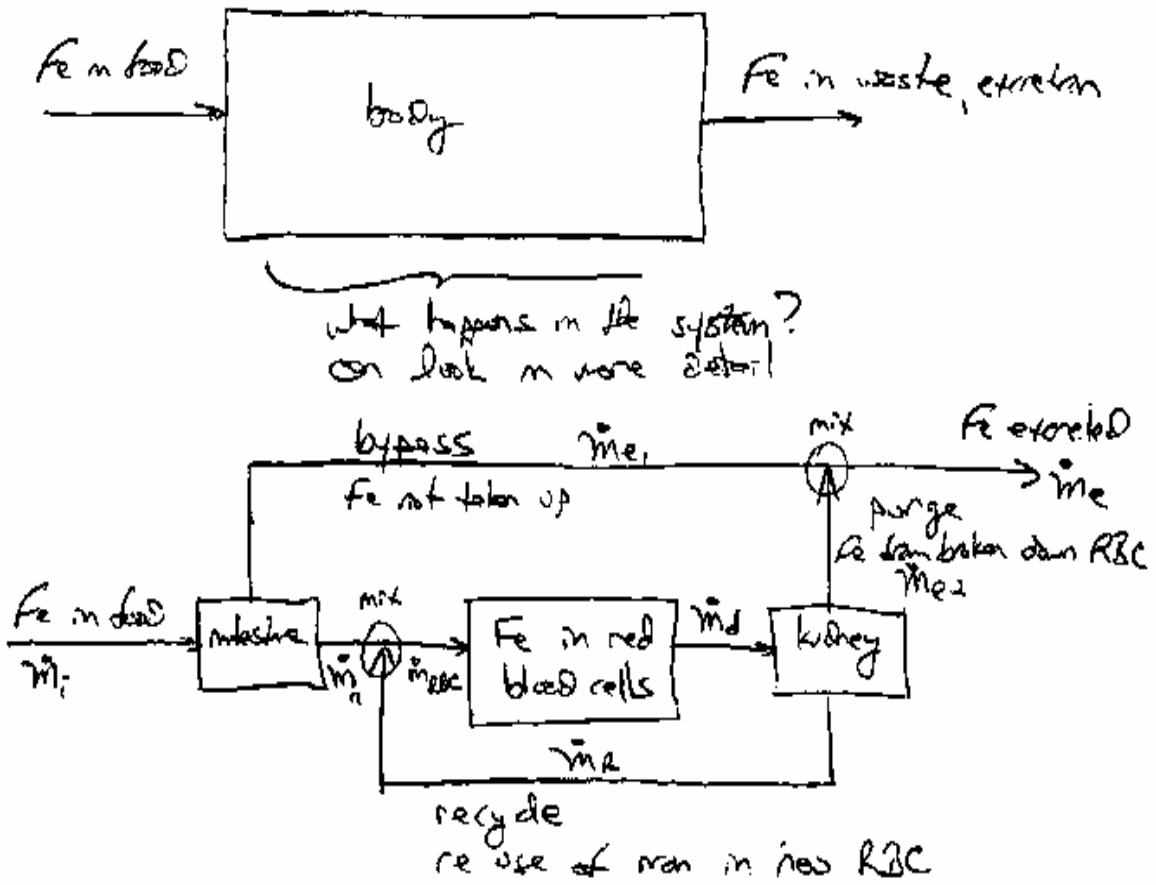
TOPICS – cont'd
- processes with recycle, bypass and purge
- human iron inventory example
- unsteady mass balances and kinetics
- microbial growth kinetics
- pharmacokinetics

RECYCLE, BYPASS and PURGE

Consider how the body handles iron (See MMD 2.5.1)



Can do mass balances around whole system (body) as well as mass balances around each subsystem or groups of subsystems including points where streams mix or are split.

Let's consider only Fe in this example

let $\dot{m}_i$ = dietary intake of iron in mg/day
$\dot{m}_a$ = iron absorbed by body in "
$\dot{m}_{e_1}$ = iron eliminated via intestine "
$\dot{m}_{e_2}$ = iron eliminated via kidney "
$\dot{m}_d$ = iron in degenerated RBC (=red blood cells) "
$\dot{m}_R$ = iron recycled "

Consider this a steady-state system with no rxns:

$$\sum_{in} \dot{m}_j = \sum_{out} \dot{m}_j$$

Can write balances around each subsystem.

intestine: $\dot{m}_i = \dot{m}_{e_1} + \dot{m}_a$ (1)

kidney: $\dot{m}_d = \dot{m}_R + \dot{m}_{e_2}$ (2)

excretion: $\dot{m}_{e_1} + \dot{m}_{e_2} = \dot{m}_e$ (3)

recycle mix: $\dot{m}_a + \dot{m}_R = \dot{m}_{RBC}$ (4)

redblood cells: $\dot{m}_{RBC} = \dot{m}_d$ (5)

Can also write balance around entire system (body)

body: $\dot{m}_i = \dot{m}_e$ (6)

In general if you have N components and M subsystems, can write N*M independent mass balance equations

there are many ways of drawing system boundaries around connected sets of subsystems; some sets of system boundaries will lead to much easier solutions than others — seeing which to choose is part of developing engineering intuition.

