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Hierachic stochastic modelling of intracellular Ca(2+) signals - a new concept based on emergent behaviour of biomolecules

Biological systems often exhibit complex spatio-temporal dynamics and are stochastic at the same time. That is a challenge for mathematical modelling, since standard techniques then either apply rude assumptions like mean-field theories, or they lead to astronomic numbers of system states. As a new concept, we formulate a theory in terms of interevent interval distributions describing mesoscopic cluster states.

Here we consider intracellular Ca(2+) dynamics, where channel clusters are known to evoke local Ca(2+) release events that eventually induce cellular concentration spikes by diffusive coupling. However, the new modeling framework can potentially also be applied to other systems consisting of coupled clusters of biomolecules, like T cell receptor clusters or chemotaxis. Describing system dynamics in terms of probability distributions instead of rate-laws implies that the model becomes non-Markovian, but it has the advantage that the shape of the distributions reflects the microscopic dynamics without considering them in detail. Moreover, probability distributions of cluster state-changes can often be measured in vivo or calculated from known constraints, in contrast to kinetic parameters of state-changes of individual proteins.

Despite of the rather complicated integral equations appearing in the complete description of the dynamics, we arrive at simple expressions for stationary statistics at regular cluster arrangements, and stochastic simulations run quite efficiently. For Ca(2+) dynamics, we verify data input and output by fluorescence microscopy in HEK cells and thus provide strong support for the proposed stochastic model. Furthermore, we find valuable robustness properties of the stochastic mechanism, which might be one of the reasons for ubiquity of the Ca(2+) signalling toolkit in cell signalling.

Publications: Thurley and Falcke, PNAS 108:427-32 (2011); Thul, Thurley and Falcke, Chaos 19:037108 (2009).