Characterising relationships between model parameters for biocircuit design

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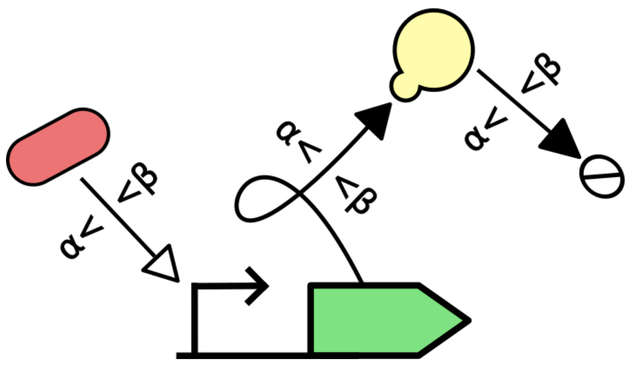
Overview

- We advocate for treating genetic circuit model parameters as sets, rather than scalars.
- Relationships between parameter sets encode information about host-circuit interactions.
- Knowledge of the context-sensitivity of one parameter can allow inferences about the context-sensitivity of others.



Introduction

- Many aspects of the host organism can interact with a genetic circuit and affect its output[1]. Parameter optimisation abstracts away these complex host-circuit interactions.
- We hypothesise that qualitative relationships between parameters optimised for different hosts encode information about the host-circuit interactions.
- Most optimisation methods produce *scalar* parameters [3] which are limited in the qualitative information they can reveal.
- Set-membership estimation produces *regions* of the parameter space which agree with the observations, providing a richer description of relationships between parameters.

Model

- Steady-state data for three genetic constructs coupling protein expression to an inducible promoter were taken from [4].
- A simple analytical model with three parameters was used for this initial investigation.
- The three constructs differ only in the promoter used to control expression of the output protein.
- This simulates different 'transcriptional contexts' of a host organism, and allows for assumptions about the inter-model relationships for some model parameters.

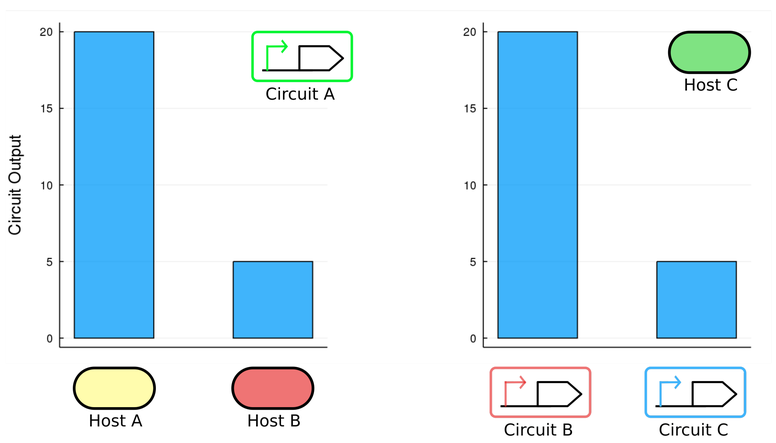


Figure 1: An identical circuit placed in different 'transcriptional contexts' is conceptually equivalent to placing circuits with different transcriptional components in the same host.

Method

Set-inversion via interval analysis [2] was used to identify the feasible parameter sets for three constructs.
The set-inversion can be thought of as computing the set of feasible parameter vectors $\mathbb{P} \subset \mathbb{R}^n$

$$\mathbb{P} = \{\vec{p} \quad | \quad f(\vec{p}) \in [lb, ub]\} \tag{1}$$

for a model f and bounded-error observed output $[lb, ub]$.

