Spatiotemporal coordination of the cell division cycle

Thibeau Wouters

Under supervision of Lendert Gelens and Daniel Ruiz Réynes

January 31, 2022

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Introduction

Me:

- Master thesis with Nikolay Bobev at ITF
- Research internship at *Laboratory for Dynamics in Biological Systems* (DiBS), Department of Cellular and Molecular Medicine

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Motivation: from experiments to theory

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- Life: *Xenopus laevis* frog eggs
- Experiments: cell cycle oscillations in extracts. Waves coordinate cell cycles in space
- Theory: understand the observations

Figure: A *Xenopus laevis* frog. [2]

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What about the internship?

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Figure: A *Xenopus laevis* frog. [2]

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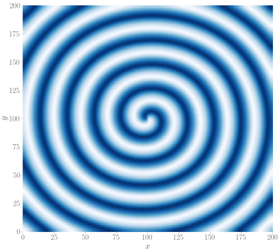
- **Goal:** Model spiral waves and study their properties.



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The FitzHugh-Nagumo model

The FitzHugh-Nagumo (FHN) eqs [3, 4] are *reaction-diffusion* eqs modelling concentrations of chemicals:

$$\begin{cases} \partial_t u &= \varepsilon^{-1}\left(v - \frac{1}{4}u(u^2-4)\right) + D_u \nabla^2 u \\ \partial_t v &= a - u + D_v \nabla^2 v\,. \end{cases} \qquad (\nabla^2 = \partial_x^2 + \partial_y^2)$$

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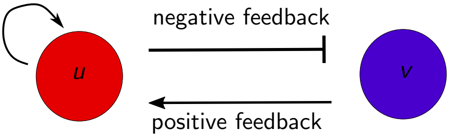
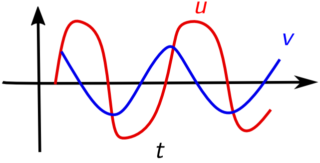
Reactions with positive and negative feedback loops give oscillations [5, 6]:





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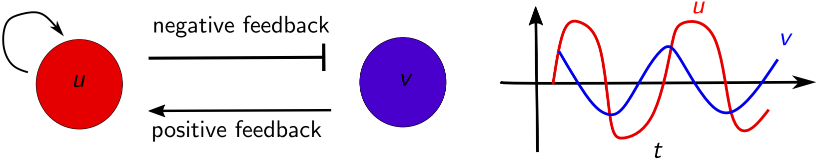

Diffusion couples oscillators in space. They can synchronise and create coherent wave patterns.

Wave patterns

Besides spirals, we also study target patterns. They are generated by **pacemakers** [6]: regions oscillating faster than their surroundings ($P_i < P_o$). Which pattern (target/spiral) emerges depends on the IC:

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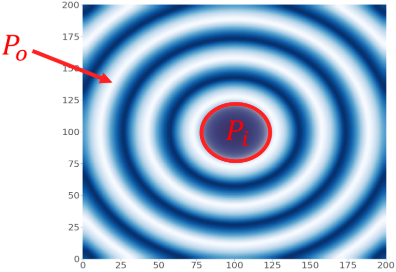
IC = homogeneous + pacemaker

$\Downarrow$



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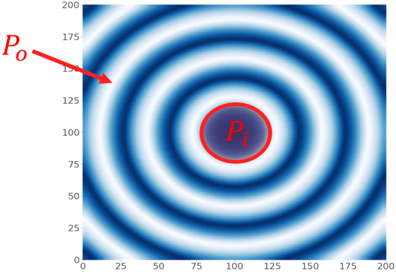
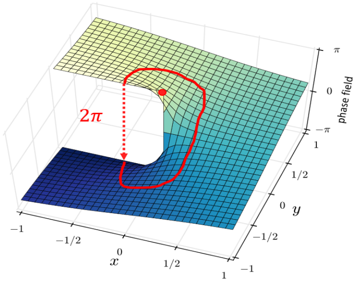


IC = topological defect [7, 8]

(= heterogeneous)



⇓

spirals

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Speeds of wave patterns

Q1: How do the **properties (speeds, periods)** of the wave patterns depend on the parameters of the FHN equations (ε, a, D_u/D_v,...)?

