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Taking a break from chemotherapy to fight drug-resistance: The cases of Cancer and HIV/AIDS*

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Abstract— **In this work, we present how optimized treatment interruptions during chemotherapy may be used to control drug-resistance, a major challenge for clinicians worldwide. Specifically, we examine resistance in cancer and HIV/AIDS. For each disease, we use mathematical models alongside real data to represent the respective complex biological phenomena and optimal control algorithms to design optimized treatment schedules aiming at controlling disease progression and patient death. In both diseases, it is shown that the key to controlling resistance is the optimal management of the frequency and magnitude of treatment interruptions as a way to facilitate the interplay between the competitive resistant/sensitive strains.**

I. Introduction

Drug-resistance is a major drawback of chemotherapy and one of the biggest challenges of treatment design. Drug-resistance occurs when some fraction of a living population develops resistance to drugs, thus evading eradication. Several types of resistance may be encountered: innate or acquired, reversible, and dose-dependent. Resistance is a result of genetic instabilities and mutations. These mutations may occur in the locations targeted by drugs; therefore, although there may be some cells that continue to be affected by drugs, there may also exist others that are not suppressed. These form the resistant population; they replicate despite chemotherapy.

Research has identified various treatment modifications to minimize the risk of developing resistant strains, however no radical solution to this problem exists. Clinical tests on a regular basis are important because they can indicate whether the patient is developing resistance or not. Combination treatment, i.e. administration of several drugs, also helps fight resistance; nevertheless, it is not always effective. In some cases, if the population is resistant to one drug, it is sometimes resistant to similar drugs in the same family. This is known as cross-resistance and explains why some drugs will not be effective even though they have not been used before. While the likelihood of a population being resistant to all drugs is unlikely, especially since different drugs may attack different cellular processes, the large number of cells in a population make this a plausible scenario. In fact, clinical studies in the UK [1] identified that a large percentage (42%) of HIV patients were resistant to all known drugs.

The above limitations of continuous therapy have led some researchers to examine taking a break from therapy with a planned timescale and close monitoring. A drug holiday is associated with the re-emergence and predominance of a more sensitive population in patients with resistant strains [2]. A better response is therefore experienced when therapy is re-initiated. This "reversion phenomenon" can be seen in Fig. 1 and can be explained as follows. The large number of mutations facilitates the emergence of a resistant population that replicates despite drugs. These mutations however also make it "less fit" when compared to the wild-type population. Thus, while during therapy it will prevail and grow, in a drug-free medium it will be outcompeted by the sensitive population. In the case of cancer, for example, the sensitive tumor cells will outcompete the resistant ones in the fight for nutrients and will prevail given no drug. In HIV/AIDS, the resistant virus is "less fit" when fighting for CD4+ T-cells (main target of HIV; orchestrate the immune response), hence it will eventually reduce in numbers. The reverse is true during therapy.

In this work, we use mathematical modeling and optimal control techniques to examine the promising potential of treatment interruptions as means to controlling drug-resistance in two diseases: cancer and HIV/AIDS. The paper is structured as follows. In Section II, we formulate mathematical models to represent the complex biological mechanisms in cancer and HIV/AIDS. Our modeling work makes use of real data in an attempt to present results that capture reality as

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closely as possible. Finally, in Section III we employ optimal control to formulate chemotherapy schedules with optimized treatment interruptions and illustrate the results with simulations.

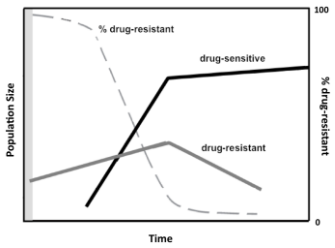

Fig. 1. Dynamics during a treatment break. Note the shift to a drug-sensitive population for patients with drug resistance during the break. Figure reproduced from [2] and is based on clinical tests from 11 HIV patients.

II. Mathematical models

A. Model of Cancer Progression

Cancer is a leading cause of death worldwide. It is an evolutionary disease, where a cell population shows inefficient control of its proliferation. Many management options exist for cancer: surgery, chemotherapy, and radiotherapy. Issues faced in cancer include: metastasis, drug-related toxicity, and drug-resistance, which we deal with herein.

