Lecture 4: Importance of Noise and Fluctuations

Jordi Soriano Fradera

Dept. Física de la Matèria Condensada, Universitat de Barcelona
UB Institute of Complex Systems

September 2016

1. Noise in biological systems

■ Generally, ‘noise’ in a living system refers to background fluctuations of diverse origin and structure that interact with the system of interest.

■ ‘Noise’ has a stochastic nature. Its exact value cannot be predicted along time, but it is bounded and can be mathematically quantified.

■ One distinguishes between intrinsic and extrinsic noise.

▫ **Intrinsic noise**: it results form the probabilistic character of the biochemical reactions. It is inherent to the dynamics of any genetic or biochemical system.

▫ **Extrinsic noise**: it is associated to random fluctuations in environmental parameters, e.g. cell-to-cell variability, temperature, pH,…

These sources of noise may overlap with the inherent nonlinear behavior of living systems (i.e. sensitivity to initial conditions and chaos). Identifying and quantifying all sources of observed variability may be impossible!

1. Noise in biological systems

Impossibility in isolating all sources of noise

Analyze the system and quantify the most important noise

Model the system including the effect of noise

You may get surprises!

Paradigm shift!

Noise may be the driver of system's behavior

(spontaneous patterns, neuronal activity)

The system is more efficient with noise

(genes, bacteria…)

What you identified as noise is actual system's behavior!

(brain's resting state)

2. Description of noise

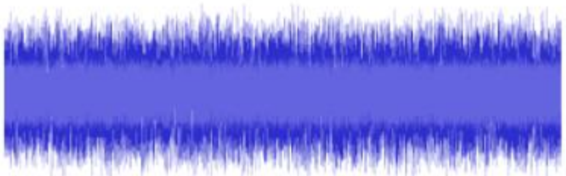
■ Noise is typically described in terms of its frequency contents or mathematical properties.

$$P(f) \sim f^{-\gamma}$$

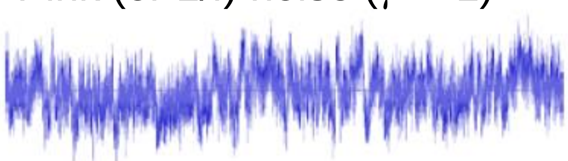
"characteristic" of the noise

intensity frequency

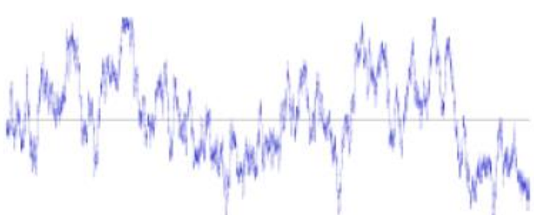
White noise (γ = 0)

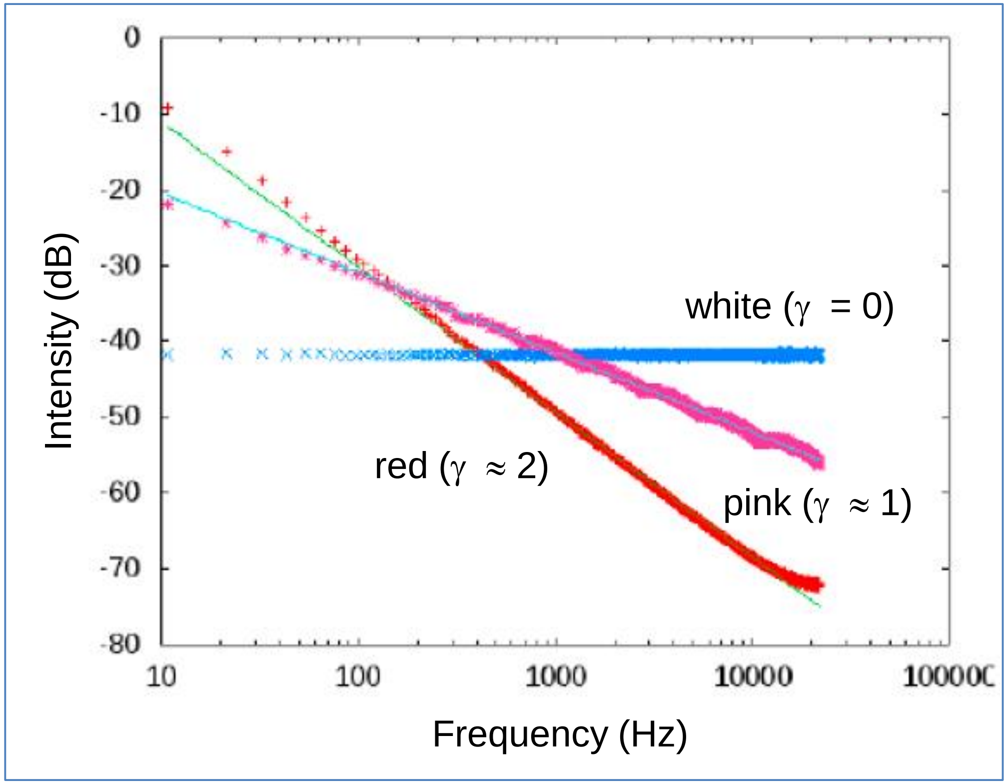


Pink (or 1/f) noise (γ = 1)



Red noise (γ = 2)





