Department of Computer Science

Precise Parameter Synthesis for Stochastic Biochemical Systems (Technical Report)

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Abstract. We consider the problem of synthesising rate parameters for stochastic biochemical networks so that a given time-bounded CSL property is guaranteed to hold, or, in the case of quantitative properties, the probability of satisfying the property is maximised/minimised. We develop algorithms based on the computation of lower and upper bounds of the probability, in conjunction with refinement and sampling, which yield answers that are precise to within an arbitrarily small tolerance value. Our methods are efficient and improve on existing approximate techniques that employ discretisation and refinement. We evaluate the usefulness of the methods by synthesising rates for two biologically motivated case studies, including the reliability analysis of a DNA walker.

1 Introduction

Biochemical reaction networks are a convenient formalism for modelling a multitude of biological systems, including molecular signalling pathways, logic gates built from DNA and DNA walker circuits. For low molecule counts, and under the well-mixed and fixed volume assumption, the prevailing approach is to model such networks using continuous-time Markov chains (CTMCs) [12]. Stochastic model checking [18], e.g. using `PRISM` [19], can then be employed to analyse the behaviour of the models against temporal logic properties expressed in CSL (Continuous Stochastic Logic) [2]. For example, one can establish the reliability and performance of DNA walker circuits by means of properties such as "what is the probability that the walker reaches the correct final anchorage within 10 min?". Since DNA circuits can implement biosensors and diagnostic systems, ensuring appropriate levels of reliability is crucial to guarantee the safety of deploying molecular devices in healthcare applications.

Stochastic model checking, however, assumes that the model is fully specified, including the kinetic rates. In view of experimental measurement error, these are rarely given precisely, but rather intervals of values. The *parameter synthesis problem*, studied for CTMCs in [14], assumes a formula and a model whose rates are given as functions of model parameters, and aims to compute the parameter valuations that guarantee the satisfaction of the formula. This allows one, for example, to determine the ranges of parameter values for a given level of reliability and performance, which can provide important feedback to the designers of biosensors and similar molecular devices, and thus significantly extends the power of stochastic model checking.

In [14], the parameter synthesis problem was solved for CTMCs approximately, and only for probabilistic time-bounded reachability. In this paper, we address the parameter synthesis problem for stochastic biochemical reaction networks for the full time-bounded fragment of the (branching-time) logic CSL [2]. We formulate two variants: *threshold synthesis*, which inputs a CSL formula and a probability threshold and identifies the parameter valuations which meet the threshold, and *max synthesis*, where the maximum probability of satisfying the property and the maximizing set of parameter valuations are returned.

We develop efficient synthesis algorithms that yield answers with arbitrary precision. The algorithms exploit the recently published parameter exploration technique that computes safe approximations to the lower and upper bounds for the probability to satisfy a CSL property over a fixed parameter space [7]. In contrast to the exploration technique our algorithms automatically derive the satisfying parameter regions through iterative decomposition of the parameter space based on refining the preliminary answer with additional decompositions up to a given problem-specific tolerance value. We also show that significant computational speed-up is achieved by enhancing the max synthesis algorithm by sampling the property at specific points in the parameter space. We demonstrate the usefulness of the method through two case studies: the SIR epidemic model [17], where we synthesize infection and recovery rates that maximize the probability of disease extinction, and the DNA walker circuit [10], where we derive the rates that ensure a predefined level of reliability.

Related work. The parameter synthesis problems have been studied for discrete-time Markovian models in [13, 8]. The approach applies to unbounded temporal properties and is based on constructing a rational function by performing state elimination [13]. For CTMCs and bounded reachability specifications, the problem can be reduced to the analysis of the polynomial function describing the reachability probability of a given target state [14]. The main limitation here is the high degree of the polynomials, which is determined by the number of uniformization steps. Therefore, in contrast to our method, only an approximate solution is obtained using discretization of parameter ranges. When considering linear-time specifications, specific restrictions can be placed on the rate function to result in a smooth satisfaction function (i.e. having derivatives of all orders). In that case the function can be approximated using statistical methods which leverage the smoothness [6]. A concept similar to smoothness, uniform continuity, can be used to obtain an unbiased statistical estimator for the satisfaction function [15]. Both methods approximate parameter synthesis using confidence intervals. Inference of parameter values in probabilistic models from time-series measurements is a well studied area of research [1, 5], but different from the problem we consider. Interval CTMCs, where transition rates are given as intervals, have been employed to obtain a three-valued abstraction for CTMCs [16]. In contrast to parametric models we work with, the transition rates in interval CTMCs are chosen nondeterministically and schedulers are introduced to compute lower and upper probability bounds.

2 Background

We state preliminary definitions relevant to the study of Parametric Continuous Time Markov Chains [14, 7] that permit formal analysis of probabilistic models with uncertain parameters [22].

A *Continuous Time Markov Chain* (CTMC) is a tuple $\mathcal{C} = (S, \pi_0, \mathbf{R})$ where S is a finite set of states, $\pi_0 : S \to \mathbb{R}_{\geq 0}$ is the initial distribution and $\mathbf{R} : S \times S \to \mathbb{R}_{\geq 0}$ is the rate matrix. A transition between states $s, s' \in S$ can occur only if $\mathbf{R}(s, s') > 0$ and in that case the probability of triggering the transition within t time units equals $1 - e^{-t\mathbf{R}(s,s')}$. The time spent in s, before a reaction occurs, is exponentially distributed with rate $E(s) = \sum_{s' \in S} \mathbf{R}(s, s')$, and when the transition occurs the probability of moving to state s' is given by $\frac{\mathbf{R}(s,s')}{E(s)}$. Let $\mathbf{E}$ be a $S \times S$ diagonal matrix such that $\mathbf{E}(s_i, s_i) = E(s_i)$, and define the generating matrix by setting $\mathbf{Q} = \mathbf{R} - \mathbf{E}$. Then a vector $\pi_t : S \to \mathbb{R}_{\geq 0}$ of the transient probabilities at time t is given by $\frac{d\pi_t}{dt} = \pi_t \mathbf{Q}$ such that $\pi_t = \pi_0 e^{\mathbf{Q}t}$. Using standard uniformisation the transient probability at time t is obtained as a sum of state distributions after i discrete-stochastic steps, weighted by the probability of observing i steps in a Poisson process. Let $\mathbf{P} = \mathbf{I} + \frac{1}{q}\mathbf{Q}$ be the uniformised matrix, where $q \geq \max\{E(s) - \mathbf{R}(s, s) \mid s \in S\}$ is called the uniformisation rate. The transient probabilities π_t are computed as $\pi_t = \pi_0 \sum_{i=0}^{k_\epsilon} \gamma_{i,qt} \mathbf{P}^i$ where $\gamma_{i,qt} = e^{-qt} \frac{(qt)^i}{i!}$ denotes the i-th Poisson probability for a process with rate qt, and k_ϵ satisfies the convergence bound $\sum_0^{k_\epsilon} \gamma_{i,qt} \geq 1 - \epsilon$ for some $\epsilon > 0$. The Poisson terms and summation bound can be efficiently computed using an algorithm due to Fox and Glynn [11].

