ACID BASE AND THE REGULATION OF RESPIRATION *

Summary: The avenues of CO₂ transport are discussed followed by a detailed look at blood acid-base balance and the role of CO₂ in this balance. The Davenport diagram is introduced as a means of visualizing acid base disturbances and compensations.

I. THE ACID-BASE BALANCE OF THE BLOOD AND ITS REGULATION:
   A. Introduction to and Review of pH Buffers:
      1. Plasma pH is tightly regulated; we want to consider some of the factors that are involved in the determination and regulation of blood-acid base balance.
      2. Let's remind ourselves that buffers exist when we have a solution of a weak acid and its conjugate base and that they RESIST BUT THEY DO NOT PREVENT pH CHANGES.
      3. In the body, we generally deal only with weak acids (the stomach being one big exception). We can describe the state of a weak acid in terms of the degree of dissociation of the weak acid:

         1. HA ⇌ H⁺ + A⁻

         where HA is the acid and A⁻ is its conjugate base.

         The mass-action ratio or DISSOCIATION CONSTANT (K) for this reaction is:

         2. \[ K = \frac{[H^+][A^-]}{[HA]} \]

         by re-arranging equation #2, we can write:

         3. \[ [H^+] = K^+ \frac{[HA]}{[A^-]} \]

         we can convert this into an equation with a log form:

         4. \[ \log [H^+] = \log K + \log \left( \frac{[HA]}{[A^-]} \right) \]

         This can be simplified: since \( pH = - \log [H^+] \); thus we can multiply the equation #4 by -1 and then substitute \( pH \) for \( -\log[H^+] \):

         5. \[ - \log [H^+] = - \log K - \log \left( \frac{[HA]}{[A^-]} \right) \]

         or (next page)

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6. \[ \text{pH} = - \log K + \log \left( \frac{[\text{conjugate base}]}{[\text{acid}]} \right) \]

If we now define the **negative log of the dissociation constant** as being the \( pK_a \), we can re-write eq.6 as:

7. \[ \text{pH} = pK_a + \log \left( \frac{[\text{conjugate base}]}{[\text{acid}]} \right) \]

This equation is known as the **HENDERSON-HASSELBALCH EQUATION**

Now let's consider an important special case that explains what the \( pK_a \) is and what it means. **Suppose we wish to know the pH where buffer is most effective.** Obviously, this will be the pH where the concentrations of the conjugate base and acid are equal since a disturbance in either direction can be resisted. If we substitute equal values for these two species into the Henderson-Hasselbalch equation:

8. \[ \text{pH} = pK_a + \log \left( \frac{[\text{A}^-]}{[\text{HA}]} \right) \]

and since \([\text{A}^-] = [\text{HA}]\), then

9. \[ \text{pH} = pK_a \]

Here are a few common misconceptions to **get over now** -- before we go on further in our discussions of acid base:

First and foremost, **the only thing that matters in determining pH is the[H⁺]**. Notice that it is determined by the pKa, concentrations of the weak acid and conjugate base -- not by just one of these factors.

So -- the [base] is not a primary concern. Base only matters to the extent that the base helps to determine the amount of H⁺ in the solution. The same thing can be said for the concentration of the weak acid.

Notice that if more acid dissociates, the pH goes down as expected. But **what commonly surprises folks is that the concentration of the base increases**. Free yourself of the notion that every base molecule somehow finds every H⁺ and reacts with and neutralizes it. An instant of thought shows this to be total bunk, yet it is a very common notion for people to have. Finally, notice that the pKa says something about the relative mix of acid and base at a given [H⁺] -- as it should since it is the negative log of the dissociation constant. More about this below, just think about it for the moment.
Thus, the $pK_a$ gives the pH where a buffer is most effective. We can graph the behavior of a buffer system with respect to how $pH$ changes as the system is titrated:

![Graph showing pH changes around the pKa](image)

Note that for approximately +/- 1 pH unit around the $pK_a$ the buffer is very effective at resisting the effects of adding or removing $H^+$. Thus, the value of the $pK_a$ when compared to the actual $pH$ of the system is an indication of the buffering ability or contribution of the given buffer.

Suppose that the pKa (see above) of an acid is 6.1 (e.g., carbonic acid) as we will treat it in the body. It is now placed in a chemical environment such that other compounds add or remove $H^+$ to the solution (i.e., it is placed in a solution where it can act as a pH buffer).

