Sensitivity analysis and parameter estimation of leukopoiesis model with two delays

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Outline

- Motivation
- Leukopoiesis model with two delays
- Solution method
- Clinical data
- Numerical tests
- Concluding remarks

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Motivation

Blood cells production and regulation

Haematopoietic pluripotent stem cells (HSCs) in bone marrow give birth to the three blood cell types.

Growth factors or Colony Stimulating Factors (CSF) – specific proteins that stimulate the production and maturation of each blood cell type.

Blast cells – blood cells that have not yet matured.

Blood cell type	Function	Growth factors
Erythrocyte	Transport oxygen to tissues	Erythropoietin
Leukocyte	Fight infections	G-CSF, M-CSF, GM-CSF, Interleukins
Thrombocyte	Control bleeding	Thrombopoietin

Leukopoiesis – process of production and regulation of white blood cells (T- and B-lymphocytes, NK cells, monocytes, granulocytes, eosinophils, and basophils)

Blood pathologies

Various hematological diseases (including leukemia) are characterized by abnormal production of particular blood cells (matured or blast).

Main stages in the therapy of blood diseases:

TBI: Total body irradiation (TBI) and chemoterapy – kill the ”tumour” cells, but also the healthy ones.

BMT: Bone marrow transplantation (BMT) – stem cells of a donor (collected under special conditions) are put in the peripheral blood.

After BMT, HSCs have to:

1. find their way to the stem cell niche in the bone marrow; and
2. selfrenew and differentiate to regenerate the patient’s blood system.

Adequate computer models would help medical doctors to

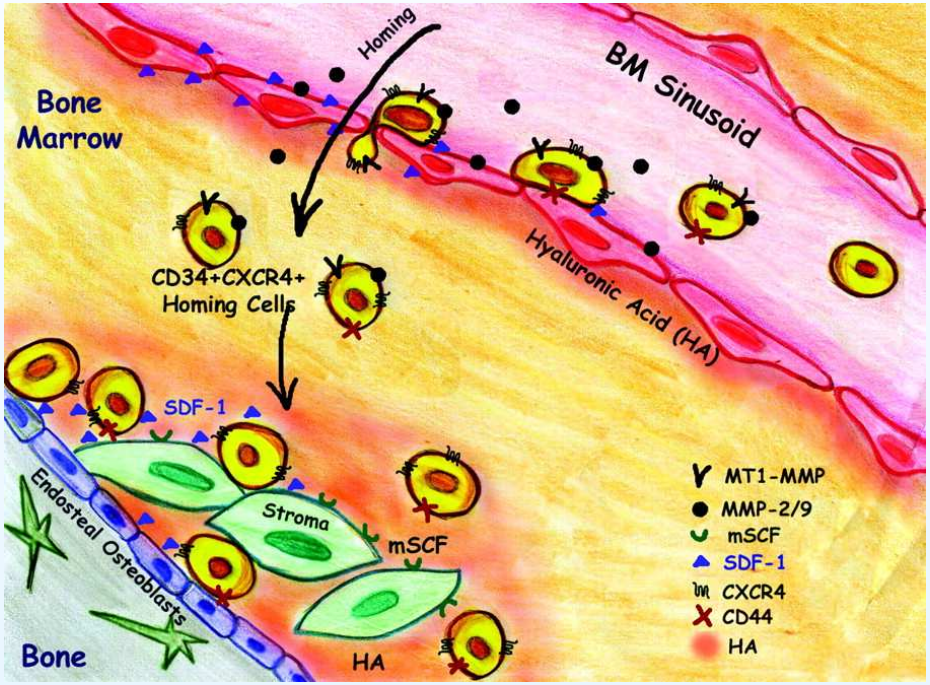
- understand better the HSCs migration and differentiation processes;
- design nature experiments for validation of hypotheses;
- predict the effect of various treatment options for specific blood diseases;

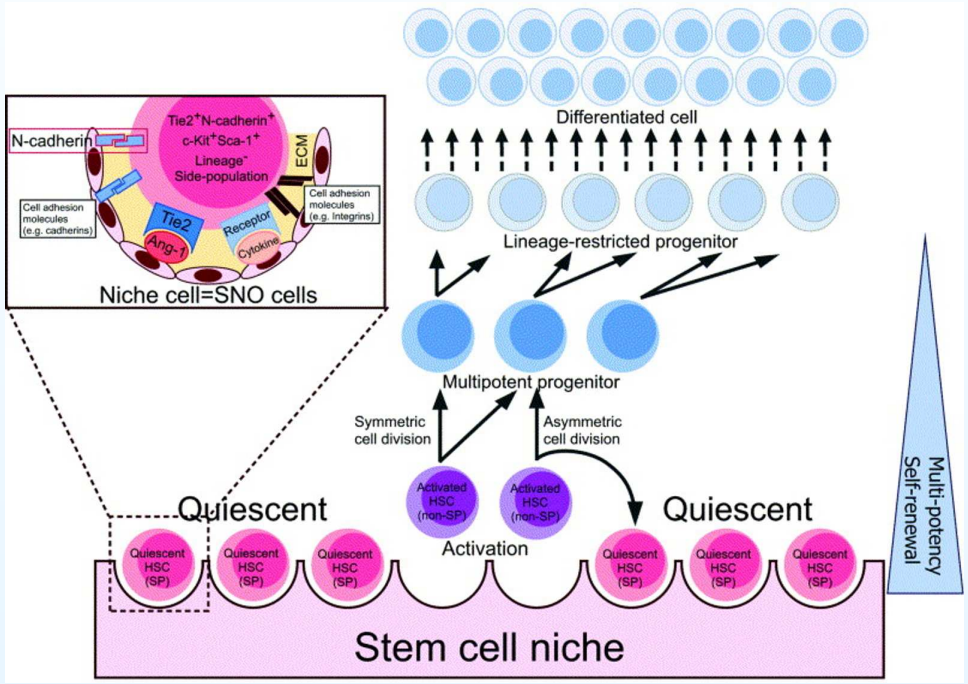
Current stage: Tune parameters of leukopoiesis model on the base of clinical data for T, B and NK cells.

