SADIO Electronic Journal of Informatics and Operations Research

http://www.dc.uba.ar/sadio/ejs

vol. 8, no. 1, pp. 25-34 (2008)

# On Artificial Gene Regulatory Networks

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**Abstract**

Gene regulatory networks (GRNs) represent dependencies between genes and their products during protein synthesis at the molecular level. At the present there exist many inference methods that infer GRNs form observed data. However, gene expression data sets have in general considerable noise that make understanding and learning even simple regulatory patterns difficult. Also, there is no well-known method to test the accuracy of inferred GRNs. Given these drawbacks, characterizing the effectiveness of different techniques to uncover gene networks remains a challenge. The development of artificial GRNs with known biological features of expression complexity, diversity and interconnectivities provides a more controlled means of investigating the appropriateness of those techniques. In this work we introduce this problem in terms of machine learning and present a review of the main formalisms that have been used to build artificial GRNs.

**Keywords:** Gene Regulatory Networks, Artificial GRNs, bioinformatics

## 1 Introduction

A crucial objective of functional genomics is the study of the role of genes in the DNA (Deoxyribonucleic Acid) as protagonist "actors" during the initial mechanism of protein synthesis. How does the sequence of a strand of DNA (a gene) correspond to the amino acid sequence of a protein? This concept is explained by the central dogma of molecular biology, which states that DNA is transcribed into mRNA (messenger Ribonucleic Acid) and then, mRNA is translated into a protein, as shown in Figure 1.

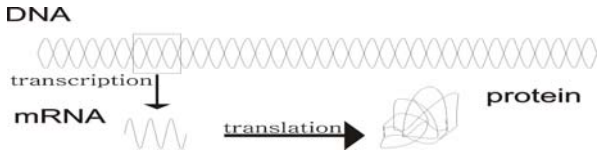


**Fig. 1.** Protein synthesis scheme.

However, how each gene impacts on (*regulates*) the synthesis of each protein remains unknown, and therefore the problem of discovering the gene regulation interactions constitutes a great challenge. From the joining of these interactions emerges a gene network that represents the whole regulation mechanism of the organism.

In this context, bioinformatics plays an essential role in the development of algorithms that enables the reconstruction of gene networks. Nowadays, this problem is being tackled with several machine learning strategies, achieving different degrees of success [1]. However, some drawbacks are being found as these strategies evolve. First of all, most of them begin the studies from data sets that are sometimes scarce, as large amounts of information are needed to accomplish reliable results. Also, this information generally contains noise that makes it difficult to perform the inference methods.

All of these negative aspects gave rise to a new tendency that follows the idea of building artificial GRNs (aGRNs) as a means of acquiring sufficient reliable data. In this sense, aGRNs can be used for validation purposes. It is important to remark that, in the present, there is no literature review on the main methods that are being employed to build aGRNs. The rest of the article is organized as follows: in section 2, a detailed explanation of the problem of gene regulation is presented; later, the main machine learning approaches developed to infer GRNs are described; in section 4 aGRNs are introduced and the state of the art in this area is reviewed; finally, conclusions are put forward.

## 2 Regulatory network's inference

An organism's genetic information is stored in one or more distinct DNA molecules; each called a *chromosome*. All of the genetic information of an organism, taken together as a whole, is referred to as its *genome*. The primary role of nucleic acids is to carry the encoding of the primary structure of proteins. Each non-overlapping triplet of nucleotides, called a *codon*, corresponds to a particular amino acid, which in turn groups with other amino acids to construct a particular protein.

DNA contains a large amount of information in addition to the coding sequences of proteins. Every cell in the body has the same DNA, but each cell type has to generate a different set of proteins, and even within a single cell type, its needs change throughout its life. An increasing number of DNA signals that appear to play a role in the control of expression are being characterized. There are a variety of signals identifying where proteins begin and end, where splices should occur, and a detailed set of mechanisms for controlling which proteins should be synthesized and in what quantities.

