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Toward simple *in silico* experiments for drugs administration in some cancer treatments

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Abstract.— We present some “in silico” experiments to design combined chemo- and immunotherapy treatment schedules. We introduce a new framework by combining flatness-based control, which is a model-based setting, along with model-free control. The flatness property of the used mathematical model yields straightforward reference trajectories. They provide us with the nominal open-loop control inputs. Closing the loop via model-free control allows to deal with the uncertainties on the injected drug doses. Several numerical simulations illustrating different case studies are displayed. We show in particular that the considered health indicators are driven to the safe region, even for critical initial conditions. Furthermore, in some specific cases there is no need to inject chemotherapeutic agents.

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Keywords: Biomedical control, cancer, nonlinear control, fault accommodation, flatness-based control, model-free control, shooting method.

1. INTRODUCTION

We consider drug injections scheduling for cancer treatments from a control point of view (see, *e.g.*, Chap. 10 in Padmanabhan *et al.* (2021) for bibliographical references). Among the many models which have been used, those stemming from an earlier work of Stepanova (1979) are quite popular. Most appealing are several publications by d’Onofrio and different coauthors: see especially d’Onofrio *et al.* (2012). Such approaches to chemo- and immunotherapy led in recent years to promising control-theoretic investigations: see, *e.g.*, Alamir (2014); Schättler & Ledzewicz (2015) and references therein; Moussa *et al.* (2020); Sharifi *et al.* (2017, 2020a). They employ various optimization techniques which are related to optimal control, model predictive control, and robust control.

We explore here another route via tools which are combined here for the first time, although they both gave rise to an abundant literature in control engineering:

- (1) *Flatness*-based control (see Fliess *et al.* (1995, 1999); and Sira-Ramírez & Agrawal (2004); Lévine (2009); Rudolph (2021)) is a model-based approach which has

been well received in many industrial domains. See, *e.g.*, Bonnabel & Claves (2020) for tower cranes.

- (2) Besides being useful in concrete case-studies (see, *e.g.*, Amasyali *et al.* (2020); Park & Olama (2021); Park *et al.* (2021); Telsang *et al.* (2021); Tumin *et al.* (2021) for energy management), *model-free* control in the sense of Fliess & Join (2013, 2021) has already been illustrated in biomedicine (MohammadRidha *et al.* (2018); Bara *et al.* (2018); Faraji *et al.* (2021)) and in bioengineering (Truong *et al.* (2021)). Note that the terminology “model-free control” has been used many times with different definitions: see Chareyron & Alamir (2009) in oncology.

Our *virtual patient* is modeled through two ordinary differential equations presented by d’Onofrio *et al.* (2012). This system is trivially flat with obvious *flat outputs*. The design of suitable reference trajectories with the corresponding open-loop controls becomes straightforward. A major source of uncertainty, according to Sharifi *et al.* (2020a), is the unknown fluctuation of the drug delivery to the tumor, which should be related to actuators faults, *i.e.*, to a classic topic in fault-tolerant control (see, *e.g.*, Noura *et al.* (2015)). It has been already noticed that model-free control is well-suited for dealing with actuators

faults: see Fliess & Join (2013) for an academic example and Lafont *et al.* (2015) for a concrete case-study. The loop is therefore closed via model-free control. Let us emphasize the following points:

- 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.

Our paper is organized as follows. Section 2 presents the dynamical model of the virtual patient, Section 3 reviews briefly flatness-based control, and model-free control. Numerical simulations are presented in Section 4. Section 5 contains some suggestions for future research on: 1) the possible medical impact of our *in silico* experiments, 2) some aspects related to *systems biology*, 3) new control paradigms which might be derived from the methods developed here.

See Fliess *et al.* (2021) for a first draft.

2. VIRTUAL PATIENT DYNAMICAL MODEL

We consider the model presented in d'Onofrio *et al.* (2012)

$$\dot{x} = -\mu_C x \ln\left(\frac{x}{x_\infty}\right) - \gamma xy - x u \eta_x \quad (1)$$

$$\dot{y} = \mu_I (x - \beta x^2) y - \delta y + \alpha + y v \eta_y \quad (2)$$

x , y are, respectively, the number of tumor cells and the immune cell density; the control variables u and v are the cytotoxic and immune-stimulation drugs; the parameters μ_C , μ_I , α , γ , δ , x_∞ are positive. The terms η_x , η_y , $0 \leq \eta_x \leq 1$, $0 \leq \eta_y \leq 1$, are inspired by Sharifi *et al.* (2020a): they represent the uncertain and fluctuating parts of drugs which are delivered to the tumor. The definition as well as the numerical values of these parameters can be found in Table 1.

