(Entropic) Stochastic Resonance in Biological Systems at Mesoscale

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As interconnected, flexible system it is, bio-soft matter manifests its own unique transition dynamics in a thermally fluctuating environment. The stochastic resonance (SR), a novel cooperative phenomenon due to coupling of an ambient noise and an external signal, is studied for a number of bio-soft matter systems such as ion channels and biopolymers. Due to the flexibility and susceptibility to thermal fluctuation, the systems manifest many new features of the entropic stochastic resonance.

What are the roles of thermal energy or noise

$k_B T$ (T : body temperature) **?**

Stochastic Resonance (SR):

A counter-intuitive phenomenon, where background noises (fluctuations) are not harmful but can be instrumental in enhancing synchrony and resonance of a nonlinear system to a small periodic signal.

A periodic signal so weak to be normally detected can be enhanced due to resonance and coherence between the signal and the noise.

[L. Gammatoni et al, *Review of Modern Physics 70,(1998)*].

Examples ; Periodic recurrence of an ice age , Benzi et al, J. Phys. A, 1981
-Climate Noise
; Crayfish enhancement of information transfer in crayfish mechanoreceptors, J. K. Douglass, Nature, 1993-Sound Noise

There are now a wide variety of SR manifestations and applications in nature and technology, such as signal processing, nonlinear optics, solid state devices, sensory neurons

Are there any SR for biological systems that live on thermal noise?

A simple example:

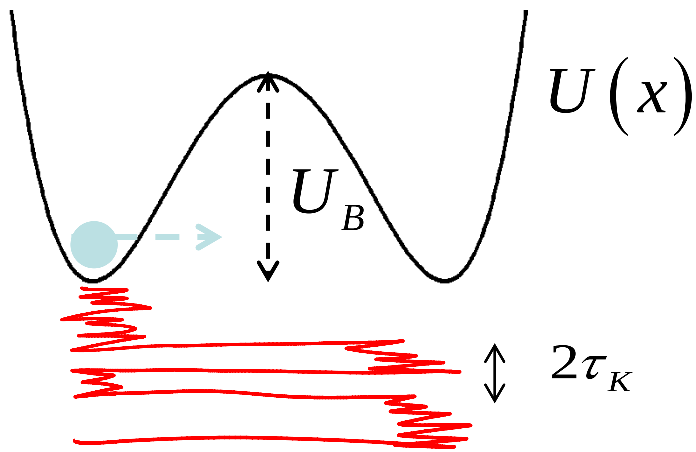
A Brownian Particle hopping in a double-well potential $U(x)$

$$\gamma \dot{x} = -\frac{\partial U(x)}{\partial x} + \xi(t)$$

a Gaussian, white noise

$$\langle \xi(t)\xi(0)\rangle = 2\gamma D\delta(t)$$

D: Strength of noise, $\boldsymbol{k_B T}$ for thermal cases



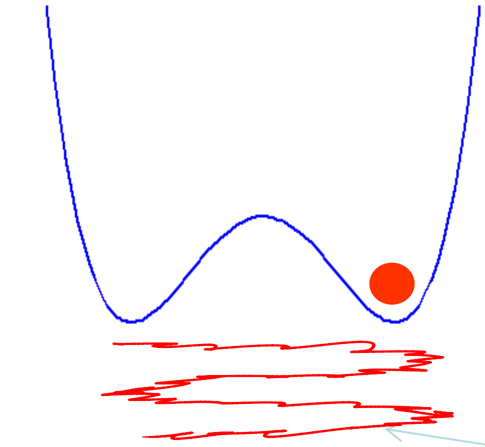
For $U_B \gg D$, the average (Kramers) rate of the barrier crossing is

$$R_K = \frac{\omega_0 \omega_B}{2\pi\gamma} e^{-\frac{U_B}{D}} \equiv \tau_K^{-1}$$

$\omega^2 = U''(x^*)$

Arrhenius

τ^K (D): The Kramers (mean crossing) time

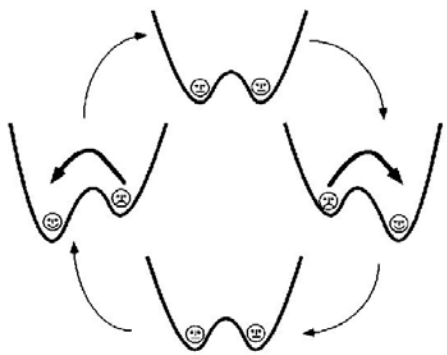


In the presence of a small time-periodic force

$$\gamma \dot{x} = -\frac{\partial U(x)}{\partial x} + F_0 \cos(\Omega t) + \xi(t)$$

At a non-vanishing optimal noise-strength D:

$$2\tau_K(D) \approx 2\pi/\Omega$$



the hopping dynamics tends to maximally coherent (synchronous) to the periodic driving.

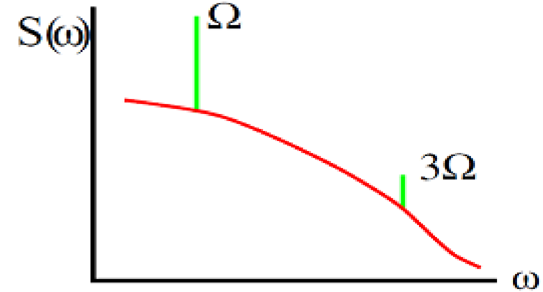
Measures of SR: 1) signal-to-noise ratio (SNR): Resonance

$$\mathrm{SNR} = S(\omega)/S_0(\omega)$$

Power spectrum

$$S(\omega) = \frac{1}{2\pi}\int_{-\infty}^{\infty} dt\, e^{i\omega t} < x(t)x(0) >$$

$$S_0(\omega) = \frac{1}{2\pi}\int_{-\infty}^{\infty} dt\, e^{i\omega t} < x(t)x(0) >_0$$



