



**HAL**  
open science

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

Michel Fliess, Cédric Join, Kaouther Moussa, Seddik M Djouadi, Mohamed W Alsager

### ► To cite this version:

Michel Fliess, Cédric Join, Kaouther Moussa, Seddik M Djouadi, Mohamed W Alsager. Toward simple in silico experiments for drugs administration in some cancer treatments. BMS 2021 - 11th IFAC symposium on Biological and Medical Systems (BMS 2021), Sep 2021, Ghent, Belgium. 10.1016/j.ifacol.2021.10.263 . hal-03299417v2

**HAL Id: hal-03299417**

**<https://polytechnique.hal.science/hal-03299417v2>**

Submitted on 10 Nov 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Michel Fliess<sup>\*,†</sup> Cédric Join<sup>\*\*,†</sup> Kaouther Moussa<sup>\*\*\*</sup>  
Seddik M. Djouadi<sup>\*\*\*\*</sup> Mohamed W. Alsager<sup>\*\*\*\*</sup>

\* LIX (CNRS, UMR 7161), École polytechnique, 91128 Palaiseau,  
France (e-mail: Michel.Fliess@polytechnique.edu).

\*\* CRAN (CNRS, UMR 7039), Université de Lorraine, BP 239,  
54506 Vandœuvre-lès-Nancy, France  
(e-mail: cedric.join@univ-lorraine.fr)

\*\*\* Université Grenoble Alpes, CNRS, Grenoble INP, GIPSA-lab,  
38000 Grenoble, France (e-mail: kaouther.moussa@gipsa-lab.fr)

\*\*\*\* Department of Electrical Engineering and Computer Science,  
University of Tennessee, Knoxville, TN 37996, USA  
(e-mail: mdjouadi@utk.edu, malsager@vols.utk.edu)

† A.L.I.E.N., 7 rue Maurice Barrès, 54330 Vézelize, France  
(e-mail: {michel.fliess, cedric.join}@alien-sas.com)

**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.

Copyright © 2021 The Authors. This is an open access article under the CC BY-NC-ND license (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

**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 & Clayes (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)

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

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

$x$ ,  $y$  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  $\mu_C$ ,  $\mu_I$ ,  $\alpha$ ,  $\gamma$ ,  $\delta$ ,  $x_\infty$  are positive. The terms  $\eta_x$ ,  $\eta_y$ ,  $0 \leq \eta_x \leq 1$ ,  $0 \leq \eta_y \leq 1$ , 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
$\mu_C$	tumor growth rate	$1.0078 \cdot 10^7$ cells/day
$\mu_I$	tumor stimulated proliferation rate	$.0029 \text{ day}^{-1}$
$\alpha$	rate of immune cells influx	$.0827 \text{ day}^{-1}$
$\beta$	inverse threshold	$.0031$
$\gamma$	interaction rate	$1 \cdot 10^7$ cells/day
$\delta$	death rate	$.1873 \text{ day}^{-1}$
$\eta_x$	chemotherapeutic killing parameter	$1 \cdot 10^7$ cells/day
$\eta_y$	immunotherapy injection parameter	$1 \cdot 10^7$ cells/day
$x_\infty$	fixed carrying capacity	$780 \cdot 10^6$ cells

Table 1.

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

- (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  $\nu_1, \dots, \nu_m$  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  $\eta_x$  and  $\eta_y$  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;  $\alpha_x$  (resp.  $\alpha_y$ ) 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  $u_{\text{CL}}, v_{\text{CL}}$  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  $\eta_x$  and  $\eta_y$ , 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  $\eta_y$ . 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).

## REFERENCES

- Alamir M. (2014). Robust feedback design for combined therapy of cancer. *Optim. Control Appl. Meth.*, 35, 77-88.
- Amasyali K., Chen Y., Telsang B., Olama M., Djouadi S.M. (2020). Hierarchical model-free transactional control of building loads to support grid services. *IEEE Access*, 8, 219367-219377.
- Bara O., Fliess M., Join C., Day J., Djouadi S.M. (2018). Toward a model-free feedback control synthesis for treating acute inflammation. *J. Theoret. Bio.*, 448, 26-37.

