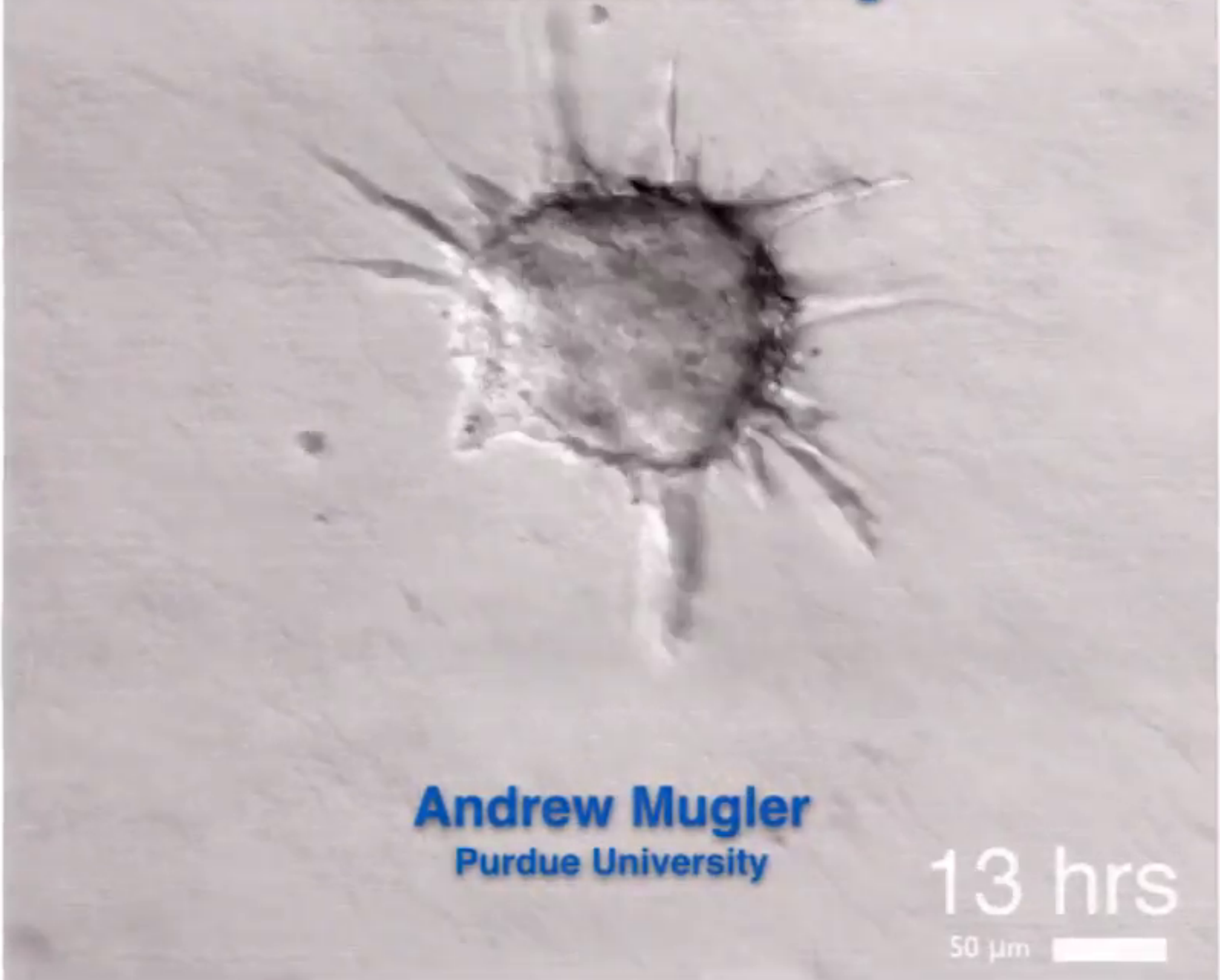
Fundamental limits to the precision of multicellular sensing



Andrew Mugler
Purdue University

Cheung et al,
Cell, 2013

Fundamental limits to the precision of multicellular sensing

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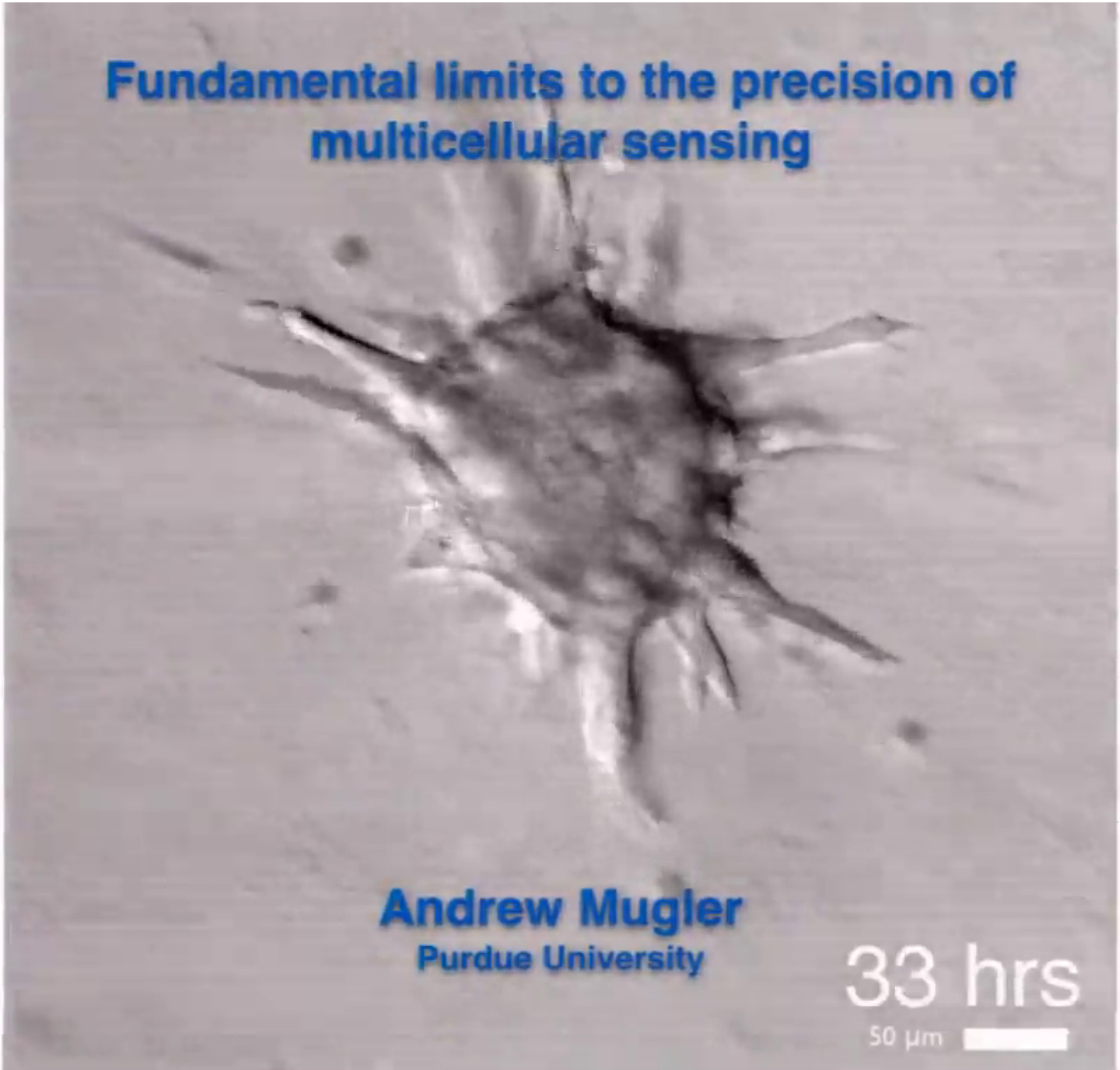
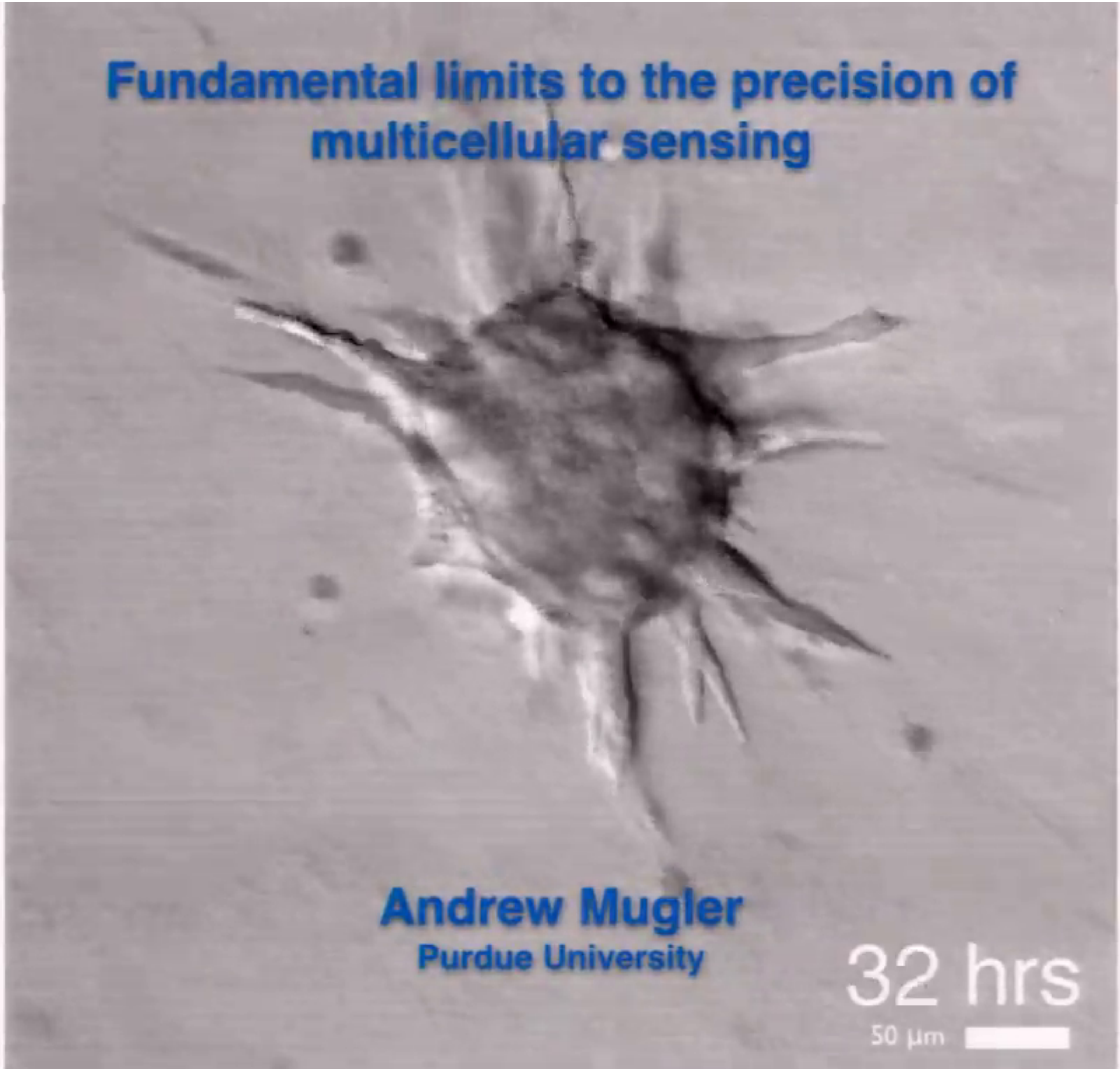
Purdue University



