Computer modelling of hematopoiesis with applications to blood pathologies

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Main ongoing projects (funded by the Bulgarian NSF):

DO 02-115/2008, Svetozar Margenov

Center of excellence on supercomputer applications
`http://parallel.bas.bg/CE_SuperCA/`

DO 02-147/2008, Ivan Lirkov

Large Scale Scientific Computating in Advanced Multiscale Simulation

DO 02-214/2008, Gergana Bencheva

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`http://delta.bas.bg/~cmblood`

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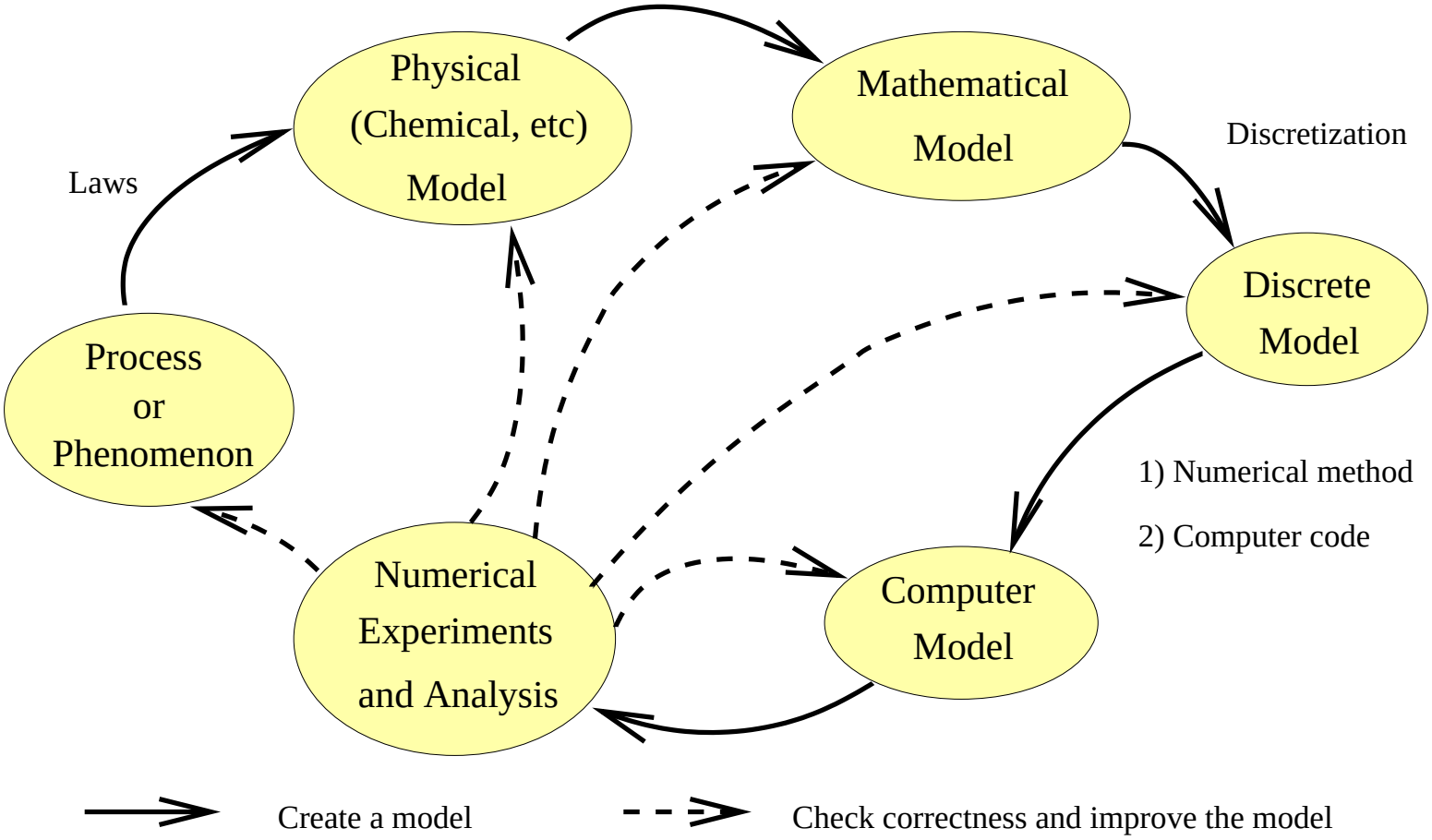
Motivation

Computer modelling stages



Computer modelling ...

... includes:

- mathematical model, adequately describing the results of planned experiments and observations
- numerical methods for discretization of differential and/or integral equations
- efficient methods and algorithms for solution of the obtained after discretization systems of linear algebraic equations
- algorithms for visualization and analysis of the results of the performed numerical experiments
- high performance computer programs, which use in maximum degree the potential and architecture of the contemporary computing systems

... gives possibilities for:

- Economy of expensive laboratory and nature experiments
- Determination of characteristics of new materials and technologies, as well as investigation of processes for which direct measurements and observations are impossible
- Substantial acceleration of the development process
- Real time processes' management

Blood cells production and regulation

Haematopoietic pluripotent stem cells (HSCs) in bone marrow (BM) give birth to the three blood cell types, due to their
a) rapid migratory activity and ability to ”home” to their niche in BM;
b) high self-renewal and differentiation capacity.

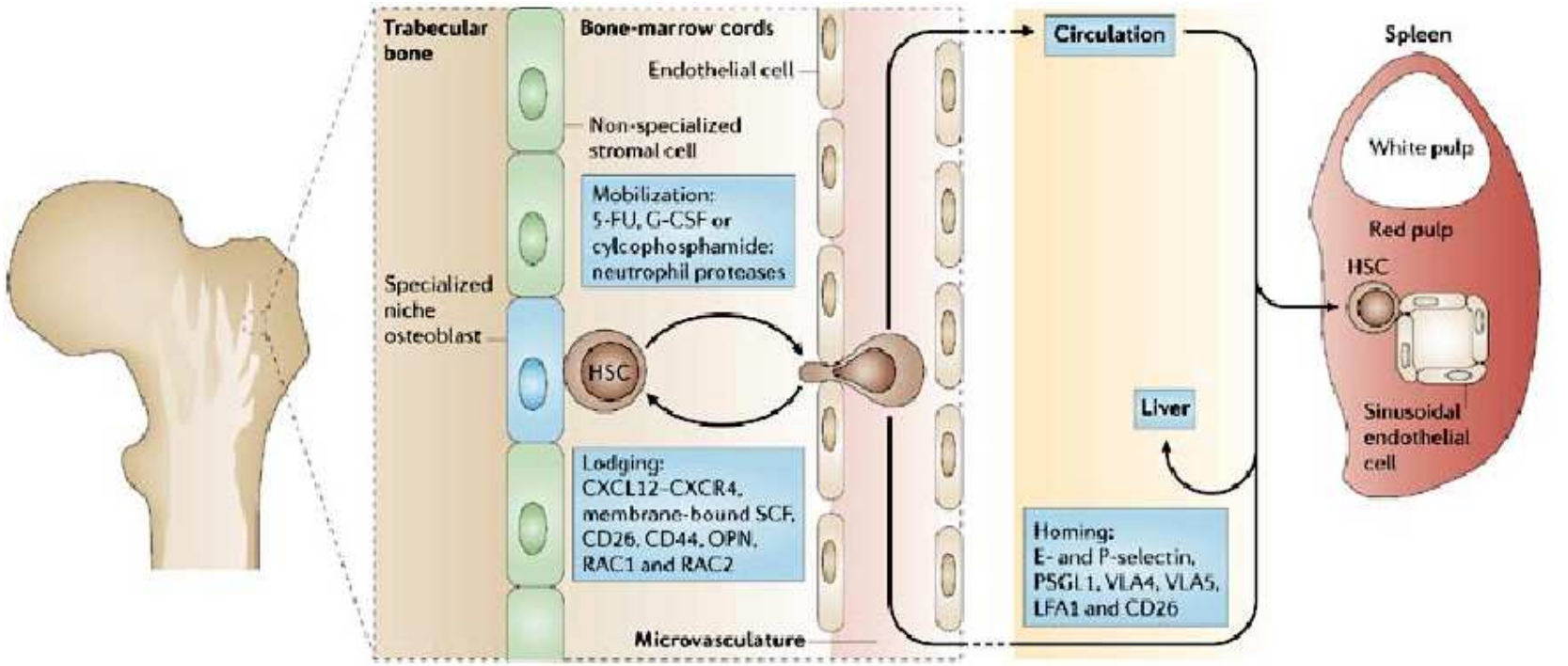
Growth factors or Colony Stimulating Factors (CSF) – specific proteins that stimulate the production and maturation of each blood cell type.

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)

HSCs mobilization, homing and lodging

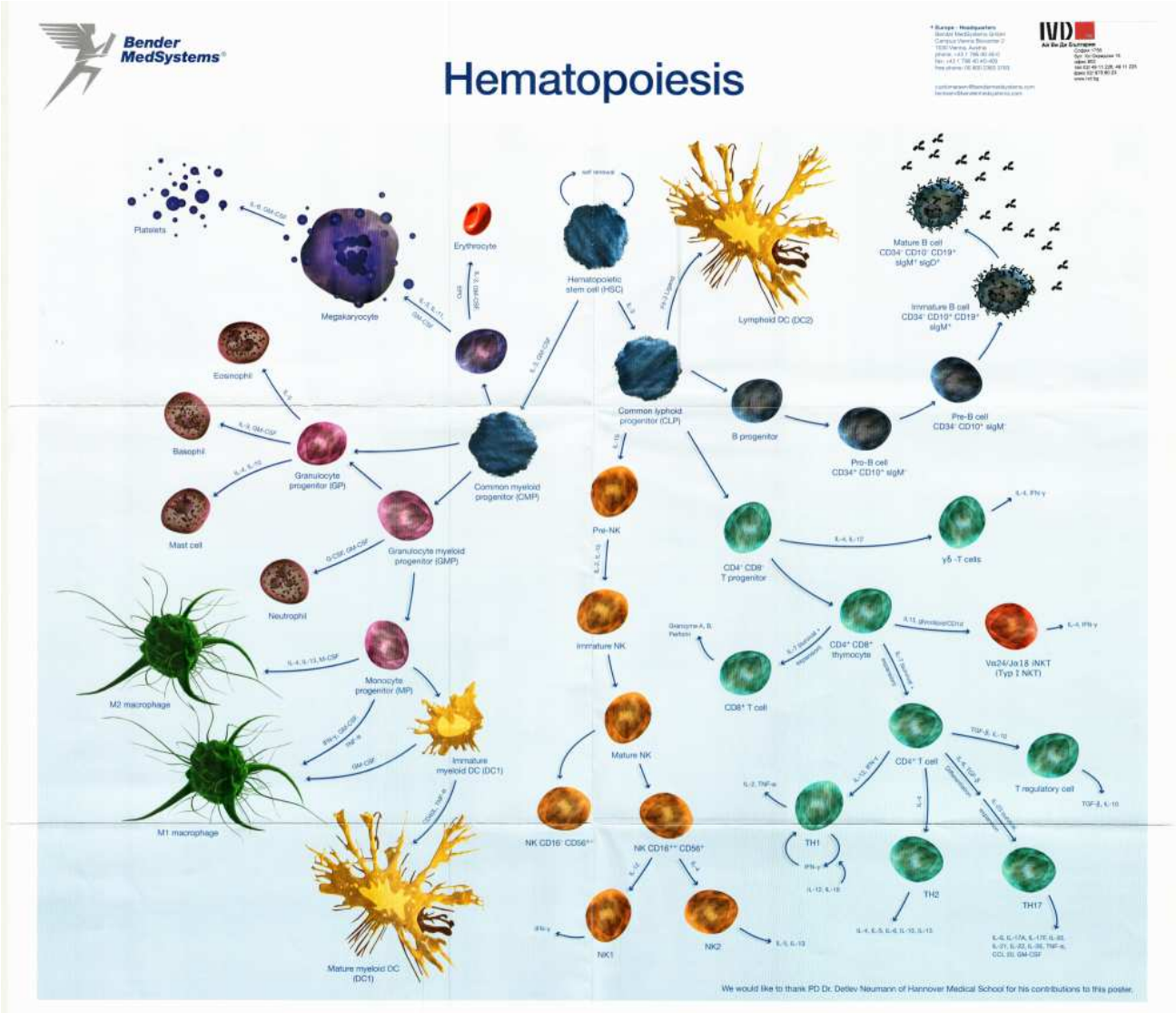


Wilson *et al. Nature Reviews Immunology* **6**, 93–106 (February 2006) | doi:10.1038/nri1779

