

A COMPARISON OF GENETIC NETWORK MODELS

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With the completion of the sequencing of the human genome, the need for tools capable of unraveling the interaction and functionality of genes becomes extremely urgent. In answer to this quest, the advent of microarray technology provides the opportunity to perform large scale gene expression analyses. Recently, genetic networks were proposed as a possible methodology for modeling genetic interactions. Since then, a wide variety of different models have been introduced. However, it is, in general, unclear what the strengths and weaknesses of each of these approaches are and where these models overlap and differ. This paper compares different genetic modeling approaches that attempt to extract the gene regulation matrix from expression data. A taxonomy of continuous genetic network models is proposed and the following important characteristics are suggested and employed to compare the models: (1) inferential power; (2) predictive power; (3) robustness; (4) consistency; (5) stability and (6) computational cost. Where possible, synthetic time series data are employed to investigate some of these properties.

1 Introduction

Genetic network models are typically constructed in order to extract the ‘gene regulation matrix’, that describes which genes regulate each other and how environmental inputs affect gene expression. This matrix can be employed to figure out how genes act ‘in concert’ to achieve specific phenotypic characteristics. The genetic modeling process usually starts out with the construction of a (parameterized) model that describes the regulation process. Such models are usually inspired by existing biological knowledge about gene-gene interactions, gene product degradation, responses of genes to specific inputs etc. In addition, gene expression data sets that contain measured time responses of the studied genes to various stimuli are used to infer the unknown parameters of the model. A wide variety of approaches for the inference of genetic networks from data have been proposed (see Sec. 2). The contributions of this work are the following: (1) a taxonomy of the existing repertoire of genetic network models is proposed (Sec. 2); (2) several properties which are considered to be important for successful genetic network modeling are introduced (Sec. 3); (3) models are compared with respect to these properties (Sec. 3) and (4) where applicable properties are further investigated empirically (Sec. 4).

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This evaluation results in some preliminary conclusions (Sec. 5).

2 Model Descriptions

This comparison will focus on continuous models^{1,2,3,4,5,6,7,8,9,10}, i.e. models which do not require explicit discretization of the measured input data prior to the inference process. Boolean networks¹¹, Bayesian networks¹² and Qualitative models¹³ are therefore excluded. Studying the continuous models reveals that they can be divided into three categories: (1) methods based on pair-wise comparisons, (2) methods that model rough networks of gene-interactions and (3) more complex models that also describe intermediate products, such as proteins.

2.1 Pair-wise Methods

These methods construct relationships between genes based solely on pair-wise comparisons. Therefore, they do not take into account interactions where the resulting expression-level of one gene is governed by the *combined* action of multiple other genes. Because these methods have no actual model that describes *exactly how* genes are activated by external inputs and other genes, no predictions of gene expression can be made. We now elaborate on two of these methods that were recently introduced.

Arkin and Ross '97: Correlation Metric Construction (CMC) The CMC method¹ first computes the magnitude and position at which the maximal (time-shifted) cross-correlation occurs. This provides a measure of similarity and temporal ordering, respectively. Then a distance matrix, D , is constructed, by comparing, for each pair of genes, their similarities to other genes. The significant eigenvalues of the constructed distance matrix provides an indication of the intrinsic dimensionality of the system. Single linkage hierarchical clustering is employed to find a singly linked tree that connects associated genes. This tree (association diagram) is augmented with directional and time-lag information, revealing temporal ordering.

Chen, Filkov and Skiena '99: Activation/Inhibition Networks The method proposed by Chen *et al.*² expresses regulation based on whether peaks in one signal precede peaks in another signal. After thresholding and clustering, resulting in a set of prototype signals, each prototype is represented as a series of peaks. For each pair of prototypes three scores are computed, representing a possible activating, inhibiting or unmatching relationship. The regulation matrix is inferred by taking for each pair of genes the highest of these three scores.

