Observer-Based Efficiency Enhancement in Cell-Cycle Specific Therapies

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Cell-Cycle Specific Drugs

\[ G_1 \] Preparation (DNA Synthesis)
\[ S \] DNA Duplication
\[ G_2 \] Preparation
\[ M \] Cell Division (Mitosis)

Cell-Cycle Specific Drugs

$G_1$ Preparation (DNA Synthesis)

$S$ 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

\[ \dot{L} = \alpha L \ln \frac{\theta_L}{L} - \mathcal{L}_1(c)L, \quad L(0) = L_0, \]
\[ \dot{N} = \beta N \ln \frac{\theta_N}{N} - \mathcal{L}_2(c)N - \mathcal{E}(L)N, \quad t \in [0, T], \]
\[ c = c(t) \in [0, c_{\text{max}}], \quad N = N(t) \geq N_-, \quad N(0) = N_0. \]

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

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

\[
\frac{dN}{dt} = cC - fN + g\frac{T^2}{h + T^2}N - pNT - K_N (1 - e^{-M})N, \tag{2}
\]

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

\[
\frac{dC}{dt} = \alpha - \beta C - KC(1 - e^{-M})C, \tag{4}
\]

\[
\frac{dM}{dt} = -\gamma M + v_M(t), \tag{5}
\]

\[
\frac{dI}{dt} = -\mu_I I + v_I(t) \tag{6}
\]

\[
D = d \frac{(L/T)^l}{s + (L/T)^l} \tag{7}
\]

Mixed immunotherapy and chemotherapy of tumors
Standard Control-related works: A few examples

Hahnfeldt et al. Cancer Research 1999

\[
\begin{align*}
\dot{p} &= -w_1 p \ln\left(\frac{p}{q}\right) - w_2 pv_2 \\
\dot{q} &= w_3 p - (w_4 + w_5 p^{2/3})q - w_6 v_1 q \\
\dot{y}_1 &= v_1 \\
\dot{y}_2 &= v_2
\end{align*}
\]

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 !)

\[
\dot{T} = f(T) - T \left[ \sum_{i=1}^{q} \sum_{j=1}^{m} \frac{\kappa_j}{q} (1 - \cos(\varphi_{ij})) \right] D \\
\dot{\varphi}_{ij} = \omega_j + \delta_{ij} \\
\dot{D} = -\lambda D + \alpha u
\]

- **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
- **\(\omega_j\)**: Pulsation of mode \(j\) (= \(\frac{2j\pi}{T_c}\))
- **\(\delta_{ij}\)**: Discrepancies
Constraints

\[ \dot{T} = f(T) - T \left[ \sum_{i=1}^{q} \sum_{j=1}^{m} \frac{\kappa_{ij}}{q} (1 - \cos(\varphi_{ij})) \right] \]

\[ \dot{\varphi}_{ij} = \omega_{j} + \delta_{ij} \]

\[ \dot{D} = -\lambda D + \alpha u \]

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

\[ \forall k \in \{1, \ldots, M\}, \int_{0}^{T_c} u_k(\tau)d\tau = \Delta_k \]
Problem Statement

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

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

satisfying the constraints:

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

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

while maximizing the drug’s effect.
Sketch of the solution

Discrete-time Observer for $G$

\[
\begin{align*}
\begin{bmatrix} \hat{T} \\ \hat{\psi} \end{bmatrix}^+ &= \bar{A}_2 \begin{bmatrix} \hat{T} \\ \hat{\psi} \end{bmatrix}^+ + \frac{\bar{B}_2}{2} \left[ f(T) + f(T^+) \right] + L_2 (T - \hat{T}) \\
\hat{z}^+ &= \bar{A}_1 \hat{z} + L_1 \left[ -\frac{\hat{\psi}}{T_D} - \sum_{j=1}^{m} \kappa_j - C \hat{z} \right] \\
\hat{G} &= -\frac{\hat{\psi}}{T_D}
\end{align*}
\]

LP-solver

\[
\begin{align*}
\mathbf{u}_k^* \leftarrow \max_{\mathbf{u}_k(\cdot)} \left[ \int_0^{T_c} D_k(\tau) \hat{G}_k(\tau) d\tau \right] \\
\text{under the constraints (}\forall \tau) \\
\dot{D}_k(\tau) &= -\lambda D_k(\tau) + \alpha u_k(\tau) \\
\int_0^{T_c} u_k(\tau) d\tau &\leq \Delta_k \\
0 &\leq u_k(\tau) \leq u_{max}
\end{align*}
\]
Validation scenarios

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

\[ \dot{G} = -\lambda D + \alpha u \]

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

**Comparison:** Proposed vs uniform:

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

M. Alamir, IEEE CDC, Las Vegas, USA, December 2016
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**Case 1:** \( T_c = 1, \Delta_k = 4 \)

Evolution of the tumor size (T)

Evolution of drug injection intensity u

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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.