Mathematical modelling of heterogeneous stem cell-based systems

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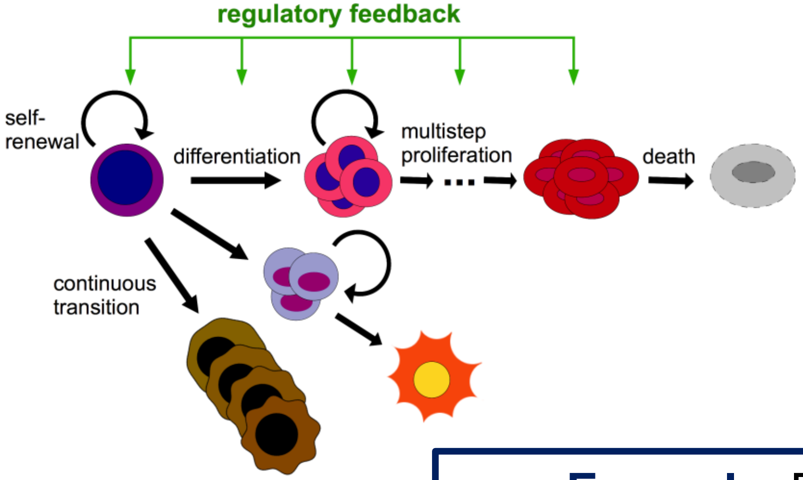
Content of this talk

Population dynamics models of stem cell-based systems:

- **Within-system heterogeneity:**
  - Different models and model-based data analysis on example of hematopoiesis and neurogenesis
- **New challenges arising from new technology for data aquisition** (linking single cell data with mechanistic models)
  - Structured population models in measure spaces

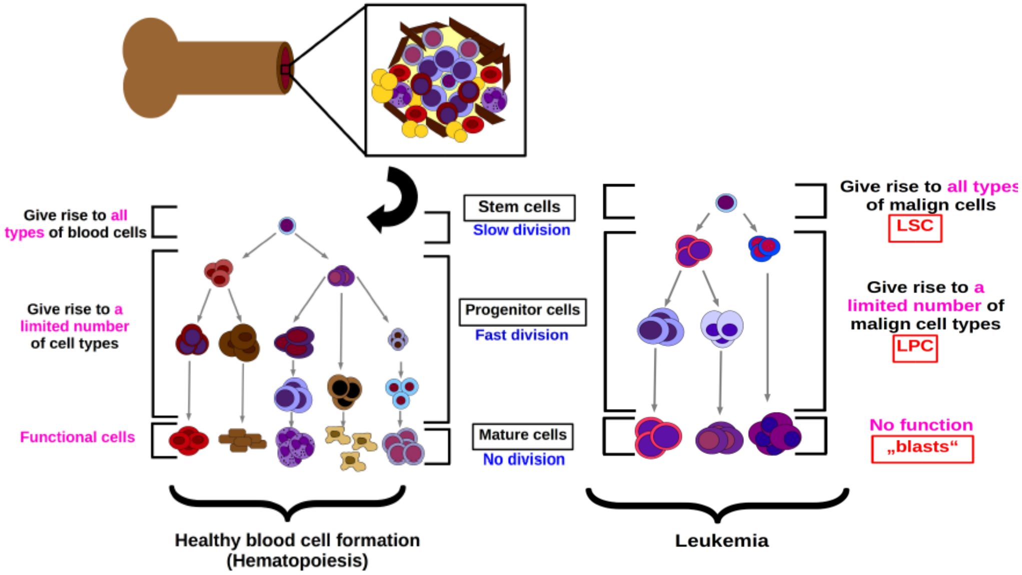
Stem cells – fundamental component of organ physiology



Tree-like structure of cell lineages:

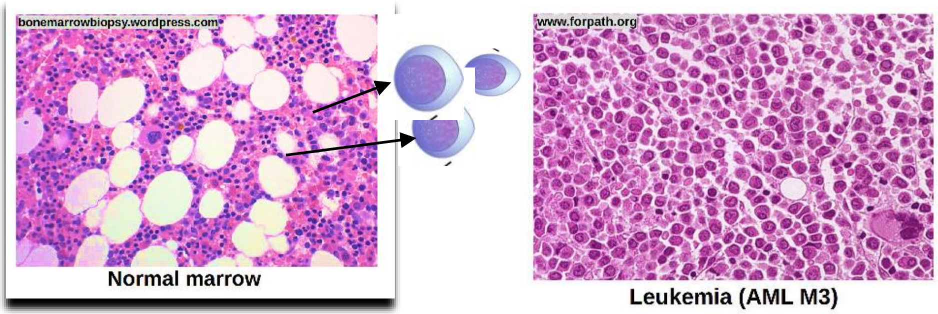
- discrete and continuous cell state transitions
- bifurcation points

Example: Blood production system



Spatial structure?

Heterogeneous cell systems (spatially statistically homogeneous)

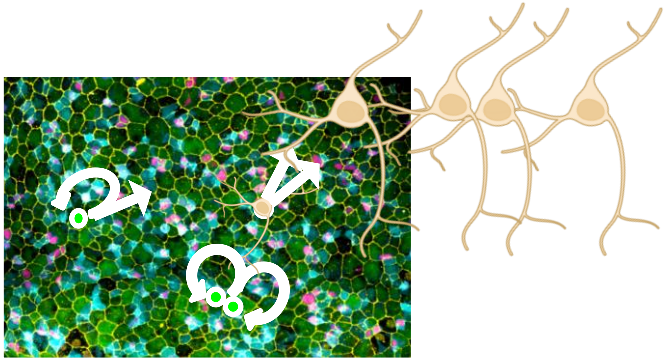

bonemarrowbiopsy.wordpress.com

Normal marrow

www.forpath.org

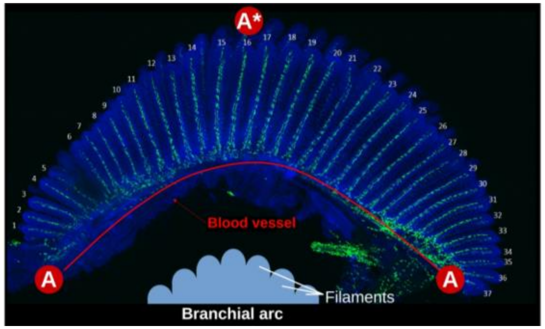
Leukemia (AML M3)

Hematopoietic niche

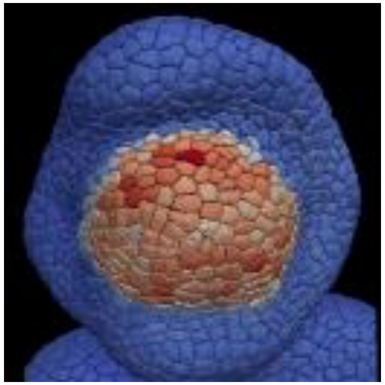


Neural stem cell niche

Developmental systems with spatial organisation/structure



Branching structures



Growing structures

New challenges: Single cell data showing large heterogeneity

Single-cell data analysis:

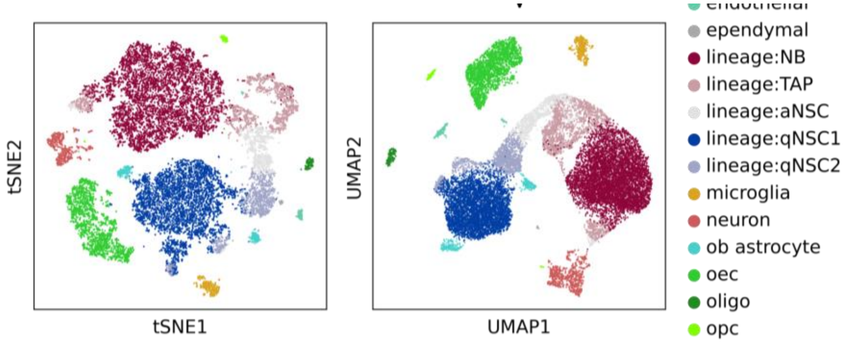
Single-cell sequencing

```
AGTTCTCCTCGTTTGTTATGTTCGGGATGCAGCTGGACATACATTCCCAC
ACAGACCATATAATCCTATTTATCCACGCTATGAATCATATGCGTAAAGT
TTTCCGCTCCTTTAGTGGCTTGAGGATTTAAAACAGTTACAAACAGGGCT
GCTCGTTCGGATCTTCGAGGGAGTCTAGTCATTCGCACTCACATGAGGTT
```

	PC1	PC2	…	PCN
cell1	.52	-1.07		.68
cell2	.70	.58		.52
⋮				
cellN	-.58	-1.08		.49

Dimensiality reduction (PCA)

Two-dimensional “embeddings”



Data show single cell heterogeneity in a high-dimensional space of transcriptome-based features

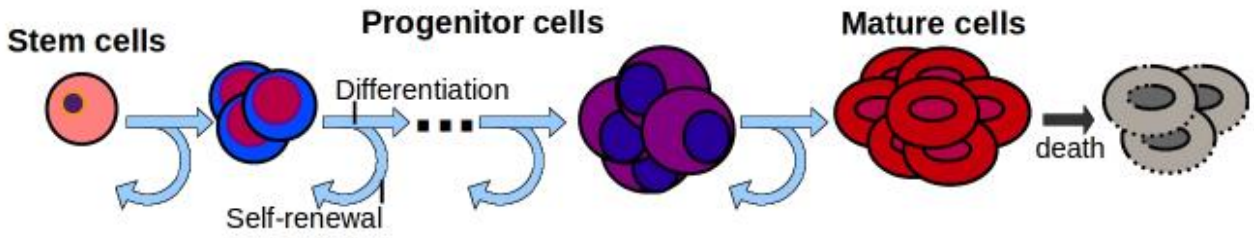
Can we use the data for mechanistic modelling?

Kalamakis,…, Marciniak-Czochra and Martin-Villalba, *Cell*, 2019

Discrete or continuous lineages?

On example of granulopoiesis

Multi-compartmental models



Population dynamics model:

$$\frac{du_i}{dt} = \underbrace{(2a_i - 1)p_i u_i}_{\text{self-renewing proliferation}} + \underbrace{2(1 - a_{i-1})p_{i-1} u_{i-1}}_{\text{differentiation from more primitive cells}};$$

Key model parameters:

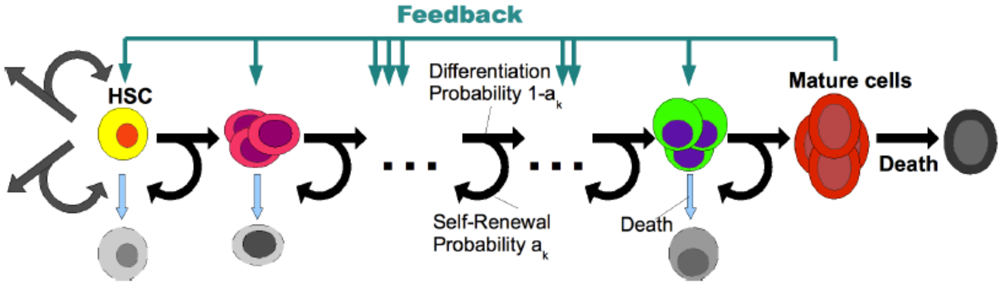
- **Proliferation rate**
  (number of divisions per time unit)
- **Death rate**
  (average deaths per time unit)
- **Self-renewal probability /fraction**

regulatory feedbacks ?

