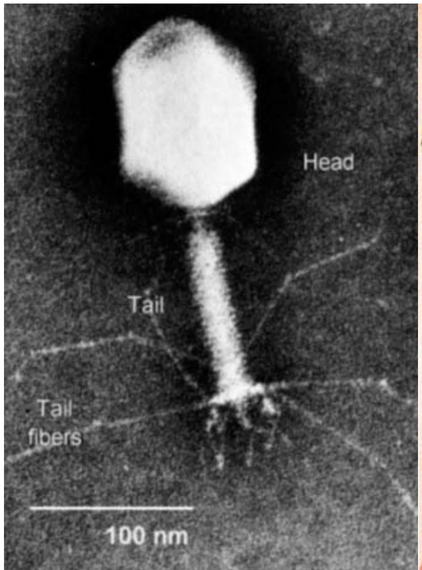
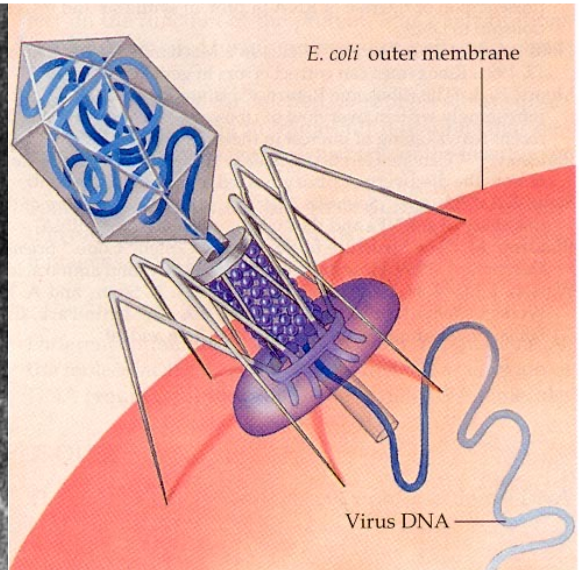
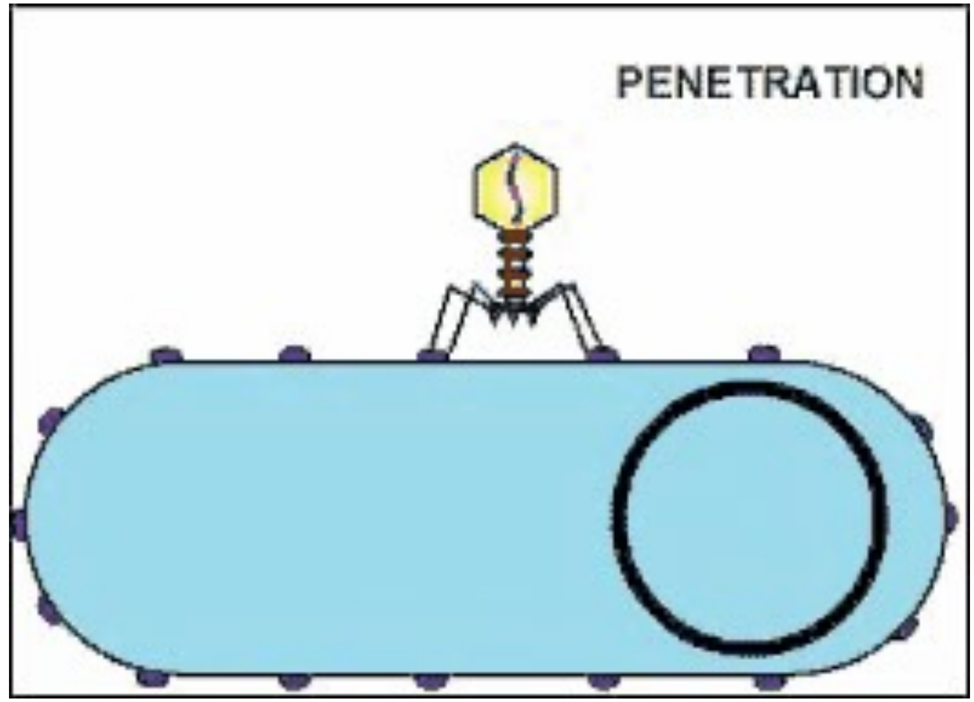
Motivation: Bacteriophage





