Towards a non-equilibrium statistical mechanics approach of biological systems

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Molecular motors

bacteria
$\sim 10^{-6}$ m

eukaryote cells

social insects
$\sim 10^{-2}$ m

bird and fish
$\sim 10^{-1}$ m

Mammals
$\sim 10^0$ m

collective behavior at various scales
spontaneous self-organized flows?

we observe a flow if we apply a difference of pressure, or due to a difference in potential energy.

in a glass, the water will not spontaneously start moving in a given direction.

Lithograph August Mayer
In active or living systems the situation is different...

We observe a flow if we apply a difference of pressure, or due to a difference in potential energy.

In a glass, the water will not spontaneously start moving in a given direction.

Quincke rollers in confinement

the examples we are going to visit today...

spontaneous behaviors/flows in biological systems

Peruani, Deutsch, Bär, PRE (2006)
Peruani et al., PRL (2012)
Weitz, Deutsch, Peruani, PRE (2015)
Collective effects in myxobacteria

Multicellular organization in myxobacteria

Transition from individual to collective behavior
(i.e. from "unicellular to multicellular")

uncoordinated behavior → Complex collective behavior

bacteria hunting in clusters (individual phase)

under starvation:
aggregation centers are formed

a morphogenetic process starts involving highly coordinated cell movements, that culminates with the formation of a fruiting body.

Reichenbach 1965

Zusman 2007
Collective effects in myxobacteria

Multicellular organization in myxobacteria

Transition from individual to collective behavior (i.e. from "unicellular to multicellular")

uncoordinated behavior → Complex collective behavior

Self-organized patterns we want to explain...

clusters  |  vortex aggregates
---|---

network patterns  |  fruiting bodies

1. Life-cycle:
   - Vegetative growth cycle and swarming
   - Germination
   - Myxospore
   - Fruiting body

2. Examples:
   - Reichenbach 1965
   - Zusman 2007

Peruani
Collective effects in myxobacteria

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Self-organized patterns we want to explain...

network patterns  fruting bodies

clusters  vortex aggregates
Collective effects in myxobacteria

- **Motility engines in *Myxococcus xanthus***:

  - Type IV pili
  - Slime secretion
  - Focal adhesion points

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Myxobacteria (speed = 0.025 to 0.1 μm/s)
Cyanobacteria (speed = 10 μm/s)
Cytophaga-Flavobacterium (speed = 2 to 4 μm/s)
• **How do M. xanthus cells communicate?**

  • A quorum sensing diffusive mechanism to trigger the life cycle.
  • There is no evidence of a *guiding chemotactic signals* involved in *collective motion*.
  • Cells exchange C-signal which controls cell reversal (it requires cell-cell contact).

• **Cell reversal and C-signal:**

  Igoshin & Oster 2003
Which mechanism is used by the cells to coordinate their motion?

- Is there a hidden guiding chemotactic signal?
- Can slime trail following cause these effects?
- Is there a cell-density sensing mechanism that controls cell speed causing of these effects?
- What is the minimal mechanism that can produce these effects?
Collective effects in myxobacteria

Self-propulsion of bacteria + elongated shape
= collective behavior?

What macroscopic effects emerge in a system of self-propelled liquid crystals?
Collective effects in myxobacteria

• A simple physical model: bacteria as self-propelled rods

We consider the over-damped situation in which we have:

\[ \dot{x}_i = \mu \left[ -\nabla U_i + F V(\theta_i) + \sigma_i(t) \right] \]

\[ \dot{\theta}_i = \frac{1}{\zeta_\theta} \left[ -\frac{\partial U_i}{\partial \theta_i} + \xi_i(t) \right] \]

Self-Propelling force/stress

\[ V(\theta) \equiv (\cos(\theta), \sin(\theta)) \]

\[ V(\theta) \cdot V_\perp(\theta) = 0 \]

noise

The interactions come from a conservative potential

\[ U_i = U(x_i, \theta_i) = \sum_{j=1; j \neq i}^{N} u_{i,j} \]

