Towards a non-equilibrium statistical mechanics approach of biological systems

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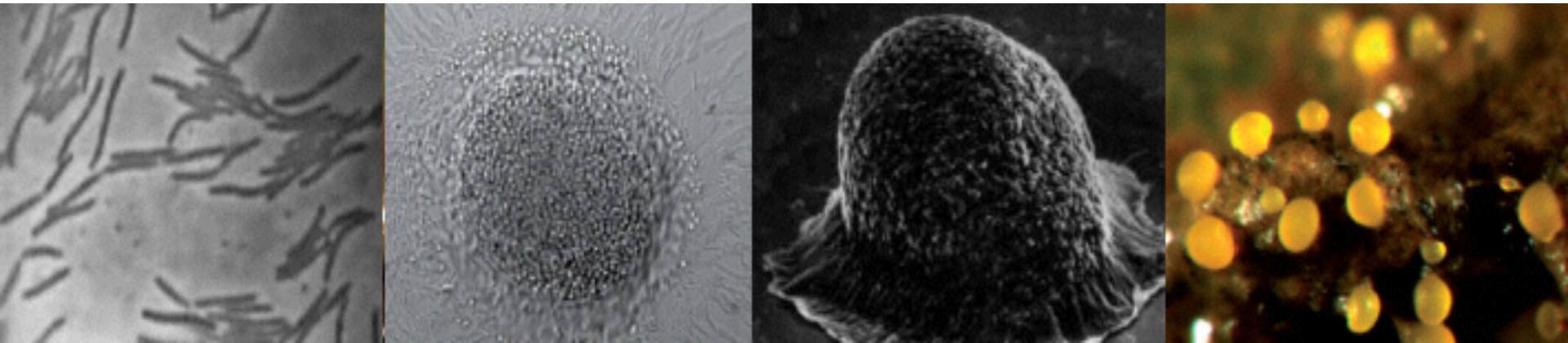
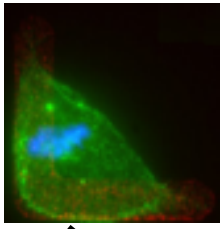
LPC - Clermont - Feb. 2017

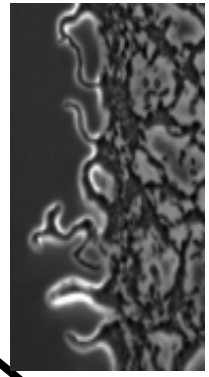


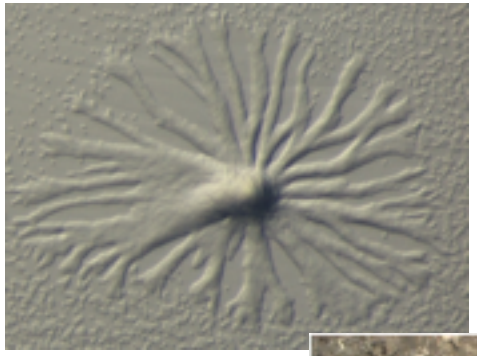
collective behavior at various scales

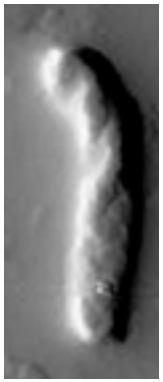
Peruani



Molecular motors







bacteria

~10^{-6} m

eukaryote cells

social insects

~10^{-2} m

bird and fish

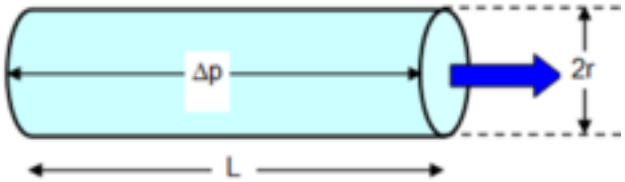
~10^{-1} m

Mammals

~10^{0} m

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

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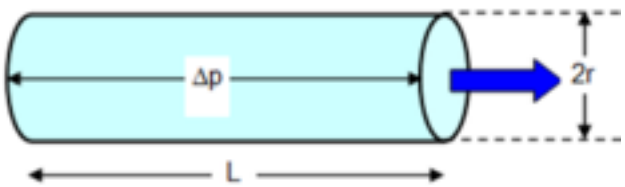
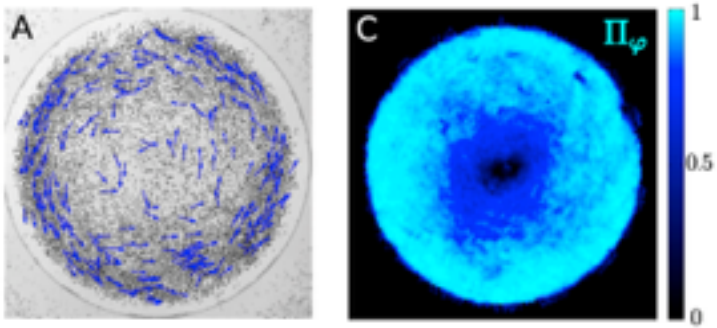


in a glass, the water will not spontaneously start moving in a given direction

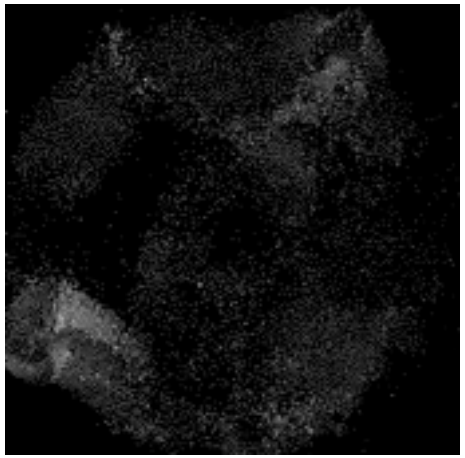
Lithograph August Mayer

in active or living systems the situation is different…



quincke rollers in confinement

A. Bricard et al. Nature Comm. 6, 7470 (2015)



the examples we are going to visit today…

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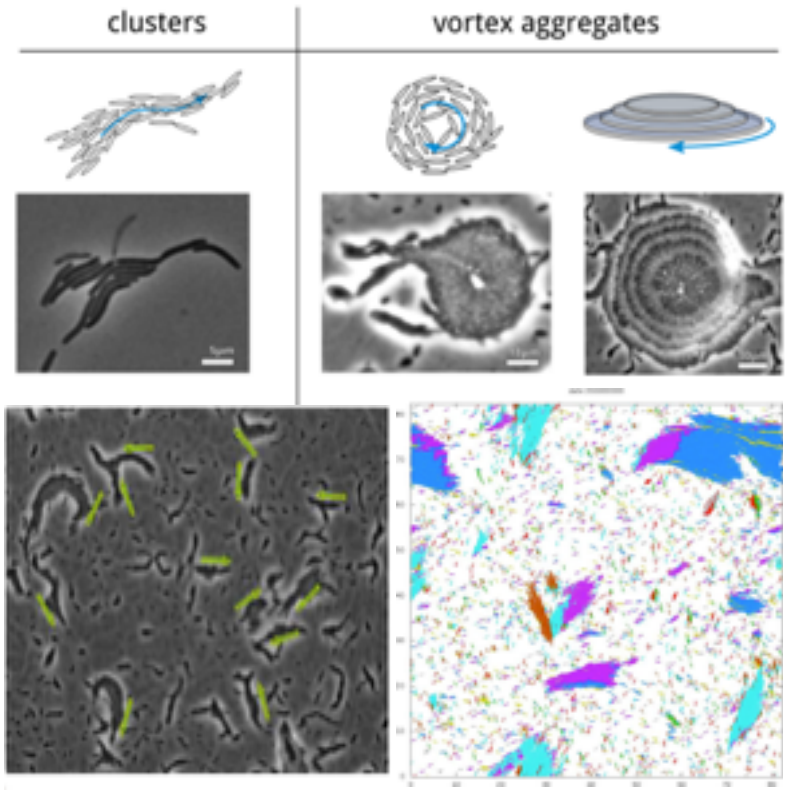
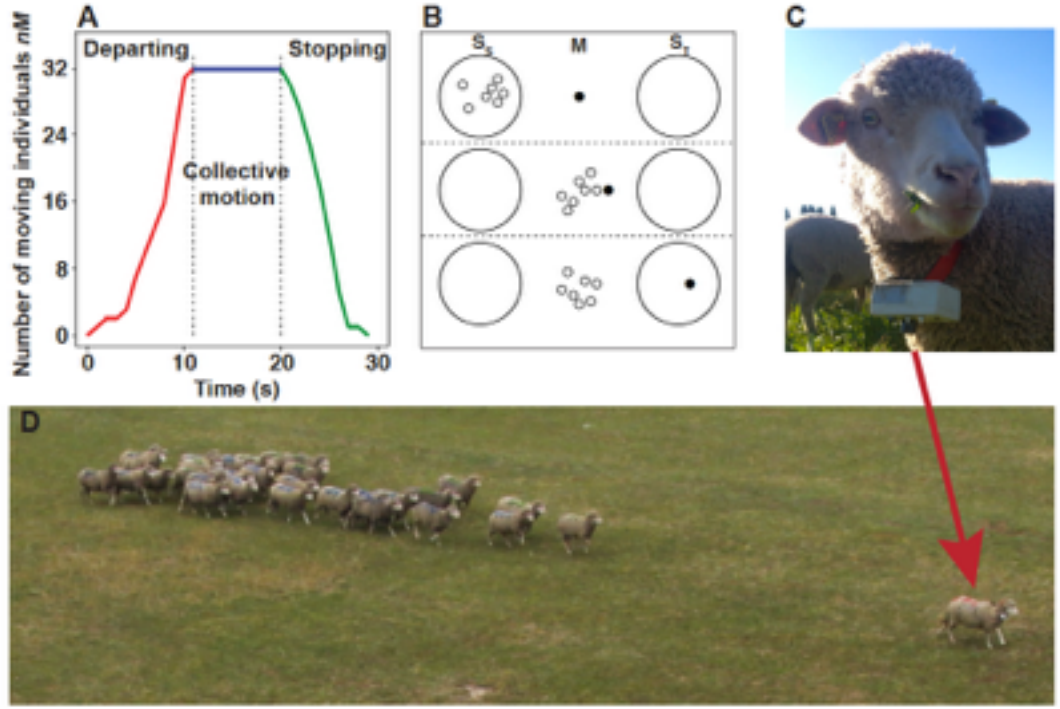
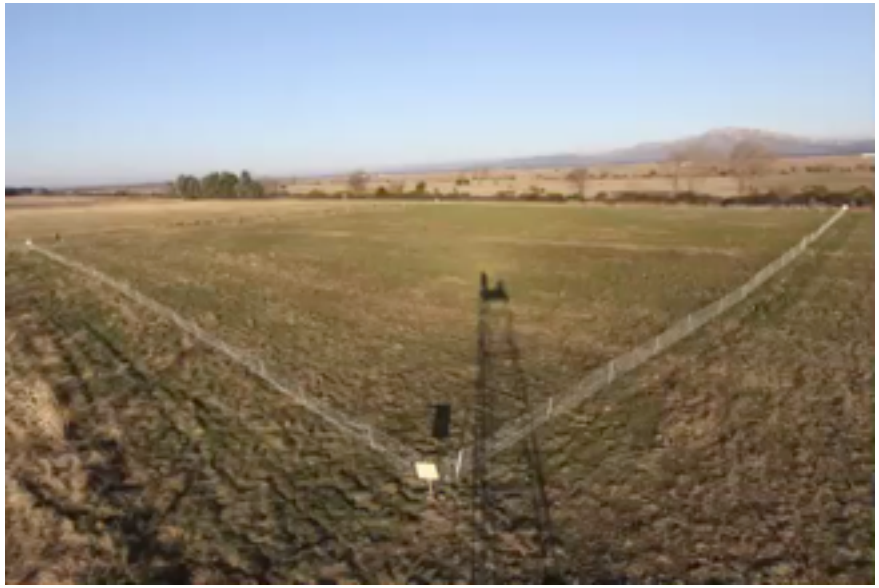




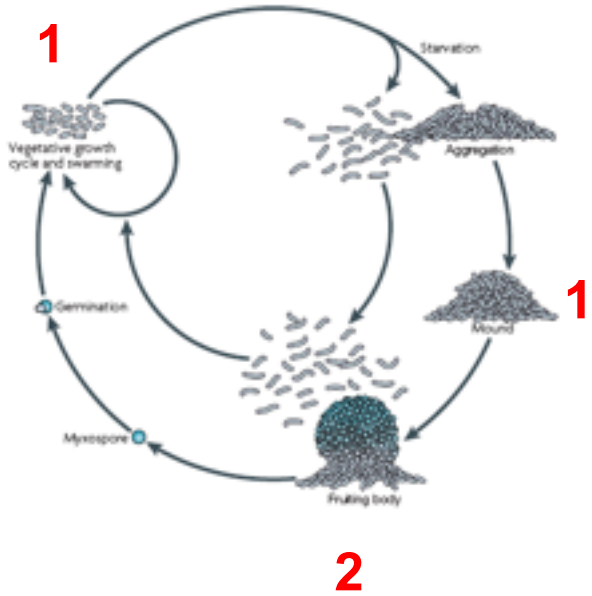


spontaneous behaviors/flows in biological systems

Peruani, Deutsch, Bär, PRE (2006)
Peruani et al., PRL (2012)
Weitz, Deutsch, Peruani, PRE (2015)
Toulet, Gautrais, Bon, Peruani, PLoS ONE (2015)
Ginelli*, Peruani*, Pillot, Chate, Theraulaz, Bon, PNAS (2015)

Collective effects in myxobacteria

life-cycle

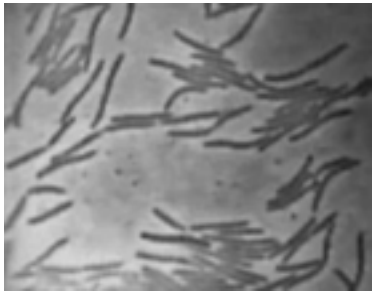


Multicellular organization in myxobacteria

Transition from individual to collective behavior

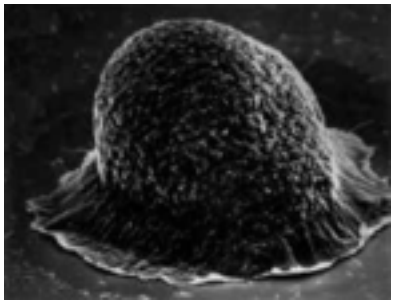
(i.e. from "unicellular to multicellular")

uncoordinated behavior → Complex collective behavior

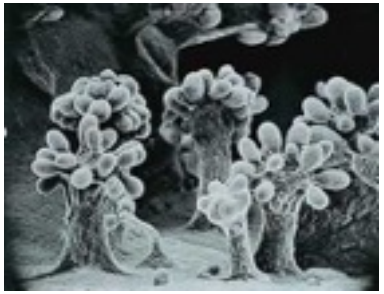


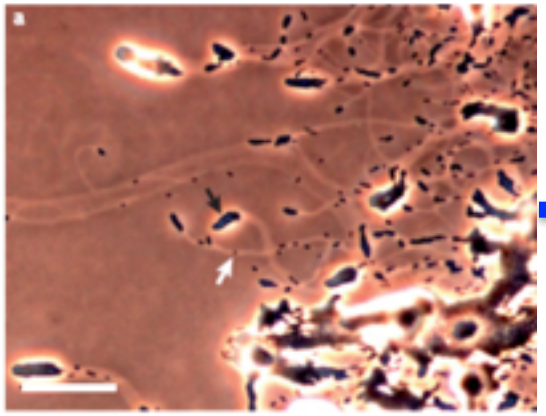
Reichenbach 1965

2



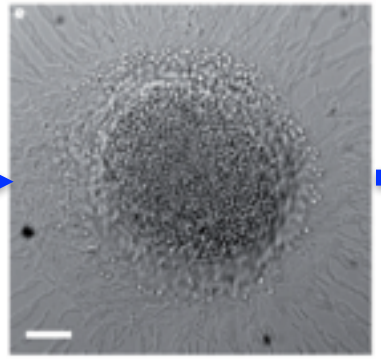
Zusman 2007





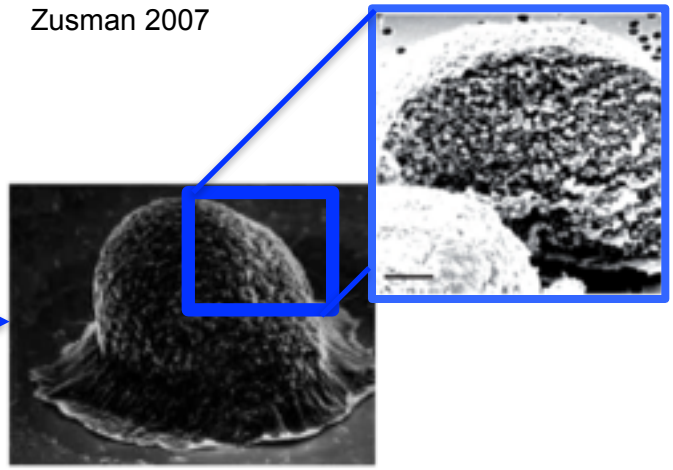
bacteria hunting in clusters

(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.