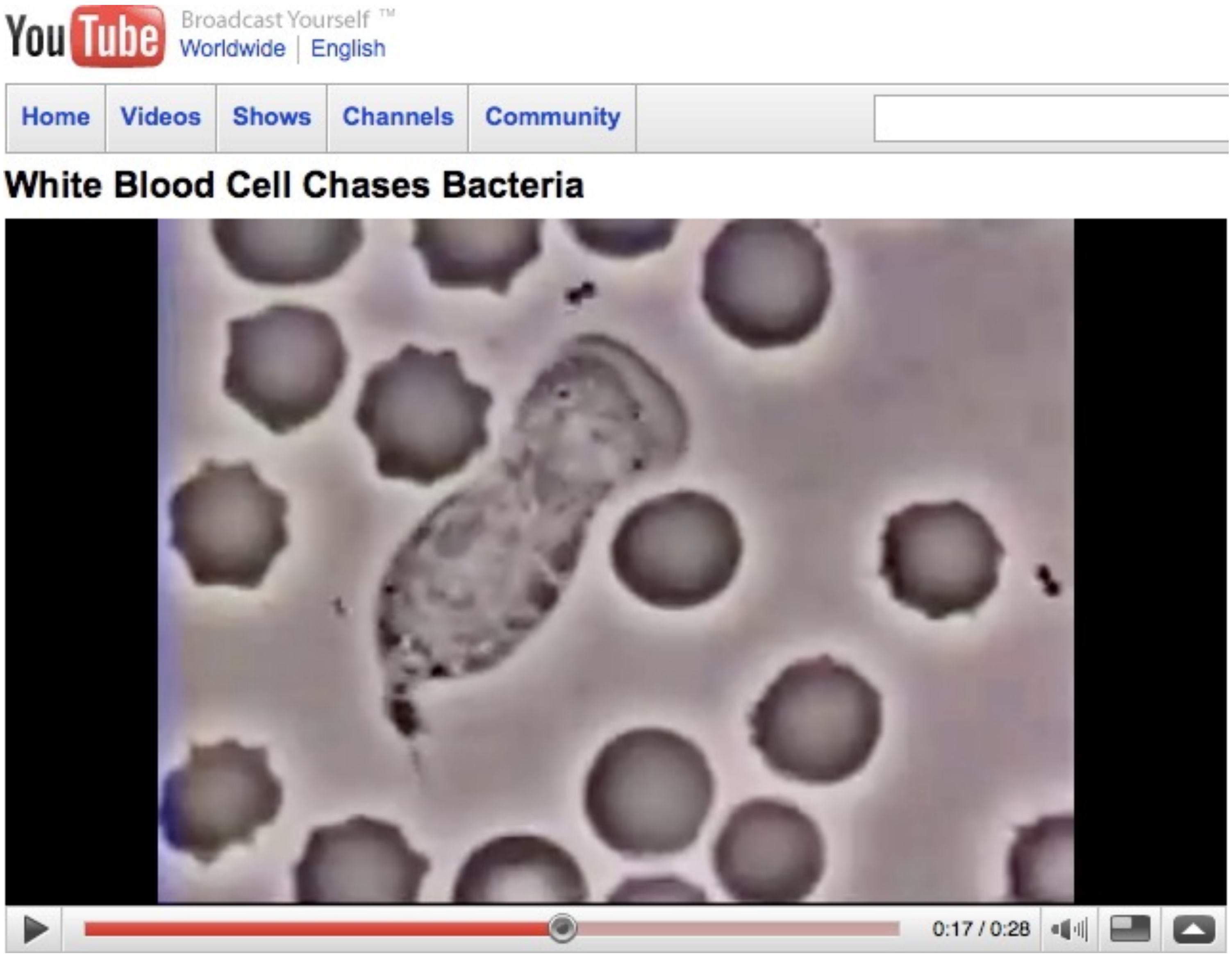


100-parts autonomous machine to search for, recognize & land on a target cell, drill a hole & inject DNA, which is self-assembled!

