Collective cell behaviour

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(USRA 2023)

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Collective cell behaviour

Important in embryo development, dynamics and organization of tissues, wound healing, and in disease (cancer metastasis)

Neural crest cell migration

- Initiate formation of organs, limbs, etc
- Long migration to target sites

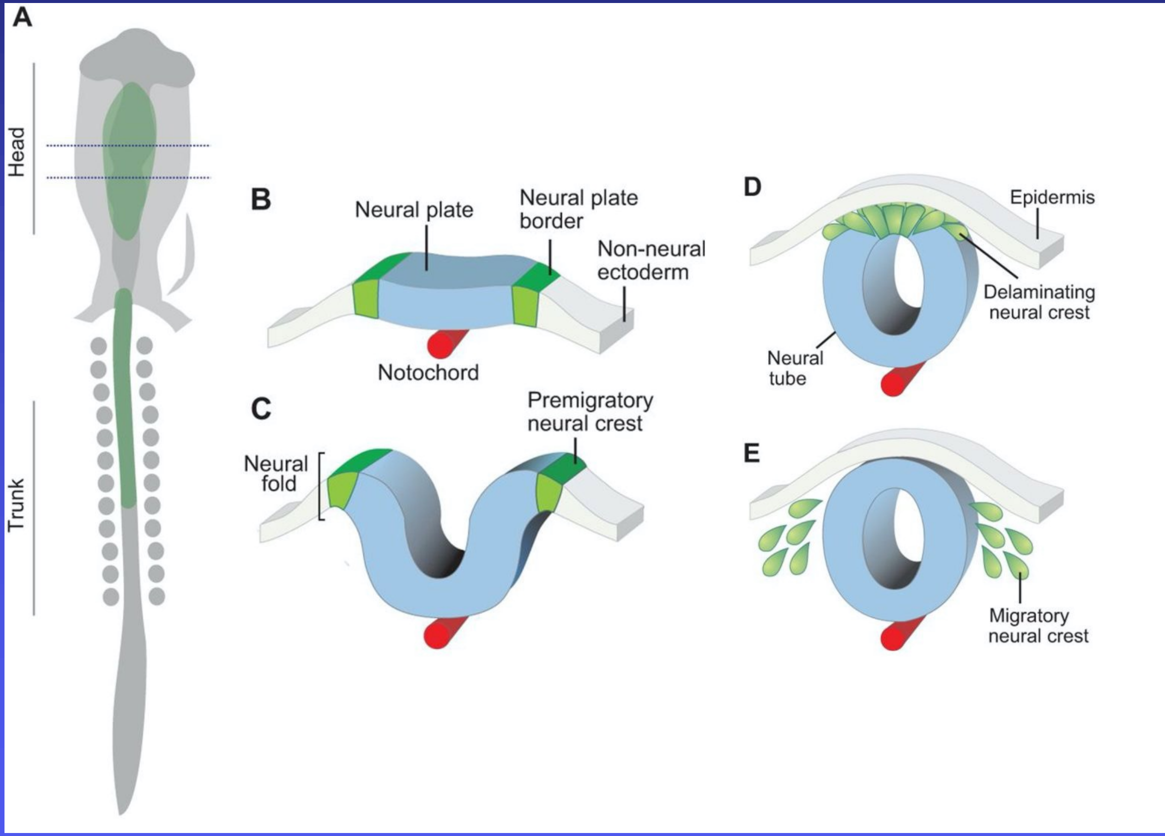
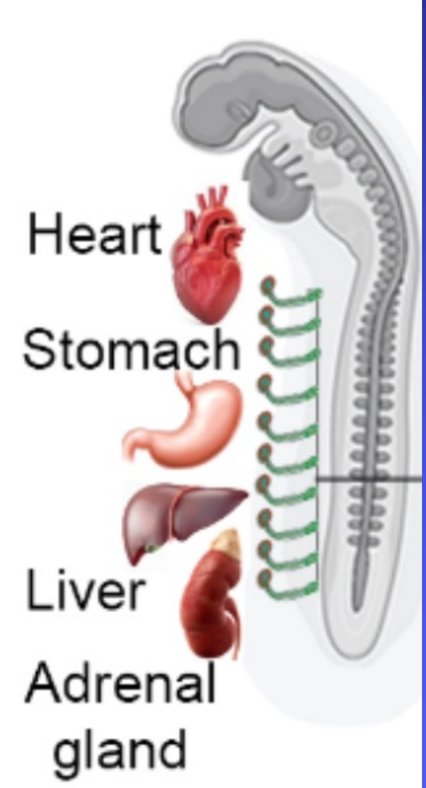


Image: P Kulesa

Project motivated by Paul Kulesa lab



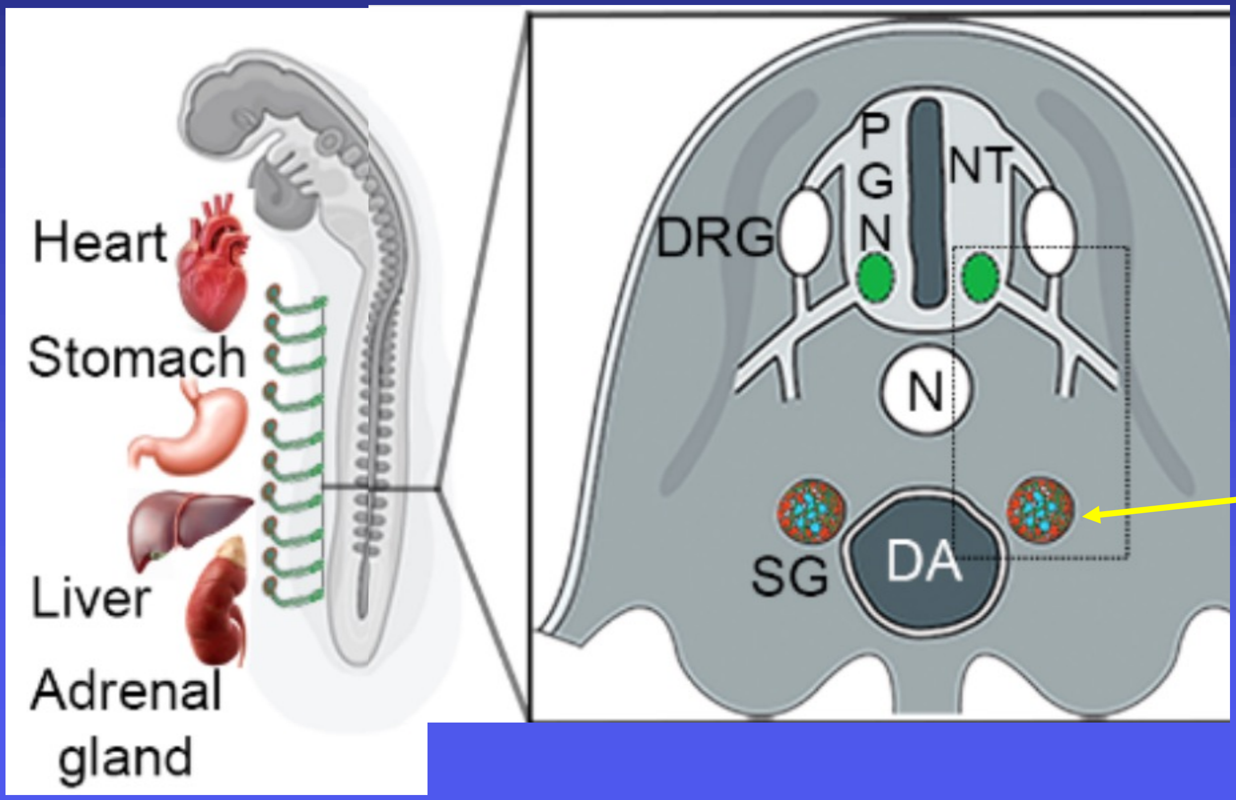
Sympathetic nervous system development in chick embryo

Kasemeier-Kulesa JC, Morrison JA, Lefcort F, Kulesa PM. (2015) TrkB/BDNF signalling patterns the sympathetic nervous system. Nature comm. 6(1):8281.

Image: P Kulesa

Sympathetic nervous system

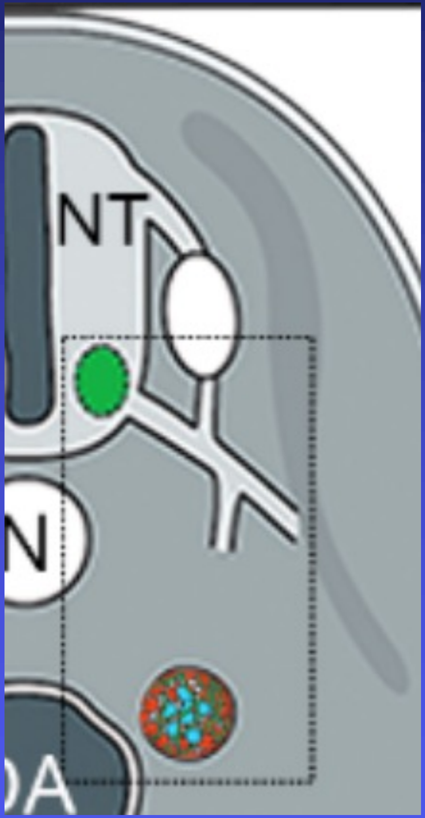
- Formed by migrating cluster of NCCs



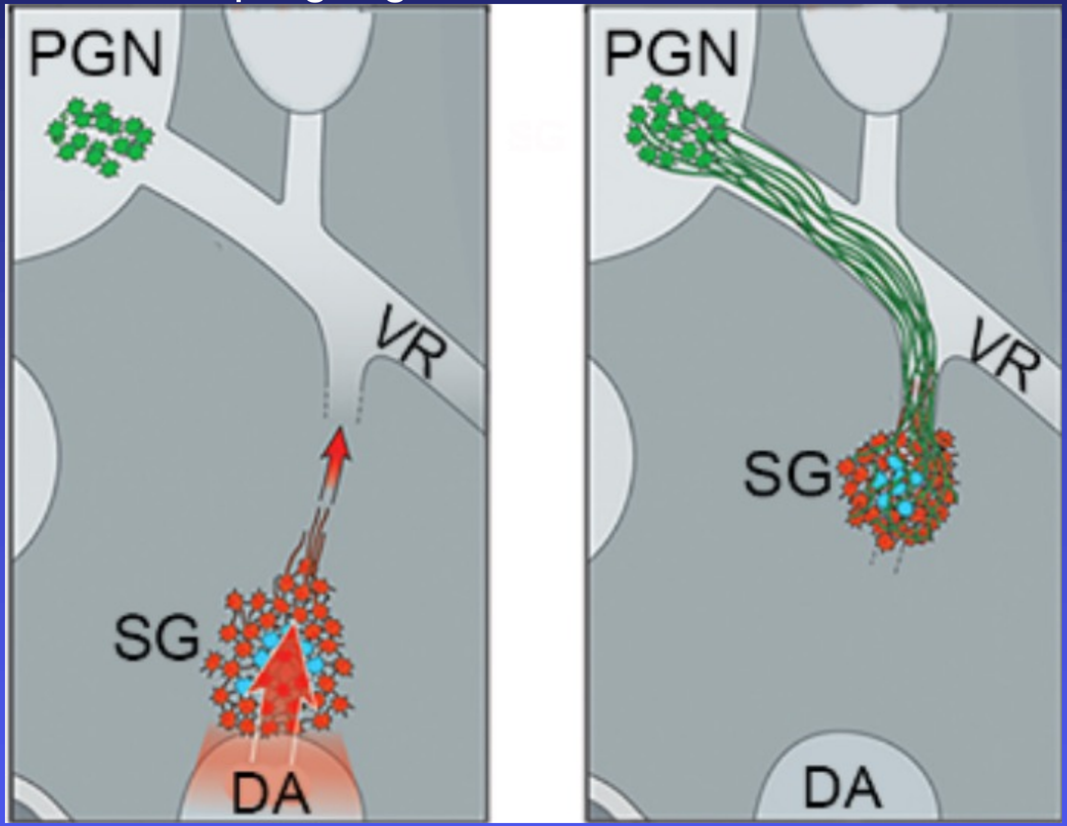
Sympathetic ganglia

Image: P Kulesa

Sympathetic ganglia migration



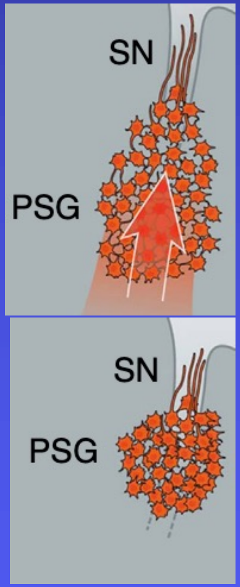
preganglionic neurons

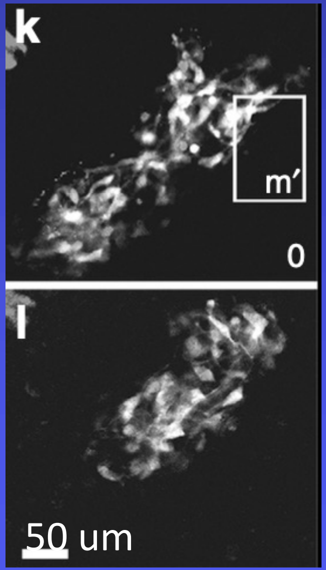


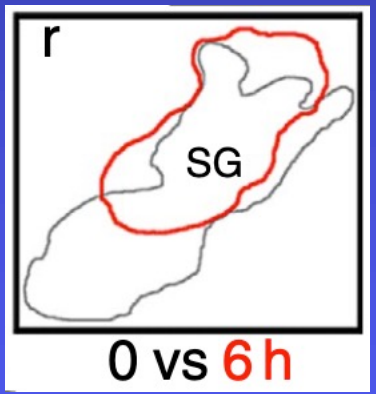
Dorsal aorta

Cluster compactness

- Directed migration of loosely connected cells, local and non-local contacts with neighbours
- Later: cells reorganize to form tight cohesive cluster







Questions

- How do cells stay together?
- What influences affect cluster cohesion, compactness, shape?
- What initiates and guides the migration?
- How does the cluster find its target?

