Path optimization in alchemical free energy calculations

Ryan Muraglia[1]

[1]Program in Computational Biology & Bioinformatics
Duke University

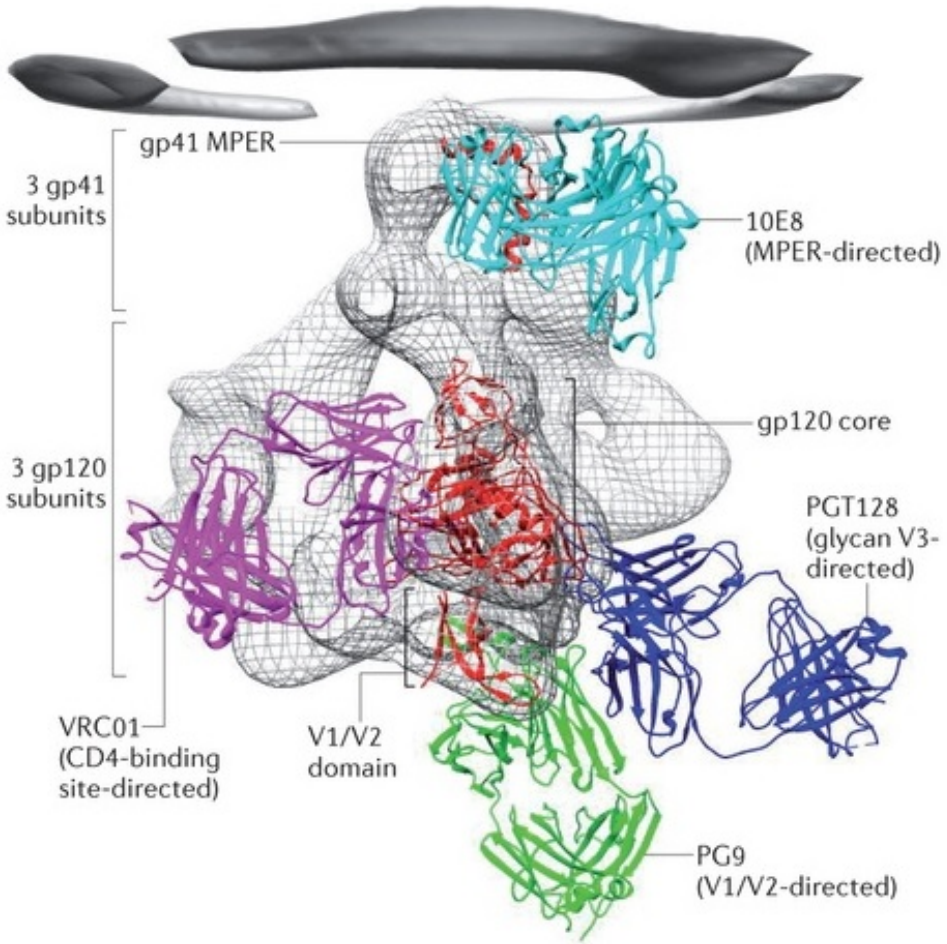
July 19, 2016

Outline

Modulating binding in biological systems

Rational molecular design

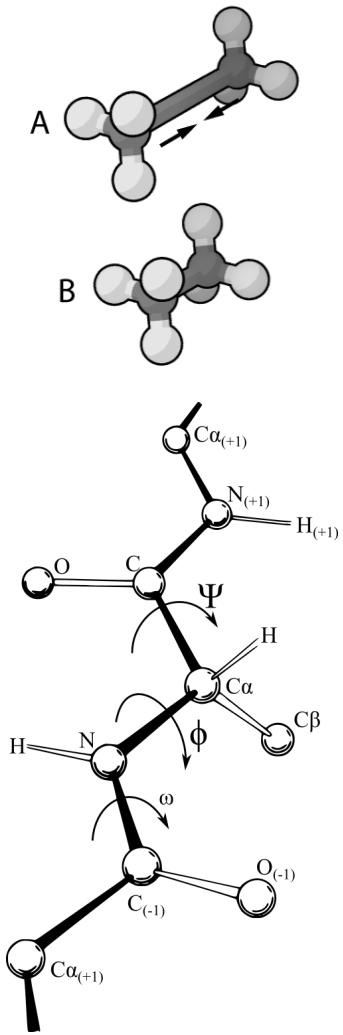
- Free energy of binding determines behavior of system
- Changes to the ligands affect the free energy
- Predict change in free energy for a given set of ligand mutations
- Select mutations with desired properties (enhance or destabilize binding)



P.D. Kwong, J.R. Mascola, G.J. Nabel, *Nat. Rev. Immunol.* **13**, 693 (2013)

A probabilistic representation of molecules

- Atomic coordinates: $r \equiv \{\boldsymbol{r_1}, ..., \boldsymbol{r_N}\}$
- Atomic momenta: $p \equiv \{\boldsymbol{p_1}, ..., \boldsymbol{p_N}\}$
- State representation: $x \equiv \{r, p\}$
- Kinetic energy: $K(p) = \sum_{i=1}^{N} \frac{p_i^2}{2m_i}$
- Potential energy:
  $U(r) = U_{bond} + U_{angle} + U_{dihedral} + U_{elec} + U_{vdW}$
- Hamiltonian: $H(x) = K(p) + U(r)$
- Boltzmann weight: $q(x) = \exp(-\beta H(x))$
- Partition function: $Z = \int_{\Omega} \exp(-\beta H(x)) dx$
- Probability of state: $p(x) = q(x)/Z$
- Free energy: $G = -\beta^{-1} \log(Z)$



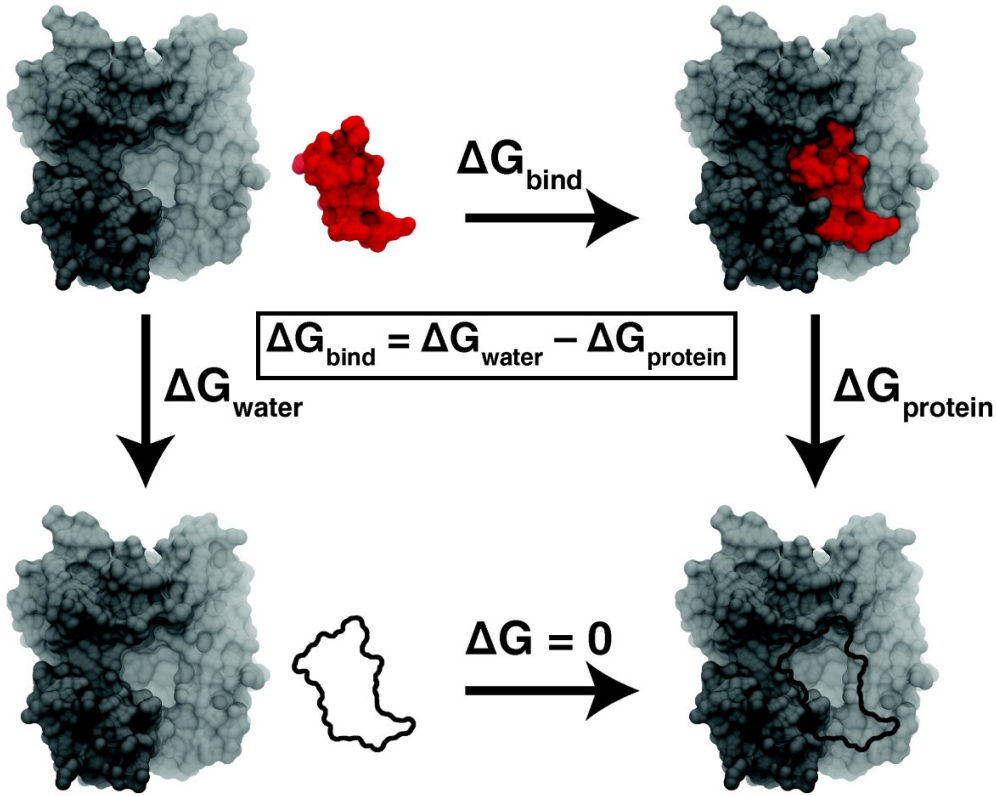
Wikimedia Commons

The thermodynamic cycle

Free energy differences can be expressed in terms of the ratio of partition functions:

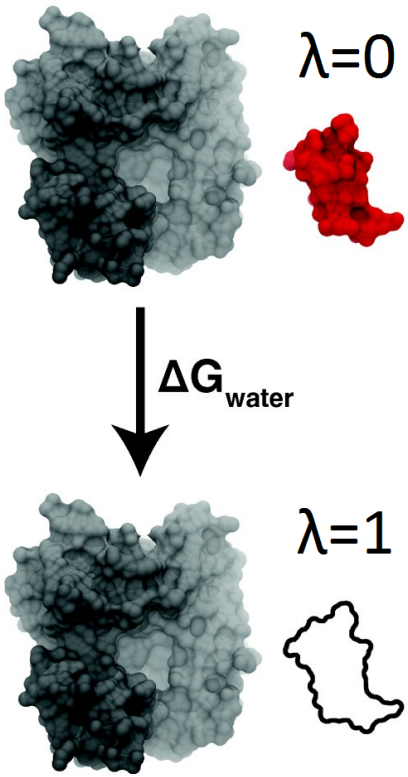
$$\begin{aligned}\Delta G_{bind} &= G_B - G_U \\ &= -\beta^{-1} \log(Z_B/Z_U)\end{aligned}$$

Many valid combinations of partition functions are accessible via a thermodynamic cycle.



J.D. Durrant, J.A. McCammon, *BMC Biol.* **9**, 71 (2011)

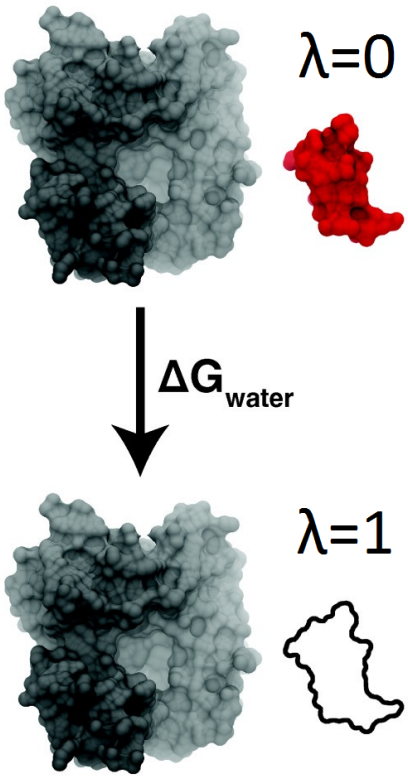
Exponential averaging and alchemical intermediates



- Exponential averaging (EXP) estimator:
  $\Delta G_{0\to 1} = -\beta^{-1} \log E_0[\exp(-\beta(U_1(x) - U_0(x))]$
- Common problem: as the overlap between p_0 and p_1 decreases, the accuracy of the estimator deteriorates.

J.D. Durrant, J.A. McCammon, *BMC Biol.* **9**, 71 (2011)

Exponential averaging and alchemical intermediates



- Exponential averaging (EXP) estimator:
  $\Delta G_{0\to 1} = -\beta^{-1} \log E_0[\exp(-\beta(U_1(x) - U_0(x))]$
- Common problem: as the overlap between p_0 and p_1 decreases, the accuracy of the estimator deteriorates.
- Solution: construct intermediate states, divide and conquer.
  $\Delta G_{0\to 1} = -\beta^{-1} \log \left(\frac{Z_1}{Z_{0.5}} \frac{Z_{0.5}}{Z_0} \right)$

λ scaling

Define intermediate states with the potential:

$$U(\lambda) = \lambda U_1 + (1 - \lambda) U_0$$

J.D. Durrant, J.A. McCammon, *BMC Biol.* **9**, 71 (2011)

Bridge sampling estimators

The Bennett acceptance ratio (BAR) method is part of the broader class of bridge sampling estimators, commonly used to estimate ratios of normalizing constants.

The bridge sampling identity

$$r \equiv \exp(-\beta \Delta G) = \frac{Z_1}{Z_0} = \frac{E_0[q_1(x)\alpha(x)]}{E_1[q_0(x)\alpha(x)]}$$

This can be approximated by Monte Carlo integration:

The bridge sampling estimator

$$\hat{r} = \frac{\frac{1}{n_0}\sum_{j=1}^{n_0} q_1(x_{0j})\alpha(x_{0j})}{\frac{1}{n_1}\sum_{j=1}^{n_1} q_0(x_{1j})\alpha(x_{1j})}$$

where $\{x_{i1}, ..., x_{in}\}$ are draws from p_i, $i = 0, 1$.

The BAR estimator

BAR's α function

$$\alpha \propto (s_1 q_1 + s_0 r q_0)^{-1}$$

where $s_i = n_i/(n_0 + n_1)$.

This α minimizes the asymptotic variance of $\log(\hat{r})$.

The iterative BAR estimator

$$\hat{r}^{(t+1)} = \frac{\frac{1}{n_0}\sum_{j=1}^{n_0}\left[\frac{l_{0j}}{s_1 l_{0j} + s_0 \hat{r}^{(t)}}\right]}{\frac{1}{n_1}\sum_{j=1}^{n_1}\left[\frac{1}{s_1 l_{1j} + s_0 \hat{r}^{(t)}}\right]}$$

where $l_{ij} = q_1(x_{ij})/q_0(x_{ij})$, $j = 1, ..., n_i$, $i = 0, 1$

Outline

1. Free energy calculation primer
2. Proof of concept
   - Gelman and Meng's result
   - Defining the augmented λ space
   - Exhaustive search
3. Sequential Monte Carlo for path traversal
   - Path sensitivity for SMC
   - Path selection and the multi-armed bandit
4. Full grid optimization
   - pCrooks - a new estimator
   - Q-learning

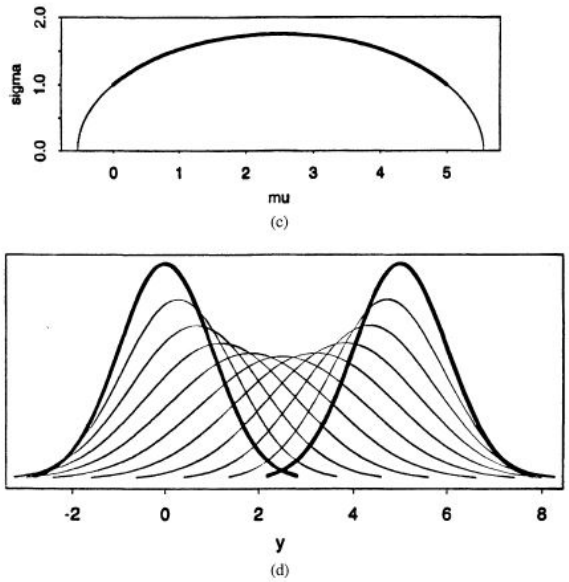
Optimal bridging densities

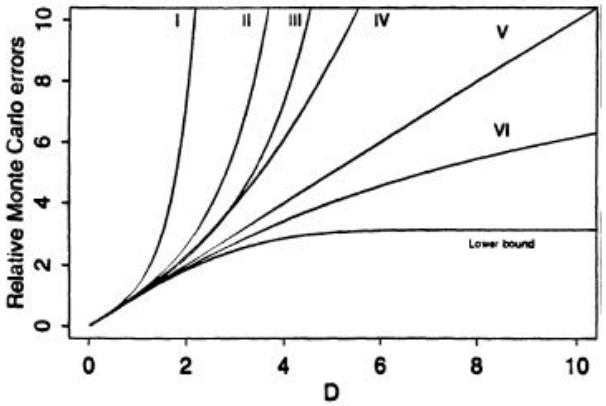
λ scaling

Define intermediate distributions with the potential:

$$U(\lambda) = \lambda U_1 + (1 - \lambda) U_0$$

Selecting an appropriate number and placement of intermediates can have a profound effect on the free energy estimation.





