This supplementary document provides the supporting materials for the manuscript **"State reduction for network intervention with probabilistic Boolean networks"**, including the relevant theorem for computing transition probabilities of different types of probabilistic Boolean networks (PBNs) and the additional simulation results.

*** Note:** The order of the references in this file is *not* identical to the order in the manuscript. The list of references cited in this file can be found on the last page.

Theorems and Proofs

State transition probabilities for PBNs

The computation of the transition probabilities between states in PBNs has been discussed in several papers [Brun *et al*., 2005, Pal *et al*., 2006, Qian *et al*., 2009]. We re-iterate them in the following theorem:

Theorem 1: The transition probabilities from $\mathbf{x}$ to $\mathbf{y}$ for a BNp and an instantaneously random PBN are given by

$$p(\mathbf{x},\mathbf{y}) = \mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}(1-p)^n + \mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}, \tag{1}$$

where $\eta(\mathbf{x},\mathbf{y})$ is the Hamming distance between $\mathbf{x}$ and $\mathbf{y}$, and $\mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}$ is the indicator function that takes value 1 if $\mathbf{f}(\mathbf{x}) = \mathbf{y}$ according to the truth table and is equal to 0 otherwise; and

$$p(\mathbf{x},\mathbf{y}) = \sum_{j=1}^{m} c_j \mathbf{1}_{[\mathbf{f}_j(\mathbf{x})=\mathbf{y}]}(1-p)^n + \mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}, \tag{2}$$

respectively. The transition probability from $(r,\mathbf{x})$ to $(s,\mathbf{y})$ for a context-sensitive PBN is given by

$$\begin{aligned} p(\{r,\mathbf{x}\},\{s,\mathbf{y}\}) &= \mathbf{1}_{[s=r]}((1-q)+qc_r)\{\mathbf{1}_{[\mathbf{f}_r(\mathbf{x})=\mathbf{y}]}(1-p)^n + \mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}\} \\ &+ \mathbf{1}_{[s\neq r]}qc_s\{\mathbf{1}_{[\mathbf{f}_s(\mathbf{x})=\mathbf{y}]}(1-p)^n + \mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}\}, \end{aligned} \tag{3}$$

where r, s denote the rth and sth context BNp, which are the BNps at time $t+1$ and t.

Proof: With perturbation, the dynamics of a BNp can be analyzed as a homogeneous irreducible finite Markov chain $\mathbf{X}_t$ with the state space $\{0,1\}^n$. The state transitions of a BNp over time are governed by transition rules $\mathbf{f}$ and perturbation. Implicitly, we assume that there is an i.i.d. random perturbation vector $\gamma \in \{0,1\}^n$, where the ith gene flips if the ith component of γ is equal to 1. Here, $p = P\{\gamma_i = 1\} = E[\gamma_i]$ is the same for all the genes. If $\mathbf{X}_t \in \{0,1\}^n$ is the state of the network at time t, then the next state $\mathbf{X}_{t+1}$ is either $\mathbf{f}(\mathbf{X}_t)$ with probability of $(1-p)^n$ or $\mathbf{X}_t \oplus \gamma$ with probability $1-(1-p)^n$ (at least one perturbation), where $\oplus$ is component-wise addition modulo 2. For each pair of states $\mathbf{x}$ and $\mathbf{y}$, We write the transition probability from $\mathbf{x}$ to $\mathbf{y}$ at arbitrary time t as $p(\mathbf{x},\mathbf{y}) = P[\mathbf{X}_{t+1} = \mathbf{y}|\mathbf{X}_t = \mathbf{x}]$. This probability is

a weighted sum of two transition probabilities:

$$p(\mathbf{x},\mathbf{y}) = \mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}(1-p)^n + p_{\mathbf{x}}(\mathbf{y})[1-(1-p)^n], \tag{4}$$

where $\mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}$ is the indicator function that takes value 1 if $\mathbf{f}(\mathbf{x}) = \mathbf{y}$ according to the truth table and is equal to 0 otherwise, and $p_{\mathbf{x}}(\mathbf{y})$ is the probability that the perturbation moves from $\mathbf{x}$ to $\mathbf{y}$. With $\eta(\mathbf{x},\mathbf{y})$ as the Hamming distance between $\mathbf{x}$ and $\mathbf{y}$, we can write:

$$p_{\mathbf{x}}(\mathbf{y}) = \mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}\frac{p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}}{1-(1-p)^n}.$$

Plugging this into (4), we obtain (1). Based on this, we can derive the transition matrix P of the underlying Markov chain by computing all of its matrix entries.

