Modelling hematopoietic stem cells

and their interaction with the bone marrow micro-environment.

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The First Nordic Biomathematics Days, Helsinki
October 22^{nd}, 2019

Introduction and brief outline

- Brief introduction to stem cells.

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- Development of a mathematical model.
- Some basic features of the model.
- What does the model tell us?

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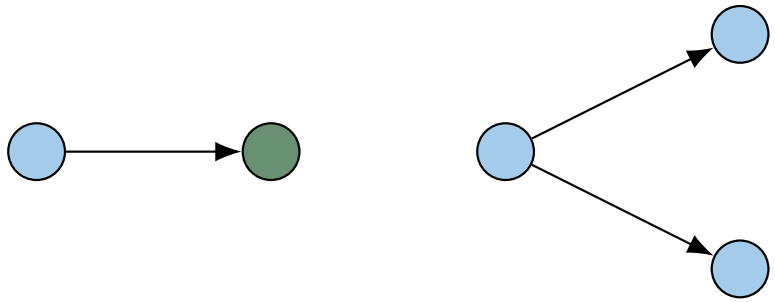

where ● are stem cells and ● is a differentiated/progenitor cell.

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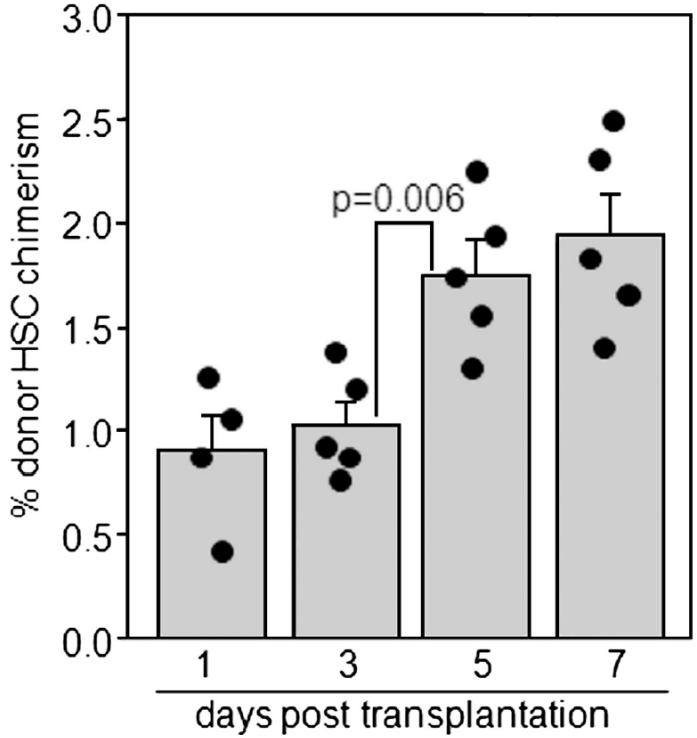

Figure: Mouse experiment data (**?**)

Hematopoietic stem cells and the bone marrow

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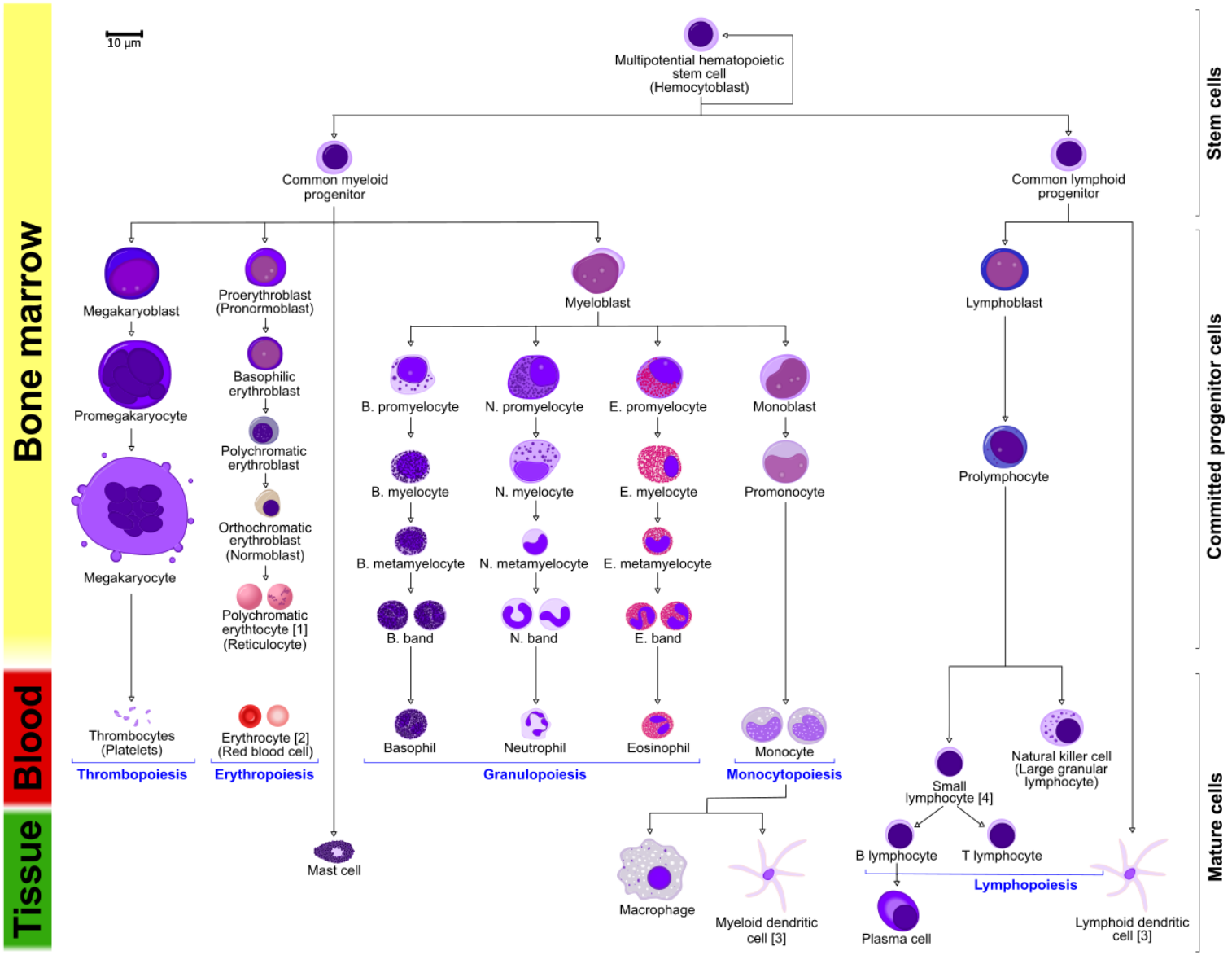

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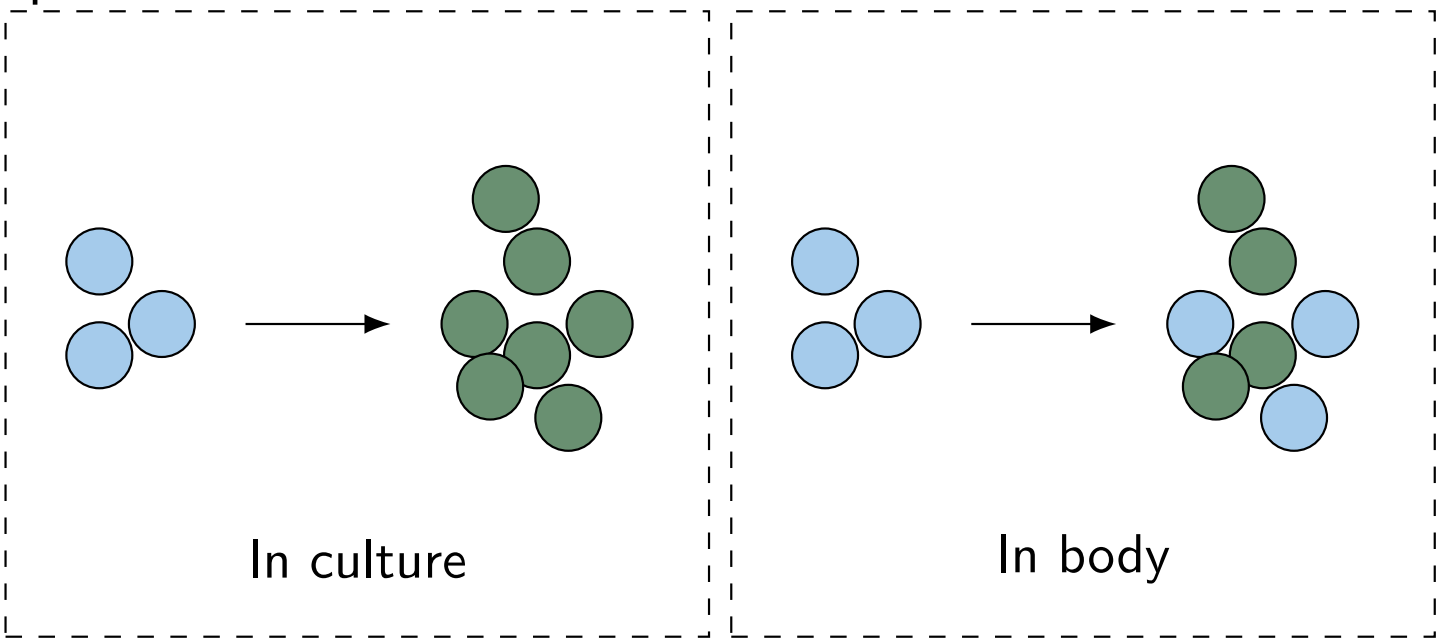
(**?**), (Wang, Stiehl et al. 2017), (**?**), (**?**).