(i) At a $pH$ of 7.4, in what form is most of this acid-base system -- acid or conjugate base? (ii) How about at $pH$ 6.1? (iii) At $pH = 5.0$? (iv) Which of these solutions has the most free $H^+$? (v) The least?

**ANS:** (i) conjugate base, (ii) equal, (iii) acid, (iv) $pH$ 5.0, (v) $pH$ 7.4. Be able to explain all these answers in some detail.

There is one other factor that is important in understanding the effectiveness of a buffer system: the **AMOUNT (usually the equivalent of the CONCENTRATION) of the buffer**. Thus, even if a buffer is operating far from its $pK_a$, it can still be an important buffer if enough of it is present. The reason is that the ability to release or absorb a given number of $H^+$ ions is not only related to the pKa vs. $pH$ but also to the total number of molecules available to react.

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4. The important buffers in the blood are the **bicarbonate buffer system**, the **phosphate** (H$_2$PO$_4^-$ $\leftrightarrow$ HPO$_4^{2-}$) buffer, and **hemoglobin**.
   a. Phosphate and Hb are important since their pK$_a$'s (meaning the overall pK$_a$ for Hb) are close to the physiological range.
   b. Hb is especially important since there is so much
   c. Bicarbonate is important due to its **abundance**. Its pK$_a$ is **6.1** (remember this number).

5. In organisms, we must deal with several acid-base systems that are in action simultaneously. As a reminder, the primary ones that we need to consider are:
   (i) H$_2$CO$_3$ $\leftrightarrow$ HCO$_3^-$ (bicarbonate buffer system)
   (ii) H$_2$PO$_4^-$ $\leftrightarrow$ HPO$_4^{2-}$ (phosphate buffer system)
   (iii) R-NH$_3^+$ $\leftrightarrow$ R-NH$_2$ (proteins and a. acids, Hb is most important in the plasma).

The strength of the phosphate buffer system is partially controlled hormonally via the action of **CALCITONIN** and **PARTHORMONE** and their actions on the phosphate pool in the bones -- both can affect phosphate levels by changing the net addition of subtraction of Ca$^{++}$ salts in the bones.

6. **In a given body "compartment"** (such as the plasma or the intracellular fluid, etc.), the **pH** is the same for all of these acid-base systems since they are all in equilibrium with the same pool of H$^+$.  
   a. We can state a rule called the **ISOHYDRIC PRINCIPLE**: if we know the ratio of $K$ * $[HA] / [A^-]$ for any one buffer of a complex set of buffers, we know it for all of them since we can write the following relationship (eq. #4) for each buffer system:

   \[
   [H^+] = K_1 * \frac{[HA_1]}{[A_1^-]}; \quad \text{and} \quad [H^+] = K_2 * \frac{[HA_2]}{[A_2^-]}
   \]

   or more completely:

   \[
   [H^+] = K_1 \frac{[HA_1]}{[A_1^-]} = K_2 \frac{[HA_2]}{[A_2^-]} = K_3 \frac{[HA_3]}{[A_3^-]} = K_4 \frac{[HA_4]}{[A_4^-]} etc., \quad etc.
   \]

   b. Thus, although all of the buffer systems help to determine the plasma pH, we only need to study one of them in order to understand the overall action of the PLASMA BUFFER SYSTEM.
7. The buffer system that we study and monitor the most is the bicarbonate buffer system. By doing this, we know much of what is happening in the other systems, since a disturbance in any one buffer affects all of the systems.

8. In addition, the bicarbonate buffer system is of interest since it is the one that can be changed the most rapidly — since the system is in equilibrium with CO₂, any change in respiration will change this system. Thus, we know that most short-term regulation of plasma pH is achieved through the regulation of the bicarb. system.

