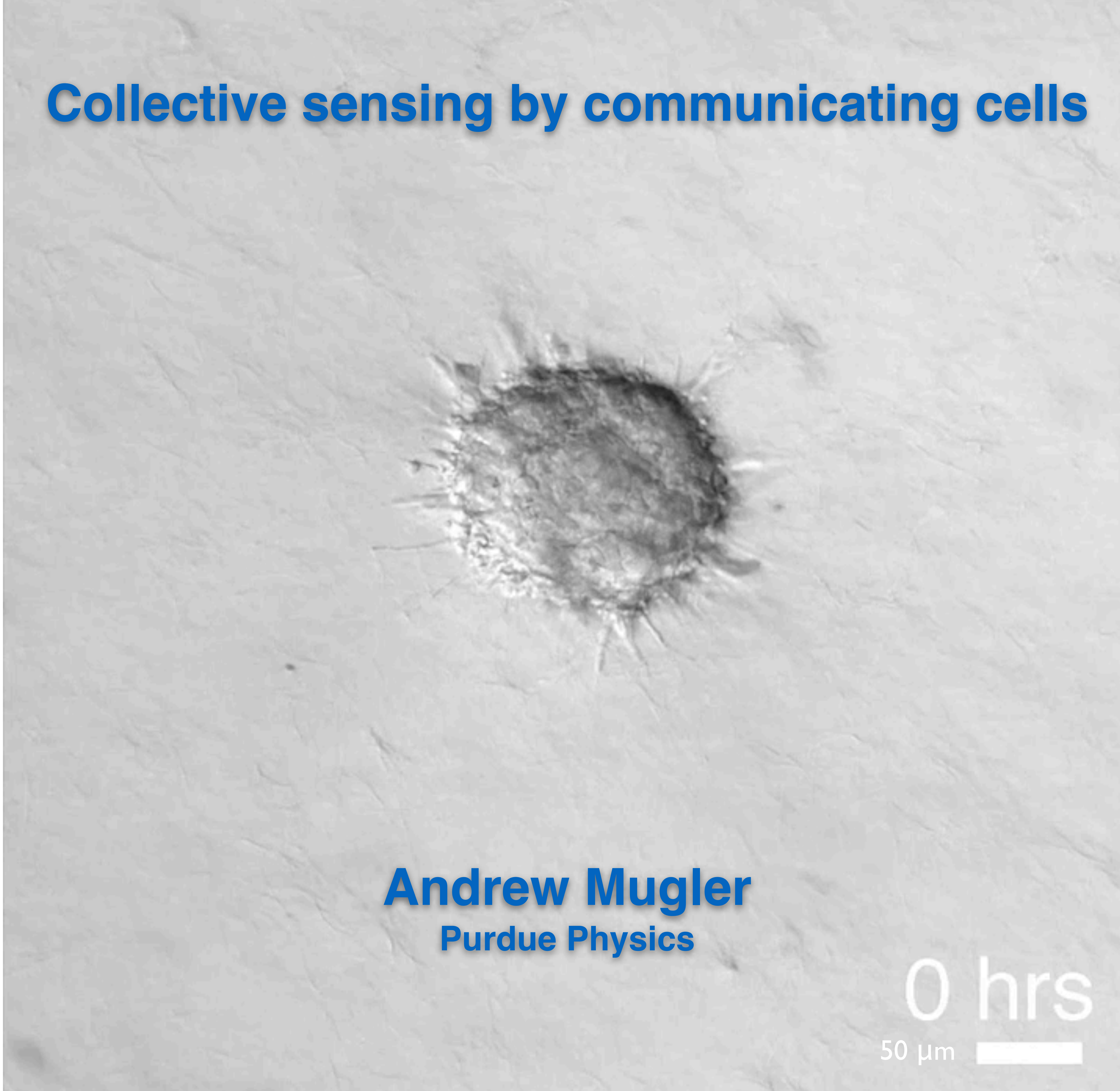
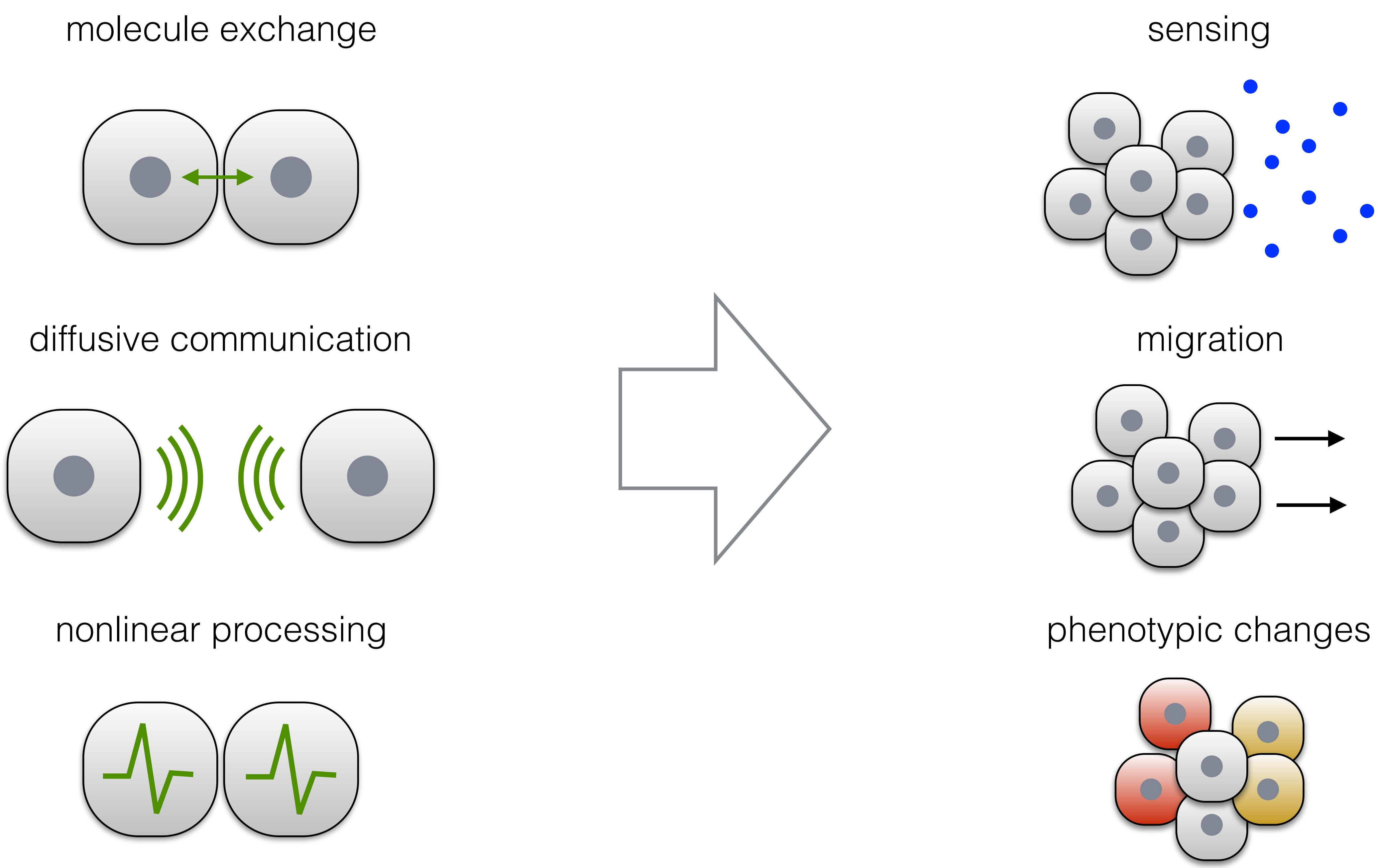
Collective sensing by communicating cells



Andrew Mugler
Purdue Physics

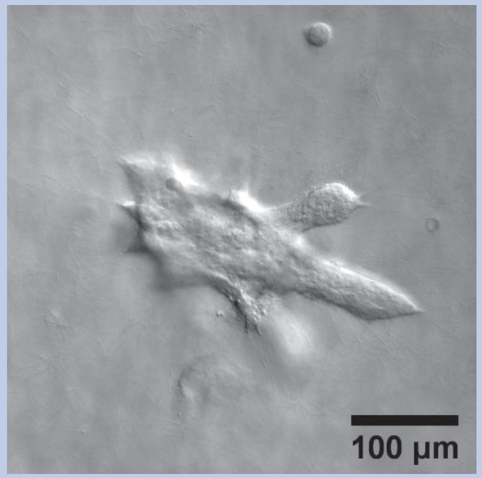
Cheung et al,
Cell, 2013

From communication to collective behavior



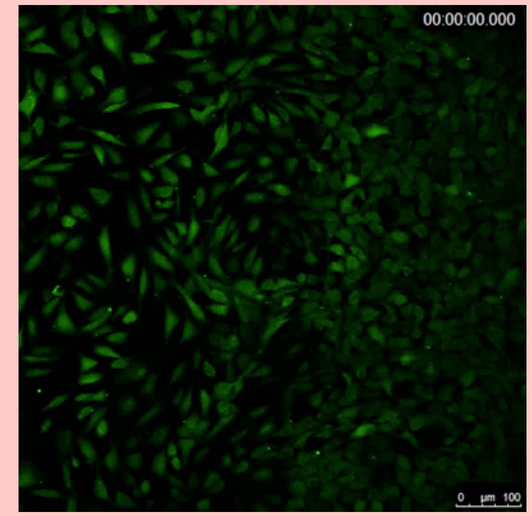
Physics of collective cell behavior

Collective EGF sensing in organoids



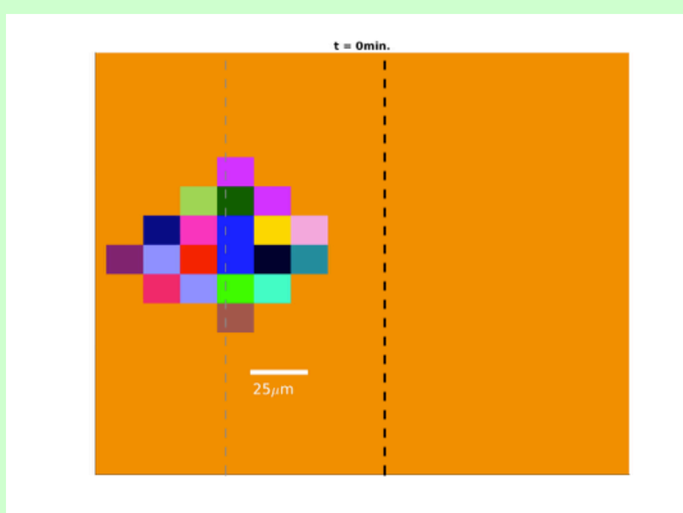
Mugler, Levchenko, Nemenman, *PNAS*, 2016
Ellison, **Mugler**, Brennan, et al, *PNAS*, 2016

Collective ATP sensing in fibroblasts



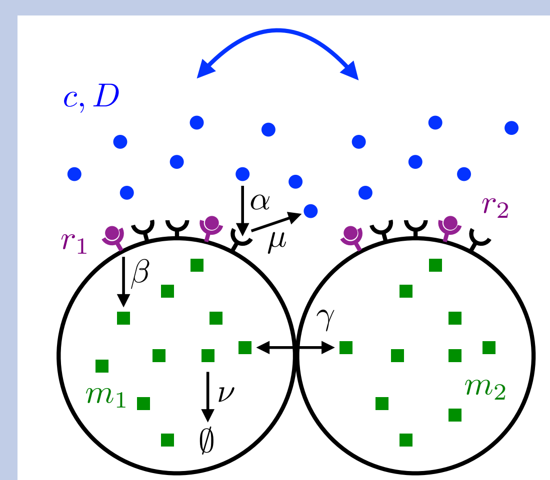
Potter*, **Byrd***, **Mugler**, Sun, *PNAS*, 2016

Collective cell migration



Varennes, Han, **Mugler**, *Biophys J*, 2016

Theory of collective sensing

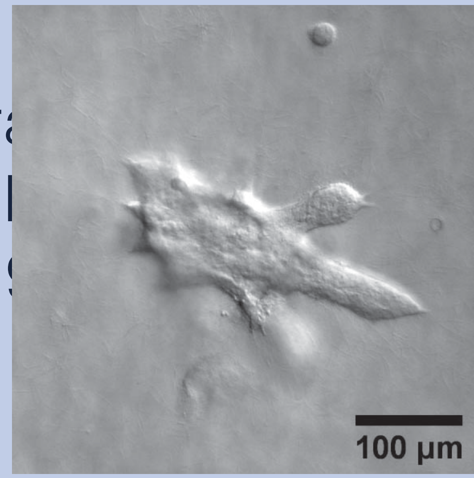


Fancher, **Mugler**, submitted

Physics of collective cell behavior

Collective EGF sensing in organoids

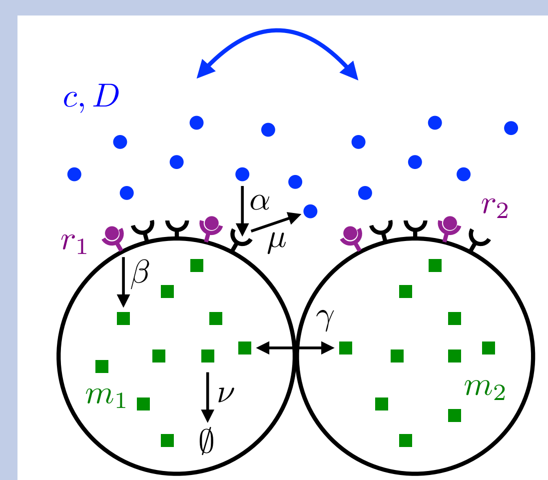
Concentra
sensing (I
Purcell, 1



Mugler, Levchenko, Nemenman, *PNAS*, 2016
Ellison, **Mugler**, Brennan, et al, *PNAS*, 2016