### 2.1 Genetic Regulation

As it was aforementioned, each cell has the same DNA. Nevertheless, the DNA in some cells codes for the proteins needed to function as, say, a muscle, and other code for the proteins to make the lens of the eye. The difference lies in the *regulation* of the genetic "machinery". At any particular time, a particular cell is producing only a small fraction of the proteins coded for in its DNA. And the amount of each protein produced must be precisely regulated for the cell to function properly. The cell will change the proteins it synthesizes in response to the environment or other factors. The mechanisms that regulate this process constitute a finely tuned, highly parallel system with extensive feedback and complex control structure. Besides, this intricate mechanism is not yet well understood [2].

Genes are generally said to be on or off (or *expressed/not expressed*), although the amount of protein produced is also important. The production process is controlled by a complex collection of proteins in the nucleus of eucaryotic cells that influence which genes are expressed. Perhaps the most important of these proteins are the *histones*, which are tightly bound to the DNA in the chromosomes of eucaryotes. Histones are some of the most conserved proteins in all of life. There are almost no differences in the sequence of plant and mammalian histones, despite more than a billion years of divergence in their evolution. Other proteins swarm around the DNA, some influencing the production of a single gene (either encouraging or inhibiting it), while others can influence the production of large numbers of genes at once.

In this manner, gene regulatory networks (GRNs) dynamically orchestrate the level of expression for each gene in the genome by controlling whether and how vigorously that gene will be transcribed into RNA. Each RNA transcript then operates as the template for synthesis of a specific protein by the process of translation. A simple GRN would consist of one or more input signaling pathways, regulatory proteins that integrate the input signals, several target genes, and the RNA and proteins produced from those target genes. Input signaling pathways transduce cellular signals to a group of regulatory proteins called transcription factors. Transcription factors activated by the signals then interact, either directly or indirectly, with DNA sequences belonging to the specific genes they regulate.

## 3 Computational Inference of Gene Regulatory Networks

Inference techniques use gene expression data in order to discover the structure of the GRNs. The term ***gene expression data*** refers to the measured abundances of mRNA of a subset or all genes in the genome of an organism. Such measurements are usually performed using microarrays, a revolutionary technology for collecting gene expression data on a genome-wide scale, providing a unique possibility to gain insight into a cell's state. A description of microarray techniques is given in [3].

For computational purposes, expression data can be viewed as a matrix **E** that contains time-series, where rows correspond to genes and columns to the samples – also called *conditions* - taken at different time points. A matrix element $e_{ij}$ contains the measured expression value or a derived statistic for the corresponding gene *i* and sample *j*. For example, an expression matrix for *n* genes under *m* conditions is shown in Figure 2.

| | *condition 1* | *condition 2* | … | *condition m* |
|---|---|---|---|---|
| *gene 1* | $e_{11}$ | $e_{12}$ | … | $e_{1m}$ |
| *gene 2* | $e_{21}$ | $e_{22}$ | … | $e_{2m}$ |
| … | … | … | … | … |
| *gene n* | $e_{n1}$ | $e_{n2}$ | … | $e_{nm}$ |

**Fig. 2**. Gene expression data matrix structure.

Several inference methods have been proposed to perform the reverse engineering of GRNs from gene expression matrices. In general, these approaches consist in identifying correlations among the expression values ($e_{ij}$ entries of **E**) of the genes under different conditions, and then, to infer regulation associations from these correlations.

The basic idea behind these methodologies is that the expression value of a gene represents an indicator of its degree of activity. In this context, a significant change (increment or decrement) in the expression value of a gene *i* from the condition *j* to the condition *j+1*, represents a transition in the *gene state* from a non-active state (*underexpressed*) to an active state (*overexpressed*) or viceversa. This yields to a binary matrix obtained by a discretization procedure. Using these discretized data, it is possible to analyze when two o more genes have a similar (or opposite) behavior pattern over some time period, this relation among their activity patterns indicate the potential existence of a regulation link among them. Finally, it is possible to reconstruct the graph that represents the GRN by interconnecting the different regulation links discovered by the inference method. The whole process is shown in Figure 3.

