How does clinical data fit into two leukopoiesis models?

Gergana Bencheva

Institute for Parallel Processing

Bulgarian Academy of Sciences

gery@parallel.bas.bg

Contents

- Motivation
- Two leukopoiesis models
- Solution method
- 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.

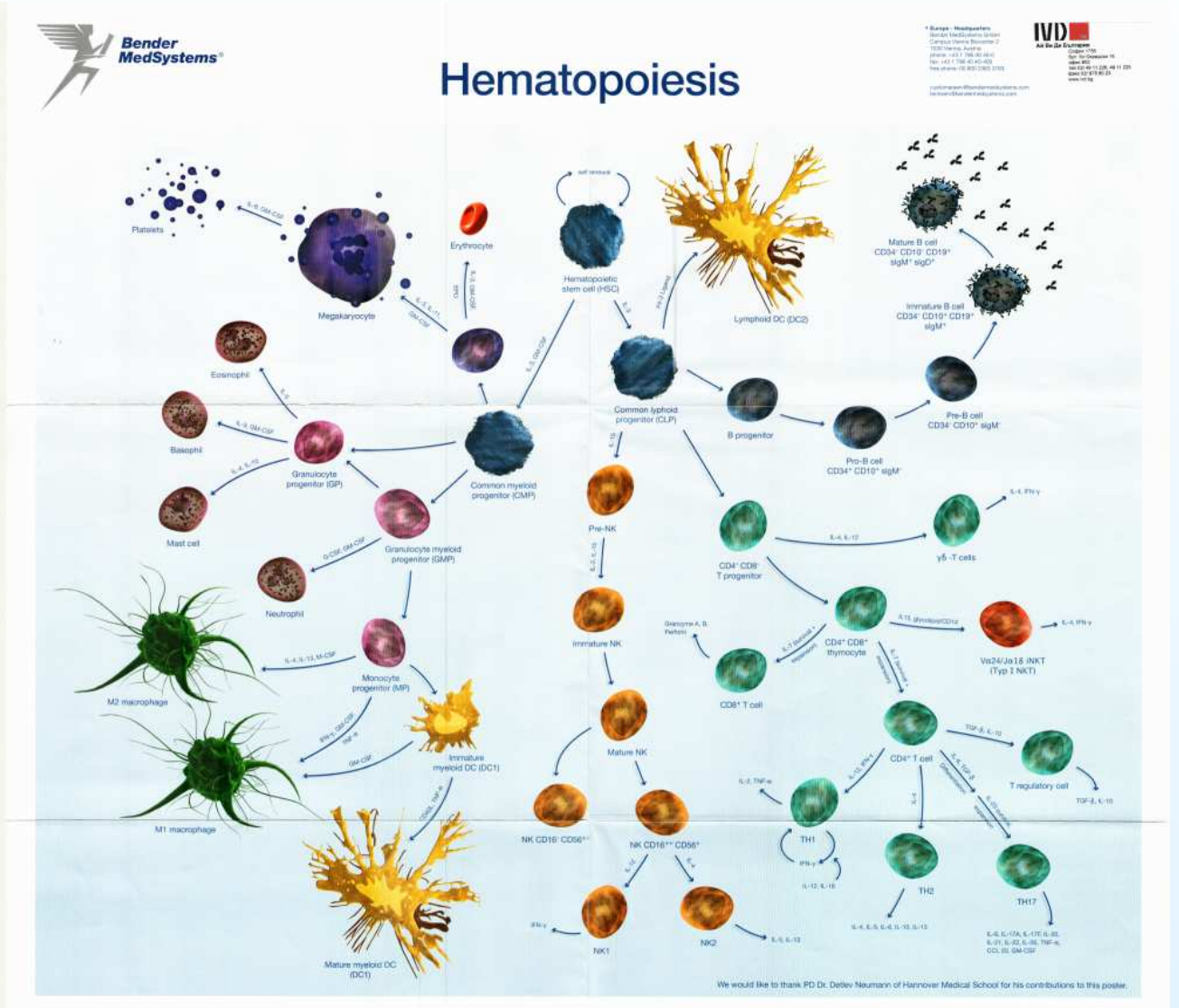
Growth factors or Colony Stimulating Factors (CSF) – specific proteins that stimulate the production and maturation of each blood cell type.