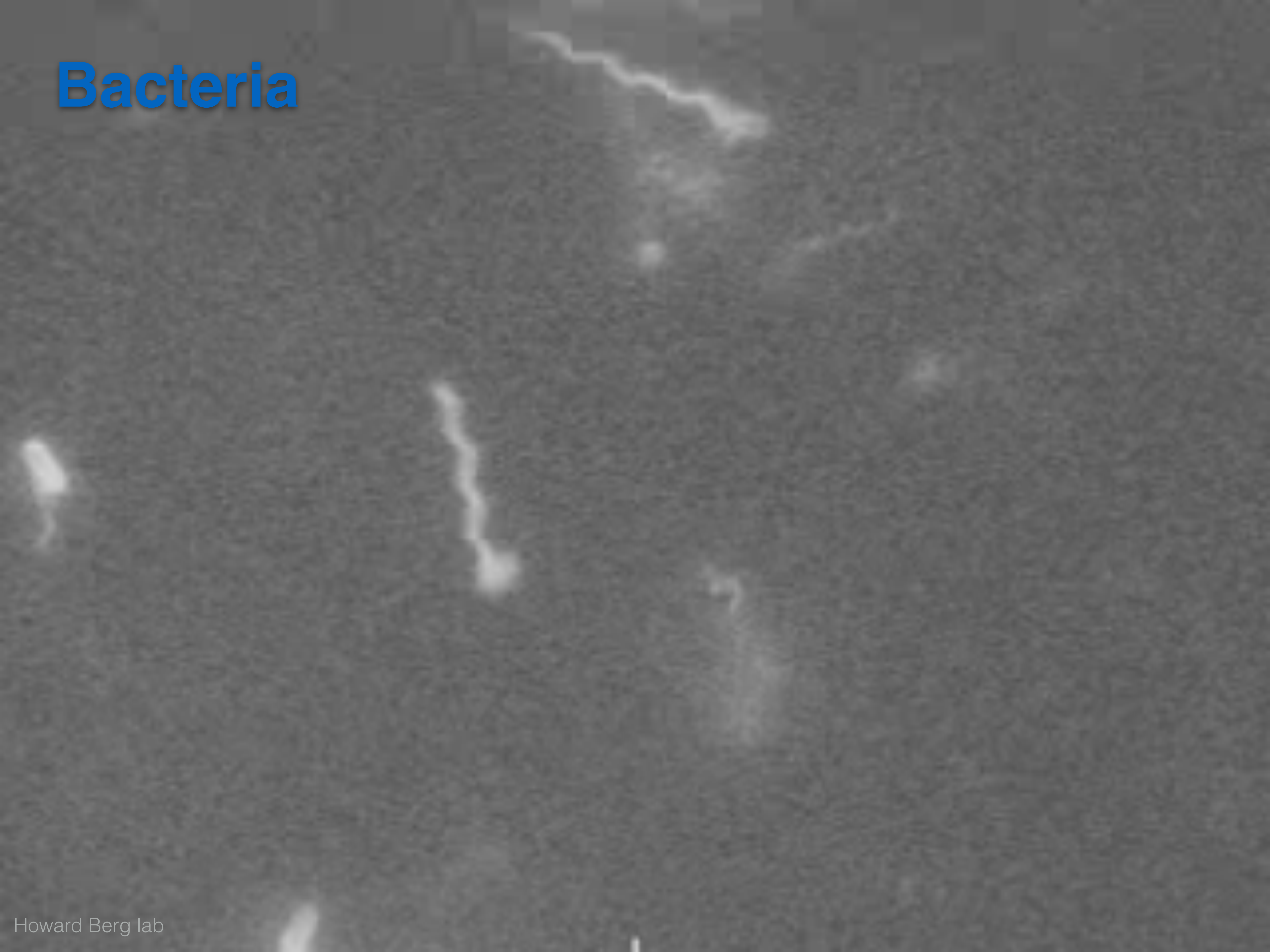
Gradient sensing

Theory of collective sensing

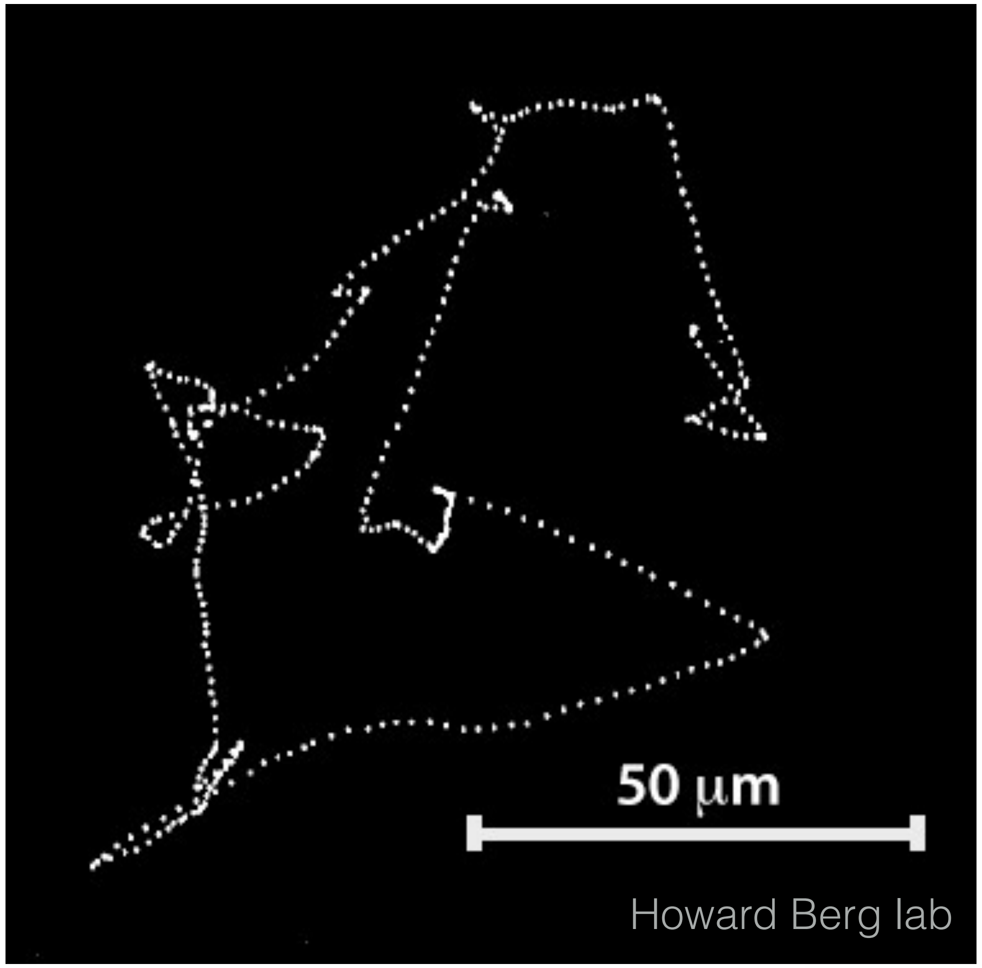


Fancher, **Mugler**, submitted

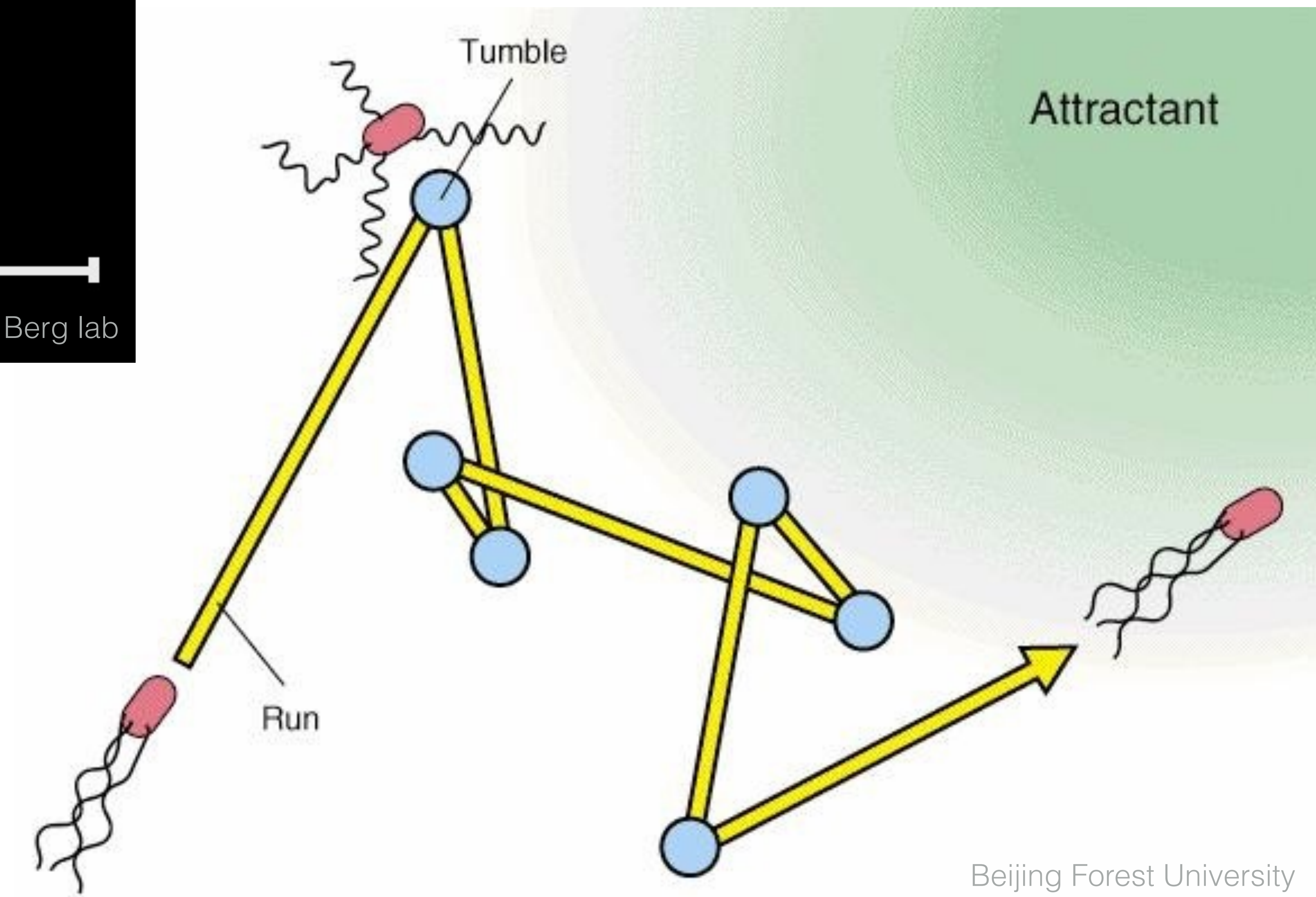
Bacteria



Howard Berg lab



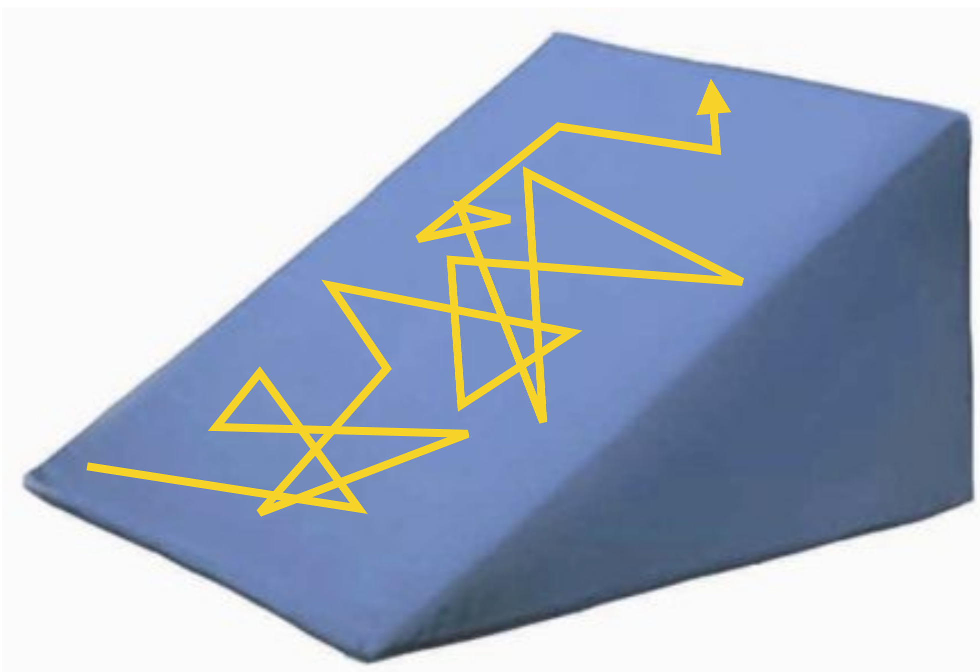
50 μm
Howard Berg lab



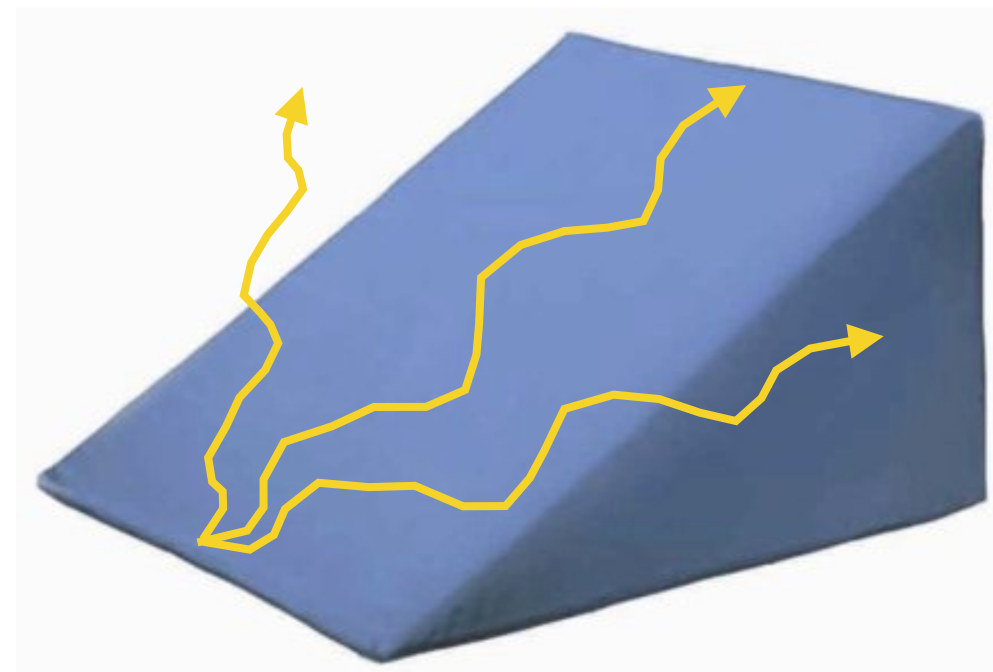
Tumble
Attractant
Run
Beijing Forest University

Should the minimum run time be…

…long?



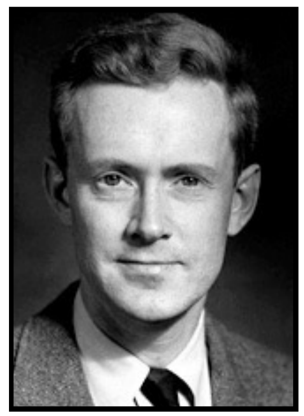
…or short?



PHYSICS OF CHEMORECEPTION

BIOPHYSICAL JOURNAL VOLUME 20 1977

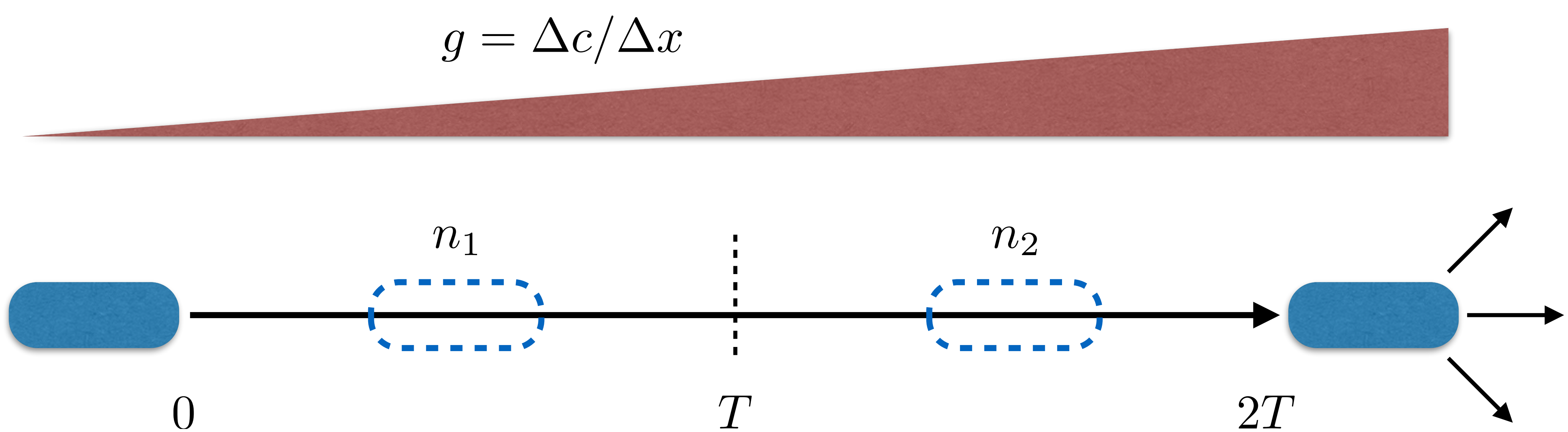

Howard Berg


Edward Purcell

It's all about counting molecules.

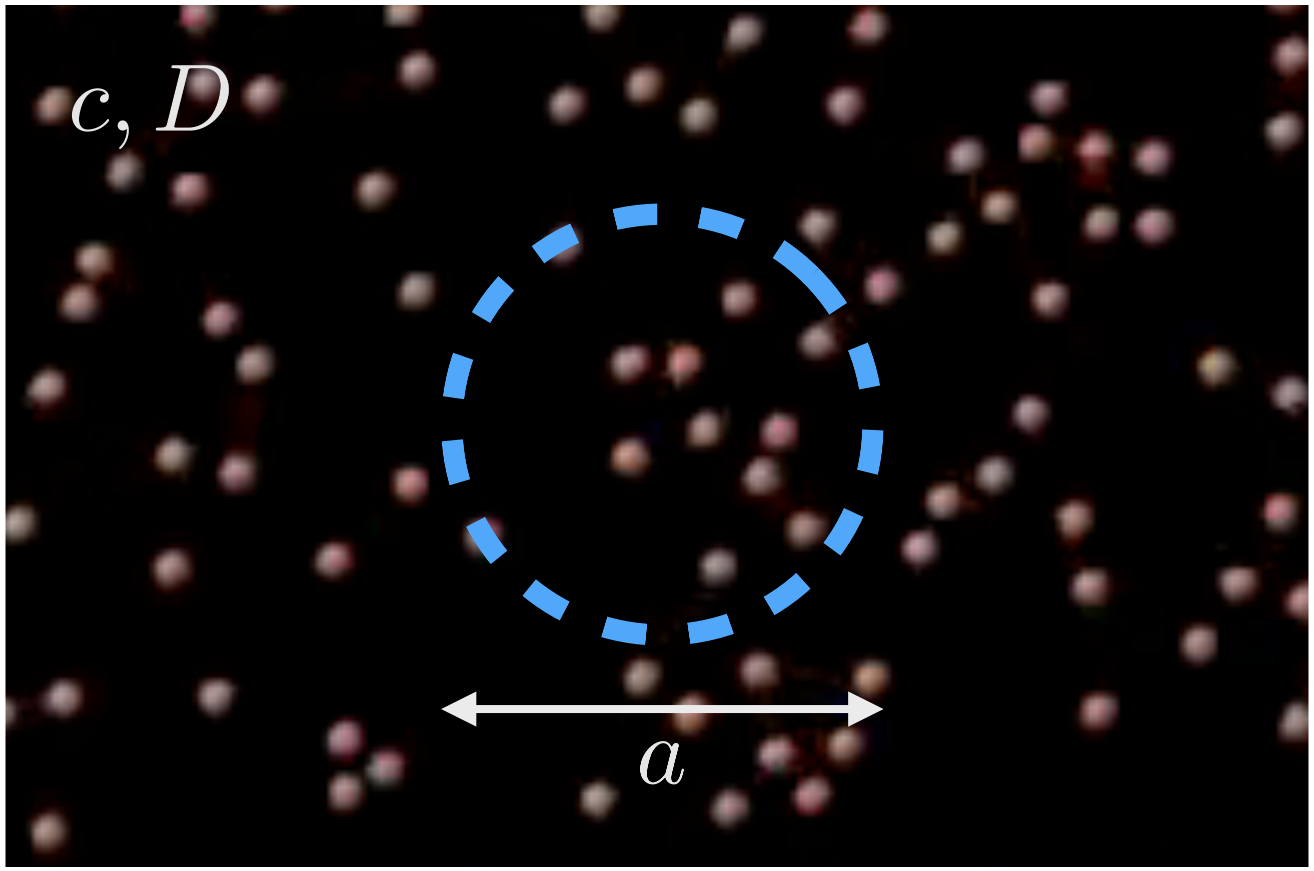
A good measurement requires

$$\bar{n}_2 - \bar{n}_1 > \sigma_{n_2 - n_1}$$



PHYSICS OF CHEMORECEPTION

BIOPHYSICAL JOURNAL VOLUME 20 1977



Poisson statistics:

$$\bar{n} \sim a^3 c \qquad \sigma^2 = \bar{n}$$

Diffusive refreshing:

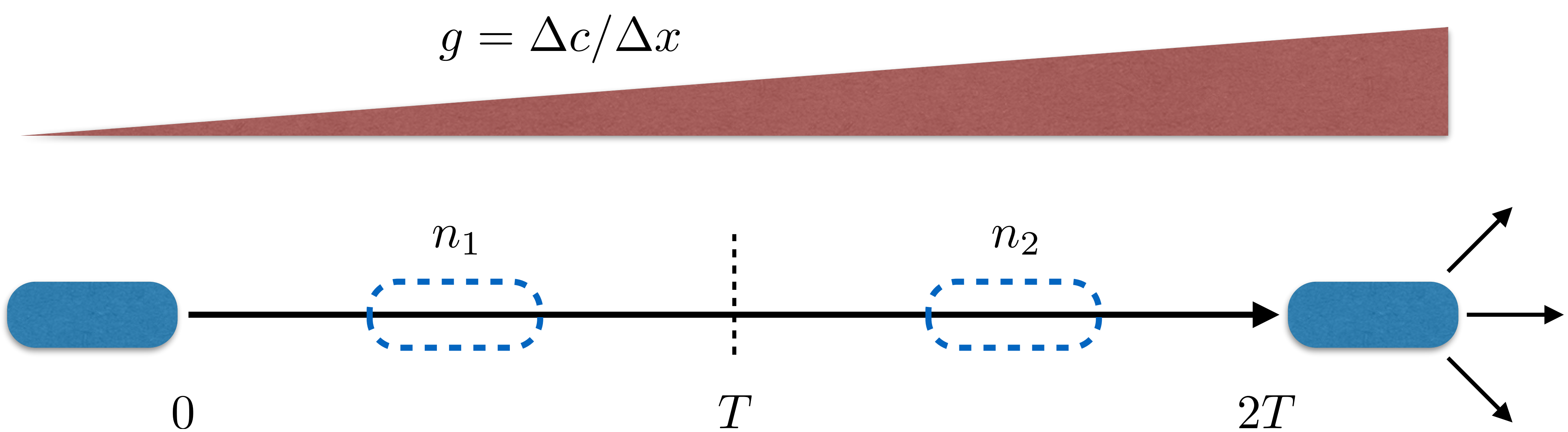
$$\sigma^2 \to \frac{\bar{n}}{T/(a^2/D)}$$

"Berg-Purcell limit":

$$\frac{\sigma}{\bar{n}} \sim \frac{1}{\sqrt{TDac}}$$

PHYSICS OF CHEMORECEPTION

Biophysical Journal Volume 20 1977



A good measurement requires $$\Delta\bar{n} \sim a^3 g v T > \sigma \sim \frac{a^3 c}{\sqrt{TDac}}$$

or $$T > \left(\frac{c}{g^2 v^2 D a}\right)^{1/3} \sim 0.5 \text{ s}$$

1 mM (c)

1 mM/mm (minimum detectable gradient) (g)

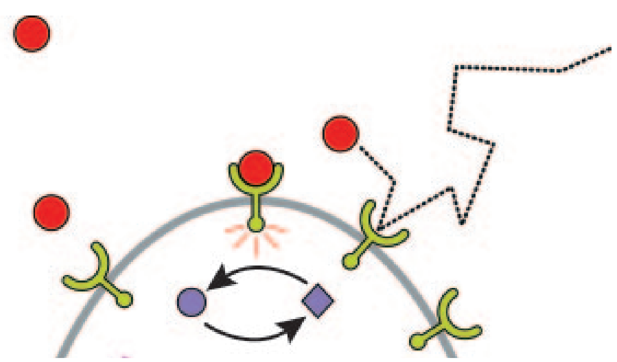
15 μm/s (v)

1000 μm²/s (D)

1 μm (a)

And typical bacteria run times are 1 s.

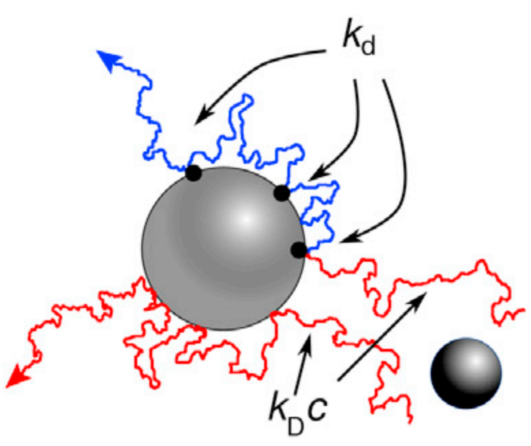
The Berg-Purcell limit persists



Using the fluctuation-dissipation theorem:

Bialek & Sateyeshgar, *PNAS*, 2005

$$\frac{\delta c}{c} = \sqrt{\frac{1}{\pi D \sigma c T} + \frac{2}{k_a c(1-\overline{n})T}}.$$



Using reaction-diffusion theory:

Kaizu et al, *Biophys J*, 2014

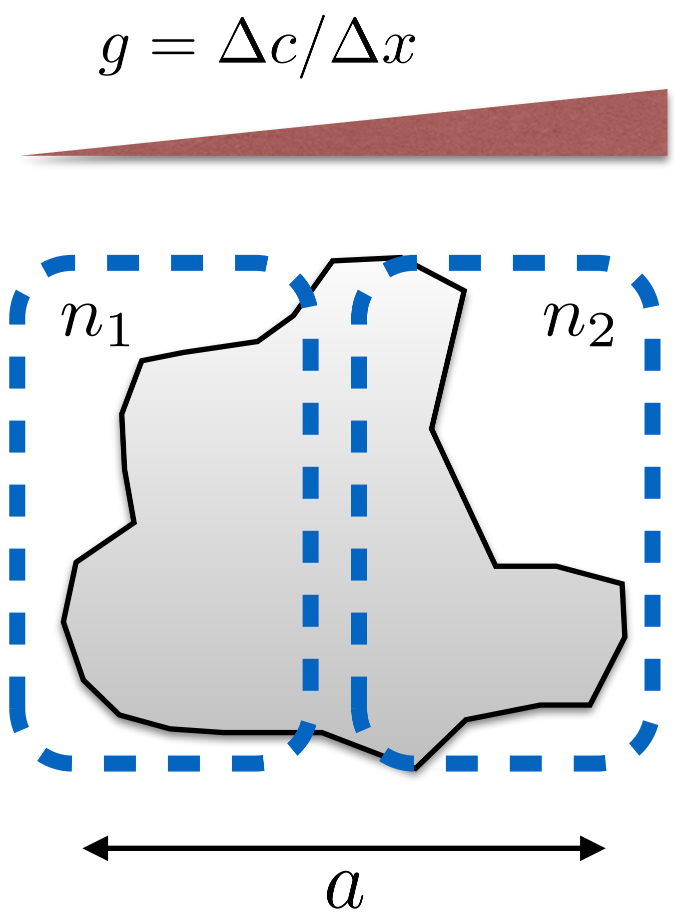
$$\frac{\delta c}{c} = \sqrt{\frac{1}{2\pi\sigma D c(1-\overline{n})T} + \frac{2}{k_a c(1-\overline{n})T}}.$$

Berg-Purcell term sets the “noise floor”

Amoeba

Firtel lab

Gradient sensing in larger cells



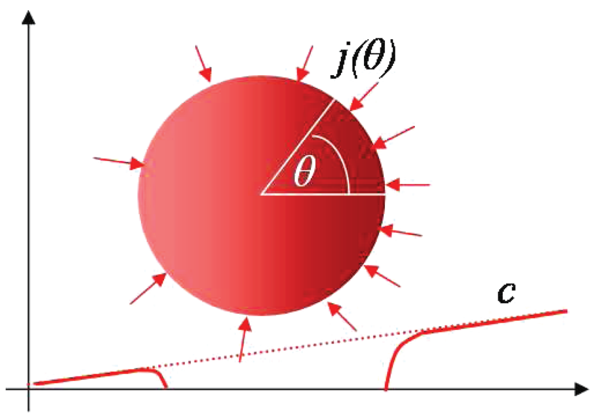
Difference in molecule numbers: $\Delta \bar{n} \sim a^3 \Delta c = a^3 g a$

Diffusive fluctuations: $\sigma \sim \dfrac{a^3 c}{\sqrt{TDac}}$

Error in gradient sensing: $\dfrac{\delta g}{g} = \dfrac{\sigma}{\Delta \bar{n}} \sim \sqrt{\dfrac{c}{g^2 a^3 T D}}$

Or $$\boxed{\frac{\delta g}{c/a} \sim \frac{1}{\sqrt{TDac}}}$$ Berg-Purcell limit

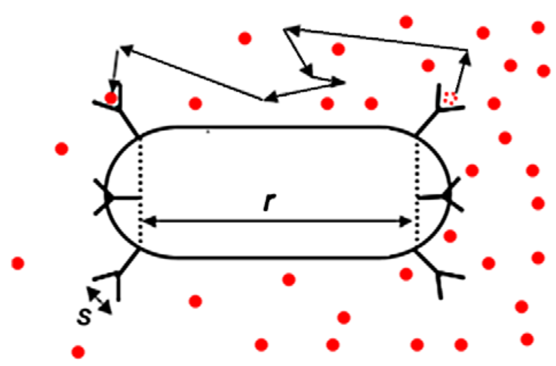
Once again, the Berg-Purcell limit persists



Using an analogy to electrostatics:

Endres & Wingreen, *PNAS*, 2008

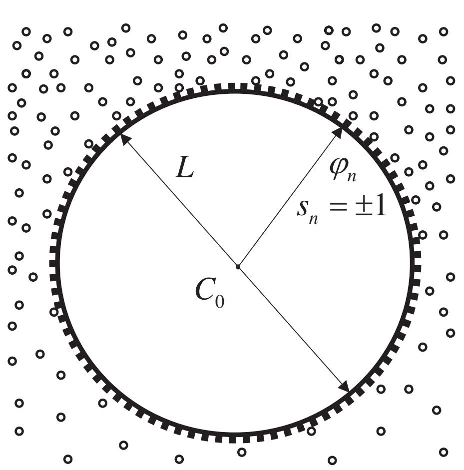
$$\frac{\langle(\delta c_{\vec{r}})^2\rangle}{(c_0/a)^2} = \frac{1}{4\pi D a c_0 T},$$



Using the fluctuation-dissipation theorem:

Endres & Wingreen, *Prog Biophys Mol Biol*, 2009

$$\frac{\left\langle[\delta(c_1 - c_2)]_\tau^2\right\rangle / r^2}{(c_0/r)^2} = \frac{1}{\pi D a' c_0 \tau}$$

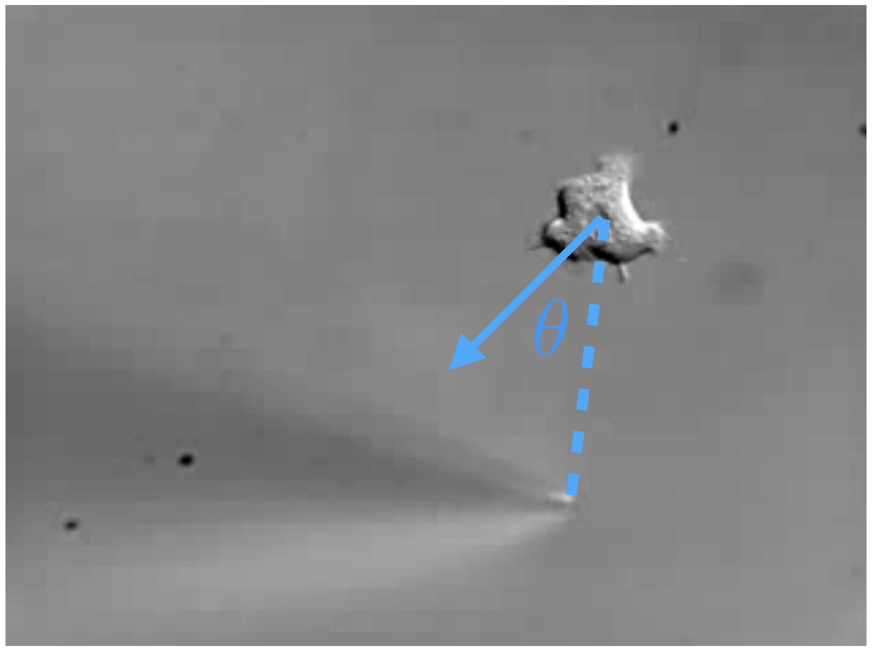


Modeling as an Ising spin chain:

Hu et al, *PRL*, 2010

$$\sigma^2_{p,\mathcal{T}} \gtrsim \frac{8}{\pi \mathcal{T} D L C_0}$$

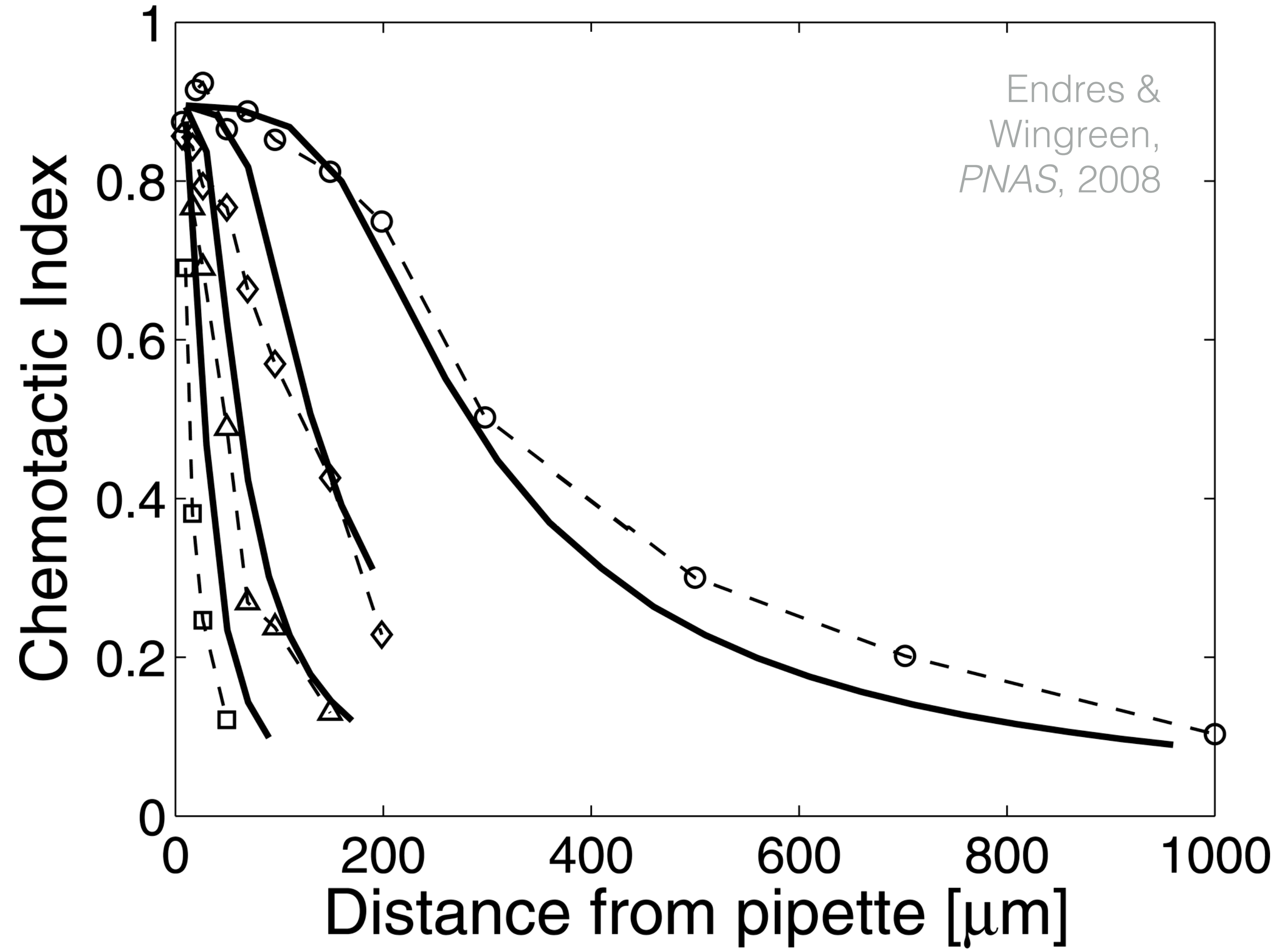
Amoebae appear to approach the limit



Chemotactic index $= \langle \cos\theta \rangle$

where θ is a function of

$$\frac{\delta g}{c/a} \sim \frac{1}{\sqrt{TDac}}$$



One free parameter: $T \approx 3.2$ s

And typical amoebae response times are 5-10 s.

Physics of collective cell behavior

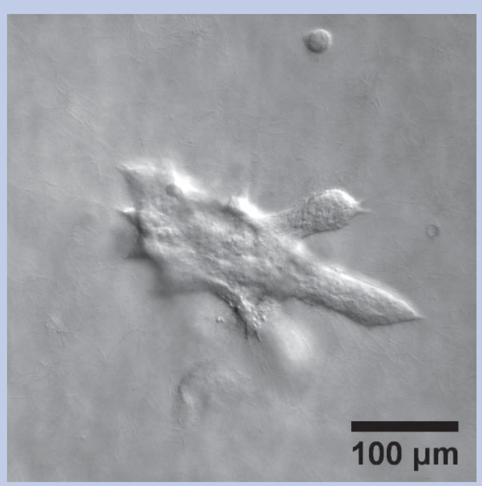
What are the fundamental limits to cellular sensing?

Concentration sensing (Berg & Purcell, 1977)

Gradient sensing

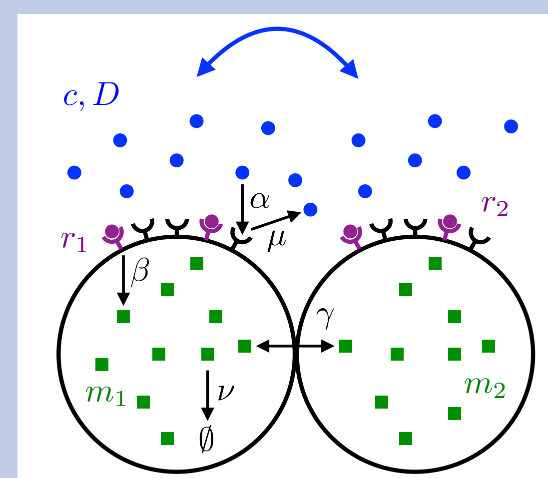
Can cells surpass these limits by communicating?

Collective EGF sensing in organoids



Mugler, Levchenko, Nemenman, *PNAS*, 2016
Ellison, **Mugler**, Brennan, et al, *PNAS*, 2016

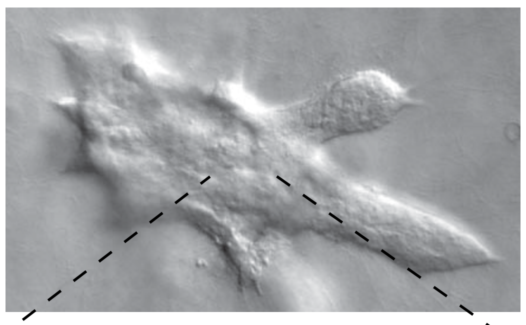
Theory of collective sensing



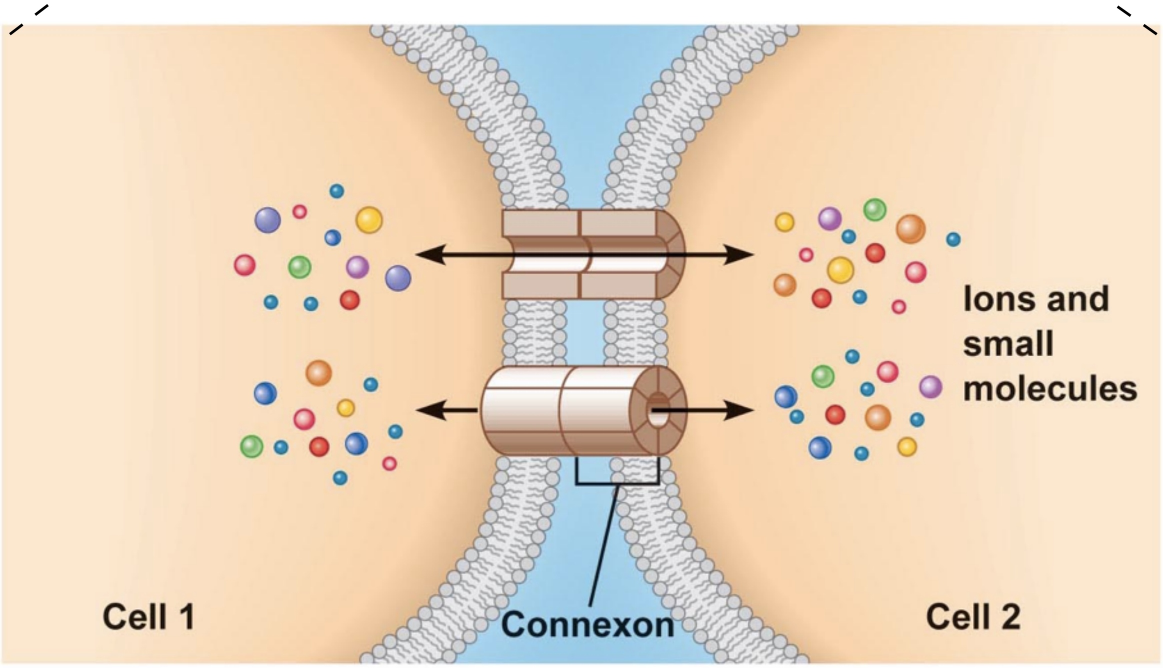
Fancher, **Mugler**, submitted

Cell-cell communication

Juxtacrine signaling (short-range)



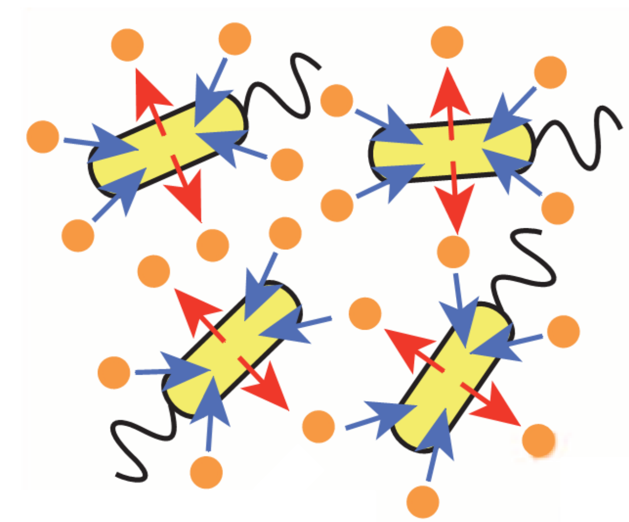
Gap junctions



Autocrine signaling (long-range)

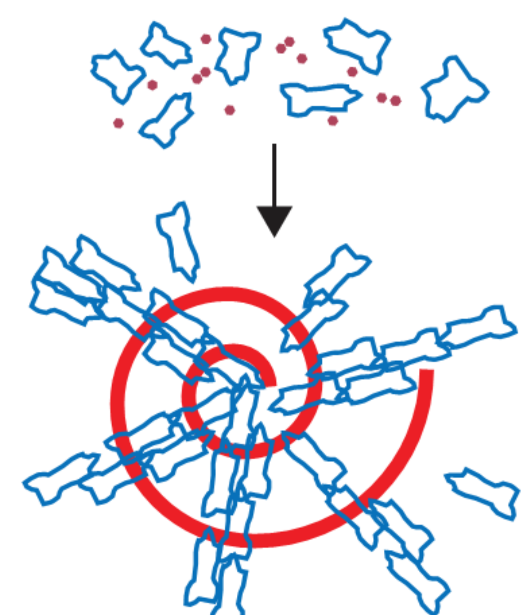
Bacteria

Youk & Lim, *Science*, 2014

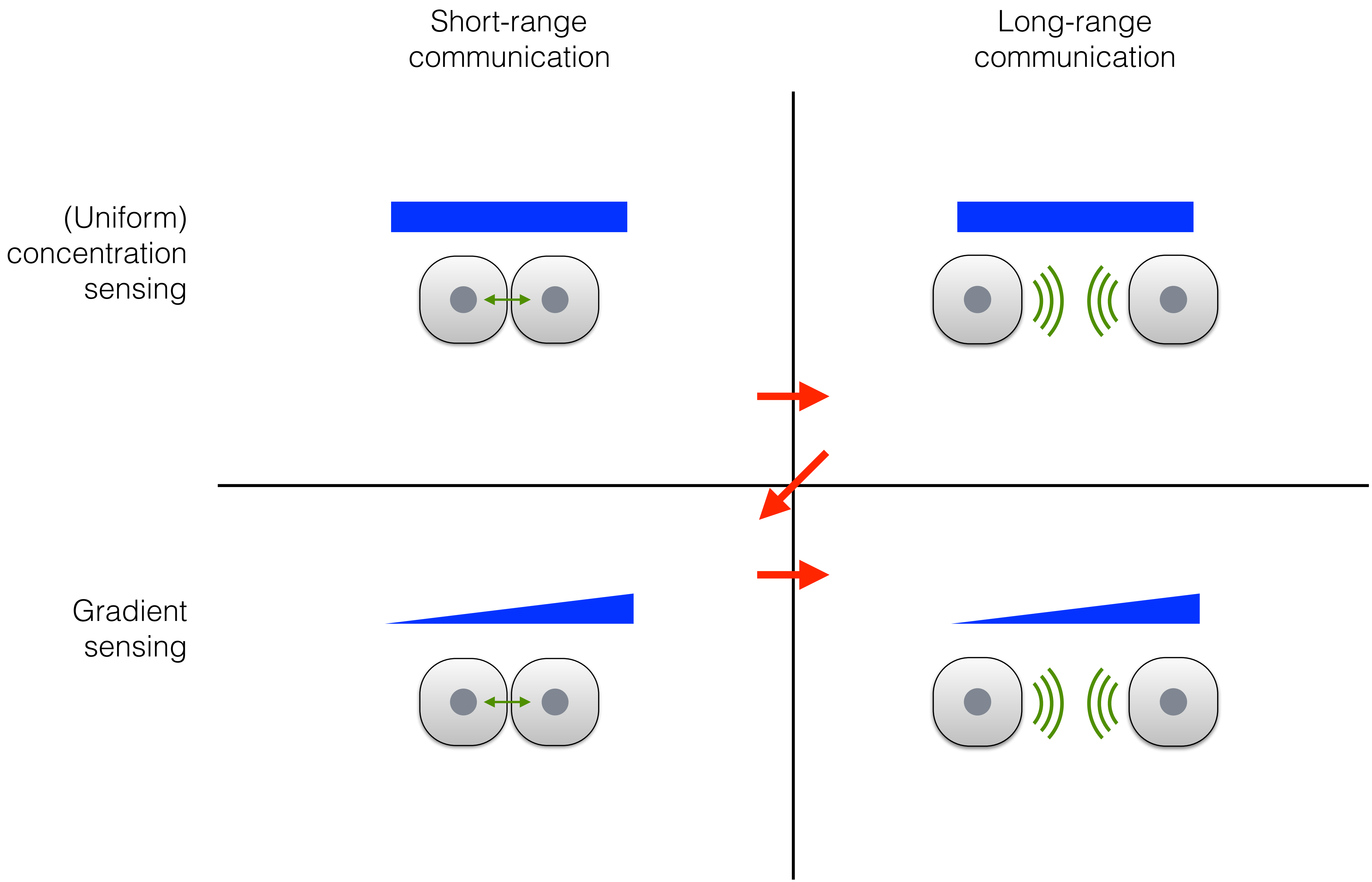


Amoebae

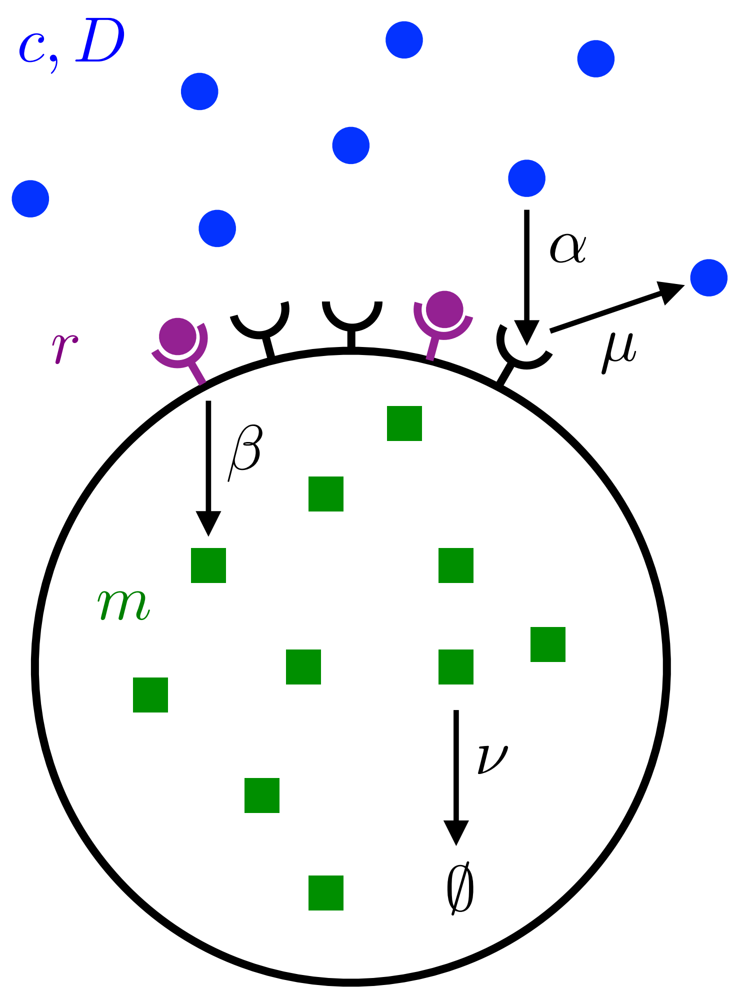
Mehta & Gregor, *Curr Opin Gen Dev*, 2010



