Appropriate time to apply control input to complex dynamical systems

Ali Ebrahimi1, Abbas Nowzari-Dalini2, Mahdi Jalili3 & Ali Masoudi-Nejad1*

Controlling a network structure has many potential applications many fields. In order to have an effective network control, not only finding good driver nodes is important, but also finding the optimal time to apply the external control signals to network nodes has a critical role. If applied in an appropriate time, one might be to control a network with a smaller control signals, and thus less energy. In this manuscript, we show that there is a relationship between the strength of the internal fluxes and the effectiveness of the external control signal. To be more effective, external control signals should be applied when the strength of the internal states is the smallest. We validate this claim on synthetic networks as well as a number of real networks. Our results may have important implications in systems medicine, in order to find the most appropriate time to inject drugs as a signal to control diseases.

Applications of control theory is no longer confined to a small technical system and has been recently expanded into complex network systems1-5. The aim of a control system is to look for a sequence of interventions in the network, so that the state of the nodes is hierarchically changed to a desired reference condition6,7. Finding driver nodes is an essential step toward controlling a dynamical system. The study of network controllability and determining the minimum number of driver nodes3, has attracted much attention within the community of network science and dynamical systems9-15. Various applications have for network control technology16-20.

There is a rich literature on theoretical and empirical studies which have examined how a dynamical system responds to external signals21-27. The degree of flexibility of a dynamical system has been introduced and the interaction between the flexibility values of a dynamical system and the effect of an external signal applied to the network has been examined22. In another work, the effect of local divergence on the synchronization capabilities of paired oscillators as well as the effect of slow transition have been investigated and some of the dynamical systems' conditions have been depicted, under which the highest ability to synchronize these oscillators could be achieved23. Moreover, concerning the connection between noise in a dynamical system and its stability, random intermittent stabilization based on discrete-time or time-delay feedback has been examined25. It has also been proved that a dynamical system stimulated by a noisy input with a time delay can produce the same effects as a dynamical system with a typical delay stimulated by the same noise27.

In a network system, the set of driver nodes with the minimal size is often not unique28. Choosing the best driver nodes to control have an active research topic within the community of network science29,30. To select a set of driver nodes to facilitate an optimal control of the network, one should further consider some important secondary issues, such as minimizing the amount of energy required for the control5,31,32, decreasing mediator nodes as well as the possible side effect of the control process15 and the number of control steps13.

Determining a set of driver nodes for an optimal control of a network is a necessary but inadequate action. Moreover, identifying the type of interventions, which should be applied to the network, is of the utmost importance. To minimize the energy required to control a network, it is crucial to determine the time that the inputs should be fed into the network such that the control performance is maximized.

As an example, in Bioinformatics, suppose we would like to input the signals into some effective agents to induce the apoptosis of cancer cells and eliminate this type of cells under minimum effort (energy)34-36. Taking the state of network variables and the internal fluxes into account, lack of knowledge about the best time for applying the external signals is a major challenge. As another example37-39, imagine a person would like to take control of a society or make some changes in the way a community is being led. If we assume that people are network nodes in this community, considering the fact that network nodes are under the influence of signals that

1Laboratory of Systems Biology and Bioinformatics (LBB), Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran. 2School of Mathematics and Computer Science, University of Tehran, Tehran, Iran. 3School of Engineering, RMIT University, Melbourne, Australia. *email: amasoudin@ut.ac.ir
agree or disagree to alterations in a particular subject within a population, thereby within their various communications, it is critical to find the best time when one can input the signals into the network. In this manuscript, we propose a methodology to determine the optimal time to apply the external inputs to driver nodes. We apply the proposed method on some real networks and reveal its effectiveness.

Results

States of individual nodes in complex dynamical network systems often undergo continuous changes based on their interactions with other nodes. Our aim is to find the best time that an external input can be applied to nodes in order to have maximum control impact. Our methodology is based on the connection between the strength of the system’s internal fluxes and the effect of the external signals on the system. As an external signal is applied to the network, the existing interaction between network nodes and the adjacent systems is ignored and only the network’s internal connections are taken into account in order to calculate the study the relationship between the strength of internal fluxes and effect of the external control.

Let’s consider a directed network $G$ with $n$ nodes with equations of motion described by the

$$\dot{X}(t) = AX(t) + BU(t) \tag{1}$$

where $A$ is the connectivity matrix between the nodes, $X$ is the state vector, $U$ is the input vector and $B$ determines the driver nodes to which the external input should be applied. The solution to the above equation will be

$$X(t) = e^{At}X(0) \tag{2}$$

if there are not any external signals, and

$$X(t) = e^{At}X(0) + \int_0^t e^{A(t-T)}BU(T)dT \tag{3}$$

if the external signals are applied to the network.

