Comparative Analysis of Solution Methods for Delay Differential Equations in Haematology

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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.

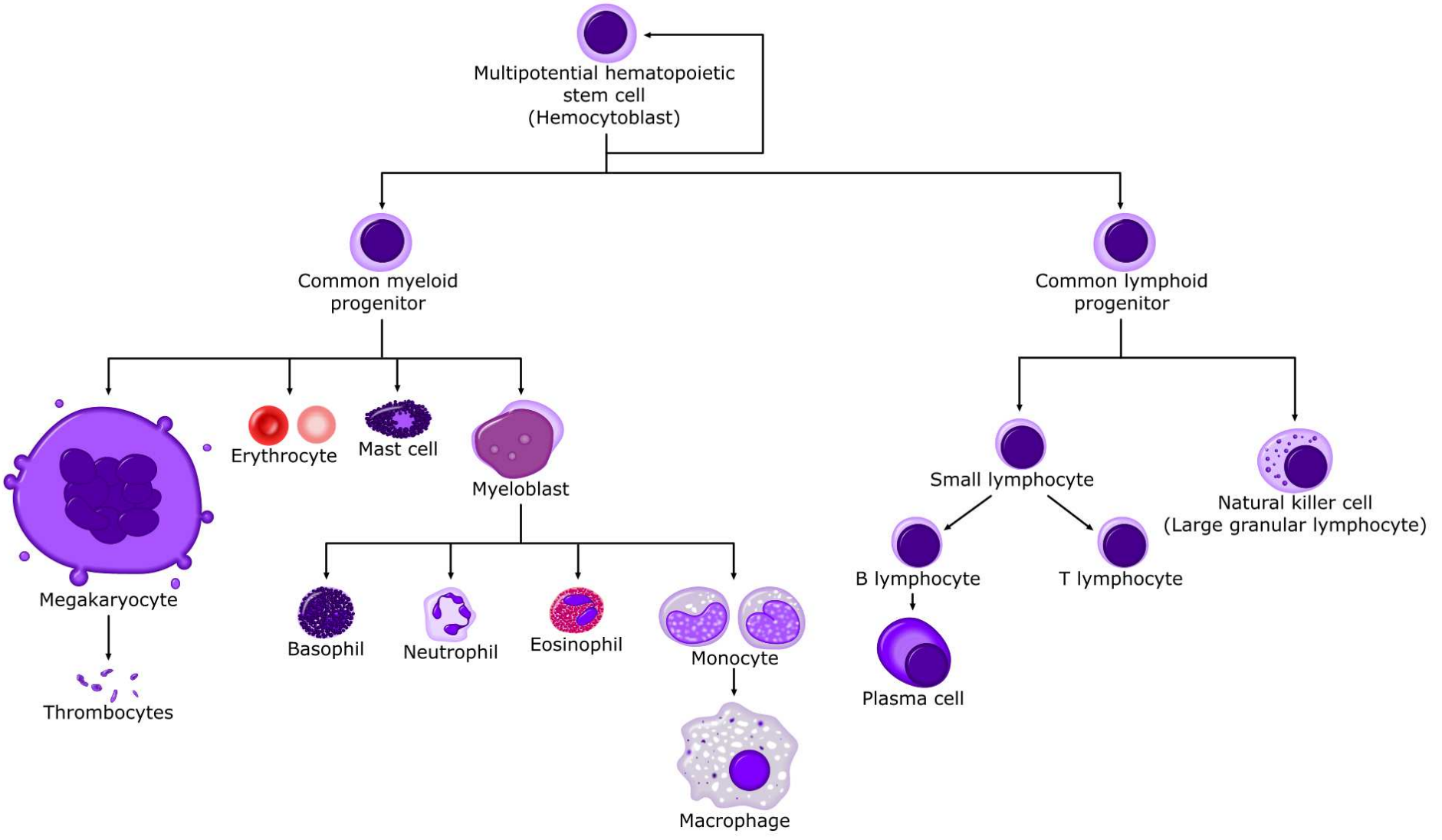
Growth factors or Colony Stimulating Factors (CSF) – specific proteins that stimulate the production and maturation of each blood cell type.

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.