M-C, Stiehl, Jäger, Ho, Wagner, Stem Cells Dev, 2009

Example of granulopoiesis: Model of a regulatory feedback

Competition for signalling factors



Dynamics of signaling molecules

(cytokines; G-CSF):

$$\boxed{\frac{dS(t)}{dt} = \alpha - \mu S(t) - \beta u_n(t)S(t)}$$

Quasi steady state approximation (Tikhonov Thm.)

$$s(t) = \frac{1}{1 + ku_n(t)} \in [0,1], \quad \text{where } s(t) := \tfrac{\mu}{\alpha} S(t) \text{ and } k := \tfrac{\beta}{\mu}.$$

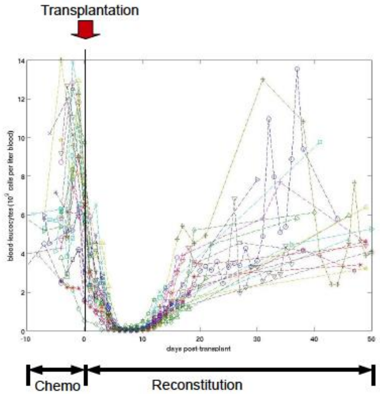
Regulation modes:

Proliferation: $p_i(s(t)) := p_i s(t) = \frac{p_{i,max}}{1+ku_n(t)}$

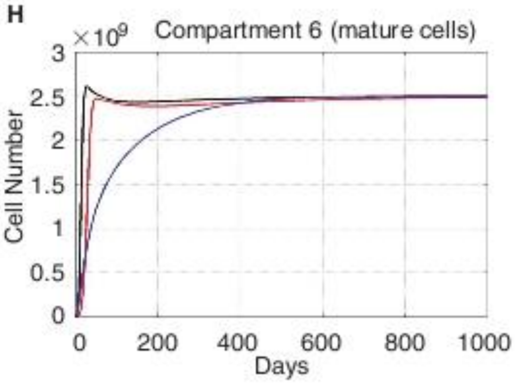
Self-renewal: $a_i(s(t)) := a_i s(t) = \frac{a_{i,max}}{1+ku_n(t)}$

Example of granulopoiesis: Data-based model selection

Data on hematopoietic reconstitution



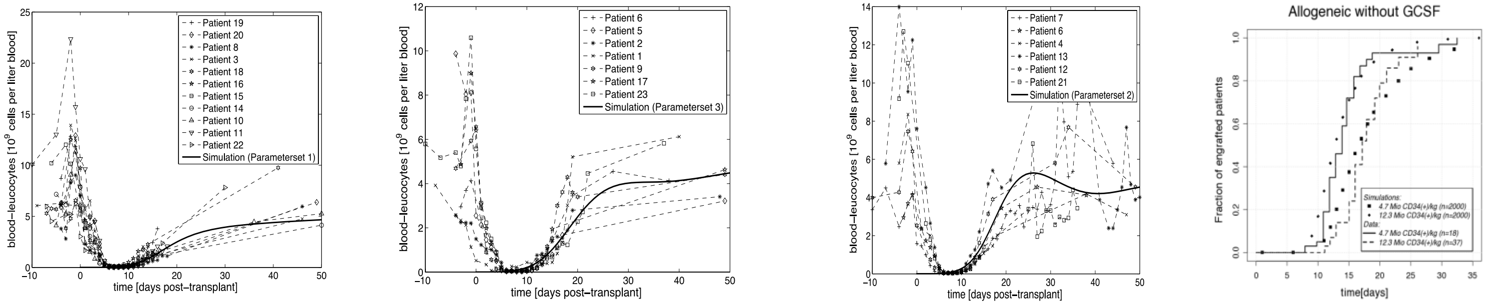
Model fit



Regulation of self-renewal fractions is the most effective mechanism of hematopoietic reconstitution

:

Model validation using Individual patient data and large patient groups



Stiehl, Ho, Marciniak-Czochra, BMT, 2014

Dynamics of the model

- Trivial steady state - unstable (unless it is the only equilibrium)
- Semi-trivial steady state: $(0,..0,\bar{u}_k,..,\bar{u}_n)$ - linearly unstable iff there exists a steady state with more positive components
- Unique positive steady state: $(\bar{u}_1,..,\bar{u}_n)$ - globally stable ?
  - Global stability for the 2-compartment model

$$L(u_1(t),u_2(t)) := \frac{1}{p_1 G(\bar{u}_2)} L_{21}(t,u_1(t),u_2(t)) + \frac{1}{d_2} L_{22}(t,u_1(t),u_2(t))$$

with $G(\xi) = 2(1 - a_1/(1+ku_2))$ and

$$L_{21}(t,u_1,u_2) := \frac{u_1}{\bar{u}_1} - 1 - \ln\frac{u_1}{\bar{u}_1},$$

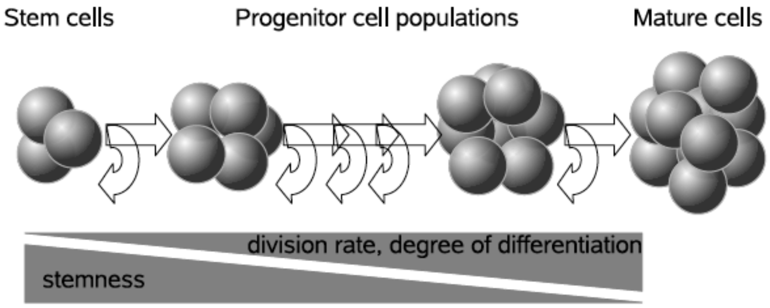
$$L_{22}(t,u_1,u_2) := \frac{u_2}{\bar{u}_2} - 1 - \frac{1}{\bar{u}_2}\int_{\bar{u}_2}^{u_2} \frac{G(\bar{u}_2)}{G(\xi)}\,d\xi.$$

- Hopf bifuraction and oscillations in the 3-compartment model and in the structured population model.

Knauer, Stiehl, Marciniak-Czochra, JMB, 2020
Getto, Nakata, Marciniak-Czochra, 2013

Population dynamics models of cell lineages

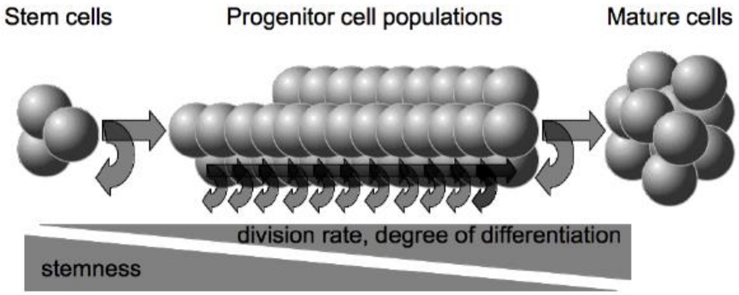
Multi-compartmental models



$$\begin{aligned}\frac{du_1}{dt} &= p_1(u_1,s) - g_1(u_1,s) - d_1 u_1,\\ \frac{du_i}{dt} &= g_{i-1}(u_{i-1},s) + p_i(u_i,s) - g_i(u_i,s) - d_i u_i,\\ \frac{du_n}{dt} &= g_{n-1}(u_{n-1},s) - d_n(u_n,s).\end{aligned}$$

What is the number of compartments?

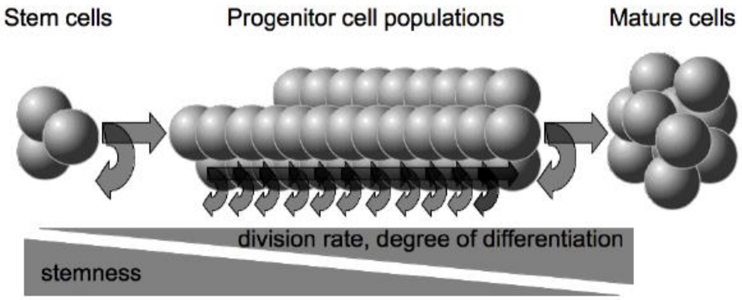
Continuous models



$$\partial_t u(x,t) + \partial_x[g(x,v(t))u(x,t)] = p(x)u(x,t)$$

What is x? How to identify g(x,.)?

Continous maturation model?



stem cells

$$\frac{d}{dt}w(t) = [2a_w(s)-1]p_w(s)w(t) - d_w w(t),$$

progenitors

$$\begin{aligned} \partial_t u(x,t) + \partial_x[g(x,s)u(x,t)] &= p(x,s)u(x,t) - d(x)u(x,t), \\ g(0,s)u(0,t) &= 2[1-a_w(s)]p_w(s)w(t), \quad t>0, \end{aligned}$$

mature cells

$$\frac{d}{dt}v(t) = g(x^*,s)u(x^*,t) - \mu v(t),$$

$$g(x,v) = 2[1 - \tfrac{a(x)}{1+kv(t)}]p(x),$$

$$a_w = a(0), \qquad p_w = p(0), \qquad 0 < a_w = a(0) \leq 1,$$

Signal intensity: $s = s[v(t)] = \dfrac{1}{1+kv(t)},$

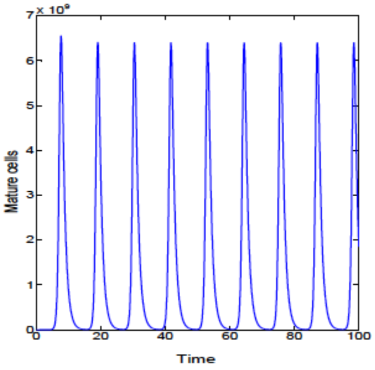
Doumic, Marciniak-Czochra, Perthame, Zubelli, SIAM Appl. Math. 2011

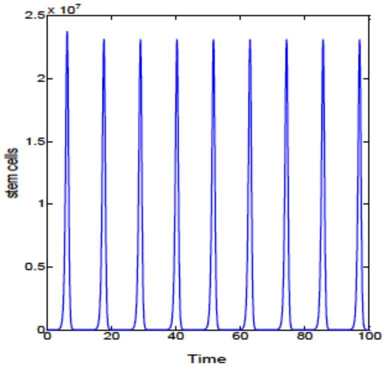
Different structure of stationary solutions and dynamics

- Similar conditions as in the multi-compartmental model but there exist no semitrivial stationary solutions

$$\begin{cases} \bar{v} &= \frac{2a_w - 1}{k}, \\ \bar{u}(x^*) &= \frac{\mu}{kp(x^*)} \; \frac{a_w(2a_w - 1)}{2a_w - a(x^*)}. \end{cases}$$

- Structure of stationary solutions as in 2-compartment model but dynamics may exhibit oscillations (Hopf Bifurcation)

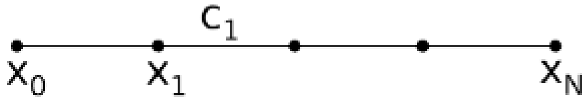




Doumic, Marciniak-Czochra, Perthame, Zubelli, SIAM Appl. Math. 2011

Link between the two models

Unexpected: Different structure of the steady states



Can we obtain the continuous model in a limit from the discrete model?

$$
\begin{aligned}
\frac{du_1}{dt} &= p_1(u_1, s) - g_1(u_1, s) - d_1 u_1, \\
\frac{du_i}{dt} &= g_{i-1}(u_{i-1}, s) + p_i(u_i, s) - g_i(u_i, s) - d_i u_i, \\
\frac{du_n}{dt} &= g_{n-1}(u_{n-1}, s) - d_n(u_n, s).
\end{aligned}
$$

$$g_i(u_i, s) = 2[1 - \frac{a(x)}{1+kv(t)}]p$$

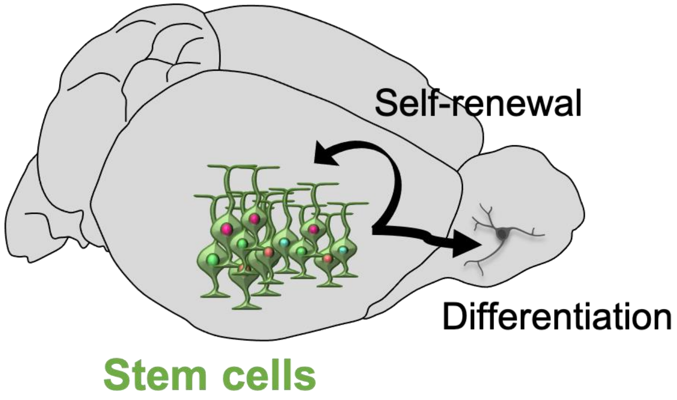
Answer: No! Only if we assume that differentiation is independent of the proliferation

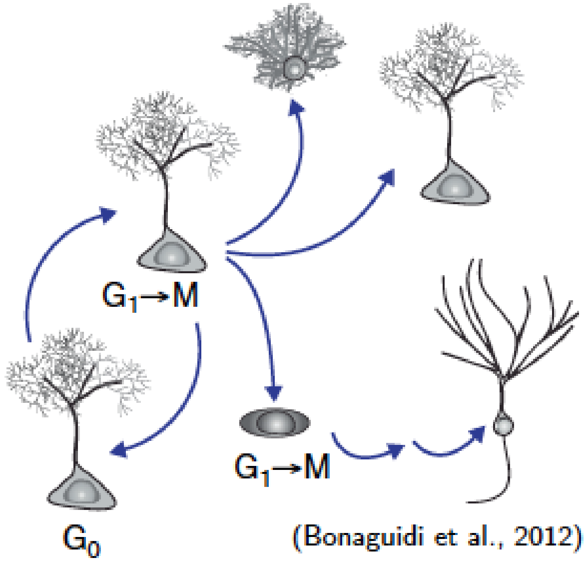
Doumic, Marciniak-Czochra, Perthame, Zubelli, SIAM Appl. Math. 2011

