Title: The rocky road from non-equilibrium work to free energy

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Abstract: Although a few of very promising methods now exist for extracting free energy profiles of a many-body system from non-equilibrium work performed on it the implementation of these methods have proven to be non-trivial. These methods (most notable of all the Jarzynski equality the FR method and the Brownian dynamic FDT) typically require a proper sampling of the work performed on the system along many trajectories in the available phase space that connect the desired initial and final macrostates. One requires a transparent way of sampling the work performed on the system along each trajectory and then to assign residual work values to each 'bin' along the range under study. This becomes a seemingly arbitrary process when done along steered molecular dynamics trajectories. As a result of Brownian motions the system will repeatedly pass back and forth the boundaries of each bin along the reaction path and proper sampling of non-equilibrium work becomes challenging.A method for measuring non-equilibrium work in such cases will be presented with discussions on error analysis and how to address the issue of correlations among adjacent samplings of work for each bin. Applications of this method to a test system and also to a couple of peptide-membrane systems will be presented and discussed as well as the relative reliability of the results based on theoretical arguments and the agreement among different methods.

The rocky road from non-equilibrium work to the free energy profile

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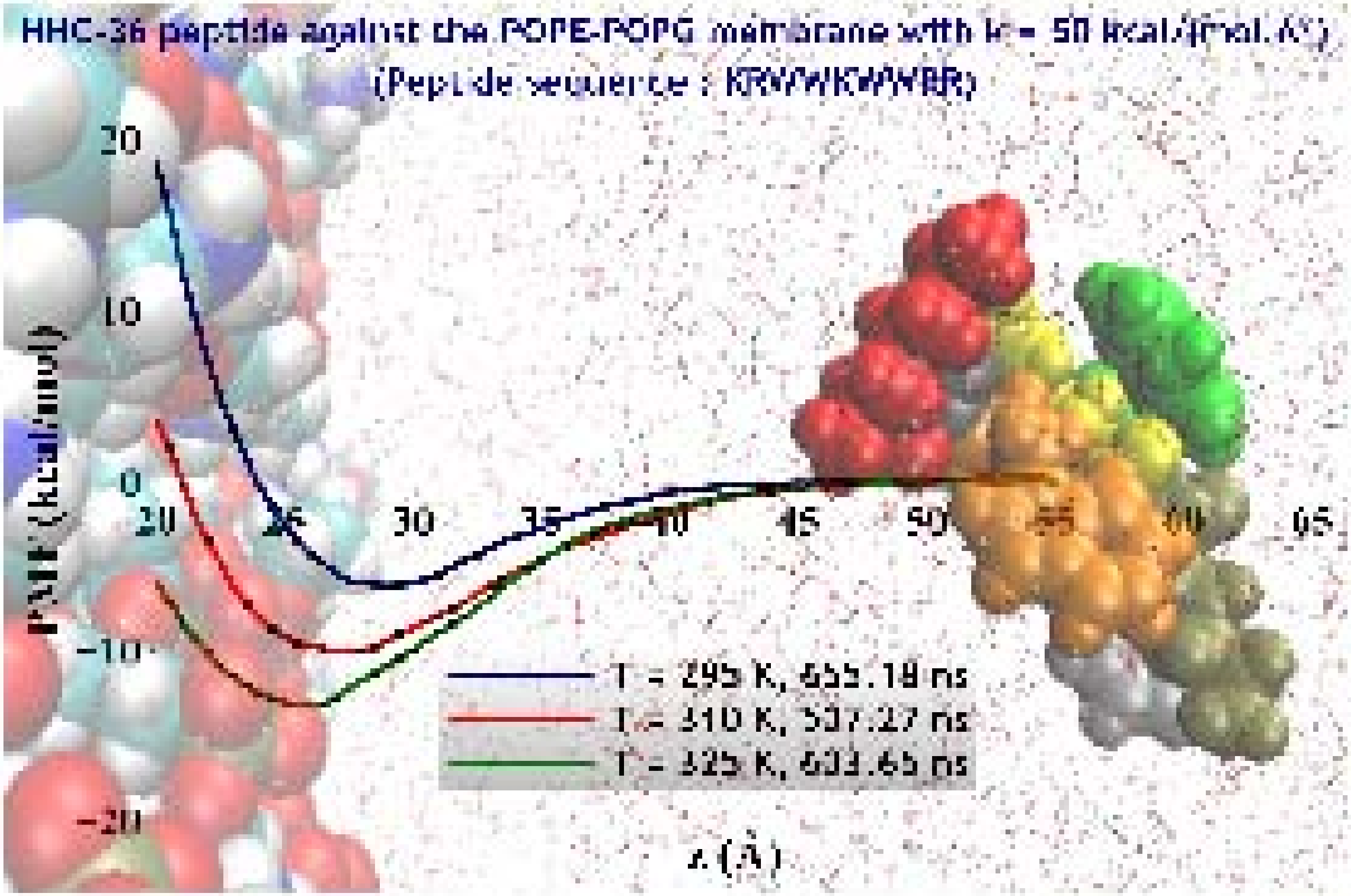
Goal: to find the potential of mean force for a (relatively) large biomolecular system from non-equilibrium processes