9. We can re-write the Henderson-Hasselbalch eq. (# 7) for the bicarb system:

\[ \text{pH} = pK_a + \log \left( \frac{[\text{HCO}_3^-]}{\text{acid}} \right) \]

10. Now, recall that the acid, \( \text{H}_2\text{CO}_3 \), is in equilibrium with dissolved CO₂. This means that in effect the CO₂ acts as if it were part of the acid pool. Thus, the amount of acid available for this buffer system is more like the sum of the \( \text{H}_2\text{CO}_3 \) and dissolved CO₂ than it is the \( \text{H}_2\text{CO}_3 \) by itself. Since the equilibrium of the reaction CO₂ + H₂O \( \rightleftharpoons \) carbonic acid is far to the left (there are about 500 molecules of CO₂ per molecule of \( \text{H}_2\text{CO}_3 \) (acid) at equilibrium), and since CO₂(d) is easy for us to measure, we can use dissolved CO₂ as a stand-in for carbonic acid. To do this we re-write equation #10 as follows:

\[ \text{pH} = pK_a + \log \left( \frac{[\text{HCO}_3^-]}{\alpha_{\text{CO}_2} P_{\text{CO}_2}} \right) \]

11. We are able to do this since \( \alpha \text{ CO}_2 * P_{\text{CO}_2} \) determines the amount of CO₂ that is in solution. Please see the note in your textbook about the value of the \( pK_a \) for the carbonic acid/bicarbonate system.

! In human plasma at 37°C the value of \( \alpha \text{ CO}_2 \) is given as 0.03 m molsCO₂/L solution * torr

B. To describe the behavior of acids and bases in the body, physiologists have developed a very useful but complicated graph known as the Davenport Diagram.
1. Since we are studying acid-base via the bicarbonate buffer system, we will be interested in inter-relating the following variables: pH, [bicarbonate], and $P_{CO_2}$. Notice that these are all variables in the Henderson-Hasselbalch eq. for bicarb buffer given above (#12).

2. We will start by plotting a graph of [HCO$_3^-$] vs. pH. These two are selected because they are easily measurable attributes of a plasma sample.

3. Next, we will use the Henderson-Hasselbalch eq. to plot a number of lines called ISOPLETHS. These are lines that are calculated for a constant value of $P_{CO_2}$ with the amount of bicarbonate being varied. Typically these are plotted for reasonable values of $P_{CO_2}$ in normal and abnormal states. A good range is +/- 20 torr from the "normal" arterial $P_{CO_2}$ of 40 torr. Our Davenport diagram now looks like this:

![Graph showing isopleths for different $P_{CO_2}$ values.]

Please note that these isopleths are only approximately of the correct form -- the correct ones can be easily calculated using the Henderson-Hassalbach equation.

4. Next, we can put in some data that is obtained empirically: the BLOOD BUFFER LINE. This is simply the buffer line for [bicarb] vs. pH when a sample of blood is titrated with acid or base. The line has a distinctive shape that is determined by the following:

(a) Obviously, as more base is added the pH will increase since $H^+$ ions are removed by reaction with some of the added base.

(b) In addition, since we are dealing with a buffer system, as we add $OH^-$ (base) and $H^+$ in the blood is consumed, the HCO$_3^-$ will also decrease as some of the HCO$_3^-$ loses a H$^+$ to become CO$_3^{2-}$. The Davenport diagram with a blood buffer line will look like the graph below:
On the plot, N (which should exactly intersect the 40 isolpeth and blood buffer line) represents the normal point for arterial blood: $pH = 7.4$, $P_{CO_2} = 40$ torr, and $[HCO_3^-] = 24$ mM. Thus (when the solubility of $CO_2$, 0.03 mmols/(l sol'n * torr), is considered) the ratio of bicarbonate to $CO_2$ is 20 to 1. This will always be the case when a pH of 7.4 is obtained with the bicarb. buffer. Know this point! (It is valid for humans and some other mammals).

C. Now let’s use the graph to explore what happens when various disturbances occur.

1. Suppose that we place the subject on a respirator and turn it up such that the $V_E$ is much too great. Obviously, the subject is HYPERVENTILATING (or I should say, we are forcing him/her to hyperventilate). What will happen?
   a. As we will see in the next class, $P_{ACO_2}$ will decrease in hyperventilation. The result is that the $P_{aCO_2}$ also decreases since arterial gas is in equilibrium with the alveolar value. Thus the bicarb/$CO_2$ increases from 20:1 and the blood becomes more alkaline.
   b. How will the blood change with respect to $pH$ and $[HCO_3^-]$? Note that essentially we are titrating the blood by removing acid. Thus, the change is described shifts along the blood-buffer curve, with the final resting point being equal to the intersection of the blood line and the $P_{CO_2}$ isopleth of the hyperventilating lung. (See the following graph).
What will happen when the subject (starting from normal) HYPOVENTILATES?

