

Math 462 Project

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1 Introduction

The numbers of Notch (N_P) and Delta (D_P) molecules changing over time due to random reactions motivates us to employ a stochastic model. Each reaction happens with a certain probability per unit time. However, we want to show that, in the large-number limit, the expected values $E[N_P]$ and $E[D_P]$ follow the deterministic ODEs:

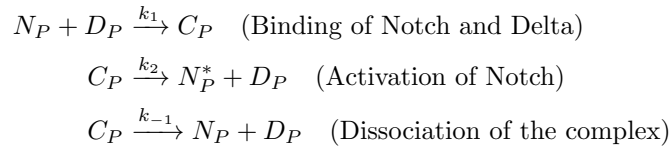
$$\begin{aligned}\frac{dN_P}{dt} &= F(D_{\text{neighbour},P}) - \mu N_P \\ \frac{dD_P}{dt} &= G(N_P) - \rho D_P\end{aligned}$$

We establish a detailed stochastic model for Notch-Delta signalling, ensuring that it converges to the deterministic ODE model under suitable regularity conditions. The system is described by a continuous-time Markov process (CTMC) and then derive the expected value equations to show how it approximates the deterministic model.

2 Stochastic Model for Notch-Delta Signalling

2.1 Chemical Reactions and Propensities

To construct a probabilistic model, we define the stochastic dynamics of the Delta-Notch interaction as a set of discrete reaction events. We introduce the following reactions:



where:

- C_P represents the Notch-Delta complex in cell P .
- k_1 is the rate at which Notch and Delta bind to form a complex.
- k_2 is the rate at which the complex activates Notch, producing an intracellular signal.
- k_{-1} is the dissociation rate of the complex back into Notch and Delta.

Reactions describing Notch and Delta production and degradation are summarized in the table below:

Reaction	Reaction Equation	Associated term
Notch production	$N_P \rightarrow N_P + 1$	$F(D_{\text{neighbour},P})$
Notch degradation	$N_P \rightarrow N_P - 1$	μN_P
Delta production	$D_P \rightarrow D_P + 1$	$G(N_P)$
Delta degradation	$D_P \rightarrow D_P - 1$	ρD_P

Table 1: A summary of Notch and Delta production and degradation reactions

where:

- $F(D_{\text{neighbour},P})$ is an increasing function describing the effect of Delta on Notch production.
- $G(N_P)$ is a decreasing function representing Notch inhibiting Delta.

2.2 Chemical Master Equation and State Probabilities

Let $P(N_P, D_P, C_P, t)$ be the probability that the system is in state (N_P, D_P, C_P) at time t . The probability evolves according to the chemical master equation (CME):

$$\begin{aligned} \frac{dP}{dt} = \sum_{\text{all reactions}} [\text{gain term} - \text{loss term}] \\ \frac{dP(N_P, D_P, C_P, t)}{dt} = k_1(N_P - 1)(D_P - 1)P(N_P - 1, D_P - 1, C_P + 1, t) \\ + k_{-1}(C_P + 1)P(N_P + 1, D_P + 1, C_P - 1, t) \\ + k_2(C_P + 1)P(N_P, D_P, C_P - 1, t) \\ + F(D_{\text{neighbour},P})P(N_P - 1, D_P, C_P, t) \\ + G(N_P)P(N_P, D_P - 1, C_P, t) \\ + \mu(N_P + 1)P(N_P + 1, D_P, C_P, t) \\ + \rho(D_P + 1)P(N_P, D_P + 1, C_P, t) \\ - (k_1 N_P D_P + k_{-1} C_P + k_2 C_P + \mu N_P + \rho D_P)P(N_P, D_P, C_P, t). \end{aligned}$$

2.3 Expected Value Approximation

To derive the deterministic equations, we compute the expected values:

$$\begin{aligned} E[N_P] &= \sum_{N_P} N_P P(N_P, D_P, C_P, t) \\ E[D_P] &= \sum_{D_P} D_P P(N_P, D_P, C_P, t) \\ E[C_P] &= \sum_{C_P} C_P P(N_P, D_P, C_P, t) \end{aligned}$$