Potential of mean force

- Consider a thermodynamical system undergoing a transition from an initial macrostate A to a final macrostate B, characterized by values x_A and x_B of a reaction coordinate x.
- x is a variable in the system, like the volume of a gas, or the position of the center of mass of a molecule against a cell membrane
- The potential of mean force (PMF), $\Phi(x)$ is defined as the free energy of the system as a function of x, (thermodynamically) averaged over all other coordinates and momenta in the system:

$$e^{-\beta . \Phi(x')} = \int dr\, dp\, \delta(x - x')\, e^{-\beta . H(r,p)}$$

General non-equilubrium work theorems

First came Jarzynski (1997): $e^{-\beta\Delta\Phi_{AB}} = \langle e^{-\beta W_{A\to B}} \rangle$

And then Crooks' theorem (1998): $\frac{\langle f(W_{A\to B})\rangle_F}{\langle f(-W_{A\leftarrow B})e^{-\beta(W_{A\leftarrow B})}\rangle_R} = e^{-\beta\Delta\Phi_{AB}}$

From which, the FR method emerged (2006): $\Delta\Phi_{AB} = \frac{\langle W_{A\to B}\rangle - \langle W_{A\leftarrow B}\rangle}{2}$

And more recently (2008), Chen: $e^{-\beta\Delta\Phi_{AB}} = \frac{\langle e^{-\frac{1}{2}\beta W_{A\to B}}\rangle}{\langle e^{-\frac{1}{2}\beta W_{A\leftarrow B}}\rangle}$

These relations are generally correct, as long as the conditions assumed in their derivation (e.g. Brownian dynamics of the system under consideration) are met.

However, their convergence for a finite number of samplings is not always satisfactory.

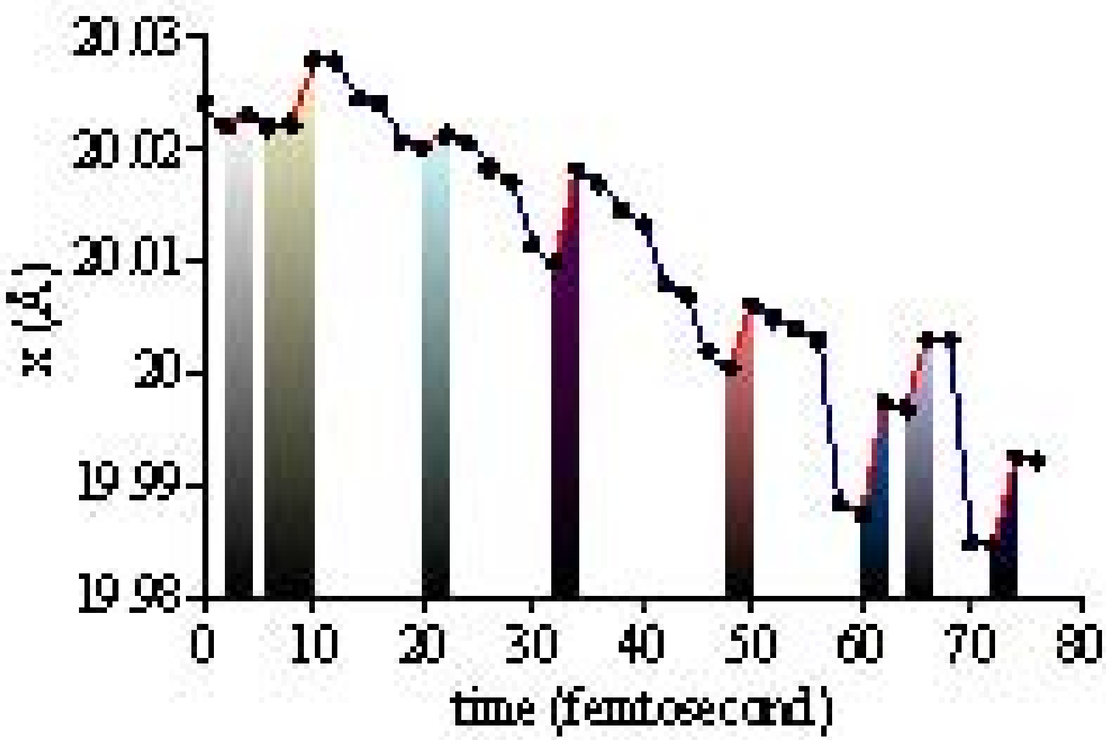
Implememnting a steered molecular dynamics (SMD) simulation

