# BIOMAT 2011

International Symposium on
Mathematical and Computational Biology

*edited by*

Rubem P Mondaini

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Santiago, Chile, 5 – 10 November 2011

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*Federal University of Rio de Janeiro, Brazil*



World Scientific

NEW JERSEY · LONDON · SINGAPORE · BEIJING · SHANGHAI · HONG KONG · TAIPEI · CHENNAI

*Published by*

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

*USA office:* 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

*UK office:* 57 Shelton Street, Covent Garden, London WC2H 9HE

**British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library.

**BIOMAT 2011**

**International Symposium on Mathematical and Computational Biology**



ISBN-13 978-981-4397-70-4

ISBN-10 981-4397-70-9

Printed in Singapore by World Scientific Printers.

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## Preface

At the end of the BIOMAT 2010 International Symposium, which was organized as a joint meeting with the 2010 SMB Annual Meeting, we have made an announcement of the decision of organizing the next series of the BIOMAT Symposia, to start on 2011, in other developing countries and the city of Santiago de Chile was chosen to held the BIOMAT 2011 International Symposium on November, 05 -10, 2011. Even on account of all difficulties associated to meagre financial funds in Chile, we can report that the members of the Local Organizing Committee have done their best to follow at least the traditional guidelines under the continuous advice of the BIOMAT Consortium and its organization of the BIOMAT Symposium series since its inception in Rio de Janeiro on April 2001. This was done in spite of several unexpected facts coming from the hard necessary work to circumvent local emergencies. It was a test for their competence on their first experience of collaborating in full with the organization of an international conference.

We are then indebted to the representatives and authorities of the two local universities - Catholic University del Maule and Pontifical Catholic University of Valparaiso for their offer of fifty hotel daily rates to support the BIOMAT 2011 Keynote Speakers, the bags for the delegates, the coffee-breaks and the Reception Cocktail. The prestige of the BIOMAT Consortium was felt to be necessary for the agreement of five out of ten Keynote speakers to pay for their air tickets. We thank very much indeed these friends and colleagues of the BIOMAT Consortium. They deserve the best in career and personal life for their readiness to collaborate. We also take this opportunity to register that the Consortium got an invaluable financial help from the International Union of Biological Sciences - IUBS. We send to the IUBS Vice-President, Prof. John Jungck and the IUBS Executive Director, Dr. Nathalie Fomproix, our warmest thanks for their collaboration with the BIOMAT 2011 International Symposium on Mathematical and Computational Biology.

Unfortunately, we have also to report that the BIOMAT Consortium has spent all its remaining emergency money this time in the realization of another step of this International Symposium series. However we are happy with the accomplishment of BIOMAT Consortium duties and fundamental mission of collaborating with the Local Scientific development with another international meeting of the BIOMAT Symposium series.

We would like to thank the members of the BIOMAT Consortium Administrative Staff for the year 2011 - Sandro Pereira Vilela, Wanderson da Rocha and Alejandra Guerrero Troyo, for their expertise with certificates, registration and general information given to delegates. Reinaldo Viana Alvares has collaborated with the photographic record of the conference. Sandro Pereira Vilela has been working with the Consortium and the publishers to provide a LaTeX version fo all accepted papers.

The editor of this book series as the President of the BIOMAT consortium and on behalf of this non-profit scientific association sends the best wishes for future productive work to all attendants, delegates, local organizers and Keynote Speakers. He thanks his daughter Cecilia Mondaini, for her technical collaboration and readiness at solving daily bureaucratic problems which cannot be solved in time by someone in charge of so many responsibilities. He feels also indebted to his wife Carmem Lucia for her love, patience and continuous advice which helps to support the disappointments of a long academic life and to his two years old youngster son Romolo Mondaini who has promised to attend the next BIOMAT International Symposium.

