Comparing Models of Delta-Notch Signalling

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Introduction

Introduction

The Signalling Pathway

- Ligands bind to a Notch receptor.
- This releases NICD in the cell.
- NICD promotes Notch, inhibits Delta, and promotes Serrate.
- *Cis-inhibition* occurs between molecules from the same cell.

Previous Models

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We investigate how the results of these models change under the **Stochastic Differential Equation** (SDE) and **Agent-Based** formalisms.

Our Assumptions

- All ligands are Delta molecules (so we ignore Serrate).
- Delta molecules only bind to Notch receptors from neighbouring cells.
- Reaction events follow a Poisson point process.
- Notch and Delta production are hill functions of NICD.

Our Chemical Equations

Consider a cell A with neighbour B. The Notch, Delta, and NICD concentrations of cell A are given by N_A, D_A, and I_A respectively (and similarly for cell B).

1. $N_A + D_B \to I_A$: Binding event.
2. $N_A \to \emptyset$: Notch decay.
3. $D_A \to \emptyset$: Delta decay.
4. $I_A \to \emptyset$: NICD decay.
5. $\emptyset \to N_A$: Notch production.
6. $\emptyset \to D_A$: Delta production.

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In the **SDE** model, we reintroduce randomness by adding an independent *Wiener Process* to each equation in the ODE model. This recreates some the stochasticity of the agent-based model.

Derivation

Preliminaries and Assumptions

Reaction	Rate	Description
$N_A + D_B \to I_A$	$k_T N_A D_B$	A Notch receptor from cell A binds to a delta ligand from cell B, triggering the release of NICD in cell A.
$N_A \to \emptyset$	γN_A	A Notch receptor from cell A decays.
$D_A \to \emptyset$	γD_A	A Delta receptor from cell A decays.
$I_A \to \emptyset$	$\gamma_I I_A$	A NICD molecule from cell A decays.
$\emptyset \to N_A$	$H^+(I_A)$	A Notch receptor in cell A is produced
$\emptyset \to D_A$	$H^-(I_A)$	A Delta ligand in cell A is produced

Table 1: A list of possible reactions and their rates in a cell A with neighbour B.

Preliminaries and Assumptions

Since there are 6 possible reactions per cell, a system with k cells will have $6k$ possible reactions to keep track of.

In the following derivations, we focus on tracking a single cell (cell A) for simplicity.

Derivation of Kolmogorov Forward Equation

Let us define

- $P(n, d, i, t)$: the probability of having n Notch receptors, d Delta ligands, and i NICD molecules at time t.
- D_{ext}: the average Delta concentration over all neighbours of cell A.

The KFE describes how $P(n, d, i, t)$ changes over a small time step Δt:

$$
\begin{aligned}
P(n, d, i, t + \Delta t) = P(n, d, i, t) \\
&+ P(n-1, d, i, t) \cdot H^+(i)\Delta t \quad \text{(Notch production)} \\
&+ P(n, d-1, i, t) \cdot H^-(i)\Delta t \quad \text{(Delta production)} \\
&+ P(n+1, d, i, t) \cdot \gamma(n+1)\Delta t \quad \text{(Notch decay)} \\
&+ P(n, d+1, i, t) \cdot \gamma(d+1)\Delta t \quad \text{(Delta decay)} \\
&+ P(n, d, i+1, t) \cdot \gamma_I(i+1)\Delta t \quad \text{(NICD decay)} \\
&+ P(n+1, d, i-1, t) \cdot k_T(n+1)D_{ext}\Delta t \quad \text{(Trans-activation)} \\
&- P(n, d, i, t) \cdot [H^+(i) + H^-(i) + \gamma n + \gamma d + \gamma_I i + k_T n D_{ext}]\Delta t
\end{aligned}
$$

Derivation of Kolmogorov Forward Equation

Rearranging to find the time derivative and taking the limit as $\Delta t \to 0$:

$$\begin{aligned}\frac{\partial P(n,d,i,t)}{\partial t} &= P(n-1,d,i,t)\cdot H^{+}(i)\\ &+ P(n,d-1,i,t)\cdot H^{-}(i)\\ &+ P(n+1,d,i,t)\cdot \gamma(n+1)\\ &+ P(n,d+1,i,t)\cdot \gamma(d+1)\\ &+ P(n,d,i+1,t)\cdot \gamma_I(i+1)\\ &+ P(n+1,d,i-1,t)\cdot k_T(n+1)D_{ext}\\ &- P(n,d,i,t)\cdot [H^{+}(i)+H^{-}(i)+\gamma n+\gamma d+\gamma_I i+k_T n D_{ext}]\end{aligned}$$

Matrix Formulation

The Kolmogorov forward equation can be expressed in matrix form as:

$$\frac{d\vec{P}(t)}{dt} = \mathbf{A}\vec{P}(t)$$

where $\vec{P}(t)$ is a column vector containing the probabilities for all possible states, and $\mathbf{A}$ is the transition rate matrix.
Each entry $A_{i,j}$ represents the transition rate from state i to state j. The diagonal elements $A_{i,i}$ contain the negative sum of all outgoing rates from state i.

Matrix Formulation

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Each state in our system is described by (n,d,i), but the matrix form needs a single index.

We flatten the 3D state space into a 1D list.

- We encode (n,d,i) into a single index — just like how multidimensional data (e.g., images, simulation grids) are stored in computer memory.

Matrix Formulation

To construct the matrix **A**, we first establish a one-to-one mapping between the three-dimensional state space (n, d, i) and a one-dimensional index k.

We set n_{max}, d_{max}, and i_{max} as large enough bounds for Notch, Delta, and NICD in cell A. These define the size of our 3D "box" of possible states.
Remark: These are not strict limits but chosen large enough to technically capture all relevant dynamics.

