Modelling hematopoietic stem cells

and their interaction with the bone marrow micro-environment.

Rasmus Kristoffer Pedersen

Collaboration with Thomas Stiehl, Johnny Ottesen and Morten Andersen
rakrpe@ruc.dk
Roskilde University, Denmark

Stem Cell Modelling Day
September 18^{th}, 2019

Introduction and brief outline

- Brief introduction to mathematical modelling.

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- Brief introduction to stem cells.

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

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- A way to test hypotheses

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Stem cells

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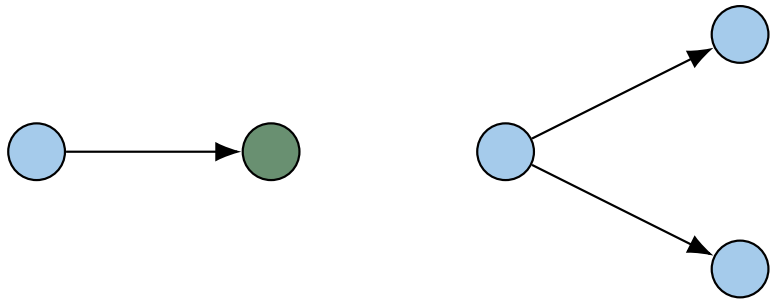

where ● are stem cells and ● is a differentiated/progenitor cell.

Stem cells (As seen by a mathematician)

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- Very hard to measure *in vivo*.

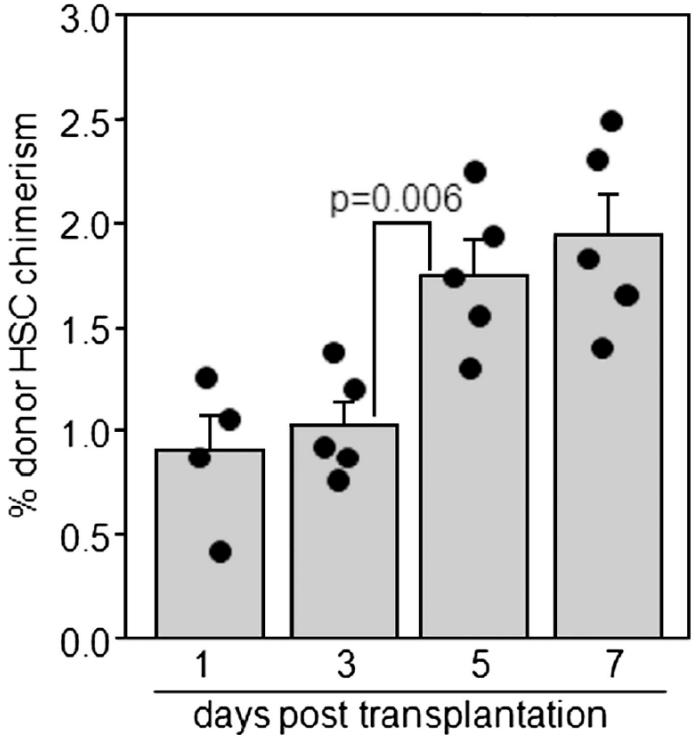

Figure: Mouse experiment data (Bhattacharya et al., 2009)

Hematopoietic stem cells and the bone marrow

- *Cancitis* group at RUC: Modelling of development and treatment of blood cancers (leukemias), in particular Myeloproliferative Neoplasms (MPNs).

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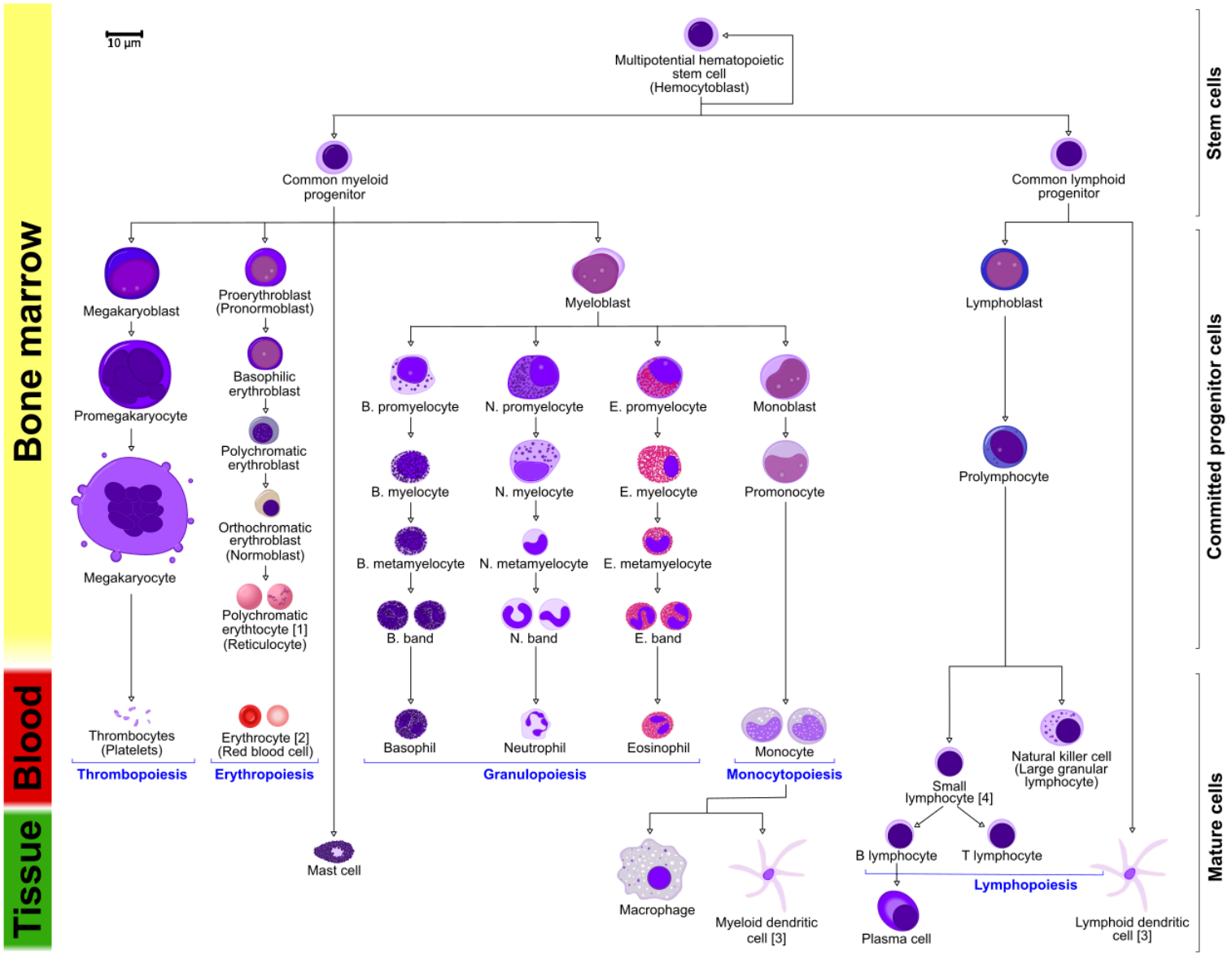

