Nonequilibrium thermodynamics of small systems

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Outline

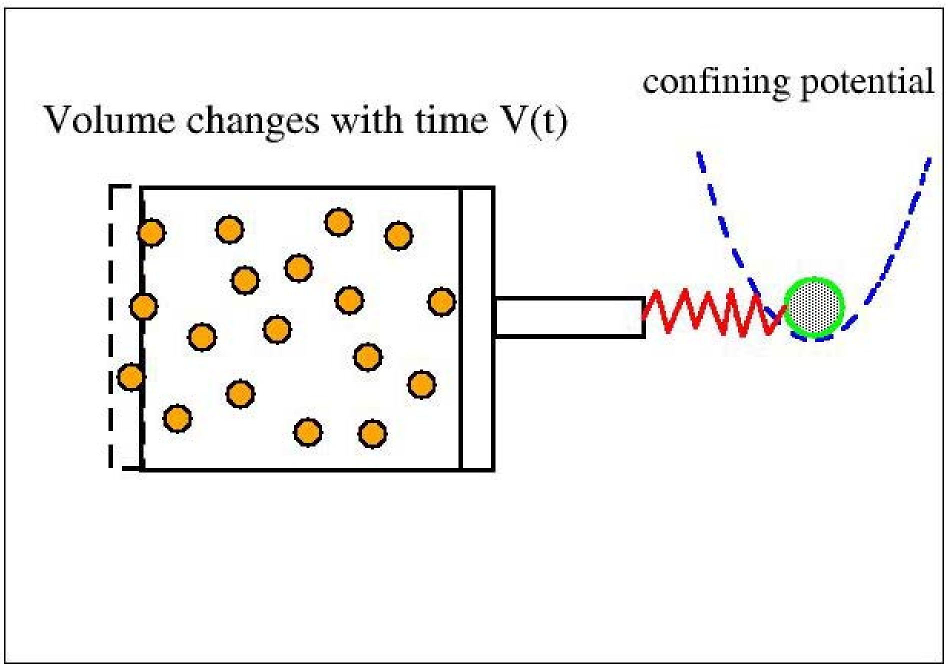
- Lecture I: **Fluctuation theorems**
  - Nonequilibrium states
  - The nonequilibrium equality
  - The fluctuation theorem
- Lecture II: **Single molecule experiments**
  - Introduction
  - RNA pulling experiments
  - Free energy recovery using FT

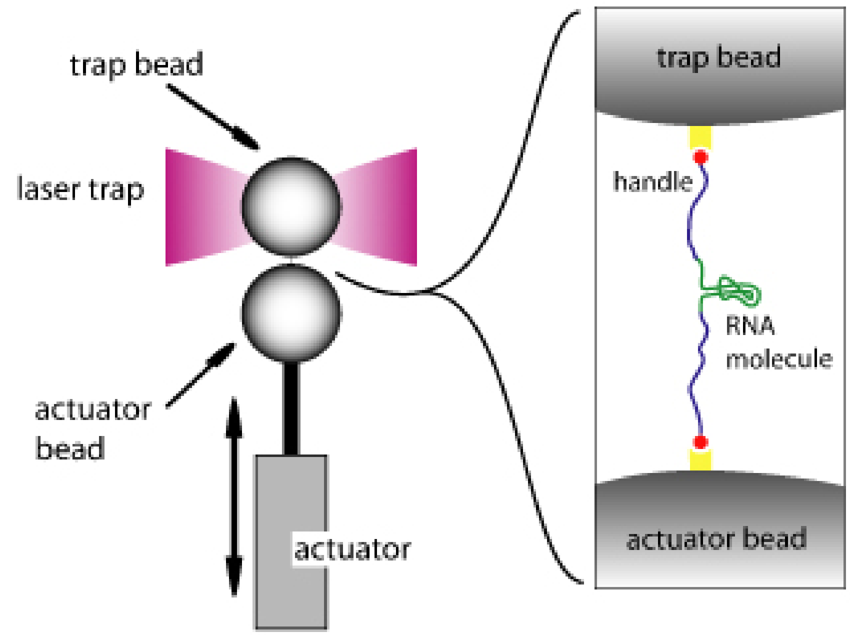
Lecture I: **Fluctuation theorems**

Nonequilibrium states

- **Nonequilibrium transient states**

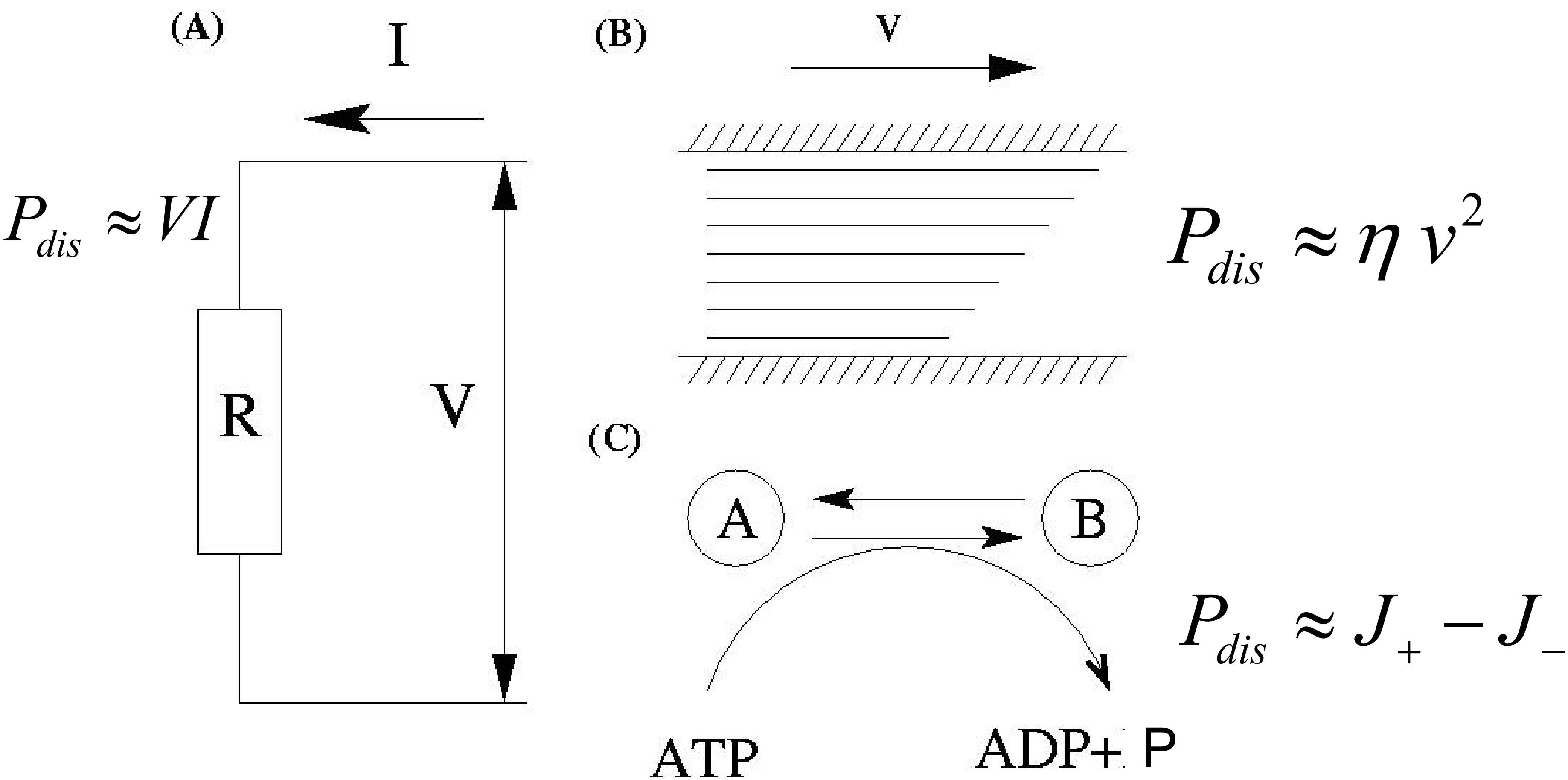
  Initially in equilibrium but driven out of equilibrium