See [How coronavirus works]

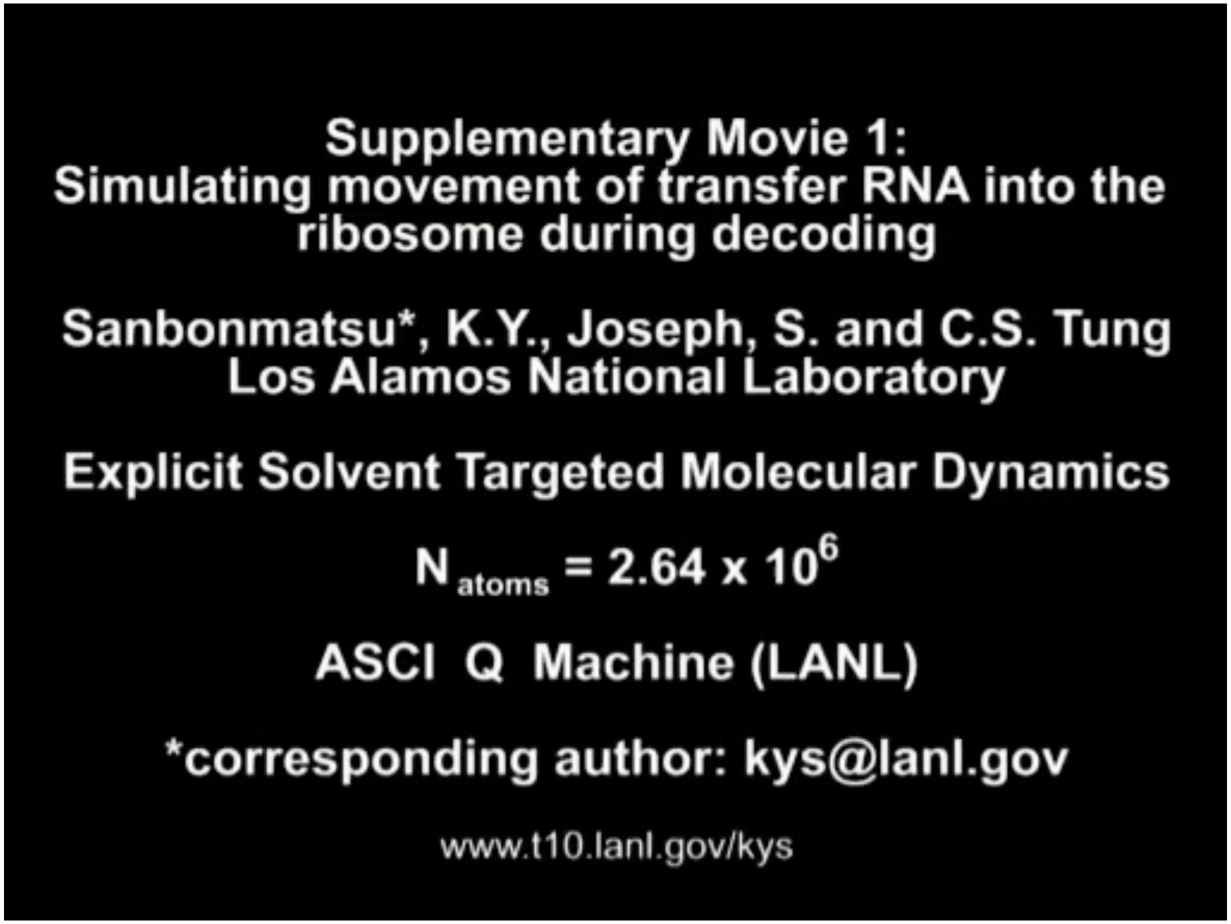
None of the methods we have learned can simulate this

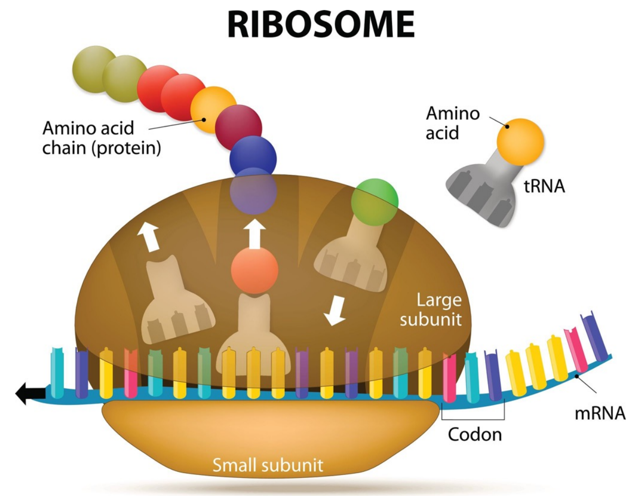
White Blood Cell Chases Bacteria



http://www.youtube.com/watch?v=JnlULOjUhSQ&eurl=http://video.google.com/videosearch?q=White%20Blood%20Cell%20Chases%20Bacteria&oe=utf-8&rls=org.mozilla:&feature=player_embedded