nature REVIEWS IMMUNOLOGY

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

Differentiation stages in haematopoiesis



http://www.bendermedsystems.com/

Blood pathologies

Various hematological diseases (including leukaemia) 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 shorten the period in which the patient is missing his/her effective immune system.

Need for computer simulation

The approach ”trial-error” is not recommended for dealing with questions related to understanding and predicting of human physiological processes in health and disease.

Development of software tools for real-time data-driven simulation of haematopoiesis will give possibility to

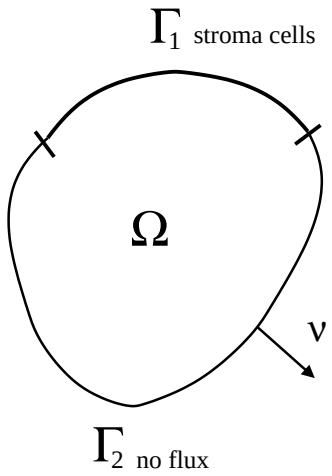
- understand better the HSCs migration and differentiation processes;
- design nature experiments for validation of hypotheses;
- predict the effect of various treatment options for patients with specific hematological diseases;

Chemotactic HSCs movement

Involved data

Unknowns:

$s(t,x)$ – concentration of stem cells in Ω
$a(t,x)$ – concentration of chemoattractant
$b(t,x)$ – concentration of stem cells bound to stroma cells at the boundary part Γ_1



Parameters:

ε – random motility coefficient of HSCs
$\chi(a)$ – chemotactic sensitivity function
D_a – diffusion coefficient of chemoattractant
γ – consumption rate-constant for SDF-1
$c(x)$ – concentration of stroma cells on Γ_1
$\beta(t,b)$ – proportionality function in the producton rate of chemoattractant

$$\Omega \in R^2$$
$$\partial\Omega = \Gamma_1 \cup \Gamma_2$$
$$\Gamma_1 \cap \Gamma_2 = \emptyset$$

A. Kettemann, M. Neuss-Radu, Derivation and analysis of a system modeling the chemotactic movement of hematopoietic stem cells, Journal of Mathematical Biology, 56, (2008), 579-610.

The model

$$\begin{cases} \partial_t s &= \nabla \cdot (\varepsilon \nabla s - s \nabla \chi(a)), \quad \text{in } (0,T) \times \Omega \\ \partial_t a &= D_a \Delta a - \gamma a s, \quad \text{in } (0,T) \times \Omega \end{cases}$$

$$-(\varepsilon \partial_\nu s - s \chi'(a) \partial_\nu a) = \begin{cases} c_1 s - c_2 b, & \text{on } (0,T) \times \Gamma_1 \\ 0, & \text{on } (0,T) \times \Gamma_2 \end{cases}$$

$$D_a \partial_\nu a = \begin{cases} \beta(t,b) c(x), & \text{on } (0,T) \times \Gamma_1 \\ 0, & \text{on } (0,T) \times \Gamma_2 \end{cases}$$

$$\partial_t b = c_1 s - c_2 b, \text{ on } (0,T) \times \Gamma_1 \text{ and } b = 0, \text{ on } (0,T) \times \Gamma_2$$

$$s(0) = s_0,\ a(0) = a_0 \text{ in } \Omega, \text{ and } b(0) = b_0 \text{ on } \Gamma_1$$

Existence of unique solution is ensured by

$$c \in H^{\frac{1}{2}}(\partial\Omega),\ \beta \in C^1(R \times R, R),\ \chi \in C^2(R)$$

$$0 \le c(x) \le \bar{c}, x \in \Gamma_1 \text{ and } c \equiv 0, x \in \Gamma_2$$

$$\beta(0, b_0) = 0,\ 0 \le \beta(t,b) \le M,\ \left|\frac{\partial \beta}{\partial b}(t,b)\right| \le M_s,\ \left|\frac{\partial \beta}{\partial t}(t,b)\right| \le M_t$$

$$\chi \in \{\chi \in C^2(R) | 0 \le \chi(a), 0 \le \chi'(a) \le C_\chi, |\chi''(a)| \le C'_\chi, a \in R\}$$

Methods and software

Software: COMSOL Multiphysics (http://www.comsol.com)

PDE mode – system of 2 PDEs + ODE on the boundary
Positivity property – $s(t),\ a(t),\ b(t) \geq 0$ for all $t \geq 0$, whenever $s(0),\ a(0),\ b(0) \geq 0$

- Nonlinearities – Automatic choice of nonlinear solver;
- Discretization on space: Finite Element Method – nonuniform mesh
  Finite Difference Method (FDM), Finite Element Method (FEM), Finite Volume Method (FVM)
- Discretization on time
  FDM; θ-scheme (Forward/Backward Euler, Crank-Nicolson); Fractional step and operator splitting methods.
- Solution methods – BDF for time integration; Implicit Euler + PARDISO or GMRES/ILU for linearised system

A. Quarteroni, A. Valli, Numerical Approximation of Partial Differential Equations, Springer Ser. in Comp. Math., Springer, 1997.
V. Thomée, Galerkin Finite Element Methods for Parabolic problems, Springer Ser. in Comp. Math., Springer, 1997.

Nonlinearities

- Newton methods

  Assume we have to solve a nonlinear operator equation $F(x) = 0$ wherein $F : D \in X \to Y$ for Banach spaces X, Y endowed with norms $||\cdot||_X$ and $||\cdot||_Y$. Let F be at least once continuously differentiable. Suppose we have a starting guess x^0 of the unknown solutions x^* at hand. Then successive linearization leads to the general Newton method
  $F'(x^k)\Delta x^k = -F(x^k),\ x^{k+1} = x^k + \Delta x^k,\ k = 0, 1, \ldots$.

  P. Deuflhard, Newton Methods for Nonlinear Problems, Springer Ser. in Comp. Math., Springer, 2004.

- Bifurcation analysis
  Reaction diffusion equations often depend on various parameters, e.g. temperature, catalyst and diffusion rate, etc. Moreover they form normally a nonlinear dissipative system, coupled by reaction among different substances. The number and stability of solutions of a reaction diffusion system may change abruptly with variation of control parameters. Correspondingly we see formation of patterns in the system. This kind of phenomena is called bifurcation.

  Z. Mei, Numerical Bifurcation Analysis for Reaction-Diffusion Equations, Springer Ser. in Comp. Math., Springer, 2000.

Numerical tests

Test data: $\Omega = (0, 1.5) \times (0, 1),\ \Gamma_1 = \{x_1 = 1.5\},\ \Delta t = 0.1$

$c(x_2) = 0.01(1 + 0.2\sin(5\pi x_2)),\ \beta(t, b) = V(t)\beta^*(b)$ with

$$V(t) = \left\{ \begin{array}{ll} 4t^2(3 - 4t) & \text{for } t \leq 0.5 \\ 1 & \text{for } t > 0.5 \end{array} \right\} \text{ and } \beta^*(b) = \frac{0.005}{0.005 + b^2}$$

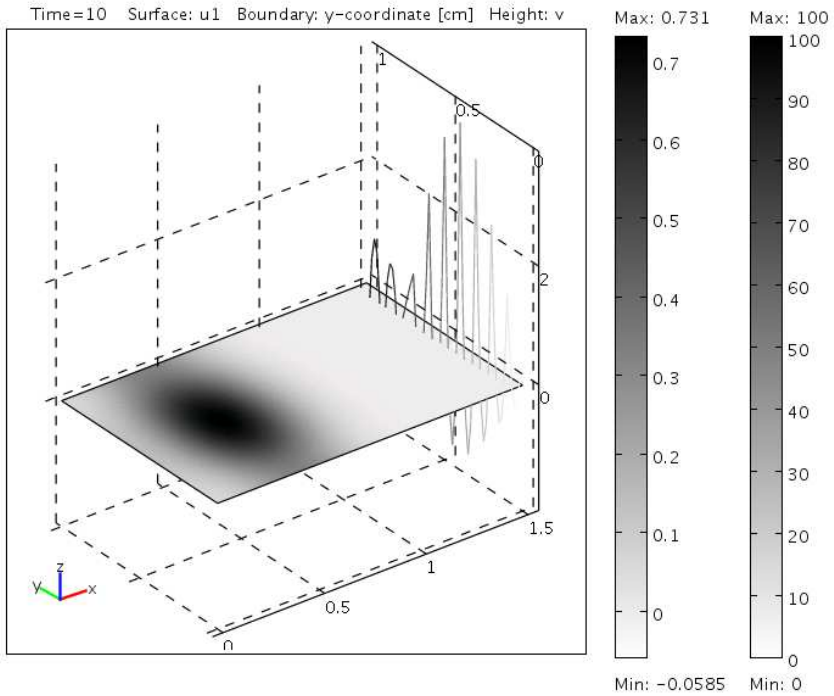
$$\chi(a) = 10a \qquad \chi(a) = \log(a)$$

$$\varepsilon = 0.0015, D_a = 2, \gamma = 0.1, c_1 = 0.3, c_2 = 0.5$$

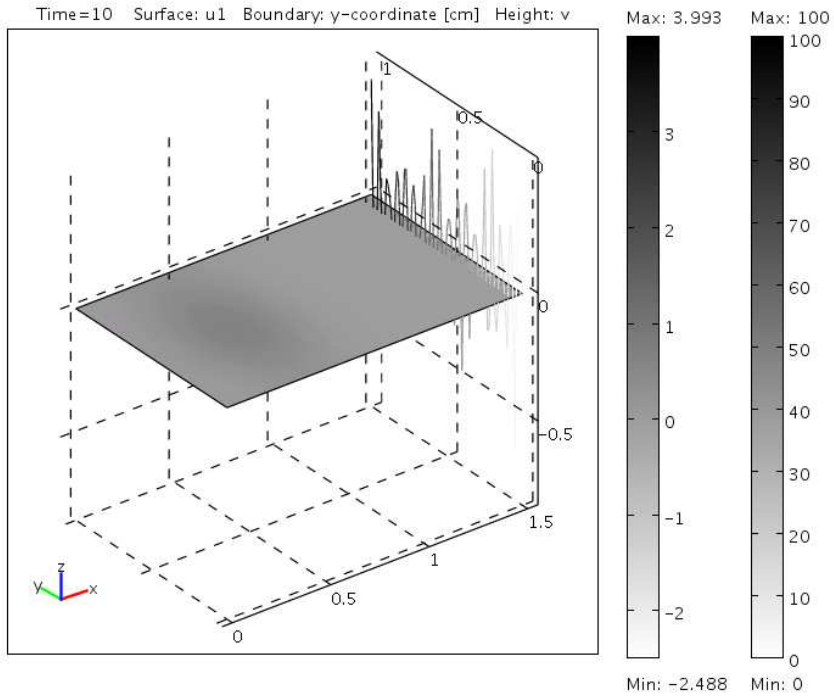
$$a_0 = 0, b_0 = 0 \text{ and}$$

$$s_0(x_1, x_2) = \left\{ \begin{array}{ll} (1 + \cos(5\pi(x_1 - 0.4)))sin(\pi x_2), & \text{for } 0.2 \leq x_1 \leq 0.6 \\ 0 & \text{otherwise} \end{array} \right.$$

Model data – $s(t,x)$ and $b(t,x)$, $T = 10$, GMRES/ILU.

