harmacokinetic

ations

First in Man: Animal to Human

Typically mice, rats, dogs to man

Compartmental models

Scale volumes and clearances using allometric principles

Doesn't take into account differences in body composition

"Blurring" of clearance & volume (distribution or absorption masked as clearance)

PBPK models

Define model as physiological and pharmacological parameters

"Swap" the physiological parameters for a new species

Keep the pharmacological parameters the same

(or vice versa for predicting a new drug in the same species!)

PBPK model parameters

Physiological

Organ size/volume

Organ blood flow

Organ composition (e.g. lipid content)

Organ enzyme contents

Haematocrit/plasma protein concentrations

Pharmacological

Partition coefficient

Free fraction

Kb values (binding)

Extraction ratio

Km values (enyzmes)

The Standard Sheep

Example of physiological data from the literature

Table 1
Data and references for a 45 kg standard sheep

	Organ size[a]	Reference	Weight (kg)	Perfusion (ml/min/100 g)	Flow (ml/min)	Reference	%CO
Blood	0.057	(Craigmill, 2003; Grimes, Buss, & Brace, 1987; Norberg et al., 2005)	2.56	11.9	5342		100
Lung	0.010	(Gardner et al., 2005; Hales, 1973)	0.45	11.9	5342		100
Brain	0.002	Hales (1973)	0.09	63	57	(Hales, 1973; Upton, Grant, & Ludbrook, 1994)	1.04
Heart	0.0037	Gardner et al. (2005)	0.167	160	266	(Hales, 1973; Talke et al., 2000)	4.89
Liver (PDV+artery)	0.016	(Barnes et al., 1983; Boxenbaum, 1980; Burrin, Ferrell, Britton, & Bauer, 1990; Craigmill, 2003; Gardner et al., 2005)	0.72	na	2581[b]	(Hales, 1973; Runciman, Mather, Ilsley, Carapetis, & Upton, 1984b; Talke et al., 2000)	47.40
PDV–stomach	0.032	Burrin et al. (1990)	1.45	70	1015	(Hales, 1973; Hales & Fawcett, 1993)	
PDV–small intestine	0.017	Burrin et al. (1990)	0.79	120	942	(Hales, 1973; Hales & Fawcett, 1993)	
PDV–large intestine	0.015	Burrin et al. (1990)	0.69	60	414	(Hales, 1973; Hales & Fawcett, 1993)	
PDV–spleen	0.0023	Gardner et al. (2005)	0.105	200	210	(Hales, 1973; Hales & Fawcett, 1993)	
Kidneys	0.0046	(Burrin et al., 1990; Craigmill, 2003; Gardner et al., 2005; Gilbert, Lang, Grant, & Nijland, 2005; Hales, 1973)	0.207	440	911	(Di Giantomasso, Morimatsu, May, & Bellomo, 2004; Hales, 1973; Hales & Fawcett 1993; Runciman, Ilsley, Mather, Carapetis,& Rao, 1984a; Ullman, Eriksson, & Rundgren, 2001)	16.73
Fat	0.168	Craigmill (2003)	7.56	6	454	(Barnes et al., 1983; Hales & Fawcett, 1993)	8.33
Muscle	0.277	(Craigmill, 2003; Hales, 1973)	12.47	6	748	Hales and Fawcett (1993)	13.74
Other (skin, marrow)	0.103	Hales (1973)	4.64	7	325	(Hales & Fawcett, 1993; Midtgard, Hales, Fawcett, & Sejrsen,, 1987)	5.97
Bone	0.070	Davies, Tan, and Broad (1884)	3.15	na			
GI contents	0.130	(Aziz, Murray, & Ball, 1992; Craigmill, 2003)	5.85	na			
Fleece	0.091	Schinckel (1955)	4.10	na			

Upton, J Pharmacol Toxicol Methods 2008; 58:198-205

The Standard Pig

Table 2
Data and references for a 25 kg Standard Pig

	Organ size[a]	Reference	Weight (kg)	Perfusion (ml/min/100 g)	Flow (ml/min)	Reference	%CO
Blood	0.06	(Buur, Baynes, Craigmil, et al., 2005; Buur, Baynes, Smith, et al., 2006; Vinegar, 1999)	1.200	10.3	2060	(Buur et al., 2005, 2006; Duddy et al., 1984; Vinegar, 1999)	
Lung	0.01	(Buur et al., 2005, 2006; Vinegar, 1999)	0.200		2060	(Buur et al., 2005, 2006; Vinegar, 1999)	
Brain	0.004	(Buur et al., 2005, 2006; Vinegar, 1999)	0.080	76.0	61	(Buur et al., 2005, 2006; van Woerkens, Duncker, Huigen, R. J., van der Giessen, & Verdouw, 1990; van Woerkens et al., 1992; Vinegar, 1999)	3.0
Heart	0.0037		0.074	120.0	89	(Duddy et al., 1984; van Woerkens et al., 1990, 1992)	4.3
Liver (PDV+artery)	0.0294	(Buur et al., 2005, 2006; Court et al., 2003; Vinegar, 1999)	0.588	107.0	629	(Buur et al., 2005, 2006; Duddy et al., 1984; Thein, Becker, Anetzberger, Hammer, & Messmer, 2003; van Woerkens et al., 1990, 1992; Vinegar, 1999)	30.5
PDV–stomach	0.007	Phuc and Hieu (1993)	0.140			van Woerkens et al. (1990, 1992)	
PDV–small intestine	0.025	Phuc and Hieu (1993)	0.500			van Woerkens et al. (1990, 1992)	
PDV–large intestine	0.018	Phuc and Hieu (1993)	0.360				
PDV–spleen	0.002	Phuc and Hieu (1993)	0.040				
Kidneys	0.004	(Buur et al., 2005, 2006; Vinegar, 1999)	0.080	360.0	288	(Buur et al., 2005, 2006; Duddy et al., 1984; Vinegar, 1999)	14.0
Fat	0.3	(Buur et al., 2005, 2006; Vinegar, 1999)	6.000	6.0	360	(Buur et al., 2005, 2006; Duddy et al., 1984; Vinegar, 1999)	17.5
Muscle	0.4	(Buur et al., 2005, 2006; Vinegar, 1999)	8.000	6.5	520	(Duddy et al., 1984; van Woerkens et al., 1990, 1992)	25.2
Other (skin, marrow)	0.0569		1.138	10.0	114	van Woerkens et al. (1990, 1992)	5.5
Bone	0.07		1.400				
GI contents	0.01		0.200				

Upton, J Pharmacol Toxicol Methods 2008; 58:198-205

Scaling body composition

Body composition varies with species

Sheep vs Pig

Standard sheep

17% fat and 28% muscle

Liver blood flow is 47% of cardiac output

Standard pig

30% fat and 40% muscle

Liver blood flow is 30% of cardiac output

Scaling size within a species

Animals come in different sizes, even within a species

To generate a simulated population:

1. Assume % body composition is the same

2. Scale organ size relative to the standard size

$$\text{OrganSize}_i = \text{OrganSize}_{std} * \left(\frac{\text{Weight}_i}{\text{Weight}_{std}}\right)^{1} * N\left(1, 0.08^2\right)$$

$$\text{OrganFlow}_i = \text{OrganFlow}_{std} * \left(\frac{\text{Weight}_i}{\text{Weight}_{std}}\right)^{0.75} * N\left(1, 0.15^2\right)$$