Approach: 'Measure' wave speeds c and envelope speeds C_ℓ from simulations:

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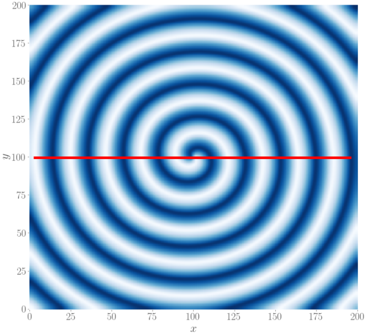

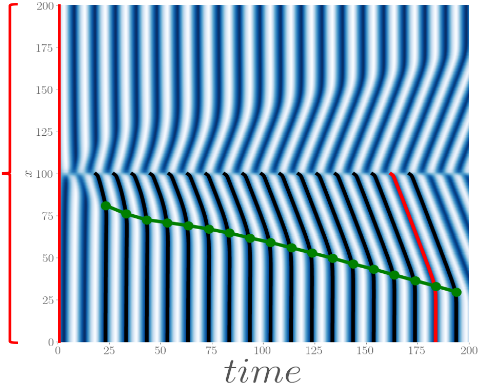

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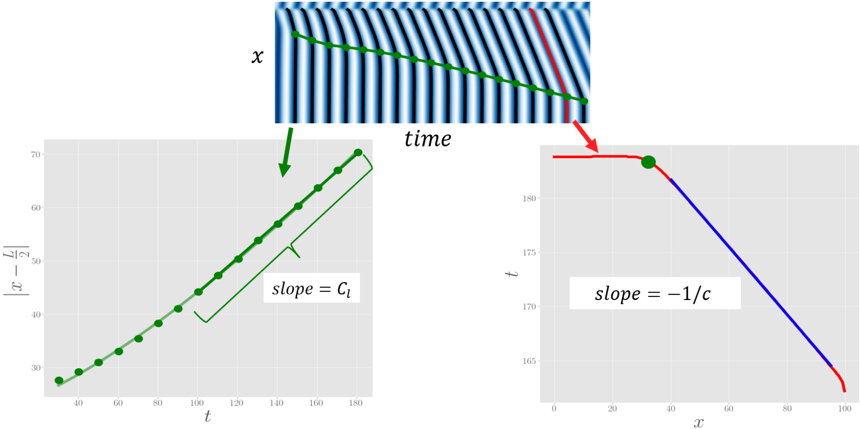
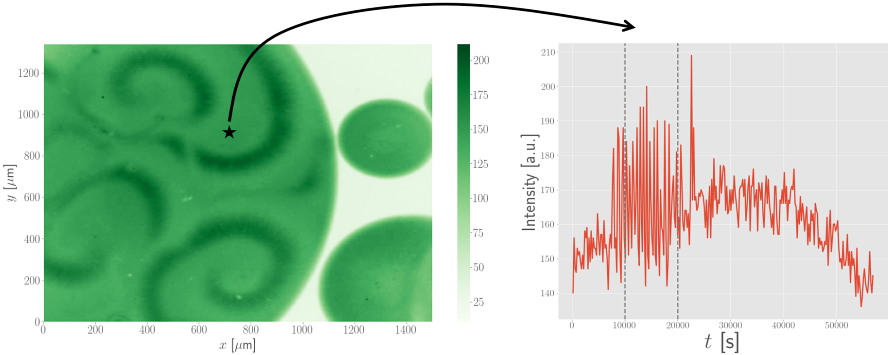