We assume a set K of model parameters. The domain of each parameter $k \in K$ is given by a closed real interval describing the range of possible values, i.e, $[k^\perp, k^\top]$. The *parameter space* $\mathcal{P}$ induced by K is defined as the Cartesian product of the individual intervals: $\mathcal{P} = \bigtimes_{k \in K} [k^\perp, k^\top]$. Therefore, $\mathcal{P}$ is a hyper-rectangular space. A *parameter point* $p \in \mathcal{P}$ is a valuation of each parameter k. Subsets of the parameter space are also referred to as *parameter regions* or *subspaces*. $\mathbb{R}[K]$ denotes the set of polynomials over the reals $\mathbb{R}$ with variables $k \in K$.

Parametric Continuous Time Markov Chains (pCTMCs) [14] extend the notion of CTMCs by allowing transition rates to depend on model parameters. Formally, a pCTMC over a set K of parameters is a triple $\mathcal{C} = (S, \pi_0, \mathbf{R})$ where s and π_0 are as above, and in this case $\mathbf{R} : S \times S \to \mathbb{R}[K]$ is the parametric rate matrix. Given a pCTMC $\mathcal{C}$ and a parameter space $\mathcal{P}$, we denote with $C_\mathcal{P}$ the (possibly uncountable) set $\{\mathcal{C}_p \mid p \in \mathcal{P}\}$ where $\mathcal{C}_p = (S, \pi, \mathbf{R}_p)$ is the instantiated CTMC obtained by replacing the parameters in $\mathbf{R}$ with their evaluation in p.

We consider the time-bounded fragment of CSL [2] to specify behavioural properties, with the following syntax. A state formula Φ is given as $\Phi ::= \mathsf{true} \mid a \mid \neg\Phi \mid \Phi \wedge \Phi \mid P_{\sim r}[\phi] \mid P_{=?}[\phi]$, where ϕ is a path formula given as $\phi ::= \mathsf{X}\ \Phi \mid \Phi\ \mathsf{U}^I\ \Phi$, a is an atomic proposition, $\sim \in \{<, \leq, \geq, >\}$, $r \in [0, 1]$ is a probability threshold and I is a bounded interval. Using $P_{=?}[\phi]$ we specify properties which evaluate to the probability that ϕ is satisfied. The synthesis methods presented

in this paper can be directly adapted to the time-bounded fragment of CSL with the reward operator [18], but, for the sake of simplicity, here we present our methods only for the probabilistic operator P.

Let ϕ be a CSL path formula and $\mathcal{C}_{\mathcal{P}}$ be a pCTMC over a space $\mathcal{P}$. We denote with $\Lambda : \mathcal{P} \to [0,1]$ the *satisfaction function* such that $\Lambda(p) = P_{=?}[\phi]$, that is, $\Lambda(p)$ is the probability of ϕ being satisfied over the CTMC $\mathcal{C}_p$. Note that the path formula ϕ may contain nested probabilistic operators, and therefore the satisfaction function is, in general, not continuous.

Biochemical reaction networks provide a convenient formalism for describing various biological processes as a system of well-mixed reactive species in a volume of fixed size. A CTMC semantics can be derived whose states hold the number of molecules for each species, and transitions correspond to reactions that consume and produce molecules. Bounds on species counts can be imposed to obtain a finite-state model. The rate matrix is defined as

$$\mathbf{R}(s_i, s_j) \stackrel{def}{=} \sum_{r \in \mathsf{reac}(s_i, s_j)} f_r(K, s_i) \tag{1}$$

where $\mathsf{reac}(s_i, s_j)$ denotes all the reactions changing state s_i into s_j and f_r is the *stochastic rate function* of reaction r over parameters $k \in K$. In this paper we assume *multivariate polynomial* rate functions that include, among others, mass-action kinetics where $k \in K$ represent kinetic rate parameters.

Figure 1 illustrates a running example, a simple birth-death process with an uncertain parameter k_1 representing the birth rate. It depicts the corresponding pCTMC and the satisfaction Λ for a simple reachability property.

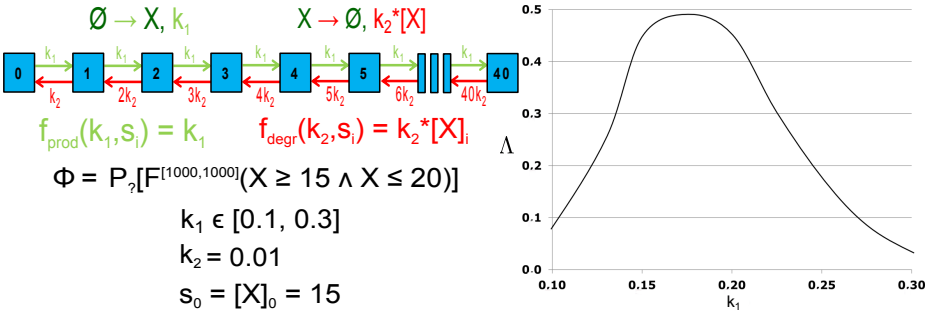


Fig. 1. Left: The example model contains one species X with the population bounded by 40, two reactions, production of X ($\emptyset \to X$ with rate k_1) and degradation of X ($X \to \emptyset$ with the rate $k_2 \cdot [X]$, $k_2 = 0.01$), and the initial population of $X = 15$. The corresponding pCTMC has 41 states (initial state s_0 corresponds to the state with initial population). The formula Φ represents the quantitative property "What is the probability that the population of X is between 15 and 20 at time 1000?" The parameter space $\mathcal{P}$ is given by the interval of the stochastic rate constant $k_1 \in [0.1, 0.3]$. **Right:** The satisfaction function Λ.

3 Problem Definition

We consider pCTMC models of biochemical reaction networks that can be parametric in the rate constants and in the initial state. We introduce two parameter synthesis problems for this class of models: the *threshold synthesis* problem that, given a threshold $\sim r$ and a CSL path formula ϕ, asks for the parameter region where the probability of ϕ meets $\sim r$; and the *max synthesis* problem that determines the parameter region where the probability of the input formula attains its maximum, together with an estimation of that maximum. In the remainder of the paper, we omit the min synthesis problem that is defined and solved in a symmetric way to the max case.

In contrast to previous approaches that support only specific kinds of properties (e.g. reachability as in [14]), we consider the full time-bounded fragment of CSL with rewards, thus enabling generic and more expressive synthesis requirements. Moreover, the variants of the synthesis problem that we define correspond to qualitative and quantitative CSL formulas, which are of the form $P_{\geq r}[\phi]$ and $P_{=?}[\phi]$, respectively. Solutions to the threshold problem admit parameter points left undecided, while, in the max synthesis problem, the set of maximizing parameters is contained in the synthesis region. Our approach supports arbitrarily precise solutions through an input tolerance that limits the volume of the undecided region (in the threshold case) and of the synthesis region (in the max case). To the best of our knowledge, no other synthesis methods for CTMCs exist that provide guaranteed error bounds.

Problem 1 (Threshold Synthesis). Let $\mathcal{C}_{\mathcal{P}}$ be a pCTMC over a parameter space $\mathcal{P}$, $\Phi = P_{\geq r}[\phi]$ with $r \in [0,1]$ be a CSL formula and $\varepsilon > 0$ a volume tolerance. The *threshold synthesis* problem is finding a partition $\{T, U, F\}$ of $\mathcal{P}$, such that:

1. $\forall p \in T.\ \Lambda(p) \geq r$; and
2. $\forall p \in F.\ \Lambda(p) < r$; and
3. $\mathrm{vol}(U)/\mathrm{vol}(\mathcal{P}) \leq \varepsilon$

where Λ is the satisfaction function of ϕ on $\mathcal{C}_{\mathcal{P}}$; and $\mathrm{vol}(A) = \int_A 1 d\mu$ is the volume of A.