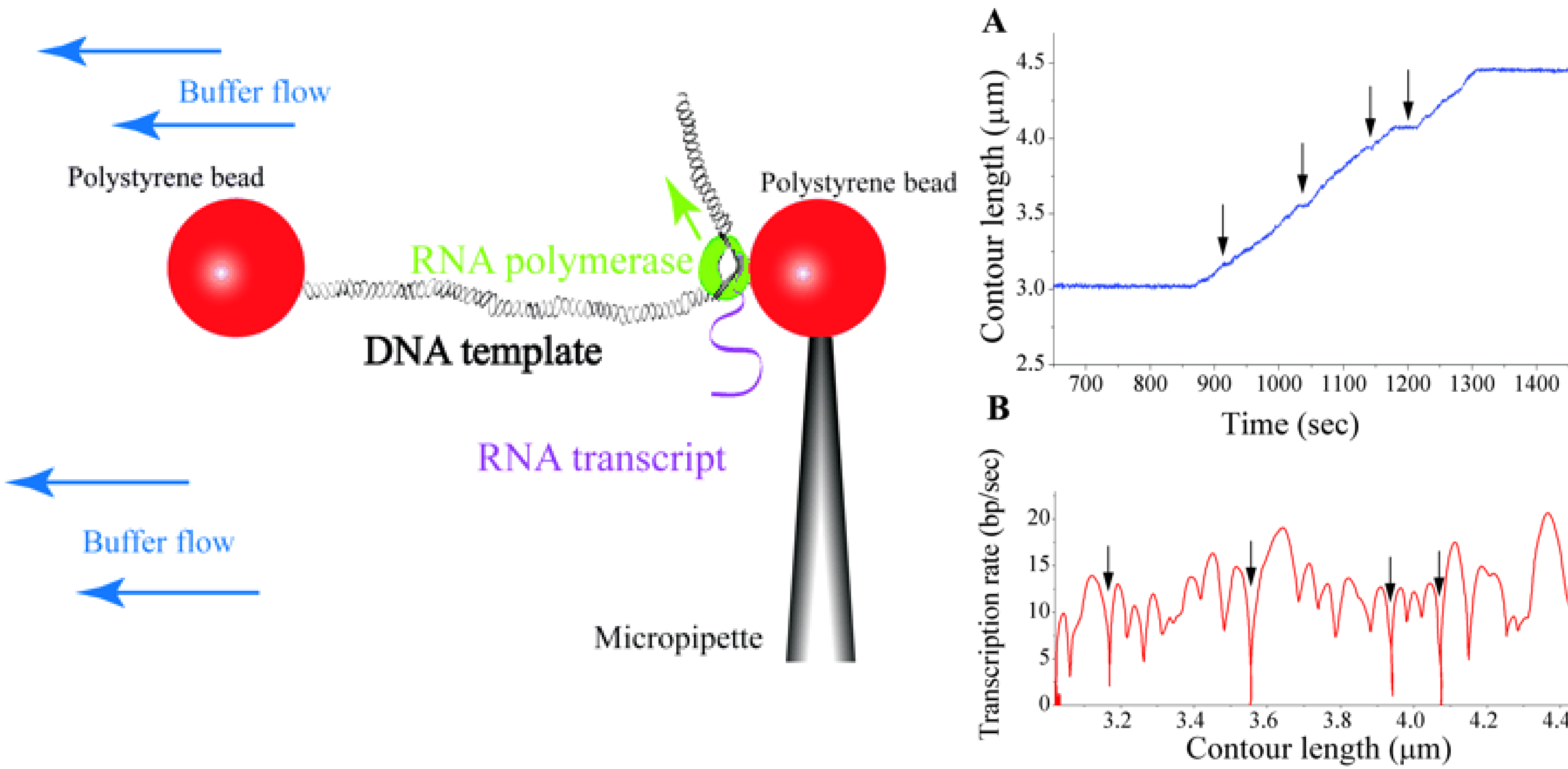




- **Nonequilibrium steady states**

  (non-Gibbsian state where net heat or mass is exchanged between the system and the surroundings)

