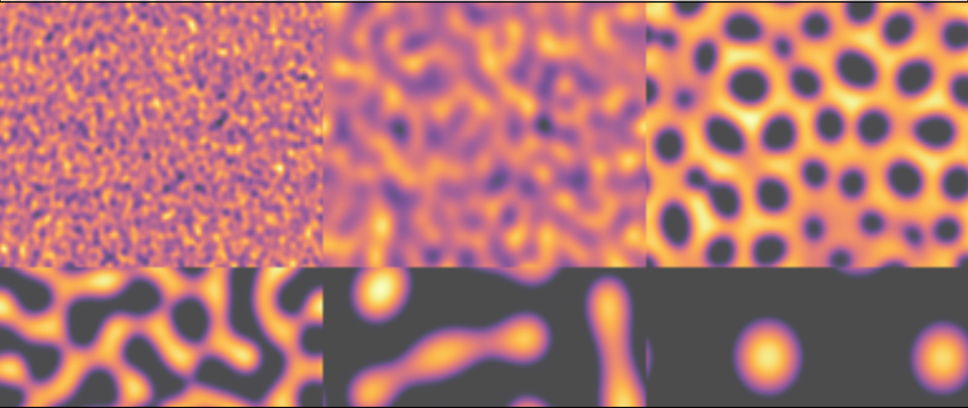
Numerical Aspects of nonequilibrium dynamics
Institut Henri Poincaré, Paris
April 25, 2017

Courant NYU



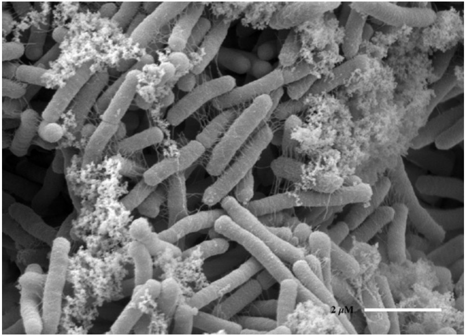
Non-equilibrium self-organization of motile bacteria with fluctuating population and speed

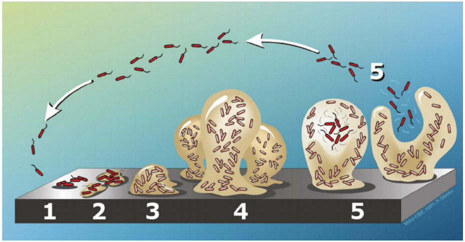
Tobias Grafke, M. Cates, E. Vanden-Eijnden

Collective behavior of bacteria

Bacteria show complex collective behavior

- For example, bacteria such as *E. Coli* are capable of **active propulsion**, i.e. have a free-swimming (*planktonic*) stage.
- They are capable of sensing their environment through **quorum sensing**, density-dependent gene regulation.
- They stick to surface to form **biofilms**, high density colonies.
- They exhibit **cyclic**/time-periodic behavior: Biofilm formation, maturation, dispersion, planktonic stage.
- All these are controlled by highly complex bio-chemical processes.





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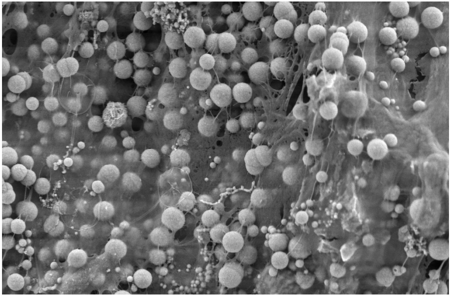

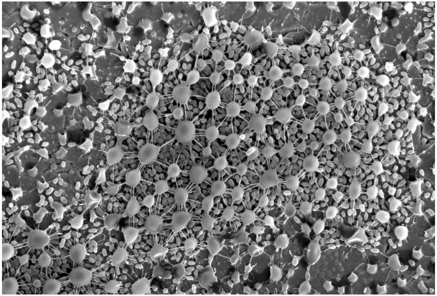

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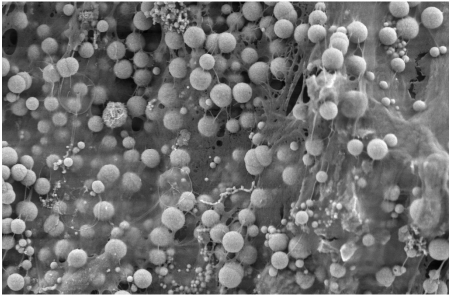
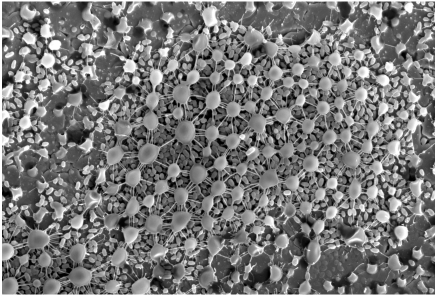




Statistical mechanics of active matter

Stepping away from the biological complexity: Is it possible to describe similarly complex life-cycles as **emergent behavior** of a large number of simple **individual agents** subject to a small number of collective rules?

