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Dynamical structure analysis of sparsity and minimality heuristics for reconstruction of biochemical networks

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Abstract— **Network reconstruction, i.e. obtaining network structure from input-output information, is a central theme in systems biology. A variety of approaches aim to obtaining structural information from available data. Previous work has introduced dynamical structure functions as a tool for posing and solving the network reconstruction problem. Even for linear time invariant systems, reconstruction requires specific additional information not generated in the typical system identification process. This paper demonstrates that such extra information can be obtained through a limited *sequence* of system identification experiments on structurally modified systems, analogous to gene silencing and overexpression experiments. In the absence of such extra information, we discuss whether combined assumptions of network sparsity and minimality contribute to the recovery of the network dynamical structure. We provide sufficient conditions for a transfer function to have a completely decoupled minimal realization, and demonstrate that every transfer function is arbitrarily close to one that admits a perfectly decoupled minimal realization. This indicates that the assumptions of sparsity and minimality alone do not lend insight into the network structure.**

I. Introduction

One of the fundamental issues in the identification of dynamical systems is that of accurately determining a system's structure; that is, the presence or absence of causal relationships between any two variables in a system. Structure identification has generated especially high interest among biologists studying biochemical networks. Frequently, even a simple understanding of the causal dependencies between variables can lead to valuable scientific progress. For example, the knowledge of whether one species affects another can be useful in designing a drug to inhibit a certain, undesired reaction while leaving other reactions unaffected.

Different approaches to the reconstruction problem favor different types of data, such as chemical concentration data (steady-state or time-series measurements) or quantified system parameters (such as rate constants or molecular weights). It is of interest to know whether certain types of data about a system are more useful than others for network reconstruction. Results reported in [1] and [2] showed that network reconstruction techniques involving perturbations to network parameters have much higher predictive accuracy than those which rely solely on data obtained from changes to initial concentration levels. Given a nonlinear system of differential equations $\dot{x} = f(x)$, the authors in [1] propose a method to find a best fit for the elements of the Jacobian of $f(\cdot)$, $\mathbf{F} = \{\partial f_i/\partial x_j\}$, from time-series data obtained by perturbing parameters such as temperature or pH of the chemical solution. A nonzero element F_{ij} represents a causal dependency of x_i on x_j; the magnitude and sign of F_{ij} represent the strength and nature (activation or inhibition) of this dependency.

Other algorithms common in the literature utilize probabilistic methods such as Dynamic Bayesian Networks, or information-theoretic techniques ([3], [4], [5]) to find the best possible fit–within a pre-defined family of possible models–to input-output data. Some of these methods use data from perturbation experiments, similar to the ones described above, while others (e.g. ARACNe, [5]) only require that data contain considerable "phenotypic variations of a given cell type." To maintain computational tractability, algorithms involving Dynamic Bayesian Networks typically assume a system is discrete-time. As a result, they do not accurately describe the continuous reaction environment of biochemical systems.

In the absence of data obtained from perturbations to structural parameters, other approaches such as [6] and [7] attempt to reconstruct biochemical networks by assuming that the network exhibits a sparse connection topology. Such methods can involve fitting a chemical network to time-series data in a way that the 1-norm of the reaction rates for the system is minimized [6], or setting a limit on the number of states that can influence any given state. Another assumption often used is that all states in the system are measured [7]. In this paper we examine the utility of such assumptions in reconstructing the network.

Many of the properties common to most biological networks–large numbers of system variables, high noise and inaccuracy levels in data sets, nonlinearities–pose special challenges to network reconstruction. In [8], [9] we have shown that even with the assumption of linearity, time-invariance, absence of noise and continuous measurement for all time (basically enabling perfect identification of the transfer function) the causal interconnection structure between the measured states cannot be reconstructed. In particular, in [8] we introduced the notion of *dynamical structure function* as a representation of a linear, time-invariant (LTI) system that captures the network structural information at the resolution of the observed variables. When the transfer function associated with a particular network is given, the results of [8], [9] allow us to precisely characterize the necessary additional information required to recover the associated network structure (either dynamic or Boolean).

