Classification and stability analysis of travelling wave solutions for a model of collective cell migration.

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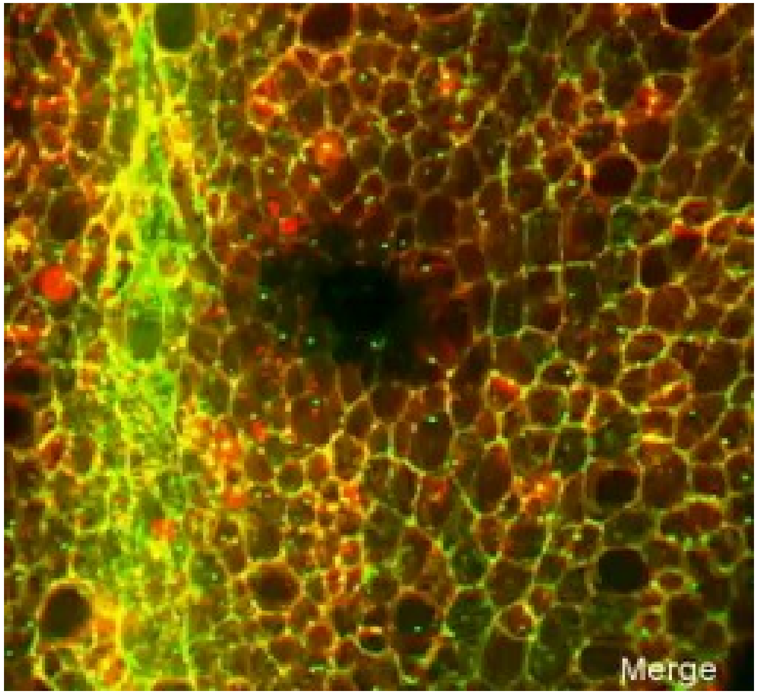
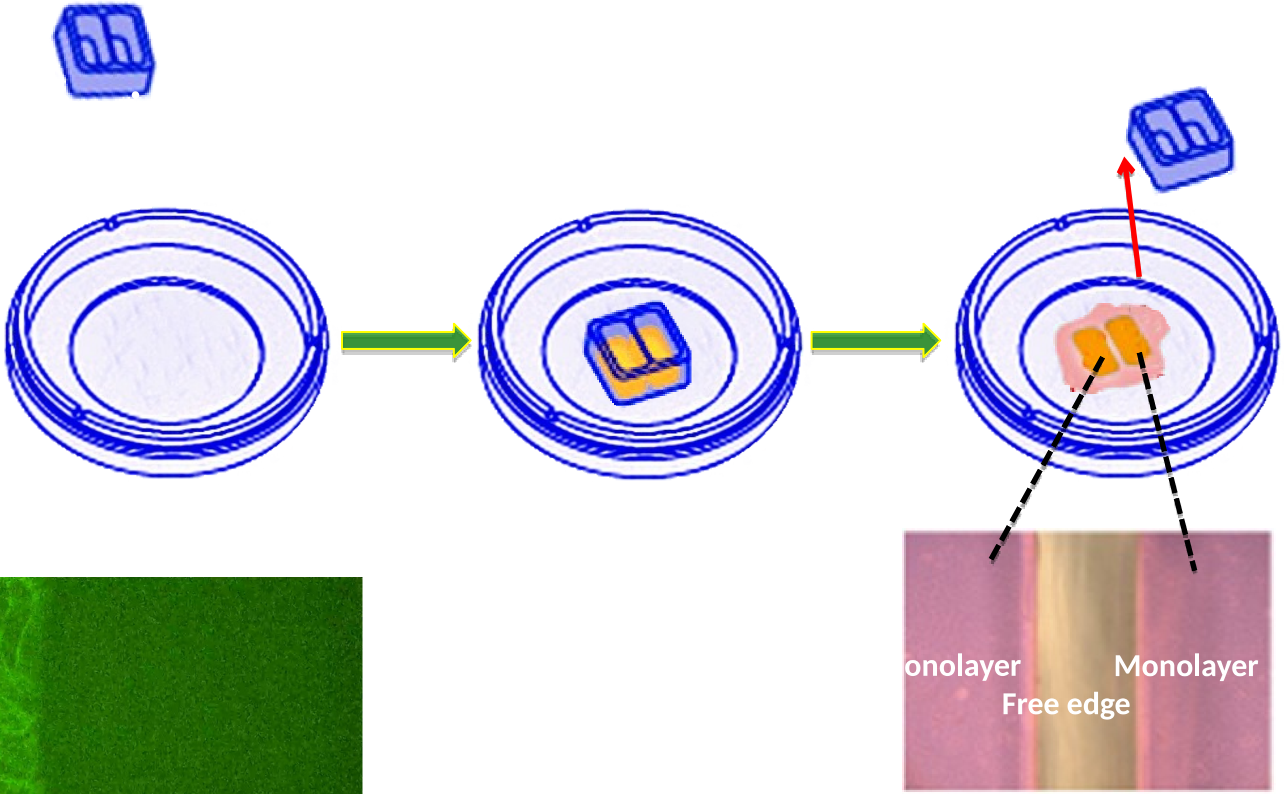
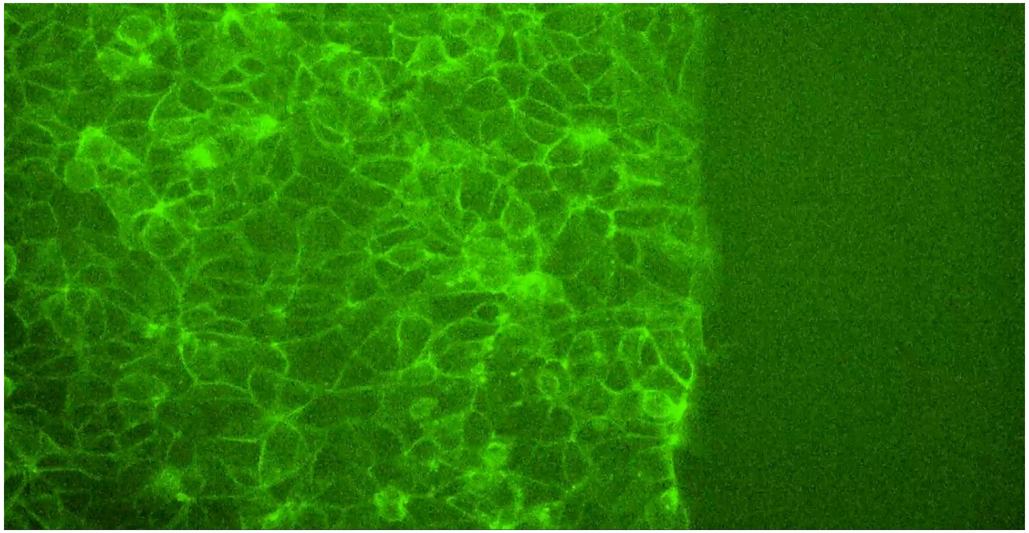
- Physiological conditions: **tissue morphogenesis, wound healing**
- Pathophysiological condition: **cancer invasion.**
- coordination through **cell-cell junctions (mechanosensation)**.



JCB 2013; Antunes

Migration (model wound) assays

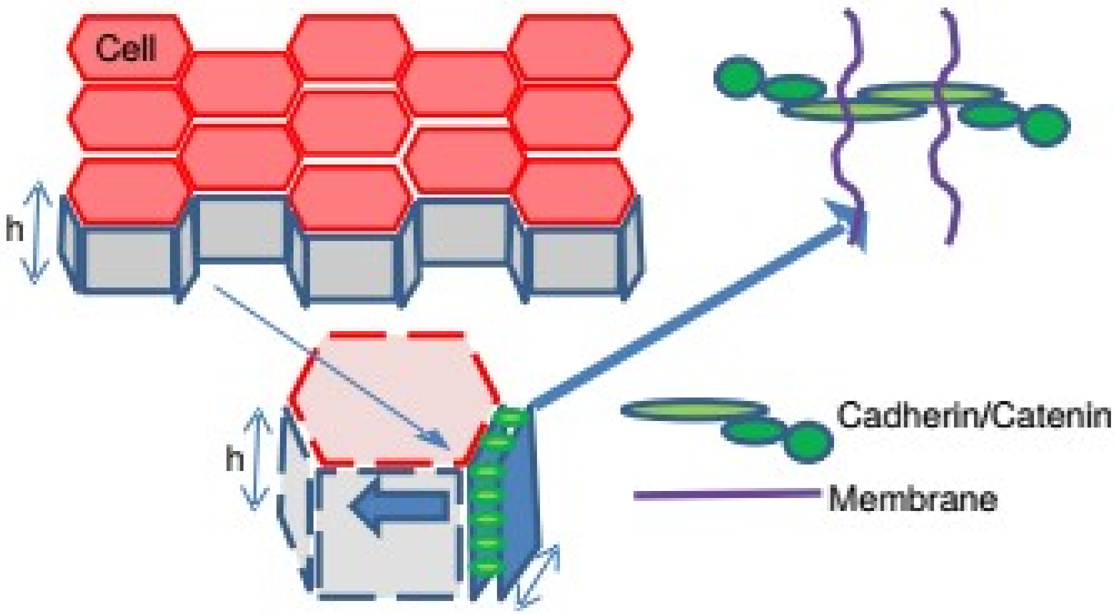




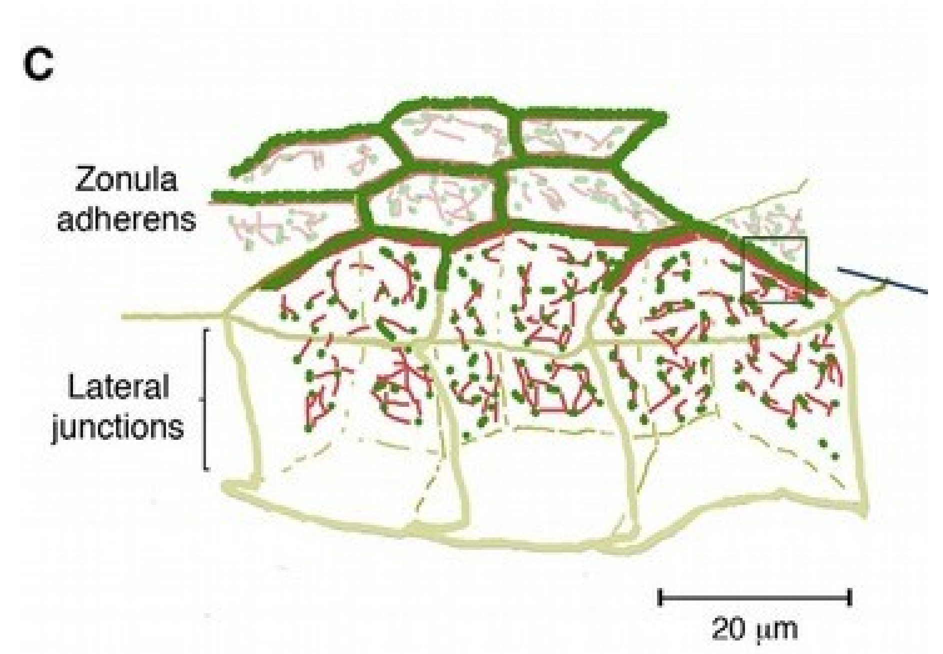
Collective motion of MCF-7 cells. (Shafali Gupta, IMB-UQ)

