On Process Rate Semantics

Luca Cardelli

Microsoft Research

Abstract

We provide translations between process algebra and systems of chemical reactions. We show that the translations preserve discrete-state (stochastic) and continuous-state (concentration) semantics, and in particular that the continuous-state semantics of processes corresponds to the differential equations of chemistry based on the law of mass action. The novel semantics of processes so obtained equates processes that have the same state occupation dynamics, but that may have different interaction interfaces.

1 Introduction

We study *stochastic interacting processes*: a simple compositional model of stochastic systems, with a natural semantics in terms of continuous time Markov chains. These interacting processes can be translated by an intuitive procedure into a set of chemical reactions from which a continuous semantics can be extracted in the form of Ordinary Differential Equations (ODEs). Such a translation establishes a precise connection between process algebra models of biochemical systems, and more traditional models based on chemistry and ODEs.

Process algebra interactions are at first sight richer than chemical interaction, so it is not immediately clear that the ODEs extracted from the chemical translation faithfully represent the behavior of the processes according to the processes' own semantics. The correspondence is fairly obvious when the process interactions are *detangled*, meaning when each interaction channel has exactly one source of inputs and one source of outputs. Then, each interaction channel corresponds exactly to a chemical reaction between two chemical species, and in fact the translation from chemistry back to processes produces detangled systems. In general, though, process interactions can be *entangled*, meaning that there can be many sources of inputs and outputs on each channel. This is a convenient feature that supports compact ways of organizing models: its effectiveness is indicated by the fact that detangled system can be N^2 bigger than corresponding entangled systems. In this paper we show that these more general process models are still faithful: both the Markov and ODE dynamics of the chemical reactions extracted from process models match the intrinsic dynamics of the processes themselves.

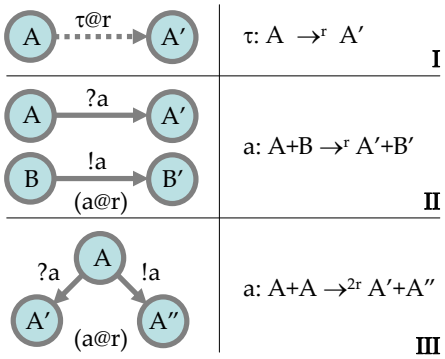


Figure 1 Automata and chemistry

A simple example can illustrate the potential problem with such a correspondence. In this introduction we limit our discussion to *automata*, which are those processes that do not "split" dynamically

into more processes, and that can be conveniently drawn as transition diagrams. (Automata are not sufficient to model all of chemistry, however, because a molecule can split into two.) In Figure 1 we have three basic situations and their chemical interpretation as changes in molecule numbers [23][24].

In Figure 1.I, an automaton in state A can move to state A′ at a specified rate r, by a spontaneous delay transition τ@r. The "chemical" interpretation is a unary reaction $A \to^{r} A'$ (the intended sense of "chemical reaction" is discussed in Section 3). In a population of such automata, each transition decrements the number of automata in state A, and increments the number of automata in state A′.

In Figure 1.II, we have two species of automata: the ones in state A can perform an *input* ?a on a *channel* a, and move to state A′, provided that each can coordinate its transition with another automaton in state B that at the same time performs an *output* !a on the same channel a, to move to state B′. Each channel has a fixed associated rate, a@r. The coordinated transitions between a pair of automata models the collision between a pair of molecules resulting in a chemical reaction; therefore the chemical interpretation is $A+B \to^{r} A'+B'$. In a population of automata, each such reaction results in decrementing the number of automata in states A and B, and incrementing the number of those in states A′ and B′.

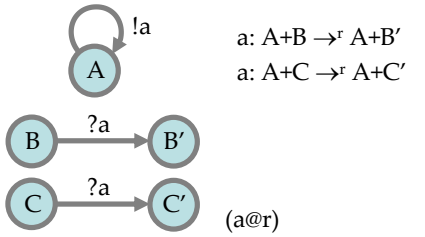


Figure 2 Two reactions on one channel

In Figure 1.III, we have the situation where an automaton in state A can choose to either perform an input ?a and move to A′, or an output !a and move to A″. One lone automaton can do nothing, but if we have two such automata, they can interact, one moving to state A′ and the other to state A″ (in two possible symmetric ways, hence the reaction rate is doubled). The chemical interpretation is $A+A \to^{2r} A'+A''$.

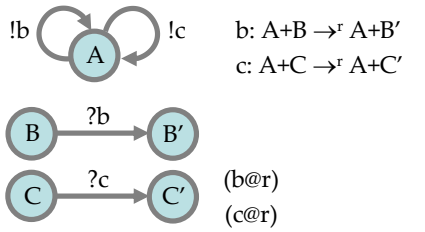


Figure 3 Two reactions on two channels

Finally, note that in Figure 1 the chemical reactions are tagged by the name of the channel on which the corresponding interaction happens (or by τ for delays); it is tempting to think of the name of the channel as identifying the chemical reaction: automata interacting on multiple channels would be involved in multiple reactions.

So far so good: these examples are representative of the complete endeavor of translating automata to chemistry. Apart from reactions that "split" molecules, we can also see intuitively how we can go back from chemistry to automata: the chemical species become automata states, and chemical reactions become either delay transitions, or binary interactions on a channel (using the name of the reaction as the name of the channel), which move automata from one state to another.

But now consider the automata in Figure 2, and the two corresponding chemical reactions derived by observing the state transitions that happen as a result of input/output interactions. Both reactions naively get the same name, because they both result from interactions on channel a. So, how would we go back from reactions to automata in this case? The names of chemical reactions should make no difference to their dynamics, so let us give them different names b,c. Translating backward to automata, we now get the automata in Figure 3, which are not the ones we started from. Or, conversely, if we start from the different automata in Figure 3 we get the same chemical reactions as in Figure 2, although named differently.

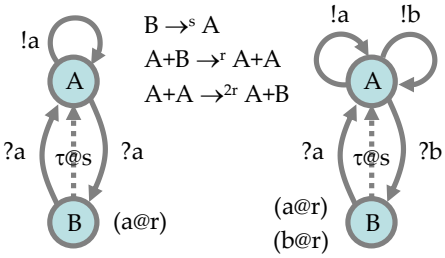


Figure 4 Same chemistry

The worrying issue is then the following. We have two apparently different sets of automata, with different interaction interfaces (a vs. b,c) that produce the same chemistry. Chemistry prescribes the rate at which numbers of molecules change over time. So, those two sets of automata should be *equivalent* at least in terms of the rate at which the occupations of automata states change over time. Now, is that true? If not, we could have little confidence that process-based models of biochemical systems yield the expected results. If the previous example is not sufficiently worrisome, consider the two automata in Figure 4, entangled on the left and detangled on the right. They induce the same set of chemical reactions, but it is not obvious that as populations they have the same rate behavior.

In this paper we show that, yes, all processes resulting in the same chemistry are equivalent, according to the intrinsic rate semantics of the processes themselves. Furthermore, we are able to compare processes that do not have the same chemistry: the automaton in Figure 5 (note: b@r/2), as we shall see, has the same rate behavior as those in Figure 4. In this case, the induced chemical reactions are different, but when computing the respective chemical rate equations, those reactions turn out to be trivially equivalent. By using our main results, we eventually show that any automaton has a rate-equivalent detangled automaton, which can be N^2 bigger. Since detangled automata are in simple correspondence with systems of reactions, it follows that automata can in general be N^2 more compact in representing chemical systems.

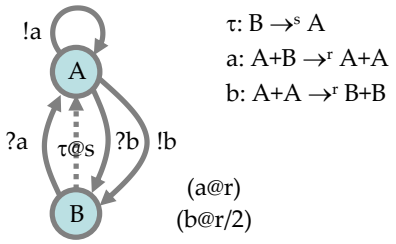


Figure 5 Rate equivalent to Figure 4

This paper is organized as follows. In Section 2 we introduce syntax for stochastic processes and for chemical reactions, and we show how to translate from one to the other. In Section 3 we give the stochastic semantics of process and the stochastic semantics of chemical reactions, both as continuous time Markov chains, and we show that they are equivalent under the translations. In Section 4 we first give the interpretation of chemical reactions in terms of Ordinary Differential Equations (by the law of mass action). That is standard, but it is subtly different from the stochastic semantics of chemical reactions, so we present it via formal translations between discrete and continuous chemical systems. We then give a novel semantics of processes in terms of ODEs (the *process rate equations*), and we show that it is equivalent to the mass action semantics under the translations. In Section 5 we show by an example that the Markov chain and the differential equation semantics are in the fact different. We also summarize the running examples used in the previous sections, and we revisit the examples from the Introduction. In the Conclusions we discuss the compactness of process representations, and the related work. The pattern of Figure 6 is used in thumbnails guides to the various sections.