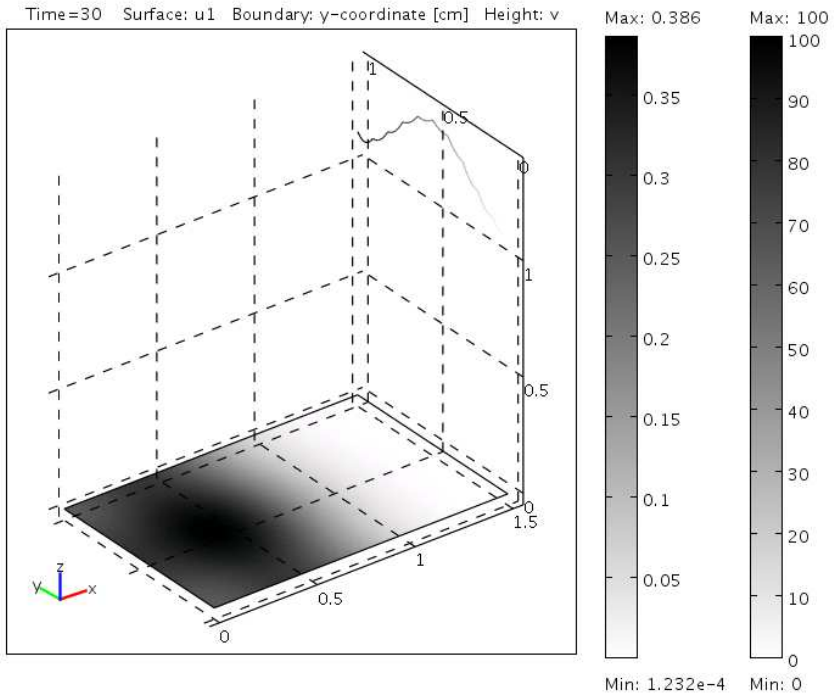


dof = 1723

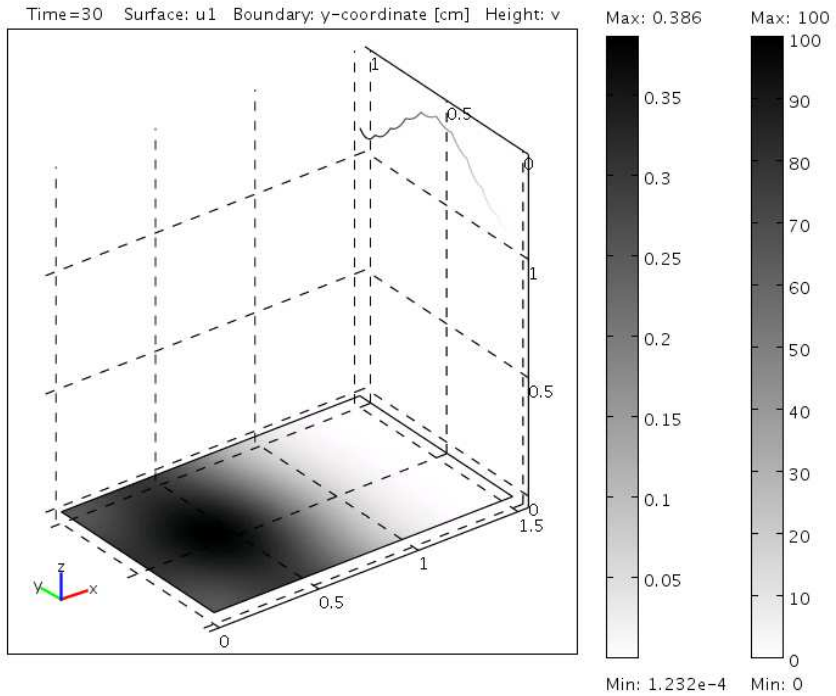


dof=6643

Model data – $s(t,x)$ and $b(t,x)$, $T = 30$, GMRES/ILU.

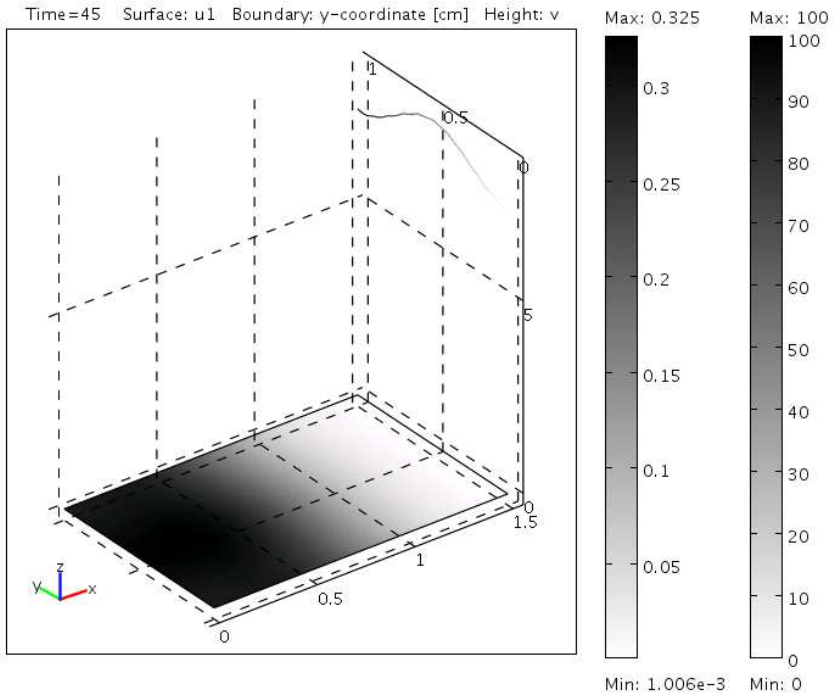


$\chi = 10a$

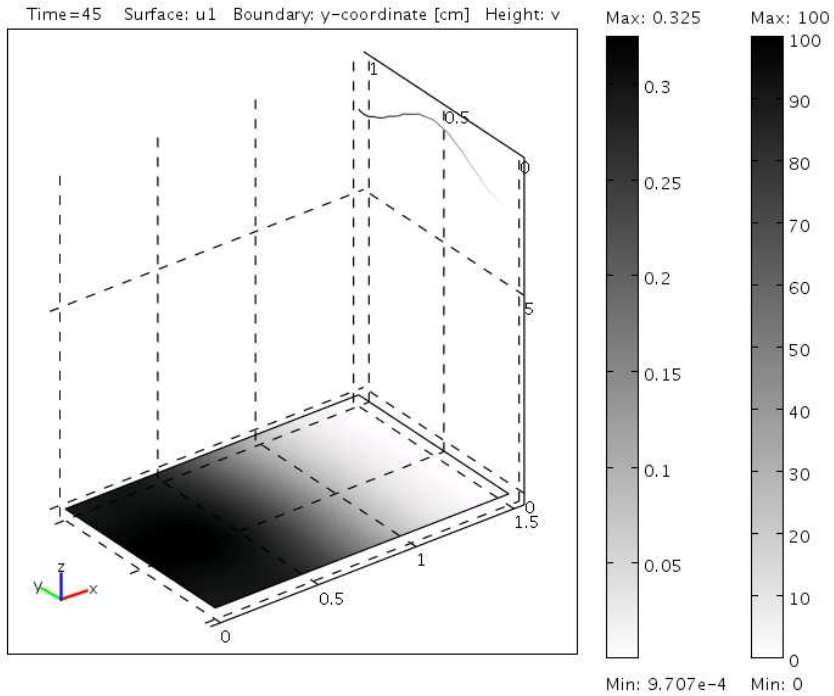


$\chi = log(a)$

Model data – $s(t,x)$ and $b(t,x)$, $T = 45$.

