QBM LECTURE SERIES, LMU MUNICH
14 MAY 2021

IN-DEPTH LECTURE

Stem Cells as Self-renewing Many-Particle Systems

Jörg, Kitadate, Yoshida and Simons, *Annu. Rev. Cond. Mat. Phys.* 12, 135–153 (2021)

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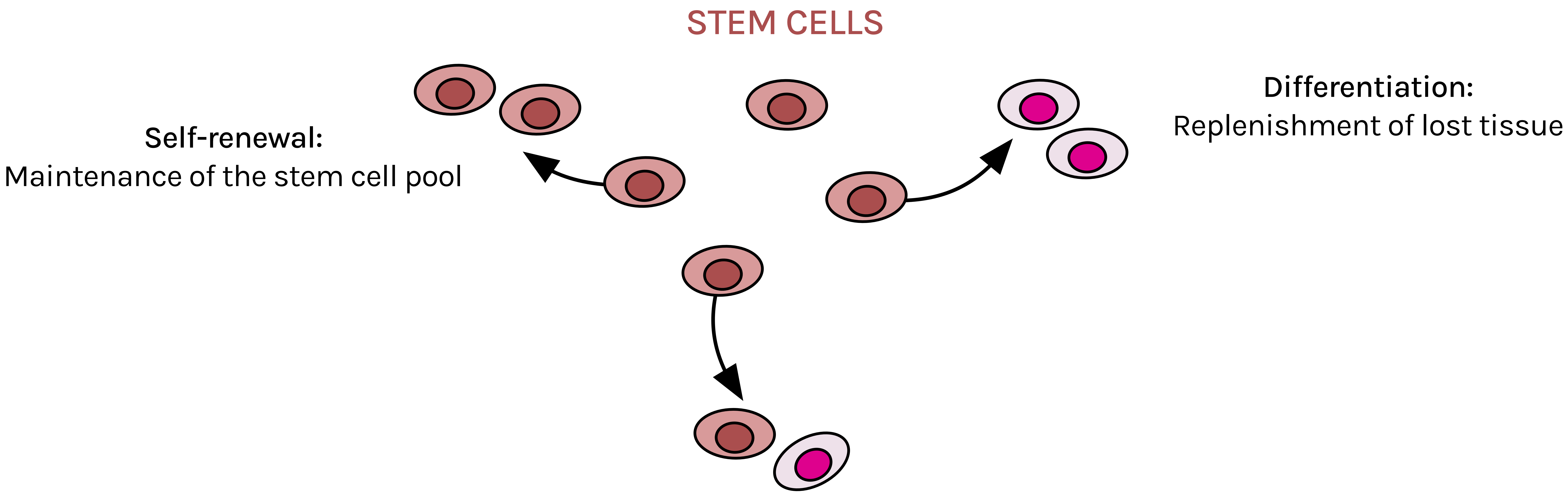
Aim of this lecture

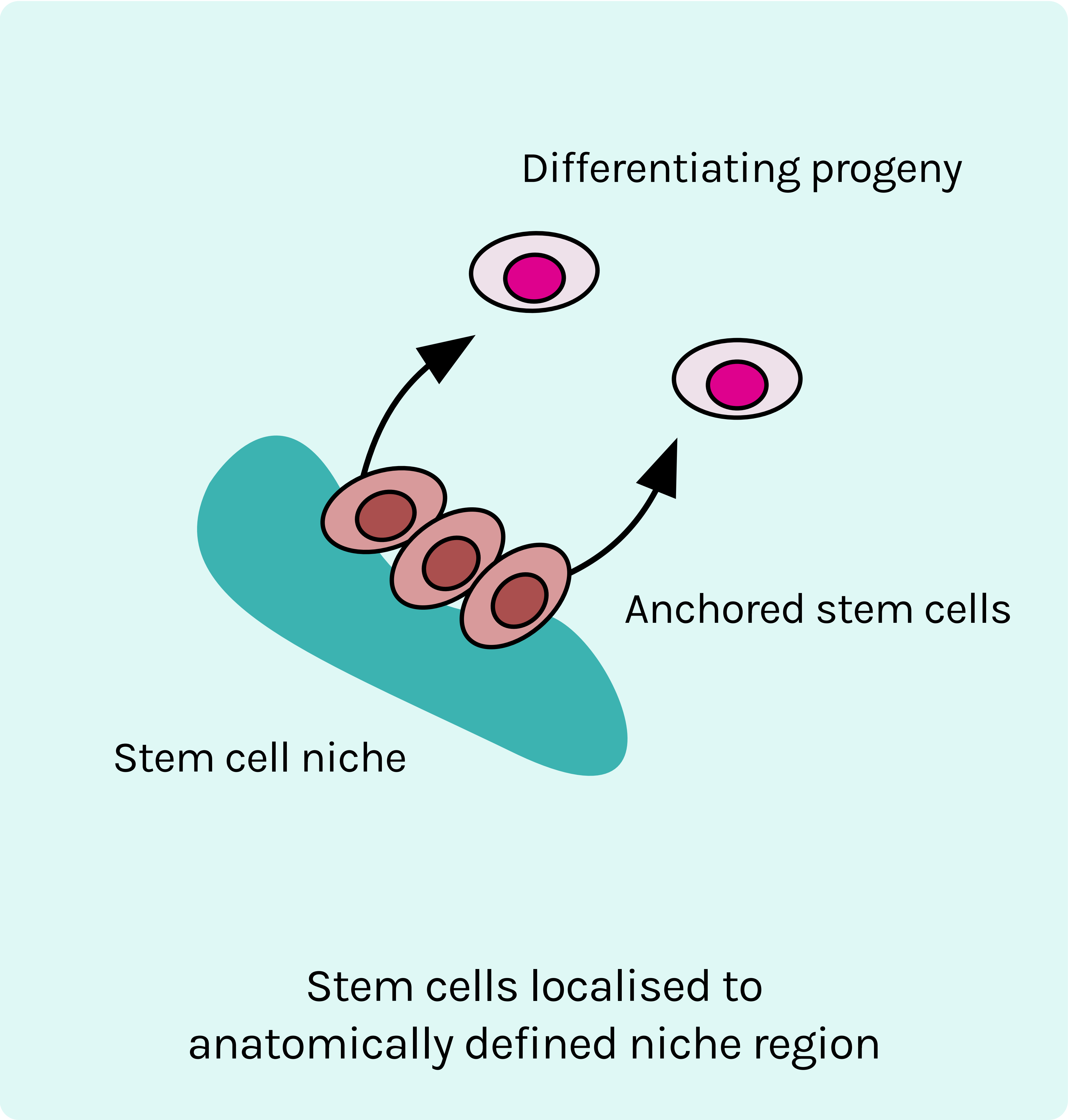
- How to **build a model** of stem cell homeostasis
- Understand basics of **stochastic stem cell fate**
- Analytically and numerically analyse **clonal dynamics**
- Address **spatial fluctuations** in cell density
- Address density **front propagation**

Stem cells self-renew and replenish lost cells

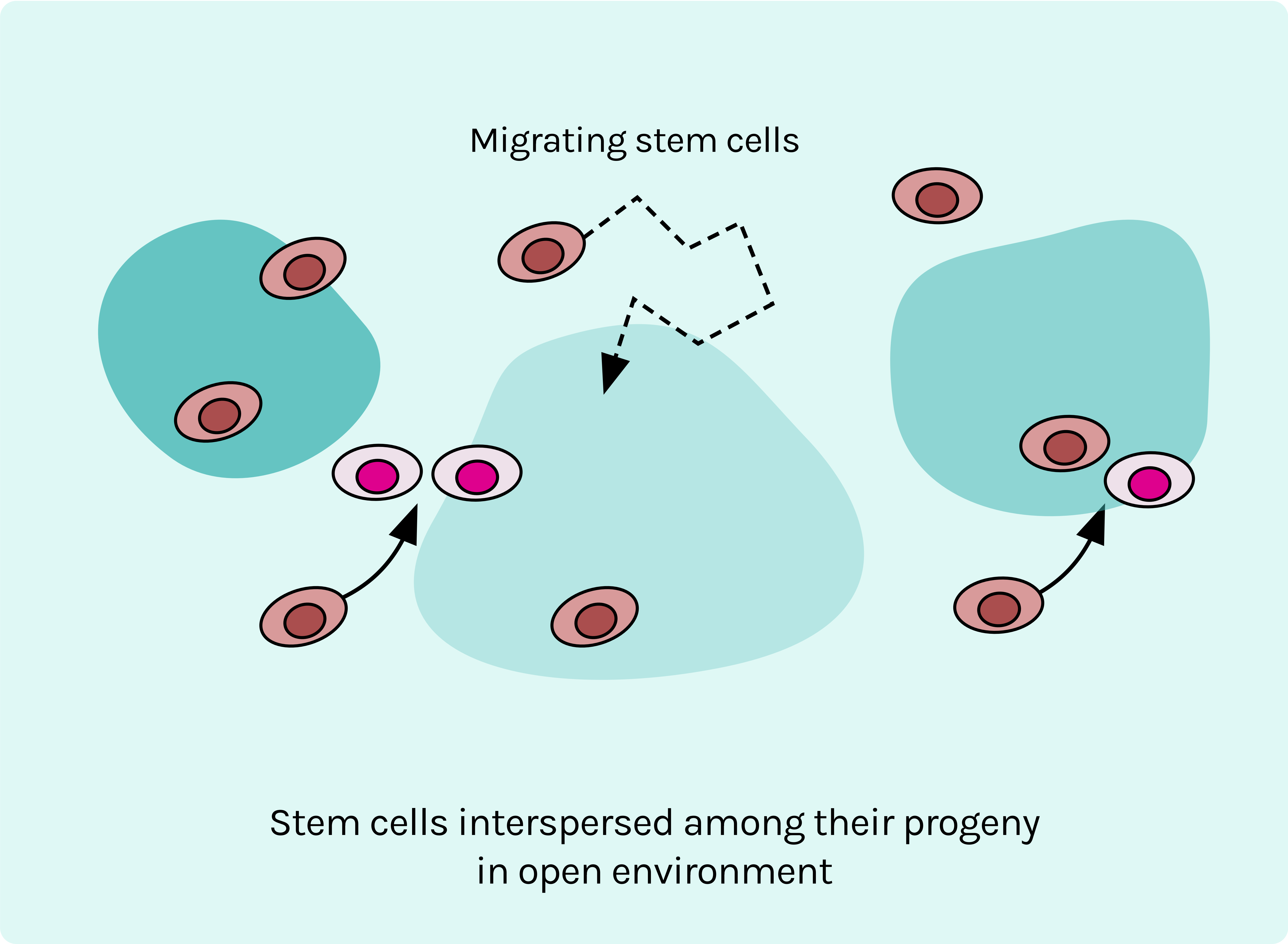


Types of stem cell niches: “definitive” vs. “open” niches

Definitive niche environment



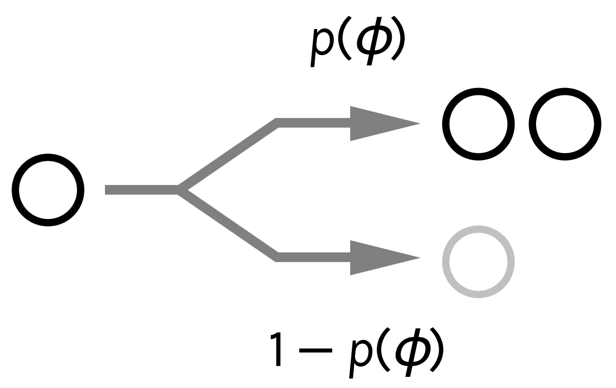
Open niche environment



Ingredients for a generic model of stem cell homeostasis

Stochastic stem cell fate

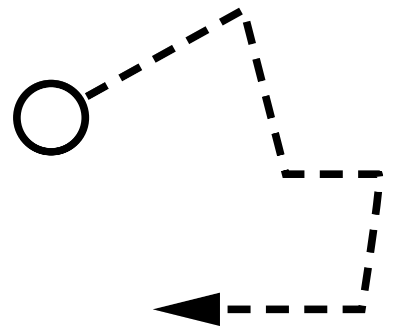
duplication



loss
(through differentiation)

- We dont consider asymmetric divisions.
- Probability p may depend on external factors.

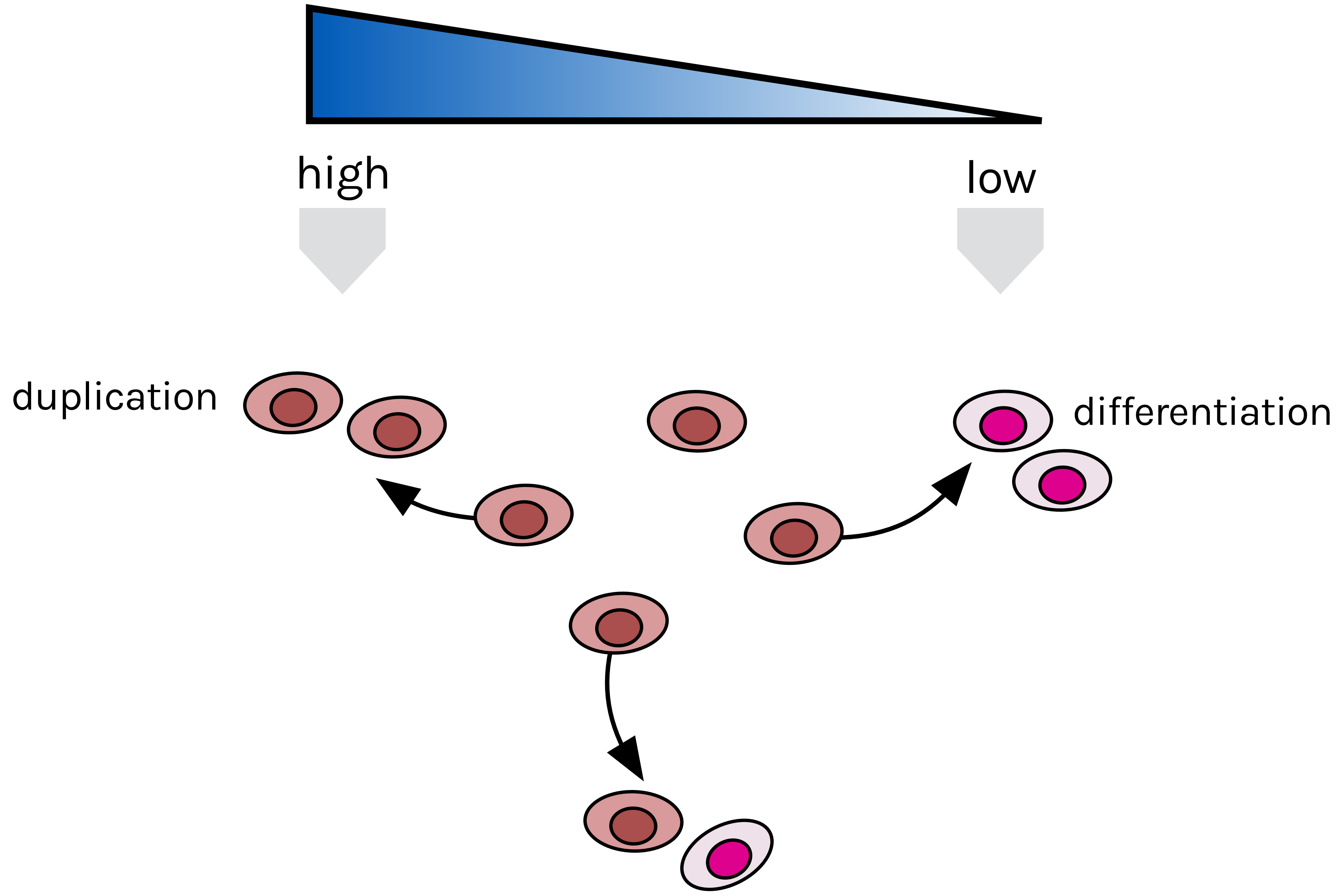
Stem cell rearrangement



through active cell migration or displacement

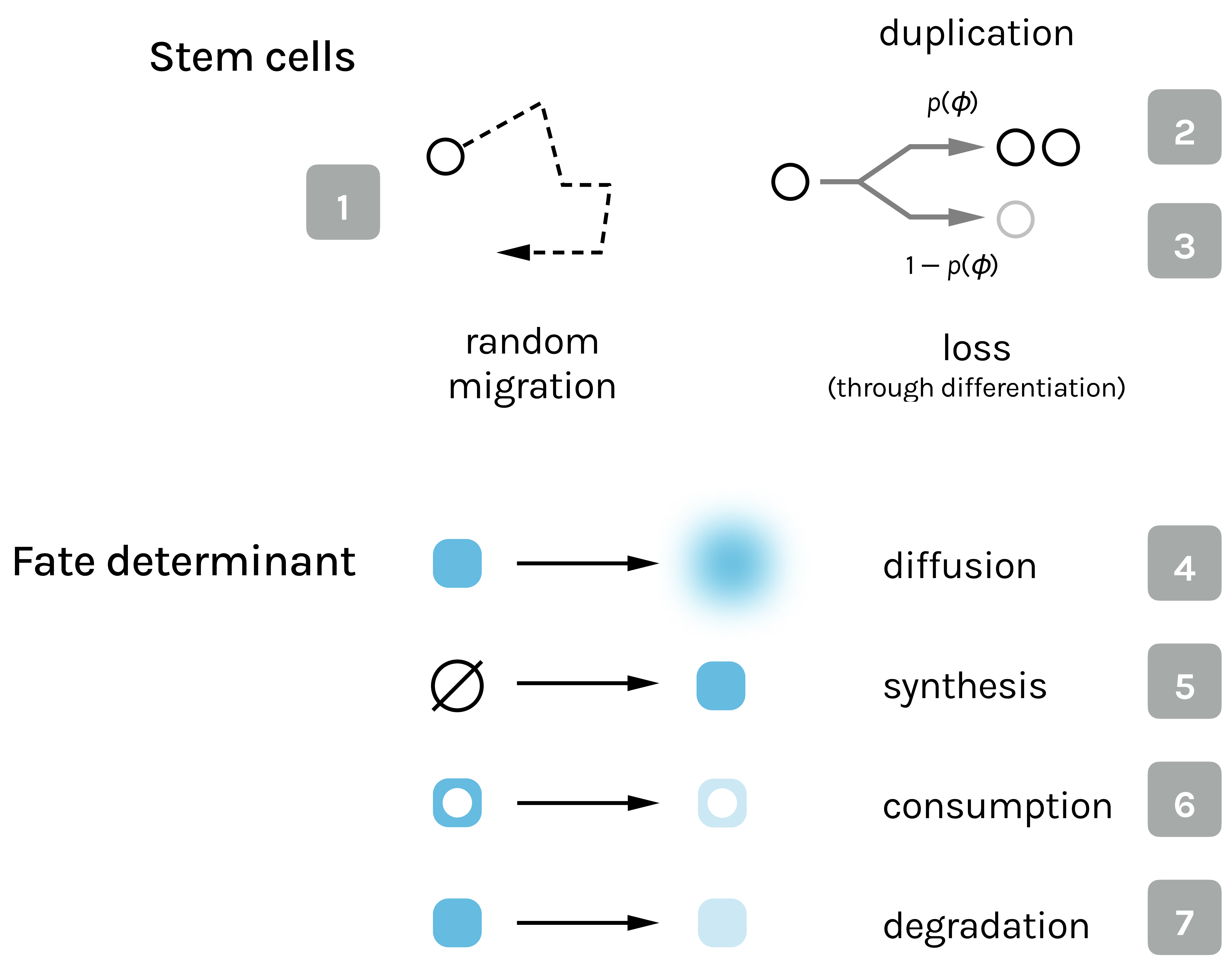
Stem cell fate regulation

Concentration of a fate determinant



Numerous other mechanisms possible.