Collective effects in myxobacteria

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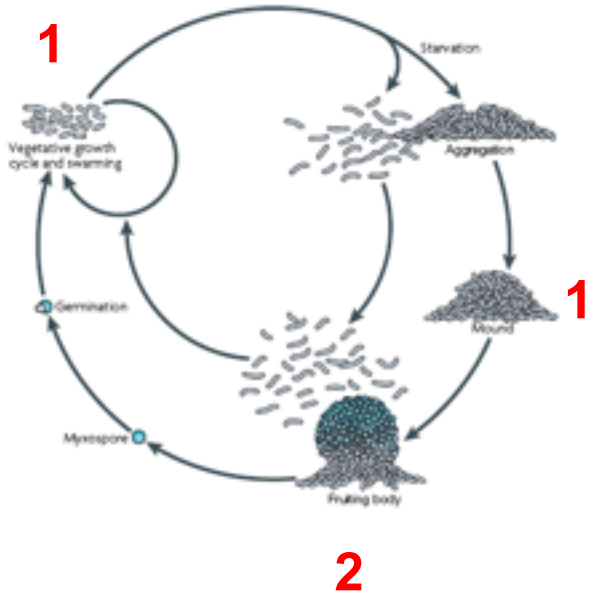
life-cycle



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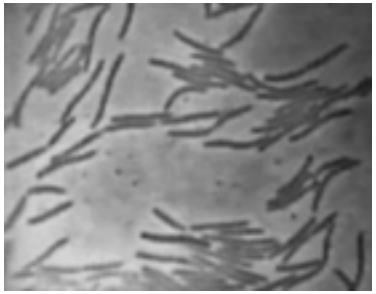

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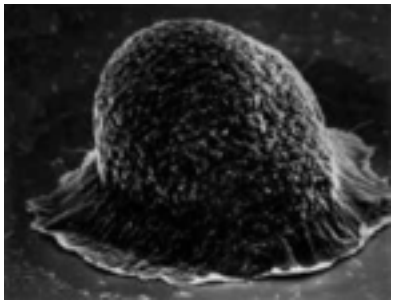

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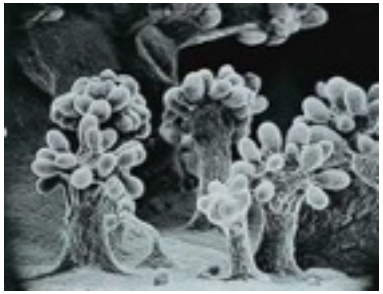
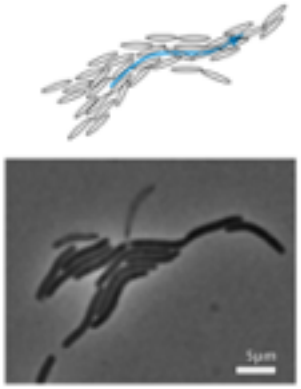
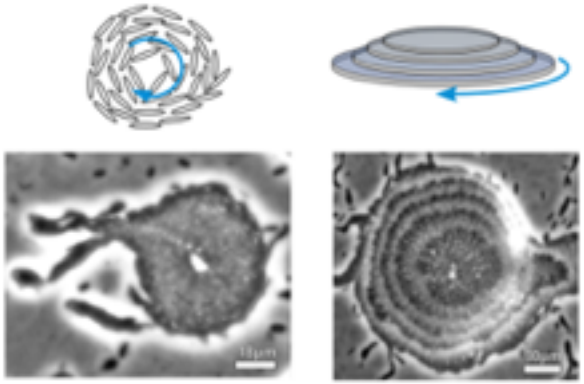


Self-organized patterns we want to explain…

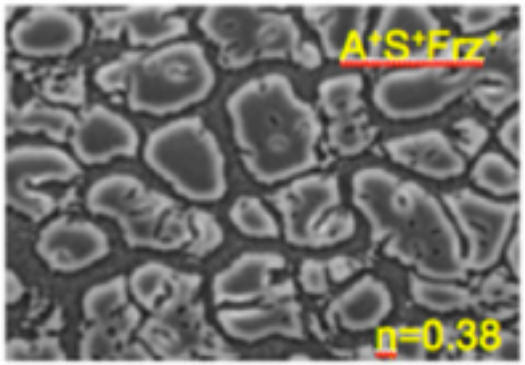
clusters



vortex aggregates



network patterns

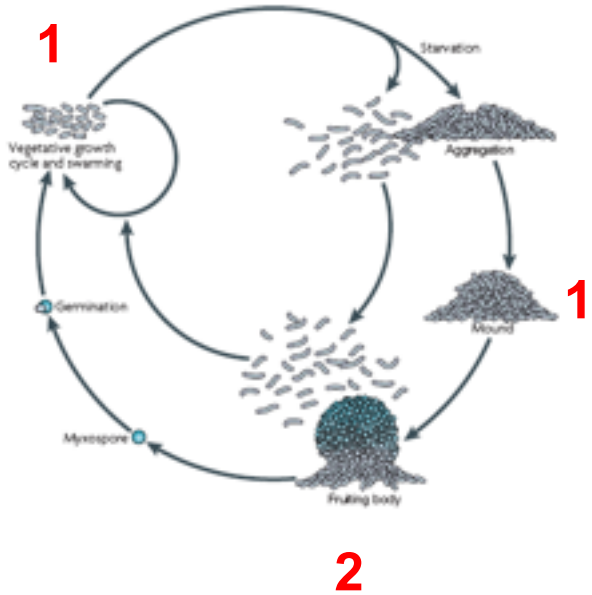


fruiting bodies

Collective effects in myxobacteria

Peruani

life-cycle



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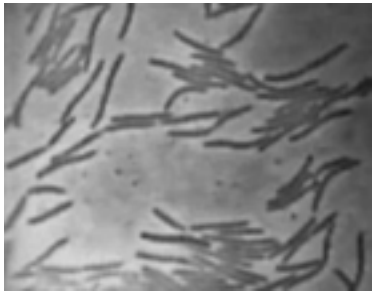

Reichenbach 1965

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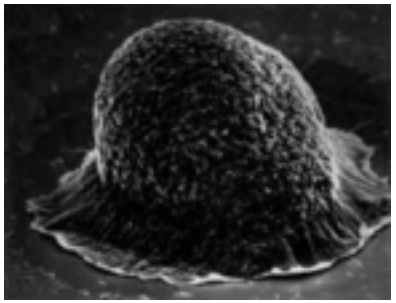

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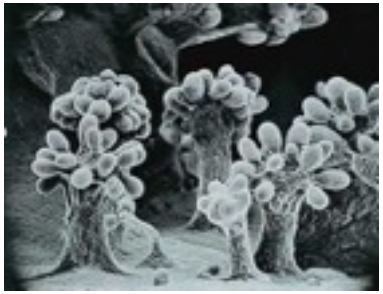

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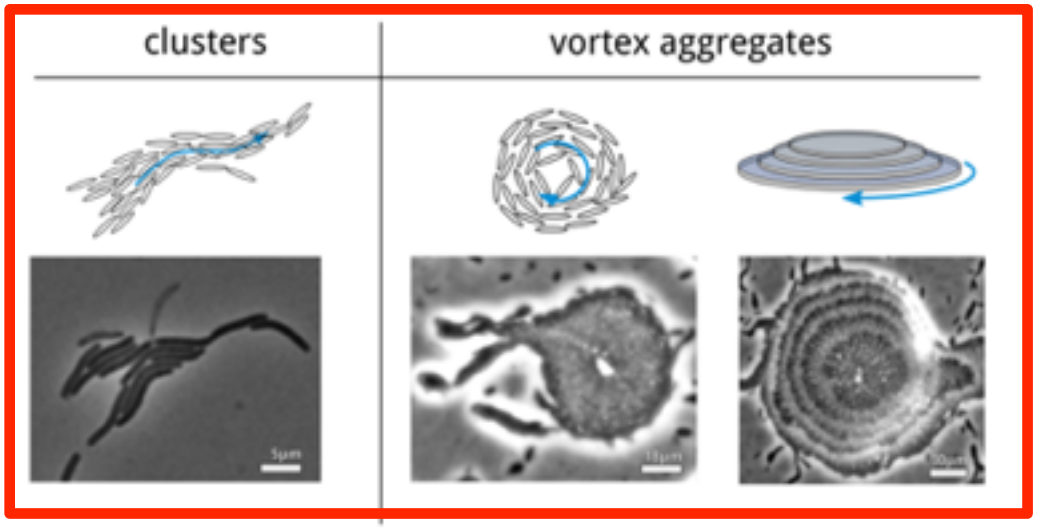
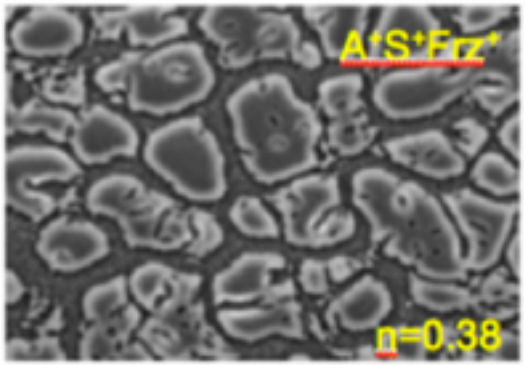


network patterns

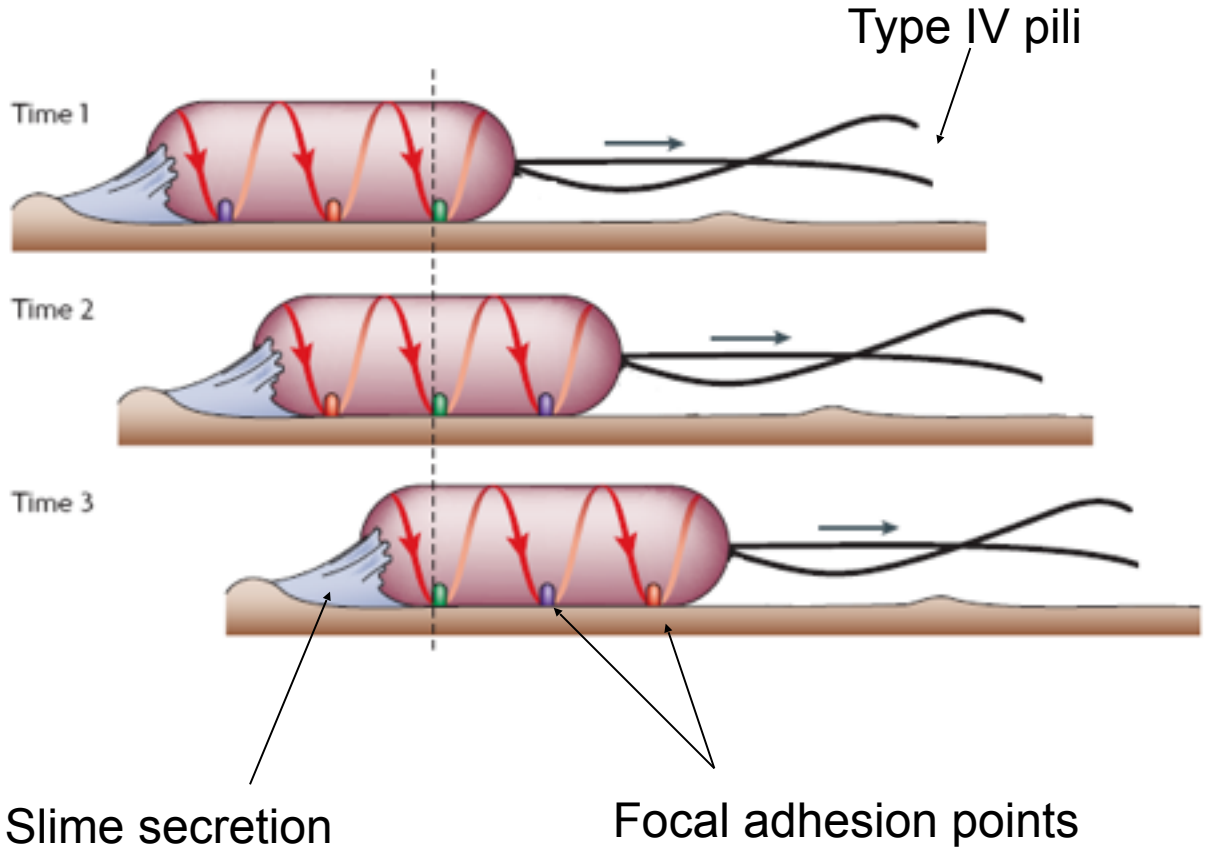


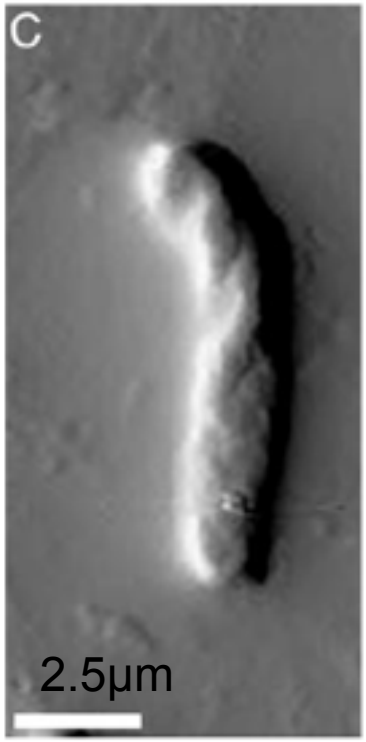
fruiting bodies

Collective effects in myxobacteria

Peruani

- **Motility engines in Myxococcus xanthus:**





Pelling 05

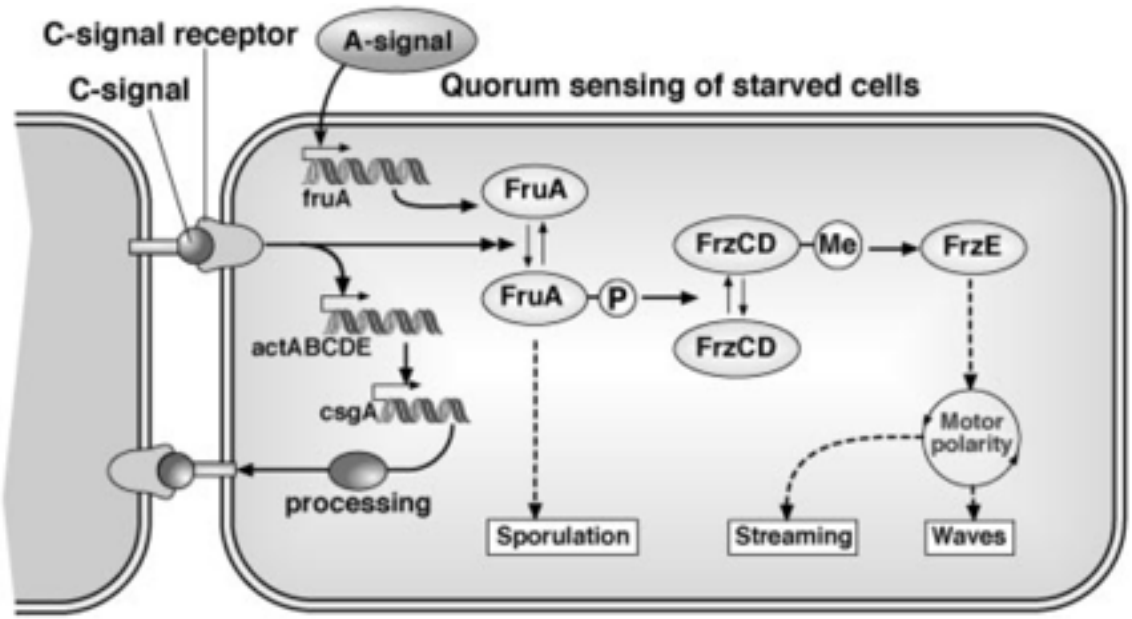
Myxobacteria (speed = 0.025 to 0.1 µm/s)
Cyanobacteria (speed =10 µm/s)
Cytophaga-Flavobacterium (speed = 2 to 4 µm/s)

Collective effects in myxobacteria

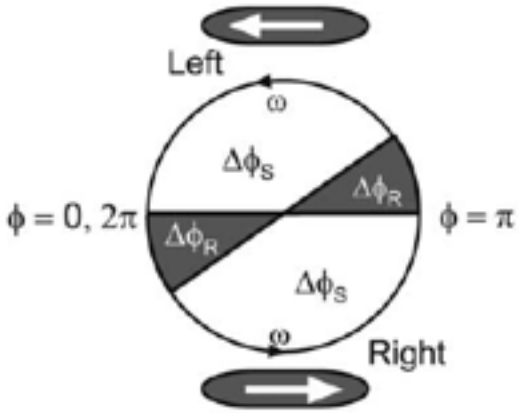
- **How do M. xanthus cells communicate?**

  - 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

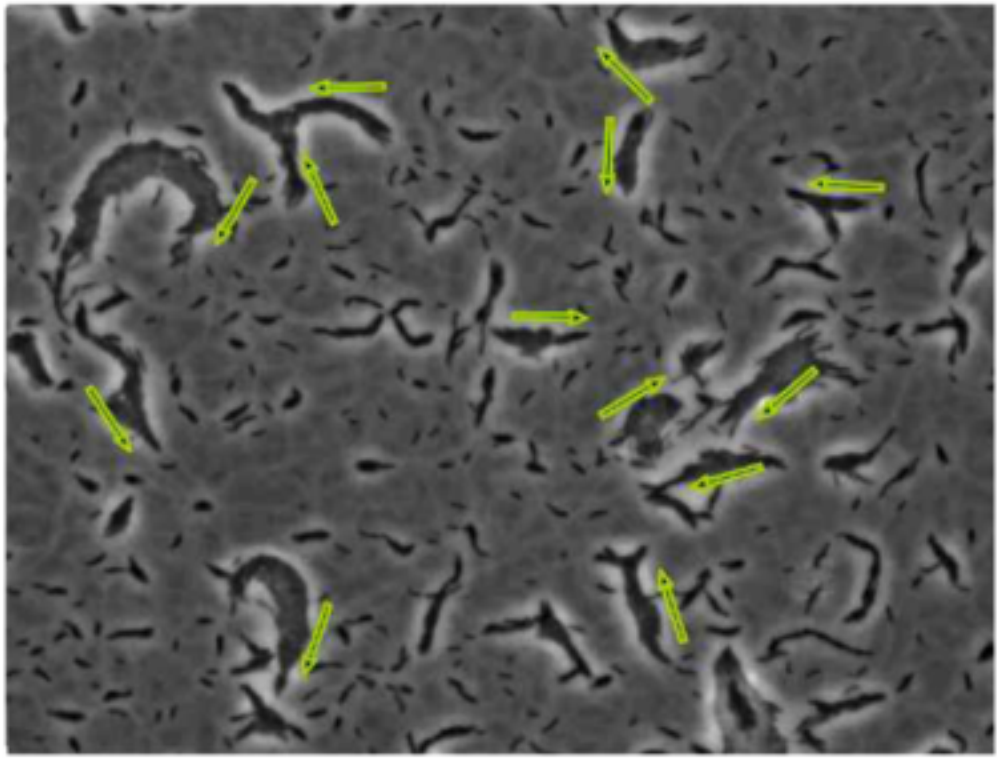


Internal clock

Collective effects in myxobacteria

Peruani

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

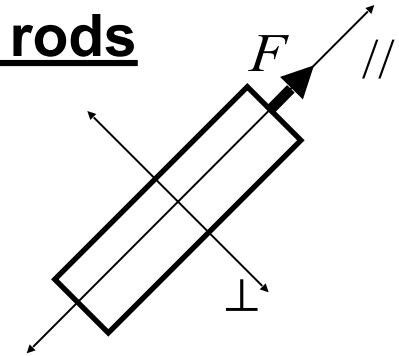
Self-propulsion of bacteria + elongated shape

= collective behavior ?

What macroscopic effects emerge

in a system of self-propelled liquid crystals?

