A basic approach to body pH

THE PHYSICAL DISTANCE BETWEEN EUROPE AND NORTH AMERICA IS PERHAPS A FEW THOUSAND kilometers but from a acid base point of view, we are talking light years. It is sad that acid-base (which should be *relatively* easily understood, now that we have modern computers to do the dirty work for us) is plagued by unnecessary argument. Particularly vituperative comments have come from Severinghaus and Siggaard-Andersen, criticising the work of Stewart and the "strong ion difference" concept. We believe that although Siggaard-Andersen has made a massive contribution to the understanding of acid-base, Stewart has provided a sound mathematical approach which is of great use in understanding acid-base. This article briefly examines Peter Stewart's approach to acid-base. It's best read carefully, but you can jump straight to the calculator, a Java applet that implements his model!

Basis

This web page makes few assumptions about your knowledge. It should be easily *understood* by anyone with a high-school education and a bit of a background in clinical medicine and physiology. We try to keep things simple - if you feel that our tone is patronising, then you are probably too advanced to be reading such simple stuff! Note that *a bit of spadework is still required* to work through the maths - pen and paper remain a wonderful medium for this! Because solutions for the more complex equations require the use of computers, we use a tiny little bit of "computerspeak" - as little as we can get away with! We do however feel obliged to use a star (*) to indicate multiplication and a slash (/) for division. This page does **not** assume that you can speak a computer language.

Remember from physiology that if you have two substances A and B reversibly combining to form substance C, that when the reaction is at equilibrium the equation governing the equilibrium is:

$$[A] * [B] = K * [C]$$

where K is the rate constant for the reaction.

Throughout the body pH is vitally important. Anyone who has a blood pH of below 7.0 is likely to die soon if this isn't corrected. Likewise, a pH of over 7.6 is frequently associated with serious illness and death. Remember that pH is the log of the reciprocal of the hydrogen ion concentration. Why use such a convoluted measure, and not just talk about the concentration of hydrogen ions? The answer is mainly historical but also perhaps reflects the ongoing inability of humans to cope with concepts that cannot be counted on fingers (with perhaps a little help from the toes)! Rather talk about pH 7 than $1 * 10^{-7}$ mol/litre, or (god forbid!) 100 nanomol/l of hydrogen ion.

Unfortunately, such terminology has only served to complicate things, especially when we start plotting how pH changes when we change another ion concentration - we have to continually remember that we are dealing with non-linear axes on any graph we might draw. We will try and clear up some of the confusion. It goes without saying that in any solution mass is conserved (the amount of each component remains constant unless some of that substance is added or removed, either physically or by participating in a chemical reaction), and that any aqueous solution is **electrically neutral** (the number of positive ions equals the number of negative ones). But let's review a few other fundamental definitions:

What is an acidic solution?

We define an acidic solution as one that has a higher concentration of hydrogen ions than of hydroxyl ions. A basic solution is the reverse of this, and a solution is acid-base neutral in the rare circumstance where the concentrations are exactly the same! Simplistically, we then say that an **acid** is something that makes a solution more acidic, while a **base** does the opposite! Note that already the Scandinavian hackles rise, as they fashionably follow Bronsted with his definition of an acid as a "proton donor" and so on - but we have done nothing wicked - we simply use a convenient definition that will have great utility in the clinical arena. We are not pooh-poohing Bronsted, we are simply applying a useful label!

What is a strong electrolyte?

Another convenience is to categorise substances that dissociate when put into water (electrolytes) into two groups. If they dissociate almost totally in the pH range we are interested in, we call them **strong electrolytes** - if only partially dissociated, they are **weak**. Note that we will also refer to ion concentrations in units of *moles of charge* rather than moles of substance, as we are after all more interested in the ionic (charge) properties of the substance than actual concentrations. For example, if each ion has a charge of +2 (say Calcium) then there are twice as many moles of charge as there are moles of calcium.

{ A convenient shorthand is use of the term *normal*, for example if we have 1 mole of Sodium Sulphate in a litre of water, then the solution is *2 normal in the sodium ion* (there are two mol of Na^+ per litre), as well as being 2 normal in sulphate (there is only one mole of SO_4^{--} but it has a charge of 2-). Also note that technically we should be talking about "effective concentration" (or "activity") of an ion rather than concentration, as the two may differ. But for most ions in physiological solutions, the difference is not significant. }

Here is a list of common strong ions (in biological solutions):

- Na^+, K^+, Ca^{++}, Mg^{++}
- Cl^-, $SO4^{--}$
- $lactate^-$

Weak electrolytes (at physiological pH) include the carbon dioxide / bicarbonate system, and reactions involving the proteins found in some body fluids.

What body compartments are there?

In all biology, approximations are necessary. Although each of the perhaps 10^{14} cells in the body is unique, we can define groups of cells and treat them as single entities. Likewise, we have identifiable subsets of body fluids that we can define and analyse. Important components are

- Intracellular fluid

- Interstitial (tissue) fluids including lymph but excluding blood plasma
- Blood plasma
- Gastric secretions
- Pancreatic secretions

  ..but of course there is also..

- Bile
- Saliva
- Fluid within the small bowel
- fluid within the large bowel
- Cerebrospinal fluid
- Synovial fluid (and fluid within bursas)
- The aqueous humour
- .. and so on!

We will concentrate on the first five 'compartments'.