Cheung et al.
Cell 2013

Fundamental limits to the precision of multicellular sensing



Andrew Mugler

Purdue University

Cheung et al, *Cell.* 2013

Fundamental limits to the precision of multicellular sensing

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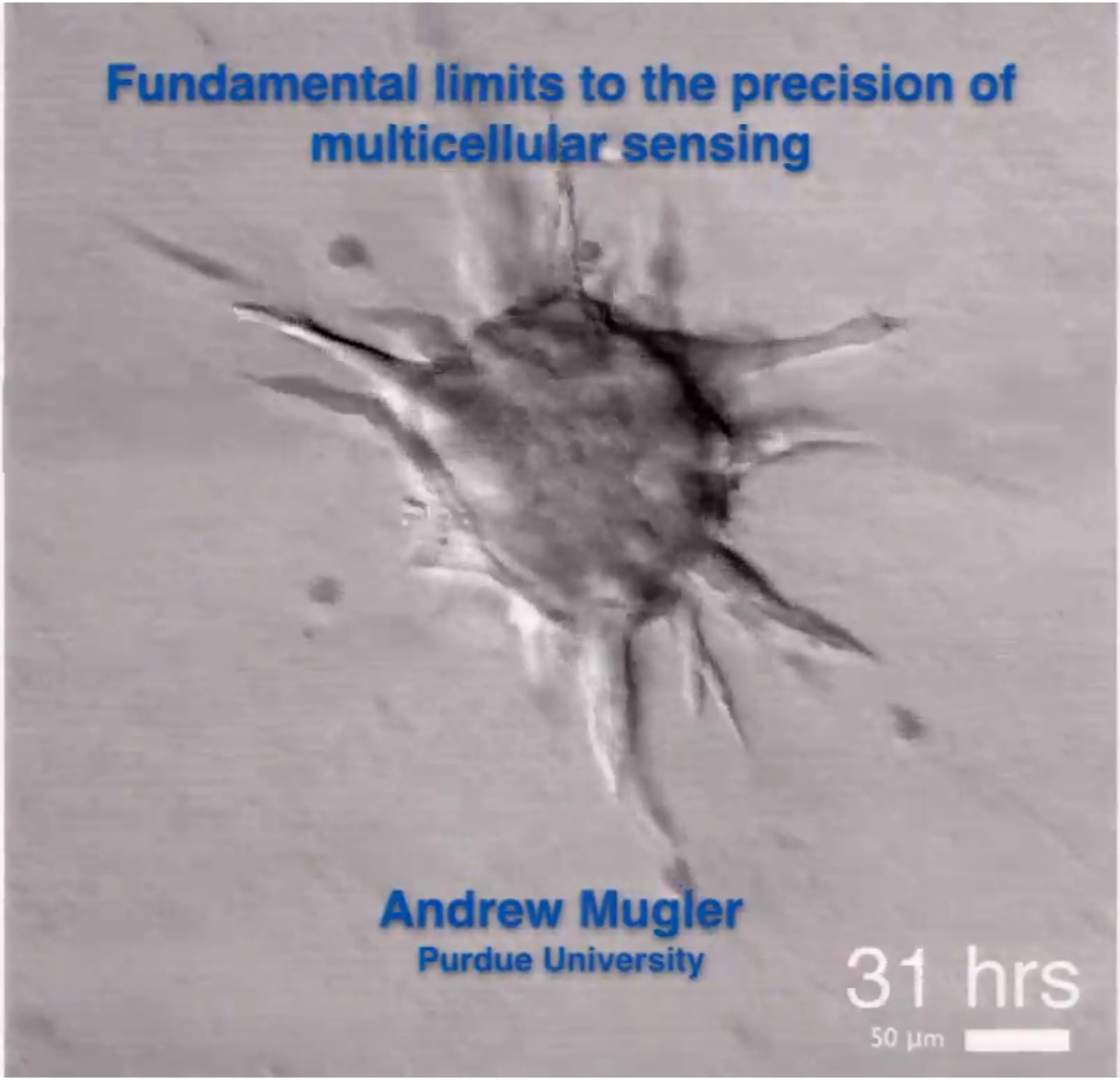
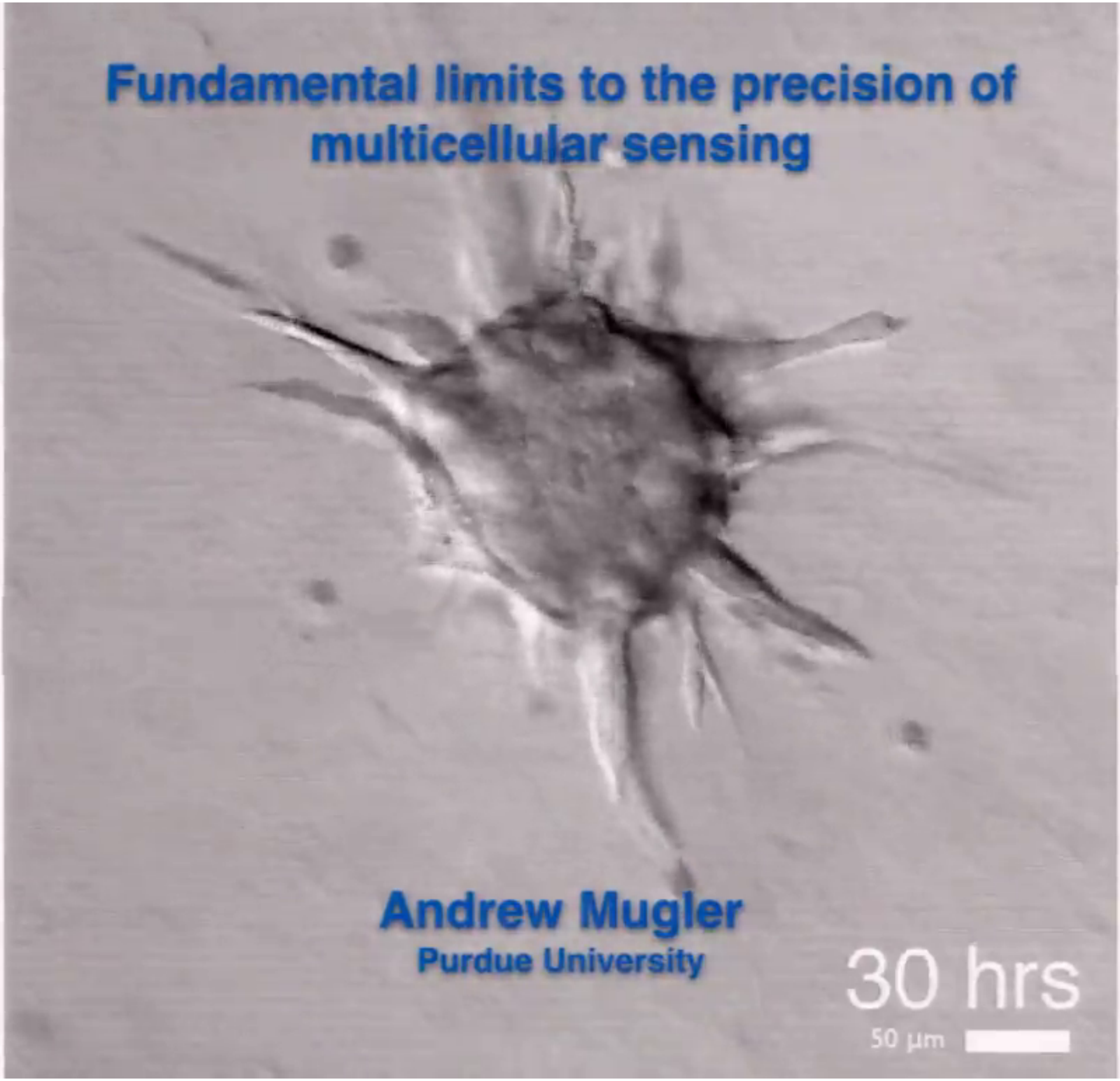
Purdue University



Cheung et al, *Cell*, 2013

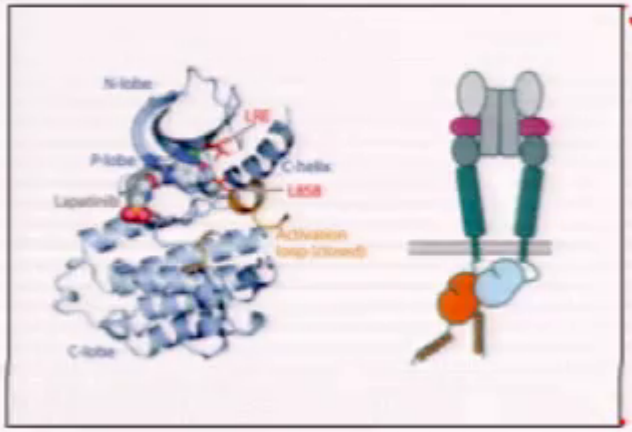
Fundamental limits to the precision of multicellular sensing

Andrew Mugler
Purdue University



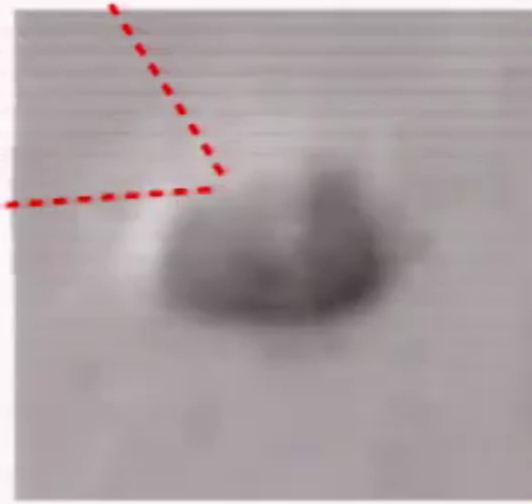
Cheung et al.,
Cell, 2013

Life is multi-scale



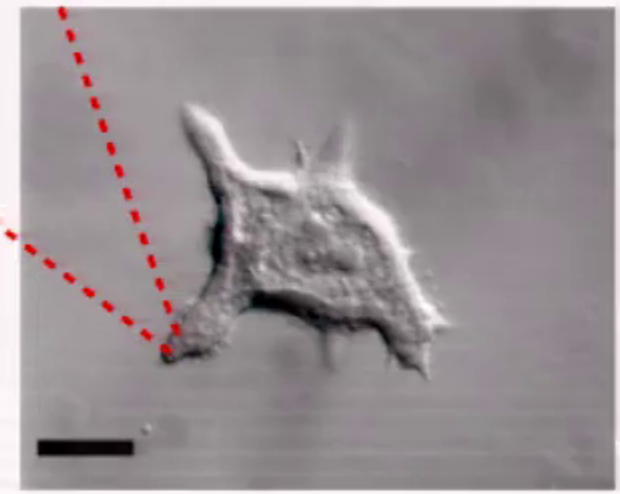
da Cunha Santos et al. *Ann Rev Pathol Mech Dis.* 2011

