Pharmacokinetic Analysis
A Historical Perspective

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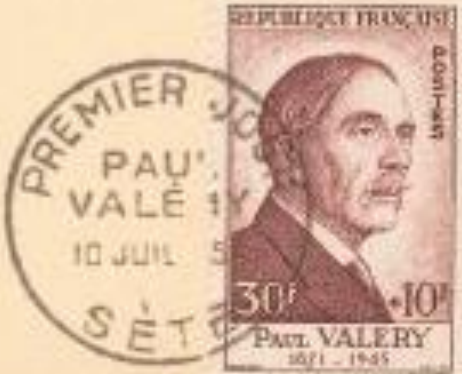
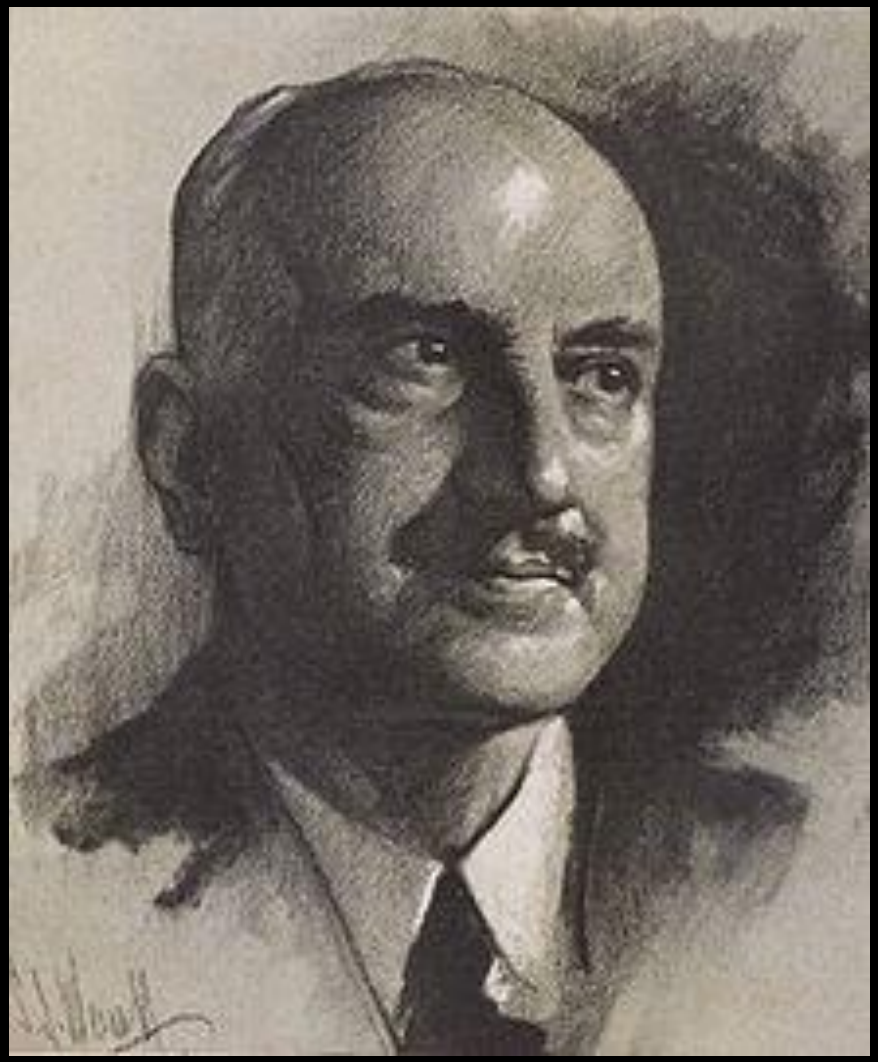


Nous entrons dans l'avenir à reculons

We enter the future backwards

Variété, la Politique de l'esprit



George Santayana
(1863-1952)

Those who cannot remember the past are condemned to repeat it

Reason in Common Sense, 1905: 284.

Pharmacokinetics

- Pharmacokinetics is the science of the quantitative analysis of the interaction between an organism and a drug.

F H Dost

Der Blütspiegel. Kinetic der Konzentrationsablaüfe in der Frieslaufflüssigkeit, 1953

Pharmacokinetics

- Pharmacokinetics is the study of the kinetics of absorption, distribution, metabolism, and excretion of drugs and their corresponding pharmacological, therapeutic, or toxic effects in animals and man. The development of mathematical models is virtually essential to the interpretation of kinetic phenomena.

JPB Editors, 1973

Pharmacokinetics

- Pharmacokinetics is the mathematical analysis of the absorption, distribution, and elimination of drugs as a function of time in animals and humans.

Buchanan, 1847

- The brain content of anaesthetics determines the depth of narcosis and depends on the arterial concentration, which is in turn related to the concentration of inhaled ether.
- The speed of recovery is related to redistribution of ether in the body
- Calculated the amounts of ether inhaled, exhaled, and retained during induction

A Buchanan. Physiologic effects of the inhalation of ether. London Medical Gazette 1847; 39: 715-7.