For instantaneously random PBNs, we assume that we select one function from among $\mathbf{f}_1,\cdots,\mathbf{f}_k$, representing one of constituent BNps, with probabilities $\mathbf{c} = \{c_1,\cdots,c_k\}$ at any time point t. Therefore, the transition probability for the state pair $\mathbf{x}$ and $\mathbf{y}$ can be written according to (2).

The transition probability for context-sensitive PBNs is more complicated because $P_{\mathbf{x}}(\mathbf{y})$ depends on the function $\mathbf{f}_j$ selected at time t. The state space of the underlying Markov chain for context-sensitive PBNs is in fact the joint space of the gene expression states and the constituent BNps. At each time point t, a random decision is made according the switching probability q as to whether to switch the network function for the next state transition. If a decision is made to switch the network function, then a new network function is chosen from $\mathbf{F} = \{\mathbf{f}_1,\cdots,\mathbf{f}_k\}$ with the probability of choosing $\mathbf{f}_j$ being the selection probability c_j and the selection for the next transition is not conditioned by the current network and the current network can also be selected. Thus, the transition probability of the underlying homogeneous Markov chain $(J_t,\mathbf{X}_t)$ is given by (3), where r,s denote the rth and sth BNp, which are the BNps at time $t+1$ and t. ■

Structure of state transition probability matrices

For BNps, since $p(\mathbf{x},\mathbf{y}) = \mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}(1-p)^n + \mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}$ in (1), all the entries in P have two terms $\mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}(1-p)^n$ and $\mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}$. We note that the first term is the multiplication of the probability of no random flipping $(1-p)^n$ with the indicator $\mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}$ determined by the Boolean functions $\mathbf{f}$ given in the BNp. We denote $q(\mathbf{x},\mathbf{y}) = \mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}$. The second term is determined by the Hamming distance between $\mathbf{x}$ and $\mathbf{y}$ as explained in the above proof. We denote it $h(\mathbf{x},\mathbf{y}) = \mathbf{1}_{[\mathbf{y}\neq\mathbf{x}]}p^{\eta(\mathbf{x},\mathbf{y})}(1-p)^{n-\eta(\mathbf{x},\mathbf{y})}$. Hence, $p(\mathbf{x},\mathbf{y}) = (1-p)^n q(\mathbf{x},\mathbf{y}) + h(\mathbf{x},\mathbf{y})$ for any entry in the transition matrix P. Thus, we can write $P = (1-p)^n F + H$ as given in the manuscript. Each entry in F corresponds to $q(\mathbf{x},\mathbf{y})$ and each entry in H corresponds to $h(\mathbf{x},\mathbf{y})$. We can derive similar decompositions of the transition matrices for both instantaneously random and context-sensitive PBNs. Obviously, H is the same for all PBNs with the same number of genes and F is determined by the regulatory rules or Boolean functions $\mathbf{f}$ given in the PBNs.

As $q(\mathbf{x},\mathbf{y}) = \mathbf{1}_{[\mathbf{f}(\mathbf{x})=\mathbf{y}]}$, for singleton attractors, we have $q(\mathbf{x},\mathbf{x}) = 1$ and $q(\mathbf{x},\mathbf{y}) = 0, \forall \mathbf{y} = \mathbf{x}$. Hence, if we organize the transition matrix P by grouping singleton attractors together as we did in the manuscript, we have

$$P = (1-p)^n F + H, \text{where } F = \begin{pmatrix} F' & \mathbf{0} \\ \mathbf{0} & I \end{pmatrix},$$

where I is the identity matrix corresponding to all the singleton attractors and F' is determined by the regulatory rules for other states.

