Please note: Several slides containing unpublished data have been removed from this PDF file.

Other slides (marked with ★) that were not shown in the talk have been included in this PDF

Recent progress in fluctuation theorems and free energy recovery

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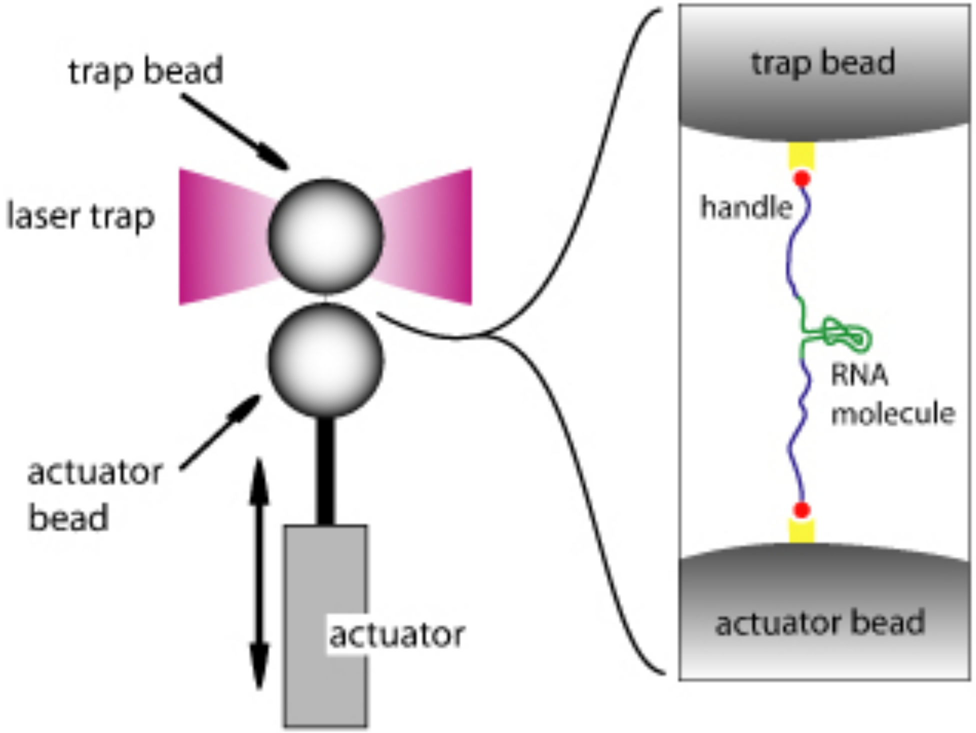
DPG conference, Dresden 14-18 March 2011

Nonequilibrium transient states

Initially in equilibrium but driven out of equilibrium by externally controlled forces




The Nonequilibrium Thermodynamics of Small Systems

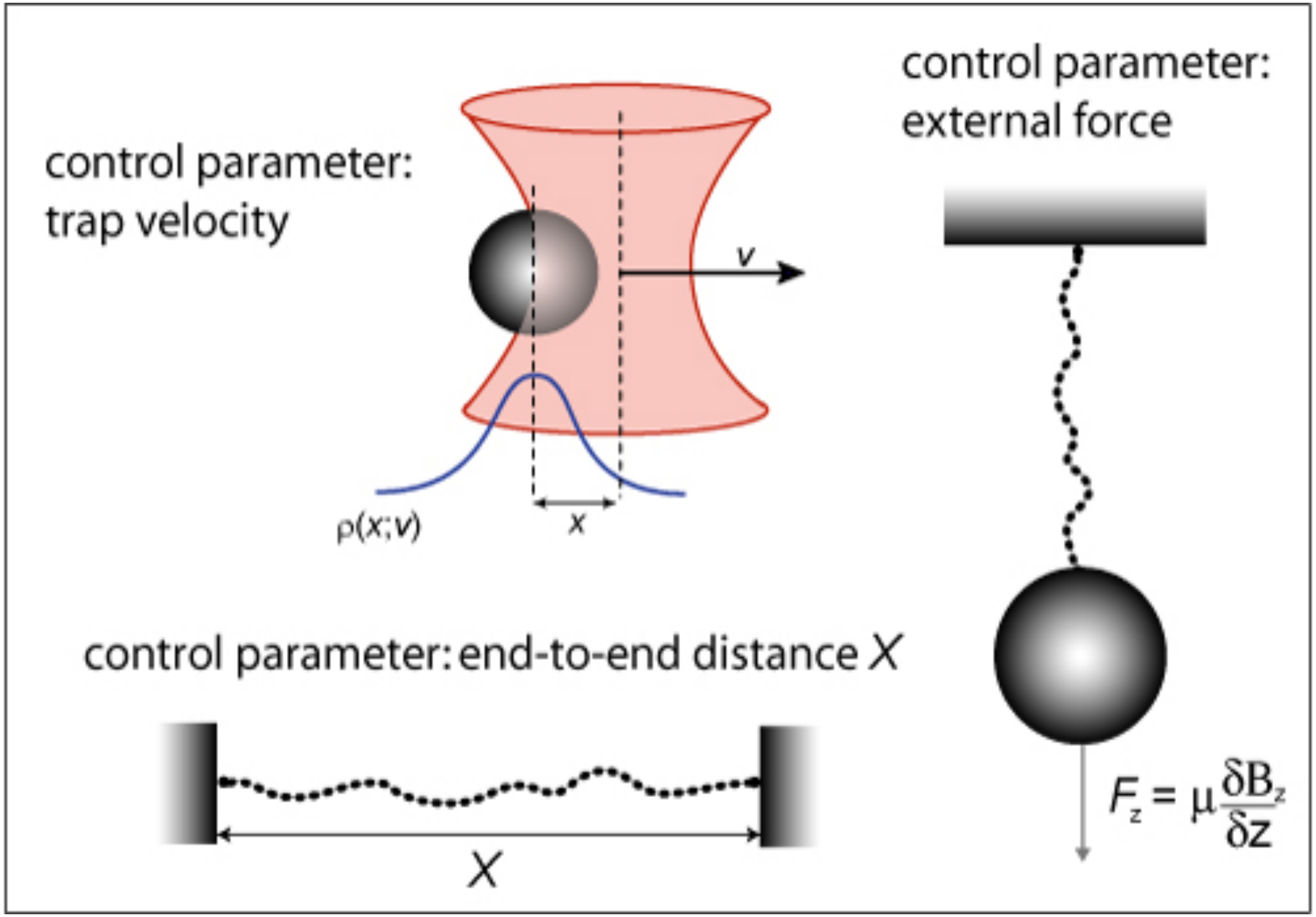
The interactions of tiny objects with their environments are dominated by thermal fluctuations. Guided by theory and assisted by new micromanipulation tools, scientists have begun to study such interactions in detail.

C. Bustamante, J. Liphardt, F. R., Physics Today, vol. 58, 43-48 (2005)

Main concepts

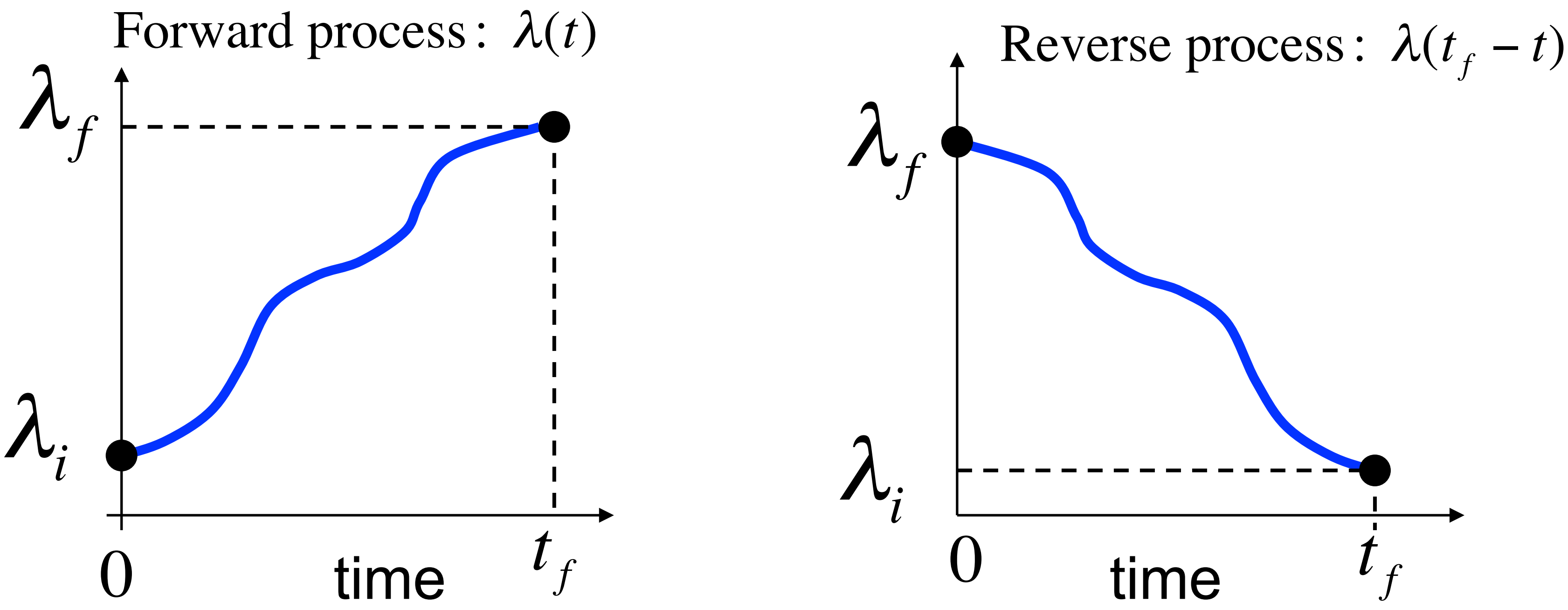
- **Configuration**
- **Path Γ**: sequence of configurations
- **Control parameter** $\lambda(t) \equiv \{\lambda_0, \lambda_1, \ldots, \lambda_k, \ldots, \lambda_M\}$
  - It fully specifies the nonequilibrium experiment
  - In small systems the equation of state depends on which quantity is the control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

Control parameter



Crooks fluctuation relation

(G. E. Crooks, PRE 1998)