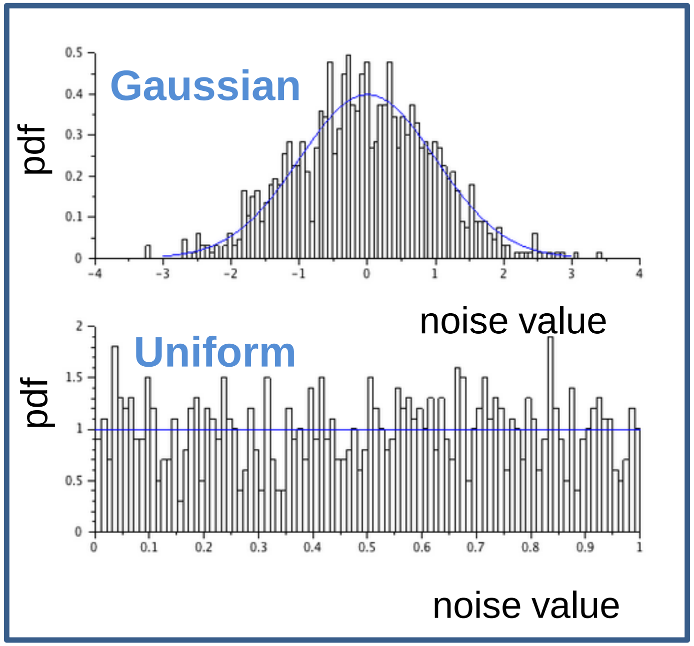
2. Description of noise

■ **White noise** if one of the most commonly used descriptors for fluctuations in biological systems.

▫ One distinguishes between **uniform white noise** and **Gaussian white noise**, depending on their distribution of values.

▫ **Gaussian white noise** reflects well fluctuations in the biological environment due to thermal agitation. It also accounts for measured variability in the state and behavior of biological units such as cells size, gene expression levels, concentration of proteins....

$$\xi(t) = \frac{1}{\sigma\sqrt{2\pi}} exp\left[\frac{-(t-\mu)^2}{2\sigma^2}\right]$$



Gaussian white noise is very useful to introduce variability in mathematical models

▫ White noise occurrence is treated as uncorrelated, i.e. $C(t,t') = \langle \xi(t)\, \xi(t') \rangle \simeq \delta(t-t')$

▫ **1/f noise** is also important, and has been measured in heart beat variability and neuronal populations firing.

3. Noise and equations: additive or multiplicative?

■ When modelling a biological system, noise can be introduced in the model either in an additive manner or in a multiplicative one. Both scenarios would lead to very different results!

▫ Depending on the model and the analysis of interest, one can use one way or the other, or both to account for different sources/interactions with noise.

Example 1: In a reaction-diffusion system, noise can be introduced additively to account for **fluctuations in the species**:

$$\begin{cases} \dfrac{\partial U}{\partial t} = f(U,V) + D_U \nabla x + \xi(U) \\ \dfrac{\partial V}{\partial t} = g(U,V) + D_U \nabla y \end{cases}$$

Example 2: Noise can be introduced multiplicatively to account for **fluctuations in the interactions**:

$$\begin{cases} \dfrac{\partial U}{\partial t} = f(U,V) \cdot \zeta(U) + D_U \nabla x \\ \dfrac{\partial V}{\partial t} = g(U,V) + D_U \nabla y \end{cases}$$

Example 3: Or can be included everywhere, even in space to account for a **changing environment**:

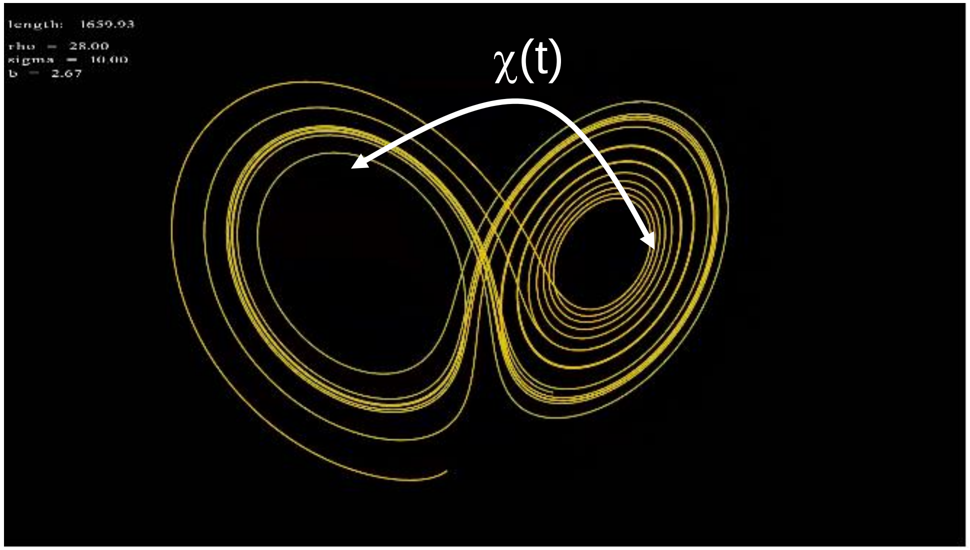
$$\begin{cases} \dfrac{\partial U}{\partial t} = f(U,V) \cdot \zeta(U) + D_U \cdot \nabla(x + \chi(x)) + \xi(U) \\ \dfrac{\partial V}{\partial t} = g(U,V) + D_U \cdot \nabla(y + \chi(y)) \end{cases}$$

4. In biophysics… think of noise in a positive way

From a **physical** perspective:

■ Noise helps dissipative linear systems (e.g. a harmonic oscillator with damping) to keep operating ➡ Linear systems are not useless anymore.