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Acquisition of this necessary information instead requires several independent structural perturbations to a system and observation of the dynamic behavior of each such modified system. We describe how structural modifications to a network, such as the commonly available biological experiments gene silencing (or knockout) and overexpression, can successfully yield a network's dynamical structure. We also explore the implications of coupling assumptions of system minimality and sparsity on dynamical structure identification.

In Section II, we review some important theoretical properties of dynamical structure developed in [8], [9]. Section III shows that the information necessary to obtain a system's dynamical structure can be found by performing experiments on a set of well-defined structural modifications to the original system such as gene silencing and gene overexpression. In the absence of such experiments, we show in Section IV that, without such information, reconstruction of the full system dynamics between observable network components is not possible, even under a combined minimality and sparsity assumption. Section V concludes giving future direction.

II. Dynamical Structure

Our work in [8], [9] introduced several important concepts related to dynamical structure, which we summarize here. We consider an LTI system of form

$$\begin{array}{rcl} \begin{bmatrix} \dot{y} \\ \dot{x}_h \end{bmatrix} & = & \begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix} \begin{bmatrix} y \\ x_h \end{bmatrix} + \begin{bmatrix} B_1 \\ B_2 \end{bmatrix} u \\ y & = & \begin{bmatrix} I & 0 \end{bmatrix} \begin{bmatrix} y \\ x_h \end{bmatrix} \end{array} \quad (1)$$

where $x = \begin{bmatrix} y' & x_h' \end{bmatrix}' \in \mathbb{R}^n$ is the full state vector, $y \in \mathbb{R}^p$ is a partial measurement of the state, x_h are the $n-p$ "hidden" states, and $u \in \mathbb{R}^m$ is the control input. Taking the Laplace transforms of the signals in (1) and solving for X_h gives $X_h = (sI - A_{22})^{-1} A_{21} Y + (sI - A_{22})^{-1} B_2 U$. Substituting into the Laplace transform of the first equation of (1) then yields $sY = WY + VU$, where $W = A_{11} + A_{12}(sI - A_{22})^{-1} A_{21}$ and $V = A_{12}(sI - A_{22})^{-1} B_2 + B_1$. Let D be the matrix composed of the diagonal elements of W. We equivalently obtain, $(sI - D)Y = (W - D)Y + VU$. Note that $W - D$ is a matrix with zeros on its diagonal, and that D is a diagonal matrix of proper rational functions. We thus have

$$Y = QY + PU \quad (2)$$

where

$$Q = (sI - D)^{-1}(W - D) \text{ and } P = (sI - D)^{-1} V \quad (3)$$

Definition 2.1: Given the system (1), we define the *dynamical structure function* of the system to be (Q, P), where Q and P are the *internal structure* and *control structure*, respectively, and given as in (3).

Lemma 2.2: The dynamical structure function (Q, P) of any system of the form given in (1) exists and is unique. It is related to the transfer function, G, of the system by

$$G = (I - Q)^{-1} P. \quad (4)$$

The advantages of working with the matrix pair (Q, P) as opposed to (W, V) are described in [8], [9]. The dynamical structure function is invariant to any change of coordinates (and corresponding change of structure) involving only the hidden states; such information is suppressed in this description of the system. We conclude from this and Lemma 2.2 that the dynamical structure function of a system contains more information than the transfer function, and less information than the state-space representation.

Theorem 2.3 (Reconstruction from G): Given any $p \times m$ transfer function G, with $p > 1$ and no other information about the system, dynamical or Boolean reconstruction is not possible. Moreover, for *any* internal structure Q there is a dynamical structure function (Q, P) consistent with G.

In particular, this shows that the use of criteria such as sparsity or decoupledness to guide our selection of a proposal internal structure Q can be misleading. If one were to optimize for decoupledness, for example, a dynamical structure $(0, G)$ could always be found, regardless of the actual underlying network structure. Thus, if we are to use such criteria, they must be firmly justified a priori.

Theorem 2.4 (Partial Structure Information): Given a $p \times m$ transfer function G, dynamical structure reconstruction is possible from partial structure information if and only if $p - 1$ elements in each column of $\begin{bmatrix} Q & P \end{bmatrix}'$ are known that uniquely specify the component of (Q, P) in the nullspace of $\begin{bmatrix} G' & I \end{bmatrix}$.