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)

Differentiation stages in haematopoiesis



http://www.bendermedsystems.com/

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:

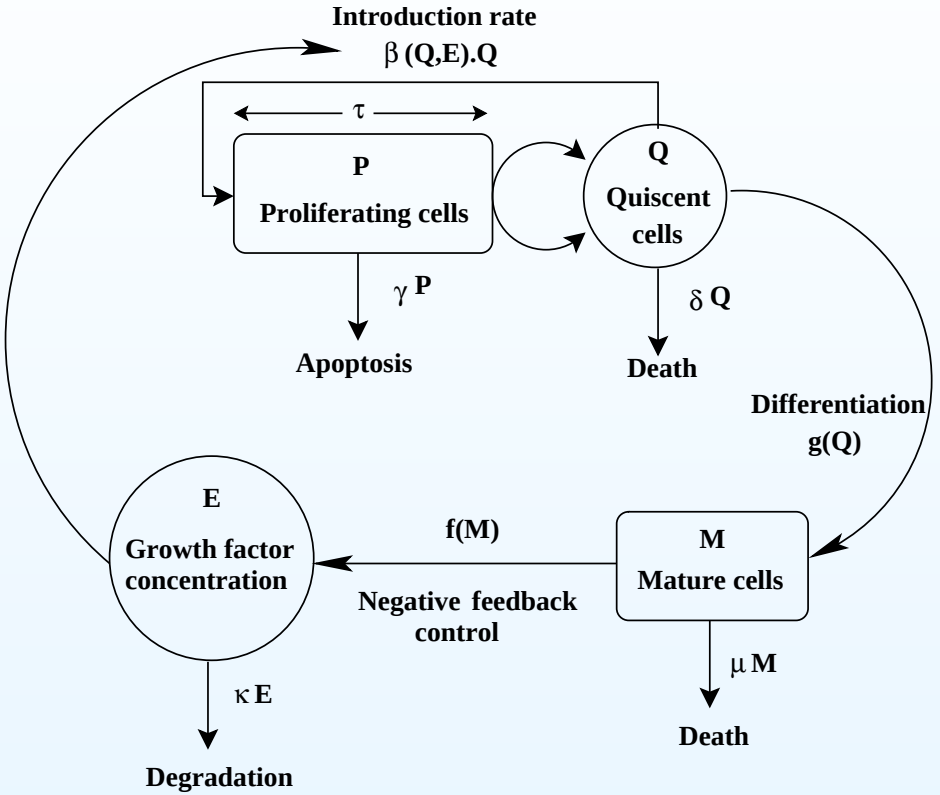
TBI: Total body irradiation (TBI) and chemoterapy – kill the "tumour" cells, but also the healthy ones.

BMT: Bone marrow transplantation (BMT) – stem cells of a donor (collected under special conditions) are put in the peripheral blood, from where they have to:
1) find their way to the stem cell niche in the bone marrow; and afterwards
2) selfrenew and differentiate to regenerate the patient's blood system.

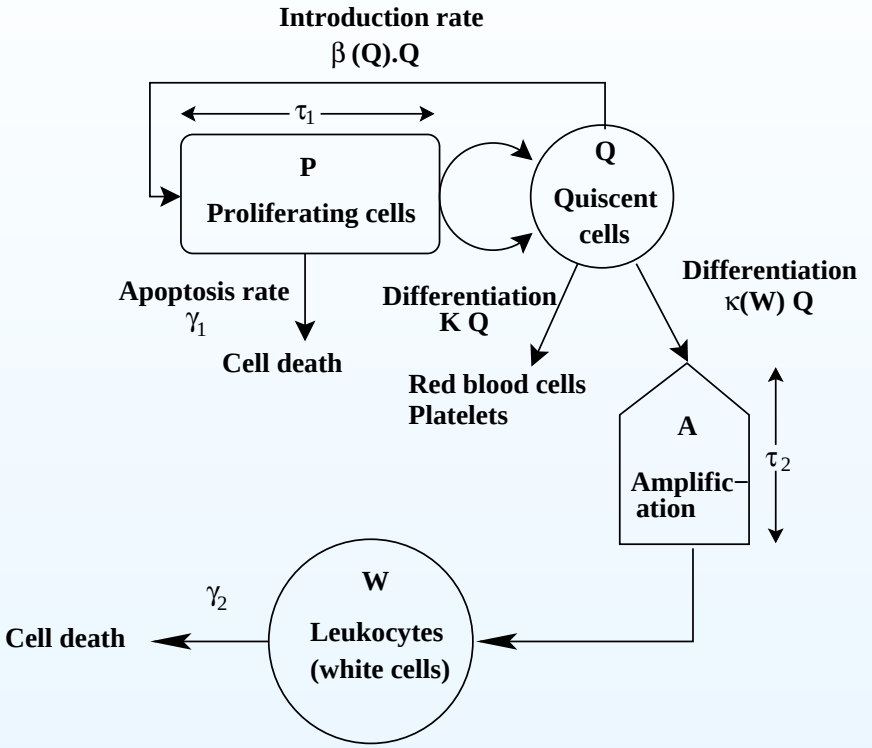
Current stage: Compare clinical data and computer simulations with two leukopoiesis models.

