ETH zürich

Travelling waves emerge from coupled oscillators during vertebrate body segmentation.

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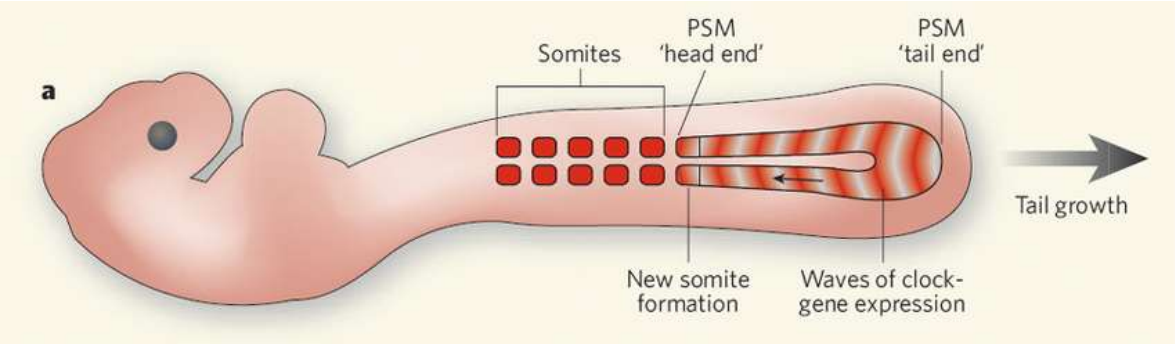
Iber‘s group

Vertebrate body segmentation (Somitogenesis)

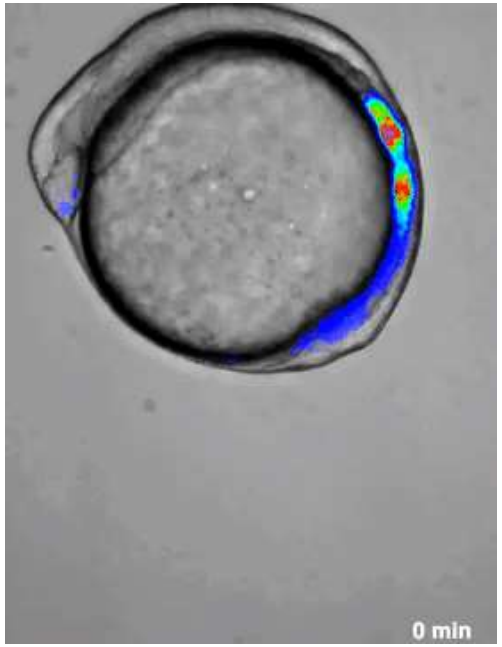
Somites are paired blocks of mesoderm that form along the anterior-posterior axis of the developing embryo in segmented animals.

Somites give rise to segmental structures such as vertebrae, ribs, and skeletal muscles.



Somites are formed periodically. ~2h in mouse and chicken, ~30 min in zebrafish.

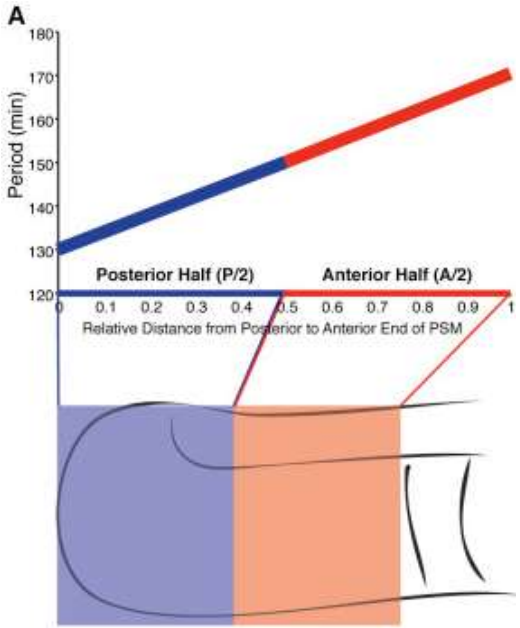
The period of somite formation is controlled by travelling waves of gene expression.



Credit:
Oates lab

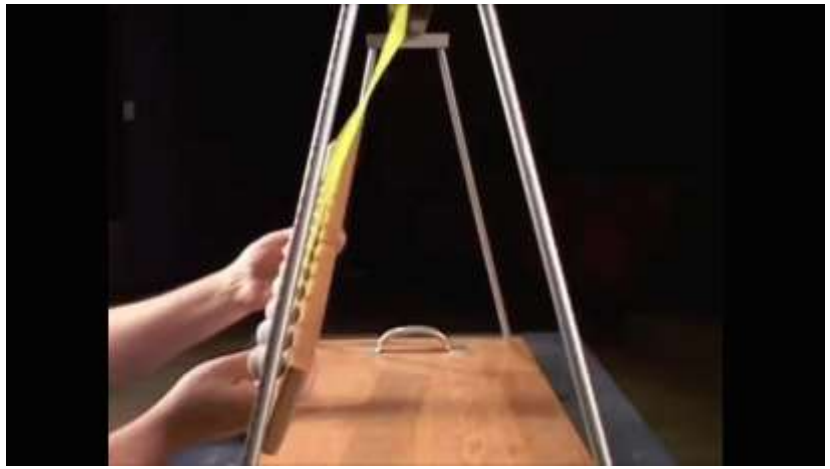
Traveling waves emerge from period gradient.