molecular
nm

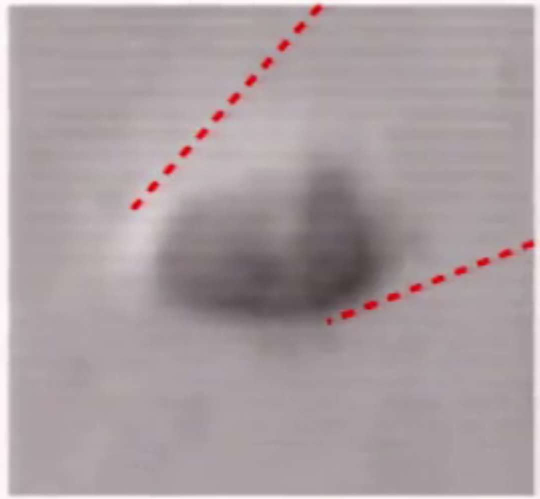


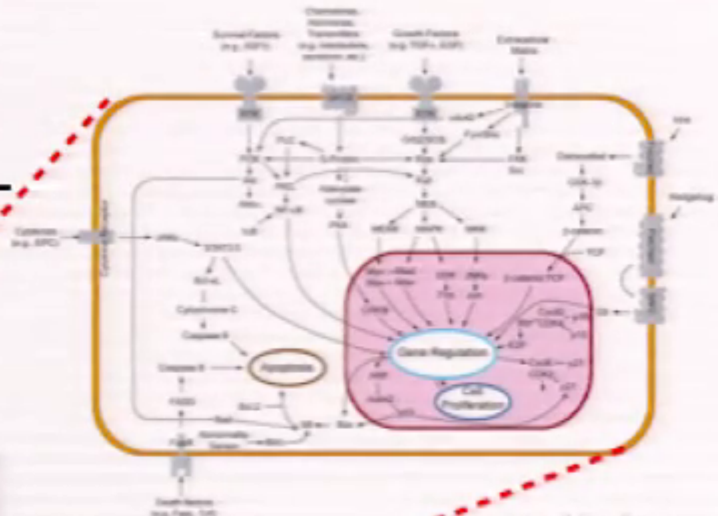
cellular
µm

multicellular
mm



Life is complex

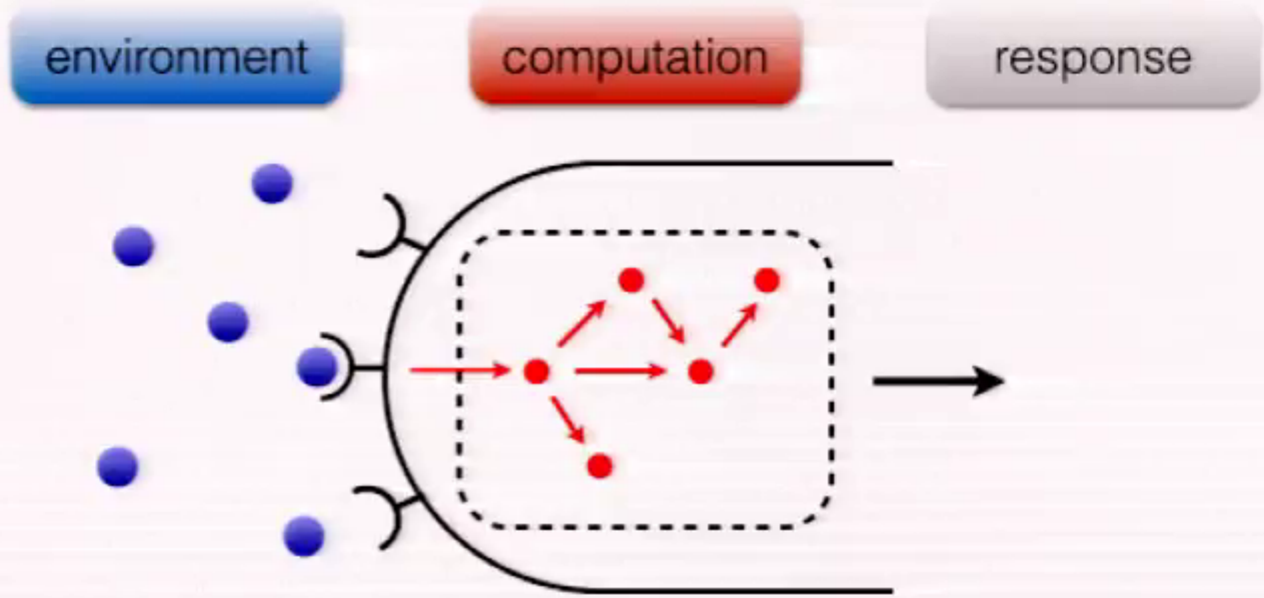




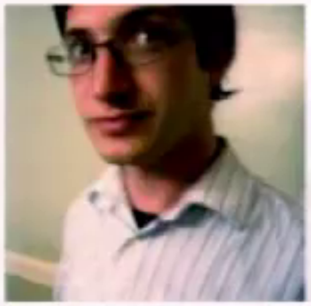
wikipedia

Can we understand complex,
multi-scale processes from simple principles?

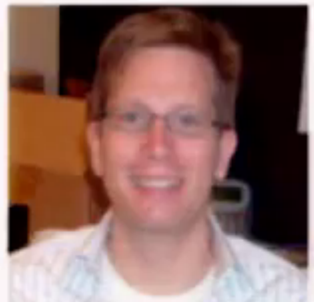
Minimal modeling approach



- Physical limits set by environment — diffusion, fluctuations, …
- Basic mechanisms of computation — simple network models
- Falsifiable predications for response — quantitative experiments



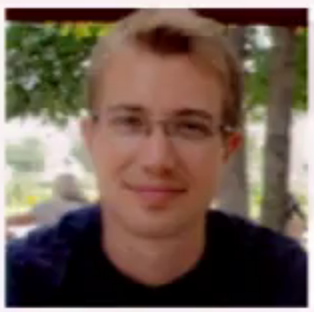
Matt Brennan
Johns Hopkins



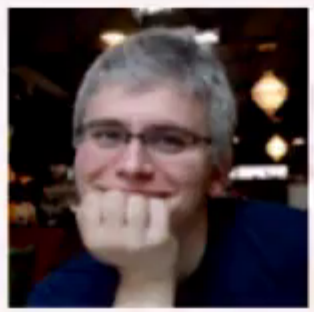
Andrew Ewald
Johns Hopkins

David Ellison
Johns Hopkins

Andre Levchenko
Yale



[Me]
Purdue

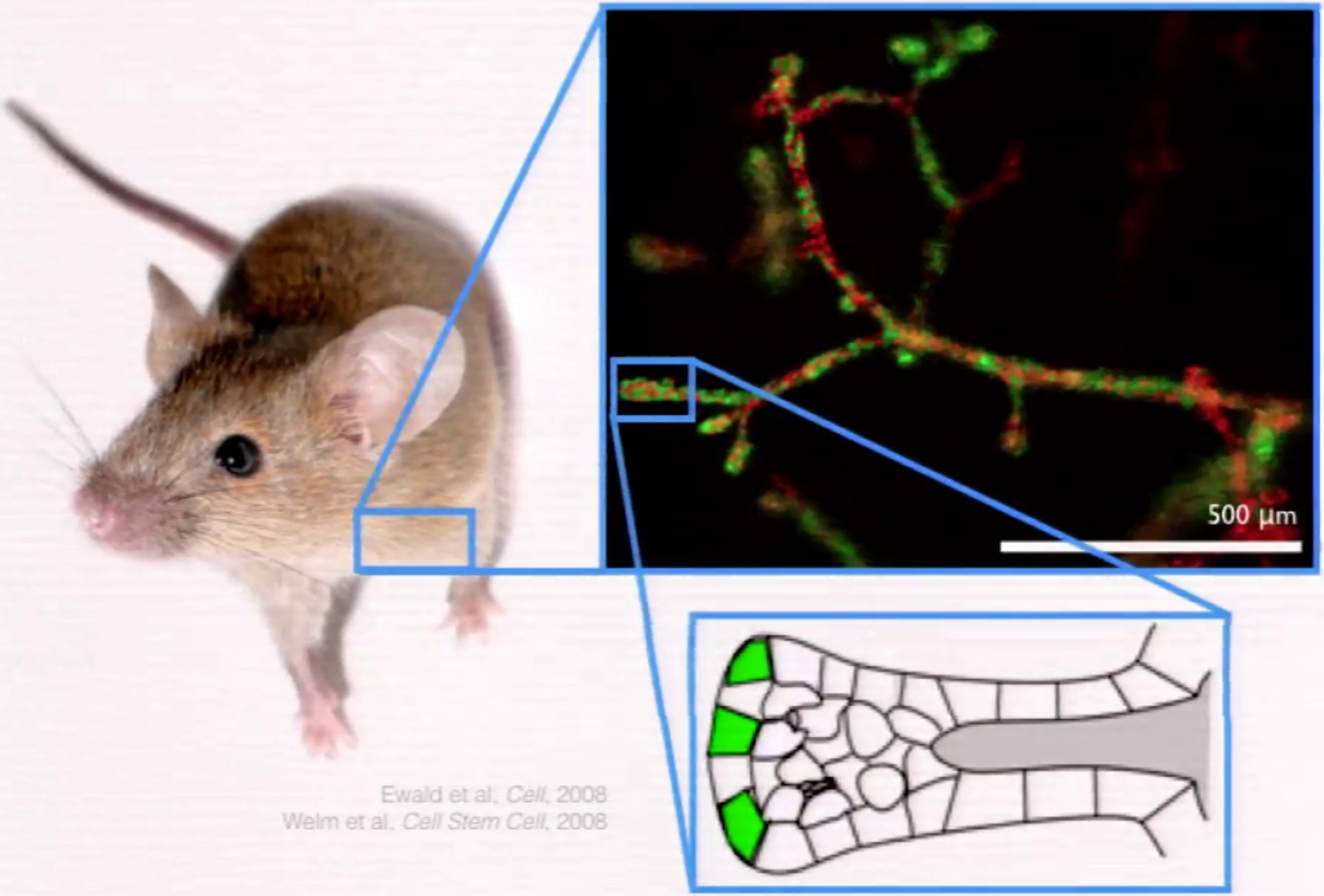


Ilya Nemenman
Emory

Can cells sense better together than they can alone?

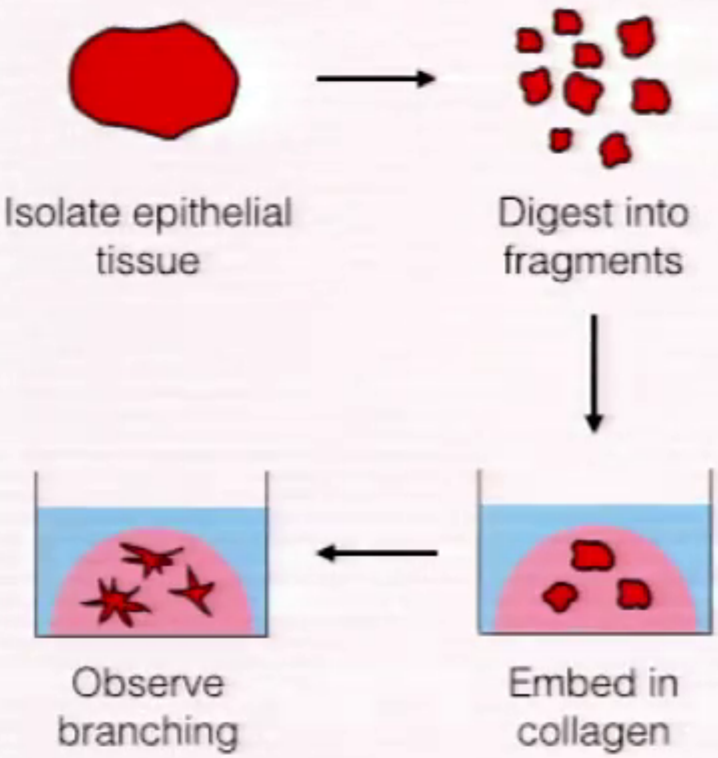
How?