In the Methods section, we prove a theorem which specifies that the maximum effect of input signals to control a system will be produced when the system’s internal fluxes are weak. A dynamical system will have strong internal fluxes when it is not in a steady-state mode or when the equilibrium of the system could be related to the positive and negative signals that are balanced. In such case, external control signals often have minimal effect on the system’s performance. Our proposed method is based on this principle.

Let’s denote the network internal signals of nodes by $h(t)$. This function is differentiable at every point, when the left- and right-hand derivatives are equal, and the derivative is the degree of stimulation or the tendency for the movement of state of node. We know that the derivative of a function is zero if and only if the function is positioned at the extremum points, where the systems is its steady-state. The strength of the input signals is a function of the extent of movement in the preequilibrium, the duration of the stay in the equilibrium and the network structure.

To evaluate the above idea, here we present evidence on both synthetic and real networks. We compute the relationship between the strength of network’s internal fluxes and the degree of effectiveness of external input signals on the network. Negative correlation coefficient between the strength of the internal fluxes and the effect of the external inputs denotes an inverse association between them. Our results show that when the strength of internal fluxes is high, the impact of external input signals on the network will be low, and vice versa.

As shown below, the functions $f(t)$ and $g(t)$, respectively, are employed to measure the strength of internal network fluxes and the degree of the effectiveness of external signals. The function $f(t)$ determines the sum of the derivatives of the states at time $t$ by applying the following equation:

$$f(t) = \sum_n |\dot{X}(t)| \text{ s.t } |\dot{X}(t)| = \sqrt{Re^2(\dot{X}(t)) + Im^2(\dot{X}(t))} \tag{4}$$

where $n$ is the number of nodes and $Re$ and $Im$ are the real and imaginary parts of the complex number, respectively. The function $g(t)$ is obtained from the following equation:

$$g(t) = \sum_n |Y(t+m) - Z(t+m)| \tag{5}$$

where $Z(t+m)$ specifies the state of the nodes without applying the external signals to the system after $m$ steps, and $Y(t+m)$ determines the state of the nodes by applying the signals to the system at time $t$ after $m$ steps.

Based on the states obtained in the previous step and the available signals, the state of network nodes is obtained as:

$$X(t) = e^{A}X(t-1) + \int_{1}^{T} e^{A(t-T)}BU(T)dT = e^{A}X(t-1) + \int_{1}^{T} e^{-AT}BU(T)dT = e^{A}X(t-1) + A^{-1}(1-e^{-A}) \times U \tag{6}$$

and

$$e^{A} = M \hat{e} M^{-1}$$
in which
where \( \lambda_1, \lambda_2, \ldots, \lambda_n \) are eigenvalues and \( m_1, m_2, \ldots, m_n \) are eigenvectors of \( A \). In order for the matrices \( M \) and \( A \) to be invertible, \( \det(A) \neq 0 \), and \( A \) must have \( n \) distinct eigenvalues.

Figure 1 represents a toy network. We take the initial states of the nodes as \([1, 1, 1, 1, 1]^T\) and the time intervals as \( t = 1 \) to 20. At times \( t = 1, 5, 10, 15 \), and 20, a signal with the value of 1 is applied to the nodes of the network. Thus, the amount of internal fluxes of the network at \( t = 1, 5, 10, 15 \) and, 20 will be high; otherwise it will be low (blue curves). At any specific time, different input signals are applied to the network, and the correlation coefficient between \( f \) and \( g \) is calculated. There exist two strategies for applying the signal at time \( t \). In the first strategy, the signal is applied at the first step, and there are not any signals in the next \( m-1 \) steps. While in the other strategy, a continuous signal with a length of \( m \) is applied to the network. The value of \( m \) is 5 or 20.

**Results on synthetic networks.** A directed network \( G(A) \) (with 100 nodes), in which \( A \) has 100 distinct eigenvalues and \( \det(A) \neq 0 \), was randomly generated with different average degrees of 10, 25 and 50. To prevent an increased state of the network, the weight of edges was considered \( \pm 0.01 \), and the state of each node was initially set one. Then, an interval with 100 steps was considered, and signals with size 1 were applied to the network at times 0, 20, 40, 60, 80 and 100. Based on the algorithm that we have provided in order to find the driver nodes with the minimal mediator nodes, the network driver nodes are specified and then applied these signals to either (i) all nodes, or (ii) only driver nodes. At any time from 1 to 100, signals with different sizes \( \{U = -100, -10, -1, -0.1, 0.1, 1, 10, 100\} \) were applied to the network. Then, the correlation coefficient between \( f \) and \( g \) was calculated based on both the single and continuous signals \( (m = 5 \) and 20). Figure 2 shows \( f \) and \( g \) in a sample network with an average degree of 10, and when an input signal with a value of \( -100 \) was applied to all nodes in 20 consecutive steps. Figure 3 (Fig. 4) show the correlation coefficient between \( f \) and \( g \) when the input signals are applied to all (driver) nodes. It is seen that when the control is applied to all nodes, the correlation takes a larger absolute value than the case when the control is applied to only driver nodes. Furthermore, as the network become denser (i.e. their average degree increases), the correlation becomes stronger.

