Deep Reinforcement Learning for Control of Probabilistic Boolean Networks

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Abstract. Probabilistic Boolean Networks (PBNs) were introduced as a computational model for studying gene interactions in Gene Regulatory Networks (GRNs). Controllability of PBNs, and hence GRNs, is the process of making strategic interventions to a network in order to drive it from a particular state towards some other potentially more desirable state. This is of significant importance to systems biology as successful control could be used to obtain potential gene treatments by making therapeutic interventions. Recent advancements in Deep Reinforcement Learning have enabled systems to develop policies merely by interacting with the environment, without complete knowledge of the underlying Markov Decision Process (MDP). In this paper we have implemented a Deep Q Network with Double Q Learning, that directly interacts with the environment – that is, a Probabilistic Boolean Network. Our approach develops a control policy by sampling experiences obtained from the environment using Prioritized Experience Replay which successfully drives a PBN from any state towards the desired one. This novel approach sets the foundations for overcoming the inability to scale to larger PBNs and opens up the spectrum in which to consider control of GRNs without the need of a computational model, i.e. by direct interventions to the GRN.

Keywords: Controllability, Complex Networks, Gene Regulatory Networks, Machine Learning, Markov Process, Q-Learning

1 Introduction

Gene activities in an organism are interdependent, thus studying each gene independently, albeit important, it provides limited knowledge on how a perturbation or change in specific genes affects the rest of the cell. Systems Biology focuses on understanding the underlying dynamics and structure of a Gene Regulatory Network (GRN) by studying the multivariate interactions of its components e.g. genes and proteins [1].

Controllability in this context refers to the process of discovering strategies to cause such perturbations by targeted interventions to the state of a cell (gene expression) aiming to drive a cell from its current state to some other more desirable state by influencing its dynamics. Such interventions can be regulated aiming to reduce undesirable functionality and potentially have a positive therapeutic effect in various diseases such as cancer.

Numerous mathematical and computational methods have been developed in order to represent GRNs and used to determine such control strategies. Boolean Networks (BNs) were
introduced by [2] and is the model that has received the most attention. A Boolean Network is comprised of a number of nodes representing the genes of a GRN and gene expression is quantized as binary values \{0, 1\}, namely ON (1) or OFF (0). The expression level of each gene in a Boolean Network at each time step is governed by logical functions defined for that gene as well as the expression level of other genes interacting with it. However, transitions from one state to another in Boolean Networks is fully deterministic, thus allowing the possibility of not accurately modelling the behavior of a Gene Regulatory Network. Their yet simple model has provided useful insights to the complex dynamics of regulatory networks [3], [4], [5], [6].

Probabilistic Boolean Networks (PBNs) have received less attention probably due to their intrinsically more complex and non-deterministic nature. PBNs are an extension to BNs [7]. They share the same principles in regard to quantization of gene expression, but state transitions at each time step are governed by Boolean functions assigned to each gene with some probability. Thus, the probability of transitioning from one state to another (state transition probability) is dependent on the probability of specific functions being assigned to each gene at each time step, making such transitions highly non-deterministic. It has been shown that state transitions of PBNs can be studied under the context of Markov Chains (MCs) and form a homogenous MC [7]. PBNs are thus able to cope with the inherent uncertainty found in the studies of biological systems.

Genes in biological systems have been shown to exhibit sudden emergence of ordered collective behavior [8] which is manifested in PBNs as irreducible sets of states and absorbed states, also known as attractors [9]. Correspondence to such attractors has been observed in biological cell functions such as growth or quiescence [8], [10]. Proliferation and Apoptosis, behaviors found in cancerous cells, are characterized by such collective gene behavior and in the context of PBNs can be understood as attractors [8]. A perturbation on the state of a GRN that may be the result of external causes such as the environment a patient may reside in, or from internal causes such malfunctions of other organs in the body, may drive the cellular state of that GRN towards some undesired gene collective behavior as the ones mentioned above. Thus, it becomes clear that targeted interventions to specific genes can potentially transition the state of a cell from an undesired attractor e.g. cancerous state, to a desirable one where the GRN ceases to exhibit functionality such as uncontrollable cell proliferation.

Deep Reinforcement Learning and Deep Learning in general, have received much attention recently mostly due to the continuous increase in computational power. These approaches have shown to yield state of the art results, exceeding human performance in a number of domains e.g. see [11], [12]. A Reinforcement Learning algorithm, also known as an agent, is concerned with the interaction of such agent with an environment in order to determine actions that aim to maximize some notion of cumulative reward by performing these actions on the environment and observing the state changes and the rewards received. In this paper we focus on Deep Reinforcement Learning and more specifically on the use of a Deep Q Network. A DQN is a function approximator with parameters \( \theta \), trained using a variant of Q Learning [14] and stochastic gradient descent. In the case of [13], a DQN was used to learn how to play Atari games by directly interacting with the game’s environment without knowledge of its underlying dynamics, while storing experiences in a memory buffer which were then sampled to train the network using Experience Replay (ER) [15].
Since Deep Reinforcement Learning has successfully been applied to such large state spaces such as the Atari games, it is normal to wonder whether we can borrow some of these ideas to adapt in the context of controllability of PBNs. In this paper, we explore a novel approach to controlling PBNs. We have implemented two improvements on DQNs and ER, that is Double Q Learning [16] adapted for Deep Reinforcement Learning [17] and Prioritized Experienced Replay [18] which we apply to the problem of controlling PBNs. To the best of our knowledge no other Deep Reinforcement Learning approach has been applied to this problem.

The proposed approach requires no knowledge of the state transition probabilities, also known as transition probability matrix of the PBN or the probabilities related to Boolean functions assigned to each node. Our goal is to train a DQN which we also refer to as the agent, to discover a successful strategy that can be used to make appropriate interventions at each state in order to drive the PBN towards a desired attractor or in the context of GRNs, desired collective behavior of genes. We explore this controllability problem by allowing the agent to make the minimum possible interventions at each time i.e. a maximum of one gene intervention is allowed at each time step. Our solution does not focus on a specific PBN model of a GRN but shows how the agent successfully learns to control a PBN with zero knowledge of its underlying dynamics, implying that any GRN of such complexity could be controlled. We show that the proposed approach successfully determines a strategy to control PBNs from any current state towards a desired attractor by targeted gene interventions.

To summarize our contributions here, are as follows:

- We propose a novel approach that applies Deep Reinforcement Learning to the problem of PBN controllability.
- We provide a solution to the problem of control by limiting the possible interventions per time step to a maximum of one intervention in order to make such interventions as less invasive as possible to the PBN, while considering all nodes as a potential intervention point.
- We propose a solution that learns how to control a PBN without having any knowledge of the PBN’s structure, connectivity, state transition probabilities or assigned Boolean functions to its nodes, while also setting the foundations for a solution that can scale to large PBNs.
- Finally, given sufficient biologically related technology that allows isolation and interaction with GRNs, this approach could be used to learn to control GRNs directly without the need of a computational model.

The remainder of this paper is structured as follows. Section II briefly reviews previous approaches to controllability and advancements in Deep Reinforcement Learning. Section III introduces general concepts around Markov Decision Processes in order to set the stage for PBNs and the main idea behind the Q-Learning algorithm. Section IV proceeds to introduce and explain PBNs. Section V presents the problem of controllability in the context of PBNs. Then Section VI explores the mechanics of a Double Deep Q Network with Prioritized Experience Replay in more detail. Section VII briefly explains the PBN as an environment for Reinforcement Learning. Section VIII proceeds to discuss our experiments and results. Finally, Section IX includes concluding remarks and suggestions for future work.
2 Related Work

Perhaps one of the most popular solutions that successfully controls PBNs was developed by [19] where the authors make use of dynamic programming [20] and full knowledge the state transition matrix of the PBN in order to minimize a cost function aiming at developing an optimal control strategy that determines the optimal interventions required to control a PBN from some state $s$ to some terminal state $s'$ in finite time horizon. In this implementation the authors allow up to $n$ simultaneous gene interventions ($n$ being the size of the PBN i.e. number of nodes), which implies that the Markov Chain of the PBN with such interventions becomes ergodic [9].

In [9] the authors utilize the state transition matrix of a PBN and the concept of mean first passage time is used to determine the genes that would probabilistically minimize the time steps required for desired state transitions to occur.

These methods make use of the state transition probabilities defined by the full knowledge of a PBN’s Markov Decision Process (MDP), which restricts controllability to a limited size PBN. One of the reasons is that determining the state transition matrix for large GRNs to model as PBNs is challenging from a biology perspective. Most importantly though, the state-space (cardinality) grows exponentially ($2^n$, where $n$ in the number of PBN nodes) as the PBN size increases and the problem can fall into the ‘Curse of Dimensionality’ as explained by Richard Bellman [20].

