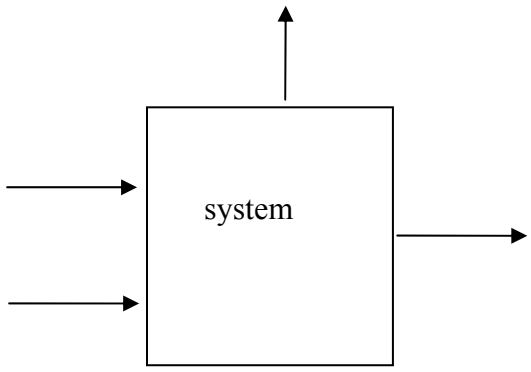
TOPICS
- general mass balance (conservation of mass) equation
- special cases of the general mass balance
- types of systems (batch=closed and continuous=open) and application of the general mass balance
- general method of solution of mass balance problems
- blood tracer example
- cellular stoichiometry example
- processes with recycle, bypass and purge
- human iron inventory example
- kinetics
- microbial growth

Systems Engineering in Biology

At a basic life level, life processes convert certain raw materials, such as glucose, into other materials, such as proteins or DNA. Processes that happen in one location, say inside one type of organelle, are linked to processes elsewhere, say other organelles in the same cell, other cells, or other organs. To understand how these processes are coordinated, it is necessary to keep track of all the material that comes and goes in a biological system. This leads to the concept of a **mass balance**.

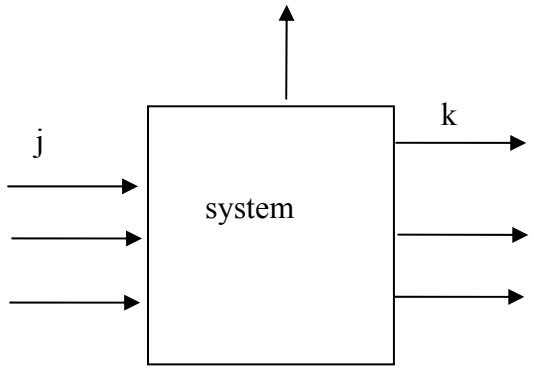
A mass balance is an accounting of the mass within a system that has one or more inlets or outlets. The mass within a system may change with time, in which case we perform an **unsteady-state** mass balance, or the mass within a system may be constant over time, in which case we perform a **steady-state** mass balance.



The concept of a mass balance is based on the simple statement that **mass is conserved.** Except for nuclear processes, mass is neither created nor destroyed. This is the **Law of Conservation of Mass**. The molecules that make up the mass may change if chemical reactions occur, but the total mass does not change. If one or more chemical reactions do occur in the system, stoichiometric relationships derived from balanced chemical reactions may be used to connect the consumption of one species with the production of another species.

General Mass Balance Equation

The general mass balance on a system is constructed as follows. Consider a system with multiple inlets, j = 1 … # inlets, and outlets, k = 1 … # outlets, and multiple components, i = 1 … # chemical species, that pass through the various inlets and outlets:



Let's consider how the mass (or moles) of the i^{th} species in the system can change with time:

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 of Accumulation of i^{th} species

= Total Amount of i in – Total Amount of i out + Amount i Generated by Reaction

Special Cases of the General Mass Balance

If we have the special case of steady-state operation, then the derivative with respect to time is zero, and we have

steady-state

$$0 = \sum_{j}^{all\ inlets} \dot{m}_{j,i} - \sum_{k}^{all\ outlets} \dot{m}_{k,i} + R_{sys,i}$$

If we have the special case of a non-reacting system, then $R_{sys,i} = 0$, and we have

non-reacting system

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

and a steady-state, non-reacting system follows

steady-state, non-reacting

$$0 = \sum_{j}^{all\ inlets} \dot{m}_{j,i} - \sum_{k}^{all\ outlets} \dot{m}_{k,i}$$

Types of Systems

Two important classifications of systems are **batch (closed)** and **continuous (open)**.

batch: everything is added to the system at some time t_o, a process takes place for some amount of time, and then the system is emptied (e.g., baking a cake in an oven)

continuous: material flows in and/or out of the system on a continuous basis (e.g., a running car engine)

Industrially, there are many examples of each. Many pharmaceutical manufacturing processes are batch. Many petrochemical production processes are continuous. Many physiological examples exist for each as well. Digestion is approximately a batch process. If you eat a big meal, some digestion has started before you finish eating. This is considered a "semi-batch" process. Batch processes are also key to the field of *pharmacokinetics*, the study of how drugs are distributed throughout the body over time – this is essential to defining dosage regimens.

