Stochastic gene expression model and structured nonlinear cell population model

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In this talk, I will present a work in progress on cell differentiation models. The objective of this work is to combine stochastic single-cell gene expression models and structured cell population models. The general idea is that of the "Waddington epigenetic landscape", which suggests that cell fates are attractors of an underlying gene regulatory network. We are interested in this context how a cell population can achieve homeostasis. To keep things simple, we focus on a one-dimensional state-space (a single protein that self-regulate its own production), and highlight the role of the bursting (randomly intermittent) production of proteins and of the asymmetric repartition of proteins between daughter cells at division.

We start from the well-established bursting gene expression model. The first step to go from a stochastic single-cell gene expression model to a cell population model is to include the division mechanism. The latter is obviously responsible of the growth of the population, and interacts with the cellular content with possible molecular segregation at division. Using the framework of Markov processes, following a single cell line, the study of the probability density function (of the number of proteins in a cell) leads to a Fokker-Planck-like equation that is a linear (mass-preserving) integro-differential equation

$$\frac{\partial u(t,x)}{\partial t} = \underbrace{-\lambda_b(x)u(t,x) + \int_0^x \lambda_b(y)u(t,y)\kappa_b(x,y)dy}_{\text{Bursting (gain)}} \underbrace{-\lambda_d(x)u(t,x) + \int_x^\infty \lambda_d(y)u(t,y)\kappa_d(x,y)dy}_{\text{Division (loss)}}$$

Under specific choice of bursting (κ_b) and division (κ_d) kernel, we obtain fairly general results for the long time behavior of such equations. Such cases lead to analytic solutions, suitable for a P-bifurcation study (number of modes of the stationary states) and waiting time caracterisation.

Finally, I will adress the issue of modelling the behavior of the whole population (rather than a single cell line). This leads to nonlinear structured cell population model, with nonlinear division rate,

$$\begin{aligned}\frac{\partial u(t,x)}{\partial t} = &-\lambda_b(x)u(t,x) + \int_0^x \lambda_b(y)u(t,y)\kappa_b(x,y)dy \\ &- \lambda_d(x,S)u(t,x) + 2\int_x^\infty \lambda_d(y,S)u(t,y)\kappa_d(x,y)dy - \mu(x)u(t,x),\end{aligned}$$

with $S = \int_0^\infty \psi(x)u(t,x)dx$. I will give specific cases (constant division and death rates) where we obtain convergence towards non-trivial steady-states. With the help of numerical simulations, I will discuss the occurence of oscillations, and the influence of the bursting mechanism and the asymmetry of division for the homeostasis to be achieved.

This work is performed during my stay as a "post-doc" in the MATCH laboratory, at the University of Heidelberg, under the supervision of Anna Marciniak-Czochra. It has also been done in collaboration with Marta Tyran-Kaminska (Institute of Mathematics, University of Silesia, Poland) and Michael C. Mackey (CAMBAM, McGill University, Canada).