Two leukopoiesis 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

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

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

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

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

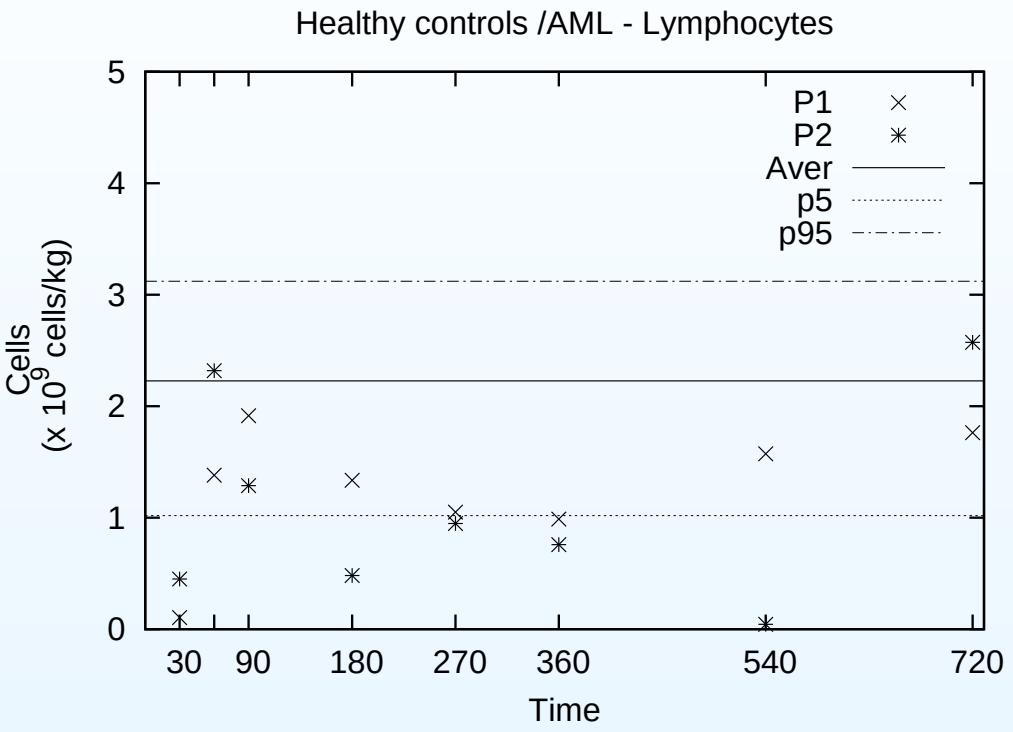
Provided clinical data

- 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), 1, 2, 3, 6, 9, 12, 18, 24 months after BMT.
- Diseases – Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), Acute Myelogeneous Leukemia (AML)

