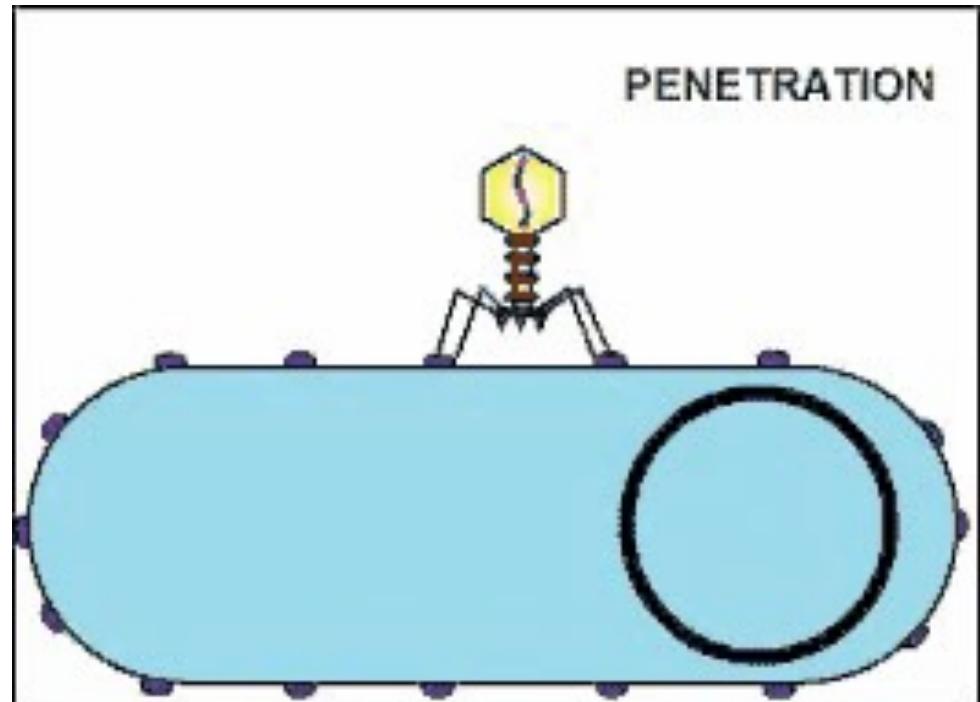
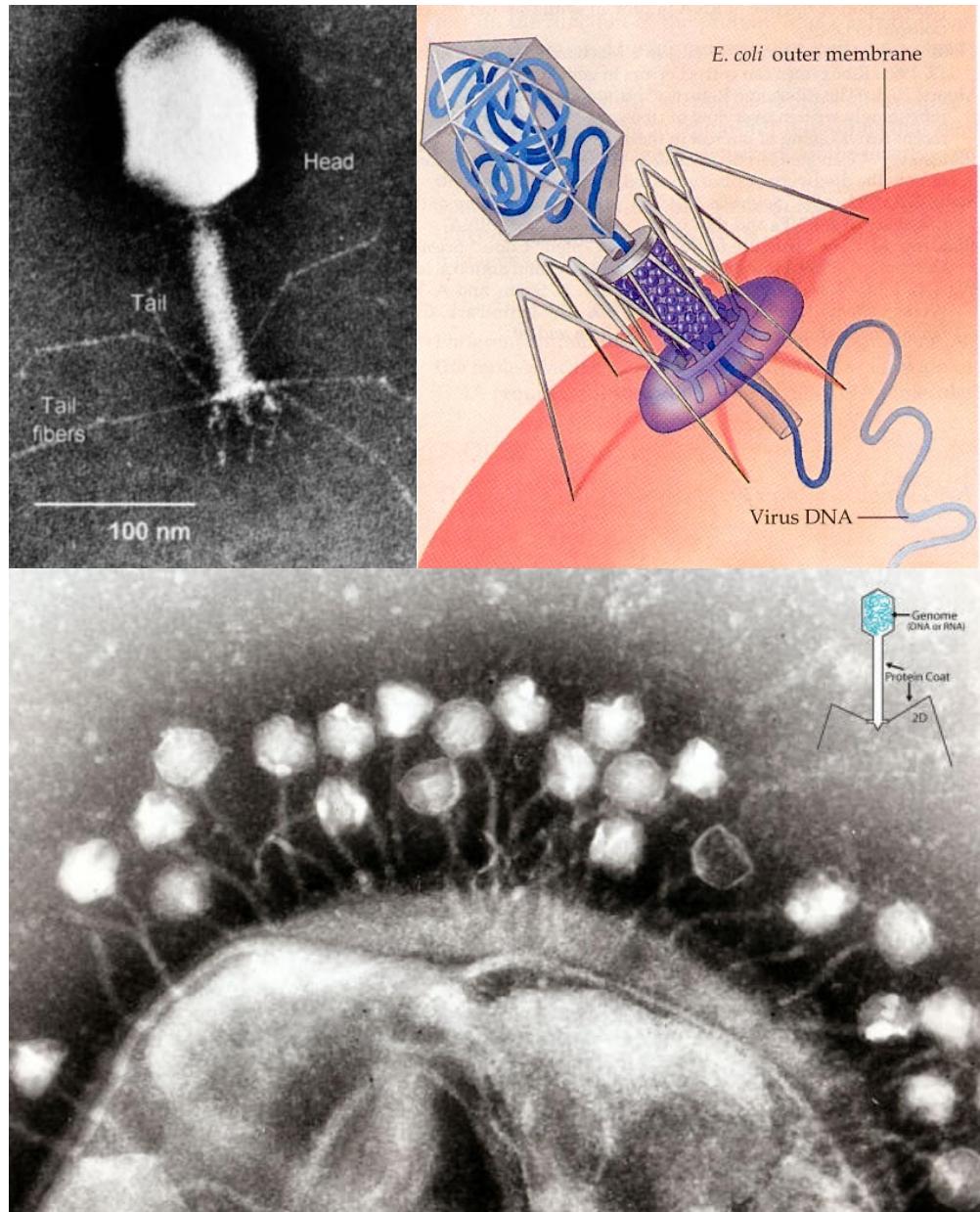