Some examples of continuous processes in the body include kidney dialysis, and blood circulation.

NOTE, careful selection of the system is very important: performing mass balances for different (but related) systems will give you different types of insight to a problem. In some cases, careful selection of system boundaries may permit a previously un-solvable mass balance to become solvable.

Suppose we want to think about delivering a drug to the body by having a patient swallow a pill. The pill is digested completely after the input (ingestion) is done. This is a batch process if you consider that (the system) = (the stomach in between fill and empty cycles).

What if (the system) = (the pill)?

What different types of information could be obtained?

Application of the general mass balance equations to different types of process systems.

Batch

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

Between t_o and t_{final}, there are no inlet or outlet flows, the system just reacts.

Can a batch system be operated at steady-state?

$$0 = R_{sys,i}$$

This would just mean that nothing happens. For the cake-baking analogy, we'd add our flour, sugar, etc., but then we wouldn't turn the oven on.

How to solve the batch material balance equation? This is a differential equation that must be *integrated* by the separation of variables technique.

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

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

$$\int_{m_{sys,i}(t=t_o)}^{m_{sys,i}(t=t_{final})} dm_{sys,i} = \int_{t_o}^{t_{final}} R_{sys,i}dt$$

The left-hand side is readily integrated:

$$m_{sys,i}(t=t_{final}) - m_{sys,i}(t=t_o) = \int_{t_o}^{t_{final}} R_{sys,i}dt$$

If species i does not participate in the reaction, then $R_{sys,i} = 0$ for that species and its mass does not change. To solve such material balance problems, we need to have mathematical expressions for the reaction rate R. Specifying such relationships is called *kinetics*.

Continuous Systems

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

If we have the special case of steady-state operation, then the derivative with respect to time is zero, and we have

steady-state

$$0 = \sum_{j}^{all\ inlets} \dot{m}_{j,i} - \sum_{k}^{all\ outlets} \dot{m}_{k,i} + R_{sys,i}$$

If we have the special case of a non-reacting system, then $R_{sys,i} = 0$, and we have

non-reacting system

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

and a steady-state, non-reacting systems balance follows

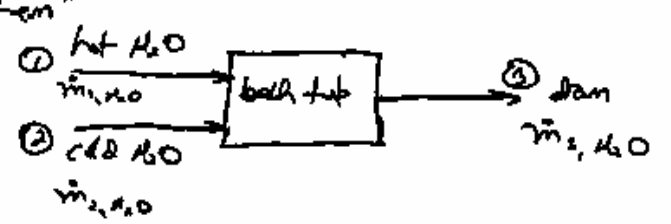
steady-state, non-reacting

$$0 = \sum_{j}^{all\ inlets} \dot{m}_{j,i} - \sum_{k}^{all\ outlets} \dot{m}_{k,i}$$

Terminology note: **steady-flow** operation means that all of the flow rates in the system are constant, i.e. the flow rates, $\dot{m}$, don't change over time. For the purposes of Intro to BME, we will typically assume that all of our problems involving continuous processes are operated under steady-flow conditions.

Solving Mass Balance Problems

1. draw and label input-output diagram that defines "system"



total ent (flow)
component ent (flow)
or
component conc.
define component variables

2. Select basis for problem – an amount or flow rate in system. Sometimes basis will be obvious, other times may need to assume a basis

3. write mass balances and special relations

note, if balancing molecules and if N different types of molecules present, can write

N molecule balances
1 total mass (mole) balance
N+1 equations

But: only N equations will be independent; pick the N easiest equations to use

if balancing atoms and if N different types of atoms present, can write

N atom balances
1 total atom balance
N+1 equations

But: only N equations will be independent; pick the N easiest equations to solve

Special relations: reaction stoichiometry, yields, RQ, proportions, all additional info.

4. assess DoF : can prblm be solved?

DoF = # unknowns − # eqs/cons

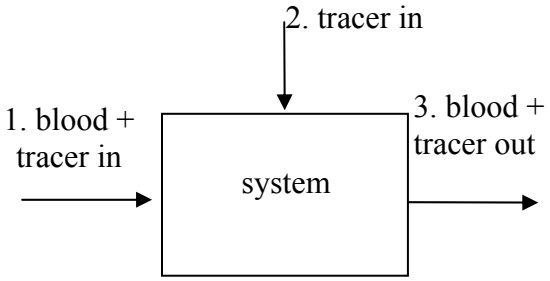
5. outline soln to problem

6. solve problem

7. think: does soln make sense?

