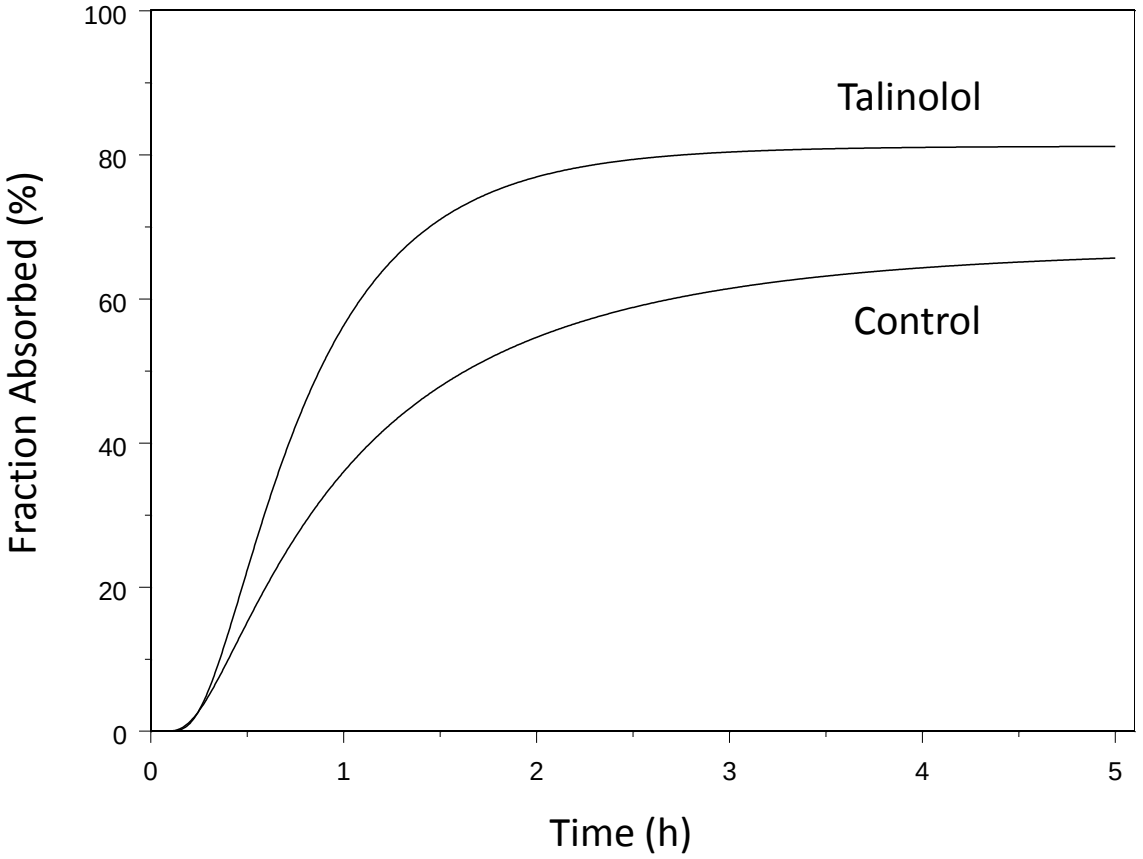


first-order absorption model



Weiss et al, J Clin Pharmacol.,2011

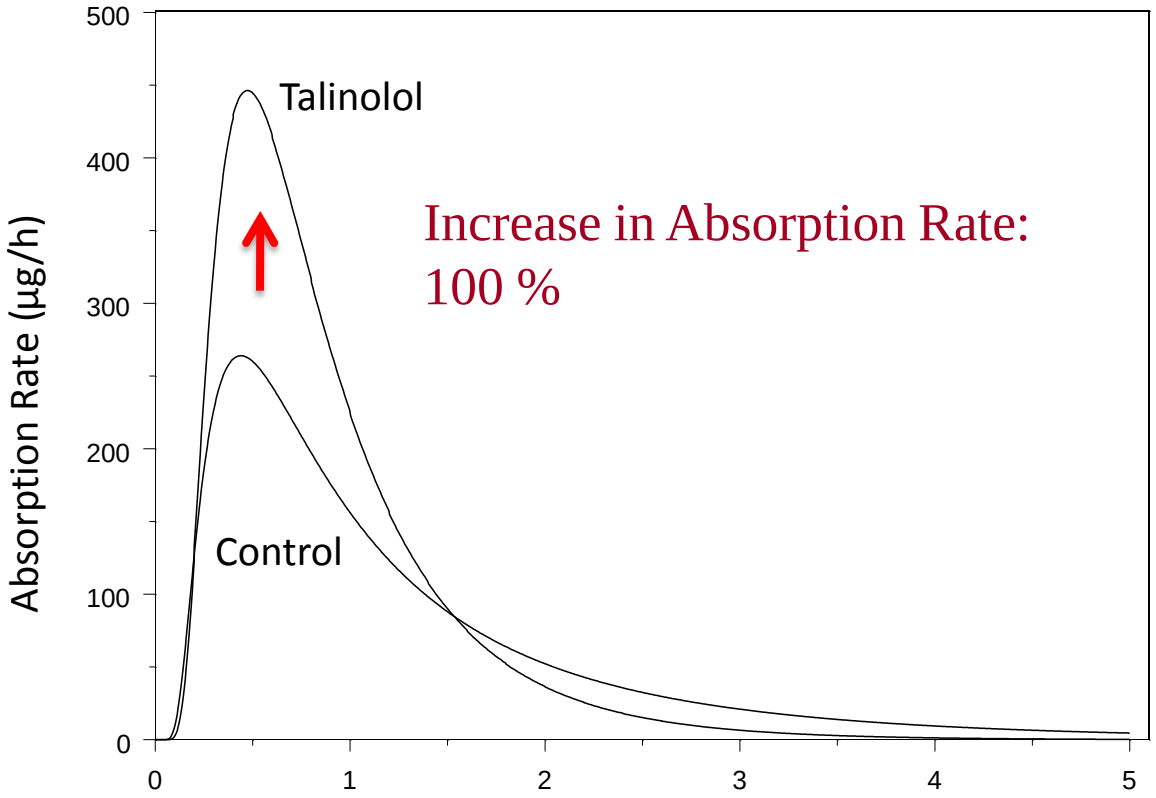
Effect of P-Glycoprotein Inhibition: Bioavailability