Intrinsically **out-of-equilibrium** system: Statistical mechanics of **active matter**

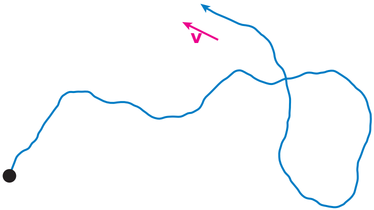
Continuum description of motile bacteria

- Self-propelled bacteria modeled as **active Brownian motion**:

  For position $X \in \Omega \subset \mathbb{R}^d$, direction $\hat{n} \in S^{d-1}$, and location dependent swim speed $v(X) \in \mathbb{R}$

  $$\dot{X} = v(X)\hat{n}\,,$$
  $$d\hat{n} = \tau^{-1/2} P \circ dW\,, \qquad P = \mathrm{Id} - \hat{n}\hat{n}^T$$

  Direction diffuses on S^{d-1} with tumbling rate τ^{-1}.



active Brownian motion†

- Limit $\tau \to 0$ yields Brownian motion

$$dX = \sqrt{2D(X)} \circ dW \qquad \text{with diffusivity} \qquad D(x) = \tau v^2(x)$$

† *M. Cates, J. Tailleur (2015)*

Continuum description of motile bacteria

Cates & Tailleur

Now consider N such particles with position $X_i, i \in \{1, \dots, N\}$.

To model **quorum sensing**, introduce scale δ over which particles feel each other's influence,

$$dX_i = \sqrt{2D(\rho_{N,\delta}(t, X_i))} \circ dW_i$$

with

$$\rho_{N,\delta}(t,x) = \int_\Omega \phi_\delta(x-y)\rho_N(t,y)\,dy, \qquad \rho_N(t,x) = \frac{1}{N}\sum_{j=1}^{N}\delta(x - X_j(t))$$

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In the limit $N \to \infty$, yields closed integro-differential equation for $\rho_N \to \rho$,

$$\partial_t \rho = \nabla \cdot (D(\rho_\delta)\nabla\rho + \tfrac{1}{2}D'(\rho_\delta)\nabla\rho_\delta), \qquad \rho_\delta(t,x) = \int_\Omega \phi_\delta(x-y)\rho(t,x)\,dy$$

in the sense that

$$\forall\, \epsilon, T > 0: \quad \lim_{N\to\infty} \mathbb{P}\Big(\sup_{0\le t\le T}\Big|\frac{1}{N}\sum_{j=1}^N f(X_j(t)) - \int_\Omega \rho(t,x) f(x)\,dx\Big| > \epsilon\Big) = 0$$

Continuum description of motile bacteria

To make this closed in $\rho(t,x)$, consider $D(\rho) = D_0 e^{-\rho}$, and expand in $\delta \ll 1$,

$$\rho_\delta(x) \approx \rho(x) + \tfrac{1}{2}\delta^2 \partial_x^2 \rho(x)\,.$$

Then we obtain an **effective diffusion** equation

$$\partial_t \rho = \nabla \cdot (D_e(\rho)\nabla\rho - \delta^2 \rho D(\rho)\nabla\Delta\rho)$$

with diffusivity

$$D_e(\rho) = D(\rho) + \tfrac{1}{2} D'(\rho)\rho\,.$$

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Despite non-equilibrium microscopic model, continuum model restores **detailed balance**

$$\partial_t \rho = \nabla \cdot (\rho D(\rho) \nabla (\delta E/\delta\rho))$$

with

$$E(\rho) = \int_\Omega (\rho \log \rho - \rho + f(\rho) + \tfrac{1}{2}\delta^2 |\nabla\rho|^2)\, dx\,, \quad f'(\rho) = \tfrac{1}{2}\log D(\rho) \quad \text{(free energy)}$$

("Thermodynamic mapping" depends on regularization, not preserved by original Cates & Tailleur)

Motility induced phase separation

$$\partial_t \rho = \nabla \cdot (D_e(\rho)\nabla\rho - \delta^2 \rho D(\rho)\nabla\Delta\rho)\,,$$
$$D_e(\rho) = D(\rho) + \tfrac{1}{2}D'(\rho)\rho$$

$D(\rho) > 0$ **diffusivity**, but $D_e(\rho) < 0$ possible!

