Fluctuations and structure in a flocking epithelium

Francesco Ginelli

SUPA, Department of Physics and ICSMB, University of Aberdeen, UK

University of Milan and

IFOM-FIRC Institute of Molecular Oncology,

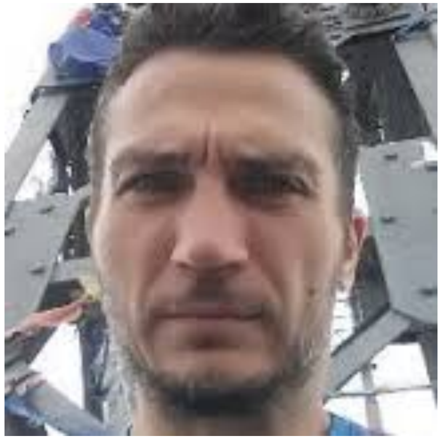
Fabio Giavazzi

Roberto Cerbino

Chiara Malinverno

Salvatore Corallino

Giorgio Scita



EPSRC

Pioneering research and skills

MARIE CURIE ACTIONS

1495

UNIVERSITY OF ABERDEEN

Introduction: active matter

Active particles are able to extract and dissipate energy from their surroundings to produce systematic and coherent motion

- Energy enters and exits the system → out of equilibrium
- Energy is spent to perform actions, typically move (self-propel) in a non-thermal way
- In active systems, energy is injected and dissipated in the bulk, not from the boundaries, in a way that does not explicitely breaks any simmety

Flocking active matter

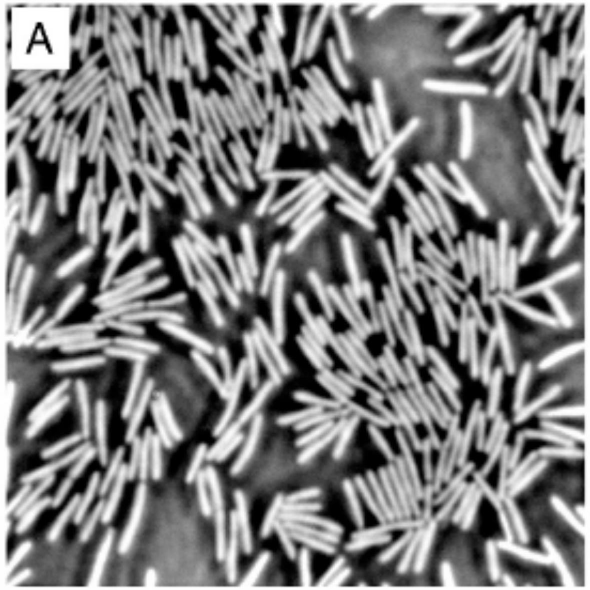
spontaneous symmetry breaking to collective motion

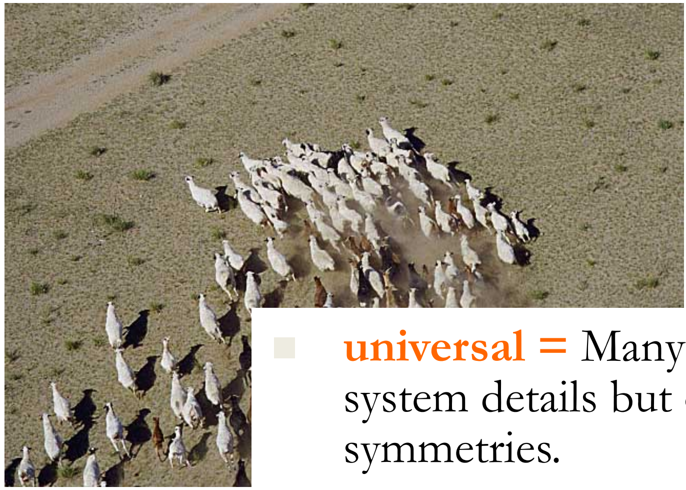
Starlings flock - Predation attempt in Rome

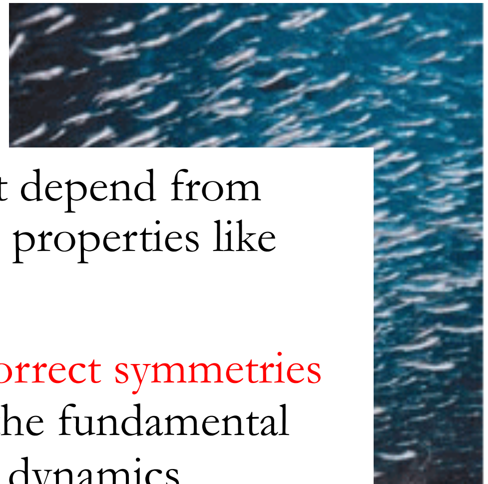
thanks to STARFLAG Project & Claudio Carere, Istituto Superiore di Sanità - Roma - Italy

Collective motion (flocking) at all scales

- From the largest mammals to bacteria, and even within the cell.
- Large groups with **local interactions** only, without leaders, without ordering field
- **Collective motion** as a **spontaneous symmetry breaking** phenomenon:
- **Underlying universal properties!**







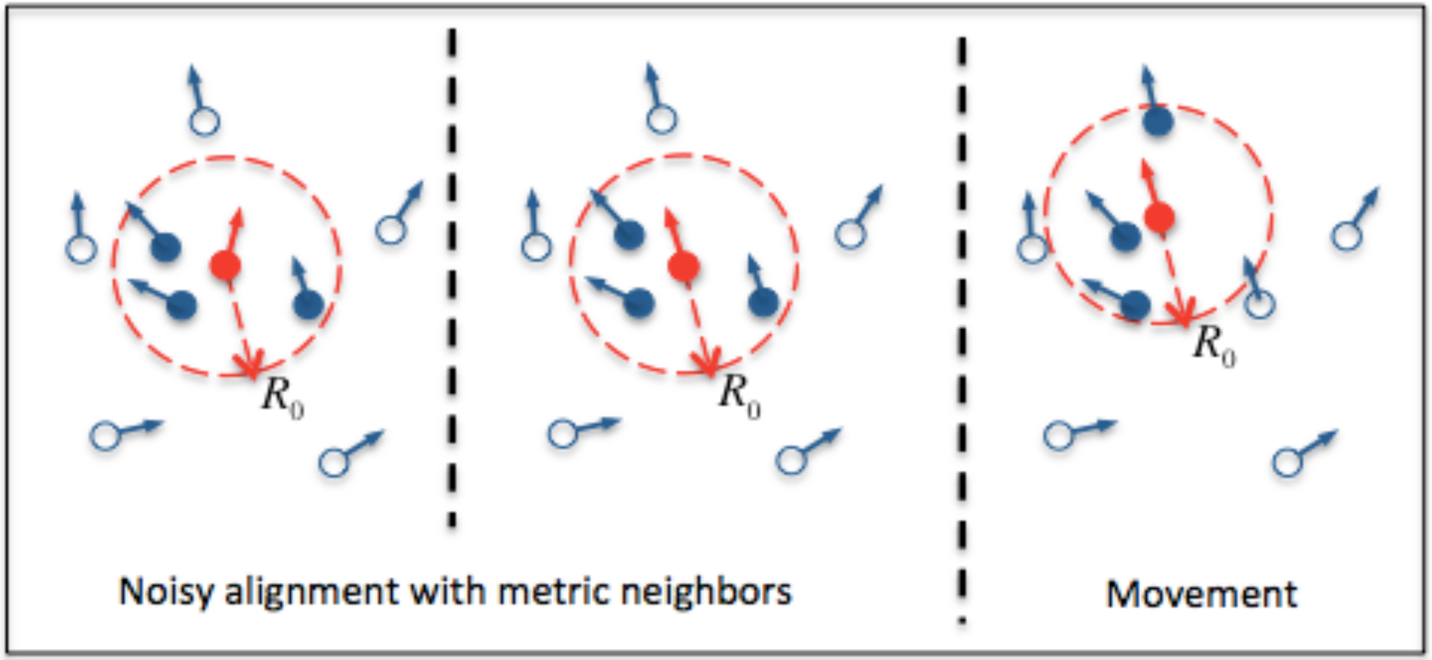
- **universal =** Many properties do not depend from system details but only from general properties like symmetries.
- Simple models, equipped with the correct symmetries and conservation laws, can capture the fundamental long range features of the collective dynamics

The Vicsek model ("moving XY spins")

Vicsek et al, PRL (1995)

- Off lattice self propelled particles that move with constant speed v_0
- Local *ferromagnetic (or polar)* alignment with local neighbors (inside a metric range R_0.)
- Environmental **white noise**

In d=2 one may write the VM as



The Vicsek universality class

Which essential ingredients you find in the VM?