Method	Equation	$g(z)$	$R_i =$	$\lambda_i =$
Mjolsness '00 ³	(1)	$\frac{1}{1+e^{-z}}$	R_i	λ_i
Spirov '97 ⁴	(1)	$\frac{1}{1+e^{-z}}$	R_i	λ_i
Wahde '99 ⁵	(1)	$\frac{1}{1+e^{-z}}$	R_i	R_i
Weaver '99 ⁶	(2)	$\frac{1}{1+e^{-z}}$	R_i	0
Someren '00 ⁷	(2)	z	1	0
D'Haeseleer '99 ⁸	(2)	z	1	0

Table 1: Deviation of each network model with respect to the general equations (1 & 2).

2.2 Rough Network Models

These networks directly model effects that result from the combination of different input genes, by means of a weighted sum of their expressed levels. The term 'rough' refers to the fact that the influence of all intermediate products are summarized in the linear gene-to-gene relationship. These weights provide information about the relationships between genes, i.e. zero weights indicate the absence of interaction and a positive or negative weight corresponds to stimulation or repression. The absolute value of a weight corresponds to the strength of the interaction. All network models can be represented in the following generalized differential equation:

$$\frac{dx_i(t)}{dt} = R_i \cdot g \left(\sum_{j=1}^J W_{i,j} x_j(t) + \sum_{k=1}^K V_{i,k} u_k(t) + B_i \right) - \lambda_i x_i(t) \quad (1)$$

or difference equation of similar form:

$$x_i[t+1] = R_i \cdot g \left(\sum_{j=1}^J W_{i,j} x_j[t] + \sum_{k=1}^K V_{i,k} u_k[t] + B_i \right) - \lambda_i x_i[t] \quad (2)$$

with the following (biological) interpretations:

- $g(\cdot)$: monotonic regulation-expression (activation) function
- $x_i(t)$, $x_i[t]$: gene expression of gene i at time instance t .
- R_i : rate constant of gene i .
- $W_{i,j}$: strength of control of gene j on gene i
- $u_k(t)$, $u_k[t]$: k -th external input at time instance t .
- $V_{i,k}$: influence of the k -th external input on gene i .
- B_i : basal expression level of gene i .
- λ_i : degradation constant of the i -th gene expression product.

All rough models included in this comparison are a specific instance of one

Method	Pre-Processing	Structuring	Inference
Mjolsness '00	-	EM-Clustering	SA
Spirov '97	-	-	GA + SA + GD
Wahde '99	-	-	GA
Weaver '99	Normalization	-	De-squashing + LR
Someren '00	Normalization + Thresholding	Hierarchical Clustering	LR
D'Haeseleer '99	Interpolation	-	LR

Table 2: Methodology to infer parameters. EM = Expectation Maximization, SA = Simulated Annealing, GA = Genetic Algorithm, GD = Gradient Descent, LR = Linear Regression

of these generalized equations. An overview of the network models is given in Table 1. Table 2 summarizes the algorithms employed to infer the model parameters from measured mRNA levels.

2.3 Complex Networks

These networks are more complex in that they not only model interactions between genes based on measured mRNA levels, but also explicitly model their intermediate products, such as proteins and metabolites. Consequently, their parameters cannot be inferred from data-sets that contain only measurements of mRNA levels, since explicit knowledge about the expression levels of the intermediates are necessary (see Chen⁹). However, in this comparison we used the model of Savageau¹⁰ to generate realistic gene-expression data to test the other modeling approaches.

Savageau '99 The genetic network model proposed by Savageau¹⁰ models mRNA, protein and metabolite expression levels. The changes in the expression level of a given chemical species are modeled as follows:

$$\frac{dx_i}{dt} = \alpha_i \prod_{j \in \mathcal{S}_I} x_j^{W_{i,j}} - \beta_i \prod_{k \in \mathcal{S}_D} x_k^{W_{i,k}} \quad (3)$$

The first term constitutes an activation term (\mathcal{S}_I being all activating species) and the latter a degradation term (\mathcal{S}_D being species involved in degradation). The 'product-power law' formulation results in expression levels that behave non-linearly, but remains an easily interpretable format. This model contains a large number of parameters in comparison to the rough and pair-wise models which makes the inference process particularly difficult.

