Computer modelling of hematopoiesis with applications to blood pathologies

Gergana Bencheva

Institute for Parallel Processing, Bulgarian Academy of Sciences

Acad. G. Bontchev Str. Bl. 25A, 1113 Sofia, Bulgaria

gery@parallel.bas.bg

Department of Scientific Computations

http://parallel.bas.bg/SciComp/

Main ongoing projects (funded by the Bulgarian NSF):

DO 02-115/2008, Svetozar Margenov

Center of excellence on supercomputer applications

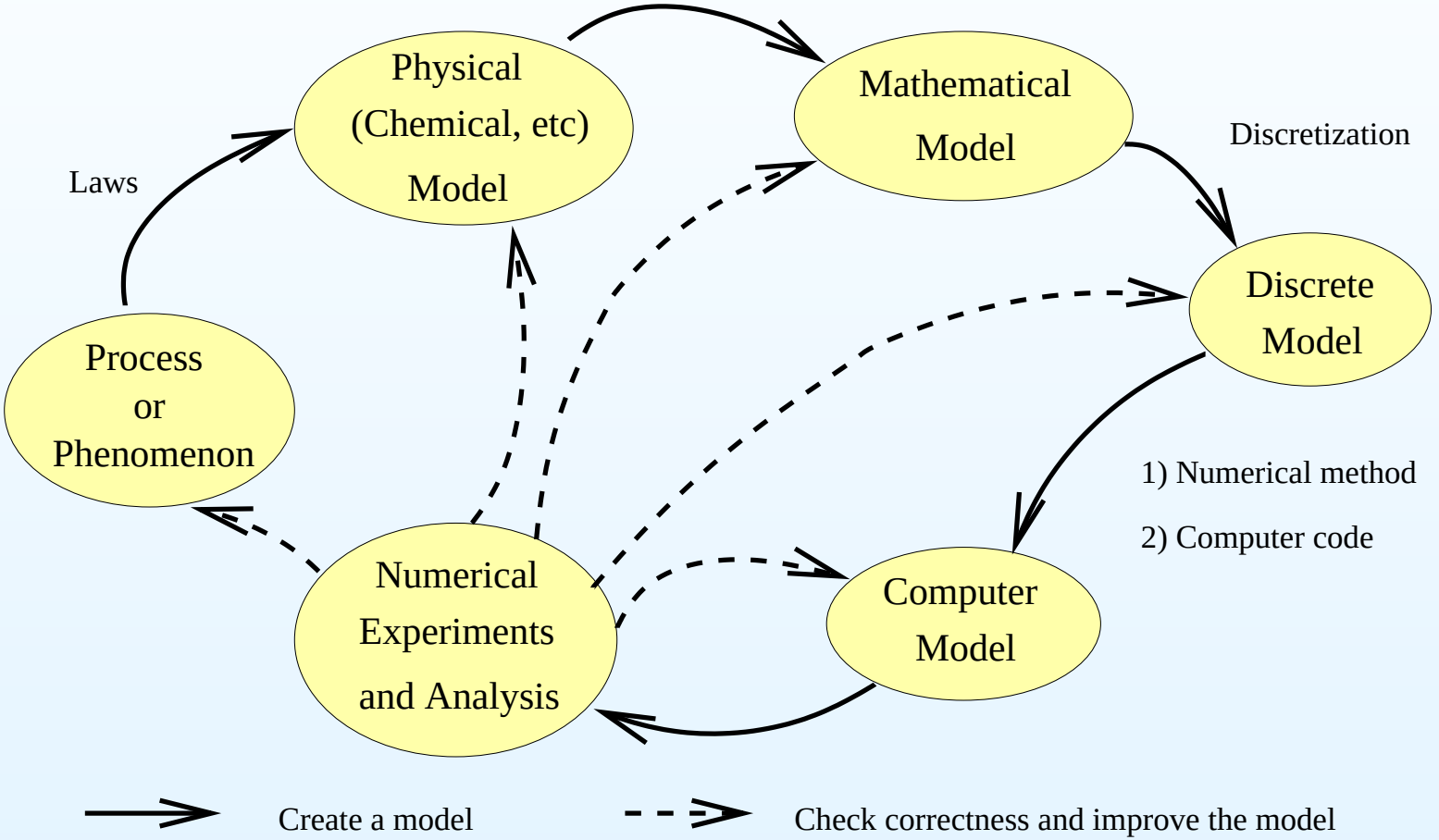
DO 02-147/2008, Ivan Lirkov

Large Scale Scientific Computating in Advanced Multiscale Simulation

DO 02-214/2008, Gergana Bencheva

Computer modelling of haematopoiesis with applications to blood pathologies

Computer modelling stages



Contents

- Motivation
- Chemotactic movement of HSCs
  – the model
  – numerical tests
- Regeneration of blood system
  – two models
  – clinical data
  – numerical tests
- Concluding remarks

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 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.

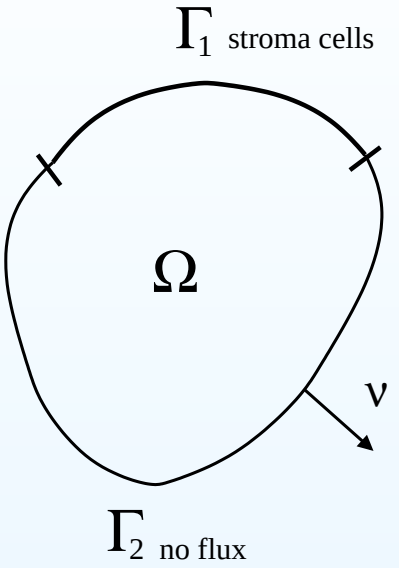
Adequate computer models would help medical doctors to shorten the period in which the patient is missing his/her effective immune system.

Chemotactic movement of HSCs

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

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

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

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

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

Numerical tests

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

PDE mode – system of 2 PDEs + ODE on the boundary
BDF for time integration; Automatic choice of nonlinear solver;
Implicit Euler + PARDISO or GMRES/ILU for linearised system.

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

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

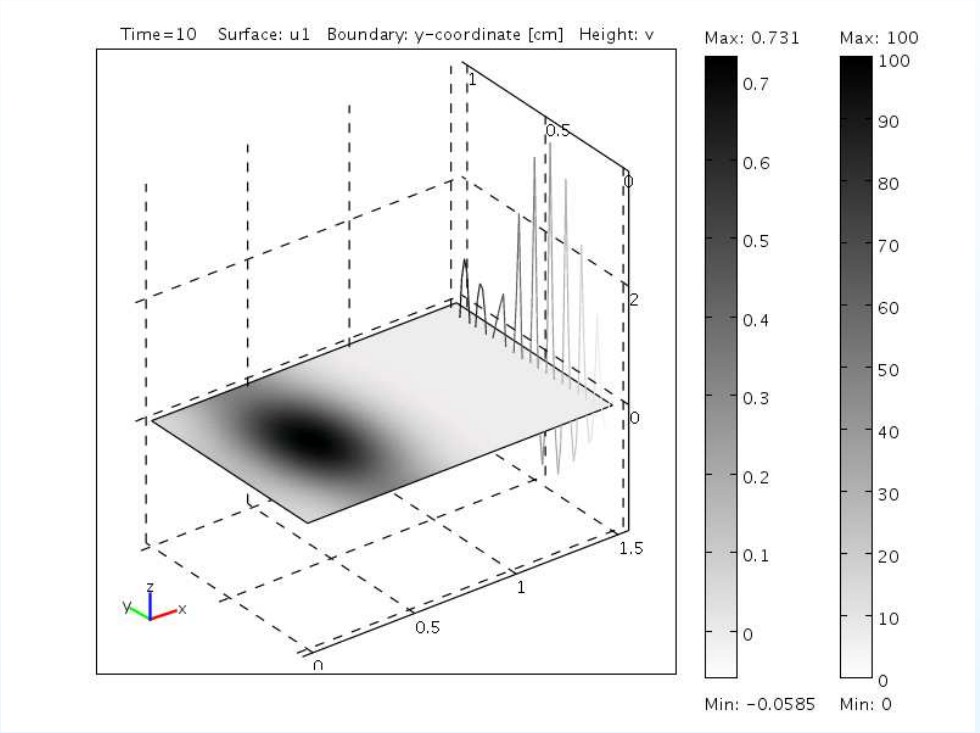
$$\chi(a) = 10a \qquad \chi(a) = \log(a)$$

