Numerical Methods in Cancer Models

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Plan

- What is cancer?
- Delayed differential equations
- Agent-based models
- PDEs
Delayed Differential Equations in Cancer Models
Analysis & Numerical Methods

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Montréal, May 2013
Outline

1 Motivation
   - Cancer Immunology
   - Stem Cell Transplantation

2 Properties
   - Zero Crossings
   - Time Scales

3 Numerical Methods

4 Stability in the delays space
Outline

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What is leukemia?

**Normal cells:** stem cells turn into mature cells

**Leukemia:** A malignant transformation of a stem cell or a progenitor cell
- Myeloid or Lymphocytic
- Acute or Chronic
CML

3 phases
- **Chronic**: uncontrolled proliferation
- **Accelerated**
- **Acute**: Uncontrolled proliferations. Cells do not mature

Philadelphia chromosome
- Translocation (9;22)
- Oncogenic BCR-ABL gene fusion
- The ABL gene expresses a tyrosine kinase. Growth mechanisms
- Easy to diagnose
- Drug targeting this genetic defect (a tyrosine kinase inhibitor)
Treating leukemia

- Chemotherapy
- Bone Marrow or Stem Cell transplant
  - Chemo + radiotherapy + transplantation
- Imatinib (Gleevec)
  - Molecular targeted therapy - suppresses the corrupted control system
  - $32K-$98K/year
Problems with existing therapies

- **Remission vs. Cure:** Can CML be cured?
  - Yes! but only with a bone marrow (or stem cell) transplant
  - Requires a (matching) donor
  - A risky procedure (+ unpredictable side effects)

- **Imatinib?** Does not cure the disease: stopping it causes a relapse

- **New Medical Data:** There is an anti-leukemia immune response (Lee lab)

- The **strength** and **dynamics** of the specific anti-leukemia immune response can be measured
  - Number of cells
  - Activity (count signaling molecules)
A different immune response for each patient. However:

- At the beginning of the treatment: no immune response
- Peak: around 6-12 months (after starting the drug treatment)
- Later: waning immune response

**Question:**

What is the relation between the dynamics of the cancer, the drug, and the immune response?
Ingredients:

- Leukemia cells: stem cells, , fully functional cells
- Mutations, Drug (Imatinib), Anti leukemia immune response

Kim, Lee, Levy: PLoS Computational Biology, ’08
Michor et al. (Nature 05). Cronkite and Vincent (69), Rubinow (69), Rubinow & Lebowitz (75), Fokas, Keller, and Clarkson (91), Mackey et al (99,...), Neiman (00), Moore & Li (04), Michor et al (05), Komarova & Woodarz (05).
Motivation
Properties
Stability in the delays space
Numerical methods

The immune response to leukemia
Stem cell transplantation

Michor’s model + immune response

Cells without mutations:

\[
\begin{align*}
\dot{y}_0 &= [r_y(1-u) - d_0]y_0 - q_c p(C, T)y_0, \\
\dot{y}_1 &= a_y y_0 - d_1 y_1 - q_c p(C, T)y_1, \\
\dot{y}_2 &= b_y y_1 - d_2 y_2 - q_c p(C, T)y_2, \\
\dot{y}_3 &= c_y y_2 - d_3 y_3 - q_c p(C, T)y_3.
\end{align*}
\]

Anti-cancer T cells:

\[
\begin{align*}
\dot{T} &= s_t - d_t T - p(C, T)C + 2^n q_T p(C_{nT}, T_{nT})C_{nT}, \\
p(C, T) &= p_0 e^{-c_n C} kT, \\
C &= \sum (y_i + z_i), \\
C_{nT} &= C(t - nT).
\end{align*}
\]
Accounting for the immune response

Motivation
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No immune response
Leukemia
T cells

Cell Concentration (k/µL)
0
0.01
0.02
0.03
0.04
0.05
0.06

Time (months)
0 10 20 30 40 50

0

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Stopping imatinib (simulation)

Cell Concentration (k/µL) vs Time (months)

- Leukemia
- \(1000 \times T\) cell concentration
- Imatinib removed at month 12

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Cancer vaccines: a mathematical design

Inactivated leukemia cells

\[ \dot{V} = -d_V V - q_c p(C, T) V + s_V(t) \]