2) Power Amplification factor: $P = \frac{S(\Omega)}{(2\pi)^2 F_o^{\ 2}}$

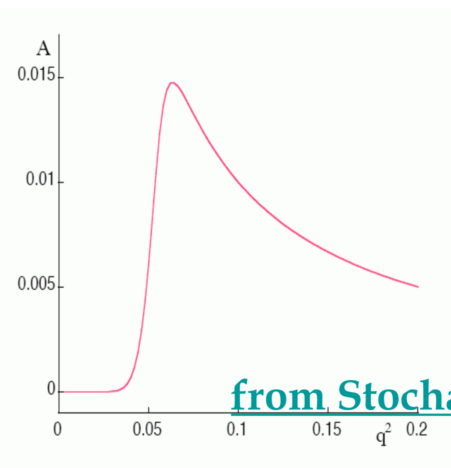
Linear Response Theory→

$$\langle x(t)\rangle == |\chi(\Omega,\mathcal{D})| F_o \cos(\Omega t - \phi)$$

$$P = |\chi(\Omega,\mathcal{D})|^2$$

tends to be at a maximum at $\tau_K(\mathcal{D}) \sim \Omega^{-1}$

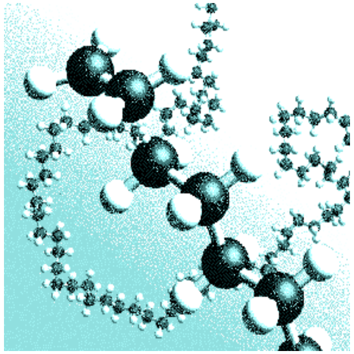
Maximum Power Amplification



from Stochastic resonance - Scholarpedia

The bio-soft matter lives on thermal fluctuations (noises). How about the SR in bio-soft matter ?

1)Bio-soft matter is flexible and susceptible to thermal fluctuation at ambient temperature.



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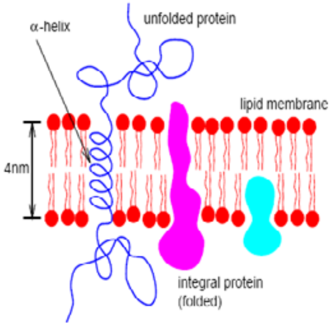
- **Interconnectivity → Cooperativity, Collective Excitations of Low Energies (~ $k_B T$ ~1/40 eV)**

- **Flexibilty due to**

Weak (Electrostatic) Interactions in WATER < 10 $k_B T$
***e.g.*,Hydrogen-Bonding, Hydrophobic/**
Hydrophilic Interactions,Van der Waals,
Screened Coulomb Interactions---



2) Added to the thermal fluctuation, there are plenty of athermal, nonequilibrium noises in vivo.

3) Can a particular mode out of the nonequilibrium noises, although weak, synchronize (SR) the transition dynamics of bio-soft matter systems?

Stochastic Resonance in Bio-Soft Matter

I. Stochastic resonance of a flexible chain crossing over a barrier

*EPL, **90** (2010)*

Mesfin Asfaw and W.S.

II. Stochastic resonance in an ion channel

*Eur. Phys. J. B **69**, (2009)*

Yong Woon Parc, Duk-Su Koh and W. S

III. The folding-unfolding transition dynamics of a stretched RNA hairpin,

PNAS 2012

Won Kyu Kim, Changbong Hyeon and W. S

IV. The Stochastic Resonance in a stretched wormlike chain,

JCP 2012

Won Kyu Kim and W. S.,

Coarse-Grained Descriptions

Mesoscopic degree of freedom ***q*** *(or a few* ***q's****)*

$$e^{-F(q)/k_BT} = Tr_{\Gamma/q}\, e^{-H(\Gamma)/k_BT}$$

The integration over all microscopic degrees of freedom but ***q***

The effective Hamiltonian or free energy function $F(q)$ must depend on temperature *T*. It has the entropic contribution.

A simple (Markovian) equation of motion for the **q(t)** is

$$\gamma \dot{q} = -\frac{\partial F(q)}{\partial q} + \xi(t)$$

$$< \xi(t)\xi(0) >= 2\gamma k_B T \delta(t)$$

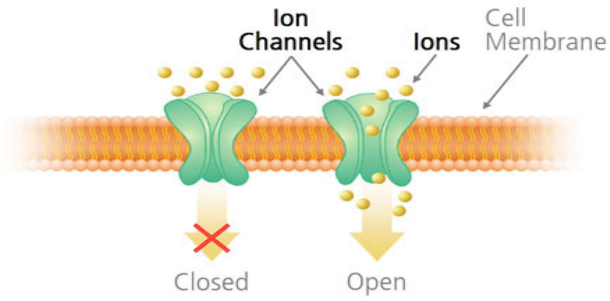
I. Stochastic resonance in an ion channel

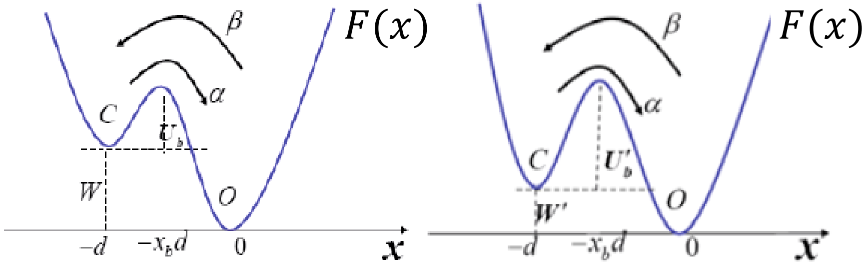
(*Y. W. Parc, D. Koh, W.S, EPJB, (2009)*)

1)A voltage gated ion channel can open and close depending upon external voltage .

2)Biological channels have flexible macromolecular structures(membrane proteins) so that they are susceptible to thermal (internal) noise, which can induce conformational transitions, dramatically affecting channel gating.