Outline of this talk



Concentration sensing by a single cell



$$C + U \underset{\mu}{\overset{\tilde{\alpha}}{\rightleftharpoons}} R \qquad R \xrightarrow{\beta} R + M$$

$$M \xrightarrow{\nu} \emptyset$$

$$\dot{c} = D\nabla^2 c - \delta(\vec{x})\dot{r} + \eta_c$$

$$\dot{r} = \alpha c(\vec{0}, t) - \mu r + \eta_r \qquad (\alpha \equiv \tilde{\alpha} r_{\mathrm{total}})$$

$$\dot{m} = \beta r - \nu m + \eta_m$$

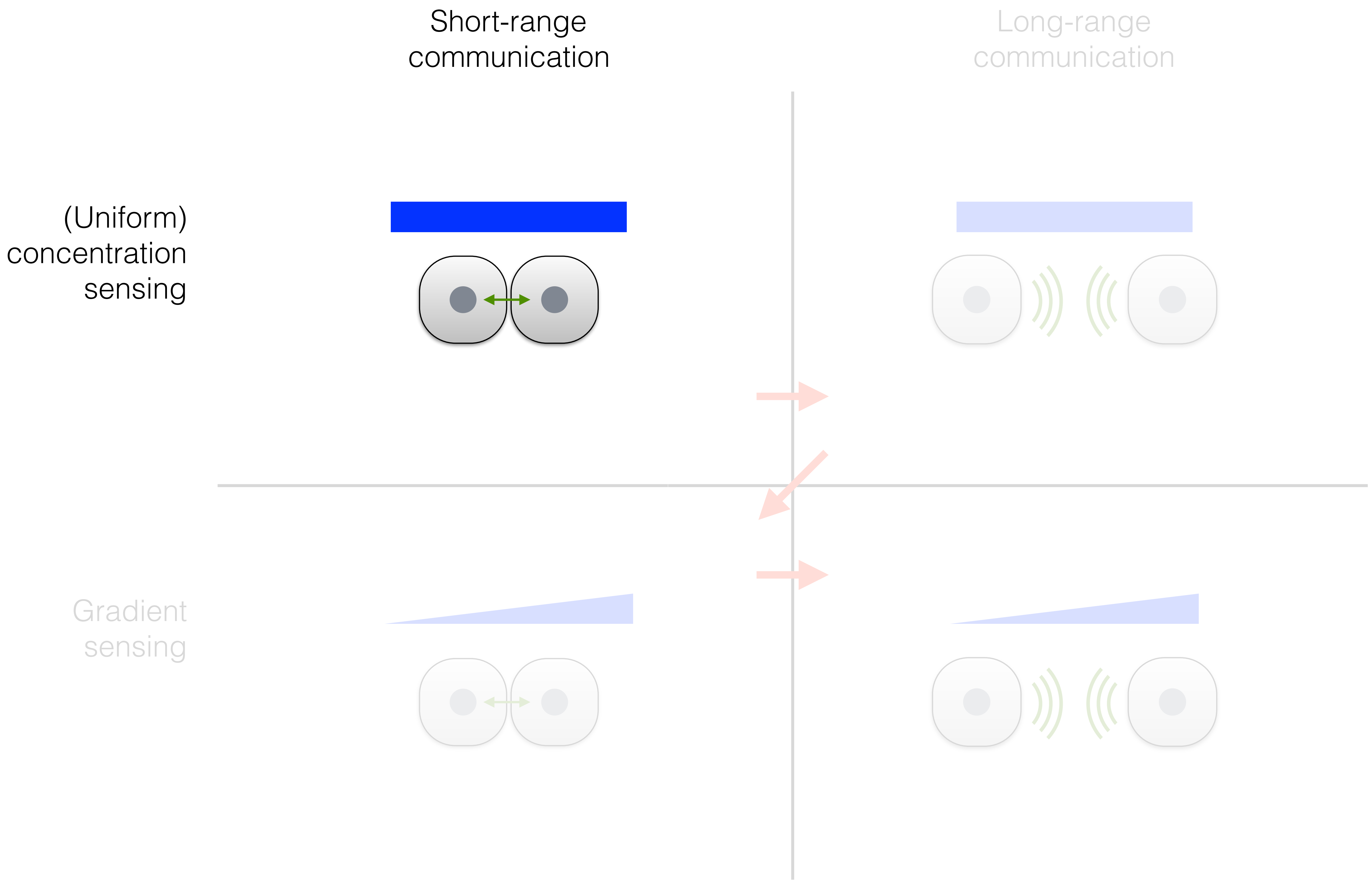
$$\boxed{\frac{\sigma_m^2}{\bar{m}^2} = \underbrace{\frac{1}{2}\frac{1}{\pi a \bar{c} D T}}_{\text{extrinsic noise}} + \underbrace{\frac{2}{\mu T \bar{r}} + \frac{2}{\nu T \bar{m}}}_{\text{intrinsic noise}}}$$

extrinsic noise — intrinsic noise

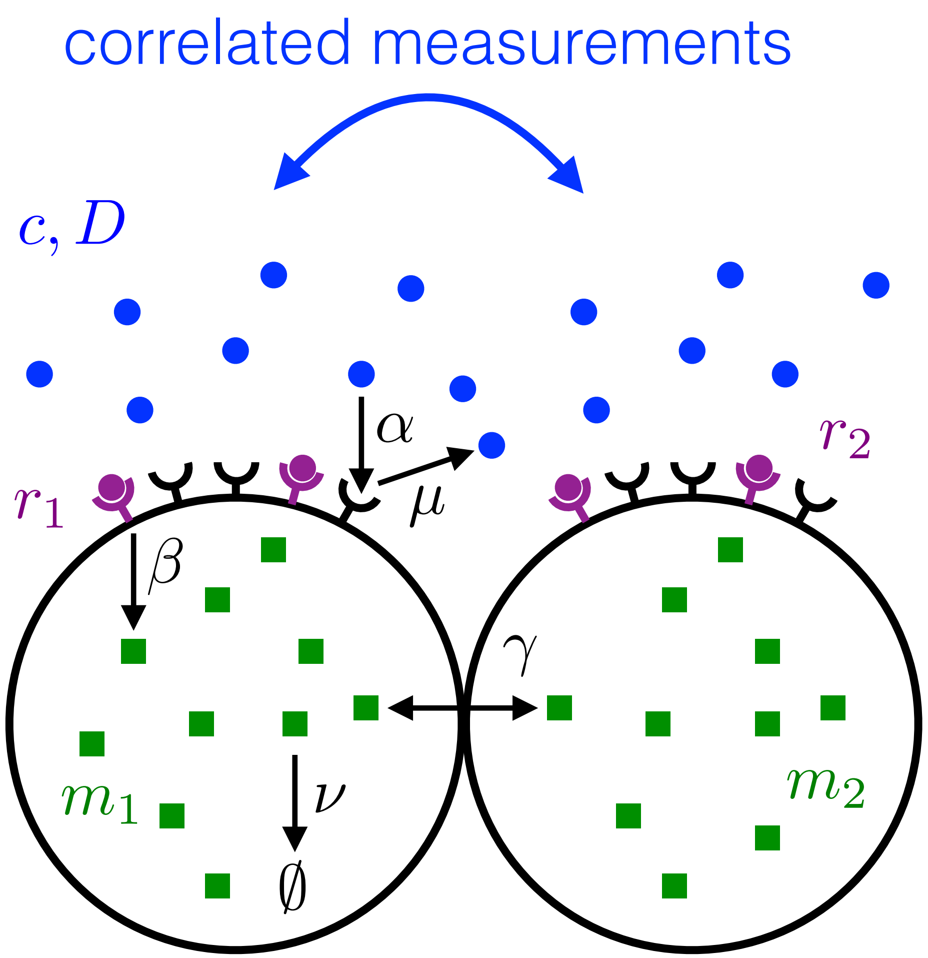
See also:

- Gardiner, *Handbook of stochastic methods*, 1985
- Bialek & Setayeshgar, *PNAS*, 2005

Outline of this talk



Conc. sensing with short-range communication



$$\dot{c} = D\nabla^2 c - \sum_{i=1}^{N} \delta(\vec{x} - \vec{x}_i)\dot{r}_i + \eta_c$$

$$\dot{r}_i = \alpha c(\vec{x}_i, t) - \mu r_i + \eta_{ri}$$

$$\dot{m}_i = \beta r_i - \nu m_i + \gamma \sum_{j \in \mathcal{N}_i} (m_j - m_i) + \eta_{mi}$$

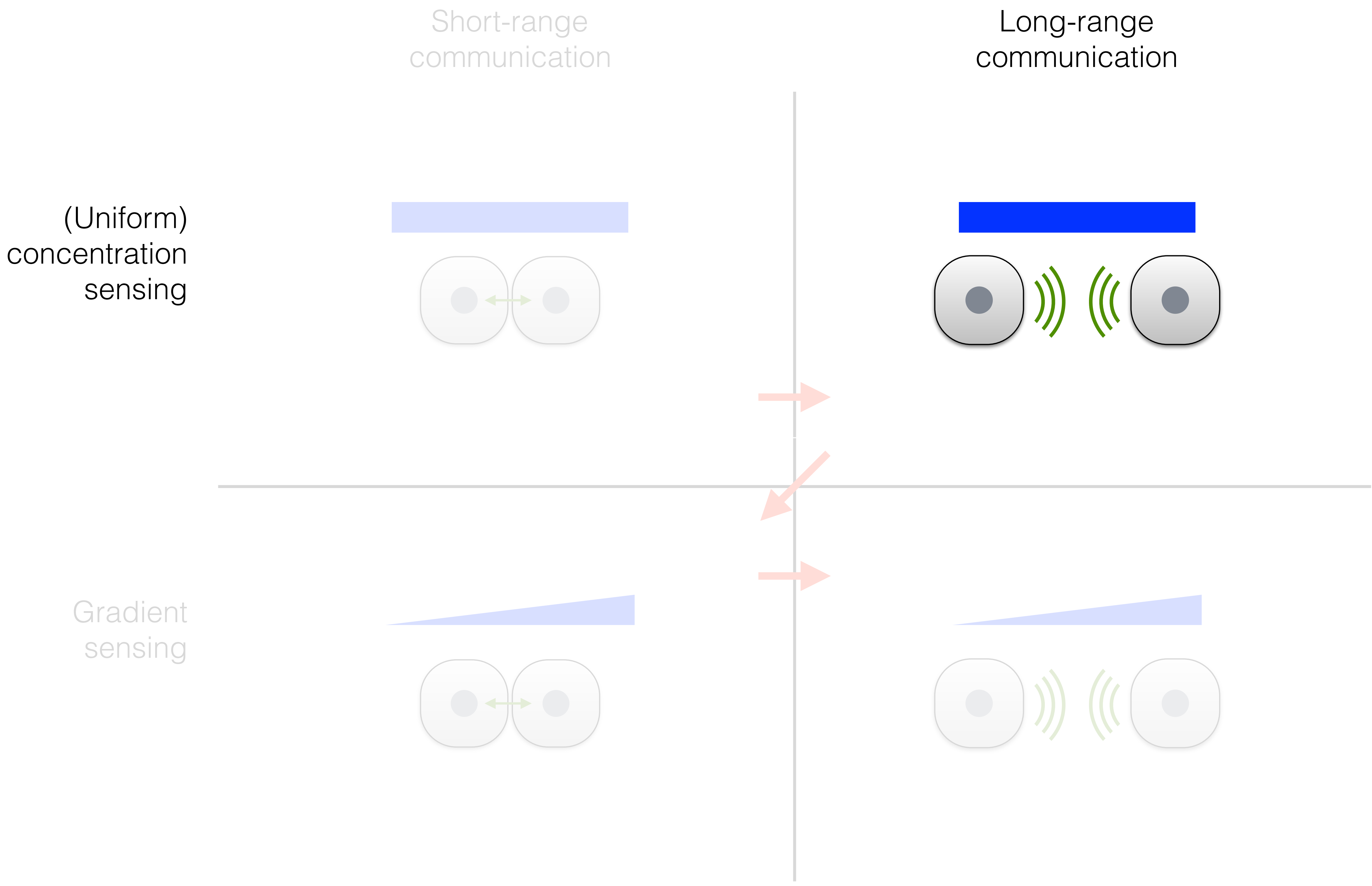
$$N = 2: \quad \frac{\sigma_m^2}{\bar{m}^2} = \frac{3}{8}\frac{1}{\pi a \bar{c} D T}, \quad \gamma \gg \nu$$

Note: $\frac{3}{8} > \frac{1}{2} \times \frac{1}{2}$

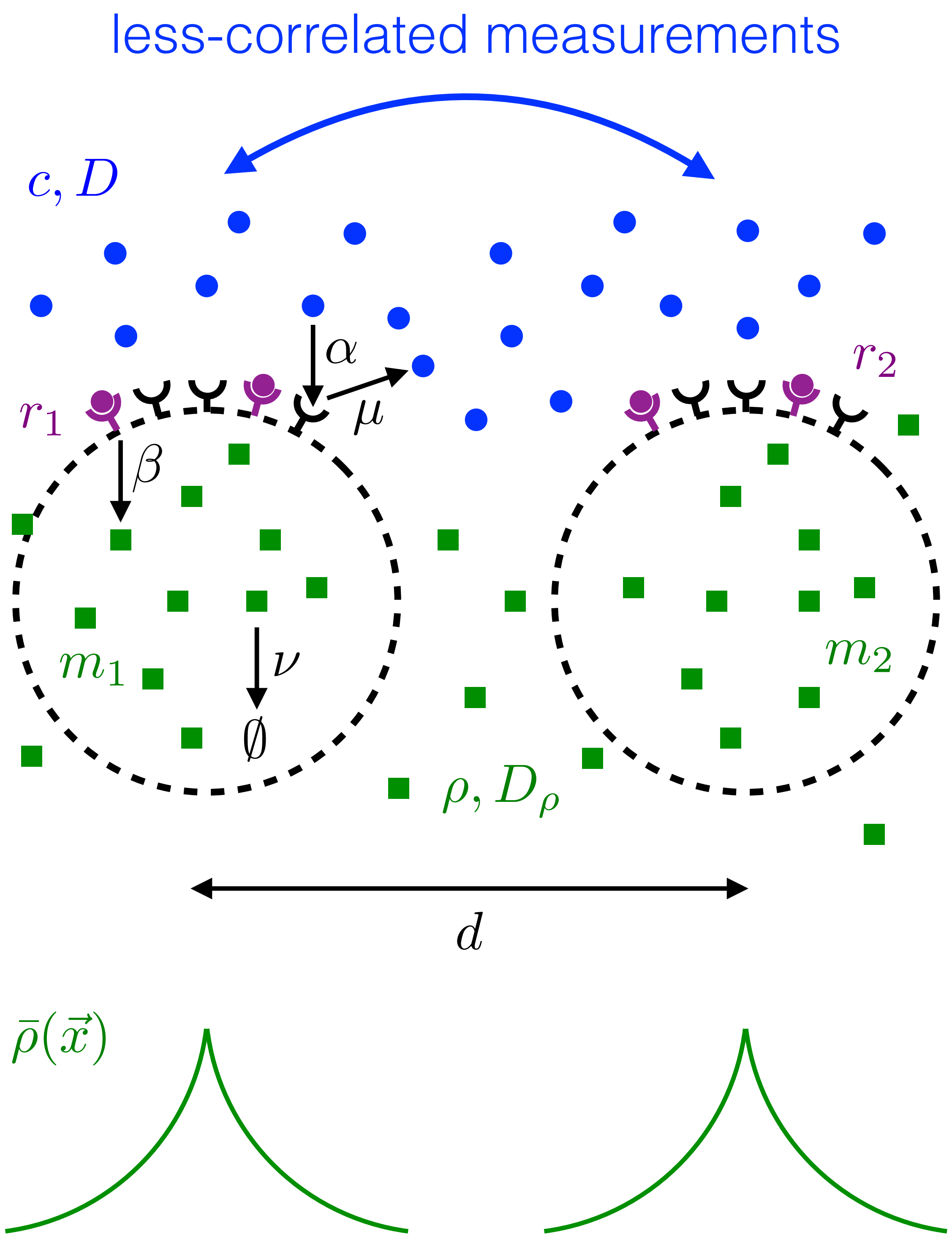
single cell — two cells

Fancher & Mugler, arXiv:1603.04108

Outline of this talk



Conc. sensing with long-range communication



$$\dot{c} = D\nabla^2 c - \sum_{i=1}^{N} \delta(\vec{x} - \vec{x}_i)\dot{r}_i + \eta_c$$

$$\dot{r}_i = \alpha c(\vec{x}_i, t) - \mu r_i + \eta_{ri}$$

$$\dot{\rho} = D_\rho \nabla^2 \rho - \nu\rho + \sum_{i=1}^{N} \delta(\vec{x} - \vec{x}_i)(\beta r_i + \eta_{pi}) + \eta_d$$

and $\quad m_i(t) = \int_{V_i} d^3x\,\rho(\vec{x}, t)$

$$N = 2: \quad \frac{\sigma_m^2}{\bar{m}^2} = \left[\frac{9d^2 + 16a^2}{2(3d + 2a)^2}\right] \frac{1}{\pi a \bar{c} D T}$$

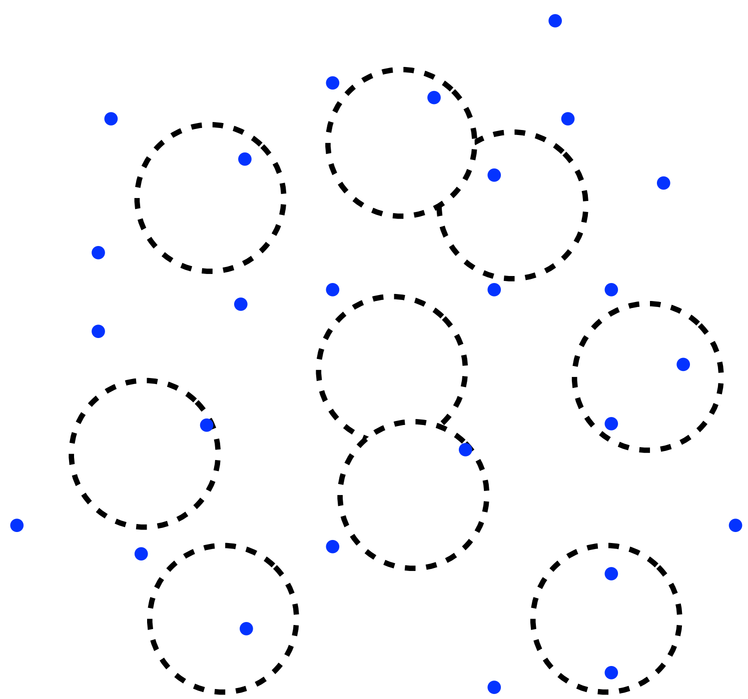
But $\frac{2}{5} > \frac{3}{8}$ $\qquad \frac{2}{5}, \quad d = d^* = \frac{8}{3}a$

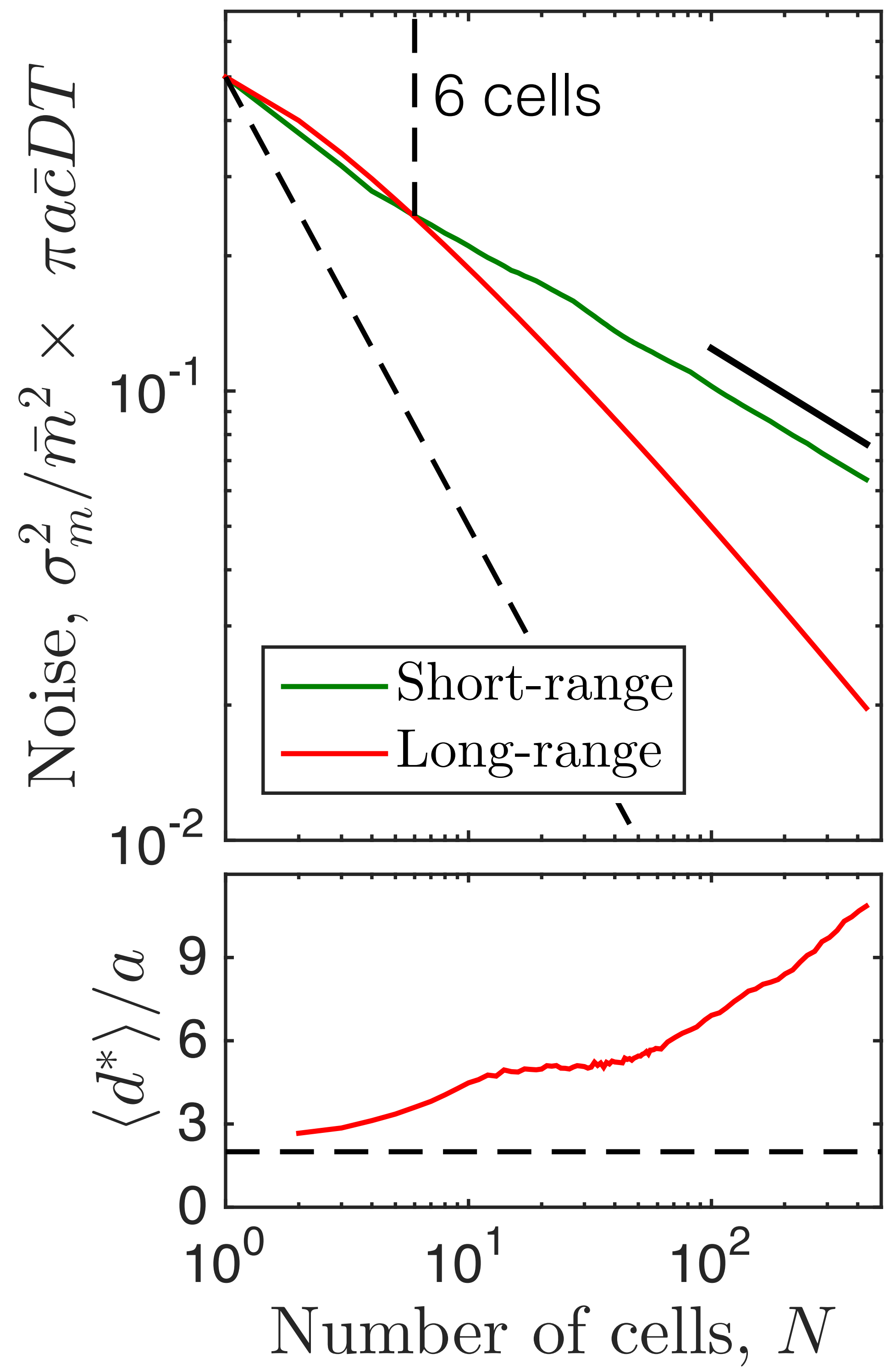
long-range $\quad$ short-range

Fancher & Mugler, arXiv:1603.04108

Conc. sensing with long-range communication

Optimized configuration of cells:



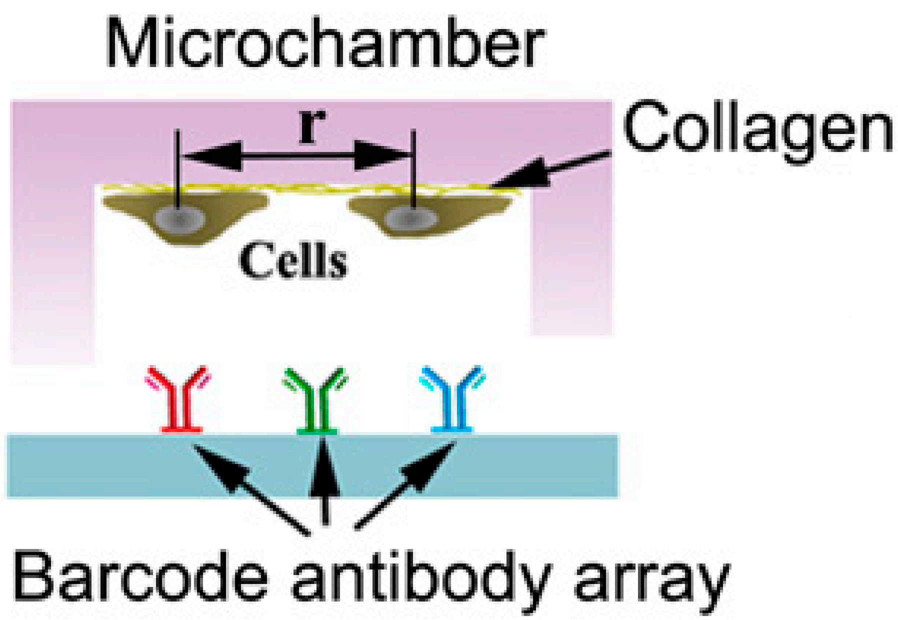


- Long-range communication outperforms short-range, even for small populations
- Optimal separation can be many cell radii