Motivation: Bacteriophage



**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

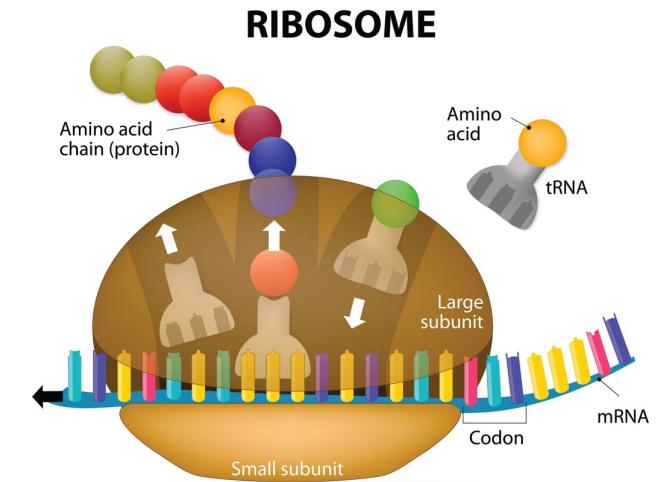
Home Videos Shows Channels Community

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

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

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

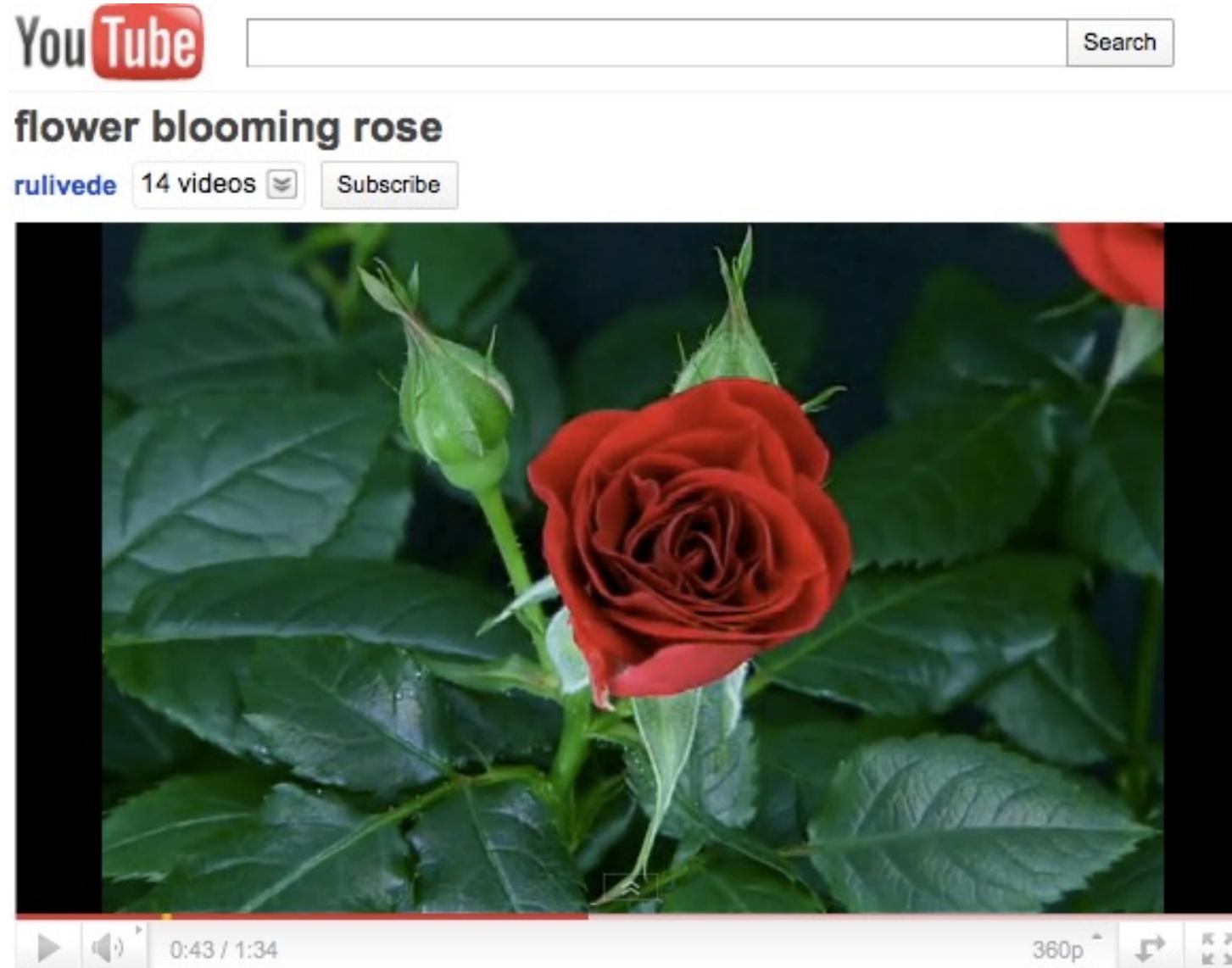
<http://sanbonmatsu.org/images/03456Movie1.mov>

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 Perez¹, Blas P. Uberuaga², Yunsic Shim³,
