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DOI:
10.1109/TCBB.2018.2804395

Document Version
Peer reviewed version

Citation for published version (Harvard):
Mu, C, Dittrich, P, Parker, D & Rowe, J 2018, 'Organisation-Oriented Coarse Graining and Refinement of Stochastic Reaction Networks', *IEEE - ACM Transactions on Computational Biology and Bioinformatics*. https://doi.org/10.1109/TCBB.2018.2804395

Organisation-Oriented Coarse Graining and Refinement of Stochastic Reaction Networks

Chunyan Mu, Peter Dittrich, David Parker, Jonathan E. Rowe

Abstract—Chemical organisation theory is a framework developed to simplify the analysis of long-term behaviour of chemical systems. In this work, we build on these ideas to develop novel techniques for formal quantitative analysis of chemical reaction networks, using discrete stochastic models represented as continuous-time Markov chains. We propose methods to identify organisations, and to study quantitative properties regarding movements between these organisations. We then construct and formalise a coarse-grained Markov chain model of hierarchic organisations for a given reaction network, which can be used to approximate the behaviour of the original reaction network. As an application of the coarse-grained model, we predict the behaviour of the reaction network systems over time via the master equation. Experiments show that our predictions can mimic the main pattern of the concrete behaviour in the long run, but the precision varies for different models and reaction rule rates. Finally, we propose an algorithm to selectively refine the coarse-grained models and show experiments demonstrating that the precision of the prediction has been improved.

Index Terms—stochastic reaction networks, probabilistic model checking, organisation theory, coarse-graining, refinement.

1 Introduction

In this paper, we study reaction networks and chemical organisation theory, in particular, investigating the applicability of formal verification to their analysis. Reaction networks are widely used in modelling chemical and biological phenomena. For example, the BioModels Database [18] contains more than one hundred thousand reaction network models of bio-molecular systems [5]; additionally, large-scale processes like infection dynamics, evolutionary population dynamics [22], or social systems [24] can be modelled by reaction networks. A reaction network describes the structure of interactions between system elements in a formal and intuitively clear way. However, as a consequence of non-linear interactions, feedback loops, and large state spaces the implied overall dynamics can be difficult to understand and to analyse.

Chemical organisation theory [7], [10] provides a way to analyse complex dynamical networks and reason about the long-term behaviour of chemical systems. The complex network is decomposed into a set of sub-networks called "organisations". An *organisation* is a set of objects (for example, the species or molecules in a reaction system) which are closed and self-maintaining. Informally, *closed* means that no new object can be produced by the interactions within the set, and *self-maintaining* means that no object of the set disappears from the system, i.e., every consumed object of the set can be generated within the set. The concept of organisation allows us to lift the complex reaction network to a hierarchic structure including all stable states and states depicting accumulating molecules regarding to the organisations. The dynamics of the complex state space of the reaction network can then be mapped to movements among the set of organisations. Building a chemical organisation-based model thus helps us to model the structure and behaviour of complex reaction networks, and to simplify the dynamical analysis of the overall system.

In order to study the evolution of reaction networks, we apply probabilistic model checking, a formal verification technique for modelling and analysis of systems with stochastic behaviour. It has been used to study models across a wide range of application domains, including chemical and biological systems. Probabilistic model checking is based on the exhaustive construction and analysis of a state-based probabilistic model, typically a Markov chain or variant. In this work, we model the reaction networks as continuous-time Markov chains. Quantitative properties of interest about the system being analysed are formally specified using temporal logic. Here we use CSL (Continuous Stochastic Logic) [2] with rewards, a quantitative extension of the temporal logic CTL.

Specifically, we apply CSL model checking of continuous-time Markov chains to investigate connections between chemical organisations using model decompositions into strongly connected components (SCCs). We develop an algorithm to automatically find organisations, and then perform a quantitative dynamical analysis in terms of organisations, asking, for example, "what is the probability of moving from one organisation to another?" or "what is the expected time to leave an organisation?" We implement our techniques as an extension of the probabilistic model checking tool PRISM [17], and illustrate the approaches on a set of example reaction networks.

A coarse grained Markov chain model of hierarchical organisations for a given reaction network is then constructed as a result, and we prove that this yields safe approximations to the dynamical properties of the original

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Manuscript received April XX, 2017; revised August XX, 2017.

concrete model. Approximating and predicting the system behaviour over time is another direct application of our coarse grained model, which can save significant time and space comparing with doing prediction by using the original concrete model. Specifically, we study the following question: "Given a coarse-grained model and a fixed volume of the chemical species, what is the probability distribution of the molecular population after t time units?". Our experiments show that our prediction can mimic the main pattern of concrete behaviour in the long run, but the precision varies for different models and rates of their reaction rules. In order to improve the precision of the approximation and prediction, we develop an algorithm to selectively refine the coarse-grained models. The basic idea is that we partition the abstract states of the coarse-grained model using k-means clustering techniques. Our experiments show that the precision of the prediction is improved as a result.

This paper is an extended version of [21]. It also contains extra examples, experiments for performance comparisons and, in particular, the method for refinement of the coarse-grained models.

Related work. There are various approaches to modelling the dynamics of reaction networks. Feinberg and Horn [9] proposed methods to identify *positive* stationary states in which *all* molecular species are present in a network. Heinrich and Schuster [13] study network structure based on *flux modes*, each of which specifies a set of reaction rules that can take place at a steady state and thus implies a set of species participating in those reactions. Species relating to a flux mode were not required to be *self-maintaining* or *closed* however. We are more interested in the stationary states in which a *subset* of species are present, which is formalised in organisation theory [7]. In that area, the focus was typically on *qualitative* properties, and ODEs [8], approximating the evolution of reaction networks in *continuous* dynamical systems. Kreyssig et. al [15] studied the effects of small particle numbers on long-term behaviours in *discrete* biochemical systems. We build on their notion of discrete organisation but focus on *quantitative* analysis of the transitive dynamics among the organisations, which was not considered in [15]. Other approaches for approximate analysis of discrete models of reaction networks include the use of Linear Noise Approximation [4], the Central Limit Approximation [3] and "sliding window" abstractions [25].

Outline. This paper is organised as follows. Section 2 gives an overview of probabilistic model checking. Sections 3 and 4 present the details of modelling chemical reaction networks as CTMCs and introduce definitions for building connections with chemical organisation theory. Section 5 proposes methods for a quantitative organisation-based analysis. Section 6 formalises the definition of the organisation-based interval coarse-grained model, which safely approximates the probabilistic behaviours of the system, but may suffer from over-estimation. Section 7 demonstrates how to use our organisation-oriented coarse-grained model to predict system behaviour over time evolution. For the purpose of improving the precision of the approximation and prediction, Section 8 proposes an algorithm to selectively refine the the coarse-grained models, and shows how precision of the analysis is improved by the refinement. Section 9 draws conclusions.

2 Probabilistic Model Checking

Probabilistic model checking is a variant of *model checking* [6], a well-established formal method to automatically verify the correctness of real-life systems. Classical model checking answers the question of whether the behaviour of a given system satisfies a property or not. It thus requires two inputs: a description of the system and a specification of one or more required properties of that system, normally in temporal logic (such as CTL or LTL).

In probabilistic model checking, the models are extended with information about the likelihood that transitions take place. In practice, these models are usually Markov chains or Markov decision processes. In this work, we model the reaction systems as continuous-time Markov chains (CTMCs). Properties expressed in temporal logic are also of a quantitative nature. For instance, instead of verifying that "species A eventually vanishes", we ask that "what is the probability of species A eventually vanishing?". In this work, we use the temporal logic Continuous Stochastic Logic (CSL) [1], [2].

The remainder of this section reviews some preliminary definitions for the probabilistic model checking techniques that we use in this paper.

2.1 Continuous-Time Markov Chains

Continuous-Time Markov Chains are widely used in fields such as performance analysis or systems biology to model systems with stochastic real-time behaviour. Formally, we define them as follows.

Definition 1 (CTMC). A CTMC is a tuple $\mathcal{A} = (Q, Q_0, \Delta, L)$, where: Q is a finite set of states; $Q_0 \subseteq Q$ is the set of initial states; $\Delta : Q \times Q \to \mathbb{R}_{\geq 0}$ is the transition rate matrix; $L : Q \to 2^{AP}$ is a labelling function assigning, to each state $q \in Q$, a set of atomic propositions, from a set AP, that are true in q.

The transition rate matrix Δ assigns a *rate* to each pair of states in the CTMC, which is used as the parameter of an exponential distribution.

2.2 Continuous Stochastic Logic

In this work, the probabilistic temporal logic CSL (Continuous Stochastic Logic) is used to formally represent properties of reaction networks. It was originally introduced by Aziz et al. [1] and extended by Baier et al. [2]. The extended version allows for the specification of reward (or cost) properties, to reason about rewards (or costs) that have been attached to a CTMC. The extended version of CSL that we use allows us to represent properties such as "the probability of all of species A degrading within t time units is at most 0.1" or "the expected time elapsed before a B molecule first appears is at most 10".

Definition 2 (CSL syntax). An (extended) CSL formula is an expression Ψ derived from the grammar:

$$\Psi \quad ::= \quad \texttt{true} \mid p \mid \neg\Psi \mid \Psi \wedge \Psi \mid \mathtt{P}_{\bowtie\lambda}(\Psi\ U^I\ \Psi) \mid \mathtt{S}_{\bowtie\lambda}(\Psi) \mid \mathtt{R}_{\bowtie r}[\Diamond\Psi]$$

where $p \in AP$ is an atomic proposition, $\lambda \in [0,1]$ is a probability threshold, $r \in \mathbb{R}_{\geq 0}$ is a reward threshold, $\bowtie \in \{<, \leq, \geq, >\}$ and I is an interval of $\mathbb{R}_{\geq 0}$.

