How Cells Know Where They Are

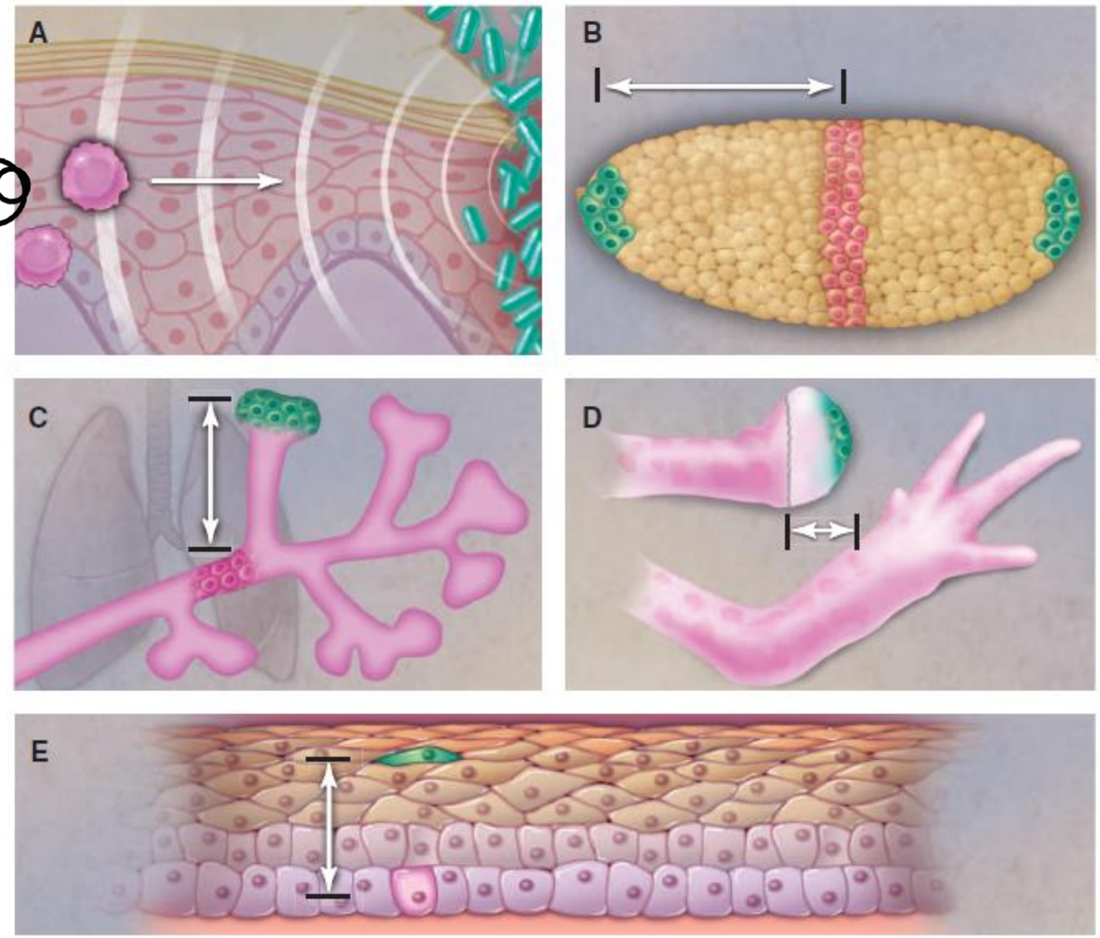
Arthur D. Lander

Development, regeneration, and even day-to-day physiology require plant and animal cells to make decisions based on their locations. The principles by which cells may do this are deceptively straightforward. But when reliability needs to be high—as often occurs during development—successful strategies tend to be anything but simple. Increasingly, the challenge facing biologists is to relate the diverse diffusible molecules, control circuits, and gene regulatory networks that help cells know where they are to the varied, sometimes stringent, constraints imposed by the need for real-world precision and accuracy.

Science 22 February 2013:
Vol. 339 no. 6122 pp. 923-927
DOI: 10.1126/science.1224186

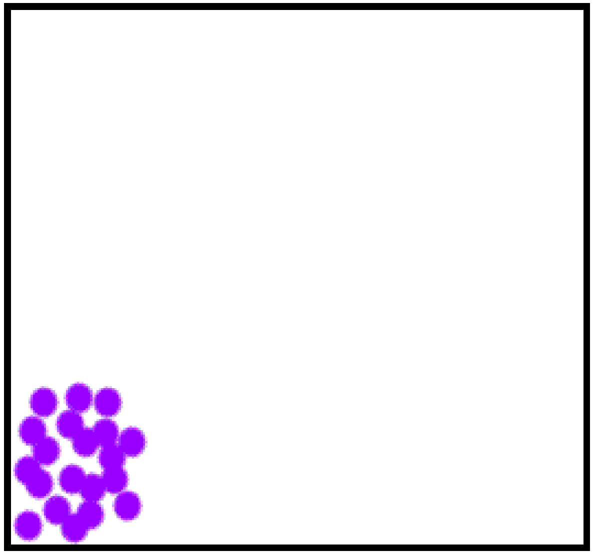
2013. 06. 22.
Jonggwan Lee

Introduction



Cells have to locate themselves for development, regeneration, and even for day-to-day physiology.