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1. A simple case - Pure Water

Water is weird. This weirdness is the basis of life. Among its most peculiar characteristics are:

- Strongly ionic substances dissociate when placed in water
- Water itself dissociates, but only a little
- Water contains a lot of water!

The last statement deserves a bit of explanation. Because water molecules are small (molecular weight of just $16+1+1 = 18$) the molar concentration of water is enormous - about 55.3 mol/litre at 37 degrees C. There are a billion times fewer hydrogen ions than there are water molecules in a glass of water. Remember that even the hydrogen ion is a convenient fiction - it's just a simple symbol (H^+) for a statistically very complex association between a proton and a whole lot of surrounding water molecules that the proton finds very attractive. The life of the common proton is far more complex than even the most Byzantine modern TV soap opera!

Water dissociates as follows:

$$H_2O <<<===> H^+ + OH^-$$
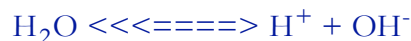
{ This is a very rapid reaction indeed, and we will always assume that equilibrium is reached instantaneously in biological solutions. }

At equilibrium, the following equation must hold:

$$[H^+] * [OH^-] = K_W * [H_2O]$$

As we've already implied by saying that water doesn't dissociate very much, the dissociation constant K_W is rather small, in fact, about $4.3 * 10^{-16}$ Eq/l at 37° Celsius. This is really *tiny*. Also note that K_W varies rather remarkably with temperature - for example at 25 C it is about $1.8 * 10^{-16}$ Eq/l ! If you're smart, you'll immediately realise that the pH of a glass of water

changes dramatically as its temperature changes! Further contemplation will also assure you that we can assume a new constant

$$K_W' = K_W * [H_2O]$$

because the tiny changes in water concentration will be totally insignificant compared with the total amount of water present.

K_W' is just a convenient label for the product of the two constants, K_W and the molar concentration of water.

{ As an aside, you can approximate the value of K_W' by: $K_W' = 8.754 * 10^{-10} * e^{(-1.01*10^6) / T^2}$ where temperature T is expressed in degrees Kelvin}

Okay, so how do we find the pH of pure water?

From the above we know that

$$[H^+] * [OH^-] = K_W'$$

But it is clear that even if we know K_W', we still need to find one of the other variables, the hydroxyl ion concentration, if we are to determine the hydrogen ion concentration. Fortunately, in pure water the only ions present are hydrogen ion and hydroxyl ion, so if the water is to be <u>electrically neutral</u> then:

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

We now have two simultaneous equations, and it is easy to see that $[H^+] = [OH^-]$, so $[H^+]$ is the square root of K_W'. We can also see the practical significance of our <u>definition</u> of an acid-base neutral solution - if the hydrogen and hydroxyl ion concentrations are the same, then

$$[H^+] * [H^+] = K_W'$$

which is another way of saying that **a solution is acid-base neutral if the hydrogen ion concentration is equal to the square root of the K_W'**. The definitions of acid (acidic) and alkaline (basic) solutions follow accordingly:

A solution is acidic if $[H^+] > ROOT (K_W')$

A solution is basic if $[H^+] < ROOT (K_W')$

where "ROOT" is just our way of saying that we are taking a square root.

2. Strong ions in Water

Take some water. Add strong electrolytes, such as NaOH and HCl, which we know will almost completely dissociate. We now have a heady mix of water, Na^+, Cl^-, H^+ and OH^- ions. What will happen to the hydrogen ion concentration in this mix?

We already know that water dissociation constrains us to:

$$[H^+] * [OH^-] = K_W' \quad .. \text{ Equation \#0}$$

and we can readily deduce that electrical neutrality ensures that:

$$[H^+] - [OH^-] + [Na^+] - [Cl^-] = 0 \quad .. \text{ Equation \#1}$$

We can therefore substitute $K_W'/[H^+]$ for $[OH^-]$ in Equation #1, and determine $[H^+]$. We get an equation:

$$[H^+] - K_W'/[H^+] + [Na^+] - [Cl^-] = 0$$

which we can readily tweak by multiplying throughout by $[H^+]$:

$$[H^+]^2 + [H^+] ([Na^+] - [Cl^-]) - K_W' = 0$$

At last! A use for quadratic equations!
The above is a standard quadratic equation of the form:

$$a*x^2 + b*x + c = 0$$

We know from our high school days that the solution of such an equation is given by:[1]

$$x = - b/2a +- \textbf{ROOT (} (b/2a)^2 - c/a \textbf{)}$$

Substituting in for a=1 b= $[Na^+] - [Cl^-]$ and c = $- K_W'$ this gives us the formula:

$$[H^+] = \textbf{-} ([Na^+] - [Cl^-])/2 + \text{ROOT} (([Na^+] - [Cl^-])^2/4 + K_W')$$

If we know the amount of sodium and chloride ion in solution, we can readily determine the hydrogen ion concentration. Even more elegantly, we can determine the result for any solution containing only strong ions! We simply fill in the concentrations of those ions in solution, where we had Na and Cl! The perceptive reader will realise that it is only the *difference* in ionic concentrations that matter - we can abbreviate the above equation to:

$$[H^+] = \text{ROOT} (K_W' + SID^2/4) - SID/2 \quad .. \text{ Equation \#2}$$

where **SID** is our abbreviation for the difference between the concentrations of the strong base cations (eg Na^+) and the strong acid anions (eg Cl^-). SID is what Stewart calls the **Strong Ion Difference** .. an extremely useful concept. For a detailed consideration of this elegant solution, see Stewart's book. Similarly,

$$[OH^-] = \text{ROOT} (K_W' + SID^2/4) \textbf{+} SID/2 \quad .. \text{ Equation \#3}$$

Note that if SID is negative, then the hydrogen ion concentration is always greater than the hydroxyl ion concentration. The converse holds for a positive SID. In these solutions it is clear that if the hydrogen ion concentration changes the **SID must have changed**.