Taking the time derivative:

$$\frac{dE[N_P]}{dt} = \sum_{N_P} N_P \frac{dP(N_P, D_P, C_P, t)}{dt}.$$

Substituting from the CME, we obtain:

$$\frac{dE[N_P]}{dt} = -k_1 E[N_P]E[D_P] + k_{-1}E[C_P] + k_2 E[C_P] + F(E[D_{\text{neighbour},P}]) - \mu E[N_P].$$

Similarly, for Delta:

$$\frac{dE[D_P]}{dt} = -k_1 E[N_P]E[D_P] + k_{-1}E[C_P] + G(E[N_P]) - \rho E[D_P].$$

For Complexes, we start with the transition terms in the CME.

$$\begin{aligned} \frac{dP(N_P, D_P, C_P, t)}{dt} = & +k_1(N_P - 1)(D_P - 1)P(N_P - 1, D_P - 1, C_P + 1, t) \\ & +k_{-1}(C_P + 1)P(N_P + 1, D_P + 1, C_P - 1, t) \\ & +k_2(C_P + 1)P(N_P, D_P, C_P - 1, t) \end{aligned}$$

We compute the expected value for complexes, $E[C_P]$, and substitute into the time derivative expression:

$$\frac{dE[C_P]}{dt} = k_1 E[N_P]E[D_P] - (k_{-1} + k_2)E[C_P] - k_{-1}$$

Rearranging, we get the final form:

$$\frac{dE[C_P]}{dt} = k_1 E[N_P]E[D_P] - (k_{-1} + k_2)E[C_P].$$

Using the main equation derived above, we substitute dP/dt for each reaction.

For Notch production, we expand:

$$\sum_{N_P} N_P [F(D_{\text{neighbour},P})P(N_P - 1, D_P, C_P, t) - F(D_{\text{neighbour},P})P(N_P, D_P, C_P, t)]$$

Shifting the sum over N_P gives:

$$\sum_{N_P} (N_P + 1)F(D_{\text{neighbour},P})P(N_P, D_P, C_P, t) - \sum_{N_P} N_P F(D_{\text{neighbour},P})P(N_P, D_P, C_P, t)$$

Rearranging:

$$\sum_{N_P} F(D_{\text{neighbour},P})P(N_P, D_P, C_P, t) = E[F(D_{\text{neighbour},P})]$$

Thus, the equation simplifies to:

$$\frac{dE[N_P]}{dt} = E[F(D_{\text{neighbour},P})] - \mu E[N_P]$$

Similarly, for Delta:

$$\frac{dE[D_P]}{dt} = E[G(N_P)] - \rho E[D_P]$$

2.4 The Mean-Field Approximation

In general, expected values of nonlinear functions like $E[F(D_P)]$ are not necessarily equal to $F(E[D_P])$. However, under large-number assumptions, fluctuations around the mean become small (due to the law of large numbers), and we approximate:

$$E[F(D_{\text{neighbour},P})] \approx F(E[D_{\text{neighbour},P}])$$

$$E[G(N_P)] \approx G(E[N_P])$$

This assumes that each individual cell's fluctuations average out in large populations.

2.5 Deterministic Model Recovery

Substituting these approximations into our equations:

$$\frac{dE[N_P]}{dt} = F(E[D_{\text{neighbour},P}]) - \mu E[N_P]$$

$$\frac{dE[D_P]}{dt} = G(E[N_P]) - \rho E[D_P]$$

Thus, we recover the deterministic system:

$$\frac{dN_P}{dt} = F(D_{\text{neighbour},P}) - \mu N_P$$

$$\frac{dD_P}{dt} = G(N_P) - \rho D_P$$

The calculation confirms that in the large-number limit, the stochastic model converges to the deterministic ordinary differential equation (ODE) system. This implies that as the molecular count increases, transitioning the system to a more macroscopic scale, the stochastic model naturally aligns with the deterministic framework.

2.6 Convergence to the Deterministic Model

To show convergence, define fluctuations:

$$X = N_P - E[N_P], \quad Y = D_P - E[D_P], \quad Z = C_P - E[C_P].$$

Taking expectations:

$$\frac{dE[X]}{dt} = -\mu E[X], \quad \frac{dE[Y]}{dt} = -\rho E[Y], \quad \frac{dE[Z]}{dt} = -(k_{-1} + k_2)E[Z].$$

These decay exponentially, meaning that as time progresses:

$$E[X], E[Y], E[Z] \rightarrow 0.$$

Thus, the stochastic model converges to the deterministic ODE model as molecule numbers increase.