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Robust model invalidation for chemical reaction networks using generalized moments

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Abstract— **Many biomolecular systems can be described by chemical reaction networks, however, there may be several candidate networks based on the known biology for a particular system. Determining which chemical reaction network models are inconsistent with observed data can be done via model invalidation. In this work, we formulate and solve a robust version of the model invalidation problem for the case where only measurements from the stationary distribution are available. This problem corresponds to determining if an observed distribution could have been generated by the given chemical reaction network for some value of the parameters, plus a perturbation of bounded size with respect to total variation distance. The main technical tool we introduce to solve the problem is a set of generalized moments that make the problem amenable to an algorithmic solution.**

I. INTRODUCTION

Many systems of interest in synthetic and systems biology can be modeled by stochastic chemical reaction networks. These models describe the evolution of the molecular counts of each species as a continuous-time Markov chain over the non-negative lattice [3]. For many design problems in synthetic biology, one must select molecules that implement a specific set of chemical reactions from a set of available molecules. Therefore, determining from experimental data whether a particular set of candidate molecules implements the desired model is highly relevant for design. One framework for deciding if a model is "correct" is *model invalidation*. In this framework, the experimental data is either consistent or inconsistent with a given model. If the data is inconsistent with the model, then the model is invalidated: we know that the model is incorrect in the sense that it could not have generated the data. On the other hand, if the data is consistent with the model, the model may or may not have generated the data [4], [22].

Approaches to check if data invalidates the model have been developed for ordinary differential equation models of biological systems [21], [13], [23], [8], which are applicable when one wishes to model how the mean of a population of cells evolves over time. However, in many cases of interest, experiments are performed wherein a large population of cells is cultured, and at certain times the distribution of the species across the population is measured using techniques such as flow cytometry [2] or single cell RNA sequencing [12]. Such distributional data has been used for identifying the parameters of chemical reaction networks [18], [15], [17]. However, the problem of model invalidation from distributional data is largely unexplored. A special case of distributional data is when only samples from the stationary distribution are measured, which is the case we focus on in this work. To allow for the possibility that the observed empirical distribution is perturbed in some way from the stationary distribution of the idealized chemical reaction network model, e.g. by outliers or finite sample effects, we study a *robust* model invalidation problem that requires the observed distribution to be sufficiently far in total variation distance from all stationary distributions achievable by the model before we invalidate the model. In this setting, the model invalidation problem can be naturally formulated as a nonconvex quadratic program, where the nonconvexity arises through the bilinear constraints between the (unknown) parameters and the probability mass function given by the chemical master equation (CME) at steady state. Such a quadratic program cannot be solved in practice, since the number of decision variables is equal to the number of relevant microstates, which even for small systems may be extremely large or infinite. Our approach summarizes the stationary distribution using finitely many "exponentially weighted moments," which we introduce. In this way, we obtain a much smaller, though still nonconvex, quadratic program that can be solved for biologically relevant systems using commercial software such as Gurobi [1].

Our approach uses methods that are similar to the semidefinite and linear programming approaches to bounding the moments of the stationary distribution [10], [7]. Such methods are based on the fact that the lower order moments must satisfy certain constraints, which come from the CME [9], and the fact that one can describe the set of moments achieved by any probability distribution using semidefinite programming [14]. However, when the maximum molecular counts of the species are unbounded, the total variation distance between two distributions cannot be bounded from below by comparing finitely many moments of the two distributions. This is due to the fact that small perturbations in total variation can cause unbounded changes in the moments, and results in an inability to robustly invalidate a model using finitely many moments. To resolve this issue, we introduce a novel family of generalized moments which are better suited to the model invalidation problem for chemical reaction networks in the sense that the total variation distance between two distributions can be underapproximated by comparing finitely many of our generalized moments.

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The remainder of the paper is organized as follows. In Section II, we provide mathematical background and introduce our definition of robust model invalidation. In Section III, we introduce these generalized moments and show how to construct sets where the first k generalized moments of the stationary distribution must lie. Then, in Section IV we exploit this construction to give a solution to the robust model invalidation problem. We illustrate our method by applying it to a particular chemical reaction network in Section V, and provide concluding remarks and directions for future work in Section VI.

II. PROBLEM SETTING

A. Notation and mathematical background

We denote by $\mathcal{P}(\mathcal{D})$ the set of all probability distributions supported on the set $\mathcal{D}$. Where possible, we denote random variables by uppercase symbols, e.g. X, and the value of random variables on a particular event by lowercase symbols, e.g. x. The *total variation distance* between two probability distributions ν and ρ in $\mathcal{P}(\mathbb{Z}^n_{\geq 0})$, the set of probability distributions over $\mathbb{Z}^n_{\geq 0}$, is defined as

$$d_{TV}(\nu,\rho) = \sup_{S\subseteq\mathbb{Z}^n_{\geq 0}} |\nu(S)-\rho(S)|$$

where $\nu(S) = \sum_{\boldsymbol{x}\in S}\nu(\boldsymbol{x})$ and $\rho(S) = \sum_{\boldsymbol{x}\in S}\rho(\boldsymbol{x})$. We will make use of the fact that since ν and ρ are supported on $\mathbb{Z}^n_{\geq 0}$, $d_{TV}(\nu,\rho) = \frac{1}{2}\|\boldsymbol{p}-\boldsymbol{q}\|_1$, where $\boldsymbol{p}$ and $\boldsymbol{q}$ are vectors comprised of the values $\nu(\boldsymbol{x})$ and $\rho(\boldsymbol{x})$ for $\boldsymbol{x}\in\mathbb{Z}^n_{\geq 0}$ respectively.

