A different model for signaling cascades

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Covalent modification cycles are one of the major intracellular signaling mechanisms, both in prokaryotic and eukaryotic. Each cycle is formed by two interconvertible forms of a signaling protein: the protein is activated by the addition of a phosphate group and inactivated by the removal of this phosphate. The most studied example of covalent modification cycles is phosphorylation-dephosphorylation of proteins, representing one of the basic motifs of cell signaling. Several signaling pathways are constituted by a cascade of those basic units, in such a way that the activated protein in one cycle promotes the activation of the next protein in the chain. The functional significance of these cascades in signal transduction is multiple.

Much has been done regarding the mathematical modeling of signaling cascades. In a recent article we have unveiled interesting properties of these cascades by proposing a novel model. Starting from a complete mechanistic kinetic description of a cascade composed by an arbitrary number of cycles, we have derived for the first time a consistent approximation of the chain with one variable per cycle. The achieved model is different from existing models in the literature for signaling cascades, which are mostly phenomenological, like the phenomenological extension of the Goldbeter-Koshland biochemical switch **[1]**. In our new derivation a feedback from each unit to the previous one arises naturally from the biochemistry involved, conferring novel properties to this description.

The approximation behind our simplified model is the quasi-steady state one. Interestingly and for a single enzymatic irreversible scheme, it was proposed that the parameter domain for which the standard quasi-steady state assumption (sQSSA) is valid can be considerably extended by a change of variables, what has been called the total quasi-steady state approximation (tQSSA) **[2]**.

The tQSSA has already been successfully applied to single covalent modification units and to models coupling low number of these units. We here explore the extension of our description for signaling cascades formed by an arbitrary number of units but using the tQSSA instead of the sQSSA. We obtain a generalization of our previous model, for which we analyze and compare the dynamics under both approximations and their ranges of applicability. We find that the parameter domain for which the extended model is valid overlaps the domain of validity of our previous model and, even more, can match the complete description of the system for a wide range of substrate and enzyme concentrations.

[1] Goldbeter, A., Koshland Jr., D. E. (1981). An amplified sensitivity arising from covalent modification in biological systems. Proc. Natl. Acad. Sci. USA 78(11), 6840-6844.

[2] Borghans, J. A., De Boer, R. J., Segel, L. A. (1996). Extending the quasi-steady state approximation by changing variables. Bull. Math. Biol. 58(1) 43-63.