Upton, J Pharmacol Toxicol Methods 2008; 58:198-205

Scaling organ distribution

Consider a membrane-limited model

Measured apparent distribution volumes (V_{app}), permeabilty (PS) and blood flow (Q)

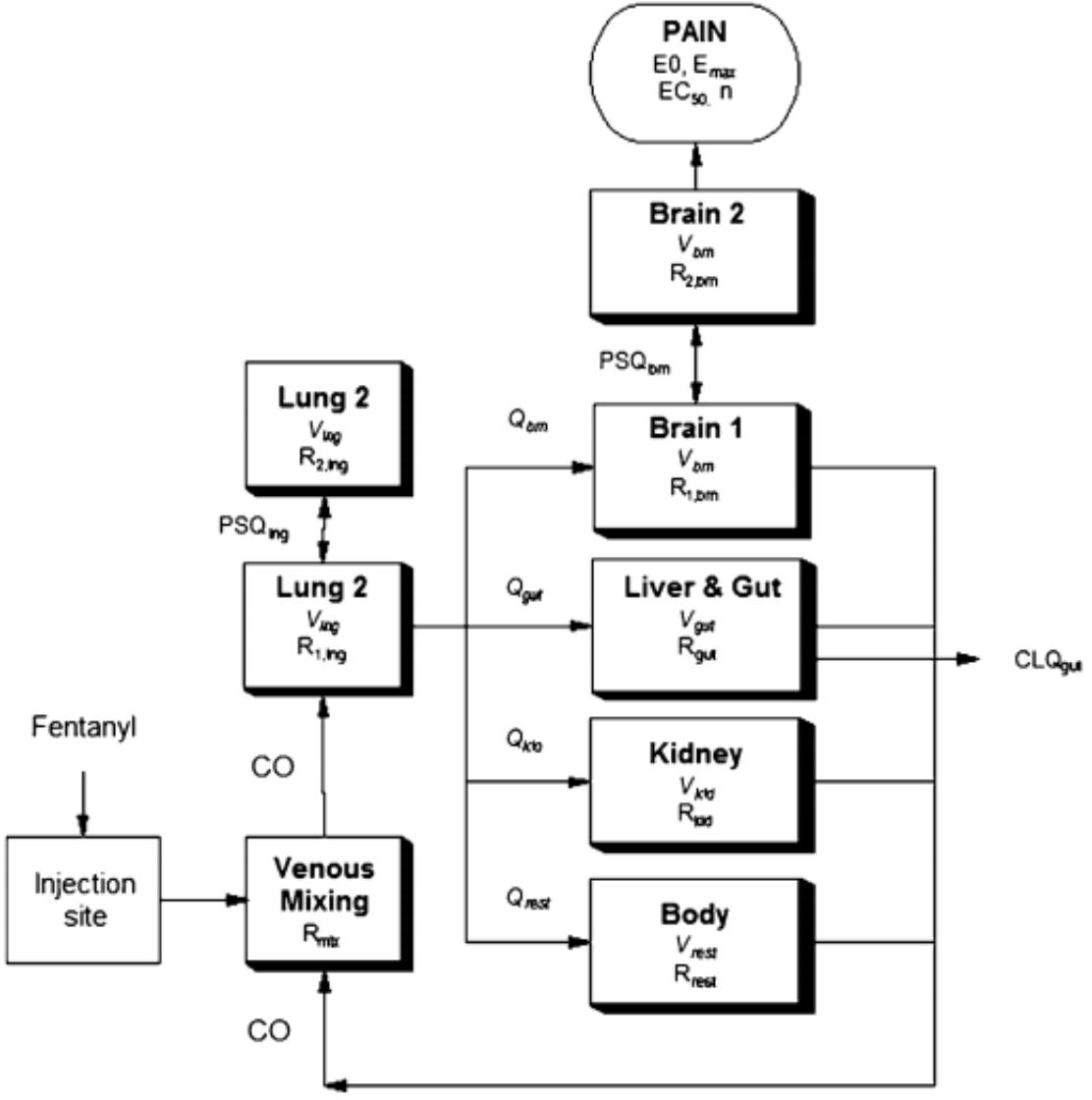
ANIMAL		MAN
Dimensioned	Dimensionless	Dimensioned
$V_{app,a}$ (L)	$R = V_{app,a}/V_{real,a}$	$V_{app,m} = R.V_{real,m}$ (L)
PS_a (L/min)	$PSQ = PS_a/Q_a$	$PS_m = PSQ.Q_m$ (L/min)

Scaling organ elimination

Measured organ clearance (CL) blood flow (Q)

ANIMAL		MAN
Dimensioned	Dimensionless	Dimensioned
CL_a (L/min)	$E = CL_a/Q_a$	$CL_m = E.Q_m$ (L/min)

A recirculatory model of fentanyl in man



Scaling membrane limited distribution

Table 3 Estimated lung and brain kinetics of fentanyl in man

Organ	Parameter	Value	Unit	Dimensionless parameter	Value
Lung	Weight	0.91	kg		
	Flow	6.31	L/min		
	V_1	12.89	L	R_1	14.156
	PS	1.56	L/min	PSQ	0.247
	V_2	29.55	L	R_2	32.44
Brain	Weight	1.311	kg		
	Flow	0.686	L/min		
	V_1	0.065	L	R_1	0.05
	PS	2.88	L/min	PSQ	4.21
	V_2	7.13	L	R_2	5.44

Values were estimated via allometric scaling of data collected in sheep [3]

Upton et al., J Pharmacokinetic Pharmacodyn 2012; 39: 561-76

A recirculatory model of fentanyl in man

Table 6 Pharmacological parameter values for the Standard Man model

Parameter symbols	Description	Value	SD	Origin
R_{mix}	Venous mixing compartment, fraction of body weight	0.0253	na	Fitting Scott data
$R_{1,lng}$	Partition coefficient of first lung compartment	14.16	na	Scaled sheep model
PSQ_{lng}	Permeability ratio of lung as fraction of CO	0.247	na	Scaled sheep model
$R_{2,lng}$	Partition coefficient of second lung compartment	32.4	na	Scaled sheep model
$R_{1,brn}$	Partition coefficient of first brain compartment.	0.05	na	Scaled sheep model
PSQ_{brn}	Permeability ratio of brain as fraction of cerebral blood flow	4.21	na	Scaled sheep model
$R_{2,brn}$	Partition coefficient of second brain compartment	5.44	na	Scaled sheep model
R_{vis}	Partition coefficient of visceral compartments (liver and kidney)	5.08	1.64	Fitting Scott data
CLQ_{gut}	Extraction ratio across liver and gut	0.437	0.0081	Fitting Scott data
R_{rest}	Partition coefficient of rest of body compartment	6.59	0.042	Fitting Scott data
$R_{1,arm}$	Partition coefficient of first arm compartment.	0.247	na	Fitting Moksnes data
PSQ_{arm}	Permeability ratio of arm as fraction of muscle blood flow	0.345	na	Fitting Moksnes data
$R_{2,arm}$	Partition coefficient of second arm compartment	2.30	na	Fitting Moksnes data

Upton et al., J Pharmacokinetic Pharmacodyn 2012; 39: 561-76

Intravenous Magnesium

Used for a number of diseases, including preeclampsia

Relaxes smooth muscles in blood vessels

- Lowers systemic vascular resistance
- Decreases mean arterial blood pressure
- Increases in cardiac output

Dosing is often empirical, based on observed cardiovascular variables

Magnesium Pharmacokinetics

The clearance of magnesium is renal, but it can be reabsorbed or excreted in the tubules, as dictated by homeostatic requirements