1. Conservation of particles number

2. A continuous symmetry can be spontaneously broken (to polar order) by local interactions

3. Particles are self propelled, i.e. they move and (being interactions local, $R_0 << L$) exchange neighbors

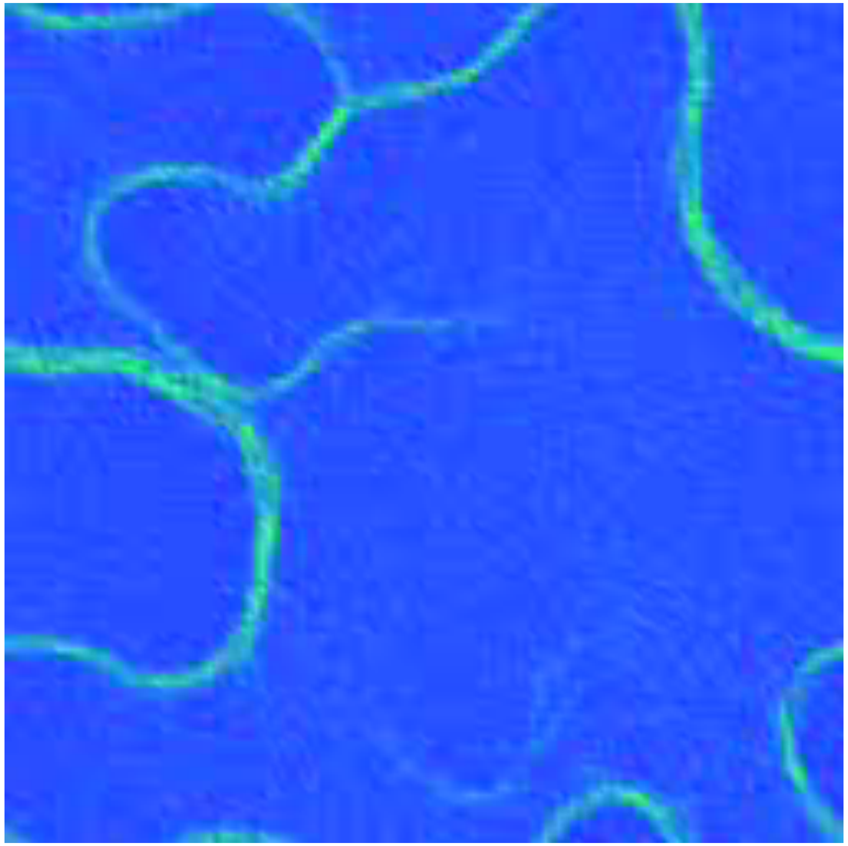
The system is far from equilibrium !!

4. No momentum conservation, no Galileian invariance, overdamped dynamics

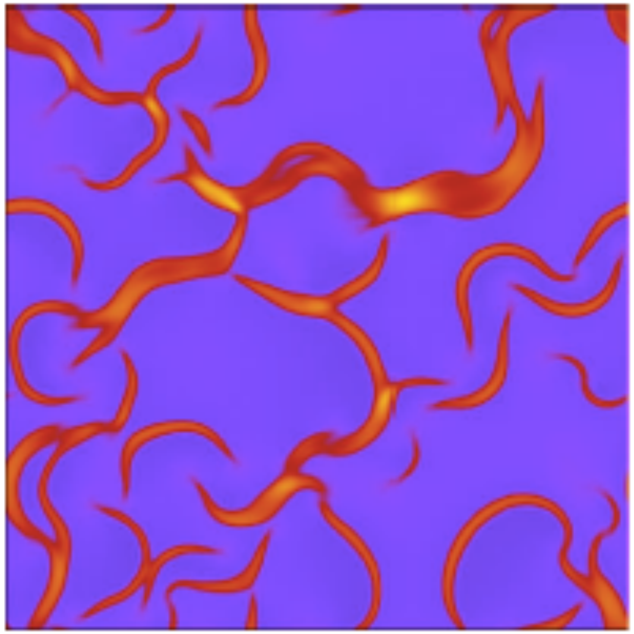
Our self-propelled particles move over a dissipative substrate (or in a viscous medium) which acts as a momentum sink

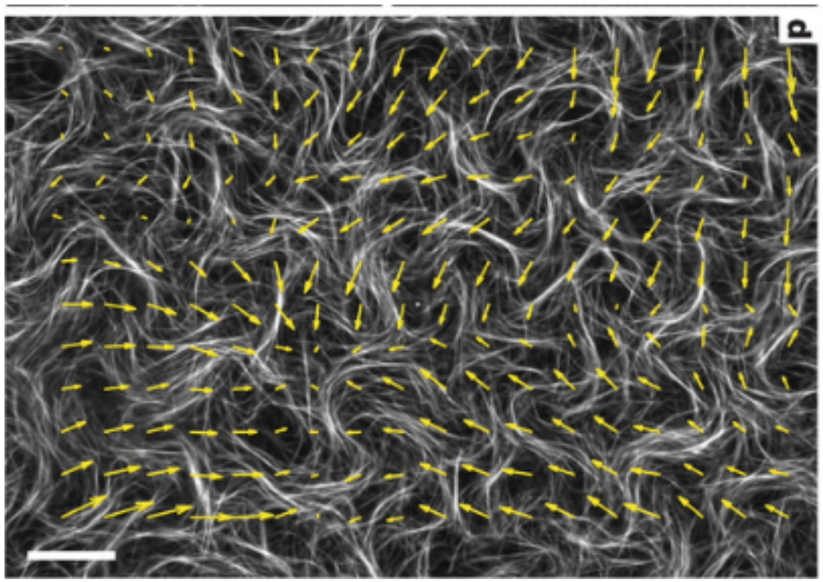
Interlude -- Instabilities in nematic Vicsek-like models

F. Ginelli et al. PRL **104** 184502 (2010).
S Ngo, et al. PRL **113**, 038302 (2014).



(d)





Dogic lab, Nature 2012

Hydrodynamic description (Toner & Tu theory)

$$\partial_t \rho + \nabla \cdot (\mathbf{v}\rho) = 0$$ continuity eq.

$$\partial_t \mathbf{v} + \mathbf{\Lambda}[\nabla \mathbf{v}\mathbf{v}] = U(\rho, |\mathbf{v}|)\mathbf{v} + \mathbf{D}[\nabla\nabla\mathbf{v}] + \mathbf{F_P} + \mathbf{f}$$

advective

$$\mathbf{\Lambda}[\nabla \mathbf{v}\mathbf{v}] \equiv \lambda_1(\mathbf{v}\cdot\nabla)\mathbf{v} + \lambda_2(\nabla\cdot\mathbf{v})\mathbf{v} + \lambda_3\nabla(|\mathbf{v}|^2)$$

Some kind of material derivative (time + convective derivatives), but with extra terms since Galileian invariance is broken

Can be derived either by:

1. **Phenomenological hydrodynamics**

2. **Direct coarse-graining: e.g. Kinetic approaches (Boltzmann-Ginzburg-Landau approach)**

J. Toner, Y. Tu, Phys Rev Lett 75 4326 (1995); , Phys Rev E 58 4828 (1998).

Hydrodynamic description

$$\partial_t \rho + \nabla \cdot (\mathbf{v}\rho) = 0$$

$$\partial_t \mathbf{v} + \mathbf{\Lambda}\left[\nabla \mathbf{v}\mathbf{v}\right] = U(\rho, |\mathbf{v}|)\mathbf{v} + \mathbf{D}\left[\nabla\nabla\mathbf{v}\right] + \mathbf{F_P} + \mathbf{f}$$

Diffusive, viscous terms

$$\mathbf{D}\left[\nabla\nabla\mathbf{v}\right] \equiv D_1\nabla(\nabla\cdot\mathbf{v}) + D_2(\mathbf{v}\cdot\nabla)^2\mathbf{v} + D_3\nabla^2\mathbf{v};$$

Hydrodynamic description

$$\partial_t \rho + \nabla \cdot (\mathbf{v}\rho) = 0$$

$$\partial_t \mathbf{v} + \mathbf{\Lambda}\,[\nabla \mathbf{v}\mathbf{v}] = U(\rho, |\mathbf{v}|)\mathbf{v} + \mathbf{D}\,[\nabla\nabla \mathbf{v}] + \mathbf{F_P} + \mathbf{f}$$

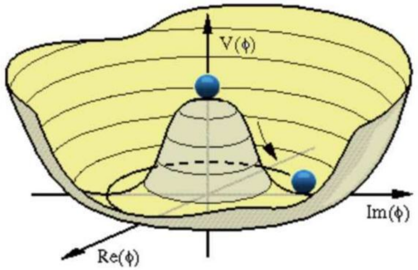
Spontaneous symmetry breaking

pressure

$$\mathbf{F_P} \equiv -\nabla P_1 - \mathbf{v}\,(\mathbf{v} \cdot \nabla P_2)$$

$$P_i(\rho) = P_i^0 + \sum_{n=1}^{\infty} \sigma_{i,n}(|\vec{v}|)\delta\rho^n$$

$$U = \mu(\rho) - \beta(\rho)|\mathbf{v}|^2$$



$$v_0(0) = \sqrt{\mu/\beta},$$

Hydrodynamic description

$$\partial_t \rho + \nabla \cdot (\mathbf{v}\rho) = 0$$

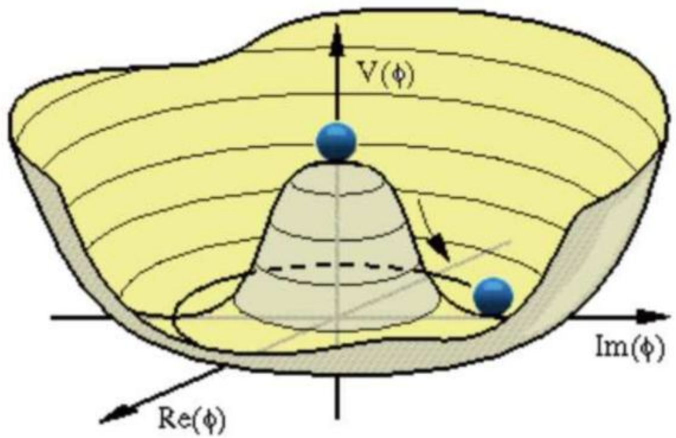
$$\partial_t \mathbf{v} + \boldsymbol{\Lambda}\left[\nabla \mathbf{v}\mathbf{v}\right] = U(\rho, |\mathbf{v}|)\mathbf{v} + \mathbf{D}\left[\nabla\nabla \mathbf{v}\right] + \mathbf{F}_{\mathbf{P}} + \mathbf{f}$$

$$< f_i(\mathbf{r}, t) f_j(\mathbf{r}', t') >= \Delta \delta_{ij} \delta^d(\mathbf{r} - \mathbf{r}')\delta(t - t')$$

order parameter $\Phi(h) \equiv |\langle \mathbf{v}(\mathbf{r}, t)\rangle|$

Spontaneous symmetry breaking of a continuous symmetry + non-equilibrium effects

In the symmetry-broken state, large wavelength velocity fluctuations are easily excited and decay slowly (Nambu-Goldstone modes)