Transfer RNA in Ribosome





Ribosome synthesizes proteins by binding messenger RNA & transfer RNA

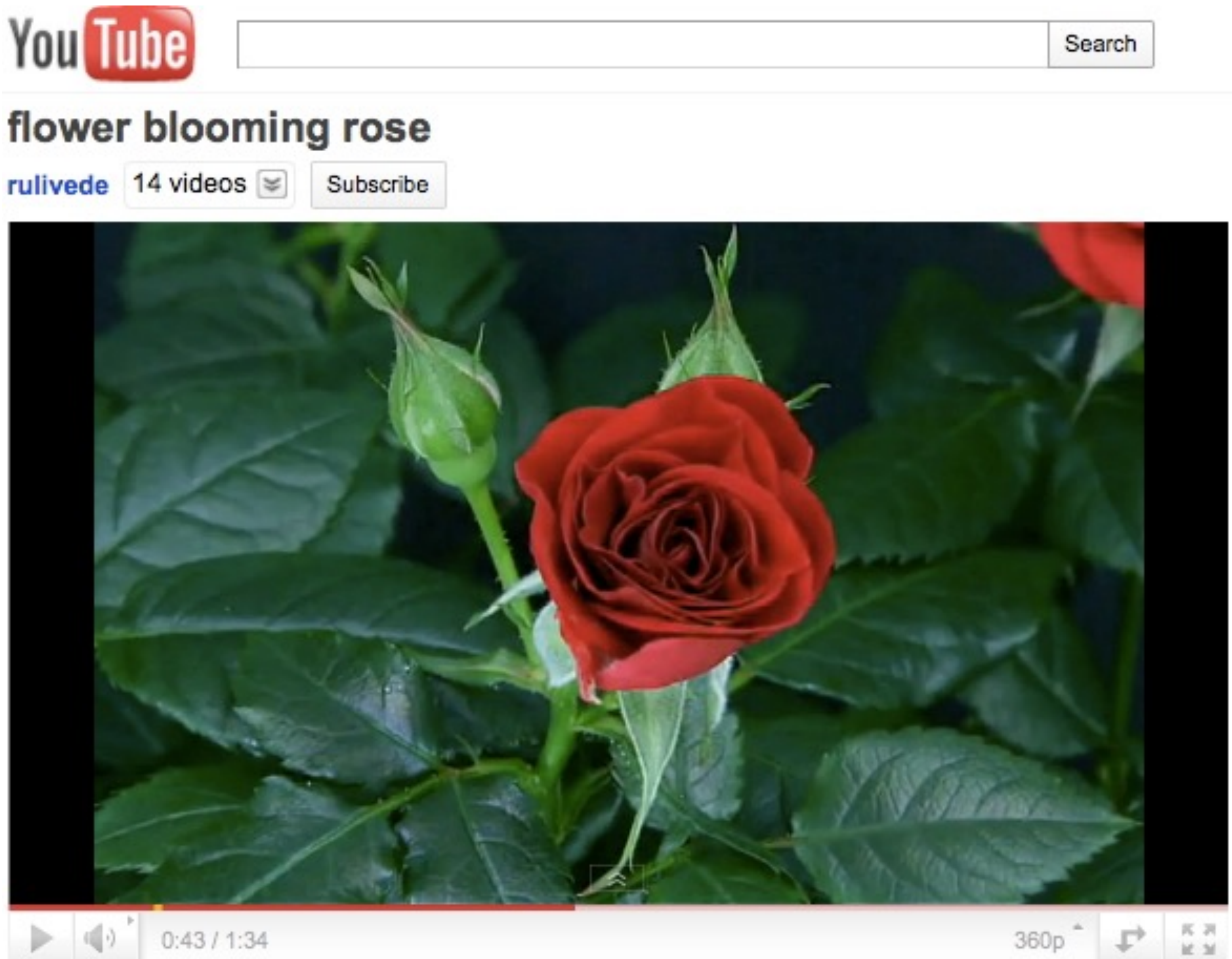
https://www.lanl.gov/projects/karissa/images/03456Movie1.mov

Long-time dynamics *via* a series of rare events!

Time Lapse Simulation?