Predominant loss from blood is by cellular uptake. This occurs in all tissues, and is potentially blood flow (cardiac output) dependent

A Study of Magnesium in Sheep

A chronically instrumented sheep preparation

Training data set (30 mmol over 2 min)

Arterial blood samples for PK

Cardiovascular measurements

LVEDP - Left ventricular end diastolic pressure

MAP - Mean arterial blood pressure

SVR - Systemic vascular resistance

CO - Cardiac output

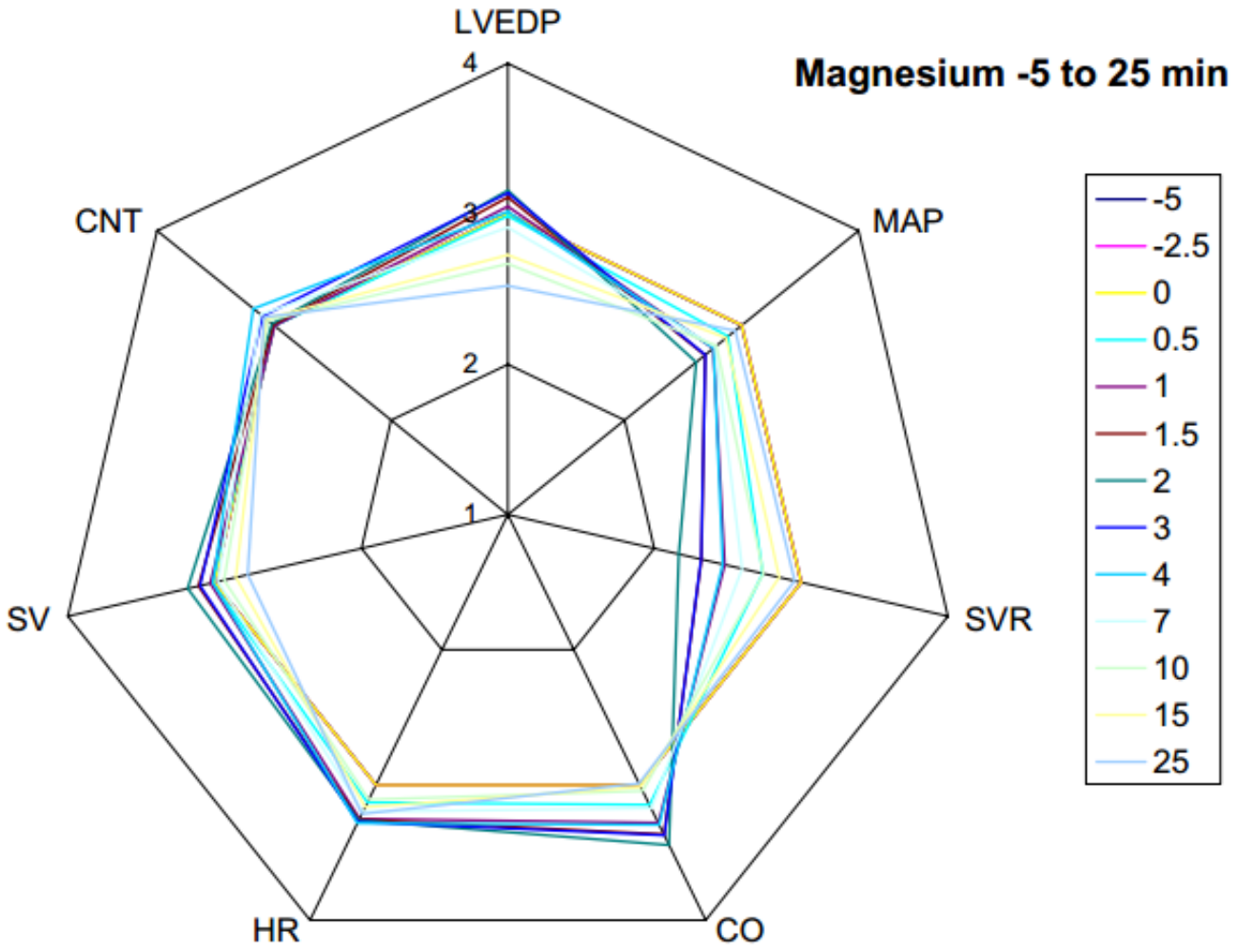
HR - Heart Rate

SV - Stroke Volume

CNT - Contractility

Magnesium - Observed data

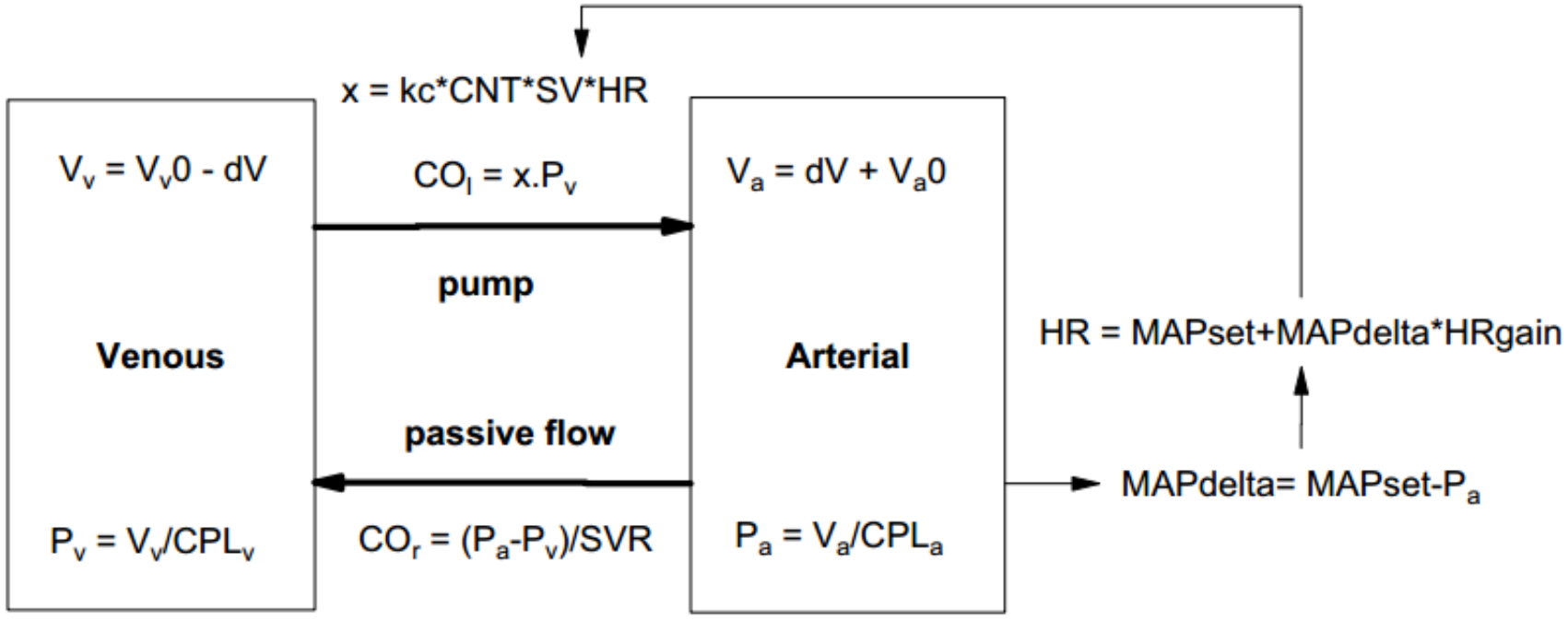
3 = baseline; 2 = baseline/2; 4 = baseline.2