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

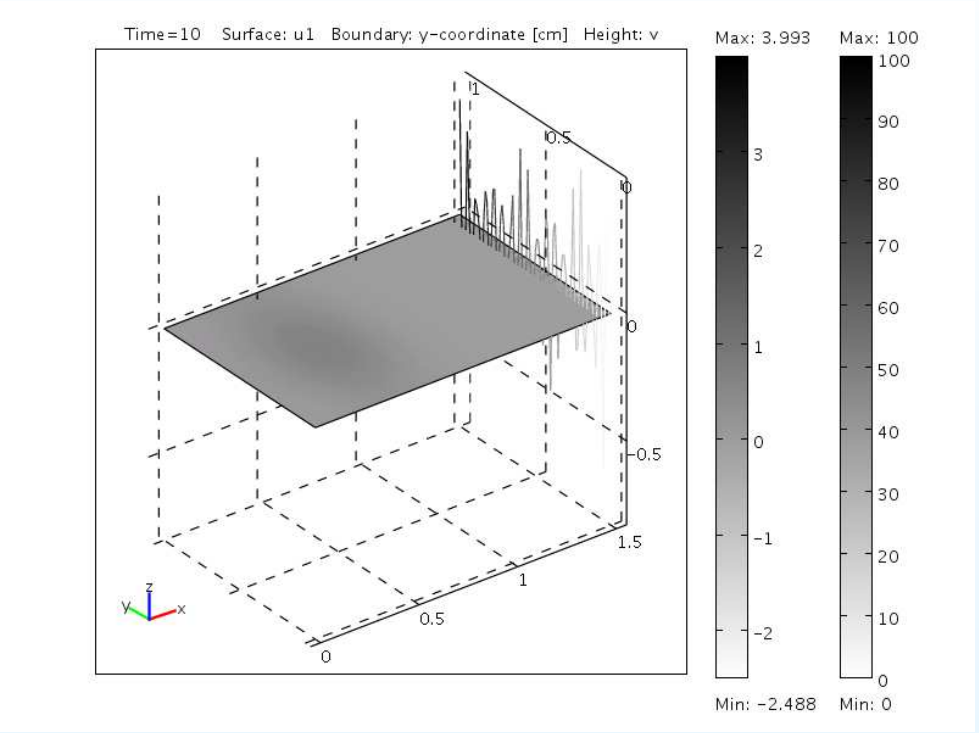
$$a_0 = 0, b_0 = 0 \text{ and}$$

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

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

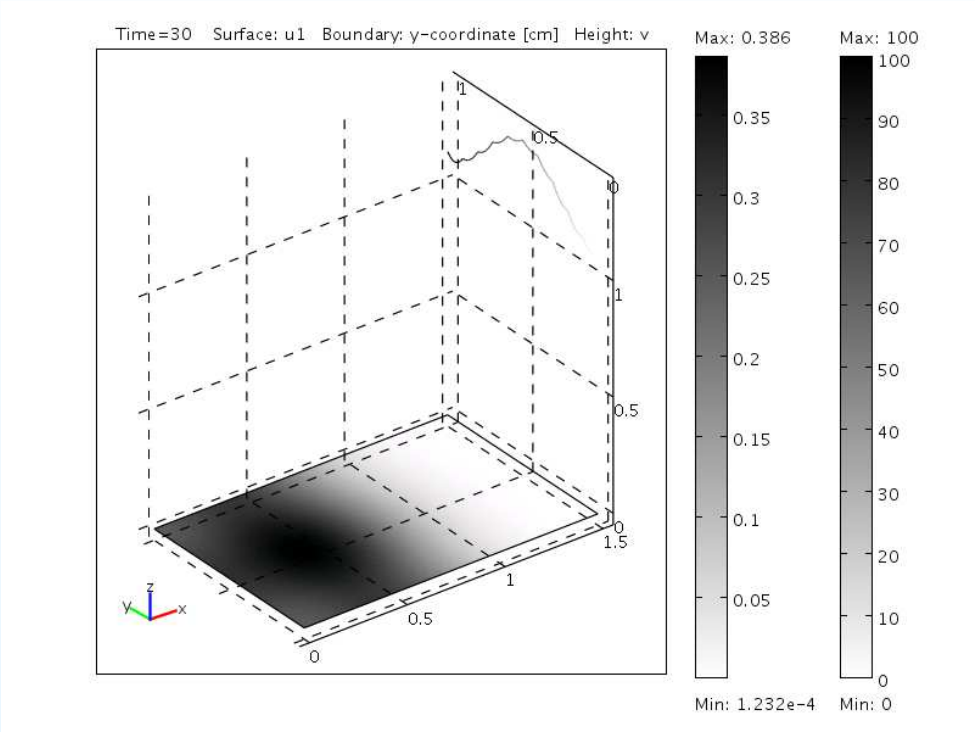


dof = 1723

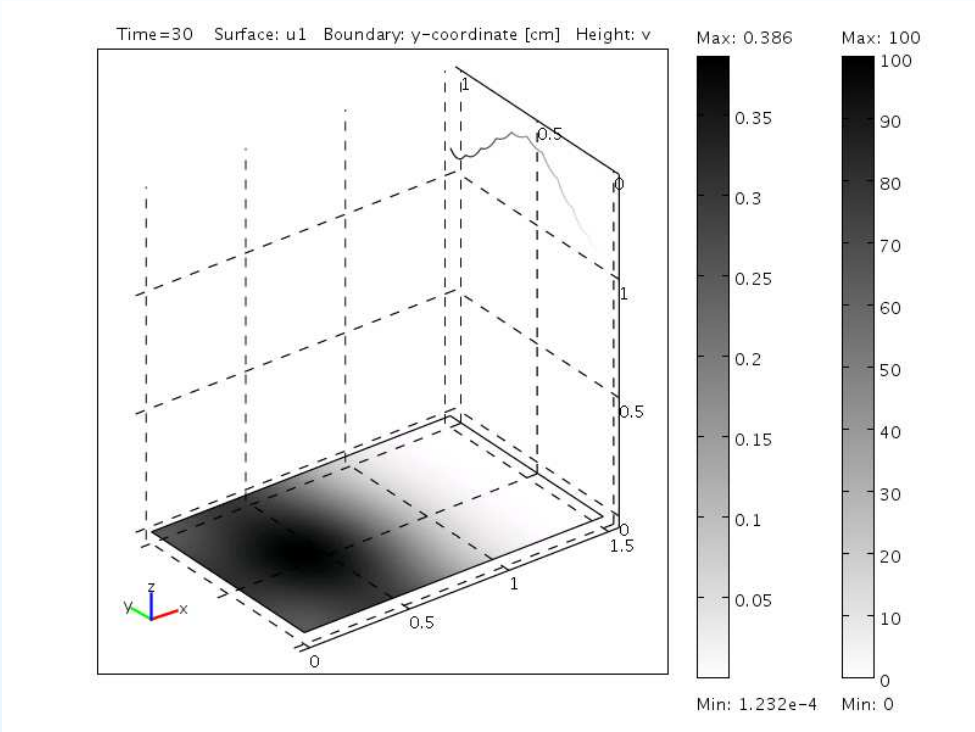


dof=6643

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