Increase in *F*: 21 %

Weiss et al, J Clin Pharmacol,2011

Effect of P-Glycoprotein Inhibition Absorption Rate



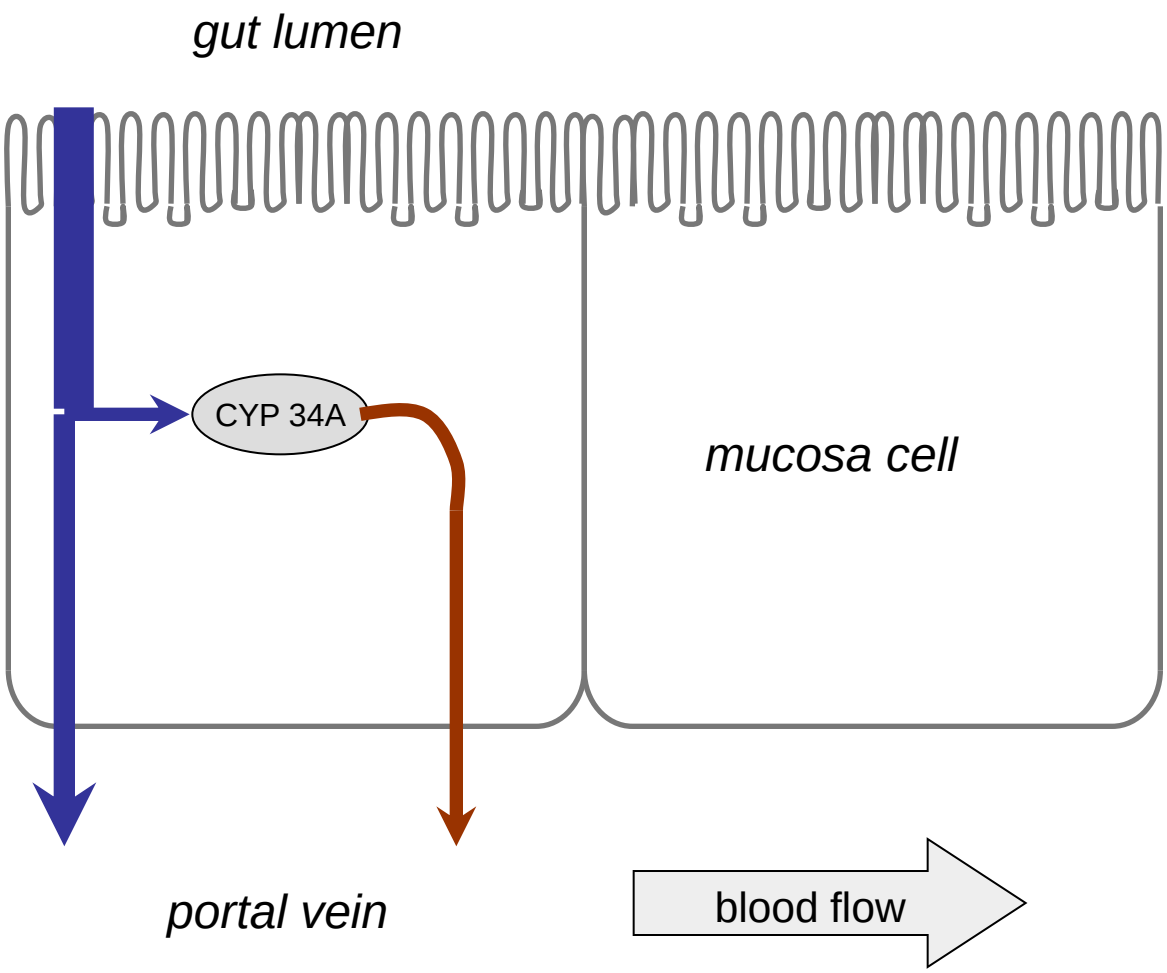
Weiss et al, J Clin Pharmacol,2011

	Digoxin Alone		Digoxin+ Talinolol	
Parameters	**Population Mean**	**Interpatient % CV**	**Population Mean (%RSE)**	**Interpatient %CV (%RSE)**
MAT (h)	1.32	17	0.88 (20)**	31 (50)
CV_A^2	0.89	38	0.45 (51)*	63 (92)
F (%)	67.1	14	81.2 (17)*	9 (66)
$f_{A,max}$ (µg/h) [a]	278	26	499**	34

[a]Maximum absorption rate

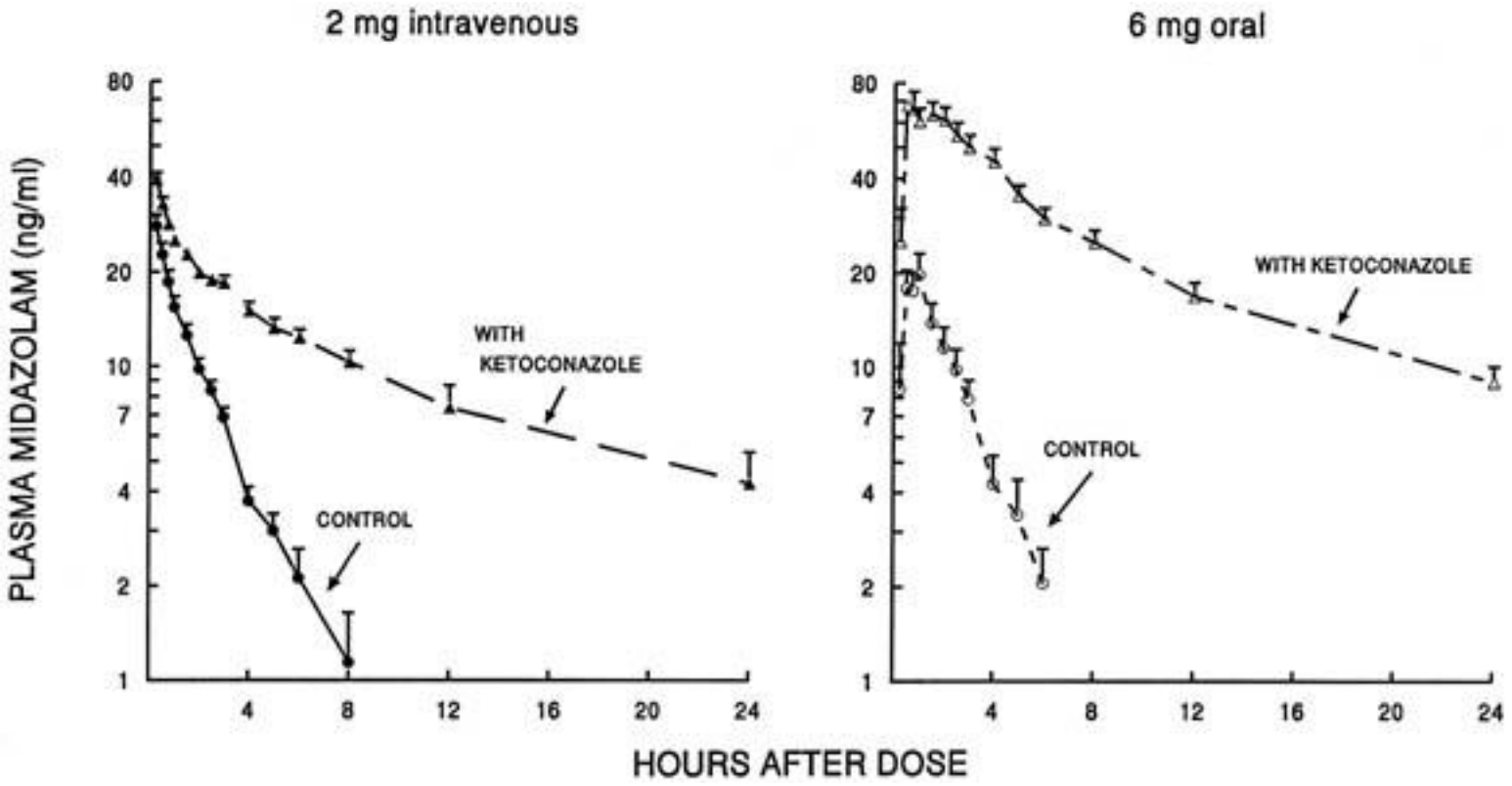
Weiss et al, J Clin Pharmacol,2011

Intestinal First Pass Metabolism



Ketoconacole increases AUC of Midazolam

Inhibition of intestinal and hepatic Cytochrome P450 3A



AUC_{iv} ↑ × 5

AUC_{or} ↑ × 16

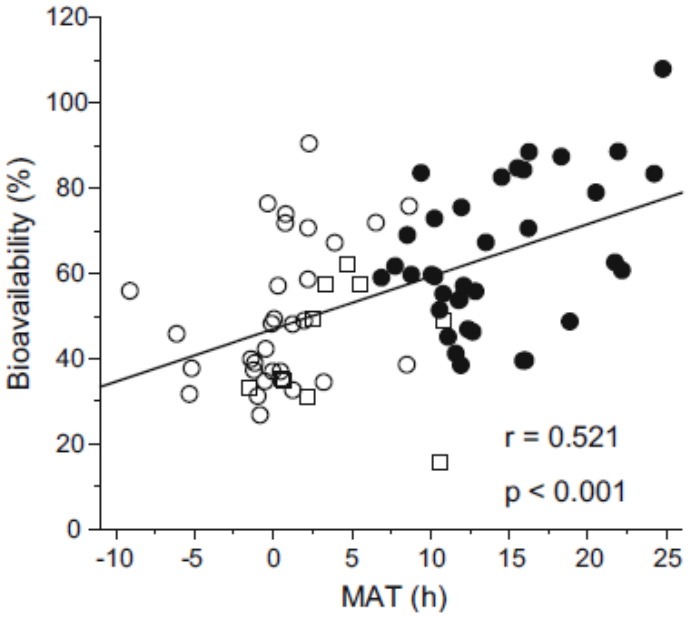
CL_{int} ↓ by 84 %

F ↑ 25% → 80%

Tsunoda et al., Clin Pharmacol & Ther, 1999

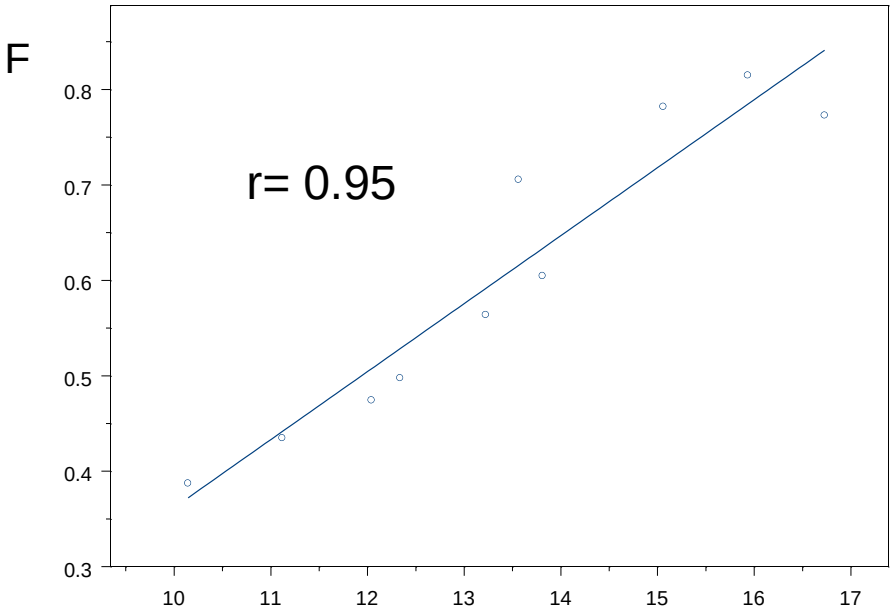
Bioavailabilty of Propiverine increases with dissolution time