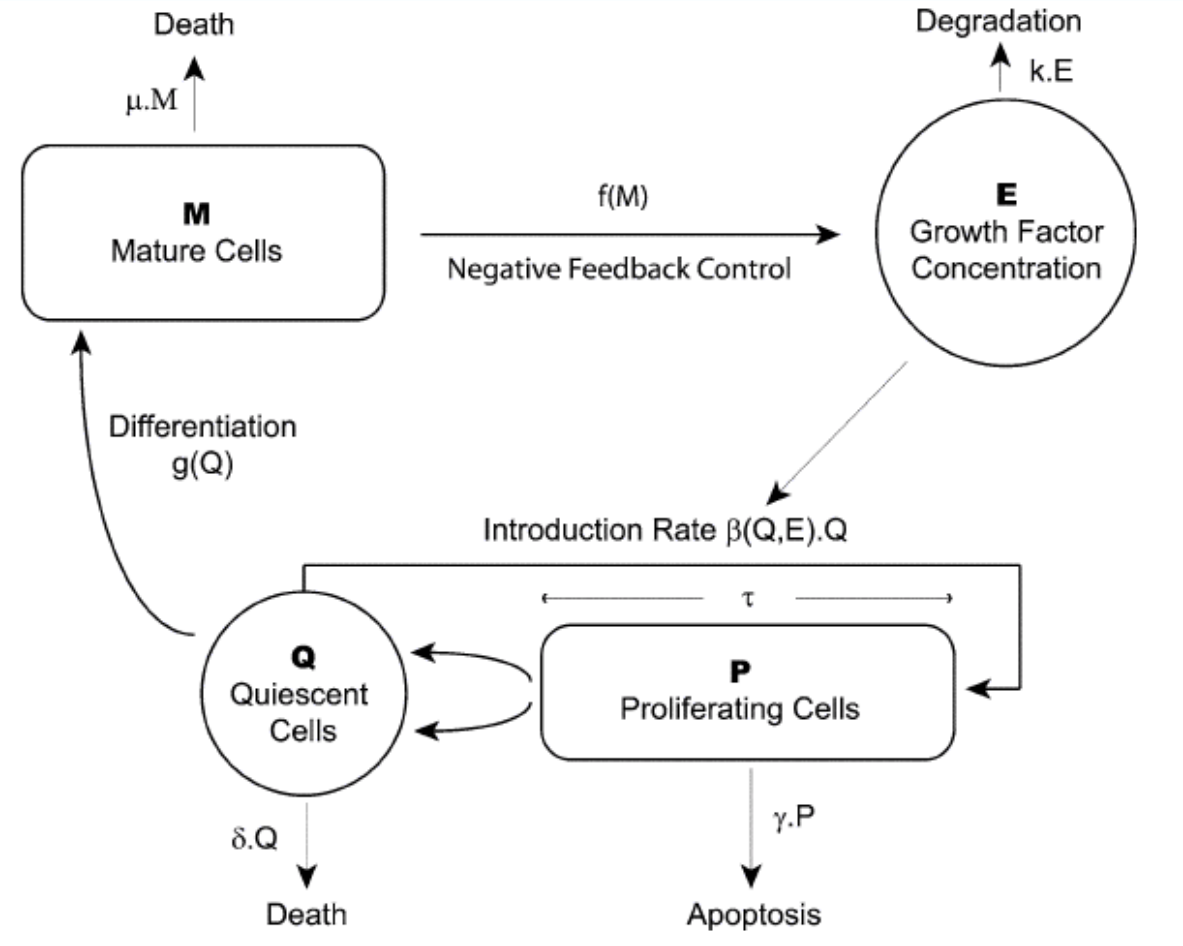
Development of software tools for real-time data-driven simulation of haematopoiesis will give possibility to

- 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;

Current step: comparison of some already existing solvers

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:

$$0 < \delta + g'(0) < \beta\left(0, \frac{f(0)}{k}\right) \text{ and}$$

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

Solution methods

What is XPPAUT?

"A tool for simulating, animating and analyzing dynamical systems." (G. B. Ermentrout)

Some of the features:

- brings together useful algorithms for solving various types of equations, including DDEs;
- contains the code for bifurcation program AUTO;
- provides means for visualisation of the solution;
- portable on various systems and its building requires the standard C compiler and Xlib.