Tailoring mathematical approach to the character of data sets

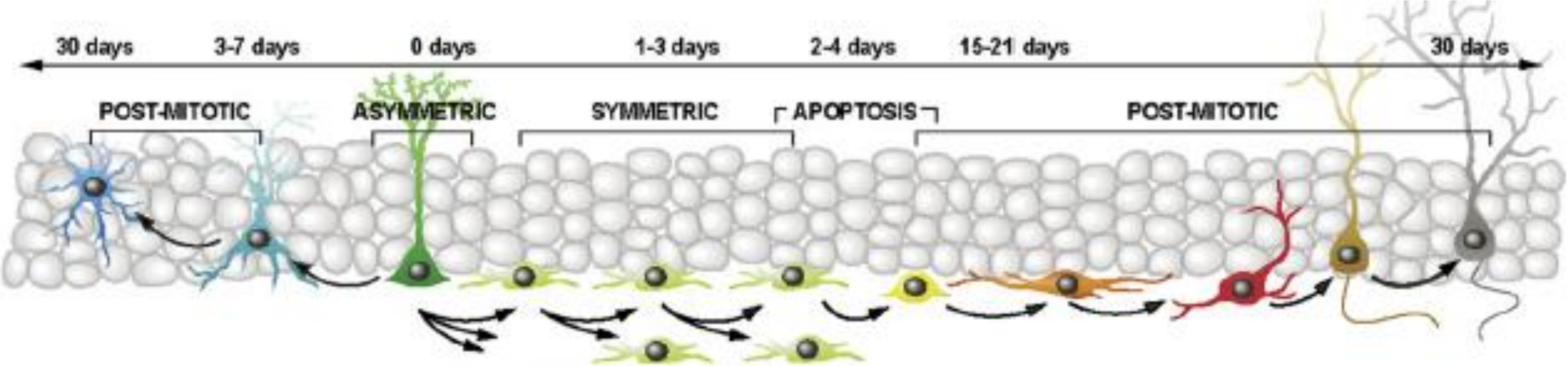
On example of neurogensis

Neural stem cell (NSC) system in adult mouse





(Bonaguidi et al., 2012)



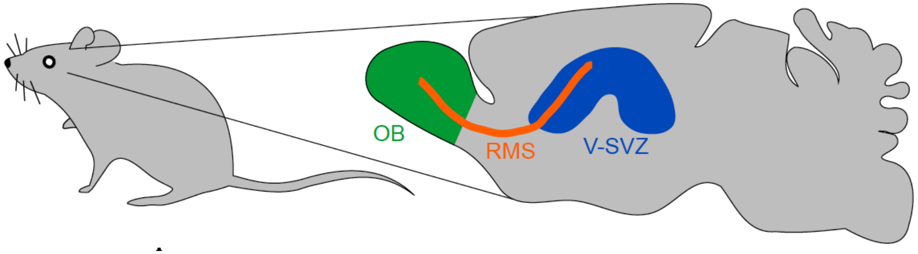
Data: SVZ and hippocampus of adult mice

- classical population data
- single cell transcriptomics

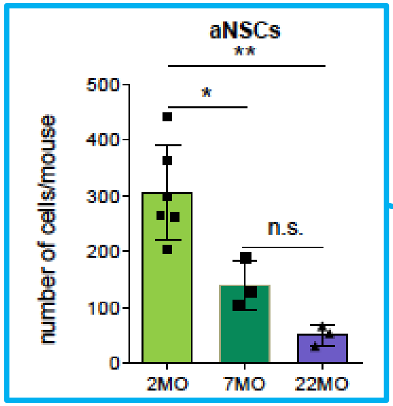
Modelling stem cell-based systems on example of adult neurogenesis:

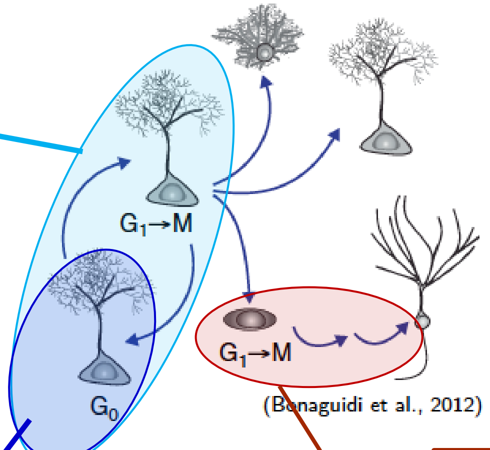
→ Basic compartmental model
→ Nonlinear feedbacks and model selection
→ Application to brain cancer (GBM)

Age-related changes in different cell populations



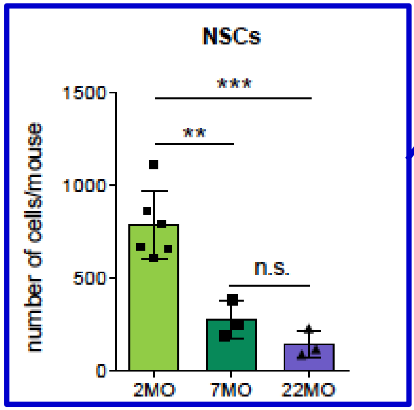
FACS
Analysis
(Glast+Prom1+)

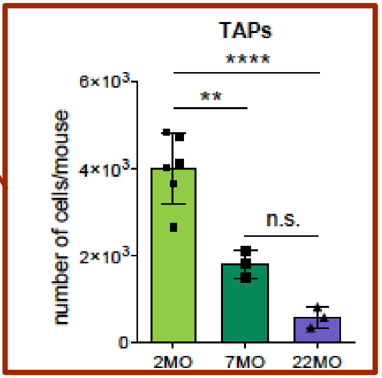




(Bonaguidi et al., 2012)

How can we explain the dynamics of NSC system?



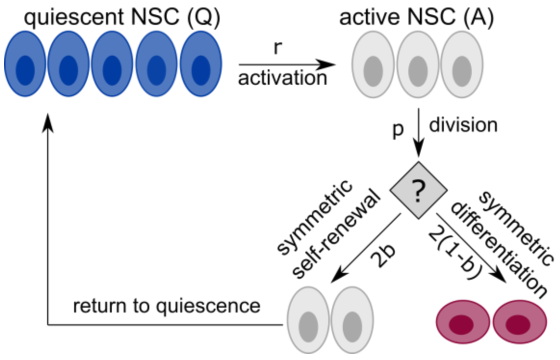


Kalamakis,…, Marciniak-Czochra and Martin-Villalba, *Cell*, 2019

Mathematical model

NSC system

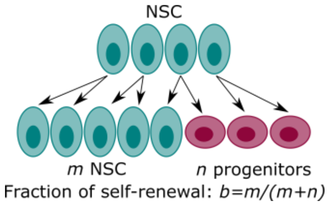
Processes



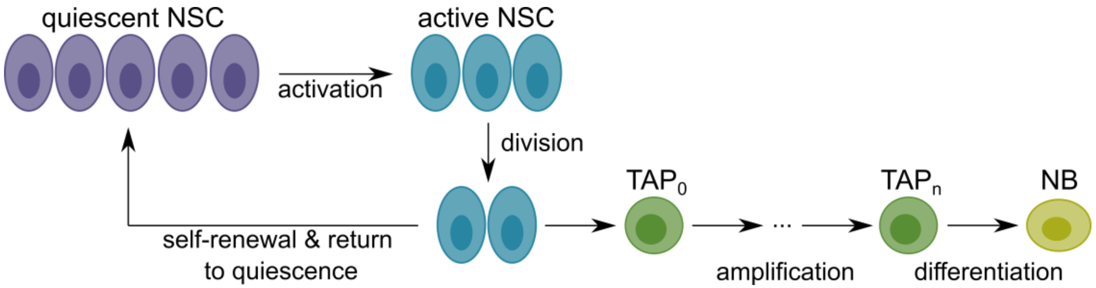
Mathematical model

$$\frac{d}{dt}Q = -rQ + 2bpA$$

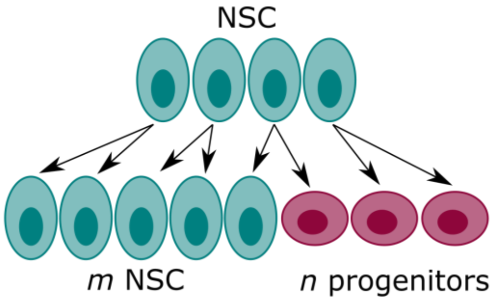
$$\frac{d}{dt}A = rQ - pA$$



Including additional data:



What is the effective self-renewal parameter?



b in the NSC model

$$\frac{d}{dt}\begin{pmatrix}\mathrm{qNSC}\\ \mathrm{aNSC}\end{pmatrix}(t)=\begin{pmatrix}-r & 2bp\\ r & -p\end{pmatrix}\begin{pmatrix}\mathrm{qNSC}\\ \mathrm{aNSC}\end{pmatrix}(t)$$

a in the HSC model

$$\frac{d}{dt}\,\mathrm{NSC(t)}=(2a-1)p\,\mathrm{NSC(t)}$$

The effective self-renewal parameter for the single SC compartment model is a function of *b* and *r*.

In the linear case:

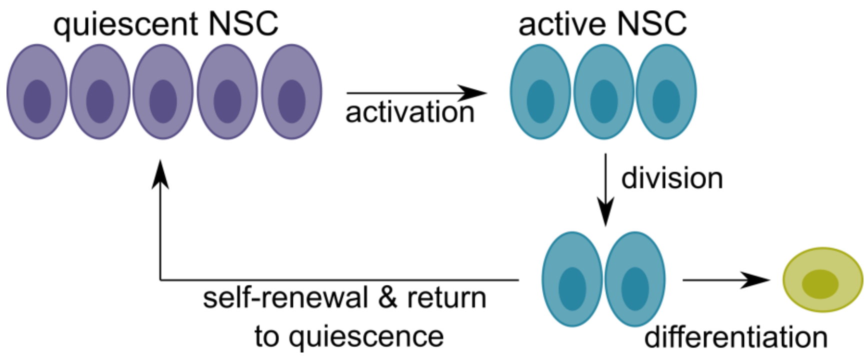
$$\frac{A}{Q+A}=F^*_{A_2}\Leftrightarrow Q+A=\frac{A}{F^*_{A_2}}$$

$$\frac{d}{dt}(Q+A)=(2b-1)pA=(2b-1)pF^*_{A_2}(A+Q)$$

$$a=\frac{(2b-1)F^*_{A_2}+1}{2}$$

but $F^*_{A_2}$ depends also on *r*

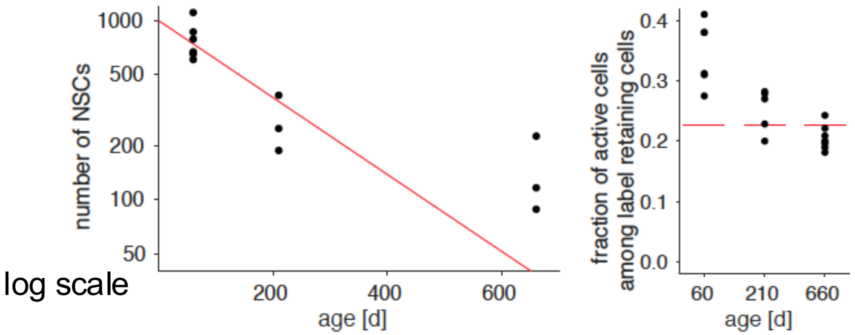
Stem cells dynamics


quiescent NSC
activation
active NSC
division
self-renewal & return to quiescence
differentiation

$$\frac{d}{dt}Q = -rQ + 2bpA$$
$$\frac{d}{dt}A = rQ - pA$$

Linear model:

- Decline of cell numbers
- Convergence of fractions of cell numbers to a quasi-stationary distribution
- Does not match the data!



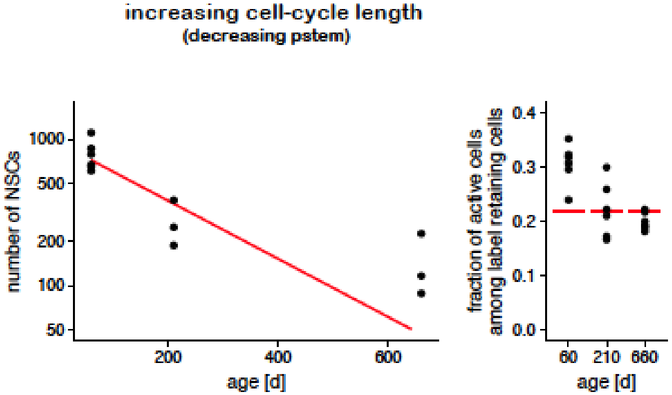
What mechanisms prevent the NSC pool from depletion?