**Results on real networks.** Like the previous section, the correlation coefficient between \( f \) and \( g \) at the given time intervals was calculated under different settings. The results obtained from \( U = \pm 1 \) were listed in Table 1 and those obtained from different sizes of \( U \) were presented in Fig. 5. The results obtained from different sizes of \( U \) show that the correlation coefficient between \( f \) and \( g \) is close to \(-1\), except for the case of small-size input signal \( (U = \pm 0.1) \). Similar to synthetic networks, the correlation is stronger when the input signal is applied to all nodes rather than only drivers, which is somehow expected.
Conclusions

A dynamical network is controllable if the state of its nodes can be steered from any initial value to a desired final value in a finite time. Often, external control signals are applied to a number of select nodes, called drivers, to control the networks. In some applications, it is critical to apply control signals in appropriate times to obtain the maximum control performance. If control signals are applied at appropriate times, the network might be controlled with smaller control signals, and thus less energy. Therefore, one may optimize the energy required for the control. In this manuscript, we proposed a methodology to find the best times to apply the external control signals to network nodes. We showed that applying the external signals to the network is most efficient when the value of positive and negative internal fluxes of the system is small. Under this condition, there would be no opposite forces in the system, and thus even small control signals could be effective.

Methods

State-variable response of linear systems. In a network with dynamics of motion as $X(t) = AX(t) + BU(t)$, if there are no external signals, the state of the nodes will be obtained from the equation:

$$X(t) = e^{At}X(0)$$

(8)

If an external signal is applied to the network, the state will be obtained using the following equation:

Figure 2. The graph shows $f$ and $g$ in a network with 100 nodes and average degree $\langle k \rangle = 10$. The initial value of the state of nodes is considered to be 1. (a) The horizontal axis represents the intervals from $t = 1$ to $t = 100$, where the input signal is applied to the network at $t = 1, 20, 40, 60, 80, 100$. (b) The function $g$ where an input signal with a value of -100 is to all nodes in 20 consecutive steps.

Figure 3. The correlation coefficient between $f$ and $g$. In random networks with size 100 and different average degree $\langle k \rangle$. The Absolute value of correlation coefficient is high in all cases except in cases when the value of the input signal is very small. $U = -100, -10, -1, -0.1, 0.1, 1, 10, 100$ are the input signal. The input signal is applied to all nodes (a) in 5 Consecutive steps, (b) in 20 Consecutive steps, (c) Single signal applied to the whole nodes with $m = 5$, and (d) Single signal applied to the whole nodes and $m = 20$. The graphs show the average value with bars corresponding to the standard deviation over 20 realizations.
State transition matrix. The state of network nodes is obtained from the following equations:

\[ X(t) = e^{At}X(0) + \int_0^t e^{A(t-T)}BU(T)dT \]

(9)

**State transition matrix.** The state of network nodes is obtained from the following equations:

\[
X(t) = e^A X(t-1) + \int_{t-1}^t e^{A(t-T)}BU(T)dT = e^A X(t-1) + \left( \int_{t-1}^t e^{-A}dT \right) \times U = e^A X(t-1) + A^{-1}(1 - e^{-A}) \times U
\]

and \( e^A = M \hat{e} M^{-1} \) which

\[
M = [m_1|m_2|\ldots|m_n] \quad \text{and} \quad \hat{e} = \begin{bmatrix}
\hat{e}_1^1 & 0 & 0 \\
0 & \hat{e}_2^2 & 0 \\
. & . & . \\
0 & 0 & \hat{e}_n^n
\end{bmatrix}_{n \times n}
\]

(11)

\( \lambda_1, \lambda_2, \ldots, \lambda_n \) and \( m_1, m_2, \ldots, m_n \) are eigenvalues and eigenvectors of the matrix A, respectively.
Theorem In a Linear Time Invariant (LTI) system, the maximum effect of the input signals will be produced when the internal fluxes of the system are weak.

