Towards Real-Time Data-Driven Computer Simulation of Blood Cells Production and Regulation

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Motivation

Blood cells production and regulation

Haematopoietic pluripotent stem cells (HSCs) in bone marrow give birth to the three blood cell types.

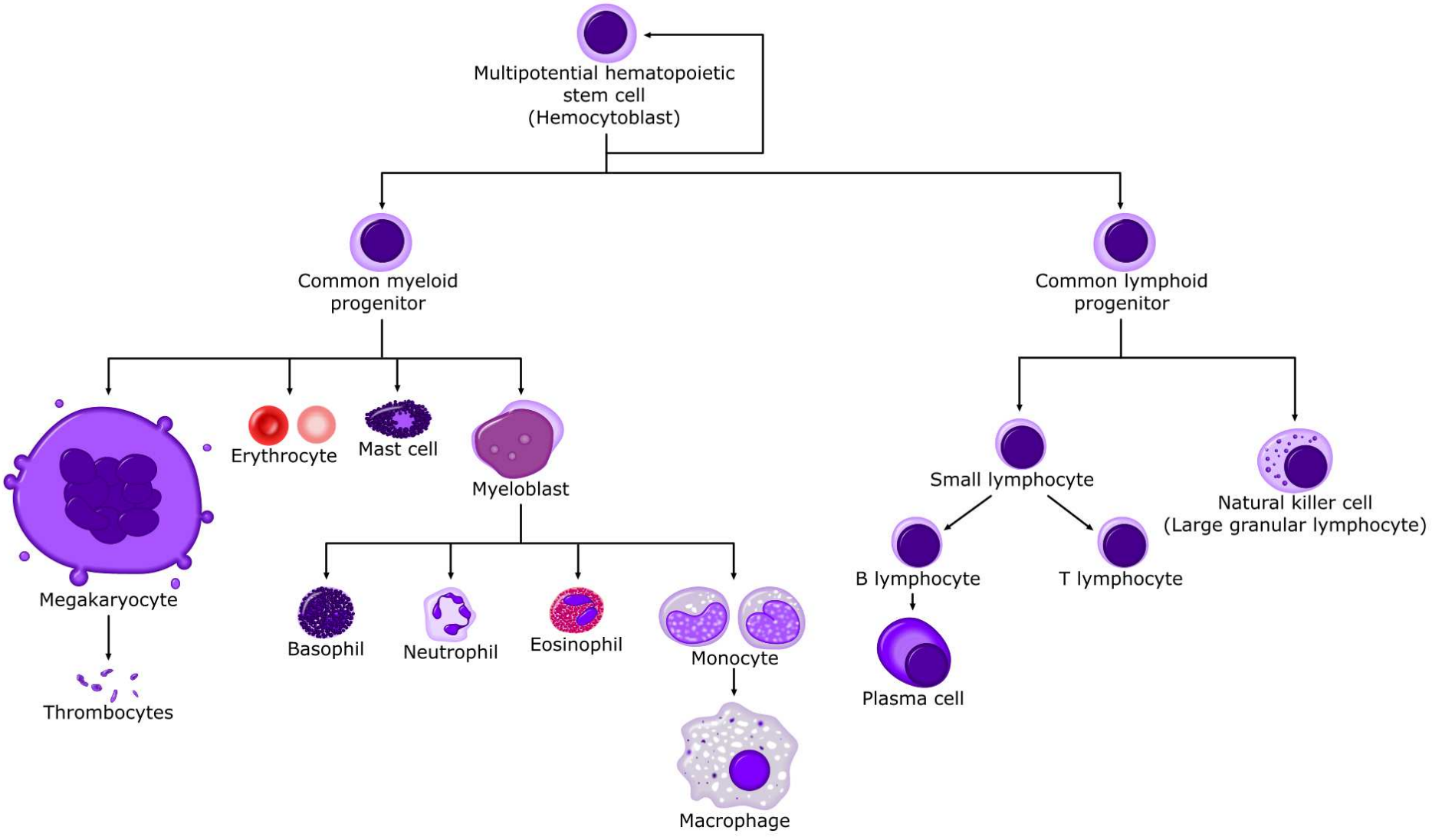
Growth factors or Colony Stimulating Factors (CSF) – specific proteins that stimulate the production and maturation of each blood cell type.