We call disturbances of acid base balance that are caused by mismatches in ventilation compared to demand as being **RESPIRATORY in nature**, they result in either a pH that is higher than normal (**RESPIRATORY ALKALOSIS**) or lower (**RESPIRATORY ACIDOSIS**).

2. Likewise suppose that the subject consumed or produced a large amount of acid. What would happen? The acid would react with HCO$_3^-$, thus we know this parameter would drop. In addition, the pH would also fall since not all the H$^+$ that is being added to the blood would be removed. This would be seen as the arterial Davenport value leaving the blood buffer line and traveling down the $P_{CO_2} = 40$ isopleth a distance determined by the amount of bicarbonate consumed. Notice that once again the bicarb./$CO_2$ drops below 20:1 and the pH falls. (See the following graph)

Describe what happens when a large amount of base is consumed.

3. When excess acid or base is introduced through either diet or via metabolic (including disease states) processes, we term the condition **NON-RESPIRATORY ACIDOSIS** or **ALKALOSIS**. An older alternative term that we will also use is **Metabolic alkalosis or acidosis**.

Based on the location of someone’s blood gas point, how would you distinguish between Non-respiratory and Respiratory Blood gas disturbances? Between Acidosis and Alkalosis? Use the blood buffer line and the $P_{CO_2}$ isopleths as your reference points.
Different types of alkalosis and acidosis can be easily identified on this graph by their position. Any disturbance along the $P_{CO_2} = 40$ isopleth such that the $[HCO_3^-]$ differs from 24 mM is considered to have a non-respiratory cause since normal $P_{CO_2}$ is maintained. If the $[HCO_3^-]$ is greater than 24 mM, the condition is termed non-respiratory alkalosis; if below 24 mM it is termed non-respiratory acidosis. By contrast, conditions which involve $P_{CO_2}$ values that are different from 40 are said to be respiratory in cause. In their pure sense they are essentially the titration of blood with different amounts of CO$_2$ from 40 -- if more, it is respiratory acidosis (due to extra carbonic acid); if less it is respiratory alkalosis.

Finally, note that it is possible to have more than one condition at a time. For instance, non-respiratory acidosis and respiratory acidosis. Locate such a point. Again please note that these isopleths and the blood buffer are only approximately of the correct form -- the correct isopleths can be calculated using the Henderson-Hassalbach equation and the blood buffer line must be determined empirically.

D. COMPENSATION FOR ACID BASE DISTURBANCES.

1. pH is a tightly regulated variable -- disturbances are potentially life threatening.

2. If an acid base disturbance occurs, there are several things that can be done to restore the body to normal pH. In the following discussion, we will assume that the disturbance (such as hyperventilation) cannot simply be reversed. What can be done then?

   a. Irreversible respiratory disturbances. Here the $P_{CO_2}$ is either too high or low. To return to normal pH when $P_{CO_2}$ cannot be changed requires that
bicarb be either lost or gained -- thereby restoring the 20:1 ratio of bicarbonate to CO₂.

1. The **kidneys** are a major avenue of **bicarbonate and H⁺ removal and conservation**.
2. The **level of bicarb can be adjusted by either increasing or decreasing bicarb. elimination in the urine or by doing the opposite with H⁺ elimination**.

b. **Irreversible metabolic (non-respiratory) disturbances**: the $P_{CO₂}$ is normal but bicarb. levels are off the normal blood buffer line intersection for the given $P_{CO₂}$:
   1. Compensation is via **the respiratory system** where the $P_{CO₂}$ can be changed.
   2. This of course will also indirectly affect the bicarb system.

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? Show how (using the Davenport diagram) compensation would occur to NON-RESPIRATORY ALKALOSIS. To RESPIRATORY ACIDOSIS.

3. To remind ourselves of the roles of the kidney and lung in the regulation of acid-base, we often restate the Henderson-Hasselbalch relationship as:

$$pH = pK_a + \log \frac{\text{kidney}}{\text{lung}}$$

(note that this relationship is only useful for animals such as mammals that regulate $P_{CO₂}$ in the respiratory exchanger and H⁺ and HCO₃⁻ in the kidney.

II. The Regulation of Breathing:

A. Introduction:

1. In the first set of notes on respiration, we overviewed general models of respiratory gas exchange that contained two convective steps (ventilation and circulation) and two diffusive steps (tissue/blood and blood/alveolar space). We also considered how O₂ and CO₂ are carried in the blood and we have just finished discussing how CO₂ relates to acid/base. We are now in a position to look at the overall regulation of this exchange process.

