1.1: The System

10.1.1: The 'New Paradigm'?

Recently, attention has shifted to a quantitative physicochemical approach to acid-base physiology. Many of the generally accepted concepts of hydrogen ion behaviour (as discussed above) are viewed differently and indeed are often shown to be wrong! This analysis introduced by Peter Stewart \(^1,2\) in 1978 \(^3\) provides a chemical insight into the complex chemical equilibrium system known as acid-base balance. The impact of the Stewart analysis has been slow in coming but there has been a recent resurgence in interest, particularly as this approach provides explanations for several areas which are otherwise difficult to understand (eg dilutional acidosis, acid-base disorders related to changes in plasma albumin concentration). [As discussed in section 1.1, the majority of this book covers the traditional acid-base approach.]

Stewart's book now online

Peter Stewart's influential 1981 book ("How to Understand Acid-Base") \(^1\) has long been out-of-print and it has been difficult for many people to obtain access to a copy. Recently, Stewart's widow has given the copyright on the book to Paul Elbers from Amsterdam and Paul has placed the whole book on-line at his new website [http://www.AcidBase.org](http://www.AcidBase.org)

The interested reader is referred to Bellomo(1999)\(^4\) and the associated review articles in that edition of Current Opinion in Critical Care where the 'new paradigm' of Stewart's acid-base approach is considered with the enthusiasm of the true believer.
Undoubtedly the physiochemical approach will become more important in the future and this chapter provides an introduction. A bit of background is necessary first.

10.1.2: Terms & Concepts

This approach requires a consideration of solutions as systems. In particular:

"... it is a general property of systems that the quantitative results of several interacting but independent mechanisms can not be explained or understood solely in terms of the action of any single one of these mechanisms." (Stewart 1983, p1444-5)

A simple introduction to the concepts and the terms which are used by Stewart is necessary to understand the framework in which he discusses acid-base chemistry in the body. A biological fluid is a very complex dynamic system but useful analysis is possible by considering the chemical species involved and how they interact chemically with each other. Consider the argument developing in this way:

- There are often multiple mechanisms involved in influencing the particular concentration of any single chemical species.
- Hydrogen ion is an example of one of these species whose concentration is dependent on several interacting chemical mechanisms (equilibriums).
- Finally (and rapidly) these multiple mechanisms must come into equilibrium and the \([H^+]\) in the solution at that point in time is determined.
- An attempt to calculate the equilibrium concentration of any species must take into account all the mechanisms involved.
- This is not quite as difficult as may be supposed because certain simplifications are possible. (These will be considered later).
- Finally, a formula for the calculation of the equilibrium value of a chemical species (eg \([H^+]\)) can be obtained. The equation for \([H^+]\) is complex but solution of it is easy and quick on a computer.

What we are planning to do is to decide what it is that determines \([H^+]\) (and the other chemical concentrations) in a biological solution by considering the several interacting mechanisms involved. One aim is to develop a formula for calculating \([H^+]\), but more importantly a new understanding of how acid-base physiology really works at the chemical level should be gained.

The concentrations of the various chemical species present are the variables whose values are used in the equations. From the perspective of considering a biological solution as a system of interacting chemical species, we can consider these variables as being of two types. All the variables can be classified as either dependent variables or as independent variables. This is extremely important in discussing cause and effect so first consider the meaning of these terms:

**Dependent and Independent Variables**

**Dependent variables** have values which are determined internally by the system. They
are determined by the equations (chemical equilibria) which determine the system and can be altered only by changes in the values of the independent variables.

**Independent variables** have values which are determined by processes or conditions which are external to the system; they are imposed on the system rather than being determined by it.