Modelling of the HSCs and their niches

Experimental observation:



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Central hypothesis:
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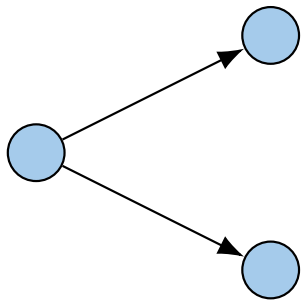

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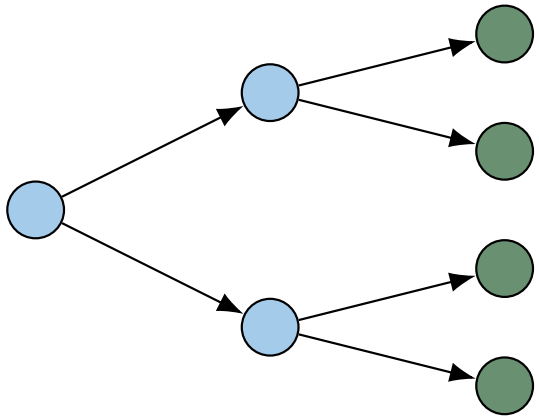

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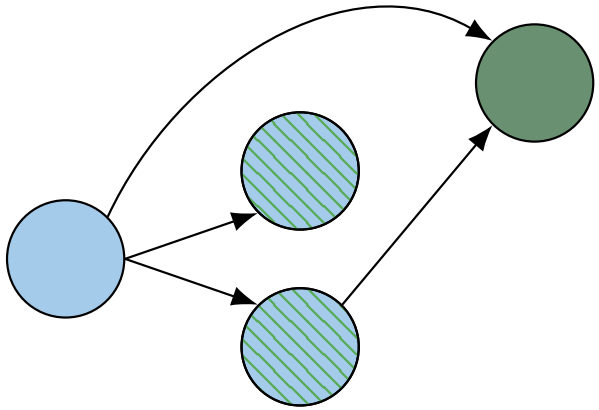

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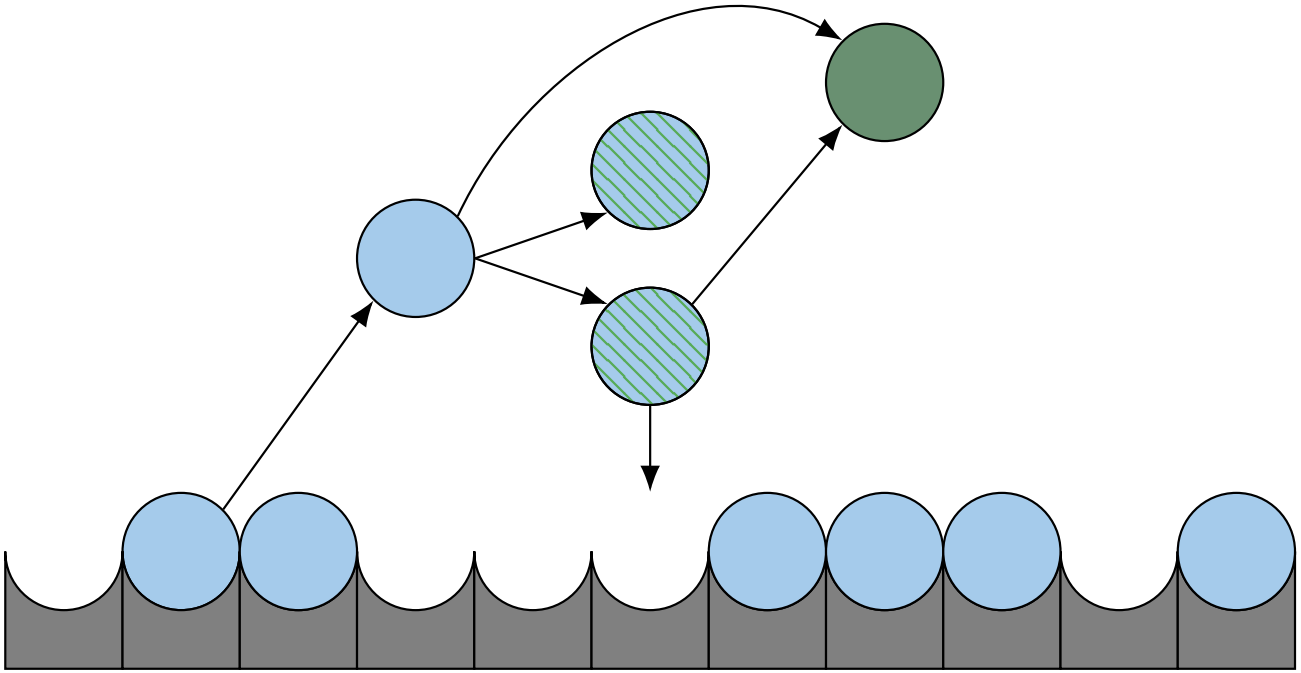

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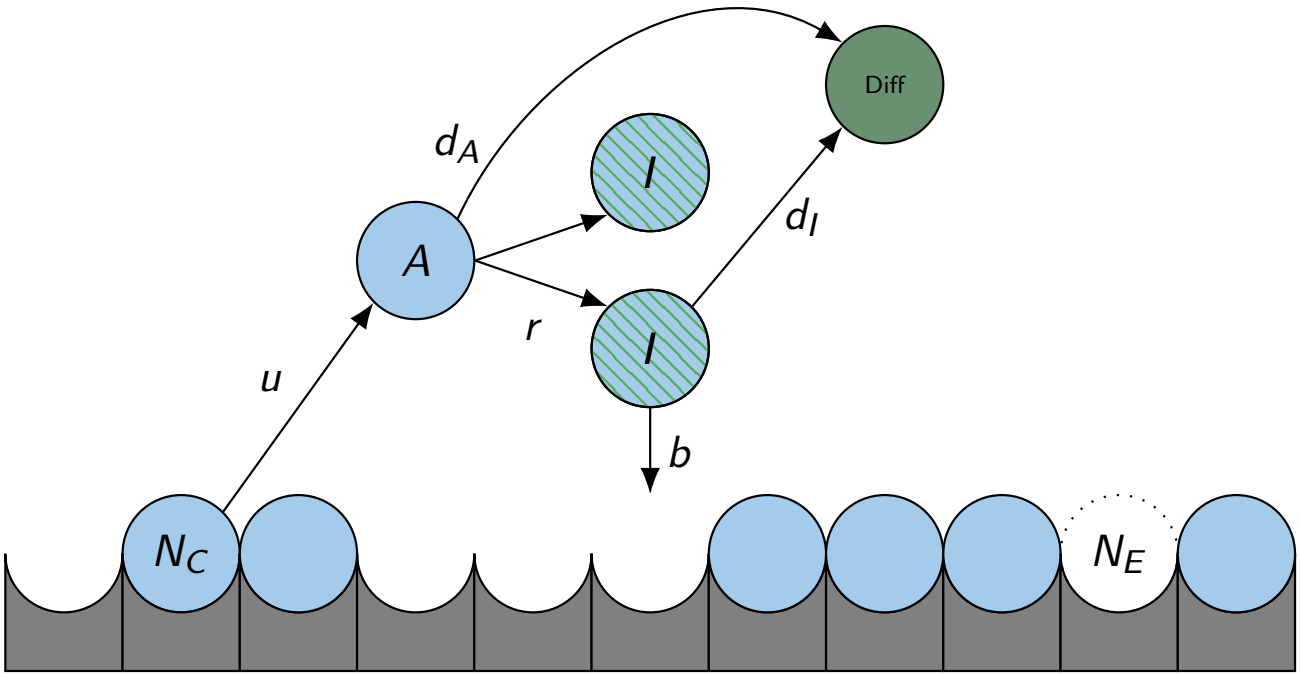
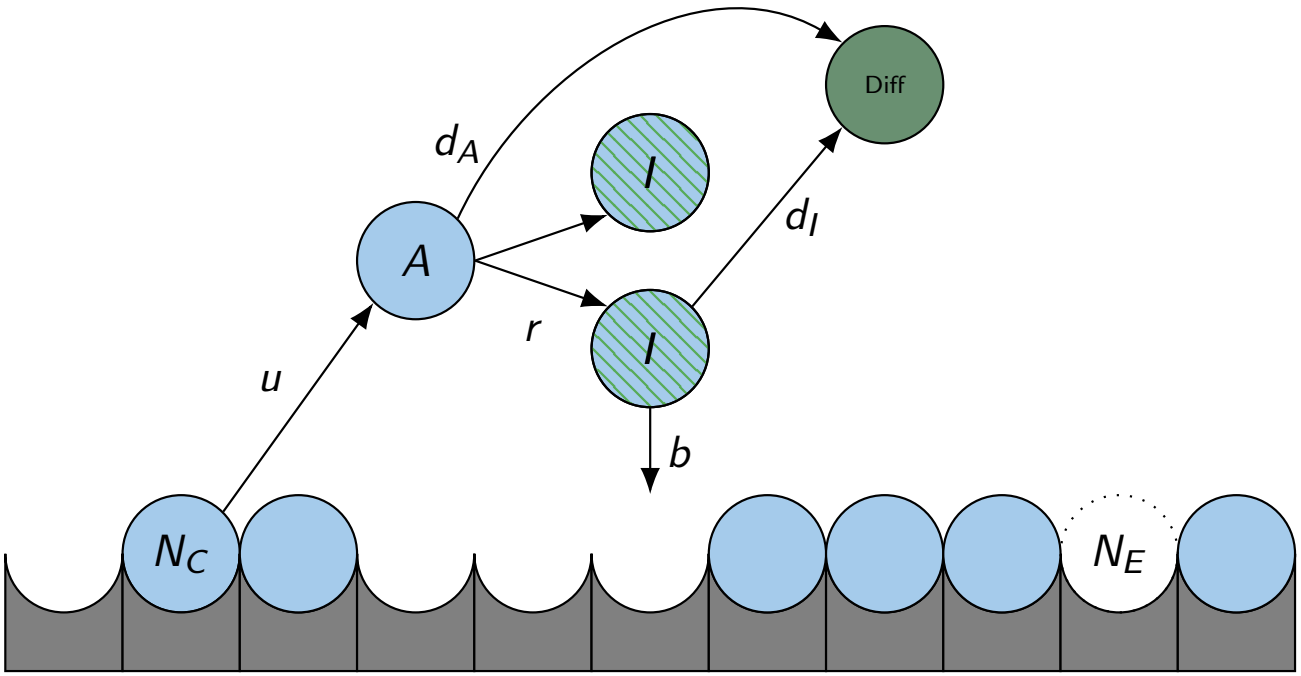


N_C: Niche-bound, A: Active, I: Inhibited, N_E: Empty niches

Competition for niche-space



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Considering multiple subpopulations of stem cells:
Work of Thomas Stiehl $\Rightarrow$ Healthy and malignant cells compete for a shared niche.

