Controllability analysis of networks

Anna Lombardi and Michael Hörnquist*
Department of Science and Technology, Linköping University, SE-601 74 Norrköping, Sweden
(Received 30 June 2006; revised manuscript received 5 April 2007; published 15 May 2007)

The concept of controllability of linear systems from control theory is applied to networks inspired by biology. A node is in this context controllable if an external signal can be applied which can adjust the level (e.g., protein concentration) of the node in a finite time to an arbitrary value, regardless of the levels of the other nodes. The property of being downstream of the node to which the input is applied turns out to be a necessary but not a sufficient condition for being controllable. An interpretation of the controllability matrix, when applied to networks, is also given. Finally, two case studies are provided in order to better explain the concepts, as well as some results for a gene regulatory network of fission yeast.

DOI: 10.1103/PhysRevE.75.056110 PACS number(s): 89.75.Fb, 87.10.+e, 87.17.Aa

I. INTRODUCTION

Biological networks, such as those describing gene regulation, can be seen as dynamical systems. Some structural characteristics of these networks have been identified [1] but the exploration of the dynamical implications is still in its infancy. The area attracts people from various fields, such as statistics, mathematics, computer science, biology, control theory, and, of course, physics. From a physics perspective, it is interesting both to model the dynamics of a specific system directly with differential equations [2], and to search for mechanisms that have built these kinds of networks [3]. The goal of this paper is to show how control theory can be applied to networks, namely, how the concept of controllability can be taken into consideration. In network theory, a node N_1 in a directed network is often said to be controlled by another node N_2 if there is a directed path from N_2 to N_1. Control theory, instead, uses the term controllability to describe the behavior of the network on the basis of the dynamical model. This latter definition of controllability applied to networks provides an insight to the behavior that could be missed by just looking at the network in terms of paths between nodes. The novelty here is the application of the concept of controllability from control theory to networks in a systematic way. Although both the concept of controllability and the representation of networks as digraphs are well known, this kind of systematic study has not, to the best knowledge of the present authors, been performed yet.

A network can be seen as a dynamic system with external inputs acting on it and the interactions between the components can be represented with a graph. The question whether it is possible to control each node from the input raises, and the notion of controllability can help to answer it. Often, it is tacitly assumed that a node can be controlled by the nodes upstream of it [4]. However, looking at controllability in this new context of control theory, we obtain useful information on how a node can be controlled going beyond the concept of just being downstream of another node. An interpretation of the controllability matrix is also given based on the gain of different paths from the input to the nodes. The paper is structured as follows. Section II introduces in a tutorial manner the notion of controllability for linear systems. Section III applies the concept of controllability to networks and gives an interpretation in this context. Section IV explains the notions previously introduced with two case studies. Section V describes the results for a gene regulatory network of fission yeast from the literature. Finally, Sec. VI contains conclusions and mentions some future directions for research.

II. CONTROLLABILITY

A linear system within control theory is often described in terms of state equations as

$$\dot{x}(t) = Ax(t) + Bu(t). \tag{1}$$

Here $x \in \mathbb{R}^n$ is the internal state of the system (often referred to as "the state") and u is an input (scalar) signal applied to one of the units of the system (in a more general framework, the input signal u can be both vector valued and/or applied to more than one unit, but this is of no interest for the present presentation). The factors A and B are matrices, of dimensions $n \times n$ and $n \times 1$, respectively, where A is called the "state-transition matrix" and B for us has only one nonzero element. Often, one also considers an output equation $y(t) = Cx(t) + Du(t)$, with C and D as matrices. For the present paper, however, this output equation is irrelevant and therefore discarded.

A natural question to ask is if we can find an input signal $u(t)$ which will take the system to any desired state in a finite time [5]. In the general case, when the matrices A and B vary in time, the concept of controllability is tied to a specific, finite time interval denoted $[t_0, t_f]$ with $t_f > t_0$. Then, the following definition of controllability is widely accepted. The linear state equation (1) is controllable on $[t_0, t_f]$ [6] if given any initial state $x(t_0) = x_0$ there exists a continuous input signal $u(t)$ such that the corresponding solution of Eq. (1) satisfies $x(t_f) = 0$. Note that due to the linearity, a system in the state $x(t) = 0$ will remain in that state if the input signal is turned off, i.e., if $u(t) = 0$.

