Bio-Systems Modeling and Control

Lecture 24
Compartmental Modeling

Main Literature Sources:

- Robert Northrop “Endogenous and Exogenous Regulation and Control of Physiological Systems”, Chapman & Hall / CRC Press 2000.
- Lecture Notes: Dr. Alicia McDonough (USC Medical School) (Core Principles System, HO-Phy 1) “Compartmental Organization of the Body: Fluid and Electrolyte Homeostasis” (2003)

Modeling Goal: Closed-Loop Control of Drug Concentration

In many scenarios

- post-operative hypertension,
- post-operative pain,
- blood glucose concentration,
- cancer chemotherapy drug concentration,
- depth of anesthesia

drug must be administered to the body under controlled conditions.

Modeling Goal: Closed-Loop Control of Drug Concentration

- Usual drug input routes:
  - intravenous infusion,
  - bolus injection,
  - pills swallowing,
  - aerosol or gas inhalation

Godfrey's Definition of a Compartmental System

"… a finite number of homogeneous, well-mixed, lumped subsystems, called compartments which exchange a substance with each other and with the environment, so that the quantity or concentration of material within each compartment may be described by a first-order differential equation…"

(continued on the next slide)

Godfrey's Definition of a Compartmental System (cont'd)

"…A compartmental system may be used to model either the kinetics of one substance, in which case the compartments occupy different spaces and the inter-compartment transfers represent flow of material from one location to another, or the kinetics of two or more substances (such as drug and its metabolites) in which case different compartments may occupy the same space, and some of the inter-compartment transfers represent transformations from one substance to another."

(From Godfrey's 1983 book)

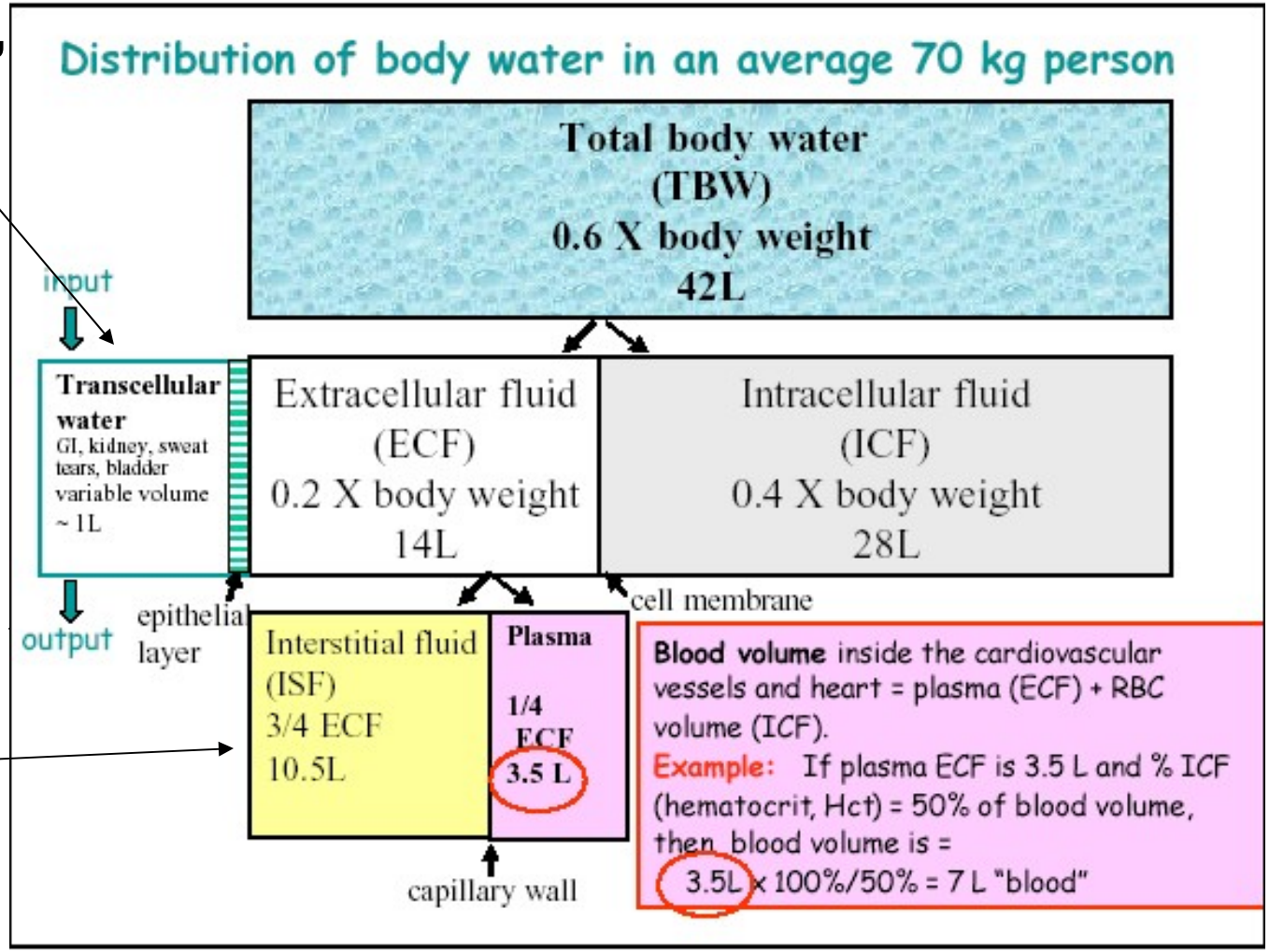
In other words:

- We look at the human organism as distinct body fluid compartments, separated by distinct barriers.
- The focus is on physical factors – volume, ionic composition and the forces that maintain differences between compartments.
- Volume and ionic compositions may be disrupted by infusion of dilute or concentrated solutions → Need to understand the effect on body fluids and composition.

Distribution of body water in average 70 kg person

Saliva, sweat, stomach fluids, tears

Tissue gel, at low concent. of proteins, compared to plasma in the capillaries



Relationships between Body Fluid Compartments - 1

- ICF is separated from ECF by the cell membrane (plasma membrane) which contains specific transporters capable of selective transport of solutes.
- ECF is made up of plasma and interstitial fluid (ISF) compartments.
- Plasma is the ECF in the cardiovascular space, separated from the ISF by the vascular capillary endothelium (capillary wall layer that performs filtration, preventing proteins from going through).

Relationships between Body Fluid Compartments - 2

- Solute and water movement between plasma and ISF occur by filtration through capillary pores, depending upon physical forces.
- Transcellular fluid (TCF) compartments interface with the external environment and provide input and output routes.
- Epithelia capable of very selective transport of solutes and water separate TCF from the ECF. These epithelia are critical for matching input to output to maintain homeostasis of the ECF bathing the cells.

