

Phase waves in spermatogenesis

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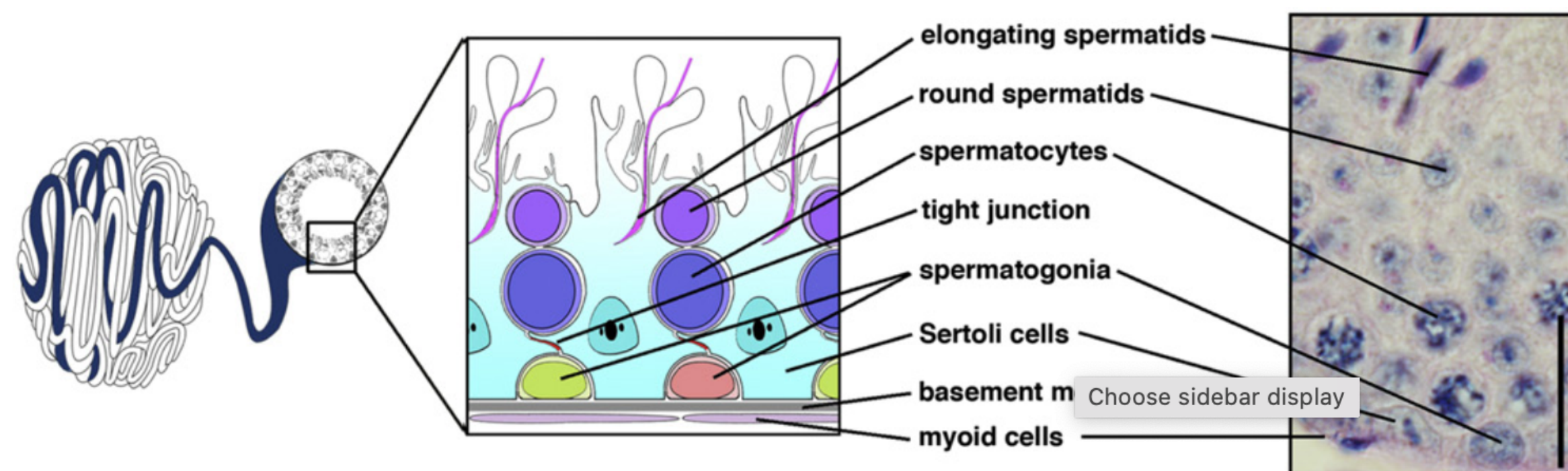
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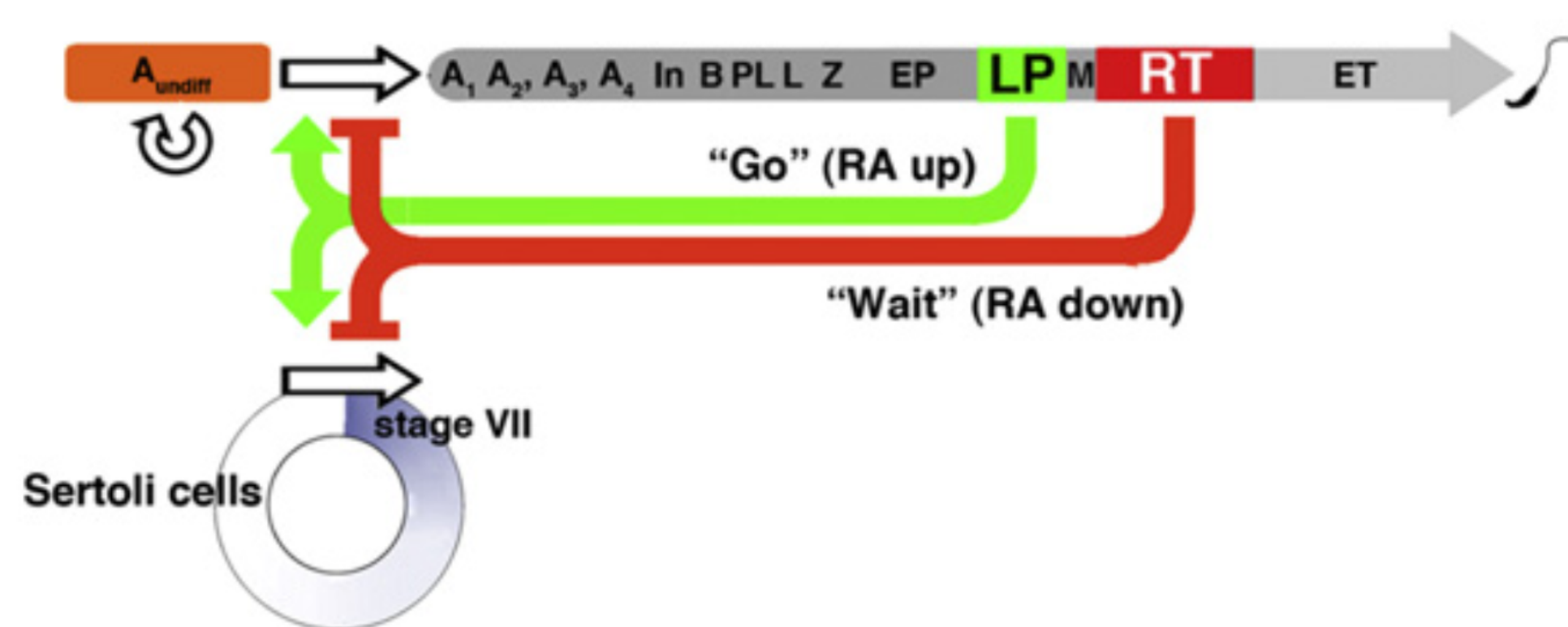