Mechanosensitive coupling

Cell-cell adhesion



Cortex contractility



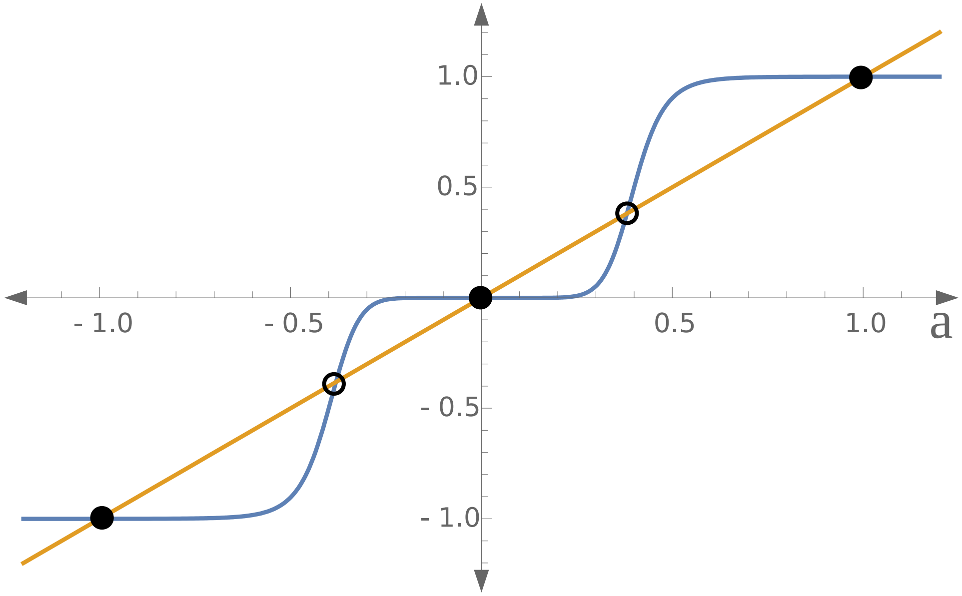
From Charras, Yap.
Current Biology 2018

Minimal model for motile machinery (polarization) of a single cell

$$\textit{Steady state:} \quad \frac{\beta}{\gamma} a = M_n(a)$$

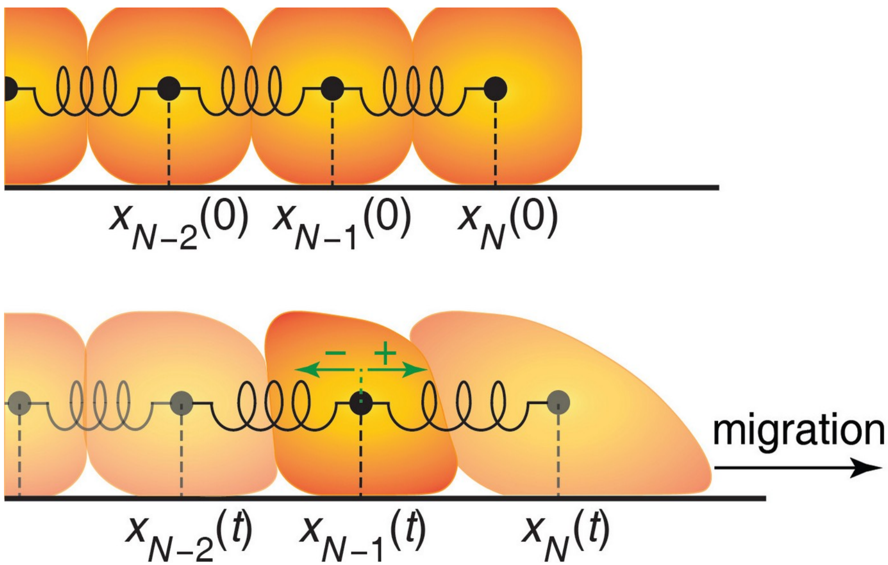
$$\begin{cases} \dot{a} = -\beta a + \gamma \dot{x} \\ \dot{x} = M_n(a) \end{cases}$$

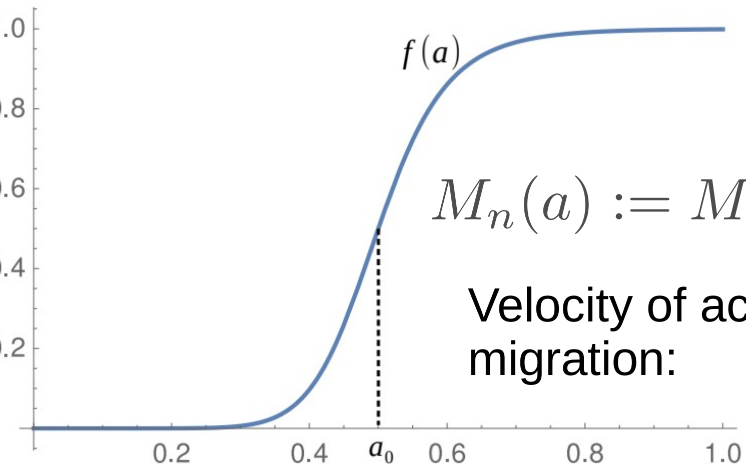
a ... *polarity*,
$\dot{x}$ ... *velocity*,
β ... *depolarisation*,
γ ... *polarisation*



$$M_n(a) := M_{max} \frac{a}{|a|} \frac{|a|^n}{|a|^n + \alpha^n}$$

1D toy model for collective cell migration





$$M_n(a) := M_{max} \frac{a^n}{a^n + \alpha^n}$$

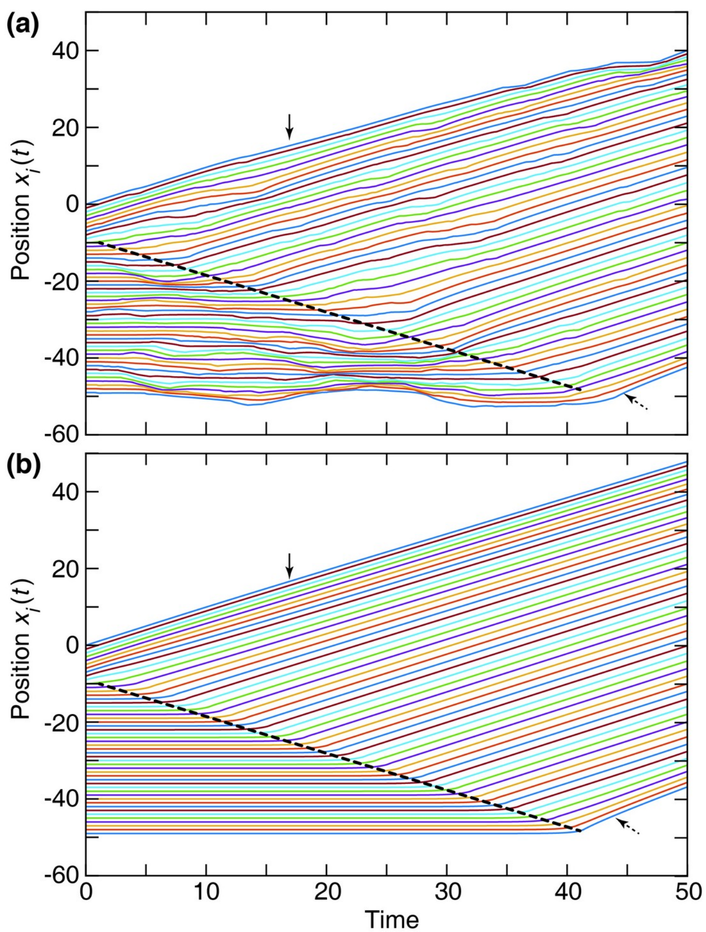
Velocity of active migration:

$$\begin{cases} \dot{x}_i = \dfrac{\kappa}{\eta} \underbrace{\left(x_{i+1} - x_i - l_0 - (x_i - x_{i-1} - l_0)\right)}_{x_{i+1} - 2x_i + x_{i-1}} + M_n(a_i) \\ \dot{a}_i = -\beta\, a_i + \gamma\, \dot{x}_i \end{cases}$$

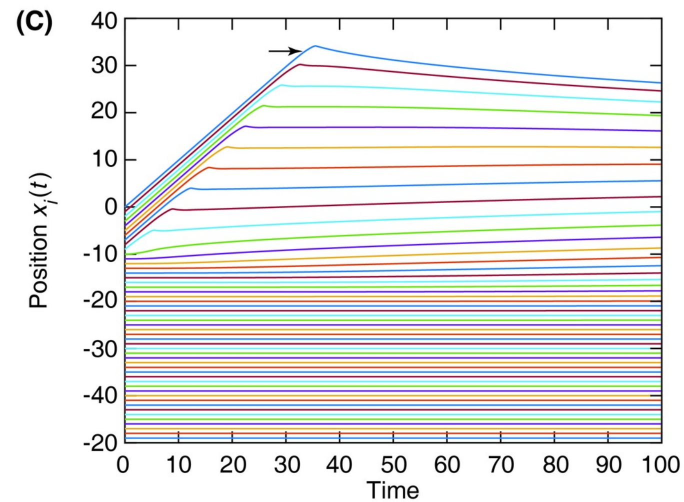
x_i ... position of cell i, a_i ... polarity of cell i
η...drag friction, β...depolarization, γ...self-excitation, l_0.... equilibrium length, κ...contractility

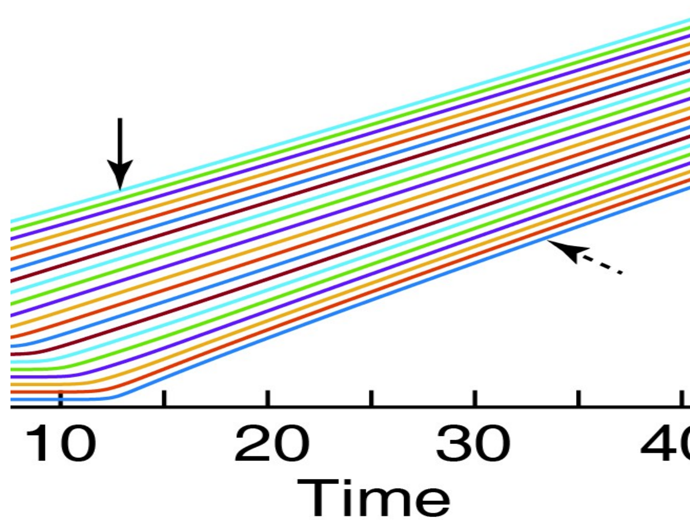
Numerical results

Polarization wave $(\kappa=0.1)$



Depolarization wave $(\kappa=0.1, \alpha=0.8)$





What determines the speed of the polarization wave?