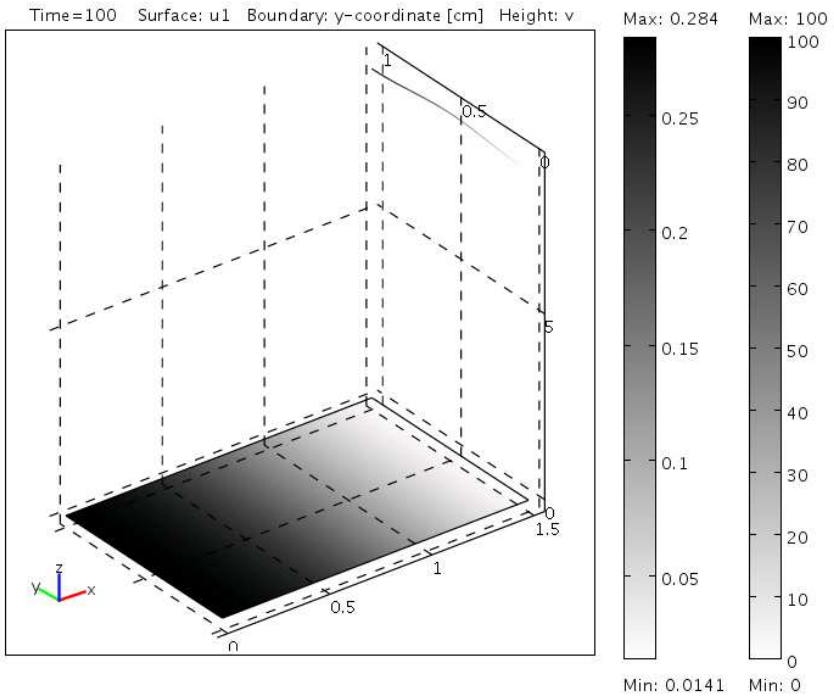


GMRES/ILU

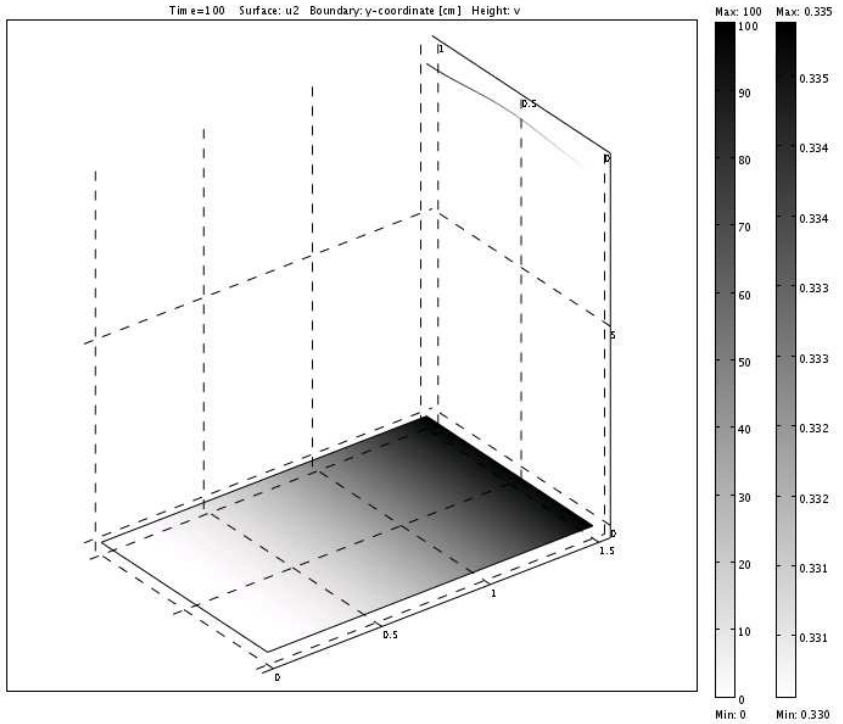


PARDISO

Model data – solution $T = 100$, GMRES/ILU.



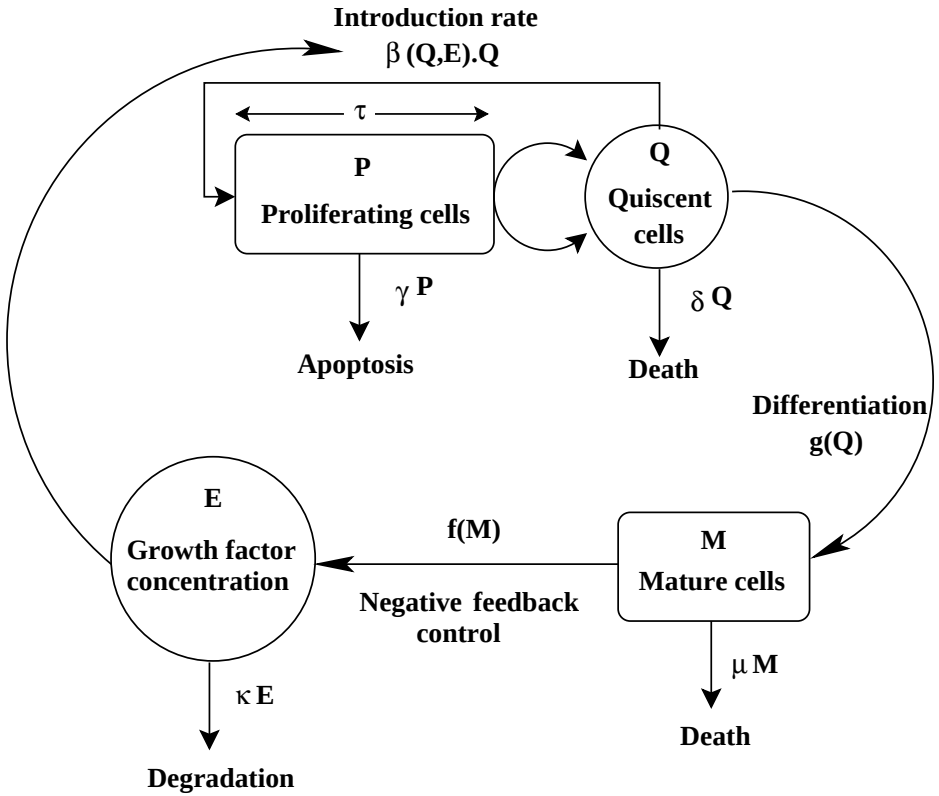
s(t,x) and b(t,x)



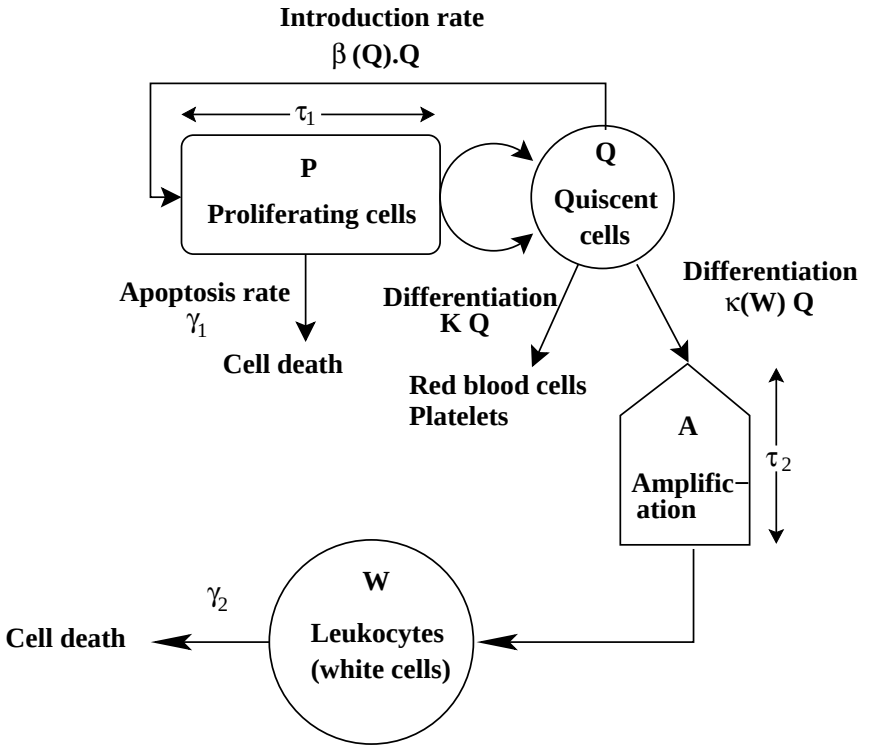
$a(t, x)$ and $b(t, x)$

Regeneration of blood system

Two models – involved data



Growth factors model (GFM)



Leukopoiesis model (LM)

[GFM] M. Adimy, F. Crauste, S. Ruan, Modelling Hematopoiesis Mediated by Growth Factors with Applications to Periodic Hematological Diseases, Bulletin of Mathematical Biology, 68 (8), (2006), 2321–2351.

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

Description of parameters and functions

Stem cells – P in proliferating phase, Q in quiscent phase
Growth factor – E, Mature cells – M, Leukocytes – W

Proliferating phase duration – τ, τ_1
Amplification phase duration – τ_2
Amplification parameter – $A = \alpha 2^i$, with
$\alpha \in (0, 1)$ – survival rate, i – number of generations

Apoptosis rate – γ, γ_1
Death rate – κ (for E), μ (for M), γ_2 (for W), δ (for Q)

Introduction rate – $\beta(Q, E)$, $\beta(Q)$
Differentiation – $g(Q)$, K, $k(W)$

GFM system of DDEs

$$\text{(GFM)} \begin{cases} \dfrac{dQ}{dt} = -\delta Q(t) - g(Q(t)) - \beta(Q(t), E(t))\, Q(t) \\ \qquad\qquad +2e^{-\gamma\tau}\beta(Q(t-\tau), E(t-\tau))\, Q(t-\tau) \\ \dfrac{dM}{dt} = -\mu M(t) + g(Q(t)) \\ \dfrac{dE}{dt} = -kE(t) + f(M(t)) \end{cases}$$

$$Q(t) = Q_0(t),\ M(t) = M_0(t),\ E(t) = E_0(t),\ t \in [-\tau, 0]$$

Delay τ corresponds to the cell cycle duration.
$Q(t) \geq 0,\ M(t) \geq 0,\ E(t) \geq 0,\ k > 0,\ \mu > 0$

Existence of nontrivial positive steady-state is ensured by:

$0 < \delta + g'(0) < \beta\left(0, \dfrac{f(0)}{k}\right)$ and

$$0 \leq \tau < \tau_{max} := \frac{1}{\gamma} \ln \left(\frac{2\beta\left(0, \frac{f(0)}{k}\right)}{\delta + g'(0) + \beta\left(0, \frac{f(0)}{k}\right)} \right)$$

LM system of DDEs

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

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

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

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

Methods and software

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)

Runge-Kutta methods

Let $b_i, a_{ij} \in \mathbf{R}$ $(i, j = 1, \ldots, s)$ and $c_i = \sum_{j=1}^{i-1} a_{ij}$. The s-stage Runge-Kutta (RK) method for solution of $y' = f(t, y),\ y(t_0) = y_0$ is defined by

$$k_i = f(t_0 + c_i h, y_0 + h \sum_{j=1}^{s} a_{ij} k_j)\ i = 1, \ldots, s$$

$$y_1 = y_0 + h \sum_{i=1}^{s} b_i k_i$$

Explicit RK: if $a_{ij} = 0$ for $i \leq j$
Diagonal implicit RK (DIRK): if $a_{ij} = 0$ for $i < j$ and at least one $a_{ii} \neq 0$.
Singly DIRK: if $a_{ij} = 0$ for $i < j$ and $a_{ii} = \gamma \neq 0$ for $i = 1, \ldots, s$.
Implicit RK: all other cases.

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)

Dealing with delays

Discrete DDEs, where only finite number of past values of the variable are involved.

Delay τ (always non-negative) can be *constant* ($\tau = const$), *time dependent* ($\tau = \tau(t)$) or *state dependent* ($\tau = \tau(t, y(t))$).

Breaking points (primary discontinuities) – the solution possesses only a limited number of derivatives, the *order* of the breaking point, and remains piecewise regular between two consecutive such points.

Locating the breaking points and including them into the mesh is a crucial issue on the numerical integration of DDEs, because any step-by-step method attains its own order of accuracy provided that the solution sought is sufficiently smooth in the current integration interval.

A. Bellen, N. Guglielmi, S. Maset, Numerical methods for delay models in biomathematics, In: A. Quarteroni, L. Formaggia, A. Veneziani (Eds.) Complex Systems in Biomedicine, Springer-Verlag Italia, Milano 2006, 147-185.

Provided 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; ranges for lymphocytes $0 - 0.2 \times 10^6$ cells/mL
- G-CSF is applied every day during the first month – 5-10 mcg/kg of bw NEUPOGEN-Filgrastim http://www.neupogen.com/pi.html spec. act. $1.0 \pm 0.6 \times 10^8$ U/mg; half-life 3.5 h; 300 mcg/mL or 600 mcg/mL.
- Statistical data for T, B and NK cells and their subpopulations at several stages: before BMT (D) and 1, 2, 3, 6, 9, 12, 18, 24 months after BMT.
- Diseases – Morbus Hodgkin (MH), Non-Hodgkin's Lymphoma (NHL), Acute Myelogeneous Leukemia (AML), Multiple Myeloma (MM).