numerical integration



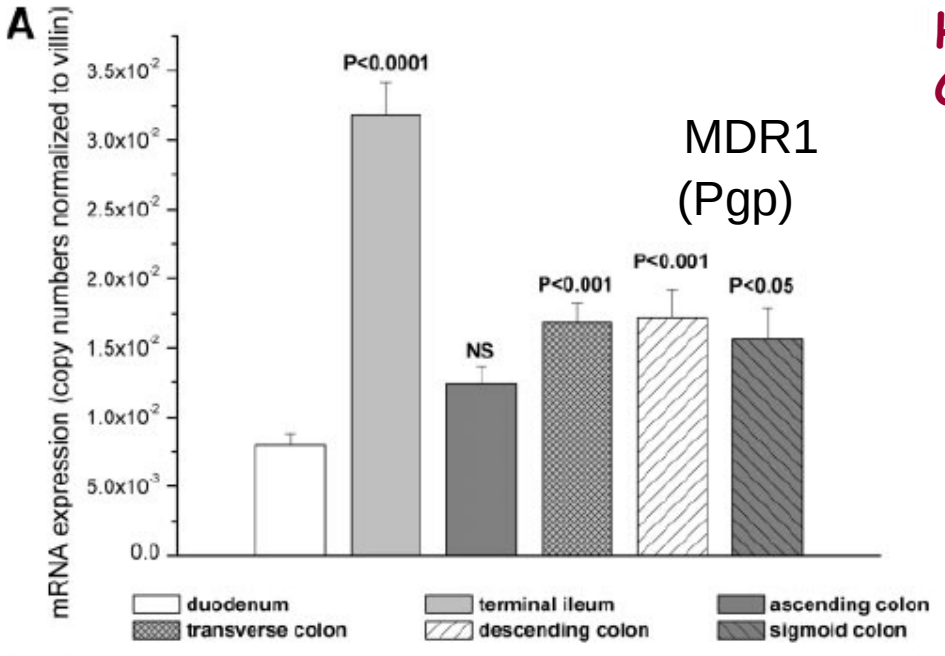
May et al., Eur J Clin Pharmacol, 2008

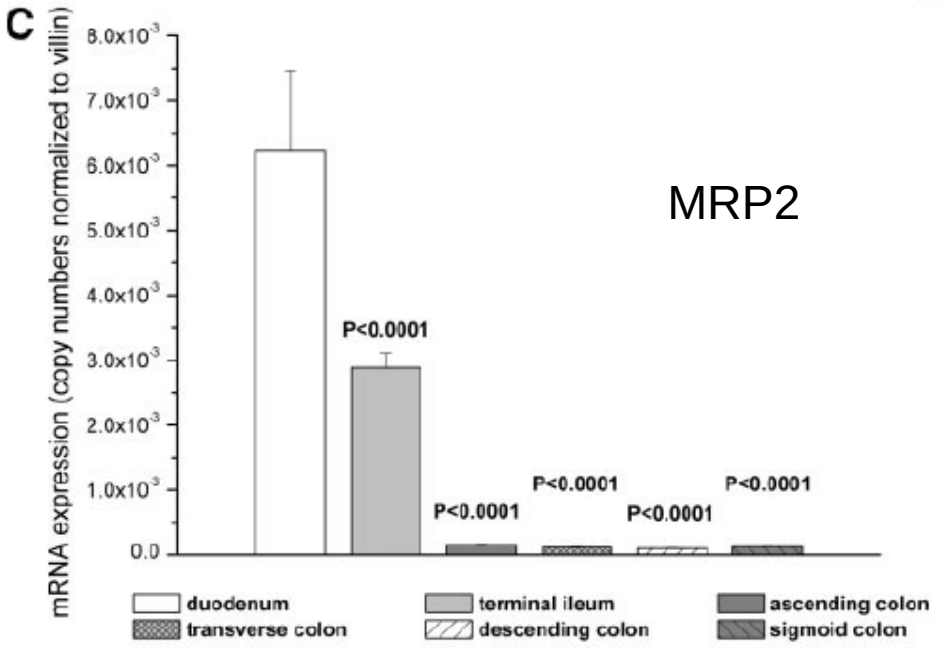
IG-absorption model



Re-analyisis of extended release data using a population approach

Heterogeneity of gastrointestinal CYP and transporter expresssion



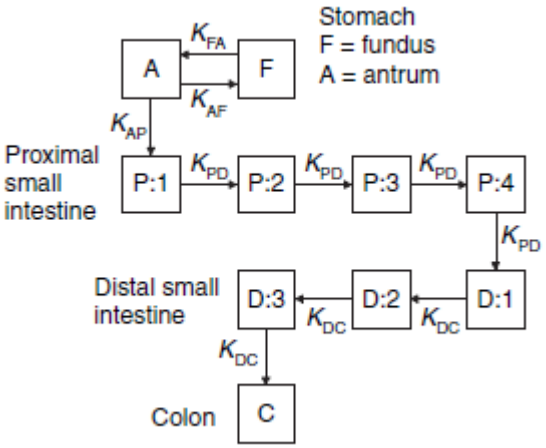


The expression of mRNA for **CYP3A4**, **Pgp, and MRP2** was highest in jejunum and decreased toward more distal regions.

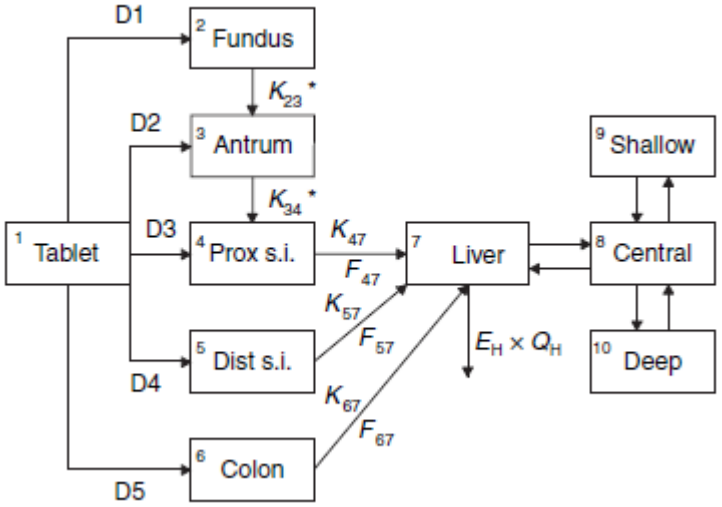
Berggren et al.,Mol. Pharm, 2007

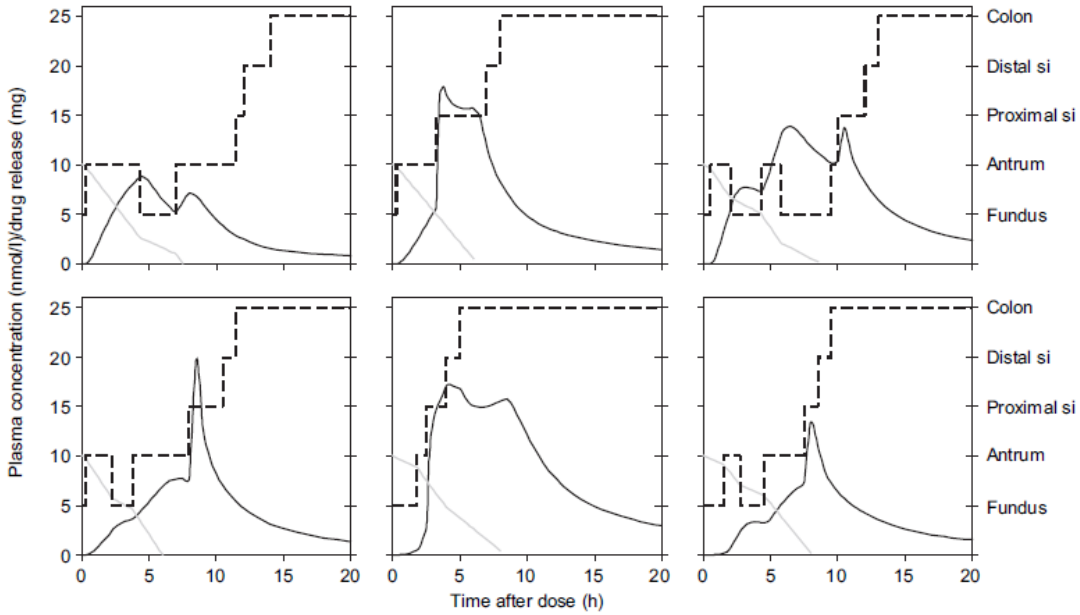
Zimmermann et al., Drug Metab Dispos 2005