DOF Analysis (preliminary)

$$DOF = \underbrace{(\dot{m}_i, \dot{m}_a, \dot{m}_2, \dot{m}_{e_1}, \dot{m}_{e_2}, \dot{m}_e, \dot{m}_{RBC}, \dot{m}_d)}_{8 \text{ unknowns}} - \underbrace{(\text{mass balances around intestine, kidney, excretion, recycle mkt, RBC cells, body})}_{5 \text{ equations}}$$

$= 3$ must specify 3 pieces of info to be able to solve

- Can specify dietary intake of iron, $\dot{m}_i$ (can use this as a basis)
- Can specify recycle efficiency $\varepsilon = \dot{m}_R / \dot{m}_d$,
  i.e. what fraction of Fe from broken down RBCs is internally recycled?

Let's set dietary intake as 8 mg/day ⇔ basis (minimum daily requirement) and assume $\varepsilon = 0.80$ 80% recycle efficiency ⇒ $\dot{m}_R / \dot{m}_d = 0.80$ (1)

- further, we can use some physiological data (RBC inventory, iron content and lifetime) to estimate $\dot{m}_d$, the rate of iron turn over from RBC degradation
  each adult has ~ 5 L blood
  there are about 15 g Hb / 100 mL blood
  MW hemoglobin is 64,500 g/mol and there are 4 Fe per hemoglobin (Hb)
  RBC have lifetime of 120 days

$$\dot{m}_d = \frac{(5\text{ L blood})\left(\frac{15\text{ g Hb}}{0.1\text{ L blood}}\right)\left(\frac{\text{mol Hb}}{64{,}500\text{ g Hb}}\right)\left(\frac{4\text{ mol Fe}}{\text{mol Hb}}\right)\left(\frac{55.847\text{ mg Fe}}{\text{mol Fe}}\right)}{120\text{ days}}$$

$$\dot{m}_d = 21.51 \text{ mg Fe/day}$$

Now can solve,

① $\Rightarrow \dot{m}_i = \dot{m}_e = 8$ mg/day

④ $\Rightarrow 0.80 = \dot{m}_R / 21.51 \Rightarrow \dot{m}_R = 21.51$ mg/day

⑤ $\Rightarrow \dot{m}_d = \dot{m}_{ABC} = 21.51$ mg/day

④ $\Rightarrow \dot{m}_a + 17.21 = 21.51 \Rightarrow \dot{m}_a = 4.30$ mg/day

② $\Rightarrow 21.51 = 17.21 + \dot{m}_{e_2} \Rightarrow \dot{m}_{e_2} = 4.30$ mg/day

③ $\Rightarrow \dot{m}_{e_1} - 4.30 = 8 \Rightarrow \dot{m}_{e_1} = 3.70$ mg/day

i.e. $\dot{m}_a = \dot{m}_{e_2}$ ...

Sig figs? Limited precision of given flow rate: Directly

$\dot{m}_i = \dot{m}_e$	=	8	mg/day
$\dot{m}_d = \dot{m}_{ABC}$	=	22	"
$\dot{m}_a = \dot{m}_{e_2}$	=	4	"
$\dot{m}_{e_1}$	=	4	"
$\dot{m}_R$	=	17	"

Think: All $\dot{m} \geq 0$ as expected

$\dot{m}_R > \dot{m}_i$ Typically, with regards, there is more recirculating within system than there is added to system

note $\frac{\dot{m}_R}{\dot{m}_i} = \frac{17 \text{ mg/day}}{8 \text{ mg/day}} \sim 2\times$

Parameter study – operating diagram

We may be short one or more pieces of info (DOF > 0) and/or may want to know how one or more unknowns change as a function of another

e.g. Suppose we don't know ε, the recycle efficiency. We could solve problem as a function of ε and see how other variables depend on ε ⇒ may be able to place bounds on the unknown ...

e.g. What fraction of iron intake will be eliminated by intestine ($\dot{m}_{e1}/\dot{m}_i$) as a function of ε?

intestine: $\dot{m}_i = \dot{m}_{e1} + \dot{m}_a$

$$\Rightarrow \frac{\dot{m}_{e1}}{\dot{m}_i} = 1 - \frac{\dot{m}_a}{\dot{m}_i}$$

recycle mix: $\dot{m}_a + \dot{m}_R = \dot{m}_{RBC} = \dot{m}_d$

$$\Rightarrow \frac{\dot{m}_a}{\dot{m}_d} + \frac{\dot{m}_R}{\dot{m}_d} = 1 \quad (\dot{m}_R \to \varepsilon)$$

