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Optimal Objective-Based Experimental Design for Uncertain Dynamical Gene Networks with Experimental Error

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Abstract

In systems biology, network models are often used to study interactions among cellular components, a salient aim being to develop drugs and therapeutic mechanisms to change the dynamical behavior of the network to avoid undesirable phenotypes. Owing to limited knowledge, model uncertainty is commonplace and network dynamics can be updated in different ways, thereby giving multiple dynamic trajectories, that is, dynamics uncertainty. In this manuscript, we propose an experimental design method that can effectively reduce the dynamics uncertainty and improve performance in an interaction-based network. Both dynamics uncertainty and experimental error are quantified with respect to the modeling objective, herein, therapeutic intervention. The aim of experimental design is to select among a set of candidate experiments the experiment whose outcome, when applied to the network model, maximally reduces the dynamics uncertainty pertinent to the intervention objective.

Index Terms

Dynamical model; dynamics uncertainty; experimental design; mean objective cost of uncertainty (MOCU); network intervention; experimental error

1 Introduction

A major goal in systems biology is to characterize the way biological entities interact with each other. A collection of interacting entities can be modeled by a mathematical framework called a network and be represented by a graph [1]. Generally, in a network, the interacting entities are represented by nodes and the interactions among entities are represented by edges [2]. To construct a gene network one needs to look up pertinent biological information in biological databases [3]. The available knowledge is mainly in the form of biological pathways, containing information about interactions among entities. Network dynamics involves state evolution over time as entities change through interactions and is central to drug design, whose objective is to change the dynamical behavior of the network to avoid

undesirable phenotypes [4], [5]. Generally, network dynamical models embrace dynamics uncertainty because the available prior knowledge is very limited [6]–[8]. It is desirable to reduce dynamics uncertainty to attain more reliable dynamical models and consequently improve the performance of the designed intervention. This can be accomplished by conducting additional biological experiments. However, biological experiments are often expensive and time consuming. In this manuscript, our concern is to rank experiments based on the information each can provide. Using such a strategy, the experiments with higher ranks are suggested to be conducted first. This technique is called *experimental design*.

Experimental design first emerged in machine learning and statistics where the information content of an experiment was measured as the decrease in the entropy of the model resulting from the experiment [9]. Since high-dimensional and nonlinear dynamical models suffer from a large number of unknown parameters and both *in vitro* and *in vivo* biological experiments are expensive and time consuming, experimental design is of high practical significance in systems biology [10], [11] and has attracted significant attention in recent years [12]–[14]. However, most of the existing methods only consider the statistical information of the model represented by measures such as the Fisher information matrix or entropy and do not take into account the ultimate goal of using network models, which is designing therapeutic interventions.

Key to experimental design is the quantification of uncertainty relative to its effect on the ultimate objective, that being intervention. Thus, we use the *mean objective cost of uncertainty* (MOCU) [15] for uncertainty quantification. MOCU measures the deterioration in the performance of the network, subjected to intervention, resulting from the presence of uncertainty. Based on MOCU, we develop an objective-based experimental design method to reduce dynamics uncertainty in dynamical models. We use the recently proposed dynamical modeling methodology in [16] to obtain the dynamical model of the network. Given all possible network dynamical models compatible with the prior knowledge, a distribution governing the network initial conditions, a class of interventions, and a set of candidate experiments, an objective-based optimal experimental design problem is to find the experiment yielding the largest reduction of the pertinent uncertainty that affects operational cost. In our case, an optimal experiment results in the minimum expected remaining MOCU, as in [17], [18]. However, there are two critical differences relative to the latter studies: (1) the model used herein is interaction-based at the biochemical level, rather than an abstract Boolean network, and it involves priority labels to determine regulation when more than a single action is possible at a time point; (2) when there is a likelihood for experiments to give erroneous estimations, we include this likelihood in our experimental design framework through measuring the increased cost induced due to experimental error – in particular, uncertainty is assumed to arise from uncertain priority labels, experiments are conducted to determine priority labels, and we take into account the further uncertainty resulting from experimental error.

The remainder of this paper is organized as follows. Section 2 is devoted to a review of the dynamical modeling approach proposed in [16]. In Section 3, we formulate the problem of experimental design for uncertain dynamical models and also develop a framework for defining experiments and applying interventions to the model. Section 4 presents the

proposed experimental design approach. The simulation results on both synthetic networks and real pathways are provided in Section 5. Finally, Section 6 concludes the paper.

2 Preliminaries

2.1 Network Model

A network model $M = (N, E)$ consists of a set of nodes N , representing the entities, and a set of hyper-edges, or simply edges (a hyper-edge is an edge with multiple inputs/outputs), E , representing the interactions. We denote the i -th node by n_i and the j -th edge by e_j . Each node has a *value*, where the abstract term “value” is interpreted based on the characteristics of the entity represented by the node. Thus, it represents the concentration level of a protein/chemical or the expression level of a gene, indicating whether the gene is active or inactive. We assume that nodes take non-negative integer values. Hence, the state of a network with m nodes, $N = \{n_1, n_2, \dots, n_m\}$, is a vector $x \in \mathbb{Z}_{\geq 0}^m$ being the set of non-negative integers, where each element of x is a node value. Each edge has a set of input/output nodes and possibly control (activator/inhibitor) nodes. We assume that an edge (interaction) can dynamically happen if all its input and activator nodes are nonzero and its inhibitor nodes are zero. Then, we update the values of the nodes associated to that edge. If e_i^I, e_i^O , and e_i^C denote the input, output, and control nodes for e_i , respectively, we update the nodes based on the following rules:

$$e_i^I \leftarrow e_i^I - 1,$$

$$e_i^O \leftarrow e_i^O + 1,$$

$$e_i^C \leftarrow e_i^C. \quad (1)$$

Each edge may also have a set of labels, called *edge priority labels*, characterizing the dynamics of the corresponding interaction. These are assigned to an edge based on prior knowledge or an earlier measurement made on the interaction. For instance, consider two edges $(e_1, e_2) \in E$, where both can dynamically happen. A priority label $e_1^{\text{prio}} > e_2^{\text{prio}}$ infers that when both interactions can happen at the same time based on the values of their respective nodes, only e_1 should be processed in the dynamics of the network.

2.2 Dynamic Trajectories

Given a network model $M = (N, E)$ and an initial condition vector x_0 , the network state vector x can be updated at each time step based on the method proposed in [16]. We denote by x_k the network state vector at the k -th time step. In most practical cases, knowledge of all network parameters that affect the network dynamics is not available because these parameters cannot be measured or observed. This is equivalent to some missing priority labels for the set of edges. The current study concerns model uncertainty resulting from

missing edge priority labels. Therefore, for a given M and x_0 , different updates of the state vector can be computed, these being referred to as *dynamic trajectories*, and denoted by $T_{x_0}^M$. Each trajectory $t \in T_{x_0}^M$, is a possible sequence of interactions that can take place over time. For instance, $t = \{e_i, e_j, \dots\}$, is a trajectory for which in the first time step interaction i (edge e_i) happens, in the second time step interaction j takes place, and so on.