■ Noise cooperates with nonlinearity to enable and enhance key functions in the system ➡ Exploration by switching orbits and attractors.



■ Fluctuations in nonlinear systems are particularly efficient at the vicinity of bifurcations. Fluctuations can induce phase-transitions.

4. In biophysics… think of noise in a positive way

From a **biological** perspective:

■ Noise causes adaptability and promotes flexibility → Evolution → Survival.

■ Noise may drive dynamics at local levels and allow regular oscillations at the global level → Noisy neurons but reliable brain.

■ Noise enhances mobility and cooperativity among molecular machinery.

■ Noise enhances the detection of signals.

Let’s see some examples!

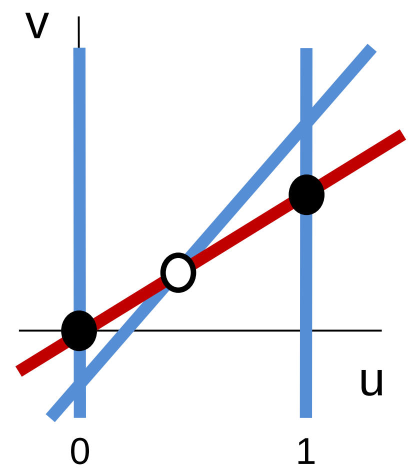
5. Action of noise in bistable systems.

■ Bistable systems are those that switch from two stable fixed points. Noise facilitates that the system switches from one to another **without** any external drive or control.

■ However, in bistables systems, noise shapes a new scenario: **excitability.**

■ Consider the following beautiful model:

$$\begin{cases} \dfrac{\partial u}{\partial t} = \dfrac{1}{\varepsilon} f(u,v), \\[2ex] \dfrac{\partial v}{\partial t} = g(u,v), \end{cases} \qquad \begin{cases} f(u,v) = u(1-u)\left(u - \dfrac{v+b}{a}\right), \\[2ex] g(u,v) = \gamma u - v, \end{cases}$$



▫ Analysis of the nullclines:

u-nullcline: $u(1-u)\left(u - \dfrac{v+b}{a}\right) = 0 \longrightarrow \begin{cases} u = 0 & \forall\, v \\ u = 1 & \forall\, v \\ v = au - b. \end{cases}$

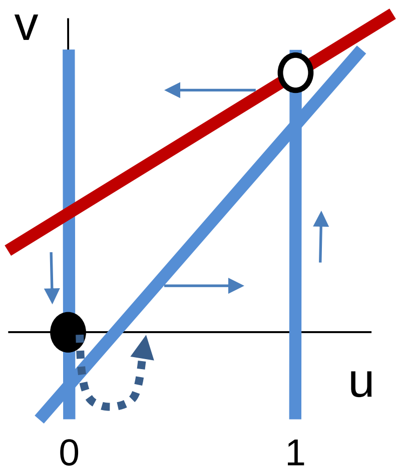
2 stable
1 unstable

v-nullcline: $\longrightarrow \quad v = \gamma u.$

5. Action of noise in bistable systems.

■ In this conditions the system will fluctuate between the two fixed points.

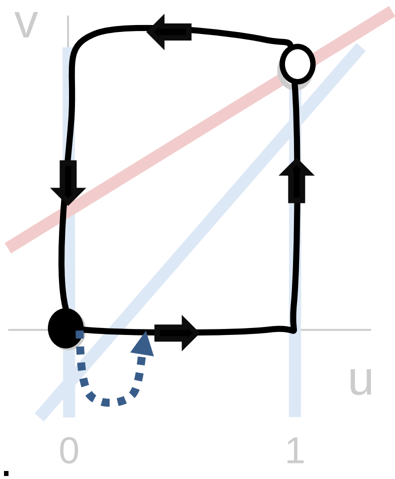
■ However, if the v-nullcline goes up, there are only 1 stable and 1 unstable.



▫ We now pay attention to the vector fields. If the system moves towards the right and crosses the u-nullcline it will make an excursion and come back to the fixed point. This is known as **excitable behavior**!

5. Action of noise in bistable systems.

- In this conditions the system will fluctuate between the two fixed points.
- However, if the v-nullcline goes up, there are only 1 stable and 1 unstable.



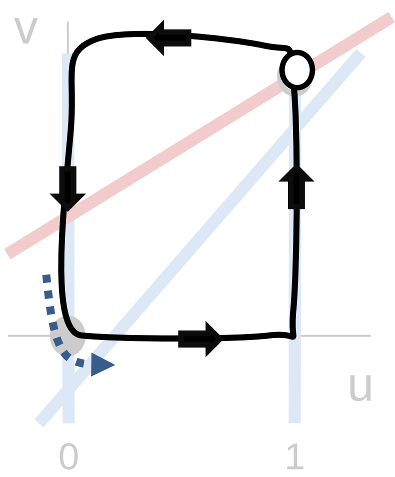
▫ We now pay attention to the vector fields. If the system moves towards the right and crosses the u-nullcline it will make an excursion and come back to the fixed point. This is known as **excitable behavior**!

▫ Noise naturally drives the system to a state to start the excursion.

▫ **Neurons are excitable cells**, so noise allows them to spontaneously fire.

