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CML dynamics: Optimal control of age-structured stem cell population

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Abstract

This paper is devoted to the optimal control of an age-structured system, describing the evolution of normal and leukemic hematopoietic stem cells (HSC) under therapy. The optimal control represents the drug dosage over a fixed length of time. We give evidence that the discrete scheme, derived from our model, is consistent; moreover, the continuous dependence of the solution with respect to the initial data is proved. We prove the existence of an optimal control providing a unique solution to our model. Numerical simulations show that the division rate of leukemic HSC plays a crucial role when determining the optimal control. When the division rate decrease with age of cells, drug therapy should be administered at full dosage at the beginning. Next, it is piecewise continuous in time. When older leukemic HSC have a larger capacity of division, the optimal dosage increases to the maximum value, and then decreases over time.

Keywords: Hematopoietic stem cells; Drug therapy; Chronic myeloid leukemia; Partial differential equations; Optimal control

1. Introduction

Hematopoiesis is a physiological process referring to the production of blood cells (red blood cells, white cells and platelets). Blood cells originate from hematopoietic stem cells (HSC) in the bone marrow, which represent a self-renewing population, able to differentiate into mature cells. Hematopoiesis often reveals some abnormalities causing a disturbance of homeostasis, and leading to hematological diseases. Initially described in 1845, chronic myeloid leukemia (CML) is a common hematological disease, with an incidence of 1–1.5 cases per 10^5 individuals per year [9]. The molecular mechanisms involved in CML are defined in [19]; indeed, CML results from a chromosomal aberration of HSC, since an exchange of genetic particles between chromosomes 9 and 22 combines two genes: the Abl gene of chromosome 9 and the Bcr gene of chromosome 22. The produced gene Bcr–Abl codes for a fusion protein with tyrosine kinase activity and entails a disorder in hematopoiesis. Leukemic cells proliferate abnormally and spread to blood inducing hypertrophied spleen. Despite targeted cancer drugs, imatinib mesylate constitutes the main treatment of CML with posology varying from 400 to 800 mg per day [10,27]. Affected individuals respond to imatinib with

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