- Bonnabel S., Clayes X. (2020). The industrial control of tower cranes: An operator-in-the-loop approach. *IEEE Contr. Syst. Magaz.*, 40, 27-39.
- Cacace F., Cusimano V., Germani A., Palumbo A., Papa F. (2018). Closed-loop control of tumor growth by means of anti-angiogenic administration. *Math. Biosci. Engin.*, 15, 827-839.
- Carraro T., Geiger M., Körkel S., Rannacher R. (Eds) (2015). *Multiple Shooting and Time Domain Decomposition Methods*. Springer.
- Chareyron S., Alamir M. (2009). Model-free feedback design for a mixed cancer therapy. *Biotech. Progr.*, 25, 690-700.
- Del Vecchio M., Murray R.M. (2015). *Biomolecular Feedback Systems*. Princeton University Press.
- Faraji B., Gheisarnejad M., Rouhollahi K., Esfahani Z., Khooban M.H. (2021). Machine learning approach based on ultra-local model control for treating cancer pain. *IEEE Sensors J.*, 21, 8245-8252.
- Fliess M., Join C. (2013). Model-free control. *Int. J. Contr.*, 86, 2228-2252.
- Fliess M., Join C. (2021). An alternative to proportional-integral and proportional-integral-derivative regulators: Intelligent proportional-derivative regulators. *Int. J. Robust Nonlinear Contr.*, 2021.  
<https://doi.org/10.1002/rnc.5657>
- Fliess M., Join C., Moussa K., Djouadi S.M., Alsager M. (2021). Preliminary *in silico* experiments: Towards new cancer treatments? *bioRxiv*,  
<https://doi.org/10.1101/2021.04.06.438636>
- Fliess M., Lévine J., Martin P., Rouchon P. (1995). Flatness and defect of non-linear systems: introductory theory and examples. *Int. J. Contr.*, 61, 1327-1361.
- Fliess M., Lévine J., Martin P., Rouchon P. (1999). A Lie-Bäcklund approach to equivalence and flatness of nonlinear systems. *IEEE Trans. Automat. Contr.*, 44, 922-937.
- Hahnfeldt P., Panigrahy D., Folkman J., Hlatky L. (1999). Tumor development under angiogenic signaling: A dynamical theory of tumor growth, treatment response, and postvascular dormancy. *Cancer Res.*, 59, 4770-4775.
- Kovács L., Szeles A., Sági J., Drexler D.A., Rudas I., Harmati I., Sági Z. (2014). Model-based angiogenic inhibition of tumor growth using modern robust control method. *Comput. Meth. Program. Biomed.*, 114, e98-e110.
- Lafont F., Balmat J.-F., Pessel N., Fliess M. (2015). A model-free control strategy for an experimental greenhouse with an application to fault accommodation. *Comput. Electron. Agricult.*, 110, 139-149.
- Meurer T. (2013). *Control of Higher-Dimensional PDEs – Flatness and Backstepping Designs*. Springer.
- Lévine J. (2009). *Analysis and Control of Nonlinear Systems: A Flatness-based Approach*. Springer.
- MohammadRidha T., Ait-Ahmed M., Chaillous L., Krempf M., Guilhem I., Poirier J.Y., Moog C.H. (2018). Model free iPID control for glycemia regulation of type-1 diabetes. *IEEE Trans. Biomed. Eng.*, 65, 199-206.
- Moussa K., Fiacchini M., Alamir M. (2020). Robust optimal scheduling of combined chemo- and immunotherapy: Considerations on chemotherapy detrimental effects. *Amer. Contr. Conf.*, Denver.