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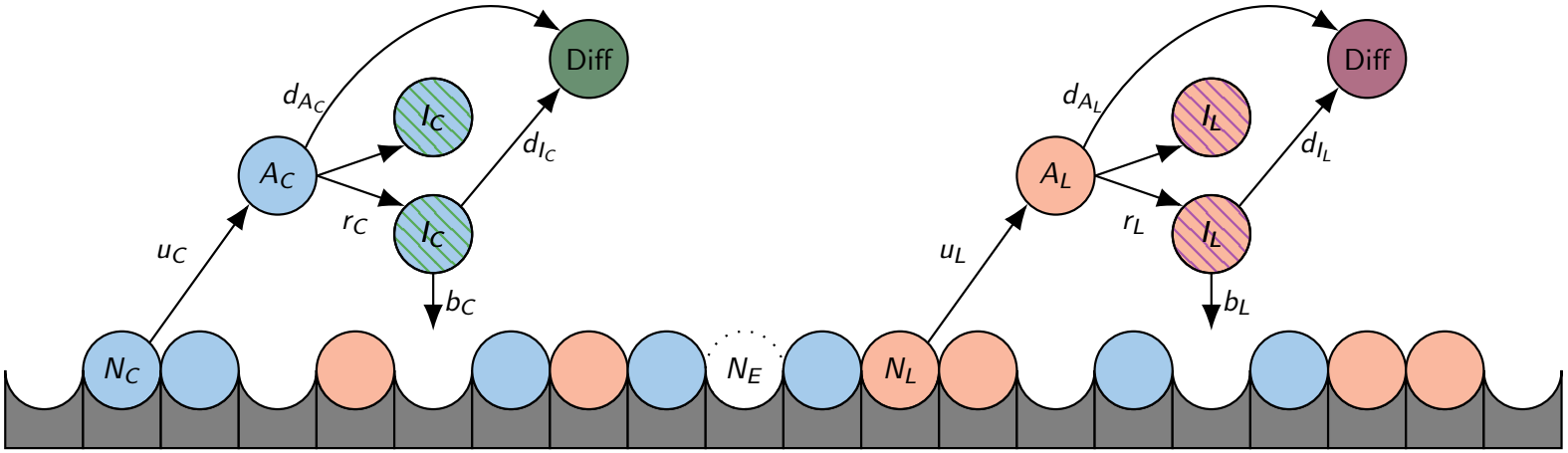

N_C: Niche-bound C-type, A_C: Active C-type, I_C: Inhibited C-type
N_L: Niche-bound L-type, A_L: Active L-type, I_L: Inhibited L-type
N_E: Empty niches.

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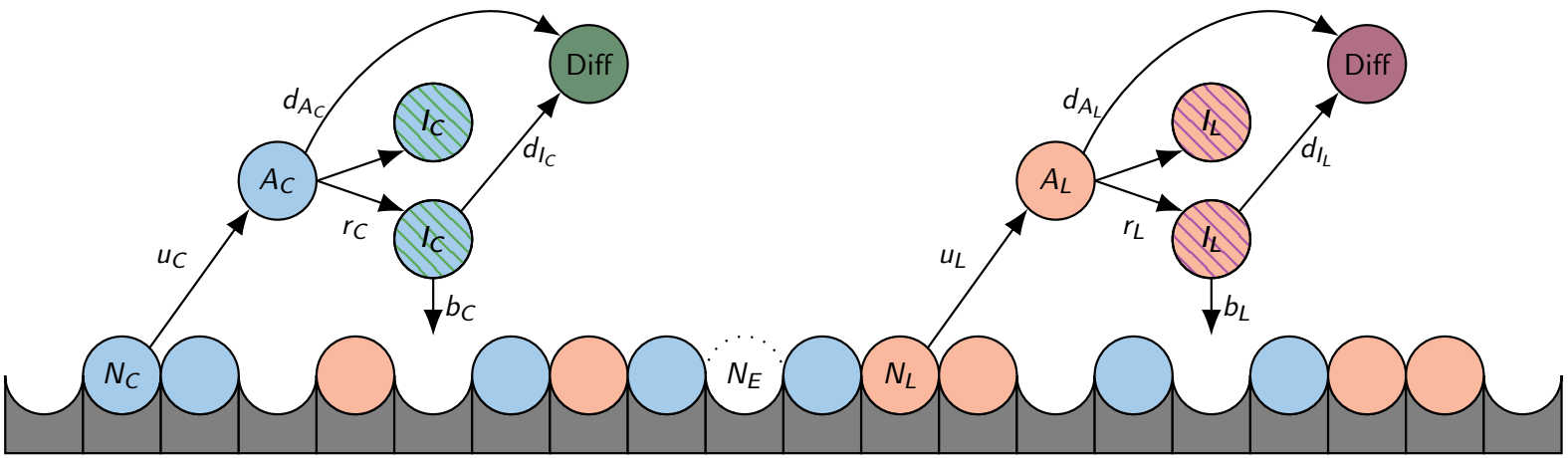

$$\frac{dN_E}{dt} = -b_C N_E I_C + u_C N_C - b_L N_E I_L + u_L N_L$$

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$$\frac{dI_C}{dt} = -b_C N_E I_C + 2 r_C A_C - d_{I_C} I_C \qquad \frac{dI_L}{dt} = -b_L N_E I_L + 2 r_L A_L - d_{I_L} I_L$$

$$\frac{dA_C}{dt} = u_C N_C - r_C A_C - d_{A_C} A_C \qquad \frac{dA_L}{dt} = u_L N_L - r_L A_L - d_{A_L} A_L$$

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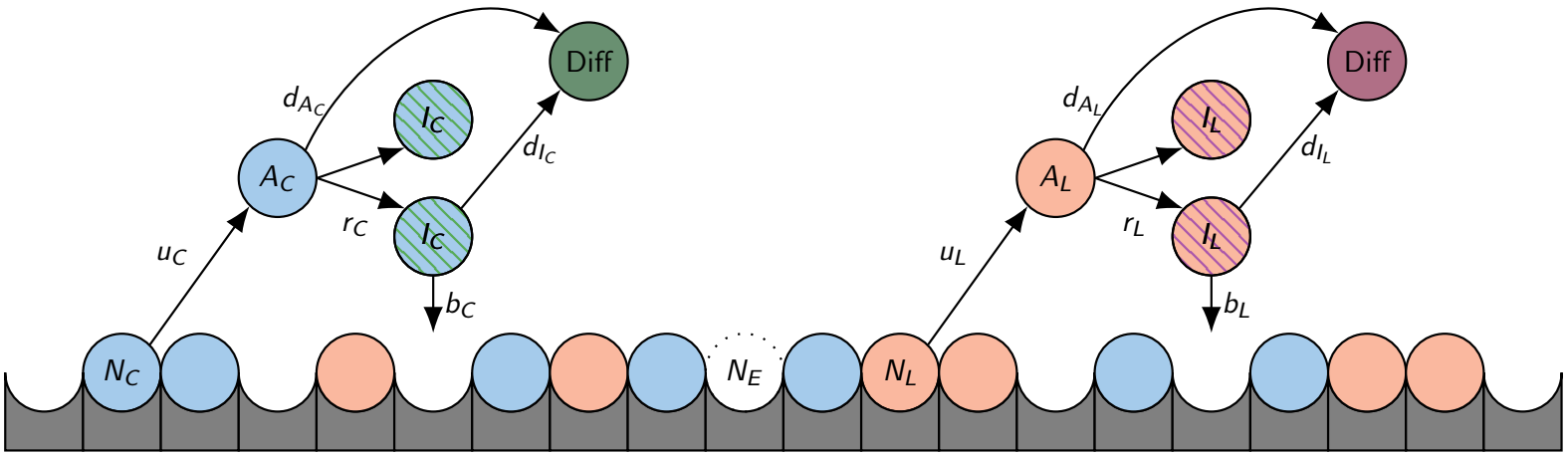
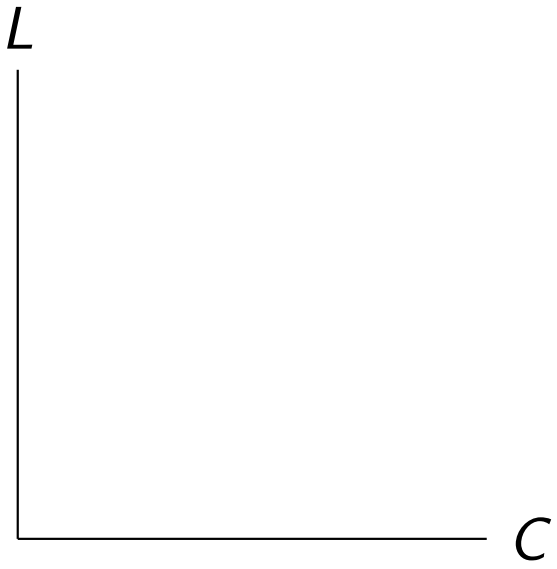