- Time is discretized into time-steps, typically of length 2 fs each
- System evolves one time-step at a time (Solving equations of motions numerically)
- A harmonic potential (i.e. a spring) is often employed to apply force in the desired direction (restraint)
- The spring will serve both as the steering tool and as the force measurement device

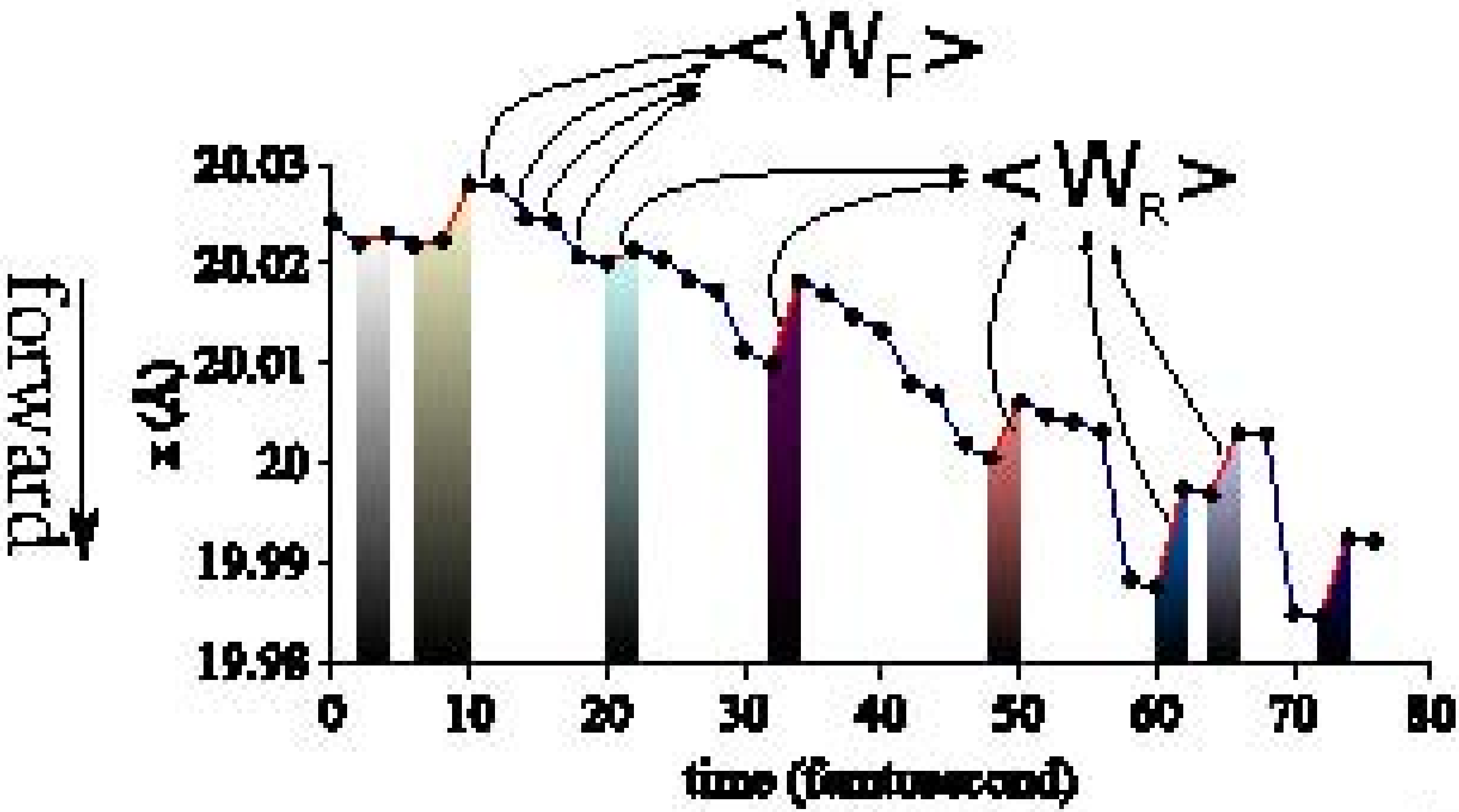
Drawback: Any spring of finite stiffness will inevitably do an imperfect steering against random graininess of the molecular system with Brownian motions.

