# Delay models for cancer and tumor growth

Maria Barbarossa

Technische Universität München M6

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# Outline

# Overview

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# Delay Differential Equations

A delay differential equations (DDEs) problem has the form:

$$\dot{y}(t) = f(t, y(t-\tau_1), \cdots, y(t-\tau_n)), \quad t \geq t_0 \tag{1}$$

$$y(t) = \phi(t), \quad t \leq t_0. \tag{2}$$

where

- $y$ is a physical quantity which changes over time
- Changes in $y$ at time $t$ depend also on the past, not only on $t$
- $\phi(t)$ is the history function.

[ R. Driver(1977), A. Bellen(2003)]

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In this lecture we will only consider mathematical models with constant delays.

# Main differences between ODEs and DDEs

- History function ($\phi(t)$) instead of an initial value ($y_0$)
- Initial discontinuity ($y'(t_0)^+ \neq \phi'(t_0)^-$) and its propagation (*cascade of discontinuities*)
- For the same solution, more than one history function may exist
- Depending on regularity of $\phi(t)$, there can be a unique solution or more solutions
- Lack of regularity in the initial function $\phi(t)$ can cause termination of solution after some bounded interval
- Depending on the delay, the solution can become unstable.

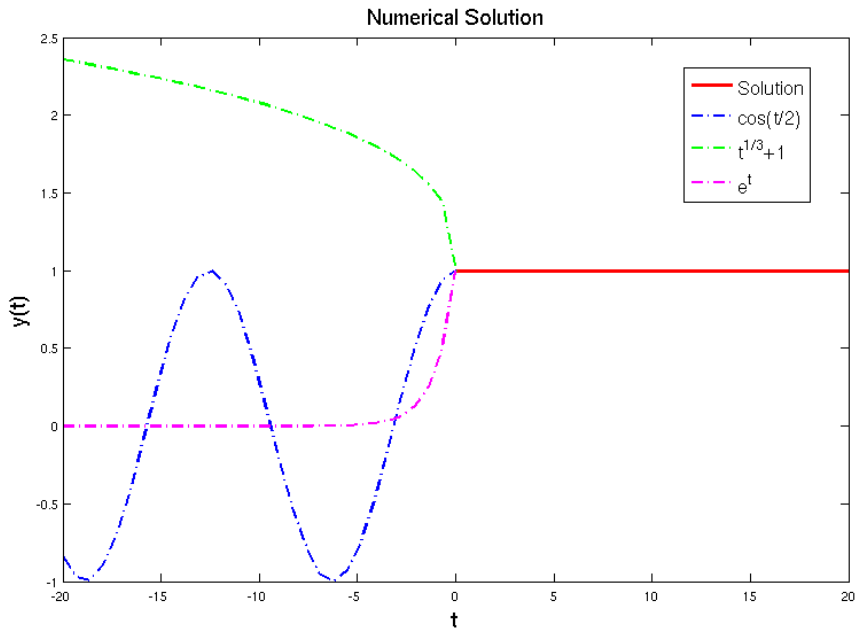
# Main differences between ODEs and DDEs

An example for non-injectivity of initial data.

The following equation

$$\dot{y}(t) = y(t-1)\,(y(t)-1)\,,\ t \geq 0 \tag{3}$$

has the constant solution $y(t) \equiv 1$ in $[0, \infty)$ for any initial function $\phi(t),\ t \in [-1, 0]$ such that $\phi(0) = 1$.



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In biological and mechanical processes we find often “physical“ delays. Delay Equations are used to make the mathematical model closer to the real phenomenon.

Examples of delay mathematical models in biology:

[ N. MacDonald(1989), H. Smith(2010)]

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- Physiology (delays in regulation processes, e.g. Mackey-Glass model for blood cells production)
- Neurology (e.g. delay to express the synaptic processing time)

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As next we will see two examples from the population biology.