Widmark & Tandberg, 1924

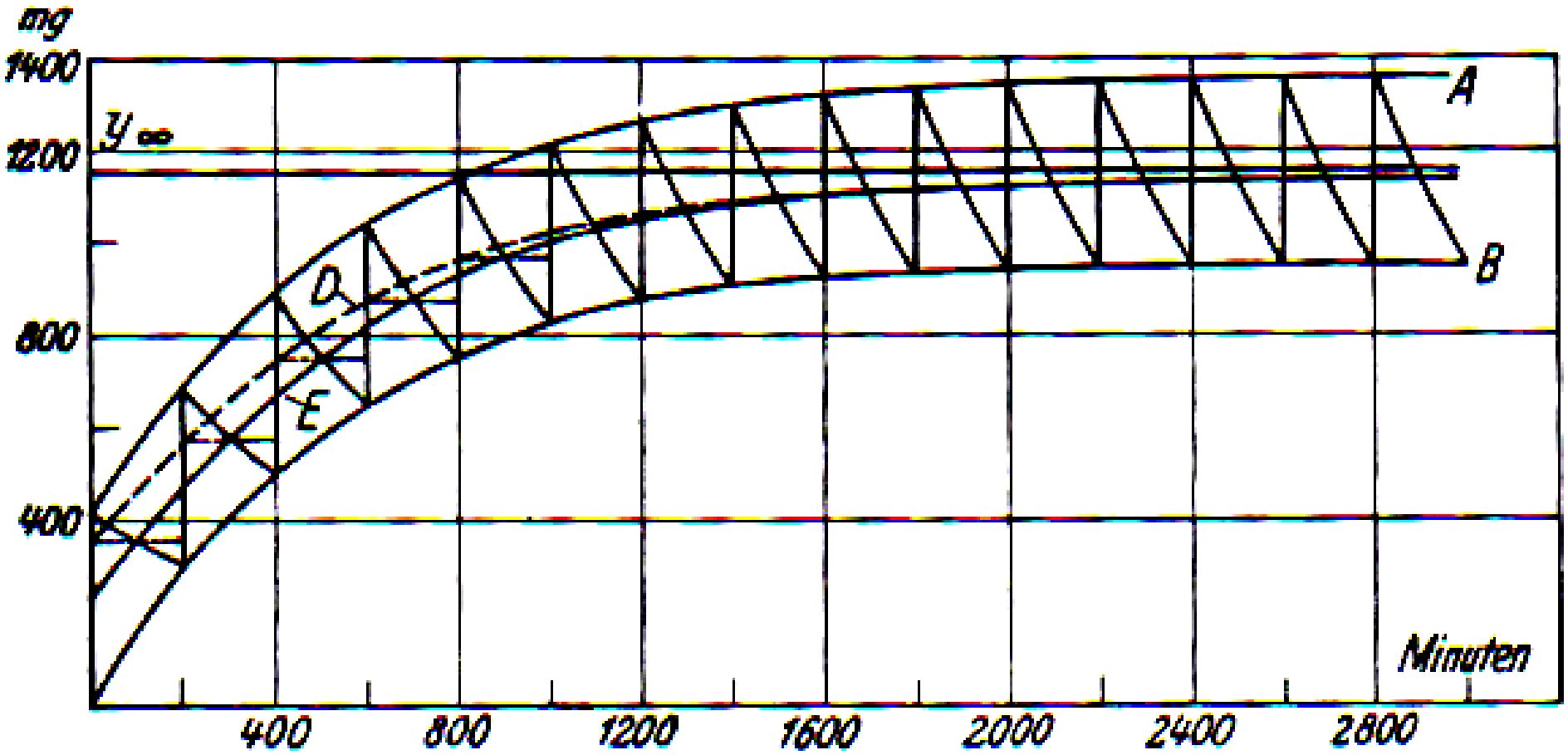


Abb. 2. Intermittente Zufuhr. Konstanten wie in Abb. 1. Verlauf der Kurven *A*, *B*, *D* und *E*.

Widmark E, Tandberg J. Uber die bedingungen für die Akkumulation Indifferenter Narkotika: Theoretische Berechnungen. Biochemische Zeitschrift 1924; 147: 358-69.

One-compartment model

$$dC/dt = -kC$$

$$C(t) = C(0)e^{-k_{10}t}$$

$$C(t) = C_{ss}(1-e^{-k_{10}t})$$

Physiological correlates

$$V = \bar{t}Q$$

$$\bar{t} = \frac{\int_0^\infty tC\,dt}{\int_0^\infty C\,dt}$$

Hamilton WF, Moore JW, Kinsman JM, Spurling RG. Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Am J Physiol 1931; 99: 534-51.

Physiological correlates

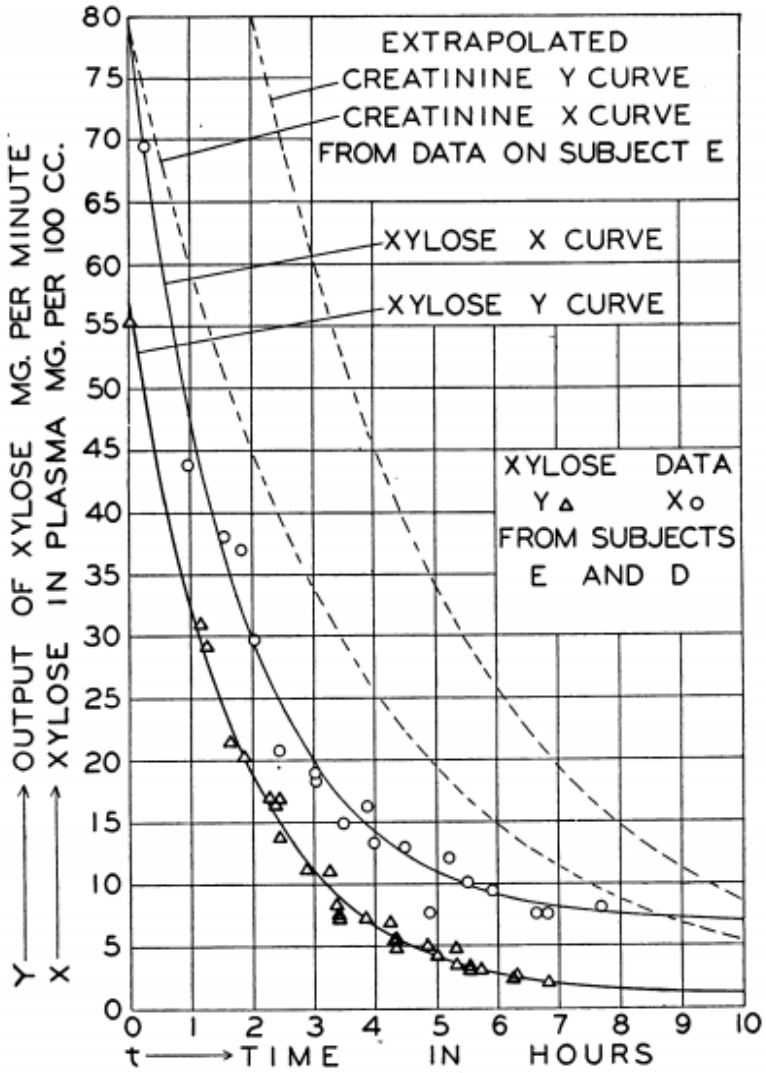


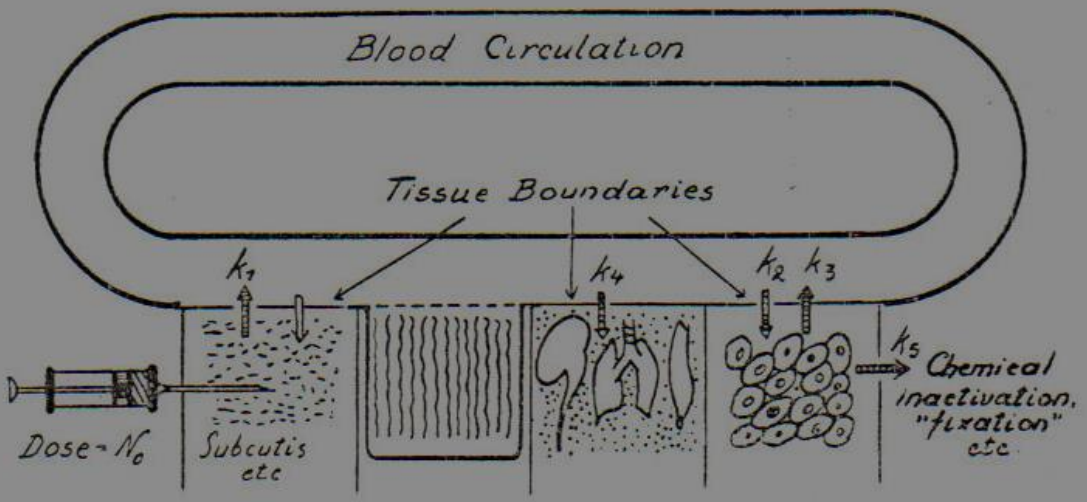
FIG. 1. TIME CHANGE IN PLASMA CONCENTRATION AND RATE OF OUTPUT OF XYLOSE IN MAN

Dominguez R, Pomerene E.
On the renal excretion of xylose.
J Clin Invest 1934; 13(5): 753-66.