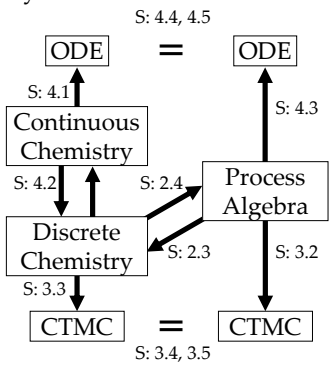


Figure 6 Paper Outline

2 Interactions vs. reactions

In this section we introduce two simple notations: one for processes, slightly generalizing the interacting automata of the Introduction, and one for basic chemical reactions, and we show how to translate from one notation to the other. These translations are to be intended as converting between two equivalent representations of discrete-state continuous-time systems, as elaborated in Section 3.

2.1 Processes

We introduce a subset of π-calculus and of CCS [19] enriched with transition rates [21]: the *Chemical Ground Form* (CGF), which is sufficient for representing the dynamics of chemical reactions. The concepts we need from process algebra are: *complementary synchronous interactions* (*input* '?' and *output* '!') modeling collisions between molecules, *stochastic delays at rate r* ($\tau_{(r)}$) corresponding to molecular decay, *channels with stochastic rate r* ($a_{(r)}$, $b_{(r)}$, ...) corresponding to molecular interaction surfaces; *parallel composition* (|) modeling concurrent activities; and *guarded choice* (⊕) modeling races between events.

2.1–1 Definition: Chemical Ground Form (CGF)

E ::= 0 ⋮ X=M, E	Reagents	(empty, or a reagent X=M and Reagents)
M ::= 0 ⋮ π;P ⊕ M	Molecule	(empty, or an interaction π;P and Molecule)
P ::= 0 ⋮ X | P	Solution	(empty, or a variable X and Solution)
π ::= $\tau_{(r)}$ ⋮ ?$a_{(r)}$ ⋮ !$a_{(r)}$	Interaction prefix	(delay, input, output)
CGF ::= E,P	Chemical Ground Form	(Reagents with initial Solution)

A chemical ground form (CGF, Definition 2.1–1, where the symbol '⋮' separates syntactic alternatives) has a finite set E of *reagents* X_i=M_i (named molecules) for distinct *variables* X_i naming chemical species, and *molecules* M_i describing the interaction capabilities of the corresponding species. The possible process *interactions* π are: *delay* $\tau_{(r)}$ at *rate* r (where r is a positive real), *input* ?$a_{(r)}$ on *channel* a at rate r, and *output* !$a_{(r)}$ on channel a at rate r (each channel always has the same rate). In the syntax of molecules, each interaction π leads to releasing a *solution* P (a multiset of variables). We use ⊕ for *choice*, | for *parallel composition*, and 0 for the empty reagent, the empty molecule, and the empty solution. Trailing 0's are usually left implicit, and we use | also as an operator over the syntax: if P and P' are 0-terminated lists of variables, according to the syntax above, then P|P' means appending the two lists into a single 0-terminated list. Therefore, if P is a solution, then 0|P, P|0, and P are syntactically equal.

A CGF (E,P) is a set of reagents E together with *initial conditions*, which are a solution P. If an X occurs in some M_i or P, but is not a reagent in E, we assume the existence of a reagent X = 0. We write E.X for the molecule associated to X in E, and X∈E to indicate that X is a reagent in E.

A CGF is in *automata form*, if there is no occurrence of parallel composition except in the initial conditions (corresponding to the notions of *finite control* [9] and *regularity* [13]). In such a case, the CGF can be drawn as a collection of automata, as in the figures in the Introduction. A CGF is *detangled* if each channel a occurs once as ?a and once as !a: there is a direct correspondence between detangled CGFs and chemical reaction systems.

Some simple examples follow; these will become our running examples.

2.1–2 Basic examples

Unary reaction

E: X = $\tau_{(r)}$;0 — The reagent X that transitions to 0 after a stochastic delay of rate r.

Hetero reaction

E: X = ?$a_{(r)}$;0, Y = !$a_{(r)}$;0 — The reagent X that interacts with reagent Y on channel a at stochastic rate r, and then both reagent transition to 0.

Homeo reaction

E: X = ?$a_{(r)}$;0 ⊕ !$a_{(r)}$;0 — The reagent X that interacts with another copy of X on channel a.

2.2 Chemical reactions

We now define systems of simple chemical reactions, to which we later give both discrete-state and continuous-state semantics. There are only three kinds of chemical reactions of interest to us. First, a molecule may spontaneously degrade into components; this is a *unary reaction*. Second, two molecules of different species may collide and produce other molecules; this is a *hetero (binary) reaction*. Third, two molecules of the same species may collide and produce other molecules; this is a *homeo (binary) reaction*. We deal with the two cases of binary reactions together, unless we need to distinguish them. Therefore, we have the following syntax for chemical reactions:

2.2–1 Definition: Chemical reactions

X	$\rightarrow^r$	$Y_1 + \ldots + Y_n + 0$	Unary	$(n \geq 0)$
$X_1 + X_2$	$\rightarrow^r$	$Y_1 + \ldots + Y_n + 0$	Binary	$(n \geq 0)$

We can ignore reactions between three or more molecules, because of the unlikelihood under normal conditions of finding three or more molecules at the same time in the same place, and with the right energy and orientation to produce a reaction: "Genuinely *trimolecular* reactions do not physically occur in dilute fluids with any appreciable frequency. *Apparently* trimolecular reactions in a fluid are usually the combined result of two bimolecular reactions and one monomolecular reaction, and involve an additional short-lived species." [11]. So, for example, $2H + O \rightarrow H_2O$ should be interpreted as $\{H + H \rightarrow H_2,\ H_2 + O \rightarrow H_2O\}$, or as $\{H + O \rightarrow OH,\ H + OH \rightarrow H_2O\}$.

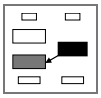
2.2–2 Definition: Systems of chemical reactions

Let X_i be a set of chemical species, with $i \in 1..m$. Let J be an index set for naming reactions. Let $j \in 1..n$, and let $\rho \in 1..n \rightarrow J$ be the injective reaction-naming function. A *system of chemical reactions* C has the form:

$$C = \{\rho_j : Lhs_j \rightarrow^{r_j} Rhs_j\}$$

where each Lhs has the form X or X_1+X_2 (with possibly $X_1=X_2$), and each Rhs has the form $X_1+...+X_{k_j}+0$ for $k_j \geq 0$ (trailing 0's are usually omitted). If P and Q are two Rhs's, then P+Q means appending the two 0-terminated sums into a single 0-terminated sum; therefore 0+P, P+0, and P are syntactically equal. The rates r_j are positive reals.

Therefore, a system of chemical reactions is defined to be a finite set of reactions that are uniquely named (this is an important invariant for our translations). Each reaction, $\rightarrow^r$, has a *(base) rate*, r, with bigger base rates meaning faster reactions. The exact interpretation of r depends critically on whether we consider a discrete or continuous semantics, as we discuss later. A common interpretation of these reactions is that they happen in a constant volume, at constant temperature, and in a *well-stirred solution*, so that the probability of two molecules reacting is independent of their position.



2.3 From process reagents to chemical reactions

We show how to convert a set of process reagents, E (Definition 2.1–1), into a system of chemical reactions Ch(E) (Definition 2.2–2). This is achieved by producing a unary reaction for each $\tau_{(r)}$ delay in E, a hetero reaction for each pair ?a, !a of interactions in different molecules of E, and a homeo reaction for each pair of interactions ?a, !a in the same molecule of E (with doubled rate).

2.3–1 Definition: From process reagents E to chemical reactions Ch(E)

$$
\begin{aligned}
&Ch(E) = \\
&\quad \{(\langle X.i\rangle\colon X \to^{r} P)\ s.t.\ E.X.i = \tau_{(r)};P\} \cup \\
&\quad \{(\langle X.i,Y.j\rangle\colon X + Y \to^{r} P + Q)\ \ s.t.\ X{\neq}Y \text{ and } E.X.i = ?a_{(r)};P \text{ and } E.Y.j = !a_{(r)};Q\} \cup \\
&\quad \{(\langle X.i,X.j\rangle\colon X + X \to^{2r} P + Q)\ \ s.t.\ E.X.i = ?a_{(r)};P \text{ and } E.X.j = !a_{(r)};Q\}
\end{aligned}
$$

When embedding a P from E into a chemical reaction, we implicitly change all process "|" to chemical "+". Note that Ch(E) is a proper system of chemical reactions, where by definition the reactions must be uniquely named. We in fact have unique tags for reactions: either a singleton ‹X.i› or an ordered pair ‹X.i,Y.j›, where M.i is the i-th summand in molecule M, and X.i refers to the summand (E.X).i. This tagging allows us to easily account for multiplicity of equal reactions (whose rates must be summed), and to generally track them in proofs.