Continuum limit

$\rho = \rho(t, x) \ldots.$ *cell density*

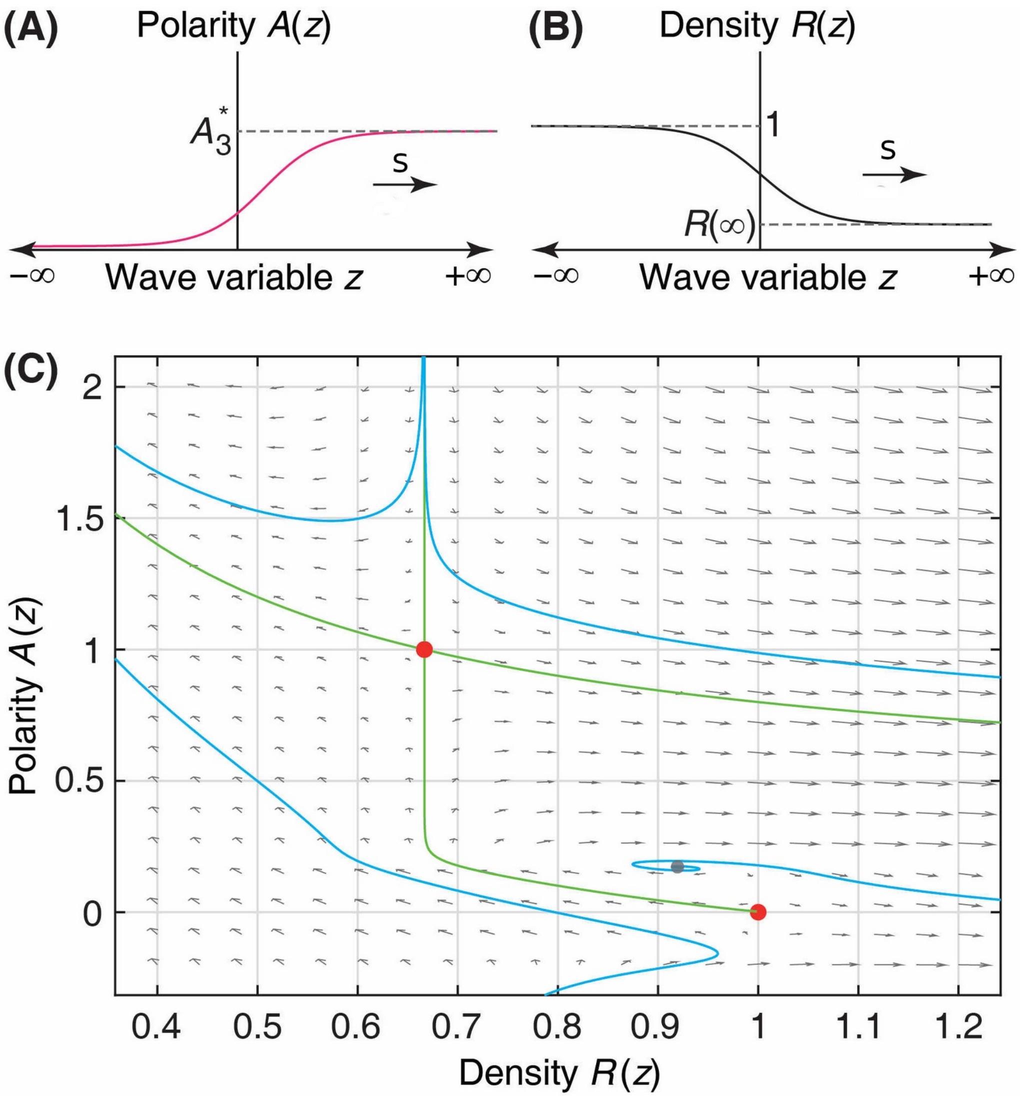
$a = a(t, x) \ldots.$ *polarity*

$$\begin{cases} \dfrac{\partial \rho}{\partial t} + \dfrac{\partial}{\partial x}(\rho v) = 0 \ , \\ \dfrac{\partial a}{\partial t} + v \dfrac{\partial a}{\partial x} = -a + v \ . \end{cases} \qquad v = M_n(a) - \kappa \frac{1}{\rho^3} \frac{\partial \rho}{\partial x} \ .$$

with parameters κ and α after non-dimensionalisation

Traveling wave ansatz

$$\rho(x,t) = R(x - st)\ ,$$
$$a(x,t) = A(x - st)\ .$$



$$\begin{cases} R' = \dfrac{R^2}{\kappa}\Big(R(-s + M_n(A)) + s\Big)\ , \\ A' = 1 - R\left(\dfrac{-1}{s}A + 1\right)\ . \end{cases}$$

stable steady states:

$(R_{-\infty}, A_{-\infty}) = (1, 0)$

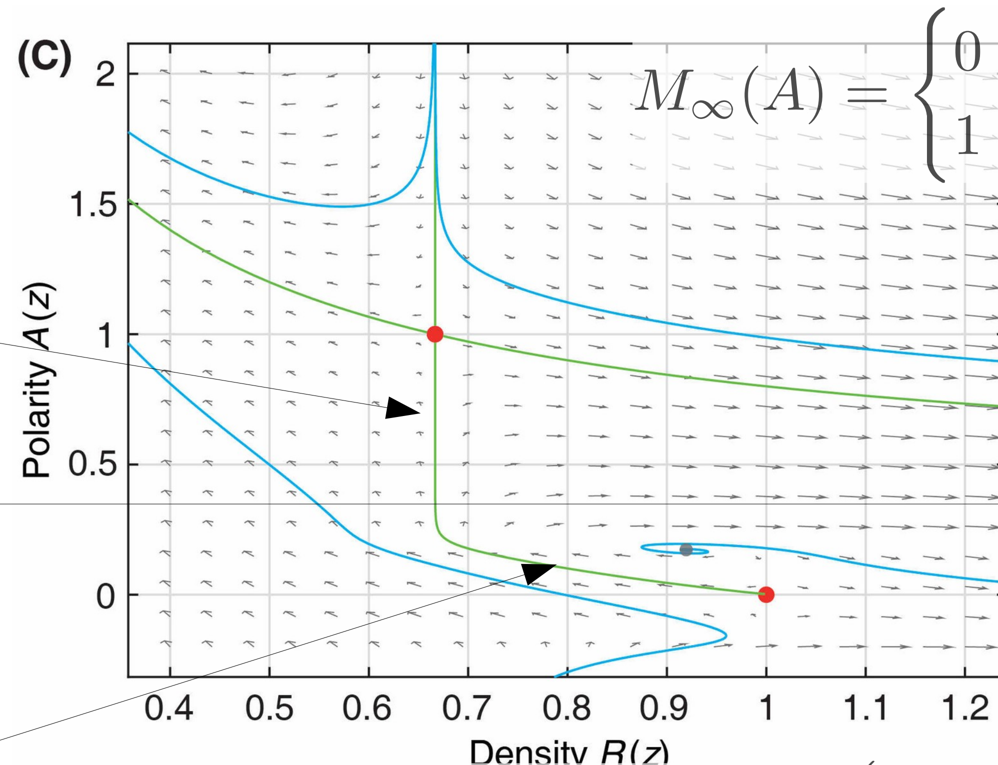
$(R_{\infty}, A_{\infty}) = \left(\dfrac{s}{s-1}, 1\right)$

Travelling wave III: explicit solution

$$M_\infty(A) = \begin{cases} 0 & A < \alpha\,, \\ 1 & A > \alpha\,. \end{cases}$$

$$R(z) = \rho_\infty$$

$$A(z) = 1 + (\alpha - 1)e^{\frac{-z}{1-s}}$$



α

$$R(z) = g^{-1}\left(\frac{-sz}{\kappa} + G\right) \quad \text{where} \quad g(y) := 1/y + \log(1/y - 1) \quad \text{and} \quad G = g\left(\frac{s_1}{s_1 - 1}\right)$$

$$A(z) = \frac{-s\kappa}{s^2+\kappa}\left(\frac{1}{g^{-1}\left(G + \frac{-sz}{\kappa}\right)} - 1\right) + \frac{\left(\alpha(s^2+\kappa) - s\kappa\right) g^{-1}(G) + s\kappa}{g^{-1}(G)(s^2+\kappa)}\left(\frac{\frac{1}{g^{-1}(M)} - 1}{\frac{1}{g^{-1}\left(G + \frac{-sz}{\kappa}\right)} - 1}\right)^{\frac{\kappa}{s^2}}$$