Jacques G. Amar³ and Arthur F. Voter¹

Decaheme Cytochrome MtrF Adsorption and Electron Transfer on Gold Surface

Tao Wei,^{*,†} Heng Ma,[†] and Aiichiro Nakano^{*,‡,§,||,¶}

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

Lin Lin¹, Mohan Chen², Chao Yang¹ and Lixin He²



Washington, DC



Goyang, Korea

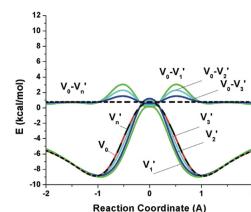
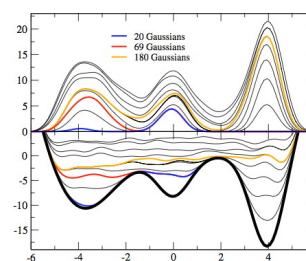
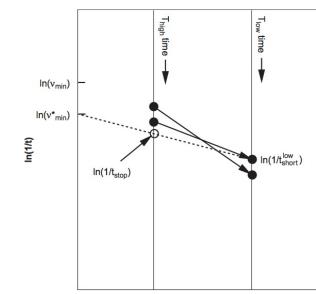
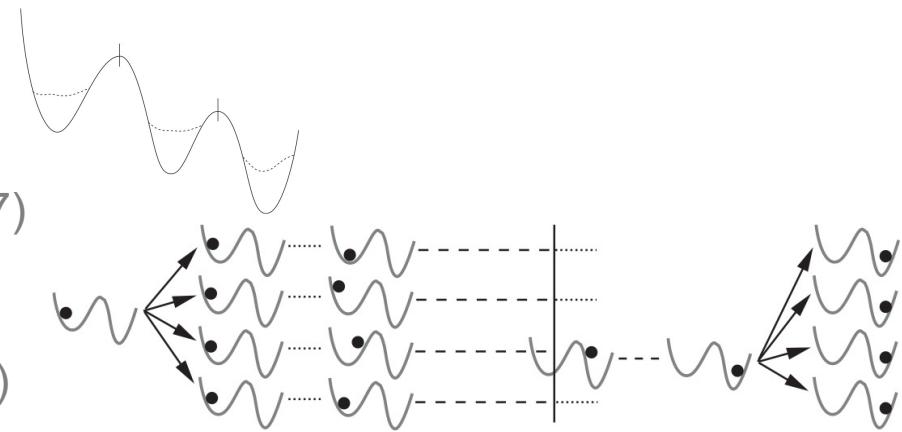