Physiological correlates

$$\frac{dA}{dt} = V\frac{dC}{dt} + VkC$$

Teorell, 1937



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	—	V_3	—
Concentration	x/V_1	y/V_2	—	z/V_3	—
Perm. coeff	k_1'	—	k_4'	k_2'	—
Velocity constant out	$k_1 = k_1'/V_1$	—	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	—	not existing	$k_2 = k_2'/V_2$	—
Name of process	Resorption	—	Elimination	Tissue take up -"- output	Inactivation

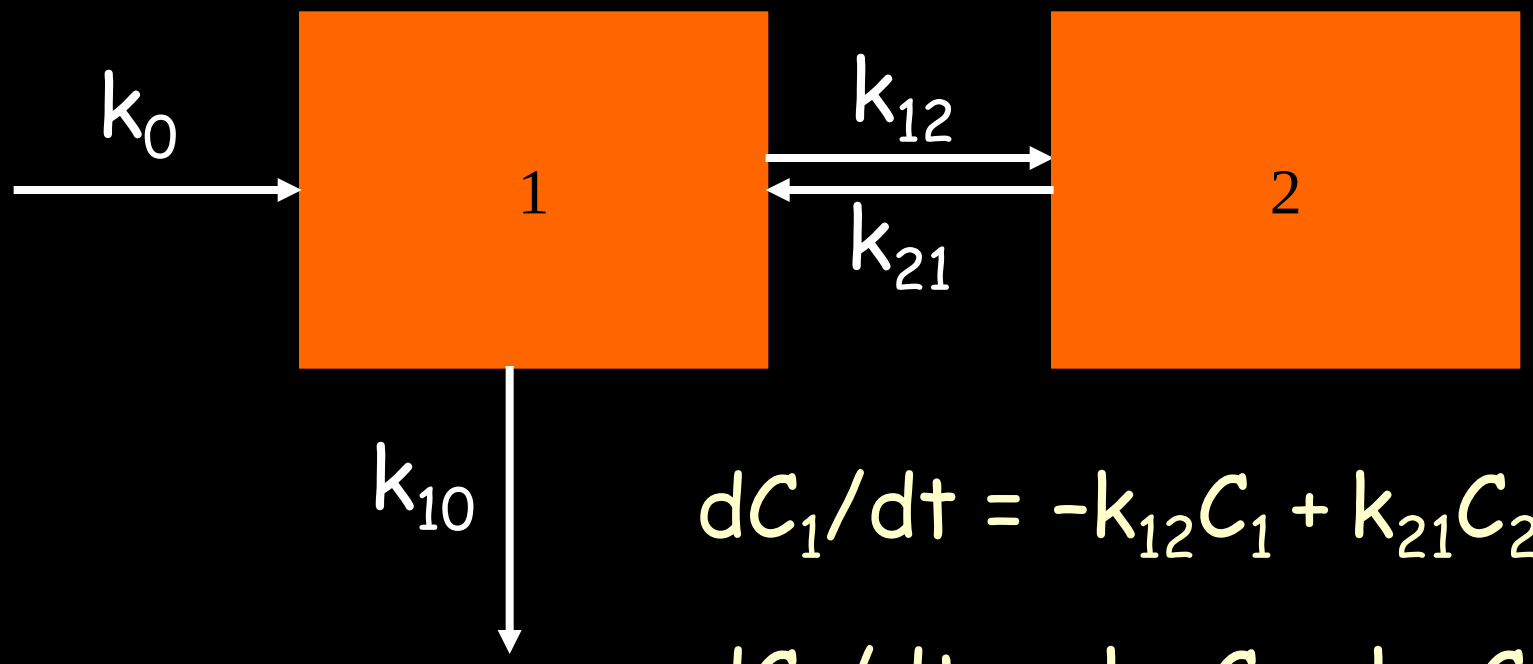
Teorell T. Kinetics of distribution of substances administered to the body.

I. The extravascular modes of administration.

II. The intravascular modes of administration.

Arch Int Pharmacodyn Ther 1937; 57: 205-25 & 226-240.

Two-compartment model



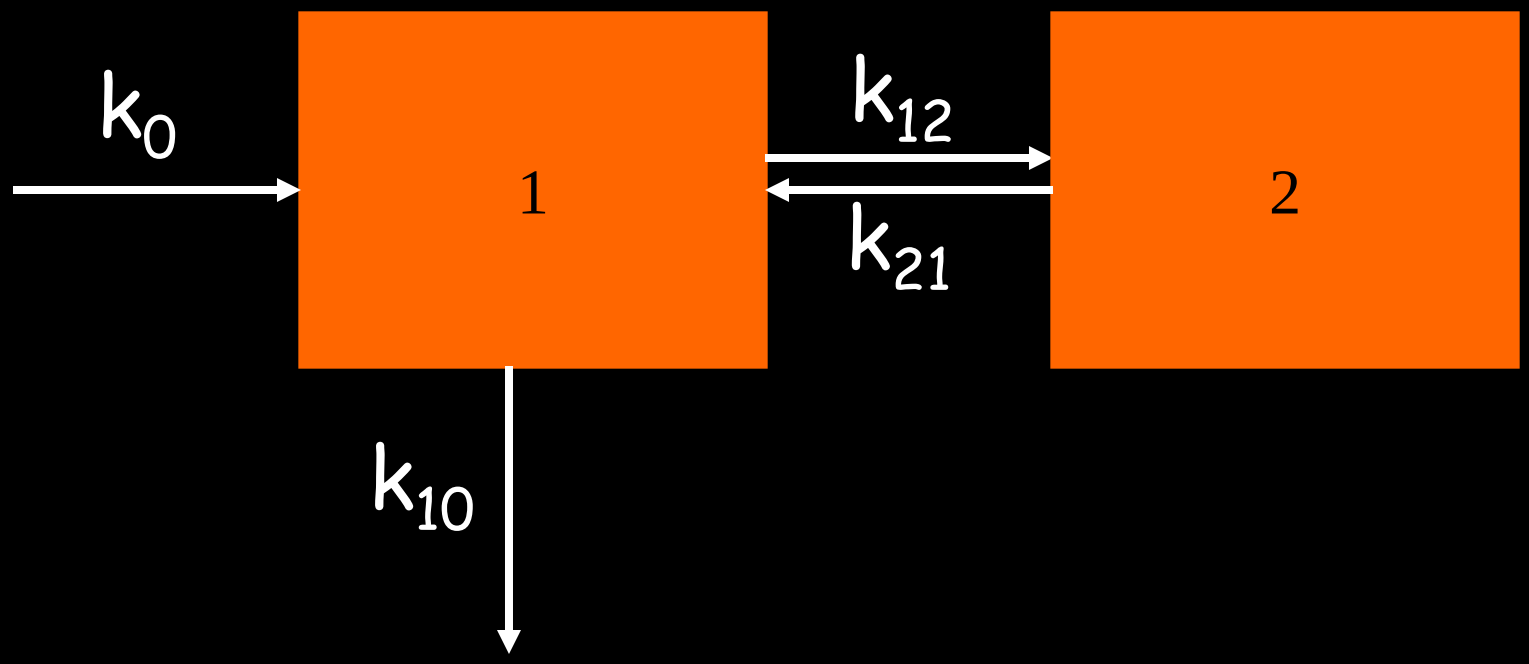
$$dC_1/dt = -k_{12}C_1 + k_{21}C_2 - k_{10}C_1$$