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



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

Self-Propelling force/stress

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

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

noise

$$\mathbf{V}(\theta) \equiv (\cos(\theta), \sin(\theta))$$

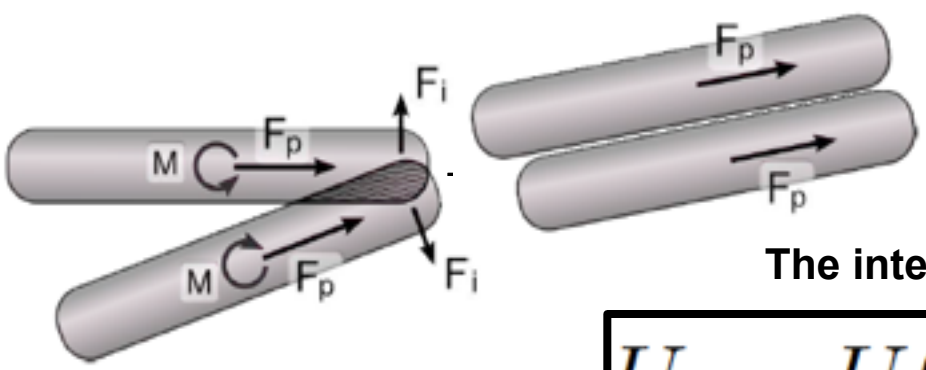
$$\mathbf{V}(\theta).\mathbf{V}_\perp(\theta) = 0$$

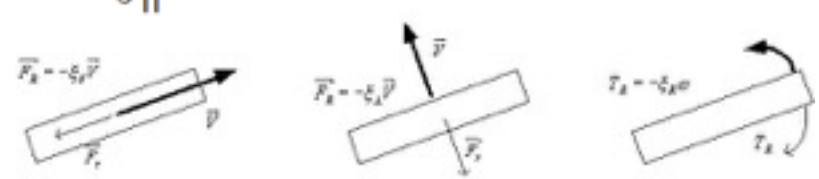
mobility tensor

$$\boldsymbol{\mu} = \zeta_\parallel^{-1}\mathbf{V}(\theta_i)\mathbf{V}(\theta_i) + \zeta_\perp^{-1}\mathbf{V}_\perp(\theta_i)\mathbf{V}_\perp(\theta_i)$$

friction coefficients

$\zeta_\parallel$ $\zeta_\perp$ ζ_θ



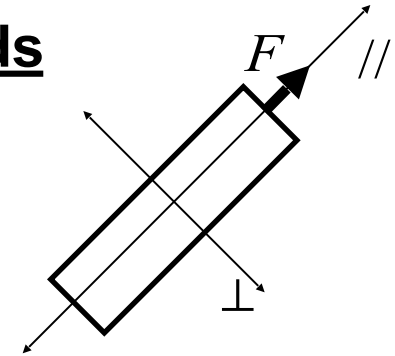


The interactions come from a conservative potential

$$U_i = U(\mathbf{x}_i, \theta_i) = \sum_{j=1;j\neq i}^{N} u_{i,j}$$

Peruani, Deutsch, and Bär, PRE (2006)

• A simple model of physical active Brownian rods



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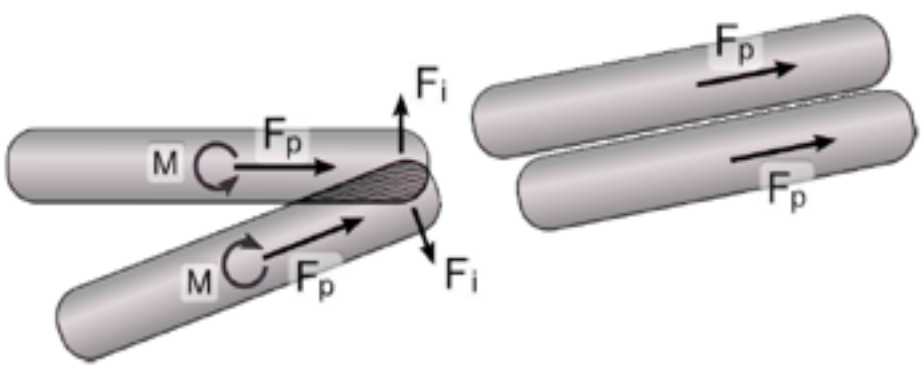
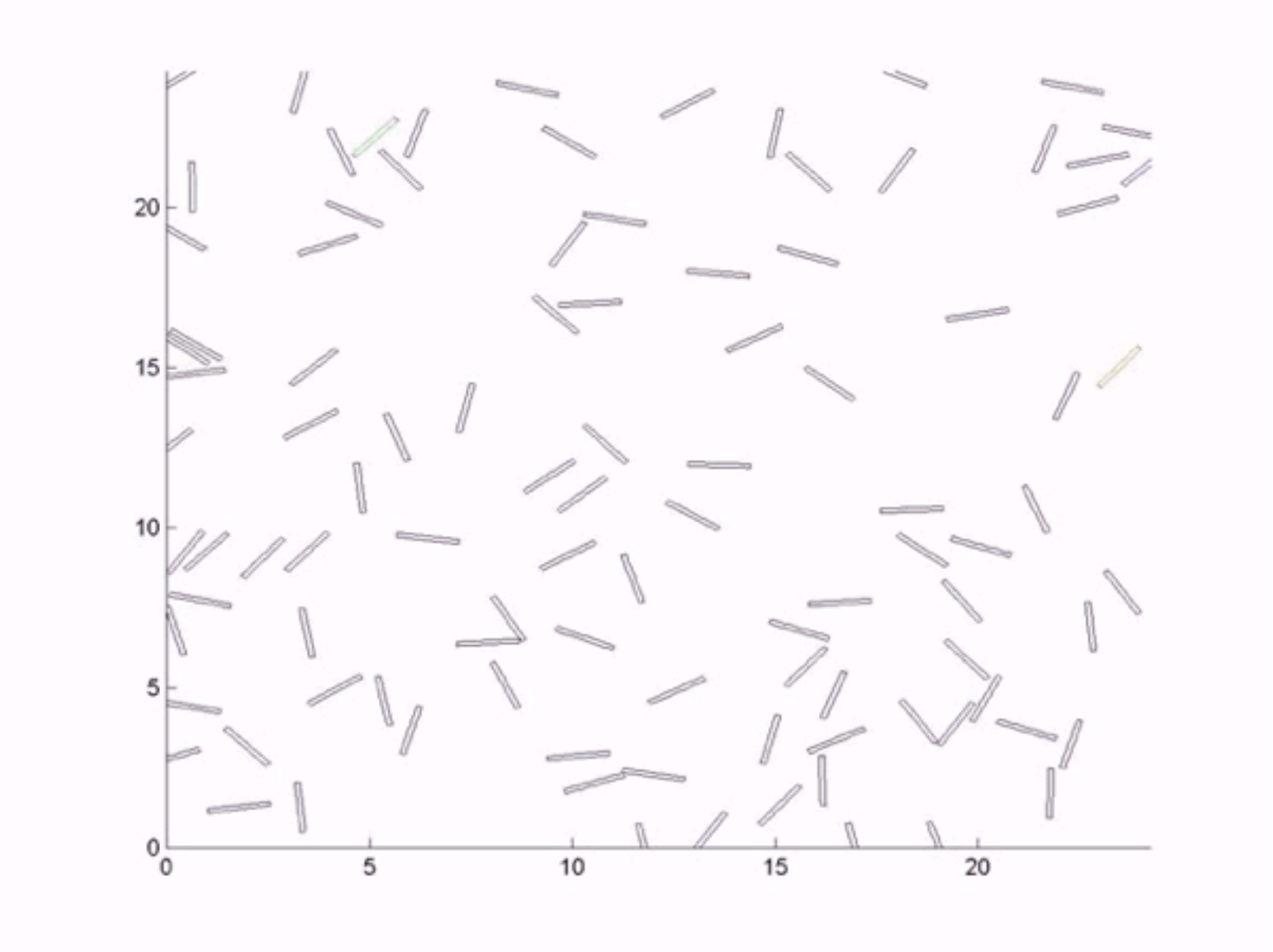


Peruani, Deutsch, and Bär, PRE (2006)

Collective effects in myxobacteria

Peruani

[particles form clusters and move together without any attractive force or communication]

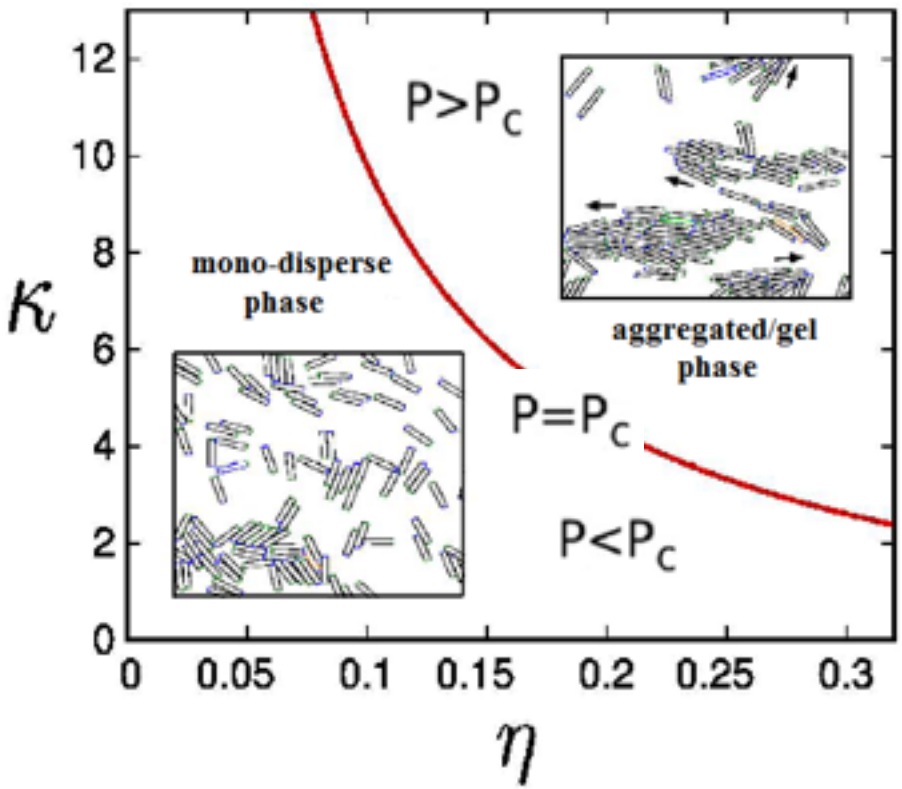


How to characterize the collective properties of a SP rod system?

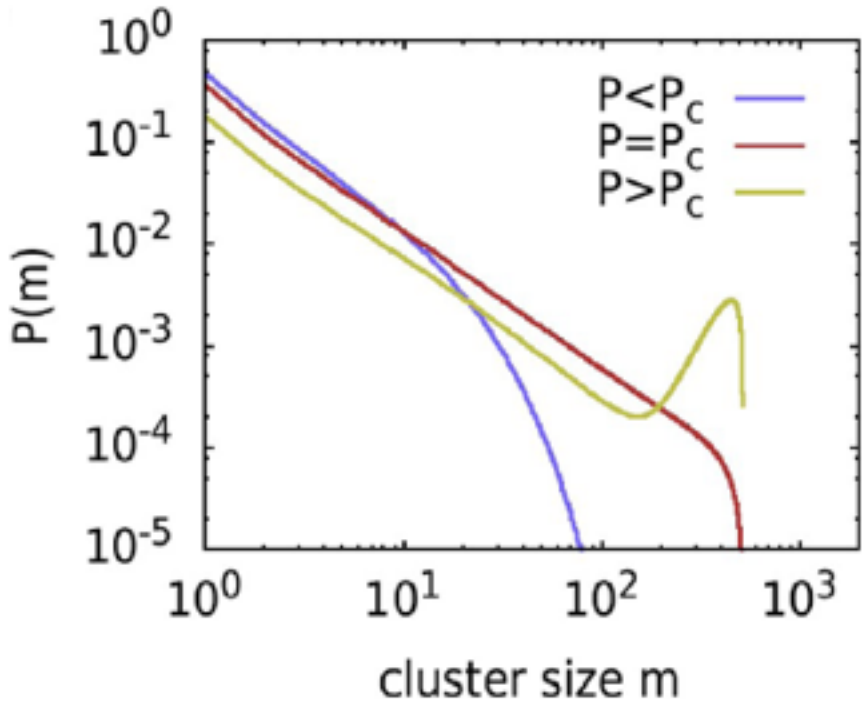
Collective effects in myxobacteria

Peruani

How to characterize the collective properties of a SP rod system?



P=density!



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 <u>dilute</u> and an "<u>collective</u>" phase.

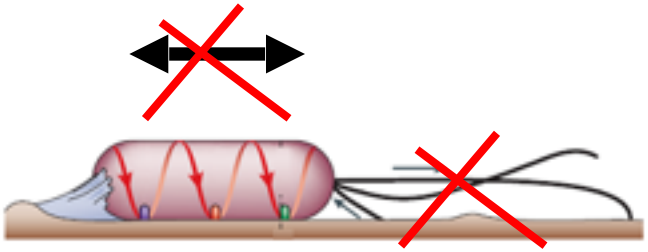
Collective effects in myxobacteria

Peruani

What kind of clustering properties exhibit real myxobacteria ?

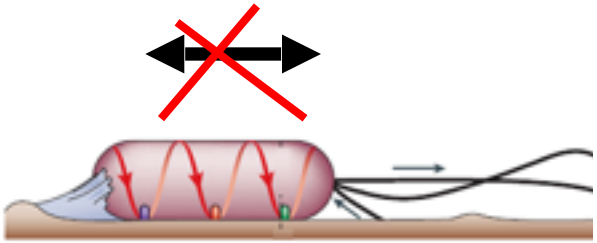
- **Experiments with:**

***A+S-Frz-* mutants**



* Cells do not reverse
* Social motility engine – off
* Advent. motility engine - on

***A+S+Frz-* mutants**



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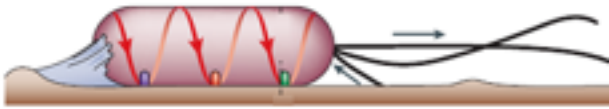
Wild-type



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F. Peruani et al. Phys Rev Lett (2012); J. Starruss et al. Interface Focus (2012)

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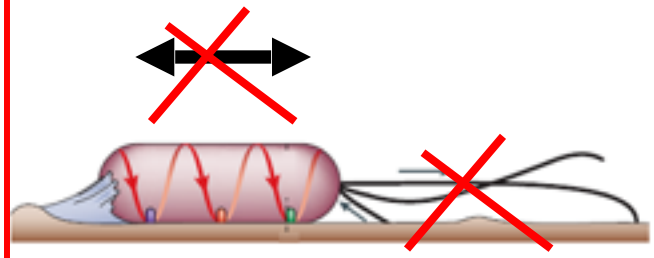
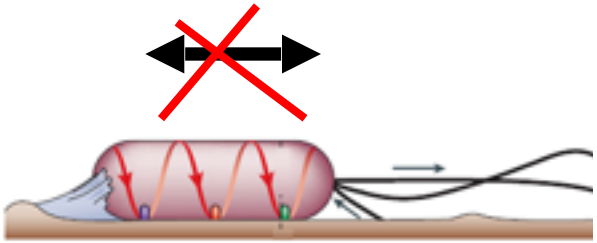
- **Experiments with:**

***A+S-Frz-* mutants**



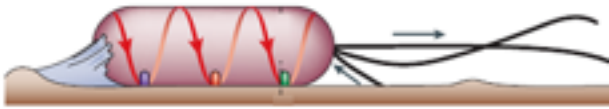
* Cells do not reverse
* Social motility engine – off
* Advent. motility engine - on

***A+S+Frz-* mutants**



* Cells do not reverse
* Social motility engine – on
* Advent. motility engine - on

Wild-type

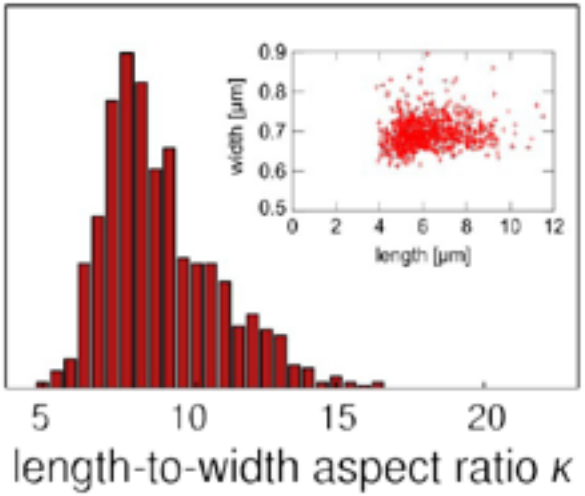


* Cells do reverse
* Social motility engine – on
* Advent. motility engine - on

Collective effects in myxobacteria

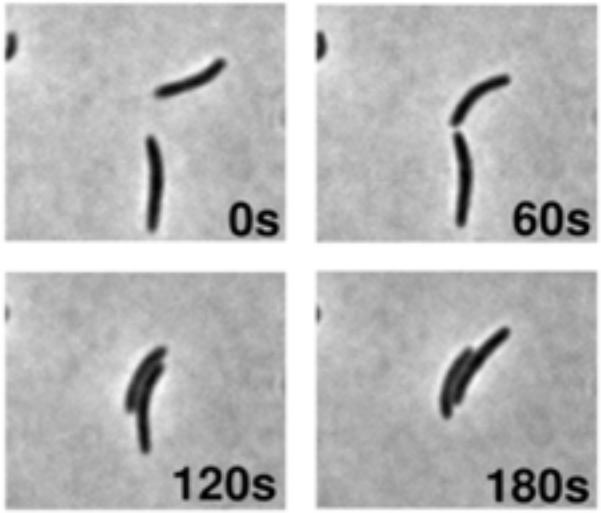
Peruani

- **Alignment and clustering (A+S-Frz- & A+S+Frz-)**

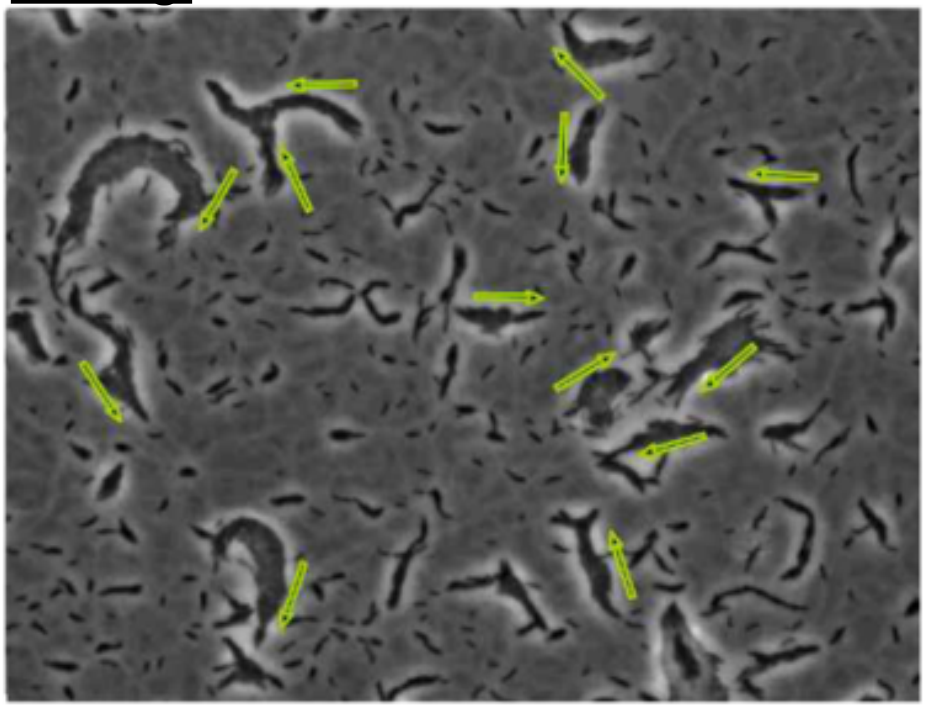


- **Gliding speed = 3.10 ± 0.35 μm/min**
- **W=0.7 μm, L=6.3 μm, a=4.4 μm**
- **κ=8.9 ± 1.95**

Cell collision leads to alignment:

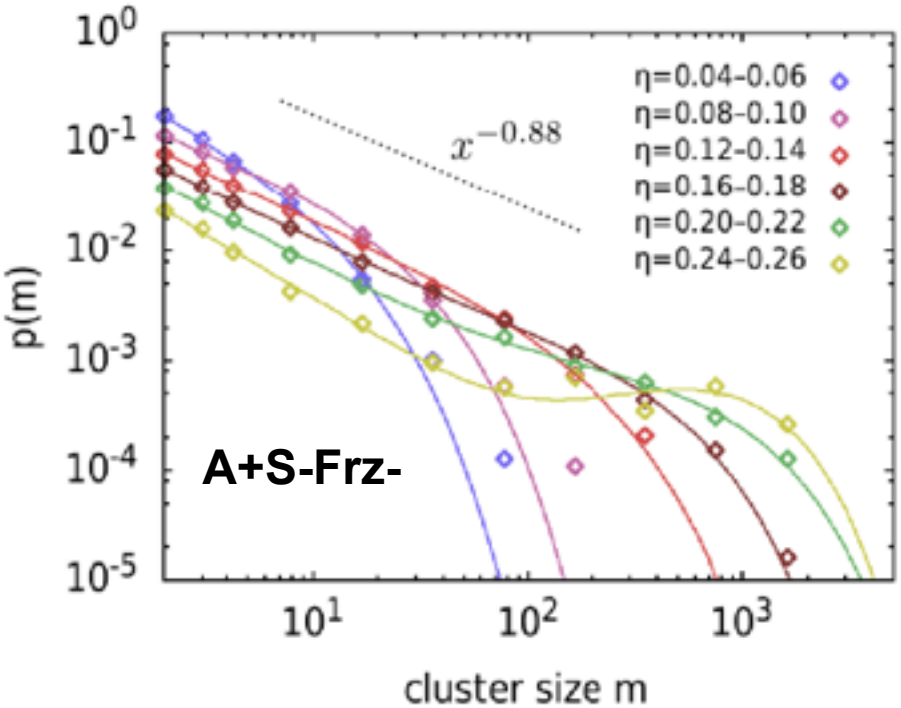


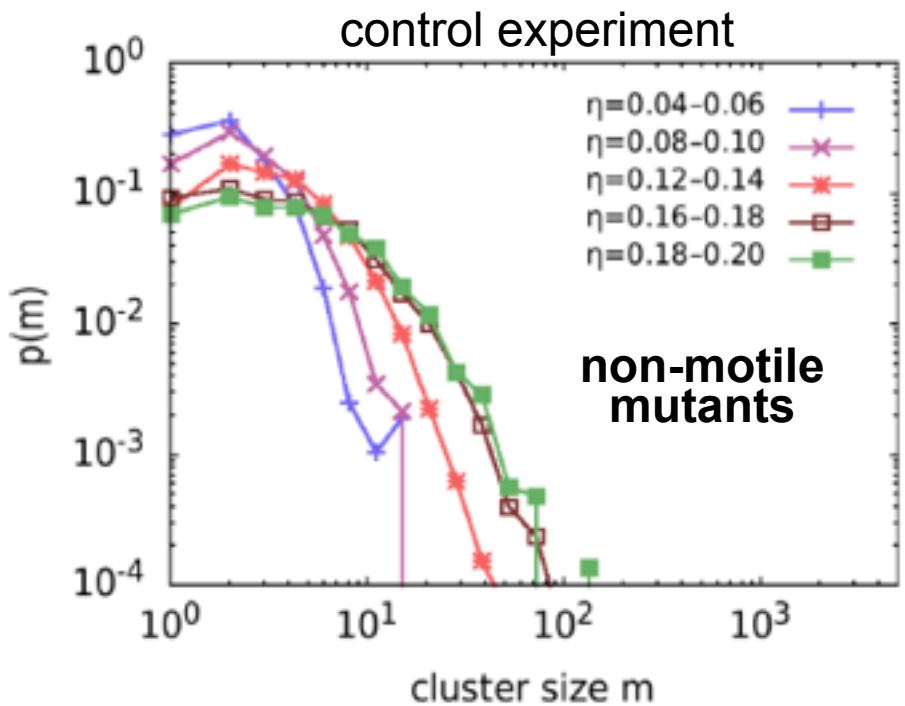
Moving clusters of bacteria are formed:



Collective effects in myxobacteria

- **Steady state cluster size distribution is a function of the density**





The packing fraction η 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 η.

