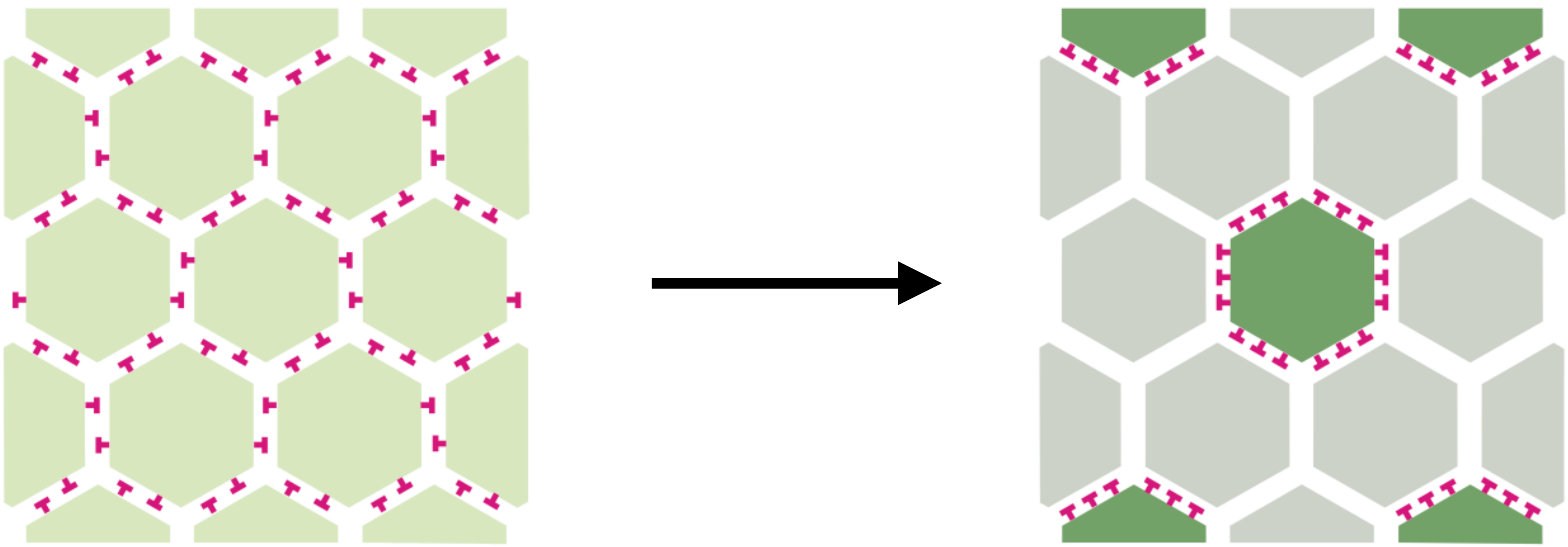
ILAS Seminal-E2:

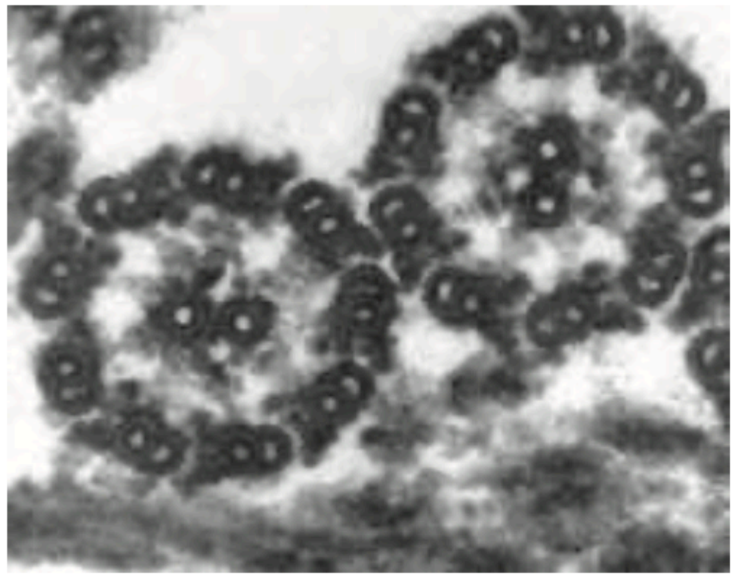
Pattern formation in biology:

the Notch-Delta mechanism



Life is full of patterns at various length-scales

Phillips “Physical Biology of the Cell”



