Lecture #11 Free energy Measurement 11·4

Review CTMC github.com/gecrooks/LectureNotes220b

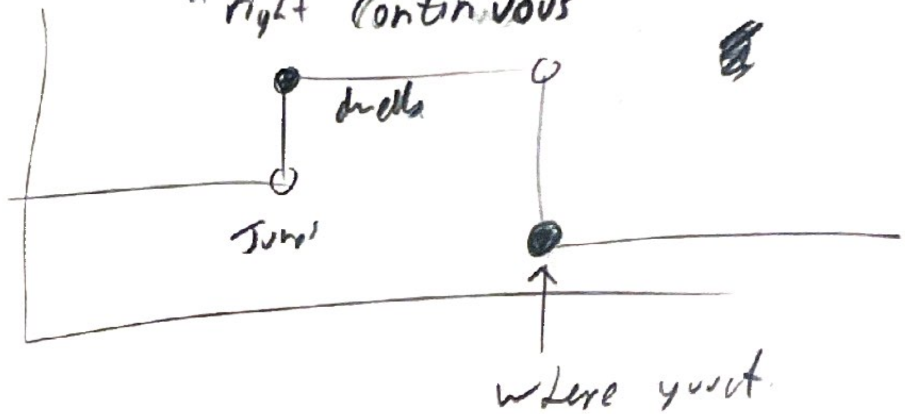
$p(t) = e^{Qt} p$

$\frac{dp}{dt} = Qp$

$$Q \text{ or } R = \begin{array}{c|ccc} & 1 & 2 & 3 \\ \hline & -\lambda_i & \lambda_{12} & \lambda_{13} \\ \text{out} & \lambda_{21} & -\lambda_i & \lambda_{23} \\ & \lambda_{31} & \lambda_{32} & -\lambda_i \end{array} \quad \text{in}$$

$\sum_j Q_{ji} = 0$

"right continuous"



Survival function

$$s(t+s) = s(t)\, s(s)$$

$$s(nt) = s(t)^n$$

$$s(n) = s(1)^n \equiv e^{n \ln s(1)}$$

$\lambda = -\ln s(1)$

Examples

Chemical Reactions

Gillespie dynamics

#11

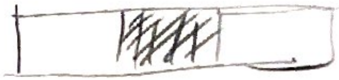
11.2

Markov Processes

CTMP

↓ Brownian dynamics

Lin Response



sometime an extra 'i'

Review CTMC

Langevin dynamics

	Classical	pre QM	Mixed QM
CT: $p(t) = e^{Qt} p(0)$, $\frac{dp(t)}{dt} = Qp$	Fokker-Plank: $\rho(t) = e^{-\mathcal{L}t} \rho(0)$, $\frac{\partial \rho}{\partial t} = -\mathcal{L}\rho$ Liouvillian	Hamiltonian: $\lvert\psi_t\rangle = e^{-iHt} \lvert\psi_0\rangle$, $\frac{d\psi}{dt} = -iH\lvert\psi_0\rangle$	$\rho(t) = e^{\mathcal{L}t} \rho(0)$, $\frac{d\rho}{dt} = \mathcal{L}\rho$ Lindbladian
DT: $p(t) = M_t\, p(0)$, $M_t = e^{+Qt}$	Discrete time. MD Molecular dynamics	Unitary: $\lvert\psi_t\rangle = U \lvert\psi_0\rangle$	$\rho(t) = S\, \rho(0)$ CPTP Maps

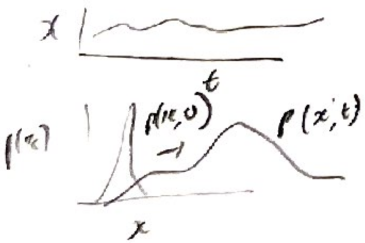
completly positive trace-preserving map
Quantum channel.