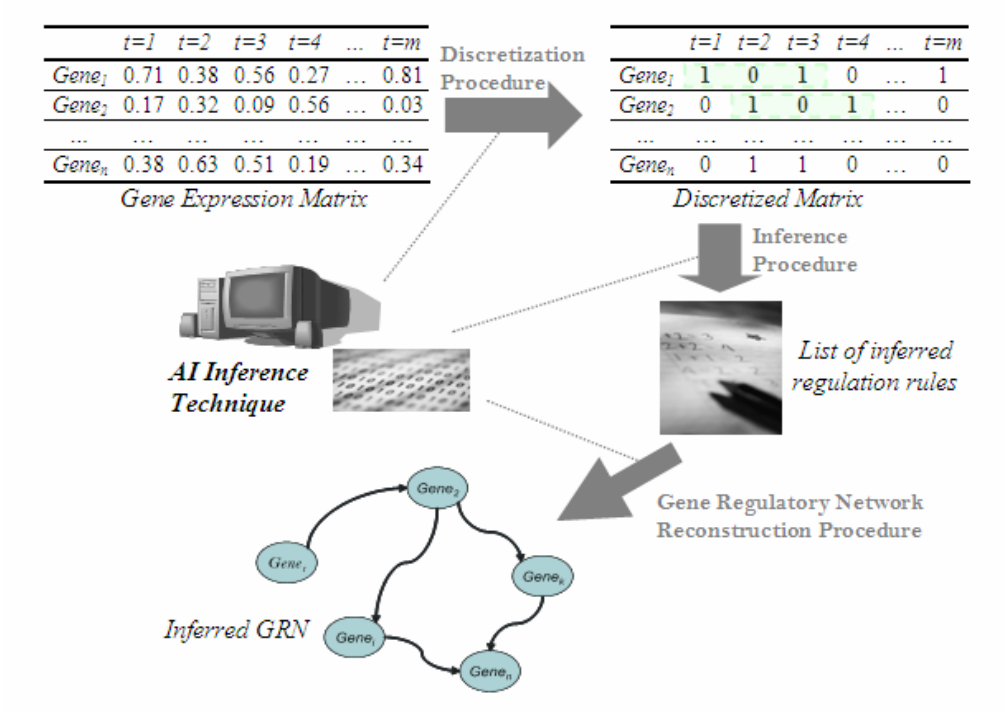


**Fig. 3**. From the gene expression matrix to the GRN.

### 3.1 GRN Inference Techniques: State-of-Art

Following these central ideas, several statistical and artificial intelligence methods have been proposed to perform the inference of GRNs [1, 4, 5]. Clustering algorithms represented one of the first approaches to supporting the large-scale identification of regulatory modules [6, 7]. An important limitation of this approach is that it assumes that co-expression is always equivalent to regulation. Moreover, this method implies symmetric and simultaneous relationships between the genes, which may not always correspond to real biological phenomena.

As regards machine learning, Boolean Networks were one of the first models used in GRNs inference [8], [9], and several variations of this approach have been published recently [10]. These models basically aim to infer logical rules from a discretization of the gene expression matrix. Although these models can be easily applied, they depend on the arbitrary discretization of the gene expression values [11], which imposes strong assumptions and restrictions about the biological system under study. Evolutionary computation have also imparted the basis for several approaches to inferring GRNs. Ando *et al.* [12] presented an algorithm that combines genetic programming with the minimum least squares method. This technique infers a differential

equation system that represents regulation interactions between genes. Although this method may be robust in statistical terms, the algorithm was only tested on small GRNs (ten genes) and the authors detected important scalability limitations when applied to more complex data. Iba and Mimura [13] proposed an iterative inference approach based on a genetic algorithm (GA) whose learning process was guided by a molecular biologist. The main goal was to allow the expert to perform interactive analysis and validation of the results based on the introduction of new constraints until a GRN with a high level of predictive confidence was achieved. One of the most important drawbacks of this methodology is that it requires the biologist to have a good understanding of the dynamics of the GA in order to select optimum learning parameters.

With respect to the Bayesian Networks research line [14], [15], [16]. These methods employ conditional probabilistic distributions for gene interactions modeling. Despite the strong theoretical rationale behind these approaches, the exponential explosion of the parameter space required for these models together with the large quantity of data needed to make reliable inferences, reduce their capacity to infer complex GRNs using gene expression data only. Moreover, the Bayesian Network models are inherently static. Since they are acyclic directed graphs, they can not represent auto-regulation or time-course regulation in a straightforward way [4].

