Towards computer modelling of the therapy of leukaemia

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Motivation

Chemotactic movement of HSCs

Regeneration of blood system

Concluding remarks

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

Contents

Motivation

Chemotactic movement of HSCs

Regeneration of blood system

Concluding remarks

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

Motivation

Motivation
- Haematopoiesis
- Blood pathologies

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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

Motivation
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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

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- Involved data
- The model
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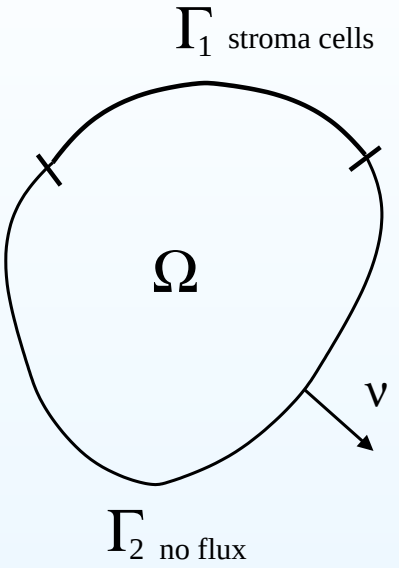
Involved data

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.

Motivation

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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

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

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

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

$$0 \le \chi(a), 0 \le \chi'(a) \le C_\chi, |\chi''(a)| \le C'_\chi$$

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

PDE mode – system of 2 PDEs + ODE on the boundary
Implicit Euler + direct solver for linearised system; BDF for ODE.

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

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

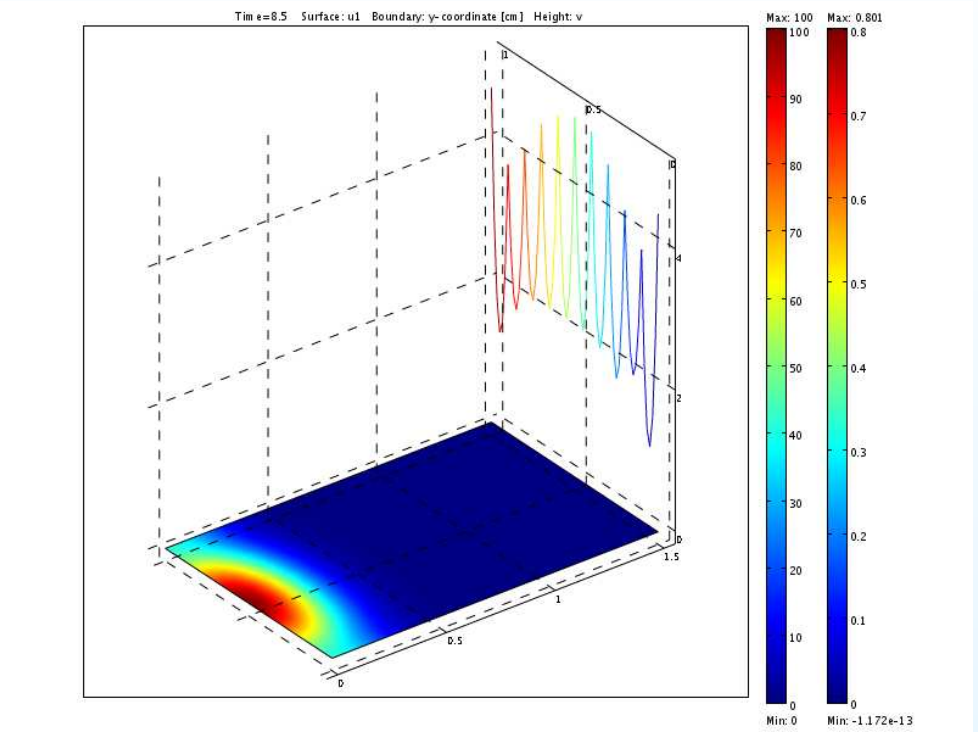
$$\chi(a) = 10a \quad \chi(a) = \log(a)$$