B. Stochastic chemical reaction networks

We consider a continuous-time Markov chain model of a chemical reaction network (CRN) consisting of n species with molecular counts $\boldsymbol{X}(t) = [X_1(t),\ldots,X_n(t)]^T$ evolving via r reactions $(\boldsymbol{\xi}^i_r)^T\mathbf{X} \xrightarrow{\theta_i} (\boldsymbol{\xi}^i_p)^T\mathbf{X}$. When reaction i fires, the species counts $\boldsymbol{X}$ changes by $\boldsymbol{\xi}^i = \boldsymbol{\xi}^i_p - \boldsymbol{\xi}^i_r$. Each reaction occurs stochastically at rate $q_i(\boldsymbol{x})$, which is proportional to $\theta_i \geq 0$, the reaction rate constant of reaction i. Specifically, we consider CRNs with only zeroth, first, and second order reactions. A zeroth order reaction is of the form $\emptyset \xrightarrow{\theta_i} (\boldsymbol{\xi}^i_p)^T\mathbf{X}$, and has propensity $q_i(\boldsymbol{x}) = \theta_i$. A first order reaction is of the form $\mathrm{X}_s \xrightarrow{\theta_i} (\boldsymbol{\xi}^i_p)^T\mathbf{X}$ for some s, and has propensity $q_i(\boldsymbol{x}) = \theta_i x_s$. A second order reaction is of the form $\mathrm{X}_s + \mathrm{X}_{s'} \xrightarrow{\theta_i} (\boldsymbol{\xi}^i_p)^T\mathbf{X}$ for some s, s', and has propensity $q_i(\boldsymbol{x}) = \theta_i x_s x_{s'}$ if $s \neq s'$, and propensity $q_i(\boldsymbol{x}) = \frac{1}{2}\theta_i x_s(x_s-1)$ if $s = s'$. Since we assume that there are no third order or higher order reactions, for all i, $q_i(\boldsymbol{x})$ is a polynomial of degree less than or equal to two. The Chemical Master Equation (CME) describes the time evolution of the probability mass function of the species counts:

$$\frac{d}{dt}\mathbb{P}\left[\boldsymbol{X}(t)=\boldsymbol{x}\right] = \sum_{i=1}^r q_i(\boldsymbol{x}-\boldsymbol{\xi}^i)\mathbb{P}\left[\boldsymbol{X}(t)=\boldsymbol{x}-\boldsymbol{\xi}^i\right] - \sum_{i=1}^r q_i(\boldsymbol{x})\mathbb{P}\left[\boldsymbol{X}(t)=\boldsymbol{x}\right].$$

In this work we assume that $\boldsymbol{X}(t)$ is ergodic, and as such the CME has a unique steady state solution, which is the stationary distribution of $\boldsymbol{X}(t)$.

For any function $h:\mathbb{Z}^n_{\geq 0}\to\mathbb{R}$ we have the corresponding *generalized moment* $\mathbb{E}\left[h(\boldsymbol{X})\right]$, when the expectation exists. When this expectation is differentiable, we have that

$$\frac{d}{dt}\mathbb{E}\left[h(\boldsymbol{X})\right] = \mathbb{E}\left[\sum_{i=1}^r q_i(\boldsymbol{X})\left(h(\boldsymbol{X}+\boldsymbol{\xi}^i)-h(\boldsymbol{X})\right)\right], \quad (1)$$

whenever the right hand side is finite. For a proof of this formula see Lemma 2.1 in [9]. We refer the interested reader to [3] for a deeper background on Continuous Time Markov Chain models of CRNs.

C. Robust model invalidation

Given a CRN with unknown reaction rate constants $\boldsymbol{\theta}\in\Theta$, let $\pi(\boldsymbol{x};\boldsymbol{\theta})$ denote the stationary distribution. Given an observed distribution $\hat{\pi}$, the model is invalidated if no value of $\boldsymbol{\theta}\in\Theta$ reproduces the observed distribution, i.e. if there does not exist a $\boldsymbol{\theta}\in\Theta$ such that $\pi(\boldsymbol{x};\boldsymbol{\theta})$ matches the observed distribution. To account for the possibility of measurement error, in this work we consider a robust variant of model invalidation, which we formally define as follows:

Definition 2.1: Given a CRN model with parameters $\boldsymbol{\theta}\in\Theta$ and stationary distribution $\pi(\boldsymbol{x};\boldsymbol{\theta})$, an observed distribution $\hat{\pi}(\boldsymbol{x})$, and a threshold $\eta\geq 0$, $\hat{\pi}(\boldsymbol{x})$ *robustly invalidates the model with threshold* η if there does not exist $\boldsymbol{\theta}\in\Theta$ such that $d_{TV}(\pi(\cdot;\boldsymbol{\theta}),\hat{\pi})\leq\eta$.

Our notion of robust model invalidation can capture multiple effects. For example, if ζ fraction of samples are corrupted, e.g. drawn from an arbitrary distribution ν, the observed distribution with infinitely many samples is

$$\hat{\pi} = (1-\zeta)\pi(\cdot;\boldsymbol{\theta}) + \zeta\nu. \quad (2)$$

Since it follows that $d_{TV}(\hat{\pi},\pi(\cdot;\boldsymbol{\theta}))\leq\zeta$, one can pick $\eta=\zeta$ and be guaranteed that if $\hat{\pi}$ robustly invalidates the model $\pi(\cdot;\boldsymbol{\theta})$ with threshold η, then $\hat{\pi}$ could not have been generated by (2) for any $\boldsymbol{\theta}\in\Theta$ and any distribution ν. Alternatively, robust model invalidation can capture $\hat{\pi}$ being an arbitrary "perturbation" in total variation distance to $\pi(\cdot;\boldsymbol{\theta})$, representing the fact that CRN models are rarely perfect descriptions of biological systems. In Remark 4.3, we will see another motivation for our definition of robust model invalidation through its connection to hypothesis testing.

Remark 2.1: One could define robust model invalidation using a different metric on the space of probability distributions. However, in addition to total variation distance capturing certain unmodeled effects, as noted above, it will be seen to be computationally convenient in Section IV.

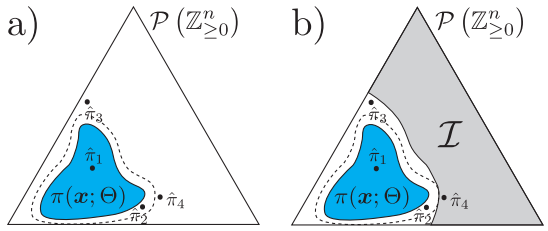


Fig. 1: Model invalidation setup. a) Robust model invalidation. $\mathcal{P}(\mathbb{Z}^n_{\geq 0})$ is the space of all probability distributions supported on the nonnegative integer lattice. The set $\pi(\boldsymbol{x};\Theta) = \{\pi(\boldsymbol{x};\boldsymbol{\theta})|\boldsymbol{\theta}\in\Theta\}$ is all distributions that correspond to some $\boldsymbol{\theta}\in\Theta$. The dashed line shows the set of all distributions $\nu\in\mathcal{P}(\mathbb{Z}^n_{\geq 0})$ such that $d_{TV}(\pi(\cdot;\boldsymbol{\theta}),\nu)\leq\eta$ for some $\boldsymbol{\theta}\in\Theta$. Distribution $\hat{\pi}_1$ is in $\pi(\boldsymbol{x};\Theta)$ and does not invalidate the model, $\hat{\pi}_2$ is within η in total variation of $\pi(\boldsymbol{x};\Theta)$ and so does not robustly invalidate the model with threshold η. Distributions $\hat{\pi}_3$ and $\hat{\pi}_4$ are not within η of $\pi(\boldsymbol{x};\Theta)$ in total variation, and so each robustly invalidates the model with threshold η. b) Algorithm for model invalidation. The set $\mathcal{I}$ shows the set of distributions for which a particular algorithm declares that $\hat{\pi}$ robustly invalidates the model with threshold η. In this case, only $\hat{\pi}_4$ would result in the algorithm returning "robustly invalidates," whereas $\hat{\pi}_1$ through $\hat{\pi}_3$ would result in the algorithm making no declaration.