Yes, it's called accelerated dynamics

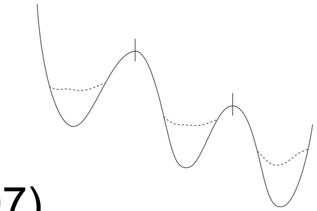
D. Perez *et al*., *Ann. Rep. Comput. Chem.* **5**, 79 ('09)



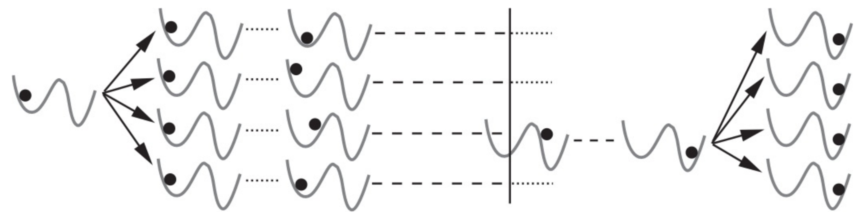
http://www.youtube.com/watch?v=HnbMYzdjuBs&feature=related


Accelerated Molecular Dynamics Methods: Introduction and Recent Developments
Danny Perez[1], Blas P. Uberuaga[2], Yunsic Shim[3], Jacques G. Amar[3] and Arthur F. Voter[1]
Accelerating atomic orbital-based electronic structure calculation via pole expansion and selected inversion
Lin Lin[1], Mohan Chen[2], Chao Yang[1] and Lixin He[2]
Decaheme Cytochrome MtrF Adsorption and Electron Transfer on Gold Surface
Tao Wei,*,† Heng Ma,† and Aiichiro Nakano*,‡,§,∥,⊥
STOP

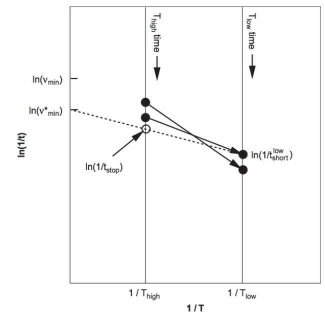
Accelerated Molecular Dynamics



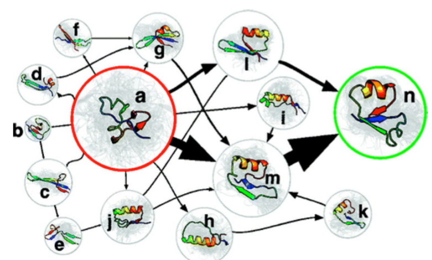
- **Hyperdynamics**
  A. F. Voter, *J. Chem. Phys*. **106**, 4665 ('97)



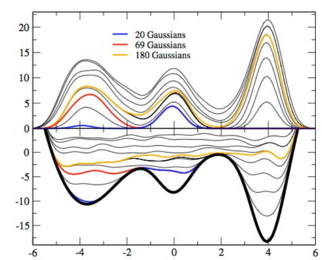
- **Parallel replica dynamics**
  A. F. Voter, *Phys. Rev. B* **57**, R13985 ('98)



- **Temperature accelerated dynamics**
  M. R. Sorensen & A. F. Voter, *J. Chem. Phys*. **112**, 9599 ('00)

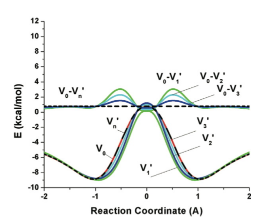


- **Markov state model**
  V. Pande, *et al*., *Methods* **52**, 99 ('10)