Parameter	Definition	Numerical Value
μ_C	tumor growth rate	$1.0078 \cdot 10^7$ cells/day
μ_I	tumor stimulated proliferation rate	$.0029 \text{ day}^{-1}$
α	rate of immune cells influx	$.0827 \text{ day}^{-1}$
β	inverse threshold	$.0031$
γ	interaction rate	$1 \cdot 10^7$ cells/day
δ	death rate	$.1873 \text{ day}^{-1}$
η_x	chemotherapeutic killing parameter	$1 \cdot 10^7$ cells/day
η_y	immunotherapy injection parameter	$1 \cdot 10^7$ cells/day
x_∞	fixed carrying capacity	$780 \cdot 10^6$ cells

Table 1.

This system has three equilibria corresponding to $\dot{x} = \dot{y} = u = v = 0$:

- (1) a locally stable equilibrium $x = 73$, $y = 1.32$ which corresponds to a benign case;
- (2) an unstable saddle point $x = 356.2$, $y = 0.439$, which separates the benign and malignant regions;
- (3) a locally stable equilibrium $x = 737.3$, $y = 0.032$, which is malignant.

The idea behind controlling such systems consists in driving the state trajectories from the region of attraction of the malignant equilibrium (critical case) to the region of attraction of the benign equilibrium. The simulations that are presented in this paper will show that the state trajectories are driven to the benign equilibrium under control action (drug delivery) for different settings.

3. CONTROL METHODOLOGY

3.1 Flatness property

A control system with m independent control variables is said to be (*differentially*) *flat* if, and only if, there exists m system variables y_1, \dots, y_m , the *flat outputs*, such that any system variable z , the control variables for instance, may be expressed as a *differential* function of y_1, \dots, y_m , *i.e.*, $z = \Phi(y_1, \dots, y_m, \dots, y_1^{(\nu_1)}, \dots, y_m^{(\nu_m)})$, where the derivation orders ν_1, \dots, ν_m are finite. A linear system is flat if, and only if, it is controllable. Thus flatness may be viewed as another extension of Kalman's controllability.

Equations (1)-(2) yield

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

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

The above equations show immediately that System (1)-(2) is flat; x , y are flat outputs.

3.2 Reference trajectory and nominal open-loop control

One of the main benefits of flatness is the possibility of easily deriving a suitable reference trajectory and the corresponding nominal open-loop control. For a given reference trajectory $x^*(t)$, $y^*(t)$, the corresponding nominal control variables

$$u^*(t) = X(x^*(t), \dot{x}^*(t), y^*(t)) \quad (3)$$

$$v^*(t) = Y(y^*(t), \dot{y}^*(t), x^*(t)) \quad (4)$$

might exhibit unacceptable negative values. Define therefore the nominal open-loop control variables

$$u_{OL}(t) = u^*(t) \text{ if } u^*(t) \geq 0, \quad u_{OL}(t) = 0 \text{ if } u^*(t) < 0$$

$$v_{OL}(t) = v^*(t) \text{ if } v^*(t) \geq 0, \quad v_{OL}(t) = 0 \text{ if } v^*(t) < 0$$

3.3 Closing the loop via model-free control

From a control-engineering standpoint the terms η_x and η_y should be related to actuators faults. Introduce therefore the two “decoupled” *ultra-local models* (Fliess & Join (2013); Lafont *et al.* (2015)):

$$\dot{z}_x = F_x + \alpha_x u_{MFC}, \quad \dot{z}_y = F_y + \alpha_y v_{MFC}$$

where $z_x = x - x^*$, $z_y = y - y^*$ are the tracking errors; α_x (resp. α_y) is a constant parameter which is chosen by the practitioner such that \dot{x} and $\alpha_x u$ (resp. \dot{y} and $\alpha_y v$) are of the same order of magnitude; F_x and F_y , which are data-driven, subsume the poorly known structures and disturbances. A real-time estimation (Fliess & Join (2013)) of F_x , F_y are given by