▫ The addition of noise in *u* opens a completely new dynamic scenario.

$$\begin{cases} \dfrac{\partial u}{\partial t} = \dfrac{1}{\varepsilon} f(u,v) + \dfrac{\partial^2 u}{\partial x^2} + \xi(u,t) \\ \dfrac{\partial v}{\partial t} = g(u,v), \end{cases}$$

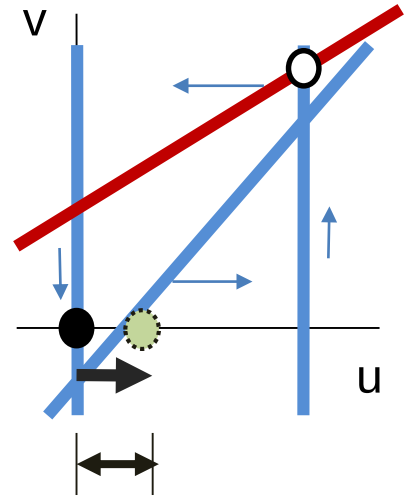


▫ If the noise is very strong, the system can be in a **perpetual oscillatory state**, i.e. never resting.

5. Action of noise in bistable systems.

■ This model also helps illustrating an important concept in neuroscience: the threshold for firing.

The system has to be driven to the unstable region to start the excursion as an excitable cell.



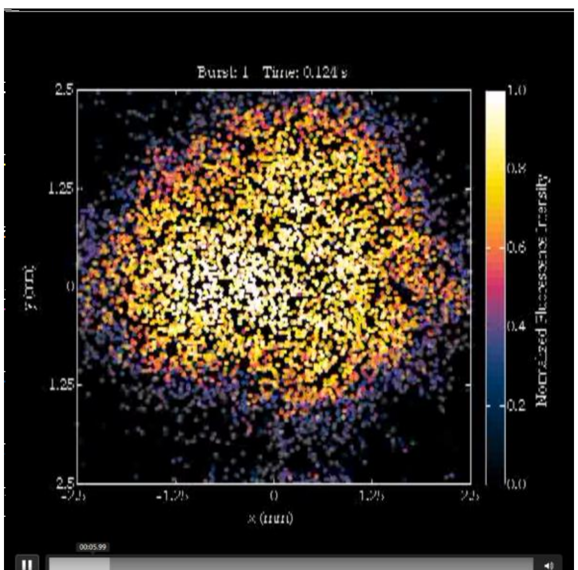
threshold for firing

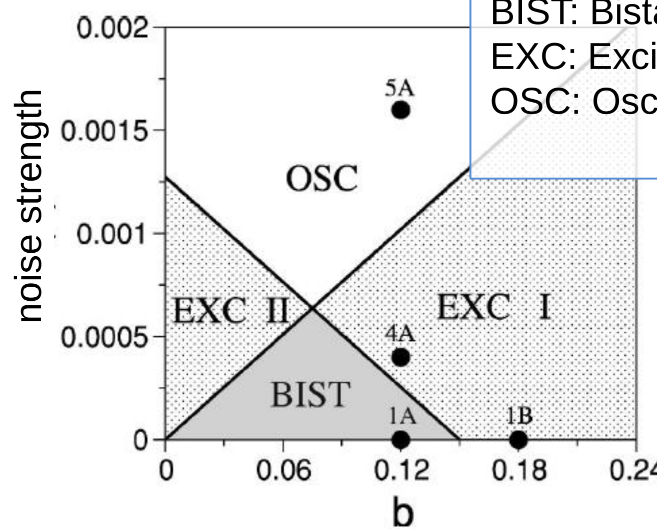
5. Action of noise in bistable systems.

▫ These mechanisms allow a neuronal system to be always active without the need of an external clock, and in general allow bistable systems to be much more powerful.

▫ The strength of the noise, combined with the parameters of the model allow for a very rich dynamics.

▫ Note that by adding diffusion we can naturally create traveling pulses in the excitable and oscillatory states, and **maintained by noise**.





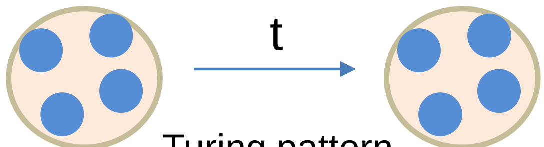
BIST: Bistable
EXC: Excitable
OSC: Oscillatory

6. Action of noise in reaction-diffusion systems

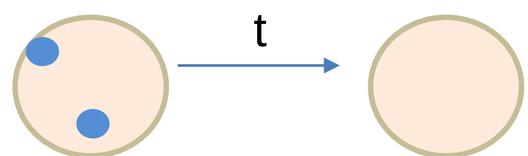
■ We have seen that RD systems only need small fluctuations in the concentration of species to trigger the formation of a pattern.

$$\begin{cases} \dfrac{\partial U}{\partial t} = f(U,V) + D_U \nabla x + \boxed{\xi(U)} \\ \dfrac{\partial V}{\partial t} = g(U,V) + D_U \nabla y \end{cases}$$

■ However, noise can induce the formation of transitory patterns, a feature observed in experiments, in which spots of some species appear in the cell membrane.



