Lectures in Physiology

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Contents

1 Introductory Lectures and some Biophysics

Lecture 1
Introduction to the course

Introduction to the course

This is :

1. Zoology 355, Principles of Physiology

Instructor:

1. Ralph A. Ackerman

   The laboratory is run by David Vleck, who knows as much physiology as me or perhaps more!

2. Office Rm 601, Sci II

3. email racker@iastate.edu

4. Office Hours: By arrangement, right after your lab is good but contact me by email first and we will set the time. You can also try walking in but I am in and out.

Lecture Times

1. 1100 hrs Monday, Wednesday and Friday

Laboratory

1. Various times in rm 626, Science II—check your schedule

Textbook

1. Berne, R.M., M.N. Levy, B.M. Koeppen and B.A. Stanton 1998 (4rd Edition). Physiology. Mosby Year Book. 1131pps.

   This is a good but quite demanding textbook. It is typically used in a medical school setting and those of you whom go on to med school or one of the health related professions, may well see it again or a book like it. Is it too "tough" for undergraduates, such as you? No, I don't think so but you are free to disagree. You are going to have to work at the text; i.e. read the thing and correlate what I say in class with what is written in the text.

Lecture Handout

I use a lot of graphical and cartoon materials during the lecture, rather than have you distracted trying to copy these, I make copies and compile them into handout that I will give out prior to the lecture. They are yours and you can take notes on the them (and probably ought to).

Examinations

Really Important Stuff

1. Motivational Philosophy (for lack of a better expression)

   This course is not intended as a "flunk out" course. A "C" in this course is an average grade and is intended as such. The course is aimed at the top half of the class and perhaps a bit higher. My intention is to push you just a bit. My expectation is that everybody who enrolls in this course can pass the course, if they are willing to do the work. Moreover, I am very willing and interested in working with any student who wants to learn physiology, whether they are "A" students or "D" students. Those of you who stay the course and pass are going to learn a lot of physiology.

2. Lecture Style

   - Quantitative and graphical models
   - More interest in the forest than the trees. But you really need to know the trees (i.e. details) too. There is a lot of new language which you will have to pick up—mostly on your own.
   - Sheer memorization will take you only so far in this course. You have to learn how the systems that we study operate.

3. Course Coverage—What is this course about

   - Mammalian Physiology But only from a few mammals (the medically relevent mammals, which are taken to be human models—mice, rats, cats, dogs, pigs etc.)
   - Models, conceptual and quantitative. Which describe how animals work!!

How should you learn the material

- Take good lecture notes
- Read the text carefully
- Correlate the text with the lecture notes
- Review the material shortly after the lecture. Study in groups can be very useful

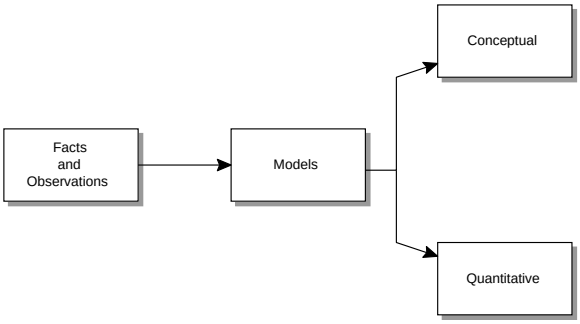


Figure 1: n1l1.eps

- Construct concepts maps of the material to pick out the important elements
- Understand qualitatively how models work
- Learn sufficient detail to understand and explain the models
- Explain the model to others—group work again

What do I want you to learn

1. How do Animals Work

   This is what physiology is all about. The emphasis is on animal as an intact organism; that is, the "whole" animal.

   There are many levels of organization (here is a concept map):

   What we are interested in is **Integrative Physiology (Biology)**

Models and Modelling

I have actually give you some models already!

1. Models in Physiology

   - What is a model
   - Models are never, never perfect.
   - Models can't be proven but they can be tested. Or rather predictions made by models can be tested
   - What kinds of models are there?.
   - Verbal.
   - Quantitative.
   - Physical.

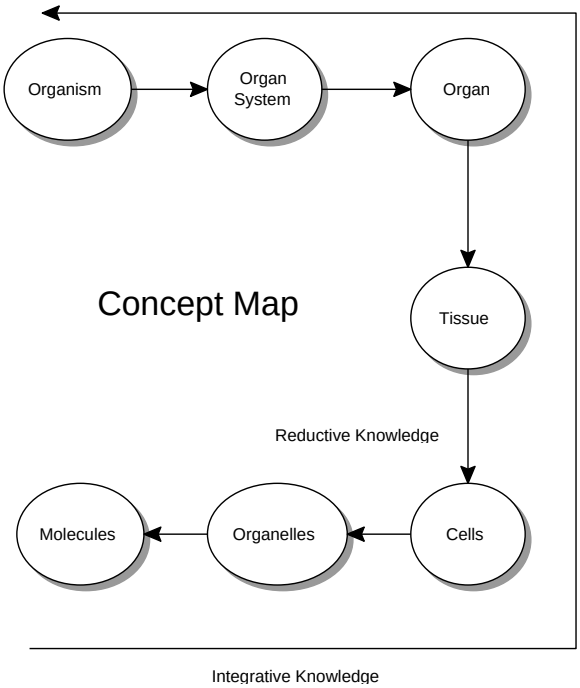


Figure 2: n2l1.eps

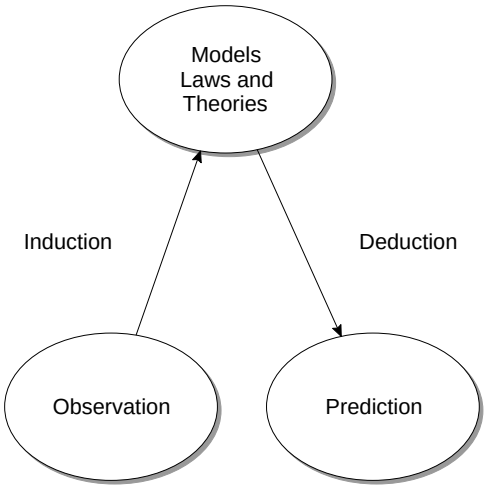


Figure 3: n3l1.eps

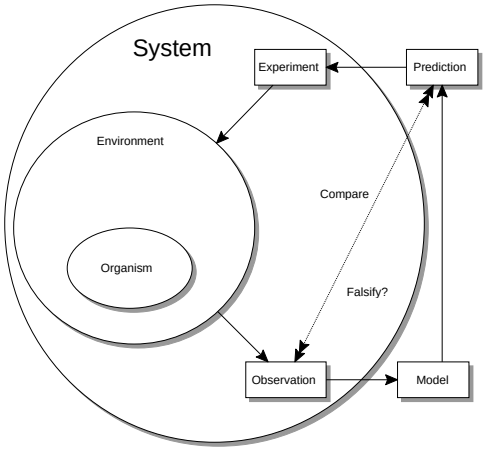


Figure 4: n4l1.eps

- Abstract.

  Remember that a picture is worth a 1000 words (to use an old saw), well it is true. This is why we are going to do a lot of graphical work. Good graphs summarize succinctly, an enormous quantity of verbal description. I tend to think in graphs rather than equations (contrary to what some of you may think), so visual representation of models is important to me, personally, and to you, because it is how I teach! Pay a lot of attention to the graphs and figures that I use!!!

Some Important Processes

1. Transport –Moving materials and energy around
2. Regulation –Control of important variables and process, control systems
3. Integration –Homeostasis, something like keeping the system in a normal state using transport and regulation.

Some Important Concepts: the Physiologist's Toolbox

1. Equilibrium
2. Steady-state
3. Unsteady-state

A simple model: the balance

1. A mass balance
2. Transport Models

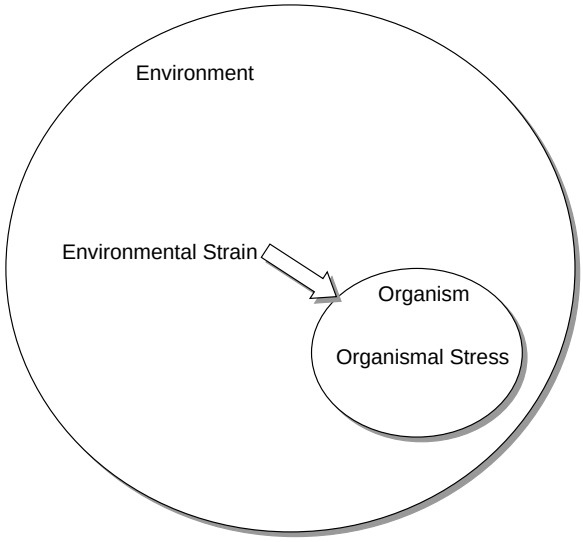


Figure 5: n5l1.eps

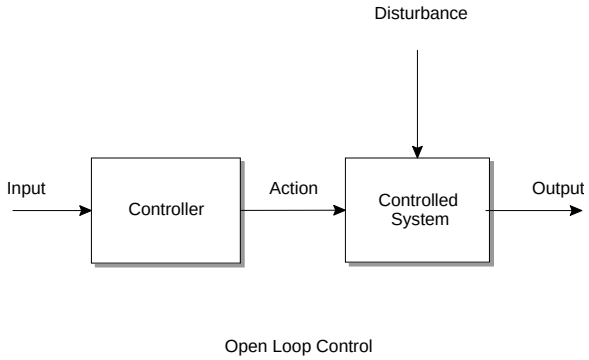


Figure 6: n6l1.eps

Other kinds of models

1. Stress-Strain

The Balance Model

$$\text{Change of Material or energy in system} = \text{Quantity In} - \text{Quantity Out} + \text{Production} - \text{Consumption} \quad (1)$$

$$\Delta\text{Mass} = +\Sigma\text{inputs} - \Sigma\text{outputs} \pm \Sigma\text{generation} \quad (2)$$