~~Brownian Motion~~

Langevin dynamics

$\rho(t) = \mathcal{L}_L\, \rho(0)$

$x \longrightarrow x'$



FT Experiments

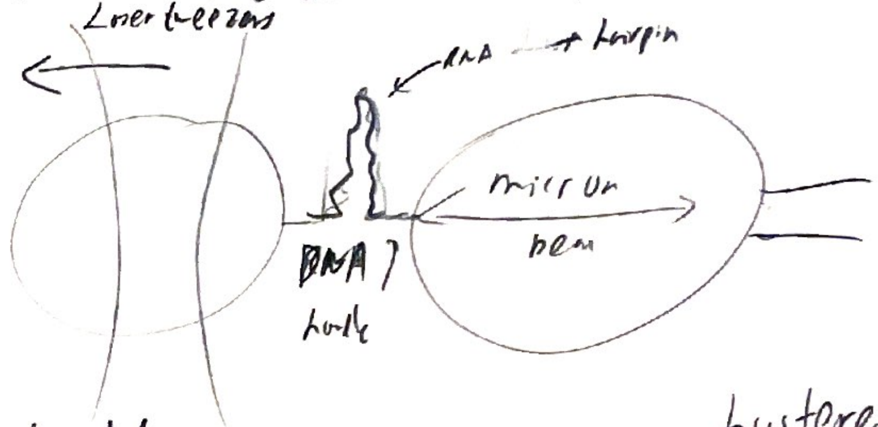
Transient Protocol

$$\frac{P_\Lambda(x)}{P_{\tilde\Lambda}(\tilde x)} = e^{+\beta W - \beta\Delta F}$$

$$\frac{P_\Lambda(+W)}{P_{\tilde\Lambda}(-W)} = e^{+\beta W - \beta\Delta F}$$

$$\langle e^{-\beta W}\rangle = e^{-\beta\Delta F}$$

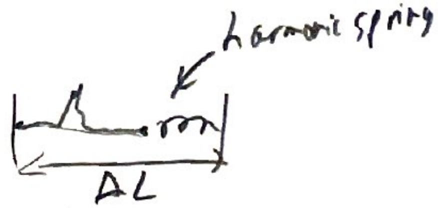
Hummer & Szabo 2001

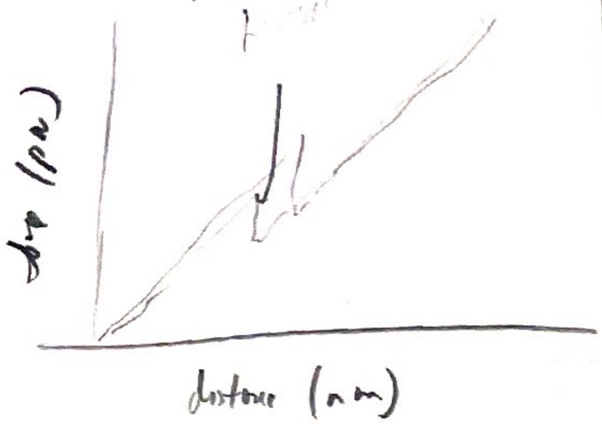


<u>Bustamante lab</u>

Liphardt et al 2002

Collin et al 2005





11·4

Free Energy

Thermodynamic Integration

$$\Delta F = W^{rev}$$ Quasistatic

$$D(X \| \tilde{X}) = \sum P(\tilde{X}) \ln \underbrace{\frac{P_{\lambda}(X)}{P_{\hat{\lambda}}(\tilde{X})}}_{0} = 0$$

$$1 = e^{+\beta W - \beta \Delta F} \qquad \beta \Delta F = \beta W$$

Quasi-static is

(Microscopic Reversible) $\beta \Delta E$ for

Helmholtz versus Gibbs

$$\Delta F = \Delta E - T\Delta S$$

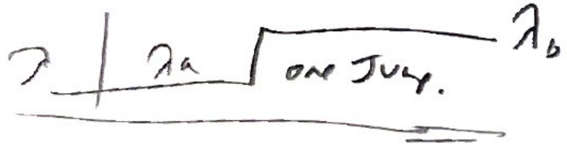
$$\Delta G = \Delta E + p\Delta V - T\Delta S$$