$\to 0\ (as\ z \to -\infty)$ $\quad = 0 \quad$ $\to \infty\ (as\ z \to -\infty)$

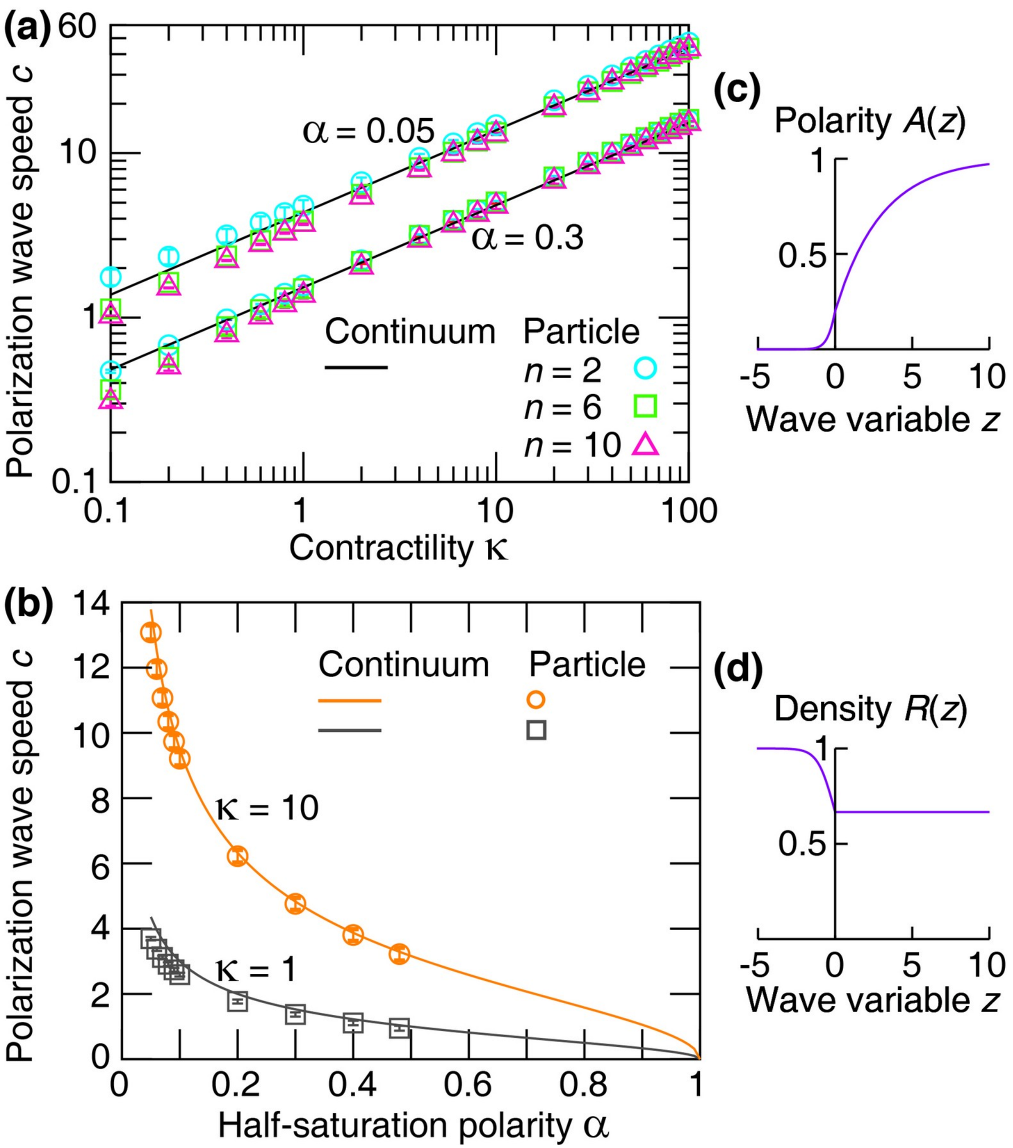
Travelling wave speed

$$s = -\sqrt{\kappa\left(\frac{1}{\alpha}-1\right)}\,.$$

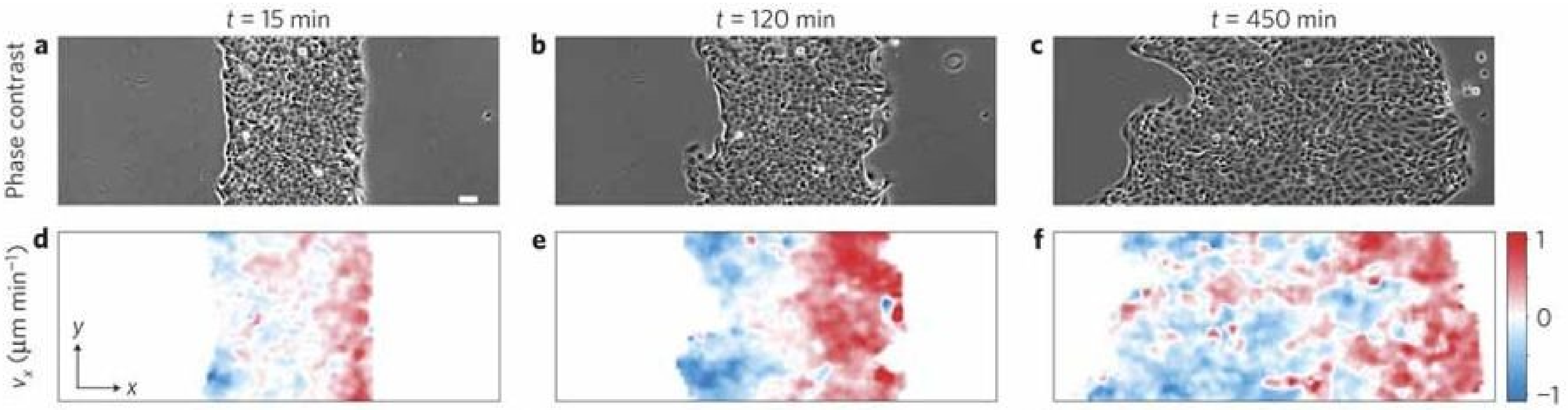
$$A_1(z) = \begin{cases} s_1\alpha\left(1-\frac{1}{g^{-1}\left(G-\frac{zs_1}{\kappa}\right)}\right), & z<0 \\ 1+(\alpha-1)e^{\frac{z}{s_1-1}}, & z\geq 0 \end{cases}$$

$$R_1(z) = \begin{cases} g^{-1}\left(G-\frac{zs_1}{\kappa}\right), & z<0 \\ \frac{s_1}{s_1-1}, & z\geq 0 \end{cases}$$

where $g(y) = \frac{1}{y} + \log\left(\frac{1}{y}-1\right)$ and $G = g\left(\frac{s_1}{s_1-1}\right)$.



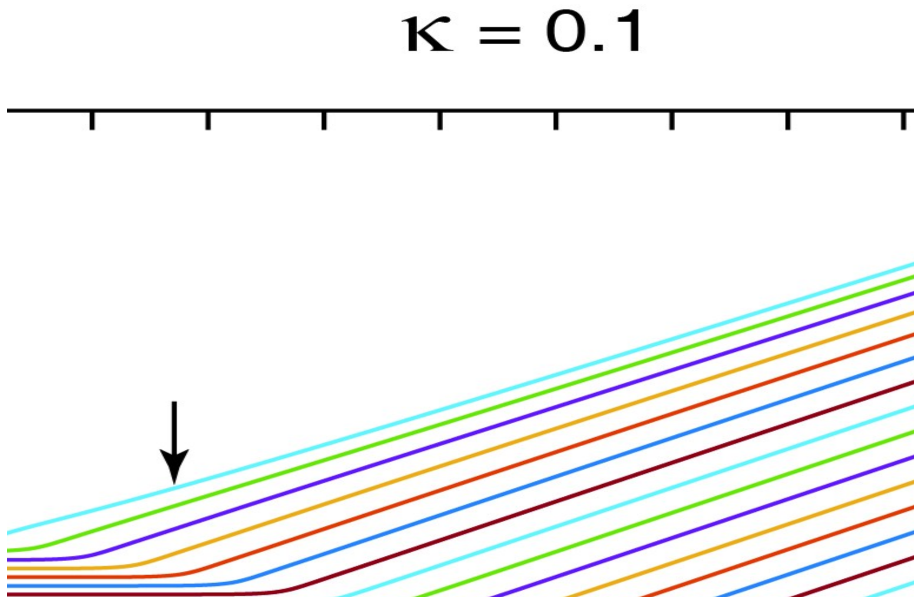
Polarization wave



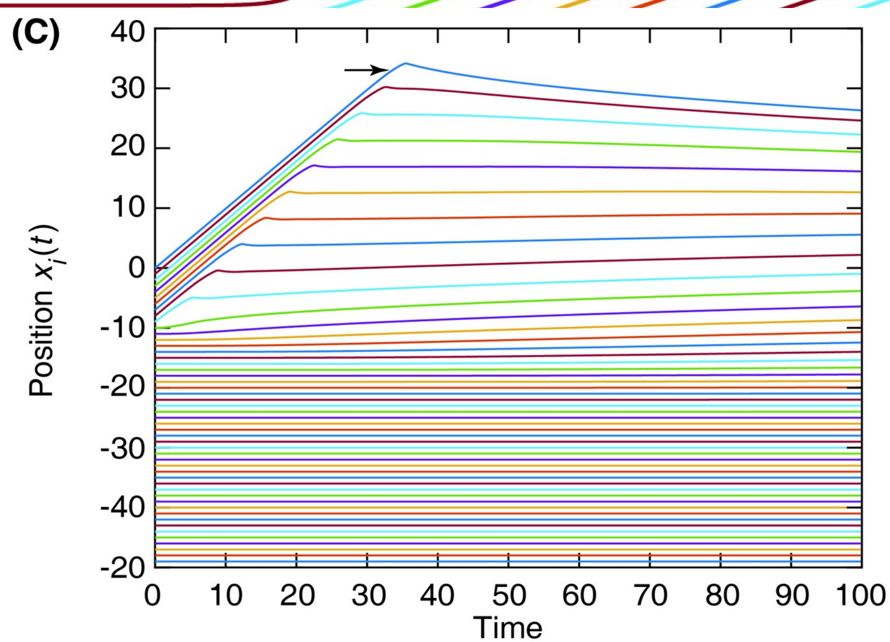
Treppat e.a., Nat. Phys., 2012

Depolarization wave

Polarisation



Depolarisation



$$\tilde{\rho}(\tilde{t}, \tilde{x}) = \rho(t, x)$$

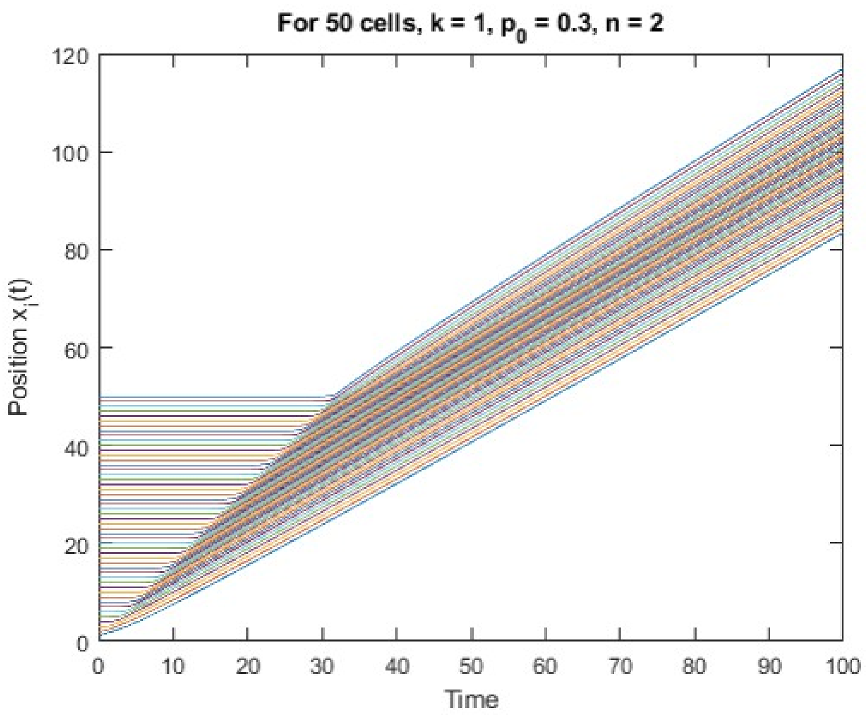
$$\tilde{a}(\tilde{t}, \tilde{x}) = 1 - a(t, x)$$

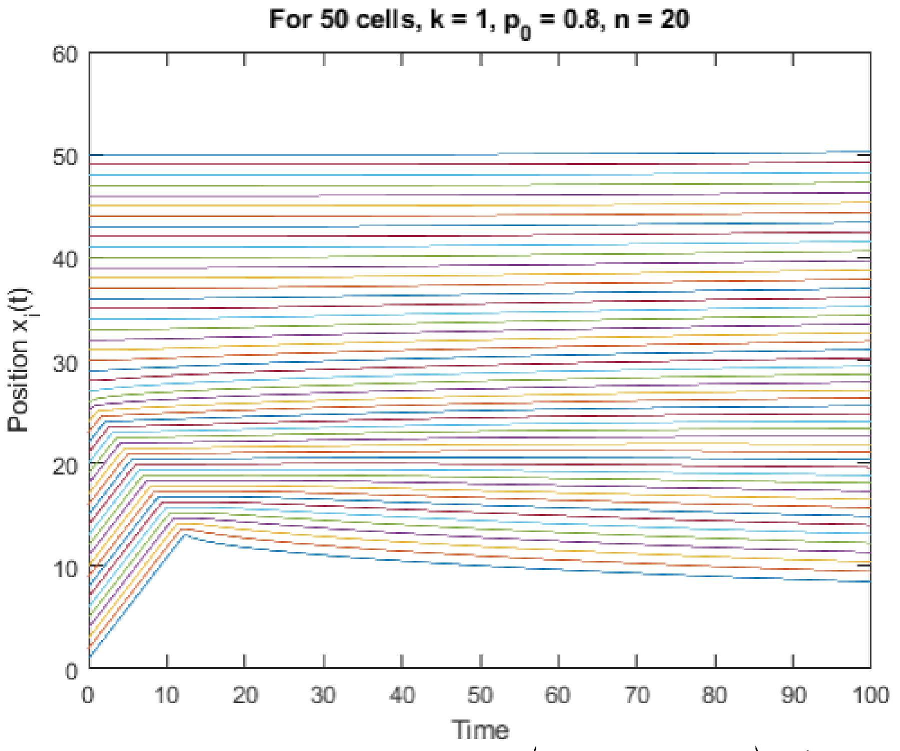
$$\tilde{M}(\tilde{a}) = 1 - M(1 - \tilde{a})$$

$$\tilde{v} = 1 - v$$

$$\begin{pmatrix} \tilde{t} \\ \tilde{x} \end{pmatrix} = \begin{pmatrix} t \\ t - x \end{pmatrix}$$