Problem 2 (Max Synthesis). Let $\mathcal{C}_{\mathcal{P}}$ be a pCTMC over a parameter space $\mathcal{P}$, $\Phi = P_{=?}[\phi]$ be a CSL formula and $\epsilon > 0$ a probability tolerance. The *max synthesis* problem is finding a partition $\{T, F\}$ of $\mathcal{P}$ and probability bounds $\Lambda^{\perp}$, $\Lambda^{\top}$ such that:

1. $\Lambda^{\perp} - \Lambda^{\top} \leq \epsilon$;
2. $\forall p \in T.\ \Lambda^{\perp} \leq \Lambda(p) \leq \Lambda^{\top}$; and
3. $\exists p \in T.\ \forall p' \in F.\ \Lambda(p) > \Lambda(p')$.

where Λ is the satisfaction function of ϕ on $\mathcal{C}_{\mathcal{P}}$.

Figure 2 illustrates the thresholds synthesises (left) and the max-synthesis (right) for the running example. Note that we need to consider a probability tolerance to control the inaccuracy of the max probability, and in turn of region T. Indeed, constraining only the volume of T gives no guarantees on the precision of the maximizing region.

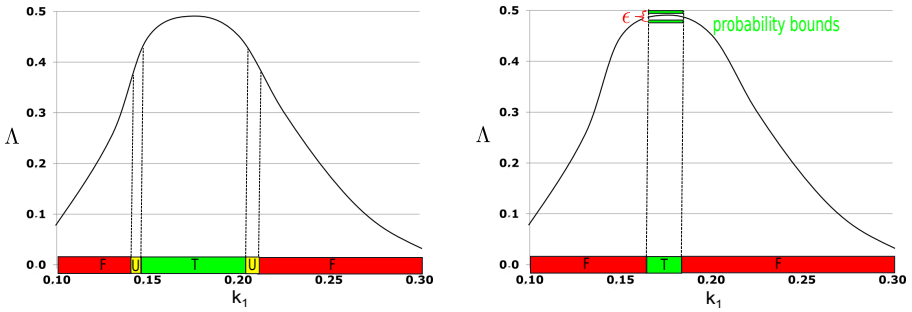


Fig. 2. The threshold synthesis (left) and the max-synthesis (right) for the running example of Fig. 1, for volume tolerance $\varepsilon = 5\%$ and probability tolerance $\epsilon = 2\%$.

4 Computing Lower and Upper Probability Bounds

This section presents a generalization of the parameter exploration procedure originally introduced in [7]. The procedure takes a pCTMC $\mathcal{C}_{\mathcal{P}}$ and a CSL path formula ϕ, and provides safe under- and over-approximations for the minimal and maximal probability that $\mathcal{C}_{\mathcal{P}}$ satisfies ϕ, that is, lower and upper bounds $\Lambda_{\min}$ and $\Lambda_{\max}$ satisfying $\Lambda_{\min} \leq \min_{p\in\mathcal{P}} \Lambda(p)$ and $\Lambda_{\max} \geq \max_{p\in\mathcal{P}} \Lambda(p)$. The accuracy of these approximations is improved by partitioning the parameter space $\mathcal{P}$ into subspaces and re-computing the corresponding bounds, which forms the basis of the synthesis algorithms that we discus in the next section. For now we focus on obtaining approximations $\Lambda_{\min}, \Lambda_{\max}$ for a fixed parameter space $\mathcal{P}$. The model-checking problem for any time-bounded CSL formula reduces to the computation of transient probabilities [3], and a similar reduction is applicable to the computation of lower and upper bounds. Following [7], to correctly handle nested probabilistic operators, under- and over-approximations of the satisfying sets of states in the nested formula are computed.

We now re-state the transient probabilities as given by standard uniformisation and include the dependency on the model parameters in our notation, so that $\pi_{t,p} = \pi_0 \sum_{i=0}^{k_\epsilon} \gamma_{i,qt} \mathbf{P}_p^i = \sum_{i=0}^{k_\epsilon} \gamma_{i,qt} \tau_{i,p}$ where $\mathbf{P}_p$ is the uniformised rate matrix obtained from the rate matrix $\mathbf{R}_p$ and $\tau_{k,p} = \pi_0 \mathbf{P}_p^k$ is the probability evolution in the discretized process. Observe that if some functions $\pi_i^{\min}$ and $\pi_i^{\max}$ can be obtained such that for any step i,

$$\tau_i^{\min} \leq \min_{p\in\mathcal{P}} \tau_{i,p} \text{ and } \tau_i^{\max} \geq \max_{p\in\mathcal{P}} \tau_{i,p} \tag{2}$$

then robust approximations $\pi_t^{\min} = \sum_{i=0}^{k_\epsilon} \gamma_{i,qt} \tau_i^{\min}$ and $\pi_t^{\max} = \sum_{i=0}^{k_\epsilon} \gamma_{i,qt} \tau_i^{\max}$ provide the bounds $\Lambda_{\min}$ and $\Lambda_{\max}$ that we seek. As usual, the vector ordering in Equation 2 holds element-wise. If we assume that some functions $f_k^{\min}, f_k^{\max}$ exist such that $f_k^{\min}(\tau_i^{\min}) = \tau_{i+k}^{\min}$ and $f_k^{\max}(\tau_i^{\max}) = \tau_{i+k}^{\max}$ then recursively the terms in Equation 2 for all i are obtained, given that the first k terms for $\tau_i^{\min}, \tau_i^{\max}$ are known. We now note that the functions

$$f_k^{\min}(\tau_i^{\min}) = \min_{p\in\mathcal{P}} \tau_i^{\min} \mathbf{P}_p^k \text{ and } f_k^{\max}(\tau_i^{\max}) = \max_{p\in\mathcal{P}} \tau_i^{\max} \mathbf{P}_p^k \tag{3}$$

can be under- and over-approximated using analytical methods when the parametric rate matrix $\mathbf{R}_p$ employs low-degree polynomial expressions. Provided that $\mathbf{R}_p(s_i, s_j)$ is a polynomial of at most degree d over the parameter space, the degree of $\tau_{k,p}(s) = \pi_0 \mathbf{P}_p^k(s)$ is at most kd.

Here we present an efficient method to obtain approximations using $k = 1$ when $\mathbf{R}_p$ is a *multi-affine function*, i.e. a multivariate polynomial where each variable has degree at most 1, thus generalizing the result of [7] where only the case $k = 1$ and $d = 1$ is considered. Recalling that $\mathcal{P}$ is a hyper-rectangular parameter space, we exploit the property [4, 21] that any multi-affine function f defined on a hyper-rectangular domain R is such that

$$\min_{p \in R} f(p) = \min_{v \in V_R} f(v) \text{ and } \max_{p \in R} f(p) = \max_{v \in V_R} f(v) \tag{4}$$

where V_R is the set of vertices of R. For each state s, we consider function $f_{1,s}^{\max}$ such that $\tau_{i+1}^{\max}(s) = f_{1,s}^{\max}(\tau_i^{\max})$. Following [7] we get that

$$f_{1,s}^{\max}(\tau_i^{\max}) = \tau_i^{\max}(s) + \frac{1}{q} \cdot \max_{p \in \mathcal{P}} \{\text{inflow}_s(p) - \text{outflow}_s(p)\} \tag{5}$$

where for the parameter valuation p, $\text{inflow}_s(p) = \sum_{s' \in S} \mathbf{R}_p(s', s) \cdot \tau_i^{\max}(s')$ represents the probability inflow to s and $\text{outflow}_s(p) = \sum_{s' \in S} \mathbf{R}_p(s, s') \cdot \tau_i^{\max}(s)$ represents the probability outflow from s.

