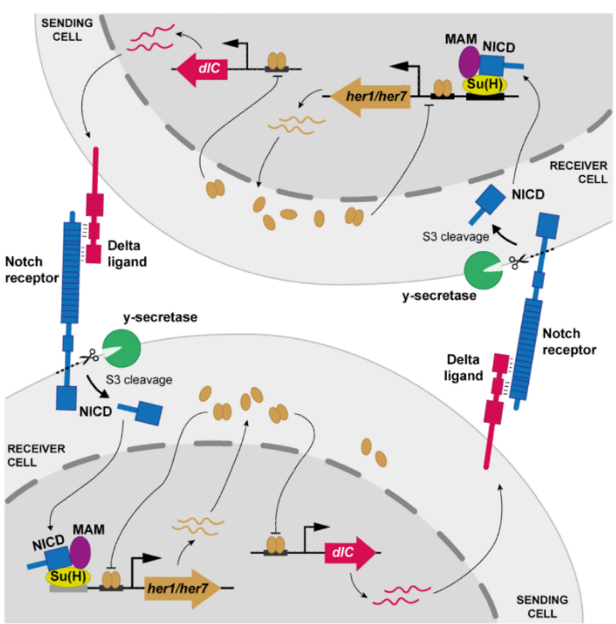
Setup:

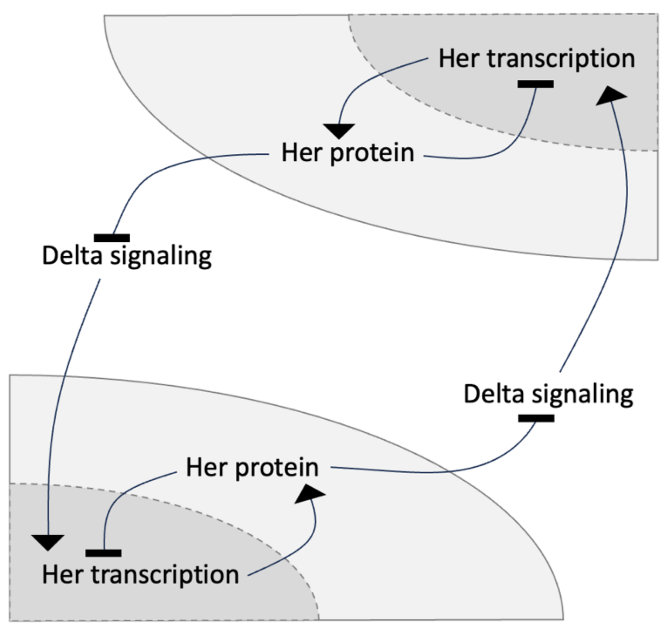
Download and unzip the “Coupled_oscillator” folder in your Noto instance
Open a terminal from within the “Coupled_oscillator” folder
Run “`kbuilder_create cosc2 requirements.txt`”
Refresh window
Open “her_sync_05.ipynb”
Select kernel “cosc2” in top right corner (start python kernel)
You can now run the notebook with all required packages

Exercises:

We will use a mathematical simulation to observe how complex behavior can appear in a system of two communicating cells. Remember to record the output and values you used to run the model for each exercise question. Each time you change the value, you can run the new simulation and generate the plots by running the entire notebook.



Delta-Notch and Her molecular signaling



Simplified interaction diagram

Loureiro, Cristina, Olivier F. Venzin, and Andrew C. Oates. "Generation of patterns in the paraxial mesoderm." *Current topics in developmental biology* 159 (2024): 372-405.

Week 1: Lateral inhibition

1. We are starting with weak signaling between cells. For low coupling, set Ks to high (>0.9). Start by varying the relative values of production (ν) and decay (μ). Try both high and low values.
    a. How does the ratio production:decay affect the final Her concentration in each cell? Does the initial concentration matter?
    b. Is there a difference between the coupled and the uncoupled model?

2. Chose a production and decay rate (you can use the recommended values or something near). Now change Kh, the relative strength of autoinhibition. Remember, a low Kh value is high strength, and a high Kh value is low strength.
    a. How does the behavior change?
    b. What is the difference between changing the production:decay ratio, and changing the strength of autoinhibition?

3. Set Kh to a moderate value (around 0.4). We will now add cell-cell communication by setting Ks to a low value (i.e. strong signaling coupling).
    a. What happens now that you increased signal coupling?
    b. How does the strength of coupling affect the coupled model when compared to the uncoupled behavior?
    c. What happens when the cells start out at almost identical or identical concentrations?

4. We will now add noise to the data. Chose to either add noise to the decay rate or the production rate by setting the noise values to μ or ν and by uncommenting/commenting the corresponding equation in the **coupled model.**
    a. How does adding noise affect the behavior you see?
    b. Does increasing the noise strength (sigma_x1) change the behavior of the cells?

5. Time to sample the space. Test out different behaviors by changing only starting concentration, production/decay rates, Kh, Ks, and the noise strength.
    a. How much does cell-cell communication matter in terms of cell behavior?
    b. Can you get any interesting behavior that you have not seen in the above exercise?
    c. Can you make a cell with lower starting concentration inhibit a neighbor with larger concentration?

Week2: Oscillatory behavior

Last week we explored the behavior of the model when the time delay was short. In essence the cells could sense almost immediately the concentration of Her in the cell and its neighbor. We will now look at what happens when there is a bit of delay between the concentration of Her and the time the cell can actually respond to that concentration.

Set the values of the model to ones where you observed lateral inhibition, also make sure you are using the model **without noise**.

1. Test higher values for time delay of autoinhibition (τh).
   a. As you increase values, what type of behavior do you see?
   b. Is there a difference between coupled and uncoupled cells?

2. Chose an autoinhibition delay value where you get stable oscillations. Now change the relative value of signaling delay (τs).
   a. How does changing the time delay of cell coupling affect the Her levels within the cell?
   b. What differences do you observe between the coupled and uncoupled model?
   c. What biological mechanisms could explain a time delay between the Her levels and when the cells sense the level? What about for sensing the neighbor's level of Her?

3. Chose a signaling delay where you get synchronous oscillations when coupled.
   a. Change the strength of Kh or Ks. How does increasing or decreasing this affect oscillation synchronization?
   b. What biological mechanism is a Hill equation often used to simulate? In this model, what do the Kh and Ks parameters conceptually represent (i.e., what is their effect on the system)?

4. Add noise back into the model. Remember to choose either noise in production or decay rates and uncomment the corresponding equation.
   a. How does noise affect the oscillation? What happens when you change the magnitude of the noise?
   b. Compared to lateral inhibition, how sensitive do the oscillations seem to noise?
   c. What underlying biological mechanism could the noise be representing?