*Electronic address: micho@itn.liu.se

More interesting for us, because one can obtain easily interpretable results, is the case of a time-invariant linear system (i.e., the matrices A and B do not depend on time). The controllability property is now independent of the particular interval $[t_0, t_f]$, and a necessary and sufficient condition for controllability of the linear system is the following: A time-invariant linear system (1) is controllable if and only if (see theorem 9.5 in Ref. [6]) the controllability matrix

$$C_0 = [B\ AB \cdots A^{n-1}B] \tag{2}$$

has full rank, i.e.,

$$\text{rank } C_0 = n. \tag{3}$$

The subscript zero is introduced in order not to confuse the controllability matrix C_0 with the matrix C in the output equation. The matrix B from Eq. (1) will always have n rows and in our case one column with only one nonzero element, and constitutes the first column of the controllability matrix C_0. The second column of C_0 is in this case the matrix product AB, the third column is A^2B, and so on.

Note that the formulation above presupposes linear equations. For a nonlinear system, it is not possible directly to build the controllability matrix (2) and therefore to use the condition (3). However, it is often fruitful to linearize the governing equations in a neighborhood of an equilibrium point, and this paper will focus only on the linear case, which then almost always represents a good starting point when analyzing a system. The system from biology we use as an example in Sec. V is indeed shown to be possible to describe also with linear equations.

III. GRAPHS AND NETWORKS

The linear system given in (1) can be seen as a realization of a graph [7]. The corresponding graph has as many nodes as number of components of the state x, and a link between two nodes are given by the existence of a nonzero element in the matrix A. In other words, from A we obtain the adjacency matrix for the graph if we replace all nonzero elements with unity (in some texts, this is the transpose of the adjacency matrix). In particular it results in a directed graph, a digraph, where each node is labelled as an integer i, $i=1,\ldots,n$ and described by a real number x_i. An edge is drawn whenever a node j affects directly the rate of change of a variable x_i. The element a_{ij} of the matrix A in Eq. (1) represents the weight of the arc going from node j to node i. In this context, the input u in Eq. (1) is seen as an external node affecting the node corresponding to the nonzero element of the matrix B.

The term "controllability" is sometimes applied to directed networks in the sense that upstream nodes are supposed to control downstream nodes, i.e., one considers only whether there is a path from one node to another. In order to avoid confusion, we will in this paper only use the word "controllability" the way it is introduced in Sec. II. It turns out in our case studies below that these two concepts do not coincide, where being downstream is a necessary but not sufficient condition for being independently controlled.

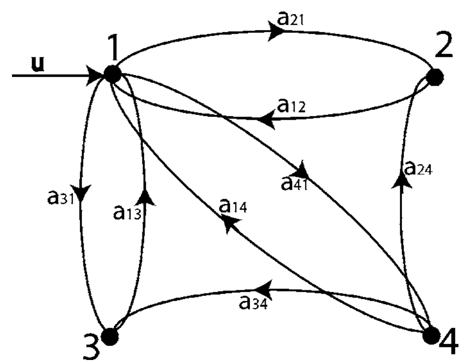

FIG. 1. Network with four nodes; the corresponding controllability matrix is rank deficient.

When speaking of controllability of networks and the input signal u is a scalar, the controllability matrix (2) acquires a particular meaning. The element c_{ij} of the matrix C_0 denotes the gain of all the paths going from the input u to the node i along $(j-1)$ links (or along j links, in case we consider the input as an external node). The particular case of 0 links denotes the case of the input applied directly on the node. In the next section two case studies will illustrate in details the interpretation given for the controllability matrix for a graph.

IV. CASE STUDIES

In the previous section the concept of controllability for a graph has been introduced and an interpretation of the controllability matrix has been given. These concepts are now illustrated with two case studies. Let the network have four nodes and the input be applied to node 1 making $B = [1\ 0\ 0\ 0]'$. In both examples considered, the networks are strongly connected, i.e., there is a directed path (often longer than one edge) between every pair of nodes, but it will be shown that in one case the controllability matrix has not full rank.

