Efficient unbiased sampling of protein dynamics using reinforcement learning

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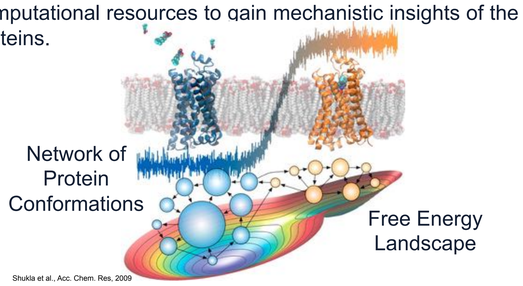
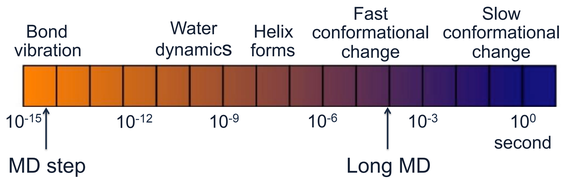
It is challenging to sample rare events via simulations.

Molecular dynamics (MD) simulations capture the atomistic details of the motions of atoms. We need powerful computational resources to gain mechanistic insights of the proteins.



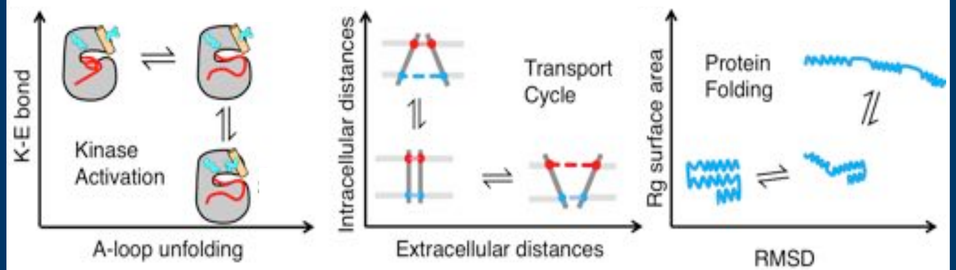
The main challenges in molecular dynamics simulations are simulation timescale and accuracy.



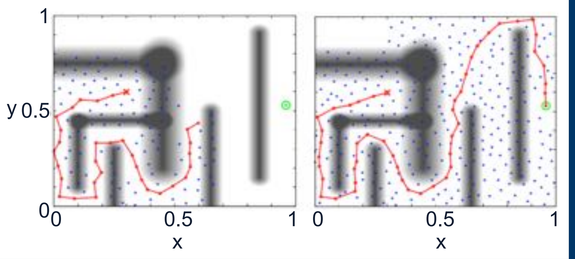
What is REinforcement learning based AdaPtive sampling?

REAP the rewards using Reinforcement Learning.

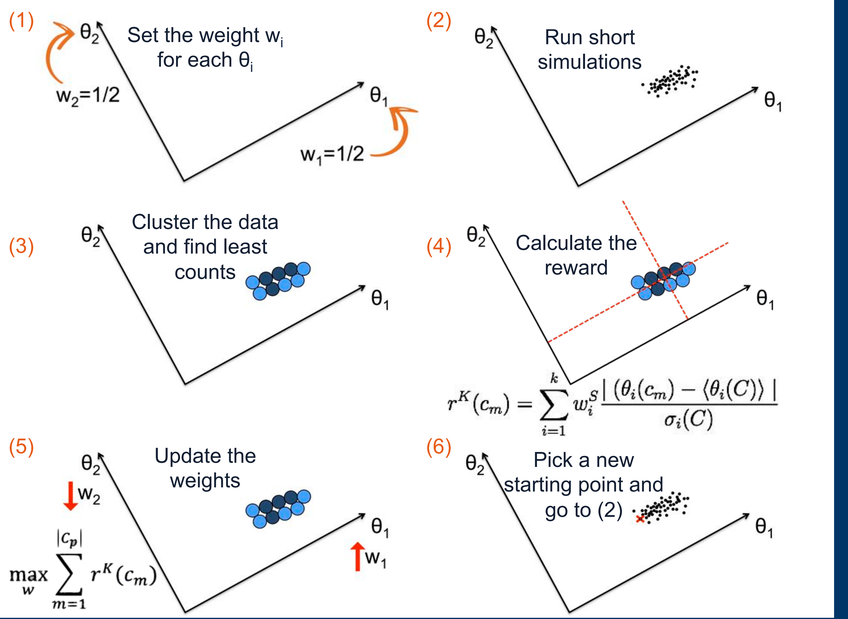
As one reaction coordinate is important for sampling, the other becomes less relevant.