   2. The first point is that this regulation is achieved in the convective processes since they are under the control of the nervous system. Diffusive changes tend to follow changes in blood flow and ventilation. For the moment then, we will focus on ventilation. We also should mention that **both the respiration and circulation must be regulated together** in order to deliver adequate oxygen and remove CO₂ so as to not prevent acid-base disturbances. Here is a very important summary of the ways that convection controls diffusion and that circulation and ventilation inter-act:

   (a) As you should recall from the general respiration model in the first set of notes, the main places regulation can occur are in the two
convective steps -- **ventilation of the lungs** and **circulation** (which is essentially ventilation of the tissues).

(i) Notice that we cannot really make regulatory changes in the diffusion between blood and lungs except as a result of changes in circulation or ventilation. For instance, deeper ventilation (larger tidal volume) will result in:

   a) **increased area as more alveoli are opened** in different parts of the lungs. Thus area is really determined by ventilation depth. It will also increase the average diffusion distance somewhat but not as much as you might think since the main effect of a larger tidal volume is to open more alveoli until very large lung volumes are reached.

   b) **increased partial pressure gradient as the \( P_{O_2} \) is increased and the \( P_{CO_2} \) is decreased in the alveoli.** Changes in circulation also affect this gradient since for a given tissue metabolism, the lower rate of circulation the lower the blood \( P_{O_2} \) and higher the blood \( P_{CO_2} \). To make things simple, we will simply assume that the blood arrives in the lungs with constant values of CO\(_2\) and O\(_2\).

(ii) Similarly, increases in circulation have the effect of:

   a) **keeping average partial pressure gradients of the two respiratory gases higher in a capillary for a given metabolic rate** and thereby increasing movement of the gases;

   b) they are **usually accompanied by opening of more blood vessels to a particular tissue** as we will see when we examine the regulation of microcirculation. The result of this is to **increase area** (more vessels opened per unit volume of tissue) and **decrease average diffusion distance**.

(iii) **for this packet, we will simply assume that the circulation increases or decreases to match tissue need. Therefore, we will only be concerned with how the ventilation system also changes to match need.**

(iv) We will also need to keep in mind what we learned in the last packet dealing with CO\(_2\) -- **respiration is used not only to provide oxygen but also as a primary means to regulate the overall acid-base balance of the body!!!**

B. **General Regulation of Ventilation in Mammals:** Since the goals of breathing and circulation is to (i) maintain adequate oxygen delivery and (ii) to help maintain pH by adjusting CO\(_2\) elimination it would make sense to monitor the concentration of these two gases and make regulatory adjustments accordingly.

1. **\( P_{O_2} \):** Under most conditions at the altitude a species evolved at (we will take this to be near sea level (i.e., below 5000 feet for the purposes of this discussion) the \( P_{A_{O_2}} \) (Alveolar \( P_{O_2} \)) is never so low that the blood Hb
isn't saturated. This is due to the position of the loading region of the \( O_2 \)-Hb dissociation curve. Thus, under these conditions, arterial \( O_2 \) is very poor potential regulator of respiration since changes in arterial \( P_{O_2} \) make little difference in the amount of oxygen contained in the blood.

a. The major \( O_2 \) sensors are located in the CAROTID BODIES that are in a sinus of the internal carotid artery. They measure oxygen content and therefore, they simply would not respond to a slight under-ventilation that results in a drop in \( P_{O_2} \) so long as the blood is still essentially saturated. Put another way, such a small change makes no difference to the tissue's ability to obtain oxygen and so it is ignored (in fact, it is not even registered!).

b. On the other hand, if \( P_{O_2} \) gets low enough so that blood is no longer saturated, then \( P_{O_2} \) is a very potent stimulus of respiration. The relationship is summarized later on a graph on the next page.

c. These receptors are ancient. As you will recall from the textbook, their action produces what is normally the critical signal in the regulation of ventilation by fishes. We have maintained them, but as we will shortly see, under normal atmospheric conditions, they are not too important to us. However, under conditions of low ambient oxygen -- as are often faced by fishes, they become very important.

