Bio-221 - Exercise class about oscillations and traveling waves

In this exercise we are going to look at the possible origin of the traveling waves in the segmentation clock. We are going to simulate the following model for oscillatory gene expression

$$\frac{dw}{d\tau} = -w + C\frac{1}{1 + w^n(\tau - \tau_d)}$$

where w is a variable that oscillates over time and is related to the protein concentration inside the cell. The first term on the right-hand side of the equation is the degradation rate of the protein, and the second nonlinear term is its production rate. The production term is regulated by the past values of w, this is modeling the time it takes to produce a protein through transcription and translation. As soon as the final product is ready it will bind to the promoter region of its gene. The binding represses further transcription and the protein starts decaying. As the concentration decreases, the likelihood of having a protein bound to the promoter decreases and production is restarted. This interplay between production, repression and time delay results in oscillatory gene expression. We do the following exercises to relate this simple model, to what is observed in the segmentation clock.

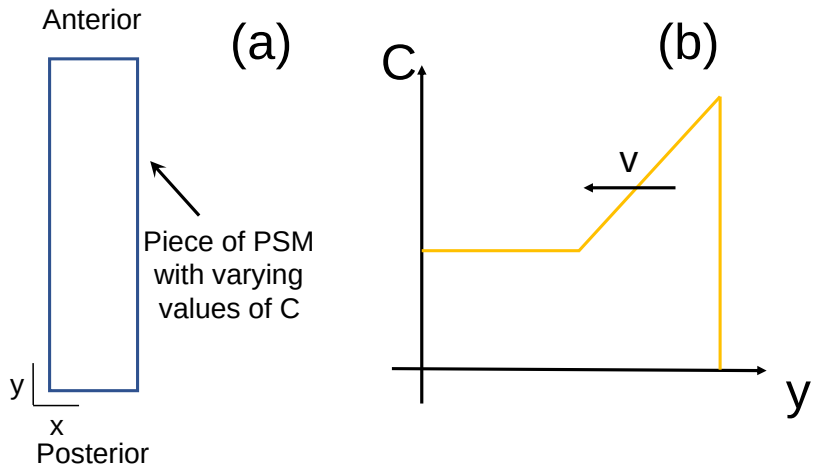
Questions

1. (Routine: Delay_oscillator.m) The second term in the model is controlled by two parameters, C which is the maximum production rate and τ_d is the delay between transcription and translation. In an experiment, the easiest thing to measure is the relationship between amplitude (A), the difference between maxima and minima, and period (T), the time between cycles. How does the relation between amplitude (A) and period (T) looks if:
    a) we keep τ_d constant and vary C?
    b) we keep C and vary τ_d?

2. (Routine: Ramp_oscillator.m) In experimental data (shown in the lecture notes) the cells dissociated from the PSM of zebrafish embryos exhibit oscillations where the amplitude increases over time. Motivated by this data, we assume that in these cells the production rate ramps up in the form $C \approx \gamma\tau$ where τ is time and γ sets the speed of concentration increase. We set the duration of the ramp the same, independent of the value of γ. Given the results from the previous exercise what kind of behavior we would expect when we change γ?

3. (Routine: Traveling_waves.m) The aim of this exercise is to see the minimal requirements to observe traveling waves at the tissue level similar to the ones we observe in experiment (see lecture notes for the segmentation clock). For this case we imagine a set of cells forming a row, where each cell has a value of C and w that

changes over time. The values of C are arranged in such a way that it forms a spatiotemporal pattern. For example, suppose you are observing the PSM and the tailbud of an embryo. At each time point each cell has a specific value of C forming a structure as in the following figure:



The values of C varies from anterior to posterior (y axis in panel (a)), an example of such profile is shown in panel (b). The values of C are arranged and change such that we would see a structure traveling from anterior to posterior with velocity v. In this exercise, simulate three spatiotemporal profiles of C and discuss the resulting pattern for w. Discuss which profile has similar features to the cyclic gene expression profile observed in experiment.

What are the take home messages of this exercise? Theoretical studies have shown that to have the wave profile like the one observed in experiments, we need a population of oscillators that slows down as they slowly travel to the anterior part of the presomitic mesoderm.

- If the cells are composed by delay genetic oscillators, then we could get this profile by regulating the production rate across the embryo.
- The amplitude increase is the reason why the oscillators slow down and a traveling wave emerges. This is consistent with observations from experimental studies.
- Very important questions arise that might be answered with further experiments, for example:
    - What modulates the C profile in the embryo?
    - Are there many factors or is it a single one that modulate this?
    - And a central question in the field, what shuts down this wave to coincide with the formation of somites?