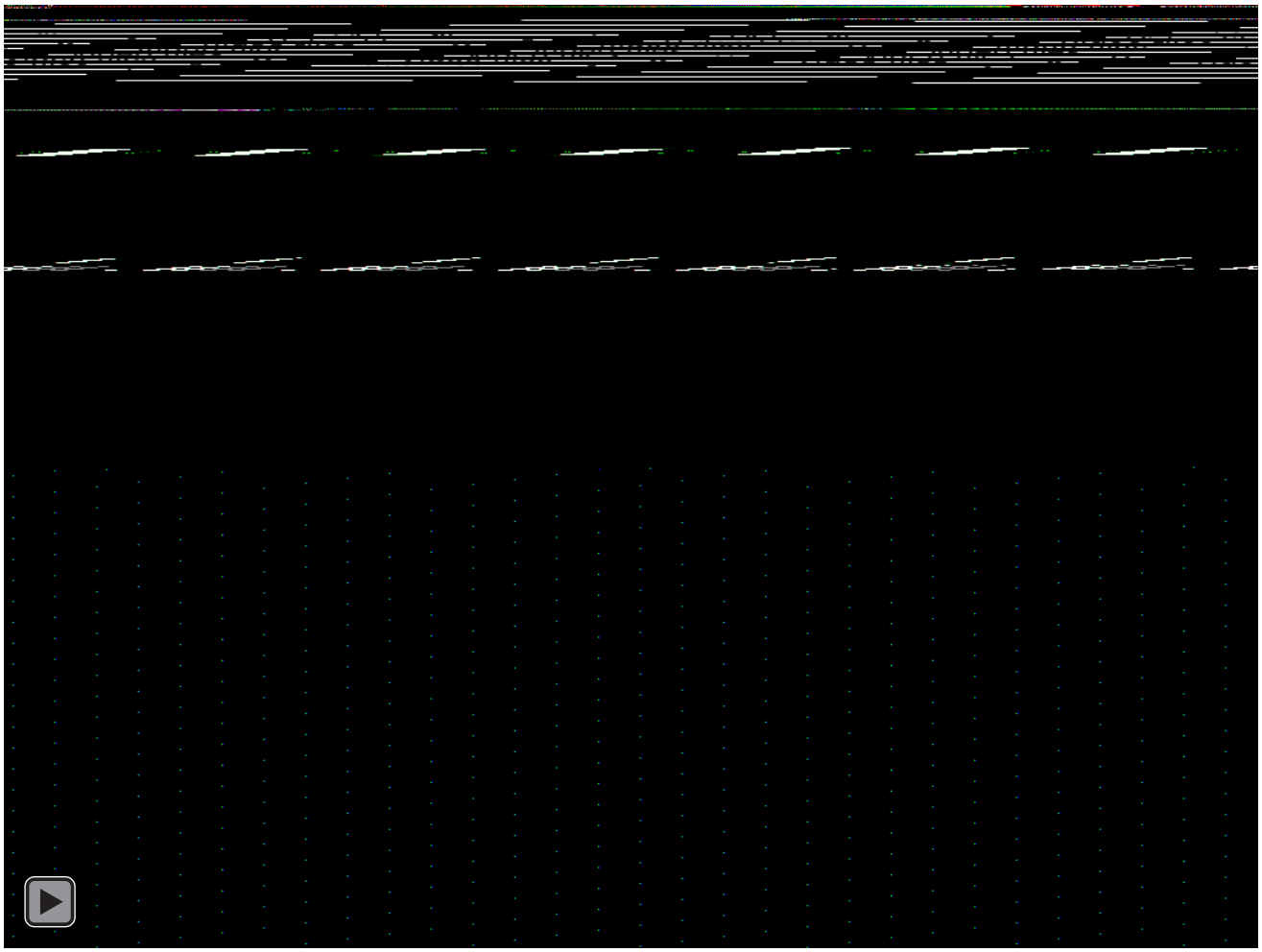
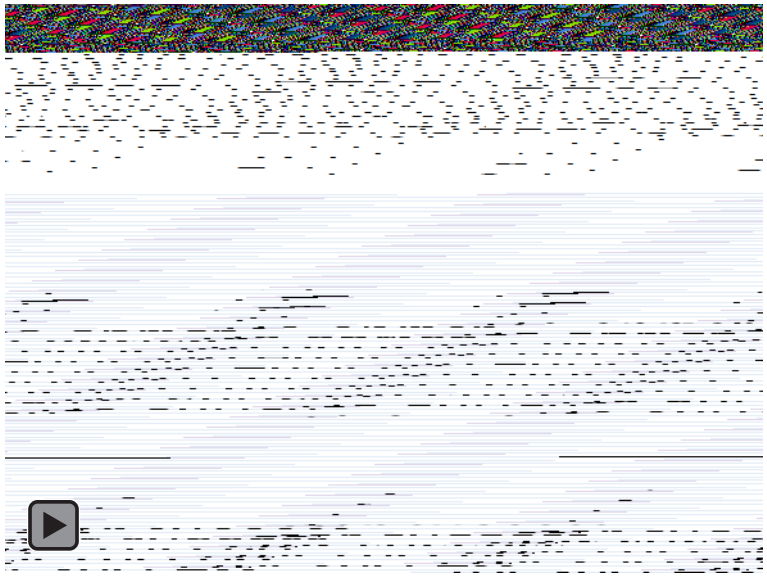
The problem with standard simulations

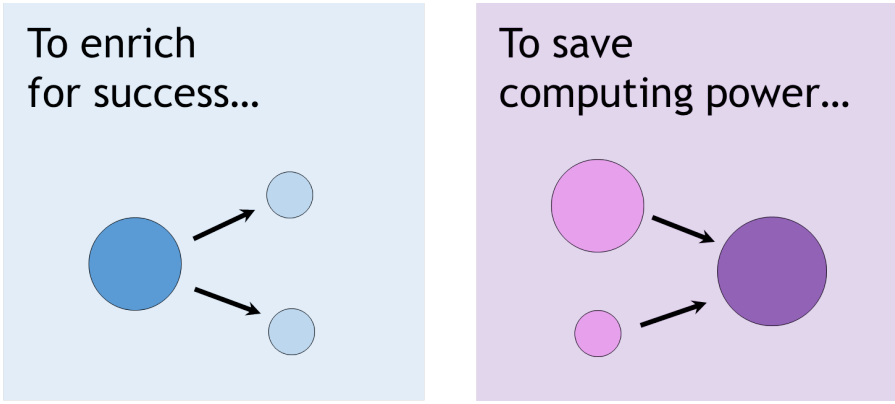


Chong, Saglam, and Zuckerman, *Curr. Opin. Struct. Biol.*, 2017.