1. Importance sampling
2. Geometric bridge sampling
3. Optimal bridge sampling

A. Gelman, X.L. Meng, *Stat. Sci.* **13**, 163 (1998)

Defining the expanded λ space

Numerous options for expansion of λ space:

- Separation of energy terms (Jiang & Roux, 2010)
  - $U(\lambda_{vdW}, \lambda_{elec}) = U_0 + U_{vdW}(\lambda_{vdW}) + U_{elec}(\lambda_{elec})$
- Addition of biasing potential (Darve et al., 2008)
- Addition of temperature ladder (Sugita et al., 2000)

Defining the expanded λ space

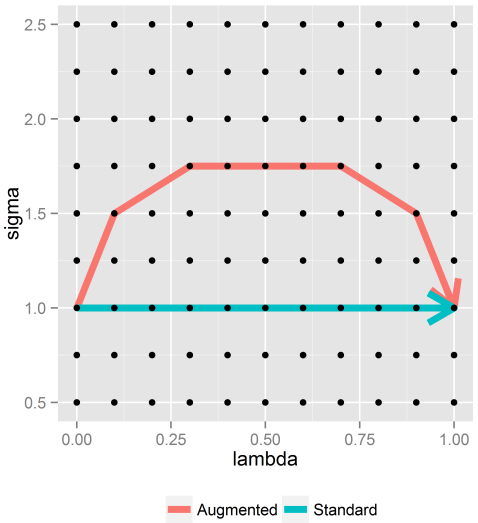
Numerous options for expansion of λ space:

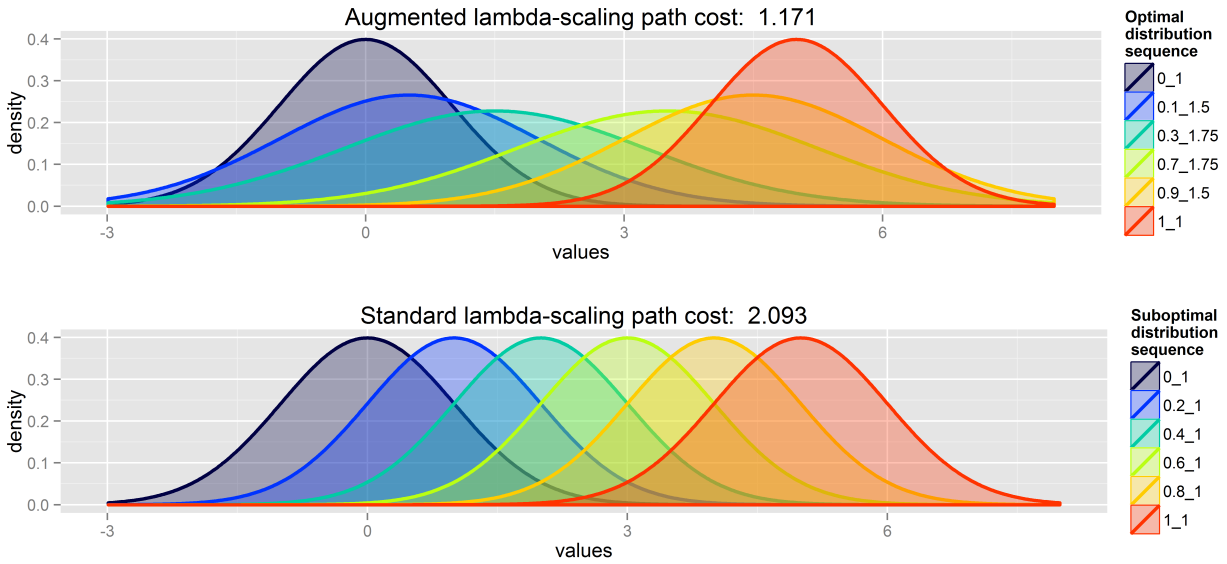
- Separation of energy terms (Jiang & Roux, 2010)
  - $U(\lambda_{vdW}, \lambda_{elec}) = U_0 + U_{vdW}(\lambda_{vdW}) + U_{elec}(\lambda_{elec})$
- Addition of biasing potential (Darve et al., 2008)
- Addition of temperature ladder (Sugita et al., 2000)

Temperature-augmented λ space

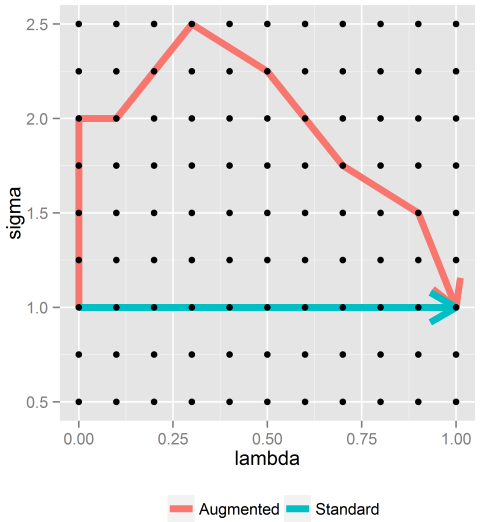
- Predictable benefits, analogous to REMD, conceptually similar to Gelman and Meng's optimal path
- Potential energy is unaffected:
  $U(x, \lambda) = \lambda U_1(x) + (1 - \lambda) U_0(x)$
- Temperature changes Boltzmann weights:
  $q(x, \lambda, \beta) = \exp(-\beta U(x, \lambda))$

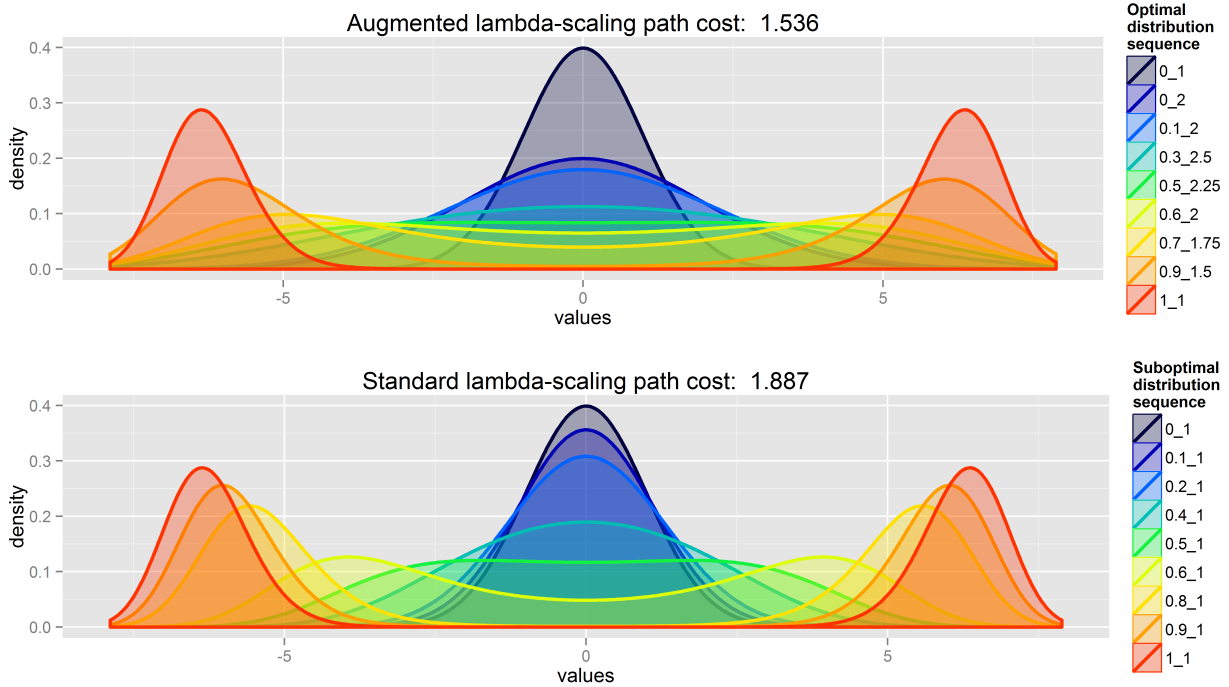
Exhaustive search I - G&M in discrete space