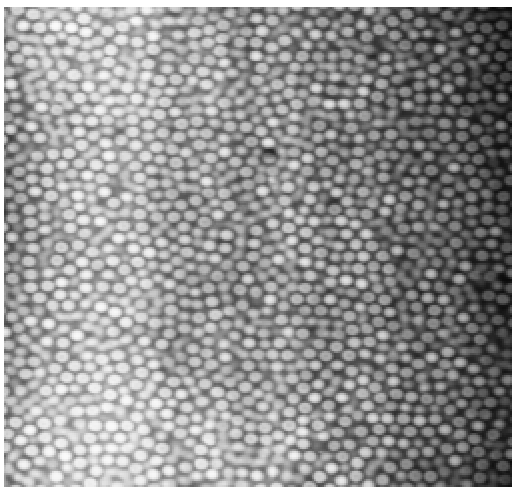


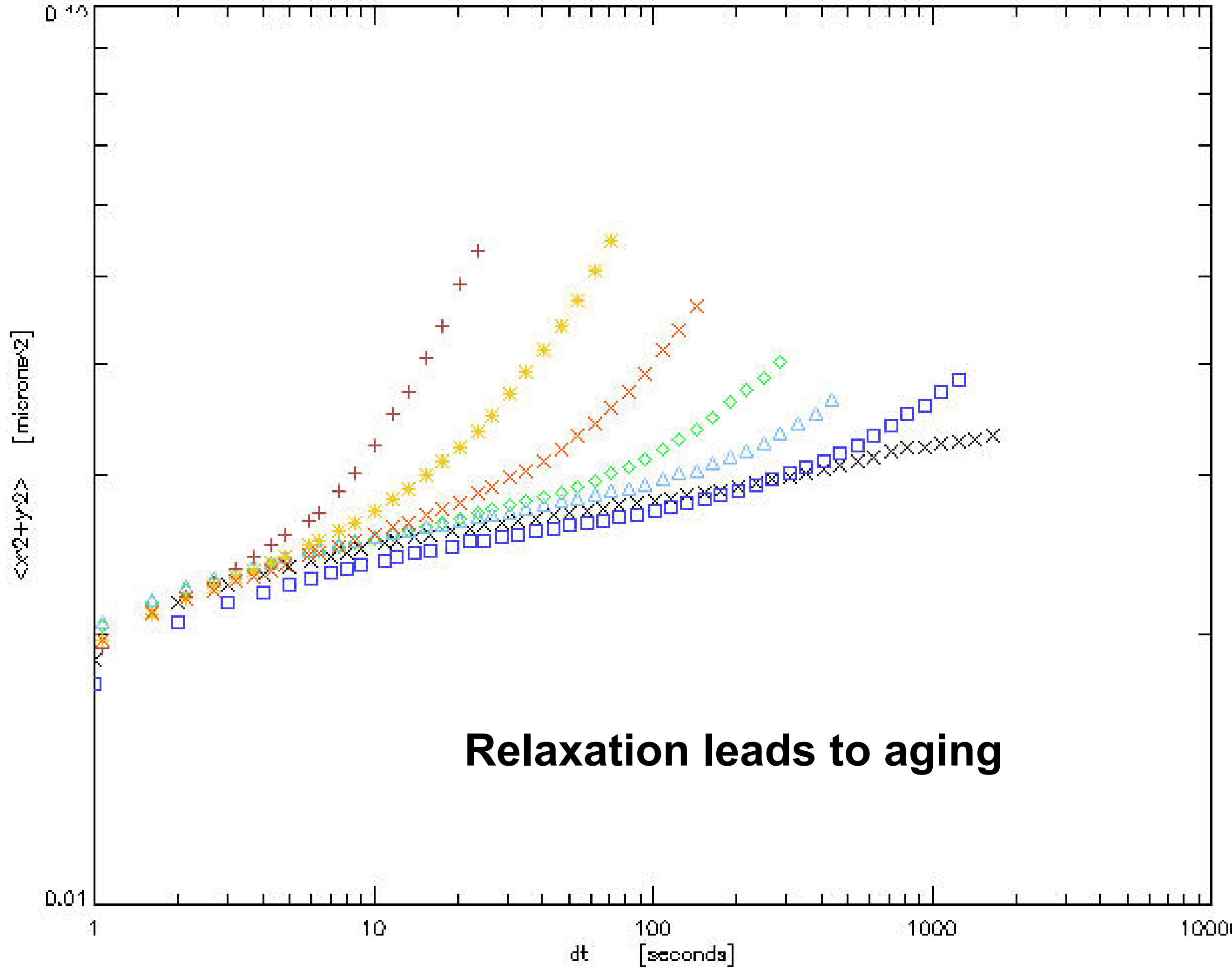


Molecular motors

- **Nonequilibrium aging states**

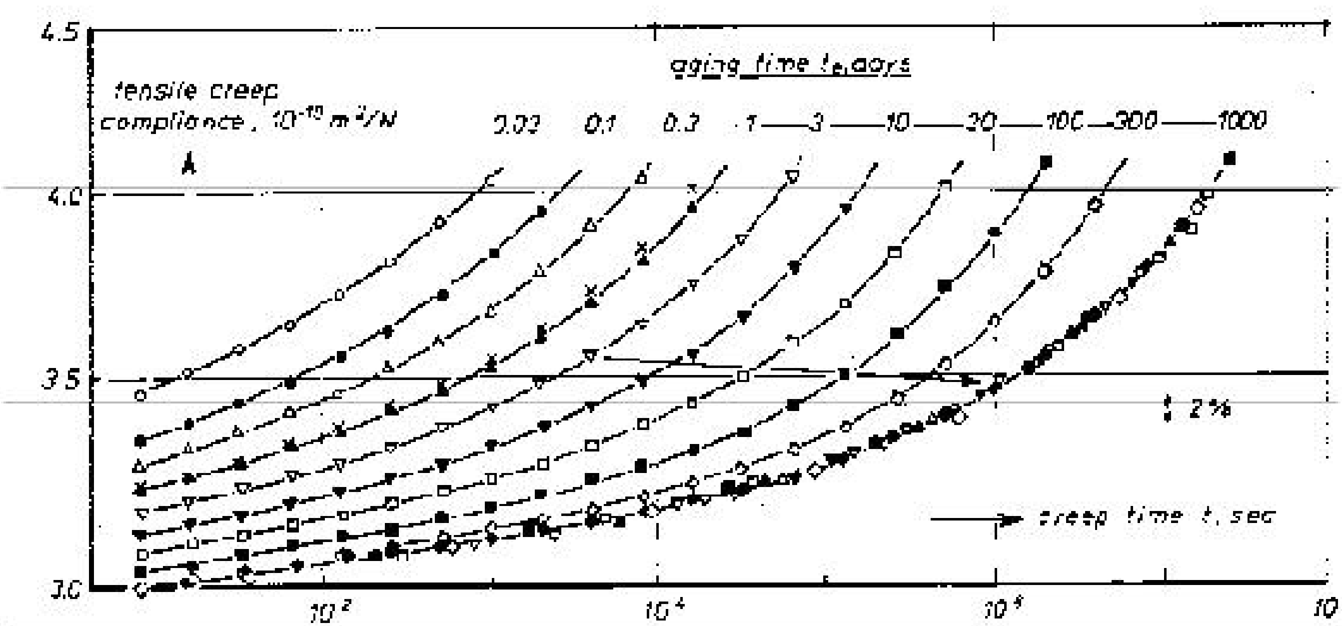
  (non-stationary state with extremely slow relaxation)





- Aging: response slows down as system gets older

(compliance in polymers, density fluctuations in supercooled liquids, polarization in dielectric glasses, magnetization in spin glasses, msd in colloids…)



Compliance of polymers, Struik in the 70’s

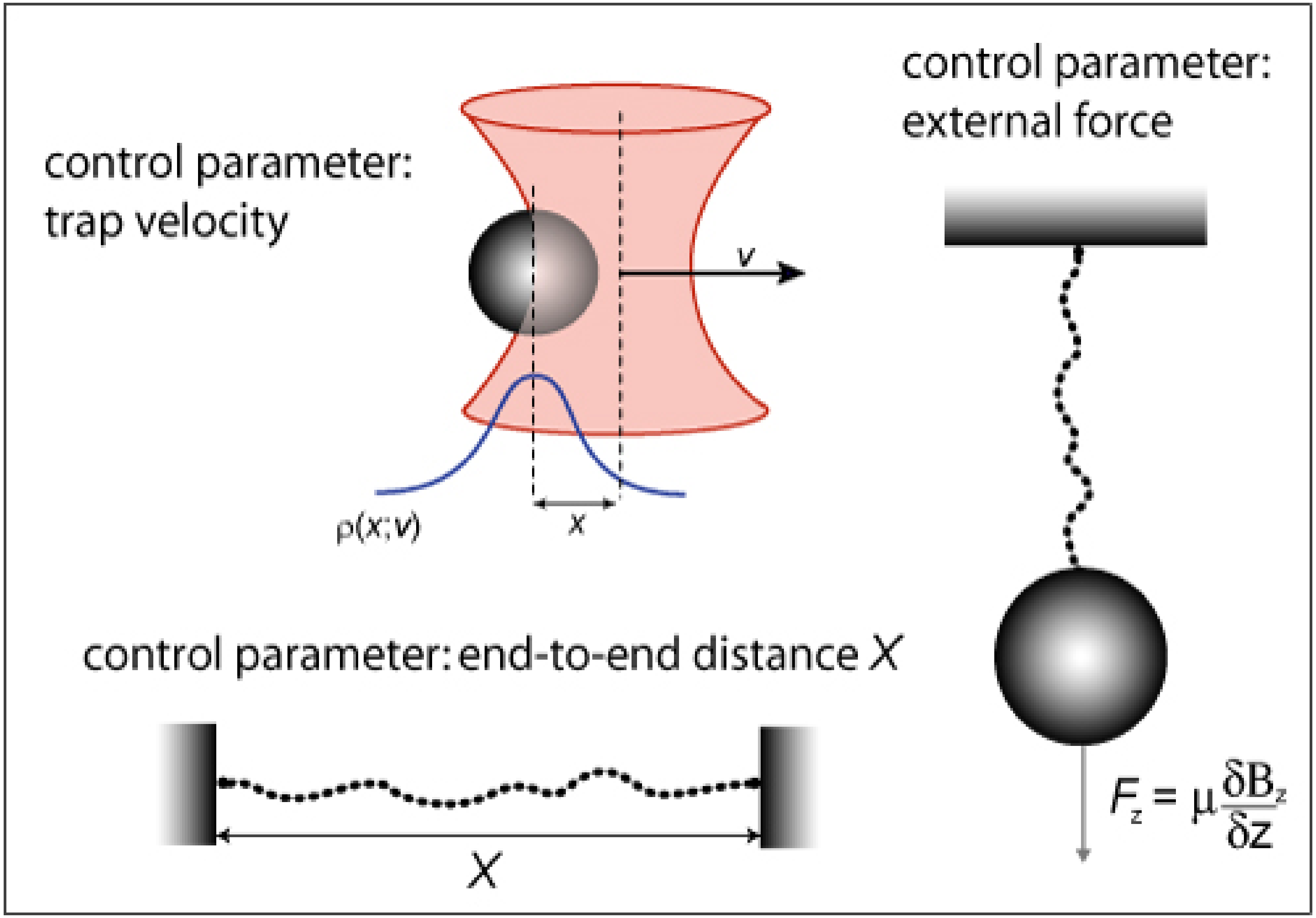
The nonequilibrium equality

(D. Evans, J. Kurchan, J. Lebowitz, H. Spohn, C. Jarzynski, G. E. Crooks, C. Maes, U. Seifert,.....)