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`

The methods

	Expl.	Impl.	FS	AS	Stiff
Runge Kutta (RK)	+		+		
Adams (AD)	+		+		
Dormand-Prince 5 (DP5)	+			+	
Backward Euler (BE)		+	+		
CVODE (CV)		+		+	+
Rosenbrock (RB2)		+		+	+

CVODE is based on C-version of LSODE, written by S. D. Cohen and A.C. Hindmarsh, LLNL.
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)

Numerical tests

Model parameters for erythropoiesis

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

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

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

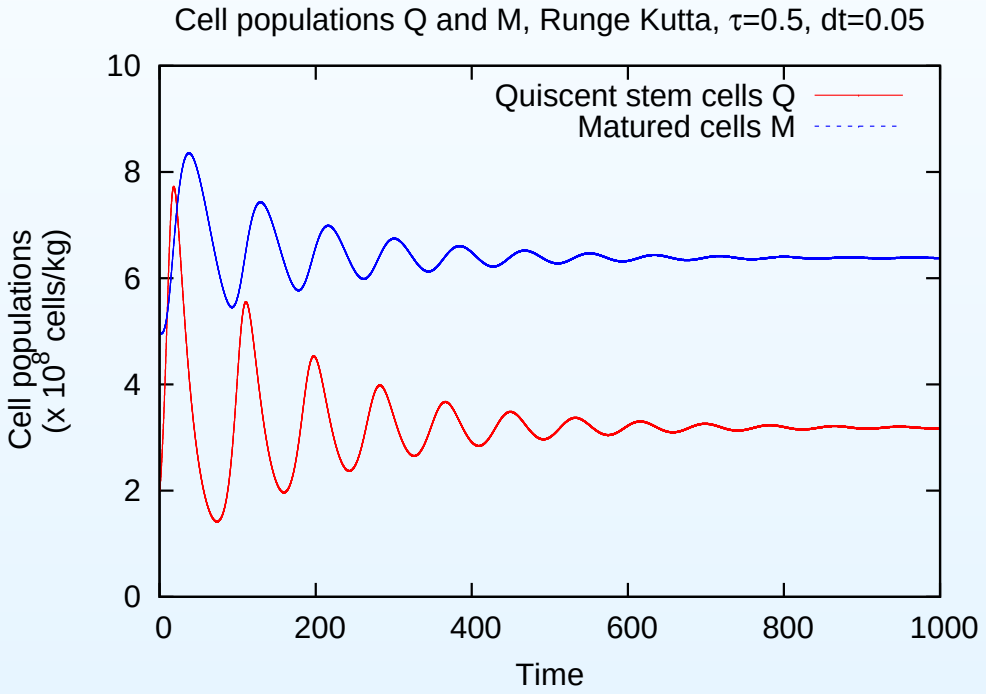
Parameter	Value in [ACR]	Range (day^{-1})
δ	0.01 day^{-1}	0 – 0.09
G	0.04 day^{-1}	0 – 0.09
β_0	0.5 day^{-1}	0.08 – 2.24
γ	0.2 day^{-1}	0 – 0.9
μ	0.02 day^{-1}	0.001 – 0.1
k	2.8 day^{-1}	—
a	6570	—
K	0.0382	—
r	7	—