As an example, consider the network model M depicted in Figure 1, where $N = \{n_1, n_2, \dots, n_{15}\}$ and $E = \{e_1, e_2, \dots, e_7\}$, and the following two initial condition vectors:

$$x_{0,1} = [1, 1, 0, 1, 0, 0, 0, 1, 0, 1, 0, 1, 0, 1, 0]^T,$$

$$x_{0,2} = [0, 1, 0, 1, 0, 1, 0, 1, 0, 1, 0, 1, 0, 1, 0]^T. \quad (2)$$

Using the updating rules in (1), for $x_{0,1}$, one may update the network state vector x in one of the following three ways (the node values that have changed or are going to change are indicated by an underline):

$$\begin{array}{ccc} \underbrace{\begin{bmatrix} 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{0,1}} & \xrightarrow{e_1} & \underbrace{\begin{bmatrix} 0 \\ 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{1,1}} \xrightarrow{e_4} \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{2,1}}, \\ \underbrace{\begin{bmatrix} 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{0,1}} & \xrightarrow{e_2} & \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{1,1}} \xrightarrow{e_5} \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{2,1}}, \\ \underbrace{\begin{bmatrix} 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{0,1}} & \xrightarrow{e_2} & \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{1,1}} \xrightarrow{e_6} \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{2,1}}. \end{array}$$

For example, in the first time step, the interactions e_1 and e_2 can happen because the input and activating nodes for e_1 , which are n_1 and n_2 , respectively, and the input nodes n_1 and n_4 for e_2 , have value of 1 in the initial condition $x_{0,1}$. For the subsequent time steps the state vector updates can be easily followed. Therefore, the set of dynamic trajectories for $x_{0,1}$ is $T_{x_{0,1}}^M = \{t_1, t_2, t_3\}$, where $t_1 = \{e_1, e_4\}$, $t_2 = \{e_2, e_5\}$, and $t_3 = \{e_2, e_6\}$. Now if one applies the priority label $e_5^{\text{prio}} > e_6^{\text{prio}}$ and updates the state vector, then the set $T_{x_{0,1}}^M$ will contain only t_1 and t_2 as given above. Also for $x_{0,2}$, we have

$$\underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{0,2}} \xrightarrow{e_3} \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}}_{x_{1,2}} \xrightarrow{e_7} \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 1 \end{bmatrix}}_{x_{2,2}},$$

and $T_{x_{0,2}}^M = \{t_1\} = \{\{e_3, e_7\}\}$.

The set of dynamic trajectories $T_{x_0}^M$ depends on the network model M , in particular its topology and edge priority labels, as well as the initial condition vector x_0 . The multiplicity of dynamic trajectories, for a given initial condition, is referred to as *dynamics uncertainty*. In this paper, our aim is to reduce the dynamics uncertainty – equivalently, the number of dynamic trajectories in the network dynamical model – by determining some missing edge priority labels. The goal of an effective experimental design is to decide which edge priority label should be determined first.

3 Problem Formulation

This section provides some definitions which are helpful in characterizing the experimental design approach.

3.1 Uncertainty Class

Based on the assumption that the network model M embraces uncertainty, we consider M as an *uncertainty class* of models M_θ , $\theta \in \Theta$, where the uncertainty vector $\theta = (\theta_1, \theta_2, \dots, \theta_U)$ represents a set of U unknown edge priority labels defined for appropriate U pairs of network edges. Each M_θ has no further dynamics uncertainty meaning that it behaves dynamically in a deterministic way for a given initial condition x_0 . Therefore, each model M_θ will have only one dynamic trajectory $t_{x_0}^{M_\theta}$ for a given x_0 . Each M_θ corresponds to one possible combination of edge priority labels. In the current formulation, Θ is the set of all possible combinations of edge priority labels. Possible models M_θ differ with each other only in the unknown edge priority labels.

For example, consider the network model M in Figure 1 and the initial conditions in (2). We obtain the following sets of trajectories: $T_{x_{0,1}}^M = \{\{e_1, e_4\}, \{e_2, e_5\}, \{e_2, e_6\}\}$ and $T_{x_{0,2}}^M = \{\{e_3, e_7\}\}$. To define the uncertainty vector, we need to find all unknown edge priority labels that induce dynamics uncertainty for each initial condition. Finding the priority labels for the pairs of edges (e_1, e_2) and (e_5, e_6) determines which dynamic trajectory happens for $x_{0,1}$; the priority label for (e_1, e_2) will choose between e_1 and e_2 at

time step 1 and the priority label for (e_5, e_6) will choose between e_5 and e_6 at time step 2 should e_2 be chosen at step 1. For $x_{0,2}$, the network model M behaves in a deterministic way as only one trajectory exists for this initial condition. Hence, we define the uncertainty vector $\theta = (\theta_1, \theta_2)$, where θ_1 is the unknown priority label for the pair (e_1, e_2) and θ_2 is the unknown label for (e_5, e_6) .

A probability distribution P_M can be associated to the uncertainty class M . To do so, for each unknown priority label θ_u defined over a pair of edges $(e_{u,1}, e_{u,2}) \in E$, one may assign a probability p_u , $0 \leq p_u \leq 1$, to the case that $e_{u,1}^{\text{prio}} > e_{u,2}^{\text{prio}}$, and $1 - p_u$ to $e_{u,1}^{\text{prio}} < e_{u,2}^{\text{prio}}$. Following this strategy, each model M_θ will have a probability $P_M(M_\theta)$ being a function of $p = (p_1, p_2, \dots, p_U)$. We assume that there is a *true*, yet unknown, network model M^* corresponding to the network under study, embracing a complete knowledge of all true edge priority labels. Thus, there exists $\theta^* \in \Theta$ such that $M_{\theta^*} = M^*$.

3.2 Dynamic Performance Error

For a given initial condition x_0 , the set of dynamic trajectories $T_{x_0}^M$ over the uncertainty class M is given by

$$T_{x_0}^M = \bigcup_{\theta \in \Theta} t_{x_0}^{M_\theta}. \quad (3)$$

Since for a given initial condition x_0 some network models M_θ might have similar dynamical behavior resulting in the same dynamic trajectory, the conditional probability $P_{T_{x_0}^M}(t)$, of each dynamic trajectory $t \in T_{x_0}^M$ given x_0 , is

$$P_{T_{x_0}^M}(t) = \sum_{\theta \in \Theta} P_M(M_\theta) \mathbb{1}_{t_{x_0}^{M_\theta} = t}, \quad (4)$$

where $\mathbb{1}_z$ is an indicator function, i.e., $\mathbb{1}_z = 1$ if z is true, and $\mathbb{1}_z = 0$ otherwise.