Questions

- How do cells stay together?
- What influences affect cluster cohesion, compactness, shape?

PLAN: - Recap of (old) agent-based modeling
- Discuss recent (continuum) theory
- Mention simulations & future prospects

Agent-based models

Keep track of positions *x*, velocities, *v*:

$$\frac{d\vec{x}_i}{dt} = \vec{v}_i.$$

Animals:

$$\frac{d\vec{v}_i}{dt} = \vec{F}_i - \xi \vec{v}_i$$

Cells:

$$\vec{v}_i \approx \frac{1}{\xi} \vec{F}_i$$

(no inertia)

Many agents

- Repulsion and attraction

$$\frac{d\vec{x}_i}{dt} = \Sigma_{i\neq j}\left(\vec{F}^r(\vec{x}_i - \vec{x}_j) - \vec{F}^a(\vec{x}_i - \vec{x}_j)\right)$$

- 1D, "Morse forces" (Exponentials)

$$F(x) = F^r(x) - F^a(x) = \text{sign}(x)\left(Re^{-|x|/r} - Ae^{-|x|/a}\right)$$

Mogilner et al (2003) JMB 47:353-89.

Remarks

- Simplify analysis to 1D
- Forces are odd functions of distance
- Superposition of Repulsion and Attraction
- Morse forces are gradients of Morse potentials. (convenient for analysis)

Mogilner et al (2003) Mutual interactions, potentials, and individual distance in a social aggregation. Journal of mathematical biology 47:353-89.

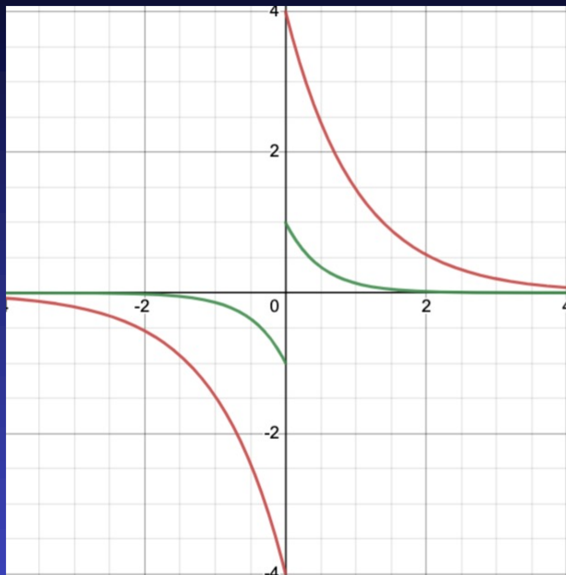
Scaled variables

- Scale force by A, distance by r:

$$x' = \frac{x}{r}, \quad \ell = \frac{a}{r}, \quad C = \frac{R}{A}.$$

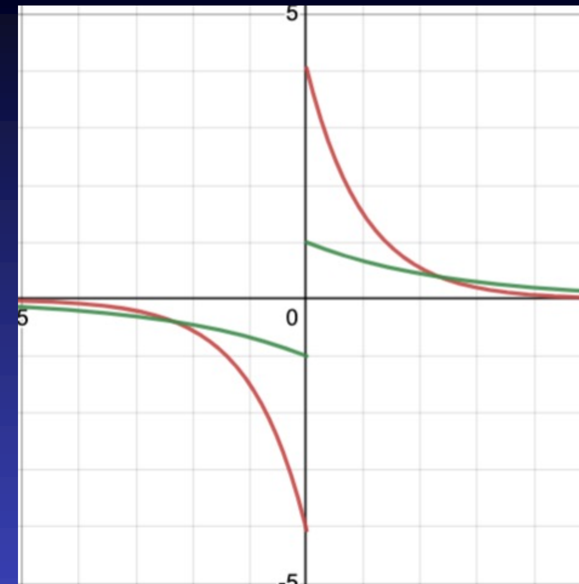
Attraction -Repulsion

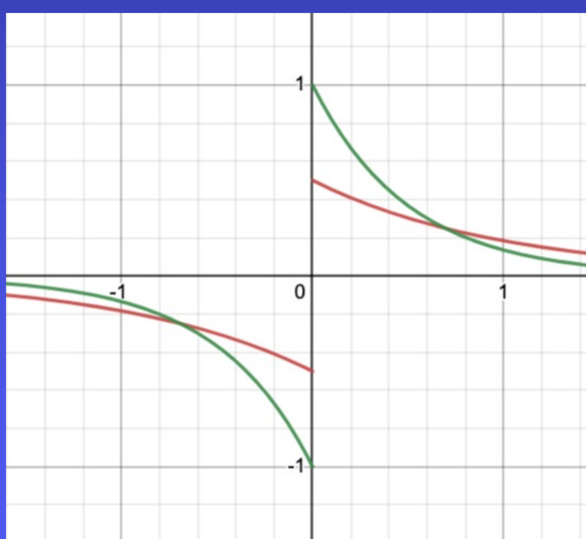
C=4, l=0.5



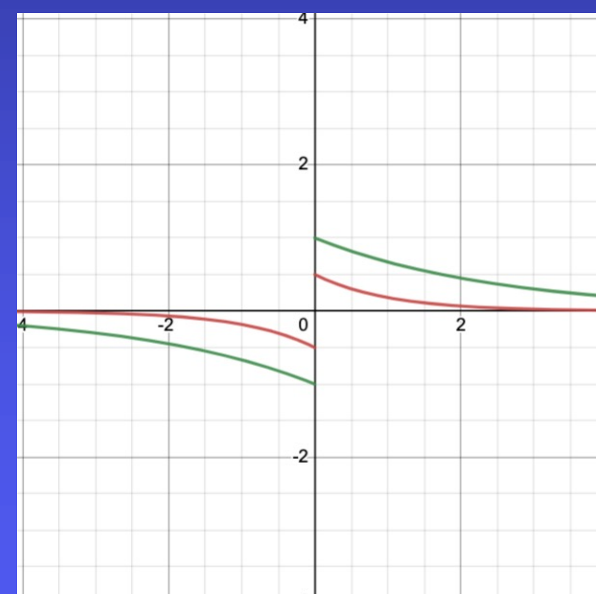
$$\ell = \frac{a}{r}, \quad C = \frac{R}{A}.$$

C=4, l=2.5





C=0.5, l=0.5

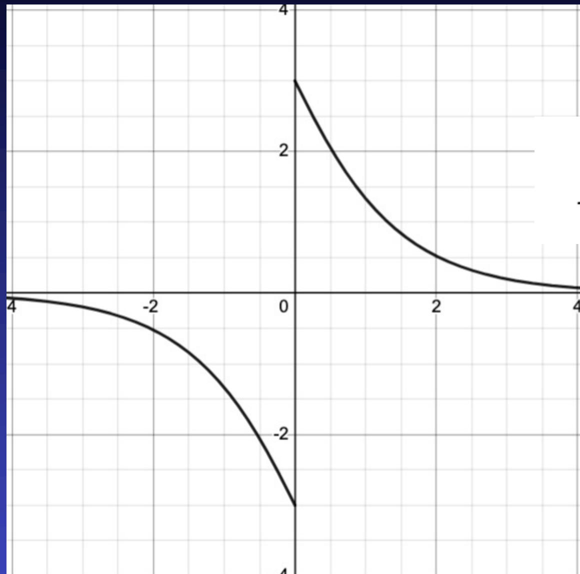


C=0.5, l=2.5

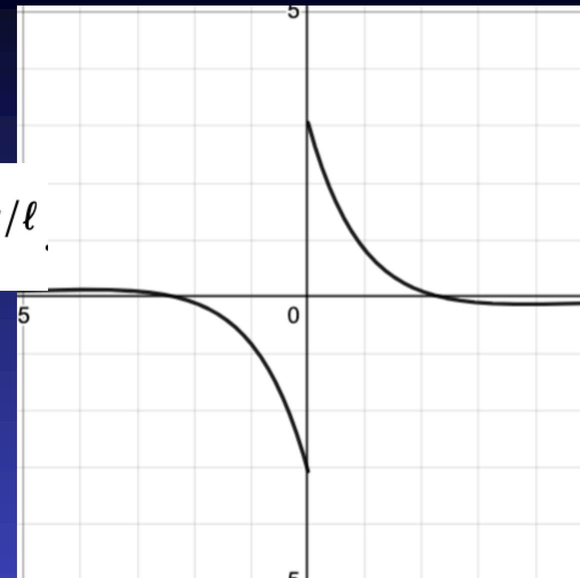
Net force

$$\ell = \frac{a}{r}, \quad C = \frac{R}{A}.$$

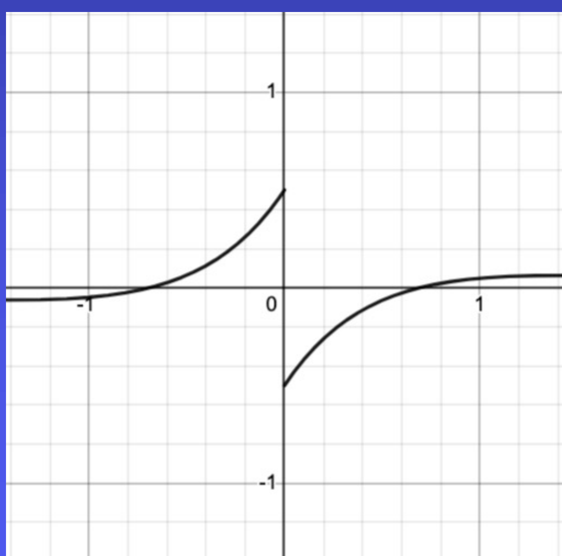
$$F(x) = Ce^{-x} - e^{-x/\ell}.$$



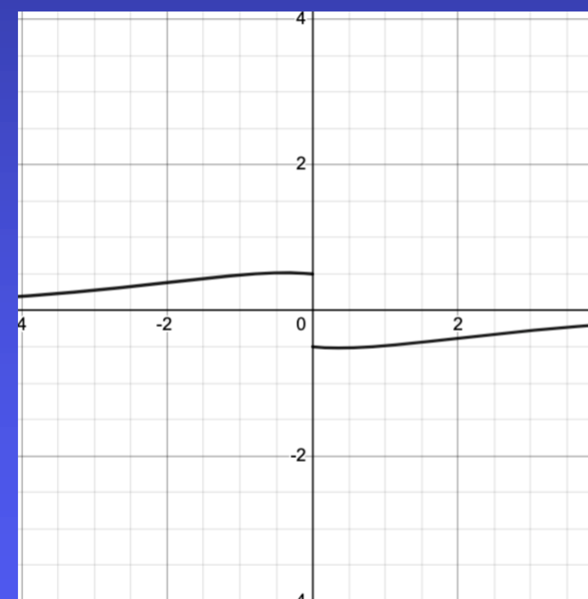
C=4, *l*=0.5



C=4, *l*=2.5



C=0.5, *l*=0.5



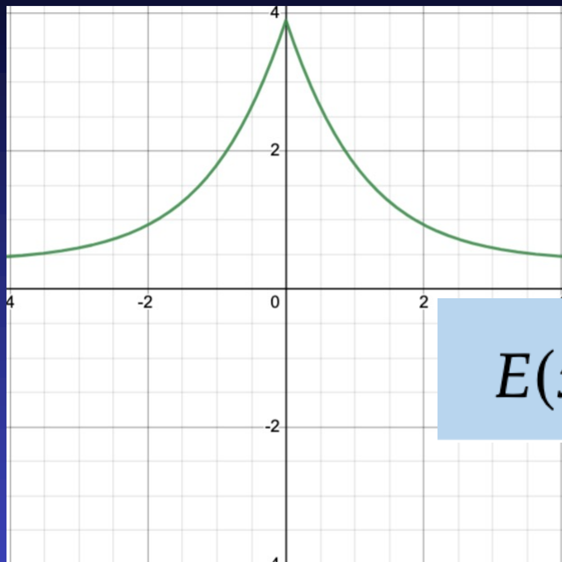
C=0.5, *l*=2.5

Potential

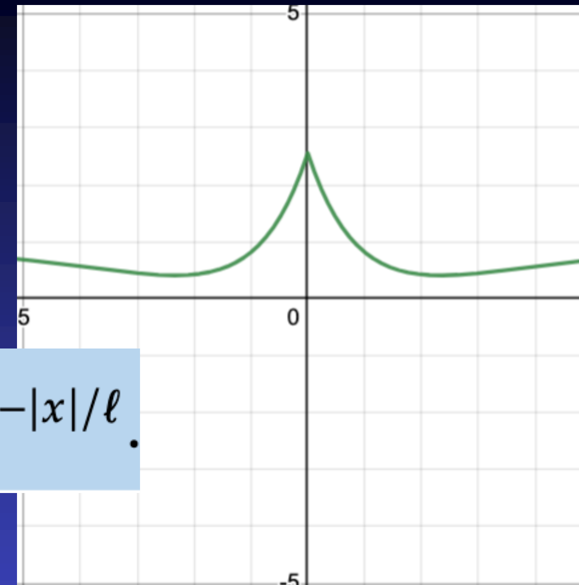
$$\ell = \frac{a}{r}, \quad C = \frac{R}{A}.$$