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

Various hematological diseases (including leukemia) are characterized by abnormal production of particular blood cells (matured or blast).

Differentiation stages in haematopoiesis



Need for computer simulation

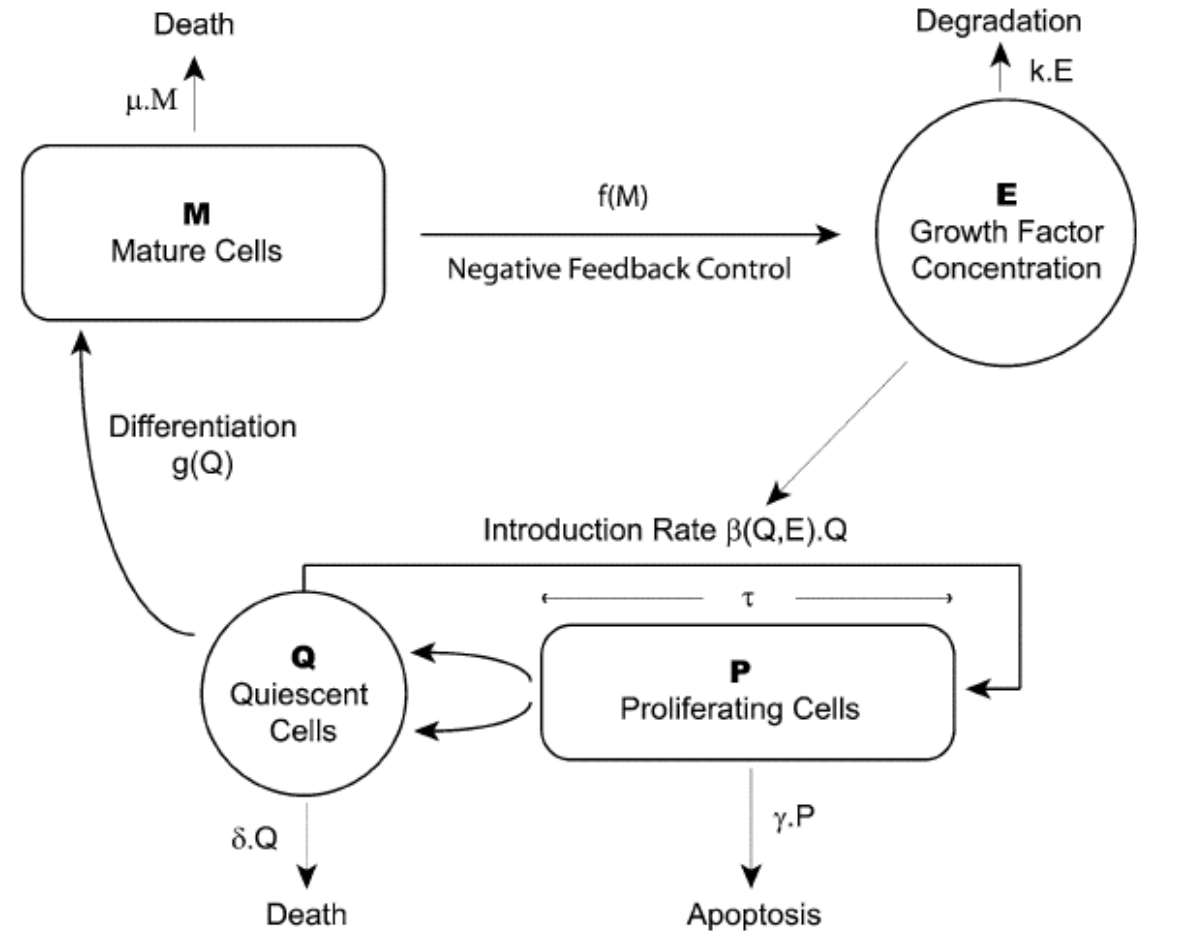
The approach ”trial-error” is not recommended for dealing with questions related to understanding and predicting of human physiological processes in health and disease.

