

Modelling Bacterial Quorum Sensing and Effects of Nutrient Availability

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Many bacteria developed a possibility to recognise aspects of their environment or to communicate with each other by chemical signals. The so-called Quorum sensing (QS) is a special case for such a communication, a regulatory system for gene expression. Such an extracellular signalling via small diffusible compounds (called autoinducers) is known for an increasing number of bacterial species, including pathogens and beneficials. Briefly, bacteria release autoinducers and simultaneously regulate target gene expression dependent on the environmental autoinducer concentration. Regulated behaviour often induces critical life style switches, thus mechanistic understanding of autoinducer regulation and its ecological significance is of high relevance for the development of treatment strategies. Typical bacterial species using QS are *Vibrio fischeri* (a marine, luminescent bacterium) and *Pseudomonas aeruginosa* (a pathogenic bacterium). Autoinducer regulation was originally assumed to be a strategy enabling life style switches dependent on the cell density (quorum sensing), [4]. Later detected influence of other aspects as mass transfer properties of the environment and cell distribution lead to the alternative concept of diffusion sensing (assuming the diffusion properties of the environment around a cell being estimated by autoinducers) and of the unifying efficiency sensing [8, 5].

We will focus on the typical QS system of Gram negative bacteria of the so-called *lux* type, named after the QS system in *V. fischeri*. Many other species have systems of similar structure. Acyl homoserine lactones (AHL), produced by an autoinducer synthase (LuxI) are acting there as signal. AHL binds to a receptor molecule (LuxR); this complex dimerises and binds to the so-called *lux* box (a special piece of DNA). Thereby, the autoinducer synthase (LuxI) and other target genes are upregulated. The AHL controls its own production, resulting in a positive feedback loop in the QS system. By a system of ODEs, the gene regulation can be modelled in detail, but it is hard to determine realistic parameter values. By quasi-steady state assumptions ([1]), this system can be reduced to just one remaining ODE

of the form

$$\dot{A} = \alpha + \beta \frac{A^2}{A_{thresh}^2 + A^2} - \gamma A - d_1 A + d_2 A_{ext}.$$

It shows up the typical behaviour of bistability with a resting state and an activated state and saddle-node bifurcations [7].

The current bacterial population density has a direct influence on the QS system, hence population dynamics has to be taken into account. This is typically considered in a batch culture (i.e., logistic growth) or a chemostat. Obviously, the nutrient availability influences the bacterial growth, and by that indirectly the QS system.

There is increasing evidence that autoinducer systems themselves are controlled by various factors, often reflecting the cells' nutrient or stress state. Further effects which cause e.g. detachment processes and heterogeneous behaviour within colonies appear. Recently, it has been suggested that such controls allow for integrating the demand of the cells for the regulated behaviour into the signal strength, generating a kind of hybrid push/pull control [6]. The factors have been shown to interfere with the autoinducer regulation pathway in various ways [2, 10]. The differences with respect to the outcomes and the reason for the variety are largely unclear. We hypothesise that different ecological and/or evolutionary impacts emerge. In this study, exemplarily three interaction patterns in *V. fischeri* are analysed by modelling:

1. Regulation of LuxR
2. Regulation of LuxI
3. Regulation of LuxI and LuxR

Aim is to understand the differences with respect to the outcomes and to estimate potential ecological respectively evolutionary consequences. Typical aspects are e.g. the range of bistability, the activation threshold and long term behaviour. From a mathematical point of view, bifurcation analysis may help to answer these questions. Mainly deterministic models are used, but we will shortly consider the potential influence of stochasticity which may be caused by small numbers of certain players in the system.

As last part, we will introduce a spatial approach, including the diffusion and transport of nutrients, respectively. As bacteria are typically growing

in small colonies and not in well-stirred cultures, spatial structures may play a major role. One typical approach for bacterial cells in a biofilm are PDE models which can be combined with the QS modelling approach (see e.g. [9, 3]). Furthermore, for simulations one can use a hybrid model combining a PDE model for the spread of substances (autoinducers, nutrients) with a cellular automata model (for the bacterial growth).

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