Each cell in the presomitic mesoderm express oscillatory genes (clock). The period of these oscillator increase from posterior to anterior.



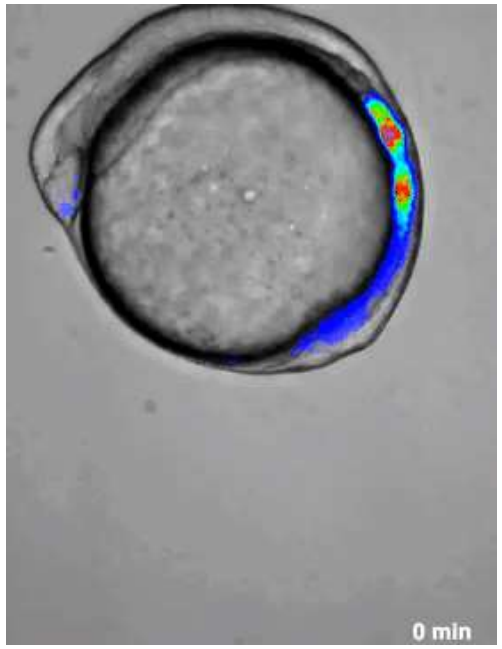
Tsiairis and Aulehla. *Cell*, (2016).

This creates a gradient in the period which leads to travelling waves.

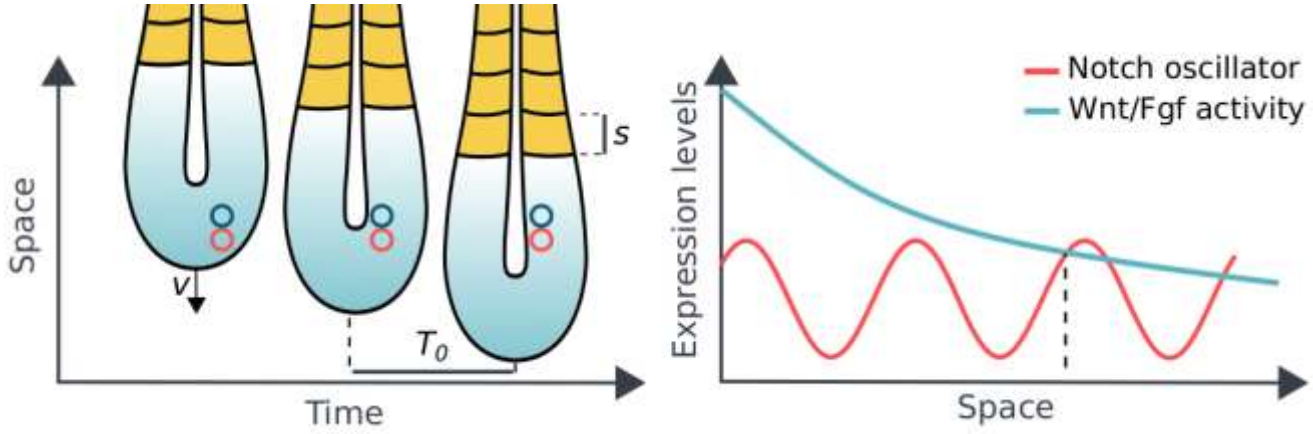


Pendulum wave experiment. from Harvard Natural Sciences Lecture Demonstrations.

During somite formation, these oscillators are coupled, which leads to synchronization.



Models of somite formation.



Clock and Wavefront model:

- Periodic somite formation due to oscillatory genes.
- Positional information: posterior-anterior signaling gradient of Fgf and Wnt.