Magnesium - PD model

A simple model of the cardiovascular system

Two "stressed" blood volumes, active pump, passive return

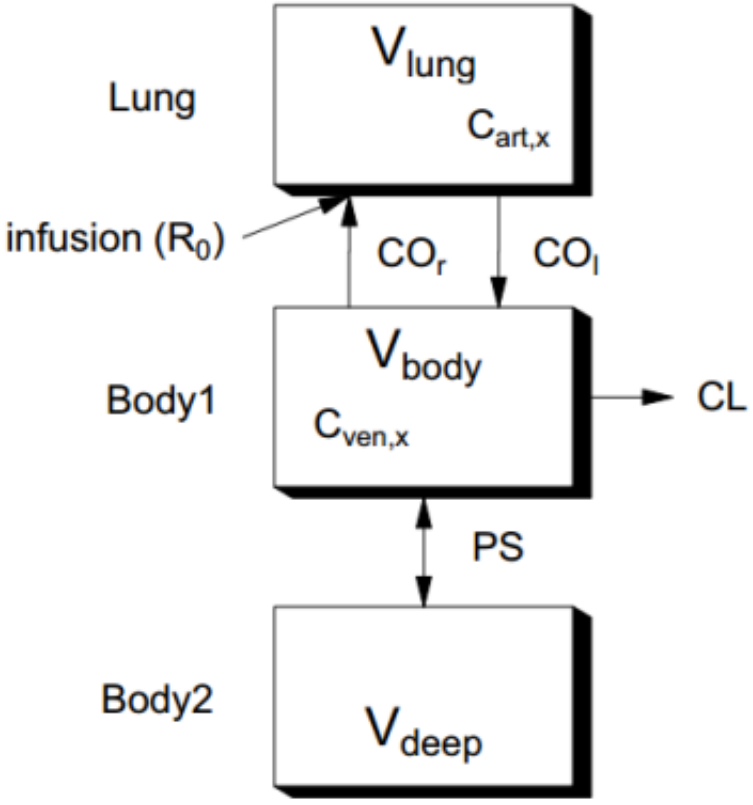


Upton & Ludbrook, BMC Pharmacology 2005; 5:5, 10 Mar

Magnesium - PK model

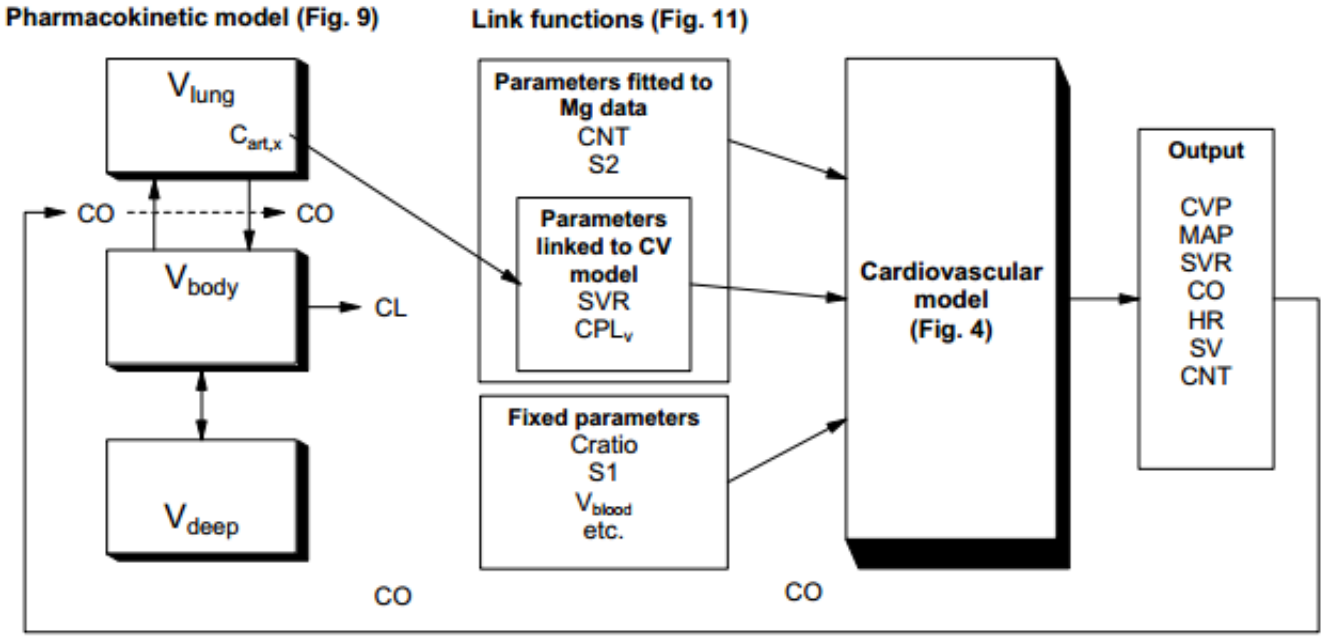
A 2 compartment recirculatory model with CO as a parameter

Distribution into intracellular stores (PS)