Introduction



$$y = \frac{v}{2k}\left(1 - e^{-2c/\sqrt{\frac{DK_m}{kr}}}\right)e^{-x/\sqrt{\frac{DK_m}{kr}}} = ae^{-x/\lambda}$$

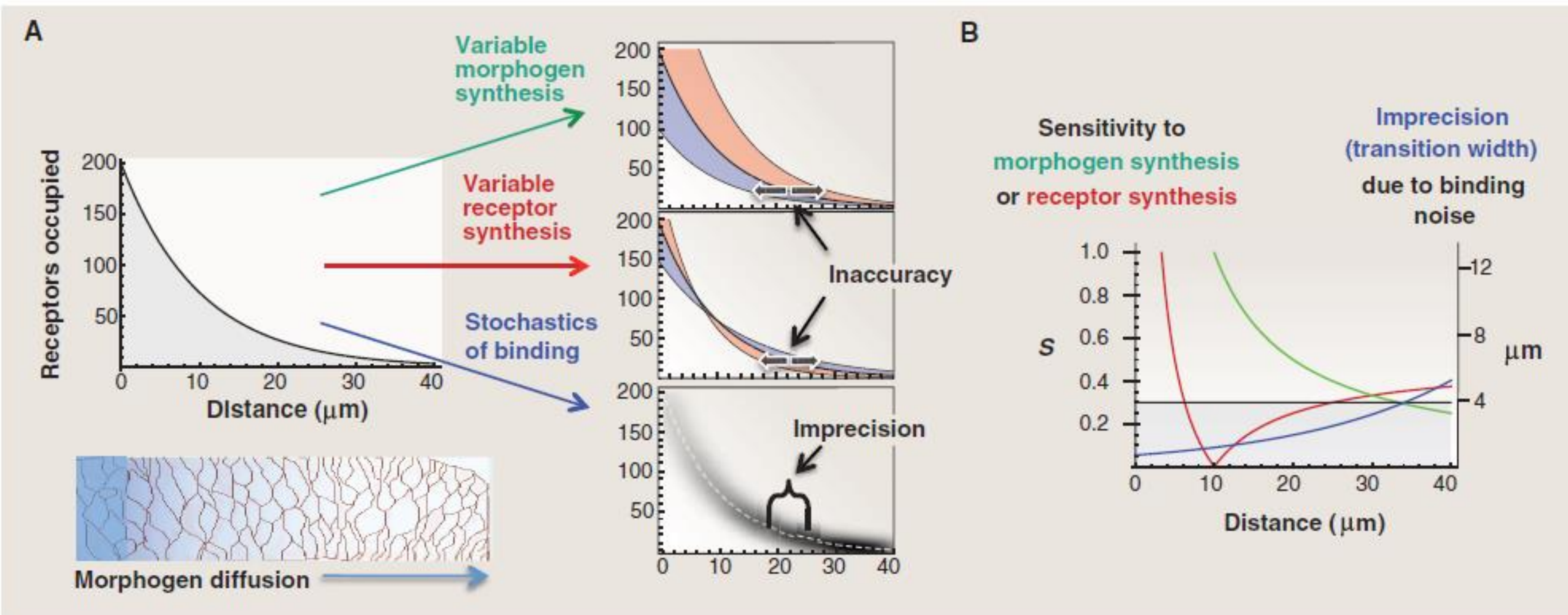
y : the concentration of occupied receptors
v : the rate of morphogen production
k : the rate constant of turnover of morphogen receptor complexes
D : the diffusivity
K_m : the Michaelis constant of receptor interaction (which combines the effects of binding and internalization)
r : the concentration of (free) receptors
c : the half-width of the production region
x : the distance from the edge of the morphogen source

To do so, they use molecular diffusion, which is the simplest way to measure the distance in microscopic world of cells.

In developmental pattern formation (morphogenesis), molecules called morphogen play central role.

Introduction

During development, high reliability is required. While diffusion process has inevitable inaccuracy & imprecision, Due to the variability in transport process or stochastic fluctuation.



In this article, mechanisms by which our cells deal with such errors to get more reliable information about their position, are introduced.

What price reliability?

Some cells increase morphogen degradation in response to morphogen signaling

decreases sensitivity to variation in morphogen production (more reliable)

makes gradients shallower.