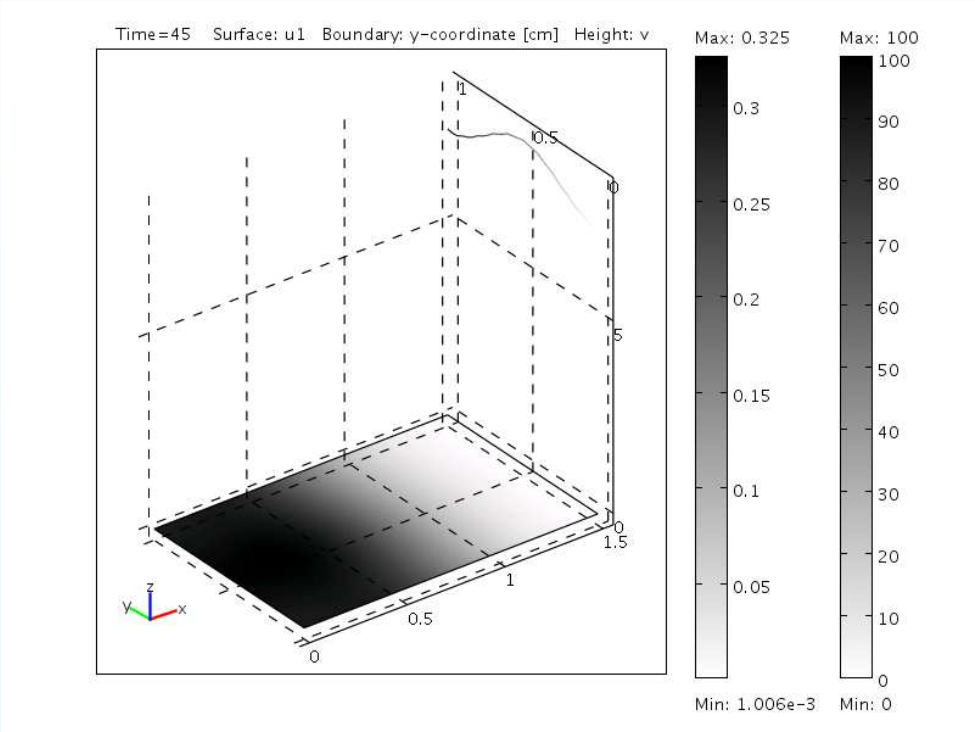


$$\chi = 10a$$

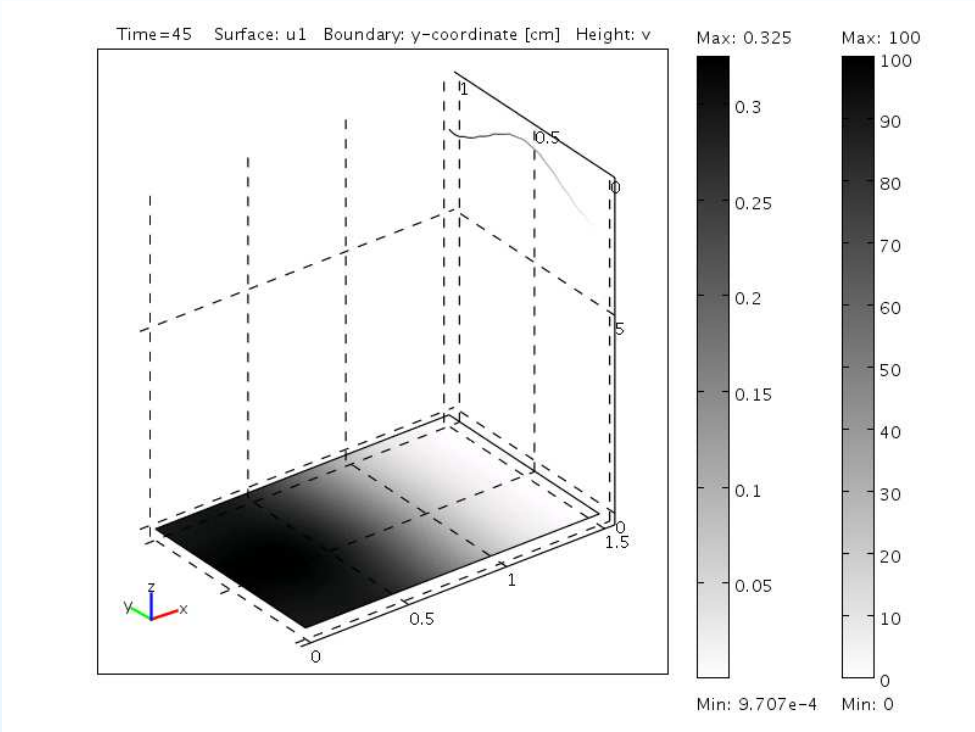


$$\chi = log(a)$$

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

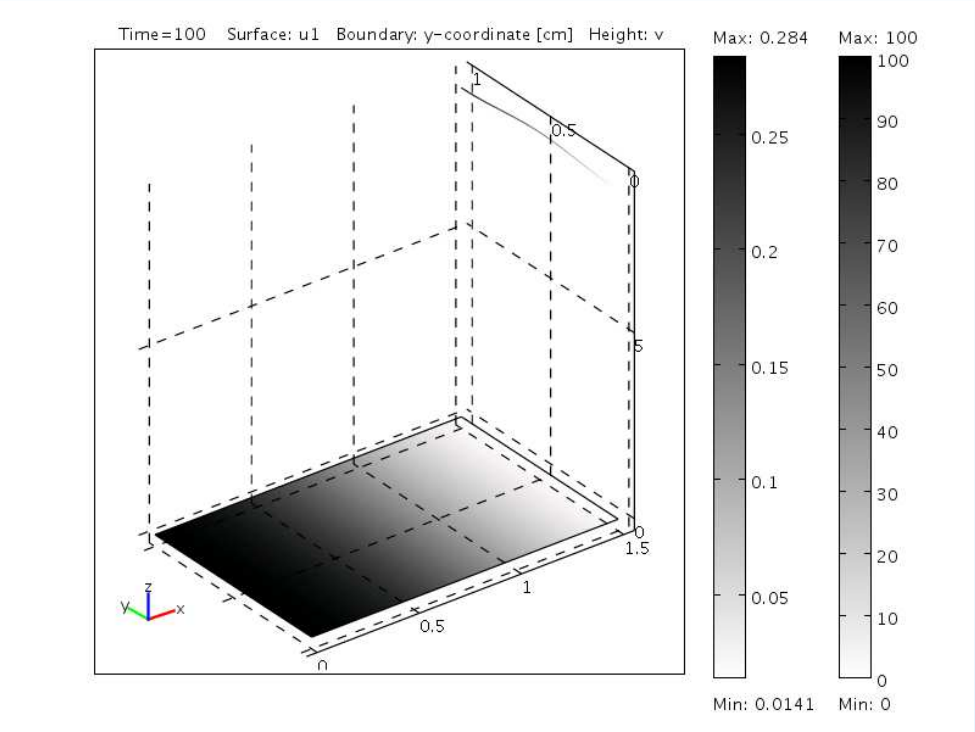


GMRES/ILU

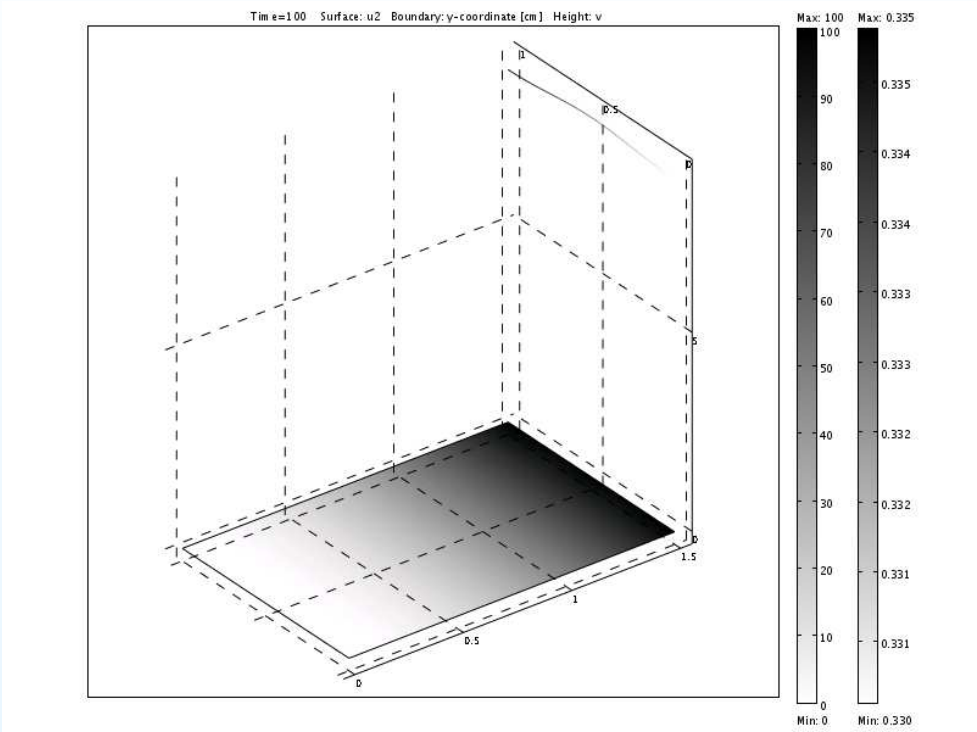


PARDISO

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



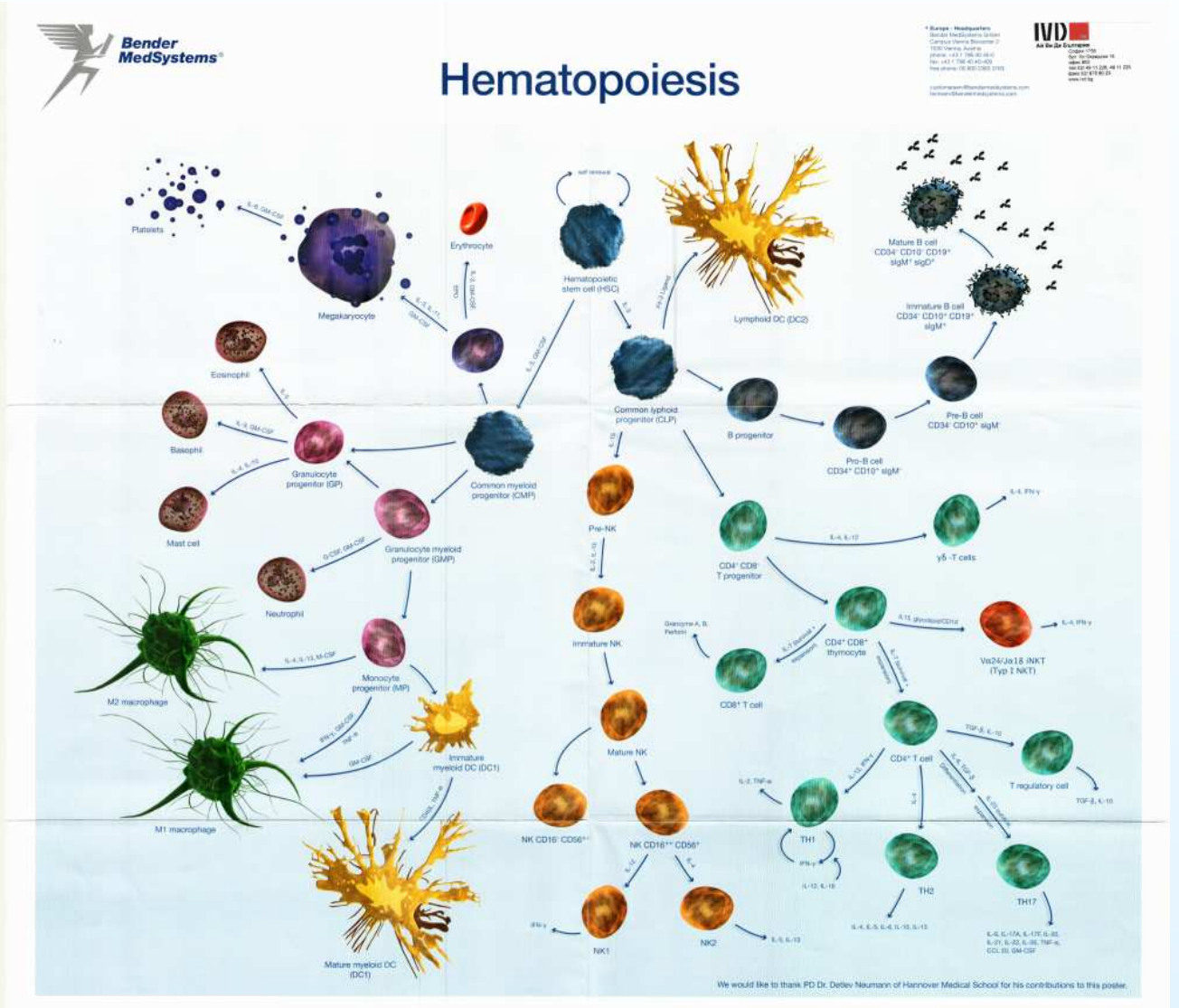
s(t,x) and b(t,x)