Remark 2.2: In most cases, $\hat{\pi}$ is computed as the empirical distribution of the data. However, since we do not require that the data be drawn from a distribution in the set $\pi(\cdot;\Theta)$, there may be reasons other than having finitely many samples that $\hat{\pi}$ deviates from $\pi(\cdot;\boldsymbol{\theta})$.

The problem we consider in this work is constructing an algorithm for robust model invalidation, that is, given a CRN model $\pi(\cdot;\boldsymbol{\theta})$ with $\boldsymbol{\theta}\in\Theta$, observed distribution $\hat{\pi}$, and a threshold η, determine if $\hat{\pi}$ robustly invalidates $\pi(\cdot,\boldsymbol{\theta})$. As shown in Figure 1, we seek an algorithm having the property that it never incorrectly declares that the observed distribution robustly invalidates the model. We do however allow the algorithm to be conservative, i.e. it may fail to declare the model robustly invalidated, even when $\hat{\pi}$ robustly invalidates the model according to Definition 2.1. This mirrors the philosophy behind model invalidation, where declaring the model robustly invalidated represents a firm belief that the model is incorrect, and the alternative is that we do not know if the model is correct or not. When using a algorithm such as the one we develop in this work, this lack of knowledge may be because $\hat{\pi}$ is close to $\pi(\cdot;\Theta)$, or it may be because $\hat{\pi}$ is not close to $\pi(\cdot;\Theta)$, but our algorithm could not prove this fact. As we will see, allowing for this type of conservatism allows us to construct a computationally efficient algorithm for robust model invalidation.

III. EXPONENTIALLY WEIGHTED MOMENTS

In this section, we introduce the generalized moments that are necessary to solve the model invalidation problem in Section IV. In Section III-A, we then show to how construct constraints that hold for the generalized moments of any distribution that is close to $\hat{\pi}$, and in Section III-B we use the CME to construct bilinear constraints relating the generalized moments of the stationary distribution and the reaction rate constants.

Let ν be a probability mass function over $\mathbb{Z}^n_{\geq 0}$ and let $\gamma>0$ such that $\frac{1}{\gamma}\in\mathbb{Z}$. For $\boldsymbol{i}=(i_1,i_2,\ldots,i_n)\in\mathbb{Z}^n_{\geq 0}$ we define

$$g_{\boldsymbol{i}}(\boldsymbol{x}) = c_{\boldsymbol{i}} e^{-\gamma\langle \mathbf{1},\boldsymbol{x}\rangle}\prod_{j=1}^n x_j^{i_j},$$

where $c_{\boldsymbol{i}} = \left(e^{-\sum_{j=1}^n i_j}\prod_{j=1}^n\left(\frac{i_j}{\gamma}\right)^{i_j}\right)^{-1}$. Observe that $0\leq g_{\boldsymbol{i}}(\boldsymbol{x})\leq 1$ for all $\boldsymbol{x}\geq 0$, and that $g_{\boldsymbol{i}}(\boldsymbol{x})$ takes value 1 at exactly $\boldsymbol{x}=\frac{1}{\gamma}\boldsymbol{i}$. We then define the exponentially weighted moments of ν as

$$\lambda_{\boldsymbol{i}}(\nu) = \mathbb{E}_\nu\left[g_{\boldsymbol{i}}(\boldsymbol{X})\right].$$

Let $k\in\mathbb{N}$. For convenience let $\phi:\mathbb{Z}_{>0}\to\mathbb{Z}^n_{\geq 0}$ be a one-to-one function such that $\phi(\{1,\ldots,K\}) = \{0,1,\ldots,k\}^n$. We define

$$\boldsymbol{g}^k(\boldsymbol{x}) = \begin{bmatrix} g_{\phi(1)}(\boldsymbol{x}) & g_{\phi(2)}(\boldsymbol{x}) & \ldots & g_{\phi(K)}(\boldsymbol{x})\end{bmatrix}^T,$$

where $K=(k+1)^n$, and

$$\boldsymbol{\lambda}^k(\nu) = \mathbb{E}_\nu\left[\boldsymbol{g}^k(\boldsymbol{X})\right].$$

Thus, for a distribution ν, $\boldsymbol{\lambda}^k(\nu)$ is the vector of all generalized moments such that the degree in each species is $\leq k$, i.e. $\lambda_{\boldsymbol{i}}$ where $\boldsymbol{i}\leq k$. It will sometimes be convenient to express $\boldsymbol{\lambda}^k(\nu)$ using matrix notation. Let $\boldsymbol{p}\in\ell_1$ be a probability vector representing $\nu\in\mathcal{P}(\mathbb{Z}^n_{\geq 0})$. We denote by $\mathcal{G}$ the matrix with $(k+1)^n$ rows and infinite columns such that $\boldsymbol{\lambda}^k(\nu)=\mathcal{G}\boldsymbol{p}$. Observe that each column of $\mathcal{G}$ will be given by $\boldsymbol{g}^k(\boldsymbol{x}^*)$ for some $\boldsymbol{x}^*\in\mathbb{Z}^n_{\geq 0}$.