Divergent vs. colliding cell layers





$$\begin{cases} R' = \frac{R^2}{\kappa}\Big(R(c + M_n(A)) - c\Big)\,, \\ A' = 1 - R\left(\frac{1}{c}A + 1\right)\,. \end{cases}$$

is invariant under:

$$\bar{R}(\bar{z}) = \left(2 - \frac{1}{R(z)}\right)^{-1}$$

$$\bar{A}(\bar{z}) = A(z)$$

$$\bar{s} = -s$$

$$\frac{d\bar{z}}{dz} = -\frac{R(z)}{\bar{R}(\bar{z})} = 1 - 2R(z)$$

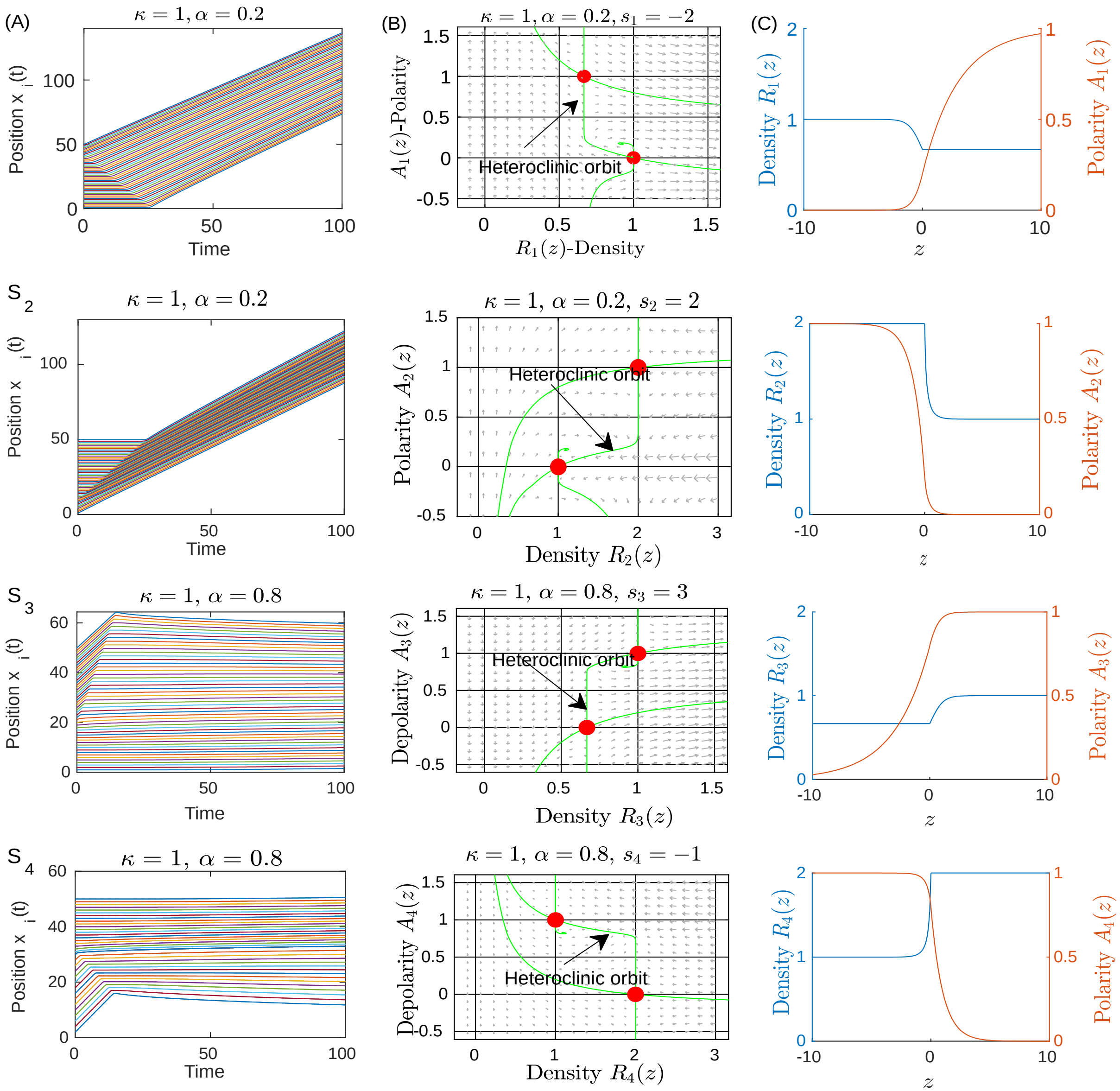
Four types of travelling wave solutions

polarisation wave of departing cell sheets.

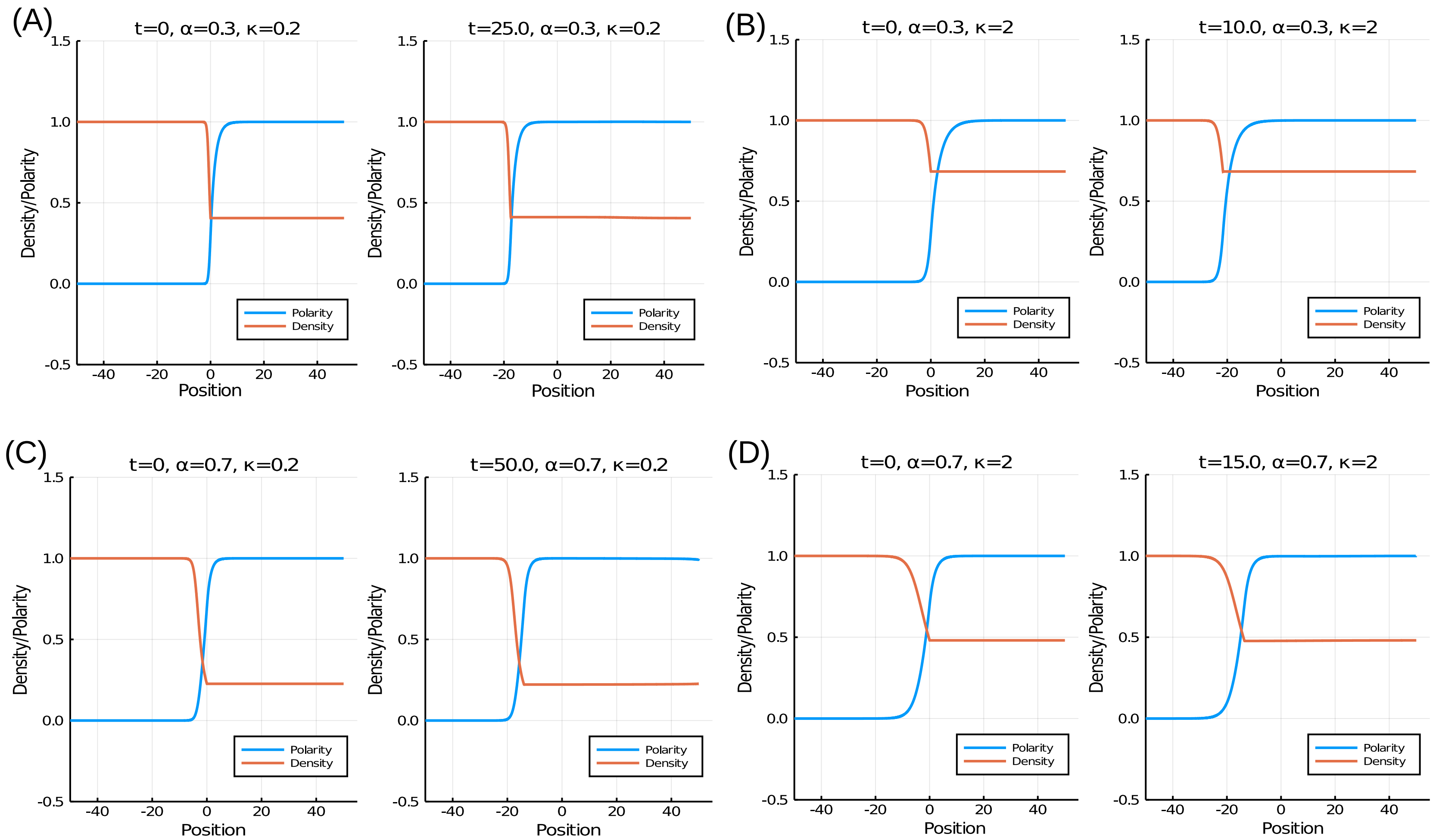
polarisation wave of colliding cell sheets.

depolarisation wave of departing cell sheets.

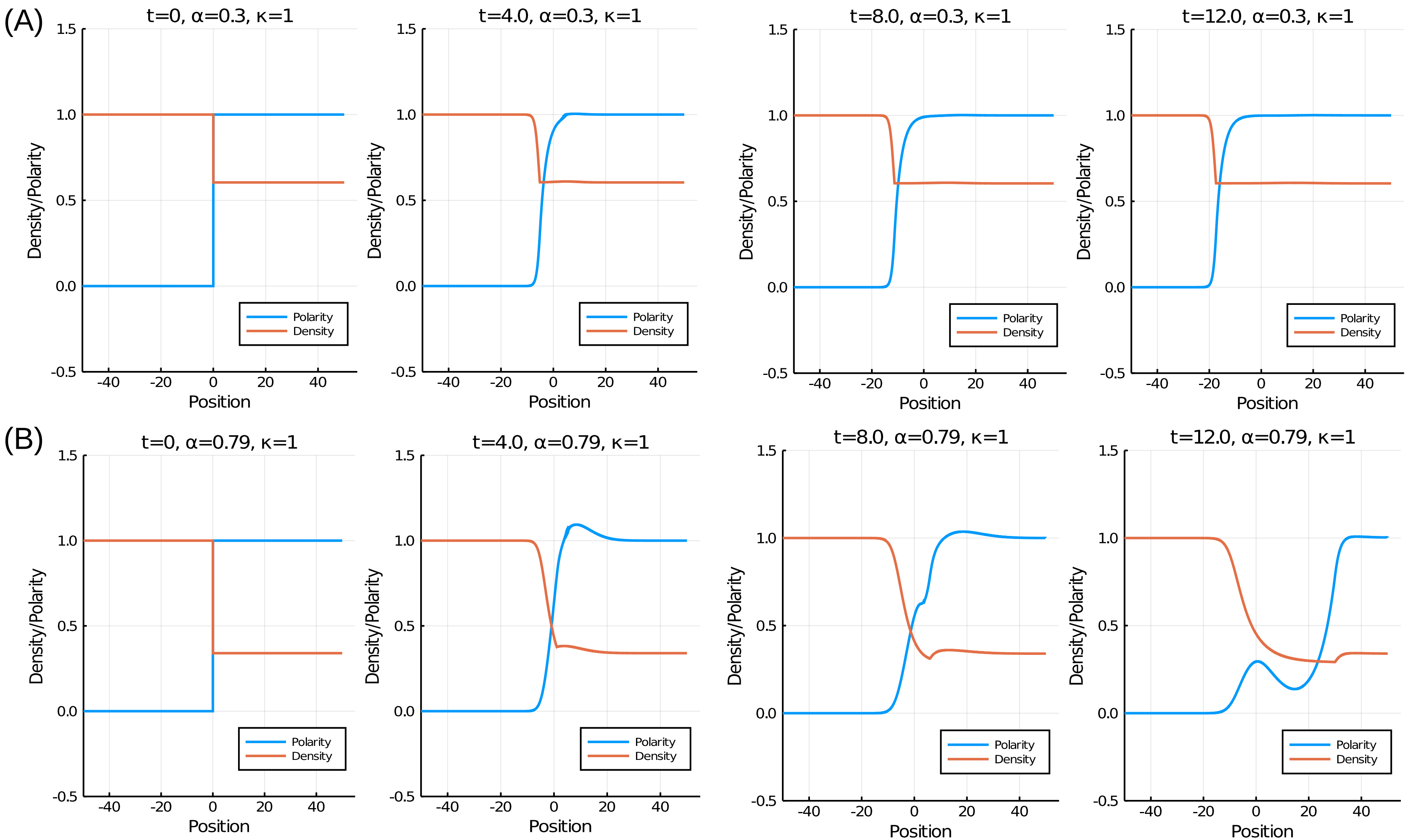
depolarisation wave of colliding cell sheets.