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

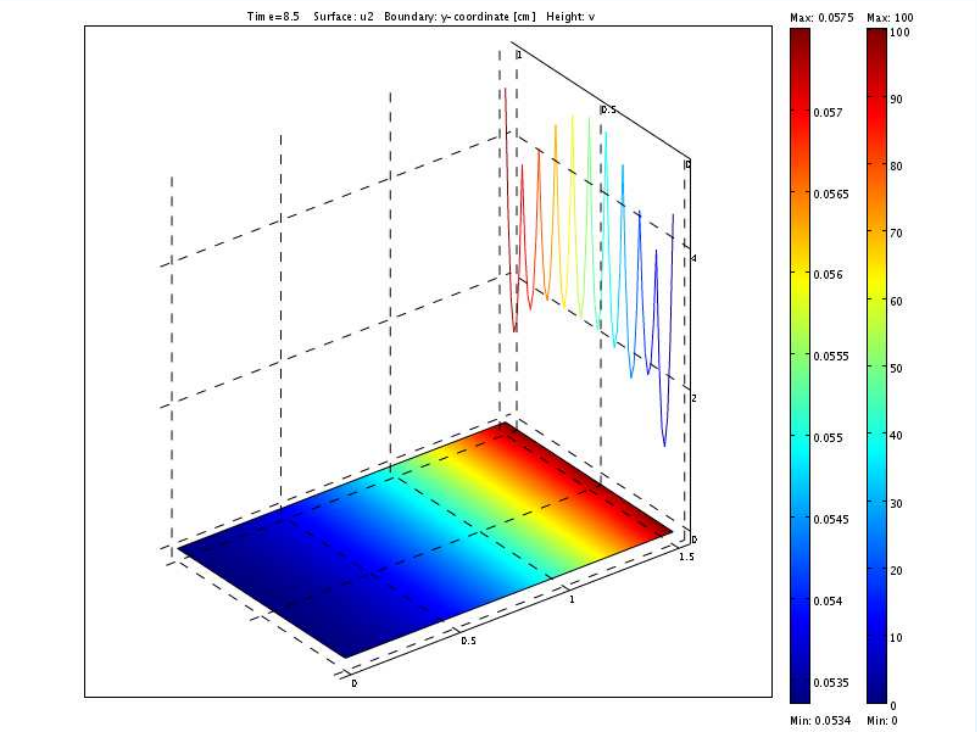
$$a_0 = 0, b_0 = 0 \text{ and}$$

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

Model data – solution for t=8.5

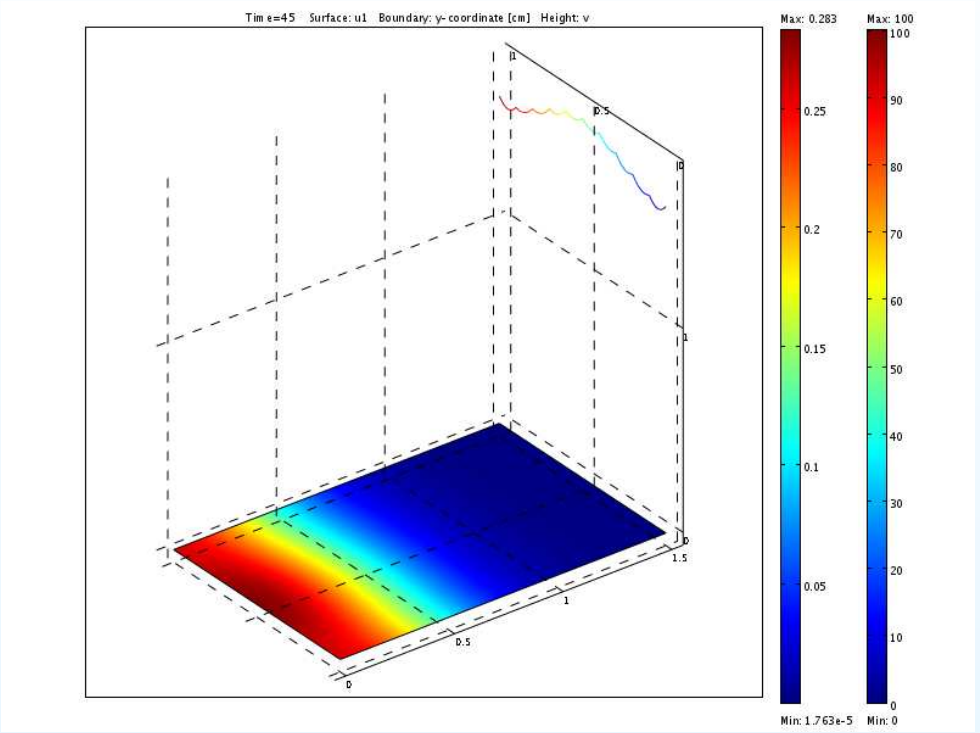


s(t,x) and b(t,x)

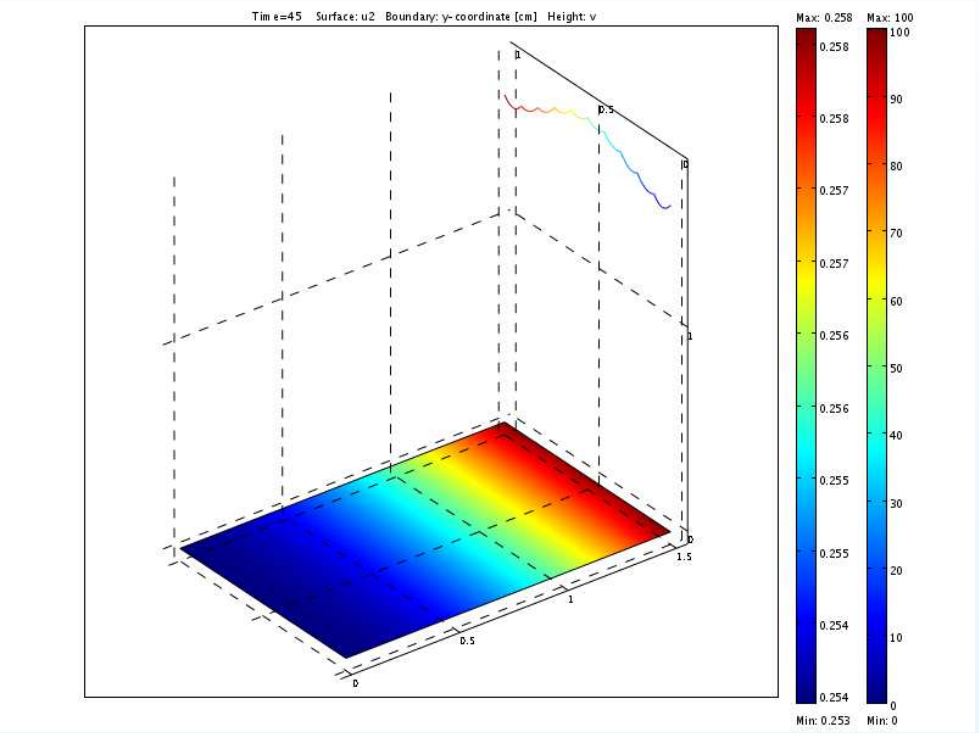


a(t,x) and b(t,x)