3 Model Evaluation

This section introduces several characteristics that are central to successful genetic network modeling and are therefore appropriate benchmarks with which genetic modeling approaches can be evaluated. These characteristics are (1) inferential power, (2) predictive power, (3) robustness, (4) consistency, (5) stability and (6) computational cost. In this section each characteristic is defined and motivated. Both pair-wise and rough network models are also subjected to a preliminary evaluation with respect to each of the characteristics. In Sec. 4 each of these models are compared empirically (where applicable) based on these characteristics. In order to simplify the discussion of the different

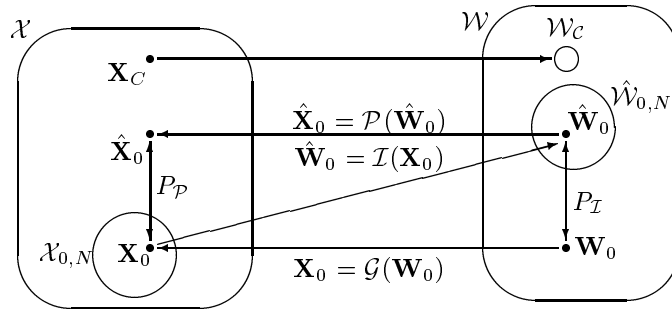


Figure 1: Graphical representation of the framework that relates the expression space (\mathcal{X}) to the gene regulation matrix space (\mathcal{W}).

characteristics, a simple framework and nomenclature (depicted in Fig. 1) is introduced. For a particular class of genetic network models, let \mathcal{W} represent the space of gene regulation matrices, with \mathbf{W} an instance of a regulation matrix. Let \mathcal{X} denote the space of expression data sets associated with \mathcal{W} , with \mathbf{X} a particular data set. For experimental purposes, a particular matrix, \mathbf{W}_0 is chosen to represent a ‘real’ network.^b Based on \mathbf{W}_0 (and initial conditions) a dataset, \mathbf{X}_0 , is generated ($\mathbf{X}_0 = \mathcal{P}(\mathbf{W}_0)$). During the *inference* step (employing one of the models described in Section 2) an estimate of \mathbf{W}_0 is obtained based solely on \mathbf{X}_0 , and this is represented as $\hat{\mathbf{W}}_0$ with $\hat{\mathbf{W}}_0 = \mathcal{I}(\mathbf{X}_0)$. $\hat{\mathbf{W}}_0$ can, in turn, be employed to make a *prediction* of the expression data, given the same initial conditions. This produces an approximation of \mathbf{X}_0 , which is denoted by $\hat{\mathbf{X}}_0$, with $\hat{\mathbf{X}}_0 = \mathcal{P}(\hat{\mathbf{W}}_0)$.

^bIn reality \mathbf{W}_0 is not known, but needs to be inferred by the genetic network algorithms. However, in synthetic experiments, we are free to choose \mathbf{W}_0 , allowing us the opportunity to verify the results produced by the algorithms.

3.1 Inferential power, P_I

Since genetic network models are primarily employed to infer regulatory interaction patterns from expression data, it is quite important that this process delivers accurate estimates of the gene regulation matrix. Inferential power is a measure of this capability.

Definition: Formally, inferential power is measured as the similarity between the actual (\mathbf{W}_0) and inferred ($\hat{\mathbf{W}}_0$) gene regulation matrices: $P_I(\mathbf{W}_0, \hat{\mathbf{W}}_0) = 0.5(1 + \rho(\mathbf{W}_0, \hat{\mathbf{W}}_0))$, with $\rho(\cdot)$ the Pearson product moment correlation.

Preliminary evaluation: Pair-wise approaches infer a regulation matrix based on pair-wise comparisons. Consequently sparse, yet greedy, sub-optimal solutions are obtained. When a gene is influenced by more than one other gene, even erroneous solutions may be obtained. Network models do not suffer from this disadvantage, but the regulation matrix is inferred *indirectly*, i.e. by minimizing the prediction error (difference between \mathbf{X}_0 and $\hat{\mathbf{X}}_0$) instead of maximizing $\rho(\mathbf{W}_0, \hat{\mathbf{W}}_0)$. This is done under the assumption that small prediction errors result in accurate regulation matrices. More definitive statements about the inferential power of individual models can only be made based on empirical evidence (Sec. 4).