Weighted ensemble MD focuses on transitions



Resampling procedure



von Neumann & Ulam “splitting strategy” (1950s)
Huber & Kim, *Biophys. Journal* (1996)
Zuckerman & Chong, *Ann. Rev. Biophys.* (2017)

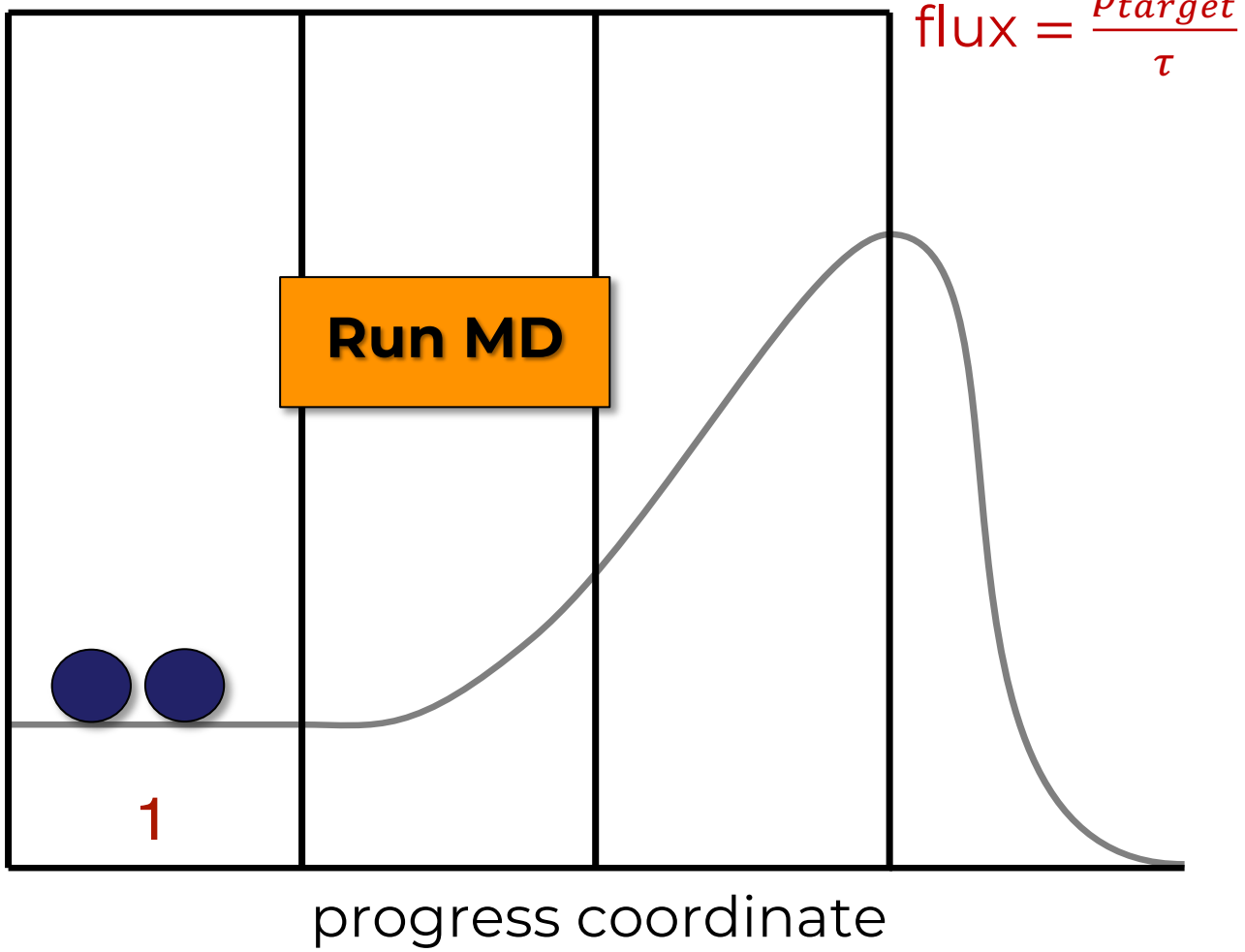
Generates **unbiased, continuous pathways and rates** with **orders of magnitude less computing** than standard MD.

Efficiency scales exponentially with the barrier.