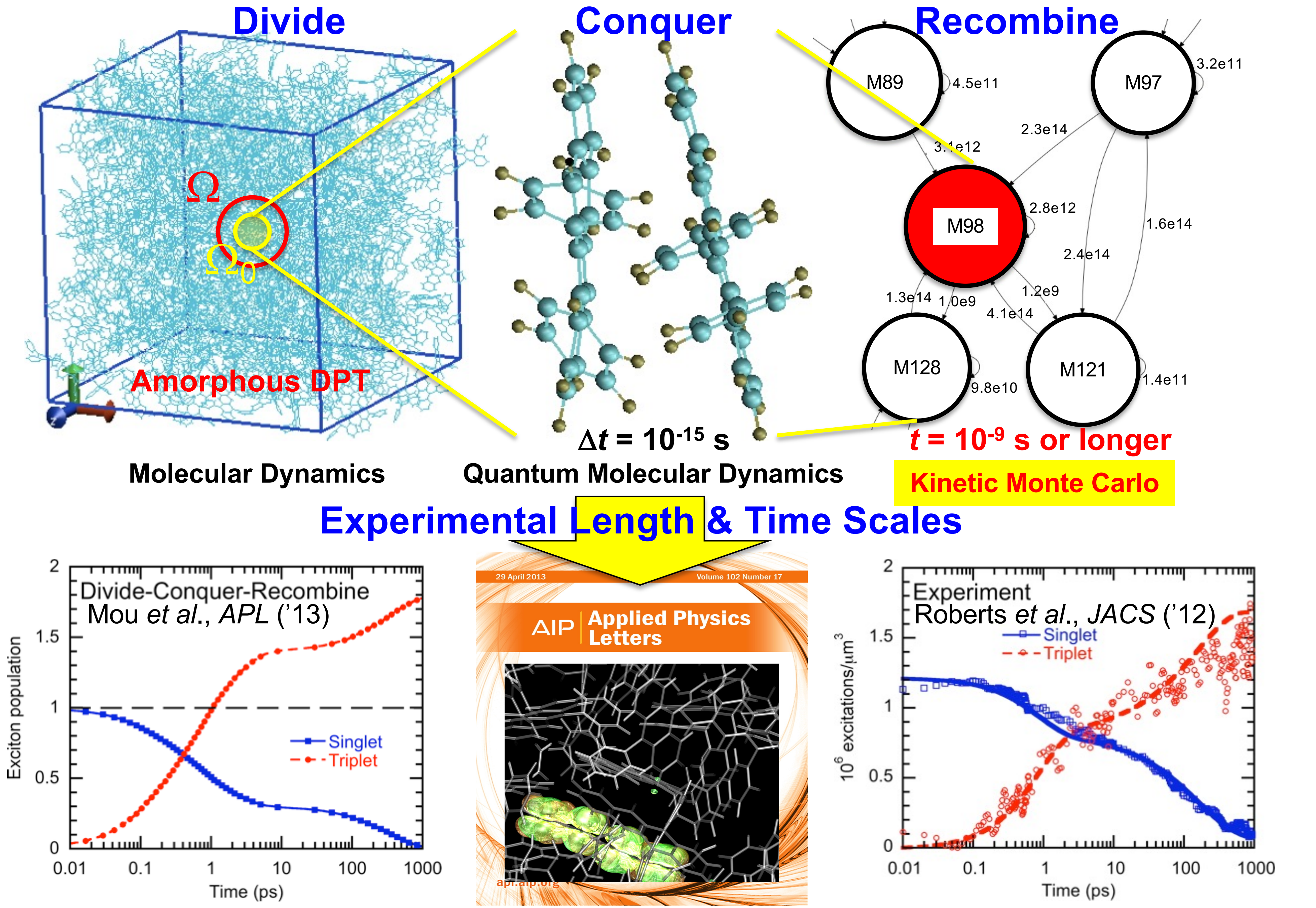
- **Metadynamics**
  A. Laio & M. Parrinello, *Proc. Nat'l Acad. Sci*. **99**, 12562 ('02)

- **Paradynamics**
  N. V. Plotnikov, S. C. L. Kamerlin & A. Warshel, *J. Phys. Chem. B* **115**, 7950 ('11)



...

