UNIVERSITÀ DEGLI STUDI FIRENZE

# Complex systems: physics beyond physics.

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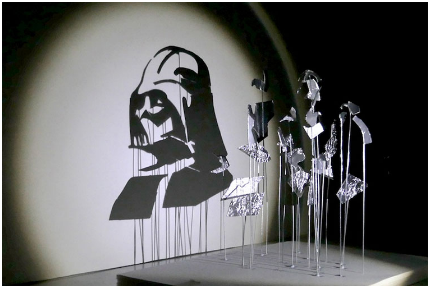
# Defining complex systems...

Complex systems is a broad term which defines a research approach to problems in many diverse disciplines.

1. Complex systems are many body systems, which exhibit emergent collective behaviours.
2. The collective behavior of their parts entails macroscopic properties that can hardly be inferred from the microscopic rules of interactions.

# The challenge.



*The whole is more than the sum of its parts* (Aristotle)

- Bridging the gap between the microscopic and macroscopic realms
- Build mathematical models of the examined problem.
- The model oughts to be simple but bear predictive power (reductionistic approach).
- Self-organization at different spatial and temporal scales

# A gallery of examples I: active matter.

Herd of sheep behaves like a fluid.

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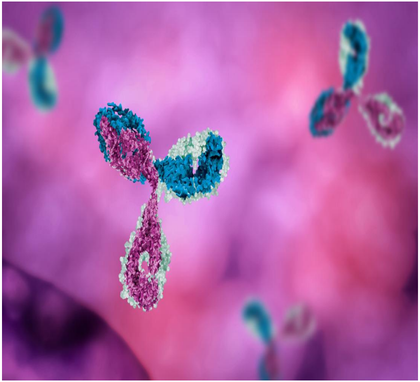
Flocking of starlings yields coherent patterns.

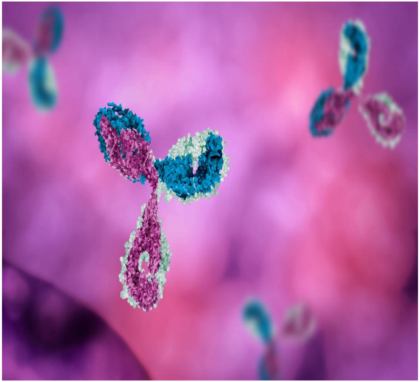
# A gallery of examples I: active matter.

Simulating the flocking in silico (courtesy of F. Ginelli).

Flocking of sterling form coherent patterns.



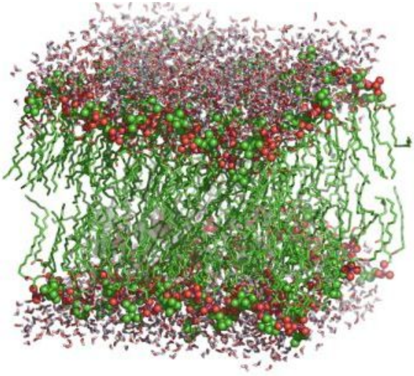
Large scale dynamics of an antibody.

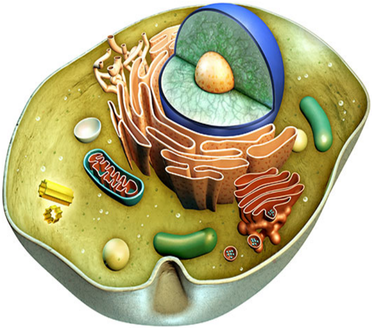


Large scale dynamics of an antibody.

ATP fueled walk of molecular motors on actin filaments.

# A gallery of examples II: biology and life sciences

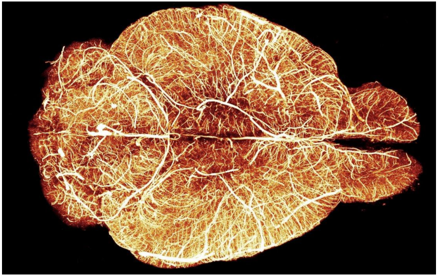




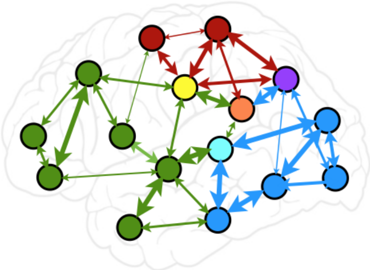
From the spontaneous assembly of lipid membranes....

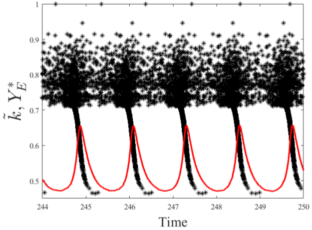
...to the complex functioning of the cellular machinery.

# A gallery of examples III: neuroscience.



Interlaced dynamics of large neuronal population (courtesy of L. Silvestri).



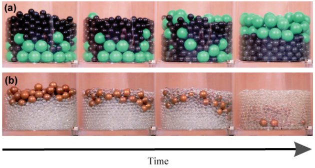


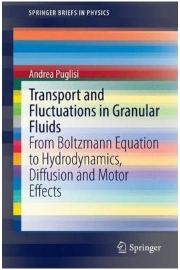

The average fields show ***global activity events***.

# A gallery of examples IV: synchronicity.

Spontaneous synchronization.

1. Oscillations are central for life (neurons, circadian clocks)
2. Individual oscillations should be coordinated to operate a system in unison.




Crowd dynamics: experiments and theory.

Granular on a vibrating plate.

# Summing up...

Investigating the dynamical evolution of an ensemble made of microscopic entities in mutual interaction constitutes a rich and fascinating problem, of paramount importance and cross-disciplinary interest.