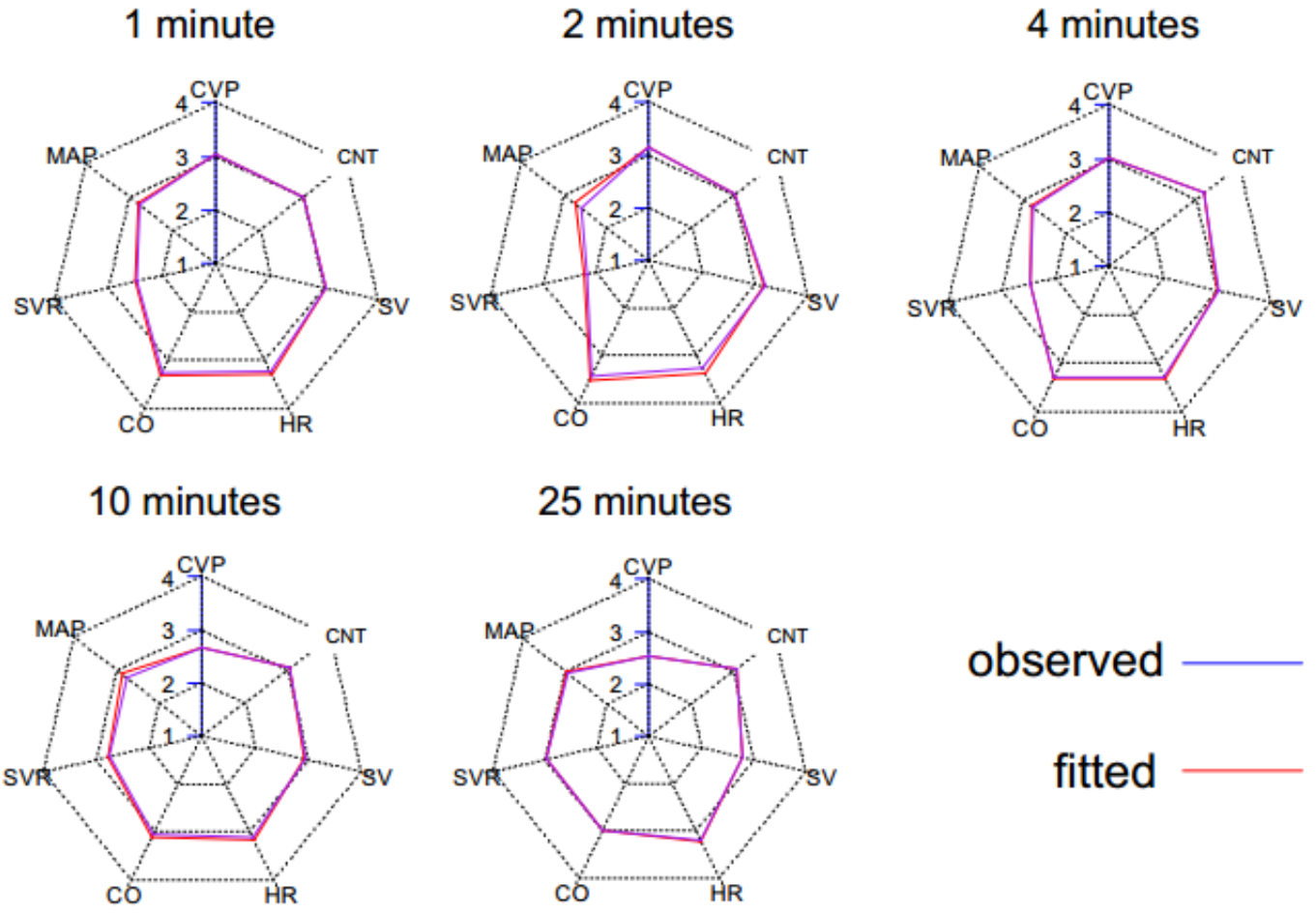


Magnesium - PKPD model

Feedback between the PK and PD models via link functions

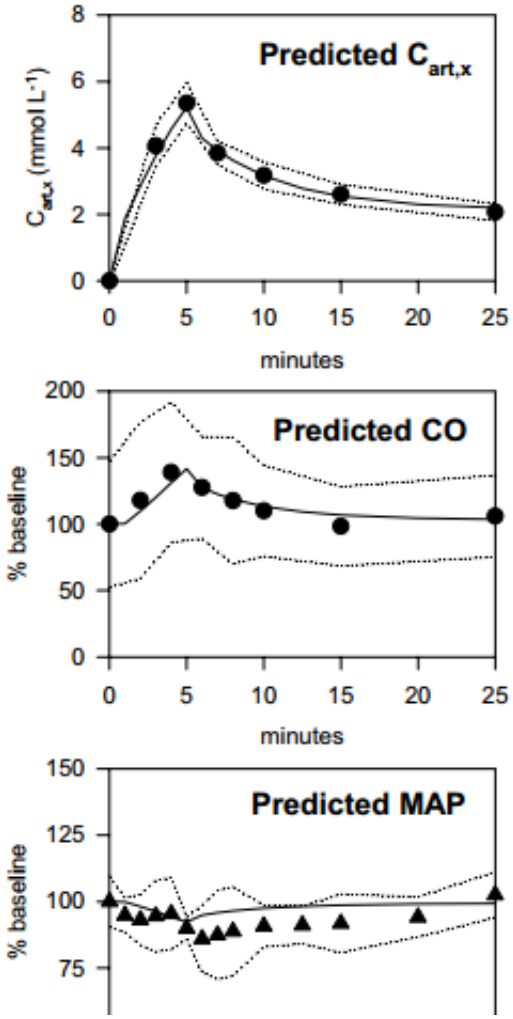


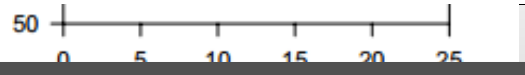
Magnesium - Observed vs Fitted



Magnesium - Validation data

Prediction of a validation data set (30 mmol over 5 min)




50
0
5
10
15
20
25

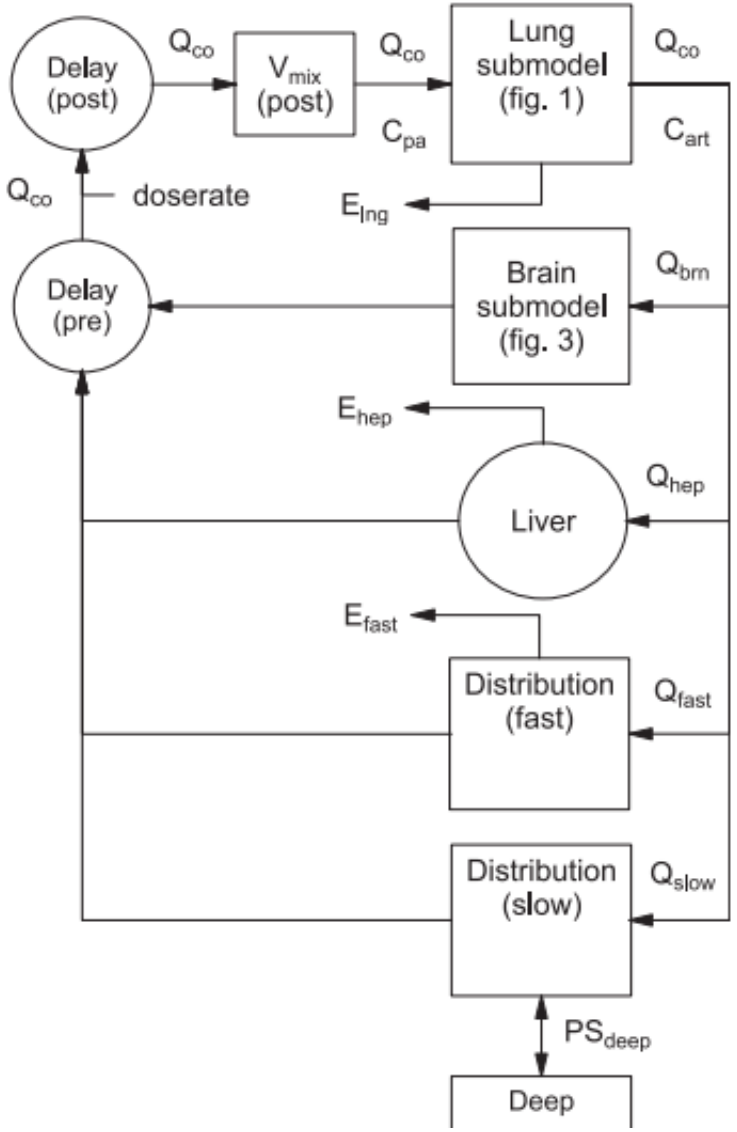
Propofol

- Intravenous anaesthetic
- GABA agonist (and other receptors)
- Depression of neuronal activity evident in the EEG
- Propofol concentration in the CNS determines the time-course of anaesthesia

Why not include the target organ in a model of propofol kinetics?