For $D(\rho) = D_0 e^{-\rho}$

- effective diffusivity

$$D_e(\rho) = D_0(1 - \tfrac{1}{2}\rho)e^{-\rho}$$

- Homogeneous configuration stable if

$$\bar\rho = \frac{1}{|\Omega|}\int_\Omega \rho(x)\,dx < 2$$

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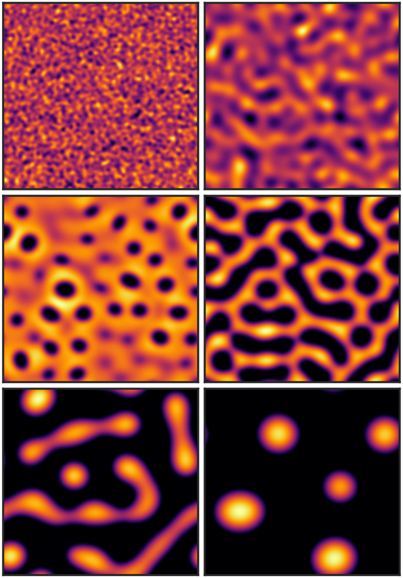
- If $\bar\rho > 2$, then **phase separation** occurs
  Feedback loop: Accumulation induced slowdown + slowdown induced accumulation



Motility induced phase separation

Up to now, single behavioral rule:

Active Brownian motion with **density dependent diffusivity**

Introduce second behavioral rule: **Population dynamics**

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Active Brownian motion with **density dependent diffusivity**

Introduce second behavioral rule: **Population dynamics**

$$A \xrightarrow{\lambda_r} A + A \qquad \lambda_r = \alpha \qquad \text{(reproduction)}$$

$$A + A \xrightarrow{\lambda_c} A \qquad \lambda_c = \alpha/\rho_0 \qquad \text{(competition)}$$

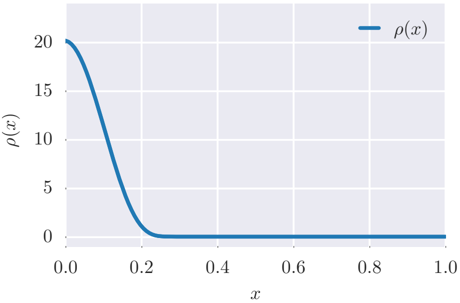
with **carrying capacity** ρ_0 and **timescale** α, leads to **logistic growth**.

$$\partial_t \rho = \nabla \cdot (D_e(\rho)\nabla\rho - \delta^2 \rho D(\rho)\nabla\Delta\rho) + \alpha\rho(1 - \rho/\rho_0)$$

- Phase separation eventually if

$$D_e(\rho_0) < 0$$

- System will drive itself into instability
- Coarsening stopped by growth, **arrested phase separation**[†]



[†] *Cates, M. E. and Marenduzzo, D. and Pagonabarraga, I. and Tailleur, J. (2010)*

Timescale separation

Consider large **timescale separation**, $\alpha \ll 1$, i.e. fast propulsion, slow reproduction

$$\partial_t \rho = \nabla \cdot (D_e(\rho)\nabla\rho - \delta^2 \rho D(\rho)\nabla\Delta\rho) + \alpha\rho(1-\rho/\rho_0)$$

Asymptotic analysis:

- Propulsion is **conservative**, $\bar\rho$ is invariant under fast dynamics
- Emergence of **slow manifold** $\mathcal{M}$,

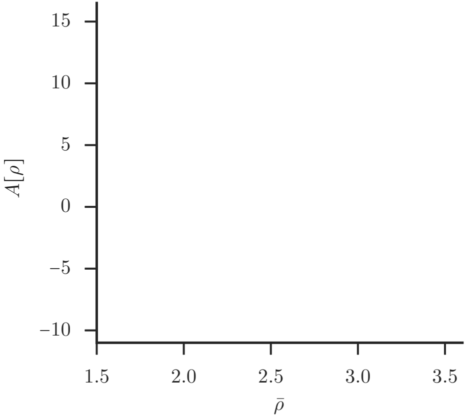
  $$0 = \nabla \cdot (D_e(\rho)\nabla\rho - \delta^2 \rho D(\rho)\nabla\Delta\rho)$$

  foliated by $\bar\rho$.
- Obtain **reduced dynamics**

  $$\dot{\bar\rho} = \alpha(\bar\rho - \overline{\rho^2}/\rho_0), \quad \rho = \rho_{\mathcal{M}}(x, \bar\rho(t))$$

- 3 regimes

$\rho_0 < \rho_S$	homogeneous solution
$\rho_S < \rho_0 < \rho_c$	limit cycles
$\rho_c < \rho_0$	two stable fixed points



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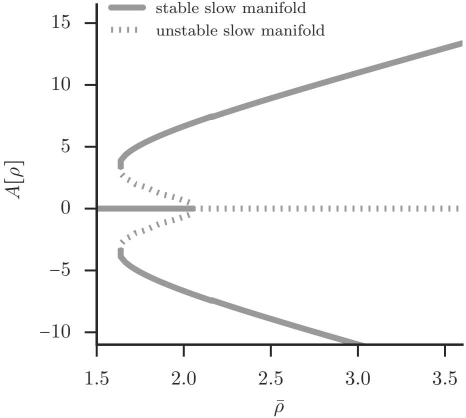