2.3–2 Basic examples

Unary reaction

E: $X = \tau_{(r)};0$ Ch(E): $\{\langle X.1\rangle\colon X \to^{r} 0\}$

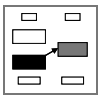
E: $X = \tau_{(r)};0 \oplus \tau_{(r)};0$ Ch(E): $\{\langle X.1\rangle\colon X \to^{r} 0,\ \langle X.2\rangle\colon X \to^{r} 0\}$

Hetero reaction

E: $X = ?a_{(r)};0,\ Y = !a_{(r)};0$ Ch(E): $\{\langle X.1,Y.1\rangle\colon X+Y \to^{r} 0\}$

Homeo reaction

E: $X = ?a_{(r)};0 \oplus !a_{(r)};0$ Ch(E): $\{\langle X.1,X.2\rangle\colon X+X \to^{2r} 0\}$



2.4 From chemical reactions to process reagents

An inverse translation maps a system of chemical reactions C (Definition 2.2–2), to process reagents Pi(C) (Definition 2.1–1), by using the distinct reaction labels in C as channel names in Pi(C). For each reaction of label v with corresponding rate s in C, we prepare a channel $v_{(r)}$ of rate r, setting r=s for unary and hetero reactions, and r = s/2 for homeo reactions. For each species X we produce an initially empty reagent, X = 0. Then we scan each chemical reaction in turn to gradually populate the reagents with summands (such summands may be tagged for convenience in proofs). For a unary reaction v: $X \to^{r} P$ we add a summand $\tau_{(r)};P$ (tagged ‹τv›) to reagent X. For a hetero reaction v: $X+Y \to^{r} P$ we add a summand $?v_{(r)};P$ (tagged ‹?v›) to reagent X and a summand $!v_{(r)};0$ (tagged ‹!v›) to reagent Y. For a homeo reaction v: $X+X \to^{r} P$ we add two summands $?v_{(r/2)};P$ (tagged ‹?v›) and $!v_{(r/2)};0$ (tagged ‹!v›) to reagent X. We also implicitly change all chemical "+" to process "|", which incidentally means that Pi(C) is not necessarily in automata form.

2.4–1 Definition: From chemical reactions C process reagents Pi(C)

$$
\begin{aligned}
Pi(C) = \{(X = \ & \oplus((v\colon X \to^{r} P) \in C)\ of\ (\tau_{(r)};P :\langle \tau v\rangle) \ \oplus \\
& \oplus((v\colon X+Y \to^{r} P) \in C \text{ and } Y{\neq}X)\ of\ (?v_{(r)};P :\langle ?v\rangle) \ \oplus \\
& \oplus((v\colon Y+X \to^{r} P) \in C \text{ and } Y{\neq}X)\ of\ (!v_{(r)};0 :\langle !v\rangle) \ \oplus \\
& \oplus((v\colon X+X \to^{r} P) \in C)\ of\ (?v_{(r/2)};P :\langle ?v\rangle \oplus !v_{(r/2)};0 :\langle !v\rangle)) \\
& s.t.\ X \text{ is a species in C}\}
\end{aligned}
$$

2.4–2 Basic examples

Unary reaction

C: $\{v: X \to^r 0\}$ Pi(C): $X = \tau_{(r)};0$

Hetero reaction

C: $\{v: X+Y \to^r 0\}$ Pi(C): $X = ?v_{(r)};0, \quad Y = !v_{(r)};0$

Homeo reaction

C: $\{v: X+X \to^r 0\}$ Pi(C): $X = ?v_{(r/2)};0 \oplus !v_{(r/2)};0$

The labels associated to binary reactions are turned into channels v that occur exactly once as input ?v and once as output !v in the translated process reagents Pi(C), which is thus detangled.

2.4–3 Proposition: Pi(C) is detangled.

If C is a system of chemical reactions, then Pi(C) is detangled.

That is, each channel occurs once as ?v and once as !v.

Proof

By definition, systems of chemical reactions are uniquely labeled. By definition of Pi(C), for each $v: X+Y \to^r P$ in C, Pi(C) contains one ?v as a summand of X and one !v as a summand of Y. And for each $v: X+X \to^r P$ in C, it contains one ?v and one !v as summands of X. □

The tags ‹τv›,‹?v›,‹!v› attached to the detangled summands of Pi(C) are thus unique. Tags of the form ‹?v› and ‹!v› simply repeat the information at the head of their summand; only tags ‹τv› add information about the reaction v which they came from. We can thus use these tags as indexes in the corresponding molecules, writing M.‹...› for M.i when ‹...› tags the i-th summand of M. For example:

***Reactions* C:** $\{a: A+A \to^r B+A,\ b: B+A \to^s A+A,\ c: B \to^t A\}$

***Tagged processes* Pi(C)**: $A = ?a_{(r)};(B \mid A) :‹?a› \oplus !a_{(r)};0 :‹!a› \oplus !b_{(s)};0 :‹!b›$
$B = ?b_{(s)};(A \mid A) :‹?b› \oplus \tau_{(t)};A :‹τc›$

***Tag indexing in* Pi(C)**: $B.‹?b› = B.1 = ?b_{(s)};(A \mid A), \quad B.‹τc› = B.2 = \tau_{(t)};A, \quad$ etc.

***Reactions* Ch(Pi(C)):** $\{‹A.1,A.2›: A+A \to^r B+A,\ ‹B1.A.3›: B+A \to^s A+A,\ ‹B.2›: B \to^t A\}$
$= \{‹A.‹?a›,A.‹!a››: A+A \to^r B+A,\ ‹B‹?b›.A.‹!b››: B+A \to^s A+A,\ ‹B.‹τc››: B \to^t A\}$

We thus obtain:

2.4–4 Proposition: C vs. Ch(Pi(C))

There is a bijection between the labels of Ch(Pi(C)) and C such that related reactions are equal:

Ch(Pi(C)) =
$\{(‹X.‹τv››: X \to^r P)\ s.t.\ (v: X \to^r P) \in C\} \cup$
$\{(‹X.‹?v›,Y.‹!v››: X + Y \to^r P)\ s.t.\ (v: X + Y \to^r P) \in C\} \cup$
$\{(‹X.‹?v›,X.‹!v››: X + X \to^r P)\ s.t.\ (v: X + X \to^r P) \in C\}$

Proof

We recall the definition of Pi(C).X (the X component of Pi(C)):

$Pi(C).X = \quad \oplus((v: X \to^r P) \in C)\ of\ (\tau_{(r)};P :‹τv›) \quad \oplus$
$\oplus((v: X+Y \to^r P) \in C \text{ and } Y \neq X)\ of\ (?v_{(r)};P :‹?v›) \quad \oplus$
$\oplus((v: Y+X \to^r P) \in C \text{ and } Y \neq X)\ of\ (!v_{(r)};0 :‹!v›) \quad \oplus$
$\oplus((v: X+X \to^r P) \in C)\ of\ (?v_{(r/2)};P :‹?v› \oplus !v_{(r/2)};0 :‹!v›)$

and the definition of Ch(-), instantiated to Ch(Pi(C)):

$$\begin{aligned}&\mathrm{Ch}(\mathrm{Pi}(C)) = \\ &\quad \{(\langle X.i\rangle: X \to^{r} P)\ \textit{s.t.}\ \mathrm{Pi}(C).X.i = \tau_{(r)};P\} \cup \\ &\quad \{(\langle X.i,Y.j\rangle: X + Y \to^{r} P + Q)\ \ \textit{s.t.}\ X{\neq}Y \text{ and } \mathrm{Pi}(C).X.i = ?v_{(r)};P \text{ and } \mathrm{Pi}(C).Y.j = !v_{(r)};Q\} \cup \\ &\quad \{(\langle X.i,X.j\rangle: X + X \to^{2r} P + Q)\ \ \textit{s.t.}\ \mathrm{Pi}(C).X.i = ?v_{(r)};P \text{ and } \mathrm{Pi}(C).X.j = !v_{(r)};Q\}\end{aligned}$$