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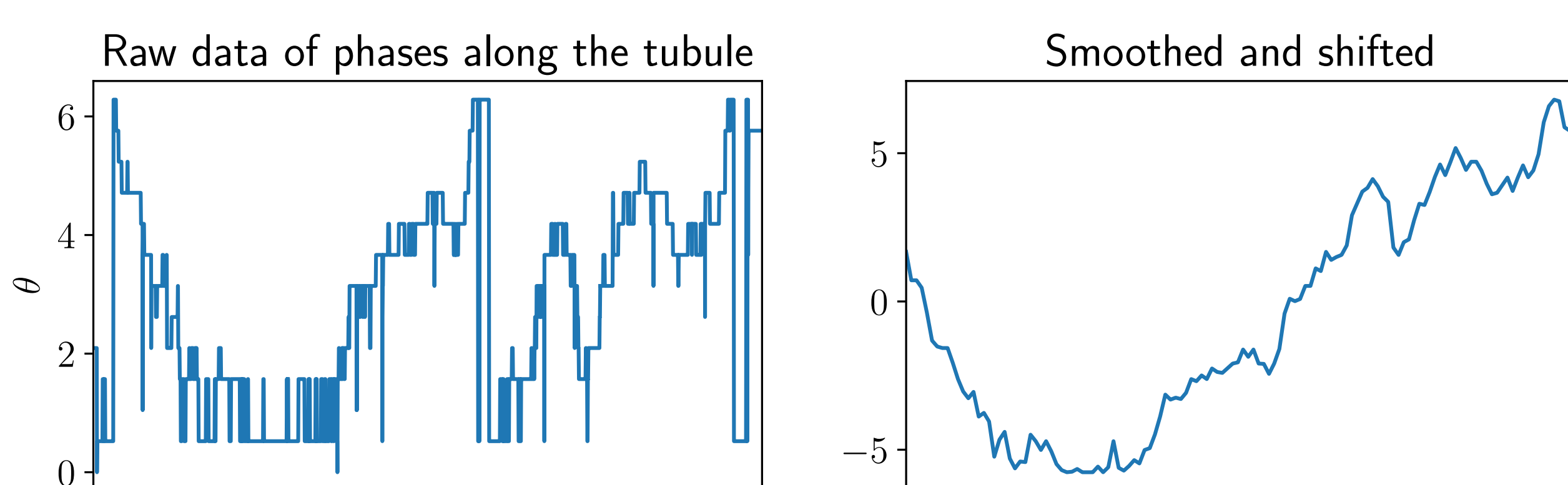
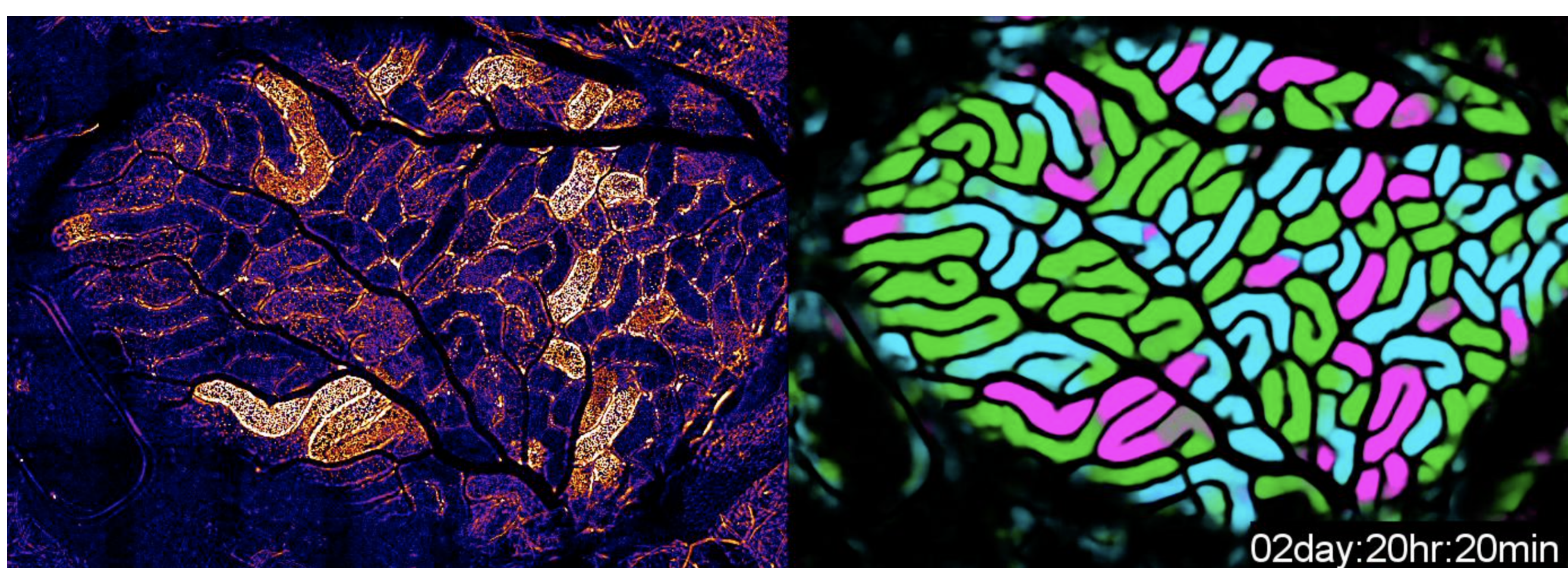
Spermatogenesis and the seminiferous cycles