Rubem P. Mondaini
President of the BIOMAT Consortium
Chairman of the BIOMAT 2011 Scientific Advisory Committee

Santiago de Chile, November 2011

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# APPLICATION OF HYBRID DISCRETE-CONTINUOUS MODELS IN CELL POPULATION DYNAMICS

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The paper is devoted to the development and to applications of hybrid models in biology and medicine. In this approach, biological cells are considered as discrete or individual objects, intracellular regulatory networks are described by ordinary differential equations, biochemical species in the extracellular matrix by partial differential equations. Cells interact with each other mechanically and biochemically, they can divide, differentiate or die by apoptosis. Cell fate is determined by intracellular and extracellular regulation. We apply these modelling tools to study biological pattern formation and to investigate various biological processes, such as blood cell production and blood flows.

## 1. Hybrid models with off-lattice cell dynamics

Hybrid models is a new method to describe cell population dynamics well adapted to study complex multi-scale biological phenomena. They are more and more used nowadays for various biological and medical applications.

We develop a hybrid model with off-lattice cell dynamics. The model is schematically explained in Figure 1. In this approach, cells are considered as discrete objects. They can interact with each other and with the surrounding medium mechanically and biochemically. Cells have the ability to move, grow, divide, differentiate and die by apoptosis. The fate of each cell is determined by intracellular and extracellular regulatory networks. Intracellular regulatory networks are described by ordinary differential equa-

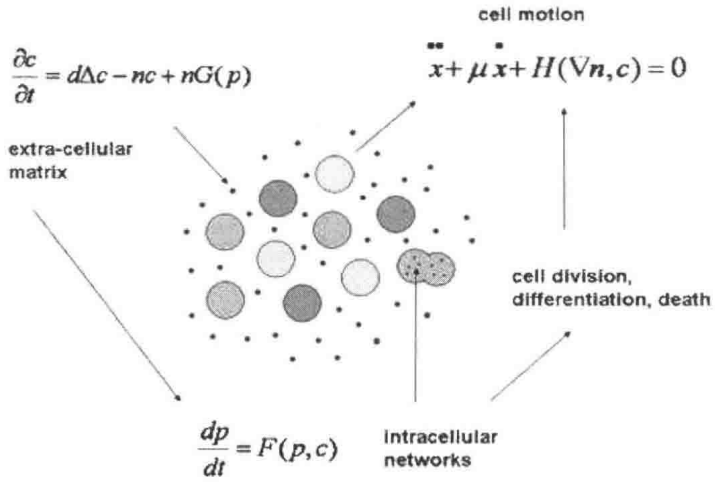


Figure 1. Schematic representation of the hybrid model. Cells are considered as elastic balls, intracellular regulatory networks are described by ordinary differential equations. They determine cell proliferation, differentiation, death by apoptosis. Extracellular biochemical species are described by partial differential equations. They can influence intracellular regulation. Cell displacement is reduced to the motion of their centers.

tions:

$$\frac{du_i(t)}{dt} = F(u_i(t), u(x_i, t)), \tag{1}$$

where $u_i$ is a vector of intra-cellular concentrations of cell $i$, $u$ is a vector of extra-cellular concentrations, $F$ is a vector of reaction rates which is specified for each particular application. Intra-cellular concentrations $u_i$ are supposed to be uniformly distributed inside the $i$th cell. Therefore these functions depend on time $t$ and they are independent of the space variable $x$. Values of intracellular concentrations can be different in different cells. At the same time, they can be influenced by extra-cellular concentrations $u(x, t)$. We will see below that cell motion will be reduced to motion of their centers. The value of the extra-cellular concentration in the right-hand side of equation (1) is taken at the center $x_i$ of the $i$th cell.

The extracellular regulatory network [18] is described by reaction-diffusion equations:

$$\frac{\partial u}{\partial t} = D\Delta u + G(u, c), \tag{2}$$

where $c$ is the local cell density, $G$ is the rate of consumption or production of different species by cells, which will be specified in the following section,

$D$ is the extracellular diffusion rate. Numerical solution of these equation is based on conventional implicit finite-difference alternative direction method. A specific feature of this model is that cells are not necessarily small in comparison with the space step of the numerical mesh. A local cell concentration $c$ is computed as total cell area inside each square of the grid.