Blood Tracer Experiment example (MMD example 2.4.4):

A tracer is used to determine a patient's blood flowrate. For safety purposes, this tracer could be a normally occurring metabolite. The normal concentration of this tracer in the blood is 100 parts per million, where 1 ppm = 1 mg/kg. Inject 1000 mg of tracer into the blood over a period of five minutes and measure the downstream concentration. We find the downstream concentration is 4000 ppm. Determine the mass flowrate of blood.

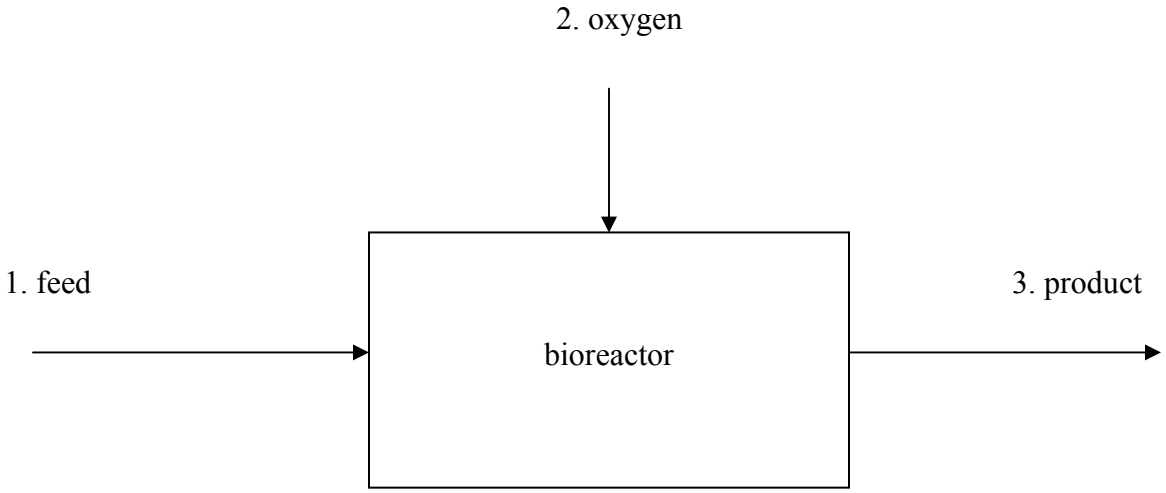


Cellular Stoichiometry example:

Consider the continuous aerobic growth of a bacterium on glucose and ammonia according to the stoichiometry:

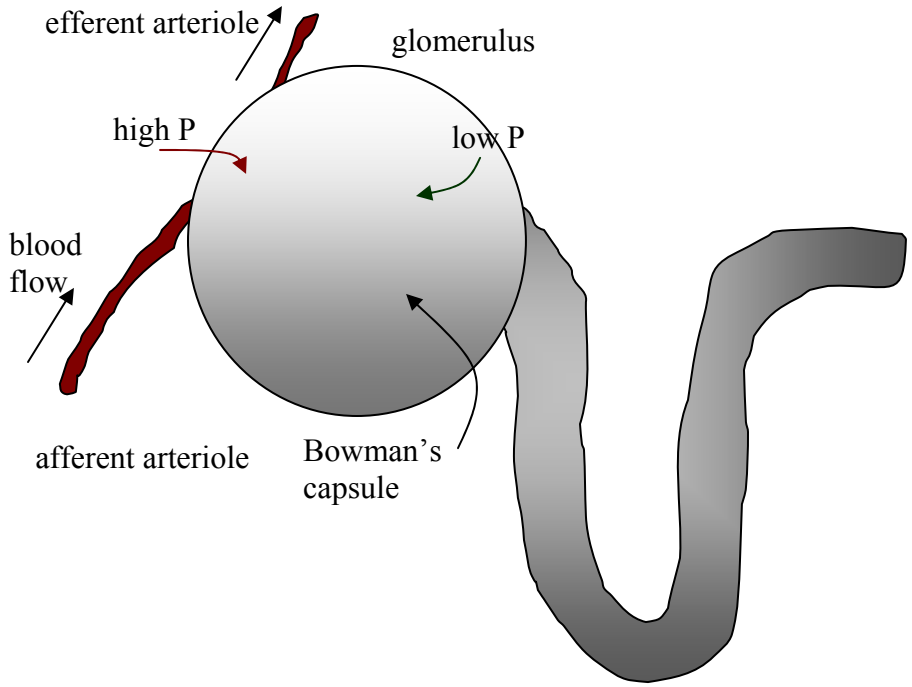
$$0.25\ C_6H_{12}O_6 + 0.20\ NH_3 + 0.37\ O_2 \rightarrow CH_{1.67}N_{0.20}O_{0.27} + 0.50\ CO_2 + 0.97\ H_2O$$

A biotech company is interested in producing 100 g/hr of bacteria (on a dry basis). A feed stream containing 0.27 g/L glucose and 0.019 g/L ammonia is available. What feed stream flow rate, in g/hr, and O_2 flow rate, in g/hr, will be required? Assume all liquid streams have a density similar to water and that all O_2 is consumed. What will the composition of the product stream be?