In the epithelium of mouse seminiferous tubules, the production of mature sperm from undifferentiated stem cells occurs in a periodic fashion, known as the “seminiferous cycle”. During such a cycle, Sertoli cells change their function in accordance with the differentiation of germ cells under the regulation of retinoic acid (RA) signalling.



Recently, the intensity of RA signalling has been observed to exhibit travelling phase waves along the length of the seminiferous tubules.



Model for local oscillations: delayed differential equation

We construct a time-delayed model for the local cyclic behaviour, incorporating the feedback mechanisms between the RA concentration ϕ and germ line differentiation,

$$\partial_t \phi = \underbrace{\mu h(\phi_\tau)}_{\text{Pos. feedback}} + \underbrace{\nu \bar{h}(\phi_{\tau+\epsilon})}_{\text{Neg. feedback}} - \underbrace{\kappa \phi}_{\text{Degradation}}$$

where ϕ_τ denotes the time-delayed concentration $\phi(t - \tau)$, $h(x) = \frac{x^n}{1+x^n}$ and $\bar{h}(x) = 1 - h(x)$.

Linear stability analysis

- Linearise around the uniform steady state.
- Set the growth rate to be complex: $\lambda = \sigma + i\omega$.
- Set $\sigma = 0$ and numerically solve for the boundary values of (τ, ϵ) , marked as orange dotted lines on the right.