Hybrid cell-based and continuum theory of competition for fate determinants



Model equations

1 $$\frac{\mathrm{d}\mathbf{x}_i}{\mathrm{d}t} = \sqrt{2\eta}\boldsymbol{\xi}_i(t)$$

Random walk in *d* dimensions

$$\langle \xi_i^\alpha(t)\xi_j^\beta(t')\rangle = \delta_{\alpha\beta}\delta_{ij}\delta(t-t')$$

2 $$\mathrm{S} \xrightarrow{p\lambda} \mathrm{S}+\mathrm{S}$$

3 $$\mathrm{S} \xrightarrow{(1-p)\lambda} \varnothing$$

Poissonian birth-death processes

Probability for duplication:

$$p = \frac{(\phi/\phi_0)^n}{1+(\phi/\phi_0)^n}$$

$$p \to \begin{cases} 1 & \phi\to\infty \\ 1/2 & \phi=\phi_0 \\ 0 & \phi = 0 \end{cases}$$

Fate determinant concentration field

$$\frac{\partial\phi}{\partial t} = D\nabla^2\phi + \nu J(\mathbf{x}) - \gamma Q(\phi,\rho) - \kappa\phi$$

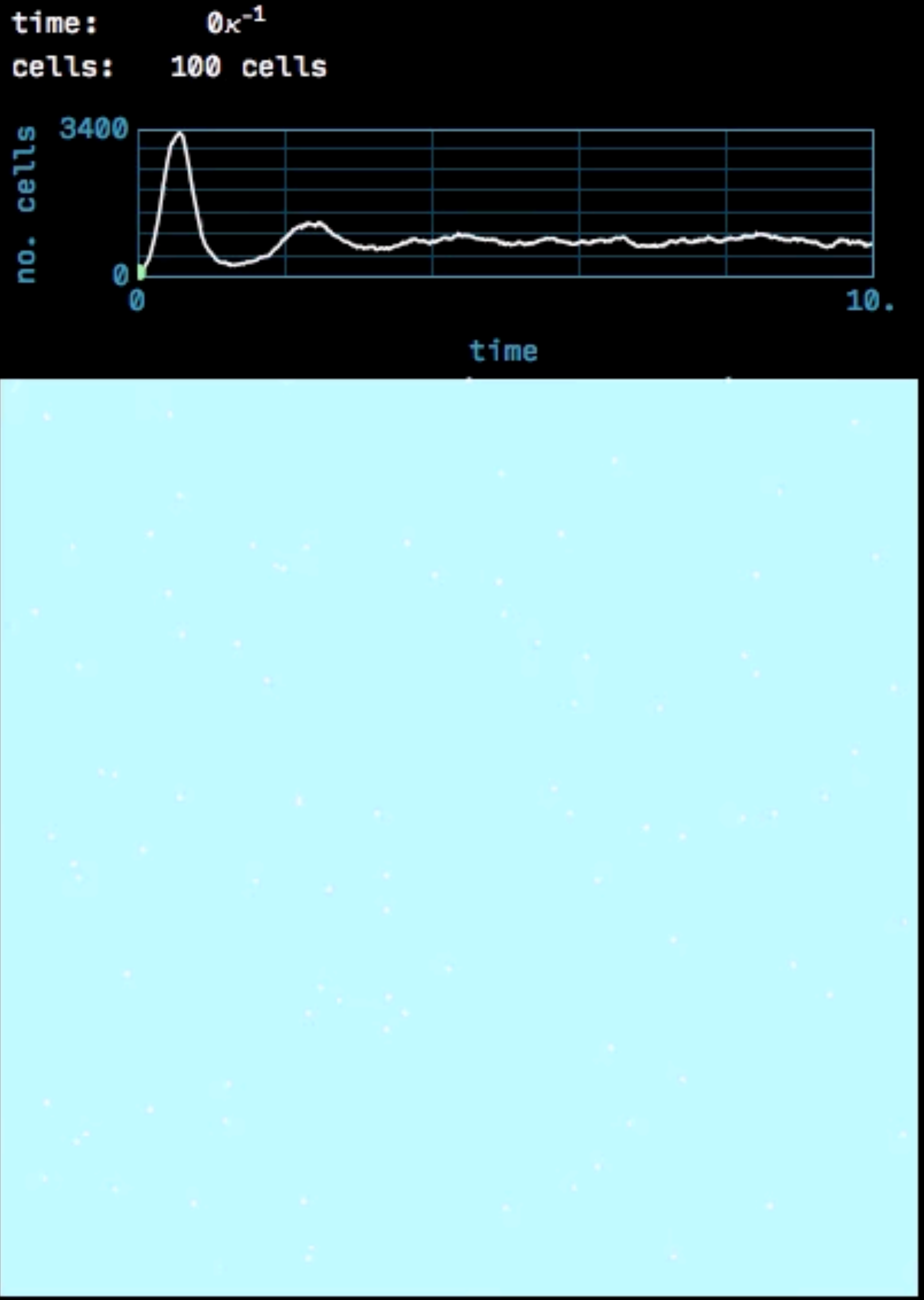
4 5 6 7

Stem cell density: $\rho(\mathbf{x},t) = \sum_i \delta(\mathbf{x}-\mathbf{x}_i(t))$

Jörg et al., *Annu. Rev. Cond. Mat. Phys.* **12**, 135–153 (2021)

Example simulation

Equilibration to homeostasis



Particle-based simulation of stem cells
+
space-discretised simulation of the concentration field

In **homeostasis**, average cell density and average concentration are arranged such that cells duplication and differentiation balance.

$$p \approx 1/2$$

Today's menu: How to approach model calculations

1. **Understanding the statistics of stem cell clones**
   (connection to experiments)
   - Consequences of **stochastic cell fate**
   - How to calculate **clone size distributions**
   - Understanding the **asymptotic** dynamics of clone sizes

2. **Understanding the phase space of the model**
   - Continuum approximation
   - Mean-field theory
   - Steady states
   - Small perturbations

3. **Understanding spatial fluctuations in many-particle systems**
   - How to quantify the spatial distribution of cells
   - How to calculate the structure factor

4. **Understanding transient population behaviour**
   - Recasting the model as a reaction-diffusion system
   - Understanding the type of density fronts
   - Calculating approximations for density front velocities

Main idea:
How to generate limiting cases or simplified versions of our full model that can be addressed analytically.

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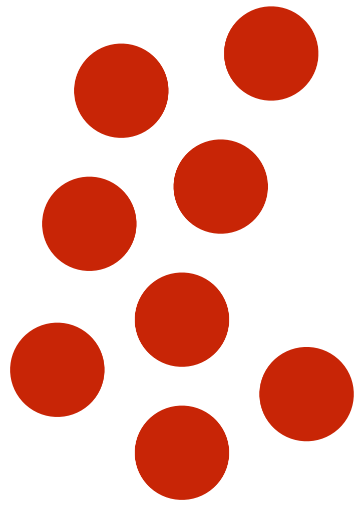
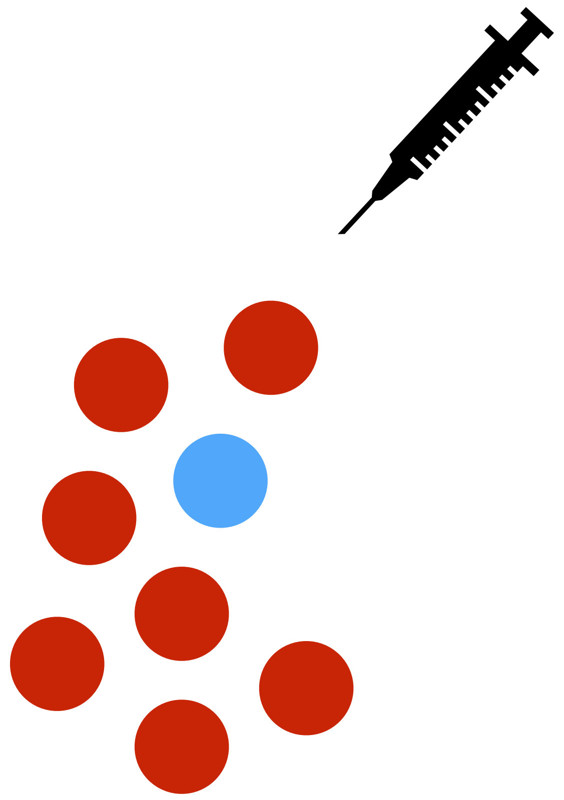
Clonal lineage tracing as a window to stem cell fates

Example:
Inducible labelling system

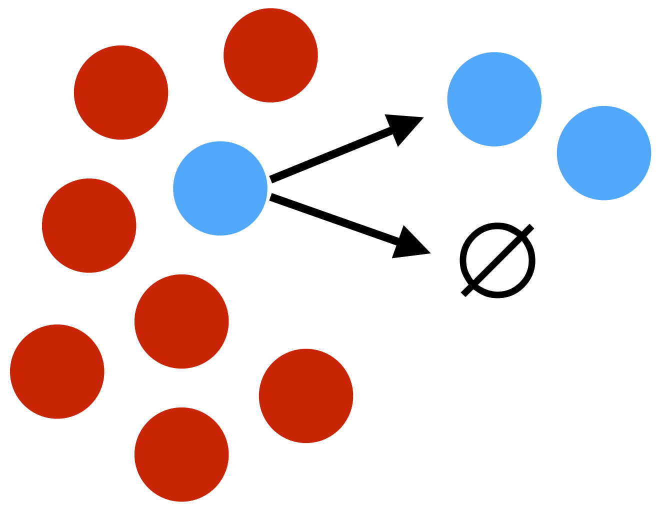
Stem cells



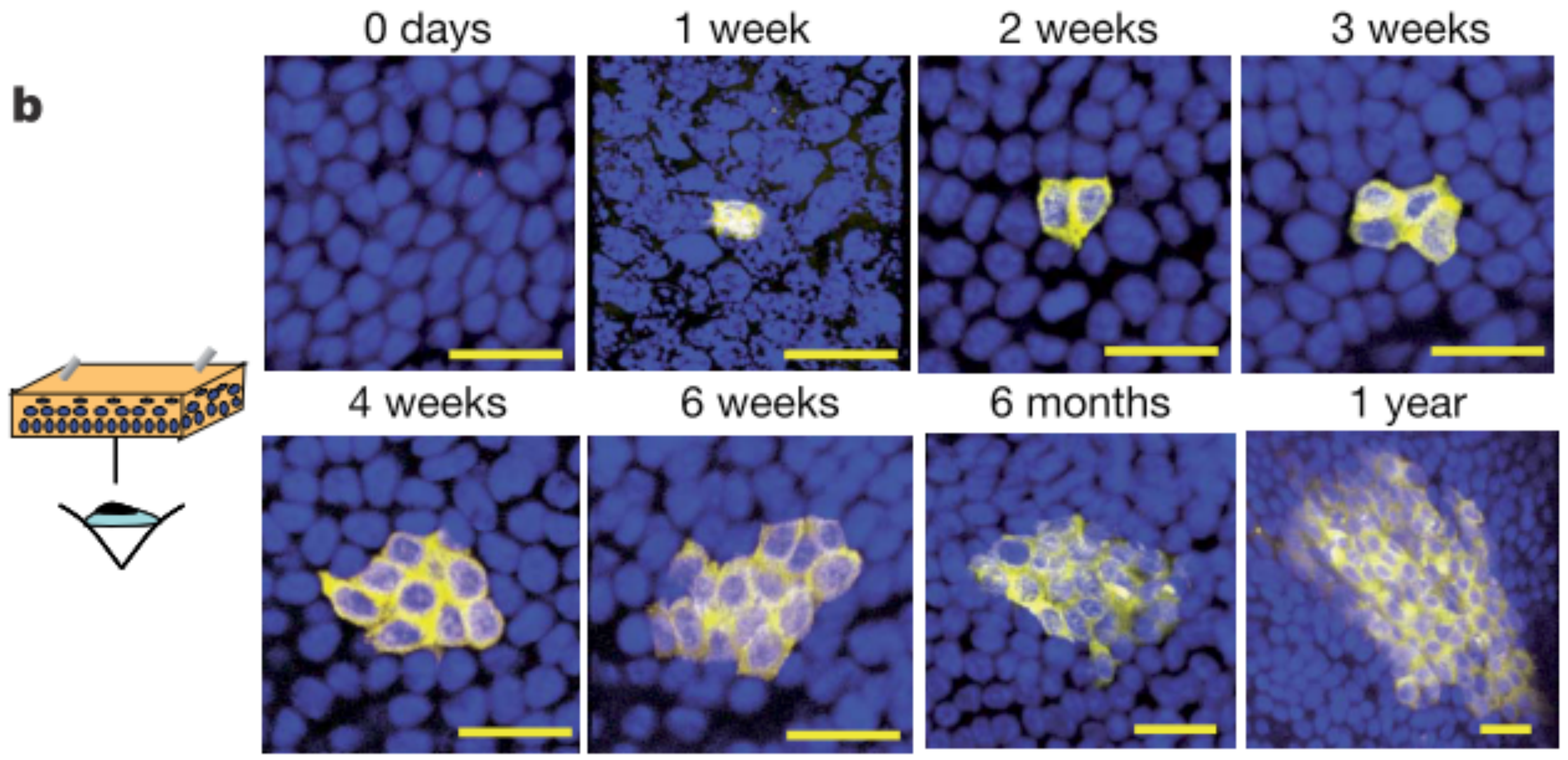
Genetically modified animal carrying a gene encoding fluorescent proteins



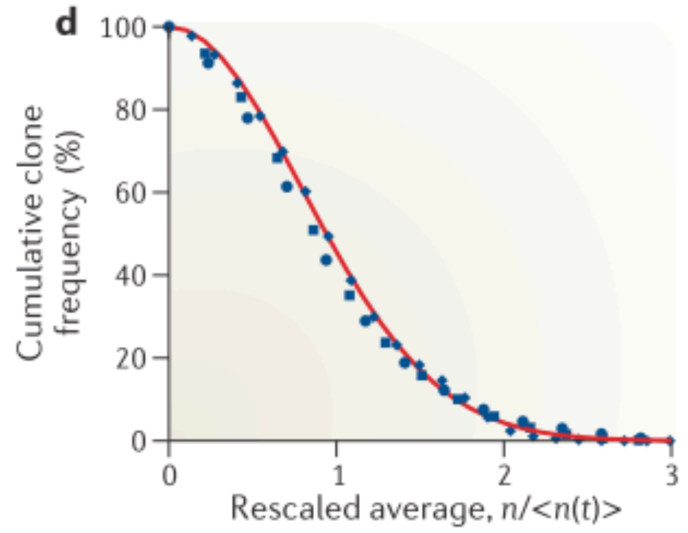
“Induction” of fluorescent gene expression by injection of an external agent

