The Total Quasi-Steady State Approximation Readily Explains the Loss of Zero-Order Ultrasensitivity at Intermediate and High Enzyme Concentrations

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Abstract

Covalent modification plays a pivotal role in many signal transduction pathways, for example in the activation of enzymes by kinases and their inactivation by phosphatases. Goldbeter and Koshland (Proc. Natl. Acad. Sci. USA (1981) 78:6840-6844) showed that these systems can possess so-called ultrasensitivity if their catalyzing enzymes operate in a regime where they follow approximate zero-order kinetics. This happens when the enzymes have high affinities for their substrates and low concentrations compared to the substrate concentrations, such that the enzymes are saturated. However, experimental data indicate that enzymes *in vivo* are present in concentrations

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similar to or higher than those of their substrates in many cases. In this case ultrasensitivity is lost even for high affinity systems. This is closely related to the breakdown of the Briggs-Haldane approximation of the kinetics, such that one must describe the system by the full set of reactions or the recent total quasi-steady state approximation. We show that the latter approach not only reproduces the presence or lack of ultrasensitivity, but in addition, and more importantly, allows a treatment in line with the one used at low enzyme concentrations thus providing a simplification compared to the use of the full system of reactions.

Keywords: Covalent modification – Goldbeter-Koshland switch – metabolic control analysis – substrate sequestration