If SID is positive and bigger than about 10^{-6} Eq/l you can see that K_W becomes insignificant,

and Equation #3 becomes very nearly the same as:

$$[OH^-] = [SID]$$

We can use this and Equation #0 to derive the hydrogen ion concentration:

$$[H^+] = K_W' / [SID]$$

{ If the SID is **negative** and bigger than about 10^{-6} Eq/l then Equation #2 simplifies out to: $[H^+] = -[SID]$ but such solutions are not commonly encountered in biological systems. }
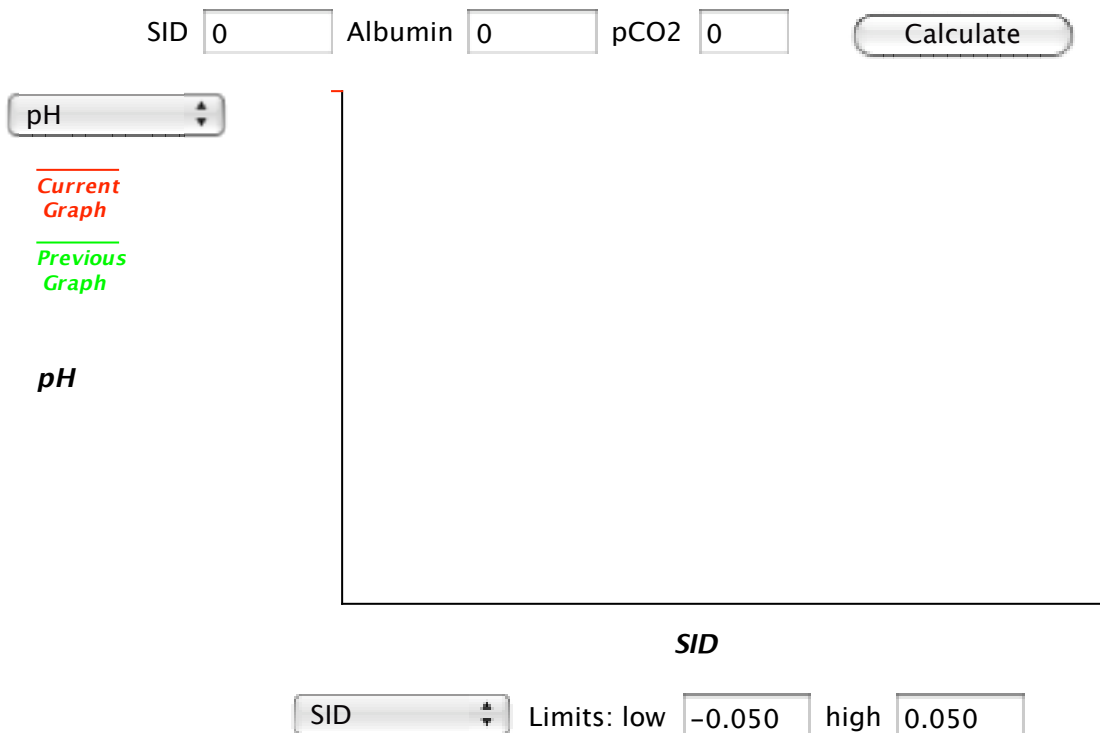
"Okay, this is all very well" you say "but **what is the practical significance of all this maths?**" Easy. The above tells us that in a solution containing strong ions, if you want to calculate the pH, you must:

1. Know the concentrations of the strong ions, and
2. Plug these values into the equations;

before you can work anything out. And if you add basic or acidic substances, you cannot just say "We added so much sodium hydroxide so the pH will change by so much". You have to work things out using the above equations. Conversely, if you know the values, they are sufficient to work out the pH.

You can also see that if we have (for example) an acidic solution and we progressively add base, there will be a sudden, rapid rise in pH as we approach the point where [SID] is zero, and then add just a tiny bit more base. Consider the following diagram (our applet) showing how pH changes with SID - Press the button!

Press the 'Calculate' Button!

SID `0`   Albumin `0`   pCO2 `0`   [Calculate]

[pH ▲▼]

_____
Current Graph

_____
Previous Graph

pH

SID

[SID ▲▼]   Limits: low `-0.050`   high `0.050`

pH is easily measured so now we finally understand the concept of "titratable acidity" of for example urine (we add base until there is a sudden rise in pH and this is the point where

"titration is complete" - that is, the SID of the solution is zero). But remember that this doesn't tell us what titratable acidity *means*, and also note that the "sudden change in pH" is an artefact induced because pH is logarithmic: nothing that dramatic happens if we look at actual hydrogen ion *concentration*! Try this - in the above applet, change the Y axis parameter from *pH* to *[H+]* and press on the **Calculate** button again!

It is instructive to read Stewart's book where he looks at titration of interstitial pH using HCl - the counter-intuitive nature of pH is clearly seen.