Crooks relation

G. E. Crooks, Phys. Rev. E. **60**, 2721 (1999)

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

For the bead in the trap: $\Delta G = 0$ and $P_F(W) = P_R(W)$

★ FREE ENERGY RECOVERY

A) The Jarzynski equality

G. Hummer and A. Szabo, PNAS **98**, 3658 (2001)

$$\Delta F = -k_B T \log < \exp\left(-\frac{W}{k_B T}\right) >_F$$

For a finite number of experiments the JE is biased

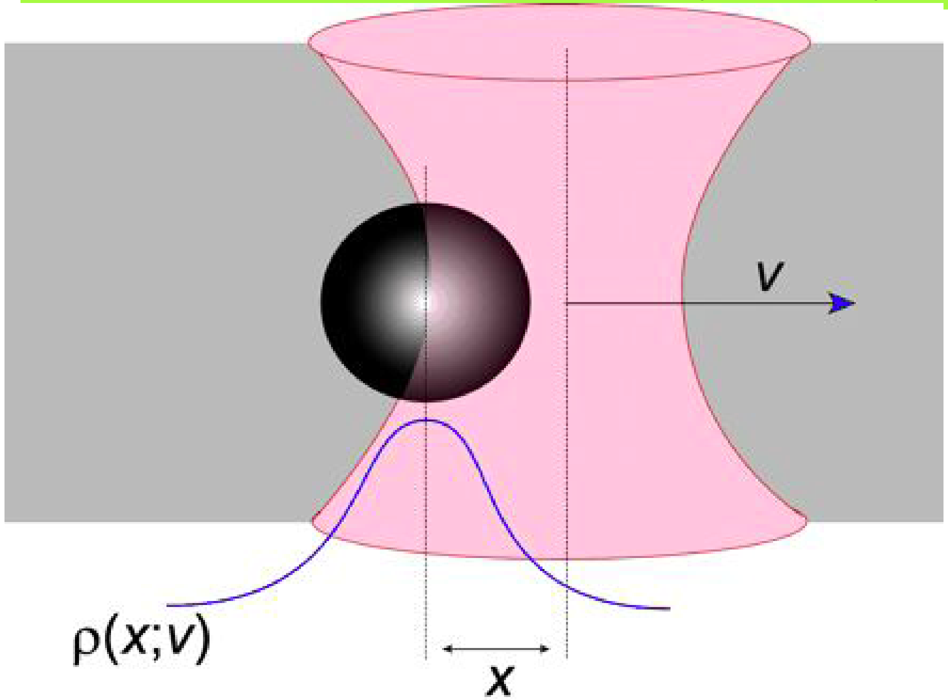
Experiments, numerical simulations and exactly solvable models

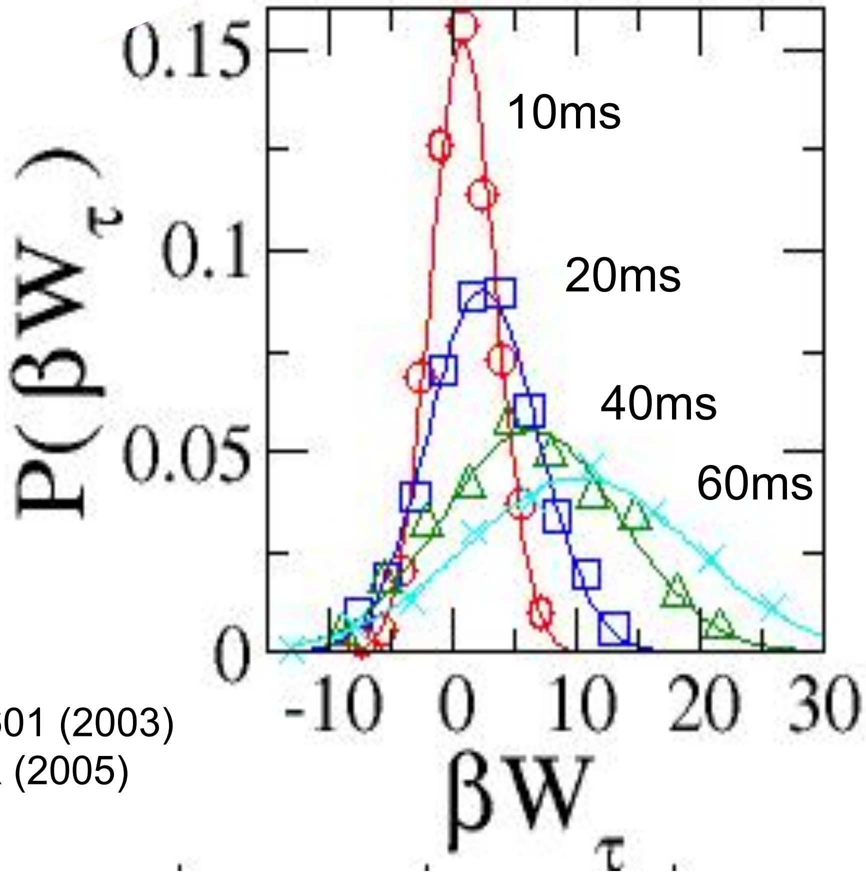
- D.Zuckerman and T.Woolf, Chem. Phys. Lett., **351,** 445 (2002); Phys. Rev. Lett. **89**, 180602 (2002).
- J. Liphardt,S. Dumont, S. B. Smith, I. Tinoco and C. Bustamante, Science **296**, 1832 (2002)
- F. Ritort, C. Bustamante and I. Tinoco, PNAS **99,** 13544 (2002)
- S. Park and K. Schulten, J. Chem. Phys. **120**, 5946 (2004).
- J. Gore, F. Ritort and C. Bustamante, PNAS **100**, 12564 (2003)
- O. Braun, A. Hanke and U. Seifert , Physical Review Letters **93,** 158105 (2004).
- F. Douarche, S. Ciliberto, N. Garnier, Europhysics Letters **70,** 593 (2005)
- R. C. Lhua and A. Y. Grossberg, Journal of Physical Chemistry B **109,** 6805 (2005)
- B. Cleuren, C. Van den Broeck and R. Kawai, Physical Review Letters **96,** 050601 (2006).
- R. D. Astumian, American Journal of Physics **74**, 683 (2006)

The Nonequilibrium Thermodynamics of Small Systems

The interactions of tiny objects with their environments are dominated by thermal fluctuations. Guided by theory and assisted by new micromanipulation tools, scientists have begun to study such interactions in detail.

C. Bustamante, J. Liphardt, F. Ritort, Physics Today, vol. 58, 43-48 (2005)

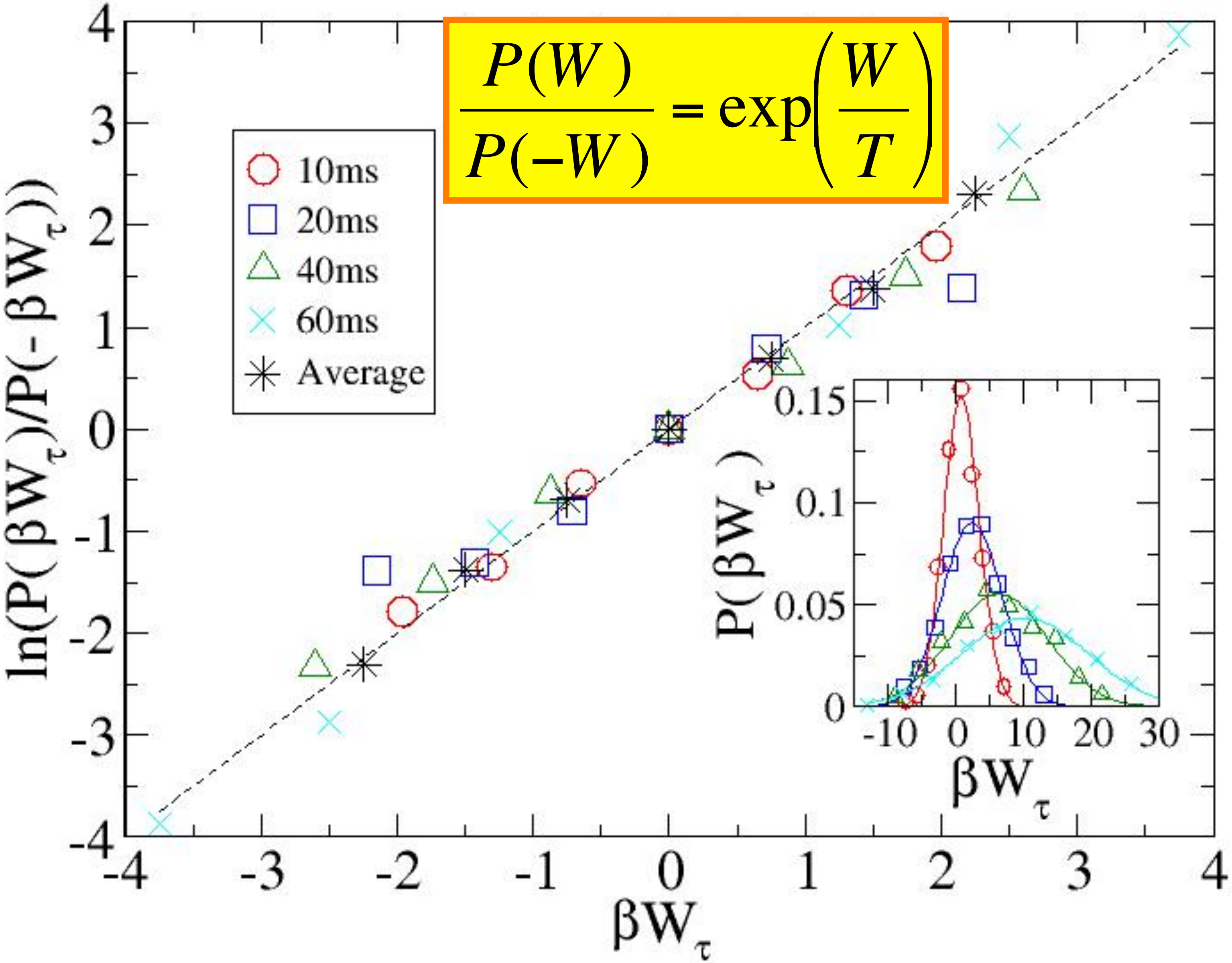




G. M. Wang et al. ,Phys. Rev. Lett. **89,** 050601 (2002)
R. Van Zon, E. G. D. Cohen, Phys. Rev. Lett. **91,** 110601 (2003)
S. Garnier and S. Ciliberto, Phys. Rev. E, **71** 060101R (2005)
E. Trepagnier et al., PNAS **101**, 15038 (2004)
Jake Siegel, Liphardt group, unpublished 2006