Kidney Function example.

The job of the kidney is to filter out toxic metabolic products such as urea from the blood. This happens in tiny structures called *nephrons*. The first part of the nephron is the *glomerulus*, where a tufted network of capillaries is surrounded by a capsule called the *Bowman's capsule*. Blood flowing into the tuft of capillaries, is laden with byproducts that are to be filtered. Blood flowing out of the capillaries is free of byproducts. The filtration is accomplished by the glomerular wall that serves as a semi-permeable membrane – it has fine pores that do not allow cells or proteins to pass out of the blood, but small molecules (such as water and urea) do pass. The liquid that passes through the glomerular wall is called the *glomerular ultrafiltrate*, that is destined to become urine. The rest of the nephron regulates the composition of the urine to maintain the body's water and salt balance. In the Bowman's capsule, the composition of the glomerular ultrafiltrate is identical to that of blood, minus the cells and proteins.



The blood flowing in the capillaries is pressurized by the heart so that it has a higher pressure than the glomerular ultrafiltrate. This *hydrostatic pressure* difference ΔP between the capillaries and the glomerular ultrafiltrate is what drives fluids across the glomerular wall for filtration.

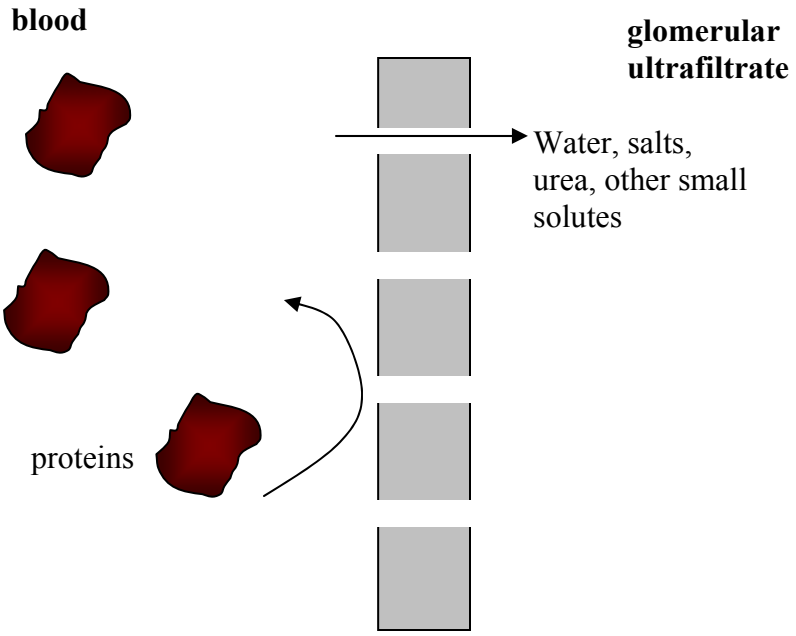
Fluid flows from regions of high hydrostatic pressure to regions of low hydrostatic pressure.

If the hydrostatic pressure difference were too large, it could be possible for too much fluid to leak out of the capillaries. The fluid flow driven by the hydrostatic pressure difference is counteracted by an *osmotic pressure* difference $\Delta\Pi$ that favors flow in the other direction (from the glomerular ultrafiltrate into the capillaries).

Fluid tends to flow from regions of low osmotic pressure to regions of high osmotic pressure.

The net flow across the glomerular wall is determined by the competition between these two opposing pressure differences.

The glomerular wall as a size-selective, semi-permeable membrane.