Four steady states:



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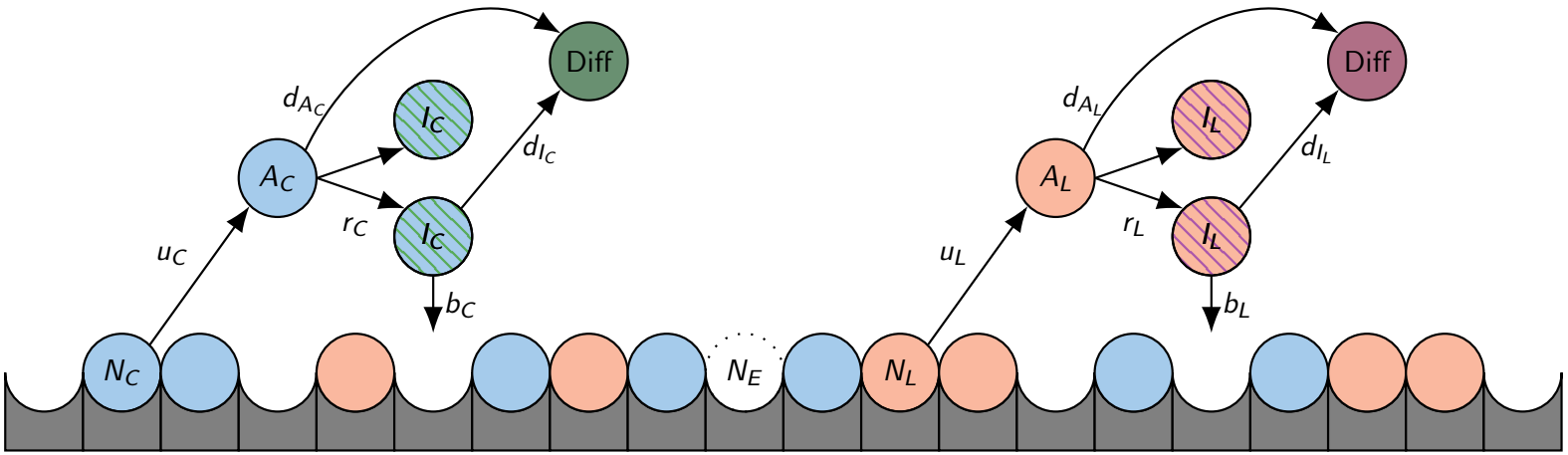

Four steady states:

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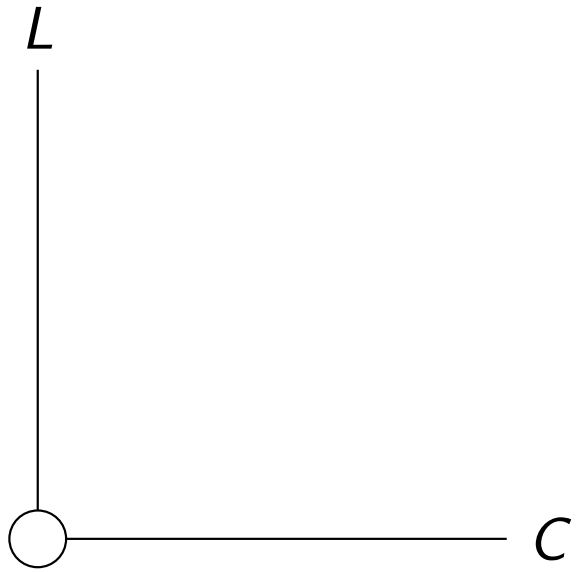

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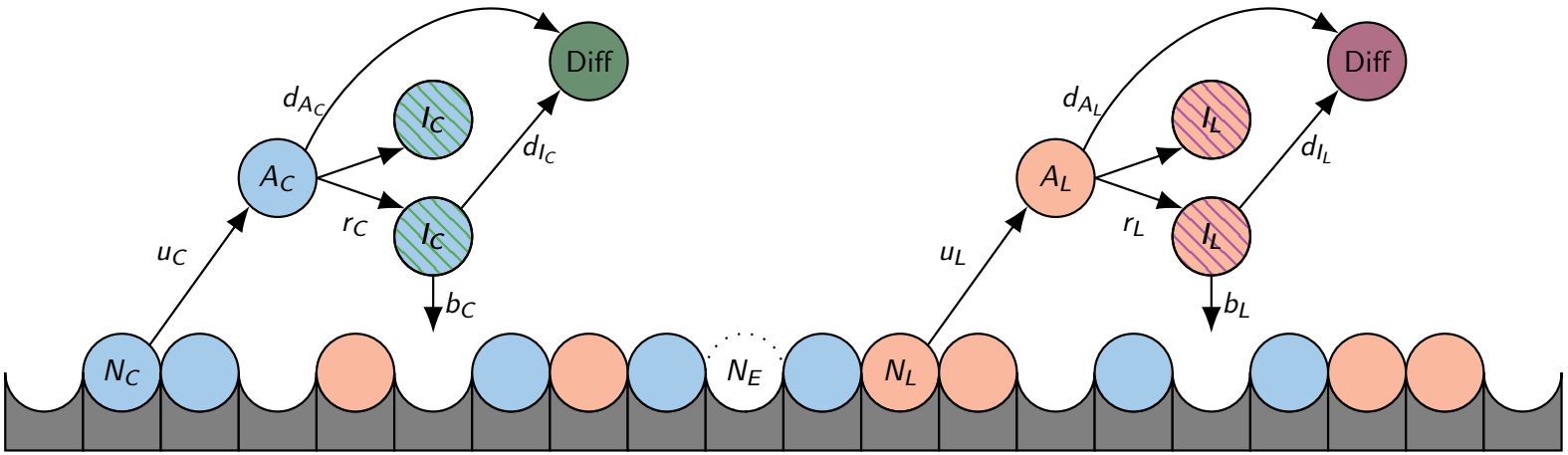
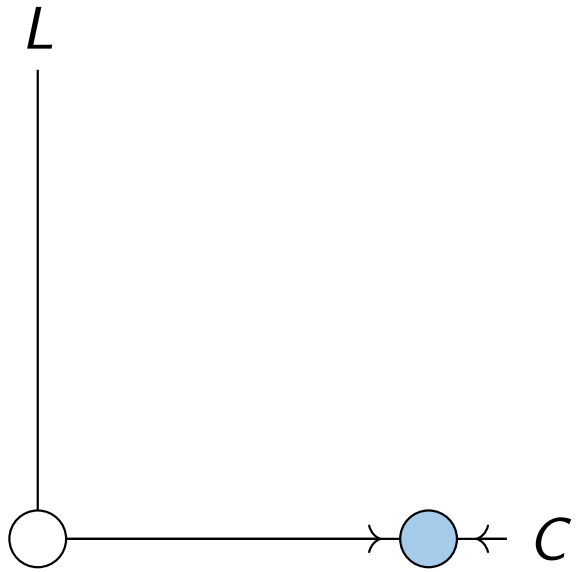


Four steady states:

- No cells (Exhaustion)
- Only C cells (Hematopoiesis)



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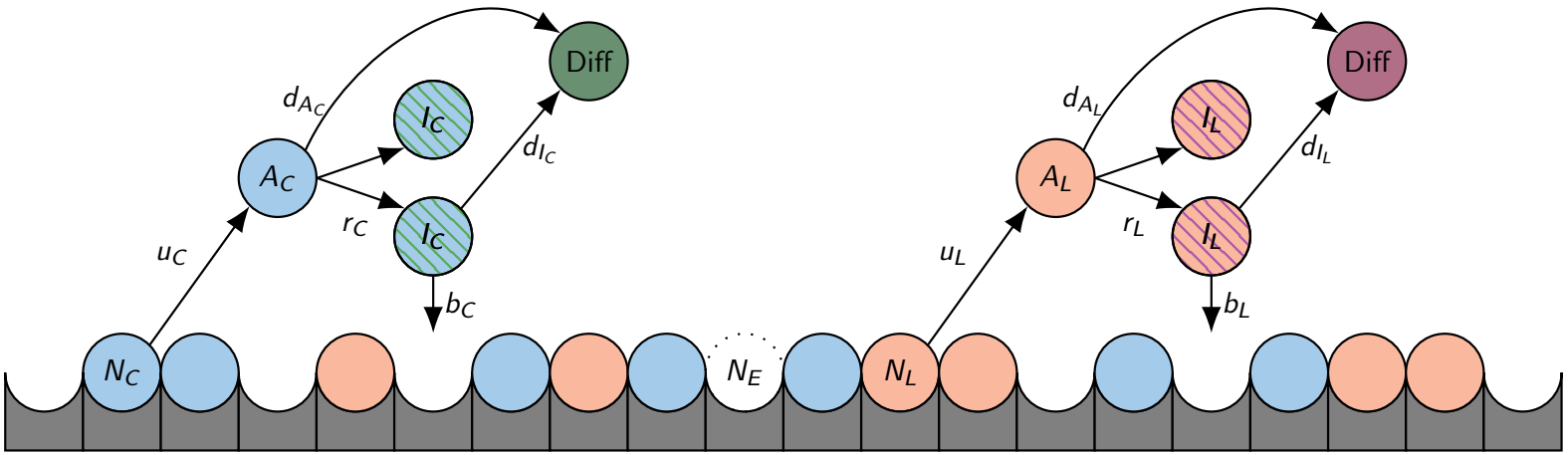