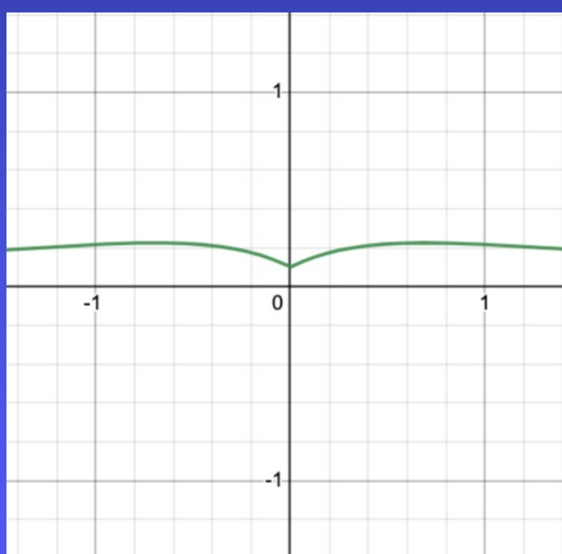
$$E(x) = Ce^{-|x|} - \ell e^{-|x|/\ell}.$$

C=4, l=0.5

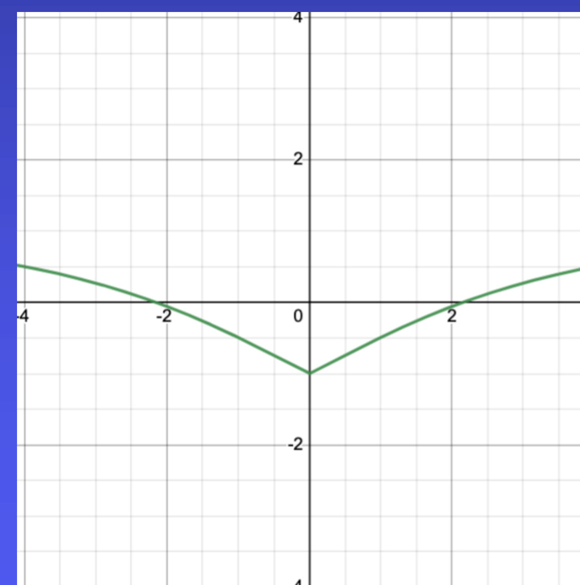


C=4, l=2.5





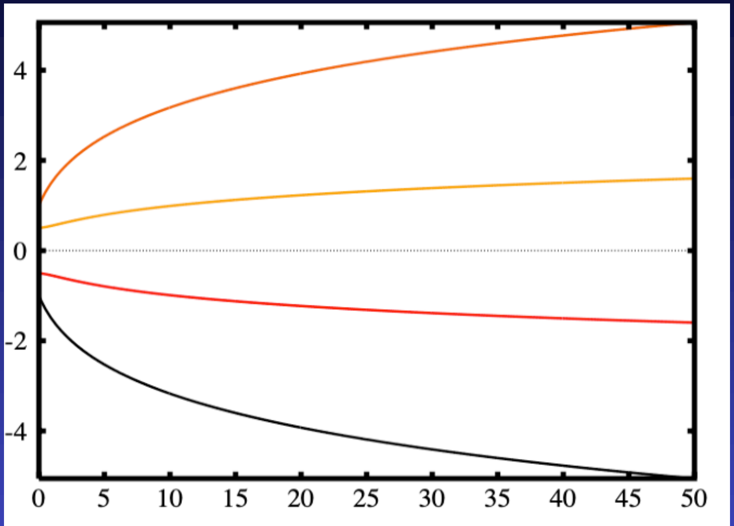
C=0.5, l=0.5



C=0.5, l=2.5

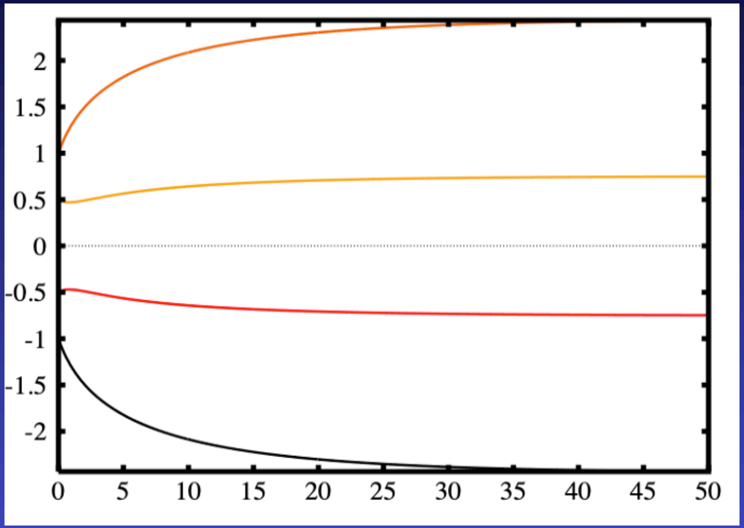
Trajectories 1D

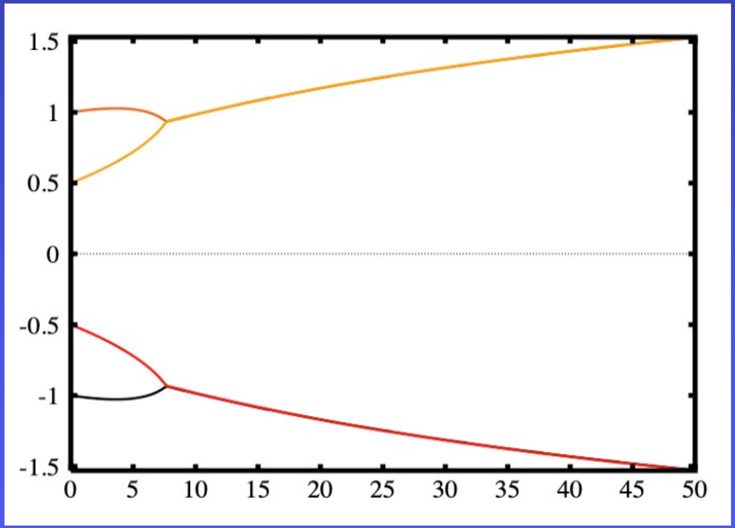
C=4, l=0.5



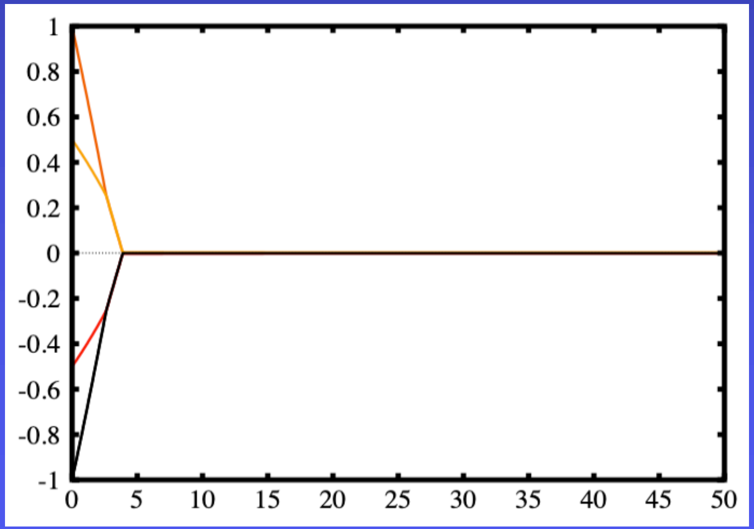
$$\ell = \frac{a}{r}, \quad C = \frac{R}{A}.$$