A multicellular sensory system

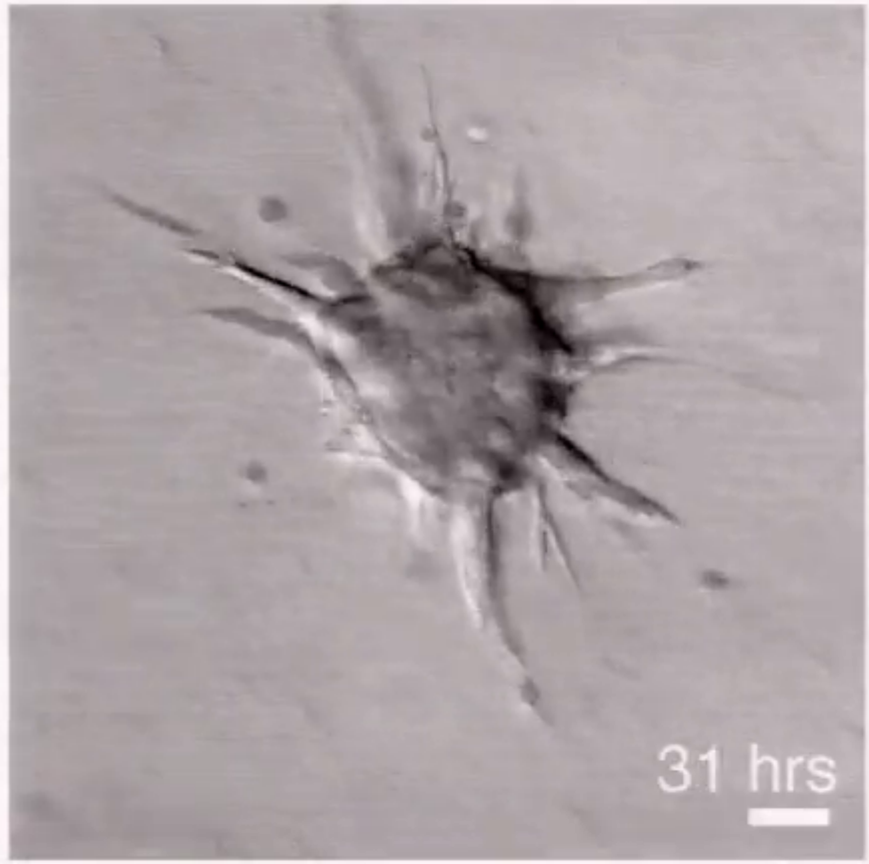


Ewald et al., *Cell*, 2008
Welm et al., *Cell Stem Cell*, 2008

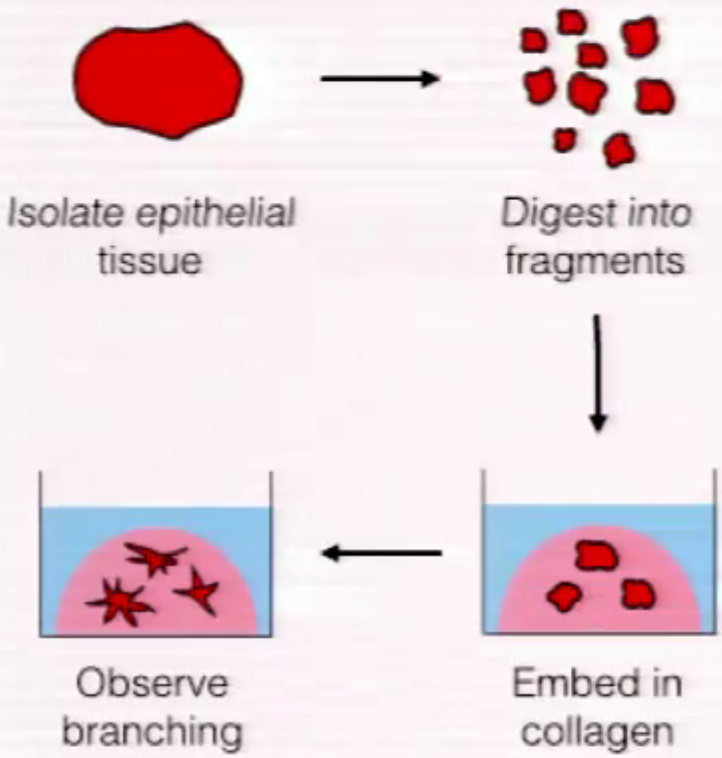
Multicellular ‘organoids’



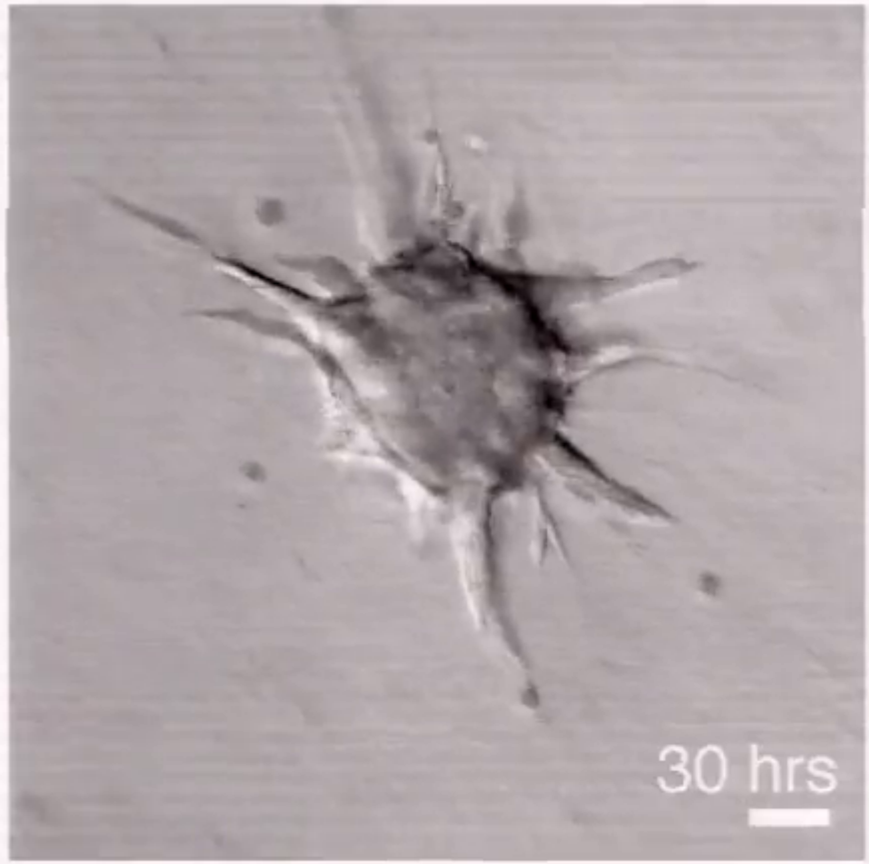
Cheung et al, *Cell*, 2013



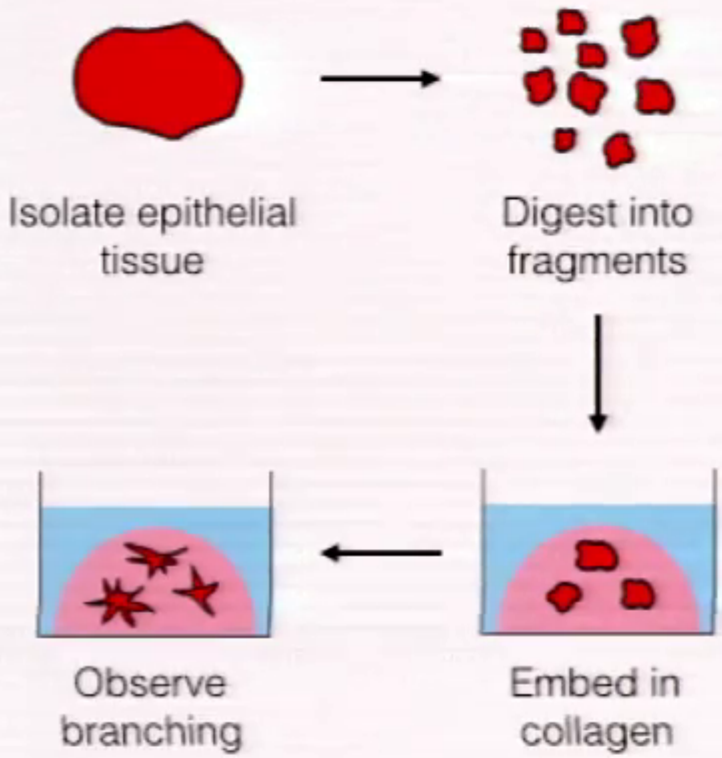
Multicellular ‘organoids’



