Understanding biological functions during Morphogenesis: quantification of experimental data

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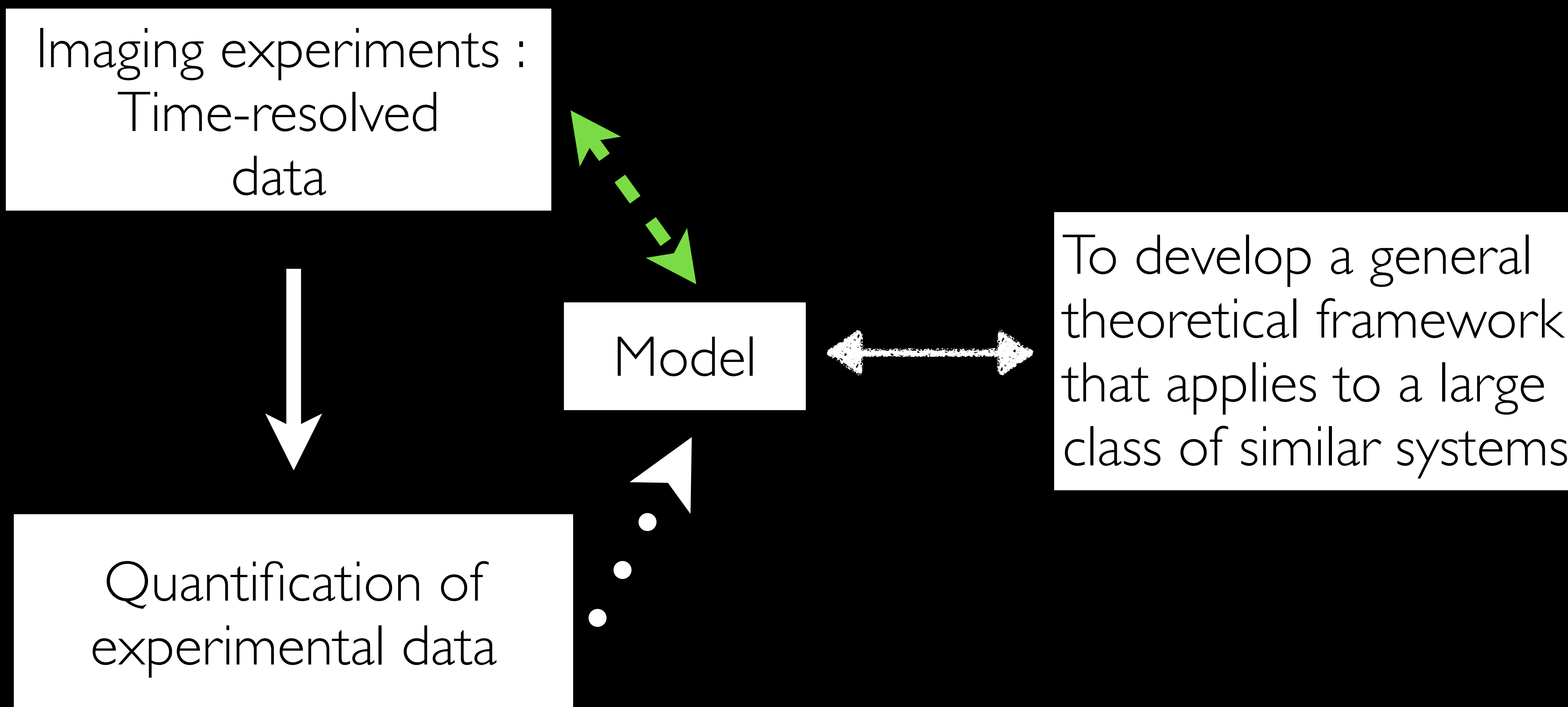
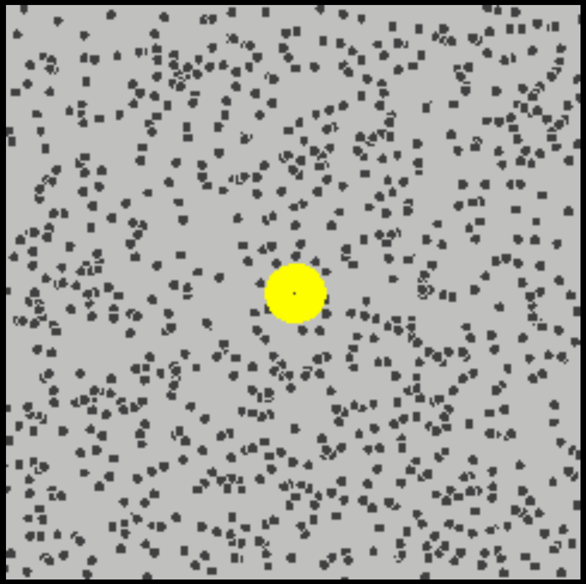
May 14, 2024

Quantification of experimental data: Building a model



Transport by simple diffusion

Mesoscopic view of diffusion



Source: Wikipedia

$$\cancel{m\ddot{\mathbf{r}}} + \gamma\dot{\mathbf{r}} = \boldsymbol{\xi}(t)$$

$$\langle \xi_i(t)\rangle = 0, \quad \langle \xi_i(t)\xi_j(t')\rangle = \Gamma\delta_{ij}\delta(t-t')$$

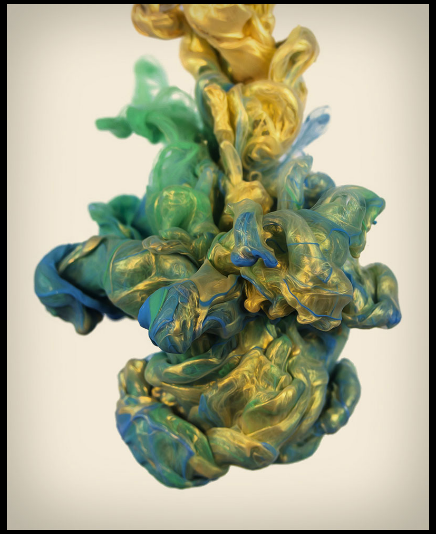
In the over damped limit

$$\dot{\mathbf{r}} = \sqrt{2D}\ \boldsymbol{\xi}(t)$$

(1) Fluctuation-Dissipation relationship: $\Gamma = 2dm\gamma K_B T$

(2) Mean-square displacement: $\langle r^2(t)\rangle = 2dDt$

Macroscopic view of diffusion



Source: ZME Science

Diffusion equation

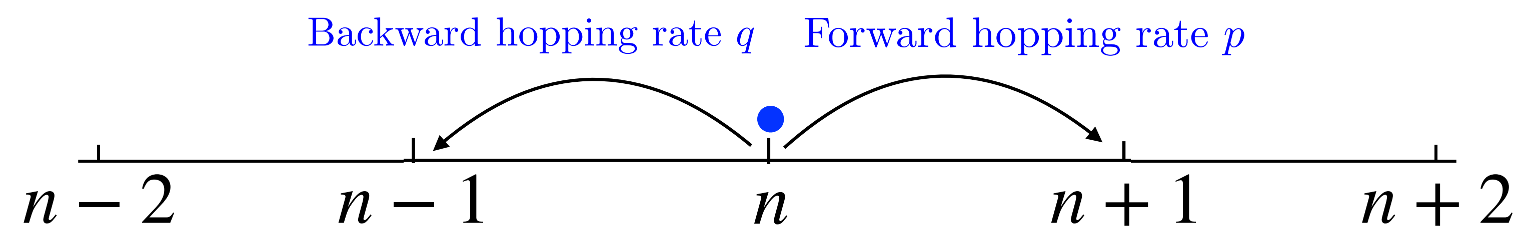
$$\frac{\partial}{\partial t}P(\mathbf{r},t) = D\frac{\partial^2}{\partial x^2}P(\mathbf{r},t)$$

$$P(\mathbf{r},t) = \frac{1}{\sqrt{4\pi dDt}}\exp\left[-\frac{(r-r_0)^2}{4dDt}\right]$$

Master equation approach

$$\frac{d}{dt}P(\mathbf{n},t) = \sum_{\mathbf{n}'}\left[W(\mathbf{n}\,|\,\mathbf{n}')P(\mathbf{n}',t) - W(\mathbf{n}'\,|\,\mathbf{n})P(\mathbf{n},t)\right]$$

Example: 1D random walk



$$\frac{d}{dt}P(n,t) = pP(n-1,t) - pP(n,t) + qP(n+1,t) - qP(n,t)$$

Let $p = q$

$$\frac{d}{dt}P(n,t) = p[P(n-1,t) + P(n+1,t) - 2P(n,t)]$$

$$\frac{d}{dt}P(n\Delta x,t) = p[P((n-1)\Delta x,t) + P((n+1)\Delta x,t) - 2P(n\Delta x,t)]$$

Let

$\lim \Delta x \to 0,$

$D = p\Delta x^2$

$$\frac{d}{dt}P(x,t) = D\frac{\partial^2}{\partial x^2}P(x,t)$$

What if $p > q$?

Intra-cellular transport, role of the dynamic cytoskeleton

Modified mean-square displacement

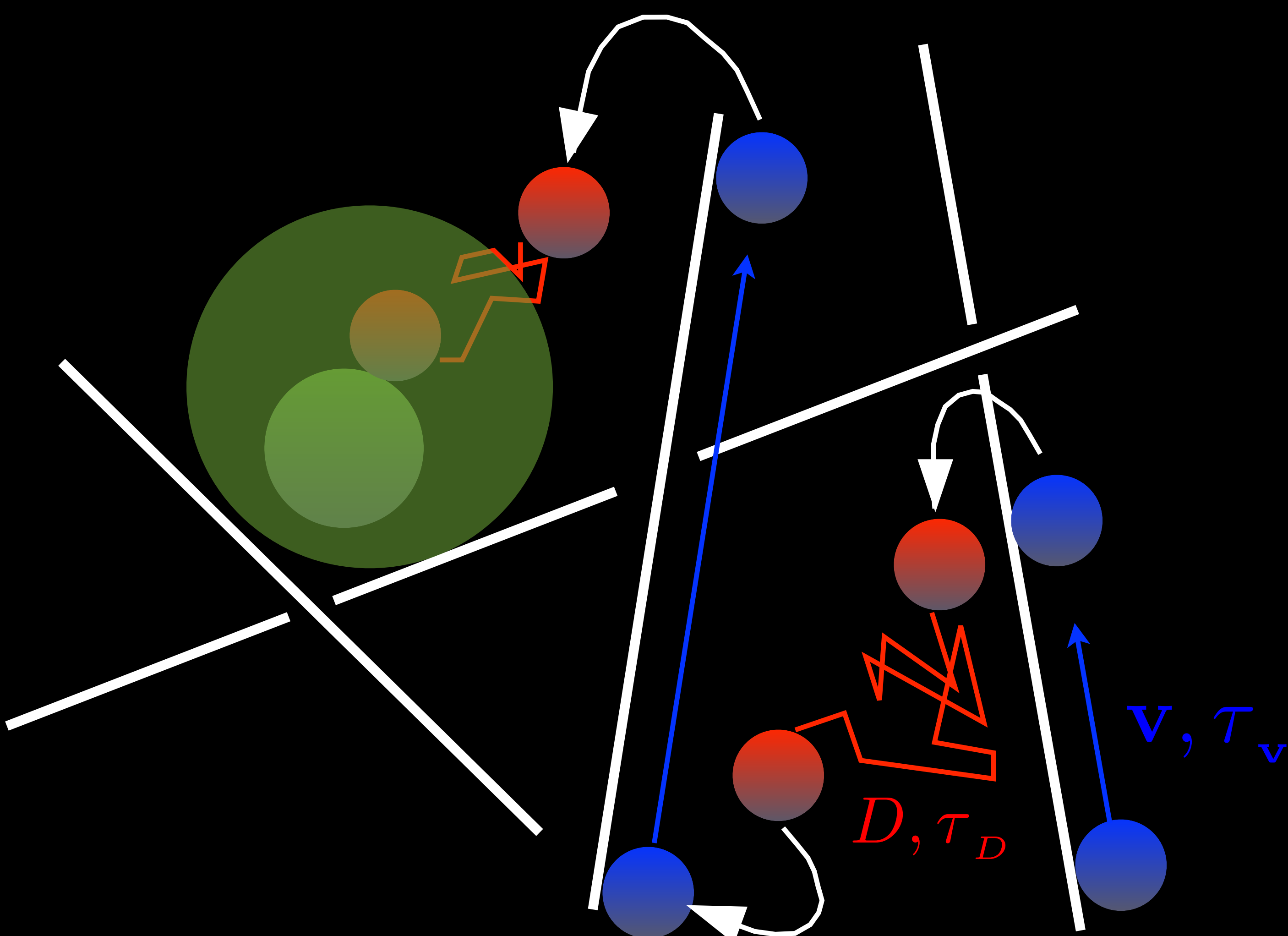
$$\langle \Delta R^2(\tau) \rangle \propto \tau^{\alpha}$$

$\alpha = 1$, for free diffusion

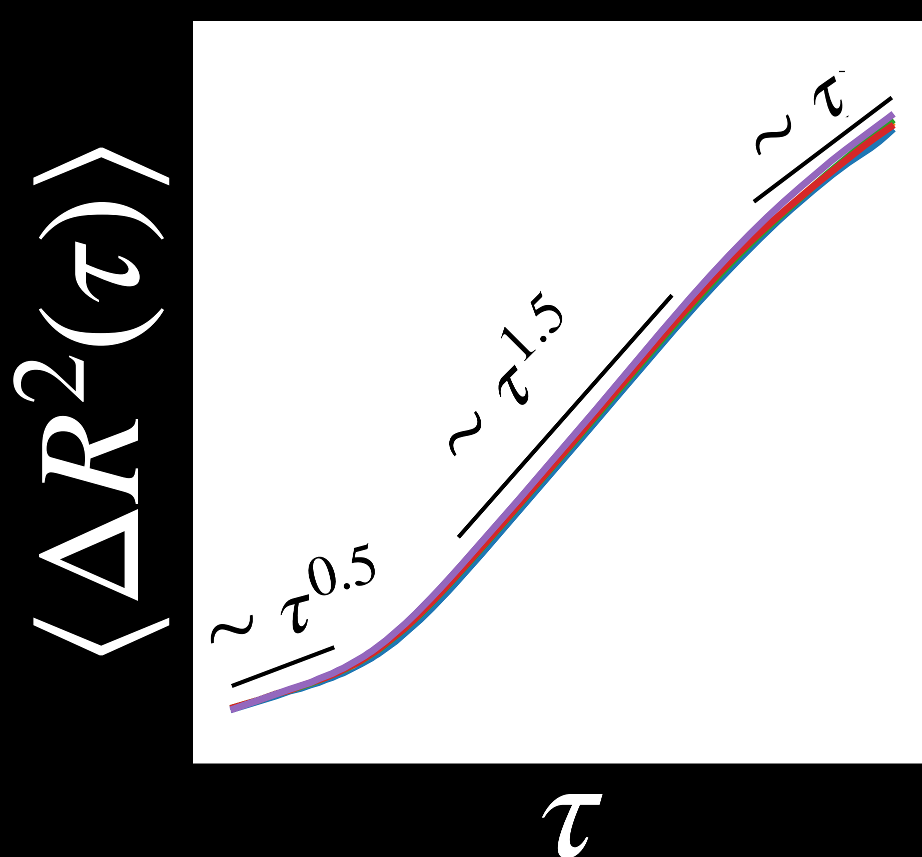
$\alpha = 2$, for ballistic motion

$\alpha < 1$, for sub-diffusion

$1 < \alpha < 2$, for super-diffusion



Loverdo et. al, Nature Physics (2008)



Sanoria et. al., PRE (2021)

MSD for an experimental trajectory

$$\langle \Delta R_t^2(\tau = k\Delta t)\rangle = \frac{1}{M-k+1} \sum_{i=1}^{M-k+1} \sum_{l=1}^{d} \left(x_{i+k-1}^l - x_{i-1}^l\right)^2$$

Extracting the transport coefficients from MSD

$$\langle \Delta R_t^2(\tau = k\Delta t)\rangle = A(k\Delta t)^\alpha$$

For $\alpha = 1$, Diffusion coefficient $D = A/2d$

What is the meaning of D for $\alpha < 1$?

$$\langle \Delta R_t^2(\tau)\rangle = A\left(\frac{\tau}{\tau_0}\right)^\alpha \qquad D = A/2d\tau_0$$

Temporal Analysis of Active and Passive Transport in Living Cells

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[2]*Laboratoire Matière et Systèmes Complexes, UMR 7057 CNRS & Université Paris Diderot, F-75205 Paris Cedex 13, France*

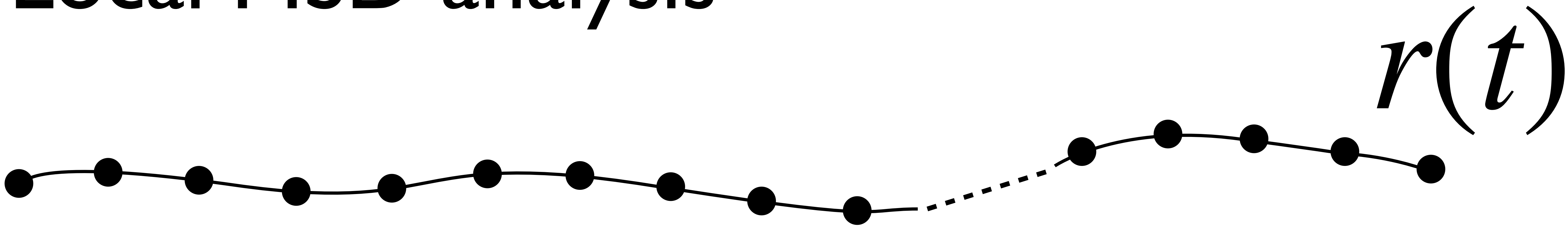
[3]*Physik Department E22, Technische Universität Munich, D-85748 Garching, Germany*

(Received 23 May 2008; published 12 December 2008)

The cellular cytoskeleton is a fascinating active network, in which Brownian motion is intercepted by distinct phases of active transport. We present a time-resolved statistical analysis dissecting phases of directed motion out of otherwise diffusive motion of tracer particles in living cells. The distribution of active lifetimes is found to decay exponentially with a characteristic time $\bar{\tau}_A = 0.65$ s. The velocity distribution of active events exhibits several peaks, in agreement with a discrete number of motor proteins acting collectively.