Fluid and Electrolyte Homeostasis

- Homeostasis: the maintenance of static or constant conditions in the internal environment.
- Internal environment: The intracellular fluid (ICF) and extracellular fluid (ECF).
- Transcellular fluid (TCF) is not included, as it typically receives highly variable input and produces highly variable output (see next figure)

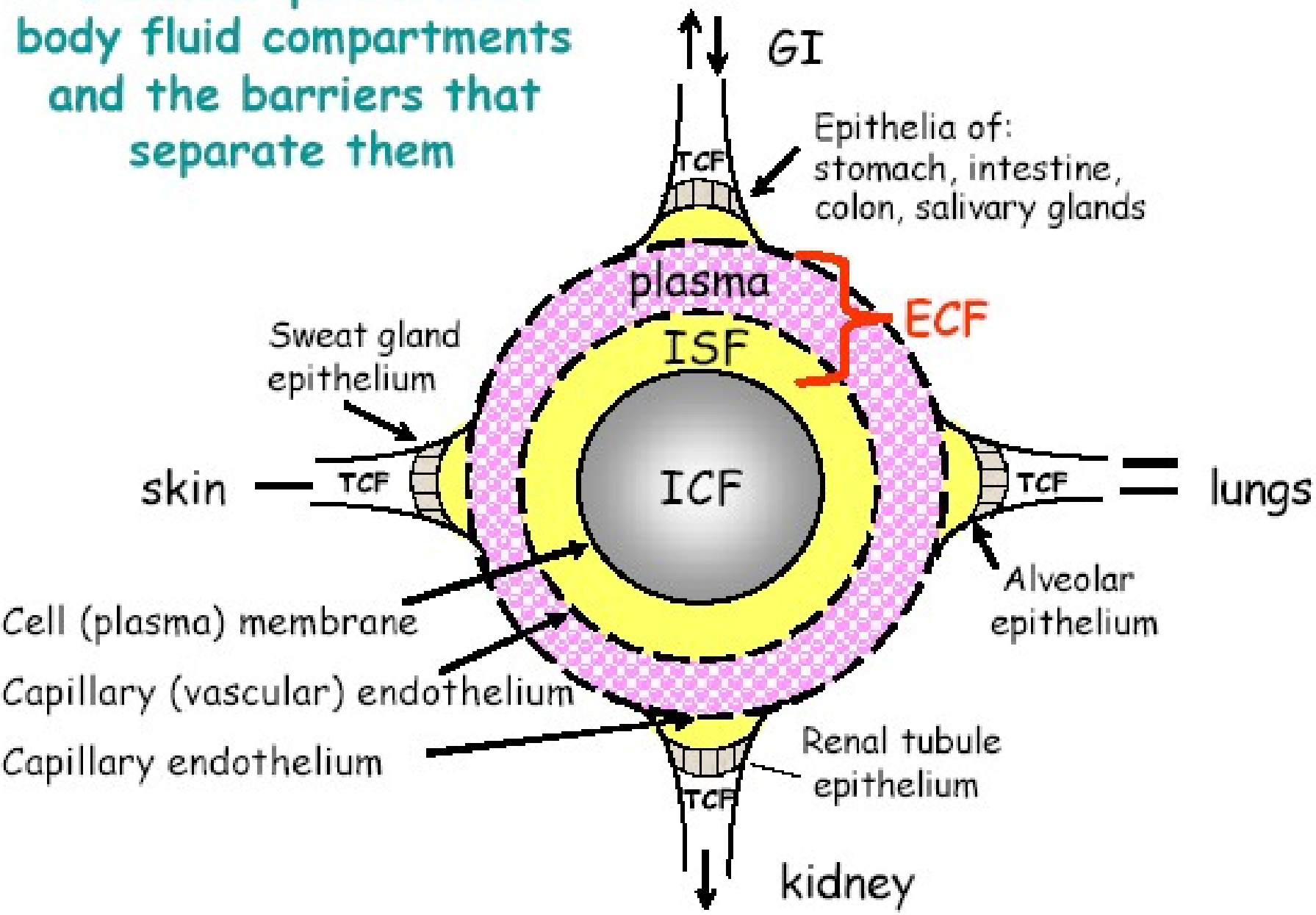
Modes of Material Transport between Compartments - 1

- Within vascular compartment: <u>convection</u> – driven by cardiac pump, good for long distances.
- Within both ICF and ECF: <u>diffusion</u> – very slow, short distances involved.
- Between plasma and interstitial fluid: <u>capillary filtration</u> driven by convection.

Modes of Material Transport between Compartments - 2

- Between interstitial fluid and intracellular fluid: <u>membrane transport</u> via the cell membrane channels.
- Between interstitial fluid and transcellular fluid: <u>epithelial membrane transport</u> across certain types of membranes in series.

Relationships between body fluid compartments and the barriers that separate them



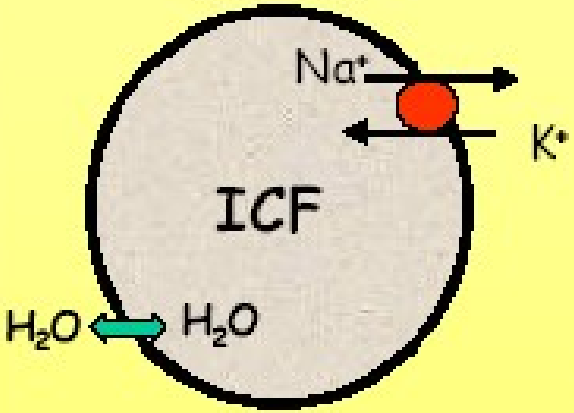
Mathematical Description of N-Compartment System - 1

- N first-order ordinary differential equations, coupled to each other.
- In Control Theory language, this is simply a state-variable model.
- There are N states (i.e. that can be initialized independently, and that at any time the values of the states fully describe the system – no need to keep records of "earlier history").

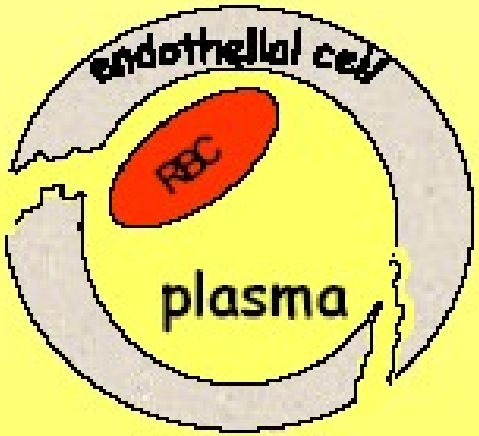
Mathematical Description of N-Compartment System - 2

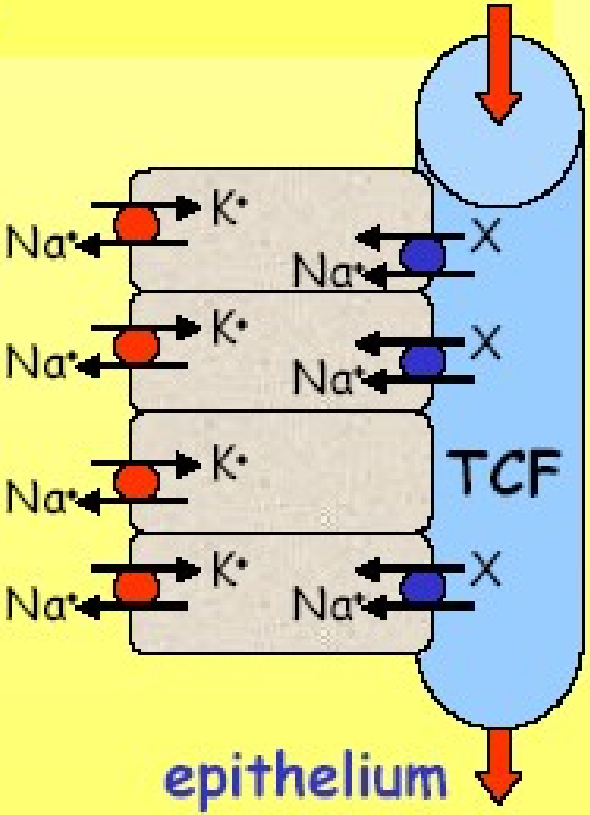
- If a chemical reaction occurs within a compartment, additional first-order ordinary differential equations, coming from the mass-action kinetics, raise the number of system states.
- As Godfrey said, we may then partition such compartments into sub-compartments, according to the different substances.