We now note that $\text{inflow}_s(p) - \text{outflow}_s(p)$ over $p \in \mathcal{P}$ is in turn a multi-affine function and, thus, according to Equation 4, its maximum is in one of the vertices of $\mathcal{P}$. This gives us an effective computation procedure for the function $f_{1,s}^{\max}$.

More advanced methods can be used, provided that the under- and over-approximations for Equation 3 are sound. Note that the solution $\pi_{t,p}(s)$ itself can be expressed as a polynomial of degree at most $k_\epsilon d$. A direct attempt to bound the polynomial expression of $\pi_{t,p}(s)$ is difficult due to the large number of uniformisation steps, k_ϵ, and previous approaches in parameter synthesis have provided an approximate solution by sampling the value of $\pi_{t,p}$ over a grid in $\mathcal{P}$ [14], rather than bounding the polynomial itself as in our approach. The computational complexity depends on the chosen rate function and the bounding method for the functions in Equation 3, but for our settings it has the same asymptotic complexity as standard uniformisation. Two approximation errors are introduced when we compute $\pi_t^{\max}$ (or $\pi_t^{\min}$). Firstly, the probabilities $\tau_i^{\max}, \tau_{i+k}^{\max}, \tau_{i+2k}^{\max}, \ldots$ are locally maximized, so that different parameter valuations are allowed at each step and for each state. Secondly, the error of over-approximating $f_k^{\max}(\tau_i^{\max})$ accumulates in $\tau_i^{\max}$ at every iteration.

5 Refinement-based Parameter Synthesis

We present algorithms to solve Problems 1 and 2, based on the computation of probability bounds introduced in Section 4 and on iterative parameter space refinement. In the max synthesis case we employ parameter sampling to enhance the synthesis procedure. We remark that our refinement procedure partitions a

Algorithm 1 Threshold Synthesis

Require: pCTMC $\mathcal{C}_{\mathcal{P}}$ over parameter space $\mathcal{P}$, CSL formula $\Phi = P_{\geq r}[\phi]$ and volume tolerance $\varepsilon > 0$
Ensure: T, U and F as in Problem 1

```
1:  T ← ∅, F ← ∅, U ← P
2:  repeat
3:      R ← decompose(U), U ← ∅
4:      for each R ∈ R do
5:          (Λ^R_min, Λ^R_max) ← computeBounds(C_R, φ)
6:          if Λ^R_min ≥ r then
7:              T ← T ∪ R
8:          else if Λ^R_max < r then
9:              F ← F ∪ R
10:         else
11:             U ← U ∪ R
12: until vol(U)/vol(P) ≤ ε        ▷ where vol(A) = ∫_A 1dμ
```

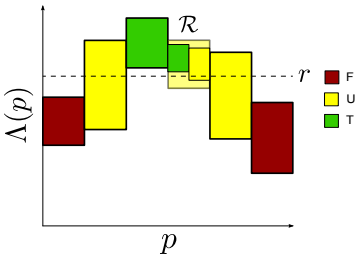


Fig. 3. Refinement in threshold synthesis with $\geq r$. Parameter values are on the x-axis, probabilities on the y-axis. Each box describes a parameter region (width), and its probability bounds (height). The refinement of $\mathcal{R}$ yields regions in T and in U.

hyper-rectangular parameter region into hyper-rectangular subspaces, which are in turn of the form required by the method in Section 4.

5.1 Threshold Synthesis

Algorithm 1 describes the method to solve the threshold synthesis problem with input formula $\Phi = P_{\geq r}[\phi]$. The idea, also illustrated in Figure 3, is to iteratively refine the undecided parameter subspace U (line 3) until the termination condition is met (line 14). At each step, we obtain a partition R of U. For each subspace $\mathcal{R} \in R$, the algorithm computes bounds $\Lambda^{\mathcal{R}}_{\min}$ and $\Lambda^{\mathcal{R}}_{\max}$ on the maximal and minimal probability that $\mathcal{C}_{\mathcal{R}}$ satisfies ϕ (line 5). We then evaluate if $\Lambda^{\mathcal{R}}_{\min}$ is above the threshold r, in which case the satisfaction of Φ is guaranteed for the whole region $\mathcal{R}$ and thus it is added to T. Otherwise, the algorithm tests whether $\mathcal{R}$ can be added to the set F by checking if $\Lambda^{\mathcal{R}}_{\max}$ is below the threshold r. If $\mathcal{R}$ is neither in T nor in F, it forms an undecided subspace that is added to the set U. The algorithm terminates when the volume of the undecided subspace is negligible with respect to the volume of the entire parameter space, i.e. $\text{vol}(U)/\text{vol}(\mathcal{P}) \leq \varepsilon$, where ε is the input tolerance. Otherwise, the algorithm continues to the next iteration, where U is further refined.

We prove an important property of the satisfaction function that guarantees termination of the synthesis algorithm for arbitrary time-bounded CSL path formulae.

Theorem 1. *For a finite-state pCTMC $\mathcal{C}$, a finite time bounded CSL path formula ϕ and a bounded parameter space $\mathcal{P}$, the corresponding satisfaction function Λ is piecewise polynomial with a finite number of subdomains.*

Proof. As proved in [14] and discussed in Section 4, for every time-bounded reachability property the corresponding satisfaction function Λ can be expressed

as a polynomial function. Following [3], where model-checking of an arbitrary nested-free CSL path formula ϕ is reduced to the computation of transient probabilities based on the modification of the rate matrix $\mathbf{R}$, we get a polynomial representation of Λ also for the nested-free fragment of time-bounded CSL. We now prove that, for any time-bounded finite path formula ϕ, the corresponding satisfaction function Λ can be expressed as a piecewise polynomial function with a finite number of subdomains.

