Supplementary Information: Dissipation reduction and information-to-measurement conversion in DNA pulling experiments with feedback

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S1 Experimental measurement of ΔG_{FU} without feedback

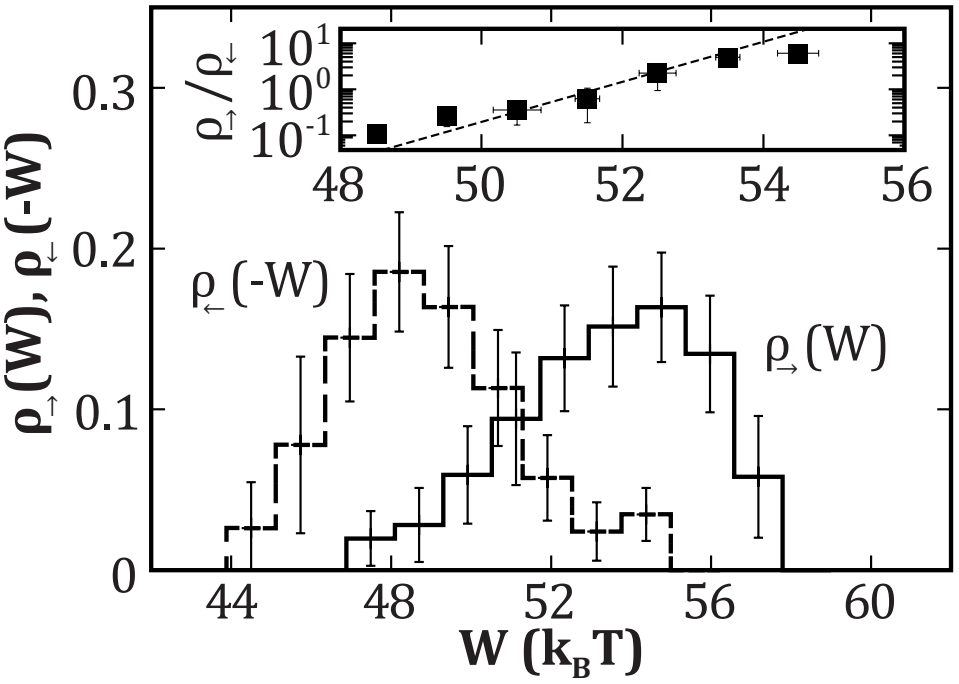

Figure S1: **Work-FT results without feedback.** In the main plot the forward (solid black line) and reverse (dashed black line) work distributions without feedback for the DNA hairpin pulled at the loading rate $r = 4$pN/s. In the inset we show the test of the Crooks-FT ($\rho(W)/\rho(-W) = \exp((W - \Delta G_{FU})/k_B T)$) from which we extract the value of ΔG_{FU}. We obtain $\Delta G_{FU} = 51 \pm 1$ k$_\mathrm{B}$T.

S2 Simulation details

To simulate pulling experiments where the trap position, λ, is the control parameter we proceed as described in references [1, 2]. Briefly, the forward and reverse trajectories are simulated as a first order Markov chain where, for a given value of λ and force, f, it is satisfied that:

$$\lambda(f) = x^{\sigma}_{DNA}(f) + x_h(f) + x_b(f) \ . \tag{S1}$$

In Eq.(S1) $x_b(f)$ is the position of the trapped bead relative to the center of the optical trap; $x_h(f)$ is the end-to-end distance of the dsDNA handles and x^{σ}_{DNA} is the end-to-end distance of the DNA hairpin, which depends on the state of the molecule ($\sigma = F, U$). The latter defines two force branches, one when the DNA hairpin is folded and the other when the hairpin is unfolded.