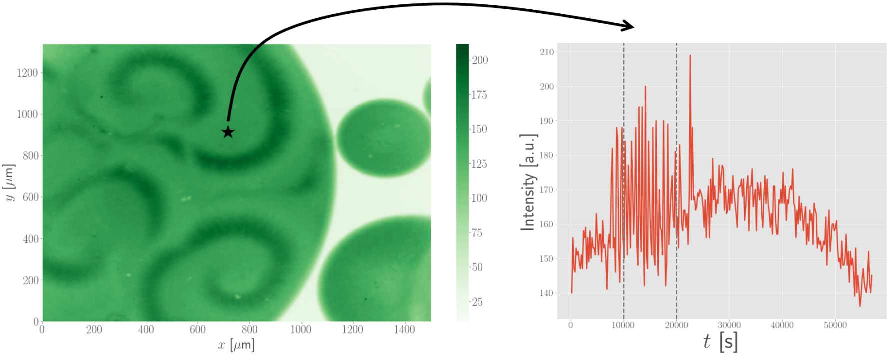
Periods of spirals

A1:



Periods of spirals

A1: Data analysis on the experiments shows periods with *spirals* are $P \sim 10 - 20$ mins, while earlier experiments with *targets* had $P \sim 30 - 40$ mins [9] .



Periods of spirals

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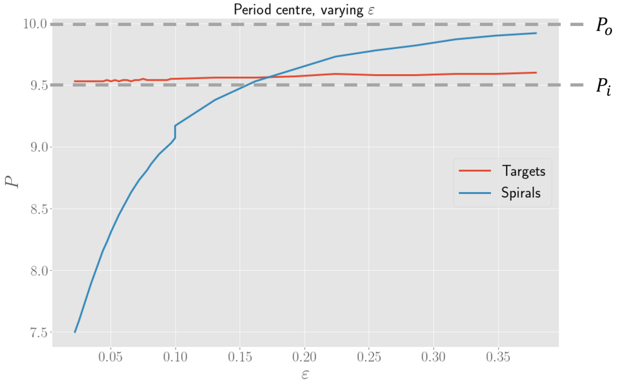
Simulations reproduce this observation.



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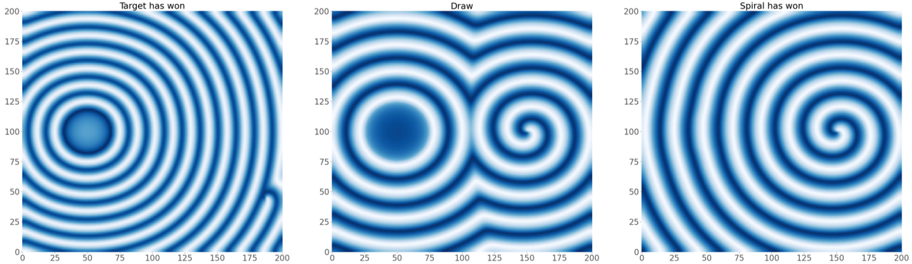
Competition between wave patterns

Q2: What if patterns **compete** (cf. video)? Which will 'win'? What is the deciding factor in this competition?



Competition results

A2: We varied ε and $h = P_o - P_i =$ period difference pacemaker and surroundings.

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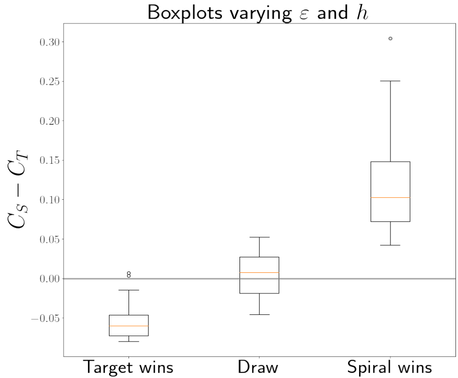
The pattern with the largest envelope speed wins in the end.



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Conclusion

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- Both theory and experiment show that periods of oscillations are lower when spirals are present.

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- Reaction-diffusion equations allow us to model and numerically study wave patterns.
- Different initial conditions cause different wave patterns (pacemaker $\rightarrow$ target, topological defect $\rightarrow$ spiral).
- Both theory and experiment show that periods of oscillations are lower when spirals are present.
- When wave patterns interact, the envelope speed decides the outcome.

References & thanks for listening!

[1] Gelens Lab, "Home." http://www.gelenslab.org/.
[Online; accessed 29-Jan-2022].