Pros:

Simple, clear predictions:

- Somite size:

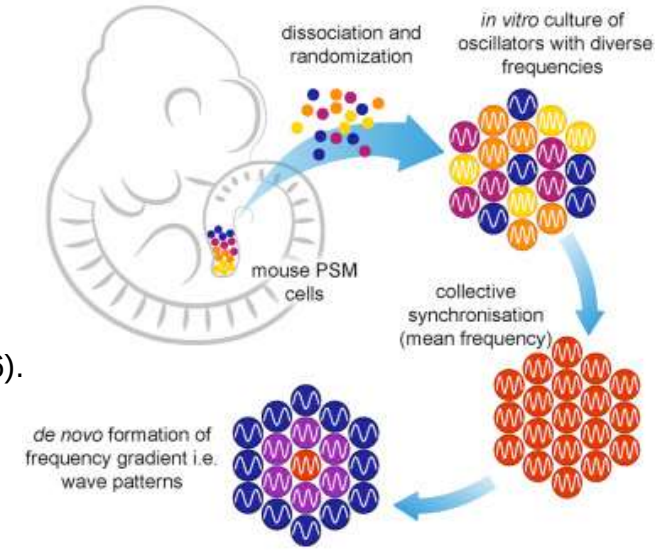
$$s = v.\ T_0$$

Cons:

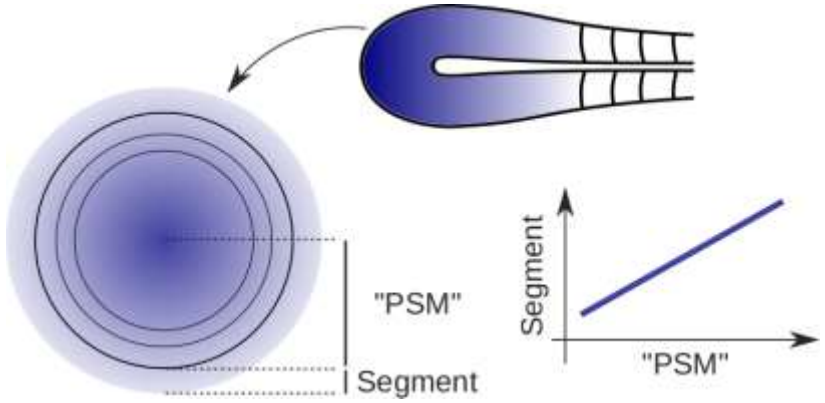
- No molecular mechanism.
- Difficult to explain scaling.

Cooke J, Zeeman EC. *J Theor Biol* (1976).

Models of somite formation.

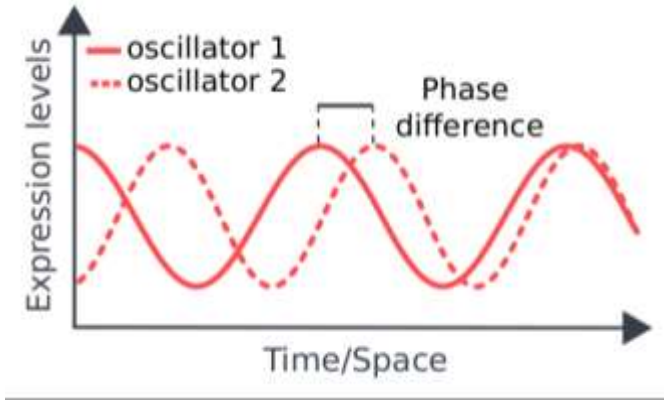


Lauschke, et al. (2013).
Tsiairis and Aulehla. (2016).



Ex vivo explant self organize forming a gradient in the period.

Size of the segment scales with the size of the tissue.



Goodwin and Cohen. (1969)
Lauschke, et al. (2013)
Beaupeux and François. (2016)

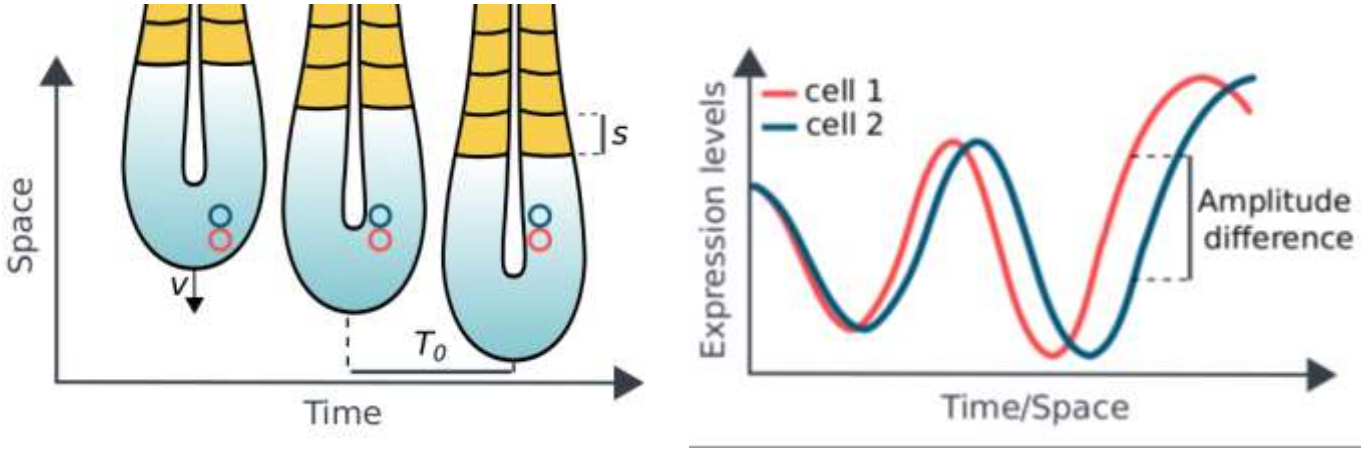
Phase difference between **two** oscillators gives the positional information.
Difficult to interpret *in vivo* data.

