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Applications Note

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SYNBADm: a tool for optimization-based automated design of synthetic gene circuits

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Abstract

Motivation: The design of *de novo* circuits with predefined performance specifications is a challenging problem in Synthetic Biology. Computational models and tools have proved to be crucial for a successful wet lab implementation. Natural gene circuits are complex, subject to evolutionary tradeoffs and playing multiple roles. However, most synthetic designs implemented to date are simple and perform a single task. As the field progresses, advanced computational tools are needed in order to handle greater levels of circuit complexity in a more flexible way and considering multiple design criteria.

Results: This works presents SYNBADm (SYNthetic Biology Automated optimal Design in Matlab), a software toolbox for the automatic optimal design of gene circuits with targeted functions from libraries of components. This tool makes use of global optimization to simultaneously search the space of structures and kinetic parameters. SYNBADm can efficiently handle high levels of circuit complexity and can consider multiple design criteria through multiobjective optimization. Further, it provides flexible design capabilities, i.e. the user can define the modeling framework, library of components and target performance function(s).

Availability and Implementation: SYNBADm runs under the popular MATLAB computational environment, and is available under GPLv3 license at https://sites.google.com/site/synbadm

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1 Introduction

Computer-aided design (CAD) is fundamental in modern engineering. During the last decade, many efforts in the context of Synthetic Biology have been dedicated to incorporate CAD as part of the forward-engineering design cycle (Arpino *et al.*, 2013). Marchisio (2014) and Huynh and Tagkopoulos (2014) offer a comprehensive review of computational tools for the design of synthetic biological circuits. The GEC language by Pedersen and Phillips (2009) and the Parts & Pools framework by Marchisio and Stelling (2008, 2011) are pioneering works conceptualizing modular computational design of synthetic gene circuits. Both tools use search algorithms not based on optimization to explore designs compatible with prespecifications. Automated design of biocircuits was first formulated as an optimization problem in Optcircuit (Dasika and Maranas, 2008) and Genetdes (Rodrigo *et al.*, 2007). Optimization-based algorithms ensure a more efficient search in the design space, attempting to find the circuit with overall best possible performance. In contrast to GEC and Parts & Pools, neither Optcircuit nor Genetdes are suitable for modular design. In terms of modularity, AutoBioCad (Rodrigo and Jaramillo, 2012), SBROME (Huynh *et al.*, 2013) and iBioSim (Myers *et al.*, 2009; Roenher and Myers, 2014) made an important step forward. SBROME allows reusing preexisting constructs, and its extension by Huynh and Tagkopoulos (2014) identifies the smallest number of modules for a specified function. iBioSim handles module reuse, operates at a low specification level and do not account for biological diversity. Biological diversity (one functional behavior can be carried out by different biological processes) is important when all topologies

including those non-intuitive or previously unknown want to be considered, allowing identifying new design principles.

Here we present SYNBADm (SYNthetic Biology Automated optimal Design in Matlab), a software toolbox that enables to automatically find biocircuit designs with pre-specified performance starting from a library of biological components, using global optimization. SYNBADm is developed aiming for optimality, modularity, biological diversity, and a high flexibility regarding the target behaviours and components. SYNBADm includes state of the art global mixed-integer nonlinear programming (MINLP) optimization solvers with proven efficiency in biocircuit design (Otero-Muras and Banga, 2014). It handles high levels of circuit complexity, and incorporates multi-objective design to find gene-circuits with best trade-offs between multiple conflicting criteria.

2 Summary of features

SYNBADm is a Matlab-based multiplatform (Windows and Linux) software toolbox for automated optimal design of gene circuits. To our knowledge, it is the first tool incorporating multiobjective (Pareto optimal) design together with a suite of robust global optimization solvers, offering:

i. flexibility for the definition of biological components (promoters, coding regions, inducers). Mass action and Hill type kinetics are currently supported;
ii. flexibility for the definition of design targets (objective functions);
iii. multi-criteria (Pareto optimal) design, finding the best trade-offs between competing design criteria (Pareto optimal solutions);
iv. simultaneous optimization of topology and parameters using a MINLP framework;
v. a suite of global optimization methods for MINLP, all providing a good compromise between diversification (exploration by global search) and intensification (local search), and ensuring robustness and efficiency;
vi. efficient dynamic simulation in Matlab and C++ (using CVODES).