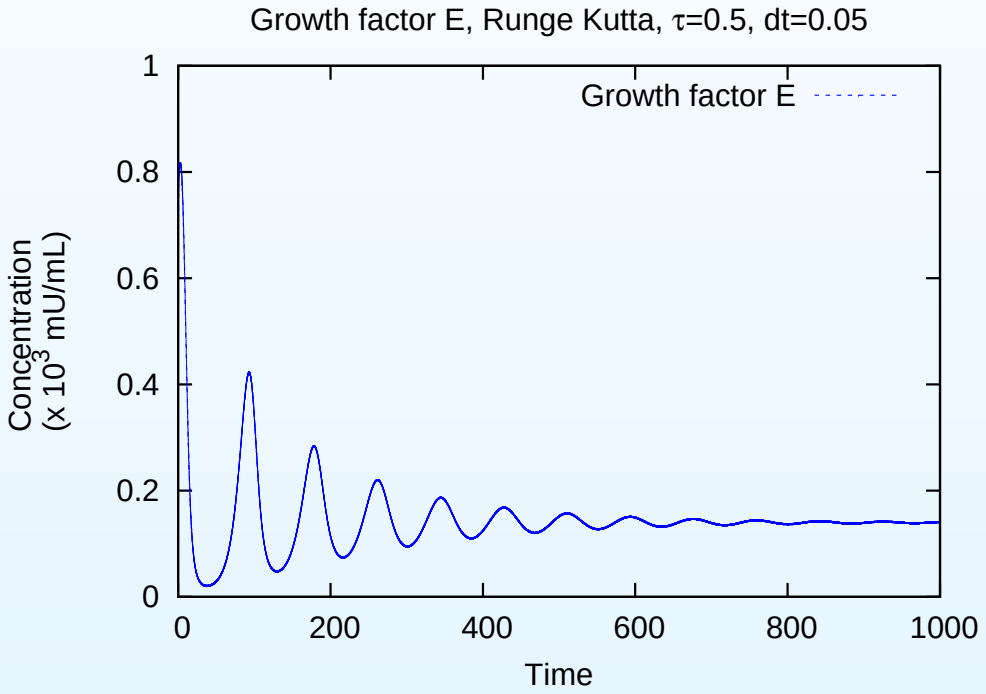
Computing time

	$\tau = 0.5$			$\tau = 1.4$			$\tau = 2.9$		
Method $\backslash dt$	0.2	0.1	0.05	0.2	0.1	0.05	0.2	0.1	0.05
RK	0.05	0.09	0.2	0.04	0.09	0.18	0.04	0.1	0.19
AD	0.02	0.04	0.1	0.03	0.05	0.1	0.02	0.05	0.1
BE	0.13	0.25	0.46	0.15	0.30	0.56	0.15	0.26	0.49
DP5 $(1.e-6)$	0.09	0.17	0.34	0.08	0.18	0.35	0.09	0.17	0.34
DP5 $(1.e-9)$	0.12	0.19	0.35	0.17	0.25	0.34	0.13	0.18	0.34
CV $(1.e-6)$	0.12	0.1	0.07	0.28	0.29	0.14	0.07	0.03	0.02
CV $(1.e-9)$	0.62	1.0	1.66	0.75	1.28	1.96	0.58	0.67	0.96
RB2 $(1.e-6)$	0.17	0.34	0.65	0.17	0.32	0.65	0.17	0.32	0.64
RB2 $(1.e-9)$	0.49	0.57	0.8	1.17	1.18	1.27	0.59	0.53	0.78

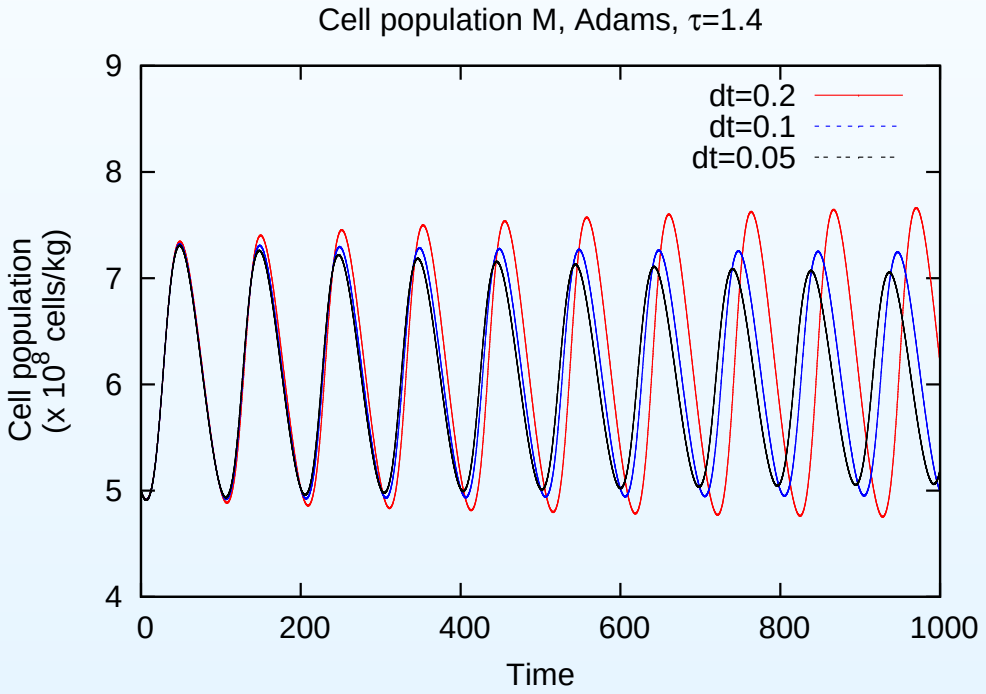
dt – step size for the fixed step integrators and output step for the others.