Theorem 2.4 identifies exactly what information about a system, beyond knowledge of its transfer function, must be obtained to perform network dynamical structure reconstruction without appeal to a priori assumptions like sparsity or parsimony, etc. This enables the design of experiments targeting precisely the extra information needed for reconstruction (see Corollary 2.5). In particular when $p = m$ and G is full rank, we observe that imposing P to be diagonal, i.e. having each input control a measured state independently, is sufficient for reconstruction.

Corollary 2.5: If $m = p$, G is full rank, and there is no prior information about the internal structure Q of the system, then the dynamical structure can be reconstructed if each input controls a measured state independently, i.e. without loss of generality, the inputs can be numbered in such an order that P is diagonal. Moreover, $H = G^{-1}$ then characterizes the dynamical structure as follows

$$Q_{ij} = -\frac{H_{ij}}{H_{ii}} \text{ and } P_{ii} = \frac{1}{H_{ii}}.$$

A special case of this corollary in [10] considers steady-state or quasi-steady-state data, which means all transfer functions G,Q and P are evaluated at $s = 0$. The drawbacks of working with steady-state measurements are seen when transfer functions have zeros at $s = 0$ and thus lack dynamical predictability, while the advantage is that such methods require much less data. In this paper, we provide a framework which precisely characterizes the amount of information required for reverse engineering the *dynamical structure* of interconnected LTI dynamical systems, i.e. the recovery of both the internal and control dynamic structure.

III. Network Reconstruction by Structural Modifications

Knowledge of a network's dynamical structure allows recovery not only of the network topology (presence or absence of connections representing the causal relationships between the network's components) but also of the dynamics of the network's constitutive systems. Since a given transfer function admits several realizations, input-output data, which allow transfer function identification, do not provide enough information to deduce a system's dynamical structure.

It follows from Theorem 2.4 and Corollary 2.5 that determination of the dynamical structure of a system with hidden states cannot be done by merely considering control input modifications. It instead necessitates structural modifications to the system. There are many ways to interact with the system to yield its dynamical structure; we present two such experiments based on gene silencing and inducible overexpression. Examples of such system modifications have special relevance in the field of systems biology.

In particular, we will consider two different types of measurements typically available to biologists, i.e. measurements of messenger RNA (mRNA) concentrations (as done by microarray techniques) and of protein concentrations.

A. Gene silencing

Perturbing the system with RNA interference (RNAi) is a relatively easy way to directly interact with a specific gene. RNAi is a structural perturbation mechanism that either inhibits gene expression at the stage of translation or hinders the transcription of specific genes. This leads to gene silencing, a term generally used to describe the "switching off" of a gene by a mechanism other than genetic modification. Gene silencing is a type of experiment that is readily available to biologists and obviously can be seen as making a modification to the structure of the biological system.

We first assume that our network has p observed states (mRNA concentrations which we can measure). We model gene silencing by RNAi as an "operator" that adds additional state variables and inputs to the system. The additional states z represent the RNAi molecule and the complex resulting from the binding of the RNAi and corresponding mRNA. Silencing an mRNA results in temporarily driving its concentration to zero. For the purpose of illustrating the methodology, we consider a simplified model where all differential equations remain the same except for the measured state y_i and the added hidden state dynamics z. This simplified model is given by

$$\begin{aligned} \dot{y}_i &= a_i \begin{bmatrix} y \\ x_h \end{bmatrix} + \bar{a}_i z \\ \dot{z} &= \bar{A}_i z + \begin{bmatrix} \bar{b}_i \\ 0 \end{bmatrix} u_i \end{aligned}$$

where a_i corresponds to the ith row of A, and $\bar{A}_i$, $\bar{a}_i$ and $\bar{b}_i$ characterize the dynamics of the added states z, and u_i is the input. Over time, silencing reduces the concentration of the ith mRNA to zero (consequently eliminating the associated protein from the network).

Performing a silencing experiment on x_i and measuring the dynamical behavior of this modified system yields a transfer function g_i, where g_i is a column vector. The control structure function p_i for this particular experiment is a column vector of the form $p_i = [0, ..., p_{ii}, ..., 0]'$, i.e. all entries are zero except the ith entry. We know this because the control input u_i affects the new hidden states z, which in turn only directly affect the measured state y_i (this may, in turn, then affect other measured states). Thus, there is only one unknown in p_i.