Figure 7: n6l1b.eps

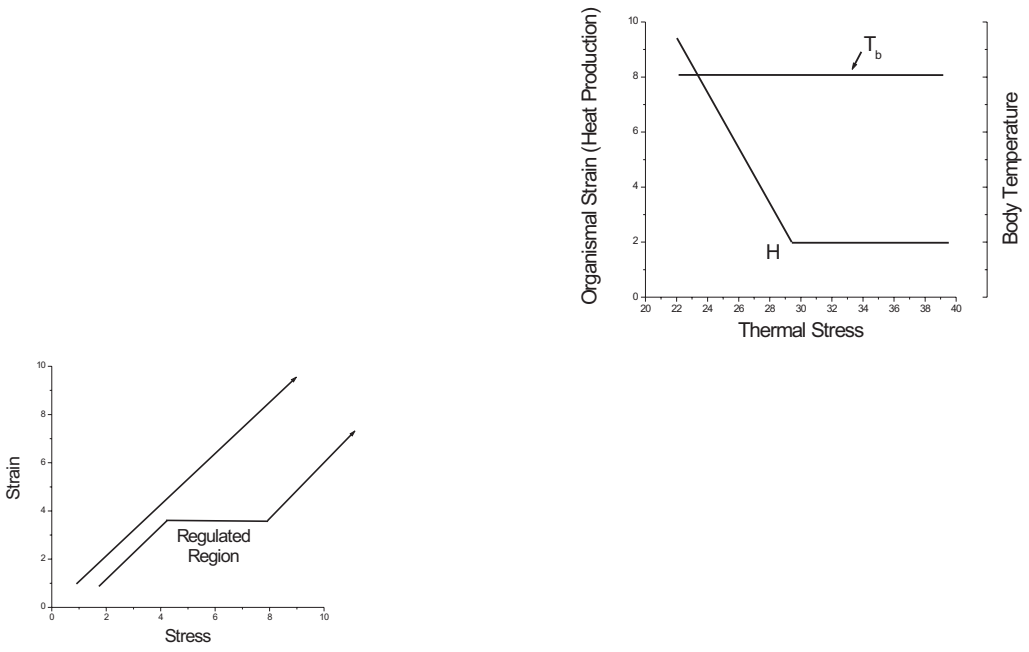


Figure 8: n7l1.eps, n8l1.eps

Figure 9: A concept map for Thermoregulation.

$$\text{Quantity Produced} = \text{Quantity Out} - \text{Quantity In} \tag{3}$$

and for materials which are consumed:

$$\text{Quantity Consumed} = \text{Quantity In} - \text{Quantity Out} \tag{4}$$

Lecture 2
Transport:Balance Models

Balance Models of Equations

$$\text{Change of Material or energy in system} = \text{Quantity In} - \text{Quantity Out} + \text{Production} - \text{Consumption} \quad (5)$$

$$\Delta\text{Mass} = +\Sigma\text{inputs} - \Sigma\text{outputs} + \Sigma\text{generation or consumption} \quad (6)$$

Direction Protocols

1. input and production are positive, +
2. output and consumption are negative, -

   Equation must be dimensionally homogeneous (or it is not an equation)

More Formally

$$\frac{dM}{dt} = \frac{I_i}{dt} - \frac{O_i}{dt} + \frac{M_i}{dt}$$

1. Now to makes things easier lets set up our system so that it is in steady-state:

   $$\frac{dM}{dt} = 0$$

   that is:

   $$0 = \frac{I_i}{dt} - \frac{O_i}{dt} + \frac{M_i}{dt}$$

   $$0 = \text{Quantity In} - \text{Quantity Out} + \text{Net Production} \quad (7)$$

2. Now we can rearrange this is a variety of ways as desired to be most useful but remembering that we have made the **steady-state** assumption.

   $$\text{Quantity Produced} = \text{Quantity Out} - \text{Quantity In} \quad (8)$$

   and for materials which are consumed:

   $$\text{Quantity Consumed} = \text{Quantity In} - \text{Quantity Out} \quad (9)$$

So lets do this on a real system that a physiologist might use–indeed David Vleck and I have both used this system.

$$O_2^{\text{Consumed}} = O_2^{In} - O_2^{Out}$$

Steady-state assumption

$$\dot{V}_{O_2} = F_{I_{O2}} \cdot \dot{V} - F_{O_{O2}} \cdot \dot{V}$$

and

$$\dot{V}_{O_2} = \dot{V} \cdot (F_{I_{O2}} - F_{O_{O2}})$$

remember that

$$C = \frac{n}{V} = \frac{P}{RT}$$

and the model becomes:

$$\dot{V}_{O_2} = \frac{1}{RT} \cdot \dot{V} \cdot (P_{I_{O2}} - P_{O_{O2}})$$

and you will see this again, in lecture and in lab!!!!

Biological Membranes

Transport across membranes

1. Fluid Mosaic Model
    - peripheral proteins
    - integral proteins.
2. Membranes are semi-permeable
    - Water soluble molecules do not go across very well do to the non-polar nature of the membrane but water does.
    - small molecules go across much more easily than do large molecules. Many large molecules such as proteins which are charged do not go across at all unless helped.

Transport

1. Passive Transport
    - Diffusion
    - Osmosis.
2. Mediated Transport
    - Protein-mediated Transport
    - Facilitated Transport.
    - Active Transport.

Passive Transport

1. Diffusion Random Molecular Motion

$$J = -DA\frac{dc}{dx}$$

Fick's First Law of Diffusion, where

- J= net rate of diffusion, $\frac{quantity}{time}$
- A= area
- $\frac{dc}{dx}$= concentration gradient
- D = diffusion constant, a constant of proportionality

$$J = -D \cdot A \cdot \frac{C_1 - C_2}{x_1 - x_2}$$

where $\frac{C_1 - C_2}{x_1 - x_2}$ is defined as a "concentration gradient"
rearranging:

$$J = -\frac{D \cdot A}{x_1 - x_2} \cdot (C_1 - C_2)$$

and $(C_1 - C_2)$ is called simple a concentration difference
rearranging again:

$$\underbrace{Flux}_{flux} = \frac{J}{A} = \overbrace{-\frac{D}{x_1 - x_2}}^{conductance} \cdot \underbrace{(C_1 - C_2)}_{force}$$

The model is now in what is called force flux form.

$$\boxed{k = \frac{D}{x} = permeability}$$

D is often determined empirically.

2. Stokes-Einstein Relation

$$D = \frac{k \cdot T}{6 \cdot \pi \cdot r \cdot \eta}$$

- k= Boltzmann's Constant
- T= Absolute Temperature ($k \cdot T$ = the average kinetic energy of molecules)
- r= molecular radium
- η = viscosity of the medium

As a rule of thumb:

$$\boxed{D = MW^{\frac{1}{3}}}$$

1. Diffusion speed

   Rapid for very short distances but speed falls off rapidly. This was all worked out by Albert Einstein!

$$\text{Average Squared Displacement} = 2 \cdot D \cdot t$$

$$\overline{(\Delta x)^2} = 2 \cdot D \cdot t$$

$$t = \frac{1}{2} \cdot \frac{\overline{(\Delta x)^2}}{D}$$

For $D = 1 \cdot 10^{-5} \frac{cm^2}{second}$

Distance	Time
um	
1	0.5 msec
10	50 msec
100	5 sec
1000	8.3 minutes
10000	14 hours

Lecture 3
More Models and Modelling

Let's recall this model again

Which models, using a mass balance, a mass flow system, that is a system with bulk flow (i.e. ventilation) through it:

$$\dot{V}_{O_2} = \frac{1}{RT} \cdot \dot{V} \cdot (P_{I_{O2}} - P_{O_{O2}})$$

Now let's do the same thing for a diffusion system

Recalling

$$0 = \text{Quantity In} - \text{Quantity Out} \pm \text{Net Production} \tag{10}$$

We can write:

$$\text{outputs} + \text{consumption} = \text{inputs} + \text{generation}$$

but, in this case we have a structure which is only consuming and not producing so:

$$\underbrace{\text{outputs}}_{=0} + \text{consumption} = \text{inputs} + \underbrace{\text{generation}}_{=0}$$

so at steady-state (and this must be the case):

$$\text{consumption} = \text{inputs}$$

symbolizing:

$$\dot{V}_{O_2} = J_{O_2}$$

and because we know that J is:

$$J = -\frac{D \cdot A}{\Delta x} \cdot (\Delta C)$$

then:

$$\dot{V}_{O_2} = -\frac{D \cdot A}{\Delta x} \cdot (\Delta C)$$

Remembering that $pV = nRT$ or $p = \frac{n}{V}RT$ so that $C = \frac{n}{V}$, then $C = \frac{P}{RT}$, so we can rewrite the model as:

$$\dot{V}_{O_2} = -\frac{D \cdot A}{x} \cdot (\frac{P^1_{O2}}{RT} - \frac{P^2_{O2}}{RT})$$

Figure 10: n1l3.eps

and collecting

$$\dot{V}_{O_2} = -\frac{D \cdot A}{x \cdot RT} \cdot (P^1_{O2} - P^2_{O2})$$

and, in force flux form:

$$\underbrace{\frac{\dot{V}_{O_2}}{A}}_{flux} = -\frac{D}{x \cdot RT} \cdot \underbrace{(P^1_{O2} - P^2_{O2})}_{force}$$

This is a bit strange and perhaps arbitrary so let's develop some intuition.