Models of somite formation

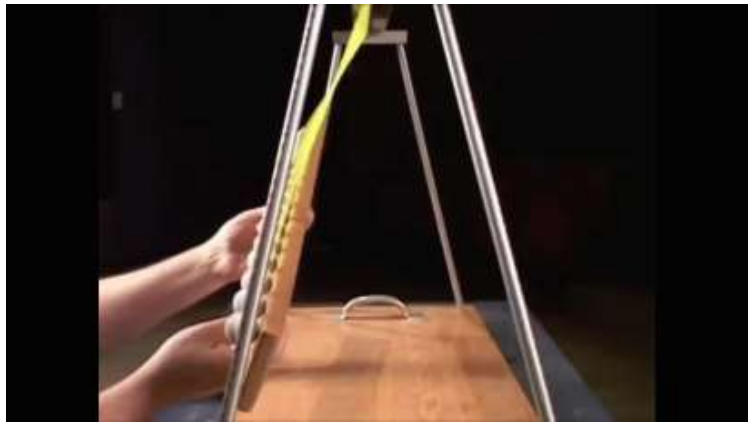
Difference in the levels of the oscillators between **neighboring cells** gives the positional information.

Differences in the levels increase in time due to differences in the period and amplitude.

Explain both *ex vivo* and *in vivo* data.

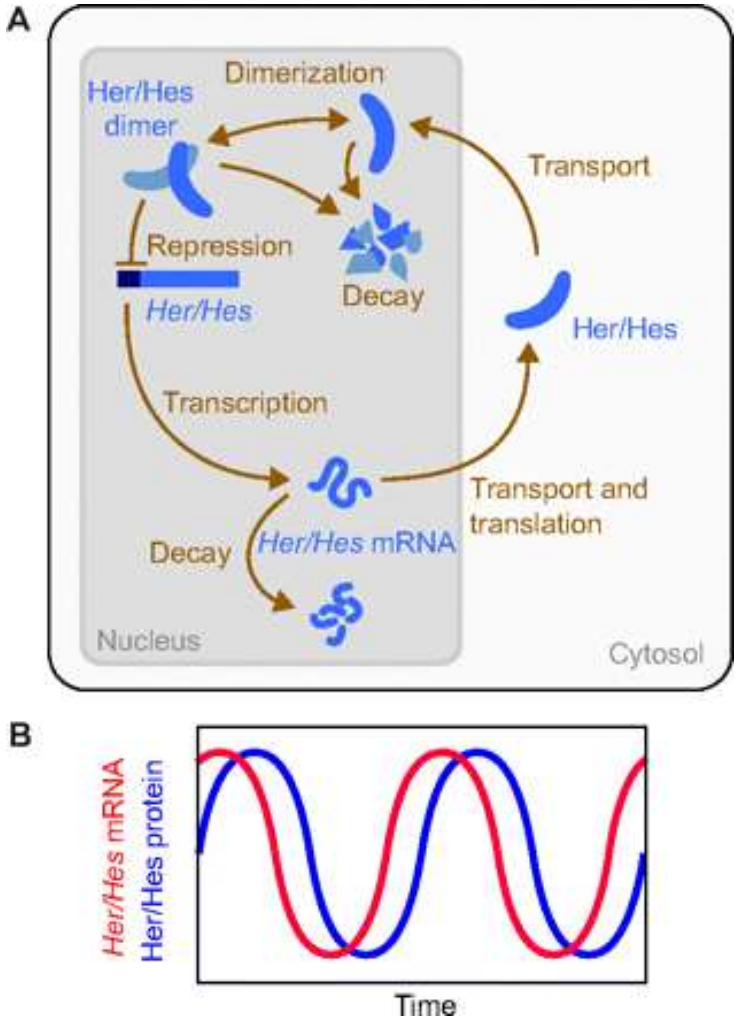


Boareto, Tomka, Iber. (2019)



Pendulum wave experiment. from Harvard Natural Sciences Lecture Demonstrations.

Notch/Hes oscillators.



Oscillations require:

- Fast degradation of Hes protein.
- Strong auto-repression.
- Delay in the auto-repression.