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

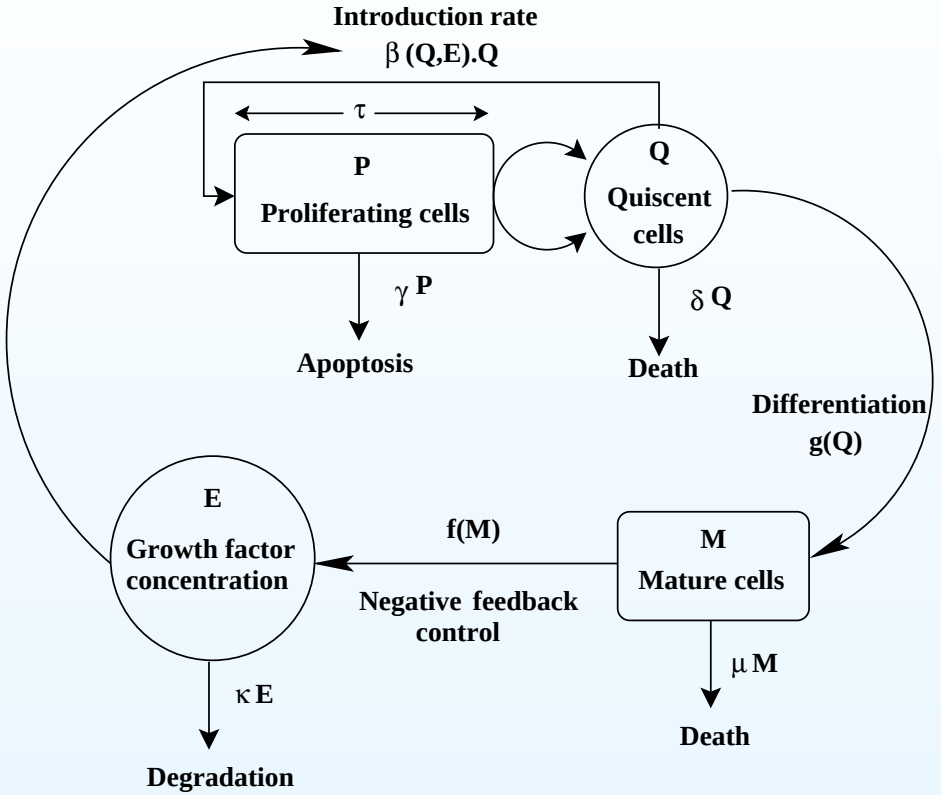
Regeneration of blood system

Differentiation stages in haematopoiesis

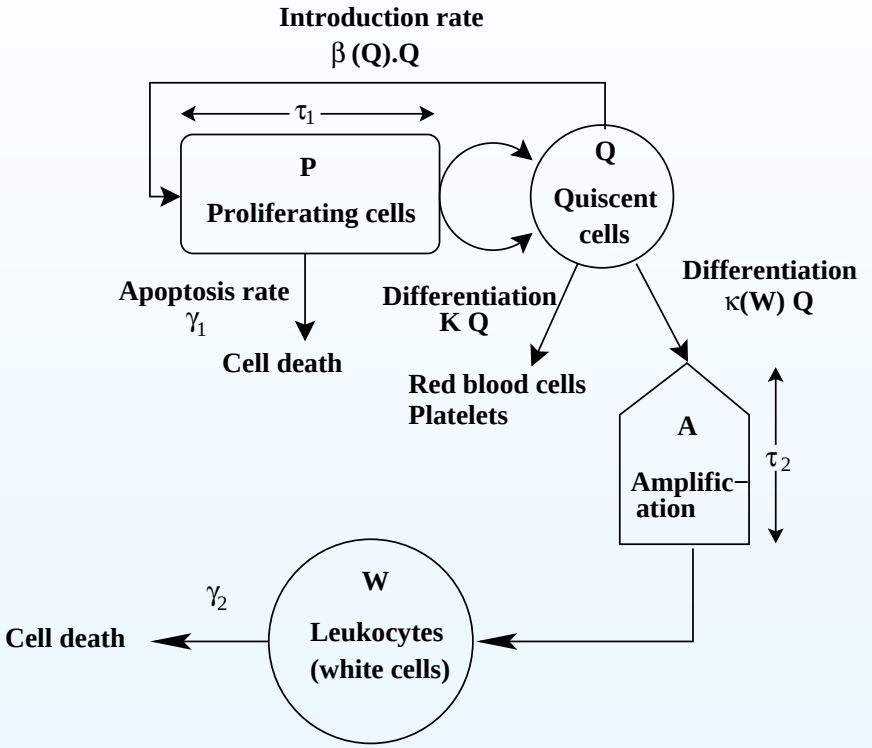


http://www.bendermedsystems.com/

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

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

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)