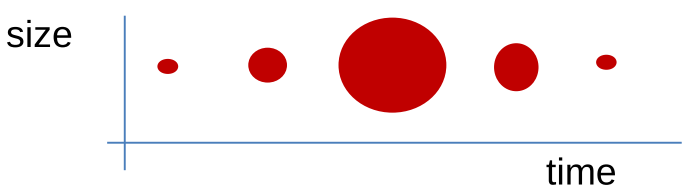
Turing pattern
(maintained in time)

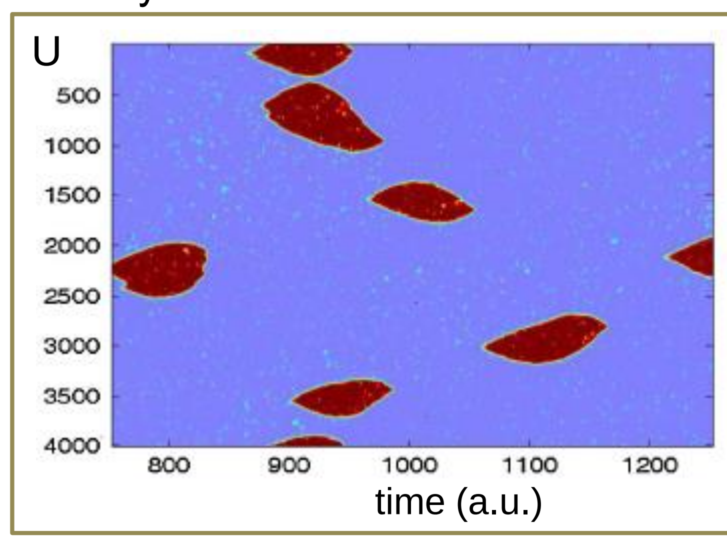


transient spots

▫ Transient spots are important for "surveillance" of the activity in the membrane.

▫ In Turing, spots typically appear for $D_V >> D_U$ (long range activator, short range inhibitor). Since cells can control diffusion, for $D_V \sim D_U$ noise suffices to provide an overshoot of U, leading to unstable spots but that survive for sufficient time.





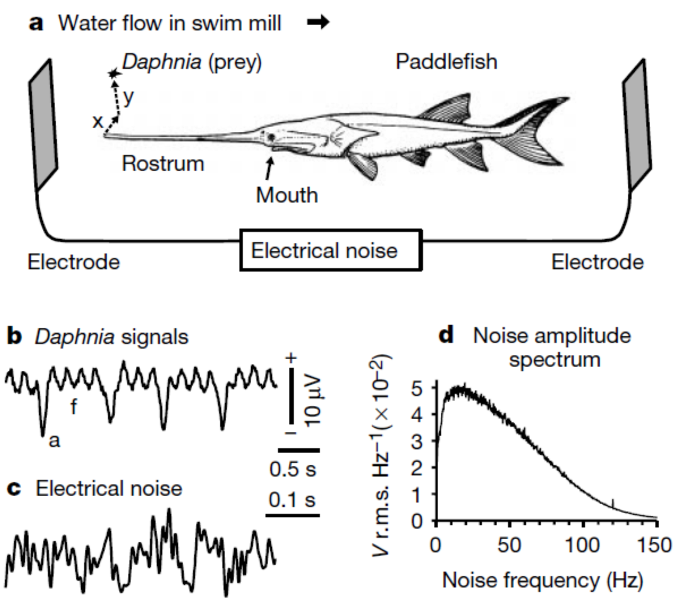
7. Stochastic resonance

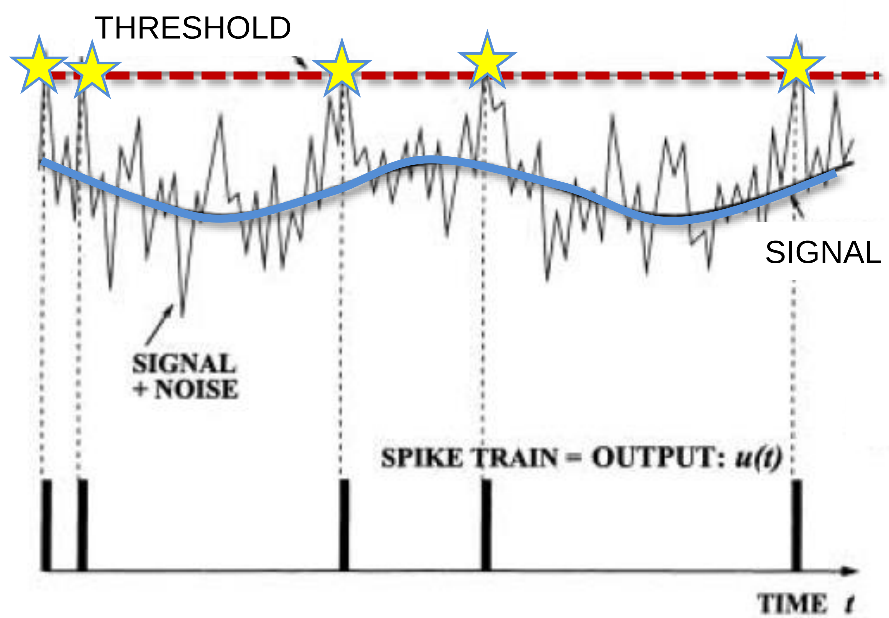
■ Stochastic resonance (1981) is the detection of small signals thanks to noise. It became popular in the context of neuroscience.

▫ Conceptually, a periodic signal of low amplitude do not lead to neuronal firing since it is below threshold.

But noise in the environment stochastically increases the strength of the signal and, at its peaks, the probability to cross the threshold is very high!

▫ SR experimental evidence was obtained when studying paddlefish and its detection of prey.