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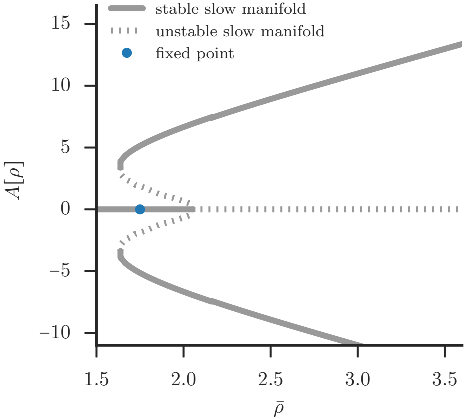

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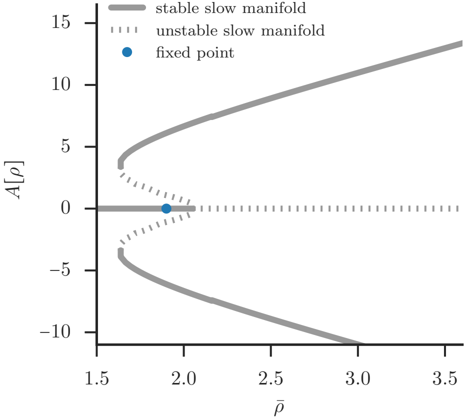

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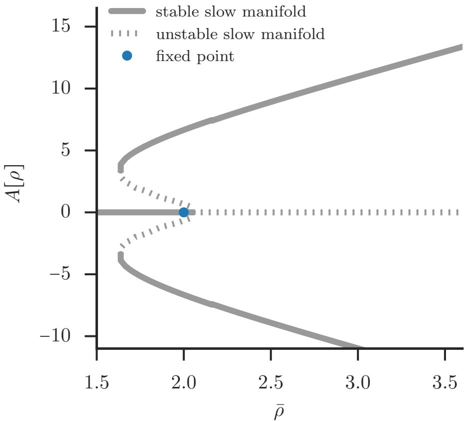

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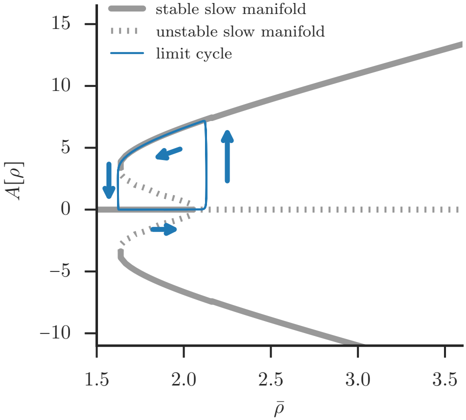

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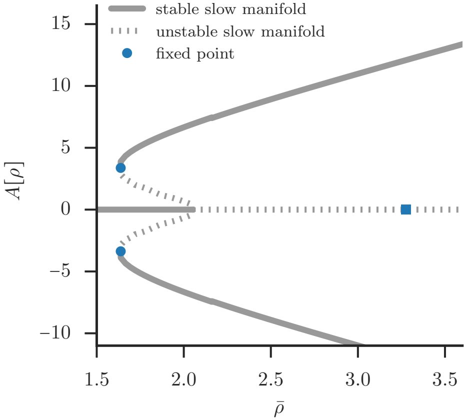

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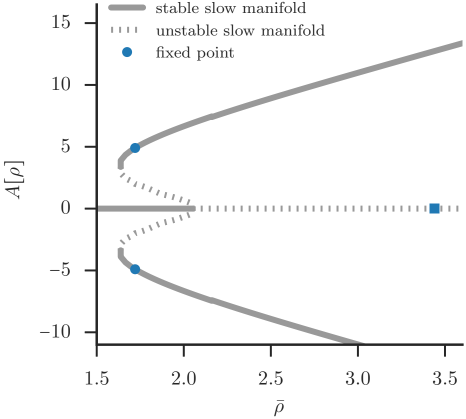

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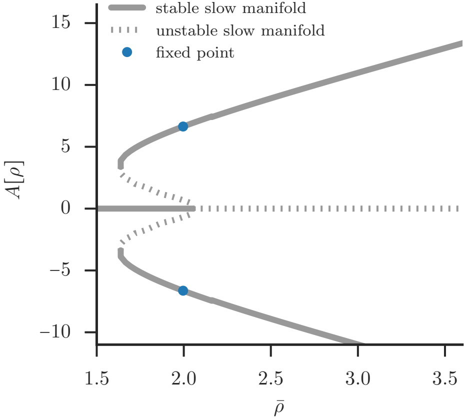

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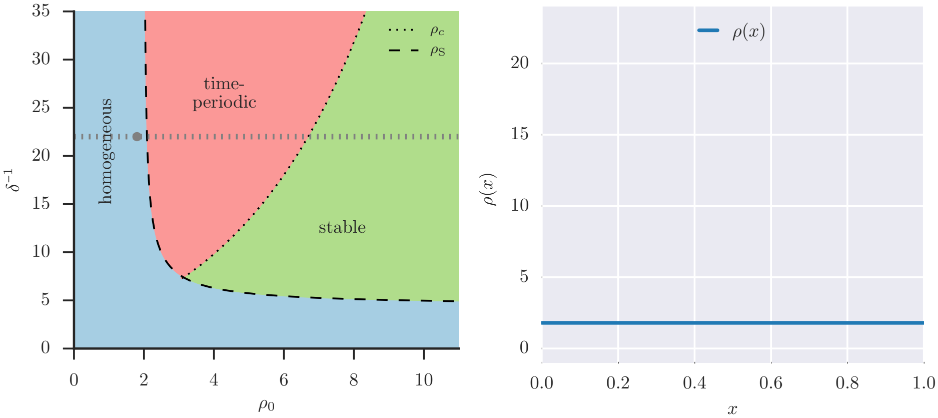