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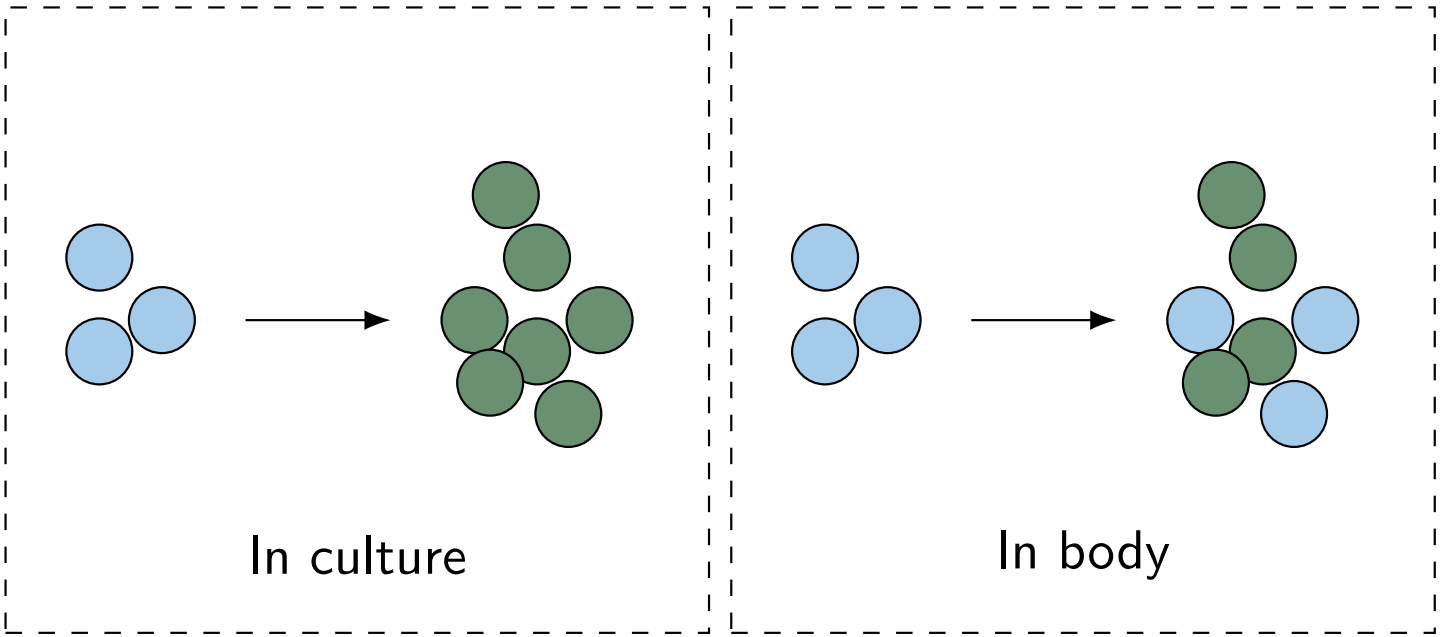
  (Ashcroft et al., 2017), (Wang, Stiehl et al. 2017), (Becker et al., 2019), (Wilson and Trumpp, 2006).

Modelling of the HSCs and their niches



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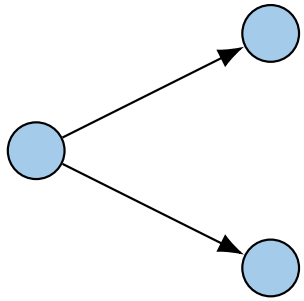

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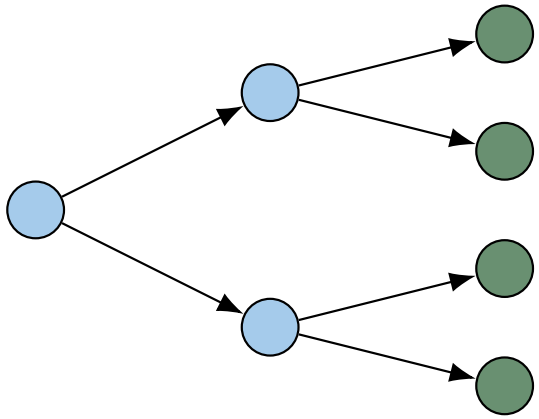

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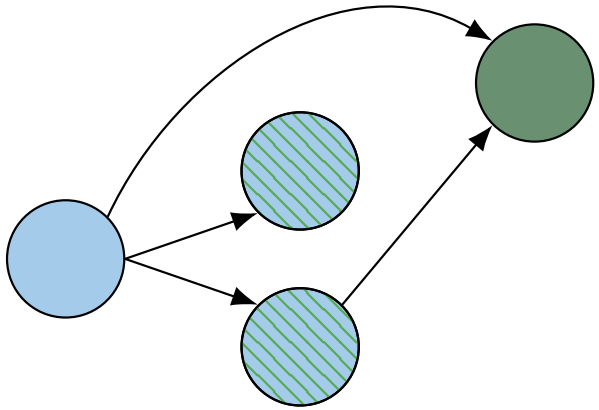

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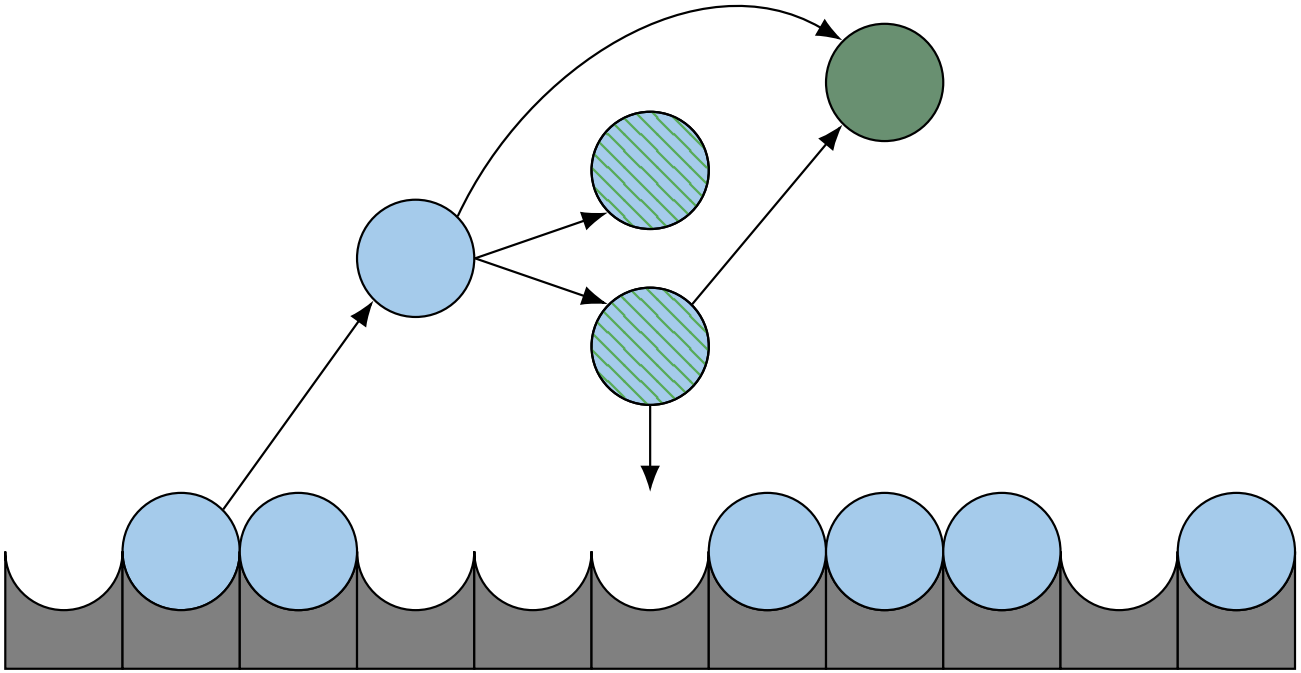