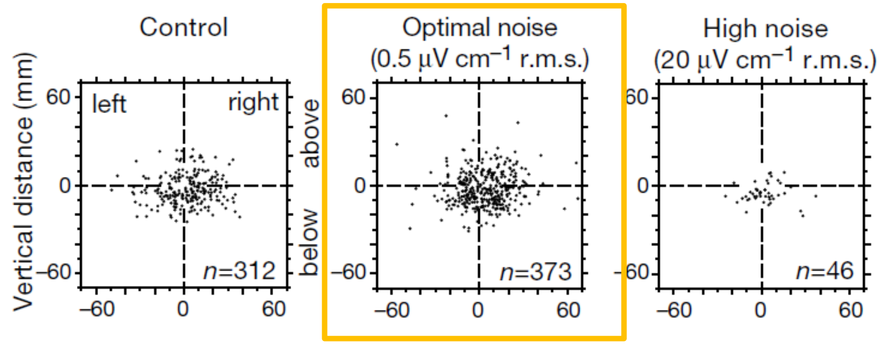




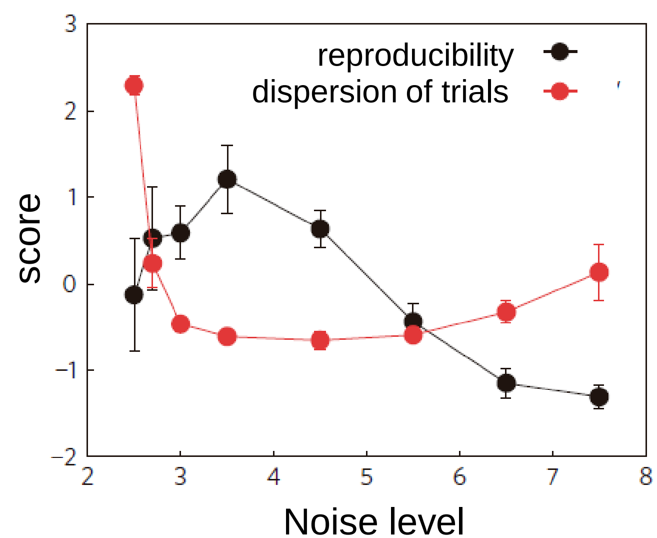
7. Stochastic resonance

▫ Noise has a range for optimal response of the system. This is a crucial aspect, and from here the term “resonance”.

- If the noise is too high, the response is noisy as well (and useless).
- If the noise is too low, no enhancement.



▫ In the last years, the term **‘stochastic facilitation’** has been introduced to refer to all those cases in which noise enhances response. Recent experiments in neuroscience showed for example that memory retrieval is enhanced by noise.

