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Traveling waves in a coupled reaction–diffusion and difference model of hematopoiesis

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Abstract

The formation and development of blood cells is a very complex process, called hematopoiesis. This process involves a small population of cells called hematopoietic stem cells (HSCs). The HSCs are undifferentiated cells, located in the bone marrow before they become mature blood cells and enter the blood stream. They have a unique ability to produce either similar cells (self-renewal), or cells engaged in one of different lineages of blood cells: red blood cells, white cells and platelets (differentiation). The HSCs can be either in a proliferating or in a quiescent phase. In this paper, we distinguish between dividing cells that enter directly to the quiescent phase and dividing cells that return to the proliferating phase to divide again. We propose a mathematical model describing the dynamics of HSC population, taking into account their spatial distribution. The resulting model is a coupled reaction–diffusion equation and difference equation with delay. We study the existence of monotone traveling wave fronts and the asymptotic speed of spread.
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1. Introduction

Hematopoiesis is the process that leads to the production and regulation of blood cells. It can be defined as a set of mechanisms that ensure the continuous and controlled replacement of the various blood cells. All blood cells arise from a common origin in the bone marrow, the hematopoietic stem cells (HSCs). These stem cells are undifferentiated and have a high proliferative potential. They can proliferate and mature to form all types of blood cells: the red blood cells, white cells and platelets. They have abilities to produce by division either similar cells with the same maturity level (self-renewal), or cells committed to one of the three blood cell types (differentiation) (see [41]). The HSCs compartment is separated into two sub-compartments: proliferating and quiescent (nonproliferating or resting). Quiescent cells represent the major part of HSC population (90% of HSCs are in quiescent phase, also called G_0-phase, [43]). Proliferating cells are actually in the cell cycle where they are committed to divide during mitosis at the end of this phase. After division, the two newborn daughter cells, either enter directly into the quiescent phase (long-term proliferation), or return immediately to the proliferating phase to divide again (short-term proliferation), [2,20,38]. More details about HSC dynamics can be found, *e.g.* in [22]. We will take here into account spatial cell distribution inside the bone marrow.

It is believed that several hematological diseases are due to some abnormalities in the feedback loops between different compartments of hematopoietic stem cell populations. Among a wide variety of disorders affecting blood cells, myeloproliferative diseases are of great interest. They are characterized by a group of conditions that cause blood cells to grow abnormally. They include chronic myelogenous leukemia, a cancer of white blood cells. Myeloproliferative disorders usually originate from the HSC compartment: an uncontrolled proliferation in the HSC compartment can perturb the entire system and leads to a quick proliferation. The excessive proliferation of malignant HSCs changes normal cell distribution in the bone marrow. If the proliferation of malignant HSCs is sufficiently fast, then the disease can invade the whole bone marrow. The propagation of malignant HSCs may correspond to traveling wave fronts of a reaction–diffusion equation.

The first mathematical model of HSC dynamics has been introduced in 1978 by Mackey, [26], inspired by works of Burns and Tannock, [15]. Mackey proposed a system of two uncoupled delay differential equations to describe the dynamics of HSC populations, and applied his model to a blood disease, aplastic anemia. The delay describes the average cell cycle duration. The model of Mackey stressed the influence of some factors such as the apoptotic rate, the introduction rate, the cell cycle duration, playing an important role in the appearance of periodic solutions. Since then, Mackey's model has been improved by many authors, including Mackey and co-authors, [8–10,27,28,31,32], Adimy and co-authors, [1–6], and the references therein.

Traveling wave fronts have been widely studied for reaction–diffusion equations modeling a variety of biological phenomena (see for instance, [13,21,33,39] and the references therein), and for time-delayed reaction–diffusion equations (see [12,37,40,44,45]). In [25], the authors considered a HSC dynamics model that took into account spatial diffusion of cells. The investigators have simply added a diffusion term to the corresponding delay differential equation. But in recent years it has become recognized that there are modeling difficulties with this approach (see [11,34]). The problem is that individuals have not been at the same point in space at previous times. To attempt to address this difficulty, we use a general principle by which certain retarded differential equations can be obtained from age-structured population models or renewal equations (see [11,34,40]).

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