We consider cells as elastic balls. Under the assumption of small deformations, we can express the force acting between them as a function of the distance between their centers. Thus, the force between two particles with centers at $x_i$ and $x_j$ is given by a function $f(d_{ij})$ of the distance $d_{ij}$ between the centers. It is zero if the distance is greater than the sum of their radii. To describe the motion of a particle, we should determine the forces acting on it from all other particles and possibly from the surrounding medium. We describe the motion of each cell by the displacement of its center by Newton's second law:

$$m\ddot{x}_i + \mu m\dot{x}_i - \sum_{j \neq i} f(d_{ij}) = 0, \tag{3}$$

where $m$ is the mass of the particle, the second term in left-hand side describes the friction by the surrounding medium, the third term is the potential force between cells. The force between two spherical particles is considered in the form

$$f(d_{ij}) = \begin{cases} K\dfrac{d_0 - d_{ij}}{d_{ij} - d_0 + 2H_1}, & d_{ij} < d_0, \\ 0, & d_{ij} \geq d_0 \end{cases} \tag{4}$$

where $d_0$ is the sum of cell radii, $K$ is a positive parameter, and $H_1$ accounts for the compressible part of each cell. The force between the particles tends to infinity when $d_{ij}$ decreases to $d_0 - 2H_1$. On the other hand, this force equals zero if $d_{ij} \geq d_0$. More detailed discussion of the model and various test cases and examples are presented in [2,3].

Cells can divide, die by apoptosis or differentiate. Their fate is determined by intra-cellular concentrations. In particular, if a concentration of an intra-cellular protein exceeds some critical value, the cell divides, if a concentration of another protein reaches its critical value, the cell differentiates. These assumptions are simplified but still realistic from the biological point of view. In the numerical model, if a cell dies by apoptosis, it is removed from the computational domain. Before a cell divides, it increases its area. It can preserve a circular shape during its growth or, if we need

to compute more precisely the forces acting between the cells, it can take an $\infty$-shape specific for cells in the process of division.

We presented in this section a general description of the hybrid model. For each particular biological process, we need to describe the corresponding intracellular and extracellular regulation, cell behavior, possible feedback from other organs. We illustrate it in the next section how it works to model erythropoiesis, red blood cell production in the bone marrow. In Section 3 we use this approach to study blood flows where we take into account plasma, blood cells, cell interaction between each other and with vessel walls. Here we need to give a more detailed description of simple flows (homogeneous Newtonian fluids) and elastic properties of erythrocytes.

## 2. Modelling hematopoiesis

Hematopoiesis is the process of blood cell production in the bone marrow. It is extremely complex and intensive, with about $10^{11}$ cell produced in human body every day. There are numerous regulatory mechanisms in the bone marrow and from other organs. We illustrate modelling of hematopoiesis with one of its lineages, erythropoiesis, production of red blood cells.

### 2.1. *Intracellular and extracellular regulations in erythropoiesis*

**Intracellular regulation.** A simplified model of intracellular regulation in erythroid progenitors is reduced to two proteins, ERK and Fas. Their concentrations are described by ordinary differential equations.

$$\frac{dE}{dt} = (\alpha(Epo, GF) + \beta E^k)(1 - E) - aE - bEF, \tag{5}$$

$$\frac{dF}{dt} = \gamma(F_L)(1 - F) - cEF - dF, \tag{6}$$

The form of these equations and the values of parameters are discussed in [2], [3]. It is chosen in such a way that it describes a possible choice of erythroid progenitors between self-renewal, differentiation and apoptosis. If the concentration of Fas reaches its critical value during the cell cycle, then the cell will die by apoptosis. If the value of ERK reaches its critical value, then at the end of the cell cycle the cell will divide and give two erythroid progenitors. If neither Fas nor ERK reach their critical values, then at the end of the cell cycle the cell divides and gives two differentiated cells. This choice is influenced by the hormones Epo and GK whose level

is considered to be constant in this model, by Fas-ligand and the growth factor produced by the macrophage.