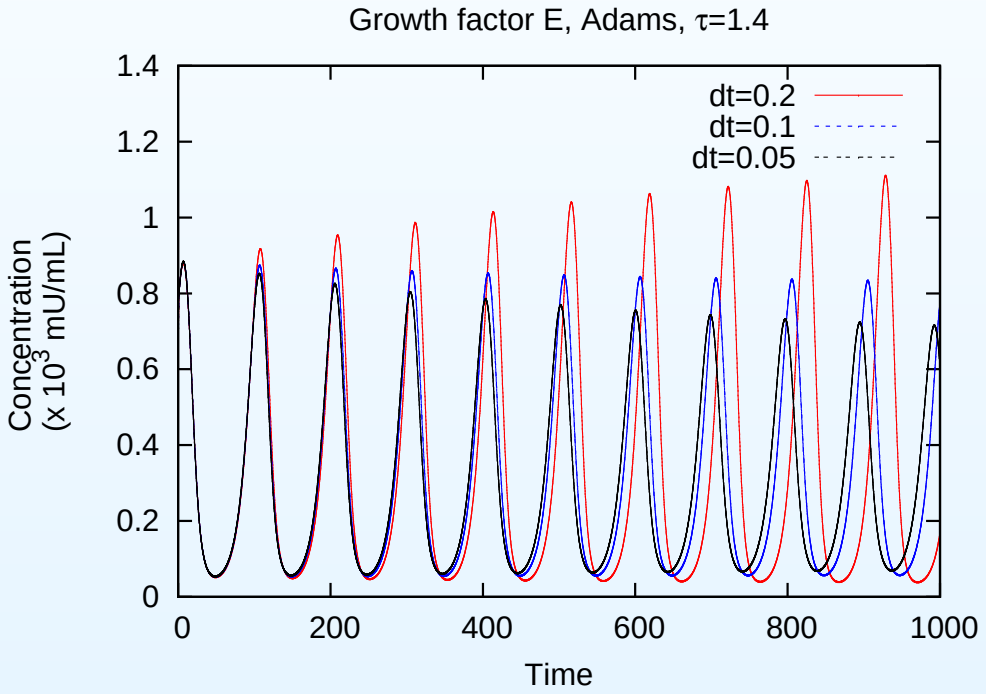
Solution with Runge Kutta for $\tau = 0.5$



