

# 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:

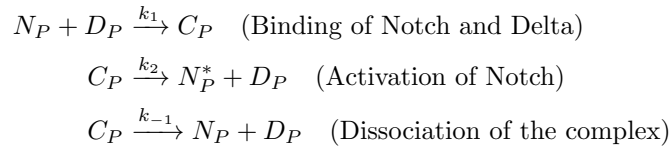
$$\begin{aligned}\frac{dN_P}{dt} &= F(D_{\text{neighbour},P}) - \mu N_P \\ \frac{dD_P}{dt} &= G(N_P) - \rho D_P\end{aligned}$$

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:



Shouldn't the binding equation use  $\bar{D}_P$  (i.e. the delta concentration in neighbouring cells) instead of  $D_P$ ? Also, I think this would be a good place to state the assumptions you used to derive these equations. The start of section "2. The Model" in Collier et al. contains some more information about interpreting  $N$  and  $D$  that might be useful to read through.

I'm also unsure about the activation equation, because it implies that a complex is splitting to form an  $N_P^*$  (what makes this different from  $N_P$ , by the way?) and a  $D_P$ . I think something like  $C_P \xrightarrow{k_2} N_P^* + D_P$  might be more accurate.

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	$N_P \rightarrow N_P - 1$	$\mu N_P$
Delta production	$D_P \rightarrow D_P + 1$	$G(N_P)$
Delta degradation	$D_P \rightarrow D_P - 1$	$\rho D_P$

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):

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

I think there are a couple mistakes in this equation. For example, in the first term, we're looking at the probability of a binding event, which creates one  $C_P$  and destroys a  $N_P$  and a  $D_P$ . Therefore, I believe we need to be in state  $(N_P + 1, D_P + 1, C_P - 1)$  in order for a binding event to take us to state  $(N_P, D_P, C_P)$ . I think the first term should be the following, although I could be mistaken.

$$k_1(N_P + 1)(D_P + 1)P(N_P + 1, D_P + 1, C_P - 1, t)$$

I think some of the other terms have similar issues. I'm also still unsure about the difference between the unbinding ( $k_{-1}$ ) and activation ( $k_2$ ) reactions. What assumptions are you making?

## 2.3 Expected Value Approximation

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

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

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

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

Taking the time derivative:

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

This looks good and makes sense to me.

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:

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

I'm not sure how you got to here, but the equation makes sense.

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:

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

Isn't this just the previous equation without the  $k_{-1}$ ? I also think you're missing an  $E[C_P]$ :

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

and then you can do some simple algebra to get rid of the last term.

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

For Notch production, we expand:

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

Where does this equation come from?

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.