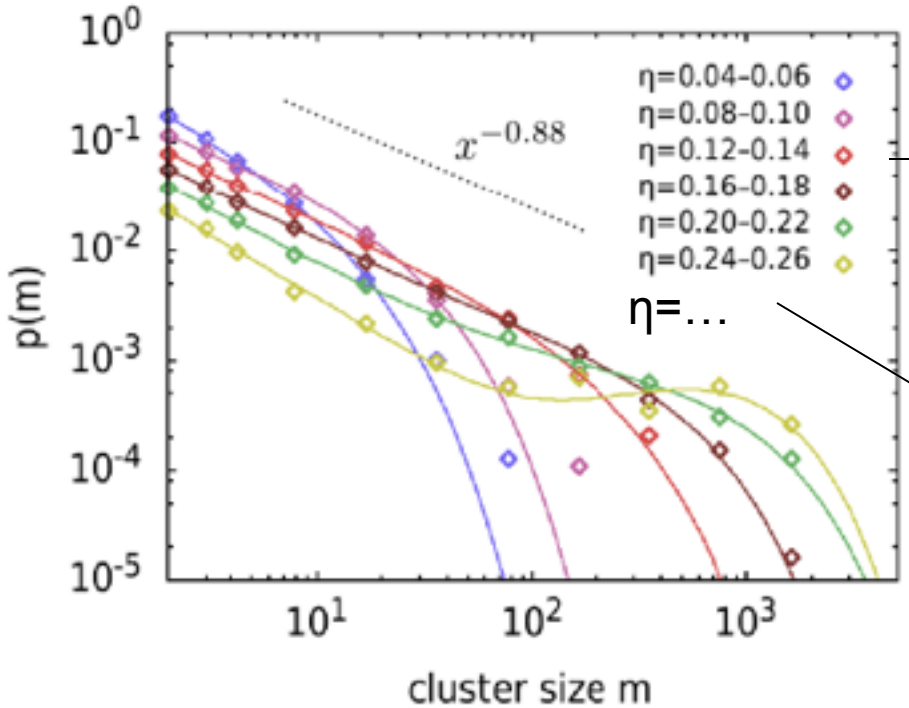
The exponent at the critical density (0.88) is also in the range expected by the theory!

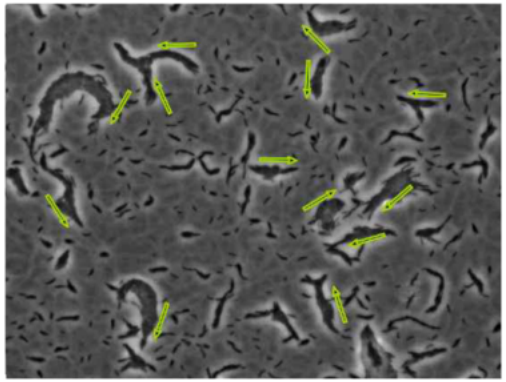
Peruani et al., PRL (2012)

Collective effects in myxobacteria

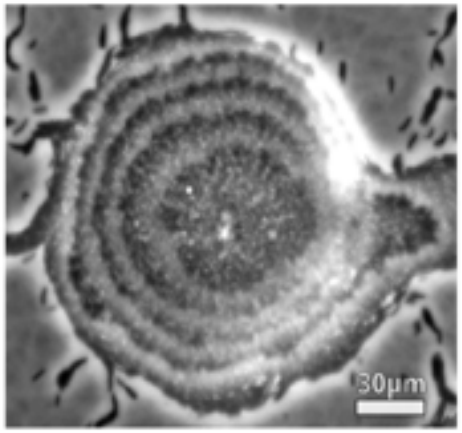
Peruani

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





Moving clusters



Aggregate formation

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

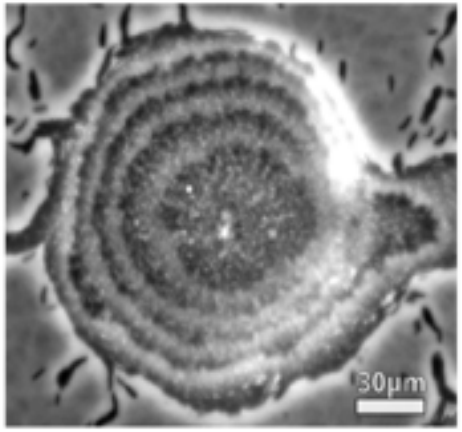
Starruss, Peruani, al., Interface Focus (2012)

Collective effects in myxobacteria

How can we understand the formation of these aggregates?

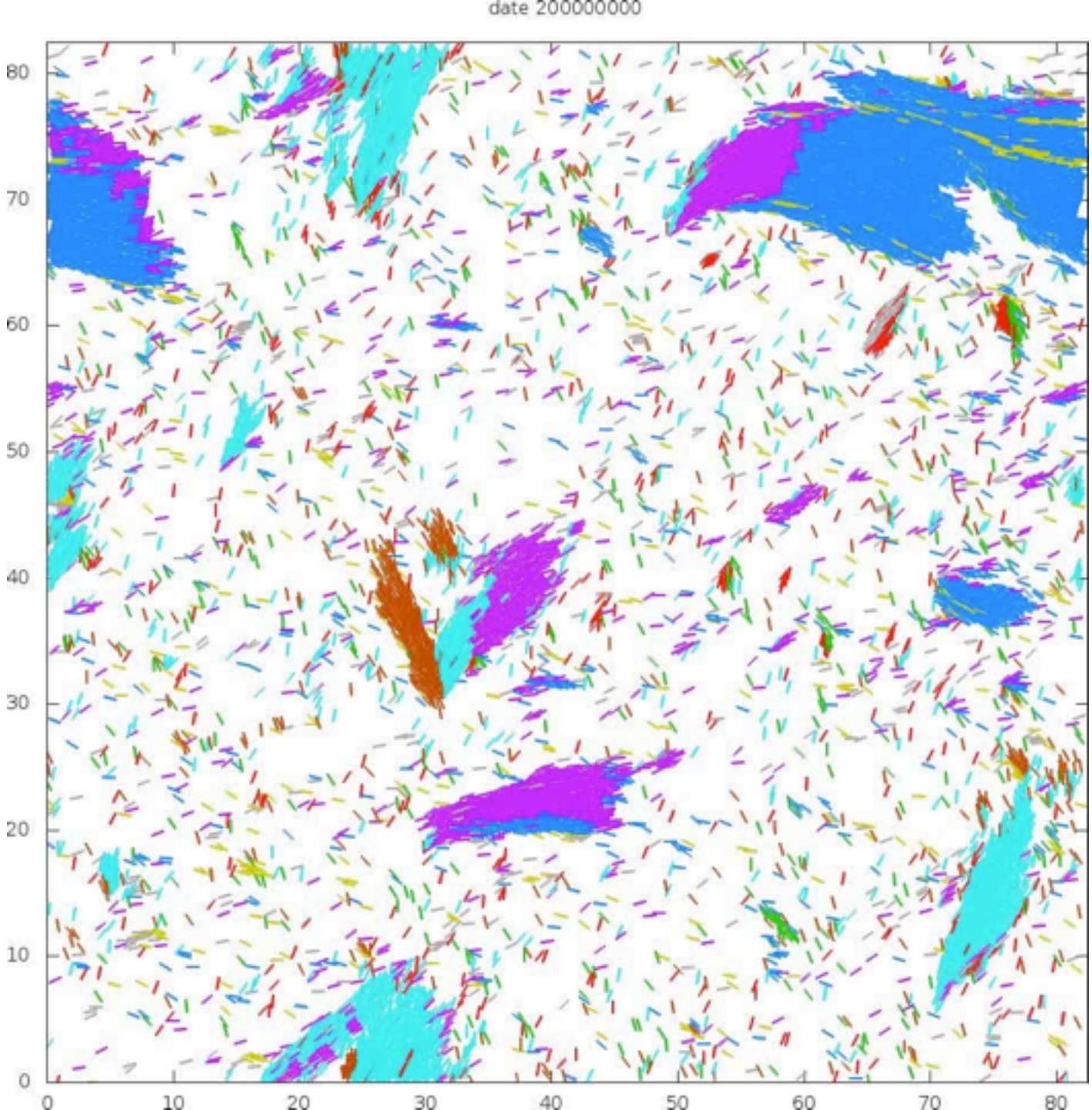
Does this mean the the self-propelled rod model either failed or that is not sufficient to explain these patterns?

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



?

Aggregate formation


date 200000000
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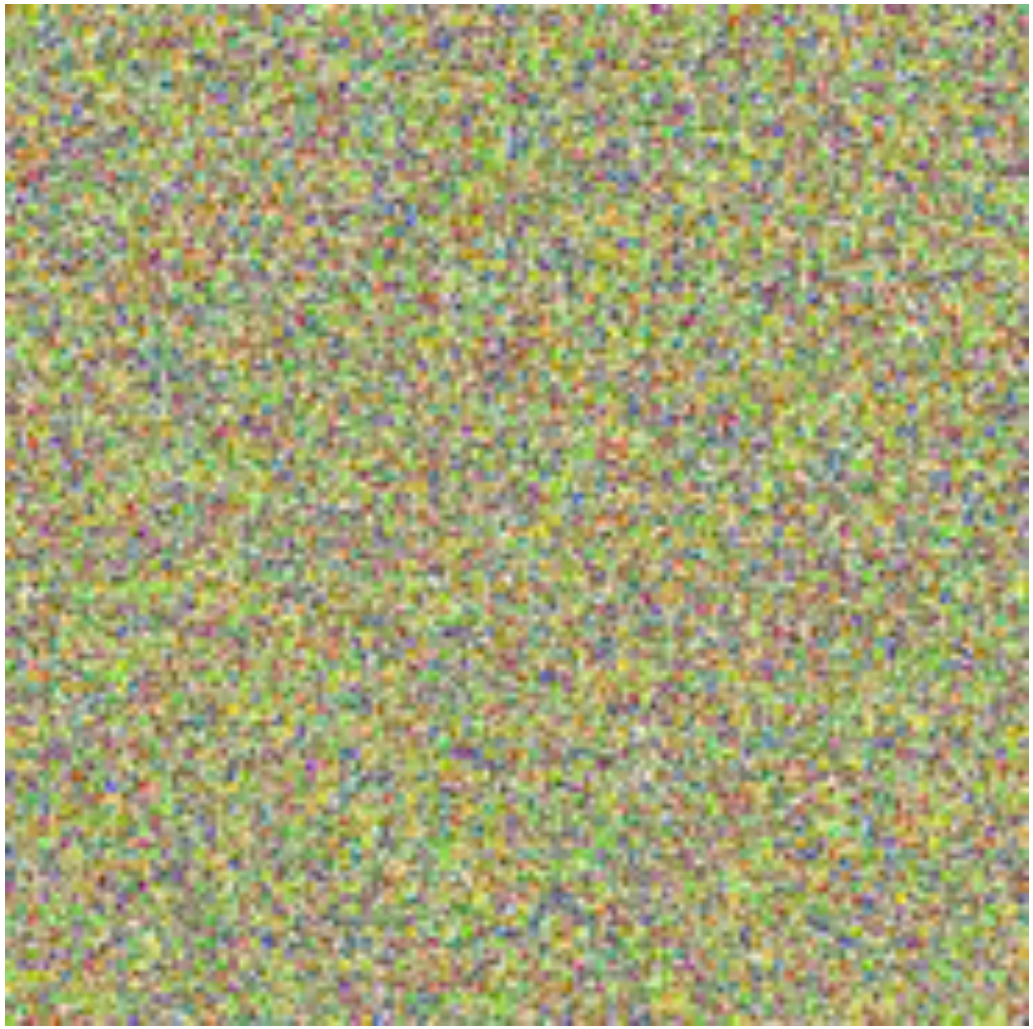
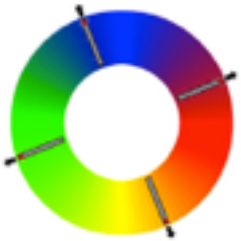
Collective effects in myxobacteria

at large densities and very large system sizes…



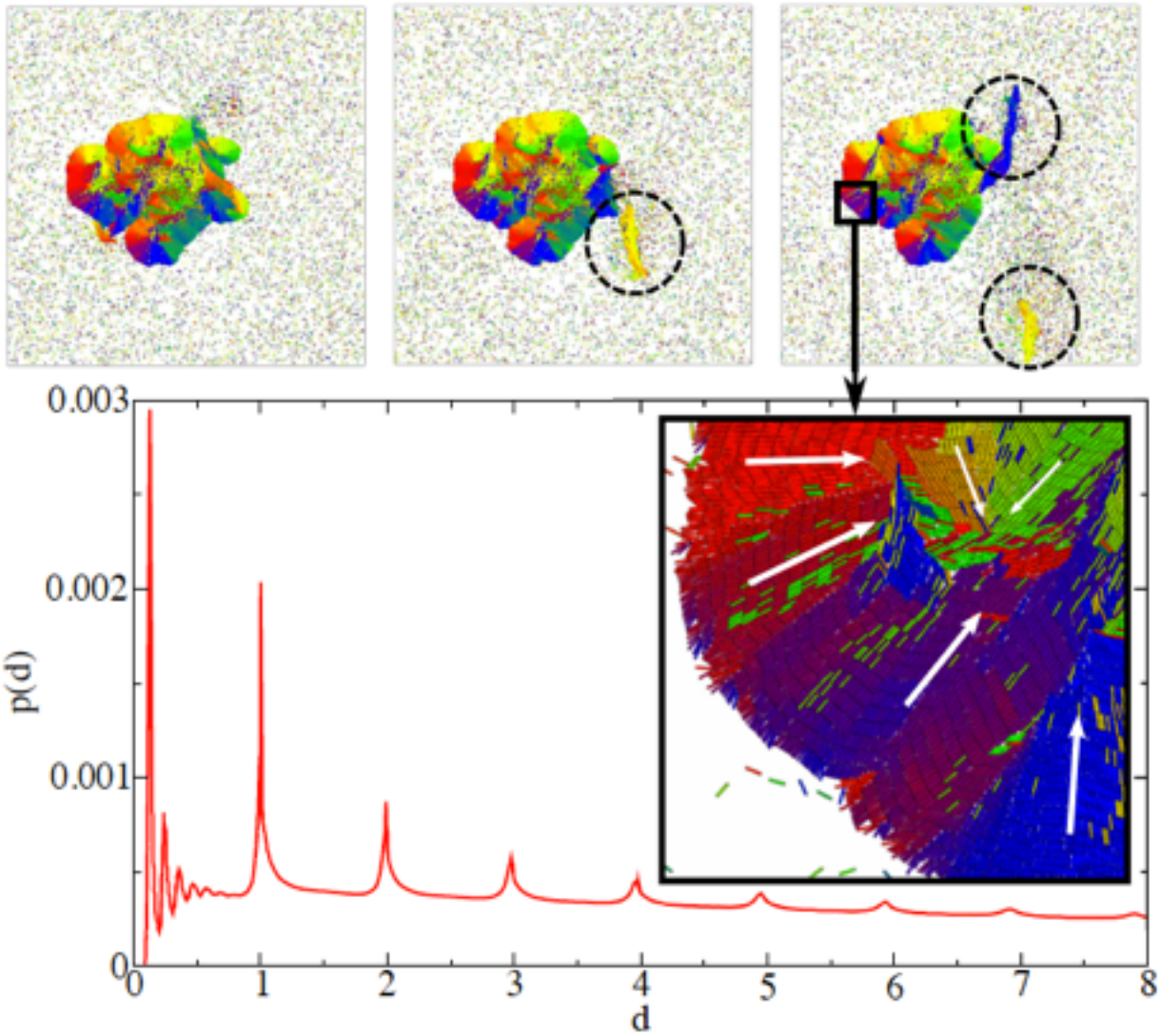


we learn that aggregates are also formed as in the experiments!

Collective effects in myxobacteria

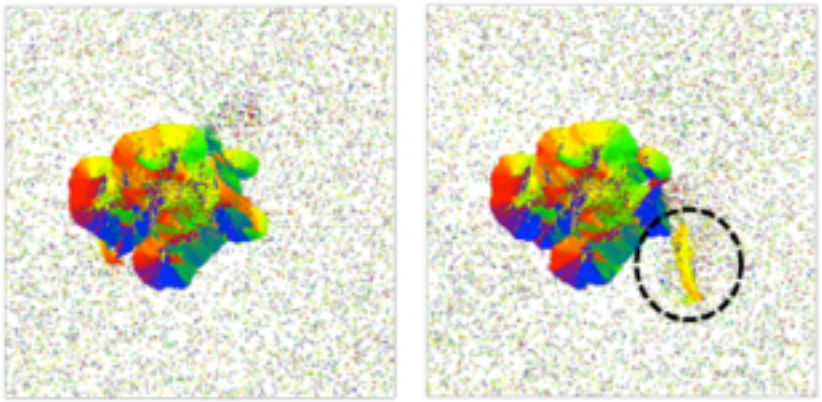
Peruani

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

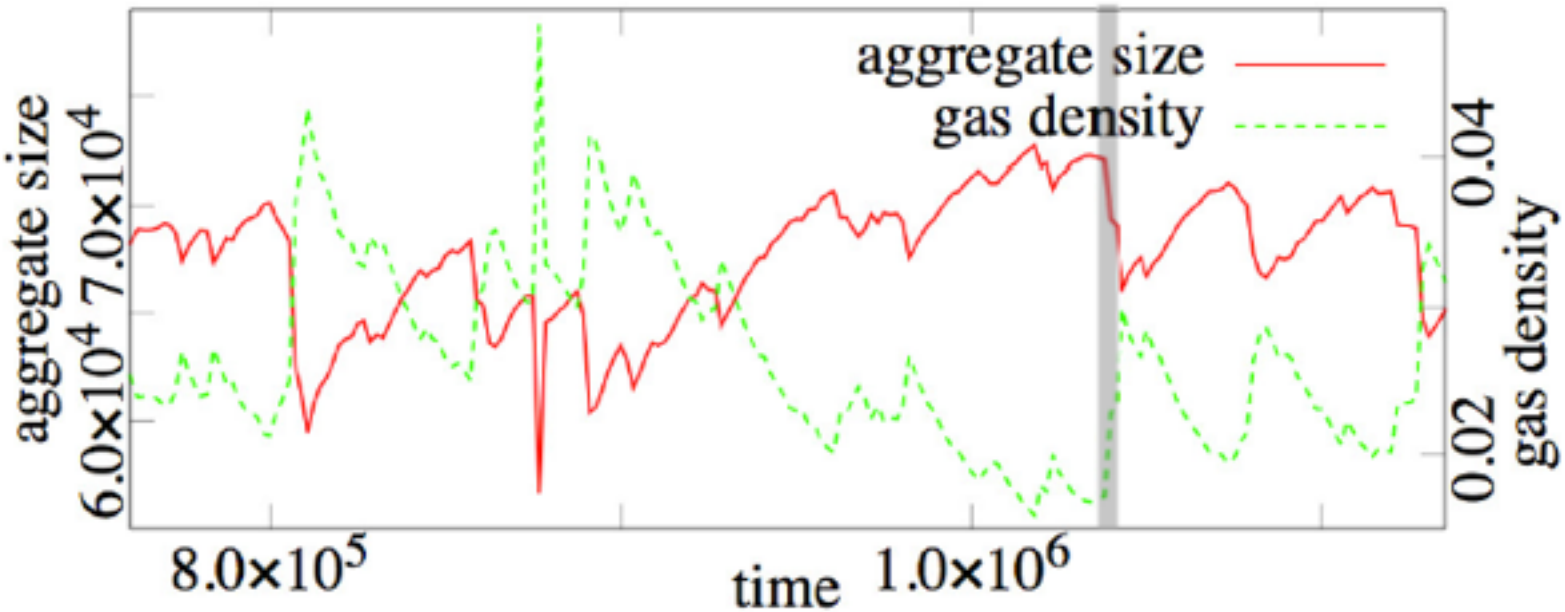


Collective effects in myxobacteria

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



S. Weitz, A. Deutsch, F. Peruani, PRE 92, 012322 (2015)

What have we learned ?