Model data – solution for t=45

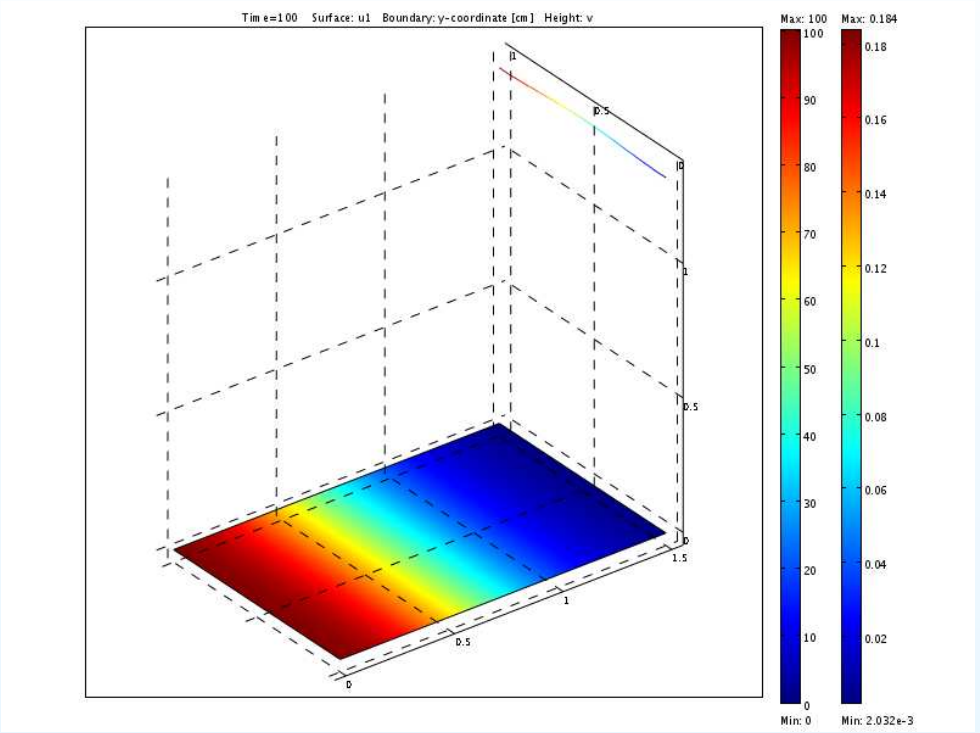


s(t,x) and b(t,x)

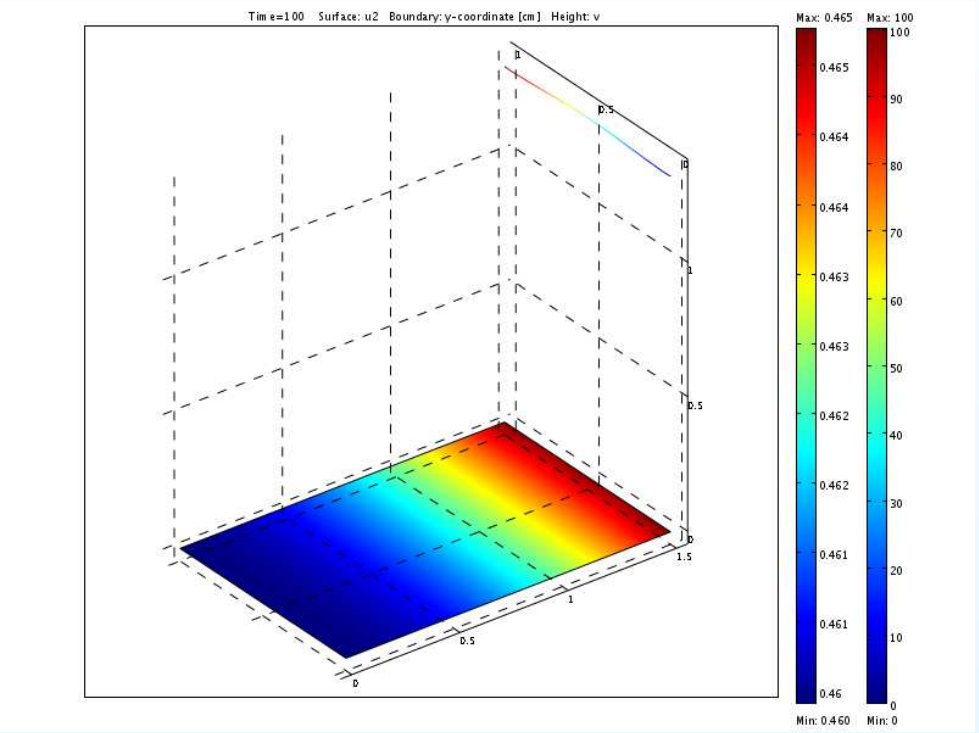


a(t,x) and b(t,x)

Model data – solution for t=100

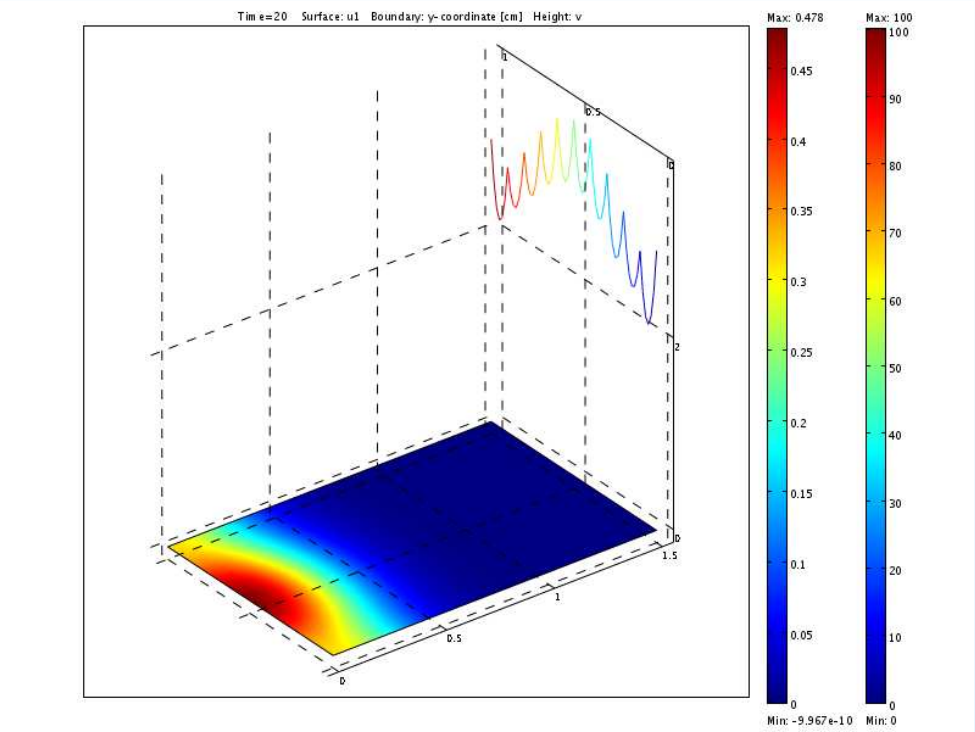


s(t,x) and b(t,x)