C=4, l=2.5





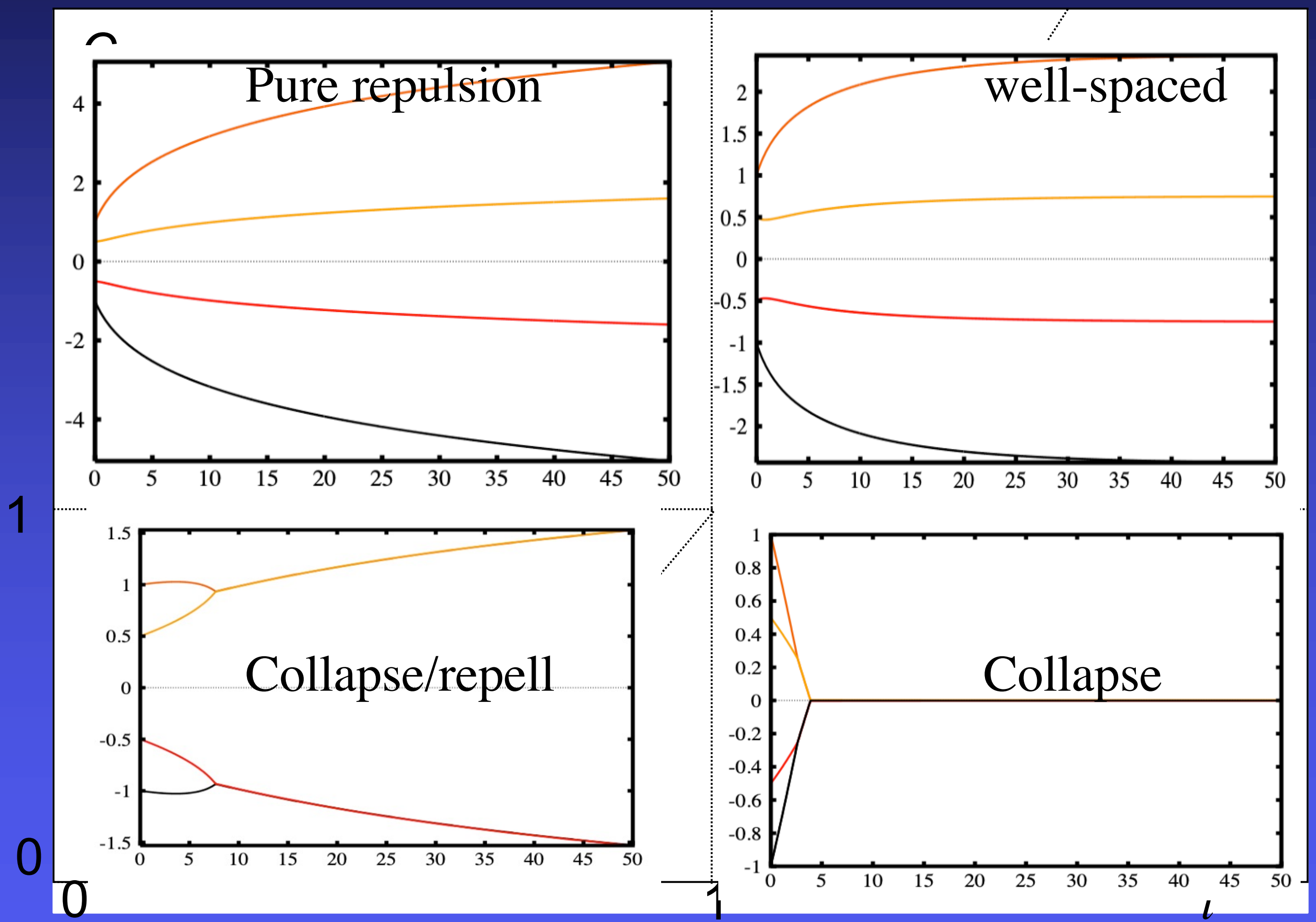
C=0.5, l=0.5



C=0.5, l=2.5

Parameter regimes

$C = \frac{R}{A}$

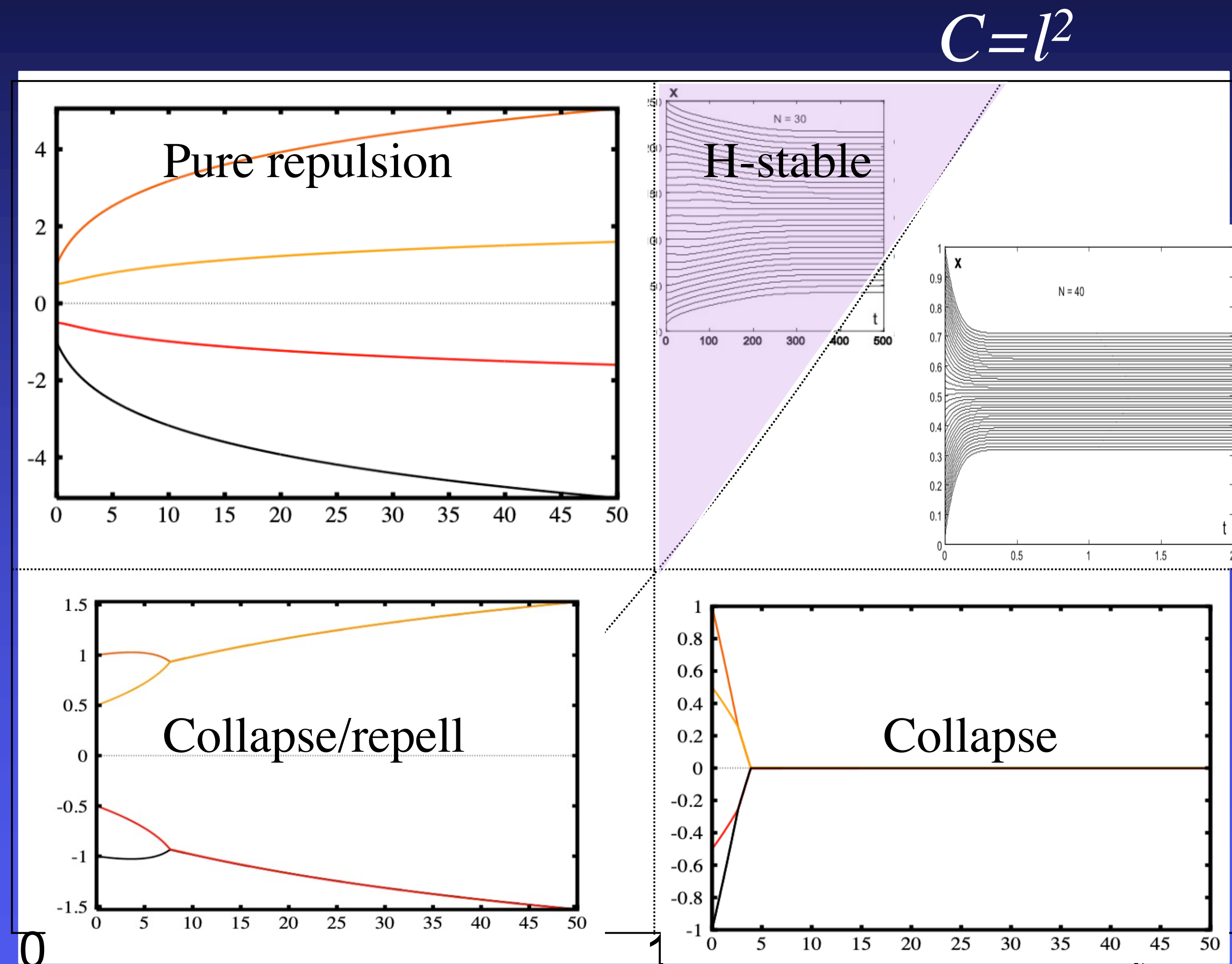


$\ell = \frac{a}{r}$

Distance between agents

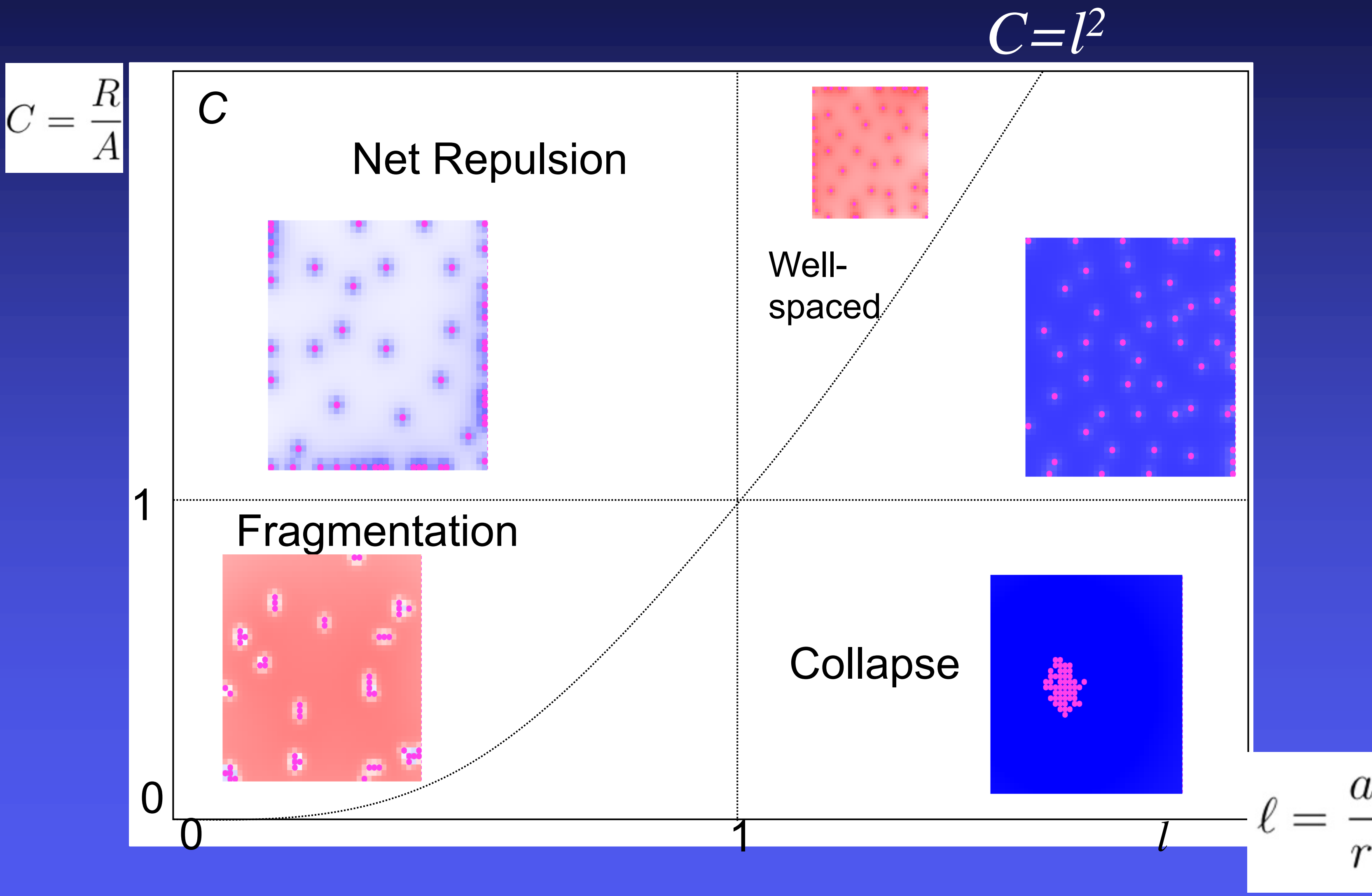
$$\delta = \sqrt{12\frac{C-\ell^2}{C-1}}.$$

$$C = \frac{R}{A}$$



$$\ell = \frac{a}{r}$$

Same idea in 2D



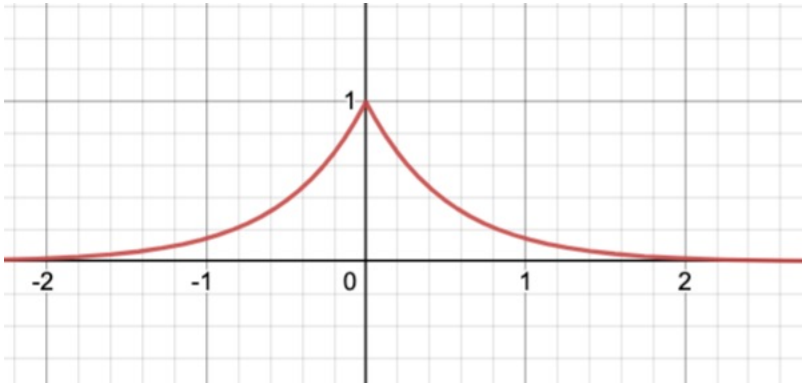
Biological "Morse forces"

- Cell secretes attractant and/or repellent
- Chemical(s) diffuse, decay
- Cells move up/down gradients (chemotaxis)

1 space dimension

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - kc.$$

$$c(x) = C_0 \exp(-x/\lambda), \quad \lambda = \sqrt{D/k}$$

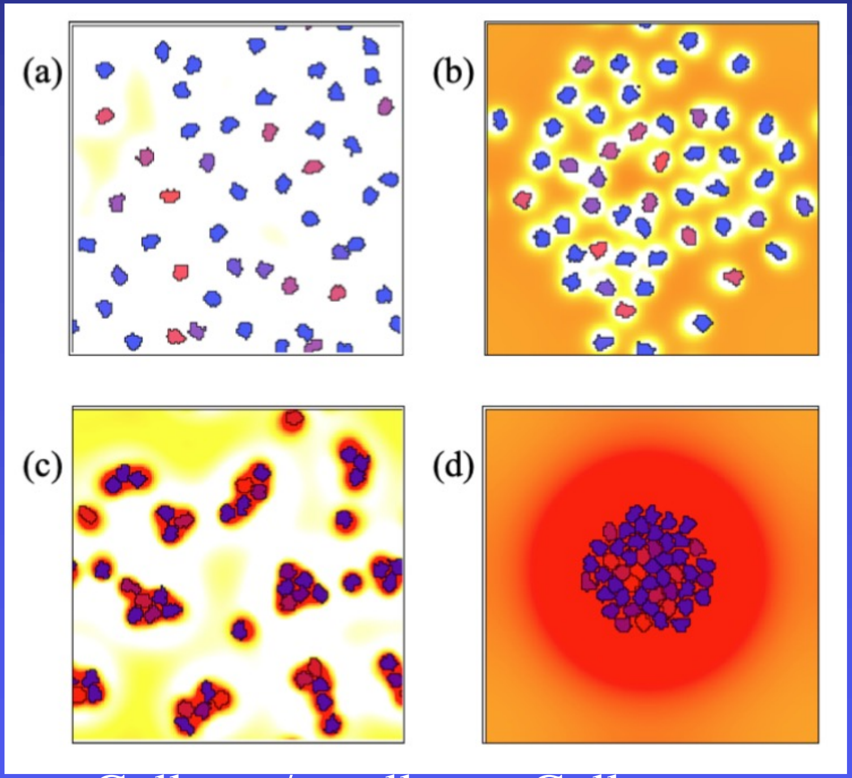


Alex Mogilner (1990's)

Hybrid model

- Chemotaxis with attractant and repellent

Pure repulsion   Well-spaced



Collapse/repell   Collapse

Morpheus
Multicellular Simulation
TU Dresden

Continuum Limit

- From ABM to continuum model:

For large number (N) of agents, associate a density with the superposition

$$\rho(\vec{x}, t) = \frac{1}{N} \sum_{i=1}^{N} \delta(\vec{x} - \vec{x}_i(t))$$

Typical nonlocal PDE

Falcó, Baker, Carrillo (2023) A local continuum model of cell-cell adhesion. SIAM J Appl Math 27:S17-42.

Directed motion (speed *v*), governed by potential function

$$\frac{\partial \rho}{\partial t} = -\nabla \cdot (\rho \vec{v}), \quad \textbf{where} \quad \vec{v} = -\nabla (W * \rho)$$

- In 1D:

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial x} \cdot (\rho v), \quad v = -\frac{\partial (W * \rho)}{\partial x}$$

$$W * \rho = \int K(x - s) \rho(x, t) dx$$

(“Nonlocal model”)

- No flux BCs as $x \rightarrow$ +/- infty

Comments

- Ignore random motion - get variational system (Cahn-Hilliard type free energy)
- Assume: potentials not too long-ranged
- Approximate convolution with Taylor series (up to 2nd order).