Proof If the dynamics of the systems are regarded as
\[
X(t) = e^{At}X(0) + \int_0^t e^{A(t-T)}BU(T)dT
\]  

(12)
The first part of the formula is derived from the initial conditions of the system, while the second part is derived from the input signals. So, the fraction
\[
\frac{\int_0^t e^{A(t-T)}BU(T)dT}{e^{At}X(0)}
\]  

(13)
specifies the effect of the input signals based on the initial conditions of the system. By removing \(e^{At}\) from the fraction and the placement of the equation
\[
X(0) = A^{-1}(\dot{X}(0) - BU(0))
\]  

(14)
in the fraction, we will acquire the following equation:
\[
\int_0^t e^{A(t-T)}BU(T)dT \quad \frac{e^{At}X(0)}{\dot{X}(0) - BU(0)} = \frac{\int_0^t e^{-AT}BU(T)dT}{A^{-1}(\dot{X}(0) - BU(0))}
\]  

(15)
When the numerator of the fraction is constant, the maximum value will be obtained when the denominator of the fraction converges to zero. Thus, the value of \(AX(0)\) will converge toward zero: \((AX(0) = \dot{X}(0) - BU(0) \approx 0)\) and this would be achieved when the internal fluxes of the system are weak.

Received: 3 February 2020; Accepted: 12 November 2020
Published online: 16 December 2020