A. Exponentially weighted moments of distributions close to $\hat{\pi}$

We now consider the set of values of $\boldsymbol{\lambda}^k(\nu)$ for some probability distribution ν that is within η of $\hat{\pi}$ in total variation. These values are given by the set $\Lambda^k(\hat{\pi},\eta)$, defined formally as

$$\Lambda^k(\hat{\pi},\eta) = \left\{\boldsymbol{\lambda}^k(\nu)\middle|\nu\in\mathcal{P}(\mathbb{Z}^n_{\geq 0})\text{ s.t. }d_{TV}(\nu,\hat{\pi})\leq\eta\right\}.$$

In this section we give one approach to producing an outer approximation of $\Lambda^k(\hat{\pi},\eta)$. Let us define c_λ as the maximum 2-norm discrepancy between $\boldsymbol{\lambda}^k(\hat{\pi})$ and any vector of generalized moments of a distribution that is within η of $\hat{\pi}$ in total variation distance:

$$c_\lambda(\hat{\pi},\eta) = \sup_{\nu\in\mathcal{P}(\mathbb{Z}^n_{\geq 0}):d_{TV}(\nu,\hat{\pi})\leq\eta}\|\boldsymbol{\lambda}^k(\nu)-\boldsymbol{\lambda}^k(\hat{\pi})\|_2.$$

We have that $\left\{\boldsymbol{\lambda}\middle|\|\boldsymbol{\lambda}-\boldsymbol{\lambda}^k(\hat{\pi})\|_2\leq c_\lambda(\hat{\pi},\eta)\right\}\supseteq\Lambda^k(\hat{\pi},\eta)$. We now show how to compute upper bounds on c_λ, which can then be used to create an outer approximation to $\Lambda^k(\hat{\pi},\eta)$. We start by observing that

$$c_\lambda(\hat{\pi},\eta) = \sup_{\boldsymbol{p}\in\ell_1:\boldsymbol{p}\geq 0,\ \sum_i p_i=1,\ \|\boldsymbol{p}-\hat{\boldsymbol{p}}\|_1\leq 2\eta}\|\mathcal{G}(\boldsymbol{p}-\hat{\boldsymbol{p}})\|_2, \quad (3)$$

where $\hat{\boldsymbol{p}}$ is the probability vector representation of $\hat{\pi}$. Define e_λ as

$$e_\lambda = \sup_{\tilde{\boldsymbol{p}} \in \ell_1 : \|\tilde{\boldsymbol{p}}\|_1 \leq 2\eta, \sum_i \tilde{p}_i = 0} \|\mathcal{G}\tilde{\boldsymbol{p}}\|_2. \tag{4}$$

Since the feasible set in (4) is a superset of the feasible set in (3), e_λ provides an upper bound on c_λ. Since (4) is a convex maximization problem, to compute e_λ we must check the value of $\|\mathcal{G}\tilde{\boldsymbol{p}}\|_2$ at every extreme point of the feasible set. This is formalized, with the extreme points given explicitly, in Lemma 3.1.

Lemma 3.1: Let $H = \{\boldsymbol{p} \in \ell_1 | \sum_i p_i = 0,\ \|\boldsymbol{p}\|_1 \leq 2\eta\}$, $K \in \mathbb{R}^{m \times \infty}$ have finite absolute row sums, and $\boldsymbol{b} \in \mathbb{R}^m$. For $i, j \geq 1$, let $\boldsymbol{v}_{ij} = \eta\boldsymbol{\delta}_i - \eta\boldsymbol{\delta}_j$ where $\boldsymbol{\delta}_i$ is the i^{th} canonical unit vector in ℓ_1. We have that

$$\sup_{\boldsymbol{p} \in H} \|K\boldsymbol{p} + \boldsymbol{b}\|_2 = \sup_{1 \leq i,j} \|K\boldsymbol{v}_{ij} + \boldsymbol{b}\|_2.$$

Proof: See [11]. ∎

Lemma 3.1 implies that

$$e_\lambda = \sup_{i,j \geq 1} \|\mathcal{G}\boldsymbol{v}_{ij}\|_2 = \sup_{\boldsymbol{x}, \boldsymbol{x}' \in \mathbb{Z}^n_{\geq 0}} \eta \|\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}')\|_2,$$

where $\boldsymbol{v}_{ij} = \eta\boldsymbol{\delta}_i - \eta\boldsymbol{\delta}_j$. Partition $\mathbb{Z}^{2n}_{\geq 0}$ into three sets,

$$S^1_{N'} = \left\{(\boldsymbol{x}, \boldsymbol{x}') \in \mathbb{Z}^{2n}_{\geq 0} \middle| \boldsymbol{x}, \boldsymbol{x}' \leq N'\right\},$$
$$S^2_{N'} = \left\{(\boldsymbol{x}, \boldsymbol{x}') \in \mathbb{Z}^{2n}_{\geq 0} \middle| \boldsymbol{x}, \boldsymbol{x}' \not\leq N'\right\},$$
$$S^3_{N'} = \left\{(\boldsymbol{x}, \boldsymbol{x}') \in \mathbb{Z}^{2n}_{\geq 0} \middle| \boldsymbol{x} \not\leq N' \text{ or } \boldsymbol{x}' \not\leq N', \text{but not both}\right\}.$$

Here, $\boldsymbol{x} \leq N'$ means that every elements of $\boldsymbol{x}$ is less than or equal to N', and $\boldsymbol{x} \not\leq N'$ means that at least one element of $\boldsymbol{x}$ is greater than N'. Additionally, let

$$B_{N'} = \left\{\boldsymbol{x} \in \mathbb{Z}^n_{\geq 0} \middle| \boldsymbol{x} \leq N' \text{ and } \exists i \text{ s.t. } x_i = N'\right\},$$

which the set of points in $\mathbb{Z}^n_{\geq 0}$ on the "boundary" of the subset where $\boldsymbol{x} \leq N'$. Let

$$e^1_\lambda(N') = \eta \cdot \max_{(\boldsymbol{x}, \boldsymbol{x}') \in S^1_{N'}} \|\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}')\|_2,$$
$$e^2_\lambda(N') = \eta \cdot \sup_{(\boldsymbol{x}, \boldsymbol{x}') \in S^2_{N'}} \|\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}')\|_2,$$
$$e^3_\lambda(N') = \eta \cdot \sup_{(\boldsymbol{x}, \boldsymbol{x}') \in S^3_{N'}} \|\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}')\|_2.$$

Since $S^1_{N'} \cup S^2_{N'} \cup S^3_{N'} = \mathbb{Z}^{2n}_{\geq 0}$, we have that

$$e_\lambda(N') = \max\left\{e^1_\lambda(N'), e^2_\lambda(N'), e^3_\lambda(N')\right\}.$$

One can compute $e^1_\lambda(N')$ since it is a maximum over a finite number of points. However, it is not obvious how to compute $e^2_\lambda(N')$ and $e^3_\lambda(N')$. Let

$$\tilde{e}^2_\lambda(N') = 2\eta \max_{\boldsymbol{x} \in B_{N'}} \|\boldsymbol{g}^k(\boldsymbol{x})\|_2,$$

and

$$\tilde{e}^3_\lambda(N') = \eta \cdot \max_{\boldsymbol{x} \in \mathbb{Z}^n_{\geq 0}, \boldsymbol{x} \leq N'} \|\boldsymbol{g}^k(\boldsymbol{x})\|_2 + \eta \cdot \max_{\boldsymbol{x} \in B_{N'}} \|\boldsymbol{g}^k(\boldsymbol{x})\|_2.$$

Define

$$\tilde{e}_\lambda(N') = \max\left\{e^1_\lambda(N'), \tilde{e}^2_\lambda(N'), \tilde{e}^3_\lambda(N')\right\}.$$

For sufficiently large N', $e_\lambda \leq \tilde{e}_\lambda(N')$, with the bound becoming tight as $N' \to \infty$. This is formalized in the following lemma.

