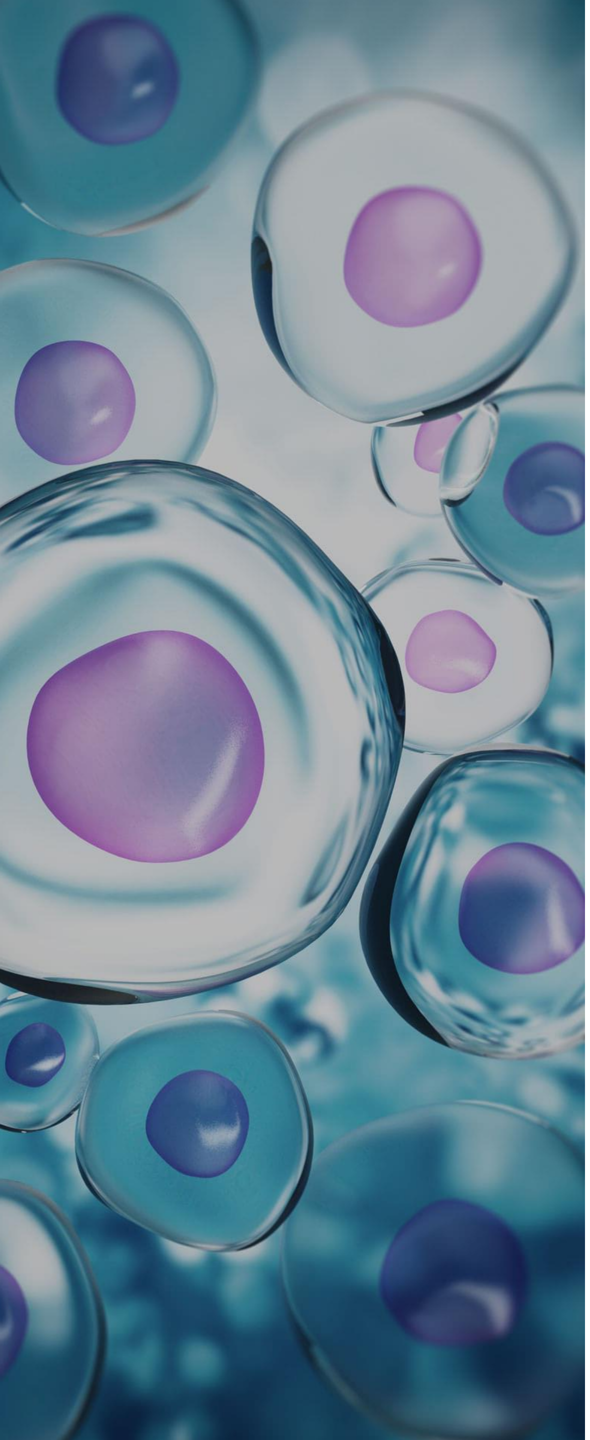

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The University of Edinburgh

Volume Exclusion in Stem Cell Homeostasis

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Linus Schumacher

Ramon Grima

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What is a stem cell?