Gaps & Gamblegrams

Electrical neutrality in solution demands that Equation #1 is satisfied - the sum of [negative] and [positive] ions is always zero. This is conveniently represented by two adjacent bar plots as shown in the following illustration (after Stewart, p43).
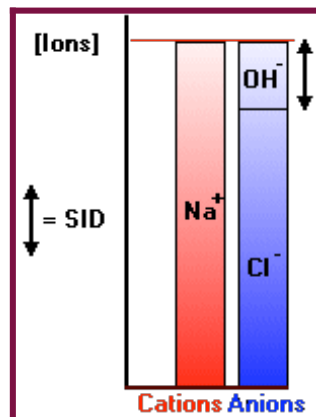

The solution is a simple one containing $[H^+]$, $[OH^-]$, $[Na^+]$ and $[Cl^-]$. The bar plot (Gamblegram) clearly shows the disposition of ions. The minuscule amount of H^+ ion is not shown. Such plots can be used for far more complex solutions, often with unmeasured ions (where the term "gap" is often used, as in "anion gap"). It is crystal clear from the plot that the SID is equal to the amount of hydroxyl ion. In alkaline solutions the SID will be positive, in acidic, negative.

3. A more complex setup - Adding a weak electrolyte

Adding a weak electrolyte (one that only partially dissociates in the pH range we are considering) complicates things rather a lot. In body fluids such as plasma, the most important weak electrolyte is albumin, but the principles hold for all weak electrolytes.

A weak acid

Let's look at the case of a weak acid, HA (such as albumin) that dissociates to form H^+ and A^-, as follows:

$$HA <===> H^+ + A^-$$
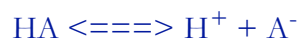
As above, we can work things out if we have the correct numbers, and plug them into the relevant equations. Two of the equations we already know, those governing the dissociation of water and the requirement for electrical neutrality (slightly modified to include the dissociated anion A^-, derived from the acid):

$$[H^+] * [OH^-] = K_W' \quad \text{.. Equation \#0}$$

$$[H^+] + [OH^-] + [SID] + [A^-] = 0 \quad \text{.. Equation \#1A}$$

The other two equations are not too difficult, as they are based on the dissociation of the acid, and the necessity for conservation of the total amount of acid, which we abbreviate to A_{TOT}. These are (in turn):

$$[H^+] * [A^-] = K_A * [HA] \quad \text{.. Equation \#4}$$

$$[HA] + [A^-] = [A_{TOT}] \quad \text{.. Equation \#5}$$

Unfortunately for people such as myself who are used to counting on their fingers, the solution of the above four equations is based on cubic equations. Fortunately, when we use digital computers to solve such equations, the difficulty evaporates! We explore this below. When we actually go to the bother of solving the equations, we reach several initially rather counter-intuitive conclusions.

1. The weak acid is only really important in the range where SID is between zero and $[A_{TOT}]$. Outside this range the hydrogen ion concentration changes in much the same way as it does without the presence of the weak acid. When [SID] is negative, then $[A^-]$ becomes tiny, and so $[H^+]$ approximates − [SID].

   On the other hand, with [SID] > $[A_{TOT}]$, OH^- have to fill the gap between the two (for $[A^-]$ can't of course exceed $[A_{TOT}]$), so $[OH^-] = [SID] - [A_{TOT}]$. Consider the following:

Press the 'Calculate' Button!

SID `0`   Albumin `0`   pCO2 `0`   (Calculate)

| pH ⇅ |

Current Graph

Previous Graph

pH

SID

[SID ⇅] Limits: low `−0.020` high `0.050`
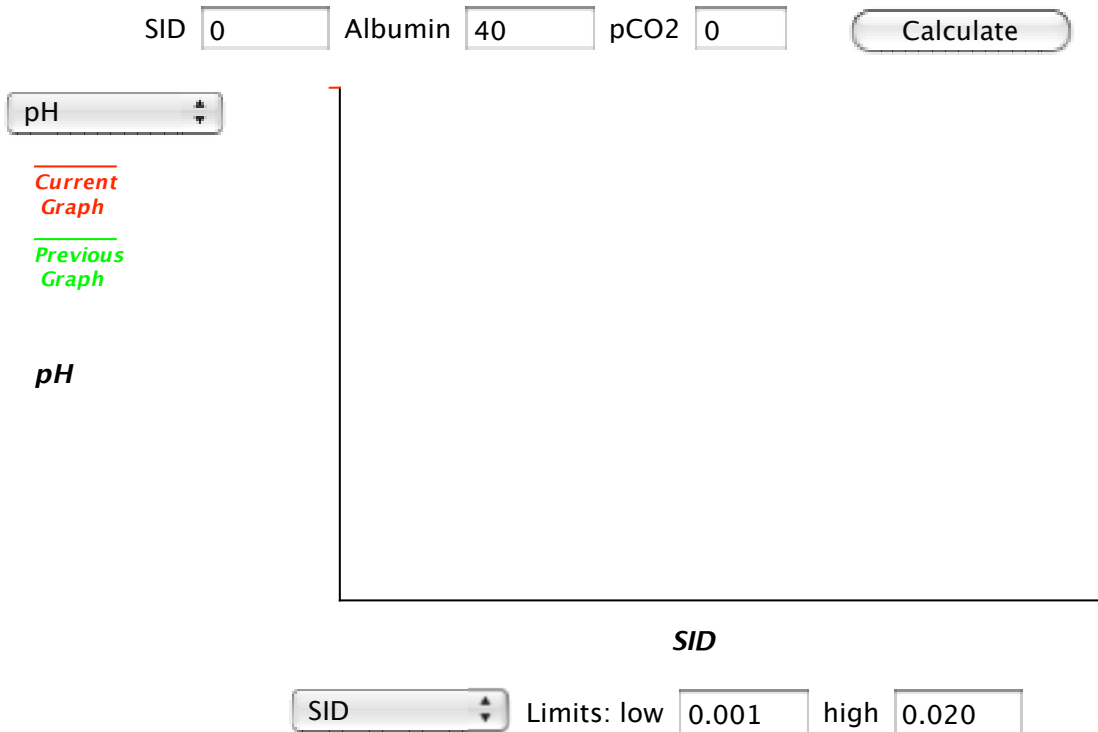
Click on **Calculate** and then change the Albumin value to say 40, and click once