- Noura H., Theilliol D., Ponsart J.-C., Chamseddine A. (2009). *Fault-tolerant Control Systems: Design and Practical Applications*. Springer.
- d’Onofrio A., Ledzewicz U., Schättler H. (2012). On the dynamics of tumor-immune system interactions and combined chemo- and immunotherapy. A. d’Onofrio, P. Cerrai, A. Gandolfi (Eds.): *New Challenges for Cancer Systems Biomedicine*, Springer, pp. 249-266.
- Padmanabhan R., Meskin N., Al Moustafa A.-I. (2021). *Mathematical Models of Cancer and Different Therapies – Unified Framework*. Springer.
- Park B., Olama M. (2020). A model-free voltage control approach to mitigate motor stalling and FIDVR for smart grids. *IEEE Trans. Smart Grid*, 12, 67-78.
- Park B., Zhang Y., Olama M., Kuruganti T. (2021). Model-free control for frequency response support in microgrids utilizing wind turbines. *Elec. Power Syst. Res.*, 194, 107080.
- Pellegrini E., Russell R.P. (2020). A multiple-shooting differential dynamic programming algorithm. Part 1: Theory. *Acta Astronaut.*, 170, 686-700.
- Rudolph J. (2003). *Flatness Based Control of Distributed Parameter Systems*. Shaker Verlag.
- Rudolph J. (2021). *Flatness-Based Control: An Introduction*. Shaker Verlag.
- Schättler H., Ledzewicz U. (2015). *Optimal Control for Mathematical Models of Cancer: An Application of Geometric Methods*. Springer, 2015.
- Sharifi N., Ozgoli S., Ramezani A. (2017). Multiple model predictive control for optimal drug administration of mixed immunotherapy and chemotherapy of tumours. *Comput. Meth. Program. Biomed.*, 144, 13-19.
- Sharifi N., Zhou Y., Holmes G., Chen Y. (2020a). Overcoming channel uncertainties in touchable molecular communication for direct-drug-targeting-assisted immuno-chemotherapy. *IEEE Trans. Nanobiosci.*, 19, 249-258.
- Sharifi N., Ali M., Holmes G., Chen Y. (2020b). Blind obstacle avoidance using taxicab geometry for Nanorobot-Assisted direct drug targeting. *42nd Int. Conf. IEEE Engin. Med. Biol. Soc.*, Montreal.
- Sira-Ramírez H., & Agrawal S.K. (2004). *Differentially Flat Systems*. Marcel Dekker.
- Sira-Ramírez H., Luviano-Juárez A., Ramírez-Neria M., Zurita-Bustamante E.W. (2017). *Active Disturbance Rejection Control of Dynamic Systems – A Flatness-Based Approach*. Butterworth-Heinemann.
- Stepanova N.V. (1979). Course of the immune reaction during the development of a malignant tumour (*in Russian*). *Biophysics*, 24, 917-923.
- Telsang B., Amasyali K., Chen Y., Olama M., Djouadi S. (2021). Power allocation by load aggregator with heterogeneous loads using weighted projection. *Energy Buildings*, 242, 110955.
- Truong C.T., Huynh K.H., Duong V.T., Nguyen H.H., Pham L.A., Nguyen T.T. (2021). Model-free volume and pressure cycled control of automatic bag valve mask ventilator. *AIMS Bioengin.*, 8, 192-207.
- Tumin W., Olama M.M., Djouadi S.M. (2021). Adaptive Control for Residential HVAC Systems to Support Grid Services. *IEEE Power Energ. Soc. Innov. Smart Grid Techno. Conf.*, Washington.