Lemma 3.2: For any integer $N' > k/\gamma$ we have that

$$e_\lambda \leq \tilde{e}_\lambda(N').$$

Furthermore, $\lim_{N' \to \infty} \tilde{e}_\lambda(N') = e_\lambda$.

Proof: See [11]. ∎

Based on Lemma 3.2 we can construct an outer approximation to $\Lambda^k(\hat{\pi}, \eta)$, as given in the following theorem.

Theorem 3.1: For any integer $N' > k/\gamma$ we have that

$$\left\{\boldsymbol{\lambda} \middle| \|\boldsymbol{\lambda} - \boldsymbol{\lambda}^k(\hat{\pi})\|_2 \leq \tilde{e}_\lambda(N')\right\} \supseteq \Lambda^k(\hat{\pi}, \eta).$$

Proof: Observe that $c_\lambda \leq e_\lambda$. The result then follows from Lemma 3.2. ∎

We now give another type of constraint that $\boldsymbol{\lambda}^k(\nu)$ satisfies for all ν such that $d_{TV}(\nu, \hat{\pi}) \leq \eta$. We exploit that fact that for certain values of γ and k, the elements of $\boldsymbol{\lambda}^k$ are constrained to be approximately in a lower dimensional subspace of $\mathbb{R}^{(k+1)^n}$. If we can find a $T \in \mathbb{R}^{m \times (k+1)^n}$ such that the nullspace of T is the subspace of $\mathbb{R}^{(k+1)^n}$ that $\boldsymbol{\lambda}^k$ is close to, $\|T\boldsymbol{\lambda}^k\|_2$ will be small. We first give a general method for bounding

$$c_T = \sup_{\nu \in \mathcal{P}(\mathbb{Z}^n_{\geq 0}) : d_{TV}(\nu, \hat{\pi}) \leq \eta} \|T\boldsymbol{\lambda}^k(\nu)\|_2 \tag{5}$$

for an arbitrary T. Then, we give a heuristic for selecting T. Our development of the bound on c_T proceeds similarly to our bound on c_λ. Let

$$e_T = \sup_{\boldsymbol{p} : \sum_i p_i = 0, \|\boldsymbol{p} - \hat{\boldsymbol{p}}\|_1 \leq 2\eta} \|T\mathcal{G}\boldsymbol{p}\|_2. \tag{6}$$

From the fact that the feasible set is larger in (6) than in (5) we have that $c_T \leq e_T$. An equivalent expression for e_T is

$$e_T = \sup_{\tilde{\boldsymbol{p}} : \sum_i \tilde{p}_i = 0, \|\tilde{\boldsymbol{p}}\|_1 \leq 2\eta} \|T\boldsymbol{\lambda}^k(\hat{\pi}) + T\mathcal{G}\tilde{\boldsymbol{p}}\|_2.$$

By using Lemma 3.1 we can write e_T as

$$\begin{aligned} e_T &= \sup_{i,j \in \mathbb{Z}_{>0}} \|T\boldsymbol{\lambda}^k(\hat{\pi}) + T\boldsymbol{v}_{ij}\|_2, \\ &= \sup_{\boldsymbol{x}, \boldsymbol{x}' \in \mathbb{Z}^n_{\geq 0}} \|T\boldsymbol{\lambda}^k(\hat{\pi}) + \eta T\left(\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}')\right)\|_2. \end{aligned}$$

Similarly to our approach to bounding e_λ we define

$$e^1_T(N') = \max_{(\boldsymbol{x}, \boldsymbol{x}') \in S^1_{N'}} \|T\boldsymbol{\lambda}^k(\hat{\pi}) + \eta T(\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}'))\|_2,$$
$$e^2_T(N') = \sup_{(\boldsymbol{x}, \boldsymbol{x}') \in S^2_{N'}} \|T\boldsymbol{\lambda}^k(\hat{\pi}) + \eta T(\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}'))\|_2,$$
$$e^3_T(N') = \sup_{(\boldsymbol{x}, \boldsymbol{x}') \in S^3_{N'}} \|T\boldsymbol{\lambda}^k(\hat{\pi}) + \eta T(\boldsymbol{g}^k(\boldsymbol{x}) - \boldsymbol{g}^k(\boldsymbol{x}'))\|_2.$$

Since $S^1_{N'} \cup S^2_{N'} \cup S^3_{N'} = \mathbb{Z}^{2n}_{\geq 0}$, we have that

$$e_T(N') = \max\left\{e^1_T(N'), e^2_T(N'), e^3_T(N')\right\}.$$

One can compute $e^1_T(N')$, but we must bound $e^2_T(N')$ and $e^3_T(N')$. Let

$$\tilde{e}^2_T(N') = \|T\boldsymbol{\lambda}^k(\hat{\pi})\|_2 + 2\eta\|T\|_2 \max_{\boldsymbol{x} \in B_{N'}} \|\boldsymbol{g}^k(\boldsymbol{x})\|_2$$

and

$$\tilde{e}_T^3(N') = \max_{\boldsymbol{x}\in\mathbb{Z}^n_{\geq 0}, \boldsymbol{x}\leq N', \kappa\in\{+1,-1\}} \|T\boldsymbol{\lambda}^k(\hat{\pi}) + \kappa\eta T\boldsymbol{g}^k(\boldsymbol{x})\|_2 + \eta\|T\|_2 \cdot \max_{\boldsymbol{x}\in B_{N'}} \|\boldsymbol{g}^k(\boldsymbol{x})\|_2.$$

We define

$$\tilde{e}_T(N') = \max\left\{e_T^1(N'), \tilde{e}_T^2(N'), \tilde{e}_T^3(N')\right\},$$

and have the following lemma, which establishes that $\tilde{e}_T(N')$, with N' sufficiently large, can be used to bound e_T.