We first replace the numerical indices with the tags from Pi(C), which are unique:

$$\begin{aligned}&\mathrm{Ch}(\mathrm{Pi}(C)) = \\ &\quad \{(\langle X.\langle \tau v\rangle\rangle: X \to^{r} P)\ \textit{s.t.}\ \mathrm{Pi}(C).X.\langle \tau v\rangle = \tau_{(r)};P\} \cup \\ &\quad \{(\langle X.\langle ?v\rangle,Y.\langle !v\rangle\rangle: X + Y \to^{r} P + Q)\ \ \textit{s.t.}\ X{\neq}Y \text{ and } \mathrm{Pi}(C).X.\langle ?v\rangle = ?v_{(r)};P \text{ and } \mathrm{Pi}(C)(Y).\langle !v\rangle = !v_{(r)};Q\} \cup \\ &\quad \{(\langle X.\langle ?v\rangle,X.\langle !v\rangle\rangle: X + X \to^{2r} P + Q)\ \ \textit{s.t.}\ \mathrm{Pi}(C).X.\langle ?v\rangle = ?v_{(r)};P \text{ and } \mathrm{Pi}(C).X.\langle !v\rangle = !v_{(r)};Q\}\end{aligned}$$

We then have, by definition of Pi(C).X, that:

$$\{(\langle X.\langle \tau v\rangle\rangle: X \to^{r} P)\ \textit{s.t.}\ \mathrm{Pi}(C).X.\langle \tau v\rangle = \tau_{(r)};P\} = \{(\langle X.\langle \tau v\rangle\rangle: X \to^{r} P)\ \textit{s.t.}\ (v: X \to^{r} P){\in}C\}$$

$$\begin{aligned}&\{(\langle X.\langle ?v\rangle,Y.\langle !v\rangle\rangle: X + Y \to^{r} P + Q)\ \ \textit{s.t.}\ X{\neq}Y \text{ and } \mathrm{Pi}(C).X.\langle ?v\rangle = ?v_{(r)};P \text{ and } \mathrm{Pi}(C).Y.\langle !v\rangle = !v_{(r)};Q\} \\ &= \{(\langle X.\langle ?v\rangle,Y.\langle !v\rangle\rangle: X + Y \to^{r} P + 0)\ \ \textit{s.t.}\ (v: X{+}Y \to^{r} P){\in}C\} \quad \text{(where Q must be 0, and P+0=P)}\end{aligned}$$

$$\begin{aligned}&\{(\langle X.\langle ?v\rangle,X.\langle !v\rangle\rangle: X + X \to^{2r} P + Q)\ \ \textit{s.t.}\ \mathrm{Pi}(C).X.\langle ?v\rangle = ?v_{(r)};P \text{ and } \mathrm{Pi}(C).X.\langle !v\rangle = !v_{(r)};Q\} = \\ &= \{(\langle X.\langle ?v\rangle,X.\langle !v\rangle\rangle: X + X \to^{2r} P + 0)\ \ \textit{s.t.}\ (v: X{+}X \to^{2r} P){\in}C\} \quad \text{(where Q must be 0, and P+0=P)}\end{aligned}$$

We thus obtain the statement. □

We conclude this section with some syntactic properties of detangled automata that are used later. Given process reagents E, we have from Proposition 2.4–3 that Pi(Ch(E)) is detangled. But given E in automata form, Pi(Ch(E)) is not necessarily in automata form, so unfortunately we cannot "draw" the detangled version of E as automata. However, Pi(Ch(E)) is close to being in automata form, and we can thus find a related Detangle(E) that is both detangled and in automata form. We show later that E and Detangle(E) are in fact semantically equivalent.

2.4–5 Definition: Detangled automaton

Let E be in automata form. Then Detangle(E) is defined to be the same as Pi(Ch(E)), but where any pair or summands $?v_{(r)};(X|Y|0)$, $!v_{(r)};0$ occurring anywhere in Pi(Ch(E)) is replaced by the pair $?v_{(r)};(X|0)$, $!v_{(r)};(Y|0)$ respectively.

2.4–6 Proposition: Detangled automaton

If E is in automata form then Detangle(E) is in automata form.

Moreover, Ch(Detangle(E)) and Ch(Pi(Ch(E))) have the same reactions.

Proof

Let T,U denote either a singleton list X|0 or 0. Since E is in automata form, each of its molecule summands has the form $\tau_{(r)};T$, $?v_{(r)};T$, or $!v_{(r)};T$. Then, all reactions in Ch(E) have the form $X \to^{r} T$, $X+Y \to^{r} T+U$, or $X+X \to^{2r} T+U$. Hence, each summand in Pi(Ch(E)) has the form $\tau_{(r)};T$, $?v_{(r)};(T|U)$, or $!v_{(r)};0$. Moreover, Pi(Ch(E)) is detangled (Proposition 2.4–3): for each $?v_{(r)};(T|U)$ there is exactly one $!v_{(r)};0$ with the same v. Detangle(E) is also detangled, and is in automata form because whenever T|U contains two variables, it is split in two so that all the summands have again the form $\tau_{(r)};T$, $?v_{(r)};T$, or $!v_{(r)};U$. Note that splitting T|U is ambiguous if e.g. T=X|0 and U=0, but in such a case the summands are already in automata form, and they are not modified. It follows from Definition 2.3–1 that Ch(Detangle(E)) and Ch(Pi(Ch(E))) have the same reactions, noting that (T+U)+0 and T+U are syntactically equal (Definition 2.2–2). □

3 Discrete-state semantics

In this section we give a semantics to both processes and reactions over a discrete state space. The aim is to give meaning to the definitions of Section 2, and to show that the translations between processes and reactions are sound. However, the overall goal of the paper is to define a semantics of processes over a continuous state space, which is the subject of Section 4. Therefore, Section 3 has been organized so that it can be easily skipped, although it can help in understanding the connections between discrete and continuous systems.

3.1 Continuous time Markov chains

The stochastic semantics of both processes and reactions can be given as Continuous Time Markov Chains (CTMCs) [6][2][12][14][15]. A CTMC tracks the evolution of a system through state transitions weighted by stochastic rates. We obtain CTMCs from the collapsing of Labeled Transition Graphs (LTG), which are structures that can be easily extracted from processes and reactions.

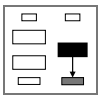
Semantically, a (discrete) *state* is a multiset of molecules. For a solution P (Definition 2.1–1), we indicate by $P^\dagger$ the normalized form of P where the variables are sorted in lexicographical order, possibly with repetitions. That is, $P^\dagger$ is a canonical representation of the multiset corresponding to P. Let $P^\dagger.m$ be the m-th variable in $P^\dagger$, and $P^\dagger \setminus m_1..m_k$ be $P^\dagger$ with the variables of indices $m_1..m_k$ removed. Let #X(P) be the number of instances of X in solution P.

3.1–1 Definition: Labeled Transition Graph (LTG) and associated CTMC

A node (*state*) of a *labeled transition graph* (*LTG*) is a normalized solution $P^\dagger$. An arc (*transition*) of an LTG is a quadruple $\langle l, P^\dagger, r, Q^\dagger\rangle$, written $(l: P^\dagger \rightarrow^r Q^\dagger)$, where $P^\dagger$ is the source state, $Q^\dagger$ is the target state, r is a positive real, which is the rate of the transition, and l is a label, out of an index set, that is used to account for multiplicity of transitions that are otherwise equal. An *LTG*, Ψ, is a set of such quadruples.

If Ψ is an LTG, then the associated *continuous time Markov chain* (*CTMC*) $|\Psi|$, is the set of the triples $\langle P, r, Q\rangle$, written $(P \rightarrow^r Q)$, with P≠Q, obtained by summing the rates of all the quadruples in Ψ that have the same P and Q: $|\Psi| = \{\langle P,r,Q\rangle \text{ } s.t. \text{ } \exists\langle l,P,r',Q\rangle\in\Psi$ with P≠Q, and $r = \Sigma r_i \text{ } s.t. \text{ } \langle l_i{:}P,r_i,Q\rangle \in \Psi\}$.

Therefore, a CTMC is a (possibly infinite) graph with at most one arc between any two nodes, with no self-arcs (because they have a null dynamic effect), and with a rate associated to each arc. From such a graph G, we can easily extract the Q-matrix of a continuous time Markov chain as normally presented, by setting $Q_{ij} = r$ if i≠j and $\langle i, r, j\rangle \in G$, and $Q_{ii} = -\Sigma_{j\neq i}Q_{ij}$. The *master equation* of the Markov chain can then be derived by considering the conditional probability distribution $p_i(t)$ of the system being in state i at time t given the initial conditions [25]. We stop short of probability theory, and of issues of minimization of the Q-matrix, since it is sufficient for us to show that certain systems have the same CTMC graph. More generally, a theory of equivalence of processes or reactions should consider equivalence at the level of probability distributions [2][7][14].



3.2 Discrete-state semantics of processes

We now describe how to produce a Labeled Transition Graph from a Chemical Ground Form (E,P). The set Next(E,P) is the set of all the transitions $(l: P^\dagger \rightarrow^r S^\dagger)$ from the current state $P^\dagger$ arising from the definitions of E. This set is then closed under next transitions. Let E.X be the molecule defined by X in E, and M.i be the i-th summand in a molecule of the form $M=\pi_1;P_1\oplus\ldots\oplus\pi_n;P_n$. The transition labels used are either of the form {m.X.i} or {m.X.i, n.Y.j} where m,n,i,j are positive integers, X,Y are species names, m.X.i are ordered triples and {..., ...} are unordered pairs.