Tokyo, Japan

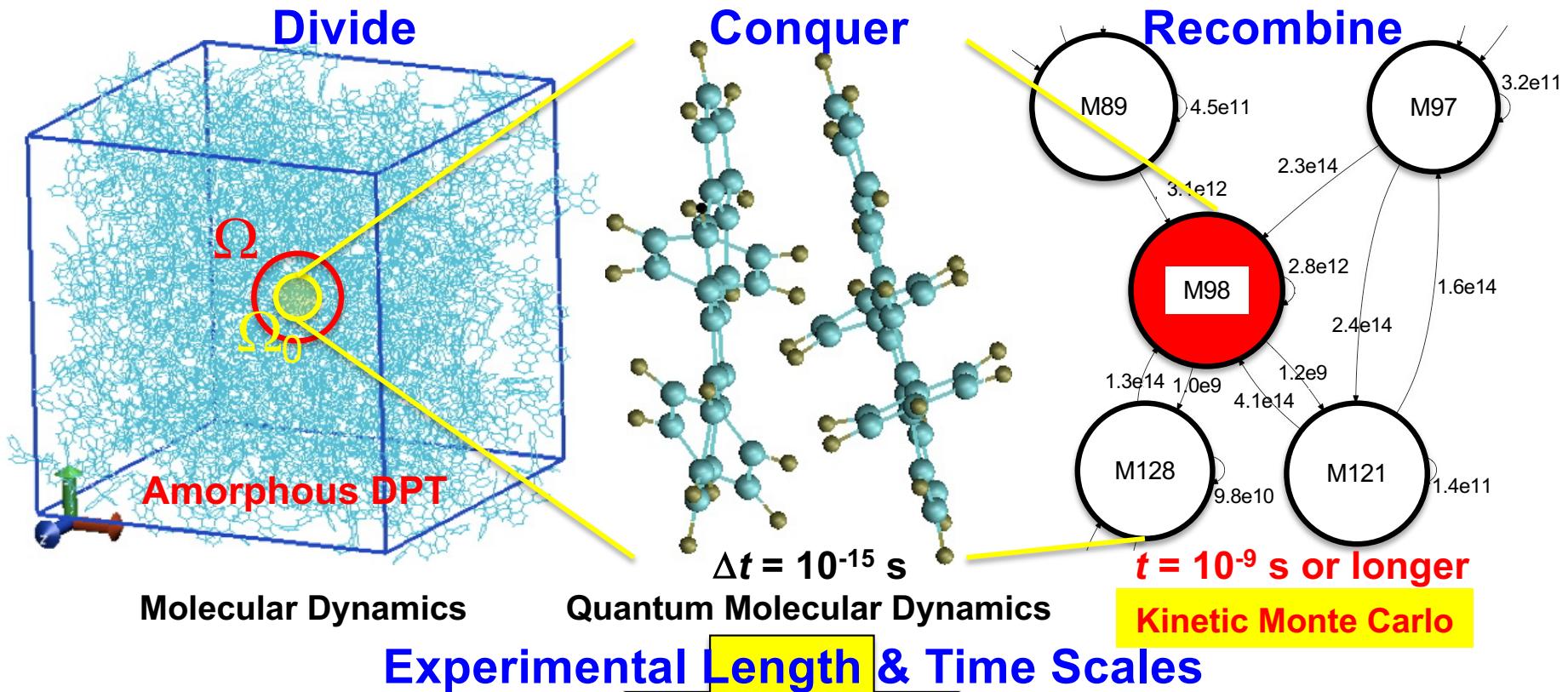
Accelerated Molecular Dynamics

- **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)