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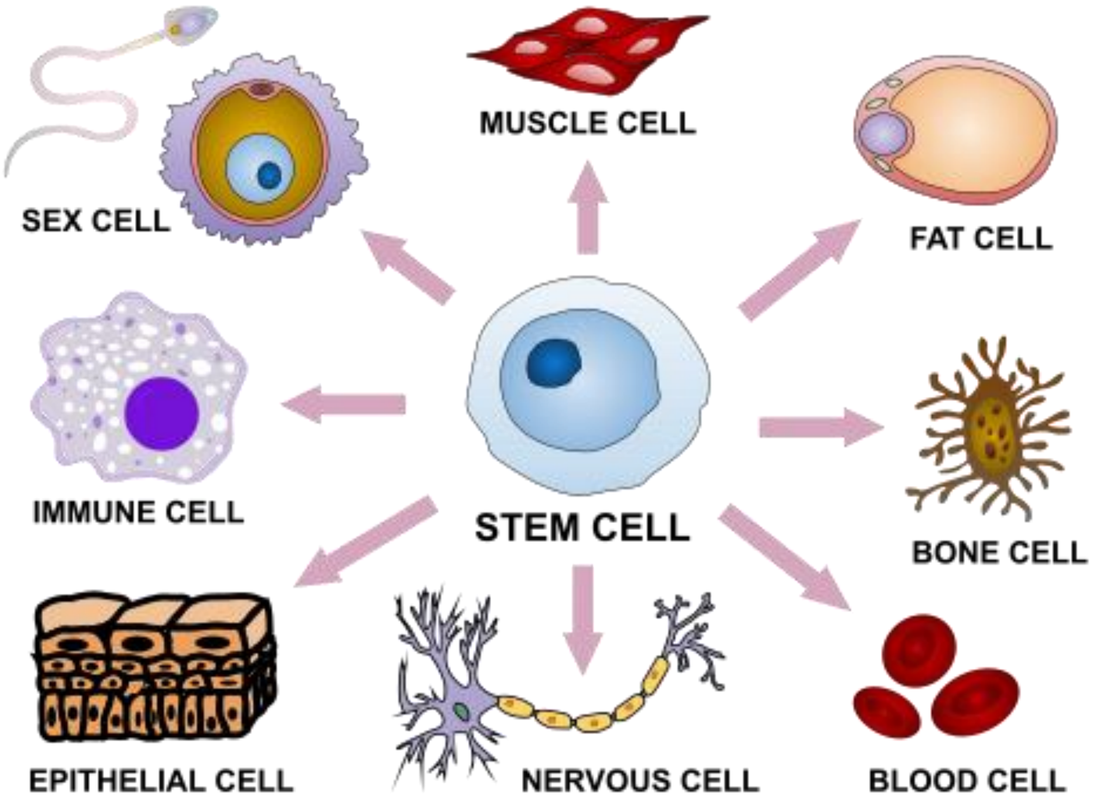
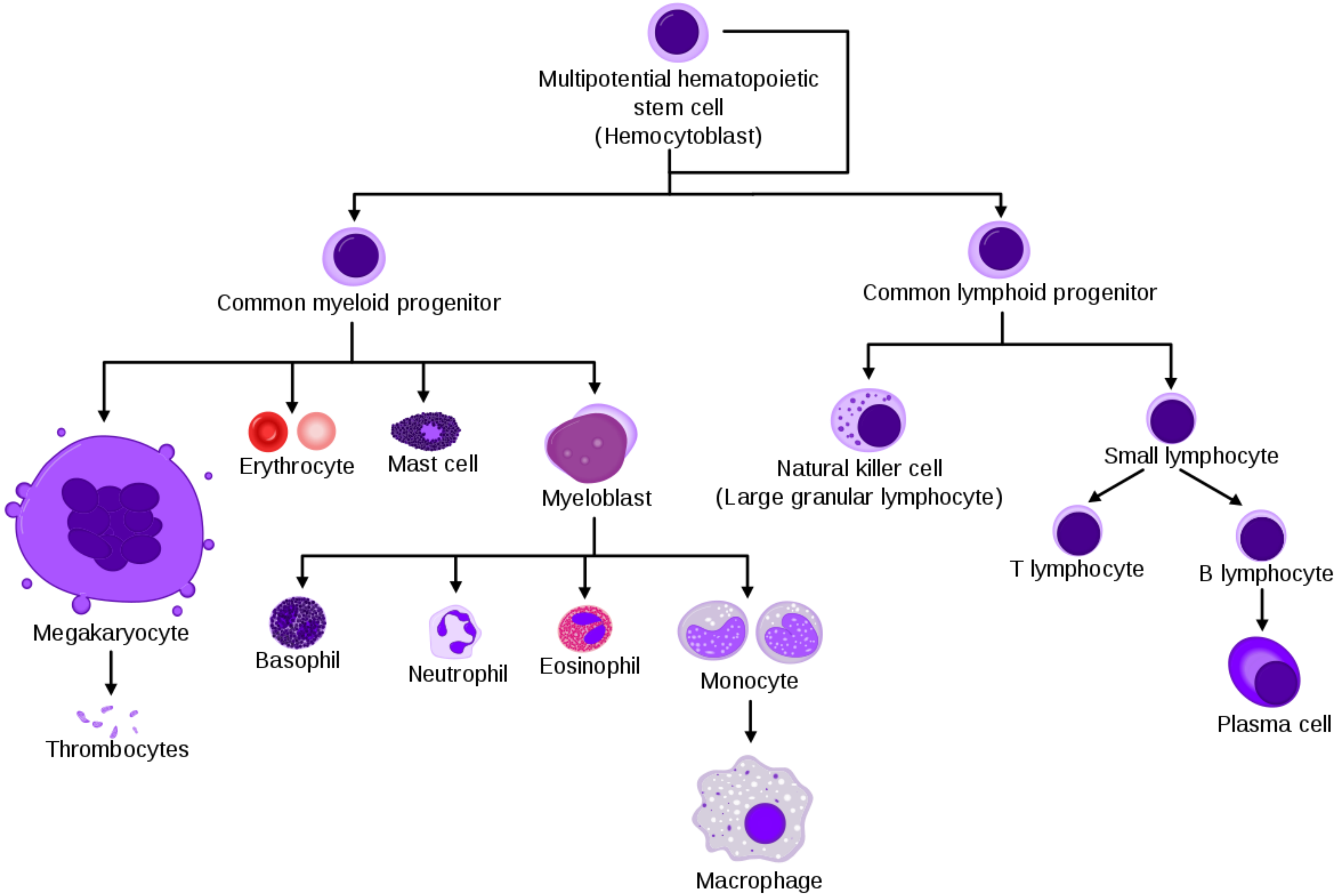
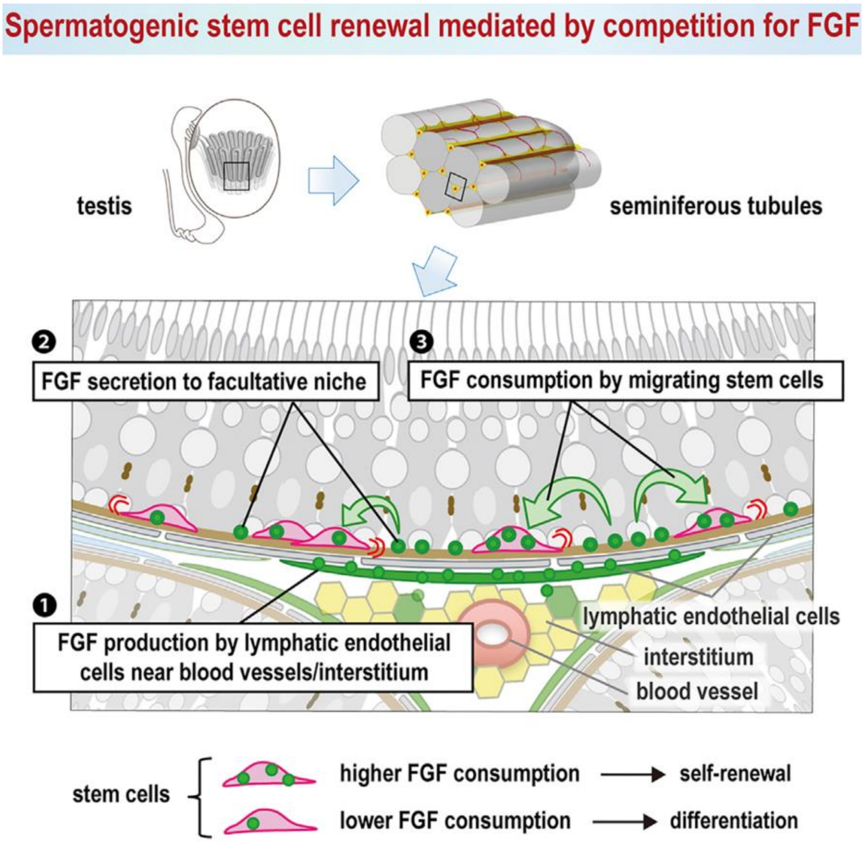