★ Transient fluctuation relation

$$\frac{P(W)}{P(-W)} = \exp\left(\frac{W}{T}\right)$$



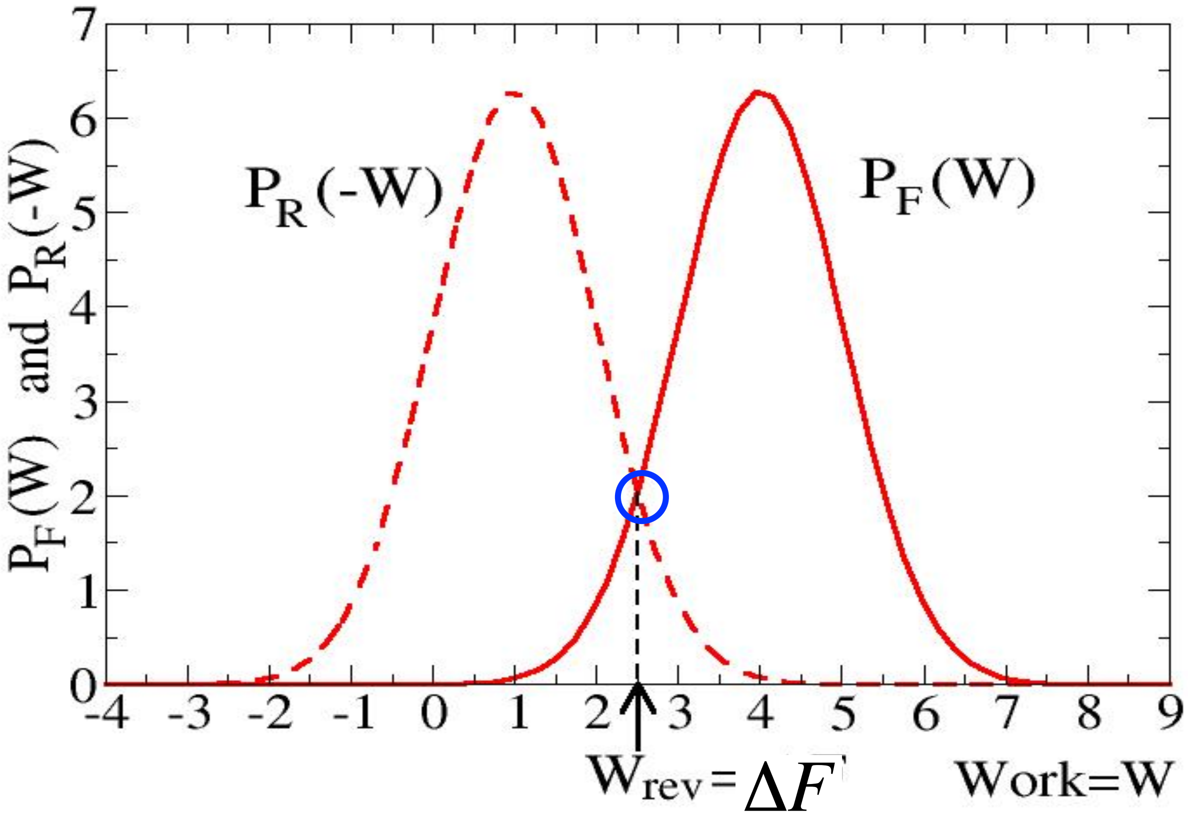
Jake Siegel, Liphardt group, unpublished 2006

B) Bidirectional methods

C. H. Bennett, J. Comp. Phys. **22,** 245 (1976)
M. R. Shirts, E. Bair, G. Hooker, and V. S. Pande, Phys. Rev. Lett. **91**, 140201 (2003)
D. D. L. Minh and A. B. Adib, Phys. Rev. Lett. **100**, 180602 (2008)

Less biased than the JE

For $W = \Delta F \Rightarrow P_F(W) = P_R(-W)$



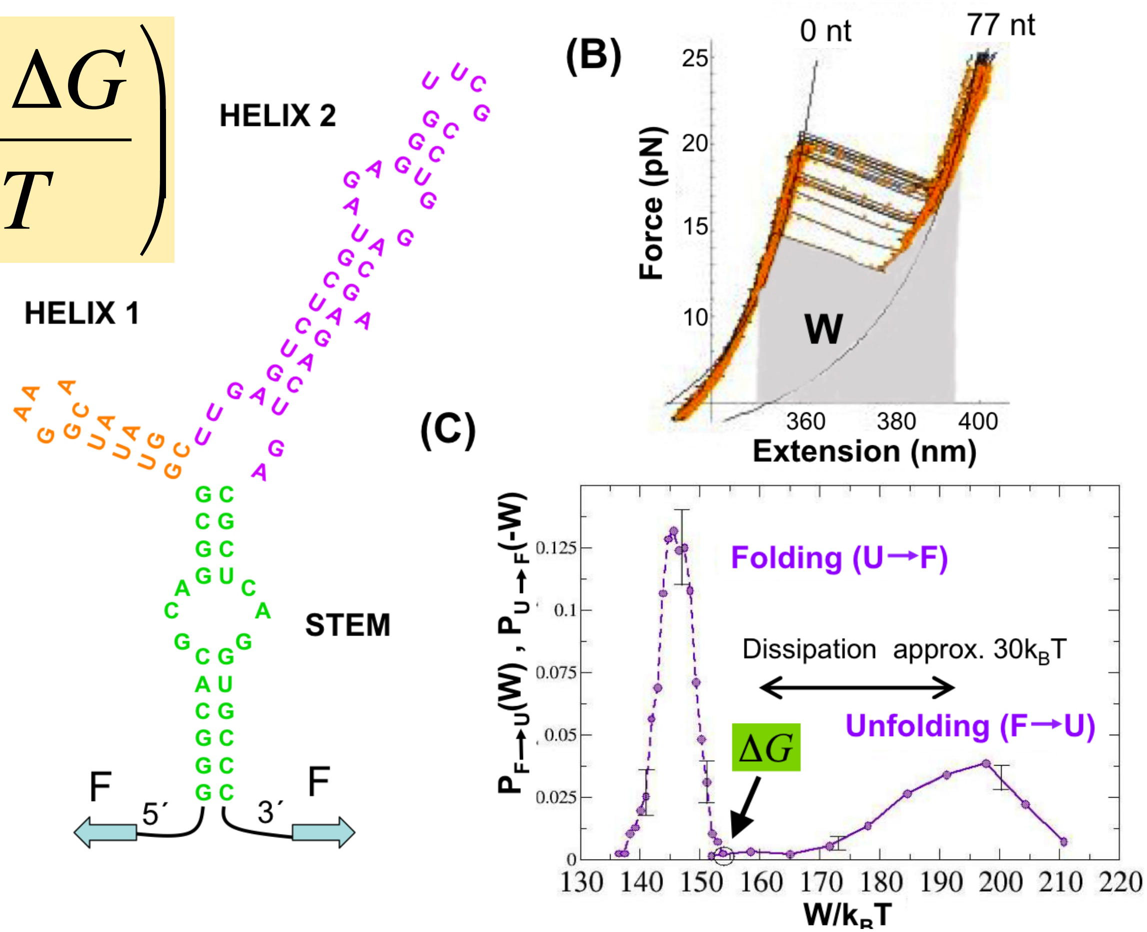
Vol 437|8 September 2005|doi:10.1038/nature04061 nature

LETTERS

Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies

D. Collin[1]*, F. Ritort[2]*, C. Jarzynski[3], S. B. Smith[4], I. Tinoco Jr[5] & C. Bustamante[4,6]

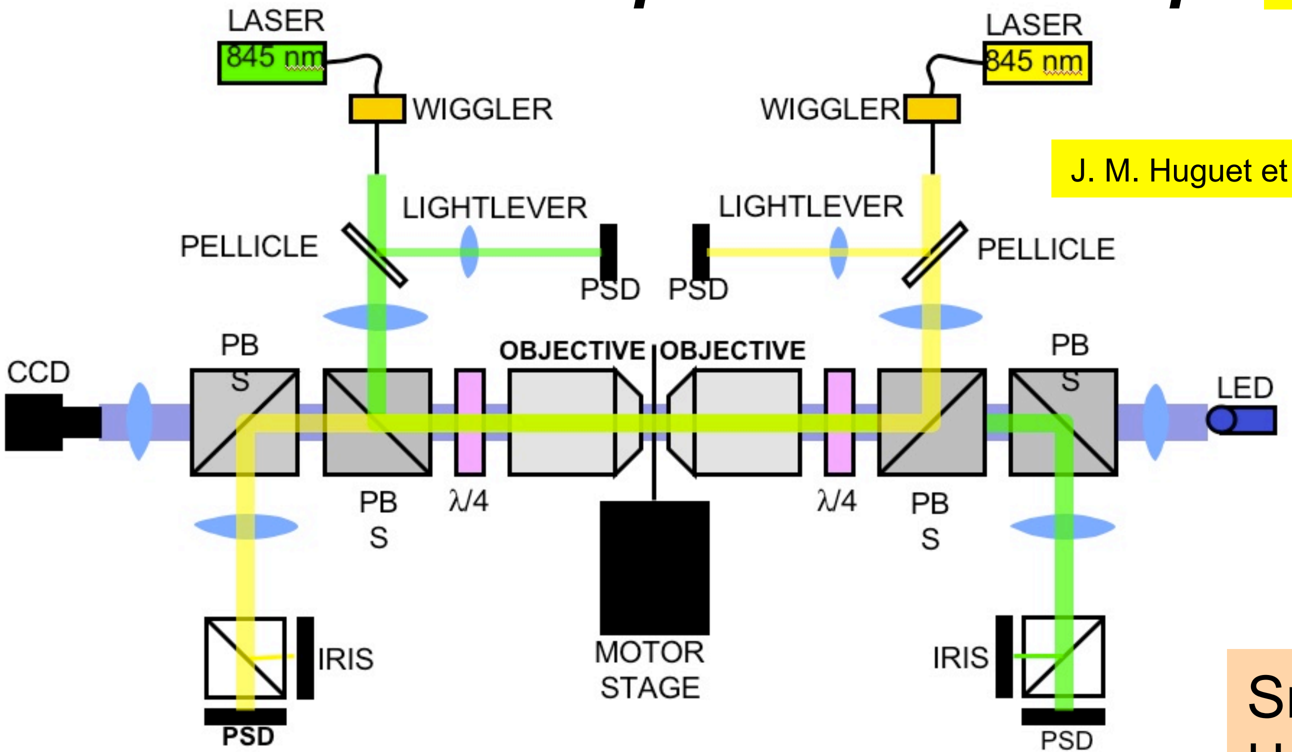
$$\frac{P_U(W)}{P_R(-W)} = \exp\left(\frac{W-\Delta G}{k_B T}\right)$$