Lemma 3.3: For any integer $N' > k/\gamma$ we have that

$$e_T \leq \tilde{e}_T(N').$$

Furthermore, $\lim_{N'\to\infty} \tilde{e}_T(N') = e_T$.

Proof: See [11]. ∎

Based on Lemma 3.3 we can construct an outer approximation of $\Lambda^k(\hat{\pi}, \eta)$, which we formalize in the following theorem.

Theorem 3.2: For any integer $N' > k/\gamma$ we have that

$$\{\boldsymbol{\lambda} | \|T\boldsymbol{\lambda}\|_2 \leq \tilde{e}_T(N')\} \supseteq \Lambda^k(\hat{\pi}, \eta).$$

Proof: Observe that $c_T \leq e_T$. The result then follows from Lemma 3.3. ∎

While there are many methods to select a matrix T, and Theorem 3.2 will hold for any matrix T, we wish to choose a T so that the intersection of the sets given in Theorems 3.1 and 3.2 is a good outer approximation of $\Lambda^k(\hat{\pi}, \eta)$. Here we simply give a heuristic for selecting T, which is inspired by moment closure techniques for the standard moments [19]. Let $\boldsymbol{\lambda}^k$ be partitioned into $\boldsymbol{\lambda}^k = \begin{bmatrix}(\boldsymbol{\lambda}^{0:k-2})^T & (\boldsymbol{\lambda}^{k-1:k})^T\end{bmatrix}^T$, where $\boldsymbol{\lambda}^{0:k-2}$ is composed of the elements corresponding to $g_{\boldsymbol{i}}(\boldsymbol{x})$ with $\boldsymbol{i} \leq k-2$ and $\boldsymbol{\lambda}^{k-1:k}$ is composed of all the other elements. Note that the existence of such a partitioning requires a particular choice of ϕ. For some choices of γ and k, it will be true that there exists $\tilde{T} \in \mathbb{R}^{\dim \boldsymbol{\lambda}^{k-1:k} \times (k+1)^n}$ such that

$$\forall \nu \in \mathcal{P}(\mathbb{Z}^n_{\geq 0}) \text{ s.t. } d_{TV}(\nu, \hat{\pi}) \leq \eta,\ \boldsymbol{\lambda}^{k-1:k} \approx \tilde{T}\boldsymbol{\lambda}^{0:k-2}.$$

This expresses the idea that at least for distributions close to $\hat{\pi}$, one can approximate $\boldsymbol{\lambda}^{k-1:k}(\nu)$ by a linear combination of the elements of $\boldsymbol{\lambda}^{0:k-2}$. A heuristic for picking such a $\tilde{T}$ is based on least squares,

$$\tilde{T} = G_{N''}^{0:k-1}\left(G_{N''}^{k-1:k}\right)^{\dagger},$$

where $G_{N''} = \begin{bmatrix}G_{N''}^{0:k-1} \\ G_{N''}^{k-2:k}\end{bmatrix}$ is the matrix formed from the columns of $\mathcal{G}$ corresponding to $\boldsymbol{x} \leq N''$, and N'' is picked such that most of the probability mass of $\hat{\pi}$ is contained in the region $\boldsymbol{x} \leq N''$. We than pick $T = \begin{bmatrix}\tilde{T} & I\end{bmatrix}$. While we have not justified that the approximation will be good, the correctness of the robust model invalidation method we introduce in Section IV depends only upon Theorem 3.2, which holds for any matrix T, and thus using a heuristic for selecting T does not affect the rigor of our results.

B. Exponentially weighted moments of the stationary distribution

Here we show that when $\pi(\boldsymbol{x};\boldsymbol{\theta})$ is the stationary distribution of the CME, $\boldsymbol{\lambda}^k(\pi(\cdot;\boldsymbol{\theta}))$ must satisfy particular constraints. Specifically, letting $\omega(\boldsymbol{x}; t, \boldsymbol{\theta})$ be the solution to the CME, we define $A^k(\boldsymbol{\theta}) = \sum_{i=1}^r \theta_i A_i^k$ as the matrix valued function such that

$$\frac{d}{dt}\boldsymbol{\lambda}^{k-2}(\omega(\cdot;t,\boldsymbol{\theta})) = A^k(\boldsymbol{\theta})\boldsymbol{\lambda}^k(\omega(\cdot;t,\boldsymbol{\theta})), \tag{7}$$

when such an $A^k(\boldsymbol{\theta})$ exists. For the stationary distribution $\pi(\boldsymbol{x};\boldsymbol{\theta})$, setting $0 = \frac{d}{dt}\boldsymbol{\lambda}^{k-2}(\pi(\cdot;\boldsymbol{\theta}))$ we have the constraints

$$0 = A^k(\boldsymbol{\theta})\boldsymbol{\lambda}^k(\pi(\cdot;\boldsymbol{\theta})). \tag{8}$$

We stress that the existence of such constraints is a property of the particular generalized moments that we have chosen, and in general, for a set of functions $g_{\boldsymbol{i}}(\boldsymbol{x})$, no such constraints exist. However, a similar property does hold for the standard moments, i.e. expectations of monomials with respect to $\boldsymbol{X}$ [10], [7].

Theorem 3.3: Let $\omega(\boldsymbol{x}; t, \boldsymbol{\theta})$ be the solution to the CME, and let $\pi(\boldsymbol{x};\boldsymbol{\theta})$ be the stationary distribution of the CME, both parameterized by the reaction rate constants $\boldsymbol{\theta}$. Let $\boldsymbol{\lambda}^k(\pi(\cdot;\boldsymbol{\theta}))$ be the vector of generalized moments corresponding to $\pi(\boldsymbol{x};\boldsymbol{\theta})$. Then, there exists $A^k(\boldsymbol{\theta}) \neq 0$ linear in $\boldsymbol{\theta}$ satisfying (7) and (8) for all $\boldsymbol{\theta}$ such that $\boldsymbol{X}(t)$ is ergodic.