Initial data for the patients with AML and MH

Patient	Disease	Weight	HSCs CD34+	volume
P1	AML	70 kg	4.32×10^6 cells/kg	500 mL
P2	AML	95 kg	1.69×10^6 cells/kg	500 mL
P3	MH	75 kg	6.00×10^6 cells/kg	300 mL
P4	MH	71 kg	6.48×10^6 cells/kg	500 mL

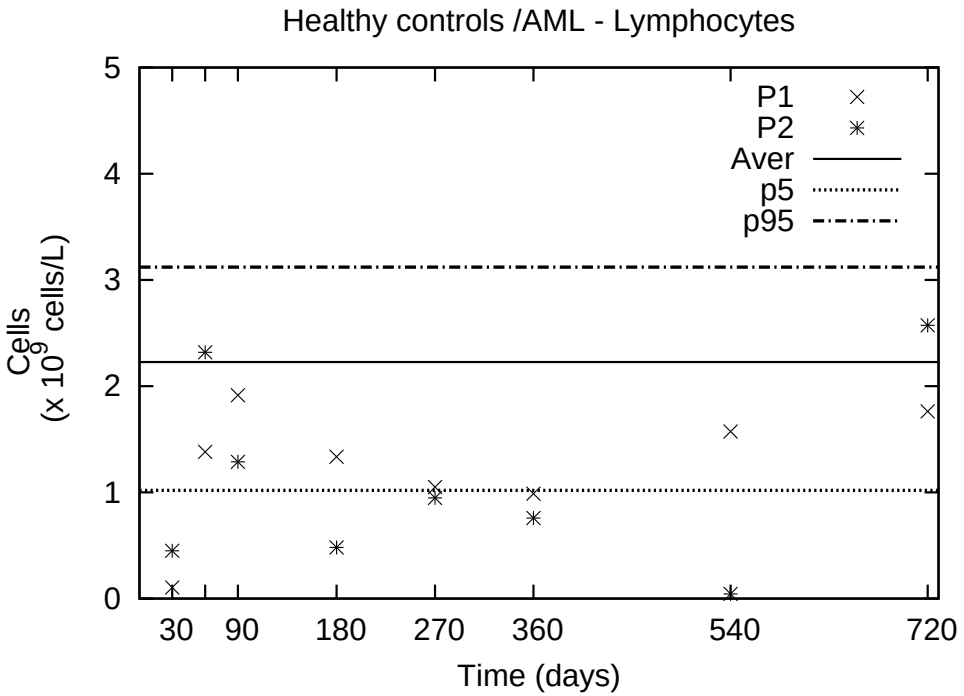
Two patients with AML

N	Date	Stage	Lymphocytes CD 45 AC	B cells CD19 AC	T cells CD3 AC	NK cells CD 56 AC	T_n AC
P1	11/11/05	D	571	5	491	33	114.36
	01/12/05	E1	104	1	90	8	27.8
	16/01/06	E2	1382	15	1172	104	222.83
	06/02/06	E3	1914	57	1501	226	249.66
	10/05/06	E6	1336	123	1017	107	232.02
	30/08/06	E9	1049	156	703	103	75.70
	14/11/06	E12	988	270	600	121	108.01
	09/05/07	E18	1573	267	959	215	215.84
	21/10/08	E24	1763	924	924	400	333.00
P2	11/10/06	D	1946	25	1721	53	160.01
	01/11/06	E1	450	30	410	19	39.70
	07/12/06	E2	2319	32	2082	121	103.35
	17/01/07	E3	1287	97	1061	84	92.55
	25/04/07	E6	481	62	380	25	20.19
	04/07/07	E9	947	9	886	31	155.05
	17/10/07	E12	759	1	729	17	115.22
	27/05/08	E18	44	0	43	1	23.41
	16/10/08	E24	2572	2279	2291	208	182.61

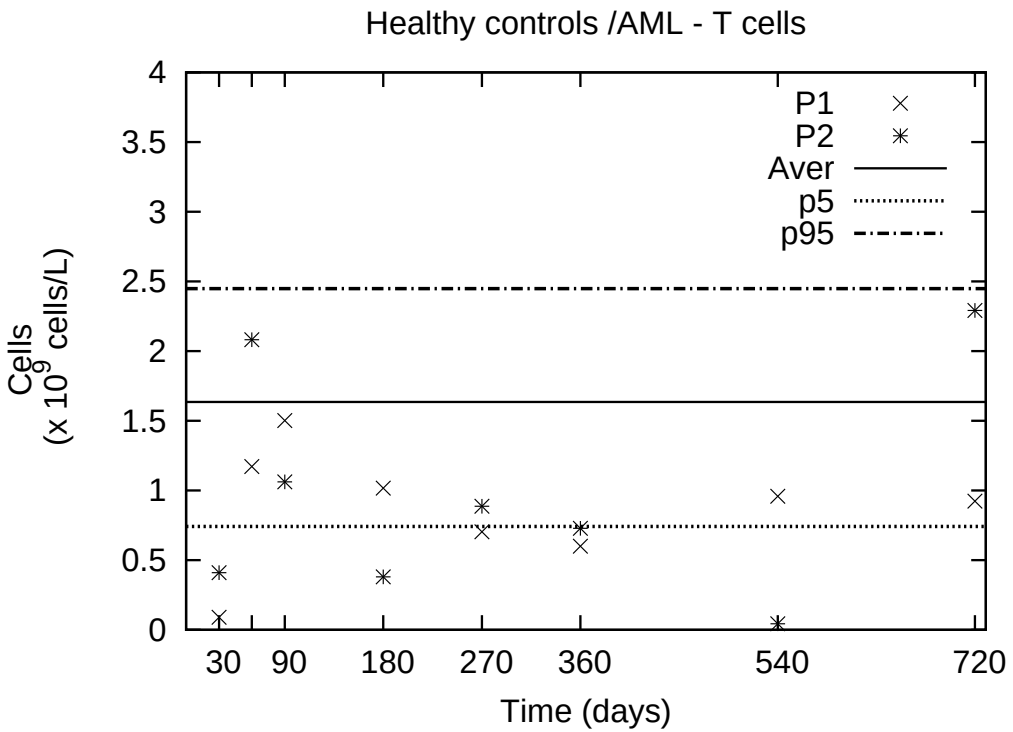
Two patients with MH

N	Date	Stage	Lymphocytes CD 45 AC	B cells CD19 AC	T cells CD3 AC	NK cells CD 56 AC	T_n AC
P3	28/02/06	D	491	33	394	41	31.19
	21/03/06	E1	142	16	122	14	11.03
	08/05/06	E2	2482	119	2179	144	74.71
	06/06/06	E3	1263	279	867	66	28.35
		E6					
	12/12/06	E9	850	117	607	73	16.52
	07/03/07	E12	995	161	677	132	51.34
	10/10/07	E18	1199	246	704	223	57.93
	31/10/08	E24	1233	677	676	152	152.68
P4		D					
	26/09/06	E1	291	1	255	17	22.37
	27/10/06	E2	169	6	104	54	3.22
	01/12/06	E3	1076	173	603	274	41.42
	02/04/07	E6	739	126	434	111	6.04
	04/06/07	E9	1820	96	1330	309	30.04
	05/10/07	E12	1043	73	609	348	16.02
	22/02/08	E18	1155	9	680	448	17.99
	18/08/08	E24	690	434	436	231	13.05

Healthy controls vs patients with AML after BMT

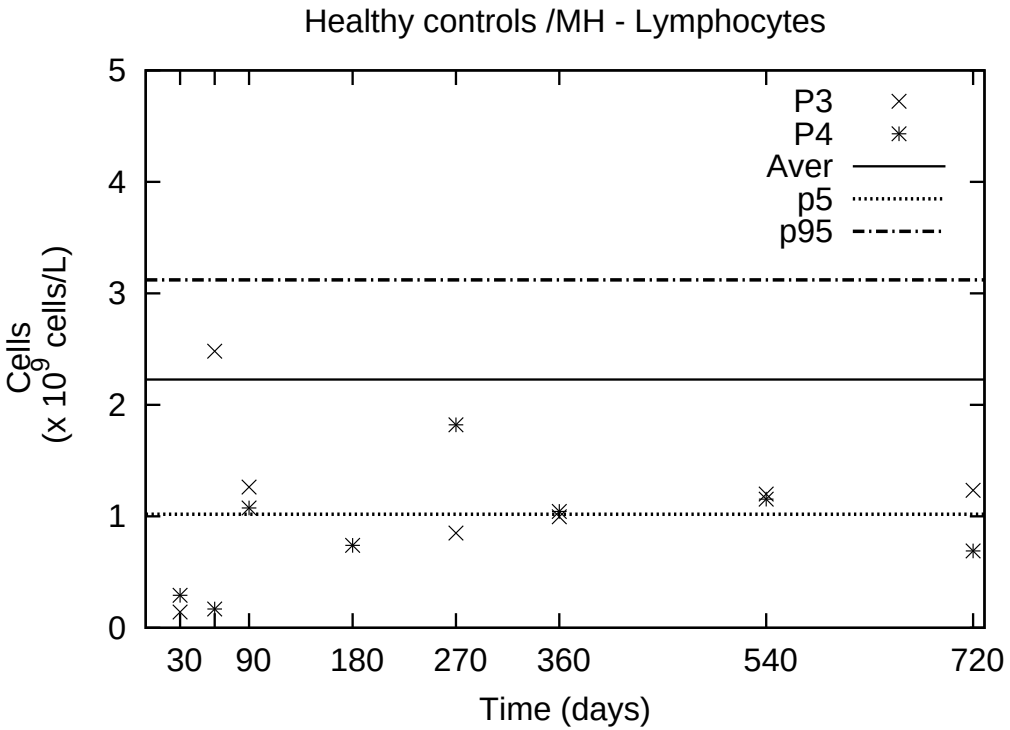


Lymphocytes (CD 45 AC)