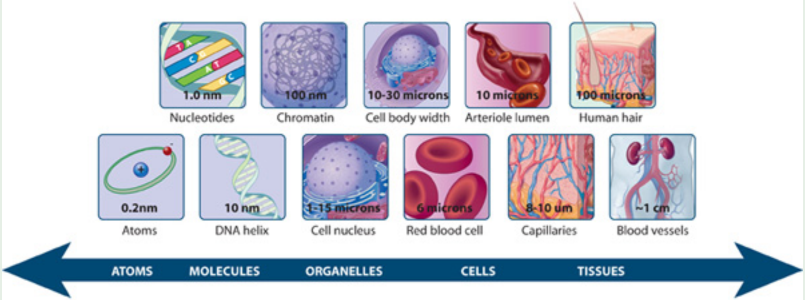
**Spontaneous self-organization**

- Complex microscopic interactions can eventually yield to macroscopically organized patterns.
- Temporal and spatial order manifests as an emerging property of the system dynamics.

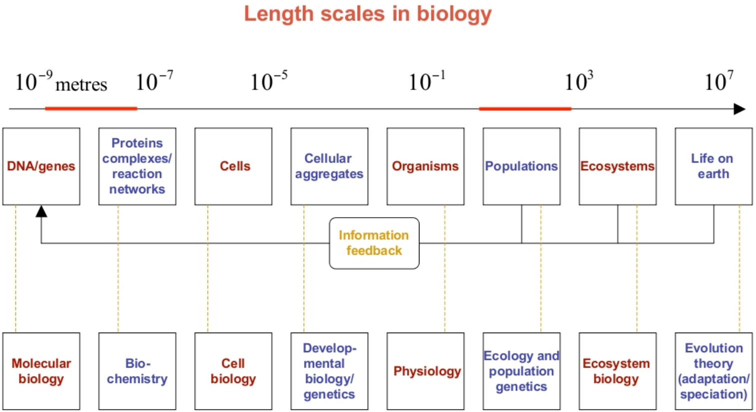
# Defining micro and macro

## The example of life sciences

- Hierarchical dependence and multi-level structure.
- Non linear interactions.
- Simulations/dynamical models needed to fully appreciate the mutual dependences among constituents.



# From individuals to populations



## Model the dynamics of the population involved (family of homologous chemicals)

### From the microscopic picture ...

- Assign the microscopic rules of interactions
- Discrete, many particles model

### Deterministic formulation (continuum limit hypothesis)

- Differential equations
- No fluctuations allowed

### Stochastic model (respecting the intimate discreteness)

- Stochastic processes
- Statistical, finite sizes fluctuations

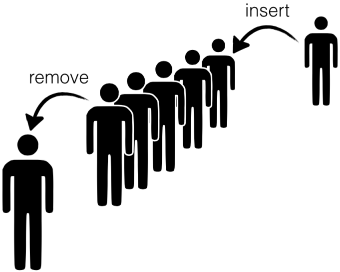
# Take home messages

1. Finite size corrections do matter: macroscopic order, both in time and space, can emerge as mediated by the microscopic disorder (inherent granularity and stochasticity)

2. Endogenous fluctuations cannot be neglected in systems made by finite constituents and may act as a factual drive for the implementation of dedicated functions

# Example 1: birth/death processes.

- Bacteria dynamics.
- Demography.
- Queueing theory.




1. Simple model of population growth.
2. Individuals enter/exit the community.

1. Universal grammar of the chemical equations.
2. Moves occur with given probabilities.
3. Stochasticity and fluctuations are at play.

$$E \xrightarrow{b} X$$
$$X \xrightarrow{d} E$$

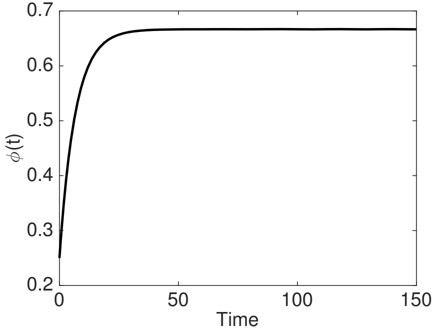
- $X$ is one element of the population.
- $E$ stands for an empty space.
- $n_E + n_X = N$, the size of the system.

# Dynamical evolution for the averaged system

- Average over different histories (trajectories), $< n_X >$
- Wash out noise and fluctuations.
- Deterministic evolution of the mean concentration, $\phi =< n_X > /N$

$$\frac{d\phi}{dt} = b(1-\phi) - d\phi$$

- First oder ODE
- The system converges to the stable equilibrium $\phi^* = b/(b+d)$



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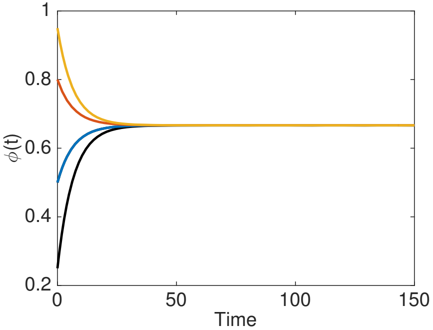
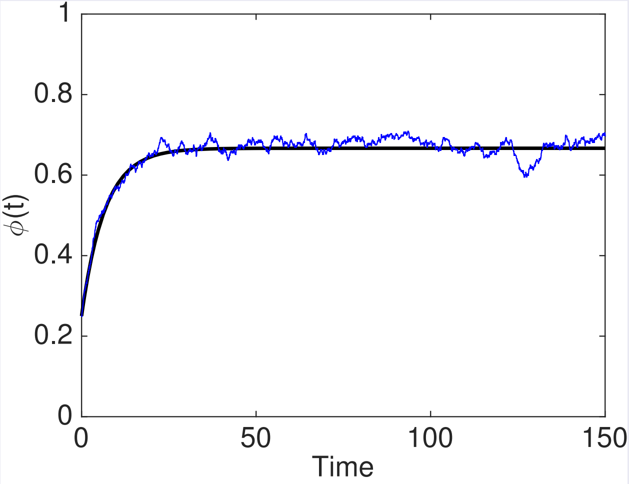