Proof: We show that $A^k(\boldsymbol{\theta})$ can be obtained by writing the derivatives of $\boldsymbol{\lambda}^{k-2}(t)$ as a linear combination of the elements of $\boldsymbol{\lambda}^k(t)$. For any multi index $\boldsymbol{i} \leq k-2$, we have from (1) that

$$\frac{d\lambda_{\boldsymbol{i}}(\omega(\cdot;t,\boldsymbol{\theta}))}{dt} = \mathbb{E}\left[\sum_{j=1}^r q_j(\boldsymbol{X})\left(g_{\boldsymbol{i}}(\boldsymbol{X}+\boldsymbol{\xi}^j) - g_{\boldsymbol{i}}(\boldsymbol{X})\right)\right],$$

$$= \mathbb{E}\left[\sum_{j=1}^r q_j(\boldsymbol{X})\left(c_{\boldsymbol{i}}e^{-\gamma\langle\mathbf{1},\boldsymbol{X}+\boldsymbol{\xi}^j\rangle}\prod_{s=1}^n (X_s+\xi_s^j)^{i_s} - c_{\boldsymbol{i}}e^{-\gamma\langle\mathbf{1},\boldsymbol{X}\rangle}\prod_{s=1}^n (X_s)^{i_s}\right)\right],$$

$$= \mathbb{E}\left[c_{\boldsymbol{i}}e^{-\gamma\langle\mathbf{1},\boldsymbol{X}\rangle}\sum_{j=1}^r q_j(\boldsymbol{X})\left(e^{-\gamma\langle\mathbf{1},\boldsymbol{\xi}^j\rangle}\prod_{s=1}^n (X_s+\xi_s^j)^{i_s} - \prod_{s=1}^n (X_s)^{i_s}\right)\right],$$

where all expectations are with respect to $\boldsymbol{X} \sim \omega(\cdot;t,\boldsymbol{\theta})$. One can see that under our assumption that $q_j(\boldsymbol{x})$ is a polynomial of order 2 or less, $\frac{d}{dt}\lambda_{\boldsymbol{i}}(t)$ can be written as a linear combination of the elements of $\boldsymbol{\lambda}^k$. Additionally, since $q_j(\boldsymbol{x})$ is linear in θ_j, one can see that $\frac{d}{dt}\lambda_{\boldsymbol{i}}(t)$ is linear in $\boldsymbol{\theta}$. Thus, but setting $0 = \frac{d}{dt}\lambda_{\boldsymbol{i}}(t)$ for $0 \leq \boldsymbol{i} \leq k-2$, justified by the boundedness of $\boldsymbol{g}^k(\boldsymbol{x})$ and the ergodicity of $\boldsymbol{X}(t)$, we have the desired result for the generalized moments of the stationary distribution. ∎

IV. ROBUST MODEL INVALIDATION

In this section we present the main result of this work, an algorithm that can certify that an observed distribution is farther than η from $\pi(\boldsymbol{x};\Theta)$ in total variation distance. We consider feasibility problem (10), which is a nonconvex quadratically constrained program due to the $0 = \left(\sum_{i=1}^{r}\theta_i A_i^k\right)\boldsymbol{\lambda}$ constraint. The decision variables are $\boldsymbol{\theta} \in \mathbb{R}^r$ and $\boldsymbol{\lambda} \in \mathbb{R}^{(k+1)^n}$, and we assume for simplicity that $\Theta \subseteq \mathbb{R}^r_{>0}$ is a polyhedral set.

$$\|\boldsymbol{\lambda} - \boldsymbol{\lambda}^k(\hat{\pi})\|_2 \leq \tilde{e}_{\boldsymbol{\lambda}}(N') \tag{10a}$$

$$\|T\boldsymbol{\lambda}\|_2 \leq \tilde{e}_T(N') \tag{10b}$$

$$0 = \left(\sum\nolimits_{i=1}^{r}\theta_i A_i^k\right)\boldsymbol{\lambda} \tag{10c}$$

$$\boldsymbol{\theta} \in \Theta \tag{10d}$$

As formalized in Theorem 4.1, if we can show infeasibility of (10), then we have a method to robustly invalidate a model. We note that despite the fact that (10) is nonconvex, it has only $r+(k+1)^n$ variables, and thus the size of (10) can be controlled by our choice of k. We will see in an example that $(k+1)^n$ can be made far smaller than the number of variables needed to naively represent $\pi(\boldsymbol{x};\boldsymbol{\theta})$ to within η in total variation distance. Nonconvex quadratically constrained feasibility problems can be solved by commercial solvers such as Gurobi, using a spatial branch and bound method [1].

Theorem 4.1: Consider a CRN with stationary distribution $\pi(\cdot;\theta)$ and parameters $\boldsymbol{\theta} \in \Theta$ and let $\eta \geq 0$ be a threshold. Let $N' > k/\gamma$. For an observed distribution $\hat{\pi}$, if (10) is infeasible, then the model $\pi(\boldsymbol{x};\boldsymbol{\theta})$ is robustly invalidated with threshold η by $\hat{\pi}$.

Proof: We prove the contrapositive. Suppose the model $\pi(\boldsymbol{x};\boldsymbol{\theta})$ is not robustly invalidated with threshold η by $\hat{\pi}$. Then, exists $\boldsymbol{\theta}^* \in \Theta$ such that $d_{TV}(\pi(\cdot;\boldsymbol{\theta}^*),\hat{\pi}) \leq \eta$. We show that (10) is feasible. We have that $\|\boldsymbol{\lambda}^k(\pi(\cdot;\boldsymbol{\theta}^*)) - \boldsymbol{\lambda}^k(\hat{\pi})\|_2 \leq \tilde{e}_{\boldsymbol{\lambda}}(N')$ and $\|T\boldsymbol{\lambda}^k(\pi(\cdot;\boldsymbol{\theta}^*))\|_2 \leq \tilde{e}_T(N')$ from Theorems 3.1 and 3.2. Additionally, since $\pi(\cdot;\boldsymbol{\theta}^*)$ is the stationary distribution of the CRN with parameters $\boldsymbol{\theta}^*$, we have that $0 = \left(\sum_{i=1}^{r}\theta_i A_i^k\right)\boldsymbol{\lambda}^k(\pi(\cdot;\boldsymbol{\theta}^*))$ from Theorem 3.3. Hence, $\boldsymbol{\lambda}^k(\pi(\cdot;\boldsymbol{\theta}^*))$ is a solution to (10), which completes the proof. ∎

Remark 4.1: Instead of solving the feasibility problem (10), one can compute η^*, the minimum η such that (10) is feasible. Then, $d_{TV}(\hat{\pi},\pi(\cdot;\Theta)) \geq \eta^*$, and so we have a lower bound on how much the observed distribution deviates from the model.