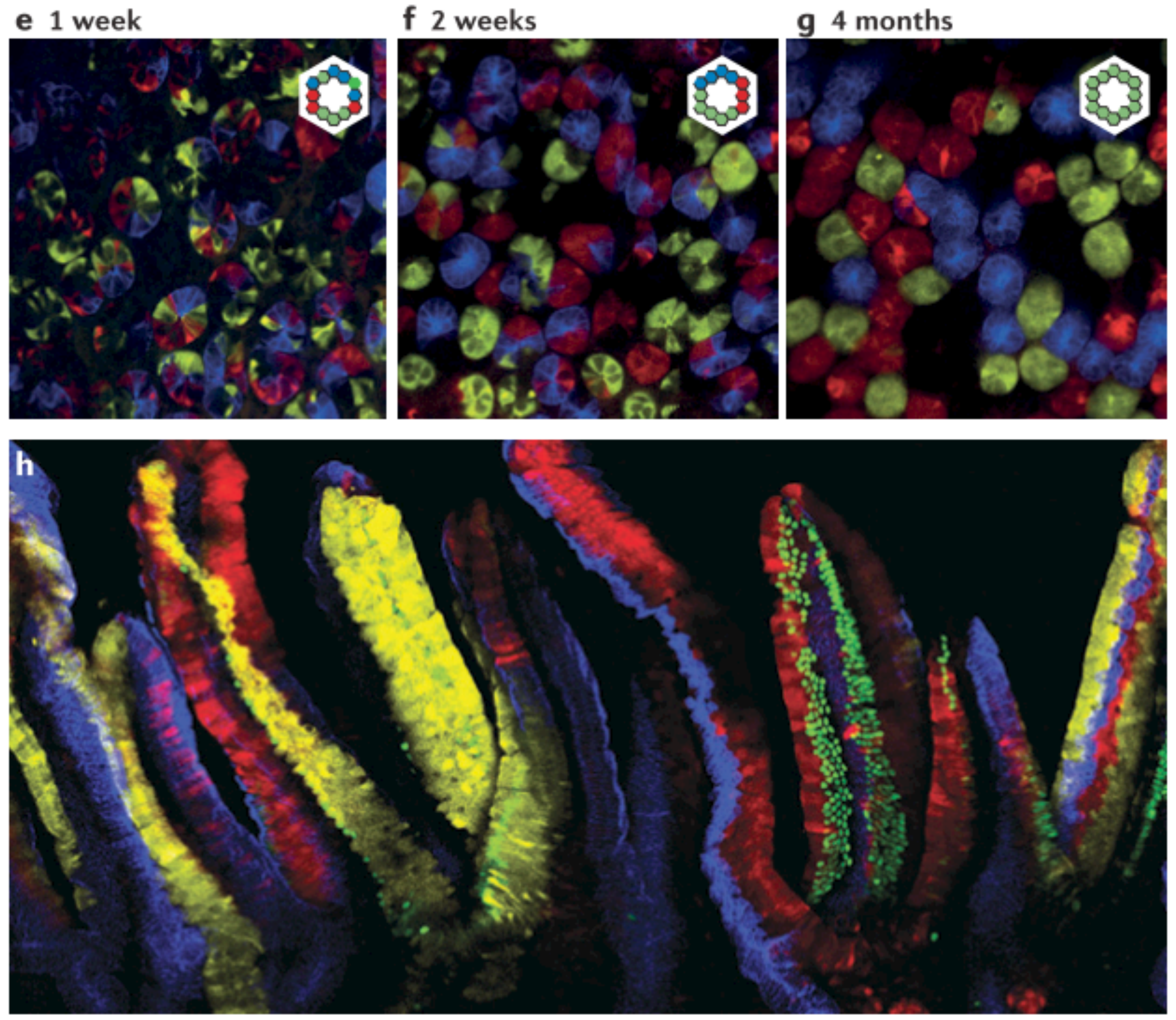


Lineage tracing: tracking the progeny of a single stem cell over time



Example:
Multicolour mosaic labelling





intestinal epithelium

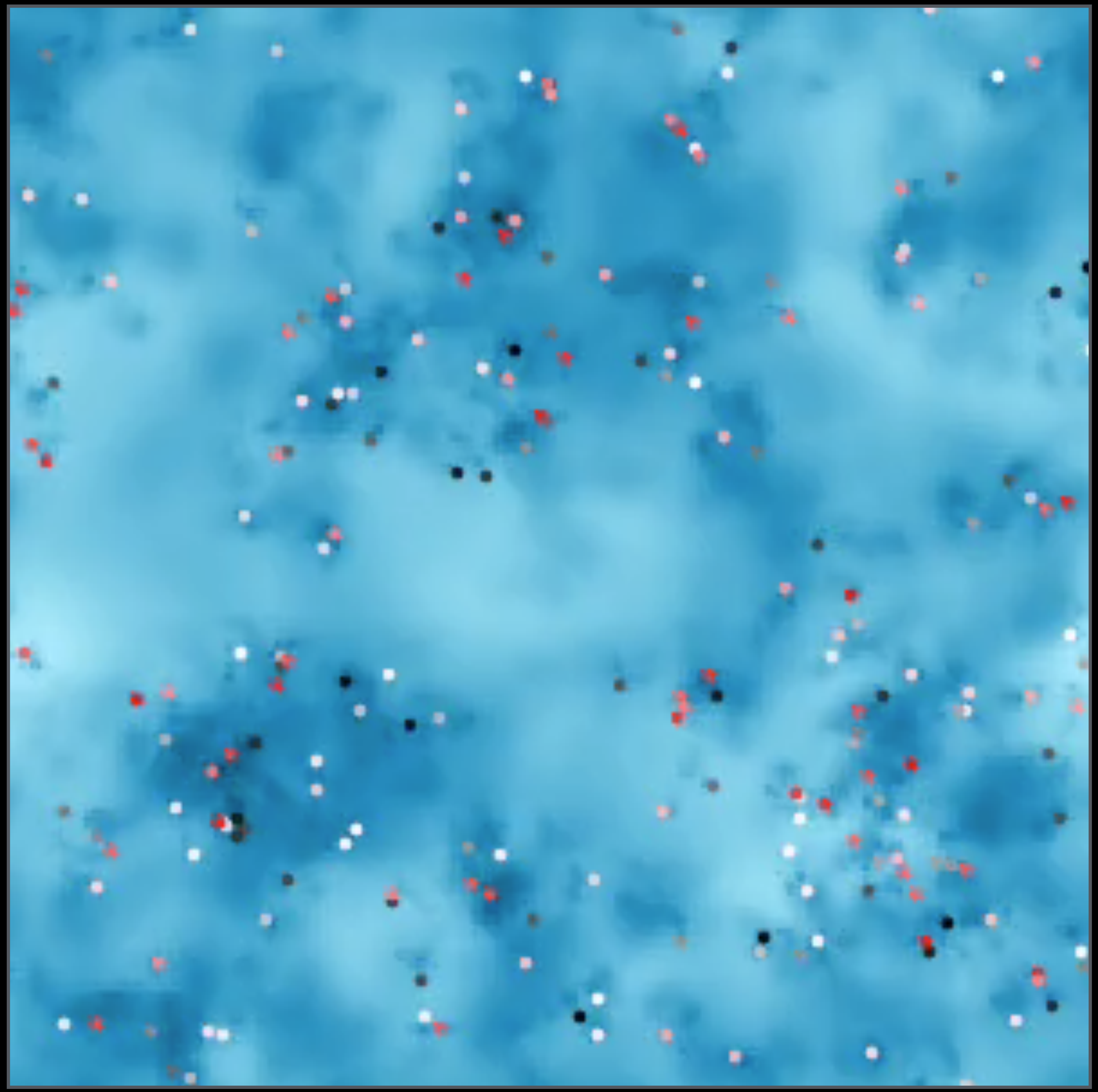
Kretzschmar and Watt, *Cell* **148**, 33–45 (2012); Blanpain and Simons, *Nat. Rev. Mol. Cell Biol.* **14**, 489–502 (2013); Clayton et al., *Nature* **446**, 185–189 (2007)

Long-term dynamics of stem cell clones in homeostasis

Labelled progeny of individual stem cells ("clones") are lost and replaced in a characteristic way until the system reaches monoclonality.

Homeostatic state

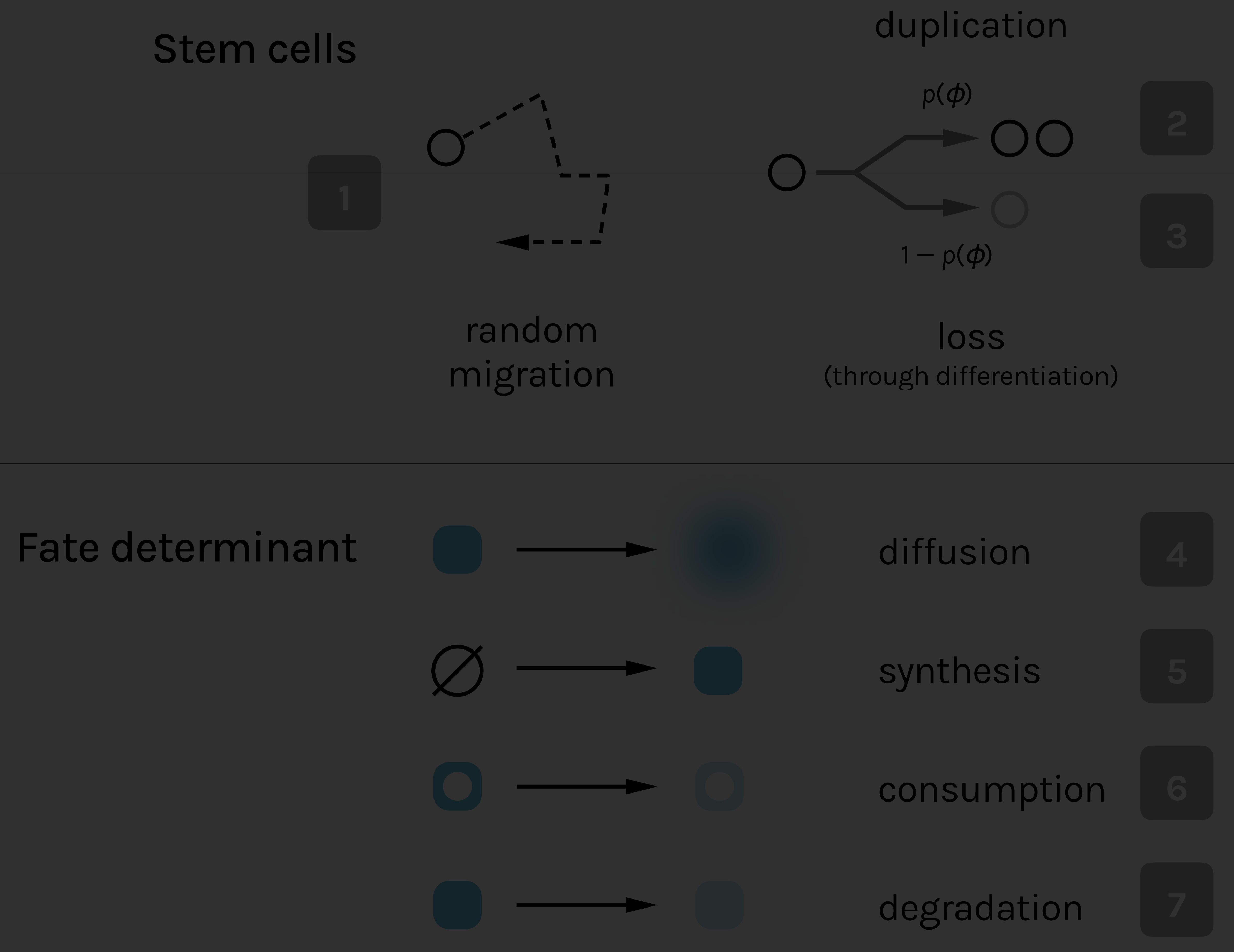
$$p \approx 1/2$$



2D (p.b.c.)

quasi 1D (p.b.c.)

Hybrid cell-based and continuum theory of competition for fate determinants



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2 $$\mathrm{S} \xrightarrow{p\lambda} \mathrm{S} + \mathrm{S}$$

3 $$\mathrm{S} \xrightarrow{(1-p)\lambda} \varnothing$$

Poissonian birth-death processes

Probability for duplication:

$$p \approx 1/2$$

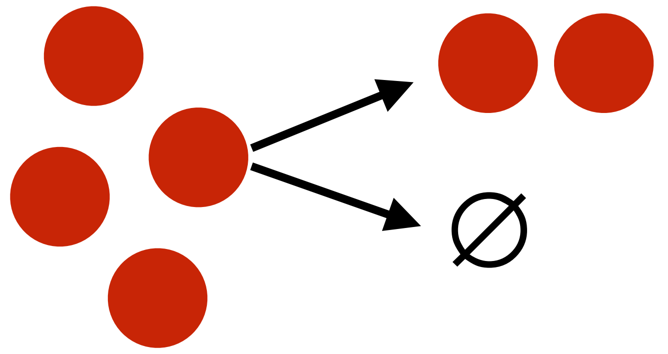
Reaction-diffusion equation

$$\frac{\partial \phi}{\partial t} = D\nabla^2\phi + \nu J(\mathbf{x}) - \gamma Q(\phi, \rho) - \kappa\phi$$

4 5 6 7

Stem cell density: $\rho(x,t) = \sum_i \delta(x - x_i(t))$

Clonal dynamics in zero dimensions



Structureless pool of cells
(cell-intrinsic homeostasis)

$n \ldots$ clone size, $\alpha = p\lambda$ (duplication rate) , $\beta = (1-p)\lambda$ (differentiation rate)

Avg. clone size	Individual clones
$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha n - \beta n$	$\mathrm{S} \to \begin{cases} \mathrm{S}+\mathrm{S} & \text{rate } \alpha \\ \varnothing & \text{rate } \beta \end{cases}$ Poisson processes
$n \propto \mathrm{e}^{(\alpha-\beta)t}$	$\langle n \rangle \propto \mathrm{e}^{(\alpha-\beta)t}$

$\alpha > \beta \rightsquigarrow$ exponential growth of n

$\alpha = \beta \rightsquigarrow n = \text{const.}$ (homeostasis)

$\alpha < \beta \rightsquigarrow$ exponential loss of n

$$\frac{\partial P(n,t)}{\partial t} = \alpha(n-1)P(n-1,t) - \alpha n P(n,t) + \beta(n+1)P(n+1,t) - \beta n P(n,t)$$

$$P(n,0) = \delta_{n,1}$$

Master equation

Solution:

$\alpha \neq \beta$
$(p \neq 1/2)$

$$P(n,t) = \begin{cases} [1-\beta f(t)][1-\alpha f(t)][\alpha f(t)]^{n-1} & n > 0 \\ \beta f(t) & n = 0 \end{cases}$$

$$f(t) = \frac{\mathrm{e}^{(\alpha-\beta)t} - 1}{\alpha \mathrm{e}^{(\alpha-\beta)t} - \beta}$$

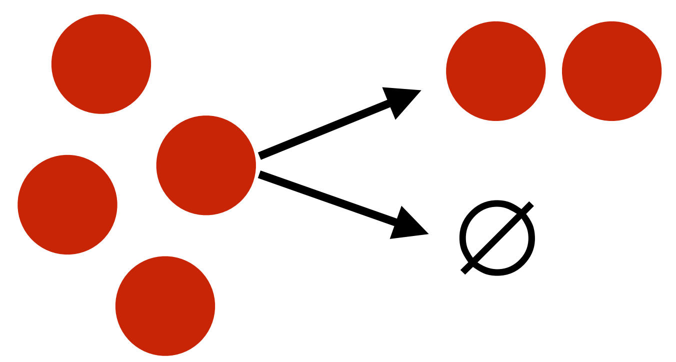
Homeostatic case

$\alpha \to \beta$
$(p \to 1/2)$

$$P(n,t) = \begin{cases} \frac{(\alpha t)^{n-1}}{(1+\alpha t)^{n+1}} & n > 0 \\ \frac{\alpha t}{1+\alpha t} & n = 0 \end{cases}$$

Bailey, *"The elements of stochastic processes"*, John Wiley & Sons (1964)

In experiments, we observe only the **surviving population (*n* ≥ 1)**



Structureless pool of cells
(cell-intrinsic homeostasis)

$\alpha \to \beta$
$(p \to 1/2)$

$$P(n,t) = \begin{cases} \dfrac{(\alpha t)^{n-1}}{(1+\alpha t)^{n+1}} & n > 0 \\ \dfrac{\alpha t}{1+\alpha t} & n = 0 \end{cases}$$

Homeostatic case

$$P_*(n,t) \equiv \frac{P(n,t)}{1-P(0,t)} = \frac{1}{\alpha t}\frac{1}{(1+[\alpha t]^{-1})^n} \to \frac{1}{\alpha t}\mathrm{e}^{-\frac{n}{\alpha t}}$$

Clone size distribution of the surviving population (*n* ≥ 1)

$$\langle n(t)\rangle_* \to \alpha t$$

Average surviving clone size

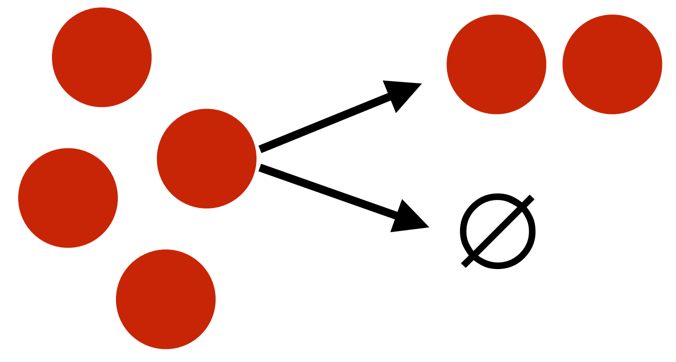
$$P_*(n,t) = \frac{1}{\langle n(t)\rangle_*}\mathrm{e}^{-n/\langle n(t)\rangle_*}$$

Scaling form of the clone size distribution

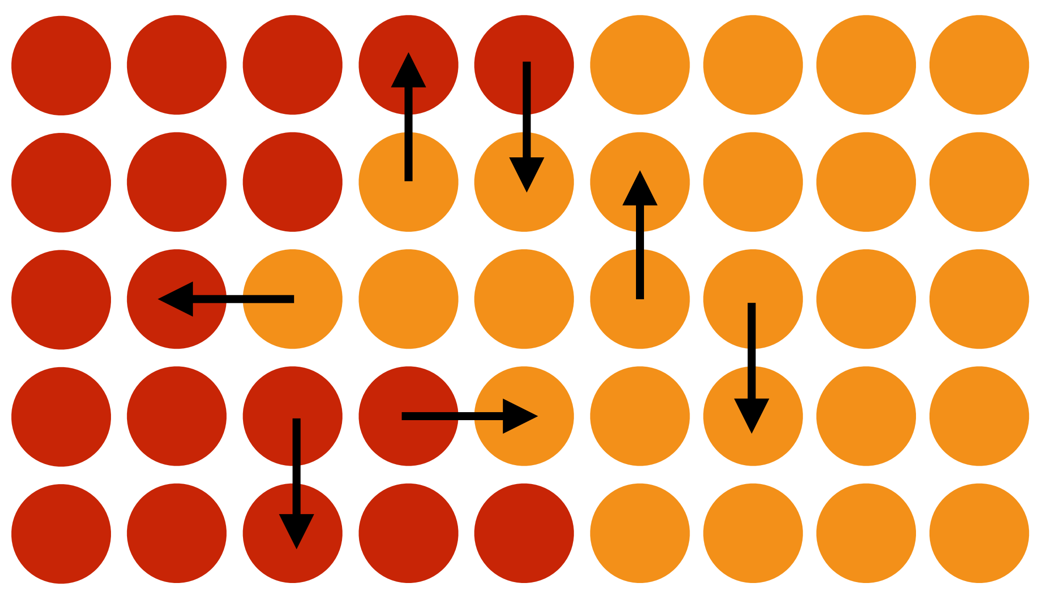
$$C_*(n,t) = \sum_{n' \geq n} P_*(n',t) = \mathrm{e}^{-n/\langle n(t)\rangle_*} = g\left(\frac{n}{\langle n(t)\rangle_*}\right)$$

Cumulative clone size distribution

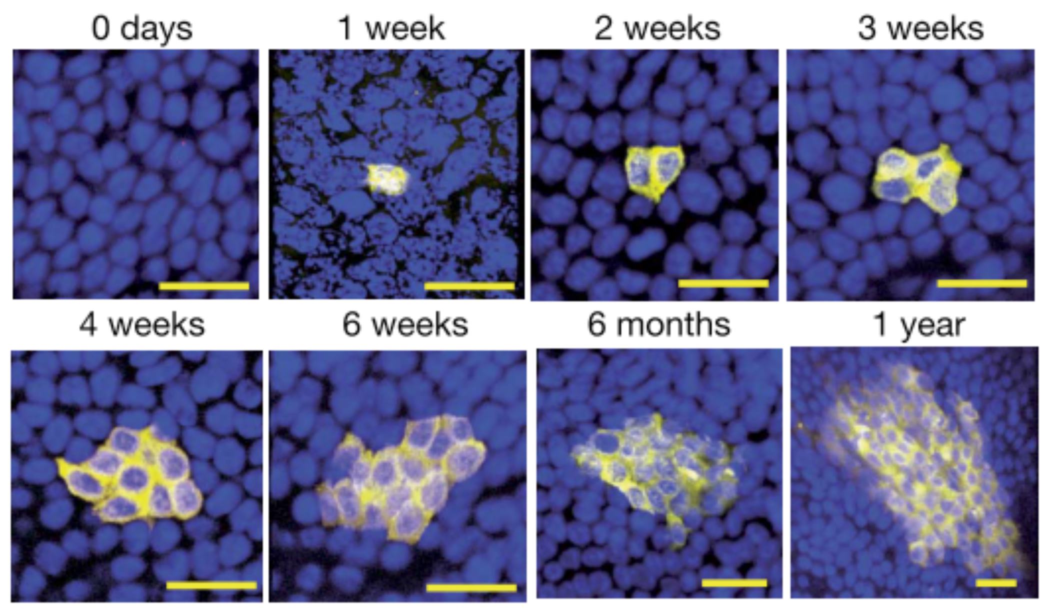
In the homeostatic regime ($p = 1/2$):
Details of the scaling behaviour depend on the dimensionality of the system



Structureless pool of cells
(cell-intrinsic homeostasis)



Spatially extended system
("Voter model") with
stochastic loss and replacement
(cell-extrinsic homeostasis)



Clayton et al., *Nature* **446**, 185–189 (2007)

$$C_*(n,t) = g(n/\langle n \rangle_*)$$

Cumulative clone size distribution of the surviving population

$$\langle n(t) \rangle_* \sim \begin{cases} \sqrt{\lambda t} & d = 1 \\ \lambda t / \ln \lambda t & d = 2 \\ \lambda t & d \geq 3 \end{cases}$$

Mean clone size of the surviving population

$$g(x) = \begin{cases} \mathrm{e}^{-\pi x^2/4} & d = 1 \\ \mathrm{e}^{-x} & d \geq 2 \end{cases}$$

Scaling function

Needs work to derive these behaviours!