microtubules

100 nm

5 cm

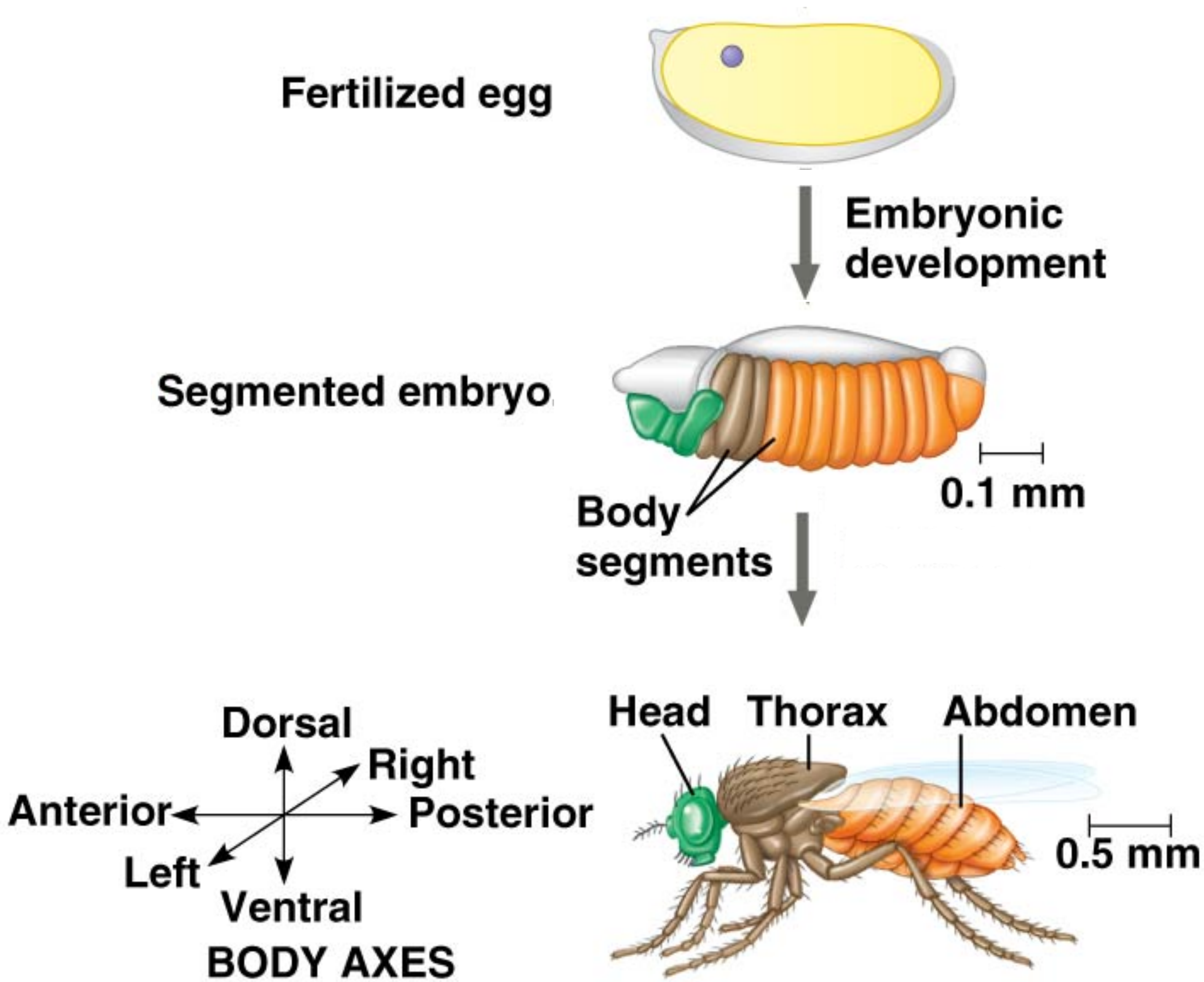
1 m

5 m

These patterns are often the result of self-organization, thanks to the interactions between the (simpler) components of the system

