1 Background Information

Sources: Boareto et al., 2015, Bray, 2006

Binding of the Delta ligand from cell B to the Notch receptor on cell A results in the *cleavage* (removal) of both the ligand and receptor. This interaction triggers the release of NICD (Notch Intracellular Domain) in cell A, which *promotes* Notch and *inhibits* Delta.

- The Serrate (Jagged) ligand can also bind to Notch. Unlike Delta, NICD promotes Jagged, which creates a double-positive feedback loop.
- Interaction between Delta ligands and Notch receptors from the same cell (cis-interaction) removes both molecules and does not trigger the release of NICD.

2 Collier et al., 1996

Collier et al. make the following five modelling assumptions:

1. Cells interact through Delta-Notch signalling if and only if they are adjacent.
2. Production of Notch is an increasing (hill) function of Delta in neighbouring cells.
3. Production of Delta is a decreasing (hill) function of Notch in the same cell.
4. Production of Notch and Delta is balanced by decay proportional to concentration.
5. Low levels of Notch cause the primary fate, high levels cause the secondary fate.

Define the following variables:

- τ: time
- N_P: notch activity (concentration) in cell P
- D_P: delta activity (concentration) in cell P
- $\overline{D}_P$: average delta activity in neighbours of P
- N_0: typical notch activity (across all cells)
- D_0: typical delta activity (across all cells)
- μ: The decay rate for notch (assumed constant)
- ρ: The decay rate for delta (assumed constant)

Then, define the following system of differential equations, where $F : [0, \infty) \to [0, \infty)$ is a continuous increasing function and $G : [0, \infty) \to [0, \infty)$ is a continuous decreasing function.

$$\frac{d(N_P/N_0)}{d\tau} = F(\overline{D}_P/D_0) - \mu N_P/N_0$$
$$\frac{d(D_P/D_0)}{d\tau} = G(N_P/N_0) - \rho D_P/D_0$$

This equation is inherently nondimensional, since N_P/N_0 and D_P/D_0 have no units.

Remark: The notch activity can also be taken to be the number of complexes formed by the binding of notch to its activated ligand delta (Collier et al. 1996).

2.1 Deriving a Probabilistic Model

We will make the assumption that each cell has N notch molecules (which can be in a complex, or not). As we did above, define $\overline{D}$ to be the average number of active delta molecules in neighbouring cells. Let k_b be the binding rate and k_u the unbinding rate. Let $p_n(t)$ be the probability there are n complexes at time t. Then, define the Kolmogorov forward equation:

$$\begin{aligned} p_n(t+\Delta t) = p_{n-1}(t) \cdot \underbrace{(N-(n-1))(\overline{D}-(n-1))k_b\Delta t}_{\text{P(binding)}} \\ + p_n(t) \cdot \underbrace{(1-(N-n)(\overline{D}-n)k_b\Delta t)}_{\text{P(no binding)}} \cdot \underbrace{(1-nk_u\Delta t)}_{\text{P(no unbinding)}} \\ + p_{n+1}(t) \cdot \underbrace{(n+1)k_u\Delta t}_{\text{P(unbinding)}} \end{aligned}$$

Rearranging this equation (and cancelling out the term with Δt^2) we get:

$$\begin{aligned} p_n'(t) &= p_{n-1}(t) \cdot (N-(n-1))(\overline{D}-(n-1))k_b \\ &\quad - p_n(t) \cdot (N-n)(\overline{D}-n)k_b - p_n(t) \cdot nk_u \\ &\quad + p_{n+1}(t) \cdot (n+1)k_u \end{aligned}$$

Let $C(t)$ be the number of complexes at time t. From the equation above, we have:

$$y(t) = \mathbb{E}[C(t)] = \sum_{n=0}^{N} np_n(t) \Rightarrow y'(t) = \sum_{n=0}^{N} np_n'(t)$$

Now, we substitute $p_n'(t)$ for the expression derived above:

$$\begin{aligned} y'(t) = &\sum_{n=2}^{N} np_{n-1}(t)(N-(n-1))(\overline{D}-(n-1))k_b \\ &- \sum_{n=1}^{N-1} np_n(t)(N-n)(\overline{D}-n)k_b - \sum_{n=1}^{N} n^2p_n(t)k_u \\ &- \sum_{n=1}^{N-1} np_{n+1}(t)(n+1)k_u \end{aligned}$$

We will need to reindex the p_{n-1} and p_{n+1} terms. To do this, begin by rewriting:

$$\begin{aligned} y'(t) = &\sum_{n=2}^{N} (n-1+1)p_{n-1}(t)(N-(n-1))(\overline{D}-(n-1))k_b \\ &- \sum_{n=1}^{N-1} np_n(t)(N-n)(\overline{D}-n)k_b - \sum_{n=1}^{N} n^2p_n(t)k_u \\ &- \sum_{n=1}^{N-1} (n+1-1)p_{n+1}(t)(n+1)k_u \end{aligned}$$

Now, perform reindexing on the p_{n-1} and p_{n+1} terms:

$$
\begin{aligned}
y'(t) = & \sum_{n=1}^{N-1}(n+1)p_n(t)(N-n)(\overline{D}-n)k_b \\
& - \sum_{n=1}^{N-1} np_n(t)(N-n)(\overline{D}-n)k_b - \sum_{n=1}^{N} n^2 p_n(t)k_u \\
& + \sum_{n=2}^{N}(n-1)p_n(t)nk_u
\end{aligned}
$$

Now, we cancel out like terms to get the following:

$$
y'(t) = \sum_{n=1}^{N} p_n(t)(N-n)(\overline{D}-n)k_b - \sum_{n=1}^{N} np_n(t)k_u
$$

Therefore,

$$
y'(t) = (N-y)(\overline{D}-y)k_b - yk_u
$$

Note that the $(N-y)(\overline{D}-y)$ term is an increasing function of $\overline{D}$, which means that it satisfies the conditions imposed by the Collier et al. (1996). However, it is not a hill function, which means the authors made different assumptions about the system.