Exhaustive search II - Generalized to other distributions

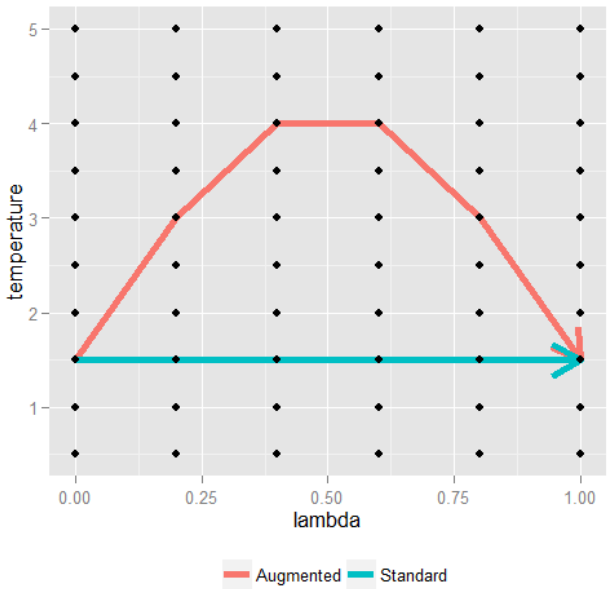


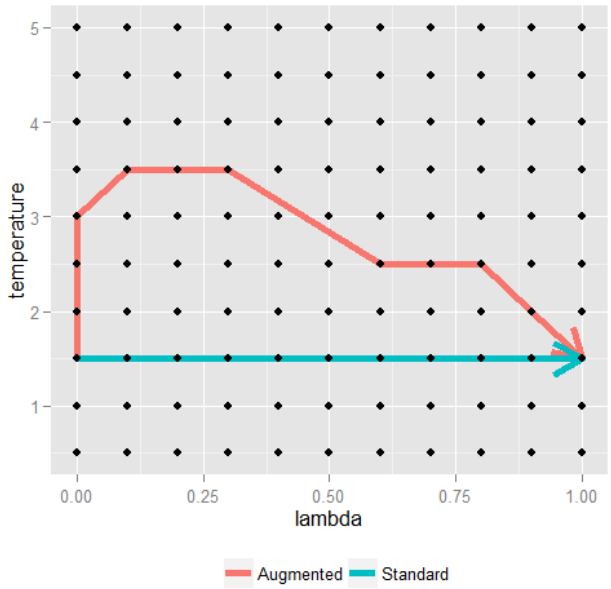


Exhaustive search III - Cost-adjusted varBAR

Asymptotic variance of the BAR estimator

$$\mathrm{var}(\widehat{\Delta G}) = \frac{1}{N}\left[\left\langle \frac{1}{2+2\cosh(\widehat{\Delta G}-\Delta U(x)-M)}\right\rangle^{-1} - \left(\frac{N}{N_0}+\frac{N}{N_1}\right)\right]$$