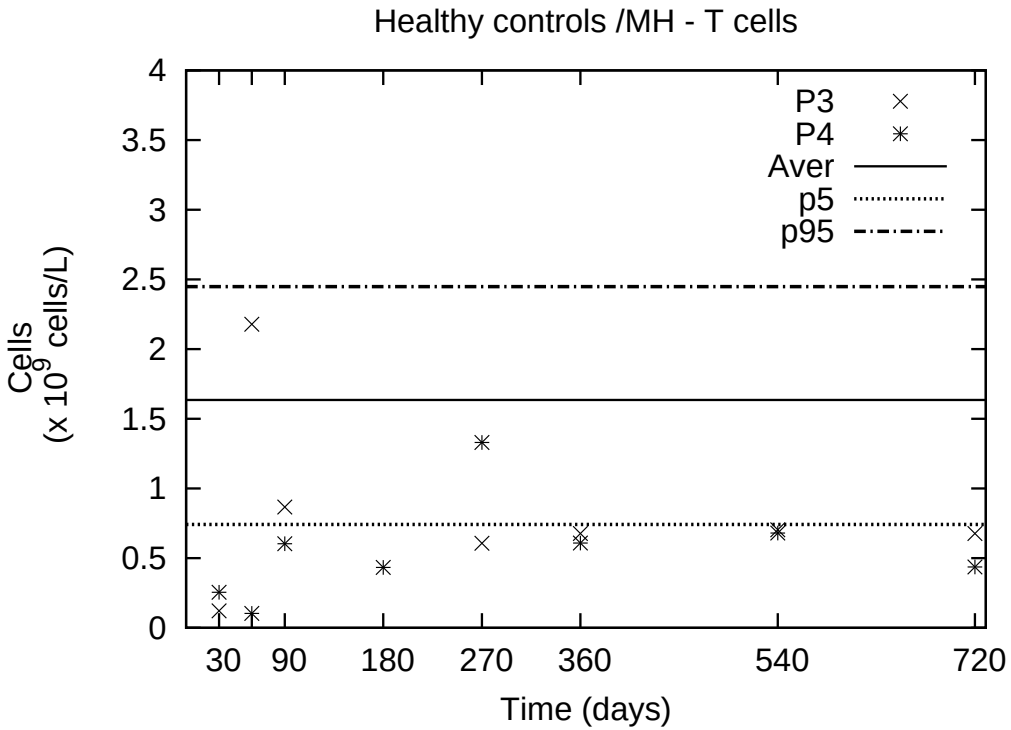


T cells (CD 3 AC)

Healthy controls vs patients with MH after BMT



Lymphocytes (CD 45 AC)



T cells (CD 3 AC)

Numerical tests – model parameters

GFM

$$\beta(E) = \beta_0 \frac{E}{1+E}, \qquad \beta_0 > 0$$
$$g(Q) = GQ, \qquad G > 0$$
$$f(M) = \frac{a}{1+KM^r}, \qquad a, K > 0, r > 0$$

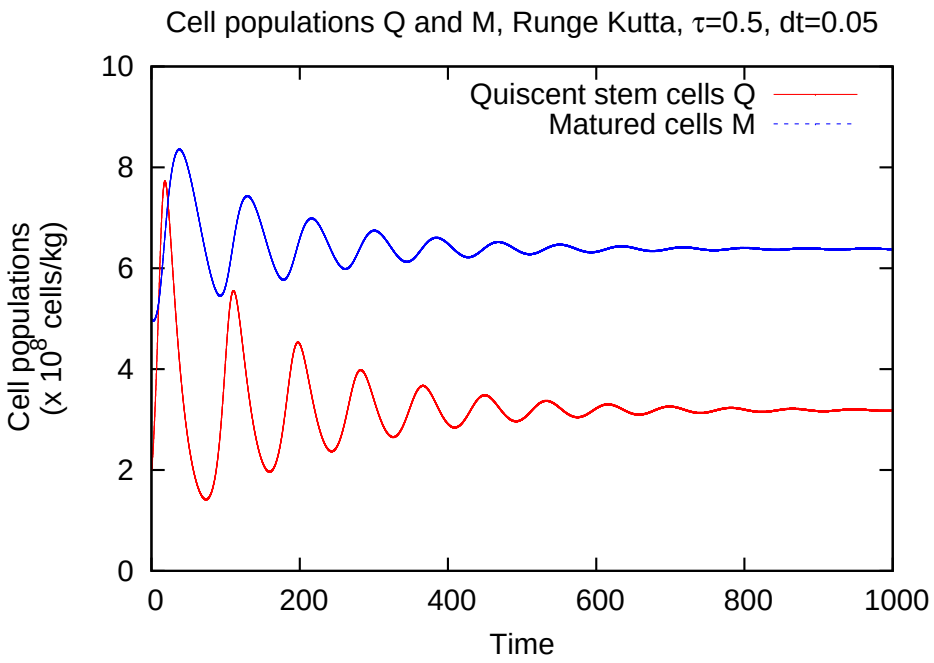
Param	Value	Range (day^{-1})
δ	0.01 day^{-1}	0 – 0.09
G	0.04 day^{-1}	0 – 0.09
β_0	0.5 day^{-1}	0.08 – 2.24
γ	0.2 day^{-1}	0 – 0.9
μ	0.02 day^{-1}	0.001 – 0.1
k	2.8 day^{-1}	—
a	6570	—
K	0.0382	—
r	7	—

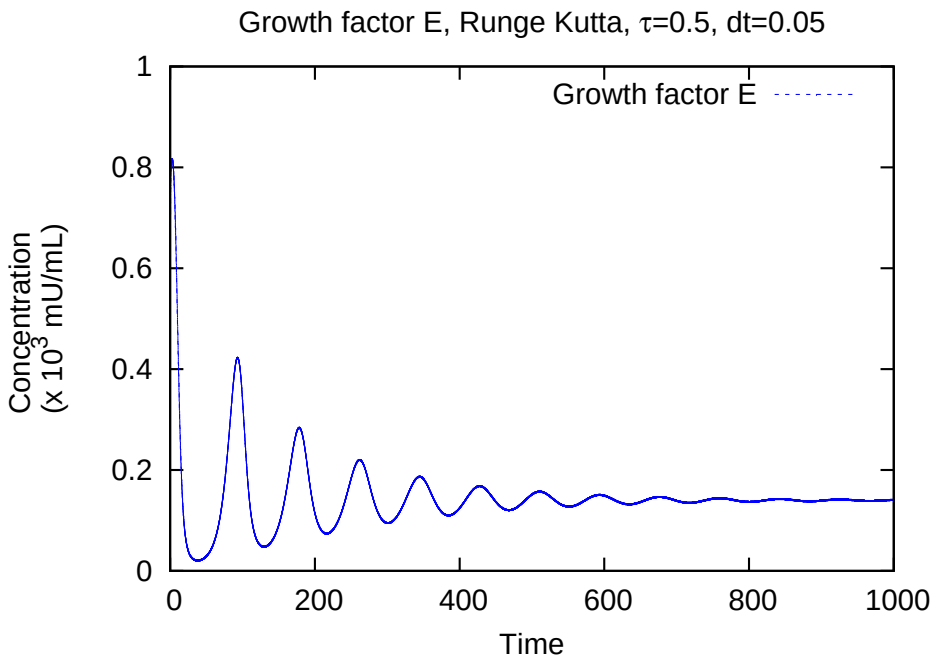
LM

$$\beta(Q) = \frac{\beta_0}{1+Q^n}, \qquad \beta_0 > 0$$
$$k(W) = \frac{k_0}{1+W^m}, \qquad k_0 > 0$$
$$A = \alpha 2^i, \qquad \alpha \in (0,1)$$

Param	Value
β_0	1.77 day^{-1}
k_0	0.1 day^{-1}
n	3
m	2
γ_1	0.1 day^{-1}
γ_2	2.4 day^{-1}
K	0.02 day^{-1}
A	20

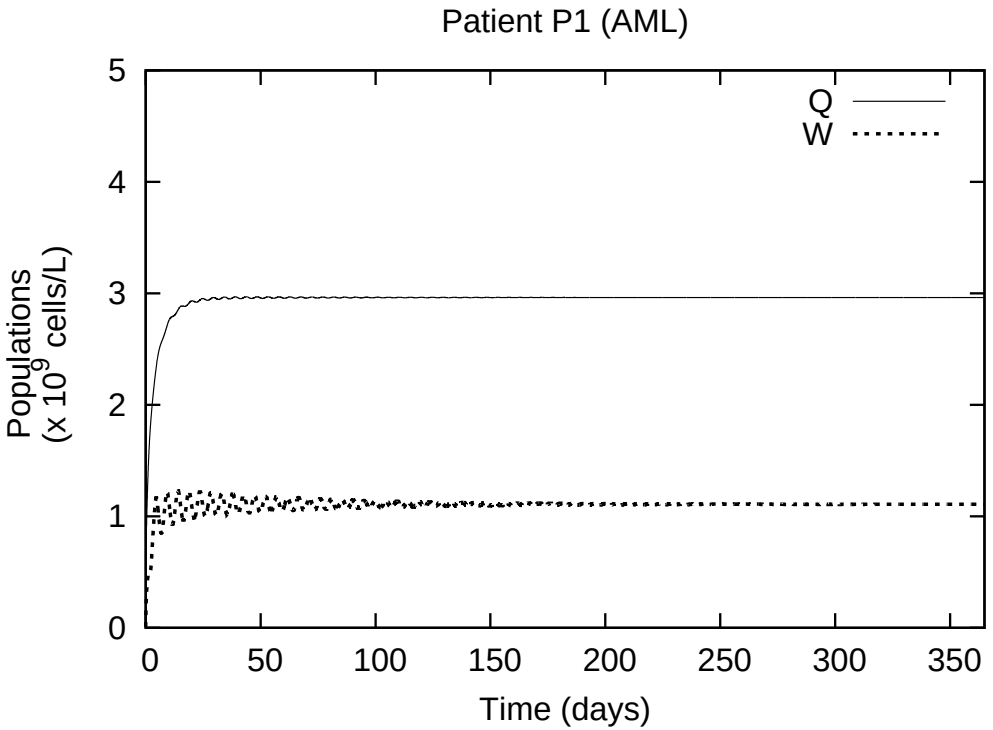
Erythropoiesis, model data from [GFM], $\tau = 0.5$

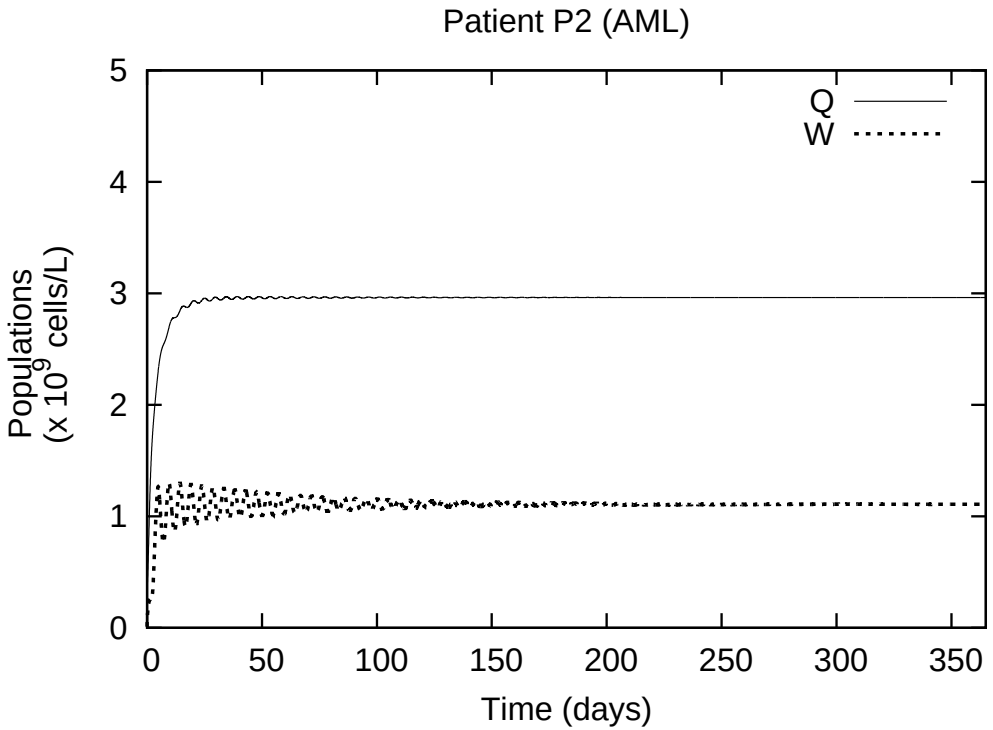




GFM failed with initial data for WBC and G-CSF and various sets of parameters

Results W(t), Q(t), model data from [LM] – AML





Patient P1:

$Q(0) = 0.61(\times 10^9)$ cells/L,

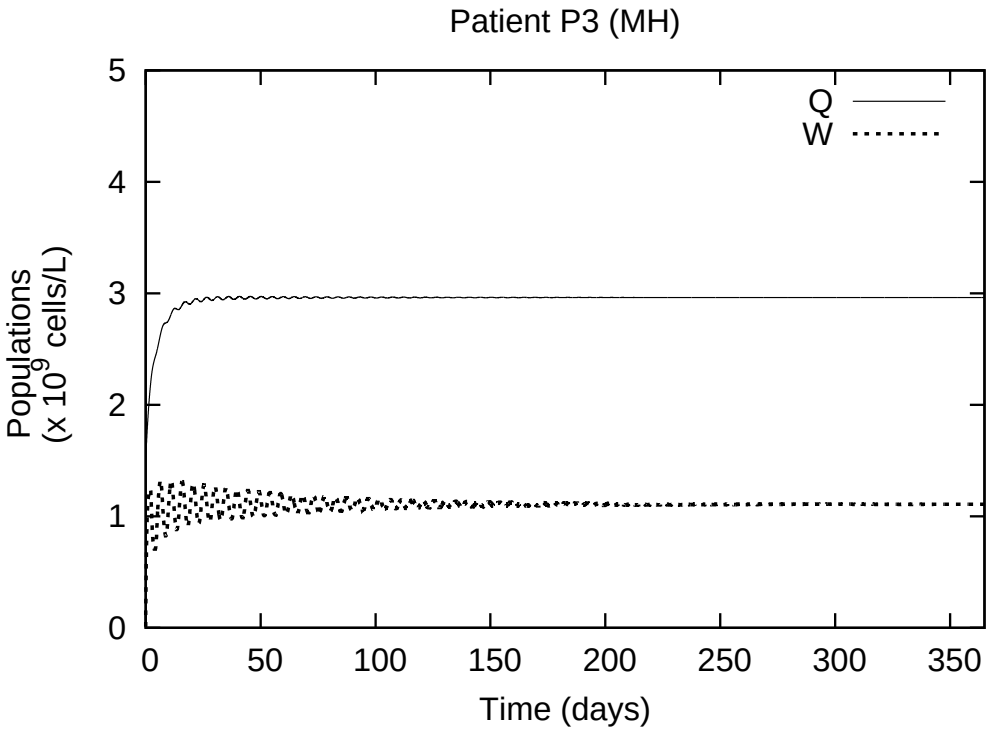
$W(0) = 0.01(\times 10^9)$ cells/L

Patient P2:

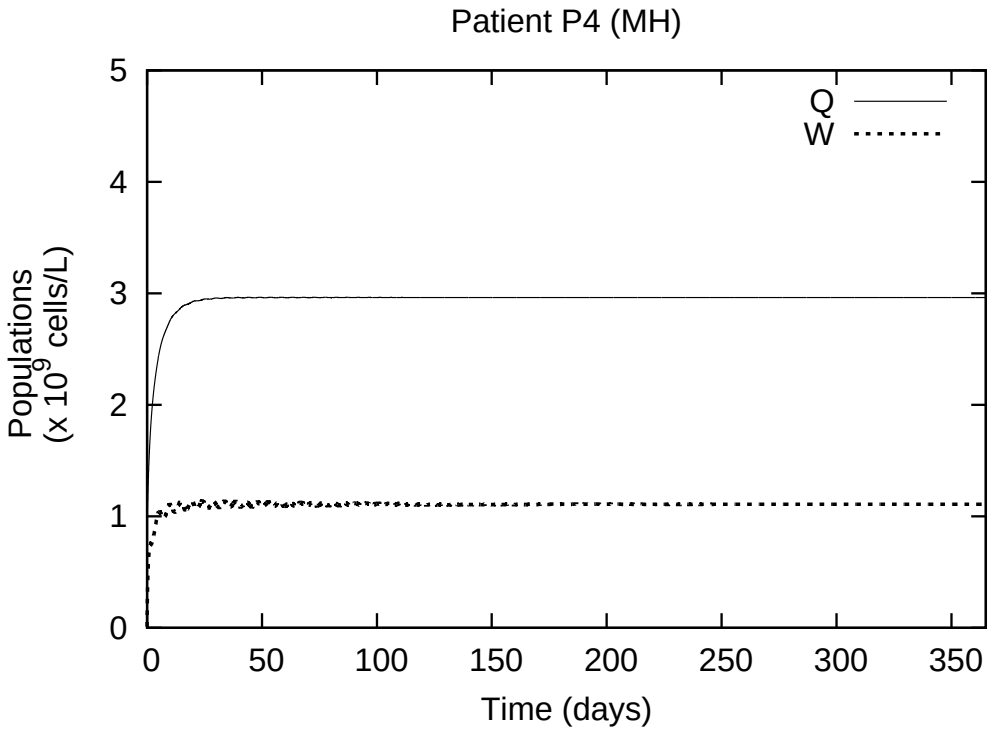
$Q(0) = 0.32(\times 10^9)$ cells/L,

$W(0) = 0.01(\times 10^9)$ cells/L

Results W(t), Q(t), model data from [LM] – MH

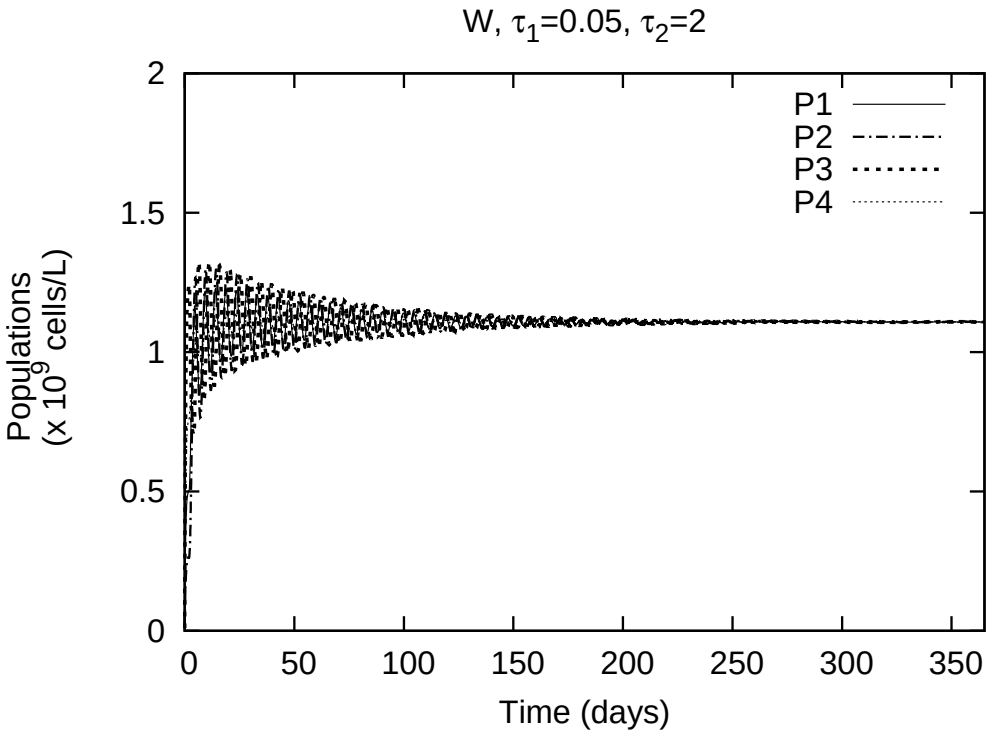


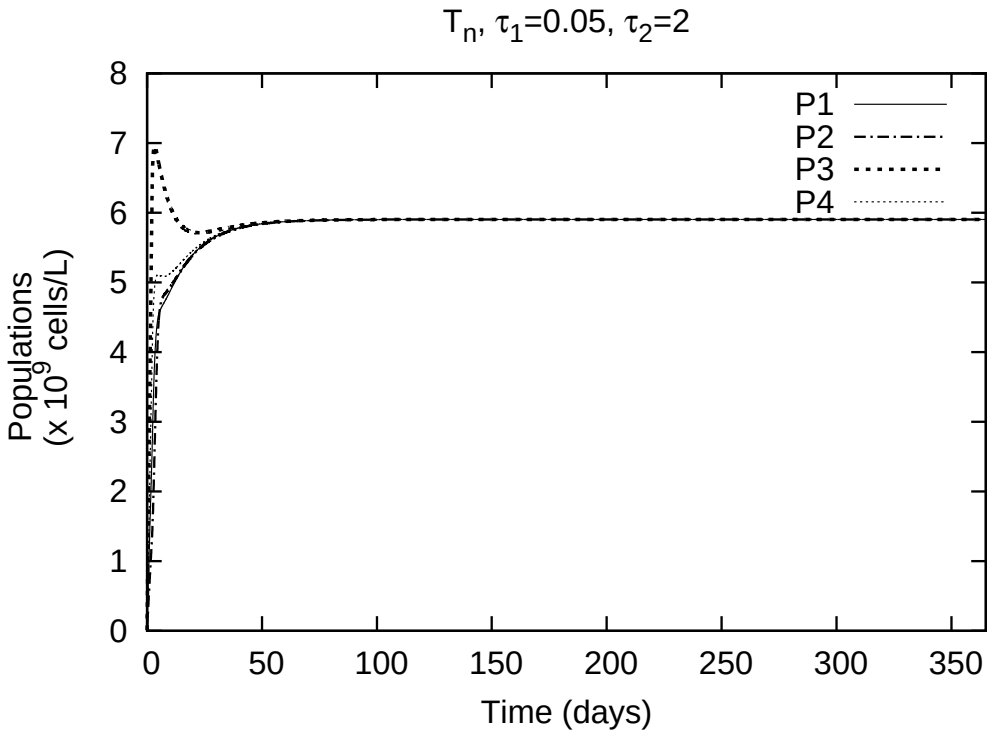
Patient P3:
$Q(0) = 1.5(\times 10^9)$ cells/L,
$W(0) = 0.01(\times 10^9)$ cells/L



Patient P4:
$Q(0) = 0.92(\times 10^9)$ cells/L,
$W(0) = 0.01(\times 10^9)$ cells/L