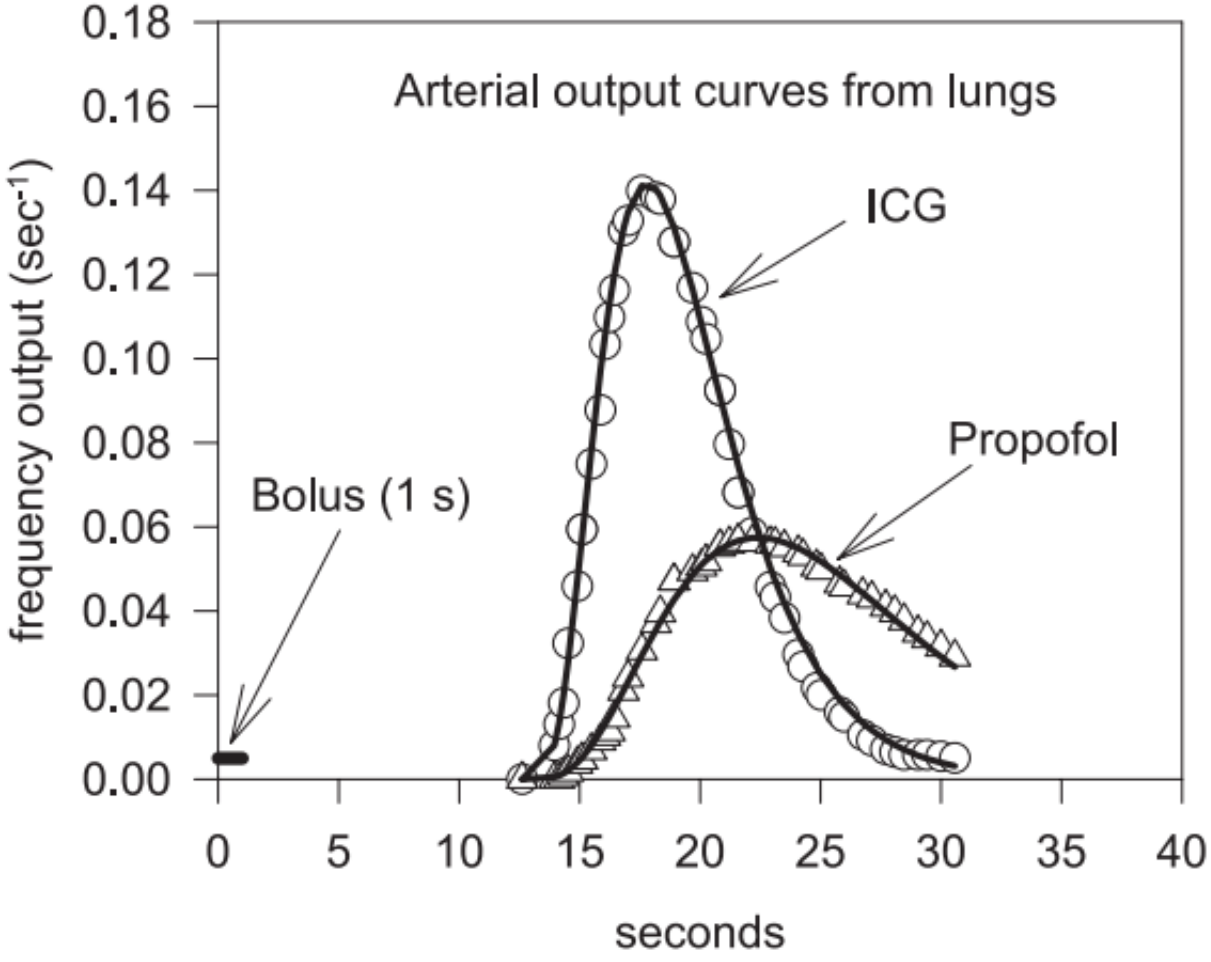
Upton & Ludbrook, Anesthesiology 2005; 103:344-52

Propofol - Recirculatory Model



Propofol - Lung Sub-model

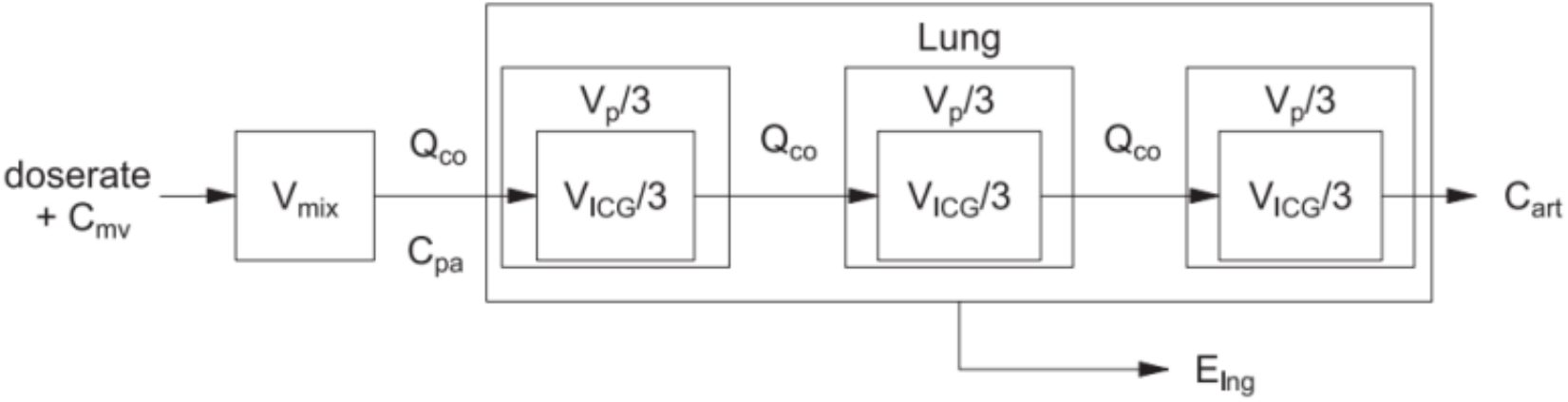
ICG = concurrent intra-vascular marker



Propofol - Lung Sub-model

Flow = Cardiac output (Q_{co})

Input = Pulmonary artery (C_{pa}); Output = Aorta (C_{art})



Propofol - Brain Sub-model

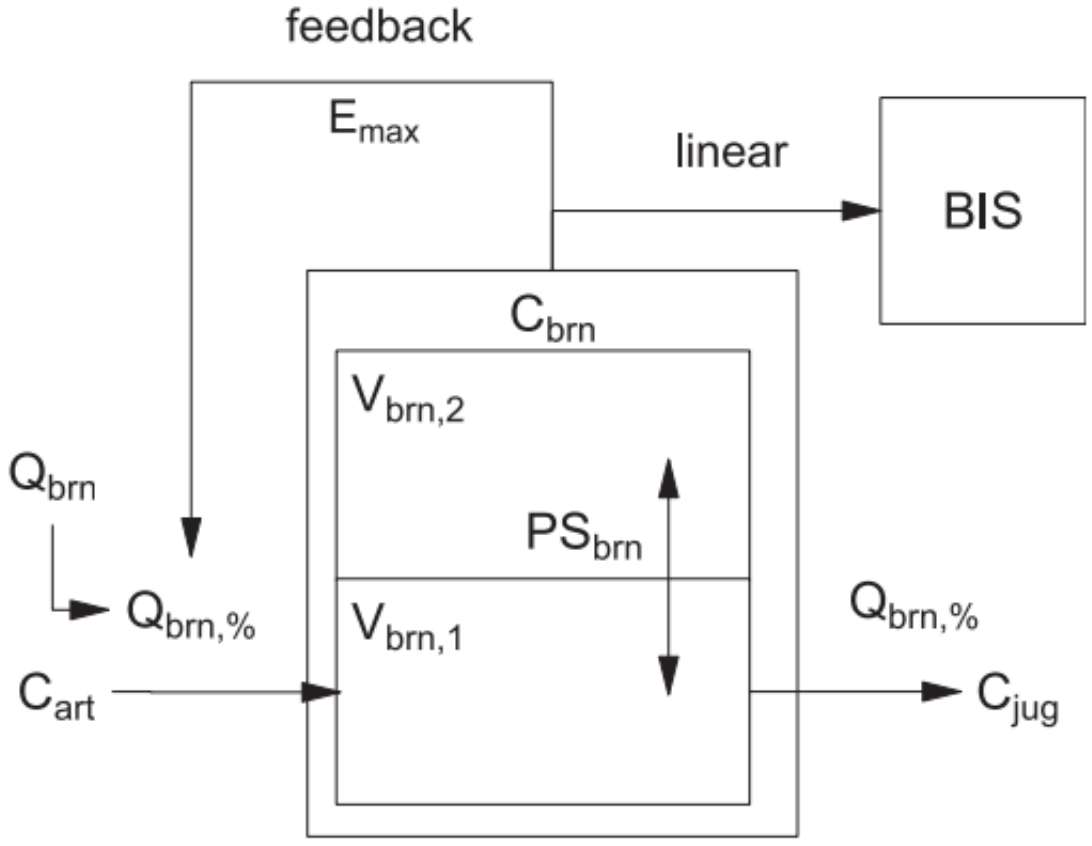
Input = Aorta (C_{art}); Output = Jugular bulb (C_{jug})