# Visualizing fluctuations via numerical simulations.

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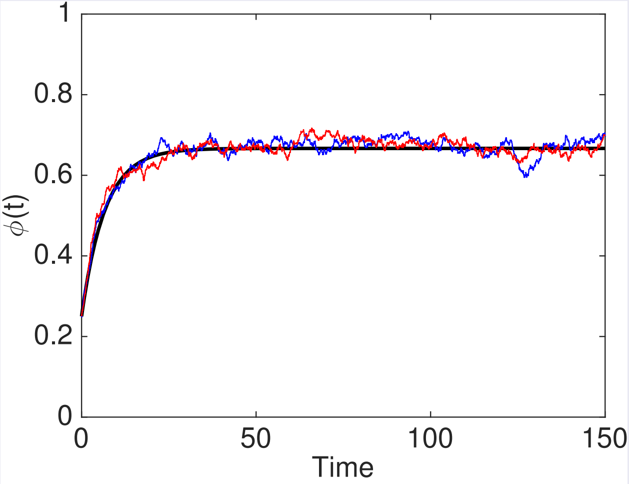


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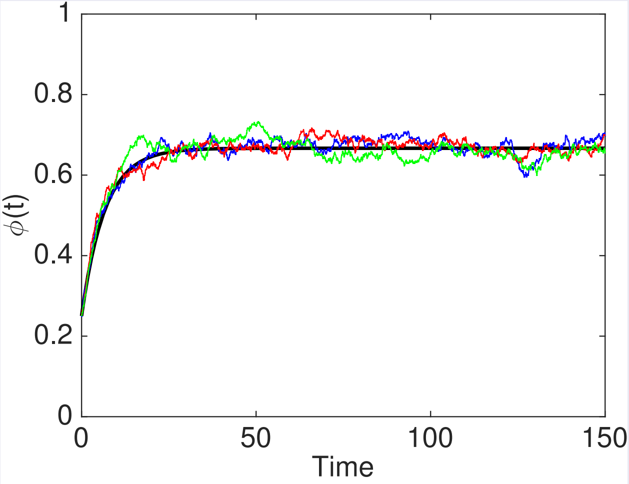


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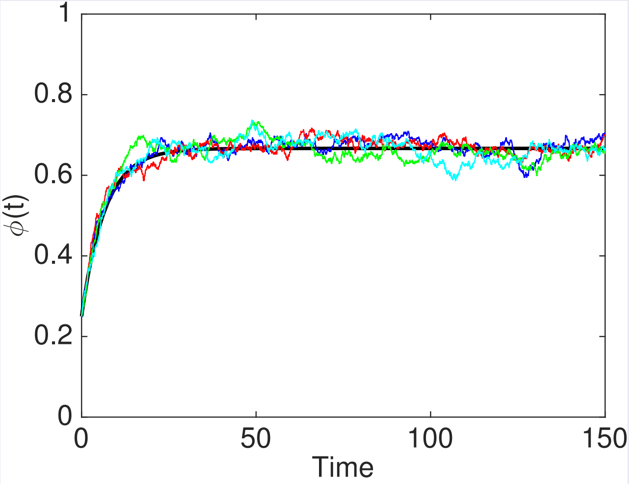


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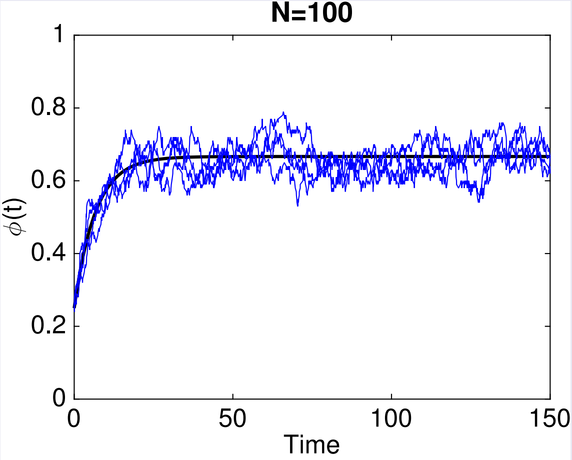


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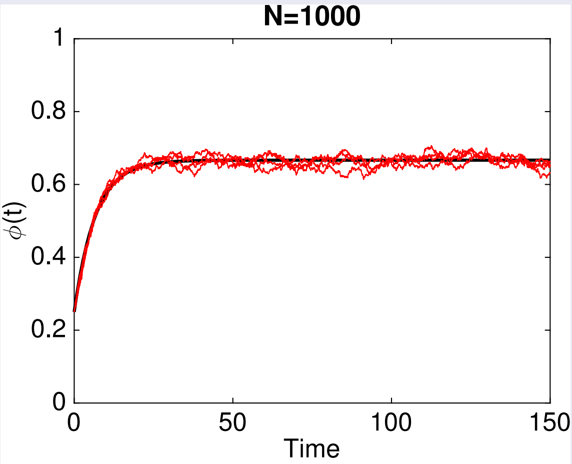


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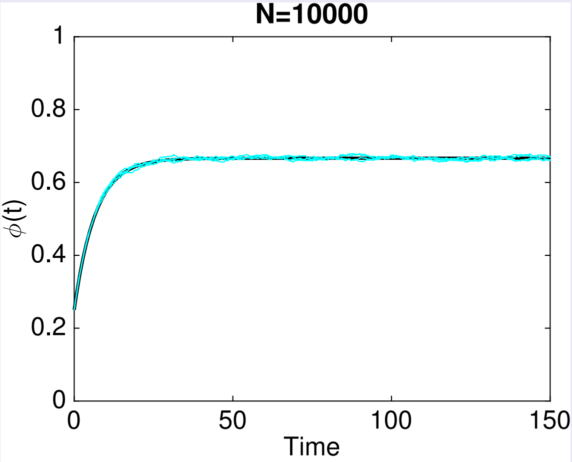


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# Shedding light on fluctuations: formal tools.