more. The difference between the two curves is clearly seen - albumin only really has an effect between an SID of zero and an SID of about 0.02. (An albumen of 40 g/litre more-or-less corresponds to an A_{TOT} of 0.016 Eq/l, perhaps a bit less)!

2. Inside this range of 0 .. $[A_{TOT}]$, hydrogen ion concentration changes **more** rapidly with [SID] than is the case where no weak acid is present! This **destroys our conventional view** that weak acid "buffers" lessen the impact of a pH change - the presence of a weak acid causes $[H^+]$ to change more rapidly with changing [SID] !

Press the 'Calculate' Button!

SID `0`   Albumin `40`   pCO2 `0`   (Calculate)

| pH ⇕ |

___
Current Graph

___
Previous Graph

pH

SID

[SID ⇕]   Limits: low `0.001`   high `0.020`

Click on the above graph to get the picture with an albumin of 40g/l, and then decrease the albumin to 0 and click again - notice how the new, red, albumin-free graph changes LESS steeply! Wham!

3. The point where $[H^+] = [OH^-]$ is **NOT** necessarily where $[SID] = [A_{TOT}]$!

It is best to play extensively with the actual equations in order to see how truly non-intuitive their effects are! Remember that in order to predict any result of altering the nature of a strong ion solution containing a weak acid, we need to know:

1. [SID]
2. $[A_{TOT}]$
3. K_A
4. K'_W

Without even one of these four, you are stymied, and cannot for example predict pH. Note that in this example, (as in all the others on this page) we have **dependent** and **independent** variables. Things that we change by external maneuvers (such as [SID] or $[A_{TOT}]$) are independent variables.

Values that respond to such changes (e.g. pH) are dependent variables.

> **WE MUST KNOW ALL THE INDEPENDENT VARIABLES**
> **IN ORDER TO CALCULATE THE DEPENDENT ONES!**

A weak base

Calculations for a weak base are similar to the case of the weak acid above. In an analogous way, added weak base is most effective in the SID range zero to $-[B_{TOT}]$. The difference is that buffering here does occur: the base flattens the $[H^+]$ versus $[SID]$ curve very effectively!

Solving equations using computers

If you've successfully come this far, the following section should not be beyond your capabilities, even if computers scare you witless! You may however skip the following computerese. If you choose to read it, then also get a piece of paper and write down the equations, and work things out. We take the equations from above:

$$[H^+] * [OH^-] = K_W' \quad .. \text{ Equation \#0}$$

$$[H^+] + [OH^-] + [SID] + [A^-] = 0 \quad .. \text{ Equation \#1A}$$

$$[H^+] * [A^-] = K_A * [HA] \quad .. \text{ Equation \#4}$$

$$[HA] + [A^-] = [A_{TOT}] \quad .. \text{ Equation \#5}$$

Our approach:

1. First, we identify the independent variables (K_W', $[SID]$, $[A_{TOT}]$ and K_A), and the dependent ones ($[H^+]$, $[OH^-]$, $[HA]$ and $[A^-]$).

2. Next, eliminate all the dependent variables apart from $[H^+]$ from the equations. We do this by substitution -
   we can derive that:

   $$[OH^-] = K_W' / [H^+] \quad \text{(from Equation \#0)}$$

   $$[HA] = [A_{TOT}] - [A^-] \quad \text{(from Equation \#5)}$$

   and by substituting the latter into Equation #4,
   $$[A^-] = Ka * [A_{TOT}] / ([H^+] + K_A)$$

3. We substitute these values into Equation #1A, and we get:

$$\mathbf{[SID] + [H^+] - K_W' / [H^+]] - K_A * [A_{TOT}] / (K_A + [H^+]) = 0}$$
$$.. \text{ Equation \#6}$$

One can sit down and turn the above into a third order polynomial, but because we are simple-minded people, we will abbreviate it to:

$$F([H^+]) = 0$$

Look at Equation #6 carefully - assume we know the value of $[H^+]$. If we fill in *this* value, then the left hand side of the equation will be zero (of course). But let's say we are not quite sure of $[H^+]$. We guess its value. Plug *this* guessed value in, and we find something very exciting - if the guessed value is too big, then when we plug in the value, the result is **positive**. And if the guess is too small, the result is **negative**. From the *sign* of the result, we know whether our guess was too big or too small. We have a way of testing our guesses! Even better, if we have a guess that is too big and one that is too small, we *know* that the true value must be somewhere in between, so we can progressively narrow down the true range within which our target lies. We will never quite reach a "true" value for $[H^+]$, but we can get as close as we jolly well like, effectively conquering our cubic equation!