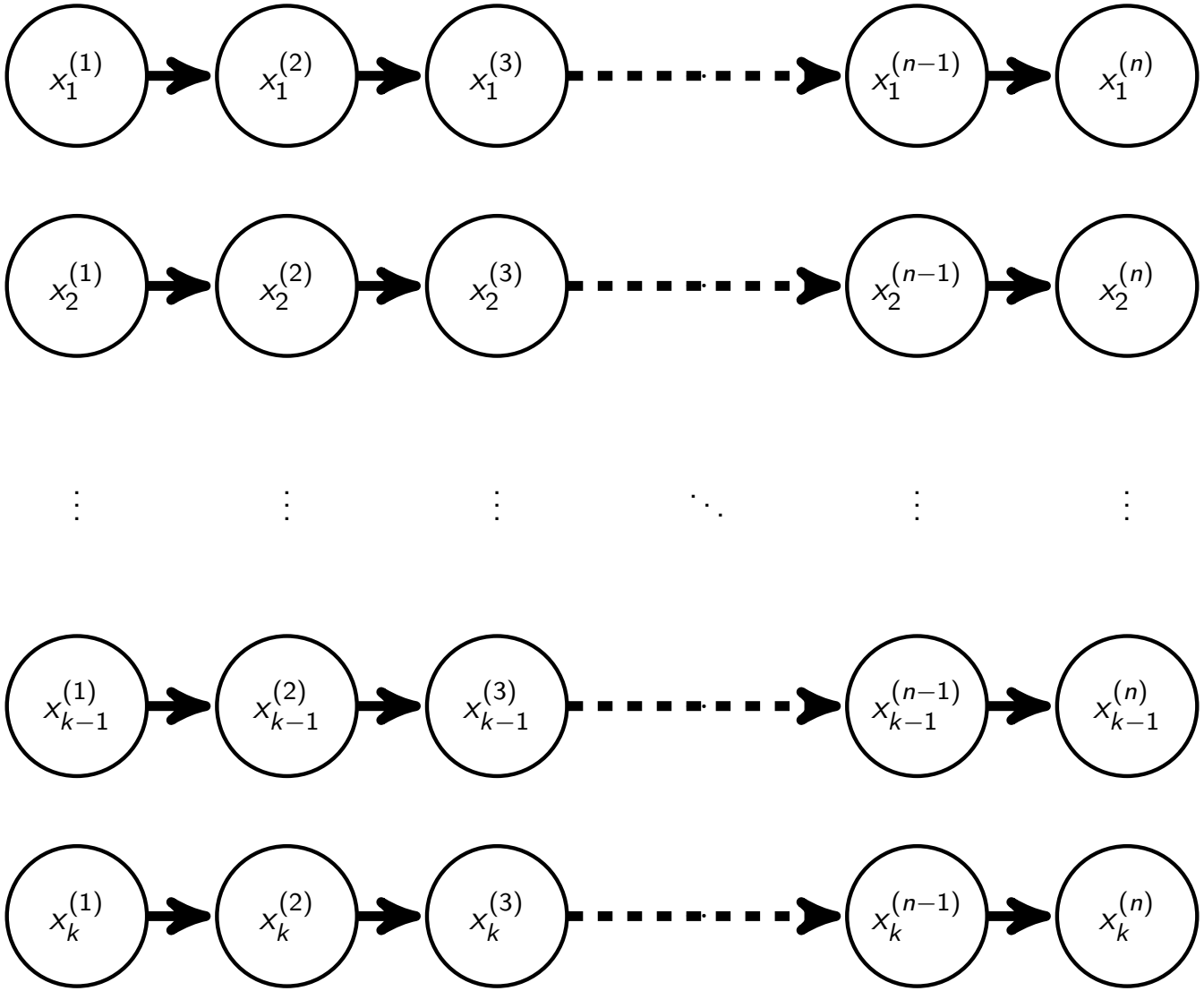
	Left
Aug	3.18E-4
Std	5.07E-4

	Right
Aug	5.93E-5
Std	7.03E-5

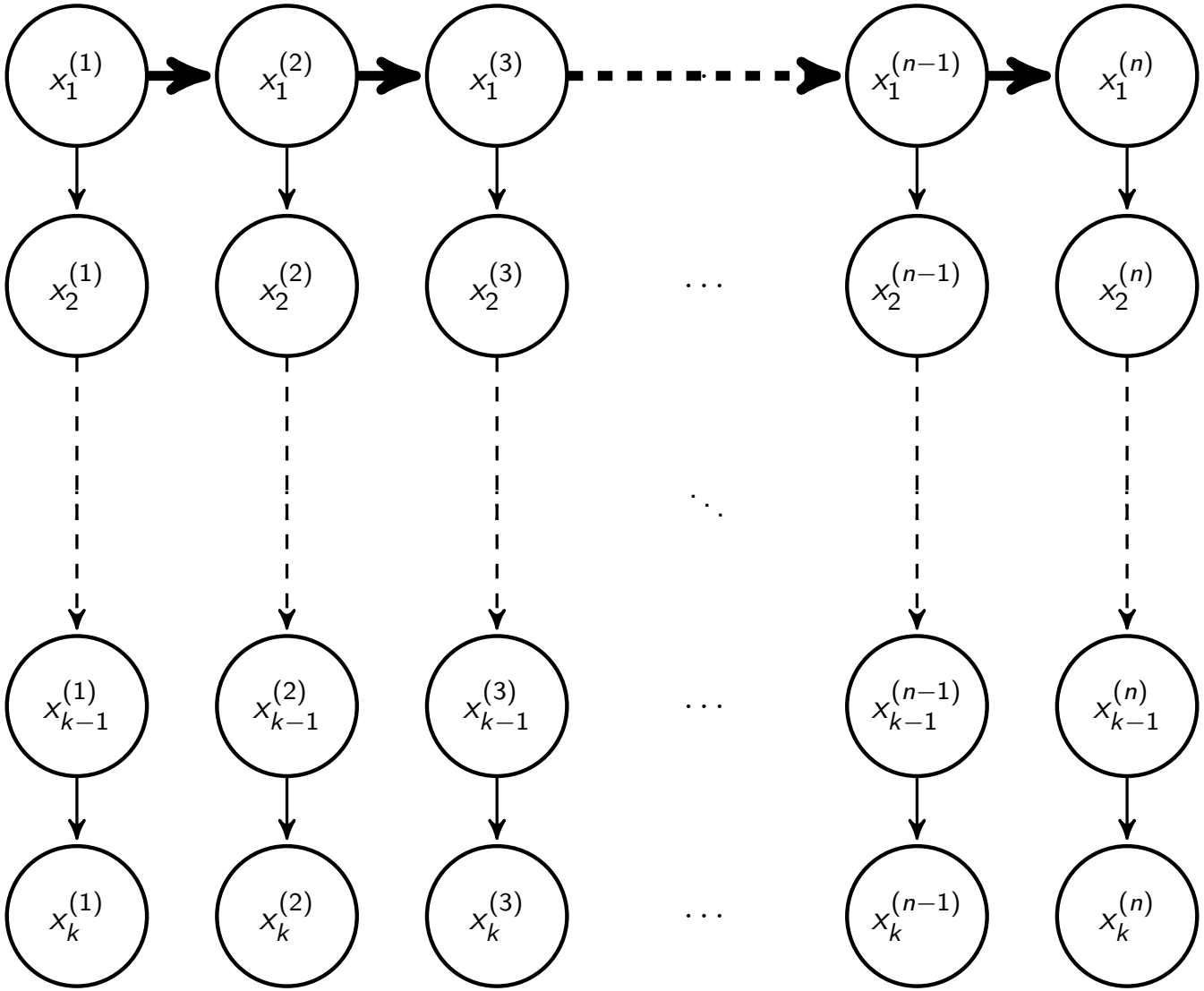
Two sides of path optimization

- Up to now, we've been focused on optimizing the reaction coordinate - the constituent states of the alchemical path.
- The manner in which we traverse a given path represents a complementary side to path optimization.
- To obtain n draws for a path with k states, each with a relaxation time of τ, would require $\mathcal{O}(\tau k n)$ computation with equilibrium sampling.
- A sequential sampler with transition cost τ', where $\tau >> \tau'$ can accomplish the equivalent task in $\mathcal{O}((\tau + (k-1)\tau')n)$ time, representing a significant cost reduction.

Graphical representation of (non)equilibrium samplers



Graphical representation of (non)equilibrium samplers



Analogous SMC estimators

The k-th distribution can be approximated as: $p_k \sim w_k x_k$, where w_k is the normalized incremental weight, given by $\tilde{w}_k = q_k(x_{k-1})/q_{k-1}(x_{k-1})$ for an MCMC transition kernel.

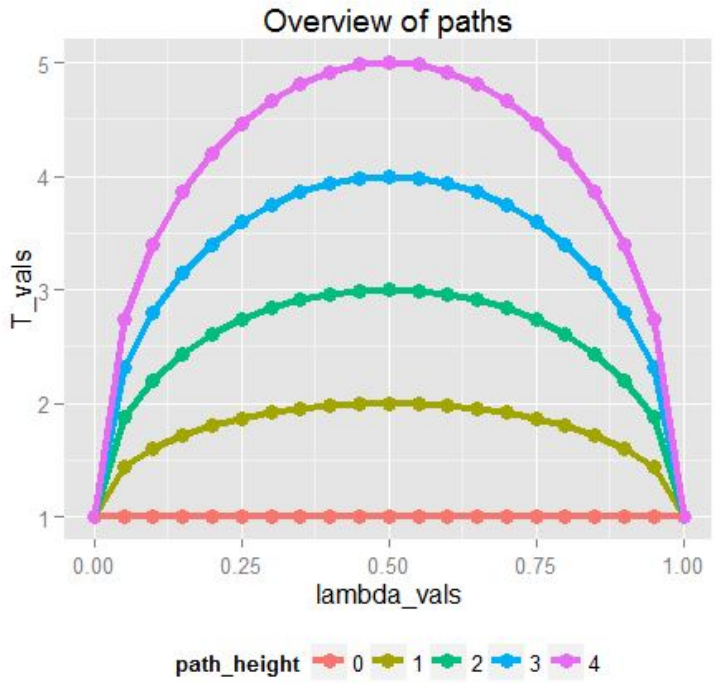
AIS - Annealed importance sampling

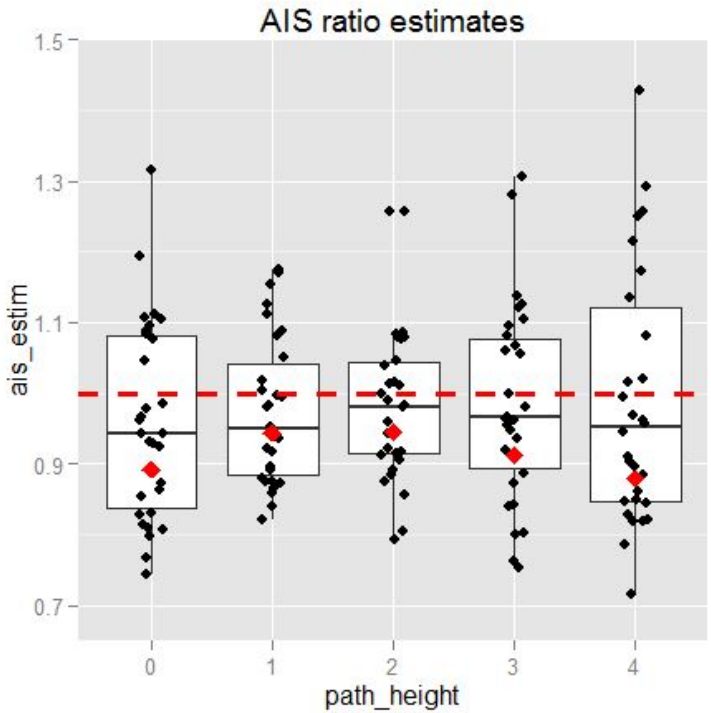
$$\hat{r} = E_{0\to 1}[\exp(-\beta w_1)]$$