Let $\phi = (P_{\sim_1 r_1}[\psi_1])\ U^I\ (P_{\sim_2 r_2}[\psi_2])$ be a nested CSL path formula where $i \in \{1,2\}$, $\sim_i \in \{<, \leq, \geq, >\}$, $r_i \in [0,1]$, $I \in \mathbb{R}$ is a bounded interval and ψ_i is an unnested time-bounded CSL path formula. Let $\Lambda_s^{\psi_i}$ denote the satisfaction function for ψ_i and the initial state $s \in S$. Since, for each $s \in S$, $\Lambda_s^{\psi_i}$ is a polynomial function (i.e. $\Lambda_s^{\psi_i} - r_i = 0$ has a finite number of roots), there exists a finite partition R_s^i of $\mathcal{P}$ that separates parameters yielding different satisfaction values of $\Lambda_s^{\psi_i}(p) \sim_i r_i$:

$$\forall \mathcal{R} \in R_s^i : (\forall p \in \mathcal{R} : \Lambda_s^{\psi_i}(p) \sim_i r_i)\ \vee\ (\forall p \in \mathcal{R} : \Lambda_s^{\psi_i}(p) \not\sim_i r_i). \tag{6}$$

Let R_1 and R_2 be partitions of $\mathcal{P}$, then $R_1 \odot R_2 = \{\mathcal{R}'_1, \ldots, \mathcal{R}'_n\}$ is a minimal common cut of R_1 and R_2 defined as a minimal partition of $\mathcal{P}$ that satisfies:

$$\forall 1 \leq j \leq n : (\exists \mathcal{R}_1 \in R_1 : \mathcal{R}'_j \subseteq \mathcal{R}_1)\ \wedge\ (\exists \mathcal{R}_2 \in R_2 : \mathcal{R}'_j \subseteq \mathcal{R}_2). \tag{7}$$

Clearly, if R_1 and R_2 are finite then $R_1 \odot R_2$ is finite as well. Since S is finite, the partition R of $\mathcal{P}$ defined as $R = \bigodot_{s \in S, i \in \{1,2\}} R_s^i$ is also finite. For $p \in \mathcal{P}$, let $Sat^{\psi_i}(p) = \{s \in S \mid \Lambda_s^{\psi_i}(p) \sim_i r_i\}$ be a satisfaction set. Then, for each subspace $\mathcal{R} \in R$, it holds that $\forall p_1, p_2 \in \mathcal{R} : Sat^{\psi_1}(p_1) = Sat^{\psi_1}(p_2)\ \wedge\ Sat^{\psi_2}(p_1) = Sat^{\psi_2}(p_2)$. Let $\phi' = Sat^{\psi_1}(p)\ U^I\ Sat^{\psi_2}(p)$ and Λ' denote its satisfaction function ($Sat^{\psi_i}(p)$ can be expressed using atomic propositions). Since for all $p \in \mathcal{R}$ the same set of states satisfies $P_{\sim_i r_i}[\psi_1]$, then $\Lambda(p) = \Lambda'(p)$. Note that ϕ' is an unnested CSL path formula, and thus Λ' (and Λ) can be expressed as a polynomial function. Given the finite partition R of $\mathcal{P}$, we get that the function Λ on $\mathcal{P}$ is a piecewise polynomial function with a finite number of subdomains. Similarly, we can show the existence of a finite partition of $\mathcal{P}$ for an arbitrarily nested finite time-bounded CSL path formula. □

The theorem also implies that Λ has a finite number of discontinuities. As shown in [7], if the satisfaction function Λ is continuous on a region $\mathcal{R}$ then for any $\delta > 0$ there exists a finite partition R' of $\mathcal{R}$ such that for each subspace $\mathcal{R}' \in R' : \Lambda^{\mathcal{R}'}_{\max} - \Lambda^{\mathcal{R}'}_{\min} < \delta$. Therefore, the synthesis algorithm always terminates since only a finite number of refinements reducing the area of the undecided parameter region needs to be performed to obtain the desired precision.

The initial decomposition of the parameter space is guided by a priori sampling of probability values. In Algorithm 2 (procedure decompose in Algorithm 1), we present a heuristic for providing a good initial decomposition of the parameter space, assuming a hyper-rectangular parameter space. The idea, illustrated also in Figure 4, is based on sampling a number of probability values (through

Algorithm 2 Sampling-guided parameter decomposition in threshold synthesis

Require: Parameter region $\mathcal{R} = [l_1, u_1] \times \ldots \times [l_m, u_m]$ and number of samples n
Ensure: Hyper-rectangular partition of $\mathcal{R}$, $\bar{R}$

1: $(p_1, \ldots, p_n) \leftarrow \mathsf{Uniform}(\mathcal{R}, n)$
2: **for** $i \leftarrow 1, \ldots, n$ **do**
3: $\quad P_i \leftarrow \mathsf{Discretize}(\Lambda(p_i))$
4: **for** $k \leftarrow 1, \ldots, m$ **do** ▷ number of parameters
5: $\quad \bar{R}_k \leftarrow \emptyset$
6: $\quad (p_{1_k}, \ldots, p_{n_k}) \leftarrow \mathsf{sort}((p_1, \ldots, p_n), k)$
7: $\quad l \leftarrow l_k$
8: $\quad$ **for** $i \leftarrow 1, \ldots, n-1$ **do**
9: $\quad\quad$ **if** $P_{i_k} \neq P_{(i+1)_k}$ **then**
10: $\quad\quad\quad u \leftarrow \left(p_{1_k}(k) + p_{(i+1)_k}(k)\right)/2$
11: $\quad\quad\quad \bar{R}_k \leftarrow \bar{R}_k \cup \{[l, u]\}$
12: $\quad\quad\quad l \leftarrow u$
13: $\quad \bar{R}_k \leftarrow \bar{R}_k \cup \{[l, u_k]\}$
14: $\bar{R} \leftarrow \bigtimes_{k=1}^{m} \bar{R}_k$
15: **if** $|\bar{R}| = 1$ **then**
16: $\quad \bar{R} \leftarrow \bigtimes_{k=1}^{m} \{[l_k, (l_k + u_k)/2], [(l_k + u_k)/2, u_k]\}$

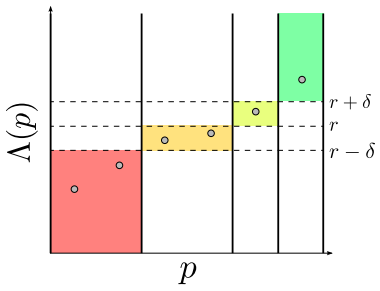


Fig. 4. Sampling-guided refinement of parameter space in threshold synthesis

standard model checking) and on finding a partition that sets apart sampled parameters with probabilities that satisfy and violate the threshold $\geq r$. In particular, we identify the following groups of probability values (procedure Discretize, line 3): $\{[0, r-\delta), [r-\delta, r), [r, r+\delta), [r+\delta, 1]\}$, where $\delta > 0$ is a tolerance value that helps in identifying regions close to the threshold. Ideally, a parameter region whose samples all have probabilities in the interval $[0, r-\delta)$ is very likely to lie below the threshold r, and therefore to be in the F-set, while a region with sampled probabilities in $[r+\delta, 1]$ is expected to be in the T-set. Regions whose sampled probabilities are close to the threshold are more likely to be further decomposed. Then, for each parameter, a splitting point is placed between each pair of consecutive samples located in different probability groups (lines 10-14). This requires processing each parameter individually, and sorting the samples in ascending order (lines 5-17). If the resulting decomposition has only one element, meaning that no splitting points were found with sampling, standard bisection is applied (lines 19-21).