HSCs after transplantation ...

1. find their way to the stem cell niche in the bone marrow; and ...

2. self-renew and differentiate to regenerate the patient's blood system



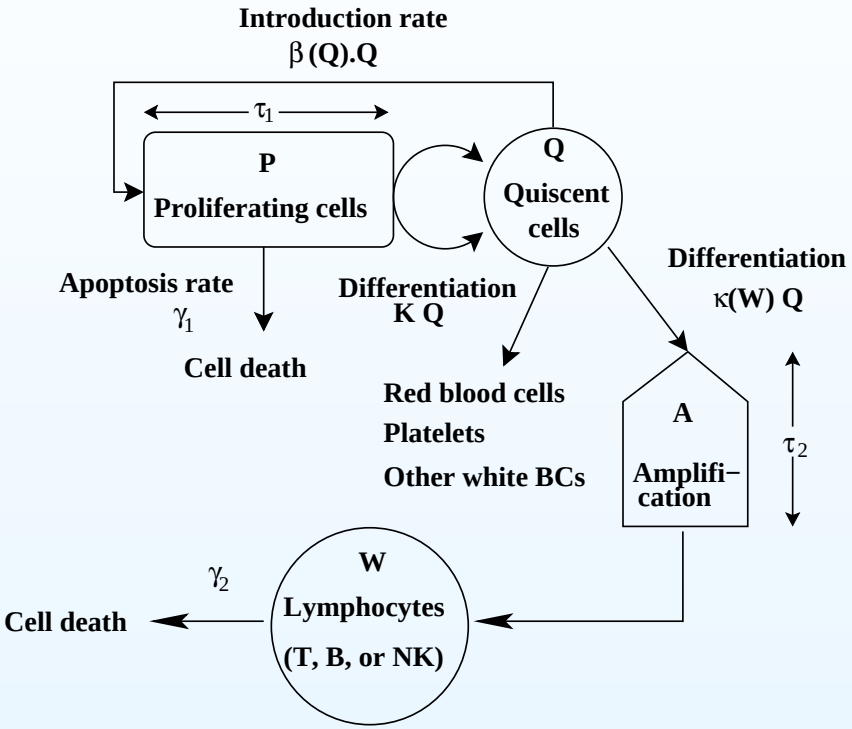


T. Lapidot, A. Dar, O. Kollet, How do stem cells find their way home?, Blood, Vol. 106(6), (2005), 1901–1910.

T. Suda, F. Arai, A. Hirao, Hematopoietic stem cells and their niche, Trends in Immunology, Vol. 26(8), (2005), 426–433.

Leukopoiesis model

Involved data



P – HSCs in proliferating phase

Q – HSCs in quiscent phase

W – Matured white blood cells

τ_1 – Proliferating phase duration

τ_2 – Amplification phase duration

$A = \alpha 2^i$ – Amplification parameter, with

$\alpha \in (0, 1)$ – survival rate

i – number of generations

$\beta(Q)$ – Introduction rate

$K, k(W)$ – Differentiation rate

γ_1 – Apoptosis rate of P

γ_2 – Death rate of white blood cells

Apoptosis rate of Q is included in K

[LM] *M. Adimy, F. Crauste, S. Ruan, Periodic oscilations in leukopoiesis models with two delays, Journal of Theoretical Biology 242, (2006), 288–299.*

LM system of DDEs

$$\begin{cases} \dfrac{dQ}{dt} &= -[K + k(W(t)) + \beta(Q(t))]Q(t) \\ & \quad +2e^{-\gamma_1\tau_1}\beta(Q(t-\tau_1))Q(t-\tau_1) \\ \dfrac{dW}{dt} &= -\gamma_2 W(t) + Ak(W(t-\tau_2))Q(t-\tau_2) \end{cases}$$

$$Q(t) = Q_0(t),\ W(t) = W_0(t),\ t \in [-\tau^*, 0],\ \tau^* = max\{\tau_1, \tau_2\}$$

Delay $\tau_1 \geq 0$ corresponds to the cell cycle duration.
Delay $\tau_2 \geq 0$ corresponds to the amplification phase duration.
$Q(t) \geq 0,\ W(t) \geq 0$

Existence of nontrivial positive steady-state is ensured by:

$(2^{-\gamma_1\tau_1} - 1)\beta(0) > k(0) + K$ and
the function $Q \mapsto Q\beta(Q)$ is decreasing in (Q_0, Q_1), where

$$Q_0 = \beta^{-1}\left(\frac{k(0)+K}{2^{-\gamma_1\tau_1}-1}\right) \text{ and } Q_1 = \beta^{-1}\left(\frac{K}{2^{-\gamma_1\tau_1}-1}\right)$$

Solution methods

Solution methods

XPPAUT is "A tool for simulating, animating and analyzing dynamical systems." (G. B. Ermentrout)

B. Ermentrout, *Simulating, analyzing and animating dynamical systems: a guide to XPPAUT for researchers and students,* SIAM, 2002

`http://www.math.pitt.edu/~bard/xpp/xpp.html`

XPPAUT implementation of the methods:

	Expl.	Impl.	FS	AS	Stiff
Runge Kutta (RK)	+		+		
Dormand-Prince 5 (DP5)	+			+	
Rosenbrock (RB2)		+		+	+

Rosenbrock is based on Matlab version of the two step Rosenbrock algorithms.

Delay equations are solved by storing previous data and using cubic polynomial interpolation to obtain the delayed value.