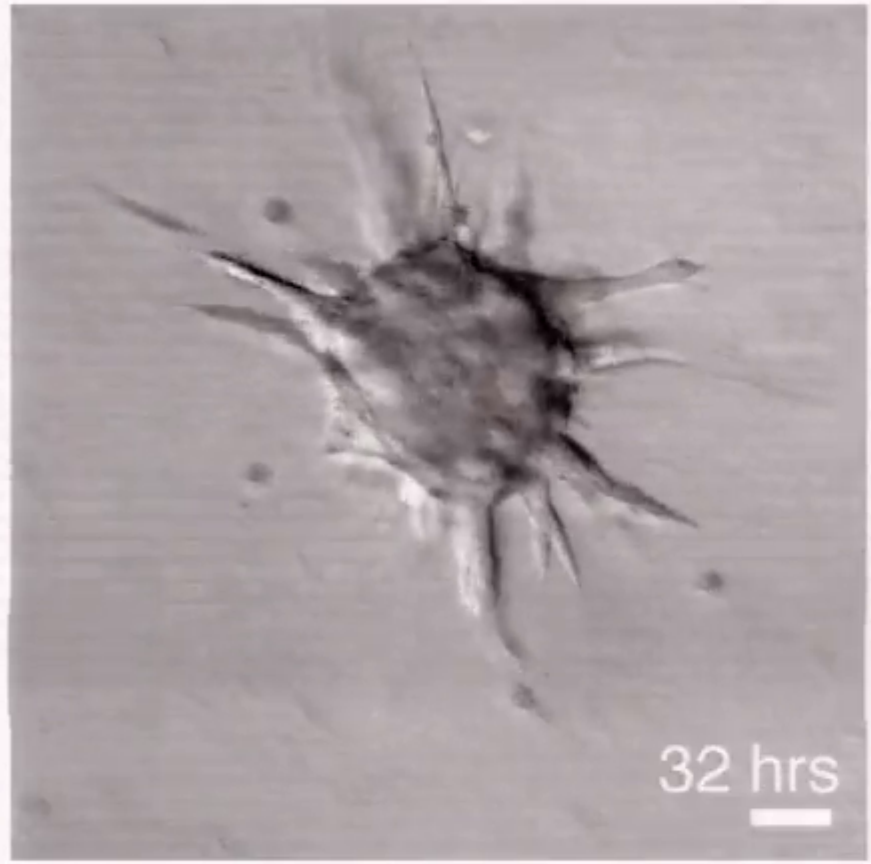
Cheung et al, *Cell*, 2013



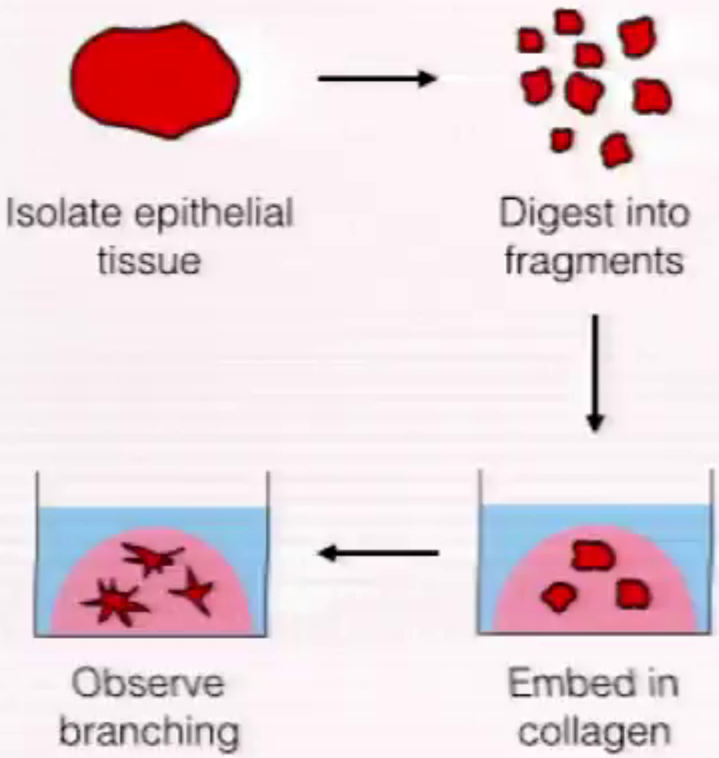
Multicellular ‘organoids’



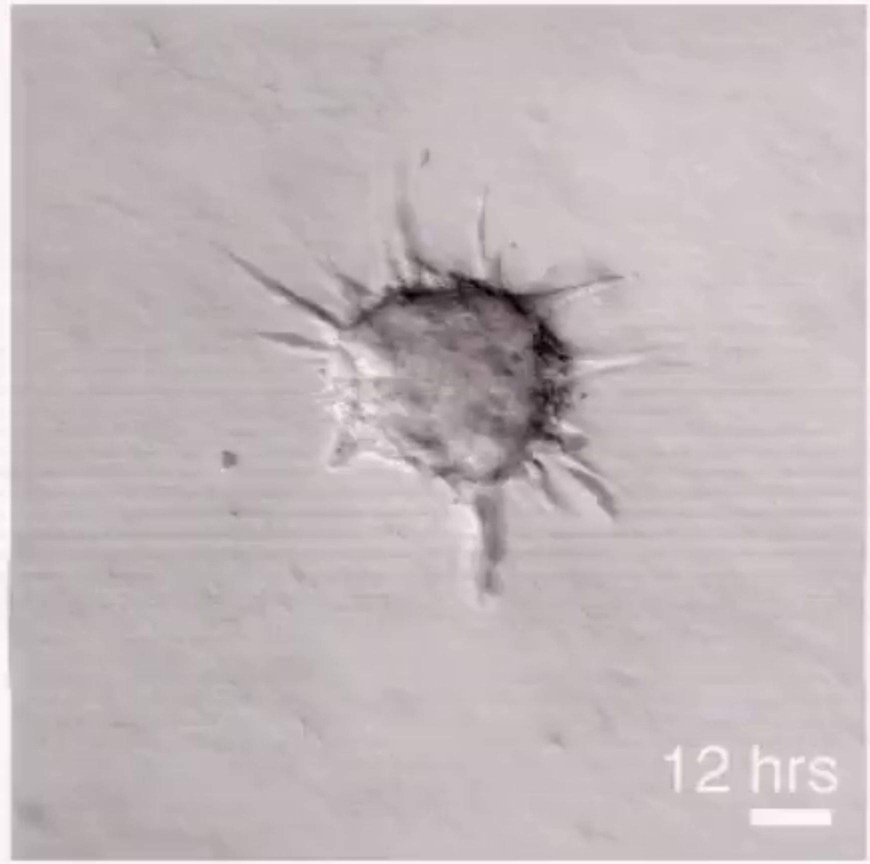
Cheung et al, *Cell*, 2013



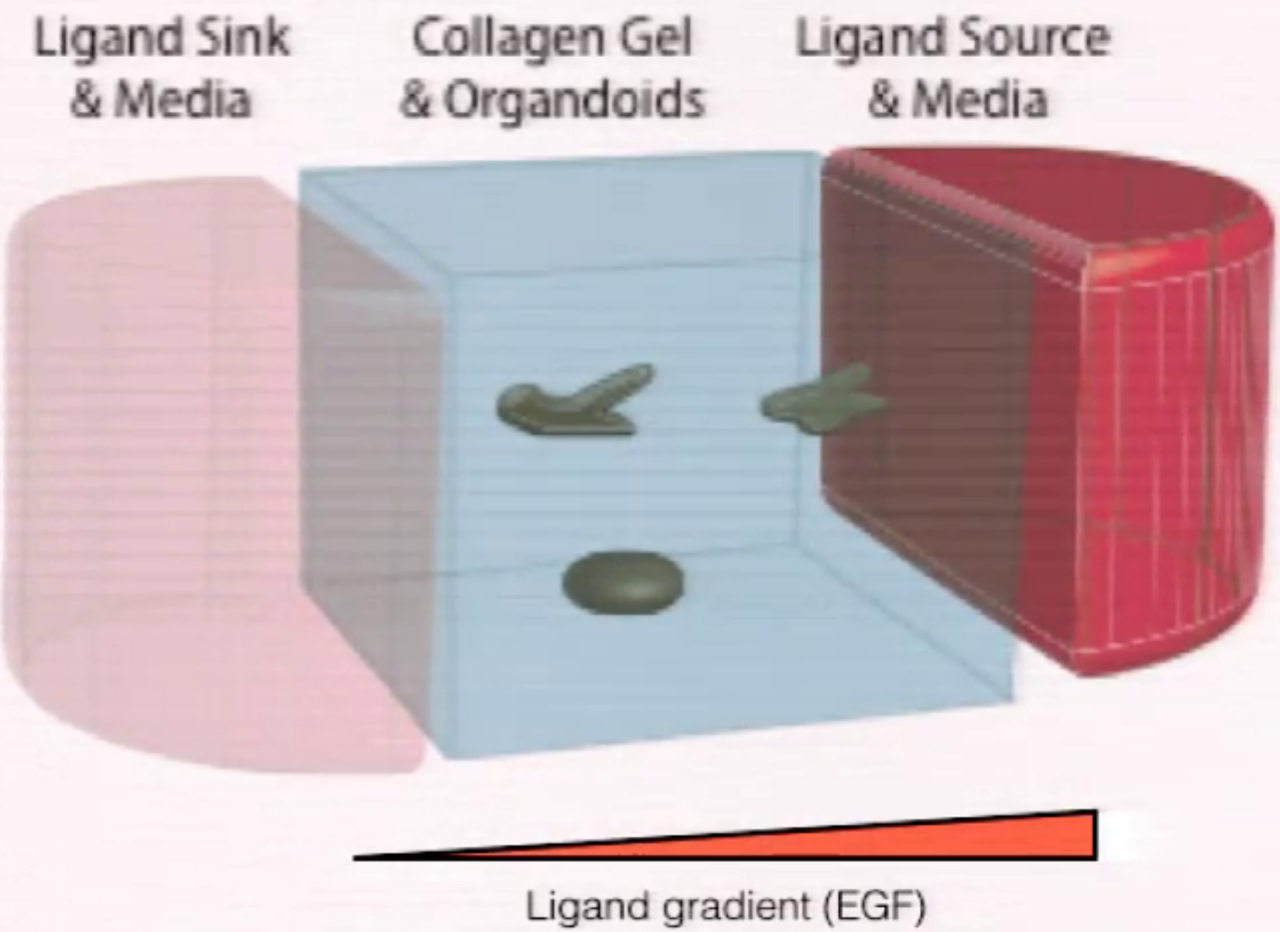
Multicellular 'organoids'