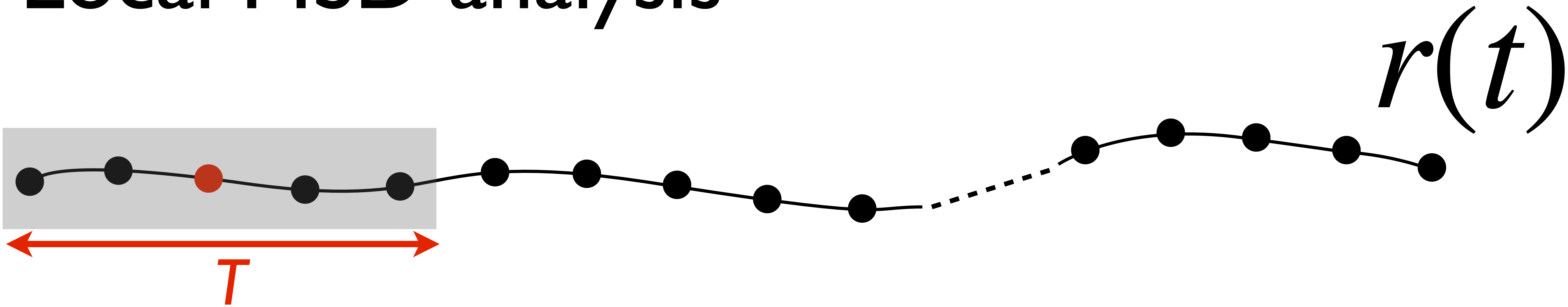
DOI: 10.1103/PhysRevLett.101.248103 PACS numbers: 87.16.Uv, 83.10.Pp, 87.16.Ln, 87.16.Wd

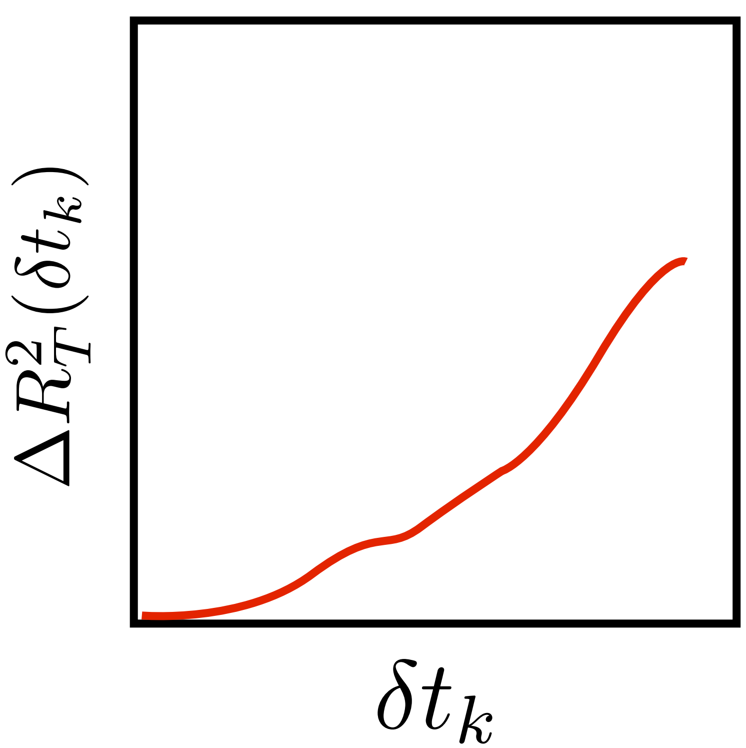
Local MSD analysis



Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

Local MSD analysis

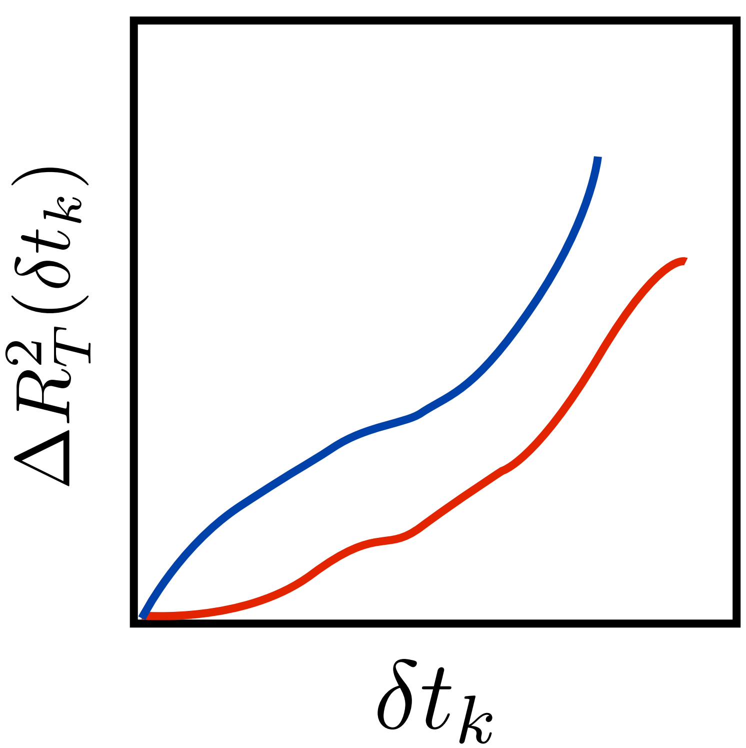




$$\Delta R_t^2(k\Delta t) = \langle (\mathbf{R}(t'+k\Delta t) - \mathbf{R}(t'))^2 \rangle_{-(T/2)<t'<(T/2)},$$

Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

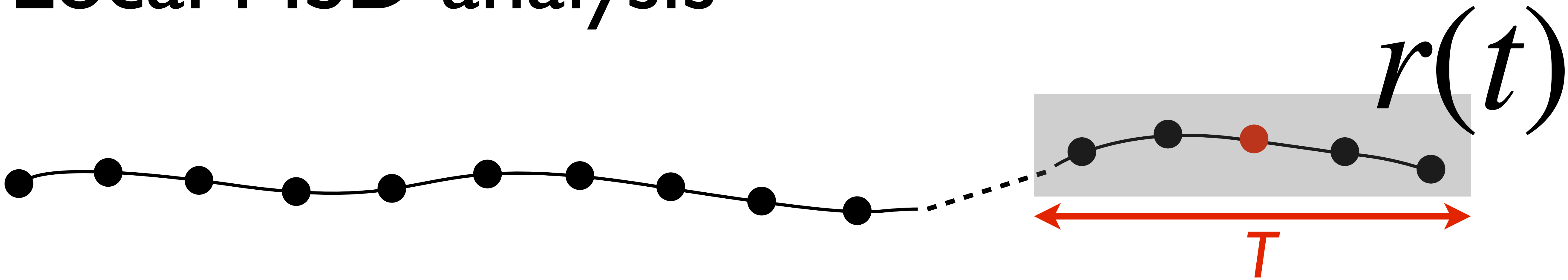
Local MSD analysis

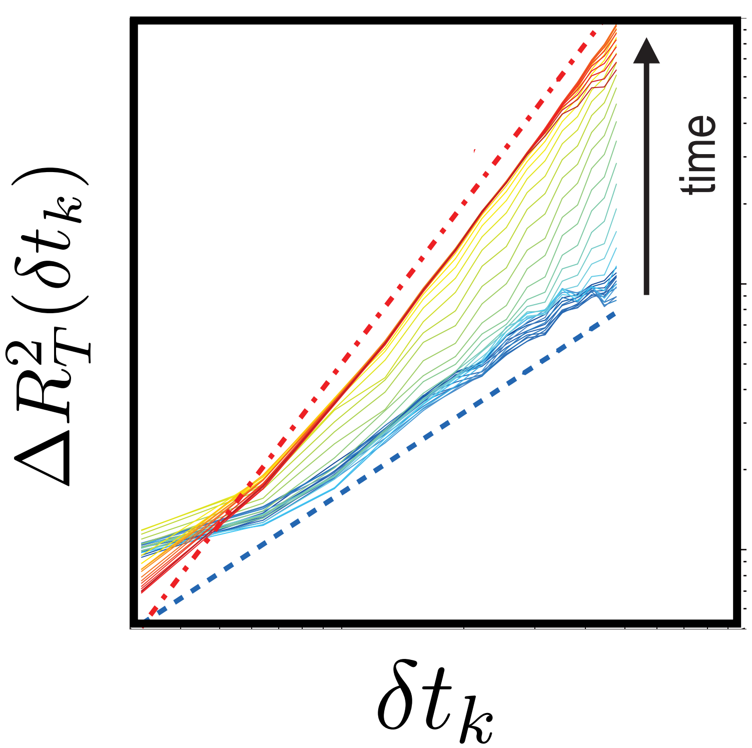


$$\Delta R_t^2(k\Delta t) = \langle (\mathbf{R}(t' + k\Delta t) - \mathbf{R}(t'))^2 \rangle_{-(T/2)<t'<(T/2)},$$

Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

Local MSD analysis





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Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

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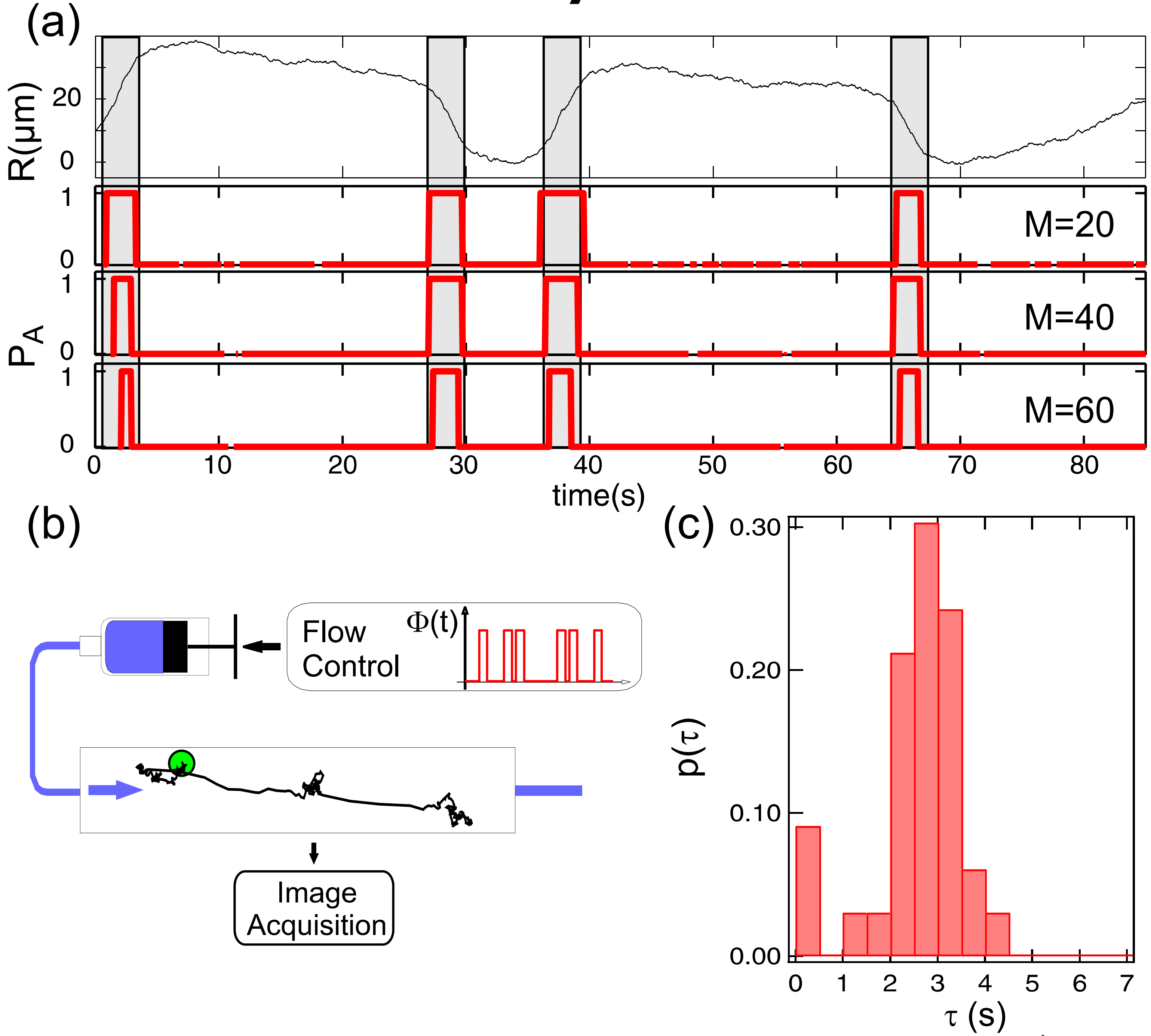
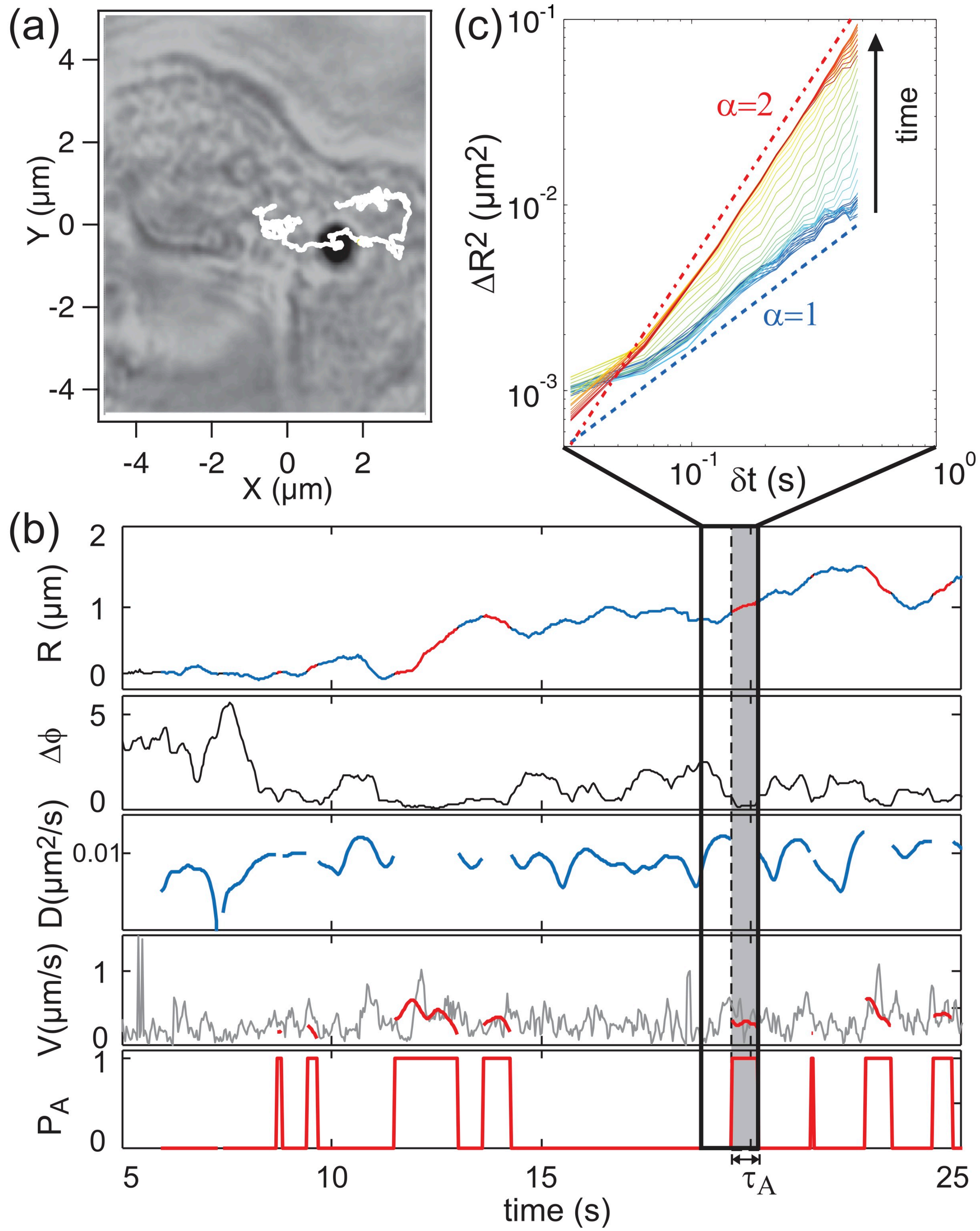


$$\Delta\phi_t(\delta t) = \langle(\phi(t' + \delta t) - \phi(t'))^2\rangle^{1/2}_{-(T/2)<t'<(T/2)}$$

$$p_A = \begin{cases} 1 & \text{if } \alpha = 2 \pm \sigma_\alpha \wedge \Delta\phi = 0 \pm \sigma_\phi \\ 0 & \text{otherwise} \end{cases}$$

