Outline

- ▷ Signaling and Diffusion
- ▷ The cable equation
- ▷ Traveling waves
- ▷ Multidimensional cable equation
- ▷ Lab session

Diffusion and random walks

Unit mass particle moving randomly along x–axis:

- $x = mh$, $h =$ space–step;
- $t = N\tau$, $\tau =$ time–step;
- $p(x, t) =$ probability to find the particle at position x and time t.

Objective: take the limit $h \to 0$ and $\tau \to 0$.

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The position x is a random variable. We have:

$$\mathbb{E}[x] = 0, \qquad \mathbb{V}\mathrm{ar}[x] = \mathbb{E}[x^2] = Nh^2 = t\frac{h^2}{\tau}.$$

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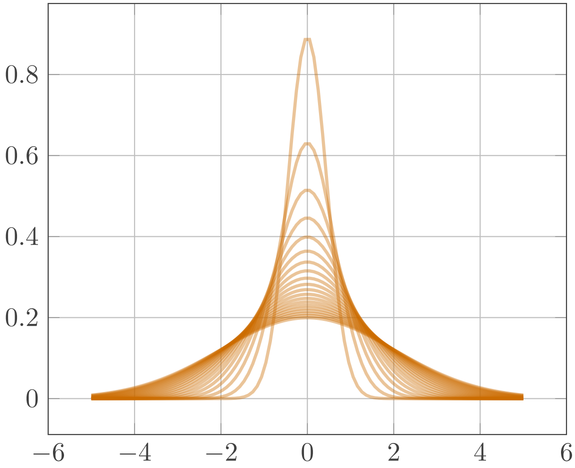
Now we compute the limit, so $p(x,t)$ satisfies the diffusion equation:

$$\boxed{\frac{\partial p}{\partial t} = \mathsf{D}\frac{\partial^2 p}{\partial x^2}, \qquad \mathsf{D} := \lim_{h,\tau\to 0}\frac{h^2}{2\tau}.}$$

Not rigorous, $p(x,t)$ should be a *probability density* in the limit.

Fundamental solution for $D = 1,\ T \in [0, 2]$



Diffusion distance and other effects

In $\mathbb{R}^n$ we have $\mathsf{D} := \lim_{h,\tau\to 0} \frac{h^2}{2n\tau}$: dimension matters! [Youtube]

On average, we reach a point at distance L in about $T \sim \frac{L^2}{2n\mathsf{D}}$.

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Example Smoke in the air $\sim$ 0.22 cm/s^2.

$$\begin{array}{lcl} L = \ \ 1 \text{ cm} & \rightarrow & T = 1 \text{ second} \\ L = 10 \text{ cm} & \rightarrow & T = 1 \text{ minutes} \\ L = \ \ 1 \text{ m} & \rightarrow & T = 2 \text{ hours} \\ L = 10 \text{ m} & \rightarrow & T = 9 \text{ days} \end{array}$$

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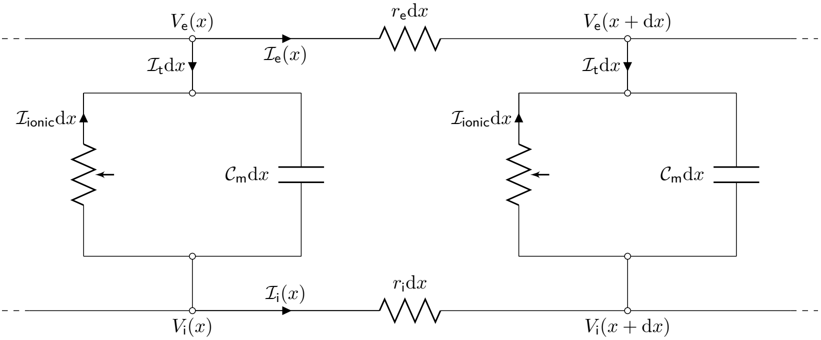
In the air, diffusion alone is not enough: indeed, turbulence is the missing ingredient (advection dominated process).