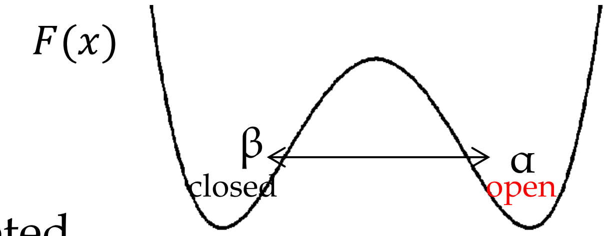
Two State-Free energy landscape and Gating





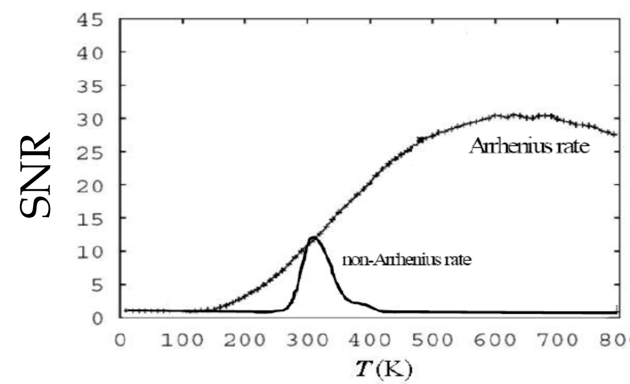
The reaction coordinate (degree of freedom) $q = x$ is the position of the gating charge.

SR in ion channel

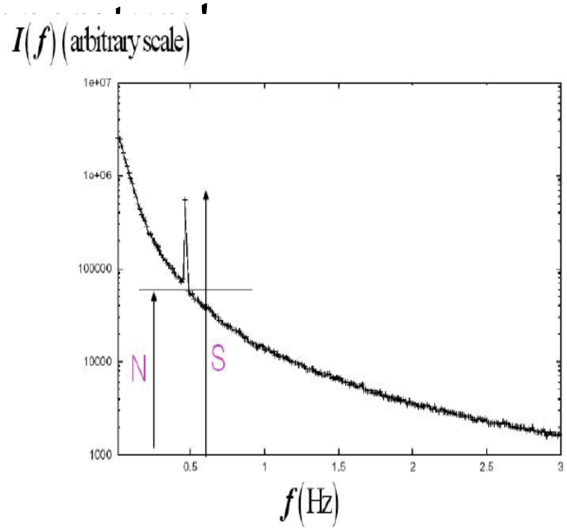


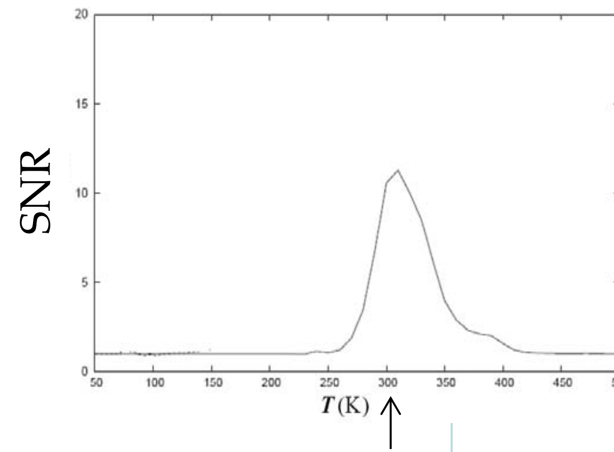
x= position of gate charge

The double well model for (non-Arrhenius) gating rates (open←→closed state) were adapted Using experimental data for guinea pig ileal muscle channels (on the half-activated voltage where the opening and closing rates are equal)



An SR occurs at T=310 K, which is just the pig’s body ter





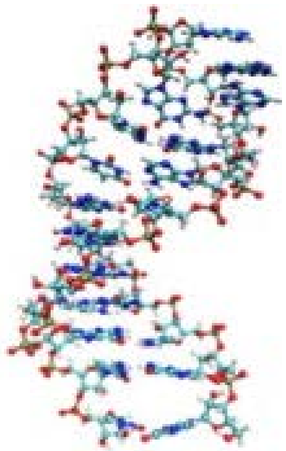
→Body temperature is not an accident but the outcome of nature’s selection!!

The SR peak at 310K

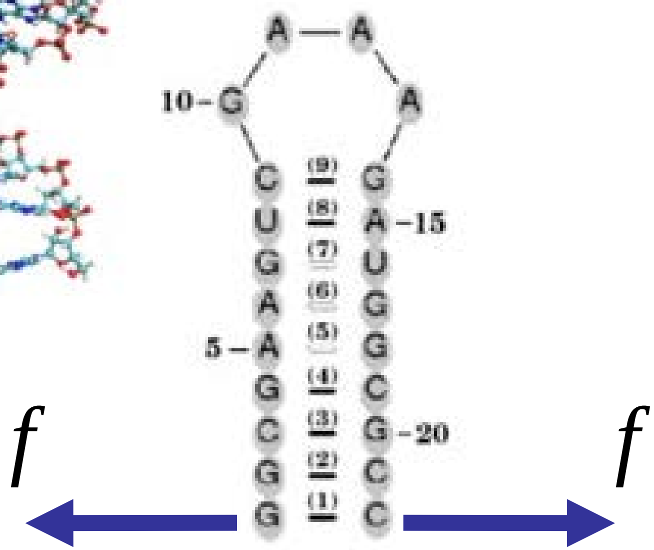
“The quest for the smoking gun proving that evolution itself has been directed by unavoidable ambient fluctuations---”

Eur. Phys. J. B **69, 1–3 (2009)**
Editorial: **Stochastic Resonance: A remarkable idea that changed our perception of noise**
L. Gammaitoni1, P. Hanggi, P. Jung, and F. Marchesoni