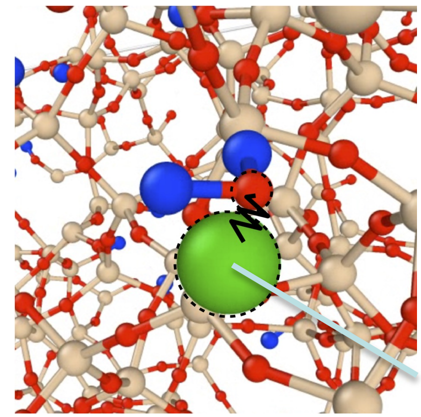
Divide-Conquer-Recombine KMC

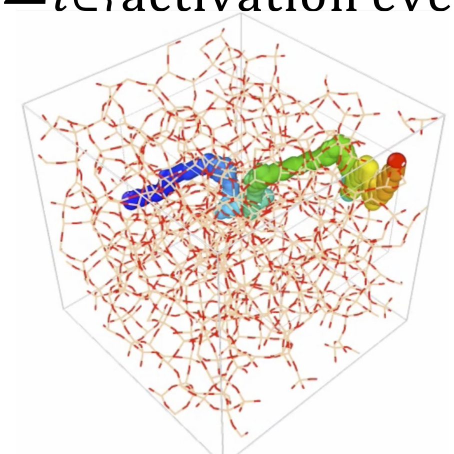


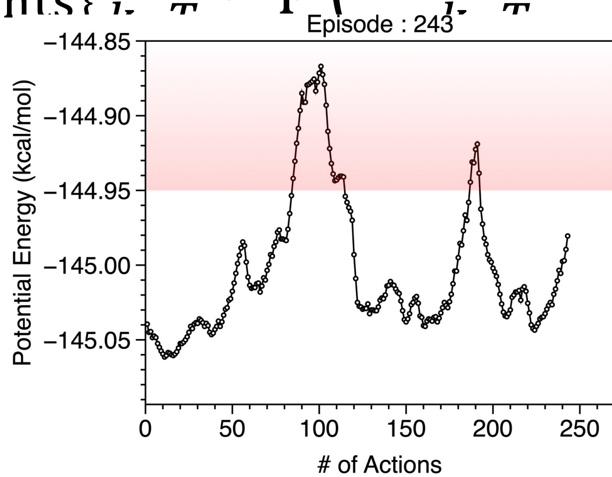
Reinforcement Learning for Long-Time Dynamics

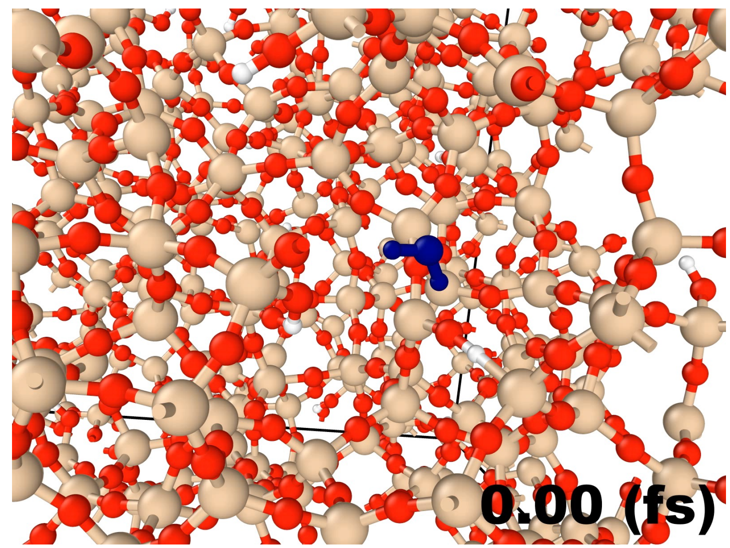
- **Reinforcement learning agents autonomously discover low-activation-barrier migration pathways to study long-time dynamics**
- **Multiple agents share experience using an asynchronously updated replay buffer** [Silver *et al.*, *Nature* **529**, 484 ('16)]
- **Estimate migration time based on the transition-state theory:**

$$t_{\mathrm{migration}} = \sum_{i \in \{\mathrm{activation\ events}\}} \frac{\hbar}{k_B T} \exp\left(\frac{E_i^{\mathrm{activation}}}{k_B T}\right)$$