Polynomial Optimization and Integer Programming [21] approaches, are two methods that do not make use of the state transition matrix and can be more effective in larger PBNs. In addition, a number of other approaches have been proposed [22], [23], [24], [25], [26], [27], [28], [29], [30] which develop control techniques for PBNs. However, they all require and are dependent on prior knowledge of the connectivity, state transition probabilities or probability of Boolean functions being assigned to each of the PBN’s nodes. Nevertheless, it is important to examine the case where no knowledge of the PBN’s underlying dynamics exists. Such can be the case when limited amount of biological studies have been conducted on a GRN and sufficient data is not available to determine the network’s dynamics [24].

Perhaps the most similar approaches to our proposed method are the use of fitted Q Iteration [31], the use of Q Learning [32] and the application of an LCS [33] variable called XCS [34], which is trained with a variant of Q Learning. The former approach focuses explicitly on controlling Gene Regulatory Networks and is concerned with driving two specific proteins to a target region in the state-space. The second focuses on the control problem of a melanoma case PBN that aims to reduce the probability of a state with up-regulation of the WNT5A gene to occur by single control of the Pirin gene. Finally, the latter successfully applies XCS to the control problem of BNs [3] which evolves a set of control rules in order to drive BNs from any state towards an attractor.

Even though these approaches do not require any knowledge of the underlying dynamics of a PBN, they suffer from the fact that as the state space of the PBN exponentially increases, the computational complexity also increases, yielding these techniques unable to scale further than a few nodes. Hence, motivated by the fact that available work on control of PBNs without knowledge of the underlying dynamics is scarce and limited in its application we explore in this paper the application of a non-linear function approximator; that is a Double Deep Q Network in order to address this issue.
One of the main contributions of a Deep Q Network [13] is that it overcomes the issue of scalability found in other Q Learning implementations. The state-space of Atari games is very large and solving it with classical Q Learning [14] is impractical. However, a DQN exceeded human performance on three of the Atari games and outperformed all other previous approaches for the rest.

A number of improvements have been proposed to the original DQN implementation that result in more successful learning. One of the improvements has to do with the use of Double Q Learning [16] with DQNs (also known as Double DQN or DDQN) [17] which performed significantly better compared to the original DQN implementation on the same Atari games.

Both of these approaches [13], [17] use Experience Replay (ER) [15] during training of the network. ER is the process of storing experiences, that is information regarding the agent’s interaction with the environment which are then uniformly sampled from replay memory and used during training to optimize the network’s parameters. The main motivation behind the use of ER, is that it breaks the strong temporal correlations of experiences caused by always optimizing the network according to its current interaction with the environment and avoids the possibility of rapid forgetting of experiences that rarely occur. Prioritized ER (PER) [18] was proposed as an improved alternative to ER that prioritizes the sampling of experiences, with the motivation that the DQN can learn more from some experiences than others. DDQN with PER was tested on 49 Atari games and was shown to outperform the original DQN with ER on 41 of them [18].

3 Preliminaries

In this section we briefly discuss Markov Chains and Markov Decision Processes which describe an environment in the context of Reinforcement Learning. We also refer to the Q Learning algorithm in order to lay the foundations that make Reinforcement Learning a suitable solution to the problem of PBN controllability.

Markov Decision Process

A Markov Chain is a mathematical framework that models a sequence of stochastic events, where the probability of an event occurring at the next time step is conditioned only to the event at the current time step and not the events that occurred prior to that. In other words, every state in the Markov Chain must satisfy the following Markov Property:

\[ P[s_{t+1} | s_t] = P[s_{t+1} | s_t, s_{t-1}, \ldots, s_0] \]  

(1)

where \( P[s_{t+1} | s_t] \) is the probability at time step \( t \) of transitioning from state \( s_t \) to \( s_{t+1} \) at the next time step.

Then for a current state \( s_t = i \) and next state \( s_{t+1} = j \) the transition probability from \( i \) to \( j \) can be written as:

\[ P_{ij} = P[s_{t+1} = j | s_t = i] \]  

(2)
We can now construct the state transition matrix $P$ of size $n \times n$, where $n$ is the number of states. Each entry at $P$ is a probability $P_{ij}$ (so that $P_{ij} = P_{ij}$) that defines the probability of transitioning from each current state $i$ for $i \in n$ to every possible next state $j$ so that:

$$\sum_{j=1}^{n} P_{ij} = 1. \quad (3)$$

We define a Markov Decision Process (MDP) [35] as a tuple of a finite set of states $S$ where every state satisfies the Markov Property, a finite set of possible transformations or in other words actions that can be performed on $s \in S$, defined by $A$, the state transition matrix $P$ and a reward function $R^s_\tau$ which is the expected reward at the next time step conditioned to the current state $s$ and action $a \in A$ defined as follows:

$$R^s_\tau = E[R_{t+1} \mid s_t = i, A_t = a], \quad (4)$$

where $E$ indicates the expected value of a random variable\(^1\) and $R_{t+1}$ indicates the value obtained by performing $a$ at state $s_t$ which is referred to as the reward received at the next time step $t + 1$.

We can now revisit the state transition probability $P_{ij}$ and condition it to some action $a \in A$. $P_{ij}$ can then be written as:

$$P^a_{ij} = P[S_{t+1} = j \mid s_t = i, A_t = a] \quad (5)$$

which shows the probability of transitioning from state $i$ to $j$ after performing action $a$ on the environment at time step $t$. One could initially think of $P_{ij}$ as the ‘intrinsic’ probability of an environment changing states due to its internal dynamics. Then action $a$ could be seen as an external agent acting on that environment and affecting the probability of some transition.

Then if we assume that we select an action at some state with some probability according to policy $\pi(\cdot): S \to A$ then we can say that $\pi(a \mid s)$ is the probability of selecting action $a$ at state $s$, where clearly $\sum_{a \in A} \pi(a \mid s) = 1$. Then the following is true for the transition probability from current state $i$ to $j$ and expected reward:

$$P^\pi_{ij} = \sum_{a \in A} \pi(a \mid i) \ P^a_{ij} \quad (6)$$

$$R^\pi_i = \sum_{a \in A} \pi(a \mid i) \ R^a_i \quad (7)$$

\(^1\) The expected value of a discrete random variable is the average of all possible values that the variable can take weighted by the probability of that value to actually occur.
where $P_{ij}$ is the sum of the probabilities of transitioning from current state $i$ to $j$ given every possible action $a$ on that state, weighted by the probabilities of taking that action as indicated by policy $\pi()$. $R_i^a$ is the expected reward of being at state $i$ and taking every possible action $a$, weighted by the probability of taking that action according to $\pi()$.

We have outlined the basics of a Reinforcement Learning environment in terms of an MDP and can now proceed the discussion towards finding an \textit{optimal policy}. There are a number of algorithms, either model-based\(^2\) or model free\(^3\), that can achieve this, but for the purpose of this paper we only focus on Q-Learning as it is the main component of a DQN.

Assuming that actions are selected at each time step according to some \textit{(behavior) policy} $\pi()$; $S \rightarrow A$, then the true value; that is the \textit{actual} expected reward of taking action $a \in A$ at state $s$ and then continue to select actions according to $\pi()$ at each time step is defined as follows:

$$Q_\pi(s, a) = E[R_1 + \gamma R_2 + \gamma^2 R_3 + \ldots + \gamma^{t-1} R_t | S_0 = i, A_0 = a]$$ (8)

where $\gamma$ is the discount factor which is used to ensure convergence of the algorithm and also determines the tradeoff between immediate and future rewards. For example, future rewards are unknown to the agent thus it may be more convenient to value immediate rewards more by setting $\gamma$ to a small value. The action-value function $Q_\pi(s, a)$ shows the cumulative expected total reward after taking action $a$ at state $s$ and then continue selecting actions for every state according to some policy $\pi$ discounted by $\gamma^{t-1}$, until some final state. The exponent of $\gamma$, $t$, corresponds to the time step the reward was received, where we assume for convention that the first time step begins at $t = 0$.

In the above scenario we can clearly state that optimal action-value function $Q^*(s, a) = \max Q_\pi(s, a)$. That is, instead of selecting an action probabilistically for each state, we select the action that yields the highest expected cumulative future reward. We refer to \textit{optimal policy} as the process of greedily selecting action $a$ that yields $\max Q_\pi(s, a)$. Hence, by greedily selecting the action at each state that has been shown to maximize future rewards i.e. has the maximum expected reward, we maximize the agent’s probability of actually receiving the maximum possible reward during interaction with the environment from some initial state to some final state. This is true as $Q^*(s, a)$ obeys an important identity known as \textit{Bellman Equation}\(^{[20]}\). As shown in the rest of this section however, in order to act greedily we must have first approximated the true value of $Q^*$.

\textbf{Q-Learning}

The goal of a Reinforcement Learning agent is to maximize the reward received at the end of an episode in the context of PBNs\(^4\), where an episode is a sequence of states of the environment starting from some initial state $s$ to some terminal state $s'$. This can be achieved by approximating the actual $Q^*(s, a)$ and then greedily selecting the action that returns the

\(^2\) Model-based methods in the Reinforcement Learning context are methods that require full knowledge of the MDP i.e. the state transition matrix $P$.