A. Case A: Rank deficiency

Consider the network with links as shown in Fig. 1. The corresponding state-transition matrix for the network of Fig. 1 is given by

$$A = \begin{bmatrix} 0 & a_{12} & a_{13} & a_{14} \\ a_{21} & 0 & 0 & a_{24} \\ a_{31} & 0 & 0 & a_{34} \\ a_{41} & 0 & 0 & 0 \end{bmatrix}, \tag{4}$$

with $a_{ij} \neq 0$ unless otherwise stated in the matrix, and the controllability matrix by

$$C_0 = \begin{bmatrix} 1 & 0 & a_{12}a_{21} + a_{13}a_{31} + a_{14}a_{41} & a_{12}a_{24}a_{41} + a_{13}a_{34}a_{41} \\ 0 & a_{21} & a_{24}a_{41} & a_{12}a_{21}^2 + a_{31}a_{21}a_{13} + a_{41}a_{21}a_{14} \\ 0 & a_{31} & a_{34}a_{41} & a_{21}a_{31}a_{12} + a_{13}a_{31}^2 + a_{41}a_{31}a_{14} \\ 0 & a_{41} & 0 & a_{21}a_{41}a_{12} + a_{31}a_{41}a_{13} + a_{14}a_{41}^2 \end{bmatrix}. \quad (5)$$

Figure 1 and the matrix (5) together give the interpretation of the controllability matrix for a graph. We see that it is possible to go from the input at node 1 to nodes 2, 3, and 4 in one step and therefore the corresponding elements c_{22}, c_{32}, and c_{42} are nonzero and given by the gain of the path a_{21}, a_{31}, and a_{41}, respectively. Let us now consider the element c_{13} of the matrix C_0: it represents the gain of all possible paths going from the input at node 1 back to node 1 in two steps. It is possible to go from the input to node 1 in two steps following three different paths: going to node 2 through the arc with gain a_{21} and coming back through the arc with gain a_{12}, the total gain of the path is $a_{21}a_{12}$. Similarly it is possible to go through the arcs with gains a_{31} and a_{13} and through the arcs with gains a_{41} and a_{14}. The total gain of all possible paths going from the input to node 1 in two steps is given by $a_{12}a_{21}+a_{13}a_{31}+a_{14}a_{41}$, that is, exactly the element c_{13} of the controllability matrix (5).

The controllability matrix (5) has rank 3 and this means, according to condition (3), that the network is not controllable. Indeed rows 2, 3, and 4 of the controllability matrix (5) have together rank 2, i.e., they are linearly dependent (for certain values of a_{ij}, it might happen that one of them gets independent as a kind of "accidental degeneracy" when the other two become parallel). This implies that nodes 2, 3, and 4 of the network cannot be controlled independently. This property can also be seen by simulating the system (1) and plotting the components of the state vector with respect to time. The system given by Eq. (1) with the initial state as zero has been simulated with the matrix A given in Eq. (4) with all the nonzero elements replaced by random numbers normally distributed (zero mean and unit variance, but the exact values are not important here). The input is a square wave applied to node 1. In Fig. 2 one can see how the nodes 2, 3, and 4 of the state vector seem to be correlated in time, and indeed the corresponding time derivatives of these signals are found to be linearly dependent.

Figure 2 also illustrates how node 1 is uncorrelated from the other nodes, and this corresponds to the fact that row 1 of the controllability matrix (5) is linearly independent from the other rows. Here, we find how the vector containing the time-derivatives of the signal for node 1 is linearly independent to the time derivatives of the signals of the other nodes.

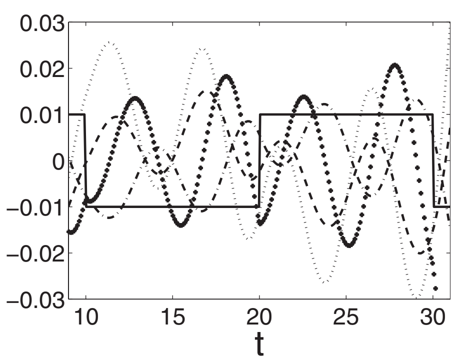

FIG. 2. Time development of the nodes of the network depicted in Fig. 1 (case A). The solid curve is the input signal, the plus signs is for node 1, the dashed curve for node 2, the dash-dotted curve for node 3, and the dotted curve for node 4. The second to fourth rows in the controllability matrix have rank 2, i.e., the rank is not full, and one can see how the nodes 2, 3, and 4 covary. Further, the vectors containing the time-derivatives of these signals are found to be linearly dependent. The first and third row, e.g., in the controllability matrix (5) are linearly independent, and one can see how the nodes do not covary. Consequently, the vectors containing the time-derivatives of these signals are linearly independent.