Data obtained from similar silencing experiments on each of the p measured states gives us a transfer function $G = [g_1 \ g_2 \ \cdots \ g_p]$ and a diagonal $P = \text{diag}(p_{11}, p_{22}, ..., p_{pp})$. We know that the $p-1$ nondiagonal terms on each row of P are zero; thus, the conditions of Theorem 2.4 are satisfied and, as a result, we can solve for the dynamical structure. The number of independent RNAi experiments required to reconstruct the network is exactly p.

Measuring protein concentrations rather than mRNA requires our corresponding simplified model to be a little different, taking into account the dynamical effects of gene silencing on protein concentration levels. However, by a similar argument, we can still choose the corresponding control structure P to be a diagonal matrix. In particular, the measured states do not directly depend on the new hidden states, but rather on the control input. The measured proteins in turn affect the mRNA concentrations (which are hidden states in this situation). Bringing the mRNA concentrations to zero will eventually lead the associated protein to degrade and approach zero. It follows that p of these experiments will also enable dynamical structure reconstruction.

B. Inducible overexpression

As a second set of structural perturbation experiments we consider inducible overexpression. Overexpression of a gene may be constitutive or inducible, through introduction of a transgene into the host which is specifically designed to increase the abundance of the desired transcript. Inducible overexpression uses a chemical to activate the inserted transgene, temporarily driving the concentration of a particular measured state to a large value.

The target specificity of these methods allows us to control a gene's expression without directly affecting other genes in the network. Putting these modifications in terms of a general network, overexpression of a state makes the effects of other states on the overexpressed state negligible, while preserving the effects of the overexpressed state on other states. These experiments can affect the system slightly or severely depending on which state is modified (Figure 1).

We can posit a simple model of inducible overexpression in a similar way to the above model of gene silencing. In this case, z is a single molecule representing a promoter for gene i. The concentration of mRNA corresponding to y_i will then increase to a high value, affecting other measured concentrations. This results in a p_i that, as before, has only one nonzero entry. In a similar way, we can show that inducibly overexpressing all measured states leads to

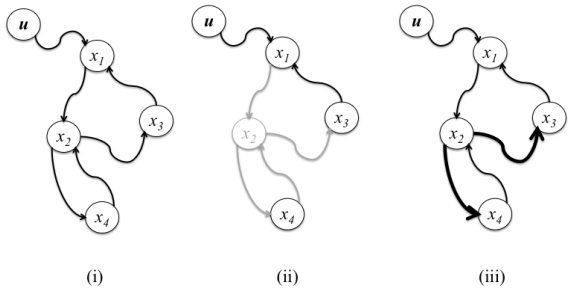

Fig. 1. A sample network (i) with four observed states and one input, and the resulting network when x_2 is silenced (ii) or overexpressed (iii). Grey arrows represent inhibited connections or states while thick arrows show connections that have been strengthened.

a diagonal P and allows us to reconstruct the dynamical structure of the network. As before, a similar argument follows if protein concentrations are measured instead of mRNA.

IV. Decoupled Structures and Network Sparsity

In the absence of extra information obtained from such experiments as silencing and overexpression, we investigate whether the use of a combined sparsity and minimality assumption can contribute to the recovery of the network dynamical structure. In particular, we are interested in determining whether the use of a sparsity assumption about the control or internal structure can contribute to the recovery of its dynamical structure. Sparsity has been considered as a natural assumption in the literature, mainly on the basis that many biochemical networks exhibit relatively few connections among system states.

Since the control structure P may reflect the introduction of artificial stimuli to the system, its structure conveys no information about the causal relationships between internal components of the network under consideration. In particular, a sparsest network structure implies as few as possible internal causal relationships between the components of the network. Thus a sparsest realization should be understood as a sparsest internal structure, Q, consistent with the input-output dynamics given by G. We learned in Theorem 2.3 that any transfer function G admits a perfectly sparse, or decoupled internal structure ($Q = 0$). As a consequence, sparsity alone cannot be used to recover dynamical structure.