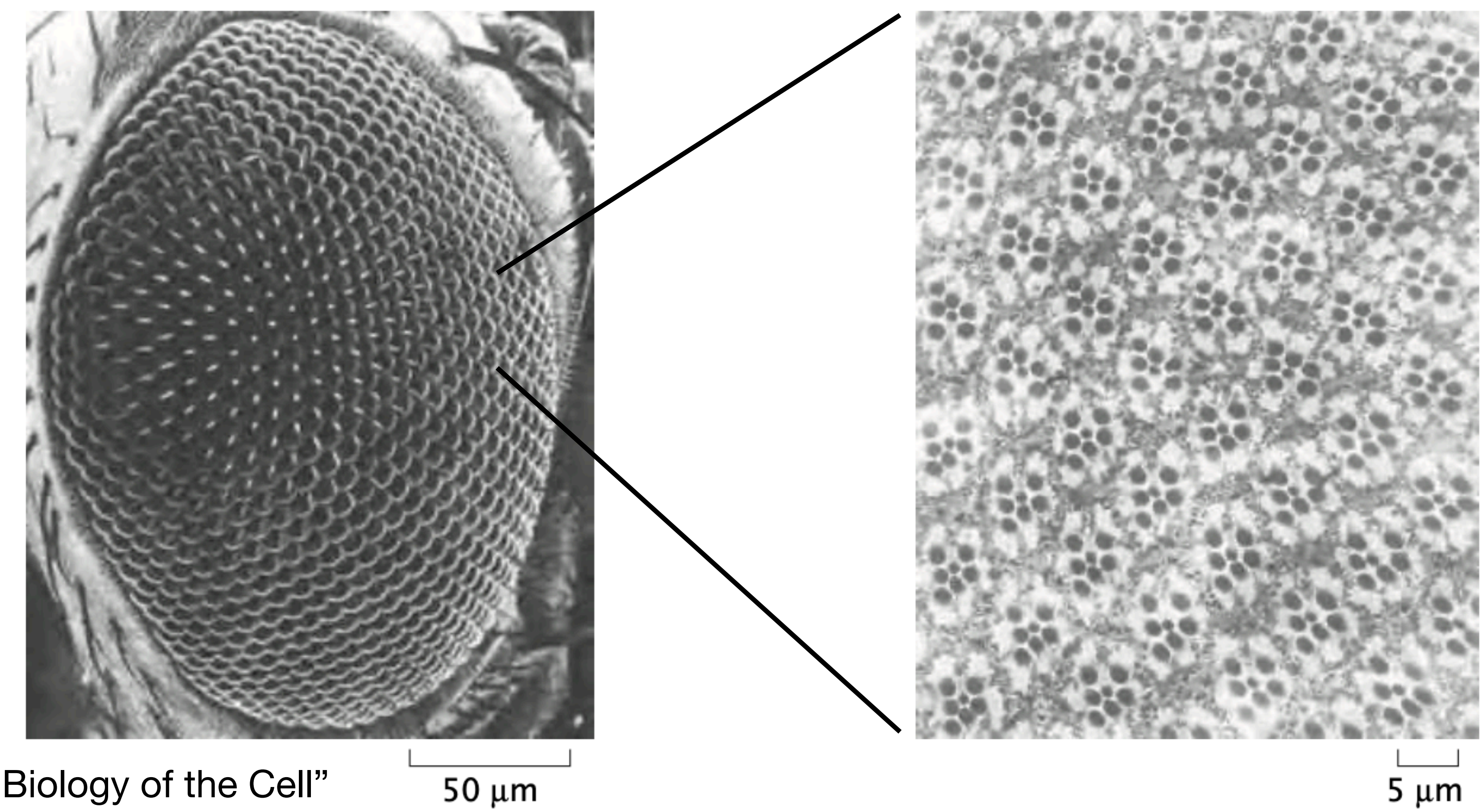
Example: pattern formation during development

Fertilized eggs appears simple and mostly “symmetric”, but adult organism are complex and organized along distinct asymmetric axes. Formation or regular patterns is critical for development.



Example: Drosophila compound eyes

The eye of Drosophila, as well as other insects and crustaceans, is composed of many units called ommatidia (~800), each composed of various cell types (~20). Such alternating pattern of cell differentiation arises from a uniform undifferentiated epithelial tissue.



Phillips “Physical Biology of the Cell”

How can such complex regular patterns spontaneously arise in animal tissues?

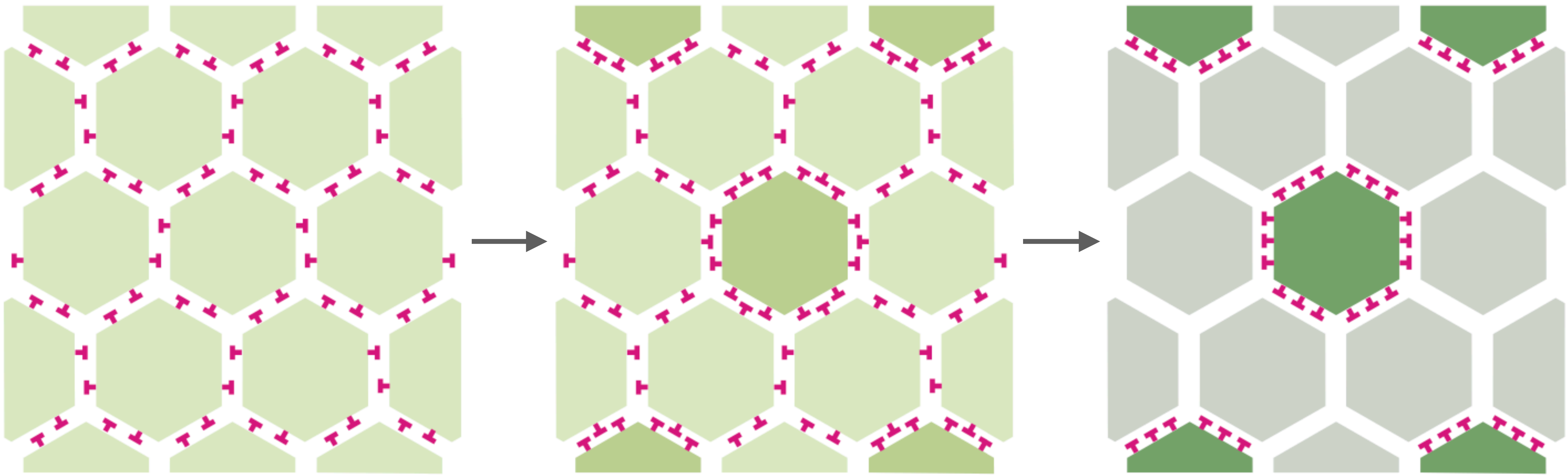
Cell-cell communication allows the generation of regular patterns from initially uniform tissues