Fancher & Mugler, arXiv:1603.04108

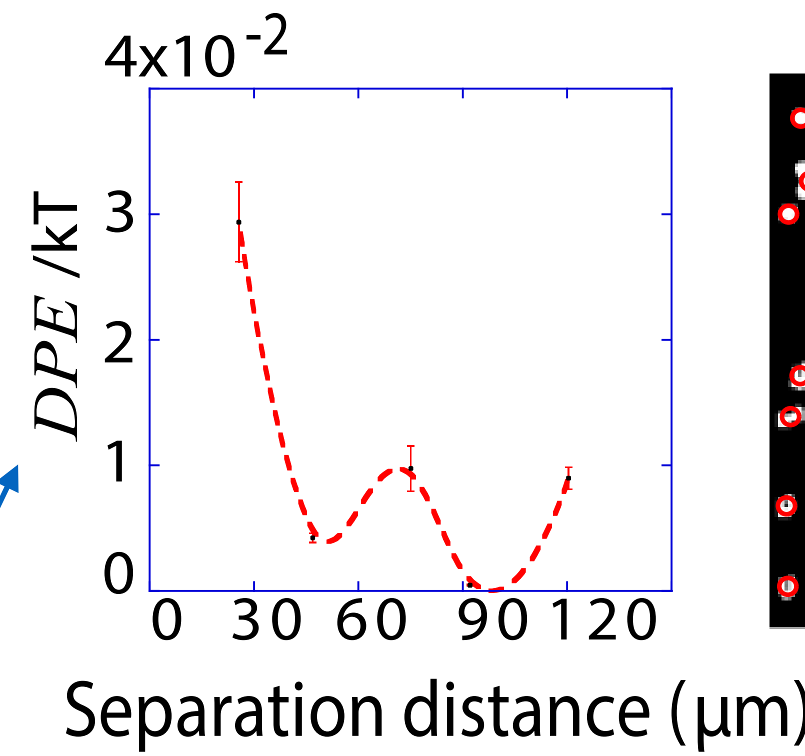
Glioblastoma cellular architectures are predicted through the characterization of two-cell interactions

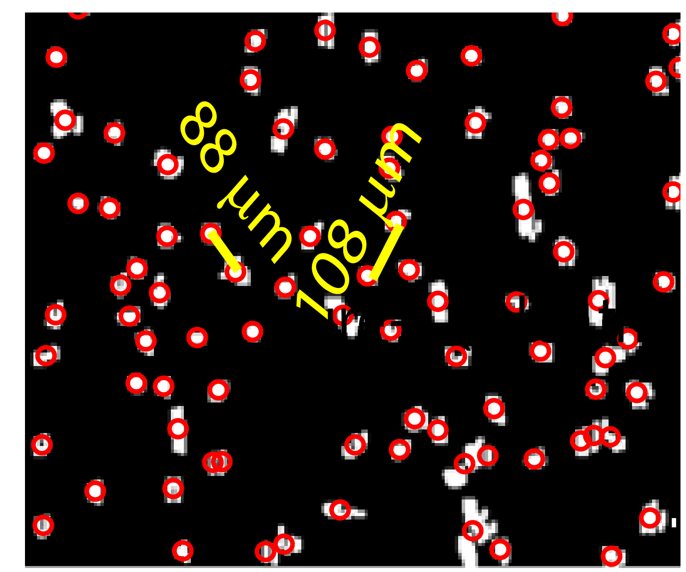
Nataly Kravchenko-Balasha[a,1], Jun Wang[a,1], Francoise Remacle[b,c], R. D. Levine[c,d,2], and James R. Heath[a,d,2]



(to detect autocrine factors)

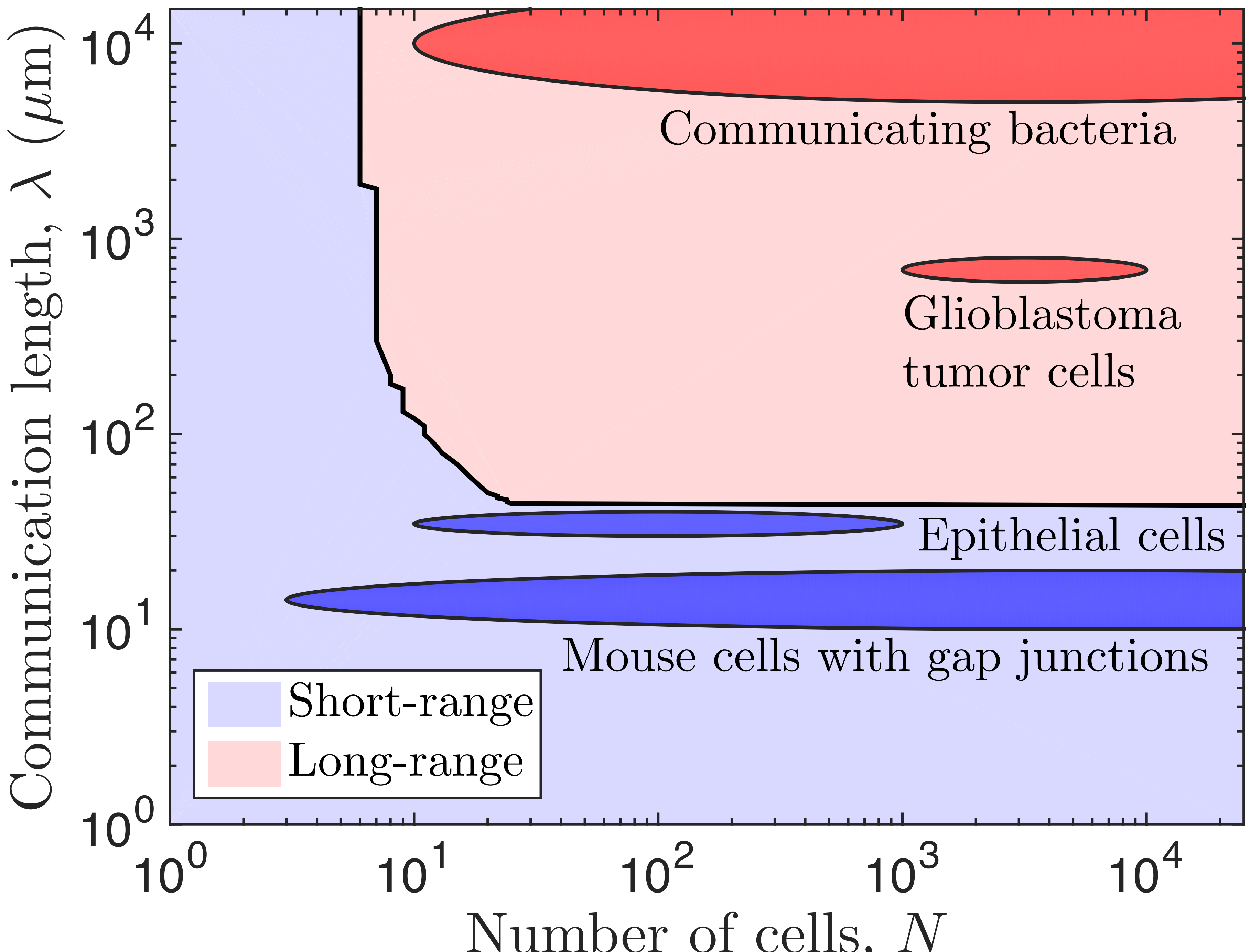
“Noise”





PNAS | **April 29, 2014** | vol. 111 | no. 17 | **6521–6526**

Phase diagram of optimal sensing strategy



Communicating bacteria: Stewart, *J Bacteriol*, 2003; Trovato et al, *FEMS Microbiol Lett*, 2014; Shaefer et al, *Method Enzymol*, 2000

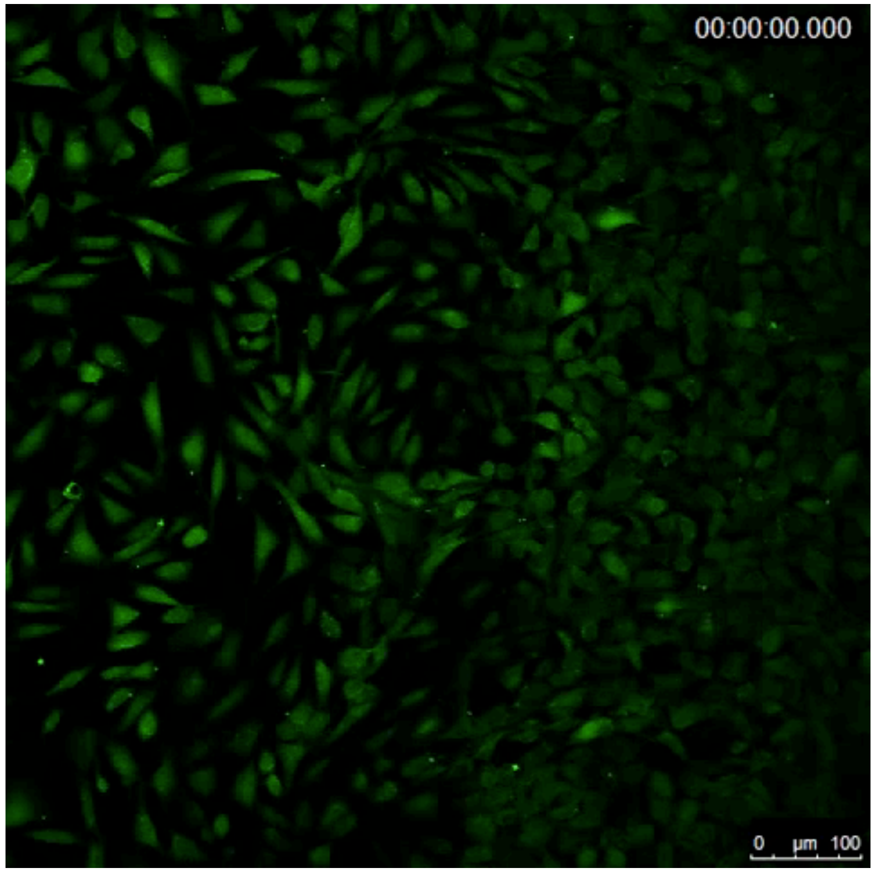
Glioblastoma tumor cells: Kravchenko-Balasha et al, *PNAS*, 2014; Goodhill, *Eur J Neurosci*, 1997; Miura & Tanaka, *Math Model Nat Phenom*, 2009; Marino & Giotta, *Nephrol Dial Tranpl*, 2007; Yen et al, *PLoS ONE*, 2011

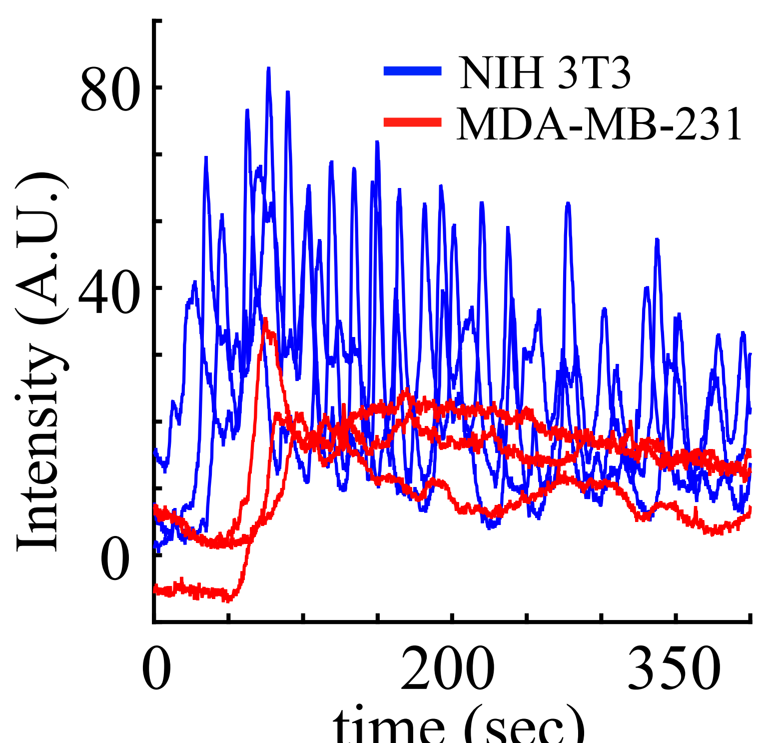
Epithelial cells: Ellison et al, *PNAS*, 2016; Lu et al, *Dev Biol*, 2008

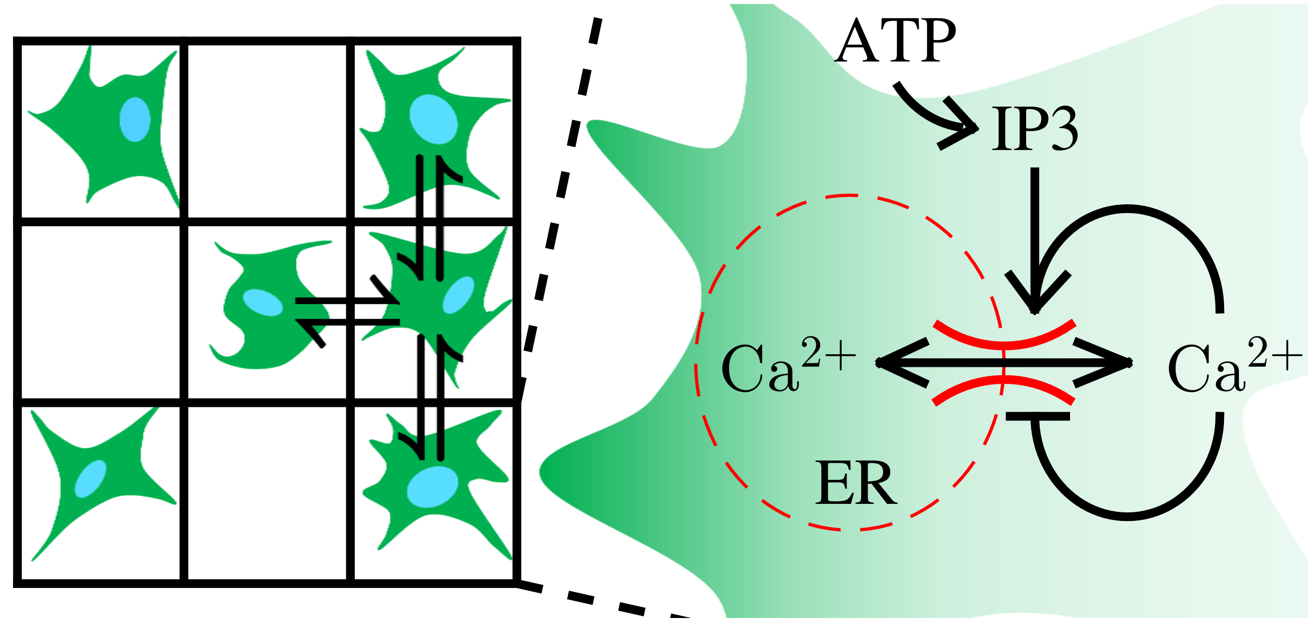
Mouse cells with gap junctions: Elfgang, et al, *J Cell Biol*, 1995