Sudbury, *J. Appl. Probab.* **13**, 355–356 (1976)
Sawyer, *J. Appl. Probab.* **16**, 482–495 (1979)
Bramson and Griffeath, *Probability Theory and Related Fields* **53**, 183–196 (1980)

In the homeostatic regime ($p = 1/2$): Details of the scaling behaviour depend on the dimensionality of the system

Cumulative clone size distribution of the surviving population

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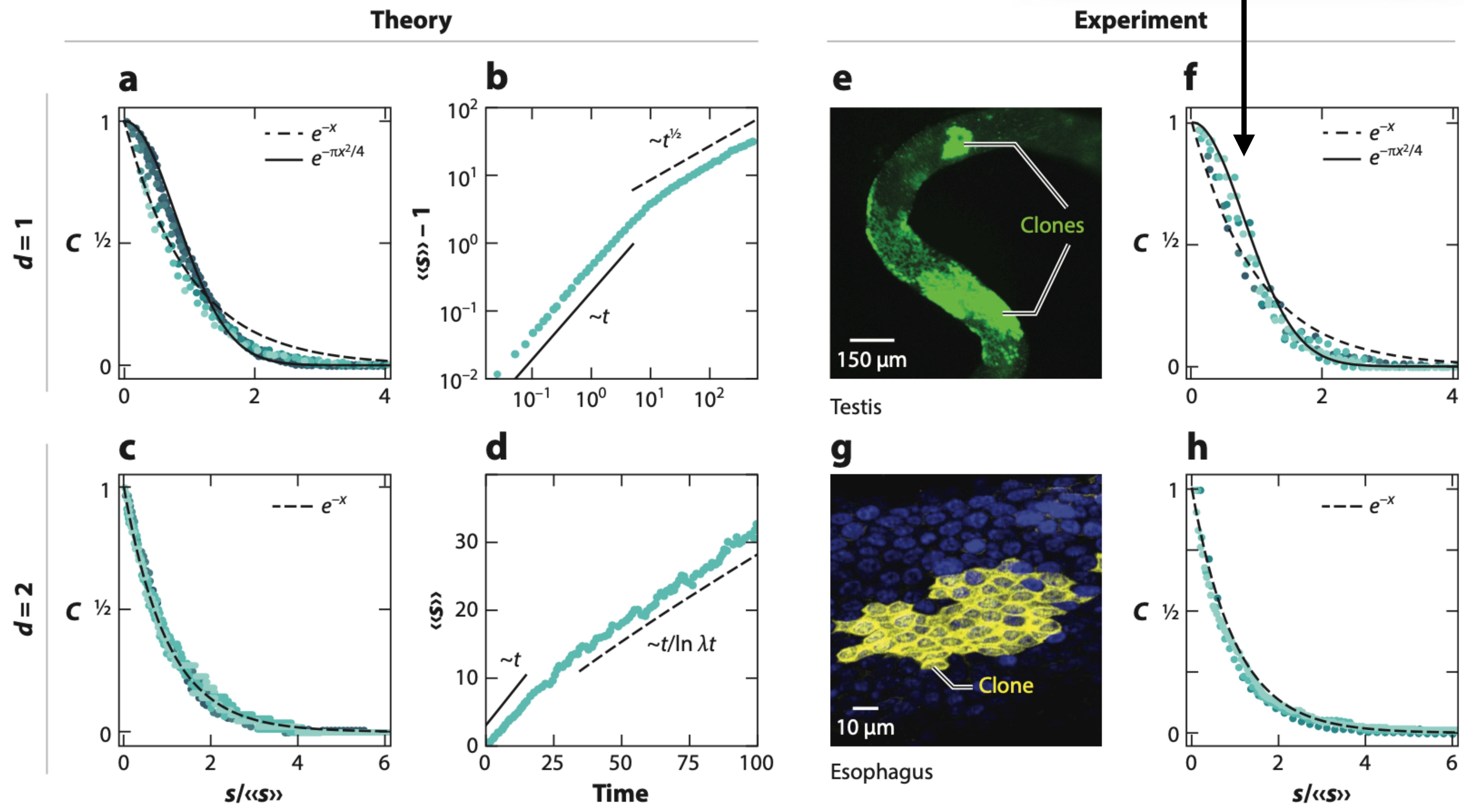
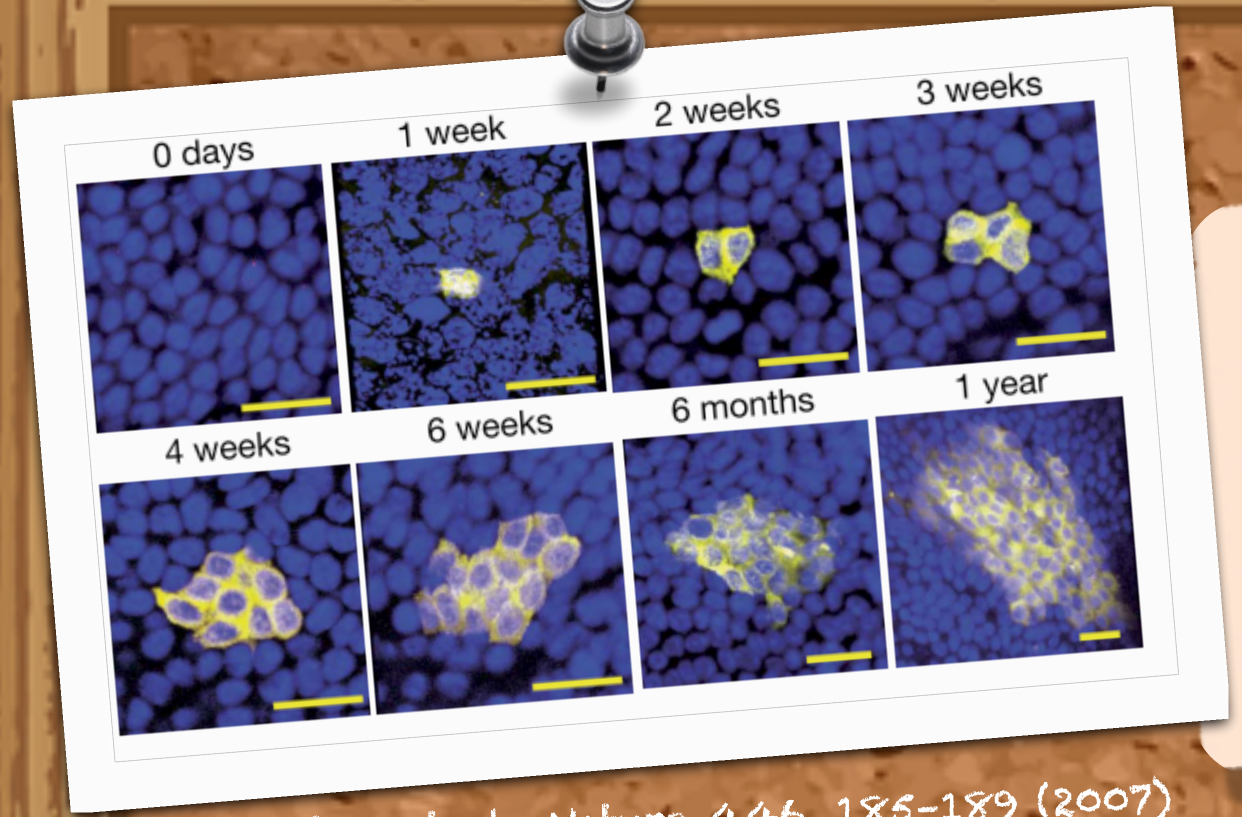
$$g(x) = \begin{cases} \mathrm{e}^{-\pi x^2/4} & d = 1 \\ \mathrm{e}^{-x} & d \geq 2 \end{cases}$$

Rescaled data points from all time points



Hara et al., *Cell Stem Cell* **14**, 658–672 (2014)
Doupé et al., *Science* **337**, 1091–1093 (2012)
Jörg et al., *Annu. Rev. Cond. Mat. Phys.* **12**, 135–153 (2021)

Summary: Clonal dynamics



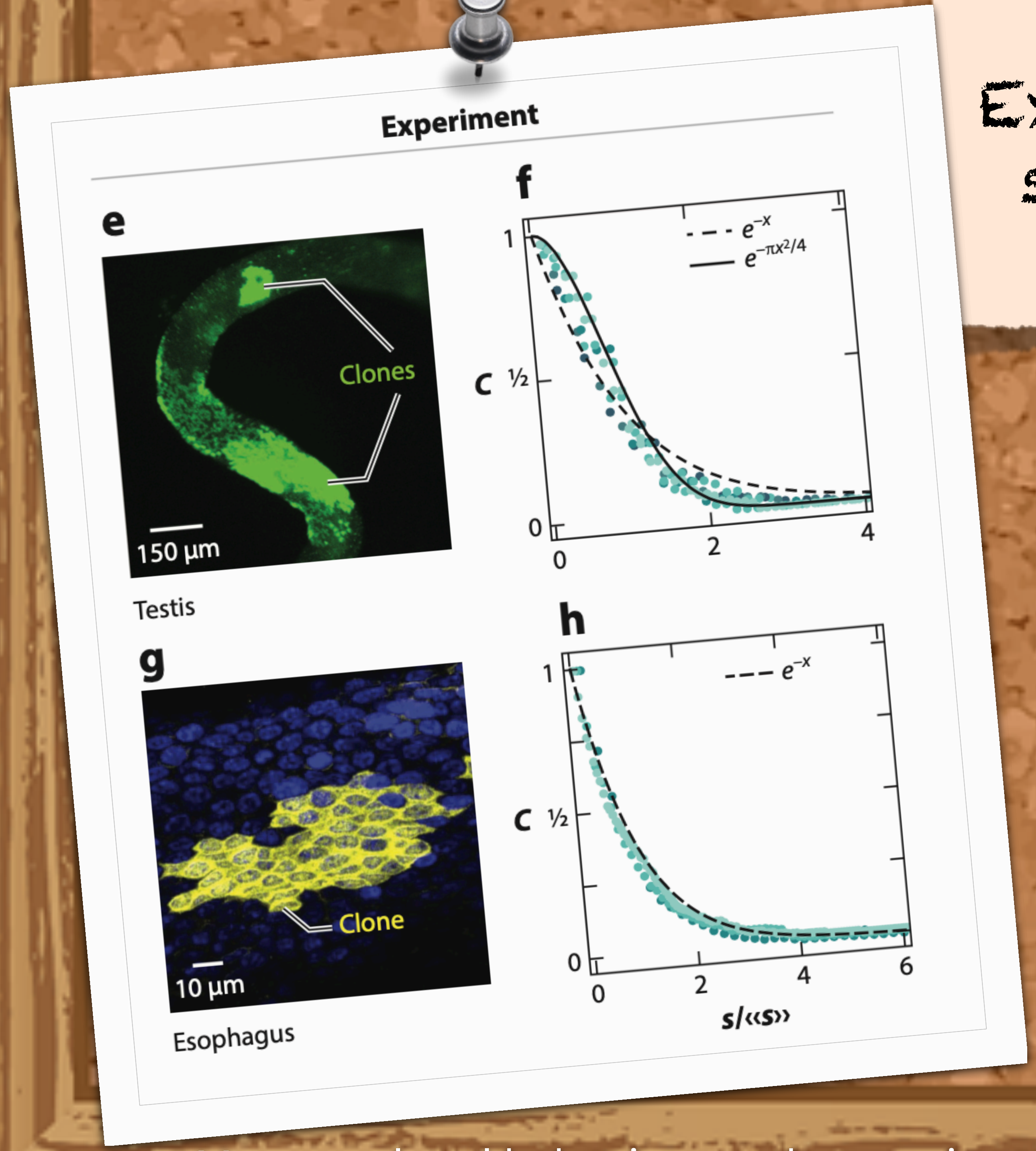
Clayton et al., Nature 446, 185–189 (2007)

Lineage tracing as an experimental window to resolve individual stem cell fate

Theoretical model of stochastic stem cell fate assuming equipotency

$$\mathrm{S} \xrightarrow{p\lambda} \mathrm{S} + \mathrm{S}$$

$$\mathrm{S} \xrightarrow{(1-p)\lambda} \varnothing$$



Experimental clone size distributions

Scaling clone size distributions and average clone size (depends on dimensionality)

$$C_*(n,t) = g(n/\langle n\rangle_*)$$

Corroboration of theoretical assumptions (stochastic fate, equipotency)

More on clonal behaviour and scenarios with competitive advantage of individual clones: Jörg et al., *Annu. Rev. Cond. Mat. Phys.* **12**, 135–153 (2021)

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Deriving a continuum approximation of our hybrid model

Hybrid particle-based and continuum theory models are hard to treat analytically.

Let's try to approximate it by a stochastic field theory.

$$\mathbf{x}_1, \ldots, \mathbf{x}_{N(t)} \to \rho(\mathbf{x}, t) = \sum_i \delta(\mathbf{x} - \mathbf{x}_i(t))$$

—> describe particles by fields.

$$\mathrm{S} \xrightarrow{p\lambda} \mathrm{S} + \mathrm{S}$$

$$\frac{\mathrm{d}\mathbf{x}_i}{\mathrm{d}t} = \sqrt{2\eta}\boldsymbol{\xi}_i(t)$$

$$\mathrm{S} \xrightarrow{(1-p)\lambda} \varnothing$$

Density representation of random walks
Dean, *J. Phys. A* 29 (1999)

System-size expansion
See e.g., v. Kampen's
"Stochastic Processes in Physics and Chemistry"

$$\frac{\partial \rho}{\partial t} = \eta \boldsymbol{\nabla}^2 \rho + \boldsymbol{\nabla} \cdot \sqrt{2\eta\rho}\boldsymbol{\xi} + \lambda[2h(\phi) - 1]\rho + \sqrt{\lambda\rho}\zeta \ ,$$

Stem cell density

$$\frac{\partial \phi}{\partial t} = D\boldsymbol{\nabla}^2\phi + \nu - \gamma h(\phi)\rho - \kappa\phi$$

Fate determinant concentration

$$h(\phi) = \frac{(\phi/\phi_0)^n}{1 + (\phi/\phi_0)^n}$$

Just our original equation for the diffusible fate determinant – it's already a field.

$$\langle \zeta(t)\zeta(t') \rangle = \delta(t - t')$$
$$\langle \xi^i(t)\xi^j(t') \rangle = \delta_{ij}\delta(t - t')$$

See also: Yamaguchi et al., *Phys. Rev. E* **96**, 012401 (2017)

Helpful limiting case: Steady state in the mean-field limit

$$\frac{\partial \rho}{\partial t} = \eta \nabla^2 \rho + \nabla \cdot \sqrt{2\eta\rho}\boldsymbol{\xi} + \lambda[2h(\phi) - 1]\rho + \sqrt{\lambda\rho}\zeta \ ,$$

Stem cell density

$$\frac{\partial \phi}{\partial t} = D\nabla^2 \phi + \nu - \gamma h(\phi)\rho - \kappa\phi$$

Fate determinant concentration

$$h(\phi) = \frac{(\phi/\phi_0)^n}{1 + (\phi/\phi_0)^n}$$

"Mean-field" approximation in the absence of noise (well-mixed reactor at high densities):

$$\rho(\mathbf{x}, t) = \rho(t) \qquad \boldsymbol{\xi} \to 0$$
$$\phi(\mathbf{x}, t) = \phi(t) \qquad \zeta \to 0$$

$$\dot{\rho} = \lambda[2h(\phi) - 1]\rho$$
$$\dot{\phi} = \nu - \gamma h(\phi)\rho - \kappa\phi$$

ODE system

Two steady states (stability mutually exclusive):

$$\rho(t) = \text{const.}$$
$$\phi(t) = \text{const.}$$

homeostasis

$$\begin{pmatrix} \rho_* \\ \phi_* \end{pmatrix} = \begin{pmatrix} 2(\nu - \kappa\phi_0)/\gamma \\ \phi_0 \end{pmatrix}$$

synthesis rate

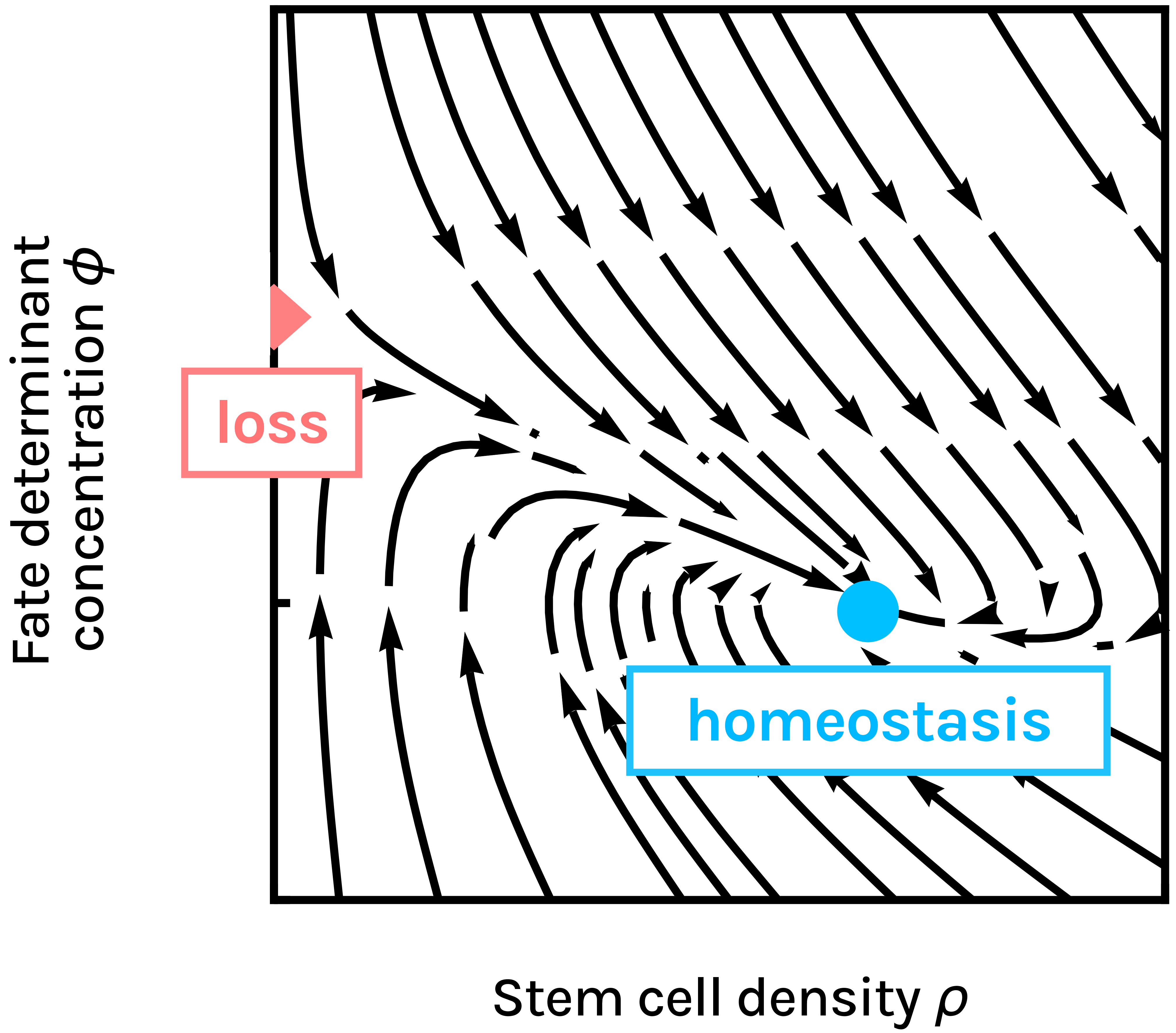
concentration for which h = 1/2

loss

$$\begin{pmatrix} \rho_\times \\ \phi_\times \end{pmatrix} = \begin{pmatrix} 0 \\ \nu/\kappa \end{pmatrix}$$

balance of synthesis and degradation

Competition for fate determinants leads to a state where self-renewal and differentiation exactly balance



homeostasis

$$\begin{pmatrix} \rho^* \\ \phi^* \end{pmatrix} = \begin{pmatrix} 2(\nu - \kappa\phi_0)/\gamma \\ \phi_0 \end{pmatrix}$$

loss

$$\begin{pmatrix} \rho^\times \\ \phi^\times \end{pmatrix} = \begin{pmatrix} 0 \\ \nu/\kappa \end{pmatrix}$$