This can be easily modelled:

$$\frac{d}{dt}m = g[t-\tau] - bm,$$

$$\frac{d}{dt}p = am - bp,$$

Notch/Hes oscillators.

Exercise 2. Mechanistic model of body segmentation.

In 2003, Julian Lewis proposed a simple model that describes the dynamics of *her* genes (*Hes* in mammals) providing a mechanistic molecular model for the intracelular oscillator that controls body segmentation in zebrafish (Lewis 2003). The model consists in the dynamics of *her* mRNA (m) and protein (p) given by the following delayed differential equations:

$$\frac{d}{dt}m = g[t-\tau] - bm, \tag{4}$$

$$\frac{d}{dt}p = am - bp, \tag{5}$$

where τ represents the delay, b represents mRNA and protein degradation rate, and a represents the translational rate. The production rate of *her* mRNA in the time t is defined by the following function:

$$g[t] = kH^{-}(p[t]) \tag{6}$$

where k is the basal production rate, $p[t]$ represents the amount of *her* proteins in the time t and H^{-} is a negative Hill function: $H^{-}(x) = \frac{1}{1+(x/x_0)^n}$.

Exercise 2.

A) Show that in the absence of delay ($\tau = 0$), the ODE system is a stable focus. Plot the nullclines.

B) Find the eigenvalues of the DDE system. Assuming small delays, show that the solution of the system has a Hopfield bifurcation (goes from has a stable focus to a oscillatory solution) when

$$\tau = \frac{2}{nbH^+(p^*)} \tag{7}$$

where $(m, p) = (m^*, p^*)$ is the equilibrium point of the ODE system.

C) Show that at the Hopfield bifurcation, the period of oscillations is

$$T_{Hopf} = \frac{\pi}{b}\sqrt{\frac{1 + \frac{nb^2}{2}H^+(p^*)\tau^2}{1 + nH^+(p^*)}}. \tag{8}$$

Hint: The eigenvalues of the DDE system can be obtained by solving the determinant:

$$\det(-\lambda I + A_0 + A_1 e^{-\lambda\tau}) = 0 \tag{9}$$

where the caracteristic equation of the DDE system is:

$$\frac{d\mathbf{x}}{dt} = A_0\mathbf{x}(t) + A_1\mathbf{x}(t - \tau). \tag{10}$$

Also, assume that for small delays:

$$e^{-\lambda\tau} \simeq 1 - \lambda\tau + \frac{\lambda^2\tau^2}{2}. \tag{11}$$

Exercise 2.

Solving the ODE system

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

$$m = \frac{kH^{-}(p)}{b} \tag{9}$$

and

$$m = \frac{bp}{a} \tag{10}$$

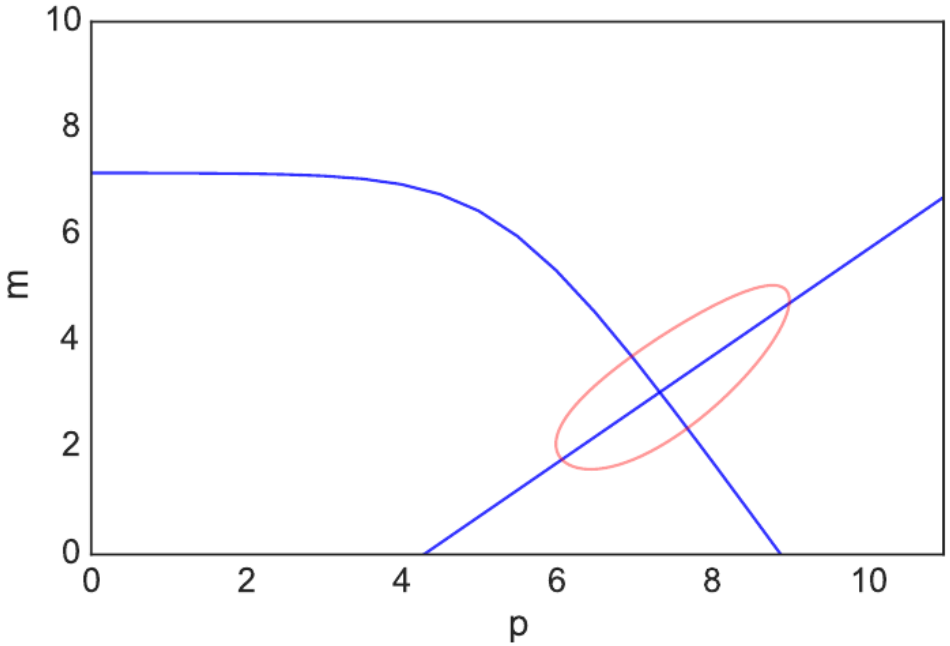


Figure 3: *Nullclines and oscillatory path. Blue lines represent the nullclines of the ODE system. Red line show the solution of the DDE system for* $\tau = 10$ *min. Parameters:* $b = 0.23$, $a = 4.5$, $p_0 = 40$, $n = 2$, $k = 33$.