All derivations that follow have been taken from: F. Ritort, *Nonequilibrium fluctuations in small systems: From physics to biology,* To be published in Advances in Chemical Physics

- **Configuration**
- **Path**: sequence of configurations
- **Control parameter** $\boxed{\lambda(t) \equiv \{\lambda_0, \lambda_1, \ldots, \lambda_k, \ldots, \lambda_M\}}$
  - It fully specifies the nonequilibrium experiment
  - In small systems the equation of state depends on which quantity is the control parameter
  - The system can reach thermal equilibrium for a fixed value of the control parameter

Control parameter



Kinetics

- Master equation

$$\boxed{\frac{\partial P_\lambda(C)}{\partial t} = \sum_{C'} W_\lambda(C' \to C) P_\lambda(C') - \sum_{C'} W_\lambda(C \to C') P_\lambda(C)}$$

- Microscopic reversibility

$$\boxed{\frac{W_\lambda(C \to C')}{W_\lambda(C' \to C)} = \frac{P_\lambda^{eq}(C')}{P_\lambda^{eq}(C)}}$$

- Observables and expectation values

$$\boxed{< A(t) >= \sum_{\Gamma} A(\Gamma) P(\Gamma)}$$

The equality (I)

Step 1

$$< A >= \sum_{\Gamma} A(\Gamma) P_{\lambda_0}(C_0) \prod_{k=0}^{M-1} W_{\lambda_k}(C_k \to C_{k+1}) =$$

$$= \sum_{\Gamma} A(\Gamma) P_{\lambda_0}(C_0) \prod_{k=0}^{M-1} \left[W_{\lambda_k}(C_{k+1} \to C_k) \frac{P^{eq}_{\lambda_k}(C_{k+1})}{P^{eq}_{\lambda_k}(C_k)} \right] =$$

$$\sum_{\Gamma} A(\Gamma) P_{\lambda_0}(C_0) \exp\left[\sum_{k=0}^{M-1} \log\left(\frac{P^{eq}_{\lambda_k}(C_{k+1})}{P^{eq}_{\lambda_k}(C_k)} \right) \right] \prod_{k=0}^{M-1} \left[W_{\lambda_k}(C_k \to C_{k+1}) \right]$$

The equality (II)

Step 2: Define

$$\boxed{A(\Gamma) = \exp\left(-S(\Gamma)\right) = \frac{f(C_M)}{P_{\lambda_0}(C_0)} \prod_{k=0}^{M-1} \left(\frac{P^{eq}_{\lambda_k}(C_k)}{P^{eq}_{\lambda_k}(C_{k+1})} \right)}$$

We get:

$$\boxed{< \exp(-S) >= \sum_{\Gamma} f(C_M) \prod_{k=0}^{M-1} W_{\lambda_k}(C_{k+1} \to C_k) = 1}$$

Jarzynski equality, Kawasaki identity, Generalized FDT by G. N. Bochkov and Y. E. Kuzovlev

Various results:

- **Total entropy**

$$\boxed{S(\Gamma) = \underbrace{\sum_{k=0}^{M-1} \log\left[\frac{P^{eq}_{\lambda_k}(C_{k+1})}{P^{eq}_{\lambda_k}(C_k)}\right]}_{S_p(\Gamma)} + \underbrace{\log\left(P_{\lambda_0}(C_0)\right) - \log\left(f(C_M)\right)}_{B(\Gamma)}}$$

Entropy production

Boundary term

- **Second law:**

$$< \exp(x) > \;\geq\; \exp(< x >) \quad \Rightarrow \quad \boxed{< S > \geq 0}$$

Nonequilibrium transient states (I)

- Canonical ensemble: N,V,T are constant

$$P_{\lambda}^{eq}(C)=\frac{\exp\left(-\beta\, E_{\lambda}(C)\right)}{Z_{\lambda}}=\exp\left(-\beta\, E_{\lambda}(C)+\beta\, F_{\lambda}\right)$$

$$\beta=\frac{1}{T}$$

- The entropy production is the heat Q

$$S_p(\Gamma)=\sum_{k=0}^{M-1}\log\left[\frac{P_{\lambda_k}^{eq}(C_{k+1})}{P_{\lambda_k}^{eq}(C_k)}\right]=\beta\sum_{k=0}^{M-1}\left(E_{\lambda_k}(C_k)-E_{\lambda_k}(C_{k+1})\right)=\beta Q(\Gamma)$$

- The boundary term is

$$B(\Gamma)=\log\left(P_{\lambda_0}(C_0)\right)-\log\left(f(C_M)\right)=\log\left(P_{\lambda_0}^{eq}(C_0)\right)-\log\left(P_{\lambda_M}^{eq}(C_M)\right)=$$
$$=\beta\left(E_{\lambda_M}(C_M)-E_{\lambda_0}(C_0)-F_{\lambda_M}+F_{\lambda_0}\right)=\beta\left(\Delta E(\Gamma)-\Delta F\right)$$

Nonequilibrium transient states (II)

- First law:

$$B(\Gamma) = \beta\left(\Delta E(\Gamma) - \Delta F\right) \Rightarrow S(\Gamma) = S_p(\Gamma) + \beta\left(\Delta E(\Gamma) - \Delta F\right);$$
$$TS(\Gamma) = TS_p(\Gamma) + \Delta E(\Gamma) - \Delta F = Q(\Gamma) + \Delta E(\Gamma) - \Delta F = W(\Gamma) - \Delta F$$

- Second law:

$$< S > \geq 0 \Rightarrow < W > \geq \Delta F$$

- Total entropy is the dissipated work:

$$W_{\mathrm{dis}}(\Gamma) = TS(\Gamma) = W(\Gamma) - \Delta F$$

The fluctuation theorem

Forward (F) path

$$\Gamma \equiv C_0 \xrightarrow[\lambda_0]{} C_1 \xrightarrow[\lambda_1]{} \ldots \rightarrow C_{M-1} \xrightarrow[\lambda_{M-1}]{} C_M$$

Reverse (R) path

$$\Gamma^* \equiv C_M \xrightarrow[\lambda_{M\text{-}1}]{} C_{M-1} \xrightarrow[\lambda_{M-2}]{} \ldots \rightarrow C_1 \xrightarrow[\lambda_1]{} C_0$$

$$P_F(\Gamma) = \prod_{k=0}^{M-1} W_{\lambda_k}(C_k \rightarrow C_{k+1})$$

$$P_R(\Gamma^*) = \prod_{k=0}^{M-1} W_{\lambda_{M-k-1}}(C_{M-k} \rightarrow C_{M-k-1}) = \prod_{k=0}^{M-1} W_{\lambda_k}(C_{k+1} \rightarrow C_k)$$

Step 1

$$\frac{P_F(\Gamma)}{P_R(\Gamma^*)} = \prod_{k=0}^{M-1} \left(\frac{P^{eq}_{\lambda_k}(C_{k+1})}{P^{eq}_{\lambda_k}(C_k)} \right) = \exp\left(S_p(\Gamma)\right) = \exp\left(\frac{Q(\Gamma)}{T} \right)$$

- Heat and work are antisymmetric against path reversal

$$\boxed{Q(\Gamma^*) = -Q(\Gamma) \quad ; \quad W(\Gamma^*) = -W(\Gamma)}$$

and therefore also: $\boxed{S(\Gamma^*) = -S(\Gamma)}$

Remember

Step 2

$$\boxed{S(\Gamma) = S_p(\Gamma) + \log\left(P^{eq}_{\lambda_0}(C_0)\right) - \log\left(P^{eq}_{\lambda_M}(C_M)\right)}$$

$$P_F(S) = \sum_{\Gamma} P^{eq}_{\lambda_0}(C_0) P_F(\Gamma) \delta(S(\Gamma) - S) =$$
$$\sum_{\Gamma} P^{eq}_{\lambda_0}(C_0) P_R(\Gamma^*) \exp\left(S_p(\Gamma)\right) \delta(S(\Gamma) - S) =$$
$$\sum_{\Gamma} P^{eq}_{\lambda_M}(C_M) P_R(\Gamma^*) \exp\left(S(\Gamma)\right) \delta(S(\Gamma) - S) =$$
$$\exp(S) \sum_{\Gamma^*} P^{eq}_{\lambda_M}(C_M) P_R(\Gamma^*) \delta(S(\Gamma^*) + S) = \exp(S) P_R(-S) \quad .$$