Anti-cancer T cells

\[ \dot{T} = s_t - d_T T - p(C, T)(C + V) + 2^n p(C_n T_n)(q_T C_{nT} + V_{nT}) \]
Model populations

- **Host Cells**
  - Cancer
  - Anti-donor T cells
  - General blood cells

- **Donor cells**
  - Anti-cancer T cells (cancer-specific)
  - Anti-host T cells
  - General blood cells
Everything takes time
Anti-Cancer T Cells

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T \text{C}/T \text{C} Interaction

Ignore
React
Proliferate
Reload
Die or Become anergic

T \text{C}/C Interaction

Survive
Perish

\sigma

\kappa\text{T}_C

T \text{C}

\nu

\rho

q_1^{T\text{C}/C}

q_2^{T\text{C}/C}

q_3^{T\text{C}/C}

p_1^{T\text{C}/C}

p_2^{T\text{C}/C}

p_1^{T\text{D}/T\text{C}}

p_2^{T\text{D}/T\text{C}}

k\text{T}_\text{D}\text{T}_\text{C}

k\text{T}_\text{C}

\nu

\sigma

\tau

\nu

\sigma

\tau

\nu

\sigma

\tau

\nu

\sigma

\tau

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Antithose T Cells

- **Motivation**
  - Immunological response to leukemia
  - Stem cell transplantation

- **Properties**
  - Numerical methods
  - Stability in the delays space

- **Stem Cell Transplantation**

- **Interaction**
  - Anti-Host T Cells
  - $\rho_{H/C}$ Interaction
  - $p_{1H/C}^T$
  - $p_{2H/C}^T$
  - $k_{CT_H}$
  - Proliferate
  - $n\tau$
  - React
  - Reload
  - $\nu$
  - $q_{1H/C}^T$
  - $q_{2H/C}^T$
  - $q_{3H/C}^T$

- **Death**
  - $p_{1H}^T$
  - $p_{2H}^T$
  - $d_{TH}$

- **Survive**
  - $p_{2D/T_H}^T$
  - $S_{2D}$
  - Proliferate
  - $n\tau$
  - React
  - Reload
  - $\nu$
  - $q_{1H/T_D}^T$
  - $q_{2H/T_D}^T$

- **Perish**
  - $p_{1D/T_H}^T$
  - $p_{2D/T_H}^T$

- **Die or become anergic**
  - $q_{3H/T_D}^T$

- **No flow**
  - $q_{3H/T_D}^T = 0$

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Anti-Donor T Cells

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General Donor and Host Blood Cells

Stem Cells

\[ D \]

\[ S_D \]

\[ p_{1/D} k D T_D \]

\[ d_D \]

\[ T_D/D \text{ Interaction} \]

\[ \rho \]

\[ \text{Death} \]

\[ \text{Perish} \]

Stem Cells

\[ H \]

\[ S_H \]

\[ p_{1/H} k H T_H \]

\[ d_H \]

\[ T_H/H \text{ Interaction} \]

\[ \rho \]

\[ \text{Death} \]

\[ \text{Perish} \]
Cancer Cells

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C/T\_H Interaction

Perish

p_{1/T_H}^{C/T_H}k_{T_H}C

r_C

logistic growth

C/T\_c Interaction

Perish

p_{1/T_c}^{C/T_c}k_{T_c}C

Death rate is included in net logistic growth term

Death

C/T Interaction

\( \rho \)

\( \rho \)
\[
\frac{d T_H}{d t} = -d_{T_H} T_H - kCT_H - kT_D T_H - kHT_H \\
+ p_{2}^{T_H/C} kC(t - \sigma) T_H(t - \sigma) + p_{2}^{T_D/T_H} p_{2}^{T_H/T_D} kT_D(t - \sigma) T_H(t - \sigma) \\
+ p_{2}^{T_H/H} kH(t - \sigma) T_H(t - \sigma) \\
+ 2^n p_{1}^{T_H/C} q_{1}^{T_H/C} kC(t - \rho - n\tau) T_H(t - \rho - n\tau) \\
+ 2^n p_{1}^{T_H/H} q_{1}^{T_H/H} kH(t - \rho - n\tau) T_H(t - \rho - n\tau) \\
+ 2^n p_{2}^{T_D/T_H} p_{1}^{T_H/T_D} q_{1}^{T_H/T_D} kT_D(t - \rho - n\tau) T_H(t - \rho - n\tau) \\
+ p_{1}^{T_H/C} q_{2}^{T_H/C} kC(t - \rho - \nu) T_H(t - \rho - \nu) \\
+ p_{1}^{T_H/H} q_{2}^{T_H/H} kH(t - \rho - \nu) T_H(t - \rho - \nu) \\
+ p_{2}^{T_D/T_H} p_{1}^{T_H/T_D} q_{2}^{T_H/T_D} kT_D(t - \rho - \nu) T_H(t - \rho - \nu).
\]
Time Delays