Another problem is that diffusion dissipates energy, so the signal is attenuated on long distances.

Idea: invest some energy to “rekindle” the process (reaction). [Youtube].

Electric analogue of the cellular membrane



$$\begin{aligned}
\mathcal{C}_{\mathsf{m}} &= \text{membrane capacitance,}\\
\mathcal{I}_{\mathsf{ionic}} &= \text{ionic currents,}\\
V_{\mathsf{i,e}} &= \text{intra– and extra–cellular electric potential,}\\
r_{\mathsf{i,e}} &= \text{intra– and extra–cellular resistence.}
\end{aligned}$$

Equation and dimensionless form

$$\boxed{p\left(\mathcal{C}_{\mathsf{m}}\frac{\partial V}{\partial t}+\mathcal{I}_{\mathsf{ionic}}(V,t)\right)=\frac{1}{r_{\mathsf{e}}+r_{\mathsf{i}}}\frac{\partial^2 V}{\partial x^2}.}$$

- $\dfrac{1}{R_{\mathsf{m}}}=\left.\dfrac{\mathrm{d}\mathcal{I}_{\mathsf{ionic}}}{\mathrm{d}V}\right|_{V=V_0}$ is the membrane conductance;
- $\lambda_{\mathsf{m}}=\sqrt{\dfrac{R_{\mathsf{m}}}{p(r_{\mathsf{i}}+r_{\mathsf{e}})}}$ is the typical length–scale of the problem;
- $\tau_{\mathsf{m}}=\mathcal{C}_{\mathsf{m}}R_{\mathsf{m}}$ is the typical time–scale of the problem.

After rescaling the variables $x\mapsto\frac{x}{\lambda_{\mathsf{m}}}$ and $t\mapsto\frac{t}{\tau_{\mathsf{m}}}$ we obtain:

$$\boxed{\frac{\partial V}{\partial t}=\frac{\partial^2 V}{\partial x^2}+f(V,t).}$$

Reaction term and boundary conditions

The cable equation is reaction–diffusion PDE, and it can be reinterpreted as a infinite dimensional ODE:

$$\dot{\mathbf{u}} = \mathsf{A}\mathbf{u} + f(\mathbf{u}, t).$$

Equilibria, stability, attractors, etc... can be defined in this context.

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We need additional information to define the problem:

- **Initial condition**: $V(x, 0) = ...;$
- **Boundary conditions**:
  - Voltage–clamp: $V(x_b, t) = V_b;$
  - Short–circuit: $V(x_b, t) = 0;$
  - Current injection: $\partial_x V(x_b, t) = -r_\mathsf{i}\lambda_\mathsf{m}\mathcal{I}(t);$
  - Sealed ends: $\partial_x V(x_b, t) = 0.$

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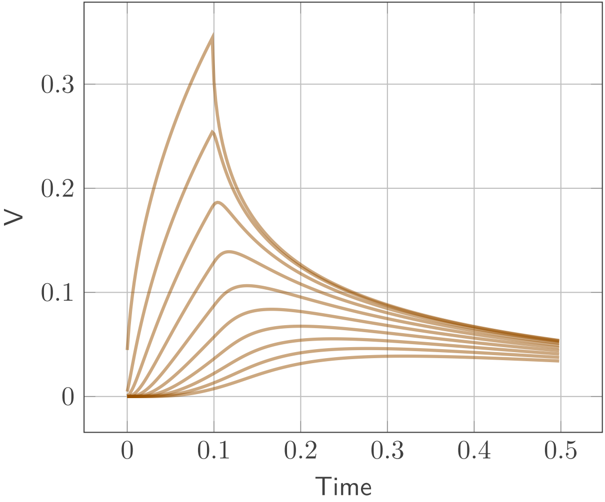
The reaction term $f(V, t)$ is generally:

- highly non–linear for excitable systems;
- a linear resistance $f(V) = -V$ for dendrite (passive systems).