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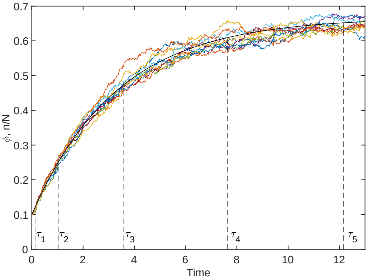
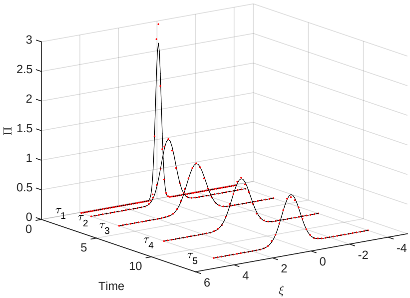
**c.** The master equation yields the deterministic ODE, performing the limit $N \to \infty$ (fluctuations fade away).

**d.** For large or moderate $N$, fluctuations play a role. The master equation reduces to a Fokker-Planck equations for the distribution of fluctuations.

# The predictive power of the theory.




Theory (black line) and simulations (red dots) agree nicely.




Sampling the distribution of fluctuations $\xi$ at different times ($\tau_i$).

R. Arbel-Goren et al. *Life* (2018).

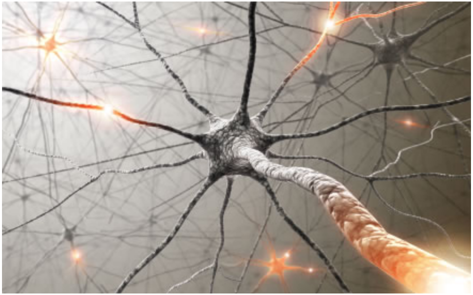
# Up to now...

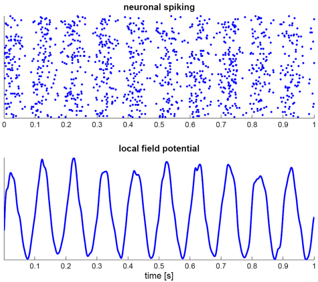
1. Systems composed by a finite set of interacting constituents, say $N$, are subject to fluctuations .
2. Fluctuations are endogenous, as stemming from the finite size $N$.
3. They fade away when $N \to \infty$.
4. Stochastic contributions can be studied with appropriate tools.
5. For the case at hand, the endogenous stochastic drive results in a noisy perturbations around the deterministic solution.

Is this the rule? Can we expect peculiar features to emerge from the inherent stochasticity?

# Example II: modeling the brain dynamics

- A neuron is an excitable cell that processes information through electrical and chemical signals.
- Neurons come in a variety of shapes and morphologies (excitatory and inhibitory neurons).
- Neurons can be grouped in homologous families, referred to as populations.

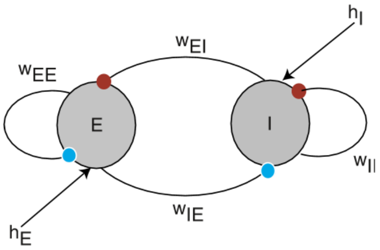




# The Wilson-Cowan model

## Excitator (x) vs. inhibitor (y)

$$\dot{x} = -\alpha_E x + f(w_{EE}x - w_{EI}y + h_E)$$
$$\dot{y} = -\alpha_I y + f(w_{IE}x - w_{II}y + h_I)$$




where:

- $w_{ij}$, $i, j = I, E$ are positive defined parameters.
- $h_E$ and $h_I$ stand for the external stimuli.
- $f(s) = 1/(1 + \exp(-s))$ is a sigmoid function.

1. The original model is deterministic in nature.
2. Stochastic (birth/death) versions also exist.
3. Role of endogenous (finite size/volume) fluctuations.

# A minimal stochastic E-I model.

Label $X$ and $Y$ individual excitatory and inhibitory elements.

## Birth-death scheme

$$\varnothing \xrightarrow{f[s_x]} X \qquad \varnothing \xrightarrow{f[s_y]} Y$$
$$X \xrightarrow{1} \varnothing \qquad Y \xrightarrow{1} \varnothing$$

where:

- $s_X = -r\left(\frac{n_Y}{V} - \frac{1}{2}\right)$.
- $s_Y = r\left(\frac{n_X}{V} - \frac{1}{2}\right)$.
- $r > 0$ is the only free parameter.
- $n_X$ and $n_Y$ identify the number of elements of type $X$ and $Y$.

## Logic flow

a. Introduce $P_{\boldsymbol{n}}(t)$ to label the probability for the system to be in state $\boldsymbol{n} = (n_X, n_Y)$ at time $t$.

b. The dynamics of the system is governed by a master equation.

c. Perform a Kramers-Moyal expansion, $1/\sqrt{V}$ acting as small parameter.

# Fluctuating hydrodynamic approximation

$$\dot{x} = -x + f\left[-r(y-\frac{1}{2})\right] + \frac{1}{\sqrt{V}}\left[x + f\left(-r(y-\frac{1}{2})\right)\right]^{1/2}\eta_x$$

$$\dot{y} = -y + f\left[r(x-\frac{1}{2})\right] + \frac{1}{\sqrt{V}}\left[y + f\left(r(x-\frac{1}{2})\right)\right]^{1/2}\eta_y$$

- stochastic non linear equations.
- multiplicative noise.
- $\eta_x$ and $\eta_y$ are delta correlated Gaussian variables.