Identification of outmost transient states

For an arbitrary outmost transient state $\mathbf{y}$, we have $q(\mathbf{x},\mathbf{y}) = 0, \forall \mathbf{x}$ as $\mathbf{f}(\mathbf{x}) \neq \mathbf{y}$ since there is no state transition from any state $\mathbf{x}$ to $\mathbf{y}$. Hence, $p(\mathbf{x},\mathbf{y}) = (1-p)^n q(\mathbf{x},\mathbf{y}) + h(\mathbf{x},\mathbf{y}) = h(\mathbf{x},\mathbf{y}), \forall \mathbf{x}$. When we have small perturbation probability, for example, $p < 0.1$, $\sum_{\mathbf{x}} p(\mathbf{x},\mathbf{y}) = \sum_{\mathbf{x}} h(\mathbf{x},\mathbf{y})$ is very small. For general PBNs, we have $\sum_{\mathbf{x}} p(\mathbf{x},\mathbf{y}) < \min_j c_j (1-p)^n$. For BNps, we have $\sum_{\mathbf{x}} p(\mathbf{x},\mathbf{y}) < (1-p)^n$.

Simulation results

This document contains the more detailed simulation results for the networks presented in the manuscript.

Performance comparison for randomly generated networks

Degree of reduction

The number of remaining states m' reflects the degree of the reduction and it also determines the computational complexity for finding both BOA and SSD control policies using reduced networks. We study the effectiveness of the proposed state reduction procedure by running simulations of 1000 randomly generated networks with with 6, 8, 10 and 12 genes. Table 1 provides the average numbers of final remaining states and their standard deviations for networks with different numbers of genes. It clearly shows that the degree of the reduction increases with the increasing number of genes in networks.

Preservation of long-term network dynamics

We study the the proportional change of stationary mass for the critical states to investigate the effects of the reduction on the long-term network behavior. Table 2 gives the average proportional changes of steady-state probabilities for critical states and their standard deviations with more digits than those given in the manuscript. We noticed that the standard deviations are relatively large (around $1 \sim 4$ times) comparing to small average proportional changes, especially for instantaneously random PBNs. To make sure that

Table 1: The average number of remaining states $\mu_{m'}$ and their standard deviations $\sigma_{m'}$ after reduction for random BNps and instantaneously random PBNs with different numbers of genes n

		BNp				PBN			
n		6	8	10	12	6	8	10	12
L=1	$\mu_{m'}$	27.17	80.11	239.84	708.28	43.00	136.11	423.92	1289.30
	$\sigma_{m'}$	6.29	21.65	77.19	254.65	5.56	22.12	79.41	295.81
L=2	$\mu_{m'}$	17.34	44.33	114.72	295.03	37.43	108.56	303.03	818.30
	$\sigma_{m'}$	5.59	16.38	51.64	148.09	6.54	23.32	74.89	250.96

the state reduction procedure works reasonably well for most of the random networks, we further plot the histograms of the actual proportional changes for critical stationary masses for 1000 random PBNs with 6 and 10 genes in Fig. 1 in addition to Fig. 3 for 10-gene BNps in the manuscript. We find that for 6-gene PBNs with $L = 1, 2$ layers of transient states removed, 93.9% and 93.8% of random networks have less than 0.2 proportional change for critical states' steady-state probabilities, respectively; for 10-gene PBNs with $L = 1, 2$ layers removed, 99.3% of random networks in both cases have less than 0.2 proportional change. Although the degree of reduction for PBNs is smaller, it is clear that the reduction preserves better the long-term dynamics comparing to BNps. Along with the results shown in the manuscript, this demonstrates that the reduction procedure generally preserves the network dynamics. Therefore, the proportional changes are similarly small for networks with different numbers of genes. This is promising as we have shown that the degree of reduction increases with the number of genes for both BNps and PBNs in the previous experiments. We conjecture that with larger networks, we can reduce the state space greatly with the long-run network behavior preserved.