Dendritic conduction

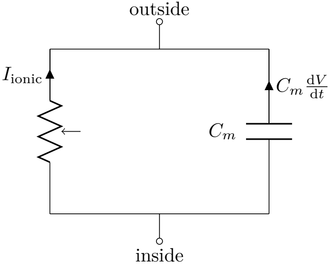


Excitable cells

We consider now an excitable cell, so $f(V)$ is one of the (several) models available in the literature (see previous lecture).

A general model could be:

$$\begin{cases} \dfrac{\partial V}{\partial t} = \dfrac{\partial^2 V}{\partial x^2} + f(V, \mathbf{w}, \mathbf{c}), \\ \dfrac{\partial w_i}{\partial t} = \alpha_i(V)\big(1 - w_i\big) + \beta_i(V) w_i, \\ \dfrac{\partial \mathbf{c}}{\partial t} = \mathbf{h}(V, \mathbf{w}, \mathbf{c}), \end{cases}$$



where the 2nd equation describes gating variables (i.e. ionic channels dynamics), and the 3rd describes intracellular ionic concentrations.

Models in literature: *FitzHugh–Nagumo* (2 eq.), *Fenton–Karma* (4), *Luo–Rudy* (9), *Ten Tusscher–Panfilov* (18), *Flaim* (80), . . .

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We focus on the simplest version of non–linearity:

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- $V \equiv 0$, stable;
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- Possibly many others (non trivial): see lab session.

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Solution must be continuous, so we have to connect those two states.
$\Rightarrow$ Travelling waves.

Construction of traveling waves

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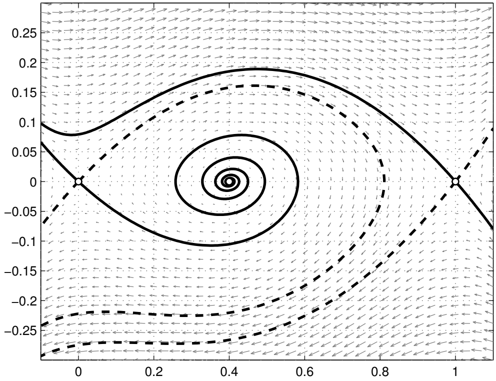
$$\text{Find } (U,c) \text{ s.t.} \quad \begin{cases} -cU'(\xi) = U''(\xi) + f(U(\xi)), & \xi \in \mathbb{R}, \\ U(-\infty) = 1,\ U(+\infty) = 0. \end{cases}$$

Analysis with PPlane.



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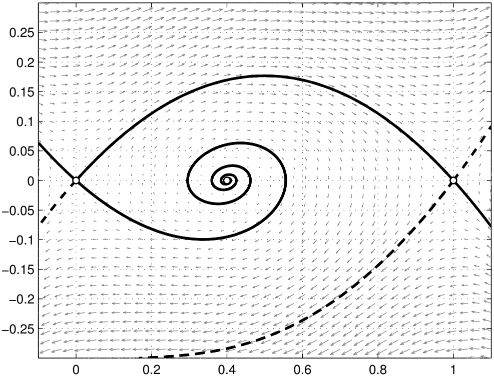
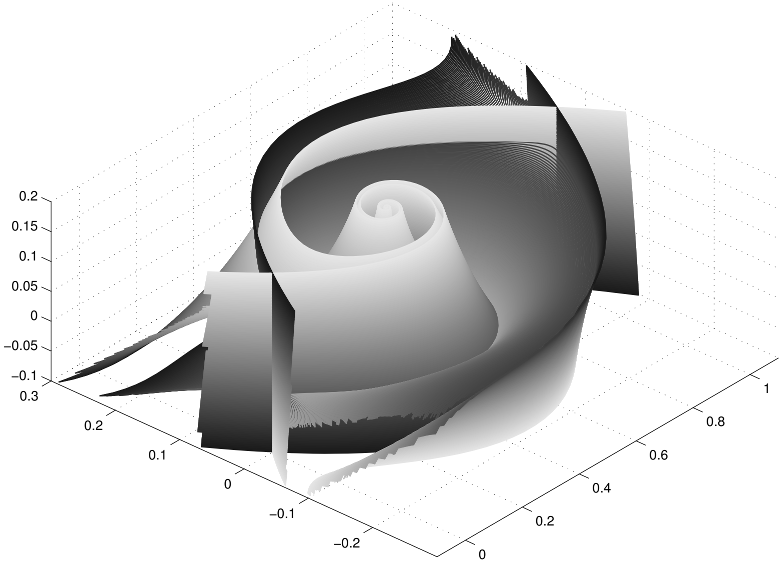