[2] Cambridge University, "Xenopus." https://www.cam.ac.uk/research/research-at-cambridge/animal-research/about-our-animal-research/which-types-of-animals-do-we-use/xenopus.
[Online; accessed 29-Jan-2022].

[3] R. FitzHugh, "Mathematical models of threshold phenomena in the nerve membrane," *The bulletin of mathematical biophysics*, vol. 17, no. 4, pp. 257–278, 1955.

[4] J. Nagumo, S. Arimoto, and S. Yoshizawa, "An active pulse transmission line simulating nerve axon," *Proceedings of the IRE*, vol. 50, no. 10, pp. 2061–2070, 1962.

[5] J. Rombouts and L. Gelens, "Analytical approximations for the speed of pacemaker-generated waves," *Phys. Rev. E*, vol. 104, p. 014220, Jul 2021.

[6] J. Rombouts and L. Gelens, "Synchronizing an oscillatory medium: The speed of pacemaker-generated waves," *Phys. Rev. Research*, vol. 2, p. 043038, Oct 2020.

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[8] M.-A. Bray and J. Wikswo, "Use of topological charge to determine filament location and dynamics in a numerical model of scroll wave activity," *IEEE Transactions on Biomedical Engineering*, vol. 49, no. 10, pp. 1086–1093, 2002.

[9] F. E. Nolet, A. Vandervelde, A. Vanderbeke, L. Piñeros, J. B. Chang, and L. Gelens, "Nuclei determine the spatial origin of mitotic waves," *Elife*, vol. 9, p. e52868, 2020.

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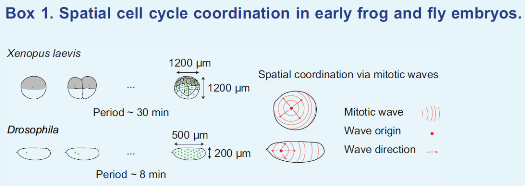
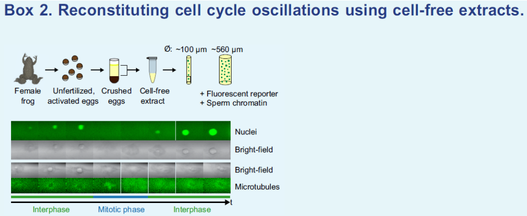
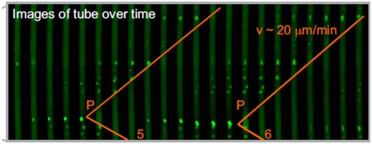
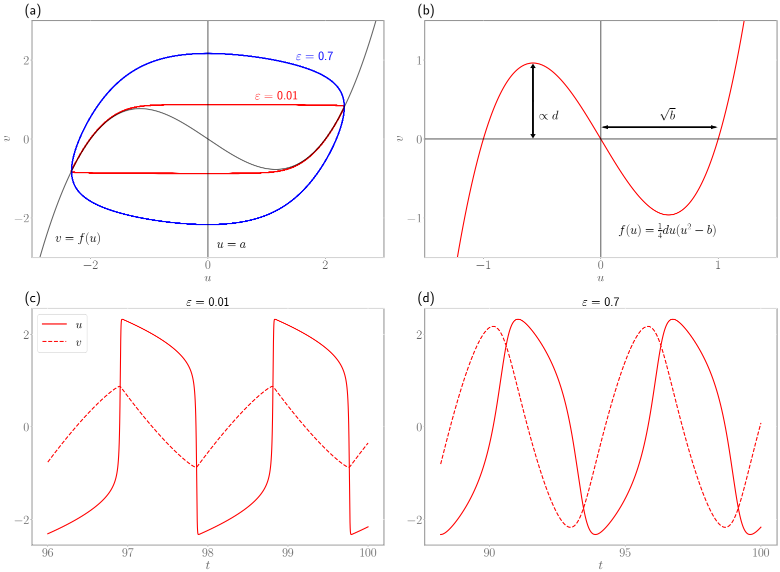
Extracts