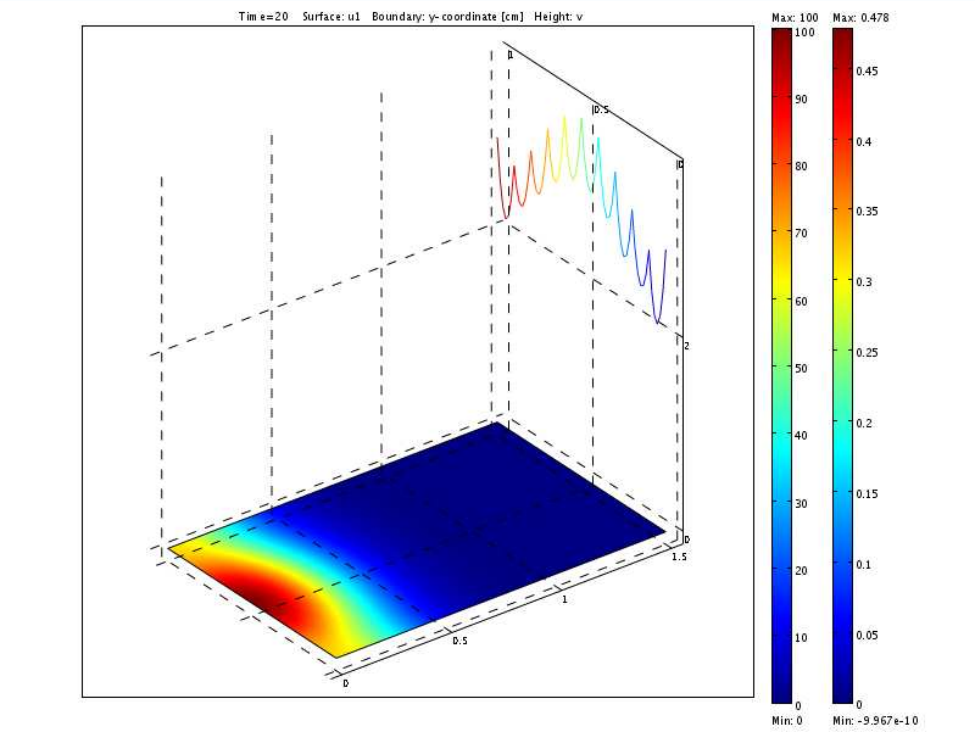


a(t,x) and b(t,x)