Homogeneous regime:

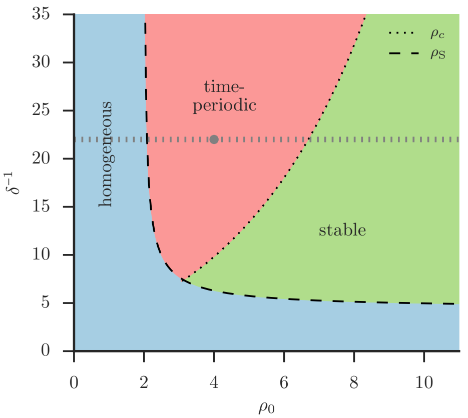
$$\rho_0 < \rho_c$$

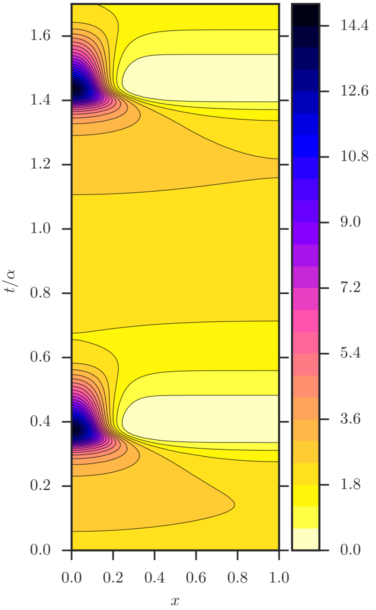
$$\Omega = [0, 1]$$

Neumann boundary conditions,

$$\partial_x \rho(0) = \partial_x \rho(1) = 0$$

Timescale separation

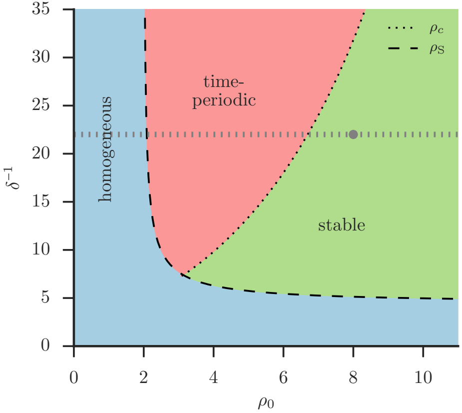


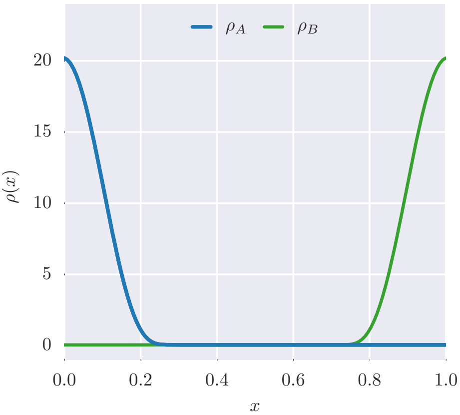


Time periodic regime:

$$\rho_c < \rho_0 < \rho_S$$

Timescale separation





Stable regime:

$$\rho_c < \rho_0$$

$$\Omega = [0, 1]$$

Neumann boundary conditions,

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The effect of fluctuations

$$\partial_t \rho = \nabla \cdot (D_e(\rho)\nabla\rho - \delta^2 \rho D(\rho)\nabla\Delta\rho) + \alpha\rho(1 - \rho/\rho_0)$$

- Is a **law of large numbers** (LLN) for $N \to \infty$ (where N typical number of particles)
- Gaussian fluctuations around these dynamics captured by **central limit theorem** (CLT)
- We are interested in long time behavior: **Large deviation theory** (LDT)
- Both **propulsion** and **reproduction** are subject to fluctuations for finite N.

