Calculating Low Energy Reaction Pathways in Proteins and RNA: A QM/MM Implementation of the Nudged Elastic Band (NEB) Method

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Abstract

We have implemented a simulated annealing based version of nudged elastic band (NEB) within an early version of AMBER 9 and successfully used it to find low energy pathways for conformational changes in protein and RNA based systems. By implementing a coupled QM/MM potential model that combines a region of chemical interest, described quantum mechanically, with a classical region, described by the AMBER force field equation, we have been able to find low energy reaction pathways involving bond breaking and formation in protein and RNA systems.

NEB Background

In nudged elastic band (NEB), the minimum energy path for a conformational change is quantified with a series of images of the molecule describing the path[1,2]. The images at the end points are fixed in space. Each image in-between is connected to the previous and next image by "springs" along the path that act to keep each image from sliding down the energy landscape onto adjacent images. The pathway represents the trajectory that a molecule follows through the conformational change and this pathway can be derived independently of the timescale of the conformational change. NEB derives from the plain elastic band method, pioneered by Elber and Karplus[3]. This method found low energy paths, but tended to cut corners in the energy landscape. NEB prevents corner cutting by truncating the spring forces in directions perpendicular to the tangent of the path. Furthermore, the forces from the molecular potential are truncated along the path, so that images remain evenly spaced along the path.

Along the direction of the path, the force on each image is governed by virtual springs that serve to fix the position of each image relative to the adjacent image so that the images follow the path. Perpendicular to the path, each image responds to the potential of the energy landscape as determined by the force field. The total force, F, is then:

$$F_i = F_i^{\perp} + F_i^{\parallel}$$

$$F_i^{\perp} = -\nabla V(P_i) + \left(\left(\nabla V(P_i)\right).\tau\right)\tau$$

$$F_i^{\parallel} = \left[\left(k_{i+1}(P_{i+1} - P_i) - k_i(P_i - P_{i-1})\right).\tau\right]\tau$$

where, N is the number of atoms per image, F_i is the force on image i, P_i is the 3N dimensional position vector of image i, k_i is the spring constant between image i-1 and image i, V is the potential described by the force field, and ∇ is the 3N dimensional tangent unit vector that describes the path.

References

1) Jonsson, H., Mills, G., Jacobsen, K.W., 'Nudged elastic band method for finding minimum energy paths of transitions.', in Classical and Quantum Dynamics in Condensed Phase Simulations. (Berne, B.J., Ciccoti, G., Coker, D.F., eds.), 1998, pp385-404, World Scientific, Singapore.

2) Mills, G., Jonsson, H., 'Quantum and thermal effects in H2 dissociative adsorption: Evaluation of free energy barriers in multidimensional quantum systems.' Phys. Rev. Lett., 1994, *72*, 1124-1127.

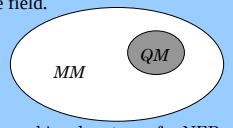
3) Elber, R., Karplus, M., 'A method for determining reaction paths in large molecules: Application to myoglobin.' Chem. Phys. Lett., 1987, *139*, 375-380.

QM/MM Background

The QM/MM approach to molecular dynamics combines a quantum mechanical (QM) potential with a more *approximate* molecular mechanical (MM) potential.

$$E_{system} = E_{MM} + E_{QM} + E_{QM/MM}$$

We have implemented this in a pre-release version of AMBER 9 so that the part of the system that is of chemical interest (*e.g.* the active site) can be treated with a semi-empirical quantum part and the rest with the classical AMBER force field.



QM/MM has some big advantages for NEB calculations:

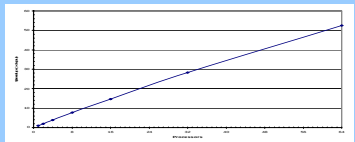
- MM calculations do not allow for bond breaking or formation. Therefore without a QM potential NEB is restricted to conformational changes.
- Pure QM calculations are very computationally costly. QM/MM provides an acceptable tradeoff between the accuracy of a QM potential and the speed of an MM potential.