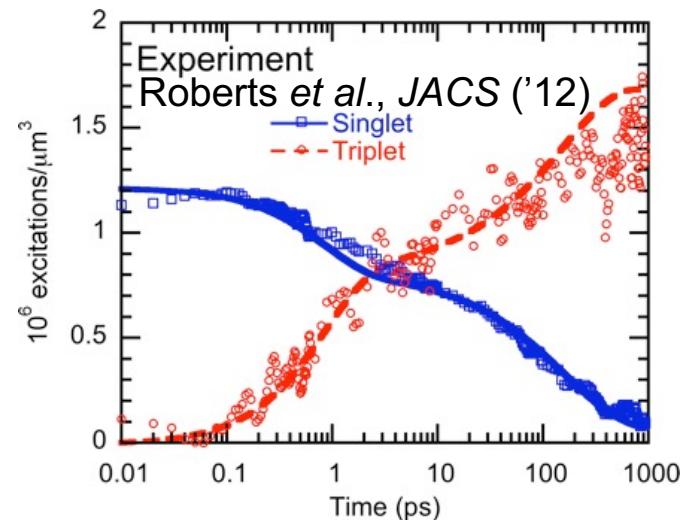
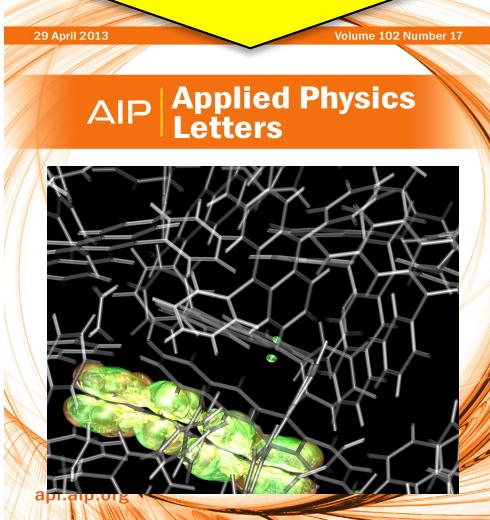
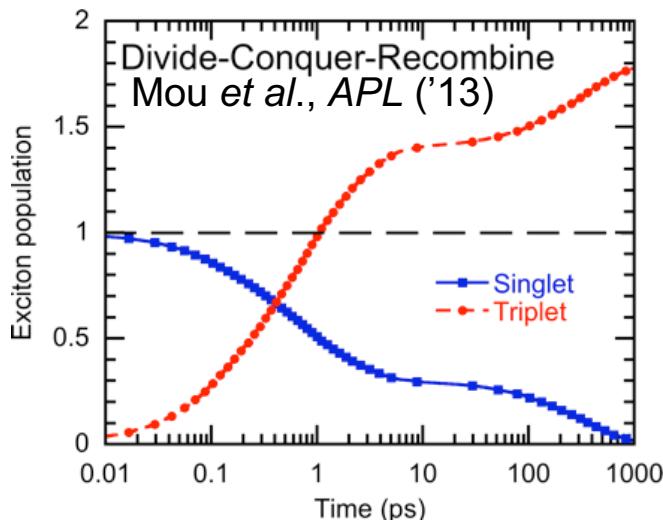
The slide contains several diagrams and plots. At the top right is a schematic of parallel replica dynamics showing multiple parallel paths for a system moving between energy minima. Below it is a plot of natural logarithms of rates versus inverse temperature $1/T$, showing a linear relationship with points for $\ln(v_{min})$, $\ln(v^*_{min})$, $\ln(1/t_{stop})$, and $\ln(1/t_{stop}^{low})$. To the right is a plot of probability density versus a coordinate s for different numbers of Gaussians (20, 69, 180). On the left is a diagram of a Markov state model showing states a through n connected by arrows representing transitions.