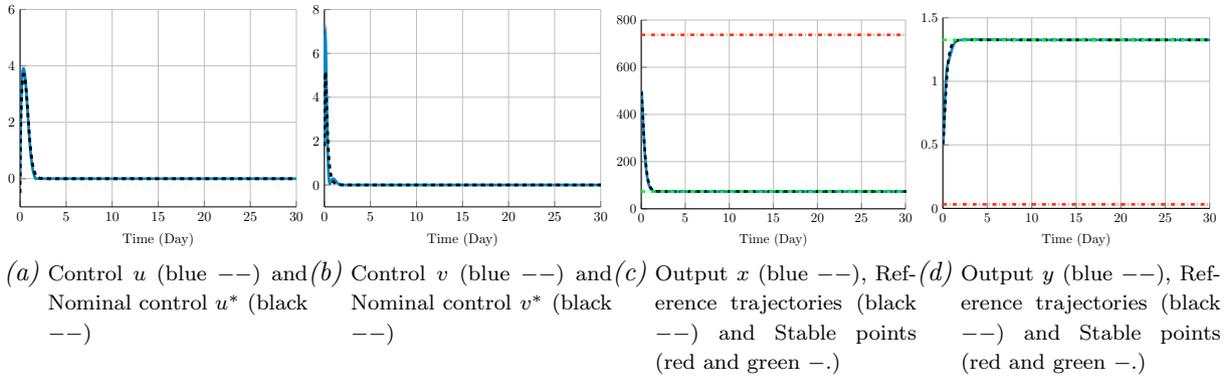


Figure 1. Fast trajectory

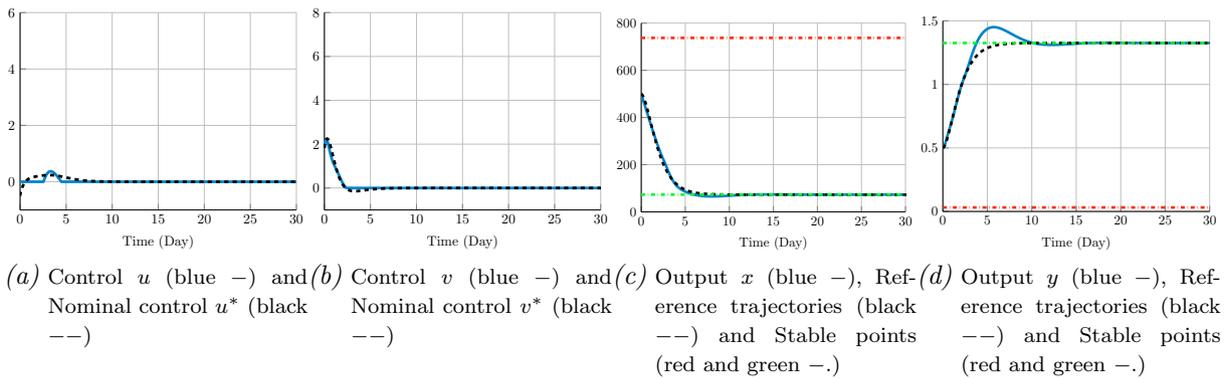


Figure 2. Slow trajectory

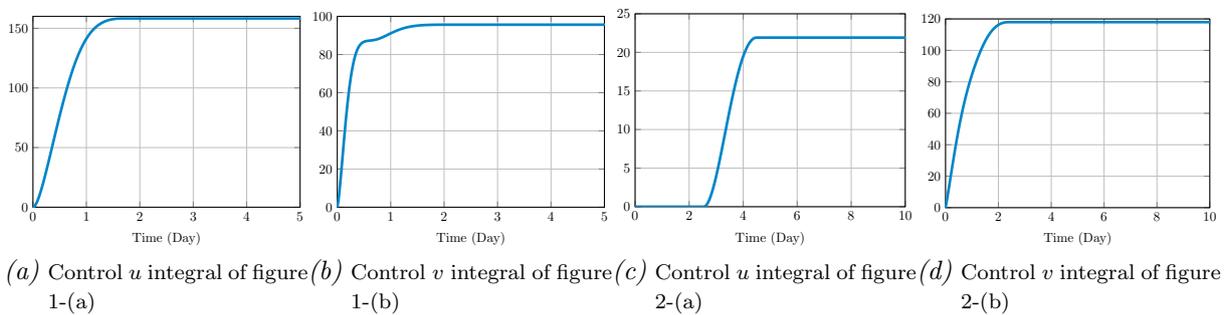


Figure 3. Comparison between total drug injections

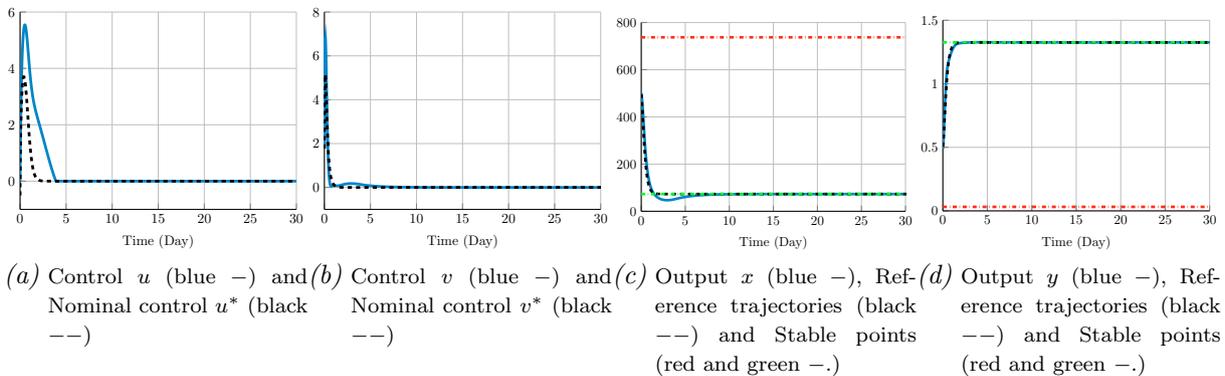


Figure 4. Unknown variation of  $\eta_x$

