Part 2-3e: Signaling and non-linear dynamics - Full

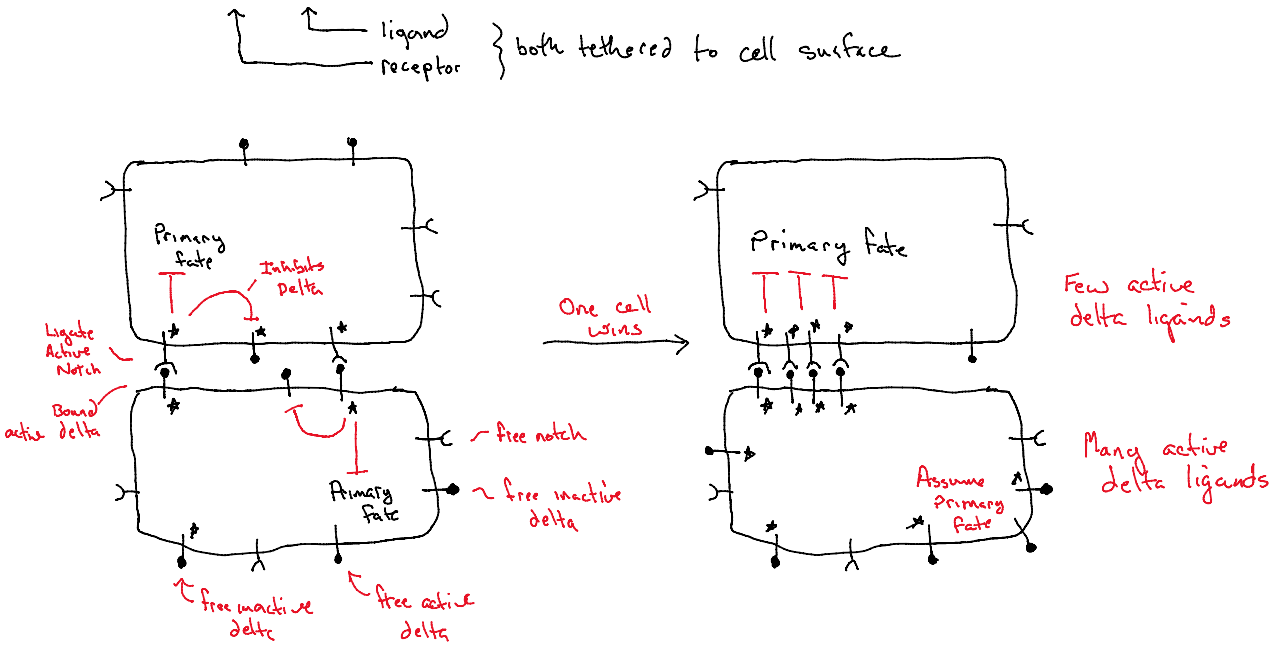
Tuesday, May 5, 2020 12:51 PM

5. Pattern formation through contact inhibition

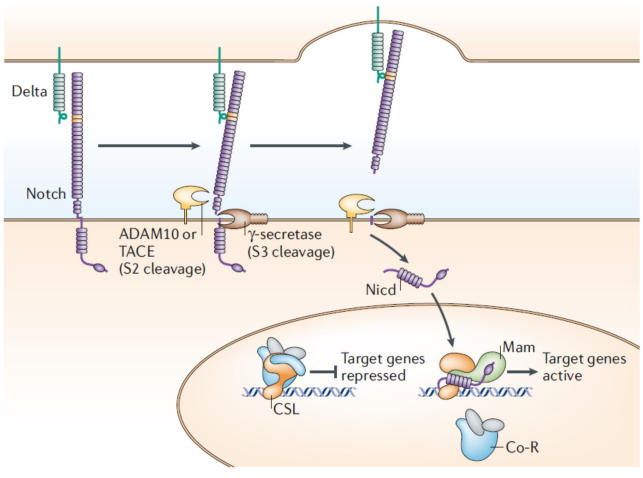
   a. **Concept**: Once one cell assume a fate, it can block a nearby cell from choosing the same fate

   b. **Mechanism - Lateral Inhibition**: Feedback mechanism between nighboring cells amplifies the differences between them
      i. Generates "salt and pepper" patterns
      ii. Note: Later activation also exists. Feedback amplifies similarities between neighboring cells; helps make noisy developmental programs where you don't want to amplify noise run more smoothly

   c. **Example - Notch-Delta**:



Notch activation



Bray, Nat. Rev. Molec. Cell. Biol.