$$\Rightarrow \dot{m}_a = \dot{m}_d (1 - \varepsilon)$$

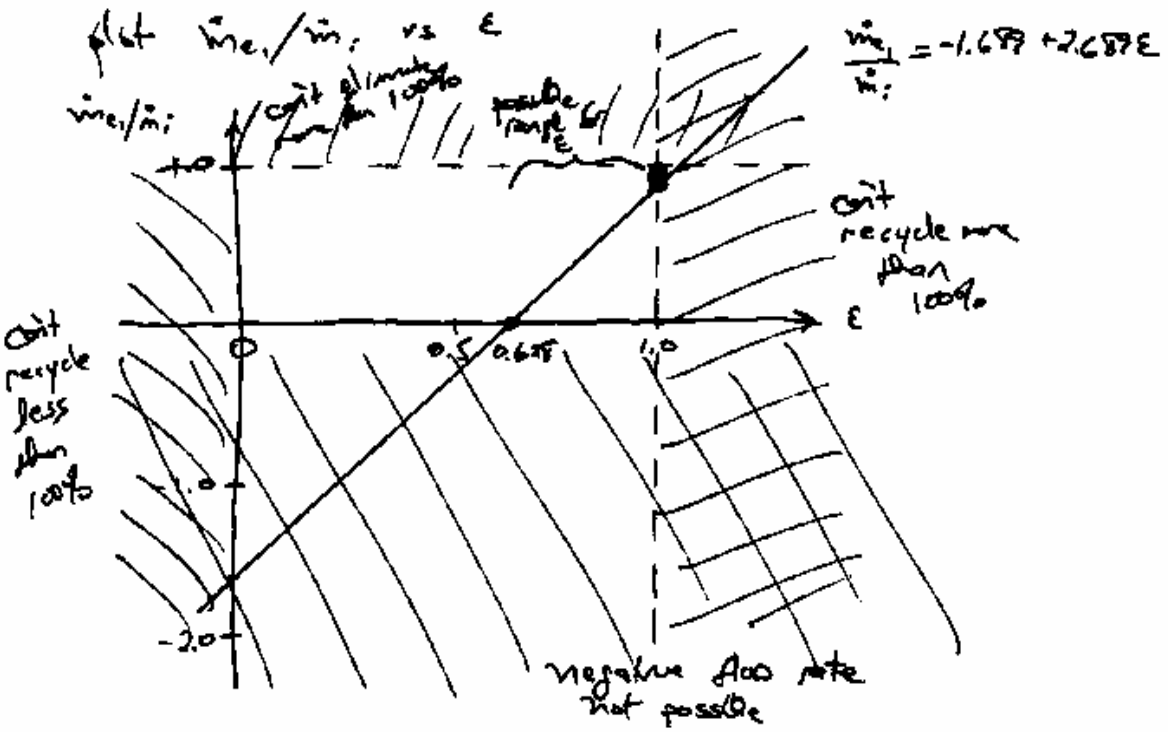
RBC turn over rate

$\dot{m}_d$ = 21.51 mg Fe/day

$$\therefore \frac{\dot{m}_{e1}}{\dot{m}_i} = 1 - \frac{\dot{m}_d (1-\varepsilon)}{\dot{m}_i}$$

$\dot{m}_i$ = 8 mg Fe/day ← minimum daily requirement

$$\frac{\dot{m}_{e1}}{\dot{m}_i} = 1 - 2.689(1-\varepsilon) = -1.689 + 2.689\varepsilon$$



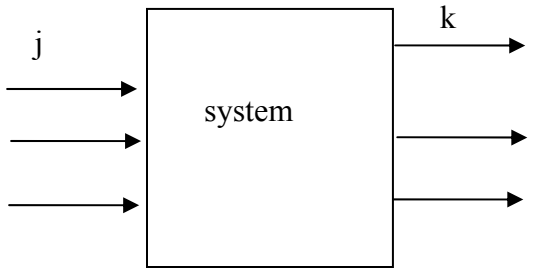
So, better have $\varepsilon \geq 62.8\%$, else will become iron deficient as even with $\dot{m}_{e,1} \to 0$, will not be able to take in enough Fe at minimum daily requirement to keep up with the RBC turnover

If recycle were perfect, $\varepsilon = 1.0$, all iron taken in would be excreted.

Unsteady Mass Balances

Recall the general mass balance analysis.

The general mass balance on a system is constructed as follows. Consider a system with multiple inlets j and outlets, k, and multiple components i that pass through the various inlets and outlets:



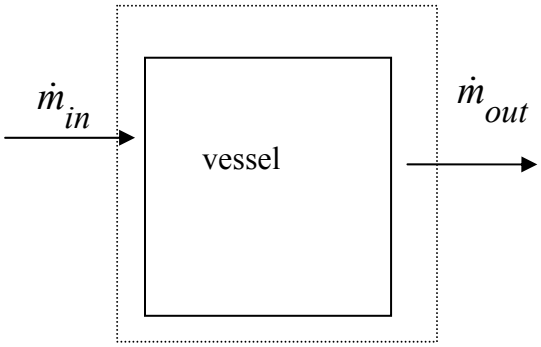
Let $\dot{m}_{j,i}$ represent the mass or molar flowrate of species i in input j, and $\dot{m}_{k,i}$ represent the mass or molar flowrate of species i in outlet k. Then, mathematically we write the mass balance on the total mass (or moles) of species i contained in the system as

$$\frac{dm_{sys,i}}{dt} = \sum_{j}^{all\ inlets} \dot{m}_{j,i} - \sum_{k}^{all\ outlets} \dot{m}_{k,i} + R_{sys,i}$$

where the term on the left is **derivative of the mass (or moles) of i with respect to time**. The last term, $R_{sys,i}$ is the rate at which species i is produced inside the system. (If species i is consumed inside the system, then $R_{sys,i}$ is a negative number.) This is the mathematical equivalent of

Amount in – Amount out + Amount Generated by Reaction = Amount of Accumulation

Consider a pumping liquid into a vessel while liquid drains out the other end.



If we consider m, the mass of water in the sink, as a function of time, we balance the inlet to the system and the outlet from the system and write:

$$\frac{dm}{dt} = \dot{m}_{in} - \dot{m}_{out} + R$$

Water is not generated in the sink, so R is zero. If the inlet and outlet flow rates are not equal, m changes with time. Thus if we specify constant values for $\dot{m}_{in}$ and $\dot{m}_{out}$, we find m as a function of time by integrating

$$dm = \left(\dot{m}_{in} - \dot{m}_{out}\right)dt$$

$$\int_0^{m(t)} dm = \int_0^t \left(\dot{m}_{in} - \dot{m}_{out}\right)dt$$

$$m(t) - 0 = \left(\dot{m}_{in} - \dot{m}_{out}\right)(t - 0)$$
$$m(t) = \left(\dot{m}_{in} - \dot{m}_{out}\right)t$$

This was a simple example where we had an unsteady mass balance without any generation term. Sometimes, unsteady mass balances will involve one or more generation terms (R).

