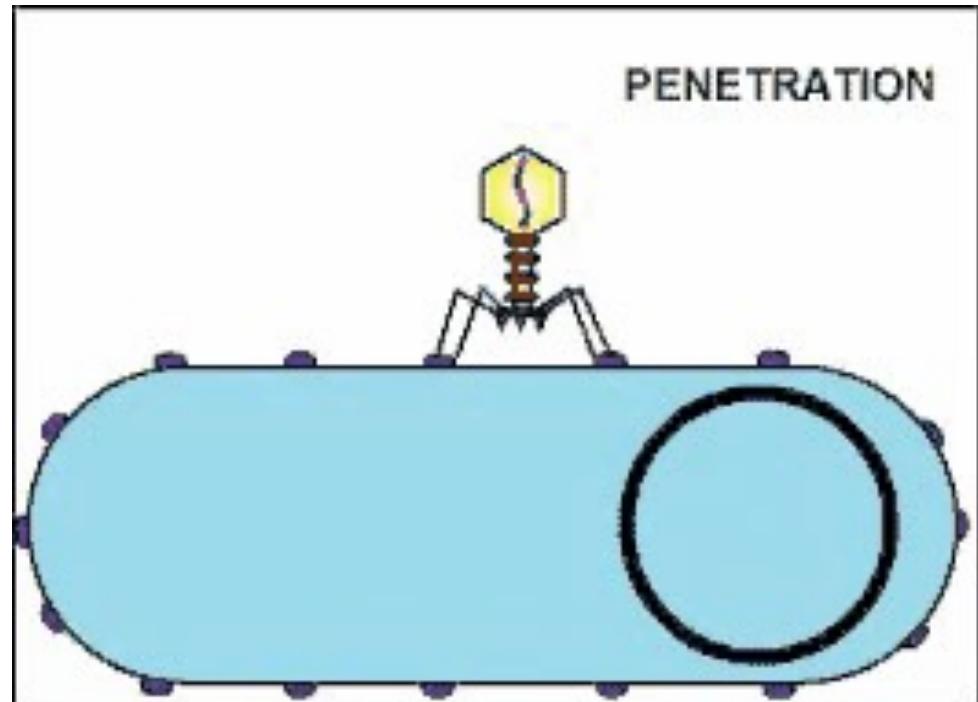
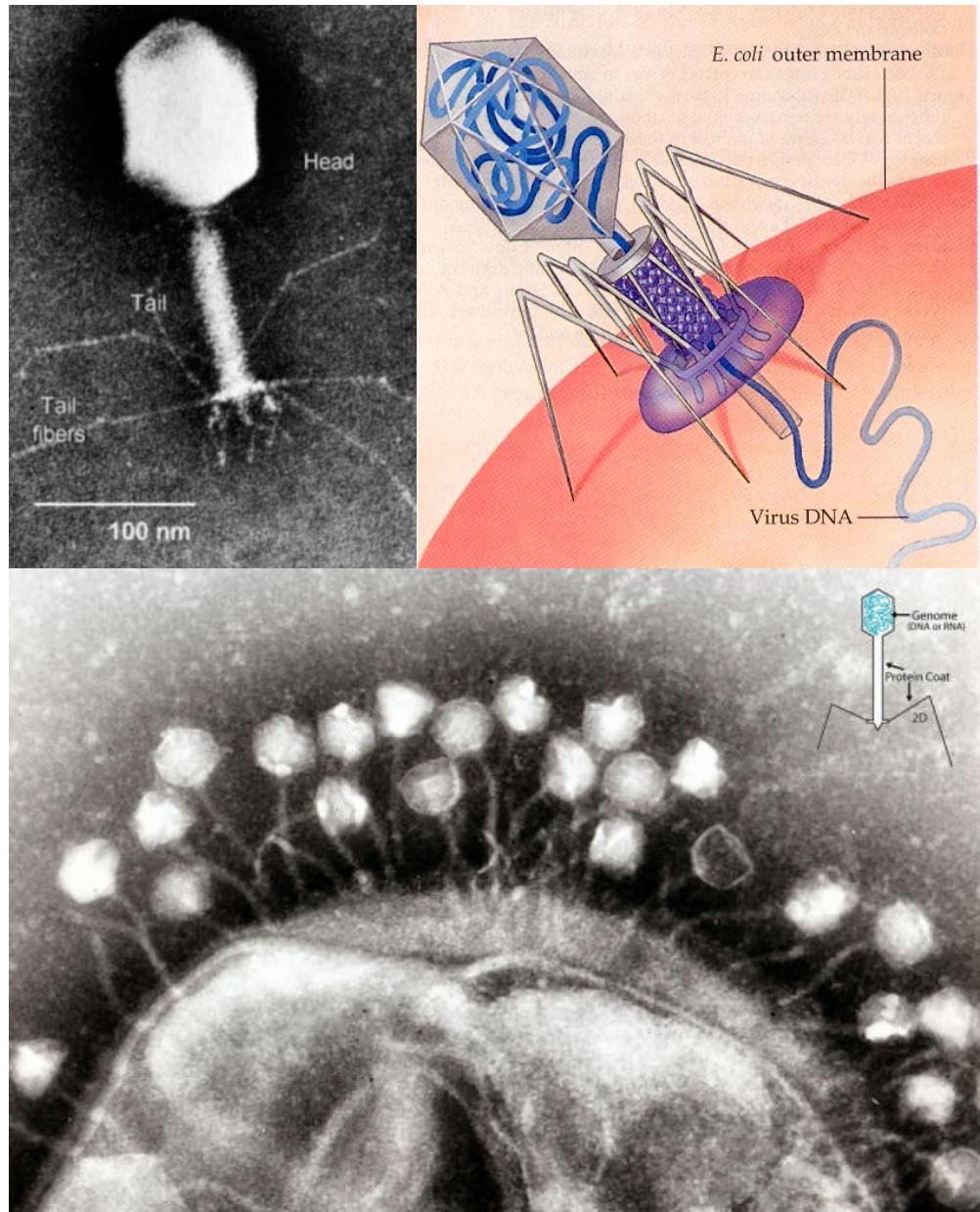