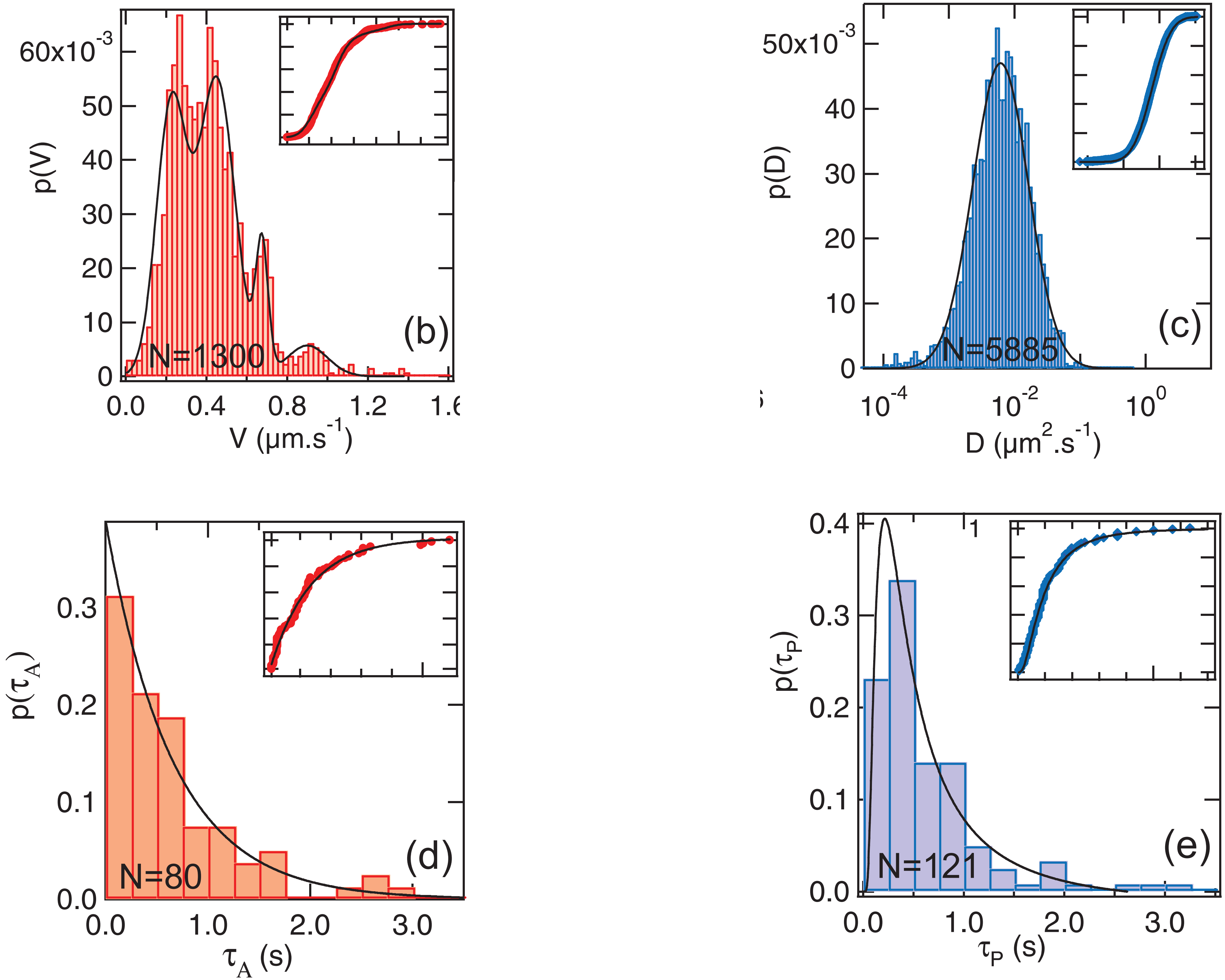
Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

Local MSD analysis



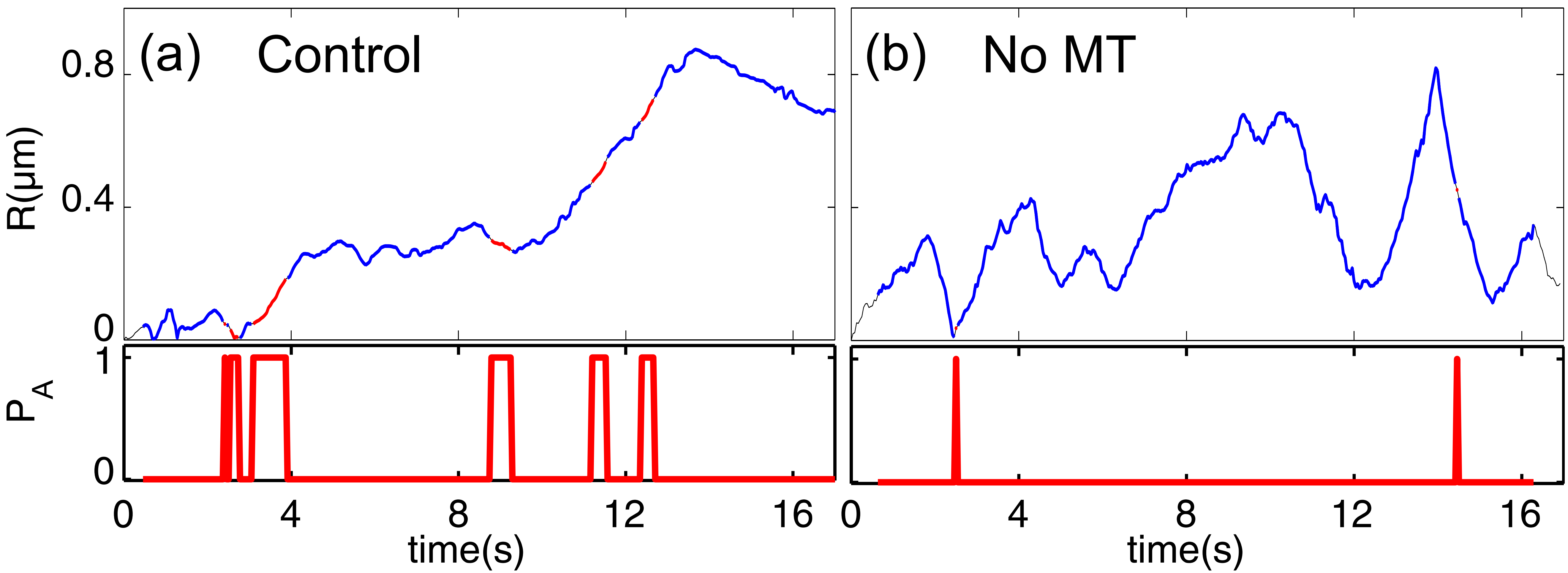
Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

Local MSD analysis



Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

Local MSD analysis: Without microtubules



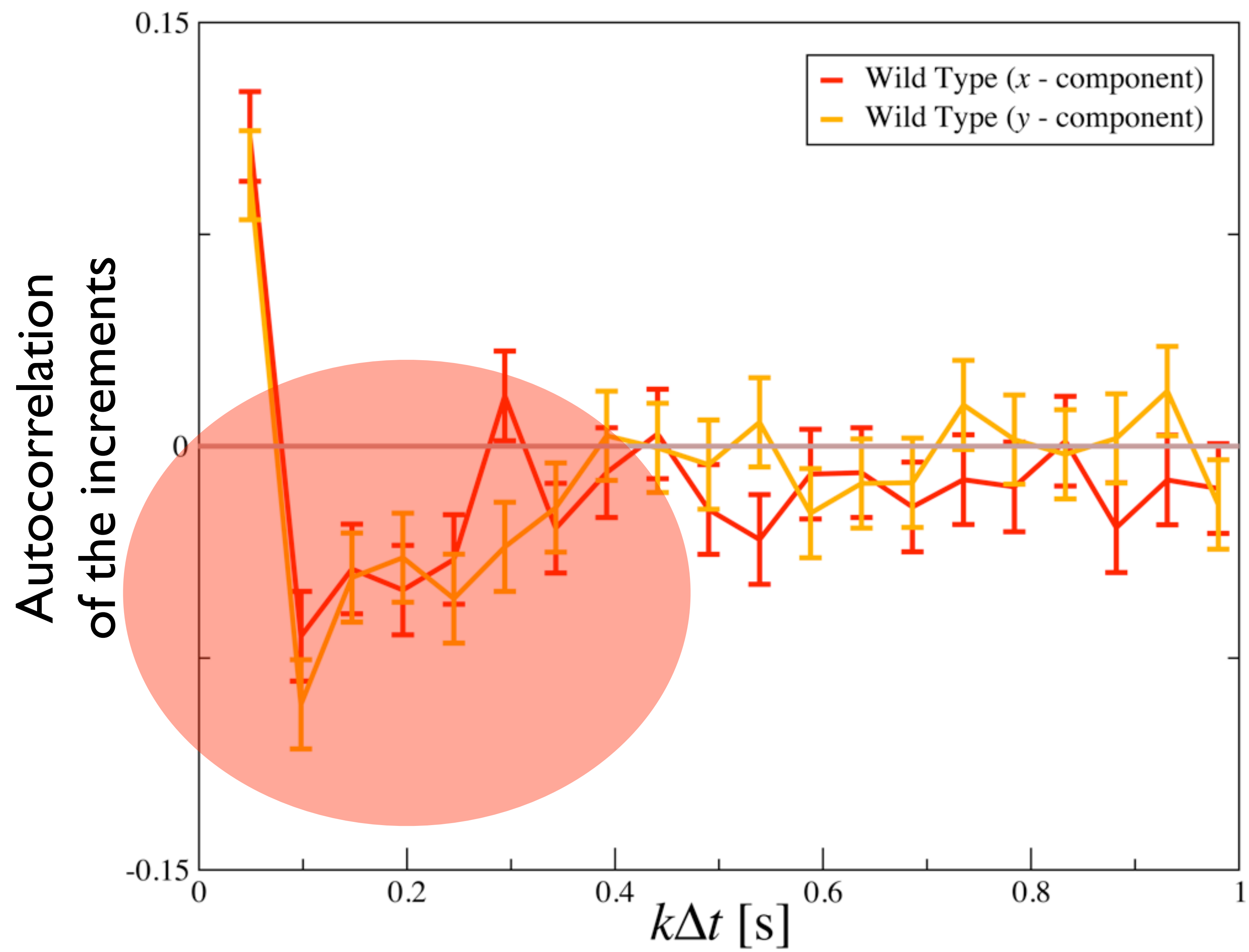
Arcizet et. al. Phys. Rev. Lett., **101**, 248103 (2008)

Auto-correlation of the increments

$$\rho_k = \frac{\langle \Delta x_i \Delta x_{i+k} \rangle}{\langle \Delta x_i^2 \rangle}$$

$$\mathrm{Var}(\rho_k) \approx \frac{1 + 2\sum_{j=1}^{\nu}\left(1 - \frac{j}{n}\right)\rho_j^2}{(n-k)(1 + 2\nu/n - \nu^2/n^2)}$$

Is the sub-diffusive behavior related to the velocity auto-correlation?



Otten et. al. Biophysical J (2012)

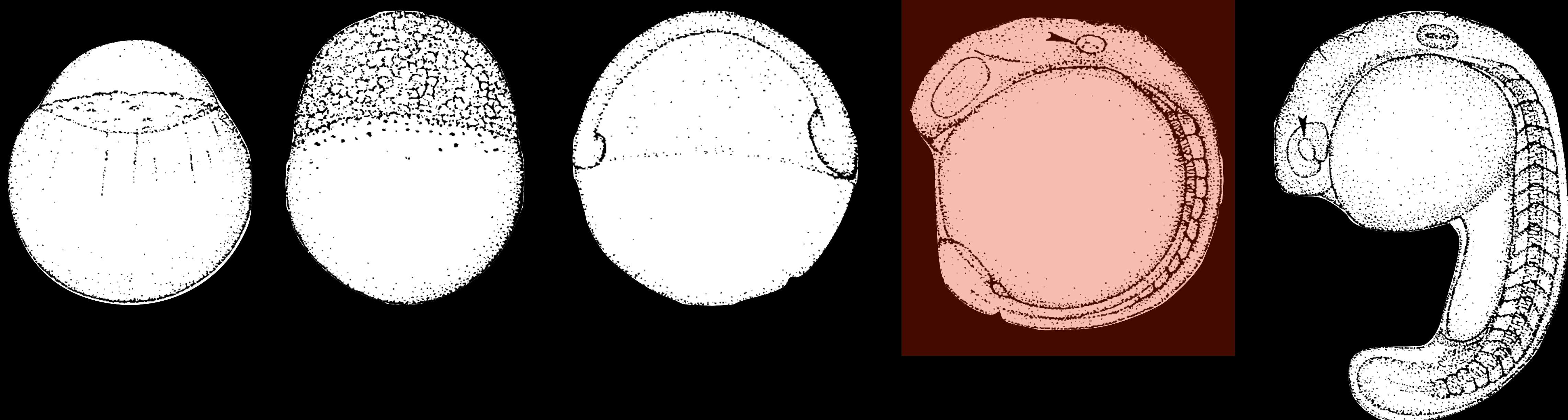
What if you have multiple cell tracks?

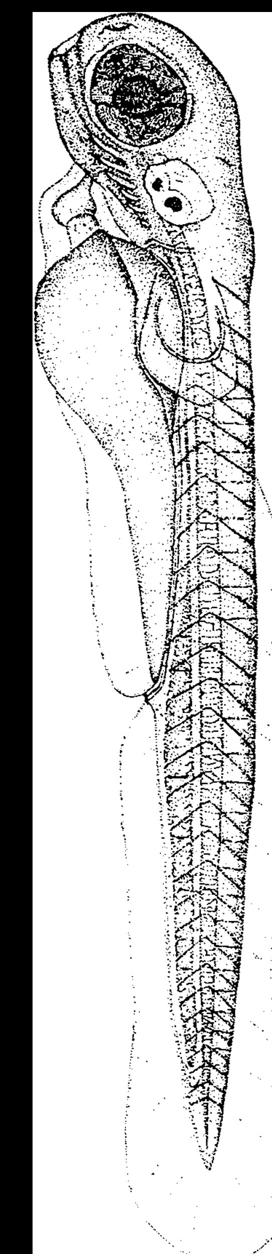
Morphogenesis

Formation of complex shapes

Developmental Cycle in zebrafish

0h 3.3h 5.7h 14h 19.5h 72h

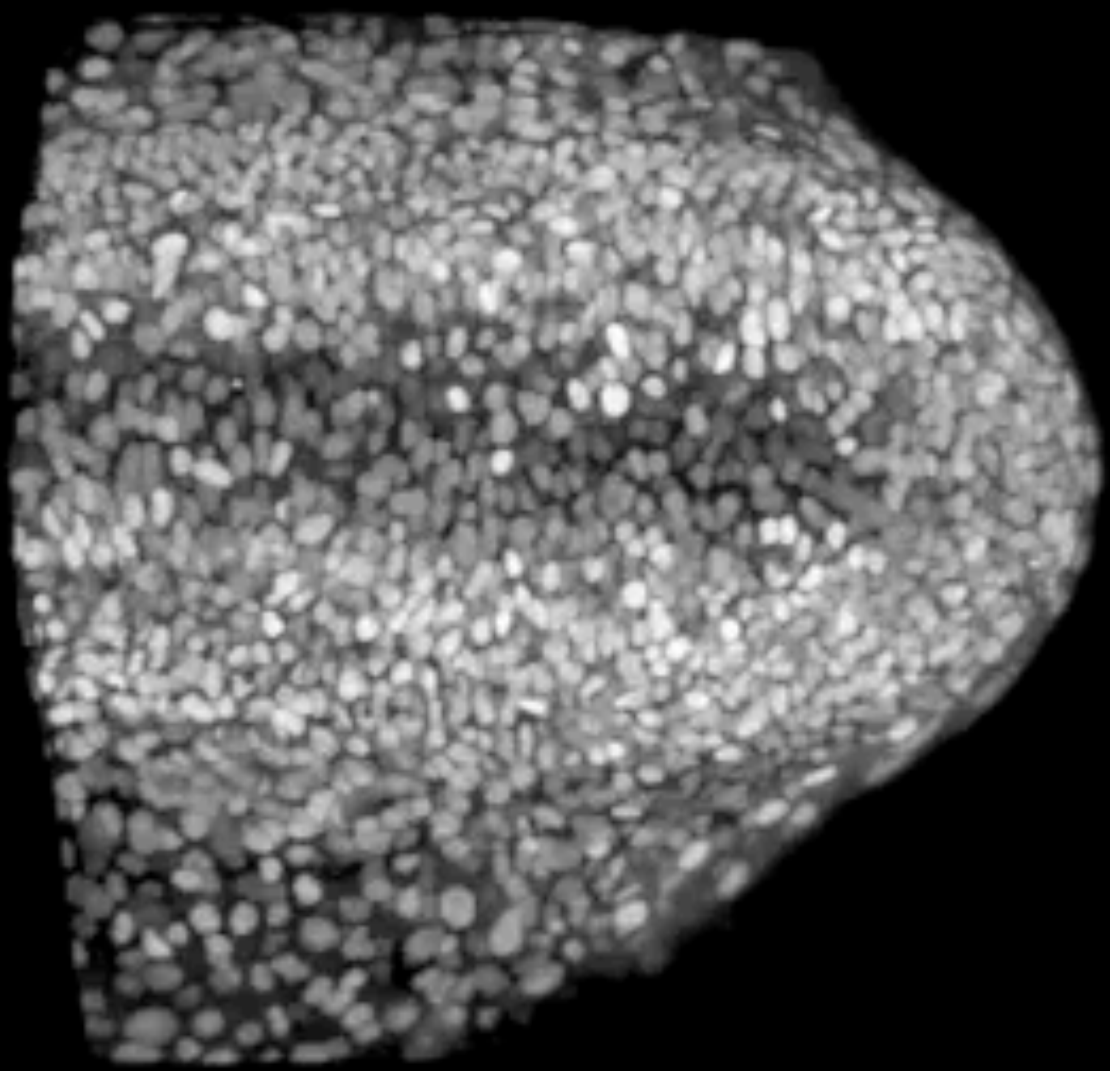




Kimmel et. al. (1995),
Solnica-Krezel (2006)