[ N. MacDonald(1989), H. Smith(2010)]

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Also known as **logistic delay equation**.

$$\dot{P}(t) = rP(t)(1 - P(t - \tau)/K)$$

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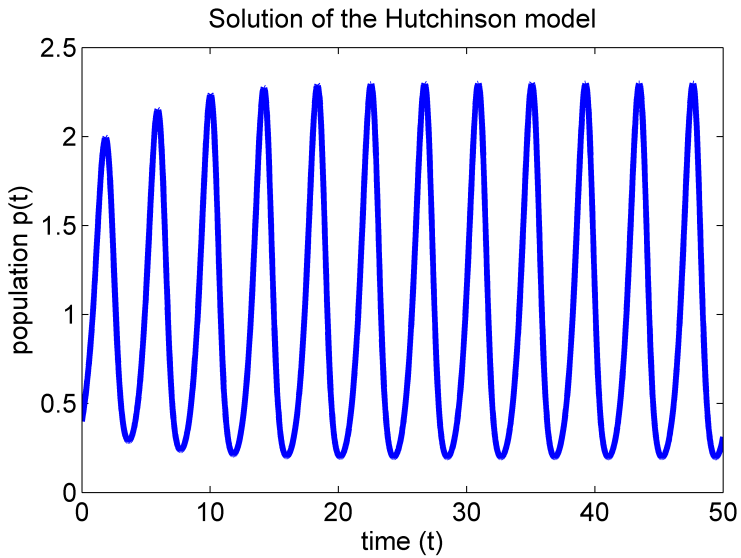
Interesting results: E.g. with $\tau = 1$ and $r > \pi/2$
$\Rightarrow$ Oscillations could be found! (more about this later)



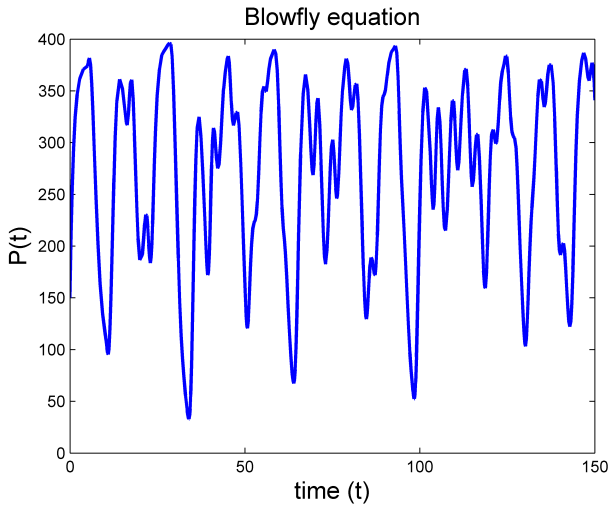

[G.E. Hutchinson, (1948)]

# Blowfly equation

The **blowfly equation** describes the (adult) population of flies $P$ at time $t$.

$$\begin{aligned} \dot{P}(t) &= b(P(t-\tau))P(t-\tau) - \mu(P(t))P(t), \\ P(t) &= \phi_0(t), \ t \leq 0 \end{aligned}$$

Here the delay occurs in the birth-term $b$: individuals have to grow up before they can reproduce.




[J. Perez, C. Malta and F. Coutinho,(1978)]

# Overview

# Linearization

We give here a short introduction to the stability theory of DDEs with help of an example.

The Hutchinson Equation

$$\dot{P}(t) = P(t)(1 - P(t - \tau)) \tag{4}$$

has two steady states $P_0^* = 0$, $P^* = 1$.

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has two steady states $P_0^* = 0$, $P^* = 1$.

We linearize at $P^*$:

$$P(t) = 1 + p(t) \;\Rightarrow\; \frac{dp(t)}{dt} \approx -p(t - \tau).$$

# Characteristic roots

We look for solutions of $p(t)$ in the form $p(t) = e^{\lambda t}$ and get the **characteristic equation**

$$\lambda = -e^{-\lambda\tau}. \tag{5}$$

Zeros of (5) are called **characteristic roots**.

Result: The fixed point solution $P^*$ of (4) is stable if and only if $Re(\lambda) < 0$ for all characteristic roots.

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**Result:** The fixed point solution $P^*$ of (4) is stable if and only if $Re(\lambda) < 0$ for all characteristic roots.

Consider complex roots in the form $\lambda = \mu + i\omega$ and separate the real part from the imaginary one in (5)

$$\mu = -e^{-\mu\tau}cos(\omega\tau) \quad \omega = e^{-\mu\tau}sin(\omega\tau).$$

Stability is affected by the values of $\tau$: stability loss when $\mu(\tau)$ first crosses the imaginary axis. It can be shown that $0 < \tau < \frac{\pi}{2}$ is the condition for stability of $P^*$. For $\tau > \frac{\pi}{2}$ the solution shows an oscillatory behavior.