Does anyone remember this

$$E = IR$$

Can you put this into a force-flux form?

1. What is the force—what drives the flow of electrons?
2. What is the flux, what is moving?

$$\underbrace{I}_{flux} = \frac{1}{R} \cdot \underbrace{\Delta E}_{force}$$

and now

$$\frac{1}{R} = \text{Conductance} = C$$

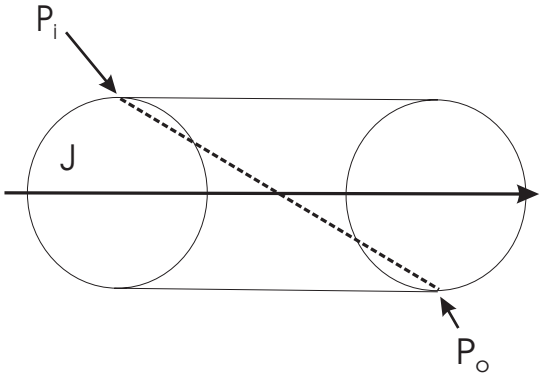


Figure 11: n2l3.ps

In the case of our diffusion force-flux model

$$\text{Conductance}_{O2} = C_{O2} = \frac{-D \cdot A}{x \cdot R \cdot T}$$

and

$$\dot{V}_{O_2} = \underbrace{C_{O2}}_{\text{oxygen conductance}} \cdot (P^1_{O2} - P^2_{O2})$$

Sometimes,

$$C = k \cdot A = k' \cdot A$$

and now

$$C = \underbrace{k'}_{permeability} \cdot A$$

Ok, lets switch again quickly back to fluid flow

1. What flows through the tube? —-$\dot{V}_{fluid}$
2. What drives fluid through the tube? —$(P_{in} - P_{out})$
   so
   $$\dot{V}_{fluid} \propto (P_{in} - P_{out})$$
3. What resists flow through the tube? —-resistance or R
4. So the model must look like this

$$\dot{V}_{fluid} = \frac{1}{R}(P_{in} - P_{out})$$

5. Poisuille's Law

$$Q = \frac{\pi r^4}{8\eta l} \cdot (P_{in} - P_{out})$$

$$\underbrace{Q}_{flux} = \overbrace{\frac{\pi r^4}{8\eta l}}^{conductance} \cdot \underbrace{(P_{in} - P_{out})}_{force}$$

6. And what does this tell us about flow through tubes

Lecture 4
Osmosis

I want to talk about Osmosis today

> **Osmosis** is defined as the flow of water across a **semi-permeable** membrane from a compartment in which the solute concentration is lower to one in which the solute concentration is greater. *Physiology, Berne et al. 4th ed.*
>
> The spontaneous movement of water across a membrane driven by a gradient of water concentration is called **osmosis**. *Medical Physiology, Rhoades and Tanner*
>
> This diffusion of water across a selectively permeable membrane is a special case of passive transport called **osmosis**. *Biology. Campbell 4th ed.*

What is it

1. There isn't much doubt that osmosis seems to be one of the more important features of organismal and cellular physiology
2. It is the fundamental force in determining fluid movement across membranes and similar barriers
3. It describes the fluid flow of water due to concentration differences in solute different sides of a permeable or semi-permeable barrier (i.e. a membrane)
4. It appears to occur because the pressure in the water is lowered when solute is added to it and the more solute, the lower the pressure
5. It is one of the colligative properties

   That occur when solute is added ($\uparrow$) to solution

   - vapor pressure $\downarrow$
   - melting point. $\downarrow$
   - freezing point. $\downarrow$

     $$\boxed{1\text{M} = -1.86C}$$

   - boiling point. $\uparrow$
   - osmotic pressure. $\uparrow$

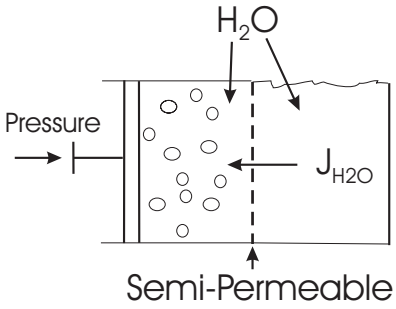


Figure 12: n1l4.ps

What isn't it

1. It is not diffusion of water models (it is bulk flow)
2. It is not due to concentration differences in water (hmmmmm)
3. Well understood–but that is ok we can still work with it

The Toolbox Again

1. Concentration Definitions

Molarity	M	$\frac{\text{moles of solute}}{\text{liters of solution}}$
Formality	F	$\frac{\text{moles of solute}}{\text{liters of solution}}$
Molality	m	$\frac{\text{moles of solute}}{\text{kg of solution}}$
Mole Fraction	x	$\frac{\text{moles of solute}}{\text{moles of solute + moles of solvent}}$
Normality	N	$\frac{\text{equivalents of solute}}{\text{liters of solution}}$

2. Pressure
   - positive pressure
   - negative pressure.

absolute pressure vs gauge pressure

760 mmHg = 760 torr = 1.01325 bar = 0.101325 Jcm^{-3}=101.325 kPa

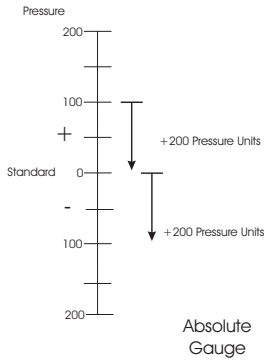


Figure 13: n2l4.ps

Back to Osmosis

Van't Hoff's Law

$$\pi = i \cdot R \cdot T \cdot m$$

- π = osmotic pressure
- i = # of molecules form by dissociation of solute
- R = gas constant
- T = absolute temperature (Kelvin)
- m = molal concentration $\frac{molesofsolute}{kgH2O}$

adding solute somehow confers a negative pressure in the solvent (solution). more typically the law looks like this

$$\pi = iRTC$$

or

$$\pi = CRT$$

1. But a correction is needed: not all solutes are equally active and activity is effected by concentration. The idea of ideal solute here! An osmotic coefficient (ϕ) is needed
2. for example $\phi = 0.93$ for NaCl (sodium cloride)

3. And we can define the osmolar concentration (the units are osmoles

$$\phi \cdot i \cdot C = \text{osmolar concentration}$$

another term for this is osmotically effective concentration

So lets do a simple model for osmotic flow

1. driving force

$$\pi_1 - \pi_2 = \Delta\pi$$

$$\Delta\pi = RT\phi iC_1 - RT\phi iC_2 = RT\phi i(C_1 - C_2)$$

2. flux

$$\frac{\dot{V}_{water}}{A}$$

3. conductance

$$L = \text{permeability}$$

4. The model

$$\frac{\dot{V}_{water}}{A} = L \cdot (\pi_1 - \pi_2)$$

but notice that π is negative (osmotic pressures are negative), so:

$$\frac{\dot{V}_{water}}{A} = L \cdot (-\pi_1 - (-)\pi_2)$$

and so

$$\frac{\dot{V}_{water}}{A} = L \cdot (-\pi_1 + \pi_2)$$

5. Another correction factor is needed The reflection coefficient (σ). Not all solutes are equally permeant or impermeant as the case might be.

   - $\sigma = 1$ when the solute is fully permeant
   - $\sigma = 0$ when the solute is fully impermeant

   So our model looks finally like this:

$$\dot{V}_{water} = \sigma \cdot A \cdot L \cdot (\pi_2 - \pi_1)$$

Great, but what is really happening to cause water to flow?

Lecture 5
Membrane Potentials

An interesting thing happens when you construct a microelectrode system and use it to measure the difference in charge across the biological membrane.

As you approach the membrane your volt meter reports that the voltage difference between the microelectrode and the reference electrode is 0 mV's. However, as the electrode encounters then pierces the membrane the voltage quite suddenly becomes negative on the order of several 10's of mV's (usually from -30 to -100 or so mV).
This phenomenon is the basic observation or foundation of what can be called bioelectricity.

1. 1780's
    - Luige Galvani
    - Alessandro Volta.——controversy over the nature of bioelectricity
2. 1850's
    - Dubois Raymond First measured a Δ P
3. 1900's
    - Helmholst
    - Nernst.

      both first properly explained the phenomenon and their work serves as the basis for all subsequent work.