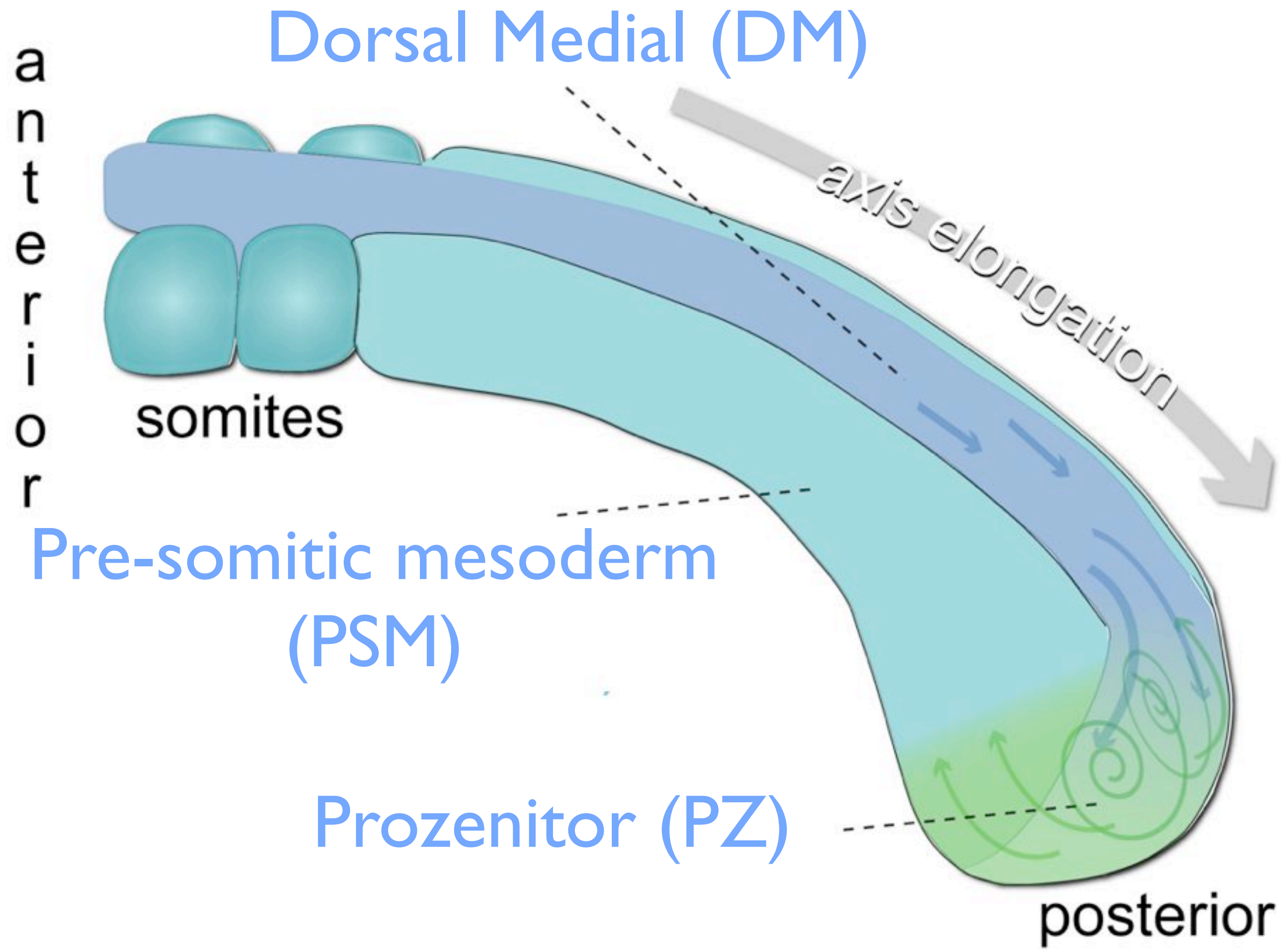
Experiments: Confocal Microscopy

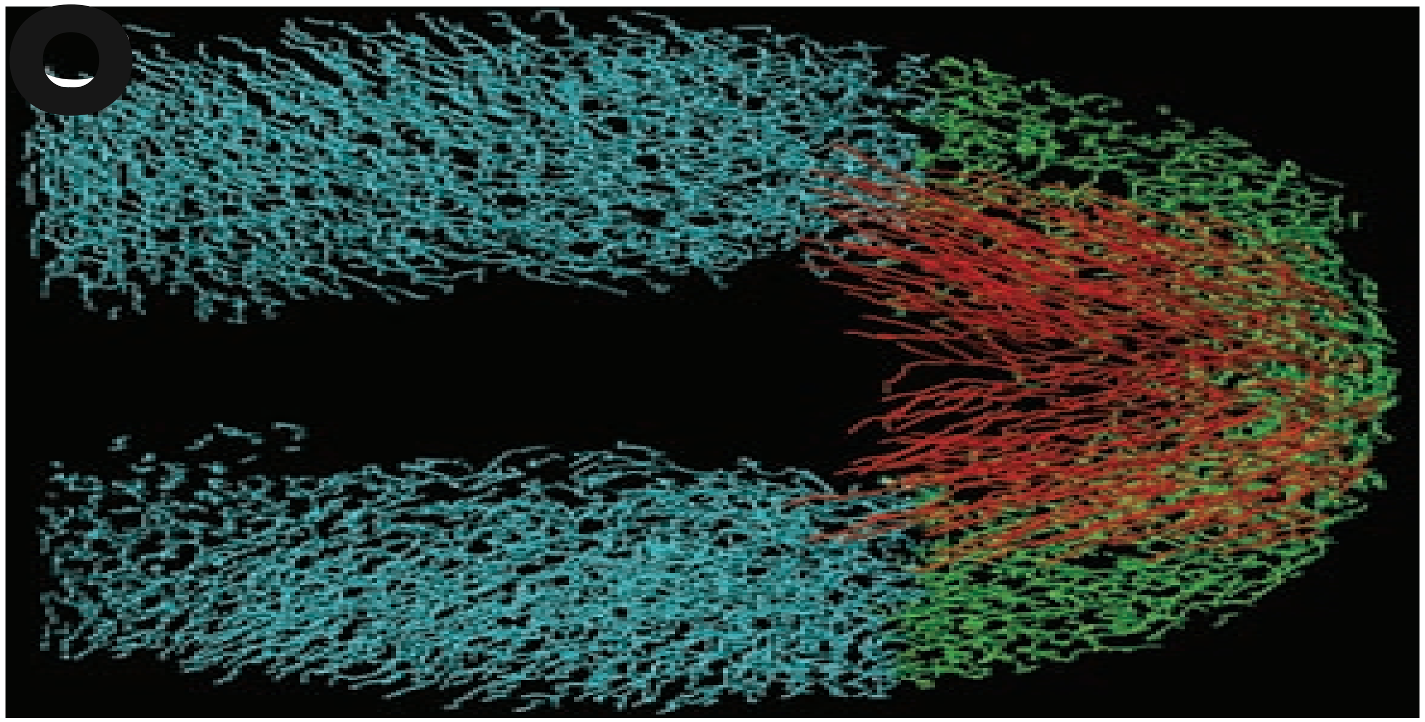
Andrew Lawton



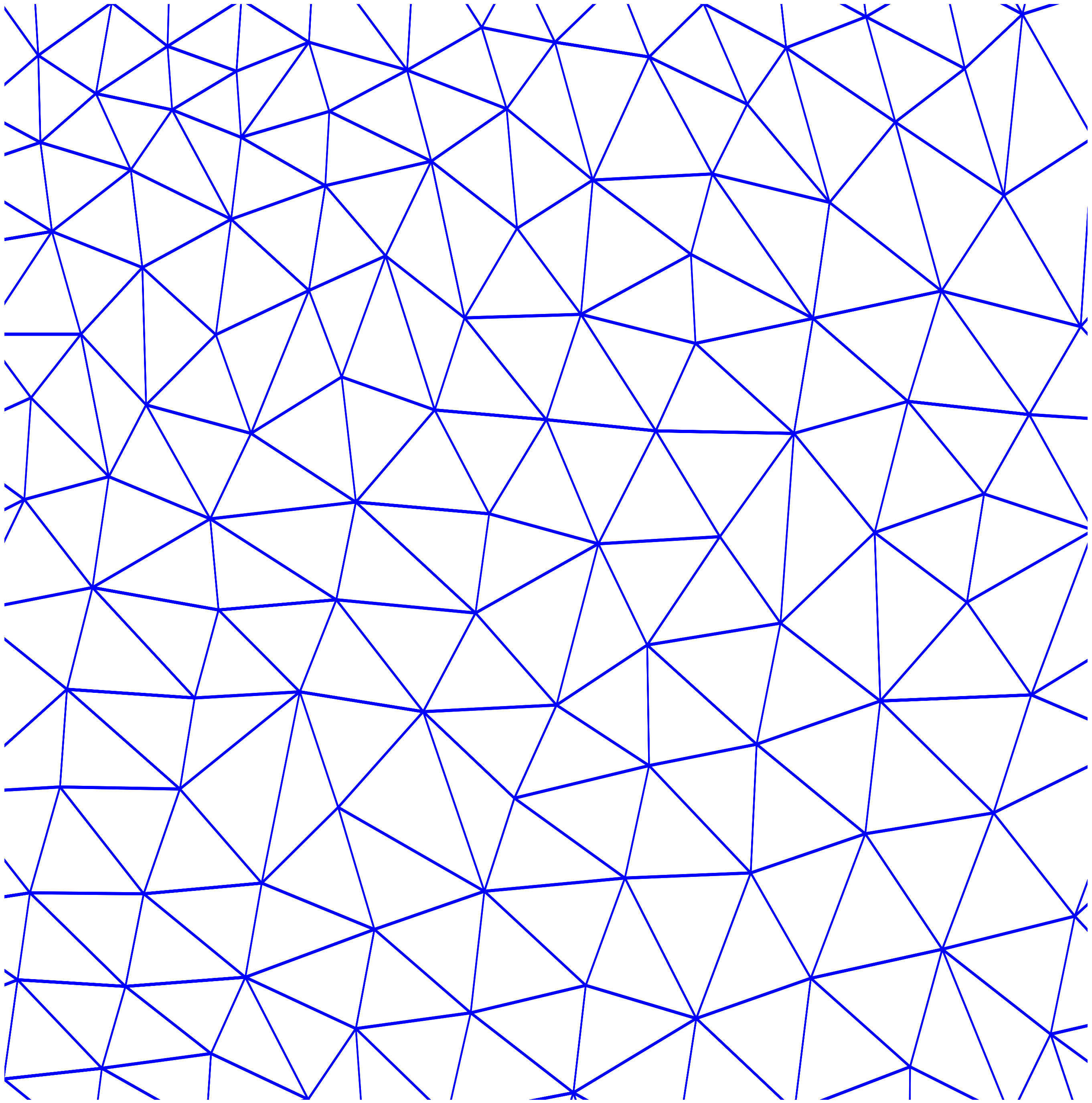
Movie: Nicolas Dray

Lawton et. al., *Development* (2013)





Lawton et. al., *Development* (2013)



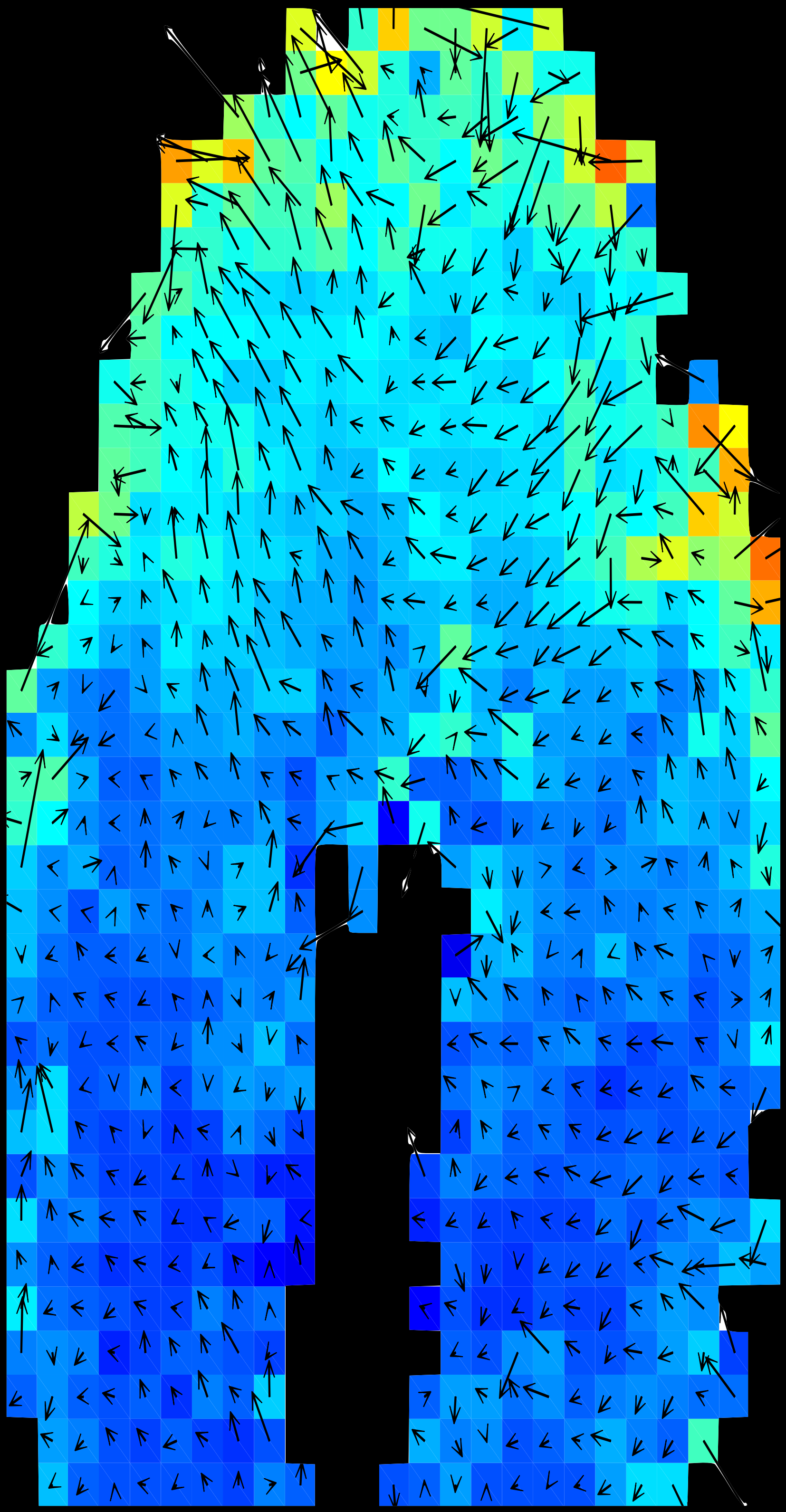
Matlab:

1. Delaunay Triangulation: Create a meshwork of triangles

2. pdegrad3: calculates the velocity gradient at the cell centres

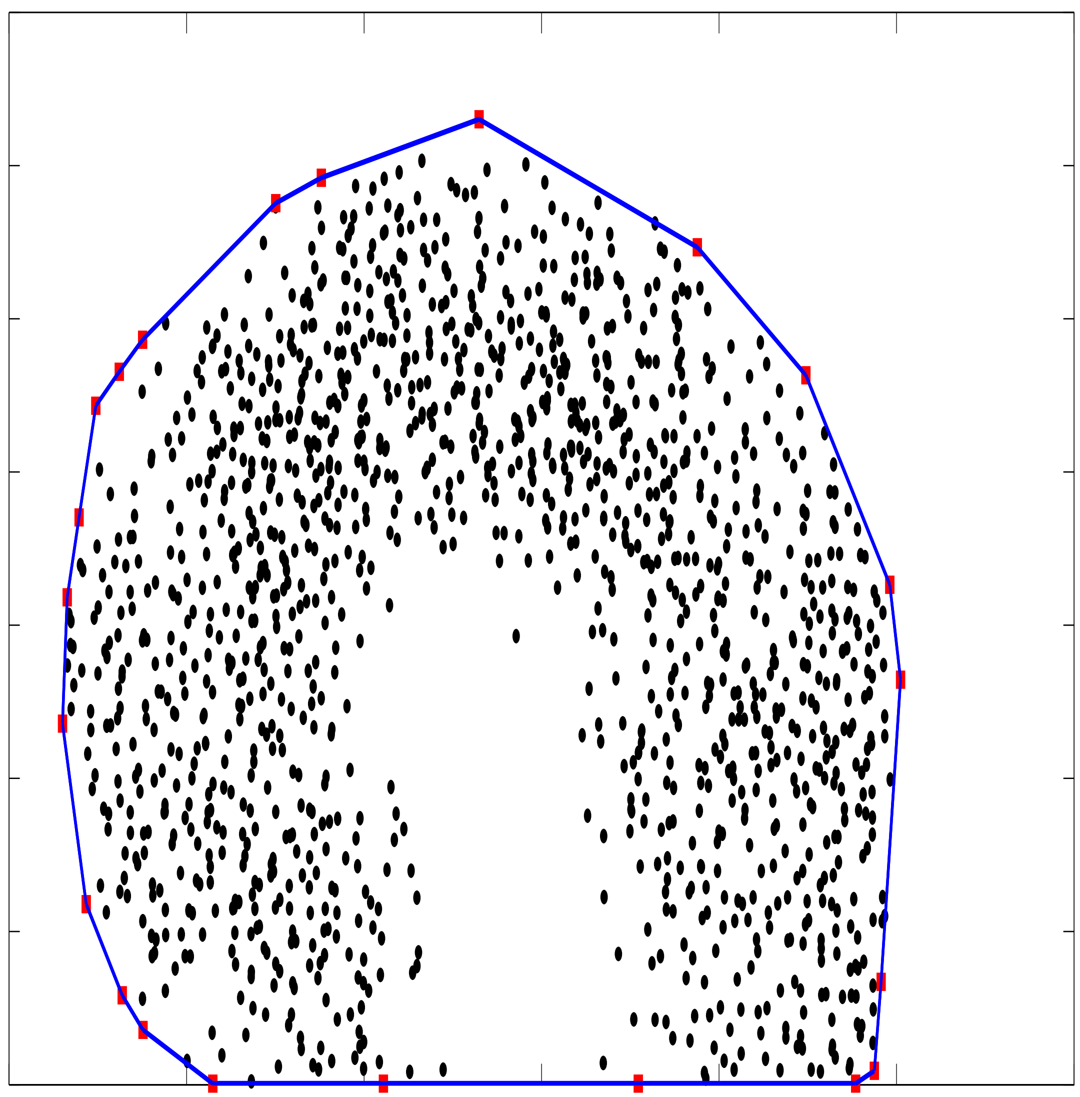
3. pdeprtni3: interpolates the value at the vertices

