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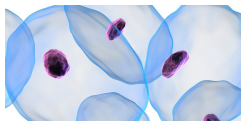

Sequence to Function: Modelling the relationship between DNA sequences and synthetic circuit responses for biosafety

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Type of thesis: Computational

Required competences: Knowledge of ODE models for synthetic biology (e.g. from SSB50806, SSB30806 or SSB31806) and ability to code in Python (e.g. from INF22306, BIF30806, or the SSB courses mentioned).

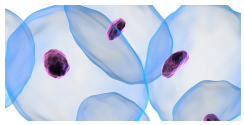
Acquired competences: Model fitting to data. Knowledge of synthetic biology construct design. If applicable, stochastic simulation methods.

Date: 04-10-22

Description

An important strand of synthetic biology is to design circuits for the purposes of biosafety. This, generally, means that networks have two features: reduced leaky (unintentional) expression of system outputs, and inducibility such that the system only functions in tightly controlled, specific conditions. To achieve this functionality, inducible riboswitches have been described in the literature (Isaacs et al., Gallagher et al.). Due to the tight folding of RNA strands, leaky transcription is prevented. By including inducible RNA unfolding and/or binding of complementary strands, a system's functionality can be tightly controlled. However, data obtained from the SSB lab suggests that experimental context matters – the same system shown to work in *E. coli* does not function when put into *P. putida*, both important species for synthetic biology applications.

Mathematical models are used to understand (and hypothesise) how differences in experimental conditions can lead to altered system functionality. For this project, we require the development of a novel mathematical model for our inducible riboregulator



system. Srinivas et al. have already shown how such DNA/RNA-based networks can be constructed mathematically, and we will use these ideas as a starting point to develop our equations. Alongside our equations, we need to understand how fast transcription and translation processes occur to "parameterise" our model. Recent developments in synthetic biology have led to the ability to predict transcription/translation efficiency from a DNA or RNA sequence and structure (Fornace et al., Hossain et al., LaFleur et al.). We will combine these tools with data-fitting strategies to build a model that matches the data we have available. With this model to hand, we will then explore under which conditions the riboregulatory switch functions (or not) and try to propose novel sequence designs that provide the function we desire (i.e. back-calculate DNA/RNA sequences and structures that would be of interest to test given a successful model simulation).

It is rare to find such sequence-based mathematical models of synthetic circuits in the published literature, so we have a lot of scope to discuss and develop new methodology pipelines.

References

Fornace, M. E., et al. (2020) *ACS Synthetic Biology* **9:** 2665-2678

Hossain, A., et al. (2020) *Nature Biotechnology* **38:** 1466-1475

LaFleur, T. L., et al. (2022) *Nature Communications* **13:** 5159

Gallagher, R. R., et al. (2015) *Nucleic Acids Research* **43:** 1945-1954

Isaacs, F. J., et al. (2004) *Nature Biotechnology* **22:** 841-847

Srinivas, N., et al. (2017) *Science* **358:** eaal2052