B. Case B: Full rank

Let the network be with the links as shown in Fig. 3. Compared with case A (Fig. 1), the only differences are that the link between nodes 2 and 4 has been reversed, and that the link from node 1 to node 3 now goes from node 3 to node 4. Although this similarity, the corresponding controllability matrix, with the same input as in case A, has full rank. This implies that all the nodes can be controlled independently by a signal to the first one. Note that this means that any state, i.e., any values of the four nodes, can be obtained by sending

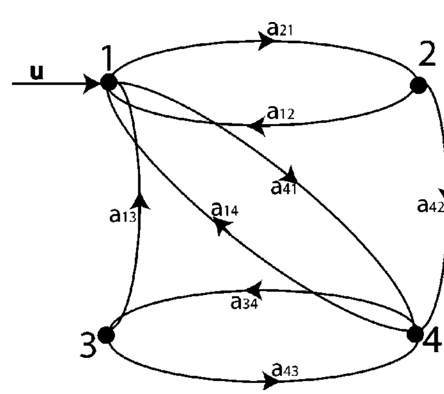

FIG. 3. Network with four nodes; the corresponding controllability matrix has full rank.

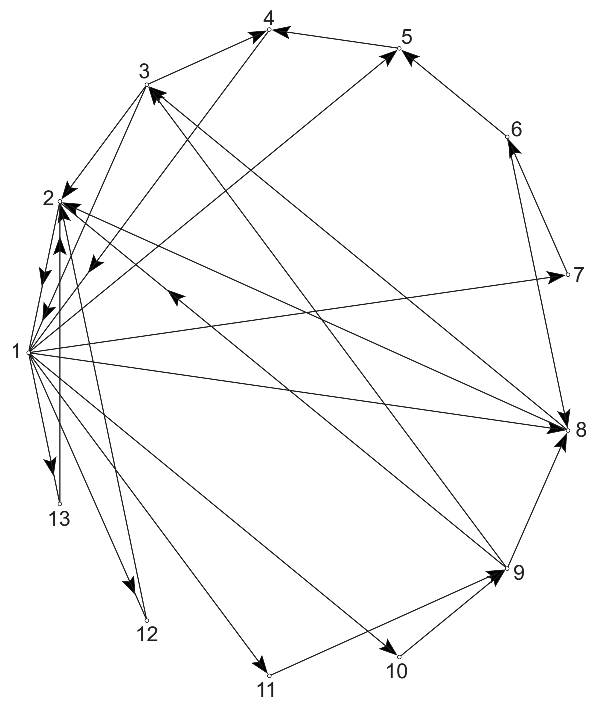

FIG. 4. Directed graph for the model of the cell cycle regulation of fission yeast [9]. (Graph drawn with Pajek [10].)

a signal into node one. However, the result does not tell us how to determine which signal to use for obtaining a desired state. That issue is far beyond the scope of the present paper to discuss.

V. NETWORK FOR CELL CYCLE REGULATION OF FISSION YEAST

In this section a biological network is taken into consideration and the concepts illustrated in Secs. II and III are applied to it. The system is a dynamical model describing the cell cycle regulation of fission yeast [8]. The differential equations of the nonlinear model can be found in Table I in Ref. [8], where the variables correspond to protein or protein complex concentrations. In Ref. [9] a piecewise linear version of this model is obtained. It is based on the fact that the biological system, apart from being large and complex, also is robust and sparse. The result is a piecewise *linear* system whose behavior can be described by a directed graph which is represented in Fig. 4. In the Appendix is reported what each node of the graph represents.

Once the directed graph is available, it is possible to determine a formal description of the system in terms of state variables (1), even if we do not know the exact values of the nonzero parameters a_{ij}. As an illustration, let us first apply the input to node 1 and compute the controllability matrix. If we look, for example, at the possible paths in two steps from the input at node 1 to node 2, it is possible to go through node 8, 12, or 13. This result appears in the controllability matrix as $c_{2,3}=a_{2,8}a_{8,1}+a_{2,12}a_{12,1}+a_{2,13}a_{13,1}$. All other elements can be determined likewise, but we refrain from reporting them here.

An interesting result comes from the analysis of the controllability matrix in different cases when the input is applied on each node at a time. Every time the input is applied on node i, the corresponding controllability matrix is computed: C_{0_i}, $i=1,\ldots,13$. For each matrix C_{0_i}, the rows that are linearly dependent are determined. It is found, e.g., that rows 7, 10, 11, 12, and 13 are linearly dependent for any input node (except, of course, when the input is applied to one of these nodes themselves). This observation reflects, e.g., that a single input cannot control the units TF, Slp1_T, IEP, Wee1, and Cdc25 (nodes 7, 10, 11, 12, and 13) independently of each other. These units are spread temporally all over the cell cycle, and our results indicate the fact that once the cycle has passed the point "start," it will proceed even if the extracellular signals that triggered the process is removed [11].