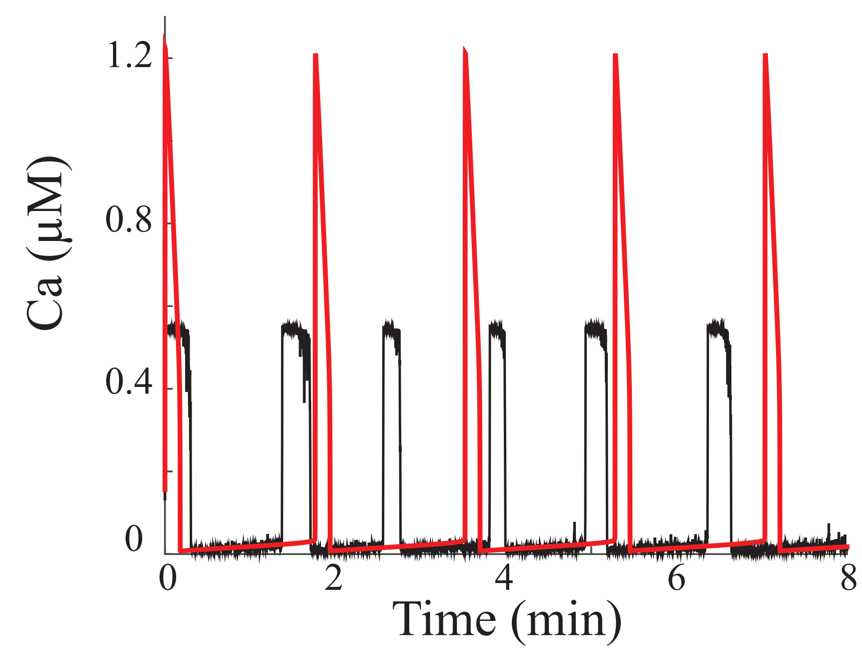
Fancher & Mugler, arXiv:1603.04108

Collective ATP sensing in fibroblasts



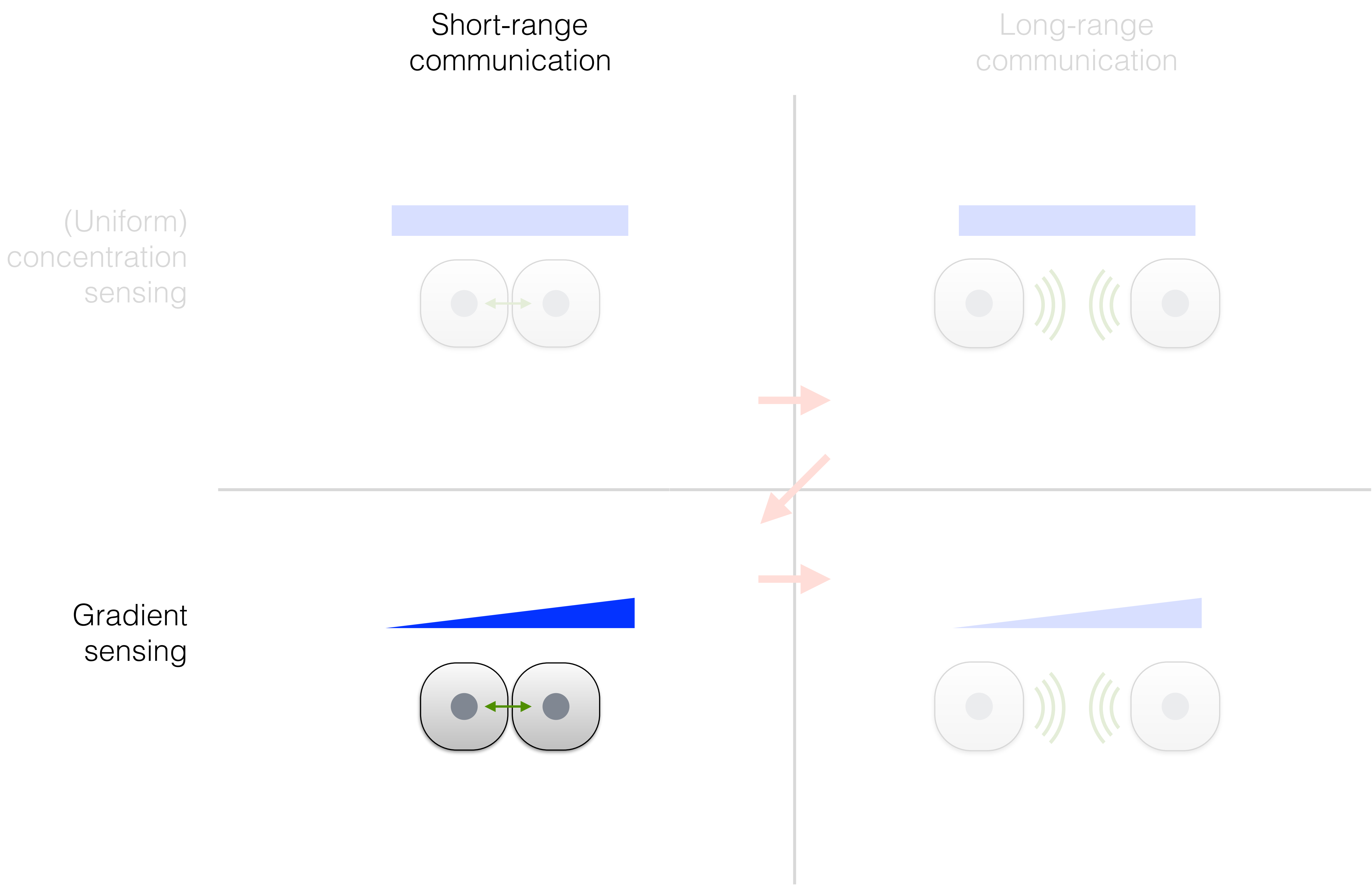




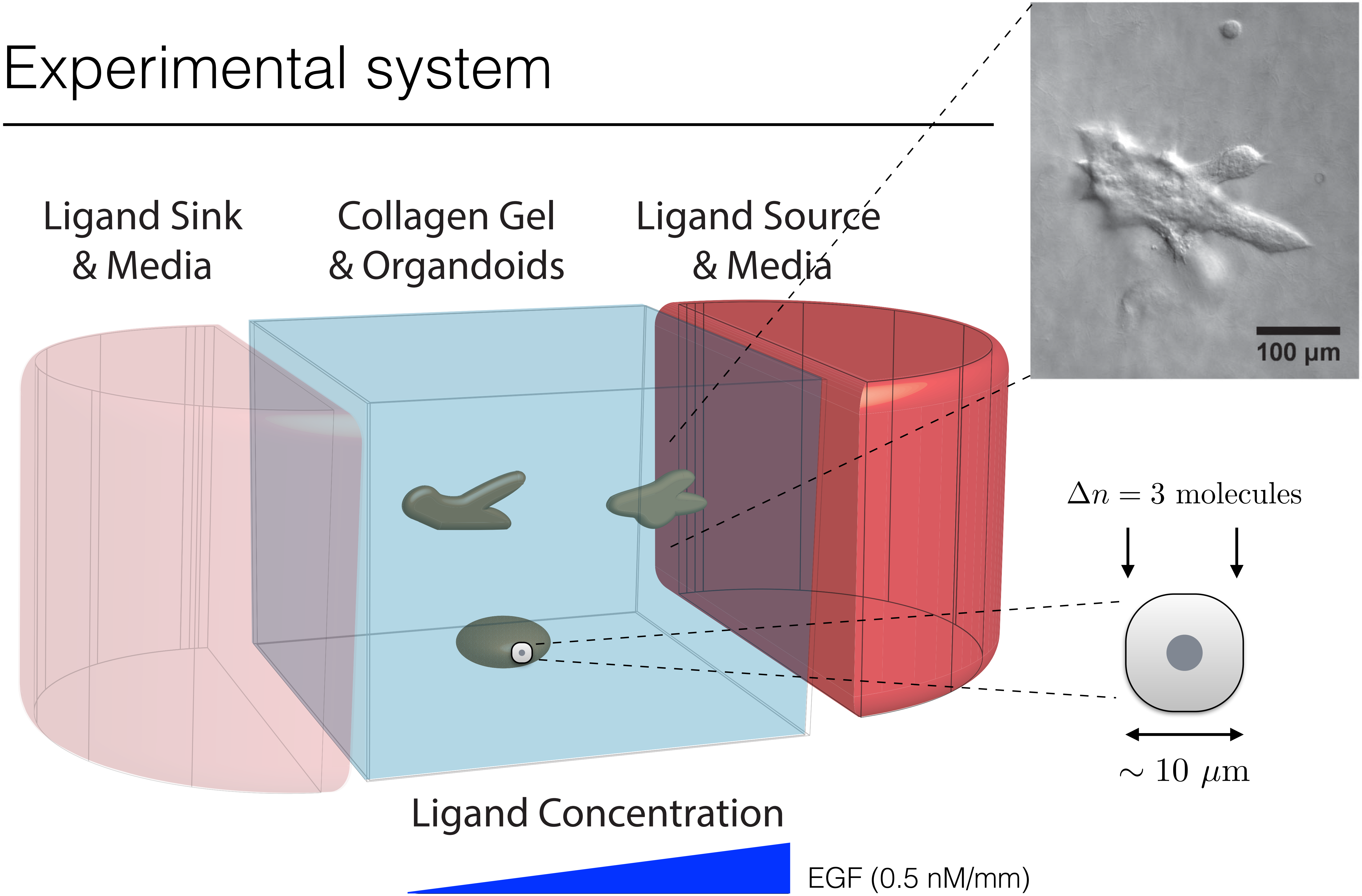


Potter*, Byrd*, Mugler, Sun, *PNAS*, 2016

Outline of this talk

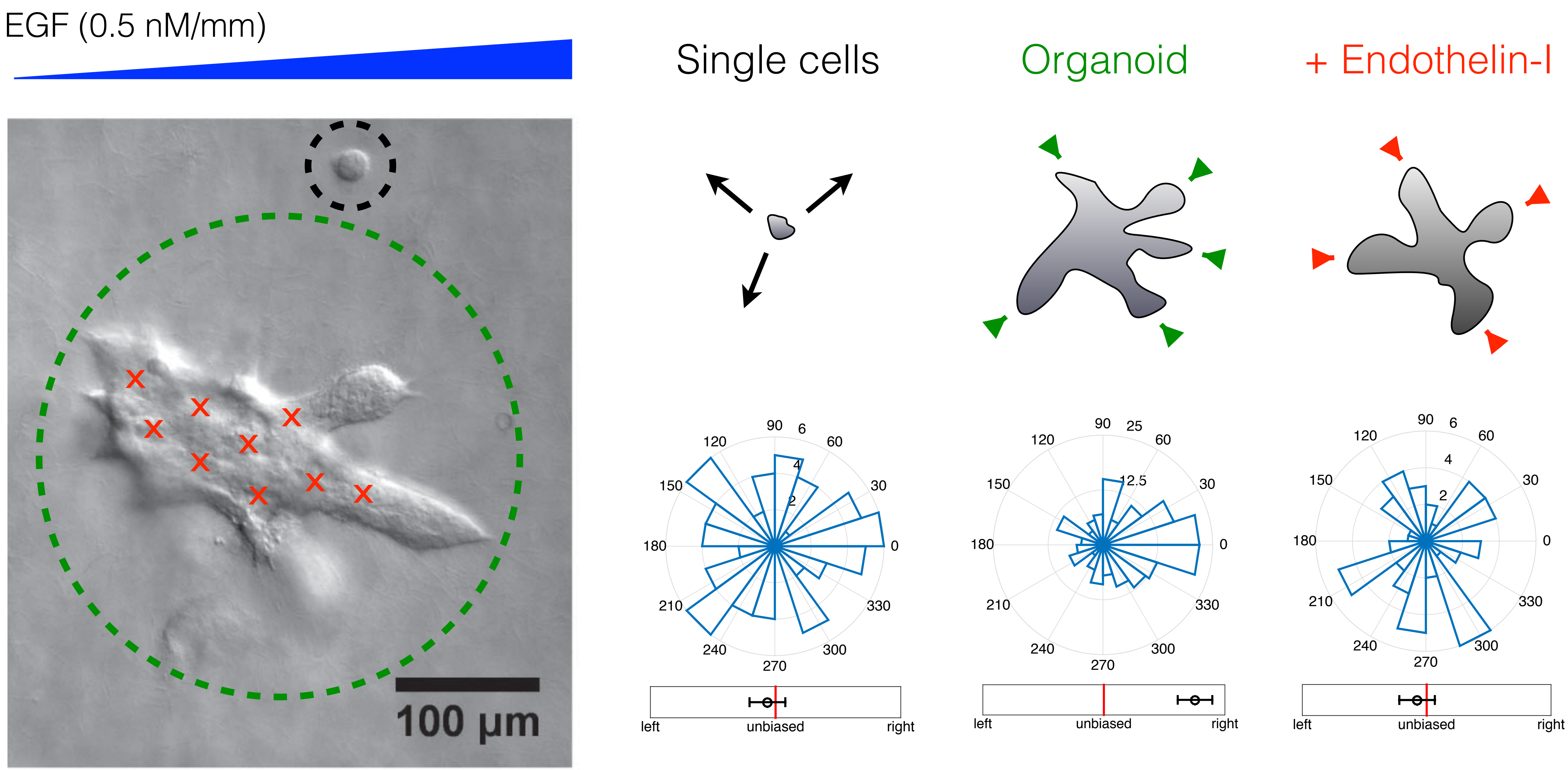


Experimental system



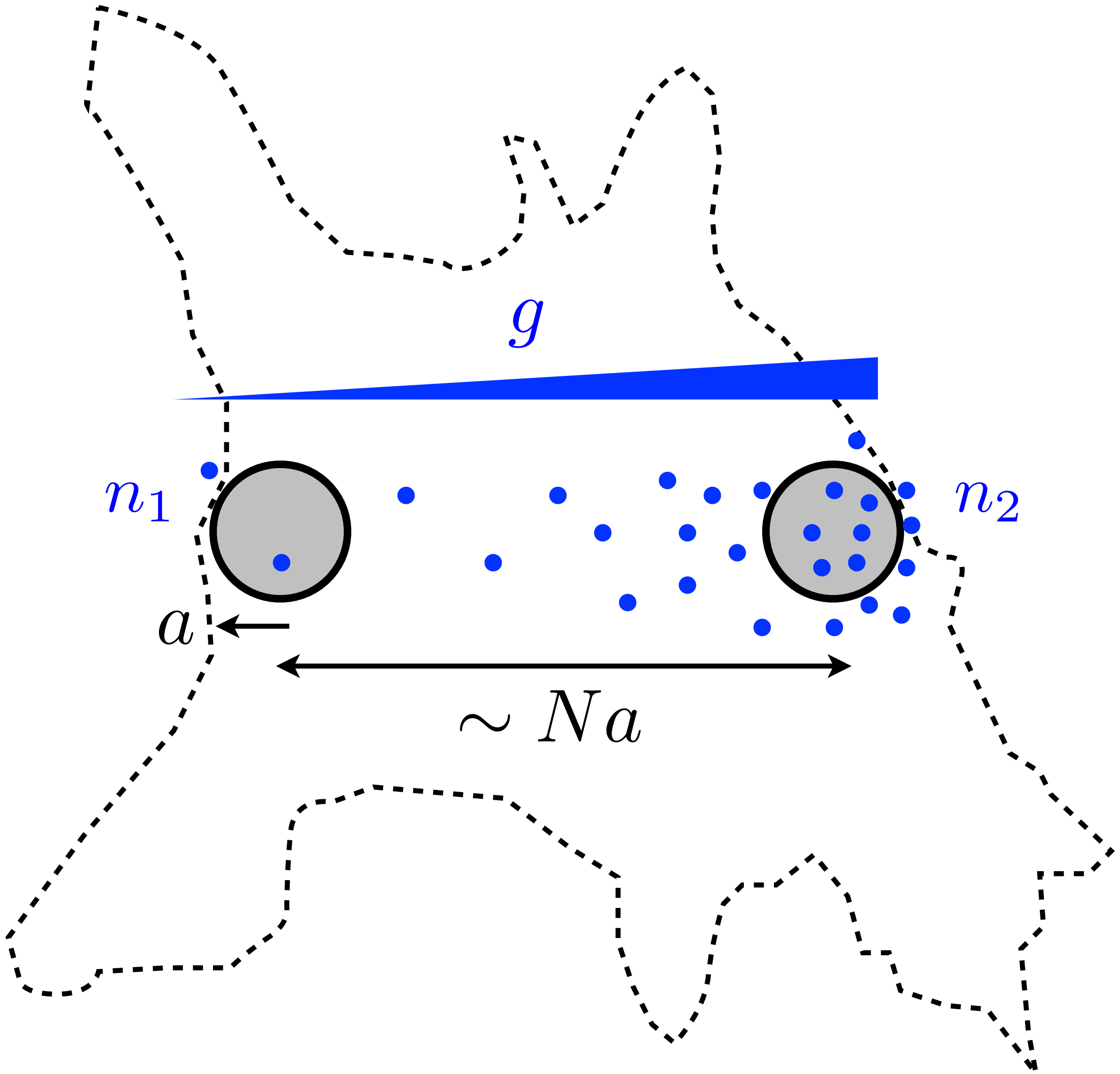
Ellison, Mugler, Brennan, et al, *PNAS*, 2016

Collective sensing



Ellison, Mugler, Brennan, et al, *PNAS,* 2016

Gradient sensing: Berg-Purcell estimate



Difference in molecule numbers:

$$\Delta\bar{n} \sim a^3 \Delta c = a^3 g(Na)$$

Diffusive fluctuations:

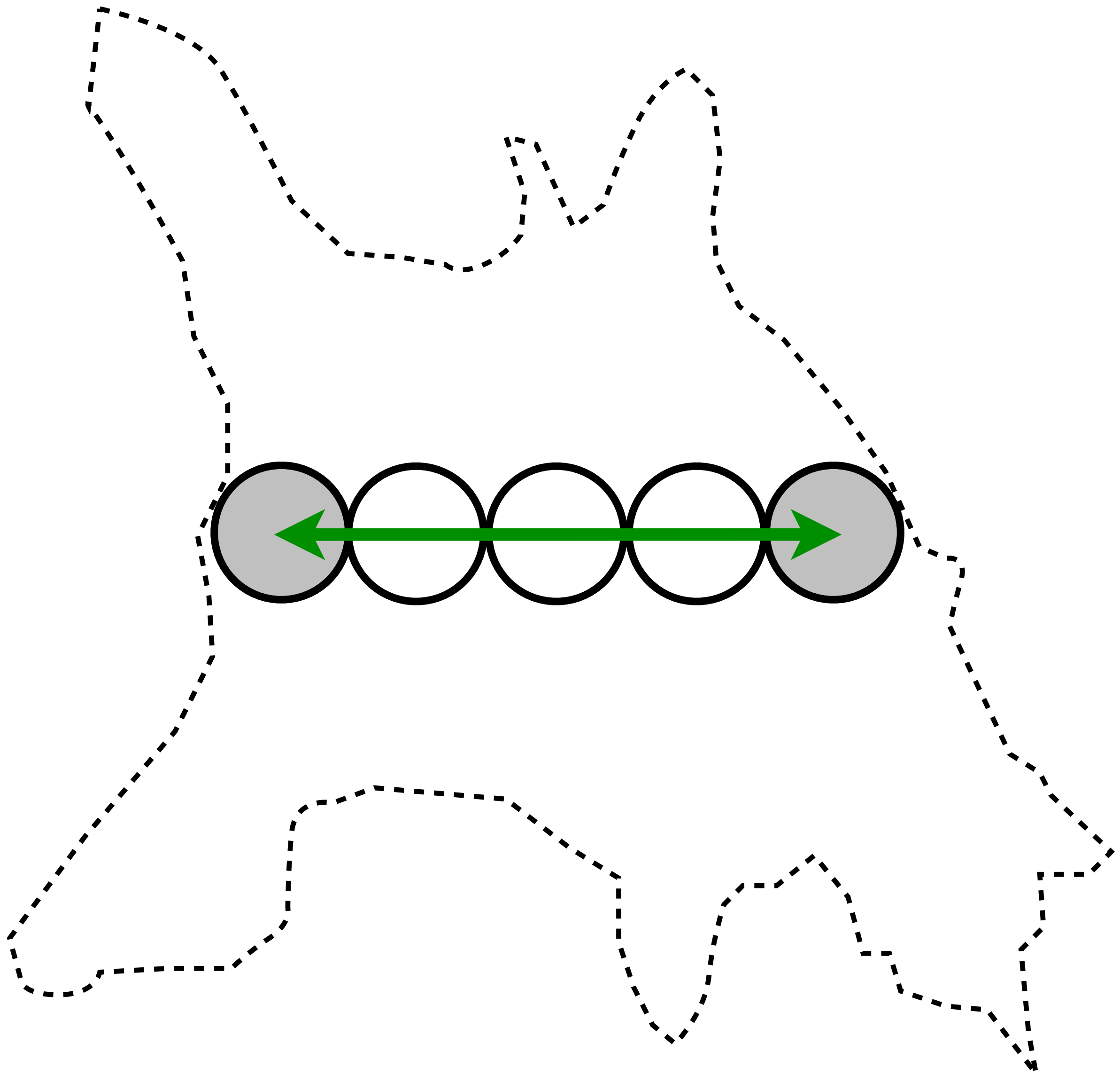
$$\sigma \sim \frac{a^3 c}{\sqrt{TDac}}$$

Error in gradient sensing:

$$\frac{\sigma_g}{g} = \frac{\sigma}{\Delta\bar{n}} \sim \frac{1}{gNa}\sqrt{\frac{c}{TDa}}$$

Mugler, Levchenko, Nemenman, *PNAS,* 2016

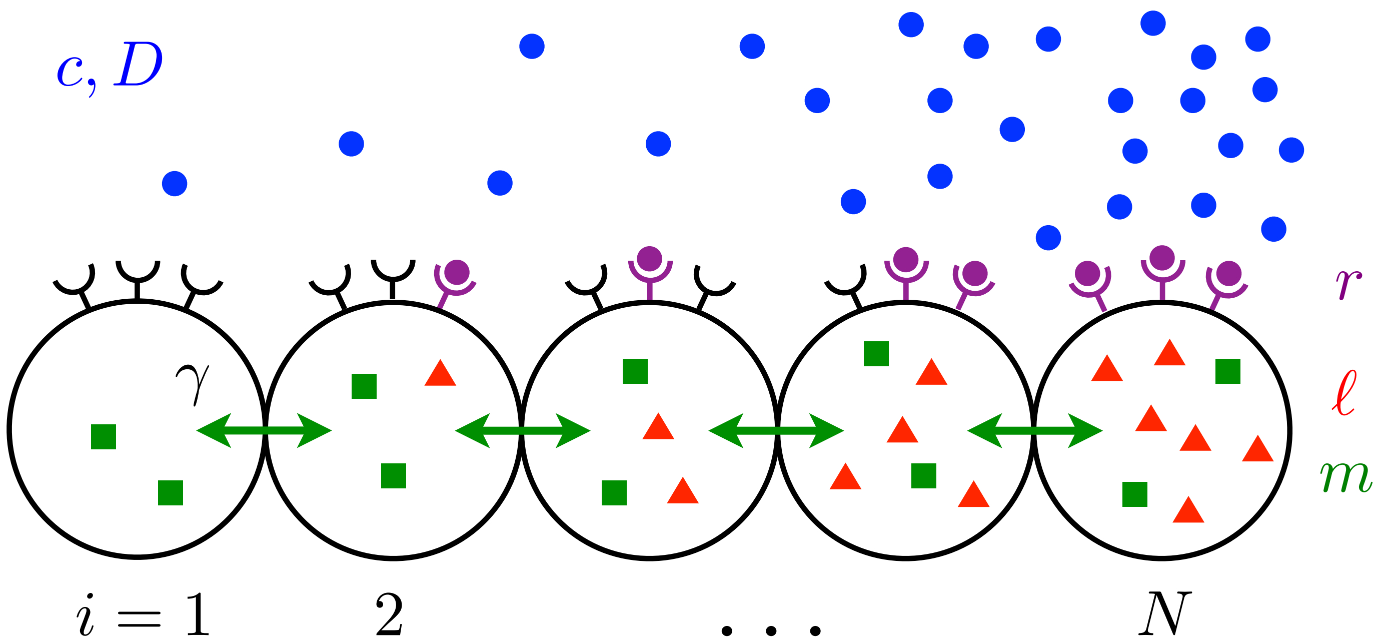
Gradient sensing: Berg-Purcell estimate

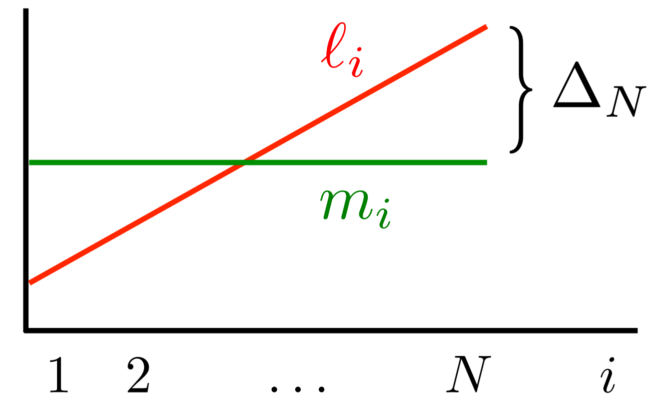


Compartments need to *communicate* to integrate information.

Mugler, Levchenko, Nemenman, *PNAS,* 2016

Gradient sensing w/ short-range communication





"Local excitation—global inhibition (LEGI)":

Levchenko & Iglesias, *Biophys J*, 2002

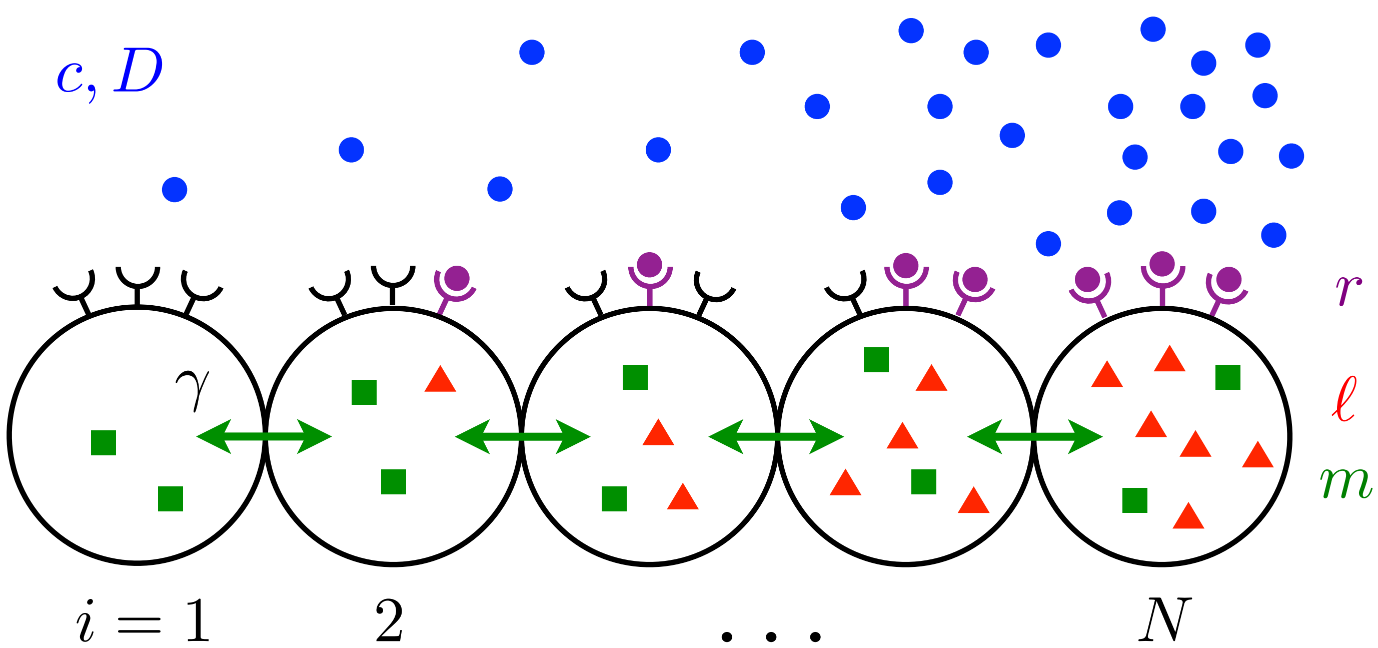
local species: ℓ_i → readout (edge cell): $\Delta_N = \ell_N - m_N$

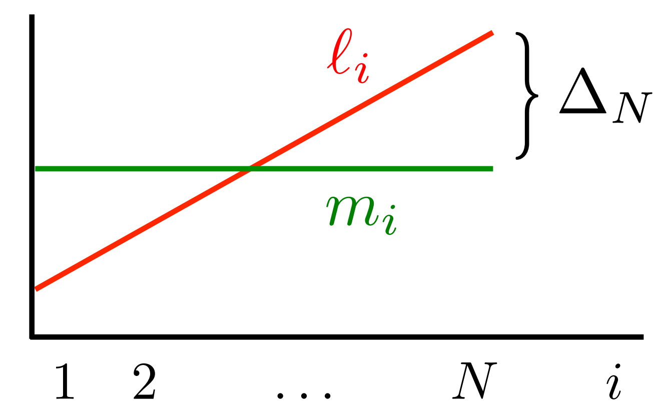
global species: m_i ⊣

For 2D, 3D systems, see:
Smith*, Fancher*, Levchenko, Nemenman, Mugler, *Phys Biol*, 2016

