Lecture 2: The Systems Approach for Linear Systems

In bioengineering, you encounter many types of systems you may need to model. The skills needed to build models for the different systems are slightly different, yet have similarities, and often yield equations and thus solutions with similar properties. The systems approach helps use a similar set of skills to build the models. We describe here linear systems, but in many cases, especially for chemical systems, the modeling approach can be expanded to include nonlinear systems.

- Electrical systems
  - current flow and voltage across neurons & muscles
  - Electrocardiograms, defibrillators, and other devices
- Fluidic systems
  - lung mechanics
  - vascular mechanics
  - microfluidic devices
- Mechanical systems
  - orthopedic mechanics
  - muscle contraction, cytoskeletal filaments
  - biomaterial mechanics
- Chemical systems
  - Metabolism
  - Signaling and Hormone Pathways
  - Drug dosing (Pharmacokinetics)

We will describe the systems approach by relating it to electrical systems, and then will expand it to each of these 4 types of systems. In each case, we will follow the same general D.I.E.S.E process for building a model:

- **D**iagram. We translate as many assumptions as possible into a diagram of the syatem, and then write out any additional assumptions that are not included in the diagram.
- **I**dentify. Define the parameters and variables by indicating them in the diagram where possible. Then list the parameters and variables in sets and identify which are described in the problem statement and their meaning vs intermediate variables that are introduced to build the model, but may be removed during simplification.
- **E**quations. Write out all the equations relevant to this problem. We will learn below about two types of equations: the element equations and the conservation equations. You may also need to translate other assumptions into equations. If there are any assumptions that were not used to build the diagram, you probably need to convert this to an equation. Although it is possible that an assumption is only used to justify the use of a simpler model by leaving out other processes, you need to ask if the model you built will always match the set of assumptions. At the end, you should have one differential equation for every variable you have defined.
- **S**implify the model to remove intermediate variables, reduce the number of equations, and provide a set of differential equations. Identify the initial conditions for each.
- **E**rror check for completeness and dimensional analysis.

All of these systems have two types of system variables.

- Effort is like potential energy and is what pushes the system, such as voltage in electrical, pressure in fluidic, force in mechanical, and chemical potential in chemical systems. Following the symbols for the electrical system, we use V for effort.
- Flow is like kinetic energy and is the movement of mass or material in the system, such as current in electrical, volumetric flow in fluidic, velocity in mechanical, and chemical flux in chemical systems. Following the symbols for the electrical system, we use I for flow.

There are three types of elements in all of these systems. Each element has a different equation relating effort to flow.

- Damping, or Resistance, R, for electrical systems, dissipates energy
  - flow is proportional to effort: $V = IR, I = \frac{1}{R}V$
- Storage, or Capacitance), C, for electrical systems stores potential energy
  - flow is proportional to the derivative of effort: $I = C\frac{dV}{dt}$.
  - equivalently, effort proportional to the integral of flow $V = \frac{1}{C}\int Idt$.
- Inertance, or Inductance, L, for electrical systems, stores kinetic energy
  - effort proportional to the derivative of flow, $V = L\frac{dI}{dt}$,
  - equivalently, flow proportional to the integral of effort: $I = \frac{1}{L}\int Vdt$.

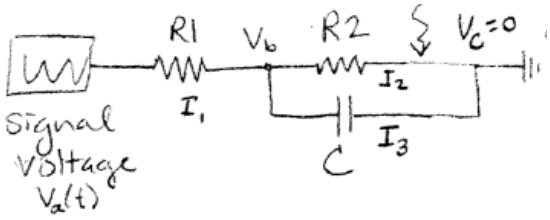
In addition to the element equations, you need the conservation laws to complete the mathematical models. These take the general form of conservation of energy, or effort and conservation of mass, or flow. For the electrical system, these take the form of Kirchoff's laws:

- Effort equation: The voltage drop around a loop sums to zero (so the voltage drop in paths in series must be identical.) $\sum V = 0$ on a loop
- Flow equation: The current entering any node must sum to zero (or the current in must equal the current out). Note that a capacitor is not a node. $\sum I = 0$ on a node

Electrical Example

Problem: You connect a voltage generator to a ground through two resistors (R1 and R2) in series, and place a capacitor (C) in parallel with the resistor (R2) closest to ground. Initially, all currents and voltages are zero. What is the current through the second resistor?