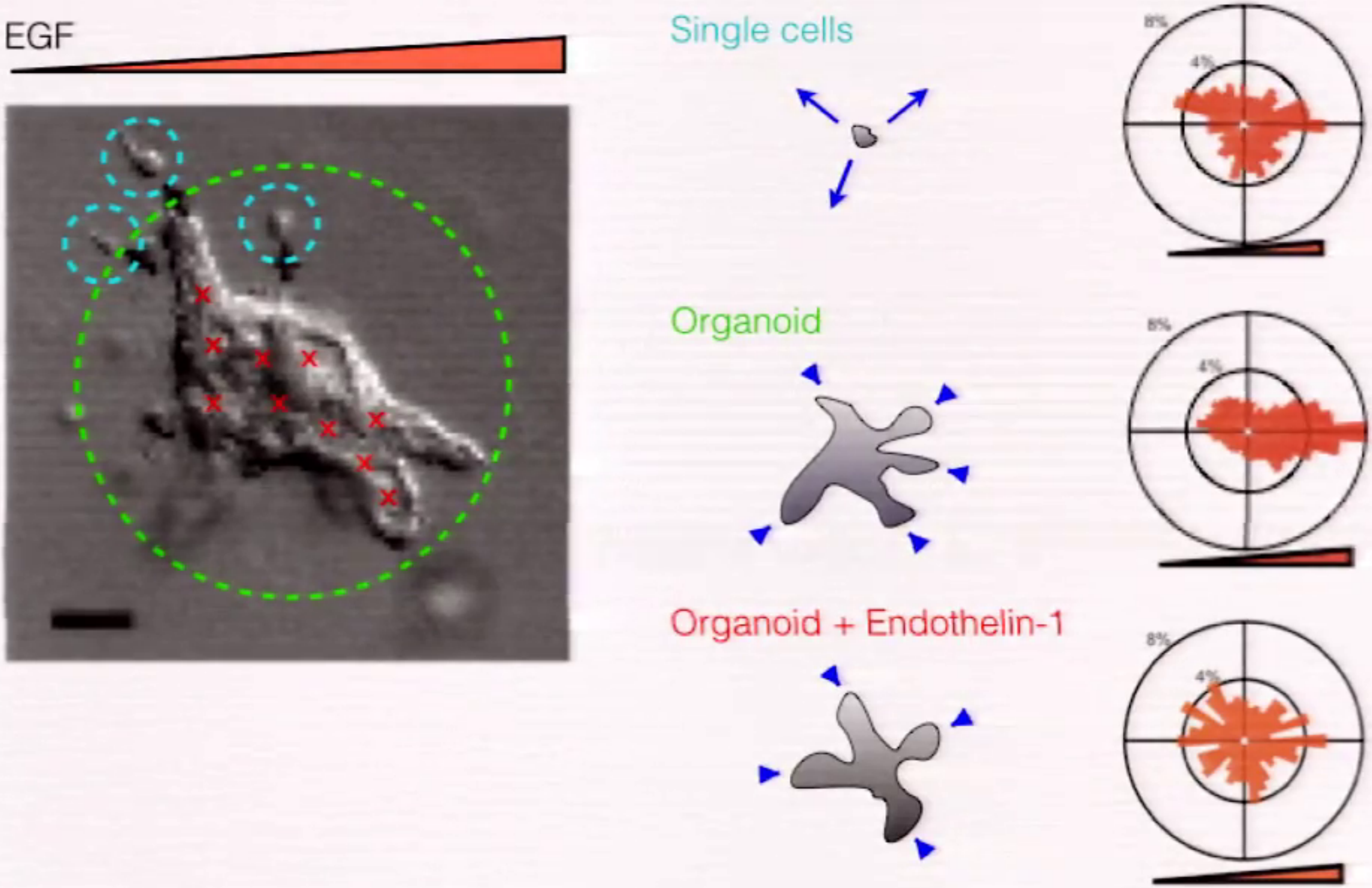
Cheung et al, *Cell*, 2013



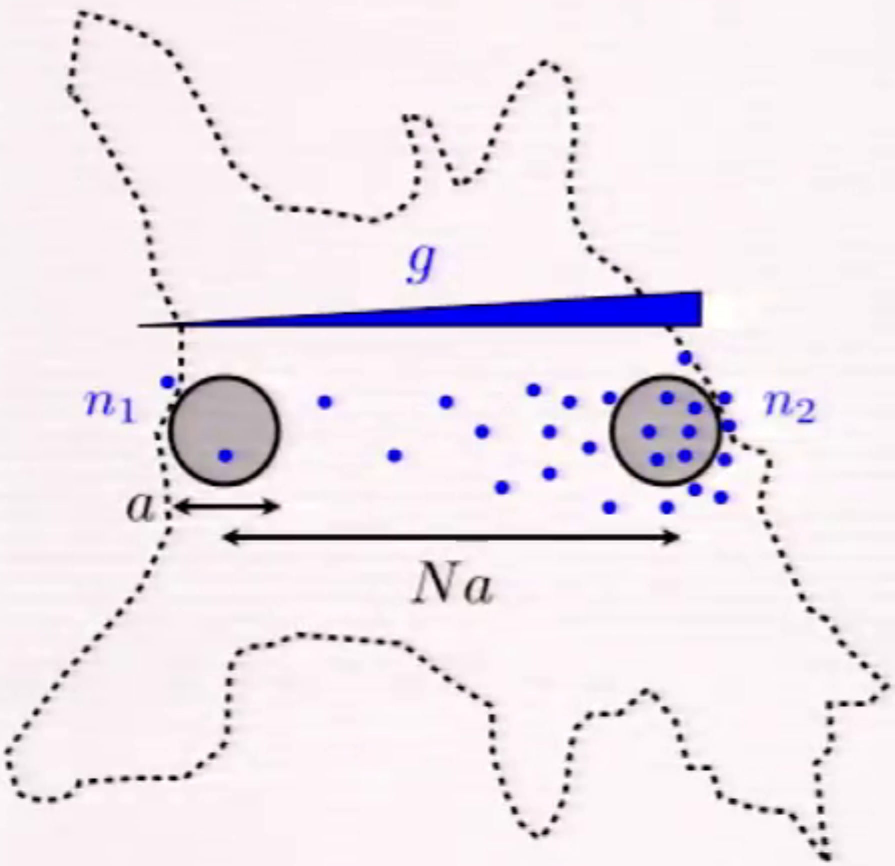
Microfluidic device



Evidence of *collective* sensing



Constructing a model



Difference in molecule numbers:

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

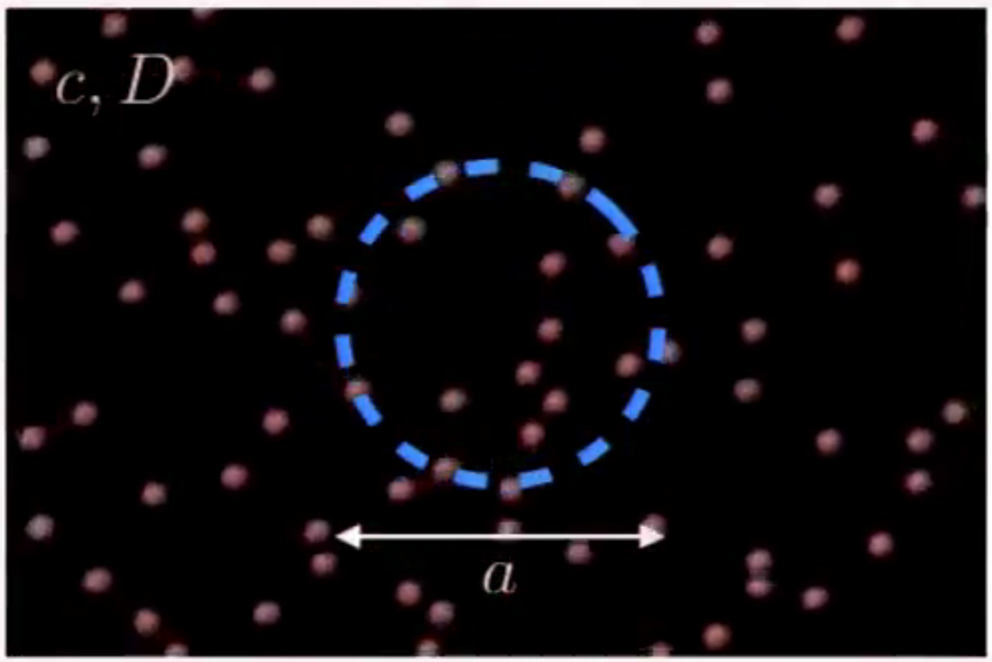
There will be *fluctuations*.
What is the error?

PHYSICS OF CHEMORECEPTION

BIOPHYSICAL JOURNAL VOLUME 20 1977

Howard Berg

Edward Purcell



Poisson statistics:

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

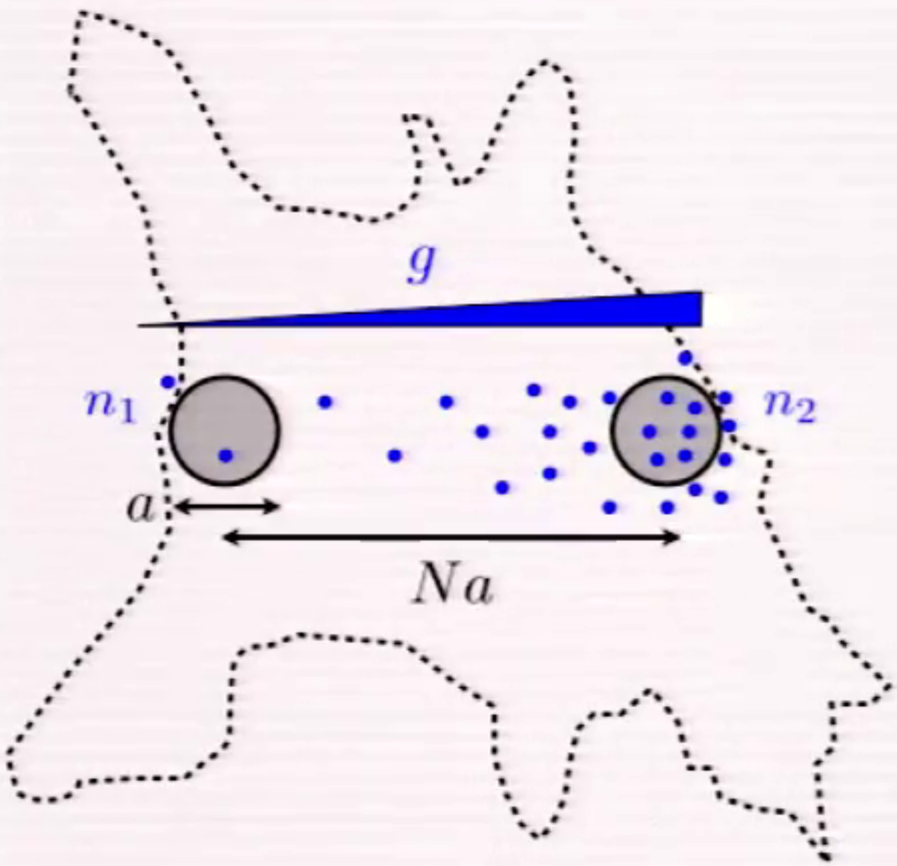
Diffusive refreshing:

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

"Berg-Purcell limit":

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

Constructing a model



Difference in molecule numbers:

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

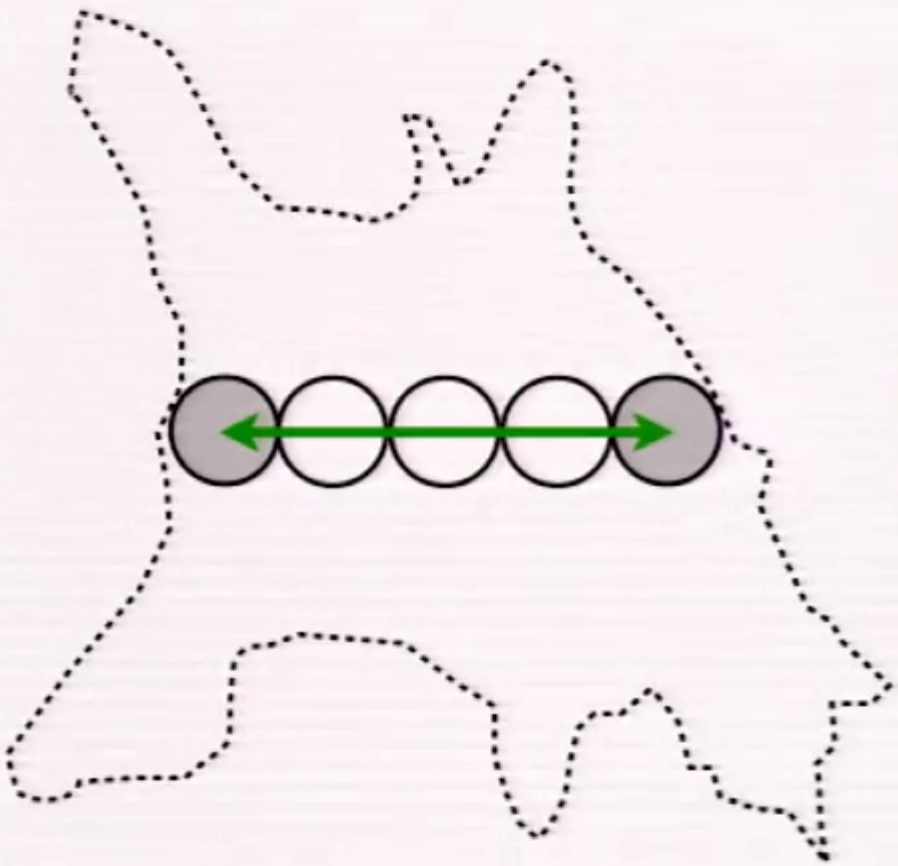
There will be *fluctuations*.
What is the error?