E. Hairer, (S.P. Norsett), G. Wanner, Solving ordinary differential equations I, II, Springer Ser. in Comp. Math., Springer, 2000 (part I), 2002 (part II)

Clinical data

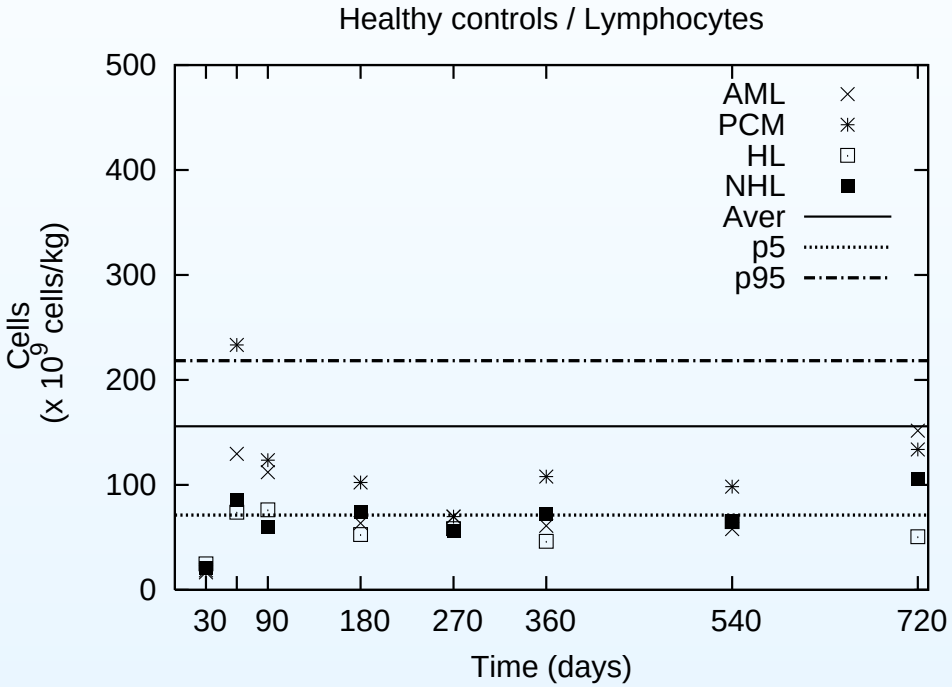
Clinical data

- Gathered amount of HSC (CD34+) – initial value for Q; Minimal required amount 2×10^6 cells/kg, optimal 5×10^6 cells/kg;
- After BMT – no blood system, i.e. initial values for matured cells are almost equal to 0; Range of circulating WBC in peripheral blood after chemotherapy is $0 - 0.014 \times 10^9$ cells/kg, $W_0 = 0.007 \times 10^8$ cells/kg.
- G-CSF is applied every day during the first month (NEUPOGEN – Filgrastim; GRANOCYTE – Lenograstim);
- Statistical data for T, B and NK cells and their subpopulations before BMT (D) and 1, 2, 3, 6, 9, 12, 18, 24 months after BMT.
- Diseases – Hodkin's Lymphoma (HL), Non-Hodgkin's Lymphoma (NHL), Plasma Cell Myeloma (PCM), Acute Myelogeneous Leukemia (AML)

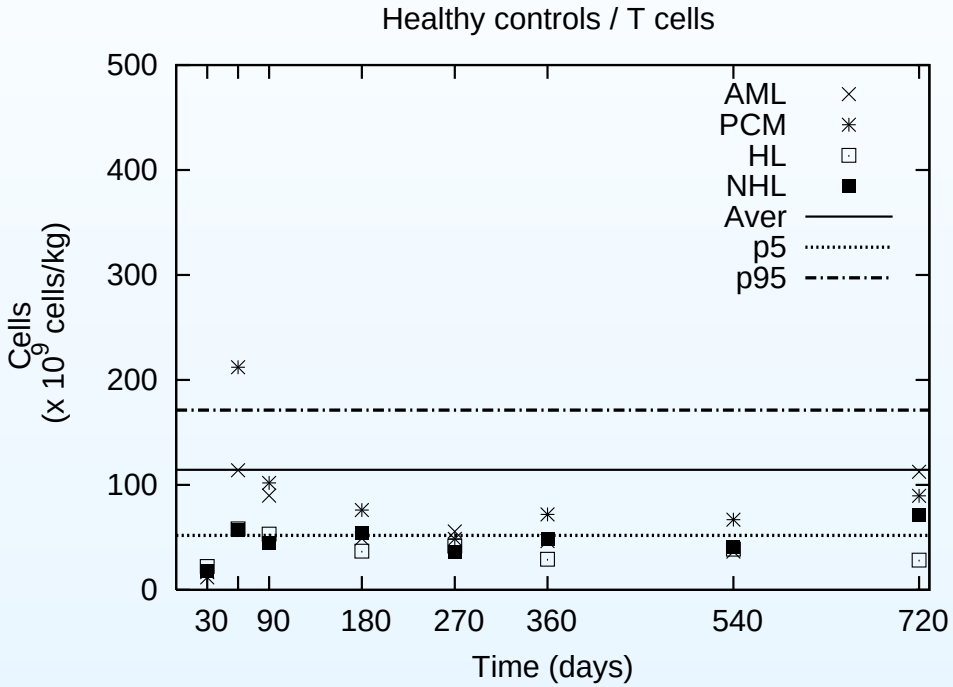
Dis.	N. P.	Weight (kg)	Age (y)	HSCs (c/kg)	Vol. (ml)
HL	9	74.22	30.56	5.06×10^6	422.22
NHL	7	77.71	38.43	4.87×10^6	457.14
PCM	4	72.75	54.75	4.67×10^6	550.00
AML	3	83.33	39.00	2.15×10^6	633.33