Solution:



1. Diagram the system
   a. See figure to the right.
   b. The only assumption not addressed in the diagram is that all currents and voltages are zero at the start, which translates to $I_1(0) = I_2(0) = I_3(0) = 0, V_b(0) = 0$
2. Identify parameters and variables.
   - The three parameters are R_1, R_2, and C, given in the problem statement.
   - The voltage signal in the voltage generator is a time dependent parameter (or forcing function), which we are calling V_a.

- We are asked to find the current through the second resister, which we have defined in the diagram as I_2. This is our dependent variable of interest.
- The three remaining variables (V_b, I_1, I_3) are intermediate variables that we would love to remove. So four total.
- Note that we can define the ground as 0, so Vc = 0.

3. **E**quations:
   - Define the element equations:

$$(V_a - V_b) = R_1 I_1$$

$$V_b = R_2 I_2$$

$$I_3 = C\frac{dV_b}{dt}$$

   - Conservation of energy around a loop tells us that the voltage drop across both R2 and C is both Vb, which we already used implicitly.
   - Conservation of mass on the node b gives:

$$I_1 = I_2 + I_3$$

   - Note that we have 4 equations, and four dependent variables. So we know we have enough to solve the problem.
4. **S**implify. Substitute some equations for others in order to remove the intermediate variables to obtain an equation for the desired unknown, I_2, in terms of the parameters, R_1, R_2, C, V_a. This is left as an exercise for the reader. Initial condition is $I_2(0) = 0$.

$$\frac{dI_2}{dt} = \frac{V_a(t)}{CR_2R_1} - \frac{R_1 + R_2}{CR_2R_1} I_2(t)$$

5. **E**rror Check.
   - Completeness: we have one equation and one initial condition for one unknown variable, I_2, since $V_a(t)$ is known.
   - Dimensional analysis: you can quickly confirm that each term has units of A/s.

Fluidic Models

Fluidic systems are the most analogous to electrical models.

- Effort (V) is pressure (P).
- Flow (I) is volumetric flow (Q).
- Damping (R) is fluid resistance (R), so $P = QR, Q = P/R$
- Storage (C) is Compliance (C) so $Q = C\frac{dP}{dt}$.
- Inertance (L) is Fluid inertia (L), so $P = L\frac{dQ}{dt}$
- Effort equation: The pressure drop around a loop sums to zero (so the pressure drop in paths in series must be identical.)
- Flow equation: The volumetric flow entering any node must sum to zero (or the flow in must equal the flow out of a node).

However, the diagrams for fluidic systems can be difficult to diagram. Even if the device can be described as a discrete set of channels with different properties, these channels do not relate in

any orderly way to the elements as defined for the systems approach. A channel with only resistance can be modeled as a resistor between two nodes that indicate the pressure at the inlet and outlet of the channel. However, a channel with only compliance cannot be drawn like a capacitor in the same way, since this would stop the flow through that channel. Instead, the capacitance of a channel or element is modeled as a shunt compliance between the pressure inside the channel and that outside the channel. If the same channel has both compliance and resistance, then the pressure changes inside the channel, and the only way to model this is to replace the tubing with a series of resistors and shunt compliances.