3.2 Prediction power, P_P

Prediction power is reflected in the prediction accuracy, i.e. how closely $\hat{\mathbf{X}}_0$ approximates \mathbf{X}_0 . For network models, regulation matrices are inferred by minimizing prediction error. It is therefore important to gain insight into the relationship between P_P and P_I for the different models in the comparison.

Definition: For a given expression data set, \mathbf{X}_0 , and the predicted approximation thereof, $\hat{\mathbf{X}}_0$, prediction power is expressed as $P_P = 1/(1 + E_{\text{MSE}})$, with the mean squared error given by $E_{\text{MSE}}(\mathbf{X}_0, \hat{\mathbf{X}}_0) = \frac{1}{TN} \sum_{i,t} (X_0(i, t) - \hat{X}_0(i, t))^2$.

Preliminary evaluation: It is to be expected that more complex models, such as the network models containing non-linearities and larger parameter sets have *potentially* greater predictive power than simpler network models such as the linear models proposed by D'Haeseleer⁸ and van Someren⁷. However, more complex models require more training data (or regularization constraints) and non-deterministic inference algorithms (such as a GA⁵ or SA³) that do not guarantee convergence to a global minimum, possibly resulting in a sub-optimal value for P_P . To shed more light on these issues, an empirical investigation was performed (Sec. 4).

3.3 Robustness

Noise is an ever present phenomenon that always needs to be dealt with. Gene expression measurements are particularly noisy and it is therefore important to know to what degree an accurate gene regulation matrix will be extracted in the presence of noise.

Definition: Let $\mathcal{X}_{0,N} \subset \mathcal{X}$ denote the set of expression data sets that are obtained when noise, $\mathbf{N}(0, \sigma)^c$, is added to \mathbf{X}_0 , i.e. $\mathcal{X}_{0,N} = \{\mathbf{X}_{0,\sigma} | \mathbf{X}_{0,\sigma} = \mathbf{X}_0 + \mathbf{N}(0, \sigma), \sigma \in [0, \sigma_{\text{MAX}}]\}$. (See also Fig. 1). Let $\hat{\mathcal{W}}_{0,N}$ denote the set of regulation matrices that are obtained by performing inference on each element of $\mathcal{X}_{0,N}$, i.e. $\hat{\mathcal{W}}_{0,N} = \{\hat{\mathbf{W}}_{0,\sigma} | \hat{\mathbf{W}}_{0,\sigma} = \mathcal{I}(\mathbf{X}_{0,\sigma}), \mathbf{X}_{0,\sigma} \in \mathcal{X}_{0,N}\}$. A measure of robustness, $P_{\mathcal{R}}$, is defined as the minimal correlation amongst the inferred regulation matrices in $\hat{\mathcal{W}}_{0,N}$: $P_{\mathcal{R}} = \min_{\{\hat{\mathbf{W}}'_{0,\sigma}, \hat{\mathbf{W}}_{0,\sigma}\} \in \hat{\mathcal{W}}_{0,N}} [0.5(1 + \rho(\hat{\mathbf{W}}_{0,\sigma}, \hat{\mathbf{W}}'_{0,\sigma}))]$.

Preliminary evaluation: None of the techniques contain features that were explicitly included to increase robustness. However, some implicit characteristics may improve robustness, For example: 1) several techniques^{2,3,7} perform a clustering step prior to the inference step which could increase robustness since inference is performed on the prototypes (*averaged* signals in a cluster); 2) CMC¹ also employs an averaging process (cross correlation) which could contribute to increased robustness and 3) the method proposed by Chen et al.² may also result in improved robustness by creating a filtered signal representation prior to the inference step. However, robustness can be most effectively evaluated empirically by monitoring the behavior of $P_{\mathcal{R}}$ as a function of the noise level, σ .