Trumpet plot

$K_1 = 1$

Problem - long times, lots of noise

Thermodynamic Perterbation   Free Energy Perturbation (FEP)   Zwanzig 1954



$$-\ln\langle e^{-\beta\Delta E}\rangle = -\ln\sum_x P(x|\lambda_a)\, e^{-\beta[E(x,\lambda_b)-E(x,\lambda_a)]}$$

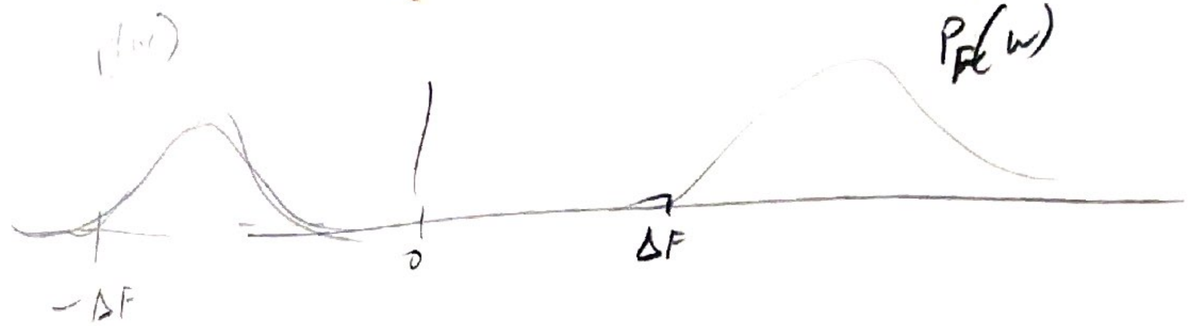
$$= -\ln\sum_x e^{\beta F_a - \beta E(x,\lambda_a)}$$

$$= \beta F(\lambda_b) - \beta F(\lambda_a)$$

(example : widom insertion)

$\langle e^{-\beta W}\rangle = e^{-\beta\Delta F}$, but with one <u>Jump</u>

11.6



Jarzynski

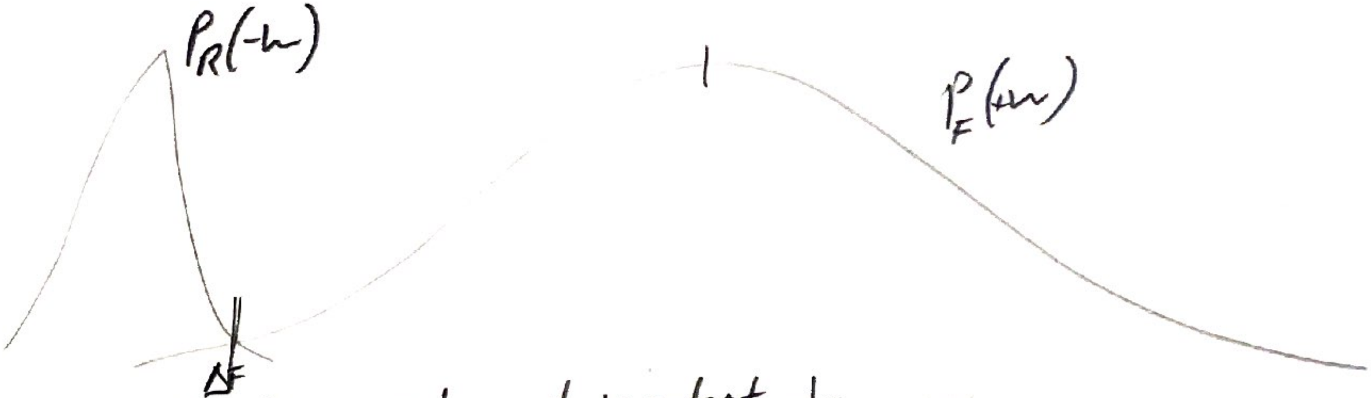
$$\langle e^{-\beta W}\rangle = e^{-\beta \Delta F}$$