Pattern can arise due to lateral inhibition with feedback

In the undifferentiated tissue, cells display a uniform amount of ligand (T, recognized by receptors on neighboring cells)

When concentrations are not perfectly equal, an higher amount of ligands on a cell can inhibit ligand production on neighboring cells

Differences are amplified, resulting in the generation of an alternating pattern of **high**- and **low**-ligand cells, which then differentiate into different cell types

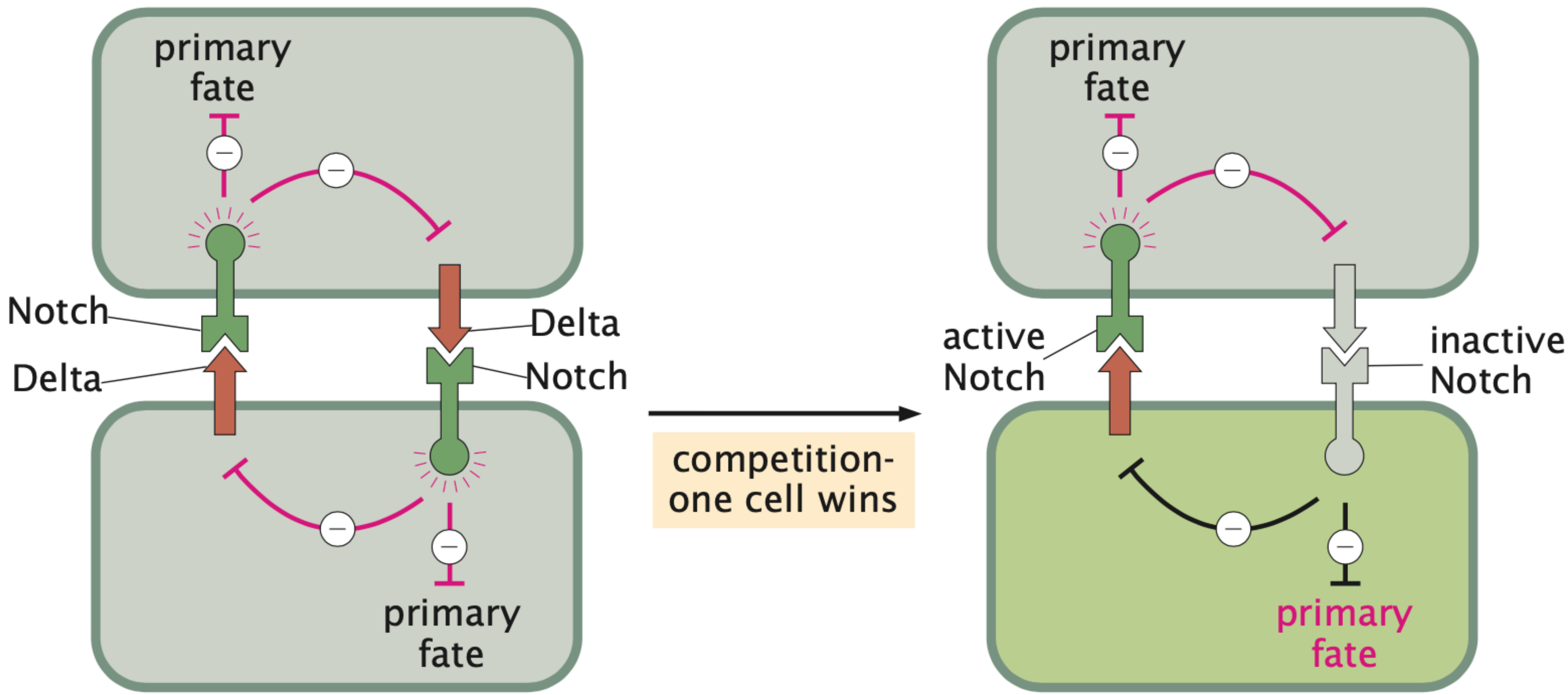


Phillips “Physical Biology of the Cell”