— Traveling waves —

Heteroclinic bifurcation



Solution

Existence, uniqueness (up to translations) and stability for general bistable nonlinearities (not only cubic).

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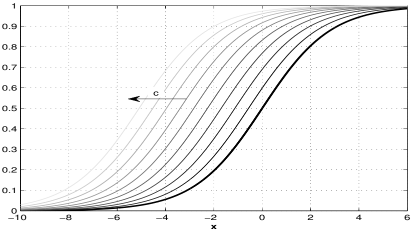
Exact solution for cubic nonlinearity:

$$U(x,t) = \frac{1}{2}\left[1 + \tanh\left(\frac{x+ct}{\varepsilon}\right)\right],$$

$$c = \frac{\lambda_{\mathsf{m}}\sqrt{2a}}{2\tau_{\mathsf{m}}}(1-2\alpha),$$

$$\varepsilon = \frac{4\lambda_{\mathsf{m}}\sqrt{2}}{\sqrt{a}}. \qquad \approx \text{front thickness.}$$

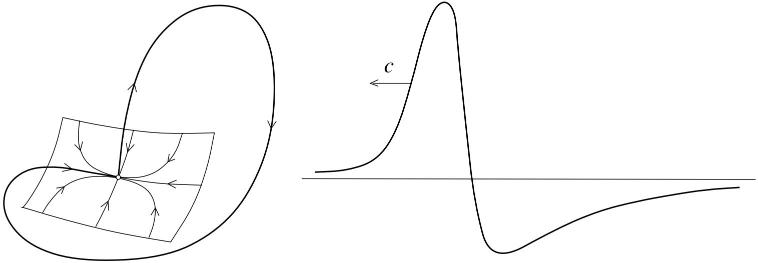


Extension to FitzHugh–Nagumo (recovery)

Not trivial, there are several analytical results but the spectrum of solutions is vast.

Pulse waves: the objective is to find a homoclinic orbit of the system obtained from the substitution $V(x,t) = U(x+ct)$, since we connect the resting state with itself.

The system is in $\mathbb{R}^3$, and the origin is a saddle point. The stable manifold in 2d, plus a 1d unstable manifold.



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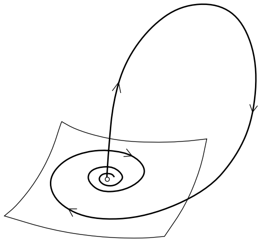

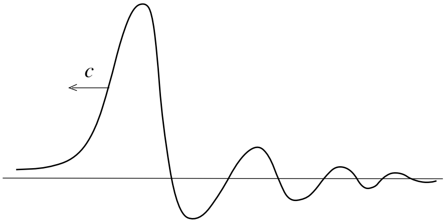

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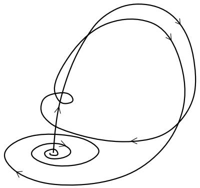

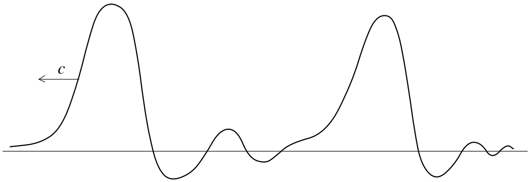

Informal generalization

$$\tau \frac{\partial V}{\partial t} = \nabla \cdot (\mathsf{D} \nabla V) + f(V, t).$$

Remark: We only substitute the diffusion, with D a symmetric positive–definite tensor of conductivity.