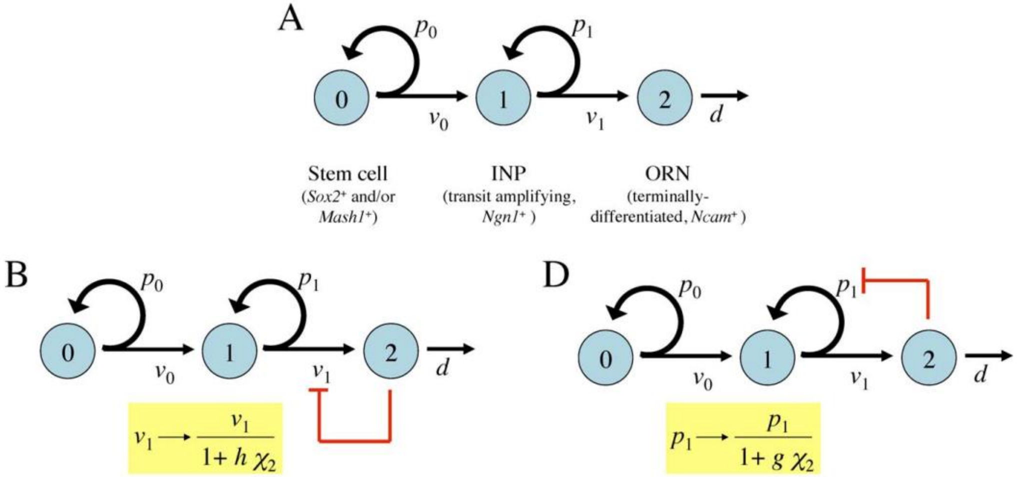
- Self-renewal
- Tissue formation and repair

Example: hematopoietic system



Example: regulatory mechanisms



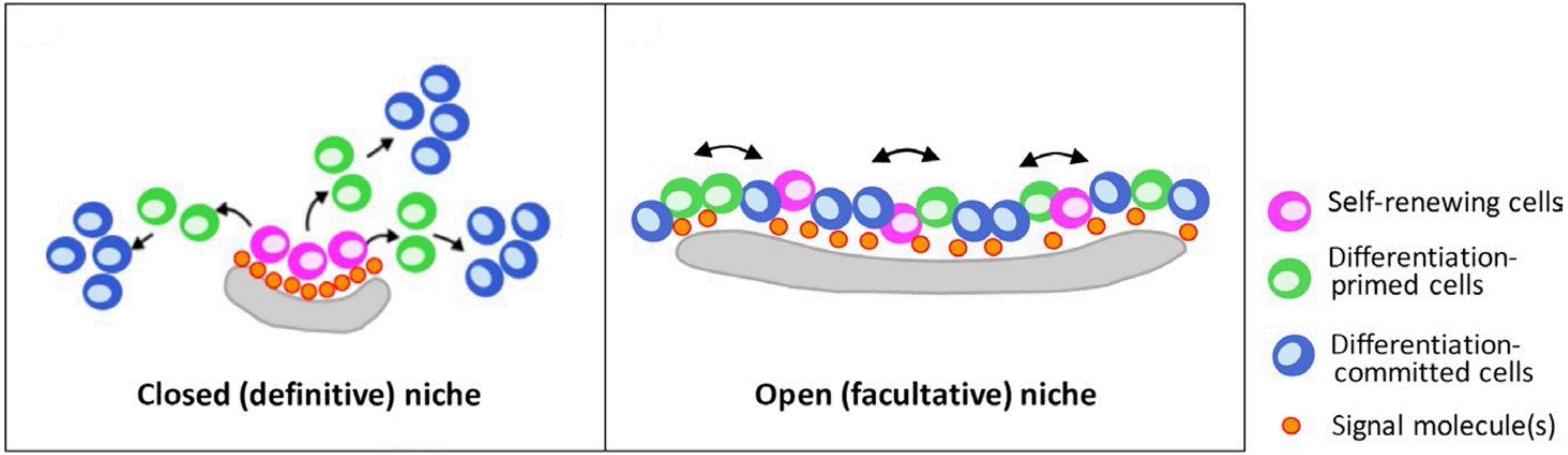


- Deterministic models
- Ordinary differential equations

Kitadate et al. (2019)

Lander et al. (2009)

The stem cell niche



- Intestinal crypt
- Bulge (hair follicles)
- Bone marrow (HSCs)
- Mouse testis (SSCs)

Yosihda et al. (2018)

Key questions

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- Is volume exclusion capable of explaining homeostatic behavior in SC populations?
- What are the main hallmarks of volume exclusion as a regulatory mechanism?
- How can we identify the presence or absence of this particular mechanism in different tissues? How can we distinguish it from other regulatory mechanisms?