Box 1. Spatial cell cycle coordination in early frog and fly embryos.
Xenopus laevis
1200 µm
1200 µm
Period ~ 30 min
Drosophila
500 µm
200 µm
Period ~ 8 min
Spatial coordination via mitotic waves
Mitotic wave
Wave origin
Wave direction

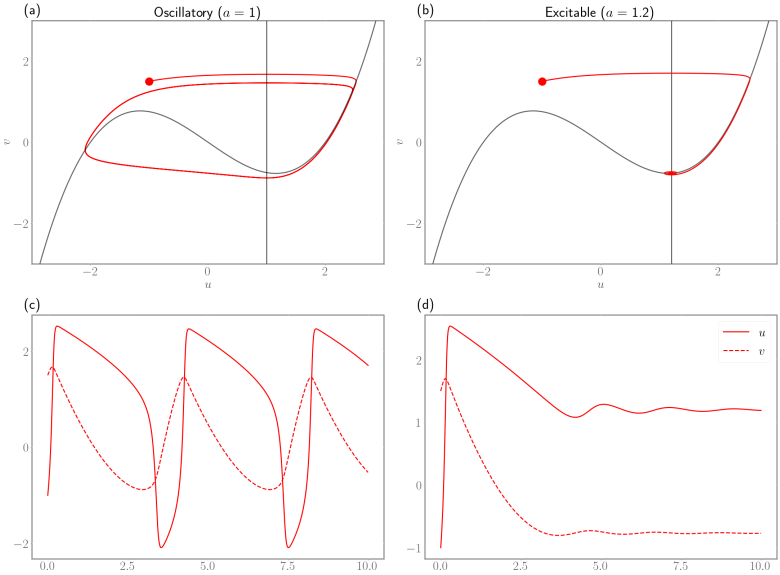

Box 2. Reconstituting cell cycle oscillations using cell-free extracts.
Ø: ~100 µm ~560 µm
Female frog
Unfertilized, activated eggs
Crushed eggs
Cell-free extract
+ Fluorescent reporter
+ Sperm chromatin
Nuclei
Bright-field
Bright-field
Microtubules
t
Interphase
Mitotic phase
Interphase


Images of tube over time
v ~ 20 µm/min
P
P
5
6

Phase space & ε controls shape oscillations



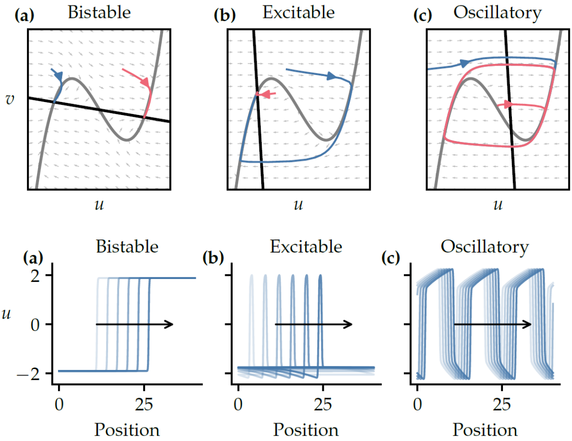
a and oscillatory vs. excitable



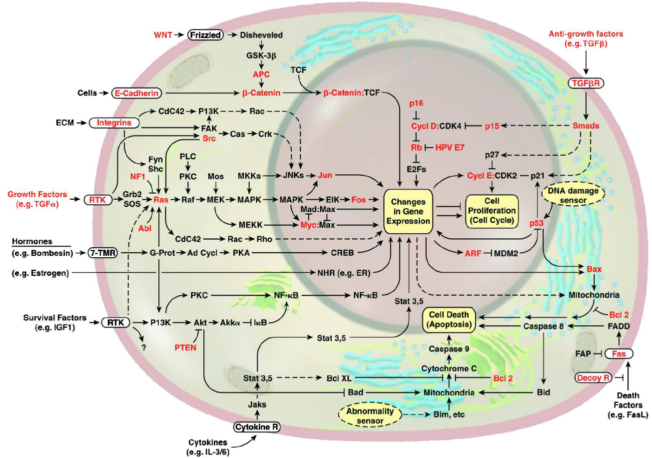
a, b and three regimes

Generalisation of FHN equations:

$$\begin{cases} \partial_t u &= \varepsilon^{-1}\left(v - \frac{1}{4}u(u^2-4)\right) + D_u \nabla^2 u \\ \partial_t v &= a - u - bv + D_v \nabla^2 v \,. \end{cases}$$