Properties of barriers between body fluid compartments



ECF = ISF





cell membrane between ICF and ECF

capillary endothelium between plasma and ISF

epithelium between ECF and transcellular fluid (TCF)

Example 1: Two linear compartments

- A molecule C is synthesized in the cell's mitochondria at a rate of Q_o.
- Its concentration in the mitochondria is C_m [μg/l].
- It diffuses out of the mitochondria and into the cytoplasm, where its concentration is C_c.
- It next diffuses through the cell membrane to an almost zero-concentration environment at the ECF.
- The two compartments are (1) the mitochondria, and (2) the cytoplasm around the mitochondria.

Mathematical Model of the two linear compartments example

$$V_m \frac{dC_m}{dt} = Q_o - K_{12}(C_m - C_c)$$

$$V_c \frac{dC_c}{dt} = K_{12}(C_m - C_c) - K_2 C_c$$

- This a simple (Fick's Law) diffusion model.
- The rate of synthesis of the substance Q_o is viewed as an <u>external input</u> to the first compartment.
- The two concentrations are the states of the model.

State-Variable Model of the two linear compartments example

$$V_m \frac{dC_m}{dt} = Q_o - K_{12}(C_m - C_c)$$

$$V_c \frac{dC_c}{dt} = K_{12}(C_m - C_c) - K_2 C_c$$

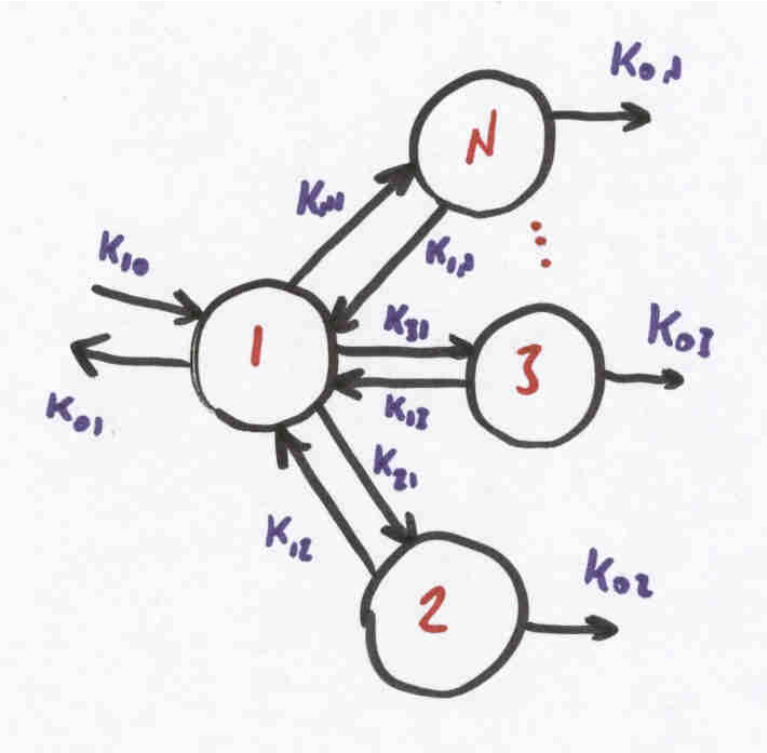
$$\Downarrow$$

$$\frac{dC_m}{dt} = -\frac{K_{12}}{V_m} C_m + \frac{K_{12}}{V_m} C_c + \frac{1}{V_m} Q_o$$

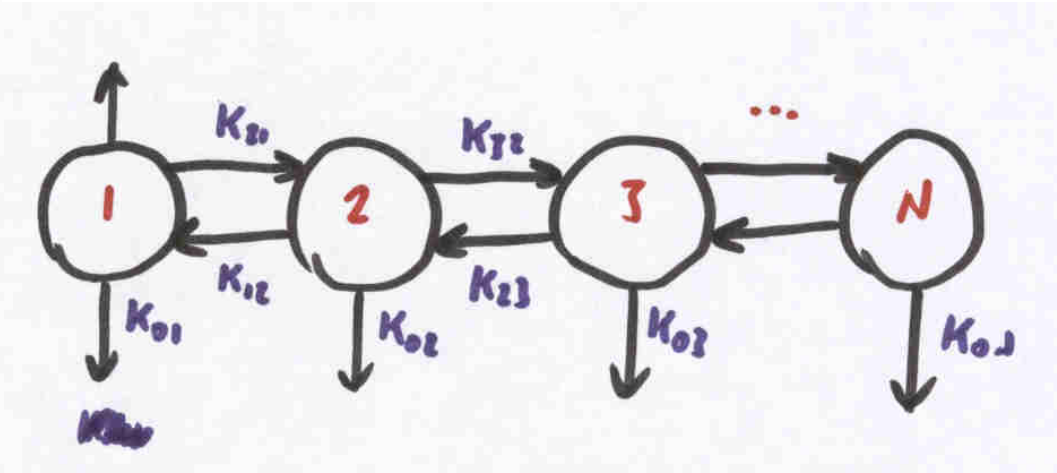
$$\frac{dC_c}{dt} = \frac{K_{12}}{V_c} C_m - \frac{K_{12} + K_2}{V_c} C_c$$

- One can now create a simulation model using two integrators.
- Diffusion rate constants have the units [liters/min]