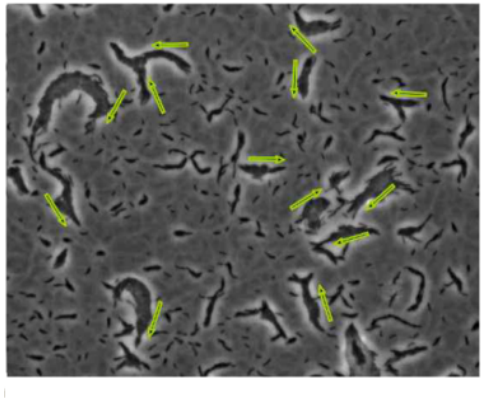
And what is the advantage of using mathematical models?

Collective effects in myxobacteria

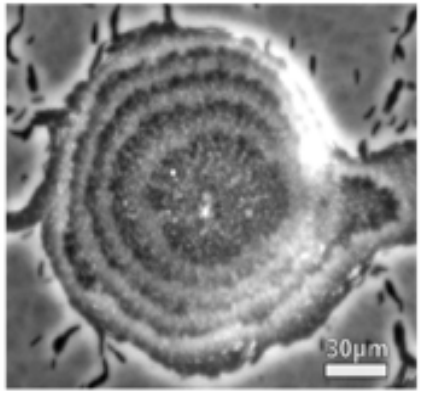
What have we learned ?

And what is the advantage of using mathematical models?

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?

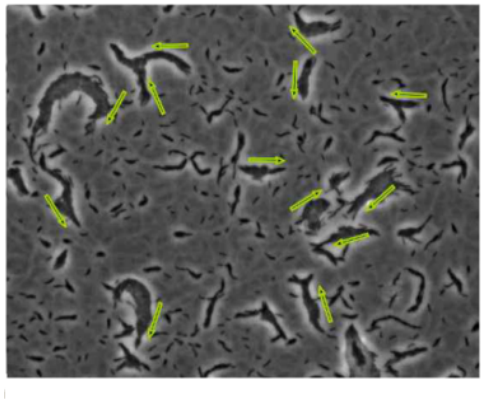
(let us remember that the usual explanation, i.e. chemotaxis, seems not to be working here)

Collective effects in myxobacteria

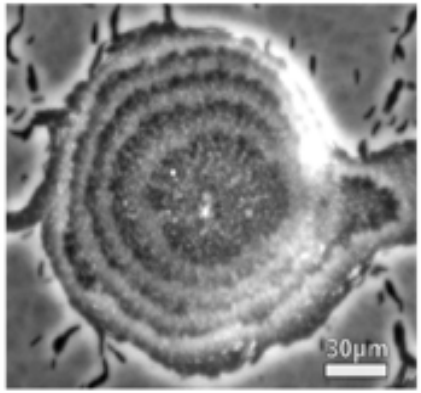
What have we learned ?

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

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

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

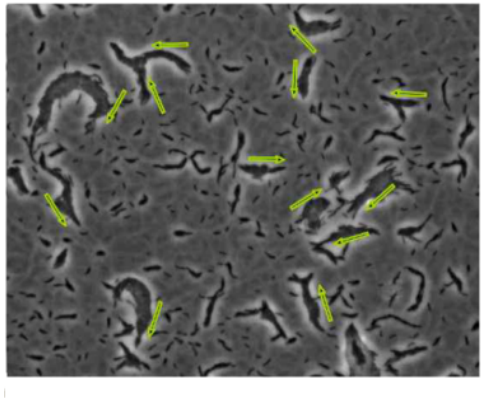
We provided a proof of principle for the proposed mechanisms.

Collective effects in myxobacteria

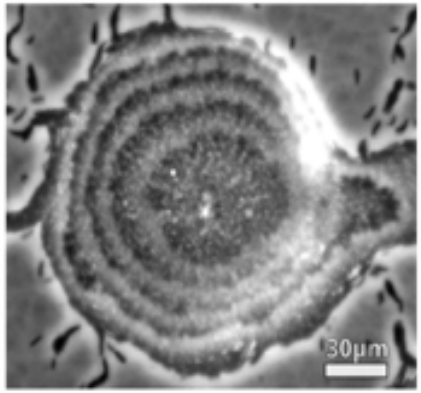
What have we learned ?

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



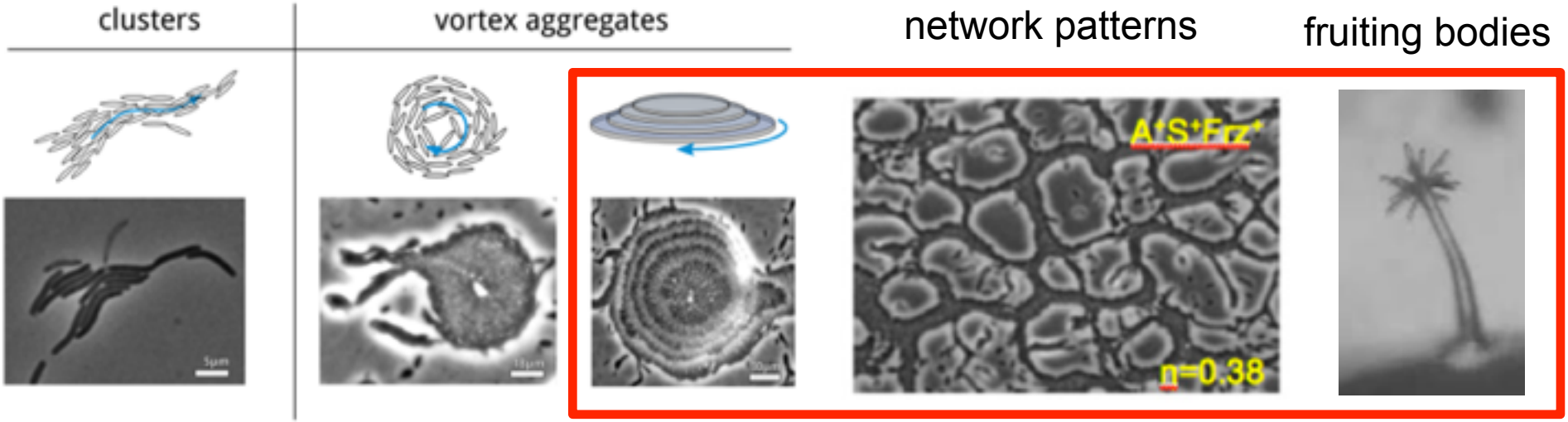
formation of aggregates

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 cluster and aggregates!

(and we have seen that these patterns produce with the mathematical model are quantitatively consistent with the empirical observations)

What is next?


clusters
vortex aggregates
network patterns
fruiting bodies
A+S+Frz+
n=0.38

collective effects in sheep

Peruani

collective effects in sheep

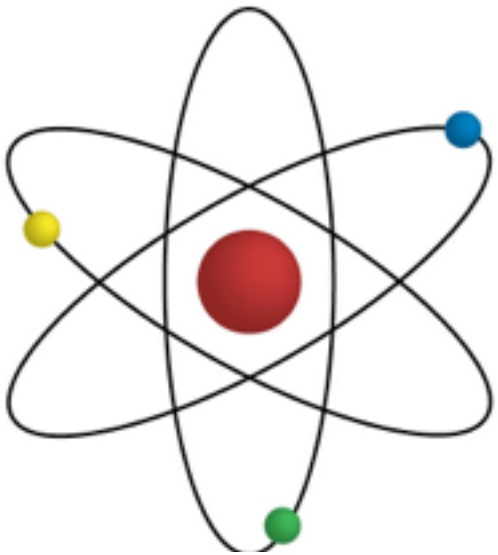
when we look at animal groups, we aim at:

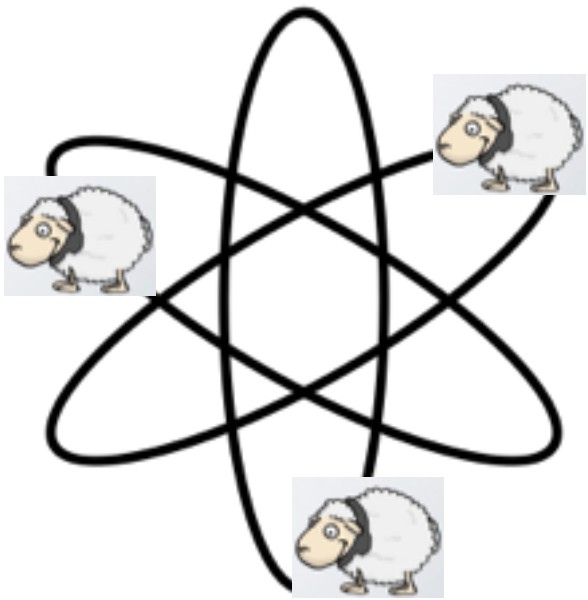
1. Identify the underlying behavioral rules

2. Characterize the emerging macroscopic patterns

Movies from youtube…

collective effects in sheep





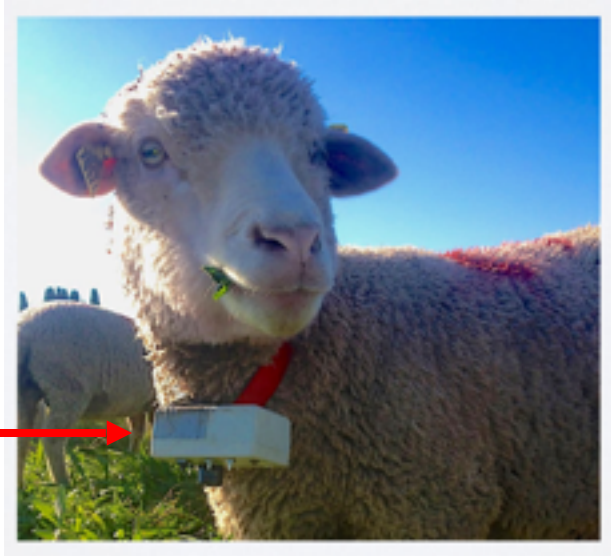
object of study: atom

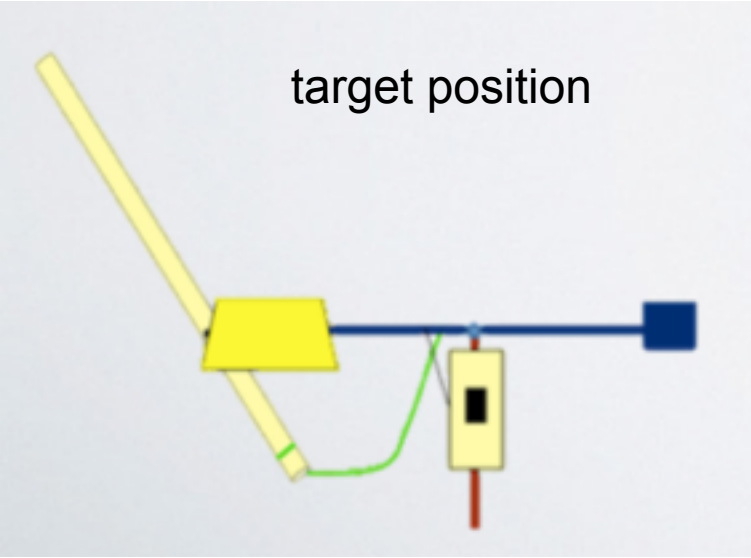
object of study: group of sheep

to study its properties, we perturb it! → here, we will apply the same logic!