5.2 Max Synthesis

Algorithm 3 is used to solve the max synthesis problem, which returns the set T containing the parameter valuations that maximize $\Phi = P_{=?}[\phi]$ and the set F not yielding the maximum value of Φ. Let R be a partition of T. For each subspace $\mathcal{R} \in R$, the algorithm computes bounds $\Lambda^{\mathcal{R}}_{\min}$ and $\Lambda^{\mathcal{R}}_{\max}$ on the maximal and minimal probability that $\mathcal{C}_{\mathcal{R}}$ satisfies Φ (line 5). The algorithm then rules out subspaces that are guaranteed to be included in F, by deriving an under-approximation (MLB) to the maximum satisfaction probability (line 7). If $\Lambda^{\mathcal{R}}_{\max}$ is below the under-approximation, the subspace $\mathcal{R}$ can be safely added to the

Algorithm 3 Max Synthesis

Require: pCTMC $\mathcal{C}_{\mathcal{P}}$ over parameter space $\mathcal{P}$, CSL formula $\Phi = P_{=?}[\phi]$ and probability tolerance $\epsilon > 0$
Ensure: $\Lambda^{\perp}$, $\Lambda^{\top}$, T and F as in Problem 2
1: $F \leftarrow \emptyset$, $T \leftarrow \mathcal{P}$
2: **repeat**
3: $R \leftarrow \mathsf{decompose}(T)$, $T \leftarrow \emptyset$
4: **for each** $\mathcal{R} \in R$ **do**
5: $(\Lambda^{\mathcal{R}}_{\min}, \Lambda^{\mathcal{R}}_{\max}) \leftarrow \mathsf{computeBounds}(\mathcal{C}_{\mathcal{R}}, \phi)$
6: $\mathsf{MLB} \leftarrow \mathsf{getMaximalLowerBound}(R)$
7: **for each** $\mathcal{R} \in R$ **do**
8: **if** $\Lambda^{\mathcal{R}}_{\max} < \mathsf{MLB}$ **then**
9: $F \leftarrow F \cup \mathcal{R}$
10: **else**
11: $T \leftarrow T \cup \mathcal{R}$
12: $\Lambda^{\perp} \leftarrow \min\{\Lambda^{\mathcal{R}}_{\min} \mid \mathcal{R} \in T\}$
13: $\Lambda^{\top} \leftarrow \max\{\Lambda^{\mathcal{R}}_{\max} \mid \mathcal{R} \in T\}$
14: **until** $\Lambda^{\top} - \Lambda^{\perp} < \epsilon$

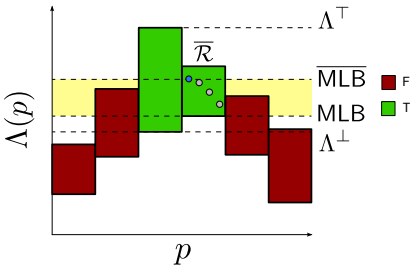


Fig. 5. Refinement in max synthesis. The two outermost regions (in red) cannot contain the maximum, as their upper bound is below the maximum lower bound (MLB) found at region $\overline{\mathcal{R}}$. The maximum lower bound is improved by sampling several points $p \in \overline{\mathcal{R}}$ and taking the highest value ($\overline{\mathsf{MLB}}$) of the satisfaction function $\Lambda(p)$. The yellow area highlights the improvement.

set F (line 9). Otherwise, it is added to the set T. The bound MLB is derived as follows. In the naive approach, the algorithm uses the maximum over the least bounds in the partition of T, that is, $\mathsf{MLB} = \max\{\Lambda^{\mathcal{R}}_{\min} \mid \mathcal{R} \in R\}$. Let $\overline{\mathcal{R}}$ be the region with highest lower bound. The sampling-based approach improves on this by sampling a set of parameters $\{p_1, p_2, \ldots\} \subseteq \overline{\mathcal{R}}$ and taking the highest value of $\Lambda(p)$, that is, $\mathsf{MLB} = \max\{\Lambda(p_i) \mid p_i \in \{p_1, p_2, \ldots\}\}$. Although regular CSL model checking is nearly as expensive as the computation of the bounds for a pCTMC, the bound obtained by the sampling method excludes more boxes (see Figure 5), which in turn leads to fewer refinements in the next iteration.

We perform additional checks (not reported in Algorithm 3), using volume tolerance ε, for detecting and discarding regions containing points of jump discontinuity that might prevent the algorithm from reaching the target accuracy and thus from terminating. In particular, each subspace $\mathcal{R}$ included in the region T with volume $\mathrm{vol}(\mathcal{R}) < \varepsilon$ that does not satisfy the probability tolerance ϵ (i.e. $\Lambda^{\mathcal{R}}_{\max} - \Lambda^{\mathcal{R}}_{\min} \geq \epsilon$) is labelled as a possible jump discontinuity. Such subspaces are reported and discarded from the termination condition (line 12 and 13 in Algorithm 3).

Algorithm 4 illustrates a version of the procedure $\mathsf{getMaximalLowerBound}$ in Algorithm 3, enhanced with sampling of probability values. This procedure computes an under-approximation to the maximum probability value, given as input a parameter decomposition R that contains the regions left to analyse. This algorithm firstly identifies the region $\overline{\mathcal{R}}$ having the highest lower probability bound (line 1 of Algorithm 4). This value provides an under-approximation to the maximum probability, and is the best value obtainable using only the computation of lower and upper bounds. Then, the under-approximation is refined by sampling a number of points in $\overline{\mathcal{R}}$ and by taking the maximum probability (computed

Algorithm 4 Sampling-guided computation of a maximal lower bound

Require: Parameter decomposition R and number of samples n
Ensure: $\overline{\mathsf{MLB}}$, an improved lower bound for max probability in R
1: $\overline{\mathcal{R}} = \arg\max_{\mathcal{R} \in R} \Lambda^{\mathcal{R}}_{\min}$
2: $(p_1, \ldots, p_n) \leftarrow \mathsf{Uniform}(\overline{\mathcal{R}}, n)$
3: $\overline{\mathsf{MLB}} \leftarrow \max_{p_i} \Lambda(p_i)$

through standard model checking) among those points (lines 2-3). Indeed, the strategy of sampling probability values in $\overline{\mathcal{R}}$ ensures that we can compute a better under-approximation with respect to the lower probability bound in $\overline{\mathcal{R}}$, taken as the best under-approximation when parameter sampling is not applied.

The overall time complexity of the synthesis algorithms is directly determined by the number of subspaces that need to be analysed to obtain the desired precision. This number depends on the number of unknown parameters, the shape of the satisfaction function and the type of synthesis. In practice, the algorithms scale exponentially in the number of parameters and linearly in the volume of the parameter space.

6 Results

We demonstrate the applicability and efficiency of the developed algorithms on two case studies.

6.1 Epidemic model

The SIR model [17] describes the epidemic dynamics in a closed population of susceptible (S), infected (I) and recovered (R) individuals. In the model, a susceptible individual is infected after a contact with an infected individual with rate k_i. Infected individuals recover with rate k_r, after which they are immune to the infection. We can describe this process with the following biochemical reaction model with mass action kinetics: $i : S + I \xrightarrow{k_i} I + I, r : I \xrightarrow{k_r} R$. We represent the model as a pCTMC with k_i and k_r as parameters, and initial populations $S = 95$, $I = 5$, $R = 0$. We consider the time-bounded CSL path formula $\phi = (I > 0)U^{[100,120]}(I = 0)$, specifying behaviour where the infection lasts for at least 100 time units, and dies out before 120 time units. Model parameters and the property are taken from [6], where the authors estimate the satisfaction function for ϕ following a Bayesian approach[3].

