Ordinary Differential Equation (ODE) Models of Cancer-Immune Interactions

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Overview

The Immune System

- The immune system defends the body against infections and abnormal cells.
- Composed of:
  - **Innate immunity:** fast, non-specific (e.g., macrophages, NK cells)
  - **Adaptive immunity:** slower, specific, with memory (e.g., T cells, B cells)
- **T cells:**
  - **$CD8^+$ T cells:** directly kill infected or cancerous cells.
  - **$CD4^+$ T cells:** help other immune cells through cytokine signaling.
- **Immune surveillance:** the immune system constantly checks for abnormal or foreign cells.

Cancer

- Cancer is the uncontrolled growth of abnormal cells in the body.
- **Hallmarks of tumor cells:**
  - Self-sufficiency in growth signals
  - Insensitivity to anti-growth signals
  - Resistance to cell death (Apoptosis)
  - Angiogenesis
  - Invasion & Metastasis

The Immune System and Cancer

- **Immune surveillance:** T cells and NK cells can detect and destroy abnormal cells, including cancerous ones.
- **Tumor-immune dynamics:**
  - The immune system may control small tumors for years.
  - Some cancer cells develop ways to avoid or suppress immune attacks.
- **Immune evasion:**
  - Tumors may downregulate immune-activating signals.
  - They may express immune checkpoint molecules or recruit suppressive cells.
- These complex interactions between cancer and the immune system can be explored using mathematical models.

Ordinary Differential Equations in Biology

- **What are Ordinary Differential Equations?** Equations used to describe how a system changes over time
- **Why Use ODEs?**
  - Capture dynamics of populations (e.g., bacteria, immune cells).
  - Model interactions between biological entities (e.g., predator–prey).
- ODEs can reveal steady states, growth/decay patterns, and oscillations, helping predict system behavior under varying and complex conditions.
- **Use in Tumor-Immune Models:** Tumor cells and immune cell populations can be represented using variables, allowing study of their interactions.

One Equation Tumor Growth Models

Simple equation for tumor growth:

$$\frac{dx}{dt} = x\, f(x), \qquad f(x) = p(x) - d(x)$$

- $x(t)$: tumor cell population at time t $(x(0) > 0)$.
- $p(x)$: per-capita **proliferation** rate; $d(x)$: per-capita **death** rate.
- **States:**

$$\begin{cases} p(x) > d(x) & \Rightarrow \text{growth} \\ p(x) = d(x) & \Rightarrow \text{dormancy} \\ p(x) < d(x) & \Rightarrow \text{decay} \end{cases}$$

Two-Equation Tumor-Immune Interaction Models

Immune cell interactions with tumors can be described with two equations.

Predator–prey model: immune cells are predators, tumor cells are prey.

$$\frac{dx}{dt} = xf(x) - d_x(x,y), \qquad \frac{dy}{dt} = p_y(x,y) - d_y(x,y) - a_y(y) + \phi(t),$$

- x: size/density of tumor cells y: size/density of effector (immune) cells
- a: apoptosis $\phi(t)$: treatment

Steady States

- A **steady state** (or equilibrium) is a value $\bar{x}$ such that the system remains there:
$$f(\bar{x}) = \bar{x}.$$
- **Stable steady state:** When the system is disturbed it returns to $\bar{x}$. (eg. a ball in a valley)
- **Unstable steady state:** When the system is disturbed it does not return to $\bar{x}$. (eg. a ball at the top of a hill)

Stability

- Start with solution: $x_n = \bar{x} + x'_n$, where x'_n is a small perturbation.
- Then
$$x'_{n+1} = x_{n+1} - \bar{x} = f(x_n) - \bar{x} = f(\bar{x} + x'_n) - \bar{x}.$$
- Linearize:
$$x'_{n+1} \approx a\, x'_n, \qquad a = f'(\bar{x}).$$
- **Stability:** $\bar{x}$ is stable if $|a| < 1$, the system will return to $\bar{x}$.

Bifurcation

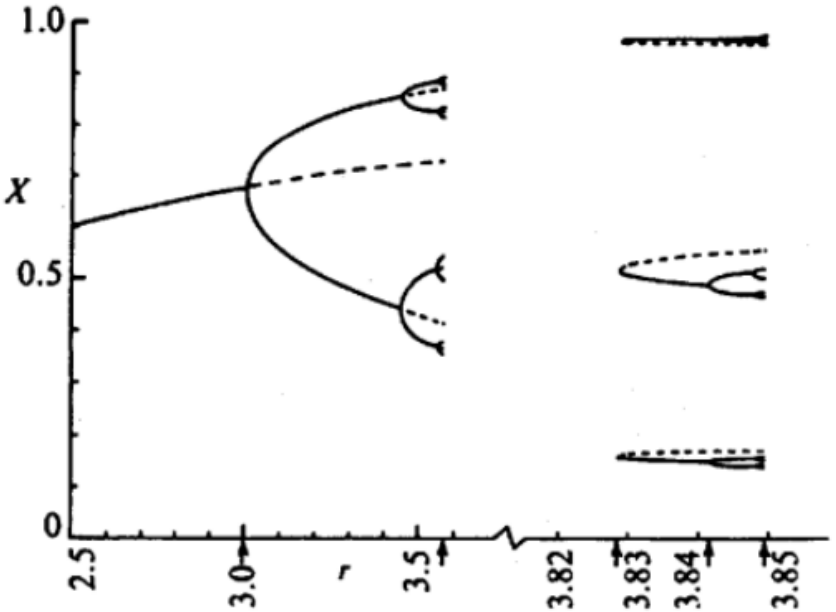

Figure 1: Bifurcation Diagram

Key ideas

- **Horizontal axis:** parameter value (e.g., r).
- **Vertical axis:** represents magnitudes of steady states of the equation.
- **Branches:** represents dependence of state level on parameter.
- **Bifurcation points:** where a change in the parameter's value changes the qualitative behaviour of the dynamical system (e.g. changes in number/stability of steady states, steady states may appear or disappear, oscillating steady states)