When a new erythroid progenitor appears, we need to specify the initial values of intracellular proteins ERK and Fas. Daughter cells inherit half of the amount of Erk and Fas of the mother cells.

**Extracellular regulation.** Differentiated cells produce Fas-ligand ($F_L$). Its concentrations are described with the following reaction-diffusion equations

$$\frac{\partial F_L}{\partial t} = D_{F_L}\Delta F_L + W_{F_L} - \sigma_{F_L}F_L, \tag{7}$$

Fas-ligand increases intracellular Fas concentration of neighbouring cells through membrane receptors. When the concentration of the extracellular Fas-ligand is high, it stimulates apoptosis, when it is intermediate it stimulates differentiation of erythroid progenitors.

Growth factor (GF) produced by macrophage stimulates self-renewal of erythroid progenitors. Its concentration can be described by the equation

$$\frac{\partial GF}{\partial t} = D_{GF}\Delta GF + W_{GF} - \sigma_{GF}GF. \tag{8}$$

### 2.2. *Modelling erythropoiesis in vitro and in vivo*

We now put together intracellular and extracellular regulations briefly described in Section 2.1 and cell dynamics described in Section 1. We begin with modelling experiments on cell cultures with macrophage. The cell culture contains a macrophage (big cell in the center in Figure 2.2), erythroid progenitors neighboring to macrophage (adherent cells, AC), erythroid progenitors located at some distance from the macrophage (non-adherent cells, NAC), differentiated cells, reticulocytes. The red region around reticulocytes shows Fas-ligand produced by these cells and promoting differentiation and apoptosis of erythroid progenitors. The green substance is growth factor produced by macrophage and stimulating self-renewal of erythroid progenitors. The results of the numerical simulations are in a good agreement with the experiments on cell cultures with macrophage [19]. Cell structure with a macrophage inside, reticulocytes outside and erythroid progenitors between them corresponds to organization of erythroblastic islands in the bone marrow [5].

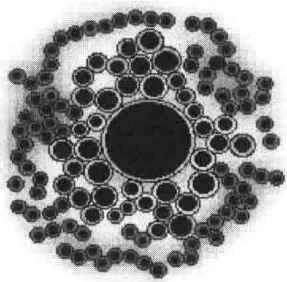

Figure 2. In the cells culture, progenitors AC are yellow, progenitors NAC are light blue, differentiated AC are dark blue and differentiated NAC are purple. Fas-ligand is red and GF is green. Colourful figures can be seen at http://www.biomat.org/biomat/ColourfulFiguresPKurbatovaNEymardATosenbergerVVolpert .htm

Numerical simulation on another in vitro experiment is shown in Figure 2.2. In this case, the cell culture contains erythroid progenitors, reticulocytes and mature erythrocytes.

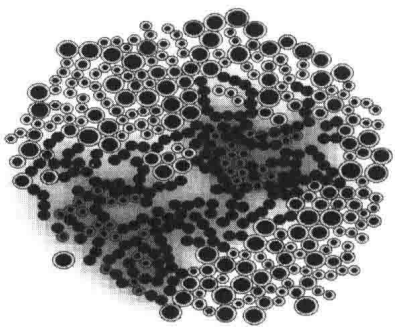

Figure 3. Growth of cells culture. After several divisions, progenitors (yellow) become reticulocytes (blue) which produce a growth factor: Fas-ligand (red halo). After one cycle, reticulocytes become erythrocytes (purple): cells do not divide in this model. Colourful figures can be seen at http://www.biomat.org/biomat/ColourfulFiguresPKurbatovaNEymardATosenbergerVVolpert .htm

## 3. Dissipative particle dynamics and blood flows

Dissipative particle dynamics is a method to simulate systems of particles. It originates from molecular dynamics where each particle moves according to Newton's second law. The difference between two methods is in the form of forces acting between the particles. In molecular dynamics, it is