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Investigating the use of Boolean networks for the control of gene regulatory networks

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ABSTRACT

The behaviour of biological cells emerges from complex patterns of interactions between genes and their products, known as gene regulatory networks (GRN). An important aim of biology is to control the dynamics of GRNs, in order to push a cell towards or away from certain behaviours. This could potentially be done by coupling a synthetic GRN to an existing biological GRN. In this work, we use Boolean networks, a methodology for modelling and simulating GRNs, to investigate the potential for doing this. Our results demonstrate that Boolean networks can be optimised to control other Boolean networks, and that the approach scales well as the target network size increases.

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1. Introduction

Complex networks are all around us: social networks, financial networks, ecological networks. Because of their ubiquity and their profound effects upon our lives and livelihood, there has been an increasing interest in controlling the dynamical behaviour of these networks [22]. However, complex networks have a range of properties that make them intrinsically difficult to control [43]. Much of the existing research in this area has focused on analytical methods, typically making use of conventional control theoretic approaches. This has resulted in control methods that can be applied to certain types of complex network, for instance those with particular relationships between their structure and dynamics [22], and those with restricted topologies [11]. In this work, we take a more empirical approach, using evolutionary algorithms to explore the space of control interventions, and thereby automatically discovering interventions that are suitable for particular complex networks.

We consider the control of gene regulatory networks (GRNs) in particular. These are biochemical networks that involve genes and their protein products, especially the transcription factors that allow a gene to regulate another gene's expression. GRNs are fundamental to the behaviour of biological organisms, and control both the internal functions of individual biological cells and the overall development of multicellular organisms. In recent decades, there has been a concerted effort to characterise and map the GRNs of various organisms. However, there has been relatively little advancement in the control of GRNs. The benefits of controlling GRNs would be considerable, particularly from the perspective of medicine: for instance, being able to transition a cell from a cancerous state to a non-cancerous state, or being able to target the differentiation of a stem cell into a particular tissue type [32,22].

In this paper, we focus on the use of Boolean networks [29] for modelling, simulating and controlling GRNs. A Boolean network is a considerably simplified model of a biological GRN. Nevertheless, there are numerous example of successfully using Boolean networks to capture the structure and dynamics of real biochemical networks [28,4,48,17,55,16,31,47,21,44]. Boolean networks have also been adopted as a more general model of complex networks, and studies of their dynamical behaviour have given considerable insight into the properties of real world networks [5]. Perhaps lesser known, however, are the uses of Boolean networks (and computational models of GRNs more generally) within the computational intelligence and artificial life communities, where they are seen as a form of artificial intelligence somewhat akin to neural networks [39]. An example is the use of Boolean networks as robotic controllers [46], where they have shown the ability to generate robust control decisions through the analysis of environmental

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inputs—which, in many respects, is comparable to the kind of control behaviour that biological GRNs carry out.

The work reported in this paper brings together the different roles of Boolean networks: using them both as a simulatable model of biological GRNs, and as a control system. More precisely, we use evolutionary algorithms to discover Boolean networks that can control the dynamics of other Boolean networks. We consider a number of things: the ability of evolutionary algorithms to optimise Boolean networks, the general ability of Boolean networks to control other Boolean networks, and the effect that topology has on both the difficulty of the control problem and the ability of the controllers. The eventual goal of this research is to design controllers for real biological GRNs, and to then implement these within biological cells. The use of Boolean networks is appropriate in this respect, since Boolean logic can be readily refined into biochemical implementations using synthetic biology principles [45].

This work builds upon initial results reported in [53]. In this paper, we report the results of a broader set of experiments using significantly larger Boolean networks and scale free Boolean networks. We also present first results showing that our method can control trajectories in a Boolean model of a real biological circuit. The paper is organised as follows: Section 2 reviews related research in the areas of Boolean modelling and control. Section 3 describes the methods used in this work, including a formal definition of Boolean networks and an overview of evolutionary algorithms. Section 4 presents results and analysis, and Section 5 concludes.