Patients' data compared with healthy controls

Main populations



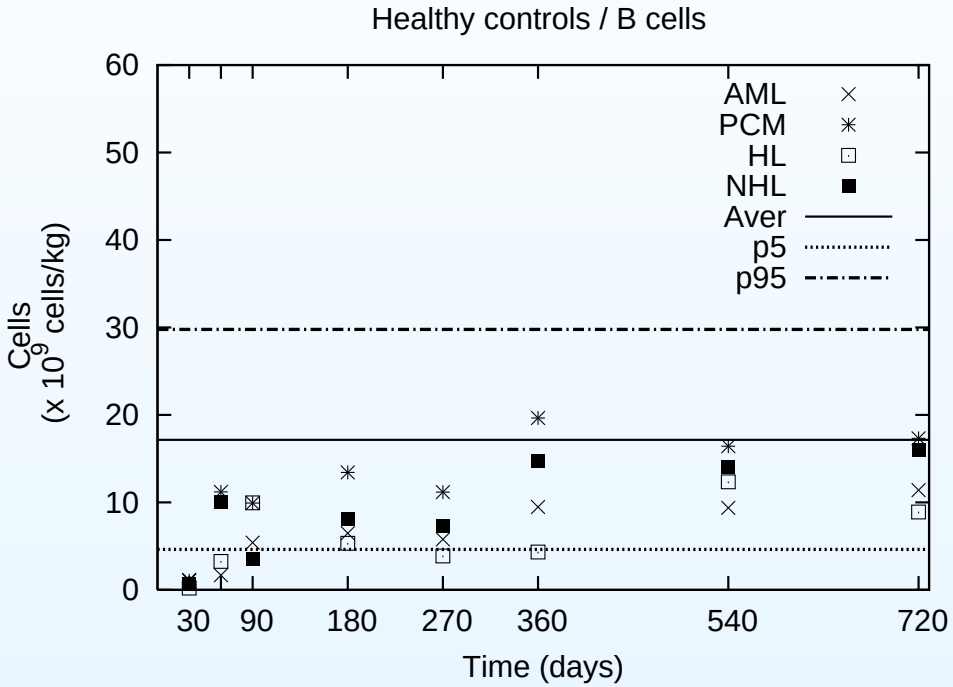
Lymphocites



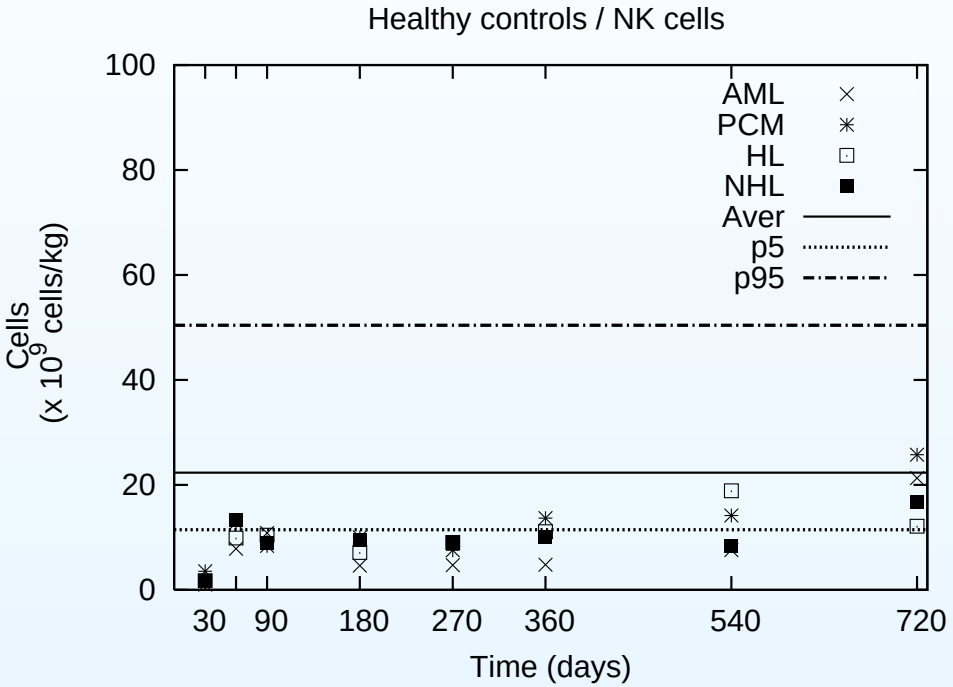
T cells

Patients' data compared with healthy controls – II

Main populations



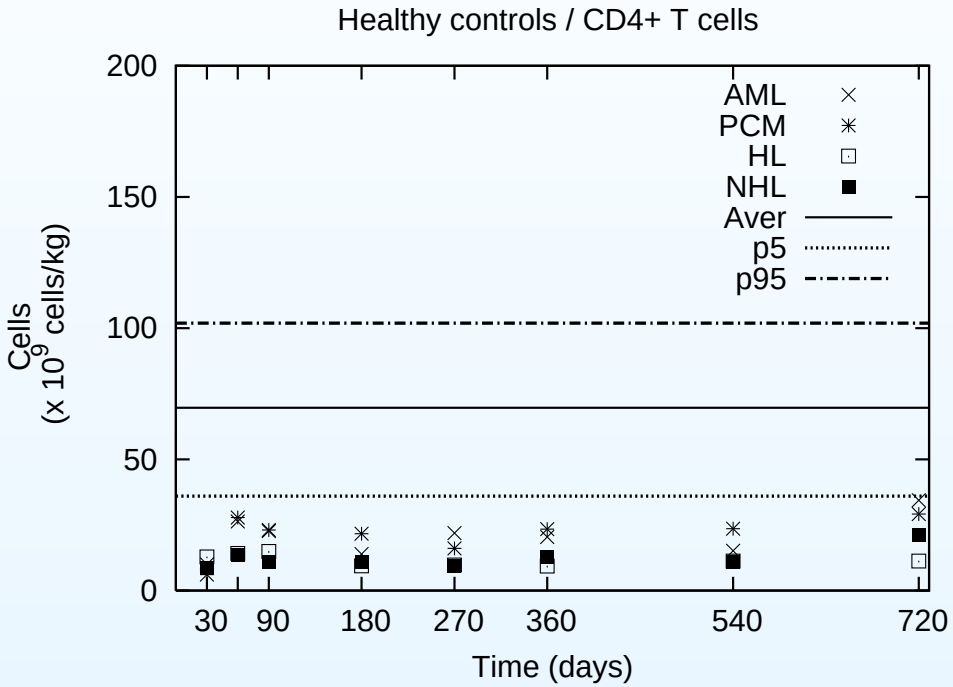
B cells



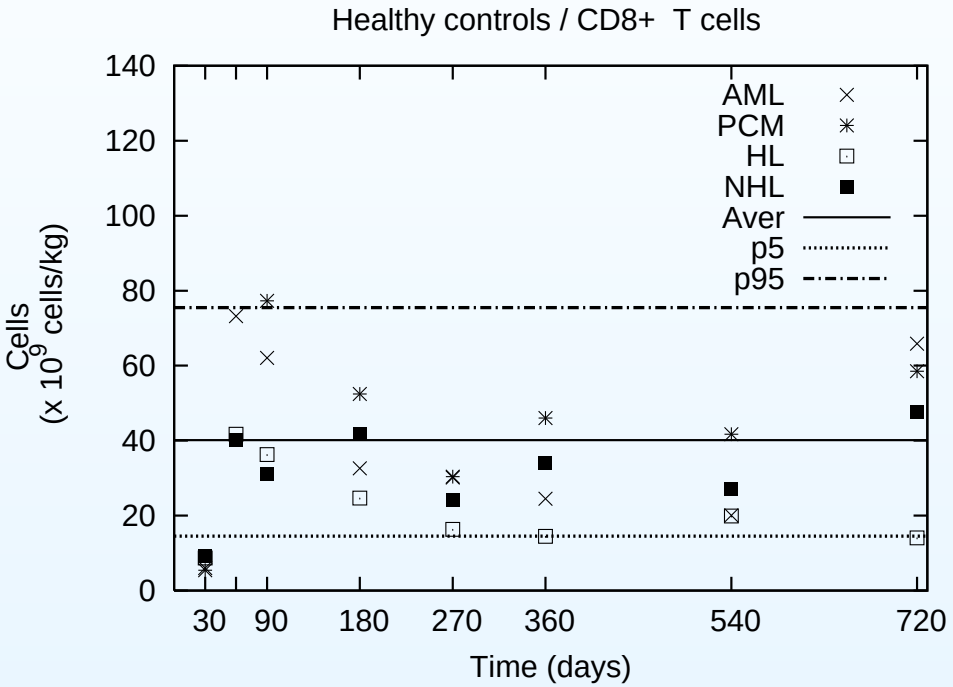
NK cells

Patients' data compared with healthy controls – III

Small populations



CD4+ T cells



CD8+ T cells

Numerical tests

Model parameters

$$\beta(Q) = \frac{\beta_0 \theta_1^n}{\theta_1^n + Q^n}, \beta_0, \theta_1 > 0,\ k(W) = \frac{k_0 \theta_2^m}{\theta_2^m + W^m}, k_0, \theta_2 > 0,$$