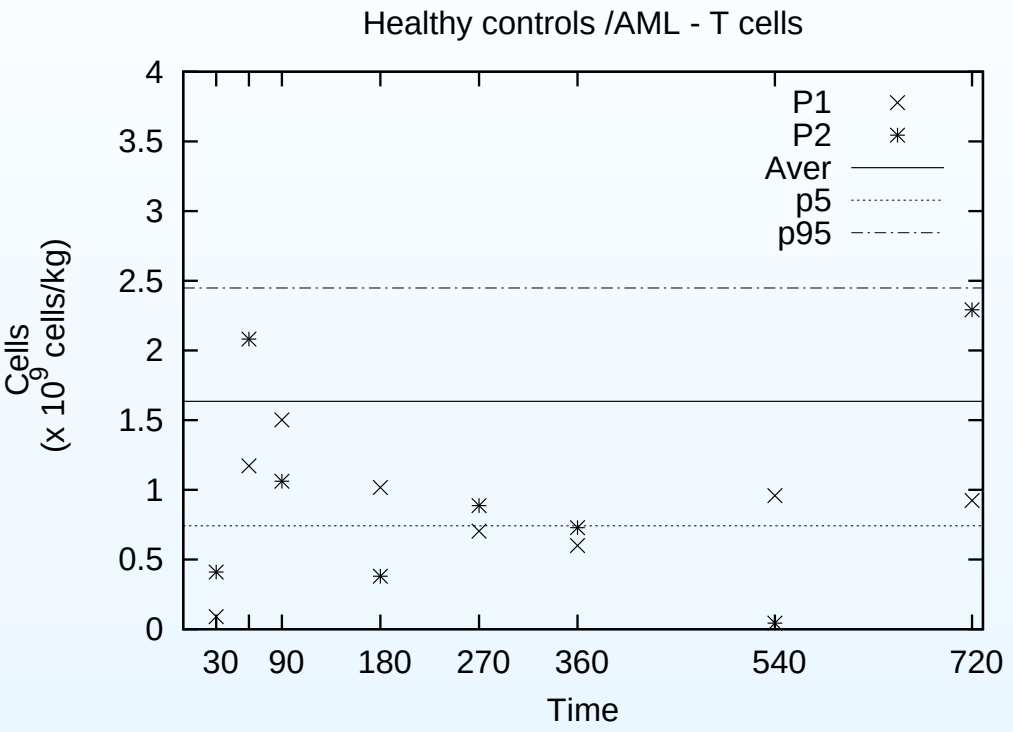
2 patients with AML

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

Healthy controls vs patients with AML



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

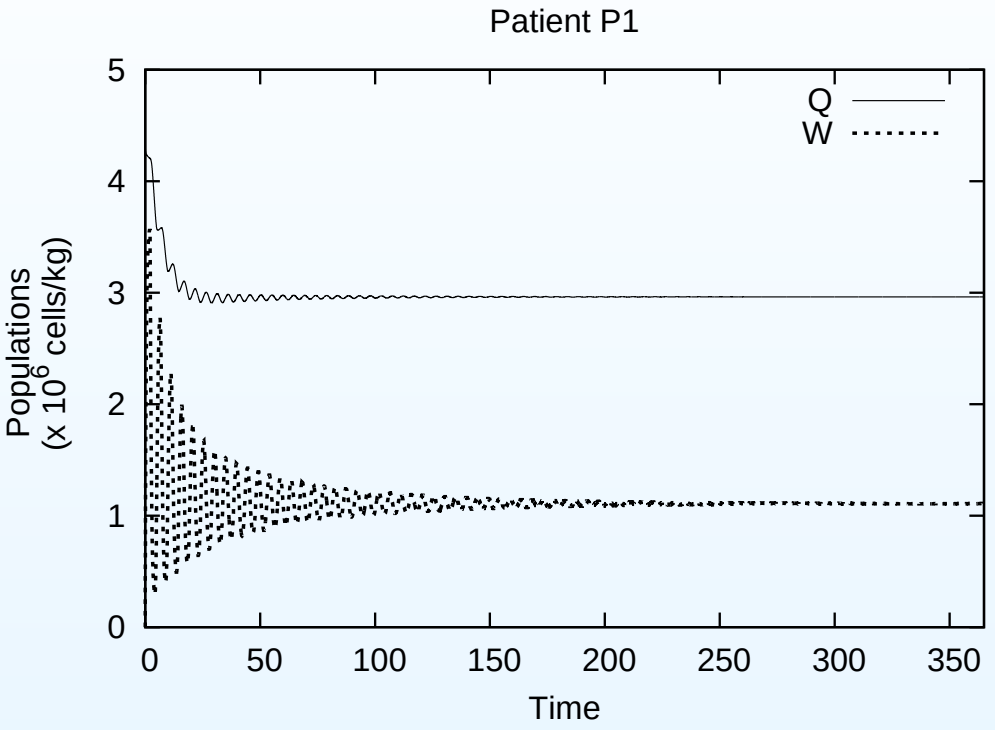
$$\beta(Q) = \frac{\beta_0}{1+Q^n}, \qquad \beta_0 > 0$$