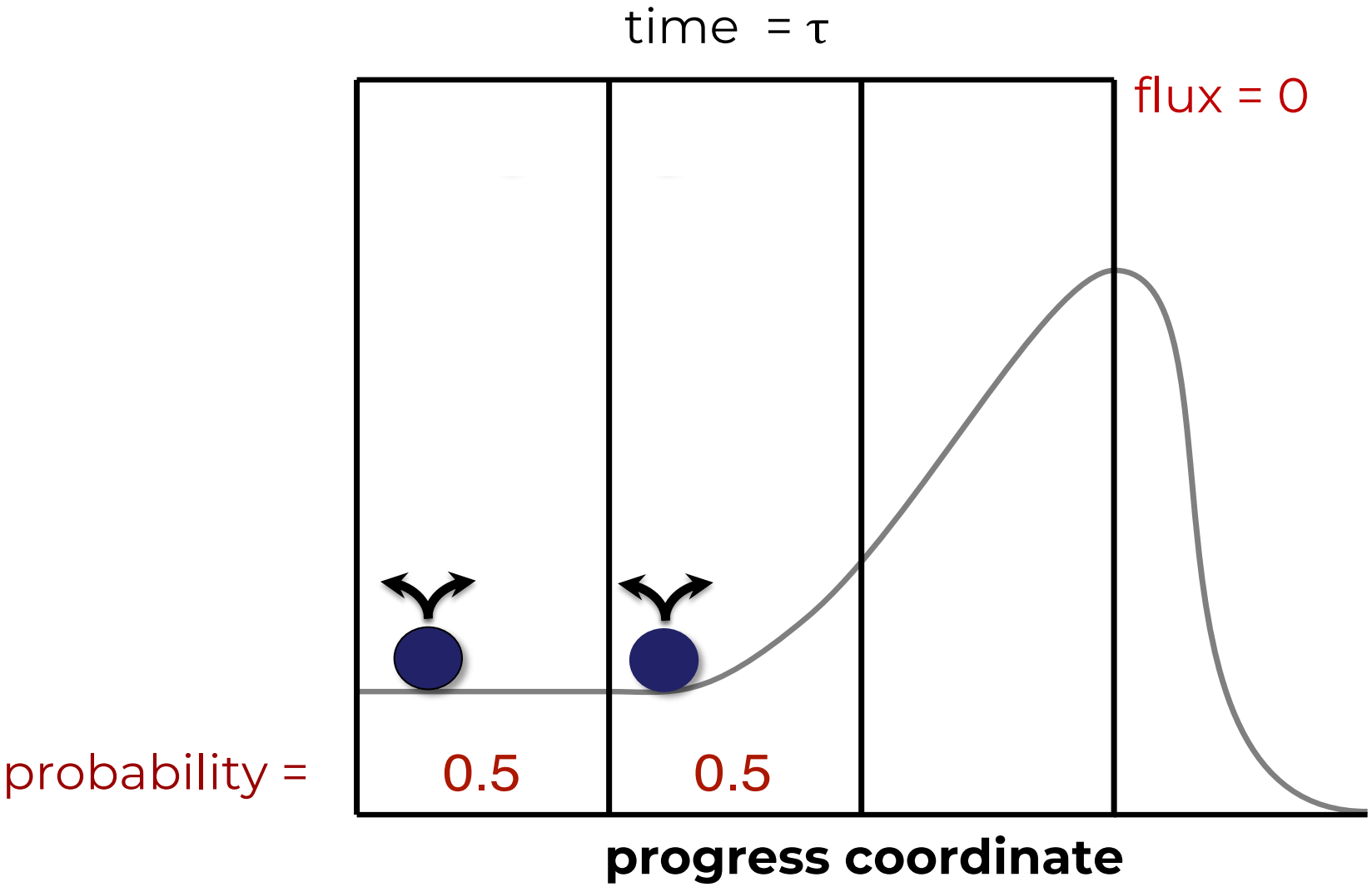
τ = 100 ps

How does resampling work?