Mugler, Levchenko, Nemenman, *PNAS,* 2016

Gradient sensing w/ short-range communication





$$\dot{c} = D\nabla^2 c - \sum_{i=1}^{N} \delta(\vec{x} - \vec{x}_i)\dot{r}_i + \eta_c$$

$$\dot{r}_i = \alpha c(\vec{x}_i, t) - \mu r_i + \eta_{ri}$$

$$\dot{\ell}_i = \beta r_i - \nu \ell_i + \eta_{\ell i}$$

$$\dot{m}_i = \beta r_i - \nu m_i + \gamma(m_{i-1} + m_{i+1} - 2m_i) + \eta_{mi}$$

$$\Delta_N = \ell_N - m_N$$

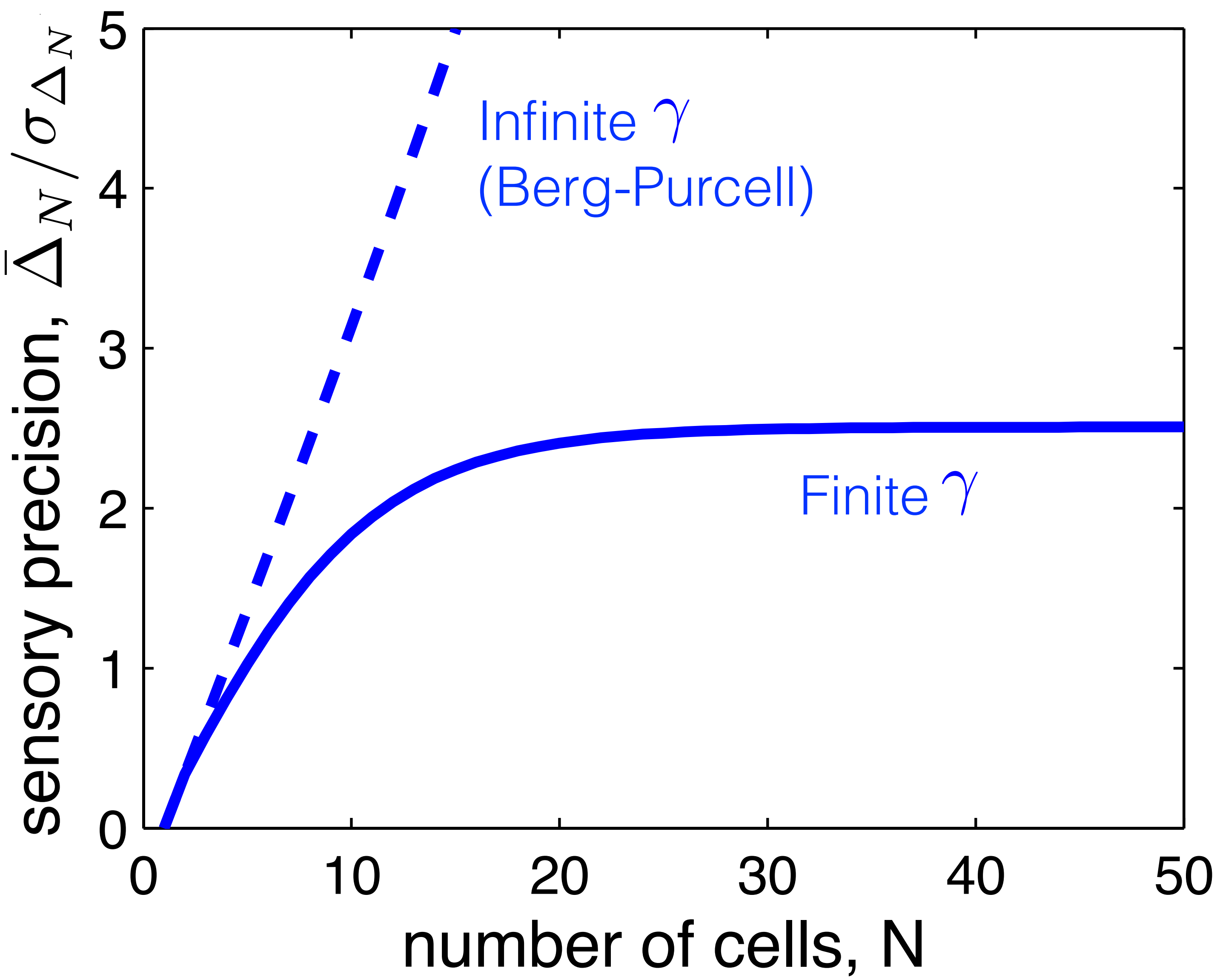
Readout noise:

$$\frac{\sigma^2_{\Delta_N}}{\bar{\Delta}^2_N}$$

For 2D, 3D systems, see:
Smith*, Fancher*, Levchenko, Nemenman, Mugler, *Phys Biol*, 2016

Mugler, Levchenko, Nemenman, *PNAS*, 2016

Finite communication bounds sensory precision

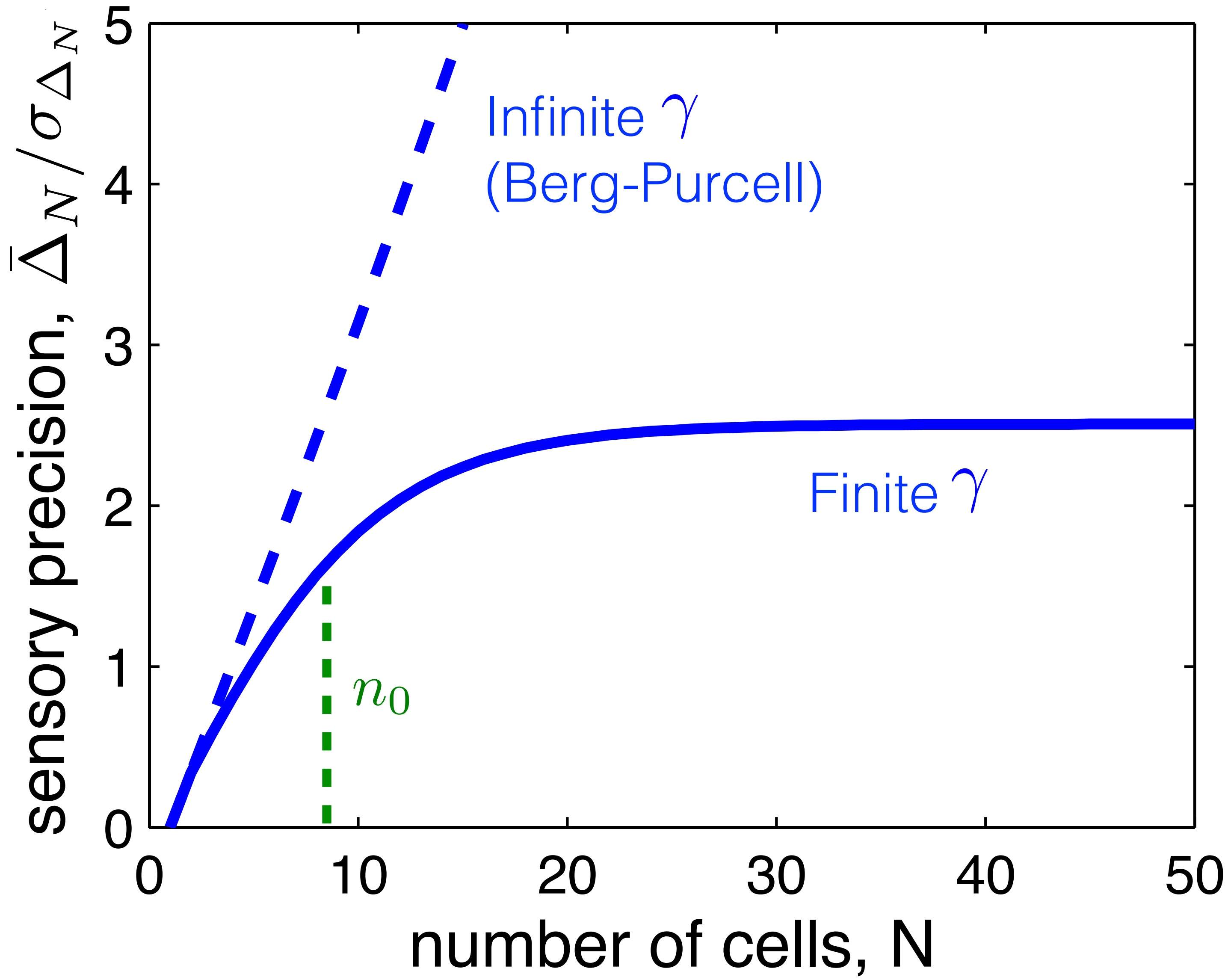


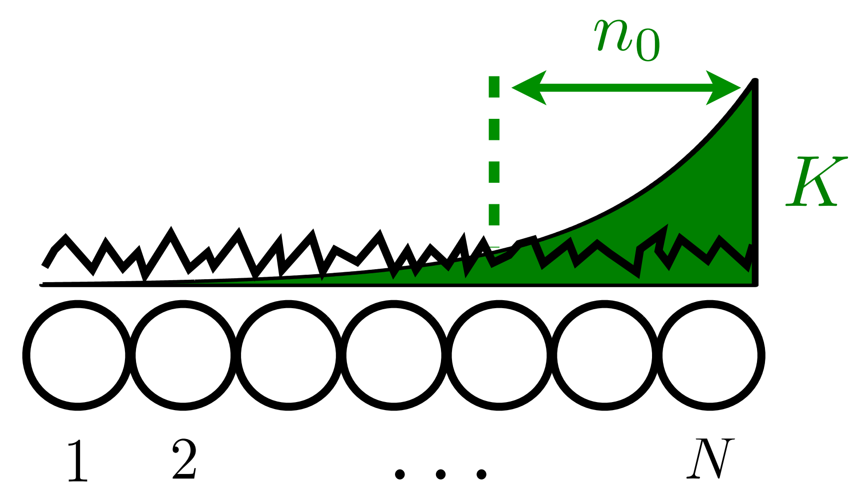
Beyond a certain size, there is no further benefit

Mugler, Levchenko, Nemenman, *PNAS*, 2016


peas
bees
knees
cheese
fleas?
katerawlings.com

Finite communication bounds sensory precision





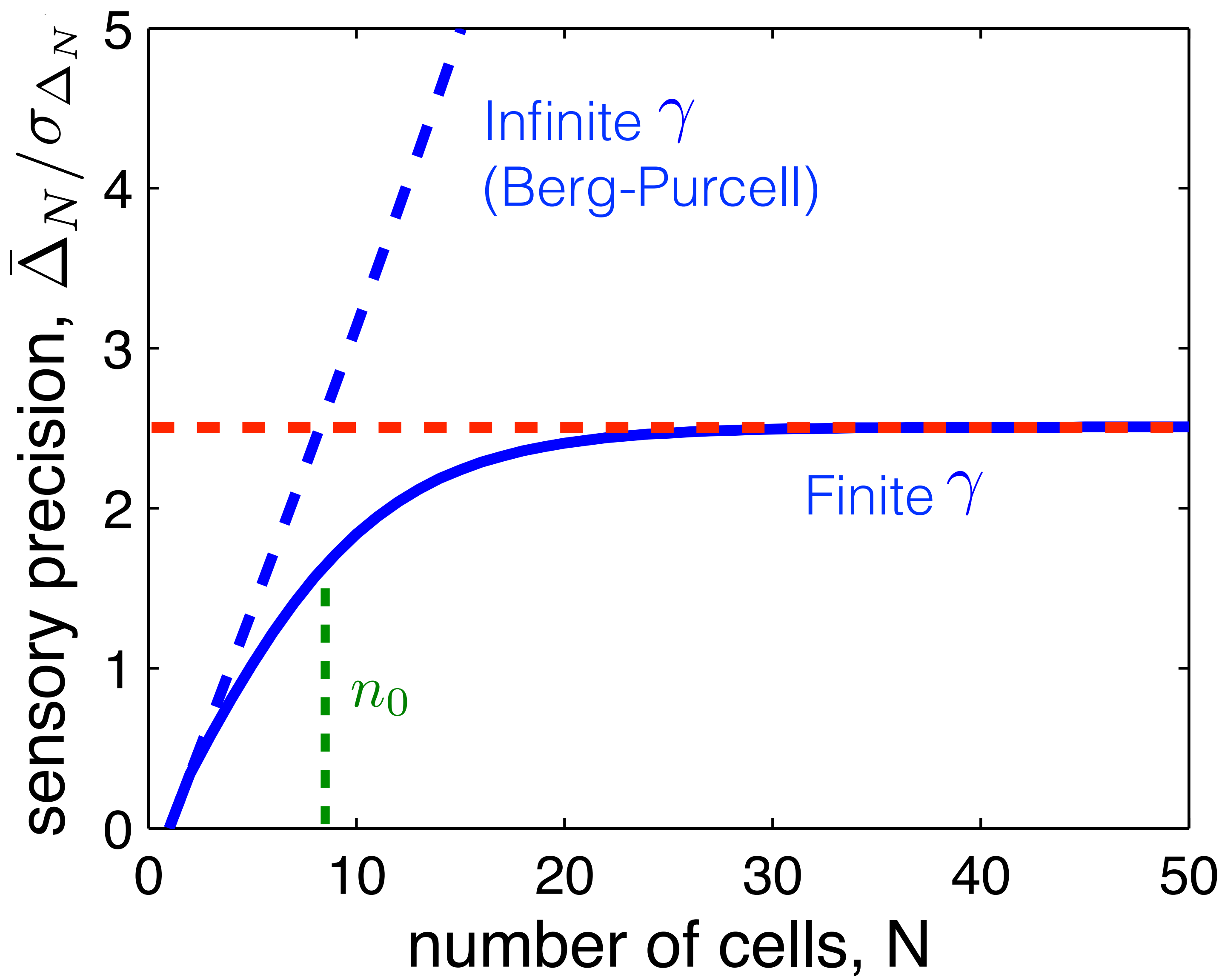
$$\bar{m}_N = \frac{\beta}{\nu} \sum_i K_i \bar{c}_{N-i}$$

$$n_0 = \sqrt{\gamma/\nu}$$

communication length scale

Mugler, Levchenko, Nemenman, *PNAS,* 2016

Finite communication bounds sensory precision



Berg-Purcell:

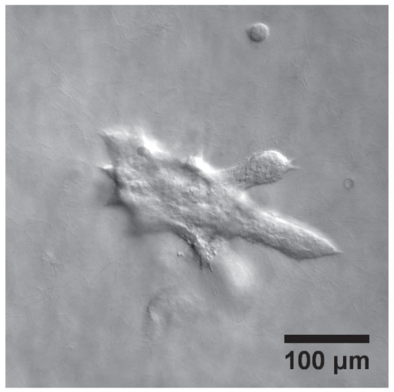
$$\frac{\sigma_g}{g} \sim \frac{1}{gNa}\sqrt{\frac{c}{TDa}}$$

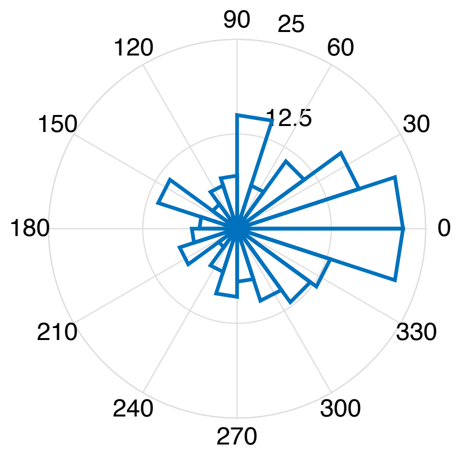
Minimal noise w/ communication:

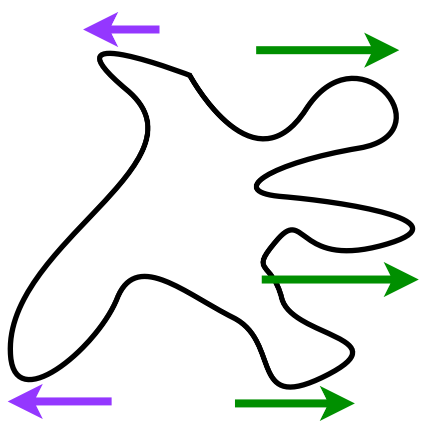
$$\frac{\sigma_{\Delta_N}}{\bar{\Delta}_N} \gtrsim \frac{1}{gn_0a}\sqrt{\frac{c_{\text{eff}}}{\pi TDa}}$$

Mugler, Levchenko, Nemenman, *PNAS,* 2016

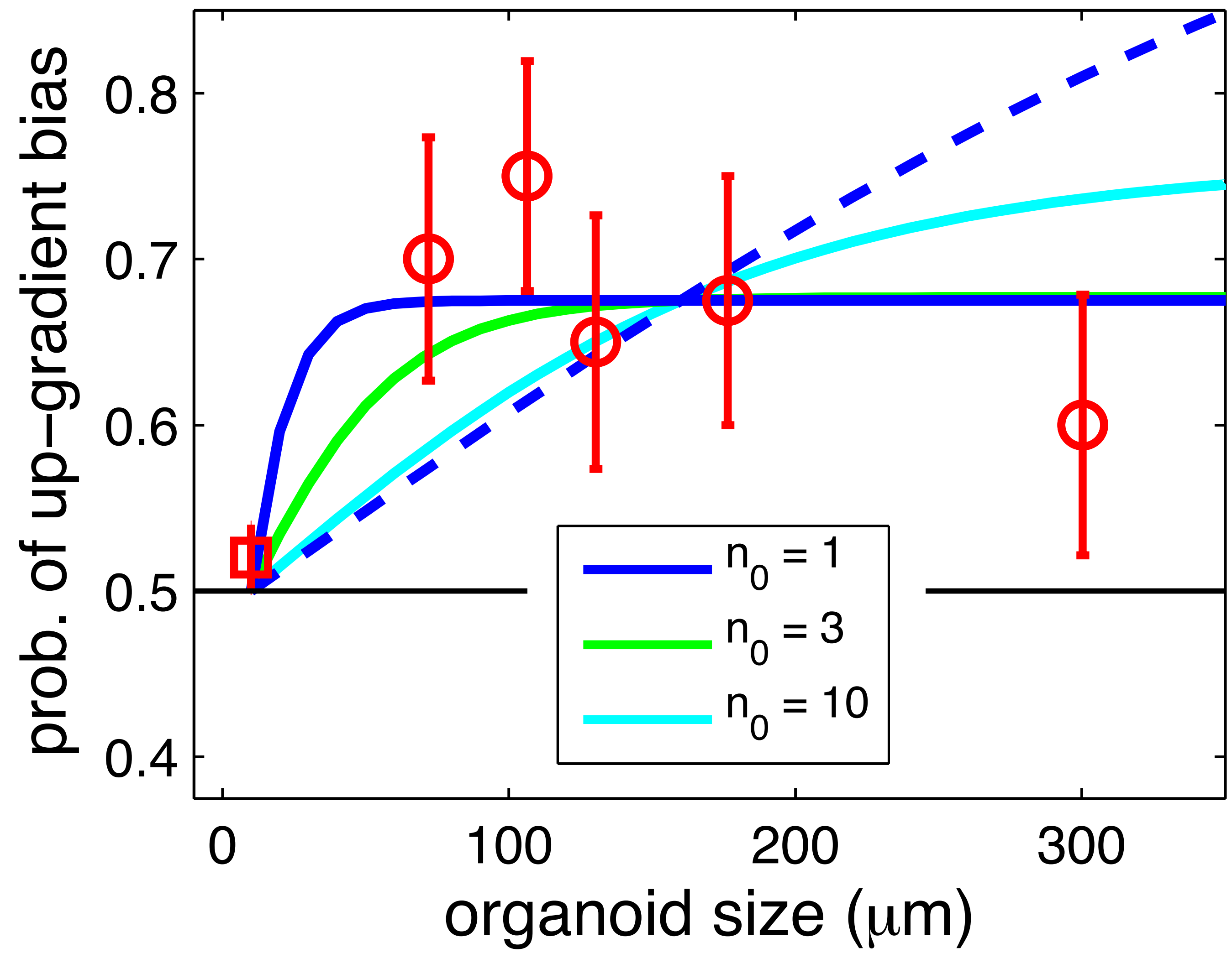
Comparing theory with experiment







$$P(L_U > L_D)$$

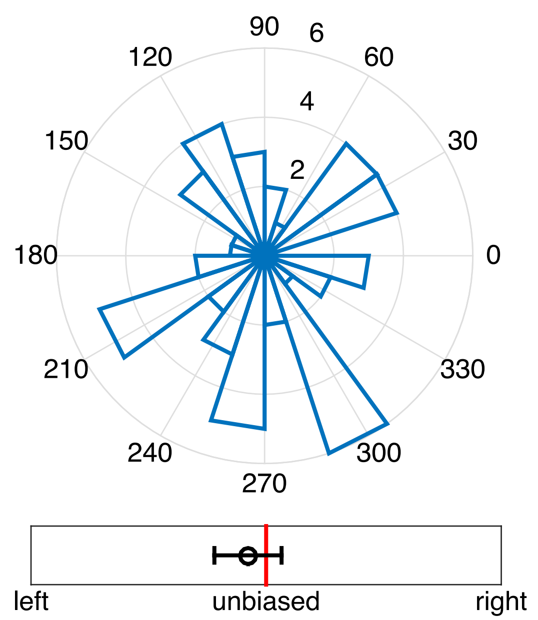


Communication length scale: $2.9 < n_0 < 4.2$ cells

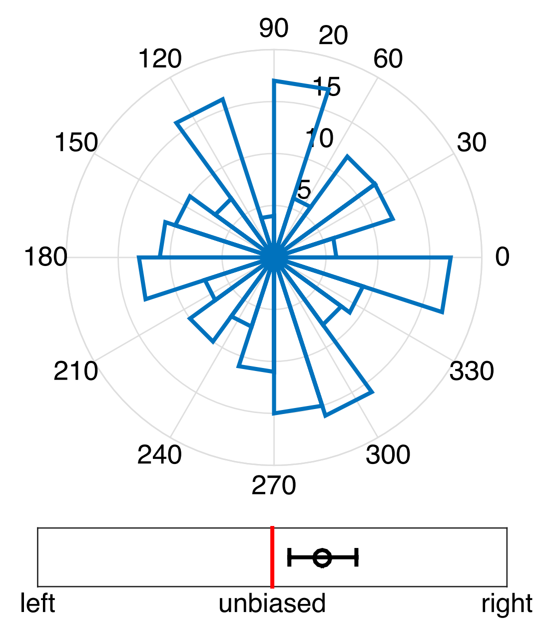
Ellison, Mugler, Brennan, et al, *PNAS*, 2016