CFT - Crooks fluctuation theorem

$$\hat{r} = \frac{E_{0\to 1}[(1+\exp(\beta w_1 + C))^{-1}]}{E_{1\to 0}[(1+\exp(\beta w_0 - C))^{-1}]}$$

SMC methods are sensitive to path choice





Adaptive sample allocation

To efficiently select a best path when their qualities are not known *a priori*, sample usage must be partitioned between two conflicting tasks:

- Exploration of poorly characterized paths
- Exploitation of the putative optimal path

Adaptive sample allocation

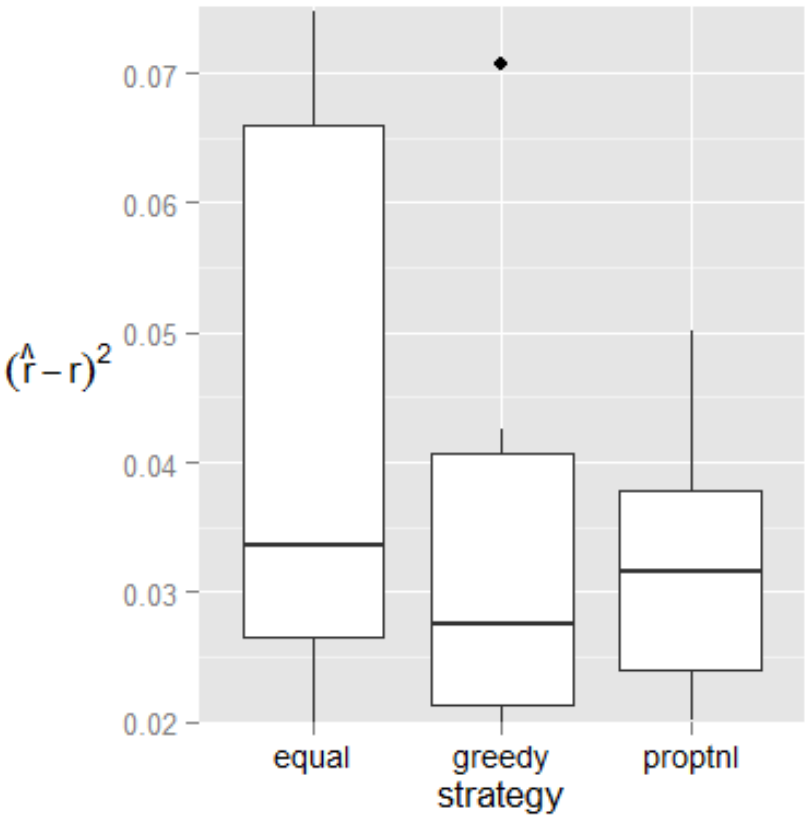
To efficiently select a best path when their qualities are not known *a priori*, sample usage must be partitioned between two conflicting tasks:

- Exploration of poorly characterized paths
- Exploitation of the putative optimal path

The multi-armed bandit problem

Given k non-overlapping paths of unknown variance and N particles with which to sample, what is the optimal sample allocation strategy that will minimize the variance of the overall free energy estimate?

Comparison of simple bandit strategies



- Equal: allocate particles equally to paths, regardless of estimated variances
- Greedy: after initial equal allocation learning period, allocate all particles to best-guess minimum variance path
- Proptnl: after initial equal allocation learning period, allocate particles to paths inversely proportional to their estimated variances

Limitations of SMC and the bandit framework

The multi armed bandit is a suitable formulation when selecting between enumerated paths, but situations can arise where we have no preconceived notion of the underlying state space, and what an acceptable path looks like.

A method that encompasses path discovery, refinement and selection is a necessity for more general applications.

Because SMC estimators operate on full paths, they are not well suited to contexts in which we build paths edge-by-edge.

Edgewise decomposable SMC estimators

seqBAR - sequential BAR

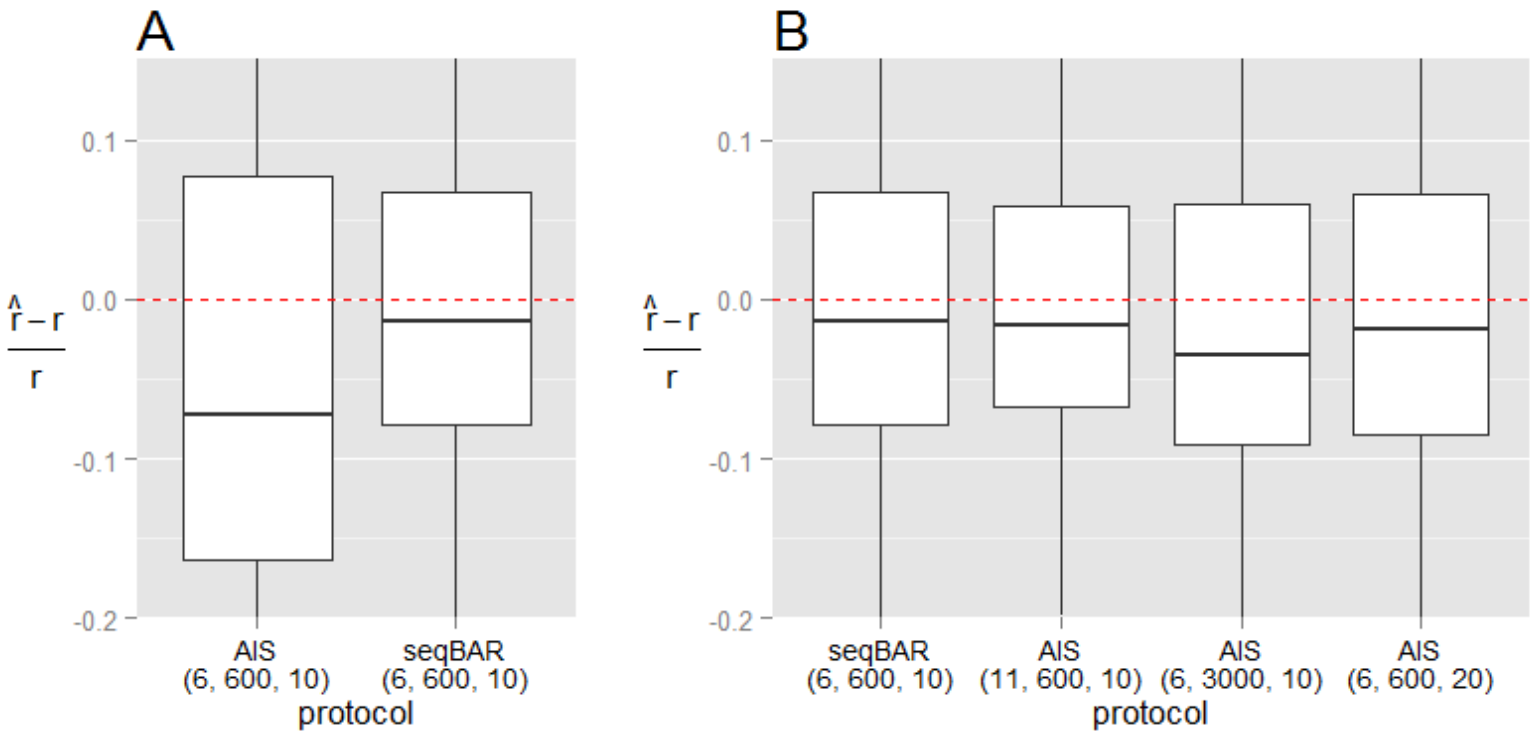
Approximate equilibrium distributions by resampling: redraw n particles from the multinomial distribution where the probabilities are the particle weights.
Use resampled, unweighted particles in BAR equation.