[J.D. Murray,(2001)]

# A general result by Cooke and Van den Driessche

More in general, it is possible to reduce the characteristic polynomial to the form

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau}.$$

The following result holds:

**Theorem**

*Let $P$ and $Q$ be analytic functions in a right half-plane $Re(z) > -\delta$, with $\delta > 0$. If the following conditions are verified*

- *$P(z)$ and $Q(z)$ have no common imaginary zero.*
- *$\overline{P(-iy)} = P(iy)$ and $\overline{Q(-iy)} = Q(iy)$ for $y \in \mathbb{R}$.*
- *$P(0) + Q(0) \neq 0$.*
- 
- *$F(y) \equiv |P(iy)|^2 - |Q(iy)|^2$ for $y \in \mathbb{R}$ has at most a finite number of real zeros.*

*Then*

- *If $F(y) = 0$ has no positive roots, the delay problem has the same stability properties of the ODE problem, for all $\tau > 0$.*
- *If $F(y) = 0$ has at least one positive root and each positive root is simple, then as $\tau$ increases, stability switches may occur. There is a $\tau^*$ such that the equation is always unstable for $\tau > \tau^*$.*

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We will see some examples for these different cases and spend some time with delays related to the cell cycle.

# Overview

# Burkowsky:a computer tool to predict the tumor growth

- Assume to deal with an avascular solid tumor.
- The tumoral mass is assumed to be a sphere. Tumor's growth is related on the concentration of oxygen($\sigma(r)$), which varies depending on the distance from the surface of the tumor. Below a certain oxygen concentration level $\sigma_{nec}$ cell death occurs.
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- During the final stages of tumor growth the tumoral sphere is made up of concentric shells (necrotic core, dormant cells, partially proliferating cells, freely proliferating cells)
- On entering the necrotic core a cell does not immediately expel inhibitory chemicals: such a phenomenon occurs after a time $\tau$ (the delay). Thus if a necrotic core is formed at time $\bar{t}$, at any time $t \geq \bar{t} + \tau$ we assume the existence of a necrotic sphere with radius $r_n(t - \tau)$ surrounded by an outer layer of dead cells awaiting lysis.

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**Results:** If the delay $\tau$ is larger than zero, the tumor may experience a temporary regression. Further conditions for an equilibrium in the tumor size were found.

[F. Burkowsky,(1977)]

# Byrne: Model formulation

In the following we present two models by H. Byrne (1997) to describe the evolution of radially symmetric avascular multicellular spheroids. The following assumptions are common to both models.

- The tumor grows until nutrient concentration ($\sigma(r,t)$) at the center of the tumor decreases below a threshold value $\sigma_{nec}$.
- $r$ denotes distance from the center of the tumor, $R(t)$ is the outer radius, $r_n(t)$ is the radius of the necrotic mass.
- Nutrient consumption is described by a reaction-diffusion equation in the proliferating rim $(r - r_n)$.
- Tumor growth = net cell proliferation - apoptotic cell loss - necrotic cell loss

$$R^2 \frac{dR}{dt} = S - A - N.$$

- At any point within the central core, necrotic cell loss occurs at constant rate $s\lambda$:

$$N = \int_0^{r_n} s\lambda r^2 dr = \frac{s\lambda r_n^2}{3}.$$

# Byrne: Delay in cell proliferation rate

- There is a delay $\tau \geq 0$ between the time at which cell commences mitosis and the time at which the daughter cells are produced.
- Local cell proliferation rate at time $t$ is proportional to the nutrient concentration at time $t - \tau$ (when the cells entered mitosis).
- The outer radius of the tumor is:

$$\frac{3R^2}{s}\frac{dR}{dt} = \underbrace{3\int_{r_n(t-\tau)}^{R(t-\tau)} \sigma r^2 dr}_{\text{Proliferation}} - \underbrace{\tilde{\sigma}(R^3 - r_n^3)}_{\text{Apoptosis}} - \underbrace{\lambda r_n^3}_{\text{Necrosis}} .$$

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**Results:** From numerical simulations the author concludes that the introduction of a nonzero delay does not affect the limiting behavior of the tumor (if it explodes or converges to a steady state), but simply modifies the details of the tumor evolution (e.g. oscillatory dynamics) and increases the time taken to reach the equilibrium value.