Network diagrams & complexity of the cell



Numerical integration details

Numerical integrations are done using:

- Python, Numpy, Matplotlib, Scipy,...,
- in a square domain of side length $L = 200$, divided into N^2 grid points, usually $N = 200$, with no-flux boundary conditions,
- integrated with the forward Euler scheme, $\mathrm{d}t = 0.01$ (usually) and for a time $T = 1000$,
- with default parameter values $a = 0, D_u = 1, D_v = 0.1, \varepsilon = 0.1$,
- time-steps are rescaled using a space-dependent factor, to simulate pacemaker domains and have identical background oscillation periods fixed between several simulations.

Large simulations are done using the HPC cluster of supercomputers, provided by the FWO.

Initial conditions for the topological defect

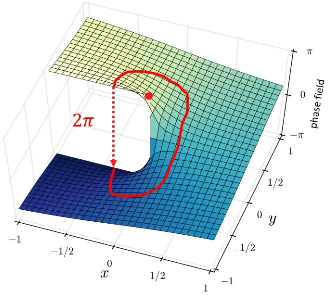
Our IC for the topological defect:

$$u_0(x, y) = \frac{(x - x_0)}{L}, \quad v_0(x, y) = \frac{(y - y_0)}{L},$$

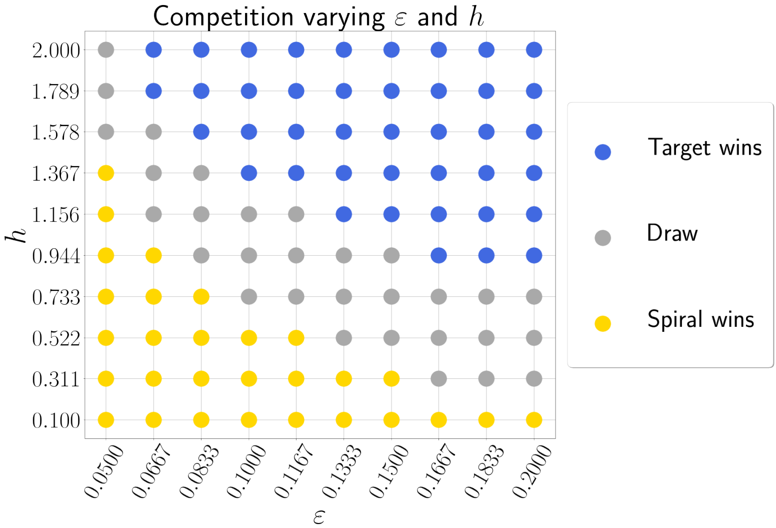
with usually $x_0 = y_0 = 0$: spiral tip at $\left(\frac{L}{2}, \frac{L}{2}\right)$. The phase field is defined as

$$\varphi(u_0, v_0) = \texttt{atan2}\left(u_0, v_0\right).$$

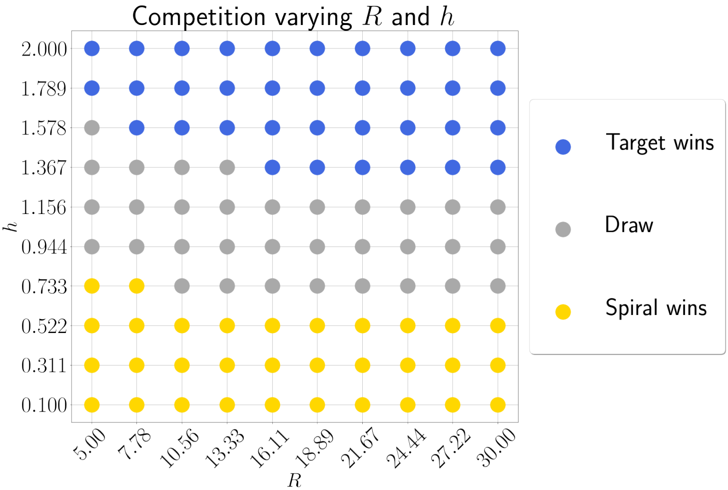
For the above IC, this is precisely the usual atan2 plot as shown earlier:



Competition results



Competition, varying R and $h = P_o - P_i$



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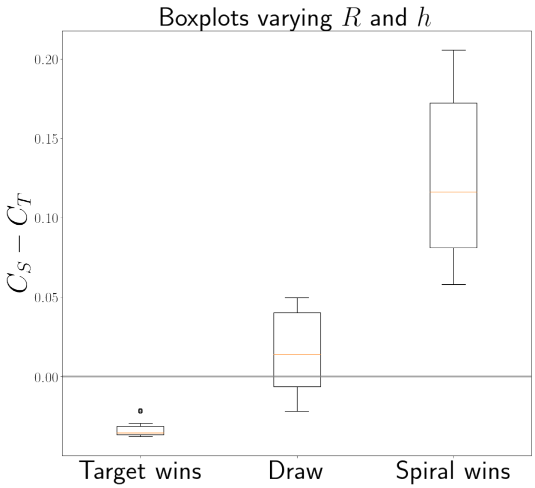

Outlook

Recall goal of DiBS:

- Do topological defects arise in experiments?
- Parameters of the model are constants: unlikely for real biological systems. What would happen if they vary?
- Continue studying interaction between patterns:
  - What about 2 pacemakers, or 2 spirals?
  - What if pacemakers and topological defects overlap? Observed in experiments!

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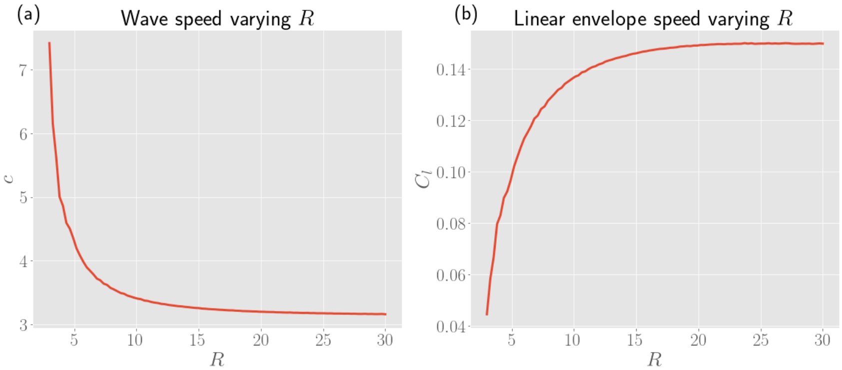
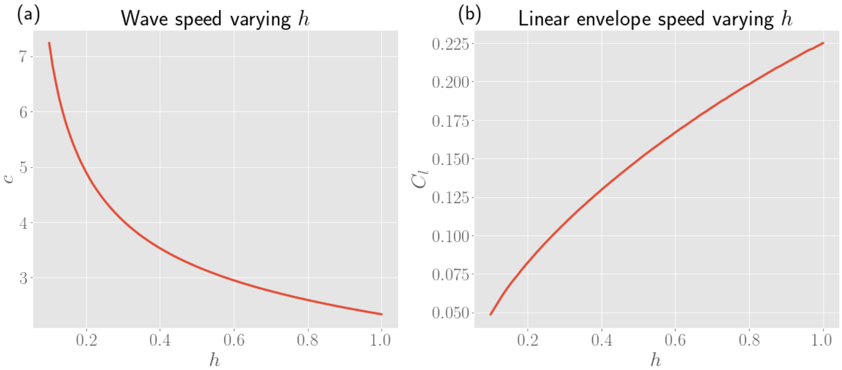
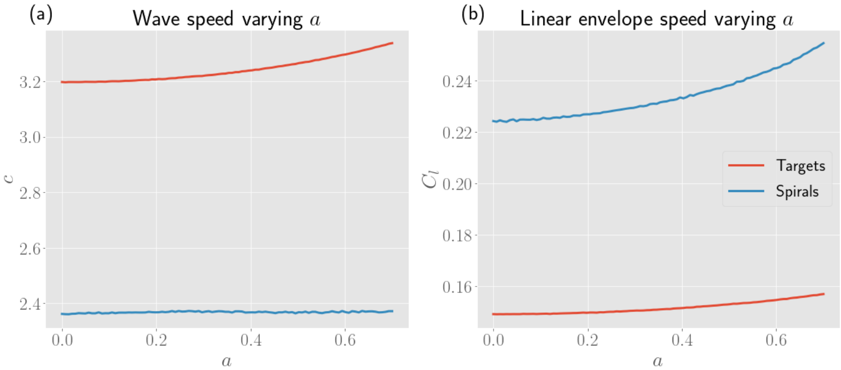
Varying R for targets