Cell population models

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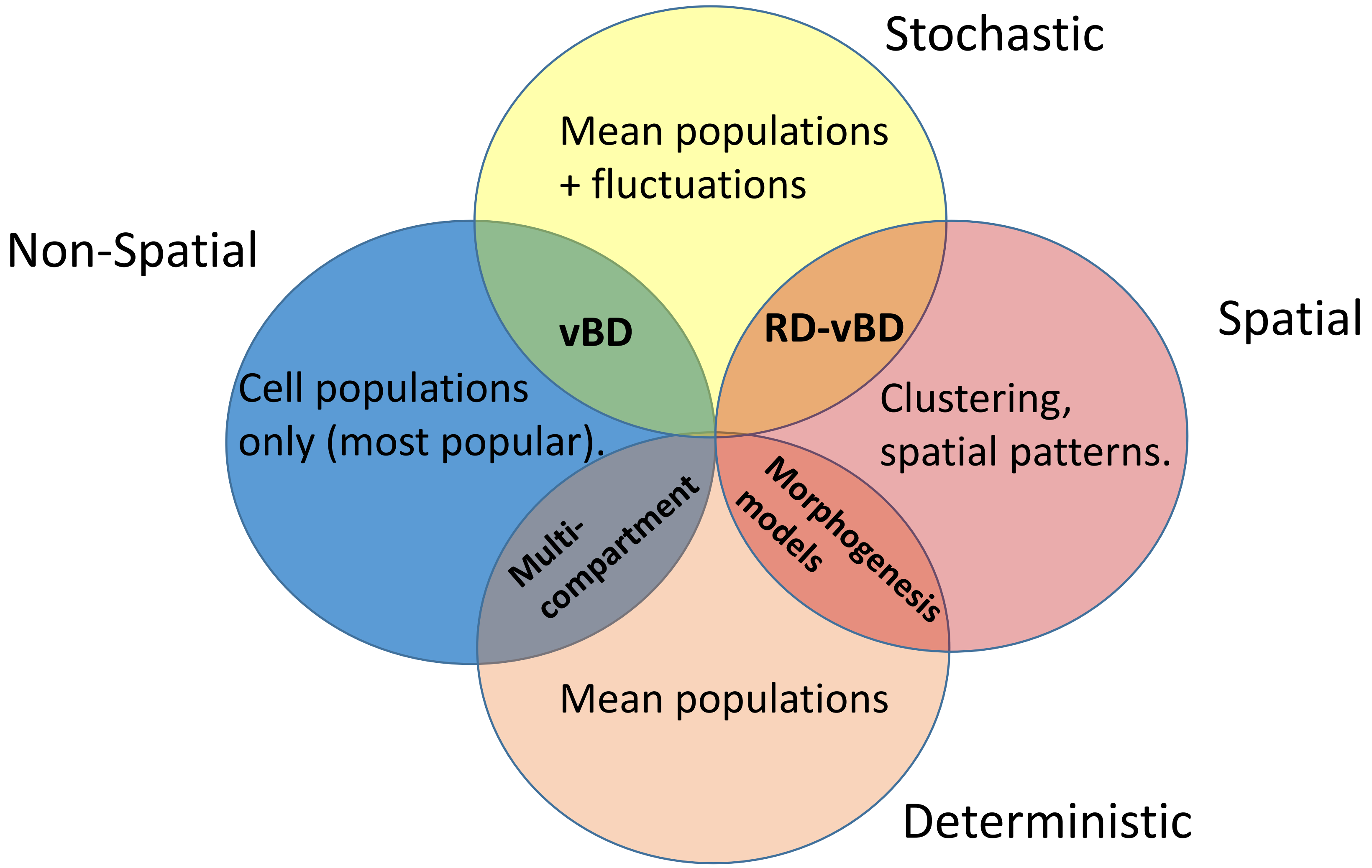

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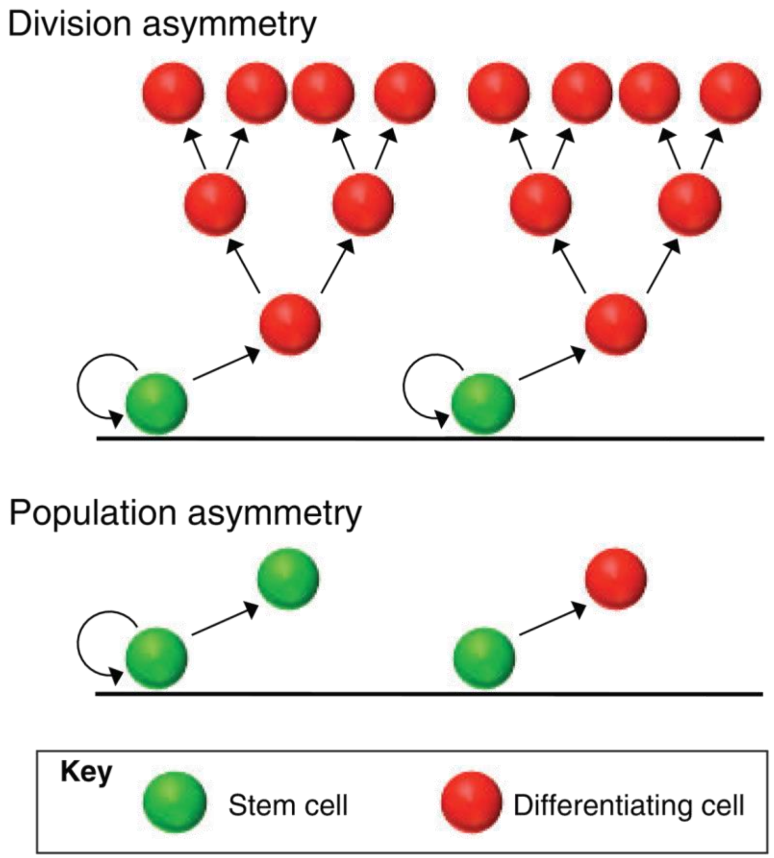
Critical Birth and Death Process (CBD)



Klein and Simons (2011)