Co-R

Bray, Nat. Rev. Molec. Cell. Biol. (2016); 7: 678-89

Two-cell Model:

$$\frac{dN_1}{dt} = F(D_2) - \gamma_N N_1 \qquad \text{(F = Activation fxn)}$$

$$\frac{dD_1}{dt} = G(N_1) - \gamma_D D_1 \qquad \text{(G = Inhibition fxn)}$$

$$\frac{dN_2}{dt} = F(D_1) - \gamma_N N_2$$

$$\frac{dD_2}{dt} = G(N_2) - \gamma_D D_2 \qquad (1)$$

N_x = Active notch in cell x
D_x = Active delta in cell x
F [=] Activation fxn
G [=] Inhibition fxn
γ [=] degradation const.

Assuming that N_x, D_x are already normalized by their max values, system can be made dimensionless by subbing, $\tau = \gamma_N t$

$$\Rightarrow \quad \frac{dN_1}{d\tau} = f(D_2) - N_1 \qquad (2)$$

$$\frac{dD_1}{d\tau} = (g(N_1) - D_1)\nu \qquad (3)$$

$$\frac{dN_2}{d\tau} = f(D_1) - N_2 \qquad (4)$$

$$\frac{dD}{d\tau} = (g(N_2) - D_2)\nu \qquad (5)$$

where: $\tau = \gamma_N t$

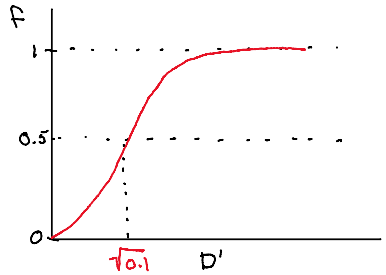
$\nu = \gamma_D / \gamma_N$

~ indicates other cell

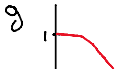
Obtain $f(D')$ and $g(N)$ from experiments (Sprinzak, Nature 2010)

$$f(D') = \frac{F(D')}{\gamma_N} = \frac{D'^2}{0.1 + D'^2}$$

eqn. (6)

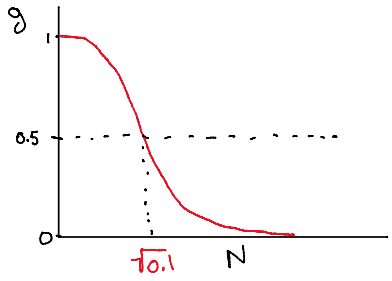


$$g(N) = \frac{G(N)}{\gamma_-} = \frac{1}{1 + 10N^2}$$



$$g(N) = \frac{G(N)}{\gamma_0} = \frac{1}{1 + 10N^2}$$

eqn. (7)



Consider case when $\nu >> 0$

$\Rightarrow D_1, D_2$ quickly relax to steady-state values (QSSA)

$$\frac{1}{\nu}\frac{dD_1}{d\tau} = g(N_1) - D_1 \approx 0 \quad \text{for very large } \nu$$

$$\frac{1}{\nu}\frac{dD_2}{d\tau} = g(N_2) - D_2 \approx 0 \quad \text{for very large } \nu$$

$\Rightarrow g(N_1) \approx D_1$

$g(N_2) \approx D_2$

Plug into (2), (4):

$$\frac{dN_1}{d\tau} = f(g(N_2)) - N_1 \qquad (8)$$

$$\frac{dN_2}{d\tau} = f(g(N_1)) - N_2 \qquad (9)$$

Geometric Soln-Phase Portrait:

Nullclines:

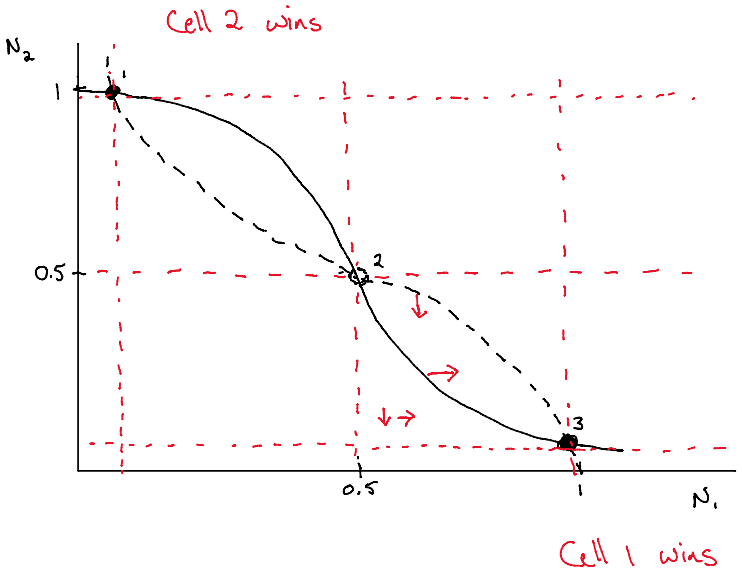
$$\frac{dN_1}{d\tau} = 0 \Rightarrow N_1 = f(g(N_2))$$