Velocity fluctuations

↕

Density fluctuations

Hydrodynamic theory predicts universal long-ranged properties

E.g.: equal time correlation functions and structure factors in the homogeneous, ordered phase

$$S(\mathbf{q},t) \equiv \langle \delta\hat{\rho}(\mathbf{q},t)\delta\hat{\rho}(-\mathbf{q},t)\rangle \sim \frac{1}{q^{\sigma}} \quad \text{for } q \to 0$$

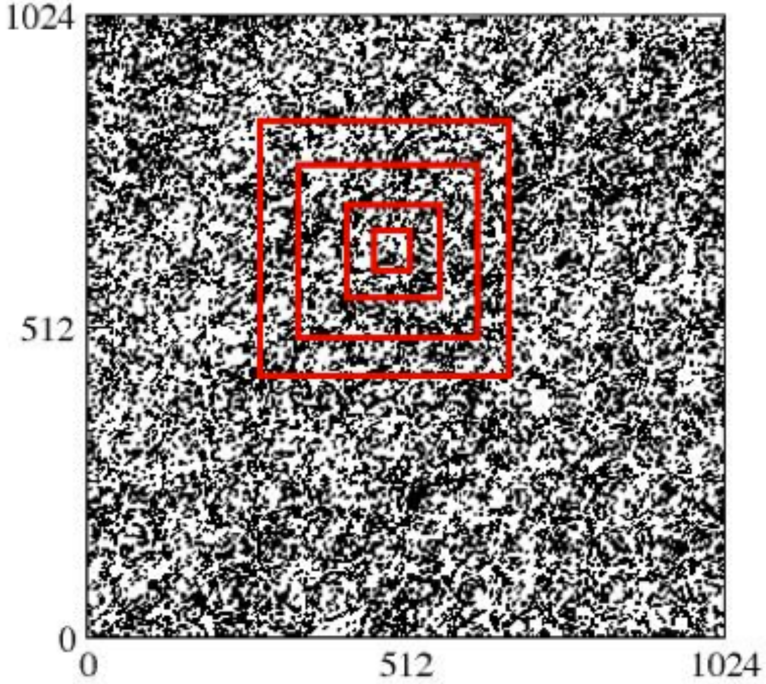
$$C_v(\vec{R}) = \langle \delta\vec{v}(\vec{r}+\vec{R},t)\cdot\delta\vec{v}(\vec{r},t)\rangle = |R_\perp|^{2\chi} f_v\left(\frac{|R_\parallel|/l_0}{(|R_\perp|/l_0)^{\xi}}\right)$$

Scaling exponents are known under some RG conjectures, e.g:

$$\chi = \frac{3-2d}{5}, \quad \zeta = \frac{d+1}{5}. \qquad \sigma = \frac{2}{5}(d+1)$$

Giant Number Fluctuations

- Fluctuations in average number of particles are anomalously large:



$$\langle n \rangle = \rho_0 \, \ell^d$$

$$\Delta n = (\langle (n_t - \langle n \rangle)^2 \rangle)^{1/2}$$

$$S(\mathbf{q} \to 0) = \rho_0 \left[\frac{\Delta n^2}{\langle n \rangle} \right]_{n \to \infty}$$

$$S(\mathbf{q} \to 0) \sim \frac{1}{q^\sigma} \sim \ell^\sigma \quad \Rightarrow \quad \Delta n \sim \langle n \rangle^{1/2 + \sigma/(2d)}$$

Good agreement between theory and numerical simulations

Some open issues

No clear-cut experimental measures of giant-number fluctuations in polar flocking systems

(for nematic: *Nishiguchi, Nagal, Chate and Sano, 2017 Phys. Rev. E 95 020601(R)*)

What about dense systems where steric interactions are important/dominate ?

- MIPS and/or non-equilibrium clustering effects, even in disordered phase
  (Anomalous density fluctuations at the mesoscopic scale)
- As long as the systems **flows** (not jammed) and does not phase segregates, hydrodynamics should hold at some large scale
- What about small and meso-scales (typically the biologically relevant ones) which are not captured by hydrodynamics?

Cellular migration

- Wound healing
- Embryogenesis
- Spreading of cancer cells
- …

nature materials

ARTICLES

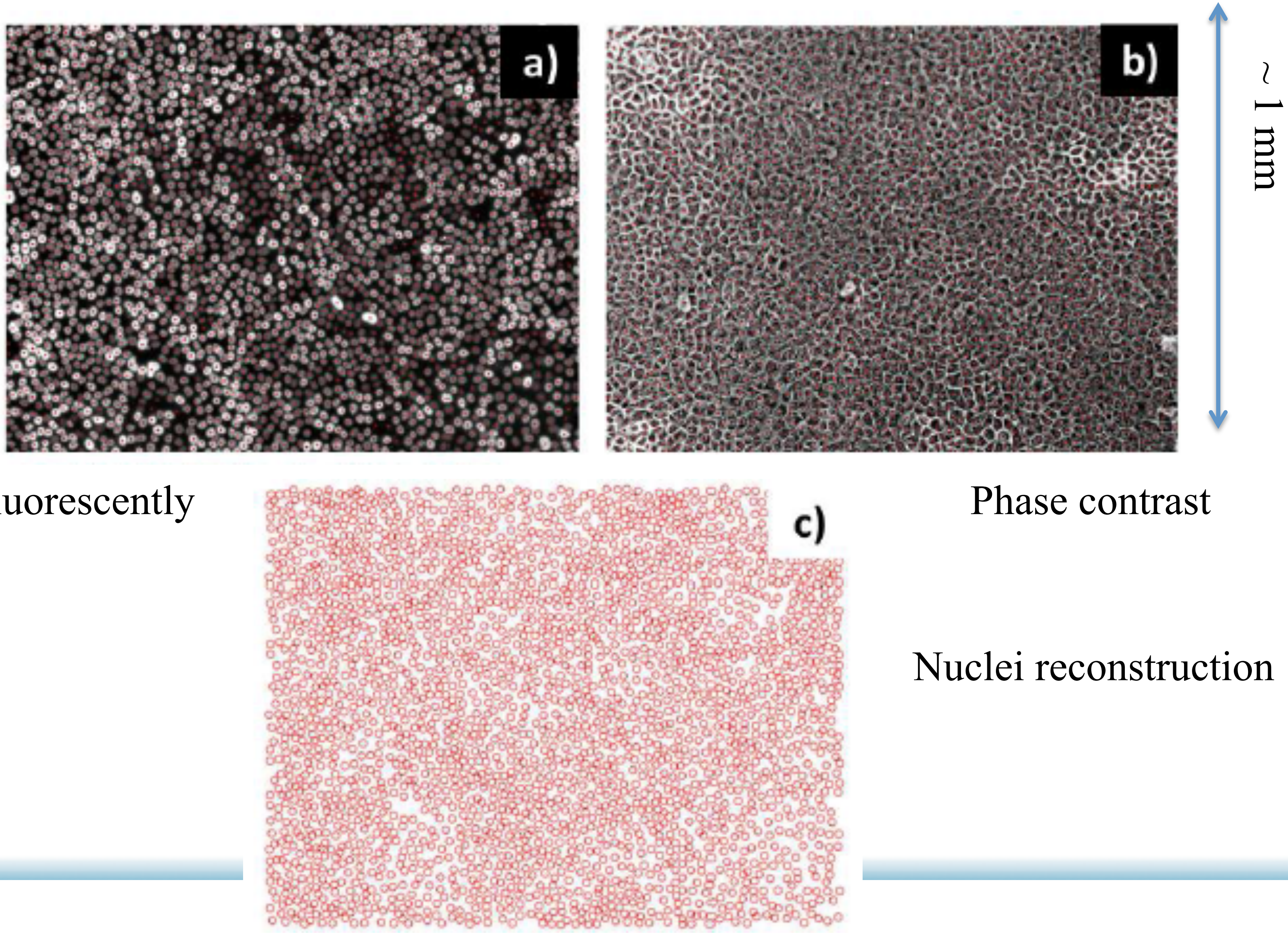
PUBLISHED ONLINE: 30 JANUARY 2017 | DOI: 10.1038/NMAT4848

Endocytic reawakening of motility in jammed epithelia

Chiara Malinverno[1†], Salvatore Corallino[1†], Fabio Giavazzi[2★], Martin Bergert[3], Qingsen Li[1], Marco Leoni[4], Andrea Disanza[1], Emanuela Frittoli[1], Amanda Oldani[1], Emanuele Martini[1], Tobias Lendenmann[3], Gianluca Deflorian[1], Galina V. Beznoussenko[1], Dimos Poulikakos[3], Kok Haur Ong[5], Marina Uroz[6,7,8,9], Xavier Trepat[6,7,8,9], Dario Parazzoli[1], Paolo Maiuri[1], Weimiao Yu[5], Aldo Ferrari[3★], Roberto Cerbino[2★] and Giorgio Scita[1,10★]

Cell tissue **Lab grown human mammary epithelial MCF-10A cells.**

Seeded in well plates and cultured to obtain a large (~ 10^6 cells) hyperconfluent monolayer