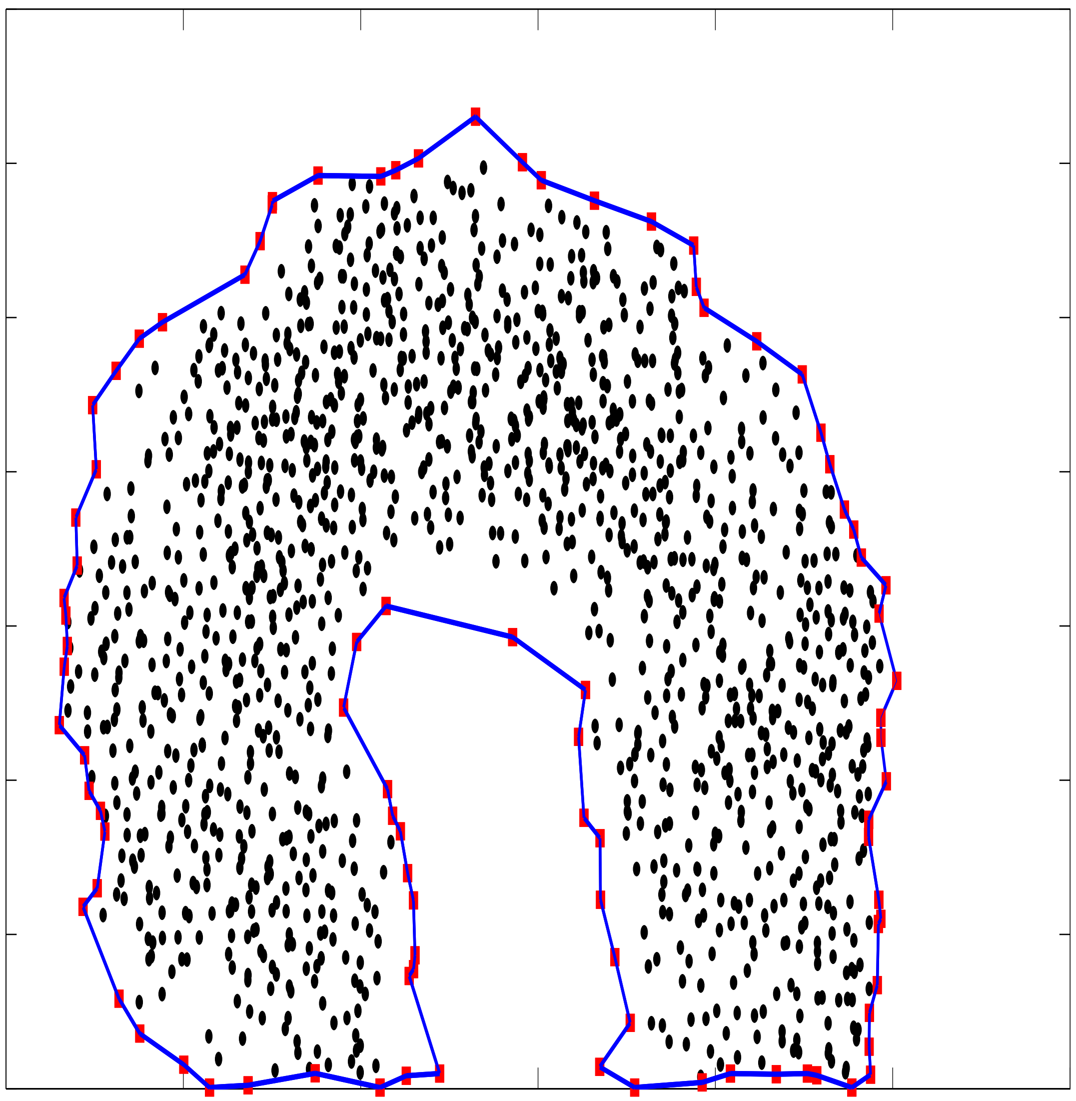
Vorticity Vector Map



Lawton et. al., *Development* (2013)

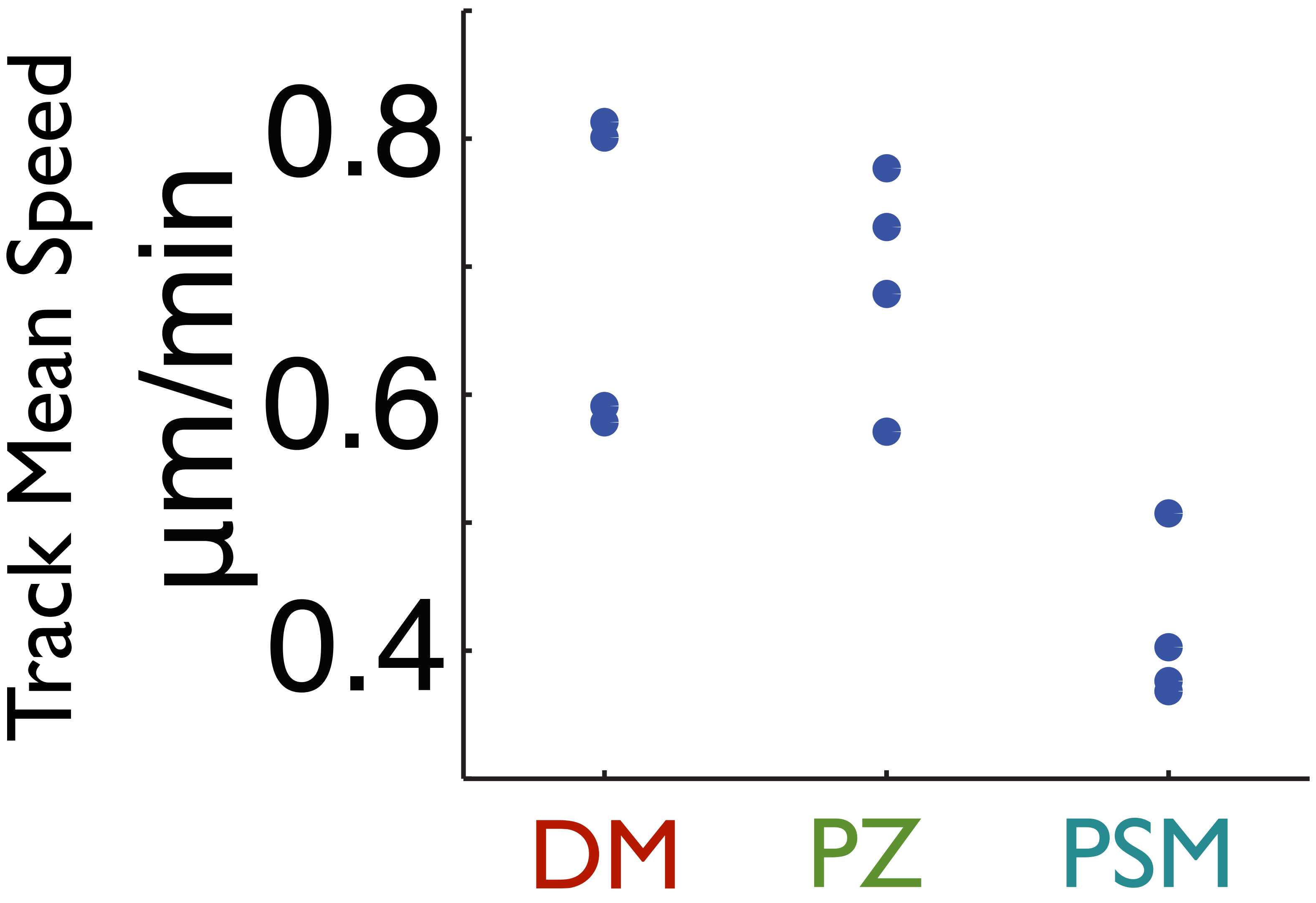
Alpha Shapes

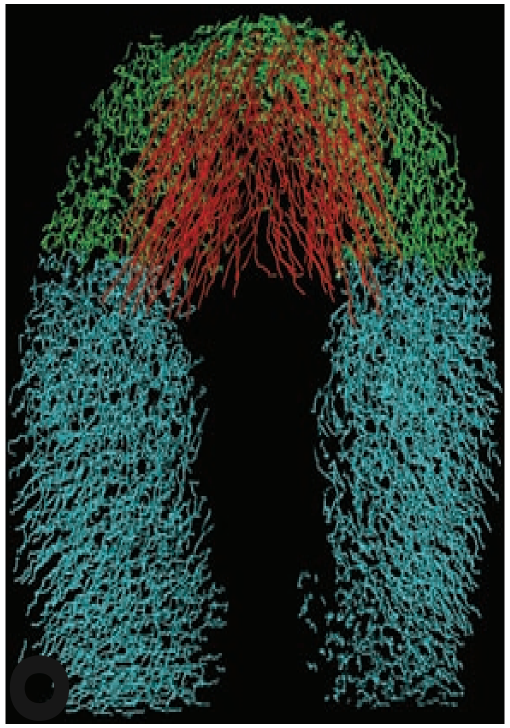




alphaShape(x,y,R)

Track Mean Speed

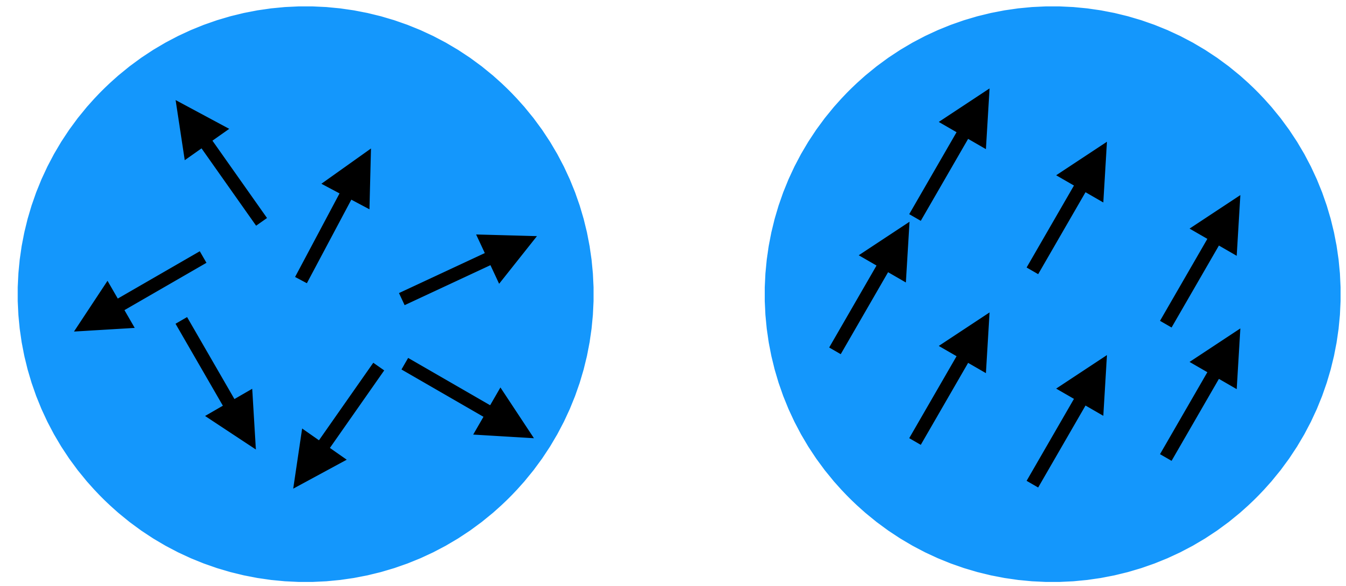




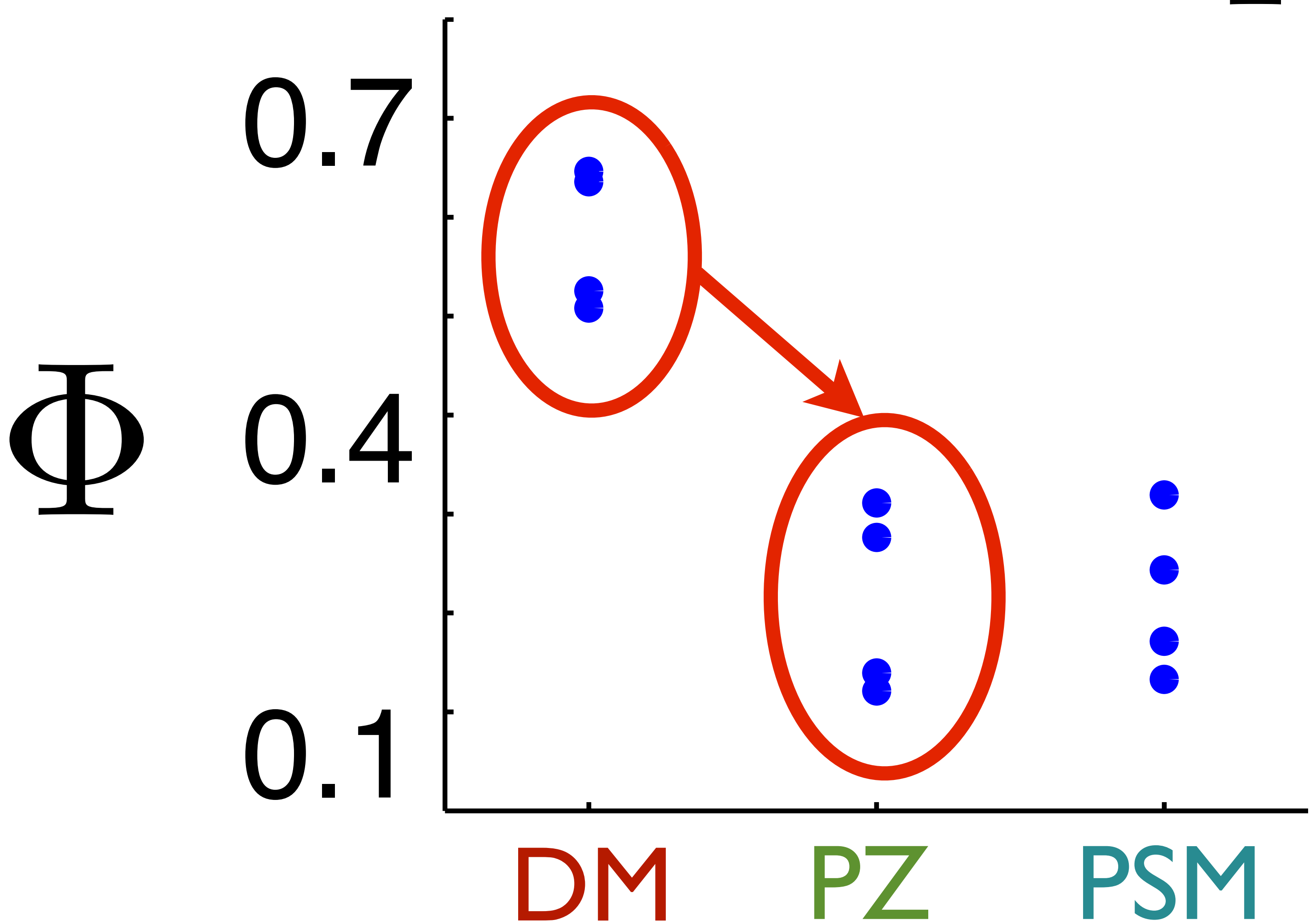
Lawton et. al., *Development* (2013)

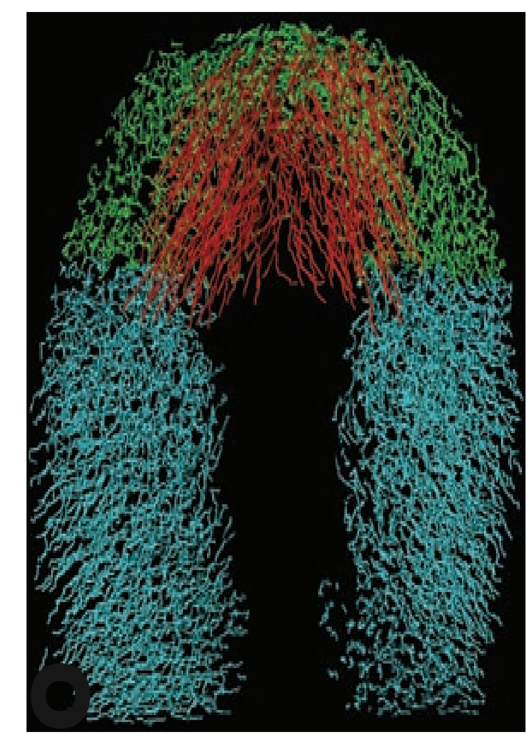
Polarization

$$\Phi = \left| \frac{1}{N} \sum_{i=1}^{N} \frac{\mathbf{u_i}}{|\mathbf{u_i}|} \right|$$