Common Architectures for Higher-Order Compartment Models

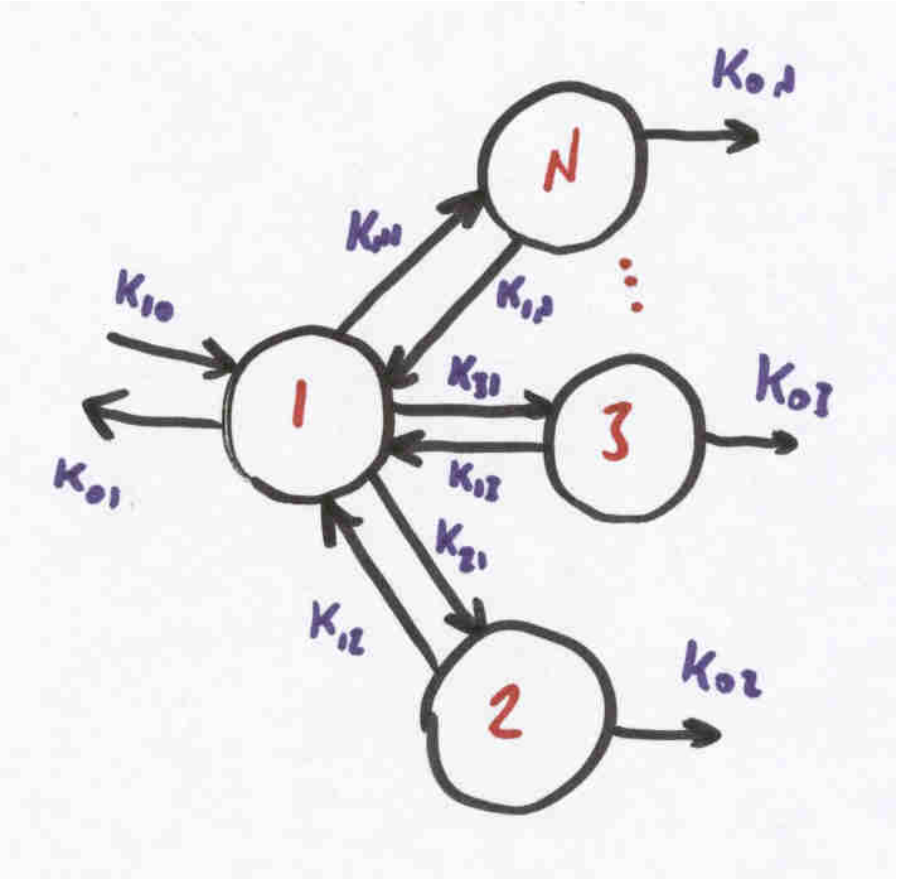


Mammilary Model



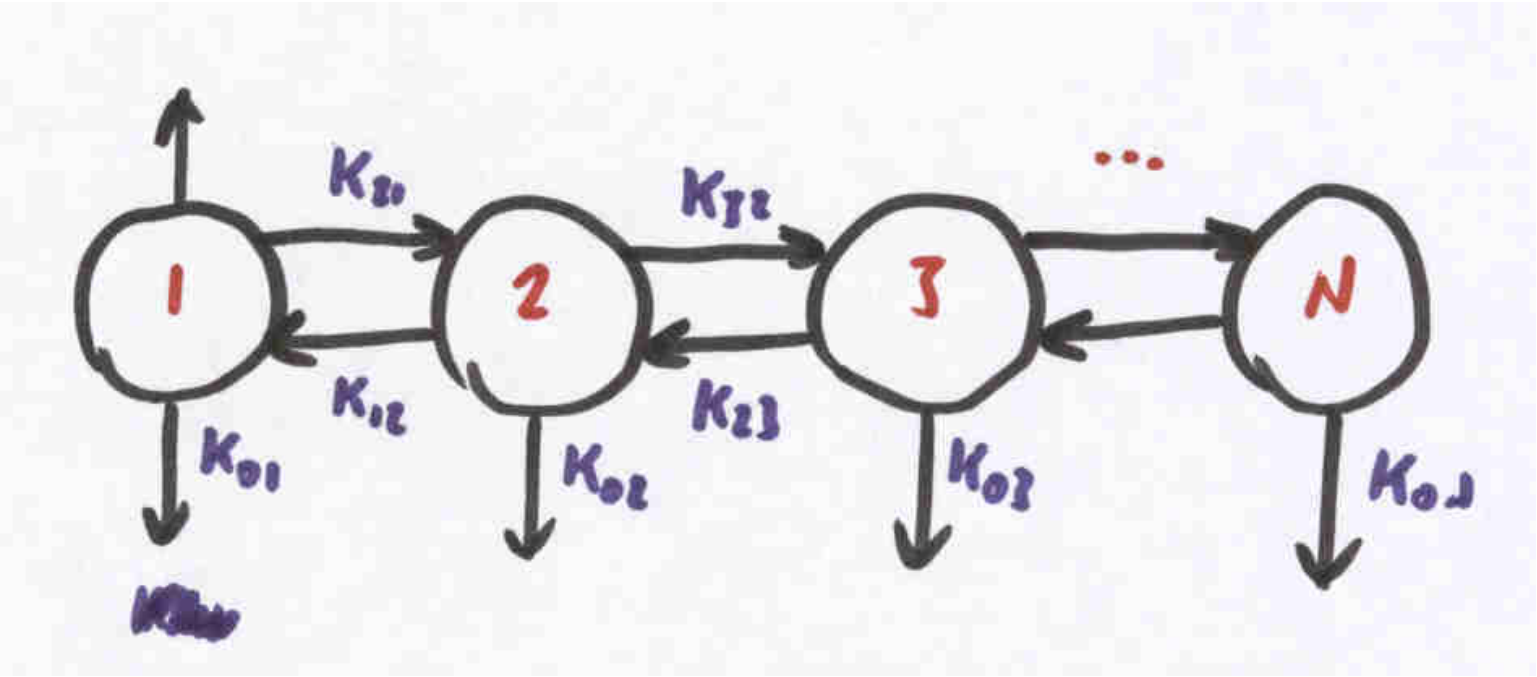
Catenary Model

Mammilary Models



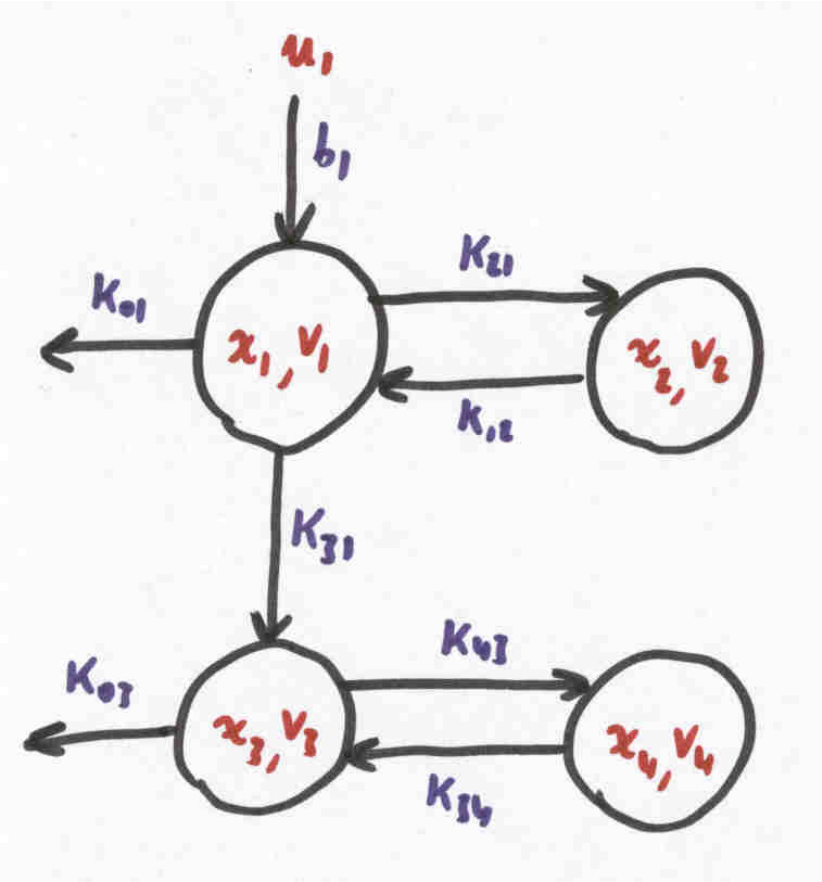
- A central compartment exchanges material with two or more peripheral compartments.
- Peripheral compartments do not directly exchange material with each other.