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

Relative error in gradient sensing:

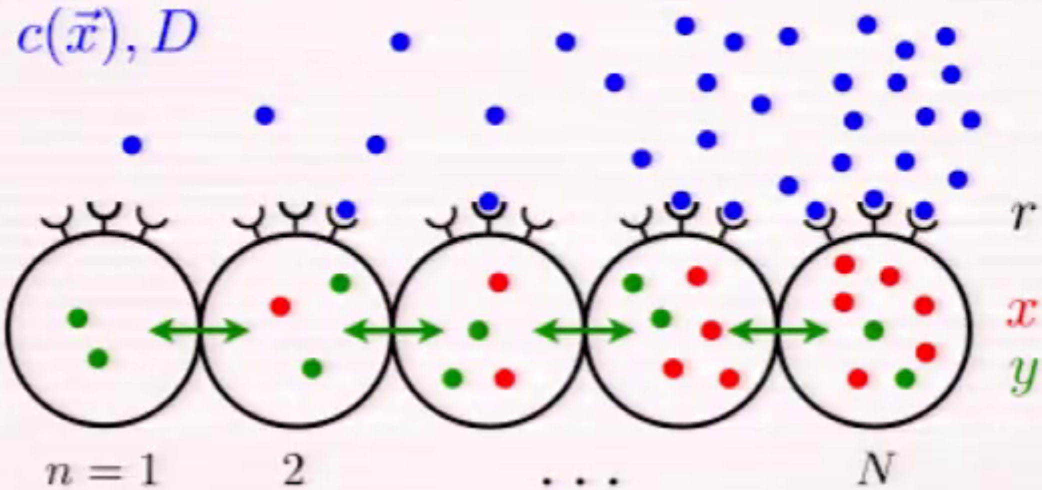
$$\frac{\delta g}{g} = \frac{\sigma}{\Delta\bar{n}} \sim \frac{1}{gNa}\sqrt{\frac{c}{TDa}}$$

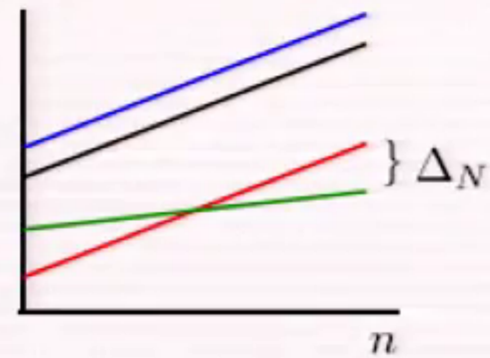
Constructing a model



Compartments need to *communicate* to integrate information.

Model of sensing with communication





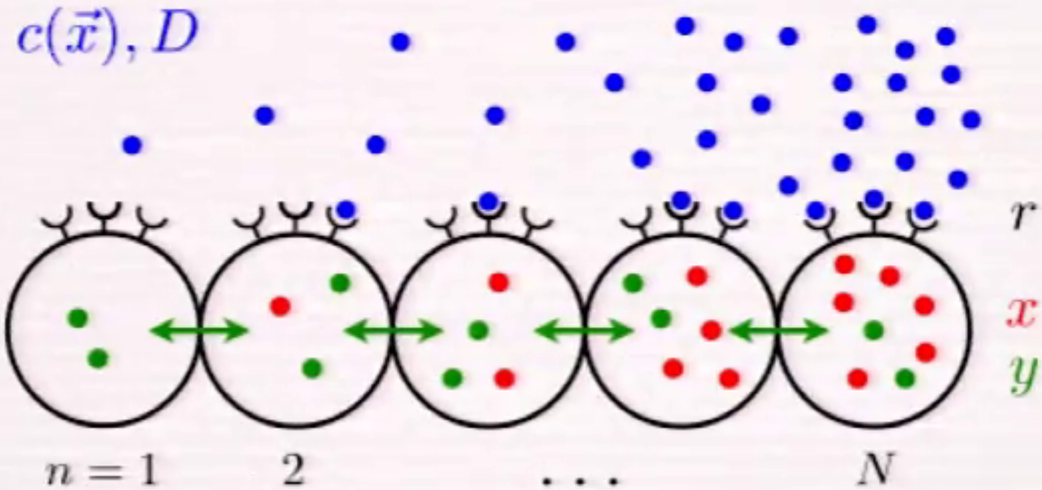
Levchenko & Iglesias, *Biophys J* 2002

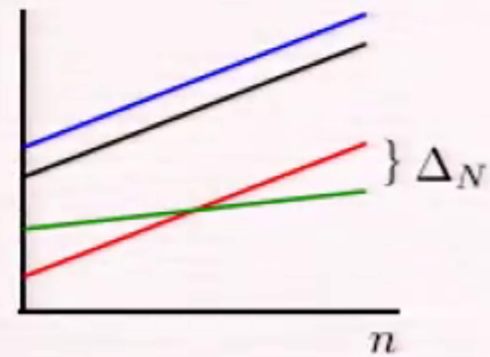
local species: x_n

global species: y_n

readout (edge cell): $\Delta_N = x_N - y_N$

Model of sensing with communication





Use fluctuation-dissipation theorem and linear response theory to find

$\delta\Delta_N/\bar{\Delta}_N$

$$\dot{c} = D\nabla^2 c - \sum_{n=1}^{N} \delta(\vec{x} - \vec{x}_n)\dot{r}_n$$

$$\dot{r}_n = \alpha c_n - \mu r_n + \eta_n$$

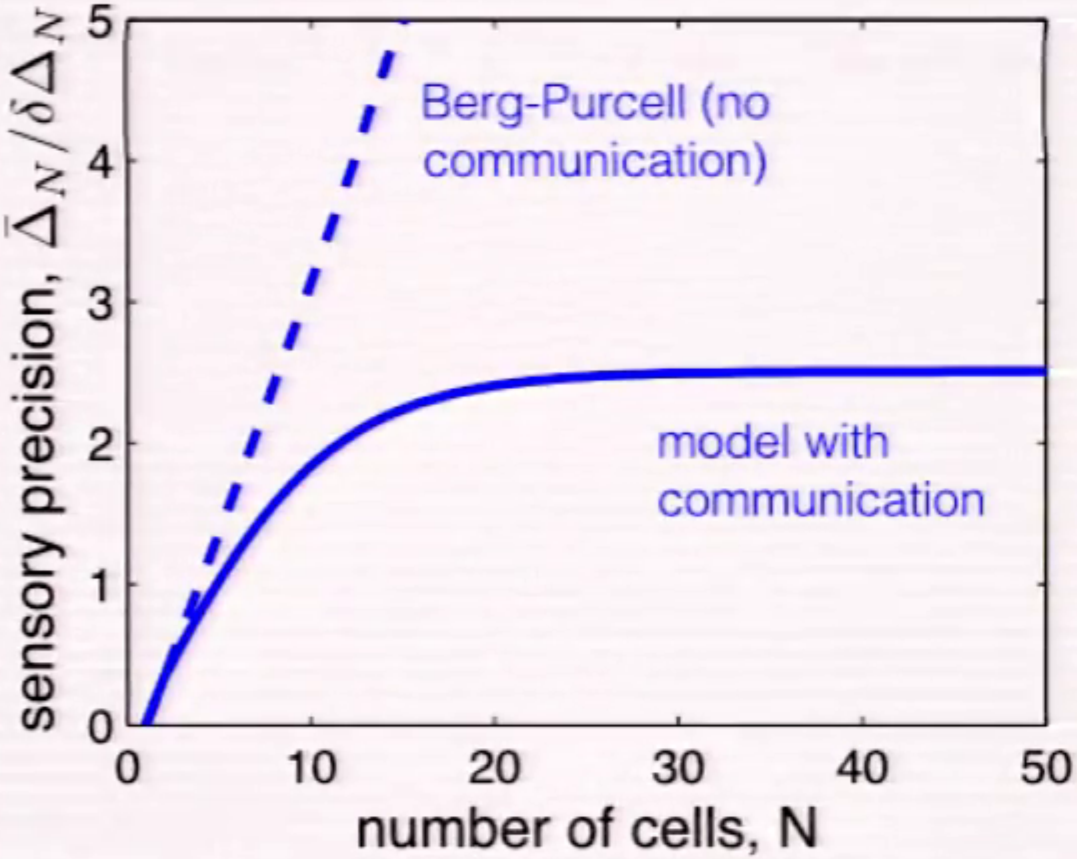
} Equilibrium binding

$$\dot{x}_n = \beta r_n - \nu x_n + \xi_n$$

$$\dot{y}_n = \beta r_n - \nu y_n + \gamma(y_{n-1} + y_{n+1} - 2y_n) + \chi_n$$

} Production, degradation, exchange

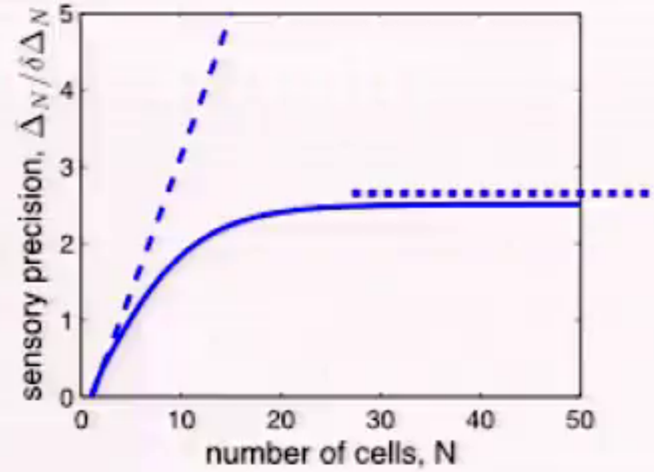
The need to communicate places a new limit



Beyond a certain size, there is no further benefit


peas
bees
knees
cheese
fleas?

Fundamental limit



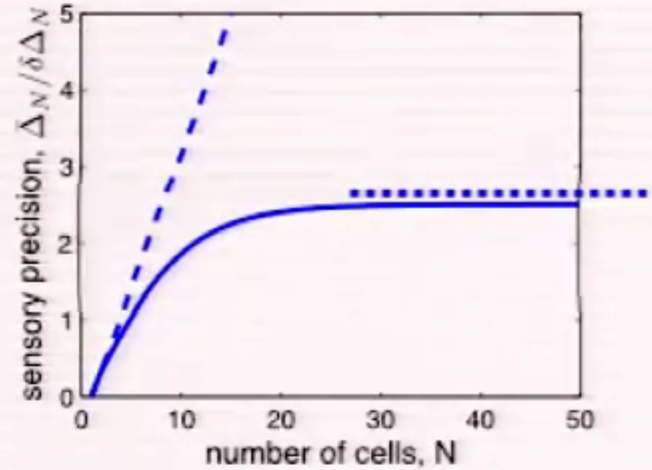
Berg-Purcell:

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

Model with communication:

$$\frac{\delta \Delta_N}{\bar{\Delta}_N} \gtrsim \frac{1}{gn_0 a}\sqrt{\frac{c_{\text{eff}}}{\pi T D a}}$$