$$dC_2/dt = -k_{21}C_2 + k_{12}C_1$$

$$C(t) = C_1(0)e^{-\lambda_1 t} + C_2(0)e^{-\lambda_2 t}$$

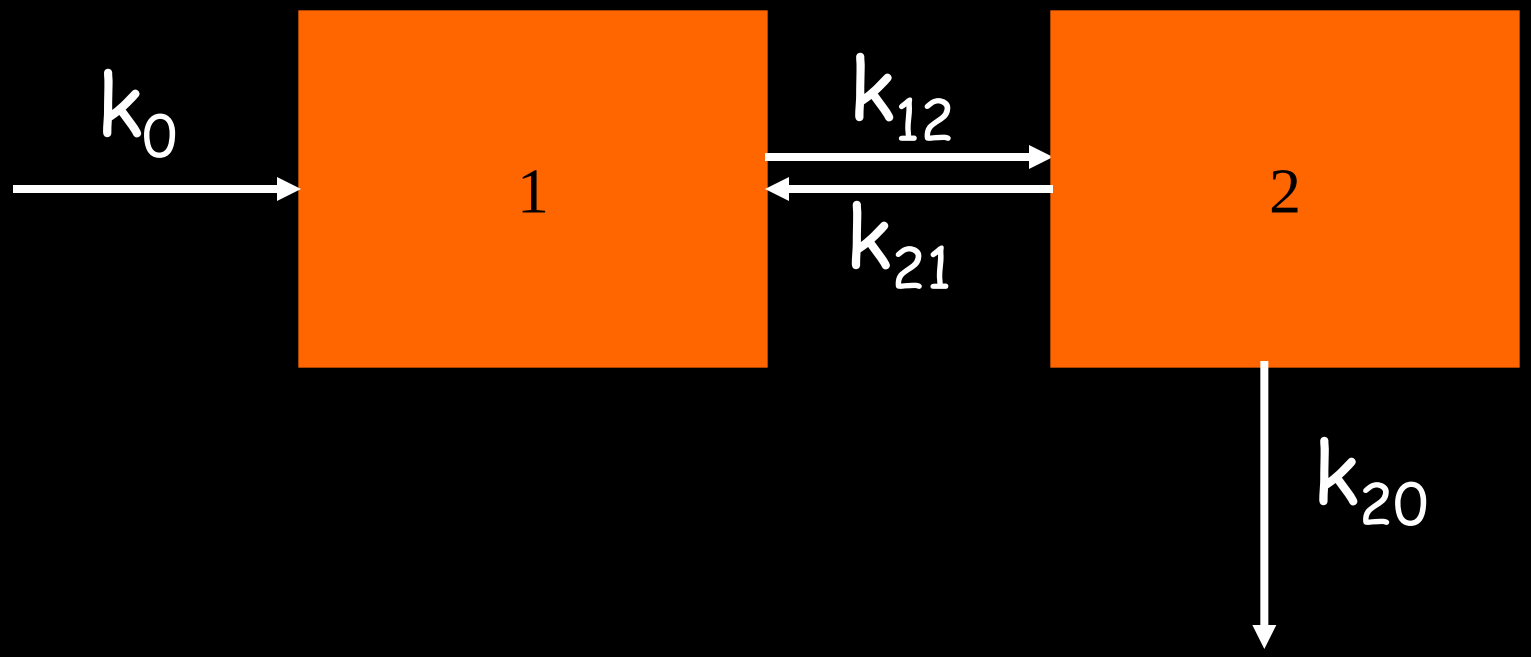
$$C_p = Ae^{-\alpha t} + Be^{-\beta t}$$