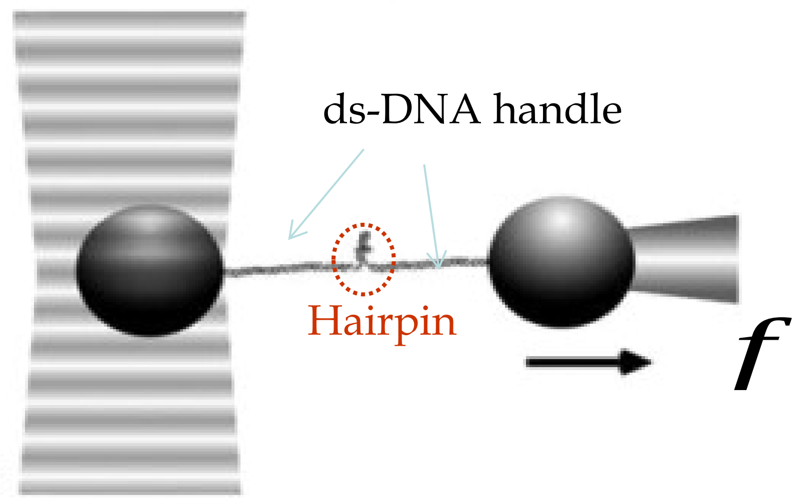
II. SR in a RNA hairpin under tension



e.g.) P5GA
RNA hairpin : 22 nucleotides (~10 nm)



RNA hairpin placed under tension in optical traps



[PNAS **103**, 6075(2006)]

Simulation via Self-Organized Polymer Model (SOP)

Coarse-grained molecular model [C.Hyeon et al, Biophys. J. 92, 731 (2007), PNAS 105, 9604 (2008)]

$$H_{SOP} = -\frac{kR_0^2}{2}\sum_{i=1}^{N-1}\ln\left[1-\frac{(r_{i,i+1}-r^o_{i,i+1})^2}{R_0^2}\right]$$

Chain elasticity (FENE)

$$+\sum_{i=1}^{N-3}\sum_{j=i+3}^{N}\epsilon_h\left[\left(\frac{r^o_{i,j}}{r_{i,j}}\right)^{12}-2\left(\frac{r^o_{i,j}}{r_{i,j}}\right)^{6}\right]\Delta_{i,j}$$

LJ potential for RNA native structure

$$+\sum_{i=1}^{N-3}\sum_{j=i+3}^{N}\epsilon_l\left(\frac{\sigma}{r_{i,j}}\right)^{6}(1-\Delta_{i,j})+\sum_{i=1}^{N-2}\epsilon_l\left(\frac{\sigma^*}{r_{i,i+2}}\right)^{6}$$

Self-avoidance

$N=22$, $k=20$kcal/(mol Å), $R_0=0.2$nm, $\varepsilon_h=0.7$kcal/mol, $\varepsilon_l=1$kcal/mol, $\sigma=0.7$nm, $\sigma^*=0.35$nm, $T=300$K

Overdamped Brownian dynamics simulation (SOP)

$$\vec{r}_{\alpha,i}(t+\Delta t)=\vec{r}_{\alpha,i}(t)+\frac{\Delta t}{\zeta}\left(-\frac{\partial H_{SOP}}{\partial r_{\alpha,i}}+f\delta_{i,22}\hat{e}_z+\vec{\xi}_{\alpha,i}(t)\right)$$

$$\vec{r}_{i=1}(t)=0$$

α : x,y,z, i : segment

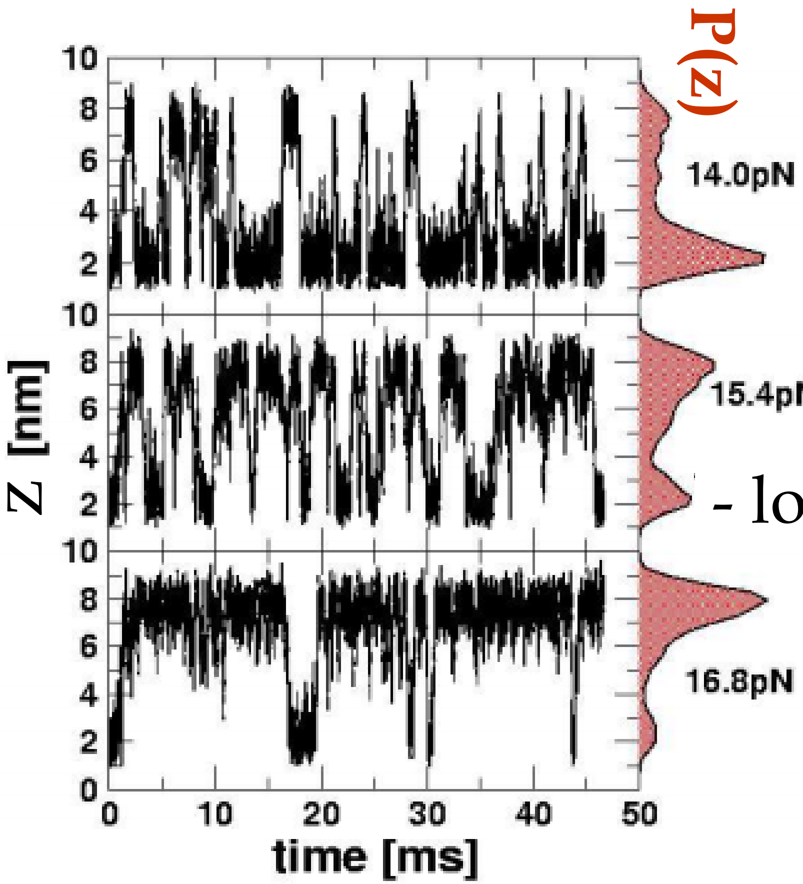
ζ : friction constant

Random noise

$$\langle\xi_{\alpha,i}(t)\xi_{\beta,j}(0)\rangle = 2\zeta k_B T\delta_{\alpha\beta}\delta_{ij}\delta(t)$$