Final result (FT):

$$\boxed{\frac{P_F(S)}{P_R(-S)} = \exp(S)}$$

Consequences

- Nonequilibrium equality:

$$\boxed{\exp(-S)P_F(S) = P_R(-S) \Rightarrow (\text{integrate}) \ \left\langle \exp(\text{-}S) \right\rangle_F = 1}$$

- Jarzynski equality and Crooks relation:

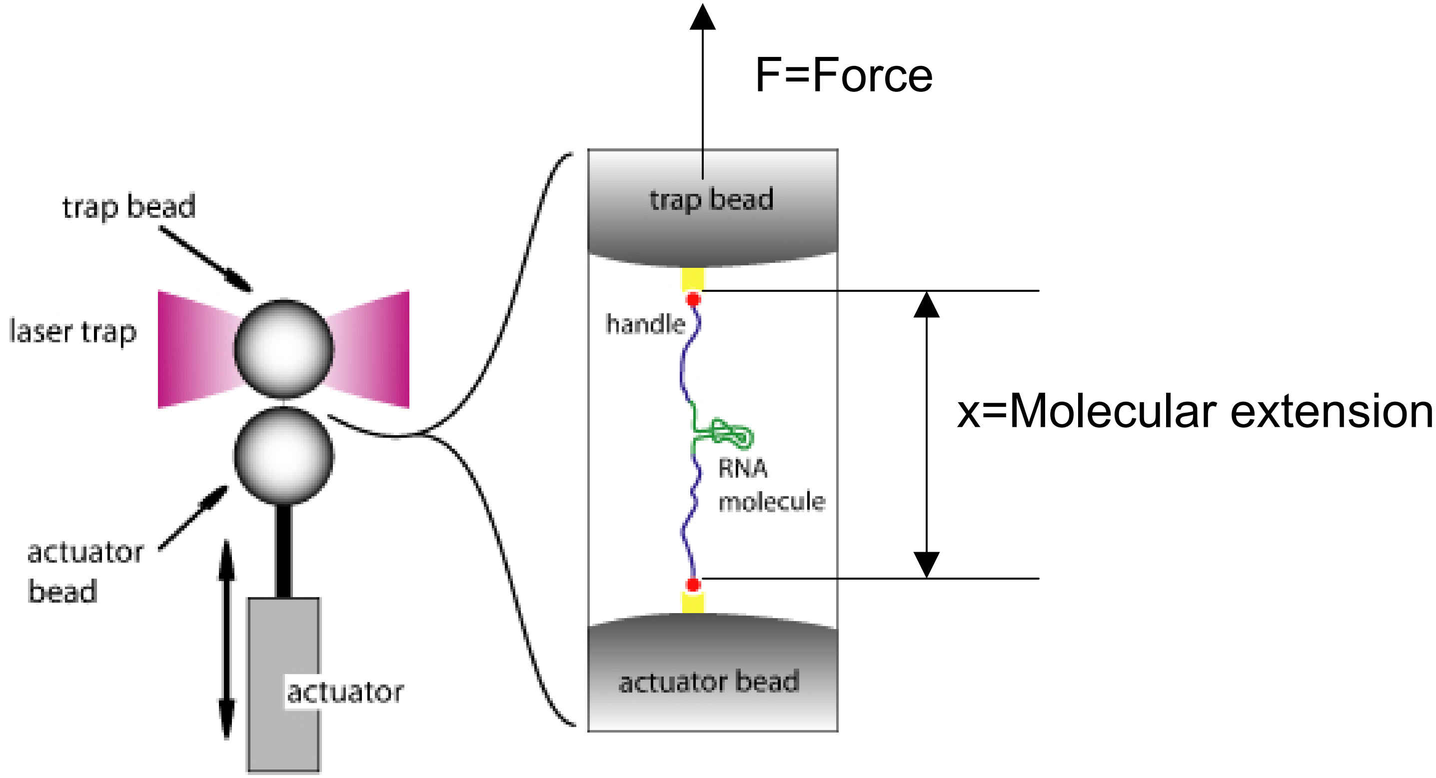
$$\boxed{\left\langle \exp\left(\text{-}\frac{W_{dis}}{T} \right) \right\rangle_F = 1} \qquad \boxed{\frac{P_F(W)}{P_R(-W)} = \exp\left(\frac{W_{dis}}{T} \right) = \exp\left(\frac{W - \Delta F}{T} \right)}$$

- Gaussian processes,

$$\left\langle \exp\left(\text{-}\frac{W_{dis}}{T} \right) \right\rangle_F = \exp\left(\text{-}\frac{\langle W_{dis} \rangle_F}{T} + \frac{\sigma_W^2}{2T^2} \right) = 1 \Rightarrow \boxed{\sigma_W^2 = 2T \langle W_{dis} \rangle_F}$$

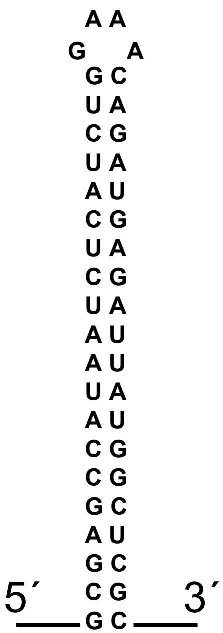
Lecture II: **Single molecule experiments**