We consider two compartments consisting of drug-sensitive and resistant cells and we denote the numbers of cells by T_S and T_R, respectively. The total cancer load is denoted by T_T. Once a sensitive cell undergoes cell division, the mother cell dies and one of the daughters remains sensitive. The other cell changes into resistant with probability μ_{SR}, where $0<\mu_{SR}<1$. Similarly, when a resistant cell undergoes cell division, then the mother cell dies, and one of the daughters remains resistant. Moreover, as shown experimentally [3] a resistant cell may mutate back into sensitive with a probability μ_{RS}. Denoting the inverses of the transit times of cells through the populations by α, then:

$$\frac{dT_S(t)}{dt} = -aT_s(t) + (1-u(t))(2-\mu_{SR})aT_S(t) + \mu_{RS}a\varphi T_R(t) - r_1 T_S T_R \quad (1)$$

$$\frac{dT_R(t)}{dt} = -a\phi T_s(t) + (2-\mu_{RS})a\varphi T_R(t) + (1-u(t))\mu_{SR}aT_S(t) - r_2 T_R T_S \quad (2)$$

$$T_T(t) = T_S(t) + T_R(t) \quad (3)$$

where the first terms on the right hand sides reflect mother cell death, the second terms are the return flows into the compartments, and the third terms are cross-over flows. The reduced fitness of the resistant tumor and the competition with the sensitive population are included in the model via φ and competition constants r_1, r_2 ($r_1< r_2$). u(t) is drug efficacy, with 0 and 1 indicating no treatment and full treatment) and is given by (4) where C(t) is concentration at the tumor site and IC_{50} (4.12 $ngml^{-1}$ [4]) is median inhibitory concentration.

$$u(t) = \frac{C(t)}{C(t) + IC_{50}} \quad (4)$$

Our model predictions alongside tumor data for total cancer [5] are depicted in Fig. 2 (*Left*). In [5], 25 $mgkg^{-1}$ of docetaxel i.v. once weekly resulted in drug-resistance. Examining mice T10, we note the treatment response initially; however, it is evident that following the first two doses, resistant tumor emerges and prevails over sensitive resulting in total cancer rapid growth. Resistance to docetaxel was also verified experimentally. Whereas the sensitive strain is controlled by drugs, the resistant one grows exponentially. It is evident that if this mouse were to continue receiving this treatment, cancer load would reach the maximum allowable size in mice experiments (4000 mm^3 [6]) short after that, hence treatment failure (Fig. 2 (*Right*)).

We used gPROMS^{TM} [7] to solve our model. To estimate the unknown parameters we employed Maximum Likelihood and obtained α=0.171 d^{-1}, μ_{SR}=0.109, μ_{RS}=0.014. φ was set to 0.9 and r_1,r_2 to $5x10^{-6}$, $1.1x10^{-4}$ $mm^{-3}d^{-1}$, respectively. Note that $\mu_{SR}>\mu_{RS}$, thus assuming that mutation of T_S to T_R is more likely to occur, which is the case encountered in reality. Moreover, $r_2>r_1$ follows experimental consensus that T_R is less fit when competing for natural resources. Drug concentrations are based on a 3-compartmental PK model trained on docetaxel data [8] (results not shown here). The model captures the phenomena during resistance emergence and replicates data, thus it could be utilised to examine treatment breaks using optimal control as a way to control resistance.

B. Model of HIV/AIDS

HIV infection can be characterized as a disease of the immune system. The main target of HIV are CD4+ T-cells, the cells that orchestrate the body's immune response. The HIV life cycle directly or indirectly causes a reduction in T-cells, thus rendering the immune system unable to defend itself against infections, hence progression to AIDS and death occurs soon after (Fig. 4).

The following are considered in the HIV model: T, uninfected T-cells; M, uninfected macrophages; V_1 (V_2), sensitive virus (resistant); V_T, total virus; T_1(T_2), T-cells infected by V_1(V_2);

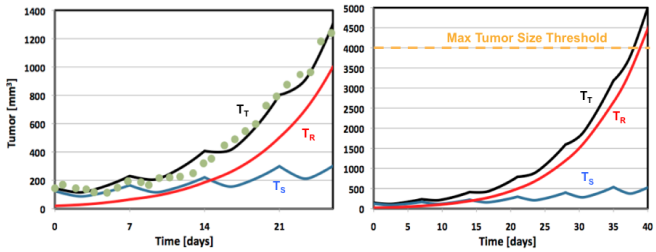

Fig. 3. *Left*: Model results for total tumor T_T volume with data (●) for mice receiving docetaxel once weekly [5]. Drug-resistant (T_R) and drug-sensitive tumor (T_S). *Right*: Long-term model predictions for tumor volume according to the schedule in [5].

$T_{L1}(T_{L2})$, latently-infected T-cells by $V_1(V_2)$; $M_1(M_2)$, macrophages infected by $V_1(V_2)$, and; CTL, cytotoxic T-lymphocyte population. The model is given by Eqs (5)-(15) and a detailed description is given in [9]. The reduced fitness of V_2 in terms of infecting and replicating capacity is given through φ. μ is the probability of a mutation per replication cycle (V_1 to V_2, and vice-versa). u_1 and u_2 represent the efficacy of drugs RTIs and PIs, respectively and may be calculated using (4).