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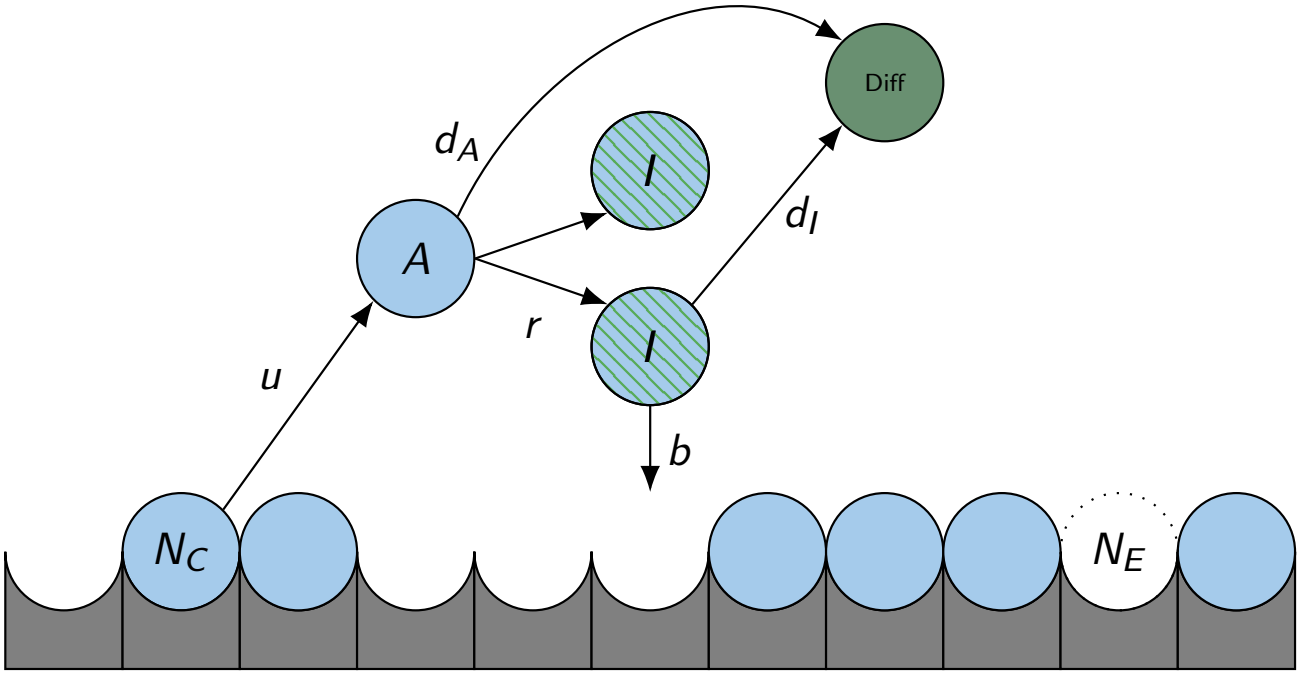

N_C: Niche-bound, A: Active, I: Inhibited, N_E: Empty niches

Modelling of the HSCs and their niches

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$$\frac{dN_E}{dt} = -bN_E I + uN_C$$
$$\frac{dN_C}{dt} = bN_E I - uN_C$$
$$\frac{dI}{dt} = -bN_E I + 2rA - d_I I$$
$$\frac{dA}{dt} = uN_C - rA - d_A A$$

Initial analysis of the mathematical model

- The total number of niches (empty or cell-bound) are constant.

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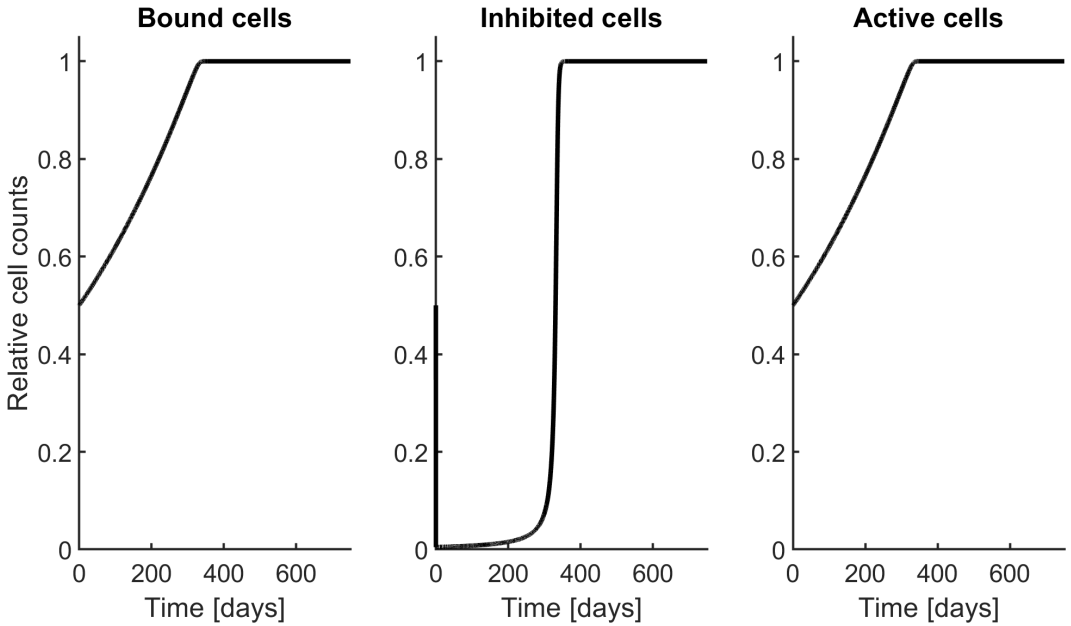

