

# *Modelling Biochemical Reaction Networks*

## *Lecture 22: Somitogenesis and delay-induced oscillations*

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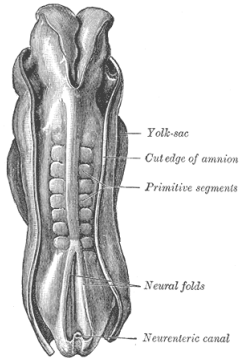
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## *Recommended reading*

- ▶ Lewis, *Curr. Biol.* **13**, 1398 (2003).

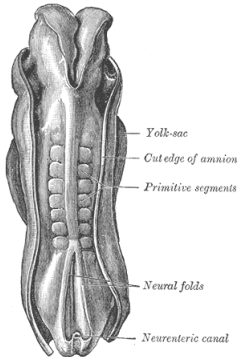
## Somites



Human embryo  
Source: *Gray's Anatomy*, 20th edition (public domain)

- ▶ **Somites** are masses of cells that develop in rows on each side of the neural tube in vertebrates.
- ▶ Formerly known as primitive segments
- ▶ Somites develop into vertebrae, ribs and lateral muscles.

## *Somitogenesis*



- ▶ Somites are formed from two rods of tissue to either side of the neural tube called the **presomitic mesoderm (PSM)**.
- ▶ Somites form in pairs starting at the anterior (head) end.
- ▶ The PSM grows during somite formation at a rate that roughly matches the shortening due to differentiation into somites at the anterior end.

## *Somitogenesis*

- ▶ The **clock and wavefront** model postulates a biochemical oscillator (a clock) as well as a boundary between the PSM and somites (wavefront).
- ▶ Several variations on clock and wavefront model explain somitogenesis somewhat differently.
- ▶ One possibility is that the clock only functions at the posterior end, so cells growing away from this end acquire a fixed phase (part of the cycle).

This phase is carried with the cells as they are pushed forward by cell division at posterior end.

Oscillator phase eventually determines the boundaries of a somite.

Some other factor (e.g. decay of a chemical) determines how long a group of cells will move away from the tail before they differentiate into a somite.

## *The clock*

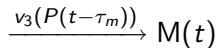
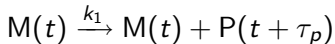
- ▶ In zebrafish, a new somite is made every 30 min, and the Her1 protein and its mRNA oscillate with the same period.
- ▶ Her1 represses the transcription of its own gene.
- ▶ Another protein called Her7 behaves similarly.  
Knocking out both Her1 and Her7 abolishes organized somitogenesis.  
Knocking out just one of the two produces similar, but less severe effects.
- ▶ Her1, Her7 and their genes and mRNAs could be the key components of the somitogenesis clock.

## *A Her1 oscillator model*

- ▶ For simplicity, consider only Her1 protein (P) and mRNA (M).

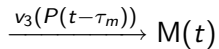
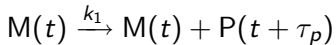
### Assumptions:

- ▶ The ribosome occupies the translation start site for a negligible time.
- ▶ Translation takes time  $\tau_p$ .
- ▶ Transcription takes time  $\tau_m$  and is inhibited by P.
- ▶ Transcription inhibition is rapid, reversible, and cooperative.



$$v_3(P) = \frac{v_{3,\max}}{1+P^2/K^2}$$

## *Clock equations*



$$v_3(P) = \frac{v_{3,\max}}{1 + P^2/K^2}$$

$$\frac{dP}{dt} = k_1 M(t - \tau_p) - k_2 P$$

$$\frac{dM}{dt} = v_3(P(t - \tau_m)) - k_4 M$$



## *Clock equations*

*A trick to simplify the equations*

$$\begin{aligned}\frac{dP}{dt} &= k_1 M(t - \tau_p) - k_2 P \\ \frac{dM}{dt} &= v_3(P(t - \tau_m)) - k_4 M\end{aligned}$$

- ▶ Let  $m(t) = M(t - \tau_p)$ .
- ▶ Take a derivative with respect to  $t$ :

$$\frac{dm}{dt} = \left. \frac{dM}{dt} \right|_{t-\tau_p} = v_3(P(t - \tau_p - \tau_m)) - k_4 m$$

- ▶ Define  $\tau = \tau_p + \tau_m$  and we have a one-delay problem.