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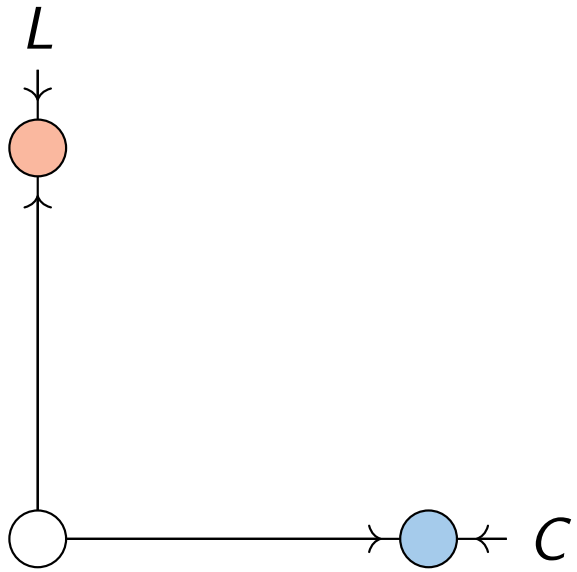
- Only L cells (Full blown disease)



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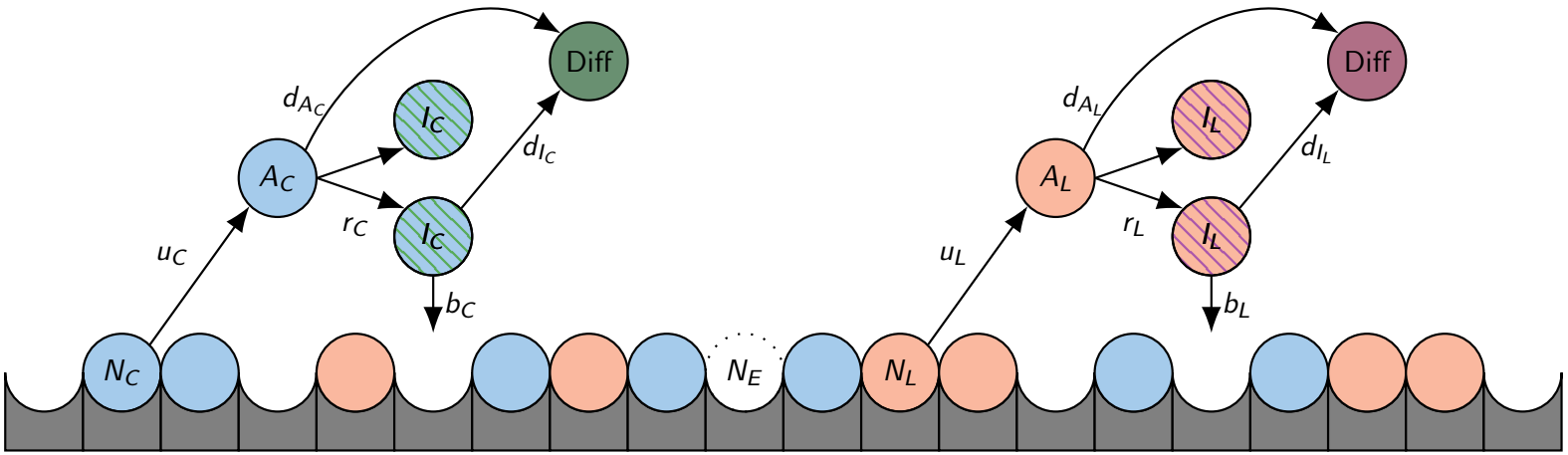

Four steady states:

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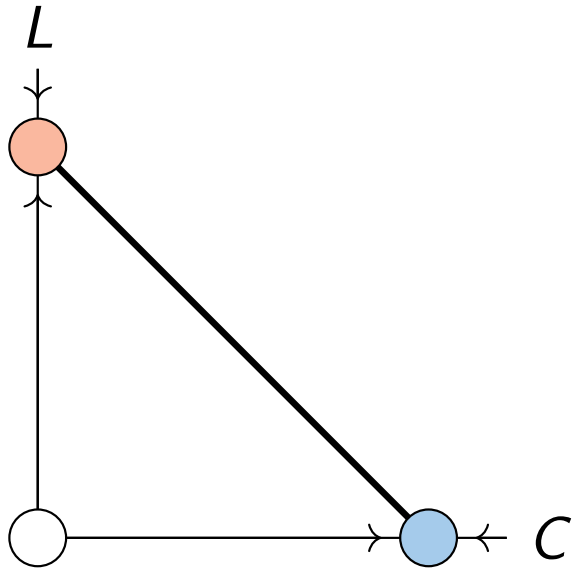
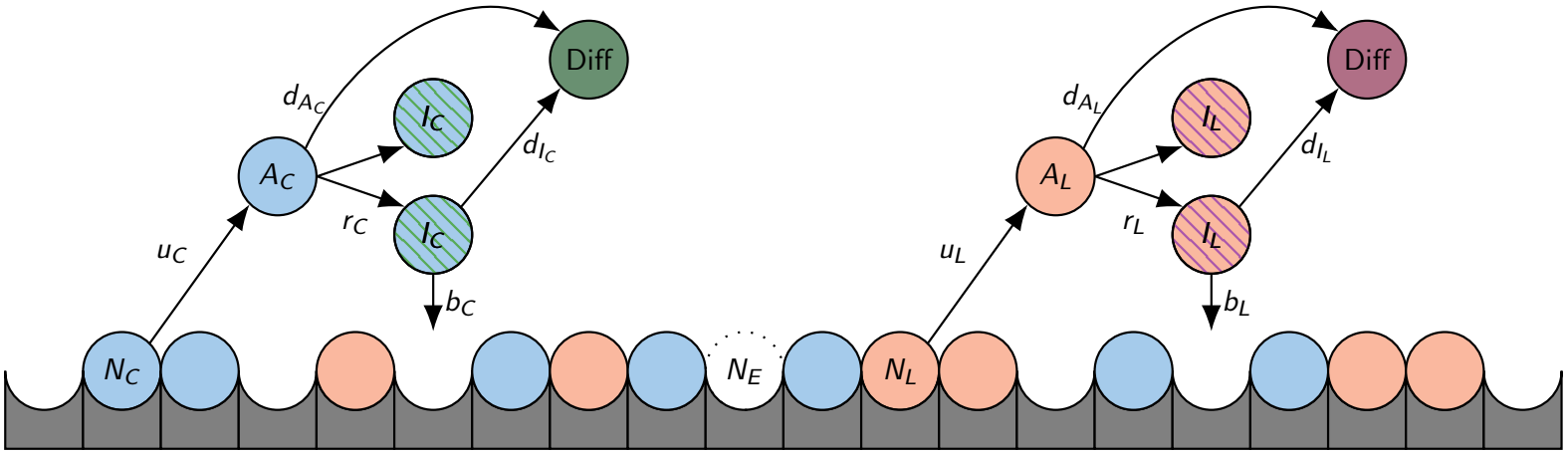
- Co-existence (Suppressed disease?)



Competition for niche-space - Fitness

$$F_C = \frac{b_C}{d_{I_C}} \frac{(r_C - d_{A_C})}{(r_C + d_{A_C})} \quad \text{and} \quad F_L = \frac{b_L}{d_{I_L}} \frac{(r_L - d_{A_L})}{(r_L + d_{A_L})}$$



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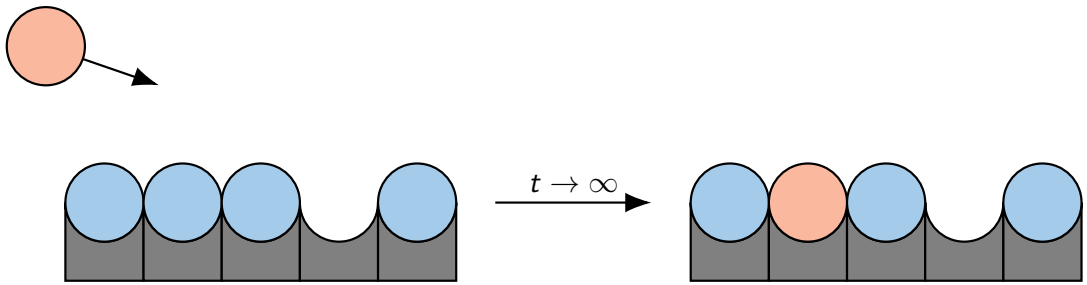

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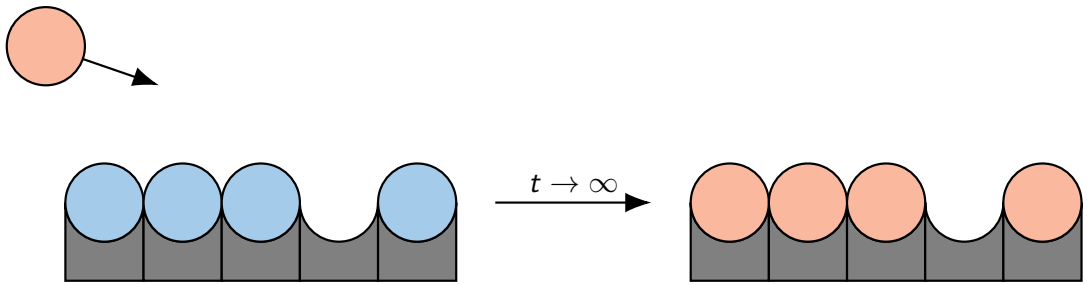