CSL formulas are evaluated over the states of a Markov chain. A state q satisfies $\mathtt{P}_{\bowtie\lambda}(\psi)$ if the probability of taking a path from q satisfying ψ is in the interval specified by $\bowtie \lambda$. Here, the path formula ψ is an "until" operator: $\Psi\ U^I\ \Psi'$ asserts that Ψ' is satisfied at some future time point within interval I, and that Ψ is true up until that point. Common derived operators include: "eventually" $\Diamond^I \Psi := \mathtt{true}\ U^I\ \Psi$ and "always" $\Box^I \Psi := \neg\Diamond^I \neg\Psi$. For example, $\mathtt{P}_{\leq\lambda}(\Box^I \Psi) \equiv \mathtt{P}_{\geq 1-\lambda}(\Diamond^I \neg\Psi)$.

The S operator describes the steady state (long-run) behaviour of the CTMC. The formula $\mathtt{S}_{\bowtie\lambda}(\psi)$ specifies that the steady-state probability of being in a state satisfying ψ meets the bound $\bowtie \lambda$. The R operator is used for reward properties: $\mathtt{R}_{\bowtie r}[\Diamond\Psi]$ is true from state q if the expected reward cumulated before a state satisfying Ψ is reached meets the bound $\bowtie r$. Rewards and costs are treated identically: here, we will use the R operator to formalise properties about the expected time elapsing before an event's occurrence.

We omit a full definition of the semantics of CSL with respect to a Markov chain. Full details can be found in, for example, [2].

3 Modelling Reaction Networks with CTMCs

A reaction network consists of a set of molecules (or, molecular species to be more precise) and a set of reaction rules.

Definition 3. A *reaction network* is a pair $(\mathcal{M}, \mathcal{R})$ consisting of a set of possible molecular species $\mathcal{M}$, and a set $\mathcal{R} \subseteq \mathcal{P}_M(\mathcal{M}) \times \mathcal{P}_M(\mathcal{M})$ of possible reactions among those species, where $\mathcal{P}_M(\mathcal{M})$ denotes the set of all multisets of elements over the set $\mathcal{M}$. For a reaction $(R, P) \in \mathcal{R}$, the multisets R and P denote the reactants and products of the reaction, respectively, and we write $R(s)$ and $P(s)$ for the number of molecules of species s consumed by (reactants) and produced by (products) the reaction, respectively.

For simplicity, we write $s_1 + s_2 + \cdots + s_n \to s'_1 + s'_2 + \cdots + s'_{n'}$ instead of $(\{s_1, s_2, \ldots, s_n\}, \{s'_1, s'_2, \ldots, s'_{n'}\}) \in \mathcal{R}$ to denote the existence of a reaction.

There are multiple ways in which we can obtain a dynamical model given a reaction network. One way is to consider (real-valued) concentrations of each molecular species and then represent the (deterministic) behaviour of the reactions as a set of ordinary differential equations. Here, we take a *discrete, stochastic* view of the network, modelling the (integer-valued) population count of each species and considering its evolution as a stochastic process, and in particular as a continuous-time Markov chain [12]. The latter is particularly appropriate when the numbers of molecules can be assumed to be relatively small in practice, and is the approach that we take in this work.

Furthermore, we will also assume that the reaction network is executing within a finite volume, which is modelled by limiting the total number $N_{\mathtt{max}} \in \mathbb{N}$ of molecules that can be present at any given time [15]. We also need to define the rates at which reaction events occur in the CTMC. To retain a general approach, we allow an arbitrary function $\mathtt{rate}_r$ from reactant populations to rate values for each reaction r. A typical default, which we use in some, but not all, of our examples, is the law of mass-action, multiplying the number of molecules of each reactant by a fixed kinetic rate associated with the reaction (and assuming the stoichimetric coefficient of each reactant is at most one). This gives $\mathtt{rate}_r(q) = \lambda_r \cdot \prod_{s \in R} q(s)$ with λ_r being a kinetic rate constant for reaction r.

Definition 4 (CTMC for reaction network). Given a reaction network $(\mathcal{M}, \mathcal{R})$, a volume limit $N_{\mathtt{max}} \in \mathbb{N}$ and a rate function $\mathtt{rate}_r : \mathbb{N}^{\mathcal{M}} \to \mathbb{R}_{\geq 0}$ for each $r \in \mathcal{R}$, we define the corresponding CTMC $\mathcal{A} = (Q, Q_0, \Delta, L)$ where:

- $Q = \{q : \mathcal{M} \to \mathbb{N} \mid \sum_{s \in \mathcal{M}} q(s) \leq N_{\mathtt{max}}\}$

  is the set of population counts of $\mathcal{M}$ and Δ is defined as follows. For states $q, q' \in Q$, we write $q \xrightarrow{(R,P)} q'$ if and only if, for each species $s \in \mathcal{M}$, we have $q(s) \geq R(s)$ and $q'(s) = q(s) - R(s) + P(s)$, and $\sum_{s \in \mathcal{M}} q'(s) \leq N_{\mathtt{max}}$. Then, for any $q, q' \in Q$, we have:

- $\Delta(q, q') = \sum\{|\, \mathtt{rate}_r(q) \mid r \in \mathcal{R} \text{ and } q \xrightarrow{r} q'\}$, and we call r the transition label of $q \xrightarrow{r} q'$.

Q_0 can be any subset of Q representing initial configurations of interest, and L can be any labelling function over Q that identifies states with relevant properties.

Each state $q \in Q$ of the CTMC gives the number $q(s)$ of molecules of each species $s \in \mathcal{M}$ currently present. For a state q, we also write $\phi(q)$ for the set of molecular species that are present, i.e., $\phi(q) = \{s \,|\, q(s) > 0\}$, and define $\phi(Q') = \cup_{q \in Q'} \phi(q)$ for a set of states $Q' \subseteq Q$. We let $Acc(q) \subseteq Q$ denote the states that are reachable from q.

Example 1. Consider the reaction network $\mathcal{A}$ with species $\mathcal{M} = \{a, b\}$ and reactions $\mathcal{R} = \{a + b \to a + 2b, a \to 2a, b \to 2b, a \to \emptyset, b \to \emptyset\}$. Assume the volume of the system is $N_{\mathtt{max}} = 4$, and that the rate of each reaction rule is the multiplication of the number of the reactants. We obtain a CTMC with 15 states (see Fig. 1).

4 Chemical Organisation Theory and SCC Decomposition

Chemical organisation theory [7] provides a way to cope with the complex "constructive" dynamics of a reaction network by deriving a set of organisations [11], and then mapping the movement through a state space to a movement between organisations. Such an abstract view allows us to analyse and predict the dynamical behaviour of a complex reaction network more easily.

An organisation is a set of molecules that is algebraically *closed* and *self-maintaining*. A subset $C \subseteq \mathcal{M}$ is called "closed" if no molecules outside C can be produced by applying any reaction that uses only reactants from C; a subset $S \subseteq \mathcal{M}$ is "self-maintaining" if all reactions that are able to fire in S can occur at certain strictly positive rates without reducing the amount of any species of S.

Definition 5 (Organisation [7]). A subset of $O \subseteq \mathcal{M}$ is a chemical organisation if it is closed and self-maintaining,

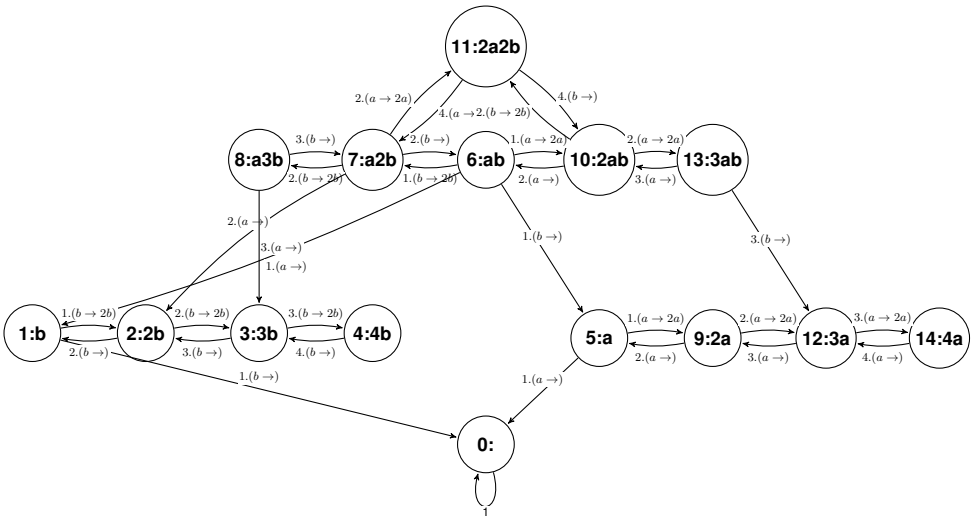


Fig. 1: State transition graph of the CTMC for Example 1. State labels show index and population count, e.g., $11 : 2a2b$ denotes that there are $2a$ and $2b$ in state 11.

that is, if for all $(R, P) \in \mathcal{R}$, $R \subseteq O$ implies $P \subseteq O$ (closure), and there exists a strictly positive flux vector $v > 0$ such that $N_O \cdot v \geq 0$ with N_O being the stoichiometric matrix of the reactions that use only reactants from O (self-maintenance).

As discussed above, we model the dynamics of a reaction network as a Markov chain. A state is defined by a discrete number for each molecular species. With a limited total amount of molecules, both cases of too few and too many molecules can prevent reaction rules being fired. As a consequence, we need to define *discrete organisations*, and the states contributing to generate them. In the following, given a state q, $\mathcal{R}_q$ denotes the reactions firing in any of the reachable states of q.

Definition 6 (Discrete organisation and internal generator [15]). Let $(\mathcal{M}, \mathcal{R})$ be a reaction network. A subset of species $D \subseteq \mathcal{M}$ is called a *discrete organisation* if there is a state $q \in Q$ such that: (i) $\phi(Acc(q)) = D$ (closure); and (ii) there is sequence of transition labels $(r_1, \ldots, r_k)$ where $r_i \in \mathcal{R}$ such that $\cup_{i=1}^{k} \{r_i\} = \mathcal{R}_q$ and $q' = (r_k \circ \cdots \circ r_1)(q)$ satisfies $\forall s \in D : q'(s) \geq q(s)$ (self-maintenance). Such a state q is called an *internal generator* of the discrete organisation.

Definition 7 (Generator). A state $q' \in Q$ is called a *generator* of organisation D iff $\exists q \in Acc(q')$ such that q is an internal generator of D.