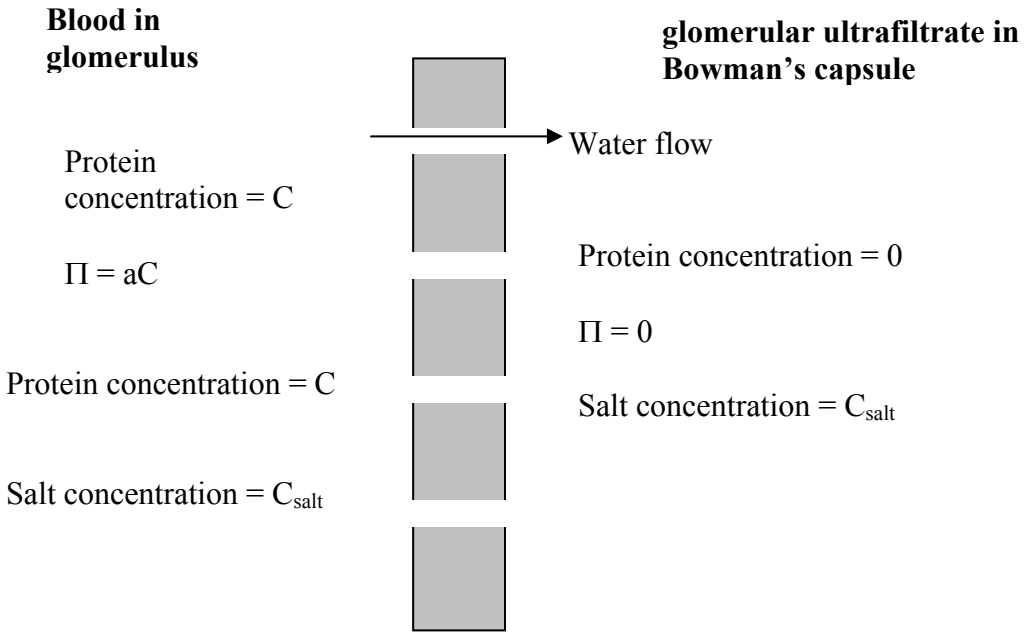


Osmotic pressure depends on the concentration of solutes in the fluid. A high solute concentration corresponds to a high osmotic pressure. Since the glomerular wall passes water and all small solutes, but blocks all proteins, the glomerular ultrafiltrate has a low protein concentration (low osmotic pressure), while the blood in the capillaries has a high protein concentration (high osmotic pressure).

Why does fluid flow from low to high osmotic pressure? The reason lies in thermodynamics, but in essence, there is a driving force for the solvent (water) to dilute the fluid with a high solute concentration. The solvent flows from the low concentration fluid to the high concentration fluid in order to equalize the solute concentrations. The interesting issue is that the solutions will never have equal concentration, since the proteins can never pass through the membrane. To first order, we can approximate the osmotic pressure by

$\Pi = a_1 C + a_2 C^2$ where the *a* constants are called virial coefficients, and C is the concentration of solute. Do not confuse the capital Greek letter Π used for osmotic pressure with the lower case Greek letter $\pi = 3.14\ldots$

The concentration of salt in the blood in the glomerulus capillaries C_{salt}^{glom} is equal to the salt concentration in the glomerular ultrafiltrate in the Bowman's capsule, C_{salt}^{bc}.
$C_{salt}^{glom} = C_{salt}^{bc} = C_{salt}$



so the salts do not contribute to the osmotic pressure difference.

As blood flows further and further through the capillaries in the glomerulus, it loses more and more water. This has the effect of making the protein concentration in the blood higher and higher. So, the osmotic pressure difference becomes higher and higher. Eventually, the osmotic pressure difference exactly equals the hydrostatic pressure difference, and no more fluid passes out of the blood.

Quantitative Model for Glomerular Ultrafiltration

Our goal is to predict how the protein concentration changes in the blood between the inlet and the outlet of the glomerulus. A byproduct of this analysis will be a method to measure how leaky the glomerular wall is.

We start by defining a volumetric flux of fluid across the glomerular wall J_v. This is the volume of fluid that crosses the wall per unit area per unit time:

$$J_v = k(\Delta P - \Delta\Pi) \quad [=] \quad \frac{volume}{area \cdot time}$$

The proportionality constant *k* is the *hydraulic permeability* of the glomerular wall. It depends on the structure and health of the nephron tissue.