**Deterministic limit, $V \to \infty$**

The deterministic model admits a fixed point $x^* = y^* = 1/2$. The linear stability analysis returns $\lambda = -1 \pm i\frac{r}{4}$

# Visualizing quasi-regular oscillations

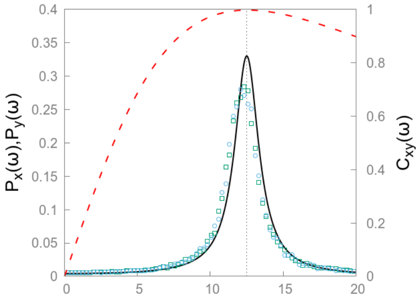
Finite size corrections do matter: macroscopic order can emerge as mediated by the microscopic disorder (inherent granularity and stochasticity)

# Fluctuations and quasi-cycles

## Linear noise approximation

- $x(t) = x^* + V^{-1/2}\xi_1$
  $y(t) = y^* + V^{-1/2}\xi_2$
- $\dot{\xi}_i = \sum_j J_{ij}\xi_j + \eta_i$ with $i = 1, 2$

where $\eta_i(t)$ is a Gaussian noise with $< \eta_i(t)\eta_j(t') > = \delta_{ij}\delta(t - t')$.




## Power spectral density matrix

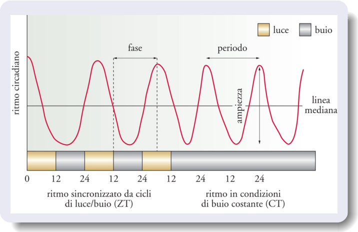
$$P_{ij}(\omega) = < \tilde{\xi}_i(\omega)\tilde{\xi}_j^*(\omega) > = \sum_{l=1}^{2}\sum_{m=1}^{2} \Phi_{il}^{-1}(\omega)\delta_{lm}\left(\Phi^\dagger\right)_{mj}^{-1}(\omega)$$

where $\Phi_{ij} = -J_{ij} - i\omega\delta_{ij}$

Fanelli et al. , *Phys. Rev. E* (2017).

# Example III: stochastic circadian clocks.

A circadian clock is a biochemical oscillator which makes it possible for the organism to adjust to the day-night cycle.



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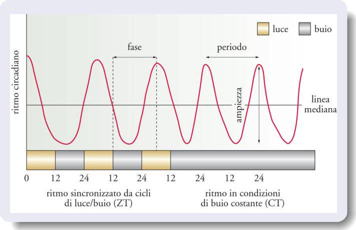


**Key properties:**

- Endogenous rhythmicity when stimuli are lacking.
- Susceptibility to external stimuli which prompt synchronization.
- Ability to adjust to temperature variation.

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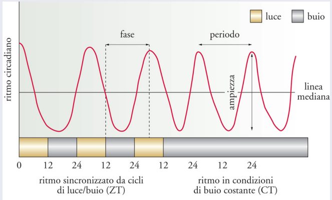


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Cyanobacteria are among the simplest organisms to possess a biological circadian clock.

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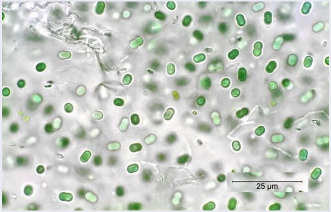

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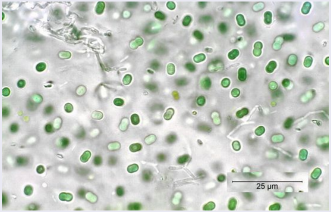


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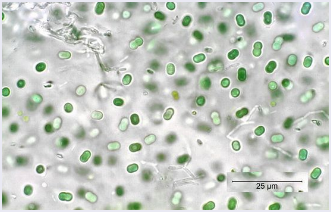


**Anabaena sp.**


The core of the circadian clock in cyanobacteria is composed by three proteins: KaiA, KaiB e KaiC.

- **KaiC** phosphorylates on sites T and S. Phosphorylation modifies the structure of the protein with the inclusion of a phosphate group $PO_4^{3-}$.

# Modeling the dynamics – 1

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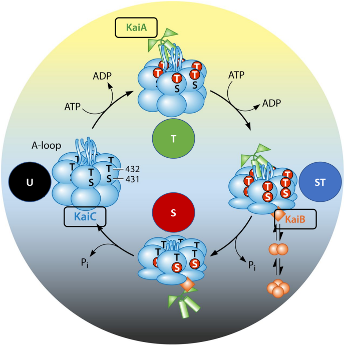


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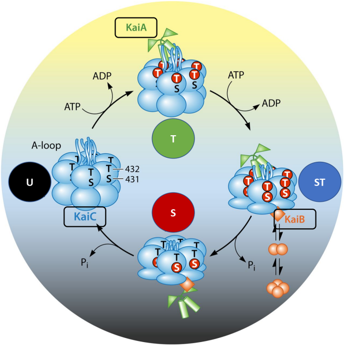


- ***KaiA*** and ***KaiB*** interact with ***KaiC*** following an ordered scheme which drives regular oscillations in the concentration of the different phosphoforms.
- **T**= T-KaiC, **D**= ST-KaiC, **S**= S-KaiC

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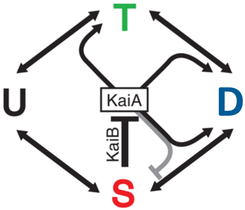


[Rust *et al.*, *Science*, 2007]

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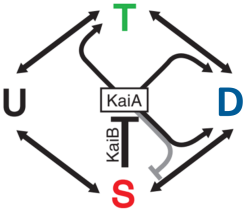