3.2–1 Definition: From a Chemical Ground Form (E,P) to a Labeled Transition Graph

Next(E,P) =
$\{(\{m.X.i\}: P^\dagger \to^r S^\dagger)$ *s.t.* $P^\dagger.m = X$ and $E.X.i = \tau_{(r)};Q$ and $S = (P^\dagger \setminus m \mid Q)\} \cup$
$\{(\{m.X.i, n.Y.j\}: P^\dagger \to^r S^\dagger)$ *s.t.* $P^\dagger.m = X$ and $P^\dagger.n = Y$ and $m \neq n$
and $E.X.i = ?a_{(r)};Q$ and $E.Y.j = !a_{(r)};R$ and $S = (P^\dagger \setminus m,n \mid Q \mid R)\}$

$LTG(E,P) = \cup_n \Psi_n$
where $\Psi_0 = Next(E,P)$ and $\Psi_{n+1} = \cup\{Next(E,Q)$ *s.t.* $Q \in states(\Psi_n)\}$

3.2–2 Basic examples

Unary reaction

(E,P): $((X = \tau_{(r)};0),\ X)$
LTG(E,P): $\{\{1.X.1\}: X \to^r 0\}$ CTMC: $\{X \to^r 0\}$

Here we have initially #X(P) = 1. Suppose P contains any number of X; then, Next(E,P) contains a number N = #X(P) of differently labeled transitions $P^\dagger \to^r Q^\dagger$, where $P^\dagger = (X \mid Q)^\dagger$. The CTMC for Next(E,P), if not empty, contains a single transition $P^\dagger \to^{r \cdot \#X(P)} Q^\dagger$. That transition is (possibly) followed, in the full CTMC, by a transition $Q^\dagger \to^{r \cdot \#X(Q)} R^\dagger$, with $Q^\dagger = (X \mid R)^\dagger$, and so on.

Hetero reaction

(E,P): $((X = ?a_{(r)};0,\ Y = !a_{(r)};0),\ X \mid Y)$
LTG(E,P): $\{\{1.X.1, 2.Y.1\}: X \mid Y \to^r 0\}$ CTMC: $\{X \mid Y \to^r 0\}$

Here we have initially #X(P) = #Y(P) = 1. Suppose P contains any number of X and Y; then, Next(E,P) contains a number N = #X(P) · #Y(P) of differently labeled transitions $P^\dagger \to^r Q^\dagger$, where $P^\dagger = (X \mid Y \mid Q)^\dagger$, since each X can interact with each Y. The CTMC for Next(E,P), if not empty, contains a single transition $P^\dagger \to^{r \cdot \#X(P) \cdot \#Y(P)} Q^\dagger$. That transition is (possibly) followed, in the full CTMC, by a transition $Q^\dagger \to^{r \cdot \#X(Q) \cdot \#Y(Q)} R^\dagger$, with $Q^\dagger = (X \mid Y \mid R)^\dagger$, and so on.

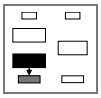
Homeo reaction

In the second clause of the definition of Next we can have X=Y (but with m≠n). For example:

(E,P): $((X = ?a_{(r)};0 \oplus !a_{(r)};0),\ X \mid X)$
LTG(E,P): $\{\{1.X.1, 2.X.2\}: X \mid X \to^r 0,\ \{2.X.1, 1.X.2\}: X \mid X \to^r 0\}$ CTMC: $\{X \mid X \to^{2r} 0\}$

Here we have initially #X(P)=2. Suppose P contains any number of X; then, Next(E,P) contains a number N = 2·(#X(P) choose 2) of differently labeled transitions $P^\dagger \to^r Q^\dagger$, where $P^\dagger = (X \mid X \mid Q)^\dagger$. That is, it contains two transitions between any choice of 2 distinct variable instances in the initial conditions, since each instance can interact with a difference instance in two possible ways. We have that N = 2·(#X(P)·(#X(P)-1)/2) = #X(P)·(#X(P)-1); the CTMC for Next(E,P), if not empty, has a single transition $P^\dagger \to^{r \cdot \#X(P) \cdot (\#X(P)-1)} Q^\dagger$. For #X(P)>>1, the rate of that transition is approximately $r \cdot \#X(P)^2$.

3.3 Discrete-state semantics of chemical reactions



In Definitions 2.2–2 we have introduced *systems of chemical reactions*, but without any initial conditions. When the initial conditions are given as a discrete molecule count for each species, we say that we have a *discrete chemical system*:

3.3–1 Definition: Discrete chemical system

A *discrete chemical system* (C,P) is a system C of chemical reactions plus a *chemical solution* P specifying the initial number of molecules of each species in the system.

For chemical solutions P we use the same syntax and conventions as for process solutions, except using chemical "+" instead of "|". We now show how to derive a Labeled Transition Graph from a discrete chemical system, again considering multisets $P^\dagger$, corresponding to syntactic solutions P, as states in the LTG. The LTG transition labels used here are either of the form {m.ρ} or {m.ρ, n.ρ} where m,n are integers, ρ are reaction labels, m.ρ are ordered pairs, and {..., ...} are unordered pairs. The set Next(C,P) is the set of the transitions $(l: P^\dagger \to^r S^\dagger)$ from the current state $P^\dagger$ arising from the reactions of C; this set is then closed under next transitions.

3.3–2 Definition: From a Discrete Chemical System (C,P) to a Labeled Transition Graph

$$\begin{aligned}
&\text{Next(C,P)} = \\
&\quad \{(\{m.\rho\}: P^\dagger \to^r S^\dagger) \textit{ s.t. } P^\dagger.m = X \text{ and } (\rho: X \to^r Q) \in C \text{ and } S = (P^\dagger \setminus m + Q)\} \cup \\
&\quad \{(\{m.\rho, n.\rho\}: P^\dagger \to^r S^\dagger) \textit{ s.t. } P^\dagger.m = X \text{ and } P^\dagger.n = Y \text{ and } m \neq n \\
&\qquad \text{and } (\rho: X+Y \to^r Q) \in C \text{ and } S = (P^\dagger \setminus m,n + Q)\} \\
&\text{LTG(C,P)} = \cup_n \Psi_n \\
&\quad \text{where } \Psi_0 = \text{Next(C,P)} \text{ and } \Psi_{n+1} = \cup\{\text{Next(C,Q)} \textit{ s.t. } Q \in \text{states}(\Psi_n)\}
\end{aligned}$$

The basic examples of reactions are very similar to the ones for processes (3.2–2), but note that there is a subtle difference in the case of homeo reactions.

3.3–3 Basic examples

Unary reaction

(C,P): $(\{\rho: X \to^r 0\},\ X)$

LTG(C,P): $\{\{1.\rho\}: X \to^r 0\}$ CTMC: $\{X \to^r 0\}$

Here we have initially #X(P) = 1. Suppose P contains any number of X; then, Next(E,P) contains a number N = #X(P) of differently labeled transitions $P^\dagger \to^r Q^\dagger$, where $P^\dagger = (X+Q)^\dagger$. The CTMC for Next(C,P), if not empty, contains a single transition $P^\dagger \to^{r\cdot\#X(P)} Q^\dagger$. That transition is (possibly) followed, in the full CTMC, by a transition $Q^\dagger \to^{r\cdot\#X(Q)} R^\dagger$, with $Q^\dagger = (X+R)^\dagger$, and so on. Note also the role of reaction labels in a system with duplicated reactions:

(C,P): $(\{\rho_1: X \to^r 0, \rho_2: X \to^r 0\},\ X)$

LTG(C,P): $\{\{1.\rho_1\}: X \to^r 0, \{1.\rho_2\}: X \to^r 0\}$ CTMC: $\{X \to^{2r} 0\}$

Hetero reaction

(C,P): $(\{\rho: X+Y \to^r 0\},\ X+Y)$

LTG(C,P): $\{\{1.\rho, 2.\rho\}: X+Y \to^r 0\}$ CTMC: $\{X+Y \to^r 0\}$

Here we have initially #X(P) = #Y(P) = 1. Suppose P contains any number of X and Y; then, Next(E,P) contains a number N = #X(P) · #Y(P) of differently labeled transitions $P^\dagger \to^r Q^\dagger$, where $P^\dagger = (X+Y+Q)^\dagger$, since each X can interact with each Y. The CTMC for Next(C,P), if not empty, contains a single transition $P^\dagger \to^{r\cdot\#X(P)\cdot\#Y(P)} Q^\dagger$. That transition is (possibly) followed, in the full CTMC, by a transition $Q^\dagger \to^{r\cdot\#X(Q)\cdot\#Y(Q)} R^\dagger$, with $Q^\dagger = (X+Y+R)^\dagger$, and so on.