Since the initial condition vector x_0 may vary, we represent the initial condition by a random vector X_0 . Now, for M and X_0 , the set T^M of all dynamic trajectories for all possible initial condition vectors is given by

$$T^M = \bigcup_{x_0 \in X_0} T_{x_0}^M. \quad (5)$$

In this context, the probability $P_{T^M}(t)$ of each dynamic trajectory $t \in T^M$ can be calculated as

$$P_{T^M}(t) = \sum_{x_0 \in X_0} P_{X_0}(x_0) P_{T_{x_0}^M}(t), \quad (6)$$

where P_{X_0} is the probability distribution of the initial conditions and $P_{T^M}^{x_0}(t)$ is given in (4).

Let $N^d \subset N$ be a subset of nodes whose final or steady-state values characterize the network dynamic performance. From a translational perspective, some node values might correspond to healthy phenotypes and some might correspond to cancerous phenotypes [19], [20]. Therefore, the network dynamic performance for each dynamic trajectory $t \in T^M$ can be evaluated based on the final/steady-state values of the nodes in N^d . Let $x_f^{d,t}$ be the final/steady-state vector corresponding to N^d and trajectory t , and v^d be the vector of desired final/steady-state values for N^d . We define the dynamic performance error $\varepsilon(t)$ for each trajectory t as

$$\varepsilon(t) := \|x_f^{d,t} - v^d\|, \quad t \in T^M, \quad (7)$$

where $\|\cdot\|$ is any appropriate norm. The average dynamic performance error $\mathcal{E}_M$ over the uncertainty class M and all initial condition vectors, is defined as the expected value of the dynamic performance error $\varepsilon(t)$ over the set T^M :

$$\mathcal{E}_M := E_{T^M}[\varepsilon(t)] = \sum_{t \in T^M} P_{T^M}(t) \varepsilon(t), \quad (8)$$

where $P_{T^M}(t)$ is obtained in (6).

3.3 Intervention

The main objective of network modeling is to derive interventions that can beneficially affect network dynamic behavior to avoid undesirable phenotypes. Two basic kinds of intervention are structural intervention, in which there is a single alteration to the gene regulatory logic, such as blocking a signal or altering the regulatory logic [21], and dynamical intervention over time in the context of control theory [22]. There has been extensive study of dynamical control in gene regulatory networks, including under model uncertainty [23]–[25], mostly in the framework of probabilistic Boolean networks [26]. In another control related work, an adaptive feedback control is used to achieve global asymptotic stability in a class of gene regulatory networks [27].

In this paper, we assume that we are able to interrupt/block a subset of interactions in a biological network. We define a class of interventions $\Psi = \{\psi_j, j \in J\}$, where each intervention ψ_j is the act of blocking the interaction (edge) $e_j \in E$ from happening, and J is the set of network edge numbers on which such blocking intervention can be applied. We emphasize that any intervention affects network dynamics and thus alters the dynamic trajectories. Let $t_{x_0}^{M_\theta}(\psi_j)$ denote the trajectory of model M_θ given the initial condition x_0 when the intervention ψ_j is applied. The dynamic performance error $\mathcal{E}_{M_\theta}(\psi_j)$, of model M_θ after applying the intervention ψ_j , is

$$\mathcal{E}_{M_\theta}(\psi_j) = \sum_{x_0 \in X_0} P_{X_0}(x_0) \varepsilon(t_{x_0}^{M_\theta}(\psi_j)), \quad (9)$$

where we used the fact that $t_{x_0}^{M_\theta}(\psi_j)$ has at most one trajectory t if it is not interrupted by intervention ψ_j . The optimal intervention for model M_θ can be found as

$$\psi_{\text{opt}}(M_\theta) := \arg \min_{\psi_j, j \in J} \mathcal{E}_{M_\theta}(\psi_j). \quad (10)$$

In the presence of uncertainty the goal is to design a robust intervention which performs optimally on average across all possible models in the uncertainty class. Applying any intervention ψ_j to the uncertainty class M results in a new set of dynamic trajectories $T^M(\psi_j)$ which can be written as

$$T^M(\psi_j) = \bigcup_{x_0 \in X_0} T_{x_0}^M(\psi_j), \quad (11)$$

where

$$T_{x_0}^M(\psi_j) = \bigcup_{\theta \in \Theta} t_{x_0}^{M_\theta}(\psi_j), \quad (12)$$

is the set of all dynamic trajectories for a given initial condition x_0 when the intervention ψ_j is applied. The new average dynamic performance error $\mathcal{E}_M(\psi_j)$ is

$$\mathcal{E}_M(\psi_j) = \mathbb{E}_{T^M(\psi_j)}[\varepsilon(t)] = \sum_{t \in T^M(\psi_j)} P_{T^M(\psi_j)}(t) \varepsilon(t), \quad (13)$$

where $P_{T^M(\psi_j)}$ is the probability distribution governing the new set of dynamic trajectories $T^M(\psi_j)$ subsequent to intervention ψ_j :

$$P_{T^M(\psi_j)}(t) = \sum_{x_0 \in X_0} P_{X_0}(x_0) P_{T_{x_0}^M(\psi_j)}(t), \quad (14)$$

where

$$P_{T_{x_0}^M(\psi_j)}(t) = \sum_{\theta \in \Theta} P_M(M_\theta)_{t_{x_0}^{M_\theta}(\psi_j)=t}, \quad (15)$$

is the probability of trajectory t , given x_0 and ψ_j .

Consistent with the terminology of [28] and [17], an *intrinsically Bayesian robust* (IBR) intervention to the uncertainty class M , denoted by $\bar{\psi}(M)$, is an intervention for which the average dynamic performance error is minimum:

$$\bar{\psi}(M) = \arg \min_{\psi_j, j \in J} \mathcal{E}_M(\psi_j). \quad (16)$$

Note the difference between the definition of model-specific optimal intervention $\psi_{opt}(M_\theta)$ in (10) and the IBR intervention $\bar{\psi}(M)$ in (16). While $\psi_{opt}(M_\theta)$ should perform optimally for a specific model M_θ relative to the distribution of initial conditions, $\bar{\psi}(M)$ should perform optimally for an uncertainty class M relative to both the distribution of initial conditions and the distribution of uncertainty class models.