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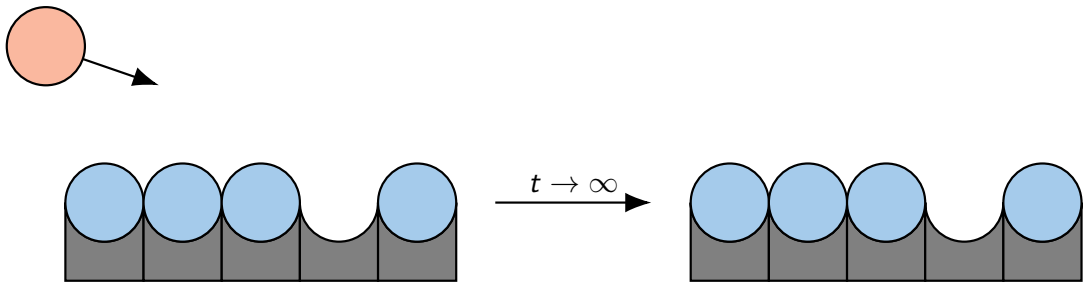

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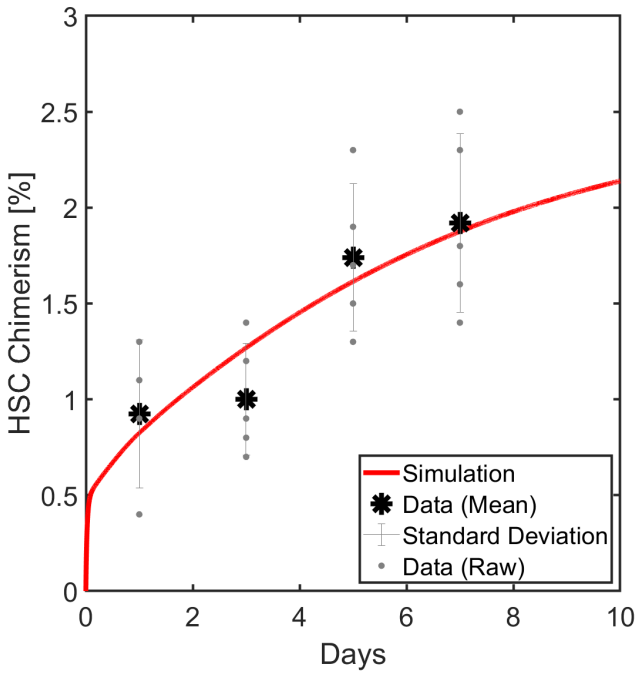

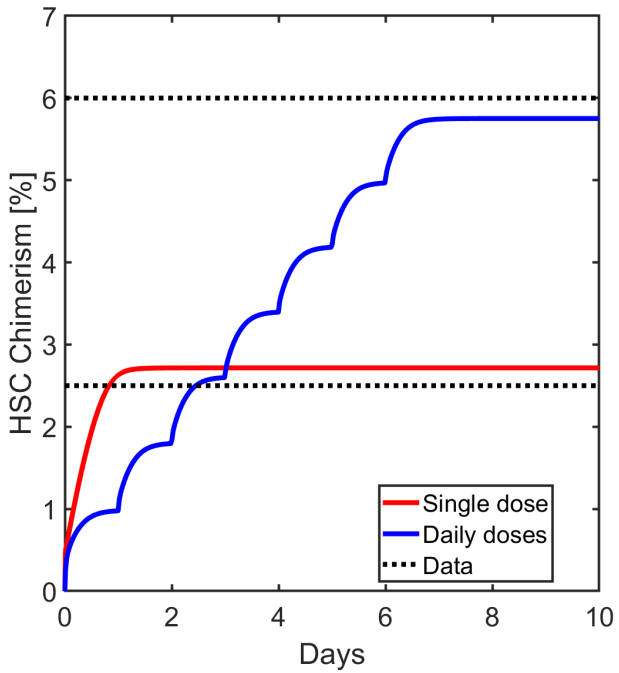

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- Some prediction/results about the significance of certain mechanisms.
- A notion of stem cell fitness.

Reducing the model

$$\frac{dN_E}{dt} = -b_C N_E I_C + u_C N_C - b_L N_E I_L + u_L N_L$$
$$\frac{dN_C}{dt} = b_C N_E I_C - u_C N_C$$
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Reducing the model

Since $N_C + N_L + N_E = K$, we set $N_E = K - N_C - N_L$:

$$\frac{dN_C}{dt} = b_C(K - N_C - N_L)I_C - u_C N_C$$
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Reducing the model

QSSA: Assuming $\dot{I_C} = 0$ and $\dot{I_L} = 0$,

$$\frac{dN_C}{dt} = \frac{2u_C}{\alpha_C + 1 - N_C - N_L} A_C - u_C N_C$$
$$\frac{dA_C}{dt} = r_C N_C - r_C A_C - d_{A_C} A_C$$
$$\frac{dN_L}{dt} = \frac{2u_L}{\alpha_L + 1 - N_C - N_L} A_L - u_L N_L$$
$$\frac{dA_L}{dt} = r_L N_L - r_L A_L - d_{A_L} A_L$$

where $\alpha_C = \frac{d_{I_C}}{b_C K}$ and $\alpha_L = \frac{d_{I_L}}{b_L K}$
(Equivalent to setting $\frac{u_C}{K} \downarrow 0$ *and* $\frac{u_L}{K}$*)*

Reducing the model

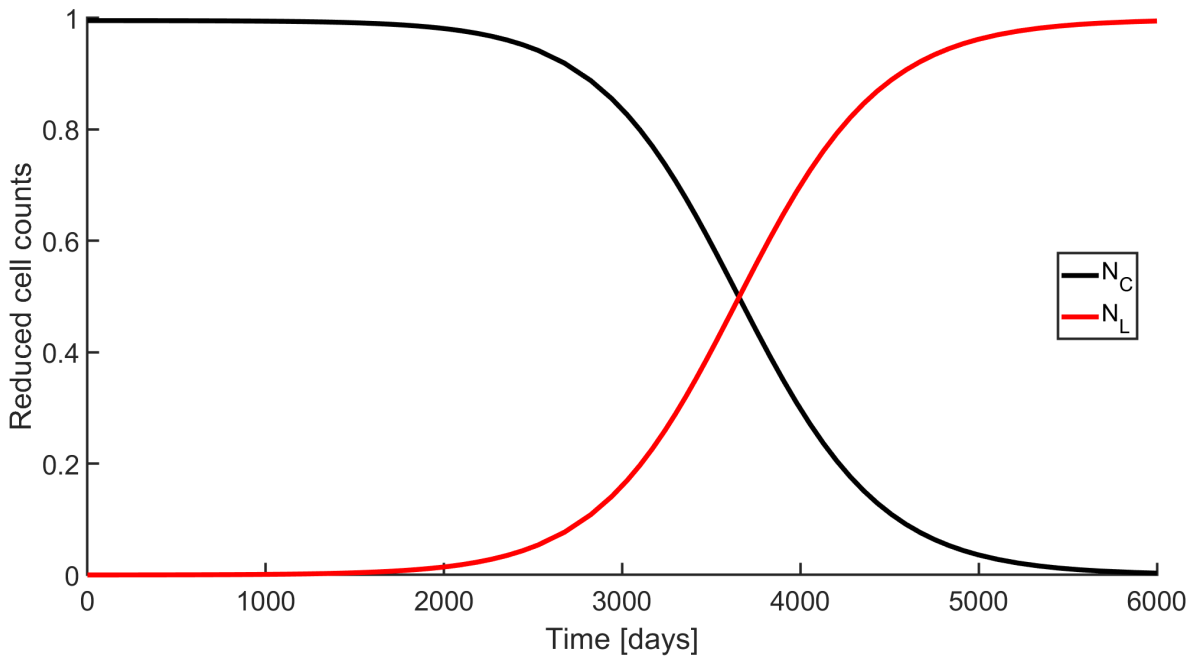
QSSA: Assuming $\dot{A_C} = 0$ and $\dot{A_L} = 0$,

$$\frac{dN_C}{dt} = u_C \left(\frac{2\rho_C(1 - N_C - N_L)}{\alpha_C + 1 - N_C - N_L} - 1 \right) N_C$$
$$\frac{dN_L}{dt} = u_L \left(\frac{2\rho_L(1 - N_C - N_L)}{\alpha_L + 1 - N_C - N_L} - 1 \right) N_L$$

where $\alpha_C = \frac{d_{I_C}}{b_C K}$, $\alpha_L = \frac{d_{I_L}}{b_L K}$, $\rho_C = \frac{r_C}{r_C + d_{A_C}}$ and $\rho_L = \frac{r_L}{r_L + d_{A_L}}$

(Also arises by setting $u_C \downarrow 0$ and $u_L \downarrow 0$)