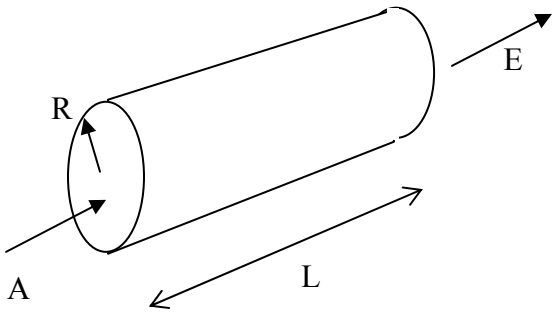
We will define the hydrostatic pressure of the blood inside the capillaries of the glomerulus as P_g and the hydrostatic pressure of the ultrafiltrate inside the Bowman's capsule as P_{bc}, and

$$\Delta P = P_g - P_{bc}$$

Likewise, we define osmotic pressures similarly, and

$$\Delta\Pi = \Pi_g - \cancel{\Pi_{bc}}^{0} = \Pi_g$$

In order to model the flux across the glomerular wall, we will need to keep track of the hydrostatic pressure gradient and the osmotic pressure gradient at all positions along the glomerulus. Since the glomerulus is a complex, convoluted tuft of capillaries, we will approximate it with a much simpler geometry, a uniform tube of length L and radius R. This tube is bathed by the fluid in the Bowman's capsule. Fluid enters the tube at the afferent (A) end and leaves at the efferent (E) end. This simplifying approximation makes the problem tractable.



Before beginning our analysis, let's consider what information is available. Micropuncture techniques make it possible to sample fluid from the afferent and efferent arterioles, but it is not possible to sample fluid from the points in between. Thus, we know typical values of the protein concentrations C_A and C_E at the afferent and efferent ends.

$C_A \sim 90$ mg/mL $\quad$ $C_E \sim 57$ mg/mL

We also know the values of the virial coefficients a_1 and a_2 for typical blood proteins,

$$a_1 = 0.16\frac{mmHg}{mg/mL} \qquad a_2 = 0.0029\frac{mmHg}{(mg/mL)^2}$$

From these we can estimate

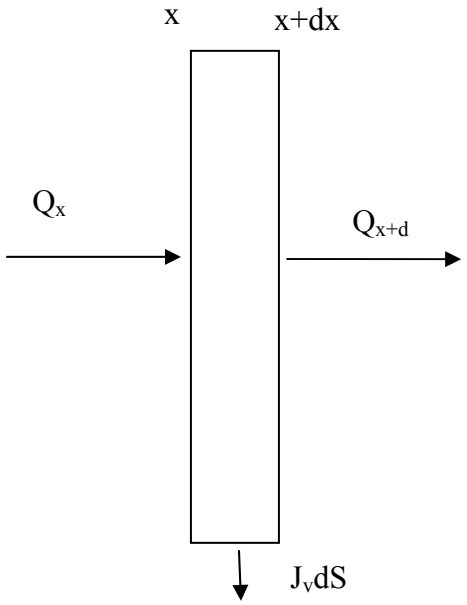
$\Pi_A \sim 35$ mmHg $\quad$ $\Pi_E \sim 19$ mmHg

Also using micropuncture, we can measure the hydrostatic pressure in the afferent and efferent arterioles. There is only a slight pressure drop between the afferent and efferent ends, so we can approximate these pressures as being equal:

$P_A \sim P_E \sim 45$ mmHg
The pressure inside the Bowman's capsule is $P_E \sim 10$ mmHg, so there is a hydrostatic pressure difference ΔP = (45 mmHg-10 mmHg) = 35 mmHg that drives ultrafiltration. This is roughly constant along the entire length of the glomerulus, but the flux does decrease further down the glomerulus due to the increasing osmotic pressure difference.

The other quantities we can measure by micropuncture are the afferent and efferent plasma flowrates Q_A and Q_E.

Conservation of Blood Plasma Mass
Our mathematical analysis begins with a material balance on the blood plasma in the capillaries. (Plasma is the name for the fluid portion of the blood minus cells and minus proteins.) The density of the blood ρ does not change as it flows through the capillaries, so it will be acceptable to perform a balance on the blood volumetric flow rather than formally considering the plasma mass flow since $Q = \dot{m}\rho$. Consider an infinitesimally small cross-sectional slice of the capillary from x to x+dx. The tube surface area corresponding to this small slice is dS. The flowrate entering is Q_x and the flowrate leaving is Q_{x+dx}. Q_{x+dx} is slightly smaller than Q_x due to the flux across the glomerular wall. The outward flow across the wall is $J_v dS$.