Ziebell,…, Marciniak-Czochra, *Development*, 2018
Kalamakis,…, Marciniak-Czochra and Martin-Villalba, *Cell*, 2019

Model-based data analysis: Testing hypotheses

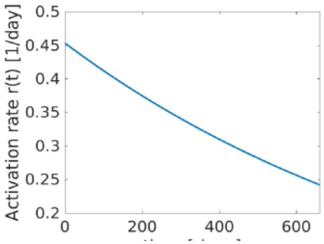
Hypothesis 1

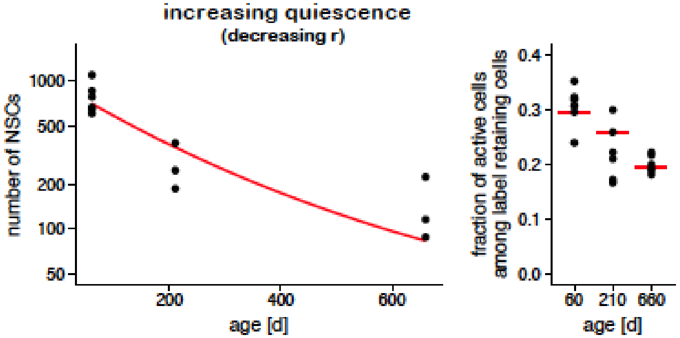
$$p(t) = p_{max} e^{-kt}$$


increasing cell-cycle length
(decreasing pstem)

Hypothesis 2

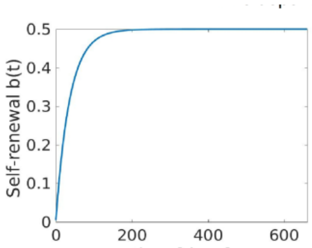
$$r(t) = r_{max} e^{-kt}$$

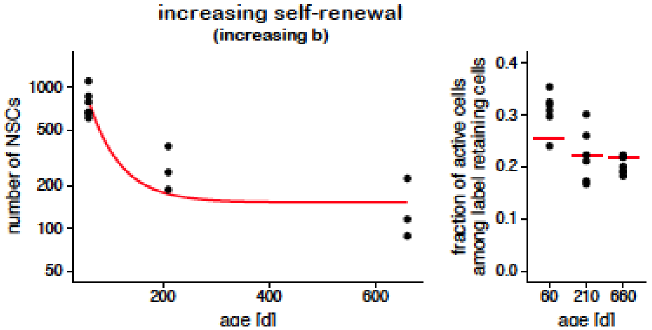



increasing quiescence
(decreasing r)

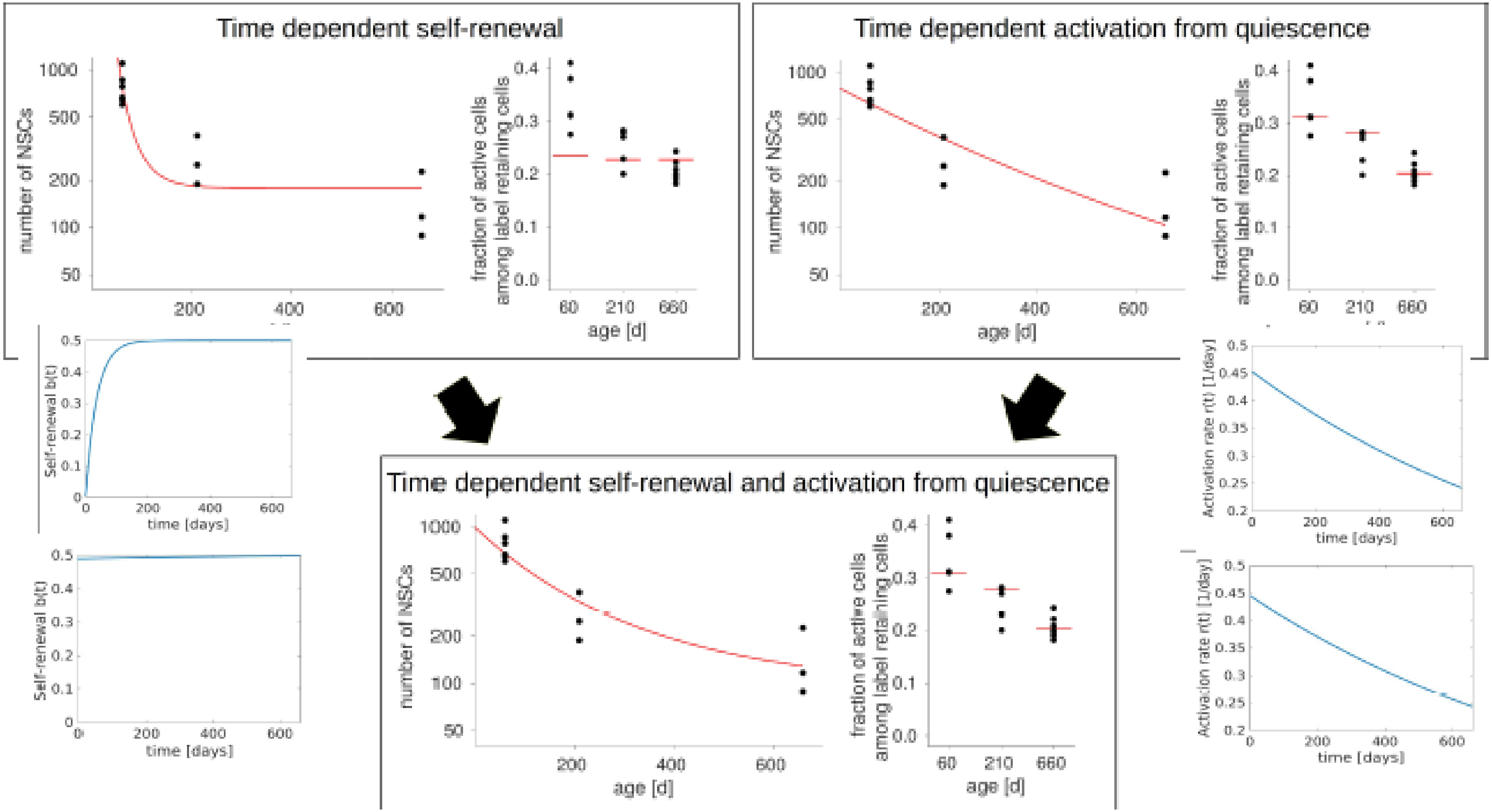
Hypothesis 3

$$b(t) = \frac{1}{2}\left(1 + e^{-\beta_b t}(2b_{\min} - 1)\right)$$



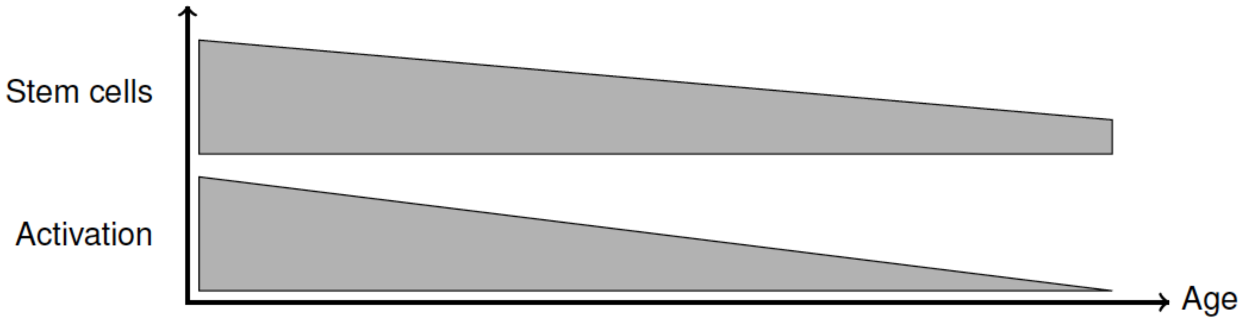

increasing self-renewal
(increasing b)

Model discrimination?



During aging stem cells become more quiescent

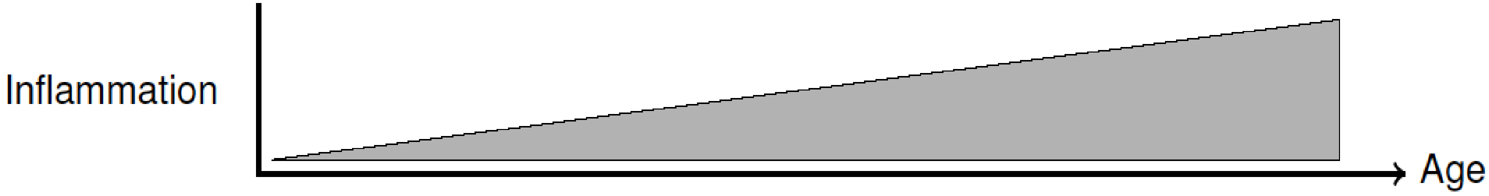
What keeps NSC quiescent?



Back to experimental data

- Bioinformatical data analysis identifies Wnt antagonist sFRP5 as a niche signal
- Model-based inference from perturbation experiments suggests that canonical Wnt activity promotes quiescence

Observation: Upregulation of expression of the interferon response genes

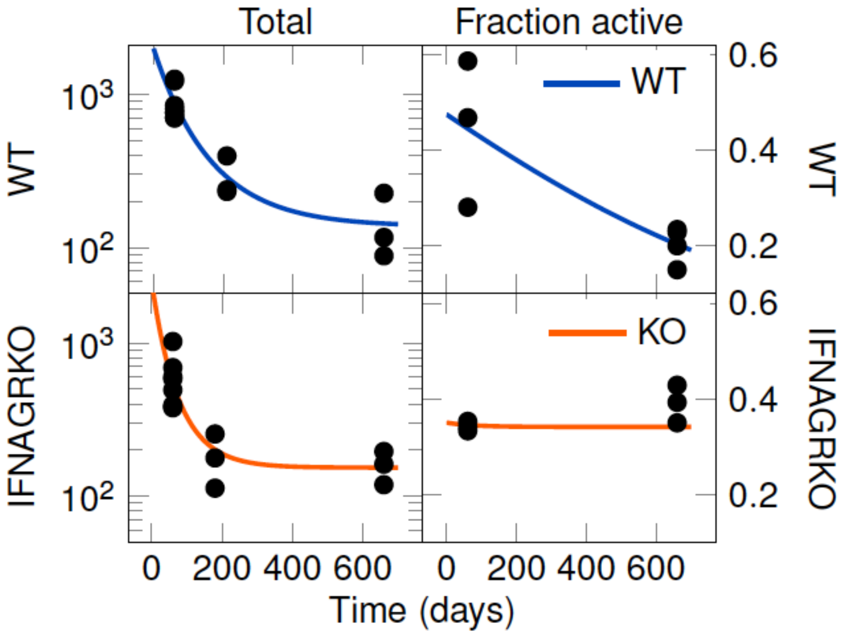


Do the niche inflamatory signals induce quiescence?

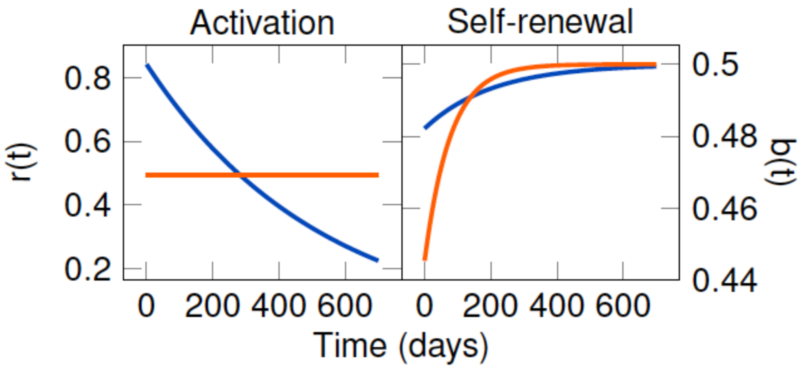
Perturbation experiment: Model-based data analysis

$$\frac{d}{dt}\mathrm{qNSC}(t) = -r \cdot \mathrm{qNSC}(t) + 2 \cdot b \cdot p_{\mathrm{stem}} \cdot \mathrm{aNSC}(t)$$

$$\frac{d}{dt}\mathrm{aNSC}(t) = r \cdot \mathrm{qNSC}(t) - p_{\mathrm{stem}} \cdot \mathrm{aNSC}(t)$$



Assumptions:
- fixed proliferation
- regulated activation
- regulated self-renewal

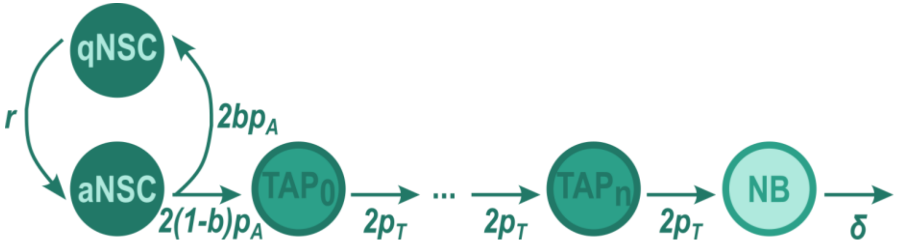


- IFN KO switches off regulation of the NSC activation
- The system compensates through an increased self-renewal

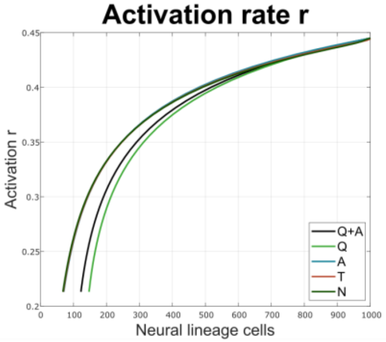
Carvajal-Ibañez, …, Marciniak-Czochra, Martin-Villalba, *EMBO Molecular Medicine*, 2023

How feedbacks depend on cell populations?