Catenary Models



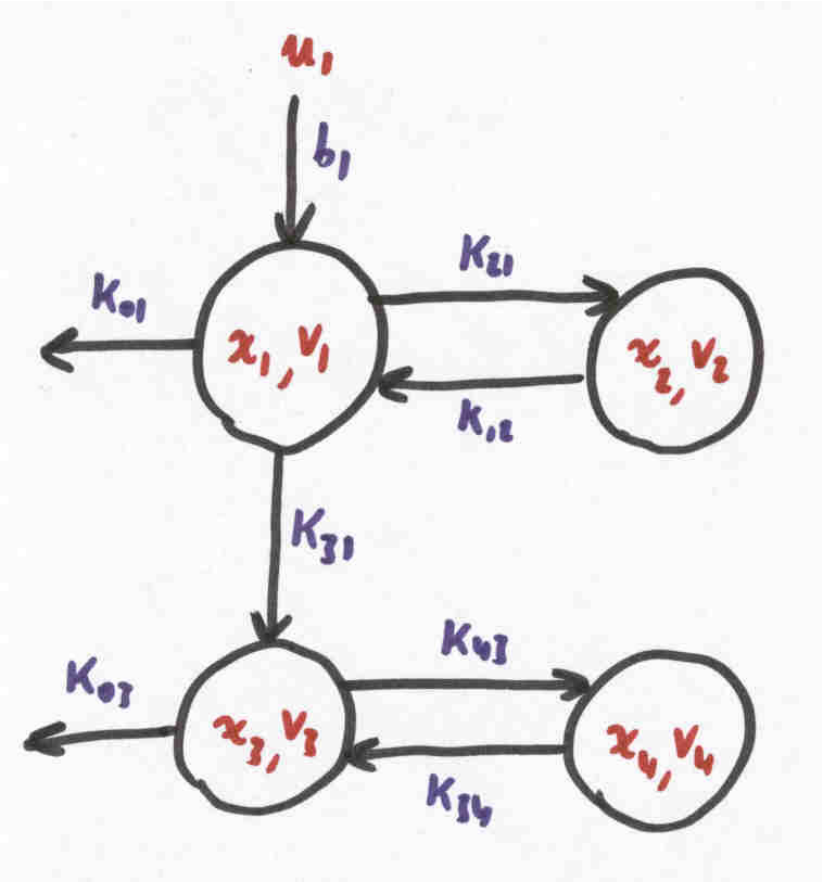
Each compartment only communicates with its two nearest neighbors

Example 2: Two-compartment-drug and two-compartment-metabolite



- It is a fourth-order system.
- Compartments 1,2 contain a drug D.
- Compartments 3,4 contain metabolite M.
- K_{31} is the mass-action rate constant governing the transformation of D into M.

Two-compartment-drug and two-compartment-metabolite (cont'd)



- Inter-compartmental mass transfer rate is proportional to the concentration in the originating compartment (in this example).
- All constants K are in [liters/minute].
- What are the system's equations?

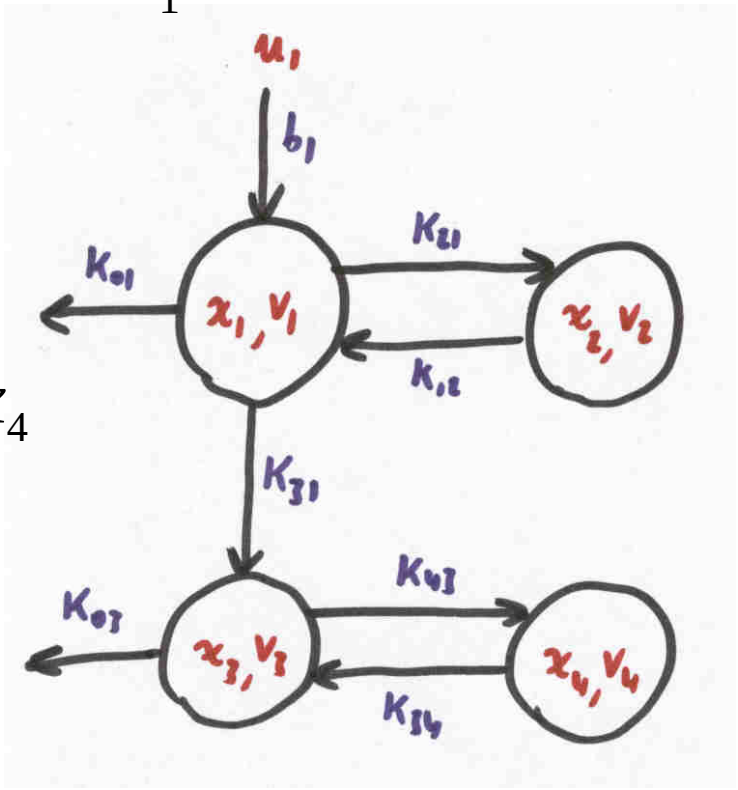
Two-compartment-drug and two-compartment-metabolite Model

$$\frac{dx_1}{dt} = b_1 u_1(t) + \frac{K_{12}}{V_2} x_2 - \frac{K_{01} + K_{21} + K_{31}}{V_1} x_1$$

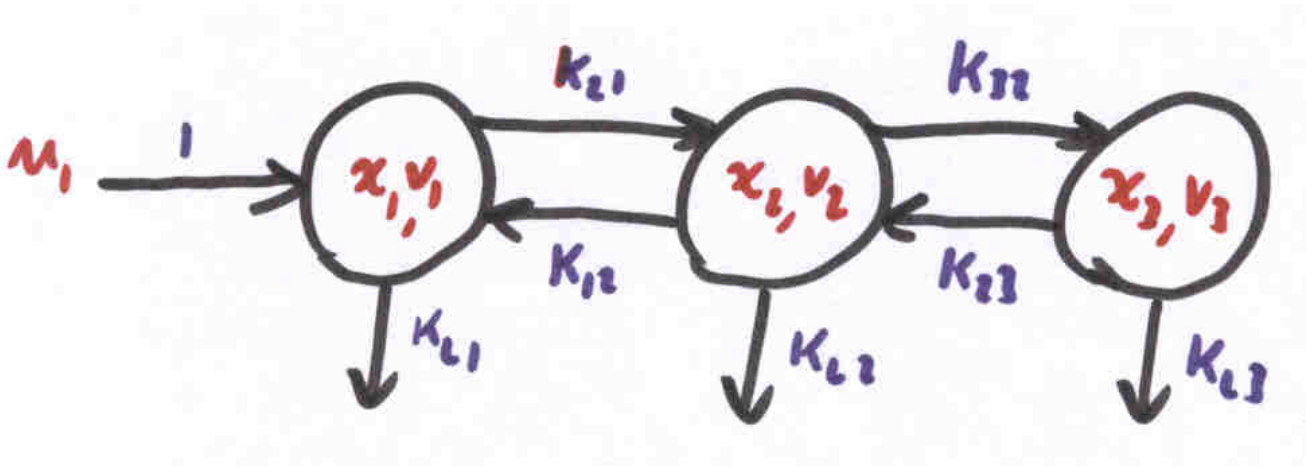
$$\frac{dx_2}{dt} = -\frac{K_{12}}{V_2} x_2 + \frac{K_{21}}{V_1} x_1$$

$$\frac{dx_3}{dt} = \frac{K_{31}}{V_1} x_1 - \frac{K_{03} + K_{43}}{V_3} x_3 + \frac{K_{34}}{V_4} x_4$$

$$\frac{dx_4}{dt} = \frac{K_{43}}{V_3} x_3 - \frac{K_{34}}{V_4} x_4$$

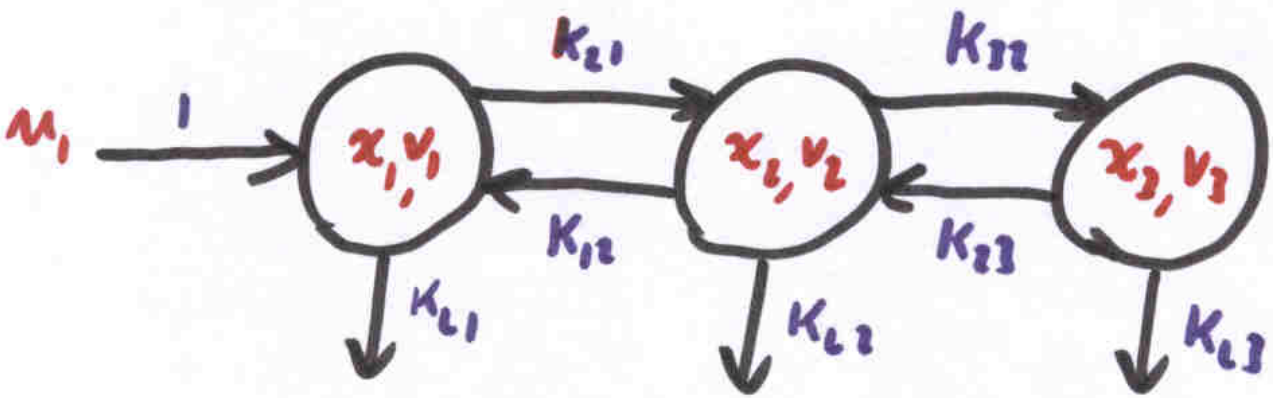


Example 3: Third-order Catenary Compartmental System



- Drug input is only to compartment 1.
- All three compartments have a certain rate of drug loss.
- Write the model.