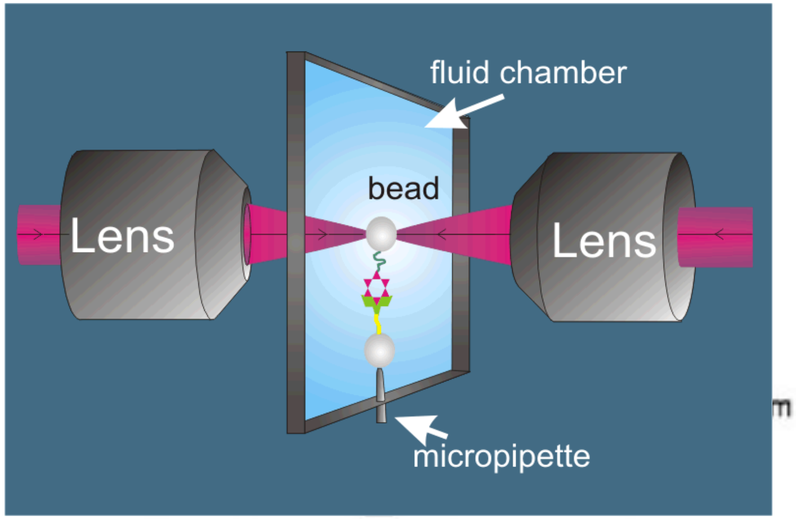
Minitweezers: Experimental set-up

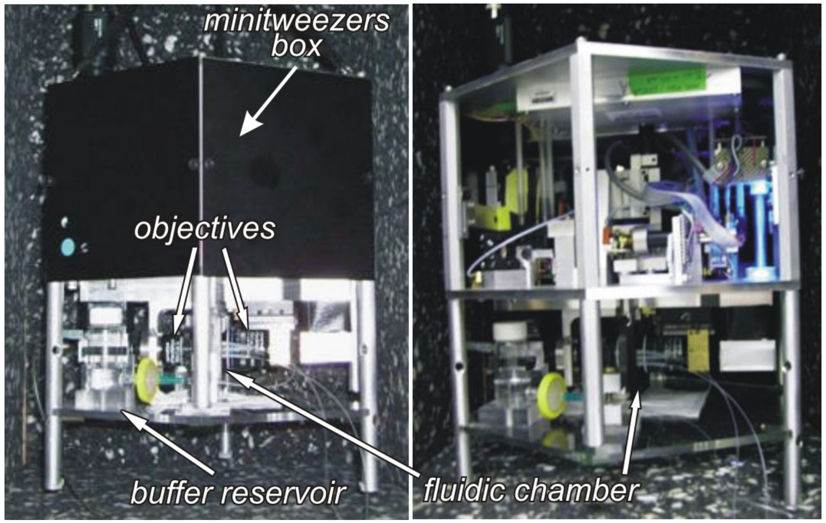
C. Bustamante and S. B. Smith et al., US Patent,**7,** 133, 132, B2 (2006)

J. M. Huguet et al., PNAS **107**: 15431-15436 (2010)

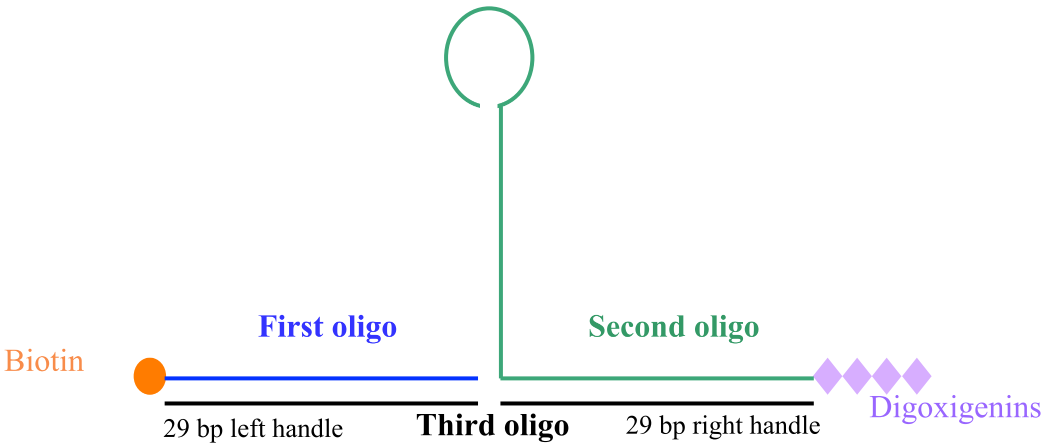


Small biosystems lab
University of Barcelona



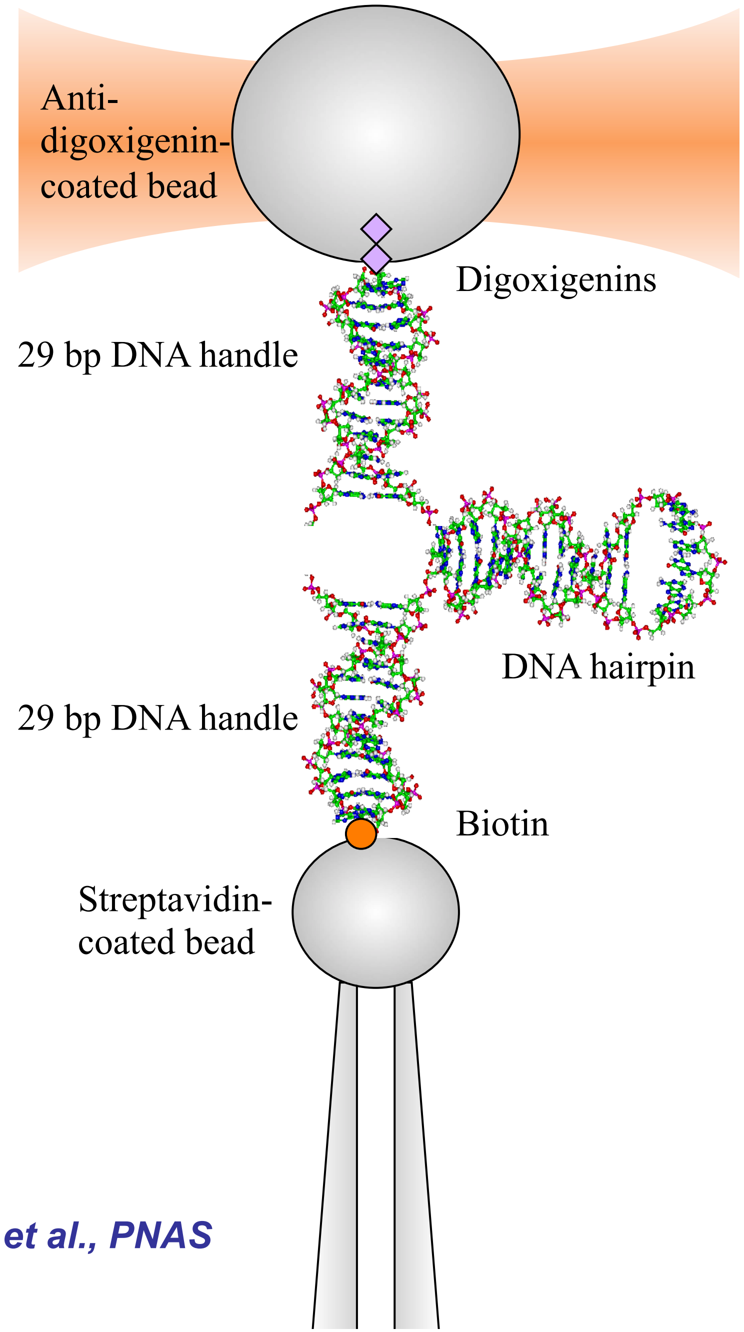


THE WORLD'S SHORTEST HANDLES



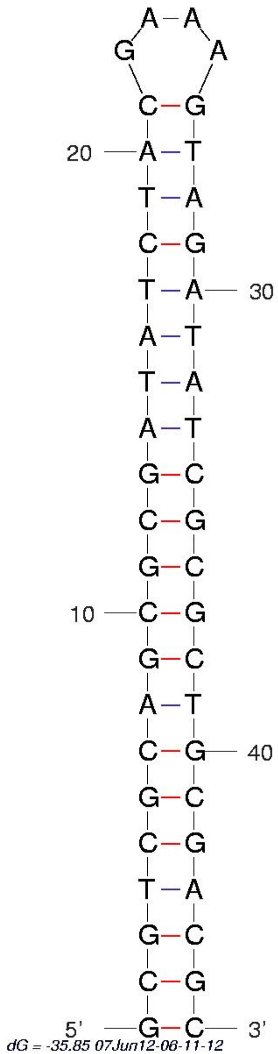
N. Forns et al., Biophys. J (vol. 100, issue 7, April 2011)

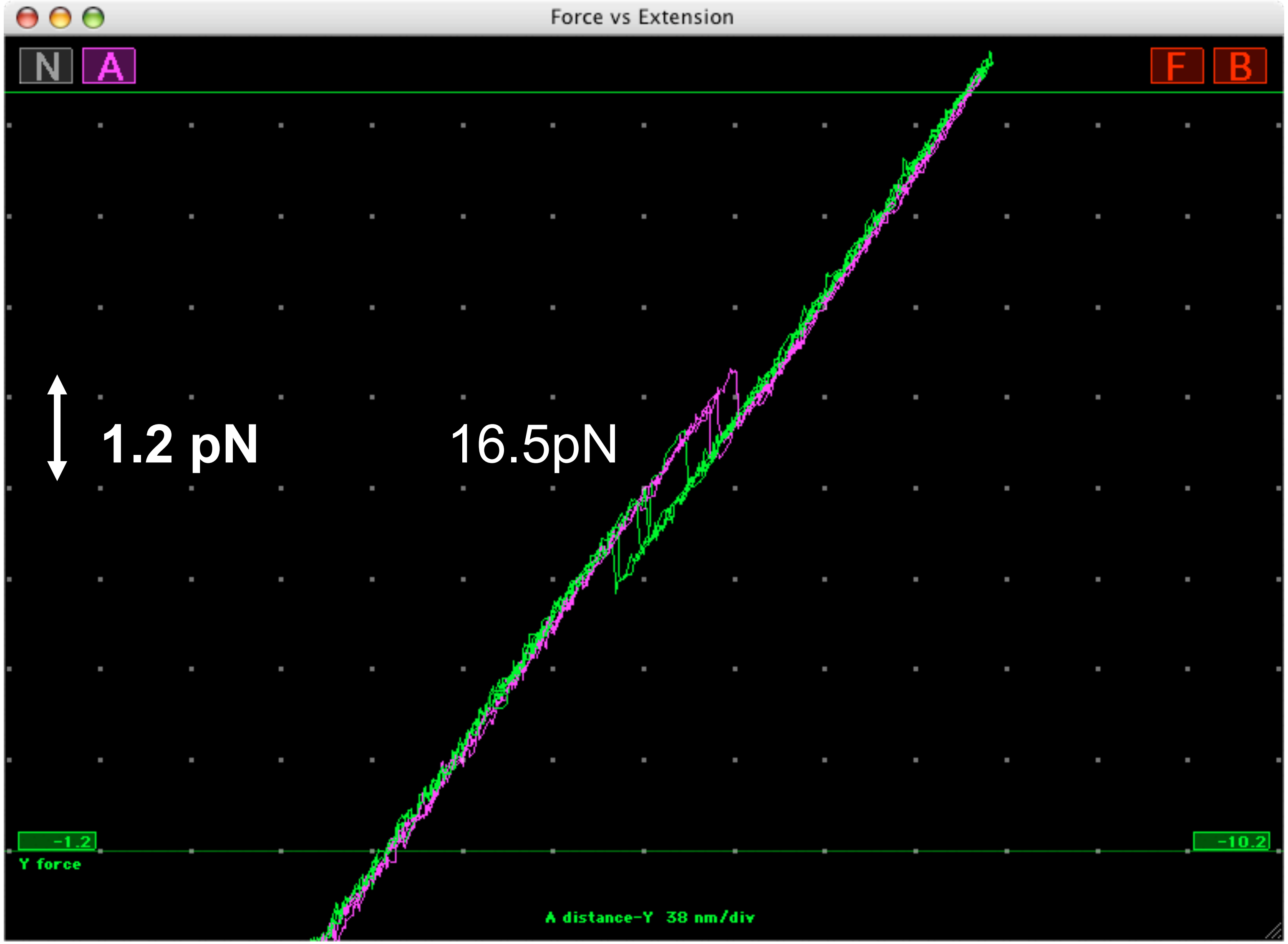
hairpin	
1st oligo	**AGTTAGTGGTGGAAACACAGTGCCAGCGC**G CGAGCCATAAT
2nd oligo	CTCATCTGGAAACAGATGAGATTATGGCTCGCA **GTTAGTGGTGGAAACACAGTGCCAGCGC**
3rd oligo	
GCGCTGGCACTGTGTTTCCACCACTAACT	