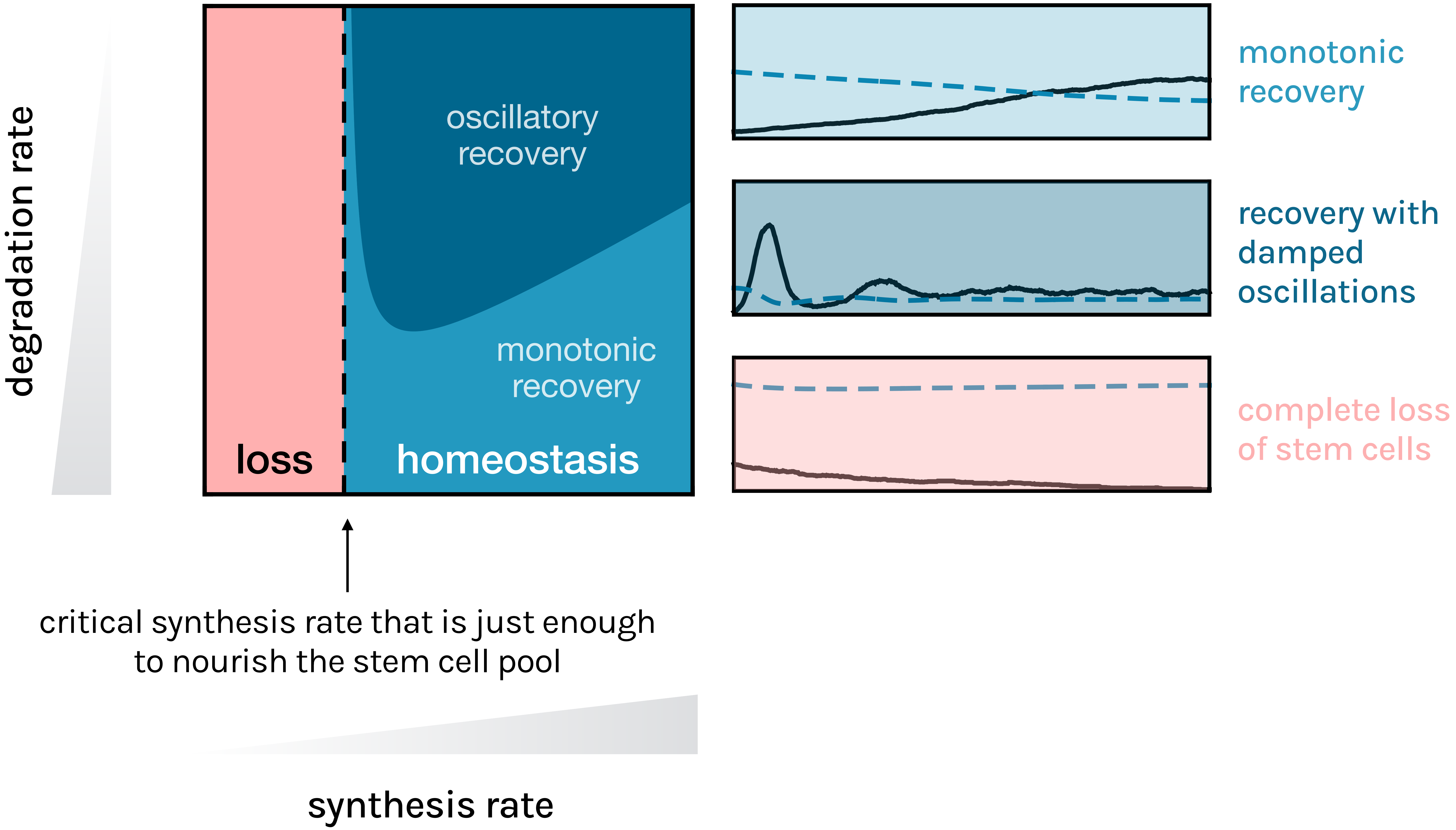
The fate determinant determines whether homeostasis is possible and the mode of recovery

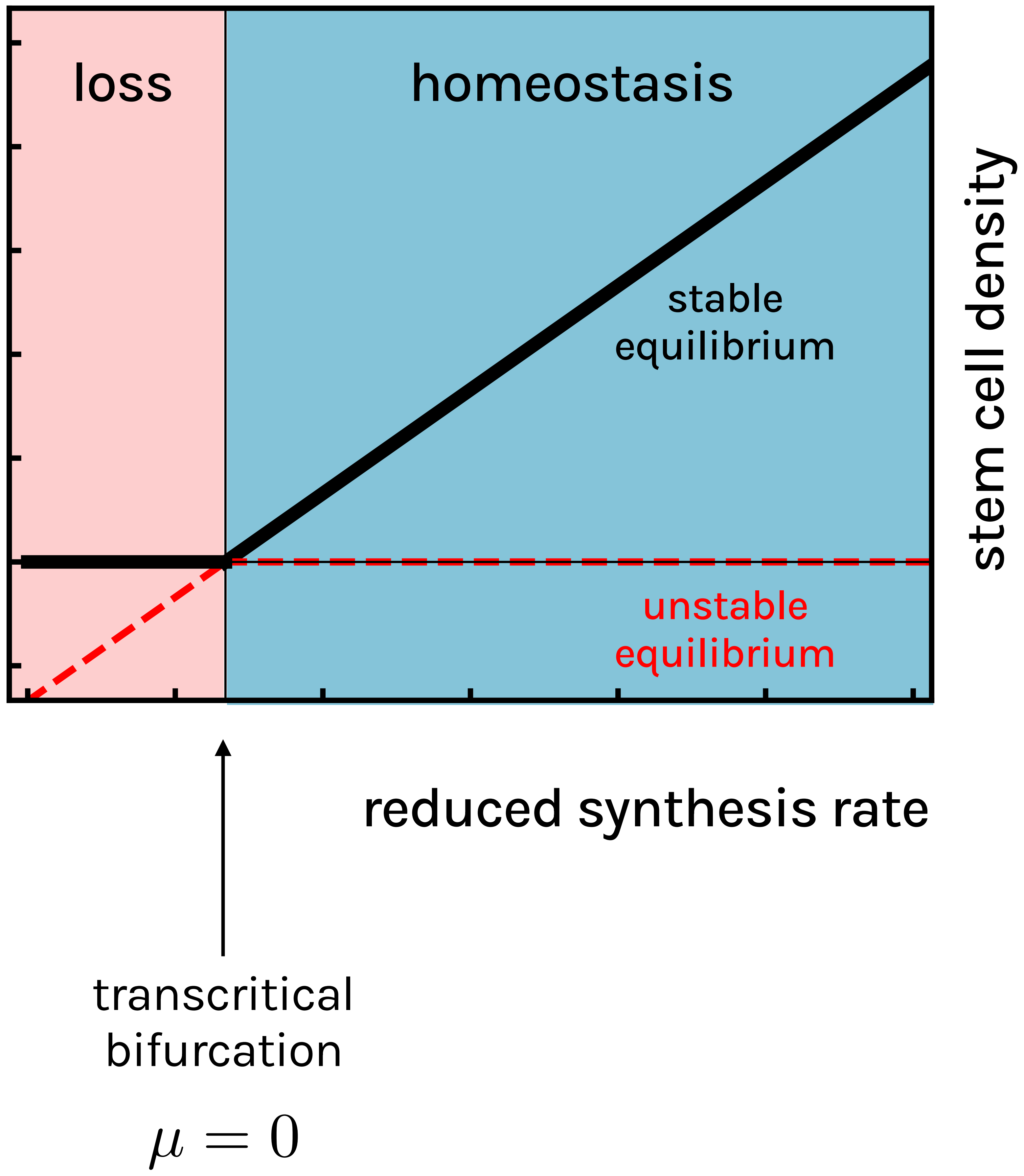
$$\dot{\rho} = \lambda[2h(\phi) - 1]\rho$$
$$\dot{\phi} = \nu - \gamma h(\phi)\rho - \kappa\phi$$

$\mu = \dfrac{\nu - \nu_c}{\nu_c}$ reduced synthesis rate

$\nu_c = \kappa\phi_0$ critical synthesis rate

Standard linear stability analysis:





Summary: Phase space

Hybrid cell-based model

Continuum approximation

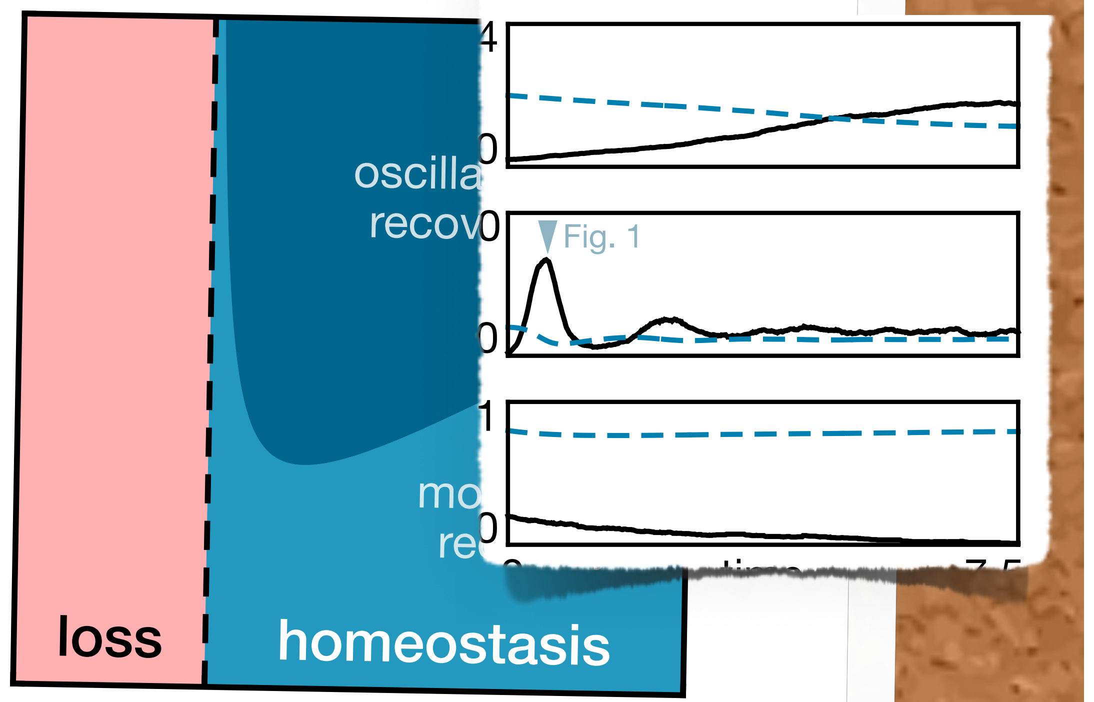
Mean-field ODEs

$$\dot{\rho} = \lambda[2h(\phi) - 1]\rho$$

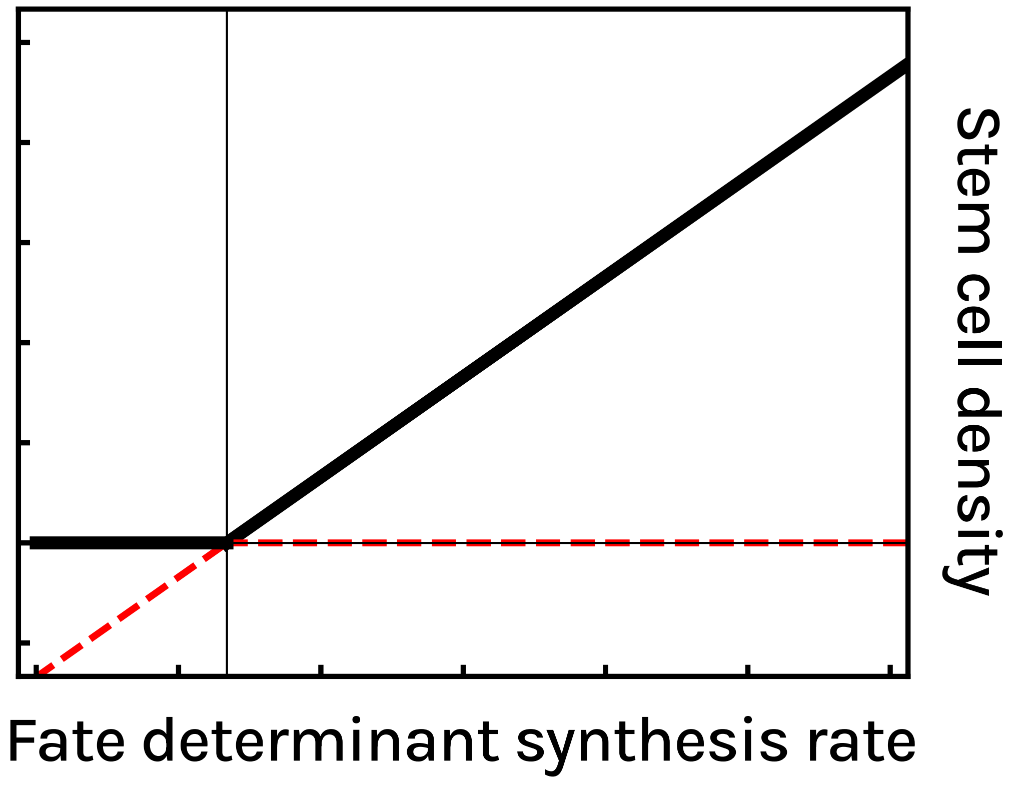
$$\dot{\phi} = \nu - \gamma h(\phi)\rho - \kappa\phi$$

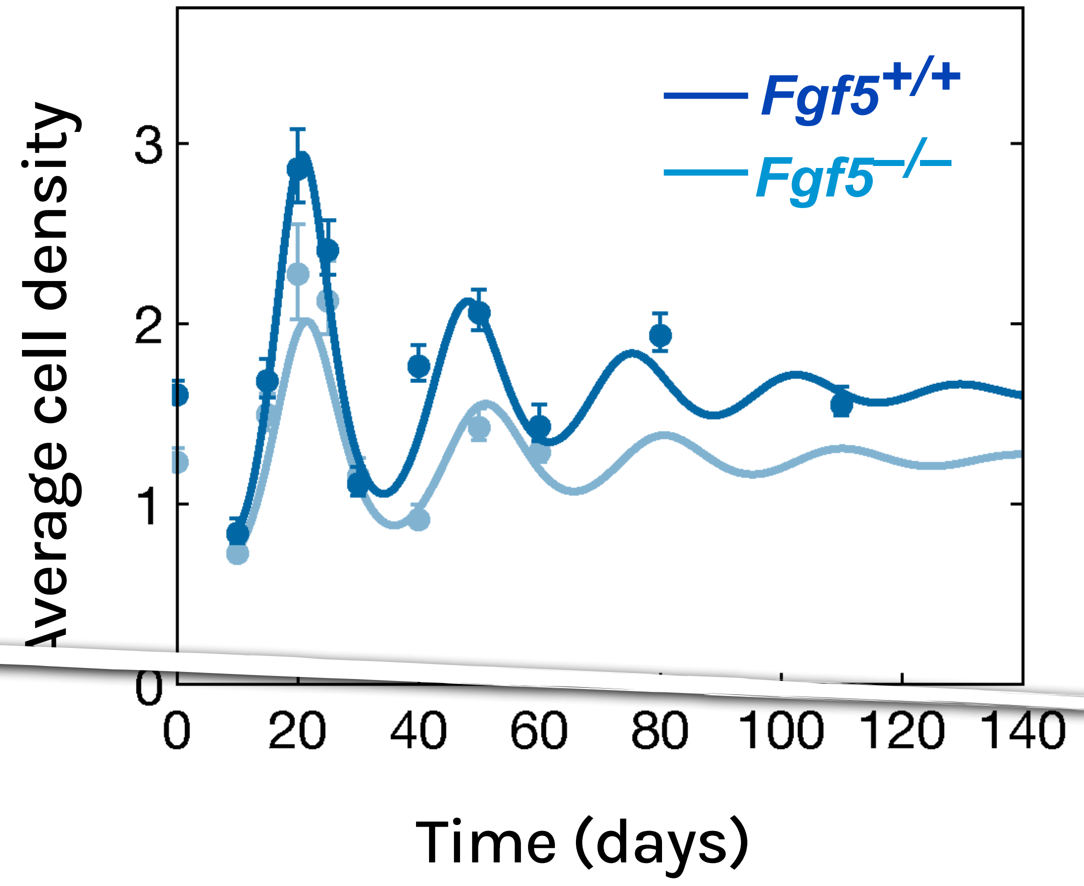
- Perturbation experiments (chemical depletion of stem cells)
- Transgenic animals and mutant with altered synthesis of fate determinants

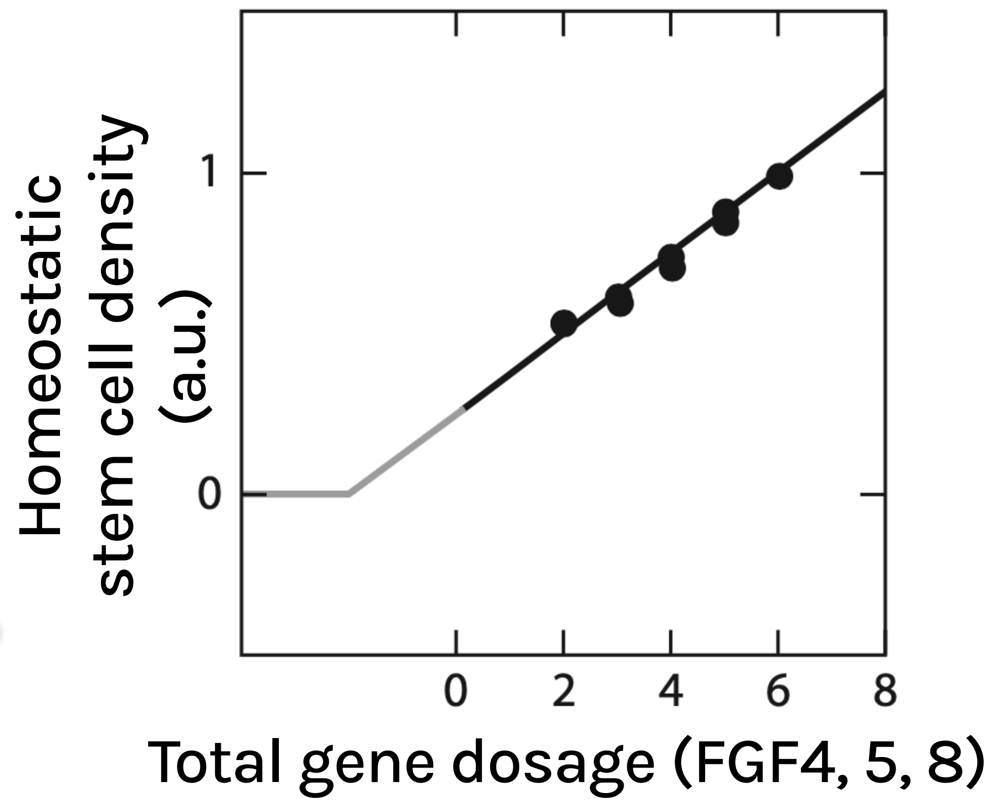
Response to perturbations



Parameter dependence of homeostatic properties







Kitadate et al., *Cell Stem Cell* **24** 1, 79 (2019)

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   - How to calculate the structure factor

