PathRover – Rapid Sampling and Optimization of Molecular Motions

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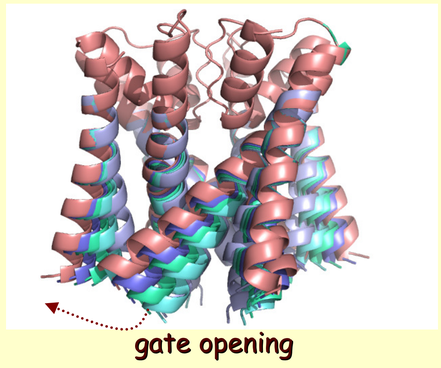
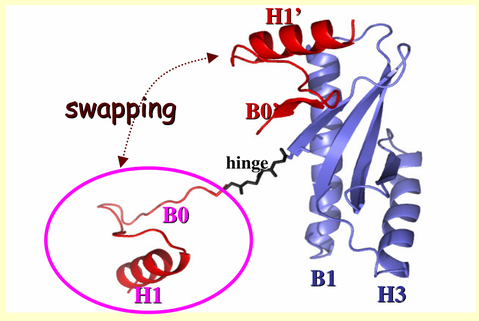
Proteins are active, flexible machines that perform a range of different functions. PathRover is a general framework for generating and optimizing collision-free and low-energy motion pathways between protein conformations while considering a wide range of degrees of freedom involved in the motion.

Protein Molecular Motion

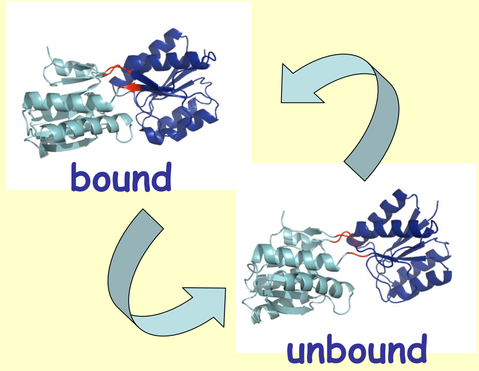
Ion Channels Gating



Domain Swapping



Substrate Binding



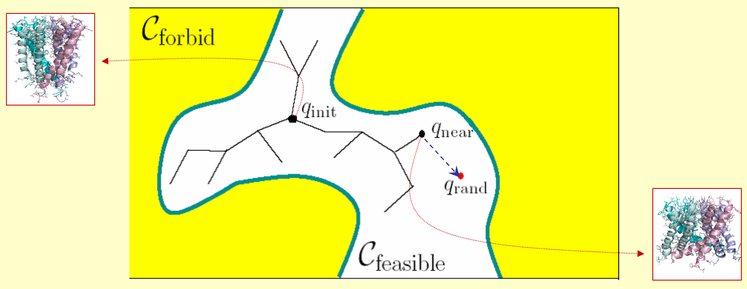
Faster Alternative to Molecular Dynamics?

Molecular Dynamics (MD) is used to predict molecular motion based on first principle physics, but it is relatively slow and cannot generate a very large number of pathways, hence a faster alternative is needed.

Algorithms for Predicting Motion in PathRover

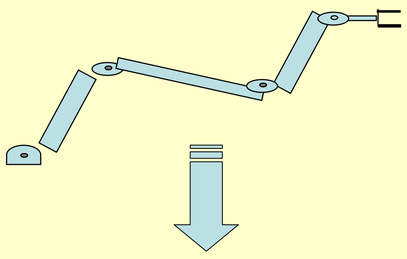
Robotic Motion Planning

Rapidly-exploring Random Trees (RRT): finding your way among obstacles [1]

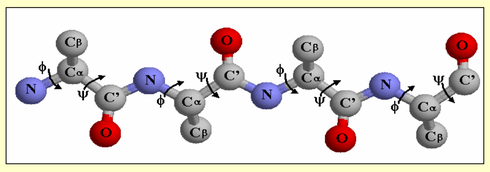


From Robotics to Biology:

Industrial robot arm: joints, links and degrees of freedom (e.g. elbow)

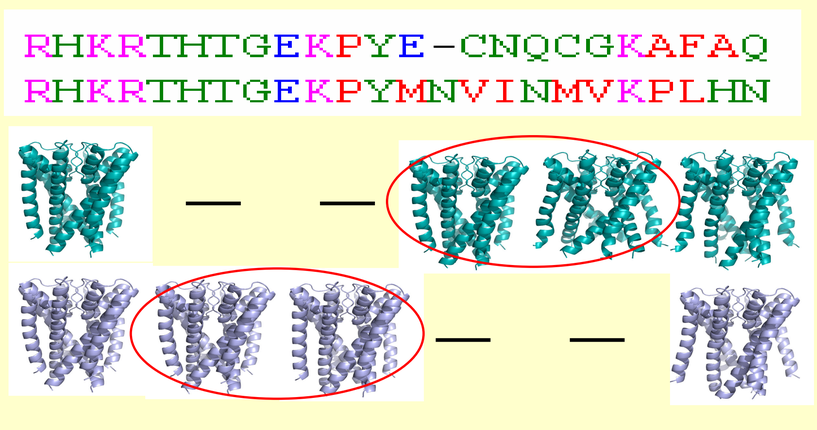


Peptide chain: joints, links and degrees of freedom ***(Φ,Ψ)***

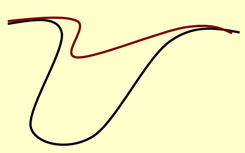


Pathway Optimization

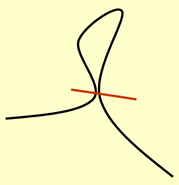
Similarity of Molecular Motion Pathways, Reminiscent of String Matching