Mechanistic modeling based on gastrointestinal tablet transit



a priori information



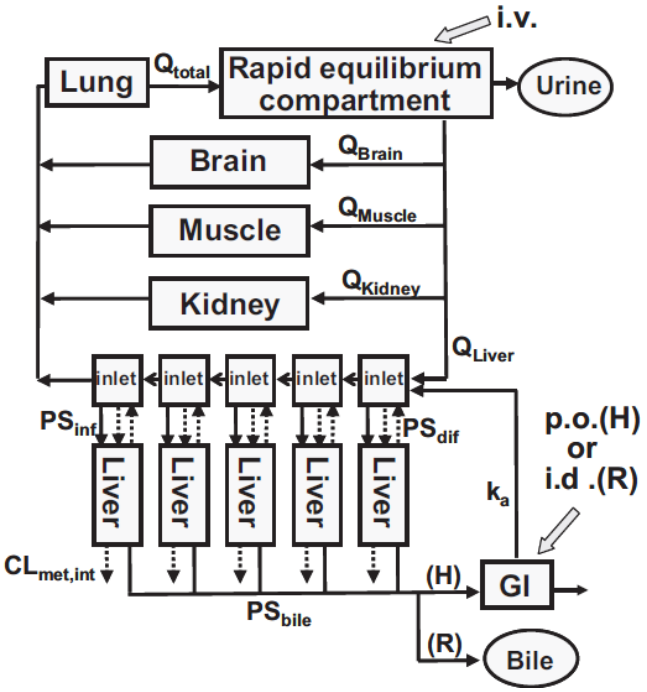


Mechanistic Modeling of a Magnetic Marker Monitoring Study Linking Gastrointestinal Tablet Transit, *In Vivo* Drug Release, and Pharmacokinetics

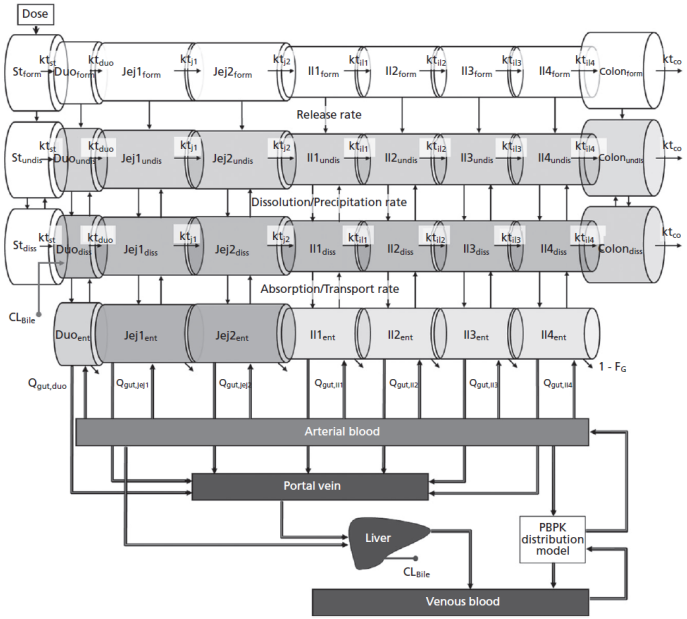
M Bergstrand[1], E Söderlind[2], W Weitschies[3] and MO Karlsson[1]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 86 NUMBER 1 | JULY 2009

