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Multiobjective H_2/H_∞ synthetic gene network design based on promoter libraries

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ABSTRACT

Some current promoter libraries have been developed for synthetic gene networks. But an efficient method to engineer a synthetic gene network with some desired behaviors by selecting adequate promoters from these promoter libraries has not been presented. Thus developing a systematic method to efficiently employ promoter libraries to improve the engineering of synthetic gene networks with desired behaviors is appealing for synthetic biologists.

In this study, a synthetic gene network with intrinsic parameter fluctuations and environmental disturbances *in vivo* is modeled by a nonlinear stochastic system. In order to engineer a synthetic gene network with a desired behavior despite intrinsic parameter fluctuations and environmental disturbances *in vivo*, a multiobjective H_2/H_∞ reference tracking (H_2 optimal tracking and H_∞ noise filtering) design is introduced. The H_2 optimal tracking can make the tracking errors between the behaviors of a synthetic gene network and the desired behaviors as small as possible from the minimum mean square error point of view, and the H_∞ noise filtering can attenuate all possible noises, from the worst-case noise effect point of view, to achieve a desired noise filtering ability. If the multiobjective H_2/H_∞ reference tracking design is satisfied, the synthetic gene network can robustly and optimally track the desired behaviors, simultaneously.

First, based on the dynamic gene regulation, the existing promoter libraries are redefined by their promoter activities so that they can be efficiently selected in the design procedure. Then a systematic method is developed to select an adequate promoter set from the redefined promoter libraries to synthesize a gene network satisfying these two design objectives. But the multiobjective H_2/H_∞ reference tracking design problem needs to solve a difficult Hamilton–Jacobi Inequality (HJI)-constrained optimization problem. Therefore, the fuzzy approximation method is employed to simplify the HJI-constrained optimization problem to an equivalent linear matrix inequality (LMI)-constrained optimization problem, which can be easily solved by selecting an adequate promoter set from the redefined promoter libraries using the LMI toolbox in Matlab.

Based on the confirmation of *in silico* design examples, we can select an adequate promoter set from the redefined promoter libraries to achieve the multiobjective H_2/H_∞ reference tracking design. The proposed method can reduce the number of trial-and-error experiments in selecting an adequate promoter set for a synthetic gene network with desired behaviors. With the rapid increase of promoter libraries, this systematic method will accelerate progress of synthetic biology design.

1. Introduction

Synthetic biology is hybrid discipline, combining elements of both engineering and science to engineer synthetic organisms. Through detailed understanding of cellular mechanisms and improved experimental techniques for manipulating cell genotypes, it has become possible to engineer a cell for the rational design of genetic and protein circuits [1]. In the past decade, synthetic biologists have built several gene networks such as toggle switches [2–5], transcriptional cascades [6], pulse generators [7], time-delayed circuits [8,9], oscillators [2,10–12] and digital logic evaluators [13,14]. The field has also yielded several technological applications and provided new avenues for drug manufacture [15,16], bio-fabrication [17], therapeutics [18,19] and biofuel production [20–22].

From the bottom-up approach, simple and well-characterized biological parts can be coupled together into more complex networks with predicted behaviors. Synthetic biologists also provide a concept that programmable cells can be constructed by designing appropriate interfaces, which couple engineered gene networks to the regulatory circuitry of the cell [23,24]. Hence,

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the well-characterized biological parts as well as a mathematical model can help us engineer a synthetic gene network. Recently, many studies have discussed computation design for synthetic gene networks. For transcription networks, their qualitative depiction and an estimation of produced proteins can be both obtained by employing mathematical modeling frameworks such as an ordinary differential equation (ODE). Kuepfer et al. developed an approach for synthetic biology based on semidefinite programming for partitioning the parameter spaces of polynomial differential equation models into the so-called feasible and infeasible regions [25]. In this approach, a feasible region refers simply to the existence of a steady state of the synthetic system. Rosenfeld et al. used time-lapse fluorescence microscopy to quantitatively analyze autoregulatory negative feedback circuits in order to test the assumption that quantitative characterization of regulatory elements can predict the behavior of gene circuits [26]. More recently, some gene circuit designs have been proposed to embed gene circuits into an existing gene network to improve its robust stability [27,28]. In the biological implementation, synthetic biologists have built the combined gene circuits to produce a push-on/push-off circuit [29] and a counter [30]. These synthetic gene networks are implemented by some basic biological parts for industrial biotechnology. Hence, the synthetic gene networks can be implemented by these basic biological parts and rational design principle [31]. From the engineering viewpoint, the design purpose in synthetic biology is to engineer a completely new gene network and then insert this gene network into a host cell to perform new tasks in spite of intrinsic parameter fluctuations and environmental disturbances on the host cell. Hence, despite intrinsic parameter fluctuations and environmental disturbances, the robust synthetic gene network is designed to achieve a desired steady state [32,33] or an H_2 optimal tracking of a desired oscillatory behavior [34]. The above robust design method is to tune some parameters of biological devices for a synthetic gene network to achieve the desired steady or oscillatory state. But, in fact, tuning the parameters of biological devices to fit the designed parameters for a real suitable biological network is currently quite a difficult or even unfeasible task for biotechnology. With this concept, we think that selecting adequate promoters from the existing promoter libraries for synthetic gene networks is more convenient than tuning the parameters of some components to achieve the designed values of synthetic gene networks.