[Rust *et al.*, *Science*, 2007]

$$\begin{cases} \dot{\phi}_T = \phi_U k_{UT} + \phi_D k_{DT} - \phi_T k_{TU} - \phi_T k_{TD} \\ \dot{\phi}_D = \phi_T k_{TD} + \phi_S k_{SD} - \phi_D k_{DT} - \phi_D k_{DS} \\ \dot{\phi}_S = \phi_U k_{US} + \phi_D k_{DS} - \phi_S k_{SU} - \phi_S k_{SD} \end{cases}$$

$$\phi_U = [\mathrm{KaiC}] - \phi_T - \phi_D - \phi_S$$

# Modeling the dynamics – 2

- **KaiC** phosphorylates on sites T and S. Phosphorylation modifies the structure of the protein with the inclusion of a phosphate group $PO_4^{3-}$.
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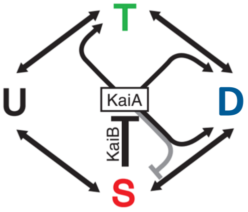


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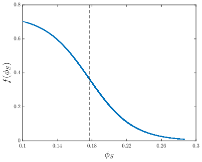
$$\boxed{k_{XY}(\phi_S) = k_{XY}^0 + k_{XY}^A f(\phi_S)}$$



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A linear stability analysis around the fixed point solution $\phi^* = \left(\phi^*_T, \phi^*_D, \phi^*_S\right)$ yields the following scenario

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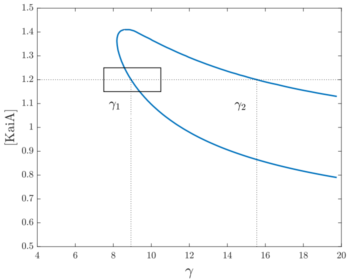

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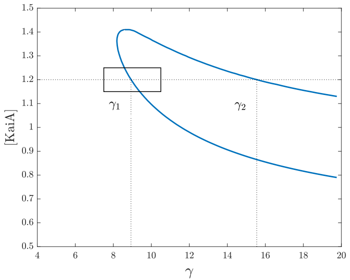
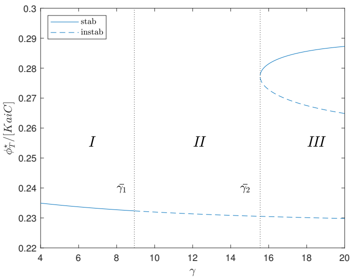
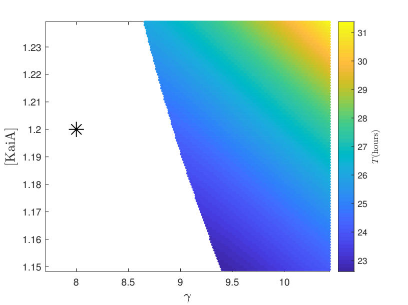



## Bifurcation diagram, $\phi_T$.



# Exploring different dynamical regimes



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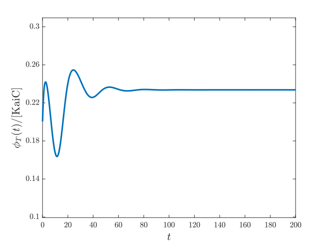


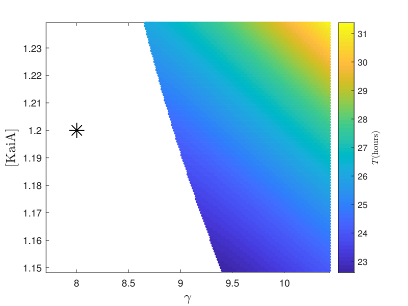

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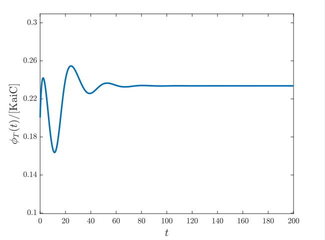
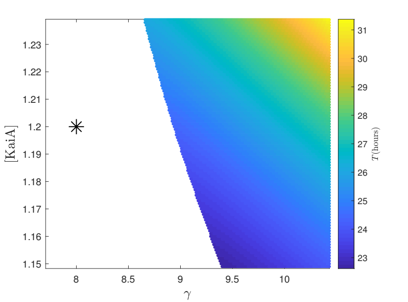
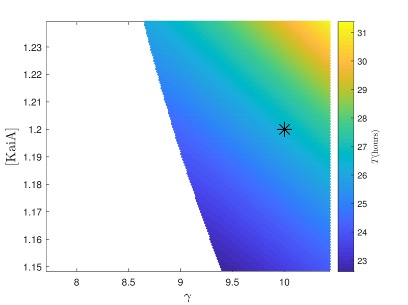



In region I the concentration of the phosphoforms of KaiC converges to a fixed point (absence of circadian cycles).

# Exploring different dynamical regimes



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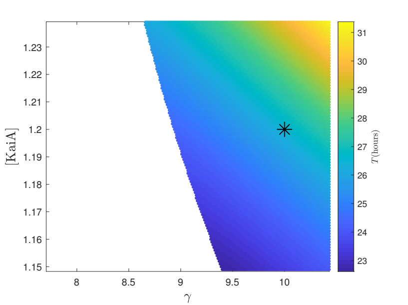


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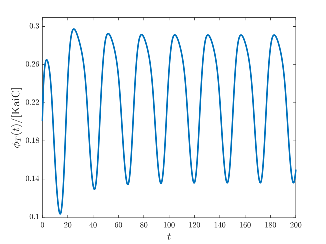

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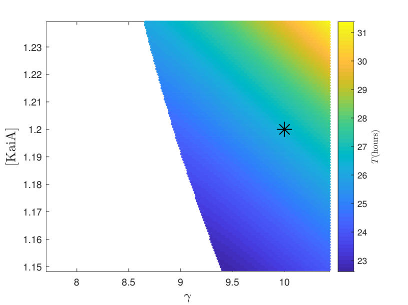


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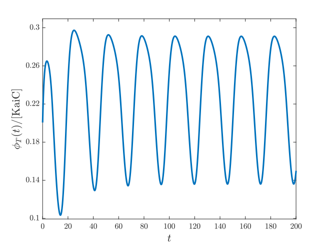


In region II the concentration of the phosphoforms of KaiC displays regular oscillations (with circadian period).