Note that drugs have no effect on V_2, which can grow despite of treatment. As discussed, owing to the reduced fitness of the drug-resistant virus, taking a break will allow the sensitive strain to re-emerge and become the dominant virus with the resistant variant experiencing decay. This reversion phenomenon can be seen in Fig. 5 (*left*) and is due to the competitive nature of the two viruses and the reduced fitness of the resistant one in terms of infecting and replicating capacity. Fig. 5 depicts the virus dynamics as given by our model for patient 226 from clinical study [10]. Several interruptions are subsequently given, however as can be seen in Fig. 5 (*right*), the resistant virus continues to grow uncontrollably, resulting in progression to AIDS soon after.

Clearly, treatment breaks helped patient 226 initially; still resistance was not controlled. We are convinced that the reasoning behind this is the fact that the magnitude and frequency of treatment breaks were not planned in an optimal manner. We investigate this next through optimal control.

III. Optimal Control

Firstly, we examine optimized continuous therapy for the HIV patient with resistance in Fig. 5. Treatment initiation occurs at point B, at which point the resistant strain is the dominant virus population. Our optimal control algorithm is:

$$\frac{dT}{dt} = s_1 + \frac{p_1(V_1+V_2)T}{V_1+V_2+C_1} + rT\left(1 - \frac{T+T_1+T_2+T_{L1}+T_{L2}}{T_{max}}\right) - \delta_1 T - (1-u_1)(k_1V_1+k_2M_1)T - \varphi(k_1V_2+k_2M_2)T \quad (5)$$

$$\frac{dT_1}{dt} = (1-u_1)\psi(k_1V_1+k_2M_1)T + \alpha_1 T_{L1} - \delta_2 T_1 - k_3 T_1 CTL \quad (6)$$

$$\frac{dT_2}{dt} = \psi\varphi(k_1V_2+k_2M_2)T + \alpha_1 T_{L2} - \delta_2 T_2 - k_3 T_2 CTL \quad (7)$$

$$\frac{dT_{L1}}{dt} = (1-u_1)(1-\psi)(k_1V_1+k_2M_1)T - \alpha_1 T_{L1} - \delta_3 T_{L1} \quad (8)$$

$$\frac{dT_{L2}}{dt} = (1-\psi)\varphi(k_1V_2+k_2M_2)T - \alpha_1 T_{L2} - \delta_3 T_{L2} \quad (9)$$

$$\frac{dM}{dt} = s_2 + \frac{p_2(V_1+V_2)M}{V_1+V_2+C_2} - (1-f_1u_1)k_4V_1M - \varphi k_4V_2M - \delta_4 M \quad (10)$$

$$\frac{dM_1}{dt} = (1-f_1u_1)k_4V_1M - \delta_5 M_1 - k_5 M_1 CTL \quad (11)$$

$$\frac{dM_2}{dt} = \varphi k_4V_2M - \delta_5 M_2 - k_5 M_2 CTL \quad (12)$$

$$\frac{dCTL}{dt} = s_3 + k_6(T_1+T_2)CTL + k_7(M_1+M_2)CTL - \delta_6 CTL \quad (13)$$

$$\frac{dV_1}{dt} = (1-u_2)(1-\mu)k_8T_1 + (1-f_2u_2)(1-\mu)k_9M_1 + \mu\varphi k_8T_2 + \mu\varphi k_9M_2 - (k_{10}T+k_{11}M)V_1 - k_{12}V_1M - \delta_7 V_1 \quad (14)$$

$$\frac{dV_2}{dt} = (1-\mu)\varphi k_8T_2 + (1-\mu)\varphi k_9M_2 + (1-u_2)\mu k_8T_1 + (1-f_2u_2)\mu k_9M_1 - (k_{10}T+k_{11}M)V_2 - k_{12}V_2M - \delta_7 V_2 \quad (15)$$

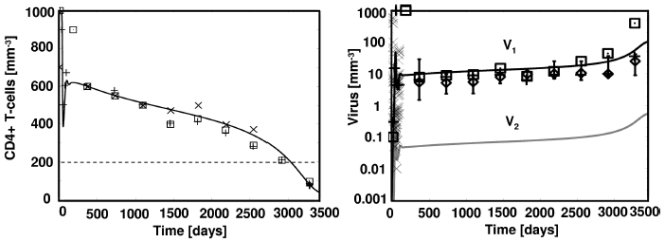

Fig. 4. T-cell (Left) and Virus (Right) dynamics for untreated progressors to AIDS with clinical data [9]. Dotted line marks progression to AIDS.