\(^3\) Model-free methods do not require knowledge of the MDP and can learn directly by observing and interacting with the environment.

\(^4\) Q-Learning can also learn in non-episodic tasks, that is tasks that do not have an explicit final state.
highest expected reward. Q-Learning is [14] a model-free, off-policy\(^5\) algorithm under the umbrella of Temporal Difference (TD) learning [36] defined as follows:

\[
Q(s_t, a_t) \leftarrow Q(s_t, a_t) + \alpha [R_{t+1} + \gamma \max_{a'} Q(s_{t+1}, a') - Q(s_t, a_t)]
\]  

(9)

where \(\{R_{t+1} + \gamma \max_{a'} Q(s_{t+1}, a')\}\) is called the TD-Target,

\[
[R_{t+1} + \gamma \max_{a'} Q(s_{t+1}, a') - Q(s_t, a_t)]
\]  

(10)

is called the TD-Error and \(\alpha\) is a constant, \(0 < \alpha \leq 1\), that determines how fast the agent forgets past experiences. \(Q^*(s, a)\) can now be approximated iteratively by selecting actions at each time step with the use of \(\epsilon\)-greedy policy algorithm, where \(\epsilon\) is the probability of randomly selecting an action \(a\) at each time step and \((1 - \epsilon)\) of greedily performing the action with the maximum expected reward determined by \(\max_{a} Q(s_t, a)\). The value of \(\epsilon\) starts from 1 and decreases towards a constant value \(\min_{\epsilon}\) at every time step. After an action is selected \(Q(s_t, a_t)\) is updated according to (9). \(Q\) has been proved to converge to \(Q^*\) with probability 1 [36]. The number of updates and environment interactions required to approximate \(Q^*\) depends on the problem domain.

Before we conclude the discussion on Markov Decision Process and Q-Learning, it is important to note that Q-Learning is a model-free algorithm. It does not require any advance knowledge of the MDP, it can directly learn by performing actions on the environment and observing rewards received as well as state transitions. As we show in the following sections if combined with a function approximator it allows for policies to be determined for large state-space problems. This is one of our main contributions of applying Deep Q Learning to the controllability problem of PBNs.

For a more detailed explanation of the above concepts the reader is referred to [14], [20], [36].

4 **Probabilistic Boolean Networks**

In this section, we briefly explain Probabilistic Boolean Networks. We only explore concepts that are useful in the context of Reinforcement Learning and our problem formulation. For a more detailed explanation the reader is referred to [7].

Probabilistic Boolean Networks (PBNs) were introduced as a framework for modelling the dynamics of Gene Regulatory Networks (GRNs). A PBN consists of \(n\) different nodes where each node corresponds to a specific gene in a GRN. Each node can take one of two binary values \(\{0, 1\}\). A node with a value of 0 represents a gene that is not expressed, while a value of 1 corresponds to a gene that is expressed in the network. The value of each node is functionally dependent on a Boolean function \(f^j_i\) assigned with some probability out of a

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\(^5\) Off-Policy refers to learning in the context of Reinforcement Learning with the use of two policies, a target policy \(\pi\) and a behaviour policy \(\mu\). As showed we use \(\epsilon\)-greedy (policy \(\mu\)) to select an action to perform on the environment, but use \(\max_{a'} Q(s_{t+1}, a')\) (policy \(\pi\)) to select an action to calculate the TD target.
set of Boolean functions $F^i$ with finite cardinality, as well as other nodes that are directly connected to that node and act as an input to the assigned Boolean function. In the case that each node is assigned a set of Boolean functions each containing only a single function then this refers to the case of standard Boolean Networks (BNs) [2]. As mentioned very briefly in Section I, PBNs are an extension to BNs allowing the assignment of a different Boolean function to a node at each time step. The motivation behind this addition is mainly to incorporate uncertainty found in the data of GRN studies and biological models themselves.

To give a formal definition of a Probabilistic Boolean Network, let us take the case of a GRN with $n$ nodes and state space $2^n$. We refer to node $i$ as $g_i$ and assume that its expression at some time step $t$ is denoted by $g_i(t)$. In other words, $g_i(t) = 1$ would indicate that gene $i$ is expressed, while $g_i(t) = 0$ vice versa. Thus, we can construct a vector $G^n(t) = \{g_1(t), g_2(t), ..., g_n(t)\}$ where $G^n(t)$ represents the state $h$ of the PBN at time $t$, also known as Gene Activity Profile (GAP) [8] in the context of GRNs. Each node $g_i$ is assigned a set of Boolean functions:

$$F^i = \{f^i_1, f^i_2, ..., f^i_{l(i)}\}$$

where $l(i)$ is the number of functions in the set $F^i$ of gene $g_i$. The value of $g_i(t + 1)$ is dependent on the values of its input nodes at time $t$ and function $f^i_k$ assigned to it. Assuming for $g_i(t + 1)$ the function selected is $f^i_k$ and input nodes $\text{inp}^i$ are $g_{a}(t), g_{b}(t)$, then $g_i(t + 1) = f^i_k(\text{inp}^i) = f^i_k(g_a(t), g_b(t))$.

Each function $f^i_k \in F^i$ has a probability of being assigned to node $g_i$ at time step $t$, $c^i_k$ where:

$$\sum_{k=1}^{l(i)} c^i_k = 1 \quad (12)$$

We assume for our implementation that assignment of Boolean functions for each node $g_i$ is independent, meaning that the probability $\mathcal{P}_{\mathcal{F}_z}$ of a specific network $\mathcal{F}_z$ to occur is:

$$\mathcal{P}_{\mathcal{F}_z} = \mathcal{P}(f^1_k, f^2_m, ..., f^n_j) = c^1_k c^2_m ... c^n_j \quad (13)$$

where the probability of $\mathcal{F}_z$ is equal to the product of the probabilities of these specific Boolean functions being selected at each time step.

Thus $\mathcal{F}_z$ is a vector function comprised of $f^1_k, f^2_m, ..., f^n_j$ and can be written as: $\mathcal{F}_z = f^1_{z_1}, f^2_{z_2}, ..., f^n_{z_n}$, where $f^1_{z_1} = f^1_k, f^2_{z_2} = f^2_m, ..., f^n_{z_n} = f^n_j$.

We can now state that the possible network realizations $N$, where $N$ is the number of vector functions, $\mathcal{F}_1, \mathcal{F}_2, ..., \mathcal{F}_N$ is:

$$N = \prod_{k=1}^{n} l(k) \quad (14)$$
Thus, the probability of transitioning from state $G^h(t) \rightarrow G^k(t + 1)$ at the next time step is:

$$P\left[[g_1(t+1), g_2(t+1), ..., g_n(t)] \mid [(g_1(t), g_2(t), ..., g_n(t))]\right] = \sum_{\mathcal{F}_t} \mathcal{P}_{\mathcal{F}_t}$$

We can now construct the transition probability matrix $P$ comprised of $n \times n$ entries where entry $P_{h,k} = T_{h,k}$ indicates the probability of transitioning from current state $h$ to every possible next state $k$.

**Example 1**

Assume that we are given a PBN of size $n = 3$, $(g_1(\cdot), g_2(\cdot), g_3(\cdot))$, where $g_i(\cdot)$ indicates the value of node $g_i$ at some arbitrary time step and three sets of vectors functions $F^1$, $F^2$, $F^3$ where:

$$F^1 = \{\text{AND, } c_1^1 = 0.95 \quad \text{OR, } c_2^1 = 0.05\}$$

$$F^2 = \{\text{OR, } c_2^2 = 1\}$$

$$F^3 = \{\text{AND, } c_1^3 = 0.73\quad \text{OR, } c_2^3 = 0.18\quad \text{XOR, } c_1^3 = 0.09\}$$

The connectivity of the PBN is shown below in Fig. 1. The truth table for that PBN is shown at Table I.