2. Related literature

2.1. Boolean modelling of biological networks

Modelling biological processes using quantitative and continuous mathematical models such as differential equations has brought important insights to systems biology [34,1]. However, these models are often inefficient when simulating larger biological networks. This has promoted interest in discrete-valued models. One such model is the Boolean network, which models gene expression as a binary process (either on or off) and regulatory interactions as Boolean functions (e.g. AND, OR, NOT). The use of binary states and Boolean functions makes them especially cheap to simulate on a computer. Numerous studies have demonstrated that, despite their apparent simplicity and high level of biological abstraction, these models are often able to capture the qualitative dynamics of biological processes. For example, [28] developed a model of the yeast transcription network, [4] successfully modelled the GRN underlying pattern formation in drosophila, [16] modelled the quorum sensing circuits of *Pseudomonas aeruginosa* and [31] developed a model of the GPR142 biological pathway in type 2 diabetes. A number of studies have applied Boolean models to cancer analysis, both by considering specific pathways [47,17,21] and through more abstract systems-level studies [26,27]. Many of these studies have carried out an attractor analysis of the resulting models in order to gain insights into the biological system's stable states [4,26,17], typically associating these with phenotypes. In [44], the authors went a stage further and identified nodes whose state would effect the accessible attractors, in effect identifying potential drug targets for preventing the expression of pathological phenotypes. Discrete models such as Boolean networks have been shown to be equivalent to continuous models when only the steady states of the system are considered [56]; however, it should be borne in mind that Boolean networks are not appropriate when a detailed quantitative understanding of a process is required. For a review of Boolean modelling in biology, see [47].

2.2. Controlling Boolean networks

Finding strategies to control Boolean networks is an important and challenging problem. The control problem is typically defined in terms of leading a Boolean network's trajectory towards a particular point in its state space, ideally by manipulating the state of a minimum group of nodes and with the aim of reaching the target state in a minimal period of time. In common with the complex networks that they model, Boolean networks have a number of characteristics that make them hard to control, including non-linear dissipative dynamics, multiple stable states and high dimensionality [43]. A number of previous works on the control of Boolean networks have been conducted [2,11,51,33,32,43,22]. Many of these use control theoretic approaches. For instance, pinning control methods have been used to stabilise the dynamics of Boolean networks, allowing particular phenotypic states to be maintained [35]. However, in general the control of Boolean networks is known to be NP-complete [2], meaning that optimal control techniques can only be applied to networks of limited size, though polynomial-time algorithms have been developed for Boolean networks with constrained topologies such as tree structures [2]. To an extent, the control problem can be made easier by identifying nodes that have dominant roles within the network (such as hubs in scale-free networks) and focusing control interventions on these [36,32]. This works well for certain kinds of network, but in general it has been shown that dynamics can not be determined by structure alone, and therefore that methods based on structural analysis will not always be effective [22].

2.3. Computation and control using gene regulatory models

In addition to modelling biological GRNs, a number of studies have shown that GRN models can be used to carry out complex computational and control behaviours that are to some degree analogous to their biological activities (see [39] for a recent review). Typically this is done by training the model using a stochastic global optimiser such as an evolutionary algorithm (see Section 3.2) so that it generates a particular behaviour. A number of approaches have used Boolean networks [19,46,24,57], including [46], where a Boolean network was used for robotic control and [10] where asynchronous multiplexing behaviours were evolved. Examples using other GRN models include medical time series classification [40], chaos control [37], games controllers [15] and image compression [54]. A number of studies have shown that Boolean networks in particular have interesting computational characteristics [42,24], and in situations where these models have been applied to control, the analysis of evolved controllers typically shows a high degree of robustness in comparison to more conventional controller architectures [46,15].

2.4. Implementing Boolean networks in cells

Part of the justification for using Boolean networks in this study is the potential for implementing them as optimised control systems within biological cells. One benefit of Boolean networks, in this respect, is that they are relatively amenable for implementation in biological cells using existing synthetic biology approaches. A key focus of synthetic biology has been on implementing digital circuits within cells, the idea being that this will allow more conventional computing approaches to be readily refined into biological systems. However, these approaches also have direct relevance to Boolean networks, since both digital circuits and Boolean networks are comprised of Boolean logic functions that can be implemented as logic gates. Synthetic biology has demonstrated that logic gates can be implemented in various biochemical forms, including proteins, RNA and DNA [45,52,50]. It is also possible to assemble these

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