Third-order Catenary Compartmental Model



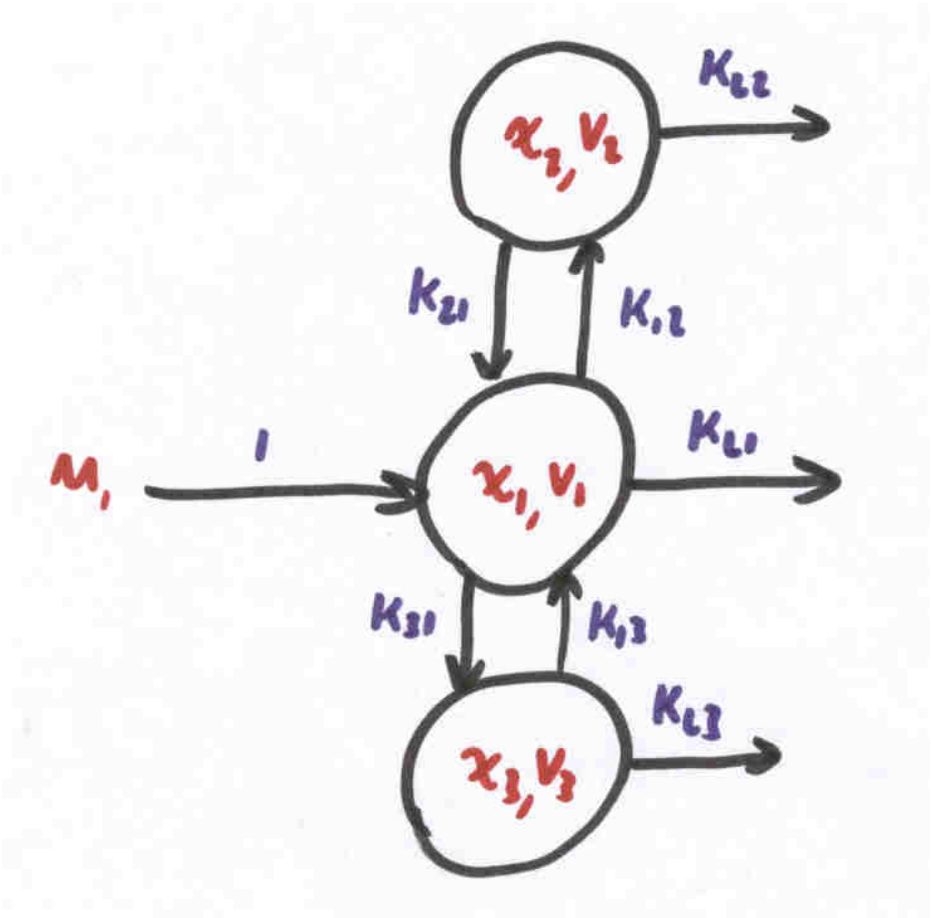
$$\frac{dx_1}{dt} = u_1(t) + \frac{K_{12}}{V_2} x_2 - \frac{K_{L1} + K_{21}}{V_1} x_1$$

$$\frac{dx_2}{dt} = -\frac{K_{L2} + K_{12} + K_{32}}{V_2} x_2 + \frac{K_{21}}{V_1} x_1 + \frac{K_{23}}{V_3} x_3$$

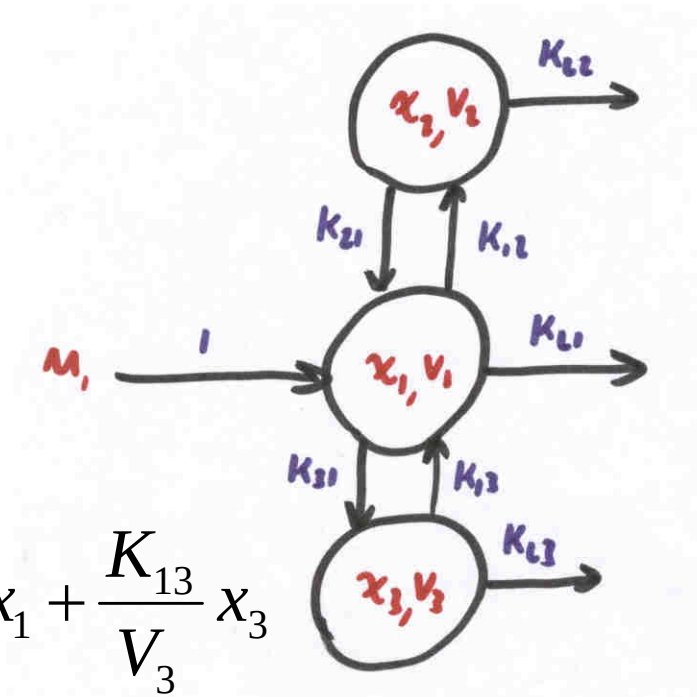
$$\frac{dx_3}{dt} = \frac{K_{32}}{V_2} x_2 - \frac{K_{L3} + K_{23}}{V_3} x_3$$

Example 4: Third-order Mammilary System

- Drug input is to compartment 1.
- All three compartments lose drug.
- Again, let us write the state-variable model:



Example 4: Third-order Mammilary System



$$\frac{dx_1}{dt} = u_1(t) + \frac{K_{12}}{V_2}x_2 - \frac{K_{L1} + K_{21} + K_{31}}{V_1}x_1 + \frac{K_{13}}{V_3}x_3$$

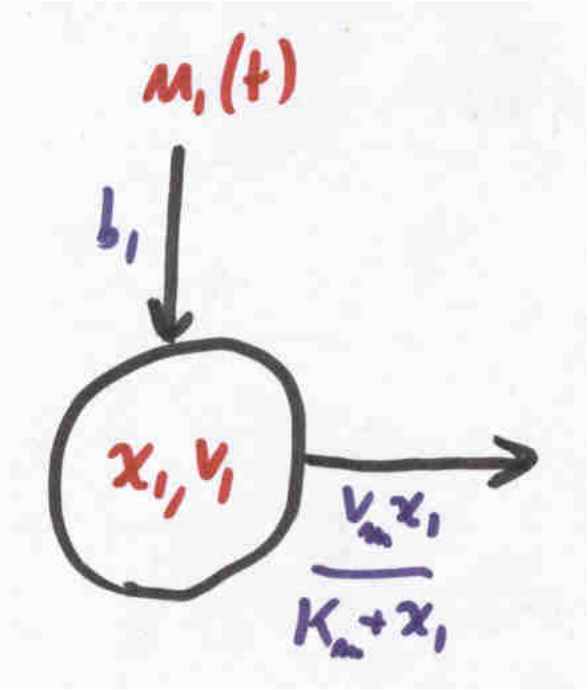
$$\frac{dx_2}{dt} = -\frac{K_{L2} + K_{12}}{V_2}x_2 + \frac{K_{21}}{V_1}x_1$$

$$\frac{dx_3}{dt} = \frac{K_{31}}{V_1}x_1 - \frac{K_{L3} + K_{13}}{V_3}x_3$$

Linear Models?