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

- understand better the 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;

Delay differential equations

Mathematical model



[ACR] 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.

System of ODEs with delay

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

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

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

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

Solution method

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.

DOPRI5 – Dormand and Prince method of order 5 for non-stiff problems.
RADAU5 – RK method based on Radau quadrature formula for stiff problems.
RETARD and RADAR5 are their modifications for DDEs

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.

Computer simulation

Computer simulation

Current step: tuning of software parameters with the help of test data from paper [ACR] and comparison of the obtained results.

Software we used: RETARD, a modification of DOPRI5 in such a way that after every successfull step of integration the coefficients of the continuous solution are written into memory. It provides a possibility to match given points of discontinuity exactly, which improves precision and computation time. (http://www.unige.ch/∼hairer/software.html)

Software used in [ACR]: dde23, a Matlab solver for DDEs written by Shampine and Thompson (http://www.radford.edu/∼thompson/webddes/)

Model parameters for erythropoiesis

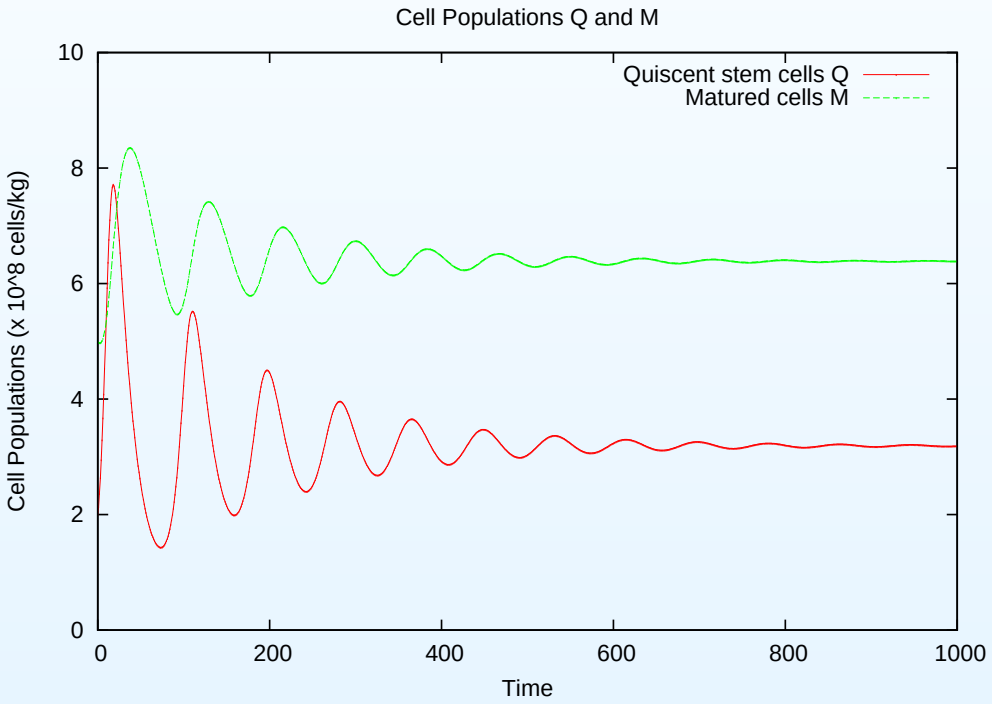
$$\beta(E) = \beta_0 \frac{E}{1+E}, \quad \beta_0 > 0 \qquad \tau \in [0, \tau_{max})$$