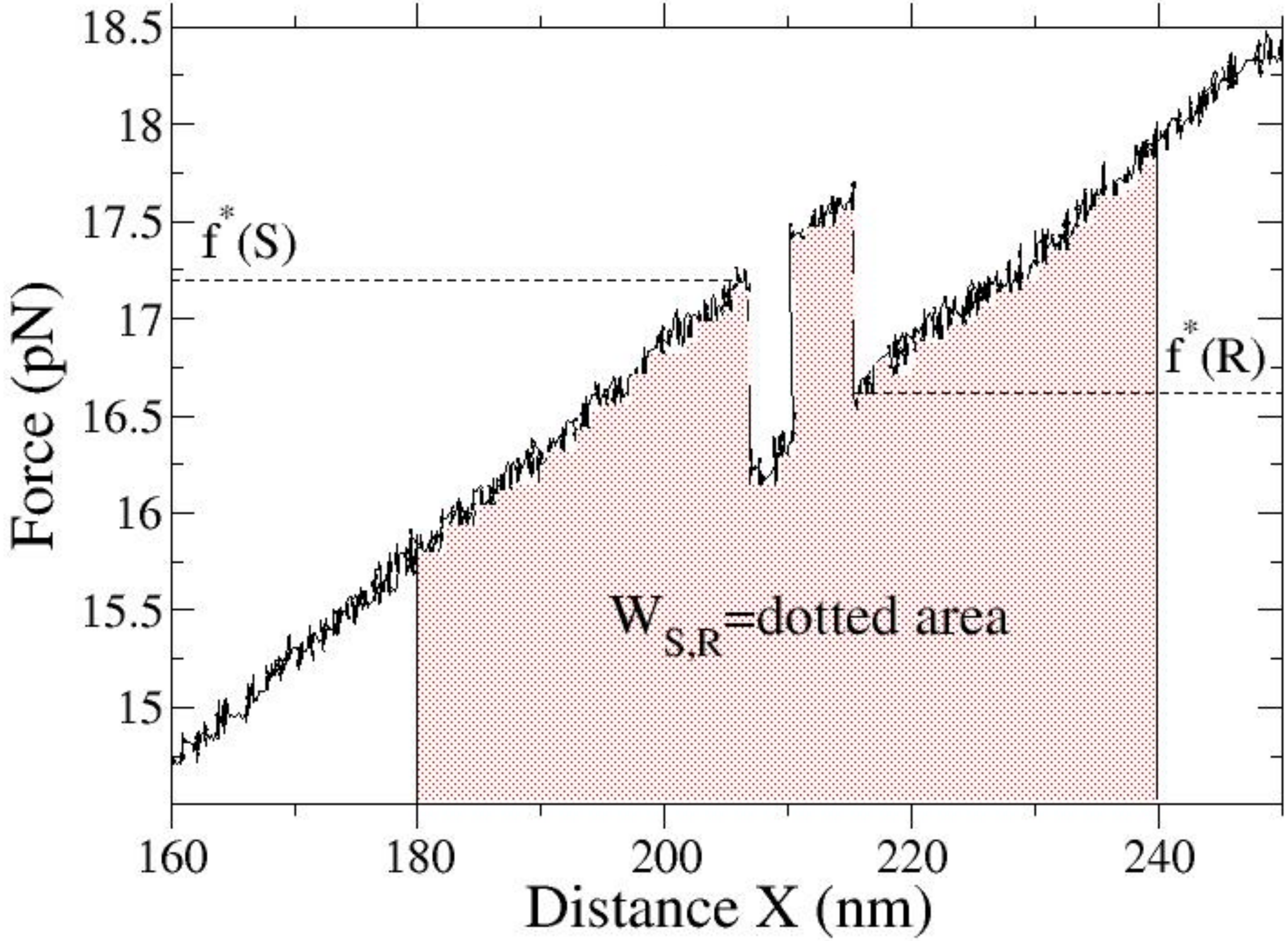
✓Experiments similar to those carried out by M. Woodside et al., PNAS vol. 103, 6190-6195 (2006)

Pulling experiments





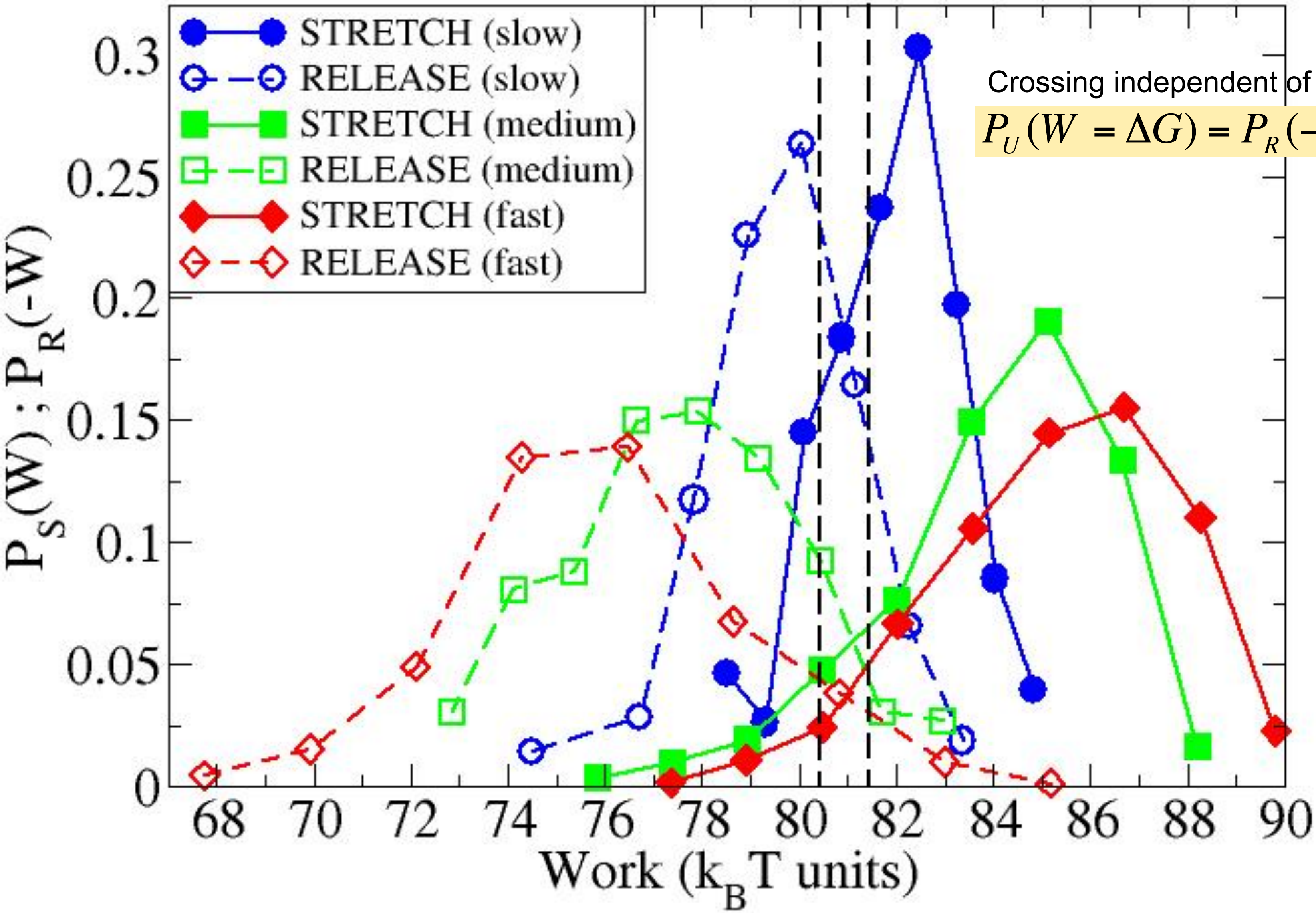
Mechanical work



Control parameter: trap-pipette distance X

Work distributions (1 , 5 , 15 pN/s)