Pattern formation through Notch-Delta lateral inhibition with feedback

Delta (D) ligands inactivate **Notch** (N) receptors in a neighboring cell, which in turn decrease Delta production in that cell

Mechanism can lead to an alternating pattern of low vs high Delta activity

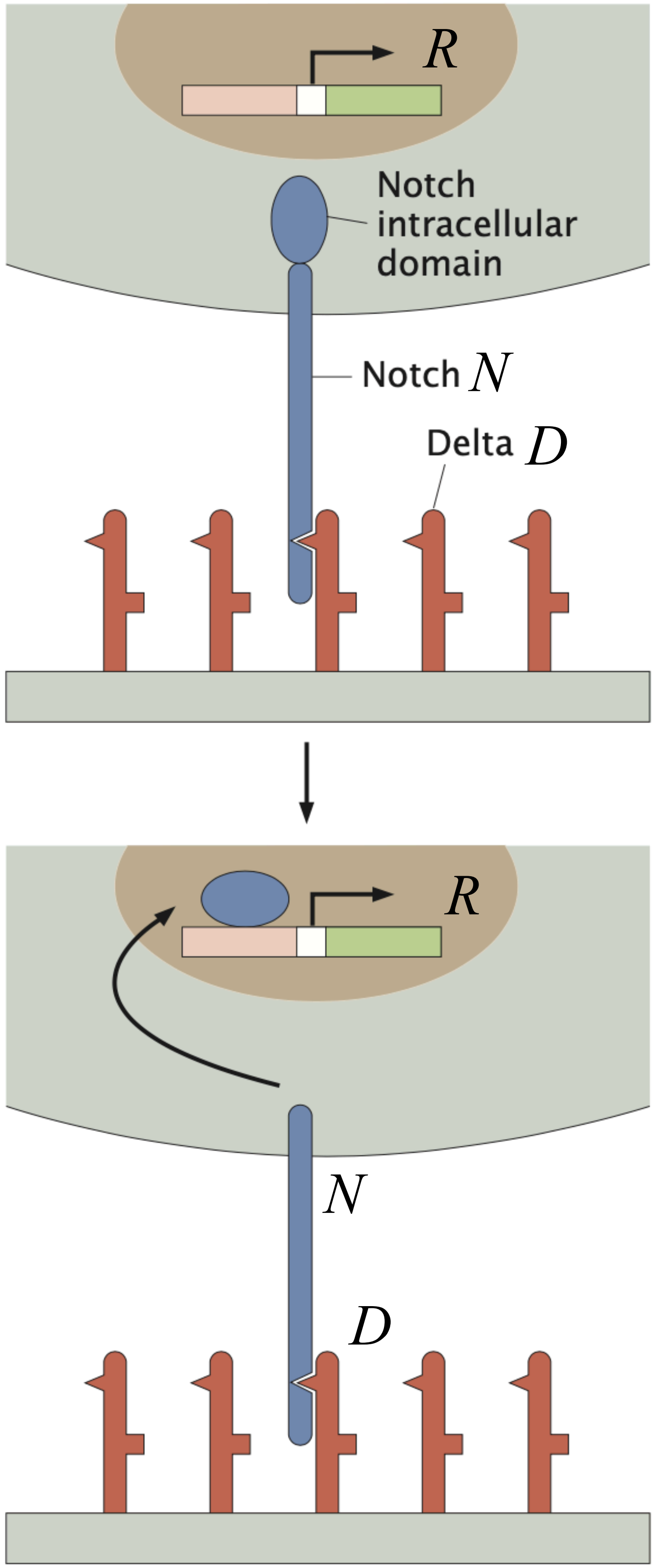


each cell tends to inhibit its neighbor

cell with active Delta specializes and inhibits its neighbor from doing likewise

Phillips "Physical Biology of the Cell"

