Von der Moleküldynamik zur Konformationsdynamik beim Entwurf von Medikamenten

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Abstract
Computational drug design requires information about the Hamiltonian dynamics of molecular systems, which is the principal basis for the so-called molecular dynamics (MD) approach. However, the corresponding initial value problems are ill--conditioned already after psec time spans. Therefore, numerical long term integration like in classical MD will, assuming ergodicity, at best supply average information, but not the desired dynamical information over msecs up to min, which is the time scale important for drug design. In order to overcome this dilemma, the conformation dynamics approach as suggested by the author, Sch\"utte, and their co-workers has been established.

The key idea of the approach is the direct identification of metastable conformations, i.e. of sets of molecular states wherein the dynamical system stays 'for a long time', once it is in there. The mathematical approach is a Markov state model, based on some self-adjoint transfer operator. Its discretization via hybrid Monte Carlo (HMC) methods generates transition matrices; in order to avoid the 'curse of dimensionality', the construction of appropriate state discretizations requires careful consideration. Once the operator has been discretized, mathematical and biochemical interest focuses on nearly uncoupled Markov chains and the corresponding metastable conformations, which can be identified together with their life spans and their transition patterns. This task called Perron cluster analysis leads to the numerical solution of a cluster eigenproblem for eigenvalues around the Perron eigenvalue 1; the talk will introduce a robust variant of such an algorithm suggested by the author and Marcus Weber. Moreover, a recent meshless discretization approach due to Weber and a statistical error estimator for its hierarchical refinement due to Susanna Röblitz (neé Kube) will be presented. Finally, a very recent approach towards the construction of the projected transfer operator via the corresponding projected infinitesimal generator due to Weber is sketched. With this recent progress, first potential drugs could be suggested, one of which is on its way to being patented. Throughout the talk, biomolecular examples will be inserted for illustration.