The number of possible network realizations at each time step is $N=6$. So, for example when we are at state 101 as we can see from the truth table there are two possible state transitions 111 and 110. There are four network realizations that can yield state 111 and two for state 110.
Thus, following equations (13) and (15):

\[
\mathcal{P}_{101,111} = \sum_{\mathcal{F}; f_1^{1,1} = 1, f_2^{1,0} = 1, f_3^{0,0} = 1} \mathcal{P}_{\mathcal{F}_i} = \mathcal{P}_{\mathcal{F}_2} + \mathcal{P}_{\mathcal{F}_3} + \mathcal{P}_{\mathcal{F}_6} + \mathcal{P}_{\mathcal{F}_4} + \mathcal{P}_{\mathcal{F}_5}
\]

\[
\mathcal{P}(f_1^{1,1}, f_2^{1,0}, f_3^{0,0}) + \mathcal{P}(f_1^{1,1}, f_2^{0,0}, f_3^{1,1}) + \mathcal{P}(f_2^{1,1}, f_1^{0,0}, f_3^{0,0}) + \mathcal{P}(f_2^{1,1}, f_1^{1,1}, f_3^{0,0}) + \mathcal{P}(f_2^{1,1}, f_1^{0,0}, f_3^{1,1})
\]

\[
= c_1^1c_2^2c_3^3 + c_1^2c_1^2c_3^3 + c_2^1c_1^2c_3^3 + c_2^1c_1^2c_3^3
\]

\[
= 0.95 \cdot 1 \cdot 0.18 + 0.95 \cdot 1 \cdot 0.09 + 0.05 \cdot 1 \cdot 0.18 + 0.05 \cdot 1 \cdot 0.09
\]

\[
= 0.27
\]

Following the same method as above we can determine: \(\mathcal{P}_{101,111} = 0.73\)

We can now construct the transition probability matrix \(P\) following (15) where:

\[
P = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0.95 & 0 & 0 & 0 & 0.05 & 0 & 0 & 0 \\
0 & 0 & 0.73 & 0.27 & 0 & 0 & 0 & 0 \\
0 & 0 & 0.69 & 0.26 & 0 & 0 & 0.04 & 0.01 \\
0 & 0 & 0.69 & 0.26 & 0 & 0 & 0.04 & 0.01 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.73 & 0.27 \\
0 & 0 & 0.09 & 0.86 & 0 & 0 & 0.01 & 0.04 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.09 & 0.91
\end{bmatrix}
\]

where for example entry (7,4) is 0.86 = \(\mathcal{P}_{\mathcal{F}_1} + \mathcal{P}_{\mathcal{F}_2}\).
With the use of the transition probability matrix $P$, we can determine the State Transition Graph (STG) of the PBN shown in Fig. 2.

| $g_1(\cdot), g_2(\cdot), g_3(\cdot)$ | $f_1^1$ | $f_2^1$ | $f_3^1$ | $f_1^3$ | $f_2^3$ | $f_3^3$ |
|------------------------------------|---------|---------|---------|---------|---------|---------|
| 000                               | 0       | 0       | 0       | 0       | 0       | 0       |
| 001                               | 0       | 1       | 0       | 0       | 0       | 0       |
| 010                               | 0       | 0       | 1       | 0       | 1       | 1       |
| 011                               | 0       | 1       | 1       | 0       | 1       | 1       |
| 100                               | 0       | 1       | 1       | 0       | 1       | 1       |
| 101                               | 1       | 1       | 1       | 0       | 1       | 1       |
| 110                               | 0       | 1       | 1       | 1       | 1       | 0       |
| 111                               | 1       | 1       | 1       | 1       | 1       | 0       |
| $c_k$                             | 0.95    | 0.05    | 1       | 0.73    | 0.18    | 0.09    |

Table 1: The truth table shows the value of each node at the next state given current state $g_1(\cdot), g_2(\cdot), g_3(\cdot)$ and selection of some Boolean function $f_k^i$ for each node with probability $c_k$.

By observing the STG one can notice that there are two sets of states that once visited the probability of transitioning to some other state outside of these sets is 0. To be exact the two sets are $\text{A}_1 = \{000\}$ and $\text{A}_2 = \{111, 010, 011, 110\}$ as shown in Fig. 3. These sets are known as attractors where $\text{A}_1$ corresponds to an absorbed state and $\text{A}_2$ to an irreducible Markov Chain [8]. $\text{A}_1$ and $\text{A}_2$ correspond to what we have referred to in Section I as collective gene behavior in the context of GRNs.

By the time $\text{A}_1$ or $\text{A}_2$ is visited the probability of visiting any other state outside the set is 0. This can easily be verified by examining $P$, where the probability of transition from 000 to 000 is $p_{000,000} = 1$ and the sum of the probabilities of transition from any state in $\text{A}_2$ to any other state in $\text{A}_2$ is also 1 as shown below:

$$\sum_{i \in \text{A}_2} \sum_{j \in \text{A}_2} p_{ij} = 1$$

(16)

Here we conclude our discussion on PBNs. For a more in-depth explanation the reader is referred to [8].

5  Controllability of Probabilistic Boolean Networks: Problem Formulation

As we showed in Section IV a PBN starting from some state will eventually transition to an attractor which is either an absorbed state or a set of states in an irreducible Markov Chain. The probability of naturally transitioning to some attractor as we will discuss in this Section is dependent on the initial state of the PBN. This behavior is natural in the context of
GRNs, thus PBNs, and cannot be avoided without some kind of intervention. However, as we explained in Section I, transitioning to some attractor may be undesired.

**Figure 2** The State Transition Graph of the PBN shows all possible state transitions from each state along with their probabilities. Some probabilities have been omitted for clarity.

**Figure 3** $A_1 = \{000\}$ and $A_2 = \{111, 010, 011, 110\}$ are the attractors of the PBN.
Controllability aims at making targeted interventions at each time step to the state of a PBN in order to decrease the probability of transitioning to an undesired attractor, while increasing the probability of visiting a desired state or attractor.

**Intervention**

Intervention in a PBN is the process of causing a perturbation to a node and changing its value from 0 to 1 or vice versa. In this paper, we attempt to control a PBN by allowing at each time step the minimum possible interventions. That is either no intervention which implies that the PBN naturally transitions to some next state as defined by its probabilities in $P$ or a maximum of one intervention to the current state. In the latter, the intervention causes the state to change to some new state which will then naturally transition to some other state according to $P$. Thus, our goal is to make the least possible such interventions in a specified time horizon in order to maximize the probability of the PBN transitioning towards a desired attractor. We define intervention at time step $t$ by:

\[
I_n(G^h(t), v)
\]

$G^h(t)$ is the state of the network at the time step $t$ of the intervention and $v$ indicates the position $v$ of the $n$ nodes in the PBN that the intervention will occur, where $v$ is an integer $v \in [0, n]$. $v = 0$ indicates no intervention and $v = i$ for $0 < i \leq n$ indicates intervention at node $g_i$.

In the experiments in Section VIII we have been concerned with maximizing the probability of a PBN transitioning towards a desired attractor. It should be noted that, our proposed method would also work for non-attractor states, the only difference being that in order to remain in a non-attractor state we should intervene indefinitely.

Let us revisit the case of the PBN analyzed in Section III. Assume that the starting distribution is uniform for all states, meaning that the probability of the PBN starting at a specific state is the same for all other states and is captured by:

\[
D^0 = \begin{bmatrix} \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{bmatrix}
\]

Let us also assume that the absorbed state in $A_1$ is a desired attractor. Throughout the rest of this paper we will refer to a desired attractor as a target attractor. It is clear that the probability of the PBN transitioning to $A_1$ is very small. To be exact, there are only two possible ways for that PBN to naturally transition to $A_1$: either starting at $A_1$ with probability $\frac{1}{8}$ or starting at state 001 and transitioning at the next time step to state 000 with probability $\frac{1}{8} \cdot 0.95$. We can now determine the probability of the PBN naturally ending up in $A_1$:

\[
\mathcal{P}[A_1 \mid D^0] = \frac{1}{8} \cdot 1 + \frac{1}{8} \cdot 0.95 = 0.24
\]

which is the probability of transitioning to attractor $A_1$ given starting state distribution $D^0$ [8]. Likewise, we can determine the probability of transitioning to $A_2$ which is $\mathcal{P}[A_2 \mid D^0] = 0.76$. 

However, as we mentioned earlier, we assume that $\mathbb{A}_2$ should be avoided. Thus, we need to determine a way to intervene in the PBN so that it maximizes the probability of transitioning to our target attractor $\mathbb{A}_1$.

**Example 2**

Assume that the PBN shown in Section IV is initialized at state 101. Then the probability of the PBN ever *naturally* transitioning to attractor $\mathbb{A}_1$ is 0. If, however, we purposely intervene at time step $t$ at state $G^{101}(t)$ as follows:

$$In(G^{101}(t), 1)$$

$G^{101}(t)$ then becomes $G^{001}(t)$. The probability now of transitioning from state $G^{001}(t)$ to $G^{000}(t + 1)$ is:

$$P_{001, 000} = 0.95$$

Thus, by making a single intervention to state $G^{101}(t)$ we have increased the probability of transitioning to $\mathbb{A}_1$ from 0 to 0.95. This is an intuitive solution that can easily be determined by just looking at the STG in Fig. 2.

If we examine the STG, we can see that another solution exists. The probability of *naturally* transitioning from state $G^{101}(t)$ to state $G^{110}(t + 1)$ is $P_{101, 110} = 0.73$ where we can intervene at first node $In(G^{110}(t + 1), 1)$. Hence $G^{110}(t + 1)$ becomes $G^{010}(t + 1)$ and the probability at the third time step of transitioning to $G^{010}(t + 2)$ is $P_{010, 010} = 0.73$ where we can make a final intervention $In(G^{010}(t + 2), 2)$ to force the network into $\mathbb{A}_1$. The probability of the above scenario is dependent on two state transitions occurring consecutively. That is, $G^{101}(t) \rightarrow G^{110}(t + 1)$ and $G^{010}(t + 1) \rightarrow G^{010}(t + 2)$ and the probability is $P_{101, 110} \cdot P_{010, 010} = 0.53$. Given the above scenario our interventions are: $In(G^{101}(t), 0)$, $In(G^{110}(t + 1), 1)$, $In(G^{010}(t + 2), 2)$. However, it is clear that this approach yields lower probability of controlling the PBN towards $\mathbb{A}_1$.