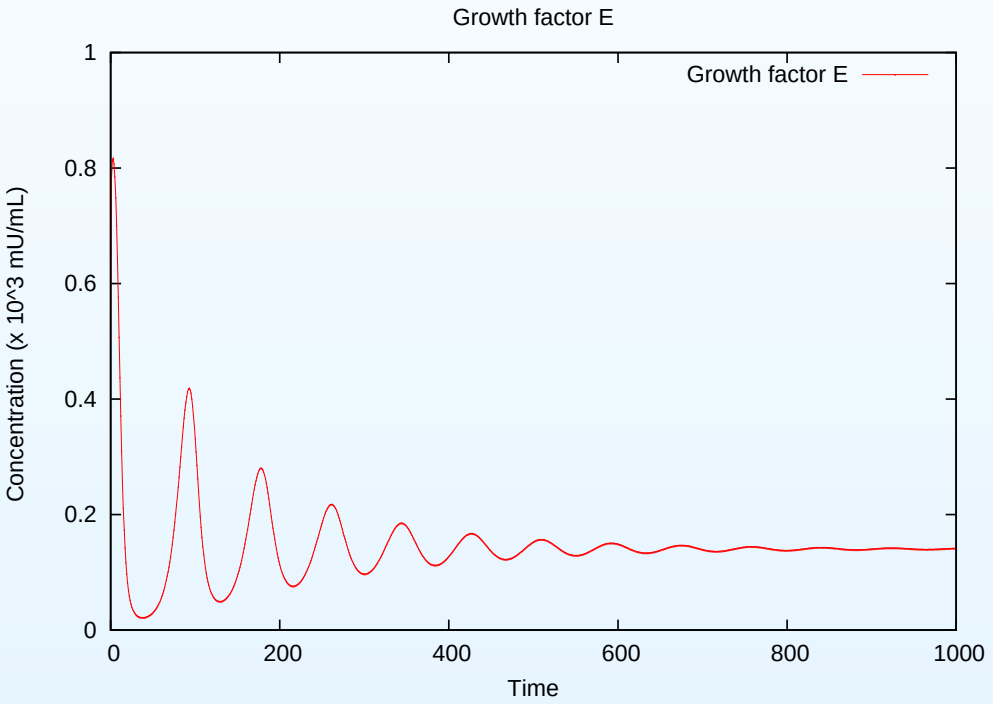
$$g(Q) = GQ, \quad G > 0 \qquad \tau_{max} = 2.99\, days$$

$$f(M) = \frac{a}{1+KM^r}, \quad a, K > 0, r > 0$$

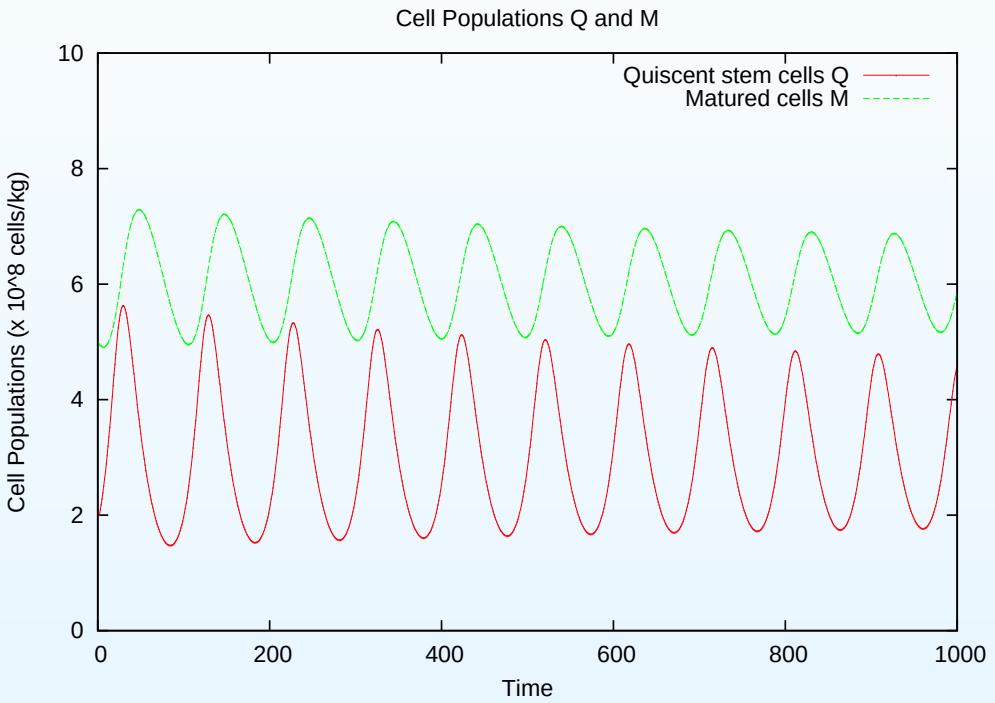
Parameter	Value in [ACR]	Range (day^{-1})
δ	0.01 day^{-1}	0 – 0.09
G	0.04 day^{-1}	0 – 0.09
β_0	0.5 day^{-1}	0.08 – 2.24
γ	0.2 day^{-1}	0 – 0.9
μ	0.02 day^{-1}	0.001 – 0.1
k	2.8 day^{-1}	—
a	6570	—
K	0.0382	—
r	7	—

