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Sustainability and long-term strategies in the modeling of biological processes. ⋆

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Abstract: In this article, we intend to explore the role of using an "infinite time horizon" framework to address the issues of sustainability and long-term strategies in the control of biological processes. We use two case study models to explain why considering a fixed or moving endpoint does not lead to the desired long-term effects. The first biological model considered concerns the spread of an infectious disease and its treatment as an infinite horizon optimal control problem. The second one deals with the metronomic chemotherapy cancer treatment over the remaining lifetime horizon of the patient. The latter is consistent with the conception of cancer as a chronic disease. Both models show structural differences in the choice of the objective functional, the first one uses a stabilization functional containing a weight function, the second one contains a damage functional which involves a density function.

Keywords: Sustainability, long-term strategies, infinite horizon, optimal control, biological processes, metronomic chemotherapy, SEIR model.

1. INTRODUCTION

In this paper we intend to investigate the role of using the infinite horizon framework to address the questions of sustainability and long-term treatment strategies while controlling biological processes.

Problems of calculus of variations and optimal control problems over unbounded intervals arise in a very natural way, when one investigates dynamic systems describing macroeconomic growth processes. These economic growth models are characterized by an objective functional which acts over an unbounded domain and usually contains a discount factor in the integral functional. Economic models which lead to infinite horizon problems of optimal control resp. calculus of variations have been considered for the very first time in Ramsey (1928). The work of Ramsey had an essential impact on the development of the modern concepts of sustainable economic growth and influenced this so far, that the consideration of an infinite time horizon in the macroscopic economic models has become common. Ramsey's ground-breaking suggestion was to model the society as an infinitely long living individual. In the years 1960 - 1970, the development of this economic area has had a great influence on the discovery of the famous maximum principle of the optimal control theory by the research group around L. S. Pontryagin, cf. Pontryagin et al. (1969), Carlson et al. (1991). Arrow and Kurz (1970), p. xviii, have explained the introduction of an infinite time planning interval as follows: *"The infinite horizon is an idealization of the fundamental point that the consequences of investment are very long-lived; any short horizon requires some methods of evaluating end-of-period capital stocks, and the only proper evaluation is their value in use in the subsequent future."*

Optimal control problems are of interest not only for economic growth models. They appear also in biological models in which the consideration of a fixed finite time horizon seems to be unnatural. It is more realistic to consider the planning time period T itself as an exponentially distributed random variable, cf. Pickenhain (2010). Last but not least, problems of asymptotic controllability of dynamic systems towards a system equilibrium can be modeled as an infinite horizon optimal control problem, cf. Kalman (1960).

Areas of applications for infinite horizon optimal control problems range from macroeconomic problems, cf. Cass (1965), Lykina et al. (2008), Magill (1982), Sethi & Thompson (2000), over problems of climate control, cf. Haurie (2003), problems of continuum mechanics, cf. Zaslavski (1995), to the problems of terror control, see Grass et al. (2008), as well as biologic problems, cf. a.o. Goh et al. (1974), Lin et al. (2010), Skritek & Veliov (2015). We focus only on the latter.

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2. PRELIMINARIES

We denote by $\mathcal{M}^n := \mathcal{M}(\mathbb{R}^+;\mathbb{R}^n)$ the space of all Lebesgue measurable functions defined on the set $\mathbb{R}^+ := [0,\infty)$ and having their values in $\mathbb{R}^n$. One calls a continuous function $\nu : \mathbb{R}^+ \to \mathbb{R}^+\backslash\{0\}$ *weight function* and *density function*, if ν belongs to the space $\mathcal{M}$ and is Lebesgue integrable over the set $\mathbb{R}^+$, i.e. $\int_0^\infty \nu(t)dt < \infty$. With a weight function $\nu \in C(\mathbb{R}^+)$ the *weighted Lebesgue* space $L_p^n(\mathbb{R}^+,\nu)$ for $1 \le p < \infty$ is introduced as follows:

$$L_p^n(\mathbb{R}^+,\nu) := \{x \in \mathcal{M}^n |\, \|x\|_p^p := \int_0^\infty |x(t)|^p \nu(t)\, dt < \infty\},$$

cf. Kufner (1985), p. 11 ff. One defines the *weighted Sobolev space* $W_p^{1,n}(\mathbb{R}^+,\nu)$ as the subspace of the weighted Lebesgue space $L_p^n(\mathbb{R}^+,\nu)$ containing all measurable functions $x(\cdot)$, which together with their generalized derivatives lie in the space $L_p^n(\mathbb{R}^+,\nu)$, see Yosida (1980), p. 49. Therefore, it follows

$$W_p^{1,n}(\mathbb{R}^+,\nu) := \{x \in \mathcal{M}^n |\, x \in L_p^n(\mathbb{R}^+,\nu), \dot{x} \in L_p^n(\mathbb{R}^+,\nu)\}.$$

For the notion of generalized derivatives we refer to the book Yosida (1980), p. 49.

3. GENERAL PROBLEM FORMULATION

First let us consider the following infinite horizon optimal control problem:

$$(P)_\infty: \quad J_\infty(x,u) = \int_0^\infty r(t,x(t),u(t))\widetilde{\nu}(t)dt \to \min\,! \quad (1)$$

$$(x,u) \in X \times U \quad (2)$$

$$\dot{x}(t) = f(t,x(t),u(t)) \text{ a. e. on } \mathbb{R}_+, \quad (3)$$

$$x(0) = x_0, \quad (4)$$

$$x(t) \in \mathcal{Z}, \quad (5)$$

$$u(t) \in U \text{ a. e. on } \mathbb{R}_+. \quad (6)$$

Here, the integral objective functional J_∞ is to be minimized with respect to all pairs (x,u) belonging to the functional spaces $X \times U$, which are at the moment abstract, and satisfying a system of ordinary differential equations, an initial condition, as well as state and control constraints. A pair (x,u) is called admissible, if all constraints (2) – (6) are fulfilled and the value of $J_\infty(x,u)$ exists and satisfies $J_\infty(x,u) > -\infty$. In the sequel, single parts of the optimal control problem will be discussed in details. We are aware that in case of infinite horizon optimal control problems there are numerous optimality definitions occurring in the literature. Here we deal only with the classical definition of optimality. In the sequel we introduce two biologic models where two different kinds of objectives are used. The first kind of the objective functional is a stabilization functional with a proper weight function inside, whereas the second one aims at minimizing the expected damage as well as treatment costs.

4. CONTROL PROBLEM OF OPTIMAL VACCINATION STRATEGY

4.1 Motivation from the point of view of epidemiology

Due to the knowledge of authors, almost all mathematical models of optimal control of infectious deceases have been considered over bounded time intervals. However, for this kind of applications consideration of optimal control problems with finite fixed horizon is questionable, and cutting the horizon often leads to results which contradict the principle of sustainability. Possibility and also importance of investigating the epidemiological problems on unbounded intervals has been pointed out in Thäter et al. (2018), however without going into details and providing some results.

The known epidemiological optimal control problems do not contain any density function in the objective functional, cf. a.o. Maurer & Pinho (2016), Rachah & Torres (2015). The presence of such a density function, e.g. of a discount factor $e^{-\rho t}$ as it is typical in economic models, would be absolutely meaningful, because the objective functional often describes the vaccination and treatment costs. And as long as the decision criterion, the functional, admits an economic interpretation, the presence of a discount factor or of another weight function while working with long intervals is reasonable. The interpretation of the weight function in the objective as a density of an exponential distribution for the end time T as a random variable is meaningful as well and it is preferable to the fixation of the horizon. Moreover, the consideration of a proper weight function $e^{\varrho t}, \varrho > 0$ in the integrand of the objective functional seems to be reasonable. With such a weight function, a control can be found that stabilizes the process asymptotically and exponentially in the sense of Lyapunov. This allows new insights into optimal control of biological systems.