- Time for reactive T cell-antigen interaction = 5min
- Time for unreactive interactions = 1min
- Time for cell division = 0.5-1.5 day
- T cell recovery time after killing another cell = 1 day
Relapse

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Stability in the delays space

The immune response to leukemia
Stem cell transplantation

0 20 40 60 80 100
0 0.5 1.0 1.5 2.0
General host cells H

0 200 400 600 800
0 0.2 0.4 0.6 0.8 1.0 x 10^{-6}
Cancer cells C

0 20
0 0.5 1.0
Anti-host T cells $T_H$

ever goes to 0

eventually overwhelms $T_H$
Remission

General host cells $H$

Anti–host cells $T_H$

Cancer cells $C$

$C = 0$ at time 25.7276

Cell Concentration in $10^3$ cells/µL

Time in Days

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Oscillations

A: Stable oscillation

- Anti–host T cells
- Cancer cells
- General host cells

B: Unstable Oscillation
Extinction instead of stability

Without state constraint

- Anti–host T cells $T_h$
- Cancer cells C
- The value of C crosses 0 at time 8.0192.

With state constraint

- Anti–host T cells $T_h$
- Cancer cells C
- The value of C crosses 0 at time 8.0192, and does not recover.

The value of C crosses 0 at time 8.0192.

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Initial anti-host cells vs. initial host cells

- Higher initial host blood cell concentrations improve the chances of a successful cure.
- Greater initial anti-host T cell concentrations slightly favor the chances of cure.
A higher average number of T cell divisions favor complete remission

Higher cancer growth rate make complete remission slightly more likely
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Zero crossing: Example

A simple DDE:

\[
\frac{dx}{dt} = -rx(t - 1), \quad x(t) = 1, \quad t < 0.
\]

- Solve: \( t \in [0, 1) \).

\[
\frac{dx}{dt} = -rx(t - 1) = -r
\]

Then

\[ x = -rt + c = 1 - rt. \]

- If \( r > 0 \) then \( x(t) = 0 \) for \( T \in [0, 1) \)
Zero crossing: example

A simple DDE:

\[ \frac{dx}{dt} = -rx(t - 1), \quad x(t) = 1, \quad t < 0. \]

Proceed: \( t \in [1, 2) \)

\[ \frac{dx}{dt} = -rx(t - 1) = -r + r^2t - r^2 \]

Then

\[ x = 1 - rt + \frac{r^2}{2}(t - 1)^2. \]
Zero crossing: example

A simple DDE:

\[
\frac{dx}{dt} = -rx(t-1), \quad x(t) = 1, \ t < 0.
\]

- The general solution: \( t \in [n, n+1) \)

\[
x(t) = \sum_{k=0}^{n+1} (-r)^k \frac{(t-k+1)^k}{k!}
\]

Question:

For what \( r \) does that exist a \( T \in [n, n+1) \) such that

\[
\sum_{k=0}^{n+1} (-r)^k \frac{(T-k+1)^k}{k!} = 0?
\]
Zero crossing: example

A simple DDE:

$$\frac{dx}{dt} = -rx(t-1), \quad x(t) = 1, \quad t < 0.$$ 

The general solution: \( t \in [n, n+1) \)

$$x(t) = \sum_{k=0}^{n+1} (-r)^k \frac{(t-k+1)^k}{k!}$$

Question:
For what \( r \) does that exist a \( T \in [n, n+1) \) such that

$$\sum_{k=0}^{n+1} (-r)^k \frac{(T-k+1)^k}{k!} = 0?$$
A toy problem

\begin{align*}
x_{n+1} &= (1 - y_n)x_n \\
y_{n+1} &= -x_n^2 + k + y_n
\end{align*}

