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Competition Between Populations: Preventing Domination of Resistant Population Using Optimal Control

URSZULA FORYŚ[1*], MARIUSZ BODZIOCH[2]

1. Faculty of Mathematics, Informatics and Mechanics, University of Warsaw, Poland [ORCID: 0000-0002-6198-3667]
2. Faculty of Mathematics and Computer Science, University of Warmia and Mazury in Olsztyn, Poland [ORCID: 0000-0002-1991-5062]

* Presenting Author

Abstract: We present an optimal control problem related to the task of controlling a growth of two competing sub-populations in the context of chemical control. One of the considered sub-populations is sensitive to the chemical and the other is resistant. We use a non-standard objective functional to prevent domination of the resistant sub-population. We show that optimal control can consist of: (1) full dose, (2) no dose, (3) singular arc. We numerically check that small doses of chemicals applied according to singular control are optimal in the main part of time interval we consider.

Keywords: competition model, resistant population, optimal control problem

1. Introduction

In the real world, there is often a situation where the use of chemicals produces resistance. This is the case with bacterial populations becoming drug resistant, tumour cell populations no longer responding to chemotherapy, or pest insect populations in various habitats that become resistant to pesticides used. Over the years, the same mistake has been made in trying to use maximum doses of drugs or pesticides to wipe out the "bad" population we are fighting. However, it often did not bring the expected results. In general, when using chemicals, it is expected that the entire population will be subdivided into sub-populations with varying levels of sensitivity, from full sensitivity to full resistance. It is therefore inevitable that there appears a competition between these sub-populations. We consider two sub-populations, for simplicity and due to the fact that analysing models with more sub-populations we have got the results very similar to those for the simplified case. We expect that without external interference in the system the sensitive sub-population outcompete the resistant one. However, with prolonged usage of chemicals, the resistant sub-population wins the competition.

In our previous works related to the chemotherapy of tumours, we used optimal control trying to reconcile the two goals: minimizing the overall population size and maintaining the dominance of the sensitive sub-population over the resistant one. Preliminary results can be found in [1], while the analysis of the relevant optimal control problem is presented in [2] for the model of competing cellular sub-populations and in [3] for the three-dimensional model with varying carrying capacity.

Here we would like to study in more details the same problem for a minimal model describing competing sub-populations. In general, for short-time optimization we expect that mutation terms included into the models considered in [2,3] are less important than competition between sub-populations. Therefore, in the following we present the results of optimization for such model.

* Correspondence: Banacha 2, 02-097 Warsaw, Poland; email: urszula@mimuw.edu.pl

2. Results and Discussion

We consider the following non-dimensional competition model with an external interference

$$\frac{dn_1}{dt} = \gamma_1 n_1(1 - n_1 - n_1 n_2) - n_1 u(t), \quad \frac{dn_2}{dt} = \gamma_2 n_2(1 - n_2 - b_2 n_1),$$

where n_1 and n_2 are non-dimensional sizes of sub-populations, sensitive and resistant, respectively, γ_i is a growth rate, b_i is a competition coefficient, while $u(t)$ reflects the control (dose of chemicals). Because of the general properties of the competition model we assume $b_1 < 1 < b_2$.

The dynamics of this system is studied in the optimal control problem in which we minimize

$$J(u) = \omega(n_1(T) + n_2(T)) + \int_0^T M\big(n_1(t), n_2(t), u(t)\big)dt,$$

where the first term reflects the overall population size at the end of control action and *M* accounts for both overall population size during the control and penalization of the population to become resistant (we call the population resistant whenever $n_2 > n_1$), as well as the cost of external interference, that is

$$M(n_1, n_2, u) = \eta(n_1 + n_2) + \xi G\left(\frac{n_2 - n_1}{\epsilon}\right) + \theta u,$$

with positive coefficients. Note that as G we use the function *tanh* for numerical purposes, while in mathematical analysis it is enough to assume that this function has the same properties as *tanh*.

In the analysis of the presented control problem we use the Pontriagin Minimum Principle, formulate the adjoint system and appropriate Hamiltonian. We prove that singular control is of order 1 and satisfies the Legendre-Clebsch condition of optimality only for $n_1 > n_2$. In this case we are able to express the singular control as a function of state variables. Although we know the structure of singular control, we are not able to prove that it is optimal. Hence, we complete our theoretical analysis with numerical analysis performed, as before [2,3] in the context of tumours chemotherapy. In numerical analysis we look for 15-day treatment protocol optimal in the context described above. It occurs that numerically optimal scenario consists of two (at the beginning and the end of the therapy) short periods of maximal tolerated dose (MTD) treatment, while in between small doses of the drug (around 10% of MTD) are applied, in which singular arc is followed. This again confirms our previous findings that in general it is not good to apply MTD and smaller doses could lead to better final results.

3. Concluding Remarks

Our analytical results are obtained with reference to a general control problem and can be applied to various populations. However, in numerical simulations we focus on the response of the heterogeneous tumour to the therapy. We consider the tumour consisting of sensitive and resistant cells and find optimal control for drug-resistant tumour growth that penalizes the resistant population. The model suggests that it is desirable to leave a certain number of sensitive cells to limit the growth of resistant ones by cell competition, which is provided by singular (intermediate) chemotherapy dose.

References

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