When we have generation terms, we are dealing with **rate processes,** or the subject of **kinetics**.

Example

Consider cell growth in a batch fermentor. All nutrients are provided at the start of the process, but they are not replenished as the cells consume them.

If there are no inlets or outlets, then the general mass balance on any species i becomes

$$\frac{dm_{sys,i}}{dt} = R_{sys,i}$$

Suppose we have a batch fermentor that contains a large excess of nutrients (so we never have to worry about nutrients being depleted). How does the biomass (mass of cells) in the fermentor change with time?

Here we have a balance on one species, the cells. It is observed experimentally that the rate of cell population increase is directly proportional to the cell population. This is called Malthusian growth. So, if we define the mass of cells per unit volume in the fermentor as m, the rate of biomass increase can be written as

$R_{sys,i} = \mu m$ where μ is just a proportionality constant that can be measured experimentally.

Then, the mass balance on biomass becomes, for a constant volume system,

$$V\frac{dm}{dt} = V\mu m$$

$$\frac{dm}{m} = \mu dt$$

$$\int_{m(0)}^{m(t)} \frac{dm}{m} = \int_{0}^{t} \mu dt$$

The integral on the right hand side is the integral of a constant (k). The integral on the left gives the natural logarithm (ln) function:

$$\ln[m(t)] - \ln[m(0)] = k[t - 0]$$

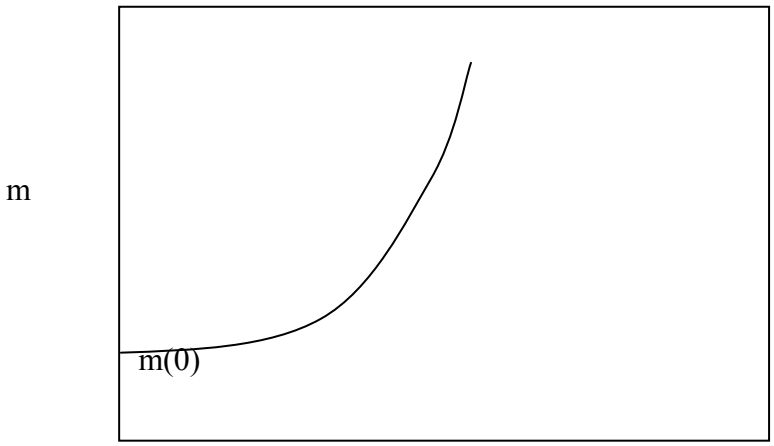
$$\ln \frac{m(t)}{m(0)} = \mu t$$

where m(0) is the mass of cells originally in the fermentor at time t = 0. We can express the biomass as a function of time by taking the exponential of both sides, since $e^{\ln x} = x$:

$$\frac{m(t)}{m(0)} = e^{\mu t}$$

$$m(t) = m(0)e^{\mu t}$$

This is an exponential function, which looks like this when plotted:

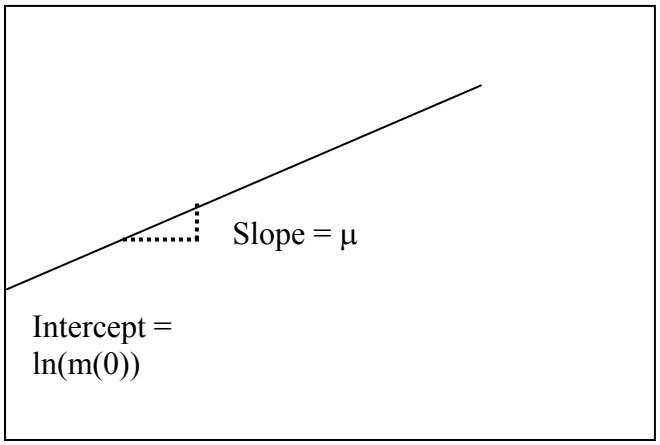


Now we can answer some questions about the population behavior over time. Often, it is important to know the population doubling time. How long will it take for the population to increase from m(0) to 2m(0)?

$$\ln \frac{2m(0)}{m(0)} = \mu t_{double}$$

$$\ln(2) = \mu t_{double}$$

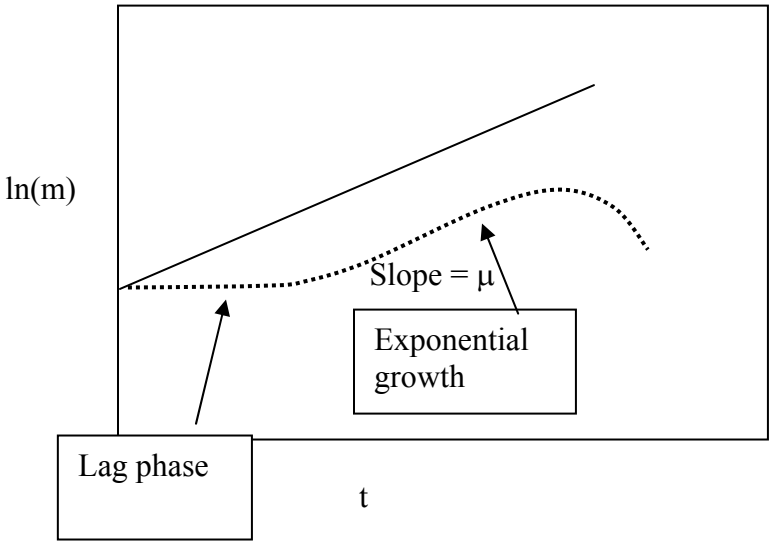
$$t_{double} = \frac{\ln(2)}{\mu}$$



What units must k have? (inverse time)

How do we experimentally determine k? Our analysis indicates that if we plot the ln(m) versus time, we should get a line with slope k and intercept ln(m(0)).