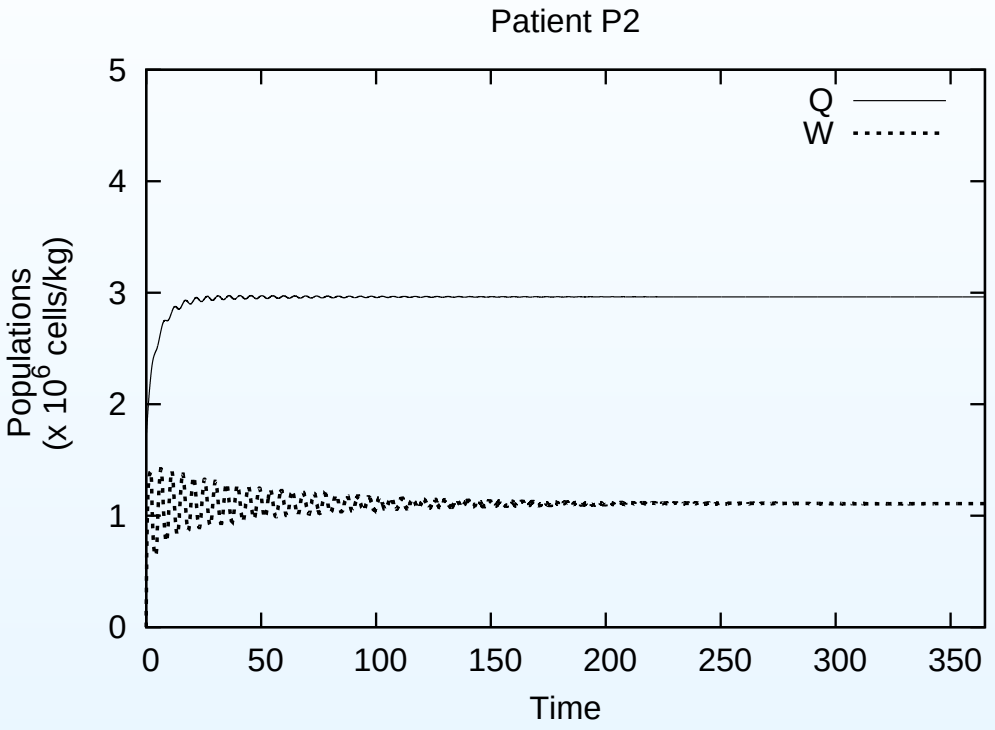
$$k(W) = \frac{k_0}{1+W^m}, \qquad k_0 > 0$$