4.2 A SEIR model for control of an infectious decease

We consider the SEIR dynamic system accordingly to Maurer & Pinho (2016), where it has been a part of an optimal control problem over a finite fixed horizon with an L_1 performance functional. The suggested SEIR model is a 4-compartment epidemiological model in which each individual of a population belongs to exactly one of four compartments at a time: S (susceptible), E (exposed), I (infected) and R (recovered). The relation $N(t) = S(t) + E(t) + I(t) + R(t)$ for the total population $N(t)$ allows us to reformulate the dynamic system in the form of a "SEIN" model which we nevertheless continue to call SEIR model:

$$\begin{aligned}
\dot{S}(t) &= bN(t) - dS(t) - cS(t)I(t) - \alpha_1 u_1(t)S(t)\\
\dot{E}(t) &= cI(t)S(t) - (e+d)E(t) - \alpha_2 u_2(t)E(t)\\
&\quad -\alpha_4 u_4(t)E(t)\\
\dot{I}(t) &= eE(t) - (g+a+d)I(t) - \alpha_3(t)u_3(t)I(t)\\
\dot{N}(t) &= (b-d)N(t) - aI(t) + \alpha_4 u_4(t)E(t)
\end{aligned}$$

where functions $u_i(\cdot)$, $i = 1,2,3,4$ denote the control functions (immunization fraction, medication, immune-boasting medication) for which the constraints $0 \le u_i(t) \le 1$ have to be fulfilled for all i and t.

The above dynamic system is affine in control $u(t)$ and suits into the class of general problem setting described in the previous section. The whole SEIR optimal control problem is a macroscopic biologic model and the corresponding infinite horizon formulation of it is very important and challenging. The consideration of an infinite time horizon in this model makes sense because there is no reason to limit the time horizon since it is not clear how long the epidemic will last.

Furthermore, instead of minimizing the number of infected individuals and the vaccination costs as it is the case in Maurer & Pinho (2016), we suggest to minimize the weighted quadratic deviation from the desired point $(S_d, E_d, I_d, R_d) \in \mathbb{R}^4$ in the state space as the objective. Since the equilibria of this dynamic system depend only on the involved parameters and do not depend on the initial condition, the unfortunate case of negative or very high positive components of equilibria can occur. Therefore, in such cases the stabilization of the system around the equilibrium is not the desired goal from the point of view of epidemiological application. For this reason, it is often useful to control the dynamics of the SEIR model so that it asymptotically converges to a specific state (S_d, E_d, I_d, R_d) desired by the decision maker.

These considerations lead to the following functional:

$$J_\infty(x,u) = \int_0^\infty \left\{ (S(t)-S_d)^2 + (E(t)-E_d)^2 + (I(t)-I_d)^2 + (R(t)-R_d)^2 + u^2(t) \right\} e^{\beta t} dt, \quad (7)$$

with $\beta > 0$. The state and control spaces are chosen in this application as follows:

$$X \times U := W_2^{1,4}(\mathbb{R}^+, e^{\beta t}) \times L_2^4(\mathbb{R}^+, e^{\beta t}).$$

After a linear shift transformation of the dynamic system, the subsequent linearization of the system around the origin and the formulation of the dual variational problem, we could successfully apply the direct dual-based pseudo-spectral solution method, cf. Kolo (2021), for different constellations of parameters and initial values. Results for one realistic parameter setting and the control-constrained optimal control problem are given in images below where already for small numbers of collocation points, e.g. 10 or 11, good convergence of the pseudo-spectral method could be achieved. The solution images reveal that all four control functions asymptotically approach some small non-zero level and remain there for the infinitely long time period, which means that the control measures have to be persistent in contrast to the strategies resulting from the fixed time horizon setting of the same problem.