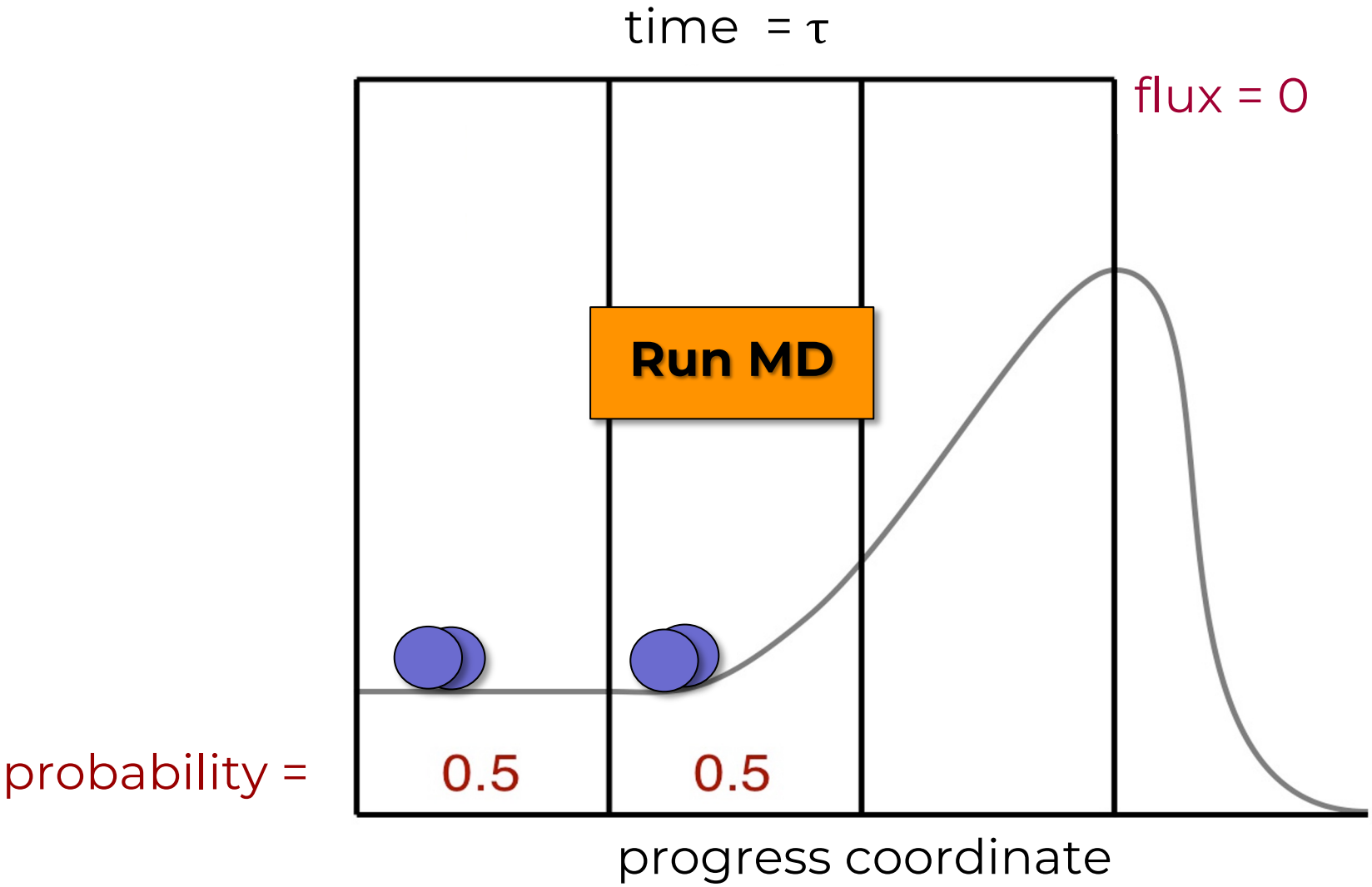
time = 0 ps



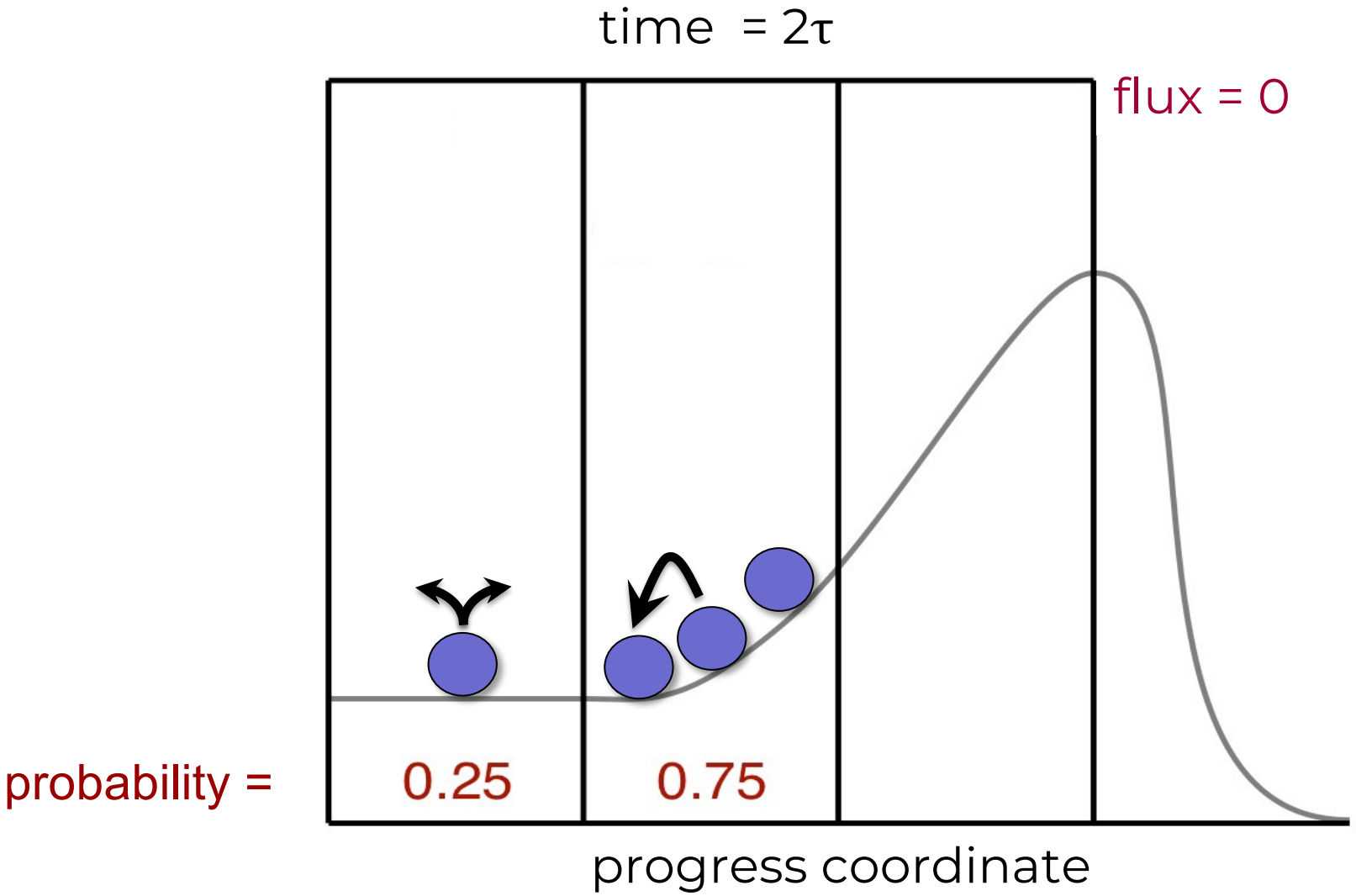
τ = 100 ps



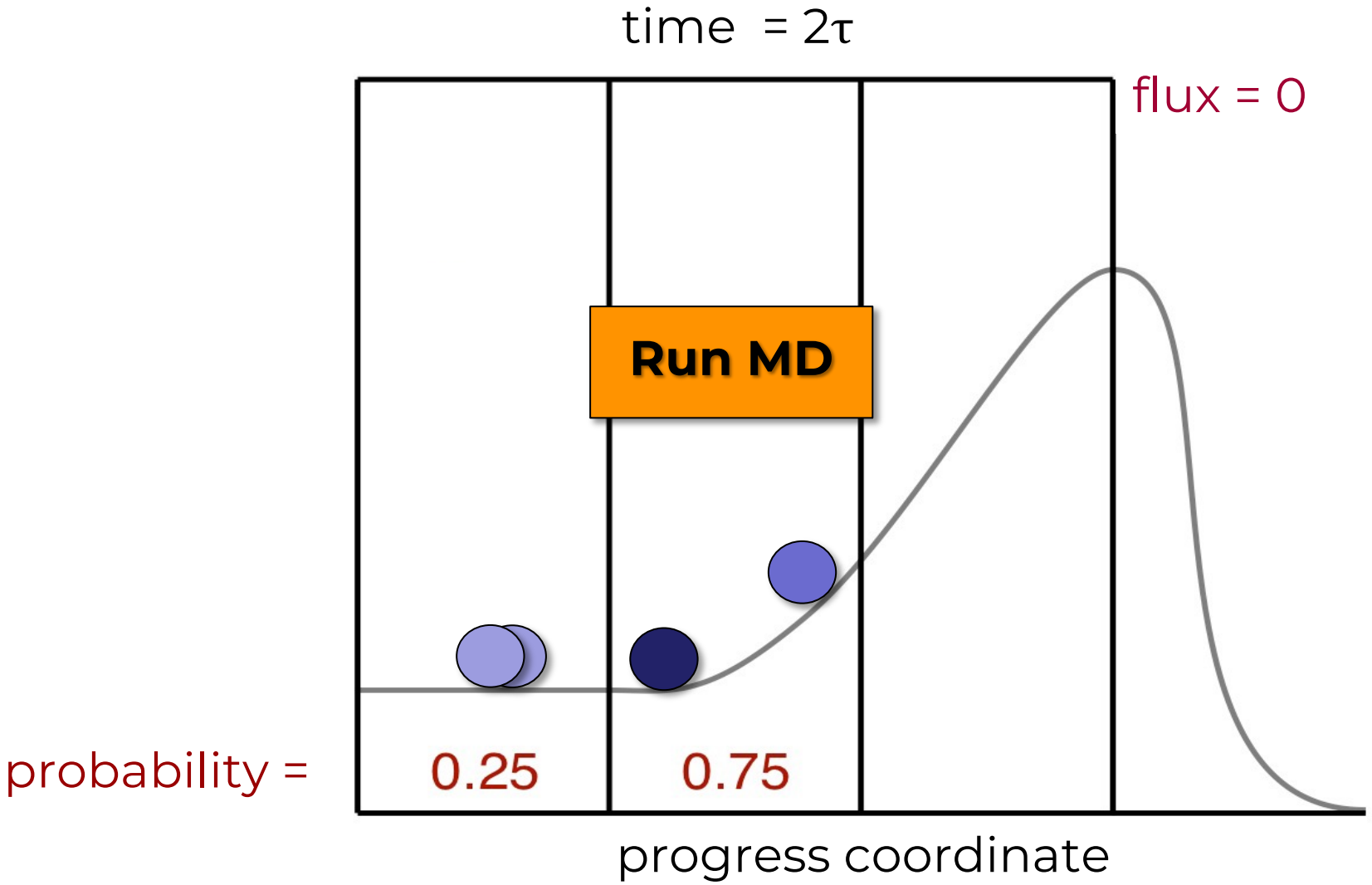
τ = 100 ps



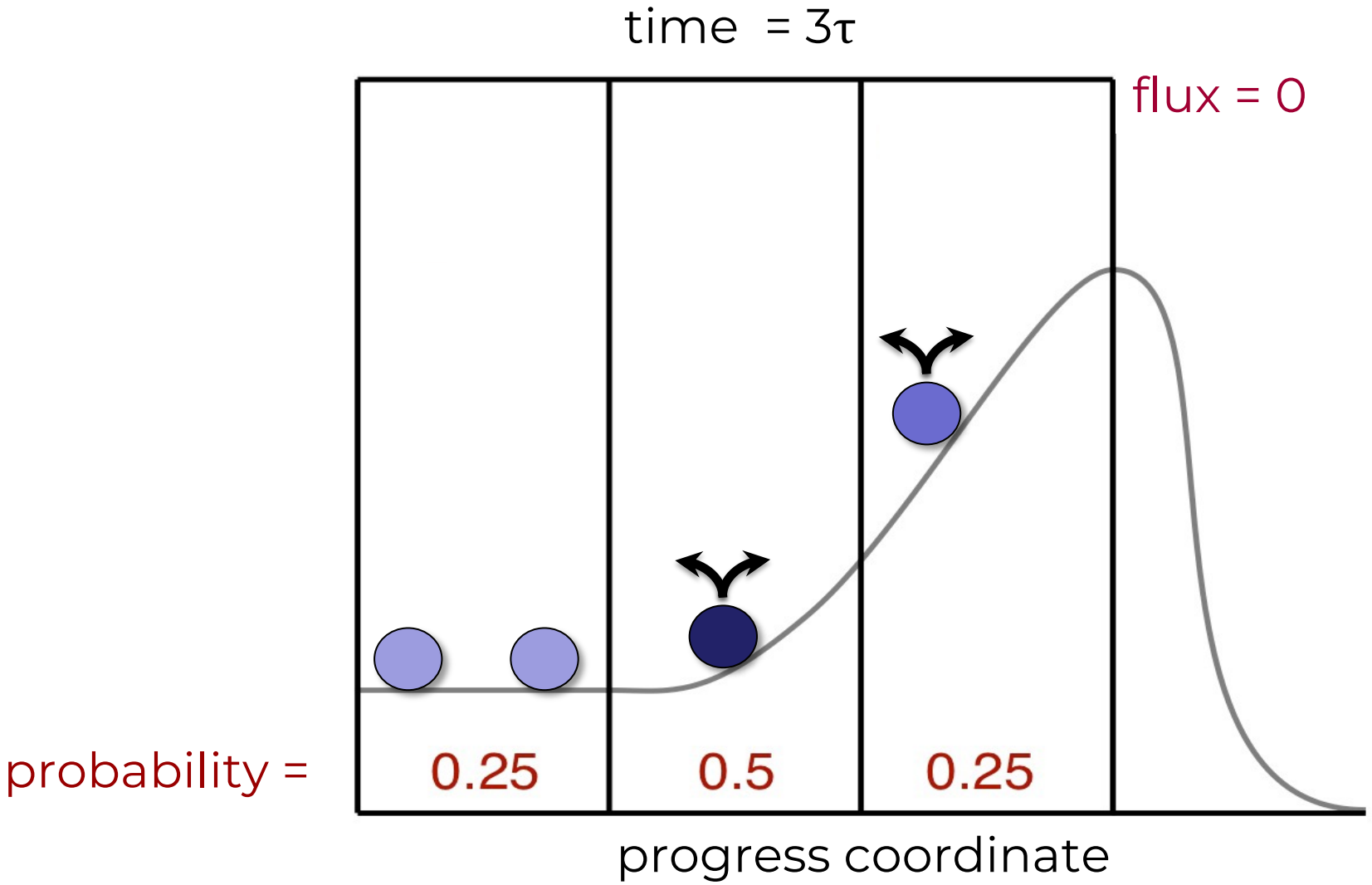
τ = 100 ps