4. **Understanding transient population behaviour**
   - Recasting the model as a reaction-diffusion system
   - Understanding the type of density fronts
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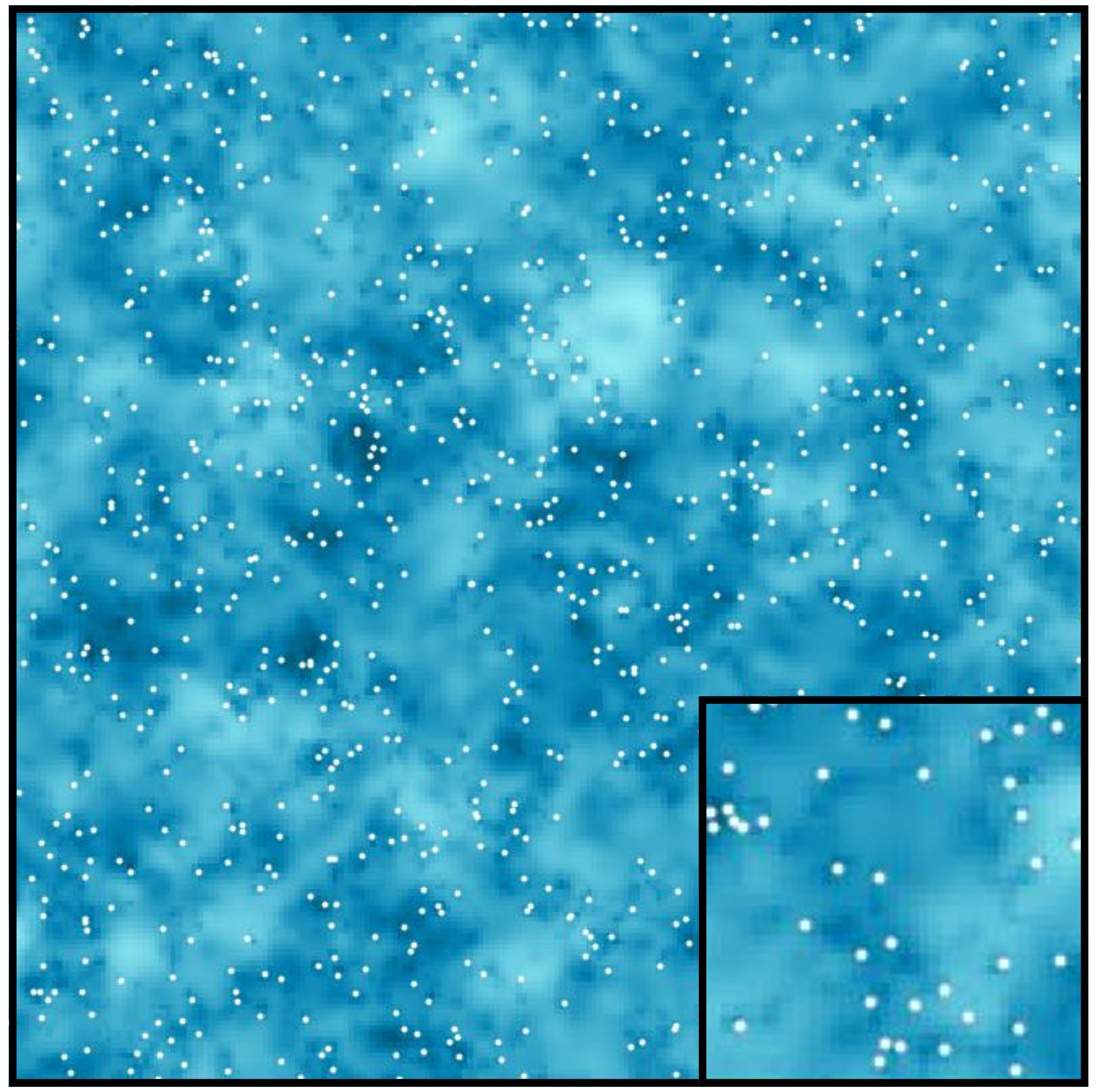
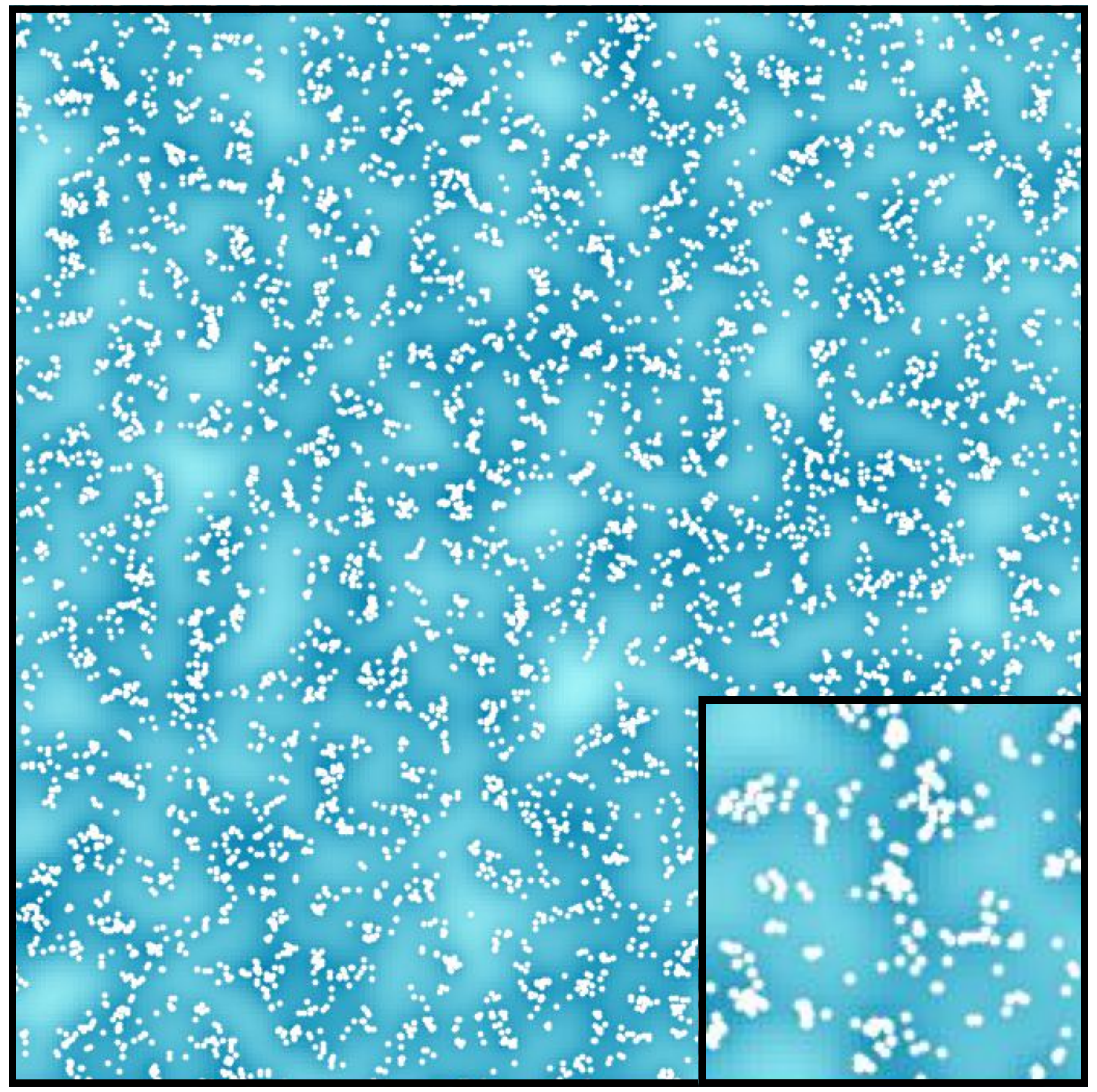
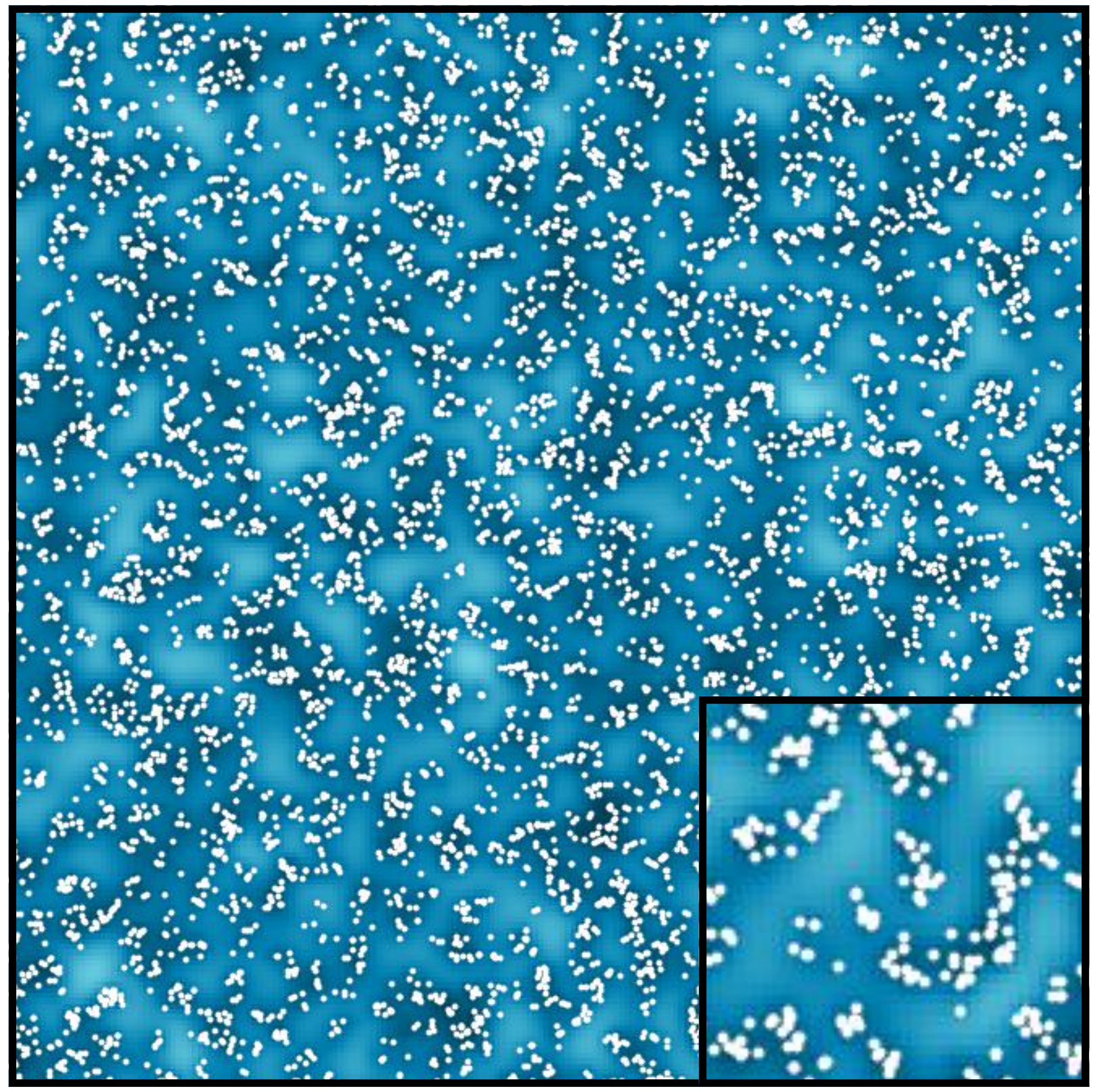
The spatial distribution of stem cells reflects the relevant time scales in the system



slow diffusion
high motility
slow proliferation



fast diffusion
low motility
fast proliferation



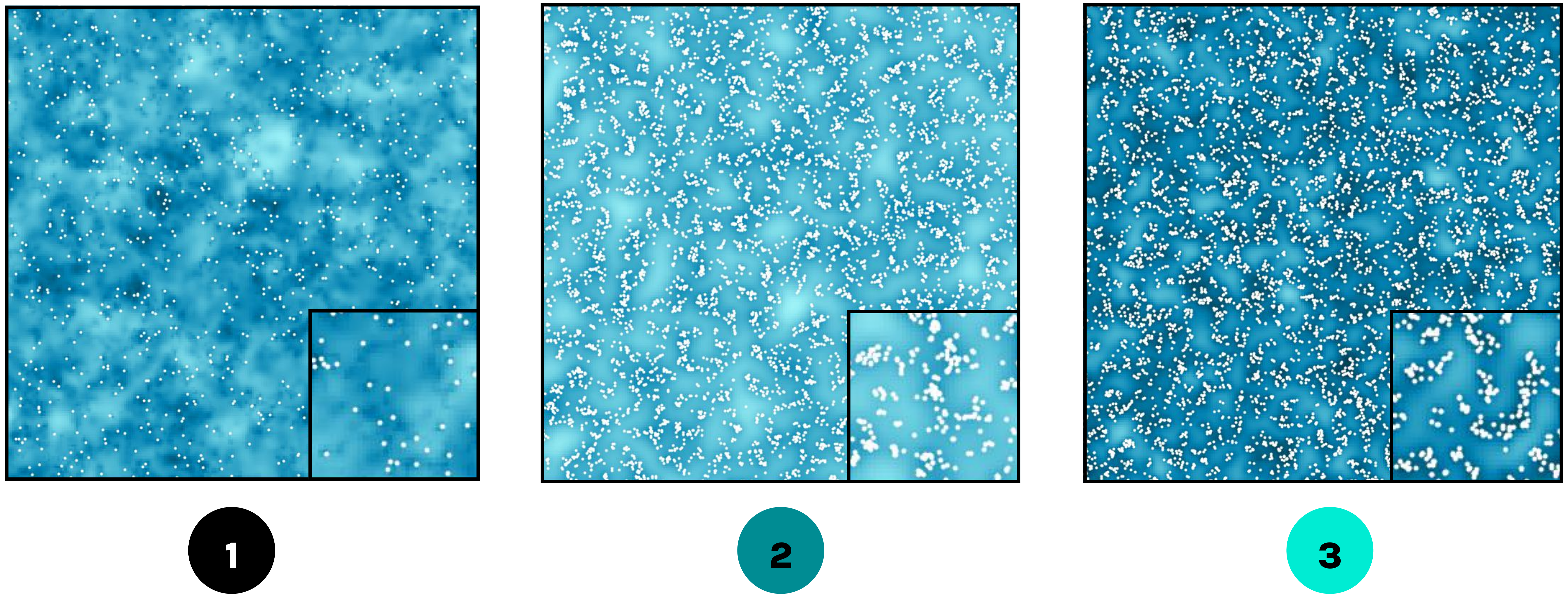
intermediate diffusion
intermediate motility
very fast proliferation

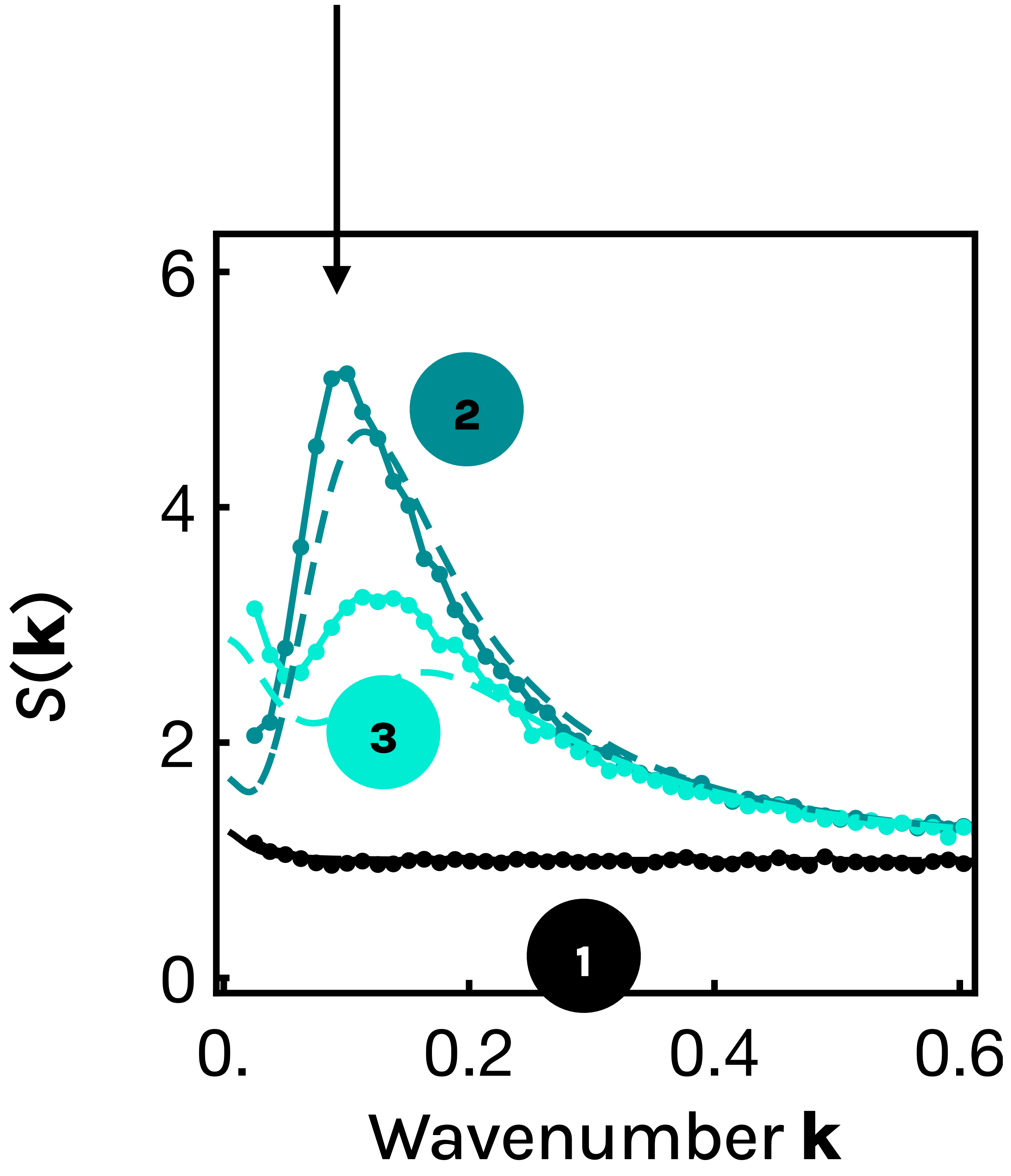
The spatial distribution of stem cells reflects the relevant time scales in the system

$$S(\mathbf{k}) = \left\langle \frac{1}{N} \left| \sum_i e^{i\mathbf{k}\cdot\mathbf{x}_i} \right|^2 \right\rangle$$

Static structure factor

Peaks of the structure factor reveal characteristic cluster length scales.





Jörg et al., *Annu. Rev. Cond. Mat. Phys.* **12**, 135–153 (2021)

Structure factor computation

Exercise [use $\rho(\mathbf{x},t) = \sum_i \delta(\mathbf{x} - \mathbf{x}_i(t))$ and $\delta\rho(\mathbf{x},t) = \rho(\mathbf{x},t) - \rho_*$.]

$$S(\mathbf{k}) = \left\langle \frac{1}{N} \left| \sum_i \mathrm{e}^{\mathrm{i}\mathbf{k}\cdot\mathbf{x}_i} \right|^2 \right\rangle = \frac{1}{\rho_*} \int \mathrm{d}^2\mathbf{x}\, \mathrm{e}^{-\mathrm{i}\mathbf{k}\cdot\mathbf{x}} \langle \delta\rho(\mathbf{0},t)\delta\rho(\mathbf{x},t)\rangle$$

Computation programme

1. Linearise the system about a reference steady state.
2. Solve the linearised system in Fourier space.
3. Calculate correlation functions in Fourier space.
4. Partial backtransform.

