Solution. Mechanistic model of Hes oscillations during vertebrate body segmentation.

Solving the ODE system

By solving the ODE system without delay we have the following nullclines:

$$m = \frac{kH^{-}(p)}{b} \tag{1}$$

and

$$m = \frac{bp}{a} \tag{2}$$

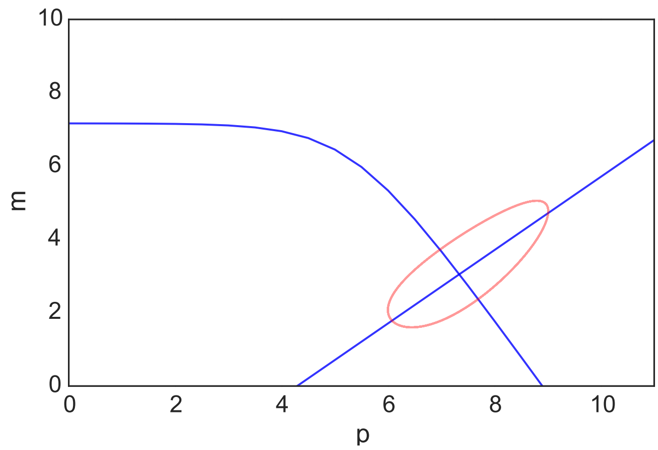

Figure 1: *Nullclines and oscillatory path. Blue lines represent the nullclines of the ODE system. Red line show the solution of the DDE system for* $\tau = 10$ *min. Parameters:* $b = 0.23$*,* $a = 4.5$*,* $p_0 = 40$*,* $n = 2$*,* $k = 33$*.*

It is easy to solve the equations without delay. We then get the following eigenvalues:

$$\lambda = -b \pm \sqrt{ka\frac{\partial H^{-}(p)}{\partial p}|_{p^*}} \tag{3}$$

where p^* is the value of p in the equilibrium and

$$\frac{\partial H^{-}(p)}{\partial p}|_{p^*} = -nH^{+}(p^*)\frac{H^{-}(p^*)}{p^*}. \tag{4}$$

From the nullclines, we have that in the equilibrium point (m^*, p^*):

$$\frac{kH^{-}(p^*)}{b} = \frac{bp^*}{a}, \tag{5}$$

and therefore,

$$\frac{H^{-}(p^*)}{p^*} = \frac{b^2}{ka}, \tag{6}$$

and with that the eigenvalues can be represented as:

$$\lambda = -b \pm ib\sqrt{nH^{+}(p^{*})}. \tag{7}$$

Therefore, the equilibrium point is a stable focus ($Re(\lambda) < 0$ and $Im(\lambda) \neq 0$). It is interesting to note that the degradation rate dominates both the real and imaginary part.

Solving the DDE system

Similarly we can solve the DDE system. In this case the eigenvalues can be obtained from the following equation:

$$(\lambda + b)^2 = ka\frac{\partial H^{-}(p)}{\partial p}|_{p^*}e^{-\lambda\tau} = -nb^2H^{+}(p^*)e^{-\lambda\tau} \tag{8}$$

which is complicated to solve.

But we can assume that the delay τ is small compared to the period of oscillation and then expand the exponential term: $e^{-\lambda\tau} \approx 1 - \lambda\tau + \frac{\lambda^2\tau^2}{2}$.

Then, the eigenvalues are:

$$\lambda = \frac{-b(2 - nbH^{+}(p^*)\tau) \pm b\sqrt{(2 - nbH^{+}(p^*)\tau)^2 - 4(1 + nH^{+}(p^*))(1 + \frac{nb^2}{2}H^{+}(p^*)\tau^2)}}{2(1 + \frac{nb^2}{2}H^{+}(p^*)\tau^2)} \tag{9}$$

and as the delay (τ) increases the real part decreases until reach a Hopfield bifurcation when $Re(\lambda) = 0$.

In the Hopfield point: $nbH^{+}(p^*)\tau = 2$ and the minimum delay for sustained oscillations is:

$$\tau = \frac{2}{nbH^{+}(p^*)}. \tag{10}$$

At this point the imaginary part is:

$$Im(\lambda) = \frac{b}{2}\sqrt{\frac{1 + nH^{+}(p^*)}{1 + \frac{nb^2}{2}H^{+}(p^*)\tau^2}}. \tag{11}$$

Then by assuming $\lambda = i\omega = i\frac{2\pi}{T_{Hopf}}$ we have that:

$$T_{Hopf} = \frac{\pi}{b}\sqrt{\frac{1 + \frac{nb^2}{2}H^{+}(p^*)\tau^2}{1 + nH^{+}(p^*)}}. \tag{12}$$

References

[1] Lewis, J. Autoinhibition with transcriptional delay: a simple mechanism for the zebrafish somitogenesis oscillator. *Current Biology.* 2003.