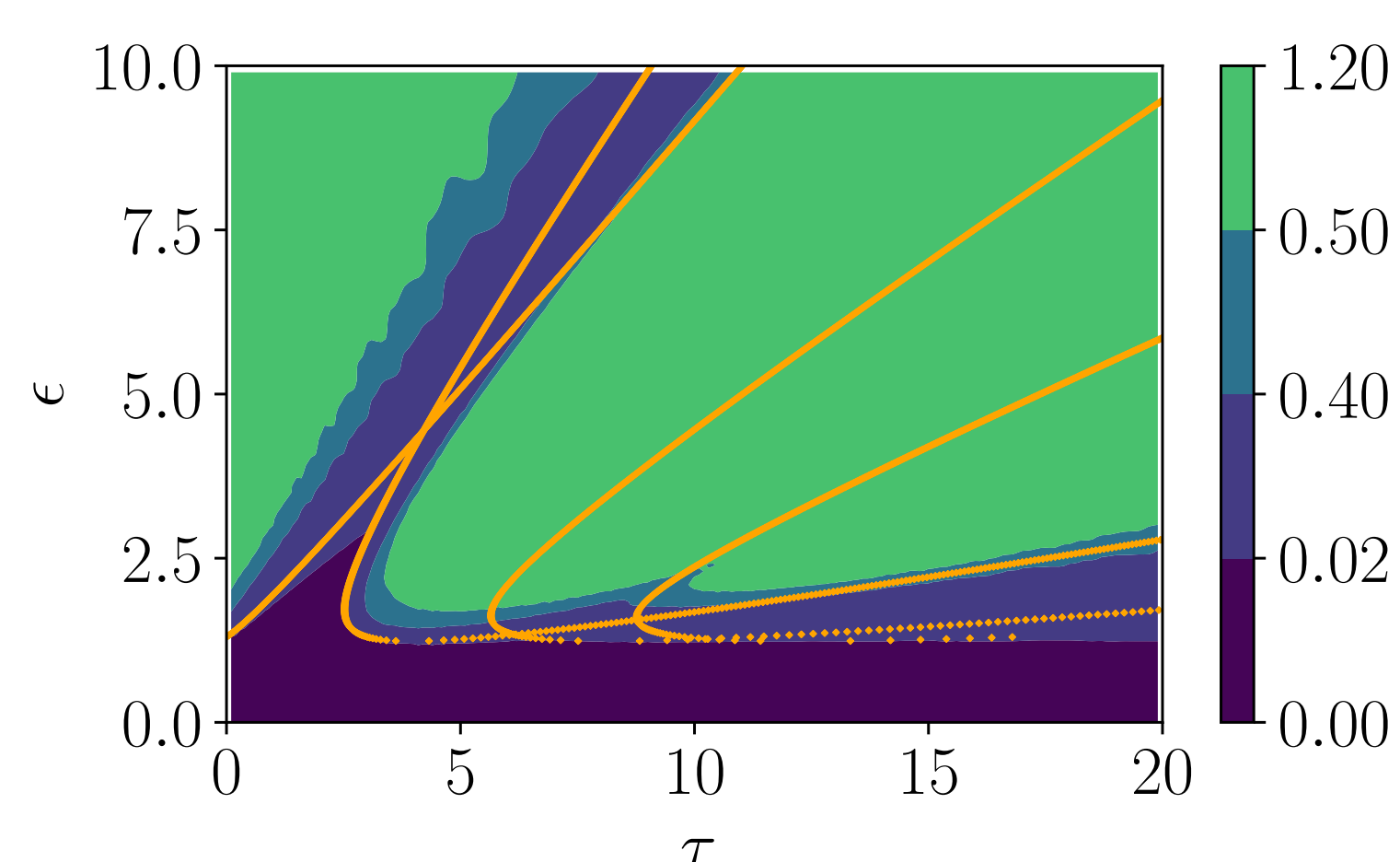
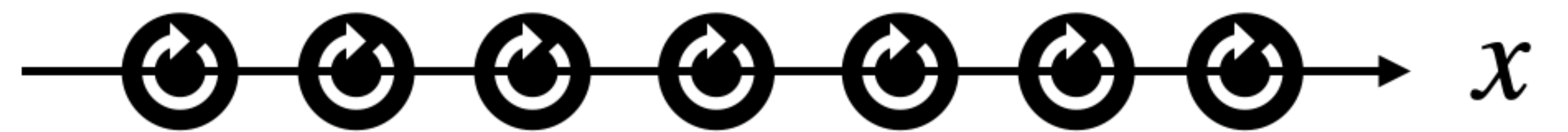


Figure: The contour map shows the amplitude of oscillations for each (τ, ϵ) value from simulation.