Numerical exploration of stability



Numerical exploration



Stability analysis- framework

Linearisation at travelling wave solution (polarisation, departing) in the moving coordinate frame z=x-st :

$$\begin{pmatrix} \partial_t \delta\rho \\ \partial_t \delta a \end{pmatrix} = \mathcal{L} \begin{pmatrix} \delta\rho \\ \delta a \end{pmatrix} = \begin{pmatrix} s\delta\rho' - (V\delta\rho + R\delta v)' \\ s\delta a' - \delta v(A' - 1) - V\delta a' - \delta a \end{pmatrix} ,$$

$$\text{where} \quad \delta v = M'(A)\delta a - \kappa \left(\frac{1}{R^3} \delta\rho \right)'$$

Eigenvalue problem ~ system of linear ODEs

$$\mathcal{T} \begin{pmatrix} \delta\rho \\ \delta v \\ \delta a \end{pmatrix} = \begin{pmatrix} \delta\rho' \\ \delta v' \\ \delta a' \end{pmatrix} - B(z,\lambda) \begin{pmatrix} \delta\rho \\ \delta v \\ \delta a \end{pmatrix} = 0 \, , \quad \text{where}$$

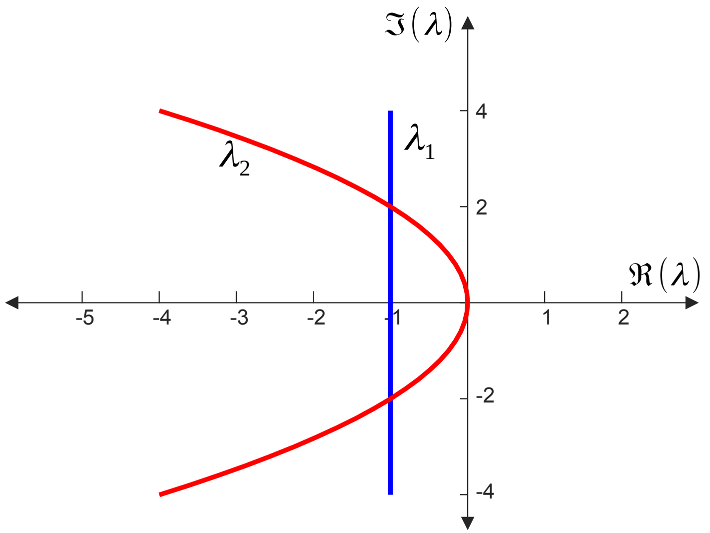
$$B(z,\lambda) = \begin{pmatrix} \frac{3\,R'}{R} & \frac{-R^3}{\kappa} & \frac{M'\,R^3}{\kappa} \\ \frac{2\,R'\,s - R^2\,\lambda}{R^3} & \frac{-R'}{R} - \frac{R\,s}{\kappa} & \frac{M'\,R\,s}{\kappa} \\ 0 & \frac{(A'-1)\,R}{s} & \frac{R\,(\lambda+1)}{s} \end{pmatrix}$$

Essential spectrum – perturbations at $\pm\infty$

Weyl's Essential Spectrum Thm: it is sufficient to consider the essential spectrum

$$\mathcal{T}_\infty \begin{pmatrix} \delta\rho \\ \delta v \\ \delta a \end{pmatrix} = \begin{pmatrix} \delta\rho' \\ \delta v' \\ \delta a' \end{pmatrix} - B_\infty \begin{pmatrix} \delta\rho \\ \delta v \\ \delta a \end{pmatrix} \,, \quad \text{where} \quad B_\infty = \begin{cases} B_-(\lambda) & z < 0 \,, \\ B_+(\lambda) & z \geq 0 \,. \end{cases}$$

Fredholm borders: dispersion relations of B^- and B^+ for purely imaginary spatial eigenvalues $i\mu$: $\lambda^1 = -1 + i\mu s$ and $\lambda^2 = -\mu^2\kappa + i\mu s$.

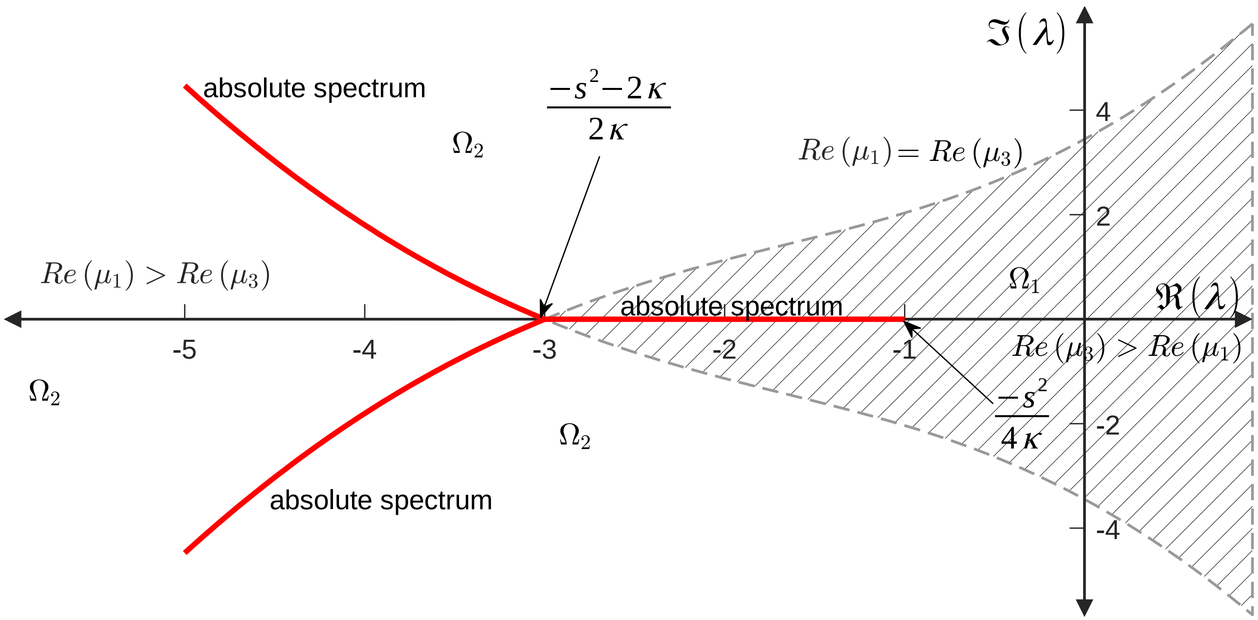


Note that the matrix (spatial) eigenvalues of $B^-(\lambda)$ are given by

$$\mu_1(\lambda) = \frac{\lambda + 1}{s} \,, \quad \mu_{2,3}(\lambda) = \frac{-s}{2\kappa} \pm \frac{\sqrt{s^2 + 4\kappa\lambda}}{2\kappa} \tag{1}$$

The matrix (spatial) eigenvalues of $B^+(\lambda)$ are multiples of (1) by $\frac{s}{s-1}$.

Absolute spectrum



as $\mathrm{Re}(\lambda \gg 1)$:

$$\mathrm{Re}(\mu_1) < \mathrm{Re}(\mu_3) < 0 < \mathrm{Re}(\mu_2)$$

Absolute spectrum: where the unstable and stable eigenspaces get mixed up (here: where $\mathrm{Re}(\mu_2)$ looses its leading position.

In red: absolute spectrum shown for $s = -2$, $\kappa = 1$.

- The **branching point** is the right extreme point of absolute spectrum
- Through the introduction of exponentially weighted spaces the **essential spectrum can be shifted** left up to the branching point.
- The **Evans function** can be extended analytically up to the branching point.

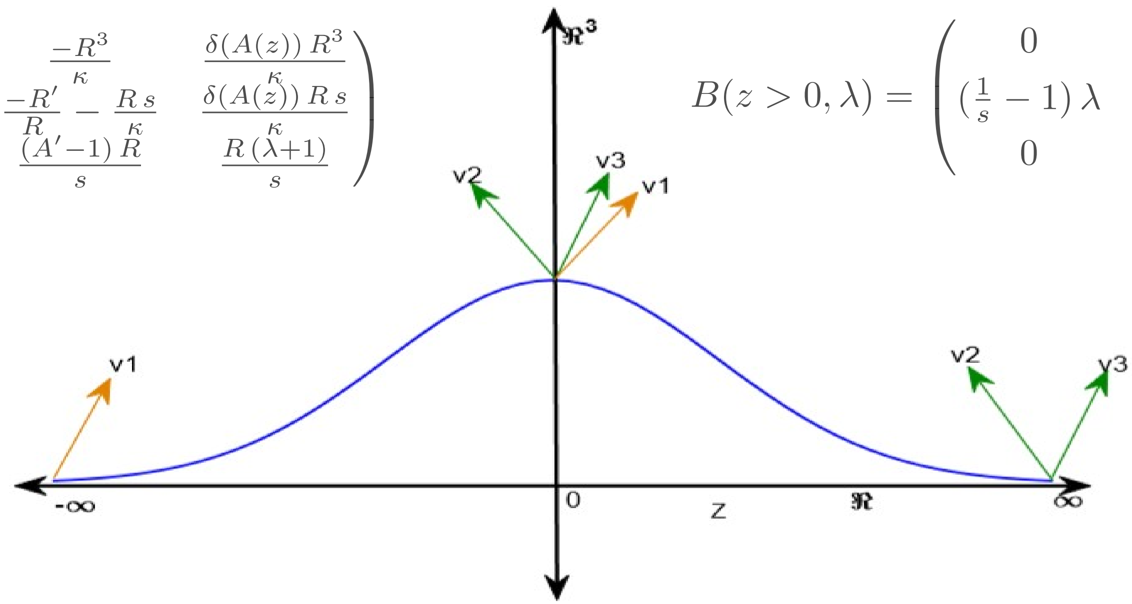
Evans function

- Construct an (integrable) perturbation originating from the unstable eigenspace of B^- and the stable eigenspace of B^+.
- Simplify B: use that $M'(\alpha) = \delta(\alpha)$ and that $R(z) = \frac{s}{s-1}$ is constant for $z > 0$.

$$B(z \leq 0, \lambda) = \begin{pmatrix} \frac{3\,R'}{R} & \frac{-R^3}{\kappa} & \frac{\delta(A(z))\,R^3}{\kappa} \\ \frac{2\,R' s - R^2\,\lambda}{R^3} & \frac{-R'}{R} - \frac{R\,s}{\kappa} & \frac{\delta(A(z))\,R\,s}{\kappa} \\ 0 & \frac{(A'-1)\,R}{s} & \frac{R\,(\lambda+1)}{s} \end{pmatrix}$$