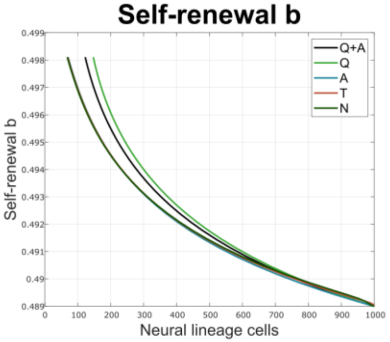
- *r* and *b* depend on subpopulations of neural lineage cells



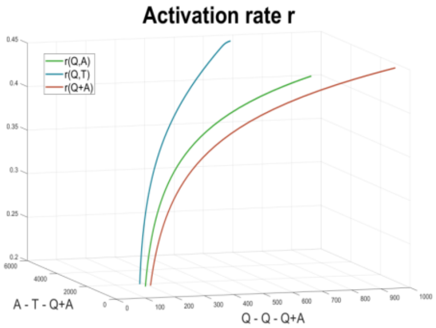
$$
\begin{aligned}
\frac{dQ}{dt} &= -rQ(t) + 2bp_A A(t)\\
\frac{dA}{dt} &= rQ(t) - p_A A(t)\\
\frac{dT_0}{dt} &= 2(1-b)p_A A(t) - p_T T_0(t)\\
\frac{dT_i}{dt} &= 2p_T T_{i-1}(t) - p_T T_i(t)\\
\frac{dT_n}{dt} &= 2p_T T_{n-1}(t) - p_T T_n(t)\\
\frac{dN}{dt} &= 2p_T T_n(t) - \delta N(t)
\end{aligned}
$$



Activation rate r



Self-renewal b



Activation rate r

➢ Activating and inhibitory Hill functions →

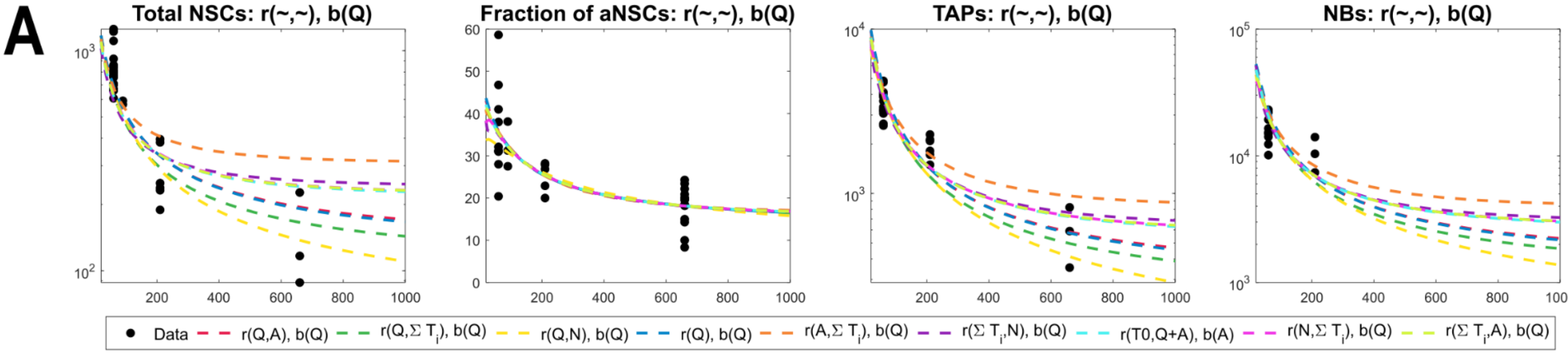
$$
\boxed{\begin{aligned}
r &= \frac{r_0 c_1(t)}{K + c_2(t)}\\
b &= \frac{b_0}{1 + \beta c_3(t)}
\end{aligned}}
$$

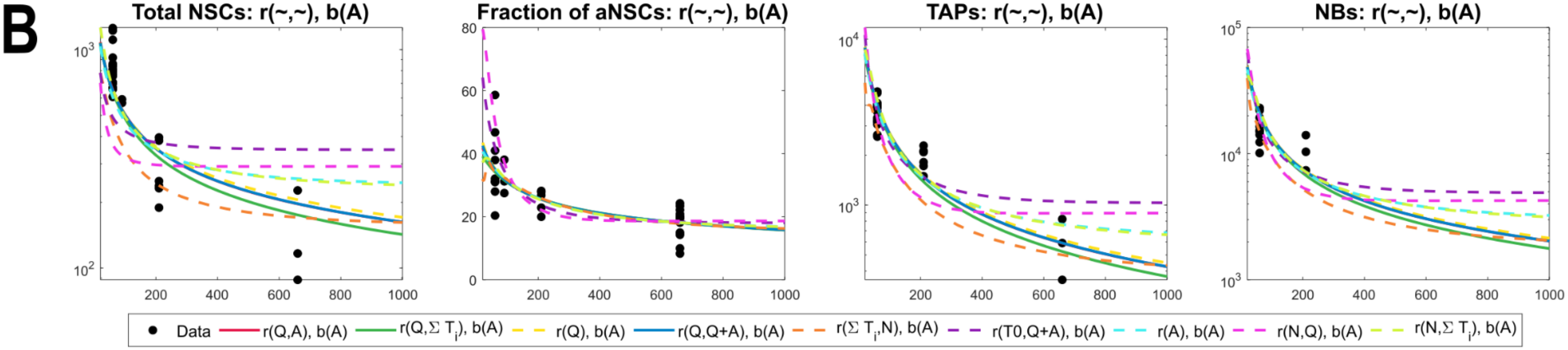
Different scenarios

- What to insert in c_i?

$$r = \frac{r_0 c_1(t)}{K + c_2(t)}$$

$$b = \frac{b_0}{1 + \beta c_3(t)}$$



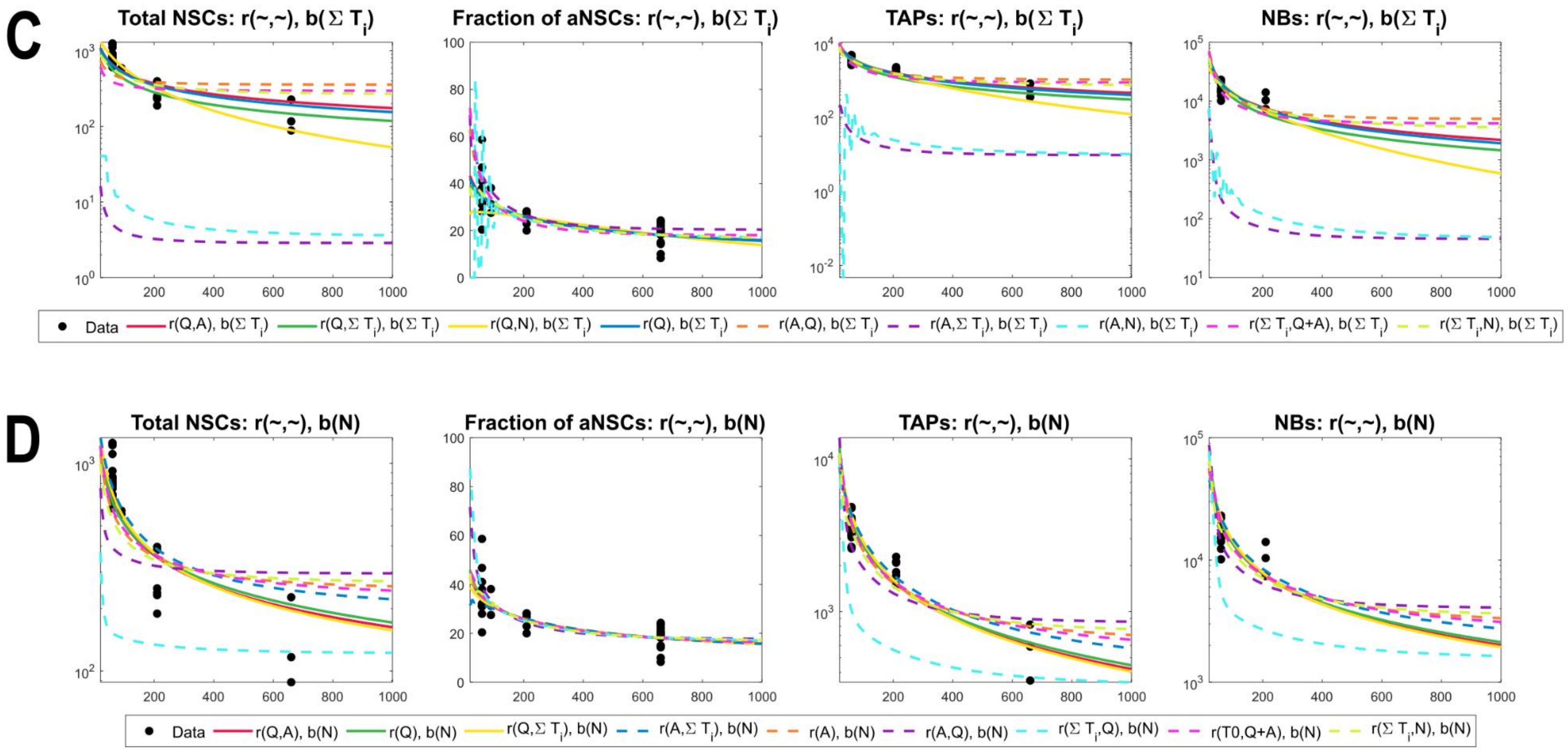


Even more scenarios

- What to insert in c_i?

$$r = \frac{r_0 c_1(t)}{K + c_2(t)}$$

$$b = \frac{b_0}{1 + \beta c_3(t)}$$



Selected scenarios

$$r(Q,A) := \frac{r_0 Q(t)}{K + A(t)}, \qquad b(A) := \frac{b_0}{1 + \beta A(t)}$$

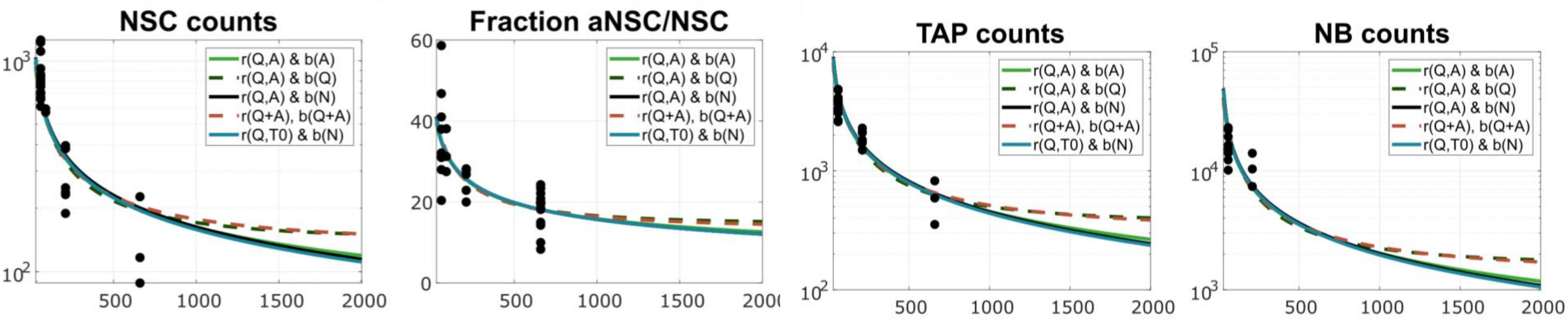
$$r(Q,A) := \frac{r_0 Q(t)}{K + A(t)}, \qquad b(Q) := \frac{b_0}{1 + \beta Q(t)}$$

$$r(Q,A) := \frac{r_0 Q(t)}{K + A(t)}, \qquad b(N) := \frac{b_0}{1 + \beta N(t)}$$

$$r(Q+A) := \frac{r_0 (Q(t) + A(t))}{K + (Q(t) + A(t))}, \qquad b(Q+A) := \frac{b_0}{1 + \beta (Q(t) + A(t))}$$

$$r(Q,T_0) := \frac{r_0 Q(t)}{K + T_0(t)}, \qquad b(N) := \frac{b_0}{1 + \beta N(t)}$$

- ➢ Q promotes activation
- ➢ Cells downstream inhibit activation



More insight from model analysis?

r(qNSC) & b(aNSC)

$$r = \frac{r_{max} \cdot Q(t)}{K + Q(t)}$$

$$b = \frac{b_{max}}{1 + \beta \cdot A(t)}$$

r(qNSC, aNSC) & b(aNSC)

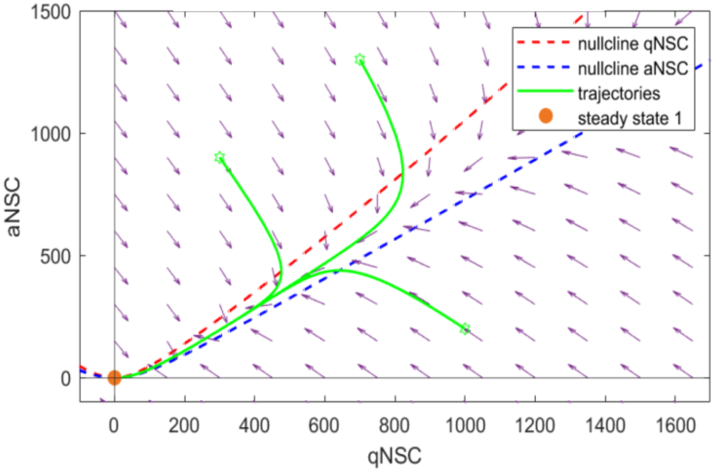
$$r = \frac{r_{max} \cdot Q(t)}{K + A(t)}$$