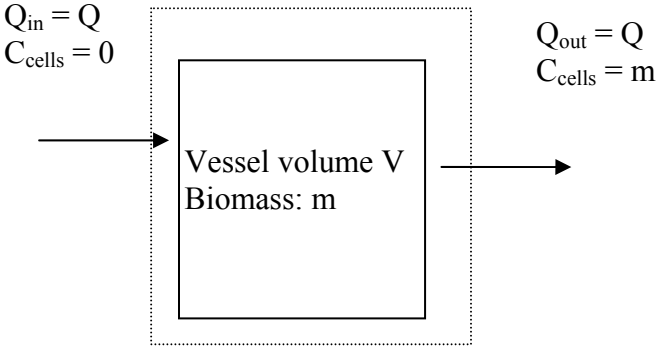
In actual practice, cell growth only follows Malthusian growth for part of the time. The complexity of cell process makes cell growth more complicated. Often one observes something more like the dashed curve in this plot.



During the lag phase, the cells adapt to their environment. Then, they grow at their fastest possible rate (exponential growth), until toxic metabolic byproducts build up and their nutrient supply starts to dwindle, at which point cells die faster than they multiply and the population begins to decrease.

It is possible to maintain a steady-state population in an open fermentor. Consider a tank containing a concentration of cells *m* that has a steady inlet flow of nutrients, and a steady outlet flow of the broth that contains cells. The volumetric flowrate in equals the volumetric flowrate out = Q. There are no cells in the inlet but the concentration of cells in the outlet is equal to the concentration inside the fermentor. We will assume that the nutrients are in excess and do not influence the growth rate.

Find the relationship between Q, m(t) and μ for the condition where the total volume in the fermentor is constant (steady-state volume). Note that the volume may be at steady-state, but the cell concentration does not necessarily have to be constant (m can be unsteady).



Balance on total fluid volume at steady-state, with no generation:

$$\frac{dV}{dt} = Q - Q = 0$$

Balance on cells:

$$\frac{Vdm}{dt} = -Qm + V\mu m$$

$$\frac{dm}{dt} = \frac{V\mu - Q}{V} m = \left[\mu - \frac{Q}{V}\right] m$$

$$\frac{dm}{m} = \left[\mu - \frac{Q}{V}\right] dt$$

$$\int_{m_o}^{m(t)} \frac{dm}{m} = \int_{o}^{t} \left[\mu - \frac{Q}{V}\right] dt$$

$$\ln \frac{m(t)}{m_o} = \left[\mu - \frac{Q}{V} \right] t$$

$$m(t) = m_o \exp\left[\left(\mu - \frac{Q}{V} \right) t \right]$$

Under what condition is the cell concentration at steady-state? When $\mu = QV$, we have $m(t) = m_o$ for all t.

If $Q/V > \mu$, then the cell concentration decreases with time – the cell growth cannot keep up with the flow through the fermentor – this is called "washout" in the language of fermentation. We literally lose our cells out the drain.

When nutrient - especially the limiting nutrient - runs low, growth rate is found to be proportional to the nutrient or substrate, S, concentration

$$\frac{R_x(t)}{V_{sys}} = k\,X^{1}(t)\,S^{1}(t)$$

1st order in X and S

k: proportionality constant

Recall case of plentiful nutrient

$$\frac{R_x(t)}{V_{sys}} = \mu_m X^{1}(t)$$

1st order in X, 0th order in S

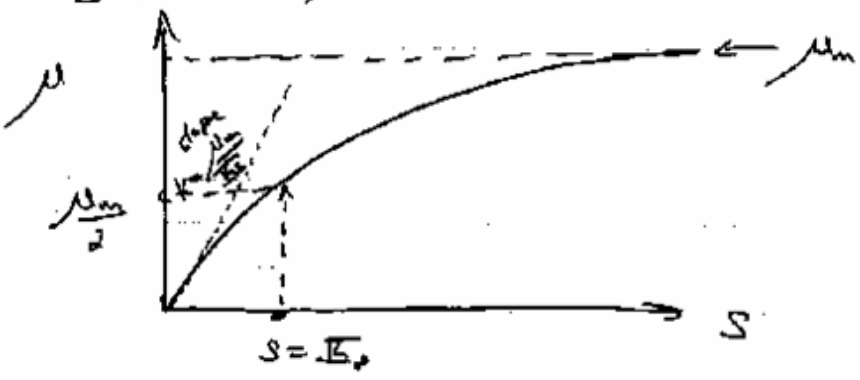
There is a model that captures both extremes and that fits empirical growth data well:

Monod model

$$\frac{R_x(t)}{V_{sys}} = \underbrace{\frac{\mu_m S(t)}{K_s + S(t)}}_{\mu} X(t)$$

