# Double Feature

## Replica Exchange Gaussian Accelerated Molecular Dynamics (ReXGaMD) Simulations

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### In Short

- Method development
- Molecular dynamics
- Enhanced Conformational Sampling
- Replica Exchange
- Gaussian Accelerated MD Simulation

Many biological processes, such as protein folding, signal transduction or ligand binding, occur on time scales which are not reachable with conventional classical all-atom molecular dynamics (MD) simulations. This shortcoming is based on the high computational demand of this technique. To overcome this problem, enhanced sampling methods aim at increasing the conformational sampling of the molecular system to capture the dynamics emerging on higher time scales. Many different approaches for enhancing the conformational sampling exist. In this project, we combine two established enhanced sampling techniques, namely, replica exchange[1] and Gaussian accelerated MD simulations[2], to further improve the sampling.

In Gaussian accelerated molecular dynamics simulations (GaMD), a boost potential following a Gaussian distribution is added to the biological system. The idea is to raise energy wells in order to decrease energy barriers separating these minima (Figure 1). By descreasing energy barriers, transitions between energy minima become more likely than on the unbiased energy landscape. Energy values larger than a pre-defined boost energy are unchanged compared to the original energy surface. The Gaussian shape of the boost potential offers a more accurate reweighting of thermodynamic observables than in the original implementation of accelerated MD simulations[3],[4].

In replica exchange, many copies of the molecular system are simulated in parallel. All of these replicas are run under different conditions (e.g. different temperatures). After a specific number of simulation steps the coordinates of two neighbouring replicas, are exchanged if a defined exchange criterion is fullfilled. This process is repeated many times (Figure 1) so that each copy of the system is simulated under different conditions. The advantage of this technique is that one replica is always run at normal conditions

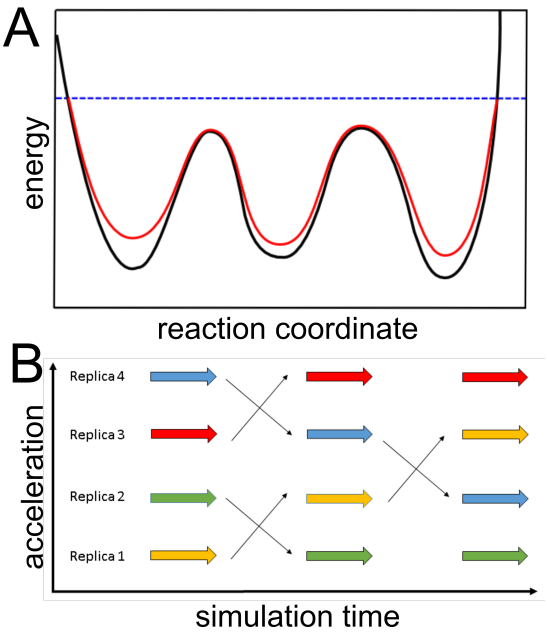


***Figure 1:** (A) Scheme of accelerated MD simulations. The black and red curves indicate the original and biased potentials, respectively. The dashed line denotes for the boost energy. (B) Scheme of replica exchange. In this example the exchange criterion is always fullfilled.*

but at different local energy minima during the simulation which allows an enhanced conformational sampling at unbiased conditions.

Our novel technique combining both enhanced sampling techniques is called replica exchange Gaussian accelerated molecular dynamics (ReXGaMD) simulations. It is already included and installed in the well-parallized sofware package NAMD on the HLRN architecture. ReXGaMD will be validated, tested and evaluated on small well-investigated molecular systems. We will sample the conformational flexibility of the backbone torsions in dialanine dipeptide, the folding of the fast-folding peptide chignolin, and the binding of benzene towards T4 lysozyme (Figure 2). The extent and efficiency of the conformational sampling compared with convential and GaMD simulations[2]. If the results show an increased performance, ReXGaMD will be applied to more complex systems, such as the tongue region of phytochromes. Here, our main intertest is to investigate protonation dependent refolding dynamics and the signal transduction.

### WWW

http://www.biomodeling.tu-berlin.de

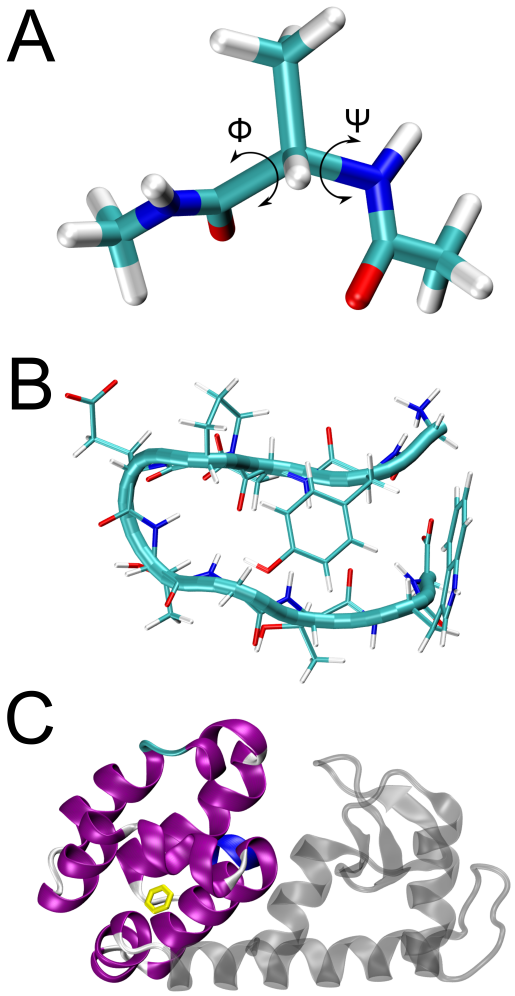


***Figure 2:*** *Test systems for ReXGaMD: (A) Flexibility of alanine dipeptide, (B) Folding of chignolin, (C) Binding of benzene to T4 lysozyme*

## More Information

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[4] Y. Miao, W. Sinko, L. Pierce, D. Bucher, R. C. Walker, J. A. McCammon, *J. Chem. Theory Comput.* **10**, 2677 (2014). doi:10.1021/ct500090q

## Funding

DFG, SFB1078