The trouble with using crude *bin-crossings*

- $\langle W_{dissipative} \rangle = \frac{\langle W_F \rangle + \langle W_R \rangle}{2} > 0$, and it is the same in forward and reverse directions
- Frequent movements of the steered object against the targeted direction introduce extra dissipative work into the estimated $\langle W_F \rangle$ and $\langle W_R \rangle$ values $\Rightarrow$ poorer convergence in $\Delta\Phi_{AB} = \frac{\langle W_{A\to B} \rangle - \langle W_{B\to A} \rangle}{2}$

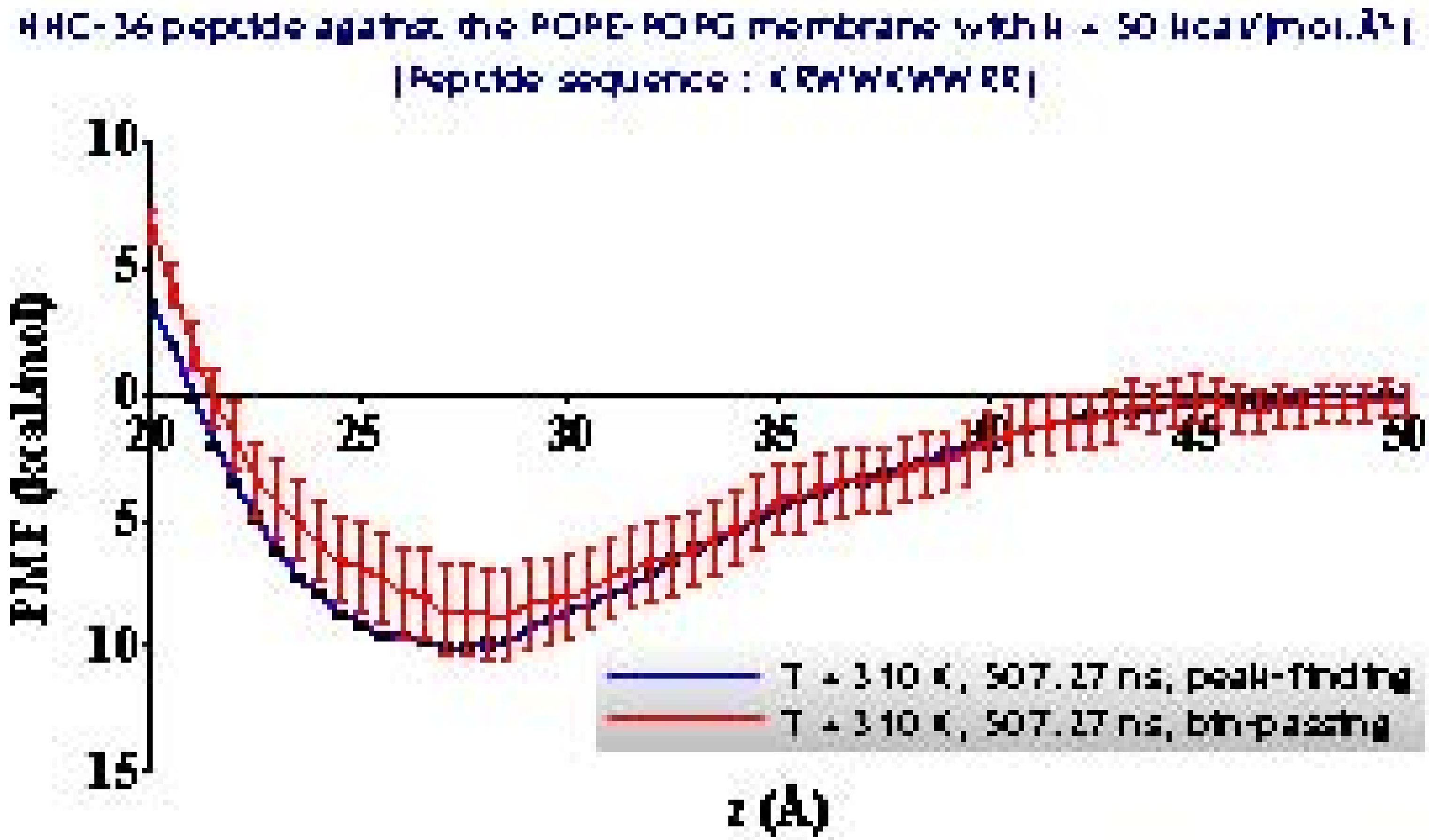


Enhanced sampling method (*bin-passing*)