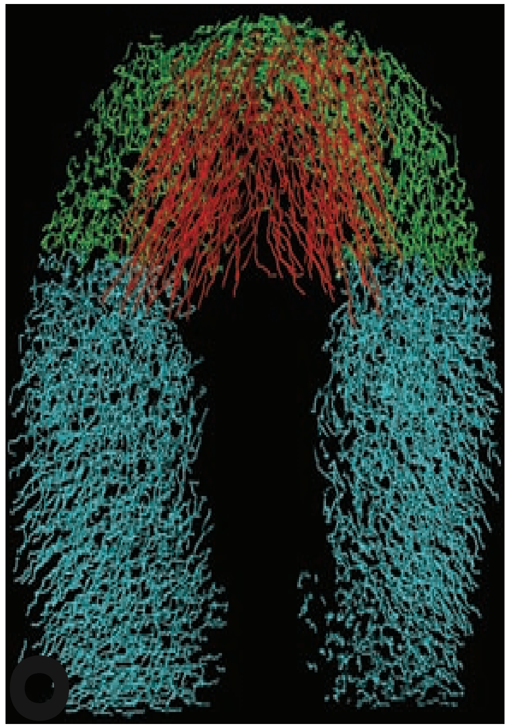
$\Phi = 0$ $\qquad$ $\Phi = 1$





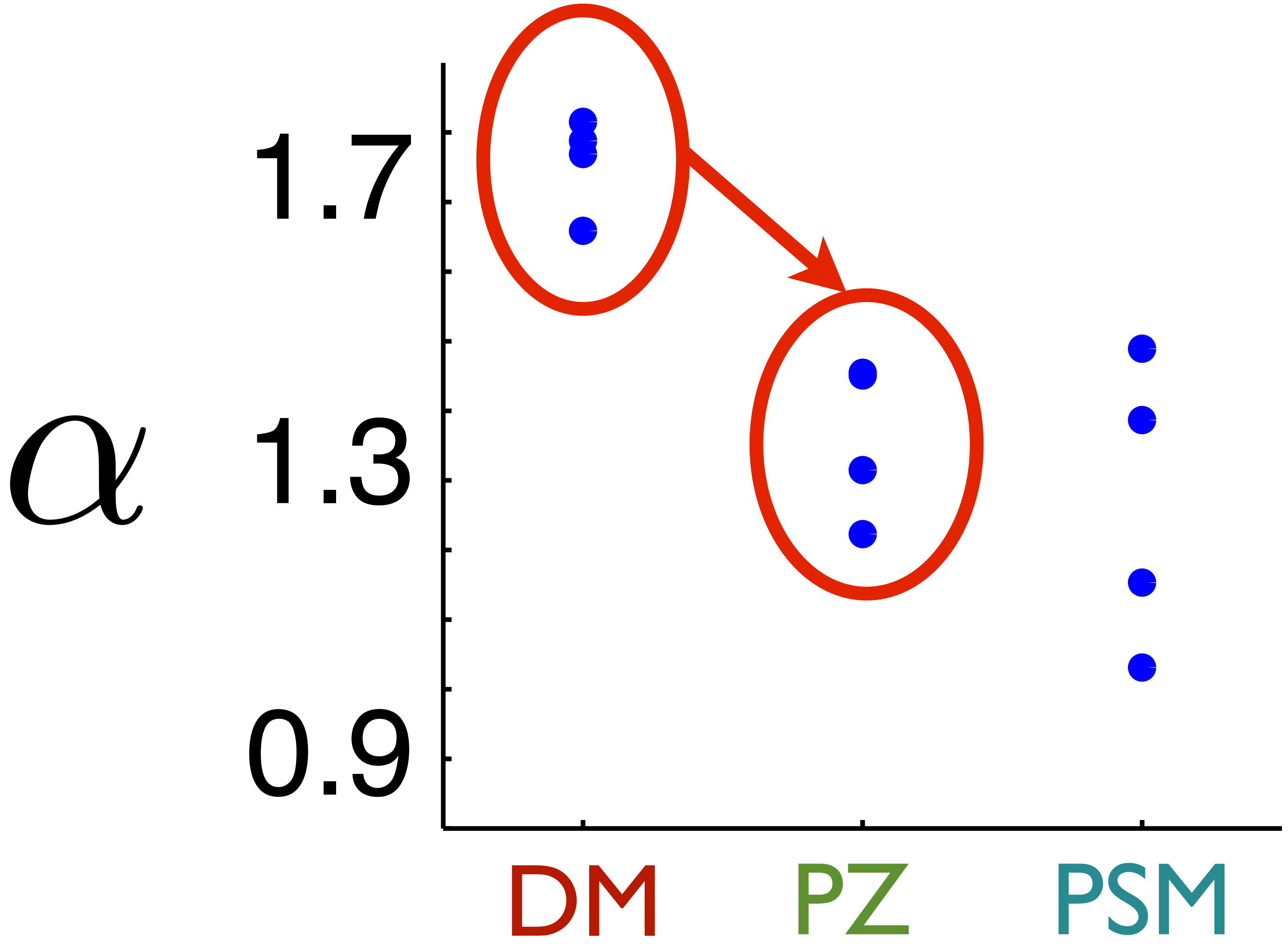
Lawton et. al., *Development* (2013)

Mean-squared displacement



$$\langle \Delta R^2(\tau) \rangle = \langle [\mathbf{R}(t+\tau) - \mathbf{R}(t)]^2 \rangle_T$$

$$\langle \Delta R^2(\tau) \rangle \sim t^\alpha$$

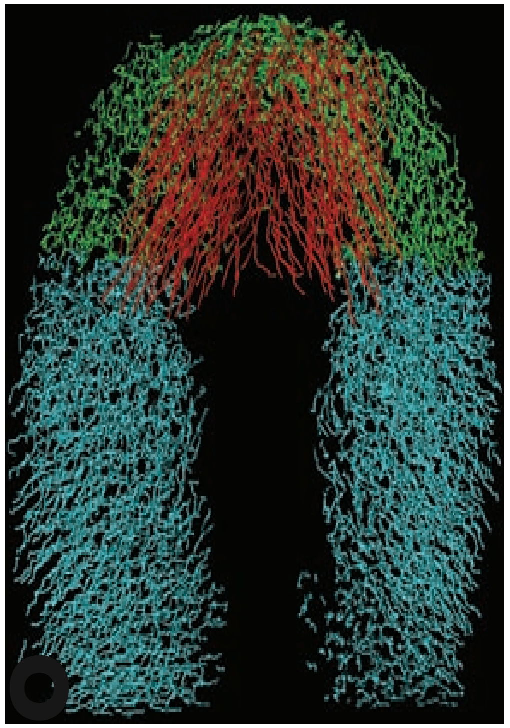


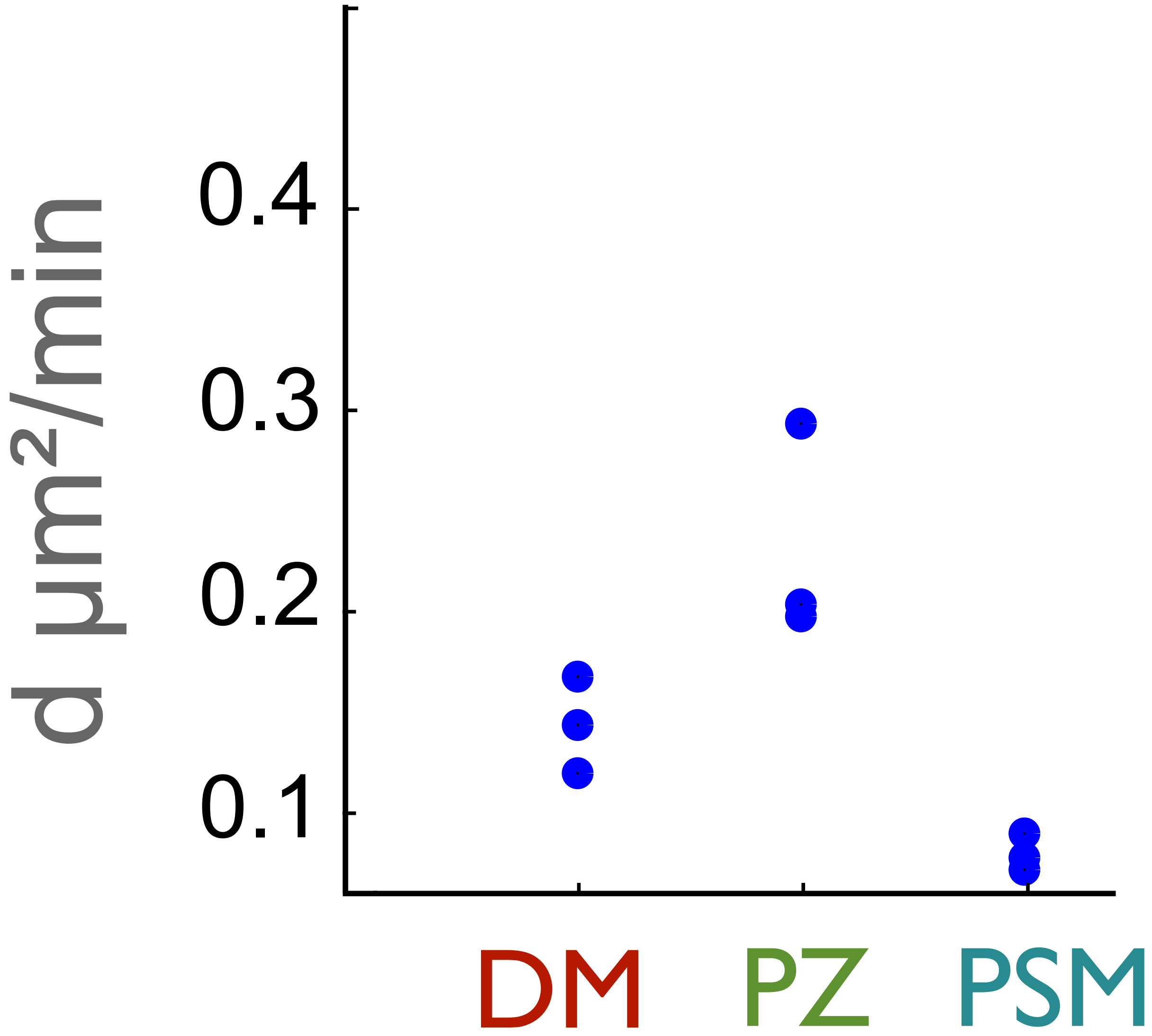
Lawton et. al., *Development* (2013)

Diffusion Coefficient

$$\langle \Delta R^2(\tau) \rangle = \langle [\mathbf{R}(t+\tau) - \mathbf{R}(t)]^2 \rangle_T$$

$$\langle \Delta R^2(\tau) \rangle \sim 6Dt + V^2 t^2$$



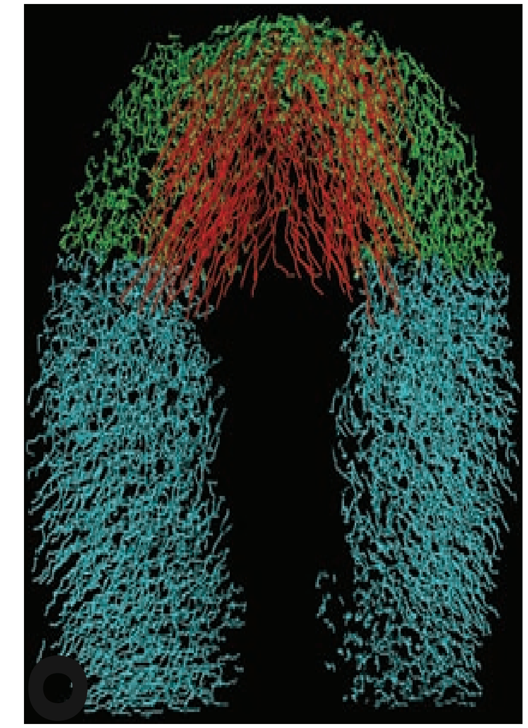


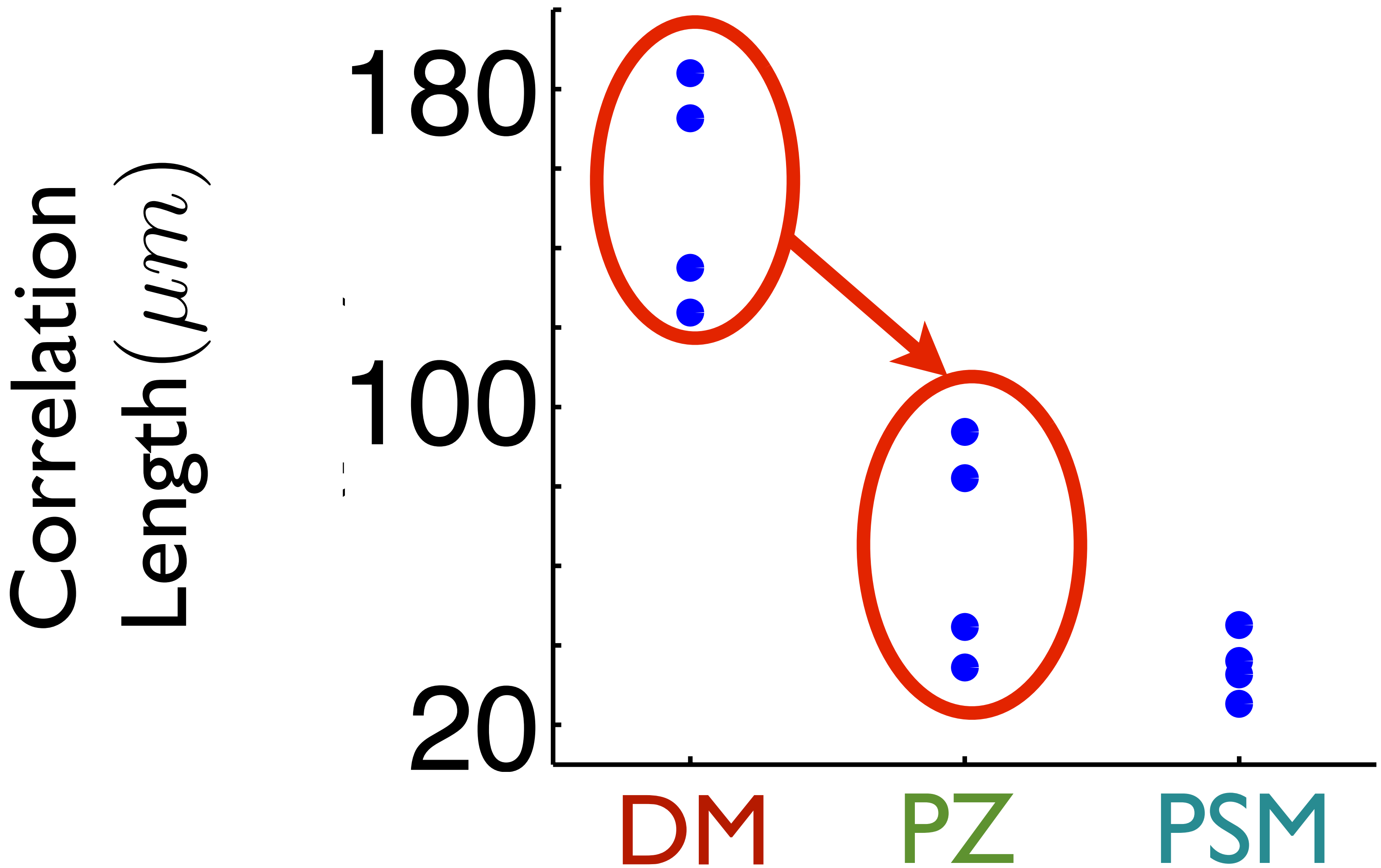
Lawton et. al., *Development* (2013)

Spatial velocity auto-correlation

$$C_u(r) = \left\langle \frac{\sum_{ij} \mathbf{u_i} \cdot \mathbf{u_j} \; \delta(r - r_{ij})}{\sum_{ij} \delta(r - r_{ij})} \right\rangle$$

$$C_u(r) \sim \exp(-r/L)$$



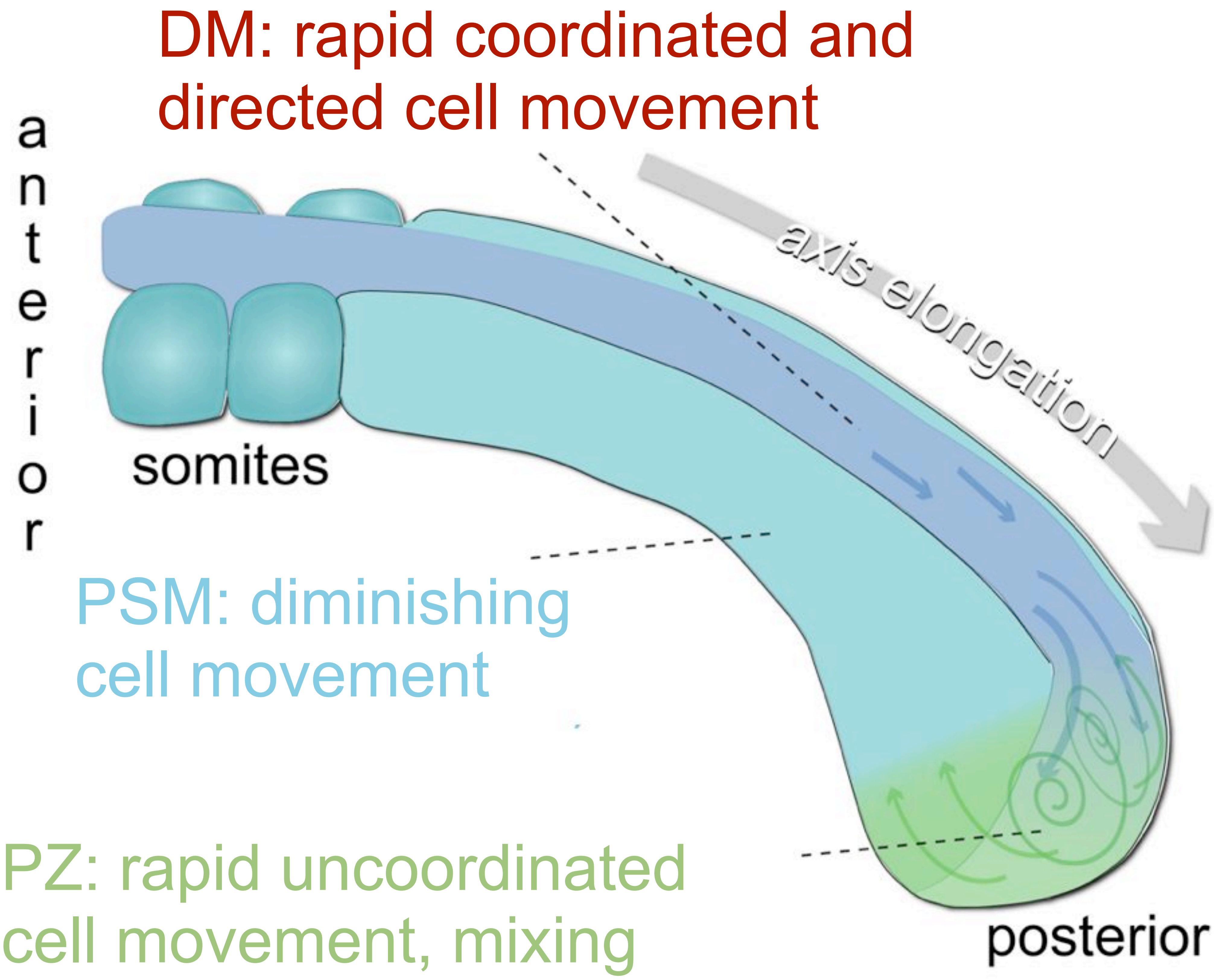


Lawton et. al., *Development* (2013)