$$F_x^{\text{est}} = -\frac{6}{\tau_x^3} \int_{t-\tau_x}^t ((t-2\sigma)x(\sigma) + \alpha_x \sigma(\tau_x - \sigma) u_{MFC}(\sigma)) d\sigma$$

$$F_y^{\text{est}} = -\frac{6}{\tau_y^3} \int_{t-\tau_y}^t ((t-2\sigma)y(\sigma) + \alpha_y \sigma(\tau_y - \sigma) v_{MFC}(\sigma)) d\sigma$$

where $\tau_x, \tau_y > 0$ are “small.” Close the loop via an *intelligent Proportional* controller, or *iP*,

$$u_{\text{MFC}} = -\frac{F_x^{\text{est}} + K_{x,P}z_x}{\alpha_x}, \quad v_{\text{MFC}} = -\frac{F_y^{\text{est}} + K_{y,P}z_y}{\alpha_y}$$

where $K_{x,P}, K_{y,P} > 0$. From $\dot{z}_x + K_{x,P}z_x = 0$, $\dot{z}_y + K_{y,P}z_y = 0$, it follows that those two gains ensure local stability around the reference trajectory.

The close-loop controls u_{CL} , v_{CL} may now be defined:

- If $u_{\text{OL}} + u_{\text{MFC}} \geq 0$, then $u_{\text{CL}} = u_{\text{OL}} + u_{\text{MFC}}$; if $u_{\text{OL}} + u_{\text{MFC}} < 0$, then $u_{\text{CL}} = 0$.
- If $v_{\text{OL}} + v_{\text{MFC}} \geq 0$, then $v_{\text{CL}} = v_{\text{OL}} + v_{\text{MFC}}$; if $v_{\text{OL}} + v_{\text{MFC}} < 0$, then $v_{\text{CL}} = 0$.

4. NUMERICAL SIMULATIONS

4.1 Presentation

A shooting method A huge number in silico experiments have been most easily performed via the flatness property, *i.e.*, via Formulae (3)-(4). It permits to select the most suitable ones with respect to boundary conditions, optimality criteria and constraints. Our approach might appear therefore as an alternative to the *shooting* methods in optimal control and numerical analysis (see, *e.g.*, Carraro et al. (2015); Pellegrini & Russell (2020)).

Time sampling and duration The duration of an experiment is 60 days. The time sampling interval is equal to 30 minutes.

Remark 1. The total simulations duration is 60 days, even though the figures are limited to 30 days for visibility reasons, since all the variables reach a steady state at this time.

4.2 Closed-loop and total amount of drugs

Set $\eta_x = \eta_y = 0.5$. This nominal value might be large according to Sharifi et al. (2020a). Figures 1 and 2 display two experiments with the same initial point $x = 500$, $y = 0.5$, which lies in the attraction region of the malignant equilibrium. The total amounts of injected drugs, which are often considered as important constraints, are given by the two integrals $\int_0^T u_{\text{CL}}(\tau)d\tau$, $\int_0^T v_{\text{CL}}(\tau)d\tau$, where T is the experiment duration. Figure 3 indicates that the quantity of drugs injected during the slow scenario is lower than in the fast one. This outcome ought to be discussed in oncology.

4.3 Other scenarios

Same initial point. Here $\eta_x = 0.31$, $\eta_y = 0.75$ are supposed to be unknown. Use the same nominal parameters as in Section 4.2, and the feedback loop of Section 3.3, with $\alpha_x = -10000$, $\alpha_y = 1$, $K_{x,P} = 100$, $K_{y,P} = 10$. The results depicted in Figures 4 and 5 show that the benign equilibrium is reached after a short period of time.

New initial point. The virtual patient is in a critical state, *i.e.*, the initial state $x = 770$, $y = 0.1$ is close to the malignant equilibrium. The time variation of η_x and η_y , which are displayed in Figure 8, are assumed to be

unknown. It is possible to cure the virtual patient without the cytotoxic drug, *i.e.*, $u_{\text{CL}} \equiv 0$. Figure 6, which should be of interest for cancerologists, exhibits a convergence to the benign equilibrium with some oscillations perhaps due to the violent fluctuations of η_y . The quality of the open loop behavior in Figure 7 is lower.