Figure 6 and Table 1 illustrate the solutions for threshold synthesis problems over one-dimensional parameter spaces (the top part of the figure, problems 1 and 2) and over a two-dimensional parameter space (the bottom part of the figure, problem 3). As we can see, a significantly higher number of refinement steps is required for parameter subspaces where the satisfaction function Λ is close to the probability threshold r.

[3] In [6], a linear-time specification equivalent to ϕ is given.

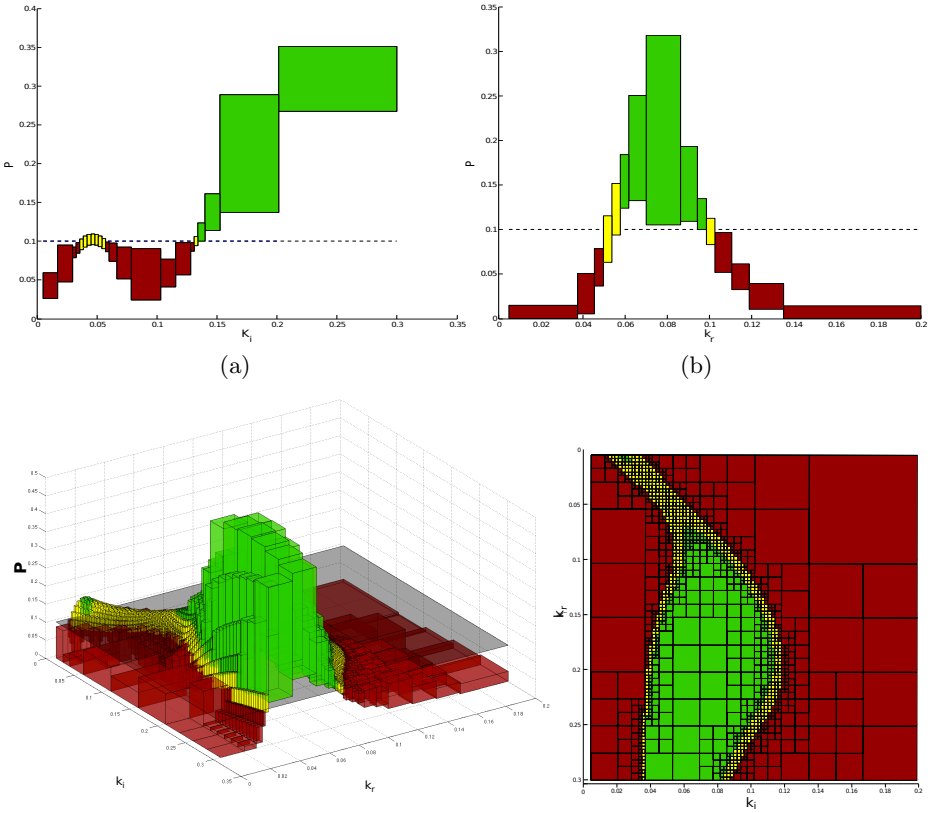
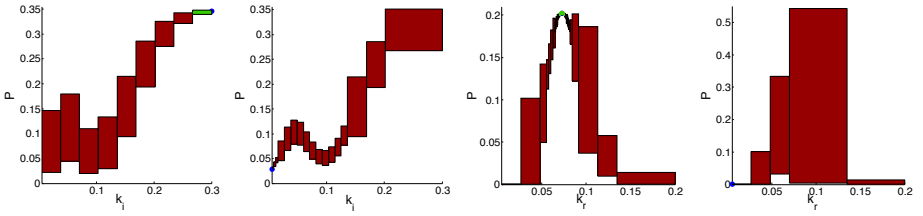


Fig. 6. Solution to threshold synthesis problems for $P_{\geq 0.1}[(I > 0)U^{[100,120]}(I = 0)]$ (the bottom part of the figure depicts two different visualizations of one solution). Volume tolerance $\varepsilon = 10\%$.

Problem	k_i	k_r	Runtime	Subspaces
1. Threshold	$[0.005, 0.3]$	0.05	42.2 s	23
2. Threshold	0.12	$[0.005, 0.2]$	26.7 s	15
3. Threshold	$[0.005, 0.3]$	$[0.005, 0.2]$	29.3 min	1320

Table 1. The computation of the synthesis problems for $P_{\geq 0.1}[(I > 0)U^{[100,120]}(I = 0)]$ using value tolerance $\varepsilon = 10\%$.

Figure 7 and Table 2 (problems 1-4) illustrate the solutions using sampling-based refinement for max and min synthesis problems over one-dimensional parameter spaces. We report that, in order to meet the desired probability tolerance, problems 2 (Figure 7b) and 3 (Figure 7c) require a high number of refinement steps due to two local extrema close to the minimizing region and a bell-shaped Λ with the maximizing region at the top, respectively. Our precise results for problem 1 (Figure 7a) improve on the estimation in [6], where in the equivalent experiment the max probability is imprecisely registered at smaller k_i values.

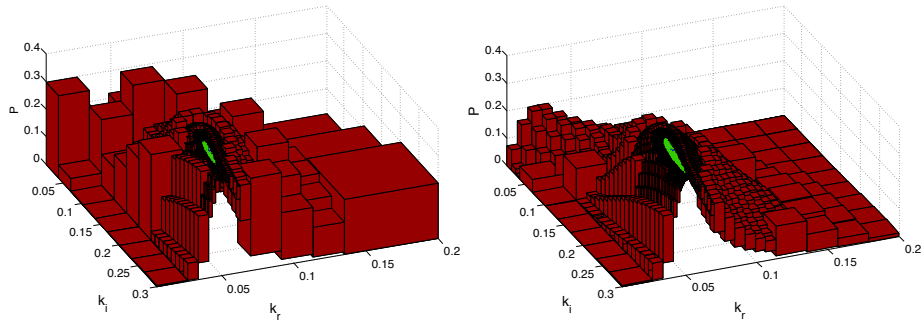


(a) (b) (c) (d)

Fig. 7. Solution to max (a,c) and min (b,d) synthesis using sampling-based refinement for $P_{=?}[(I > 0)U^{[100,120]}(I = 0)]$. Probability tolerance $\epsilon = 1\%$ (a,c) and $\epsilon = 0.1\%$ (b,d).

Problem	k_i	k_r	Runtime	Subspaces	Λ^*[%]	T
1. Max	$[0.005, 0.3]$	0.05	16.5 s	9	33.94	$[0.267, 0.3]$
2. Min	$[0.005, 0.3]$	0.05	49.5 s	21	2.91	$[0.005, 0.0054]$
3. Max	0.12	$[0.005, 0.2]$	99.7 s	57	19.94	$[0.071, 0.076]$
4. Min	0.12	$[0.005, 0.2]$	10.4 s	5	0.005	$[0.005, 0.026]$
5. Max	$[0.005, 0.3]$	$[0.005, 0.2]$	3.6 h	5817	35.01	$[0.217, 0.272] \times [0.053, 0.059]$
6. Max	$[0.005, 0.3]$	$[0.005, 0.2]$	6.2 h	10249	34.77	$[0.209, 0.29] \times [0.051, 0.061]$

Table 2. The computation of the synthesis problems for $P_{=?}[(I > 0)U^{[100,120]}(I = 0)]$ using probability tolerance $\epsilon = 1\%$ (problems 1,3,5,6) and $\epsilon = 0.1\%$ (problems 2,4). The sampling-based refinement is used except for problem 5. The minimal bounding box of T is reported in problems 5 and 6. Λ^* denotes $\Lambda^\perp$ (problems 1,3,5,6) and $\Lambda^\top$ (problems 2,4).