Matrix Formulation

For a system with "maximum" values n_{max}, d_{max}, and i_{max}, we define:

$$k(n, d, i) = n \cdot (d_{max} + 1) \cdot (i_{max} + 1) + d \cdot (i_{max} + 1) + i$$

for $0 \leq n \leq n_{max}$, $0 \leq d \leq d_{max}$, $0 \leq i \leq i_{max}$.
The inverse mapping gives:

$$n(k) = \left\lfloor \frac{k}{(d_{max} + 1) \cdot (i_{max} + 1)} \right\rfloor$$
$$d(k) = \left\lfloor \frac{k \bmod ((d_{max} + 1) \cdot (i_{max} + 1))}{i_{max} + 1} \right\rfloor$$
$$i(k) = k \bmod (i_{max} + 1)$$

Matrix Formulation

With this mapping, we can now define the elements of matrix $\mathbf{A}$. Let k and k' be the indices corresponding to states (n, d, i) and (n', d', i') respectively:

$$A_{k,k'} = \begin{cases} H^+(i) & \text{if } (n', d', i') = (n+1, d, i) \quad \text{(Notch production)} \\ H^-(i) & \text{if } (n', d', i') = (n, d+1, i) \quad \text{(Delta production)} \\ \gamma(n) & \text{if } (n', d', i') = (n-1, d, i) \quad \text{(Notch decay)} \\ \gamma(d) & \text{if } (n', d', i') = (n, d-1, i) \quad \text{(Delta decay)} \\ \gamma_I(i) & \text{if } (n', d', i') = (n, d, i-1) \quad \text{(NICD decay)} \\ k_T(n) D_{ext} & \text{if } (n', d', i') = (n-1, d, i+1) \quad \text{(Trans-activation)} \\ -v & \text{if } k' = k \quad \text{(Diagonal terms)} \end{cases}$$

Matrix Formulation

Note that $A_{k,k'}$ represents the transition rate from state k to state k'. The diagonal elements $A_{k,k}$ are the negative sum of all outgoing rates from state k:

$$A_{k,k} = -v = -[H^+(i) + H^-(i) + \gamma n + \gamma d + \gamma_I i + k_T n D_{ext} + k_T d N_{ext}]$$

where (n, d, i) is the state corresponding to index k.
The resulting matrix **A** is a sparse matrix with the following properties:

- Dimension: $(n_{max} + 1) \cdot (d_{max} + 1) \cdot (i_{max} + 1) \times (n_{max} + 1) \cdot (d_{max} + 1) \cdot (i_{max} + 1)$
- Number of non-zero elements: $\approx 7 \cdot (n_{max} + 1) \cdot (d_{max} + 1) \cdot (i_{max} + 1)$

Matrix Formulation

The corresponding transition matrix **A** would be:

$$\mathbf{A} = \begin{pmatrix} -v_{000} & \alpha_{000,001} & \alpha_{000,010} & \alpha_{000,011} & \alpha_{000,100} & \alpha_{000,101} & \alpha_{000,110} & \alpha_{000,111} \\ \alpha_{001,000} & -v_{001} & \alpha_{001,010} & \alpha_{001,011} & \alpha_{001,100} & \alpha_{001,101} & \alpha_{001,110} & \alpha_{001,111} \\ \alpha_{010,000} & \alpha_{010,001} & -v_{010} & \alpha_{010,011} & \alpha_{010,100} & \alpha_{010,101} & \alpha_{010,110} & \alpha_{010,111} \\ \alpha_{011,000} & \alpha_{011,001} & \alpha_{011,010} & -v_{011} & \alpha_{011,100} & \alpha_{011,101} & \alpha_{011,110} & \alpha_{011,111} \\ \alpha_{100,000} & \alpha_{100,001} & \alpha_{100,010} & \alpha_{100,011} & -v_{100} & \alpha_{100,101} & \alpha_{100,110} & \alpha_{100,111} \\ \alpha_{101,000} & \alpha_{101,001} & \alpha_{101,010} & \alpha_{101,011} & \alpha_{101,100} & -v_{101} & \alpha_{101,110} & \alpha_{101,111} \\ \alpha_{110,000} & 0 & H^+(0) & 0 & H^-(1) & 0 & -v_{110} & \gamma_I \\ \alpha_{111,000} & 0 & 0 & H^+(0) & 0 & H^-(1) & H^+(1) & -v_{111} \end{pmatrix}$$

where:

$$\alpha_{ndi,n'd'i'} = H^+(i) + H^-(i) + \gamma n + \gamma d + \gamma_I i + k_T n D_{ext} + k_T d N_{ext}$$

Remarks

Let us consider

- A one-cell system: $P(n, d, i, t + \Delta t)$
  A k-cell system: $P(n_1, d_1, i_1, n_2, d_2, i_2, ..., n_k, d_k, i_k, t + \Delta t)$
- D_{ext} (the average Delta concentration over all neighbours of cell A).

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- D_{ext} (the average Delta concentration over all neighbours of cell A).

The complexity of a single cell highlights the need for numerical methods to model interactions between cells.

Results

Comparing Two-Cell Models

Noise in the SDE Model

Stability Analysis

We tested model stability by perturbing 5 parameters: N_m, D_m, K_T, γ, and γ_I.

- N_m, D_m are the maximum rates of Notch/Delta production.
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Due to computational limitations, we investigated the 2-dimensional subspaces of our 5-dimensional parameter space using the following algorithm:

- Run the two-cell model on a 25×25 grid of points spanning 2 OOMs.
- Take the convex hull of the points at which the cells differentiated.

Stability Analysis

Simulations on Linear Domains

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Patterns on Linear Domains

Simulations on Hexagonal Domains

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