# Motivation: Bacteriophage



**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



Broadcast Yourself™  
Worldwide | English

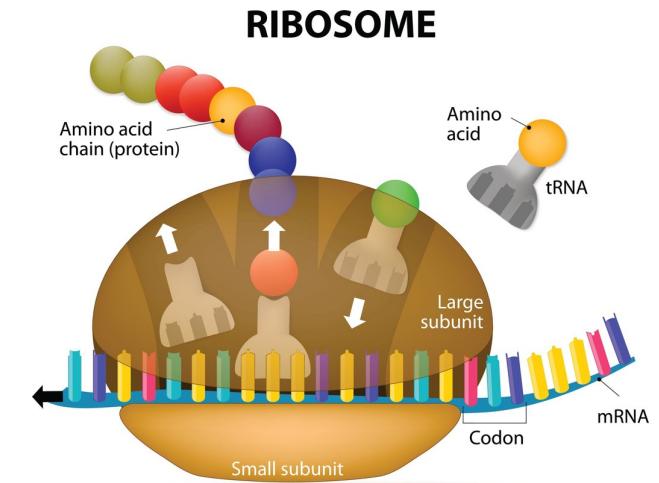
Home Videos Shows Channels Community

## White Blood Cell Chases Bacteria



[http://www.youtube.com/watch?v=JnIULOjUhSQ&eurl=http://video.google.com/videosearch?q=White%20Blood%20Cell%20Chases%20Bacteria&oe=utf-8&rls=org.mozilla:&feature=player\\_embedded](http://www.youtube.com/watch?v=JnIULOjUhSQ&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