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

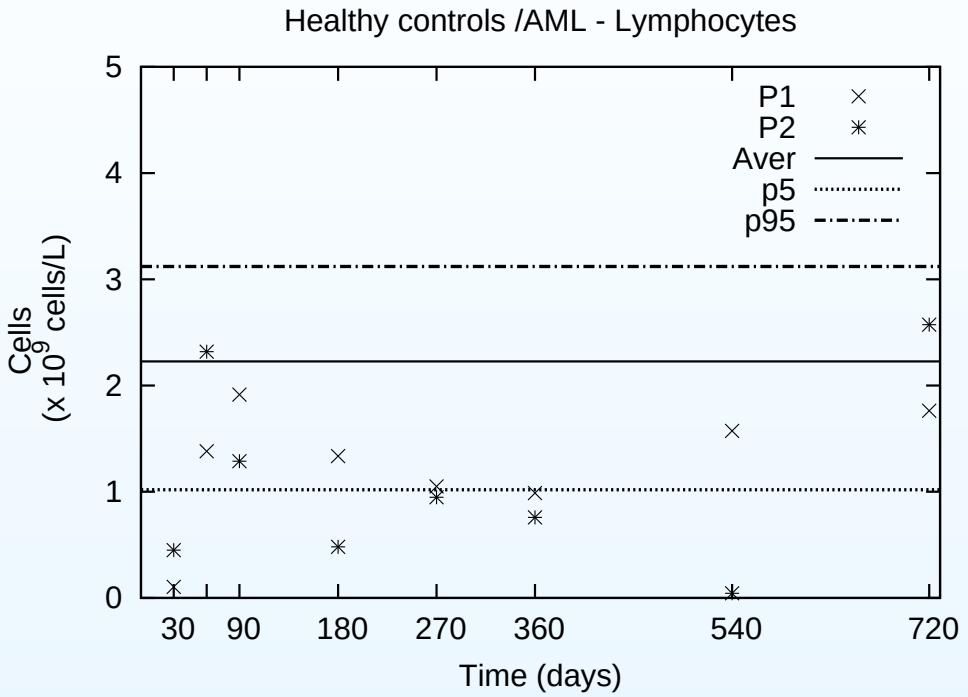
Two patients with AML

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

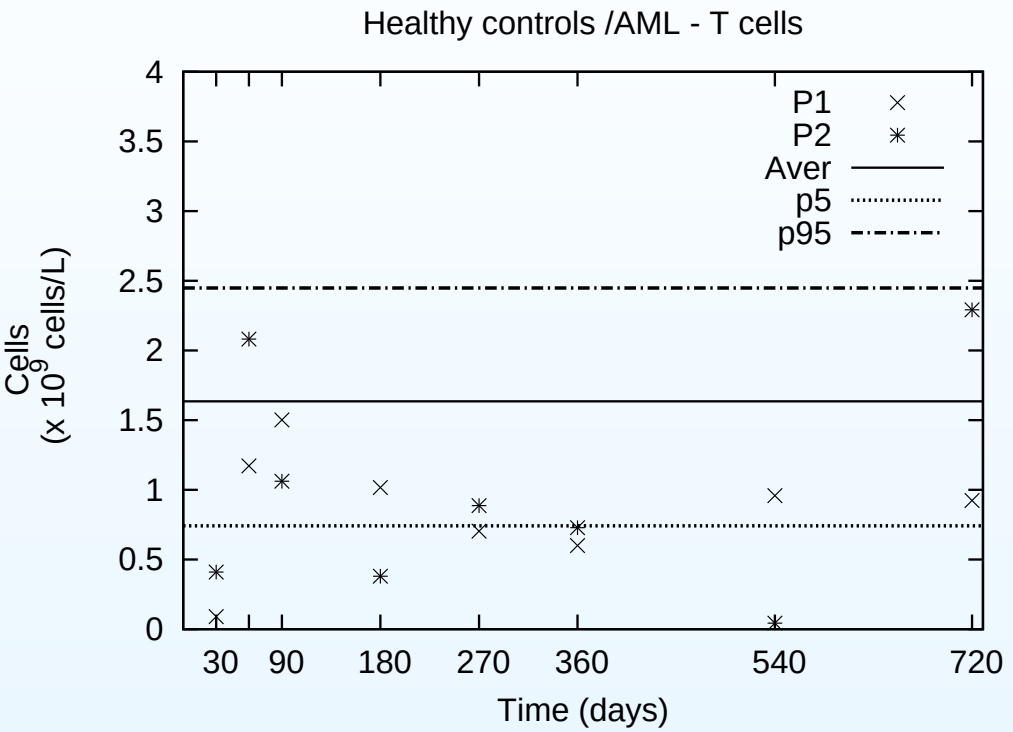
Two patients with MH

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

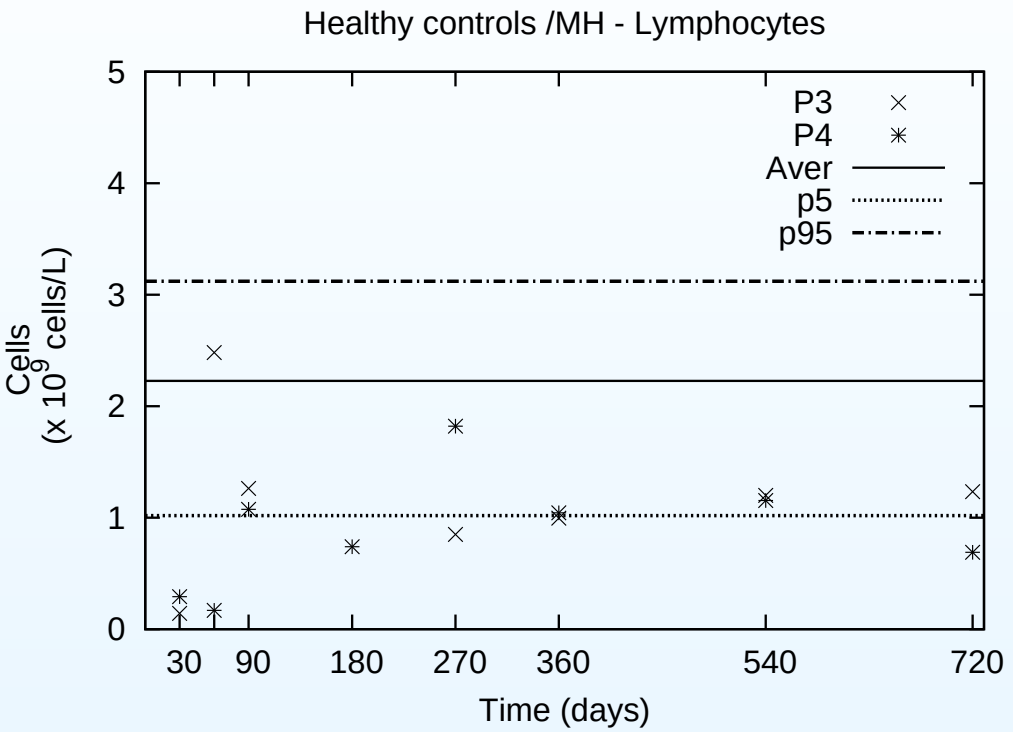


Lymphocytes (CD 45 AC)

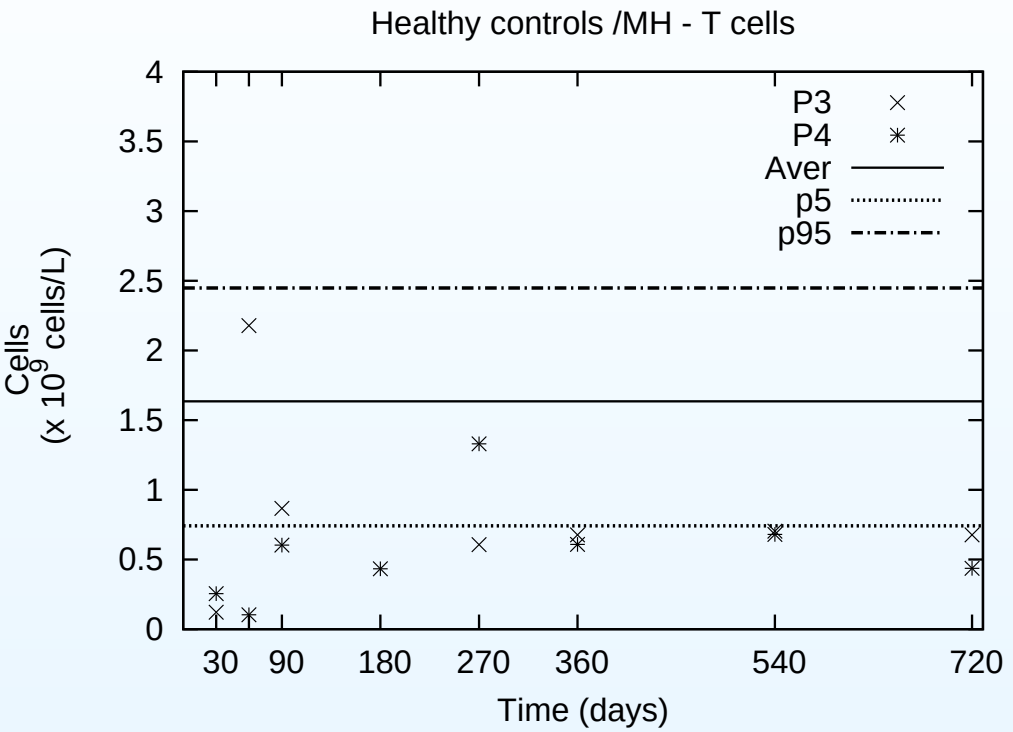


T cells (CD 3 AC)

Healthy controls vs patients with MH after BMT



Lymphocytes (CD 45 AC)



T cells (CD 3 AC)

Numerical tests – model parameters

GFM

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

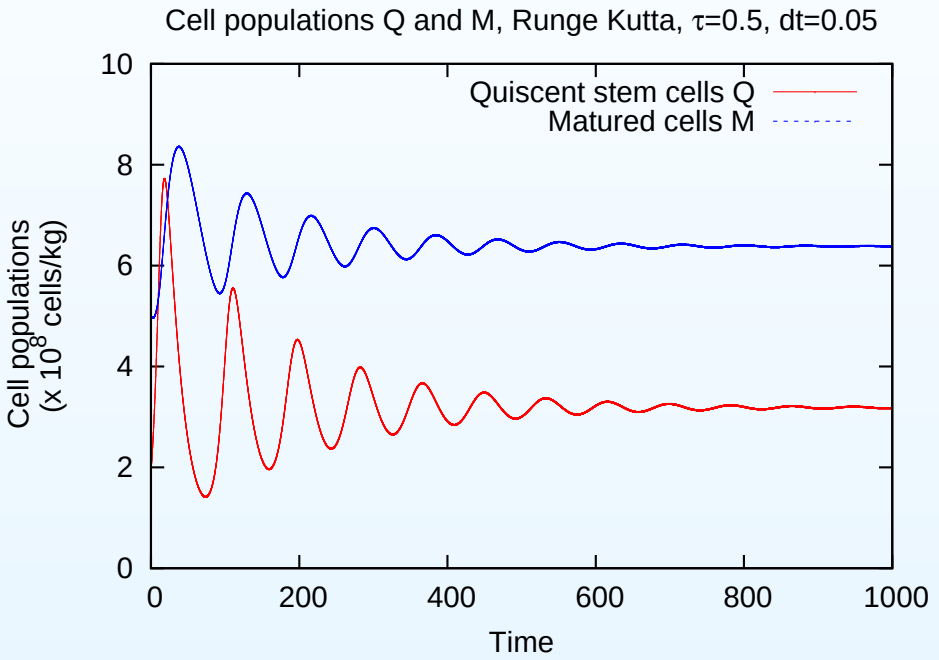
Param	Value	Range (day^{-1})
δ	0.01 day^{-1}	0 – 0.09
G	0.04 day^{-1}	0 – 0.09
β_0	0.5 day^{-1}	0.08 – 2.24
γ	0.2 day^{-1}	0 – 0.9
μ	0.02 day^{-1}	0.001 – 0.1
k	2.8 day^{-1}	—
a	6570	—
K	0.0382	—
r	7	—