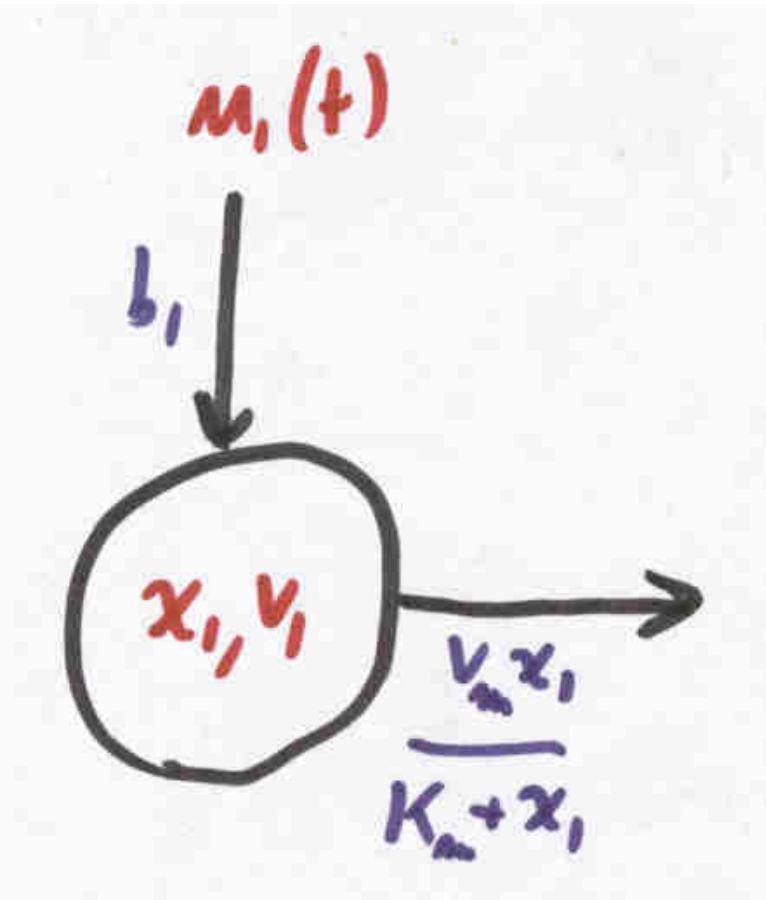
- All above typical diffusion-based compartmental modeling cases, resulted in linear models.
- Not all compartmental systems are linear.

Example 5: Nonlinear one-compartment model



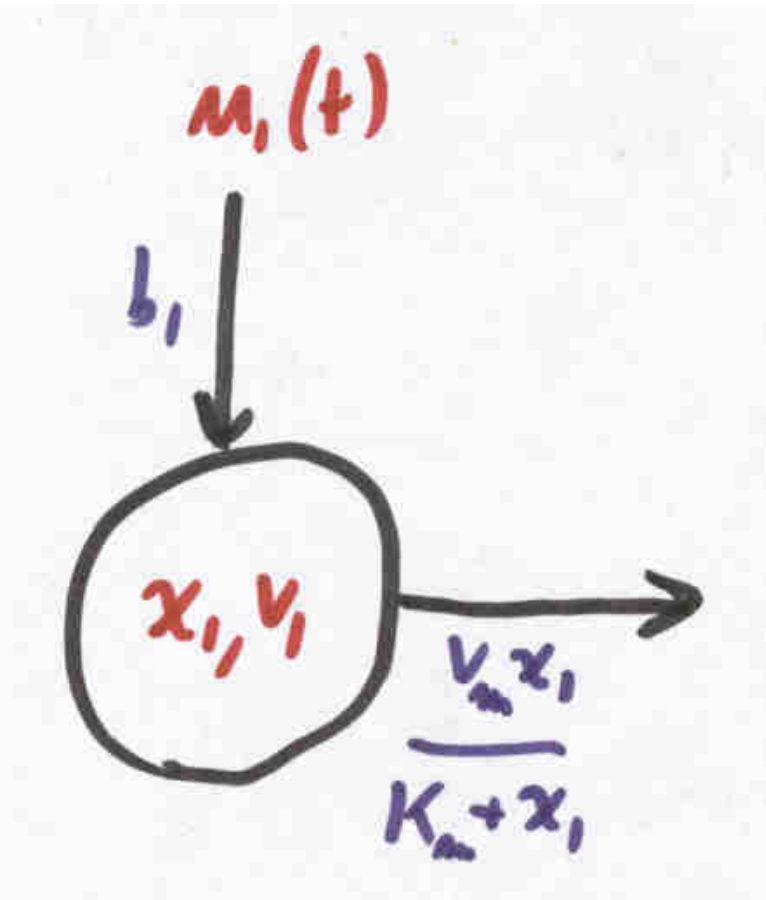
Rate of loss of a Compartment 1 substance follows a hyperbolic curve similar to the Michaelis-Menten relation.

Nonlinear one-compartment model



$$\frac{dx}{dt} = -\frac{V_m x}{K_m + x} + u(t)$$

Nonlinear one-compartment model with constant rate of drug input



$$\frac{dx}{dt} = -\frac{V_m x}{K_m + x} + u(t)$$

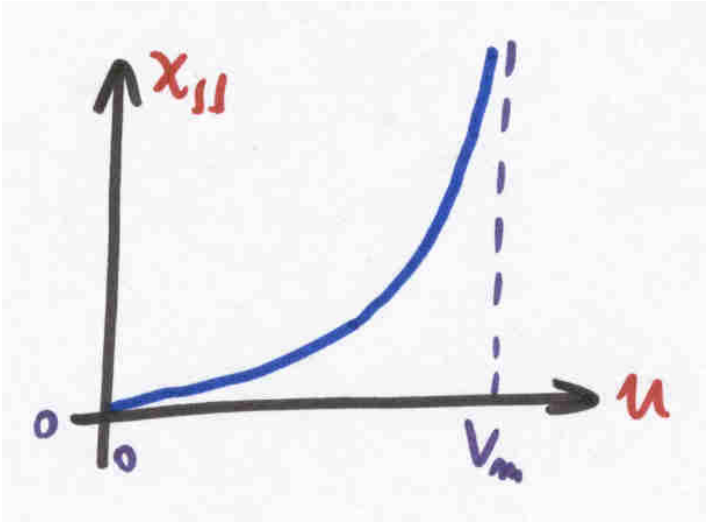
$$\Downarrow$$

$$\frac{dx}{dt} = 0 = -\frac{V_m x_{SS}}{K_m + x_{SS}} + u$$

$$\Downarrow$$

$$x_{SS} = \frac{uK_m}{V_m - u}$$

Nonlinear one-compartment model with constant rate of drug input – steady-state behavior