The effect of fluctuations: Large deviation theory

Key object: **Rate function**

$$S_T(\phi) = \frac{1}{2}\int_0^T \left|\sigma(\phi)^{-1}\left(\dot{\phi} - b(\phi)\right)\right|^2 dt = \frac{1}{2}\int_0^T \mathcal{L}(\phi, \dot{\phi})\, dt$$

associated with the S(P)DE

$$dX^\epsilon(t) = b(X^\epsilon(t))\, dt + \sqrt{\epsilon}\sigma(X^\epsilon(t))\, dW(t)$$

Then, the probability that $\{X^\epsilon(t)\}_{t\in[0,T]}$ is close to a path $\{\phi(t)\}_{t\in[0,T]}$ is

$$\mathcal{P}\left\{\sup_{0\le t\le T}|X^\epsilon(t) - \phi(t)| < \delta\right\} \asymp \exp\left(-\epsilon^{-1}S_T(\phi)\right)$$

for $\epsilon \to 0$. The problem is reduced to a **minimization** problem

$$\mathcal{P}\left\{X^\epsilon(T) \in A | X^\epsilon(0) = x\right\} \asymp \exp\left(-\epsilon^{-1} \inf_{\phi:\phi(0)=x,\phi(T)\in A} S_T(\phi)\right)$$

The effect of fluctuations: Large deviation theory

Propulsion

Gradient system

$$\partial_t \rho = -M \delta E / \delta\rho + \sqrt{\tfrac{2}{N}} M^{1/2} \eta(x,t)$$

for

$$E(\rho) = \int_\Omega (\rho \log \rho - \rho + f(\rho) + \tfrac{1}{2}\delta^2 |\nabla\rho|^2)\, dx$$

$$M(\rho)\xi = \nabla \cdot (\rho D(\rho) \nabla \xi)$$

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Large deviation Hamiltonian

$$\mathcal{H}_p(\rho,\theta) = \int_\Omega \theta\nabla\cdot(\mathcal{D}_e\nabla\rho - \delta^2\rho D\nabla\nabla^2\rho) + \tfrac{1}{2}\rho D|\nabla\theta|^2\,dx$$

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Reproduction

Poisson processes at each location for the reactions

$$A \xrightarrow{\lambda_r} A + A\,, \quad \lambda_r = \alpha \qquad \text{(reproduction)}$$

$$A + A \xrightarrow{\lambda_c} A\,, \quad \lambda_c = \alpha/\rho_0 \qquad \text{(competition)}$$

then LLN is

$$\partial_t\rho = \alpha\rho(1-\rho/\rho_0)$$

with Poisson noise.

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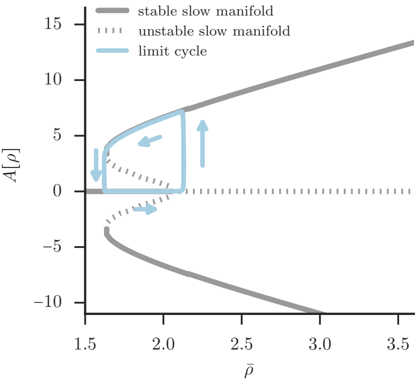
$$\mathcal{H}_r(\rho,\theta) = \alpha\int_\Omega \Big(\rho(e^\theta - 1) + \rho^2/\rho_0(e^{-\theta}-1)\Big)\,dx$$

(corresponding SPDE is ill-posed)

The effect of fluctuations: Quasi time periodic regime



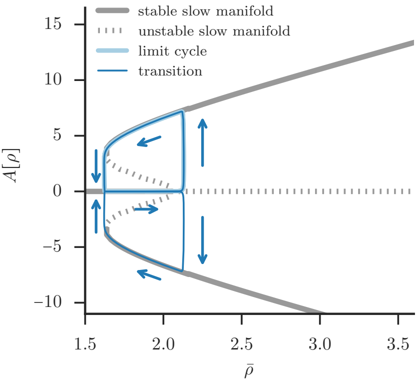
Consider $\rho_S < \rho_0 < \rho_c$

- Tiny fluctuations alter the structure of the limit cycle
- These are not rare events:

  Zero action for transition when $\alpha \to 0$

T. Grafke, M. Cates, E. Vanden-Eijnden (2017) arXiv:1703.06923

The effect of fluctuations: Quasi time periodic regime



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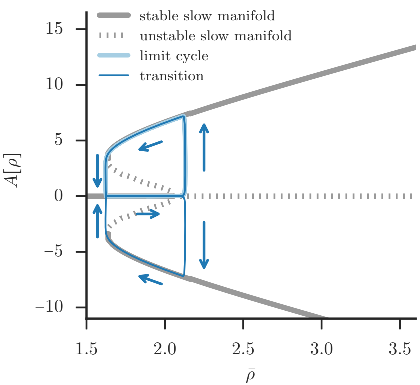

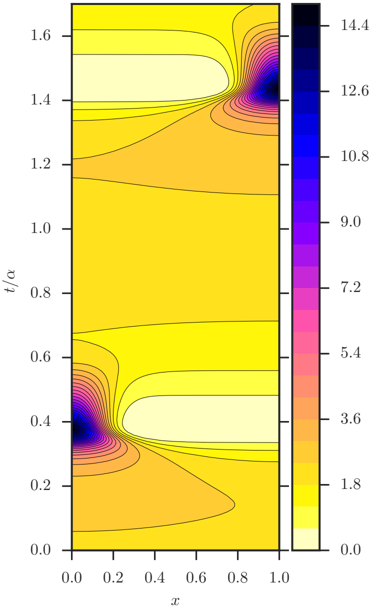

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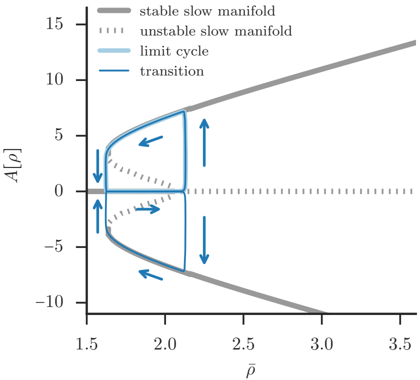