3.4 Consistency

One of the most striking properties of available gene expression data is the relatively large number of genes compared to the number of measured time-points. This so called ‘dimensionality problem’ is an important cause of inconsistency in the inferred genetic network models, and therefore an important characteristic to investigate.

Definition: A genetic network model is said to be inconsistent if multiple parameter sets can be inferred from the same expression data. Formally, for an arbitrary expression data set, $\mathbf{X}_C \in \mathcal{X}$ (See Figure 1), the following set of gene regulation matrices is defined: $\mathcal{W}_C = \{\mathbf{W}_C | \mathbf{W}_C = \mathcal{I}(\mathbf{X}_C), \mathcal{P}_{\mathcal{I}}(\mathcal{P}(\mathbf{W}_C), \mathbf{X}_C) > 1 - \epsilon\}$. The degree of consistency of a model is given by $P_C = \min_{\{\mathbf{W}_{C,i}, \mathbf{W}_{C,j}\} \in \mathcal{W}_C} [0.5(1 + \rho(\mathbf{W}_{C,i}, \mathbf{W}_{C,j}))]$.

^czero-mean, Gaussian noise with a standard deviation of σ .

Preliminary evaluation: Without a principled mechanism to select the most appropriate regulation matrix from a set of possible solutions, the inferred parameters will be meaningless. Inconsistency originates from the combination of two causes, 1) the dimensionality problem, i.e. the data represents an incomplete description of the underlying process, or 2) the predictive power of the model exceeds the intrinsic complexity of the data. The first cause can be only partly corrected by interpolation. To handle the second cause one needs to control the predictive power of the model, which can be attained by thresholding (to eliminate very noisy signals), clustering (grouping signals that cannot be distinguished by the model) and/or the introduction of appropriate constraints.

3.5 Stability

Due to limited energy and storage within a cell, concentrations of gene expression products, such as mRNA, remain bounded. All real genetic networks are therefore stable by definition. Consequently, inferred genetic network models should also be stable in order to be realistic.

Definition: A model, parameterized by a specific gene regulation matrix, is stable if the predicted expression levels remain bounded over all time, for any finite initial state. If infinitely large training sets are available, and E_{MSE} remains bounded, stability can be guaranteed. On finite data sets, the requirement for bounded E_{MSE} must be augmented by other stability requirements such as the existence of a Lyapunov function.

Preliminary evaluation: Since the pair-wise methods have no explicit model to generate signals, no indication can be given about their stability. Both linear network models^{7,8} are stable when the magnitude of the eigenvalues of the weight matrix are all smaller than or equal to one. In contrast, the network models that have a sigmoidal transfer function are ensured to have a bounded output and are therefore by definition stable. However, the plausibility of genetic network model that generates gene expression profiles that are oscillating rapidly between minimal and maximal expression bounds are questionable. None of the methods described in Section 2 are equipped with explicit mechanisms to ensure that a stable network is inferred.

3.6 Computational cost

Methods that require extremely long computation times to reach a solution are obviously undesirable, unless the additional waiting time results in substantially improved results. Methods that can not compute analytical solutions,

but rely on iterative solution approaches require, in general, much longer computation times. Empirical evaluation was employed to obtain an indication of the time required to reach a solution for each of the approaches.

4 Experimental Evaluation

Three different *types* of data sets were generated based on a given five^d gene regulation matrix with no external inputs: (1) \mathbf{D}_1 : a simple gene expression data set generated by the linear model of van Someren, (2) \mathbf{D}_2 : a data set of intermediate complexity generated by the model of Wahde and (3) \mathbf{D}_3 : the most 'realistic' data set, generated by (arguably) the most accurate model proposed by Savageau. Five datasets consisting of 25 time-points were generated of each type by using different random initial conditions. For each of these 15 datasets, ten additional sets were created by adding varying amount of noise: [1, 2, . . . , 10 %] of the average signal energy.