Structure factor computation
Step 1: Linearising the system about the homeostatic steady state

$$\frac{\partial \rho}{\partial t} = \eta \nabla^2 \rho + \nabla \cdot \sqrt{2\eta\rho}\boldsymbol{\xi} + \lambda[2h(\phi) - 1]\rho + \sqrt{\lambda\rho}\zeta \ ,$$

Stem cell density

$$\frac{\partial \phi}{\partial t} = D\nabla^2\phi + \nu - \gamma h(\phi)\rho - \kappa\phi$$

Fate determinant concentration

$$h(\phi) = \frac{(\phi/\phi_0)^n}{1 + (\phi/\phi_0)^n}$$

$$\langle \zeta(t)\zeta(t')\rangle = \delta(t - t')$$

$$\langle \xi^i(t)\xi^j(t')\rangle = \delta_{ij}\delta(t - t')$$

Homogeneous homeostatic state

$$\begin{pmatrix} \rho^* \\ \phi^* \end{pmatrix} = \begin{pmatrix} 2(\nu - \kappa\phi_0)/\gamma \\ \phi_0 \end{pmatrix}$$

Ansatz

$$\rho(\mathbf{x}, t) = \rho_* + \delta\rho$$

$$\phi(\mathbf{x}, t) = \phi_* + \delta\phi$$

$$\frac{\partial}{\partial t}\delta\rho \approx \eta\nabla^2\delta\rho + \alpha\,\delta\phi + \sqrt{2\eta\rho_*}\nabla \cdot \boldsymbol{\xi} + \sqrt{\lambda\rho_*}\zeta$$

$$\frac{\partial}{\partial t}\delta\phi \approx D\nabla^2\delta\phi - \beta\,\delta\phi - \frac{\Omega^2}{\alpha}\delta\rho$$

$$\alpha = \frac{\lambda n \rho_*}{2\phi_0} \qquad \beta = \left(1 + \frac{n\mu}{2}\right)\kappa \qquad \Omega = \sqrt{\frac{n\mu\lambda\kappa}{2}}$$

Expansion to leading order in the fluctuations

(gets rid of any multiplicative noise terms)

Structure factor computation

Step 2: Solving the linearised system in Fourier space

$$\frac{\partial}{\partial t}\delta\rho \approx \eta\boldsymbol{\nabla}^2\delta\rho + \alpha\,\delta\phi + \sqrt{2\eta\rho_*}\boldsymbol{\nabla}\cdot\boldsymbol{\xi} + \sqrt{\lambda\rho_*}\zeta$$

$$\frac{\partial}{\partial t}\delta\phi \approx D\boldsymbol{\nabla}^2\delta\phi - \beta\,\delta\phi - \frac{\Omega^2}{\alpha}\delta\rho$$

Expansion to leading order in the fluctuations

$$\hat{f}(\mathbf{k},\omega) = \int \mathrm{d}^2\mathbf{x}\,\mathrm{d}t\,\mathrm{e}^{\mathrm{i}(\omega t - \mathbf{k}\cdot\mathbf{x})} f(\mathbf{x},t)$$

Fourier convention

$$\mathrm{i}\omega\widehat{\delta\rho}(\mathbf{k},\omega) = \eta\mathbf{k}^2\widehat{\delta\rho}(\mathbf{k},\omega) - \alpha\widehat{\delta\phi}(\mathbf{k},\omega) - \hat{\psi}(\mathbf{k},\omega)$$

$$\mathrm{i}\omega\widehat{\delta\phi}(\mathbf{k},\omega) = (D\mathbf{k}^2 + \beta)\widehat{\delta\phi}(\mathbf{k},\omega) + \alpha^{-1}\Omega^2\widehat{\delta\phi}(\mathbf{k},\omega)$$

Fourier-transformed system

$$\hat{\psi}(\mathbf{k},\omega) = \sqrt{\rho_*}\int \mathrm{d}^2\mathbf{x}\,\mathrm{d}t\,\mathrm{e}^{\mathrm{i}(\omega t - \mathbf{k}\cdot\mathbf{x})}\left[\sqrt{2\eta}\boldsymbol{\nabla}\cdot\boldsymbol{\xi}(\mathbf{x},t) + \sqrt{\lambda}\zeta(\mathbf{x},t)\right]$$

Fourier-transformed aggregate noise

Structure factor computation

Step 3: Calculate the correlation functions

$$\widehat{\delta\rho}(\mathbf{k},\omega) = \frac{-\mathrm{i}\omega + D\mathbf{k}^2 + \beta}{\Delta(\mathbf{k},\omega)}\hat{\psi}(\mathbf{k},\omega) \qquad \widehat{\delta\phi}(\mathbf{k},\omega) = -\frac{\gamma}{2\Delta(\mathbf{k},\omega)}\hat{\psi}(\mathbf{k},\omega)$$

Solution of the Fourier-transformed system

$$\Delta(\mathbf{k},\omega) = (-\mathrm{i}\omega + \eta\mathbf{k}^2)(-\mathrm{i}\omega + D\mathbf{k}^2 + \beta) + \Omega^2$$

$$\langle\hat{\psi}(\mathbf{k},\omega)\hat{\psi}(\mathbf{k}',\omega')\rangle = (2\pi)^3\rho_*(2\eta\mathbf{k}^2 + \lambda)\delta(\mathbf{k}+\mathbf{k}')\delta(\omega+\omega')$$

Correlation function of the FT'ed noise

$$\langle\widehat{\delta\rho}(\mathbf{k},\omega)\widehat{\delta\rho}(\mathbf{k}',\omega')\rangle = 8\pi^3\rho_*[\omega^2 + (D\mathbf{k}^2+\beta)^2]\Lambda(\mathbf{k},\omega)\delta(\mathbf{k}+\mathbf{k}')\delta(\omega+\omega')$$

$$\langle\widehat{\delta\phi}(\mathbf{k},\omega)\widehat{\delta\phi}(\mathbf{k}',\omega')\rangle = 2\pi^3\rho_*\gamma^2\Lambda(\mathbf{k},\omega)\delta(\mathbf{k}+\mathbf{k}')\delta(\omega+\omega')$$

Correlation functions of the FT'ed fields

$$\Lambda(\mathbf{k},\omega) = \frac{2\eta\mathbf{k}^2 + \lambda}{(\omega^2 + \eta^2\mathbf{k}^4)(\omega^2 + [D\mathbf{k}^2+\beta]^2) - 2\Omega^2[\omega^2 - \eta\mathbf{k}^2(D\mathbf{k}^2+\beta)] + \Omega^4}$$

Structure factor computation
Part IV: Transform back to real time

$$(2\pi)^3\delta(\mathbf{k}+\mathbf{k}')\delta(\omega+\omega')\hat{S}(\mathbf{k},\omega) = \langle\widehat{\delta\rho}(\mathbf{k},\omega)\widehat{\delta\rho}(\mathbf{k}',\omega')\rangle$$

$$S(\mathbf{k}) = \frac{1}{2\pi\langle\rho\rangle}\int \mathrm{d}\omega\,\hat{S}(\mathbf{k},\omega)$$

$$S(\mathbf{k}) = \frac{1}{\sqrt{32}}\frac{2\eta\mathbf{k}^2+\lambda}{\beta(\mathbf{k})}\frac{\omega^+(\mathbf{k})-\omega^-(\mathbf{k})}{(D+\eta)\mathbf{k}^2+\sigma}\frac{2(D\mathbf{k}^2+\sigma)+\omega^+(\mathbf{k})\omega^-(\mathbf{k})}{\eta\mathbf{k}^2(D\mathbf{k}^2+\sigma)+\Omega^2}$$

Final result for the structure factor

$$\omega^\pm(\mathbf{k}) = \sqrt{\eta^2\mathbf{k}^4+(D\mathbf{k}^2+\sigma)^2 \pm [\eta\mathbf{k}^2+D\mathbf{k}^2+\sigma]\beta(\mathbf{k})-2\Omega^2}$$

$$\beta(\mathbf{k}) = \sqrt{(-\eta\mathbf{k}^2+D\mathbf{k}^2+\sigma)^2-4\Omega^2}$$

Bifurcation parameter ↓

$$\sigma = \kappa + \frac{\mu}{2}\lambda \qquad \Omega = \sqrt{\frac{\mu}{2}\lambda}$$

Analytical calculation of the structure factor yields further insights … or does it?

$$S(\mathbf{k}) = \frac{1}{\sqrt{32}} \frac{2\eta\mathbf{k}^2 + \lambda}{\beta(\mathbf{k})} \frac{\omega^+(\mathbf{k}) - \omega^-(\mathbf{k})}{(D+\eta)\mathbf{k}^2 + \sigma} \frac{2(D\mathbf{k}^2 + \sigma) + \omega^+(\mathbf{k})\omega^-(\mathbf{k})}{\eta\mathbf{k}^2(D\mathbf{k}^2 + \sigma) + \Omega^2}$$

$$\omega^\pm(\mathbf{k}) = \sqrt{\eta^2\mathbf{k}^4 + (D\mathbf{k}^2 + \sigma)^2 \pm [\eta\mathbf{k}^2 + D\mathbf{k}^2 + \sigma]\beta(\mathbf{k}) - 2\Omega^2}$$

$$\beta(\mathbf{k}) = \sqrt{(-\eta\mathbf{k}^2 + D\mathbf{k}^2 + \sigma)^2 - 4\Omega^2}$$

Bifurcation parameter

↓

$$\sigma = \kappa + \frac{\mu}{2}\lambda \qquad \Omega = \sqrt{\frac{\mu}{2}}\lambda$$

Limiting cases

- Pure random walkers

$$S(\mathbf{k}) = 1$$

- Pure random walkers with engrained birth-death criticality (p = 1/2)

$$S(\mathbf{k}) = 1 + \frac{\lambda}{2\eta\mathbf{k}^2}$$

(divergent for $|\mathbf{k}| \to 0$, “neutral clustering”)

Houchmandzadeh, *Phys. Rev. E* **66**, 052902 (2002)

- Full model with dynamic homeostasis (small length scale behaviour)

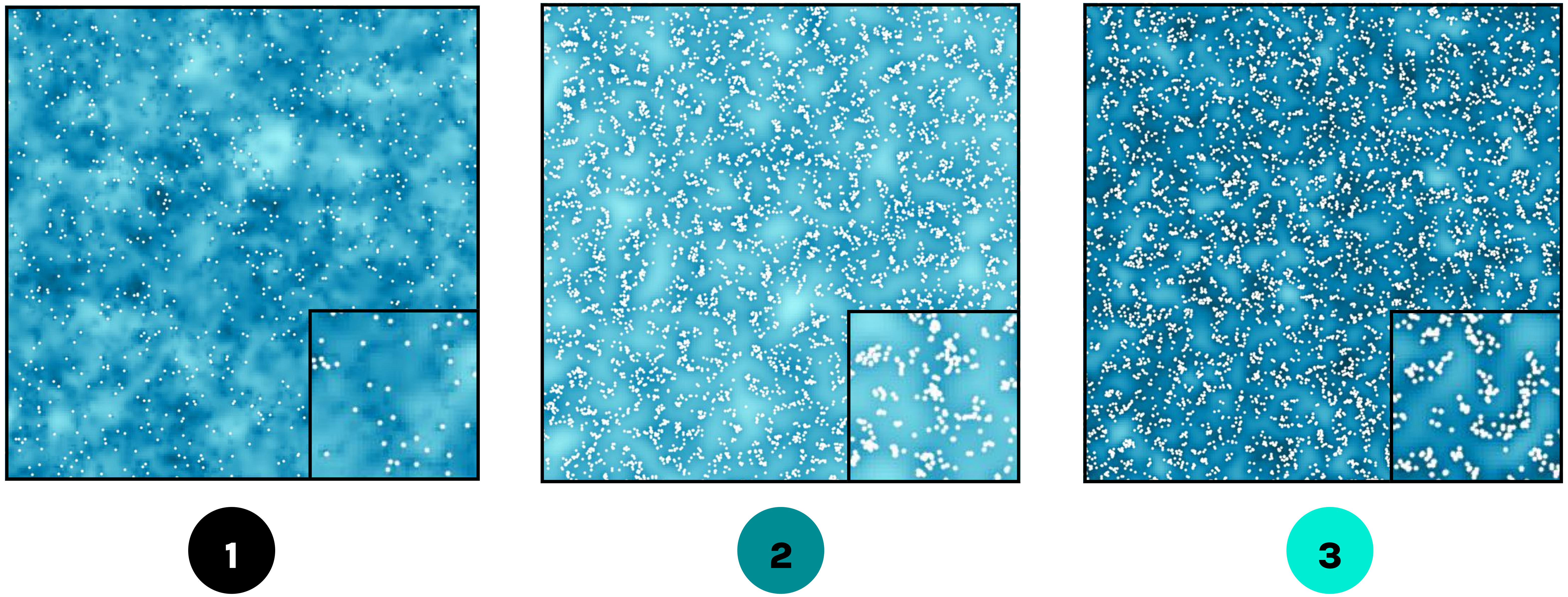
$$S(\mathbf{k}) = 1 + \frac{\lambda}{2\eta\mathbf{k}^2} + \frac{\lambda\kappa n\mu}{2} \frac{1}{(D\eta + \eta^2)\mathbf{k}^4} + O(\mathbf{k}^{-6})$$

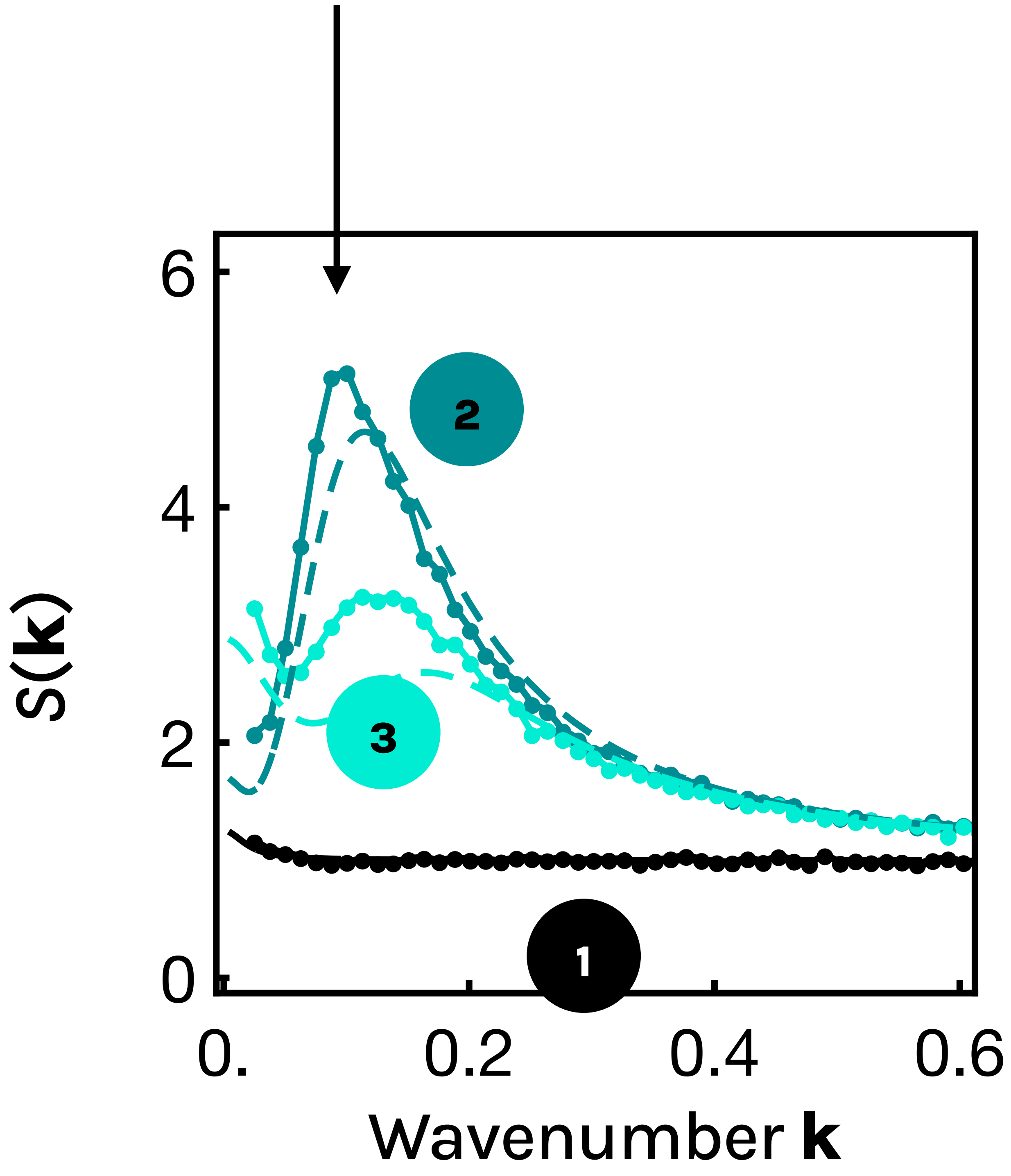
(Full expression finite for $|\mathbf{k}| \to 0$.)

A structure factor analysis reveals clustering phenomena and allows to quantify them in experiment and theory

$$S(\mathbf{k}) = \frac{1}{\sqrt{32}} \frac{2\eta\mathbf{k}^2 + \lambda}{\beta(\mathbf{k})} \frac{\omega^+(\mathbf{k}) - \omega^-(\mathbf{k})}{(D+\eta)\mathbf{k}^2 + \sigma} \frac{2(D\mathbf{k}^2 + \sigma) + \omega^+(\mathbf{k})\omega^-(\mathbf{k})}{\eta\mathbf{k}^2(D\mathbf{k}^2 + \sigma) + \Omega^2}$$

Peaks of the structure factor reveal characteristic cluster length scales.