Potential Difference

1. The problem
    - Concentration Difference
    - Charge Differences (separation of charge).
    - Osmotic Forces.

Figure 14: A charge cell

1. Ion concentration count ions
2. Charge Concentration count charges
3. Osmotic Concentration count osmotically active molecules
4. Active Transport

Concentration Cell–the tool box

Macroscopic Charge Balance

$$\sum \text{positive charge} + \sum \text{negative charge} = 0$$

We need to consider a model system called a concentration cell and essentially a series of thought experiments. A membrane separates the two sides of the cell and is semi-permeable. In this case, X^+ can move across but Y^- cannot. We set the system up so that the total concentration in side 1 is greater than the concentration in side 2 but there are equal numbers of positive and negative charge on side 1 and equal number of positive and negative charge on side 2.

$$[X^+]_1 + [Y^-]_1 \gg [X^+]_2 + [Y^-]_2$$

Now what happens:

$$[X^+]_1 \longrightarrow [X^+]_2$$

so

$$[X^+]_1 \downarrow [X^+]_2 \uparrow$$

and then

$$[^+]_1 \downarrow \longrightarrow [^+]_2 \uparrow$$

So ions are moving as well as charge. This goes on until:

$$\Delta[X] = \Delta\text{charge}$$

That is the concentration difference is opposed by a charge difference.
Can we explain this physically? Of course!!!
Lets let δ represent a very small quantity!
Suppose that δn is moved across a membrane against its concentration difference. This take work, δW_c, and that work is defined by:

$$\delta W_c = \delta n \cdot R \cdot T \cdot \ln \frac{[X^+]_1}{[X^+]_2} \tag{11}$$

Now consider the work of moving charge against its charge difference, i.e. moving positive charge from low positive to high positive charge:

$$\delta W_e = \delta n \cdot z \cdot \mathcal{F} \cdot E \tag{12}$$

At equilibrium, there is no further movement of X^+. This must mean that the work done pushing charge against a charge difference is exactly balanced by the work done pushing concentration against a concentration difference:

$$\delta W_e = \delta W_c \tag{13}$$

We can substitute the appropriate expression for the lhs (left-hand-side) and rhs (right-hand-side):

$$\delta n \cdot z \cdot \mathcal{F} \cdot E = \delta n \cdot R \cdot T \cdot \ln \frac{[X^+]_1}{[X^+]_2} \tag{14}$$

and rearrange:

$$E = \frac{R \cdot T}{z \cdot \mathcal{F}} \cdot \ln \frac{[X^+]_1}{[X^+]_2} \tag{15}$$

What does E mean? This symbol is often seen (as in $E = IR$) and it represents the voltage difference (or potential difference) across the membrane and therefore represents the membrane potential, which is what we are after.

$$E = \Delta E = E_1 - E_2 \tag{16}$$

In our model, which represents an "equilibrium" system (and this is really important), the membrane potential is proportional to the log of the ratio of the concentration of X^+ in the two compartments.

$$E_1 - E_2 = \frac{R \cdot T}{z \cdot \mathcal{F}} \cdot \ln \frac{[X^+]_1}{[X^+]_2} \tag{17}$$

The question of sign arises here. If we rearrange the equation and solve for E_1 (the "membrane potential"):

$$E_1 = E_2 + \frac{R \cdot T}{z \cdot \mathcal{F}} \cdot \ln \frac{[X^+]_1}{[X^+]_2} \tag{18}$$

but this does not make any sense. It states that the voltage in compartment 1 is more positive than the voltage in compartment 2, but we know that positive charge is moving into compartment 2 from compartment 1. Therefore the voltage in compartment 1 must be less positive (i.e. more negative) than the voltage in compartment 2:

$$E_1 = E_2 - \frac{R \cdot T}{z \cdot \mathcal{F}} \cdot \ln \frac{[X^+]_1}{[X^+]_2} \tag{19}$$

Therefore, equation 21 should look like this:

$$E_1 - E_2 = -\frac{R \cdot T}{z \cdot \mathcal{F}} \cdot \ln \frac{[X^+]_1}{[X^+]_2} \tag{20}$$

This is the Nernst Equation and it describes the potential difference due to an equilibrium concentration difference across the membrane separating the 2 compartments. Lets make the Nernst Equation a bit more convenient by putting in values for R and T, the gas constant and system temperature respectively and converting the natural log (ln) to base 10 log (log):

$$2.303 \cdot \frac{R \cdot T}{\mathcal{F}} = 60$$

then:

$$E_1 - E_2 = -\frac{60}{z} \cdot \log_{10} \frac{[X^+]_1}{[X^+]_2} \tag{21}$$

the units for the potential difference are mV (millivolts).

Lecture 6
Membrane Potential II

Lets derive the Nernst Equation in another way:

Lets derive the Nernst Equation in another, perhaps more traditional, way. We can describe the chemical potential, u, in the two compartments with:

$$u_1 = u^0 + R \cdot T \cdot \ln[x_1] + z \cdot \mathcal{F} \cdot E_1 \tag{22}$$
$$u_2 = u^0 + R \cdot T \cdot \ln[x_2] + z \cdot \mathcal{F} \cdot E_2 \tag{23}$$

Let the difference in chemical potential between the two compartments be:

$$\Delta u(x) = u_1(x_1) - u_2(x_2) \tag{24}$$

and subtract the chemical potentials for the two compartments:

$$u_1(x_1) - u_2(x_2) = \overbrace{R \cdot T \cdot \ln \frac{[x_1]}{[x_2]}}^{\text{Concentration}} + \overbrace{z \cdot \mathcal{F} \cdot (E_1 - E_2)}^{\text{charge}} \tag{25}$$

I have identified the chemical potential difference due to the charge difference and the chemical potential difference due to the concentration difference. That is, the contributions of each to the overall chemical potential difference between the compartments is identified. What we know is that at equilibrium there is no chemical potential difference across the membrane separating the compartments (why?), that is:

$$u_1(x_1) - u_2(x_2) = 0$$

so:

$$0 = \overbrace{R \cdot T \cdot \ln \frac{[x_1]}{[x_2]}}^{\text{Concentration}} + \overbrace{z \cdot \mathcal{F} \cdot (E_1 - E_2)}^{\text{charge}} \tag{26}$$

Solve for the potential (voltage) difference by rearranging:

$$(E_1 - E_2) = -\frac{R \cdot T}{z \cdot \mathcal{F}} \cdot \ln \frac{[x_1]}{[x_2]} \tag{27}$$

and we see the Nernst Equation, this time with the correct sign in place.
I stress again that the Nernst Equation describes the equilibrium potential difference due to an equilibrium concentration difference—-with the emphasis on equilibrium. Why this emphasis?

Donnan Equilibrium

We have looked at the equilibrium potential due to the concentration difference across a membrane of one ionic species, disregarding all other issues. Next, let us be a bit more realistic and add a second and third ionic species. As you can see from the concentration cells, we have $[K^+]$ and $[A^-]$ in the left side compartment, while we have $[K^+]$ and $[Cl^-]$ in the right side compartment. The total concentration in each compartment is 0.1 M. The membrane is semipermeable and will allow the $[K^+]$ and $[Cl^-]$ to move but not the $[A^-]$. In this case the $[A^-]$ represents large, negatively charged molecules such as proteins. If we set up the system and watch what happens, first we see that the $[Cl^-]$ begins to move from right to left (why?) and then the $[K^+]$ begins to follow (once again, why?). Disregarding all else, we allow this system to go to equilibrium (remember this is a thought experiment). At equilibrium, the chemical potentials should be in complete balance (i.e. nothing is moving):

$$\Delta u_{K^+} = \Delta u_{Cl^+} \tag{28}$$

Given an equilibrium state the chemical potentials (u) for the two ionic species that can move, when there is a chemical potential difference, are:

$$\Delta u_{K^+} = R \cdot T \cdot \ln \frac{[K_1^+]}{[K_2^+]} + z \cdot \mathcal{F} \cdot (E_1 - E_2) \tag{29}$$

$$\Delta u_{Cl^-} = R \cdot T \cdot \ln \frac{[Cl_1^-]}{[Cl_2^-]} - z \cdot \mathcal{F} \cdot (E_1 - E_2) \tag{30}$$

Note that the charge (z) of the Cl^- is -1, hence the change in sign. I have left the z's in to remind you of this even though the magnitude of each is 1. If we add these two chemical potentials and simplify, the result is:

$$\ln \frac{[K_1^+]}{[K_2^+]} + \ln \frac{[Cl_1^-]}{[Cl_2^-]} = 0 \tag{31}$$

Rearranging:

$$\ln \frac{[K_1^+]}{[K_2^+]} = -\ln \frac{[Cl_1^-]}{[Cl_2^-]} \tag{32}$$

Then taking the reciprocal of the Cl^- concentrations:

$$\ln \frac{[K_1^+]}{[K_2^+]} = \ln \frac{[Cl_2^-]}{[Cl_1^-]} \tag{33}$$

Taking the antilog of each side:

$$\frac{[K_1^+]}{[K_2^+]} = \frac{[Cl_2^-]}{[Cl_1^-]} \tag{34}$$

and rearranging again:

$$[K_1^+] \cdot [Cl_1^-] = [K_2^+] \cdot [Cl_2^-] \tag{35}$$

This is called a Donnan Equilibrium—it only holds if the two species are in equilibrium. Any potential resulting is called a Donnan Potential. This can be done pairwise for any ionic pair of positive and negative ions. The equation states simply, that the product of the two concentrations on one side of the membrane is equal to the product of the two concentrations on the other side (at equilibrium). OK, lets do a calculation. Let the quantity of Cl^- that moves from right to left be $b = [Cl^-]$. Then the quantity left in the right side (B) is $[Cl^-]_B = 0.1 - b$ and because, the same quantity of K^+ must follow, the quantity of K^+ left in B is $[K^+]_B = [Cl^-] = 0.1 - b$. Because there was no Cl^- in the left side (A) to begin, the quantity of Cl^- that ends up in A is $[Cl^-]_A = b$ and the quantity of $[K^+]$ that ends up in A is $[K^+]_B = 0.1 + b$. Remember that the quantity of A^- present (and trapped in A) is $A^- = 0.1M$. The Donnan equilibrium tells us that

$$[K_A^+] \cdot [Cl_A^-] = [K_B^+] \cdot [Cl_B^-] \tag{36}$$

and substituting in the appropriate variables:

$$(0.1 + b) \cdot (b) = (0.1 - b) \cdot (0.1 - b) \tag{37}$$

solving for b:

$$b = 0.0333 \tag{38}$$

Calculate the concentrations for K^+ and Cl^- in each compartment. Now calculate the equilibrium potential (the "Nernst potential") due to the concentration difference for each ionic species across the membrane. You should get something like -18 mV.
The following table was given to you in class. You should calculate the equilibrium potential for each of the ions listed and put the value in 4. If the actual potential is as listed in column 5, why are the calculated values different or similar. In what directions will $[Na^+]$, $[K^+]$ and $[Cl^-]$ move it allowed to? Now reverse the concentrations, that is the inside becomes the outside and vice versa. Recalculate the equilibrium potential and write it in the last column. What has happened to the value?