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

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

Results Q(t) and W(t), model data from paper LM

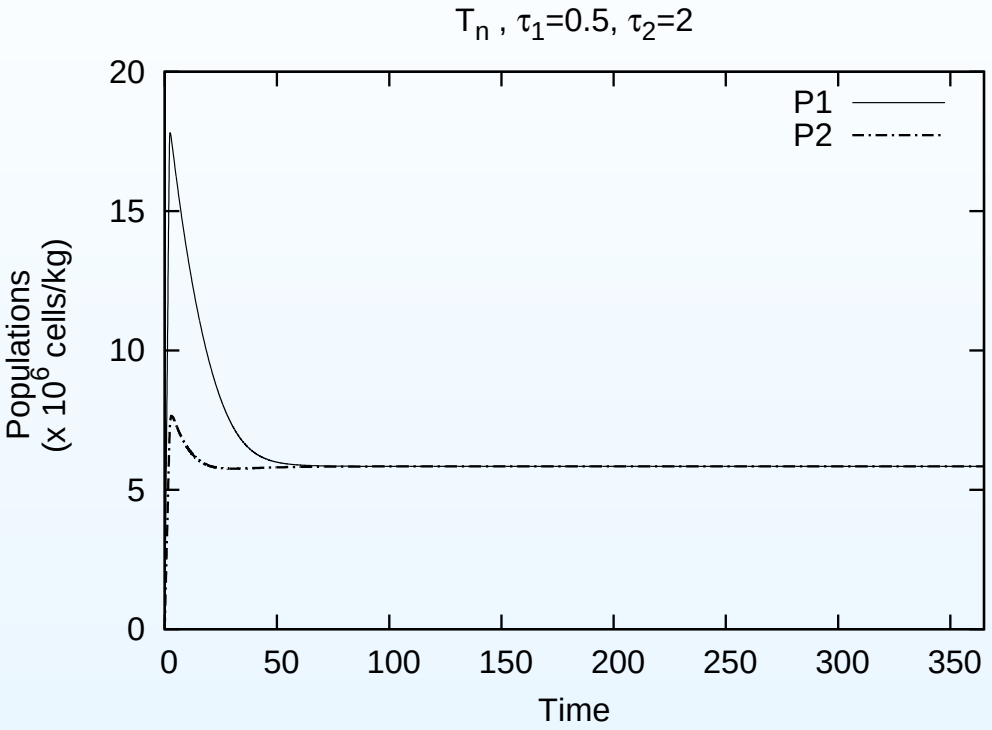




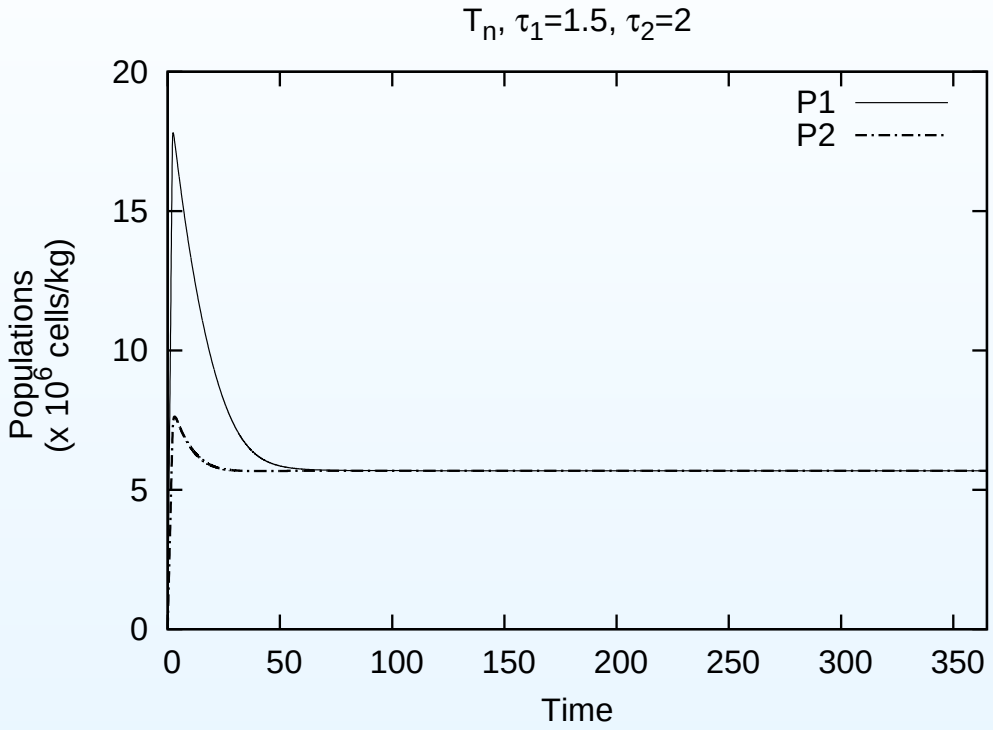
Patient P1:
$Q(0) = 4.32(\times 10^6)$ cells/kg,
$W(0) = 0$