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial x} \cdot (\rho v), \quad v = -\frac{\partial (W * \rho)}{\partial x}$$

$$v = -\frac{\partial (W * \rho)}{\partial x} \approx -\frac{\partial}{\partial x}(a_0 \rho + a_2 \rho_{xx})$$

(“Local approx”)

Local approximation

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial x}(\rho v), \quad \text{where} \quad v \approx -\frac{\partial}{\partial x}(a_0 \rho + a_2 \rho_{xx})$$

- Where a_0, a_2 are moments of the kernel
- (Kernel is even so a_1 vanishes)
- Example: Morse potentials

$$K = Rr \exp(-|x|/r) - Aa \exp(-|x|/a).$$

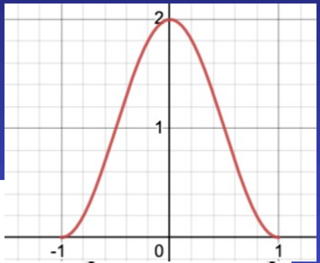
$$a_0 = \int_{-\infty}^{\infty} K(z)dz = 2(Rr^2 - Aa^2) \qquad a_2 = \frac{1}{2}\int_{-\infty}^{\infty} z^2 K(z)dz = \frac{1}{4}(Rr^4 - Aa^4)$$

Advantage of local approx:

- Explicit solution of steady state cluster dens in 1D:

$$\rho(x) = \frac{M}{2\pi}\phi\left(\cos(\phi x) + 1\right)$$

$$\phi = \sqrt{\frac{Rr^2 - Aa^2}{Rr^4 - Aa^4}}, \quad -b < x < b$$



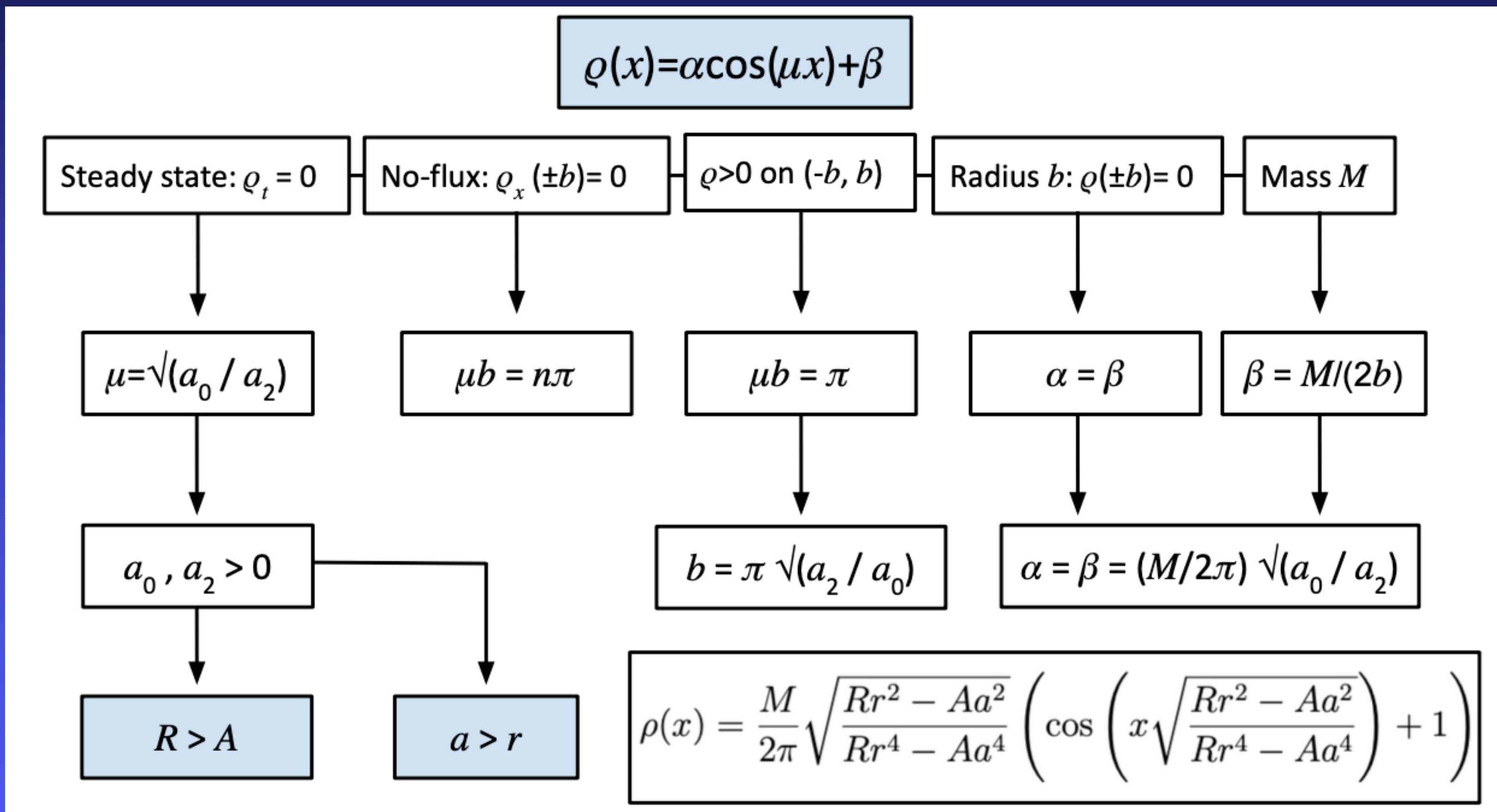
- Direct results about how magnitudes and ranges of attraction and repulsion affect cluster radius, density, etc.
- Conditions for the formation of compact cluster.

Steady state compact cluster

- Ingredients used: compact support, (radius b) variational character → $\rho(\pm b) = 0, \quad \rho_x(\pm b) = 0$
- Look for real solution for radius, b.
- Density > 0.

Shona Sinclair

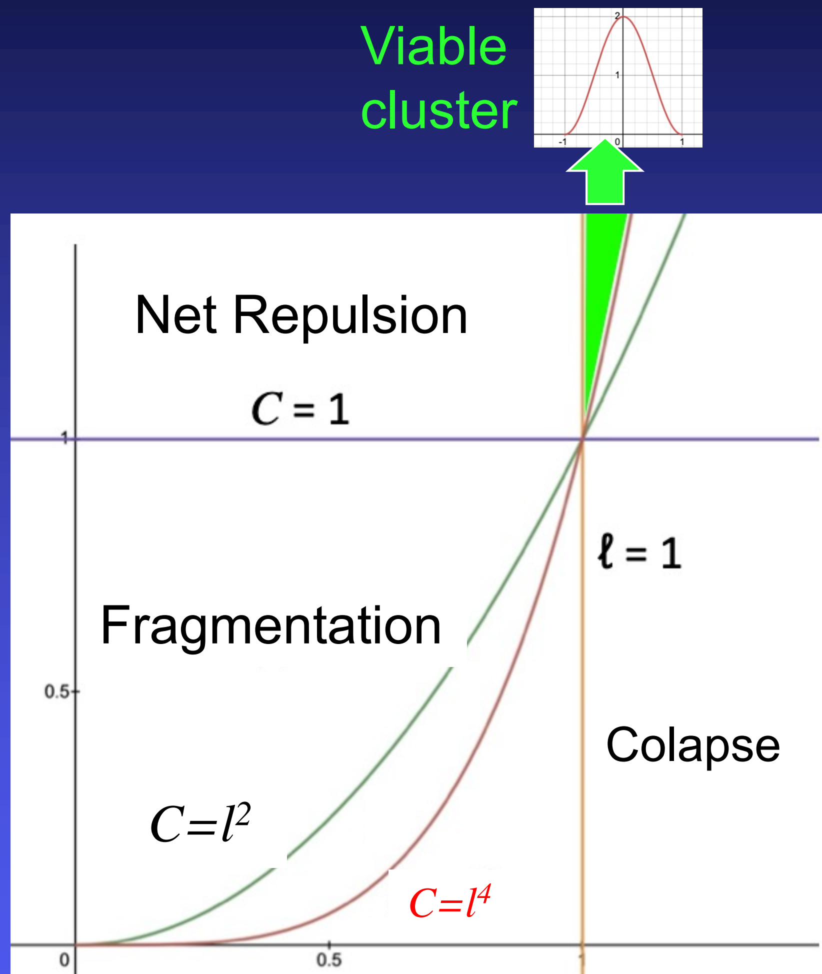
Conditions for existence



$C > 1$ $\quad$ $l > 1$

Parameter plane

- $C = \frac{R}{A}$



$\ell = \frac{a}{r}$

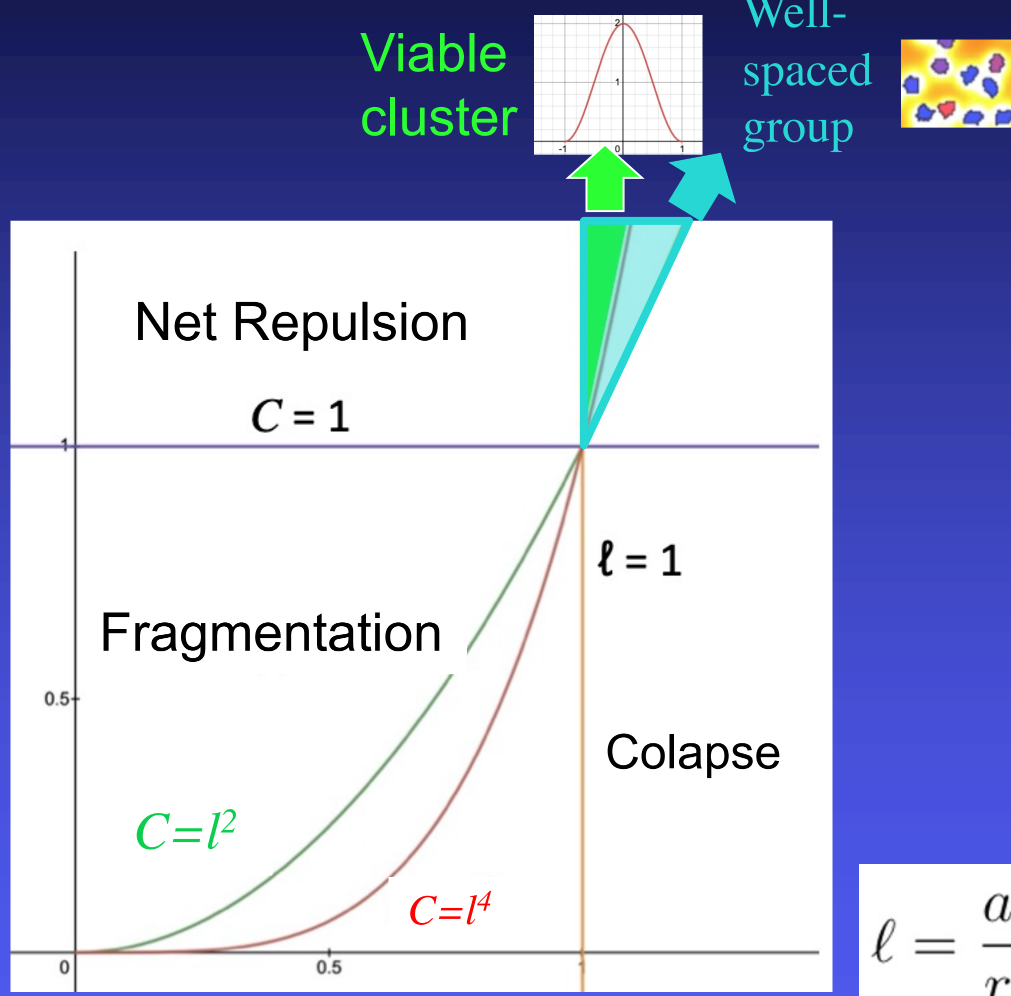
$C>1$

$l>1$

$C>l^4$

Compare to ABM results

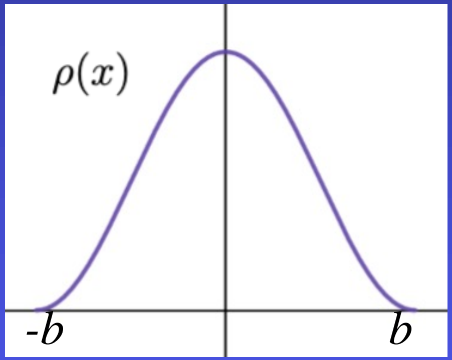
$$C = \frac{R}{A}$$



$$\ell = \frac{a}{r}$$

Cell density, cluster radius

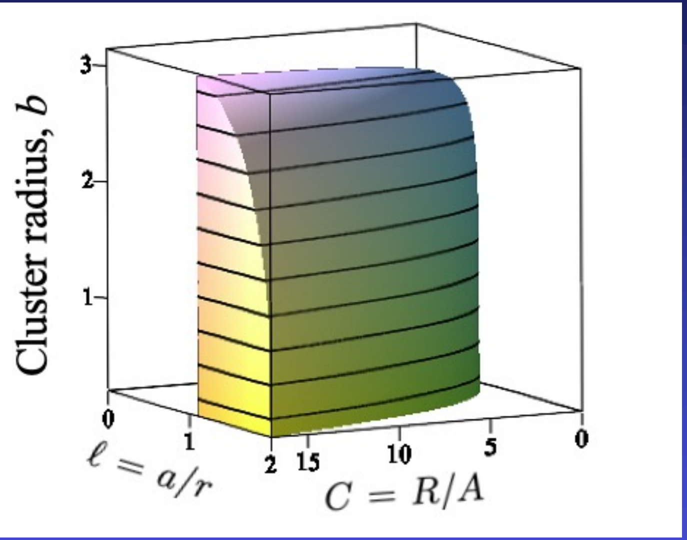
- Related to attraction-repulsion parameters:
- Density: $$\rho(x) = \frac{M}{2\pi r}\sqrt{\frac{C-\ell^2}{C-\ell^4}}\left(\cos\left(\frac{x}{r}\sqrt{\frac{C-\ell^2}{C-\ell^4}}\right)+1\right)$$
- "Shape":