Peruani, Deutsch, and Bär, PRE (2006)
A simple model of physical active Brownian rods

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\[
\begin{align*}
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\dot{\theta}_i &= \frac{1}{\zeta_\theta} \left[ -\frac{\partial U_i}{\partial \theta_i} + \xi_i(t) \right], \\
\end{align*}
\]

\[
\mu = \zeta_{||}^{-1} V(\theta_i) V(\theta_i) + \zeta_{\perp}^{-1} V_{\perp}(\theta_i) V_{\perp}(\theta_i)
\]

Peruani, Deutsch, and Bär, PRE (2006)
Collective effects in myxobacteria

[particles form clusters and move together without any attractive force or communication]
How to characterize the collective properties of a SP rod system?
How to characterize the collective properties of a SP rod system?

We can look at the clustering properties of the system!

The cluster size distribution (CSD) \( p(m) \) conveys valuable information, and indicates that there are two phases: a \textit{dilute} and an \textit{“collective”} phase.
Collective effects in myxobacteria

What kind of clustering properties exhibit real myxobacteria?

- Experiments with:

  - A+S-Frz- mutants
    - * Cells do not reverse
    - * Social motility engine – off
    - * Advent. motility engine - on

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  - Wild-type
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Collective effects in myxobacteria

- **Alignment and clustering (A+S-Frz- & A+S+Frz-)**
  
  - Gliding speed = $3.10 \pm 0.35$ μm/min
  - $W=0.7 \ \mu m$, $L=6.3 \ \mu m$, $a=4.4 \ \mu m$
  - $\kappa=8.9 \pm 1.95$

Moving clusters of bacteria are formed:

Cell collision leads to **alignment**:

- 0s
- 60s
- 120s
- 180s
Steady state cluster size distribution is a function of the density

The packing fraction $\eta$ affects the cluster size distribution (CSD) in the way predicted by the theory, i.e., there is a change in the functional form of CSD with $\eta$.

The exponent at the critical density (0.88) is also in the range expected by the theory!

Peruani et al., PRL (2012)
Collective effects in myxobacteria

• By increasing the density: moving clusters -> aggregates!

At very high densities we observe aggregates in A+S-Frz- & A+S+Frz-!

Starruss, Peruani, al., Interface Focus (2012)
How can we understand the formation of these aggregates?

Does this mean the self-propelled rod model either failed or that is not sufficient to explain these patterns?

In fact, is it really true that the self-propelled rods cannot produce aggregates?
Is the emerging order nematic?

\[ \eta = 0.3, \quad \kappa = 10 \]
Collective effects in myxobacteria

at large densities and very large system sizes...

we learn that aggregates are also formed as in the experiments!
Collective effects in myxobacteria

aggregates eject large polar clusters: active stresses play a key role!
Collective effects in myxobacteria

aggregates eject large polar clusters: active stresses play a key role!

- a giant aggregate is formed
- multiple topological defects emerge
- the elastic energy increases
- system relaxes by ejecting a polar cluster
- the background gas density increases
- the cycle starts again

What have we learned?

And what is the advantage of using mathematical models?
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There were several empirical observations, we did not know how to explain…

formation of moving clusters  formation of aggregates

How do myxobacteria self-organize in order to produce these patterns?

(let us remember that the usual explanation, i.e. chemotaxis, seems not to be working here)
What have we learned?

And what is the advantage of using mathematical models?

There were several empirical observations that we did not know how to explain…

How do myxobacteria self-organize in order to produce these patterns?

The mathematical models, together with the simulations, allow us to test various hypotheses!

We provided a proof of principle for the proposed mechanisms.
Collective effects in myxobacteria

What have we learned?

And what is the advantage of using mathematical models?

There were several empirical observations that we did not know how to explain...

formation of moving clusters  formation of aggregates

So, what have we learned?

We learned that the combined effect of being self-propelled + having an elongated cell shape is enough to produce moving clusters and aggregates!