Simulation : P5GA hairpin

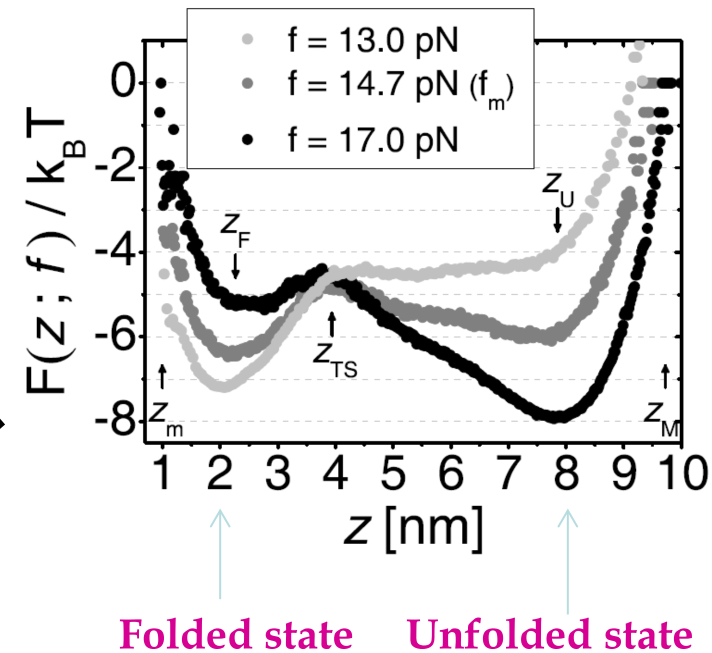
Extension Z vs. time
(simulation : P5GA (~10nm))



- log[P(z)]

=

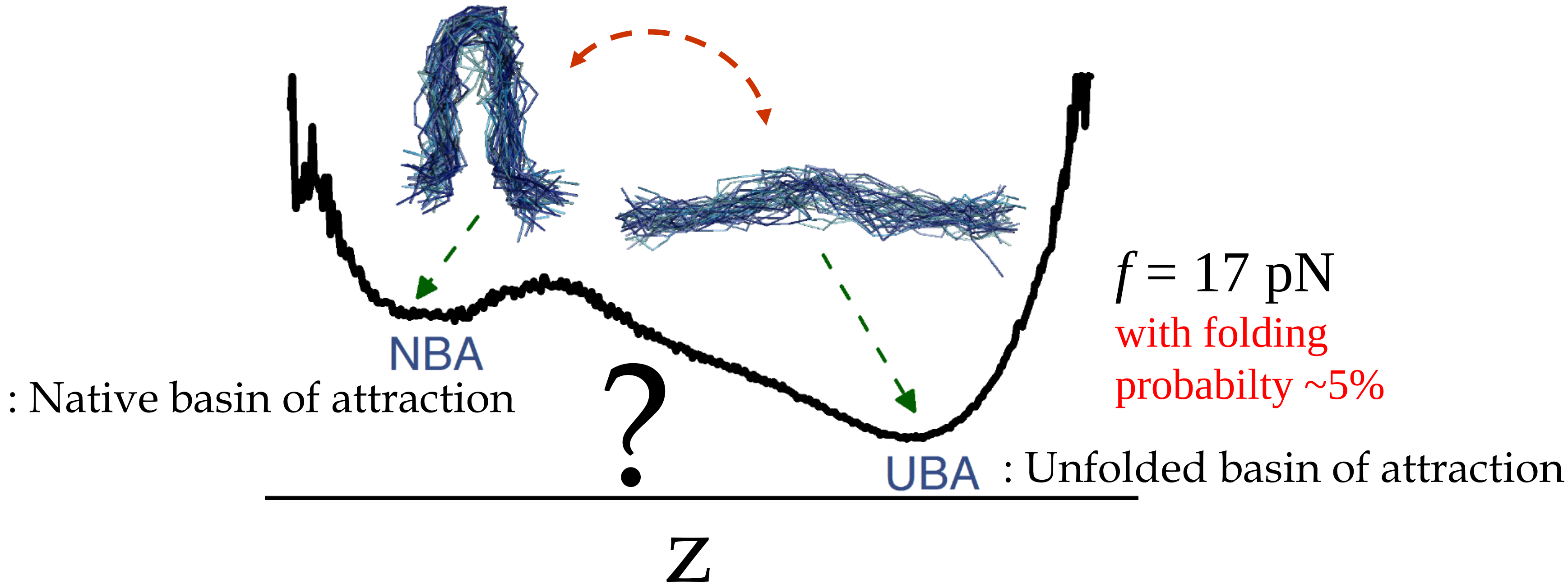
Free energy landscape



[C. Hyeon et al, CBSB07]