At heart of this biological exploration lies the fact that in Ref. [9] it is shown how the governing nonlinear equations can be approximated by piecewise linear equations where the formalism above is applicable. Fission yeast is one model organism, and there is reason to believe that properties found here will to some extent be valid also in other organisms, at least in unicellular eukaryotes. Indeed, the properties of robustness and sparsity are valid for many other organisms, and hence the linear description should not be without relevance. However, a more thorough exploration of this issue is beyond the scope of the present text.

VI. CONCLUSIONS AND OUTLOOK

In this paper, we have extended the concept of controllability from control theory into the realm of network theory for physics and systems biology. Controllability turns out to be not only a fact of a node being downstream of another node, but it depends in a more complex manner on the intrinsic structure of the network. If nodes are controllable, it implies that arbitrary values for each node can be obtained with a proper choice of the input signal. An interpretation of the controllability matrix when applied to networks has also been given. It is based on the gain of possible paths from the input to each node.

These results have been applied to two case studies of a network with four nodes; both when the corresponding controllability matrix is rank deficient and when it has full rank. Finally a gene regulatory network of yeast has been considered and the controllability has been explored.

The results presented in this paper suggest several issues to explore. For example, could this concept be a reasonable way to uncover functional modules within a biological network? How strong are the nonlinear effects in a more realistic description of other organisms than fission yeast, and how large is the neighborhood in which the linear approximation is reasonable?

ACKNOWLEDGMENTS

We thank Lic. Mika Gustafsson for valuable comments and discussions on this manuscript. Olivia Eriksson is acknowledged for drawing our attention to Ref. [9] and for providing data for the corresponding network.

APPENDIX: DIRECTED GRAPH FOR CELL CYCLE REGULATION OF FISSION YEAST

In Sec. V a directed graph for the cell cycle regulation of fission yeast (*Schizosaccharomyces pombe*, not to confuse with the more often studied baker's yeast, *Saccharomyces cerevisae*) is reported. In order to be able to compare with [8], we provide here the names of the units

Node 1:	MPF = M-phase promoting factor,
Node 2:	preMPF,
Node 3:	$Cdc13_T$,
Node 4:	Trimer,
Node 5:	$Rum1_T$,
Node 6:	SK=starter kineses (Cdc2 with Cig1, Cig2, Puc1),
Node 7:	TF=transcriptor factor for synthesis of SK,
Node 8:	Ste9,
Node 9:	Slp1,
Node 10:	$Slp1_T$,
Node 11:	IEP,
Node 12:	Wee1,
Node 13:	Cdc25.

[1] A.-L. Barabási and Z. N. Oltvai, Nat. Rev. Genet. **5**, 101 (2004).

[2] L. Chen, R. Wang, T. J. Kobayashi, and K. Aihara, Phys. Rev. E **70**, 011909 (2004).

[3] D. V. Foster, S. A. Kauffman, and J. E. S. Socolar, Phys. Rev. E **73**, 031912 (2006).

[4] N. M. Luscombe, M. M. Babu, H. Yu, M. Snyder, S. A. Teichmann, and M. Gerstein, Nature (London) **431**, 308 (2004).

[5] T. Kailath, *Linear Systems* (Prentice Hall, New York, 1980).

[6] W. J. Rugh, *Linear System Theory* (Prentice Hall, New York, 1996).

[7] D. Angeli, J. E. Ferrell, Jr., and E. D. Sontag, Proc. Natl. Acad. Sci. U.S.A. **101**, 1822 (2004).

[8] B. Novak, Z. Pataki, C. Andrea, and J. J. Tyson, Chaos **11**, 277 (2001).

[9] O. Eriksson, Y. Zhou, and J. Tegnér, in *Proceedings of 43rd IEEE Conference on Decision and Control* (Atlantis, Paradise Island, Bahamas, 2004), Vol. 1, pp. 117–123.

[10] V. Batagelj and A. Mrvar, *Pajek—Program for Large Network Analysis*, http://vlado.fmf.uni-lj.si/pub/networks/pajek/

[11] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter, *Molecular Biology of the Cell*, 4th ed. (Garland Science, London, 2002).