Comparison for t=20 – two choices of $\chi(a)$



$\chi(a) = 10a$



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

Regeneration of blood system

Differentiation stages in haematopoiesis

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- Two models
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- LM system of DDEs
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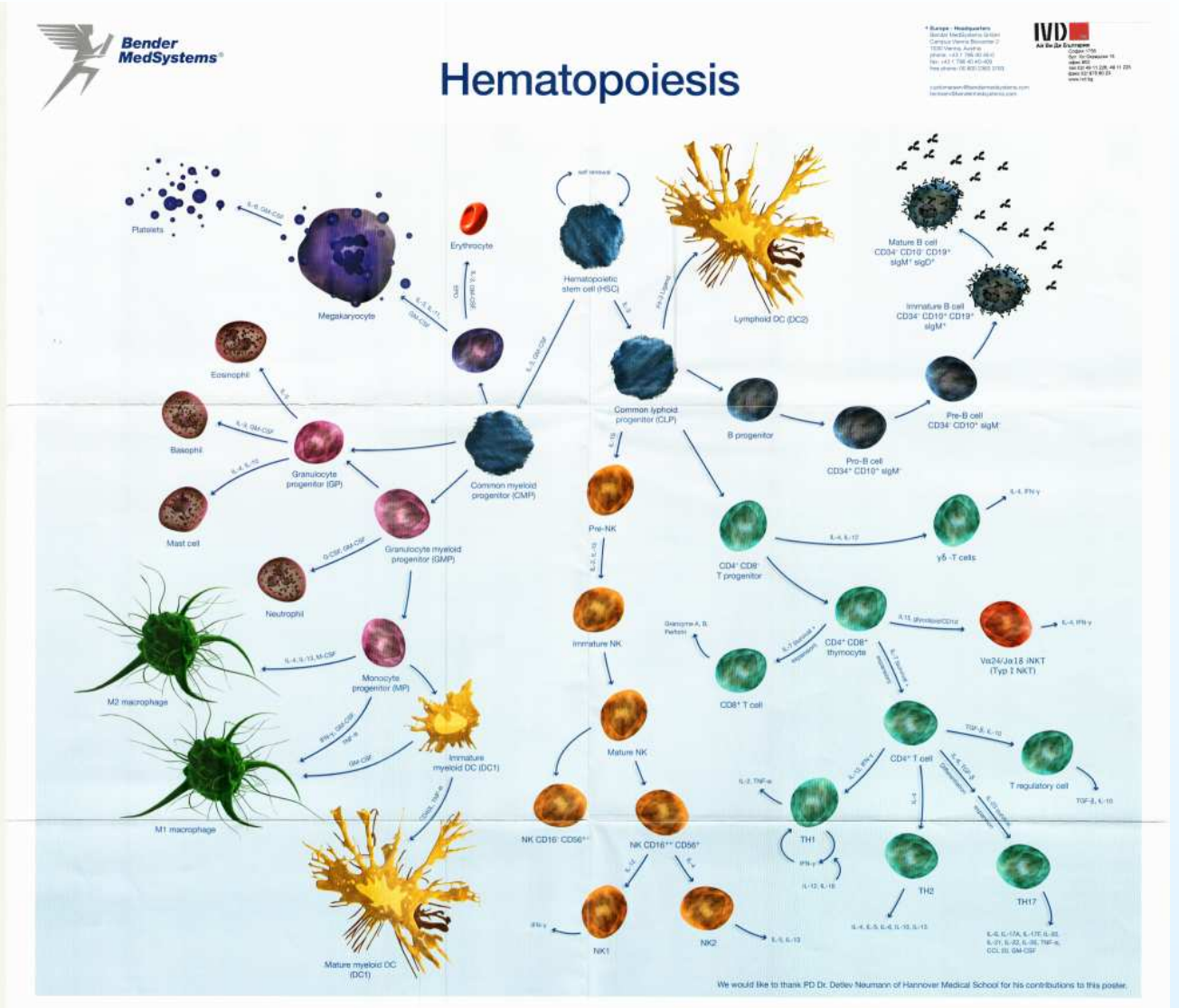
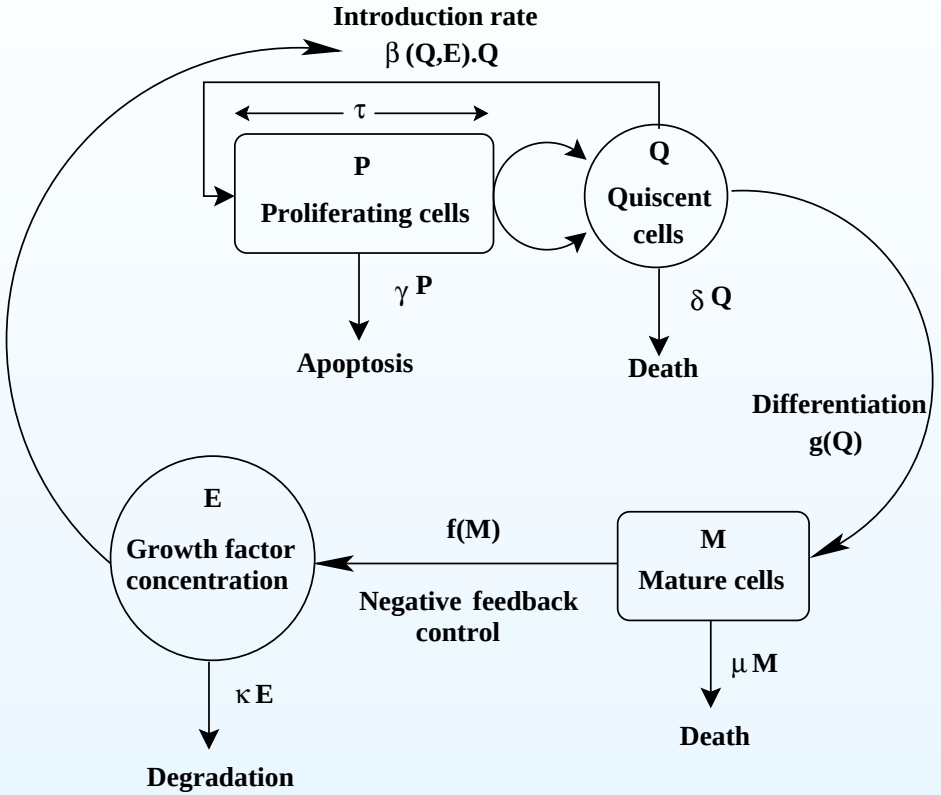
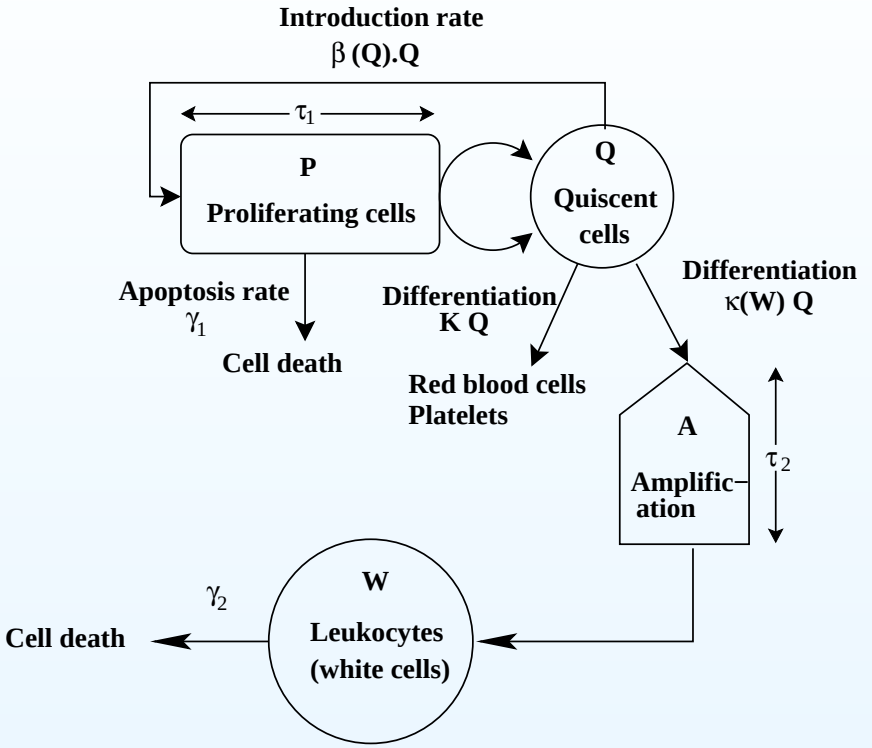


http://www.bendermedsystems.com/

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.