	Extracellular Fluid	Cytoplasm	Equilibrium Potential	Actual Potential	Calc.
	mM	mM	mV	mV	mV
Frog Muscle					
$[Na^+]$	120	9.2			
$[K^+]$	2.5	140			
$[Cl^-]$	120	3 to 4		-90	
Squid Axon					
$[Na^+]$	460	50			
$[K^+]$	10	400			
$[Cl^-]$	540	40		-70	

Conductance and Field Equations

It is useful (for the things that I will describe in lecture) to have a model of the membrane potential E_m defined in terms that include the conductance of the membrane. Recall Ohm's law (again):

$$E = IR \tag{39}$$

rearranging and expanding E:

$$I = \frac{1}{R} \cdot (E_1 - E_2) \tag{40}$$

We know have our force-flux equation, where a current flow I is driven by a voltage difference $(E_1 - E_2)$. We can define a conductance C as we did earlier, but the symbol commonly used in physiology texts is g rather than C:

$$C = g = \frac{1}{R} \tag{41}$$

and substituting:

$$I = g \cdot (E_1 - E_2) \tag{42}$$

My discussion has involved three ions (actually four but the fourth can't move) and we can write current equations for each of them. Remember, that the movement of each or all of these ions carries current because they are charged.

$$I_K = g_K \cdot (E_m - E_K) \tag{43}$$
$$I_{Na} = g_{Na} \cdot (E_m - E_{Na}) \tag{44}$$
$$I_{Cl} = g_{Cl} \cdot (E_m - E_{Cl}) \tag{45}$$
$$\tag{46}$$

Each ion has its own conductance. We know that, at equilibrium:

$$I_K = I_{Na} = I_{Cl} = 0 \tag{47}$$

Why do we know this? So:

$$g_K \cdot (E_m - E_K) = g_{Na} \cdot (E_m - E_{Na}) = g_{Cl} \cdot (E_m - E_{Cl}) = 0 \tag{48}$$

We also know that, for the membrane system that we discussed in class, $(E_m - E_{Cl}) = 0$, thus:

$$g_K \cdot (E_m - E_K) = g_{Na} \cdot (E_m - E_{Na}) = 0 \tag{49}$$

You should be able to defend the statement that $(E_m - E_{Cl}) = 0$. Solve this equation for E_m (you should be able to do this yourself):

$$E_m = \frac{g_K}{g_K + g_{Na}} \cdot E_K + \frac{g_{Na}}{g_K + g_{Na}} \cdot E_{Na} \tag{50}$$

If we let $g_{tot} = g_K + g_{Na}$, then:

$$E_m = \frac{g_K}{g_{tot}} \cdot E_K + \frac{g_{Na}}{g_{tot}} \cdot E_{Na} \tag{51}$$

This is the chord conductance equation. What if $(E_m - E_{Cl}) \neq 0$? Try and work out the appropriate form of the chord conductance equation. You can generalize for any ions that can move across the membrane in the same way. Another equation for E_m that is commonly used (and which I won't derive) is the Goldman Field Equation:

$$E_m = \frac{R \cdot T}{\mathcal{F}} \ln \frac{k_p^{K^+}[K^+]_o + k_p^{Na^+}[Na^+]_o + k_p^{Cl^+}[Cl^+]_i}{k_p^{K^+}[K^+]_i + k_p^{Na^+}[Na^+]_i + k_p^{Cl^+}[Cl^+]_o}$$

Figure 15:

Lecture 7
The Action Potential

What does an action potential look like?

1. Motoneuron
2. Skeletal Muscle
3. Cardiac Muscle
4. Description of Wave Pattern
    - Foot
    - Rising Phase.
    - Peak.
    - Falling Phase.
    - Hyperpolarizing After potential.
    - positive, negative After Potential.
5. Threshold

Figure 16:

Functional Explanation of the wave form

1. Membrane Potential Again

$$I_{K^+} = g_{K^+} \cdot (E_M - E_{K^+})$$

$$I_{Na^+} = g_{Na^+} \cdot (E_M - E_{Na^+})$$

$$I_{Cl^-} = g_{Cl^-} \cdot (E_M - E_{Cl^-})$$

Recall that the membrane potential is the weighted sum of all the voltage differences but especially K^+, Na^+ and Cl^- and that each as the respective conductance $g_{K^+}, g_{Na^+}, g_{Cl^-}$

equilibrium potential for K^+ is -100 so if $g_{K^+} \uparrow$ then membrane would hyperpolarize.

equilibrium potential for Na^+ is +60 so if $g_{Na^+} \uparrow$ then membrane would depolarizes.

equilibrium potential for Cl^- is -70 so if $g_{Cl^-} \uparrow$ then membrane would stabilize.

Figure 17:

2. Voltage Clamp

   Recall again $I = g_{ion} \cdot \Delta E$

   In the normal case:

   - I is relatively fixed
   - g_{ion} changes first
   - Δ E then changes and this is what we see as an action potential

   But what if we could fix ΔE at what ever value that we wanted? Indeed we can do this and the technique is called a voltage clamp.

   We still have $I = g_{ion} \cdot \Delta E$ as our model but now:

   - ΔE is fixed at some voltage difference
   - g_{ion} may or may not change depending on the E that we have chosen
   - if g_{ion} changes (gates open) then current flows, that is I changes

   So now instead of watching a voltage excursion, we are watching a current flow and of course, what carries the current?

   A number of experiments are possible and many were done on the squid giant axon, a nearly perfect experimental system.

   For example:

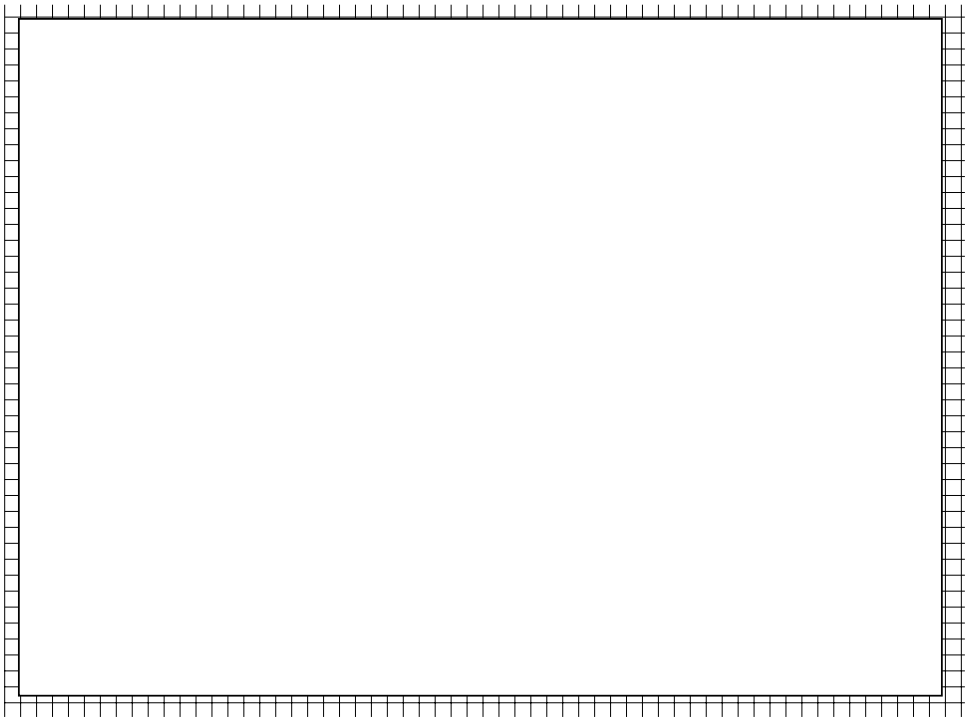


Figure 18:

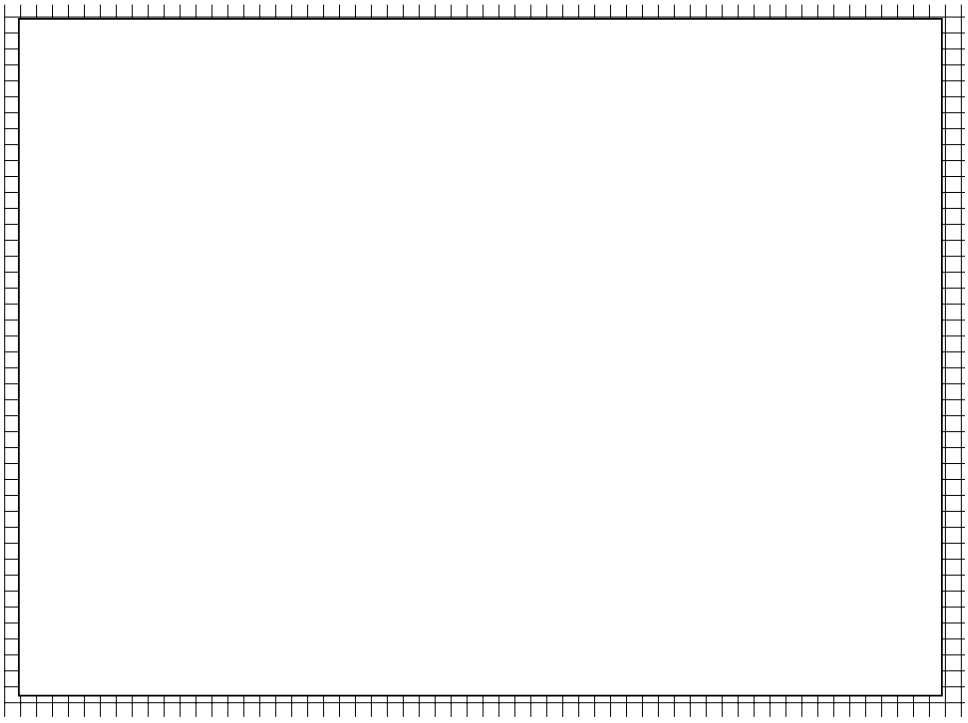


Figure 19:

Figure 20:

- Replace the outside Na^+ with Choline (positive charge and impermeant) then clamp the membrane to 0mv- the inward current disappears. Why?
- Clamp the membrane to +58mv and again the inward current disappears. Why?
-

3. Decomposing conductances

   The total current that we have been observing must be composed of the individual currents carried by the appropriate ions. We know that Cl^- is usually near its equilibrium potential so it carried little or no current. The total current must be composed of the current carried by Na^+ and the current carried by K^+.

$$TotalCurrent = K^+current + Na^+current$$

   And if we know the total current and one of the individual currents we can get the other.

   Place a figure box here

   What must be happening, of course, is that the conductances for Na^+ and K^+ must be changing.

   Note that normally conductance changes would result in a potential (voltage) change but when a voltage clamp is in use, conductance changes produce a change in current.

Figure 21:

One might ask why does current not normally change? The answer is related to the high electrical insulation of the membrane.

4. Patch Clamp

   - Gating Currents

5. Channels and Conductance The channels are thought to be controlled by "gates" in the membrane and have been studied in detail using patch clamp techniques. The opening of the gate is due to the change in voltage or potential and the channels are said to be voltage gated. This is important because there are other kinds of channels which are not voltage gated (as we shall see).

   - Na^+ Channel
     m gate
     H gate
     Channel Blockers
     Tetrodotoxin
   - K^+ Channel.
     Gates
     Channel Blockers
     TEA-Tetraethylammonium

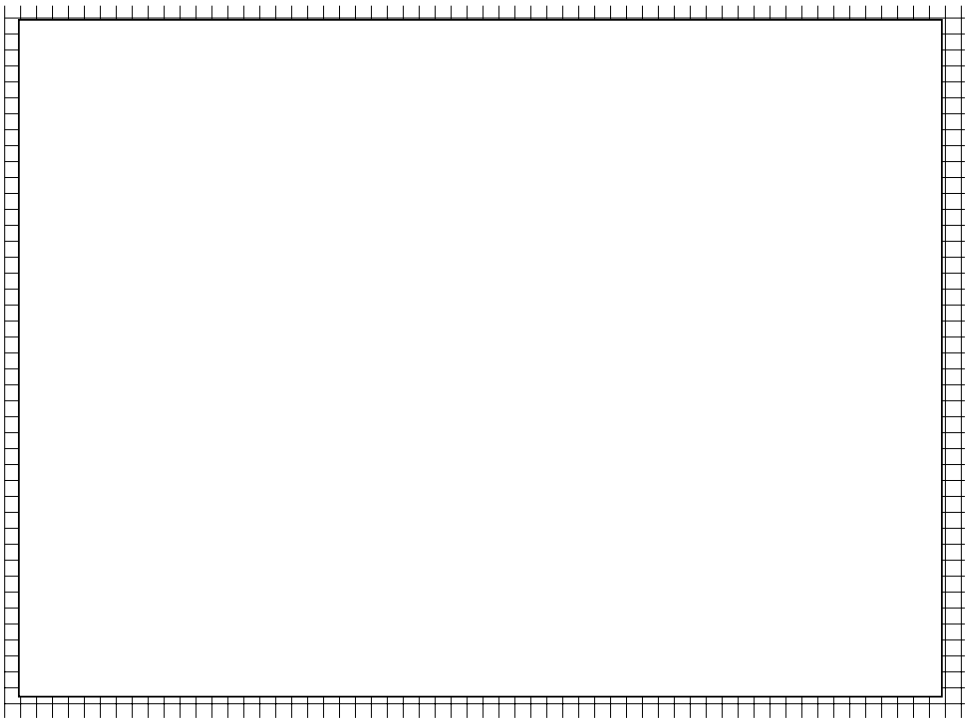


Figure 22:

Figure 23:

Figure 24:

Lecture 8
Action Potential and Axon Conduction Properties

Properties of Action potentials

1. All- or None Impulse
2. Graded potentials are different
3.
   -
   - .
   - .
   - .
   - .

Cable Properties

1. Local Response
   -
2. Electrotonic conduction
3.

2 Muscle

Lecture 10
Receptors and Signal Transmission

1.
2.
3. •
   • .
   • .
   • .
   • .

1. •
2.
3.

Lecture 11
Muscle I

Types of Muscle

1. Striated
2. Smooth
3. Cardiac
    -
    - .
    - .
    - .
    - .

Structure of Striated Muscle

1. Large Scale Structure
    - Muscle Fibers
    - Sarcolemma.
    - Myofibrils.
    - Sarcomeres.
    - filaments.
    - Sarcoplasmic Reticulum. 3T tubule
2. Molecular Structure
    - Actin
      Actin (F and G, 1 ADP/ADP 1Mg per molecule)
      Tropomyosis
      Troponin
    - Myosin.
      HMM
      LMM

Sliding Filament Theory

Lecture 12
Muscle II

Sliding Filament Theory

1.
2.
3. •
   • .
   • .
   • .
   • .

Excitation-Contraction Coupling

1. •
2.
3.

Lecture 13
Muscle III

Muscle contraction

1. Isometric
2. Isotonic
3. Tetanic contractions
    -
    - .
    - .
    - .
    - .

Length Tension Relations

1. •
2.
3.

Lecture 14
Muscle IV

Reflex Organization

1. Motor Unit
2. Reflex Hierarchy
3.
   -
   - .
   - .
   - .
   - .

Sensory Input to Reflex

1. Muscle Spindles
2. Tendon Organs
3. Spindle Function

   - Fiber Types
     extrafusal
     intrafusal
     Nuclear Bag Fibers
     Nuclear Chain Fibers
     Motor Innervation
     Afferent–Group I, Group II
     Efferent–$\beta motor, \gamma motor(static, dynamic$

3 Cardiovascular Physiology

Lecture 15
The Cardiovascular System: Heart as a Pump

Structure of the Cardiovascular System

1.
2.
3. •
   • .
   • .
   • .
   • .

Pressure and Flow

1. •
2.
3.

The Cardiac Cycle

PV Loop for the Heart

1. Correlation with Cardiac Cycle
2. Starling's Law of the Heart
3. Contractility
4. Ventricular Work

Measurement of Cardiac Output

Lecture 16
Electrical Activity of the Heart

Transmembrane Potentials

1. Types of Cardiac Action Potentials
    - Fast Response
    - Slow Response.
    - .
    - .
    - .
    - .
    - .

Natural Excitation of the Heart

1. Sinoatrial Node
2. Atrial Conduction
3. Atrioventricular Conduction
4. Ventricular Conduction
5. Reentry

Electrocardiography

1. Scalar Electrocardiography
    - P wave
    - QRS Complex.
    - T wave.
2. Standard leads

Arrhythmias

Lecture 17
Microcirculation

Descriptive Structure

1. Arterioles
2. Venules
3. Capillaries
    - Endothelium
    - Pores.
    - Tight.
    - Fenestrated.
    - Discontinuous.

Functional Properties of Capillaries

1. Vasoactive Role of Capillary
    -
2. Control of Flow
3. Capillary Exchange

Lymphatic System

Lecture 18
Hemodynamics and the Arterial System

Velocity and Pressure

1.

2.

3.

Pressure and Flow

1. Poiseuille's Law
   -
2. Resistance to Flow
   - Ohm's Law
   - Series and parallel resistances.

Determinants of Blood Pressure

1. Arterial Elasticity
2. Mean Arterial pressure
3. Arterial Pulse Pressure

4.

Lecture 19
Control of Cardiac Output:Coupling of heart and blood vessels

Vascular Function Curve

1. •

Cardiac Function Curve

1. •
2.
3.

Relating the VF curve to the CF curve

1. Cardiac Contractility
2. Blood Volume
3. Peripheral Resistance

The Two Pump System

Lecture 20
Regulation of the Heartbeat

Nervous Control of the Heart Rate

1. Parasympathetic Pathways
2. Sympathetic Pathways
3. Higher Centers
4. Reflexes
    - Baroreceptor
    - Bainbridge.
      Atrial Receptors
      ANP
    - Respiratory Sinus Arrhythmia.