5. CONTROL PROBLEM OF OPTIMAL CANCER TREATMENT STRATEGY

5.1 Motivation from the point of view of mathematical oncology

In recent years the question of modeling a low-dosed cancer treatment by means of chemotherapy agents has been paid a broad attention. It has become evident through numerous experiments that "more is not necessarily better" for certain type of cancers, cf. Schättler & Ledzewicz (2015) and references therein. The papers Klement (2000) and Browder (2000) gave birth to a new research field in medicine called metronomic chemotherapy. The two mostly spread definitions of what metronomic chemotherapy means say: "The frequent administration of chemotherapy drugs at relatively low, non-toxic doses, without prolonged drug-free breaks" and the recent one "the minimum biologically effective dose of a chemotherapeutic agent, which, when given at a regular dosing regiment with no prolonged drug-free breaks, leads to anti-tumor activity". The main assumption is that besides of a cytotoxic effect on tumor cells, small doses of a chemotherapeutic agent have both antiangiogenic and immune stimulatory effect, while toxicity level on healthy tissues stays low or even neglectful. This fact is illustrated by a generic dynamic model of cancer treatment by means of chemotherapy, cf. the book Schättler & Ledzewicz (2015):

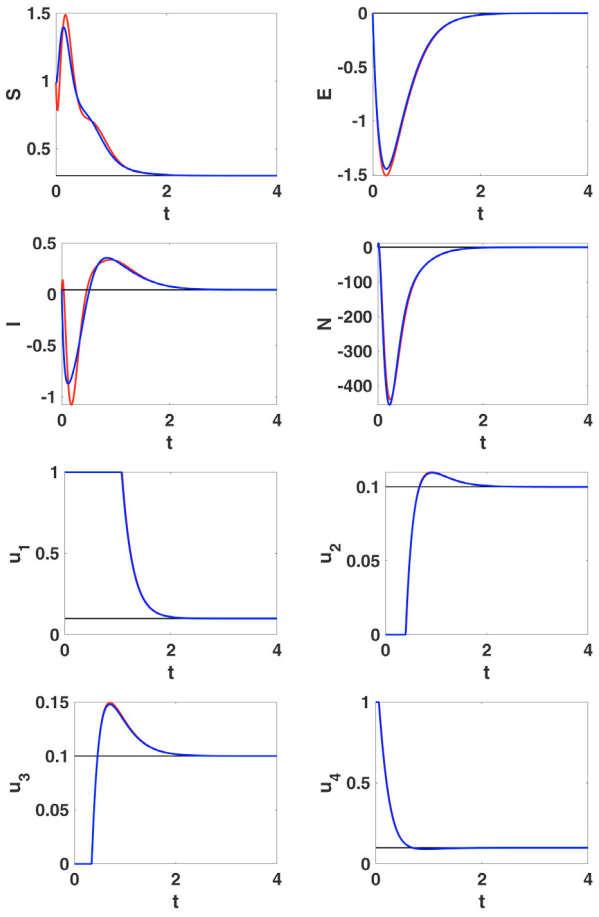

Fig. 1. Solution to the OCP of the SEIR model with infinite horizon

$$\dot{p}(t) = -\xi p(t) \ln\left(p(t)/q(t)\right) - \theta p(t) r(t) - \phi_1 p(t) u(t), \quad (8)$$

$$\dot{q}(t) = bp(t) - (\mu + dp^{2/3}(t)) q(t) - \phi_2 q(t) u(t), \quad (9)$$

$$\dot{r}(t) = \alpha(p(t) - \beta p^2(t)) r(t) + \gamma - \delta r(t) + \phi_3 r(t) u(t), \quad (10)$$

where $p(t)$, $q(t)$ and $r(t)$ denote the tumor volume, the carrying capacity of tumor vasculature and the immunocompetent cell density respectively. The control $u(t)$ stands for the dose of a chemotherapeutic agent and ξ, μ, d, β, γ, δ, $\phi_i\,(i = 1,2,3)$ are parameters of the model. In the cited source, the model has been analyzed

with respect to equilibria, their stability and bifurcations as well as an optimal control problem with a free finite terminal time T. In dependence on involved parameters, the above dynamic system may have scenarios varying from a unique, asymptotically stable benign (tumor-free) equilibrium point (situation of immune surveillance) to a multi-stable situation with both benign and malignant equilibria (co-existent equilibria) to the situation when only unique, asymptotically stable malignant (death) equilibrium point exists, cf. Schättler & Ledzewicz (2015), p. 358.