- Radius: $$b = \pi\sqrt{\frac{Rr^4 - Aa^4}{Rr^2 - Aa^2}} \quad = 2\pi r\sqrt{\frac{2(C-\ell^4)}{C-\ell^2}}$$

Cluster radius

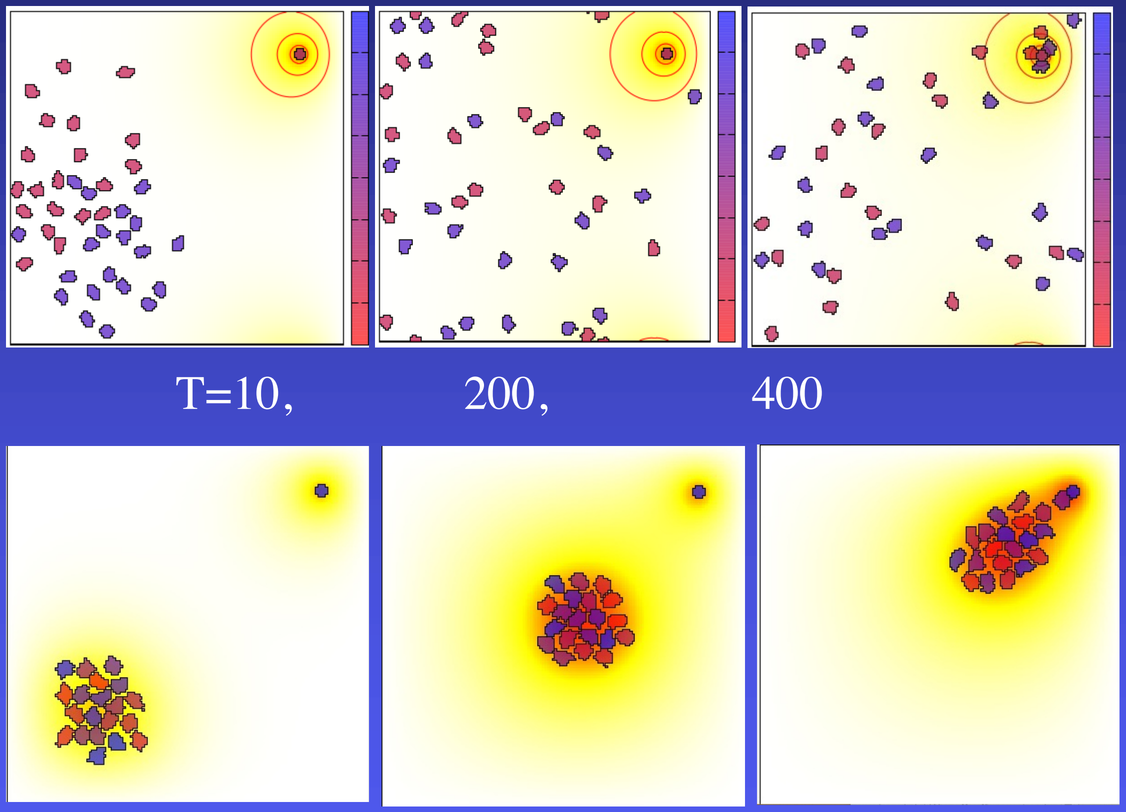
$$b = 2\pi r \sqrt{\frac{2(C - \ell^4)}{C - \ell^2}}$$



Cluster compactness as a trajectory in *Cl* space.. Changing *l=a/r* has sharper influence than changing *C=R/A*.

Simulations of cells

Use insights gained to fine-tune simulations



No cohesion

T=10, 200, 400

Cell-cell attraction

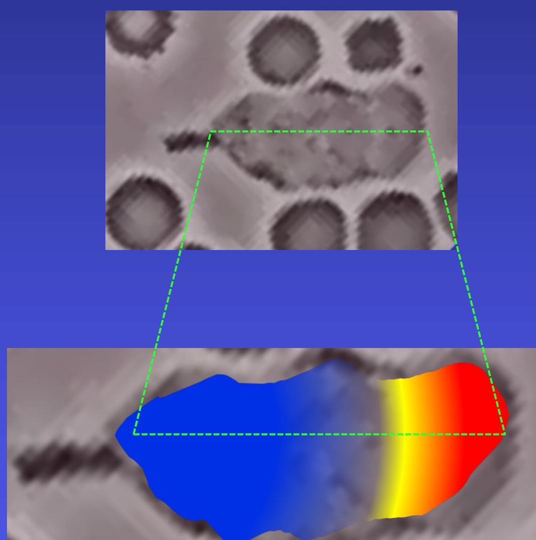
Some parallels

- Single cell ←→ cell cluster
- Animal swarm ←→ cell swarm
- Simulations ←→ analysis

How is polarity established?

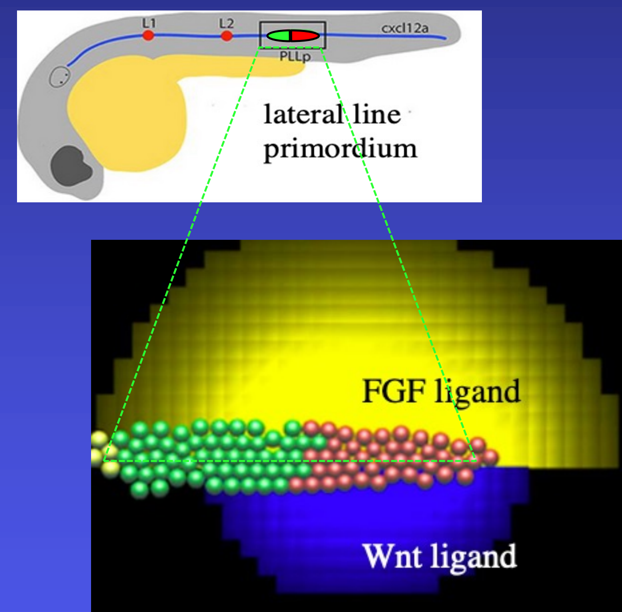
Single cell

- White blood cell (neutrophil)



Cell cluster

- In zebrafish embryo (PLLP)

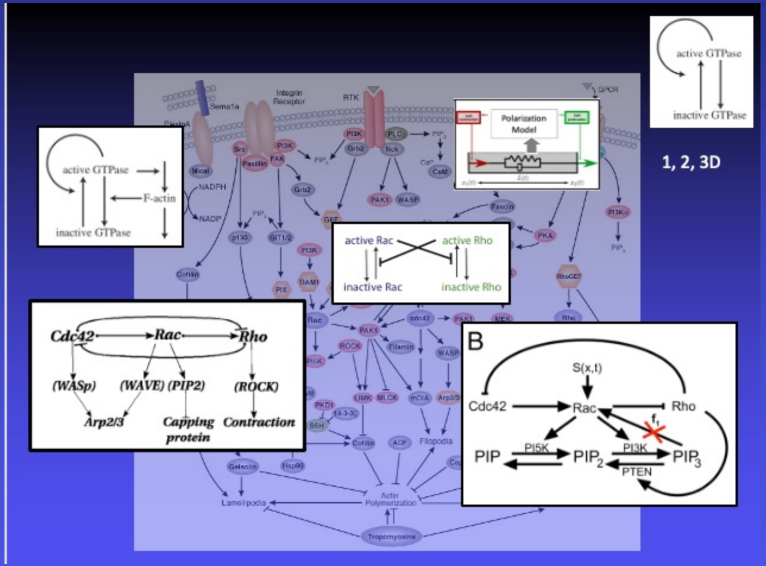


Knutsdottir et al (2017) PLoS CB.

Molecular mechanisms

Intracellular signalling

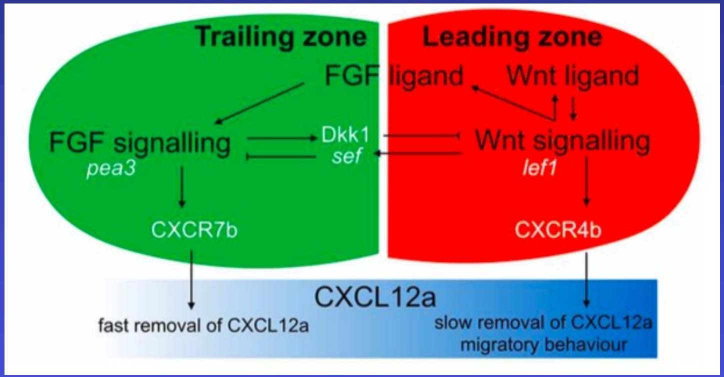
- GTPase gradients



Maree, Holmes, Mori, Jilkine, Zmurchok, Bjaskar, Rens, Buttenschoen, LEK, etc

Multicellular signalling

- Wnt-FGF gradients



Knutsdottir et al (2017) PLoS CB.

Interaction forces

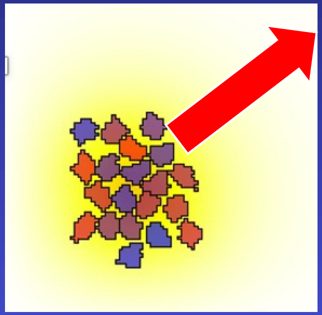
Marcoscopic

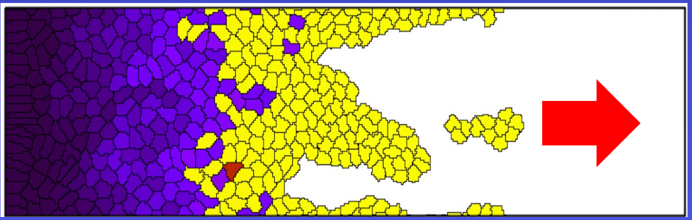
- Cohesive flock (surf scoters)

Lukeman et al (2010) PNAS 107(28)

Microscopic

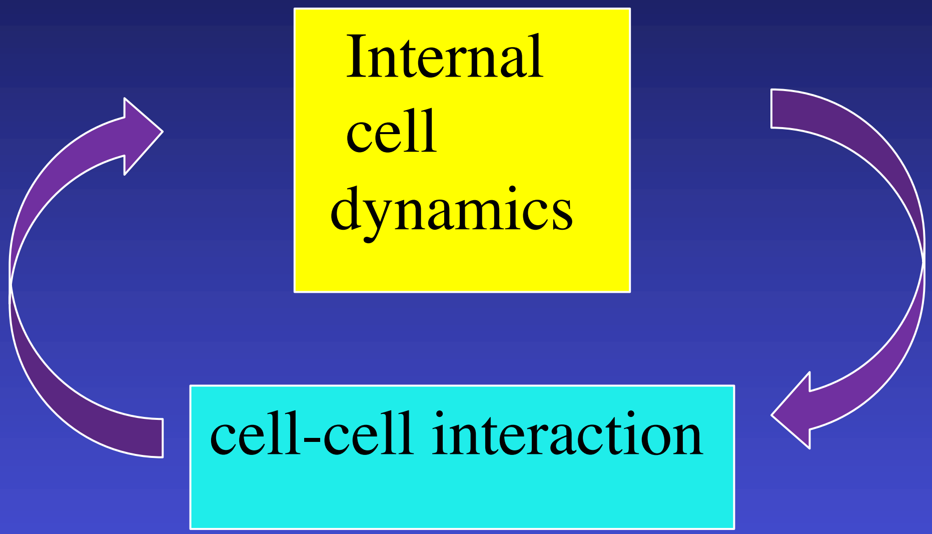
- Cell cluster





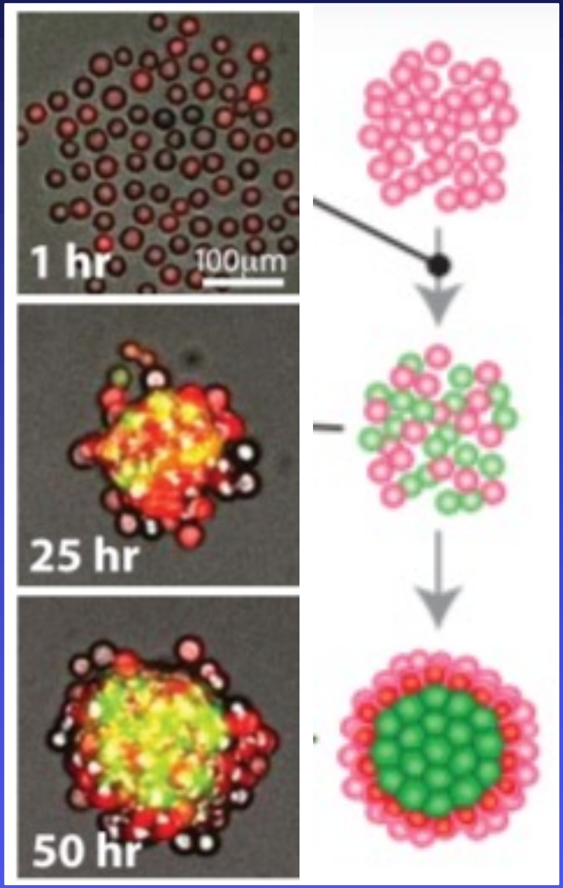
Mukhtar et al. (2022). Biophys J 121(10)