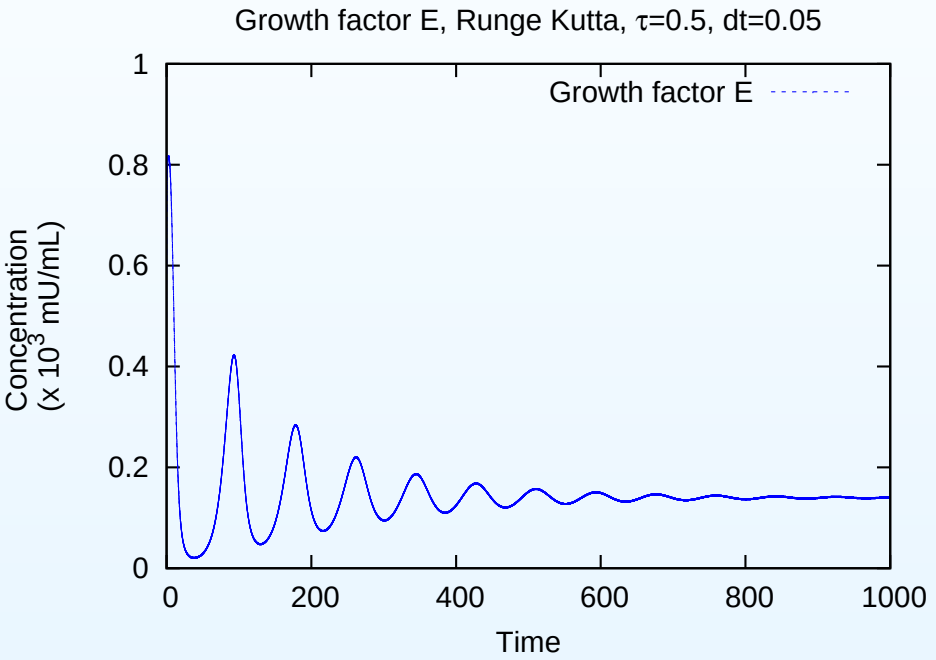
LM

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

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

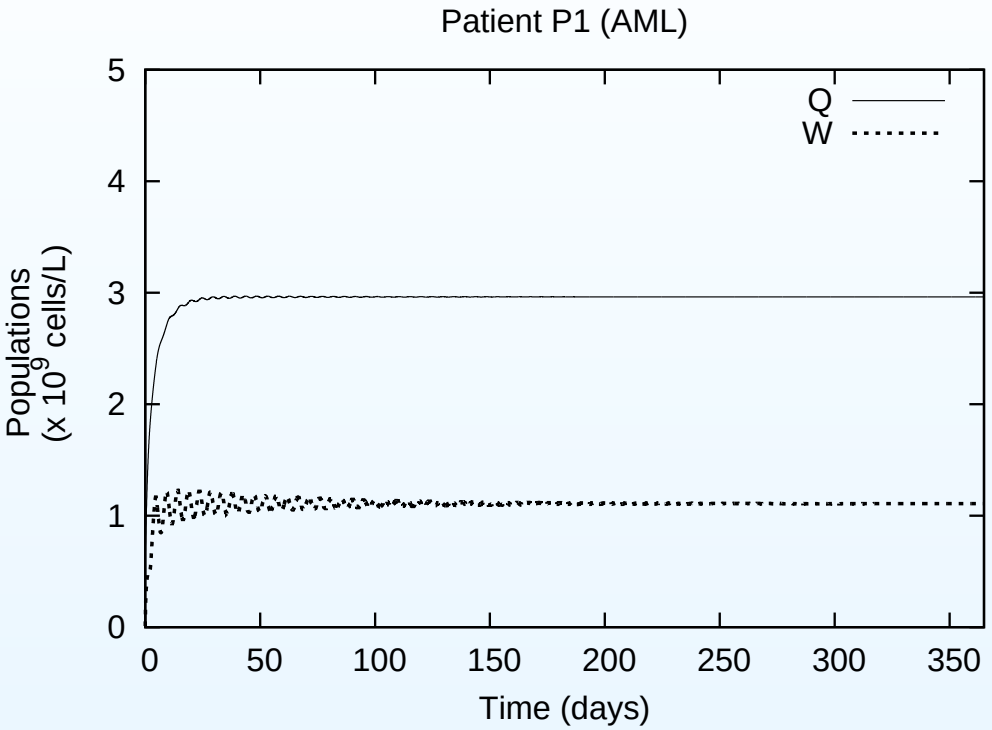
Erythropoiesis, model data from [GFM], $\tau = 0.5$