Since it is very important not only how much of drug to give, but also how to give, the finding of the drug administration regiment (protocol) becomes one of the most important tasks on the way to a successful therapy.

Our task in the present paper is to consider the problem of metronomic chemotherapy as an optimal control problem, where the tumor size and the side effects of the therapy are being minimized over the treatment horizon, which gives rise to an integral objective in Lagrange form. Through finding the optimal solution to this optimal control problem we obtain the best possible drug administration protocol automatically, including the doses and rest periods if there should be some. In case of continuous optimal solutions which are less practicable, the latter may be replaced by piecewise constant suboptimal controls which are still good enough to satisfy the treatment goal.

One of our key ideas is to assume that we have enough time to treat the patient and the goal is not to fight the cancer as fast as possible. Moreover, we consider the cancer as a chronic disease, which will be treated over the whole remaining future life time of the particular patient. The aim is to figure out whether such "chronic" formulation of the control problem leads to considerably lower doses in comparison to the short fixed finite treatment horizons. We would like to mention that through minimizing the expectation value of the cost functional the optimal control problem becomes stochastic. Nevertheless, in some cases it can easily be transformed to a purely deterministic control problem with infinite horizon.

To handle the obtained infinite horizon optimal control problem we use on the one side its rigorous formulation in weighted functional spaces. The advantage of such a functional analytical approach was addressed in details in Lykina & Pickenhain (2017) and we use it here to prove the existence of an optimal solution. According to this approach, a weighted Sobolev and a weighted Lebesgue spaces are chosen as the state space and the control space respectively. On the other side, to obtain numerical solutions to the considered problem, the open source software package OCMat was applied, which is available at http://orcos.tuwien.ac.at/research/ocmat_software/and has been described in Graß (2012). Just like the pseudospectral method used to solve the SEIR model, the continuity method of Graß (2012) avoids any truncation of the time interval. Instead, it starts at the equilibrium point, which is obviously a solution to the problem if the initial state is exactly at that equilibrium, and then continues the constant solution with respect to the initial state until the actual initial state specified in the model is reached.

5.2 Metronomic chemotherapy model with a growing force of mortality

Let a be the current age of the particular patient to be treated against cancer and T_a be the random variable denoting the future lifetime of the patient. Then our purpose is to minimize the L_2 objective functional

$$J_\infty(x,u) = E_{T_a}\left\{\int_0^{T_a} \frac{1}{2}\left(p(t)+q(t)-r(t)+u^2(t)\right)dt\right\} \quad (11)$$

with respect to all $(x,u) \in X \times U := W_2^{1,3}(\mathbb{R}^+, e^{-\rho t}) \times L_2^1(\mathbb{R}^+, e^{-\rho t})$, $(x,u) := (p,q,r,u)$ satisfying the differential equations (8) – (10). Making different assumptions about the distribution of the random variable T_a it is possible to transform the mathematical expectation value into a purely deterministic form. In this manuscript we consider the following case of a growing force of mortality, e.g.

$$\mu_a = ka^n,\ k,n>0 \quad (12)$$

and in this case, the random variable T_a is distributed with the density

$$\phi(T_a) = k(a+T_a)^n e^{-\frac{k}{n+1}((a+T_a)^{n+1}-a^{n+1})}, \quad (13)$$

which represents the density function of Weibull distribution.