*A STOCHASTIC MODEL OF STEM CELL PROLIFERATION, BASED ON THE GROWTH OF SPLEEN COLONY-FORMING CELLS**

BY J. E. TILL, E. A. McCULLOCH, AND L. SIMINOVITCH

DEPARTMENT OF MEDICAL BIOPHYSICS, UNIVERSITY OF TORONTO, AND THE ONTARIO CANCER INSTITUTE, TORONTO, CANADA

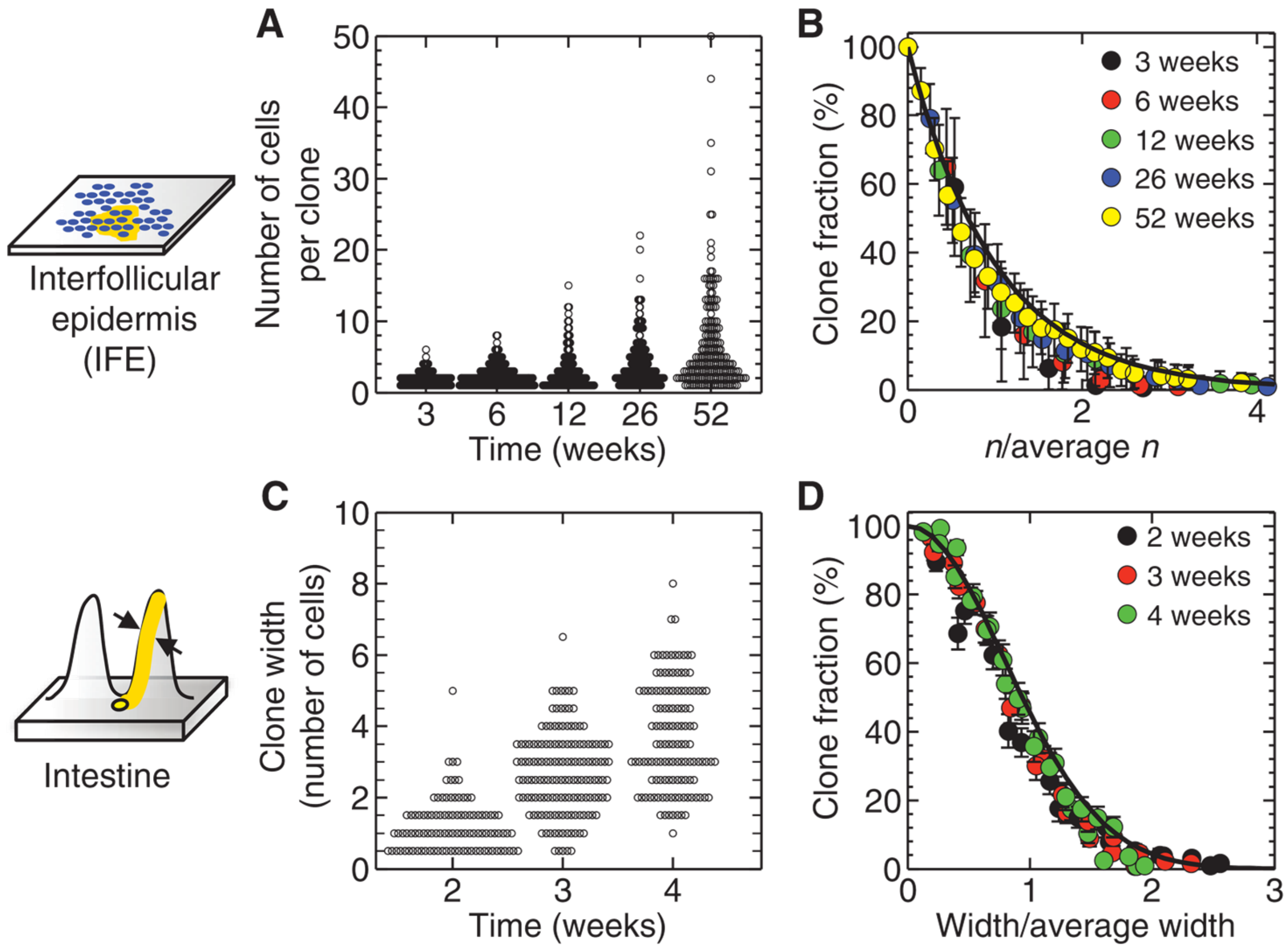
Communicated by Boris Ephrussi, November 6, 1963

- Critical BD process

$$\begin{cases} S \xrightarrow{k_1} 2S \\ S \xrightarrow{k_2} \emptyset \end{cases}$$

- Stochastic process

Clonal dynamics



Klein and Simons (2011)

Master equations

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$$\begin{cases} S \xrightarrow{k_1} 2S \\ S \xrightarrow{k_2} \emptyset \end{cases}$$

\+ Well mixed, dilute gas

$$\frac{\partial P}{\partial t} = \sum_{r=1}^{R} f_r(\mathbf{n} - S_r, t)P(\mathbf{n} - S_r, t) - \sum_{r=1}^{R} f_r(\mathbf{n})P(\mathbf{n}, t) \qquad f_r(\mathbf{n}) = k_r \Omega \prod_{i=1}^{N} \frac{n_i!}{(n_i - s_{ir})!\Omega^{s_{ir}}}$$

$$G(\mathbf{z}, t) = \sum_{n_1, \cdots, n_N = -\infty}^{+\infty} \mathbf{z}^n P(\mathbf{n}, t) \qquad P(n, t) = \frac{1}{n!} \frac{\partial^n}{\partial z^n} G(z, t)|_{z=0}$$

$$\langle n_i \rangle = \left. \frac{\partial G(\mathbf{z}, t)}{\partial z_i} \right|_{(1, \cdots, 1)} \qquad \begin{cases} \langle n_i^2 \rangle = \sum_{\mathbf{n}} n_i^2 P(\mathbf{n}, t) = \left[\frac{\partial}{\partial z_i} z_i \frac{\partial G}{\partial z} \right]_{(1, \cdots, 1)} \\ \langle n_i n_j \rangle = \sum_{\mathbf{n}} n_i n_j P(\mathbf{n}, t) = \left[\frac{\partial^2 G}{\partial z_i \partial z_j} \right]_{(1, \cdots, 1)} \end{cases}$$

Birth and death process with volume exclusion (vBD)

$$\begin{cases} S \xrightarrow{k_1} 2S \\ S \xrightarrow{k_2} \emptyset \end{cases}$$

$$\begin{cases} S + E \xrightarrow{k_1} 2S \\ S \xrightarrow{k_2} E \end{cases}$$