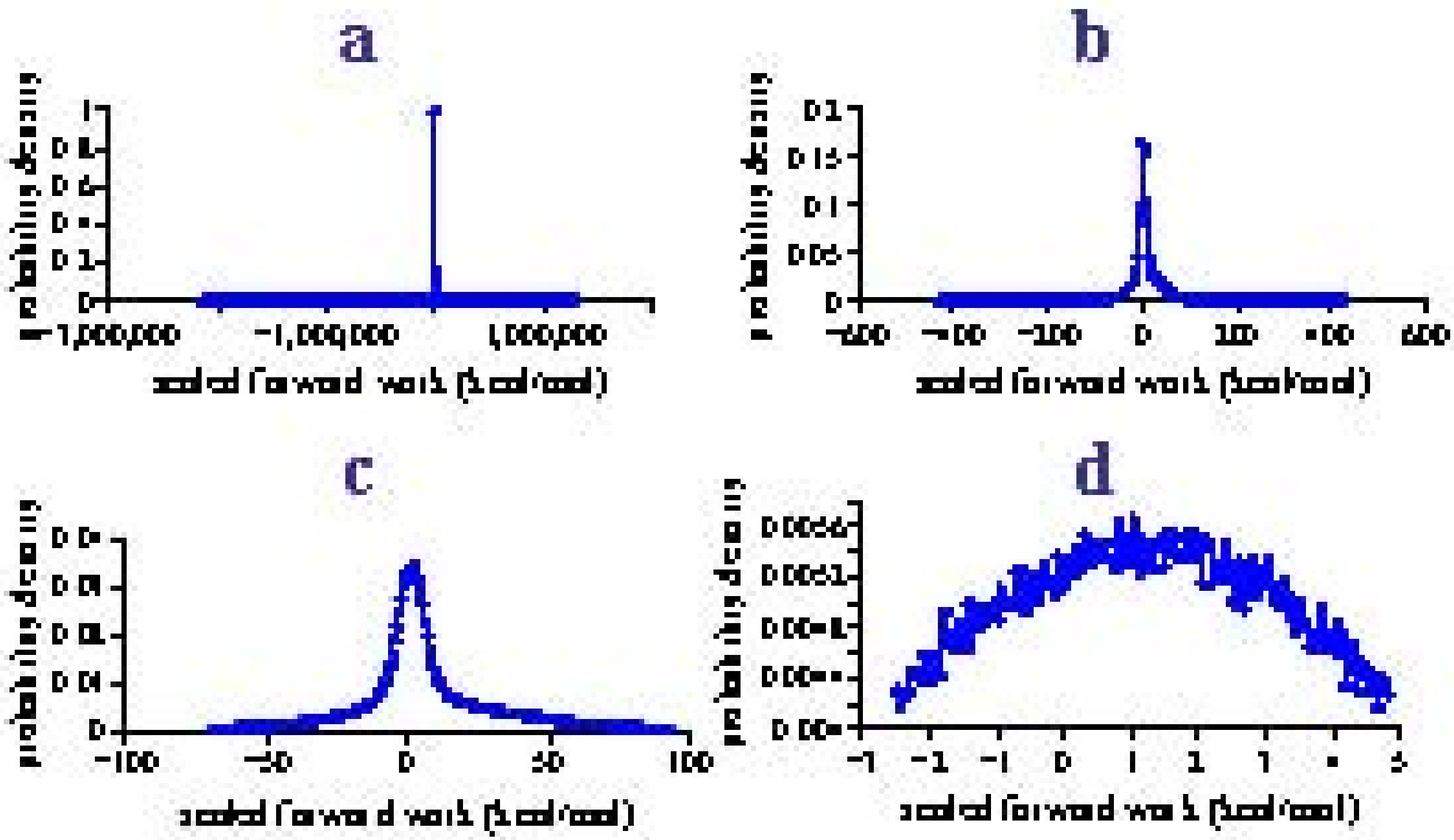
HHC-36 against a POPE/POPG membrane patch

The bin-passing method improves the convergence, but we can still do better.



The peak-finding method

Use the $W_{F(R),peak}$ instead of $\langle W_{F(R)} \rangle$ in $\Delta\Phi_{AB} = \frac{\langle W_{A\to B}\rangle - \langle W_{A\leftarrow B}\rangle}{2}$.



So...

- Restraint method for conducting non-equilibrium SMD simulations can give reliable PMFs with good convergence rates, when using the FR method
- A careful treatment of the forward and reverse work values, at time-step level, is required to achieve proper convergence
- Using $W_{F(R),peak}$ instead of $\langle W_{F(R)} \rangle$ can further the results, provided that enough statistics is available

Thanks!

Questions?