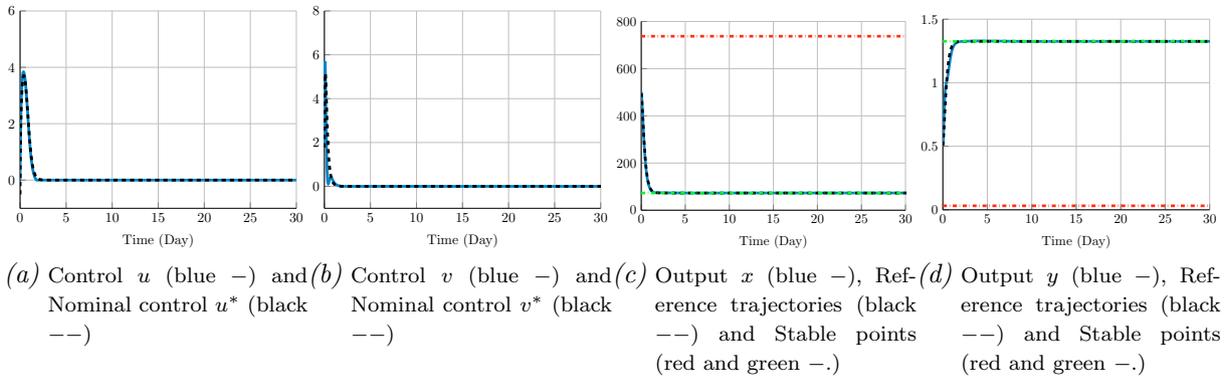


Figure 5. Unknown variation of  $\eta_y$

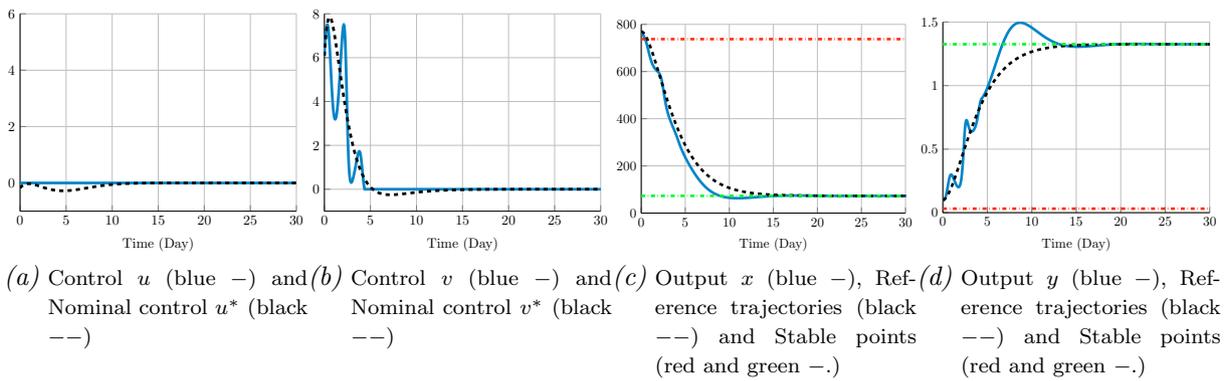


Figure 6. Very sick patient

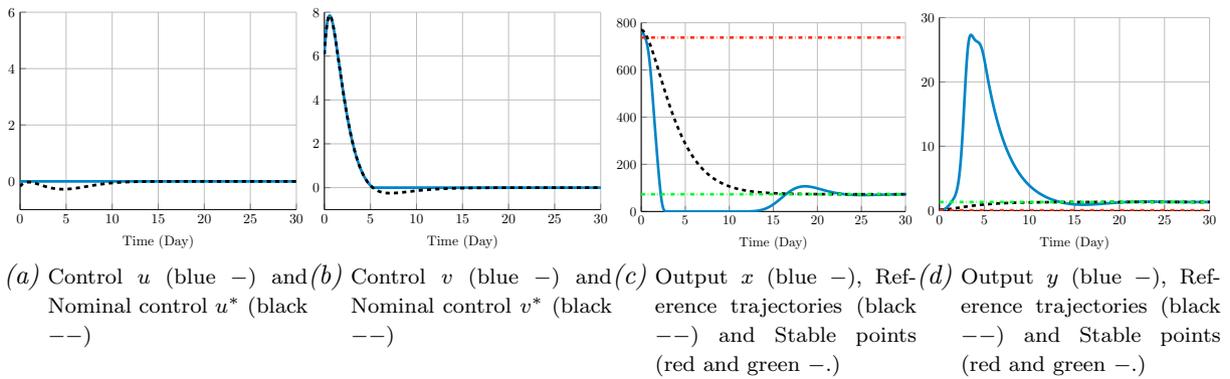


Figure 7. Open loop

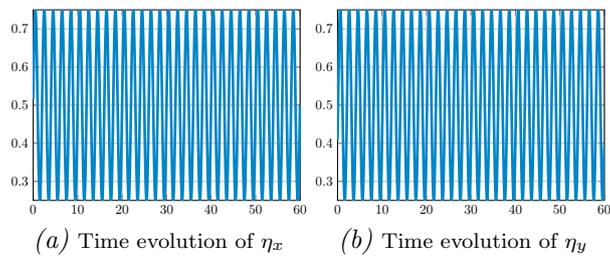


Figure 8. Fluctuation of the drug delivery