(and we have seen that these patterns produced with the mathematical model are quantitatively consistent with the empirical observations)
Collective effects in myxobacteria

What is next?

clusters | vortex aggregates
---|---

network patterns | fruiting bodies
collective effects in sheep
when we look at animal groups, we aim at:

1. Identify the underlying behavioral rules

2. Characterize the emerging macroscopic patterns
object of study: atom

object of study: group of sheep

to study its properties, we perturb it!

here, we will apply the same logic!
A simple, well-controlled experiment…

collective effects in sheep

vibrating collar

target position
A simple, well-controlled experiment...

Upon activation of the collar...

The trained individual moves toward the target position.
A simple, well-controlled experiment…

[Toulet, Gautrais, Bon, Peruani, PLoS ONE (2015)]
A simple, well-controlled experiment…
A simple, well-controlled experiment…

collective effects in sheep
A simple, well-controlled experiment…
A simple, well-controlled experiment...
A simple, well-controlled experiment...
Clip 1: The initiator provokes collective motion
collective effects in sheep

The temporal dynamics...

[Toulet, Gautrais, Bon, Peruani, PLoS ONE (2015)]
The temporal dynamics...

collective effects in sheep

$$S_S \rightarrow M \quad M \rightarrow S_T$$

excitatory

inhibitory

excitatory

inhibitory
The temporal dynamics...

\[
\mu = \alpha \frac{nM^\beta}{nS_S^\gamma}
\]

\[
\sigma = \alpha' \frac{nS_T^\beta'}{nM^\gamma'}
\]

(this is very different from physical interactions: i.e. no pairwise interactions)

(important observation: we assume that each individual is able to see all other individuals in the group)
The temporal dynamics...

\[ \mu(nM, N) = \alpha \frac{nM^\beta}{nS_S^{\gamma'}} = \alpha \frac{nM^\beta}{(N - nM)^\gamma'} \]

\[ \sigma(nM, N) = \alpha' \frac{nS_T^{\beta'}}{nM^{\gamma'}} = \alpha' \frac{(N - nM)^{\beta'}}{nM^{\gamma'}} \]
This is not all...
Clip 2: The initiator fails to provoke collective motion
The group of naïve individuals seems to reach a consensus: either all of them follow the trained individual, or none does it!

Is there a collective decision-making process? What is the mechanism behind this?
The group of naïve individuals seems to reach a consensus: either all of them follow the trained individual, or none does it!

Is there a collective decision-making process?

What is the mechanism behind this?

Two key factors: the “stimulus” time & characteristic time to react \((1/\mu)\)

**Probability plots:**

- **A:** Size 8
- **B:** Size 16
- **C:** Size 32

- \(P_F\) = prob. first follow occurs before time \(t\)
- \(P_S\) = prob. the trained individual has reached the target at time \(t\)

Notice that we have assumed that individuals in state \(S_t\) cannot induce a transition from the state \(S_s\). This implies also that the trained individual can only induce a transition if it is in motion.
Spontaneous behavior (= no leader/trained individual)… with N=100

a dilemma:
How to stay together while looking for green pastures for yourself?
How to eat without being eaten?
collective effects in sheep
collective effects in sheep
How to characterize the observed collective behavior?

![Graph showing collective effects in sheep](image)
An aggregation event:

Color indicates whether the sheep is grazing (blue), moving (green), or running (red)
An aggregation event:

fraction running

radial velocity

\[ v_r^t \equiv \langle (r_i^t - r_{cm}^t) \cdot v_i^t \rangle / \left[ ||(r_i^t - r_{cm}^t)|| ||v_i^t|| \right] \]
How is the distribution of aggregation events?

there are aggregation events of many sizes…

are these power-law distributed?

A

\[ v_{cm} \]

\[ 0 \quad 0.5 \quad 1 \]

\[ t \quad 0 \quad 100 \quad 200 \]

B

\[ P(x) \sim x^{-\gamma} \]

\[ \gamma = 1.57 \]

with

Peruani
How can we model the observed behavior?