[H. Byrne,(1997)]

# Byrne: Delay in apoptotic cell loss term

- An increase in cell proliferation leads to an increase in the concentration of many growth factors. However, it takes time for the cell to up-regulate the rate of growth factor.
- Introduce a $A_r$ rate for regulatory apoptotic cell loss and introduce $\tau$ as the time taken for changes in $A_r$
- The outer radius of the tumor is:

$$R^2 \frac{dR}{dt} = \underbrace{\int_{r_n}^{R} \sigma r^2 s \, dr}_{\text{Proliferation}} - \underbrace{\int_{r_n}^{R} \tilde{\sigma} s r^2 \, dr}_{\text{Underlaying Apoptosis}}$$

$$- \underbrace{\int_{r_n(t-\tau)}^{R(t-\tau)} s\theta(\sigma - \sigma_H) r^2 \, dr}_{\text{Regulatory Apoptosis}} - \underbrace{\int_{0}^{r_n} s\lambda r^2 \, dr}_{\text{Necrosis}}.$$

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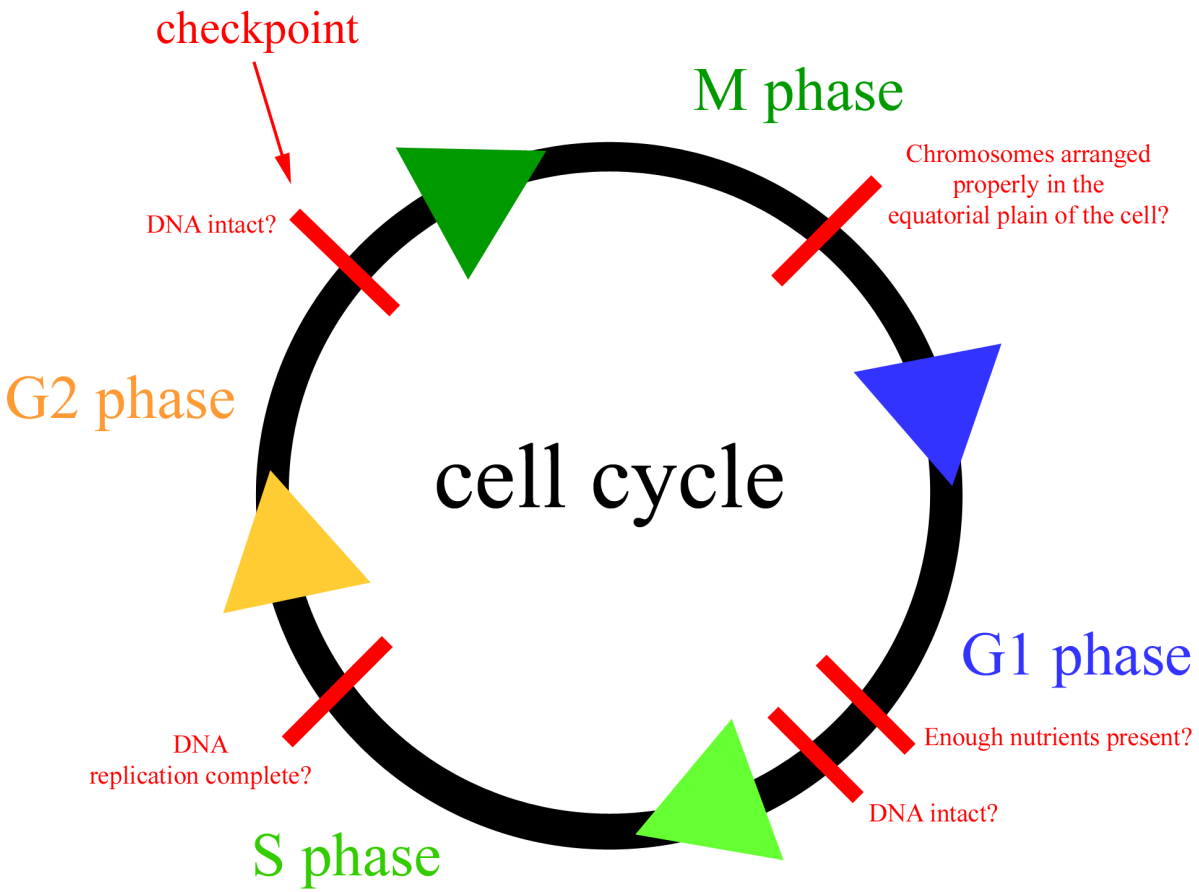
$$- \underbrace{\int_{r_n(t-\tau)}^{R(t-\tau)} s\theta(\sigma - \sigma_H) r^2 \, dr}_{\text{Regulatory Apoptosis}} - \underbrace{\int_{0}^{r_n} s\lambda r^2 \, dr}_{\text{Necrosis}}.$$

**Results:** The introduction of a nonzero delay affects the tumor's growth dynamics! Taking a parameter setting for which the ODE model ($\tau = 0$) reaches a fixed point, the author shows that small delays lead to damped oscillations around the stationary point. For large delays the steady state is no longer stable: the tumor does not proliferate any more and it turns into a necrotic mass.