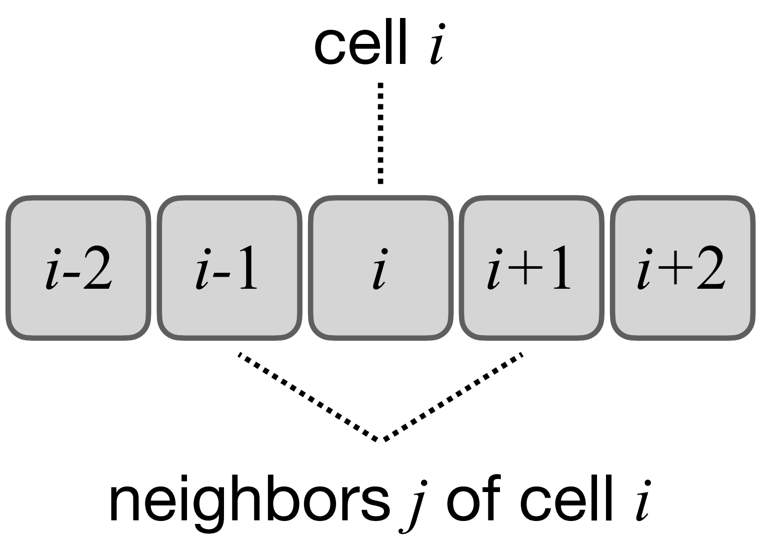
Physical basis of Notch-Delta lateral inhibition with feedback



Phillips "Physical Biology of the Cell"

- Notch receptor (N) and Delta ligand (D) in neighboring cells can form a complex (top)
- Complex formation releases Notch intracellular domain, which travels to the nucleus and activates a repressor gene R (bottom)
- The gene product of R represses Delta in its own cell

A mathematical model of Notch-Delta communication

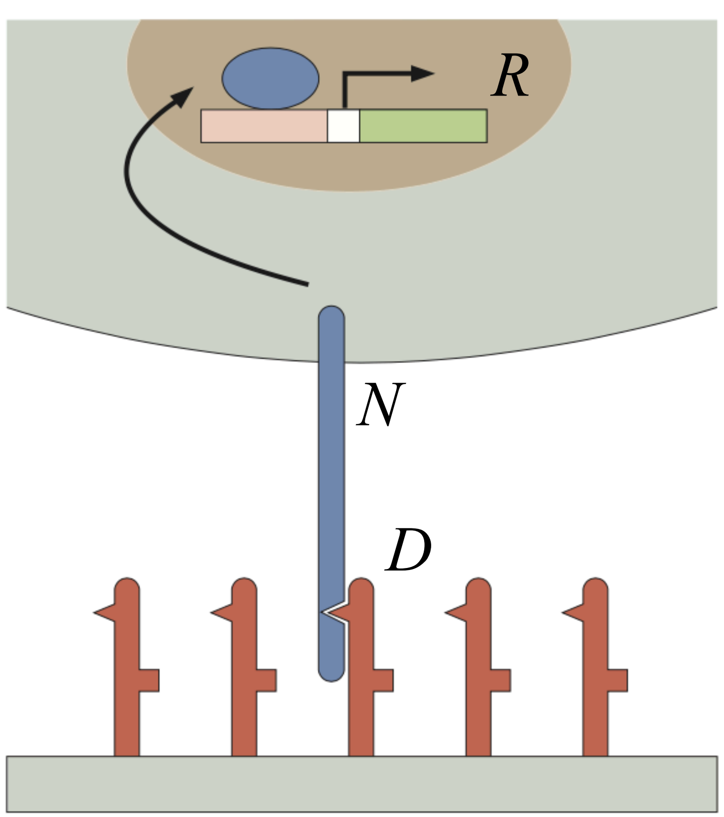


Collier et al. J. Theor. Biol. 183.4 (1996): 429
Sprinzak et al. Nature 465.7294 (2010): 86

$$\dot{N}_i = \beta_N - N_i$$

$$\dot{D}_i = \beta_D \frac{1}{1 + R_i^m} - D_i$$

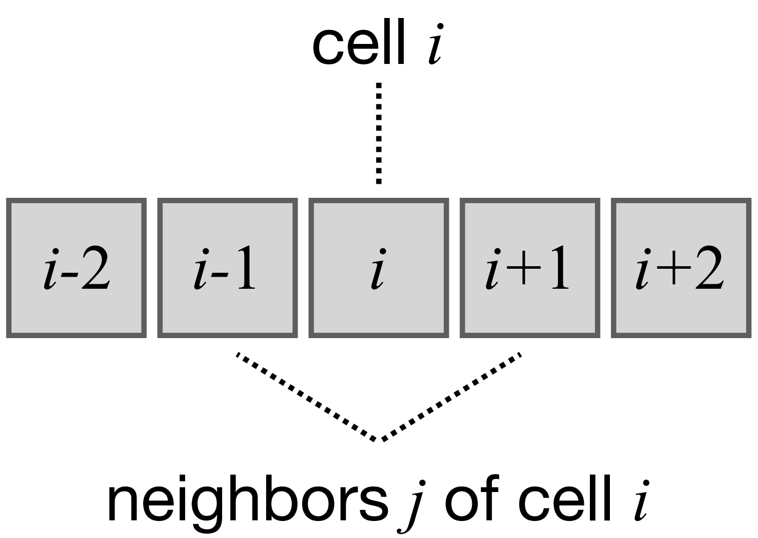
$$\dot{R}_i = \beta_R \frac{\left(N_i \langle D_j \rangle_i\right)^p}{k_{RS}^p + \left(N_i \langle D_j \rangle_i\right)^p} - R_i$$ for every cell i=1,..,M