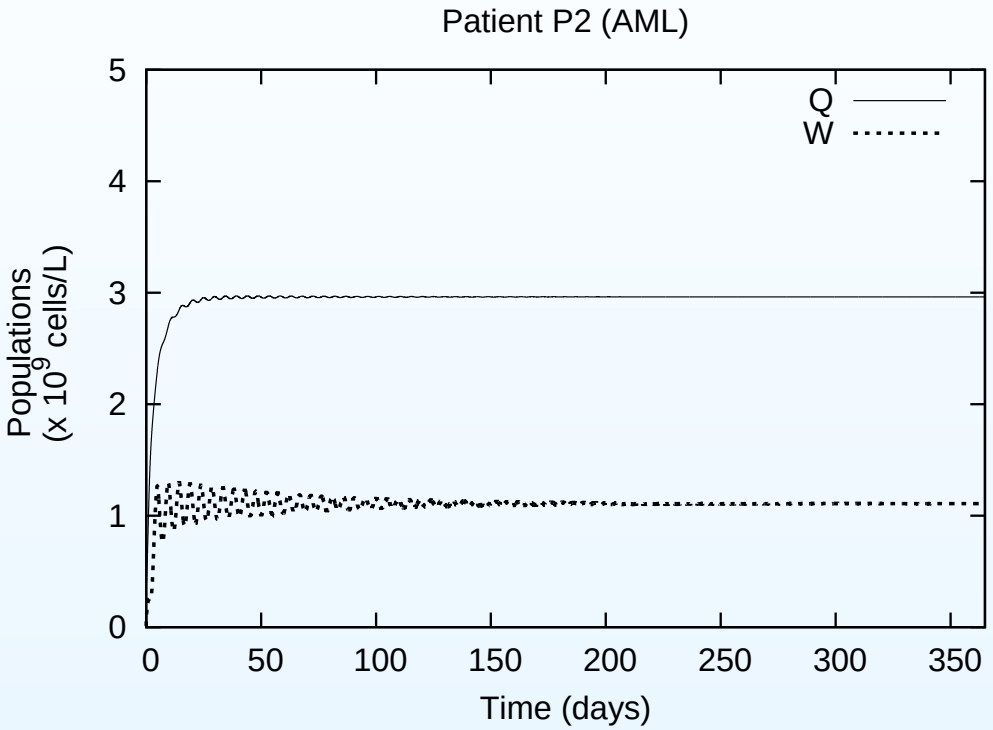




GFM failed with initial data for WBC and G-CSF and various sets of parameters

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

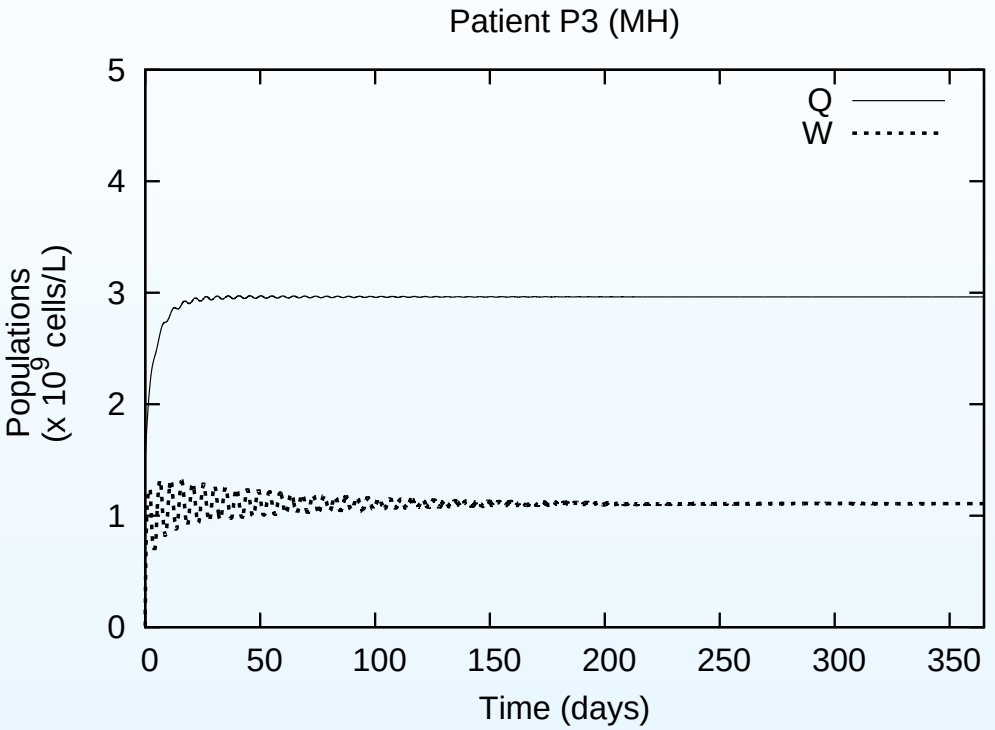


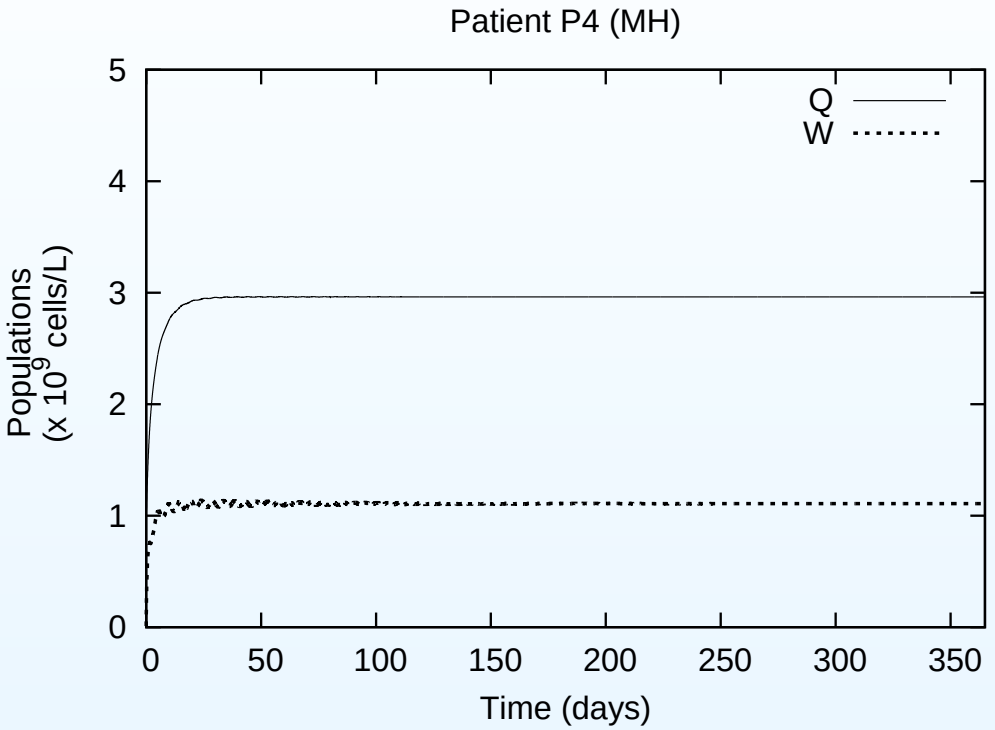


Patient P1:
$Q(0) = 0.61(\times 10^9)$ cells/L,
$W(0) = 0.01(\times 10^9)$ cells/L

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

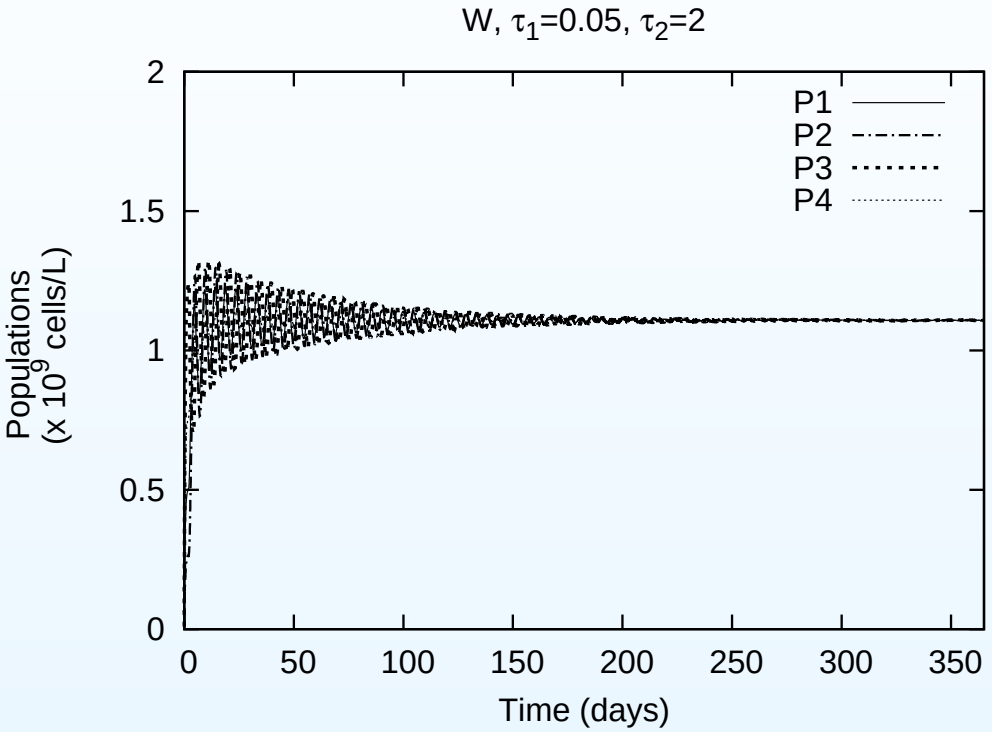


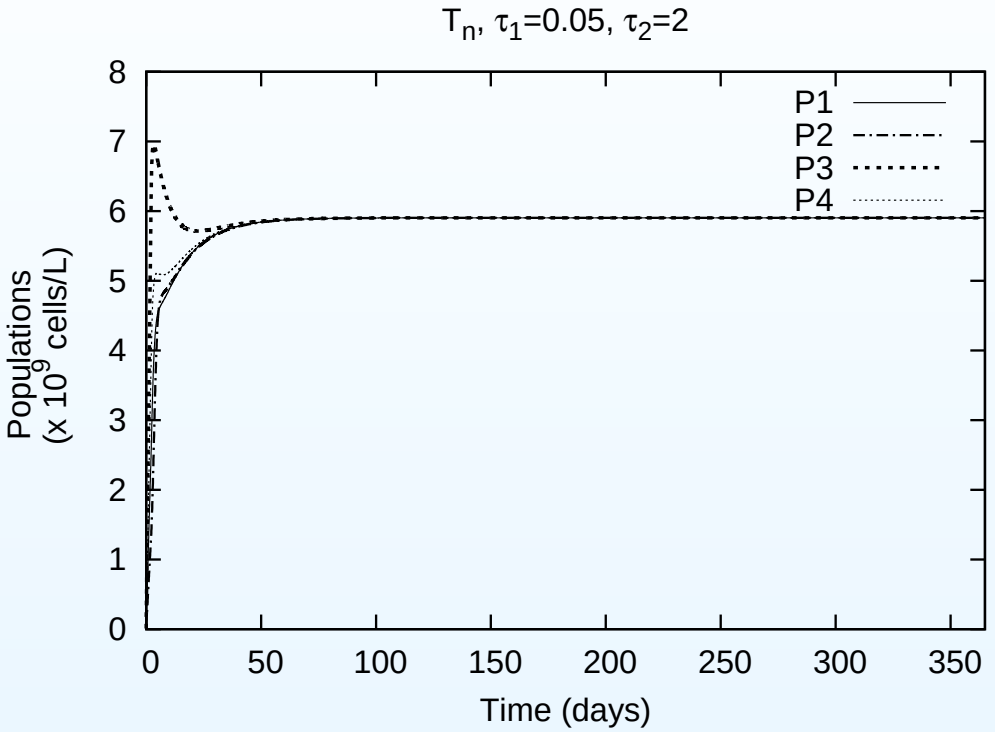


Patient P3:
$Q(0) = 1.5(\times 10^9)$ cells/L,
$W(0) = 0.01(\times 10^9)$ cells/L