Note that, in general, the organisation D generated by a state q' is not unique. However, if q is an internal generator, there is only one organisation it generates. Unless specifically stated otherwise, we say *organisation* rather than *discrete organisation* in the rest of the paper.

Example 2. The discrete organisations for Example 1 are: $\{a, b\}$, $\{a\}$, $\{b\}$, $\{\}$ and the corresponding generators are, respectively (cf. Fig 1):

- $\{6, 7, 8, 10, 11, 13\}$,
- $\{5, 6, 7, 8, 9, 10, 11, 12, 13, 14\}$,
- $\{1, 2, 3, 4, 6, 7, 8, 10, 11, 13\}$,
- $\{0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14\}$.

In order to analyse the system behaviour and perform an organisation-based quantitative analysis of the reaction network, we study the connections between chemical organisations and the decompositions into strongly connected components (SCCs) of the Markov chain.

Definition 8 (SCC [14]). A *strongly connected component* (SCC) is a maximal set of states T such that, for every pair of states $q, q' \in T$, there is a path from q to q'.

Intuitively, in the Markov chain for a reaction network, SCCs are important for an organisation-based analysis. However, some but not all SCCs correspond to organisations. In the next section, we will describe an algorithm to find organisations based on a decomposition into SCCs and then identifying those self-maintaining a set of species. We first note that *bottom* strongly connected components do relate to organisations.

Definition 9 (BSCC). A bottom strongly connected component (BSCC) is an SCC T from which no state outside T is reachable from T.

Proposition 1. Each BSCC corresponds to a (unique) organisation, which is generated (uniquely) by any state of that BSCC.

However, there are organisations whose internal generators are *not* contained in any BSCC. In order to also include such organisations, we call SCCs that correspond to an organisation *good SCCs*.

Definition 10 (Good SCC). An SCC T is called *good* if it contains a cycle of the firing of every "possible" reaction rule, i.e., those whose reactants R appear in the SCC ($R \subseteq \{\phi(q) \mid q \in T\}$).

Example 3. All SCCs are good in Example 1.

Clearly, some generators can contribute to multiple organisations. This makes it more difficult to decompose the Markov into its sets of generators. However, internal generators located in good SCCs contribute uniquely to an organisation.

Proposition 2. A generator g is an internal generator of organisation D iff it is located in a good SCC T such that: $g \in T \ \wedge \ \bigcup_{q \in T} \phi(q) = D$.

Proposition 3. Given a good SCC T, let $A = \phi(T)$, if A is closed, then A is a discrete organisation, then $\{q \mid q \in T\}$ is the set of internal generators of A.

Example 4. In Example 1, the internal generators of organisations $\{a, b\}$, $\{a\}$, $\{b\}$ and $\{\}$ are $\{6, 7, 8, 10, 11, 13\}$, $\{5, 9, 12, 14\}$, $\{1, 2, 3, 4\}$ and $\{0\}$, respectively.

5 Organisation-based Analysis of Reaction Networks

In this section, we propose techniques for quantitative organisation-based analysis of reaction networks. We first introduce an algorithm to find the set of organisations for a specific reaction network. We then use probabilistic model checking to analyse quantitative properties regarding the dynamics of the network with respect to its organisations. Such organisation-based quantitative analyses can be used to construct the structure of organisation-based coarse-grained model, and provide a framework to approximate the complex dynamical behaviours of the original reaction networks in our next step.

Algorithm 1: Finding organisations of a reaction network

Data: CTMC $\mathcal{A}$ of reaction network $(\mathcal{M}, \mathcal{R})$
Result: $\mathcal{O}$ as a set of organisations, $\mathcal{G} : \mathcal{O} \to \mathcal{P}(Q)$ as a mapping from organisations to sets of internal generators

```
O = {};
G = {};
SCC ← Tarjan(A);
SCC_G ← findGoodSCCs(SCC) ∪ BSCC;
for scc ∈ SCC_G do
    M_g ← {φ(q) | q ∈ scc} ;
    if M_g is closed then
        if M_g ∉ O then
            O ← O ∪ M_g                    /* add new organisation */ ;
            G(M_g) ← {q|q ∈ scc}           /* add new internal generators */ ;
        else
            G(M_g) ← G(M_g) ∪ {q|q ∈ scc}  /* update generators */ ;
        end
    end
end
return O, G.
```

5.1 Finding Organisations

Computing the organisations of a reaction network requires an analysis of the strongly-connected components of its Markov chain's underlying transition graph. Since every state in a good SCC is an internal generator of an organisation, we identify good SCCs to find the organisations of the reaction network. Algorithm 1 presents the procedure for finding organisations of a given reaction network modelled as a CTMC. It is based on the following procedures:

- `Tarjan`$(\mathcal{A})$ returns the set of strongly-connected components of the Markov chain $\mathcal{A}$, using Tarjan's SCC algorithm [23] on the underlying digraph;
- `findGoodSCCs`(SCC) returns the "good" part SCC_G of $\mathcal{A}$ in which each possible reaction rule is able to be fired;
- find a set of closed molecules appearing in each $scc \in \mathsf{SCC}_G$, and its relevant internal generators i.e., states in scc which generate the organisation.

5.2 Organisation-Based Probabilistic Analysis

We now illustrate, via several examples, how we derive quantitative organisation-based properties of reaction networks. We implemented the organisation and generator detection process described above in the PRISM model checker, along with a translator that converts descriptions of reaction networks into the PRISM modelling language to allow construction of the corresponding CTMC. Organisation-based properties of the network, such as probabilities (bounds or average) of the movements among organisations, or the expected time to leave or stay at an organisation, are computed using CSL formulae.

Example 5. Consider the reaction network with molecular species $\mathcal{M} = \{a, b\}$ and reactions rules include: $\{a + b \to a, a \to 2a, b \to 2b, a \to \emptyset, b \to \emptyset\}$ with stochastic rates: $\sharp a \cdot \sharp b$, $\alpha \cdot \sharp a$, $\beta \cdot \sharp b$, $(\sharp a)^2$, $(\sharp b)^2$ respectively, where $\sharp a$ denotes the number of molecules of species a (note that this example does *not* assume the law of mass action).

The resulting model is described in the PRISM modelling language. It consists of a keyword describing the model type (`ctmc`), a set of constants, and a single module whose state is represented by a set of finite-ranging variables. Each variable stores the number of each molecular species. The behaviour of the module is specified by a set of *guarded commands* of the form $[]g \to r : u$. This command is interpreted as: if the predicate g is true, then the system is updated by command u. Command u comprises one or more statements of the form $x' = \ldots$ indicating how the value of variable x is updated. The rate at which this occurs is given by r, which will be attached to the corresponding transition label in the underlying CTMC.

We show the PRISM language model for the example in Fig. 2. The resulting CTMC has 66 states and 201 transitions, and there are 4 SCCs ($\{a > 0, b > 0\}, \{a > 0, b = 0\}, \{a = 0, b > 0\}, \{a = b = 0\}$) with 1 BSCC ($\{a = b = 0\}$).

The first property we consider is the probability of moving between organisations. Specifically, the probability of moving from O_1 to O_2 can be specified in CSL as $\mathtt{P}_{=?}[\, o_1 \ U \ o_2 \,]$, where o_1 and o_2 are atomic propositions labelling states which represent internal generators of organisations O_1 and O_2. This refers to the probability of the event where O_2 is reached for the first time after leaving O_1, and is supported directly by PRISM.

In this example, all SCCs are good and each (good) SCC generates exactly one organisation. To visualise the movement between organisation, we analyse the property above for each pair of organisations and construct the abstract transition graph shown in Fig. 3. Blocks are labelled

```
//translation reaction network to PRISM model
ctmc

const int N_MAX = 10;
const double rA = N_MAX; // rA
const double rB = N_MAX; // rB
formula total = a + b;
init total <= N_MAX endinit

module RN
  a : [0..N_MAX];  // range value of specie a
  b : [0..N_MAX];  // range value of specie b

  // r1: a+b -> a
  [r1] (a*b > 0) & (a > 0) & (b > 0) & (total<= N_MAX)
       -> a*b : (a'=a) & (b'=b-1);

  // r2: a -> 2a
  [r2] (rA*a > 0) & (a > 0) & (total+1<= N_MAX)
       -> rA*a : (a'=a+1) ;

  // r3: b -> 2b
  [r3] (rB*b > 0) & (b > 0) & (total+1<= N_MAX)
       -> rB*b :  (b'=b+1) ;

  // r4: a -> 0
  [r4] (a*a > 0) & (total<= N_MAX) -> a*a : (a'=a-1);

  // r5: b -> 0
  [r5] (a*b > 0) & (total<= N_MAX) -> b*b : (b'=b-1);

endmodule
```

Fig. 2: Example 5 in the PRISM modelling language

with organisations and, for each possible transition between organisations, we show the range of probabilities (over all states in the source organisation) and the average value (over the same set of states).

We also consider the expected time to leave (the generators of) each organisation. The CSL property to specify this, for some organisation O_i, is: $\mathtt{R}_{=?}[\,\Diamond\neg o_i\,]$, where o_i is an atomic proposition as above and we use a reward that is accumulated at a rate of 1 per time unit in each state. This means that the property gives the expected time before a state *not* in O_i is reached for the first time. This value is also shown for each organisation in Fig. 3, inside the block for the corresponding organisation.

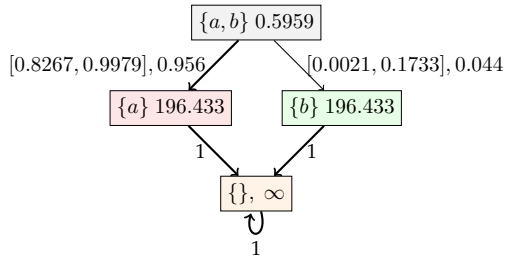


Fig. 3: Organisation movement for Example 5: transition probabilities (in bounds and averages of possible values) between generators of organisations, and the expected time to leave them. For instance, the generators of $[a, b]$ are left about every 0.5959 time steps on average, in which it visits generators of $[a]$ with probability 0.956 in average and $[0.8267, 0.9979]$ in bounds, and visits generators of $[b]$ with probability 0.044 in average and $[0.0021, 0.1733]$ in bounds.