Therefore, calculating the expectation value in the objective (11) for all $n \geq 0$ and changing the order of integration we arrive at

$$\begin{aligned}
&E_{T_a}\left\{\int_0^{T_a} \frac{1}{2}\left(p(t)+q(t)-r(t)+u^2(t)\right)dt\right\}\\
&= \int_0^\infty \left(\int_0^{T_a} \frac{1}{2}\left(p(t)+q(t)-r(t)+u^2(t)\right)dt\right) k(a+T_a)^n\\
&\qquad \cdot e^{-\frac{k}{n+1}((a+T_a)^{n+1}-a^{n+1})}dT_a\\
&= \int_0^\infty \int_t^\infty \frac{1}{2}\left(p(t)+q(t)-r(t)+u^2(t)\right)k(a+T_a)^n\\
&\qquad \cdot e^{-\frac{k}{n+1}((a+T_a)^{n+1}-a^{n+1})}dT_a dt. \quad (14)
\end{aligned}$$

Calculating the inner integral in the above expression one obtains

$$\begin{aligned}
J_\infty^2(x,u) = e^{\frac{k}{n+1}a^{n+1}} &\int_0^\infty \frac{1}{2}\left(p(t)+q(t)-r(t)+u^2(t)\right)\\
&\cdot e^{-\frac{k}{n+1}(a+t)^{n+1}}dt. \quad (15)
\end{aligned}$$

Thus, we have received a purely deterministic optimal control problem with infinite horizon, namely (15), (8) – (10).

Remark 1. It is to mention that there are distributions, such as Chen or Makeham distribution, which reflect the demographic data, and respectively the behavior of the remaining life time random variable T_a, especially of a cancer-sick person, in a more realistic way. But in our considerations we restrict ourselves by only two considered distributions, exponential and Weibull distributions, which allow the application of the described "Kamien-Schwartz-Trick" for transformation of a stochastic optimal control problem into a deterministic one.

With $n = 1$ and $\mathbf{x} := (p, q, r)$, we consider objective functional of the form

$$J^2_\infty(x,u) = e^{\frac{k}{2}a^2} \int_0^\infty \frac{1}{2}\left(p(t)+q(t)-r(t)+u^2(t)\right) e^{-\frac{k}{2}(a+t)^2} dt$$

$$= \int_0^\infty \frac{1}{2}\left(p(t)+q(t)-r(t)+u^2(t)\right) e^{-ka\cdot t - k\cdot t^2} dt. \qquad (16)$$

The whole optimal control problem reads as: minimize functional (16) with respect to all pairs

$$(\mathbf{x}, u) \in W_2^{1,3}(\mathbb{R}^+, e^{-\rho t}) \times L_2^1(\mathbb{R}^+, e^{-\rho t})$$

satisfying conditions (8) – (10) as well as control constraints

$$0 \le u(t) \le u_{max} \quad \forall\, t > 0 \qquad (17)$$

$$\int_0^\infty u(t) e^{-\rho t} dt \le d. \qquad (18)$$

In order to apply the numerical solution method mentioned above, we use the system of necessary optimality conditions given by the Pontryagin Type Maximum Principle proved in Ziemann (2019). This system also includes a necessary transversality condition of the form $\mathbf{y}(\cdot) \in W_2^{1,3}(R^+, e^{\rho t})$ which represents the essential difference to the case of a fixed finite planning horizon. We now build the Pontryagin function:

$$\begin{aligned} &H(t,\xi_1,\xi_2,\xi_3,v,\eta_1,\eta_2,\eta_3,\lambda_0=1) = \\ &-\frac{1}{2}\left(\xi_1+\xi_2-\xi_3+v^2\right) e^{-ka\cdot t - k\cdot t^2} \\ &\quad +\eta_1\cdot(-\xi\xi_1\ln(\xi_1/\xi_2) - \theta\xi_1\xi_3 - \phi_1\xi_1 v) \\ &\quad +\eta_2\cdot(b\cdot\xi_1 - (\mu + d\xi_1^{2/3})\xi_2 - \phi_2\xi_2 v) \\ &\quad +\eta_3\cdot(\alpha(\xi_1-\beta\xi_1^2)\xi_3 + \gamma - \delta\xi_3 + \phi_3\xi_3 v). \end{aligned} \qquad (19)$$