Varying h for targets

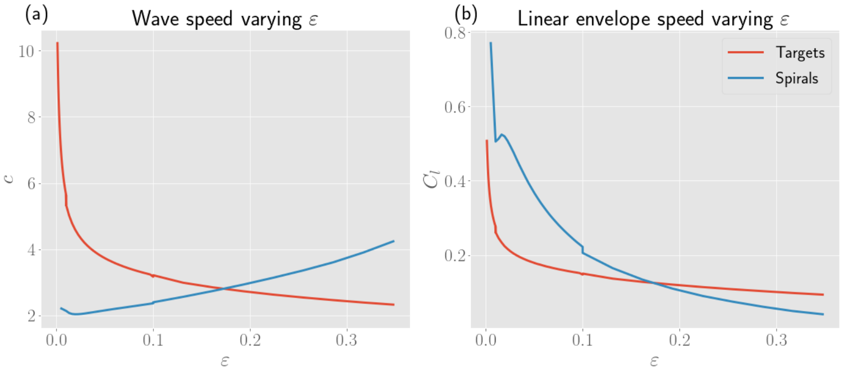


Varying a

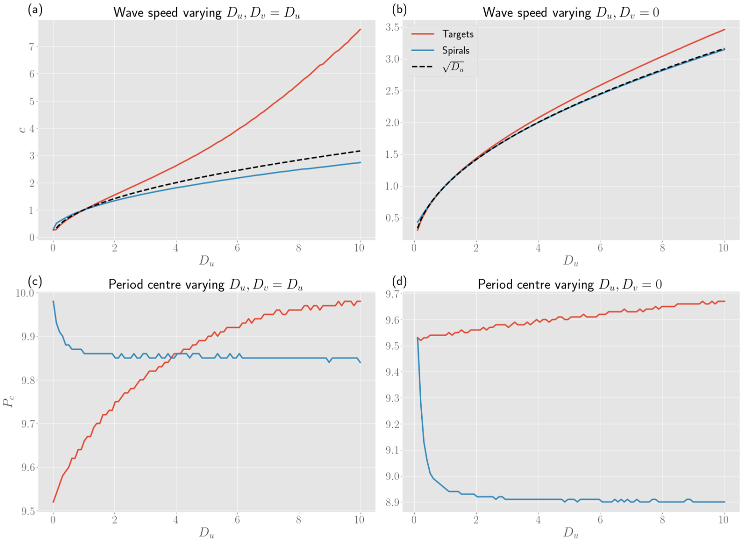


(a)
Wave speed varying a
3.2
3.0
2.8
2.6
2.4
c
0.0
0.2
0.4
0.6
a
(b)
Linear envelope speed varying a
0.24
0.22
0.20
0.18
0.16
C_l
0.0
0.2
0.4
0.6
a
Targets
Spirals

Varying ε



Varying D_u


(a)
Wave speed varying $D_u, D_v = D_u$
c
D_u
(b)
Wave speed varying $D_u, D_v = 0$
Targets
Spirals
$\sqrt{D_u}$
D_u
(c)
Period centre varying $D_u, D_v = D_u$
P_c
D_u
(d)
Period centre varying $D_u, D_v = 0$
D_u