Table 2: The average actual proportional changes for the stationary masses of critical states μ_c and their standard deviations σ_c after reduction for random BNps and PBNs with different numbers of genes n

		BNp				PBN			
n		6	8	10	12	6	8	10	12
L=1	μ_c	0.1022	0.1025	0.0989	0.1070	0.0640	0.0218	0.0107	0.0073
	σ_c	0.1231	0.1162	0.1206	0.1239	0.2271	0.0804	0.0491	0.0150
L=2	μ_c	0.1476	0.1391	0.1284	0.1367	0.0649	0.0230	0.0126	0.0091
	σ_c	0.1656	0.1535	0.1461	0.1469	0.2280	0.0803	0.0506	0.0165

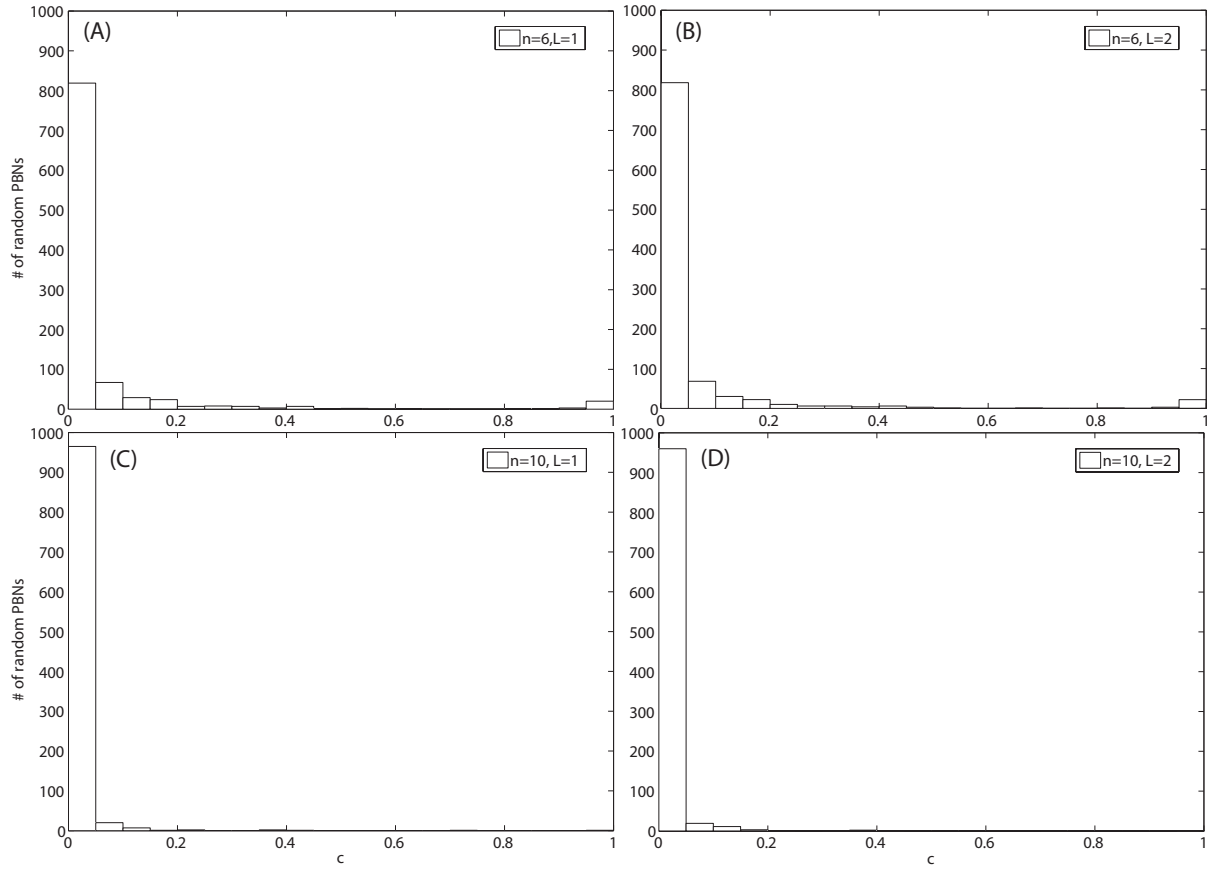

Figure 1: The histogram of actual proportional change for the stationary mass of critical states for randomly generated instantaneously random PBNs with (A) 6 genes and $L = 1$ layer of transient states removed; (B) 6 genes and $L = 2$ layer of transient states removed; (C) 10 genes and $L = 1$ layer of transient states removed; (D) 10 genes and $L = 2$ layer of transient states removed