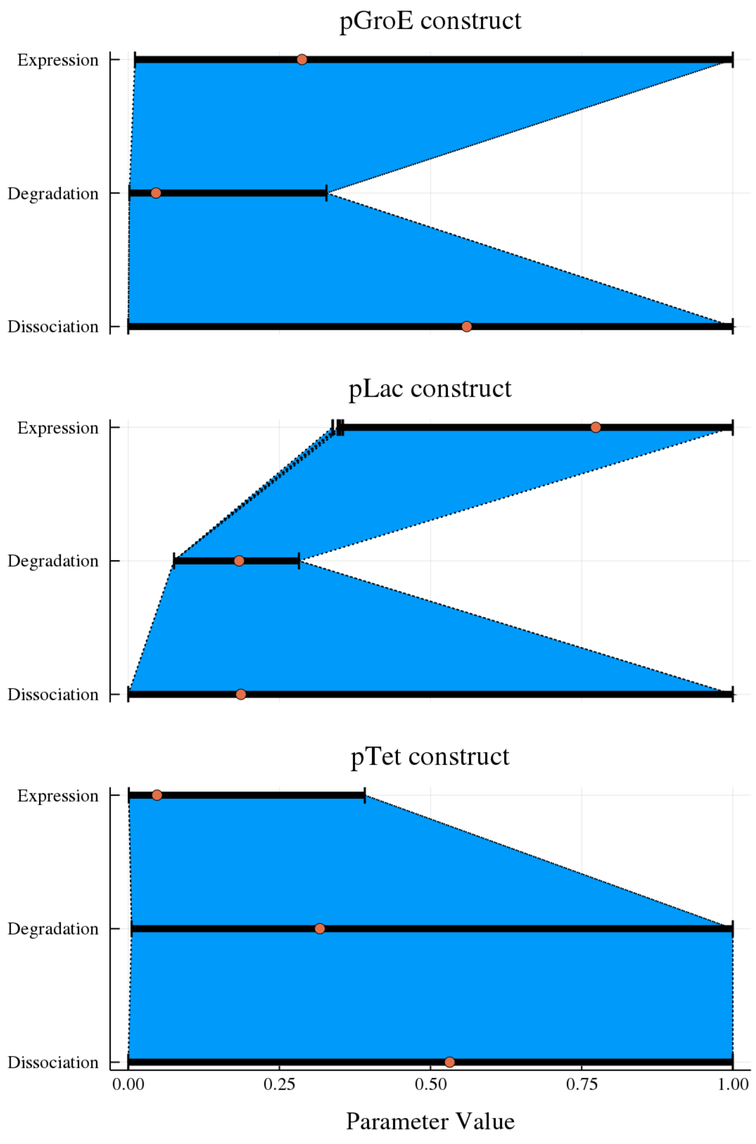


Figure 2: In blue, the complete ranges for the parameter sets. Orange dots mark the scalar parameters optimised with the Nelder-Mead method.

Analysis

- By restricting the ranges of one of the parameters it is possible to probe the parameter relationships.
- This analysis reveals that restricting parameters affects how they relate to others.
- The effects on parameter relationships depend on the modelled construct.

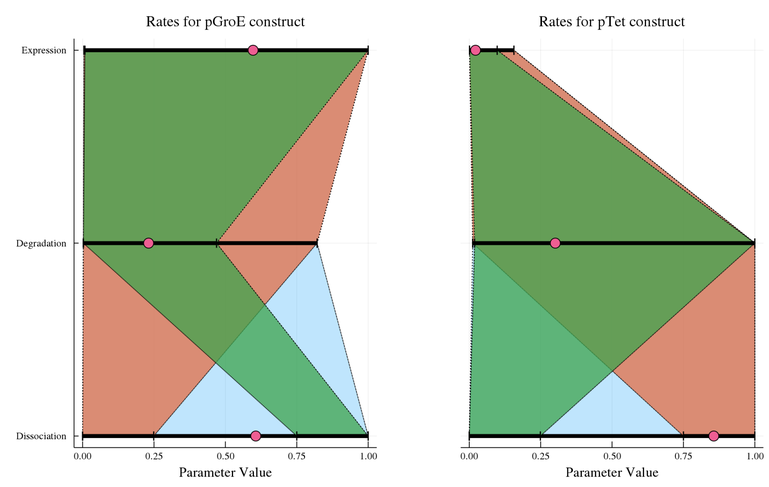


Figure 3: Restricting dissociation constant for the models affects their relationships with each other parameter differently, depending on the modeled construct.

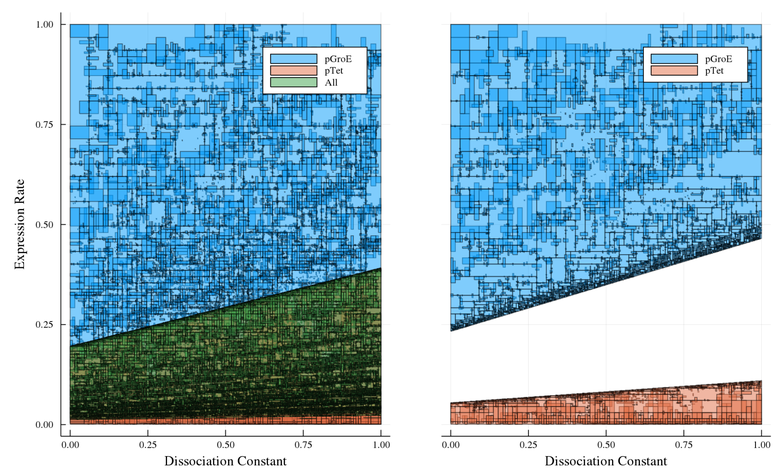


Figure 4: The 2d space of maximal expression and dissociation. The green region is feasible for both models. On the right, degradation rate is restricted to the region feasible for both models, and the green region is eliminated.

- Constructs differ only in their 'transcriptional context', so degradation rates for the output protein should lie in the intersection of the three models' degradation rates.
- Imposing this restriction on the parameter space eliminates the region where the other two parameters agree, as shown above.
- This implies the context-dependence of at least one of the other parameters.

Conclusions

- Parameter set-estimation is a complete search of the parameter space and extracts complete information about the relationships between each parameter in a model.
- By applying the analysis to more complex models and dynamics, we hope that more interesting relationships can be identified. However, there are significant methodological challenges to be overcome before analysis is tractable for more than a handful of parameters.
- Explaining how the relationships between parameters change between hosts will allow development of design tools that 'translate' genetic designs from one host to another.
- We advocate for the treatment of parameters as sets, especially when comparing models of genetic circuits inside different hosts.

References

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