5. CONCLUSION

5.1 Main goal

Some results encountered with our computer experiments might question oncologists:

- the quantity of injected drug might be lower in some slow scenario than in the corresponding fast one;
- there are critical situations where only immunotherapy matters: the cytotoxic drugs are useless.

Those startling calculations need of course to be further analyzed.

5.2 Systems Biology

In the spirit of *Systems Biology* (see, *e.g.*, Del Vecchio & Murray (2015)), let us suggest the the following research tracks:

- Examine parameter identification in Equation (1).
- Flatness-based control might be helpful elsewhere: (1) Another model due to Hahnfeldt et al. (1999) has also been investigated from a control-theoretic perspective (see, *e.g.*, Kovács et al. (2014), Schättler & Ledzewicz (2015) and references therein, Cacace et al. (2018)). It is easy to check that it is flat; (2) the unicycle in Sharifi et al. (2020b), which is used as a nanorobot for drug delivery, is well known to be flat.

5.3 New control paradigms?

The control strategy which has been developed here for oncological in silico experiments might lead to new paradigms:

- (1) Assume that we have a flat nominal system with some important uncertainties. Use open-loop flatness-based techniques. Close the loop via model-free control. What's about flatness-based control of partial differential equations (see, *e.g.*, Rudolph (2003); Meurer (2013); and references therein)?
- (2) Investigate possible connections with *Active Disturbance Rejection Control*, or *ADRC*, as presented by Sira-Ramírez et al. (2017).

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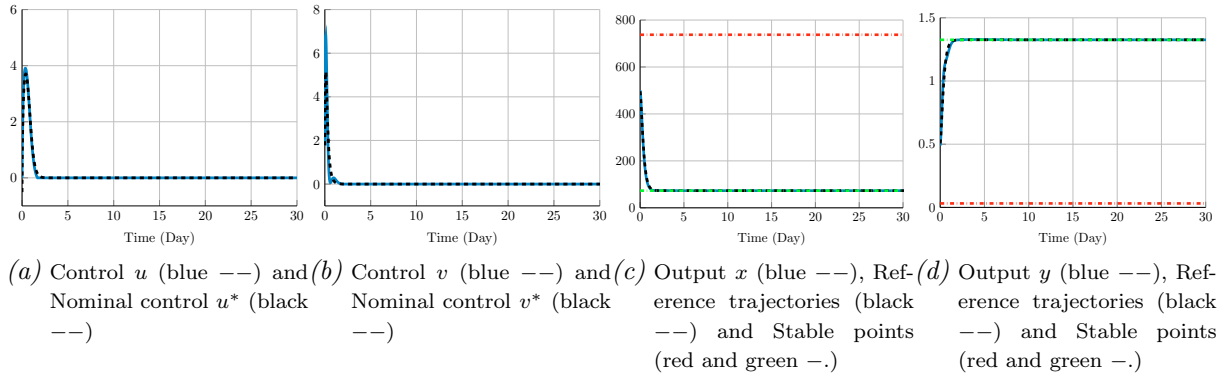


