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Live & let die - A systems biology view on cell death

Thomas Eißing[a], Madalena Chaves[a], Frank Allgöwer[a]

[a]*Institute for Systems Theory and Automatic Control, Pfaffenwaldring 9, 70569 Stuttgart, Germany, {eissing,chaves,allgower}@ist.uni-stuttgart.de*

Extended Abstract

In this keynote presentation, we will provide an introduction to systems biology, an interdisciplinary approach aimed towards a better understanding of the physical basis of life [1]. Biology is a thriving science where exciting new discoveries are made almost on a daily basis. Nevertheless, big achievements like the human genome project do not mark the completion but the beginning of the next level of understanding. Mathematical biology, metabolic engineering and chemical engineering approaches towards the cell or an organism are emerging as the "post-(gen)omic" frontiers. Whereas the "omic"-technologies produce large amounts of data, systems biology is promising to put the pieces back together by integrating knowledge using mathematical descriptions.
Exemplary we will introduce the audience to the challenges in the field of systems biology by looking at programmed cell death, also called apoptosis. Apoptosis is a molecular program by which single cells can be eliminated for the benefit of the organism as a whole. It is present in all cells of multi-cellular organisms and crucial during development and for cellular homoeostasis. The topic has attracted more than 100000 related publications in recent years. Its importance is outlined by the fact that in the adult human approximately 10 billion cells die every day to balance those reproduced during mitosis [2]. Too little apoptosis and uncontrolled reproduction are hallmarks of cancer whereas too much apoptosis is implicated in neurodegenerative diseases such as Alzheimer [3, 4].
We will overview our work on modeling biological processes mainly using the apoptosis example. We review an ordinary differential equation model describing core processes of apoptosis signaling and the idea of viewing the life and death decision as a bistable system. We illustrate how inhibitors of the key

processes can generate this bistable behavior while also filtering out noise due to stochastic influences. Further, model analysis reveals inconsistencies in the literature and help to refine the model structure. Also, while fast and irreversible on the single cell level, apoptosis is more gradual on the population level. We show how subtle differences in model parameters can give rise to this observed population heterogeneity [5, 6, 7, 8].

Employing a new conceptional modeling framework, we show how a single model can describe a population using general inhibition and activation functions. Stable steady states then translate into 0-invariant sets, which are characterized by a local notion of input to state stability (ISS) [9, 10]. This modeling framework also bridges a gap between Boolean and differential equation based modeling approaches.

In conclusion, the apoptosis example illustrates how mathematical modeling and system theoretic analysis can increase the understanding of complex biological processes and explain how malfunctions can arise. These insights will on the long term also, for example, allow a more rational approach to finding new drug targets.

Keywords

systems biology, apoptosis, bistability, ISS, invariant sets

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