[H. Byrne, (1997)]

# Overview

# The cell cycle



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- Mitosis (1-2 hours) is the cell division
- Include a delay for the length of the interphase (modelling approach introduced by Baker, 1998)
- Include interactions with cell-phase specific drugs and with the immune system

[M. Villasana and A. Radunskaya,(2003)]

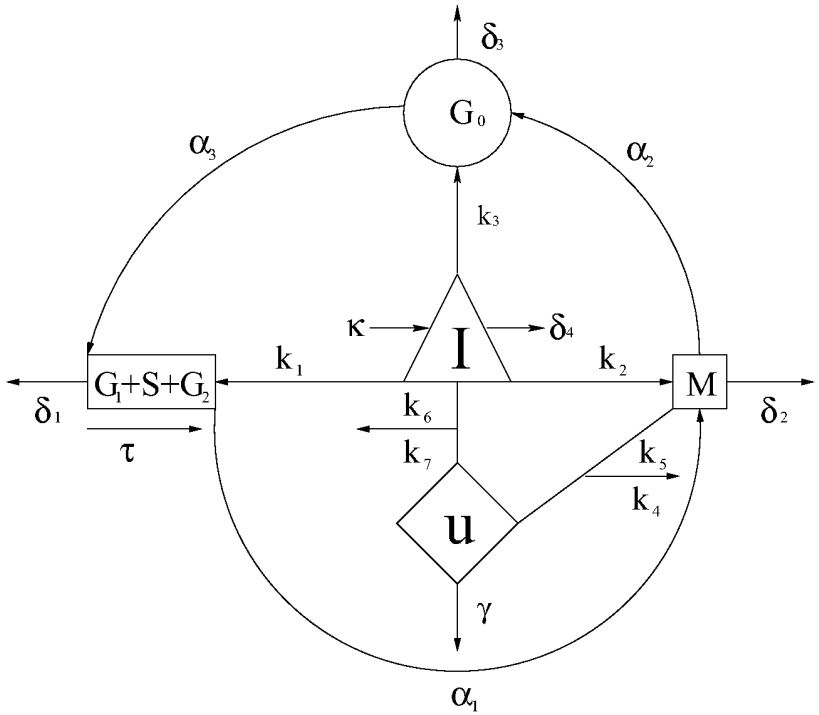
# ...but a wrong model

$$
\begin{aligned}
\dot{T}_I(t) &= 2a_4 T_M - (c_1 I + d_2) T_I - a_1 T_I(t-\tau) \quad \text{Interphase cells} \\
\dot{T}_M(t) &= a_1 T_I(t-\tau) - d_3 T_M - a_4 T_M - c_3 I T_M - \kappa_1 (1 - e^{-\kappa_2 u}) T_M \quad \text{Mitotic cells} \\
\dot{I}(t) &= k + \frac{\rho I (T_I + T_M)^n}{\alpha + (T_I + T_M)^n} - \delta_1 I - c_2 I T_I - c_4 T_M I - k_3 (1 - e^{-k_4 u}) I \quad \text{Immune system} \\
\dot{u}(t) &= -\gamma u \quad \text{Drugs}
\end{aligned}
$$

[M. Villasana and A. Radunskaya, (2003)]

# A more detailed model

Liu et al. introduce the quiescent phase and correct the model by Villasana:




[Liu et al.,(2007)]

# Liu's Model

$$
\begin{aligned}
\dot{T}_I(t) &= \alpha_3 T_Q - \alpha_1 T_I - \delta_1 T_I - k_1 I T_I && \text{Interphase cells} \\
\dot{T}_M(t) &= \alpha_1 T_I(t-\tau) - \alpha_2 T_M - \delta_2 T_M - \kappa_2 I T_M - \kappa_4 \left(1 - e^{-\kappa_5 u}\right) T_M && \text{Mitotic cells} \\
\dot{T}_Q(t) &= 2\alpha_2 T_M - \alpha_3 T_Q - \delta_3 T_Q - \kappa_3 I T_Q && \text{Quiescent cells} \\
\dot{I}(t) &= k + \frac{\rho I (T_I + T_M + T_Q)^n}{\alpha + (T_I + T_M + T_Q)^n} - \delta_4 I && \text{Immune system} \\
&\quad -(c_1 T_I + c_2 T_M + c_3 T_Q) I - \kappa_6 \left(1 - e^{-\kappa_7 u)}\right) I \\
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[W. Liu et al.,(2007)]

# Liu's Model: Analysis

- The model was rescaled and new parameter were introduced (the biological meaning goes a bit lost)
- Model analysis at different stages: first the ODE model for tumor cells only (no immune system, no drugs), then the delay model.

