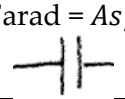
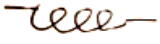
The Systems Approach

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.

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

	Mechanical	**Electrical**	**Fluidic**	**Chemical**
Effort Ψ	**Force, F (N)**	**Voltage, V (V)**	**Pressure, P (Pa)**	**Potential (Δconcentration) μ ($mol/L = M$)**
Flow ζ	**Velocity, V (m/s)**	**Current, I (A)**	**Volumetric Flow, Q (m^3/s)**	**Flux, J (mol/s)**
Damping R	Damper, b (Ns/m) 	Resistor, R (ohm =V/A) 	Fluid resistance, R (Pas/m³) 	Inverse permeability, Rc (s/L)
Storage C	Spring, k (N/m) 	Capacitor, C (Farad = As/V) 	Compliance, C (m³/Pa) 	Volume, V (L)
Inertance L	Inertia, m (kg=$Ns2/m$) 	Inductance, L (Henry =Vs/A) 	Fluid inertia, L (Pas²/m³) 	NONE

Generalized system variables

- Effort = ψ(t)
- Flow = ζ(t)

Element Equations relate flow to effort:

- Resistance R (Energy Dissipation) $\boxed{\psi(t) = R\zeta(t)}$ $V = IR$
  - Effort ~ flow
  - Flow ~ effort
- Storage C (Potential Energy) $\boxed{\psi(t) = \frac{1}{C}\int_0^t \zeta(\tau)d\tau}$ $V = \frac{1}{C}\int Idt$ or $I = C\frac{dV}{dt}$
  - Effort ~ integral of flow
  - Flow ~ derivative of effort
- Inertance L (Kinetic Energy) $\boxed{\psi(t) = L\frac{d\zeta(t)}{dt}}$ $V = L\frac{dI}{dt}$
  - Effort ~ derivative of flow
  - Flow ~ integral of effort

Conservation equations for flow and effort:

In addition to the element equations, you need the conservation laws to complete the mathematical models. These take the general form of conservation of effort (energy) and conservation of flow (mass).

- Mechanical:
  a. Conservation of energy takes the form of Newton's law: The sum of <u>forces</u> equals mass times acceleration. ($\sum F = ma$). This means that if the mass can be neglected, OR the system is at equilibrium (no acceleration), then the sum of forces is zero. In this case, forces in series are equal, so the node is pulled in equal and opposite manner, summing to zero.
  b. Conservation of mass (in the form of length): Positions and velocities in parallel must be the same, and in series, must add.
- Electrical: Kirchoff's laws (or fluid mechanics)
  a. The <u>voltage</u> (or pressure) drop around a loop sums to zero (so the voltage or pressure drop in paths in series must be identical.)
  b. The <u>current</u> (volumetric flow) entering any node must sum to zero (or the current in must equal the current out). (while charge accumulates at a capacitor (compliance), the node doesn't have capacitance (compliance.)
- Fluidic: is identical to electrical, with pressure instead of voltage and volumetric current instead of ionic current.
- Chemical: Chemical equations.
  a. conservation of mass: the change in the amount of chemical must equal the sum of the fluxes of that chemical.

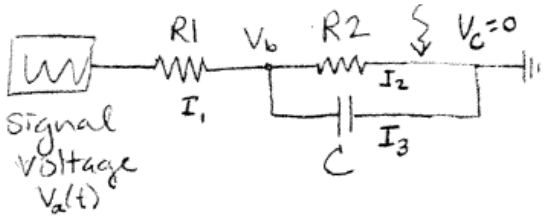
Together, the element and conservation equations make up the "E" in DIESE.

Example 1: Electrical Model

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. **D**iagram the system

2. **I**dentify 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:
   - Now 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. Initial conditions are all zero. 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.

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

5. **E**rror Check.
   - Completeness: we have one equation for one unknown variable, I_2, since $V_a(t)$ is known. We should add that $I_2(t) = 0$ is our initial condition.
   - Dimensional analysis: you can quickly confirm that each term has units of A/s.

Example 2: Fluidic Model

Fluidic systems look a lot like electrical models in the systems approach table, but they can be difficult to diagram because the same components have both compliance and resistance. The compliance in a tubing is generally modeled as a shunt compliance to the pressure outside the tubing.

For example, in my lab, we use a syringe pump attached to a microfluidic flow chamber, which has a resistance Rf, through tubing that has a complicance, 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.