Fluidic Example:

In the Thomas lab, we use a syringe pump attached to a microfluidic flow chamber, which has a resistance Rf, through tubing that has a compliance, Ct. The Pump prescribes a flow Q(t), but we want to know the flow in the flow chamber, Qf(t), since this is what the cells we study experience. Here, we ignore the resistance in the tubing and compliance of the flow chamber since they are much less than the values we include. The physical set-up is thus:

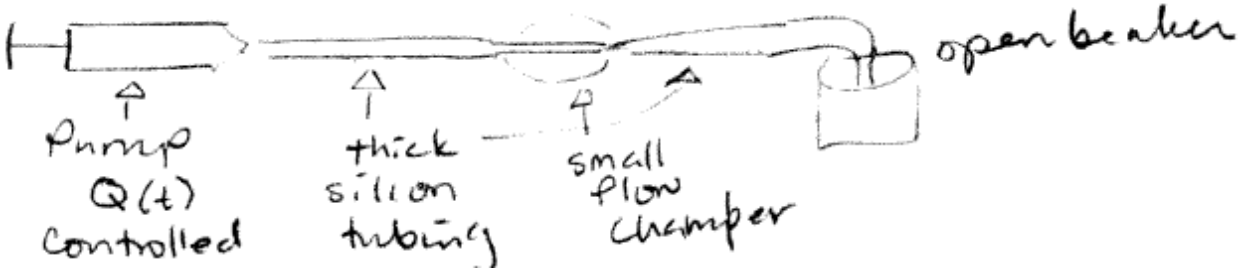
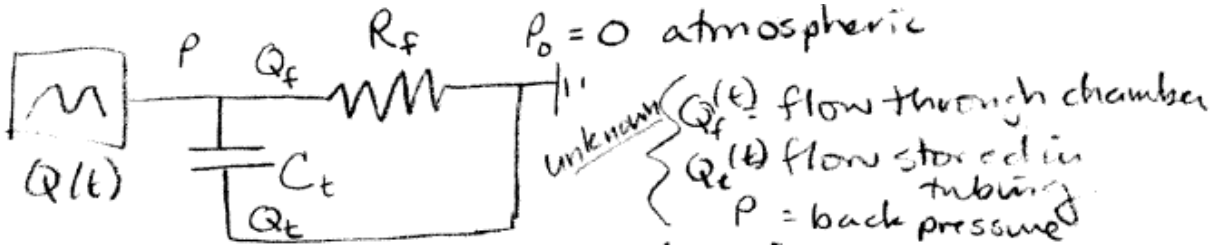


Diagram: To diagram this, you use the shunt compliance as below.



The resistance and the shunt compliance both connect to the atmospheric pressure, because the tubing after the chamber is open, and the tubing before the chamber is surrounded by atmospheric pressure. We can use our intuition to note that Qf will approach Q if the syringe pump is left for long enough at a constant flow rate. This can help you remember how to diagram shunt compliance.

Identify Parameters and variables. Recall from the problem statement that the pump will control Q, so this is a time-dependent parameter, and Qf(t) is what we want to know, since it is what the cells experience. Therefore, we want to get rid of intermediate variables Qt and P, but keep the parameters Rf and Ct.

ESE: Once diagrammed, fluidic systems are identical to the electrical systems in terms of developing the model equations. Thus, converting the diagram above into a mathematical model is left as an exercise.

Mechanical Models

Mechanical systems are quite different from electrical and fluidic models. In the diagrams, the lines indicate the distances between nodes, rather than the flow of material through elements.

- Effort (V) is force (F). A positive sign means external force is tensile.
- Flow (I) is velocity (dx/dt). A positive sign means the model is being stretched.
- Damping (R) is viscosity or damping (b), so $V = IR$ becomes $F = b\frac{dx}{dt}$
- Storage (C) is inverse spring constant (1/k) so $I = C\frac{dV}{dt}$ becomes $\frac{dx}{dt} = \frac{1}{k}\frac{dF}{dt}$, or $F = kx$.
- Inertance (L) is Intertia (m), so $V = L\frac{dI}{dt}$ becomes $F = m\frac{d^2x}{dt} = ma$
- Effort equation: Newton's law $\sum F = ma$. If mass is negligible or the system is at equilibrium, then m or a is zero, and $\sum F = 0$
- Flow equation: velocities (and distances) in around a loop are zero. $\sum \frac{dx}{dt} = 0$ around a loop. That is, lengths and velocities in parallel must be the same and in series must add.