4. How do we implement this practically? The solution is simple enough - we can write it out as a series of steps:

    1. Make two outrageously wrong guesses for $[H^+]$ - a very small and a very large one (so that you know the true value is somewhere in between). Remember these (we'll call them TOO_SMALL and TOO_BIG);

    2. Using TOO_SMALL and TOO_BIG, make a guess somewhere in between them (A cunning way of doing this is to kind of average the two numbers by multiplying them together and then taking the square root)!
        Call the value of your "guess" MY_GUESS

    3. Plug MY_GUESS into Equation #6, and take a look at the result:
        - IF the result is NEGATIVE, then MY_GUESS is too small. But MY_GUESS is still bigger than the value in TOO_SMALL, so TOO_SMALL is really far too tiny! We are absolutely sure we can replace the value in TOO_SMALL with the value in MY_GUESS. Do So.
        - OTHERWISE, if the result is POSITIVE, then MY_GUESS is too big. But wait a bit! TOO_BIG must then be enormously too big, so we can take the value from MY_GUESS and put it into TOO_BIG.

    4. Now we have a situation where one of our outrageously wrong guesses has become more accurate. You can see that every time we repeat the whole process (using the new improved guess), we progressively move both outer limits in towards the true value. When we get "close enough" to the true value, we can stop.

    5. Whew! Not too difficult. We call the above description of "how to do it" an "algorithm". The actual process by which we progressively move closer and closer to our goal is "iteration".

A program to do this

Many people are terrified of computers - an unnecessary state of mind, as all computers do is give us a way of implementing an algorithm like the one above in a fast and accurate way! In order to implement our algorithm we need to express it in an unambiguous way. We use statements written in a computer language to do so.

We will now 'formalise' the above algorithm. We won't yet write it in a specific computer language, we will just make things more precise, without (we hope) compromising readability. Our only assumptions are:

1. We have something (a function) called **ROOT** that somehow works out a square root
2. The function **F(MY_GUESS)** works out Equation #6
3. the function **ABS** works out the absolute value of a number. That is, ABS(-0.001) and ABS(0.001) give the same result, 0.001.

TEA BREAK!

If you were unwise enough to read the above in one sitting, we suggest that you take a tea break to marshal your resources!

Remember the fundamentals:

- There are complex and often non-intuitive relationships between the various components involved in acid-base.
- We must decide what are *dependent* variables and which ones are *independent*.
- If we alter an independent variable, then the dependent variables **will** change.
- If we observe a change in a dependent variable (such as $[H^+]$ or pH) then there **must have been** a change in at least one of the independent variables.

4. Strong ions with Carbon dioxide

People who are familiar with acid base as it is commonly taught, usually cut their teeth on the Henderson-Hasselbalch equation. There is little wrong with the H-H equation, other than the fact that it only represents *part of the truth*. Here we start to explore how carbon dioxide behaves, but in what we regard as the proper context. Much of the following may seem familiar, but be careful - don't lose sight of the big picture!

Take our familiar mixture of strong ions and water, and expose it to CO_2. What happens? Four things can happen to CO_2 gas when exposed to water - it can dissolve, react with water to form carbonic acid, or even form bicarbonate or carbonate ions. We will explore each of these in turn, but the two most significant reactions are the formation of carbonate and bicarbonate, as each has its own equilibrium constant. By now you will realise that these reactions with their equilibrium constants will have a profound influence on the whole system, and it is only *in the context of the whole system* that we can understand the role of carbon dioxide. Let's see:

1. **CO_2 can dissolve**, as expressed by the equation:

$$CO_{2(gas)} <=====> CO_{2\ (dissolved)}$$
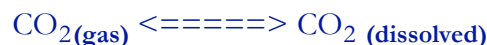
Forward Reaction	Reverse Reaction
===> Depends on partial pressure of CO_2	<=== Depends on concentration of dissolved CO_2

Rate of forward reaction = K_f * P_{CO2}	Rate of reverse reaction = K_r * $[CO_2$ $_{(dissolved)}]$

..AT EQUILIBRIUM..

$$[CO_{2(dissolved)}] = S_{CO2} * P_{CO2}$$ .. Equation #7A

For K_f/K_r we have substituted S_{CO2}, otherwise called the *Solubility of CO2*. In other words, the amount of dissolved CO_2 depends on the partial pressure of CO_2 times a rate constant. S_{CO2} is dependent on temperature, and at 37 C it is about $3.0 * 10^{-5}$ Eq/litre/mmHg. Note that if we are examining a fluid that isn't in contact with gas, we still talk about a partial pressure of that gas in solution "as if" it were exposed to, and in equilibrium with, a gas containing that gas at that partial pressure. This is just another convenient way of representing the concentration of dissolved gas in solution.

2. **CO_2 can react with water** to form carbonic acid:

$$CO_2 + H_2O <==> H_2CO_3$$

Equilibrium is represented by:

$$[CO_{2(dissolved)}] * [h30] = K * [H_2CO_3]$$ .. Equation #7B

If we treat [h30] as constant, and rearrange things a bit we get:

$$[H_2CO_3] = K_H * P_{CO_2}$$

The value of K_H at 37 C is $9 * 10^{-8}$ Eq/litre - because of this, the H_2CO_3 concentration is far smaller than the amount of dissolved CO_2.