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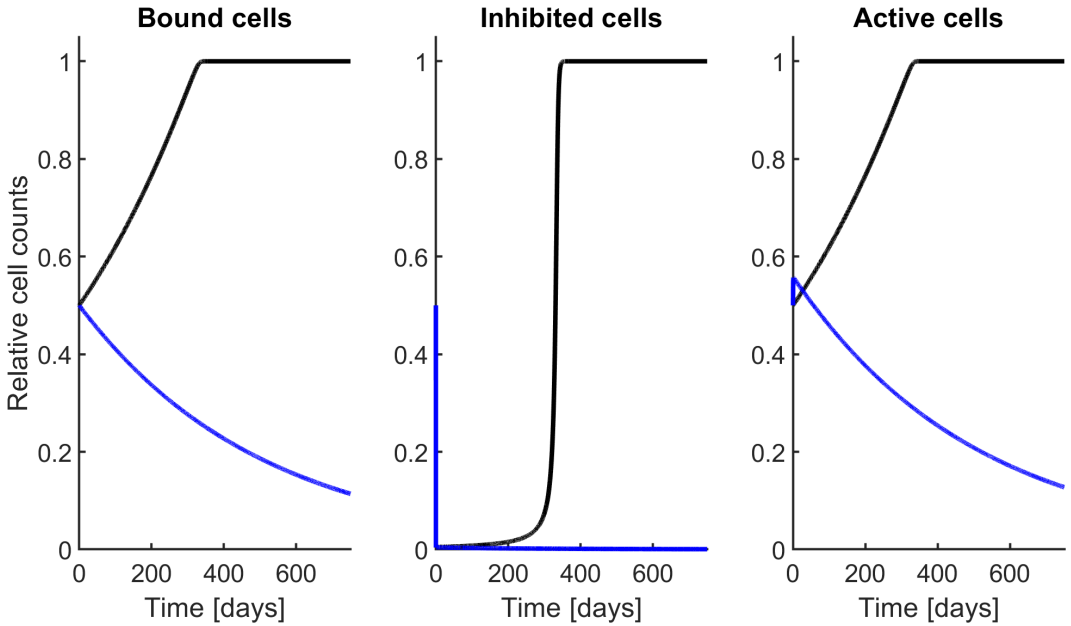

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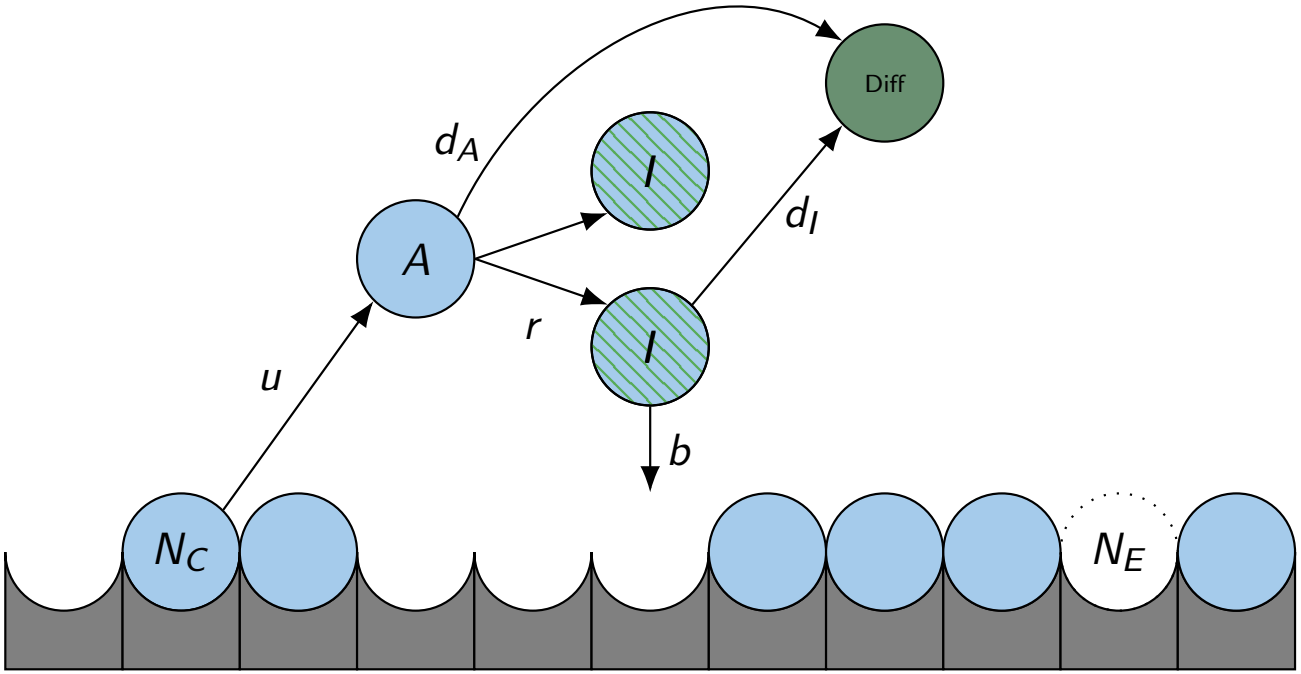
- If all niches disappear, cells die out.

Competition for niche-space



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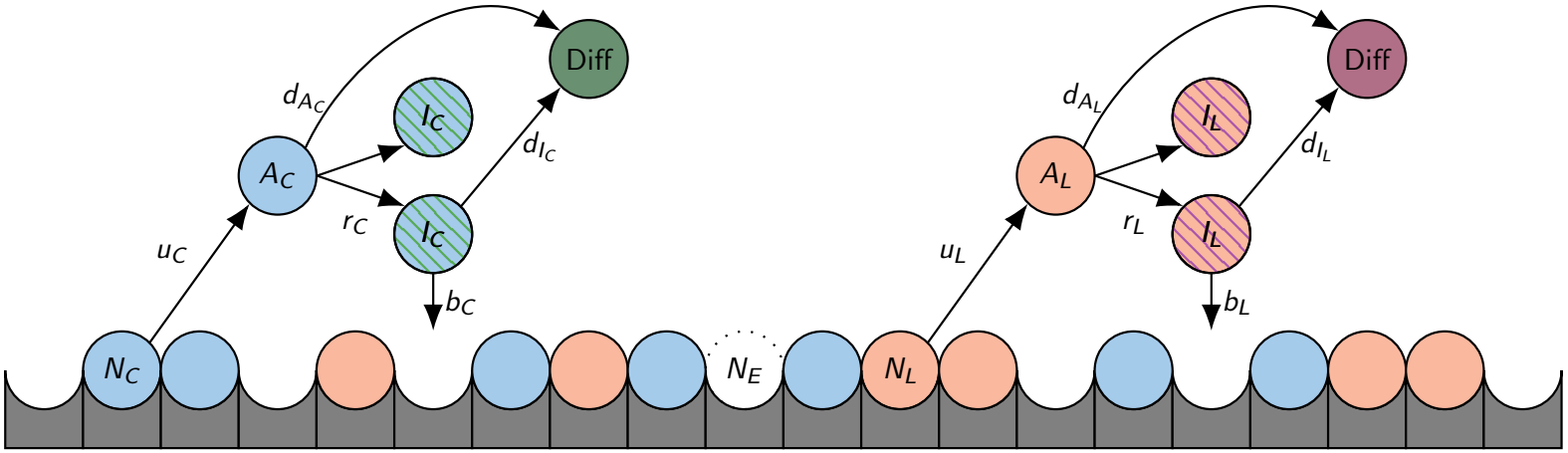

N_C: Niche-bound C-type, A_C: Active C-type, I_C: Inhibited C-type
N_L: Niche-bound L-type, A_L: Active L-type, I_L: Inhibited L-type
N_E: Empty niches.