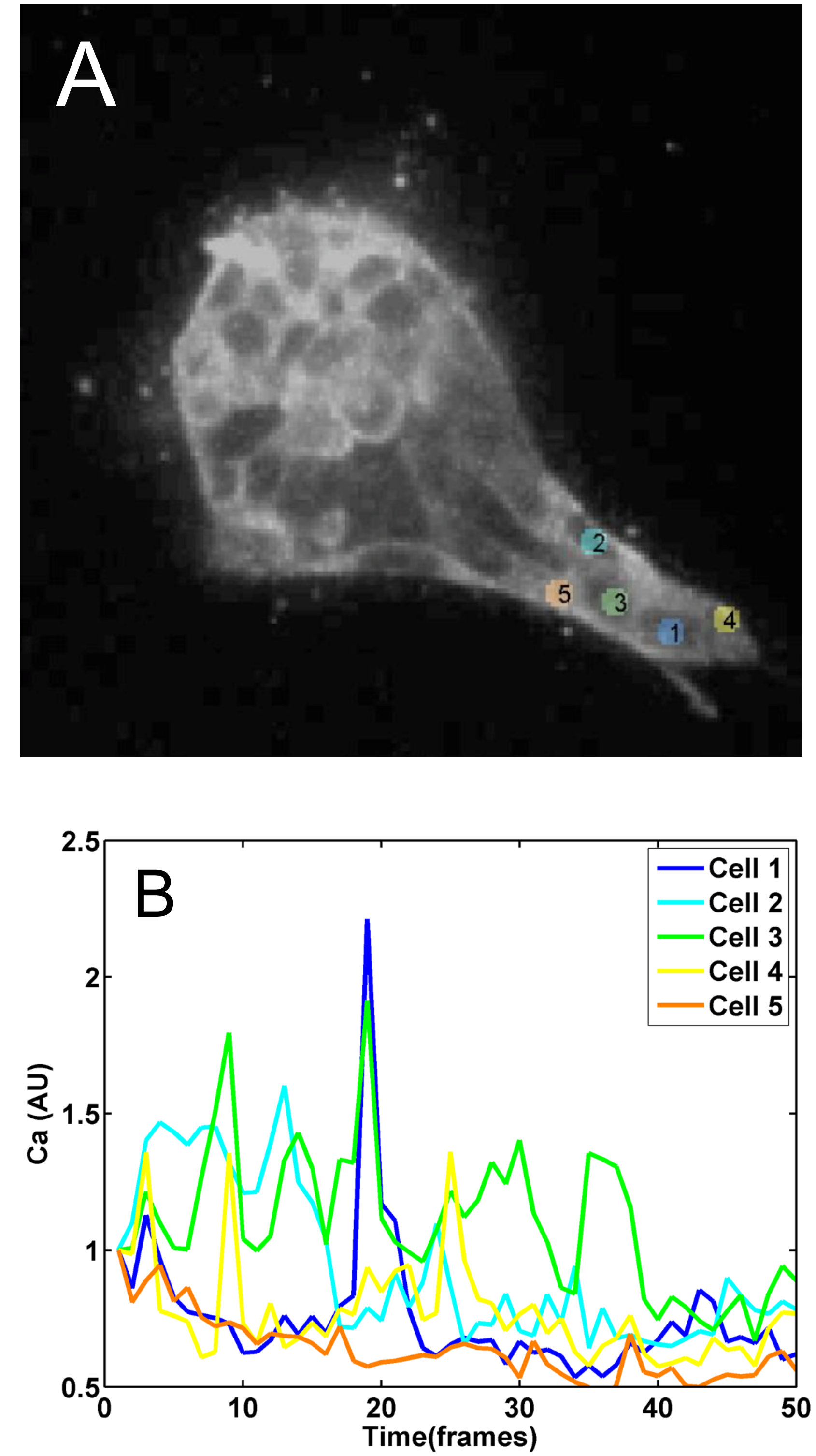
What is the communication molecule?

Gap-junction blocker:
50 nM Endothelin-I



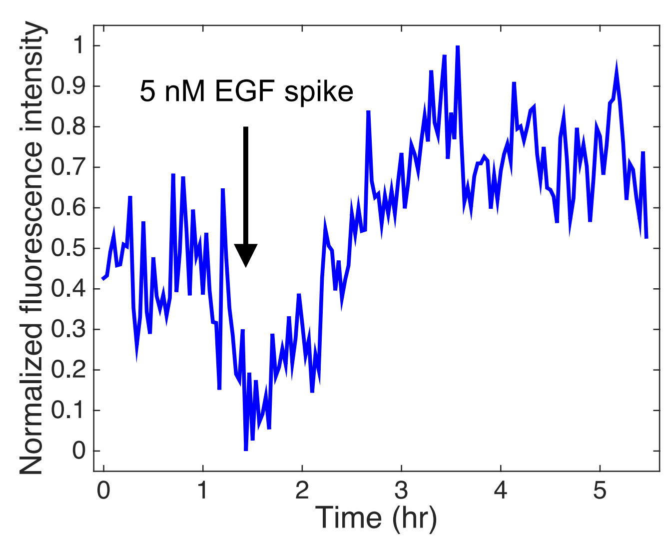
Calcium depletion:
100 nM Thapsigargin





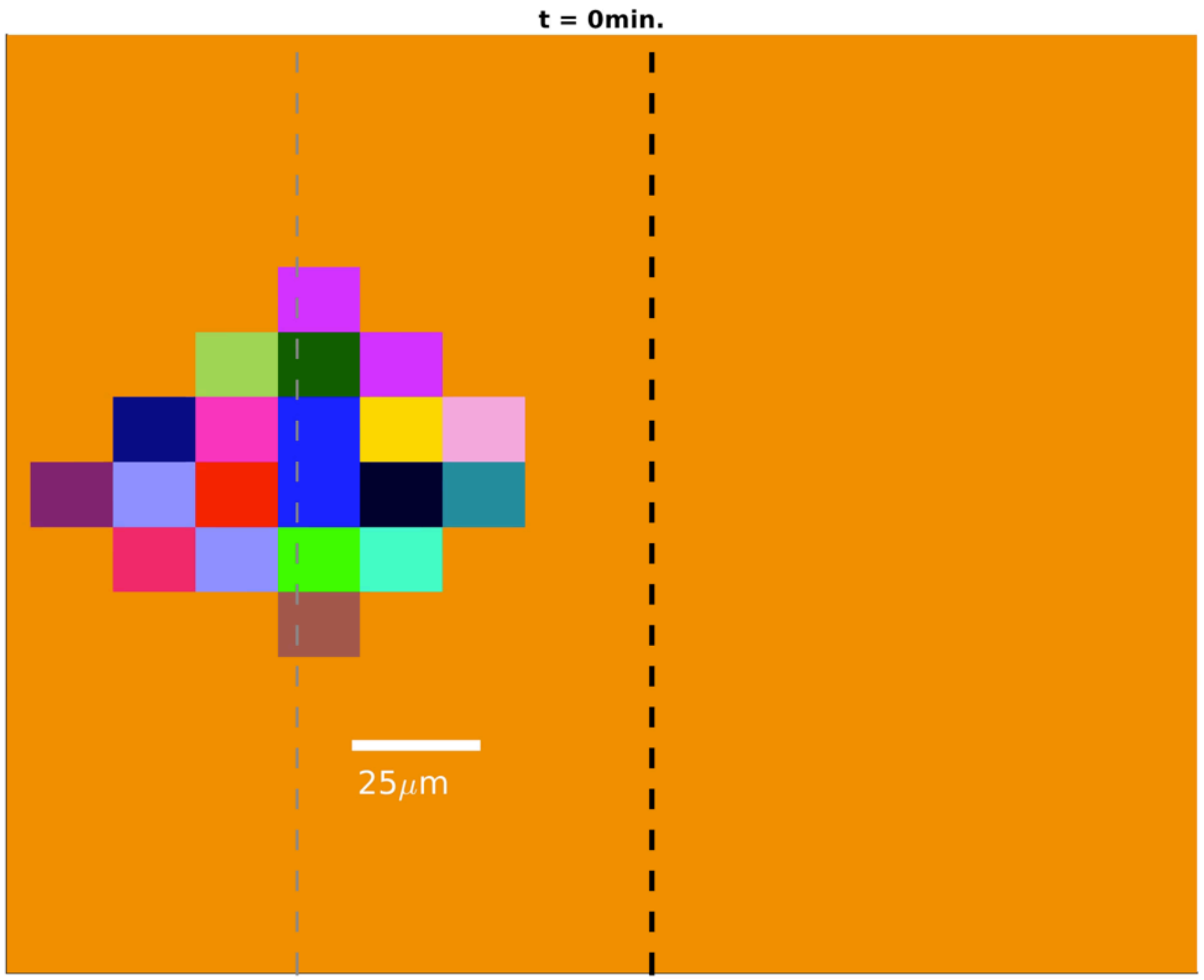
Same for:

- 50 μM Carbenoxolone
- 50 μM Flufenamic acid
- 0.5 mM Octanol

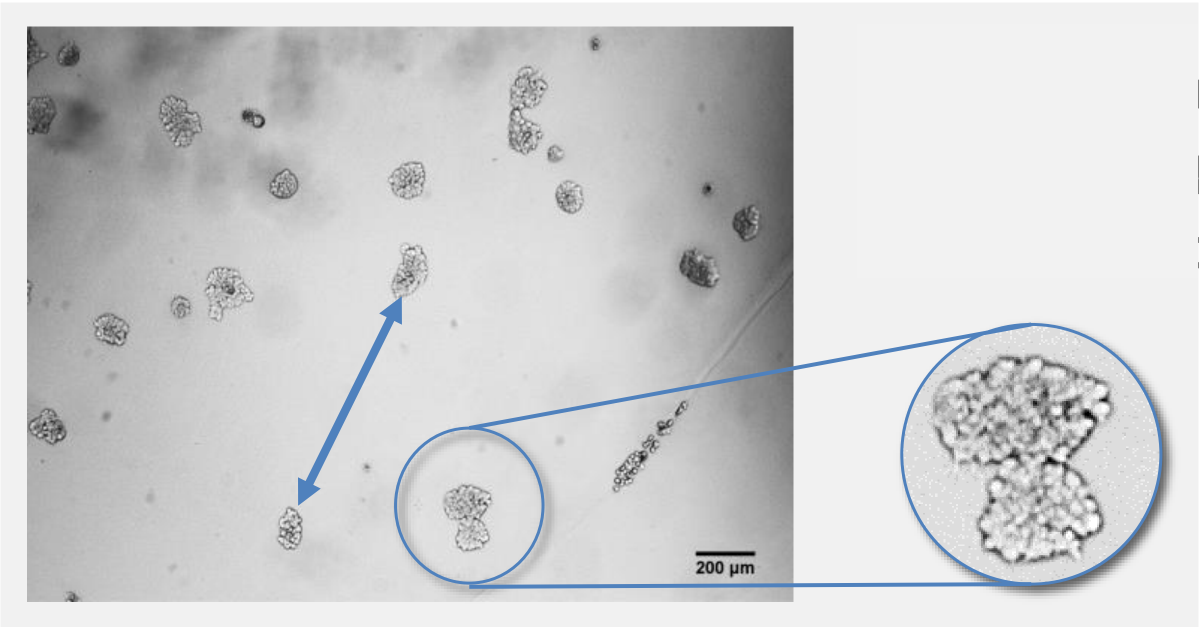


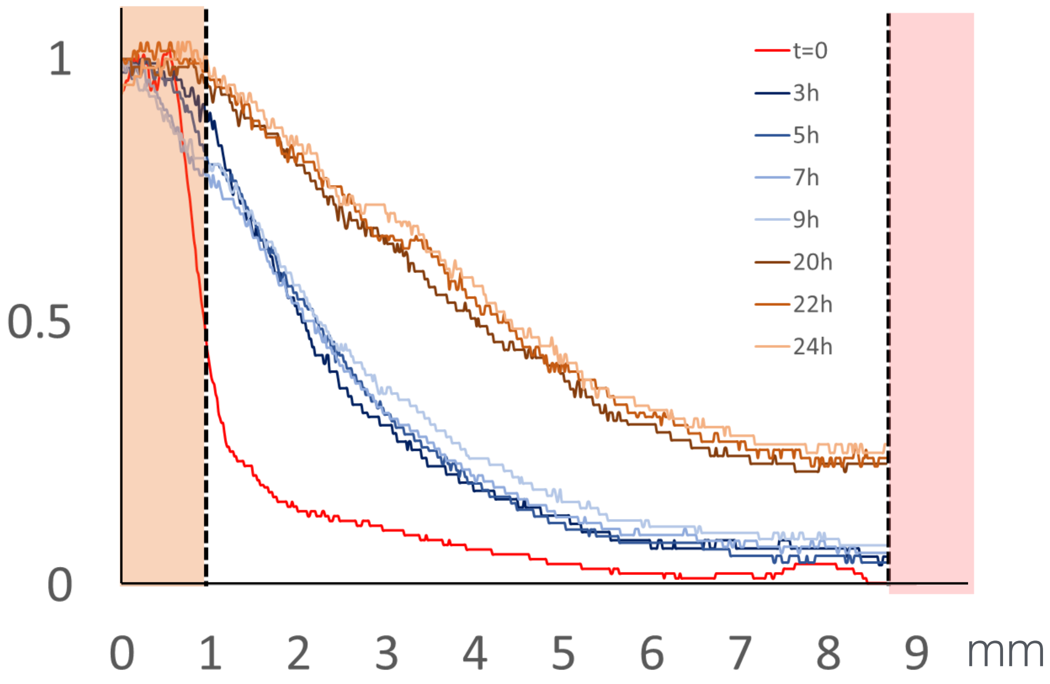
Ellison, Mugler, Brennan, et al, *PNAS,* 2016

Collective cell migration



Current work w/ Bumsoo Han, Purdue:



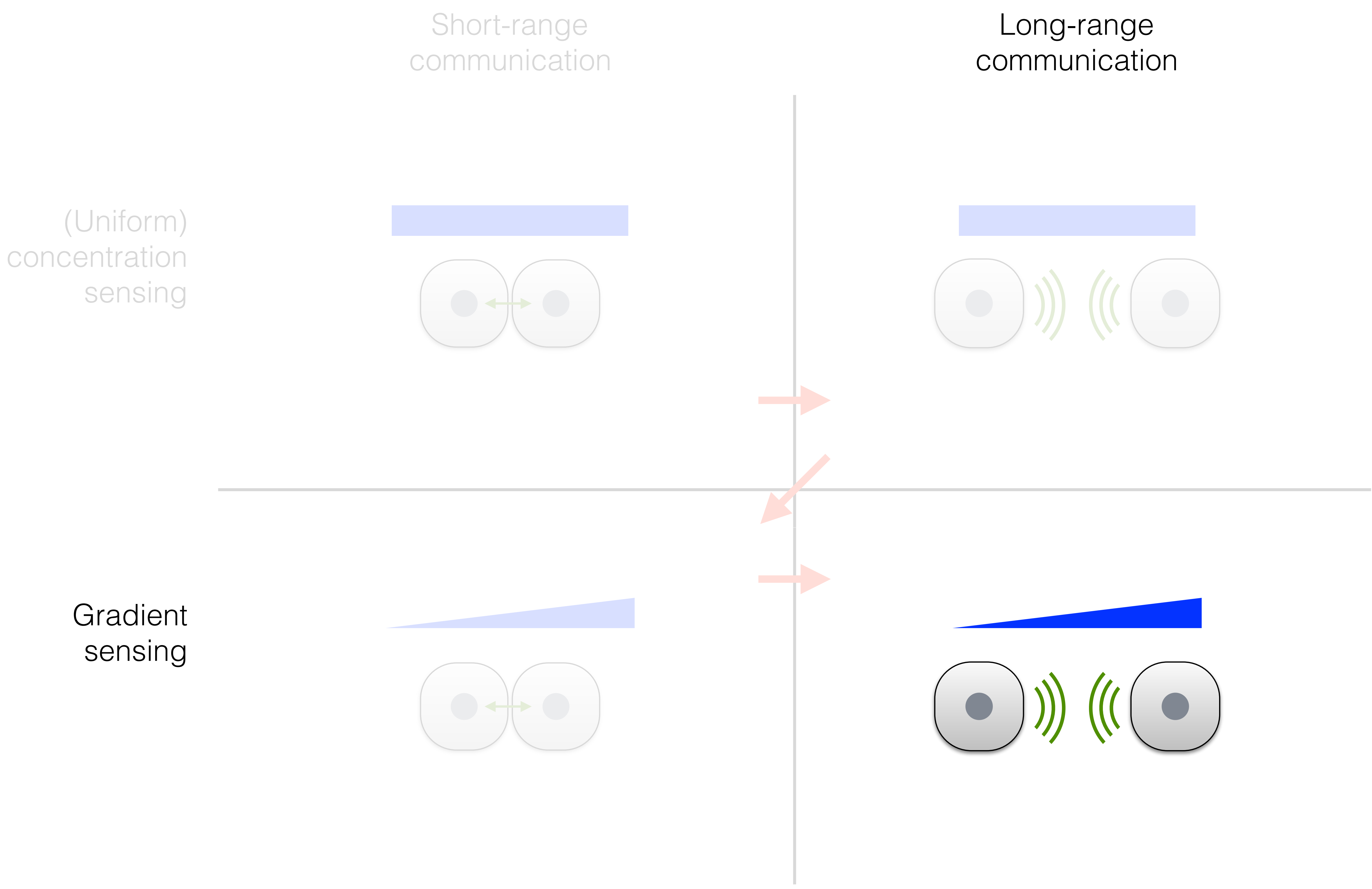


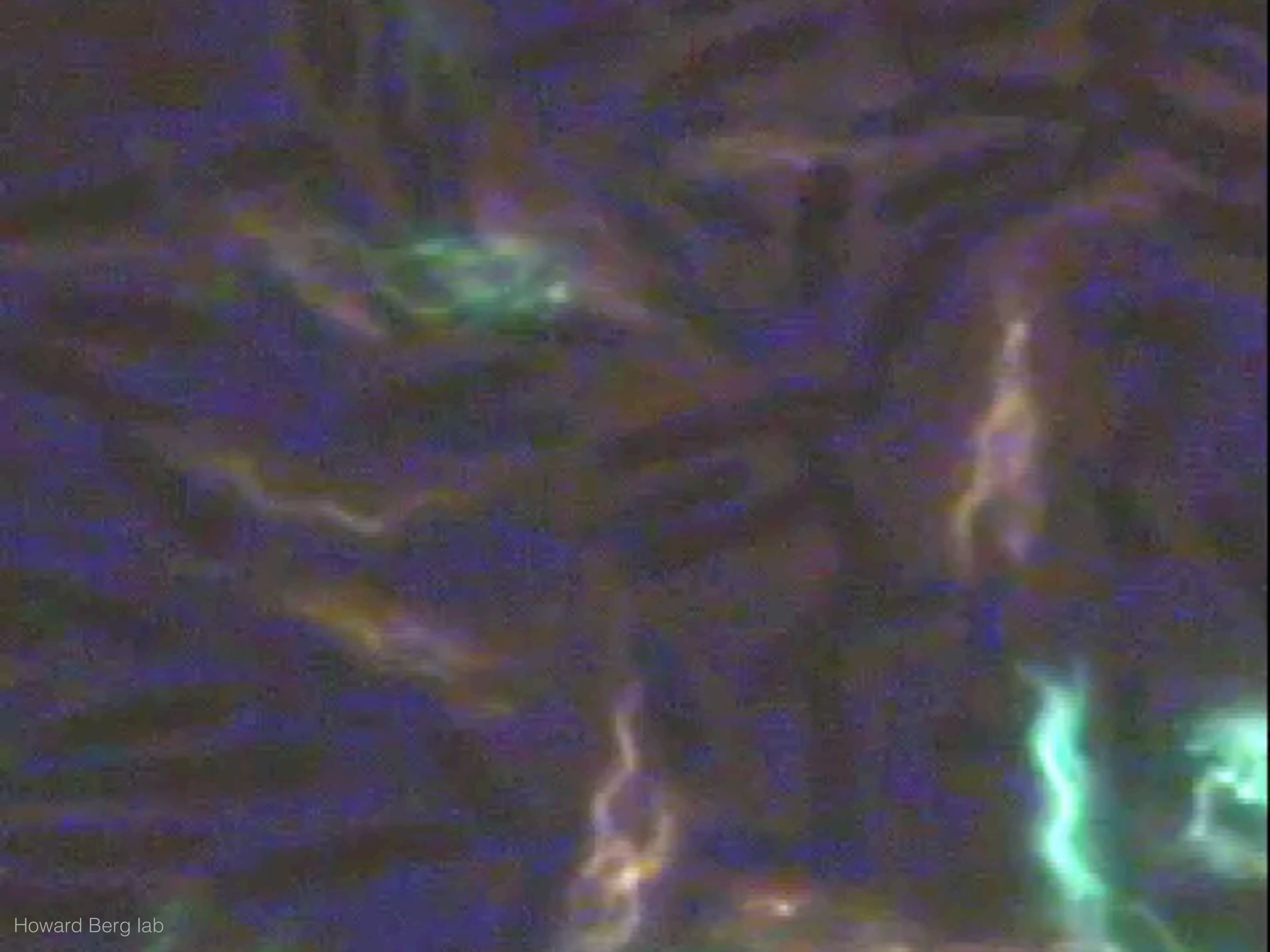
Cellular Potts model:

$$U = \sum_{\langle x,x' \rangle} J_{\sigma(x),\sigma(x')} + \lambda \sum_i \delta A_i^2$$

Varennes, Han, Mugler, *Biophys J*, 2016

Outline of this talk





Howard Berg lab

Summary

- Simple models provide powerful bounds on biological information processing
- Communication allows collective systems to outperform single cells
- Long-range communication can reduce measurement correlations, leading to optimal cell separations
- Communication is ultimately imperfect, which fundamentally limits sensory precision

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Bumsoo Han
Nicolò Michelusi

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Smith*, Fancher*, Levchenko, Nemenman, Mugler, *Phys Biol*, 2016

Fancher, Mugler, arXiv:1603.04108

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