Consider a simple analogy: A goldfish in a bowl which is full to the brim. The bowl-water-goldfish combination is the system in this example. The amount of oxygen in the solution is a dependent variable: its value at any time is determined by the rate of oxygen consumption of the goldfish and this is a process which is completely internal to the system. Now consider the volume of water in the bowl: this is an independent variable as its value is determined by factors external to the system within the bowl. If there were any reactions within the bowl that produced more water (e.g., metabolic water production by the goldfish) then it would simply overflow the edges of the full bowl. The volume would be held constant despite internal changes within the bowl. Consider further the dependent variable oxygen content in the bowl. This is not just determined by the internal process (O\(_2\) consumption by the goldfish) but is affected by the value of various independent variables such as the volume of the bowl and the temperature of the water. More oxygen will dissolve in water at a lower temperature. The temperature of the water is determined by the environmental temperature which is independent of the goldfish in bowl system. The water temperature is another independent variable.

**Why is the concept of dependent and independent variables so important?**

- The reason is that the values of all the dependent variables are determined by and can be calculated from the values of the independent variables.
- And a very important particular point: In the acid-base system in body fluids, [H\(^+\)] is a dependent variable!

The traditional analysis of acid-base makes the implicit assumption that [H\(^+\)] is an independent variable and this is wrong. Hydrogen ion concentration can therefore be calculated if the values of the independent variables are known.

**Preliminary Remarks about the Significance of this**

Now the significance of this and why it is so different from the traditional understanding may not be immediately apparent to you. So let's consider the following:

Consider a cell where H\(^+\) ions are being pumped out of a cell into the ISF.

Using the traditional approach we would predict that this would decrease the intracellular [H\(^+\)] (and increase the pH) because there is now less H\(^+\) in the ICF in that cell. But the Stewart approach would say this understanding was wrong. Because [H\(^+\)] is a dependent variable, its concentration cannot be changed in this way; its concentration can only be...
changed if the value of one of the independent variables changes and all that is happening is a pumping of H\(^+\) ions. The Stewart approach would predict that the chemical equilibria within the cell would readjust to replace any H\(^+\) lost (by being pumped out of the cell) with the result that the intracellular [H\(^+\)] would remain unchanged.

So, what really happens? Well if the pumping of H\(^+\) out of the cell was the only change occurring than the ICF [H\(^+\)] would not change and the Stewart approach would correctly predict this. The source of the replacement H\(^+\) would be an extremely small increase in the dissociation of H\(_2\)O within the cell.

But, wait a minute, surely this cannot be so. As another example, consider what happens in the parietal cells in the stomach. After a meal, the parietal cells actively pump large amounts of H\(^+\) into the gastric lumen. The [H\(^+\)] in the parietal cells decreases and this is reflected in the gastric venous blood as an increase in pH (the 'post-prandial alkaline tide').

Doesn't this mean then that the prediction of the Stewart approach is wrong afterall? Not at all. In fact, a proper analysis of this example shows that the outcome is consistent with that predicted by the Stewart approach. One important fact that has been overlooked in our analysis so far is the requirement for electroneutrality. It is just not possible to pump much H\(^+\) because this sets up a potential difference across the cell membrane. Now the cell can only tolerate an extremely tiny charge separation (and such a minute charge separation is sufficient to set up a transmembrane potential difference or RMP of say 100mV). The actual concentration difference that this RMP represents is too small to measure other than as a potential difference (ie membrane potential).

What is happening in the parietal cell is that both H\(^+\) and Cl\(^-\) are being transferred out of the cell and into the gastric lumen. Electroneutrality is maintained. The vital point to notice here is the movement of Cl\(^-\) and the effect of this. As there is no potential difference set up by pumping H\(^+\) and Cl\(^-\) together there is no electrochemical force inhibiting the movement. Consequently large amounts of Cl\(^-\) are being moved out of the cell. This causes a change in the strong ion difference (SID). Don't worry about what this means at present (it will be explained in section 10.3), just note that it is one of the independent variables in this system and thus determines the values of the dependent variables, of which [H\(^+\)] is one. The correct explanation (as provided by the Stewart approach) is that yes, the [H\(^+\)] in the gastric parietal cell does decrease but it is not the pumping of the H\(^+\) which causes this, but rather the loss of Cl\(^-\) from the cell. The loss of Cl\(^-\) changes the value of one of the independent variables.

The explanations of the two approaches as to why the [H\(^+\)] changes is quite different. The Stewart approach is the one that is correct in the sense of explaining the cause.

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**References**


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