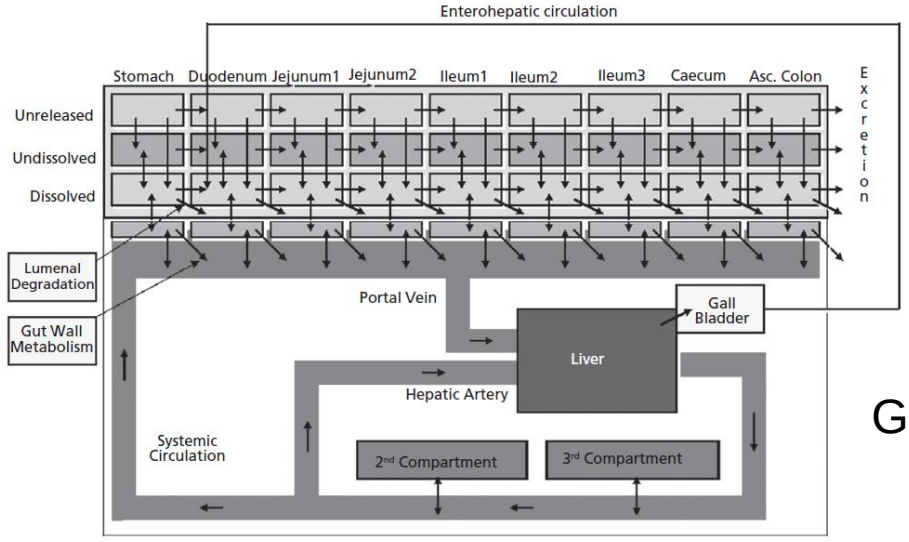
Simulation models



Watanabe et al., J Pharmacol Exp Ther, 2009



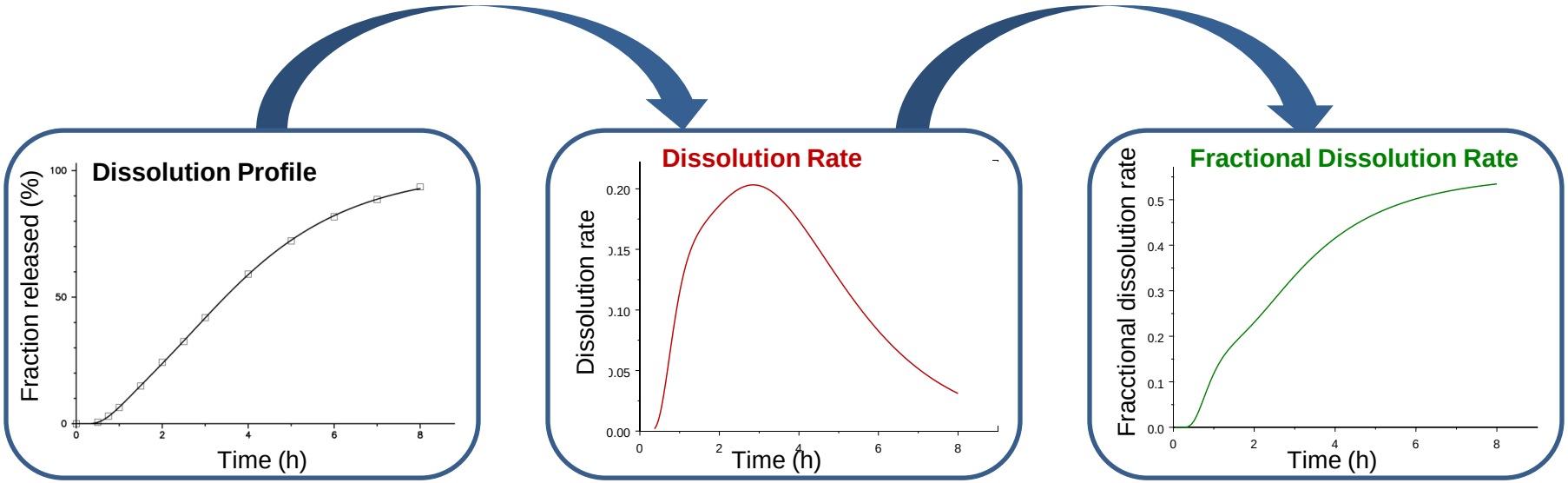
SymCyp



GastroPlus

Otsuka et al.,J Pharm Pharmacol, 2013

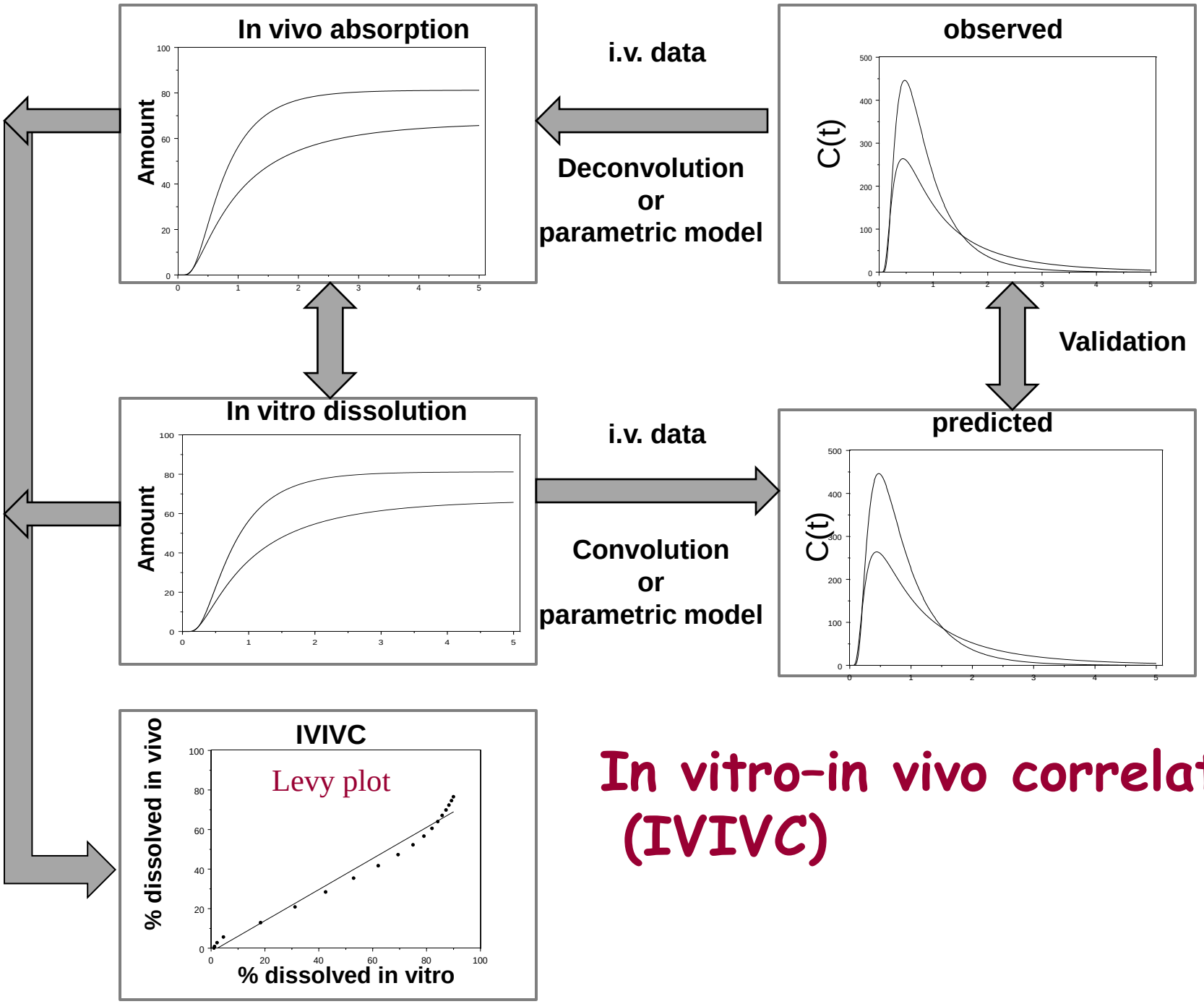
Modelling of in vitro dissolution



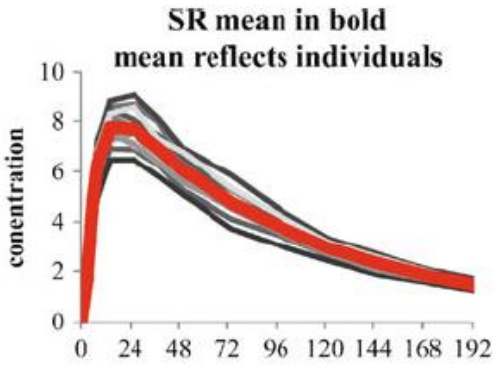
$$F(t) = \frac{A(t)}{A(\infty)} \qquad f(t) = \frac{df(t)}{dt} \qquad k(t) = \frac{f(t)}{1 - F(t)}$$

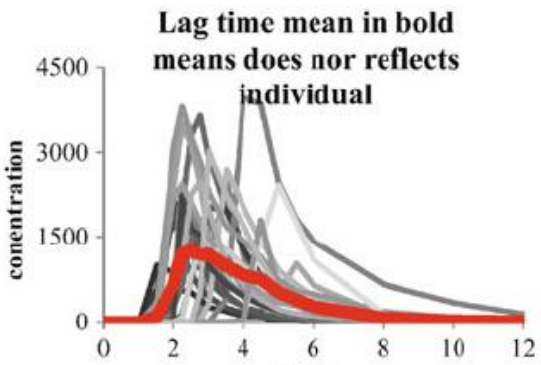
For example:

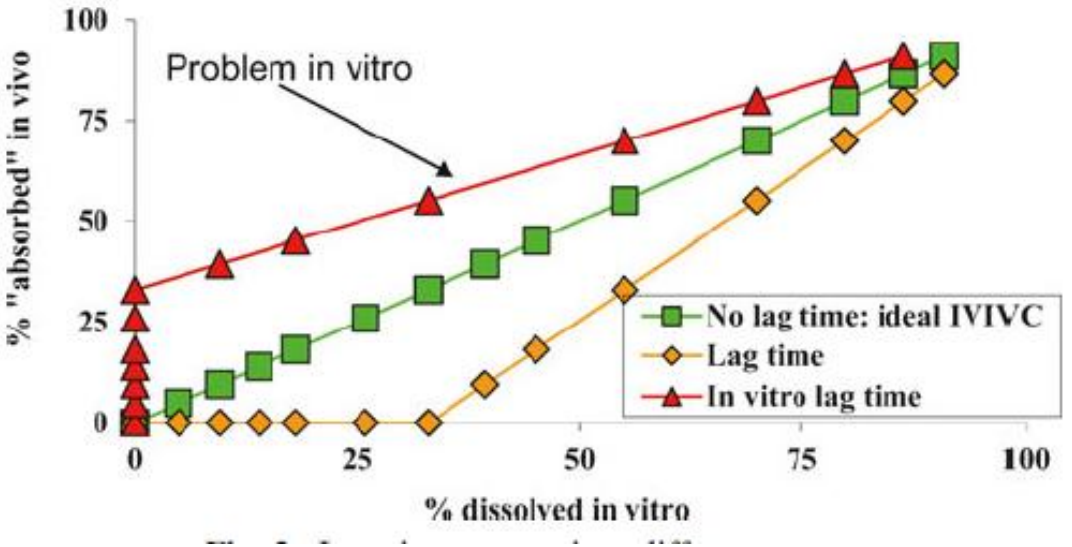
$$f_{2IG}(t) = qf_1(t) + (1-q)\,f_2(t) \qquad f_i(t) = \sqrt{\frac{MDT_i}{2\pi RD_i^2 t^3}} \exp\left[-\frac{(t - MDT_i)^2}{2RD_i^2 MDT_i t}\right]$$



In vitro-in vivo correlation (IVIVC)