Divide-Conquer-Recombine KMC



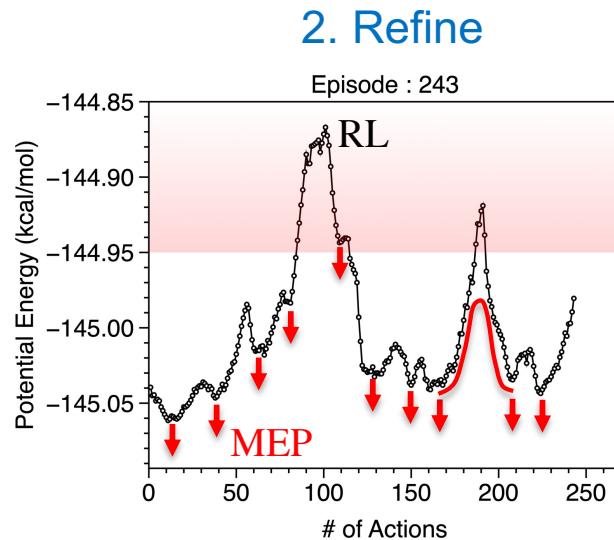
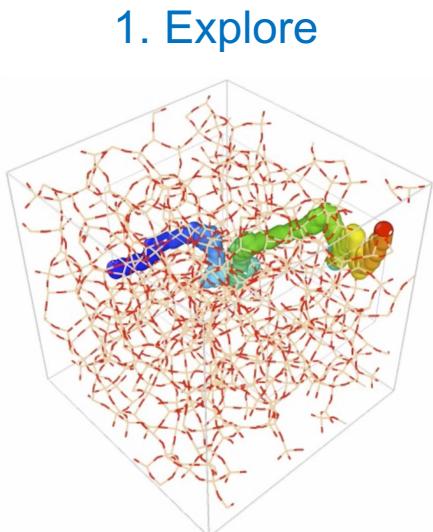
Experimental Length & Time Scales



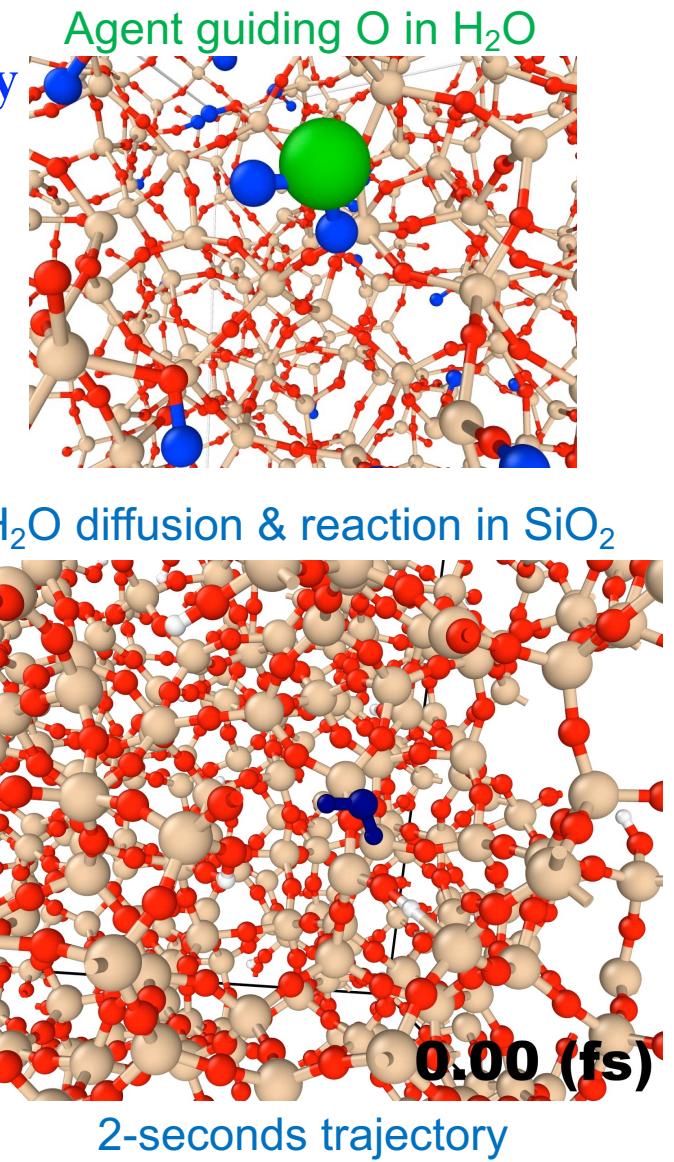
Reinforcement Learning for Long-Time Dynamics