To determine the two force branches, first we need to determine the extension of each element at a given λ, i.e., at a given force. On one hand, $x_b(f)$ satisfies:

$$|f| = k_b x_b \tag{S2}$$

being k_b the trap stiffness ($k_b = 0.068$ pN/nm). In this simple approximation (Hooke's law), the bead behaves as a Brownian particle under the action of two opposing springs (the optical trap and the molecular construct), hence the white noise due to thermal fluctuations satisfies:

$$\langle \delta x^2 \rangle = \frac{k_B T}{k^{\sigma}_{mol} + k_b} \ , \qquad \langle \delta f^2 \rangle = \frac{k_B T k_b^2}{k^{\sigma}_{mol} + k_b} \tag{S3}$$

where k^{σ}_{mol} is the stiffness of the molecular construct. It is given by $1/k^{\sigma}_{mol} = 1/k_h + 1/k^{\sigma}_{DNA}$) where k_h and k_{DNA} are the stiffness of the dsDNA handle and the DNA hairpin. These stiffness values are calculated as the derivative of the force with respect to the extension of the corresponding element (handle or molecule). Furthermore, the elastic response of the dsDNA handles and the unfolded DNA hairpin is well described by the Worm-Like Chain model,

$$f_{\mathrm{WLC}} = \frac{k_B T}{4 L_p} \left(\left(1 - \frac{x}{L_c} \right)^{-2} + 4 \frac{x}{L_c} - 1 \right) \tag{S4}$$

where k_B is the Boltzmann's constant and T is the temperature. f_{WLC} is the measured force at a given end-to-end extension of the dsDNA handles (29 base-pairs at each flanking side) and the unfolded hairpin, x; L_p is the persistence length ($L_p = 10$nm for the dsDNA handles and $L_p = 1.34$nm for the unfolded DNA hairpin [1–3]) and L_c is the contour length ($L_c = 58\mathrm{bp} \cdot 0.34\mathrm{nm/bp} = 19.72$nm for the dsDNA handles and $L_c = 25.96$nm for the unfolded DNA hairpin [1–3]). Besides, the folded DNA hairpin behaves as a dipole of length ($d_0 = 2$nm [3]) of extension:

$$x_d(f) = d_0 \left[\coth\left(\frac{d_0 f}{k_B T} \right) - \frac{k_B T}{d_0 f} \right] \tag{S5}$$

To simulate pulling experiment, we calculate the unfolding, $k_{\rightarrow}(\lambda)$, and refolding, $k_{\leftarrow}(\lambda)$, kinetic rates as

described in [4]. The kinetic rates are defined as:

$$k_{\rightarrow}(\lambda) = k_0 \exp\left(-\frac{B(\lambda)}{k_B T}\right) \tag{S6a}$$

$$k_{\leftarrow}(\lambda) = k_0 \exp\left(-\frac{B(\lambda) - \Delta G_{FU}(\lambda)}{k_B T}\right) \tag{S6b}$$

where $B(\lambda)$ is the kinetic barrier, k_0 is the attemp rate ($k_0 = 8 \cdot 10^4 s^{-1}$) and $\Delta G_{FU}(\lambda)$ is the energy difference between states F and U at a given λ. The latter is determined as:

$$\Delta G_{FU}(\lambda) = \Delta G_{FU} + \Delta W_{FU}^{DNA} + \Delta W_{FU}^{h} + \Delta W_{FU}^{b} \tag{S7}$$

where ΔG_{FU} is the folding free energy of the DNA hairpin ($\Delta G_{FU} = 51$ k$_\mathrm{B}$T); ΔW_{FU}^{DNA} is the stretching contribution of the unfolded hairpin ($W_U^{DNA} = \int_0^{x_{DNA}^U} f_{\mathrm{WLC}}(x')dx'$) minus the orientation contribution of the folded DNA hairpin ($W_F^{DNA} = \int_0^{x_{DNA}^F} f_{\mathrm{d}}(x')dx'$) with $f_d(x)$ the inverse function of Eq.(S5); ΔW_{FU}^{h} is the stretching contribution of the handles ($\Delta W_{FU}^{h} = \int_{x_h^F}^{x_h^U} f_{\mathrm{WLC}}(x')dx'$) where the limits are the end-to-end distances at a given λ evaluated at the different forces, when the hairpin is folded and unfolded; ΔW_{FU}^{b} is the work done to displace the bead with respect to the center of the optical trap between the folded and unfolded branches ($\Delta W_{FU}^{b} = \int_{x_b^F}^{x_b^U} f_{\mathrm{Hooke}}(x')dx'$).