$$\Delta F \le \langle \hat{\Delta F}_N \rangle \le \langle W \rangle$$

finite samples

$$\hat{\Delta F}_N = -\ln \sum_n e^{-\beta W_n}$$

Biased

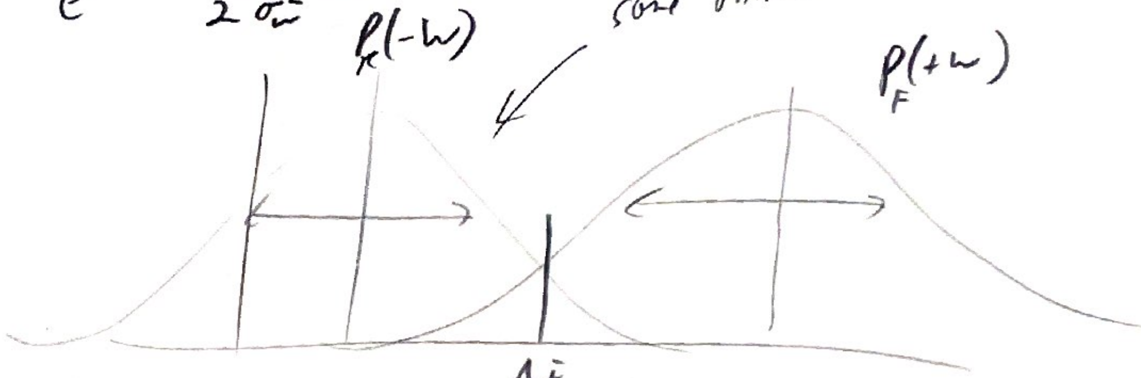


Rare events most important for

$$\langle i \rangle = \frac{\sigma_I^2}{2}$$ FD Relation

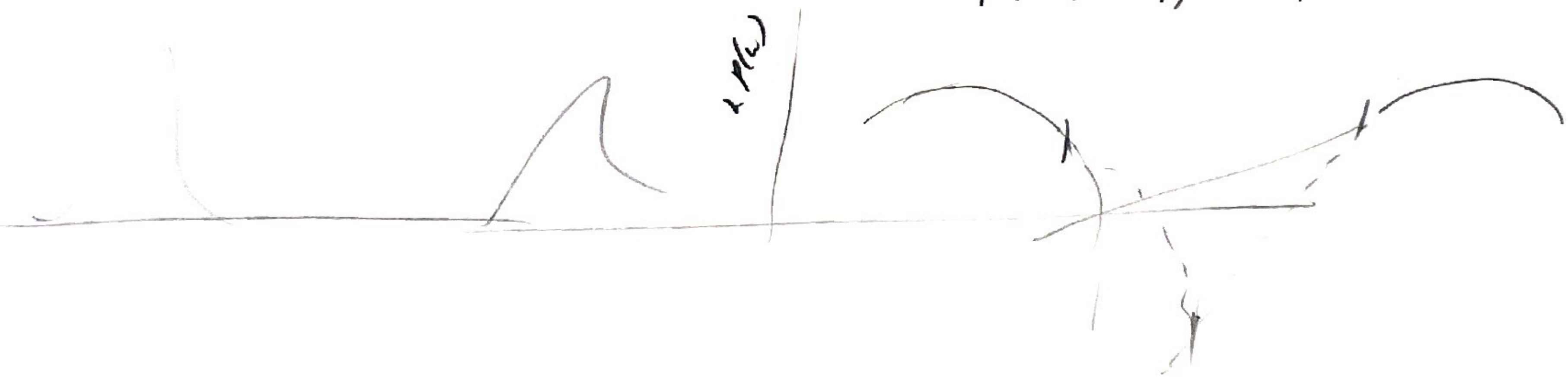
<u>Jarzynski Gaussian</u> $p(w) = e^{-\frac{(w - \langle w \rangle)^2}{2\sigma_w^2}}$