$$A = \alpha 2^i, \alpha \in (0, 1)$$

Parameter	LM
β_0 (day$^-$1)	1.77
θ_1 ($\times 10^8$ cells/kg)	1
n	3
τ_1 (day)	0.05
γ_1 (day$^-$1)	0.1
k_0 (day$^-$1)	0.1
θ_2 ($\times 10^8$ cells/kg)	1
m	2
τ_2 (day)	2
γ_2 (day$^-$1)	2.4
K (day$^-$1)	0.02
A	20

Cell type	degr. rate γ_2	source
Naive CD4+	0.0005	[1]
Naive CD8+	0.0003	[1]
T_n CD4 + CD8	0.04	[2]
B cell	0.0394	[3]
NK cell	0.0693	[4]

[1] Vrisekoop et.al. (2008)

[2] Moore, Li (2004)

[3] Macallan et.al. (2005)

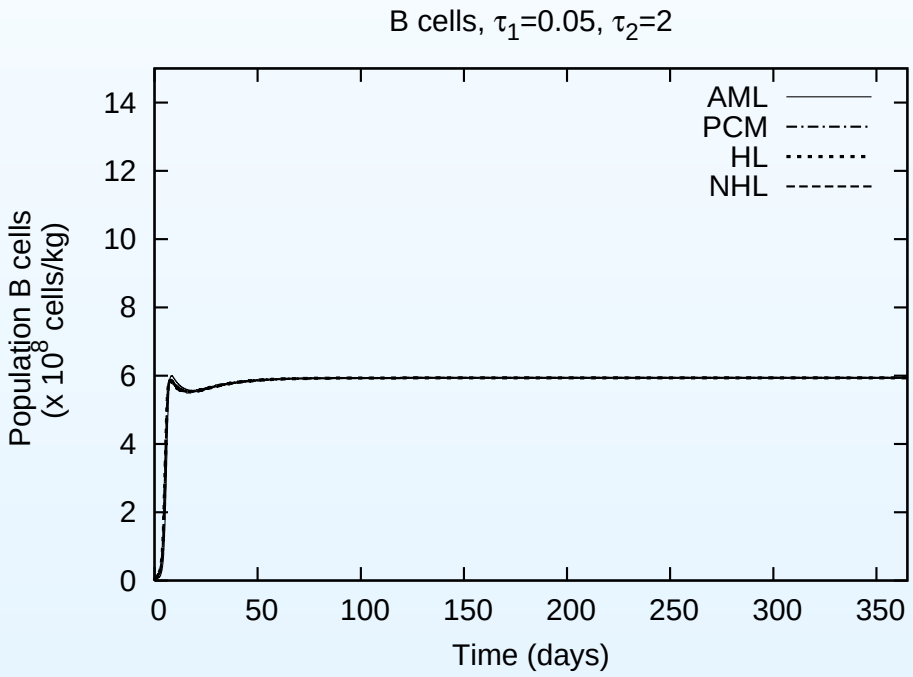
[4] Zhang et. al. (2007)