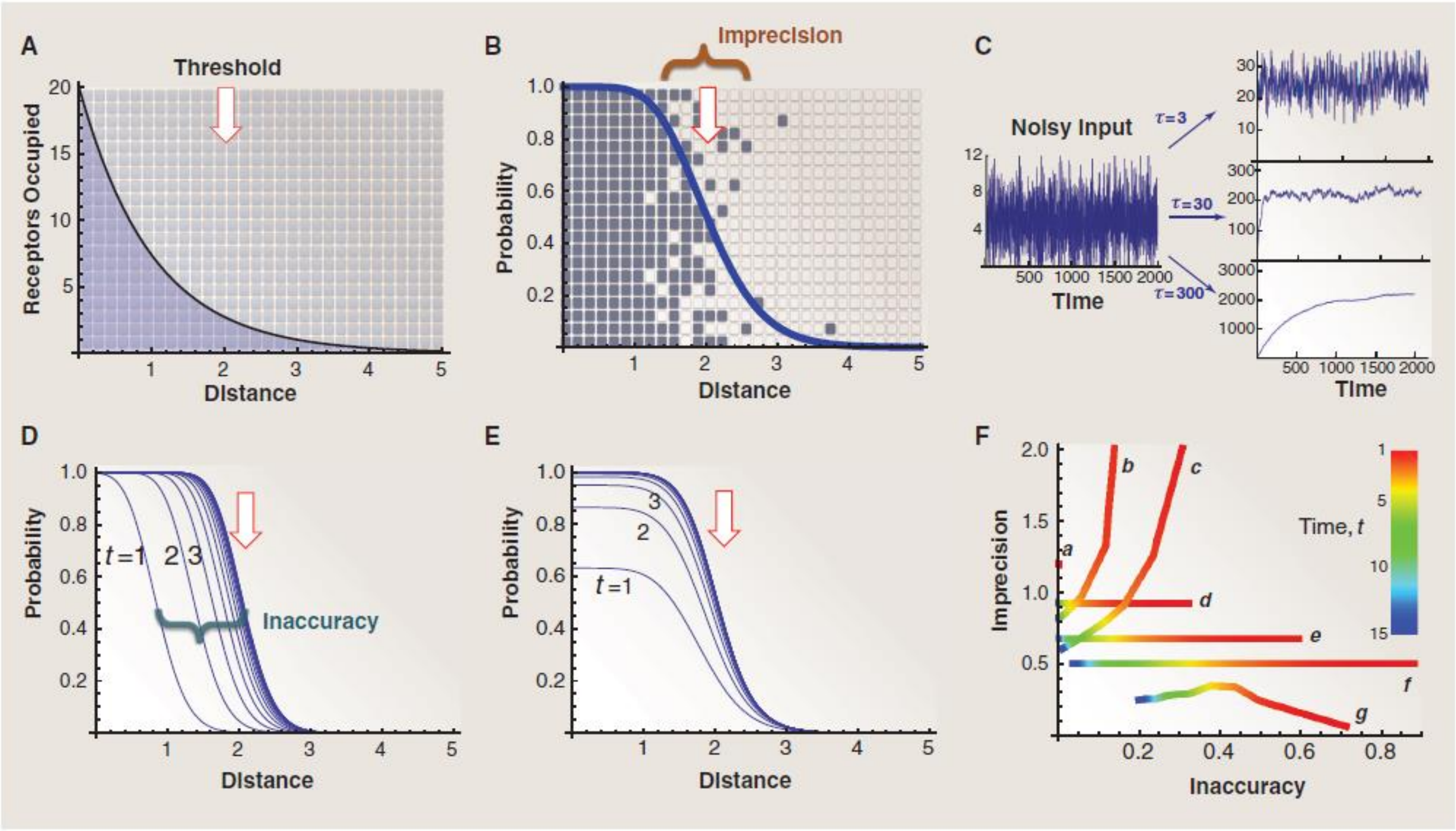
Operate in regimes of higher total morphogen

Increased recepter occupancy results into reduced stochastic fluctuations.

quickly leads to receptor saturation near the morphogen source.

Strategies that improve performance in one area typically degrade it in another.

Quality through quantity



By making combinations of measurements, cells may exploit strategies of pooled sampling.

Quality through quantity

Cells naturally pool measurements by letting intracellular signals accumulate over time : morphogen-receptor complexes may be internalized and continue to signal within endosomes.

Pooled sampling can also mean pooling different kind of data : some cells can get positional information from more than one morphogen at the same time

Measurements can also be pooled over space by sharing information with neighboring cells : In the early *Drosophila* embryo, some spatial integration happens simply by virtue of diffusion of downstream effectors of morphogen signaling from one nucleus to another.

Fixing errors before they happen

Making multiple measurements that are independent with respect to disturbances is not always feasible. In such cases, cells may exploit a different strategy, namely the disturbance compensation.

For instance, if morphogen's rate of production rises in a certain way with temperature, then measuring its abundance relative to that of some other molecule that rises in the same way with temperature will produce a temperature-corrected reading.

Any instance in which perturbations to a system have more than one predictable effect, creates an opportunity for disturbance compensation.

Summary

1. Cells can know where they are by sensing the molecular diffusion.

2. To get reliable information, cells use several noise reduction process, such as sensitivity tradeoff, measurement accumulation and ratiometric disturbance compensation.

3. Despite the existence of straightforward ways for cells to measure position, making measurements sufficiently accurate and precise is inherently challenging.

Questions remaining

1. How many of the “rulers” that cells use have we found?

2. How collaborative are most cases of positional sensing?

3. What are the primary sources of unreliability that constrain how cells in different contexts measure position?

4. To what extent can known sources of uncertainty and variability provide a satisfactory (constraining) explanation for position-sensing mechanisms we observe?