Similarly, other approaches may exist where the sequence of interventions differs according to the starting state and state transitions occurring thereafter. However, controllability is independent of the initial state as we will also see when we train the Double Deep Q Network to find a successful control policy $\pi$. Also, in our solution we do not need to have any knowledge related to the transition probabilities. The above example was used as a case to show that while more than one possible way to achieve control exists, the first of the two presented is more preferable as it will achieve the desired control with higher probability. Likewise, given enough training episodes the DQN tends towards making such interventions that increase the probability of successfully controlling the PBN with no knowledge of $P$.

### 6 Deep Q Network with Double Q Learning and Prioritized Experience Replay

Having defined the control problem in the context of PBNs, we discuss in this section the mechanics of a DQN with Double Q Learning, as well as the concept of Prioritized Experience Replay and explain why these implementation choices were made.
The main problem faced by Q-Learning (discussed in Section II & III) is that most real-world problems have very large state-action spaces. Thus, learning and storing the values of all the actions for every state separately becomes inefficient and not scalable. Instead, we can use a function approximator to learn a parametrized form \( Q(s, a; \theta) \) where \( \theta \) are the parameters of the approximator. Following equation (9) the parameter updates in the context of Q-Learning are:

\[
\theta_{t+1} = \theta_t + \alpha [R_{t+1} + \gamma \max_{a'} Q(s_{t+1}, a'; \theta) - Q(s_t, a_t; \theta)] \nabla_{\theta} Q(s_t, a_t; \theta) \tag{19}
\]

A DQN is a multilayer neural network with inputs being the current state observation of the environment and outputs a vector of the expected action values for that state \( Q(s, \cdot; \theta) \), where \( \theta \) are the network parameters. The goal of the DQN is to iteratively update \( \theta \) in order to approximate \( Q^*(s, a; \theta) \). The DQN is trained by minimizing a (different) sequence of loss functions at each iteration:

\[
L_i(\theta) = (R_{t+1} + \gamma \max_{a'} Q(s_{t+1}, a'; \theta_i) - Q(s_t, a_t; \theta))^2 \tag{20}
\]

One important suggestion by [13] was the use of a separate network to determine the TD-Target (10). The separate network (target DQN) is initialized with the same parameters as the main DQN (also called policy DQN), but has its parameters updated every \( k \) iterations. That is, the expected Q values of the target DQN are fixed and every \( k \) iterations the parameters of the policy DQN are copied to the target DQN. Thus, \( \theta_i^- \) are the parameters of the DQN at some previous iteration and \( \theta_i^- = \theta_i \) every \( k \) iterations. Using fixed Q TD-Targets avoids large oscillations in expected Q values that would be caused by immediately updating the policy network parameters at each iteration and leads to more stable learning [13].

Differentiating (20) we obtain the following gradient:

\[
\nabla_{\theta_i} L_i(\theta) = (R_{t+1} + \gamma \max_{a'} Q(s_{t+1}, a'; \theta_i^-) - Q(s_t, a_t; \theta_i^-)) \nabla_{\theta} Q(s_t, a_t; \theta) \tag{21}
\]

which can be used to update the DQN parameters using stochastic gradient descent.

**Double DQN**

Double Deep Q Network was proposed by [17]. It is an implementation of Double Q Learning [16] in the context of Deep Reinforcement Learning. Double Q Learning was proposed as an alternative to the original Q Learning which suffered from overestimation of Q values. This is caused because of the positive bias incurred due to always selecting the action with the maximum Q value as an approximation to the maximum expected reward. As discussed in Section III, Q Learning guarantees to converge to \( Q^* \) however overestimation of Q values significantly slows down learning. Double Q Learning addresses this problem with the use of two Q functions \( Q^A \) and \( Q^B \) (double estimator). The same process as the one discussed under Q Learning in Section III is followed in regard to environment interaction, however after selecting an action, \( Q^A \) or \( Q^B \) is randomly updated in terms of the other. For example, after performing action \( a \) and observing next state \( s_{t+1} \) and reward \( R_{t+1} \), if we choose to update \( Q^A \) we use \( Q^A \) to obtain the action with maximum expected reward for state \( s_{t+1} \),

\[
a' = \arg \max_a Q^A(s_{t+1}, a)
\]

and update \( Q^A \) as follows:
\[Q^a(s_t, a_t) \leftarrow Q^a(s_t, a_t) + \alpha[R_{t+1} + \gamma Q^b(s_{t+1}, a') - Q^a(s_t, a_t)] \quad (22)\]

and vice versa for the case of \(Q^B\). In the context of Deep Reinforcement Learning [17] two networks as in the case of the DQN [13] are retained and equation (20) becomes:

\[L_i(\theta_i) = (R_{t+1} + \gamma \max Q(s_{t+1}, a'; \theta_i) - Q(s_t, a_t; \theta_i))^2 \quad (23)\]

The update process remains the same where the parameters \(\theta_i\) are copied to \(\theta_i^-\) every \(k\) iterations.

**Prioritized Experience Replay**

During the training phase the agent interacts with the environment by observing state \(s_t\) and performing action \(a_t\) either randomly with probability \(\epsilon\) or greedily with probability \((1 - \epsilon)\) by selecting the action with the highest \(Q\) value. After taking action \(a_t\) at state \(s_t\), the environment transitions to state \(s_{t+1}\) and the agent receives reward \(R_{t+1}\). The transition \((s_t, a_t, R_{t+1}, s_{t+1})\) is stored in a replay (memory) buffer \(D\). This transition is an experience received at time step \(t\) where \(e_t = (s_t, a_t, R_{t+1}, s_{t+1})\). Every time step \(t\) a batch of experiences is sampled from \(D\) and used to update the Double DQN parameters.

The main advantage of using Experience Replay [15], [18] in general is that training a network from consecutive samples directly obtained from the environment is inefficient because of the strong correlations in this data, which can cause a high variance in the network parameter updates [13]. Also, rare experiences can be forgotten rapidly because of the way \(Q\) values are updated. Such experiences are useful because if the sampled experiences are dominated by frequently occurring ones, the DQN can become biased towards selecting actions that proved useful only for those. Experience Replay breaks this correlation and avoids large oscillations of the network parameters leading to more stable learning, while allowing experiences to be seen more often, hence, also avoiding rare experiences from being forgotten fast [15], [18].

Prioritized Experience Replay [18] is an improvement to the previously discussed Experience Replay that uniformly samples experiences at random from a replay memory [15]. The motivation behind Prioritized Experience Replay is that an agent can learn more from some experiences than others. Experiences with a high learning progress, measured by the magnitude of their TD-Error (11) \(\delta\), have a higher probability of being sampled.

In our implementation we use proportional prioritization compared to rank-based prioritization, as experimentally it yielded slightly better results. Thus, we focus our discussion here to proportional prioritization. For more information the reader is referred to [18].

The probability of an experience being sampled is therefore:

\[P(i) = \frac{p_i^\omega}{\sum_k p_k^\omega} \quad (24)\]

where \(p_i = |\delta| + c\) is the priority of sample \(i\), \(c\) is a small constant to prevent experiences with zero TD-Error from never being replayed and exponent \(\omega\) determines the magnitude of prioritization, where \(\omega = 0\) corresponds to the uniform case previously discussed.
However, prioritizing replay creates a bias in learning towards samples with high TD-Error as they are sampled more often. To compensate for this bias during learning Importance Sampling weights are used:

\[ w_i = \left( \frac{1}{L} \frac{1}{P(i)} \right)^\beta \]  

where \( L \) is the size of the replay memory and exponent \( \beta \) is used to anneal the amount of Importance Sampling over training episodes. In other words, \( w_i \) indicates how ‘much’ to learn for a specific sample and can be folded in the learning process as a factor in the gradient of (20):

\[ \nabla_{\theta_i} L_i(\theta) = w_i(R_{t+1} + \gamma Q(s_{t+1}, \text{argmax}_{a'} Q(s_{t+1}, a'; \theta)); \theta_i) - Q(s_t, a_t; \theta_i) \nabla_{\theta_i} Q(s_t, a_t; \theta_i) \]  

which can be used to update the network parameters using stochastic gradient descent. The unbiased nature of updates is most important towards the end of learning near convergence, as initially, the process of approximating \( Q^* \) is highly non-stationary [18]. Thus, \( \beta \) is annealed from initial value \( \beta_0 \) to 1 which is assigned only towards the end of training.

To provide a more intuitive explanation of the use of \( w_i \) one can think of Importance Sampling weights as an indication to the network of how much to change its parameters in order to minimize the large TD-Error. So, when the TD-Error is high this experience will most likely be sampled again, thus \( w_i \) indicates to the network to update its parameters, but not by much. Whereas when an experience with a low TD-Error is sampled it is very unlikely that it will be sampled again often. Thus, the network will update its parameters more aggressively towards minimizing the error, but since the error was small in the first place, not much will change as there is not a lot to learn from that experience.