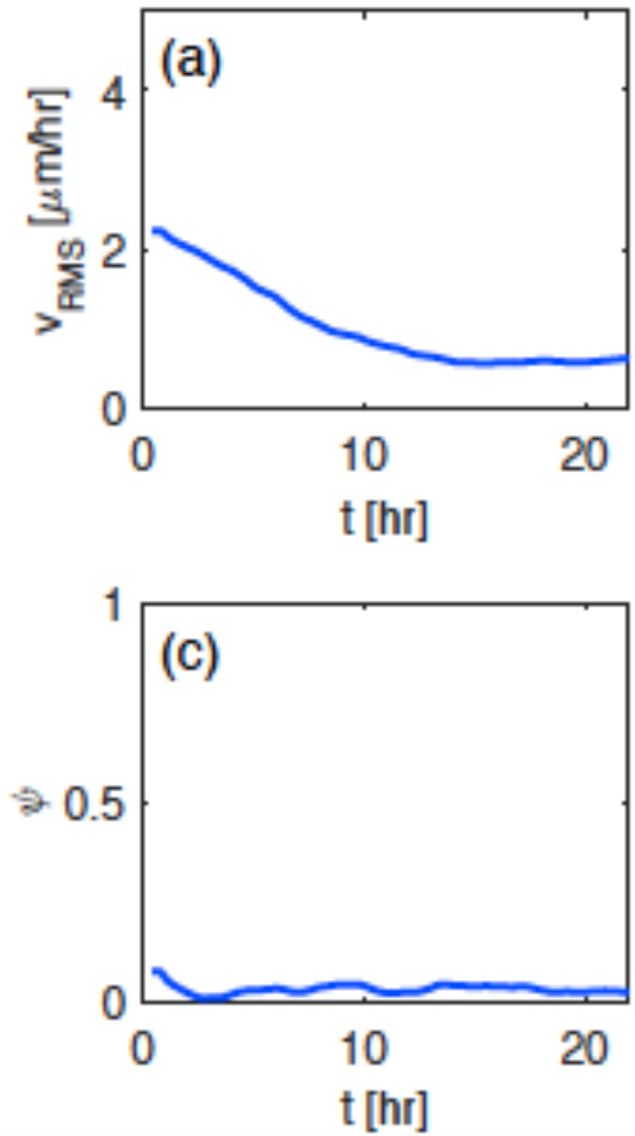


Fluorescently

Phase contrast

Nuclei reconstruction

Control tissue is disordered (and not so far from kinetic arrest



$$v_{RMS}(t) = \sqrt{\left\langle \frac{1}{M} \sum_{j=1}^{M} |\boldsymbol{v}_j^{(k)}(t)|^2 \right\rangle_k},$$

(average over 5 independent FOV, velocity measures by PIV)

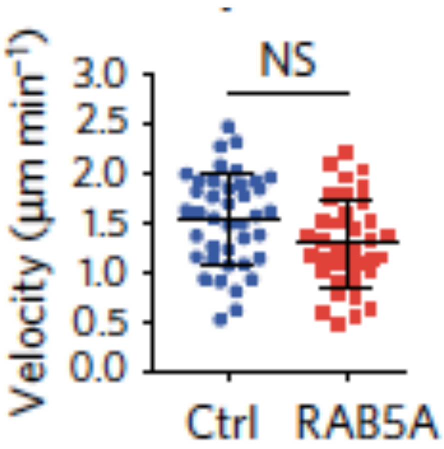
$$\psi(t) = \left\langle \left| \frac{1}{M} \sum_{j=1}^{M} \frac{\boldsymbol{v}_j^{(k)}(t)}{|\boldsymbol{v}_j^{(k)}(t)|} \right| \right\rangle_k$$

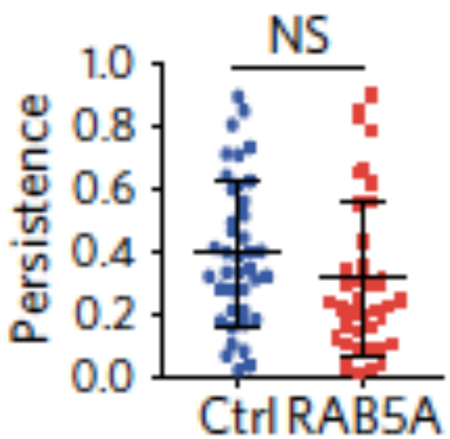
RAB5A expression

RAB5A is a protein that regulates cellular dynamics:

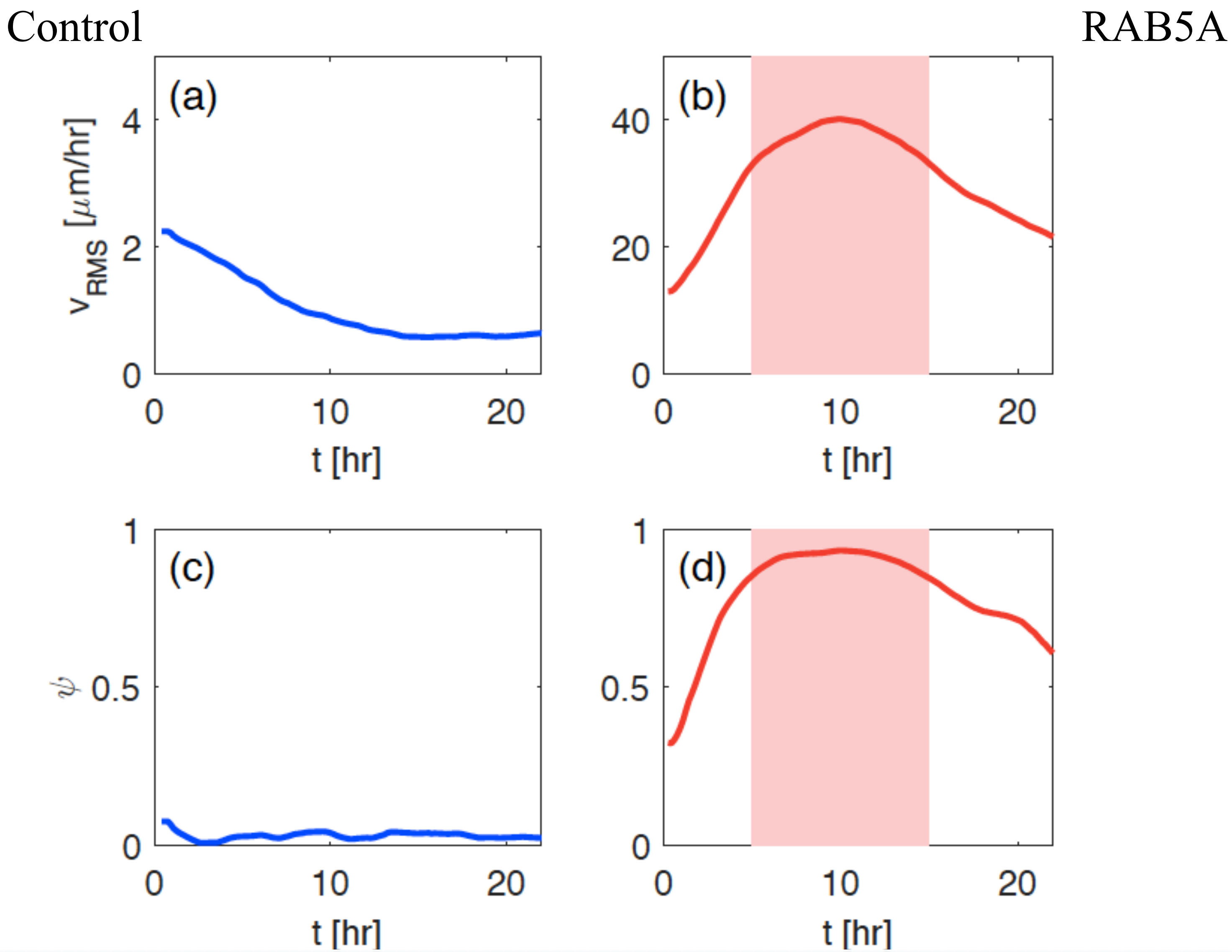
- Endocythosis
- Membrane tensions and junctions
- Promote the extension of protusions aligned to local velocity