$S + E \xrightarrow{k_1} 2S$ → Proliferation

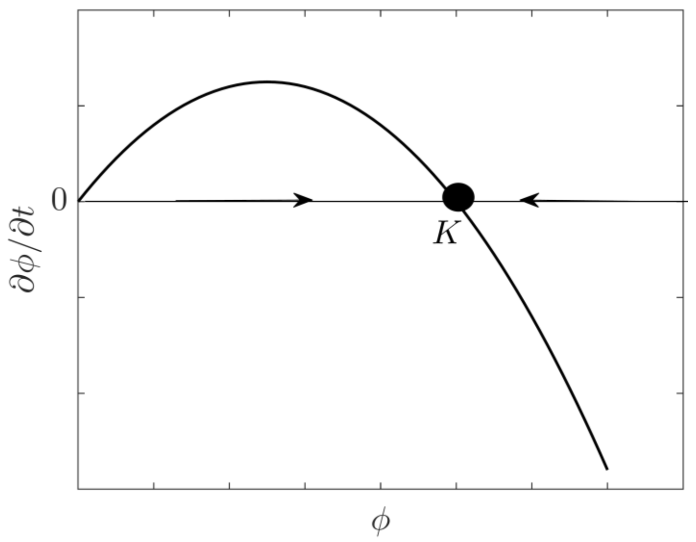
$S \xrightarrow{k_2} E$ → Death/Differentiation

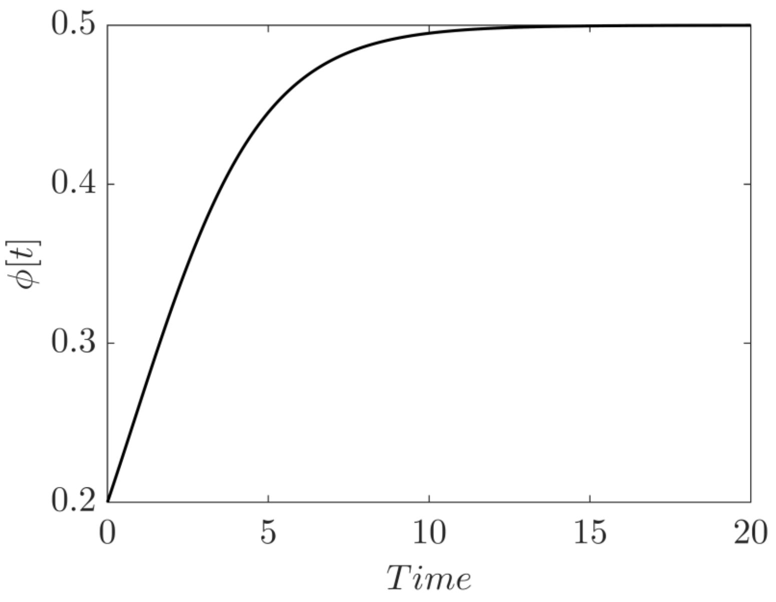
$$S + E = N$$

$$\begin{cases} \frac{d\phi_S}{dt} = k_1\phi_S(1-\phi_S) - k_2\phi_S \\ \frac{d\phi_E}{dt} = -k_1\phi_S(1-\phi_S) + k_2\phi_S \end{cases}$$