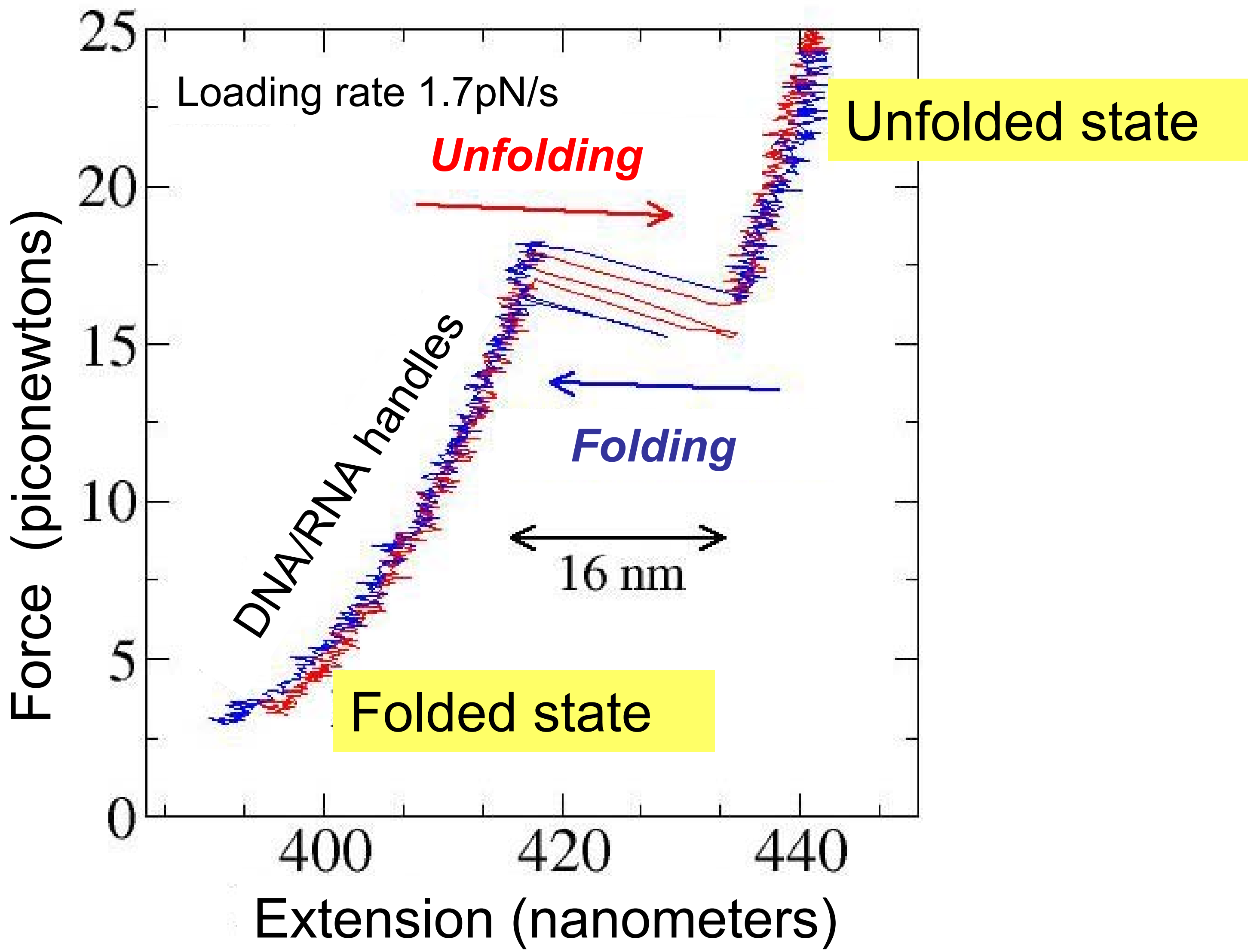
RNA pulling experiments



$$\boxed{W(\Gamma) = \int_{x_0}^{x_f} F\,dx}$$

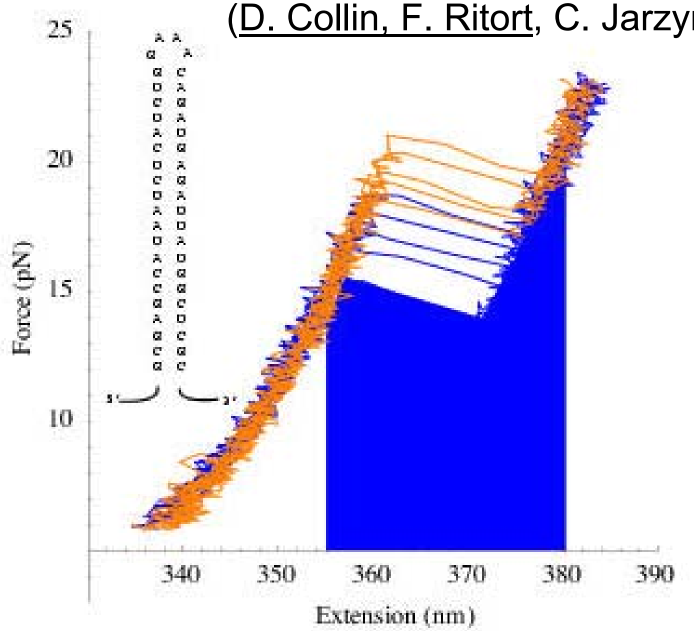
Pulling experiments





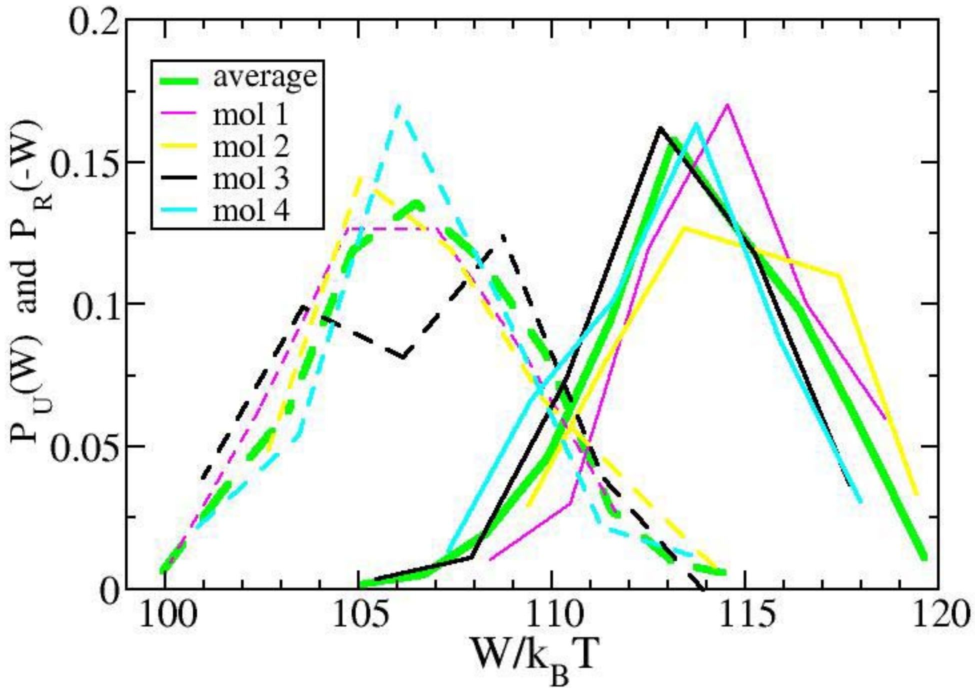
Recovery of unfolding free energies

(D. Collin, F. Ritort, C. Jarzynski, S. B. Smith. I. Tinoco, C. Bustamante, Nature, **437,** 231 (2005))