RAB5A expression does not alter the migration speed of sparsely seeded cells,

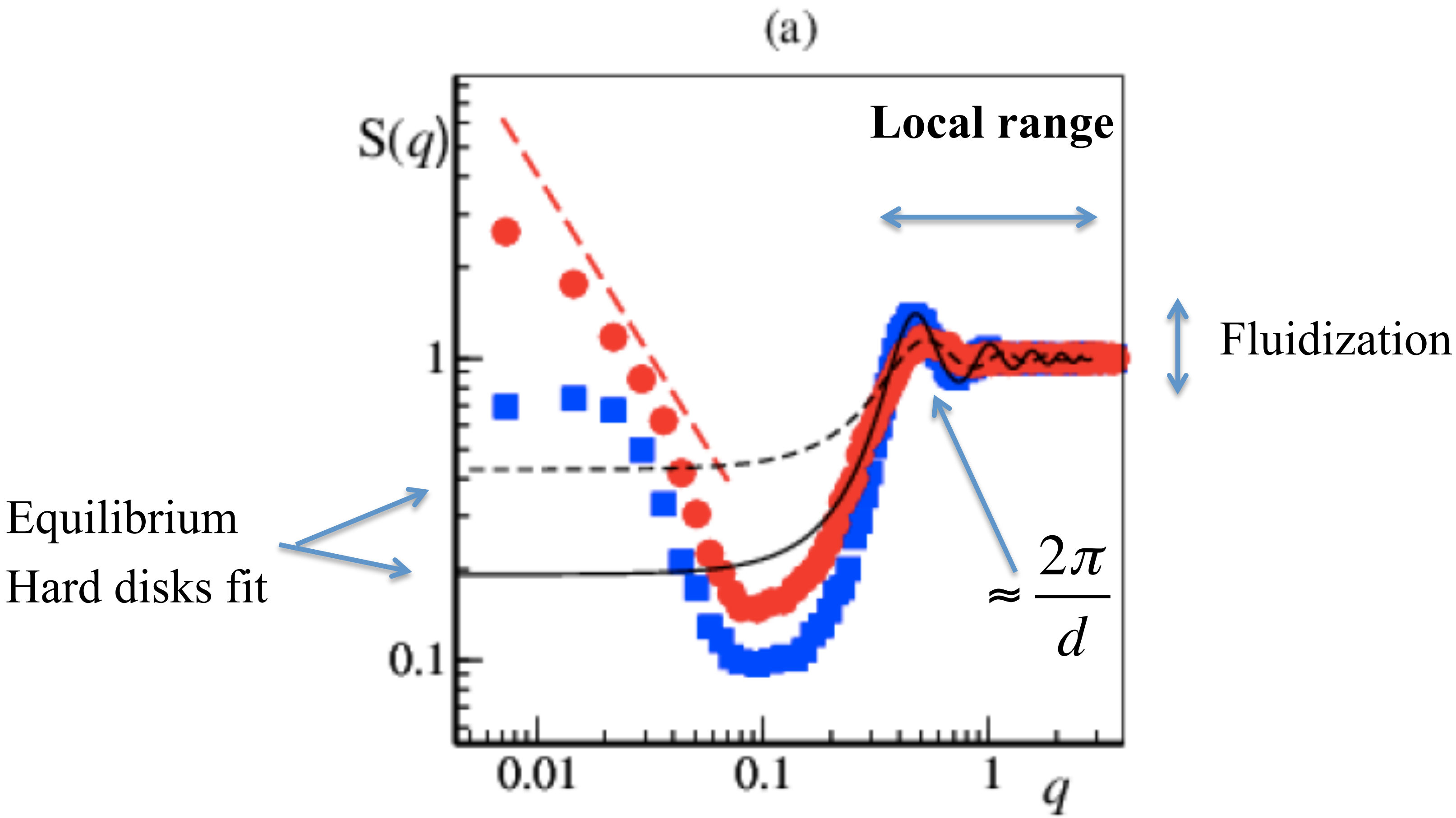




RAB5A promotes a transition to flocking and a reawakening of motility

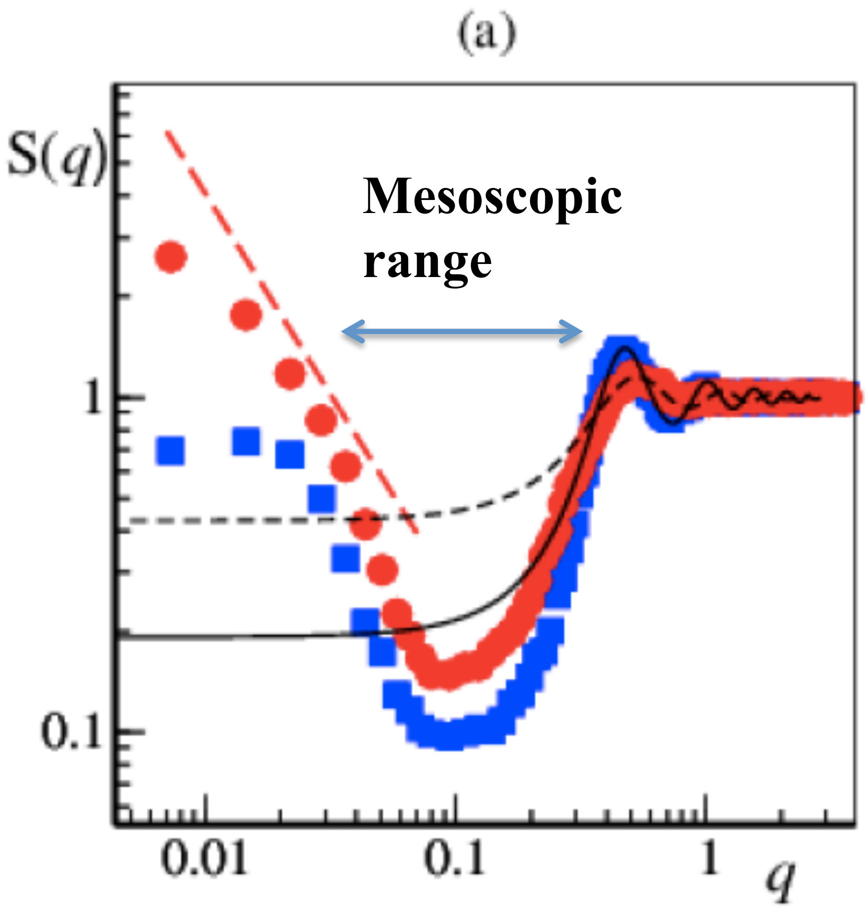


Structure factor measures



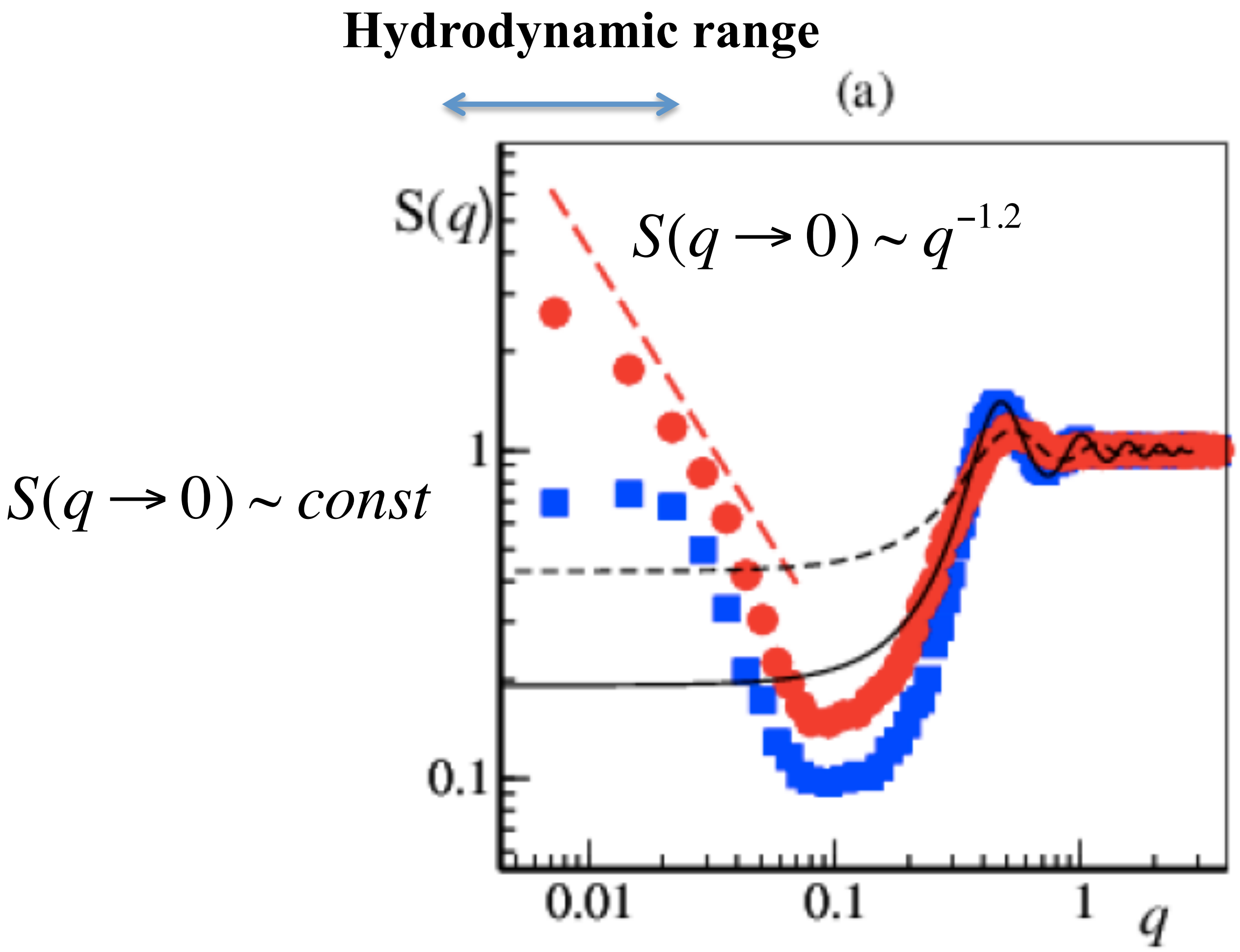
Control vs. RAB5A expressed

Structure factor measures



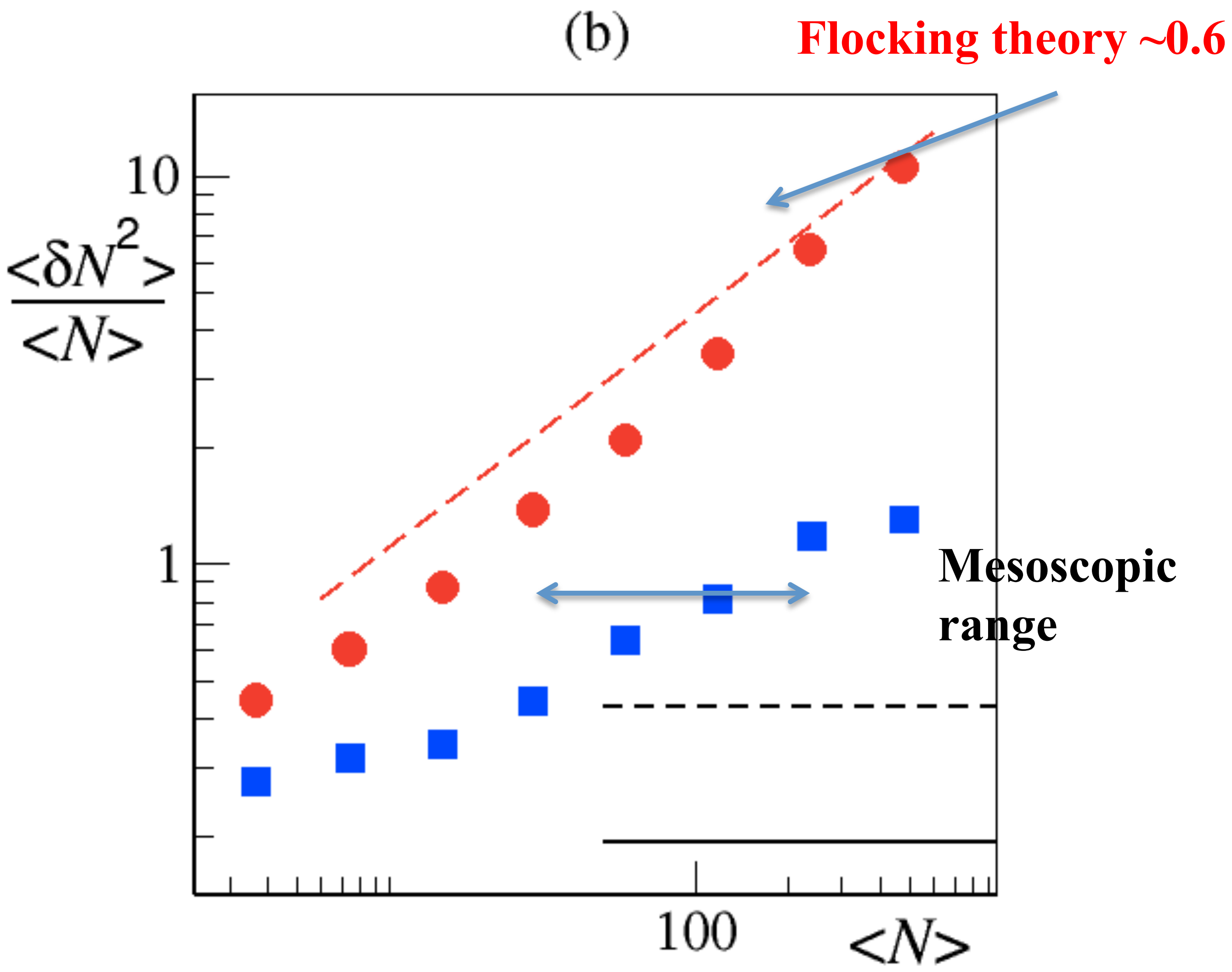
Control vs. RAB5A expressed

Structure factor measures



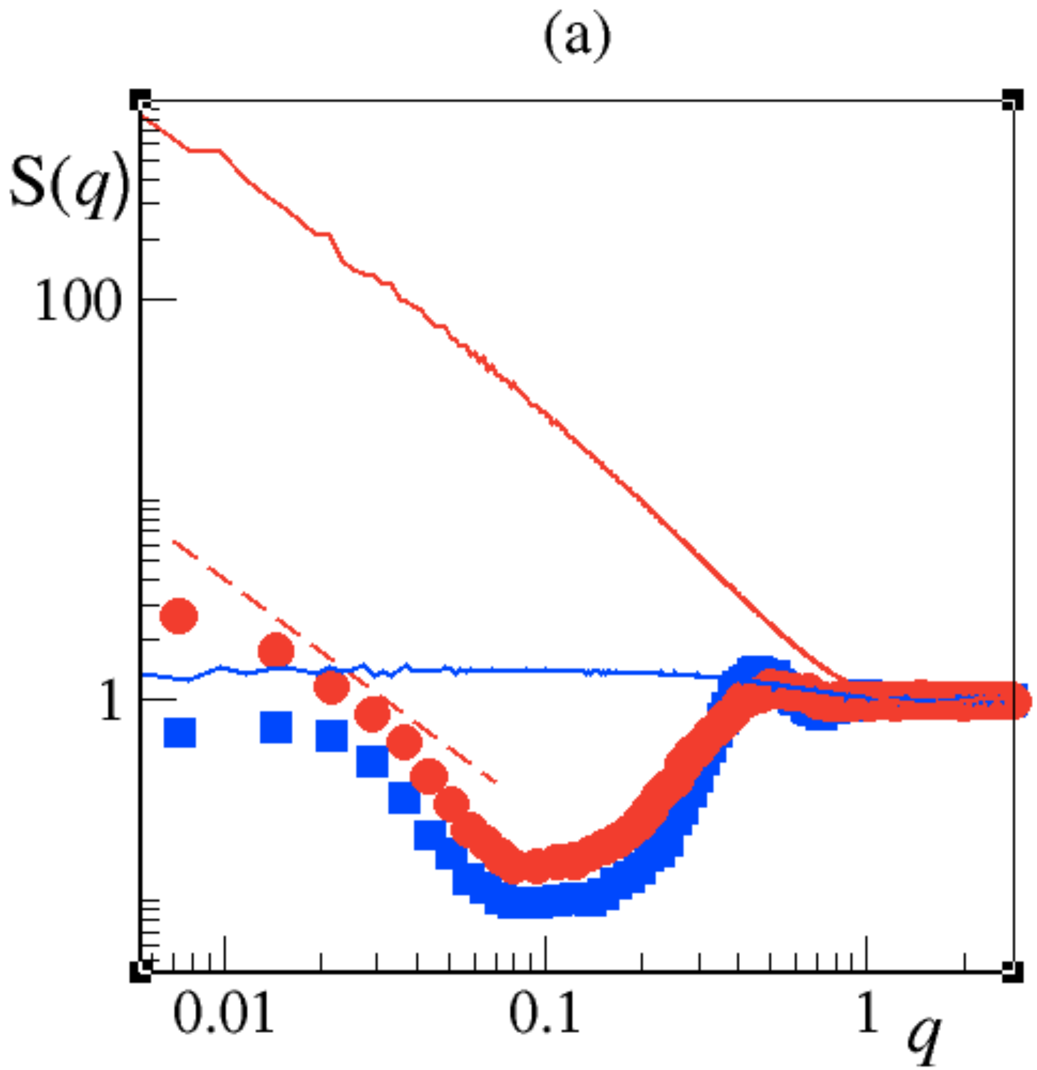
Control vs. RAB5A expressed

Giant number fluctuations



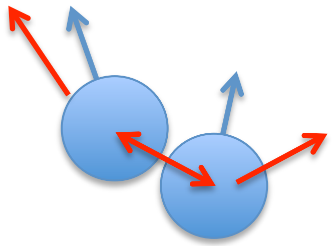
$N_c \simeq \rho_{exp}(2\pi q_c^{-1})^2 \simeq 250.$

Vicsek model only captures the hydrodynamic behavior



A better model at short scales: Collisional Vicsek model (CVM)