2.1 Problem definition

2.1.1 Library of components

Users can employ built-in libraries or easily define new libraries of components using the templates provided. SYNBADm library functions generate the necessary Matlab and C++ codes.

2.1.2 Objective functions

Users can easily define objective functions with available templates (built-in objective functions include switch-like behaviour upon induction, protein production cost and sustained oscillations).

2.1.3 Design specifications

Users can specify the minimum and maximum number of promoter-coding regions pairs allowed in the design, the optimization and integration solver options etc.

2.2 Available tasks

2.2.1 Single objective design

SYNBAD_Design_SO solves the single objective optimization problem returning the circuit (topology and parameters) with the best performance.

2.2.2 Multi-objective design

SYNBAD_Design_MO solves the multi-objective optimization problem searching for best trade-offs between competing criteria; SYNBAD_Plot_Pareto depicts the set of circuits in the Pareto front.

2.2.3 Simulation of biocircuit dynamics

SYNBAD_Simulate simulated the dynamics of biocircuit designs (time course levels of the species involved).

2.3 Illustrative examples

A number of examples are provided with the tool, including:

(i)*Design of an endogenous oscillator (single objective):* the aim is to find endogenous oscillators from a built-in library (containing 4 promoters and 11 coding regions) assuming kinetics of mass action type for transcription and translation reactions and taking into account mRNA dynamics. The target behaviour is encoded in the objective function OF_Oscil, which is optimal at a perfect (non-dumped) oscillator. Using SYNBADm we find (considering circuits with 3 promoter-transcript pairs) the sustained oscillator in Figure 1A in a short computation time.

(ii) *Design of circuit with switch-like performance upon induction at minimal protein production cost (multiple objective):* the aim is to find circuits behaving in a switch-like manner upon induction and minimizing the protein production cost from a built-in library (containing eight promoters, four transcripts and two inducers) assuming Hill kinetics for for the lumped transcription-translation

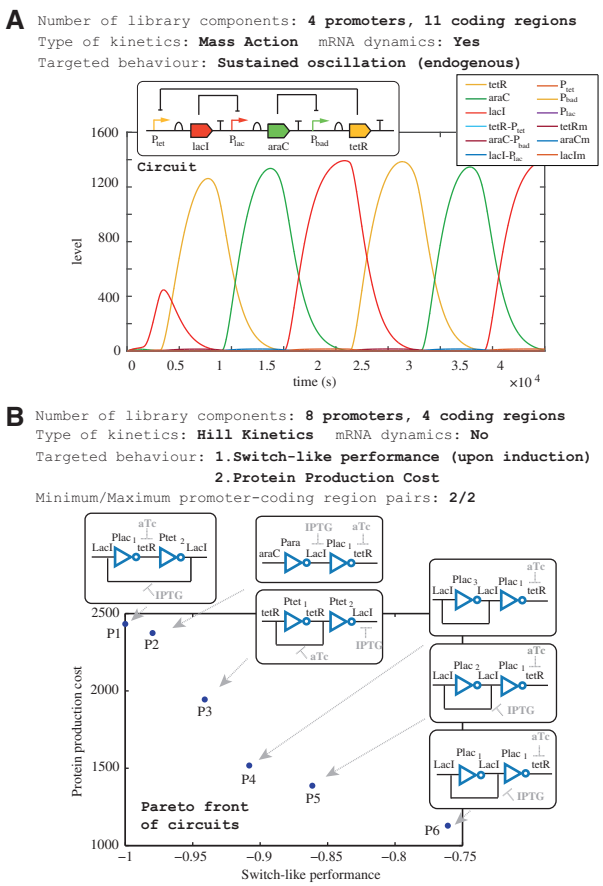

Fig. 1. SYNBADm results **(A)** Repressilator-like circuit (Elowitz and Leibler, 2008) obtained from a single objective design of an endogenous oscillator **(B)** multiple objective design of circuits with switch-like performance at optimal protein production cost

reactions. The objective functions OF_Switch and OF_Cost encode the two target criteria. Using SYNBADm we find (considering circuits with 2 promoter-transcript pairs) the Pareto front of solutions in Figure 1B.

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