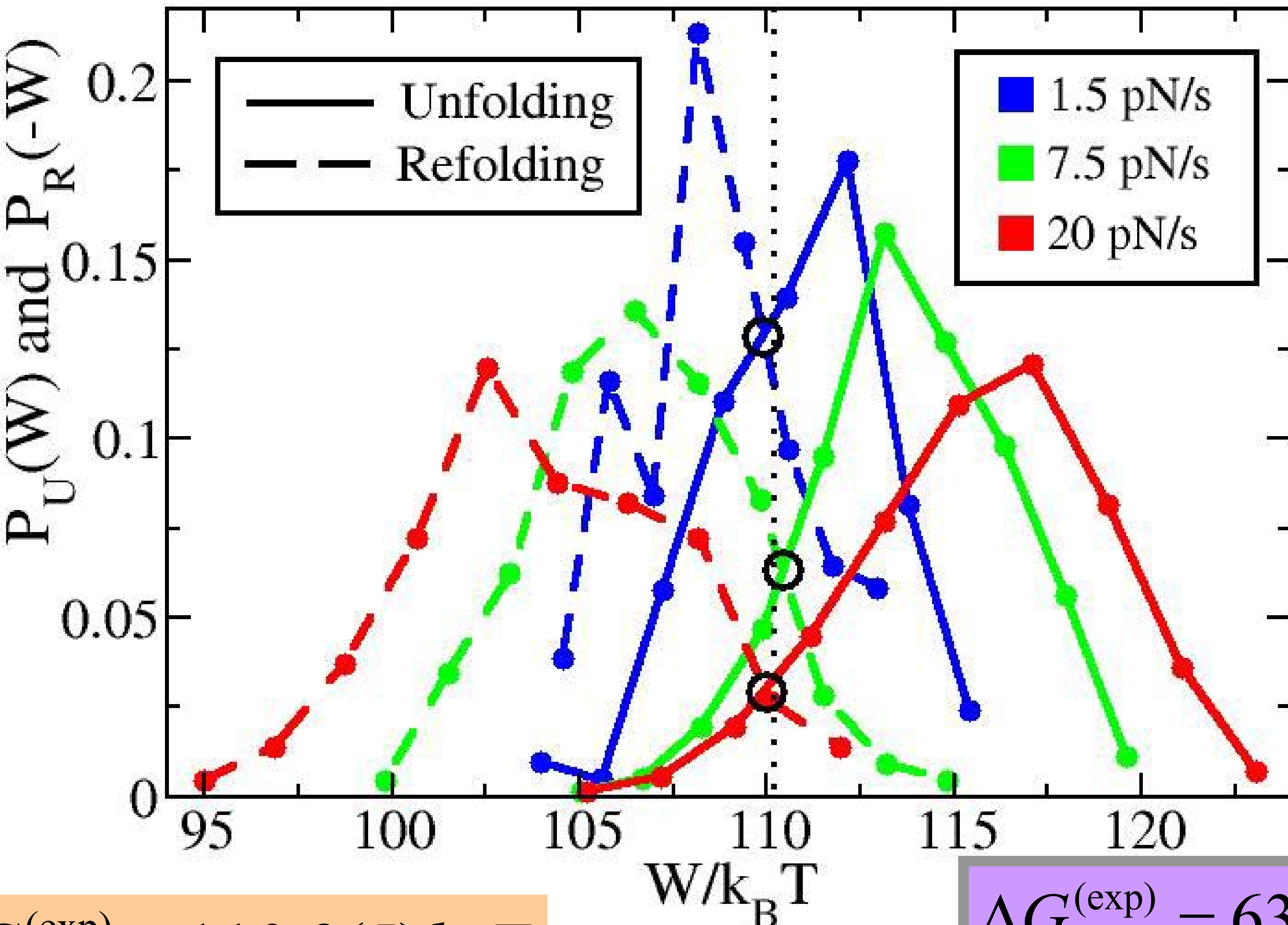


$$W = \int_{x_0}^{x_f} F dx \rightarrow P_U(W), P_R(-W)$$

Four molecules pulled at 7pN/s



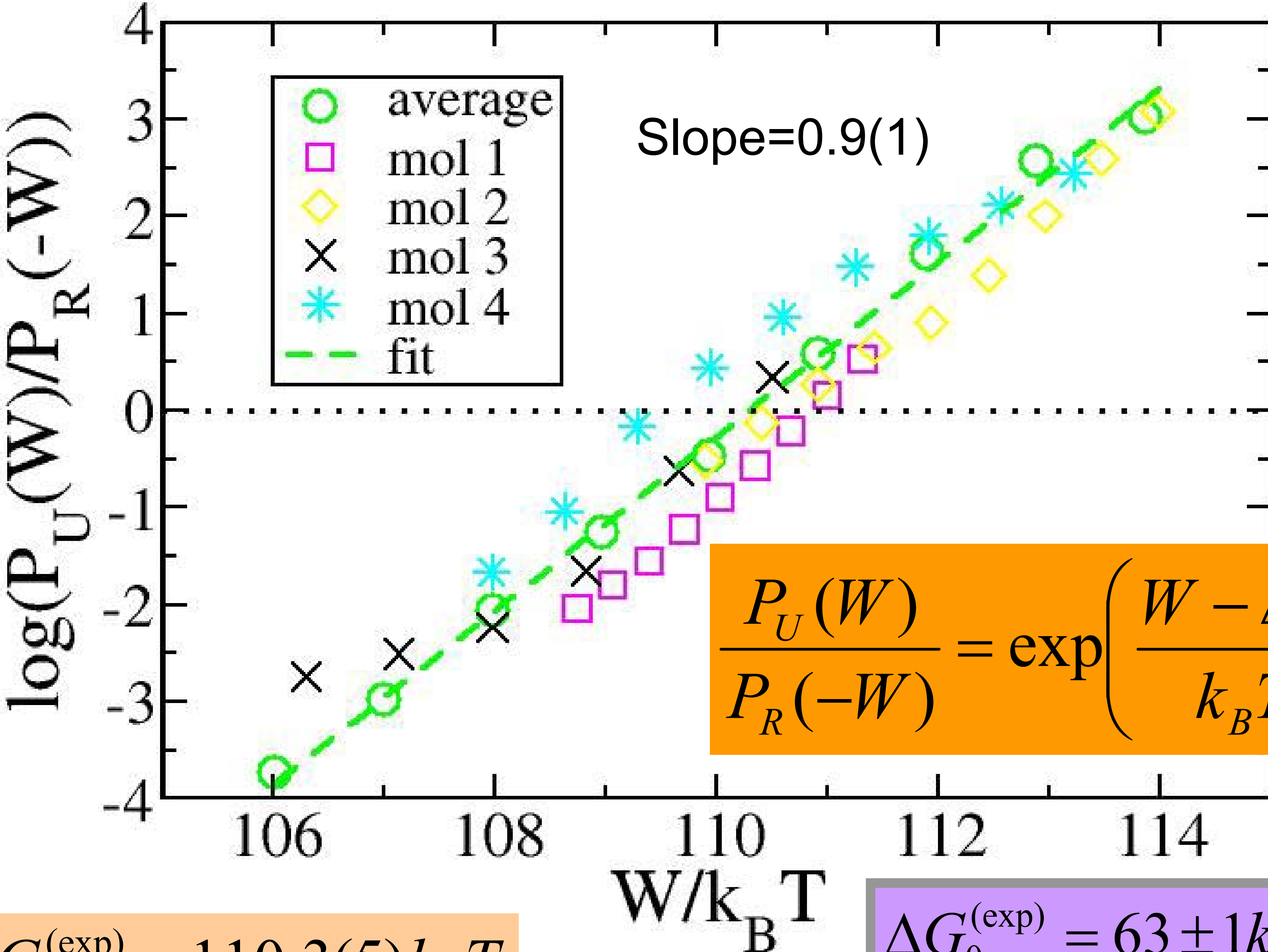
Crossing method: $\frac{P_U(W)}{P_R(-W)} = \exp\left(\frac{W - \Delta G}{k_B T}\right)$



$\Delta G^{(\exp)} = 110.3(5) k_B T$ $\xrightarrow{\text{entropic stretching}}$ $\Delta G_0^{(\exp)} = 63 \pm 1 k_B T$