Setting

$$\begin{aligned} &H_v(t,\xi_1,\xi_2,\xi_3,v,\eta_1,\eta_2,\eta_3,\lambda_0=1) = \\ &-v\cdot e^{-ka\cdot t - k\cdot t^2} - \eta_1\cdot\phi_1\xi_1 - \eta_2\phi_2\xi_2 + \eta_3\phi_3\xi_3 = 0 \end{aligned} \qquad (20)$$

and resolving this equation with respect to v we obtain

$$\begin{aligned} &v := v(t,\xi,\eta) = v(t,\xi_1,\xi_2,\xi_3,\eta_1,\eta_2,\eta_3) = \\ &(-\eta_1\cdot\phi_1\xi_1 - \eta_2\phi_2\xi_2 + \eta_3\phi_3\xi_3)\cdot e^{ka\cdot t + k\cdot t^2}, \end{aligned} \qquad (21)$$

and, consequently:

$$u^*(t) = \begin{cases} u_{max} & , \quad v(t,\mathbf{x}^*(t),\mathbf{y}(t)) \ge u_{max} \\ v(t,\mathbf{x}^*(t),\mathbf{y}(t)) & , \quad v(t,\mathbf{x}^*(t),\mathbf{y}(t)) \in (0,u_{max}) \\ 0 & , \quad v(t,\mathbf{x}^*(t),\mathbf{y}(t)) \le 0 \end{cases}$$

With the Hamiltonian $\mathcal{H}(t,\xi,\eta) := \max_{v\in[0,u_{max}]} H(t,\xi,v,\eta)$, one gets the adjoint equations $\dot{y}_i(t) = -\mathcal{H}_{\xi_i}(t,\mathbf{x}^*(t),\mathbf{y}(t))$ $(i = 1,2,3)$ building together with equations (8) – (10) the canonical system for this optimal control problem.

For our numerical computations, we have chosen the same parameter set as in Schättler & Ledzewicz (2015), p. 371, and $\rho = 0.03$, $a = 40$. In this case, the dynamic system possesses at least one stable benign equilibrium. The optimal solution can be found in Figures below, whereby the control constraint does not become active, since the largest attained value of control lies at the level of 3.85. The remarkable thing about the obtained optimal control

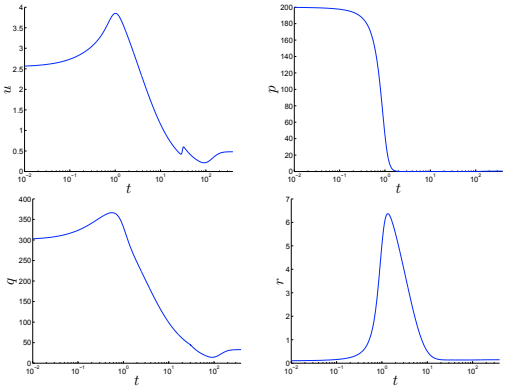

Fig. 2. Solution to the OCP of cancer treatment with infinite horizon

is that it, similarly to the solution of the SEIR model, approaches some small non-zero level and remains near it for an infinitely long time. This seems to be appropriate to the consideration and treatment of cancer as a chronic decease. Since the optimal strategy requires rather very small drug doses having also the immune-boasting effect, the patient body gains the opportunity to regenerate. This underlines the legitimacy of the treatment in terms of the sustainability principle.

6. CONCLUSIONS

In this paper, bio-medical models are formulated and addressed as control problems over an infinite time horizon. The inclusion of an infinite planning interval for the biomedical models represents an important and challenging mathematical aspect, the introduction of which turns out to be an appropriate idealization for sustainability principles that are becoming increasingly important for society at present and in the future. Both goals, optimal control and asymptotic stabilization, could be combined even in one objective functional with an infinite time horizon. In addition to the immediate interest in optimal long-term strategies, which come from the corresponding application area, the formulated biological models should serve as test problems that help to understand and illustrate mathematical phenomena.

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