Jörg et al., *Annu. Rev. Cond. Mat. Phys.* **12**, 135–153 (2021)

Summary: Structure factor calculation

Hybrid cell-based model

Continuum approximation

Linearisation about steady state

Solution in Fourier space

Calculation of correlation functions

Categorisation of the fluctuation spectrum

~~Random distribution~~

Clustering

~~Neutral clustering (diverging correlations)~~

Structure factor

$$S(\mathbf{k}) = \frac{1}{\sqrt{32}} \frac{2\eta\mathbf{k}^2 + \lambda}{\beta(\mathbf{k})} \frac{\omega^+(\mathbf{k}) - \omega^-(\mathbf{k})}{(D+\eta)\mathbf{k}^2 + \sigma} \frac{2(D\mathbf{k}^2 + \sigma) + \omega^+(\mathbf{k})\omega^-(\mathbf{k})}{\eta\mathbf{k}^2(D\mathbf{k}^2 + \sigma) + \Omega^2}$$

Kitadate et al., *Cell Stem Cell* **24** 1, 79 (2019)

Today’s menu: How to approach model calculations

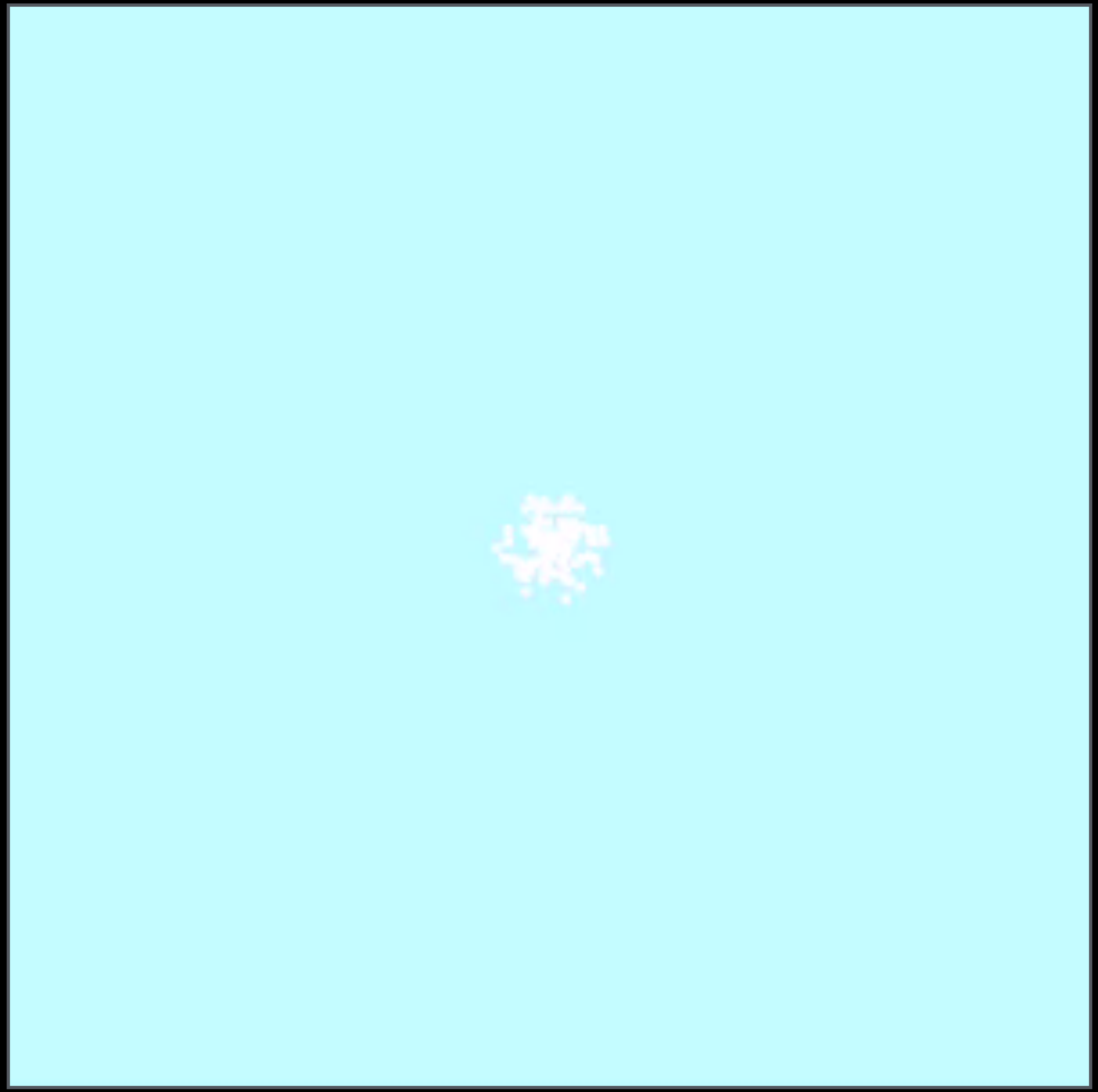
1. **Understanding the statistics of stem cell clones**
   (connection to experiments)
   - Consequences of **stochastic cell fate**
   - How to calculate **clone size distributions**
   - Understanding the **asymptotic** dynamics of clone sizes

2. **Understanding the phase space of the model**
   - Continuum approximation
   - Mean-field theory
   - Steady states
   - Small perturbations

3. **Understanding spatial fluctuations in many-particle systems**
   - How to quantify the spatial distribution of cells
   - How to calculate the structure factor

4. **Understanding transient population behaviour**
   - Recasting the model as a reaction-diffusion system
   - Understanding the type of density fronts
   - Calculating approximations for density front velocities

Front-like “invasion” of empty tissues by donor stem cells



From an initially localised population, stem cells colonise the system through a propagating density front.

(Fisher–KPP dynamics in the quasistatic limit)

Front speed computation
Step 1: Simplifying the field theory

Idea: Boil down the system to a single equation. Take limit in which fate determinant equilibrates infinitely fast.

$$\frac{\partial \rho}{\partial t} = \eta \boldsymbol{\nabla}^2 \rho + \boldsymbol{\nabla} \cdot \sqrt{2\eta\rho}\boldsymbol{\xi} + \lambda[2h(\phi) - 1]\rho + \sqrt{\lambda\rho}\zeta \ ,$$

Stem cell density

$$\frac{\partial \phi}{\partial t} = D\boldsymbol{\nabla}^2\phi + \nu - \gamma h(\phi)\rho - \kappa\phi$$

Fate determinant concentration

$$h(\phi) = \frac{(\phi/\phi_0)^n}{1 + (\phi/\phi_0)^n}$$

Simplifications: $d = 1 \ , \ \boldsymbol{\xi} \to 0 \ , \ \zeta \to 0 \ , \ D = 0 \ , \ n = 1$

Non-dimensionalisation: $\rho \to \rho/\rho_* \ , \ \phi \to \phi/\phi_0 \ , \ x \to \sqrt{\lambda/\eta}x \ , \ t \to \lambda t$

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2 \rho}{\partial x^2} + [2h(\phi) - 1]\rho$$

$$\tau\frac{\partial \phi}{\partial t} = 1 - \phi + \mu[1 - 2h(\phi)\rho]$$

$$\tau = \frac{\lambda}{\kappa} \qquad \mu = \frac{\nu - \kappa\phi_0}{\kappa\phi_0}$$

Quasi-static limit (infinitely fast equilibration of the fate determinant concentration)

$$\tau \to 0$$

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2 \rho}{\partial x^2} + \Gamma(\rho)$$

$$\Gamma(\rho) = \rho_0 - \sqrt{\rho_0^2 - \rho(1 - \rho)}$$

$$\rho_0 = \frac{1}{2} + \mu^{-1}$$

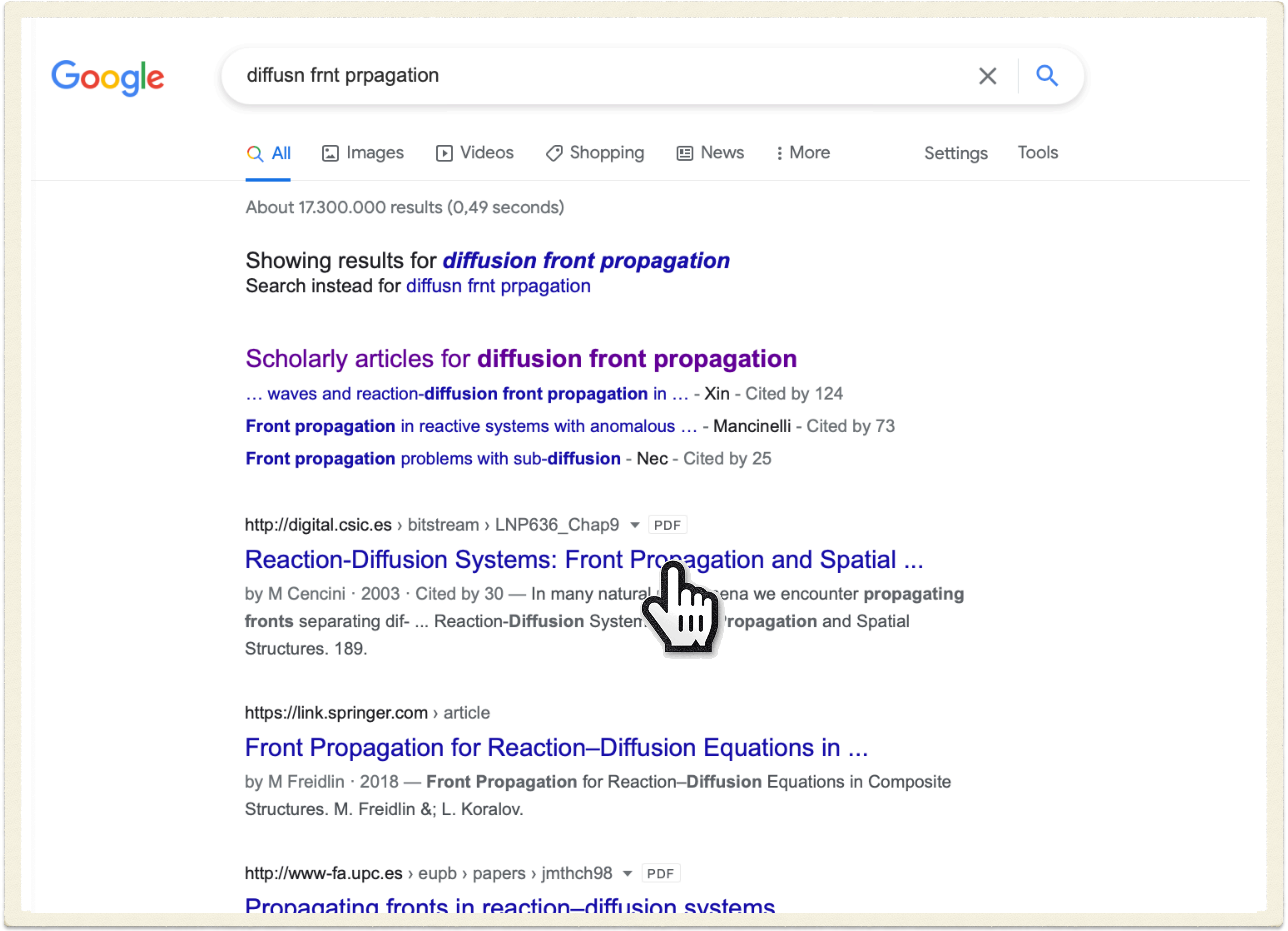
Front speed computation
Step 2: Identifying the nature of our equation

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2 \rho}{\partial x^2} + \Gamma(\rho)$$

$$\Gamma(\rho) = \rho_0 - \sqrt{\rho_0^2 - \rho(1-\rho)}$$

$$\rho_0 = \frac{1}{2} + \mu^{-1}$$

Diffusion + reaction
= Reaction-diffusion system



Front speed computation
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$$\frac{\partial \rho}{\partial t} = \frac{\partial^2 \rho}{\partial x^2} + \Gamma(\rho)$$

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$$\rho_0 = \frac{1}{2} + \mu^{-1}$$

Reaction-Diffusion Systems:
Front Propagation and Spatial Structures

Massimo Cencini[1], Cristobal Lopez[2], and Davide Vergni[3]

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understanding of it, trying to remain at an intuitive level of discussion.

First of all let us consider the general equation (1), rewritten here for convenience

$$\frac{\partial}{\partial t}\theta(x,t) = D\frac{\partial^2}{\partial x^2}\theta(x,t) + F[\theta(x,t)]\,. \quad (4)$$

Without specifying the shape of $F(\theta)$, we assume two steady states, an unstable one ($\theta = 0$) and a stable one ($\theta = 1$), i.e. $F(\theta)$ satisfies the conditions

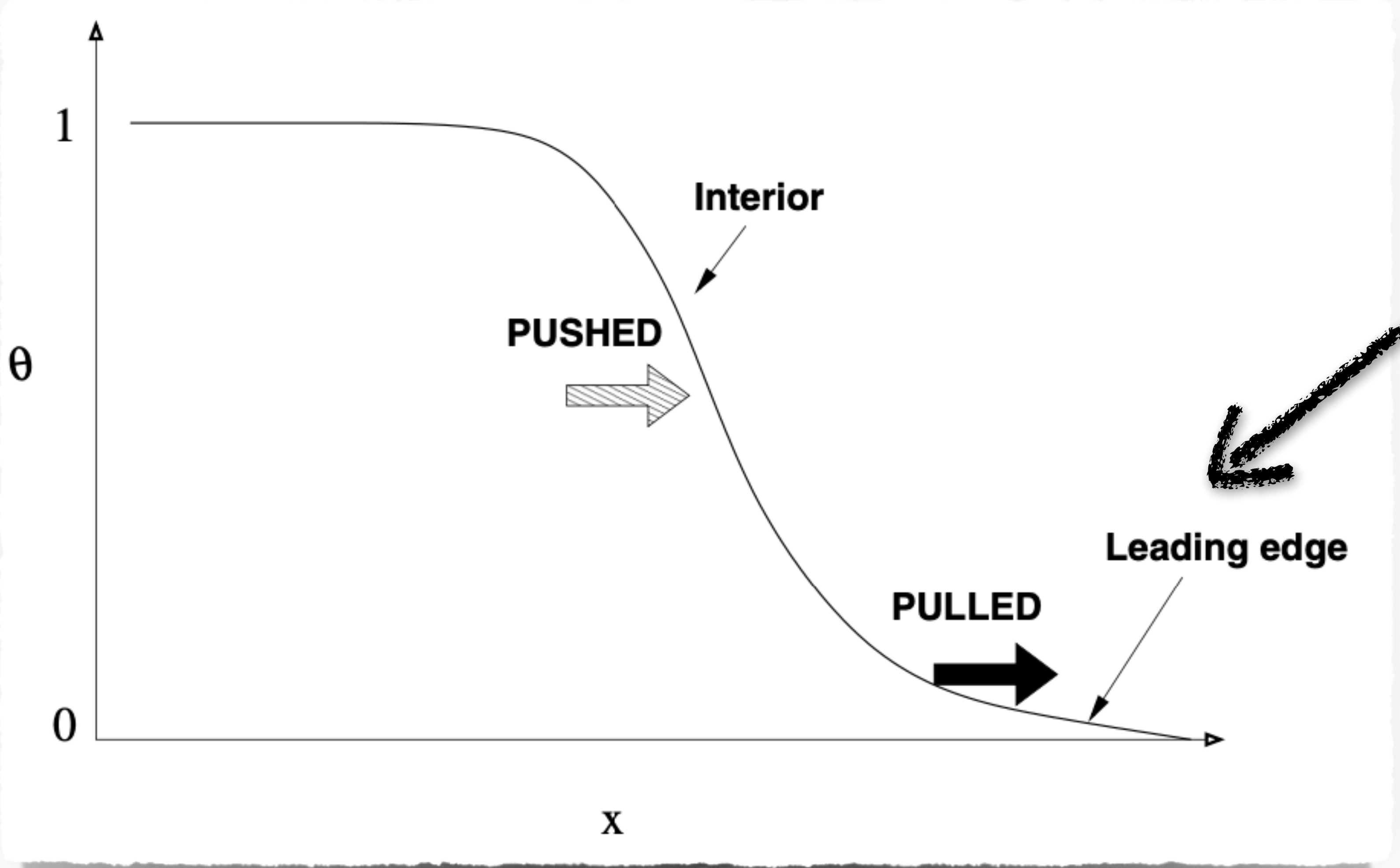
$$F(0) = F(1) = 0\,; \qquad F(\theta) > 0 \quad \text{if} \quad 0 < \theta < 1\,. \quad (5)$$

FKPP-Like Reaction Terms

Here, like Kolmogorov et al., we assume that $F(\theta)$ fulfills the conditions (5) supplemented by

$$F'(0) > 0 \quad \text{and} \quad F'(\theta) < F'(0) \quad \text{for all} \quad 0 < \theta \le 1\,, \quad (7)$$

ensuring that $F'(0) \equiv \sup_\theta\{F(\theta)/\theta\}$. Note that assumptions (5) and (7) are quite reasonable in biological problems and in some chemical reactions. Then



Our approximation is a **Fisher-KPP-type equation.**

(appears generically if propagating front is driven by "leakage" of self-maintaining states)

Front speed computation
Step 3: Compute the front speed

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2 \rho}{\partial x^2} + \Gamma(\rho)$$

$$\Gamma(\rho) = \rho_0 - \sqrt{\rho_0^2 - \rho(1-\rho)}$$

$$\rho_0 = \frac{1}{2} + \mu^{-1}$$

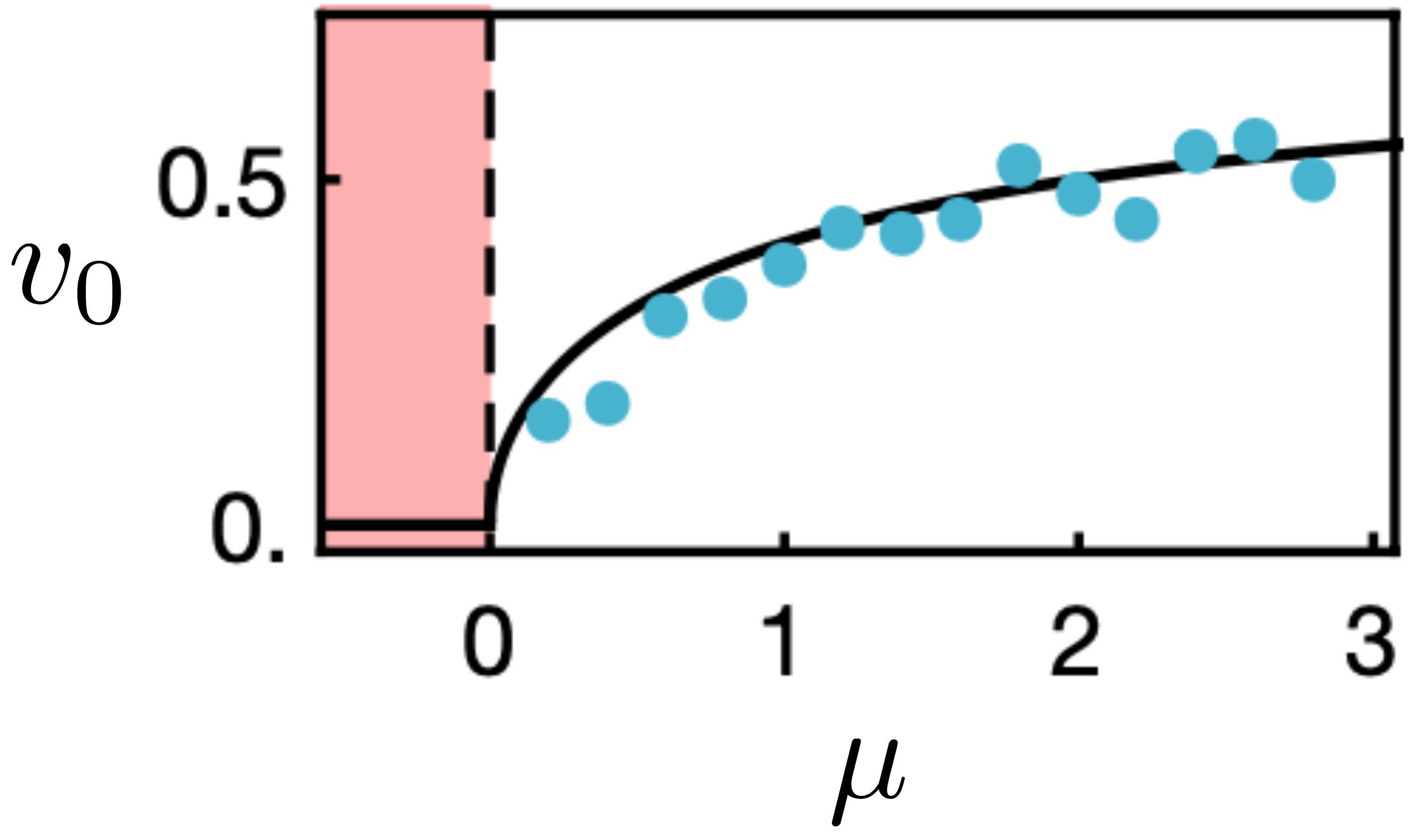
with boundary conditions $\Theta_v(-\infty)=1$ and $\Theta_v(+\infty)=0$. In the case of localized initial conditions, Kolmogorov and coworkers rigorously demonstrated, using a very interesting constructive proof, that (8) has a positive definite[2] solution with speed

$$v_0 = 2\sqrt{DF'(0)}\,. \tag{9}$$

Such a solution exists and is unique, apart from a linear transformation $x' =$

$$v_0 = \sqrt{\frac{4\eta\lambda}{1+2\mu^{-1}}}$$

Front speed
in our quasi-static limit



$\mu \to 0^+$ approaching the bifurcation from above: $v_0 \propto \mu^{1/2}$

$\mu \gg 0$ deep in the homeostatic phase: $v_0 \propto (\eta\lambda)^{1/2}$

Summary: Density front propagation

Hybrid cell-based model

↓

Continuum approximation

↓

Quasi-static limit of the fate determinant

↓

"Reaction-diffusion" equation

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2 \rho}{\partial x^2} + \Gamma(\rho)$$

Fisher-KPP type

→ Approximation for the front speed

$$v_0 = \sqrt{\frac{4\eta\lambda}{1 + 2\mu^{-1}}}$$

→ supports density front propagation ("pulled front")