Two-compartment model

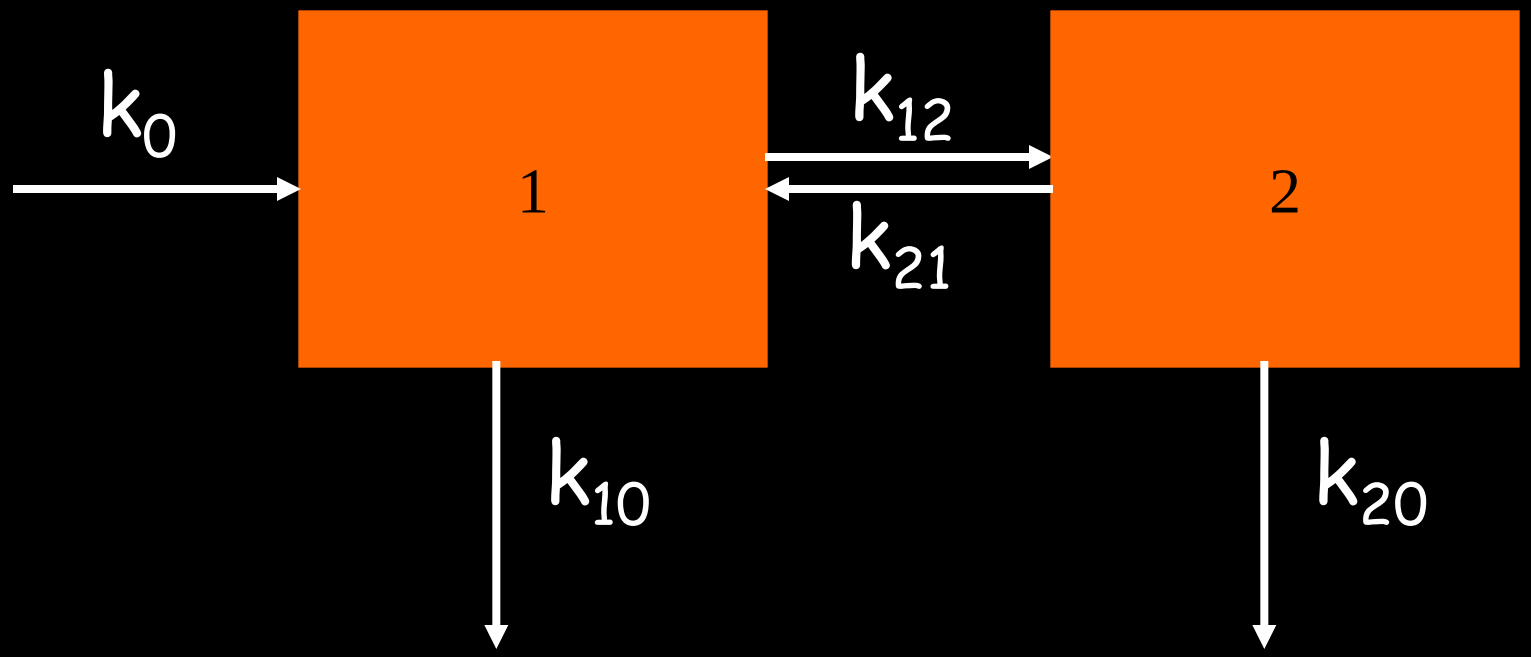


Number of solvable constants = 2n – 1

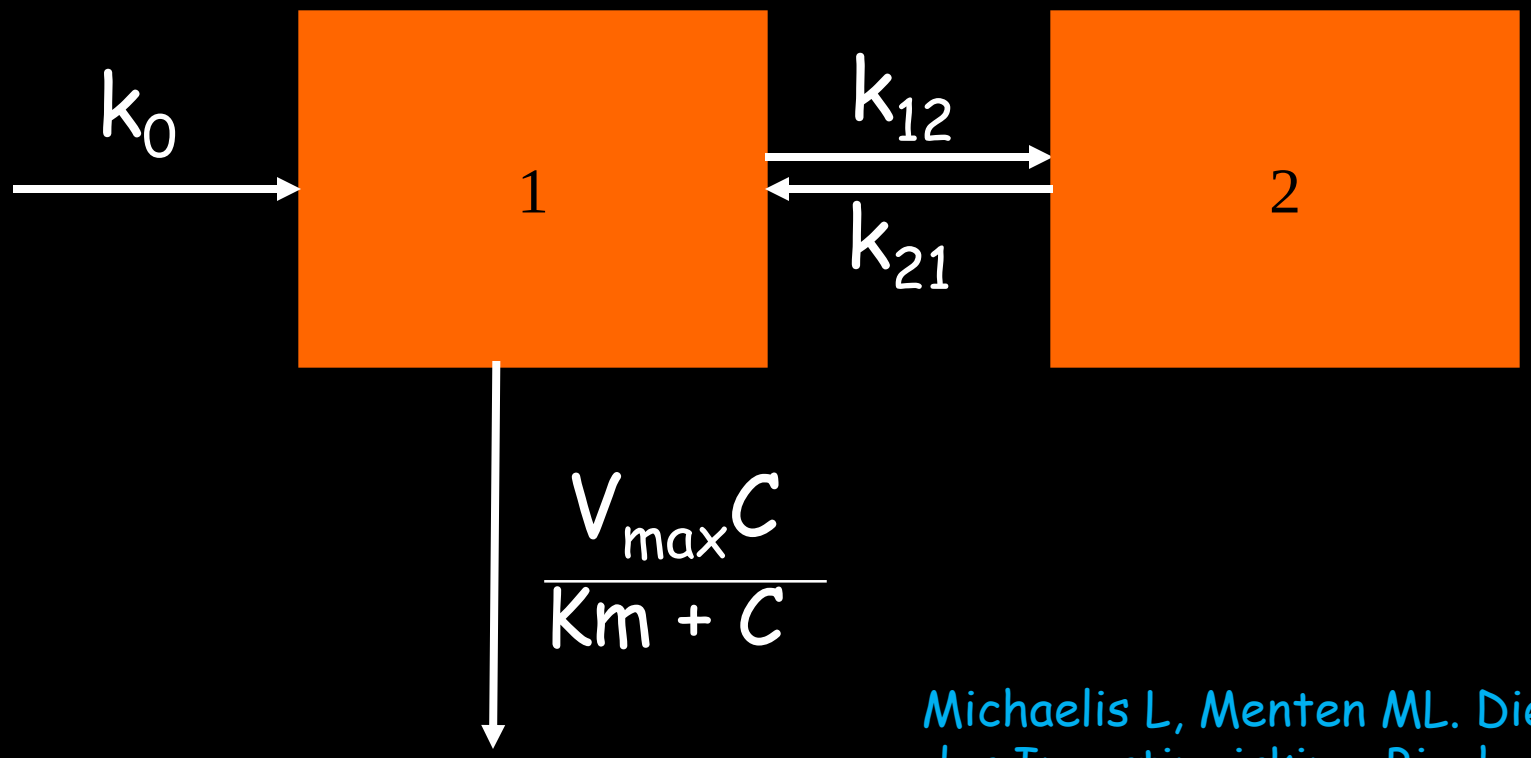
Two-compartment model



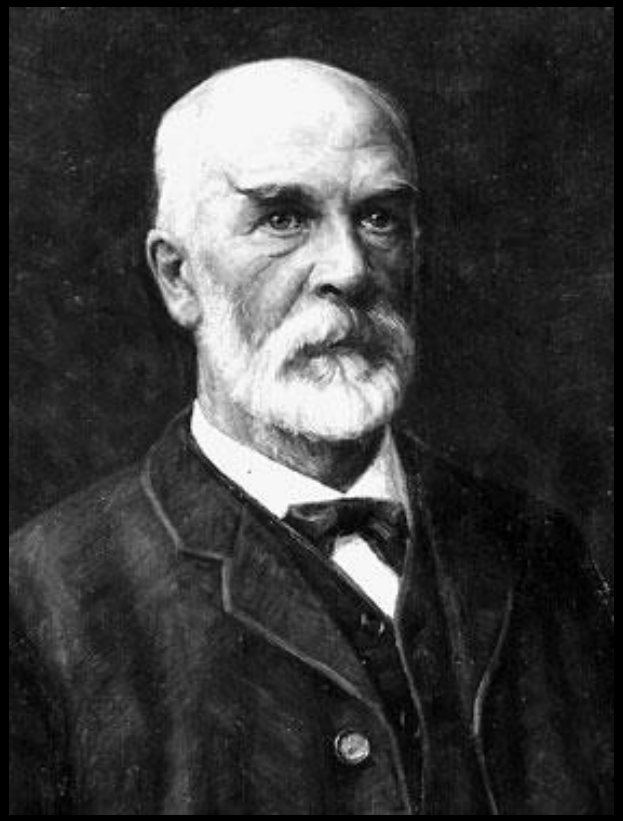
Two-compartment model



Two-compartment model



Michaelis L, Menten ML. Die Kinetik der Invertinwirking. Biochemische Zeitschrift 1913; 49: 333-69.



Cato Guldberg
1836-1902

Peter Waage
1833-1900

The law of mass action

The fundamental relationship between velocity of a chemical reaction and the concentrations of the reactants

The velocity of a reaction at equilibrium at constant temperature is proportional to the product of the concentrations of the reacting substances

Enzyme kinetics $\frac{V_{max}C}{Km + C}$

Protein binding $\frac{B_{max}C}{K_d + C}$

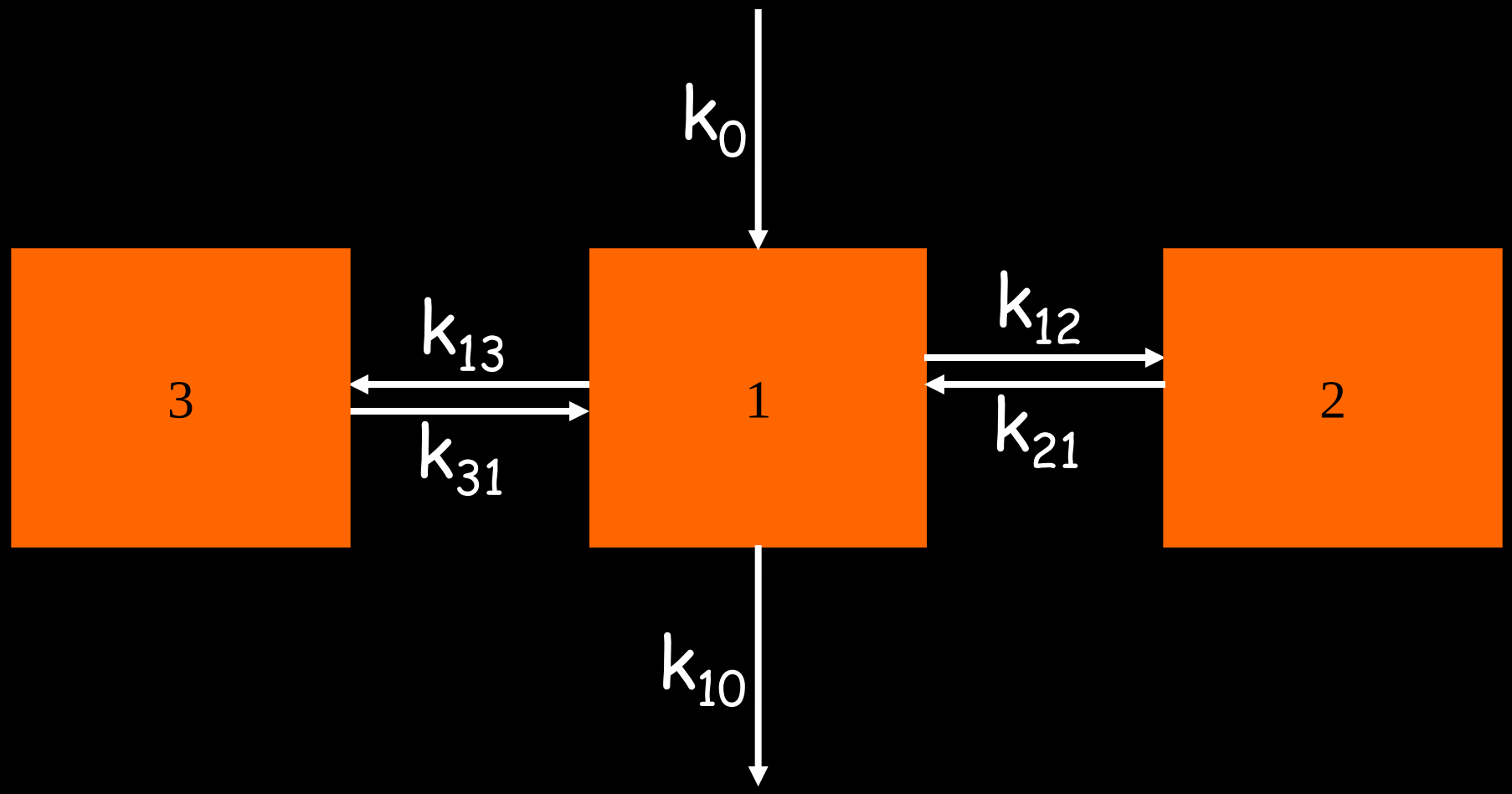
Ligand-receptor interaction $\frac{B_{max}C}{K_d + C}$

