How does clinical data fit into two leukopoiesis models?

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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.

<table>
<thead>
<tr>
<th>Blood cell type</th>
<th>Function</th>
<th>Growth factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte</td>
<td>Transport oxygen to tissues</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>Leukocyte</td>
<td>Fight infections</td>
<td>G-CSF, M-CSF, GM-CSF, Interleukins</td>
</tr>
<tr>
<td>Thrombocyte</td>
<td>Control bleeding</td>
<td>Thrombopoietin</td>
</tr>
</tbody>
</table>

**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 their therapy:

**TBI:** Total body irradiation (TBI) and chemotherapy – 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) self-renew and differentiate to regenerate the patient’s blood system.
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 stage:
Two leukopoiesis models
Involved data

Growth factors model (GFM)

Leukopoiesis model (LM)


GFM system of DDEs

\[
\begin{align*}
\frac{dQ}{dt} &= -\delta Q(t) - g(Q(t)) - \beta(Q(t), E(t)) Q(t) \\
&\quad + 2e^{-\gamma \tau} \beta(Q(t-\tau), E(t-\tau)) Q(t-\tau) \\
\frac{dM}{dt} &= -\mu M(t) + g(Q(t)) \\
\frac{dE}{dt} &= -k E(t) + f(M(t))
\end{align*}
\]

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

Delay \(\tau\) 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:

\[0 < \delta + g'(0) < \beta \left(0, \frac{f(0)}{k}\right)\] 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**

\[
\begin{align*}
\frac{dQ}{dt} &= -[K + k(W(t)) + \beta(Q(t))]Q(t) \\
&\quad + 2e^{-\gamma_1 \tau_1} \beta(Q(t - \tau_1))Q(t - \tau_1) \\
\frac{dW}{dt} &= -\gamma_2 W(t) + Ak(W(t - \tau_2))Q(t - \tau_2)
\end{align*}
\]

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

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:

<table>
<thead>
<tr>
<th>Expl.</th>
<th>Impl.</th>
<th>FS</th>
<th>AS</th>
<th>Stiff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runge Kutta (RK)</td>
<td>+</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dormand-Prince 5 (DP5)</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Rosenbrock (RB2)</td>
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</tbody>
</table>

*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.

Clinical data
Numerical tests
Model parameters
Concluding remarks
Concluding remarks

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

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Thanks to L. Gartcheva, M. Guenova
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