$$\phi(t) = \frac{K\phi_0}{(K-\phi_0)e^{-rt} + \phi_0}$$

$$r = k_1 - k_2 \qquad K = 1 - k_2/k_1$$

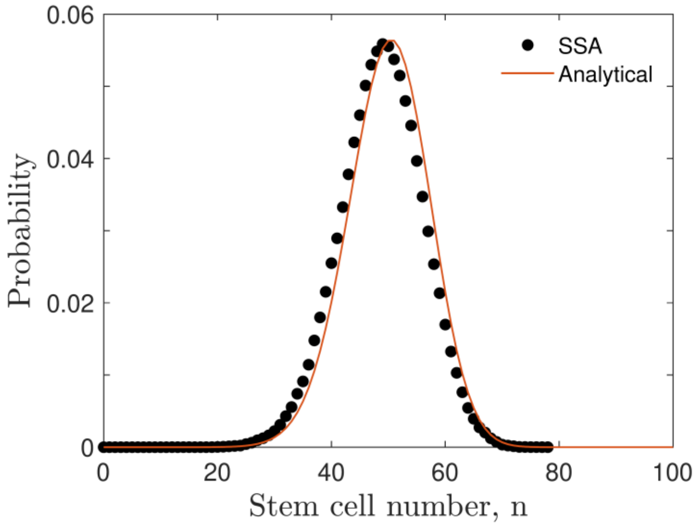


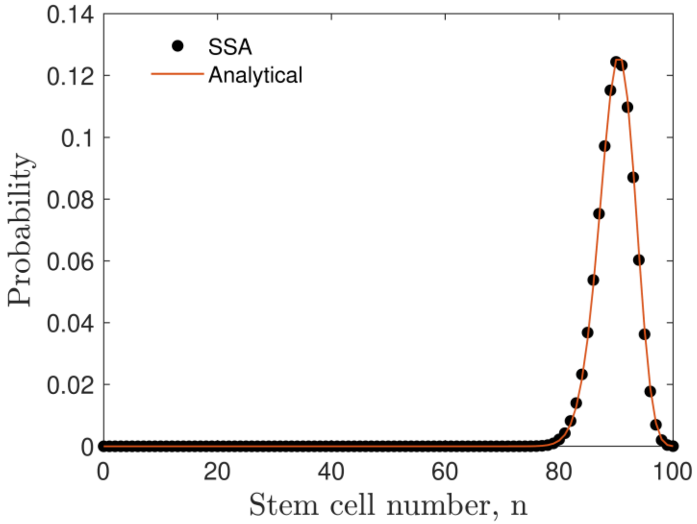


Master equation and Quasi-steady-state approximation

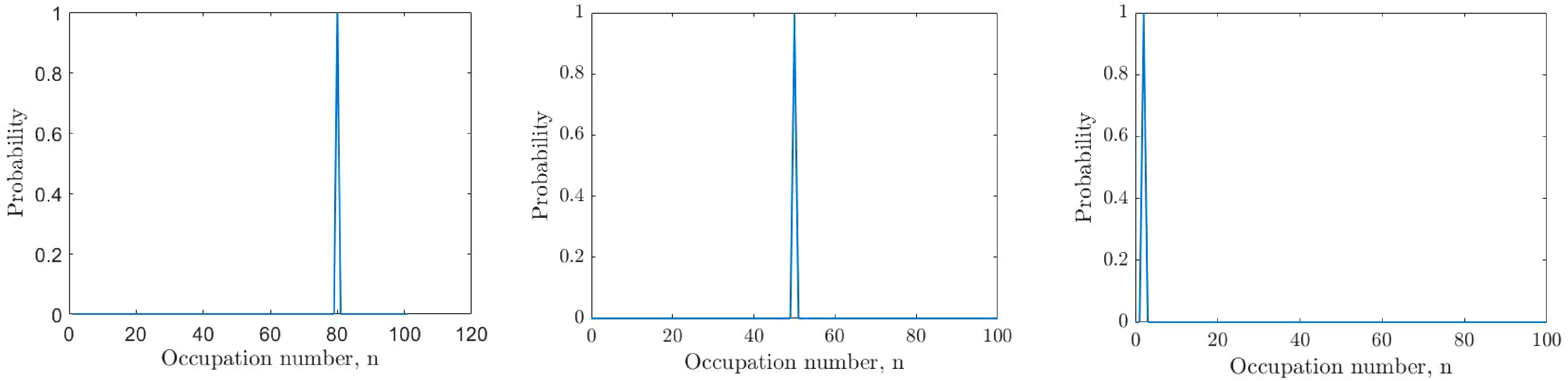
$$\begin{cases} \frac{\partial P}{\partial t} = \{(E^{-} - I)T(n \rightarrow n+1) + (E^{+} - I)T(n+1 \rightarrow n)\}P(n,t) \\ T(n \rightarrow n+1) = a_{i+1} \\ T(n+1 \rightarrow n) = b_{i-1} \\ a_i = \frac{(i-1)(n-i+1)}{N(1-\phi^*)} \quad \phi^* \in (0,1) \\ b_i = i+1. \end{cases}$$

$$\begin{cases} P_0 = 0 \\ P_1 = \frac{(N-1)}{N(2-\phi^*)-1} \frac{N^{N-1}(1-\phi^*)^(N-2)}{(N-2)!} P_N \\ P_{N-k} = \sum_{k=1}^{N-2} \frac{N^{k+1}(1-\phi^*)^k}{k!(N-k)} P_N \qquad k = 1, 2, \ldots N-2 \\ P_N = \left[1 + \frac{(N-1)}{N(2-\phi^*)-1} \frac{N^{N-1}(1-\phi^*)^(N-2)}{(N-2)!} + \sum_{k=1}^{N-2} \frac{N^{k+1}(1-\phi^*)^k}{k!(N-k)}\right]^{-1} \end{cases}$$