However, these decoupled structures with $Q = 0$ are not always realizable with a minimal system. The question thus remains whether imposition of a sparsest structure, realizable by a minimal system, may offer some insight about the dynamical structure of the system responsible for the measured data. We introduce some terminology from [11]:

Definition 4.1 (Characteristic polynomial): The *characteristic polynomial* of a proper rational transfer function matrix G is the least common multiple of the denominators of all minors of G, where a minor of a matrix A is the determinant of some square submatrix of A.

Definition 4.2 (Smith-McMillan degree): The Smith-McMillan *degree* of G, or $\delta(G)$, is the degree of the characteristic polynomial of G.

Theorem 4.3 (Minimal realization): A LTI realization of G, (A, B, C, D), is minimal if and only if $\dim A = \delta(G)$.

The requirement that $\dim A = \delta(G)$ is equivalent to the condition that the realization is both controllable and observable. Since we are only considering systems with the form shown in (1) we assume that $D = 0$ and $C = \begin{bmatrix} I & 0 \end{bmatrix}$, and refer to a system as (A, B). Note that given any minimal realization $(\bar{A}, \bar{B}, \bar{C})$, there always exists a change of coordinates leading to an equivalent minimal realization (A, B, C) with a matrix $C = \begin{bmatrix} I & 0 \end{bmatrix}$ provided that $\bar{C}$ has full row rank.

We will use these results in the next few proofs. The following assumptions hold for the remainder of the section:

- A_1: Q is a matrix of strictly proper rational transfer functions, of size $p \times p$, such that all diagonal elements of Q are 0.
- A_2: P is a matrix of strictly proper rational transfer functions, of size $p \times m$.
- A_3: D is a $p \times p$ diagonal matrix of proper rational functions.

A pair (Q, P) satisfying assumptions (A1) and (A2) is called a *dynamical structure*.

Definition 4.4: A realization (A, B) is (Q, P)-minimal if the dynamical structure of (A, B) is (Q, P) and if there is no pair $(\hat{A}, \hat{B})$, with $dim(\hat{A}) < dim(A)$, such that the dynamical structure of $(\hat{A}, \hat{B})$ is (Q, P).

Lemma 4.5: Given Q, P, and D satisfying assumptions (A1), (A2) and (A3) respectively, there exists a realization (A, B) of $\begin{bmatrix} W & V \end{bmatrix} = \begin{bmatrix} (sI - D)Q + D & (sI - D)P \end{bmatrix}$ satisfying

$$W = A_{11} + A_{12}(sI - A_{22})^{-1}A_{21} \tag{5}$$

$$V = B_1 + A_{12}(sI - A_{22})^{-1}B_2 \tag{6}$$

with the partitioning A_{11}, A_{12}, A_{21}, and A_{22} as defined in (1).

Proof: Since P and Q are strictly proper and D is proper, W and V are proper. As a consequence, a realization of the matrix transfer function $\begin{bmatrix} W & V \end{bmatrix}$ can always be obtained. Let $(\hat{A}, \hat{B}, \hat{C}, \hat{D})$ be such a realization:

$$\begin{bmatrix} W & V \end{bmatrix} = \hat{D} + \hat{C}(sI - \hat{A})^{-1}\hat{B}$$

Now set $A_{22} = \hat{A}$ and $A_{12} = \hat{C}$ and consider the partitioning $\begin{bmatrix} A_{21} & B_2 \end{bmatrix} = \hat{B}$ and $\begin{bmatrix} A_{11} & B_1 \end{bmatrix} = \hat{D}$. We then obtain

$$\begin{aligned} \begin{bmatrix} W & V \end{bmatrix} &= \hat{D} + \hat{C}(sI - \hat{A})^{-1}\hat{B} \\ &= \begin{bmatrix} A_{11} & B_1 \end{bmatrix} + A_{12}(sI - A_{22})^{-1} \begin{bmatrix} A_{21} & B_2 \end{bmatrix} \end{aligned}$$

■

Finding a realization (A, B) which is (Q, P)-minimal amounts to choosing a D (not necessarily unique) that will minimize the Smith-McMillan degree of the transfer function matrix $\begin{bmatrix} (sI - D)Q + D & (sI - D)P \end{bmatrix}$. This is easily seen since the Smith-McMillan degree of this latter matrix transfer function corresponds to the number of hidden states in the realization (A, B) (the dimension of A_{22}) obtained through the construction given in the proof of Lemma 4.5. This may or may not correspond to a minimal realization of G. In Example 4.9 we consider a transfer function whose

Smith-McMillan degree is three but for which no third-order realization has a decoupled dynamical structure $(0, G)$.

