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

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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

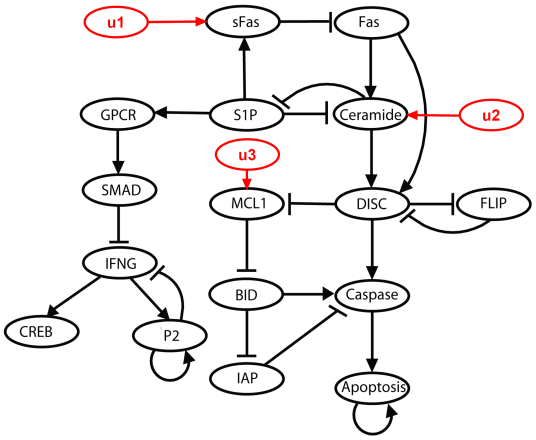

Fig. 1. The T-LGL signaling network with external control (adapted from [2]). Sharp and hammerhead arrows denote activation and inhibition respectively. The inhibitory edges from Apoptosis to other nodes are not shown for clarity. The red circles and arrows indicate the external control.

I. CASE STUDY OF THE T-LGL NETWORK

In the examples provided in the main text, we deliberately chose a mini-sized network for better illustration. However, in this section, we conduct another simulation study using a larger biological network, namely, a signaling network involved in a blood cancer called *T cell large granular lymphocyte* (T-LGL) leukemia [1], [2]. This network consists of 16 state variables and 3 control inputs, with $N = 65536$ and $M = 8$. The control inputs may represent drugs, irradiation, or other gene expression interference factors in practice. The Boolean functions for the 16 nodes (genes) are listed in Table I, and the network's structure 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 at https://github.com/ShuhuaGao/MTCBCN/tree/main/script/T-LGL.

In accordance with 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 our objective is to steer it to a healthy state 0000000000000001 (i.e., $x^{\mathrm{d}} = \delta_{65536}^{65535}$), where Apoptosis is activated. This can be easily formulated as a minimum-time control problem between the two states. However, we consider a more challenging case in which the healthy state x^{d} is a fixed point. Our goal is to design a time-optimal state feedback control law that can steer the network from an *arbitrary* initial state to the desired state x^{d} (i.e., Case 3 in the main text). Essentially, this is a time-optimal stabilization problem, previously investigated in [3], [4] (which are cited as [9], [15] in the main document).

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The algorithms were implemented using Julia 1.9.1, and experiments were conducted 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.

The results are as follows:

- The set R in Algorithm 2 contains all 65536 states, indicating 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 example, we found $T^*(\delta_{65536}^{50654}, x^{\mathrm{d}}) = 5$. This means that it takes the BCN at most 5 time steps from any arbitrary initial state to reach the desired state x^{d} under the designed time-optimal state-feedback control law.
- Our algorithms completed in less than 10 seconds, while the algebraic methods in [3], [4] were still running even after 10 hours. This significant reduction in runtime further emphasizes the efficiency advantage of the proposed approach, which also aligns with the time complexity comparison in Table I of the main text.

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