Recently, Soinov *et al.* [11] and Li *et al.* [17] approached the task of reconstructing GRNs as a classification problem. In summary, the authors proposed the application of decision trees to infer classifiers that may represent regulatory rules (relationships) between genes. They applied the C4.5 algorithm to infer the decision trees [18]. This method's computational efficiency limitations are well-known for classification problems with continuous-valued attributes [19], which is the case in the GRNs inference problem since the gene expression values are real numbers. Although this is a sound and conceptually interesting approach, it may exhibit significant predictive limitations when predicting complex GRNs are integrated by thousands of genes. This drawback was successfully addressed by Ponzoni *et al.* [20] using a combinatorial optimization learning procedure called GRNCOP, which uses a novel adaptive discretization procedure. Despite the important new features introduced by GRNCOP, this method only infers some specific time-lagged regulation patterns between genes.

### 3.1 Limitations of using real Gene Expression Matrices

All the aforementioned methods infer the GRNs from data series that generally have significant noise and, usually, the amount of information (*quantity of samples*) provided by them is not sufficient to obtain accurate GRNs. For this reason, it emerged the necessity of finding other data sources for training and testing GRN inference techniques in a more exhaustive way. In this context, several researchers have recently proposed the use of artificial GRNs (aGRNs) [21, 22]. An aGRN is a complex system which is built according to well-defined topological and kinetic properties, with the aim of generating artificial gene expression datasets that are highly reliable. In this sense, an aGRN constitutes a source of strategic data acquisition that gives unlimited 100% consistent information.

Despite of the present increasing relevance of aGRNs in the environment of bioinformatics, there is a lack of a review about the state of art in the field. More precisely, there is no article in the literature that presents an evaluation of the main approaches used to construct such kinds of networks; neither there is an analysis of the advantages or disadvantages of each methodology. Therefore, in the next section, the main formalisms used to build aGRNs, together with their pros and limitations, will be presented and discussed.

## 4 Artificial Gene Regulatory Networks

Nowadays, the most widespread manner of designing an inference technique that learns a GRN from observed data is: the researcher attains expression gene data by means of, for example, the microarray technology, and executes the inference method under development so as to learn the GRN. However, when

trying to estimate the quality of a GRN inference method, the most important measure is the degree to which the discovered GRN matches the 'real' GRN which produced the observed data. Then, since this is of course unknown in practice, the quality of a GRN can be only roughly estimated.

Under these circumstances, artificial GRNs arose as an alternative means of having access to the 'real', in fact virtual, GRN. Even though artificial GRNs do not represent any particular organism, they became very useful for this purpose as they are built according to well-defined topological and kinetic properties. Then, the process of finding a good inference method to learn GRNs starts with the implementation of an artificial GRN. The artificial GRN is later used to obtain plenty of reliable data, and then the inference method can yield the corresponding consistent GRN. In this way, the artificial and the learned GRNs can be compared, and the more they are alike, the better the inference method is. In the next paragraphs, the most relevant strategies described in the literature for this end, belonging to different research areas, will be introduced.

### 4.1 Modeling aGRNs using ODEs

*Ordinary differential equations* (ODEs) constitute a well known formalism used to build artificial GRNs starting from biological properties instead of observed data. ODEs model the concentrations of the gene and its products by time-dependent variables with values contained in the set of nonnegative real numbers.

Gene regulation is therefore modeled by rate equations expressing the rate of production of a component of the system as a function of the concentrations of other components. Rate equations have the following mathematical form:

$$\frac{dx_i}{dt} = f_i(x), 1 \le i \le n.$$

where $x = [x_1, \ldots, x_n]' > 0$ is the vector of concentrations of proteins, mRNAs, or small molecules, and $f_i : \Re^n \to \Re$ a usually nonlinear function. The rate of synthesis of $i$ is seen to be dependent upon the concentrations $x$, possibly including $x_i$.