Lemma 4.6: Given P and D satisfying assumptions (A2) and (A3) respectively, if all denominators of D are relatively prime to all the elements in P, the transfer function matrices $(sI - D)P$ and $H = [D\ (sI - D)P]$ have the same Smith-McMillan degree.

Proof: We will prove that the characteristic polynomials of H and $(sI - D)P$ are equal, by showing that the denominator of any minor of one matrix divides the characteristic polynomial of the other. First, any minor of $(sI - D)P$ is a minor of H, and so divides the characteristic polynomial of H.

Now let us consider any $r \times r$ minor x of H. If all r columns of H come from columns of $(sI - D)P$, x is a minor of $(sI - D)P$. Suppose that $m < r$ columns come from columns of $(sI - D)P$ (meaning the other $r - m$ columns are columns of D). All columns of D contain at most one nonzero element, so x is either 0 or the product of $r - m$ elements of D and an $m \times m$ minor x' of $(sI - D)P$ (or 1, if $m = 0$). Since the denominator of each element in D is unique to its row, and is found in all elements in the corresponding row of $(sI - D)P$, each of the $r - m$ denominators from D divide the characteristic polynomial of $(sI - D)P$ and are relatively prime to x', which also divides the characteristic polynomial of $(sI - D)P$. Thus their product, x, divides the characteristic polynomial of $(sI - D)P$. ∎

Recalling our objective, we want to characterize those systems which admit a minimal realization for the perfectly decoupled structure, $(0, G)$. For these systems, the dynamical structure $(0, G)$ is the sparsest minimal structure in the sense of Q. The next theorem provides conditions on G yielding a completely decoupled minimal realization.

Theorem 4.7 (Decoupled minimal realization): If each row of a $p \times m$ transfer function matrix G contains an element with a pole that is unique in its column, then G has a minimal realization whose dynamical structure is equal to $(0, G)$. For a single-input system ($m = 1$), the condition is necessary as well as sufficient.

Proof: ($\Rightarrow$) Denote by $\delta(G)$ the degree of G (which is the minimal order of a realization of G). Suppose each row in G has a pole which is unique in its column; we'll call them $\alpha_1 \in \mathbb{C}, \alpha_2 \in \mathbb{C}, \cdots, \alpha_p \in \mathbb{C}$. We will construct a diagonal transfer matrix $D(s)$, by setting $d_{ii} = s - \frac{p_i(s)}{q_i(s)}$, where $p_i(s)$ is the minimal real-valued polynomial (of degree $\delta_i \in \{1, 2\}$) for α_i, and $q_i(s)$ is a polynomial of degree $\delta_i - 1$ with normalized leading coefficient, that shares no roots with other elements in G. (If α_i is real, this makes $d_{ii} = \alpha_i$.) D is a diagonal matrix of proper rational functions, as desired, and $(sI - D)_{ii} = \frac{p_i(s)}{q_i(s)}$.

Multiplying P on the left by $(sI - D)$ removes from the ith row δ_i poles unique to that row of P, replacing them with $\delta_i - 1$ poles which do not cancel and are unique to the ith row of $(sI - D)P$. As a result, $\delta((sI - D)P) = \delta(P) - p$. By Lemma 4.6, the degree of the transfer function matrix $(sI - D)P$ is equal to the degree of $\begin{bmatrix} D & (sI - D)P \end{bmatrix}$. It follows by Lemma 4.5 that there exists a realization (A, B) of G where A_{22} is a $(n - p) \times (n - p)$ matrix (where $n = \delta(G)$), which means that A is $n \times n$. Thus (A, B) is a minimal realization of G where $Q = 0$.