**Supplementary Movie 1:  
Simulating movement of transfer RNA into the  
ribosome during decoding**

**Sanbonmatsu\*, K.Y., Joseph, S. and C.S. Tung  
Los Alamos National Laboratory**

**Explicit Solvent Targeted Molecular Dynamics**

$$N_{\text{atoms}} = 2.64 \times 10^6$$

**ASCI Q Machine (LANL)**

**\*corresponding author: kys@lanl.gov**

[www.t10.lanl.gov/kys](http://www.t10.lanl.gov/kys)

**Ribosome synthesizes  
proteins by binding  
messenger RNA &  
transfer RNA**

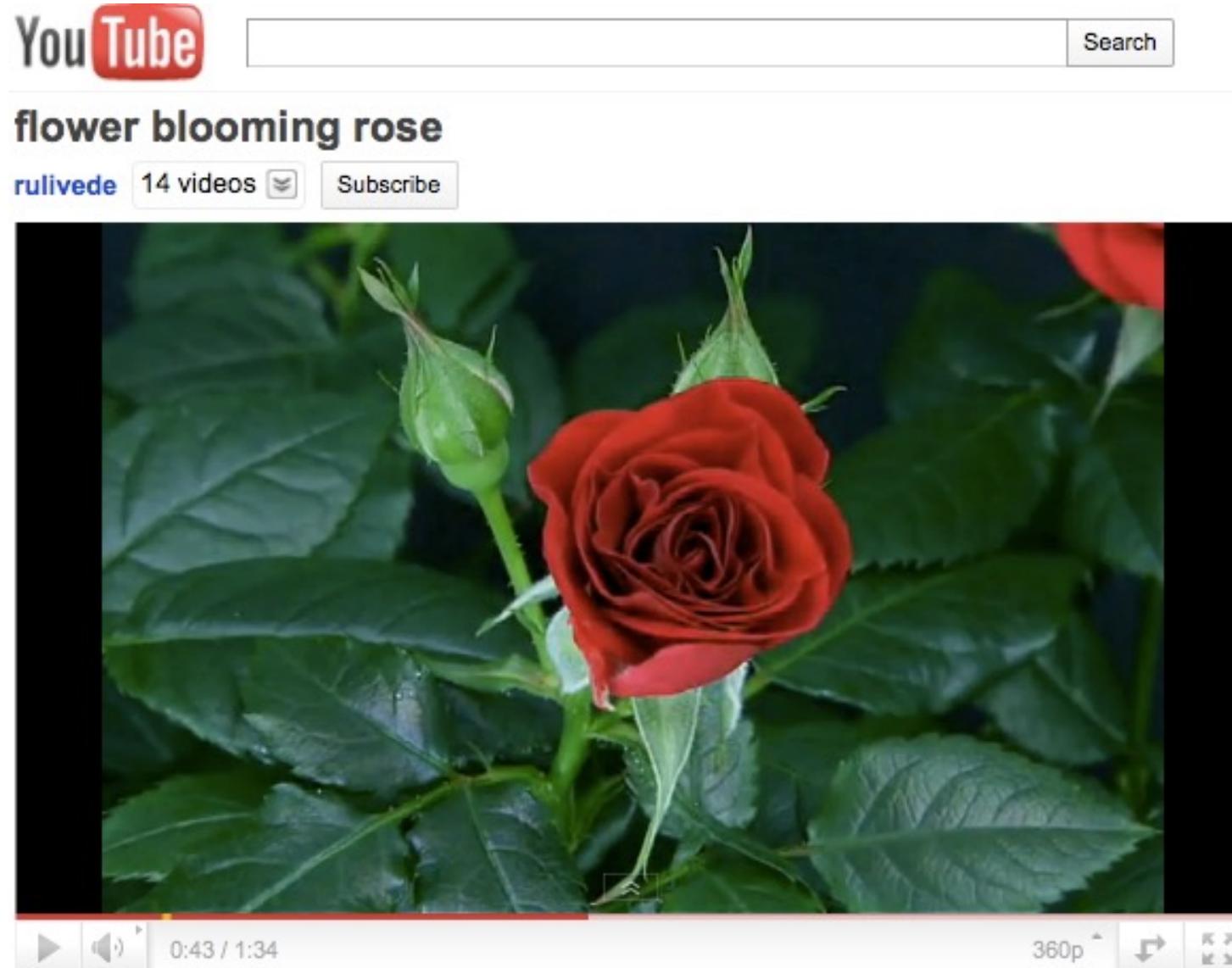
<http://sanbonmatsu.org/images/03456Movie1.mov>