3.4 Experiment

We define a laboratory testable experiment $\xi_u = \xi_u(e_{u,1}, e_{u,2})$, for $u = 1, 2, \dots, U$, over the pair $(e_{u,1}, e_{u,2}) \in E$ to have the objective of determining which of the edges (interactions) occurs in practice if both can dynamically happen at the same time. In the context of our methodology, this translates to determining the u -th unknown priority label θ_u where the experiment outcome can be applied to the uncertainty class M by assigning the corresponding edge priority label. Thus, conducting the experiment ξ_u determines the value of θ_u as

$$\theta_u = \begin{cases} 1 & \text{if } e_{u,1}^{\text{prio}} > e_{u,2}^{\text{prio}} \\ 0 & \text{if } e_{u,1}^{\text{prio}} < e_{u,2}^{\text{prio}} \end{cases}. \quad (17)$$

The set $\Xi = \{\xi_u, u = 1, 2, \dots, U\}$ of experiments is in one-to-one correspondence with the vector $\theta = (\theta_1, \theta_2, \dots, \theta_U)$ of unknown priority labels. If all experiments are performed, then we obtain the vector $\theta^* \in \Theta$ for which $M_{\theta^*} = M^*$, the true model.

4 Experimental Design

In this section, we explain how to perform experimental design in the presence and absence of experimental error.

4.1 Approach: Design without Experimental Error

For experimental design we desire a quantification of uncertainty that takes into account both the objective and the model uncertainty. In this light, the *objective cost of uncertainty* (OCU) for model M_θ is defined as the differential performance cost of applying the robust intervention $\bar{\psi}(M)$ instead of the optimal intervention $\psi_{opt}(M_\theta)$ to M_θ :

$$\mu(M_\theta) := \mathcal{E}_{M_\theta}(\bar{\psi}(M)) - \mathcal{E}_{M_\theta}(\psi_{opt}(M_\theta)). \quad (18)$$

The *mean objective cost of uncertainty* (MOCU) [15] is the expected value of $\mu(M_\theta)$ over the uncertainty class $\mathcal{M}$:

$$\mu(M) := \mathbb{E}_M [\mathcal{E}_{M_\theta}(\bar{\psi}(M)) - \mathcal{E}_{M_\theta}(\psi_{\text{opt}}(M_\theta))]. \quad (19)$$

MOCU measures the uncertainty in the model in terms of the expected increase of operational cost that it induces, i.e., the expected difference between the performance of the robust intervention (goal in the presence of uncertainty) and the model-specific optimal intervention (goal in the absence of uncertainty). Thus, MOCU can be regarded as an objective-based uncertainty quantification scheme. It should be recognized that MOCU is different from conventional uncertainty quantification methods such as entropy that do not consider the operational cost of uncertainty.

Recalling the experiment discussion in Section 3.4 and supposing that the outcome of experiment ξ_u is determined to be $\theta_u = \phi$ (which can be either 1 or 0), we define the remaining MOCU if $\theta_u = \phi$ as

$$\mu(M^{u,\phi}) = \mathbb{E}_{M^{u,\phi}} \left[\mathcal{E}_{M_\theta^{u,\phi}}(\bar{\psi}(M^{u,\phi})) - \mathcal{E}_{M_\theta^{u,\phi}}(\psi_{\text{opt}}(M_\theta^{u,\phi})) \right], \quad (20)$$

where $M_\theta^{u,\phi}$ is obtained from model M_θ by setting the u -th unknown priority label θ_u equal to ϕ , and $M^{u,\phi} = \{M_\theta^{u,\phi} | M_\theta \in \mathcal{M}\}$ is the *remaining uncertainty class* when $\theta_u = \phi$, i.e., the models in the uncertainty class $\mathcal{M}$ compatible with the outcome ϕ of the experiment ξ_u . The expectation in (20) is taken over the conditional probability distribution

$P_{M^{u,\phi}}(M_\theta^{u,\phi}) = P_M(M_\theta | \theta_u = \phi)$ governing the remaining uncertainty class $M^{u,\phi}$, and $\bar{\psi}(M^{u,\phi})$ is the robust intervention for the remaining uncertainty class $M^{u,\phi}$, which can be found in a similar way as in (16).

Corresponding to each experiment ξ_u , the expected remaining MOCU is

$$\mu^u = \mathbb{E}_{\theta_u} [\mu(M^{u,\theta_u})] = \mathbb{E}_{\theta_u} \left[\mathbb{E}_{M^{u,\theta_u}} \left[\mathcal{E}_{M_\theta^{u,\theta_u}}(\bar{\psi}(M^{u,\theta_u})) - \mathcal{E}_{M_\theta^{u,\theta_u}}(\psi_{\text{opt}}(M_\theta^{u,\theta_u})) \right] \right], \quad (21)$$

where $\mathbb{E}_{\theta_u}$ is the expectation relative to the probability distribution of the uncertain parameter θ_u . The expected remaining MOCU is the MOCU which is estimated to remain in the model after conducting the experiment. The optimal experiment possesses the minimum expected remaining MOCU [17]:

$$u^* = \arg \min_{u=1,2,\dots,U} \mu^u. \quad (22)$$

Thus, ξ_{u^*} is the experiment to be conducted first. The minimization problem in (22) can be further simplified as

$$\begin{aligned}
 u^* &= \arg \min_{u=1,2,\dots,U} \mu^u \\
 &= \arg \min_{u=1,2,\dots,U} E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}}(\bar{\psi}(M^{u,\theta_u})) - \mathcal{E}_{M_{\theta}^{u,\theta_u}}(\psi_{\text{opt}}(M_{\theta}^{u,\theta_u})) \right] \right] \\
 &= \arg \min_{u=1,2,\dots,U} \left\{ E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}}(\bar{\psi}(M^{u,\theta_u})) \right] \right] - E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}}(\psi_{\text{opt}}(M_{\theta}^{u,\theta_u})) \right] \right] \right\} \\
 &= \arg \min_{u=1,2,\dots,U} \left\{ E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}}(\bar{\psi}(M^{u,\theta_u})) \right] \right] - E_M[\mathcal{E}_{M_{\theta}}(\psi_{\text{opt}}(M_{\theta}))] \right\} \\
 &= \arg \min_{u=1,2,\dots,U} E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}}(\bar{\psi}(M^{u,\theta_u})) \right] \right],
 \end{aligned}
 \tag{23}$$

where in the fourth line we have used the law of total expectation and in the fifth line we have omitted the second term in the expression because it is not a function of the minimization argument.

4.2 Approach: Design with Experimental Error

So far, we have assumed that experiments are error free, meaning that conducting the experiment ξ_u results in the exact estimation of the uncertain parameter θ_u . However, in many biological experiments experimental error is likely to be present [29]–[33]. Experimental error might result from various sources, such as sample quality, sampling of neighboring or contaminated tissues, DNA hybridization, mechanical and optical factors, etc. Therefore, it is important to incorporate the experimental error in the experimental design process. Considering error, we denote the outcome of experiment ξ_u by a random variable $\hat{\theta}_u$. The joint probability distribution, $P_{\hat{\theta}_u, \theta_u}$, for the estimated value from experiment and the true value of the unknown parameter characterizes experimental accuracy.