A. Mossa, M. Manosas, N. Forns, J. M. Huguet, F. R., JSTAT, P02060 (2009)

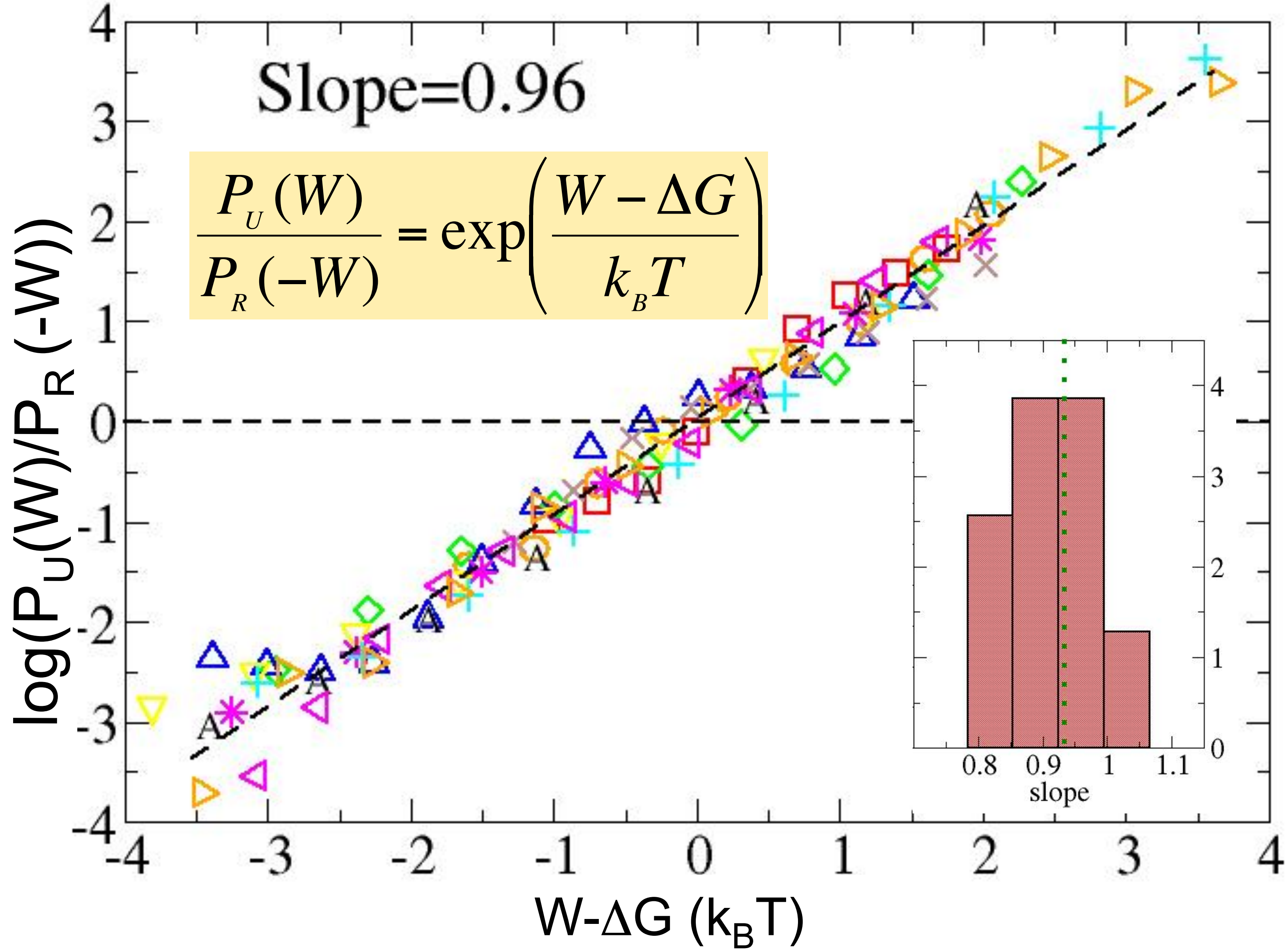


Crossing independent of loading rate

$$P_U(W = \Delta G) = P_R(-W = \Delta G)$$

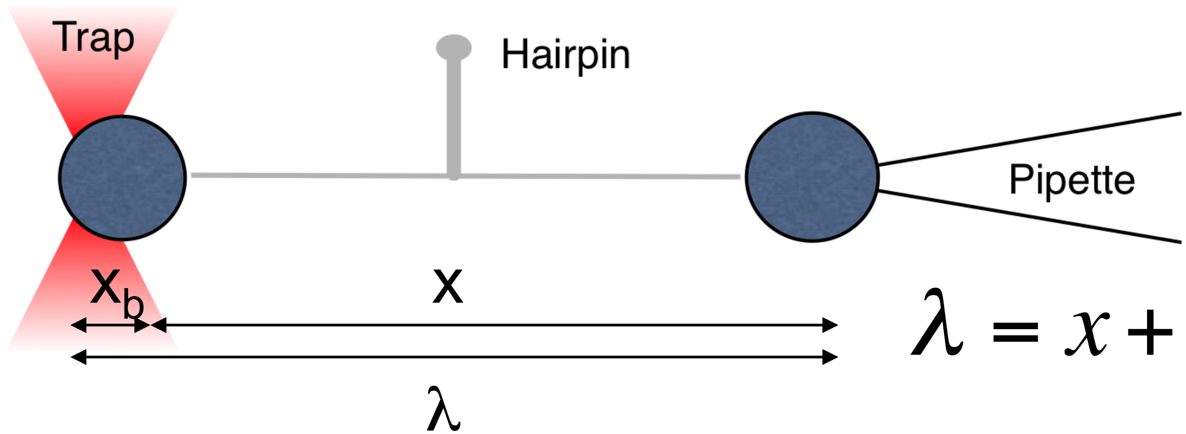
EXPERIMENTAL TEST

A. Mossa, M. Manosas, N. Forns, J. M. Huguet, F. R., JSTAT, P02060 (2009)

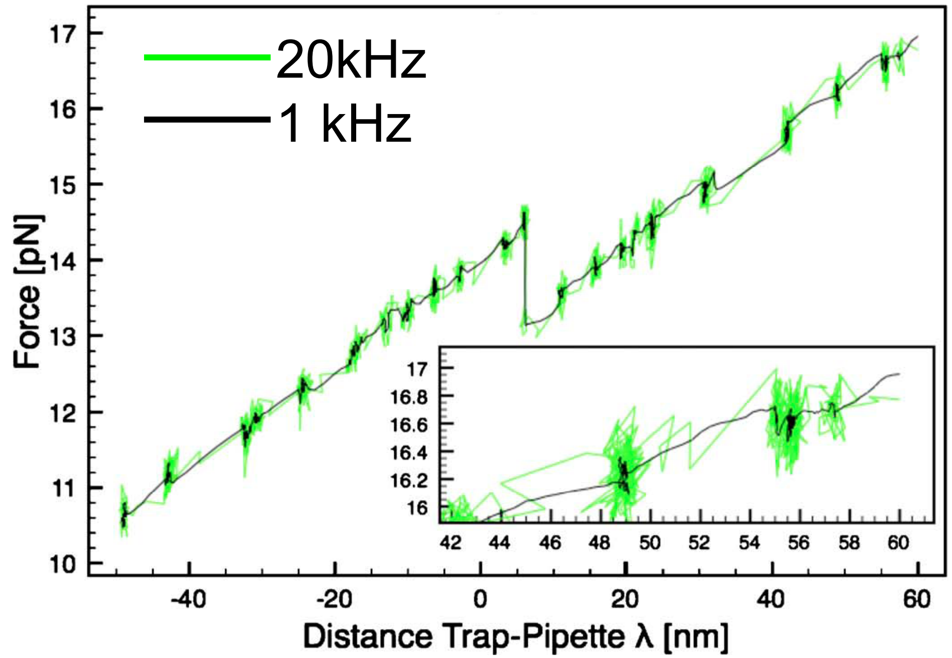


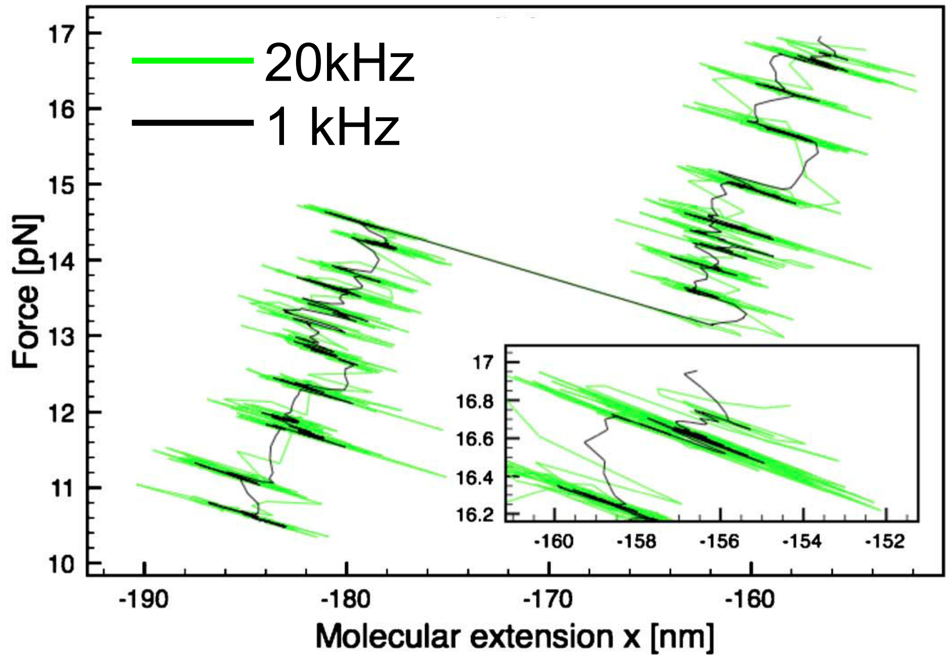
★ On the definition of mechanical work

A. Mossa, S. de Lorenzo, J. M. Huguet, F. R., J. Chem. Phys. **130,** 234116 (2009)

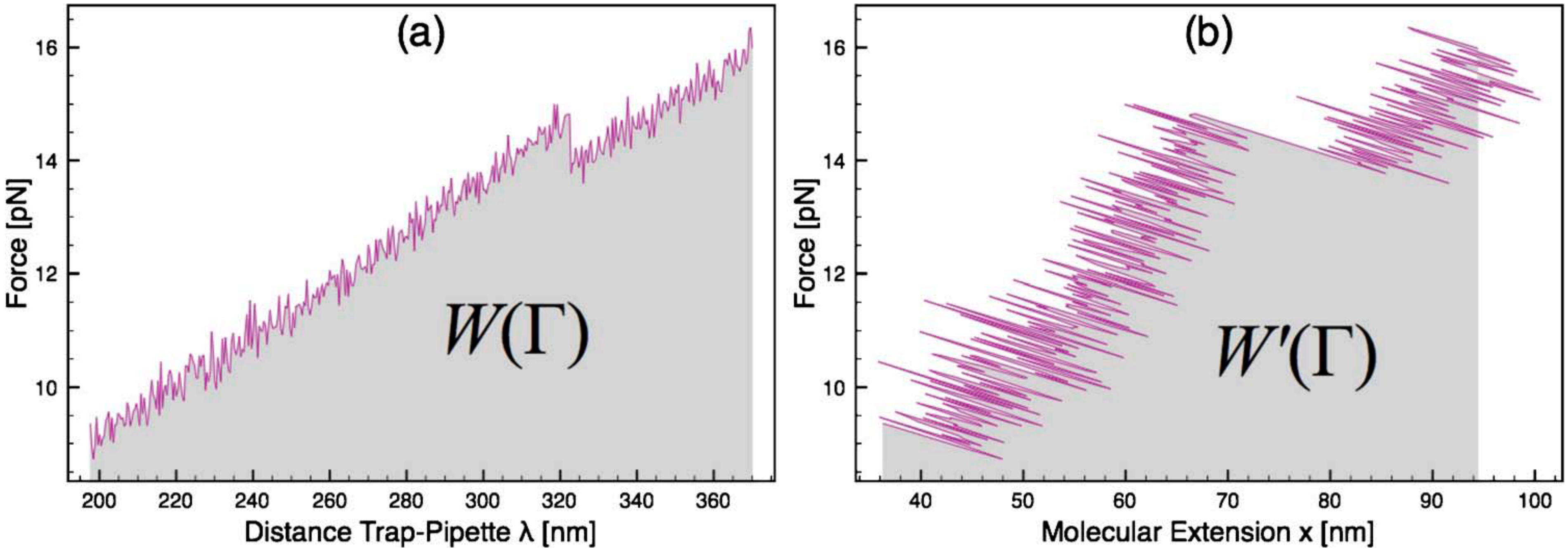


$$\lambda = x + x_b$$





Are both descriptions equivalent?



