A general model for toxin-antitoxin dynamics in bacteria like E. coli can explain persister cell formation

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Inspired by my stays at IFISC (first as a postdoc now 16 years ago) on the one hand and the tradition of the "Brussels school" (mainly at ULB) on the other hand, the Applied Physics research group at VUB recently engaged in research activities in the field of systems biology. In this contribution, my aim is to give an overview of these expanding activities.

In a first research line, we model the transcription dynamics of toxine-antitoxine modules in bacteria. Toxin-antitoxin modules are small genetic elements, omnipresent in the genomes of bacteria, which code for an intracellular toxin and its neutralising antitoxin. Toxin-antitoxin modules play a significant role in the generation of persister cells. Here, we provide an overview of several methods to simulate toxin-antitoxin modules: both deterministic modelling using ordinary differential eqs, as well as stochastic modelling using stochastic differential eqs and the Gillespie method have been studied. Protein production and degradation, negative autoregulation through DNA binding, toxin-antitoxin complex formation and conditional cooperativity are gradually integrated in these models. Finally, by including growth rate modulation, we link toxin-antitoxin module expression to the generation of persister cells.

Another modelling approach addresses the human gut microbiota: a complex ecosystem wherein many microbial species interact and which is very important for human health. How the microbial interactions contribute to the collective behavior of this ecosystem remains less understood. In our approach, we focus on small communities of a few of the key bacterial species inhabiting the gut microbiota. The long term goal of this research is to be able to predict how a bacterial population reacts to perturbation such as anti-biotic administration. Two modelling approaches are chemostat (CS) equations and Lotka-Volterra (LV) equations. CS equations are based on in vitro experiments and incorporate resource consumption. They are therefore more realistic for the human gut and more quantitative than LV eqs. LV eqs have the advantage that they are easy to use and every term has a clear biological significance which is easier to understand intuitively. Moreover, they can easily be generalized to multiple species.

In the CS modelling approach, bacterial growth is modelled with Monod-like growth kinetics. Competition and cross-feeding are taken into account through explicit modelling of the nutrient production and consumption. Comparing our theoretical predictions with experimental results on co-cultures (in collaboration with the Raes and the De Vuyst labs in Belgium), leads to a good description of (experimentally very challenging) bi- and tri-culture dynamics. Furthermore, we observe that the time that species need to adapt to their environment influences which species eventually are dominant. In a theoretical approach, we also simplify the CS equations to a minimal model that exhibits bistability. Our model is a relatively simple extension of LV eqs that is capable of describing a system of two species that is competitive as well as mutualist. Like LV equations the proposed model has an easy intuitive interpretation and can be generalized to multiple species, thus paving the way towards predictive multi-species modelling.

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[1] Gelens L, Hill L, Vandervelde A, Danckaert J, Loris R (2013) "A General Model for Toxin-Antitoxin Module Dynamics Can Explain Persister Cell Formation in E. coli". PLoS Comput Biol **9(8)**: e1003190. doi:10.1371/journal.pcbi.1003190

[2] A Vandervelde, R Loris, J Danckaert, L Gelens (2016) "Computational Methods to Model Persistence", in Bacterial Persistence: Methods and Protocols, pp. 207-240