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 methods

Clinical data

Numerical tests

Concluding remarks

- Motivation
- Two leukopoiesis models
- Solution method
- Clinical data
- Numerical tests
- Concluding remarks

Motivation

Blood cells production and regulation

Motivation
- Haematopoiesis
- Differentiation stages
- Blood pathologies
- Need for simulation

Two leukopoiesis models

Solution methods

Clinical data

Numerical tests

Concluding remarks

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

Motivation
- Haematopoiesis
- Differentiation stages
- Blood pathologies
- Need for simulation

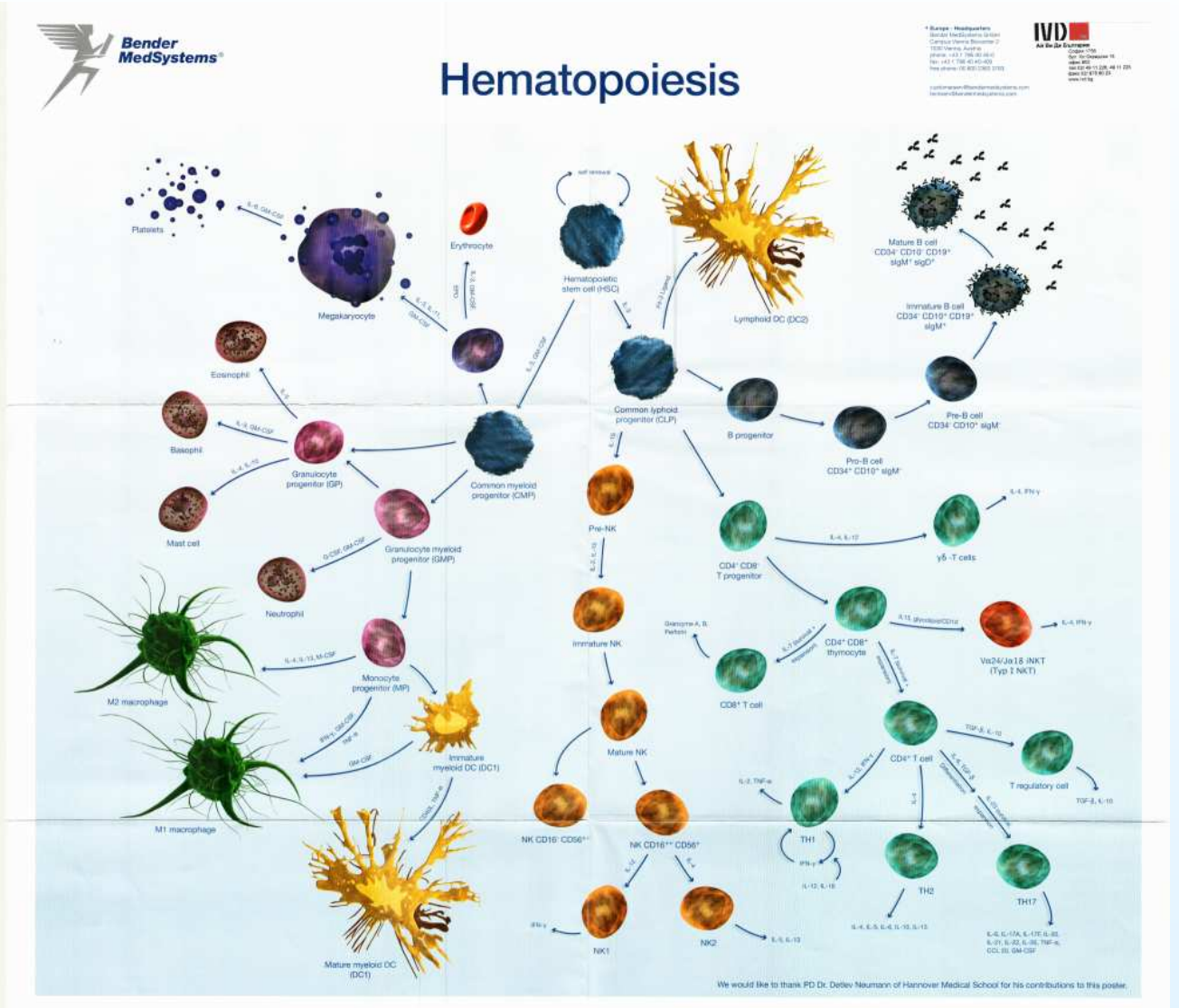
Two leukopoiesis models

Solution methods

Clinical data

Numerical tests

Concluding remarks



http://www.bendermedsystems.com/

Blood pathologies

Motivation
- Haematopoiesis
- Differentiation stages
- Blood pathologies
- Need for simulation

Two leukopoiesis models

Solution methods

Clinical data

Numerical tests

Concluding remarks

Various hematological diseases (including leukemia) are characterized by abnormal production of particular blood cells (matured or blast).
Main stages in their therapy:

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.

