Physical limits to sensing by communicating cells

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Cheung et al, Cell, 2013
From communication to collective behavior

molecule exchange

diffusive communication

active communication

sensing

migration

phenotypic changes

“Physics approach”: simple models, universal mechanisms
Physics of collective cell sensing

Collective gradient sensing in epithelial cells

Collective ATP sensing in fibroblasts

Collective tumor cell invasion

Mugler et al, PNAS 2015

with B. Sun, Oregon State

Potter, Byrd, Mugler, Sun, arXiv 2015

with B. Han, Purdue
Physics of collective cell sensing

Collective gradient sensing in epithelial cells

Do cells sense better together than they do alone?
If so, how?

Mugler et al, PNAS 2015
A multicellular sensory system

Ewald et al, Cell, 2008
Welm et al, Cell Stem Cell, 2008
Multicellular ‘organoids’

Isolate epithelial tissue

Digest into fragments

Embed in collagen

Observe branching

Cheung et al, *Cell*, 2013
**Microfluidic device**

- **Ligand Sink & Media**
- **Collagen Gel & Organdoids**
- **Ligand Source & Media**

**Ligand Concentration**
- EGF (0.5 nM/mm)
- $\sim 10 \mu m$
- $\Delta n = 3$ molecules

$\sim 10 \mu m$
Evidence of collective gradient sensing

EGF (0.5 nM/mm)

Single cells
Evidence of collective gradient sensing
Evidence of collective gradient sensing

EGF (0.5 nM/mm) Single cells Organoid + Endothelin-I
Model of collective gradient sensing

Difference in molecule numbers:

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

There will be fluctuations. What is the error?
Poisson statistics:

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

Diffusive refreshing:

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

“Berg-Purcell limit”:

$$\frac{\sigma}{\bar{n}} \sim \frac{1}{\sqrt{TDac}}$$
Model of collective gradient sensing

Difference in molecule numbers:

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There will be fluctuations. What is the error?

Relative error in gradient sensing:

$$\frac{\delta g}{g} = \frac{\sigma}{\Delta \bar{n}} \sim \frac{1}{gNa} \sqrt{\frac{c}{TDa}}$$
Model of collective gradient sensing

Compartments need to communicate to integrate information.
The basic idea: a relay channel
Model of sensing with communication

Minimal adaptive model:

\[ c(\bar{x}), D \]

\[
\Delta N = x_N - y_N
\]

Levchenko & Iglesias, Biophys J 2002
Model of sensing with communication

Minimal adaptive model:

\[ \begin{align*}
\dot{c} &= D \nabla^2 c - \sum_{n=1}^{N} \delta(\vec{x} - \vec{x}_n) \dot{r}_n \\
\dot{r}_n &= \alpha c_n - \mu r_n + \eta_n \\
\dot{x}_n &= \beta r_n - \nu x_n + \xi_n \\
\dot{y}_n &= \beta r_n - \nu y_n + \gamma(y_{n-1} + y_{n+1} - 2y_n) + \chi_n
\end{align*} \]

Use fluctuation-dissipation theorem and linear response theory to find \( \delta \Delta N / \bar{\Delta}_N \)

Equilibrium binding

Production, degradation, exchange

\( \Delta_N \)
Beyond a certain size, there is no further benefit to sensory precision. The need to communicate places a new limit.
The need to communicate places a new limit

\[ \bar{y}_N = \frac{\beta}{\mu} \sum_n K_n \bar{c}_{N-n} \]

\[ n_0 = \sqrt{\gamma/\mu} \] communication length scale

Berg-Purcell (no communication)
The need to communicate places a new limit

Berg-Purcell:
\[
\frac{\delta g}{g} \sim \frac{1}{g N a} \sqrt{\frac{c}{T D a}}
\]

Model with communication:
\[
\frac{\delta \Delta N}{\bar{\Delta}_N} \gtrsim \frac{1}{g n_0 a} \sqrt{\frac{c_{\text{eff}}}{\pi T D a}}
\]

where \( c_{\text{eff}} = \bar{c}_N + \frac{\log n_0}{2 n_0} (\bar{c}_N - n_0/2 - 2 \bar{c}_N) \)
Comparing theory with experiment

Experiment:

Theory:

\[ P(\Delta_U > \Delta_D) \]

where

\[ (\delta \tilde{\Delta})^2 \equiv (\delta \Delta)^2 + \text{downstream noise} \]
Comparing theory with experiment

- Gradient (nM/mm) vs. prob. of up-gradient bias
- Organoid size (µm) vs. prob. of up-gradient bias

Both models:
- Berg-Purcell (no communication)
- Model with communication
Comparing theory with experiment

The graphs depict the probability of up-gradient bias as a function of gradient (nM/mm) and organoid size (µm). The data points are presented with error bars, suggesting variability in the measurements. The graphs also include lines representing theoretical models: Berg-Purcell (no communication) and a model incorporating communication. The latter shows a higher probability of up-gradient bias at lower gradient values compared to the Berg-Purcell model.
Comparing theory with experiment
Comparing theory with experiment

Communication length scale: $2.9 < n_0 < 4.2$ cells
What is the molecular communicator?

Gap-junction blocker:
50 nM Endothelin-I

Same for:
• 50 μM Carbenoxolone
• 50 μM Flufenamic acid
• 0.5 mM Octanol
What is the molecular communicator?

**Gap-junction blocker:**
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100 nM Thapsigargin

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![Graph showing normalized fluorescence intensity over time with a 5 nM EGF spike.](image)
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Extensions and current work

- 2D and 3D systems
- Nonlinearity and long-range communication with A. Erez and G. Altan-Bonnet, Sloan Kettering
- Other modes of communication vs.

or
Conclusions

- Physics models provide powerful bounds on biological performance.
- Communication allows collective systems to outperform single cells.
- Communication also limits performance, since it is imperfect.
Acknowledgments

**Mugler Group @ Purdue**

Tommy Byrd  Sean Fancher  Julien Varennes

**Emory University**

Ilya Nemenman

**Yale University**

Andre Levchenko  Matt Brennan

**Johns Hopkins**

Andrew Ewald  David Ellison

**For more info**

Mugler et al, *PNAS*, Accepted (arXiv: 1505.04346)

Ellison et al, *PNAS*, In review (arXiv: 1508.04692)

**Funding**

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