Minimal model: the asymmetric Kuramoto model

Reduce the local dynamics to a simple oscillator, add nearest neighbour interactions, and assume that the natural cycle times are slightly different for each location \rightarrow the **(Asymmetric) Kuramoto Model**



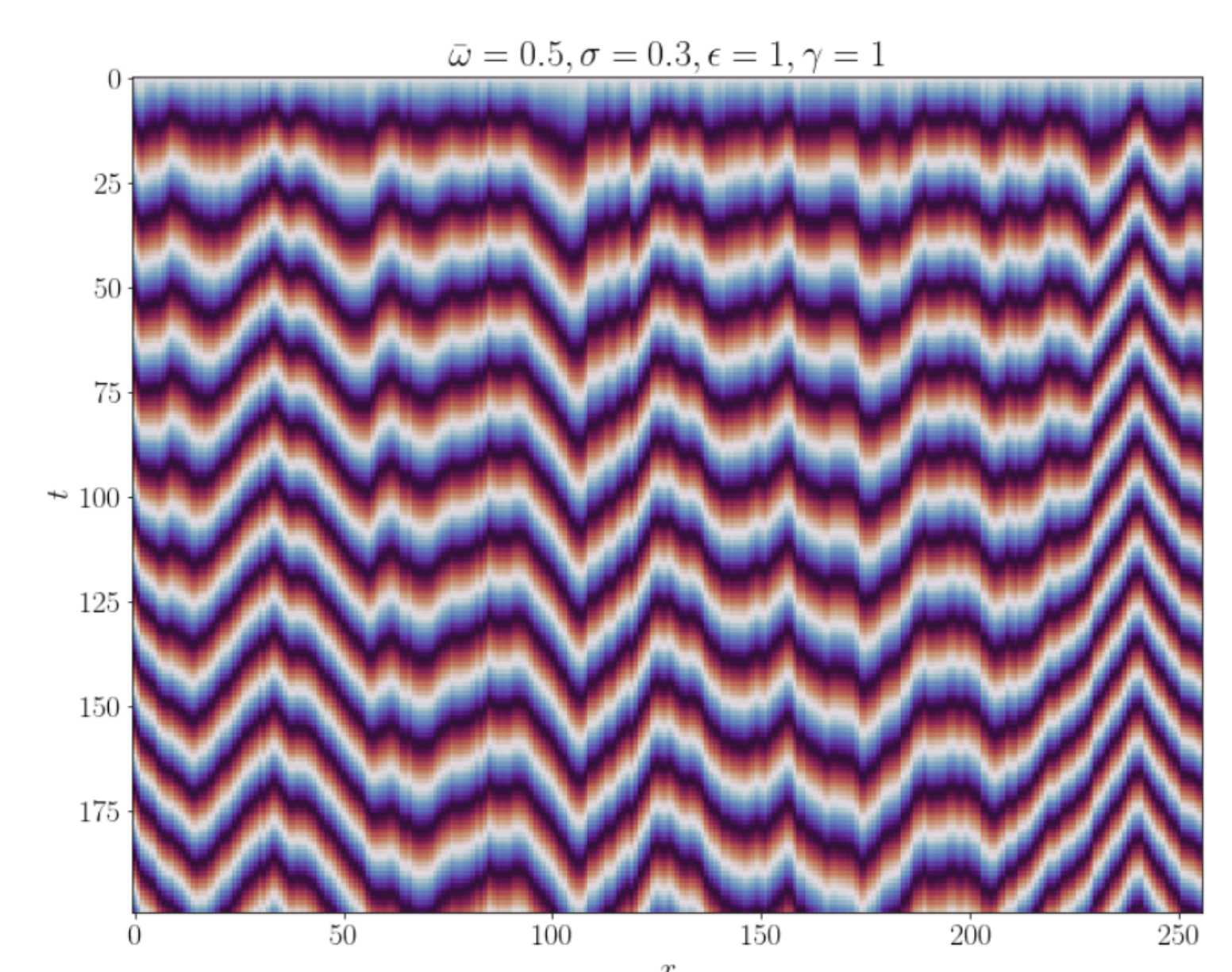
$$\partial_t \theta_i = \omega_i + \epsilon \sum_{j \in N_i} K(\theta_j - \theta_i)$$

$$K(\phi) = \sin(\phi) + \alpha(1 - \cos(\phi))$$

where ω_i 's are drawn from a normal distribution $\mathcal{N}(\bar{\omega}, \sigma^2)$ and N_i denotes the set of nearest neighbours of i .

The key features of the experimental data are captured by the minimal model,

- Travelling phase waves.
- Topological defects where velocities go in different directions.
- Variable peak to peak distances.