Shift of Undesirable stationary masses

For better performance comparison, table 3 gives the shift of average undesirable stationary masses with more digits than those given in the manuscript, in which we given the average undesirable stationary masses π_U before control (ORG) and after applying the BOA control policy based on the original network (BOA), BOA control policy induced from the reduced network with one layers of transient states grouped together (BR1), induced BOA control policy from the reduced network with two layers of transient states grouped together (BR2), induced SSD control policy from the reduced network with one layers of transient states grouped together (SSD1), and induced SSD control policy from the reduced network with two layers of transient states grouped together (SSD2), respectively. From the table, The induced SSD control policies perform slightly better than the induced BOA policies in almost all the cases for both random BNps and instantaneously random PBNs. Both of them have comparable performance with the BOA control policy derived directly based on the original networks.

Table 3: The average undesirable stationary masses π_U before and after applying control for random BNps and PBNs

	BNp				PBN			
n	6	8	10	12	6	8	10	12
ORG	0.4899	0.4977	0.4940	0.4898	0.5042	0.4950	0.4996	0.4933
BOA	0.2739	0.3023	0.3262	0.3429	0.3471	0.3830	0.3966	0.4057
$BR1$	0.3304	0.3499	0.3736	0.3817	0.3788	0.4140	0.4317	0.4404
$BR2$	0.3666	0.3878	0.4037	0.4082	0.3915	0.4273	0.4429	0.4532
$SSD1$	0.3304	0.3454	0.3733	0.3771	0.3957	0.4070	0.4144	0.4209
$SSD2$	0.3566	0.3752	0.3910	0.4000	0.4117	0.4237	0.4323	0.4400

Gastrointestinal cancer network application

Intervention performance of induced BOA and SSD control policies

In the manuscript, we only reported the intervention performance of induced SSD control policy, which achieves significant shift of SSDs towards desirable states in all the cases with $L = 1, 2, 3$ layers of transient states removed. Deriving BOA control policy requires comparing the structural properties of corresponding BOAs for the pair of states $\mathbf{x}$ and $\mathbf{x}_g$ with control gene g flipped. While as we mentioned in the manuscript, the degree of reduction in this real-world network is very large with less than 1% states remaining after reduction with $L = 3$, there is not even one pair of $\mathbf{x}$ and $\mathbf{x}_g$ both remaining after reduction. Hence, the induced BOA control policy does not perform very well. We show the undesirable stationary masses before and after applying control policies in Table 4. After removing more than one layer of transient states, the induced SSD control policy still achieves significant beneficial shift of SSDs while the induced

BOA control policy fails to shift the stationary mass beneficially. We conjecture that this is due to the well approximation of long-term network dynamics described by steady-state probabilities of the critical states by our state reduction algorithm. Table 5 shows the l_∞ norm of the proportional changes of the steady-state probabilities for the critical states $\left\| \frac{\pi_S}{\|\pi_S\|} - \frac{\pi_S^*}{\|\pi_S^*\|} \right\|_{l_\infty}$ in this cancer network.

All these experiments demonstrate that the proposed state reduction is effective and control policies derived from reduced networks are potentially helpful for developing effective intervention strategies for future gene-based therapeutics.

Table 4: Undesirable stationary masses before and after applying control for the gastrointestinal cancer network: ORG–the undesirable mass before control; BOA–the undesirable mass after applying the BOA control policy derived from the original network; BOAr–the undesirable mass after applying the induced BOA control policy derived form the reduced network with L layers of transient states removed; SSDr–the undesirable mass by the induced SSD control policy derived form the reduced network with L layers of transient states removed

L	ORG	BOA	BOAr	SSDr
1			0.2767	0.0649
2	0.5003	0.0509	0.5147	0.1508
3			0.5160	0.1942

Table 5: The proportional change of the steady-state probabilities for the critical states $c = \left\| \frac{\pi_S}{\|\pi_S\|} - \frac{\pi_S^*}{\|\pi_S^*\|} \right\|_{l_\infty}$ in the gastrointestinal cancer network with L layers of transient states removed

L	1	2	3
c	0.0140	0.0114	0.0154

References

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