Relative to θ_u being the true value of the u -th uncertain parameter and $\hat{\theta}_u$ being the outcome of experiment ξ_u , we quantify the experimental error of experiment ξ_u by

$$\mathcal{D}^u(\theta_u, \hat{\theta}_u) = E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}}(\bar{\psi}(M^{u,\hat{\theta}_u})) - \mathcal{E}_{M_{\theta}^{u,\theta_u}}(\bar{\psi}(M^{u,\theta_u})) \right], \tag{24}$$

which is the expected increased performance error across the remaining uncertainty class M^{u,θ_u} when we apply the robust intervention obtained using the experiment outcome $\hat{\theta}_u$ instead of the true value θ_u of the uncertain parameter. Similar to the approach we took for model uncertainty quantification, here we also quantify the experimental error in an objective-based manner. Since the experimental error affects network performance resulting from robust intervention subsequent to the experiment, we quantify the experimental error

relative to the false outcome $\hat{\theta}_u$ and the true value θ_u in terms of the average increased cost due to applying the robust intervention resulting from the false outcome $\hat{\theta}_u$ to the remaining uncertainty class that would be obtained if the true value θ_u is assigned to the uncertain parameter. We take the expectation of (24) with respect to the joint distribution $P_{\hat{\theta}_u, \theta_u}$ to quantify the experimental error for experiment ξ_u :

$$\mathcal{D}^u = E_{\hat{\theta}_u, \theta_u} [\mathcal{D}^u(\theta_u, \hat{\theta}_u)]. \quad (25)$$

To rank experiments in the presence of experimental error, we add $\mathcal{D}^u$ to the equation in (23), derived for the case assuming no experimental error, to obtain

$$u^* = \arg \min_{u=1,2,\dots,U} \left\{ E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}} (\bar{\psi}(M^{u,\theta_u})) \right] \right] + E_{\hat{\theta}_u, \theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}} (\bar{\psi}(M^{u,\hat{\theta}_u})) - \mathcal{E}_{M_{\theta}^{u,\theta_u}} (\bar{\psi}(M^{u,\theta_u})) \right] \right] \right\}. \quad (26)$$

We simplify (26) by using the fact that the expectation relative to the joint distribution $P_{\hat{\theta}_u, \theta_u}$ is the expectation (relative to θ_u) of the conditional expectation given θ_u :

$$\begin{aligned} u^* &= \arg \min_{u=1,2,\dots,U} \left\{ E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}} (\bar{\psi}(M^{u,\theta_u})) \right] \right] \right. \\ &\quad + E_{\theta_u} \left[E_{\hat{\theta}_u | \theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}} (\bar{\psi}(M^{u,\hat{\theta}_u})) \right] \right] \right] \\ &\quad \left. - E_{\theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}} (\bar{\psi}(M^{u,\theta_u})) \right] \right] \right\} \\ &= \arg \min_{u=1,2,\dots,U} E_{\theta_u} \left[E_{\hat{\theta}_u | \theta_u} \left[E_{M^{u,\theta_u}} \left[\mathcal{E}_{M_{\theta}^{u,\theta_u}} (\bar{\psi}(M^{u,\hat{\theta}_u})) \right] \right] \right], \quad (27) \end{aligned}$$

where the third summand follows from the fact that the expression inside the expectation operator does not depend on the outcome of experiment $\hat{\theta}_u$ and therefore we can drop $E_{\hat{\theta}_u | \theta_u}$. According to (27), for experiment ξ_u , for each possible outcome $\hat{\theta}_u$ of the experiment and each possible true value θ_u of the unknown parameter, we find the robust intervention of the remaining uncertainty class $M^{u,\hat{\theta}_u}$ corresponding to $\hat{\theta}_u$ and then calculate the average performance of the robust intervention with respect to the remaining uncertainty class M^{u,θ_u} corresponding to θ_u . Then, we take the expectation relative to the joint distribution $P_{\hat{\theta}_u, \theta_u}$ of the experiment outcome and true value. We emphasize that in the presence of experimental error, one needs to use the minimization problem in (27), which incorporates both the experimental error and the model uncertainty, instead of (23), which considers only the model uncertainty, to find the optimal experiment ξ_{u^*} to be conducted first.

When it is of interest to conduct more than one experiment, experiments can be done sequentially as follows. First the highest ranked experiment ξ_{u^*} is determined. Conduct

experiment ξ_{u^*} and apply its outcome $\hat{\theta}_{u^*}$ to the uncertainty class M which gives a remaining uncertainty class $M^{u^*, \hat{\theta}_{u^*}}$. Considering $M^{u^*, \hat{\theta}_{u^*}}$ as a new uncertainty class and removing ξ_{u^*} from the original set of candidate experiments Ξ , calculate the next optimal experiment. Repeat this process until all experiments are done.

5 Simulation Results and Performance Analysis

5.1 Synthetic Networks

To evaluate the performance of our proposed experimental design approach, we generated 50000 random synthetic network models and performed both the experimental design and random selection approaches. To generate each synthetic network, we randomly selected the number of network edges to be between 10 and 30, the number of network nodes to be between 20 and 40, and randomly associated input, output and control nodes to each network edge. For each network M , we randomly selected a set of initial condition vectors X_0 and considered a uniform distribution P_{X_0} over them. Then, we computed the dynamic trajectories T^M , based on which we defined the set Ξ of candidate experiments. We randomly chose the set of performance nodes N^d and assumed v^d is a vector of zeros of an appropriate dimension. We also randomly selected one model M^* in M as the network true model. We assume that intervention (blocking an interaction) can be applied to any network edge. As $\theta_u, \hat{\theta}_u \in \{0, 1\}$, we define the experimental error probability δ_u associated with the experiment ξ_u via the conditional probability of $\hat{\theta}_u$ given θ_u :

$$P_{\hat{\theta}_u|\theta_u}(\hat{\phi}|\phi) = \begin{cases} \delta_u & \text{if } \hat{\phi} \neq \phi \\ 1 - \delta_u & \text{if } \hat{\phi} = \phi \end{cases} \quad (28)$$

For the sake of simplicity, for the remaining of this manuscript, we assume that all experiments have the same experimental error probability δ , i.e., $\delta_1 = \delta_2 = \dots = \delta_U = \delta$. In simulations, experimental error δ varies in the interval $[0, 0.5]$.