The reaction of CO_2 with water is **SLOW** , with a half time of about 30 seconds, fortunately speeded up to microseconds by the *carbonic anhydrase* abundantly present in most tissues.

3. **H_2CO_3 thus formed can dissociate** into bicarbonate and hydrogen ions:

$$H_2CO_3 <==> H^+ + HCO_3^-$$

Equilibrium is represented by:

$$[H^+] * [HCO_3^-] = K * [H_2CO_3]$$

It follows that:

$$[H^+] * [HCO_3^-] = K_C * P_{CO2}$$ .. Equation #8

A good value for K_C is $2.6 * 10^{-11}$ $(Eq/l)^2/mmHg$.

4. Once formed, **HCO_3^- may rapidly dissociate**:

$$HCO_3^- <==> H^+ + CO_3^{2-}$$

Equilibrium is represented by:

$$[H^+] * [CO_3^{2-}] = K_3 * [HCO_3^-] \qquad .. \text{ Equation } \#9$$

A typical value for K_3 is $6 * 10^{-11}$ Eq/litre.

The big picture - finding the pH!

As usual, we need four simultaneous equations to work out all the dependent variables (given the independent ones). These are our old familiar equation #0, Equations #8 and #9, and the requirement for electrical neutrality:

$$[H^+] * [OH^-] = K_W' \qquad .. \text{ Equation } \#0$$

$$[H^+] * [HCO_3^-] = K_C * P_{CO2} \qquad .. \text{ Equation } \#8$$

$$[H^+] * [CO_3^{2-}] = K_3 * [HCO_3^-] \qquad .. \text{ Equation } \#9$$

$$[SID] + [H^+] - [OH^-] - [HCO_3^-] - [CO_3^{2-}] = 0 \qquad .. \text{ Equation } \#10$$
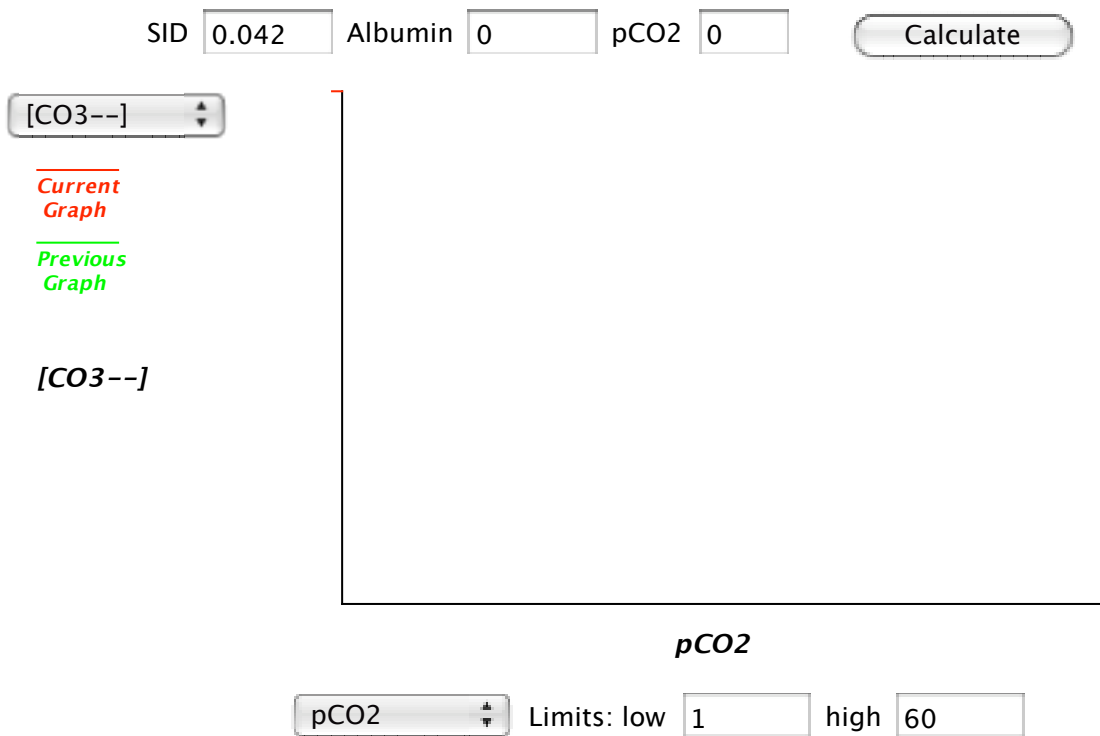
It is important to distinguish between dependent and independent variables. Bicarbonate concentration and hydrogen ion concentration are *dependent* variables, but SID and pCO2 are independent!

We work out our equation for $[H^+]$ in the same way we did in Section 3 above, and solve it using a computer, again as above. On contemplating the results thus obtained, a whole host of interesting conclusions emerge. These include:

- Where the SID is negative, the excess negative strong ions must be balanced by positive ions (H^+ being the only candidate) so OH^-, HCO_3^- and HCO_3^{2-} become rare and endangered species - their concentration becomes negligible.

- With a positive SID, $[HCO_3^-]$ very accurately approximates SID. This equality is immensely useful, and also implies that *$[HCO_3^-]$ is independent of P_{CO2} in interstitial fluid!* (at least in the physiological range).