In our implementation we make use both of a Double DQN and Prioritized Experience Replay in order to approximate \( Q^* \) and learn a policy \( \pi \) to control a PBN.

7 PBN as an environment for Reinforcement Learning

Before presenting our experiment results, in this Section we briefly discuss PBNs as an environment for Reinforcement Learning in regard to the concepts presented earlier.

As we discussed in previous sections the goal of a Reinforcement Learning agent (a Double DQN in our case) is to approximate the true \( Q \) function \( (Q^*) \) during training simply by interacting with the environment and observing state transitions and rewards received. This is critical, because as described in Section VI a Double DQN is a model free RL algorithm, meaning that this approach determines a control policy without any knowledge of the underlying dynamics of the PBN. In addition, the use of a function approximator to approximate \( Q \) eliminates the issue of storing each state-action \( Q \) value pair faced by previous methods such as those discussed in Section II.
A policy \( \pi \) can then be obtained according to the Q function approximated by the agent by acting greedily on the expected Q values; that is performing the action that maximizes the expected reward at the end of a control scenario i.e. reaching the target attractor in the context of controlling PBNs or the maximum number of time steps interventions are allowed. As we show in the Experiments & Results Section, we select the target attractor regardless of whether it is an absorbed state or an irreducible Markov Chain. The choice is based on which attractor naturally occurs the least, thus always attempting to control a PBN for the most challenging case.

In order to achieve successful control, correct reward assignments need to be made for every state transition in order for the agent to learn ‘useful’ Q values. These are then used to determine interventions that maximize the probability of a successful control.

In our implementations we chose to assign a reward of -2 for interventions (actions) that resulted in the next state being an attractor, but not the target attractor, a positive reward \( R \) greater than \( | -2 | \) for interventions that resulted in successful control and -1 for interventions that resulted in the next state being a non-attractor state. The choice behind the positive reward \( R > | -2 | \) depends on the state space of the PBN. In large PBNs successful control during training would initially occur rarely, thus a higher reward would result in a relatively higher TD-Error, hence stronger prioritization during PER and replay during learning. This is also demonstrated in the Experiments Section. The selection of -2 as a reward for non-target attractors is intuitive as entering an undesired attractor should be (highly) penalized since the PBN would exhibit some undesired behavior in the context of GRNs and may result in the PBN getting ‘trapped’ in this attractor depending on the number of maximum time steps we allow our agent to intervene. For example, if we want to attempt to control a PBN at a maximum of 5 time steps, that is by allowing at most 5 natural state transitions to occur while our agent is still allowed to intervene, if at time step 5 during training the agent directs the network to a non-target attractor the probability of eventually entering the target attractor; during when we can no longer intervene, would definitely be less than being in an a non-attractor state. The assignment of -1 for non-attractor states is so that the agent is encouraged to find interventions that will direct the network to the desired attractor as fast as possible and also avoid non-target attractors which have a greater negative reward. In other words, with that reward scheme the agent is indicated to generally prefer non-attractor states than non-target attractor states, but also avoid non-attractor states as they result in a negative reward, aiming to find the least possible interventions to reach the target attractor. It is important to note that successful control is still achievable by assigning \( R = -1 \) for all non-target attractors and non-attractor states, however we assign \( R = -2 \) for non-target attractors to emphasize the natural fact that non-target attractors are more undesirable in the context of GRNs than simple non-attractor states. In other words, the only knowledge needed to achieve control is simply the target attractor.

There is an apparent tradeoff in maximizing the probability of successful control and the number of time steps we allow the agent to intervene. Because if for example interventions are allowed for only two time steps the agent may discover interventions that achieve control less often than interventions discovered if we allowed say up to four interventions. This should be taken into account when considering control of PBNs in this case.

To explain this process in the context of MDPs and Reinforcement Learning let us give a brief example.
Example 3

Assume a PBN being in state $j$, also assume that state $x$ is our target attractor and $y$ the only other attractor. If an intervention at position $u$ is made at state $j$, $j$ then changes to some state $k$ that is identical to $j$ with the only difference being the node that the agent chose to intervene and switch its value. State $k$ at the next time step transitions with some probability defined by the underlying dynamics of the PBN; unknown to the agent, to some non-attractor state $z$ and receives reward $-1$. The experience obtained for this time step is $e_t = (s_t, a_t, R_{t+1}, s_{t+1}) = (j, u, -1, z)$. Likewise, if the agent then makes intervention at position $m$ at state $z$, $z$ then changes to $d$ and $d$ transitions to $x$ and receives reward $R$. The experience for this state is $e_t = (z, m, R, x)$. If it were to transition to $y$ the experience would be $(z, v, -2, y)$ and so on.

8 Experiment and Results

In this section we report on experiments after applying a Double DQN with Prioritized Experience Replay on PBNs of sizes $n = 7$ and $n = 10$. The experiments were run on a desktop machine of 2.60 GHz CPU, 16 GB RAM and a GeForce GTX 1080 Ti GPU. The PBN $n = 7$ was trained for 4 hours while $n = 10$ for 19 hours.

PBN with n=7

The connectivity of the PBN with 7 nodes is shown in Fig. 4 and its State Transition Graph is presented in Fig. 5. The PBN has two attractors $A_1$ and $A_2$ where $A_1 = \{0000000\}$ and $A_2 = \{1001100, 1111111, 1010001, 1111110, 1111101, 1111011, 1111010, 1111001, 1111000, 1101011, 1101010, 1101001, 1101000, 1100111, 1100110, 1100101, 1100100, 1100001, 1100000, 1101111, 1101110, 1101101, 1101100, 1100110, 1100101, 1100100, 1100001, 1100000, 1011111, 1011110, 1011101, 1011100, 1010110, 1010101, 1010100, 1010010, 1010001, 1010000, 1001111, 1001110, 1001101, 1001100, 1001010, 1001001, 1001000, 1000111, 1000110, 1000101, 1000100, 1000001, 1000000, 1011111, 1011110, 1011101, 1011100, 1011010, 1011001, 1011000, 1010110, 1010101, 1010100, 1010010, 1010001, 1010000, 1001111, 1001110, 1001101, 1001100, 1001010, 1001001, 1001000, 1000111, 1000110, 1000101, 1000100, 1000001, 1000000, 1011111, 1011110, 1011101, 1011100, 1011010, 1011001, 1011000, 1010110, 1010101, 1010100, 1010010, 1010001, 1010000, 1001111, 1001110, 1001101, 1001100, 1001010, 1001001, 1001000, 1000111, 1000110, 1000101, 1000100, 1000001, 1000000\}$ which are shown in Fig. 6.

The PBN is governed by the following Boolean functions assigned to each node. While we do not make use of any knowledge of the probabilities or the PBN’s structure in order to determine a control policy we have included them in order to demonstrate the complexity of the networks.

$$F^1 = \{\text{OR}, \ c^1 = 1\} \quad F^2 = \begin{cases} \text{AND}, & c^2_1 = 0.22 \\ \text{OR}, & c^2_2 = 0.17 \\ \text{XOR}, & c^2_3 = 0.61 \end{cases}$$

$$F^3 = \begin{cases} \text{OR}, & c^3_1 = 0.13 \\ \text{XOR}, & c^3_2 = 0.87 \end{cases} \quad F^4 = \{\text{AND}, \ c^4 = 1\}$$
Let the PBN naturally transition to attractors. We noted that attractor $A_1$ only occurs with probability $P = 0.04$, so we selected $A_1$ as our target attractor to attempt and control the PBN for the most difficult case i.e. the case where the PBN would naturally transition to this attractor only 4% of the time. We also make random interventions to the network starting from every possible state until it is controlled. That is, we make a random intervention at each time step until the PBN reaches $A_1$. We noted that the average number of interventions needed are 150. So, we decided to attempt and control the PBN by allowing at most 7 interventions or approximately 5% of the random interventions that would result in successful control. Finally, we set successful reward $R = 3$.

![Figure 4](image)

**Figure 4** The PBN is comprised of 7 nodes where $g_1$ input nodes: $(g_1, g_5)$, $g_2$ input nodes: $(g_2, g_4)$, $g_3$ input nodes: $(g_5, g_7)$, $g_4$ input nodes: $(g_3, g_6)$, $g_5$ input nodes: $(g_1, g_7)$, $g_6$ input nodes: $(g_2, g_5)$ and $g_7$ input nodes: $(g_3, g_2)$.

