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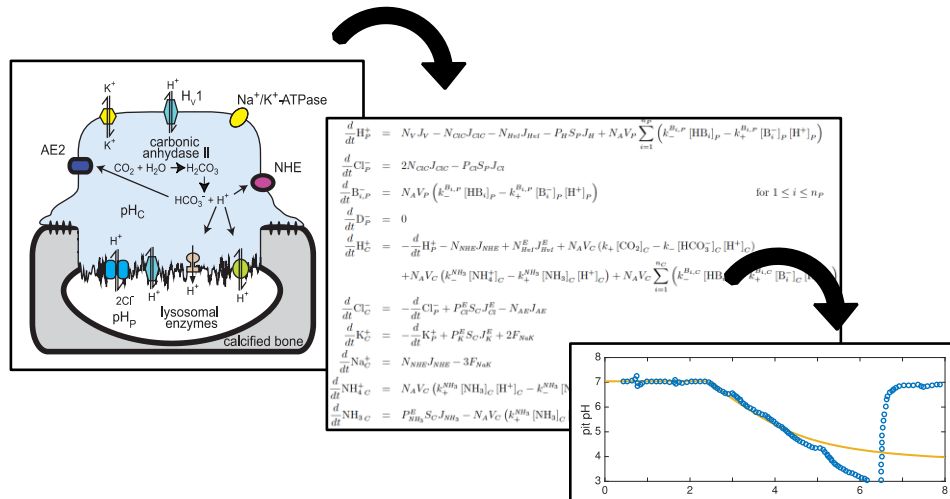
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Abstract

Bone resorption by osteoclasts occurs through the creation of a sealed extracellular compartment (ECC), or pit, adjacent to the bone that is subsequently acidified through a complex biological process. The low pH of the pit dissolves the bone mineral and activates acid proteases that further break down the bone matrix. There are many ion channels, transporters, and soluble proteins involved in osteoclast mediated resorption, and in the past few years, there has been an increased understanding of the identity and properties of some key proteins such as the ClC-7 Cl⁻/H⁺ antiporter and the H_V1 proton channel. Here we present a detailed mathematical model of osteoclast acidification that includes the influence of many of the key regulatory proteins. The primary enzyme responsible for acidification is the vacuolar H⁺-ATPase (V-ATPase), which pumps protons from the cytoplasm into the pit. Unlike the acidification of small lysosomes, the pit is so large that protons become depleted from the cytoplasm. Hence, proton buffering and production in the cytoplasm by carbonic anhydrase II (CAII) is potentially important for proper acidification. We employ an ordinary differential equations (ODE)-based model that accounts for the changes in ionic species in the cytoplasm and the resorptive pit. Additionally, our model tracks ionic flow between the cytoplasm and the extracellular solution surrounding the cell. Whenever possible, the properties of individual channels and transporters are calibrated based on electrophysiological measurements, and physical properties of the cell, such as buffering capacity, surface areas, and volumes, are estimated based on available data. Our model reproduces many of the experimental findings regarding the role of key proteins in the acidification process, and it allows us to estimate, among other things, number of active pumps, protons moved, and the influence of particular mutations implicated in disease.

Graphical Highlight



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