Conformation Dynamics in Computational Drug Design

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Abstract: Computational drug design requires information about the Hamiltonian dynamics of molecular systems, which is the principal basis for molecular dynamics (MD). 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 and Schuette has been established. The key idea of the approach is the direct identification of so-called 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 based on some self-adjoint transfer operator associated with an underlying Markov chain. Its discretization via hybrid Monte Carlo (HMC) methods generates transition matrices. Once the operator has been discretized (a hard topic of its own), interest focuses on the computation of corresponding metastable conformations, which have to 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 most recent robust version of such an algorithm is due to the author and Weber (who will give a talk later in the workshop).

Throughout the talk, biomolecular examples will be presented including, among others, epigallocatechine, some compound of green tea suspected to be a possible drug against cancer.

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