### Double DQN with Prioritized Experience Replay Architecture (PBN, $n = 7$)

We constructed a Deep Neural Network with an input layer of size $n$, two hidden layers each of 100 rectifier units and a linear output unit of size $n + 1$ where $n$ corresponds to the expected $Q$ values of the possible network interventions and the extra unit to the $Q$ value of taking no action i.e. no intervention. The behavior policy during training was $\varepsilon$-greedy with $\varepsilon$ starting at 1 and decaying to 0.01 towards the end of training, where it stays fixed. The selected discount factor $\gamma$ was set to 0.8 to weight future rewards strongly, as in PBNs the controller may end up finding the attractor after a large number of steps. For Prioritized Experience Replay we set $\omega = 0.6$ and linearly anneal $\beta$ from 0.4 to 1 after 75% of training as
in [18]. Experimentally these hyperparameter choices yielded the best noted results, but intuitively we do want to prioritize aggressively, but not dominate the sampled experiences with only large TD-Error experiences. The size of the Replay Buffer selected is 5120 in order to retain experiences for long enough, but at the same time update them often.

During training the algorithm used for optimizing the network parameters is RMSProp. We use Huber loss as the loss function to minimize the network’s TD-Error. The reason behind this choice is to avoid exploding gradients by error clipping [13]. We also sample a batch of 128 experiences from the replay memory every time we are about to update the network parameters. We train the network for 1000000 episodes and update our second estimator (target DQN) every 100 episodes. During training we evaluate the network performance by plotting the cumulative average reward per episode over all episodes shown in Fig. 7.

**Figure 5** The STG of PBN with 7 nodes is presented. We have not included the state labels for clarity reasons, but by carefully observing the STG one can notice the highly probabilistic state transitions, where one state has many possible next states.
Figure 6 Attractor $A_2$ is shown on the left and attractor $A_1$ is shown on the right.

Results (PBN, $n = 7$)

After training is complete, we evaluate the network by initializing the PBN from every possible state and attempt to control it to $A_1$ multiple times. During testing a greedy policy is used. The state of the PBN at each time step is the input to the Double DQN which outputs the expected reward for each possible intervention (including no intervention). The action with the highest expected reward is selected and performed to the environment. By allowing up to 7 interventions (as in training) we always achieved 100% controllability over all possible states.

However, one might notice that the cumulative average reward rapidly increases after about 350000 episodes which at first sight would not seem to be the expected behavior if an attractor is reached after the 7th intervention.
Figure 7 The cumulative average reward is plotted over the training episode. After 350000 episodes the cumulative reward begins to increase rapidly.

Initially, the expected graph in this case would be a rapid decrease that continues until the last episodes with a decreasing rate of decay. If we were to consider the best-case scenario for every episode; that is visiting six non-attractor states before reaching \( \mathbb{A}_1 \), the average reward would be 0.96, which does not justify an increase in the cumulative reward. However, as mentioned in Section VI we encourage our agent to make such interventions as to control the PBN with as little interventions as possible. One possible way for the agent to receive a positive reward is to avoid non-target attractor states and control the PBN with at most 3 interventions, and when more than 3 interventions are needed reduce the number of negative rewards received. Indeed, if we test the same DDQN that was trained to control the PBN by allowing a maximum number of interventions to be 7 and during testing restrict the number of interventions to 3 we get a success rate of 60%. That means that the agent determines a way to control most of the states with at most 3 interventions and that for the states where more than 3 interventions are required the agent finds a way to minimize the negative reward received; that is avoid undesired attractor states. Otherwise, we would not obtain such an increase in the average cumulative reward. We can also view this increase after plotting the average reward (not cumulative) per epoch\(^6\) as shown in Fig. 8.

Thus, we can conclude that our agent indeed tries to find the fastest possible way to control the PBN while also avoiding non-target attractor states, which in this case are states found in \( \mathbb{A}_2 \).

**PBN with \( n=10 \)**

The connectivity of the PBN with 10 nodes is shown in Fig. 9.

The PBN has 3 attractors \( \mathbb{A}_1 = \{0000000000\} \), \( \mathbb{A}_2 = \{1000000000\} \) and \( \mathbb{A}_3 = \{1111000111, 1111001110, 1010010011, 1111001011, 1111001010, 1010010010, 1111000111, 1111000110, 1000101111, 1111000011, 1111000011\}, \)

\(^6\) For our experiments one epoch corresponds to 5000 episodes of training.
Figure 8 The average reward per epoch increases until it plateaus towards the end of training, indicating that the agent has found ways to control the PBN with less interventions than initially allowed and avoids visiting non-target attractors.
Figure 9 The PBN is comprised of 10 nodes. The inputs of each node are the nodes pointing to it.

We have not presented a figure for the STG or attractors due to the large state spaces and image size constraints.
The PBN is governed by the following Boolean functions assigned to each node.

\[
F^1 = \{ OR, \quad c_1^1 = 1 \} \quad F^2 = \begin{cases} OR, & c_2^2 = 0.50 \\ AND, & c_3^2 = 0.25 \\ XOR, & c_4^2 = 0.25 \end{cases}
\]

\[
F^3 = \begin{cases} OR, & c_2^3 = 0.71 \\ AND, & c_3^3 = 0.29 \end{cases} \quad F^4 = \begin{cases} AND, & c_4^4 = 0.48 \\ OR, & c_5^4 = 0.52 \end{cases}
\]

\[
F^5 = \begin{cases} AND, & c_2^5 = 0.05 \\ XOR, & c_3^5 = 0.59 \\ OR, & c_4^5 = 0.36 \end{cases} \quad F^6 = \begin{cases} AND, & c_4^6 = 0.52 \\ OR, & c_5^6 = 0.48 \end{cases}
\]

\[
F^7 = \begin{cases} AND, & c_2^7 = 0.82 \\ XOR, & c_3^7 = 0.08 \\ OR, & c_4^7 = 0.10 \end{cases} \quad F^8 = \begin{cases} AND, & c_4^8 = 0.45 \\ XOR, & c_5^8 = 0.27 \\ OR, & c_6^8 = 0.28 \end{cases}
\]

\[
F^9 = \{ OR, \quad c_1^9 = 1 \} \quad F^{10} = \begin{cases} AND, & c_1^{10} = 0.01 \\ OR, & c_2^{10} = 0.99 \end{cases}
\]

In order to select a target attractor and set a time horizon for allowed interventions we followed the same process as in the case of the PBN with \( n = 7 \). After allowing the PBN to naturally evolve assuming a uniform starting distribution for all states we noted that \( A_1 \) only occurs with probability \( P = 0.0097, A_2 \) with probability \( P = 0.0107 \) and \( A_3 \) with probability \( P = 0.9796 \). We set our target attractor to be \( A_1 \) as its probability of naturally occurring is the least. We attempted to control the PBN starting from every possible state multiple times by random interventions and noted that the average interventions needed was 1387. We decided to allow the network to perform up to 11 interventions; that is approximately 0.8% of the average random interventions that would control the PBN. We also set the reward of successful control slightly higher than the PBN \( n = 7, R = 5 \). This PBN makes an interesting case for controllability as its possible network realizations at each time step are \( N=1296 \), which makes state transitions highly non-deterministic.

**Double DQN with Prioritized Experience Replay Architecture (PBN, \( n = 10 \))**

For this experiment we have kept most of the DDQN and PER parameters the same as for the \( n = 7 \). The size of the input and output units have been changed to match the size of the PBN and number of possible interventions. The discount factor \( \gamma \) was set to 0.9. The size of the memory buffer was changed to 10000 and we sampled experiences in batches of 1024. Finally, we let the network train for 2000000 episodes and update the second estimator every 400 episodes.

**Results (PBN, \( n = 10 \))**

After training is complete, we evaluated the network by initializing the PBN from every possible state and attempting to control it to \( A_1 \) multiple times. We followed the same greedy policy described under the PBN \( n=7 \) results. By allowing 11 interventions in this case however the agent achieved controllability on average of 99.75%. This result indicates that the network fails to always control 0.25% of the possible PBN states. As we mentioned in Section...
VII there is a tradeoff between allowed interventions and maximizing probability of controlling a state towards a target attractor. However, it is interesting to note that if we allow the same DDQN trained by allowing it to perform a maximum of 11 interventions, to perform 14 interventions during testing, it always achieved 100% controllability. The reason behind this result is in the mechanics of Q Learning. As explained in sections III and VI Q Learning aims to maximize the reward received. Hence, even if the network did not achieve in finding a policy that always achieves 100% controllability by at most 11 interventions, it manages after the 11th intervention to drive the PBN to a state that has previously been shown to evolve to states that are controllable. Thus, if the state naturally occurring after the 11th intervention has previously been controlled and the agent is allowed to intervene to that state, it will successfully drive it to the target attractor. To be more specific, let us refer to an actual control case. One of the states the DDQN often failed to control with 11 interventions is 1101101111. Over 11 time steps the DDQN makes the following interventions where the starting time step 0 is the initialized state of the PBN:

\[
\begin{align*}
\text{In}(G^{1110110111} (0), 10) & \quad \text{In}(G^{1111111011} (1), 4) \\
\text{In}(G^{1111110101} (2), 9) & \quad \text{In}(G^{1111111011} (3), 10) \\
\text{In}(G^{1111110101} (4), 10) & \quad \text{In}(G^{1101110101} (5), 10) \\
\text{In}(G^{1111110001} (6), 10) & \quad \text{In}(G^{1100010001} (7), 10) \\
\text{In}(G^{1000101010} (8), 8) & \quad \text{In}(G^{1000110000} (9), 1) \\
\text{In}(G^{0000101010} (10), 8)
\end{align*}
\]