Physical set-up:

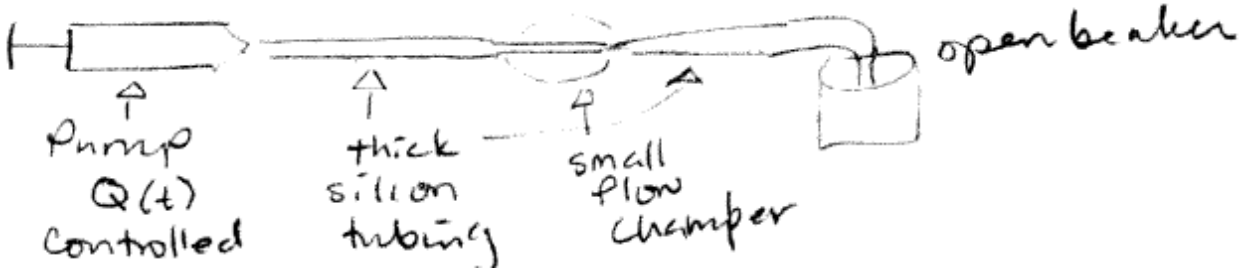
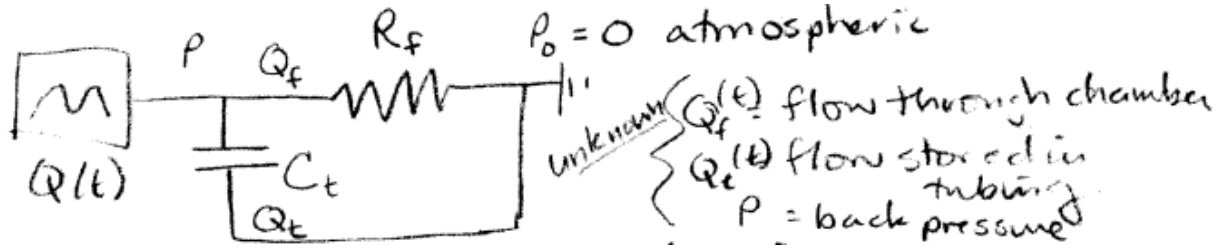


Diagram: To diagram this, you use the shunt compliance as below.



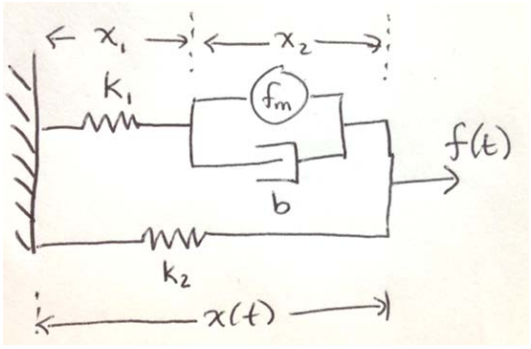
The resistance and the shunt compliance both connect to the atmospheric pressure, because the tubing after the chamber is open, and the tubing before the chamber is surrounded by atmospheric pressure. We can use our intuition to note that Qf will approach Q if the syringe pump is left for long enough at a constant flow rate. This can help you remember how to diagram shunt compliance. The novice often tries to place Rf in series with Ct, but this would cause the the flow to go to zero with a constant pressure, which is wrong; the flow should instead stabilize at some nonzero value in this condition.

Identify Parameters and variables. Recall from the problem statement that the pump will control Q, and that Qf(t) is important for the experiments, since it is the flow in the chamber experienced by the cells, as noted above. 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.

Example 3: Mechanical Model of Muscle



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 and appropriate 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!

Example 3: Chemical Model

Chemical reaction models, like we discussed in lecture 1, are often nonlinear, since the concentrations of two variables are multiplied together. However, under some assumptions, chemical reactions are linear. For example, in lecture 1, we assumed $R = R_0$, which meant that one of the reactants was a constant parameter rather than a variable and the model remained linear. Many pharmacokinetic (PK) models describe the movement of drugs between different compartments in the body and are also linear models. Thus, we do have linear chemical models. For the chemical model to require an ODE instead of a PDE, we must assume all chemicals are well-mixed within a compartment to avoid spatial variations within a compartment. However, the concentration of chemical may be different between two compartments separated by some sort of membrane or barrier. Thus, we refer to chemical models as compartmental models. However, each compartment in the model represents one variable, and different variables may reflect different chemical species (L vs C) and/or different physical compartments (blood vs intestines).

For the linear chemical system models, we need to remember the meaning of **chemical potential, $\boldsymbol{\mu}$**. This is the push for a chemical to move. 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 is 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).

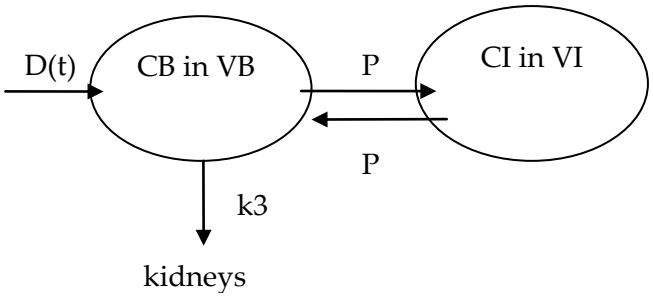
The **flux, J**, is the movement of chemical between two compartments, and has units mol/s.

The **permeability, P**, is the ease of movement between two compartments, and has units L/s. This can involve permeability of a barrier to solutes or to movement of the entire fluid between the compartments, but the units and equations are the same in both situations. The **inverse permeability, $\boldsymbol{R_C = 1/P}$**, is the resistance to movement between two compartments and is in s/L.