Finally the kinetic barrier $B(\lambda)$ can be simplified using the Bell-Evans approximation. However, as we want to see if this model fits our experiments we calculated explicitly the kinetic barrier using the Kramers solution to the one-dimensional diffusion problem in the unzipping molecular free energy landscape described by the nearest-neighbour model [4, 5]:

$$B(\lambda) = k_B T \log\left(\sum_{n=0}^{N}\sum_{n'=0}^{n} \exp\left[\frac{\Delta G_n(\lambda) - \Delta G_{n'}(\lambda)}{k_B T}\right]\right) . \tag{S8}$$

In Eq.(S8) $\Delta G_n(\lambda)$ is the free energy of the hairpin determined by the number of opened base-pairs, n, at a given λ. This energy is calculated as

$$\Delta G_n(\lambda) = \Delta G_n + \int_0^{x_n^{DNA}} f_{\mathrm{WLC}}(x')dx' + \int_0^{x_h^n} f_{\mathrm{WLC}}(x')dx' + \int_0^{x_b^n} f_{\mathrm{Hooke}}(x')dx' . \tag{S9}$$

Here, x_n^{DNA} is the extension of DNA when only n base-pairs are opened, x_h^n and x_b^n are the extension of the handles and the bead position when only n base-pairs are opened.

The simulated trajectories are generated as follows: the forward trajectory is initialized at the folded state ($n = 0$) at $\lambda_{min} = 0$nm, while the reverse one is initialized at the unfolded state ($n = N$) at $\lambda_{max} = 300$nm. During the simulation the relaxation of the handles and the bead is assumed to be instantaneous. The steps of the algorithm for the forward (reverse) process are:

1. λ increases (decreases) by the amount $r\Delta t/k_b$, were r is the loading rate and Δt is the inverse of the data acquisition frequency ($\Delta t = 0.001$s).

2. Eq.(S1) is solved according to the state of the hairpin to find the value of the force f acting on the experimental setup. Moreover, to be more realistic we added a Gaussian noise of zero mean and

variance given by Eq.(S3) to the measured λ and f.

3. We calculate the probability to observe an unfolding or folding transition as: $k_{\rightarrow}(\lambda) \cdot \Delta t$ if the molecule is folded or as $k_{\leftarrow}(\lambda) \cdot \Delta t$ if the molecule is unfolded.

4. We compare the transition probability with an uniformly distributed random number between 0 and 1. If the probability is larger than the random number we change the state of the molecule in the next step, otherwise the molecule remains in the same state.

The work done in the simulated forward and reverse trajectories is calculated as the area under the trajectory, i.e. $W = \int_{\lambda_{min}}^{\lambda_{max}} f(\lambda')d\lambda'$.