Figure 1. Fast trajectory

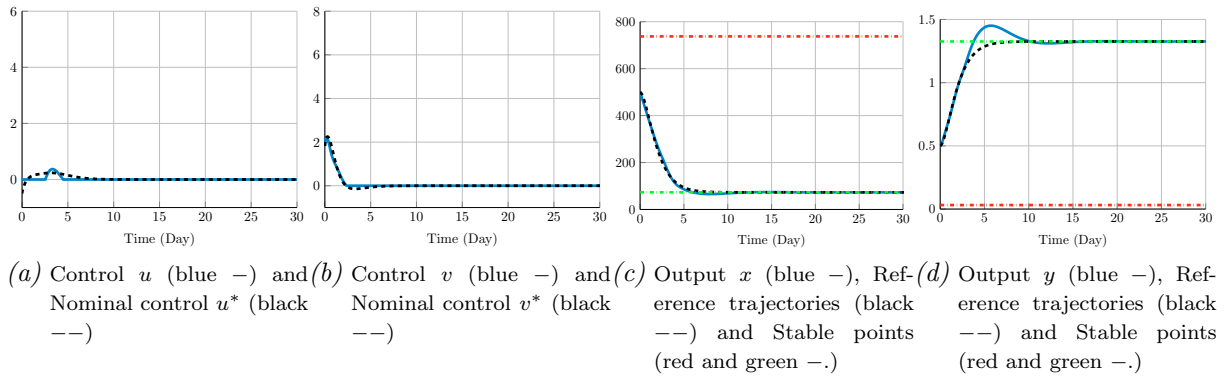


Figure 2. Slow trajectory

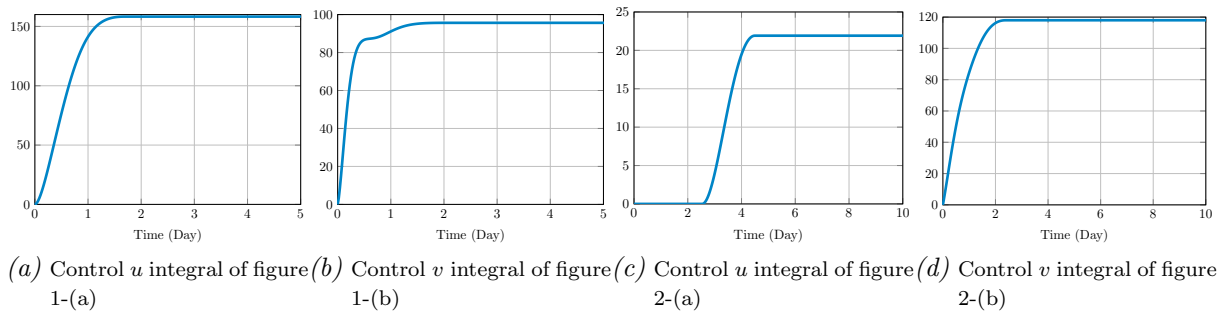
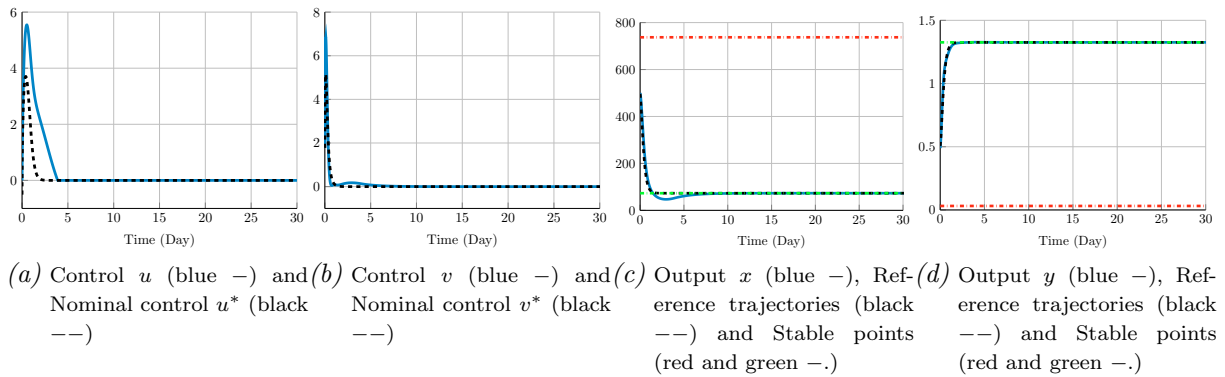