- Phase 1—explore (agent parallelism): Multiple reinforcement learning (RL) agents autonomously discover *long low-activation-barrier pathways*
- 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

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



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

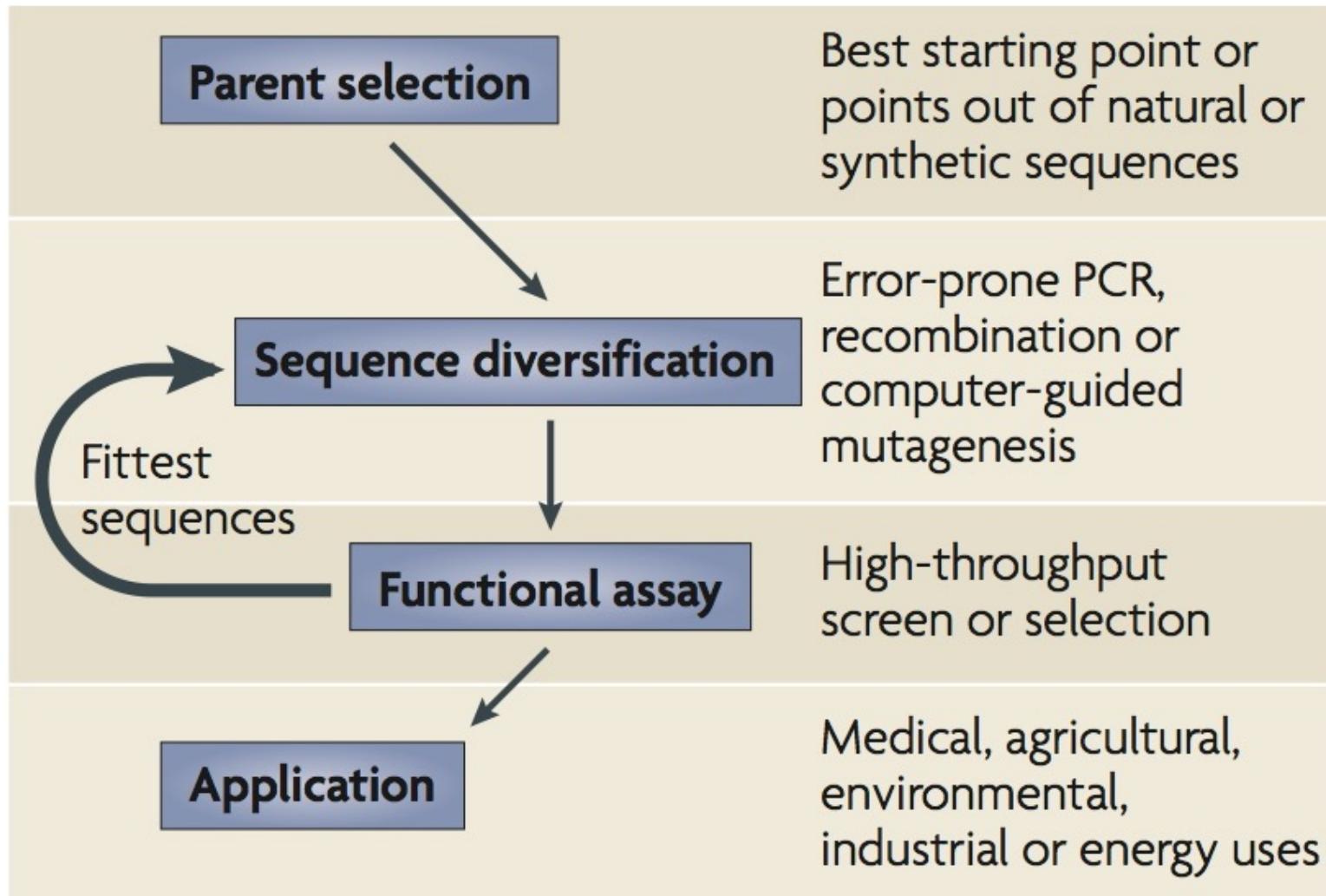


AI for long time!

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



© 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

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