Results W(t), B cells

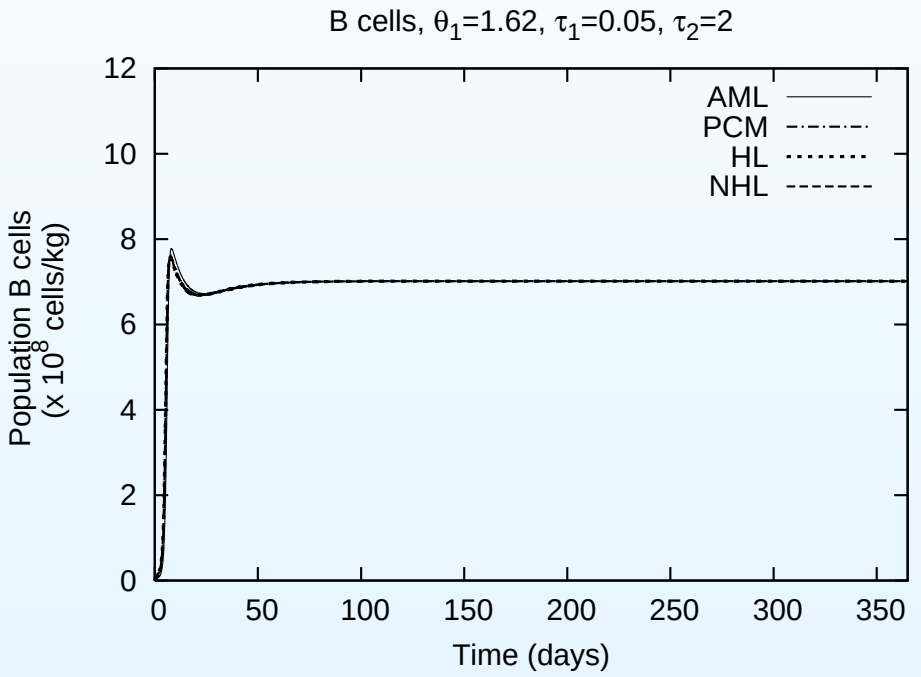
Comparison of the four diseases – AML,PCM, HL, NHL initial conditions

Healthy range for B cells: $46.2 - 297.66 \times 10^8$ cells/kg

LM parameter values with $\gamma_2 = 0.0394$



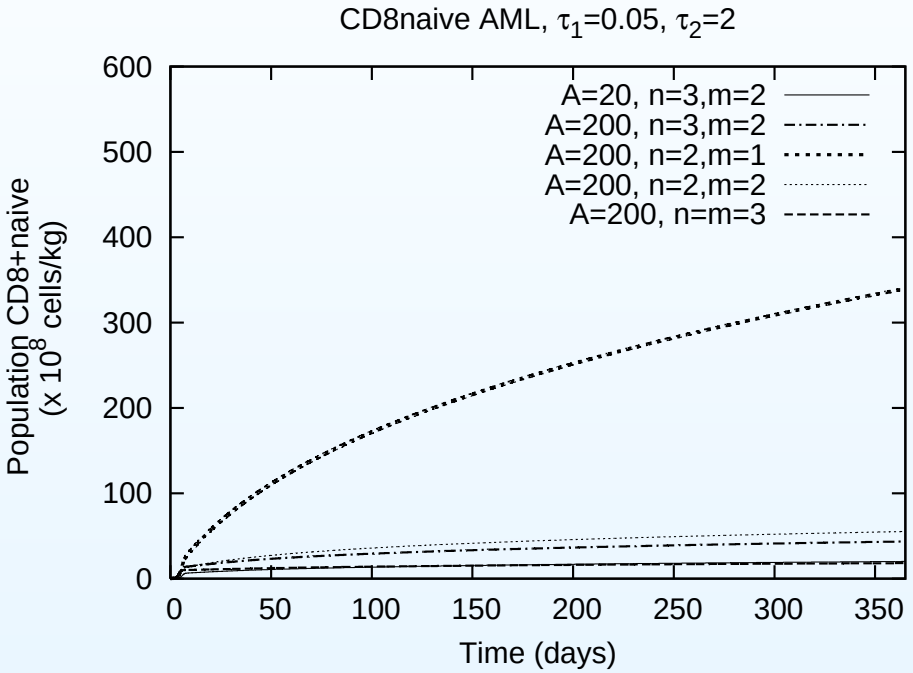
$\theta_1 = \theta_2 = 1 \times 10^8$ cells/kg

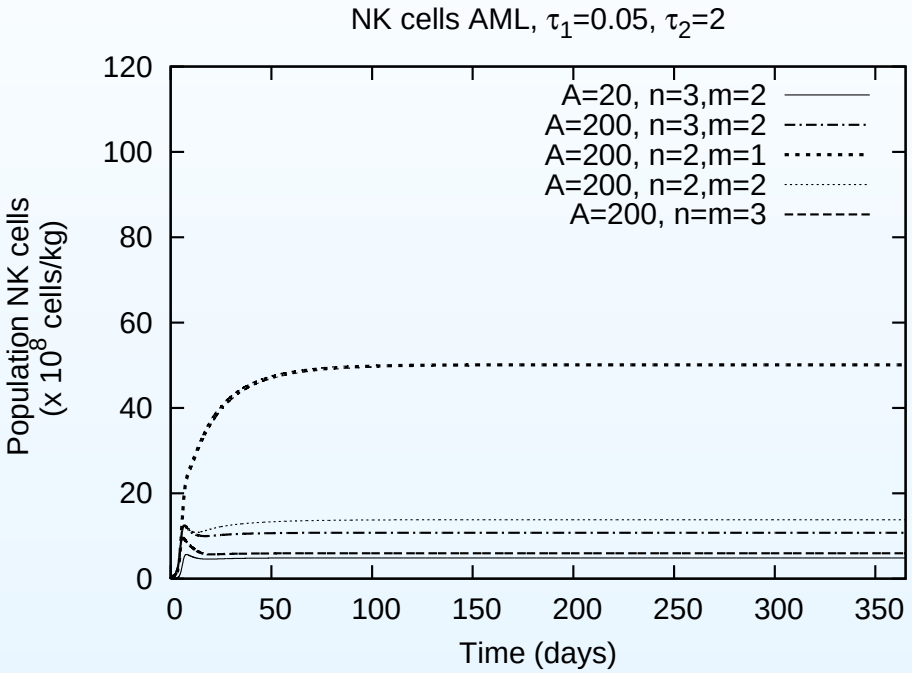


$\theta_1 = 1.62 \times 10^8, \theta_2 = 1 \times 10^8$ cells/kg

Results W(t), LM – varying A, n, m

Initial data for AML: $Q_0 = 0.0215 \times 10^8$ cells/kg, $W_0 = 0.007 \times 10^8$ cells/kg