Various powerful mathematical methods for modeling biochemical reaction systems by means of rate equations have been developed in the past century, particularly in the context of metabolic processes [23]. Using these methods, kinetic models of genetic regulation processes can be constructed by specifying the functions $f_i$. In particular, Mendes *et al.* [21] present a system that generates random artificial gene networks according to well-defined topological and kinetic properties, and they used them to run *in silico* experiments simulating real laboratory microarray experiments. A main feature of their proposal is that noise, with controlled properties, is added to the simulation results several times emulating real measurements.

A problem impeding the use of numerical techniques is the lack of *in vivo* or *in vitro* measurements of the kinetic parameters in the rate equations. Numerical parameter values are available for only a handful of well-studied systems. In contrast, in cell cycle models, as a general rule the parameter values are to chosen such that the models are able to reproduce the observed qualitative behavior. For larger models, attaining appropriate values may be difficult to achieve.

### 4.2 Modeling aGRNs using QDEs

Another important formalism developed for building GRNs are the so called *qualitative differential equations* (QDEs). The main idea behind QDEs consists of abstracting a discrete description from a continuous model and analyzing the discrete instead of continuous equations to describe conclusions about the dynamics of the system. QDEs are used in the simulation method QSIM [24].

It is important to make clear that QDEs are abstractions of ODEs, with the variables $x$ taking a *qualitative* value composed of a qualitative magnitude and direction. The qualitative magnitude of a variable $x_i$ is a discrete abstraction of its real value, while the qualitative direction is the sign of its derivative. The function $f_i$ is abstracted into a set of qualitative constraints which restrict the possible qualitative values of the variables. Given an initial qualitative state consisting of the qualitative values for $x$ at the initial time-point, the QSIM

algorithm generates a tree of qualitative behaviors. Each behavior in the tree describes a possible sequence of state transitions from the initial state. It has been proven that every qualitatively distinct behavior of the ODE corresponds to a behavior in the tree generated from the QDE, although the reverse may not be true. Some examples of the application of qualitative reasoning concepts to gene regulation are Heidtke and Schulze-Kremer [25], Akutsu *et al.* [26] and de Jong *et al.* [27].

An important drawback with qualitative simulation approaches is their limited upscalability. As a consequence the weak nature of qualitative constraints and the difficulty to identify implicit constraints, behavior trees quickly grow out of bounds. This causes the range of application of the methods to be limited regulatory systems of modest size and complexity. Systems of even a few genes related by positive and negative feedback loops cannot be handled, unless these systems have been so well-studied already that behavior prediction can be tightly constrained.

### 4.3 Modeling aGRNs using the Artifical Genome approach

Last, but not least, a novel formalism presented in the literature is called Artificial Genome (AG) [22]. The AG constitutes an evolutionary model of genetic regulatory networks, based on a representation of network encoding and dynamics. This model derives a number of specific genes and their interactions from a string of bases in an idealized manner analogous to that employed by natural DNA. The gene expression dynamics is determined by updating the gene network as if it were a simple Boolean network. This simplification is widely accepted, mainly because Boolean networks do exhibit dynamic behavior similar to that of biological cells.

Basically, they adopted Reil's artificial genome model as a representation of the way genetic encoding constrains the structure of gene regulatory networks [28]. A genome is represented by a linear sequence of ''bases'' drawn from the set {0, 1, 2, 3} (analogous to the four bases A, C, G, and T in DNA). Within this genome, every occurrence of the sequence {0 1 0 1} is identified as a promoter (analogous to the ''TATA'' sequence in biological genomes). The region between the end of a gene and the beginning of the next 0101 string becomes the promoter region for the downstream gene.

Each gene is "translated" into a gene product by incrementing each base by 1. A gene with the sequence 012130 will therefore result in a product with the sequence 123201. All of the promoter regions in the genome are searched for matches with each gene product; if a match to the product of gene **A** is found in the promoter region of gene **B**, we say that gene **A** controls gene **B**. This control may be either excitatory - **A** promotes the transcription of **B** - or inhibitory. In this way a genetic regulatory network is constructed from the randomly generated genome as shown in Figure 4.

Then, they evolve the nodes of the gene network in four different manners: synchronous deterministic (SD), synchronous nondeterministic (SND) asynchronous deterministic (AD) and asynchronous nondeterministic (AND). The fitness function is defined as $n(l/2)$, where $n$ is the number of different limit cycles found, and $l$ is the length of these limit cycles. The evolutionary algorithm works as follows: networks are built from artificial genomes generated at random, and each network is run 100 times from different initial states. The stopping criterion is of 200 generations with no improvement in fitness or 1,000 generations with no improvement in fitness over the initial network.

