Observer-Based Efficiency Enhancement in Cell-Cycle Specific Therapies

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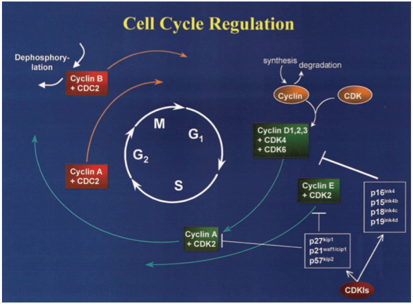
Cell-Cycle Specific Drugs



Manish et al. Cell Cycle-mediated Drug Resistance: An Emerging Concept in Cancer Therapy. *Clinical Cancer Research, 2001*

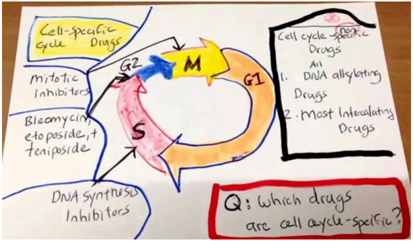
G_1 Preparation (DNA Syntesis)

S DNA Duplication

G_2 Preparation

M Cell Division (Mitosis)

Cell-Cycle Specific Drugs



Med School Radio - Simon Downes
https://www.youtube.com/watch?v=AQsGrbLxXSM

G_1 Preparation (DNA Syntesis)

S DNA Duplication

G_2 Preparation

M Cell Division (Mitosis)

Cell-Cycle specific Drugs acts *only* during a **specific phase** of the cell cycle

Standard Control-related works: A few examples

Matveev et al. Systems & Control Letters, 2002

$$\dot{L} = \alpha L \ln \frac{\theta_L}{L} - \mathfrak{L}_1(c)L, \qquad L(0) = L_0,$$

$$\dot{N} = \beta N \ln \frac{\theta_N}{N} - \mathfrak{L}_2(c)N - \Xi(L)N, \qquad t \in [0, T],$$

$$c = c(t) \in [0, c_{\max}], \quad N = N(t) \geqslant N_- \qquad N(0) = N_0.$$

Application of optimal control theory to analysis of cancer chemotherapy regimens

Standard Control-related works: A few examples

DePillis et al. J. Theor. Biology, 2005

$$\frac{dT}{dt} = aT(1-bT) - cNT - DT - K_T(1-e^{-M})T, \quad (1)$$

$$\frac{dN}{dt} = eC - fN + g\frac{T^2}{h+T^2}N - pNT - K_N(1-e^{-M})N, \quad (2)$$

$$\frac{dL}{dt} = -mL + j\frac{D^2T^2}{k+D^2T^2}L - qLT + (r_1N + r_2C)T - uNL^2 - K_L(1-e^{-M})L + \frac{p_I I}{g_I + I}L + v_L(t), \quad (3)$$

$$\frac{dC}{dt} = \alpha - \beta C - K_C(1-e^{-M})C, \quad (4)$$

$$\frac{dM}{dt} = -\gamma M + v_M(t), \quad (5)$$

$$\frac{dI}{dt} = -\mu_I I + v_I(t) \quad (6)$$

$$D = d\frac{(L/T)^l}{s+(L/T)^l} \quad (7)$$

Mixed immunotherapy and chemotherapy of tumors

Standard Control-related works: A few examples

Hahnfeldt et al. Cancer Research 1999

$$\dot{p} = -w_1 p \ln(\frac{p}{q}) - w_2 p v_2$$
$$\dot{q} = w_3 p - (w_4 + w_5 p^{\frac{2}{3}})q - w_6 v_1 q$$
$$\dot{y}_1 = v_1$$
$$\dot{y}_2 = v_2$$

Tumor development under angiogenic signaling: ...

Standard Control-related works: A few examples

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Tumor development under angiogenic signaling: ...

The majority of (optimal)-control-related works does not address the cell-cycle specific context.

The Cell-Cycle Specific (CCS) Drugs Paradigm

- CCS-Drugs are still delivered GLOBALLY
- CCS-Drugs efficiency depends on LOCAL cell phases
- Cell phases are not available

Question

How to rationally deliver drugs so that the overall efficiency is enhanced despite the above facts?

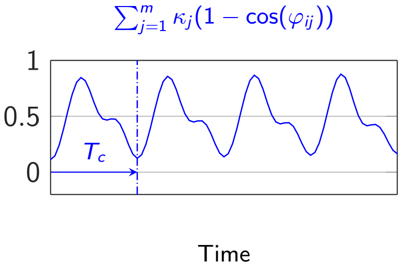
The Dynamic Model (for a POC !)

$$\dot{T} = f(T) - T \underbrace{\left[\sum_{i=1}^{q}\sum_{j=1}^{m}\frac{\kappa_j}{q}(1-\cos(\varphi_{ij}))\right]}_{G} D$$

$$\dot{\varphi}_{ij} = \omega_j + \delta_{ij}$$

$$\dot{D} = -\lambda D + \alpha u$$

T	Tumor cell's population
D	Drug's concentration
u	Drug delivery's intensity
G	Drug's efficiency gain
m	Number of modes in G
q	Number of cells
ω_j	Pulsation of mode j $(= \frac{2j\pi}{T_c})$
δ_{ij}	Discrepancies



Constraints

$$\dot{T} = f(T) - T \underbrace{\left[\sum_{i=1}^{q}\sum_{j=1}^{m}\frac{\kappa_j}{q}(1-\cos(\varphi_{ij}))\right]}_{G} D$$