Simulating Oscillatory Dynamics

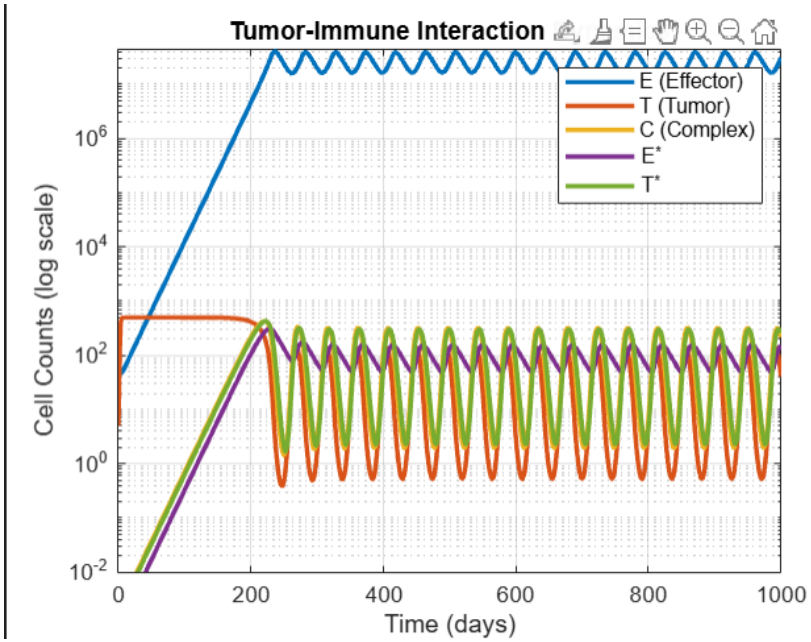

Figure 2: Oscillatory decay of tumor

- **Model:** Kuznetsov (1994) ODEs for tumor cells (T) and effector cells (E), with interaction/lysis terms and immune stimulation.
- **Solver/Code:** MATLAB `ode45`; parameters from: Interactions between the Immune System and Cancer: A Brief Review of Non-Spatial Mathematical Models
- **Plot:** Log-scale cell counts over time (days)

Impact of Parameters

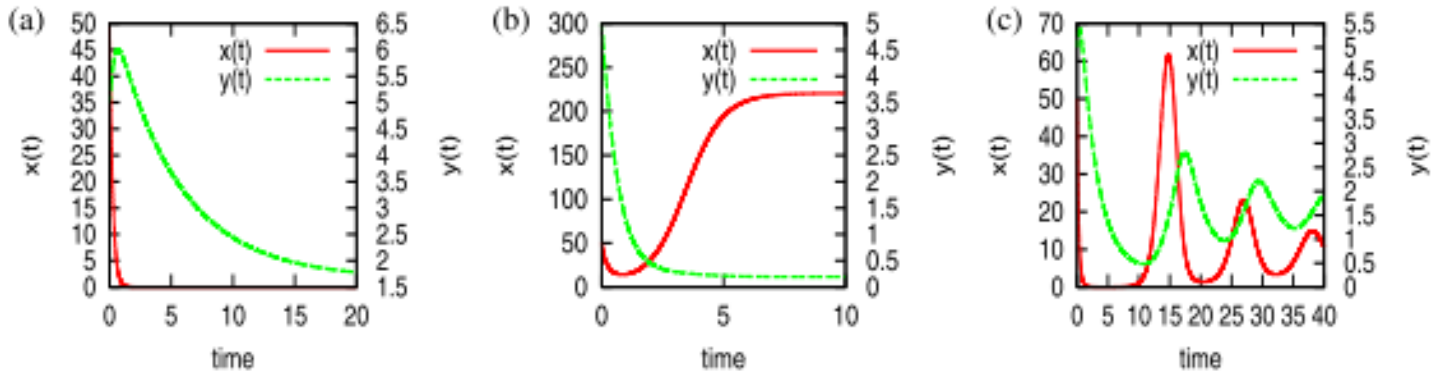

Figure 3: Effect of Parameters on System Behaviour

- **Panel A:** $s = 0.318$ (high), $d = 0.1908$ (low), $b = 2 \times 10^{-3}$ (moderate) exponential tumor decay
- **Panel B:** $s = 0.318$ (high), $d = 2.0$ (very high), $b = 4 \times 10^{-3}$ (high) tumor initially shrinks, but immune cell population decays and tumor grows again
- **Panel C:** $s = 0.1181$ (low) $d = 0.3743$ (moderate), $b = 2 \times 10^{-3}$ (moderate) tumor size decays in an oscillatory manner

Parameters:
s – immune cell recruitment rate (day^{-1})
d – immune cell death rate (day^{-1})
b – the strength to which tumor cells stimulate an immune response (cell^{-1} day^{-1})

Applications of ODEs in Cancer Immunology

- **Guide treatment choices:** Simulate effects of immunotherapies to identify strategies with the highest chance of success.
- **Predict patient outcomes:** Forecast whether a tumor will regress, remain dormant, or relapse under different conditions or treatment protocols.
- **Optimize therapy schedules:** Determine optimal doses and timing that maximize tumor destruction while minimizing side effects.
- **Explore Tumor Immune dynamics:** Identify conditions leading to steady states, oscillations, or bifurcations to better understand clinical phenomena such as remission and recurrence.
- **Test scenarios outside of clinical settings:** Explore the impact of changes in tumor growth rate, immune activation, or other variables, without needing to experiment directly on patients.

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Thank you!

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