Applying the proposed experimental design approach to each network, we calculate the optimal experiment ξ_{u^*} using (27) and apply the outcome of experiment ξ_{u^*} , i.e., $\hat{\theta}_{u^*}$, to M , thereby resulting in the remaining uncertainty class $M^{u^*, \hat{\theta}_{u^*}}$. Then, for the remaining uncertainty class $M^{u^*, \hat{\theta}_{u^*}}$, we calculate the robust intervention $\bar{\psi}(M^{u^*, \hat{\theta}_{u^*}})$, apply it to the underlying true model M^* , and obtain the dynamic performance error

$\mathcal{E}_{M^*}^{\text{exp. des.}} = \mathcal{E}_{M^*}(\bar{\psi}(M^{u^*, \hat{\theta}_{u^*}}))$. We also follow the same steps except that we select the experiment $\xi_{u'}$ using the error-free formulation in (23) instead of (27), although the

experimental error exists, and obtain $\mathcal{E}_{M^*}^{\text{exp. des. (no } \delta)} = \mathcal{E}_{M^*}(\bar{\psi}(M^{u', \hat{\theta}_{u'}}))$. We also consider randomly selecting one experiment, say ξ_{u^r} , and following the same steps to obtain the

dynamic performance error $\mathcal{E}_{M^*}^{\text{rand exp.}} = \mathcal{E}_{M^*}(\bar{\psi}(M^{u^r, \hat{\theta}_{u^r}}))$.

We define the terms ‘‘Tie’’, ‘‘Success’’, and ‘‘Failure’’ for an experiment chosen using either (23) or (27) as follows:

- Tie: $\mathcal{E}_{M^*}^{\text{exp. des.}} = \mathcal{E}_{M^*}^{\text{rand exp.}}$,
- Success: $\mathcal{E}_{M^*}^{\text{exp. des.}} < \mathcal{E}_{M^*}^{\text{rand exp.}}$,
- Failure: $\mathcal{E}_{M^*}^{\text{exp. des.}} > \mathcal{E}_{M^*}^{\text{rand exp.}}$.

As remarked earlier, the conventional approach for experimental design is based on the entropy. In this context, the information content of experiment ξ_u is defined as

$$I(M; \xi_u) = H(M) - H(M|\xi_u) = H(M) + \sum_{\theta, \phi} \Pr(\theta, \theta_u = \phi) \log_2 \Pr(\theta|\theta_u = \phi), \quad (29)$$

where $H(M)$ is the entropy of the model before conducting any experiment, $H(M|\xi_u)$ is the conditional entropy after conducting experiment ξ_u , and $\Pr(\cdot)$ is the probability operator. In our settings where all unknown priority labels are assumed to be statistically independent and each can be 1 or 0 with equal probability, $I(M; \xi_u)$ becomes $U - 1$, U being the number of candidate experiments, for each experiment ξ_u . As a result, there is no distinction between different experiments from the viewpoint of this experimental design approach. Consequently, the experimental design based on (29) would perform similarly as the random selection policy. Hence, throughout this paper when we compare our proposed method with the random selection policy, in fact, we also compare our method with the experimental design method based on (29).

In Figure 2, we show the percentage of networks for which we have obtained Tie, Success, and Failure results. The solid lines correspond to the case that the experimental error is incorporated in the experimental design (equation (27)) and the dashed lines are for the case that experiments are chosen without considering experimental error (equation (23)). Two important observations can be made from this figure. First, for any experimental error, the proposed experimental design approach performs considerably better than random experiments even if we do not consider experimental error in calculations because the percentage of Success is always significantly higher than the percentage of Failure. Second, considering experimental error in the experimental design process increases the number of networks with Success and decreases those with Failure, and this improvement becomes more considerable as the experimental error increases.

Let $\mathcal{E}_{M^*}$ be the dynamic performance error of the true network model M^* before applying any intervention. Figure 3 shows the average values of $\mathcal{E}_{M^*}^{\text{exp. des.}}$, $\mathcal{E}_{M^*}^{\text{exp. des. (no } \delta)}$, and $\mathcal{E}_{M^*}^{\text{rand exp.}}$ normalized by $\mathcal{E}_{M^*}$. For any δ , experimental design, with or without considering the experimental error, returns a lower average performance error than the random experiments. Furthermore, $\mathcal{E}_{M^*}^{\text{exp. des.}} < \mathcal{E}_{M^*}^{\text{exp. des. (no } \delta)}$ for any $\delta > 0$ and this difference becomes larger as δ increases. This figure suggests that, although considering experimental error in the experimental design helps us to achieve lower error, it is reasonable to perform experimental design even if there is no knowledge regarding the error of experiments.

Considering experimental error in the experimental design, we might find different optimal experiments for different experimental errors. Let $\xi_{u^*|\delta=0}$ denote the highest ranked experiment when there is no experimental error. Figure 4 shows the percentage of networks whose optimal experiment ξ_{u^*} for a given experimental error is different from their corresponding error-free optimal experiment $\xi_{u^*|\delta=0}$. For example, the optimal experiments for $\delta = 0$ and $\delta = 0.3$ are different for around 20% of networks. It can be seen that as the experimental error increases, ξ_{u^*} differs from $\xi_{u^*|\delta=0}$ for a larger proportion of networks. This explains the difference between the two design approaches in Figure 3: one considers δ in the calculations and one does not, and the difference becomes larger for higher δ values.

As previously explained, sequential experimental design can be performed by finding the optimal experiment ξ_{u^*} at each step. When each experiment is chosen to be done, we incorporate its outcome in the model and find the remaining uncertainty class. Then, we calculate the robust intervention of this reduced uncertainty class and record its performance error when it is applied to the underlying true model. Figure 5 shows the average performance error after conducting each number of experiments for networks with six candidate experiments when experiments are sequentially selected using the proposed experimental design method and the random selection policy. For the random selection experiment, at each step one experiment is chosen randomly among the remaining experiments. We assume that experiments are error-free, i.e., $\delta = 0$; therefore, both approaches converge to the true model M^* after conducting six experiments. As can be seen, optimal experimental design reduces the performance error much faster than the random policy. In particular, the first optimal experiment provides a majority of the reduction and almost full reduction is accomplished by two experiments. The remaining experiments determine edge priority labels having virtually no influence on the dynamical behavior of the network as it pertains to intervention.

5.2 Computational Complexity Analysis

The computational process of the proposed method can be divided into two main steps: (1) calculation of dynamic trajectories T^M , and (2) calculation of optimal experiment ξ_{u^*} . The computational complexity of the set T^M is due to performing all possible updates of the state vector at each time step and for all initial condition vectors. The major complexity in the second step is related to applying each intervention $\psi_j \in \Psi$ to each model $M_\theta \in M$ for calculating the performance error $\mathcal{E}_{M_\theta}(\psi_j)$. Since we record all updates of the network state vector over time in step 1, applying interventions in step 2 reduces to only recalling appropriate elements of such record. Thus, the computational complexity corresponding to step 2 is negligible.