**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<sup>1</sup>, Blas P. Uberuaga<sup>2</sup>, Yunsic Shim<sup>3</sup>,  
Jacques G. Amar<sup>3</sup> and Arthur F. Voter<sup>1</sup>

## Decaheme Cytochrome MtrF Adsorption and Electron Transfer on Gold Surface

Tao Wei,<sup>\*,†</sup> Heng Ma,<sup>†</sup> and Aiichiro Nakano<sup>\*,‡,§,||,¶</sup>

# Accelerating atomic orbital-based electronic structure calculation via pole expansion and selected inversion

Lin Lin<sup>1</sup>, Mohan Chen<sup>2</sup>, Chao Yang<sup>1</sup> and Lixin He<sup>2</sup>

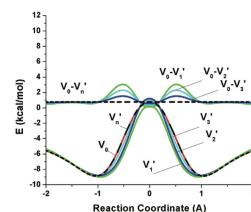
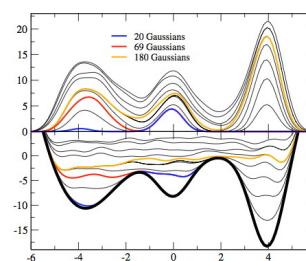
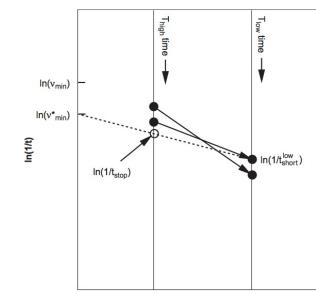
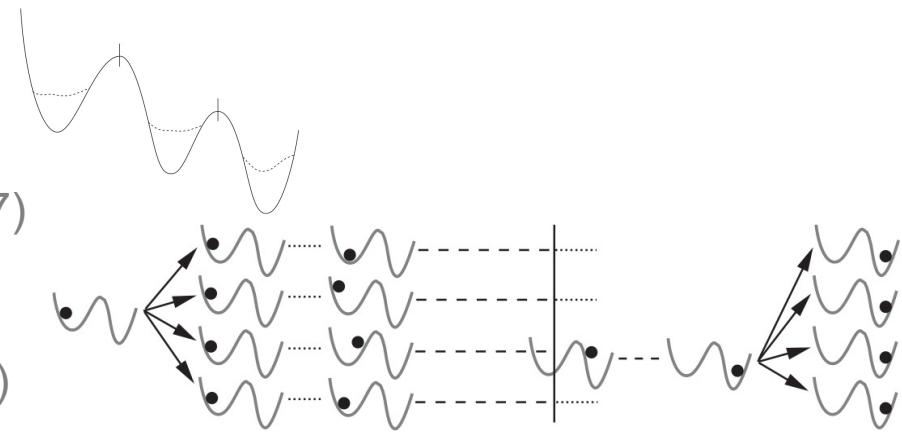