$$\dot{\mathbf{r}}_i = v_0 \hat{\mathbf{n}}(\theta_i) + \beta \sum_j^{N_0} \mathbf{F}_{ij}$$



$$\dot{\theta}_i = \frac{1}{\tau}(\theta_i - \psi_i) + \xi_i$$

$$\mathbf{v_i} \equiv \dot{\mathbf{r}}_i = v_i (\cos\psi_i, \sin\psi_i),$$

$$\mathbf{F}_{ij} = \begin{cases} 0 & \text{if } r_{ij} \equiv |\mathbf{r}_i - \mathbf{r}_j| \geq (\sigma_i + \sigma_j) \\ [r_{ij} - (\sigma_i + \sigma_j)]\, \hat{\mathbf{r}}_{ij} & \text{if } r_{ij} < (\sigma_i + \sigma_j) \end{cases}$$

$$\langle \xi_i \rangle = 0$$
$$\langle \xi_i(t) \xi_j(t') \rangle = \eta^2 \delta_{ij} \delta(t - t') .$$

Rescale time and space

$$\beta = \langle \sigma \rangle = 1$$

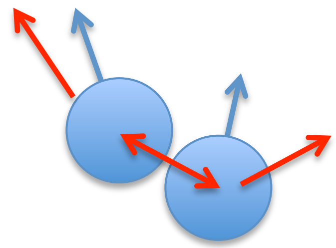
Szabo B, Szollosi GJ, Gonci B, Juranyi Z, Selmeczi D and Vicsek T 2006 Phys. Rev. E 74(6) 061908