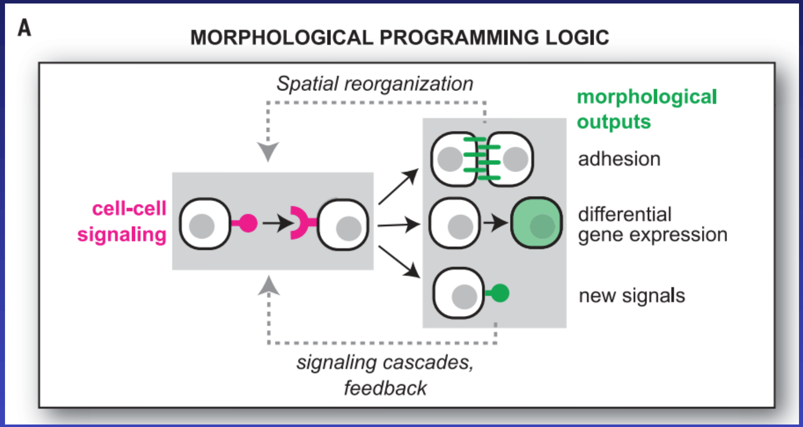
Examples: multiscale simulations

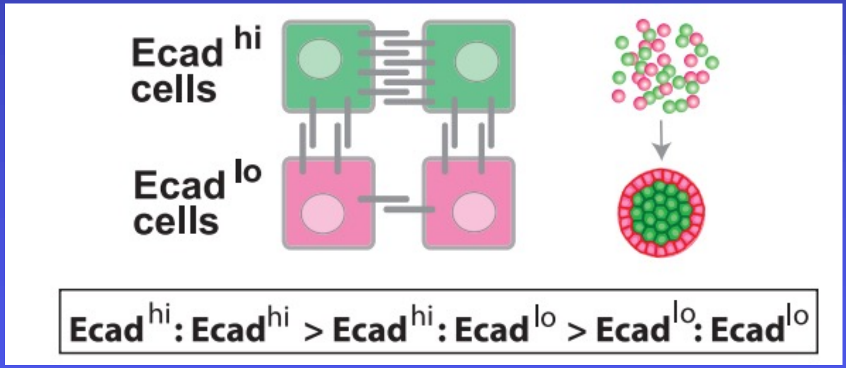


Example 1: Synthetic biology

Self-organizing cell clusters made with synthetic cell signaling.

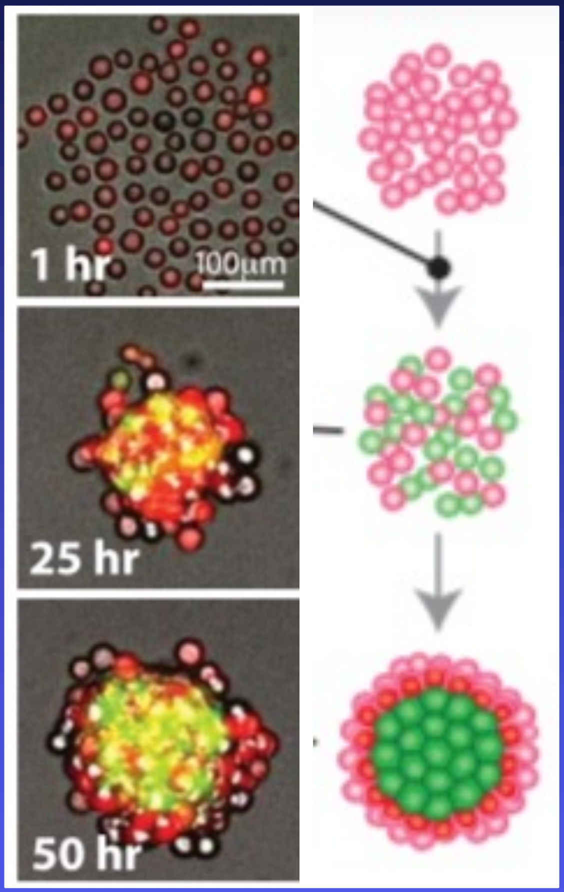




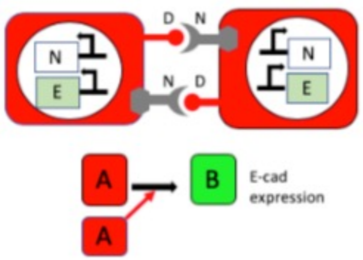


Toda et al (2018) Science, 361:156-62.(Wendell Lim's lab)

Model for cell signaling:



Toda et al (2018) Science 361



$$\frac{dN_i}{dt} = N_0\left(1 + \frac{I_i^p}{I_0^p + I_i^p}\right) - \kappa_c N_i D_i - \kappa_t N_i D_{\text{ext}}^i - \gamma N_i,$$

$$\frac{dD_i}{dt} = D_0\left(1 - \frac{I_i^p}{I_0^p + I_i^p}\right) - \kappa_t D_i N_{\text{ext}}^i - \gamma D_i,$$

$$\frac{dI_i}{dt} = \kappa_t N_i D_{\text{ext}}^i - \gamma_I I_i,$$

$$\frac{dE_i}{dt} = E_0 \frac{I_i^p}{I_0^p + I_i^p} - \gamma E_i.$$

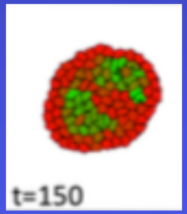
Morpheus

Multicellular simulation

TU Dresden

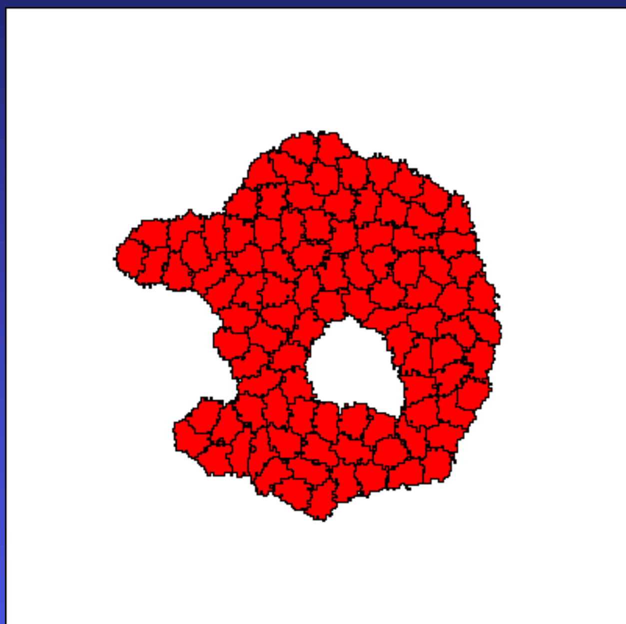
https://morpheus.gitlab.io/

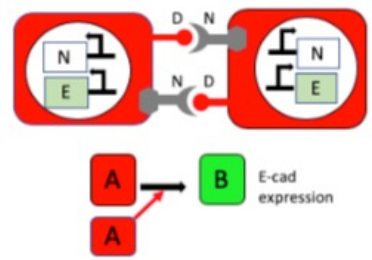
Nicola Mulberry



Mulberry & LEK (2020) Phys Biol

Emergence of tissue organization





$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = N_0\left(1 + \frac{I_i^p}{I_0^p + I_i^p}\right) - \kappa_c N_i D_i - \kappa_t N_i D_{\mathrm{ext}}^i - \gamma N_i,$$

$$\frac{\mathrm{d}D_i}{\mathrm{d}t} = D_0\left(1 - \frac{I_i^p}{I_0^p + I_i^p}\right) - \kappa_t D_i N_{\mathrm{ext}}^i - \gamma D_i,$$

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = \kappa_t N_i D_{\mathrm{ext}}^i - \gamma_I I_i,$$

$$\frac{\mathrm{d}E_i}{\mathrm{d}t} = E_0 \frac{I_i^p}{I_0^p + I_i^p} - \gamma E_i.$$

Morpheus

Multicellular simulation

TU Dresden

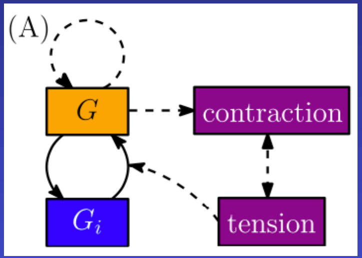
https://morpheus.gitlab.io/

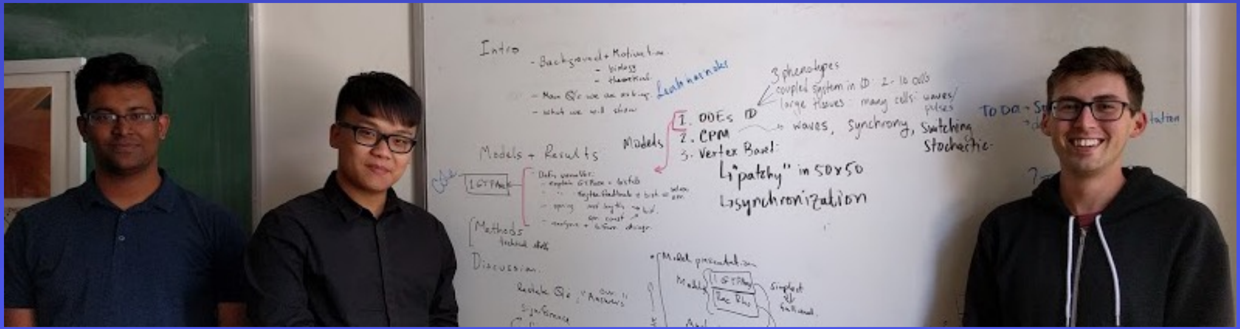
Nicola Mulberry

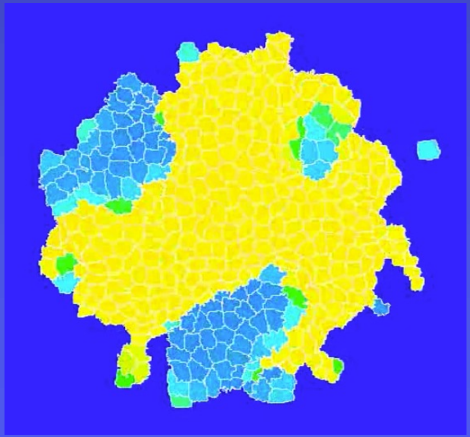
Mulberry & LEK (2020) Phys Biol

Example 2:

- Intracellular (GTPase) signaling
- GTPase affects cell spreading and contraction
- Stresses affect GTPase
- Movie