S3 Numerical simulation of hairpins L4 and L8

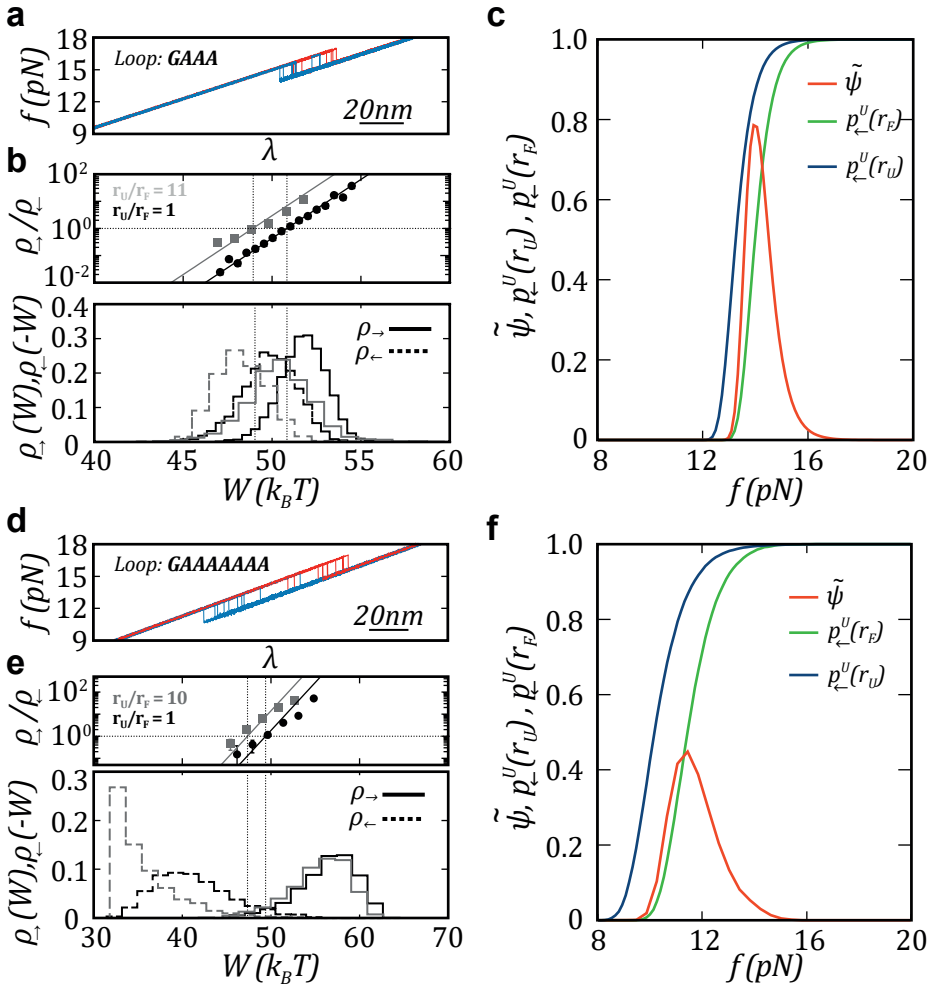

Figure S2: **Numerical simulation of hairpins L4 and L8.** (a) Simulated forward (red) and reverse (blue) FDCs without feedback for the DNA L4 hairpin. (b) Bottom: Forward work distributions (solid lines) and properly weighed reverse work distributions (dashed lines) for the non-feedback case (black lines) and the CTF with $r_U/r_F = 11$ (gray lines). Top: Test of the feedback-FT (Eq.16c) for the cases $r_U/r_F = 1$ (black circles) and $r_U/r_F = 11$ (gray squares) (c) $p^U_{\leftarrow}(\lambda, r_U)$, $p^U_{\leftarrow}(\lambda, r_F)$ and last-folding density $\widetilde{\psi}(\lambda)$ for $r_F = 5$pN/s and $r_U = 20$pN/s at different measuring points. (d) Simulated forward (red) and reverse (blue) FDCs without feedback for the DNA L8 hairpin. (e) Bottom: Forward work distributions (solid lines) and properly weighed reverse work distributions (dashed lines) for the non-feedback case (black lines) and the CTF with $r_U/r_F = 10$ (gray lines). Top: Test of the feedback-FT (Eq.16c) for the cases $r_U/r_F = 1$ (black circles) and $r_U/r_F = 10$ (gray squares). (f) $p^U_{\leftarrow}(\lambda, r_U)$, $p^U_{\leftarrow}(\lambda, r_F)$ and last-folding density $\widetilde{\psi}(\lambda)$ for $r_F = 6$pN/s and $r_U = 30$pN/s at different measuring points. In panels (c) and (f) we used force as a reference value to present the results. Force is more informative than the trap position λ_1 because the latter is defined as the relative distance between the trap position and an arbitrary initial position in the light-lever detector.