Finally, we consider the effect of making some constructive perturbation to the reaction network, by adding rules to create species with a small rate. Fig. 4 shows the results of the same analysis described above for the following constructive perturbation: $\{\emptyset \to a, \emptyset \to b\}$ both with reaction rate $\gamma = 0.01$. The result shows that, generating a and b with a small rate can cause an upward movement and slightly affect the system's behaviour. The expected time to stay in each organisation decreases since the movement flow becomes slightly faster. This meets our intuition: the upward flow introduced by the constructive perturbation leads to a smoother flow of the system.

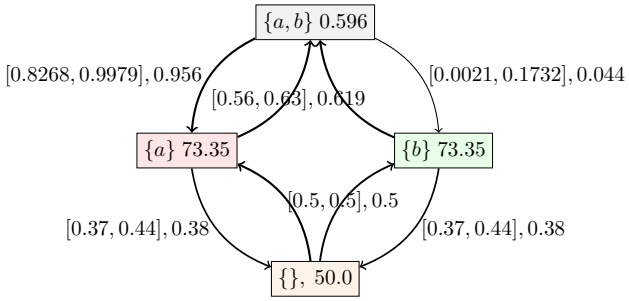


Fig. 4: Organisation-based transition model of Example 5 with constructive perturbation.

Example 6. Consider now the reaction network with $\mathcal{M} = \{a, b, c, d\}$ and $\mathcal{R} = \{a+b \to a+2b,\ a+d \to a+2d,\ b+c \to 2c,\ c \to b,\ b+d \to c,\ b \to \emptyset,\ c \to \emptyset,\ d \to \emptyset\}$ and rates (say R_1) as: $\sharp a * \sharp b$, $\sharp a * \sharp d$, $\sharp b * \sharp c$, $\sharp c$, $\sharp b * \sharp d$, $\sharp b$, $\sharp c$, $\sharp d$ respectively.

Fig. 5 shows the structure of the CTMC for $N_{\max} = 5$. Even for a small volume $N_{\max} = 5$, the structure is quite complex: 126 states, 386 transitions, 28 SCCs and 6 BSCCs.

Fig. 6 illustrates, in the same fashion as above, the transition probabilities between *all* SCCs of the CTMC, and the expected time to leave them. Note that not all SCCs are good SCCs in this example: we highlight good SCCs in colour in Fig. 6. For instance, the SCC labelled as $(99, 105; 0.25)$ is not a good one. There are two states in this SCC: state 99 ($a = 2, b = 0, c = 1, d = 1$) and state 105 ($a = 2, b = 1, c = 1, d = 1$). The set of molecules appearing in this node is closed, but reaction rules such as $c \to \emptyset$ and $d \to \emptyset$ cannot be fired within the SCC and it is therefore not good. In addition, the SCC labelled as $(12, 27; 0.25)$ is also not a good one. It contains state 12 ($a = 0, b = 0, c = 2, d = 1$) and state 27 ($a = 0, b = 1, c = 1, d = 1$). The set of molecules appeared in this node is closed, but reaction rule $c \to \emptyset$ is unable to be fired locally, i.e., this decay will only introduce transitions to other SCCs. Similar cases can happen for some of the other reaction rules.

Fig. 7 presents the transition probabilities between good SCCs only, and the expected time to leave them. Note that multiple good SCCs can contribute to the generation of one organisation. For instance, both good SCCs labelled $65\ldots$ and $98\ldots$ contribute to organisation $\{a, b, c\}$. Based on this graph, we can build up the transition graph over organisations.

Fig. 8 presents the transition probabilities between (internal generators of) organisations, and the expected time to leave each of them. It helps us to understand the movement between organisations and can be viewed as an abstract model capturing the behaviour of the reaction network at the level of organisations.

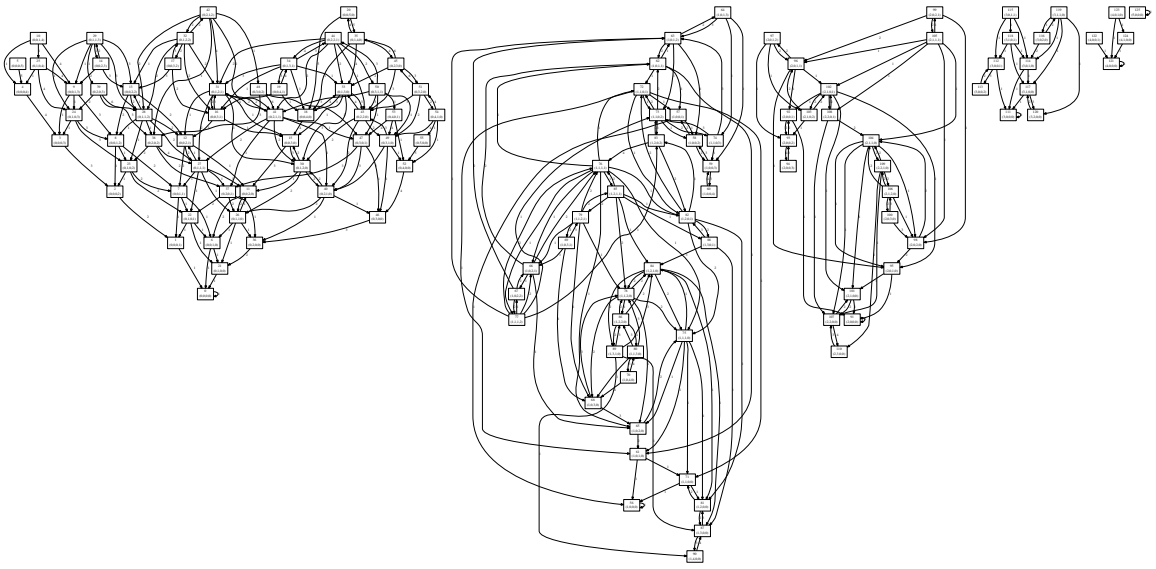


Fig. 5: CTMC for the reaction network from Example 6, with 28 SCCs and 6 BSCCs.

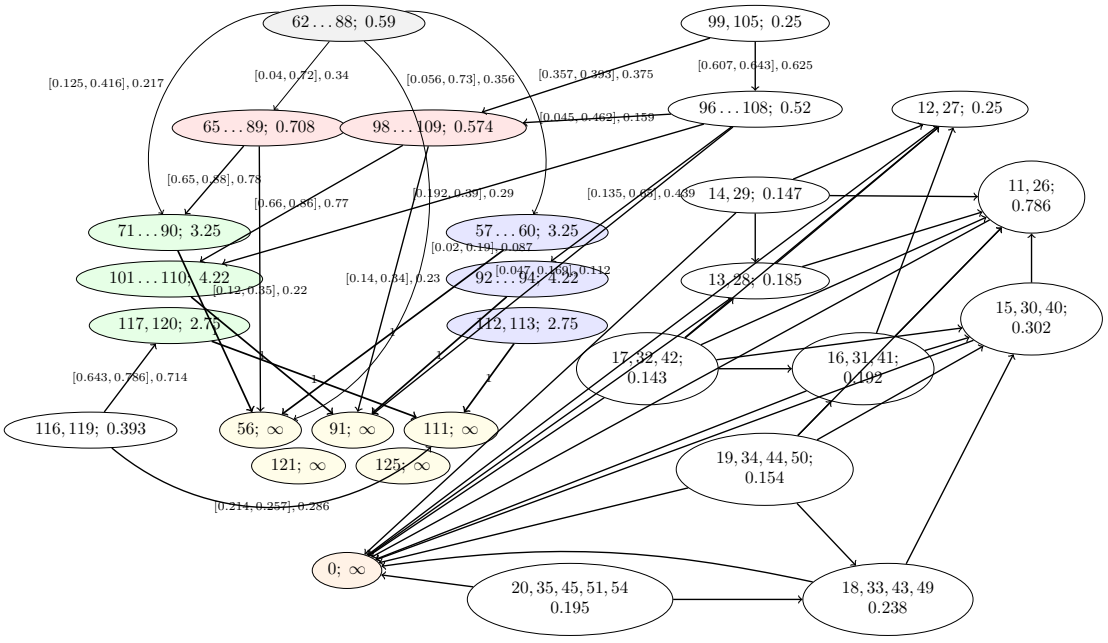


Fig. 6: Transition probabilities (bounds and averages) between all SCCs of the CTMC for Example 6 and the expected times to leave them. Probabilities annotate edges as "$[l, u], a$" for lower/upper bounds l, b and average a; states are labelled first with a list of the states in the SCC and then with the expected time to leave.

In addition, we also present transition graphs over the lattice of molecules (states in which a set of molecules in the lattice with positive numbers) for a quantitative analysis for organisations from a different point of view, see Fig. 9. The transition probabilities are given in bound. Specifically, the probability of movement from $\{a, b, c\}$ to $\{a, b\}$ can be specified as: $\mathsf{P}_{=?}[(a > 0 \wedge b > 0 \wedge c > 0)\ U\ (a > 0 \wedge b > 0 \wedge c = 0)]$. Note that Fig. 8, Fig. 9 can be used to build a coarse-grained model from a different perspective.

6 Organisation-oriented Interval Markov Chain

The organisation-oriented transition graph generated by the quantitative analysis can be used to build a coarse-grained model (with either interval based or average based probabilistic transitions). Such a coarse-grained model can mimic

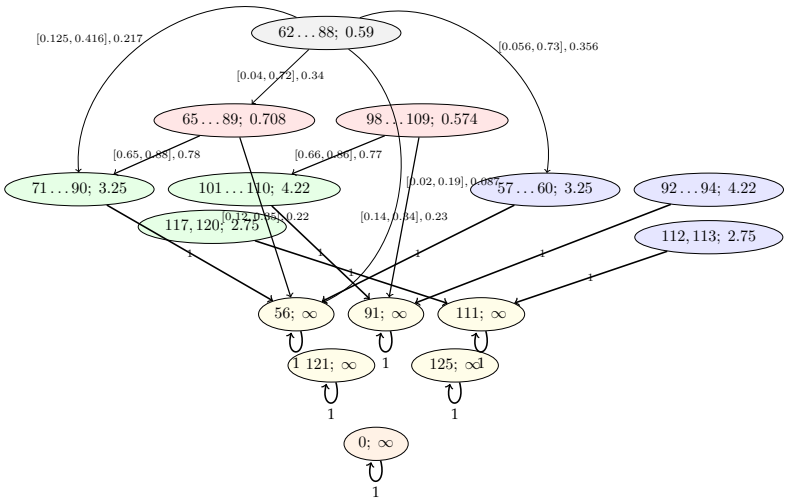


Fig. 7: Transition probabilities (bounds and average) between good SCCs for Example 6 and the expected time to leave them.