$$\Delta F = \langle w \rangle - \frac{\beta \sigma^2}{2}$$



But CLT only applies to centers

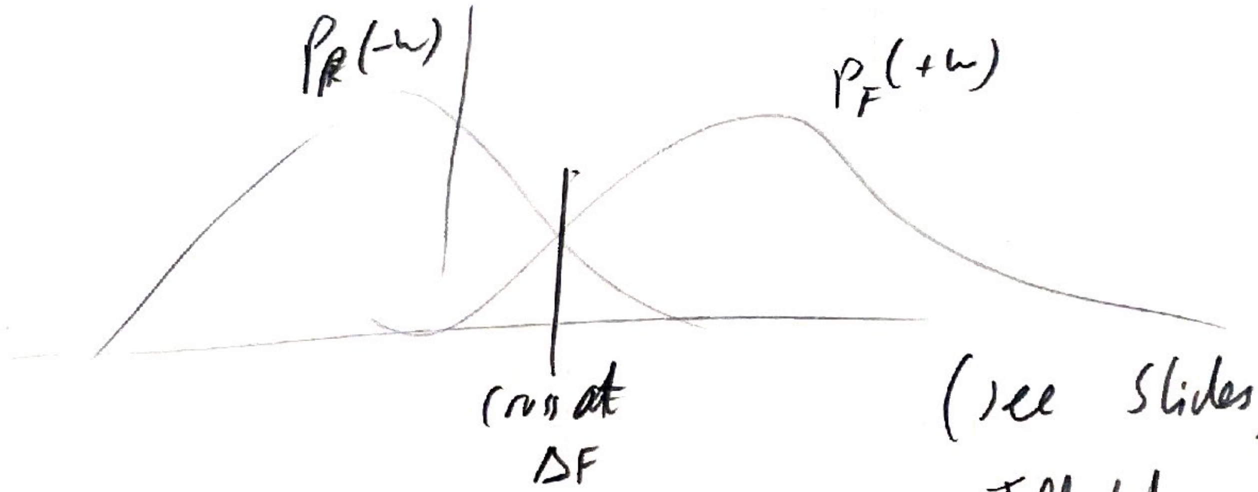
No overlap, then great uncertainty.



Crossing of work distribution

$$\frac{P_F(+w)}{P_R(-w)} = e^{+\beta W - \beta \Delta F}$$

$P_F(+w) = P_R(-w)$ when $W = \Delta F$



(see slides, Collin 2005)

Illustrative, not quantitative.

$$\frac{11 \cdot 9}{-1 \quad +\alpha}$$
$(\alpha - 1)$

Bidirectional

$$\sum_w P_F(w)\, f(+w)\, e^{-\alpha \beta W} = \sum P_R(-w)\, f(-w)\, e^{+\beta W_F - \beta \Delta F}\, e^{-\alpha \beta W_F}$$

$$e^{(\alpha-1)\beta W}$$

$$\beta \Delta F = -\ln \frac{\left\langle f(+w)\, e^{-\alpha \beta w} \right\rangle_F}{\left\langle f(-w)\, e^{-(1-\alpha)\beta w} \right\rangle_R}$$

BAR #1

$$P(A|BC) = \frac{P(A,B,C)}{P(BC)} = \frac{P(AB|C)}{P(B|C)}$$

11.10

BAR: Bennett Acceptance Ratio 1976

$P(\Delta F \mid \{w\}, \{\tilde{w}\}) = ?$

N samples from Λ, M samples from $\tilde{\Lambda}$
$w_1, w_2, w_3 \ldots w_N$ $\tilde{w}_1, \tilde{w}_2 \ldots \tilde{w}_M$

$$P(\Delta F_\Lambda \mid w, \Lambda) = P(w, \Lambda \mid \Delta F_\Lambda) \frac{P(\Delta F_\Lambda)}{P(w, \Lambda)} \propto P(w, \Lambda \mid \Delta F_\Lambda)$$

$$\frac{P(+w \mid \Lambda, \Delta F_\Lambda)}{P(-w \mid \tilde{\Lambda}, \Delta F_{\tilde{\Lambda}})} = e^{+\beta w - \beta \Delta F_\Lambda}$$

$$\frac{P(+w, \Lambda \mid \Delta F_\Lambda)}{P(-w, \tilde{\Lambda} \mid \Delta F_{\tilde{\Lambda}})} = e^{\beta w - \beta \Delta F_\Lambda} \quad \frac{P(\Lambda \mid \Delta F_\Lambda)}{P(\tilde{\Lambda} \mid \Delta F_{\tilde{\Lambda}})} = \frac{P(\Lambda)}{P(\tilde{\Lambda})} \quad = e^{\beta w - \beta \Delta F + C}$$

$$C - \ln \frac{P(\Lambda)}{P(\tilde{\Lambda})}$$

(more dissipation!)