Pathways Hybridization: optimal pathway from suboptimal segments



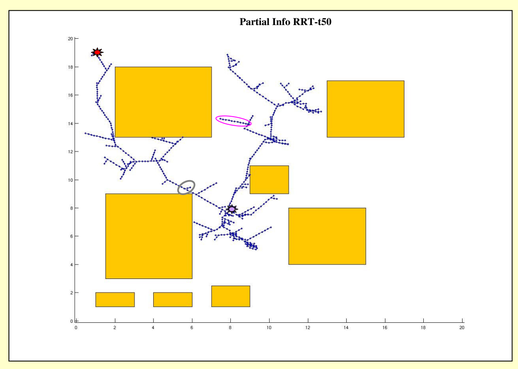
Choosing among sub-optimal alternatives



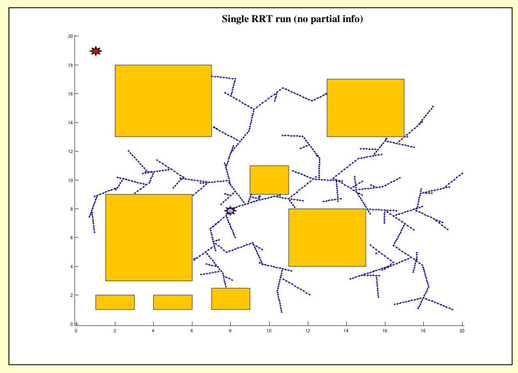
Finding Shortcuts

Incorporating Partial Information

Branch Truncation using Predicates on Partial Information



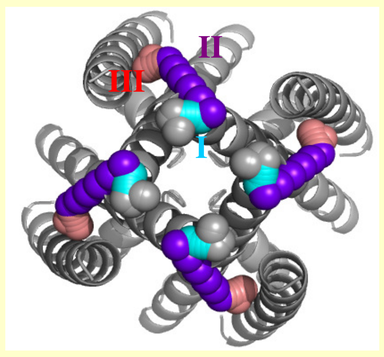
Partial Info RRT



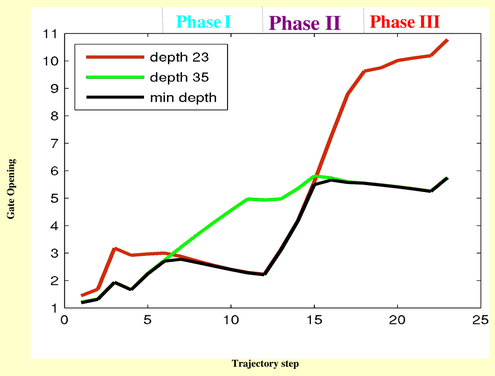
Standard RRT

Understanding Molecular Function with PathRover

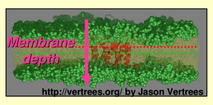
A Suggested Three Phase Secure Mechanism for Opening of a Potassium Channel: (I) unlock (II) open (III) relock

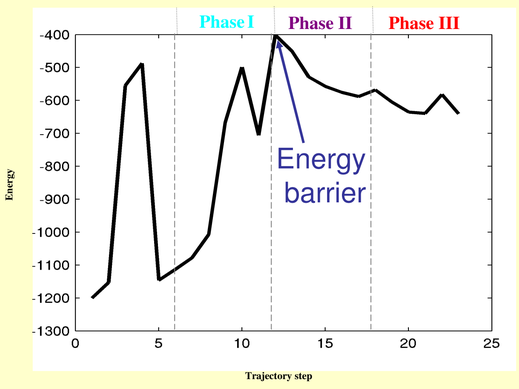


The pathway of V155 traced in spacefill balls, going through the three phases: (I) unlock (II) open (III) relock.



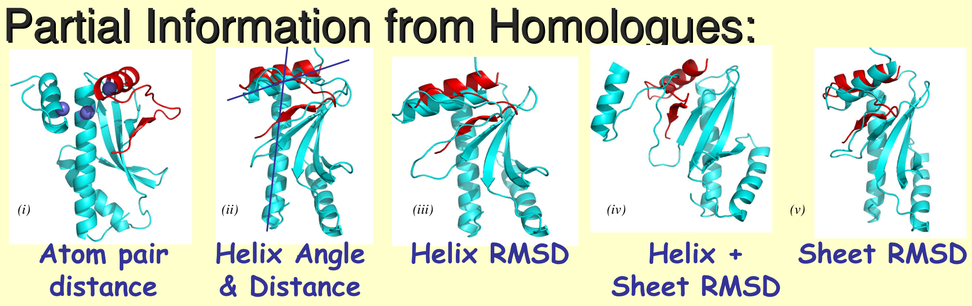
Channel first opens at depth 35Å in the membrane, and only then at depth 23Å





Energy plot through the three phases, with energy barrier crossed between phase 1 and phase 2.

Understanding Domain Swapping with Partial Information from Homologues:



Integration into Rosetta Modeling Package

Rosetta[2] is a comprehensive framework for different molecular modeling tasks. It equips PathRover with state of the art energy function, optimization and sampling protocols.

Conclusions: ***The PathRover framework complements slower molecular dynamics techniques and furthers our knowledge of protein function. Generated pathways form experimentally testable hypotheses, and can be subjected to thorough theoretical analysis. Specifically, we showed here the contribution of such analysis for examples of domain swapping and gating of Ion channels.***

References:

[1] LaValle, S.M. (2006) Planning Algorithms. *Cambridge University Press.* http://msl.cs.uiuc.edu/planning/.

[2] Rohl,C.A., Strauss,C.E., Misura,K.M. and Baker,D. (2004) Protein structure prediction using Rosetta. *Methods Enzymol,* 383, 66–93.