After the last intervention \text{In}(G^{0000101010} (10), 8) the PBN changes to 0000100000 which in this case naturally evolved to 0000000100. The DDQN achieved controllability over 0000000100 with 100% success rate. Thus, if we allowed the DDQN to intervene at time step 11 it would perform intervention \text{In}(G^{0000001010} (11), 8) which forces the PBN into \(A_1\), with 12 interventions. The fact that 14 interventions was the maximum number of interventions that always achieves controllability with 100% success rate infers that the DDQN drives the states that have to failed to be controlled with 11 interventions to states that at the next time step will always naturally transition to states that can be controlled at a maximum of 3 interventions. To further support our argument that the DDQN is encouraged to find a policy to control the PBN with the least possible interventions we can see that the cumulative average reward (Fig. 11) begins to increase after approximately 900000 episodes and the average reward per epoch (Fig. 10) is constantly increasing, which would not be justifiable if the DDQN did not achieve in finding a control policy that drives the PBN to \(A_1\) with less than 11 interventions. More specifically, in order to obtain a positive average reward, the DDQN must have found a policy that achieves controllability for the majority of states with at most 5 interventions. By testing the same DDQN again only this time by allowing up to 5 interventions the agent achieved an average controllability success rate of 75.1%.

\footnote{The reason we state often is because the next state depends on the network realization at each time step which is unknown to the agent. There are times that the DDQN achieves 100% controllability with up to 11 interventions, but that is only if a rare network realization occurs that results to an easily controllable next state.}
Similarly, as in the case of the PBN with 7 nodes we can conclude that the DDQN tends to find such interventions as to minimize the number of interventions required to control the PBN and to avoid non-target attractors when possible.

**Discussion on DDQN and PER architecture**

In order for the DDQN to successfully find a policy that controls the PBNs we had to make specific hyperparameter choices that differed for the two cases presented. We discuss here the ones that proved to have the highest effect on the quality of learning and successful control. We also assume for this discussion that controllability is attempted for the hardest case; that is that the target attractor is set to the attractor that would naturally occur with the least probability as in our experiments.

**Figure 10** The average cumulative reward begins to increase after approximately 800000 episodes indicating that the DDQN begins to find ways to control the PBN with less than 11 interventions that receive a positive average reward.

**Figure 11** The average reward per epoch is shown.
Discount factor ($\gamma$)

As explained in Section III the discount factor indicates how much future rewards are weighted in comparison to immediate rewards. The choice of $\gamma$ depends on the problem and the goal the Reinforcement Learning agent aims to achieve in the environment it interacts with. In the case of PBN controllability the goal is to reach the target attractor. However, as the size of the PBN increases positive rewards will be obtained less frequently. A small $\gamma$ will result in a positive reward received late in an episode to be very small and thus insignificant for the agent to be ‘motivated’ to perform these actions that resulted in this reward often. That is the reason we set $\gamma$ high for both PBNs and especially for the one with 10 nodes. In the case of the PBN with 7 nodes the Q values would still converge even if $\gamma$ was for example 0.4, but learning would be slower.

$\epsilon$-greedy

The value of $\epsilon$ indicates the probability of randomly performing an action to the environment or greedily selecting one according to the Q function approximated by the DDQN at each episode. The value decreases towards a $\min_\epsilon$ where it stays fixed. For large state spaces it may be important to explore aggressively at the beginning of training; that is to encourage random actions. If the agent begins to act greedily early in the training process it may end up finding a sub-optimal solution or no solution at all. Thus, by performing random actions the agent is allowed to explore the resulting state space, before it becomes more ‘confident’ and starts selecting actions greedily. The value of $\min_\epsilon$ needs to be set as to still allow the agent to act randomly throughout training yielding the possibility of potentially finding a better policy. Also, it avoids the possibility of a model overfitting; that is memorizing actions and sequence of states that can result from always performing the same actions at the same states during training. In our experiments we begin by exploring aggressively and slowly decay $\epsilon$ to 0.01 at about half of the training episodes, thus allowing the agent to perform a random action every 100 interventions.

Prioritization constant $\omega$

The value of $\omega$ indicates how much to prioritize each experience. In the case of PBNs the only actions-states that receive a positive reward are the ones resulting in successful control and hence occur less frequently. We set $\omega$ to 0.6 in order to highly prioritize the replay of these states but avoid setting it to a very high value; for example 0.9, so that our replayed samples don’t become dominated only by such experiences. As the PBN size increases we may need to set $\omega$ closer to 1, as positive rewards will occur less and less frequently.

Target Network update interval

As explained in Section VI the use of a target network is of significant importance as it results in more stable learning. The reason we increased the number of target updates from 100 (PBN, $n = 7$) to 400 (PBN, $n = 10$) is because it resulted in a more successful policy for the case of PBN with $n = 10$. There is no specific rule to determine the exact number of iterations (episodes) needed for updating the network. However, as the state-space increases updating the network less frequently allows the agent to further explore the state-space and the rewards received for each action, before updating its target. Furthermore, as discussed, we use a function approximator with parameters $\theta$ which determine the Q values for all input states. By frequently updating $\theta$ the Q values of all other states are affected leading to a
‘moving’ and unstable target. Hence, it is important to increase the iterations needed to update the target network as the PBN’s state-space we attempt to control increases, in order to allow the agent to explore potentially different and better outcomes before updating more confidently.

**Discussion on PBN size**

We have presented in this Section the detailed results of PBNs with 7 and 10 nodes in order to be able to neatly provide a clear detailed step by step explanation of our findings. However, it is important to note that the proposed approach can successfully scale to a significantly larger number of nodes depending on the computational power available. That is training a DDQN with PER to determine a successful control policy can be time consuming. Hence, doing so in a reasonable amount of time depends on the available processing power. While Q-Learning has been shown to find an optimal policy with probability 1 [37] (technical proof), in principle, it can scale to very large state spaces. However as discussed in previous sections, in practice this would require very large amounts of memory and data samples in order to obtain useful results; thus, yielding classical Q Learning impractical. Using a non-linear function approximator such as our suggested approach, addresses these issues and can theoretically scale to PBNs of sizes of hundreds of nodes. However, it is interesting to note that practically under some specific circumstances which remain an open area of research in the field of Reinforcement Learning, such as the DDQN’s architecture, non-linear function approximation may fail to converge to a good approximation of the Q function or even worse diverge [36]. Thus, while training it is important to consider tuning the specified parameters as presented in this section. Finally, it should be noted that the difficulty in achieving successful control of a PBN is also highly dependent on the number of possible network realizations at each time step. The example we presented of the PBN with 10 nodes has 1296 possible network realizations at each time step making the PBN highly stochastic and hence significantly more complex than the examples found in previous works, such as those presented in Section II. Experimentally we also noted that determining a control policy of a PBN with 15 nodes and 648 network realizations can be significantly easier than the 10 node PBN presented in this section. We hope that this approach further motivates research in the field of model-free Deep Reinforcement Learning where control of PBNs and thus GRNs, can be considered in cases where no knowledge of the PBNs underlying dynamics are known.

## 9 Conclusion and Future Work

We have presented in this paper a novel approach to the control problem of PBNs that draws upon Deep Reinforcement Learning. We showed how a Deep Q Network with Double Q Learning and Prioritized Experience Replay is used to interact with a PBN directly to develop a successful control policy by allowing at most one intervention at each time step with no knowledge of the PBN’s underlying dynamics, structure or transition probabilities.

A DDQN with PER was successfully applied to find a policy to control two highly non-deterministic PBNs. We explained how tuning the different hyperparameters can affect learning. In addition, we discussed how this approach overcomes the problem of scale in very large PBNs encountered by previous approaches. We provided a solution to the problem of control where a maximum of one intervention is allowed. Finally, given sufficient biologically related technology in the future this method could interact with GRNs directly without the need of a PBN, as it does not require any knowledge of the systems’ underlying dynamics.
One possible direction for future work concerns changes in the graph topology of the PBN (e.g., a node leaving the network, a link dropped; structural interventions) and the effect these may have on the ability of the DDQN to direct the network to a desired state. In short, it would be interesting to perform a sensitivity analysis of controllability to changes in the graph topology, in fashion similar to the study in [38]. Preliminary analysis suggests that the approach taken in this paper will be robust as there is inherent stochasticity in the dynamics of the network.

Related to this is the issue of optimal control for example as investigated by [39], which takes the form of whether the pathway (series of transitions) from the start state to the target state is optimal with respect to some cost function for the interventions.

Another possible direction for future investigation concerns the possibility of simulating GRNs graphically and allow the DDQN to retrieve environment observations directly from raw pixels rather than the binary value of the state of a PBN, further supporting the possibility of allowing direct interaction with GRNs. Finally, we aim to study whether DDQNs could potentially be used to determine the minimum required nodes to intervene in order to achieve control; also known as driver nodes [40], [41].

10 References

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