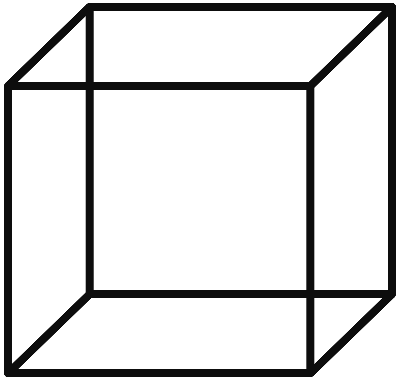


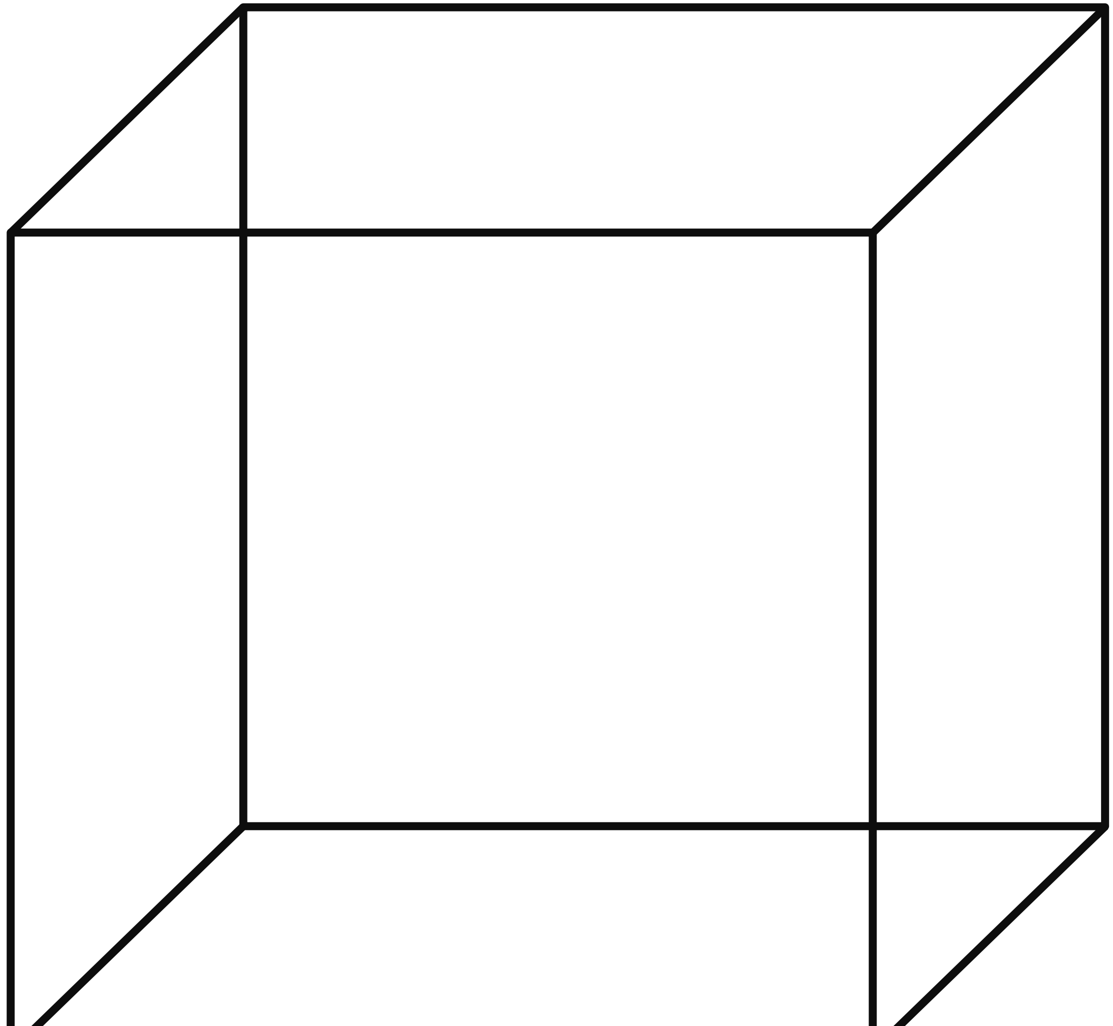
7. Stochastic resonance

■ Stochastic resonance has been extended to other scenarios, and it is viewed as an important evidence that evolution found strategies to take **advantage of noise for optimizing sensory transduction**.

▫ SR has been also observed in blood pressure control by the brain, and there has been hypothesized the existence of SR mechanisms at a molecular level

■ There is an interesting game in cognitive neuroscience illustrating SR. The shown cube makes the brain switch between two perceptions: “the cube goes deep into the plane of the screen”, or the “cube goes out the plane”. However, our brain cannot lock on any of the two configurations, except if noise is introduced and the top face changes color.



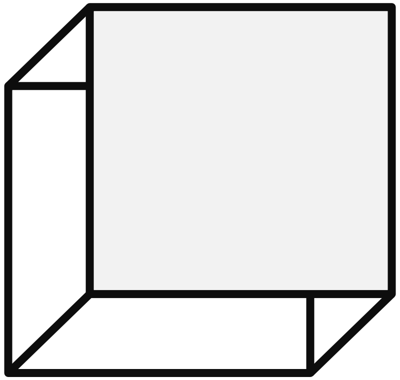


7. Stochastic resonance

■ Stochastic resonance has been extended to other scenarios, and it is viewed as an important evidence that evolution found strategies to take **advantage of noise for optimizing sensory transduction**.

▫ SR has been also observed in blood pressure control by the brain, and there has been hypothesized the existence of SR mechanisms at a molecular level

■ There is an interesting game in cognitive neuroscience illustrating SR. The shown cube makes the brain switch between two perceptions: “the cube goes deep into the plane of the screen”, or the “cube goes out the plane”. However, our brain cannot lock on any of the two configurations, except if noise is introduced and the top face changes color.



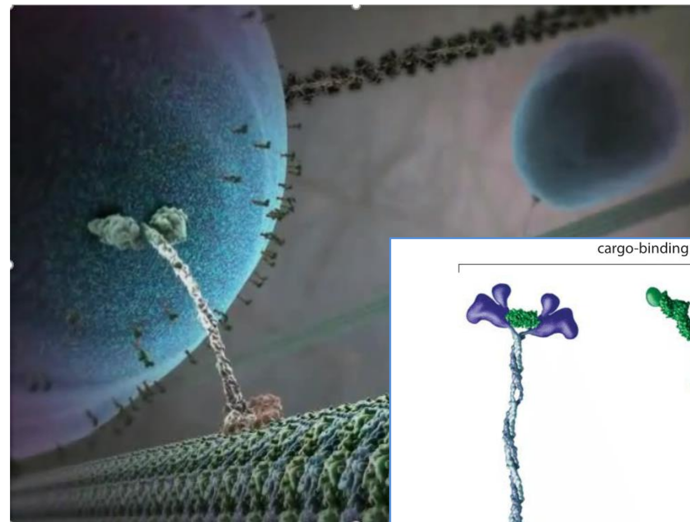
8. Action of noise in molecular machinery

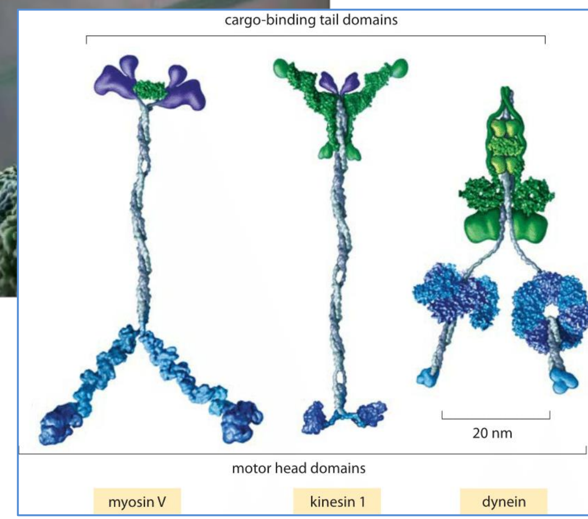
■ Molecular motors transport cargo across the cell, and by ‘walking’ on dedicated structures called microtubules.

▫ In the simplest scenario, walking requires to overcome a ratchet-like periodic potential. The ratchet prevents the motor to go back.