The map iterated twice

\begin{align*}
x_{n+2} &= (1 + x_n^2 - k - y_n)(1 - y_n)x_n \\
y_{n+2} &= -((1 - y_n)^2 + 1)x_n^2 + 2k + y_n
\end{align*}
A toy problem

\[ x_{n+1} = (1 - y_n)x_n \]
\[ y_{n+1} = -x_n^2 + k + y_n \]

The map iterated twice

\[ x_{n+2} = (1 + x_n^2 - k - y_n)(1 - y_n)x_n \]
\[ y_{n+2} = -((1 - y_n)^2 + 1)x_n^2 + 2k + y_n \]
This corresponds to...
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Approach #1

- A mesh in time that is based on the delay.
- Numerical methods for ODEs that use the mesh points only (multistep methods)
- Example:

\[
\begin{align*}
\left\{ \begin{array}{l}
y'(t) &= f(t, y(t), y(t - \tau(t))), \quad t_0 \leq t \leq t_f, \\
y(t) &= \phi(t), \quad t \leq t_0.
\end{array} \right.
\]

- A set of meshpoints:

\[
\Delta = \{t_0, t_1, \ldots, t_N = t_f\},
\]

such that \(t_n - \tau(t_n) \in \Delta\).
- Forward Euler: \(y_{n+1} = y_n + h_{n+1} f(t_n, y_n, y_q), \quad q < n\).
- Same idea with Adams-like methods, Heun, etc.
Approach #2: Feldstein

- Free the mesh selection from the delay
- Use extranodal points for the approximation of the delayed term $y(t - \tau(t))$.
- Example: $(t_0 \leq \alpha(t) \leq t)$
  \[
  \begin{cases}
  y'(t) = f(t, y(t), y(\alpha(t))), & t_0 \leq t \leq t_f, \\
  y(t_0) = y_0,
  \end{cases}
  \]

- Assume $h = (t_f - t_0)/m$. For any $t_n = t_0 + nh$, define
  \[q(n) = \text{floor} \left( \frac{\alpha(t_n) - t_0}{h} \right).\]

- A numerical method:
  \[
  \begin{cases}
  y_{n+1} = y_n + hf(t_n, y_n, z_n), \\
  y_0 = y(t_0),
  \end{cases}
  \]
  where $z_n = y_{q(n)}$, i.e., a piecewise-constant approximation of $y(\alpha(t))$.
  Alternatively, a piecewise-linear approximation:
  \[z_n = (1 - r(n))y_{q(n)} + r(n)y_{q(n)+1}.\]
Approach #3: Bellman’s method of steps

Assume a constant delay. In the first interval $[t_0, t_0 + \tau]$ the DDE has the form:

$$\begin{cases} 
  y'(t) = f(y(t), \phi(t - \tau)), \\
  y(t_0) = \phi(t_0).
\end{cases}$$

In the second interval $[t_0 + \tau, t_0 + 2\tau]$, define $y_1 = y(t - \tau)$ and $y_2(t) = y(t)$. Then:

$$\begin{cases} 
  y_1'(t) = f(t - \tau, y_1(t), \phi(t - 2\tau)), \\
  y_2'(t) = f(t, y_2(t), y_1(t)), \\
  y_1(t_0 + \tau) = \phi(t_0), \\
  y_2(t_0 + \tau) = y(t_0 + \tau)
\end{cases}$$

And so on...
For every timestep, a larger system. However, this system can be solved using standard methods for ODEs.
Approach #4: Methods based on continuous extensions

- **Continuous Extension**: very low cost method to get an accurate approximation of the solution at every point in the interval

\[
\eta(t_n + \theta h_{n+1}) = \beta_{n,1}(\theta)y_n + \ldots + \beta_{n,i_n+1}(\theta)y_{n-i_n} \\
\quad + h_{n+1}\psi(y_n, \ldots, y_{n-i_n}; \theta, g_\eta, \Delta'_n), \quad 0 \leq \theta \leq 1.
\]

where

\[
g_\eta(f, y) = f(t, y, \eta(t - \tau(t, y))).
\]

- This is how every Matlab routine provides solutions at the sampled points
Approach #4: Methods based on continuous extensions