f_m :The tension where folding/ unfolding are equally probable

A QUESTION



$$f(t) = f_m + \delta f sin(\Omega t)$$

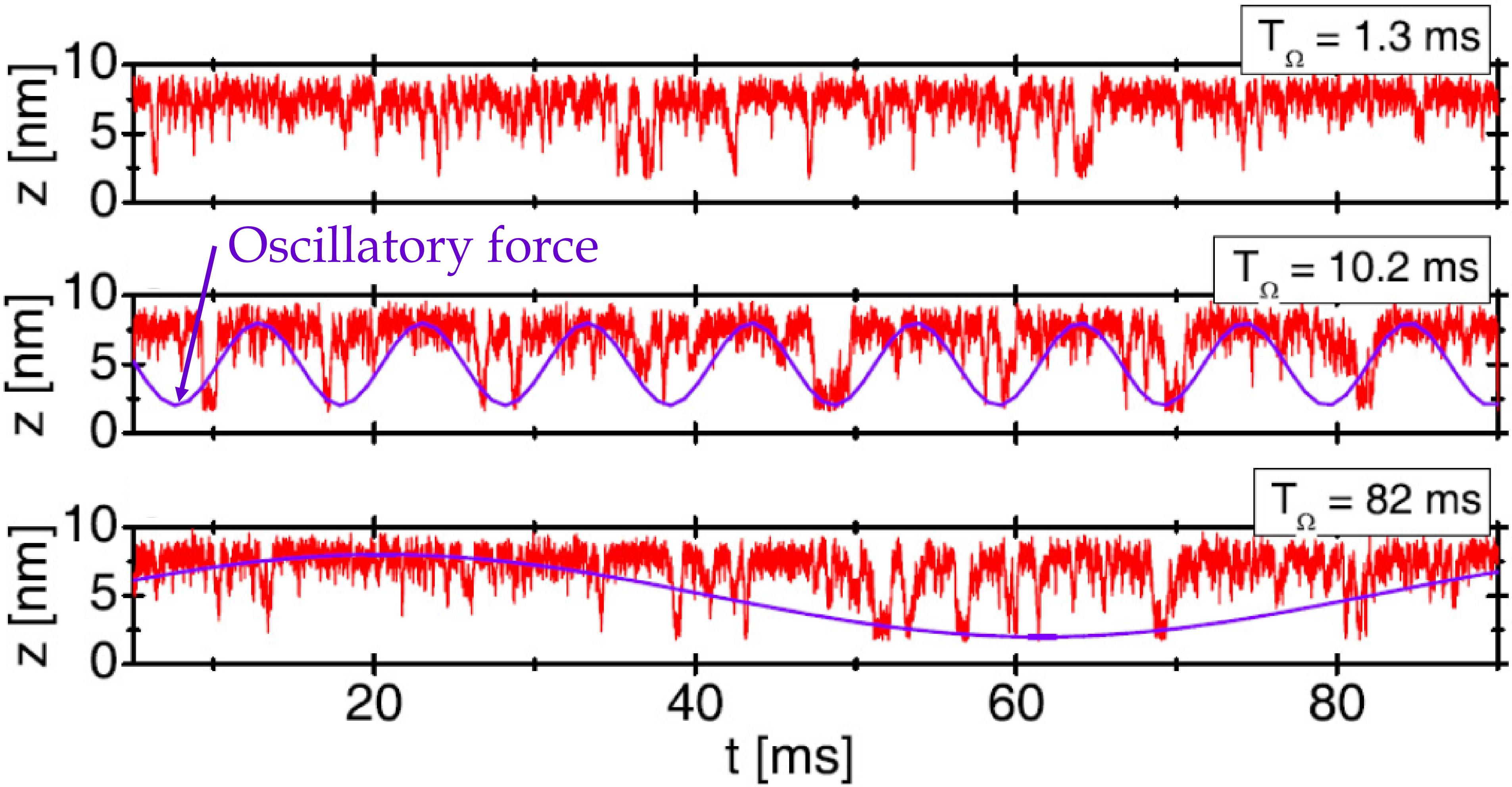
Can a small oscillatory force induce

1. coherent hopping transition(SR) to the folding state &

2. enhancement of folding transition (RA) ?

Coherent Transition (SR) in P5GA folding (SOP)

Coherent hopping transition under f = 17pN and δf = 1.4pN occurs at an **optimal** oscillatory period T_Ω = 10.2ms = $\tau_F + \tau_U$.



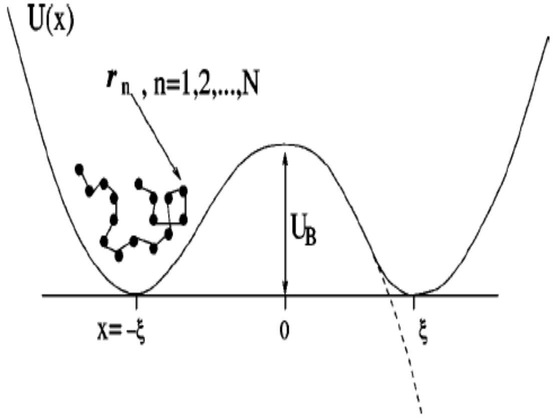
Single-Molecule Stochastic Resonance

K. Hayashi, S. de Lorenzo, M. Manosas, J. M. Huguet, and F. Ritort

Phys. Rev. X 2, 031012 – Published 24 August 2012

Stochastic resonance (SR) is a well-known phenomenon in dynamical systems. It consists of the amplification and optimization of the response of a system assisted by stochastic (random or probabilistic) noise. Here we carry out the first experimental study of SR in single DNA hairpins which exhibit cooperatively transitions from folded to unfolded configurations under the action of an oscillating mechanical force applied with optical tweezers. By varying the frequency of the force oscillation, we investigate the folding and unfolding kinetics of DNA hairpins in a periodically driven bistable free-energy potential. We measure several SR quantifiers under varied conditions of the experimental setup such as trap stiffness and length of the molecular handles used for single-molecule manipulation. We find that a good quantifier of the SR is the signal-to-noise ratio (SNR) of the spectral density of measured fluctuations in molecular extension of the DNA hairpins. The frequency dependence of the SNR exhibits a peak at a frequency value given by the resonance-matching condition. Finally, we carry out experiments on short hairpins that show how SR might be useful for enhancing the detection of conformational molecular transitions of low SNR.

