Drugs affecting differentiation and stochastic gene expression: a dynamic model of the in vitro erythroid differentiation

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Résumé

Erythropoiesis is the process by which mature red blood cells are produced by the differentiation of immature progenitors in the bone marrow. These progenitors can either keep proliferating, or engage into differentiation. Recent theoretical developments about the dynamical nature of cellular state predict that in such cell populations, the level of variability of gene expression could influence the differentiation rate.
Previous work has led to the identification of two chemical drugs, called Artemisinin and Indomethacin, which reduce both the variability of gene expression among an in vitro cell population, and its ability to differentiate. This population is composed of erythroid progenitors, which can either proliferate or differentiate into red blood cells depending on the medium in which they are grown. A problem that naturally arises from these observations, and that we propose to address in this study, is to determine whether the drop in the population of differentiated cells under drug treatment is linked to a higher mortality, or a reduced differentiation. A reduction of the differentiation rate of the erythroid progenitors would definitely link the stochasticity of gene expression with differentiation, whereas an increased mortality would not support this hypothesis.

We start by formulating a family of dynamic models, as sets of ordinary differential equations, for the in vitro erythroid differentiation, using different cell populations structures. We select the best one among this family, using information criteria based on confronting the model behavior to experimental data and results from identifiability analysis. The data that we use come from cell counts of different cell populations, at regularly spaced instants during the course of differentiation. The best model that we find comprises three cell populations at different stages of differentiation, characterized by different proliferation rates. We then predict how the values of the model parameters do vary under the drug treatments, and prove that the treatments affect both the net growth rate of the cell populations (which comprises their mortality) and their differentiation rate.

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Our work introduces the first mathematical model of in vitro erythroid differentiation. Moreover, we establish a strong link between gene expression stochasticity on the one hand, and cellular differentiation on the other one.

Mots-Clés: Erythropoiesis, Cell differentiation, Computational Modelling, Parameter Identifiability