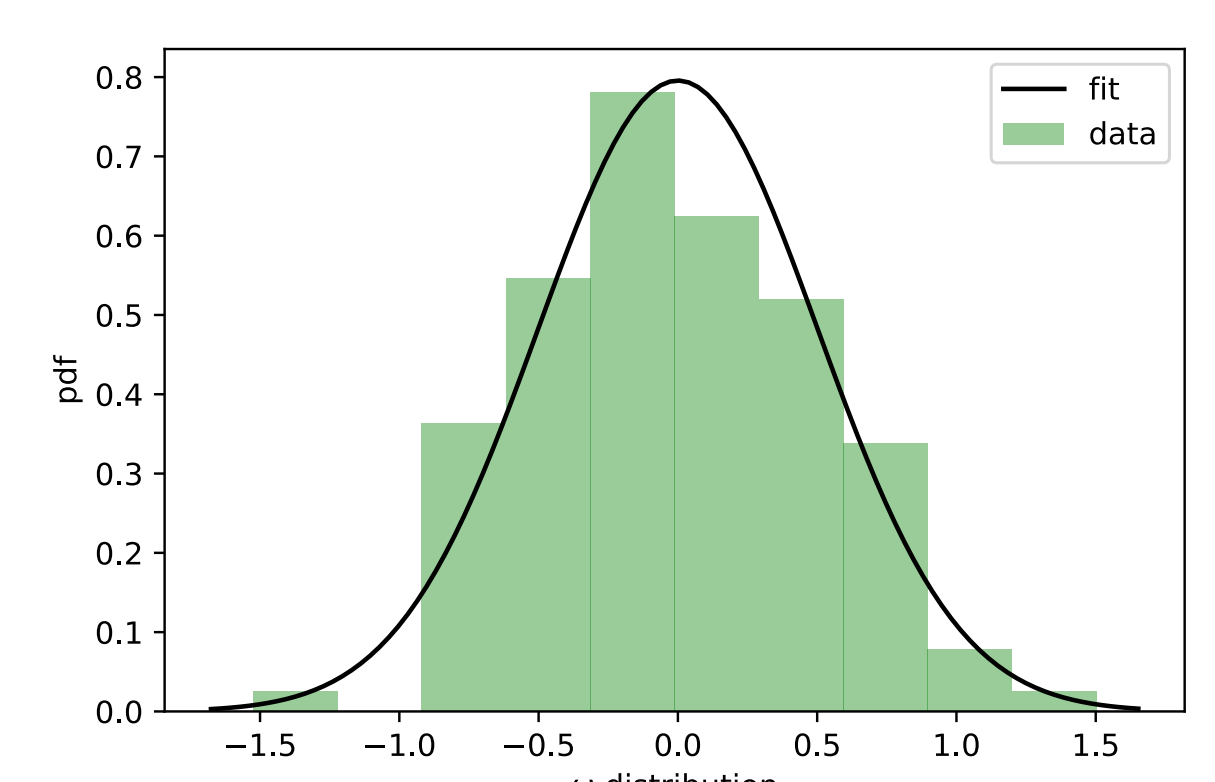
Fitting the experimental data

Assuming that the steady state is synchronised ($\theta_i(t) = \Omega t + \tilde{\theta}_i$) and the α value is known, one can infer the overall frequency Ω from the $\tilde{\theta}$ profile and substitute back to obtain the ω_i distribution:

$$\omega_i = \Omega - \epsilon \sum_{j \in N_i} K(\tilde{\theta}_j - \tilde{\theta}_i)$$

Using the Gamma distribution as prior for (σ, α) , the **fitting procedure** is as follows,

- Calculate ω_i from the phase profile for a given value of α .
- Obtain the MAP estimate for $\sigma = \sqrt{\sum_i \omega_i^2 / N}$
- Calculate the log likelihood of the ω distribution given $\mathcal{N}(0, \sigma)$.
- Minimize the log posterior over α to obtain the MAP estimate.



Conclusions and perspectives

Conclusions

- We constructed a time-delayed model for the local cyclic behaviour, incorporating the feedback mechanisms between the RA concentration and germ line differentiation.
- Having established that the local model gives rise to sustained cycles, we propose a Kuramoto-type minimal model for the spatio-temporal phase profile and fit the experimental data.

Perspectives

- Further studies of the asymmetric Kuramoto model to quantify properties such as typical wavelength and correlation functions.

References

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