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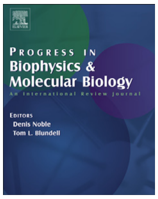

Review

Mathematical modeling of acid-base physiology

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ABSTRACT

pH is one of the most important parameters in life, influencing virtually every biological process at the cellular, tissue, and whole-body level. Thus, for cells, it is critical to regulate intracellular pH (pH_i) and, for multicellular organisms, to regulate extracellular pH (pH_o). pH_i regulation depends on the opposing actions of plasma-membrane transporters that tend to increase pH_i, and others that tend to decrease pH_i. In addition, passive fluxes of uncharged species (e.g., CO_2, NH_3) and charged species (e.g., HCO_3^-, $NH_4{}^+$) perturb pH_i. These movements not only influence one another, but also perturb the equilibria of a multitude of intracellular and extracellular buffers. Thus, even at the level of a single cell, perturbations in acid-base reactions, diffusion, and transport are so complex that it is impossible to understand them without a quantitative model. Here we summarize some mathematical models developed to shed light onto the complex interconnected events triggered by acids-base movements. We then describe a mathematical model of a spherical cells—which to our knowledge is the first one capable of handling a multitude of buffer reactions—that our team has recently developed to simulate changes in pH_i and pH_o caused by movements of acid-base equivalents across the plasma membrane of a *Xenopus* oocyte. Finally, we extend our work to a consideration of the effects of simultaneous CO_2 and HCO_3^- influx into a cell, and envision how future models might extend to other cell types (e.g., erythrocytes) or tissues (e.g., renal proximal-tubule epithelium) important for whole-body pH homeostasis.

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1. Introduction

The field of acid-base physiology has advanced significantly in recent years, thanks to the rapid accumulation of molecular biological insights—including genome-sequence data—as well as functional, biochemical, and cell biological studies. Progress with in-vitro expression systems (e.g., *Xenopus* oocytes, cells in culture) and genetically manipulated animals has produced a large amount of new data. In spite of significant progress, we are still far from fully understanding the mechanisms involved in acid-base homeostasis. For example, we are still unable to discern with certainty the relative contribution of the many simultaneous and interconnected processes (e.g., movements of numerous acid-base equivalents, equilibria of a multitude of buffers) that produce pH changes in a single living cell, let alone a tissue or the whole organism.

Understanding acid-base physiology is important because virtually every biological process is pH sensitive. Perturbations in pH can affect a variety of biological processes at the cellular, tissue, and whole-body level. At the cellular level, maintaining cytosolic pH (i.e., intracellular pH, pH_i) within a narrow range is essential for many processes to occur, including biochemical reactions, as well as the function of transporters, channels, receptors, structural proteins, and regulatory molecules (Ludwig et al., 2003; Roos and Boron, 1981; Waldmann et al., 1997). In addition, pH_i influences the luminal pH of membrane-bound intracellular organelles (e.g., endoplasmic reticulum, endosomes, mitochondria), and thereby has an indirect influence on the myriad events occurring inside these organelles (Igawa et al., 2010; Matsuyama and Reed, 2000; Roopenian and Akilesh, 2007). At the tissue level, local extracellular pH (pH_o) not only influences pH_i (Boron, 2012a; Roos and Boron, 1981) but also modulates the binding of extracellular ligands to cell-surface receptors (Roopenian and Akilesh, 2007), and a host of regional processes that include blood flow (Boedtkjer and Aalkjær, 2012), air flow in the lungs (Duckles et al., 1974; Kolobow et al., 1977; Winn et al., 1983), maintenance of appropriate corneal hydration and transparency (Li et al., 2005; Sun and Bonanno, 2003), epithelial transport, and the binding of ligands to extracellular receptors (Traynelis, 1998). At the whole-body level, the pH of blood plasma not only influences local tissue pH_o (which in turn affects pH_i) but also modulates interactions, in the plasma, of charged molecules (e.g., hormones and their carrier proteins). In the realm of patient care, plasma pH affects the electrical charge of therapeutic agents that are weak acids or weak bases, and how these agents interact with plasma proteins and distribute among the tissues (Rodgers and Rowland, 2006; Rodgers et al., 2005).

Because pH changes have such profound effects on biology, organisms have evolved a series of sophisticated mechanisms to achieve homeostasis of pH in the intracellular fluid, blood plasma, and other compartments in the body. The process by which cells or the whole body respond to perturbations in pH by tending to return pH to its initial value is known as “pH regulation”. Regulation of pH in the blood plasma—and, by extension, in the extracellular fluid—is the result of the dual action of the respiratory and renal systems, which independently control the concentrations of carbon dioxide (CO_2) and bicarbonate (HCO_3^-), the two major components of the body's most important buffering system. More specifically, the lungs regulate plasma [CO_2], whereas the kidneys, plasma [HCO_3^-].

Cells regulate pH_i by appropriately adjusting the speeds of various transporters that move acids (including hydrogen ions or protons, H^+) or bases (e.g., HCO_3^-) across the plasma membrane. The movements across the membrane of uncharged weak acids or bases (e.g., butyric acid or ammonia, NH_3), or of their charged counterparts (e.g., butyrate or ammonium, $NH_4{}^+$), can produce pH_i perturbations against which cells defend themselves using their pH_i-regulatory machinery.

Movements of acid-base equivalents across the plasma membrane—whether these movements are the insults that perturb pH_i or the regulatory responses—influence one another and alter the equilibria of numerous intracellular and extracellular buffers, thereby creating complicated interdependencies among acid-base reactions, diffusion, and carrier-mediated transport. Because of the complexity of such movements, several investigators have developed mathematical models of acid-base physiology to help in data interpretation.

In this review, first we provide an overview of acid-base physiology with special emphasis to the mechanisms of pH regulation in the body and cell. Then, we summarize mathematical models of acid-base physiology by others. Finally, we summarize the most recent models from our team.

2. Overview of acid-base physiology

2.1. Acid-base chemistry

Before reviewing how the body, tissues and cells achieve pH homeostasis, it is useful to draw our attention to the most powerful buffering system[1] in the body—the CO_2/HCO_3^- buffer pair.

Dissolved CO_2, HCO_3^-, and H^+ are related through the reactions

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3{}^- + H^+. \tag{1}$$

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[1] A buffer is any substance that tends to minimize changes in pH by reversely producing or consuming H^+.