Mfold software: $63.5 k_B T$

Experimental test of Crooks FT

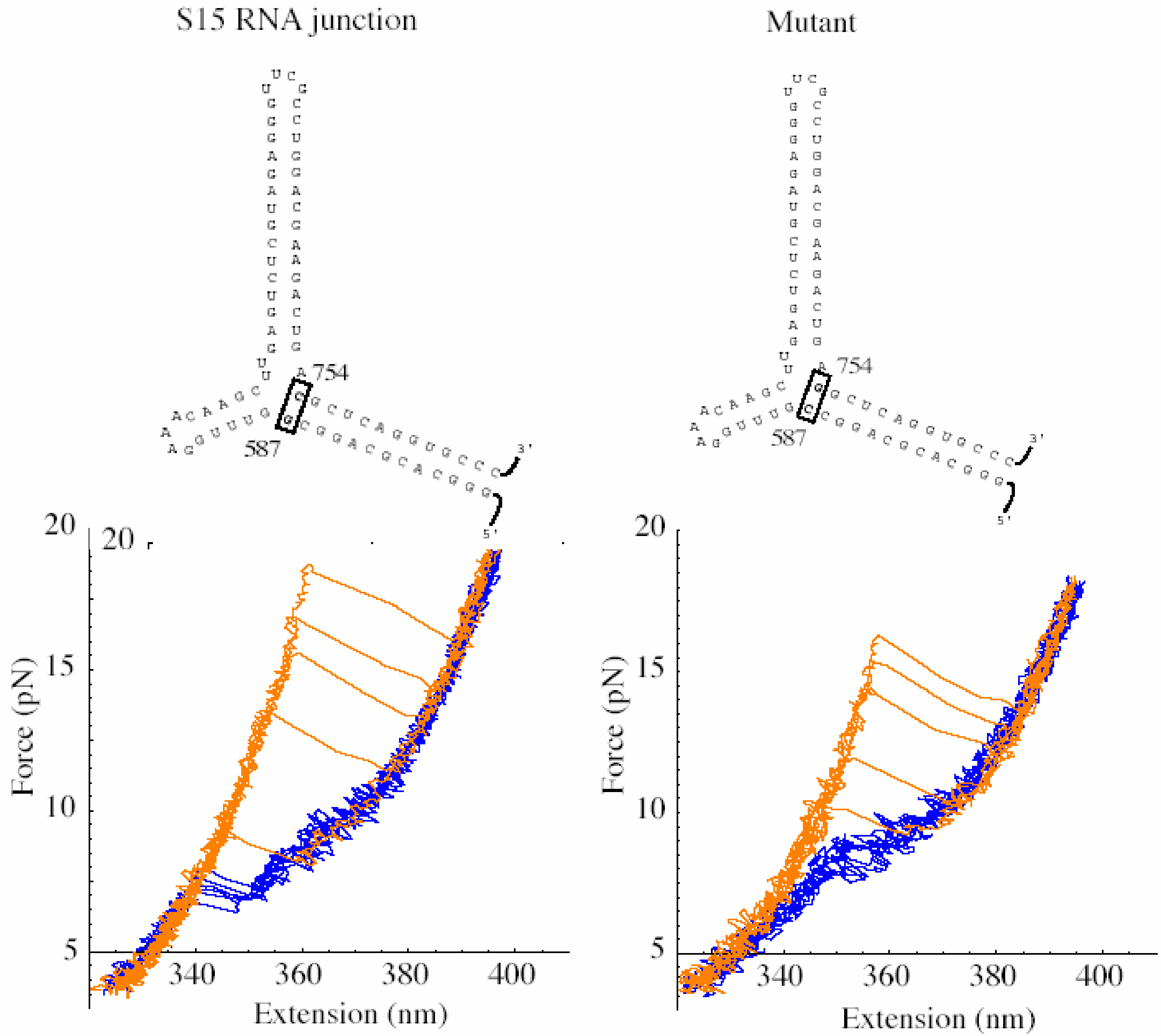


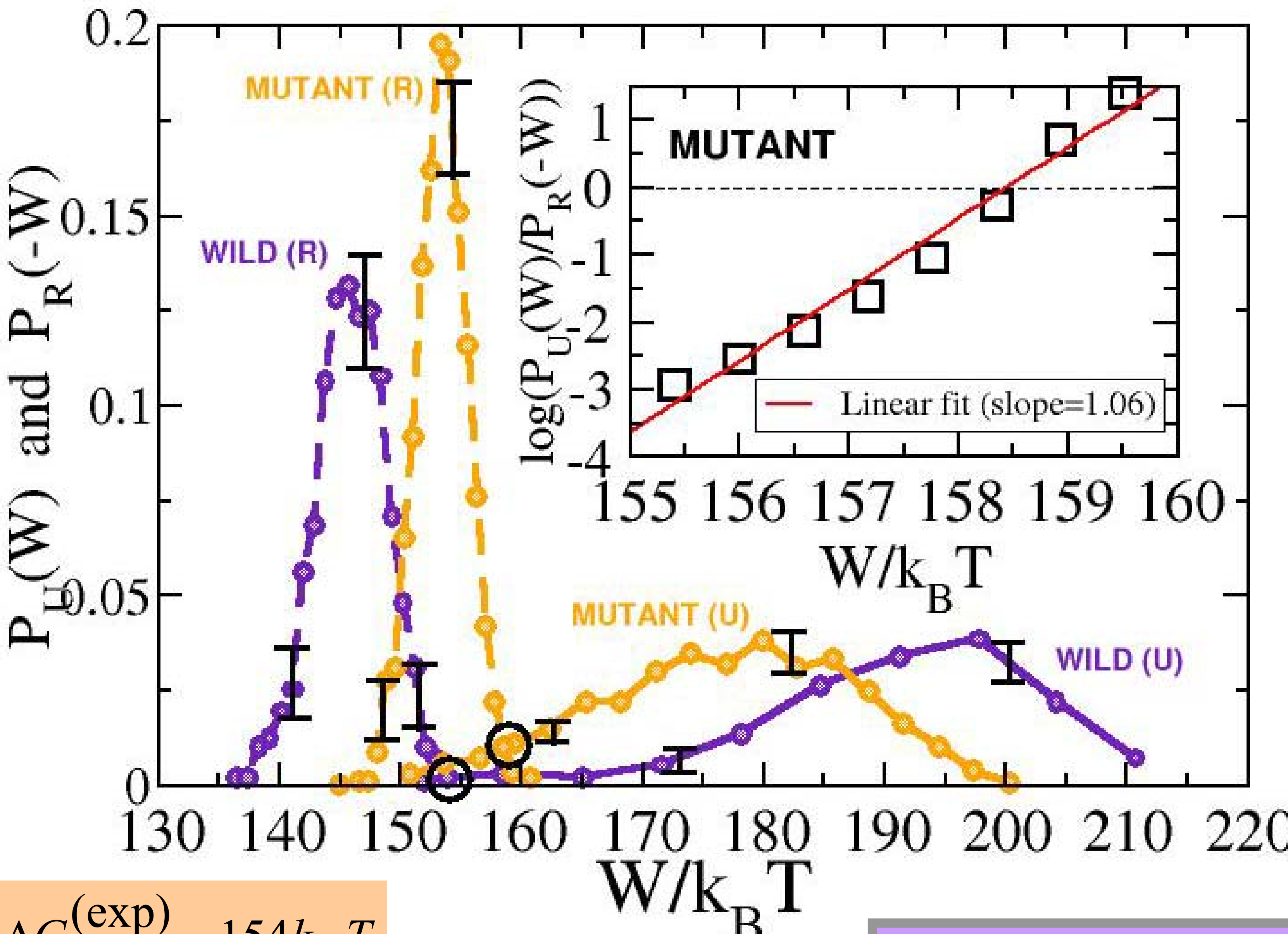
$$\frac{P_U(W)}{P_R(-W)} = \exp\left(\frac{W - \Delta G}{k_B T}\right)$$

$$\Delta G^{(\exp)} = 110.3(5) k_B T \xrightarrow{\text{entropic stretching}} \Delta G_0^{(\exp)} = 63 \pm 1 k_B T$$

Mfold software: $63.5 k_B T$

S15 three-way junction without Mg





$$\Delta G_{wild}^{(\exp)} = 154 k_B T$$

$$\Delta G_{mut}^{(\exp)} = 157 k_B T$$

$$\longrightarrow$$

$$\Delta\Delta G_0^{(\exp)} = 3 \pm 1 k_B T$$

Mfold software= $2 \pm 2 k_B T$

Maria Mañosas

Ivan Junier

Modeling unfolding of RNA and proteins

Josep Maria Huguet

Setting up the new instrument

Nuria Forns

Molecular synthesis

Sara de Lorenzo

Technician in the lab

- UC Berkeley: **Bustamante, Tinoco and Liphardt** labs
- Building the minitweezers: **Steve Smith** and **Shane Saxon**

Two predocs opening: Experimental and Theory

Publications

Relevant for the lecture:

- F. Ritort, *Nonequilibrium fluctuations in small systems: From physics to biology,* To be published in Advances in Chemical Physics
- C. Bustamante, J. Liphardt and F. Ritort, *The nonequilibrium theormodynamics of small systems*, Physics Today **58,** 43 (2005)
- D. Collin, F. Ritort, C. Jarzynski, S. B. Smith, I. Tinoco and C. Bustamante, *Recovering folding free energies of RNA molecules and experimental test of Crooks fluctuation theorem,* Nature **437,** 231 (2005)
- F. Ritort, *Work fluctuations, transient violations of the second law and free-energy recovery methods: perspectives in theory and experiments,* Seminaire Poincare **2,** 193 (2003)
- F. Ritort, *Work and heat fluctuations in two-state systems: a trajectory thermodynamics formalism,* J. Stat. Mech. (Theor. and Exp.) P10016 (2004)
- F. Ritort, C. Bustamante and I. Tinoco, *A two-state kinetic model for the unfolding of single molecules by mechanical force*, PNAS **99,** 13544 (2002)
- E. Trepagnier, C. Jarzynski, F. Ritort, G. Crooks, C. Bustamante and J. Liphardt, *Experimental test of Hatano and Sasa´s nonequilibrium steady-state equality,* PNAS **101**, 15038 (2004)

Related to the lecture:

- J. Gore, F. Ritort and C. Bustamante, *Bias and error in estimates of equilibrium free-energy differences from nonequilibrium measurements,* PNAS **100**, 12564 (2003)
- M. Manosas and F. Ritort, *Thermodynamic and kinetic aspects of RNA pulling experiments*, Biophys. J. **88**, 3224 (2005)
- F. Ritort, S. Mihardja, S. B. Smith and C. Bustamante, *Condensation transition in DNA-polyaminoamide dendrimer fibers studied using laser tweezers*, Phys. Rev. Lett **96** (2006) 118301
- M. Manosas, D. Collin and F. Ritort, *Force dependent fragility in RNA hairpins*, Phys. Rev. Lett **96** (2006) 218301
- F. Ritort, *Single molecule experiments in biological physics: methods and applications,* to be published in J. Phys. C (Condensed Matter)