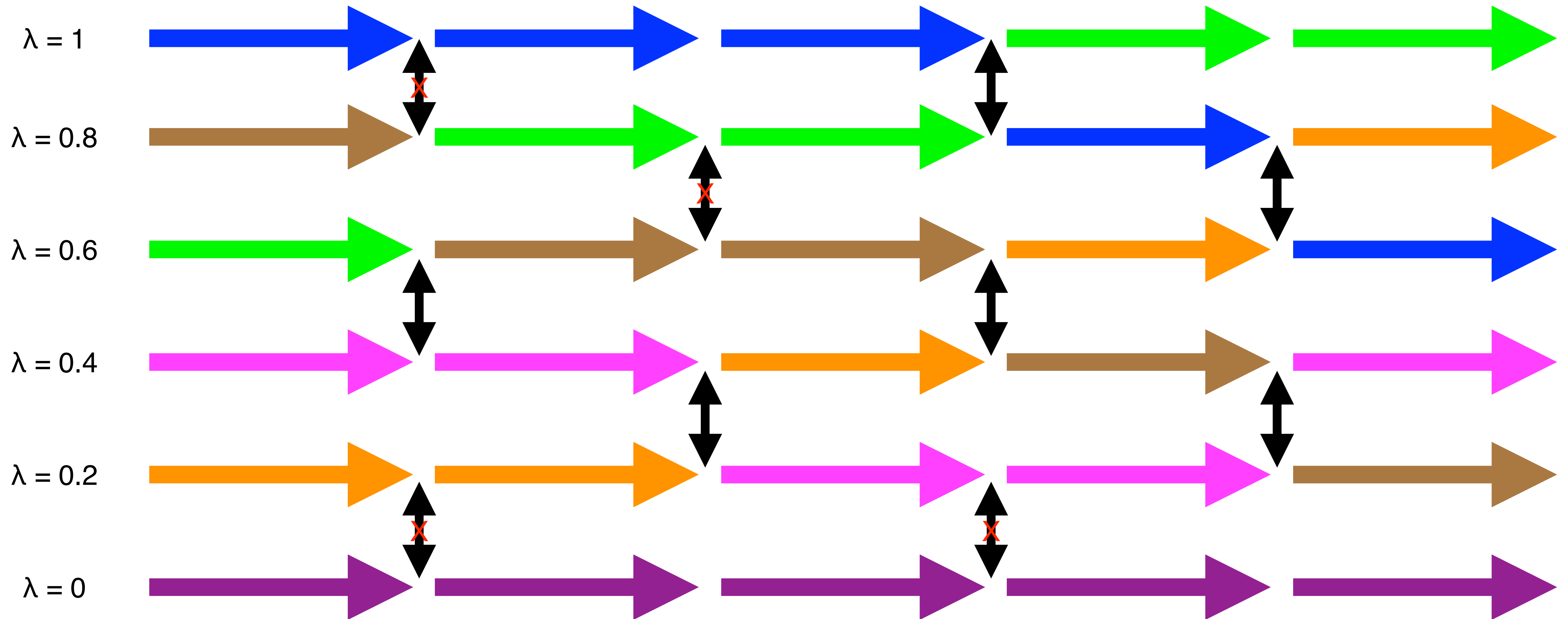# 11/18/2024 Replica exchange

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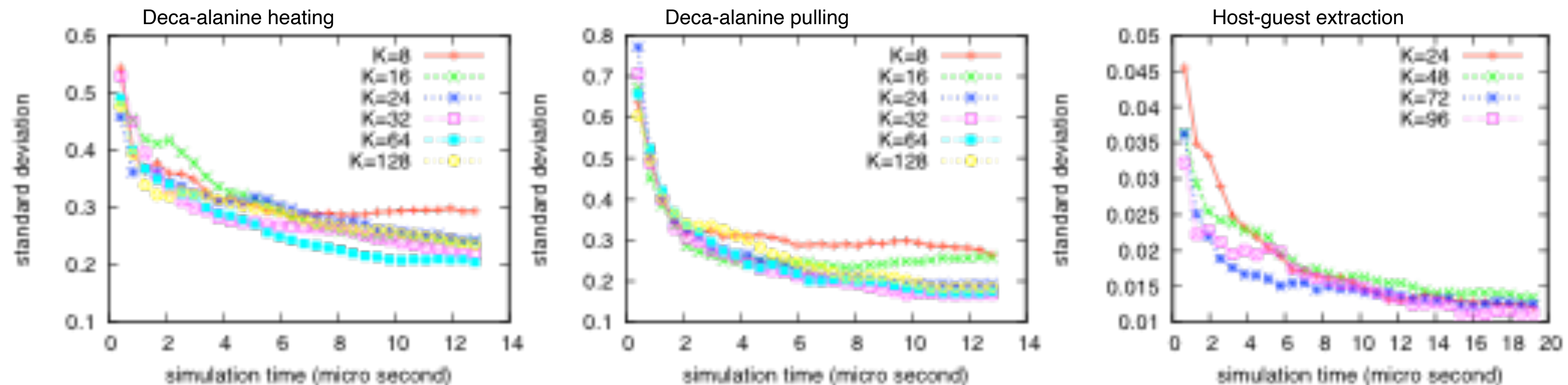
- If there are not enough states, the convergence curve levels off
- If there are enough states, the standard deviation of free energy estimates depends on the aggregate simulation time and is insensitive to the number of states.

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.