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

$$\lambda = -b \pm \sqrt{ka \frac{\partial H^-(p)}{\partial p}|_{p^*}} \tag{11}$$

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

$$\frac{\partial H^-(p)}{\partial p}|_{p^*} = -nH^+(p^*)\frac{H^-(p^*)}{p^*}. \tag{12}$$

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

$$\frac{kH^-(p^*)}{b} = \frac{bp^*}{a}, \tag{13}$$

and therefore,

$$\frac{H^-(p^*)}{p^*} = \frac{b^2}{ka}, \tag{14}$$

and with that the eigenvalues can be represented as:

$$\lambda = -b \pm ib\sqrt{nH^+(p^*)}. \tag{15}$$

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:

$$(\lambda + b)^2 = ka\frac{\partial H^-(p)}{\partial p}|_{p^*}e^{-\lambda\tau} = -nb^2H^+(p^*)e^{-\lambda\tau} \tag{16}$$

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:

$$\lambda = \frac{-b(2 - nbH^+(p^*)\tau) \pm b\sqrt{(2 - nbH^+(p^*)\tau)^2 - 4(1 + nH^+(p^*))(1 + \frac{nb^2}{2}H^+(p^*)\tau^2)}}{2(1 + \frac{nb^2}{2}H^+(p^*)\tau^2)} \tag{17}$$

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:

$$\tau = \frac{2}{nbH^+(p^*)}. \tag{18}$$

At this point the imaginary part is:

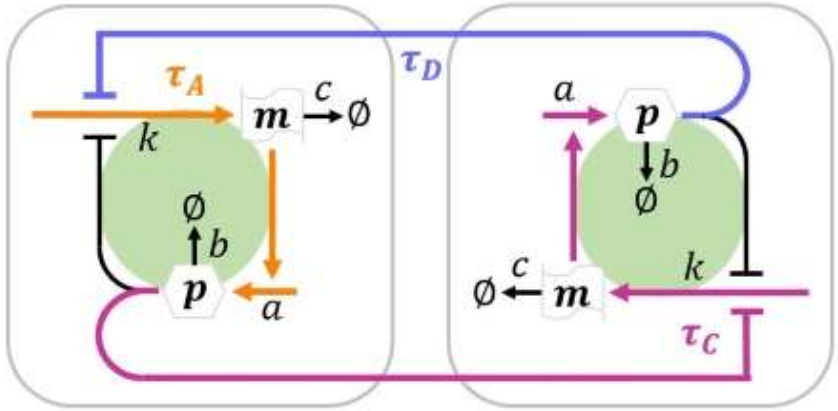
$$Im(\lambda) = \frac{b}{2}\sqrt{\frac{1 + nH^+(p^*)}{1 + \frac{nb^2}{2}H^+(p^*)\tau^2}}. \tag{19}$$

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

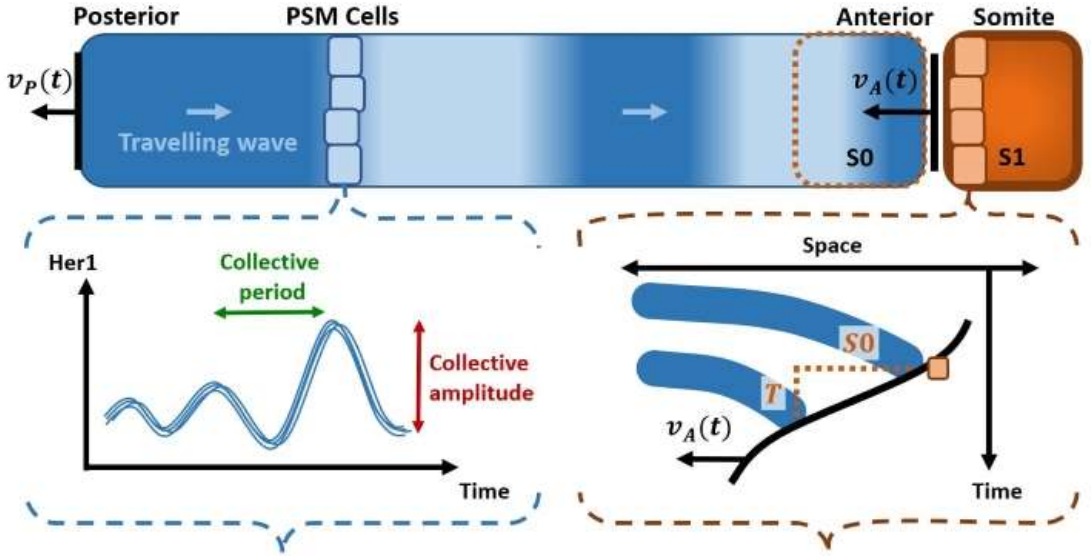
$$T_{Hopf} = \frac{\pi}{b}\sqrt{\frac{1 + \frac{nb^2}{2}H^+(p^*)\tau^2}{1 + nH^+(p^*)}}. \tag{20}$$

Coupling cellular oscillators

Oscillators coupled with a signaling delay.