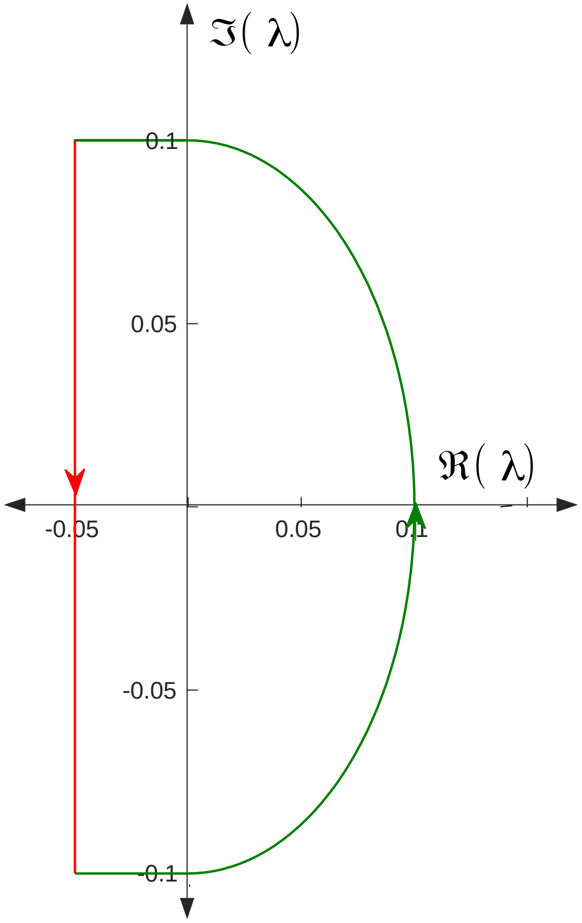
$$B(z > 0, \lambda) = \begin{pmatrix} 0 & \frac{-s^3}{\kappa\,(s-1)^3} & 0 \\ (\frac{1}{s} - 1)\,\lambda & \frac{s^2}{\kappa\,(1-s)} & 0 \\ 0 & \frac{A'-1}{s-1} & \frac{\lambda+1}{s-1} \end{pmatrix}$$

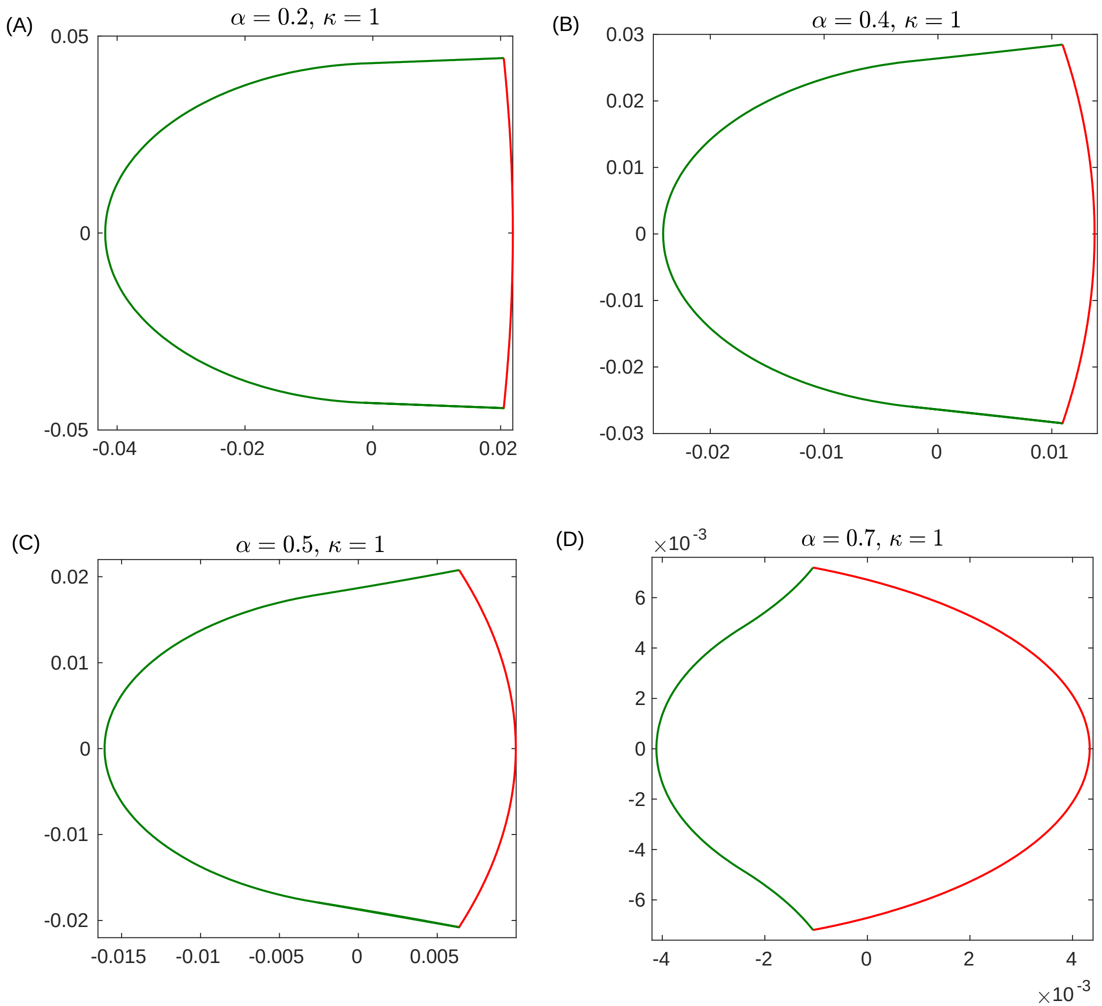
$$\begin{pmatrix} \delta\rho' \\ \delta v' \\ \delta a' \end{pmatrix} = B(z,\lambda) \begin{pmatrix} \delta\rho \\ \delta v \\ \delta a \end{pmatrix}$$



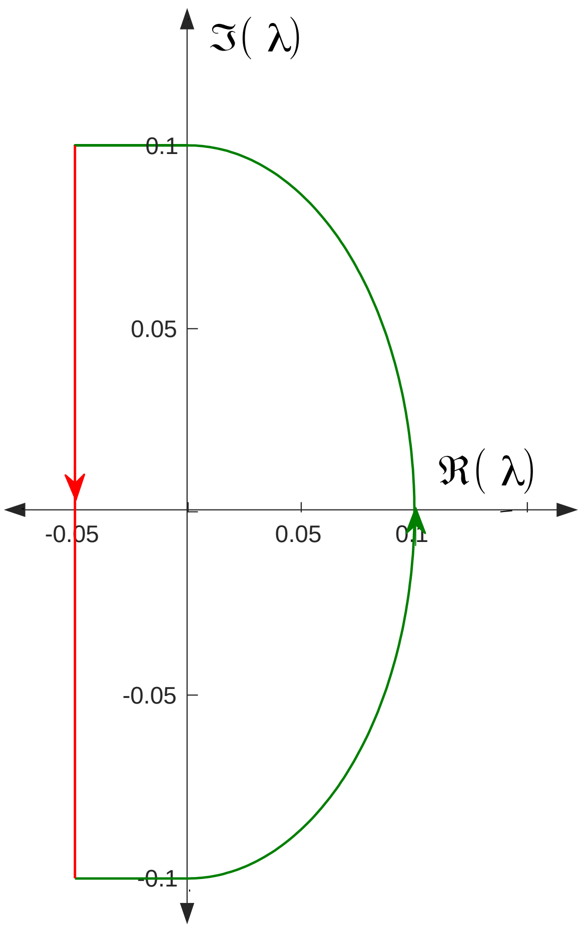
1. $v_2(z = 0^+)$ and $v_3(z = 0^+)$ can be computed exactly (constant coefficients linear system decoupled from 1st order system)
2. $v_2(z = 0^-)$ and $v_3(z = 0^-)$ can be computed exactly (jump at $z = 0$)
3. $v_1(z = 0^-)$ needs to be computed numerically
4. Zeros of the Evan's function $D(\lambda) = \det((v_1|v_2|v_3))$ characterise the point spectrum.

