“Capturing Intracellular pH Dynamics by Coupling Its Molecular Mechanisms within a Fully Tractable Mathematical Model”

Yann Bouret, Médéric Argentina, Xavier Noblin, Céline Cohen, Laurent Counillon

The distribution of charges within biological molecules determines their solubility, their folding, their activity and the spatio-temporal sequence of their interactions. In this context, the pH of the solution bathing these biological molecules is a key parameter, since its value determines the protonation of the acid-base groups that are especially abundant in macromolecular assemblies. This in turns determines the charge of biological molecules. Consequently, pH is regulated within a very narrow window in all cells, tissues and organisms. The information for intracellular pH is a convoluted interplay between the abundance and the distribution of protonable groups in biological molecules, their pKa values and the expression, stability, kinetic and affinity parameters of the pH regulating systems. We have built the first mathematical model of cytosolic pH, based on coupling the experimentally-determined kinetic equations depicting the molecular mechanisms for pumps, transporters and chemical reactions, which determine this parameter in eukaryotic cells. One of our most exciting results is the demonstration that the regulation of intracellular pH has analytical solutions that are tractable. Furthermore, this model provides both a steady state solution for intracellular pH and a reduced system of differential equations that enable to compute its dynamics under various conditions. As it is based on a system of coupled differential equations, it also computes the concentrations of all coupled ions, such as bicarbonate, sodium, chloride and potassium.

Noticeably, the different numerical values obtained from our computations are well in accordance with classical data from pH measurements taken both from the literature and from our own experiments. In particular following different perturbations, pH converges in a very robust manner to physiological values with characteristic kinetics that are in the same order of magnitude as those found experimentally.

One of our important findings was that a vanishing physiological protic perturbation systematically produces an overshoot around its steady state that we could subsequently measure using high-resolution microfluidics perfusion systems. The exact mathematical demonstration of this phenomenon is not trivial but shows that it is valid for acidification or alkalinization, and can also be expected every time a perturbation vanishes for other physiological regulation mechanisms. The biological significance of these overshoots will be discussed as our findings on pH may be generalized for example to the regulation of glycaemia, heart rate, or breathing in which overshooting effects are widely reported in the physiological and medical literature.