Results W(t), LM – varying γ_2



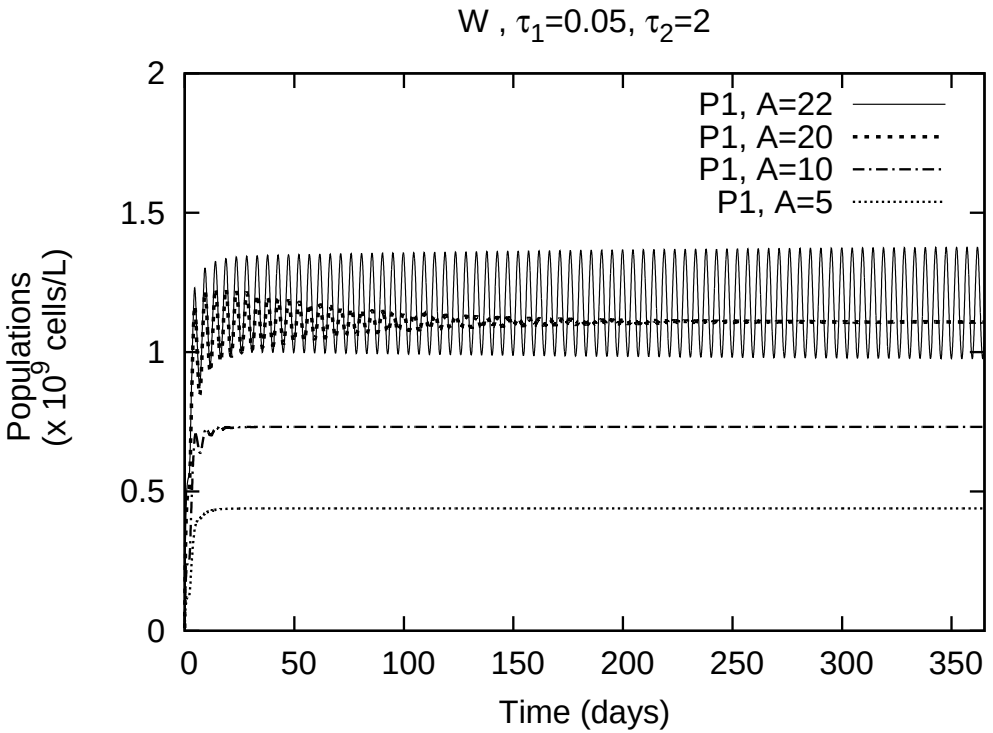


P1÷P4, W cells, $\gamma_2 = 2.4$

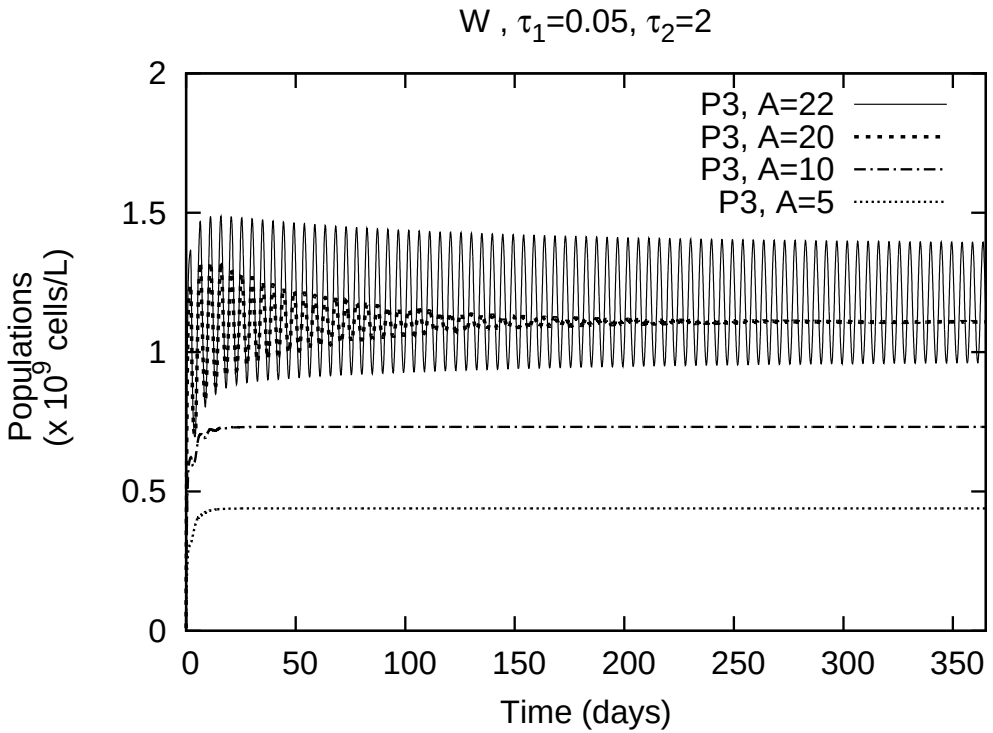
P1÷P4, T_n cells, $\gamma_2 = 0.04$

Tn cells with $\gamma_2 = 0.04$ (Moore, Li (2004))

Results W(t), LM – varying A, W cells

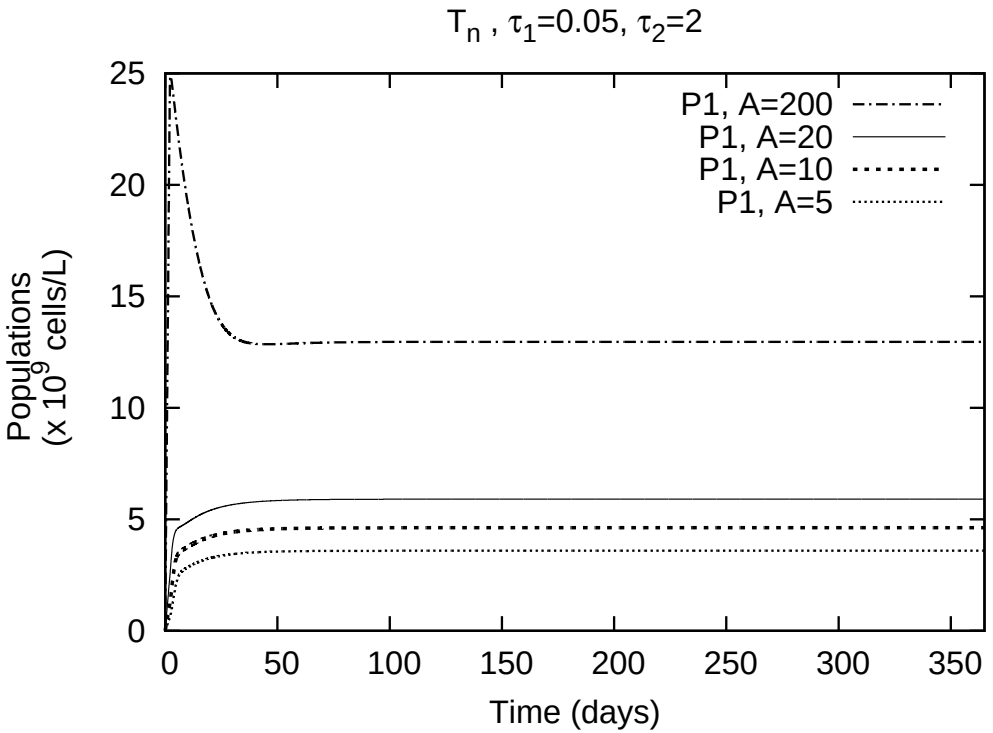


P1, W cells, $\gamma_2 = 2.4$

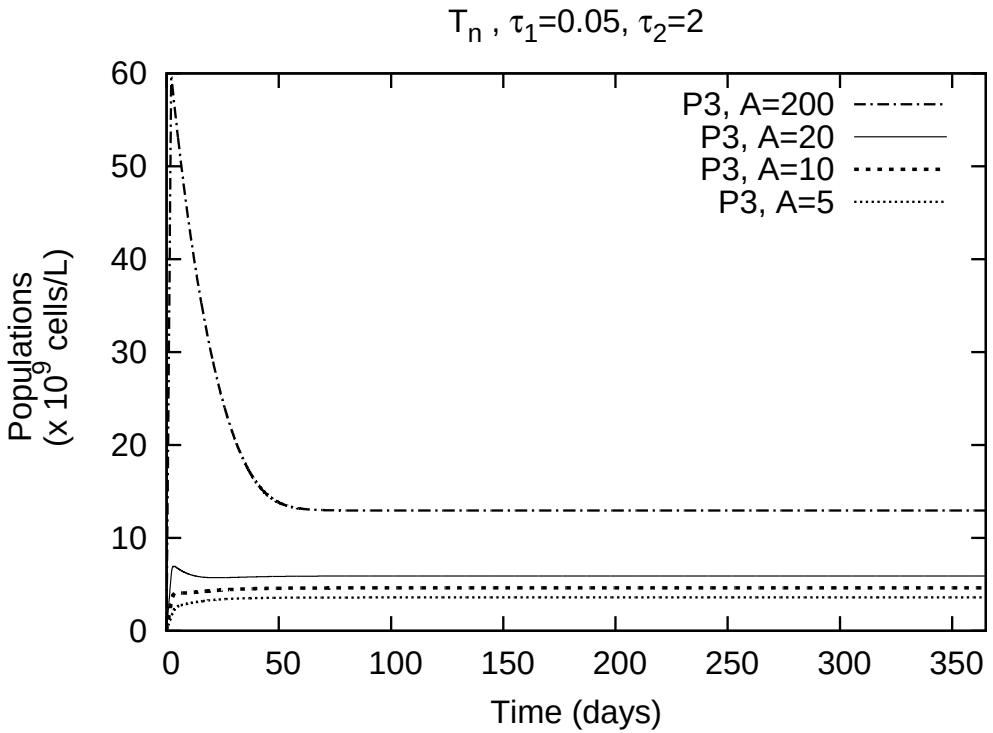


P3, W cells, $\gamma_2 = 2.4$

Results W(t), LM – varying A, T_n cells



P1, T_n cells, $\gamma_2 = 0.04$



P3, T_n cells, $\gamma_2 = 0.04$

Concluding remarks

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- Chemotactic movement:
  - Comparative analysis of solution methods in COMSOL/ other solvers
  - Positivity preserving schemes?
  - Ranges for parameters where the model works or fails?
  - Experimental/clinical data for calibration of the model?
- Regeneration of blood system:
  - Why does the GFM model "fail" with the clinical data?
  - Which parameters/functions should be changed and how, in order to have steady states of LM closer to the clinical data?
  - What is the relation between the gathered/transplanted amount of HSCs and the patient specific values of the parameters involved in the models?
- Further steps – sensitivity analysis and parameter estimation, parallel algorithms
- Possible tasks for SMM
  - Chemotaxis and COMSOL – stabilization
  - XPPAUT – comparative analysis of solution methods for LM model
  - Your interests – discretization, programming, sensitivity analysis, parameter estimation?

Acknowledgements

- Discussion with Dr. Maria Neuss-Radu was held during my HPC-EUROPA++ funded visit in HLRS and IANS, Stuttgart.
- Clinical data is provided by Dr. M. Guenova and Dr. L. Gartcheva from Laboratory of Haematopathology and Immunology, National Specialized Hospital for Active Treatment of Haematological Diseases, Bulgaria.

  – Clinical data is obtained via the Bulgarian NSF Grants TK-1603/06 and CVP-01/0119
- *This work is supported in part by the Bulgarian NSF grants DO 02-214/2008, DO 02-147/2008 and DO 02-115/2008.*

Thank you for your attention!