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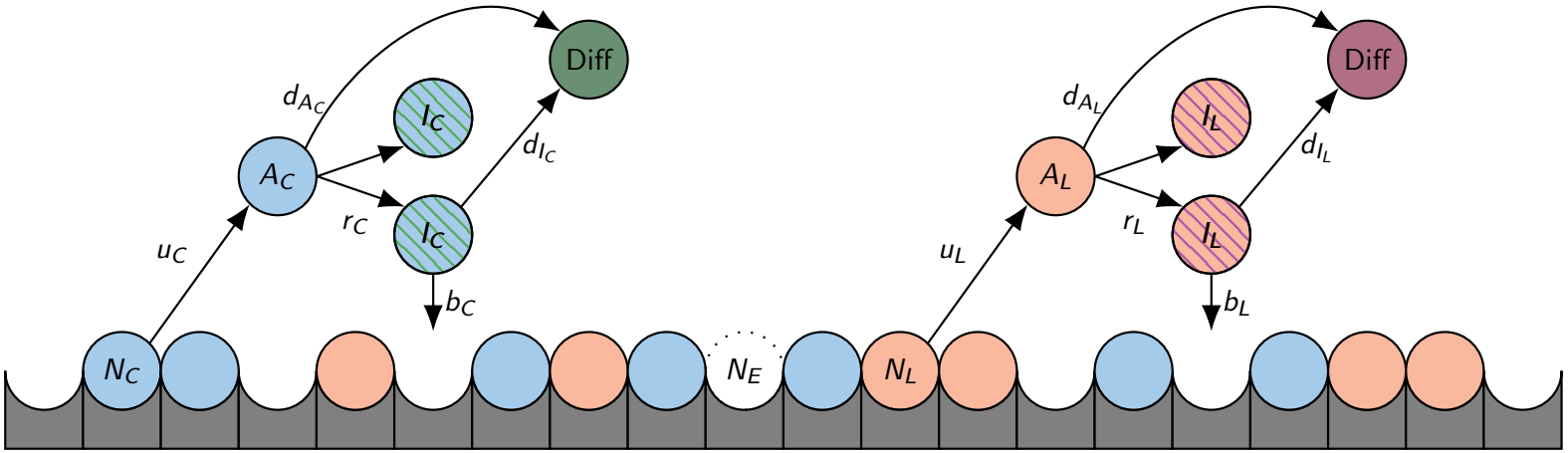

Four steady states:

- No cell (Death)
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- Only leukemic cells (Full blown disease)
- Co-existence

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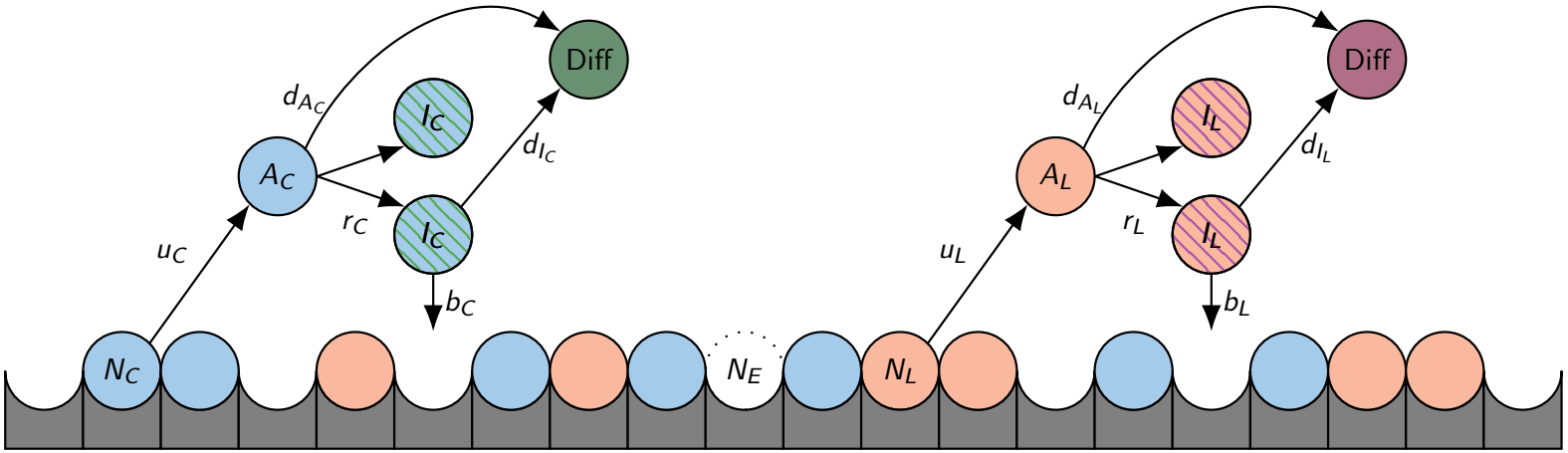

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Competition for niche-space - Fitness

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

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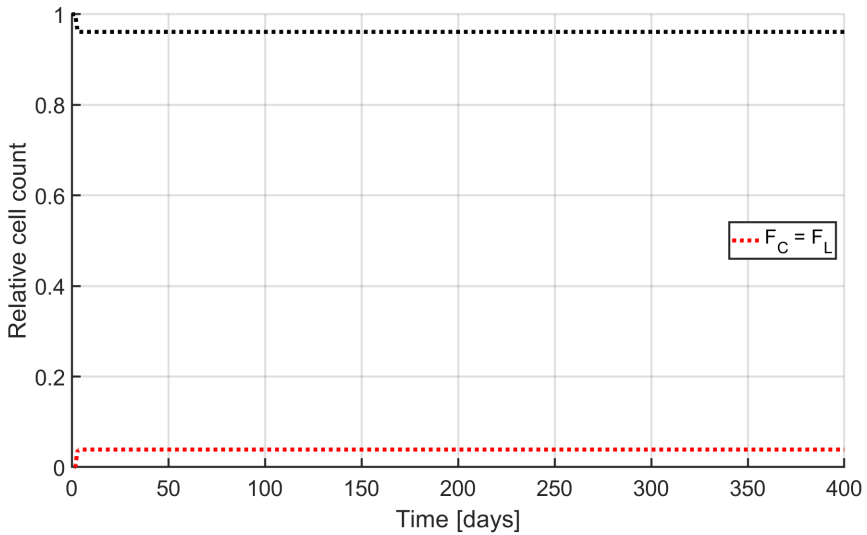
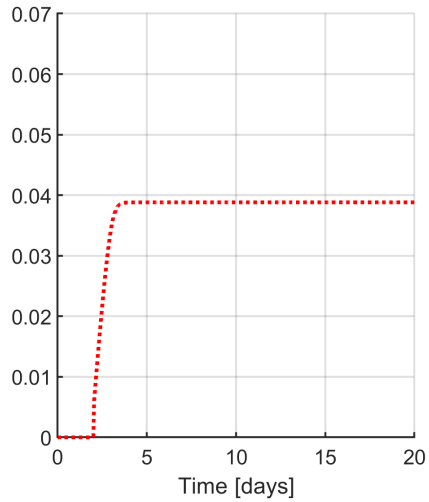
- If $F_C = F_L$ then coexistence is possible.