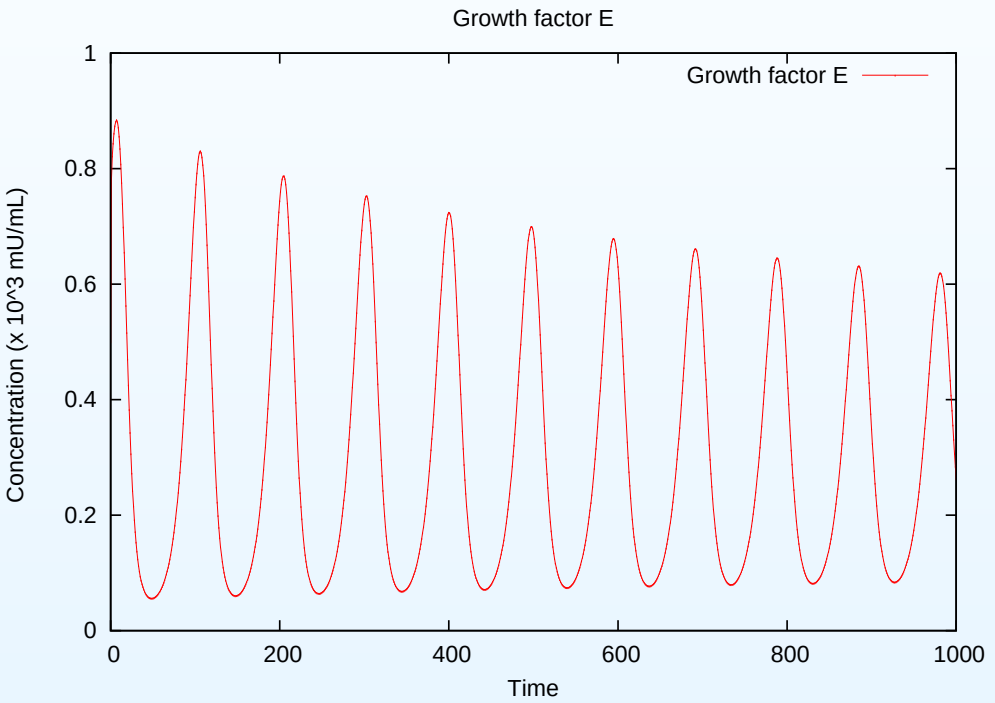
Solution for $\tau = 0.5$





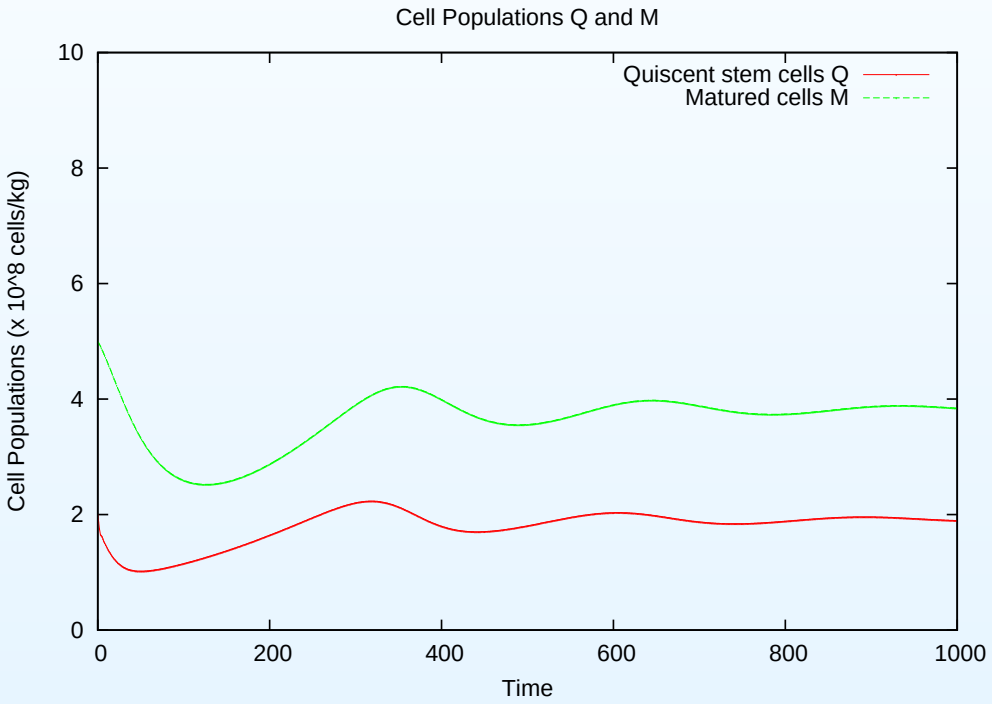
Solution for $\tau = 1.4$

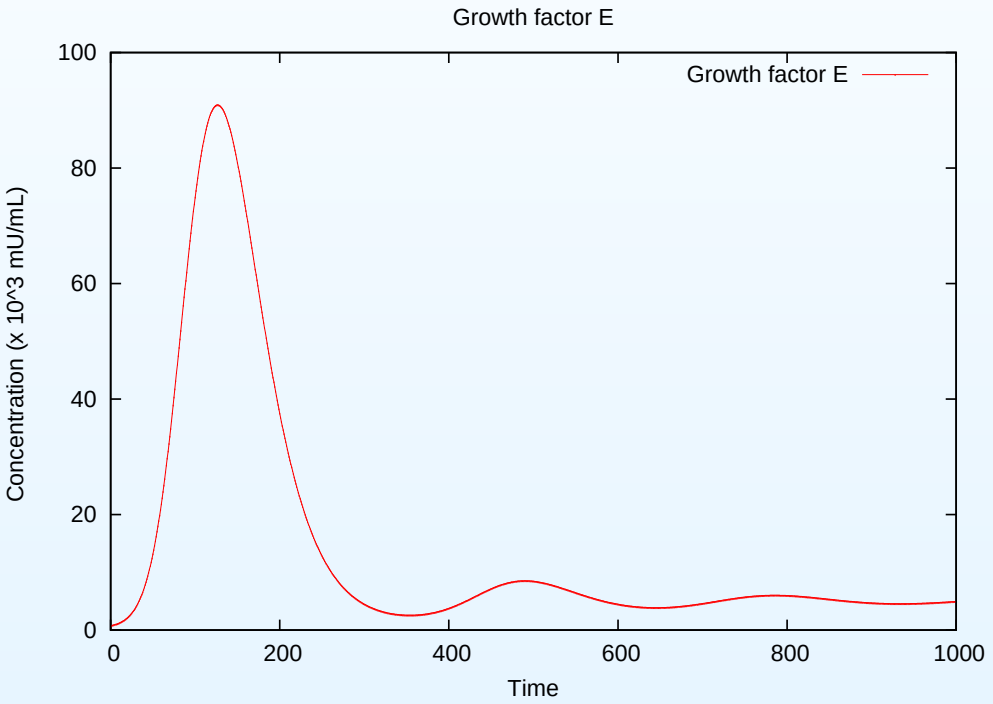




Periodic solutions are due to the Hopf bifurcation for this value of τ.

Solution for $\tau = 2.9$





Further steps

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Calibration of the model and software tools for:

- leukocytes (each of the 7 types) and thrombocytes on the base of model data, e.g. taken from papers and experiments *in vitro*;
- each of the three blood cell types on the base of real data from clinical practice, i.e. on the base of patient specific data taken *in vivo*.

These include identification of parameters and sensitivity analysis as intermediate steps.

Thank you for your attention!