Mechanical Example

Consider a model for active muscle, as diagrammed here, where $f_m(t)$ is the force generated by the muscle tissue, b is the damping of this same tissue, k_1 is the spring constant of the tendon anchoring the muscle, and k_2 is the spring constant of the sarcolemma surrounding the muscle and tendon. We want to know the external force applied by the entire system, $f(t)$, so this is the output, in response to the inputs, $f_m(t)$ and x(t), which is the length of the system *relative to its length at equilibrium*. We use the internal sign convention for forces, so that tensile force is positive and compressive negative, so that forces on a node must balance in both directions rather than sum to zero.

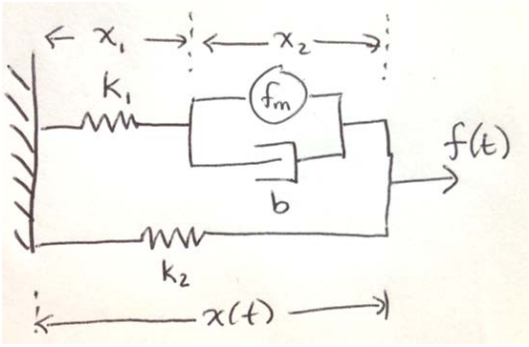


Diagram was already provided in the problem statement.

Identify parameters and variables. We want to have an equation in the variables f, x, and f_m, with parameters k_1, k_2, and b, so we want to remove internal variables x_1 and x_2

Equations. To build the model, we write the equations:

$f = k_2 x + k_1 x_1$ (from Newton's law on the two major branches, plus the element equations)

$k_1 x_1 = f_m + b\frac{dx_2}{dt}$ (from Newton's law and more element equations).

$x_2 = x - x_1$ (from conservation of length)

This gives us three equations, which is one extra for each unwanted variable, so this is probably enough. I also used all the element equations, which is usually necessary.

Simplify.

I remove x_2, with $\frac{dx_2}{dt} = \frac{dx}{dt} - \frac{dx_1}{dt}$, to get $k_1 x_1 = f_m + b\left(\frac{dx}{dt} - \frac{dx_1}{dt}\right)$

I remove x_1 by converting $k_1 x_1 = f - k_2 x$ to $x_1 = \frac{1}{k_1} f - \frac{k_2}{k_1} x$ and $\frac{dx_1}{dt} = \frac{1}{k_1}\frac{df}{dt} - \frac{k_2}{k_1}\frac{dx}{dt}$, which I can substitute into the equation I just obtained, to get $f - k_2 x = f_m + b\left(\frac{dx}{dt} - \frac{1}{k_1}\frac{df}{dt} + \frac{k_2}{k_1}\frac{dx}{dt}\right)$

I now rearrange this equation to:

$$\frac{k_1}{b} f + \frac{df}{dt} = \frac{k_1}{b} f_m + \frac{k_1 k_2}{b} x + (k_1 + k_2)\frac{dx}{dt}$$

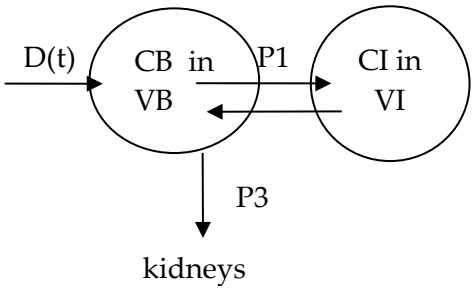
Error check.

It is complete because it relates f to fm and x using the given parameters and nothing else. (Remember what you decided in the "Identify" step.)

Dimensional analysis: all terms should have units N/s, since the second term clearly does (df/dt). k's have $\frac{N}{m}$, b's have $\frac{Ns}{m}$. (Check the systems table on page 1 of lecture 2 if you forget the units). First and third terms thus have units $\frac{N}{m}\frac{m}{Ns} N = N/s$. fourth term ($\frac{k_1 k_2}{b} x$) has units $\frac{N}{m}\frac{N}{m}\frac{m}{Ns} m = N/s$, and fifth term $(k_1 + k_2)\frac{dx}{dt}$ has units $\frac{N}{m}\frac{m}{s} = \frac{N}{s}$. Yes!