When the flux between two compartments is passive, it satisfies the system equations, $\Psi(t) = R\zeta(t)$, which translates to $\mu = J/P$, or $J = P\Delta C$. That is, flux is proportional to the chemical potential times the permeability. This relationship does not apply to active transport in the form of a fluid pump that moves volume from one compartment to another, or a transporter that pumps a specific chemical in one direction utilizing an energy source such as ATP.

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/hr). This injection is a forcing function (an input) into the system. If it is a one-time dose, we may model it as an initial condition in the blood. The permeability between the blood and interstitial fluid is P (in hr/L). Also, drug is cleared from the blood through the kidneys at a rate k_3 (in 1/hr). This is a one-directional clearance so we don't worry about the concentration in the kidneys, which will be secreted as urine. If the volume of the blood and interstitial fluid, respectively, is V_B and V_I, then how much drug is in the blood at time t?

Diagram is on the right.



Identify. The variables are C_B and C_I, the amount of drug in the blood and interstitial fluid respectively, although we don't need C_I, so it may be possible to remove it. The parameters are P, V_B, V_I, k_3 and the input is $D(t)$.

Equations.

In a chemical model, the element equations are the equations for the flux. The flux from the blood to the interstitial fluid is equal to the difference in concentrations times P. That is, $J_{Transfer} = (C_B - C_I)P$. This amount will be subtracted from the blood and added to the interstitial fluid. Sanity check: if $C_B > C_I$, material should move out of the blood.

Since we are given a rate constant (units 1/s) for the clearance, the loss of concentration from the blood to the kidneys is equal to the concentration in the blood times the clearance rate. To get the flux from the drop in concentration, we need to multiply by the volume. Thus $J_{Clearance} = k_3 C_B V_B$, which will be subtracted from the blood.

Now we apply conservation of mass to each compartment, which creates one ODE per compartment. Remember that each term should be in units of mass (e.g. mg or moles, but not M) per time, since mass, not concentration is conserved. Thus we need to multiply the concentration by the volume on each left-hand term.

$$V_B \frac{dC_B}{dt} = D(t) - J_{Transfer} + J_{Clearance}$$

$$V_I \frac{dC_I}{dt} = J_{Transfer}$$

Simplify. First replace the fluxes with the element equations we just found

$$V_B \frac{dC_B}{dt} = D(t) - (C_B - C_I)P - k_3 C_B V_B$$

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

Rearrange to obtain the equations with only the derivatives in the left hand side:

$$\frac{dC_B}{dt} = \frac{D(t)}{V_B} - \left(\frac{P}{V_B} + k_3\right) C_B + \frac{P}{V_B} C_I$$

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

Error check. The model gives equations for the two variables in terms of each other and the four parameters, so is complete and appropriate. Each term has units of mol/(Ls), so passes dimensional analysis, although I don't show the details here.

Alternative Derivations:

At this point, you may realize that the parameters P, V_B and V_I show up as the ratios P/V_B and P/V_I. We could thus use an alternative representation of this model as follows:

Let $k_1 = P/V_B$, and $k_2 = P/V_I$, and $d(t) = \frac{D(t)}{V_B}$ is the initial concentration right after dosing. Then

$$\frac{dC_B}{dt} = d(t) - (k_1 + k_3)C_B + k_1 C_I$$

$$\frac{dC_I}{dt} = k_2 C_B - k_2 C_I$$

This is a better representation of the model, since it has fewer parameters (3 instead of 4), and we probably don't know the volumes anyway. However, we needed to either know V_B or needed to measure the concentration of drug in the blood right after injection to know d(t).

You may ask why we don't develop a model using the amounts as variables instead of concentrations. Would this be simpler, since we use concentration of mass as the equations? To explore this, let's convert the original 4-parameter model to mass variables.

Let $Q_B = V_B C_B$ and $Q_I = V_I C_I$, and rearrange terms slightly

$$\frac{dQ_B}{dt} = D(t) - \left(\frac{P}{V_B} + k_3\right) Q_B + \frac{P}{V_I} Q_I$$

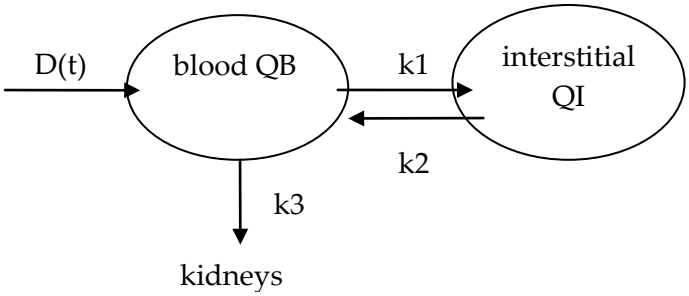
$$\frac{dQ_I}{dt} = \frac{P}{V_B} Q_B - \frac{P}{V_I} Q_I$$

We can turn this into a 3 parameter model with the same substitutions as before.

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

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

This time we have a real 3-parameter model. Because of this, many people express PK models this way. The diagram for this model is shown here. If you start with a model description in which the variables are in amounts and you are given rate constants instead of permeabilities, then you draw the diagram as we see it here.



The conservation of mass equations then are very easy to write; you write one equation for each compartment, and should add one term for each arrow leaving or entering the compartment.