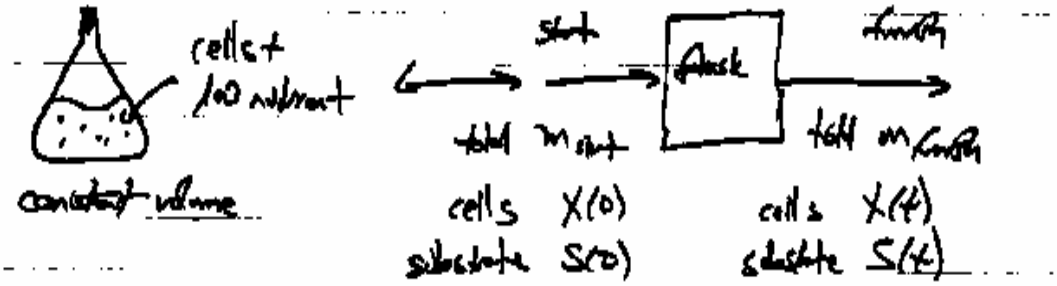
$$\lim_{S \to 0} \mu = \frac{\mu_m S(t)}{K_s} \quad (k \text{ from above})$$

$$\lim_{S \to \infty} \mu = \mu_m$$



Let's consider case where substrate conc in our closed system is low. What will cell conc do with time? Will now need to consider change of both $X(t)$ and $S(t)$ with time....
Coupled mass balances and kinetics.

So, suppose



general balance: $\frac{dm_{sys,i}}{dt} = R_i(t) \Rightarrow \frac{dC_{sys,i}}{dt} = \frac{R_i}{V_{sys}}(t)$ for constant system volume

cells: $\frac{dX}{dt} = \frac{R_x(t)}{V_{sys}} = kS(t)X(t)$

substrate: $\frac{dS}{dt} = \frac{R_s(t)}{V_{sys}} = \frac{-1}{Y_{x/s}}\frac{R_x(t)}{V_{sys}} = \frac{-1}{Y_{x/s}}kS(t)X(t)$

recall yield coefficient from stoichiometry

$Y_{x/s} \equiv \frac{\text{grams biomass produced}}{\text{grams substrate consumed}}$

relates rates of consumption and production

total: $\frac{dm_{sys}}{dt} = 0$.

Can ask questions like: "for a given amount of substrate, how much cells (biomass) can be produced?"

note: $-\frac{1}{Y_{X/S}}\frac{dX}{dt} = \frac{dS}{dt}$

finish ↑ start

$$-\frac{1}{Y_{X/S}}\int_{X(0)}^{X(t)} dX = \int_{S(0)}^{S(t)} dS$$

$$\Rightarrow \quad -\frac{1}{Y_{X/S}}\cdot\left(X(t)-X(0)\right) = S(t)-S(0)$$

$S(t) \to 0$ all consumed

$$\therefore \quad X(t) = Y_{X/S}\,S(0) + X(0)$$

If we want the details of how $X(t)$ and $S(t)$ change with time, must solve the coupled differential equations

In brief, 1. we know $S(t) = S(0) - \frac{1}{Y_{X/S}}(X(t)-X(0))$

2. can substitute in for $S(t)$ in X mass bal, solve differential equation for $X(t)$

3. plug $X(t)$ back into expression from (1) to find $S(t)$...

$$\Rightarrow \frac{S(t) + \frac{1}{Y_{X/S}}\left(X(0)-X(t)\right)}{X(t)} = \frac{S_0}{X_0}\exp\left\{-k\left(S(0)+\frac{X(0)}{Y_{X/S}}\right)t\right\}$$

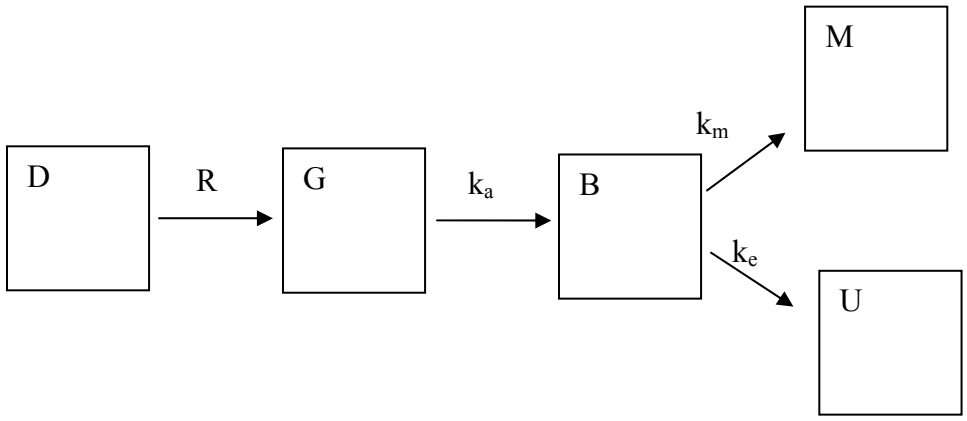
Application of Unsteady-State Material Balances: Pharmacokinetics

Pharmacokinetics concerns the rate at which drugs are absorbed by the body, distributed among the various organs and tissue types and ultimately metabolized and/or excreted from the body. The objective of pharmacokinetics is to design dosage regimens so the drug concentration in the body remains in the therapeutically active range for the longest time possible, without exceeding the toxicity threshold. The latter issue is critical – most drugs are very potent molecules, so whereas a low concentration may be beneficial, a high concentration can be lethal.