Remark 4.2: A formulation of robust model invalidation similar to (10), but using the standard moments instead of the exponentially weighted moments, is not possible. In fact, let $h_{\boldsymbol{i}}(\boldsymbol{x}) = \prod_{i=1}^{n} x_j^{i_j}$, and define

$$\boldsymbol{\mu}^k(\nu) = \mathbb{E}_\nu\left[\begin{bmatrix} h_{\phi(1)}(\boldsymbol{X}) & h_{\phi(2)}(\boldsymbol{X}) & \dots & h_{\phi(K)}(\boldsymbol{X})\end{bmatrix}^T\right],$$

the vector of standard moments of ν with $\boldsymbol{i} \leq k$. For any $\eta > 0$,

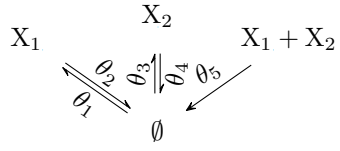
$$\sup_{d_{TV}(\nu,\hat{\pi})\leq\eta} \|\boldsymbol{\mu}^k(\nu) - \boldsymbol{\mu}^k(\hat{\pi})\|_2 = \infty,$$

which prevents us from constructing constraints analogous to (10a) using the standard moments.

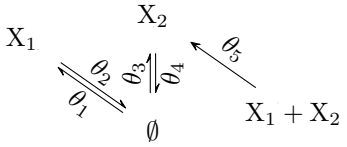
Remark 4.3: Our definition of robust model invalidation can also capture finite sample effects through a connection to hypothesis testing. Suppose we have N_s i.i.d. samples, and are trying to determine if they were drawn from $\nu \in \pi(\cdot;\Theta)$ or $\nu \notin \pi(\cdot;\Theta)$. If we consider the null hypothesis H_0 to be the former and the alternative hypothesis H_1 to be the latter, we can use (10) as a decision rule by choosing H_1 if (10) is infeasible and H_0 otherwise. As we show in the extended version [11], we can pick the threshold η such that the worst case type I error rate is less than any desired level.

V. EXAMPLE

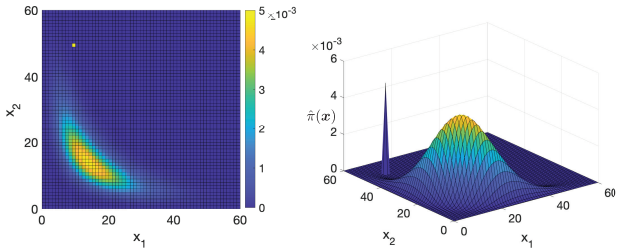
Here we present an example of our model invalidation framework applied to two different CRNs with two species, where our goal is to determine which of the two CRNs are consistent with observed data, and thus determine if the two molecules in the system are suitable for constructing a particular biomolecular circuit. One way to implement an integral controller using chemical reactions is with the *antithetic motif*, where the two controller species annihilate each other [6], [5], [20]. In order to obtain integral control using the antithetic motif, it is critical that the two species truly annihilate one another, instead of interacting via a different mechanism. We consider having measured data from the stationary distribution of a system with two species, X_1 and X_2, where it is possible that X_1 and X_2 interact through mutual degradation or that they interact by X_2 enzymatically degrading X_1. Let $\mathcal{R}_1$ be



with stationary distribution $\pi_1(\cdot;\boldsymbol{\theta})$ and associated set for the parameters of $\Theta_1 = \left\{\boldsymbol{\theta} \in \mathbb{R}^5 \middle| 1 \leq \boldsymbol{\theta} \leq 500\right\}$. The CRN $\mathcal{R}_1$ models the situation where X_1 and X_2 annihilate each other. Let $\mathcal{R}_2$ be



with stationary distribution $\pi_2(\cdot;\boldsymbol{\theta})$ and associated set for the parameters of $\Theta_2 = \left\{\boldsymbol{\theta} \in \mathbb{R}^5 \middle| 1 \leq \boldsymbol{\theta} \leq 500\right\}$. The CRN $\mathcal{R}_2$ models the situation where X_2 enzymatically degrades X_1. Consider the observed distribution $\hat{\pi}$ shown in Figure 2, generated by $\mathcal{R}_1$ mixed with outliers at a point. We select a threshold $\eta = 0.005$, and choose $k = 9$ and $\gamma = k/30$. We choose T according to the moment closure method computed with $N'' = 50$. To solve the optimization problems for this example we use the MATLAB toolbox YALMIP [16] to set up the optimization problems, and Gurobi [1] to solve them. Setting $N' = 60$ and constructing feasibility problem (10) for $\mathcal{R}_1$, we find that (10) is feasible, and thus $\hat{\pi}$ does not robustly



(a) (b)

Fig. 2: Measured distribution $\hat{\pi}$ for the example. The distribution $\hat{\pi}$, with the probability mass function shown as a heatmap in (a) and an isometric plot in (b). The distribution is $\hat{\pi} = 0.995\pi_1(\cdot;\boldsymbol{\theta}) + 0.005\mathbb{1}_{\{x_1=9,x_2=49\}}$, a mixture of the stationary distribution of $\mathcal{R}_1$ with $\boldsymbol{\theta} = [200, 1, 200, 1, 1]$, and the distribution $\mathbb{1}_{\{x_1=9,x_2=49\}}(\boldsymbol{x})$.

invalidate the model $\pi_1(\cdot,\boldsymbol{\theta})$. On the other hand, for $\mathcal{R}_2$, (10) is infeasible, and thus by Theorem 4.1 $\hat{\pi}$ robustly invalidates model $\pi_2(\cdot;\boldsymbol{\theta})$ with threshold $\eta = 0.005$. We conclude that $\mathcal{R}_2$ is not the correct model for the interaction of X_1 and X_2, and that $\mathcal{R}_1$ is a possible model for the interaction. If we know that the true model is either $\mathcal{R}_1$ or $\mathcal{R}_2$ up to a perturbation of size η in total variation distance, then we can conclude that X_1 and X_2 annihilate one another and thus are suitable for constructing an integral controller.

VI. CONCLUSION

In this work, we studied the problem of model invalidation for CRNs from the stationary distribution. Our approach makes use of the exponentially weighted moments, which we introduce, to certify that the observed distribution cannot be reproduced to within the specified tolerance in total variation by any value of the parameters. In this way we obtain a relatively small, though nonconvex, quadratic feasibility problem that can be solved by commercial software [1]. We illustrated through an example how our method can be used for determining which CRN models are consistent with observed data. Future work includes reducing the conservatism of our proposed method by considering alternative methods to construct an outer approximation of $\Lambda^k(\hat{\pi}, \eta)$, and extensions to the case where only certain species in the system are measured.

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