Need for computer simulation

Motivation
- Haematopoiesis
- Differentiation stages
- Blood pathologies
- Need for simulation

Two leukopoiesis models

Solution methods

Clinical data

Numerical tests

Concluding remarks

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

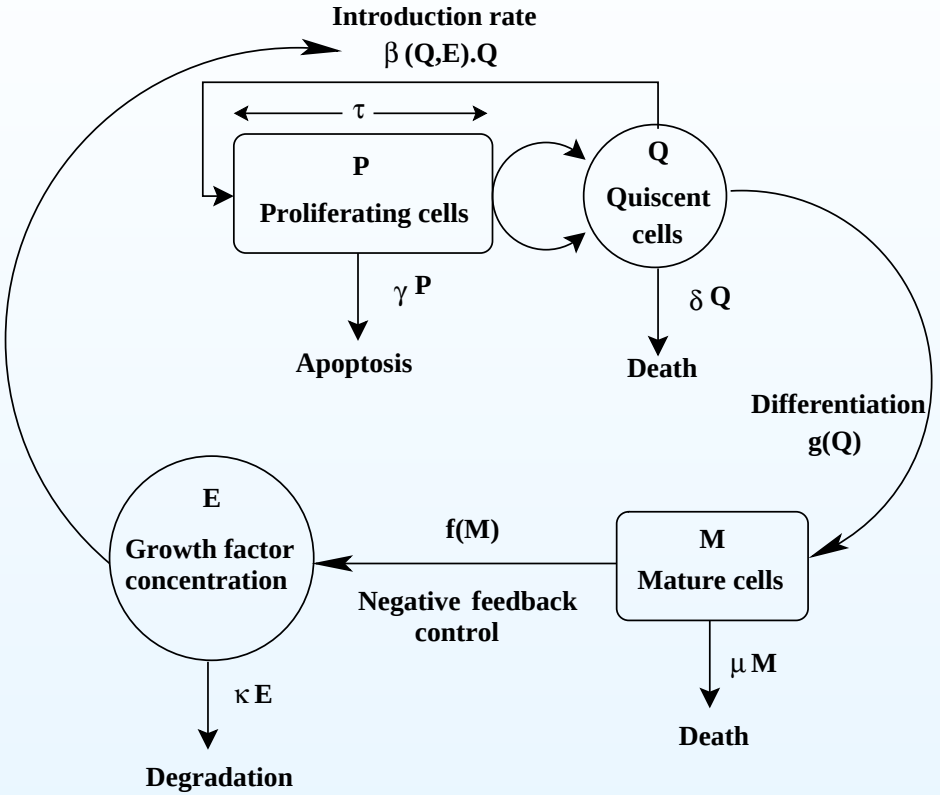
Development of software tools for real-time data-driven simulation of haematopoiesis will give possibility to

- understand better the blood cells production and regulation processes;
- design nature experiments for validation of hypotheses;
- predict the effect of various treatment options for patients with specific hematological diseases;

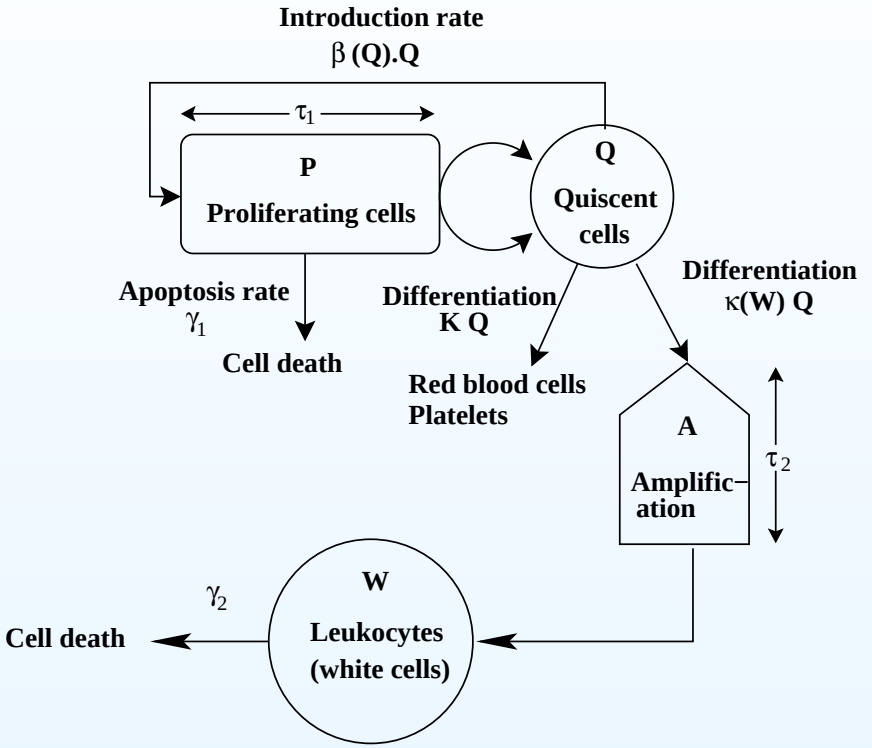
Current stage:

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.

Motivation

Two leukopoiesis models
- Involved data
- GFM system of DDEs
- LM system of DDEs

Solution methods

Clinical data

Numerical tests

Concluding remarks

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

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

Motivation
Two leukopoiesis models
- Involved data
- GFM system of DDEs
- LM system of DDEs

Solution methods
Clinical data
Numerical tests
Concluding remarks

LM system of DDEs

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

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

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

Numerical tests

Model parameters

Motivation

Two leukopoiesis models

Solution methods

Clinical data

Numerical tests

● Model parameters

Concluding remarks

Concluding remarks

Motivation
Two leukopoiesis models
Solution methods
Clinical data
Numerical tests
Concluding remarks

Concluding remarks

- What is done by now
- Open issues
- Further steps

Acknowledgements:
Thanks to L. Gartcheva, M. Guenova
This work is supported in part by the Bulgarian NSF grants DO 02-214 and DO 02-147

Thank you for your attention!