Approximate flatness-based control via a case study: Drugs administration in some cancer treatments

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Joint work with

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A better title:

In silico experiments in oncology: ...

In silico experiments (biology, medicine, ...) :
Experiments performed on computers or via computer simulations

Before *in vivo* investigations (mice, ..., human beings)

Cancer treatment via drug injections combining

1. Chemotherapy (often dangerous)
2. Immunotherapy: stimulation of immune responses (much less dangerous)

Mathematical model (d'Onofrio, Ledzewicz, Schättler (2012)):

$$
\begin{aligned}
\dot{x} &= -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - xu\eta_x \\
\dot{y} &= \mu_I \left(x - \beta x^2\right) y - \delta y + \alpha + yv\eta_y
\end{aligned}
$$

- x, y: tumor and immune cells;
- u, v: cytotoxic and immune-stimulation drugs;
- $\mu_C,\ \mu_I,\ \alpha,\ \gamma,\ \delta,\ x_\infty > 0$;
- $0 \leq \eta_x,\ \eta_y \leq 1$: uncertain and fluctuating parts of drugs delivered to the tumor (Sharifi et al. (2020))

Nominal system: $\eta_x = \eta_y = 1$

Three equilibria corresponding to $\dot{x} = \dot{y} = u = v = 0$:

1. a locally stable equilibrium which corresponds to a benign case;
2. an unstable saddle point which separates the benign and malignant regions;
3. a locally stable equilibrium which is malignant.

Drive the state variables from the region of attraction of the malignant equilibrium to the region of attraction of the benign equilibrium.

Optimal control: most popular approach

$$u = \frac{\dot{x} + \mu_C x \ln\left(\frac{x}{x_\infty}\right) + \gamma x y}{-x\eta_x} = X(x, \dot{x}, y)$$

$$v = \frac{\dot{y} - \mu_I \left(x - \beta x^2\right) y + \delta y - \alpha}{y\eta_y} = Y(y, \dot{y}, x)$$

$$\Downarrow$$

(Differential) flatness

$$\Downarrow$$

Nominal reference trajectories
and open-loop control

Fast trajectories

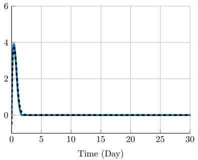
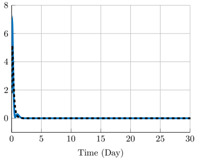


Figure: Control u (blue $--$) and Nominal control u^* (black $--$)



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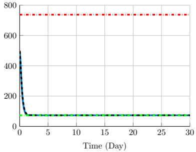


Figure: Output x (blue $--$), Reference trajectories (black $--$) and Stable points (red and green $-.$)

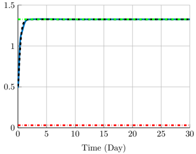
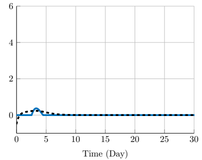


Figure: Output y (blue $--$), Reference trajectories (black $--$) and Stable points (red and green $-.$)

Slow trajectories



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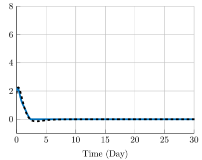

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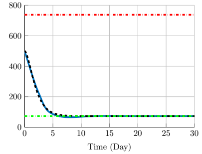

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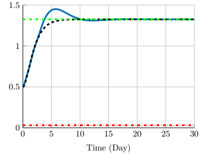

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Shooting method

Flatness $\Rightarrow$ Huge number of *in silico* trajectories[1] $\Rightarrow$ Easy selection w.r.t. optimality criteria and constraints

Example. Less drugs injections with some slow trajectories.

