

From Molecular Dynamics to Conformation Dynamics in the Virtual Drug Design Lab

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Abstract

Computational drug design requires information about the dynamics of molecular systems. The classical model consists of Hamiltonian differential equations, whose initial value problems are ill-conditioned, typically already after picoseconds. Therefore, numerical long term integration will not supply reliable dynamical information.

The talk presents the new Perron cluster analysis (better: Perron cluster cluster analysis, to be abbreviated as PCCA) that has been developed by the author, Schuette, and co-workers. Its key idea has been borrowed from early work of Dellnitz et al. on hyperbolic dynamical systems: instead of computing long term dynamics, almost invariant sets of the dynamical system are determined. However, while hyperbolic systems are characterized by the fact that their dynamics asymptotically collapses to some low dimensional attractor, the here governing Hamiltonian dynamics remains on the Hamiltonian surface and does not collapse at all – which leads to rather different mathematical and computational challenges.

Along this line, molecular dynamics is replaced by conformation dynamics, which involves the computation of metastable conformations together with their life spans and transition patterns. This is done via the numerical solution of an eigenproblem associated with some Markov operator, in particular for a cluster of eigenvalues called the Perron cluster (since it contains the Perron eigenvalue 1). Discretization of the Markov operator via Hybrid Monte Carlo (HMC) methods generates transition matrices for nearly uncoupled Markov chains, which must be identified by an efficient algorithm. In addition, the discretization itself turns out to be a challenge of its own and therefore also requires careful consideration. In order to avoid the curse of dimension, two variants have been developed: one based on temperature embedding via a Boltzmann distribution, the other one via self-organizing maps (Kohonen). Realizations of these ideas will be given in the talk.

The approach as a whole aims at the substitution of experiments in chemical labs by realistic simulations in a virtual lab. Biomolecular examples will include a patented HIV protease inhibitor, which is a potential anti-AIDS drug, or epigallocatechine, a compound of green tea, suspected to be a possible drug against cancer.