($\Leftarrow$) Let G be single-input (i.e. G is a column vector of transfer functions) and that some element in G (without loss of generality, the pth element) does not contain a unique pole. Suppose there exists a minimal realization $A, B, C = \begin{bmatrix} I_p & 0 \end{bmatrix}$ so that $Q = 0$, then A_{11} is diagonal, as is $A_{12}A_{22}^n A_{21}$ for all values of n. It follows by induction that for any power A^m of A, the submatrix A_{11}^m is also diagonal. We now consider the transfer function $\bar{G}$ consisting of the first $p - 1$ elements of G. $\bar{G}$ has the same degree as G, so the system $A, B, \bar{C}$ is a minimal realization of $\bar{G}$. However, the pth column of $\bar{C}A^k$ is uniformly zero (since the first $p - 1$ elements of the pth column of A^k are zero for all k, and $\bar{C} = \begin{bmatrix} I_{p-1} & 0 \end{bmatrix}$) so the pth column of the observability matrix is also uniformly zero. Since $(A, B, \bar{C})$ is not observable, it is not a minimal realization of $\bar{G}$, yielding a contradiction. ∎

We have characterized a class of transfer functions which always have a decoupled minimal realization. We investigate whether this lends insight into the actual dynamical structure. A few examples illustrate this result.

Example 4.8: Consider the dynamical structure

$$Q = 0; P = G_1 = \begin{bmatrix} \frac{1}{s+1} \\ \frac{2}{s^2+2} \end{bmatrix}$$

Following Lemma 4.5, choose D to give us a desired $(sI - D)$:

$$D = \begin{bmatrix} -1 & 0 \\ 0 & -\frac{2}{s} \end{bmatrix}; (sI - D) = \begin{bmatrix} s+1 & 0 \\ 0 & \frac{s^2+2}{s} \end{bmatrix}$$

$$\begin{bmatrix} W & V \end{bmatrix} = \begin{bmatrix} D & (sI - D)P \end{bmatrix} = \begin{bmatrix} -1 & 0 & 1 \\ 0 & -\frac{2}{s} & \frac{2}{s} \end{bmatrix}$$

This transfer function has a minimal realization

$$(\bar{A}, \bar{B}, \bar{C}, \bar{D}) = \left([0], \begin{bmatrix} 0 & -1 & 1 \end{bmatrix}, \begin{bmatrix} 0 \\ 2 \end{bmatrix}, \begin{bmatrix} -1 & 0 & 1 \\ 0 & 0 & 0 \end{bmatrix} \right)$$

which gives us our minimal realization of (Q, P):

$$(A, B) = \left(\begin{bmatrix} -1 & 0 & 0 \\ 0 & 0 & 2 \\ 0 & -1 & 0 \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ 1 \end{bmatrix} \right)$$

This is also a minimal realization of G, which can be seen from Theorem 4.3 since $\delta(G) = 3$. This is consistent with Theorem 4.7 as all elements of G contain a unique pole in their column.

Example 4.9: The transfer function $G_2 = \begin{bmatrix} \frac{1}{(s+1)^2(s+2)} \\ \frac{1}{(s+1)(s+2)} \end{bmatrix}$ does not admit a completely decoupled minimal realization since neither row contains a unique pole in its column, thus violating Theorem 4.7. We can see this as follows:

G_2 has a minimal realization of form $(A, B) =$

$$\left(\begin{bmatrix} -1 & 1 & 0 \\ 0 & -2 & 1 \\ 0 & 0 & -1 \end{bmatrix}, \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \right)$$

All possible minimal realizations of G_2 with desired form C can be found by performing a change of coordinates on the hidden state x_h, $x_h^* = T_1 y + T_2 x_h$, with T_2 invertible: In this case we set $T_1 = \begin{bmatrix} t_0 & t_1 \end{bmatrix}$ and $T_2 = [t_2]$, giving us

$$(\bar{A}, \bar{B}) = \left(\begin{bmatrix} -1 & 1 & 0 \\ -\frac{t_0}{t_2} & -2 - \frac{t_1}{t_2} & \frac{1}{t_2} \\ -t_0 - \frac{(t_1 - t_2)t_0}{t_2} & t_0 - 2t_1 - \frac{(t_1 - t_2)t_1}{t_2} & \frac{t_1 - t_2}{t_2} \end{bmatrix}, \begin{bmatrix} 0 \\ 0 \\ t_2 \end{bmatrix} \right)$$

We see that the term a_{12} always equals one. This implies by equation (5) that W is a 2×2 matrix whose term $w_{12} \neq 0$ since w_{12} is the sum of a_{12} and a strictly proper rational function. By equation (3), the corresponding term q_{12} of Q is also always nonzero. Therefore, given any minimal realization of G_2, y_2 directly affects y_1.