Naïve CD8+ T cells: $\gamma_2 = 0.0003$

Healthy range:

$25.41 - 193.01 \times 10^8$ cells/kg

NK cells: $\gamma_2 = 0.0693$

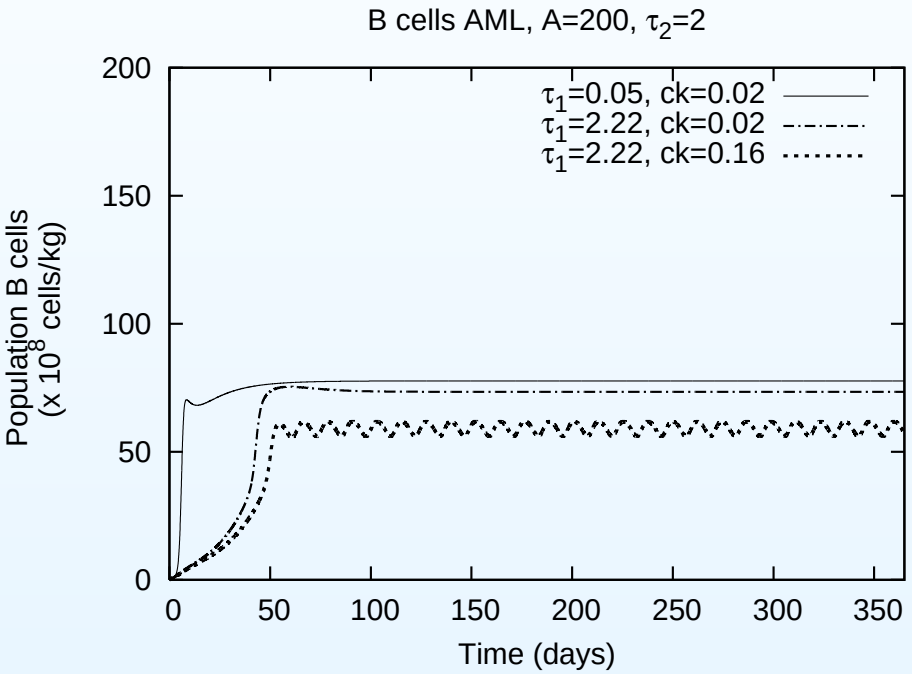
Healthy range:

$114.38 - 503.98 \times 10^8$ cells/kg

Results W(t), B cells – varying A, τ_1 and K

Healthy range: $46.2 - 297.66 \times 10^8$ cells/kg

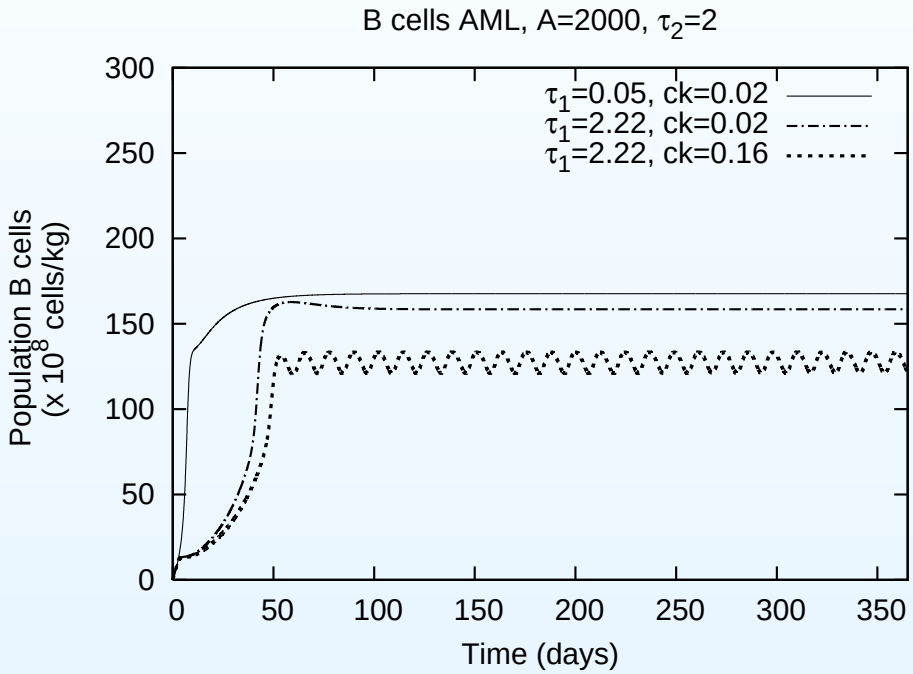
AML initial conditions, $\theta_1 = 16.2 \times 10^8$ cells/kg, $\theta_2 = 3.6 \times 10^8$ cells/kg