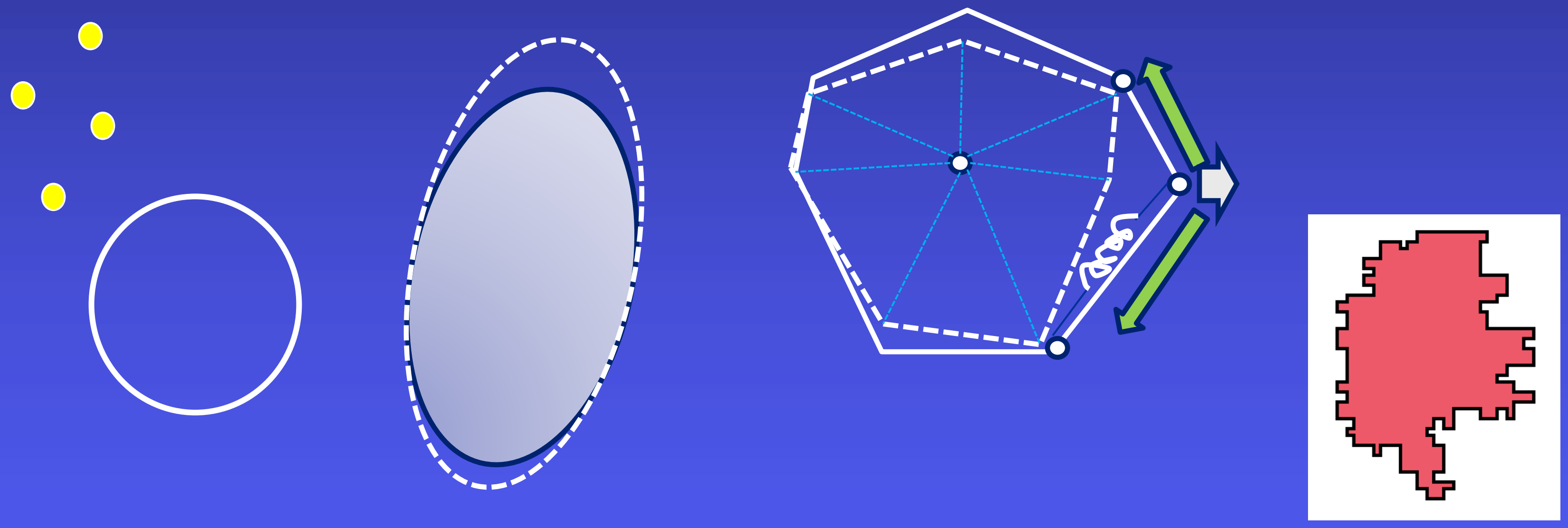


Dhananjay Bhaskar MoHan Zhang Cole Zmurchok

Zmurchok et al (2018) *Phys. Biol.* **15**

Computational methods

Cells as points, spheres, deforming ellipsoids or polygons, phase fields or Potts models

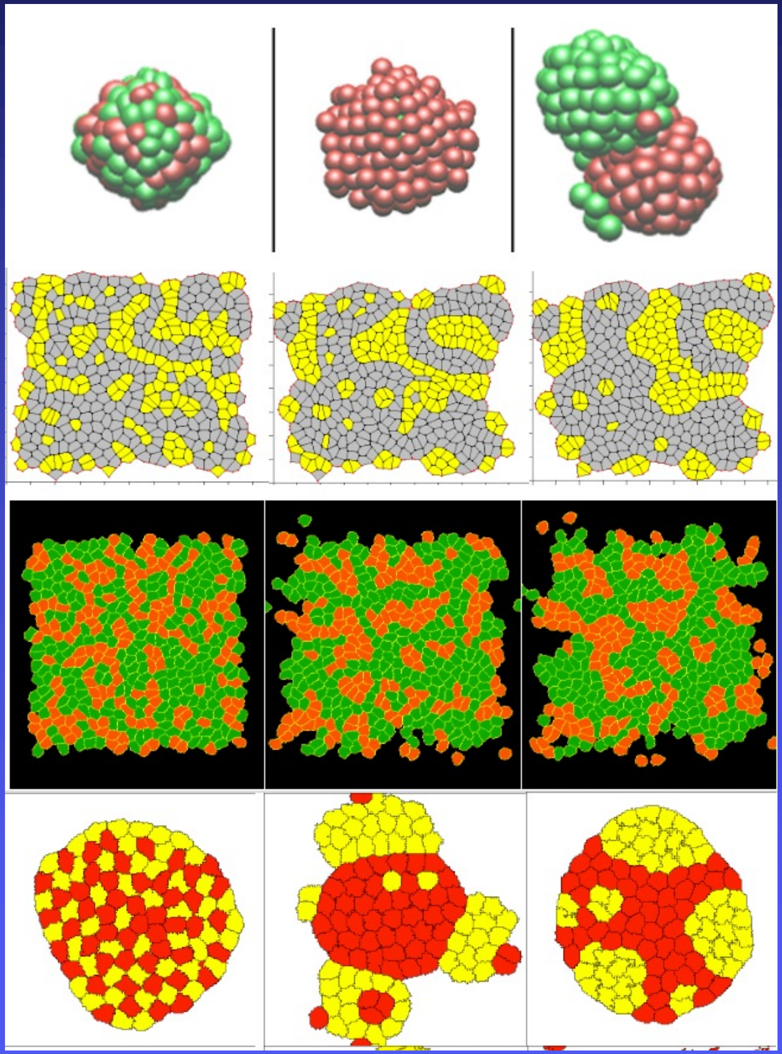


Cell sorting

Hildur Knutsdottir

Dhananjay Bhaskar

LEK



Eirikur Palsson

CHASTE

CC3D

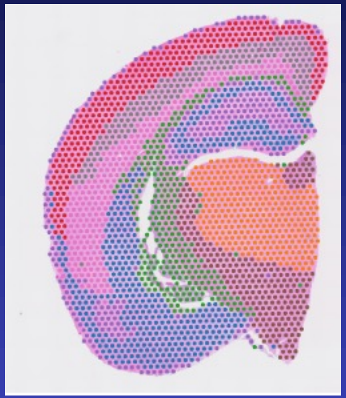
Morpheus

Morpheus

- https://morpheus.gitlab.io/
- Open source, good GUI, easy to use
- Lots of ready examples
- Growing archive of examples

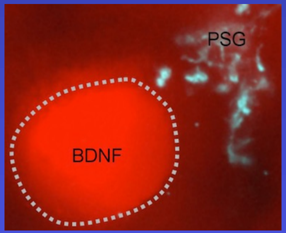
Morpheus
Multicellular Simulation
TU Dresden

Next steps



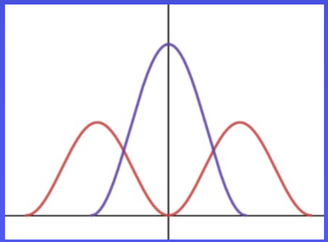
https://singulomics.com/

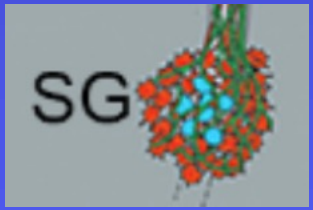
- Kulesa lab: “Spatial transcriptomics” data, identify ligan-receptor pairs over space and time (look for attractant/repellent molecules)



- “Bead” experiments & simulations

- 2-layer cluster (model extension & interpretation)

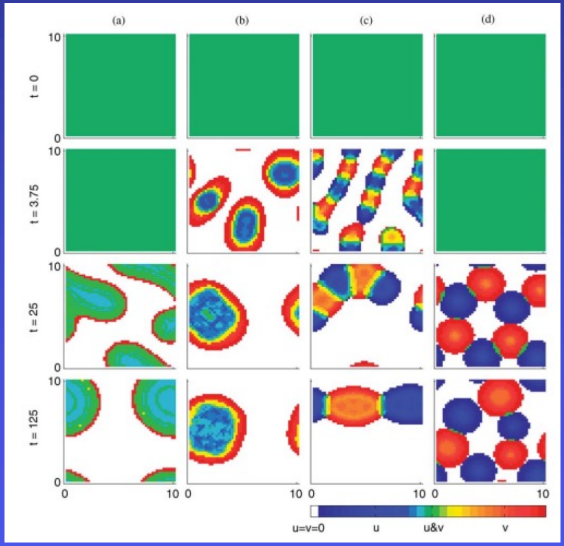




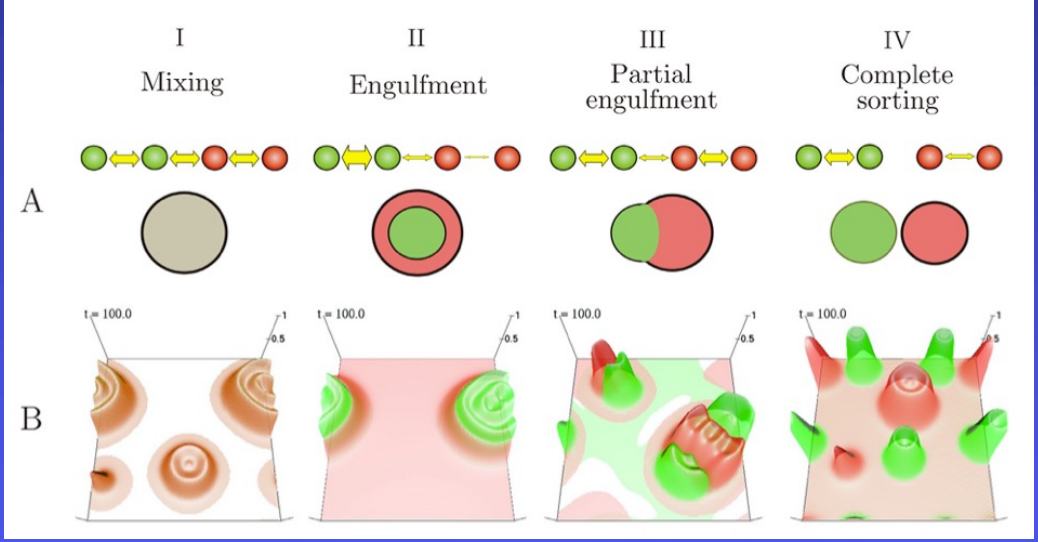
Two species continuum models

- Nonlocal and approximating (PDE) local versions

Time →



Armstrong, Painter, Sherratt (2019) JTB



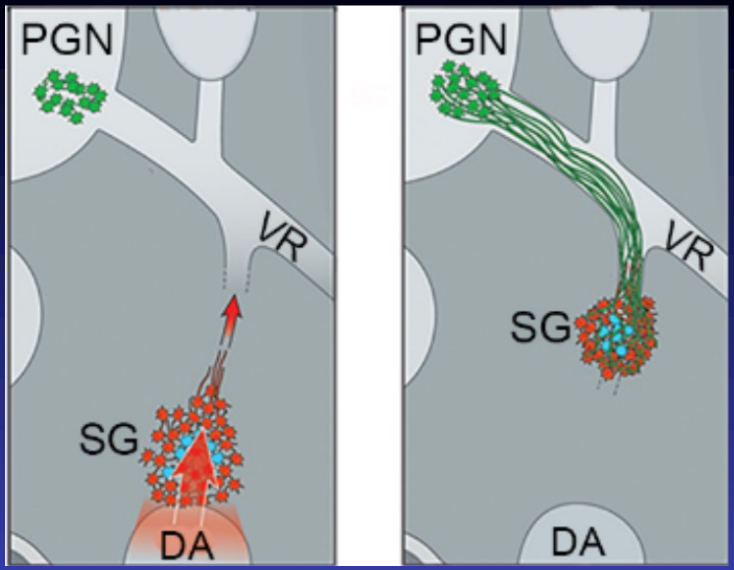
Carrillo et al (2018) JTB

Limitations & benefits

- Continuum: powerful math analysis tools, gain insights into key (dimensionless) parameters, expected range of behaviours
- Simulations: visualization and tracking of individual cells, positions, sizes, etc..
- Ideal: combine both!

THANKS FOR LISTENING

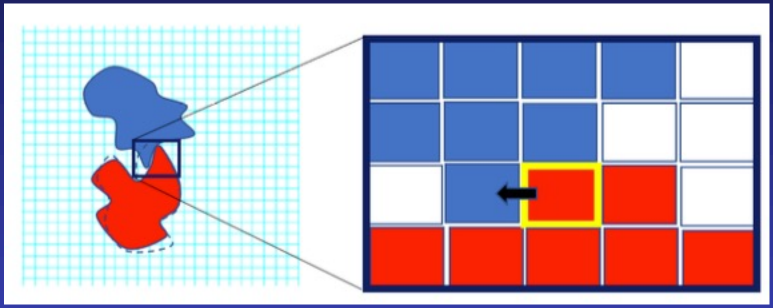
Details



- NCCs arrive near dorsal aorta (DA)
- Aggregate (EphB2/EphrinB1, N-Cadherin signaling)
- Form a cohesive cluster ("sympathetic ganglion")
- Linger for 24 h
- Start to migrate towards "ventral root" (VR)
- Meet preganglion neuron axons that secrete BDNF

Cellular Potts model

- Cell shape on a grid
- “Energetic cost”



$$H = \lambda_a (A - A_0)^2 + \lambda_p (P - P_0)^2 + JP$$

- Many cells:

$$H = \lambda_a (A - A_0)^2 + \lambda_p (P - P_0)^2 + J_{0i} P_{0i} + \frac{1}{2} \sum_{j=1}^{n} J_{ij} P_{ij}.$$

- Stochasticity

$$\mathscr{P}(\Delta H) = \begin{cases} 1 & \Delta H < 0 \\ \exp(-\Delta H / T) & \Delta H \geq 0 \end{cases}$$