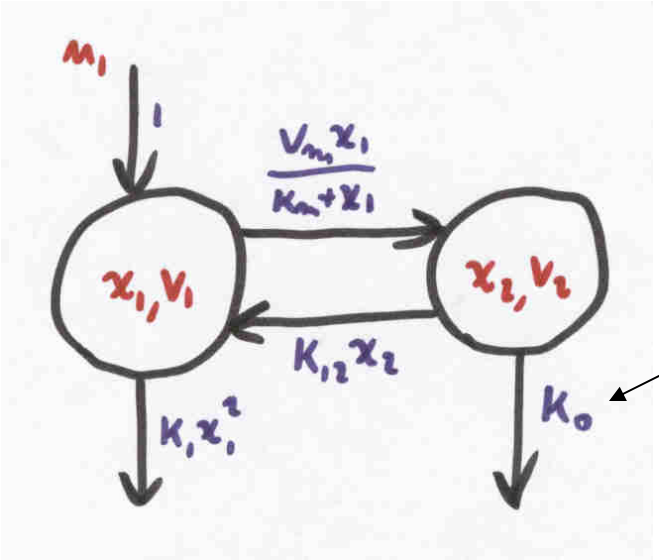


$$x_{SS} = \frac{uK_m}{V_m - u}$$

As u approaches V_m the concentration x_{SS} increases rapidly.

For u > V_m there is no steady-state: System cannot eliminate drug fast enough and it accumulate in the compartment without bound.

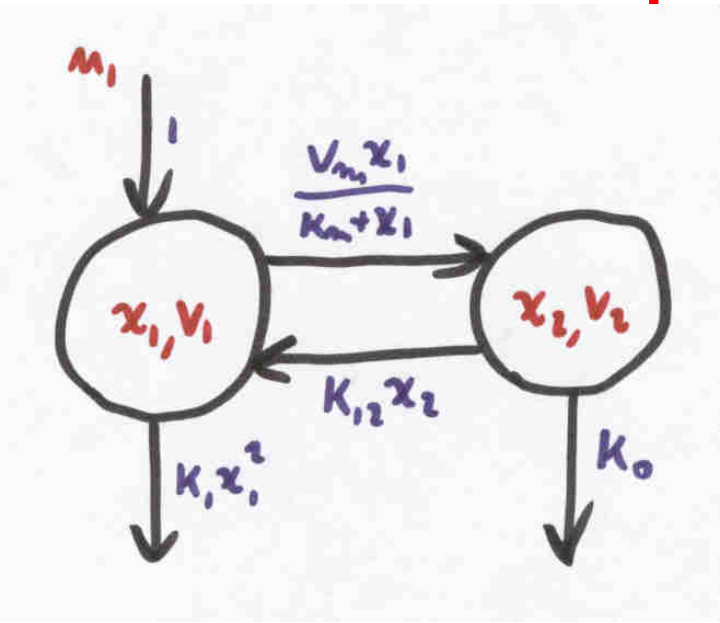
Example 6: Second-order nonlinear compartment model



Loss of drug from compartment 2 is constant K_0 (may be due to some active pumping action)

- Loss rate from compartment 1 is bi-molecular (two molecules of x_1 must combine to exit).
- Another nonlinearity: Transfer of drug from compartment 1 to 2 has Michaelis-Menten rate saturation.

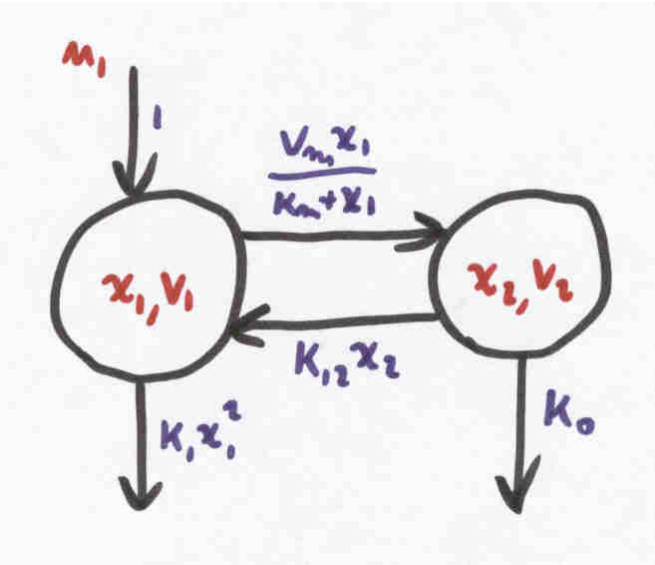
Second-order nonlinear compartment model



$$\frac{dx_1}{dt} = -K_1 x_1^{\ 2} - \frac{V_m x_1}{K_m + x_1} + K_{12} x_2 + u_1$$

$$\frac{dx_2}{dt} = \frac{V_m x_1}{K_m + x_1} - K_{12} x_2 - K_0$$

Another Second-order nonlinear compartment model



Here K_0 is a periodic time function with a period of 24 hours

$$K_0(t) = K_{02}[1 + \eta \cos(2\pi \cdot t / T)$$

$$0 \le \eta \le 1 \qquad T = 24 \cdot 60[\text{min}]$$

$$\frac{dx_1}{dt} = -K_1 x_1^{\ 2} - \frac{V_m x_1}{K_m + x_1} + K_{12} x_2 + u_1$$

$$\frac{dx_2}{dt} = \frac{V_m x_1}{K_m + x_1} - K_{12} x_2 - K_0(t)$$

The Need for System Identification

- In order to design an external drug delivery controller, we must know the parameters (coefficients) of the compartments models.
- Very often, even the number of compartments and their interconnections is not fully known.
- For identification some excitation by an external signal is needed.

Simplest Identification Approach

- People often try to assume linearity, and a specific compartmental architecture.
- Then there is a need to identify each compartment's effective volume and the rate constants determining linear loss and inter-compartmental transfer rates.
- External inputs: A set of single bolus injections to one or more compartments, one at a time.
- Injections are then followed-up by observing the compartments' <u>impulse response</u> of concentration vs. time.

Drug Infusion Methods

- Intravenous (IV) drug infusion is the most rapid means for distributing the drug to target compartments.
- IV is fastest because drug goes straight to the circulatory system. Slower infusion methods include intramuscular, subdermal etc.
- Drug may also be infused directly into the cerebrospinal fluid.

Methods for Controlling Drug Infusion Rate

- ON/OFF mode, effected by a solenoid valve, in an IV drip line.
- A syringe pump running at a constant rate can also be turned on and off.
- If the infusion rate of a syringe pump can be continuously varied between 0 and a maximum, then some sort of proportional control can be designed.
- With bolus injectors, bolus size is typically constant. We vary the frequency of injections

On-Off Controllers

- Simple, inexpensive, reliable and generally do not require a computed control algorithm (Sliding Mode Control and Minimum Time Control are well known exceptions). Drug input rate is 0 or U_{max}.
- On-Off control often results in a steady-state limit cycle (like in a thermostat action). Design should be such that no excessive oscillation frequency or amplitude develop.

Proportional Control

- Drug input rate is variable between 0 and $U_{max,}$ [μg/min] according to some pre-determined gain K.
- The linear gain operates on an error signal – the difference between a reference level and the measured level of the variable of interest.
- Choice of K requires some tuning, or pre-identification.

Nonlinearities and other non-idealities affecting Closed-Loop Drug Input Control

- Compartments parameters vary markedly from patient to patient, and also with time.
- Drug can be injected, but it cannot be un-injected. Excess drugs is generally cleared from the body naturally.
- Drug often interferes with the model, changing the model parameters.
- The compartments themselves may be nonlinear.