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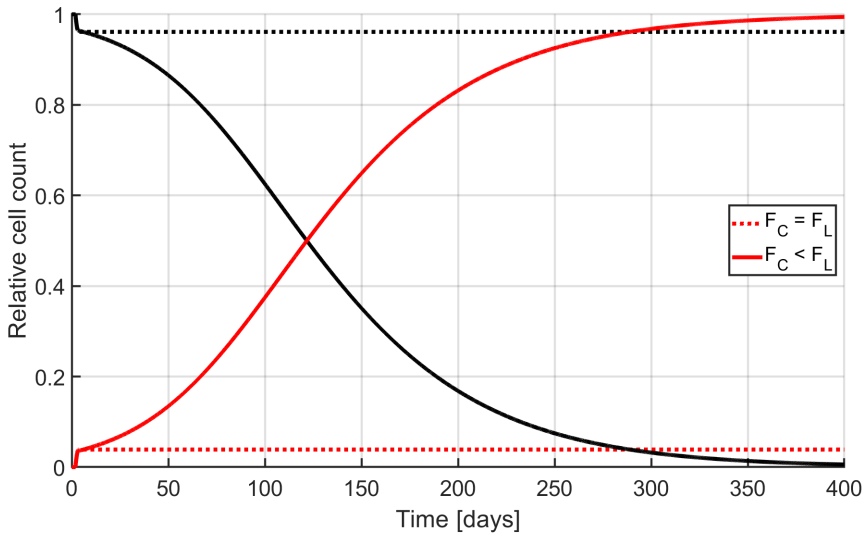

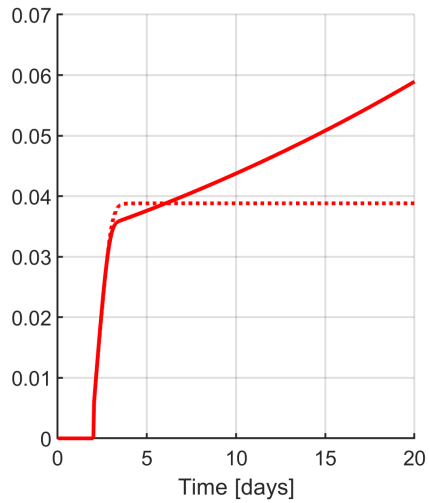

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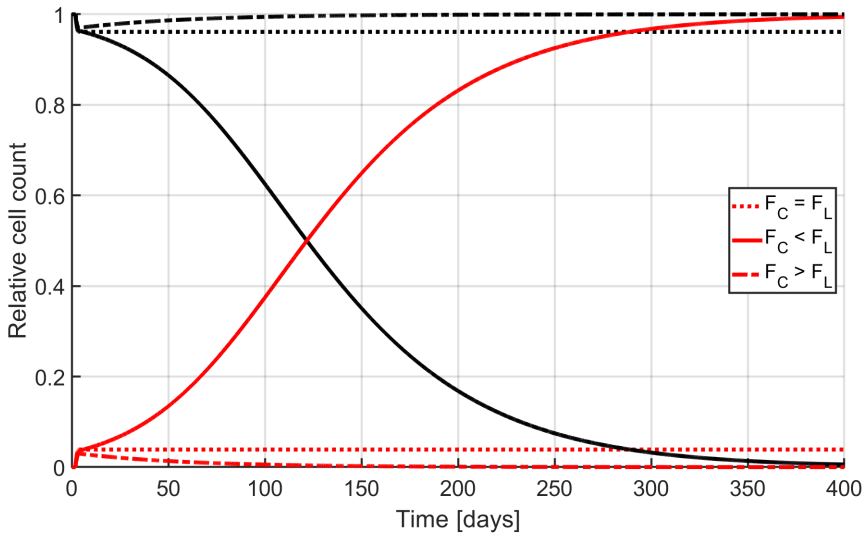
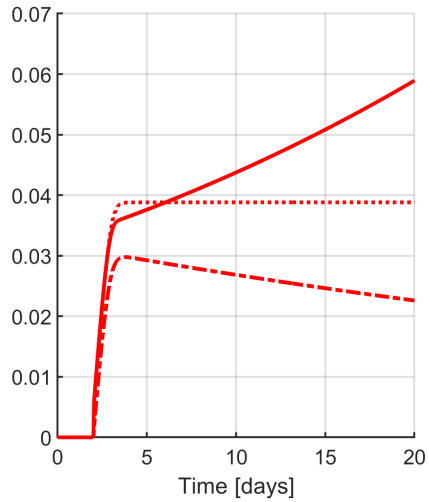
- If $F_C > F_L$ then C-type outcompetes L-type





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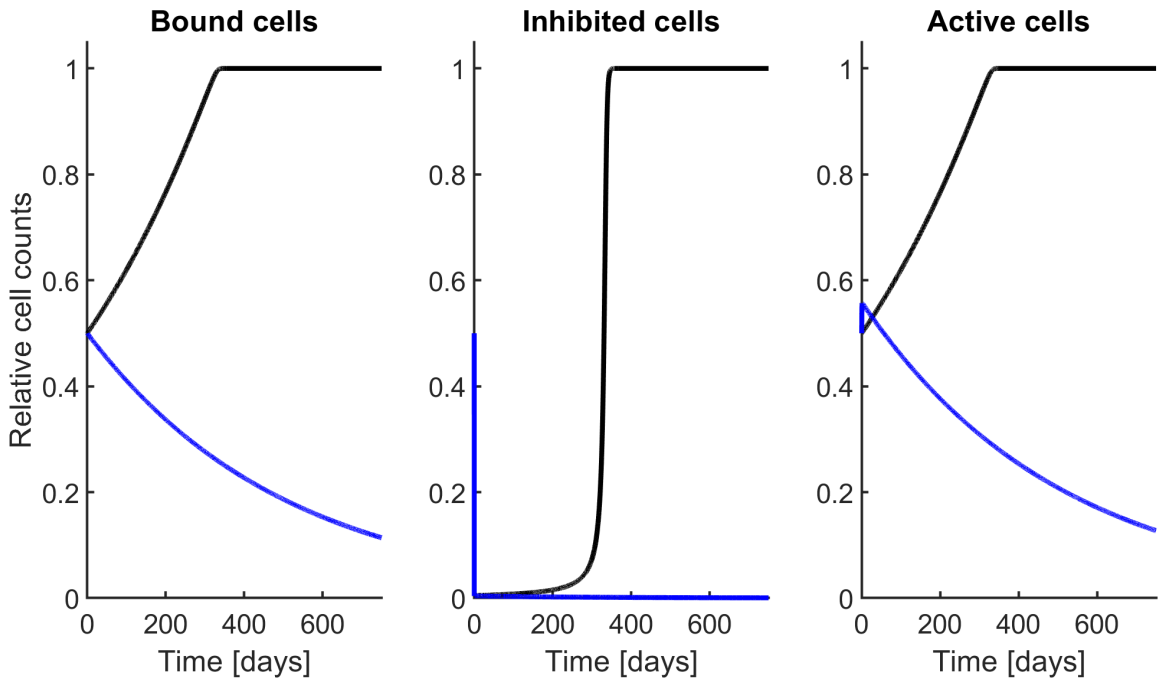