Linear Chemical Compartmental Models

Here we consider linear chemical compartmental models. A common and very useful example of a linear chemical model is pharmacokinetic (PK) models, which describe the metabolism and movement of a drug between different compartments in the body. PK models are used to design dosing regimes that will keep the concentration of a drug in the blood within the therapeutic window, meaning above the therapeutic threshold and below the toxic threshold. A "compartment" may refer to a physical compartment, such as the blood versus the urine, or in the cell cytoplasm versus nucleus. However, a compartment can also refer to two species of a chemical, such as interconversion of the cardiac drugs digitoxin and digoxin, or the phosphorylation of a protein. To use a **compartmental** model, we must assume that the each chemical species is well-mixed within the compartment, so we can neglect the specifics of the compartment geometry to avoid a PDE approach. Chemical systems are **linear** if the conversions between compartments (whether transport or chemical reactions) are either unimolecular, or the availability of other molecule(s) involved (enzyme, transport protein, reacting molecule such as water or ATP) are not affected by system state, so the effect of those other molecules can be modeled as parameters rather than dependent variables. There is no inertance in a chemical system, so a linear chemical system does not oscillate without an oscillatory input.



While we can build chemical transport models from a systems approach using a block diagram (see appendix in this lecture notes after the summary), it is much simpler to build a chemical model from a compartmental diagram. We will use a simple PK example to illustrate our approach, shown here on the right. A drug is injected at rate $D(t)$ into the blood, and transfers with permeability P1 between the blood and the interstitium, which have volumes V_B and V_I respectively. It is also filtered into the kidneys from the blood with permeability P3.

We need one equation for each compartment. Each equation will be a conservation of mass equation with a flux term for each arrow entering or leaving that compartment. Because the terms are flux, the units must be moles/sec, so if the variables are in concentrations as we used in the model here, we need to multiply by the volume. That is, the change of mass in a compartment (the volume of the compartment times the concentration), is equal to the sum of the fluxes:

$$V_i \frac{dC_i}{dt} = \sum_j J_{ij}$$

where J_{ij} is the flux (units mol/s) from compartment i to compartment j. The flux is the permeability P_{ij} (in units $\frac{mol/s}{mol/L}$, or L/s) that controls transport between j and i, times the chemical potential μ between the two compartments. The chemical potential is just the difference in concentration (units mol/L), if there is no physical contribution to chemical potential such as charge and voltage differences, or pressure. That is, $\mu = \Delta C = C_j - C_i$, and

$$J_{ij} = P_{ij}(C_i - C_j)$$

The flux may also be a prescribed input like the dosage $D_i(t)$ into compartment i.

For our example system we therefore write the following model from the diagram:

$$V_B \frac{dC_B}{dt} = P_1(C_I - C_B) - P_3 C_B + D(t)$$

$$V_I \frac{dC_I}{dt} = P_1(C_B - C_I)$$

Which we may rewrite as:

$$\frac{dC_B}{dt} = \frac{D(t)}{V_B} + \frac{P_1}{V_B} C_I - \left(\frac{P_1 + P_3}{V_B}\right) C_B$$

$$\frac{dC_I}{dt} = \frac{P_1}{V_I} C_B - \frac{P_1}{V_I} C_I$$

An alternative is to use variables with units of mass (grams or moles) instead of concentrations. In this case, we let $Q_i = V_i C_i$, so the general form of the conservation of mass equation becomes

$$\frac{dQ_i}{dt} = \sum_j J_{ij}$$

For our model, we have $Q_B = C_B V_B, Q_I = C_I V_I$, so the conservation of mass equation in terms of mass variables becomes

$$\frac{dQ_B}{dt} = P_1\left(\frac{Q_I}{V_I} - \frac{Q_B}{V_B}\right) - P_3 \frac{Q_B}{V_B} + D(t)$$

