Introduction:
Improving virtual screening through physics-based methods

CS/CME/Biophys/BMI 371

Jan. 30, 2017

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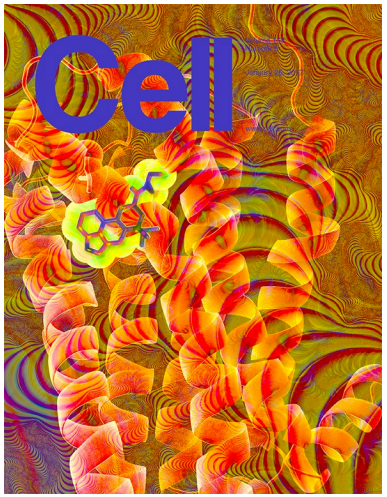
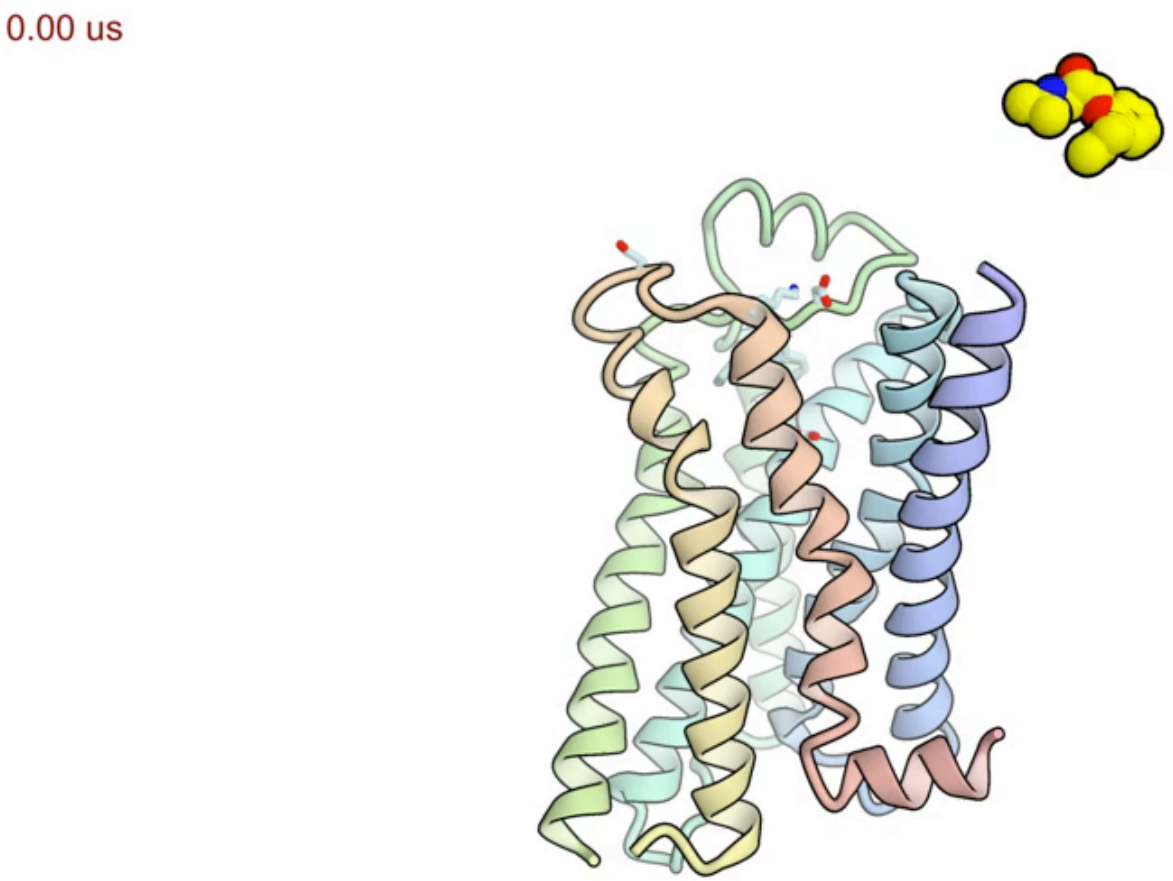
Why aren't standard (physics-based) docking methods very accurate?

- Protein flexibility
  - The binding pocket may adopt different conformations when bound to different ligands
  - Most docking protocols treat it as rigid
- Both the protein and the ligand are continually wiggling around, both before and after binding
  - Most docking protocols don't account correctly for entropic effects ("proteins and ligands like to be free")
  - They also don't account for some of the effects of water molecules



Cell, Jan. 26, 2017

In theory, we could determine binding affinity by simply running molecular dynamics simulations



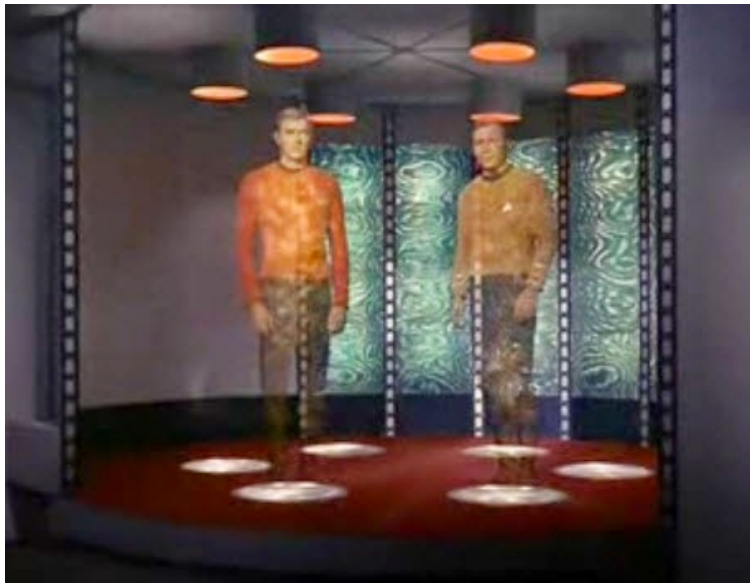
- We would watch the ligand bind and unbind multiple times and determine what fraction of the time it was bound, on average.
- This isn't practical—the simulations would need to be much, much too long

Beta-blocker alprenolol binding to an adrenaline receptor

Dror et al., *PNAS* 2011

“Alchemical” simulation methods

- Binding affinity depends on the difference in energy between the bound and unbound states
- It does ***not*** depend on the binding/unbinding pathways
- However, one needs to a pathway to compute the difference in energy
- Solution: use a *fictitious* unbinding pathway, in which the ligand gradually disappears from the binding pocket and rematerializes in water



Star Trek (?)

Another approach: exploit experimental information on protein flexibility

- If you have a very high-resolution crystal structure, you can extract information on different conformations the binding pocket can adopt in the absence of a ligand
- You can then dock to those different protein conformations
  - Include an energetic penalty for the protein conformations that are less populated in the absence of a ligand

Background material

- Ligand docking slides from CS/CME/BioE/ Biophys/BMI 279:
  - http://web.stanford.edu/class/cs279/lectures/lecture7.pdf
- Slides on the relationship between probabilities and energy of a state (the Boltzmann distribution) from CS/CME/BioE/Biophys/BMI 279:
  - http://web.stanford.edu/class/cs279/lectures/lecture3.pdf