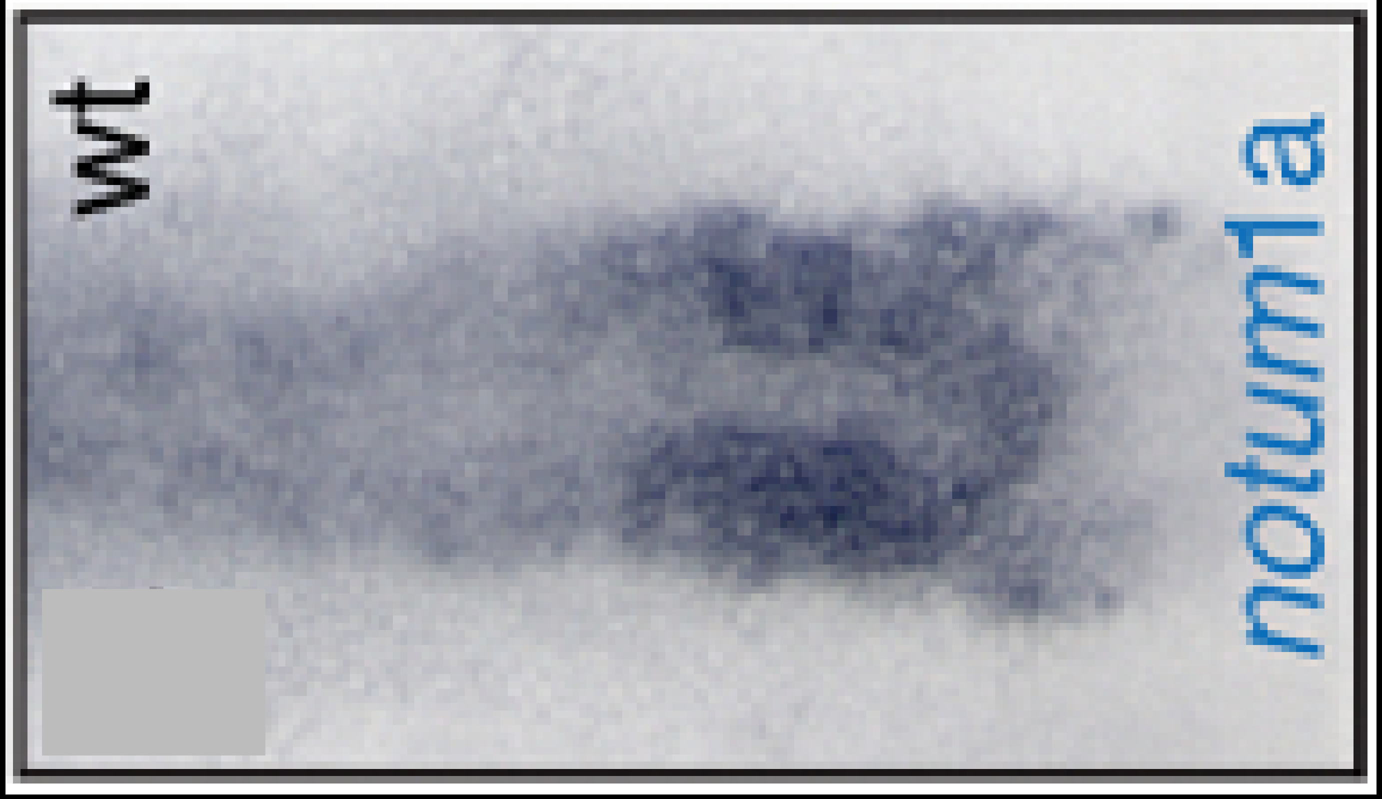
Pair distribution function

$$g(r) = \frac{1}{4\pi r^2}\frac{1}{n_c}\sum_{i}^{n_c}\sum_{j\neq i}\delta(r - r_{ij})$$

where r_{ij} is the absolute distance between the centre i and a neighbour j. Note that $g(r)$ is a distribution function (it contains a Dirac delta), meaning that to obtain a true density one needs to multiply for an appropriate spatial increment dr. Operationally, to compute

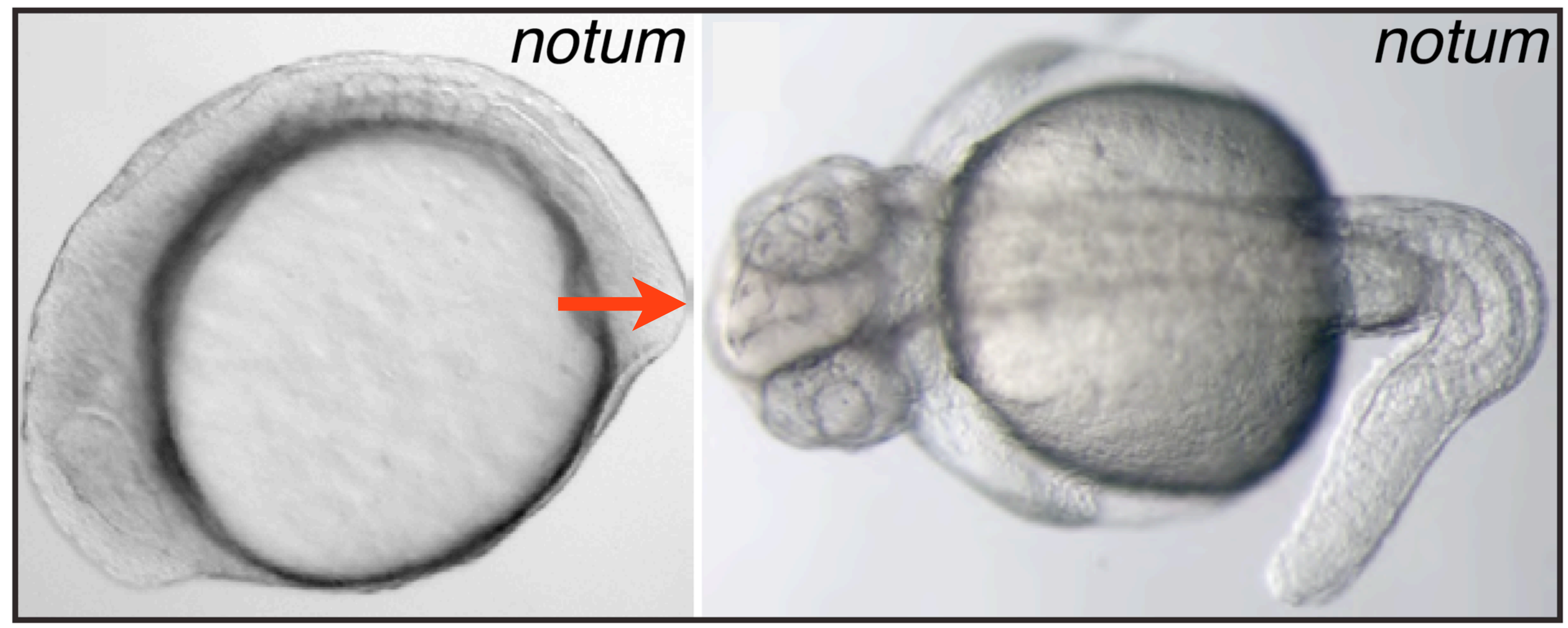

DM: rapid coordinated and directed cell movement
anterior
somites
axis elongation
PSM: diminishing cell movement
PZ: rapid uncoordinated cell movement, mixing
posterior

Transition coincides with the expression of a number of Canonical Wnt inhibitors!!

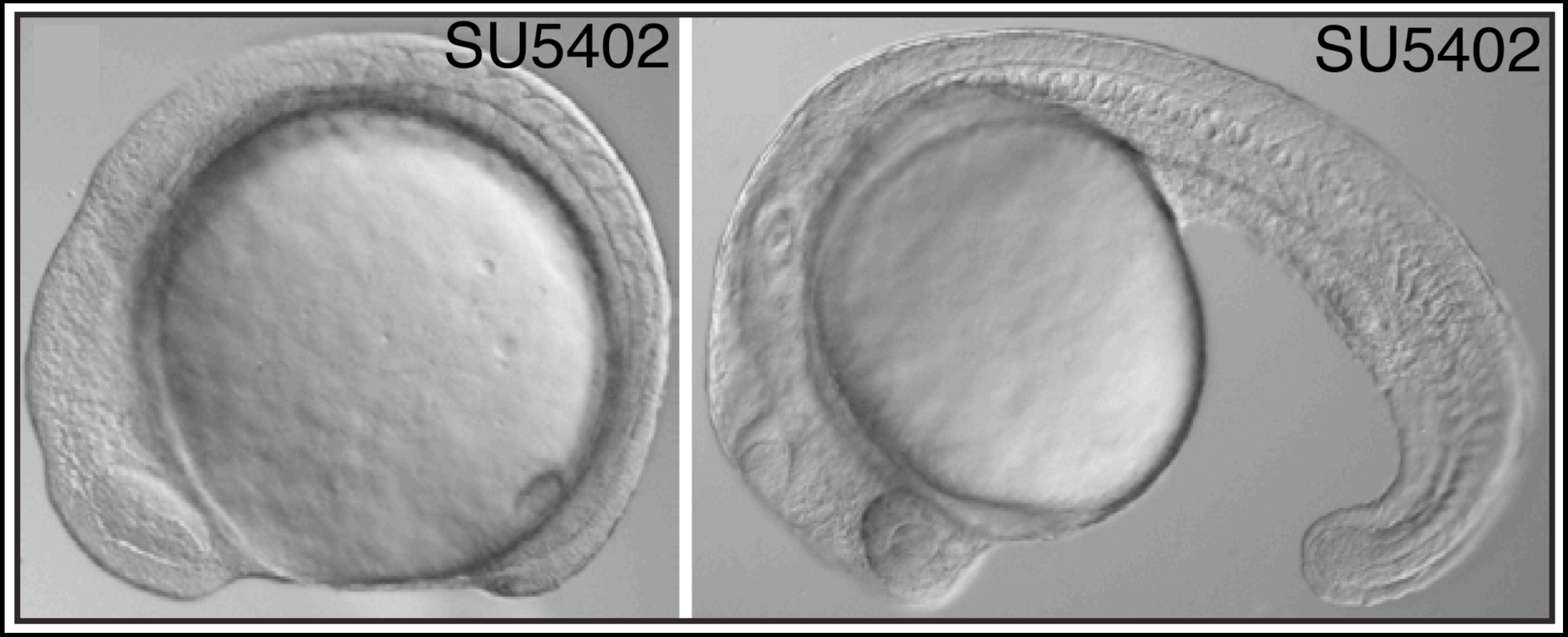


Flowers et. al, *Development* (2012)
Lawton et. al., *Development* (2013)

Wnt inhibition: notum over-expression

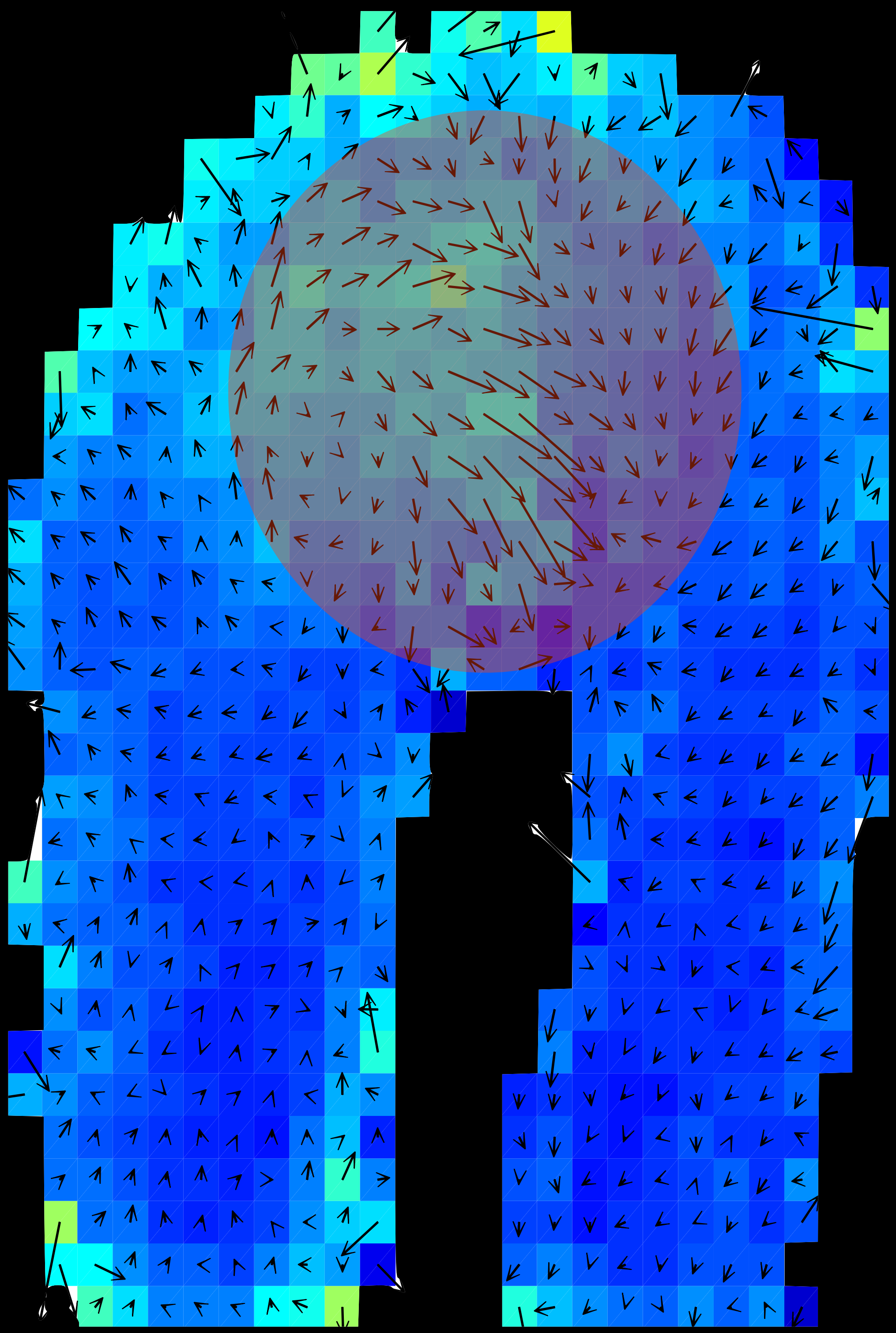


SU5402: FGF inhibition

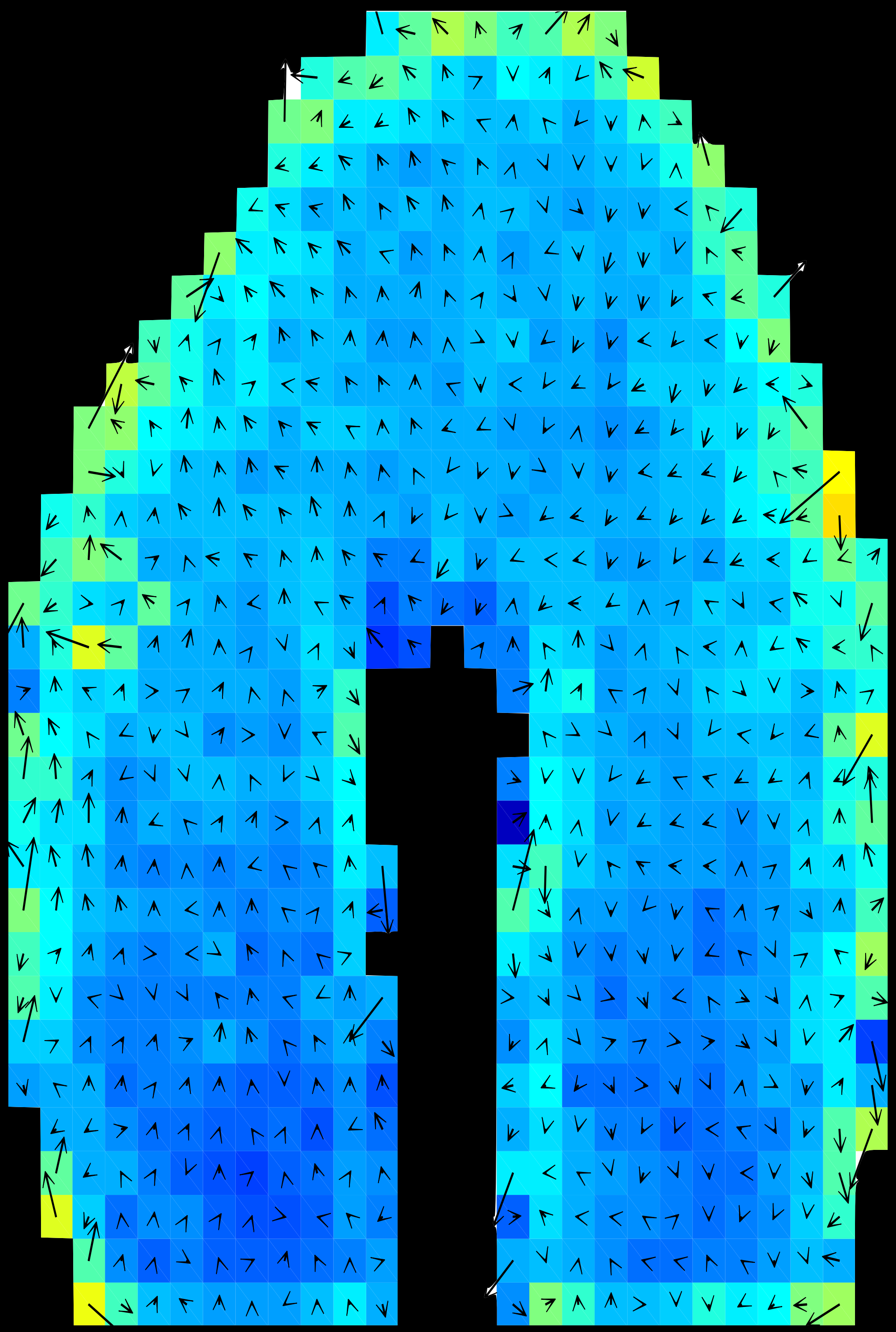


Lawton et. al., *Development* (2013)

