

We wish to develop a physiological compartmental model framework for drug pharmacokinetics based on circulatory flow, and apply it to a problem in toxicology.

- (A) Consider the 2-compartment model illustrated in Figure A on the following page, which comprises a circulatory blood plasma compartment with volume V_p and a tissue compartment with volume V_T , and drug concentrations in each being denoted by C_{IP} [moles per volume plasma] and C_{IT} [moles per volume tissue], respectively. Q_T [volume plasma per time] is the volumetric flow rate of blood plasma to and from the tissue compartment, and R_{IT} [(moles per volume tissue)/(moles per volume plasma)] is the equilibrium distribution ratio of drug concentration in the tissue relative to the plasma. Postulate that drug is infused into the plasma compartment at a constant source rate, S [moles/time], and that the drug is cleared in the tissue compartment at a rate proportional to the concentration therein with first-order rate constant k [time⁻¹]. Write the transient mass balances for $C_{IP}(t)$ and $C_{IT}(t)$; then solve these for the steady-state concentrations, and provide a conceptual interpretation of your expressions.
- (B) Now, we want to apply this framework to analysis of the toxic side-effects of a metabolic product of this drug generated in the liver, because this metabolite is toxic to bone marrow stem cells. Let the body be represented by the 5-compartment model illustrated in Figure B on a following page; this model includes compartments for circulatory blood plasma, liver, kidney, bone marrow, and “other tissues”. Associated with these compartments are corresponding drug and metabolite concentrations C_{IP} [moles drug per volume plasma] and C_{2P} [moles metabolite per volume plasma], C_{1L} [moles drug per volume liver tissue] and C_{2L} [moles metabolite per volume liver tissue], C_{1K} [moles drug per volume kidney tissue] and C_{2K} [moles metabolite per volume kidney tissue], C_{1M} [moles drug per volume marrow tissue] and C_{2M} [moles metabolite per volume marrow tissue], C_{IT} [moles drug per volume other tissue] and C_{2T} [moles metabolite per volume other tissue]; and, also associated are corresponding volumetric plasma flow rates Q_L [volume plasma per time] to-and-from liver, Q_K [volume plasma per time] to-and-from kidney, Q_M [volume plasma per time] to-and-from marrow, and Q_T [volume plasma per time] to-and-from other tissue, as indicated in the figure. Make the following postulates:
- drug is infused at a constant rate S [moles/time] into the plasma compartment;
 - drug is converted essentially instantaneously and completely in 1-to-1 stoichiometric proportion to metabolite in the liver compartment, so that the drug concentration leaving the liver, C_{1L} , can be assumed equal to zero;

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- drug and metabolite are both cleared essentially instantaneously in the kidney compartment, so that the drug and metabolite concentrations leaving the kidney, C_{1K} and C_{2K} , can be assumed equal to zero.

Write the transient mass balances for the drug and metabolite concentrations in the plasma, bone marrow, and other tissue compartments. Solve these at steady-state for the metabolite concentration in the bone marrow compartment, C_{2M} , in terms of the relevant system parameters.