# Accelerated Molecular Dynamics

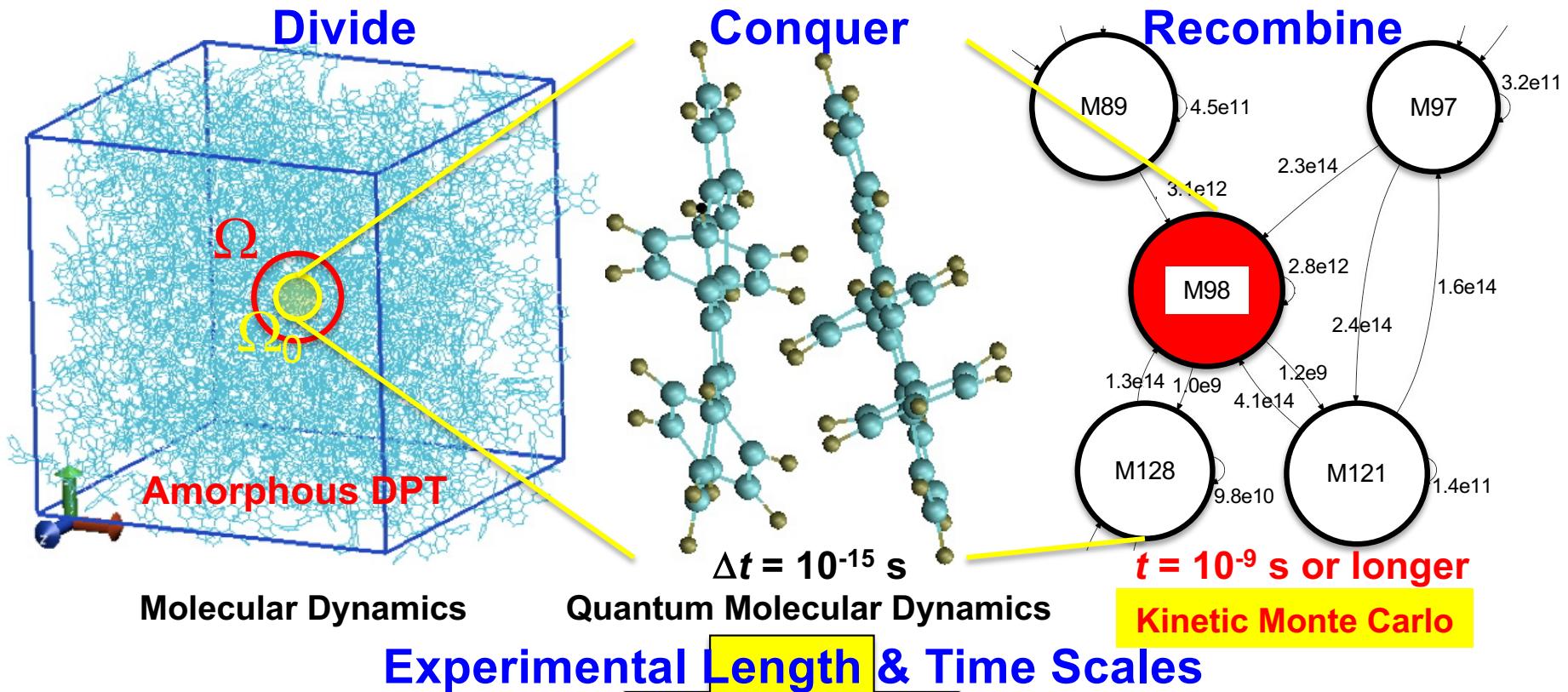
- **Hyperdynamics**  
A. F. Voter, *J. Chem. Phys.* **106**, 4665 ('97)
  - **Parallel replica dynamics**  
A. F. Voter, *Phys. Rev. B* **57**, R13985 ('98)
  - **Temperature accelerated dynamics**  
M. R. Sorensen & A. F. Voter, *J. Chem. Phys.* **112**, 9599 ('00)
  - **Markov state model**  
V. Pande, *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)

The slide contains several diagrams and plots related to molecular dynamics methods:

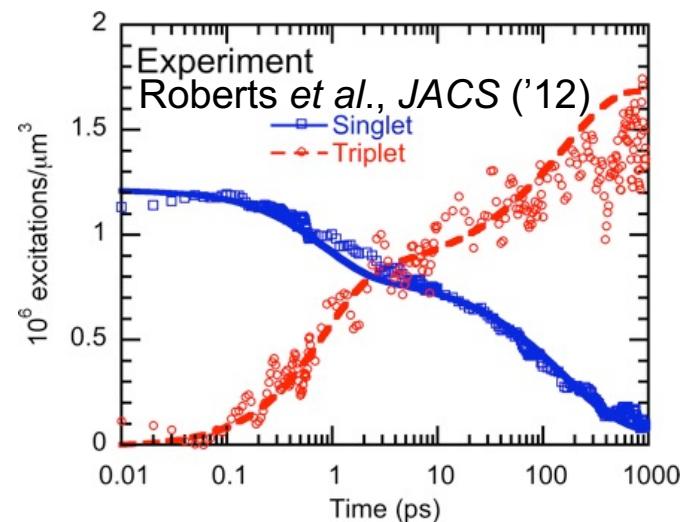
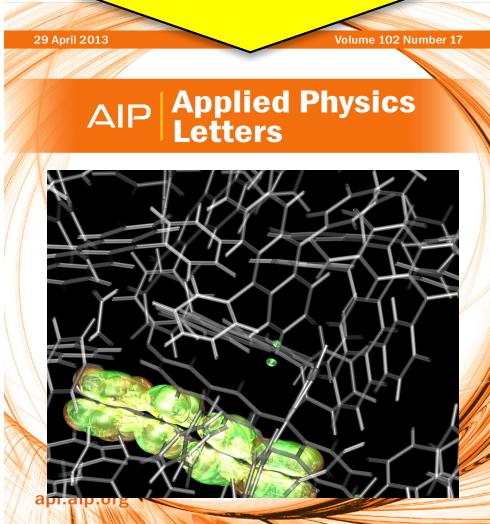
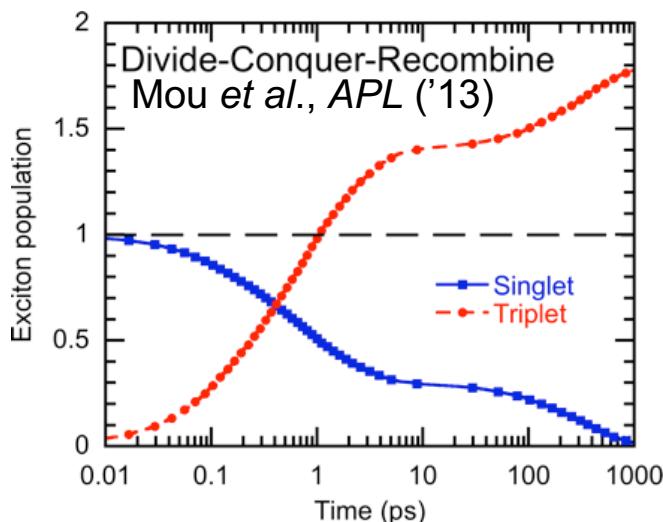
  - A schematic diagram showing multiple parallel replica trajectories starting from different initial states and converging towards a common final state.
  - A plot of natural logarithms of rates versus inverse temperature ( $1/T$ ). The y-axis includes labels for  $\ln(v_{min})$ ,  $\ln(v^*_{min})$ ,  $\ln(1/t_{stop})$ , and  $\ln(1/t_{stop}^{low})$ . The x-axis has labels for  $1/T_{high}$  and  $1/T_{low}$ .
  - A plot of probability density versus a coordinate  $s$  showing multiple Gaussian curves for different numbers of Gaussians: 20, 69, and 180.
  - A circular diagram representing a Markov State Model (MSM) with states labeled a through n. State 'a' is highlighted with a red circle, indicating it is a metastable state.