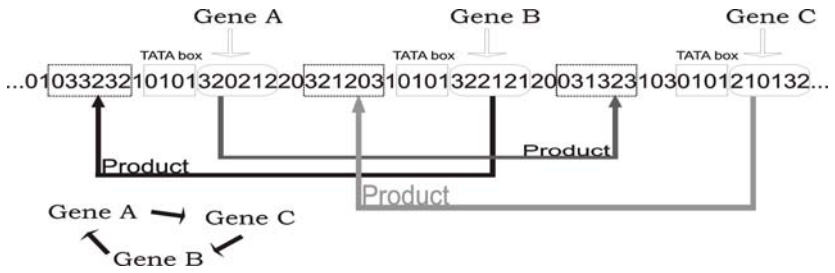


**Fig. 4.** Reil's AG model of a GRN.

The model of synchronously updated networks has shown to produce a wide range of gene network topologies, which typically lie between those of random networks and scale-free networks in terms of their degree distributions. Nevertheless, one disadvantage of the AG model is that the network dynamics relies on synchronous updating, which is biologically meaningless; when a more realistic asynchronous updating scheme is employed, the dynamic behavior collapses to a single point attractor.

Having presented the main strategies used to build and/or learn GRNs, the landscape that illustrates the current protocol and alternatives for implementing accurate methods for GRN's inference is depicted in figure 5. As it can be observed, many techniques exist in the present that can be used to infer GRNs from observed data, but the field of approaches used to build artificial GRNs is still necessitating to be explored.

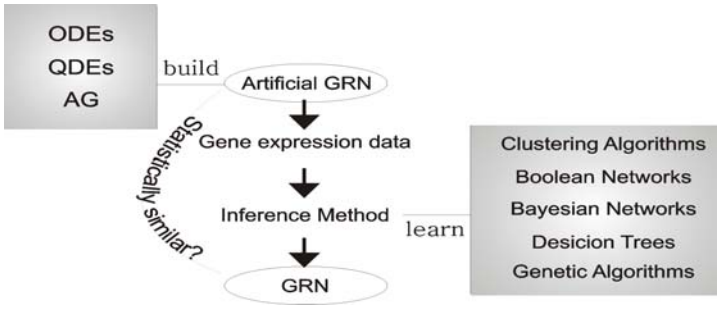


**Fig. 5**. GRNs' development and main computational formalisms

## 5 Conclusions

Artificial GRNs were introduced in this work. We have claimed on behalf of their usefulness, especially as sources of unlimited reliable data. Later we have briefly discussed in lieu of their use for validation purposes. Finally, the main focus of the work was set on the main formalisms currently being used to build aGRNs.

The first strategy we have presented was based on *Ordinary differential equations* (ODEs). The main idea behind this approach is the following one: if a gene network consists of *n* entities (proteins, mRNA, and/or small molecules), there exist *n* rate equations, one for each entity, describing its rate of synthesis and decay. As a generalization of ODEs appeared the *Qualitative differential equations* (ODEs) that contain variables that take on discrete *qualitative values* which abstract the real value. The major drawback of these two mathematical formalisms is their limited upscalability. The reason for this disadvantage is that measurements of the kinetic parameters in the rate equations are hard to attain for many organisms, this task turning out to be more difficult as the systems are bigger.

In addition, a bio-inspired method called Artificial Genome was introduced. This approach builds a network from a particular interpretation of a string of "bases", and then evolves that network in four different ways. The best results were obtained when the network was updated in a synchronous manner; nonetheless, this outcome constitutes also a negative aspect since this synchronous scheme of nodes' renovation is biologically meaningless.

## Acknoledgements

The authors would like to express their acknowledgment to the "Agencia Nacional de Promoción Científica y Tecnológica" from Argentina, for their economic support given through Grants Nº11-12778 and PICTO-UNS 917 as part of the "Programa de Modernización Tecnológica, Contrato de Préstamo BID 1728/OC-AR".

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