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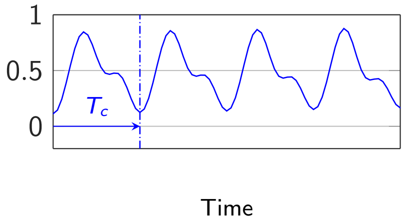
- **Sampled** measurements: (T, D)
- Treatment duration $= M \cdot T_c$
- **Upper bounds** on drug delivery:

$$\forall k \in \{1,\dots,M\}, \int_0^{T_c} u_k(\tau)d\tau = \Delta_k$$

$\sum_{j=1}^{m} \kappa_j(1-\cos(\varphi_{ij}))$



Problem Statement

Use the **measured quantities** D and T to compute, at the beginning of each period $\mathcal{T}_k$, an **optimal injection profile** $\mathbf{u}_k^* := u_k^*(\cdot)$:

$$\mathbf{u}_k := \begin{pmatrix} u_k(0) \\ u_k(\tau_s) \\ \vdots \\ u_k(T_c - \tau_s) \end{pmatrix}$$

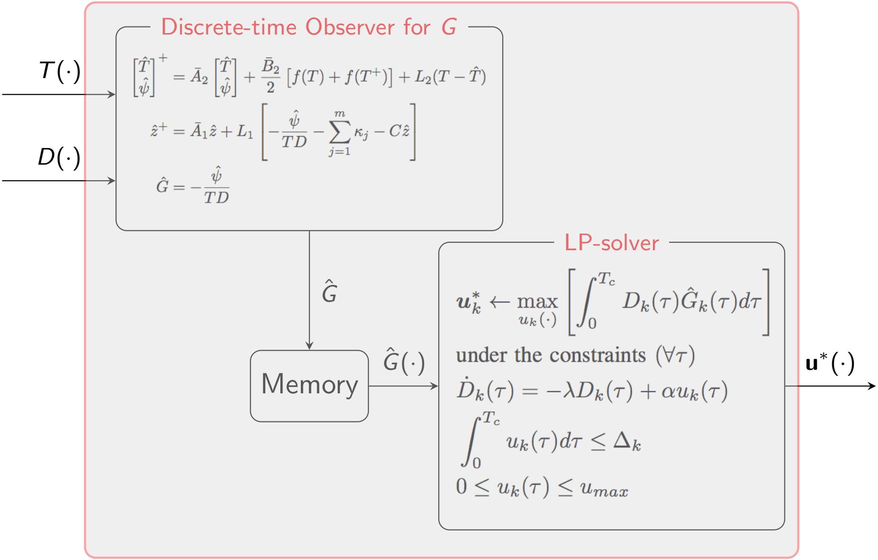
satisfying the constraints:

$$u_k(\tau) \in [0, u_{max}]$$

$$\forall k \in \{1, \dots, M\}, \int_0^{T_c} u_k(\tau) d\tau = \Delta_k$$

while **maximizing the drug's effect**.

Sketch of the solution



Validation scenarios

$$\dot{T} = f(T) - T\underbrace{\left[\sum_{i=1}^{q}\sum_{j=1}^{m}\frac{\kappa_j}{q}(1-\cos(\varphi_{ij}))\right]}_{G} D$$

$$\dot{\varphi}_{ij} = \omega_j + \delta_{ij}$$

$$\dot{D} = -\lambda D + \alpha u$$

- $f(T) = aT(1-bT)$
- $T_c \in \{1, 1.1\}$ Days
- $\tau_s = 0.1$ Days $(= 2.4\text{h})$
- $u_{max} = 8$
- $\Delta_{max} \in \{4, 1\}$
- $\kappa := (0.3, 0.006, 0.03)$
- $\delta_i := (0.04, -0.06, 0.12)$

Comparison: Proposed vs uniform:

$$u_k(\tau) = u^\dagger := \frac{\Delta_k}{T_c}$$

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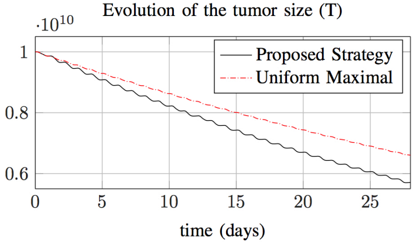
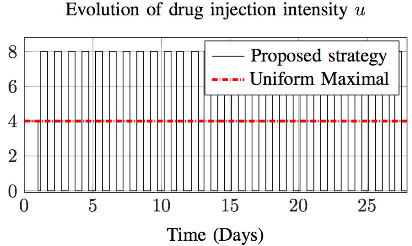
Case 1: $T_c = 1,\ \Delta_k = 4$





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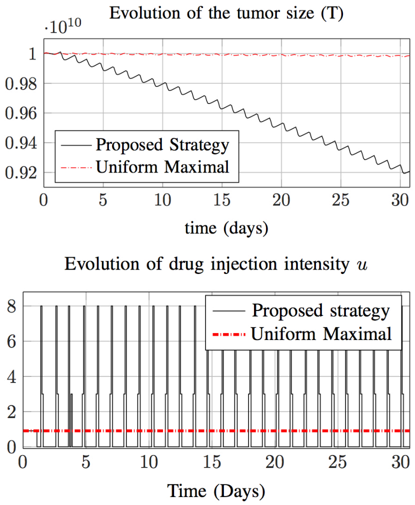
Case 2: $T_c = 1.1$, $\Delta_k = 1$



Validation scenarios

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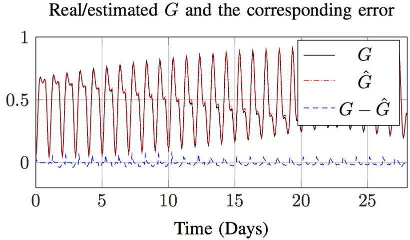
Typical observer behavior



Future work

- Use more involved cancer models:
  - combined therapy
  - multi-population models
- Deeper investigation of the phase-dependent gain's variations
- Experimental investigation with CLINATEC-CEA, Grenoble.