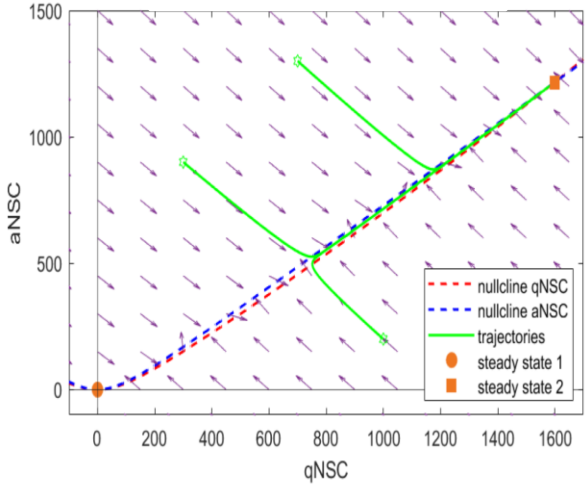
$$b = \frac{b_{max}}{1 + \beta \cdot A(t)}$$

r(qNSC, aNSC) & b(NB)

$$r = \frac{r_{max} \cdot Q(t)}{K + A(t)}$$

$$b = \frac{b_{max}}{1 + \beta \cdot N(t)}$$





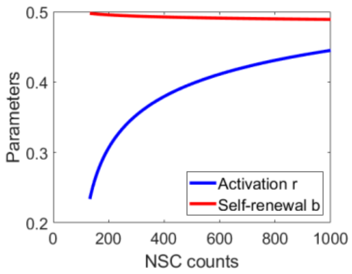
- All nonlinear models have the same structure of steady states (similar to the structure of steady states in the blood model)
- Self-renewal smaller than 0.5 implies lack of homeostasis
- Self-renewal larger than 0.5 but small yields positive steady state which however cannot be detected (is small)

Danciu, …, Marciniak-Czochra, *npj Systems Biology and Applications*, 2025

Model identifies shape of feedback, but various scenarios are equally able to recapitulate the experimental data

Activation: $r = \dfrac{r_{max} \cdot cells(t)}{K_r + cells(t)}$

Self-renewal: $b = \dfrac{b_{max}}{1 + \beta_b \cdot cells(t)}$



What does it mean in terms of molecular signaling?

$$r = r_{max} \cdot S_1$$

$$\frac{dS_1}{dt} = \underbrace{cells(t)}_{\text{Production by } \textbf{lineage cells}} - \underbrace{K_r S_1(t)}_{\text{Degradation}} - \underbrace{cells(t) S_1(t)}_{\text{Consumption by lineage cells}}$$

$$b = b_{max} \cdot S_2$$

$$\frac{dS_2}{dt} = \underbrace{1}_{\text{Production by } \textbf{niche (non-lineage cells)}} - \underbrace{S_2(t)}_{\text{Degr.}} - \underbrace{\beta_b \cdot cells(t) S_2(t)}_{\text{Consumption by lineage cells}}$$

Reverting the question: Which cells do what?

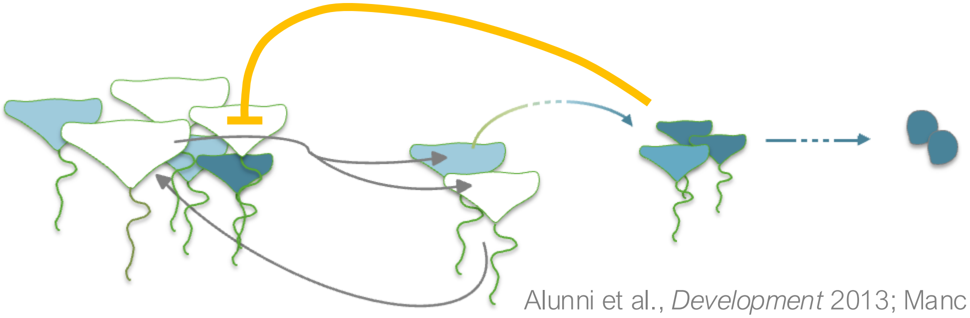
- Which cells produce and bind S_1, and which cells bind S_2?
- Which cells regulate the activation rate *r* and the fraction of self-renewal *b*?

Back to experimental evidence

Back to experimental knowledge

Delta-Notch singalling

DeltaA-Notch3 promotion of quiescence in neighboUrs



$$\frac{dS_r}{dt} = R_0 A - S_r - \beta_r S_r Q, \quad \text{with} \quad r(S_r) \sim \frac{1}{1+S_r}$$

Alunni et al., *Development* 2013; Mancini et al., *Sci. Adv.* 2023

New scenario: $r = \frac{r_1 + r_0 Q}{K + Q + A} =: r(Q, Q+A)$

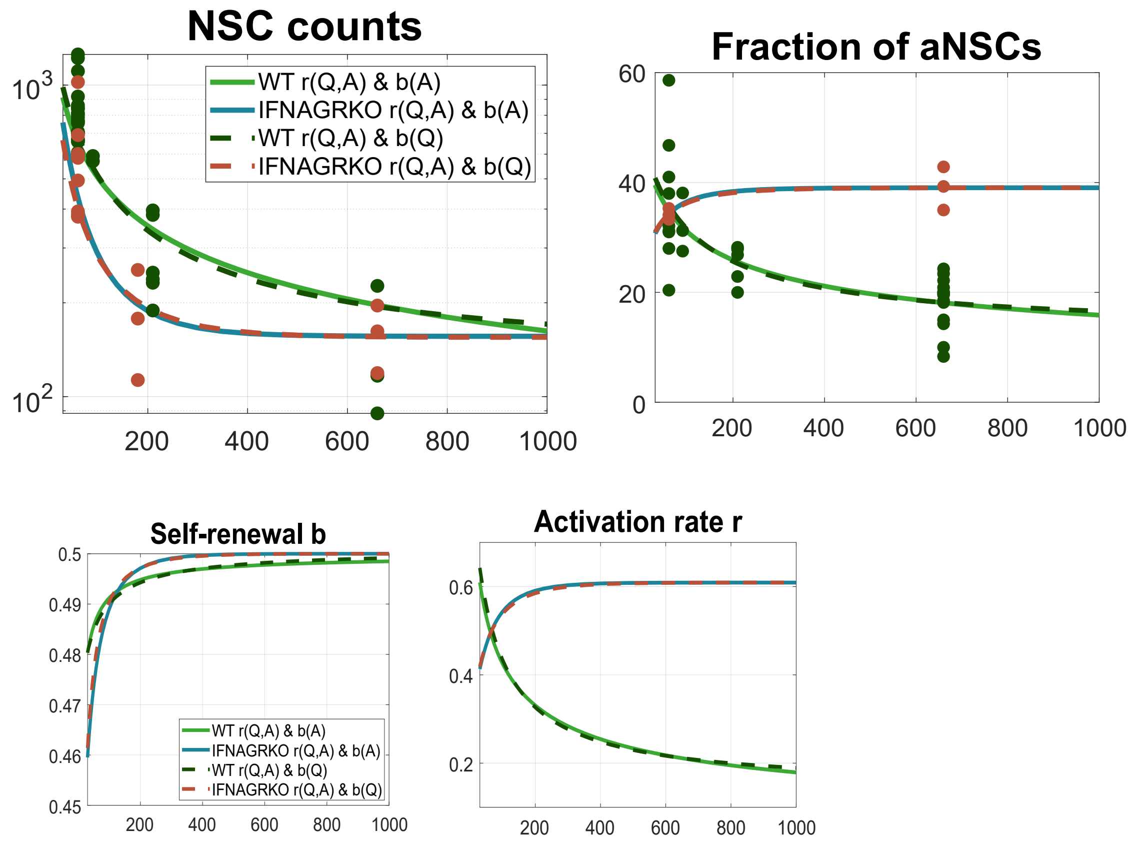
Wnt signalling can be linked to our typical b(Q) formula

$$b(Q) := \frac{b_0}{1 + \beta Q(t)}$$

- produced by the niche cells
- bound by quiescent cells

Danciu, …, Marciniak-Czochra, *npj Systems Biology and Applications*, 2025

Perturbation experiments: Inflamation


NSC counts

Fraction of aNSCs

Self-renewal b

Activation rate r

→

$$r = \frac{\boxed{r_1} + r_0 c_1}{K + c_2}$$

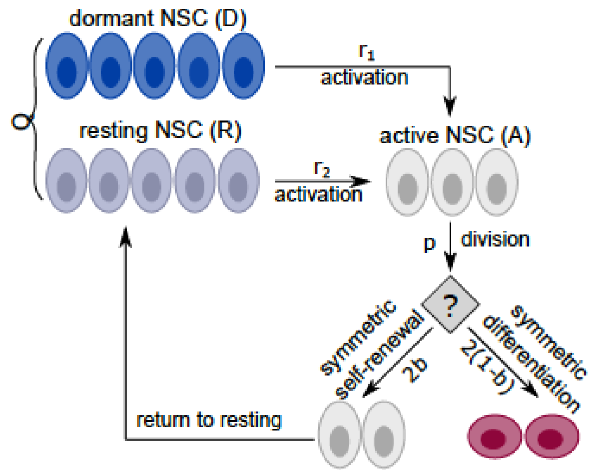
Activation regulated by the niche

- Can capture both the decreasing fraction of active cells in WT and the increasing one in KO mice
- Parameter estimation finds $r_0 \approx 0$ for INFAGRKO data
- Activation is disregulated in IFN KO and the self-renewal compensates

Danciu, …, Marciniak-Czochra, *npj Systems Biology and Applications*, 2025

Exploring inter-cellular heterogeneity

How to account for NSC heteorgeneity?

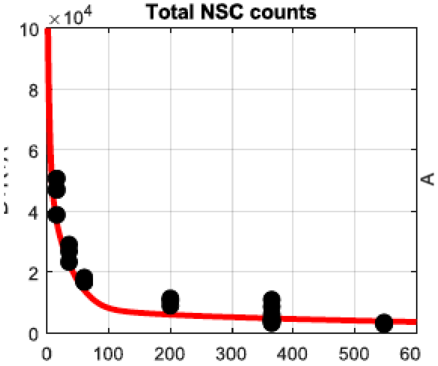


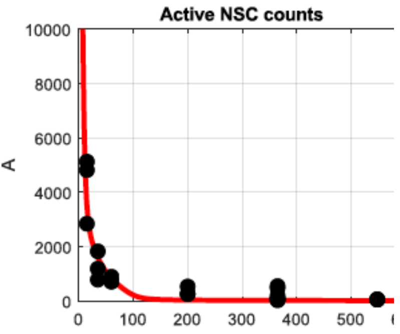
$$
\begin{aligned}
\frac{d}{dt}D &= -r_1 D \\
\frac{d}{dt}R &= -r_2 R + 2bpA \\
\frac{d}{dt}A &= r_2 R - pA + r_1 D
\end{aligned}
$$

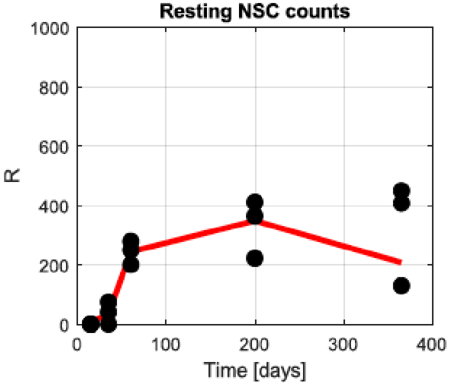
Dormant cells

Resting cells

Active cells







Estimated:

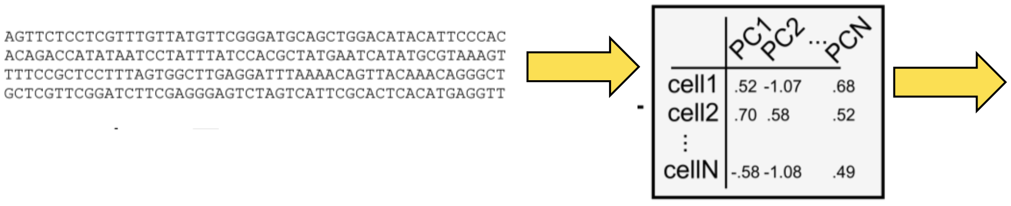
$$
\begin{aligned}
r_{max,1} &= 0.020 \\
r_{max,2} &= 3390
\end{aligned}
$$

Poulation of the quiescent stem cells is not homogeneous

Harris,…, Marciniak-Czochra and Guillemot, *Cell Stem Cells*, 2021

Population dynamics vs. single-cell data

Single-cell data analysis:



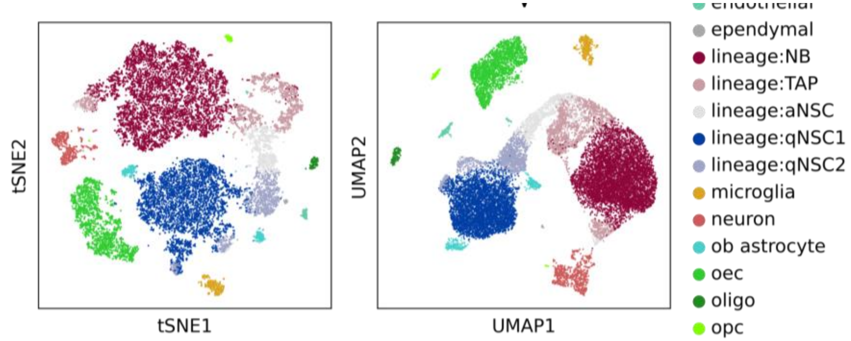
Single-cell sequencing

```
AGTTCTCCTCGTTTGTTATGTTCGGGATGCAGCTGGACATACATTCCCAC
ACAGACCATATAATCCTATTTATCCACGCTATGAATCATATGCGTAAAGT
TTTCCGCTCCTTTAGTGGCTTGAGGATTTAAAACAGTTACAAACAGGGCT
GCTCGTTCGGATCTTCGAGGGAGTCTAGTCATTCGCACTCACATGAGGTT
```

	PC1	PC2	…	PCN
cell1	.52	-1.07		.68
cell2	.70	.58		.52
⋮				
cellN	-.58	-1.08		.49

Dimensiality reduction (PCA)

Two-dimensional “embeddings”



Data show single cell heterogeneity in a high-dimensional space of transcriptome-based features

Can we use the data for mechanistic modelling?

