

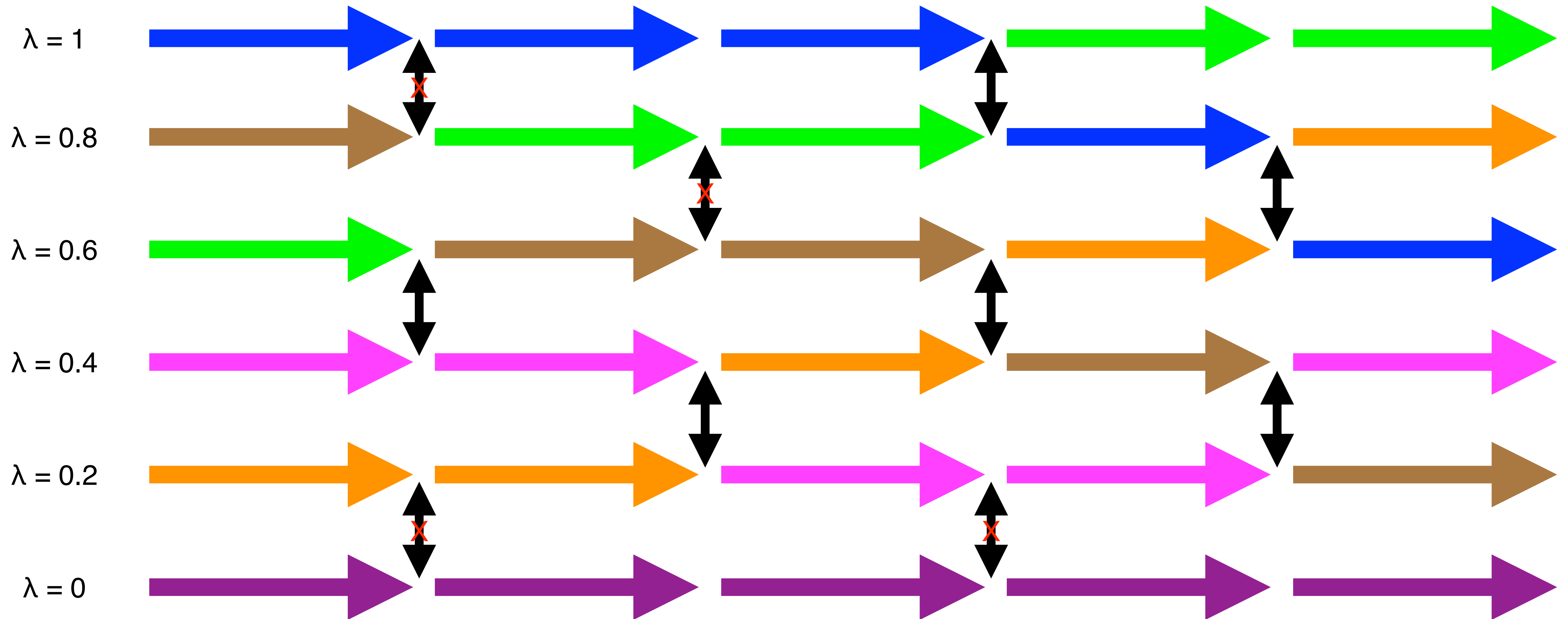
11/18/2024 Replica exchange

- The lecture will cover replica exchange
- Today's lecture is a key step towards the following learning objective: Explain key concepts related to binding free energy calculations. Compare and contrast molecular docking and binding free energy calculations.
- At the end of this module, you should be able to answer the following questions:
 - What are the benefits of performing replica exchange?
 - How do you know if there are enough states along a thermodynamic process?
- You should be able to calculate
 - expectation values
 - free energy differences between thermodynamic states

Replica exchange

- Simulations of multiple thermodynamic states with different parameters
 - originally, variation in temperature
 - often used for alchemical coupling
- Configurations from thermodynamic states are periodically swapped
 - Equivalently, thermodynamic parameters are swapped
 - Swapping satisfies detailed balance; both states sample from respective Boltzmann distributions

Swapping

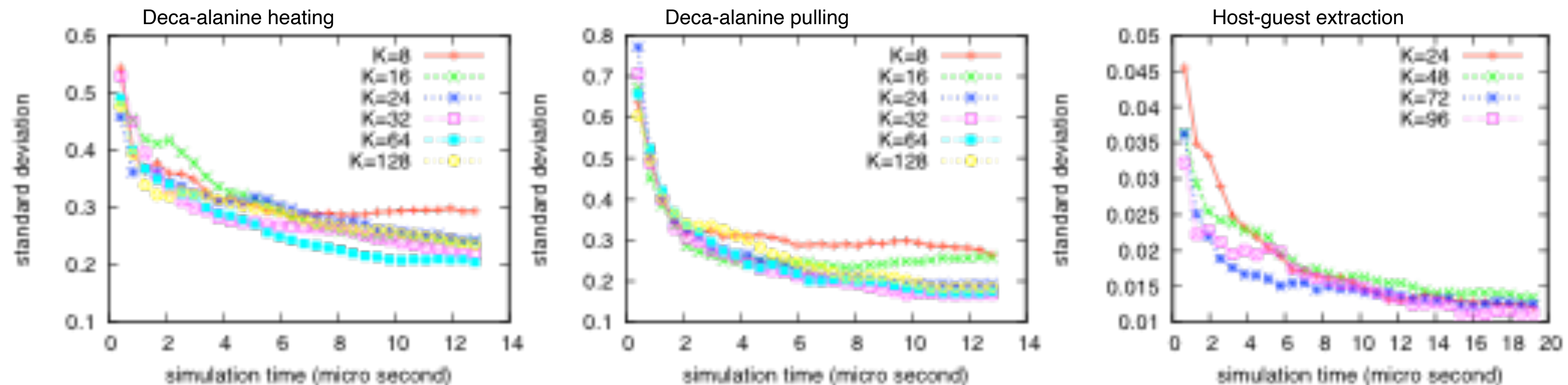


Why perform replica exchange?

- Improve mixing of MCMC chains; higher-entropy states help sample configurations in lower-entropy states
- At high temperature, energetic barriers are crossed more quickly than at low temperature
- Decoupled ligands move freely compared to bound ligands. See http://mypages.iit.edu/~dminh/images/pubs/dock_1hnn.gif.
- Minimal added computational expense

Selecting thermodynamic states

- Thermodynamic state selection has been thought to be a tricky optimization problem
- In Nguyen and Minh (2016) [1]
 - processes were simulated 100x each for each number of states, K
 - the standard deviation of the free energy was evaluated as a function of the total simulation time



- If there are not enough states, the convergence curve levels off
- If there are enough states, the standard deviation of free energy estimates depends on the aggregate simulation time and is insensitive to the number of states.

References

- [1] Nguyen, T. H.; Minh, D. D. L. Intermediate Thermodynamic States Contribute Equally to Free Energy Convergence: A Demonstration with Replica Exchange. *Journal of Chemical Theory and Computation* 2016, 12 (5), 2154–2161. <https://doi.org/10.1021/acs.jctc.6b00060>.