Henkes S, Fily Y and Marchetti M C 2011 Phys. Rev. E 84(4) 040301

A better model at short scales: Collisional Vicsek model (CVM)

$$\dot{\mathbf{r}}_i = v_0 \hat{\mathbf{n}}(\theta_i) + \beta \sum_j^{N_0} \mathbf{F}_{ij}$$

$$\dot{\theta}_i = \frac{1}{\tau}(\theta_i - \psi_i) + \xi_i$$



$$\mathbf{v_i} \equiv \dot{\mathbf{r}}_i = v_i\,(\cos\psi_i,\ \sin\psi_i),$$

Realignment timescale τ

Self-propulsion speed v_0

Packing fraction $\phi = \rho\pi\langle\sigma_i^2\rangle = 1.2$

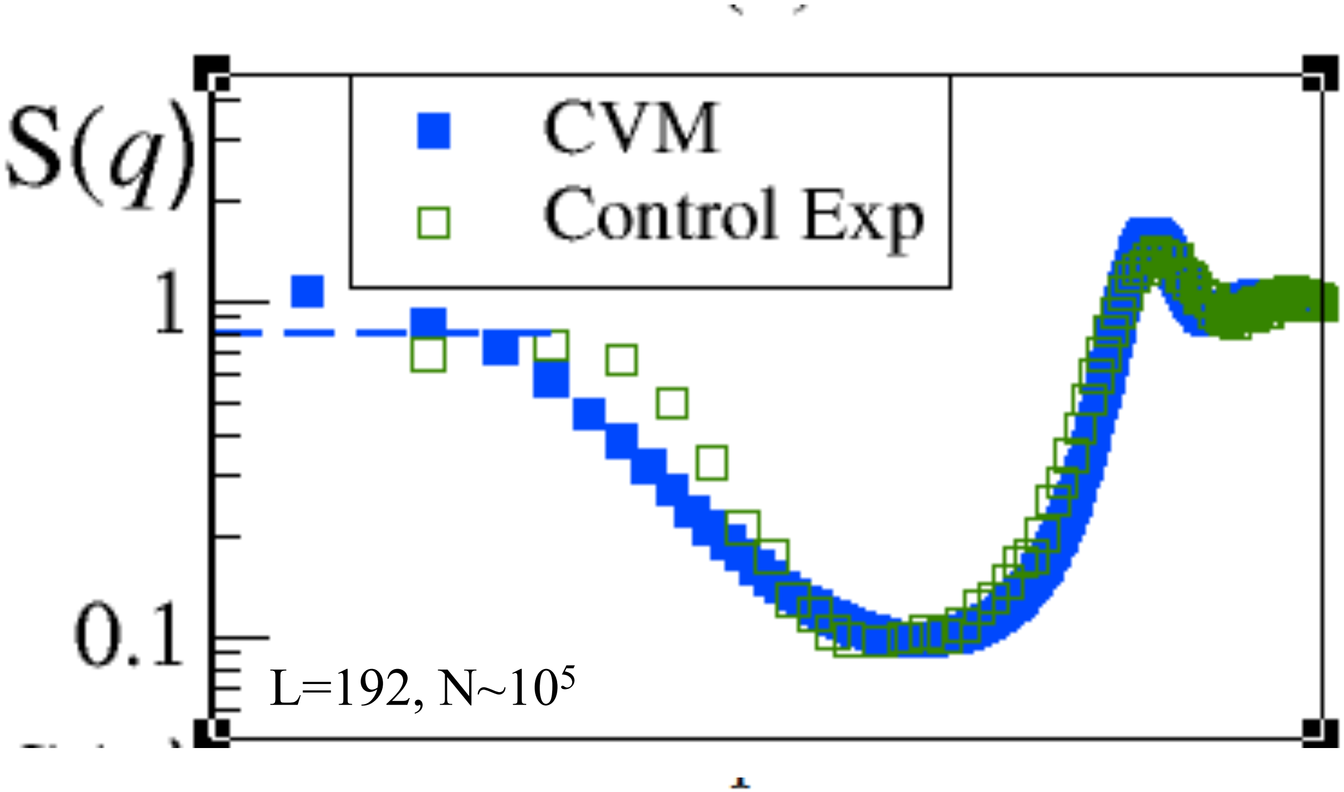
Noise $\eta = 0.45.$

Polydispersivity = 20%

Szabo B, Szollosi GJ, Gonci B, Juranyi Z, Selmeczi D and Vicsek T 2006 Phys. Rev. E 74(6) 061908

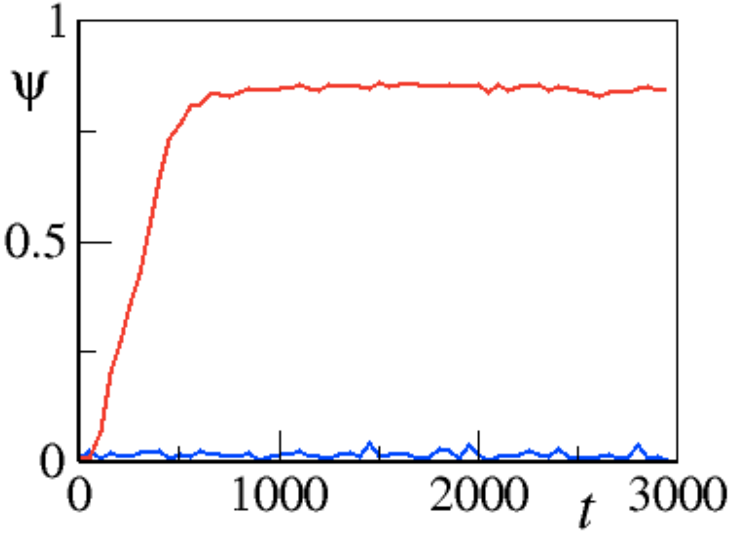
Henkes S, Fily Y and Marchetti M C 2011 Phys. Rev. E 84(4) 040301

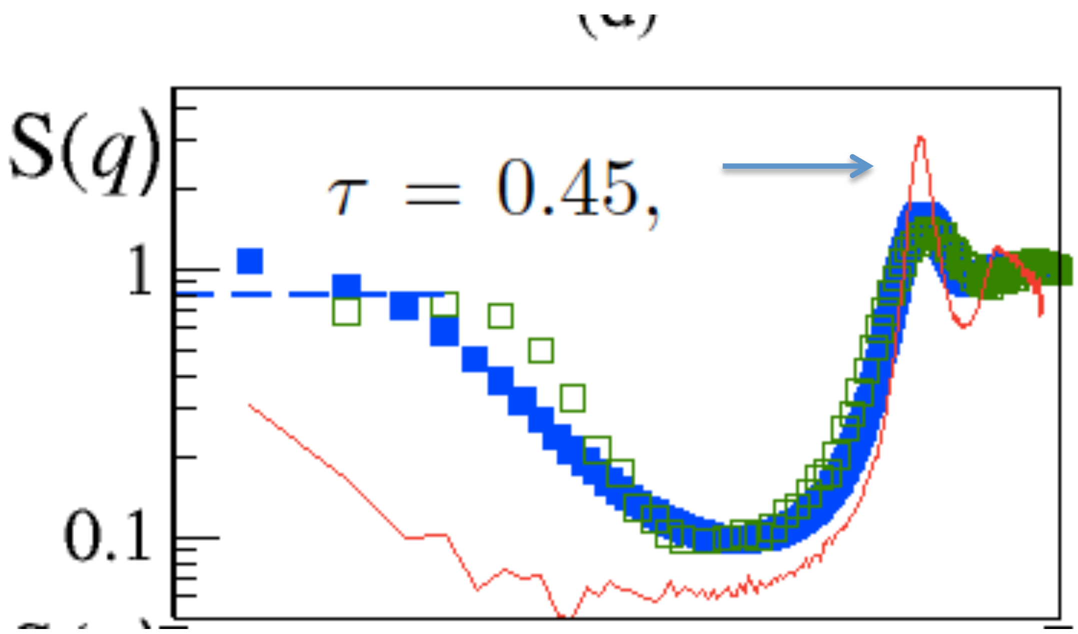
CVM – disordered (high τ)



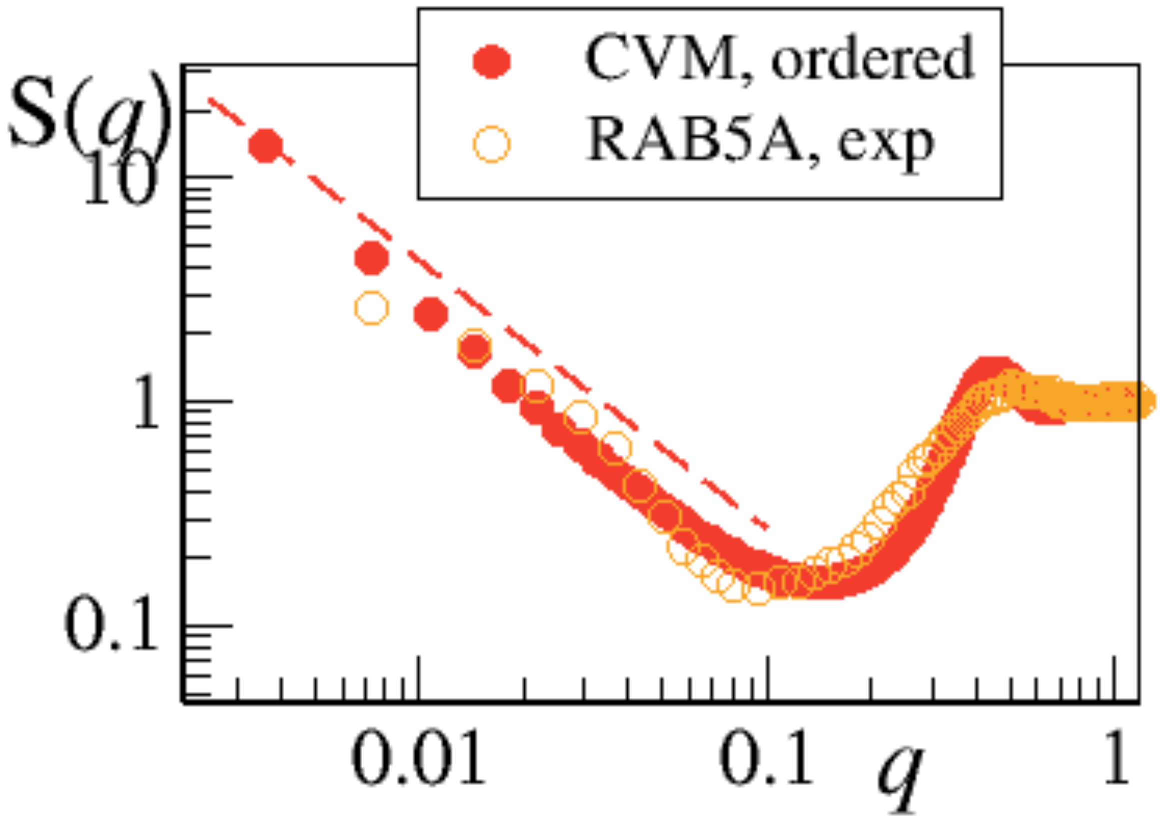
$v_0 = 0.5$ and $\tau = 5.0.$

Lowering the reorientation timescale, the system orders, but it is locally less fluid