Parallel Scaling

NEB calculations are very computationally intensive since they require calculations to be done on a number of replicas. E.g. a system of 32 replicates requires 32 times more cpu time than a regular MD simulation for a given length. Therefore scaling in parallel over many cpus is vital.

Image showing 64 NEB replicas of NMA after 10ps of heating to 300K.

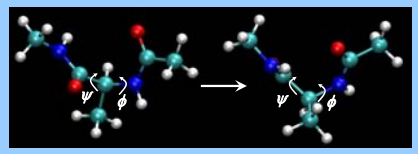
The QM part of calculation is the most time consuming so each cpu does a replica in turn. Thus as long as the number of replicas is a multiple of the number of CPUs you can run very efficiently in parallel. This enables large systems to be studied.



Calculation speedup as a function of cpus for alanine dipeptide QM NEB simulation (64 replicas) on an SGI Altix

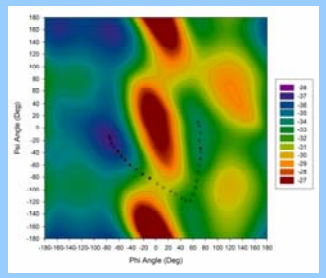
Model System

A model system is required to ensure the correct pathways are found. Alanine dipeptide has been used as a model molecule since the energy surface can be displayed topographically.



We have then used the NEB method (both QM/MM and MM) to see which pathways are found. In classical and QM/MM simulations different minima were chosen in each case to further test the method.

Classical MM Phi-Psi Map (AMBER FF02)



PM3/AMBER FF02 QM/MM phi-psi Map

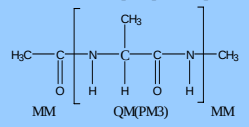
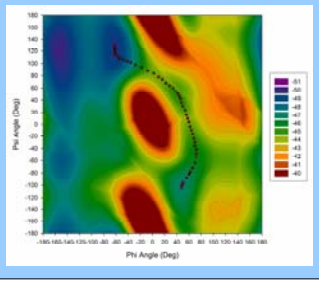
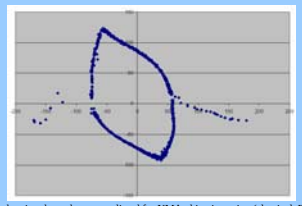


Image showing the QM and MM partitioning used in the QM/MM test. Hydrogen link atoms were placed a distance of 1 angstrom from the nitrogens along the bond vector that was broken.



Path Sampling

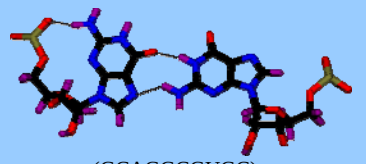
Each NEB simulation will find only one of the possible low energy pathways. Therefore it is essential that the implementation be tested to ensure it is sampling correctly. The simulated annealing procedure is repeated with different random number seeds to determine alternative pathways. The plot below shows the pathways predicted from an ensemble of 100 simulations of alanine dipeptide.



Plot showing the pathways predicted for NMA phi-psi rotation (classical, FF99) from 100 independent NEB simulated annealing runs.

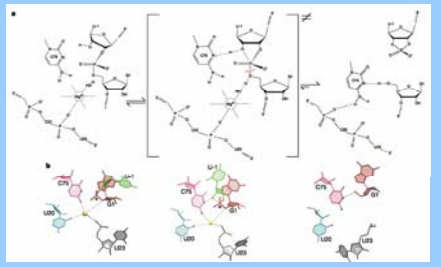
Real Systems

We are currently in the process of using this AMBER 9 implementation to study some systems of chemical and biological interest. These include using the classical implementation of NEB to study the GG mismatch conformational change in RNA and the QM/MM implementation to locate pathways for reactivity in the hepatitis delta virus (HDV) ribozyme.



r(GCAGGCGUGC)$_2$

Figure showing RNA GG Mismatch. Pathway originally proposed by Burkard & Turner. 2000. *Biochemistry 39*: 11748-11762.



Proposed mechanism for general acid-base catalysis in the HDV ribozyme. As proposed by Ke, A. *et al.* Nature, **429**, 2004, 201. It is this pathway that we are testing using the NEB approach.