Reducing the model



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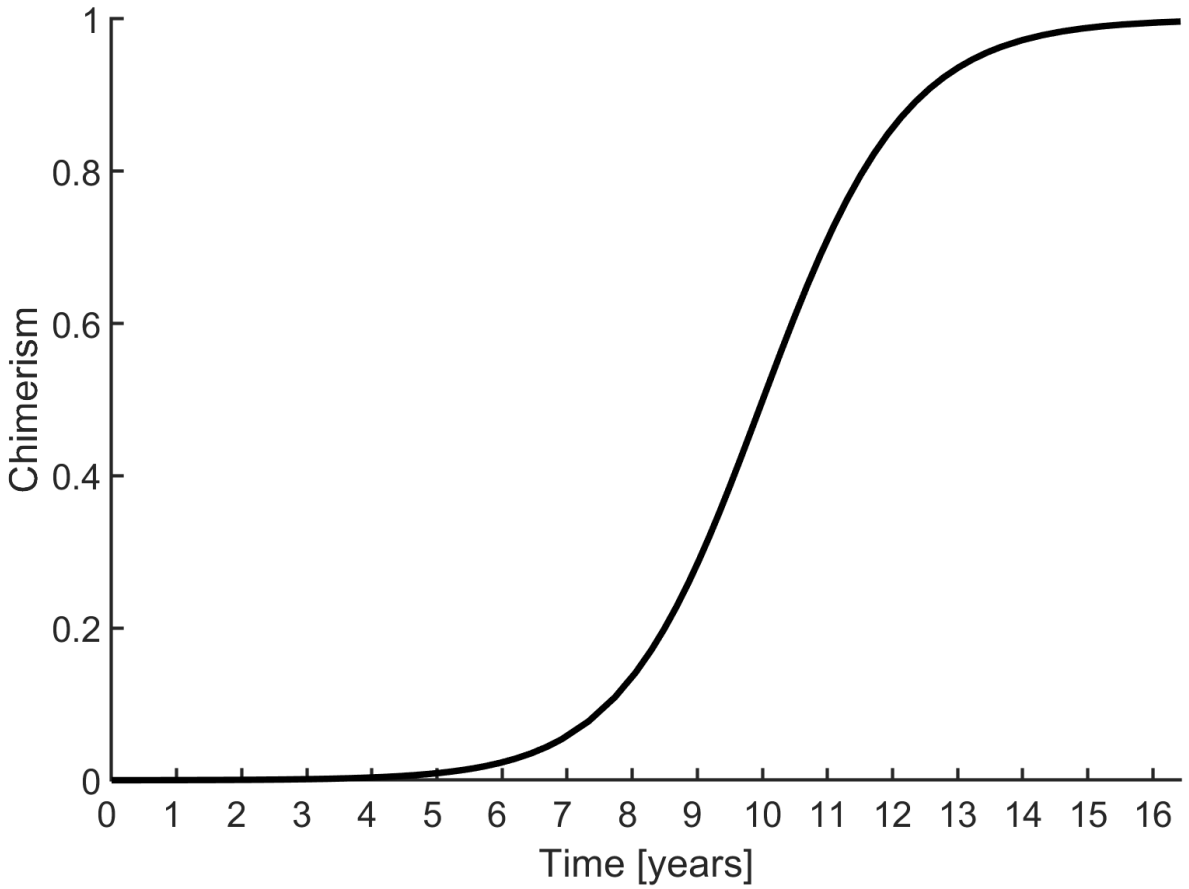
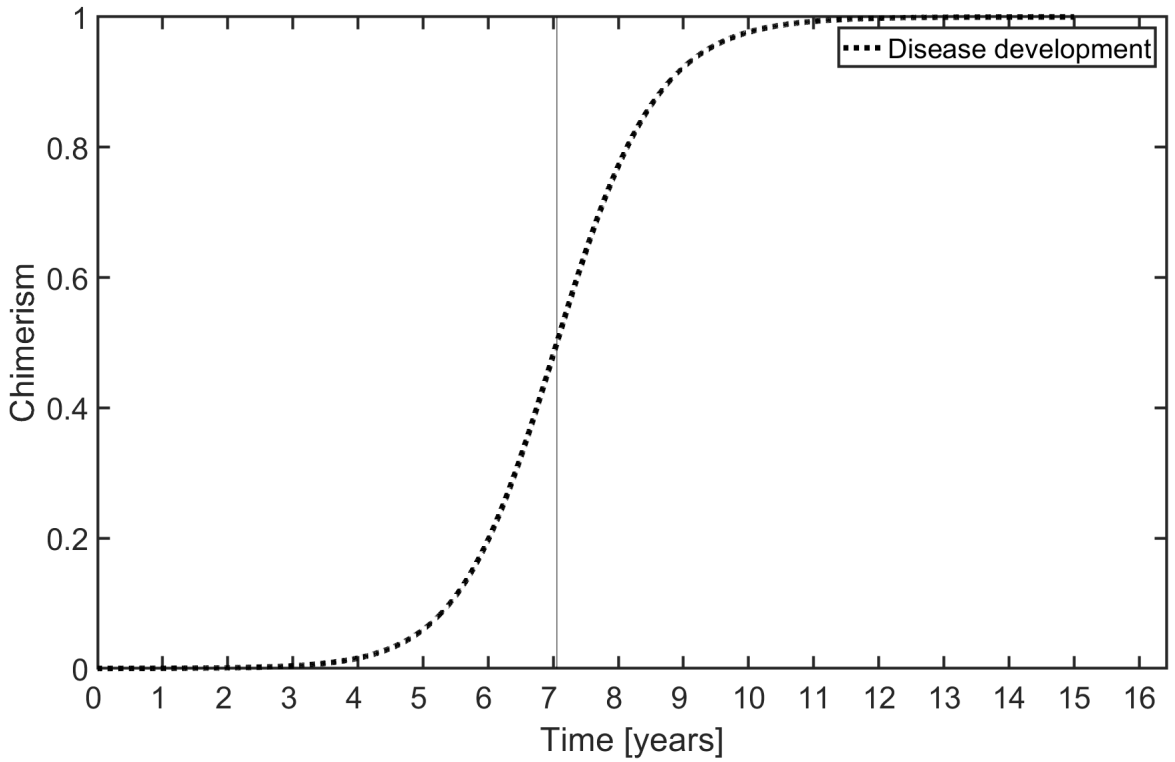


$$\text{Chimerism} = \frac{N_L}{N_C + N_L}$$

Future work: Simulated treatment in reduced model



Fitness advantage due to increased ρ_L.

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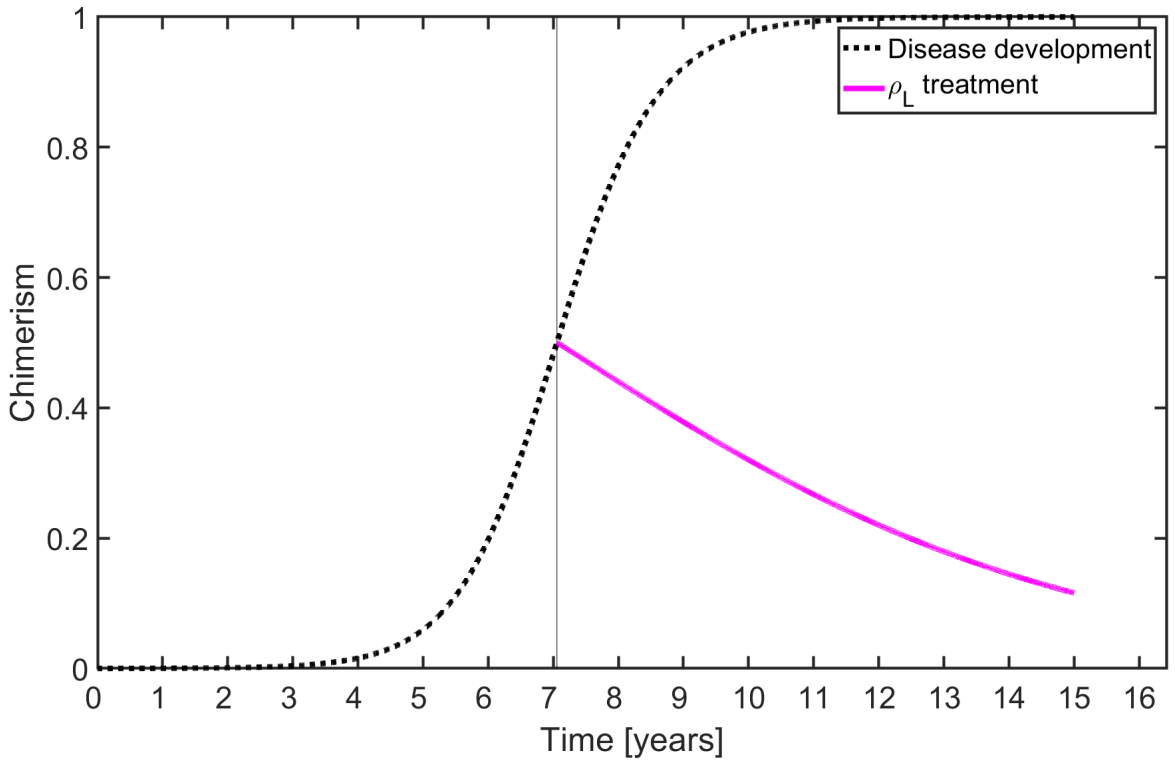

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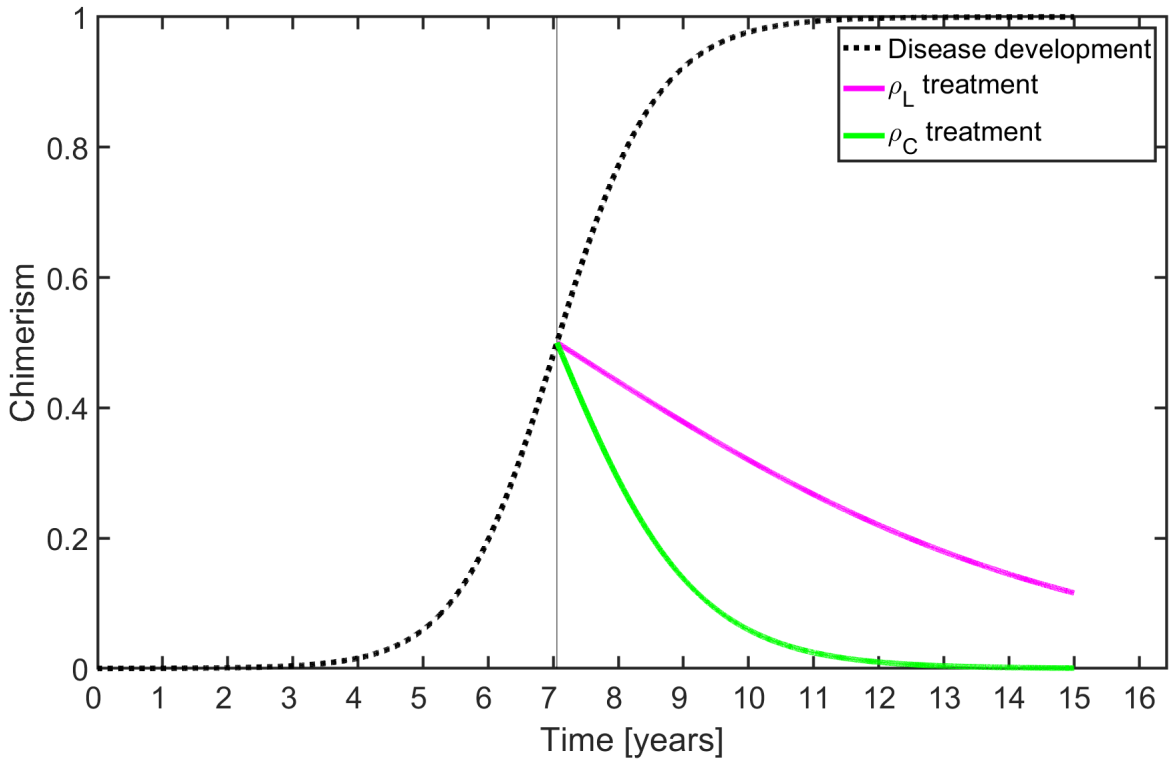