Starting from the general material balance equation for the volume V (equivalent to mass) of fluid in our small cross-section , we will cut out un-needed terms.

$$\frac{dV}{dt} = Q_x - Q_{x+dx} - J_v dS + R_{gen}$$

The kidney can be considered to operate at steady-state, so the time derivative on the left-hand side is zero, and there is no generation of blood in the capillary, so $\underline{R_{gen}} = 0$. So, the plasma material balance becomes

$$Q_{x+dx} - Q_x = -J_v dS$$

Let's divide both sides of the equation by dx

$$\frac{Q_{x+dx} - Q_x}{dx} = -J_v \frac{dS}{dx}.$$

Since the surface area S of a tube of length x is $S = 2\pi Rx$, the derivative

$$\frac{dS}{dx} = 2\pi R$$

For a tube whose total length is L, then we see that this derivative is simply equal to S/L. Our equation simplifies to

$$\frac{Q_{x+dx} - Q_x}{dx} = -J_v \frac{S}{L}$$

Take the limit as dx → 0, and the term on the right is seen to be the definition of the derivative of Q with respect to x:

$$\frac{dQ}{dx} = -J_v \frac{S}{L} = -\frac{kS}{L}(\Delta P - \Delta\Pi) = -\frac{K_f}{L}(\Delta P - \Delta\Pi)$$

$$\frac{dQ}{dx} = -\frac{K_f}{L}(\Delta P - \Delta\Pi) \quad [1]$$

where $K_f = kS$ is called the ultrafiltration coefficient. Eqn. [1] describes the conservation of blood plasma.

Conservation of Protein Mass

Next we perform a material balance on the protein in the blood plasma in the capillaries. Remember that protein does not pass out of the glomerular wall – the blood does not lose any protein. The total amount of protein flowing in the blood is equal to QC. Since the total amount of protein does not change in the blood, the mass balance equation can be reduced to

$$\frac{d(QC)}{dx} = 0 \qquad [2]$$

Equations [1] and [2] are the material balance equations.

The derivative in equation [2] can be written via the *chain rule*of calculus as

$$\frac{d(QC)}{dx} = Q\frac{dC}{dx} + C\frac{dQ}{dx}$$

Substituting from eqn [2], we can then write

$$Q\frac{dC}{dx} + C\frac{dQ}{dx} = 0$$

or

$$\frac{dQ}{dx} = -\frac{Q}{C}\frac{dC}{dx} \qquad [3]$$

Substituting eqn [1] into eqn [3], we get

$$\frac{Q}{C}\frac{dC}{dx} = \frac{K_f}{L}(\Delta P - \Delta\Pi) \quad [4]$$

Here we use our constitutive equation for osmotic pressure $\Delta\Pi = a_1C+a_2C^2$ (remember that the osmotic pressure in Bowman's capsule is zero, so $\Delta\Pi = \Pi_g$)

$$\frac{Q}{C}\frac{dC}{dx} = \frac{K_f}{L}\left(\Delta P - a_1C - a_2C^2\right) \qquad [5]$$

By solving this differential equation, we will be able to show how the protein concentration C varies along the length of the glomerulus. But – we need to do a little more work. Q varies with position due to the loss of plasma by ultrafiltration, and we know that the rate at which it is lost depends on C because of the changing osmotic pressure resistance to ultrafiltration.

We do know (eqn. [2]) that the total amount of protein is a constant, or CQ = constant. We know Q_A and C_A are available from micropuncture, so we know our constant is $CQ = C_AQ_A$.

Thus we write

$$Q = Q_A\frac{C_A}{C} \qquad [6]$$

For convenience, define a *dimensionless concentration* $C^* = C/C_A$. Thus, eqn [6] is written as

$$Q = \frac{Q_A}{C^*} \qquad [7]$$

We also define a dimensionless length x* = x/L. Substituting eqn [7] for Q, x = Lx* and C = C_AC* into eqn [5] we get

mg/mL
$$\frac{dC^*}{dx^*} = \frac{K_f C^{*2}}{Q_A}\left(\Delta P - a_1 C_A C^* - a_2 C_A^2 C^{*2}\right)$$

or

$$\frac{dC^*}{dx^*} = \frac{K_f C^{*2}\,\Delta P}{Q_A}\left(1 - \frac{a_1 C_A}{\Delta P} C^* - \frac{a_2 C_A^2}{\Delta P} C^{*2}\right) \qquad [8]$$

For the sake of clarity, let's condense some of these collections of constants as

$$F = \frac{K_f \Delta P}{Q_A} \qquad A_1 = \frac{a_1 C_A}{\Delta P} \qquad A_2 = \frac{a_2 C_A^2}{\Delta P}$$

so eqn [8] can be written more concisely as

$$\frac{dC^*}{dx^*} = FC^{*2}\left(1 - A_1 C^* - A_2 C^{*2}\right) \qquad [9]$$

You will learn this later, but to solve a differential equation, you need to specify a boundary condition. Here we define an *initial condition* at x* = 0 (the afferent arteriole inlet to the glomerulus):