$A = 200$

$\tau_1 = 0.05$ or 2.22

$K = 0.02$ or 0.16



$A = 2000$

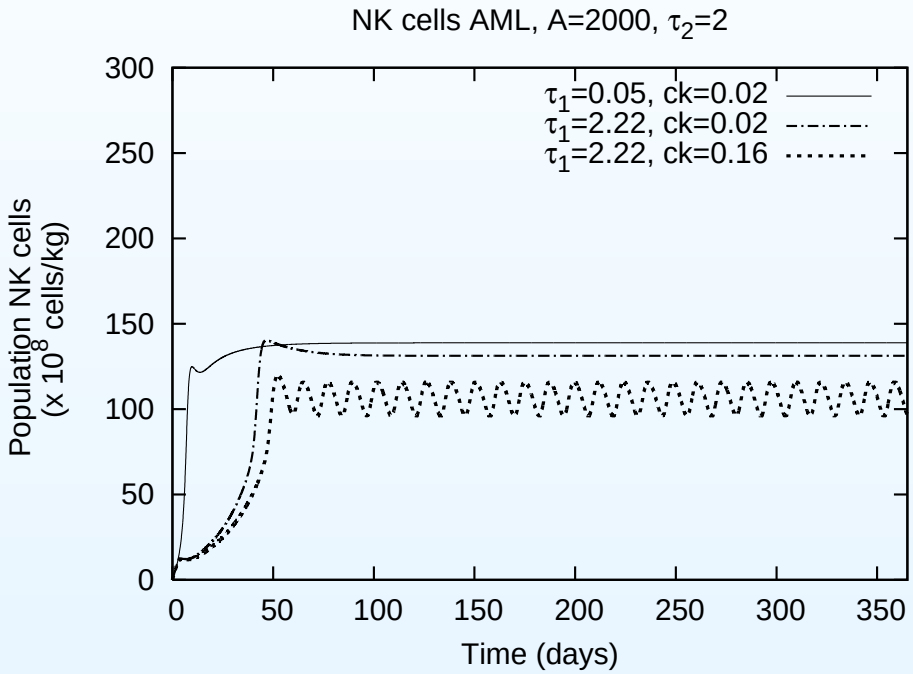
$\tau_1 = 0.05$ or 2.22

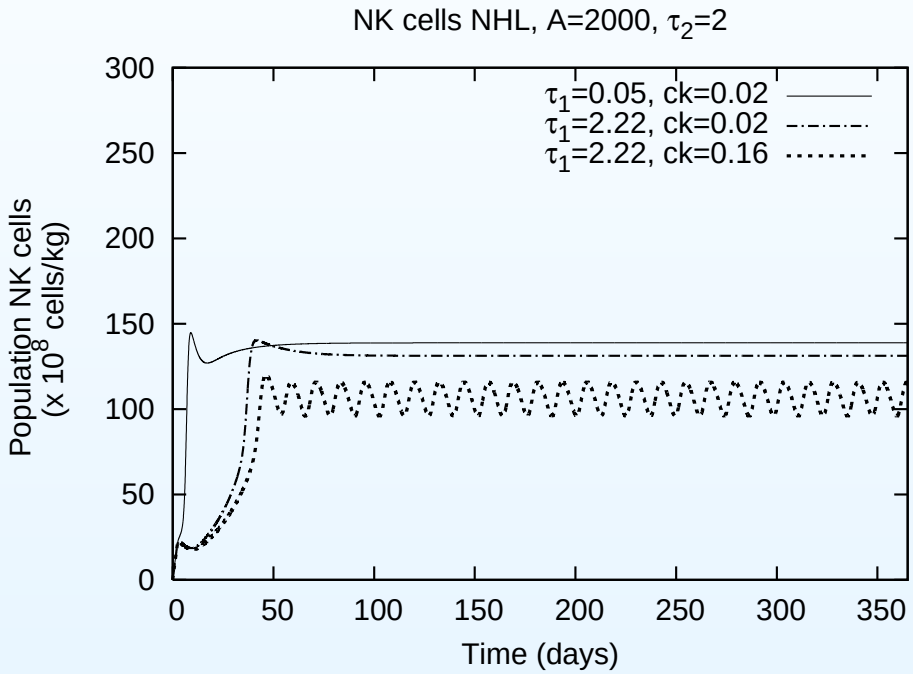
$K = 0.02$ or 0.16

Results W(t), NK cells – varying τ and K

Healthy range: $114.38 - 503.98 \times 10^8$ cells/kg

$A = 2000$, $\theta_1 = 16.2 \times 10^8$ cells/kg, $\theta_2 = 3.6 \times 10^8$ cells/kg





AML initial conditions

$\tau_1 = 0.05$ or 2.22

$K = 0.02$ or 0.16

NHL initial conditions

$\tau_1 = 0.05$ or 2.22

$K = 0.02$ or 0.16

Concluding remarks and further steps

Concluding remarks

- Change of initial condition, i.e. the amount of transplanted HSCs in various diseases, does not change the general behaviour and steady state of the population; observed differences only in the firts 50-80 days;
- Change only of γ_2, or together with other parameters, but not θ_i – populations are not in the healthy range, and no oscilating nature;
- Change of θ_i and τ_1 together with other parameters – oscilating nature is obsurved like in clinical data and for B and NK cells with $A = 2000$ the steady states are in healthy ranges.

Cell type	γ_2 (days^{-1})	HR $\times 10^8$ c/kg	Parameters
B cell	0.0394	46.2 – 297.66	$A = 200$ and $A = 2000$, $\theta_1 = 16.2 \times 10^8$, $\theta_2 = 3.6 \times 10^8$, $\tau_1 = 2.22$, $\tau_2 = 2$, $K = 0.16$
NK cell	0.0693	114.38 – 503.98	$A = 2000$, $\theta_1 = 16.2 \times 10^8$, $\theta_2 = 3.6 \times 10^8$, $\tau_1 = 2.22$, $\tau_2 = 2$, $K = 0.16$
T_n CD4 + CD8	0.04	114.50 – 490.59	the same as for NK
T naïve CD4+	0.0005	69.99 – 329.30	?
T naïve CD8+	0.0003	25.41 – 193.01	?

Ongoing and further steps

T-cell subtype	γ_2 (days^{-1})	source	HR $\times 10^8$ c/kg
Memory CD4+	0.07702	[1]	193.05 – 726.04
	0.08252	[2]	
Memory CD8+	0.08664	[1]	29.43 – 375.45
	0.07453	[2]	
Naive+ef CD4	0.06931	[1]	93.75 – 462.56 (like NK cells)
	0.04652	[2]	
Naive+ef CD8	0.11552	[1]	80.24 – 272.99
	0.14441	[2]	

[1] D.C. Macallan et.al. (2003) [2] D. L. Wallace et.al. (2004)

- Sensitivity analysis with specialized methods and software together with parameter estimation: for ODEs – SimBiology, SBML-SAT, sundials, SimLab; for DDEs – Fit parameters using curve fitting in MATLAB; develop own software;
- Add the influence of G-CSF treatment during first month after PBSCT;
- Incorporate in the model more than one type of matured blood cells.

Thank you for your attention!