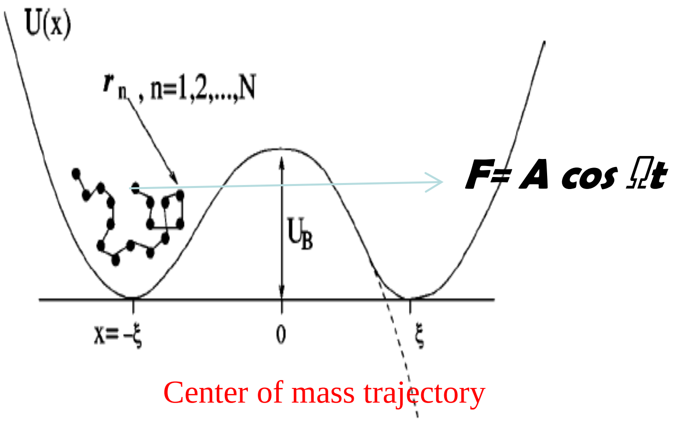
III. The Polymer Barrier Crossing



The rate of the crossing is enhanced due to the chain flexibility,
particularily in that it allow the conformational variability at the barrier top.
In particular when the chain is stretched at the barrier top, the longer chain can cross the barrier with a higher rate (99, JCP , P. J. Park & W.S, 2001, PRE, S. Lee and W.S.)

SR in Polymer Barrier Crossing

bead-spring model

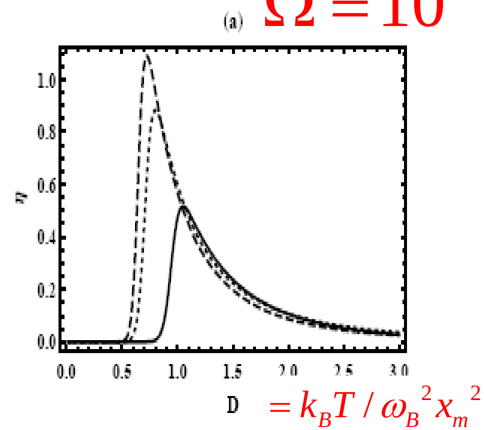


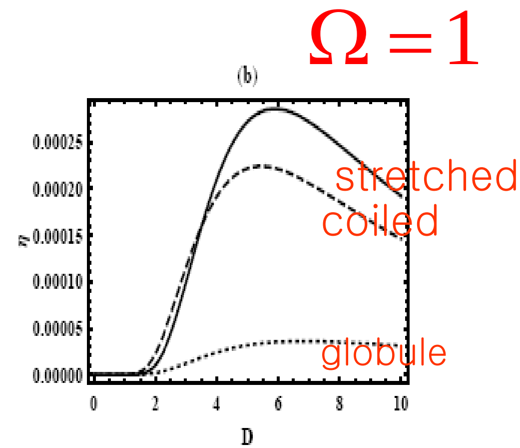
Coherence and Resonance with Minute External Forcing

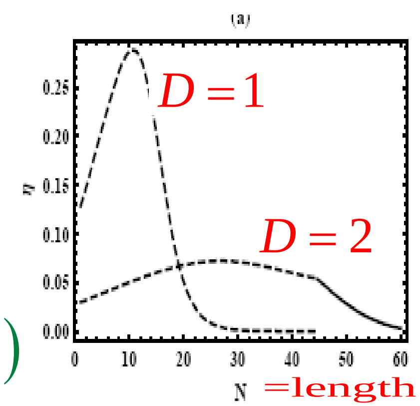
Power ampification factor

$$\eta = |\bar{\chi}(\Omega)|^2 = \left(\frac{\langle X^2\rangle}{D}\right)^2 \frac{4R^2(D)}{4R^2(D)+\Omega^2}$$

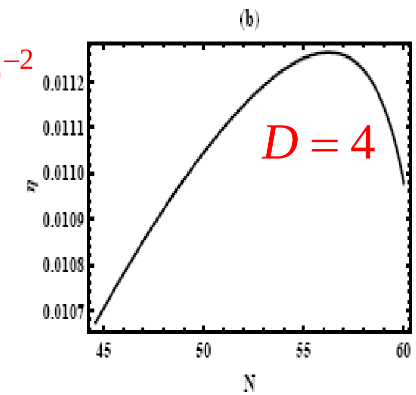
Power amplification







$\Omega = 10^{-2}$



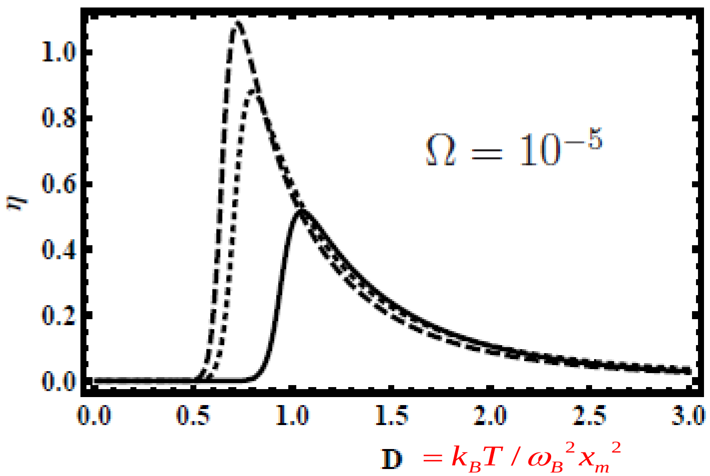
Random Hopping in the absence of a periodic driving

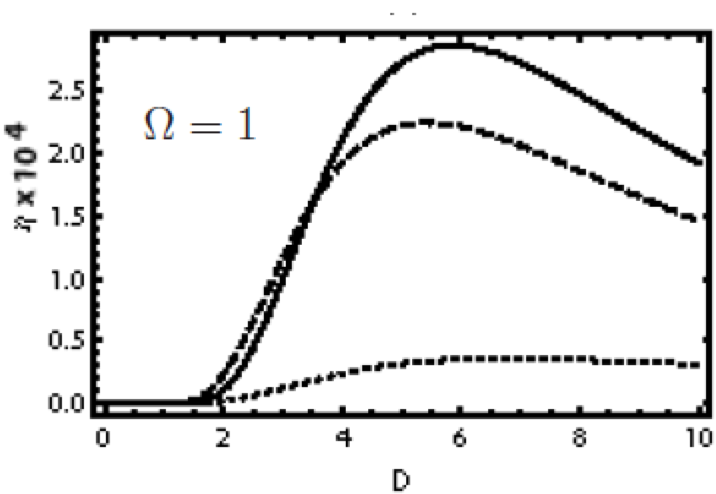
$$\bar{x}(t) = \chi(\Omega, D, N)\, AN \cos(\Omega t - \varphi)$$