Six models (Arkin, Chen, Wahde, Weaver, Someren^e and a reference model) were implemented and were trained on each of the 165 datasets. The reference model^f returns a random regulation matrix as inference and the mean of the signals as a prediction. Figure 2 depicts the measured inferential ($P_{\mathcal{I}}$) and prediction ($P_{\mathcal{P}}$) power as a function of the noise level for all the tested models on the three types of datasets^g.

Inferential power: The inferential power is judged on the noise-free dataset. Arkin performs reasonably on \mathbf{D}_1 and \mathbf{D}_2 . On \mathbf{D}_3 , Arkin is the only model that performs significantly better than the reference model. This is probably caused by the fact that the regulation matrix in \mathbf{D}_3 is sparse, a situation well suited to the single linked tree approach employed by Arkin. In contrast, Someren performs best on the simple and intermediate data-types but fails to capture the relations of the realistic dataset. The performance of the other models on \mathbf{D}_2 and \mathbf{D}_3 is indistinguishable from the reference model.

Predictive power: Predictive power is also evaluated at zero noise. Surprisingly the linear model of Someren outperforms the more complex model of Wahde on \mathbf{D}_1 and \mathbf{D}_2 in terms of prediction power^h. The good performance of Someren on \mathbf{D}_3 is probably due to the fact that \mathbf{D}_3 is generated with a sparse gene regulation matrix and the data does not fully reflect the nonlin-

^dThe number of genes was limited for practical reasons.

^eIn this experiment the models of the D'Haeseleer and Someren are equivalent.

^fThis model serves as a reference to indicate whether the other models give significant results. In the case of inferential power no correlation should correspond to $P_{\mathcal{I}} = 0.5$.

^gEach point depicts a five-fold average; standard deviations were relatively small and therefore not depicted in the interest of clarity.

^hOn \mathbf{D}_3 Wahde failed to converge to stable solutions.