Homeo reaction

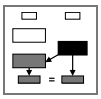
In the second clause of the definition of Next we can have X=Y (but with m≠n). For example:

(C,P): $(\{\rho: X+X \to^{r} 0\},\ X+X)$

LTG(C,P): $\{\{1.\rho,\ 2.\rho\}: X+X \to^{r} 0\}$ CTMC: $\{X+X \to^{r} 0\}$

This set contains only one transition, because the labels $\{1.\rho,\ 2.\rho\}$ and $\{2.\rho,\ 1.\rho\}$ are equal. Here we have initially #X(P)=2. Suppose P contains any number of X; then, Next(C,P) contains a number N = (#X(P) choose 2) of differently labeled transitions from $P^{\dagger} \to^{r} Q^{\dagger}$, where $P^{\dagger} = (X+X+Q)^{\dagger}$. That is, it contains one transition between any choice of 2 distinct variable instances in the initial conditions, since each instance must interact with a different instance. We thus have that $N = \#X(P)\cdot(\#X(P)-1)/2$; the CTMC for Next(C,P), if not empty, contains a single transition $P^{\dagger} \to^{r\cdot\#X(P)\cdot(\#X(P)-1)/2} Q^{\dagger}$. For #X(P)>>1, the rate of that transition is approximately $r/2\cdot\#X(P)^2$. Note that the CTMC in this example seems to have a different rate than the one in example 3.2–2, by a factor of 2, but the translations Pi(C) and Ch(E) compensate for the difference (examples 2.3–2, 2.4–2), as we show next.

3.4 Discrete-state equivalence: E ≍ Ch(E)



We can now show that the translation from processes to chemistry preserves CTMC semantics.

3.4–1 Definition: Graph equivalence (≍)

We write C ≍ C′ iff for all P, |LTG(C,P)| = |LTG(C′,P)| (with $P = X_1 + ... + X_k$)

Similarly, E ≍ E′ iff for all P, |LTG(E,P)| = |LTG(E′,P)| (with $P = X_1 \mid ... \mid X_k$)

And also, C ≍ E iff for all P, |LTG(C,P)| = |LTG(E,P)| (with P understood by context)

3.4–2 Theorem: E ≍ Ch(E)

Let E be a set of reagents and Ch(E) the corresponding reactions. Then E ≍ Ch(E).

Proof

We blur over the syntactic difference, +/|, between P in process solutions and chemical solutions. We first show that |Next(E,P)| = |Next(Ch(E),P)|; the result then follows by induction on the definitions of LTG(E,P) and LTG(C,P). For two CTMCs M,N, we say that M≤N iff for each $(P \to^{r} Q) \in M$ there is a $(P \to^{s} Q) \in N$ such that r≤s. Then, M≤N and N≤M imply M=N.

(1) We show that |Next(E,P)| ≤ |Next(Ch(E),P)| by giving a partition of Next(E,P) into singleton sets $\{(l_0{:}Q \to^{r_0} R)\}$ or pair sets $\{(l_1{:}Q \to^{r_1} R), (l_2{:}Q \to^{r_2} R)\}$, such that each partition element is mapped injectively to a transition $l{:}Q \to^{r} R$ of Next(Ch(E),P) with r_0=r or r_1+r_2=r respectively. (For self-transitions, the rates still match up as described, but neither associated CTMC contains them.) In passing, we also show that states(Next(E,P)) ⊆ states(Next(Ch(E),P)).

- Suppose $(\{m.X.i\}: U \to^{r} W) \in$ Next(E,P). Then, U=$P^{\dagger}$, and $P^{\dagger}.m = X$ and $E.X.i = \tau_{(r)};Q$ and W = $S^{\dagger}$ and $S = (P^{\dagger} \backslash m \mid Q)$. We thus have that $(\langle X.i\rangle: X \to^{r} Q) \in$ Ch(E), and hence $(\{m.\langle X.i\rangle\}: P^{\dagger} \to^{r} S^{\dagger}) \in$ Next(Ch(E),P). That is, $(\{m.\langle X.i\rangle\}: U \to^{r} W) \in$ Next(Ch(E),P). The injection is $\{m.X.i\} \to \{m.\langle X.i\rangle\}$.
- Suppose $(\{m.X.i, n.Y.j\}: U \to^{r} W) \in$ Next(E,P) with X≠Y. Then, U=$P^{\dagger}$, $P^{\dagger}.m = X$ and $P^{\dagger}.n = X$ and m≠n and $E.X.i = ?a_{(r)};Q$ and $E.Y.j = !a_{(r)};R$ and W = $S^{\dagger}$ and $S = (P^{\dagger} \backslash m,n \mid Q \mid R)$. We thus have that $(\langle X.i,Y.j\rangle: X + Y \to^{r} Q + R) \in$ Ch(E), and hence $(\{m.\langle X.i,Y.j\rangle, n.\langle X.i,Y.j\rangle\}: P^{\dagger} \to^{r} S^{\dagger}) \in$ Next(Ch(E),P). That is, $(\{m.\langle X.i,Y.j\rangle, n.\langle X.i,Y.j\rangle\}: U \to^{r} W) \in$ Next(Ch(E),P). The injection is $\{m.X.i, n.Y.j\} \to \{m.\langle X.i,Y.j\rangle, n.\langle X.i,Y.j\rangle\}$.
- Suppose $(\{m.X.i, n.X.j\}: U \to^{r} W) \in$ Next(E,P). Then, U=$P^{\dagger}$, $P^{\dagger}.m = X$ and $P^{\dagger}.n = X$ and m≠n and $E.X.i = ?a_{(r)};Q$ and $E.X.j = !a_{(r)};R$ and W = $S^{\dagger}$ and $S = (P^{\dagger} \backslash m,n \mid Q \mid R)$. Therefore, also the transition $(\{n.X.i, m.X.j\}: U \to^{r} W) \in$ Next(E,P) because of the symmetry of X. We further have that $(\langle X.i,X.j\rangle: X + X \to^{2r} Q + R) \in$ Ch(E), and hence $(\{m.\langle X.i,X.j\rangle, n.\langle X.i,X.j\rangle\}: P^{\dagger} \to^{2r} S^{\dagger}) \in$ Next(Ch(E),P). That is, $(\{m.\langle X.i,X.j\rangle, n.\langle X.i,X.j\rangle\}: U \to^{2r} W) \in$ Next(Ch(E),P). The injection is $\{\{m.X.i, n.X.j\}, \{n.X.i, m.X.j\}\} \to \{m.\langle X.i,X.j\rangle, n.\langle X.i,X.j\rangle\}$.

(2) We show that $|\text{Next}(\text{Ch}(E),P)| \le |\text{Next}(E,P)|$ by giving a partition of Next(E,P) such that each transition $l{:}Q \to^{r} R$ of Next(Ch(E),P) is mapped injectively to a partition element $\{(l_0{:}Q \to^{r_0} R)\}$ or $\{(l_1{:}Q \to^{r_1} R), (l_2{:}Q \to^{r_2} R)\}$, such that $r_0=r$ or $r_1+r_2=r$ respectively. In passing, we also show that states(Next(Ch(E),P)) $\subseteq$ states(Next(E,P)).