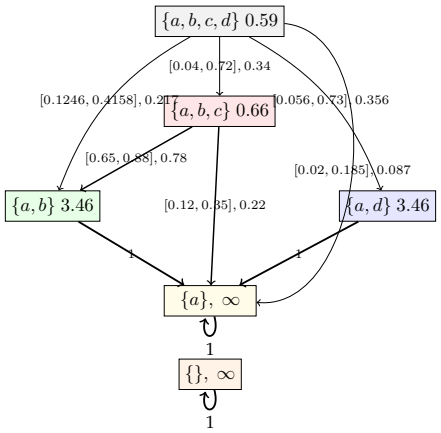


Fig. 8: Transition probabilities (bounds and average) between generators of organisations for Example 6 with $N_{\max} = 5$ and the expected time to leave them.

the complex reaction behaviours of the reaction network in an abstract way, whose state space and movement structure are much smaller. We can then perform approximation, prediction, and quantitative analysis upon the coarse-grained model in stead of the complex concrete model. This section focuses on formalising the interval-based organisation coarse-grained model. Specifically, our quantitative analysis computes an organisation-oriented interval Markov chain, in which each abstract state is specified by a set of internal generators of an organisation, and the abstract transition provides the information about the uncertainty of the abstract behaviours of the system. Probabilities of moving from one abstract state to another are given by the lower and upper bounds, which provides the under and over approximation of the concrete probabilities.

Definition 11 (Organisation-oriented interval Markov chain). An *organisation-oriented interval Markov chain* is a tuple $\mathcal{A}_I^\sharp = (Q^\sharp, Q_0^\sharp, \Delta^\sharp, L)$, where

- $Q^\sharp$ is a finite set of abstract states, each of which $q^\sharp \in Q^\sharp$ is a set of internal generators of an organisation o: $q^\sharp \subseteq \mathcal{G}_I(o)$;
- $Q_0^\sharp \subseteq Q^\sharp$ is the set of initial abstract states;
- $\Delta^\sharp : Q^\sharp \times Q^\sharp \to [lb, ub]$ is the abstract transition matrix, s.t. $\Delta^\sharp(q^\sharp, q^{\sharp\prime}) = [lb, ub]$, where lb and ub are the lower and upper bound of a set of concrete probabilistic transitions: $\{\Delta(q, q') \mid q \in q^\sharp, q' \in q^{\sharp\prime}\}$ specified in the relevant concrete model $\mathcal{A}$ respectively;
- $L : Q^\sharp \to 2^{AP}$ is a labelling function over $Q^\sharp$ that identifies properties of interest.

An *abstract path* is an execution of the organisation-oriented interval Markov chain.

Definition 12 (Abstract path). An *abstract path* $\omega^\sharp$ is a non-empty sequence of states $q_0^\sharp q_1^\sharp \ldots$, where $q_i^\sharp \in Q^\sharp$ and $\forall i. \Delta^\sharp(q_i^\sharp, q_{i+1}^\sharp) \subseteq (0, k]$ where $0 < k \leq 1$. The set of all finite and infinite paths of $\mathcal{A}_I^\sharp$ starting in state $q^\sharp$ are denoted as: $\texttt{Path}_{\texttt{fin}}^{\mathcal{A}_I^\sharp}(q^\sharp)$ and $\texttt{Path}^{\mathcal{A}_I^\sharp}(q^\sharp)$ respectively.

Definition 13 (Probability bounds of abstract paths). The lower ($\texttt{Prob}^-$) and upper bound ($\texttt{Prob}^+$) of the probability of a finite abstract path $\omega_{\texttt{fin}}^\sharp$ starting from state $q^\sharp$ are respectively:

$$\texttt{Prob}^-_{q^\sharp}(\omega^\sharp_{\texttt{fin}}) \triangleq \begin{cases} 1 & \textit{if } n = 0 \\ \texttt{Prob}^-_{q^\sharp}(\omega_0^\sharp, \omega_1^\sharp) \ldots \texttt{Prob}^-_{q^\sharp}(\omega_{n-1}^\sharp, \omega_n^\sharp) & \textit{otherwise} \end{cases}$$

$$\texttt{Prob}^+_{q^\sharp}(\omega^\sharp_{\texttt{fin}}) \triangleq \begin{cases} 1 & \textit{if } n = 0 \\ \texttt{Prob}^+_{q^\sharp}(\omega_0^\sharp, \omega_1^\sharp) \ldots \texttt{Prob}^+_{q^\sharp}(\omega_{n-1}^\sharp, \omega_n^\sharp) & \textit{otherwise} \end{cases}$$

where n denotes the length of the abstract path, $\omega_i^\sharp$ denotes the i^{th} element of $\omega^\sharp$.

We focus on the reachability properties, for instance, the probability bounds of reaching or moving to an organisation of interests from another.

Definition 14 (Reachability properties). Let $\mathcal{A}_I^\sharp$ be an organisation-based interval Markov chain. The lower

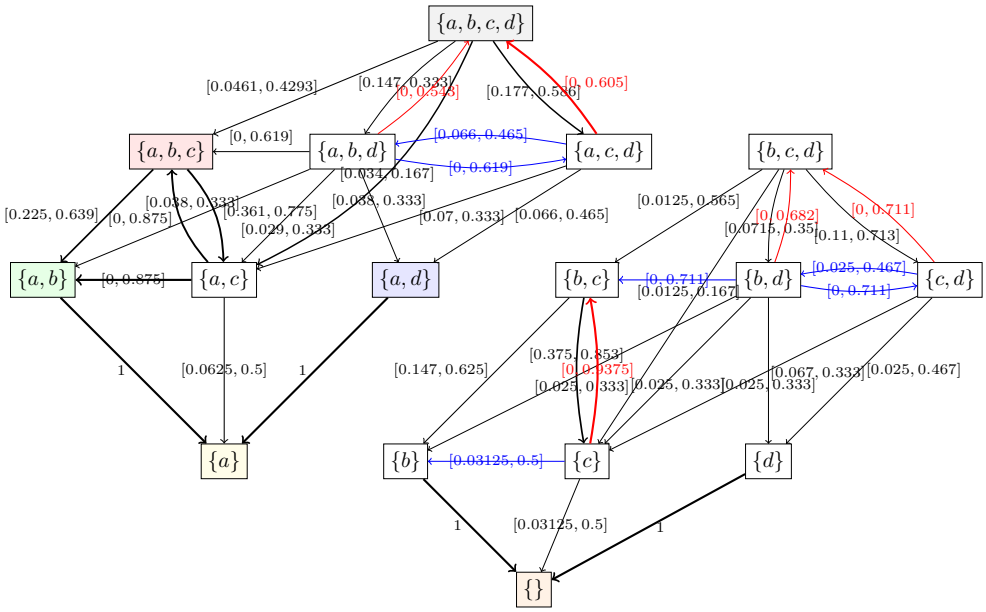


Fig. 9: Example 6: transition probabilities in bounds among the lattice of molecules

and upper bound of the probability of reaching an abstract state $q^{\sharp\prime}$ from $q^{\sharp}$ are computed by:

$$\begin{aligned}\mathtt{Reach}^{-}_{\mathcal{A}^{\sharp}_I}(q^{\sharp}, q^{\sharp\prime}) \triangleq \min\Big(\sum_{\omega^{\sharp} \in \mathtt{Path}^{\mathcal{A}^{\sharp}_I}_{\mathtt{fin}}(q^{\sharp})} \mathtt{Prob}^{-}_{q^{\sharp}}(\omega^{\sharp}) \mid \\ \omega^{\sharp}_0 = q^{\sharp} \wedge \exists i \geq 0. \omega^{\sharp}_i = q^{\sharp\prime}, 1)\end{aligned}$$

$$\begin{aligned}\mathtt{Reach}^{+}_{\mathcal{A}^{\sharp}_I}(q^{\sharp}, q^{\sharp\prime}) \triangleq \min\Big(\sum_{\omega^{\sharp} \in \mathtt{Path}^{\mathcal{A}^{\sharp}_I}_{\mathtt{fin}}(q^{\sharp})} \mathtt{Prob}^{+}_{q^{\sharp}}(\omega^{\sharp}) \mid \\ \omega^{\sharp}_0 = q^{\sharp} \wedge \exists i \geq 0. \omega^{\sharp}_i = q^{\sharp\prime}, 1).\end{aligned}$$

Our organisation-oriented interval Markov chain should safely approximate the concrete CTMC describing the probabilistic behaviours of the system.