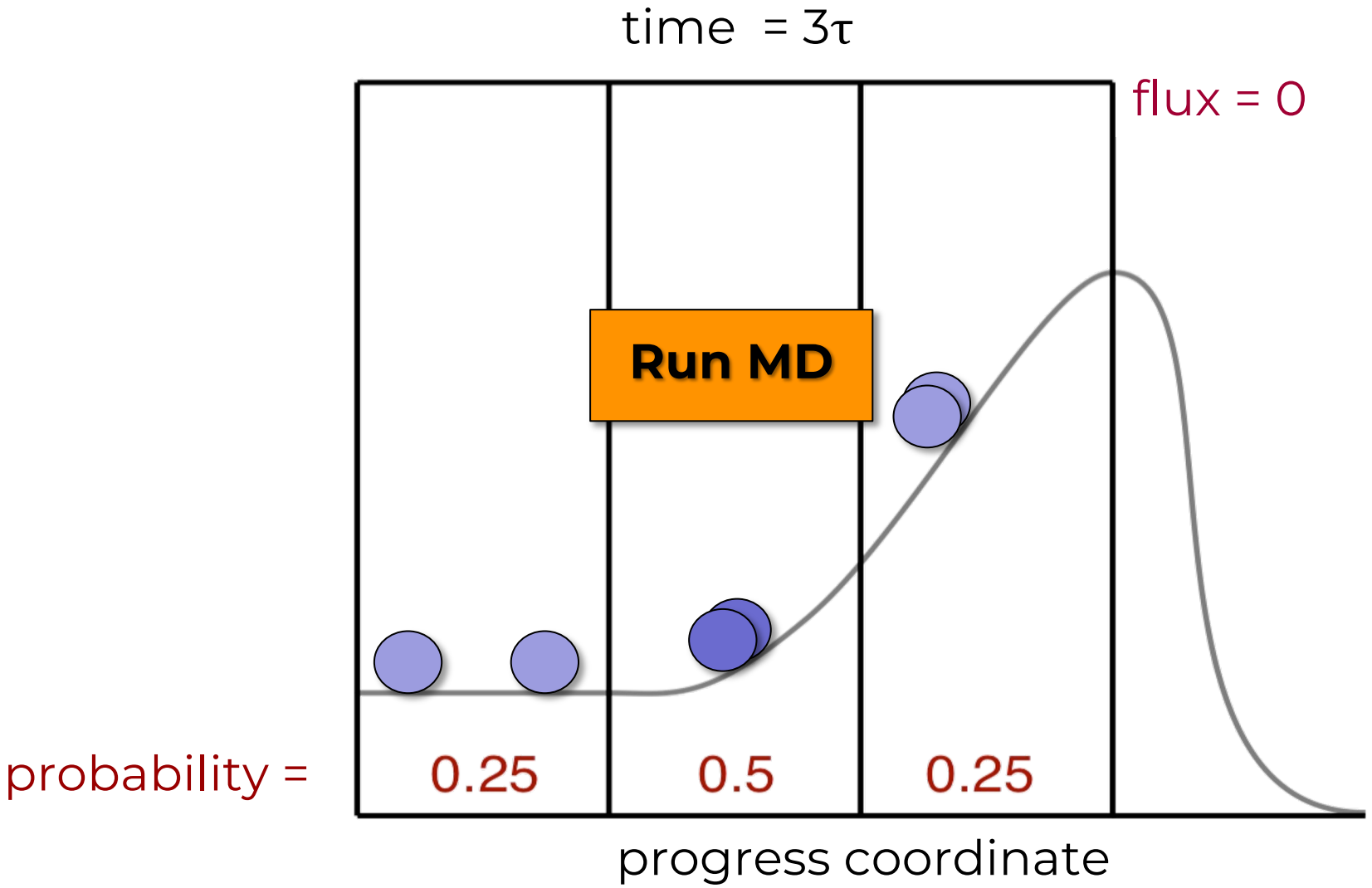
τ = 100 ps


time = 2τ
flux = 0
Run MD
probability =
0.25
0.75
progress coordinate

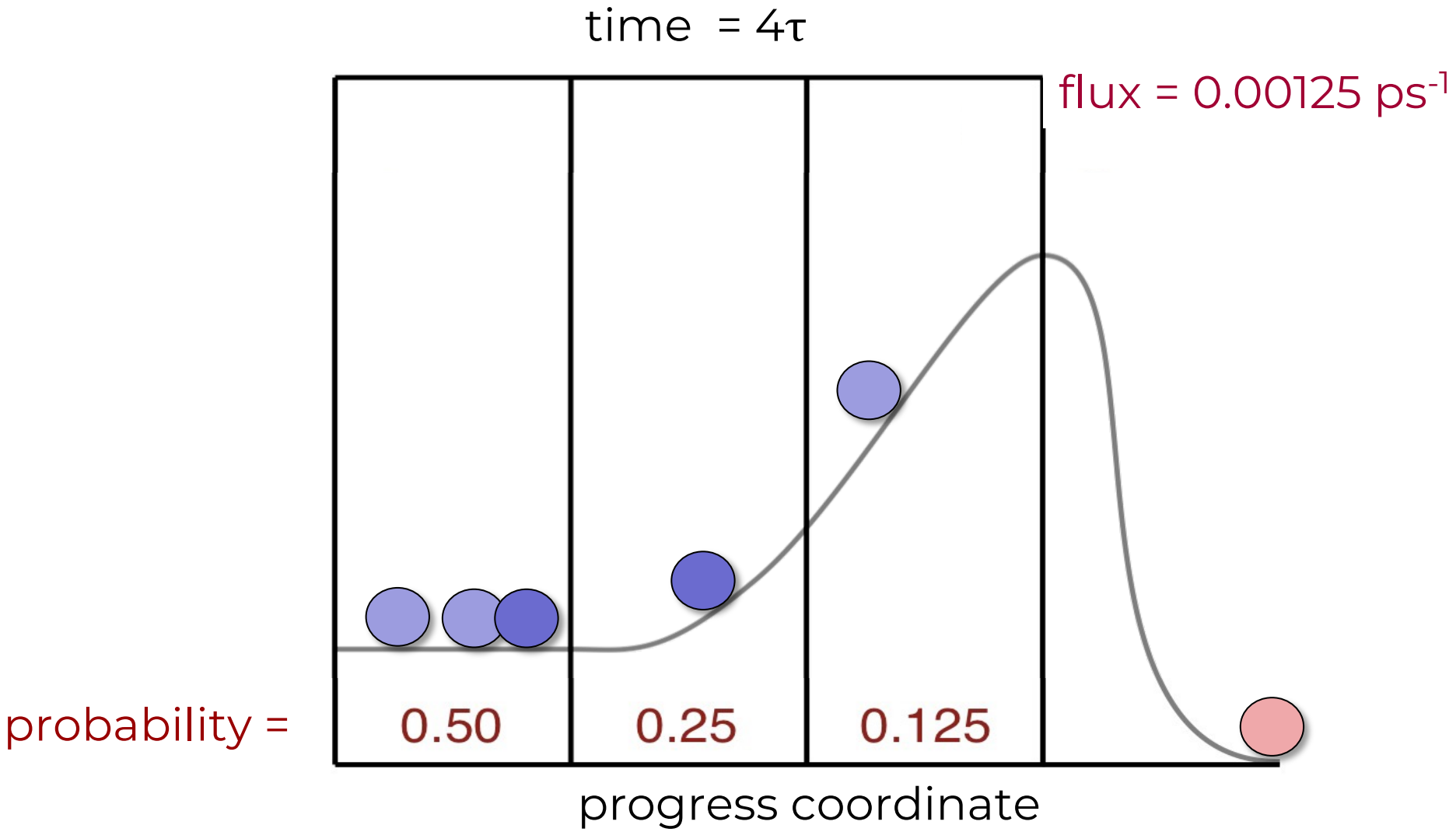
τ = 100 ps



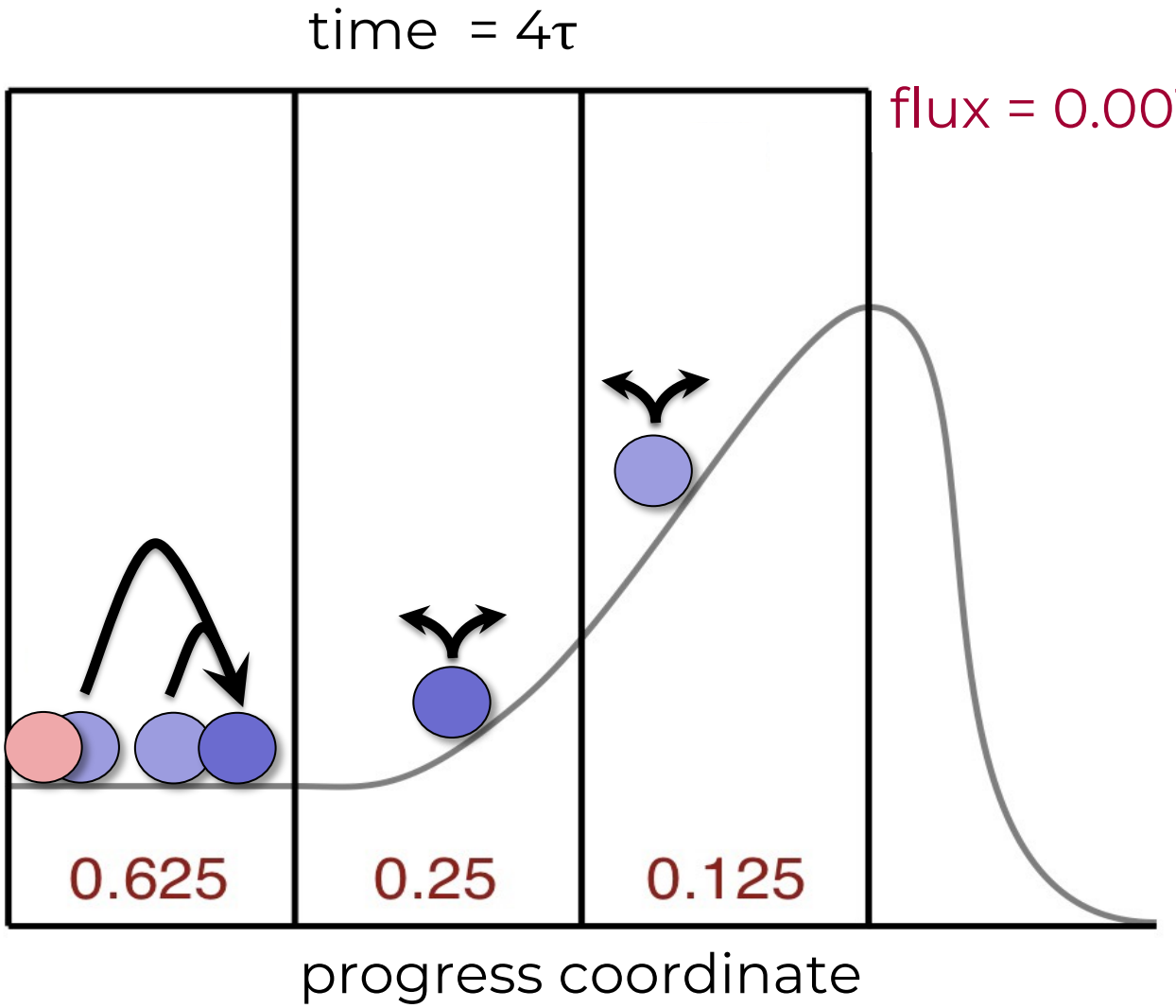