Figure 3. Comparison between total drug injections

Figure 4. Unknown variation of η_x

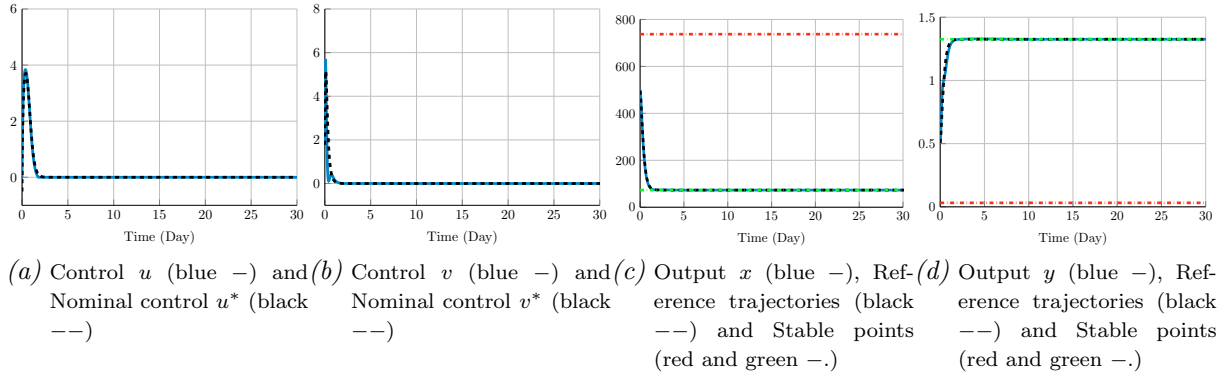
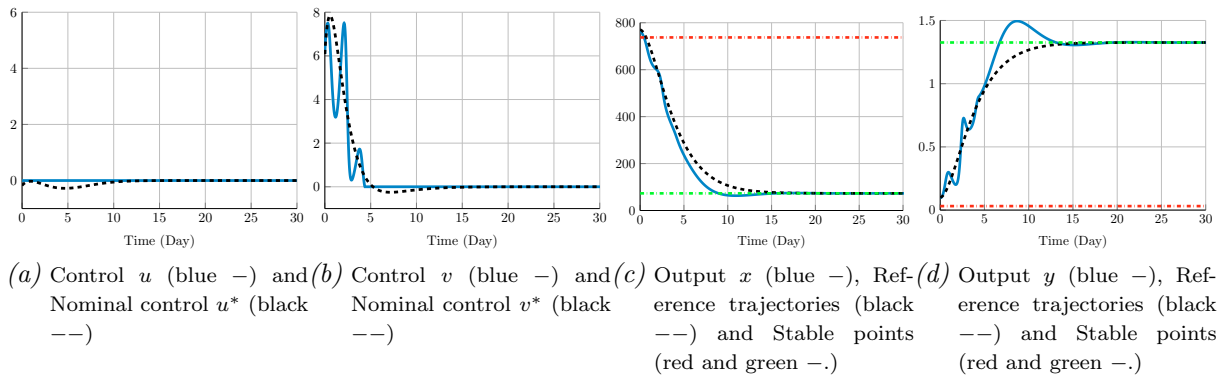
Figure 5. Unknown variation of η_y 

Figure 6. Very sick patient

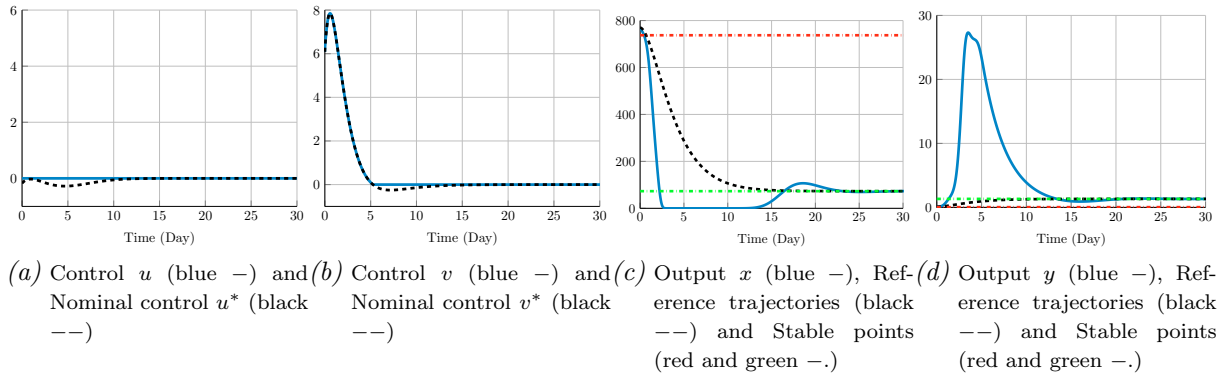


Figure 7. Open loop

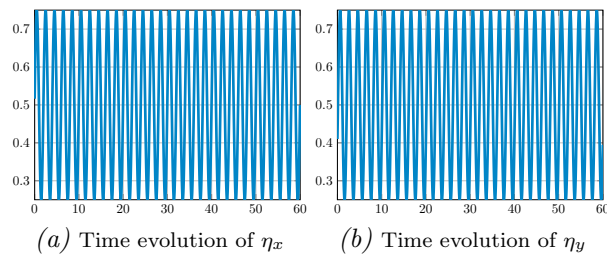


Figure 8. Fluctuation of the drug delivery