Consider the DDE

\[
\begin{align*}
y'(t) &= f(t, y(t), y(t - \tau(t, y(t)))), & t_0 \leq t \leq t_f, \\
y(t) &= \phi(t), & t \leq t_0.
\end{align*}
\]

Using continuous extensions, solving the DDE amounts to solving the ODE:

\[
\begin{align*}
w_{n+1}'(t) &= f(t, w_{n+1}(t), x(t - \tau(t, w_{n+1}(t)))), & t_n \leq t \leq t_{n+1} \\
w_{n+1}(t_n) &= y_n,
\end{align*}
\]

where

\[
x(s) = \begin{cases} 
\phi(s), & s \leq t_0, \\
\eta(s), & t_0 \leq s \leq t_n, \\
w_{n+1}(s), & t_n \leq s \leq t_{n+1}.
\end{cases}
\]

and \(\eta\) is the continuous extension interpolant.
Bellen and Zennaro, Numerical Methods for Delay Differential Equations, Oxford

Shampine and Thompson, Numerical Solution of Delay Differential Equations
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4. Stability in the delays space
Stability in the delays space

\[
d\frac{d^2x}{dt^2} + \frac{dx}{dt} + \frac{dx(t - \tau_1)}{dt} + \frac{dx(t - \tau_2)}{dt} + 8x = 0
\]
Stability crossing curves

- **Stability crossing curves**: The set of delays for which the characteristic equation has at least one imaginary zero (or pair of imaginary zeros).
- **Associated with change of stability**

Ref:
The two delays case

A DDE with two constant delays

\[ x(t) + c_1 x(t - \tau_1) + c_2 x(t - \tau_2) + c_3 x'(t) + c_4 x'(t - \tau_1) + c_5 x'(t - \tau_2) = 0. \]

The characteristic equation:

\[ h(s) = h_0(s) + h_1(s)e^{-\tau_1 s} + h_2(s)e^{-\tau_2 s}. \]

Let \( a_k(s) = h_k(s)/h_0(s) \). Then

\[ a(s, \tau_1, \tau_2) = 1 + a_1(s)e^{-\tau_1 s} + a_2(s)e^{-\tau_2 s} = 0. \]

- **Stability**: a question of the number of the roots of the characteristic equation with a real part on the right hand side of the plane.
The two delays case

For an imaginary \( s = i\omega \) to satisfy \( a(s, \tau_1, \tau_2) = 0 \), the vector corresponding to the three terms must form a triangle:

\[
a(s, \tau_1, \tau_2) = 1 + a_1(s)e^{-\tau_1 s} + a_2(s)e^{-\tau_2 s} = 0.
\]

Hence, their magnitudes must satisfy the triangle inequalities:

\[
|a_1(i\omega)| + |a_2(i\omega)| \geq 1,
\]

\[
-1 \leq |a_1(i\omega)| - |a_2(i\omega)| \leq 1.
\]
The two delays case

- The triangle inequalities determine which $i\omega$ may be zeros of $a(s)$.
- The set of all such $\omega$ are the crossing set $\Omega$.
- Any given $\omega$ defines a collection of pairs $(\tau_1, \tau_2)$.

$$
\begin{align*}
\tau_1 &= \frac{\angle a_1(i\omega) + (2u - 1)\pi \pm \theta_1}{\omega} \\
\tau_2 &= \frac{\angle a_2(i\omega) + (2v - 1)\pi \mp \theta_2}{\omega}
\end{align*}
$$

where from the law of cosine:

$$
\theta_{1,2} = \cos^{-1}\left(\frac{1 + |a_{1,2}(i\omega)|^2 - |a_{2,1}(i\omega)|^2}{2|a_{1,2}(i\omega)|}\right),
$$

and $u_0^\pm, v_0^\pm$ are the smallest possible integers such that the corresponding $\tau_{1,2}$ are nonnegative.
The two delays case

- The crossing set $\Omega$ always consists of a finite number of intervals of finite length.

- Any interval of $\omega$’s defines a collection of curves in $\mathbb{R}^2$.

- The general case is a union of the following sets:

![Graph showing different types of curves for the two delays case](image)
Example

DDE:

\[ \frac{dx}{dt} = -2x(t - \tau_1) + x(t - \tau_2). \]