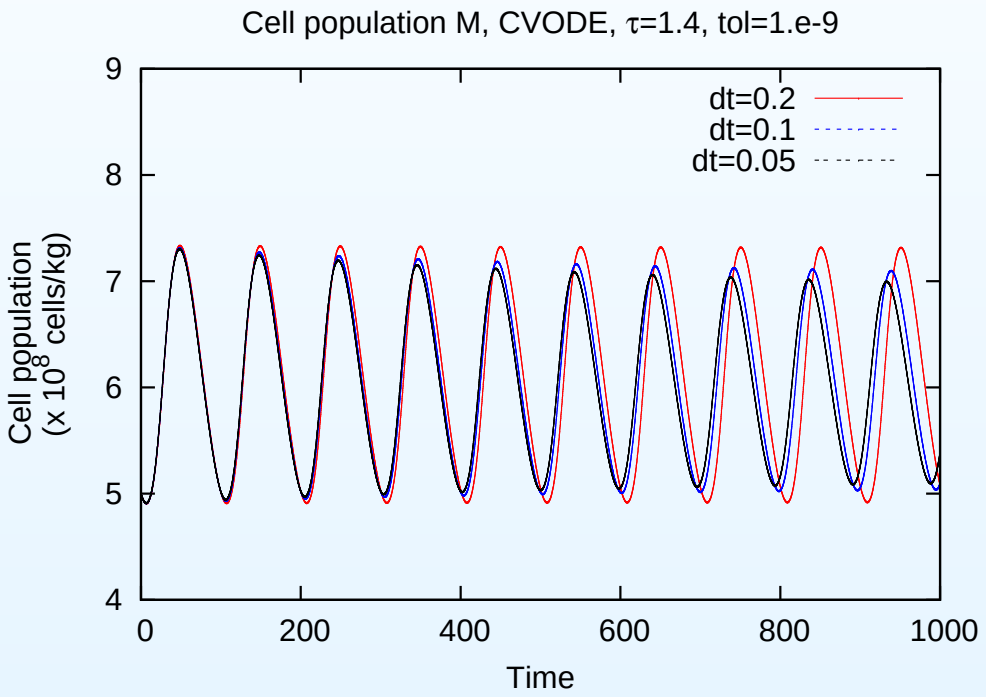


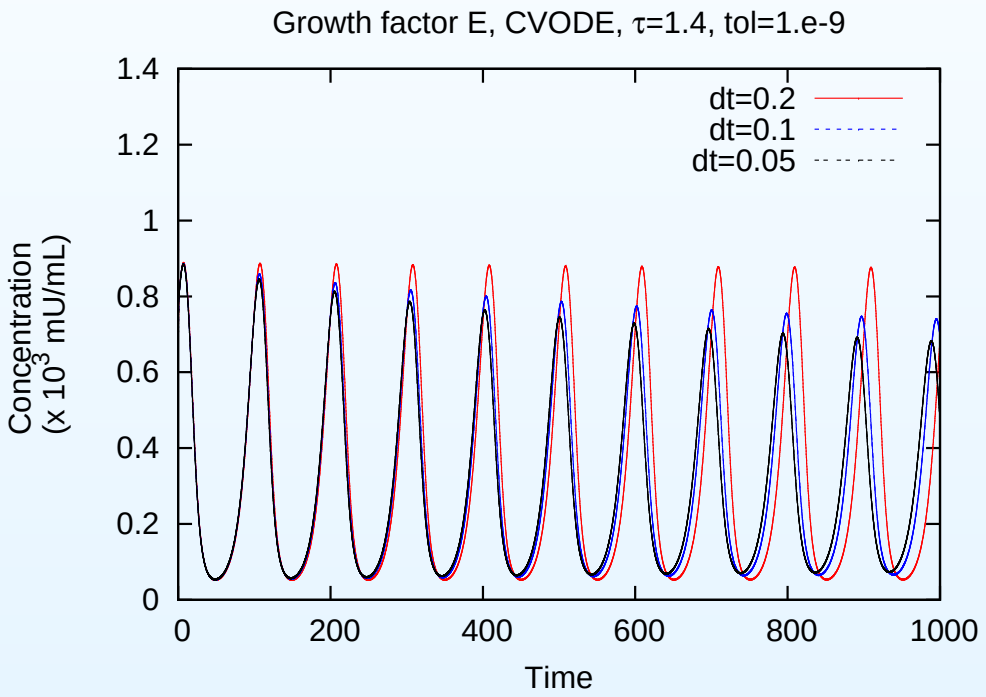
Solution with Adams for $\tau = 1.4$