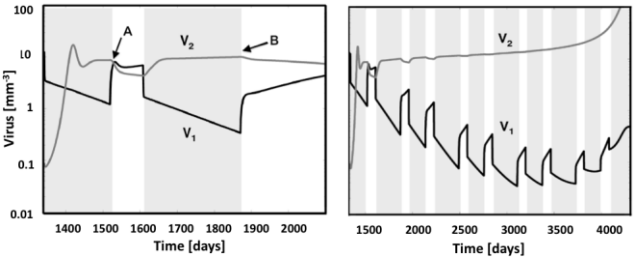

Fig. 5. Virus dynamics for a patient with resistance during on/off treatment [10]. V_2 grows uncontrollably following repeated treatment cycles.

$$\max_{u_1,u_2} \; t_f$$
$$s.t. \quad x = f(t,x,u),\; T \geq T_{AIDS} \quad (16)$$
$$t \in [t_0,t_f],\; t_f^L \leq t_f \leq t_f^U$$

where $\mathbf{x} = f(t; x; \mathbf{u})$ is Eqs (5)-(15), $t \in [t_0,t_f]$ sets the finite horizon of the optimization and T_{AIDS}= 200 mm^{-3} defines the undesirable transition from HIV to full-blown AIDS, hence corresponding to a path-constraint. In line with treatment guidelines, we administer a combination of RTI/PI drugs, where drug efficacies are set between 0 and 1. t_f is

set to $3{,}220<t_f<10{,}000$ days after initial infection. The problem is solved using Control Vector Parameterization in gPROMS. The decrease in the resistant population is not great, as it continues to grow and the patient progresses to AIDS after 4,500 days (Fig 6 (*Top*)). This further verifies that once a patient has developed severe resistance, continuous treatment cannot be effective and hence other therapy routes should be considered.

We revisit patient 226 but now examine optimized treatment interruptions. The results are depicted in Fig. 6 (*Bottom*) and it can be seen that this treatment schedule is able to control the growth of the resistant virus successfully. In fact, T-cells are kept at high levels and survival-time increases to >10,000 days. These results suggest that the key to controlling drug-resistance, the most important barrier in HIV treatment success, is the optimal management of the frequency and magnitude of treatment breaks. In this way, we facilitate the interplay between competitive sensitive/resistant strains and control their growth.

Optimized treatment interruptions may also be used to control resistance in cancer. Here, we investigate mouse T10 [5] (see Fig. 3), which developed resistance after given a continuous schedule with docetaxel. Specifically, in line with the original experiments we administer docetaxel, however this time using drug-free schedules that are determined by our optimal control scheme. It is clear that our optimized drug-free schedule is very effective and controls resistance (Fig. 7). The total tumor size following our treatment is always kept below the threshold of 4000 mm^3, which is the maximum allowable volume before the mouse is euthanized in an experimental setting. These optimized interruptions facilitate the interplay between the two tumor strains, thus controlling their grow and increasing chances of survival.

IV. Conclusion

Our work suggests that the key to controlling drug-resistance in diseases such as cancer and HIV/AIDS are optimized treatment interruptions. These leverage the competitive nature of the resistant/ sensitive strains as well as the reduced fitness of the former, thus controlling their growth. Drug-holidays offer a promising alternative to current guidelines and our results should encourage further experimental/clinical work. Towards this goal, we are currently undertaking experiments in tumor-bearing mice, which we will present in a future study.

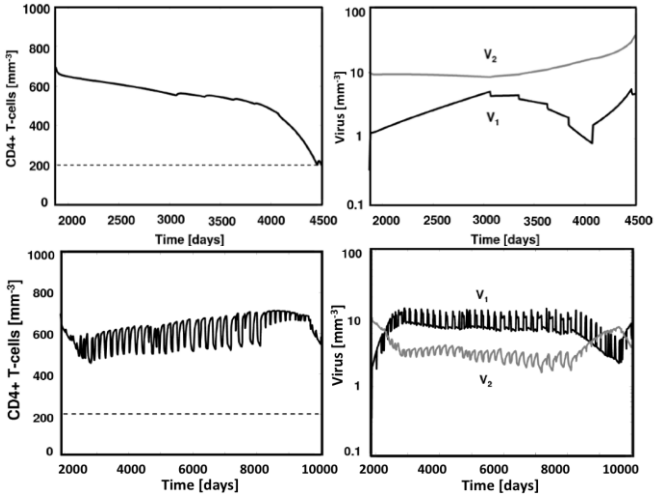

Fig. 6. T-cell and Virus dynamics for a patient with multidrug resistance (p226, [10]) during optimized treatment interruptions with RTI/ PI drugs.

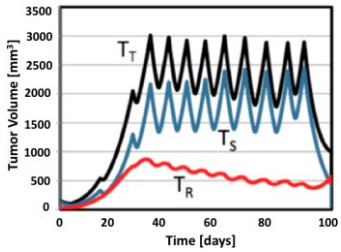

Fig. 7. Total, drug-sensitive, and drug-resistant tumor trajectories following optimized treatments interruptions with docetaxel for mouse T10 in [5].

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