# Divide-Conquer-Recombine KMC



## Experimental Length & Time Scales

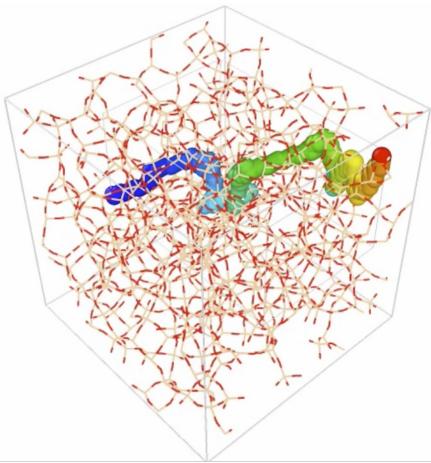


# Reinforcement Learning for Long-Time Dynamics

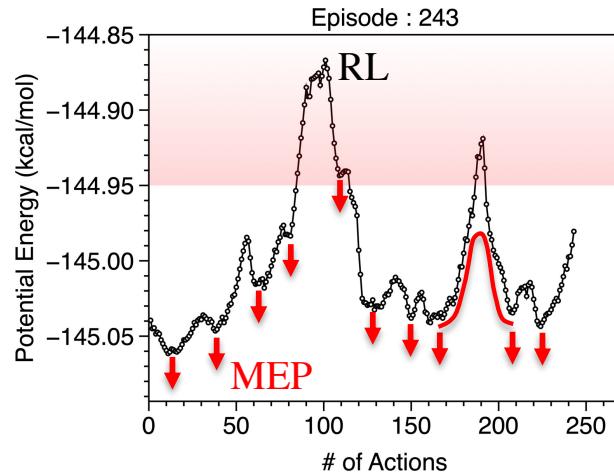
- Phase 1—explore (agent parallelism): Multiple reinforcement learning (RL) agents autonomously discover *long low-activation-barrier pathways*
- Mnih, *Nature* 518, 529 ('15); Hessel, *AAAI* 32, 11796 ('18)
- Phase 2—refine (time parallelism): Concurrent nudged-elastic-band (NEB) refinements of multiple *minimum-energy path (MEP) segments*
- Estimate time based on transition-state theory

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

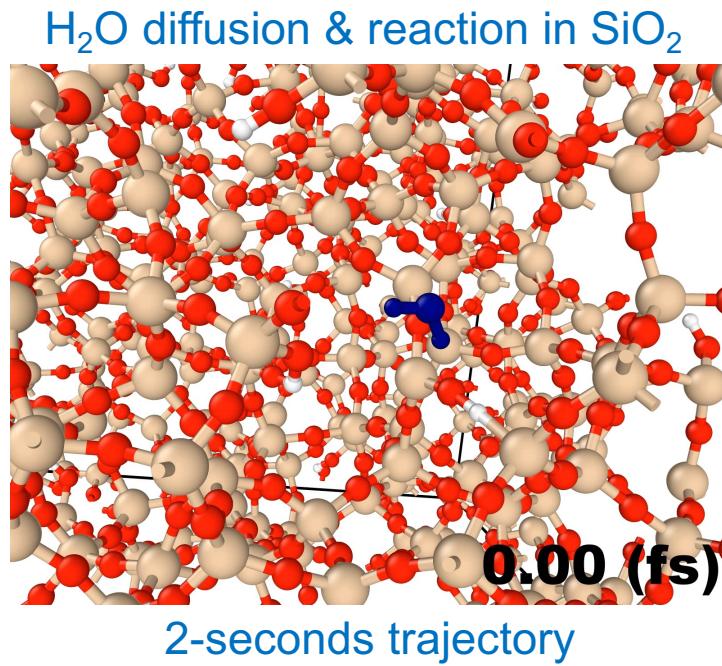
1. Explore



2. Refine



Nomura et al., *J. Phys. Chem. Lett.* 15, 5288 ('24)