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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

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

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

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

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

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Concluding remarks

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)

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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 equal to 0;
- 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 at several stages: before BMT (D) and 1, 2, 3, 6, 9, 12, 18, 24 months after BMT.
- Diseases – Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Acute Myelogeneous Leukemia (AML)

2 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	75.7
	14/11/06	E12	988	270	600	121	108.01
	09/05/07	E18	1573	267	959	215	215.84
	21/10/08	E 24	1763	924	924	400	333
P2	11/10/06	D	1946	25	1721	53	160.01
	01/11/06	E1	450	30	410	19	39.7
	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	E 18	44	0	43	1	23.41
	16/10/08	E 24	2572	2279	2291	208	182.61

Numerical tests – model parameters

GFM

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

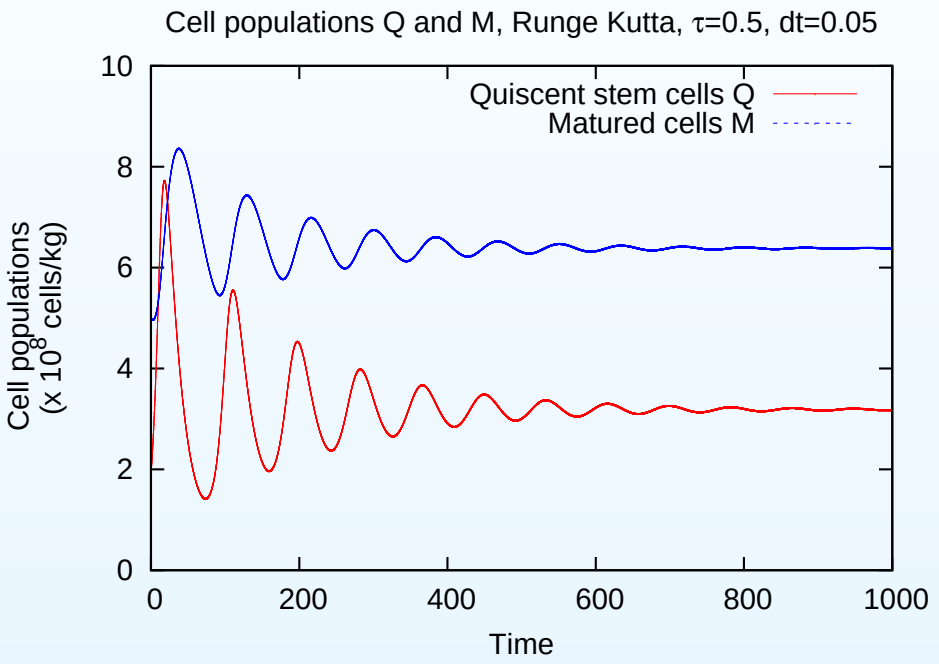
Param	Value	Range (day^{-1})
δ	0.01 day^{-1}	0 – 0.09
G	0.04 day^{-1}	0 – 0.09
β_0	0.5 day^{-1}	0.08 – 2.24
γ	0.2 day^{-1}	0 – 0.9
μ	0.02 day^{-1}	0.001 – 0.1
k	2.8 day^{-1}	—
a	6570	—
K	0.0382	—
r	7	—