2-seconds trajectory

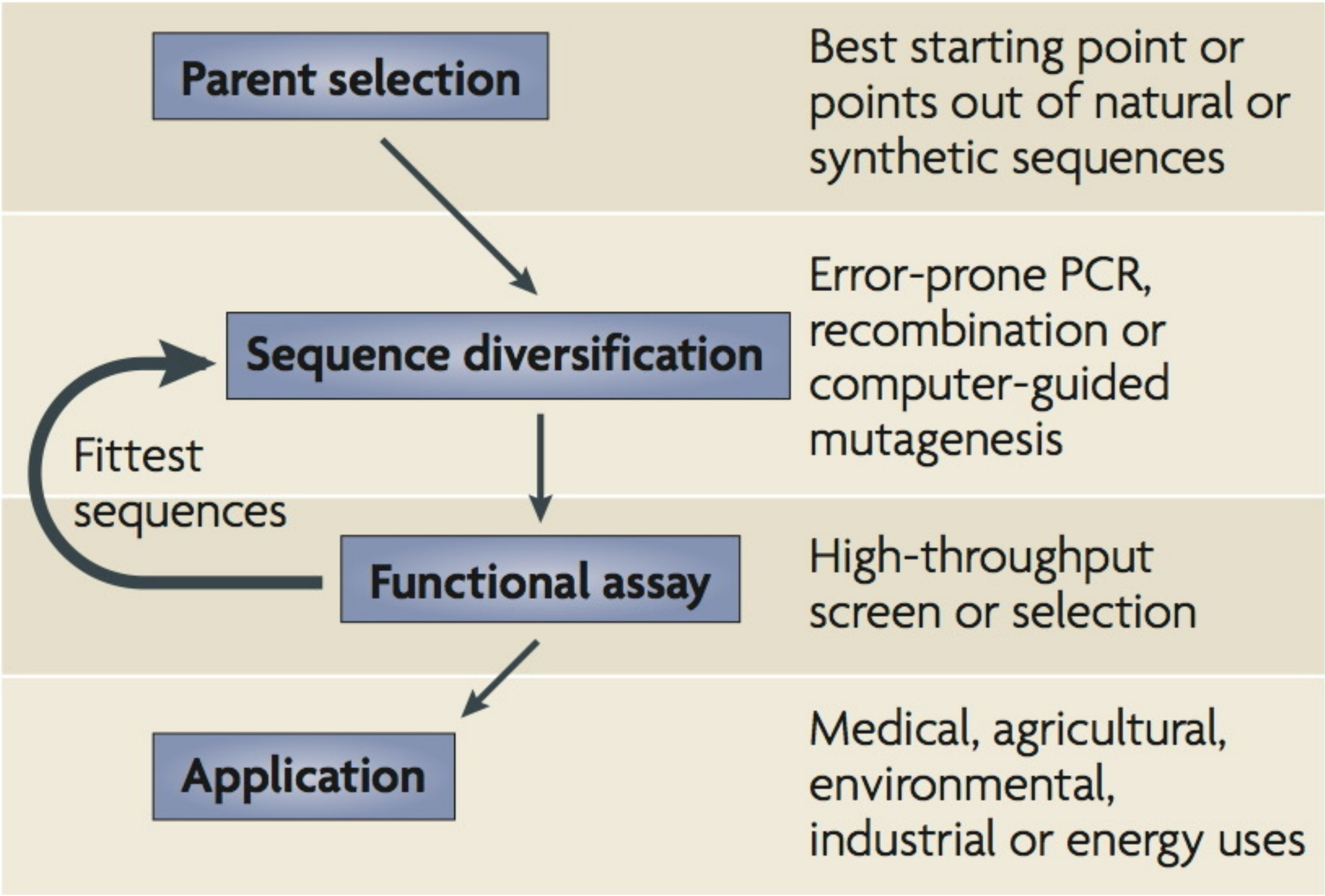
Low-activation-barrier H_2O migration pathway in SiO_2

Application to CO_2 storage through mineralization in wet silicates

Accelerated Evolution?

Directed evolution

P. A. Romero & F. H. Arnold, *Nature Rev. Mol. Cell Biol*. **10**, 867 ('09)



Accelerating directed evolution to design new materials *in silico*?

Nobel Chemistry Prize in 2018

Frances H. Arnold

Prize share: 1/2

George P. Smith

Prize share: 1/4

Sir Gregory P. Winter

Prize share: 1/4

The Nobel Prize in Chemistry 2018 was divided, one half awarded to Frances H. Arnold "for the directed evolution of enzymes", the other half jointly to George P. Smith and Sir Gregory P. Winter "for the phage display of peptides and antibodies."

Evolbability?

Abstract. Living organisms function in accordance with complex mechanisms that operate in different ways depending on conditions. Darwin's theory of evolution suggests that such mechanisms evolved through variation guided by natural selection. However, there has existed no theory that would explain quantitatively which mechanisms can so evolve in realistic population sizes within realistic time periods, and which are too complex. In this article, we suggest such a theory. We treat Darwinian evolution as a form of computational learning from examples in which the course of learning is influenced only by the aggregate fitness of the hypotheses on the examples, and not otherwise by specific examples. We formulate a notion of evolvability that distinguishes function classes that are evolvable with polynomially bounded resources from those that are not. We show that in a single stage of evolution monotone Boolean conjunctions and disjunctions are evolvable over the uniform distribution, while Boolean parity functions are not. We suggest that the mechanism that underlies biological evolution overall is "evolvable target pursuit", which consists of a series of evolutionary stages, each one inexorably pursuing an evolvable target in the technical sense suggested above, each such target being rendered evolvable by the serendipitous combination of the environment and the outcomes of previous evolutionary stages.

L. G. Valiant, *J. ACM* **56(1)**, 3 ('09)