Theorem 1 (Soundness of the abstract semantics). Let $\mathcal{A}^{\sharp}_I$ and $\mathcal{A}$ be the coarse-grained model and the relevant concrete model of a reaction network respectively, $\forall q^{\sharp} = Q, q^{\sharp\prime} = Q' \in Q^{\sharp} \subseteq Q$, we have:

$$\mathtt{Reach}^{-}_{\mathcal{A}^{\sharp}_I}(q^{\sharp}_1, q^{\sharp}_2) \leq \mathtt{Reach}^{-}_{\mathcal{A}}(Q, Q'),$$

$$\mathtt{Reach}^{+}_{\mathcal{A}^{\sharp}_I}(q^{\sharp}_1, q^{\sharp}_2) \geq \mathtt{Reach}^{+}_{\mathcal{A}}(Q, Q').$$

Proof: Let $\omega^{\sharp}$ denote an abstract path starting from $q^{\sharp}$ and reaching $q^{\sharp\prime}$. For any $\omega^{\sharp} \in \mathtt{Path}_{\mathcal{A}^{\sharp}_I}(q^{\sharp}, q^{\sharp\prime})$, such as $\omega^{\sharp}_0 = q^{\sharp}$, $\omega^{\sharp}_{|\omega^{\sharp}|} = q^{\sharp\prime}$, assume $|\omega^{\sharp}| = n \in \mathbb{N}$, and let $\omega \in \mathtt{Path}_{\mathcal{A}}(q, q')$ denote a concrete path starting from a state in Q and reaching a state Q', we have:

$$\begin{aligned}&\mathtt{Reach}^{-}(q^{\sharp}, q^{\sharp\prime}) = \sum_{\omega^{\sharp}} \mathtt{Prob}^{-}_{q^{\sharp}}(\omega^{\sharp}) \\ =\ & \sum_{\omega^{\sharp}} \Big(\mathtt{Prob}^{-}(\omega^{\sharp}_0, \omega^{\sharp}_1) \times \cdots \times \mathtt{Prob}^{-}(\omega^{\sharp}_{n-1}, \omega^{\sharp}_n) \Big) \\ =\ & \sum_{\omega^{\sharp}} \left(\prod_{i=0}^{n-1} \inf\{\mathtt{Prob}(q_i, q_{i+1}) | q_i \in \omega^{\sharp}_i, q_{i+1} \in \omega^{\sharp}_{i+1}\} \right) \\ \leq\ & \sum_{\omega^{\sharp}} \inf\{\mathtt{Prob}(q_0, q_n) | q_0 \in \omega^{\sharp}_0, q_n \in \omega^{\sharp}_n\} \\ =\ & \sum_{\omega} \inf\{\mathtt{Prob}(\omega_0, \omega_n) | \omega_0 \in Q, \omega_n \in Q'\} \\ =\ & \mathtt{Reach}^{-}(Q, Q').\end{aligned}$$

Similarly, we have $\mathtt{Reach}^{+}(q^{\sharp}, q^{\sharp\prime}) \geq \mathtt{Reach}^{+}(Q, Q')$. □

Example 7. Consider again the reaction network described in Example 6:

- by applying the coarse-grained model shown in Fig. 8, we can calculate the probability of movement from $q^{\sharp}_{\{a,b,c,d\}}$ to $q^{\sharp}_{\{a,b\}}$ is: $[0.1506, 1]$; the probability of movement from $q^{\sharp}_{\{a,b,c,d\}}$ to $q^{\sharp}_{\{a\}}$ is: $[0.2314, 1]$;
- by applying the concrete model shown in Fig. 5, we obtain the probability of movement from $Q_{\{a,b,c,d\}}$ to $Q_{\{a,b\}}$ is: $[0.1776, 0.8268]$; the probability of movement from $Q_{\{a,b,c,d\}}$ to $Q_{\{a\}}$ is: $[1, 1]$.

Note that our interval coarse-grained model safely approximates the concrete one, but may suffer from over-estimation.

7 Predicting System Behaviour over Time

This section presents an application of our organisation-oriented coarse grained model. We address the following problem: given a reaction network and a fixed number of the maximum population of the system, construct the average-based organisation coarse-grained model $\bar{\mathcal{A}}^{\sharp}$ (focus on the

average transition probabilities between abstract states for simplicity and intuition, this can be replaced by interval-based transitions directly), can we predict the behaviour of the system at any future time using $\bar{\mathcal{A}}^\sharp$? Fig. 10 captures the

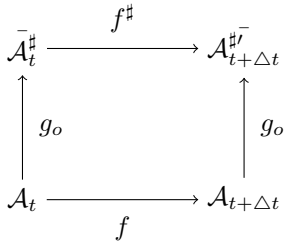


Fig. 10: Coarse graining and time evolution

idea of using an organisation-based coarse grained model to approximate the concrete one. In the concrete world, $\mathcal{A}_t$ denotes the concrete model at time t, f denotes the dynamical transition function over $\mathcal{A}_t$, and $\mathcal{A}_{t+\Delta t}$ denotes the concrete model after Δt time units; g_o denotes the organisation based coarse graining function, which maps the concrete model $\mathcal{A}_t$ (c.f. $\mathcal{A}_{t+\Delta t}$) to the average coarse-grained model $\bar{\mathcal{A}}^\sharp_t$ (c.f. $\bar{\mathcal{A}}^\sharp_{t+\Delta t}$); $f^\sharp$ denotes the coarse-graining dynamical transition function on $\bar{\mathcal{A}}^\sharp_t$.

7.1 Time evolution of the reaction networks via master equations

We apply the traditional "master equation" approach to calculate the stochastic time evolution of the reaction network. We briefly review the main features of the master equation formalism for our purpose of calculating the prediction of a reaction network at any future time. The probability function $P(X_1, X_2, \ldots, X_n; t)$ defines the probability of a number X_i of molecules of species S_i for $i \in \{1, \ldots, n\}$ at time t. This function thus describes the "stochastic state" of the system at time t. The master equation is the time-evolution equation for the function $P(t)$. Function $P(X_1, \ldots, X_n; t + dt)$ can be viewed as the sum of the probabilities of different ways that the system can reach the state $X_1, \ldots, X_n$ at time $t + dt$:

$$P(X_1, \ldots, X_n; t + dt) \quad (1)$$

$$= P(X_1, \ldots, X_n; t)(1 - \sum_{i=1}^{m} \alpha_i dt) + \sum_{j=1}^{n} \beta_j dt, \quad (2)$$

where the quantity $\beta_j dt$ denotes the probability that the system is entering the state $(X_1, \ldots, X_n)$ at time $t + dt$, and the quantity $\alpha_i dt$ denotes the probability that is leaving $(X_1, \ldots, X_n)$ at time t. Without introducing any confusion, we use $P(t)$ as an abbreviation of $P(X_1, \ldots, X_n; t)$. Consider a coarse-grained model $\bar{\mathcal{A}}^\sharp$, and any abstract state $q_i^\sharp$. Letting α_i denote the average rate of leaving state $q_i^\sharp$, i.e., $\frac{dP_i(t)}{dt} = -\alpha P_i(t)$, and E_i denote the expected time to leave state $q_i^\sharp$, we have:

$$E_i = \int_0^\infty P_i(t)dt = \int_0^\infty e^{-\alpha_i t} dt = \frac{1}{\alpha_i},$$

i.e., $\alpha_i = \frac{1}{E_i}$ is the rate of leaving $q_i^\sharp$. In addition, for any $j \neq i$ and $\Delta^\sharp(q_j^\sharp, q_i^\sharp) > 0$, similarly, $\beta_j = \frac{1}{E_j}$ is the rate of coming to $q_i^\sharp$ from $q_j^\sharp$. Therefore, for all $i \in \{1, \ldots, n\}$:

$$\frac{dP_i(t)}{dt} = -\frac{1}{E_i} P_i(t) + \sum_{j=0, j\neq i, \Delta^\sharp(q_j^\sharp, q_i^\sharp)>0}^{n} \frac{1}{E_j} P_j(t).$$

Sometimes, we use $P_{\{o|o\in O_i\}}$ to denote P_i for readability. We therefore build a set of equations for all i. By solving the set of equations, we can obtain the distributions of the system at any future time.

Example 8. Consider again Example 6. $\mathcal{M} = \{a, b, c, d\}$, $\mathcal{R} = \{a + b \to a + 2b,\ a + d \to a + 2d,\ b + c \to 2c,\ c \to b,\ b + d \to c,\ b \to \emptyset,\ c \to \emptyset,\ d \to \emptyset\}$. From the coarse-grained model shown in Fig. 8 ($N_{\max} = 5$), we construct the master equations as follows:

$$\begin{cases} \frac{dP_{\{a,b,c,d\}}(t)}{dt} & = -\frac{1}{0.59} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a,b,c\}}(t)}{dt} & = -\frac{1}{0.66} P_{\{a,b,c\}}(t) + 0.34 * \frac{1}{0.59} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a,b\}}(t)}{dt} & = -\frac{1}{3.46} P_{\{a,b\}}(t) + 0.217 * \frac{1}{0.59} P_{\{a,b,c,d\}}(t) \\ & \quad +0.78 * \frac{1}{0.66} P_{\{a,b,c\}}(t) \\ \frac{dP_{\{a,d\}}(t)}{dt} & = -\frac{1}{3.46} P_{\{a,d\}}(t) + 0.356 * \frac{1}{0.59} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a\}}(t)}{dt} & = \frac{0.087}{0.59} P_{\{a,b,c,d\}}(t) + \frac{0.22}{0.66} P_{\{a,b,c\}}(t) \\ & \quad + \frac{1}{3.46} P_{\{a,b\}}(t) + \frac{1}{3.46} P_{\{a,d\}}(t) \end{cases}$$

We solve the above equations and show in Fig. 11 a comparison between the time evolution of the reaction network via master equation simulation on (a) the organisation-based average coarse-grained model (see Fig. 8); and (b) the original concrete model (see Fig. 5). The former (6 states) takes less than a second, whereas the latter (126 states) takes approximately 1.5 minutes.