The complexity of step 1 depends on the number of trajectories and the number of time steps for each trajectory through which all updates of the state vector are possible. This does not directly depend on the number of nodes and edges in the network. For instance, there may exist a large network with few nonzero nodes giving one or a small number of trajectories; on the other hand, there can be a relatively small network with many nonzero nodes resulting in a larger set of trajectories. Let $\pi(t)$ denote the number of time steps for trajectory $t \in T^M$; hence, $\pi(T^M) = \sum_{t \in T^M} \pi(t)$. The computational complexity of the proposed

experimental design method is $\mathcal{O}(\pi(T^M))$. Table 1 summarizes the average processing time in seconds needed to perform experimental design for different values of $\pi(T^M)$ using an Intel Core 2 Duo 1.67GHz CPU.

5.3 ErbB2/ErbB3 Pathway

In this example, we considered the National Institutes of Health (NIH) ErbB2/ErbB3 pathway. The ErbB receptors play an important role in regulating cell proliferation, migration, differentiation, apoptosis, and cell motility. It has been demonstrated that the RAF/MEK pathways [34], and the PI3K/AKT pathways [35], are highly dependent on the levels of activated ErbB3. In many forms of cancer, the ErbB family members are over-expressed or mutated which makes them the therapeutic targets for many cancer drugs, examples being Lapatinib and Trastuzumab [36], [37]. To design effective therapeutic mechanisms, a reliable pathway dynamical model is needed. The developed dynamical models embrace dynamics uncertainty due to limited prior knowledge [16]; therefore, we are interested in reducing the dynamics uncertainty through the proposed experimental design approach.

The pathway network model (uncertainty class) M is plotted in Figure 6, in which the biological entities in N and interactions in E are numbered in an increasing order from top to bottom and left to right. The gray arrows indicate inputs/outputs. The blue and red arrows show activation and inhibition, respectively. More information including the biological names of the nodes and the types and references for the interactions can be found in the supplementary material to this manuscript. Table 2 describes the events/entity names and their respective node numbers in the pathway upon which the pathway dynamic performance is evaluated. The column for v^d shows the desired value for each entity which is determined according to the references given in the reference column. The desired value for those nodes that correspond to desirable events is set to 1 and for those that represent undesirable events is set to 0.

We considered 100 different initial condition vectors and a uniform distribution for P_{X_0} . We assumed that intervention (blocking an interaction) can be applied to any network edge. After computing the dynamic trajectories for each initial condition, we found the set of candidate experiments summarized in Table 3. This table also provides further details about the edges over which the candidate experiments are defined. The objective of each experiment ξ_u , $u = 1, 2, \dots, 9$, is to determine the priority between two corresponding edges as defined in (17). From Table 3, it is understood that the experiments involve determining in which interaction node n_8 , which is the ErbB2/ErbB3/neuregulin 1 beta compound, participates. Neuregulins are of high clinical significance as they play a major role in the development and maintenance of the cardiovascular [48] and the nervous systems [49]. As can be seen in Figure 6, these interactions are located upstream of the pathway; thus, determining the downstream activity depends on which of these upstream interactions occurs. We randomly selected a vector $\theta^* \in \Theta$ corresponding to a true model M^* . We performed sequential experimental design 100 times. Table 4 shows the experiments with their corresponding selection percentages obtained by the experimental design at different experimental error probability δ . As expected, for $\delta = 0$ (error-free case) a unique sequence

of experiments is always selected because the outcomes of the conducted experiments do not change for different simulation runs. When increasing δ , a large number of different sequences of experiments is obtained because, with experimental error, experiments can give either true or erroneous outcomes. Thus, when both the dynamical model and the distribution governing the model uncertainty are updated based on the outcome of a conducted experiment, the next chosen experiment might be different depending on which outcome has been observed for the previous experiment. Also, at a specific step in the sequence, the percentage of choosing the optimal experiment obtained for the error-free case decreases as δ increases. For instance, the sixth optimal experiment for the error-free case is always ξ_3 ; however, the percentage of choosing this experiment for $\delta = 0.2$ and $\delta = 0.35$ decreases to 60% and 16%, respectively.

For this example, we also conducted the following case study. We assumed that the knowledge of a subset of edges is not available; equivalently, we deleted these edges from the pathway and then performed the experimental design. We considered two cases: (1) the unknown edges are among the edges on which the candidate experiments are defined, and (2) the unknown edges are located somewhere else within the pathway. For case 1, we deleted e_6 from the pathway model, performed the experimental design and obtained the results summarized in Tables 5 and 6. As expected in this case, deleting an edge altered the experimental design results. For instance, the new set of candidate experiments in Table 5 is smaller than the original set in Table 3. Also, after removing e_6 , the first optimal experiment for the error-free case changes from determining the priority label between edges e_7 and e_9 to determining the priority label between edges e_7 and e_8 . For case 2, we deleted the subset $E_{\text{del}} = \{e_{23}, e_{24}, e_{28}, e_{32}, e_{34}, e_{38}, e_{40}, e_{46}, e_{50}\}$ from the pathway model, where no edge in E_{del} belongs to the original set of candidate experiments. In this case, the experimental design results were very similar to the original case study presented in Table 4. Therefore, this case of network incompleteness did not affect the experimental design results.

6 Conclusions

We have proposed a novel experimental design approach based on the mean objective cost of uncertainty to reduce dynamics uncertainty in a class of dynamical models at the interaction level. We have considered uncertainty due to both model incompleteness and experimental error in our formulations to find the optimal experiment relative to network intervention. We have applied the approach to randomly generated synthetic networks and the NIH ErbB2/ErbB3 pathway. We have evaluated the performance of the proposed experimental design approach compared to random experiment selection. The basic equations, (18) through (27), are general, so that the overall methodology can be applied in many circumstances, the particulars in the case of experimental error depending on the joint distribution between the true and estimated parameters.

As a final comment, we should emphasize the importance of utilizing accurate prior knowledge for the proposed experimental design framework. In the specific problem we considered in this paper, prior knowledge includes probabilities used for the unknown priority labels called the *prior distribution* in a Bayesian context, the probability distribution for the initial conditions, and the error probabilities associated to each experiment. In the

case that there is biological evidence or practical consideration, one can employ them to come up with non-uniform probability distributions. However, this should be done with careful consideration of the fact that false non-uniform distributions can degrade the experimental design performance. In general, it is suggested to use uniform distributions unless there are some clues favoring non-uniform distributions. One can also employ a prior construction methodology to refine the prior distribution. However, prior construction is not straightforward and should be done specifically for each application.

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Biographies

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Roozbeh Dehghannasiri received the B.S. degree from the University of Tehran, Iran, in 2010 and the M.A.Sc. degree from the McMaster University, Canada, in 2012, both in electrical engineering. Since 2012, he has been a Ph.D. student in the Genomic Signal Processing Laboratory at the Department of Electrical and Computer Engineering of Texas A&M University. His current research interests include computational biology, uncertainty quantification, and statistical signal processing. Mr. Dehghannasiri is the recipient of the McMaster Outstanding Thesis Research Award in 2012 and the Best Paper Award at the 12th Annual MCBIOS Conference in 2015.