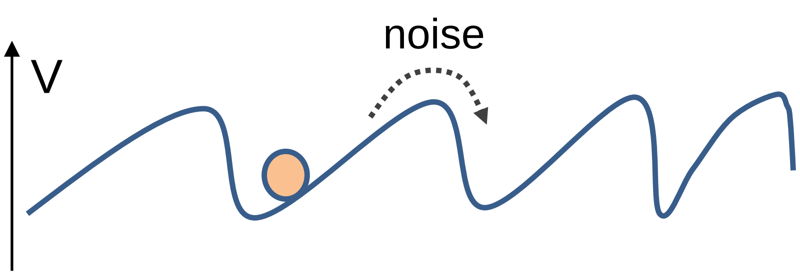
▫ Motors are often modeled as Brownian particles, so they were always seen as inefficient.

▫ Findings show that motors’ efficiency and motors’ velocity are substantially increased thanks to noise.





	Kinesin	Automobile
Size	10^{-8} m	1m
Speed	4×10^{-3} m/hr 4×10^{5} lengths/hr	10^{5} m/hr 10^{5} lengths/hr
Efficiency	~70%	~10%



8. Action of noise in molecular machinery

▫ A typical model introduces noise as thermal fluctuations in the effective diffusion of the particle. Models compared the behavior of the particle between a constant driving force and a stochastic force.

$$\begin{cases} \ddot{x} + \gamma \dot{x} = -V'(x) + a\cos(\omega t) + \sqrt{2\gamma D_T}\,\xi(t) + F, \\ \ddot{x} + \gamma \dot{x} = -V'(x) + a\cos(\omega t) + \sqrt{2\gamma D_T}\,\xi(t) + \eta(t), \end{cases}$$

External driving force

friction

potential

Particle ‘engine’

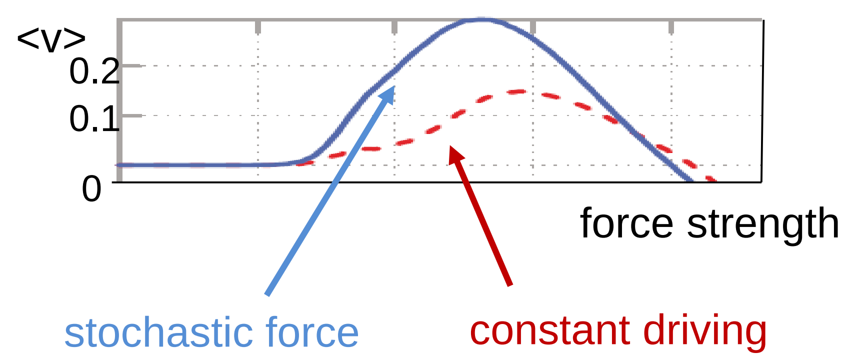
Diffusion with thermal (Gaussian) noise

Stochastic force:
(random sequence of pulses)

$$\begin{cases} \eta(t) = \sum_{i=1}^{n(t)} z_i \delta(t - t_i) \\ \langle \eta(t) \rangle = F. \end{cases}$$

▫ Calculations are difficult, but results showed that the stochastic force amplifies the ’engine’, as a resonator, increasing global efficiency and velocity.

▫ This problem illustrates the complex interplay between nonlinear dynamics and stochasticity.



End of lecture 4

TAKE HOME MESSAGE:

- Noise or stochastic fluctuations can be coupled to the behavior of nonlinear systems to give rise to new, richer scenarios.

- Noise plays an important role in biological complexity, adding variability and resources for exploration. Noise may lead a bistable system to switch faster, a bistable system to become excitable, or reaction-diffusion mechanisms to exhibit richer behaviors.

- Stochastic facilitation is a remarkable example of how Nature has taken a good advantage of noise, either for feeding or memory retrieval.

Questions and discussion aspects:

- How about the negative side of noise?

- Can we use noise in linear systems to account for variability and richer phenomenology (and forget nonlinear dynamics)?

- Has Nature adopted mechanisms to control an excess of noise? Would life be impossible in an environment too noisy?

References

▫ F. Sagués et al., “Spatiotemporal order out of noise”, Rev. Mod. Phys. (2007).
▫ J. Spiechowicz et al., “Brownian motor efficiency enhanced by nonequilibrium noise”, International Conference on Noise and Fluctuations (2015).
▫ B. Sancristóbal et al., “Collective stochastic coherence in recurrent neuronal networks”, Nat. Phys. (2016).
▫ I. Goychuk et al., “How Molecular Motors Work in the Crowded Environment of Living Cells: Coexistence and Efficiency of Normal and Anomalous Transport”, PLoS One (2014).
▫ Y. Pilpel, “Noise in Biological Systems: Pros, Cons, and Mechanisms of Control”, J.I. Castrillo, S.G. Oliver (eds.), *Yeast Systems Biology*, Methods in Molecular Biology 759 (2011).
▫ Peter Hänggi, “Stochastic Resonance in Biology”, ChemPhysChem (2002).
▫ David F. Russell, “Use of behavioural stochastic resonance by paddle ®sh for feeding”, Nature (1999),
▫ A.A. Faisal et al., “Noise in the nervous system”, Nat. Rev. Neurosci. (2008).
▫ J. Garcia-Ojalvo, “Noise-enhanced excitability in bistable activator-inhibitor media”, Phys. Rev. E (2001).
▫ I. Hecht et al., “Transient Localized Patterns in Noise-Driven Reaction-Diffusion Systems”, Phys. Rev. Lett. (2010).