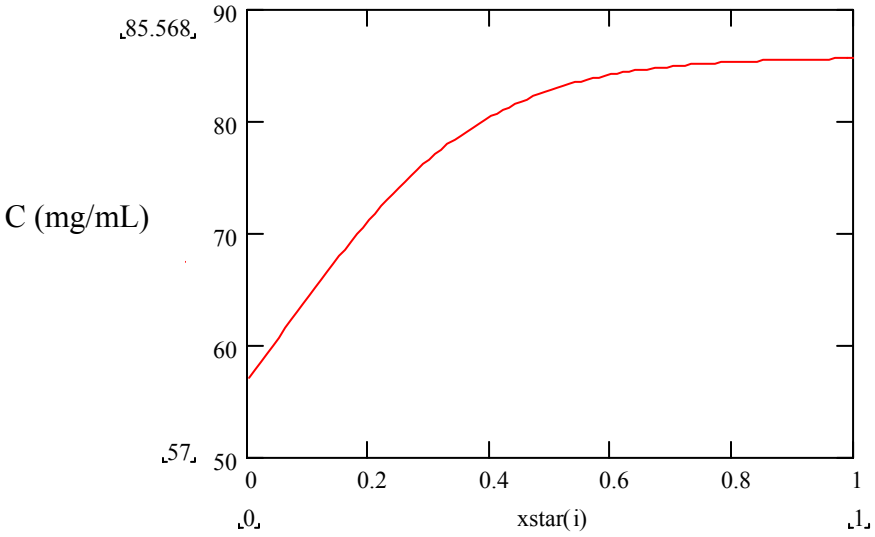
at x* = 0 C* = 1 (because C = C_A at the inlet)

We can integrate [9] by separation of variables

$$\frac{dC^*}{C^{*2}\left(1 - A_1 C^* - A_2 C^{*2}\right)} = F dx^* \qquad [10]$$

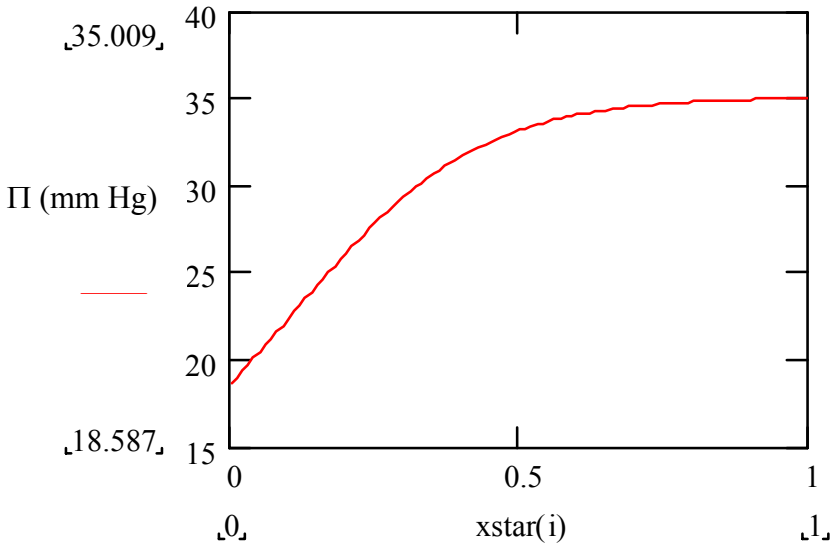
but the integral is actually quite large and cumbersome to write out. Since we are not trying to emphasize the mathematical technique but instead want to emphasize the modeling method and the predicted behavior, I have instead solved eqn [9] numerically, using the computation software package Mathcad.

The predicted behavior is shown here for Q_A = 1 nL/sec, C_A = 57 g/L, and ΔP = 35 mm Hg, with K_f specified to be 0.0784×10^{-9} , with concentration in mg/mL plotted versus dimensionless distance x* = x/L:



Notice that the protein concentration is ~ 85 mg/mL by the end of the glomerulus (x*=1), close to the typically measured value.

The osmotic pressure varies along the length of the glomerular capillaries as



Notice that by the end of the glomerulus (x* = 1), the osmotic pressure difference is 35 mmHg, matching the hydrostatic pressure difference between the glomerulus and Bowman's capsule. Once these two pressures equalize, there is no more flux of fluid across the glomerular wall, so the protein concentration ceases to increase at the same position where the osmotic pressure reaches 35 mmHg.