$$W = \int F(x,\lambda)\,d\lambda \qquad\qquad W' = \int F(x,\lambda)\,dx$$

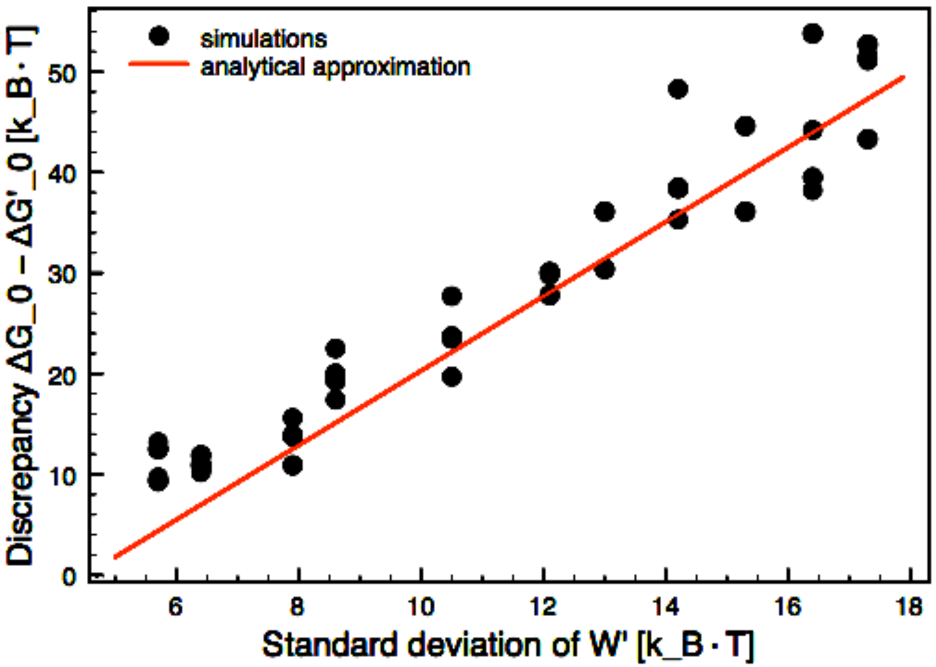
✓G. Hummer and A. Szabo, PNAS vol. 98,3658 (2001); J. M. Schurr and B. S. Fujimoto, J. Phys. Chem. B, vol. 107, 14007 (2003); L. Peliti, JSTAT 2008.

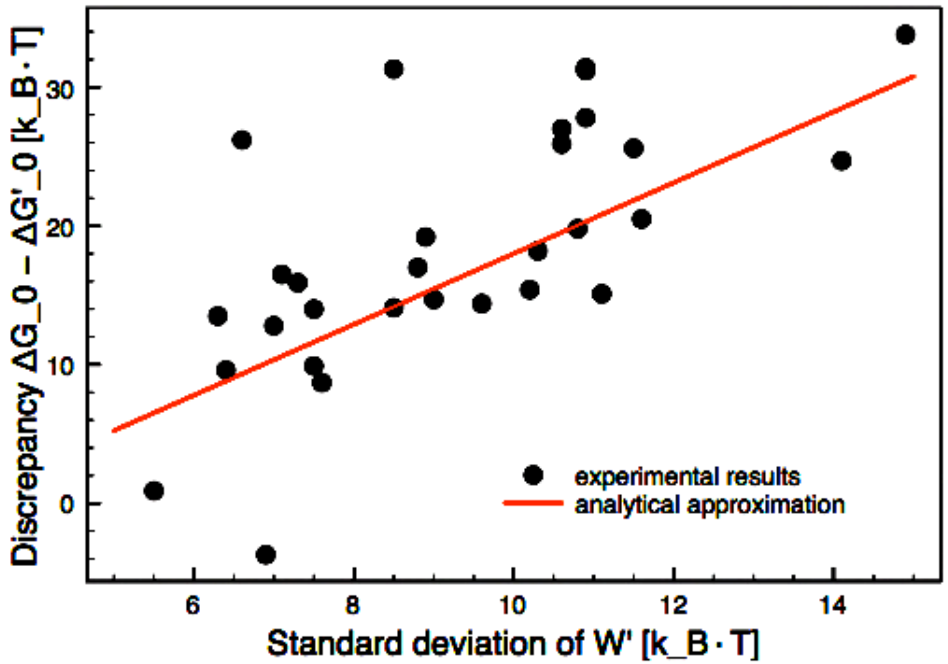
Jarzynski estimates

$$\Delta G_0 = -k_B T \log\left(\left\langle \exp\left(-\frac{W}{k_B T}\right)\right\rangle\right) \qquad \Delta G'_0 = -k_B T \log\left(\left\langle \exp\left(-\frac{W'}{k_B T}\right)\right\rangle\right)$$

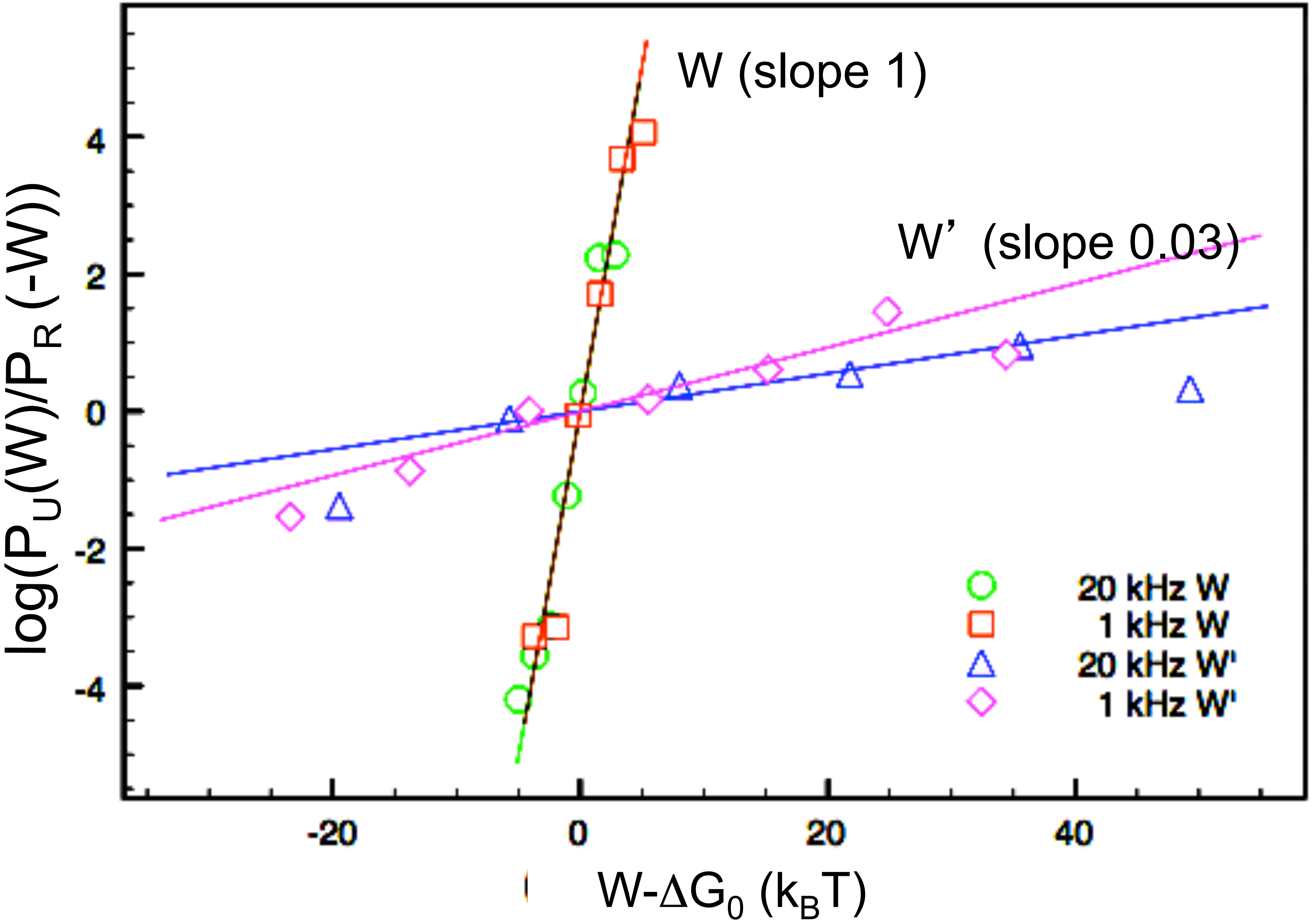
Gaussian approximation

$$W = W' + \frac{F_f^2 - F_i^2}{2k_b} \quad \Rightarrow \quad \Delta G_0 - \Delta G'_0 = -k_B T \log(n) - \sqrt{2}\,\sigma\, z(n)$$





Bidirectional methods



GENERALIZED FLUCTUATION RELATION

I. Junier, A. Mossa, M. Manosas and F. R ., Phys. Rev. Lett. **102,** 070602 (2009)

Let S_0 stand for A,B,C,..initially at λ_0 along the forward path
Let S_1 stand for A,B,C,..initially at λ_1 along the reverse path

$$\frac{p_F^{S_0\to S_1}}{p_R^{S_0\leftarrow S_1}}\frac{P_F^{S_0\to S_1}(W)}{P_R^{S_0\leftarrow S_1}(-W)}=\exp\left[\beta\left(W(\Gamma)-\Delta G_{S_0,\lambda_0}^{S_1,\lambda_1}\right)\right]$$

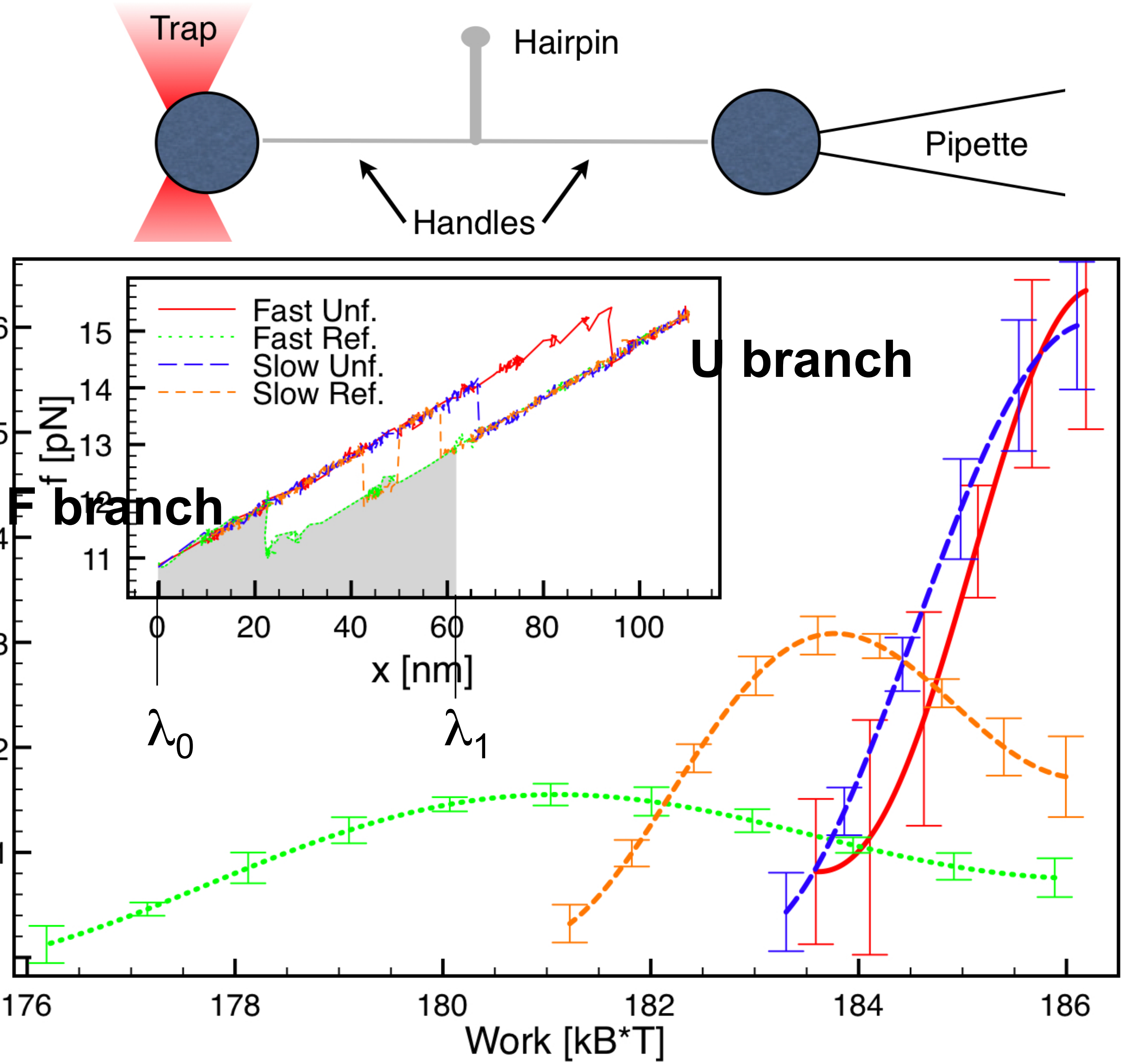
$p_F^{S_0\to S_1}$ (fraction of F paths starting at S_0 and ending at S_1