Lecture 21
The Peripheral Circulation

(a)
(b)
(c) –
– .
– .
– .
– .

(a) –
(b)
(c)

Lecture 22
Microcirculation

Descriptive Structure

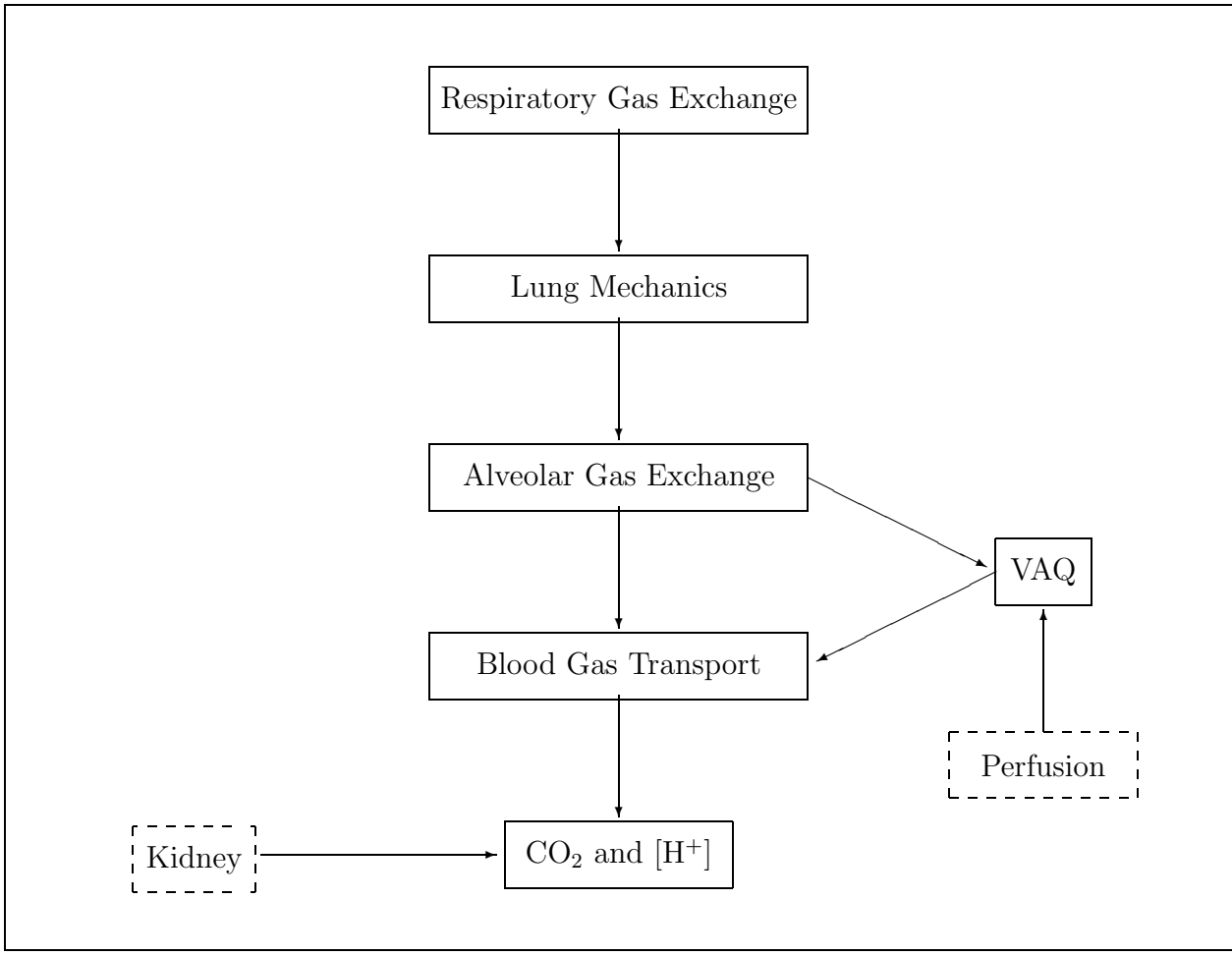
(a) Arterioles
(b) Venules
(c) Capillaries
  - Endothelium
  - Pores.
  - Tight.
  - Fenestrated.
  - Discontinuous.

Functional Properties of Capillaries

(a) Vasoactive Role of Capillary
  -
(b) Control of Flow
(c) Capillary Exchange

Lymphatic System

4 Respiratory Physiology


Respiratory Gas Exchange
Lung Mechanics
Alveolar Gas Exchange
VAQ
Blood Gas Transport
Perfusion
Kidney
CO_2 and $[H^+]$

Lecture 23
Respiration and Gas Exchange: Lung Structure and Function

(a)
(b)
(c) –
  – .
  – Tight.
  – Fenestrated.
  – Discontinuous.

Functional Properties of Capillaries

(a) Vasoactive Role of Capillary
  –
(b) Control of Flow
(c) Capillary Exchange

Lymphatic System

Lecture 24
Alveolar Gas Exchange

Another look at the lung model

(a) Lung
  - Ventilation variables
    Inspiration
    Expiration
    Dead Space
    Alveolar
    relation among ventilation variables
  - Gas Tensions.
  - Perfusion.
    Blood flow in
    Blood flow out
    Blood gas tensions

CO_2 Balance

(a) CO_2 Balance on the Lung
(b) CO_2 Balance on the Alveolar Space
(c) Solving for Dead space ventilation
(d) CO_2 Balance on the Blood

O_2 Balance

(a) O_2 Balance on the Lung
(b) O_2 Balance on the Alveolar Space
(c) O_2 Balance on the Blood

O_2-CO_2 Diagram

(a) RQ
(b) Expired Model
(c) Inspired Model

Lecture 25
Ventilation and Perfusion

(a)
(b)
(c) –
– .
– .
– .
– .

(a) –
(b)
(c)

Lecture 26
Lung Mechanics

Lung Compliance

Lung Pressure Volume Curves

(a) Air
(b) Saline Filled

Surface Active Agents and Lung Recoil

(a) Surface Tension
(b) dipalmitoyl phosphatidylcholine (DPPC)
    - Type II Alveolar epithelial cells (granular pneumocytes)
(c) LaPlace's Law
(d) Reduce work of breathing
(e) Lowers Elastic Recoil at FRC
(f) Stabilize alveolii

Chest Wall Distensibility

(a) Elastic Recoil of the chest wall
(b) Elastic Recoil of the Lung
(c) Elastic Recoil of the chest-lung system
(d) Dynamic Compliance and Lung work
    - Dynamic P-V Curve
    - Elastic Work.
    - Resistance Work.
    - Total Work.

Oxygen Cost and Efficiency of breathing

Lecture 27
Blood Gas Transport

Oxygen Cascade

Carbon dioxide Cascade

RBC's:red blood cells

(a) Non-nucleated
(b) discoid shape
(c) Fixed lifetime
  – turnover

Oxyhemoglobin equilibrium curve

(a) Plots
(b) Plasma Transport
(c) Hemoglobin
(d) Myoglobin

Hemoglobin

(a) Structure
  – Subunits
    α subunits
    β subunits
(b) Function
  – Cooperativity
  – sigmoid binding curve.
(c) Bohr Shift
  – CO_2 Bohr Shift
    very small influence
  – Fixed Acid Bohr Shift.
  – P_{50}.
  – Shape Modifiers.
    2,3 diphosphoglycerate
    temperature

Carbon Dioxide Transport

(a) Equilibrium Curve
- Plots
  Haldane Effect
- Solubility.
- Dissolved CO_2.
- Carbamino-carboxyhemoglobin.
- Bicarbonate.

	Venous	Arterial	Difference
Dissolved CO2 (vol %)	3.1	2.7	0.4
HCO3 (vol %)	47.0	43.9	3.1
Carbamino (vol %)	3.9	2.4	1.5
Total (vol %)	54.0	49.0	5.0

Form	Quantity, meqL^{-1}
dissolved	1.2
bicarbonate	19.6
carboxyhemoglobin	1.1 to 1.7

(a) Interaction of Water and CO_2

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Carbonic Anhydrase
–

(a) –
(b)
(c)

Lecture 28
Regulation of Ventilation

The respiratory system is under both automatic and conscious control. On the one hand the autonomic nervous system insures that we can breath in an appropriate way without thinking about it, whether eating, talking, excercising or during other activities. While on the other hand, we can consciously change our ventilation patterns.

Respiration is rhythmic, repeating about 12 times a minute (normally) but in contradistinction to the heart, there are no pacemakers setting the rhythm.

Brain Stem and higher

(a) Intrinsic Centers
  - Medullary respiratory centers 3 Pontine respiratory centers

(b) Extrinsic Centers
  - Cortex
  - Cerebellum.
  - Medullary vasomotor centers.

Receptors

(a) Central
  - Chemoreceptors
    Located in the brain and brain stem, lining the surface of the ventriculo-cisternal system and bathed with cerebrospinal fluid. Sensitive to P_{CO_2} and pH but not to P_{O_2}

(b) Peripheral
  - Chemoreceptors
    Carotid Bodies
    Aortic Bodies
  - Mechanoreceptors.
    Stretch Receptors

Chemical Control

Mechanical Control

Exercise

Altitude

Abnormal Patterns

(a) –
(b)
(c)

Lecture 29
Salt and Water Balance: Renal Physiology

Basic Functions

(a) Salt Balance—Ions
(b) Water Balance
(c) Acid-base Balance (Homeostasis)

Basic Anatomy

(a) Cortex
(b) Medulla
(c) Blood Supply
  - Arterial Supply
  - Venous Supply.

