Minimum-Time Control of Boolean Control Networks: A Fast Graphical Approach (Supplementary Materials)

Shuhua Gao, Jun-e Feng, Zezheng Li, Cheng Xiang, *Member, IEEE*

TABLE I
BOOLEAN RULES OF THE T-LGL BOOLEAN CONTROL NETWORK

Node	Boolean rule
CREB	IFNG $\wedge$ $\neg$Apoptosis
IFNG	$\neg$(SMAD $\vee$ P2 $\vee$ Apoptosis)
P2	(IFNG $\vee$ P2) $\wedge$ $\neg$Apoptosis
GPCR	S1P $\wedge$ $\neg$Apoptosis
SMAD	GPCR $\wedge$ $\neg$Apoptosis
Fas	$\neg$(sFas $\vee$ Apoptosis)
sFas	S1P $\wedge$ $\neg$Apoptosis $\wedge$ u_1
Ceramide	Fas $\wedge$ $\neg$(S1P $\vee$ Apoptosis) $\vee$ u_2
DISC	(Ceramide $\vee$ (Fas $\wedge$ $\neg$FLIP)) $\wedge$ $\neg$Apoptosis
Caspase	((BID $\wedge$ $\neg$IAP) $\vee$ DISC) $\wedge$ $\neg$Apoptosis
FLIP	$\neg$(DISC $\vee$ Apoptosis)
BID	$\neg$(MCL1 $\vee$ Apoptosis)
IAP	$\neg$(BID $\vee$ Apoptosis)
MCL1	$\neg$(DISC $\vee$ Apoptosis) $\wedge$ u_3
S1P	$\neg$(Ceramide $\vee$ Apoptosis)
Apoptosis	Caspase $\vee$ Apoptosis

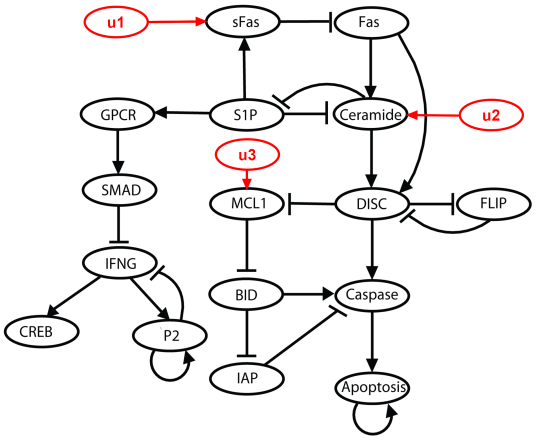

Fig. 1. The T-LGL signaling network with external control (adapted from [2]). Sharp and hammerhead arrows denote activation and inhibition respectively. The inhibitory edges from Apoptosis to other nodes are not shown for clarity. The red circles and arrows indicate the external control.

I. CASE STUDY OF THE T-LGL NETWORK

In the examples of the main text, we have examined a mini-sized network *on purpose* for better illustration. In this part, we perform another simulation study with a larger biological network, a signaling network involved in a blood cancer called the *T cell large granular lymphocyte* (T-LGL) leukemia [1], [2]. This network is composed of 16 state variables and 3 control inputs, i.e., $N = 65536$ and $M = 8$. The Boolean functions for the 16 nodes (genes) are listed in Table I, and the structure of the network is illustrated in Fig. 1. The state transition matrix of the ASSR form of this network is huge: $L \in \mathcal{L}_{65536\times 524288}$, which is computed and stored as a data file in https://github.com/ShuhuaGao/MTCBCN/tree/main/script/T-LGL.

Following the problem setting in [1], the network is initially in a diseased state $=$ 0001101000101110 (i.e., $x^0 = \delta_{65536}^{58834}$), where Caspase and Apoptosis are OFF, and we want to drive it to a healthy state 0000000000000001 (i.e., $x^{\mathrm{d}} = \delta_{65536}^{65535}$), in which Apoptosis is activated. This can be easily formulated as a minimum-time control problem between the two states. Here, we consider a more challenging case. Since the healthy state x^{d} is a fixed point, we want to design an time-optimal state feedback control law that steers the network from an *arbitrary* initial state to the desired state x^{d} (i.e., Case 3 in the main text). This is essentially a time-optimal stabilization problem that has been investigated in [3], [4] (which are cited as [8], [16] in the main document).

The algorithms are implemented with Julia 1.9.1. We did experiments on a desktop PC equipped with a 12th Gen Intel(R) Core(TM) i7-12700F 2.10 GHz CPU, 32 GB RAM, and Windows 11. Results are listed as follows.

- The set R in Algorithm 2 contains all 65536 states, which implies that the T-LGL BCN is globally stabilizable to $x^{\mathrm{d}} = \delta_{65536}^{65535}$.
- Among all the initial states $x^0 \in \Delta_N$, the largest value of $T^*(x^0, x^{\mathrm{d}})$ is 5, for instance, we found $T^*(\delta_{65536}^{50654}, x^{\mathrm{d}}) = 5$. That is, it takes the BCN at most 5 time steps from an arbitrary initial state to reach the desired state x^{d} under the designed time-optimal state-feedback control law.
- Our algorithms finished in less than 1 second, while the algebraic methods in [3], [4] were still running even after 10 hours. This dramatic runtime reduction further highlights the efficiency advantage of the proposed approach.

Shuhua Gao and Zezheng Li are with the School of Control Science and Engineering, Shandong University, Jinan 250100, China (shuhuagao@sdu.edu.cn; jingzhizz321@gmail.com).

Jun-e Feng is with the School of Mathematics, Shandong University, Jinan 250100, China (fengjune@sdu.edu.cn).

Cheng Xiang (*corresponding author*) is with the Department of Electrical and Computer Engineering, National University of Singapore, Singapore 119077 (elexc@nus.edu.sg).

REFERENCES

[1] D. Murrugarra, A. Veliz-Cuba, B. Aguilar, and R. Laubenbacher, "Identification of control targets in Boolean molecular network models via computational algebra," *BMC Systems Biology*, vol. 10, no. 1, p. 94, Dec. 2016.

[2] A. Saadatpour, R.-S. Wang, A. Liao, X. Liu, T. P. Loughran, I. Albert, and R. Albert, "Dynamical and Structural Analysis of a T Cell Survival Network Identifies Novel Candidate Therapeutic Targets for Large Granular Lymphocyte Leukemia," *PLOS Computational Biology*, vol. 7, no. 11, p. e1002267, 20111110.

[3] H. Li and Y. Wang, "Minimum-Time State Feedback Stabilization of Constrained Boolean Control Networks," *Asian Journal of Control*, vol. 18, no. 5, pp. 1688–1697, 2016.

[4] Y. Ding, Y. Guo, Y. Xie, C. Yang, and W. Gui, "Time-optimal state feedback stabilization of switched Boolean control networks," *Neurocomputing*, vol. 237, pp. 265–271, May 2017.