References
1. Medaglia, J. D., Pasqualetti, F., Hamilton, R. H., Thompson-Schill, S. L. & Bassett, D. S. Brain and cognitive reserve: translation via network control theory. *Neurosci. Biobehav. Rev.* 75, 53–64 (2017).
2. Arcelli, D., Cortellessa, V., Filieri, A. & Leva, A. In 2015 11th International ACM SIGSOFT Conference on Quality of Software Architectures (QoSA) 11–20 (IEEE).
3. Pawlicki, T. et al. Application of systems and control theory-based hazard analysis to radiation oncology. *Med. Phys.* 43, 1514–1530 (2016).
4. Mansell, W. & Marken, R. S. The origins and future of control theory in psychology. *Rev. Gen. Psychol.* 19, 425–430 (2015).
5. Liu, Y.-Y. & Barabási, A.-L. Control principles of complex systems. *Rev. Mod. Phys.* 88, 035006 (2016).
6. Duan, Z., Chen, G. & Huang, L. Complex network synchronizability: analysis and control. *Phys. Rev. E* 76, 056103 (2007).
7. Ruths, J. & Ruths, D. Control profiles of complex networks. *Science* 343, 1373–1376 (2014).
8. Kalman, R. E. Mathematical description of linear dynamical systems. *J. Soc. Ind. Appl. Math.* A 1, 152–192 (1963).
9. Liu, Y.-Y., Slotine, J.-J. & Barabási, A.-L. Controllability of complex networks. *Nature* 473, 167–173 (2011).
10. Gao, J., Liu, Y.-Y., Dsouza, R. M. & Barabási, A.-L. Target control of complex networks. *Nat. Commun.* 5, 1–8 (2014).
11. Orouskhani, Y., Jalili, M. & Yu, X. Optimizing dynamical network structure for pinning control. *Sci. Rep.* 6, 24252 (2016).
12. Yuan, Z., Zhao, C., Di, Z., Wang, W.-X. & Lai, Y.-C. Exact controllability of complex networks. *Nat. Commun.* 4, 1–9 (2013).
13. Nacher, J. C. & Akutsu, T. Structural controllability of unidirectional bipartite networks. Sci. Rep. 3, 1647 (2013).
14. Cornelius, S. P., Kath, W. L. & Motter, A. E. Realistic control of network dynamics. Nat. Commun. 4, 1–9 (2013).
15. Ebrahimi, A., Nowzari-Dalini, A., Jalili, M. & Masoudi-Nejad, A. Target controllability with minimal mediators in complex biological networks. Genomics. 112, 4938–4944 (2020).
16. Mineka, S. & Hendersen, R. W. Controllability and predictability in acquired motivation. Annu. Rev. Psychol. 36, 495–529 (1985).
17. De-Leon, S.B.-T. & Davidson, E. H. Gene regulation: gene control network in development. Annu. Rev. Biophys. Biomol. Struct. 36, 191–212 (2007).
18. Wuchty, S. Controllability in protein interaction networks. Proc. Natl. Acad. Sci. USA 111, 7156–7160 (2014).
19. Nacher, J. C. & Akutsu, T. Computational Biology of Non-coding RNA (Springer, New York, 2019).
20. Li, M., Gao, H., Wang, J. & Wu, F.-X. Control principles for complex biological networks. Brief. Bioinform. 20, 2253–2266 (2019).
21. Hu, D. & Yuan, J.-M. Time-dependent sensitivity analysis of biological networks: coupled MAPK and PISK signal transduction pathways. J. Phys. Chem. A 110, 5361–5370 (2006).
22. Marhl, M. & Perc, M. Determining the flexibility of regular and chaotic attractors. Chaos Solitons Fractals 28, 822–833 (2006).
23. Nishikawa, T. & Ott, E. Controlling systems that drift through a tipping point. Chaos 24, 033107 (2014).
24. Perc, M. & Marhl, M. Synchronization of regular and chaotic oscillations: The role of local divergence and the slow passage effect—a case study on calcium oscillations. Int. J. Bifurcation Chaos 14, 2735–2751 (2004).
25. Liu, L., Perc, M. & Cao, J. Aperiodically intermittent stochastic stabilization via discrete time or delay feedback control. Sci. China Inf. Sci. 62, 72201 (2019).
26. Capeans, R., Sabuco, I., Sanjuán, M. A. & Yorke, J. A. Partially controlling chaotic transients in the Lorenz equations. Philos. Trans. R. Soc. A 375, 20160211 (2017).
27. Bolhasani, E., Azizi, Y., Abdollahpour, D., Amjad, J. M. & Perc, M. Control of dynamics via identical time-lagged stochastic inputs. Chaos 30, 013143 (2020).
28. Zdeborová, L. & Mézard, M. The number of matchings in random graphs. J. Stat. Mech: Theory Exp. 2006, P05003 (2006).
29. Moradi Amani, A., Jalili, M., Yu, X. & Stone, L. Controllability of complex networks: choosing the best driver set. Phys. Rev. E 98, 030302(R) (2018).
30. Moradi Amani, A., Jalili, M., Yu, X. & Stone, S. Finding the most influential nodes in pinning controllability of complex networks. IEEE Trans. Circuits Syst II 64, 685–689 (2017).
31. Yan, G., Ren, J., Lai, Y.-C., Lai, C.-H. & Li, B. Controlling complex networks: How much energy is needed? Phys. Rev. Lett. 108, 218703 (2012).
32. Ma, Z. & Wang, S. Energy efficient control of variable speed pumps in complex building central air-conditioning systems. Energy Build. 41, 197–205 (2009).
33. Dai, W., Gu, Z., Lin, X., Hua, Q.-S. & Lau, F. C. In 2015 IEEE Conference on Computer Communications (INFOCOM) 648–656 (IEEE).
34. Ahmed, K., Tabuchi, Y. & Kondo, T. Hyperthermia: an effective strategy to induce apoptosis in cancer cells. Apoptosis 20, 1411–1419 (2015).
35. Loo, D. T. et al. Apoptosis is induced by beta-amyloid in cultured central nervous system neurons. Proc. Natl. Acad. Sci. USA 90, 7951–7955 (1993).
36. Fridman, J. S. & Lowe, S. W. Control of apoptosis by p53. Oncogene 22, 9030–9040 (2003).
37. Girvan, M. & Newman, M. E. Community structure in social and biological networks. Proc. Natl. Acad. Sci. USA 99, 7821–7826 (2002).
38. Liben-Nowell, D. & Kleinberg, J. The link-prediction problem for social networks. J. Am. Soc. Inform. Sci. Technol. 58, 1019–1031 (2007).
39. Borgatti, S. P., Everett, M. G. & Johnson, J. C. Analyzing Social Networks (Sage, Thousand Oaks, 2018).
40. Rowell, D. Time-domain solution of LTI state equations. Class Handout in Analysis and Design of Feedback Control System 92 (2002).
41. Ulomowicz, R. E. & DeAngelis, D. L. Network analysis of trophic dynamics in south florida ecosystems. US Geological Survey Program on the South Florida Ecosystem 114 (1999).
42. Watts, D. J. & Strogatz, S. H. Collective dynamics of ‘small-world’ networks. Nature 393, 440–442 (1998).
43. Van Duijn, M. A., Zeggelink, E. P., Huisman, M., Stokman, F. N. & Wasseur, F. W. Evolution of sociology freshmen into a friendship network. J. Math. Sociol. 27, 153–191 (2003).
44. Milo, R. et al. Network motifs: simple building blocks of complex networks. Science 298, 824–827 (2002).

Author contributions
A.E.: designed the study, implemented, analyzed and interpreted results, wrote the manuscript. A.N-D.: Assisted in interpretations and revising the manuscript. M.J.: Wrote the manuscript. A.M–N.: Assisted in interpretations and revising the manuscript. All authors approved the final version of the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to A.M.–N.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2020