The nephron

(a) Types
  - Cortical
  - Juxtamedullary.
(b) Glomerulus
  - Bowman's Capsule
(c) Tubules
  - Proximal
  - Distal.
  - Loop of Henle.
(d) Collecting Duct

Renal Function

(a) Renal Clearance
(b) Glomerular Filtration
  - GFR
(c) Renal Blood Flow
  - RPF

Regulation of GFR and RBF

5 Renal Physiology

Lecture 30
Glomerular Function

Clearance

Mass Balance on the Kidney

$$\text{input to kidney} = \text{output from kidney}$$

$$\text{Renal Artery} = \text{Renal Vein} + \text{Ureter}$$

$$P_x^a \cdot \text{RPF}^a = P_x^v \cdot \text{RPF}^v + U_x \cdot \dot{V}$$

$$P_x^a \sim U_x \cdot \dot{V}$$

$$P_x^a \cdot C_x = U_x \cdot \dot{V}$$

$$C = \frac{U_x \cdot \dot{V}}{P_x^a}$$

Glomerular Filtration Rate

$$\text{GFR} = \frac{U_{in} \cdot \dot{V}}{P_{in}}$$

Inulin is neither secreted nor reabsorbed or metabolized

fructose polysaccharide from Jerusalem Artichoke

$$\text{amount filtered} = \text{amount excreted}$$

(a) Clearance of Inulin
(b) Filtration Fraction
(c) Clearance of Creatinine
   - Kidney Disease
   - .
   - .
   - .
   - .

Renal Plasma Flow

$$\text{RPF} = \dot{V}_p = \frac{U_{PAH} \cdot \dot{V}}{P_{PAH}}$$

PAH = para amino hippurate

(a) Effective Renal Plasma Flow

–

(b)

(c)

Ultrafiltration

$$\text{GFR} = K_f[(P_{GC} - P_{BS}) - \sigma(\pi_{GC} - \pi_{BS})]$$

K_f is filtration coefficient, σ is the reflection coefficient, GC is the glomerula capillary, BS is Bowman's Space

	Males	Females
GFR	127 ml min^{-1}	118 ml min^{-1}
RPF	655 ml min^{-1}	600 ml min^{-1}

Lecture 31
Tubular Transport

Descriptive Structure

(a) Arterioles
(b) Venules
(c) Capillaries
  - Endothelium
  - Pores.
  - Tight.
  - Fenestrated.
  - Discontinuous.

Functional Properties of Capillaries

(a) Vasoactive Role of Capillary
  -
(b) Control of Flow
(c) Capillary Exchange

Lymphatic System

Lecture 32
Tubular Transport I

Tubular Reabsorption

(a)
(b)
(c) –
– .
– .
– .
– .

Tubular Secretion

(a) –
(b)
(c)

Lecture 34
Tubular Transport II

Urinary Volume and Concentration

(a) Characteristics
(b)
(c) –
– .
– .
– .
– .

(a) –
(b)
(c)

Lecture 35
Fluid Volume Regulation I

Body Fluid Compartments

(a) Volumes
(b) Composition
(c) Fluid Exchange between compartments
    –
    – .
    – .
    – .
    – .

Control of Body Fluid Osmolality

(a) Urine Concentration and Dilution
(b) ADH
(c) Thirst
(d) Free Water Clearance
(e) Osmolar Clearance
(f) $T^c_{H_2O}$
    –
(g)
(h)

Lecture 36
Fluid Volume Regulation

Control of Extracellular Fluid Volume and Regulation of Renal NaCL Excretion

(a) Effective Circulating Volume
(b) Volume Sensing
(c) Control of Na^+ Secretion
- –
- – .
- – .
- – .
- – .

(a) –
(b)
(c)

Lecture 37
Acid-Base Regulation

[H^+] and pH

$$\text{pH} = log_{10}\{\frac{1}{[H^+]}\}$$

$$\text{pH} = -log_{10}[H^+]$$

$$[H^+] = 10^{-\text{pH}}$$

The figure representing the relationship between pH and $[H^+]$ is shown. Notice that the $[H^+]$ is always very low at any physiological pH. This fact is easily overlooked when talking about pH.

The Standard View: CO_2-$[HCO_3^-]$ Buffer System

The Davenport Diagram basically represent the reaction equation:

$$[H^+] \cdot [HCO_3^-] = k \cdot [H_2CO_3]$$

and is a shorthand description of the acid-base balance in the body. We can manipulate this equation in the following ways:

$$\frac{1}{[H^+]} = \frac{1}{k} \cdot \left\{ \frac{[HCO_{-3}^-]}{[H_2CO_3]} \right\}$$

and

$$pH = pk + log_{10} \left\{ \frac{[HCO_3^-]}{[H_2CO_3]} \right\}$$

and, for humans at 38 C:

$$pH = 6.1 + log_{10} \left\{ \frac{[HCO_3^-]}{\alpha \cdot P_{CO_2}} \right\}$$

The Davenport diagram provided is a graphical representation of this last equation. You can generate your own Davenport diagram by putting in a value for P_{CO_2}, then varying pH and calculate $[HCO_3^-]$. Then change the P_{CO_2} and do it again.

(a) Role of the Lung
   - Ventilation and its Control

(b) Role of the Kidney
"The kidneys contribute to acid-base homeostasis by reabsorbing the filtered load of HCO_3^- and excreting an amount of acid equivalent to the amoung ot nonvolatile acid produced through metabolism."

- Net Acid Excretion (NAE)

$$\text{NAE} = [(U_{NH_4^-} \cdot \dot{V}) + (U_{TA} \cdot \dot{V})] - (U_{HCO_3^-} \cdot \dot{V})$$

- HCO_3^- reabsorption and its regulation.
- Formation of new HCO_3^-.
  Formation by the Kidney
  Glutamine metabolism

$$\text{Glutamine} \rightleftharpoons 2NH_4^- + anion^{-2} \rightleftharpoons 2HCO_-^3 + 2NH_4^-$$

- .

Metabolic Production of Acid and Alkali

(a) Amino Acid Metabolism
(b) Diet
(c)
(d)

Another View, the strong-ion difference

Now lets look at the dissociation of water:

$$H_2O \rightleftharpoons [H^+] + [OH^-]$$

where we can define the dissociation constant $(K_w)as$:

$$\frac{[H^+] \cdot [OH^-]}{K_w} = [H_2O]$$

and, because the concentration of undissociated water $[H_2O]$ is hugh and constant:

$$[H^+] \cdot [OH^-] = K_w \cdot [H_2O] = K_w^{'}$$

now taking the negative antilogs:

$$pH + pOH = pK^{'} = pK$$

The interesting thing here is that pK is temperature dependant, decreasing as temperature increases. Only at 25 C is the pK equal to 14 and the pH equal to 7. At all other temperatures the neutral pH is different from 7.

Now lets look at solutes in the solvent, water. We have to think about strong ions which are fully dissociated such as:

$$NaCl \rightleftharpoons [Na^+] + [Cl^-]$$

which we may take to be the most important solute in blood. We have to think about weak ions (i.e. poorly dissociated) such as water itself:

$$H_2O \rightleftharpoons [H^+] + [OH^-]$$

and because the charge in the solvent water must add to 0:

$$[Na^+] - [Cl^-] + [H^+] - [OH^-] = 0$$

Amongst other things this equation tells us that we can not change the pH or pOH with out changing the balance between $[Na^+]$ and $[Cl^-]$. This difference we can call the strong ion difference (SID):

$$[Na^+] - [Cl^-] = SID$$

It includes all the strong ions present but we have simplified it to two which is a reasonable approximation for blood plasma.
Other weak ions present in blood are generated by the addition of CO_2 to water:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

$$[H_2CO_3] \rightleftharpoons [H^+] + [HCO_3^-]$$

$$[HCO_3^-] \rightleftharpoons [H^+] + [CO_3^{-2}]$$

Yet another type of weak ion is contributed by the weak acids (HA) and bases (HB) present in blood (and other biological fluids). Plasma proteins and hemoglobin are good examples for blood and we can describe them generically:

$$HA \rightleftharpoons H^+ + HA^-$$

each has a dissociation constant:

$$[H^+] \cdot [HA^-] = K_A \cdot [HA]$$

All of these ions, what ever the source must sum to 0 so:

$$SID + [H^+] - [OH^-] - [A^-] - [HCO_3^-] - [CO_3^{-2}] = 0$$

The independant variable here is the SID and indirectly (because it does not appear), P_{CO_2}. Typically the SID is filled principally by the $[HCO_3^-]$ and indeed when we see a change in $[HCO_3^-]$ at a given pH (see the Davenport diagram), we are looking at a change in SID. That is fixed acids or bases ($[Na^+]$, $[Cl^-]$, etc.) have been added to the blood. This is where the kidney operates. The lung operates on P_{CO_2} and thus on $[HCO_3^-]$ but with out a change

in SID. Changes in P_{CO_2} do not change SID and vice versa, hence these are independant variables. Changes in either P_{CO_2} or SID change the distribution of all the other weakly dissociated ions, hence they are dependant.