Summary: At this points one may wonder so what?-- as long as adequate oxygen is delivered to the tissues, then there is no reason to worry if the \( P_{O_2} \) changes somewhat due to fluctuations in demand and ventilation.

- Under these conditions, one might assume that it is not important to regulate ventilation very precisely. In fact, if adequate oxygen were all that mattered, imprecise regulation would be OK under these conditions.
- But there is another problem and that is that if \( CO_2 \) is not eliminated at the same rate as it is produced there will be changes in overall body acid/base balance.
- As we have seen, the bicarbonate \( CO_2 \) buffer system is the most powerful one in the body since it is in such high concentration, since \( CO_2 \) is produced in all tissues and since \( CO_2 \) can easily enter or leave any tissue via diffusion.
- And, we have seen since the start of this course that CHANGES IN PH HAVE THE POTENTIAL TO CHANGE EVERY PHYSIOLOGICAL PROCESS IN THE ORGANISM since it often has potent effects on protein conformation.

2. \( P_{CO_2} \): Thus, by contrast, we are very sensitive to slight changes in \( CO_2 \) from set point. Recall that this sensitivity is possible because the \( pH \) of the body (generally a bit above 7) is maintained in a region of the \( CO_2 \)-bicarb titration curve where a slight change in bicarb. or \( CO_2 \) will cause a large change in \( pH \):
Note that this is due to operation of the system a long way from its $pK_a$. (a) CO$_2$ is sensed in certain central receptors in the hypothalamus. (i) In fact, these receptors sense pH which shouldn’t surprise you too much since it is very easy to make to a protein that is sensitive to change in pH. (ii) But a bit of deeper understanding is called for. They are still referred to as CO$_2$ receptors since the H$^+$ they sense is from CO$_2$ that diffuses into the fluid that bathes the receptors. Once it arrives, it produces carbonic acid. (iii) It is important to realize that this is H$^+$ not from exactly the same pool of H$^+$ ions that are found in the blood since highly charged H$^+$ will not readily pass the "blood/brain barrier". CO$_2$ on the other hand, has no trouble passing this barrier. (iv) These central receptors are therefore more sensitive to changes in CO$_2$ and are only indirectly influenced by other things (e.g., lactate) that change pH of the blood. They are indirectly affected because a change in pH does influence the amount of free carbon dioxide.

? How is it that a change in blood pH will change the amount of dissolved CO$_2$? What affect will an increase in lactic acid have on the concentration of CO$_2$ around central CO$_2$ receptors? What will be the effect on breathing? On arterial pH?
On arterial $P_{O2}$?

How is it possible that if this system can actually be so far away from its $pKa$? In other words, discuss the negative feedback regulation of the CO$_2$ bicarbonate system at a pH well away from its pKa (which is the pH it would tend to have in an inorganic system). Discuss the negative feedback system you learned in the first packet with respect to CO$_2$. What is the regulated variable? What is the set point? **What about this system is genetically controlled?** What are environmentally measured variables?

b. Here’s a diagram of the effects of CO$_2$ and O$_2$ on the regulation of respiration:

![Diagram of the effects of CO$_2$ and O$_2$ on the regulation of respiration](image)

From this graph you should see that if oxygen does change enough, it can become a potent stimulus for breathing. Also notice that at very large departures of CO$_2$ from normal that no further increase in minute volume occurs.

**Questions on the next page**
? Do you think the lack of further response in minute ventilation to extreme departures of $P_{CO_2}$ from normal is adaptive? Explain. Why (mechanistically) should the response change at these departures?

? Since breathing is regulated by negative feedback, explain why use of arterial CO$_2$ content for regulatory purposes will result in regulation of $P_{aO_2}$.

? Why should arterial blood gas content be monitored? Why not venous? Is the use of arterial blood an accident or is it adaptive?

-- Just for fun --

? Should it be possible to make a system that would regulate using oxygen instead of CO$_2$ that would be just a sensitive to change in gas content? (Do you think it would be easier to design through evolution a protein that would respond to oxygen or CO$_2$?) If so, what would be different about this new oxygen based system as compared to the oxygen regulated system we possess? What would be different about the set point, and regulated variable? The CO$_2$-regulated system seems to respond more or less incrementally (within limits) as the level of CO$_2$ changes. How is such an analog response generated and why might CO$_2$ be especially good for producing such a response. Would it be easy to do with oxygen? What would be a good ancestral protein from which to evolve an oxygen sensor?