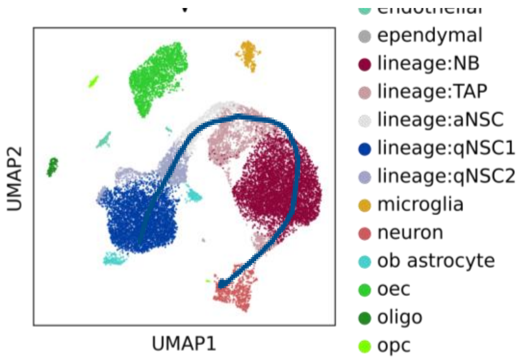
Kalamakis,…, Marciniak-Czochra and Martin-Villalba, *Cell*, 2019

From data to the underlying processes

Problems:

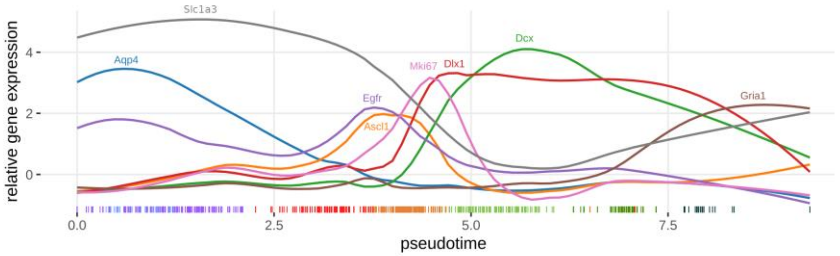
- ➢ No time resolution

Limitations of the concept of a pseudotime, i.e. a curve fitted to the data to visualise an average path of the differentiation process



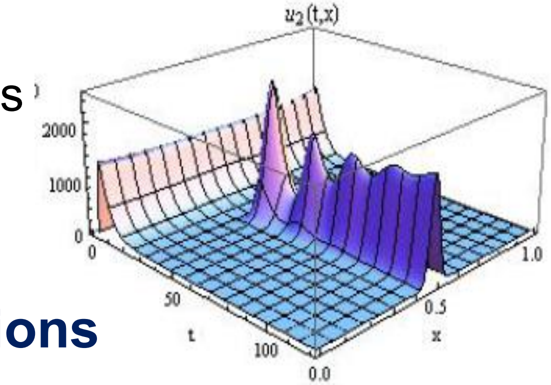
- ➢ Unclear in how far heterogeneity reflects continuity of the underlying processes

  - ➢ Clustering does not match the markers used in the population dynamics data



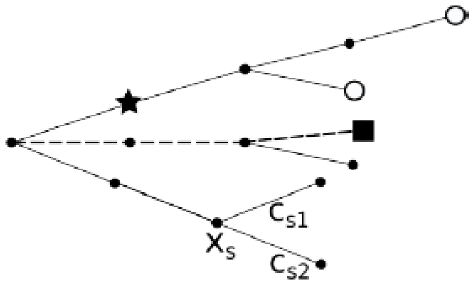
Need for a new mathematical framework?

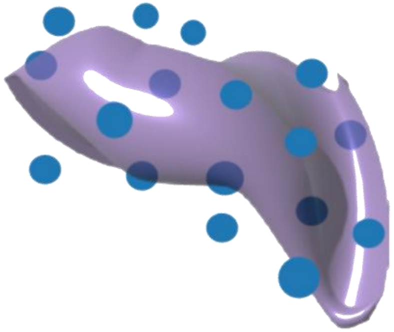
- **Concentration effects:**
  - Initial conditions describing homogeneous populations
  - Effects of nonlocal and nonlinear dynamics (e.g. selection models)



- **Co-existence of discrete and continuous transitions**

State space?





- Graphs
- Riemannian manifolds
- …

→ **Models describing evolution of measures (on metric spaces)**

(Measure) Structured Population Model

$\mu_\bullet$ denotes a family of measures $\{\mu_t\}_{t\in[0,T]}$

μ_t represents the evaluation of μ at a given time point t.

PDE formulation on $[0,\, T] \times \mathbb{R}^d$

$$\boxed{\partial_t \mu_t + \nabla_x \cdot (b(t,x,\mu_t)\mu_t) = c(t,x,\mu_t)\mu_t + \int_{\mathbb{R}^d} \eta(t,x,\mu_t)(y)\,\mathrm{d}\mu_t(y)}$$

with some initial measure $\mu_0 = \nu \in \mathcal{M}^+(\mathbb{R}^d)$ and model functions

$b : [0,\, T] \times \mathbb{R}^d \times \mathcal{M}^+(\mathbb{R}^d) \to \mathbb{R}^d,$ (flow of the vector field)

$c : [0,\, T] \times \mathbb{R}^d \times \mathcal{M}^+(\mathbb{R}^d) \to \mathbb{R},$ (growth)

$\eta : [0,\, T] \times \mathbb{R}^d \times \mathcal{M}^+(\mathbb{R}^d) \to \mathcal{M}^+(\mathbb{R}^d),$ (spread of heterogeneity)

Düll, Gwiazda, Marciniak-Czochra, Skrzeczkowski, *Cambridge Univ.* 2021

Measure spaces

Setting:

$$\mathcal{M}(S) = \{\ \mu \mid \mu \text{ is a finite and signed Radon measure}\}$$

$$\mathcal{M}^+(S) = \{\mu \in \mathcal{M}(S) \mid \mu \geq 0\}$$

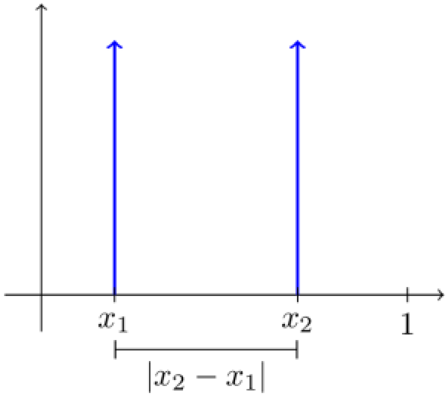
Which distance?

$$\|\mu\|_{TV} := \mu^+(S) + \mu^-(S).$$

Unfortunately, total variation generates a topology which is too strong for applications, as e.g.

$$\|\delta_a - \delta_b\|_{TV} = \delta_a(S) + \delta_b(S) = 2 \qquad \forall a \neq b$$

$\Rightarrow$ Measure solutions will not be continuous with respect to $\|\cdot\|_{TV}$



Dual bounded Lipschitz distance (flat/ Fortret-Mourier/ Kantorovich-Rubinstein norm)

Definition

The **flat norm** (or **bounded Lipschitz norm**) is defined by

$$\|\mu\|_{BL^*} = \sup\left\{ \int_S \psi \, \mathrm{d}\mu \mid \psi \in BL(S), \|\psi\|_{BL} \leq 1 \right\},$$

where the class of test functions is given by the **space of bounded Lipschitz functions**

$$BL(S) = \left\{ \psi \in C^0(S) \mid \|\psi\|_{BL} < \infty \right\}.$$

Here, $\|\psi\|_{BL} = \max\{\|\psi\|_\infty, |\psi|_{\mathbf{Lip}}\}$ with

$$\|\psi\|_\infty = \sup_{x \in S} |\psi(x)|, \qquad |\psi|_{\mathbf{Lip}} = \sup_{x \neq y} \frac{|\psi(x) - \psi(y)|}{|x - y|}.$$

Is the flat norm better for our purposes?

It defines a weaker norm than the total variation

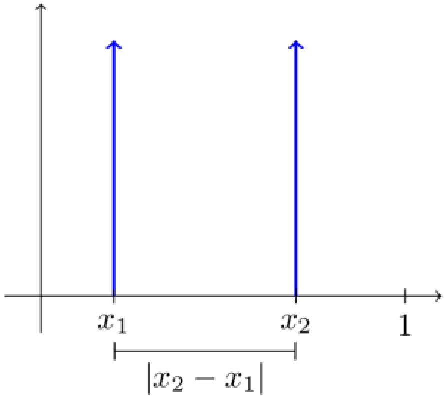
$$||\mu||_{\mathrm{BL}^*} \leq ||\mu||_{\mathrm{TV}}$$

It holds now:

$$||\delta_{x_n} - \delta_x||_{\mathrm{BL}^*} = \sup_{\substack{\psi \in \mathrm{BL}(S) \\ ||\psi||_{\mathrm{BL}} \leq 1}} |\psi(x_n) - \psi(x)| \leq d(x_n, x) \to 0 \text{ as } n \to \infty.$$

Lemma: *Let (S, d) be a metric space. Let $x, y \in S$. Then $||\delta_x||_{\mathrm{BL}^*} = 1$ and*

$$||\delta_x - \delta_y||_{\mathrm{BL}^*} = \min\{2, d(x, y)\}.$$



Functional analytic properties

$\mathcal{M}(S)$ equipped with the dual bounded Lipschitz distance

Separability

Theorem: *Let (S, d) be a separable metric space. Then the metric space $(\mathcal{M}(S), \|\cdot\|_{\mathrm{BL}^*})$ is separable.*

Completeness

Theorem: *Let (S, d) be a metric space. Then, the following equivalence holds:*

(i) $\overline{\mathcal{M}(S)}^{\|\cdot\|_{\mathrm{BL}^*}} = \mathcal{M}(S)$.

