

OPTIMAL COMBINATION TREATMENT PROTOCOLS FOR A CONTROLLED MODEL OF BLOOD CANCER**E. N. Khailov, E. V. Grigorieva, A. D. Klimenkova**

A combined treatment of blood cancer is considered on a given time interval. The treatment consists of two stages. At the first stage, the patient undergoes therapy that has a powerful effect on the body in order to eliminate the disease. At the second stage, therapy is aimed at maintaining the achieved positive effect. The moment of transition from the first stage of treatment to the second is not fixed and depends on the patient's condition. The implementation of such treatment is mathematically described by a two-dimensional Lotka–Volterra competition model whose variables are the concentrations of healthy and cancerous cells. The model contains two bounded control functions expressing the intensity of applied therapies. The quality of such combined treatment is assessed by minimizing an objective function that describes the dynamics of the concentrations of healthy and cancerous cells at the ends of the first and second stages of the total treatment period. For the theoretical analysis of this optimization problem, the Pontryagin maximum principle for hybrid control systems is applied. The results of numerical calculations performed in the BOCOP-2.2.1 environment are also presented and discussed in detail.

Keywords: blood cancer, two-dimensional Lotka–Volterra competition model, hybrid control system, optimal control, Pontryagin maximum principle.

REFERENCES

1. *World Health Organization* [site]. Available on: <https://www.who.int/news-room/fact-sheets/detail/cancer>.
2. Miller K.D., Siegel R.L., Lin C.C., Mariotto A.B., Kramer J.L., Rowland J.H., Stein K.D., Alteri R., Jemal A. Cancer treatment and survivorship statistics. *A Cancer Journal for Clinicians*, 2016, vol. 66, no. 4, pp. 271–289. doi: 10.3322/caac.21349.
3. Clapp G., Levy D. A review of mathematical models for leukemia and lymphoma. *Drug Discov. Today Dis. Models*, 2015, vol. 16, pp. 1–6. doi: 10.1016/j.ddmod.2014.10.002.
4. Chulián S., Martínez-Rubio A., Rosa M., Pérez-García V.M. Mathematical models of leukaemia and its treatment: a review. 2020. 47 p. Available on: <https://arxiv.org/pdf/2011.05881.pdf>.
5. Kuznetsov M., Clairambault J., Volpert V. Improving cancer treatments via dynamical biophysical models. *Physics of life reviews*, 2021, vol. 39, pp. 1–48. doi: 10.1016/j.plrev.2021.10.001.
6. Malinzi J., Basita K.B., Padidar S., Adeola H.A. Prospect for application of mathematical models in combination cancer treatments. *Informatics in Medicine Unlocked*, 2021, vol. 23, art. no. 100534, 15 p. doi: 10.1016/j.imu.2021.100534.
7. Khailov E.N., Grigorenko N.L., Grigorieva E.V., Klimenkova A.D. *Upravlyaemye sistemy Lotki–Vol'terry v modelirovanii mediko-biologicheskikh protsessov* [Controlled Lotka–Volterra systems in the modeling of biomedical processes]. Moscow: MAKS PRESS, 2021, 204 p. doi: 10.29003/m2448.978-5-317-06681-9.
8. Bratus' A.S., Novozhilov A.S., Platonov A.P. *Dinamicheskie sistemy i modeli biologii* [Dynamical systems and models of biology]. Moscow: Fizmatlit Publ., 2010, 400 p. ISBN: 978-5-9221-1192-8.
9. Maltugueva N.S., Pogodaev N.I. Existence of solutions to an optimal control problem for a hybrid system. *The Bulletin of Irkutsk State University. Series Mathematics*, 2017, vol. 19, pp. 129–135. doi: 10.26516/1997-7670.2017.19.129 (in Russian).
10. Dmitruk A.V., Kaganovich A.M. Maximum principle for optimal control problems with intermediate constraints. *Comput. Math. Model.*, 2011, vol. 22, no. 2, pp. 180–215. doi: 10.1007/s10598-011-9096-8.
11. Afanas'ev V.N., Kolmanovskii V.B., Nosov V.R. *Mathematical theory of control systems design*. Dordrecht: Springer, 1996, 672 p. doi: 10.1007/978-94-017-2203-2. Original Russian text published in Afanas'ev V.N., Kolmanovskii V.B., Nosov V.R. *Matematicheskaya teoriya konstruirovaniya sistem upravleniya*. Moscow: Vysshaya shkola Publ., 1998, 574 p.

12. Bonnans F., Martinon P., Giorgi D., Grélard V., Maindrault S., Tissot O., Liu J. *BOCOP 2.2.1 – user guide* [e-resource]. August 8, 2019. Available on: <http://bocop.org>.

Received May 13, 2022

Revised June 30, 2022

Accepted July 4, 2022

Evgenii Nikolaevich Khailov, Cand. Sci. (Phys.-Math.), Faculty of Computational Mathematics and Cybernetics, Lomonosov Moscow State University, Moscow, 119992, Russia,
e-mail: khailov@cs.msu.su.

Ellina Valer'evna Grigorieva, Cand. Sci. (Phys.-Math.), Prof., Department of Mathematics and Computer Sciences, Texas Woman's University, TX 76204, USA, e-mail: egrigorieva@mail.twu.edu.

Anna Dmitrievna Klimenkova, undergraduate student, Faculty of Computational Mathematics and Cybernetics, Lomonosov Moscow State University, Moscow, 119992, Russia,
e-mail: klimenkovaad@mail.ru.

Cite this article as: E. N. Khailov, E. V. Grigorieva, A. D. Klimenkova. Optimal combination treatment protocols for a controlled model of blood cancer. *Trudy Instituta Matematiki i Mekhaniki UrO RAN*, 2022, vol. 28, no. 3, pp. 222–240.