

On the Use of MPCCs in Combined Topological and Parametric Design of Genetic Regulatory Circuits

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Synthetic biology involves the assembly of biological components in a systematic and rational way to engineer functional devices, systems, and organisms [1]. A number of synthetic devices have been created over the last thirteen years, including a toggle switch [2] and a repressilator [3]. Established strategies from other engineering domains, such as feedback control, have been extended to the design of genetic circuits that govern biological functions within cells [4, 5, 6]. Simulation of the nonlinear dynamic behavior of genetic circuits has been used to explore design options. Existing design methods, however, are limited, particularly in their ability to manage large-scale genetic circuits. The dimension of successfully implemented genetic circuits, measured by the number of regulatory regions, has plateaued at six for several years [7]. While these simple systems can perform simple biological functions, they are not yet sophisticated enough to provide practical benefits. Realizing the vision of using synthetic biology to tackle grand challenges—such as biomedical therapies—will require new design principles and methodologies.

Here we introduce a new genetic circuit design technique based on direct transcription (DT), a method for dynamic system optimization. DT transforms infinite-dimensional dynamic optimization problems into finite-dimensional nonlinear programs (NLPs), and is used here to simultaneously simulate and optimize genetic circuits with respect to both time-independent parameters and system topology. This design problem is similar to more conventional engineering design problems that involve both topological and continuous design variables where nonlinear dynamic response is important. When genetic circuits are modeled using nonlinear ordinary differential equations known as the Michaelis-Menten equations, topological design decisions are modeled naturally as

complementarity constraints. This leads to a mathematical program with complementarity constraints (MPCCs), which is typically difficult to solve using standard NLP solvers because standard constraint qualifications do not hold. We explore a number of problem reformulations, and solve the genetic circuit design problem using KNITRO , a commercial implementation of an interior-point algorithm [8].

Exhaustive enumeration has been used to solve genetic circuit design problems, but is fundamentally limited in problem dimension (e.g, see the work by Ma et al. in designing three-node circuits [9]). The case study here, as in Ma’s work, focuses on designs that exhibit adaptation, i.e., the output signal returns to its original value after being disturbed by a change in input. The objective is to minimize change in output, subject to a sensitivity constraint that ensures a change in input can be detected. The problem is solved using both DT and single-shooting (i.e., nested simulation) [10, 11]. The MPCC formulation enables the solution of four-node problems, an improvement upon existing approaches and a step toward larger systems. In addition to a simultaneous solution approach for the combined topology/parameter optimization problem, a nested approach was investigated where an outer loop solves the discrete topology optimization problem (avoiding complementarity constraints), while the inner loop solves the continuous parameter optimization problem. The simultaneous approach based on DT and the MPCC formulation is shown to yield robust network topological designs that achieve adaptation.

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