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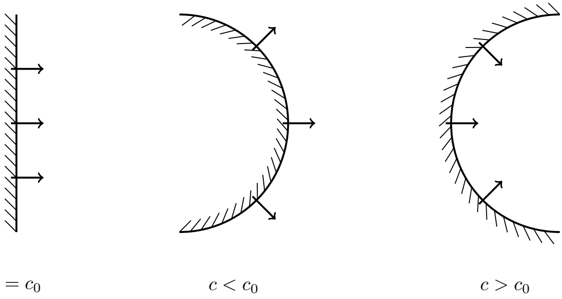
- **Planar waves:** $V(x, t) = U(x \cdot k + ct)$;
- **Spherical waves:** $V(x, t) = U(r + ct)$, $r = \|x\|$;
- **Spiral waves:** possible in $\mathbb{R}^2$, at least with FitzHugh–Nagumo;
- **Scroll waves:** possible in $\mathbb{R}^3$;
- ...

In the first two cases derivation is exactly as in one–dimensional case.

Effect of the curvature

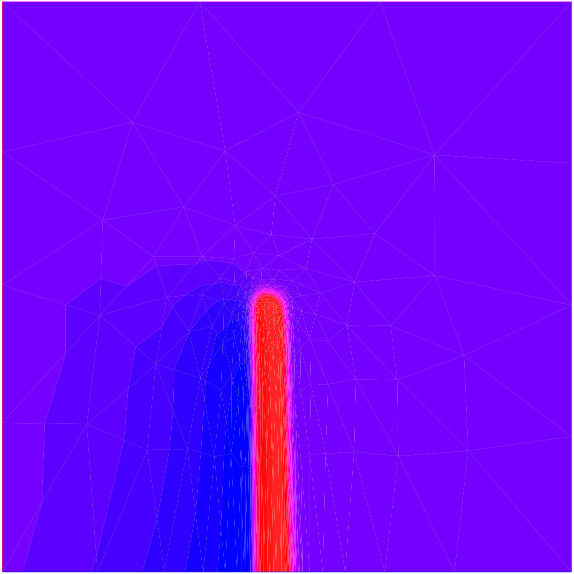


The local speed of the front depends on the curvature:

$$\boxed{c = c_0 - \kappa}$$

This is the **eikonal equation**.

Spiral waves



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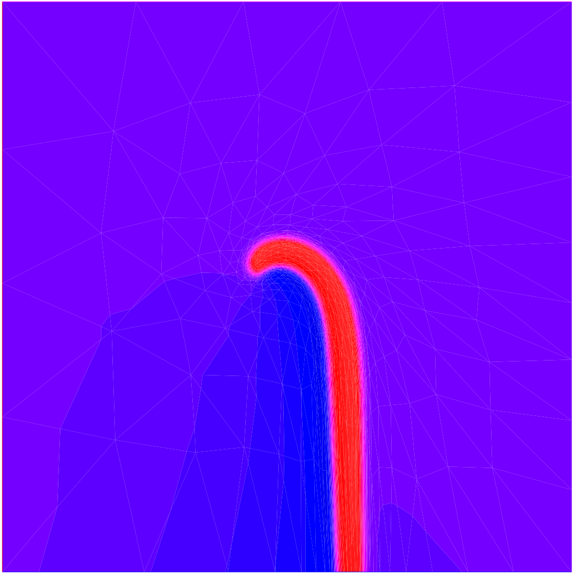