Edward R. Dougherty is a Distinguished Professor in the Department of Electrical and Computer Engineering at Texas A&M University in College Station, TX, where he holds the Robert M. Kennedy '26 Chair in Electrical Engineering and is Scientific Director of the Center for Bioinformatics and Genomic Systems Engineering. He holds a Ph.D. in mathematics from Rutgers University and an M.S. in Computer Science from Stevens Institute of Technology, and has been awarded the *Doctor Honoris Causa* by the Tampere University of Technology. He is a fellow of both IEEE and SPIE, has received the SPIE President's Award, and served as the editor of the SPIE/IS&T Journal of Electronic Imaging. At Texas A&M University he has received the Association of Former Students Distinguished Achievement Award in Research, been named Fellow of the Texas Engineering Experiment Station and Halliburton Professor of the Dwight Look College of Engineering. Prof. Dougherty is author of 16 books and author of more than 300 journal papers.

Fig. 1.

An example network used to illustrate the state vector update procedure. The gray arrows indicate inputs/outputs and the blue arrows show activation.

Fig. 2.
Percentage of networks with Tie, Success, and Failure results.

Fig. 3.
Average normalized dynamic performance error.

Fig. 4.

Percentage of networks whose highest ranked experiments ξ_{u^*} for $0 < \delta \leq 0.5$ differ from $\xi_{u^*|_{\delta=0}}$.

Fig. 5.
Average performance error after conducting sequential experiments.

Fig. 6.

Graphical representation of ErbB2/ErbB3 pathway. The gray, blue, and red arrows indicate inputs/outputs, activation, and inhibition, respectively.

TABLE 1

Average CPU processing time (in seconds) needed for different number $\pi(T^M)$ of time steps in the set of dynamic trajectories.

$\pi(T^M)$	20	60	90	140
time	0.186	0.572	0.994	1.383

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TABLE 2

The performance nodes and their desired values for ErbB2/ErbB3 pathway.

event/entity name	node number	v^d	reference
cell proliferation	n_{72}	0	[38]
cell migration	n_{59}	1	[39]
myelination	n_{71}	1	[40]
nervous system development	n_{23}	1	[41]
mammary gland morphogenesis	n_{22}	1	[42]
heart morphogenesis	n_{21}	1	[43]
Fos proto-oncogene	n_{77}	0	[44]
cholinergic receptor nicotinic alpha 1	n_{76}	0	[45]
Jun proto-oncogene	n_{78}	0	[46]
cholinergic receptor nicotinic epsilon	n_{81}	0	[47]

TABLE 3

Set of candidate experiments and the description of edges involved in the experiments for ErbB2/ErbB3 pathway.

experiment number	edges	experiment number	edges
ξ_1	(e_3, e_7)	ξ_6	(e_6, e_9)
ξ_2	(e_3, e_8)	ξ_7	(e_7, e_8)
ξ_3	(e_3, e_9)	ξ_8	(e_7, e_9)
ξ_4	(e_6, e_7)	ξ_9	(e_8, e_9)
ξ_5	(e_6, e_8)		
edge	interaction type	edge	interaction type
e_3	modification	e_8	mammary gland morphogenesis
e_6	modification	e_9	nervous system development
e_7	heart morphogenesis		

TABLE 4
Percentage of selection of each experiment for different experimental errors for ErbB2/ErbB3 pathway.

$\delta = 0$	experiment number		1st	2nd	3rd	4th	5th	6th	7th	8th	9th
	chosen experiment		ξ_8	ξ_7	ξ_9	ξ_1	ξ_2	ξ_3	ξ_4	ξ_5	ξ_6
$\delta = 0$	experiment number		1st	2nd	3rd	4th	5th	6th	7th	8th	9th
	ξ_1		-	-	28%	72%	-	-	-	-	-
	ξ_2		-	-	-	28%	72%	-	-	-	-
	ξ_3		-	-	-	-	28%	60%	-	-	12%
	ξ_4		-	-	-	-	-	40%	60%	-	-
	ξ_5		-	-	-	-	-	-	40%	60%	-
	ξ_6		-	-	-	-	-	-	-	40%	60%
	ξ_7	100%	-	-	-	-	-	-	-	-	-
	ξ_8	-	-	20%	68%	-	-	-	-	-	12%
$\delta = 0.35$	ξ_9	-	-	80%	4%	-	-	-	-	-	16%
	experiment number		1st	2nd	3rd	4th	5th	6th	7th	8th	9th
	ξ_1		-	32%	50%	4%	12%	2%	-	-	-
	ξ_2	100%	-	-	-	-	-	-	-	-	-
	ξ_3	-	-	18%	45%	2%	2%	16%	10%	5%	4%
	ξ_4	-	68%	14%	9%	9%	-	-	-	-	-
	ξ_5	-	-	18%	3%	40%	21%	11%	7%	-	-
	ξ_6	-	-	-	23%	10%	30%	21%	5%	11%	-
	ξ_7	-	-	-	16%	-	11%	21%	24%	28%	-
$\delta = 0.35$	ξ_8	-	-	-	-	19%	4%	10%	33%	34%	-
	ξ_9	-	-	-	-	8%	16%	27%	26%	23%	-

TABLE 5

Set of candidate experiments for ErbB2/ErbB3 pathway with incomplete information (case study 1).

experiment number	edges	experiment number	edges
ξ_1	(e_3, e_7)	ξ_4	(e_7, e_8)
ξ_2	(e_3, e_8)	ξ_5	(e_7, e_9)
ξ_3	(e_3, e_9)	ξ_6	(e_8, e_9)

TABLE 6

Percentage of selection of each experiment for different experimental errors for ErbB2/ErbB3 pathway with incomplete information (case study 1).

$\delta = 0$	experiment number					
	1st	2nd	3rd	4th	5th	6th
$\delta = 0.2$	chosen experiment					
	ξ_1	ξ_2	ξ_3	ξ_4	ξ_5	ξ_6
	experiment number	1st	2nd	3rd	4th	5th
	ξ_1	-	-	31%	69%	-
	ξ_2	-	-	-	31%	69%
	ξ_3	-	-	-	-	31%
$\delta = 0.35$	ξ_4	100%	-	-	-	-
	ξ_5	-	21%	67%	-	-
	ξ_6	-	79%	2%	-	-
	experiment number	1st	2nd	3rd	4th	5th
	ξ_1	-	100%	-	-	-
	ξ_2	-	-	66%	12%	-
$\delta = 0.5$	ξ_3	100%	-	-	-	-
	ξ_4	-	-	22%	17%	39%
	ξ_5	-	-	12%	15%	32%
	ξ_6	-	-	-	56%	29%
	experiment number	1st	2nd	3rd	4th	5th
	ξ_1	-	100%	-	-	-