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



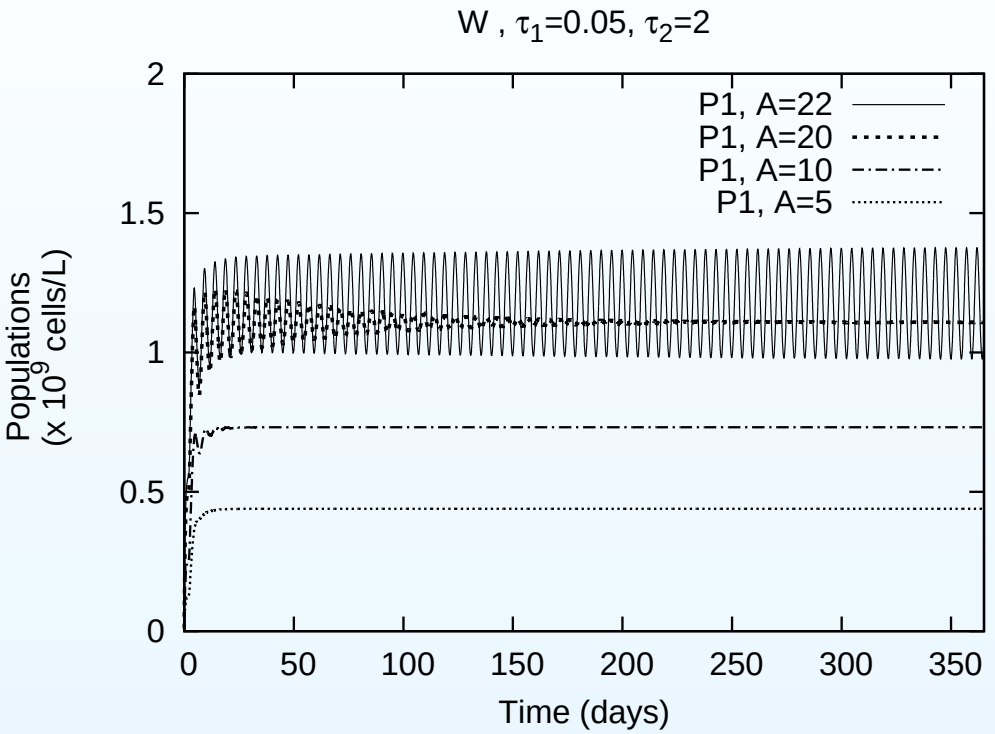


P1÷P4, W cells, $\gamma_2 = 2.4$

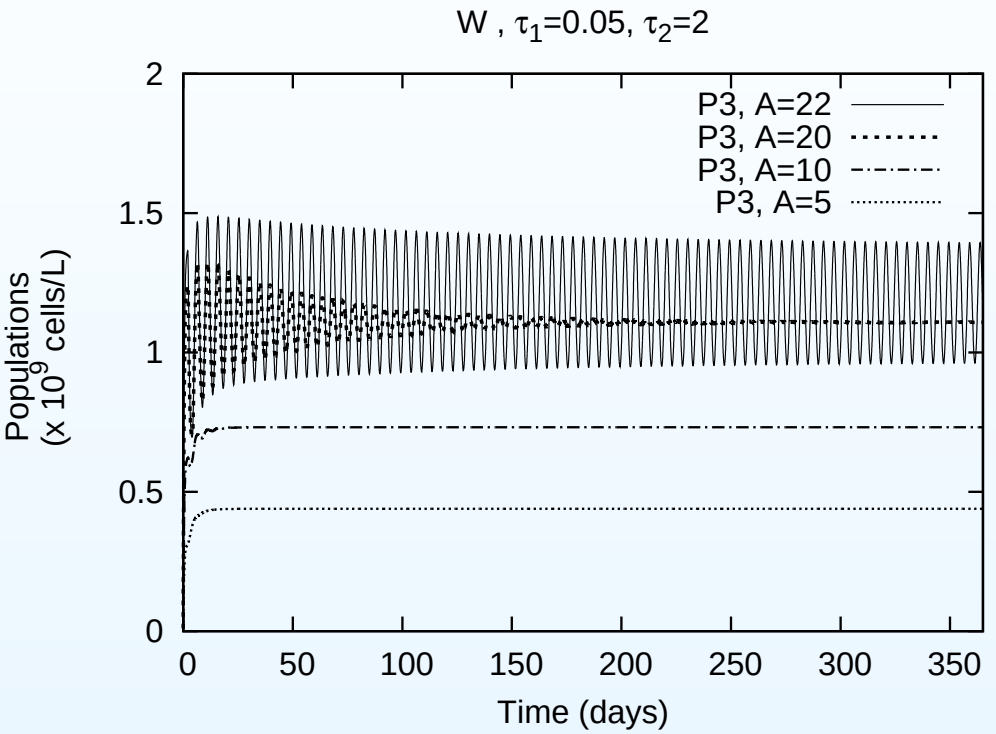
P1÷P4, T_n cells, $\gamma_2 = 0.04$

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

Results W(t), LM – varying A, W cells

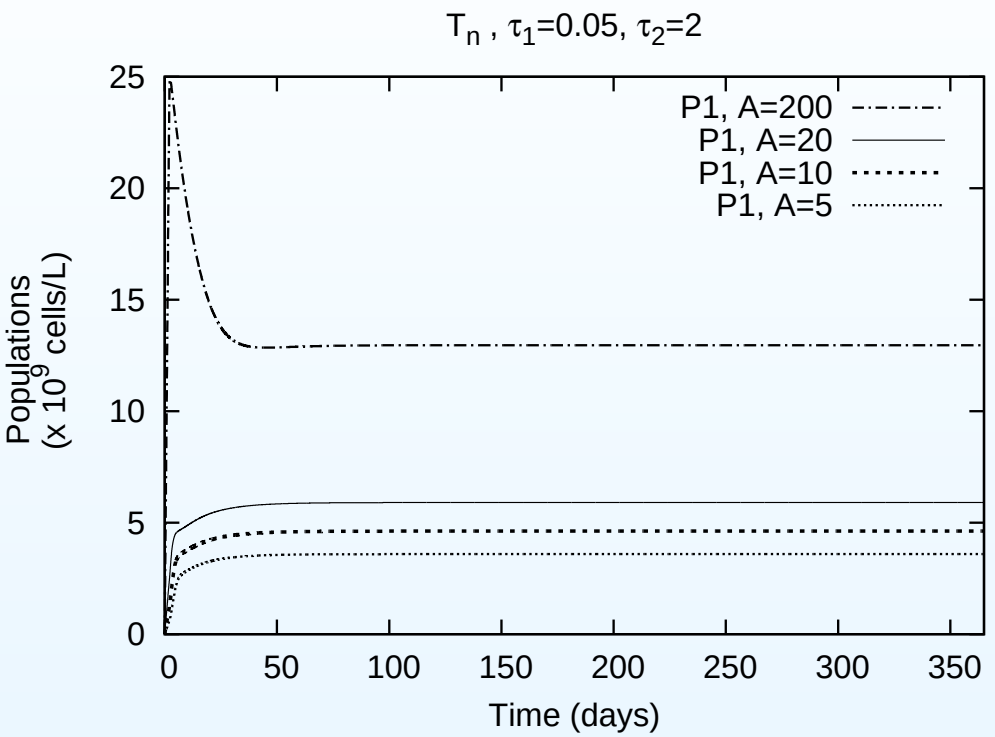


P1, W cells, $\gamma_2 = 2.4$

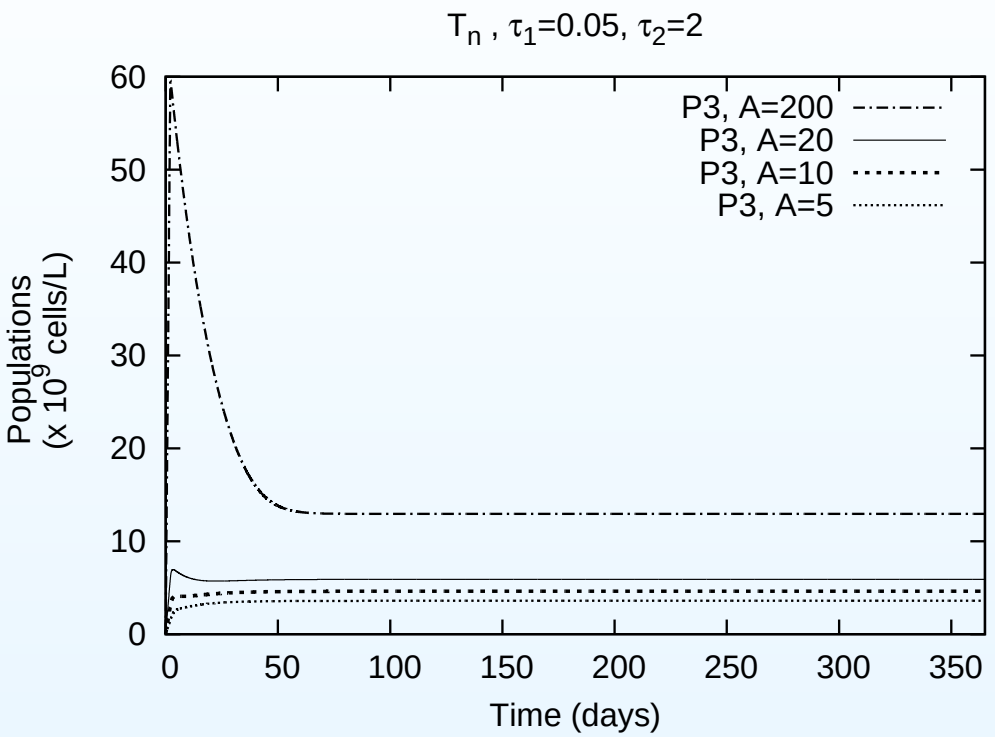


P3, W cells, $\gamma_2 = 2.4$

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

Concluding remarks

- 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

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!