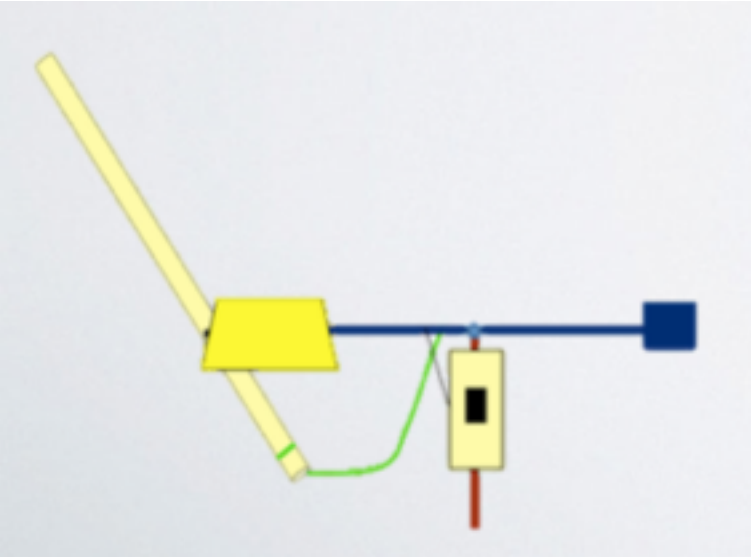
A simple, well-controlled experiment…

vibrating collar





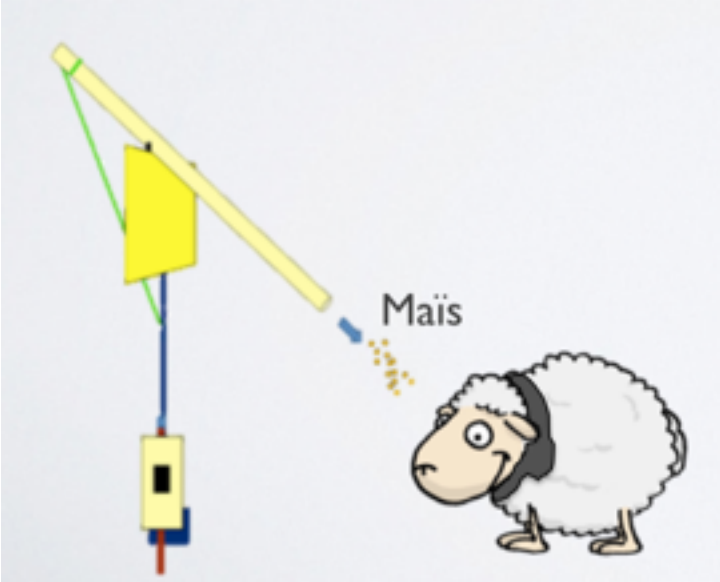
A simple, well-controlled experiment…



the trained individual moves toward the target position

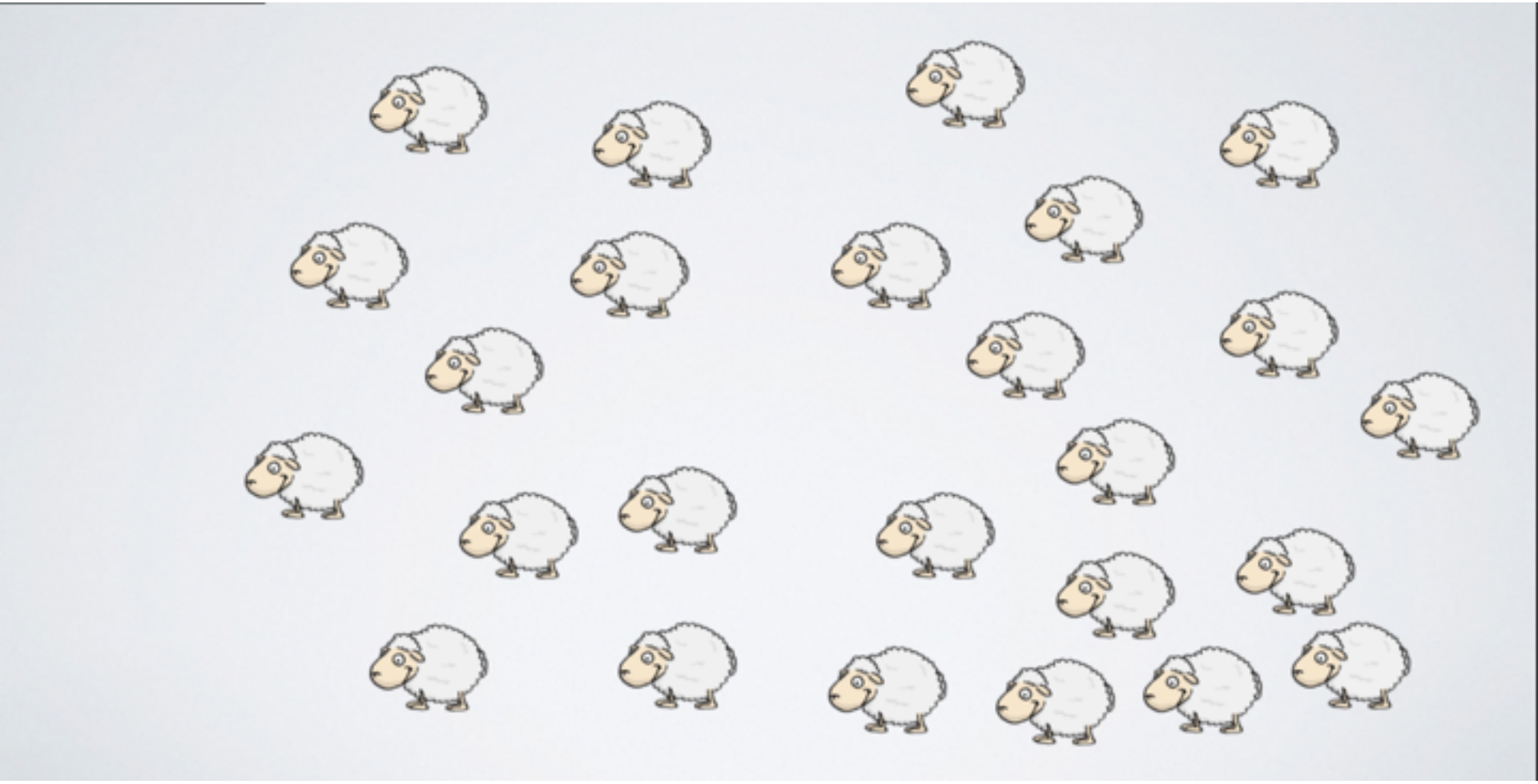
upon activation of the collar…

A simple, well-controlled experiment…

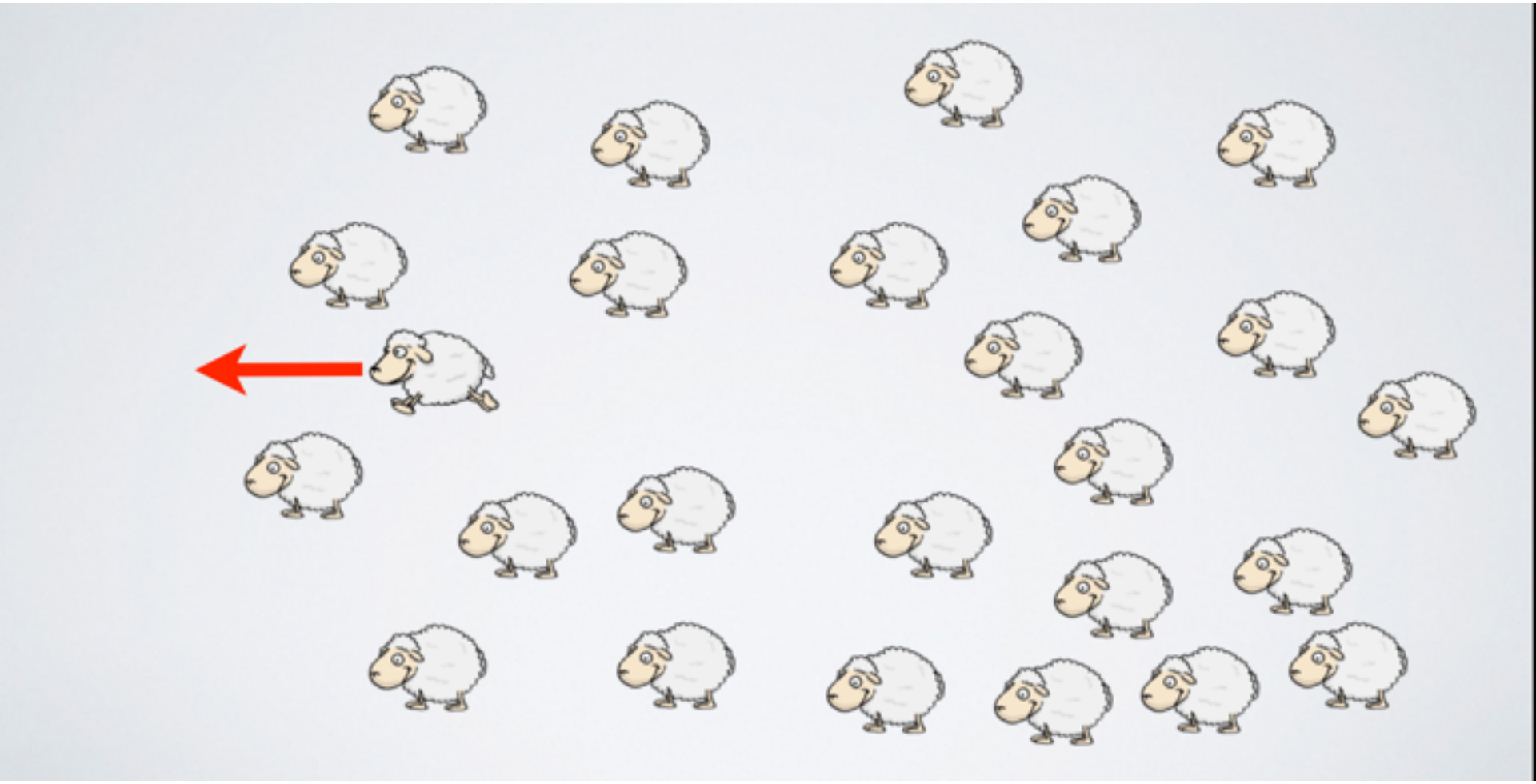


[Toulet, Gautrais, Bon, Peruani, PLoS ONE (2015)]

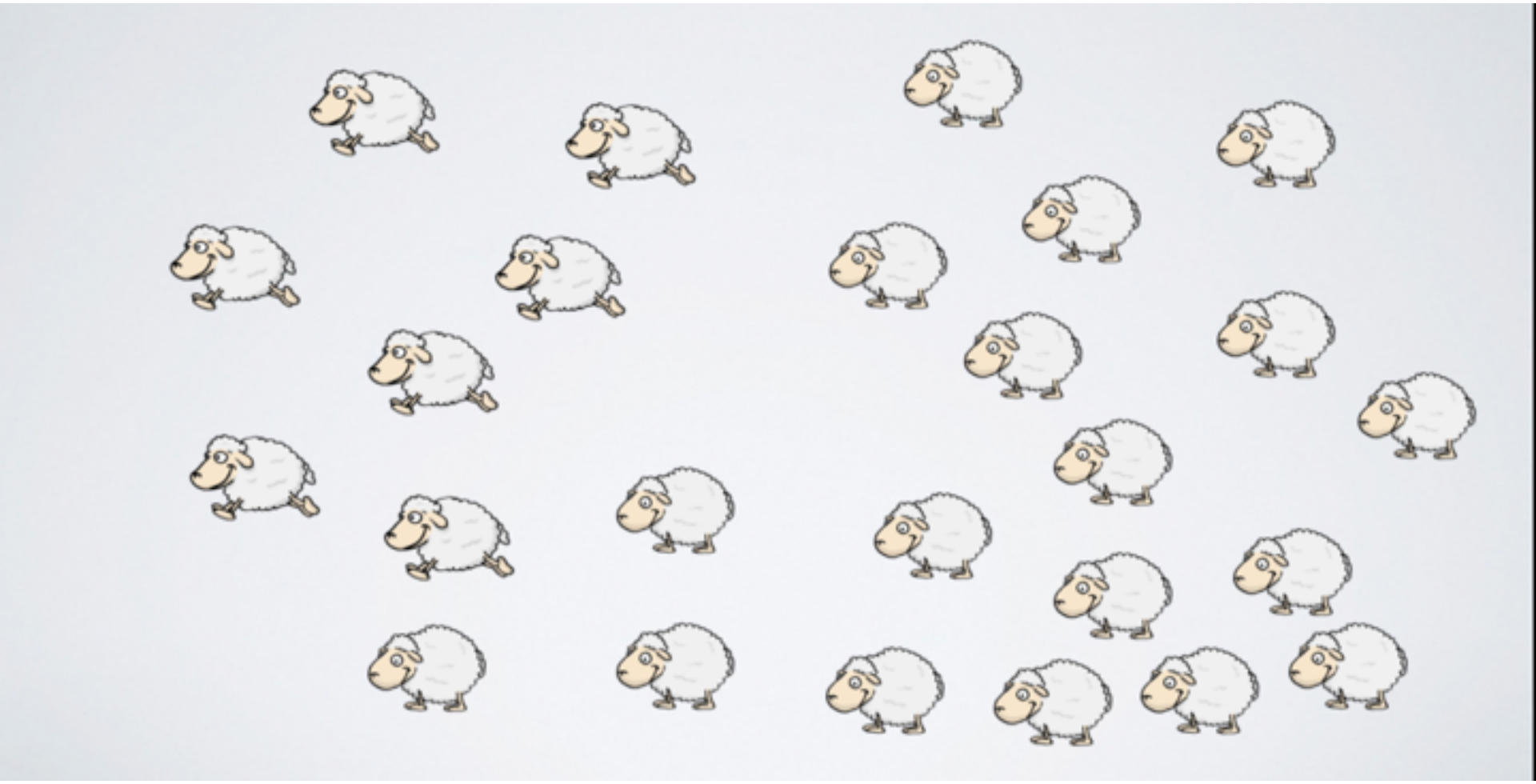
A simple, well-controlled experiment…



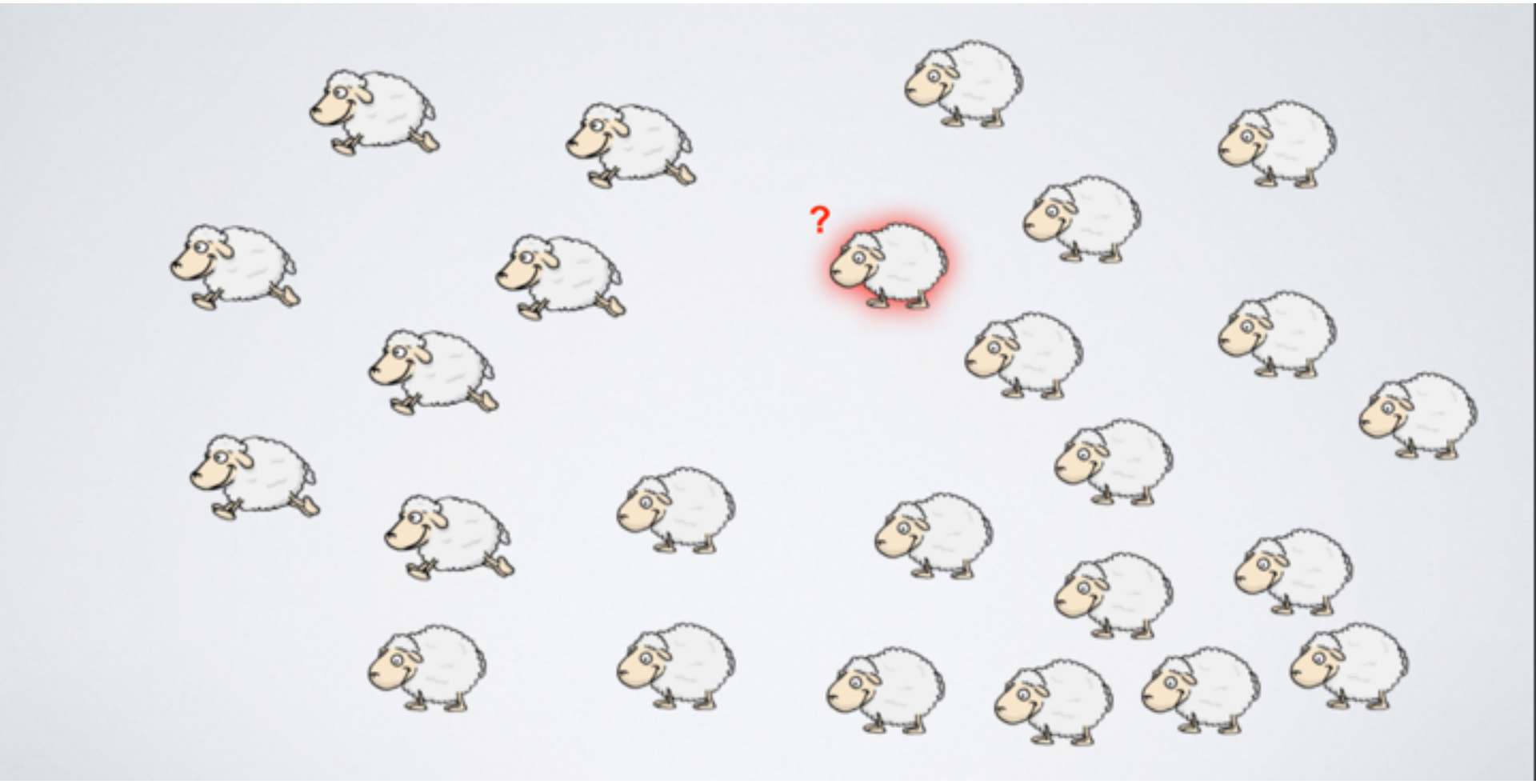
A simple, well-controlled experiment…



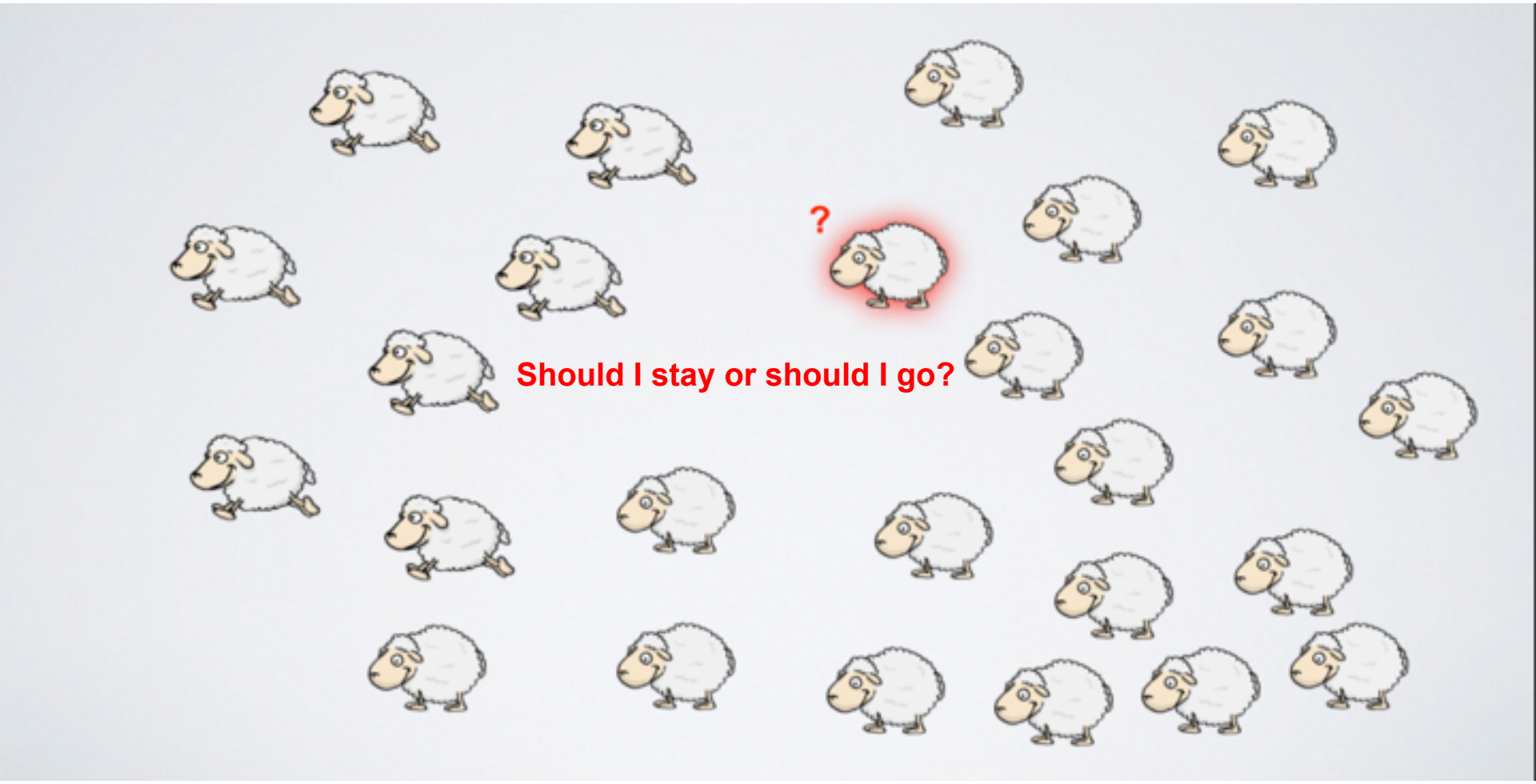
A simple, well-controlled experiment…



A simple, well-controlled experiment…



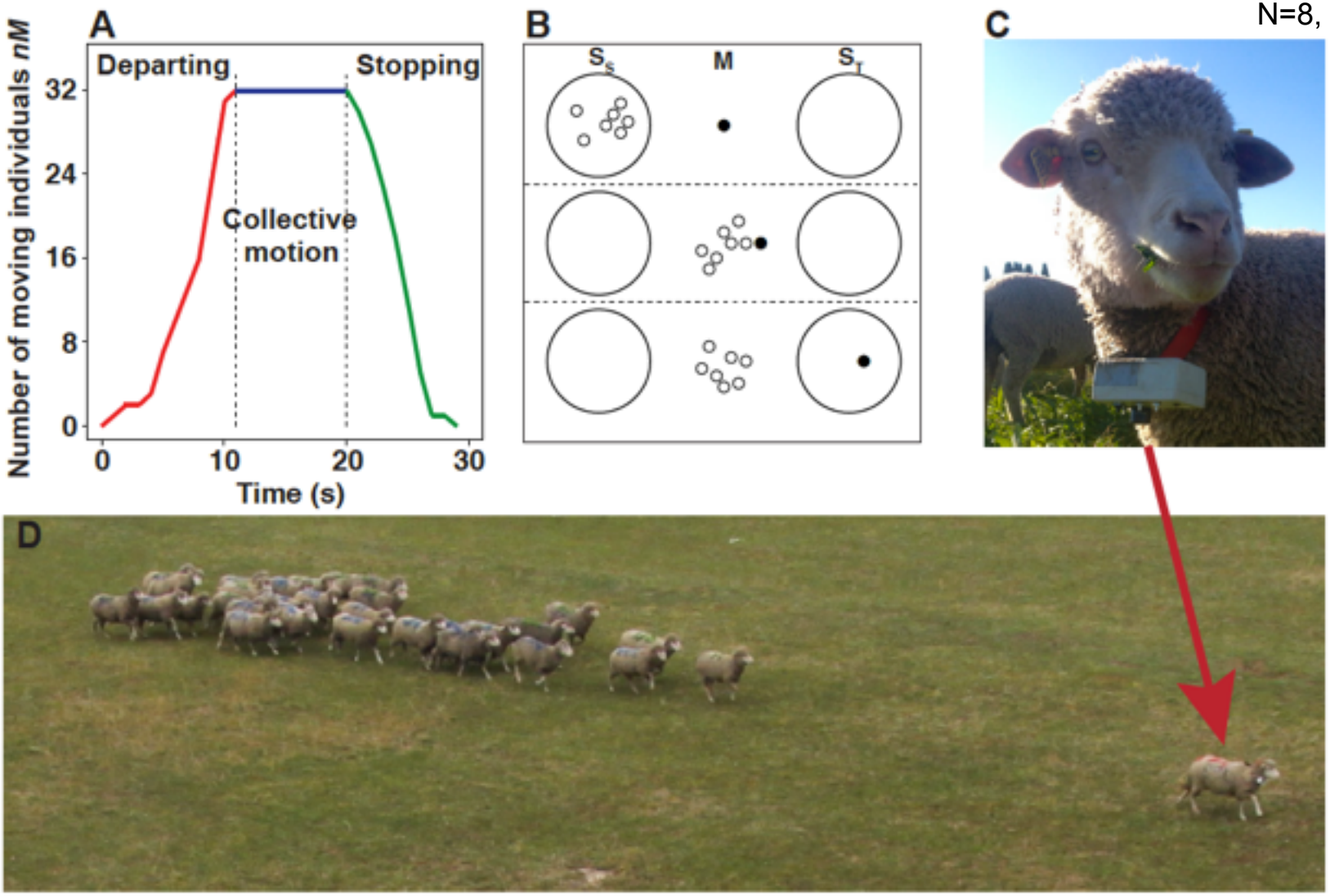
A simple, well-controlled experiment…




Clip 1:
The initiator provokes
collective motion

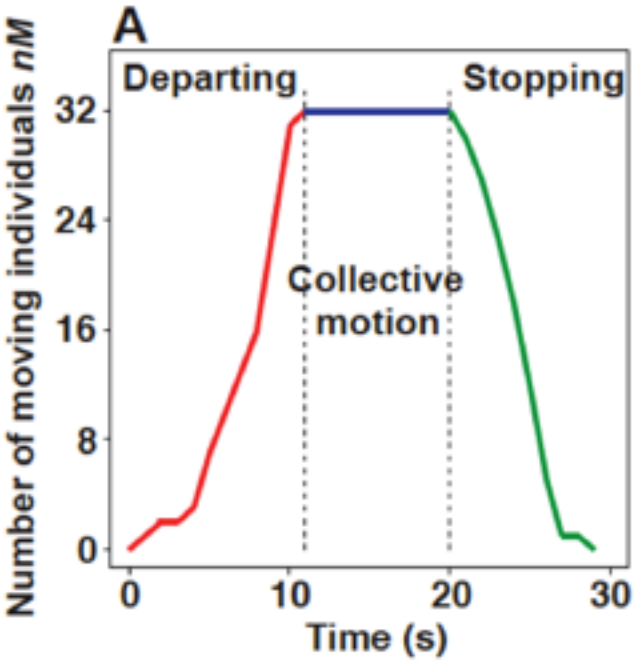
The temporal dynamics…

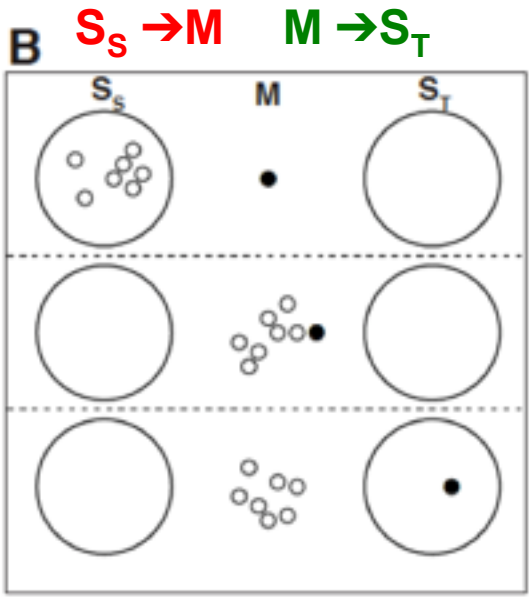
N-1 naïve indiv.
1 trained indiv.
N=8, 16, 32