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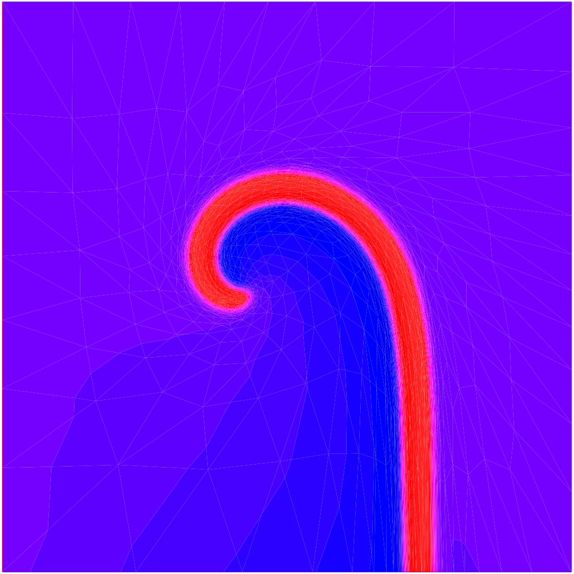

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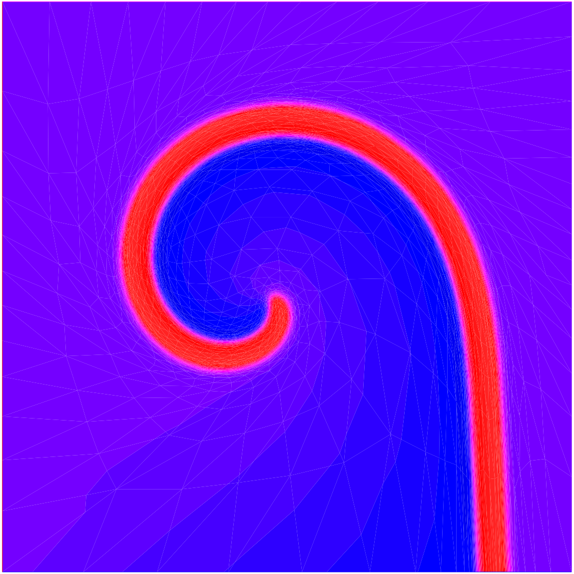

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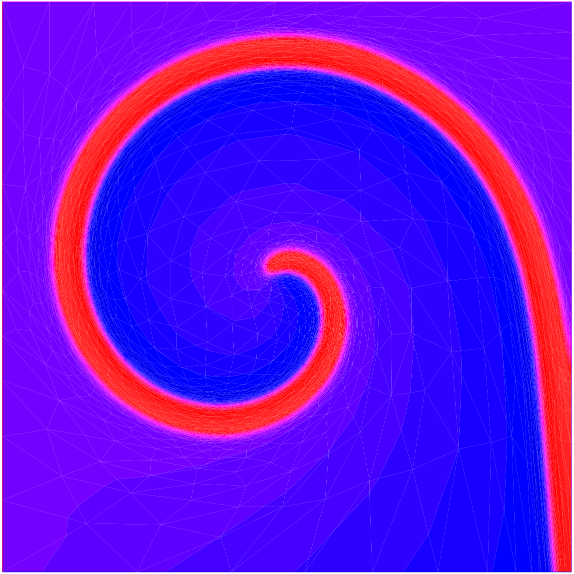

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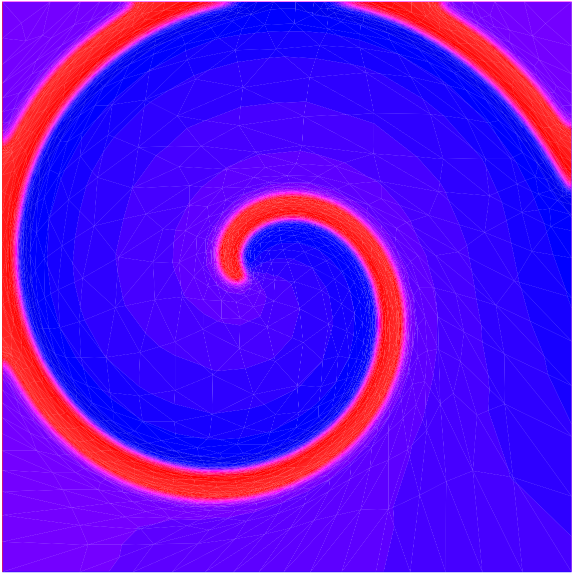