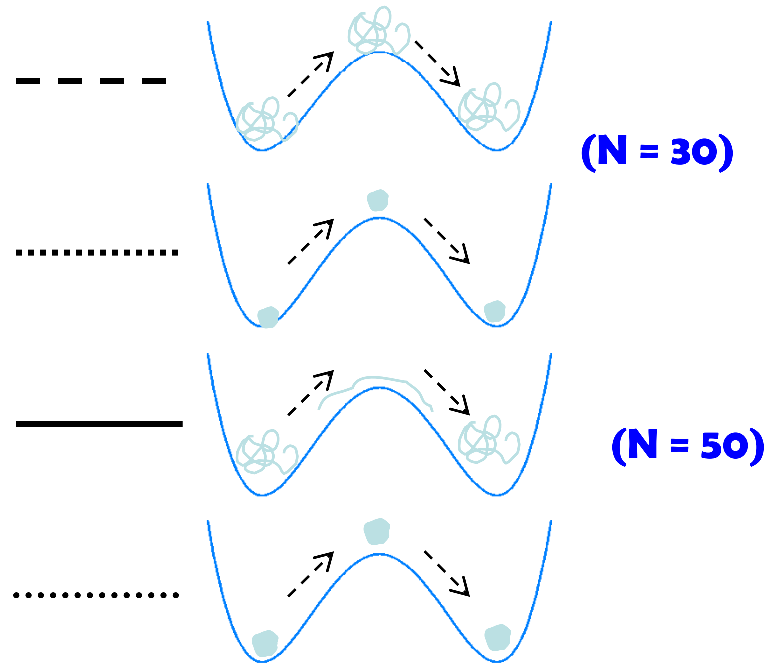
Coherent hopping to the driving at an optimal noise-strength, or an optimal chain length, or an optimal elastic constant

M.Asfew &WS –EPL 2010

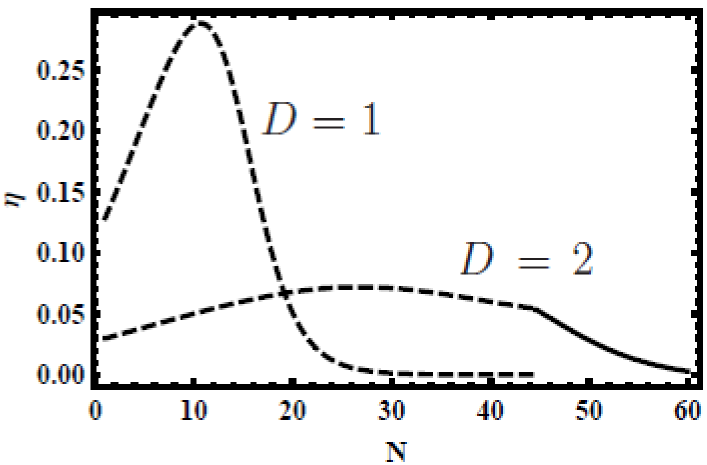
Transition Rate and Stochastic Resonance depend on the chain conformational variabilty



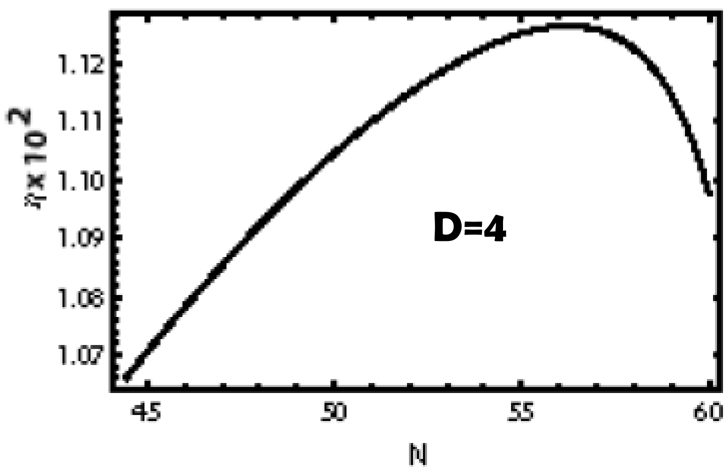


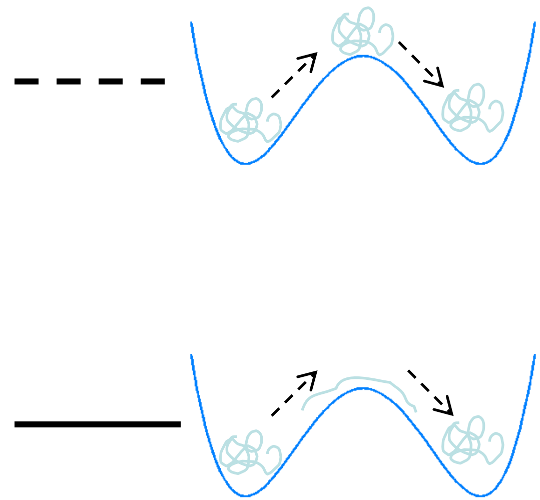


SR at an optimum chain length N



η **as a function of N**





Transition Rate and Stochastic Resonance depend on the chain conformational variabilty.

Conclusion

-Because the biological systems at mesocale live on thermal fluctuations, there are SR mechanisms with many unusual features (enhanced SR due to the structural connectivity and flexibility, selectivity of the temperature, chain length and other parameters.

-The SR is ubiquitous in bio-soft matter and can perhaps regulate the biological self-organization in various levels.