$p_R^{S_0\leftarrow S_1}$ (fraction of R paths starting at S_1 and ending at S_0

$\Delta G_{S_0,\lambda_0}^{S_1,\lambda}$ (free energy difference between substates S_0 and S_1)

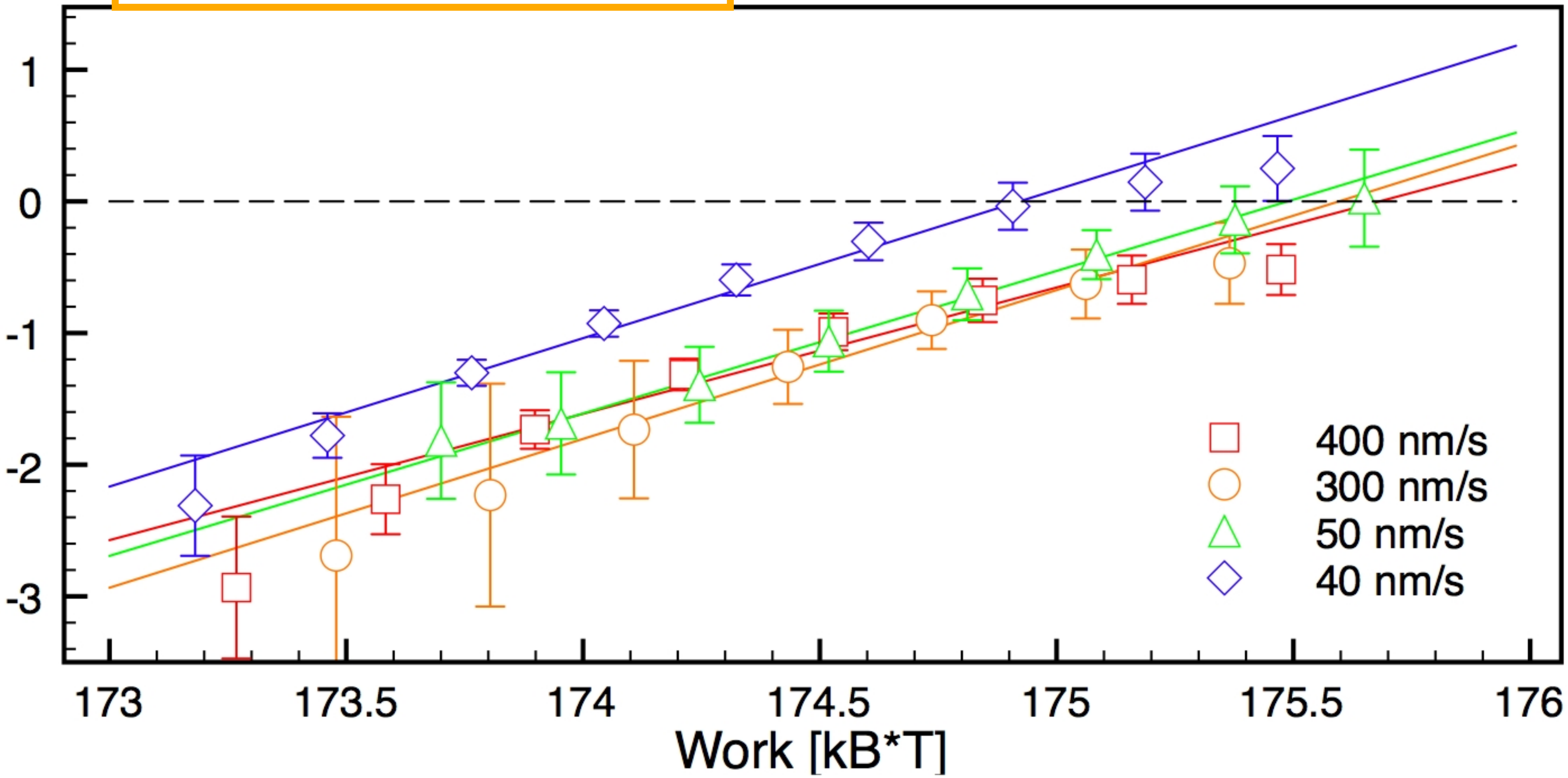
A similar relation has been obtained by P. Maragakis et al., J. Phys. Chem. B, vol. 112, 6168 (2008).

PARTIAL WORK DISTRIBUTIONS



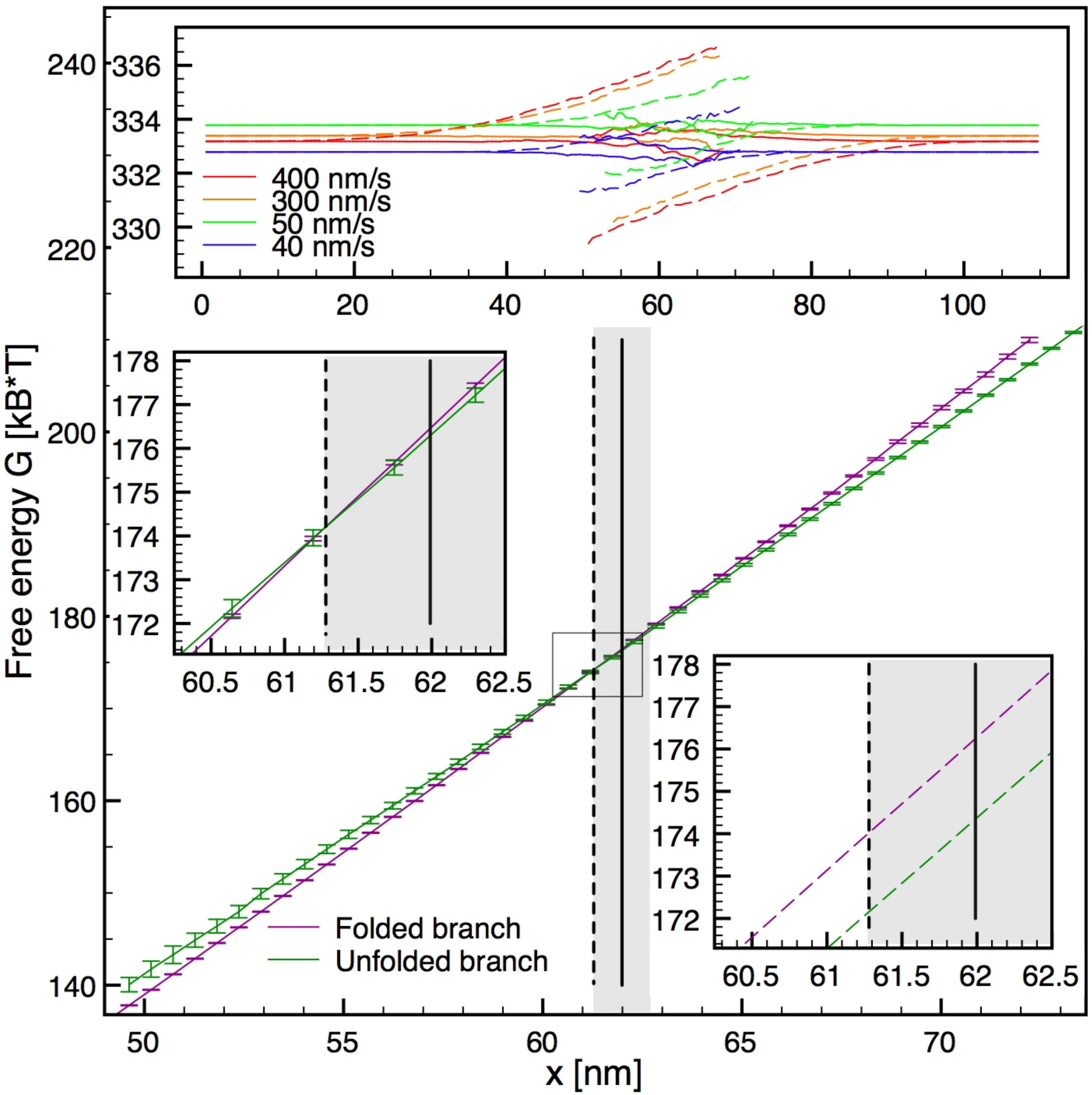
EXPERIMENTAL TEST

$$\log\left[\frac{p_F^{S_0\to S_1}}{p_R^{S_0\leftarrow S_1}}\,\frac{P_F^{S_0\to S_1}(W)}{P_R^{S_0\leftarrow S_1}(-W)}\right]$$



Slopes: 0.91, 1.07, 1.02, 1.07

★ RECOVERY OF FREE ENERGY BRANCHES



Members: **A. Alemany, J. Camunas, S. de Lorenzo, N. Forns, J. M. Huguet, K. Hayashi, I. Junier, C. Larroy, M. Manosas, A. Mossa, C. V. Bizarro, M. Ribezzi, L. Bongini, B. Rey**

FUNDING: Ministerio de Educacion y Ciencia (Spain), Instituto de Sanidad Carlos III (Spain), Generalitat de Catalunya, European Union, Human frontiers science program

Take home messages….

- Unzipping/zipping experiments provide valuable information about **thermodynamics** and **kinetics** of molecular interactions
- **Fluctuation relations** are currently used to extract free energies of native structures (nucleic acids and proteins)
- They can be used to recover free energies of **kinetic states** such as intermediates and misfolded structures
- Single molecule measurements open new perspectives to better understand **energy processes** at the molecular level with unprecedented detail