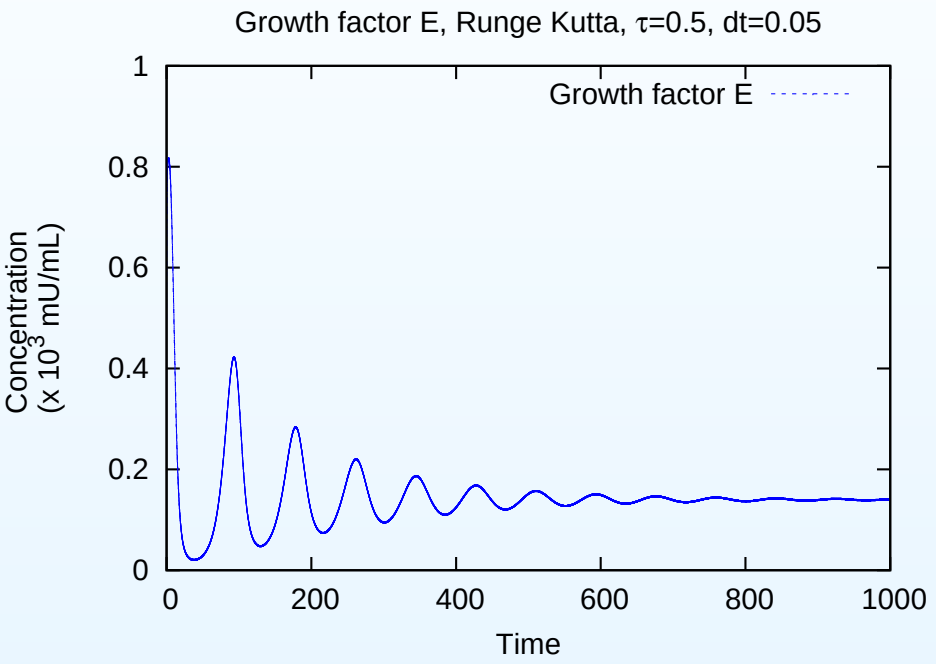
LM

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

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

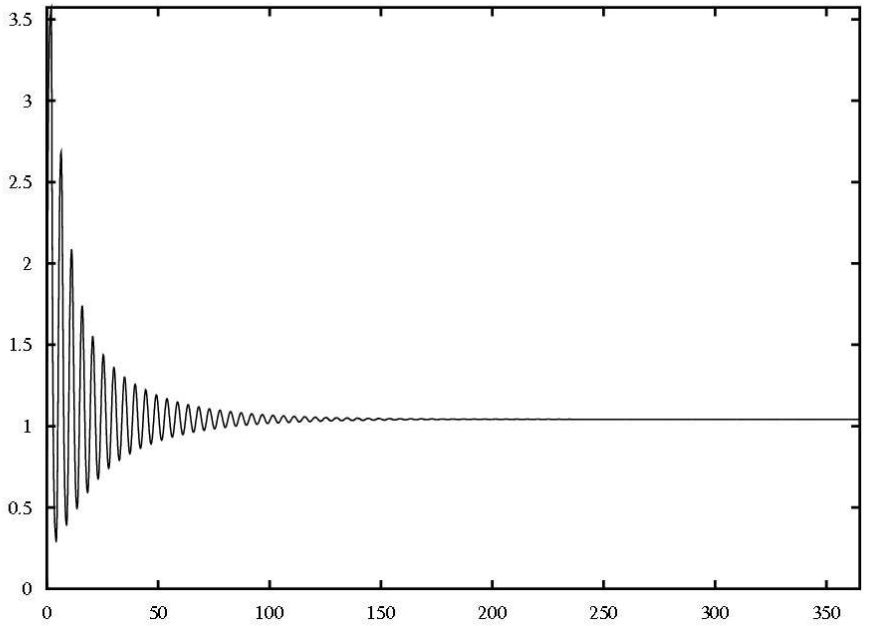
Erythropoiesis, model data from [GFM], $\tau = 0.5$