τ = 100 ps


time = 3τ
flux = 0
Run MD
probability =
0.25
0.5
0.25
progress coordinate

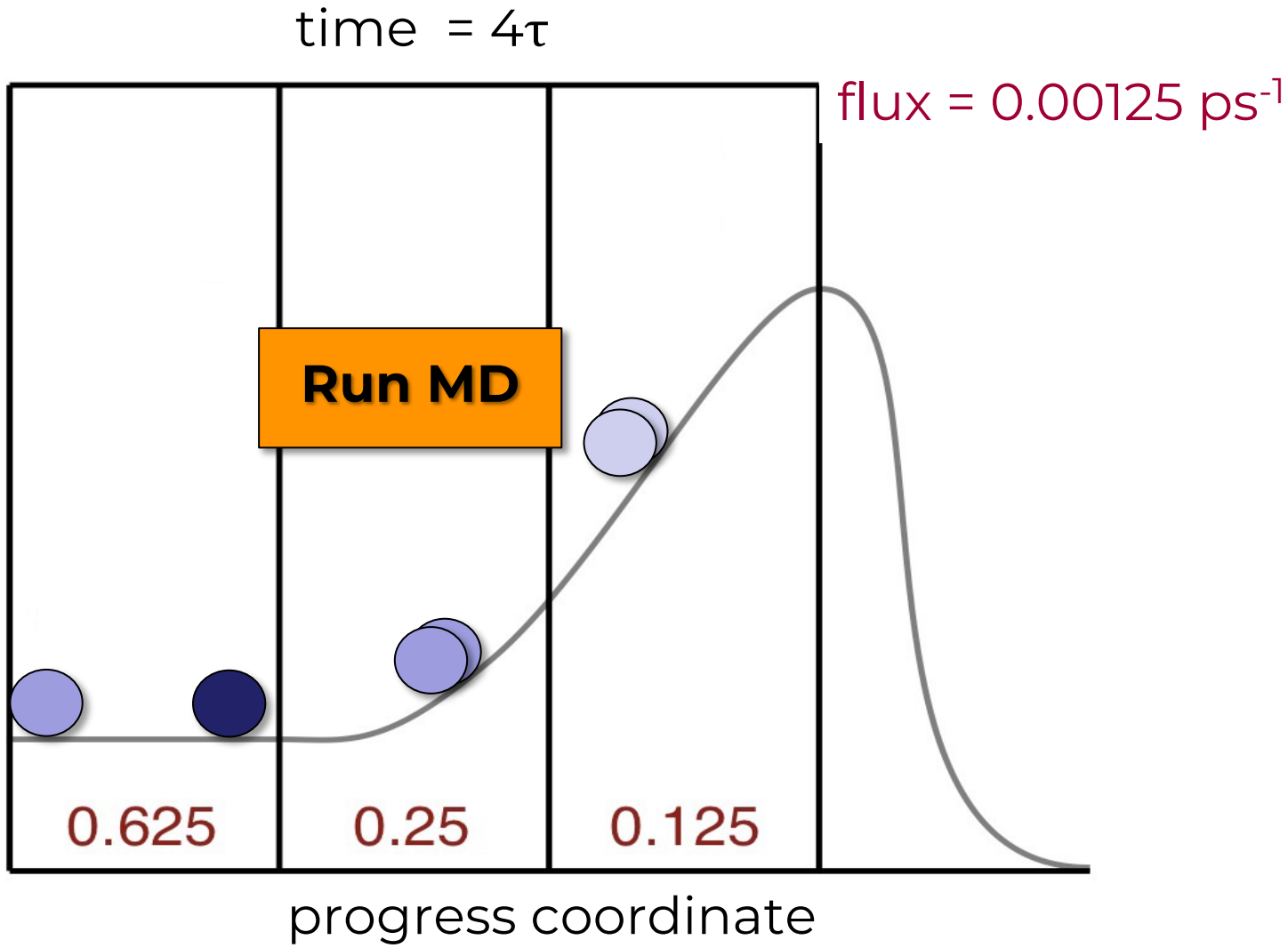
τ = 100 ps


time = 4τ
flux = 0.00125 ps-1
probability =
0.50
0.25
0.125
progress coordinate

τ = 100 ps


time = 4τ
flux = 0.00125 ps-1
probability =
0.625
0.25
0.125
progress coordinate

τ = 100 ps


time = 4τ
flux = 0.00125 ps-1
Run MD
probability =
0.625
0.25
0.125
progress coordinate

No free lunch!

May miss slow motions orthogonal to the progress coordinate.

Worse case is “brute force” sampling of orthogonal motions.

However, we can switch progress coordinates “on-the-fly.”

Weighted ensemble MD greatly extends accessible timescales