(ii) *S is uniformly discrete.* $\inf_{\substack{x \neq y \\ x,y \in A}} d(x,y) > 0$

But the positive cone $(\mathcal{M}^+(S), \rho_F)$ is complete

Sequential compatness (for tight measures)

Düll, Gwiazda, Marciniak-Czochra, Skrzeczkowski, *Cambridge Univ. Press*, 2021

PDE model: Well-posedness

$$\partial_t \mu_t + \nabla_x \cdot (b(t,x,\mu_t)\mu_t) = c(t,x,\mu_t)\mu_t + \int_{\mathbb{R}^d} \eta(t,x,\mu_t)(y)\,\mathrm{d}\mu_t(y) \qquad (1)$$

Theorem (Existence, Uniqueness and continuous dependence on model ingredients)

Under suitable assumptions, there exists a unique Lipschitz continuous solution $\mu : [0,T] \to (\mathcal{M}^+(\mathbb{R}^d), \rho_F)$ *to model* (1) *with initial measure* $\mu_0 \in \mathcal{M}^+(\mathbb{R}^d)$. *Moreover, the solution is continuous with respect to time, initial measure as well as model functions.*

Düll, Gwiazda, Marciniak-Czochra, Skrzeczkowski, *M3AS*, 2024

PDE model: Weak solutions

$$\partial_t \mu_t + \nabla_x \cdot (b(t,x,\mu_t)\mu_t) = c(t,x,\mu_t)\mu_t + \int_{\mathbb{R}^d} \eta(t,x,\mu_t)(y)\,\mathrm{d}\mu_t(y) \qquad (1)$$

Definition

A family of measures $\mu_\bullet \subset \mathcal{M}^+(\mathbb{R}^d)$ is a **measure solution** to (1) provided $t \mapsto \mu_t$ is narrowly continuous and satisfies a weak formulation for any test function $\varphi \in C^1([0,T] \times \mathbb{R}^d) \cap W^{1,\infty}([0,T] \times \mathbb{R}^d)$.

$$\begin{aligned}\int_{\mathbb{R}^d} \varphi(T,x)\,\mathrm{d}\mu_T(x) - \int_{\mathbb{R}^d} \varphi(0,x)\,\mathrm{d}\mu_0(x) &= \int_0^T \int_{\mathbb{R}^d} \partial_t\varphi(t,x)\,\mathrm{d}\mu_t(x)\,\mathrm{d}t \\ &+ \int_0^T \int_{\mathbb{R}^d} (\nabla_x\varphi(t,x) \cdot b(t,x,\mu_t) + \varphi(t,x)\,c(t,x,\mu_t))\,\mathrm{d}\mu_t(x)\,\mathrm{d}t \\ &+ \int_0^T \int_{\mathbb{R}^d} \left(\int_{\mathbb{R}^d} \varphi(t,y)\,\mathrm{d}[\eta(t,x,\mu_t)](y)\right)\mathrm{d}\mu_t(x)\,\mathrm{d}t\end{aligned}$$

Düll, Gwiazda, Marciniak-Czochra, Skrzeczkowski, *M3AS*, 2024

Duality formula

Linear transport equation in the conservative form

$$\partial_t \mu_t + \partial_x (b\, \mu_t) = 0 \quad \text{in } \mathbb{R} \times [0, T]$$

where $b : \mathbb{R} \longrightarrow \mathbb{R}$ is bounded and Lipschitz continuous and initial condition is $\mu_0 \in \mathcal{P}(\mathbb{R})$

Dual problem (backward equation)

$\varphi \in C^1(\mathbb{R} \times [0, t], \mathbb{R})$ denotes the unique solution of

$$\begin{aligned} \partial_\tau \varphi + b(x) \partial_x \varphi &= 0 \quad \text{in } \mathbb{R} \times [0, t] \\ \varphi(\cdot, t) &= \psi \quad \text{in } \mathbb{R} \end{aligned}$$

For every $\mu_0 \in \mathcal{M}(\mathbb{R})$, a solution $\mu : [0, T] \longrightarrow \mathcal{M}(\mathbb{R})$ of the linear problem in distributional sense is given by

$$\boxed{\int_{\mathbb{R}^+} \psi(x)\ \mu_t(dx) = \int_{\mathbb{R}^+} \varphi(x, 0)\ \mu_0(dx)}$$

for each time $t \in [0, T]$ and every test function $\psi \in C^1(\mathbb{R}, \mathbb{R}) \cap L^\infty(\mathbb{R}, \mathbb{R})$.

DiPerna and Lions, 1989

Roadmap of the proof: Solving the dual problem

Consider a linear version of the problem and solve the dual problem by method of characteristics.

$$\begin{cases} \partial_\tau \varphi_{\psi,t} + b \cdot \nabla_x \varphi_{\psi,t} + c\, \varphi_{\psi,t} + \int_{\mathbb{R}^d} \varphi_{\psi,t}(\tau, y)\, \mathrm{d}[\eta(\tau, x)]\,(y) = 0 & \text{in} \quad [0,t] \times \mathbb{R}^d, \\ \varphi_{\psi,t}(t, \cdot) = \psi & \text{in} \quad \mathbb{R}^d. \end{cases}$$

$$\begin{aligned} \varphi_{\psi,t}(\tau, x) = {} & \psi(X_b(t-\tau, x)) e^{\int_\tau^t c(r, X_b(r-\tau, x))\, \mathrm{d}r} \\ & + \int_\tau^t \int_{\mathbb{R}^d} \varphi_{\psi,t}(s, y)\, \mathrm{d}[\eta(s, X_b(s-\tau, x))](y) e^{\int_\tau^s c(r, X_b(r-\tau, x))\, \mathrm{d}r}\, \mathrm{d}s. \end{aligned}$$

where $X_b(t, \tau, x)$ denotes the unique solution of the ODE

$$\partial_t X_b(t, \tau, x) = b(t, X_b(t, \tau, x)) \qquad X_b(\tau, \tau, x) = x,$$

i.e. the flow generated by the vector field b.

Solution constructed using the duality formula

$$\int_{\mathbb{R}^d} \psi(x)\, \mathrm{d}\mu_t(x) = \int_{\mathbb{R}^d} \varphi_{\psi,t}(0,x)\, \mathrm{d}\mu_0(x)$$

with

$$\varphi_{\psi,t}(\tau,x) = \psi(X_b(t-\tau,x))e^{\int_\tau^t c(r,X_b(r-\tau,x))\,\mathrm{d}r}$$
$$+ \int_\tau^t \int_{\mathbb{R}^d} \varphi_{\psi,t}(s,y)\,\mathrm{d}[\eta(s,X_b(s-\tau,x))](y)e^{\int_\tau^s c(r,X_b(r-\tau,x))\,\mathrm{d}r}\,\mathrm{d}s.$$

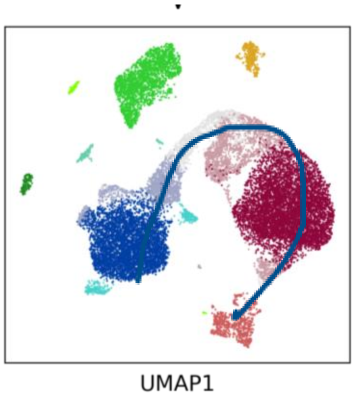
- μ_t satisfies a semigroup property
- μ_t satisfies the weak formulation

`Düll, Gwiazda, Marciniak-Czochra, Skrzeczkowski,` *`Cambridge Univ.`* `2021`

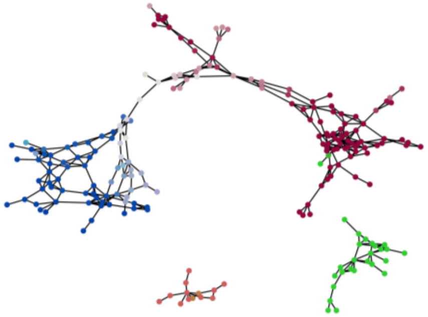
State space?

Data analysis:

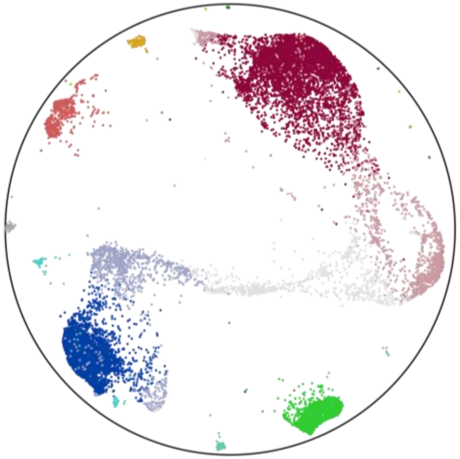
Find a correct description of the “transport” in the state space



Identifying the “pseudotime”



Topological data analysis

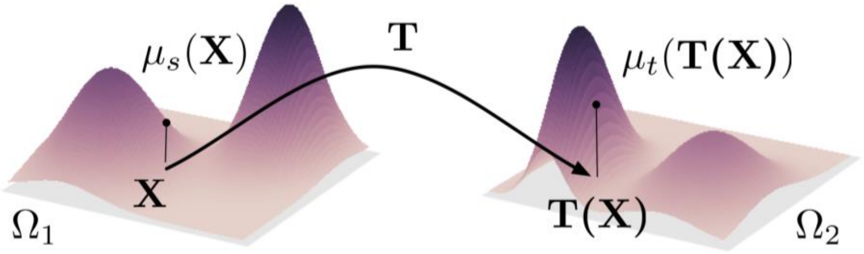


Hyperbolic geometry

Danciu, Hooli, Martin-Villalba, Marciniak-Czochra, Cells & Development, 2023

Model on a metric space

Continuous transitions in the features spaces described by push-forwards



Push-forward fromula:

$$T_{\#}\mu(B) := \mu(T^{-1}(B))$$

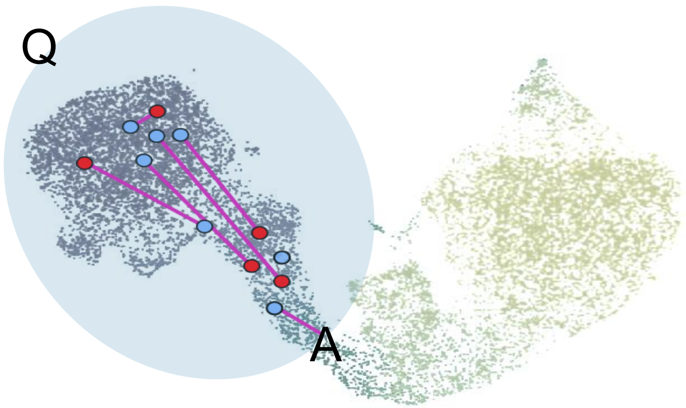
Optimal transport: $\mu_t = X(t,0,\cdot)_{\#}\mu_0(\cdot)$

Measure Structured Population Model

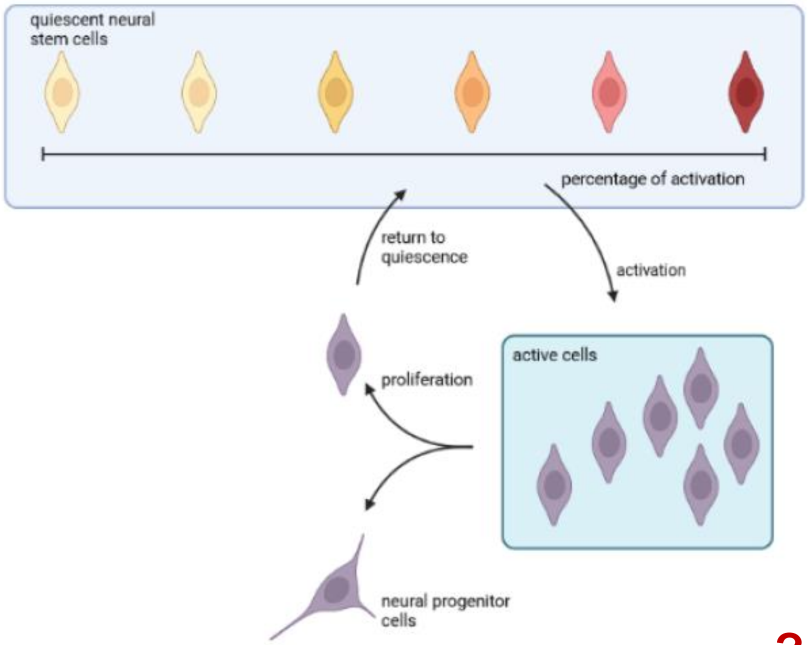
$$\mu_t = X(t,0,\cdot)_{\#}\left(\mu_0(\cdot)e^{\int_0^t c(s,X(s,0,\cdot))\,\mathrm{d}s}\right) + \int_0^t X(t,\tau,\cdot)_{\#}\left(\int_S [\eta(\tau,y)(\cdot)]\,\mathrm{d}\mu_\tau(y)e^{\int_\tau^t c(s,X(s,\tau,\cdot))\,\mathrm{d}s}\right)\mathrm{d}\tau$$

Düll, Gwiazda, Marciniak-Czochra, Skrzeczkowski, *M3AS*, *2024*

Transcriptomics-structured population model



$$
\begin{aligned}
\frac{d}{dt}Q &= -rQ + 2bpA \\
\frac{d}{dt}A &= rQ - pA
\end{aligned}
$$



$$\partial_t\mu_t + \partial_x\big(\overset{?}{\boxed{g(t,x,\mu_t)}}\mu_t\big) = -r(t,x,\mu_t)\mu_t + 2\cdot p(t,\mu_t)b(t,\mu_t)\overset{?}{\boxed{f(t,x,\mu_t)}}\mu_t(a)$$

$$\partial_t\mu_t(a) = \int_{\mathbb{R}^+} \underset{?}{\boxed{r(t,x,\mu_t)}}\,d\mu_t - p(t,\mu_t)\mu_t(a).$$

?

- derive from a particle system
- motivate experimentally

Summary: How to model heterogeneity?

- Stem cell-based systems exhibit great heterogeneity
- Functional relevance of the observed heterogeneity is not understood.
- Discrete and continuous structured population models may exhibit different dynamics
- Compartmental (ODE-based) models allow
  - linking population dynamics data with system's parameters
  - explaining age-dependent changes in neurogenesis
  - identifying within-system control mechanisms
- Linking single cell data with mechanistic mathematical modelling requires new concepts and integration of different mathematical and computational approaches.
- Structured population models can be considered in terms of measure evolutions and defined on Polish metric spaces

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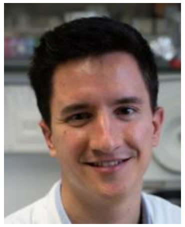
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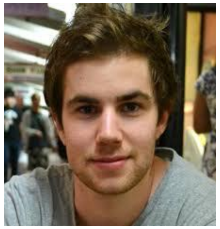
Lachlan Harris


François Guillemot