As stated in Theorem 2.3, we note that the dynamical structure $(Q = 0, P = G)$ is consistent with any transfer function, and thus with the one in Example 4.9. Nevertheless, no third order realization of G is able to generate the decoupled dynamical structure $(0, G)$, so such a realization must be of order greater than three.

The fact that any transfer function with a pole unique in its column on every row admits a completely decoupled realization implies that the existence of a completely decoupled minimal realization for a stable transfer function (biological systems are stable systems) does not yield much extra information about the system. Indeed, any stable transfer function is arbitrarily close to one that admits a decoupled minimal realization, as is summarized in the following theorem.

Theorem 4.10: Given the H_∞ norm on the set $\mathcal{G}$ of strictly proper, rational, stable $p \times m$ transfer functions, and any $\epsilon > 0$, for each $G \in \mathcal{G}$ there exists a $\hat{G} \in \mathcal{G}$ so that each row of $\hat{G}$ has a pole that is unique in its column and $||\hat{G} - G|| < \epsilon$.

Proof: For each i, select α_i to be a pole in the ith row of G with minimal real-valued polynomial $p_i(s)$. Choose γ to be the norm of the diagonal matrix with terms $(\frac{1}{p_1(s)}, \cdots, \frac{1}{p_p(s)})$. Then let $\delta = \frac{\epsilon}{2\gamma\|G\|}$. There exist $\delta_1, \cdots, \delta_p$ so the following hold: (1) $\frac{\delta_i}{p_i(s) - \delta_i}$ is stable for each i, (2) no zero of the polynomials $p_i(s) - \delta_i$ is a zero or root of any other element of G, (3) the diagonal matrix with terms $(\frac{1}{p_1(s) - \delta_1}, \cdots, \frac{1}{p_p(s) - \delta_p})$ has norm less than 2γ. Define the diagonal matrix J where $j_{ii} = \frac{p_i(s)}{p_i(s) - \delta_i}$. Let $\hat{G} = JG$. Each row of $\hat{G}$ has as unique poles the zeroes of $p_i(s) - \delta_i$:

$$\|\hat{G} - G\| = \|(J - I)G\| \leq \|J - I\|\|G\| < 2\delta\gamma\|G\| = \epsilon$$

■

Since the observed dynamics of any biological system are always susceptible to some measurement noise, we can never get an exact picture of the dynamic behavior (e.g. transfer function) of a system. Furthermore, since any observed transfer function is arbitrarily close to one that has a decoupled minimal realization, assumptions of sparsity and minimality do not appear to give us any additional insight into the true underlying dynamical structure of the network under consideration. This suggests that performing experiments similar to those mentioned in Section III may be necessary to elucidate structure; heuristics such as sparsity and minimality alone are not good enough.

V. Conclusion

We have shown in this paper that one can yield sufficient information for completely reconstructing the dynamical structure of a given LTI network by using a sufficient number of measured structural perturbations to the original system. We showed that such structural perturbation measurement can be realized using readily available experiments such as silencing and inducible overexpression of states in gene regulatory networks. This result corroborates other findings in [1], [2] which show that such perturbation experiments provide better inference of system structure than methods which only analyze the behavior of a system resulting from perturbations of its steady state. We also discussed the concepts of minimality and sparsity, and showed that such assumptions do not provide substantial information for accurately recovering dynamical structure, even when considered in combination in a linear system setting with no internal or external noise.

We are currently implementing algorithms derived from the methods described in Section III. In future work, we plan to extensively compare the results given by these techniques with those obtained using several other popular methods of predicting biological networks. Overdetermining the network with multiple measurements and best-fit techniques enables a regression fit for the dynamical structure that can make these algorithms robust to parameter and measurement noise; this is also an important topic for future analysis.

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