REAP (REinforcement learning based Adaptive samPling) is "smart" enough to determine the importance of each order parameter (OP) as it explores the landscape and rewards sampling along important OP and disregards others that do not facilitate exploration or exploitation.



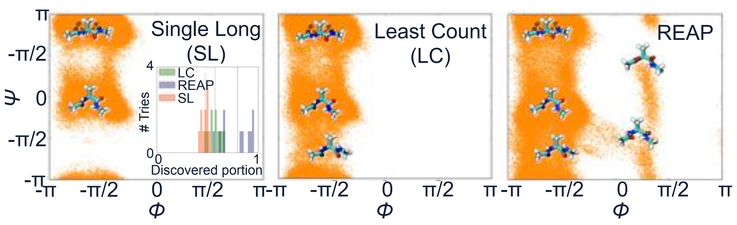
REAP Algorithm



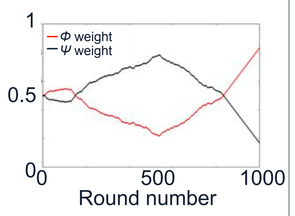
How effective is REAP?

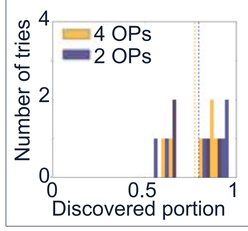
Conformational sampling: Alanine dipeptide

Total of 2 ns MD simulation of Alanine dipeptide using SL, LC, and REAP were performed. REAP samples the dihedral angle landscape more effectively in the same amount of simulation time.



The algorithm initially starts from φ direction, but quickly learns that ψ is the best to sample along

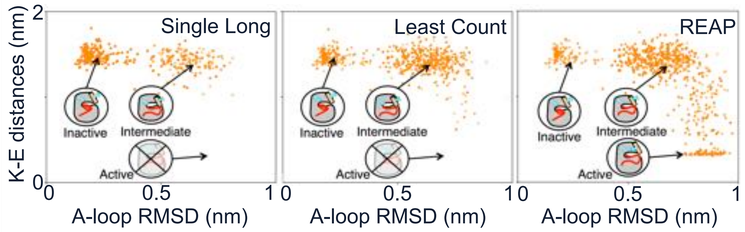


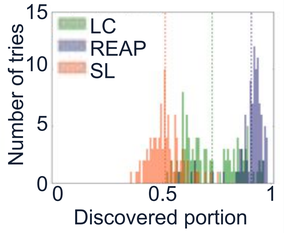


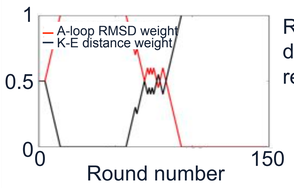
Performance of REAP using two extra OPs, θ, and ζ. Much like the results with the L landscape, sampling of 4 OPs is comparable with 2 OPs.

Enzyme activity: Src kinase activation

We furthermore demonstrated that the REAP algorithm's effectiveness in a protein system that has implications in cancer drug discovery. Total of 15 μs Monte Carlo simulations on MSM of Src kinase using SL, LC, and REAP were performed.

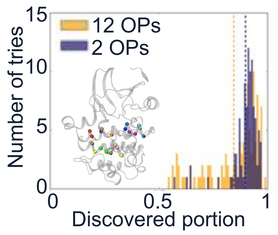






REAP initially finds sampling along the A-loop RMSD more important than K-E distance. Afterwards, the weights fluctuate until the K-E distance then becomes relevant for sampling.

Comparable result was achieved by providing 10 insignificant distances situated on the αE and αF helix (12 OPs total).



Conclusion

The proposed algorithm, REAP, has been shown to efficiently sample landscapes. It achieves this by identifying which RCs maximizes a reward function that encourages exploratory behavior. In all systems that were studied, REAP consistently outperformed the traditional simulation approach and least count based sampling when examining the distribution landscape discovered for the same simulation time.

Shamsi, Z., Cheng, J. K., & Shukla, D. REinforcement learning based Adaptive samPling: REAPing Rewards by Exploring Protein Conformational Landscapes, arXiv: 1710.00495, 2017.

Acknowledgements

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