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- Model analysis at different stages: first the ODE model for tumor cells only (no immune system, no drugs), then the delay model.
- Stability analysis carried out by investigation of the characteristic polynomial.
- Conditions for the stability of the tumor-free equilibrium were investigated.

[W. Liu et al.,(2007)]

# Liu's Model: Results

- From the simple ODE model for tumor cells only, the author can show that the resting phase $G_0$ controls cancer dynamics. Indeed if the "ingoing"-rate into the resting state is smaller than the rate of departure from the resting state, the tumor will have more proliferating cells and grow.
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- The immune system can be able to control cancer growth and under certain conditions reduce its size.
- When analysing the delay model, a stability switch due to $\tau$ can be found. When $\tau$ is larger than a threshold value $\bar{\tau}$, the cancer-free equilibrium becomes unstable. A long delay in the interphase enables cells to avoid the treatment and reenter the mitotic phase (and therefore proliferate!)

[W. Liu et al.,(2007)]

# Overview

# General considerations

A further class of models deals with interactions of tumor cells with the cells of the immune system.

These models are simplifications of the physiological phenomenon and consider mainly the following two-populations dynamics:

$$\begin{array}{ccccc} \textit{tumor cells} & \equiv & \textit{target cells} & \equiv & \textit{prey} \\ \textit{immune system cells} & \equiv & \textit{effectors} & \equiv & \textit{predators} \end{array}$$

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Hypothesis of **antitumoral immune surveillance** (Burnet,1970): the immune system patrols the cells of the body, and, upon recognition of a (group of) cell(s) that has become cancerous, it will attempt to destroy it(them), thus preventing the growth of some tumors.

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Idea: do not treat the tumor but the immune system!

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- The immune system can, in some cases, eradicate the tumor.
- The tumor may escape from the immune system control and grow.
- An equilibrium is established: the tumor survives in a microscopic (steady) state.

Idea: do not treat the tumor but the immune system!

**Immunotherapy** focuses on the stimulation of the immune system:

- **cancer vaccine** trains the immune system to recognize tumor cells as targets
- manipulation of **therapeutic antibodies** stimulates the immune system to attack the tumor

Aim: if it is not possible to eradicate the tumor, reduce its size to a life-compatible dimension.

# One of the first models

Starting from an existing ODE Model (Mayer, 1995), Búric et al. investigated the effects of time delays in the immune system response. Their motivation was essentially mathematical: since the ODE model could not describe the frequently observed, irregular or chaotic dynamics, they introduced chaotic behavior as an effect of the time delay.

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$$\begin{aligned} \dot{T} &= rT - kTI, \text{ target cells} \\ \dot{I} &= pf(aT + (1-a)T_{\tau_T}) + sg(bI + (1-b)I_{\tau_I}) - I \text{ immune agent (IS)} \end{aligned}$$

where $X := X(t)$, $X_\tau = X(t-\tau)$ and with

$$\begin{aligned} f(T) &= \frac{T^4}{1+T^4}, \text{ activation of IS due to the tumor} \\ g(I) &= p\frac{I^3}{1+I^3} \text{ self-regulation of IS} \end{aligned}$$

This model includes two constant delays for the activation of the immune system:

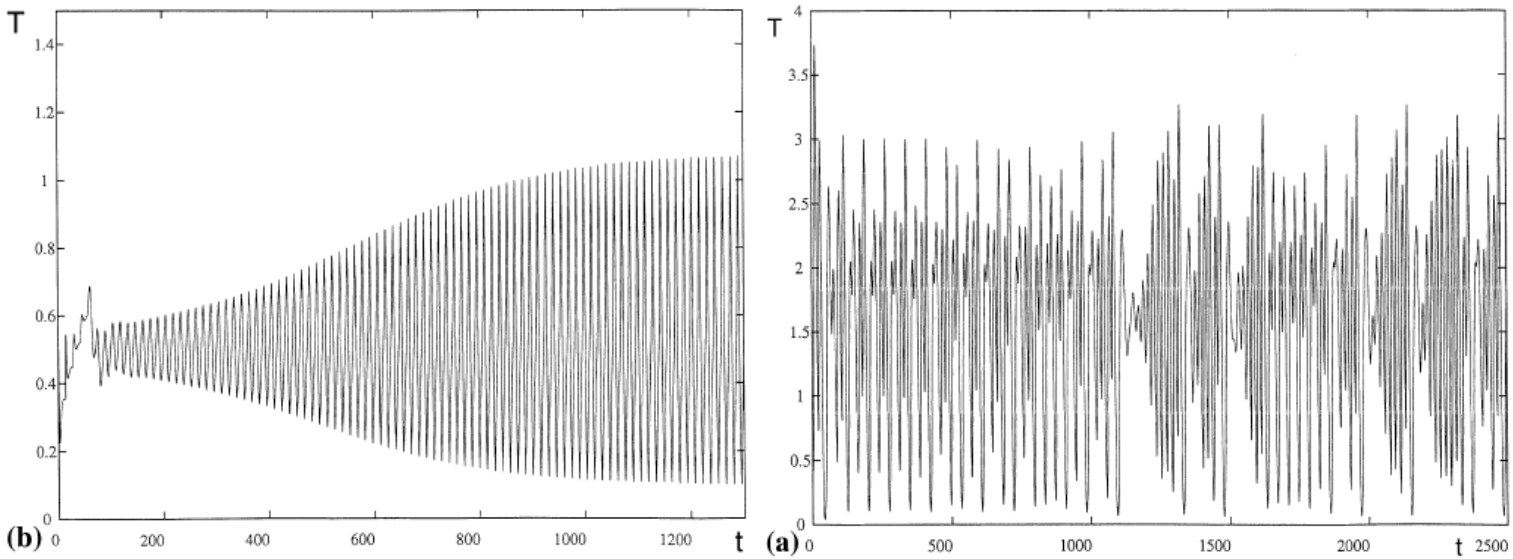
- $\tau_T$ is the delay due to the size of the tumor
- $\tau_I$ is the delay due to the self-regulation processes in the IS effectors.

[N. Burić, (2001)]

# Burić's results

The model was investigated essentially for one constant delay only (setting $a = 1$ or $b = 1$).
Varying the parameter values, different dynamics were possible.

For a delay $\tau_T$ in $f(T)$ and fixed parameter values admitting a limit cycle in the ODE model, increasing the value of $\tau_T$ a periodic orbit is found (left). For large values of $\tau_T$ the orbit becomes chaotic (left).




[N. Burić, (2001)]

# Predator-prey models by A. d'Onofrio

A. d'Onofrio worked from 2005 to a general class of predator-prey models for tumor-immune system interplay. The general model is an ODE system:

$$\begin{aligned} \dot{T} &= T(f(T) - \phi(T, I)), \text{ tumor} \\ \dot{I} &= \beta(T)I - \mu(T)I + \sigma q(T) + \theta(t) \text{ immune agent (IS)} \end{aligned}$$

- $f(T)$ is a bounded, positive, non-growing function which describes the tumor growth
- $\phi(T, I)$ is the loss of tumor cells due to the attack by the immune system
- $\sigma q(T)$, with $q(0) = 1$, represents the influx of immune cells in tumor in situ (may depend on the tumor size)
- $\beta(T)$ is a growing function of $T$ and models the stimulating effect of the tumor on immune cells proliferation
- $\mu(T)$ is the loss rate of effectors(IS) due to their interactions with the tumor
- $\theta(t)$ models the immunotherapy (constant, periodic or absent).

[A. d'Onofrio, (2005)]