Reducing the model

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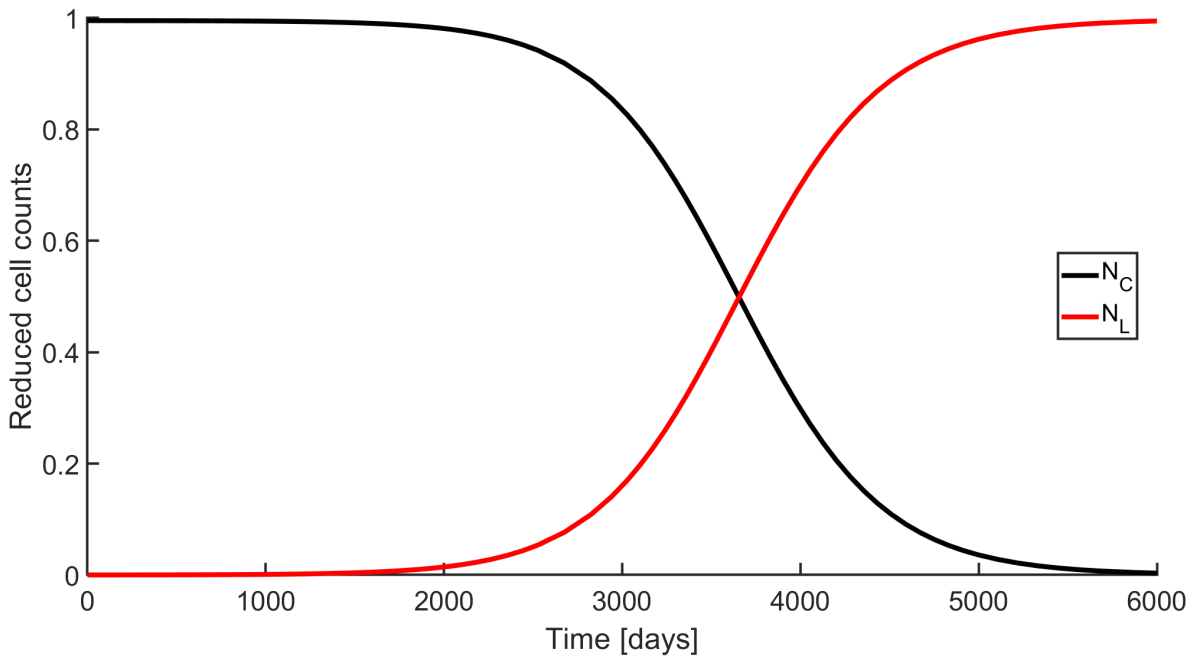
Reducing the model

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

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 $\rho_L = \frac{r_L}{r_L + d_{A_L}}$

Reducing the model



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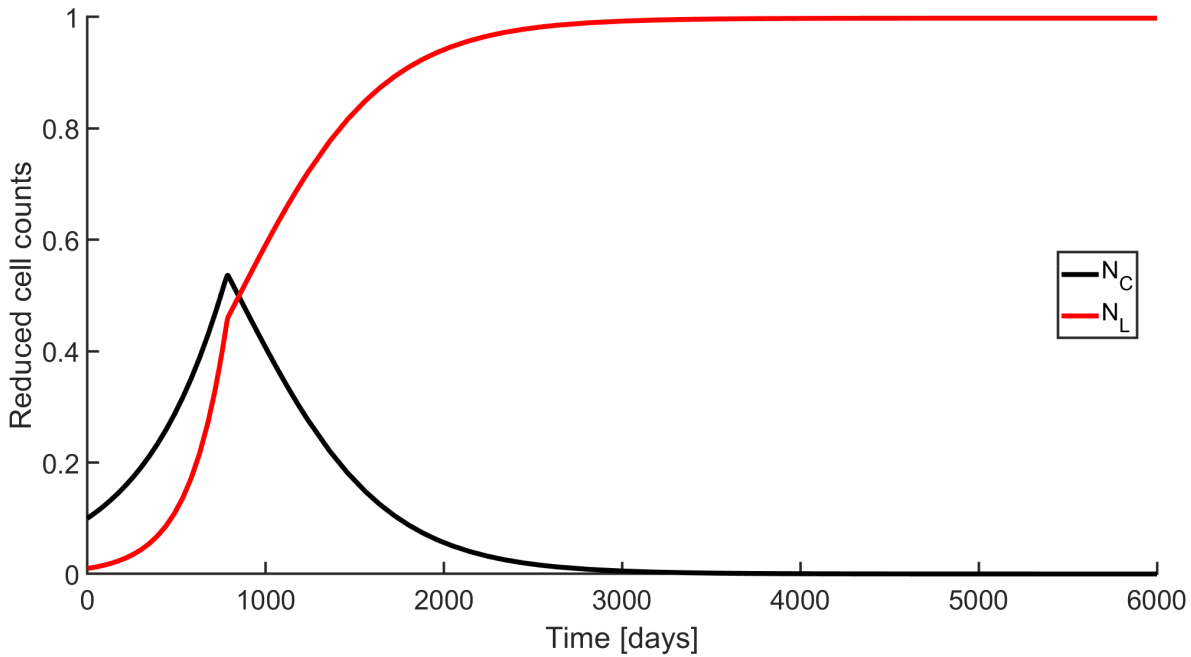