How coupled cellular oscillators can lead to emergent properties?

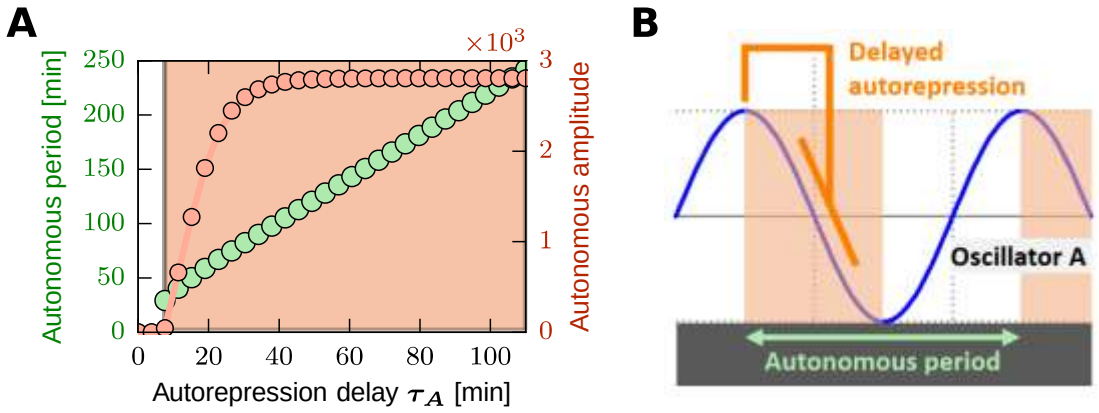


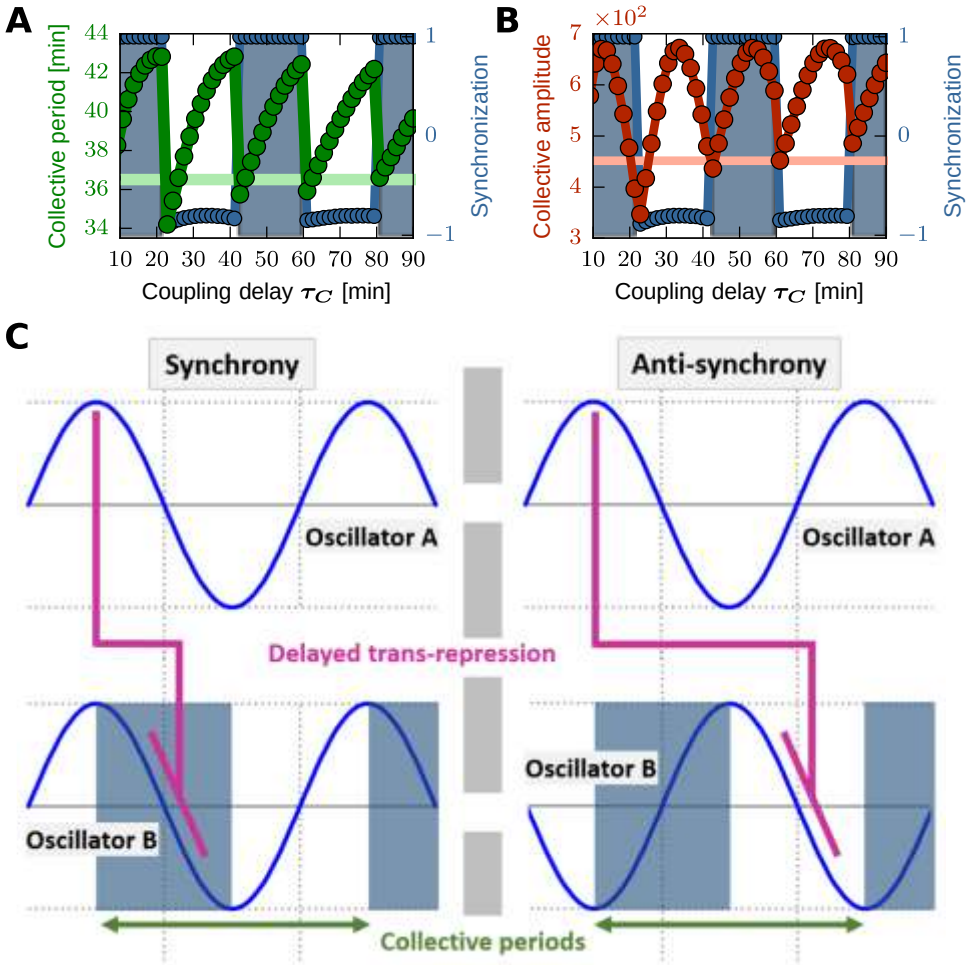
Tomas Tomka. *ETH Master Thesis.* (2017)
Tomka, Iber, Boareto. (2018)

Coupling cellular oscillators

Autorepression delay controls the period of oscillations.