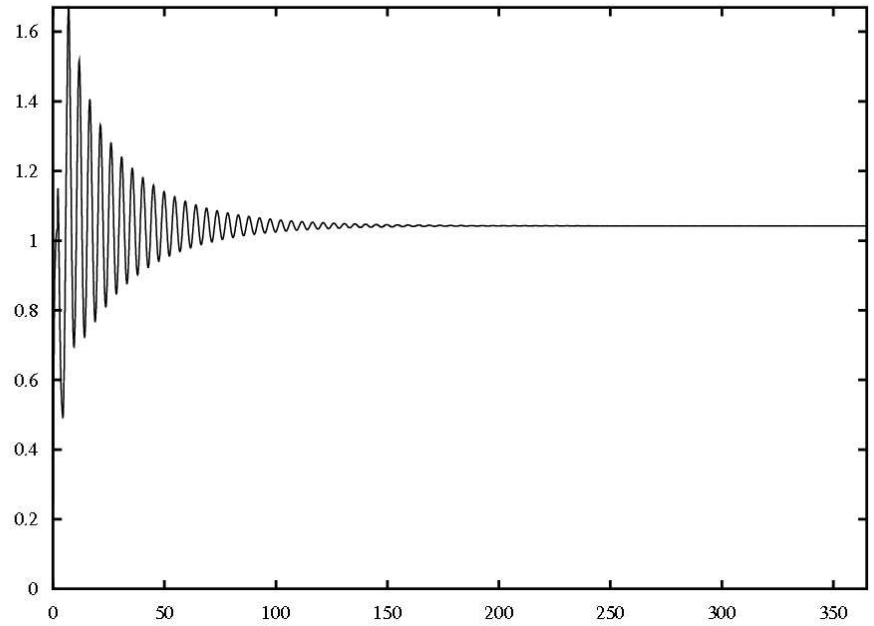


GFM failed with initial data for WBC and G-CSF and various sets of parameters

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

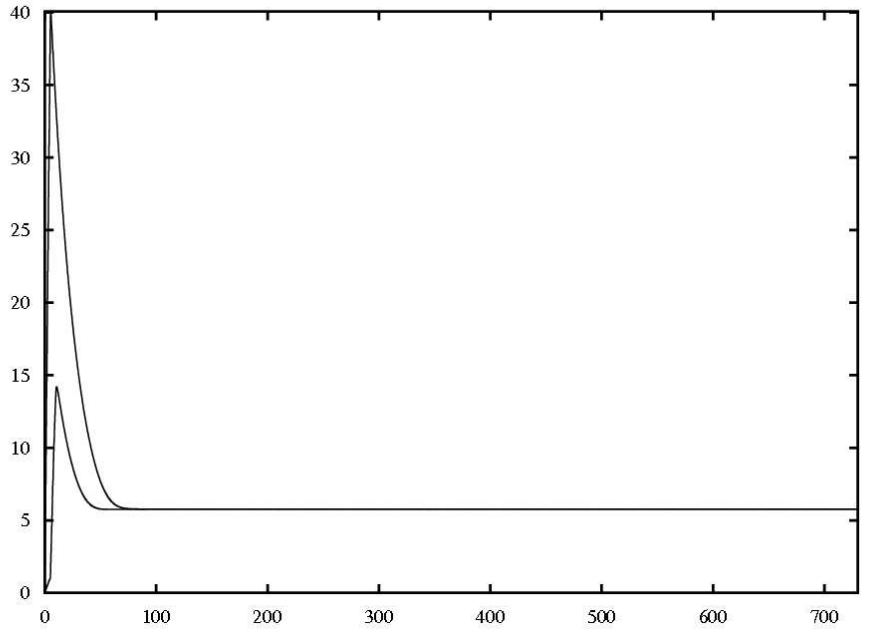


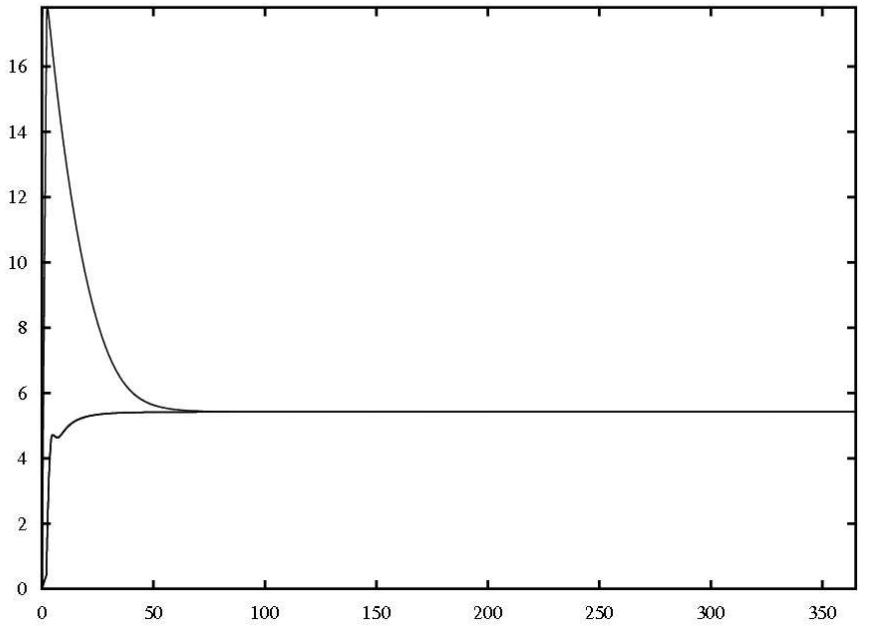
Patient P1:
$Q(0) = 4.32(\times 10^6)$ cells/kg,
$W(0) = 0$



Patient P2:
$Q(0) = 1.69(\times 10^6)$ cells/kg,
$W(0) = 0$

Results W(t), LM – varying τ



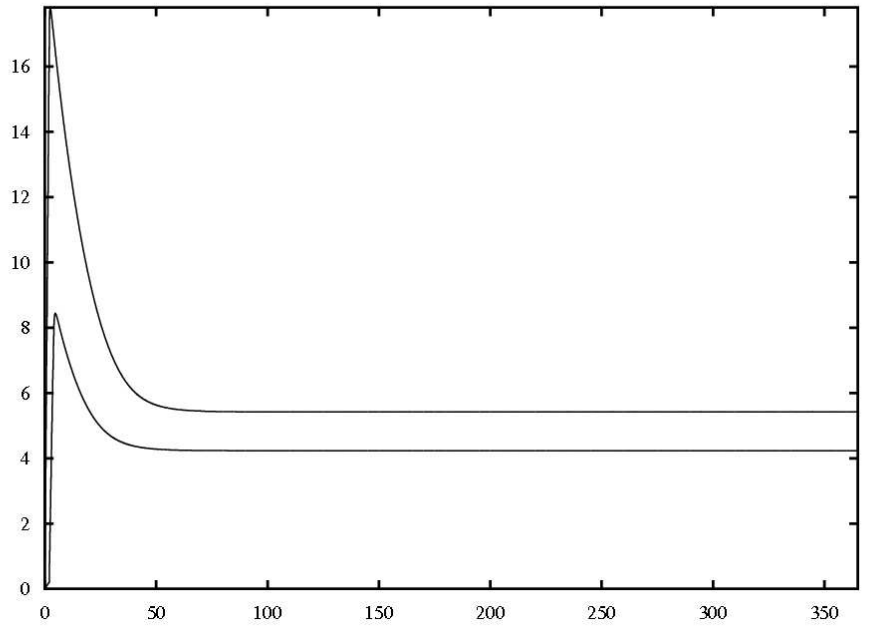


$\tau_1 = 0.5, \tau_2 = 2.$

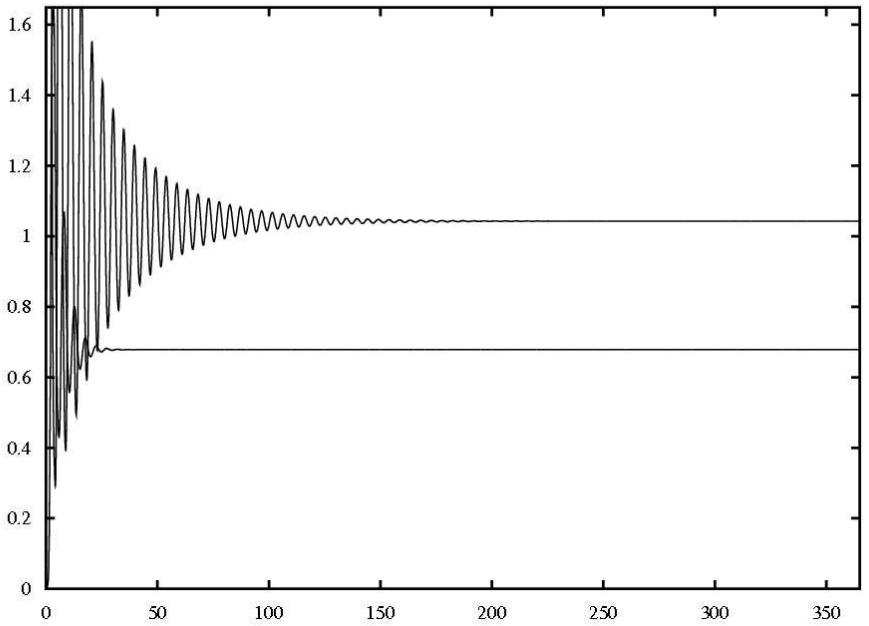
$\tau_1 = 1.5, \tau_2 = 2.$

P1 and P2 – Tn cells with $\gamma_2 = 0.04$ (Moore, Li (2004))

Results W(t), LM – varying A



$\gamma_2 = 0.04,\ A = 10, 20$



$\gamma_2 = 2.4,\ A = 10, 20$

Concluding remarks

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- Chemotactic movement:
  – Comparative analysis of solution methods in COMSOL
  – Ranges for parameters where the model works or fails?
- 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?
- 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 National Center for Hematology and Transfusiology, Bulgaria
  – *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!