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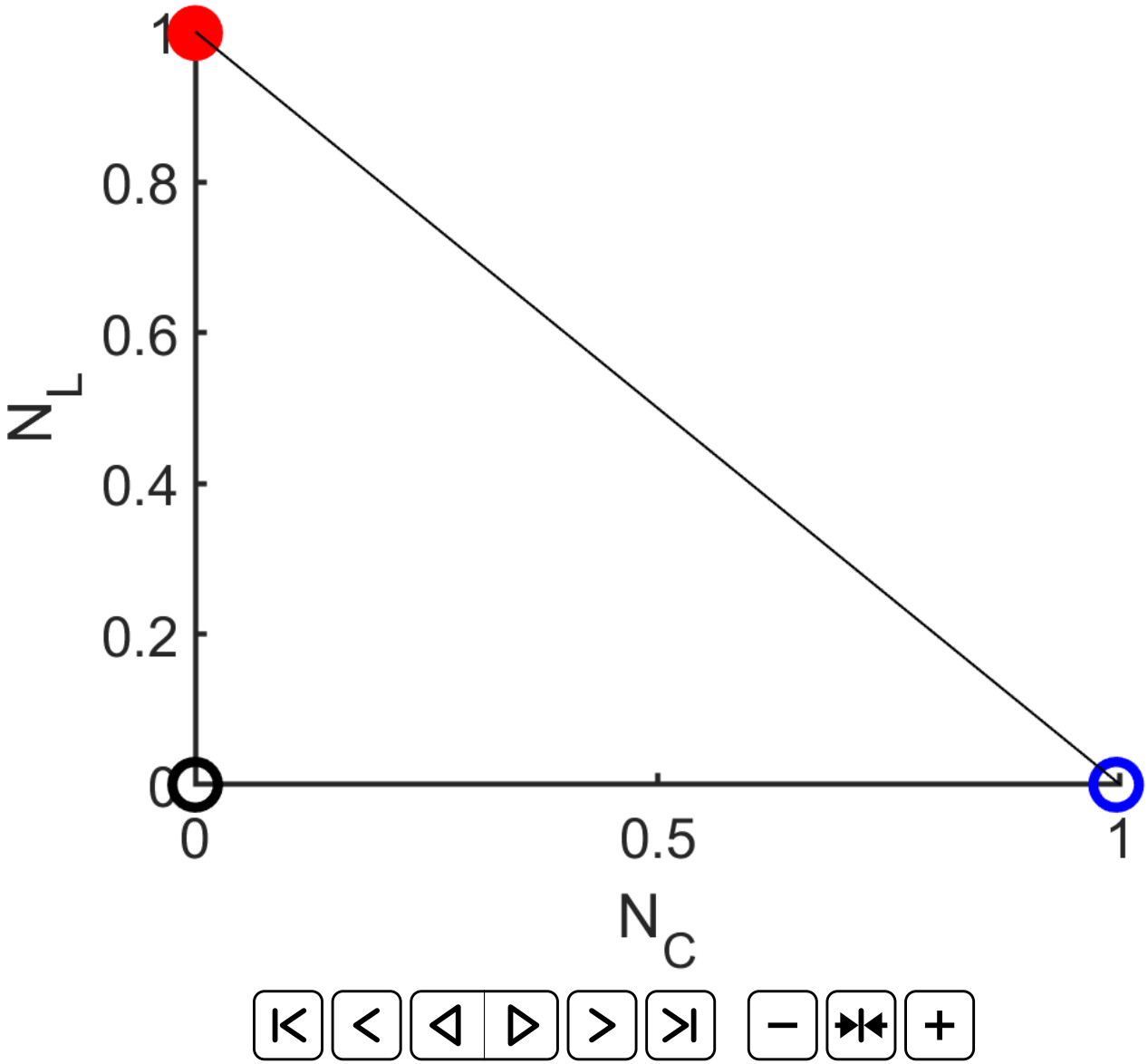
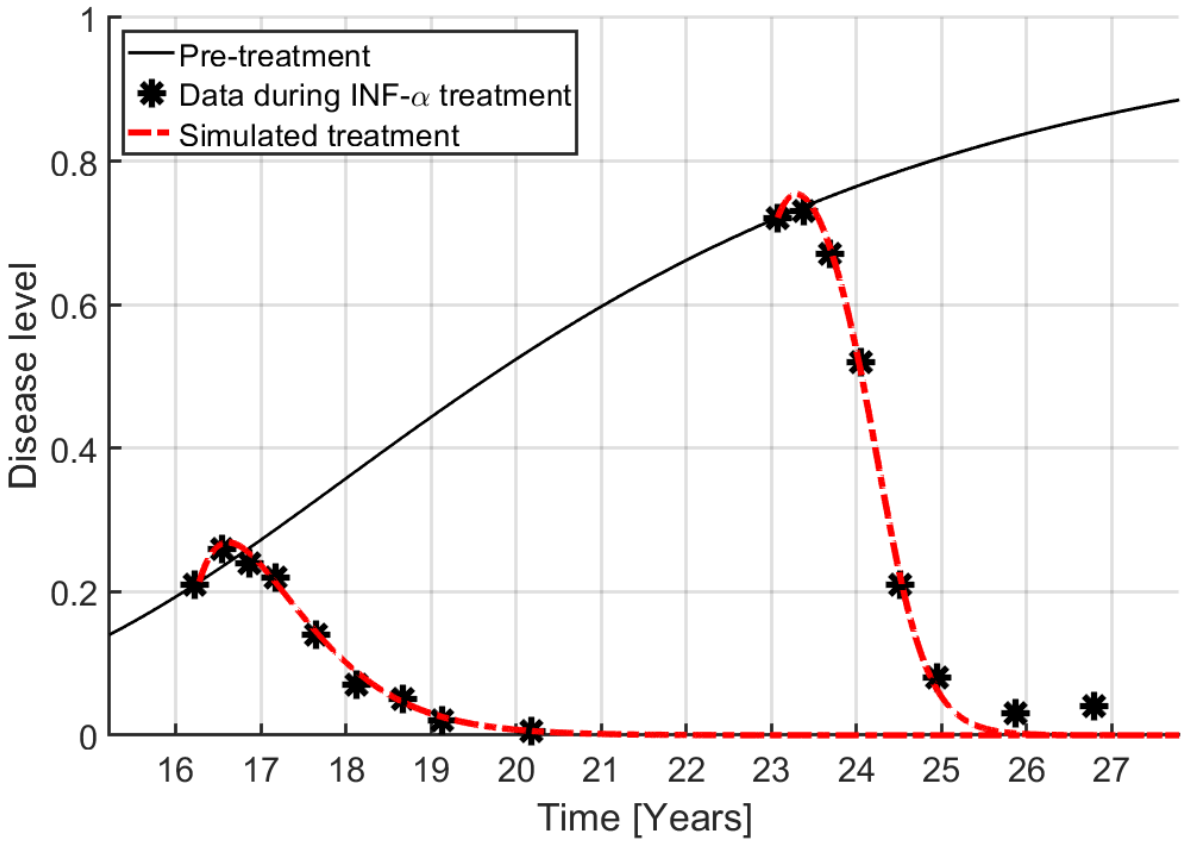


Future work: Simulating treatment



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- HSC fitness is cell intrinsic, i.e. it could be possible to determine it from studies involving only single cell types.
- By considering feedback signalling from blood, fitting with and perhaps even predicting patient-data could be possible.

Thank you for your attention.

Any questions?

References

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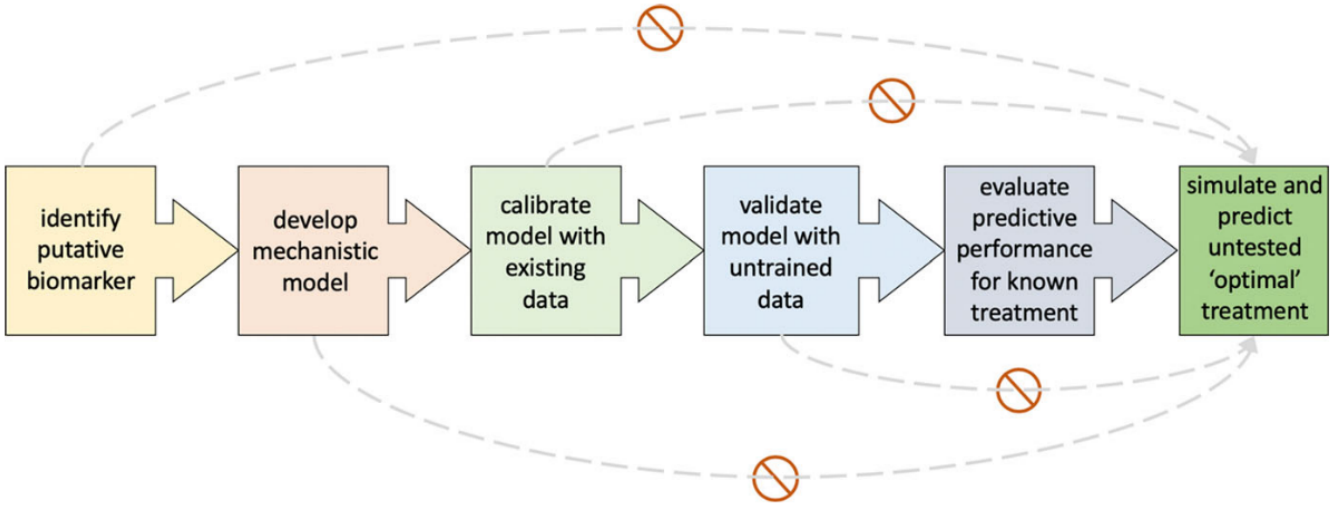
Bonus figure



(Brady and Enderling, 2019)