Ion transport $\frac{V_{max}C}{K_d + C}$

Nernst equation

Henderson-Hasselbalch equation

Three-compartment model



Br. J. clin. Pharmac. (1991), **31**, 423–427 ADONIS 030652519100082 3

Intravenous strontium gluconate as a kinetic marker for calcium in healthy volunteers

M. E. A. MORAES, J. K. ARONSON & D. G. GRAHAME-SMITH
MRC Unit and University Department of Clinical Pharmacology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE

1 We have studied the pharmacokinetics of stable strontium in 10 healthy male volunteers. We gave each volunteer 5 mmol strontium gluconate by intravenous infusion over 1 h and measured strontium concentrations in plasma and urine samples for 20 days. The plasma strontium concentration *vs* time data for each volunteer were fitted by a triexponential function using NONLIN. Compartmental model-dependent and model-independent pharmacokinetic variables were then calculated.

2 The mean half-life we report (5.4 days) is longer than that previously reported (about 2 days), since we continued sampling for 20 days. However, the rates of clearance (CL 9.4 ml min^{-1}, CL_R 5.4 ml min^{-1}, and CL_{NR} 4.0 ml min^{-1}) are similar to those previously reported, and the apparent volume of distribution at steady state (64 l) is similar to the values previously reported for the size of the exchangeable pool of both strontium and calcium.

3 The similarities in the pharmacokinetic behaviour of strontium and calcium suggest that the *in vivo* disposition of strontium may be used as a marker of calcium disposition and for studying the effects of drugs such as the calcium antagonists.

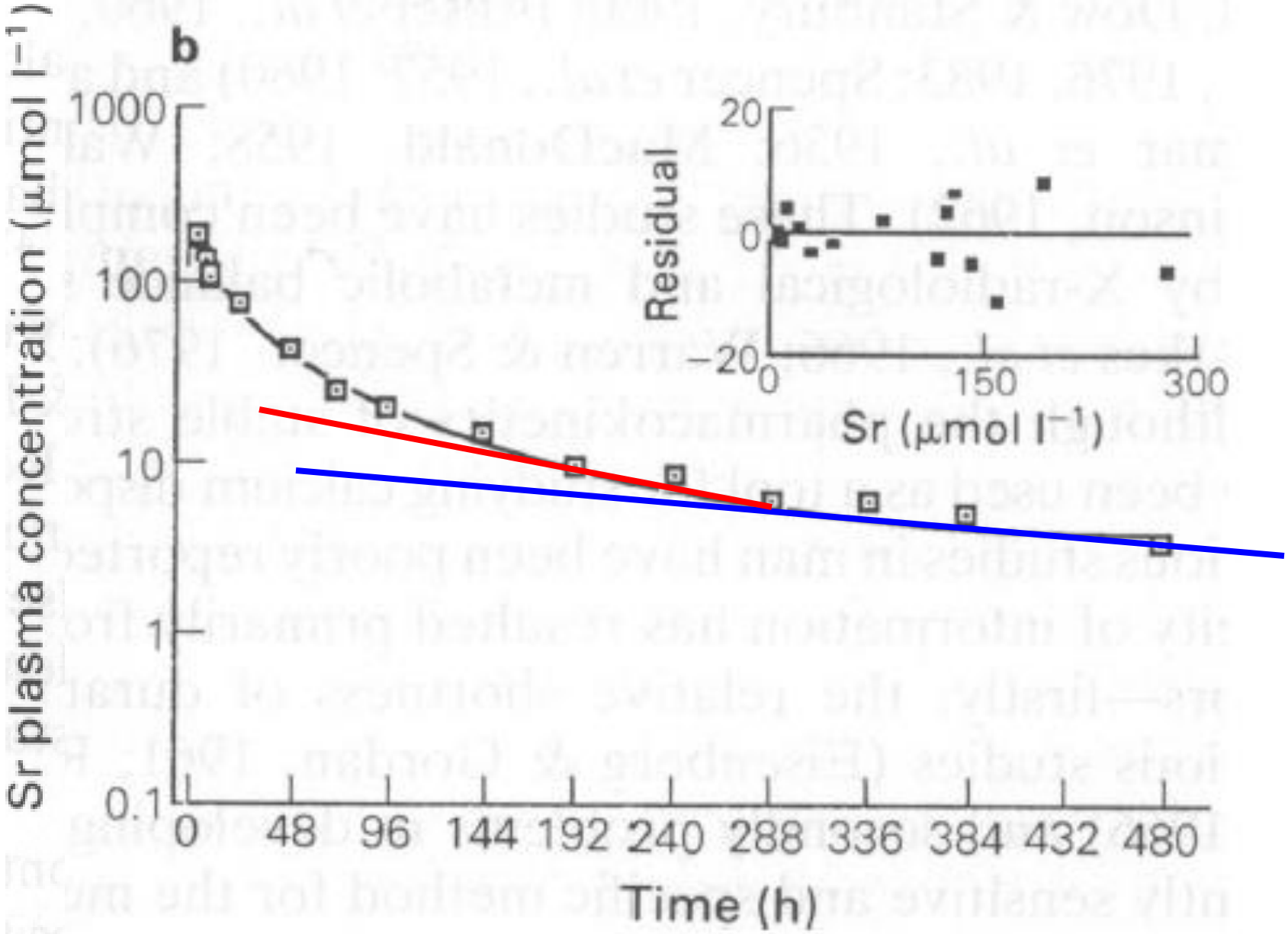
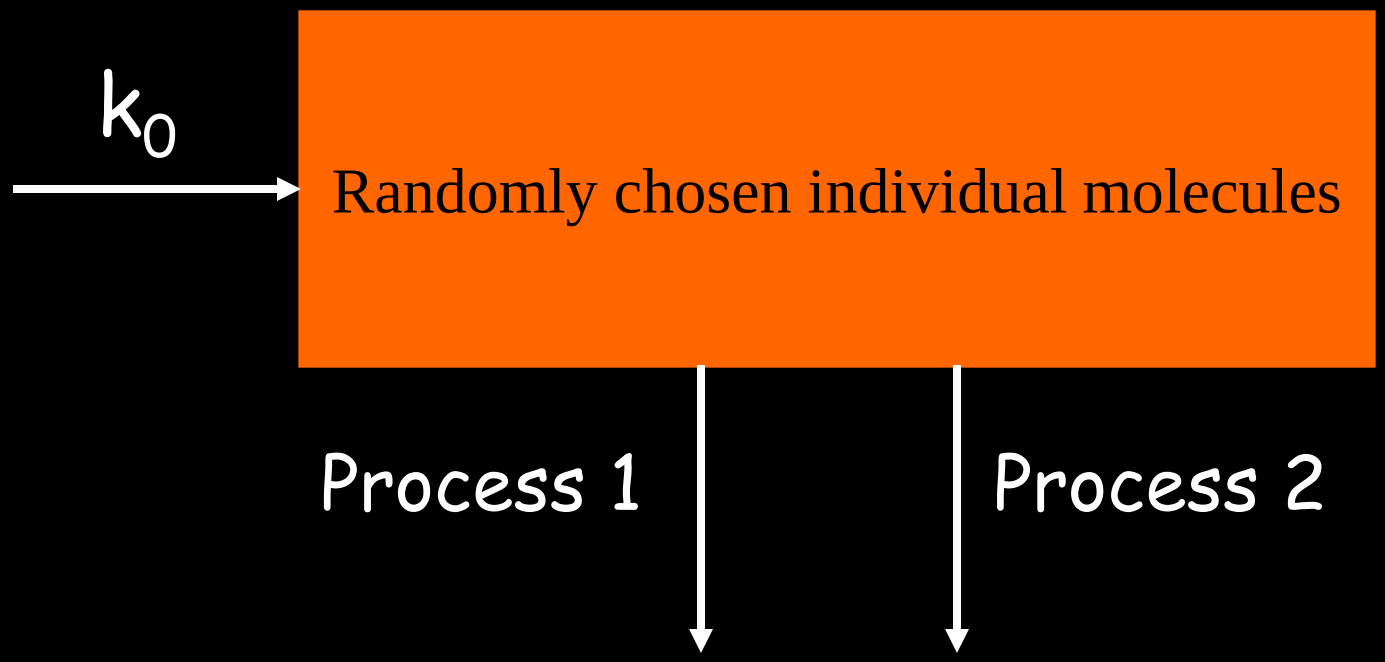