Fundamental limit

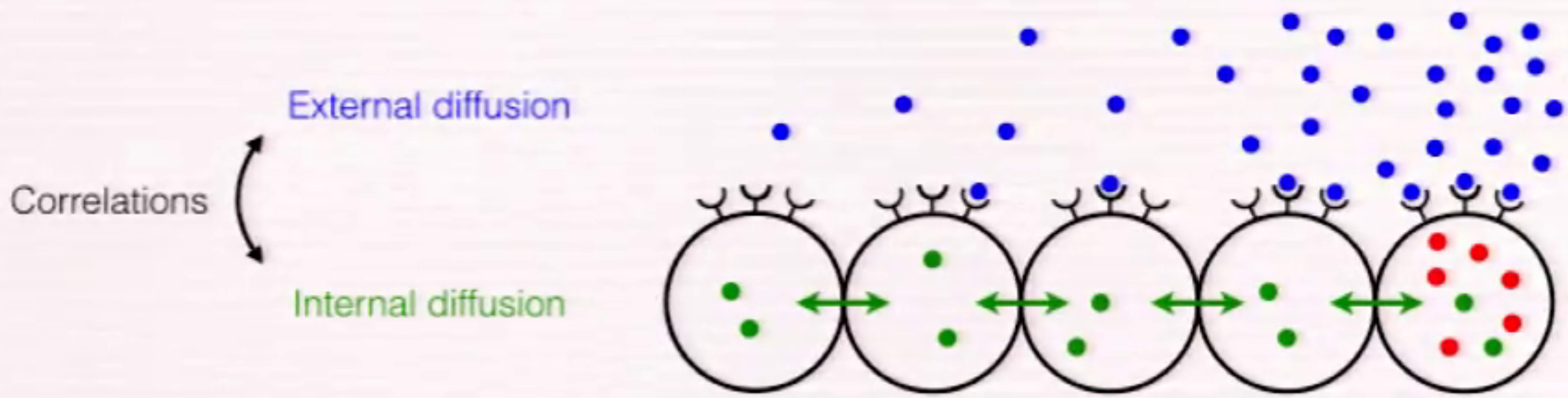


Berg-Purcell:

$$\frac{\delta g}{g} \sim \frac{1}{g\boxed{N}a}\sqrt{\frac{\boxed{c}}{TDa}}$$

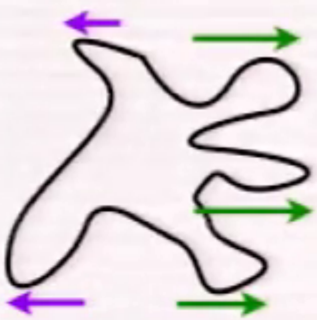
Model with communication:

$$\frac{\delta \Delta_N}{\bar{\Delta}_N} \gtrsim \frac{1}{g\boxed{n_0}a}\sqrt{\frac{\boxed{c_{\text{eff}}}}{\pi TDa}} \quad \text{where} \quad c_{\text{eff}} = \bar{c}_N + \frac{\boxed{\log n_0}}{2n_0}\left(\bar{c}_{N-n_0/2} - 2\bar{c}_N\right)$$



Comparing theory with experiment

Experiment:



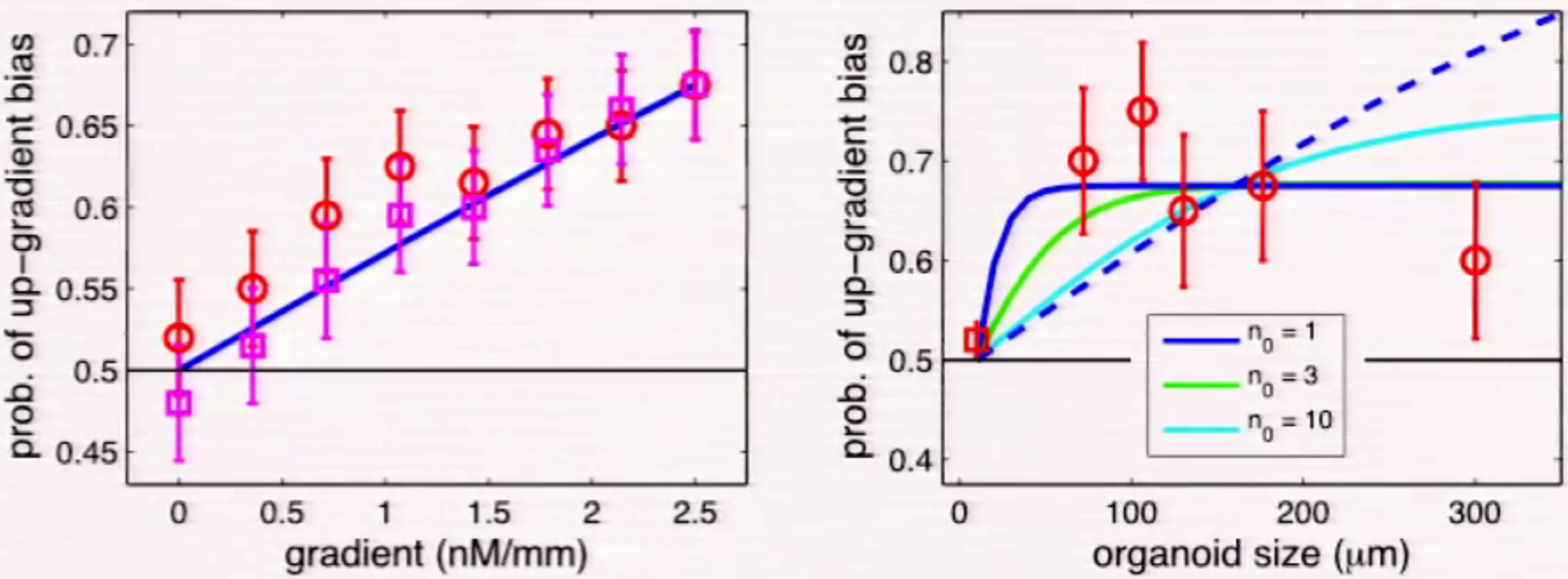
$$P(L_U > L_D)$$

Theory:

$$P(\tilde{\Delta}_U > \tilde{\Delta}_D)$$

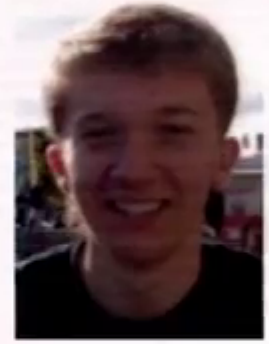
where $\left(\delta\tilde{\Delta}\right)^2 \equiv (\delta\Delta)^2 + \begin{smallmatrix}\text{downstream}\\ \text{noise}\end{smallmatrix}$

Comparing theory with experiment

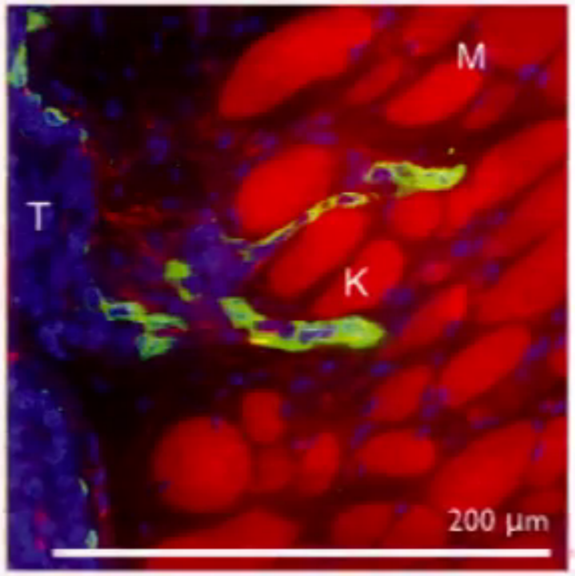


Maximum communication lengthscale: $n_0 \lesssim 4$

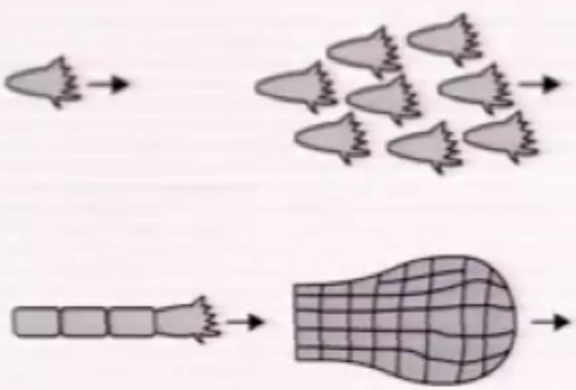
Current work: collective migration



Julien Varennes



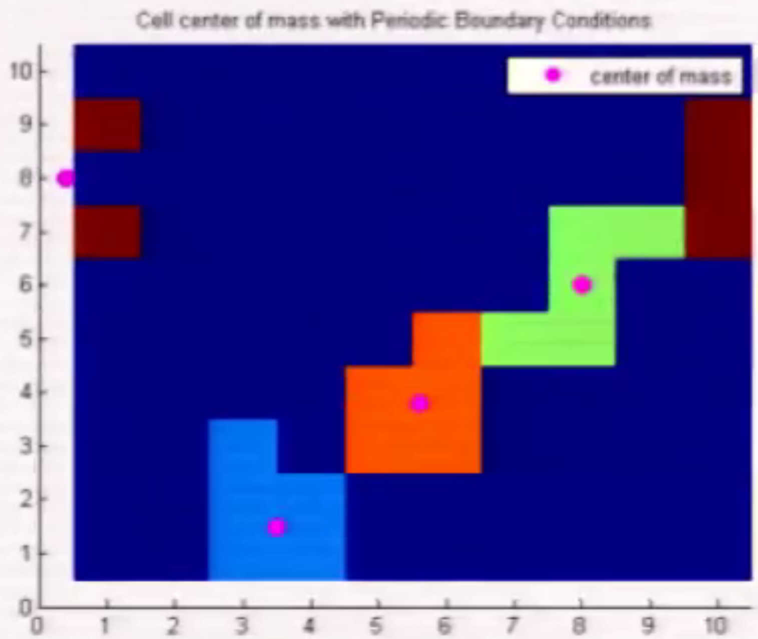
Cheung et al. *Cell* 2013



Gray et al. *Curr Opin Cell Biol*, 2010

Potts model:

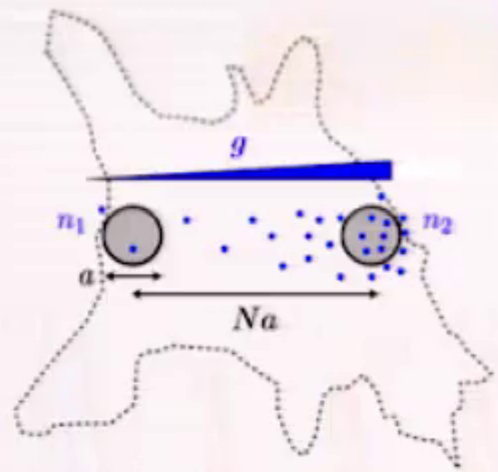
$$U = \sum_{\langle x,x' \rangle} J_{\sigma(x),\sigma(x')} + \lambda \sum_i \delta A_i^2$$

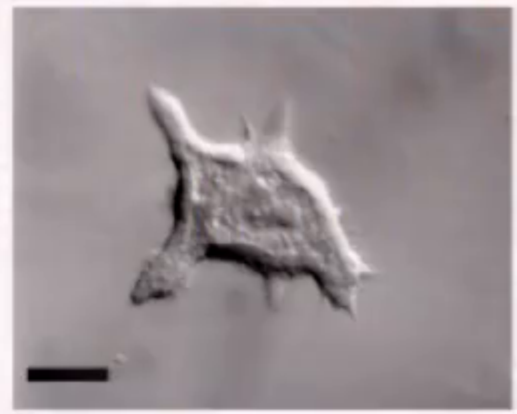


Is there an optimal cluster size?

Conclusions

- Simple estimates provide powerful bounds on biological performance
- Communication allows collective systems to outperform single cells
- Communication also *limits* performance, since it is imperfect





More info: arXiv:1505.04346