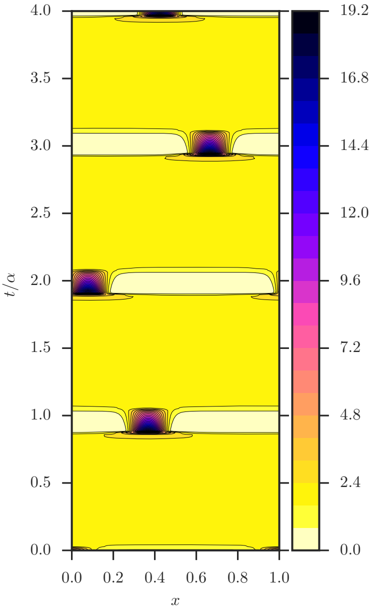

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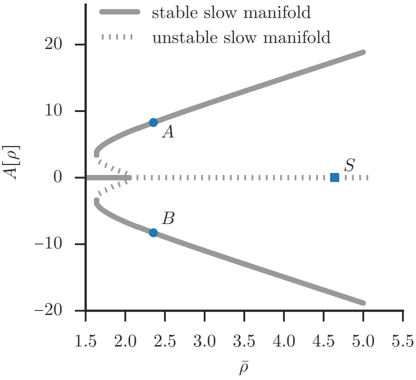
The effect of fluctuations: Metastable regime

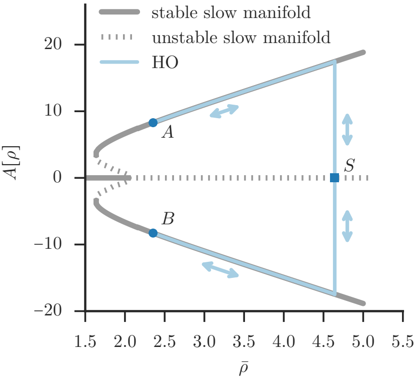


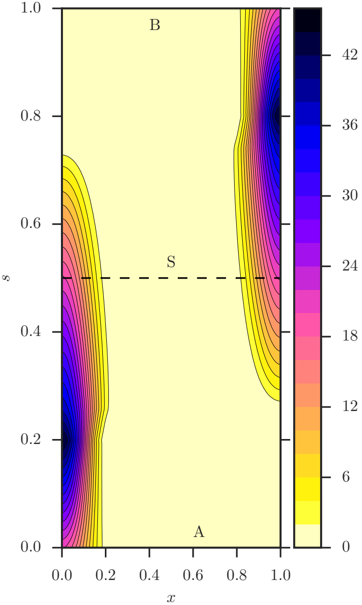
Consider $\rho_c < \rho_0$

- Fixed points become **metastable**
- Transitions between them:
  Finite action, exponentially small probability, *LDT regime*

T. Grafke, E. Vanden-Eijnden (2017) arXiv:1704.06723

The effect of fluctuations: Metastable regime





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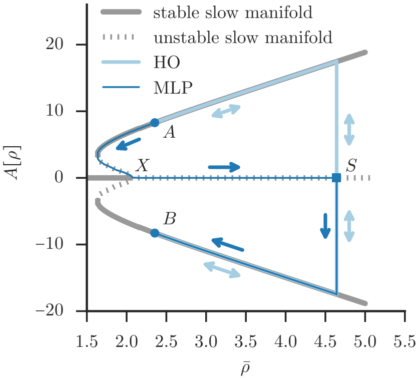

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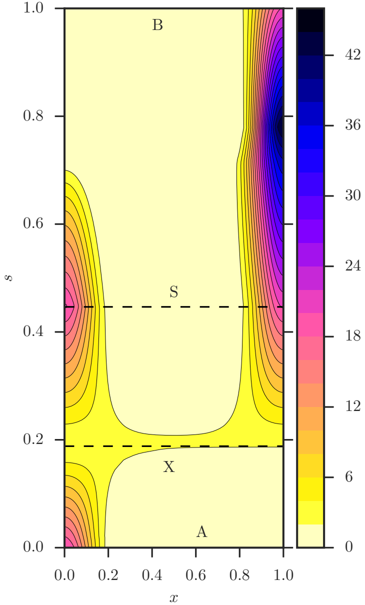