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

Results W(t), LM – varying τ



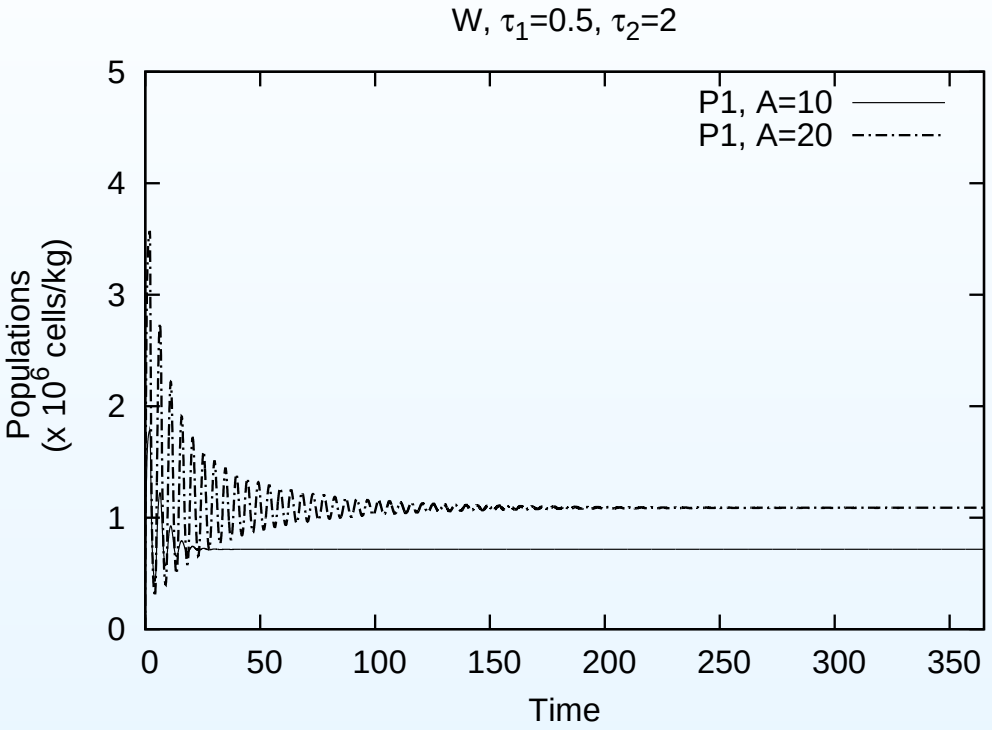
$\tau_1 = 0.5, \tau_2 = 2.$



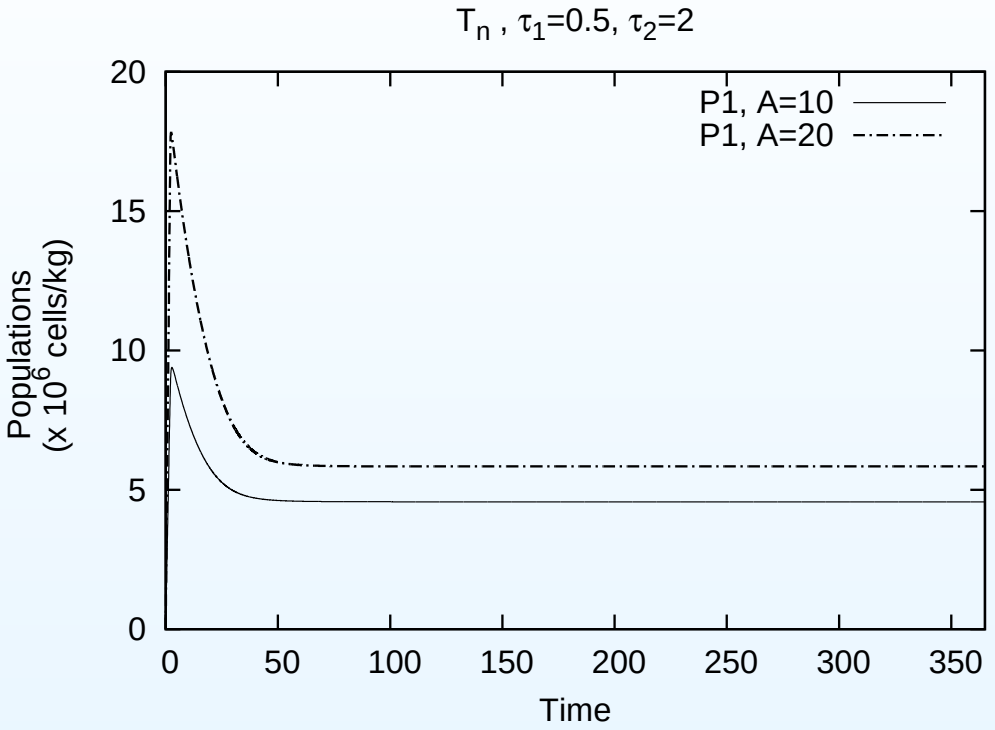
$\tau_1 = 1.5, \tau_2 = 2.$

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

Results, Patient 1, LM – varying A

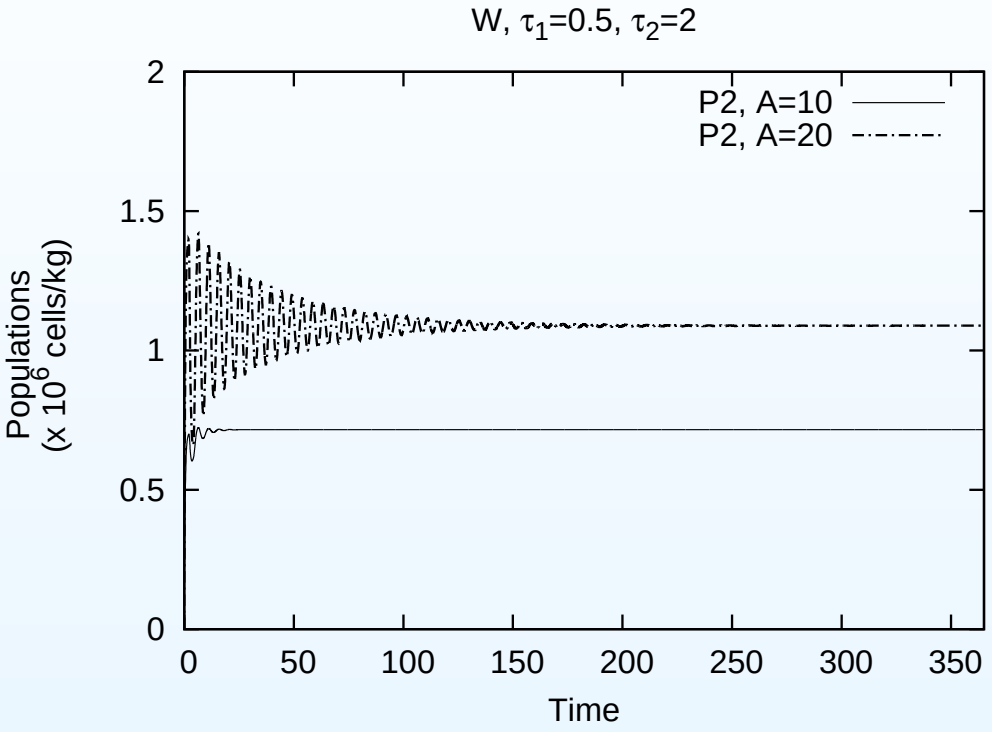


$\gamma_2 = 2.4,\ A = 10, 20$

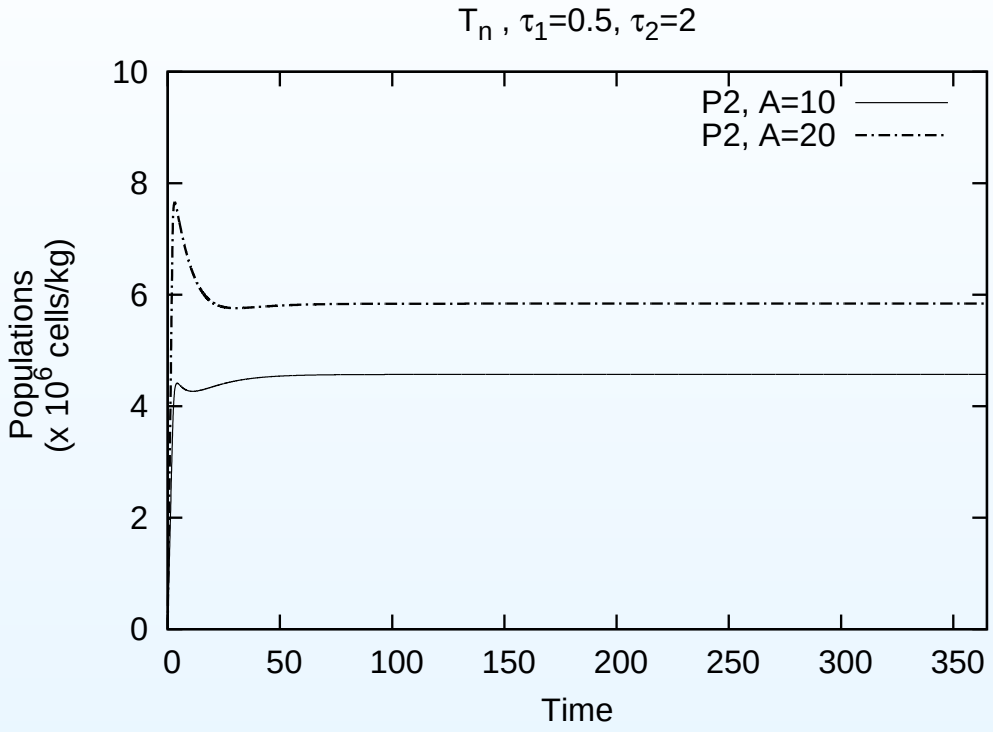


$\gamma_2 = 0.04,\ A = 10, 20$

Results, Patient 2, LM – varying A



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



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

Concluding remarks

Concluding remarks

- Open issues
  – Why does the GFM model "crash" 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 of both models

Clinical data is provided by Dr. M. Guenova and Dr. L. Gartcheva from NCHT

This work is supported in part by the Bulgarian NSF grants DO 02-214 and DO 02-147

Thank you for your attention!