[1] Compare with shooting methods in optimal control and numerical analysis

Uncertainties due to drug delivery

$$\dot{y} = F + \alpha u$$

Ultra-local model, only valid during a “very short” time window

- α constant parameter chosen by the practitioner such that αu and $\dot{y}$ are of the same magnitude.
- $F = \dot{y} - \alpha u$ carries the whole structural information of the unknown system **including** the unknown perturbations

If $n = 1$, the loop is closed with an *intelligent* Proportional controller (iP):

$$u = \frac{-F^{\text{est}} + \dot{y}^* + K_P e}{\alpha}$$

where

- $F^{\text{est}} = -\frac{6}{\tau^3} \int_{t-\tau}^{t} \left((t - 2\sigma)y(\sigma) + \alpha\sigma(\tau - \sigma)u(\sigma)\right) d\sigma$
- y^* is the output reference trajectory, which might be determined via the rules of flatness-based control;
- $e = y - y^*$: tracking error;
- K_P: usual tuning gain.

The control design boils down to a pure integrator

$$\dot{e} - K_P e = F - F^{\text{est}} \approx 0$$

Local stability via straightforward gain tuning.

Fluctuation of drug delivery

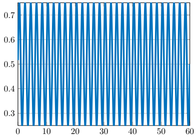


Figure: Time evolution of η_x

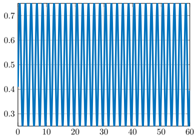


Figure: Time evolution of η_y

Very sick patient – Closed-loop control

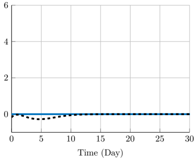
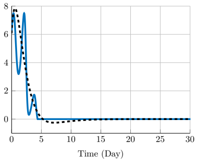


Figure: Control u (blue $-$) and Nominal control u^* (black $--$)

No chemotherapy!



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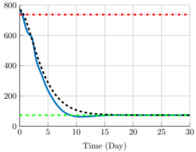

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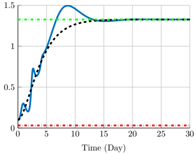

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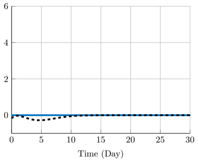
Very sick patient – Open-loop control



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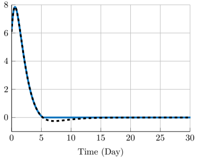

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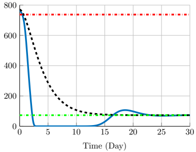

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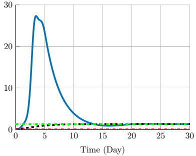

Figure: Output y (blue $-$), Reference trajectories (black $--$) and Stable points (red and green $-.$)

1. Less drugs injections with some slow trajectories
2. No need of chemotherapy in some critical situations

First concluding remarks

- The computer implementation is easy.
- Only a low computing cost is necessary.
- Some *scenarios*, i.e., *in silico* experiments, lead to unexpected results They might attract cancerologists.

Optimal control and constraints

Flatness-based control $\Rightarrow$ Shooting techniques $\Rightarrow$ Easy handling of "fuzzy" optimization and constraints

Illustrations

- Minimize $u(t)$, $0 \leq t \leq T$, **or** $\int_0^T u(t)dt$ **or** $\int_0^T (u(t))^2 dt$?
- Writing a criterion for minimizing the time duration **and** the drug quantity is **not obvious**

An epistemological detour

- Clear-cut criteria $\Longleftrightarrow$ Fundamental physical laws (variational principles)
- Applied sciences $\Rightarrow$ fuzzy criteria

Model mismatch

via model-free control

Mixing flatness-based & model-free controls

First example:

J. Villagra, D. Herrero-Pérez, A comparison of control techniques for robust docking maneuvers of an AGV. IEEE Trans. Contr. Syst. Techno., 20, 2012, 1116-1123.

Very powerful technique → a mainstay in control engineering

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Other medical references

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4. E. Manzoni, M. Rampazzo, Automatic regulation of anesthesia via ultra-local model control, IFAC PapersOnLine, 54-15, 2021, 49-54.
5. C. Join, A. d'Onofrio, M. Fliess, Toward more realistic social distancing policies via advanced feedback control, Automation, 3, 2022, 286–301.