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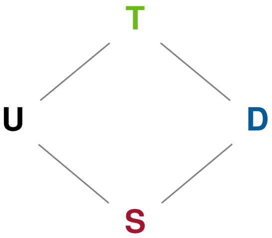

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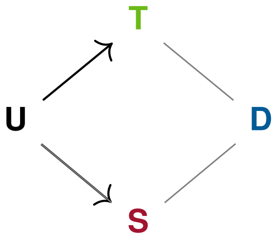


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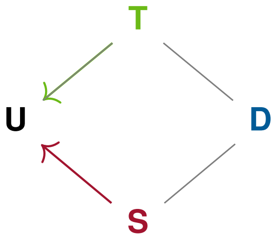


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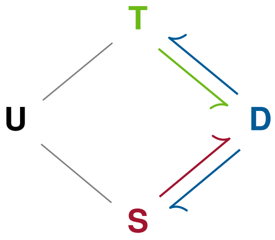


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$$\frac{\partial P(\boldsymbol{n},t)}{\partial t} = \mathbb{T}(\boldsymbol{n}|n_T-1)P(n_T-1;t) - \mathbb{T}(n_T+1|\boldsymbol{n})P(\boldsymbol{n},t) +$$

$$+\,\mathbb{T}(\boldsymbol{n}|n_S-1)P(n_S-1;t) - \mathbb{T}(n_S+1|\boldsymbol{n})P(\boldsymbol{n},t) +$$

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\begin{aligned}
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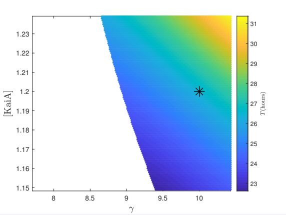
$$\boxed{\begin{aligned}\gamma &= 10\\ [\mathrm{KaiA}] &= 1.2\end{aligned}}$$



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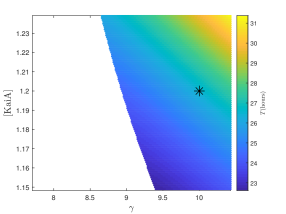


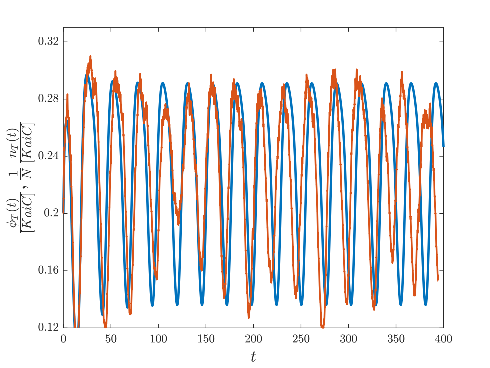

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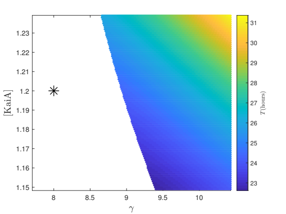

# Stochastic simulations (Gillespie algorithm)

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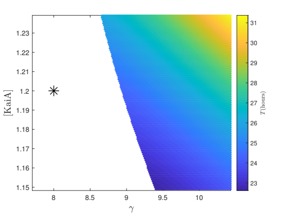


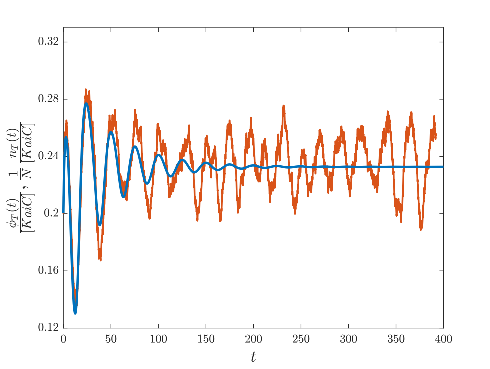


R. Arbel-Goren et al., (2020)

# Comparing with the experiments - Synechococcus el.

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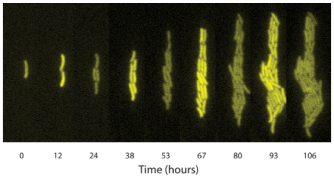


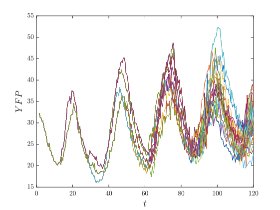


[In collaboration with J. Stavans group @Weizmann]

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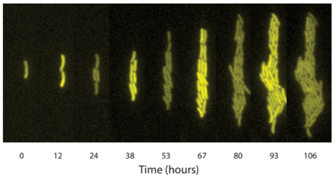
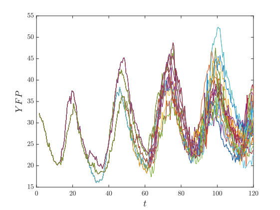
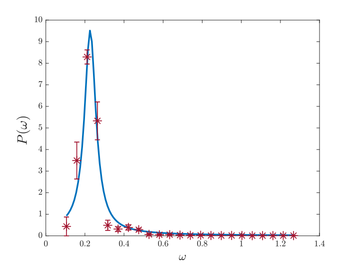
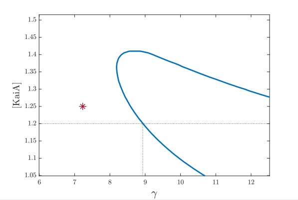


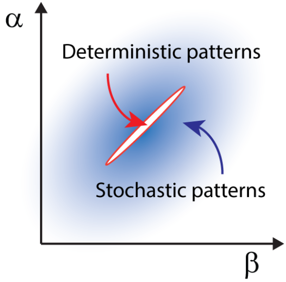

[In collaboration with J. Stavans group @Weizmann]

## Power spectrum



- Regular oscillations in time can emerge from demographic noise: order is generated from disorder.
- Endogenous noise can also seed regular patterns in space.