- Equations written so that all parameters and variables are dimensionless
- N_i, D_i, and R_i are the concentrations of Notch, Delta, and Repressor in i
- All proteins are spontaneously degraded at unit rates (terms $-N_i$ etc.)
- β_N=200, β_D=1000, β_R=3000 are the maximum rates of N, D, R synthesis
- $\langle D_j \rangle_i$ is the average of D over cells j that are neighboring i
- Exponents m and p are the cooperativities of R and the N-D complexes (e.g., m=2 $\rightarrow$ two R proteins are required to repress D)
- k_{RS} is the Michaelis-Menten constant controlling the activation of R by the N-D complex (e.g., $k_{RS} = 30000$)
- R inhibits D synthesis in the same cell, while N complex formation with neighboring D increases R activation

Adding mutual inhibition

Collier et al. J. Theor. Biol. 183.4 (1996): 429
Sprinzak et al. Nature 465.7294 (2010): 86

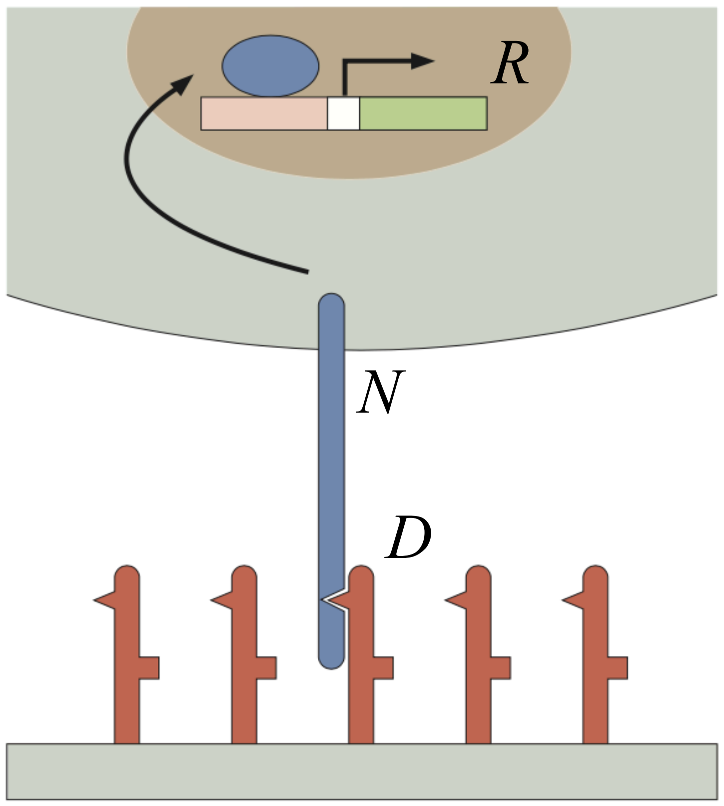


$$\dot{N}_i = \beta_N - N_i - N_i \langle D_j \rangle_i - N_i \frac{D_i}{\kappa_c}$$

$$\dot{D}_i = \beta_D \frac{1}{1 + R_i^m} - D_i - \langle N_j \rangle_i D_i - N_i \frac{D_i}{\kappa_c}$$