Many issues need to be taken into account in pharmacokinetic modeling. For example, different tissues can be quite different from other tissues in terms of their chemical characteristics. Likewise different drugs will differ in terms of their solubility characteristics. Many drugs are nonpolar. These will tend to have low solubility in the blood, but they will have high solubility in fatty tissues, which are much less polar than water. Such drugs tend to accumulate in the fatty tissues and be slowly released over time. (Some newer antibiotics exploit this phenomenon, so you only take the pills for a few days, but the antibiotic effect lasts for about 10 days.)

The most common approach to pharmacokinetic modeling is to treat the body as a set of compartments and keep track of the drug concentration as it passes from one compartment to another. This model requires rate information (hence the name pharmaco*kinetics*). to describe how fast drug gets from one compartment to another.

The simplest model is to treat the body as one compartment, but we can do better than that. In the *compartmental model* sketched below, the drug is taken as a solid pill (D) and enters the gastrointestinal tract (G), from which it passes to the rest of the body (B) and ultimately is converted to a metabolized form (M) or is excreted in the urine (U). The rate at which the drug gets from the source (pill) to the gastrointestinal tract is assumed to be a constant R, as long as the pill lasts ("zero order kinetics"). The rate at which the drug gets from one compartment to the next is assumed to be directly proportional to the concentration of the drug in the compartment that it is leaving (called first order kinetics). The proportionality constants are called rate constants.



We will use G, B, M, and U to represent the concentration of drug in the gastrointestinal tract, the rest of the body, converted to the metabolized form and excreted in the urine, respectively.

So, the rate at which drug enters the gastrointestinal tract is R. The rate at which drug is absorbed to enter the rest of the body is $k_a G$, and the rate at which the drug leaves the body to both the metabolized form and the urine is $k_m B + k_e B$. We assume that the passage of the drug from one compartment to another is irreversible. Once it leaves it does not come back around. (This assumption is often dropped for drugs that can recirculate in the body for long times, but we will keep this assumption here.)

This allows us to perform a material balance on each compartment. Initial conditions for each of these material balances are shown under each differential equation:

pill: $$\frac{dD}{dt} = -R \qquad [1]$$

at t = 0, D = D_o

gastrointestinal tract: $$\frac{dG}{dt} = R - k_a G \qquad [2]$$

at t = 0, G = 0

rest of body: $$\frac{dB}{dt} = k_a G - \left(k_m + k_e\right)B \qquad [3]$$

at t = 0, B = 0

metabolized form: $$\frac{dM}{dt} = k_m B \qquad [4]$$

at t = 0, M = 0

urine: $$\frac{dU}{dt} = k_e B \qquad [5]$$

at t = 0, U = 0

The zero concentration boundary conditions imply that there is no drug in the compartment at the start (there is nothing left over from a previously taken pill – how could this be changed if there were leftover drug in the system?)

Eqn. [1] is solved directly as

$$\int_{D_o}^{D} dD = -R\int_{0}^{t} dt$$

$$D = D_o - Rt$$

We solve eqn [2] for G(t) using the separation of variables method.

$$\frac{dG}{R - k_a G} = dt$$

$$\int_{0}^{G} \frac{dG}{R - k_a G} = \int_{0}^{t} dt$$

$$-\frac{1}{k_a}\ln\left(R - k_a G\right)\Big|_{0}^{G} = t$$

$$\ln\left(\frac{R - k_a G}{R}\right) = -k_a t$$

$$R - k_a G = Re^{-k_a t}$$

rearrange

$$G = \frac{R}{k_a}\left(1 - e^{-k_a t}\right)$$

Now to find B(t), we plug the result for G(t) into eqn [3]:

$$\frac{dB}{dt} = R\left(1 - e^{-k_a t}\right) - \left(k_m + k_e\right)B$$

This equation cannot be solved by the method of separation of variables, but it can be solved by the method of integrating factors (see p. 215 of the text for the general technique if you are interested). **Again, I emphasize that the method of solving this equation is not the point of this lecture. The point is to set up the balance equations and see how useful they are.**

The solution for B(t) is

$$B = \frac{R}{k_e + k_m}\left\{1 - e^{-\left(k_e + k_m\right)t}\right\} - \frac{R}{k_e + k_m - k_a}\left\{e^{-k_a t} - e^{-\left(k_e + k_m\right)t}\right\}$$

We could proceed to solve for the urine and metabolized form, but the drug concentration in the body is most useful for dosage regimen design. (Think of how it might be useful to solve for U(t) for drug testing purposes…)

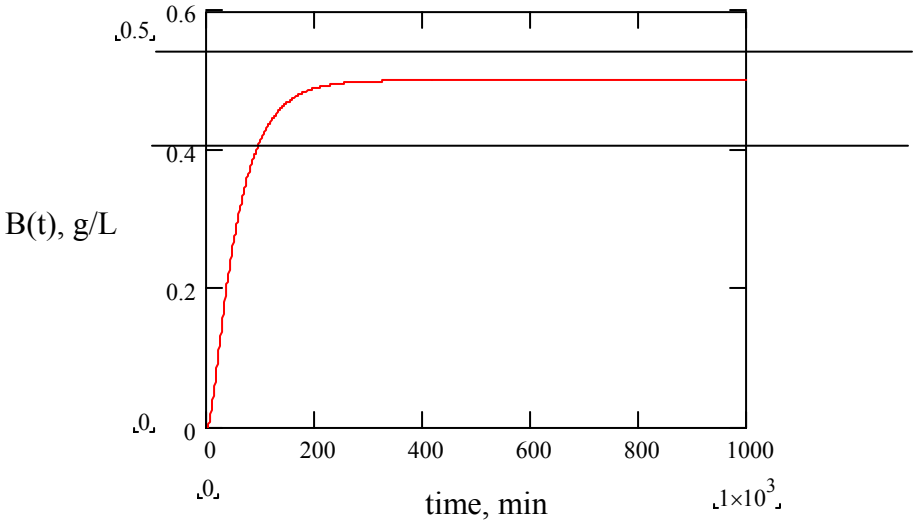
Let's plot how the drug concentration in the body (B) varies with time. For this calculation, t is in seconds, and I specified