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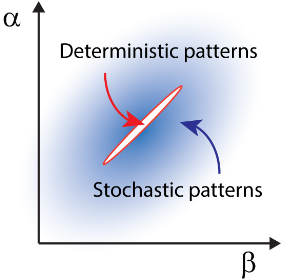
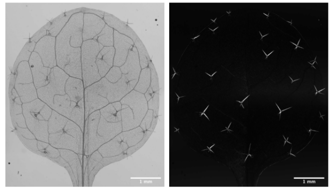
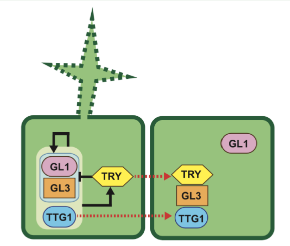



R. Arbel-Goren et al. *Life* (2018).

## Arabidopsis thaliana - I



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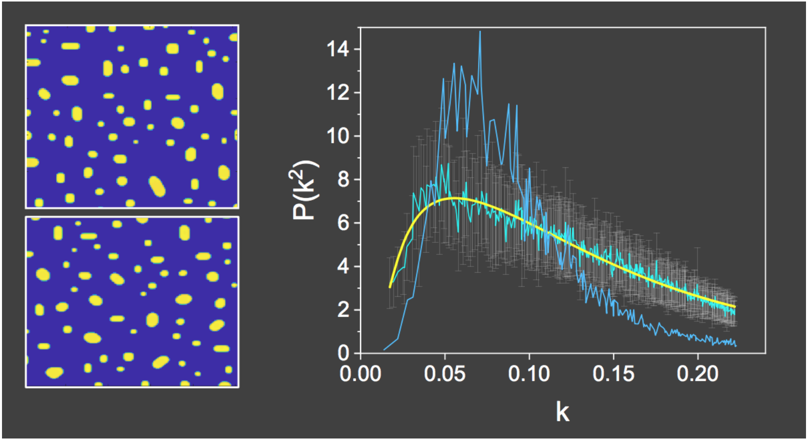


M. C. Sainz et al., in preparation (2020).

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## Synthetic bacterial populations - II

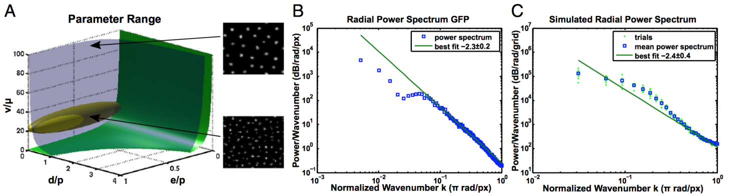
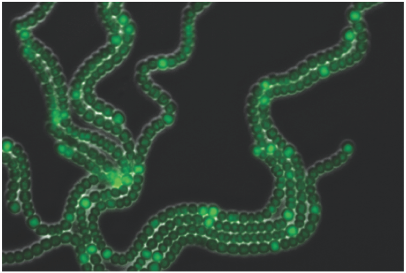


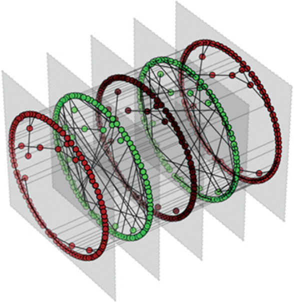

**Fig. 4.** Spectral analysis and parameter analysis. (*A*) Pattern-forming regimes in parameter space and estimated parameters for our system. Parameters above the green surface of neutral stochastic stability can form stochastic patterns, and parameters above the blue surface of deterministic neutral stability can form deterministic Turing patterns. The ratio of the diffusion coefficients $\nu/\mu$, the ratio of degradation rate to production rate $d/p$, and the ratio of production rates are estimated for our system by the yellow ellipsoid. The parameters for our system are mostly in the regime where stochastic patterns form and outside the region where deterministic Turing patterns form. Example stochastic simulations are shown for parameters drawn from a deterministic parameter region with $D_\nu/D_\mu = 100$ (*Upper Right*) and a stochastic region with $D_\nu/D_\mu = 21.6$ (*Lower Right*). (*B*) Radial power spectrum of green fluorescence and best fit power law tail with an exponent of $-2.3 \pm 0.2$. (*C*) Radial power spectrum for eight trials of our stochastic simulation, their mean, and the best fit power law tail.

D. Karig et al., *PNAS* (2018).

# Conclusions

- Spontaneous drive to self-organization in Nature.
- Regular motifs in space and time originate from a large sea of interacting individual constituents.
- Finite size corrections yield ordered macroscopic patterns.
- Stochastic patterns on heterogenous spatial supports (networks, multiplex, hypergraphs).





# Scheduled lectures

**Auditorium:** "Salle de Conférences du Dpt de Math" (**E25**) on the second floor

- ***Stochastic processes***

Wednesday February the 5th, 4:30 pm 6:30 pm

- ***Master equation***

Thursday February the 6th, 4:30 pm 6:30 pm

- ***Impact of the noise***

Tuesday February the 18th, 4:30 pm 6:30 pm

- ***Spatially extended systems***

Wednesday February the 19th, 4:30 pm 6:30 pm