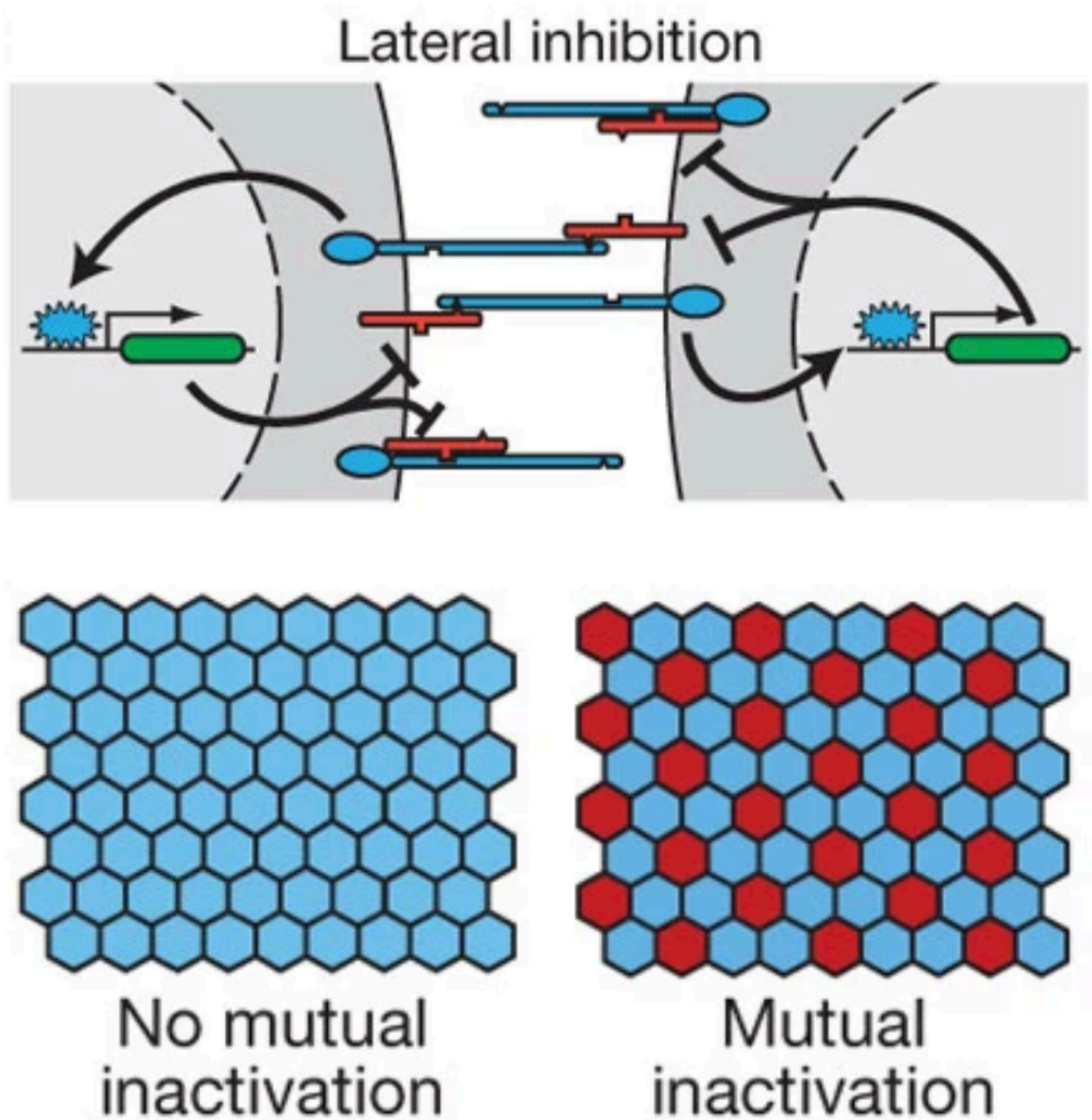
$$\dot{R}_i = \beta_R \frac{\left(N_i \langle D_j \rangle_i\right)^p}{k_{RS}^p + \left(N_i \langle D_j \rangle_i\right)^p} - R_i$$

for every cell i=1,..,M



One problem of the previous model from [Collier et al. J. Theor. Biol. 183.4 (1996): 429] is that it can lead to pattern formation in 2d only when the product of cooperativities mp is >2, for which there is not much evidence.
Experiments from [Sprinzak et al. Nature 465.7294 (2010): 86] provide instead strong evidence for mutual inhibition between Notch and Delta. Physically, when a Notch-Delta complex forms either between neighboring cells ($N_i \langle D_j \rangle_i$) or the same cell ($N_i D_i$), these complexes reduce the amount of freely available Notch and Delta that can participate in the other reactions, which can be modeled by modifying the previous equations as written above.

Adding mutual inhibition (e.g., $k_c = 0.55$) may lead to pattern formation even in the absence of cooperativity ($m = p = 1$)



Sprinzak et al. "Cis-interactions between Notch and Delta generate mutually exclusive signalling states." Nature 465.7294 (2010): 86-90.

Tasks:

A. Implement both introduced models, first for just 2 neighboring cells, and then for an array of cells in 1 dimension, using periodic boundary conditions (imagine the cells are arranged in a circle, with the first one interacting with the last). NOTE: use numpy arrays.
B. Explore the behavior of the systems for different parameters and try to reproduce past simulation results (that mutual inhibition may lead to pattern formation in the absence of cooperativity).

References:

- Phillips “Physical Biology of the Cell”. Chapter 20
- Alberts “Molecular Biology of the Cell”. Chapter 21
- Collier, Joanne R., et al. "Pattern formation by lateral inhibition with feedback: a mathematical model of delta-notch intercellular signalling." Journal of theoretical Biology 183.4 (1996): 429-446.
- Sprinzak, David, et al. "Cis-interactions between Notch and Delta generate mutually exclusive signalling states." Nature 465.7294 (2010): 86-90.
  Model used here in Supplementary Information, section IV equations 50-52