## *Clock equations*

$$\frac{dP}{dt} = k_1 m - k_2 P$$

$$\frac{dm}{dt} = v_3(P(t - \tau)) - k_4 m$$

$$\text{with } v_3(P) = \frac{v_{3,\max}}{1 + P^2/K^2}$$

- ▶ Reasonable values for parameters (from Lewis, 2003):

$$k_1 = 4.5 \text{ min}^{-1}$$

$$v_{3,\max} = 33 \text{ molecules/min}$$

$$k_2 = 0.23 \text{ min}^{-1}$$

$$K = 40 \text{ molecules}$$

$$k_4 = 0.23 \text{ min}^{-1}$$

$$\tau = 13 \text{ min}$$

## *Delay-induced instability*

- ▶ At large delays, we get oscillations, so this is a successful clock model.
- ▶ At small delays, no oscillations
- ▶ The delay destabilizes the steady state, so we call this a **delay-induced instability**.

## *Bifurcation diagram*

- ▶ Auto can't do bifurcation diagrams for delay-differential equations.
- ▶ Recall that a simple bifurcation diagram is obtained by plotting minima and maxima of a solution vs a parameter value.
- ▶ We can get some simple types of bifurcation diagrams in xppaut, but it requires a lot of setup, planning, and trial-and-error work.
- ▶ For a bifurcation diagram vs  $\tau$ , add the following line to your xppaut input file:

```
aux tau_=tau
```

This will give you a variable that is equal to  $\tau$  that you can actually plot.

## *Bifurcation diagram*

- ▶ In the Numerics menu, set the following parameters:
  - Total: 10000
  - tRansient: 9000 (We want to make sure that we are looking at the attractor and not at transient behavior.)
  - Poincare map: (M)ax/min (Plot only minima and maxima rather than the entire trajectory.)
    - Variable: P (Any variable will do.)
    - Direction: 0 (plots both minima and maxima)
    - Stop on sect: N

## *Bifurcation diagram*

- ▶ In the Viewaxes→2D dialog, set up your axes as follows:
  - X-axis: tau\_ (the auxiliary variable)
  - Y-axis: P (same variable as in the Poincaré map)
  - Xmin: 0
  - Ymin: -100
  - Xmax: 60 (no larger than the value of Delay in your input file)
  - Ymax: 3000
- ▶ Click on Graphic stuff→(E)dit curve, edit curve 0, and change the line type to 0 in the dialog that pops up. This will plot dots instead of connecting points by lines.
- ▶ Click on Graphic stuff→a(X)ex opts, then set X-org to 0. This will turn off plotting of the x axis, which otherwise interferes with our diagram.

## *Bifurcation diagram*

- ▶ Now click on Initialconds → (R)ange and fill in the dialog as follows:

Range over: tau (the parameter)

Steps: 60 (Start with a smaller value for testing.)

Start: 60

End: 0 (It's better to start in the limit-cycle regime and to work toward the bifurcation.)

Reset storage: N (Keeps the data computed in memory for each  $\tau$ .)

Use old ic's: N (When a new value of  $\tau$  is selected, the new trajectory will continue from where the old trajectory left off.)

## *Bifurcation diagram*

- ▶ Xppaut will eventually fail, with the following error message:  
Cannot zero RHS for max/min - use a variable. This means that Xppaut has entered a range where there is only a stable steady state, so there are no maxima or minima to be found.

Note: If you want to start over, you may get this message for no good reason, especially with delay equations. If this happens, just reset the initial data to the default values and run a single trajectory to reset xppaut.

- ▶ Go into the data browser and Write this data set into a file.
- ▶ Note the value of  $\tau$  (i.e. of the auxiliary variable tau\_) at which this data set ends, in this case, 8.



## *Bifurcation diagram*

- ▶ Now we want to turn off the Poincaré map: Click on Numerics→Poincare map→(N)one.
- ▶ Also in the Numerics menu, set Total to a smaller value, say 9100, and nOutput to a large value such as 200.
- ▶ We're going to do another range integration to get the steady state branch:

Range over: tau

Steps: 20

Start: 0

End: 10 (slightly larger value than where limit cycle ended in case there is bistability due to a subcritical Hopf bifurcation)

Reset storage: N

Use old ic's: Y (We want to avoid getting trapped in an unstable steady state.)

## *Bifurcation diagram*

- ▶ You will notice that, past a certain point, the values plotted fill in between the two branches of the minimum and maximum from our previous computation. Go into the data browser and figure out where this happens. In this case, you will find that  $P = 161.76$  and  $m = 8.27$  up to and including  $\tau = 7$ . After that, we start to get different values for these two variables at each computed point. The last stable point (at this resolution) is therefore  $\tau = 7$ . Redo the calculation with  $\tau = 7$  as your upper limit.

## *Bifurcation diagram*

- ▶ Click on Graphic stuff → (F)reeze → (F)reeze, and finally click on Ok without making any changes.
- ▶ Go back to the data browser and Load the file containing the minima and maxima. Click on Restore in the xppaut main window. Voilà!

