

Towards Computational Systems Biology

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For molecular systems biology to be truly quantitative, and computational systems biology to be really computational, we will need to see many technological and computational breakthroughs. I will discuss two important challenges I believe we will face in the area of cell biological and biochemical simulations.

The first is that systems biological simulations so far has undeniably been (re)discovery of the lack of high-throughput and reliable means of obtaining reaction rate coefficients, and it formed the biggest bottleneck in the biochemical modeling and simulation workflow. Many modeling projects got stuck as soon as they faced the lack of input parameters, and a common feature of the limited number of successful modeling projects has been the accumulation of a large body of kinetic studies for decades, each determined parameter for a particular enzyme corresponding to someone's doctoral degree. When we think about these systems, however, we notice that there is no such measurable physical quantities like 'net reaction rate constants', but there is only coupling of two distinct physical occurrences; diffusive encounters of reactants and subsequent interactions between them. Such decomposition into physically better defined concepts may open a pathway to an ideal combination of wet measurements and computation. I will present how recent advancements in exact Brownian dynamics methods and laser spectroscopy are making us less pessimistic.

The second challenge consists in the ubiquitous nature of cellular organisms. Extremely high densities of macromolecules (50-400 mg/ml, compare to 1-10 mg/ml typical *in vitro* conditions), called intracellular macromolecular crowding results in different equilibrium points, altered reaction rates, slow and anomalous diffusion of macromolecules, and thus modified overall behaviors and dynamical characteristics of biochemical systems. Recently it was proposed that macromolecular crowding might be the physico-chemical culprit behind the emergence of eukaryotic cells. Promising developments are ongoing in the areas of high-performance particle and lattice-based methods that can lead to direct or semi-direct modeling and simulation of crowded intracellular media. If such a grand computational challenge that requires a rigorous formal treatment, scalable numerical methods and sufficient supercomputing power comes into sight sometime in hopefully near future, that would be one great moment for computational systems biology becoming truly computational systems biology.