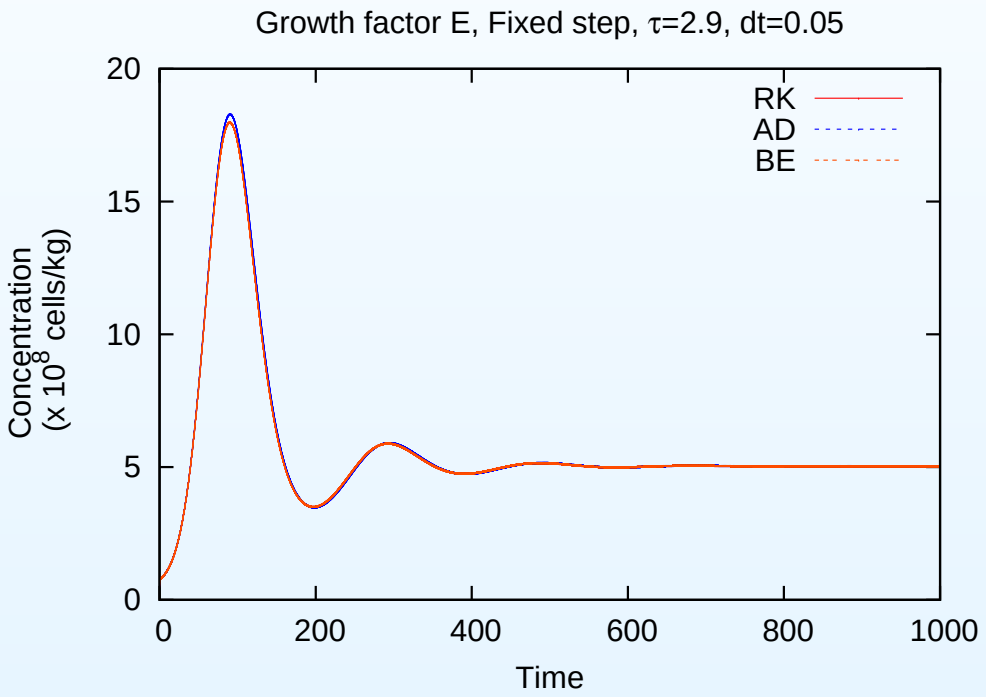


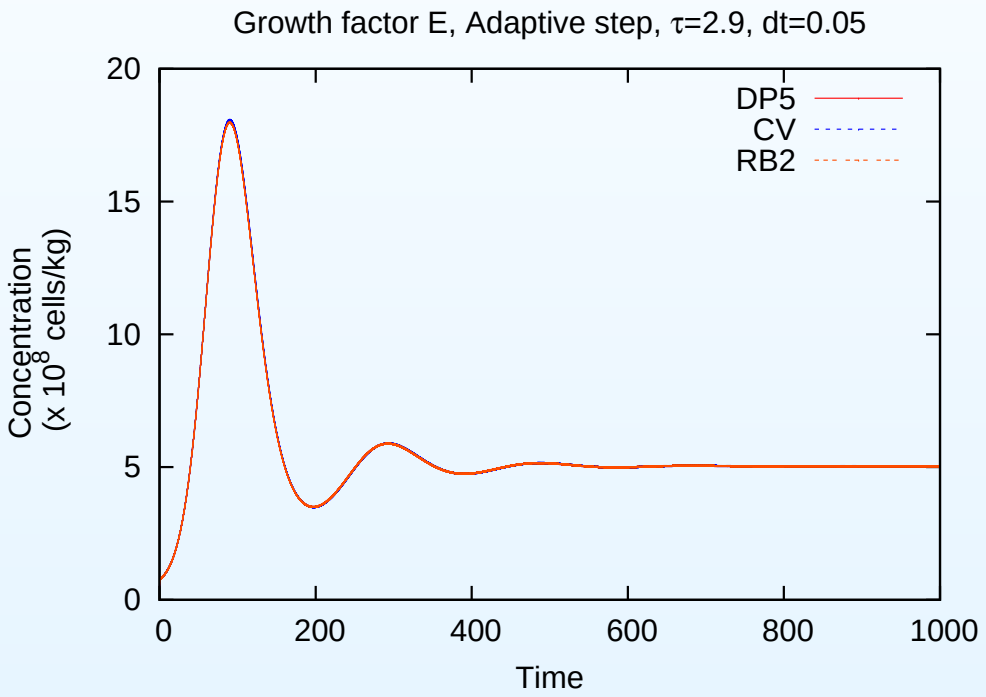
Solution with CVODE for $\tau = 1.4, tol = 1.e-9$