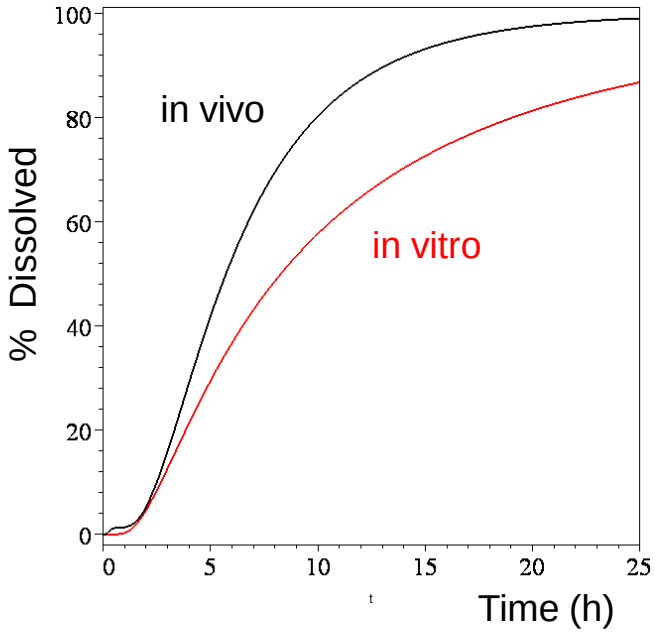


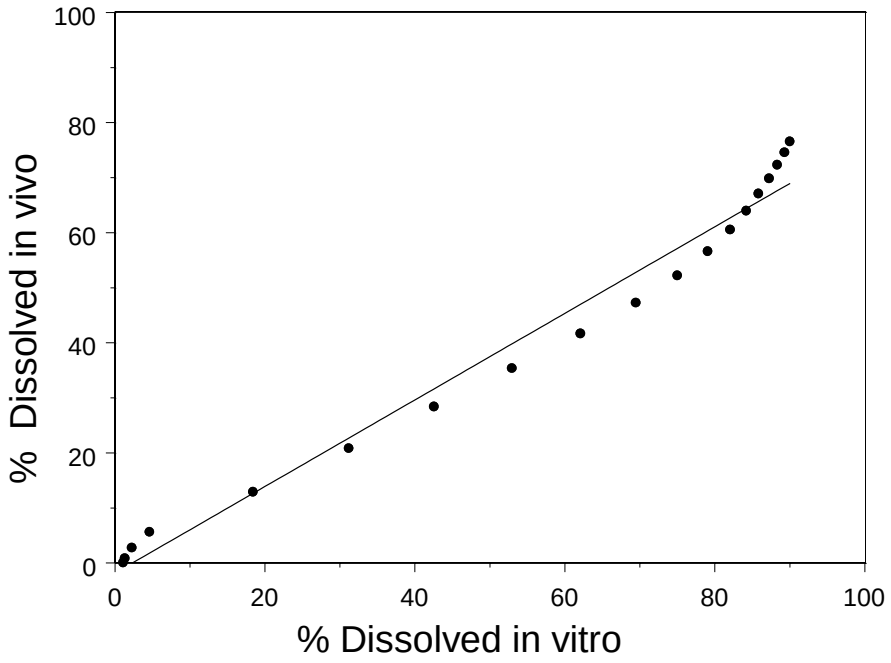


Effect of gastric emptying

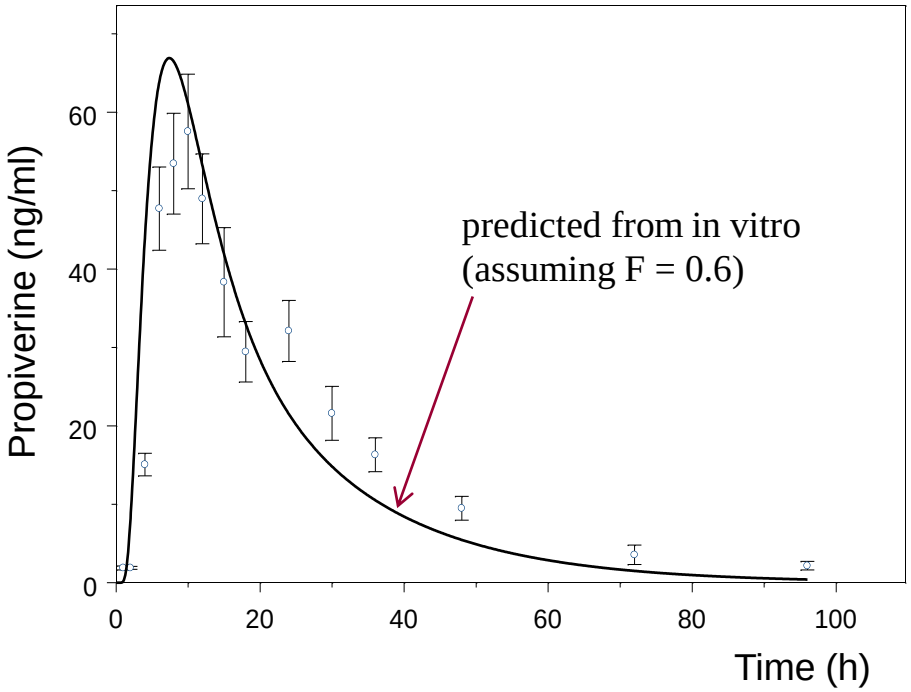
$$t_{in\ vivo} = a + bt_{in\ vivo}$$

Cardot and David, AAPS J, 2012



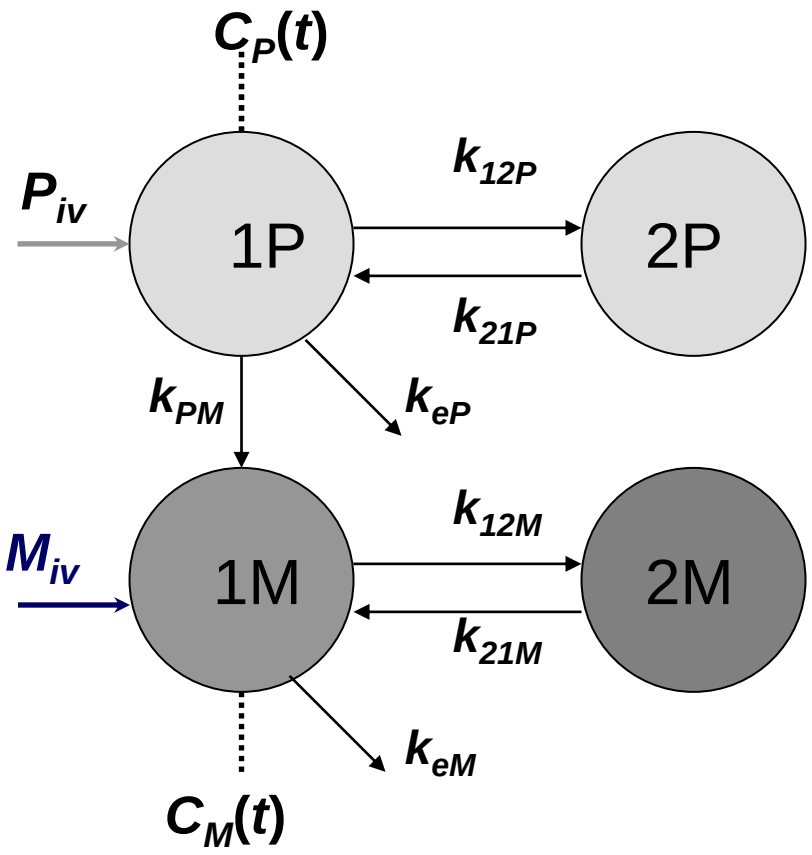


Extended release tablet



Metabolite Kinetics

Metabolite (M) formation after iv administration of parent drug (P)



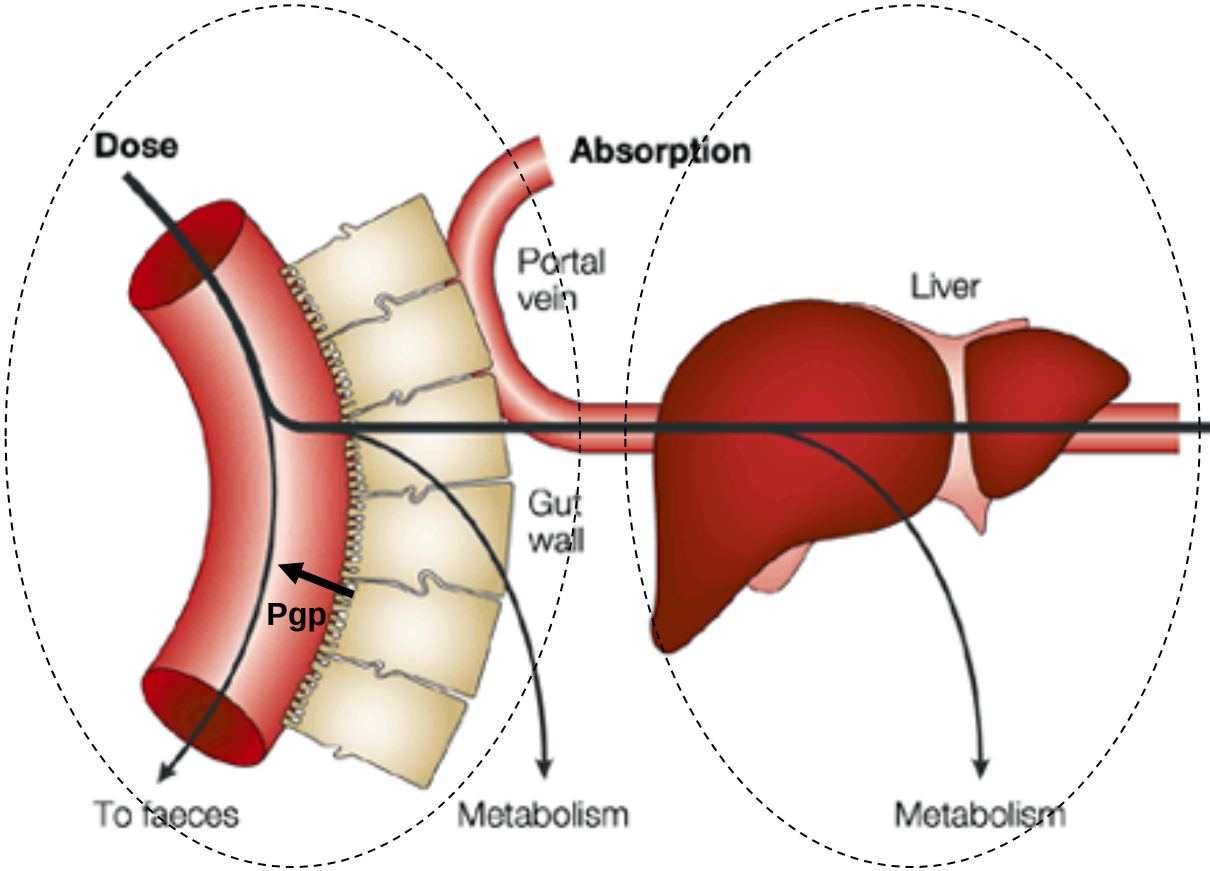
identifiable
only combinations:

$k_{eP} + k_{PM}$
k_{PM}/V_{1M}

1. Separate analysis of M disposition (M_{iv})

2. M disposition parameters fixed in fitting P and M formation data

First-pass Metabolite Formation

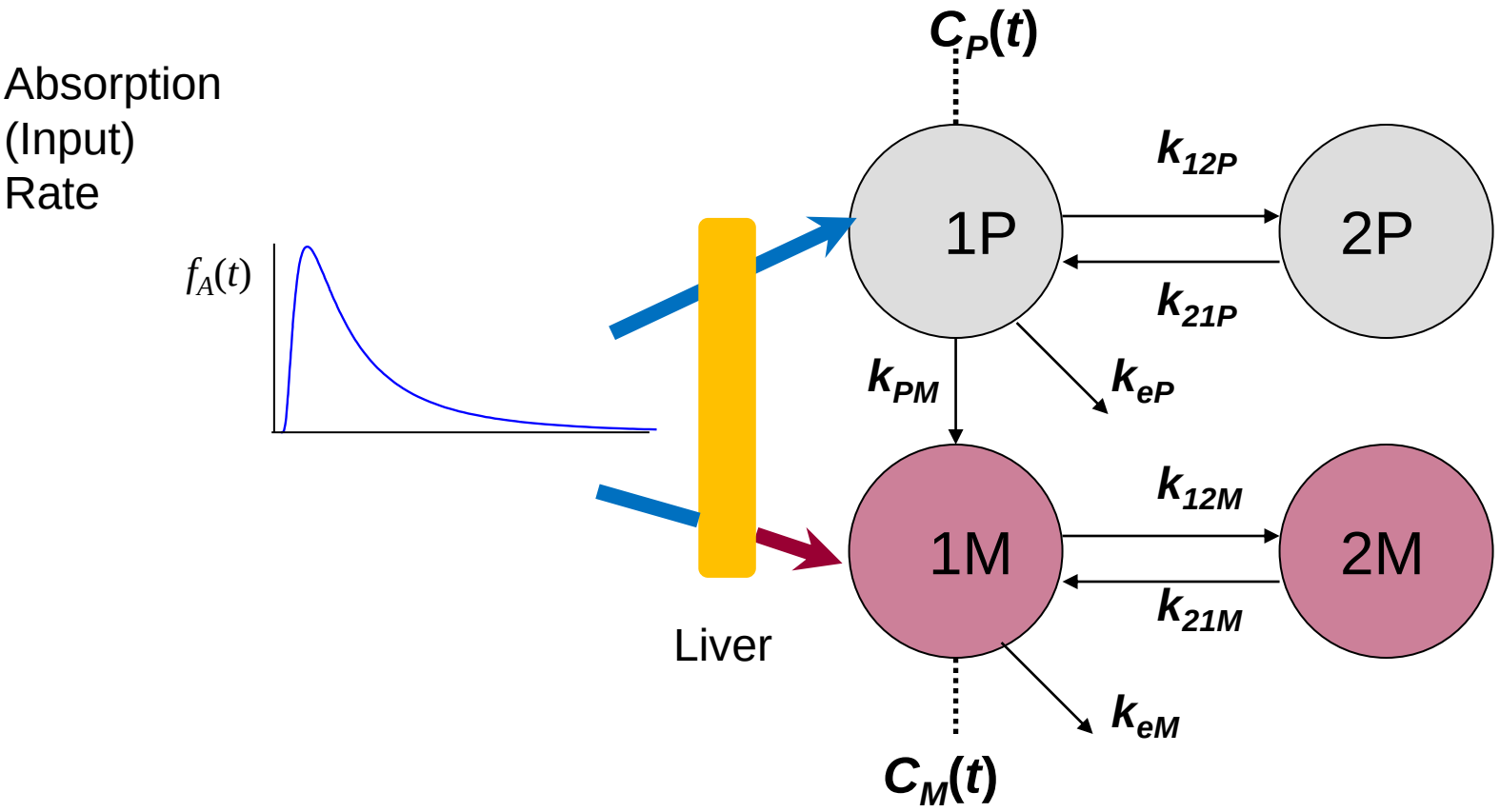


F_h Parent drug

$E_h = 1 - F_h$

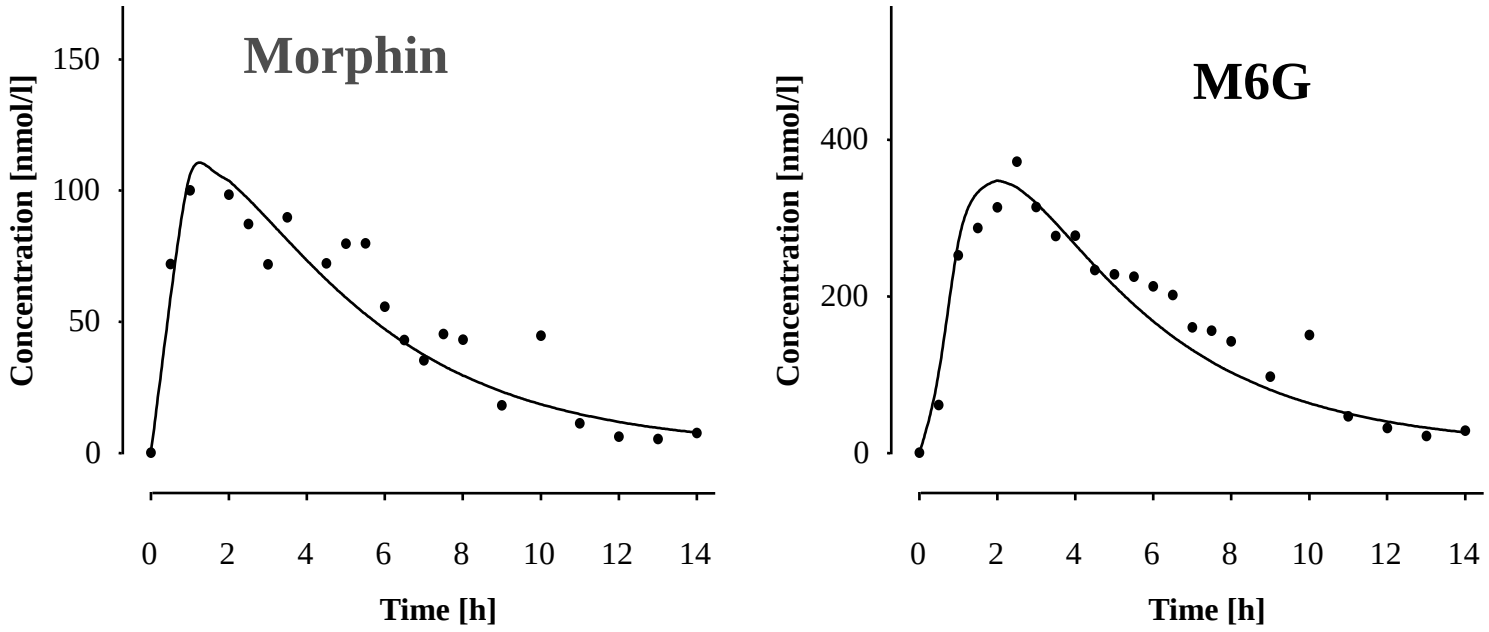
Formed metabolite

Absorption and Metabolite Kinetics



Modelling Metabolite Kinetics

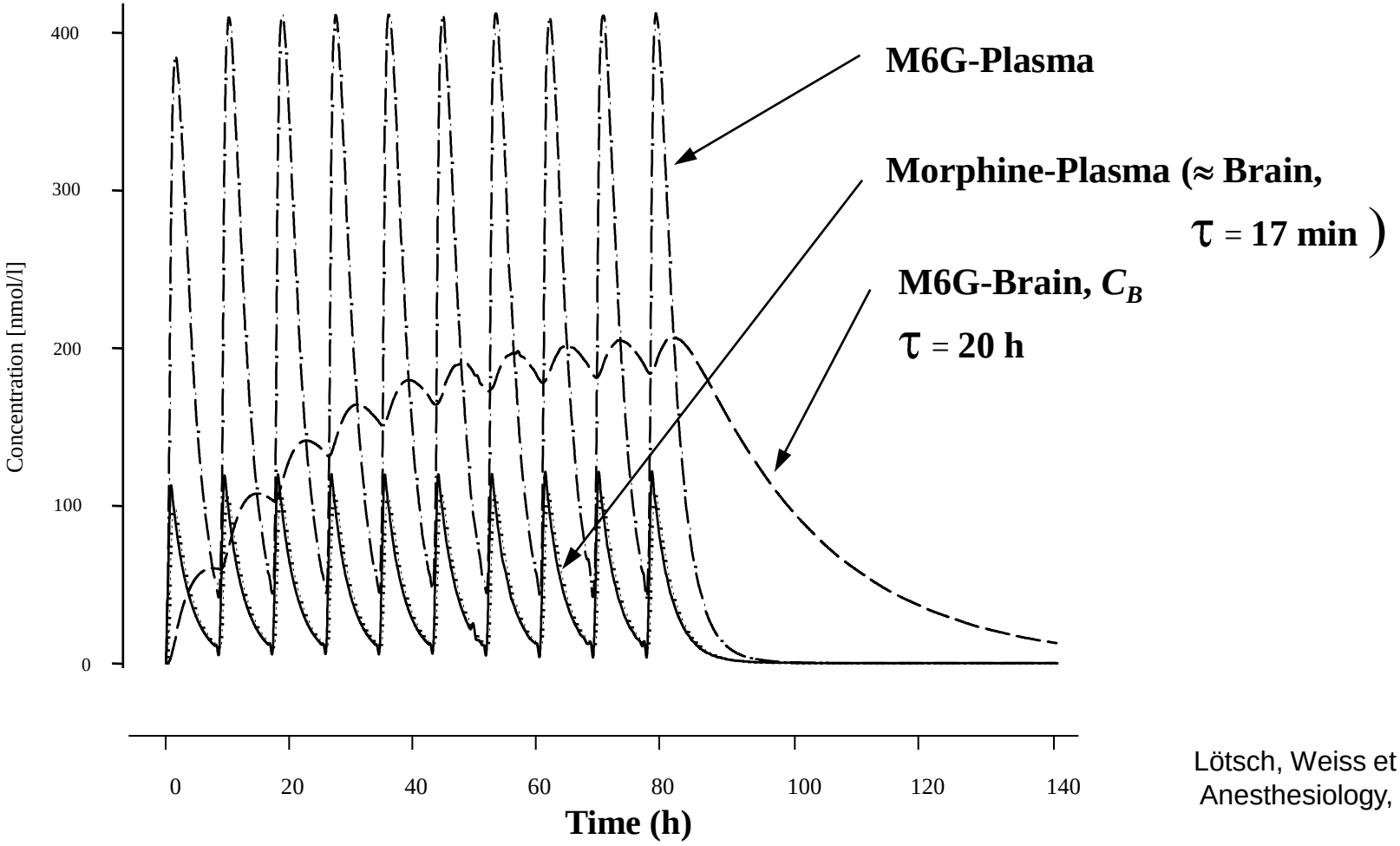
Morphin 90 mg sustained release tablet (MST®)



Lötsch, Weiss et al.: Anesthesiology, 1999.

