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Computational analysis of viable parameter spaces in high-dimensional dynamical models of biological systems

ABSTRACT

Synthetic and systems biology combine branches of biology, mathematics and engineering. Computational modelling can be applied to the study of the existing (system biology) and design of new biological systems (synthetic biology). While the topology of the biological system is in many cases well-known, the values of kinetic parameters that are required to perform computational simulations are often missing or known only partially. This can prove to be problematic since the same biological system can exhibit entirely different behaviour with different parameter values. The analysis of parameter space often applies different sensitivity analysis methods. These methods, however, prove to be problematic, when the viable parameter space is much smaller than the whole parameter space, and when the parameter space exhibits several local extrema. We propose a novel computational framework that can also deal with the systems in which existing methods prove to be inefficient. The methodology is based on the exploration of the high-dimensional viable parameter spaces with sampling, clustering and dimensionality reduction techniques. This methodology allows us to efficiently investigate the viable parameter space regions, evaluate the regions which exhibit the largest robustness and gather new insights regarding the size and connectivity of the viable parameter space. We evaluate the proposed computational framework on the repressilator model and the model of biological master-slave D flip-flop. We show that the viable parameter space of both models is complex. Furthermore, different kinetic parameters have a differently strong influence on system behaviour and its dynamics. We evaluate these parameters and show what kind of effects they exhibit. Our results should prove to be useful to the biologists to pinpoint the segments of the system, which need to be focused more precisely to achieve desired dynamics in the context of synthetic biology or to gather new knowledge in the context of systems biology.