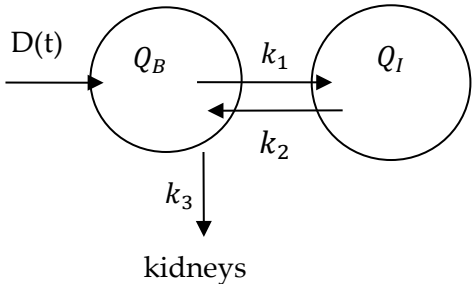
$$\frac{dQ_I}{dt} = P_1\left(\frac{Q_B}{V_B} - \frac{Q_I}{V_I}\right)$$

In this form, it is common to replace the ratios of permeability to volume with rate constants (units $1/s$). In this case, we might define: $k_1 = \frac{P_1}{V_B}, k_2 = \frac{P_1}{V_I}, k_3 = \frac{P_3}{V_B}$, which results in:

$$\frac{dQ_B}{dt} = k_2 Q_I - (k_1 + k_3) Q_B + D(t)$$

$$\frac{dQ_I}{dt} = k_1 Q_B - k_2 Q_I$$

This system may be diagrammed as follows:



Pharmicokinetic models are often used to predict the effect of drug dosing on a patient. The parameters are fit to data, usually of the concentration of drug in the blood over time. For this purpose, an empiric model would be sufficient, so it's OK to use these effective rates constants instead of attempting to identify the volumes and permeability's, which have more recognizable physical meaning.

Note that the concentration form of these equations have 4 parameters (R1, R3, VB, VI) while the mass form has 3 parameters (k1, k2, k3). However, to fit the mass model to measurements of concentration in the blood, we need to know V_B, which effectively adds a parameter.

Chemical Reaction models

When chemicals react with each other, the reaction is often written so that substrates are on the left of the reaction, and the products on the right, with an arrow indicating the direction of the reaction and a rate constant giving the speed. For example, in lecture 1, we saw two reactions:

Binding reaction: $R + L \rightarrow C$, with rate constant k_{on}, in units $M^{-1}s^{-1}$.

Unbinding reaction: $C \rightarrow R + L$, with rate constant k_{off}, in units s^{-1}.

Reactions occur at a rate that equals the rate constant times the concentrations of all substrates. That is reaction 1 occurs at a rate $k_{on}RL$, where R and L are the concentrations of receptor and ligand, respectively, while reaction 2 occurs at rate $k_{off}C$, where C is the concentration of complex. The effect of each reaction on the reactants is determined by the difference between the number of that reactant in the product minus the substrates. Thus, each reaction 1 removes one each of R and L, and adds one C. Thus reaction 1 contributes - $k_{on}RL$ to $\frac{dR}{dt}$ and $\frac{dL}{dt}$ and + $k_{on}RL$ to $\frac{dC}{dt}$. These terms are simply added to the differential equations for chemical transport.

Summary. Know the terms underlined and these concepts.

1. For linear systems, we build models with the following process.
    a. **D**iagram system and **D**escribe any additional assumptions.
    b. **I**dentify parameters and variables.
    c. **E**quations for elements and conservation laws (see table below), as well as for any additional assumptions.
    d. **S**implify the model to remove intermediate variables.
    e. **E**rror check for completeness and dimensional analysis.
2. The element and conservation equations for the systems is summarized below:

	Electrical	**Fluidic**	**Mechanical**	**Chemical**
Effort	**Voltage, V (V)**	**Pressure, P (Pa)**	**Force, F (N)**	**Potential μ (M)** $\mu = \Delta C$
Flow	**Current, I (A)**	**Volumetric Flow, Q (m^3/s)**	**Velocity, V (m/s)**	**Flux, J (mol/s)**
Damping (units)	Resistor, R (ohm =V/A) $V = IR$	Fluid resistance, R ($Pa \cdot s/m^3$) $P = QR$	Damper, b (Ns/m) $F = bdx/dt$	Inverse perm $1/P$ (s/L) $J = P\mu$
Storage (units)	Capacitor, C (Farad = As/V) $I = CdV/dt$	Compliance, C (m^3/Pa) $Q = CdP/dt$	Inverse Spring 1/k ($k\ in\ N/m$) $F = kx$	Volume, V (L) $J = V\frac{d\mu}{dt}$
Inertance (units)	Inductance, L (Henry =Vs/A) $V = LdI/dt$	Fluid inertia, L (Pas^2/m^3) $P = LdQ/dt$	Inertia, m (kg=$Ns2/m$) $F = ma$	NONE
Conservation of effort	$\sum V = 0$ on a loop	$\sum P = 0$ on a loop	$\sum F = ma$ on a node	Implicit in the storage equation
Conservation of Flow	$\sum I = 0$ on a node	$\sum Q = 0$ on a node	$\sum \frac{dx}{dt} = 0$ around a loop.	$\sum J = V\frac{dC}{dt}$