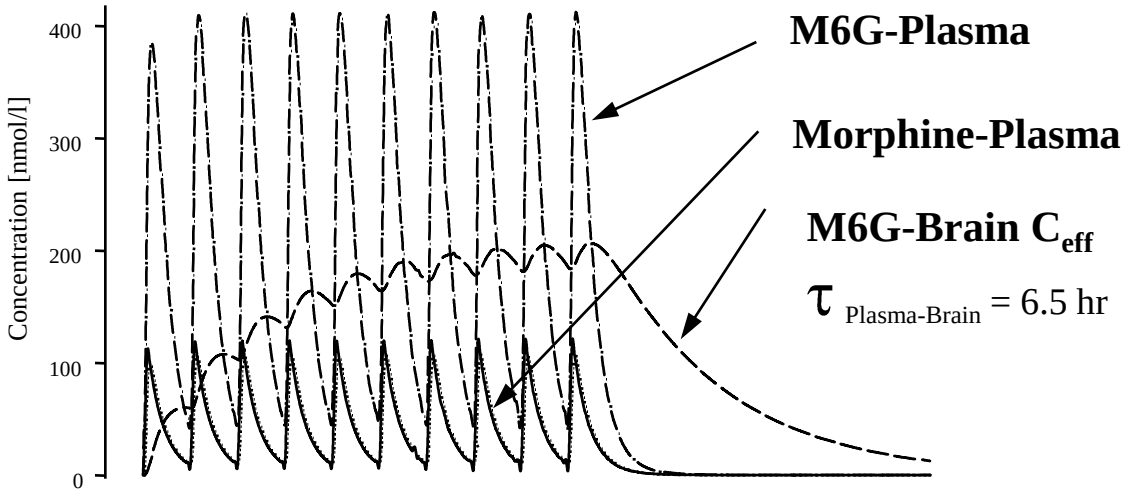
Simulation of M6G biophase concentration

(Morphin 90 mg tablets every 12 h for 5 d)

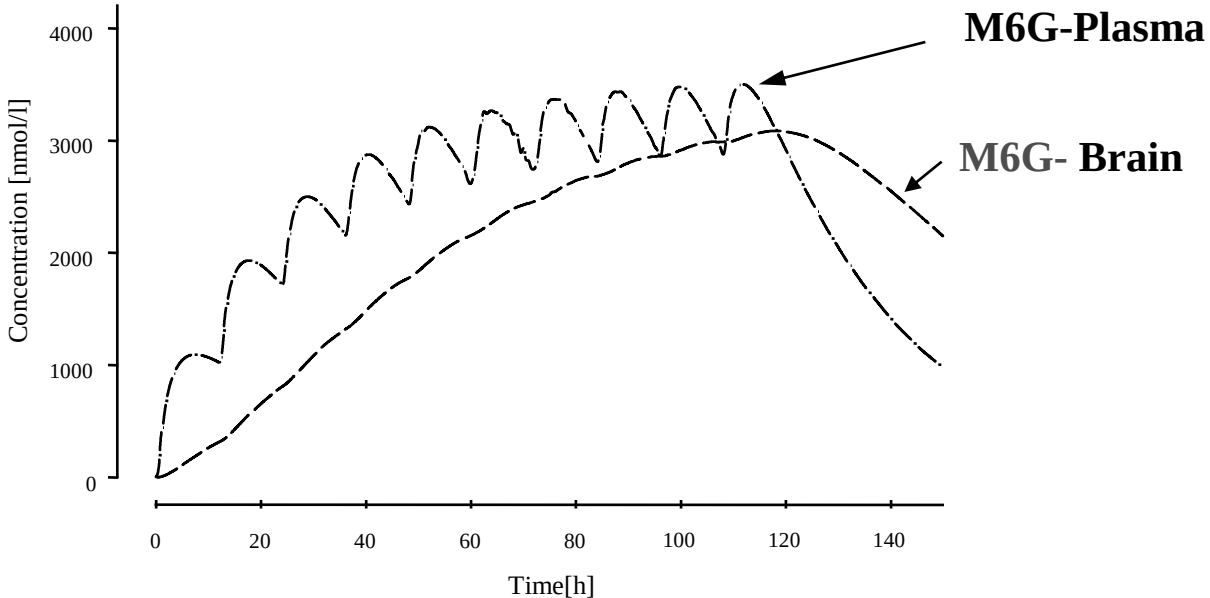


Lötsch, Weiss et al.:
Anesthesiology, 1999.

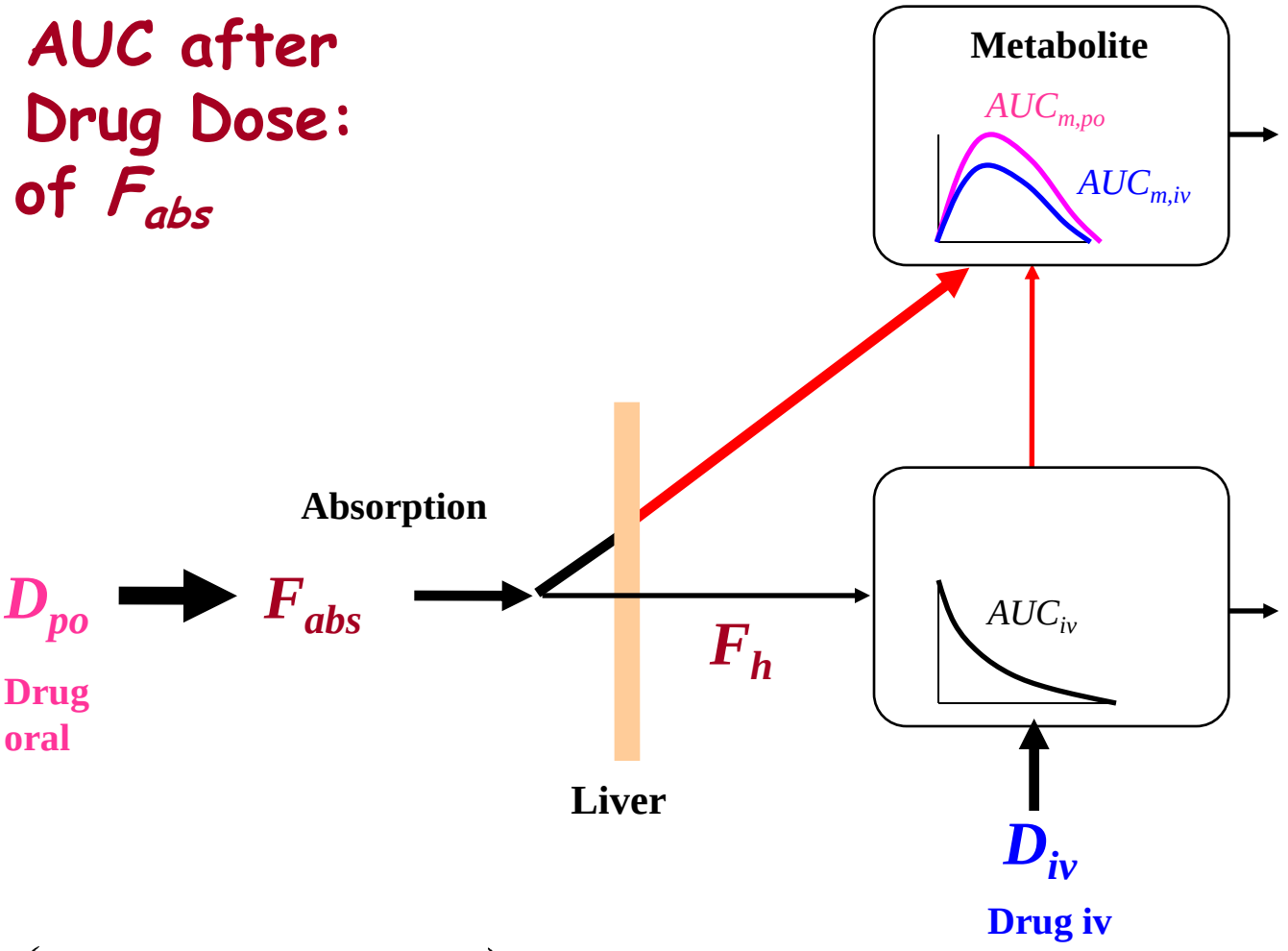
Simulation: Healthy CL_{M6G} = 162 ml/min



Renal failure: CL_{M6G} = 10. ml/min



Metabolite AUC after oral and iv Drug Dose: Estimation of F_{abs}



$$F_{abs} = F + f_m\left(\frac{AUC_{m,po}/D_{po}}{AUC_{m,iv}/D_{iv}} - F\right)$$

$$f_m = 1 - CL_R/CL$$

Weiss, Clin Pharmacokinet, 1990.

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