- Totally counter-intuitive is that $[CO_3^{2-}]$ **decreases** with increasing PCO2!! Conversely, if we lower the PCO2 enough, carbonate levels, although tiny, may rise to a point where the solubility product for calcium carbonate (10^{-8}) is exceeded. This may lower calcium levels, causing tetany! Click on the calculate button below, to see how carbonate concentration

increases as PCO2 decreases:

Press the 'Calculate' Button!

SID `0.042`   Albumin `0`   pCO2 `0`   [Calculate]

[CO3−−] ▲▼

___
Current Graph

___
Previous Graph

[CO3−−]

pCO2

[pCO2 ▲▼] Limits: low `1` high `60`

---

and a Weak Acid

The combination of strong ions, carbon dioxide and a weak acid closely models blood plasma, but also provides a fairly accurate representation of intracellular fluids. Blood plasma is rich in weak acids, the majority being proteins. For the purposes of analysis it is probably moderately accurate to regard them as being all one acid with a single A_{TOT} and single K_A. This assumption is not however central to Stewart's work - as is seen in the articles by Figge et al who extend his model with multiple K_a's.

Following the pattern we established in previous sections, we identify the independent variables ([SID], P_{CO2}, A_{TOT} which are respectively the strong ion difference, partial pressure of CO_2 and the total amount of weak acid present). In addition, we need to know K_W', K_A, K_C and K_3. Given these, we can calculate any one of eight dependent variables:

HCO_3^-, A^-, HA, CO_2 **(dissolved)**, CO_3^{2-}, H_2CO_3, OH^-, and H^+. Note that dissolved CO_2 and H_2CO_3 are easily determined from Equations #7A and #7B.

Exactly as we have done before, we derive six simultaneous equations, most of which are old friends:

$$[H^+] * [OH^-] = K_W' \quad .. \text{ Equation } \#0$$

$$[H^+] * [A^-] = K_A * [HA] \quad .. \text{ Equation } \#4$$

$$[HA] + [A^-] = [A_{TOT}] \qquad .. \text{ Equation } \#5$$

$$[H^+] * [HCO_3^-] = K_C * P_{CO2} \qquad .. \text{ Equation } \#8$$

$$[H^+] * [CO_3^{2-}] = K_3 * [HCO_3^-] \qquad .. \text{ Equation } \#9$$

and finally, to maintain electrical neutrality:
$$[SID] + [H^+] - [HCO_3^-] - [A^-] - [CO_3^{2-}] - [OH^-] = 0$$

The equation that we derive in an analogous fashion to our method <u>above</u> where we discussed a computer solution is..

$$[SID] + [H^+] - K_C * P_C / [H^+] - K_A * [A_{TOT}] / (K_A + [H^+]) - K_3 * K_C P_C / [H^+]^2 - K_W' / [H^+] = 0$$

.. and the computer approach is just the same.

"ionz" - an acid-base Calculator

Try experimenting further with our Java applet for blood plasma. This applet uses the above equation and iterative approach. First, simply press the "calculate" button. Then **play** - try seeing what happens to pH as you vary the SID and Albumin level. Then change the independent variable (on the X axis). Later you can see how other dependent variables (eg CO_3^{--}) change with variations in e.g. pCO2.

Press the 'Calculate' Button!

SID `0.042`   Albumin `43`   pCO2 `40`   [Calculate]

[pH ▲▼]

Current Graph

Previous Graph

pH

pCO2

[pCO2 ▲▼] Limits: low `20` high `60`

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Afterword

I'd like to thank everyone for their feedback (mainly positive) about this page, particularly Rinaldo Bellomo and John Kellum, who have contributed enormously to spreading the news about the physicochemical approach, and also Jon Waters, and Philip Watson. A good website that explores both the traditional, and now the Stewart approach, is that of Kerry Brandis.

Thanks too to PJ Hilton, who pointed out a typo in Stewart's book, which we carried over in a mildly embarrassing fashion.

Recent developments are explored on yet another page on anaesthetist.com. Further constructive comment is of course still welcome. By the way the actual distance between Brown University (Stewart) and Copenhagen (Siggaard-Andersen) is 5958 km, just for the record.

References

- Stewart PA *How to Understand Acid-Base. A Quantitative Acid-Base Primer for Biology and Medicine* 1981 Edward Arnold. ISBN 0-7131-4390-8. In our opinion, this book is pure gold. Get a copy!

    {It's a tragedy that Peter Stewart is dead - the man was a genius}}

- Stewart PA *Can J Physiol Pharmacol 1983 61 1444* A good overview of modern acid-base.

- Figge J, Rossing TH, Fencl V. *J Lab Clin Med 1991 117 453-67* A detailed experimental exploration of the variation of dependent variables as we alter the independent ones. Experimental validation and extension of Stewart's work. See also the following paper.

- Figge J, Mydosh T, Fencl V. *J Lab Clin Med 1992 120 713-9* A follow up on the previous article, using NMR spectroscopic measurements of the pK of histidine residues on albumin to refine their model.

- Severinghaus JW *Scand J Clin Lab Invest 1993 53 S214 99-104*. Severinghaus seems to have been smouldering for the past twenty odd years. Here, he burst into flame.

- Siggaard-Andersen O & Fogh-Andersen N *Acta Anaesthesiol Scand 1995 39 Supp 107 123-8*. It would seem clear from this article that Siggaard-Andersen has (at least partially) read Stewart. Has he understood? His "refutation" does not unfortunately explore the mathematics of Stewart's work.

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