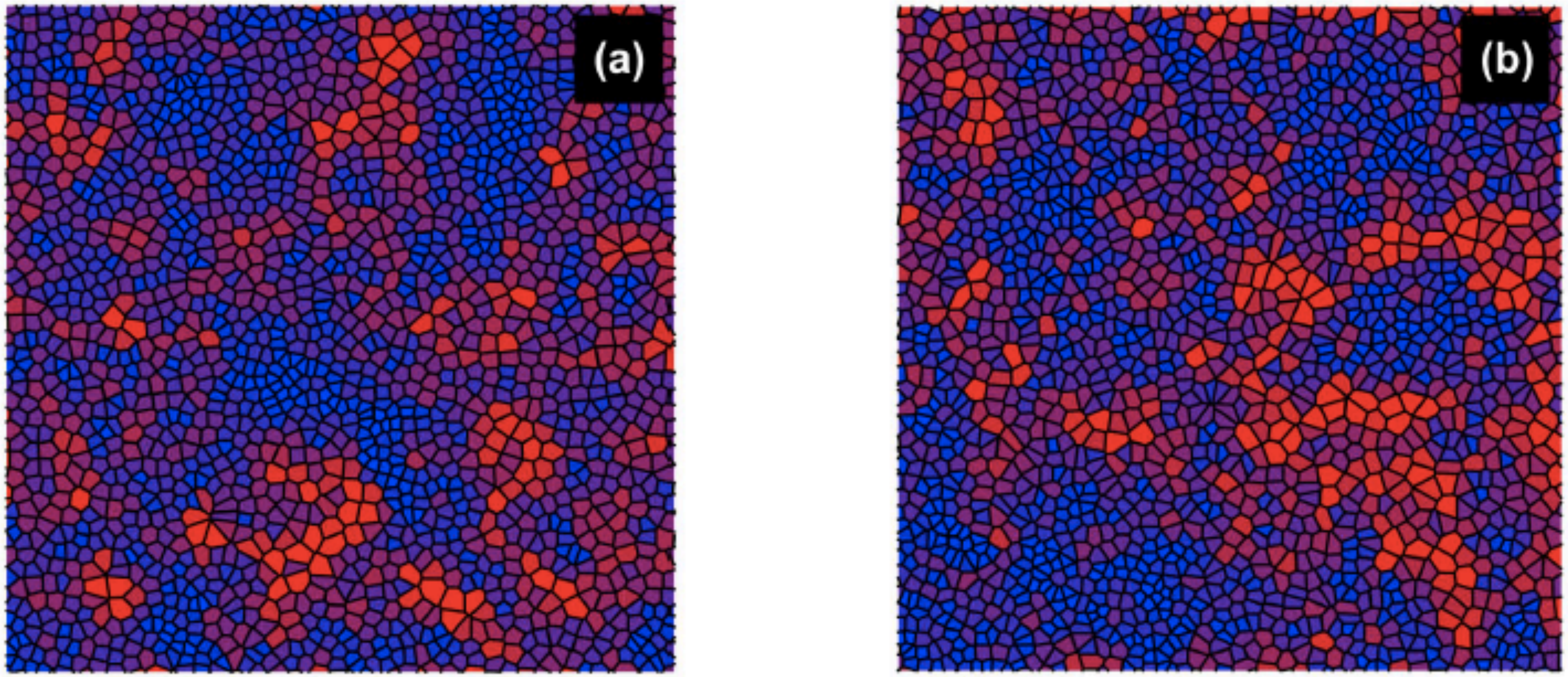


Low reorientation timescale, higher speed fluidized the flocking state

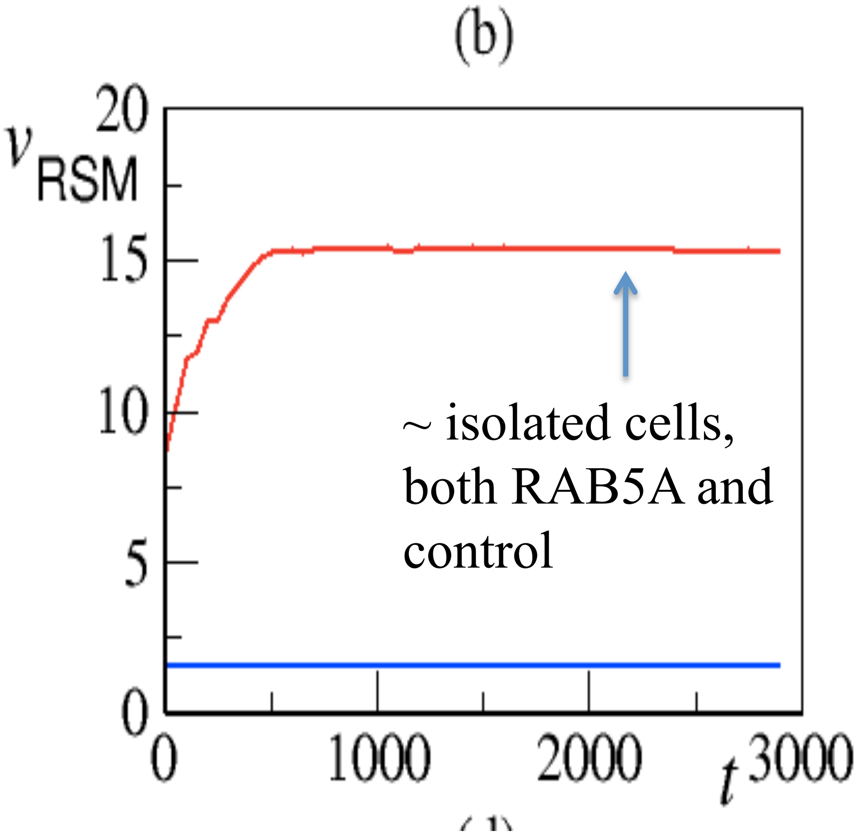


$\tau = 0.45, \qquad v_0 \approx 2.0$

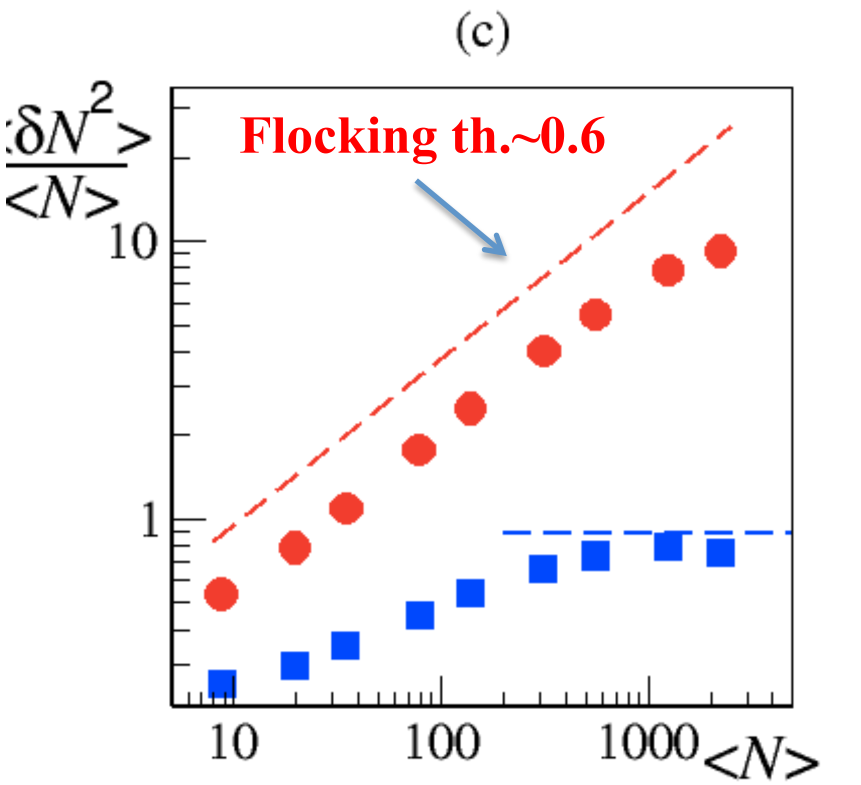
Which is which ?



Ordered, high speed vs disordered low speed CVM



Motility reawakening



GNF

Conclusions

First **experimental measure of GNF and structure** in biological active matter showing long range polar order

A **simple mechanical model** of soft self-propelled disks **reproduces fairly well a wide range of scale**, at the **local**, **mesoscopic** and **hydrodynamic** range.

At the experimental level, the flocking transition is accompanied by **local fluidization**. In simulations, this can be achieved by a large increase of self-propulsion speed. This suggests that an (indirect ?) effect of **RAB5A** expression is to **reduce the mechanical feedbacks that suppress cellular motility in the disordered control**

Perspectives

Larger FOVs, velocity fluctuations, local stresses and elastic modes