- Suppose $(\{m.\rho\}{:}\, U \to^{r} W) \in \text{Next}(\text{Ch}(E),P)$. Then $U=P^{\dagger}$, and $P^{\dagger}.m = X$ and $(\rho{:}\, X \to^{r} Q) \in \text{Ch}(E)$ and $W = S^{\dagger}$ and $S = (P^{\dagger} \setminus m + Q)$. From $(\rho{:}\, X \to^{r} Q) \in \text{Ch}(E)$ we have that $\rho=\langle X.i\rangle$ and $E.X.i = \tau_{(r)};Q$. Hence $(\{m.X.i\}{:}\, P^{\dagger} \to^{r} S^{\dagger}) \in \text{Next}(E,P)$. That is, $(\{m.X.i\}{:}\, U \to^{r} W) \in \text{Next}(E,P)$. The injection is $\{m.\langle X.i\rangle\} \to \{m.X.i\}$.
- Suppose $(\{m.\rho, n.\rho\}{:}\, U \to^{r} W) \in \text{Next}(\text{Ch}(E),P)$ with $P^{\dagger}.m = X$ and $P^{\dagger}.n = Y$ and $X \ne Y$. Then $U=P^{\dagger}$, and $m \ne n$ and $(\rho{:}\, X+Y \to^{r} T) \in \text{Ch}(E)$ and $W = S^{\dagger}$ and $S = (P^{\dagger} \setminus m,n + T)$. From $(\rho{:}\, X+Y \to^{r} T) \in \text{Ch}(E)$ we have that $\rho=\langle X.i,Y.j\rangle$ and $T=Q+R$ and $E.X.i = ?a_{(r)};Q$ and $E.Y.j = !a_{(r)};R$. Hence $(\{m.X.i,\ n.Y.j\}{:}\, P^{\dagger} \to^{r} S^{\dagger}) \in \text{Next}(E,P)$. That is, $(\{m.X.i,\ n.Y.j\}{:}\, U \to^{r} W) \in \text{Next}(E,P)$. The injection is $\{m.\langle X.i,Y.j\rangle, n.\langle X.i,Y.j\rangle\} \to \{m.X.i, n.Y.j\}$.
- Suppose $(\{m.\rho, n.\rho\}{:}\, U \to^{r} W) \in \text{Next}(\text{Ch}(E),P)$ with $P^{\dagger}.m = P^{\dagger}.n = X$. Then $U=P^{\dagger}$, and $m \ne n$ and $(\rho{:}\, X+X \to^{r} T) \in \text{Ch}(E)$ and $W = S^{\dagger}$ and $S = (P^{\dagger} \setminus m,n + T)$. From $(\rho{:}\, X+X \to^{r} T) \in \text{Ch}(E)$ we have that $\rho=\langle X.i,X.j\rangle$ and $T=Q+R$ and $E.X.i = ?a_{(r/2)};Q$ and $E.X.j = !a_{(r/2)};R$. Hence both $(\{m.X.i,\ n.X.j\}{:}\, P^{\dagger} \to^{r/2} S^{\dagger})$ and $(\{n.X.i,\ m.X.j\}{:}\, P^{\dagger} \to^{r/2} S^{\dagger}) \in \text{Next}(E,P)$. That is, $(\{m.X.i,\ n.X.j\}{:}\, U \to^{r/2} W)$ and $(\{n.X.i,\ m.X.j\}{:}\, U \to^{r/2} W) \in \text{Next}(E,P)$. The injection is $\{m.\langle X.i,X.j\rangle,\ n.\langle X.i,X.j\rangle\} \to \{\{m.X.i,\ n.X.j\},\ \{n.X.i,\ m.X.j\}\}$.

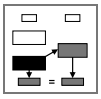
(3) We recall the definition of CTMC: $|\Psi| = \{\langle P,r,Q\rangle \textit{ s.t. } \exists \langle l,P,r',Q\rangle \in \Psi$ with $P \ne Q$, and $r = \Sigma r_i \textit{ s.t. } \langle l_i{:}P,r_i,Q\rangle \in \Psi\}$. Define the merge of two CTMCs M,N as their rate-merged union: $M \Diamond N = \{\langle P,r,Q\rangle \textit{ s.t. } \exists \langle P,r',Q\rangle \in M \cup N$, and $r = \Sigma r_i \textit{ s.t. } \langle P,r_i,Q\rangle \in M \cup N\}$; we have that $|\Psi \cup \Phi| = |\Psi| \Diamond |\Phi|$. Recall also that:

$\text{LTG}(E,P) = \cup_n \Psi_n$ with $\Psi_0 = \text{Next}(E,P)$ and $\Psi_{n+1} = \cup\{\text{Next}(E,Q) \textit{ s.t. } Q \in \text{states}(\Psi_n)\}$,
$\text{LTG}(\text{Ch}(E),P) = \cup_n \Phi_n$ with $\Phi_0 = \text{Next}(\text{Ch}(E),P)$ and $\Phi_{n+1} = \cup\{\text{Next}(\text{Ch}(E),Q) \textit{ s.t. } Q \in \text{states}(\Phi_n)\}$.

- We have already shown by **(1)** and **(2)** that $|\Psi_0| = |\Phi_0|$ and $\text{states}(\Psi_0) = \text{states}(\Phi_0)$.
- Assume $|\Psi_n| = |\Phi_n|$ and $\text{states}(\Psi_n) = \text{states}(\Phi_n)$. Then, $|\Psi_{n+1}| = |\cup\{\text{Next}(E,Q) \textit{ s.t. } Q \in \text{states}(\Psi_n)\}| = \Diamond\{|\text{Next}(E,Q)| \textit{ s.t. } Q \in \text{states}(\Psi_n)\} = \Diamond\{|\text{Next}(\text{Ch}(E),Q)| \textit{ s.t. } Q \in \text{states}(\Phi_n)\}$ (by **(1)** and **(2)** at Q) $= |\Phi_{n+1}|$. Moreover, $\text{states}(\Psi_{n+1}) = \text{states}(\cup\{\text{Next}(E,Q) \textit{ s.t. } Q \in \text{states}(\Psi_n)\}) = \cup\{\text{states}(\text{Next}(E,Q)) \textit{ s.t. } Q \in \text{states}(\Psi_n)\}) = \cup\{\text{states}(\text{Next}(\text{Ch}(E),Q)) \textit{ s.t. } Q \in \text{states}(\Phi_n)\})$ (by **(1)** and **(2)** at Q) $= \text{states}(\Phi_{n+1})$.

Therefore, by induction on n we conclude that $|\text{LTG}(E,P)| = |\text{LTG}(\text{Ch}(E),P)|$. □

3.5 Discrete-state equivalence: C ≍ Pi(C)



Be reusing the previous theorem, we can now show that, in the other direction, the translation from chemistry to processes preserves CTMC semantics.

3.5–1 Theorem: C ≍ Pi(C)

Let C be a set of reactions, and Pi(C) the corresponding reagents. Then C ≍ Pi(C).

Proof

We know from Theorem 3.4–2 that for any set of process reagents E we have E ≍ Ch(E). Hence, for any set of chemical reactions C resulting in process reagents Pi(C), we have that Pi(C) ≍ Ch(Pi(C)). Moreover, from Proposition 2.4–4 we know that Ch(Pi(C)) = C up to reaction labels (which are in bijection). Those differences do not affect the discrete semantics of chemical reactions (Definition 3.3–2) when considering the associated CTMCs, so that Ch(Pi(C)) ≍ C. Therefore, Pi(C) ≍ C. □

Finally, we can make use of the last two theorems to show that E and Detangle(E) are equivalent, in the sense of having the same Markov chain:

3.5–2 Proposition: Detangling processes and automata

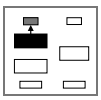
(1) If E is a set of reagents, then there is an equivalent E′ that is detangled. (Take E′ = Pi(Ch(E)).)

(2) If E is a set of reagents in automata form, then there is an equivalent E′ that is in automata form and is detangled. (Take E′ = Detangle(E).)

Proof
(1) Take E′ = Pi(Ch(E)). E′ is detangled by Proposition 2.4–3, and E′ ≋ E because E ≋ Ch(E) ≋ Pi(Ch(E)) by Theorems 3.4–2 and 3.5–1.
(2) Let Detangle(E) be the automaton obtained from E by Definition 2.4–5. By Proposition 2.4–6, Ch(Detangle(E)) and Ch(Pi(Ch(E))) have the same chemical reactions. Hence, Detangle(E) ≋ Ch(Detangle(E)) (by Theorem 3.4–2) ≋ Ch(Pi(Ch(E))) (by Proposition2.4–6) ≋ E (by Theorem 3.4–2 twice and Theorem 3.5–1). □

4 Continuous-state semantics

In this section we give the semantics of both processes and reactions in terms of Ordinary Differential Equations. We first present the standard ODE interpretation of chemical reactions in terms of changes in concentration. The main purpose of the section, however, is to assign ODEs directly to processes, and to show that process ODEs are appropriately related to chemical ODEs, via a connection between discrete and continuous chemistry.



4.1 Continuous-state semantics of chemical reactions

The International System of Units (SI) defines the following physical units, with related derived units and constants; note that *amount of substance* is a base unit in SI, like length and time:

mol	(a base unit)	mole, unit of *amount of substance*
m	(a base unit)	meter, unit of *length*
s	(a base unit)	second, unit of *time*
$L = 0.001 \cdot m^3$		liter (volume)
$M = mol \cdot L^{-1}$		molarity (concentration of substance)
$N_A : mol^{-1} \cong 6.022 \times 10^{23}$		Avogadro's number (number of particles per amount of substance)

For a substance X:*mol*, we write [X]:*M* for the concentration of X, and $[X]^\bullet : M \cdot s^{-1}$ for the time derivative of the concentration, *d*[X]/*d*t.