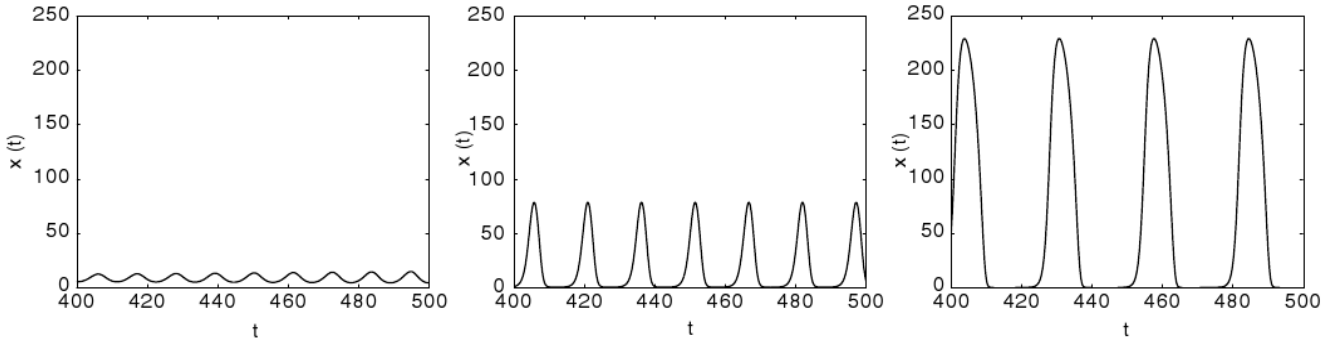
# Predator-prey models by A. d'Onofrio

In 2010 the basic ODE model was modified by including a delay for the immune system response:

$$\begin{aligned} \dot{T} &= T(f(T) - \phi(T, I)), \\ \dot{I} &= \beta(T_\tau)I - \mu(T)I + \sigma q(T) + \theta(t). \end{aligned}$$

Results:

- The stability of the disease-free equilibrium ($T = 0$) is not affected by the delay $\tau$
- Conditions for the stability of the nontrivial equilibrium $P := (\bar{T}, \bar{I})$ were given and it was further shown that there is a critical value $\tau_0$ such that: P is stable if $\tau < \tau_0$, P is unstable if $\tau > \tau_0$ and a Hopf-Bifurcation occurs at $\tau = \tau_0$ (here $\tau$ is the bifurcation parameter).




Here $\bar{T} \approx 10.925$ and $\tau = 0.3$(left plot), $\tau = 0.5$ (central plot), $\tau = 1$(right plot).

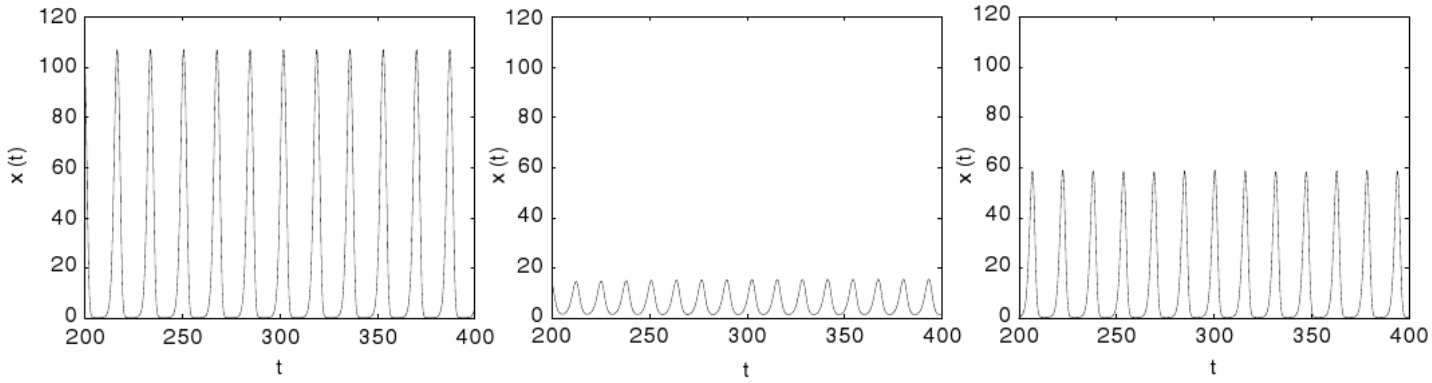
[A. d'Onofrio,(2010)]

# Predator-prey models by A. d'Onofrio

Interactions between delayed immune response and immunotherapy were investigated. The therapy was assumed to be $\omega$-periodic

$$\theta(t) = \theta_A exp\left(-\frac{1}{\gamma}\left(t - \omega\left\lfloor\frac{t}{\omega}\right\rfloor\right)\right)$$

where $\theta_A$ is the maximal 'boost' for the influx of effectors, $\omega$ is the time between two consecutive deliveries and $\gamma$ is a measure of decay time.
Results:




Here: $\tau = 0.6$:

In case of no therapy (left plot), $\gamma = 40$, $\omega = 0.1$ (central plot), $\gamma = 1.1$, $\omega = 3$(right plot).

[A. d'Onofrio,(2010)]

# Overview

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  - activation and reaction of the immune system

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