(a) (b)

Fig. 8. Solutions to max synthesis with sampling-based refinement (a) and without sampling (b) for $P_{=?}[(I > 0)U^{[100,120]}(I = 0)]$ using probability tolerance $\epsilon = 1\%$.

We also compare the solutions to the max synthesis problem over the two-dimensional parameter space obtained by applying Algorithm 3 with sampling (Figure 8a, problem 5 in Table 2) and without (Figure 8b, problem 6 in Table 2). In the former case, a more precise T region is obtained (with a volume 2.04 times smaller than in the approach without sampling), thus giving a more accurate approximation of the max probability. Sampling also allows us to rule out earlier

those parameter regions that are outside the final solution, thus avoiding unnecessary decompositions and improving the runtime (1.72 times faster than in the approach without sampling). This is visible by the coarser approximations of probabilities in the F region.

6.2 DNA walkers

We revisit models of a DNA walker, a man-made molecular motor that traverses a track of anchorages and can take directions at junctions in the track [23], which can be used to create circuits that evaluate Boolean functions. `PRISM` models of the walker stepping behaviour were developed previously [10] based on rate estimates in the experimental work. The walker model is modified here to allow uncertainty in the stepping rate, and we consider its behaviour over a single-junction circuit. Given a distance d between the walker-anchorage complex and an uncut anchorage, and d_a being the distance between consecutive anchorages, the stepping rate k is defined as:

$$k = \begin{cases} k_s & \text{when } d \leq 1.5d_a \\ c \cdot k_s/50 & \text{when } 1.5d_a < d \leq 2.5d_a \\ c \cdot k_s/100 & \text{when } 2.5d_a < d \leq 24\text{nm} \\ 0 & \text{otherwise.} \end{cases} \tag{8}$$

where the base stepping rate $k_s \in [0.005, 0.020]$ is now defined as an interval, as opposed to the original value of 0.009. We have also added factor c for steps between anchorages that are not directly adjacent, but we will assume $c = 1$ for now. The base stepping rate may depend on buffer conditions and temperature, and we want to verify the robustness of the walker with respect to the uncertainty in the value of k_s.

We compute the minimal probability of the walker making it onto the correct final anchorage (min synthesis for the property $P_{=?}[F^{[T,T]}$ finish-correct$]$) and the maximum probability of the walker making it onto the incorrect anchorage (max synthesis for the property $P_{=?}[F^{[T,T]}$ finish-incorrect). We list the probabilities at $T = 15, 30, 45, 200$ minutes in Table 3. For time $T = 30, 45, 200$, we note that the walker is robust, as the minimal guaranteed probability for the correct outcome is greater than the maximum possible probability for the incorrect outcome. For time $T = 15$ this is not the case. We also consider a property that provides bounds on the *ratio* between the walker finishing on the correct versus the incorrect anchorage. The rates $c \cdot k_s/50$ and $c \cdot k_s/100$ correspond to the walker stepping onto anchorages that are not directly adjacent, which affects the probability for the walker to end up on the unintended final anchorage. For higher values of c, we expect the walker to end up in the unintended final anchorage more often. Now we add uncertainty on the value of c, so that $c \in [0.25, 4]$, and define the performance related property $P_{\geq 0.4}[F^{[30,30]}$ finish-correct$] \wedge P_{\leq 0.08}[F^{[30,30]}$ finish-incorrect$]$, that is, the probability of the walker to make it onto the correct anchorage is at least 40% by

			Runtime		Subspaces	
Time bound	Min. correct	Max. incorrect	$\emptyset$	Sampling	$\emptyset$	Sampling
$T = 15$	1.68%	5.94%	0.55 s	0.51 s	22	11
$T = 30$	14.86%	10.15%	1.43 s	1.35 s	35	15
$T = 45$	33.10%	12.25%	3.53 s	2.14 s	61	21
$T = 200$	79.21%	16.47%	213.57s	88.97 s	909	329

Table 3. The computation of min-synthesis for $P_{=?}[F^{[T,T]}$ finish-correct] and max-synthesis for $P_{=?}[F^{[T,T]}$ finish-incorrect] using $k_s \in [0.005, 0.020], c = 1$ and probability tolerance $\epsilon = 1\%$. The runtime and subspaces are listed only for the min-synthesis (the results for the max-synthesis are similar).

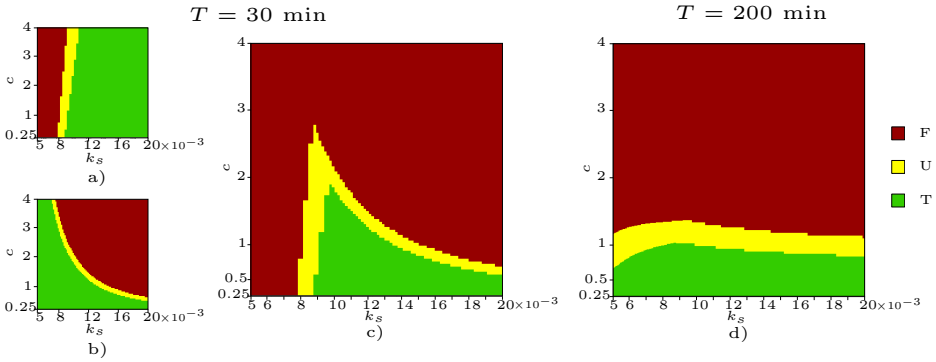


Fig. 9. The computation and results of the threshold synthesis for different formulae, using volume tolerance $\varepsilon = 10\%$. a) $\Phi_1 = P_{\geq 0.4}[F^{[30,30]}$ finish-correct], runtime 443.5 s, 2692 subspaces. b) $\Phi_2 = P_{\leq 0.08}[F^{[30,30]}$ finish-incorrect], runtime 132.3 s, 807 subspaces. c) $\Phi_1 \wedge \Phi_2$. d) $P_{\geq 0.8}[F^{[200,200]}$ finish-correct$] \wedge P_{\leq 0.16}[F^{[200,200]}$ finish-incorrect], runtime 12.3 h, 47229 subspaces.

time $T = 30$ min, while the probability for it to make it onto the incorrect anchorage is no greater than 8%. In other words, we require a correct signal of at least 40% and a correct-to-incorrect ratio of at least 5 by time $T = 30$ min. We define a similar property at time $T = 200$ min, this time requiring a signal of at least 80%: $P_{\geq 0.8}[F^{[200,200]}$ finish-correct$] \wedge P_{\leq 0.16}[F^{[200,200]}$ finish-incorrect]. The synthesized ranges of k_s and c where the properties hold are shown in Figure 9.

7 Conclusion

We have developed efficient algorithms for synthesising rate parameters for biochemical networks so that a given reliability or performance requirement, expressed as a time-bounded CSL formula, is guaranteed to be satisfied. The techniques are based on the computation of lower and upper probability bounds of [7] in conjunction with region refinement and sampling. The high computational costs observed in our case studies can be reduced by parallel processing of individual subspaces, or by utilizing advanced uniformisation techniques [20, 9]. We plan to include the synthesis algorithms in the `param` module of the `PRISM` model checker [8, 19].

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