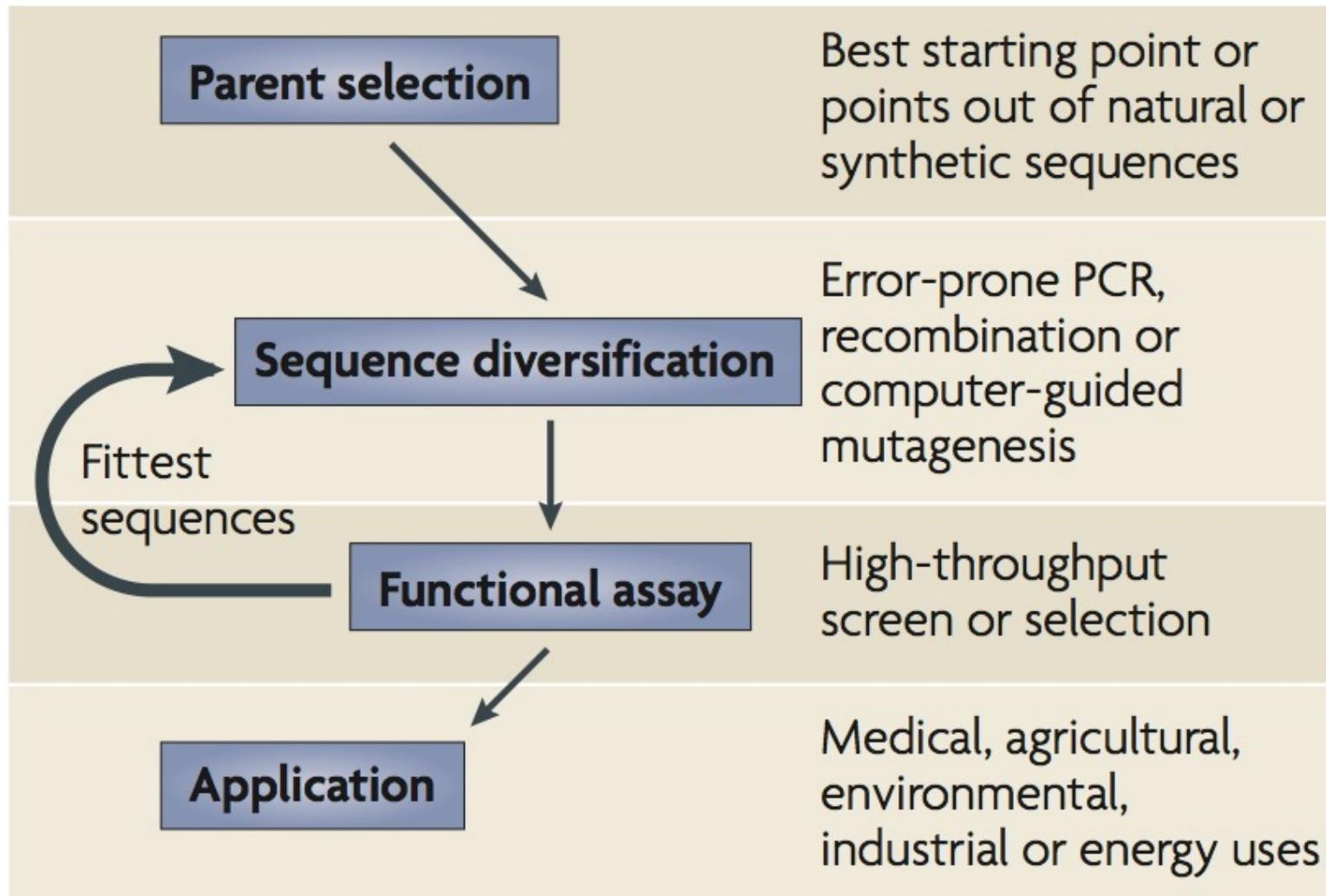


*AI for long time!*

# 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

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© Nobel Media AB. Photo: A.  
Mahmoud

**Frances H. Arnold**

Prize share: 1/2



© Nobel Media AB. Photo: A.  
Mahmoud

**George P. Smith**

Prize share: 1/4



© Nobel Media AB. Photo: A.  
Mahmoud

**Sir Gregory P.  
Winter**

Prize share: 1/4

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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)

PROBABLY

APPROXIMATELY

CORRECT

Nature's Algorithms for Learning and  
Prospering in a Complex World



LESLIE VALIANT