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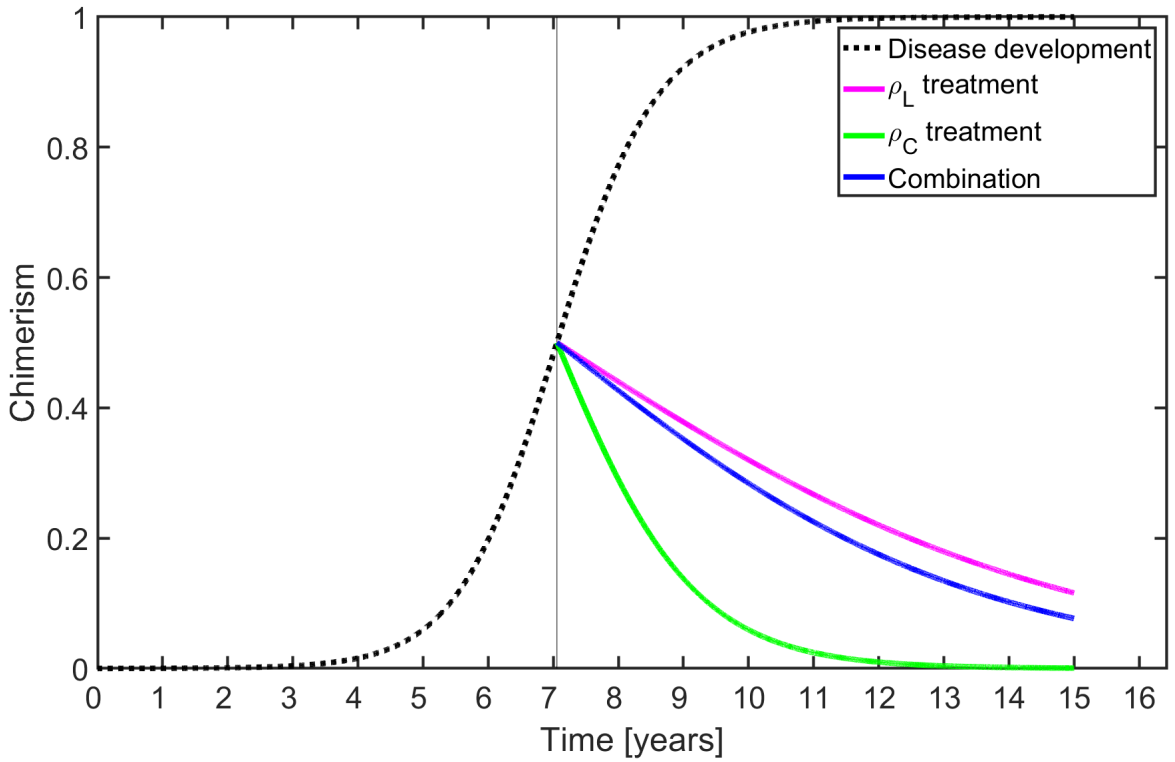
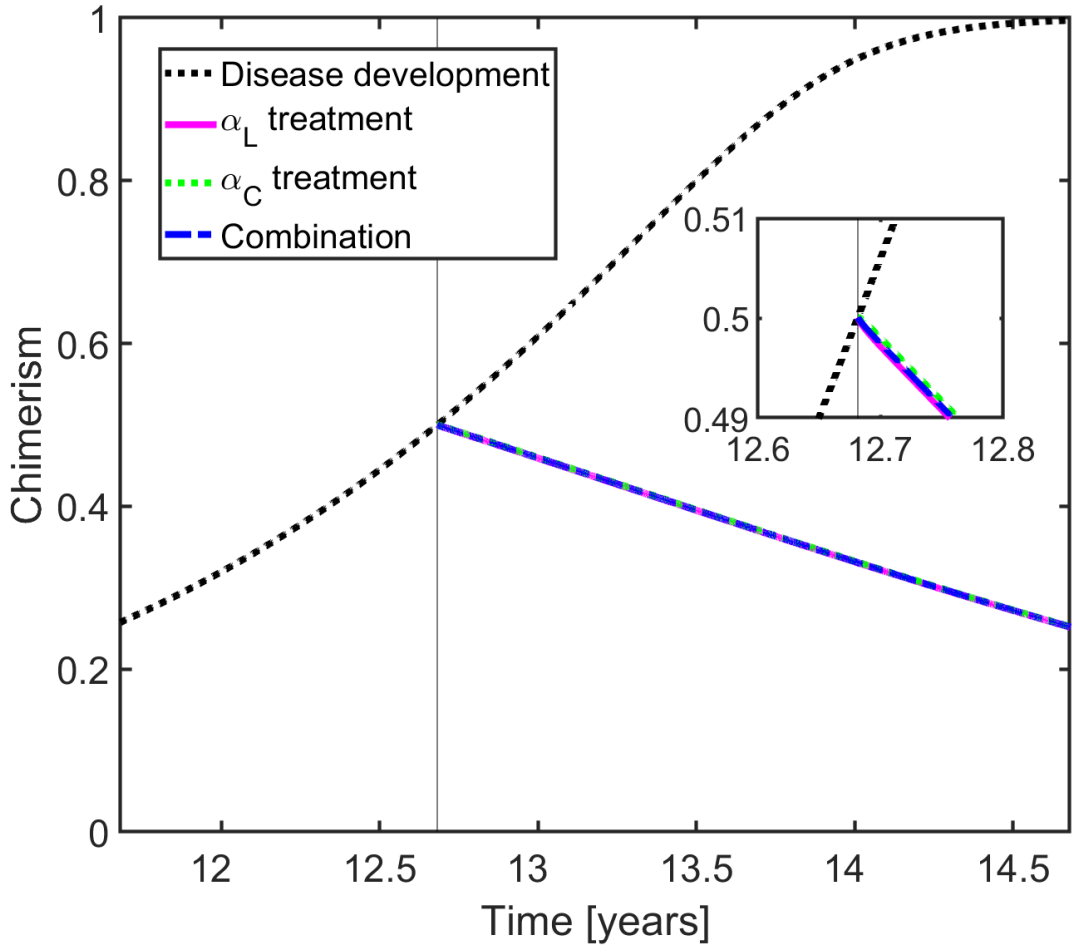


Fitness advantage due to increased ρ_L.

Future work: Simulated treatment in reduced model



Fitness advantage due to decreased α_L.

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- Improving the fitness of healthy stem cells could be more effective than decreasing the fitness of malignant cells.
- By considering feedback signalling from blood, fitting with (and perhaps even predicting) patient-data could be possible.

Thank you for your attention.

Any questions?

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References

Andersen, M., Z. Sajid, R. K. Pedersen, J. Gudmand-Hoeyer, C. Ellervik, V. Skov, L. Kjær, N. Pallisgaard, T. A. Kruse, M. Thomassen, J. Troelsen, H. C. Hasselbalch, and J. T. Ottesen
2017. Mathematical modelling as a proof of concept for MPNs as a human inflammation model for cancer development. PLOS ONE, 12(8):e0183620.

Ashcroft, P., M. G. Manz, and S. Bonhoeffer
2017. Clonal dominance and transplantation dynamics in hematopoietic stem cell compartments. PLOS Computational Biology, 13(10):e1005803.

Becker, N. B., M. Günther, C. Li, A. Jolly, and T. Höfer
2019. Stem cell homeostasis by integral feedback through the niche. Journal of Theoretical Biology, 481:100–109.

Bhattacharya, D., A. Czechowicz, A. L. Ooi, D. J. Rossi, D. Bryder, and I. L. Weissman
2009. Niche recycling through division-independent egress of hematopoietic stem cells. The Journal of Experimental Medicine, 206(12):2837–2850.

Wang, W., T. Stiehl, S. Raffel, V. T. Hoang, I. Hoffmann, L. Poisa-Beiro, B. R. Saeed, R. Blume, L. Manta, V. Eckstein, T. Bochtler, P. Wuchter, M. Essers, A. Jauch, A. Trumpp, A. Marciniak-Czochra, A. D. Ho, and C. Lutz
2017. Reduced hematopoietic stem cell frequency predicts outcome in acute myeloid leukemia. Haematologica, 102(9):1567–1577.

Wilson, A. and A. Trumpp
2006. Bone-marrow haematopoietic-stem-cell niches. Nature Reviews Immunology, 6(2):93–106.