In general, gene circuits can be constructed from a handful of basic biological parts. For example, in order to completely implement a transcription unit, one needs the promoter, ribosome binding site (RBS), protein coding region and terminator, which can be obtained from the BioBrick. However, BioBrick parts are only standardized in terms of how individual parts are physically assembled into a multi-component system, and most parts remain uncharacterized [35]. Accurate prediction and computational design for synthetic gene networks with adequate component properties have got to be developed for system-level circuitry to integrate basic parts and modules [36]. Quantitative characterization of parts is needed to be measured to improve faster construction of circuits. Kelly et al. developed standard measurement kits for characterizing BioBrick promoters and ribosome binding sites [35]. However, incomplete knowledge about components on modules makes it difficult predict the precise behaviors of synthetic gene networks. The complexity of reactions, variety of molecules, intrinsic and extrinsic disturbances all makes it hard to accurately predict the behaviors even of simpler biological devices.

More recently, Ellis et al. presented an approach that couples libraries of diversified components with *in silico* modeling to guide predictable gene network construction without the need for *post hoc* tweaking [37]. Cantone et al. created a relatively sophisticated synthetic gene network of five genes that serves as an 'oracle' that is queried by different perturbations. Finally, they tested their synthetic gene network by some methods based on ordinary differential equations, Bayesian inference and information theory to uncover the connectivity of the network [38]. Ellis et al. and Cantone et al. provided some guidance through the introduction of benchmark networks.

Next, an efficient approach for selecting suitable promoter sets from the existing promoter libraries is important for the progress of synthetic biology. Synthetic biologists can use the standard biological parts that have a clear definition of the function and interface of the device, and the operating context of the device, to measure characteristics and describe the quantitative behavior. However, at present, there is still no accepted method for synthetic biologists to efficiently select biological parts from promoter libraries for engineering a synthetic gene network with some prescribed behaviors.

In an actual real biological environment, the physical interconnections cannot be extended as in electrical and mechanical system because the interoperability has to be derived from chemical specificity of parts and their desired targets [39]. Thus rational construction in synthetic biology is always hampered by chemical specificity of biological parts. Fortunately, promoter libraries have been widely constructed and their input–output properties can be easily measured via systematic experiments. Since different promoters in promoter libraries have different biochemical kinetics, to engineer a synthetic gene network with desired behaviors by selecting some adequate promoters from promoter libraries has become possible. However, it is still difficult to directly select promoters from these promoter libraries for engineering a synthetic gene network to achieve desired behaviors because these promoters still lack promoter activities which can be easily selected for synthetic biologists. Therefore, for the convenience of design, we should redefine the promoter activities for promoters in these conventional promoter libraries so that they can be more easily selected.

In this study, we also develop a systematic method to efficiently select adequate promoters from these redefined promoter libraries so that the synthetic gene network with desired behaviors can be implemented. Based on the proposed design procedure, synthetic biologists can first create a gene circuit topology as a guide for constructing a synthetic gene network. With a reference model to generate a desired behavior to be tracked by a synthetic gene network, the proposed multiobjective H_2/H_∞ reference tracking design can efficiently select an adequate promoter set from the redefined promoter libraries. Then the synthetic gene network with a desired behavior can be achieved by employing the adequate promoter set, which can simultaneously guarantee a desired H_∞ noise filtering and H_2 optimal reference tracking. In order to meet these two design objectives, we need to solve an HJI-constrained optimization problem for the multiobjective H_2/H_∞ reference tracking design of a synthetic gene network, which is not easy solved analytically or numerically at present. We employ Takagi–Sugeno (T–S) fuzzy system to interpolate several linear systems to approximate the nonlinear gene network system. Based on the T–S fuzzy system, the HJI-constrained optimization problem for multiobjective H_2/H_∞ reference tracking design of synthetic gene networks is transformed to an equivalent LMIs-constrained optimization problem, which can be easily solved with the help of the LMI toolbox in Matlab [40]. Finally, two *in silico* design examples of selecting an adequate promoter set from the redefined promoter libraries to achieve the multiobjective H_2/H_∞ reference tracking design are given to illustrate the design procedure. Although multiobjective H_2/H_∞ control designs have been widely proposed for robust stabilization of linear and nonlinear systems [41–44], this is the first proposed method for selecting an adequate promoter set from refined promoter libraries to achieve a multiobjective