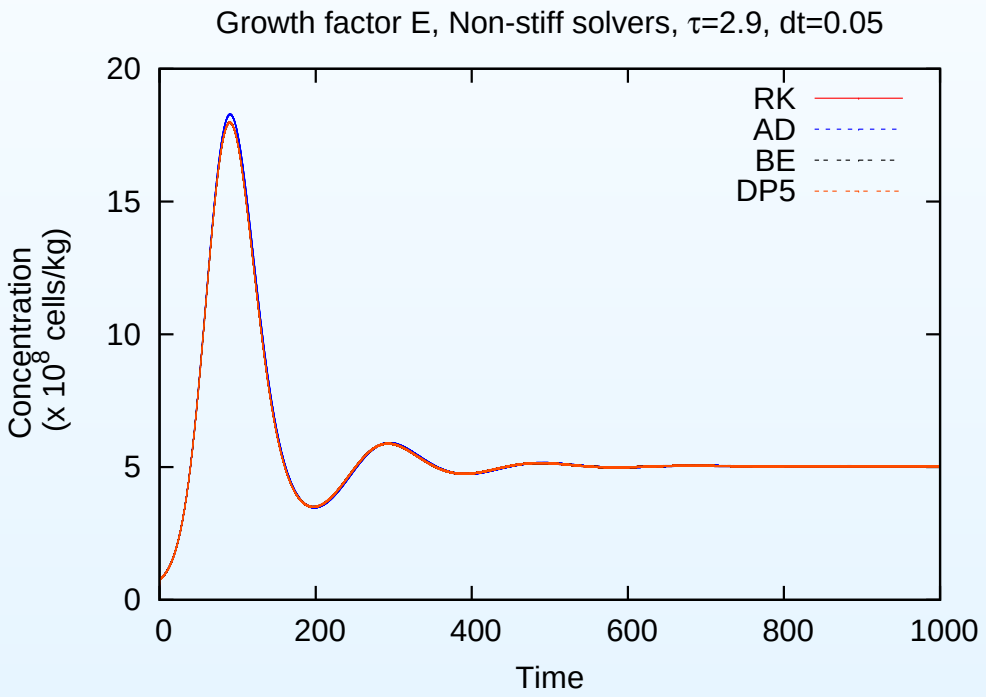


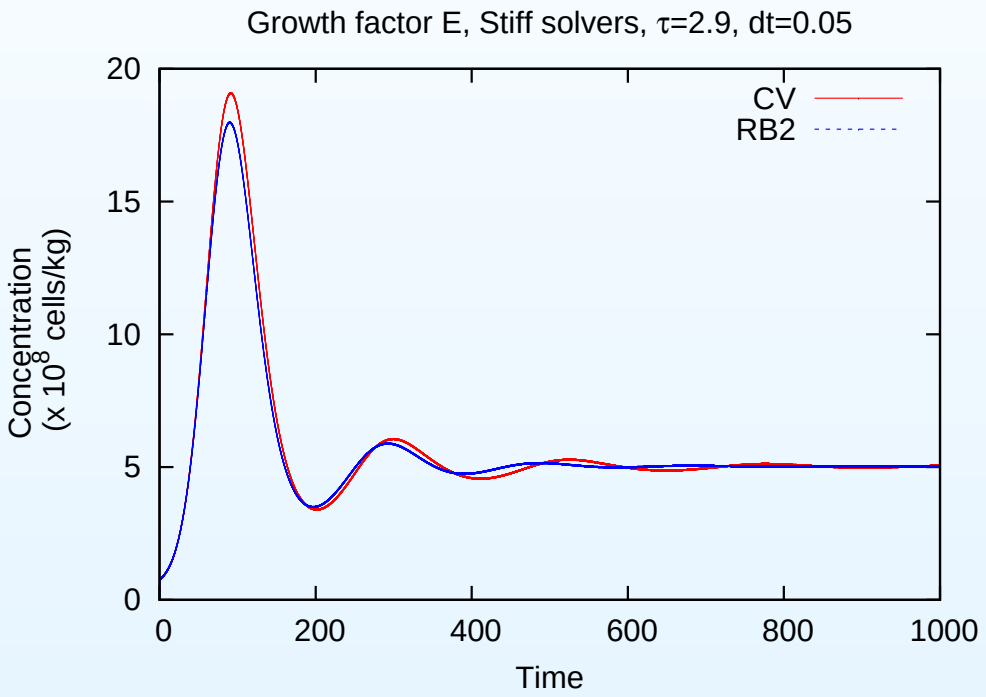
Comparison fixed/adaptive step methods for $\tau = 2.9$





Comparison nonstiff/stiff solvers 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!