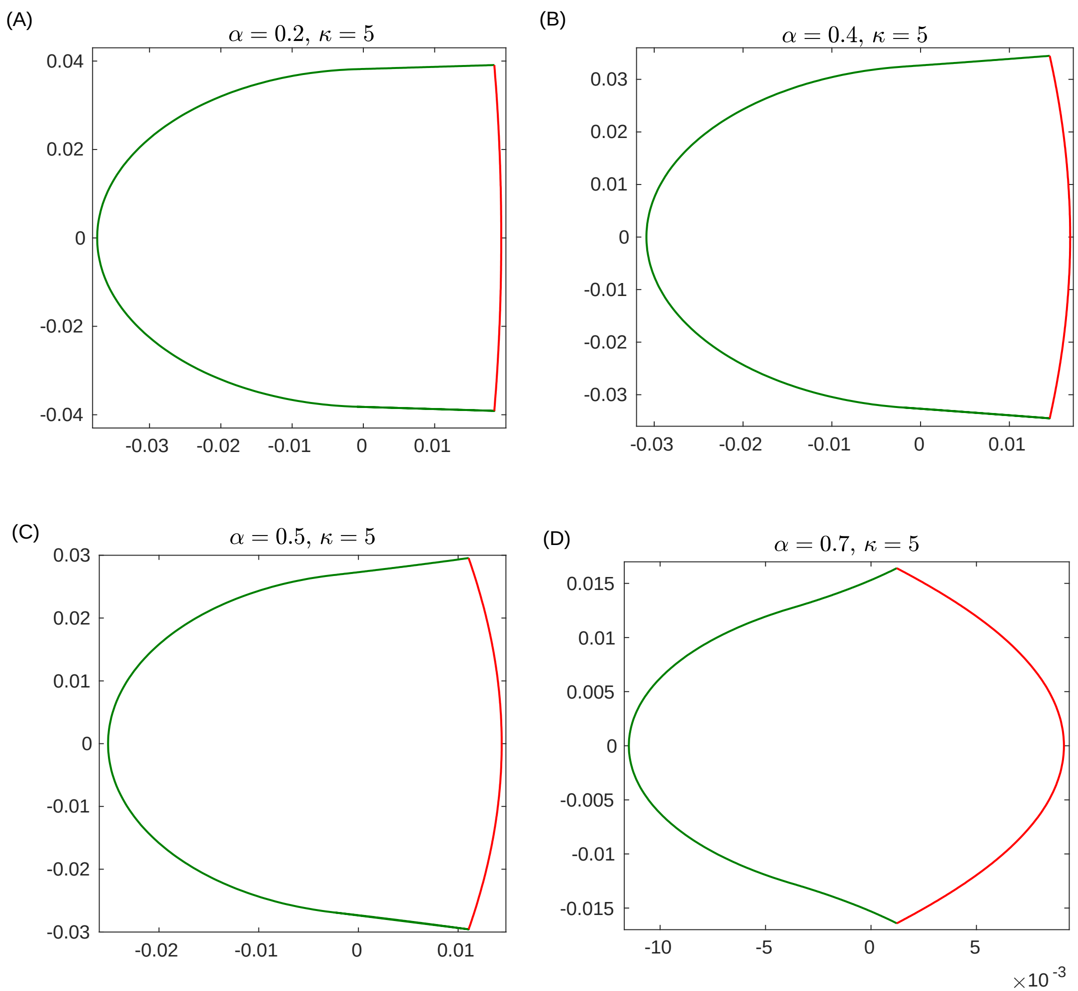
Evaluation using argument principle



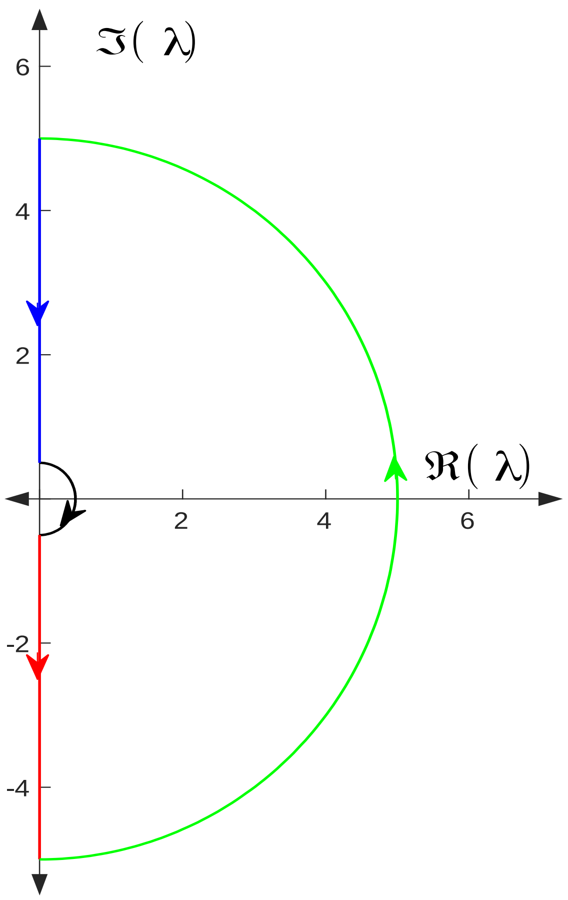


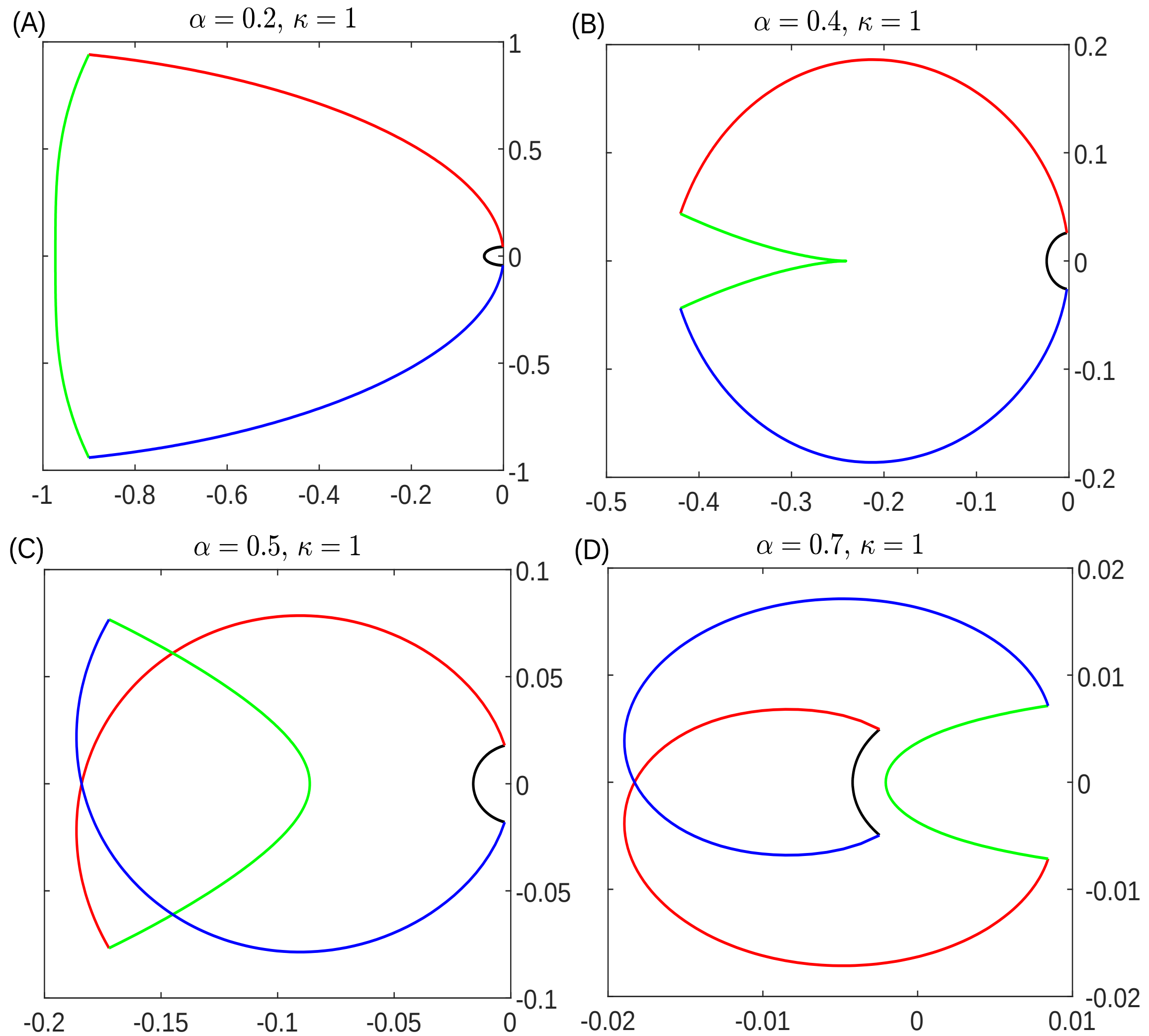
Evaluation using argument principle





Evaluation using argument principle





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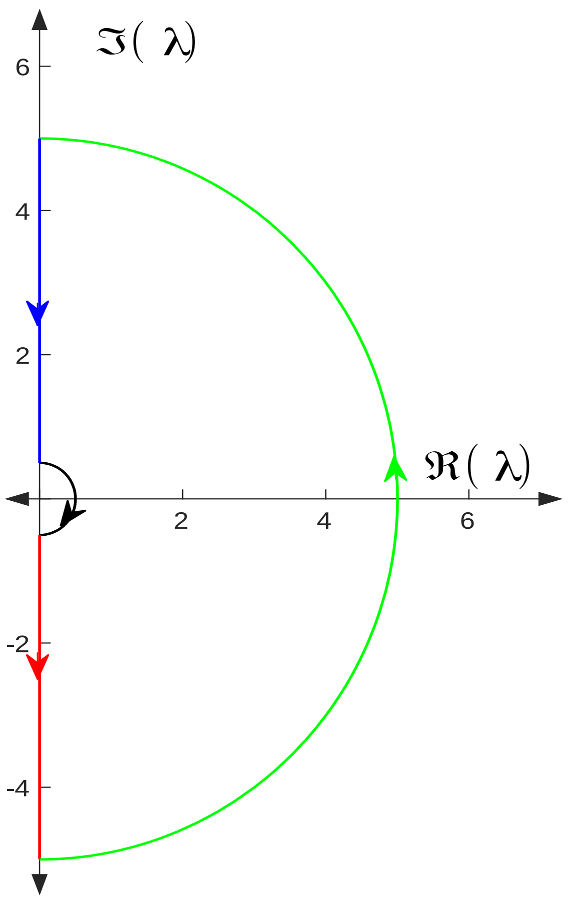

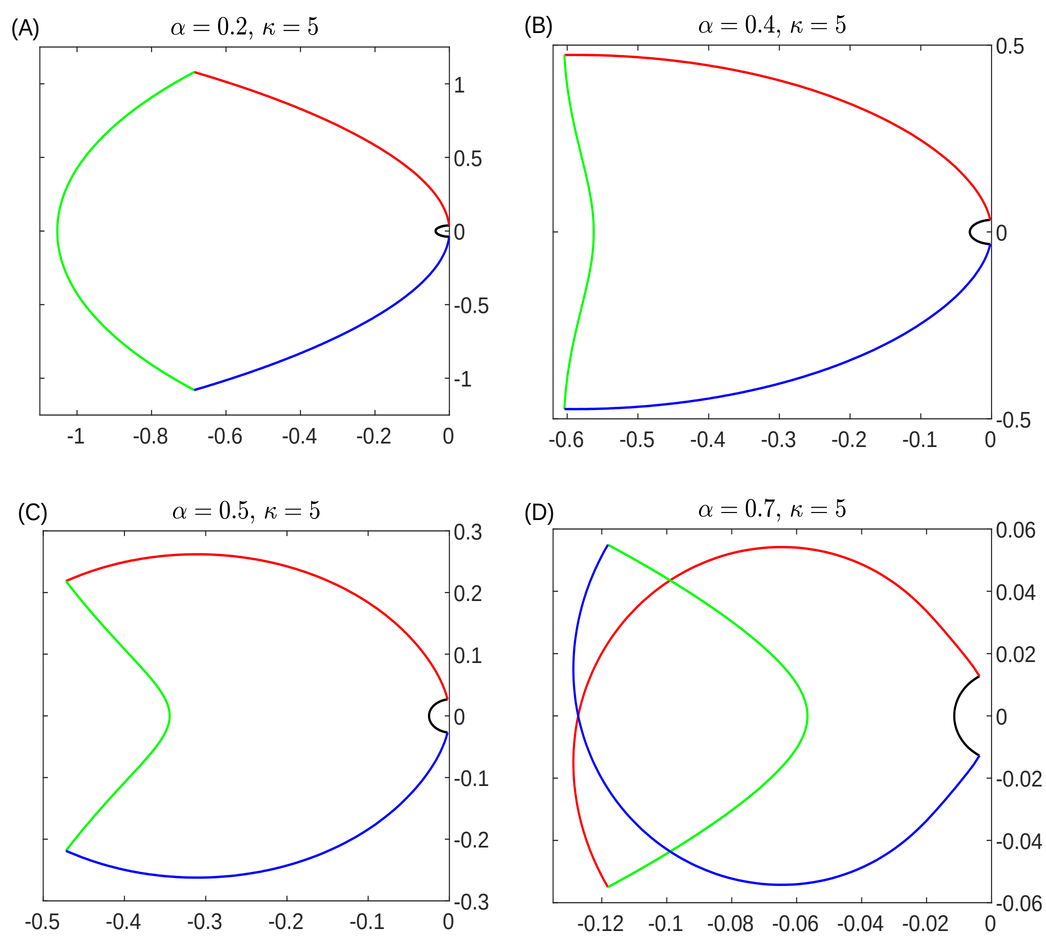

Summary

- A 1D toy model for collective migration of epithelial cells features 4 types of traveling wave solutions
  - Polarization wave triggered by departing cell sheet
  - Depolarization wave triggered by departing cell sheet
  - Polarization wave triggered by colliding cell sheet
  - Depolarization wave triggered by colliding cell sheet
- All four types of traveling wave solutions are linearly stable.
- Practical implications?
  - When moving cells collide or depart, in principle both, gradual polarization and depolarization of all cells, could occur.
  - Nevertheless, depending on sensitivity a specific scenario will occur preferentially.
- Extension to higher dimension: particle models

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Thank you

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