$$= \frac{\left(\frac{1}{1 + 10N_2^2}\right)^2}{0.1 + \left(\frac{1}{1 + 10N_2^2}\right)^2}$$

$$\frac{dN_2}{d\tau} = 0 \Rightarrow N_2 = f(g(N_1))$$

$$= \frac{\left(\frac{1}{1 + 10N_1^2}\right)^2}{}$$

$$= \frac{\left(\frac{1}{1+10N_1^2}\right)^2}{0.1+\left(\frac{1}{1+10N_1^2}\right)^2}$$



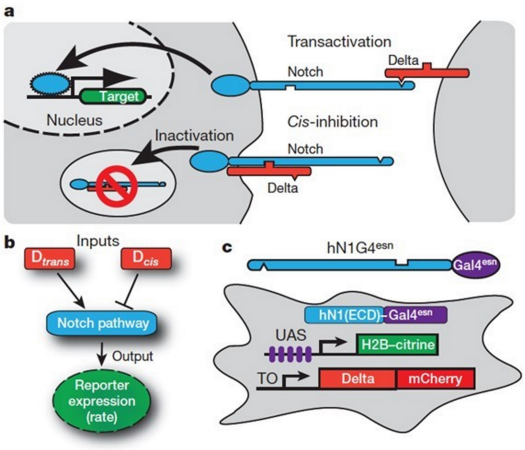
nature Vol 465|6 May 2010|doi:10.1038/nature08959

Cis-interactions between Notch and Delta generate mutually exclusive signalling states

David Sprinzak[1], Amit Lakhanpal[1], Lauren LeBon[1], Leah A. Santat[1], Michelle E. Fontes[1], Graham A. Anderson[2], Jordi Garcia-Ojalvo[3] & Michael B. Elowitz[1]

Synthetic Notch reporter. Notch cytoplasmic domain replaced with Gal4. Cleaved Gal4 activates expression of UAS promoter and downstream yellow fluorescent protein (citrine). Delta with red fluorescent protein (mCherry) can be turned on using tetracycline to active the tetracycline responsive promoter (TO).

Yellow reports active Notch. Red reports Delta levels.



Control of gene expression by Notch-Delta signaling

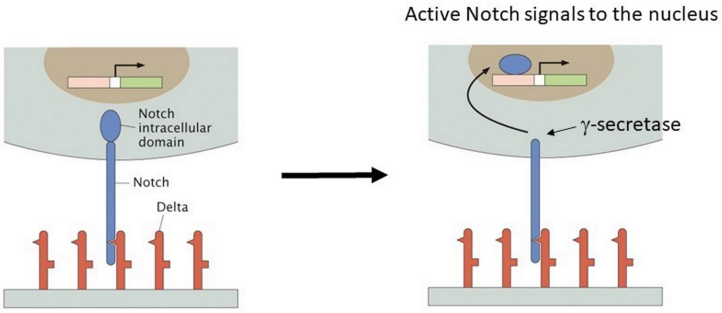
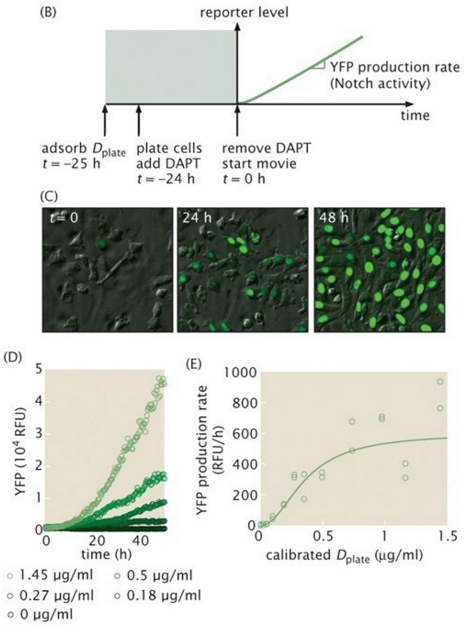


Figure 20.30 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Delta ligand absorbed on a solid substrate surface at concentration Dplate. DAPT inhibits g-secretase and added to the system to keep Notch inactive while cells are plated to the surface. DAPT washed out to allow Notch activation. YFP response measured versus time. Gives activation function.



Similar experiment conducted except Dox was added prior to DAPT washout to turn on expression of Delta in the cells. Allows for determination of inhibition function.