$$R = 0.01\frac{g}{Lmin}$$

$$k_a = 0.1 min^{-1}$$

$$k_e = 0.01 min^{-1}$$

$$k_m = 0.01 min^{-1}$$



The *therapeutic window* is defined as the region below the toxicity threshold and above the minimum concentration needed for a therapeutic effect. If the therapeutic window were indicated by the lines on the graph, this would be a very successful dosage regimen. The drug concentration in the body rapidly rises to within the therapeutic window and stays there. This is not typical! What we have shown here is the ideal of *sustained release* – the case of zero order kinetics, or a constant rate of drug release R from the pill (D). This is a highly desirable condition, and companies have been formed around technologies that *come close* to zero order release. The more typical case is where the drug release kinetics are first order.

Then, eqn [1] changes to

$\frac{dD}{dt} = -k_r D$, which is solved by separation of variables for D = D_o at t = 0 as

$$D = D_o e^{-k_r t}$$

If we plug that into eqn [2] for the concentration in the gastrointestinal tract we get

$$\frac{dG}{dt} = k_r D - k_a G$$

$$\frac{dG}{dt} = k_r D_o e^{-k_r t} - k_a G$$

with G = 0 at t = 0, this is solved (by method of integrating factors again) as

$$G = \frac{k_r D_o}{k_a - k_r}\left\{ e^{-k_r t} - e^{-k_a t} \right\}$$

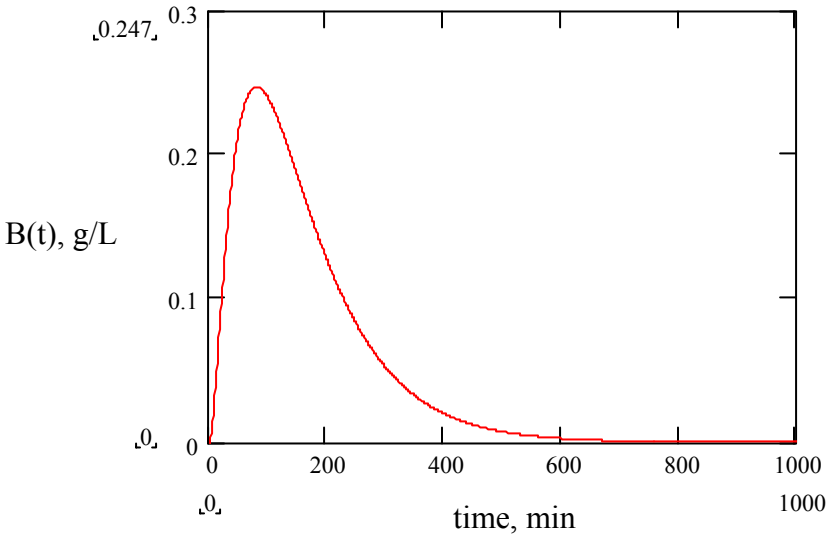
Proceeding as above, to find the concentration in the rest of the body B, we plug the result for G into eqn [3]

$$\frac{dB}{dt} = k_a \frac{k_r D_o}{k_a - k_r}\left\{ e^{-k_r t} - e^{-k_a t} \right\} - \left(k_m + k_e\right)B$$

with B = 0 at t = 0, the solution by the method of integrating factors is

$$B = \left(\frac{k_r D_o / \left(k_a - k_r\right)}{k_r - k_m - k_e} - \frac{k_r D_o / \left(k_a - k_r\right)}{k_a - k_m - k_e} \right) e^{-\left(k_m + k_e\right)t} - \frac{e^{-k_r t}}{k_r - k_m - k_e} + \frac{e^{-k_a t}}{k_a - k_m - k_e}$$

If we set $k_r = 0.01 \text{min}^{-1}$ and D_o = 1 g/L, then this is graphed as



Notice how the drug concentration in the body rises rapidly but also passes through a maximum value and drops off again.

What would happen if a second pill were taken after 200 minute? The concentration in the body would rapidly proceed even higher. This could potentially cause the concentration to exceed the toxicity threshold. To play it safe, maybe the next pill should be taken after 800 min – but then the patient would have gone about 200 minutes with virtually no drug in the body, so there is no therapy happening. This is the purpose of pharmacokinetic modeling.

To capture the effect of leftover drug from one dose to the next, we would need to solve the equations with the initial condition for each dosage set to the concentration leftover from the does before. In other words, if we take a second pill 200 min after the first pill when the concentration in the body is $B = B_{200}$, then we restart the clock and set $B = B_{200}$ at $t = 0$ and solve.

Many more complicated compartmental models are used in pharmaceutical practice than the two-compartment, irreversible model we used here.