The chemical system can be derived from the compartmental diagram in either of two forms:

- $V_i \frac{dC_i}{dt} = \sum_j P_{ij}(C_j - C_i) + D_i(t)$ where P_{ij} is permeability between compartments i and j in L/s, V_i is the volume of compartment i in L, $D_i(t)$ is input into compartment i in mole/sec, and C_i is the concentration in compartment i in mole/L.
- Add flux due to reactions; The reaction flux is volume times the rate constant times the product of the substrate concentrations. This affects substrates and products according to stoichiometry.

Appendix: using block diagrams for compartmental models.

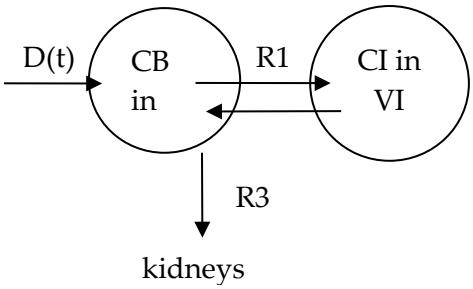
We can diagram this by drawing nodes that correspond to the amount of a chemical in a compartment. Lines between the nodes represent the effort and flow between these two compartments. While the effort and flow variables are what determine the system dynamics, we are usually interested in the concentration of a chemical in a compartment, so we want to develop a model in which effort and flow are intermediate variables that are removed for the final equations, and just keep equations for the amount or concentration of the is modeled by a variable, rather than using effort and flow as variables. While we can use the systems approach to derive the compartmental models, it is easier to start with a compartmental diagram and derive the model directly from this.

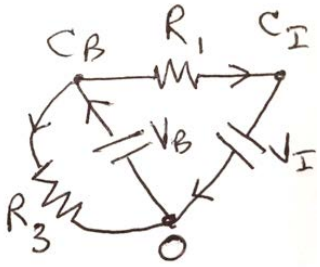
- Effort is **chemical potential, $\boldsymbol{\mu}$**. If there is a charge on the molecule, then voltage affects the chemical potential (e.g. this applies for ion channels). Similarly, a change in pressure between two compartments will push a chemical to another compartment. However, if there are no such physical effects, then $\mu = \Delta C$, the difference in concentration between the two compartments, and thus has units M (molar, or moles/liter).
- Flow is **flux, $\boldsymbol{J}$**, is the movement of chemical between two compartments, and has units mol/s.
- Damping is **inverse permeability, $\boldsymbol{R_C = 1/P}$**, where **permeability, P** is the ease of movement between two compartments, with units L/s, so $\boldsymbol{R_C}$ has units of s/L. The equation $V = IR$ thus becomes $\mu = JR_c$, or $J = P\mu$.
- Storage is the volume, $\boldsymbol{V}$, of a compartment, and has units L. The equation $I = C\frac{dV}{dt}$ thus becomes so $J = V\frac{d\Delta C}{dt}$. We can diagram this as a capacitor with parameter $\boldsymbol{V}$ that bridges between the node and ground, which as concentration 0. This, the difference in chemical potential on this element is the change in concentration, so $J = V\frac{dC}{dt}$.
- Effort equation. The sum of chemical potentials around a loop is zero. $\sum \mu = 0$ on a loop.
- Flow equation. The sum of flux at each node is zero. Note that each node has a storage element linking it to the ground, so flux through this element allows the concentration in the node to change even though the flux on a node sums to zero. $\sum J = 0$ on a node.