S4 Bias of the DTF+CTF strategy

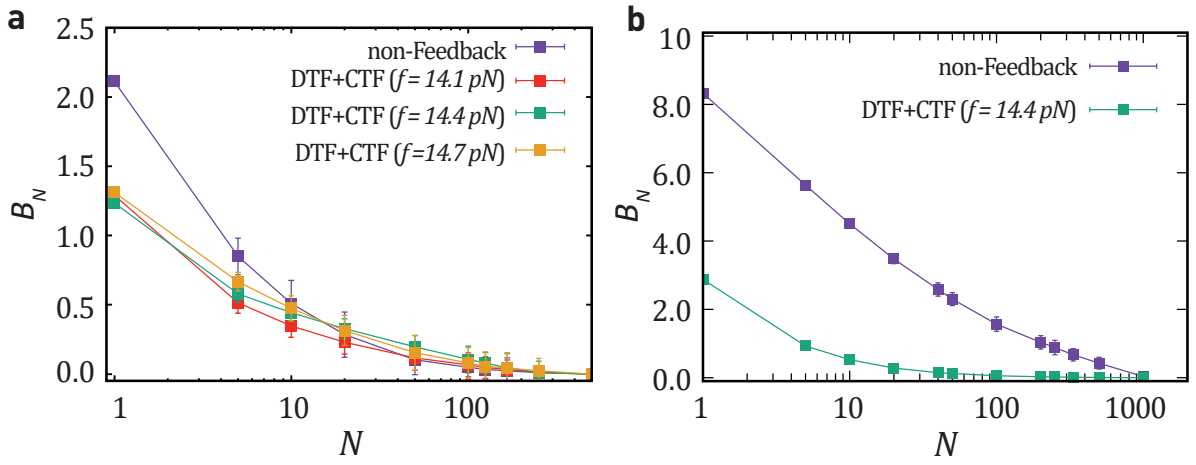

Figure S3: **Bias for the numerical simulation of the DTF+CTF strategy.** a) Bias for the DTF+CTF strategy using molecule L4. The molecule is initially pulled at $r_F = 4$pN/s with DTF until λ_1, where an observation is made. If the outcome is U then the pulling rate is switched to $r_U = 17$pN/s between λ_1 and λ_{max}. Instead, if the outcome is F the pulling rate is reduced to $r'_F = 1\text{pN/s} < r_F$ and the CTF protocol turned on. In this case, at the first unfolding event after λ_1, the pulling rate is switched to $r_U > r_F > r'_F$ until λ_{max}. In the DTF+CTF strategy both U- and F-trajectories contribute to dissipated work reduction. In the three different λ_1 the $\langle W_d \rangle$ is reduced by $\sim 1 k_B T$ respect the non-feedback case. b) Bias for DTF+CTF strategy applied to molecule L8 using the same pulling speeds than the ones used in panel a). In this case, for the studied specific conditions, the $\langle W_d \rangle$ is reduced by $\sim 6 k_B T$ respect the non-feedback case.

References

1. Evans, E. Probing the relation between force—lifetime—and chemistry in single molecular bonds. *Annu. Rev. Biophys.* **30,** 105–128 (2001).

2. Manosas, M. & Ritort, F. Thermodynamic and kinetic aspects of RNA pulling experiments. *Biophys. J.* **88,** 3224–3242 (2005).

3. Manosas, M. *Mechanical folding/unfolding of RNA molecules: Experimental facts and theoretical models* PhD thesis (Universitat de Barcelona, 2007).

4. Alemany, A. & Ritort, F. Determination of the elastic properties of short ssDNA molecules by mechanically folding and unfolding DNA hairpins. *Biopolymers* **101,** 1193–1199 (2014).

5. Koski, J. V., Kutvonen, A., Khaymovich, I. M., Ala-Nissila, T. & Pekola, J. P. On-chip Maxwell's demon as an information-powered refrigerator. *Phys. Rev. Lett.* **115,** 260602 (2015).