notum

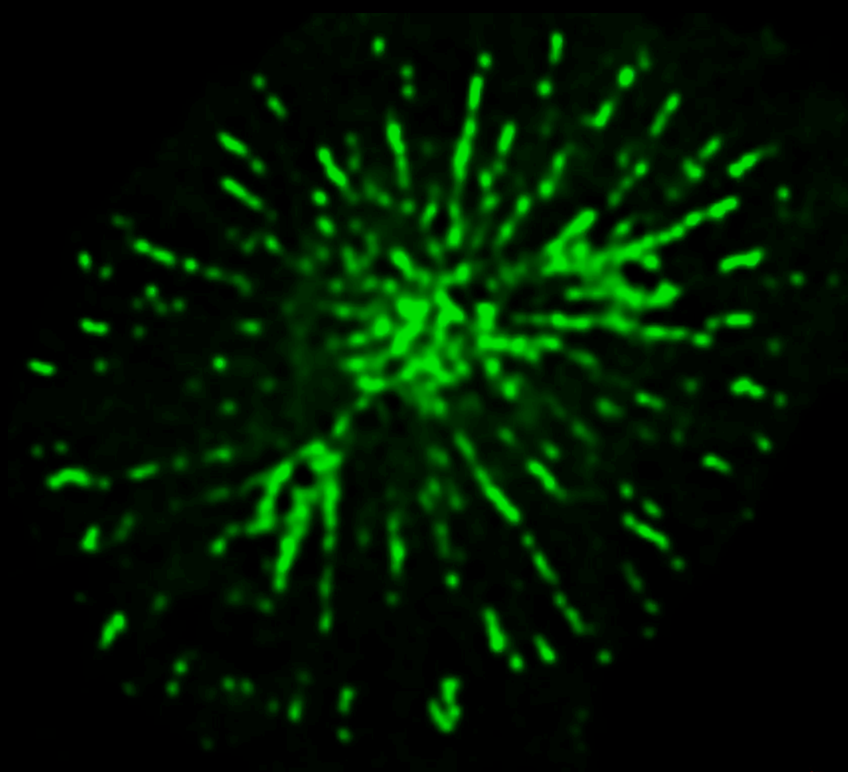


SU5402

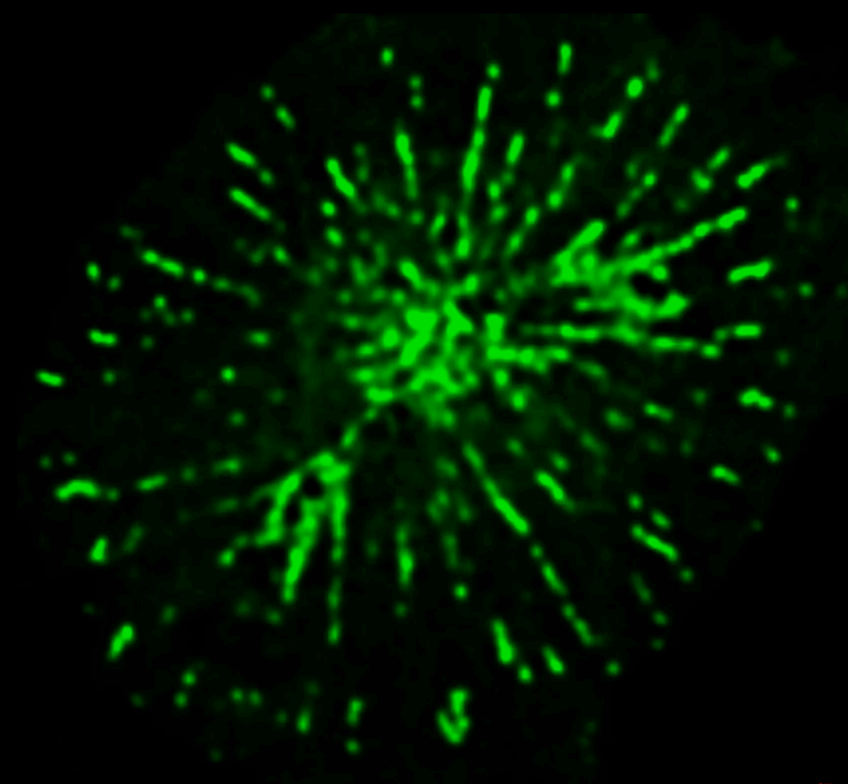


Lawton, Nandi,.......,Holley, *Development* (2013)

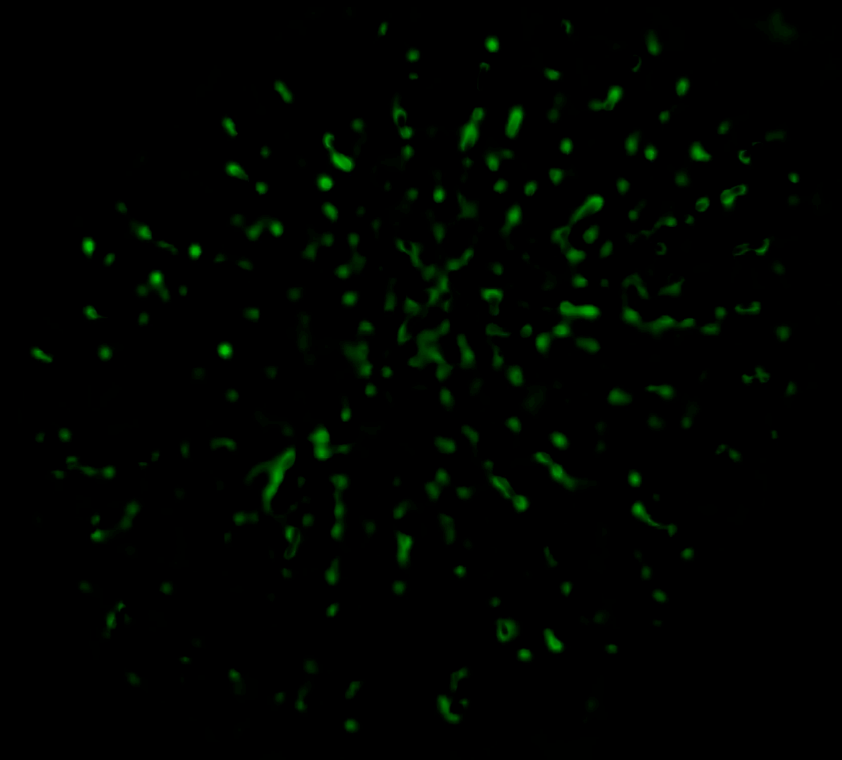
How vesicles are transported during endocytosis?



Drift Correction

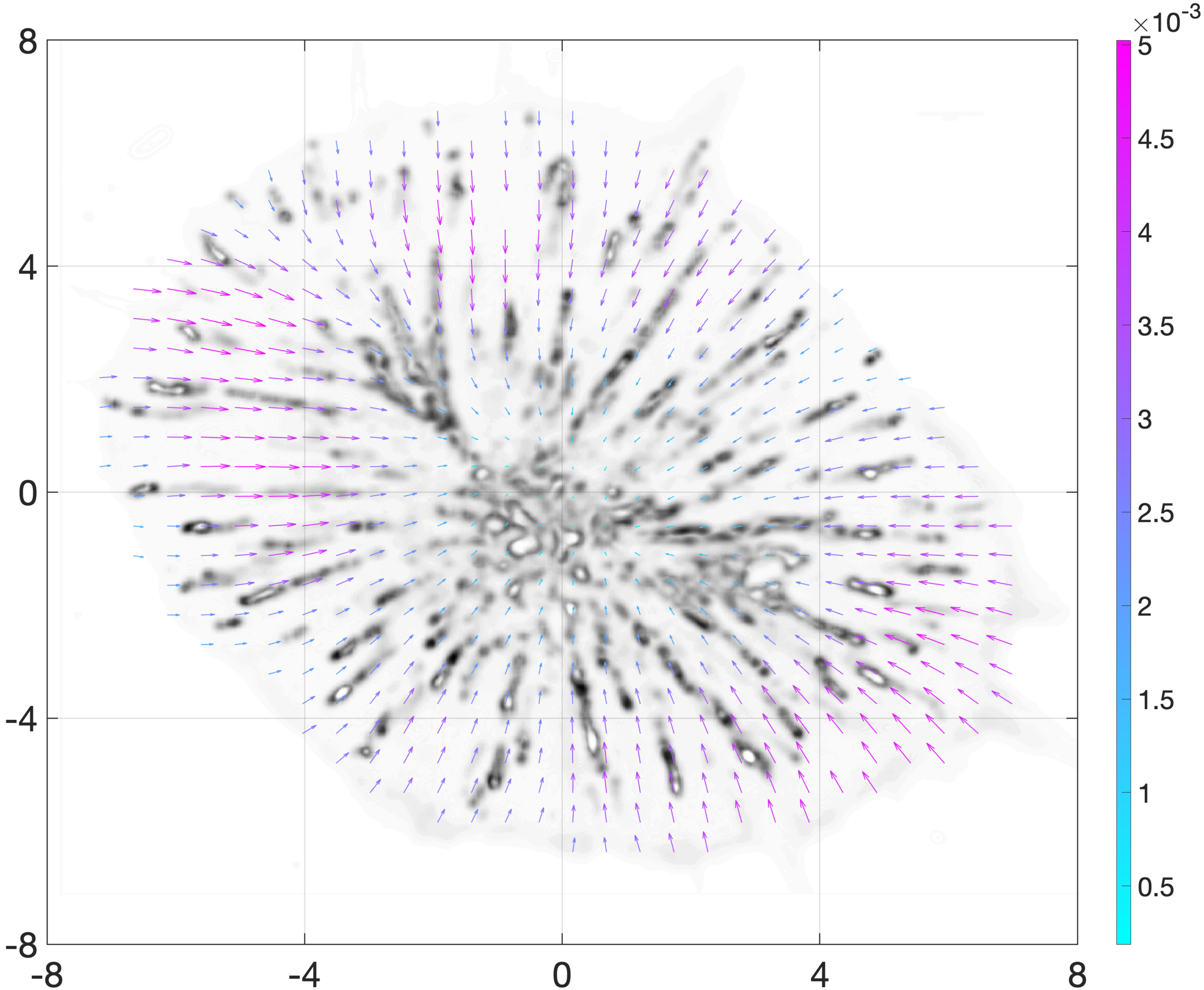


Intensity Correction



Singh et. al., biorXiv (2023)
Ganguly et. al. to be submitted (2024)

Endocytosis: Transport of *clathrin* coated vesicles



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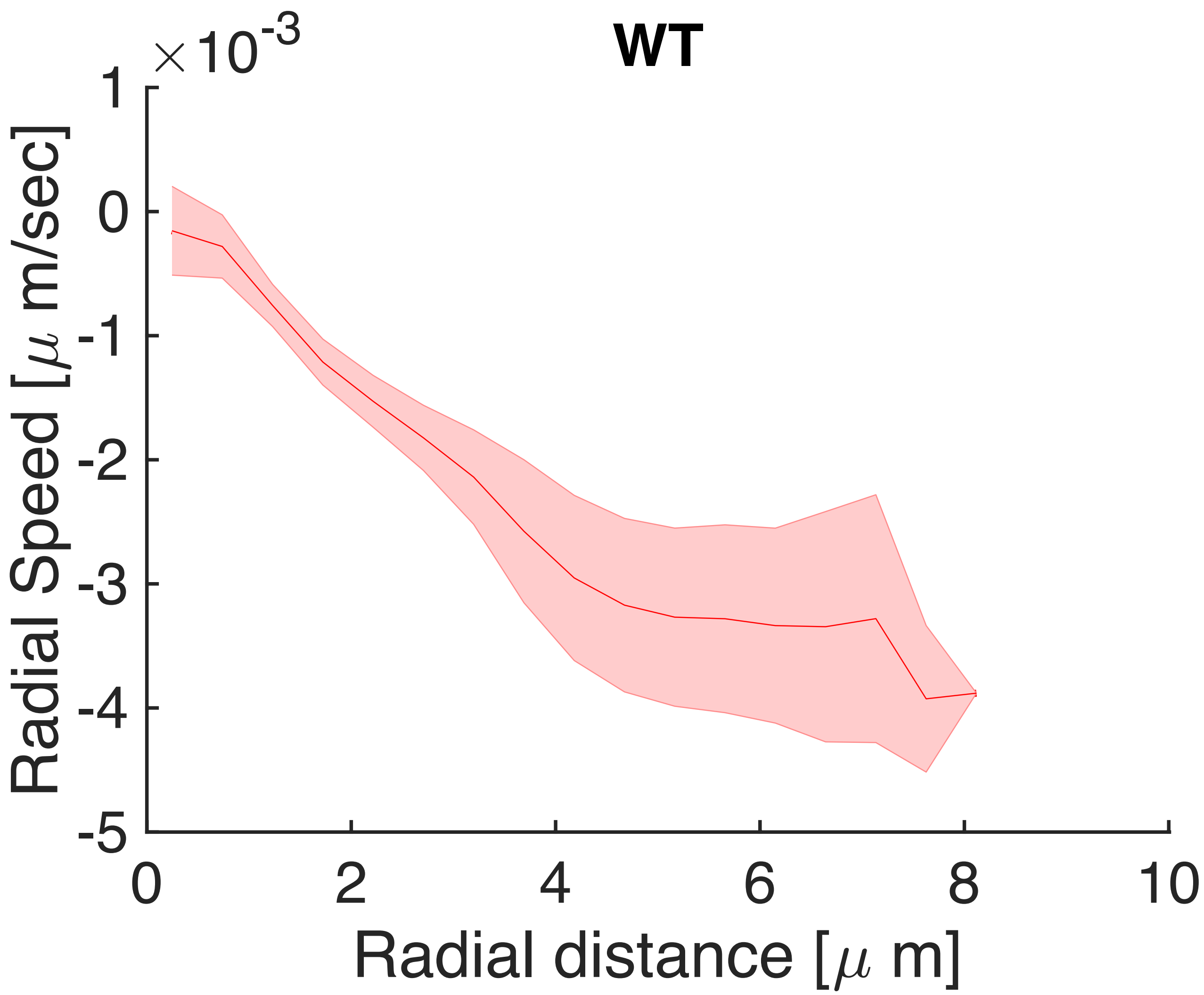

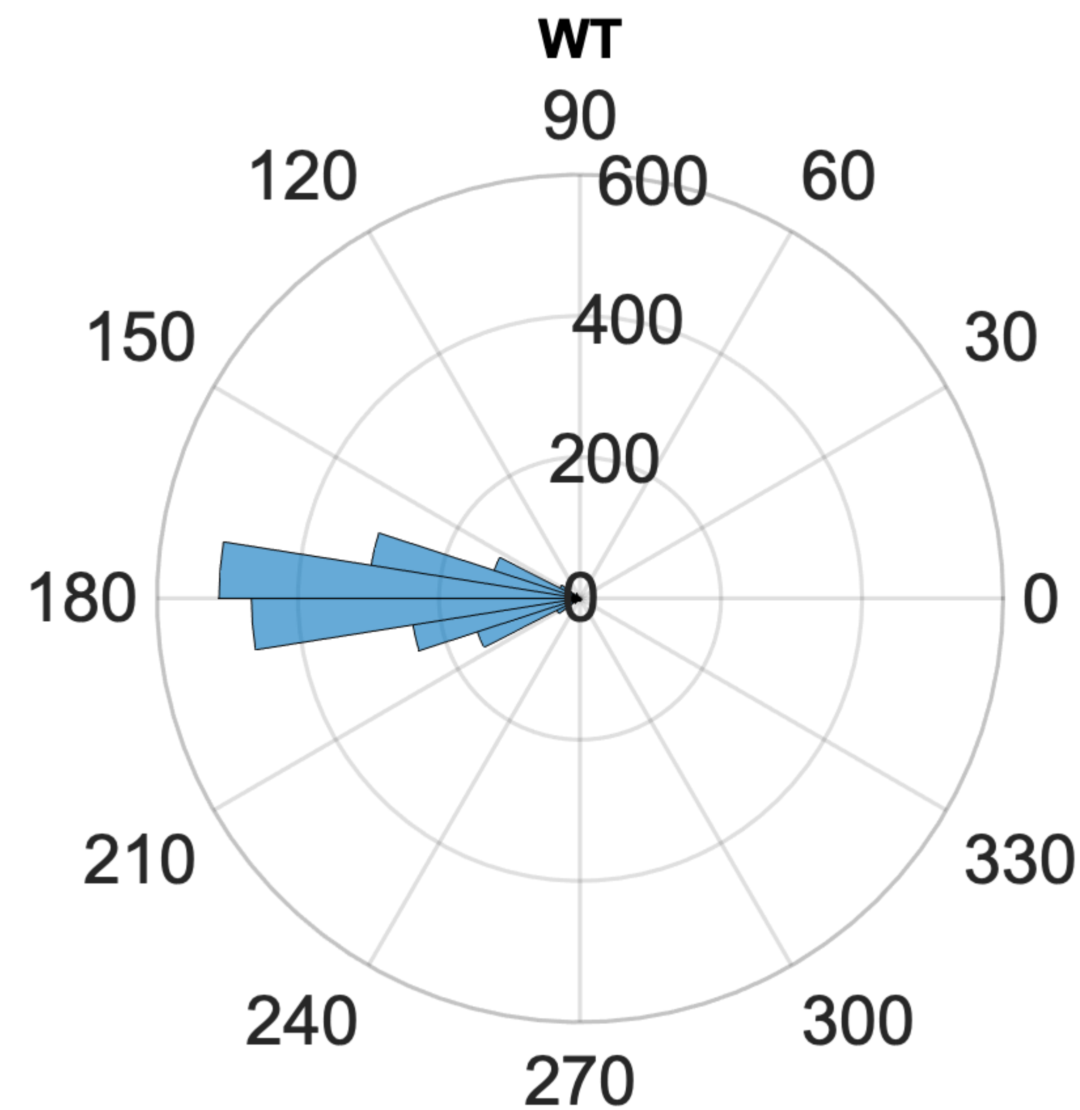

Singh et. al., biorXiv (2023)
Ganguly et. al. to be submitted (2024)

Acknowledgement

Marcus Otten
Doris Heinrich
Benjamin Lindner

Andrew Lawton
Scott Holley
Thierry Emonet

Michael J. Stulberg
Nicolas Dray
Michael W. Sneddon
William Pontius

Surya Bansi Singh
Aditya Sharma
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Funding: MATRICS (SERB), ECR (SERB), IRCC Seed Grant (IIT-B)