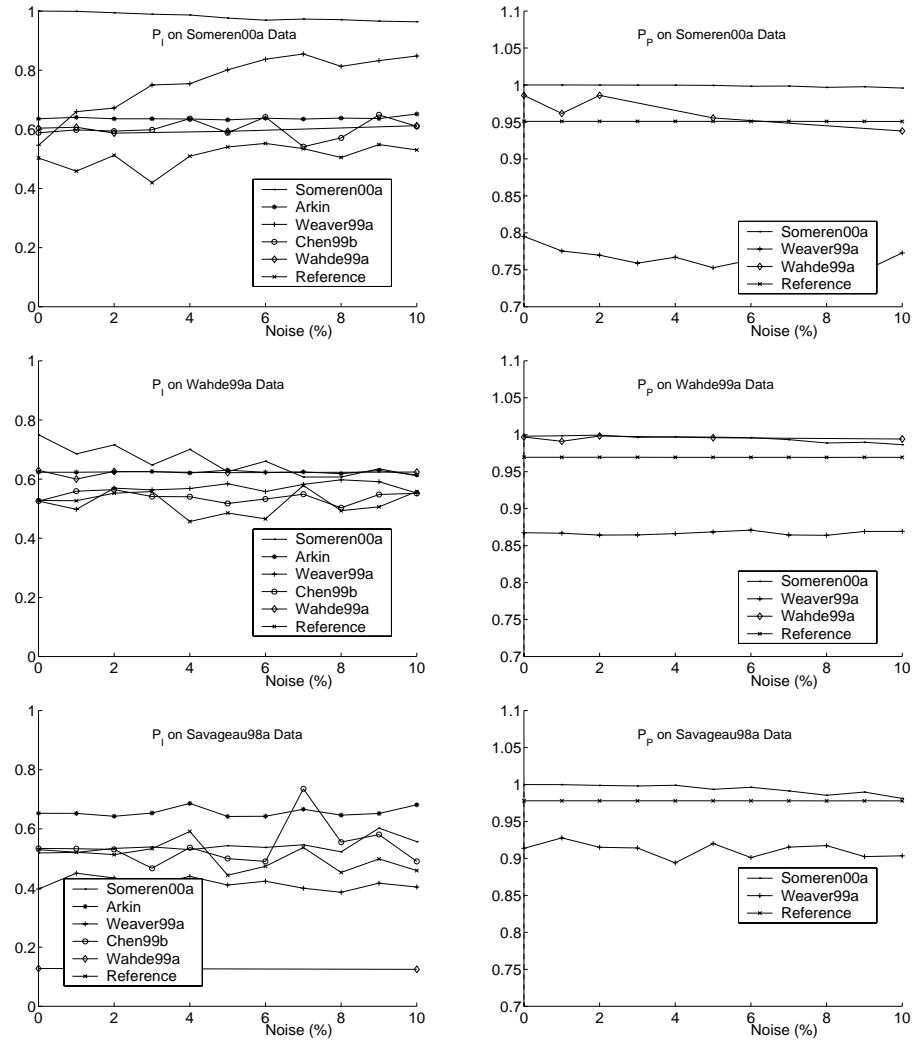


Figure 2: Inferential and prediction power (in left resp. right column) of five different models (see legend) as a function of noise-levels. Data was generated using the models of Someren, Wahde and Savageau (in top, middle and resp. bottom row).

earity of the Savageau model. This allows the Someren model to trade quality of fit for a non-sparse solution, resulting in a low inferential power. Weaver performed significantly worse than the reference model on all datasets. In this experiment no evident relation between inferential and prediction power could be observed.

Robustness: We approximate the measure of robustness proposed in Sec. 3 by the change in inferential power with increasing noise. On \mathbf{D}_1 and \mathbf{D}_2 the Someren method shows a decrease in inferential power proportional to the noise-level. In cases where the inferential power approximates the reference level, the effect of noise diminishes. Surprisingly on \mathbf{D}_1 , the inferential power of the Weaver model increases as the noise-level increases. This might be explained by the fact that noise causes the maximal signal range of the sigmoid to be overestimated causing the method to operate in its linear range, improving compatibility with the linear dataset. Arkin displays remarkable robustness on all datasets, which is probably caused by the averaging effect of the correlation measure.

Stability: Weaver's poor and unpredictable performance are probably due to the inverse sigmoid step which is sensitive to small deviations in the signals, causing the linear regression to produce unstable matrices, resulting in turn in oscillatory behavior.

Computational cost: All analytical methods performed similarly. For a single inference and prediction step the models of Arkin, Chen, Weaver and Someren took on average .6, 1.1, 1.3 and 3.8 seconds respectively. In contrast, the iterative method of Wahde often needed at least 15 minutes to converge. Given such large convergence times for a five gene network computational costs severely compromise the scalability of this approach.

5 Conclusions

In this paper a taxonomy of modeling approaches was proposed consisting of three classes: pair-wise, rough, and complex network models. In addition, a set of characteristics which are central to genetic network modeling, were proposed and a comparison of a set of models was performed based on these characteristics.

Of the pair-wise methods, CMC performed consistently and robustly achieving the best performance on the complex dataset. Due to their low computational burden, pair-wise methods may be particularly useful for extracting an initial network hypothesis, which could be further refined by more extensive models that take multiple gene interactions into account. The linear models^{7,8} performed surprisingly well compared to other rough network models. Specifically,

they achieved the highest predictive power on all data sets and were the only approaches which exhibited excellent inferential power on the simple dataset. The more complex network models performed particularly poorly in terms of inferential power. In terms of prediction power these methods either performed poorly (Weaver) or were hampered by prohibitively long computation times (Wahde).

A common theme in genetic network modeling is the fact that the gene regulation matrices are assumed to reveal the structure of the underlying genetic network. The implicit assumption is that the inferential power of the employed technique is sufficiently high. The most striking conclusion of this work is the fact that the inferential power of most techniques is surprisingly low even when very good predictive power is exhibited. In principle, more complex models should be capable of establishing both high prediction and inferential power, provided that appropriate measures are taken to adapt the model complexity to the underlying process. Currently, this is an unsolved problem. In the meantime, simple models must be employed to obtain good ‘rough’ inferential power (at high prediction power) with the additional advantage of low computational cost.

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