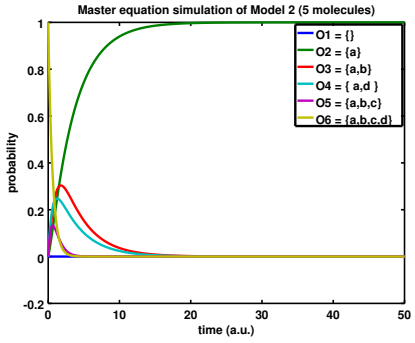
Similarly, Fig. 12 and 13 present experimental results for the case of $N_{max} = 10$ with different reaction rates. The relevant master equations are:

$$\begin{cases} \frac{dP_{\{a,b,c,d\}}(t)}{dt} & = -\frac{1}{0.99} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a,b,c\}}(t)}{dt} & = -\frac{1}{1.47} P_{\{a,b,c\}}(t) + \frac{0.4936}{0.09} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a,b\}}(t)}{dt} & = -\frac{1}{125.73} P_{\{a,b\}}(t) + \\ & \quad 0.071 * \frac{1}{0.99} P_{\{a,b,c,d\}}(t) + \\ & \quad 0.816 * \frac{1}{1.47} P_{\{a,b,c\}}(t) \\ \frac{dP_{\{a,d\}}(t)}{dt} & = -\frac{1}{125.73} P_{\{a,d\}}(t) + \frac{0.409}{0.99} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a\}}(t)}{dt} & = \frac{0.0264}{0.99} P_{\{a,b,c,d\}}(t) + \frac{0.184}{1.47} P_{\{a,b,c\}}(t) + \\ & \quad \frac{1}{125.73} P_{\{a,b\}}(t) + \frac{1}{125.73} P_{\{a,d\}}(t) \end{cases}$$

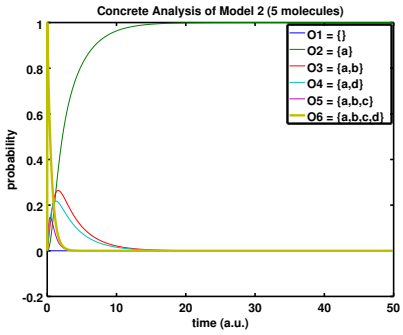
and

$$\begin{cases} \frac{dP_{\{a,b,c,d\}}(t)}{dt} & = -\frac{1}{0.6726} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a,b,c\}}(t)}{dt} & = -\frac{1}{0.633752} P_{\{a,b,c\}}(t) + \\ & \quad 0.4865 * \frac{1}{0.6726} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a,b\}}(t)}{dt} & = -\frac{1}{4.11} P_{\{a,b\}}(t) + \frac{0.1523}{0.6726} P_{\{a,b,c,d\}}(t) + \\ & \quad \frac{0.8469}{0.633752} P_{\{a,b,c\}}(t) \\ \frac{dP_{\{a,d\}}(t)}{dt} & = -\frac{1}{4.11} P_{\{a,d\}}(t) + \\ & \quad 0.2995 * \frac{1}{0.6726} P_{\{a,b,c,d\}}(t) \\ \frac{dP_{\{a\}}(t)}{dt} & = 0.0617 * \frac{1}{0.6726} P_{\{a,b,c,d\}}(t) \\ & \quad + 0.1531 * \frac{1}{0.633752} P_{\{a,b,c\}}(t) \\ & \quad + \frac{1}{4.11} P_{\{a,b\}}(t) + \frac{1}{4.11} P_{\{a,d\}}(t) \end{cases}$$

for rates R_1: $\sharp a * \sharp b$, $\sharp b * \sharp c$, $\sharp c$, $\sharp b * \sharp d$, $\sharp b * \sharp b$, $\sharp c$, $\sharp d$ and R_2: $\sharp a * \sharp b$, $\sharp b * \sharp c$, $\sharp c * \sharp c$, $\sharp b * \sharp d$, $\sharp b * \sharp b$, $\sharp c * \sharp c$, $\sharp d * \sharp d$ respectively.

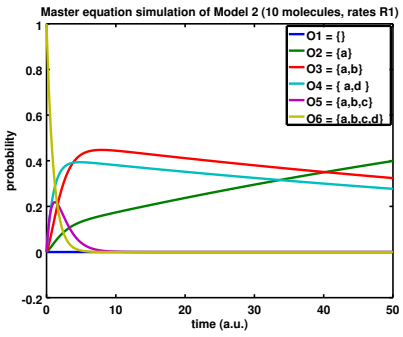


(a)

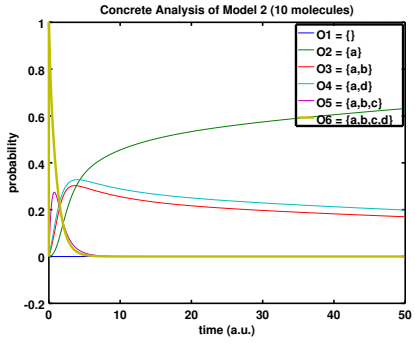


(b)

Fig. 11: Organisation dynamics predication via the average coarse-grained model (a) and the concrete model (b) of Example 6, for $N_{max} = 5$.

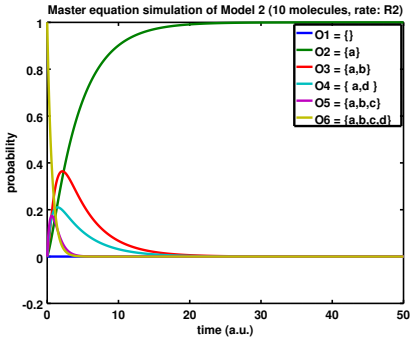


(a)

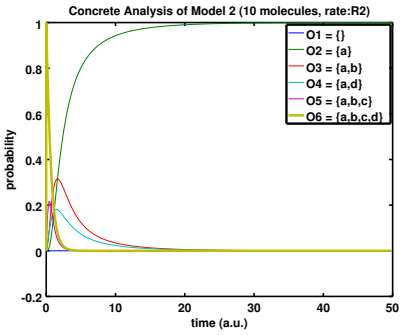


(b)

Fig. 12: Organisation dynamics predication via master equation simulation over the average coarse-grained model (a) and the concrete analysis over the original model(b) of Example 6, with $N_{\max} = 10$ and rates R_1 for each reaction rule respectively.



(a)



(b)

Fig. 13: Organisation dynamics predication via master equation simulation over the average coarse-grained model (a) and the concrete analysis over the original model (b) of Example 6, with $N_{\max} = 10$ and rates R_2 for each reaction rule respectively.

Note that the prediction by applying the abstract model produces a similar pattern of the concrete behaviour over time for this case. The precision of the results varies regarding to different models and rates of reaction rules, however the basic pattern of behaviours can be captured but the time and space spent is much smaller.

8 Refining the Coarse Graining

Our organisation-based coarse-grained model helps us to scale the complex model but may lose some precision for analysis and prediction of its time evolution (see the comparison presented in Fig. 12). To address this concern, in this section, we propose a method to refine our coarse-grained model for the purpose of improving the precision of the analysis and the prediction. The idea is that we split each abstract state with respect to the time to reach a stable state from it, since the speed to reach a stable state also heavily affects the behaviours of the reaction network system in the long term. Note that a bottom abstract state is an abstract state of the coarse-grained model without outgoing abstract transitions, which is stable and will stay there forever. A bottom abstract state is essentially a set of bottom SCCs regarding to the internal generators of an organisation, which is called "bottom SCC class".

Definition 15 (Bottom SCC class). An organisation-based abstract state $q^\sharp$ is called a bottom SCC class if it consists of a set of bottom SCCs.

We propose an algorithm to refine the organisation-based coarse-grained model. Specifically, we make a *parti-*

tion over the abstract state into a pair, one of which reaches a bottom SCC class *quickly* while the other reaches it *slowly*. Thus each abstract state is split into 2^n states if there is a path to reach n bottom SCC class. Specifically, we use the k-means ($K = 2$) refinement techniques to make the partitions.

We briefly review the basic concept of k-means clustering [20] here for our purpose of refining the abstract states. Given a set of observations $(x_1, x_2, \ldots, x_n)$, each of which is a d-dimensional real vector, k-means clustering proposes to partition the n observations into $k(\leq n)$ sets $S = \{S_1, S_2, \ldots, S_k\}$ such that the sum of distance functions of each point in the cluster to the K center is minimised, i.e., it aims to find: $\arg\min_{\mathbf{S}} \sum_{i=1}^{k} \sum_{\mathbf{x} \in S_i} \|\mathbf{x} - \boldsymbol{\mu}_i\|^2$, where μ_i is the mean of points in S_i. The basic procedure of the standard k-means algorithm [19] alternatively proceeds between two steps until the assignments in the first step no longer change: i) assign each observation to the cluster whose mean produces the least squared Euclidean distance; and ii) calculate the new means to be the centroids of the observations in the new clusters.

In our scenario, for all concrete states in an abstract state $q^\sharp \in Q^\sharp$, we calculate the expected time to reach a bottom SCC class, say $q_B^\sharp$, and get a set of observations $S = \{t_1, t_2, \ldots, t_n\}$. k-means clustering partitions the set of observations S into $K = 2$ sets: $S = \{S_1, S_2\}$, such that the sum of distance functions of each point in the cluster to the K center is minimised. The algorithm is formalised in Algorithm 3 and 2. The basic procedure is that, for any bottom SCC class $q_B^\sharp$, we partition each abstract state into a pair of states if it can reach $q_B^\sharp$ within a finite time, otherwise keep it unchanged. We then make predictions with time evolution via our refined model $\mathcal{A}_P^\sharp$ to see how the precision of the analysis and prediction is improved through our running example.

Example 9. Consider again the reaction network studied in Example 6: $\mathcal{M} = \{a, b, c, d\}$, $\mathcal{R} = \{a + b \to a + 2b,\ a + d \to a + 2d,\ b + c \to 2c,\ c \to b,\ b + d \to c,\ b \to \emptyset,\ c \to \emptyset,\ d \to \emptyset\}$. For $N_{\max} = 10$, the refined model is presented in Fig. 14 (the coarser model, but for $N = 5$ was shown previously in Fig. 8). To perform a prediction using our refined

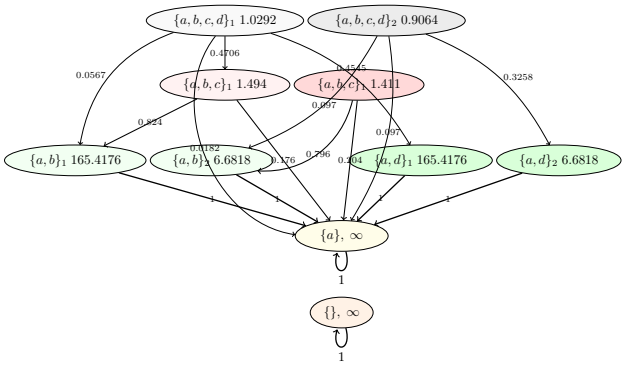


Fig. 14: Example 6: $N_{\max} = 10$, refined coarse-grained model

model, we construct the master equations as follows:

Algorithm 2: Partitioning the abstract states: `partitionAbsState`

Data: $q^\sharp, q_B^\sharp \in Q^\sharp$
Result: Refined abstract states pair $(q_{P_1}^\sharp, q_{P_2}^\sharp)$
$ResT \leftarrow$ `computeTimeToReach` $(q^\sharp \to q_B^\sharp)$;
if $ResT$ *is either* `infinite` *or* 0 **then**
  `/* if the result is infinite or 0, keep the abstract state */`
  $q_{P_1}^\sharp \leftarrow q^\sharp$;
end
else
  `/* otherwise partition` $q^\sharp$ `into two part via KMeans clustering, two clusters are created:` $ResT_1$ `and` $ResT_2$ `*/`
  $ResT_1, ResT_2 \leftarrow$ `KMeansCluster` $(ResT, 2)$;
  for *each concrete state* $q \in q^\sharp$ **do**
    if $ResT(q \to q_B^\sharp)$ *is closer to* $ResT_1$ **then**
      `/* if the time to reach` $q_B^\sharp$ `from` q `is closer to` $ResT_1$`, add` q `to` $q_{P_1}^\sharp$ `*/`
      $q_{P_1}^\sharp$.`add`(q);
    end
    else
      `/* otherwise add` q `to` $q_{P_2}^\sharp$ `*/`
      $q_{P_2}^\sharp$.`add`(q);
    end
  end
end
return $(q_{P_1}^\sharp, q_{P_2}^\sharp)$.

$$
\begin{cases}
\frac{dP_{\{a,b,c,d\}_1}(t)}{dt} &= -\frac{1}{1.0292} P_{\{a,b,c,d\}_1}(t) \\
\frac{dP_{\{a,b,c,d\}_2}(t)}{dt} &= -\frac{1}{0.9064} P_{\{a,b,c,d\}_2}(t) \\
\frac{dP_{\{a,b,c\}_1}(t)}{dt} &= -\frac{1}{1.494} P_{\{a,b,c\}_1}(t) + \frac{0.4706}{1.0292} P_{\{a,b,c,d\}_1}(t) \\
\frac{dP_{\{a,b,c\}_2}(t)}{dt} &= -\frac{1}{1.411} P_{\{a,b,c\}_2}(t) + \frac{0.5357}{0.9064} P_{\{a,b,c,d\}_2}(t) \\
\frac{dP_{\{a,b\}_1}(t)}{dt} &= -\frac{1}{165.4176} P_{\{a,b\}_1}(t) + \\
&\quad \frac{0.0567}{1.0292} P_{\{a,b,c,d\}_1}(t) + \frac{0.824}{1.494} P_{\{a,b,c\}_1}(t) \\
\frac{dP_{\{a,b\}_2}(t)}{dt} &= -\frac{1}{6.6818} P_{\{a,b\}_2}(t) + \\
&\quad \frac{0.097}{0.9064} P_{\{a,b,c,d\}_2}(t) + \frac{0.796}{1.411} P_{\{a,b,c\}_2}(t) \\
\frac{dP_{\{a,d\}_1}(t)}{dt} &= -\frac{1}{165.4176} P_{\{a,d\}_1}(t) + \frac{0.4545}{1.0292} P_{\{a,b,c,d\}_1}(t) \\
\frac{dP_{\{a,d\}_2}(t)}{dt} &= -\frac{1}{6.6818} P_{\{a,d\}_2}(t) + \frac{0.3258}{0.9064} P_{\{a,b,c,d\}_2}(t) \\
\frac{dP_{\{a\}}(t)}{dt} &= \frac{0.0182}{1.0292} P_{\{a,b,c,d\}_1}(t) + \frac{0.0142}{0.9064} P_{\{a,b,c,d\}_2}(t) \\
&\quad + \frac{0.176}{1.494} P_{\{a,b,c\}_1}(t) + \frac{0.204}{1.411} P_{\{a,b,c\}_2}(t) \\
&\quad + \frac{1}{165.4176} P_{\{a,b\}_1}(t) + \frac{1}{6.6818} P_{\{a,b\}_2}(t) \\
&\quad + \frac{1}{165.4176} P_{\{a,d\}_1}(t) + \frac{1}{6.6818} P_{\{a,d\}_2}(t)
\end{cases}
$$

Fig. 15 presents a comparison between the time evolution of the reaction network via master equation simulation using the refined coarse-grained model (a) and the exact evolution of the system using the original concrete model (b). The precision of the prediction has been improved, comparing with the results presented in Fig. 12.

9 Conclusions

This work investigates the combination of chemical organisation theory and probabilistic model checking for the

Algorithm 3: Refining the coarse-grained model

Data: Organisation-based coarse-grained model $\mathcal{A}^\sharp(Q^\sharp, Q_0^\sharp, \Delta^\sharp, L)$

Result: Refined model $\mathcal{A}_P^\sharp(Q_P^\sharp, Q_{P_0}^\sharp, \Delta_P^\sharp, L_P)$

$Q_P^\sharp = Q_{P_0}^\sharp = \{\}$;
$\Delta_P^\sharp = \{\}$;
$L_P = \{\}$;
for *each bottom scc class* $q_B^\sharp \in Q^\sharp$ **do**
  for *each abstract state* $q^\sharp \in (Q^\sharp \setminus q_B^\sharp)$ **do**
    $(q_{P_1}^\sharp, q_{P_2}^\sharp) \leftarrow$ `partitionAbsState` $(q^\sharp, q_B^\sharp)$;
    $Q_P^\sharp \cup \{q_{P_1}^\sharp\} \cup \{q_{P_2}^\sharp\}$;
    $L^\sharp(q_{P_1}^\sharp) = \{L(q) \mid q \in q_{P_1}^\sharp\}$;
    $L^\sharp(q_{P_2}^\sharp) = \{L(q) \mid q \in q_{P_2}^\sharp\}$;
    if $(q_{P_1}^\sharp \subseteq Q_0^\sharp) \wedge (q_{P_1}^\sharp \neq \{\})$ **then**
      $Q_{P_0}^\sharp \cup q_{P_1}^\sharp$;
    end
    if $(q_{P_2}^\sharp \subseteq Q_0^\sharp) \wedge (q_{P_2}^\sharp \neq \{\})$ **then**
      $Q_{P_0}^\sharp \cup q_{P_2}^\sharp$;
    end
  end
end
$\Delta_P^\sharp \leftarrow$ `computeProbBetOrgs` $(Q_P^\sharp)$;
return $\mathcal{A}_P^\sharp$.

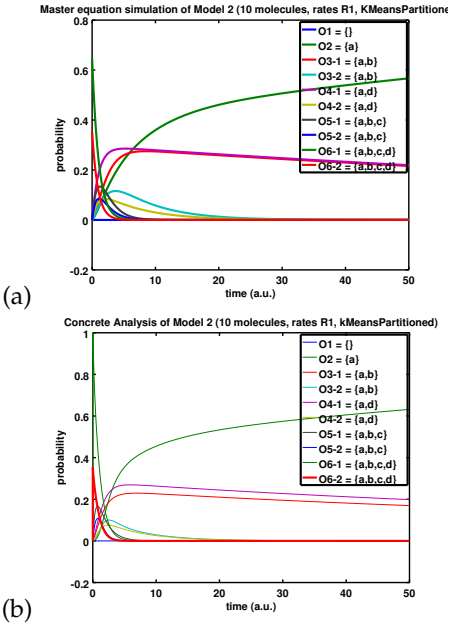


Fig. 15: Organisation k-means clustering dynamics predication via master equation simulation over the average coarse-grained model (a) and the concrete analysis over the original model (b) of Example 6, $N_{\max} = 10$.

analysis of reaction networks modelled as continuous-time Markov chains. We use model decompositions into strongly connected components (SCCs), and study the problem of how to analyse the model in terms of organisations.

We have presented an algorithm to compute a coarse-grained Markov chain model of hierarchical organisations for a given reaction network. The algorithm computes chemical organisations by identifying a set of good SCCs which can contribute to generating organisations, and building an interval Markov chain based on the organisation-based quantitative analysis. We have implemented this approach as an extension of the PRISM model checking tool and illustrate the resulting abstractions constructed for some example networks. The organisation-based coarse-grained model helps to summarise and reason about the structure and behaviour of the complex model by focusing on stable states featuring accumulating species.

In order to demonstrate the effectiveness of our approach, we show how the coarse grained model can be used to approximate the dynamic behaviour of the system over time. We apply an average-based organisation coarse-graining and compute its stochastic time evolution. The experiments show that our prediction can mimic the main pattern of concrete behaviour in the long run, but that it is possible for the interval-based organisation coarse graining to suffer from over-estimation, the extent of which varies for different models and reaction rates. Finally, to improve the precision of the approximation and predictions, we develop an algorithm to selectively refine the the coarse-grained models. The experiments demonstrate that the precision of the prediction can been improved.

In this work, we have focused on the definition and formal properties of the coarse-grained model, algorithms to construct it, and the gains it can yield when numerically solved. An important topic for further study is the overall practical performance and scalability of the approach, particularly regarding the construction of the coarse grained model. Currently, an important limitation is that the algorithm to build the abstraction is based on a decomposition into SCCs of the continuous-time Markov chain for the full concrete system. Although the basic method to compute SCCs is linear in the size of the model, as usual with such approaches, it is the large size of the state space of the model that is problematic. Furthermore, currently, the calculation of the probabilities to move between organisations is done using numerical solution of the full model. These steps, in our prototype implementation, currently represent a bottleneck for applying the techniques to very large networks.

Future work will involve adapting some of the efficient symbolic approaches [16] within the PRISM tool to the problem of building coarse grainings. In particular, SCC computation only requires the underlying graph structure of the Markov chains, for which a symbolic (binary decision diagram based) representation and manipulation could be significantly more efficient. We also believe that the computation of inter-organisation transition probabilities could then be done in a more localised fashion for each organisation, without building the full model, e.g. by adapting PRISM's "hybrid" symbolic engine [16]. This could help scale up the approach to larger, more complex networks. We also plan to investigate the differences between the 'average' and 'interval' approaches to coarse graining, and the effectiveness of different approaches to refinement.

ACKNOWLEDGMENTS

The authors acknowledge support from the European Union through funding under FP7–ICT–2011–8 project HIERATIC

(316705). We also thank the anonymous reviewers for their helpful and detailed comments.

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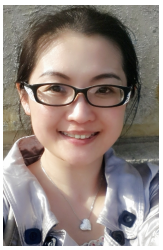

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