b
Sr plasma concentration (μmol l⁻¹)
1000
100
10
1
0.1
0
48
96
144
192
240
288
336
384
432
480
Time (h)
Residual
20
0
−20
0
150
300
Sr (μmol l⁻¹)

Table 1 The pharmacokinetics of stable strontium obtained from compartmental model-independent analysis, model-dependent analysis, and analysis of the urinary data after the intravenous administration of 5 mmol of stable strontium gluconate to 10 healthy volunteers. The results are shown as mean (s.d.)

Compartmental model-independent analysis	
$t_{1/2,z}$ (days)	5.4 (2.7)
MRT (days)	5.1 (2.1)
CL (ml min^{-1})	9.4 (3.0)
V_{ss} (l)	64 (22)
Model-dependent analysis	
$V_{ss(ij)}$ (l)	71 (25)
V_1 (l)	10 (5)
V_2 (l)	18 (9)
V_3 (l)	43 (16)
Urinary data analysis	
$t_{1/2,ur}$ (days)	4.1 (1.1)
CL_R (ml min^{-1})	5.4 (1.6)
CL_{NR} (ml min^{-1})	4.0 (1.7)

Areas and statistical moments



Areas and statistical moments

$$AUC = \int_{\infty}^{0} C dt$$

$$AUMC = \int_{\infty}^{0} tC dt$$

$MRT = AUMC/AUC$

$MAT = MRT_o - MRT_{iv}$

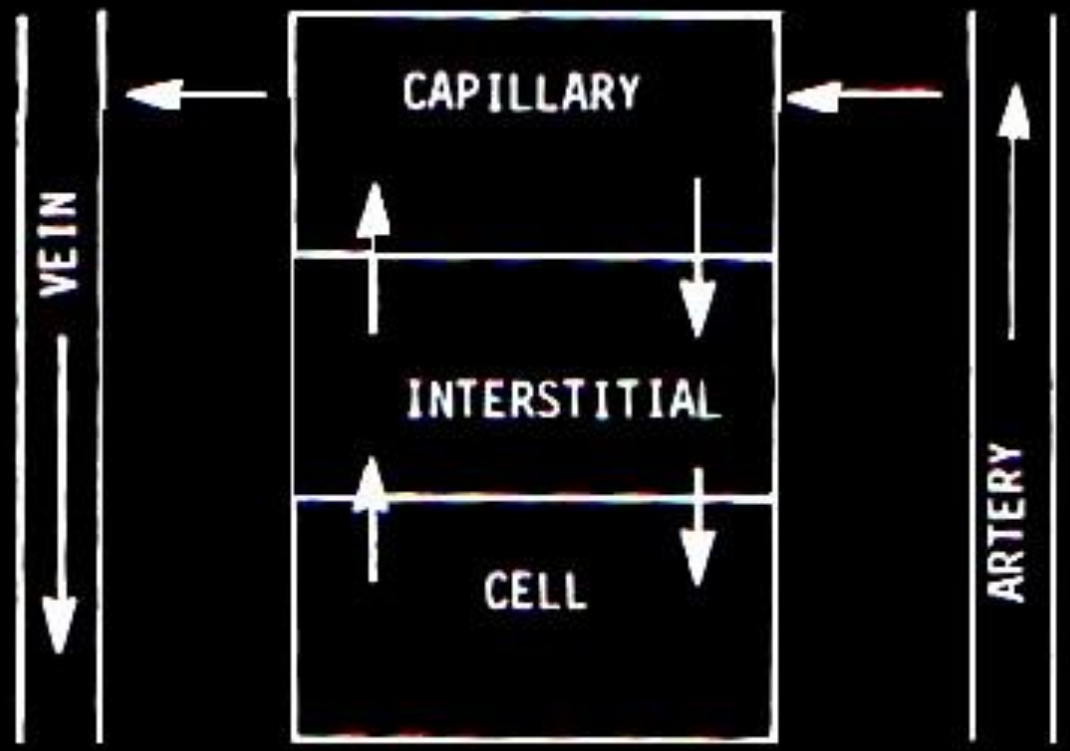
$CL = Dose/AUC$

$V = CL.MRT$

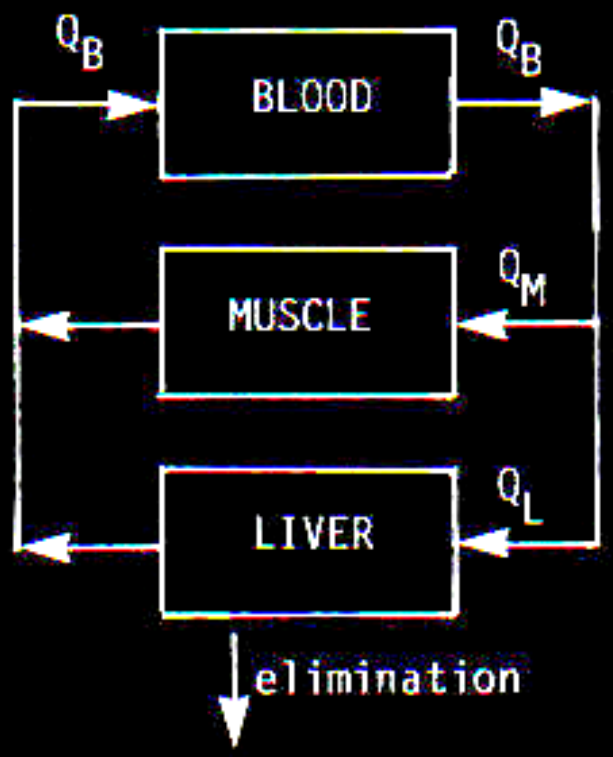
$V_{ss} = Dose.AUMC/AUC^2$

Yamaoka K, Nakagawa T, Uno T. Statistical moments in pharmacokinetics. Journal of Pharmacokinetics and Biopharmaceutics 1978; 6: 547-57.

