576e Multiscale Stochastic Simulations of the Mitogen Activated Protein (Map) Kinase Cascade

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The importance of stochasticity in biological intracellular signal networks is well established from several recent theoretical and experimental studies. Consequently, it is necessary to develop stochastic modeling and analysis tools that help to quantitatively understand the role of fluctuations and nonlinear behavior, such as bistability, in these signal networks. However, challenges typically arising from the large separation of time scales and the wide range of signaling species population sizes in a cell render exact stochastic simulation methods computationally inefficient. Recently, the tau-leap method has been introduced to cope with one of these challenges [1-3]. Other techniques have been proposed to deal with time scale separation [4, 5]. However, the disparity in time scales still plagues stochastic simulation.

In this talk, the shortcomings of current simulation tools are illustrated with the example of the epidermal growth factor (EGF) receptor induced mitogen activated protein (MAP) kinase cascade. EGF receptors belong to the receptor tyrosine kinase (RTK) family of receptors and play an important role in embryonic and postnatal development and in growth and progression of tumors. The model proposed by [6] is used for describing the signaling pathways. This model entails 106 signaling species and 296 signal transduction processes. A new multiscale stochastic simulation framework is presented that categorizes the entire network into sets of slow and fast signal species and transduction processes. This approach is reminiscent of the adiabatic elimination of variables of stochastic differential equations, works for arbitrary complex reaction networks, and can give unprecedented computational savings. A rigorous hierarchical probabilistic framework for passing information from fast processes to relatively slow processes in this new approach enables accurate predictions of the probability distribution functions at all time scales. The new multiscale stochastic simulation method is used to study the MAP kinase cascade.

References

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