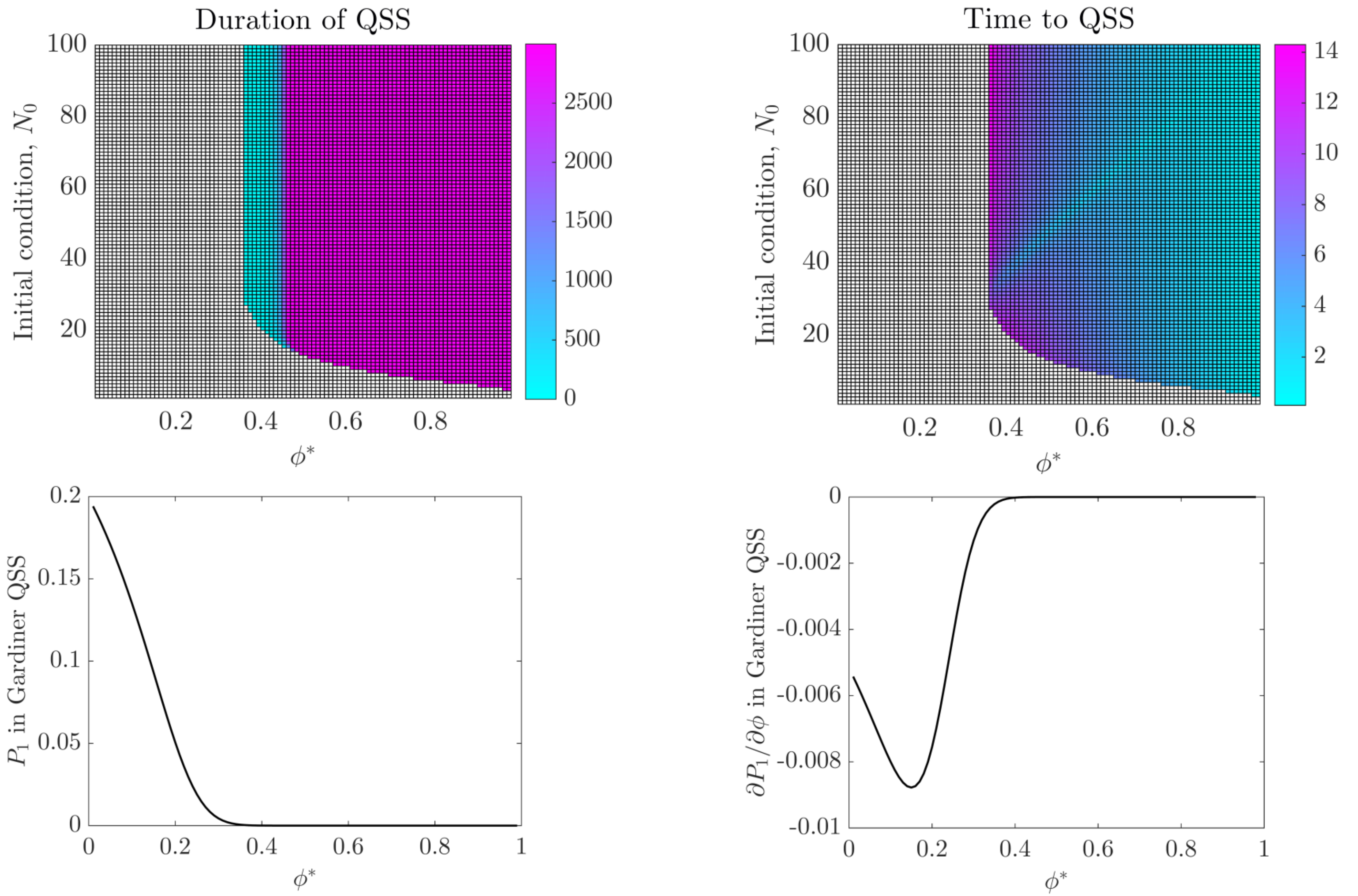




Time-dependent bi-modal behaviour



Time-dependent bi-modal behaviour



System-size expansion

Escriba aquí la ecuación.

$$\begin{cases} \frac{\partial P}{\partial t} = \{(E^- - I)T(n \to n+1) + (E^+ - I)T(n+1 \to n)\}P(n,t) \\ T(n \to n+1) = a_{i+1} \\ T(n+1 \to n) = b_{i-1} \\ a_i = \frac{(i-1)(n-i+1)}{N(1-\phi^*)} \quad \phi^* \in (0,1) \\ b_i = i+1. \end{cases}$$

ón.

$$n(t) = N\phi(t) + N^{1/2}\xi$$

$N^{1/2}$

Deterministic

N^0 Linear noise approximation (Fokker-Planck)

$$\frac{\partial \Pi}{\partial t} = [k_1(1-2\phi) + k_2]\frac{\partial}{\partial \xi}(\xi\Pi) + \frac{1}{2}\left[k_1\phi(1-\phi)) + k_2\phi\right]\frac{\partial^2 \Pi}{\partial \xi^2}$$

Higher orders

$$\begin{aligned} \frac{\partial \Pi}{\partial t} &= N^0\left\{[k_1(1-2\phi)+k_2]\frac{\partial}{\partial \xi}(\xi\Pi) + \frac{1}{2}[k_1\phi(1-\phi)) + k_2\phi]\frac{\partial^2}{\partial \xi^2}\Pi\right\} + \\ &+ N^{-1/2}\left\{\frac{\partial}{\partial \xi}(\xi^2\Pi) + \frac{1}{2}[k_2 - k_1(1-2\phi)]\frac{\partial^2}{\partial \xi^2}(\xi\Pi) + \frac{1}{6}[k_2\phi - k_1\phi(1-\phi)]\frac{\partial^3}{\partial \xi^3}\Pi\right\} + \\ &+ \sum_{r=2}^{\infty} N^{-r/2}\left\{\frac{k_1\phi(1-\phi)(-1)^{2+r} + k_2\phi}{(2+r)!}\frac{\partial^{r+2}}{\partial \xi^{r+2}}\Pi + \frac{k_2 - k_1(1-2\phi)(-1)^{r+1}}{(r+1)!}\frac{\partial^{r+1}}{\partial \xi^{r+1}}(\xi\Pi) \right. \\ &\left. - \frac{k_1(-1)^r}{r!}\frac{\partial^r}{\partial \xi^r}(\xi^2\Pi)\right\} \end{aligned}$$

Reaction-diffusion vBD process

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$$\begin{cases} S + E \xrightarrow{k_1} 2S \\ S \xrightarrow{k_2} E \end{cases}$$

$$S + E = N$$

Proliferation

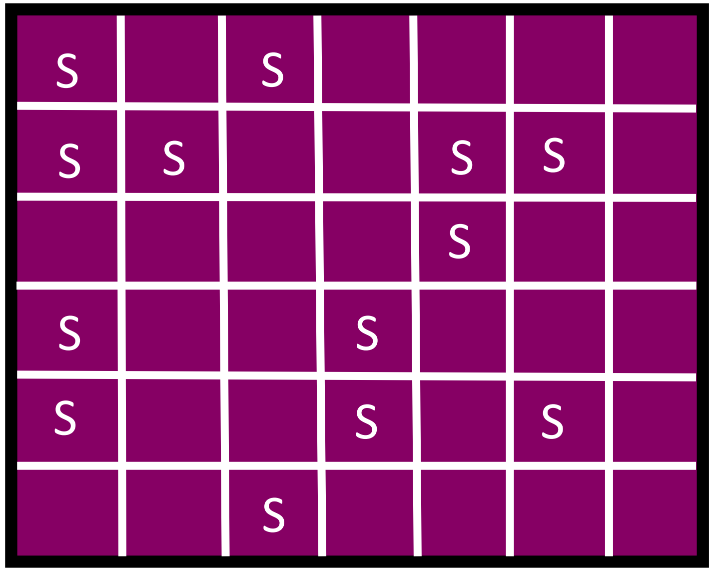
$$\begin{cases} S_i + E_j \xrightarrow{k_1} S_i + S_j \\ S_i \xrightarrow{k_2} E_i \\ S_i + E_j \xrightarrow{k_3} E_i + S_j \end{cases}$$

Death/Differentiation

Diffusion

$$S_i = 0, 1; E_i = 0, 1$$

$$\sum_i S_i + E_i = N$$



- Spatial patterns

Take home message

- Stem-cell Biology poses fascinating challenges that require physical and mathematical approaches.
- Deterministic models and their subjacent stochastic processes can differ significantly in predictions.
- Cellular and developmental biology can inspire novel mathematical/computational approaches that transcend their initial purposes.