Using a Vicsek-like model:

Transition between “behavioral states” (i.e. slow motion, fast motion, etc):

\[
p_{0\to1}(i, t) = \frac{1 + \alpha n_1^t(i)}{\tau_{0\to1}}, \quad p_{1\to0}(i, t) = \frac{1 + \alpha n_0^t(i)}{\tau_{1\to0}},
\]

\[
p_{0,1\to2}(i, t) = \frac{1}{\tau_{0,1\to2}} \left[ \frac{\ell_i^t}{d_R} (1 + \alpha m_R^t(i)) \right]^{\delta},
\]

\[
p_{2\to0}(i, t) = \frac{1}{\tau_{2\to0}} \left[ \frac{d_s}{\ell_i^t} (1 + \alpha m_S^t(i)) \right]^{\delta},
\]
How can we model the observed behavior?

Using a Vicsek-like model:

1. \[ r_i^{t+\Delta t} = r_i^t + \Delta t \, v(q_i^t) \, s_i^{t+\Delta t}, \]

2. \[ \theta_i^{t+\Delta t} = \text{Arg} \left[ \sum_{j \in \mathcal{M}_i} s_j^t \right] + \psi_i^t \quad (\text{if } q_i^t = 1), \]

3. \[ \theta_i^{t+\Delta t} = \text{Arg} \sum_{j \in \mathcal{V}_i} \left[ \delta_{2,q_j^t} s_j^t + \beta \, f(r_{ij}^t) \, e_{ij}^t \right] \quad (\text{if } q_i^t = 2) \]

Transition between "behavioral states" (i.e. slow motion, fast motion, etc):

4. \[ p_{0 \to 1}(i,t) = \frac{1 + \alpha n_1^t(i)}{\tau_{0 \to 1}}, \quad p_{1 \to 0}(i,t) = \frac{1 + \alpha n_0^t(i)}{\tau_{1 \to 0}}, \]

5. \[ p_{0,1 \to 2}(i,t) = \frac{1}{\tau_{0,1 \to 2}} \left[ \frac{\ell_i^t}{d_R} \left( 1 + \alpha m_R^t(i) \right) \right]^\delta, \]

6. \[ p_{2 \to 0}(i,t) = \frac{1}{\tau_{2 \to 0}} \left[ \frac{d_s}{\ell_i^t} \left( 1 + \alpha m_S^t(i) \right) \right]^\delta, \]
Model behavior...
Comparison between model and experiments…

collective effects in sheep
Sheep alternate periods of grazing (slowly spreading) with fast aggregation events. This seems to solve the dilemma of looking for resources, while remaining together.

Whether the distribution of aggregation events is critical (or quasi-critical) is still an open issue, but certainly a possibility.

The proposed (complex) model is able to reproduce the data. This suggests that all the mechanisms required to produce the observed phenomena is there. Which ingredients (among the many introduced) are really necessary is an open question.

Using the same theoretical framework, we can explain a large variety of collective phenomena in fundamentally different biological systems. The required theoretical framework, using the language of physics, corresponds to the theory of active particles in dissipative media, which we still do not fully understand.
Le mouton de Panurge, une réputation qui se confirme

Dans un troupeau, les moutons copient bien l’attitude de leurs voisins. La sélection naturelle aurait favorisé ce comportement d’imitation qui maximise les chances de manger sans être mangé.

Sean Bailly
collaborators related to the presented works

**Nice**
- Oleksandr Chepizkho
- Stefan Otte
- Luis Gomez Nava
- Emiliano Perez Ipiña
- Lucas Barberis
- Robert Grossmann

**Toulouse**
- Richard Bon
- Richard Gautrais
- Guy Theraulaz
- Sylvain Toulet

**Paris/Saclay**
- Hugues Chaté
- Francesco Ginelli (Aberdeen)

**Berlin & Dresden**
- Markus Bär (Berlin)
- Andreas Deutsch (Dresden)
Thanks for your attention!