pCrooks - pairwise Crooks

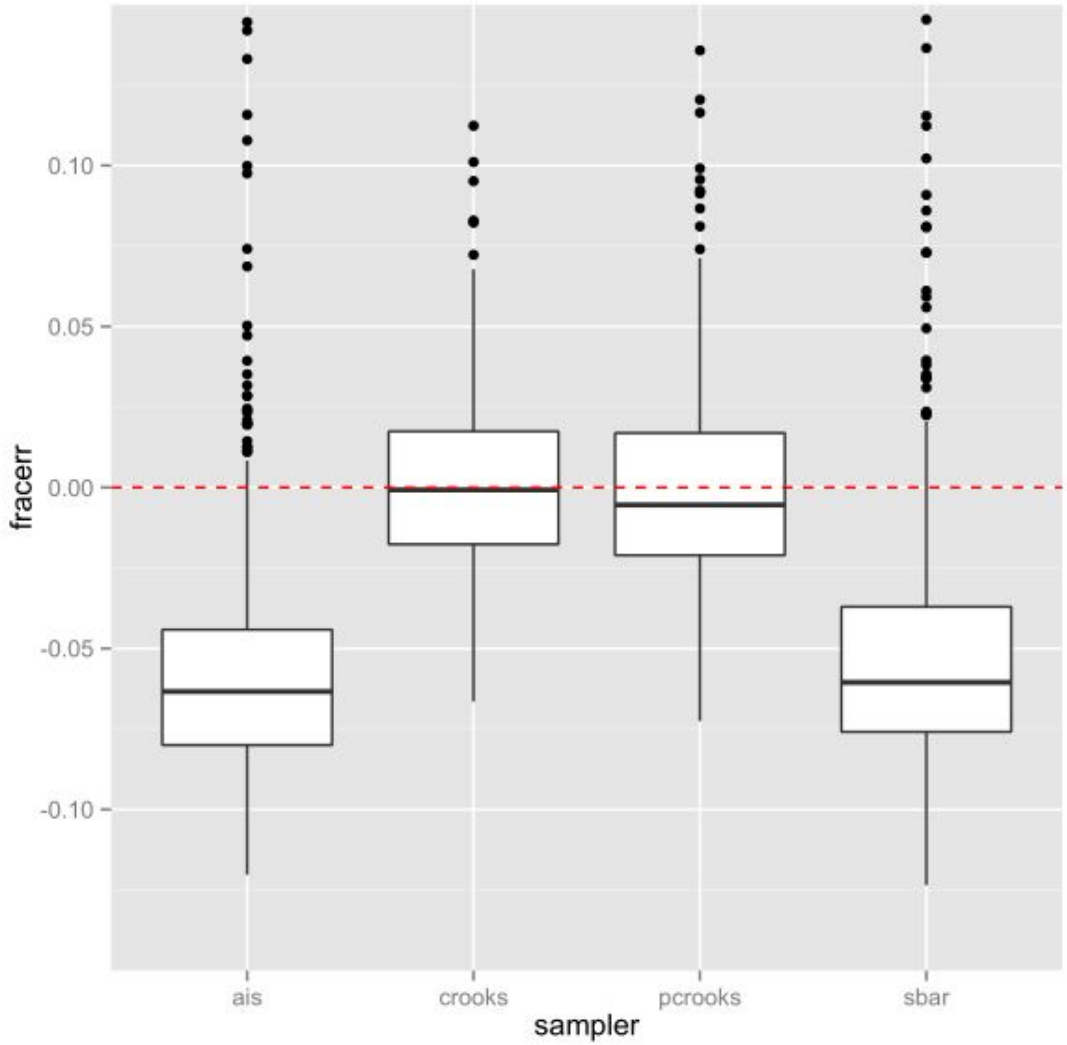
Use per-transition work-weighted distributions in a modified BAR equation:

$$\hat{r}_{A\to B} = \frac{E_{A\to B}[w_B q_B(x)\alpha(x)]}{E_{B\to A}[w_A q_A(x)\alpha(x)]}$$

SMC excels when paired with bridge sampling



pCrooks is the more robust edgewise SMC method



The Q-learning algorithm

Q-learning is a reinforcement learning technique for maximizing total reward in finite state Markov decision processes.
Q-learning accomplishes this by estimation of a Q function, which describes the expected reward for all state-action pairs in the graph.

Q-function updates

$$Q_{t+1}(s,a) = Q_t(s,a) + \alpha(R(s,a) + \gamma \max_{a'} Q_t(s',a') - Q_t(s,a))$$

$\alpha \in [0,1]$ is a learning rate, and $\gamma \in [0,1]$ is a discount factor.

The Q-learning algorithm

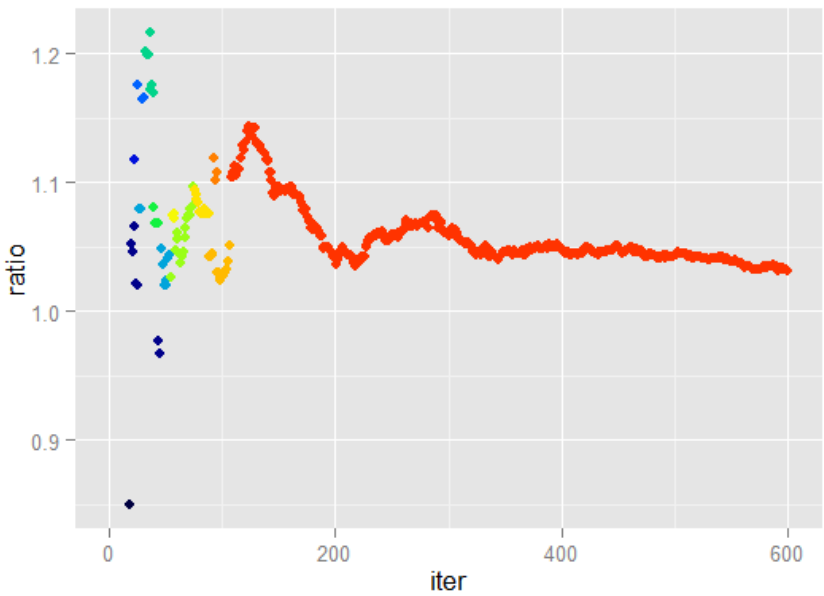
Q-learning is a reinforcement learning technique for maximizing total reward in finite state Markov decision processes.
Q-learning accomplishes this by estimation of a Q function, which describes the expected reward for all state-action pairs in the graph.