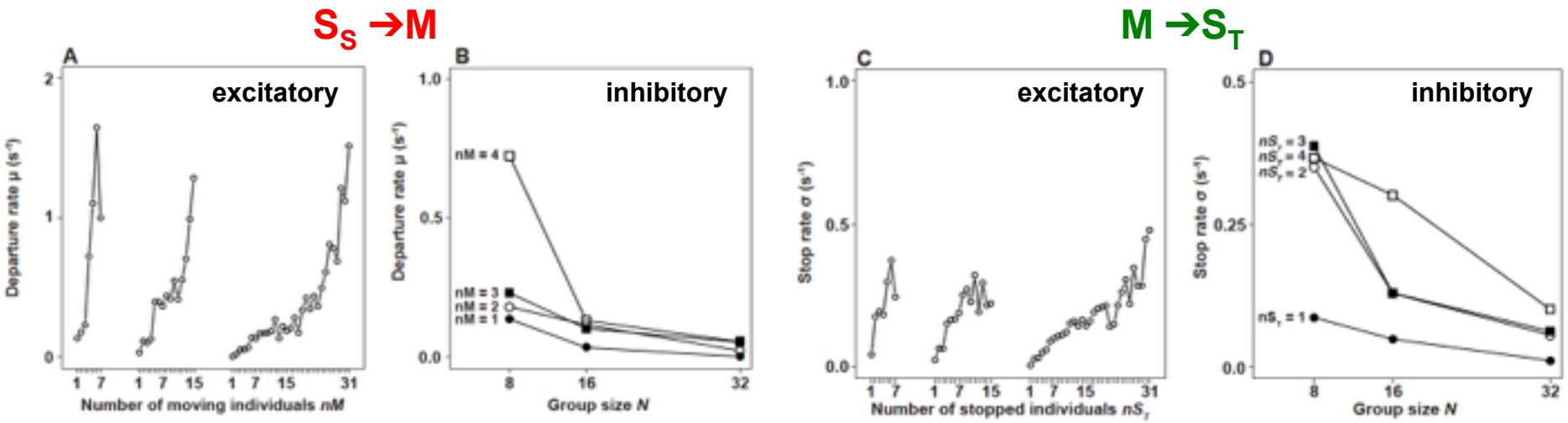


[Toulet, Gautrais, Bon, Peruani, PLoS ONE (2015)]

The temporal dynamics…







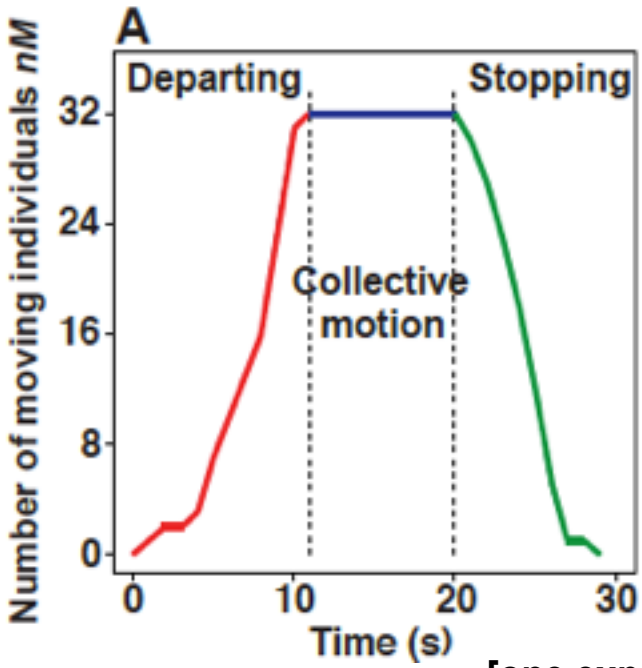
The temporal dynamics…

$$\mu = \alpha \frac{nM^{\beta}}{nS_S^{\gamma}} \qquad \sigma = \alpha' \frac{nS_T^{\beta'}}{nM^{\gamma'}}$$

$$S_S \xrightarrow{\mu} M \xrightarrow{\sigma} S_T$$

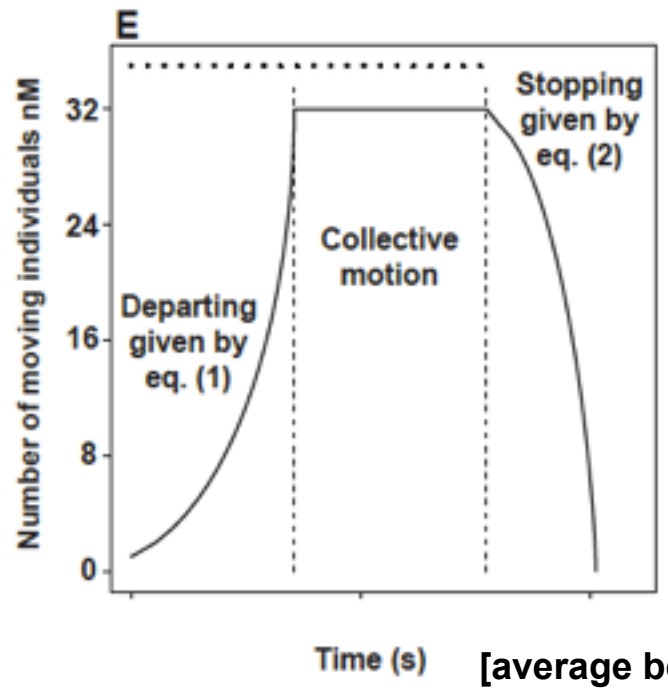
(this is very different from physical interactions: i.e. no pairwise interactions)
(important observation: we assume that each individual is able to see all other individuals in the group)

The temporal dynamics…



[one experiment]

$S_S \rightarrow M$



[average behavior]

$M \rightarrow S_T$

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

$$\sigma(nM, N) = \alpha' \frac{nS_T{}^{\beta'}}{nM^{\gamma'}} = \alpha' \frac{(N - nM)^{\beta'}}{nM^{\gamma'}}$$

This is not all…


Clip 2:
The initiator fails
to provoke
collective motion

collective effects in sheep

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?

collective effects in sheep

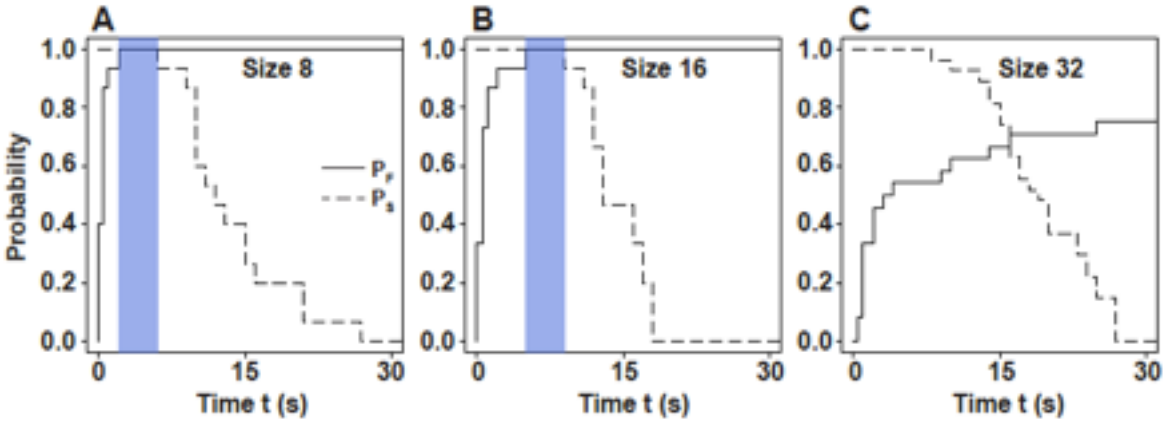
Peruani

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/μ)



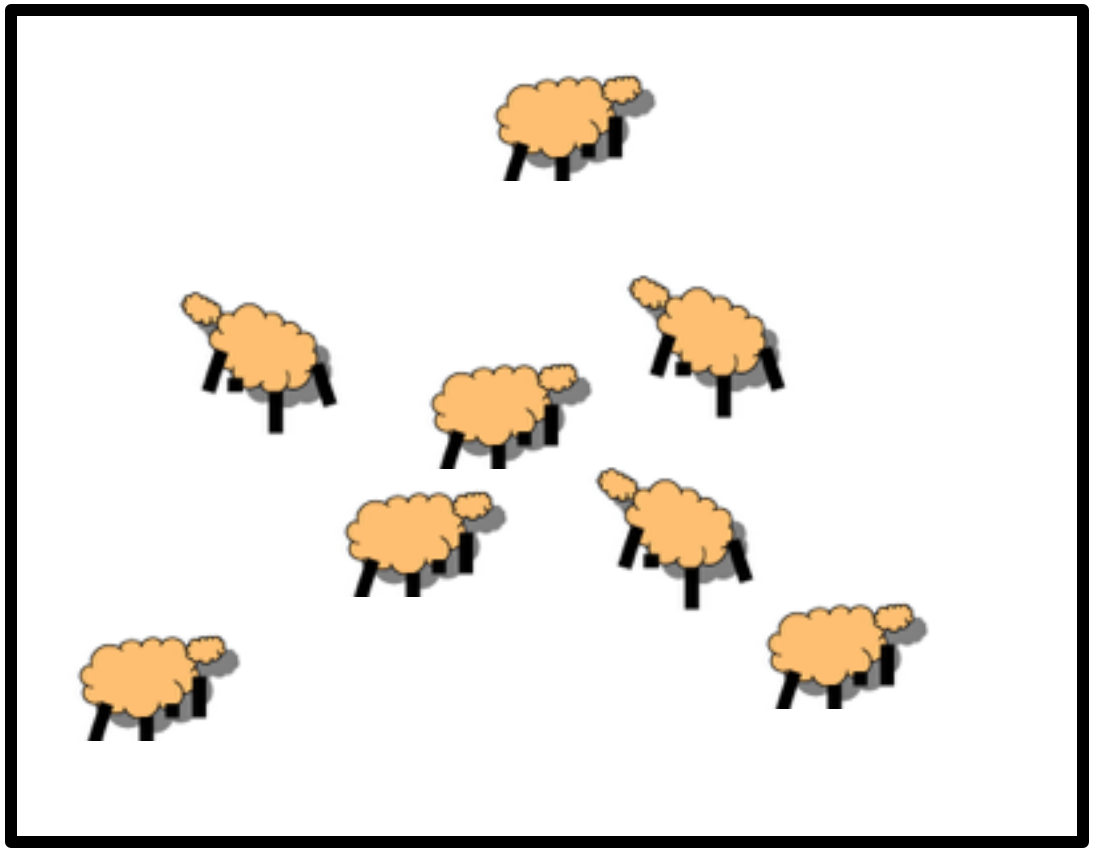
P_F=prob. first follow occurs before time t
P_S=prob. the trained individual has reached the target at time t

Notice that we have assumed that individuals in state St cannot induce a transition from the state Ss. This implies also that the trained individual can only induce a transition if it is in motion.

collective effects in sheep

Peruani

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?

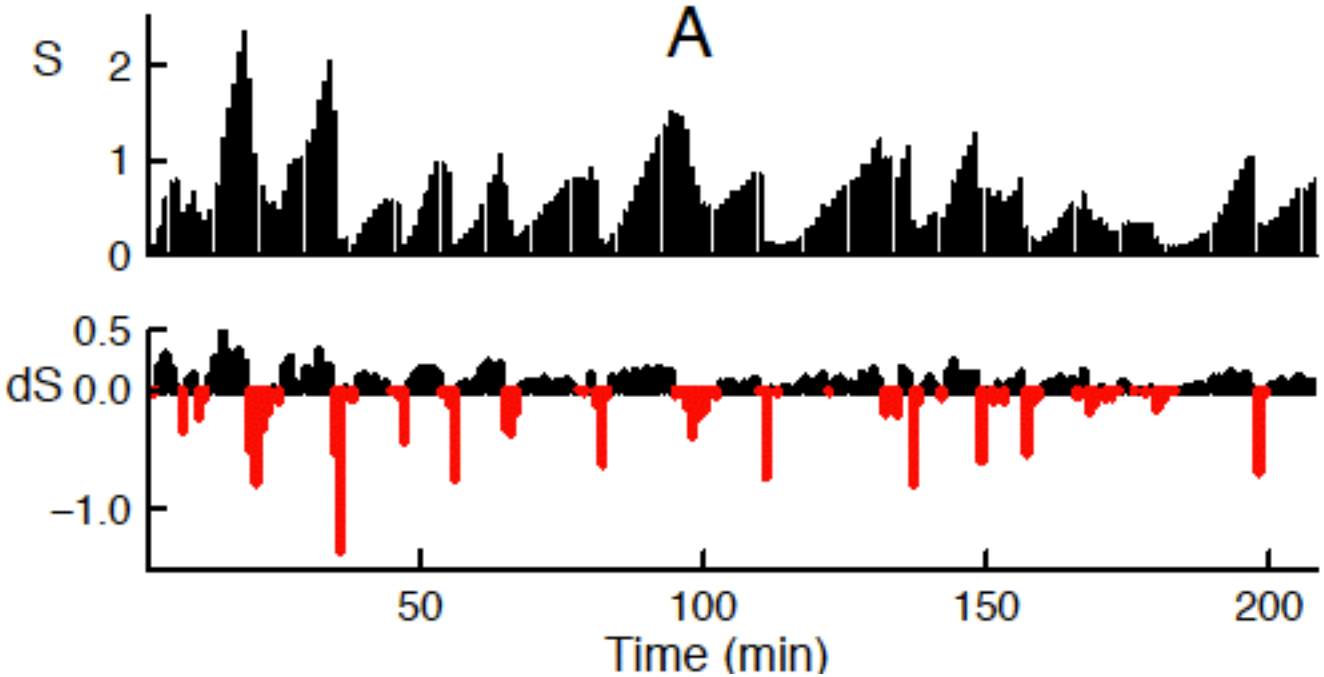
collective effects in sheep

Peruani

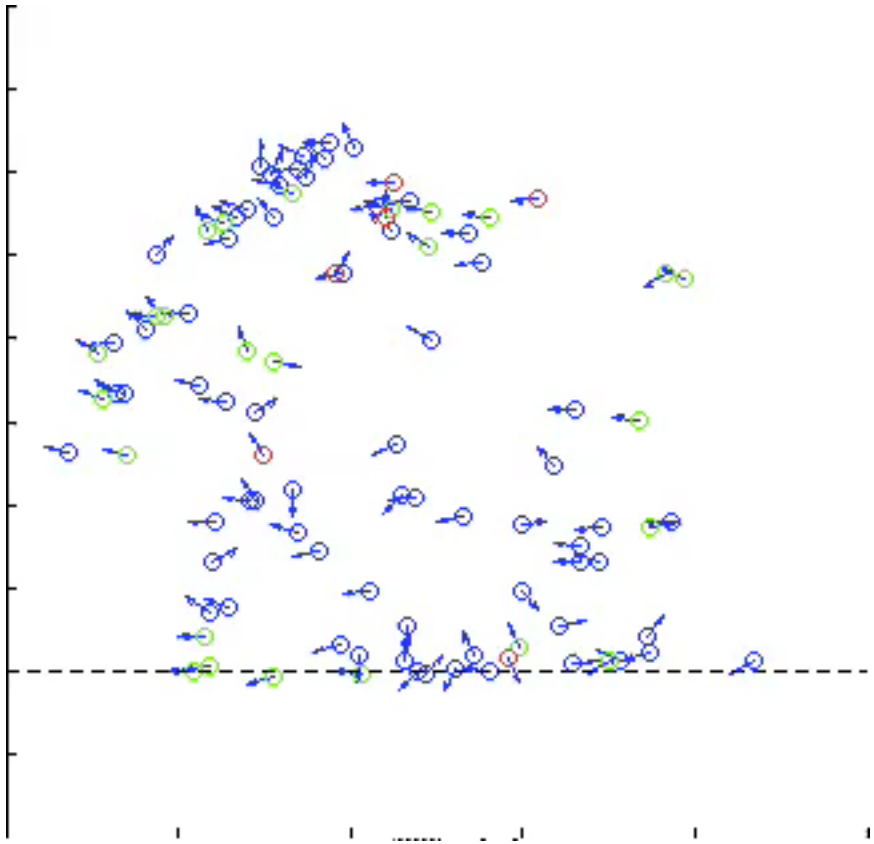
collective effects in sheep

Peruani

How to characterize the observed collective behavior?