We will now use this to derive a compartmental model, and then describe how to derive such a model without using the systems model.

Chemical Example

Problem statement: Consider a PK model where a drug is injected into the blood, and can diffuse between blood and interstitial fluid. The injection infuses a dose $D(t)$ into the blood (in moles/s). This injection is a forcing function (an input) into the system. The inverse permeability between the blood and interstitial fluid is R1 (in s/L). The drug is cleared from the blood through the kidneys with inverse permeability R3 (in s/L). This is a one-directional clearance because fluid with the solute flows into the kidneys but not back. If the volume of the blood and interstitial fluid, respectively, is V_B and V_I, then what is the concentration CB(t) in the blood?





We **D**iagram this in two ways. First, we show the fairly intuitive compartmental model on the left. Second, we draw a block diagram on the right with nodes for the concentrations, and lines for the resistances and storage elements. In the latter, each element is drawn with a direction, and is associated with a flux J_i, which is positive if material flows in the direction of the element, and a drop in chemical potential drop μ_i, which is defined as the potential at the start minus that at the end of the element. Thus, material flow in the direction of the drop in potential, just as current flows with the drop in voltage.

Identify parameters and variables. In the compartmental model, we added the intermediate variable CI, the concentration in the interstitial fluid, so we have two variables. In the block diagram, we have 4 elements (1,3,B,I) and each has a chemical potential drop and a flux for which we will use the same subscripts, so we also introduced $\mu_1, J_1, \mu_3, J_3, \mu_B, J_B, \mu_I, J_I$, as we will see in the element equations below, so we now have 10 variables. The parameters are R_1, V_B, V_I, R_3 and the input is $D(t)$.

Equations. We have four element equations:

$$J_B = V_B \frac{d\mu_B}{dt}$$

$$J_I = V_I \frac{d\mu_I}{dt}$$

$$\mu_1 = J_1 R_1$$

$$\mu_3 = J_3 R_3$$

We have an effort conservation equation for the major and the minor loops:

$$\mu_1 + \mu_I + \mu_B = 0$$

$$\mu_B + \mu_3 = 0$$

And we have flow conservation for all the nodes:

$$J_B - J_1 - J_3 + D(t) = 0$$

$$J_1 - J_I = 0$$

$$J_I - J_B + J_3 = 0$$

We now have to define the variable(s) of interest to us. We define CB and CI as the concentration in the blood and the intersitium, and thus the potential in the left and right nodes. Recall that μ_i is defined as the potential at the start minus that at the end of the element, so:

$$\mu_I = C_I$$

$$\mu_B = -C_B$$
$$\mu_3 = C_B$$
$$\mu_1 = C_B - C_I$$

We thus have 12 equations for 10 variables. We see that the effort conservation ones are redundant given the definitions above, so we have 10 linearly independent equations for 10 variables. We should be able to simplify this to 2 ODEs for our two variables (CB and CI) or to one (second order equation) in CB, as we prefer. We simplify this in the following steps:

1. Rewrite the first equations to replace all the J's with $\mu's$ in the two flux conservation equations, to get:
$$V_B \frac{d\mu_B}{dt} - \frac{\mu_1}{R_1} - \frac{\mu_3}{R_3} + D(t) = 0$$
$$\frac{\mu_1}{R_1} - V_I \frac{d\mu_I}{dt} = 0$$
2. Use the 4th set of equations to replace the $\mu's$ with the appropriate concentration expressions in the same two equations:
$$-V_B \frac{dC_B}{dt} - \frac{C_B - C_I}{R_1} - \frac{C_B}{R_3} + D(t) = 0$$
$$\frac{C_B - C_I}{R_1} - V_I \frac{dC_I}{dt} = 0$$
3. Rearrange to obtain two derivative equations:
$$V_B \frac{dC_B}{dt} = -\frac{C_B - C_I}{R_1} - \frac{C_B}{R_3} + D(t)$$
$$V_I \frac{dC_I}{dt} = \frac{C_B - C_I}{R_1}$$

We note that all terms are in units of moles per second.