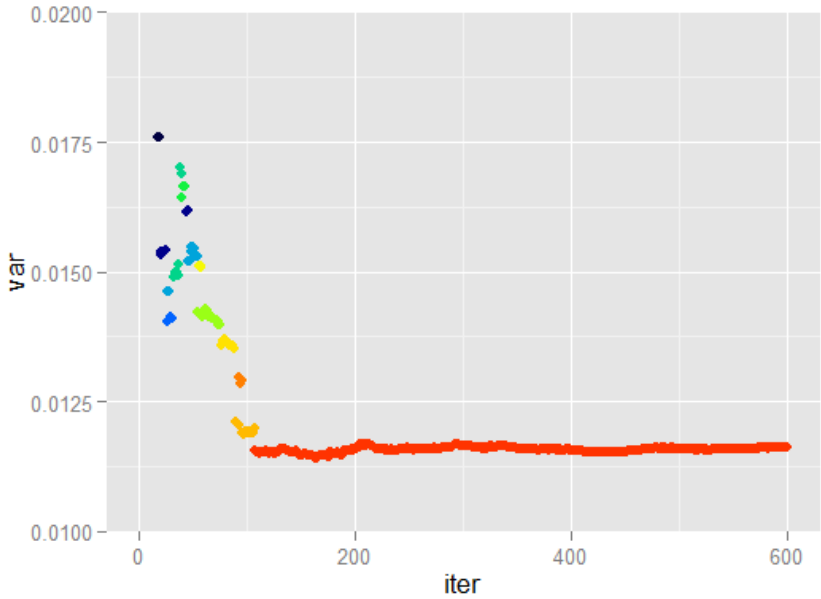
Q-function updates for minimization

$$Q_{t+1}(s,a) = Q_t(s,a) + \alpha(R(s,a) + \gamma \min_{a'} Q_t(s',a') - Q_t(s,a))$$

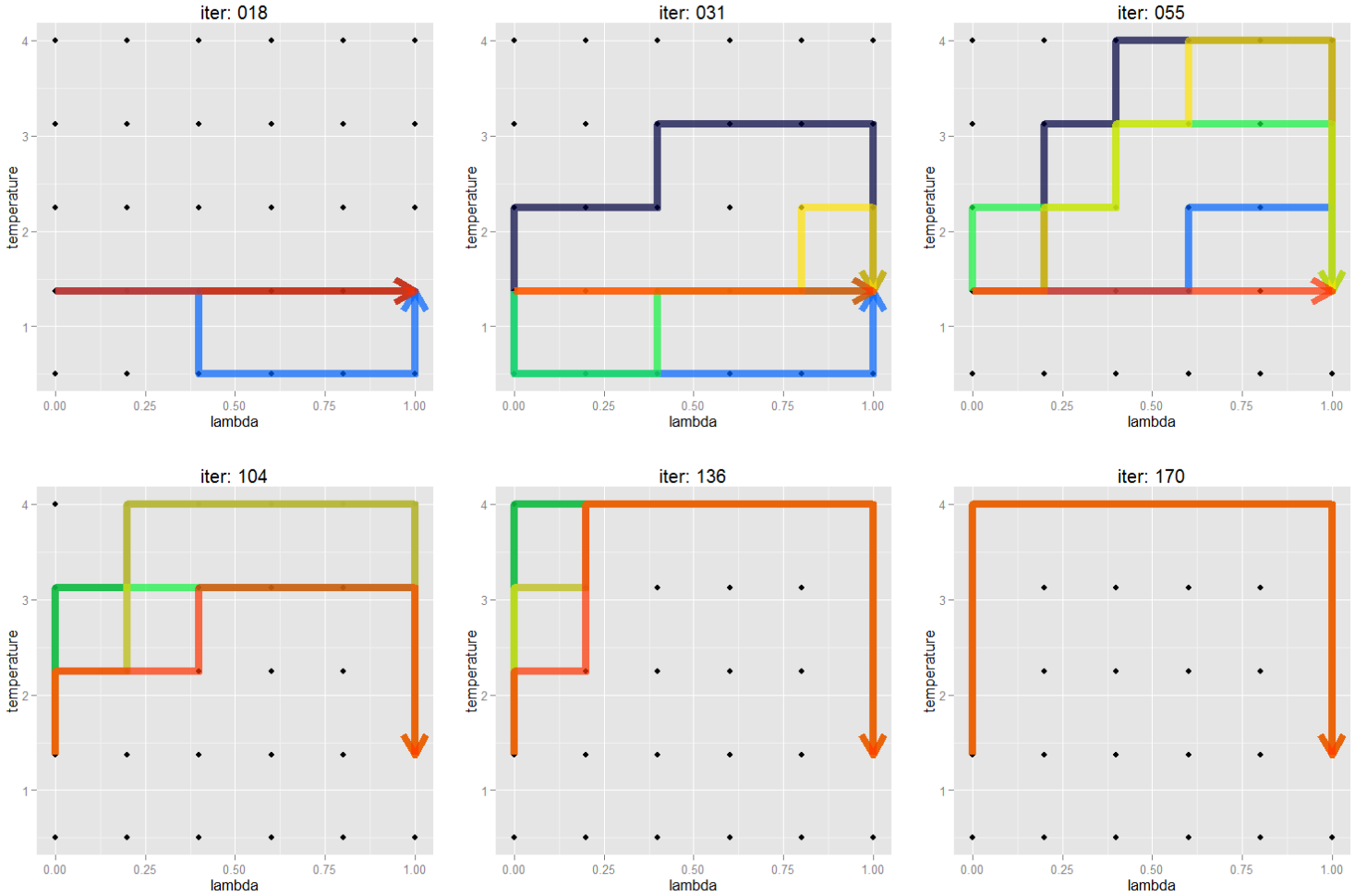
$\alpha \in [0,1]$ is a learning rate, and $\gamma \geq 1$ is a discount factor.

Fixed duration Q-learning



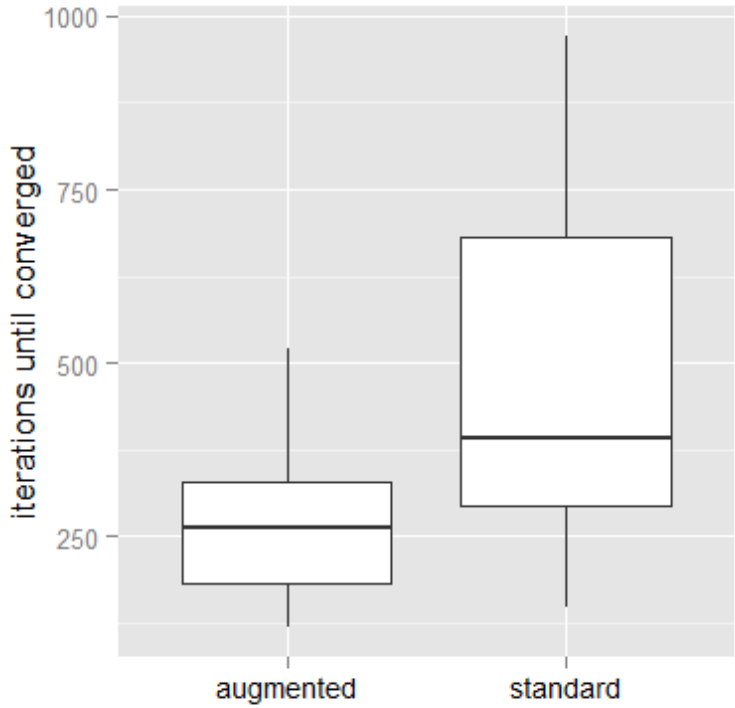


Path evolution



Ratio estimate convergence with Q-learning

- Is path searching a net benefit? Cost of path searching can be substantial - reduction from optimal path must compensate.
- Monitor convergence of three QL chains.
- Convergence achieved when each chain's $\hat{r}_i \pm \widehat{\text{var}(r_i)}$ is contained within a tolerance window surrounding the composite $\hat{r}$ ratio estimate.



Recap and conclusions

- A temperature-augmented λ space is convenient and effective for creating improved alchemical paths.
- pCrooks represents a new SMC estimator which retains desirable properties of CFT while providing valuable information about individual transitions in the path.
- Reinforcement learning techniques, like Q-learning and bandit strategies, are effective at rapidly determining improved sample allocation strategies for ratio estimation in the augmented state space.

Thank you!

Questions?