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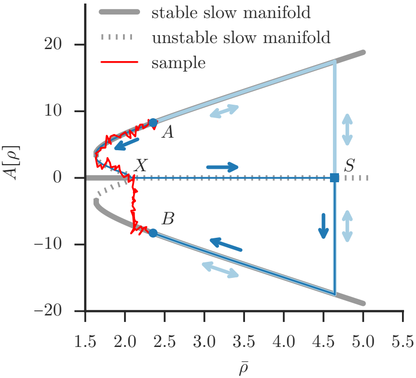
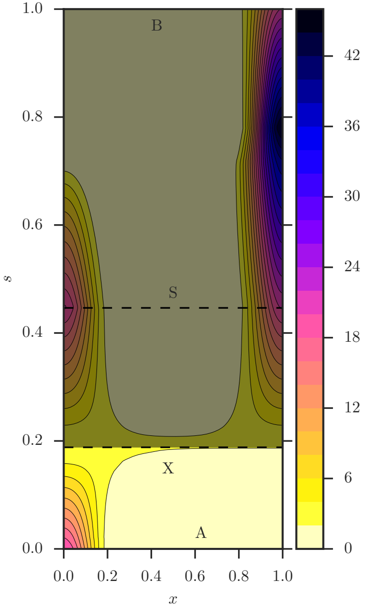




At finite N, accounting for entropy, only part of the transition with **non-zero action** is robust (and matters).

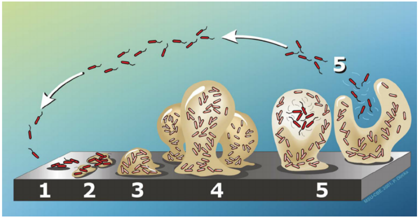
T. Grafke, E. Vanden-Eijnden (2017) arXiv:1704.06723

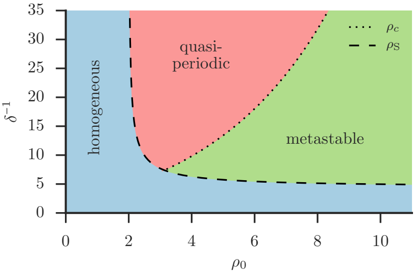
Non-equilibrium self-organization

Complex collective behavior for simple active agents:

Propulsion and **Reproduction**

- When $\rho_0 < \rho_S$, **planktonic** phase is robust.
- When $\rho_S < \rho_0 < \rho_c$, particles oscillate between **biofilm** and **planktonic** phase
- When $\rho_0 < \rho_c$, biofilms are **metastable**. They **rarely** disperse and reform by dieing out
- Full **phase diagram** depends on carrying capacity ρ_0 and **domain size** δ^{-1}.





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Numerical Computation of Large Deviation Minimizers

Main problem

For our system and observable, find the **minimizer** $\phi^\star$ such that

$$S_T(\phi^\star) = \inf_\phi S_T(\phi)\,,$$

where the minimization is over all trajectories fulfilling the boundary conditions.

The knowledge of this **minimizer** (MLP) yields

- Most probable **evolution** in time from initial state into this final configuration
- Corresponding **optimal force**, computable from auxiliary field θ
- Tail scaling behavior of the **PDF** of our observable, roughly through $\mathcal{P}\{x^\epsilon(T)\} \sim \exp(-\frac{1}{\epsilon}\inf_\phi S_T(\phi))$

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Its **computation** is challenging:

- This is an infinite-dimensional **PDE constraint optimization**. The search space is large (space-time).

  Each **iteration** we have to solve a system of coupled PDEs.
- If we are computing **transition probabilities**, we are interested in the **Quasipotential**,

  $$V(x_1, x_2) = \inf_{T>0} \inf_\phi S_T(\phi)$$

  This infimum is not attained in general, $T \to \infty$.

Challenges: Infinite transition time and geometric rate function

Quasipotential

$$V(x_1, x_2) = \inf_{T>0} \inf_{\phi} S_T(\phi)$$

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In the case $T \to \infty$, realize, that $\mathcal{H}(x, \theta) = 0$, so that

$$\int \mathcal{L}(x, \dot{x})\, dt = \int \sup_{\theta} \left(\langle \dot{x}, \theta \rangle - \mathcal{H}(x, \theta) \right) \, dt = \sup_{\theta : \mathcal{H}(x,\theta)=0} \int \langle \dot{x}, \theta \rangle \, dt$$

Effectively:

Reduce minimization over all paths to finding **geodesic** of the associated (Finsler) **metric**.

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Heymann, Vanden-Eijnden (2008), Grafke, Schäfer, Vanden-Eijnden (2017)

Summary

- Non-equilibrium statistical mechanics theory of active matter is still in its infancy
- One example is **Motility induced phase separation** — direct consequence of motile agents with density dependent drift velocity
- Adding **population dynamics** is enough to yield complex emergent behavior reminiscent of biofilm-planktonic lifecycle
- Fluctuations in MIPS + Reproduction can be analyzed by LDT
- Noise-driven spatio-temporal self-organization
  - **Limit cycles** are temporally but not spatially robust against fluctuations
  - Transitions between **metastable colonies** are out-of-equilibrium and occurs different to detailed-balance intuition
- Computation via **geometric minimization** of LDT rate function