Lab session

1d traveling waves
2d planar, circular and spiral waves

Bistable equation (non–dimensional form):

$$\begin{cases} V_t = V_{xx} - V(1-V)(V-\alpha), & x \in (-L, L), \\ V_x(-L,t) = V_x(L,t) = 0, \\ V(x,0) = V_0(x). \end{cases}$$

1. Discretize in time with backward Euler method;
2. Write the variational formulation;
3. Solve for different α and different $V_0(x)$:
   - $V_0(x) = \dfrac{1}{2}\left[1 + \tanh\left(\dfrac{\sqrt{2}}{4}x\right)\right]$;
   - $V_0(x) = \dfrac{\alpha}{2}\left[1 + \tanh\left(-\dfrac{\alpha\sqrt{2}}{4}x\right)\right]$;
   - $V_0(x) = \begin{cases} \beta & x \in (-\gamma, \gamma) \\ 0 & \text{otherwise} \end{cases}$;
   - $V_0(x) = 2\alpha \dfrac{\tanh^2(\frac{\sqrt{\alpha}}{2}x) - 1}{a_1 \tanh^2(\frac{\sqrt{\alpha}}{2}x) - a_2}$, $a_{1,2} = \frac{2(\alpha+1) \pm \sqrt{4 - 10\alpha + 4\alpha^2}}{3}$.

Multidimensional bistable equation (non–dimensional form):

$$\begin{cases} V_t = \mu \Delta V - V(1-V)(V-\alpha), & x \in \Omega = (-L, L)^2, \\ \partial_n V(x,t) = 0, & x \in \partial\Omega \\ V(x,0) = V_0(x). \end{cases}$$

1. Extend the previous code to this one;
2. Solve for different $V_0(x)$:
   - $V_0(x) = \frac{1}{2}\left[1 + \tanh\left(\sqrt{\frac{a}{8\mu}} x_1\right)\right]$;
   - As before, but in x_2–direction;
   - As before, but in direction $\mathbf{n} = \left[\begin{smallmatrix}1\\1\end{smallmatrix}\right]$;
   - $V_0(x) = \frac{1}{2}\left[1 - \tanh\left(\sqrt{\frac{a}{8\mu}} \sqrt{x_1^2 + x_2^2}\right)\right]$;
3. Find a circular front which doesn't propagate at all.

Multidimensional FitzHugh–Nagumo equation:

$$\begin{cases} V_t = \Delta V - V(1-V)(V-\alpha), & x \in \Omega = (-L,L)^2, \\ w_t = \varepsilon\left(\frac{1}{2}V - w\right), & x \in \Omega = (-L,L)^2, \\ \partial_n V(x,t) = 0, & x \in \partial\Omega \\ V(x,0) = V_0(x), & \\ w(x,0) = 0. & \end{cases}$$

1. Solve for different $V_0(x)$:
   - $V_0(x) = \begin{cases} 1 & x < 0, \\ 0 & \text{otherwise;} \end{cases}$
   - $V_0(x) = \begin{cases} 1 & \|x\| < 0.2, \\ 0 & \text{otherwise;} \end{cases}$
   - $V_0(x) = \begin{cases} 1 & \|x+0.5\| < 0.2 \text{ or } \|x-0.5\| < 0.2, \\ 0 & \text{otherwise;} \end{cases}$
2. Initialize a spiral wave;
3. Add a region of the domain where reaction is deactivated.