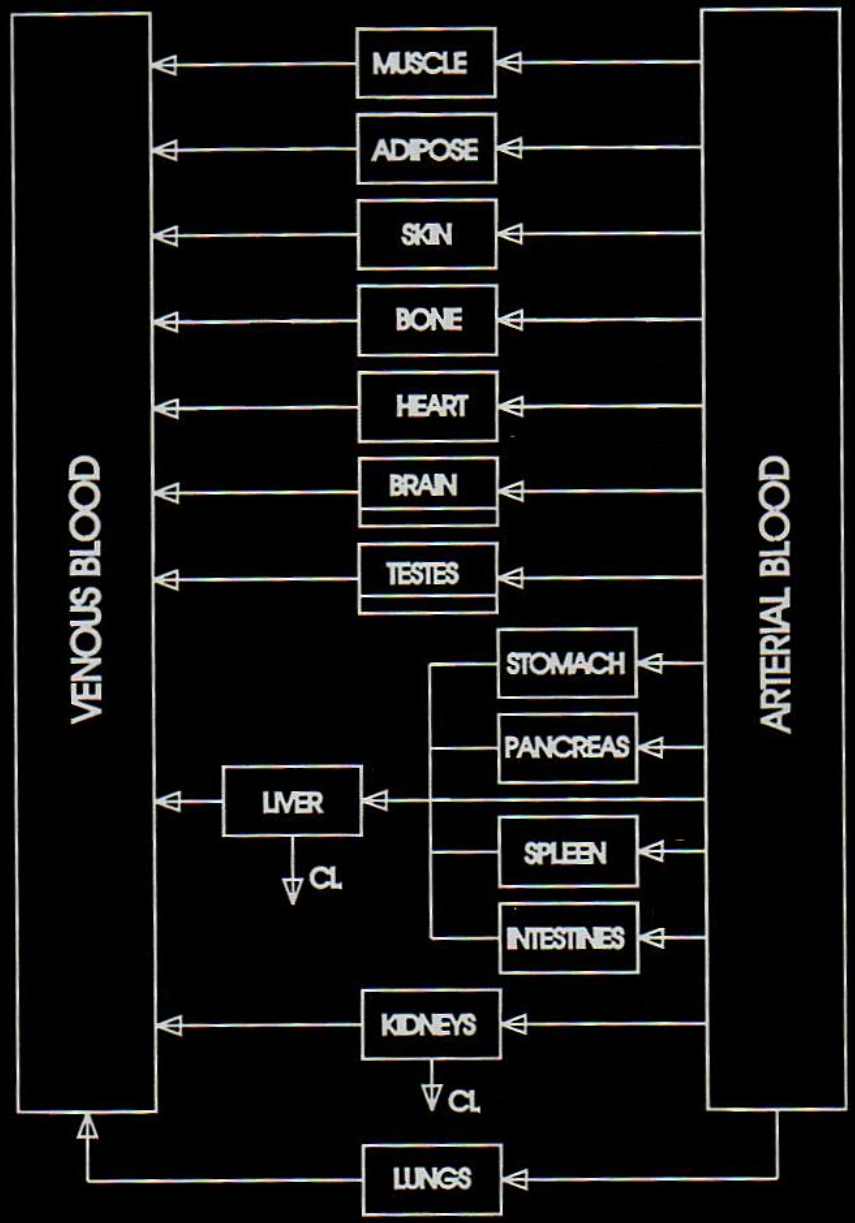
Physiology based models



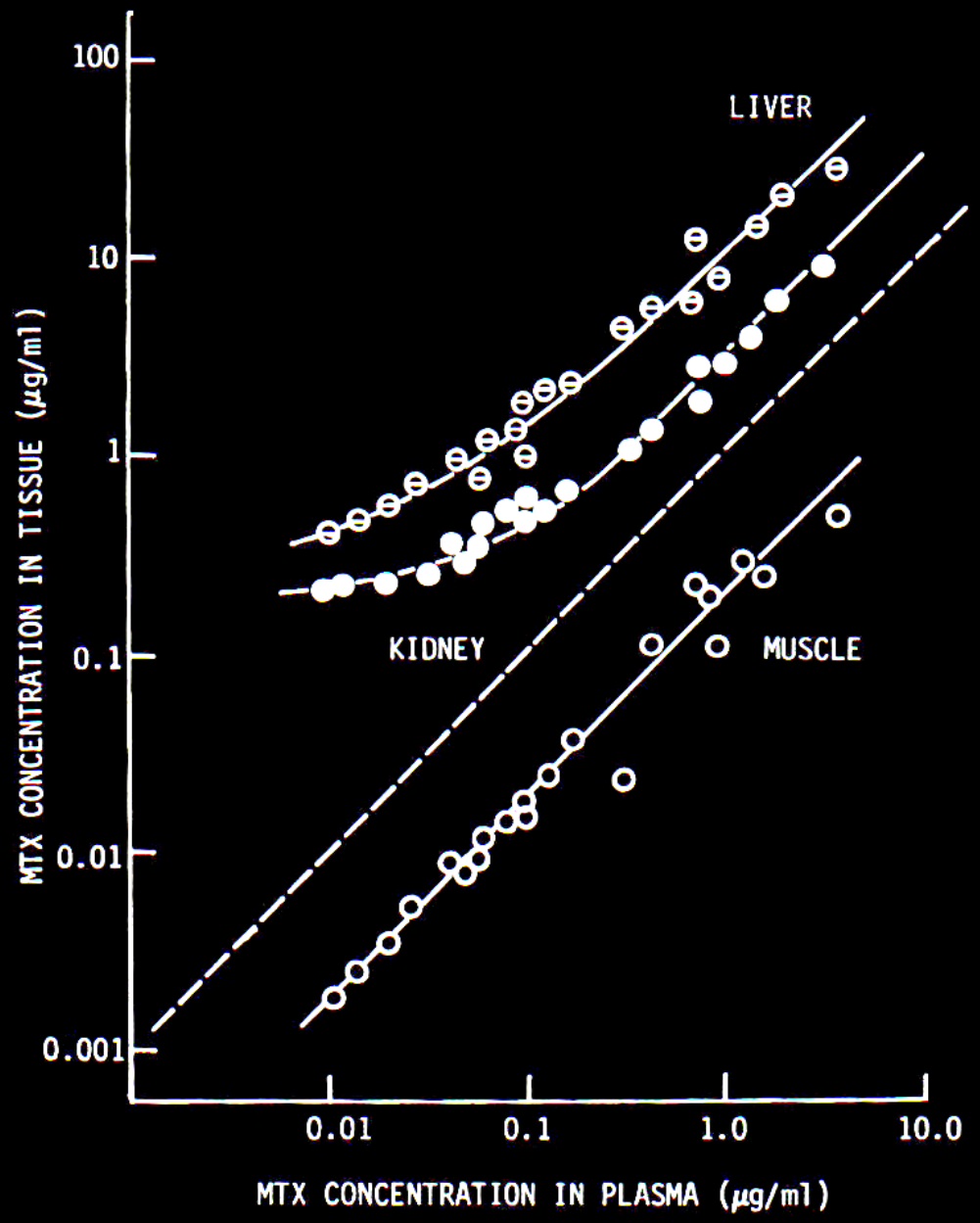
Physiology based models



Physiology based models



Physiology based models



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Some Problems of Statistics and Everyday Life

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"The best is not necessarily very good."

"Models, of course, are never true, but fortunately it is only necessary that they be useful. For this it is usually needful only that they not be grossly wrong."

"All models are wrong; some are useful"

Box GE. Robustness in the strategy of scientific model building. In: Launer RL, Wilkinson GN, editors. Robustness in Statistics. New York: Academic Press, 1979.