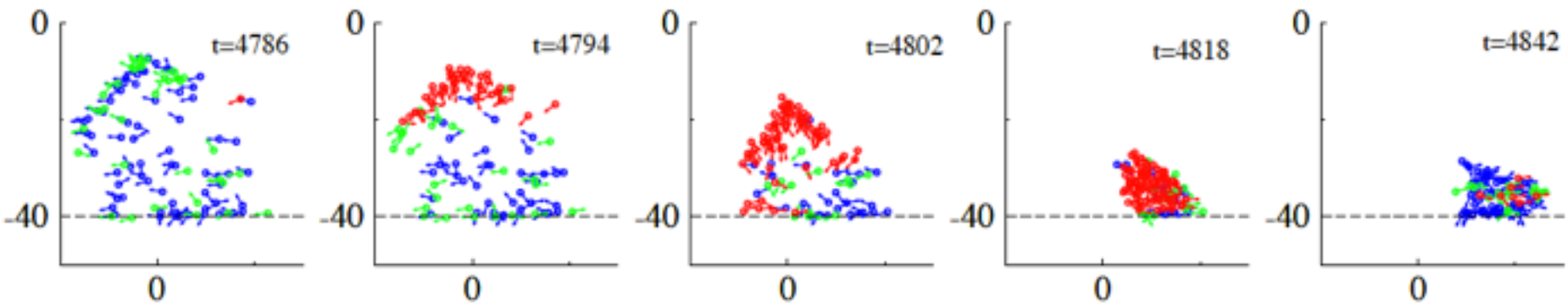


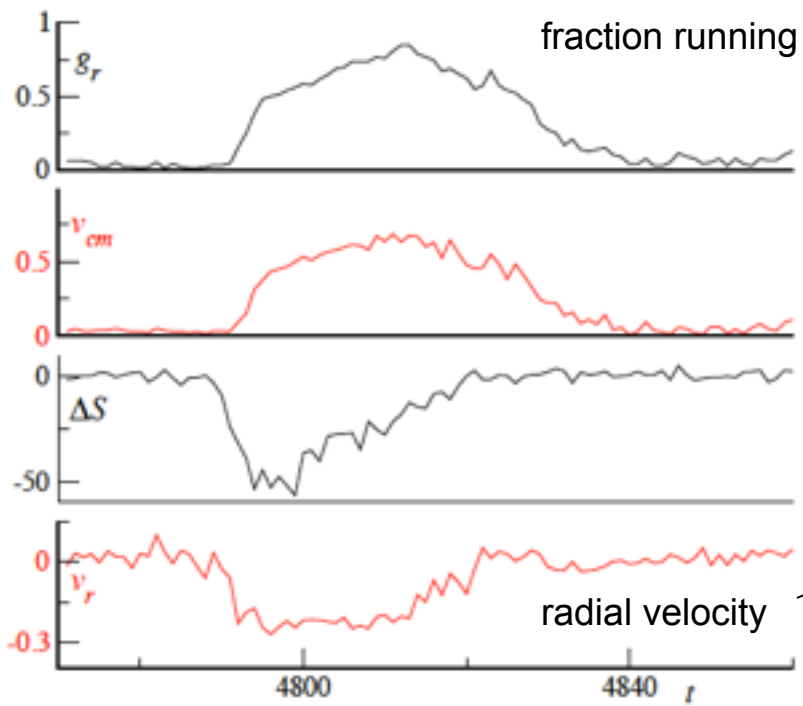
An aggregation event:



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

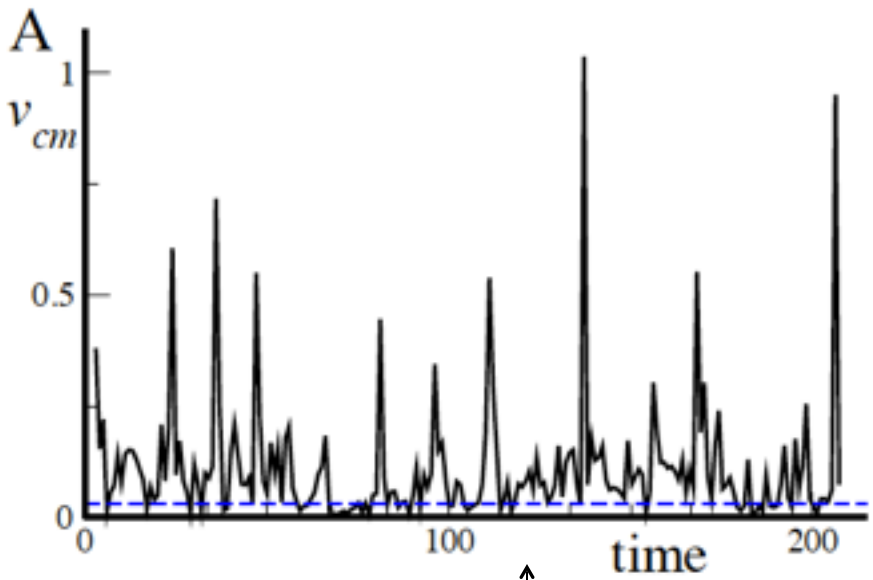
An aggregation event:

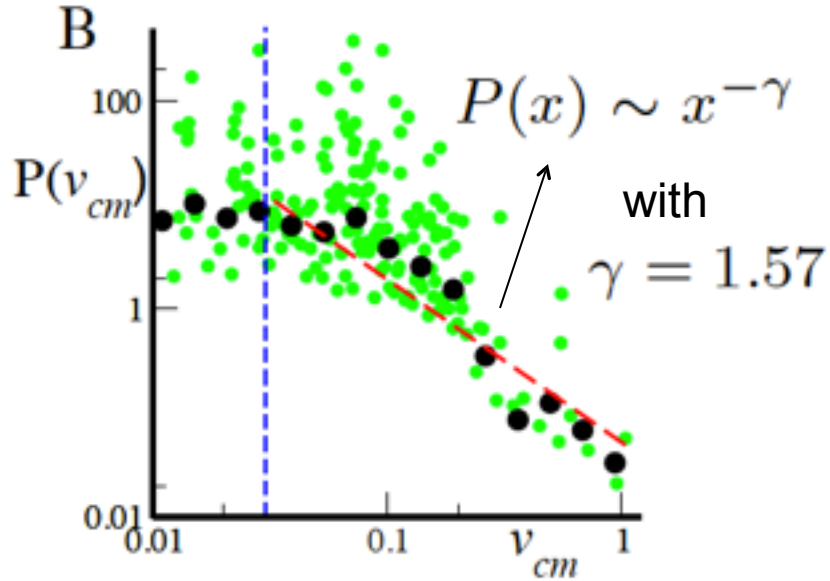


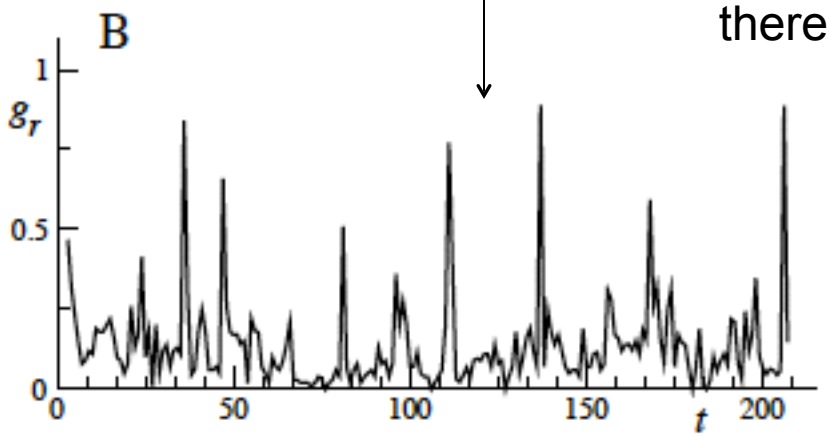


$$v_r^t \equiv \langle [(\mathbf{r}_i^t - \mathbf{r}_{cm}^t) \cdot \mathbf{v}_i^t] \,/\, [||(\mathbf{r}_i^t - \mathbf{r}_{cm}^t)||\, ||\mathbf{v}_i^t||] \rangle$$

How is the distribution of aggregation events?







there are aggregation events of many sizes…

↓

are these power-law distributed?

How can we model the observed behavior?

Using a Vicsek-like model:

$$\mathbf{r}_i^{t+\Delta t} = \mathbf{r}_i^t + \Delta t\, v(q_i^t)\, \mathbf{s}_i^{t+\Delta t}\,, \qquad [1]$$

$$\theta_i^{t+\Delta t} = \mathrm{Arg}\left[\sum_{j\in\mathcal{M}_i} \mathbf{s}_j^t\right] + \psi_i^t \quad (\text{if } q_i^t = 1)\,, \qquad [2]$$

[metric neighbors]

$$\theta_i^{t+\Delta t} = \mathrm{Arg}\sum_{j\in\mathcal{V}_i}\left[\delta_{2,q_j^t}\,\mathbf{s}_j^t + \beta\, f(r_{ij}^t)\,\mathbf{e}_{ij}^t\right] \quad (\text{if } q_i^t = 2)\,, \qquad [3]$$

[topo. neighbors]

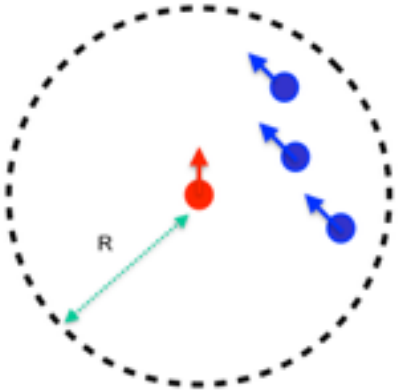
alignment

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

$$p_{0\to1}(i,t) = \frac{1+\alpha\, n_1^t(i)}{\tau_{0\to1}}\,, \quad p_{1\to0}(i,t) = \frac{1+\alpha\, n_0^t(i)}{\tau_{1\to0}}\,, \qquad [4]$$

$$p_{0,1\to2}(i,t) = \frac{1}{\tau_{0,1\to2}}\left[\frac{\ell_i^t}{d_R}\left(1+\alpha\, m_R^t(i)\right)\right]^{\delta}\,, \qquad [5]$$

$$p_{2\to0}(i,t) = \frac{1}{\tau_{2\to0}}\left[\frac{d_S}{\ell_i^t}\left(1+\alpha\, m_S^t(i)\right)\right]^{\delta}\,, \qquad [6]$$



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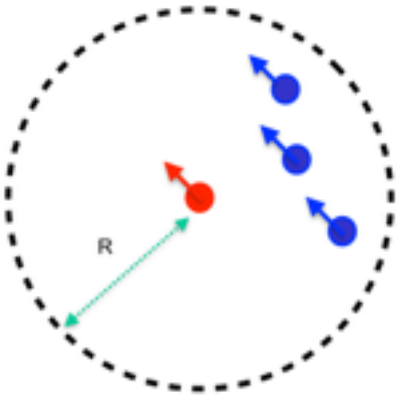
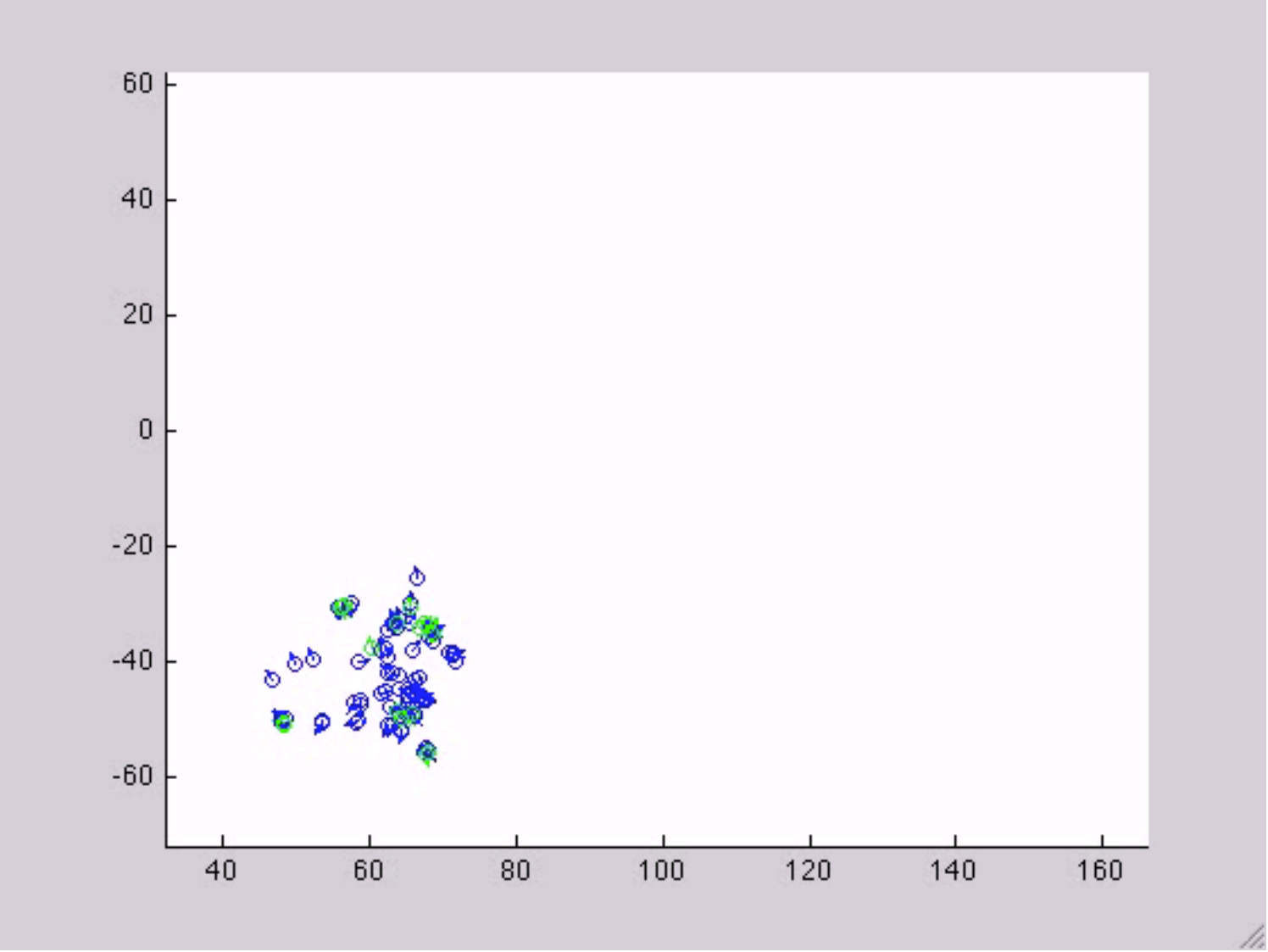
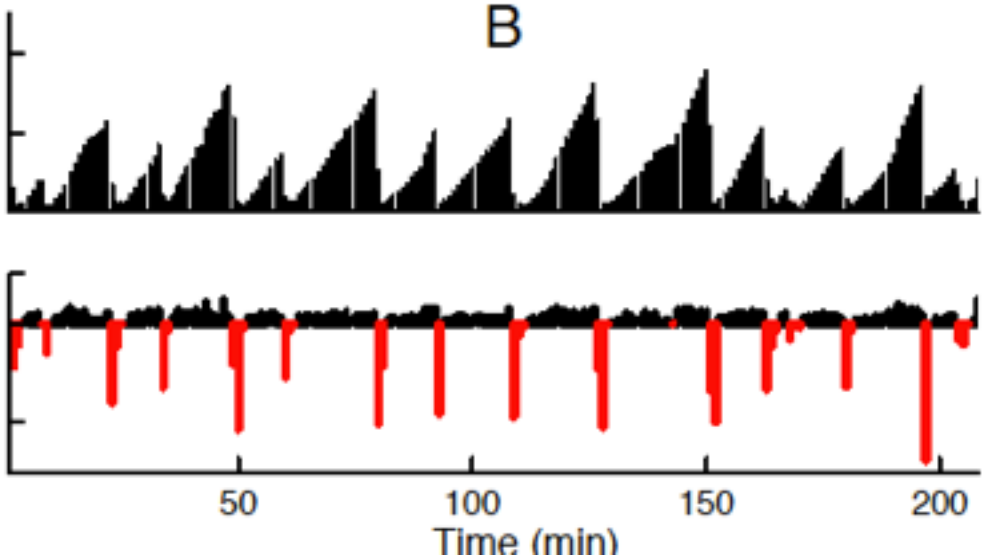
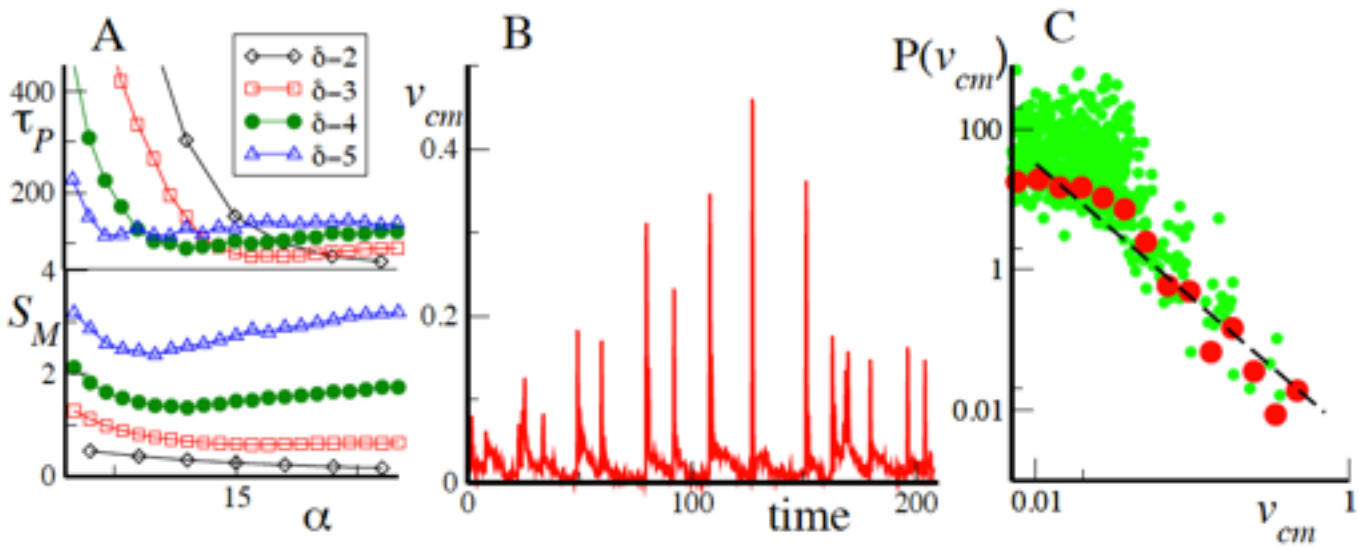


Model behavior…



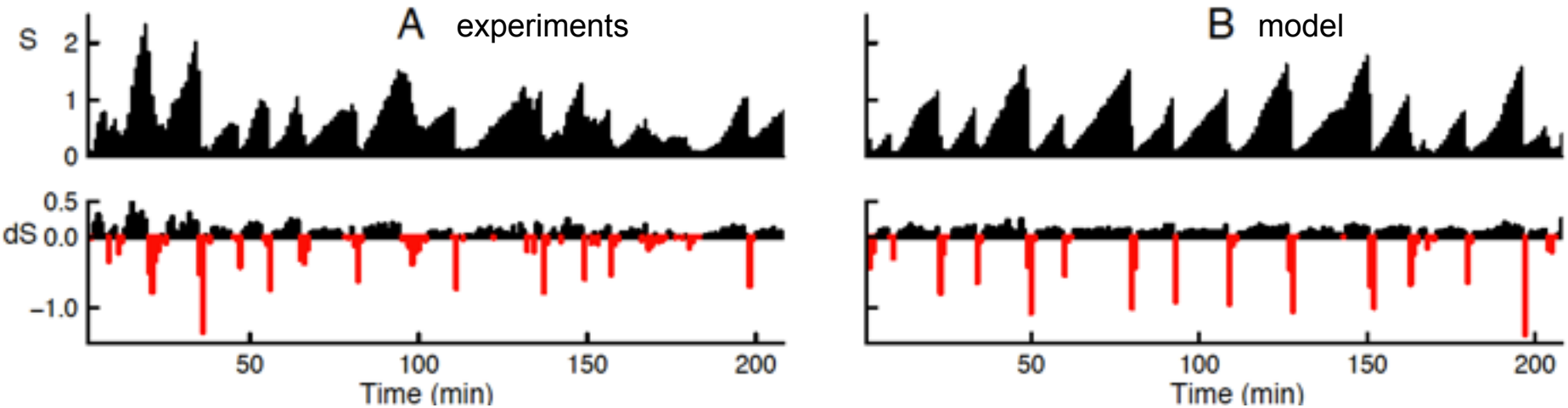
Comparison between model and experiments…





collective effects in sheep

Peruani



messages:

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.

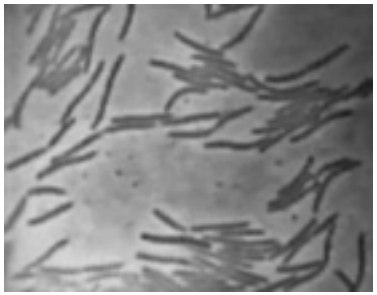
The proposed (complex) model is able to reproduce the data. This suggests that all the mechanisms required to produce the observed phenomena is there. Which ingredients (among the many introduced) are really necessary is an open question.

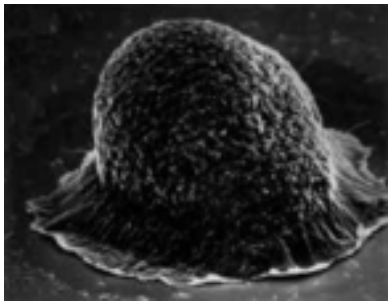
Ginelli*, Peruani*, Pillot, Chaté, Theraulaz, Bon, PNAS (2015)

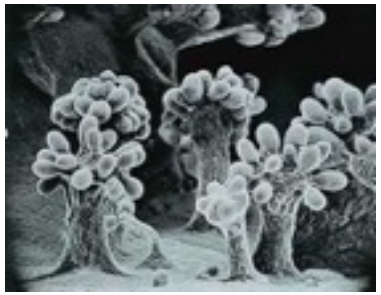
summary

Using the same theoretical framework, we can explain a large variety of collective phenomena in fundamentally different biological system

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.







some coverage on this work…

POUR LA SCIENCE.fr

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

53 5

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By Elizabeth Preston | September 29, 2015 12:40 pm

150

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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!