BAR #2 11.11

$$P(W,\lambda|\Delta F_\lambda) + P(-W,\tilde{\lambda}|\Delta F_{\tilde{\lambda}}) = \text{Const}$$

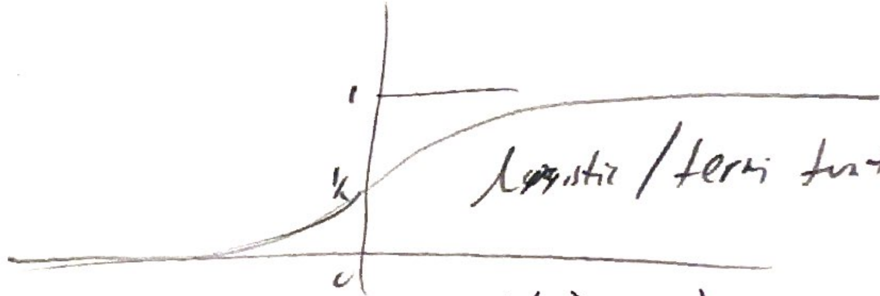
Prior.

uninformative improper prior.

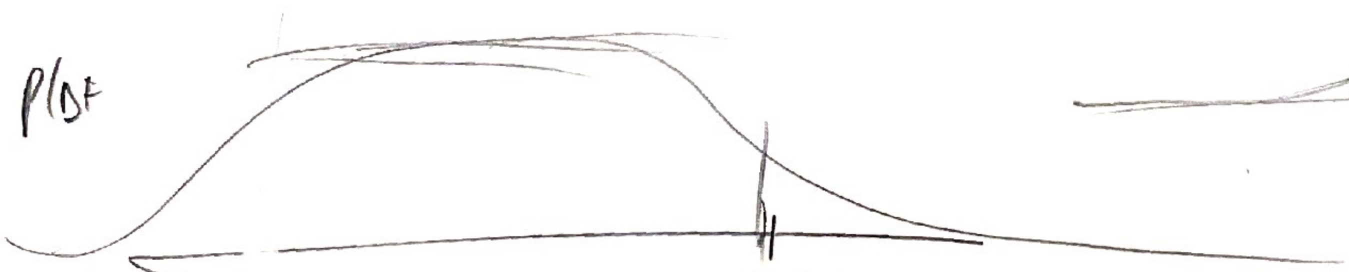
$$P(W,\lambda|\Delta F_\lambda)\left(1+e^{-\beta W+\beta\Delta F-M}\right) = \text{Const}$$

$$P(W,\lambda|\Delta F_\lambda) \propto \frac{1}{1+e^{-\beta W+\beta\Delta F-C}}$$

F.a Logistic function



$$f(x) = \frac{1}{1+e^{-x}}$$



W_{work}

each work measurement is a soft upper bound

BAR #3

11.12

$$P(\Delta F \mid \{w\}, \{\tilde{w}\}) = \prod_{n=1}^{N} \frac{1}{1+e^{-\beta W_n + \beta \Delta F + C}} \prod_{m=1}^{M} \frac{1}{1+e^{-\beta \tilde{W}_m - \beta \Delta F - C}}$$

$C = \ln \frac{P(\lambda)}{P(\hat{\lambda})} \approx \ln \frac{N+1}{M+1}$

Find Maximum

Error estimates

Bennett under

MBAR over

Bayesian expensive

Noise!

← Shirts 4 Chodera 2008

PG postdoc

Colorado MSK

(Slides →

Summary)