Signaling delay controls the synchrony of the oscillators.





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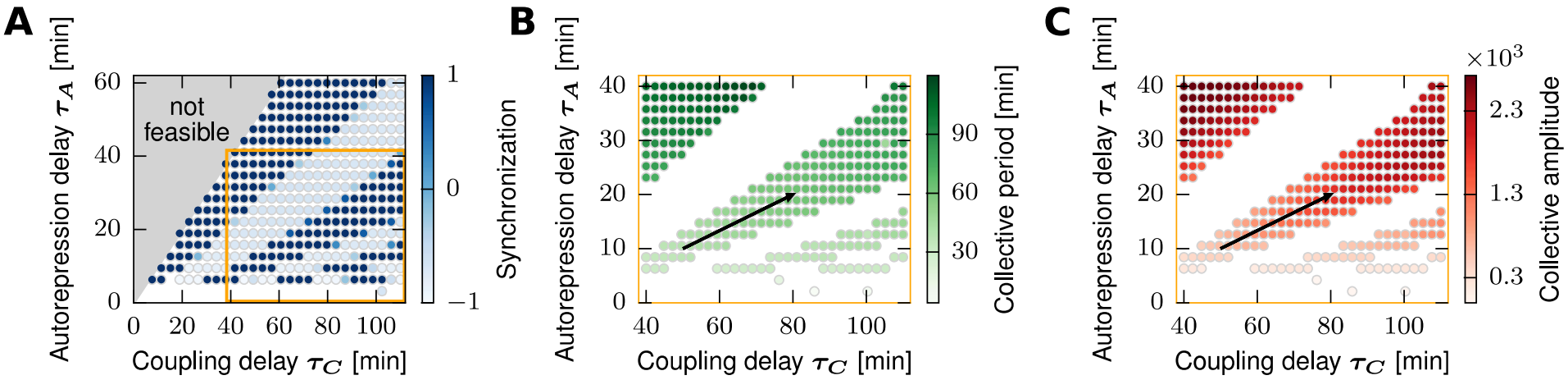
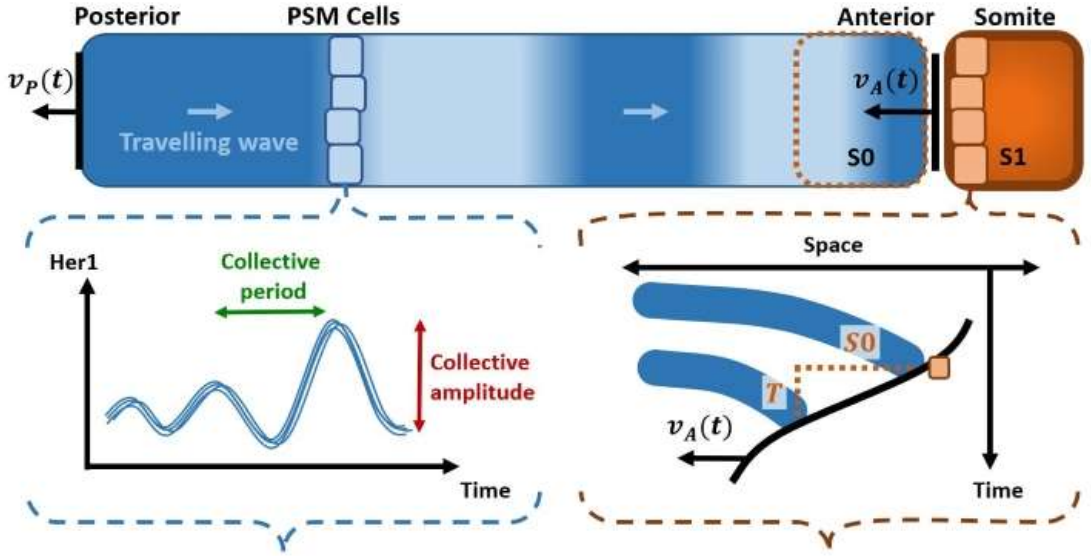
Coupling cellular oscillators



Changes in both delays are sufficient to understand the emergence of the collective period, the collective amplitude, and the synchronization of neighbouring Hes oscillators.



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