BIS = Depth of anaesthesia

Propofol - Brain Sub-model

Membrane limited model

Feedback effect on cerebral blood flow



Standard Man to Population model

This was NOT a population model!

Mean data, Standard Man physiology

Fitting in MATLAB & Simulink

Can you predict a population? Maybe…

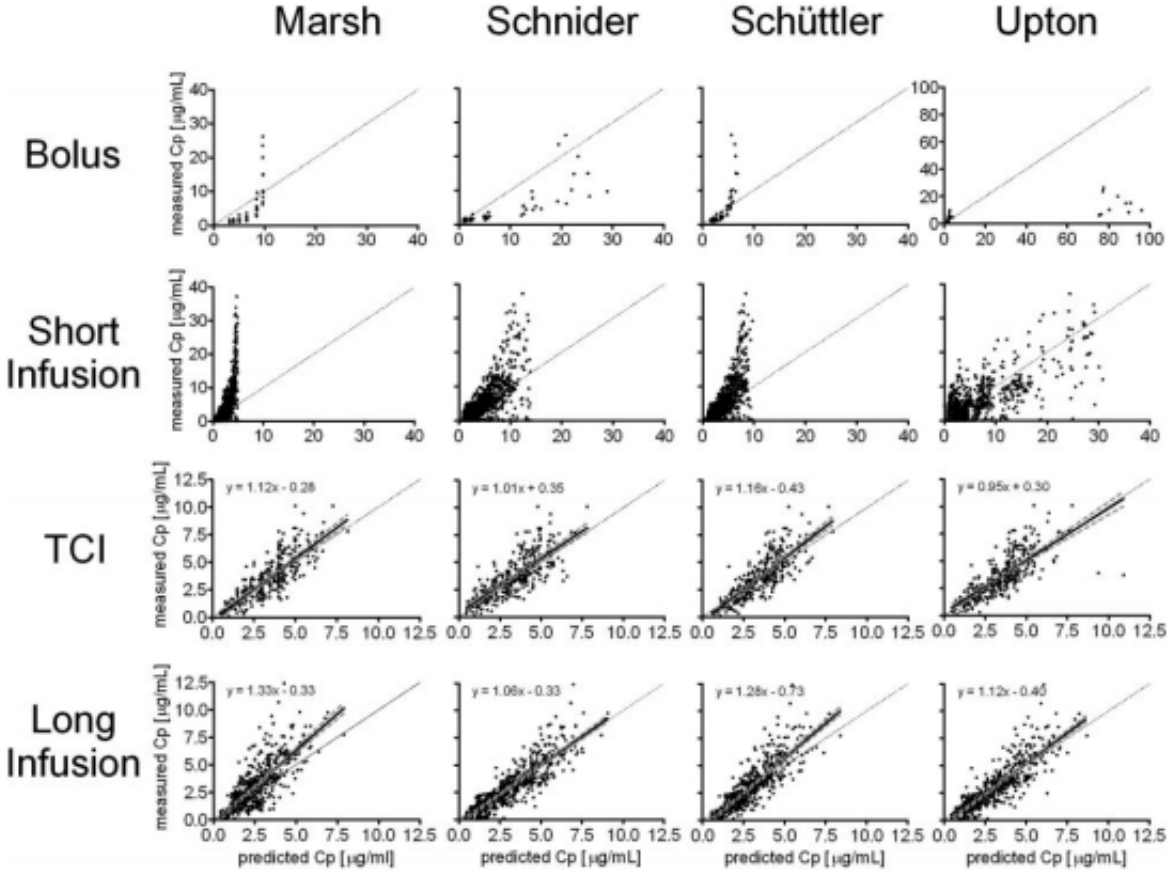
$$CO_i = 5.66 * \left(\frac{Weight_i}{70}\right)^{0.41} * \left(1.03 + 0.0295 * (Age/30) + 0.0603 * (Age/30)^2\right)$$

$$OrganSize_i = OrganSize_{std} * \left(\frac{Weight_i}{70}\right)^{1}$$

Now predict arterial propofol concentrations for an extensive database of real patients!

The harsh reality

"Performance of compartmental and physiologically-based, recirculatory pharmacokinetic models for propofol "



Masui et al., Anesthesia and Analgesia 2010; 111: 368-79

Leflunomide/Teriflunomide

undetectable parent, first-pass metabolism, blood-borne metabolism, extensive protein binding, entero-hepatic recycling, genetic influence on transporters & CYP's

Leflunomide conversion

Blood born degradation

Fentanyl in the elderly

You are a pharmacologist working in an Anaesthetic Department

What happens to the kinetics of fentanyl in the elderly?
Why do you need 1/4 of the dose of a fit young person?

