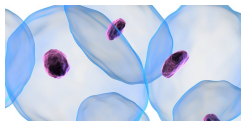
Laboratory of Systems and Synthetic Biology
www.wur.nl\ssb
www.systemsbiology.nl



Quantitative modelling of synthetic CRISPRi circuits using machine learning

Supervisors: Robert Smith (in collaboration with Luis Garcia Morales)

Contacts: robert1.smith@wur.nl

Type of thesis: Computational

Required competences: Programming knowledge in MATLAB and/or Python. Mathematical modelling knowledge will also be required in the project, e.g. from SSB30806, SSB31806 or BCT20306.

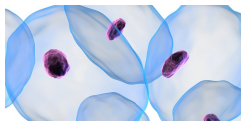
Acquired competences: Construction and analysis of mathematical models that change with time in a growing cell. We will also use machine learning algorithms (in Python) for model building.

Date: 17-08-21

Description

One of the important avenues of synthetic biology research is the (re)construction of genetic circuits and tools within host cells. These systems can then be used to control or redirect biological processes towards some researcher-defined target objective. Traditionally, transcription-translation systems have been built for these purposes, however these systems can be problematic for the host cell. The “genetic load” produced by the synthetic circuit can hamper cell growth and, ultimately, negatively impact the circuit itself. As such, recent work has replaced transcription-translation systems with CRISPRi-based networks that should have a reduced “load” on cell development (Santos-Moreno et al.). We have recently obtained a toggle-switch circuit and produced time-series data to show how toggle switches, and how the host cell develops, given different system inputs.

Given their large potential in helping design future circuits, and the data we have available, we would like to construct quantitative and predictive models of these initial systems such that we can characterise their dynamics in future. This would allow us to



predict the effects of incorporating such tools in larger, e.g. metabolic, networks. There are two levels to constructing such models. First, we need to have the correct equations. Second, we need to estimate reaction rates within the equations given the data. To answer these questions, we will trial some new machine learning methods (Rackauckas et al., Yazdani et al.). In these references, machine learning has been used to optimise reaction rates and, independently, determine mathematical terms missing from a model. However, it is not yet shown that both problems can be tackled in a single machine learning method. Based on results from this analysis, we will assess the feedback between cell growth and circuit performance using our model. Once we have a model that describes the available data, we can make statements about the function of sgRNA components in our CRISPR systems, and make predictions for novel experimental settings to be tested in future lab experiments.

References

Santos-Moreno et al. (2020) 'Multistable and dynamic CRISPRi-based synthetic circuits', *Nature Communications,* doi: 10.1038/s41467-020-16574-1

Rackauckas et al. (2020) `Universal differential equations for scientific machine learning', *arXiv*: 2001.04385

Yazdani et al. (2020) 'Systems biology informed deep learning for inferring parameters and hidden dynamics', *PLoS Computational Biology,* doi: 10.1371/journal.pcbi.1007575