The literature has no published model of fentanyl in the elderly

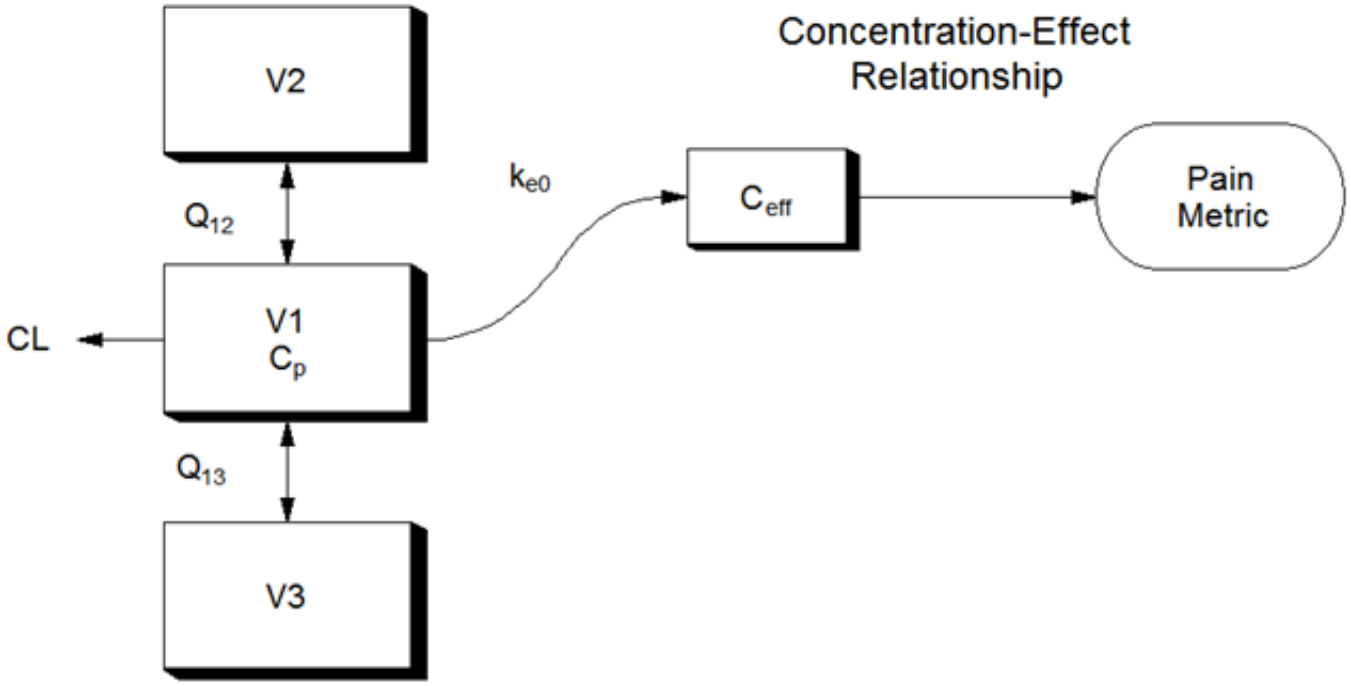
From first principles, what happens to drug kinetics when people age?

Physiology of aging

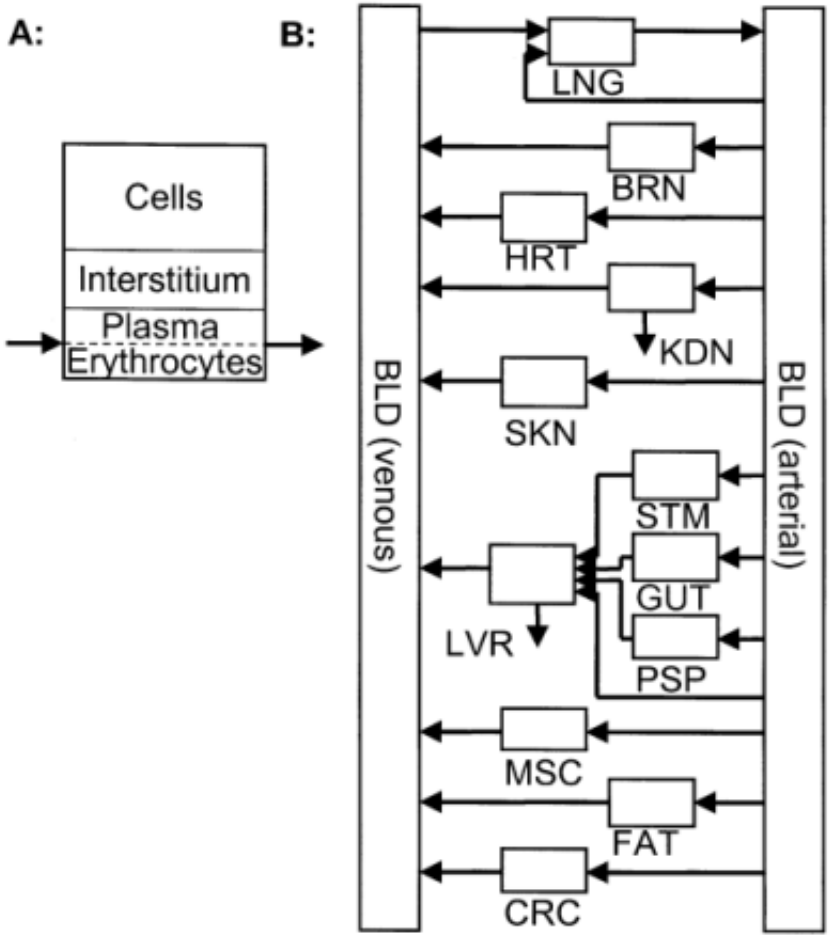
Physiological process	Magnitude	Likely kinetic/dynamic consequence	Dose strategy
Whole body			
Cardiac output	↓ 0–20%	↓ Central compartment volume ↑ Peak concentrations after bolus	•Smaller initial bolus dose •Slower injection rate
Fat Muscle mass/blood flow	↑ 10–50% then ↓ ↓ 20%	Drug specific changes in distribution volume	•Drug specific - dose based on total body weight or lean body weight
Plasma volume	Little change		
Total body water	↓ 10%	↓ Distribution volume (water-soluble drugs)	
Plasma albumin Alpha-glycoprotein Drug binding	↓ 20% ↑ 30–50% drug specific	↑ Free fraction of drug ↔ hepatic clearance of high-extraction drugs ↑ hepatic clearance of low extraction drugs ↑ cerebral uptake of drug	•Potential for changes in clearance and oral bioavailability •Potential for changes in cerebral effects
Liver & Gut			
Liver size Hepatic blood flow	↓ 25–40% ↓ 25–40%	↓ hepatic clearance of high-extraction drugs ↔ hepatic clearance of low extraction drugs	•Minimal effect on i.v. bolus •↓ Maintenance dose •Potential for changes oral bioavailability
Phase I (e.g. oxidation) Phase II	↓ 25% Little change	↓ hepatic clearance (some low extraction drugs)	•Minimal effect on i.v. bolus •↓ Maintenance dose •Potential for changes in oral bioavailability
Kidney			
Nephron mass Renal blood flow Plasma flow at 80 years Glomerular filtration rate Creatinine clearance	↓ 30% ↓ 10% per decade ↓ 50% ↓ 30–50% ↓ 50–70%	↓ clearance (polar drugs) little effect on opioids (parent compound) ↓ clearance of some active metabolites (e.g. M6G).	•↓ maintenance dose (renally cleared drugs) •Assume, and monitor for, accelerated accumulation of polar active (M6G) or toxic (M3G, norpethidine) metabolites
CNS			
Cerebral blood flow and metabolism Cerebral volume	↓ 20% ↓ 20%	↓ Distribution to the CNS ↓ Apparent volume in the CNS	•Little net effect
Active BBB transport (efflux)	↓ (drug specific)	↑ Apparent volume in the CNS ↑ Apparent increase in CNS sensitivity	•↓ Bolus dose during titration •↓ Maintenance dose
Pain threshold/sensitivity	Little change		•Need for titration unchanged
Concentration response (opioids)	↑ 50% for some opioids	↑ Response to opioids	•↓ Bolus dose during titration •↓ Maintenance dose

MacIntyre, Clinical Pain Management-Acute, Edward Arnold, 2002 pp 463

Modify this model for the elderly!



Modify this model for the elderly?



Bjorkman, J Pharmacokinet Biopharm. 1994; 22:381-410.

Conclusions

Investigate models beyond the 1, 2 & 3 compartment mamillary

Make some (informed!) assumptions, or use data beyond arm venous plasma concentrations

Old data/papers may be valuable pieces of the puzzle

Learn software to solve differential equations

There is more work to do. For example, how reliable is this equation for fit, healthy adults?

$$\text{LiverFlow}_i = 1.5 * \left(\frac{\text{Weight}_i}{70}\right)^{0.75} * \left(\frac{\text{Age}_i}{30}\right)^{x}$$