The l*aw of mass action* prescribes the evolution of a chemical system in terms of changes of concentrations of the chemical species over time. In its simplest form, it says that a reaction $X+Y \rightarrow^k Z$ has a rate k[X][Y]: the rate is proportional to the concentration of one species times the concentration of the other species by the base rate k. From the rate of the reaction we can then compute the changes of concentration of the various species: $[Z]^\bullet = k[X][Y]$ and $[X]^\bullet = [Y]^\bullet = -k[X][Y]$. The law of mass action can be formulated more generally for all forms of chemical reactions [17], and as special cases we obtain that $X \rightarrow^k Z$ has rate k[X] (the exponential decay law), and that $X+X \rightarrow^k Z$ has rate $k[X]^2$. The time course of the concentrations is often called the *mass action kinetics* of the reactions. For contrast with the discrete-state semantics, we call it here the *continuous-state* semantics, because the state space of concentrations is continuous.

The procedure for extracting the mass action ODEs from chemical reactions is standard, and can be described concisely by a formula over an appropriately indexed collection of reactions. For our purposes, we describe it in the following equivalent way, which is also standard [26]. We first build the *stoichiometric matrix*, **N**, which has one row for each species and one column for each reaction. Each cell ⟨X,ρ⟩ in the matrix contains a positive number n if n molecules of species X are produced (overall) in reaction ρ; it contains a negative number -n if n molecules of species X are removed (overall) in reaction ρ, and otherwise it contains 0. Then, we build the *vector of rate law*s, **l**, which specifies the rate law of each reaction. Namely: the rate law k[X] for unary reactions $X \rightarrow^k P$, and the rate law k[X][Y] for binary reactions $X+Y \rightarrow^k P$. Note that the rate law for homeo binary reactions $X+X \rightarrow^k P$ is therefore

defined to be $k[X]^2$, and that this is prescribed by the law of mass action. The corresponding system of ODEs is the following:

4.1–1 Definition: Chemical rate equations $[X]^\bullet_C$ (Law of mass action)

Let C be a system of chemical reactions (Definition 2.2–2). The system of ODEs for C is:

$$[\mathbf{X}]^\bullet_C = \mathbf{N}\cdot\mathbf{l}$$

where **X** is the *vector of chemical species*, of size m, and **N** is the m×n *stoichiometric matrix* with i∈1..m rows (species) and j∈1..n columns (reactions):

$N_{i,j} = \#X_i(Rhs_j) - \#X_i(Lhs_j)$ (where #X(-) is the number of occurring X's)

and **l** is *vector of rate laws* of size n:

$l_j = k_j[X]$ if $Lhs_j = X$
$l_j = k_j[X][Y]$ if $Lhs_j = X+Y$ (with possibly X=Y)

4.1–2 Basic examples

Unary reaction

the system $X \to^k 0$ gives the ODE: $[X]^\bullet = -k[X]$

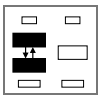
Hetero reaction

the system $X+Y \to^k 0$ gives the ODEs: $[X]^\bullet = [Y]^\bullet = -k[X][Y]$

Homeo reaction

the system $X+X \to^k 0$ gives the ODE: $[X]^\bullet = -2k[X]^2$

The factor of -2 in the equation above is due to the fact that two X are lost in the reaction; the rate of the reaction itself, according to the law of mass action, is $k[X]^2$, which would be the rate of accretion of any product on the right.



4.2 Converting between discrete and continuous chemical systems

The evolution of a chemical system according to the law of mass action depends on the initial concentrations of the species. Therefore, for a given set of chemical reactions C, the law of mass action applies to *continuous chemical systems* (C,V) which specify initial concentrations V as defined below, while it does not directly apply to *discrete chemical systems* (C,P) (Definition 3.3–1), which instead specify the initial number of molecules of each species. The relationships between continuous and discrete chemical systems is explored next.

4.2–1 Definition: Continuous chemical system.

A *continuous chemical system* (C,V) is a system C of chemical reactions plus a vector of *initial concentrations* V_X, one for each species X in the system, where V_X*: M.*

We have used "k" above for base rates in continuous systems, as opposed to "r" for base rates in discrete systems. In fact, a reaction $P \to^? Q$ can be interpreted in two ways. Either within a discrete chemical system with a given number of initial molecules (Definition 3.3–1), as a reaction $P \to^r Q$ with the base rate r describing changes in number of molecules. Or within a continuous chemical system with given initial concentrations (Definition 4.2–1), as a reaction $P \to^k Q$ with the base rate k describ-

ing changes in concentrations in the next time differential. Part of the difference is that, in general, r and k have different physical dimensions, with $r{:}s^{-1}$ always having the dimension of a pure rate, while $k{:}s^{-1}$ or $k{:}M^{-1}s^{-1}$ for unary or binary reactions (see Examples 4.2–5). Because of this, it should be clear that some conversion factor is needed. Concentration and number of molecules are related by Avogadro's number N_A and by the solution volume V. If we have a continuous system and we want to consider the corresponding discrete system, we must start by multiplying the initial concentrations by N_AV to obtain a number of molecules. But further, we must adjust the continuous-system rates k to discrete-system rates r in a corresponding way, and those are not necessarily equal.

4.2–2 Definition: Volumetric factor γ

For a given volume of solution V, the volumetric factor, of dimension M^{-1}, is:

$\gamma{:}M^{-1} = N_AV$ where $N_A{:}mol^{-1}$ and $V{:}L$

We normally use γ, instead of the related volume V.

The following translations, $Cont_\gamma$ and $Disc_\gamma$, convert a discrete chemical systems into a continuous one, and back. They are justified after the fact: *given* that discrete systems are governed by the CTMC semantics, and that continuous systems are governed by the mass action semantics, and that molecule numbers and concentrations are related by a factor γ, *then* the relationships between rates in the two kinds of systems follows. We discuss the differences between k and r with the help of our basic examples in 4.2–5, following [27].

4.2–3 Definition: $Cont_\gamma$ and $Disc_\gamma$

For a volumetric factor $\gamma{:}M^{-1}$, we define a translation $Cont_\gamma$ from a discrete chemical system (C,P), with species X and initial molecule count $\#X_0 = \#X(P)$, to a continuous chemical system (C,V) with initial concentration $[X]_0 = V_X$. The translation $Disc_\gamma$ is its inverse, up to a rounding error $\lceil \gamma[X]_0 \rceil$ in converting concentrations to molecule counts. Since γ is a global conversion constant, we later usually omit it as a subscript.

$Cont_\gamma(X \to^r P)$	$= X \to^k P$	with $k = r$,	$r{:}s^{-1}$	$k{:}s^{-1}$
$Cont_\gamma(X+Y \to^r P)$	$= X+Y \to^k P$	with $k = r\gamma$	$r{:}s^{-1}$	$k{:}M^{-1}s^{-1}$
$Cont_\gamma(X+X \to^r P)$	$= X+X \to^k P$	with $k = r\gamma/2$	$r{:}s^{-1}$	$k{:}M^{-1}s^{-1}$
$Cont_\gamma(\#X_0)$	$= [X]_0$	with $[X]_0 = \#X_0/\gamma$	$X_0{:}mol$	$[X]_0{:}M$
$Disc_\gamma(X \to^k P)$	$= X \to^r P$	with $r = k$,	$k{:}s^{-1}$	$r{:}s^{-1}$
$Disc_\gamma(X+Y \to^k P)$	$= X+Y \to^r P$	with $r = k/\gamma$	$k{:}M^{-1}s^{-1}$	$r{:}s^{-1}$
$Disc_\gamma(X+X \to^k P)$	$= X+X \to^r P$	with $r = 2k/\gamma$	$k{:}M^{-1}s^{-1}$	$r{:}s^{-1}$
$Disc_\gamma([X]_0)$	$= \#X_0$	with $\#X_0 = \lceil \gamma[X]_0 \rceil$	$[X]_0{:}M$	$X_0{:}mol$

It is sometimes convenient to consider $Pi_\gamma(C) =_{def} Pi(Disc_\gamma(C))$, and $Ch_\gamma(P) =_{def} Cont_\gamma(Ch(P))$, mapping directly between process reagents and continuous chemical systems based on a given γ.

4.2–4 Discussion: γ=1

As a special case, consider γ=1. Then, with a major caveat, the discrete and continuous system are identical, and we can take the initial number of molecules equal to the initial concentration of each species (up to rounding). The caveat is that in the case of homeo reactions we must adjust k = r/2. In practice, we often wish to use $Disc_\gamma$ to go from a continuous system (with mass action rates and concentrations taken from the literature) to a discrete system (for discrete simulation). We can then simply set γ=1, which chemically ($\gamma=N_AV$) means that we are simulating a volume of size $1/N_A$. However, if the resulting rounding error $\lceil \gamma[X]_0 \rceil$ is too large, and we end up with too few molecules of some spe-

cies, then we may wish to change γ to a more comfortable value. In that case, Definition 4.2–3 gives the proper scaling for all rates and quantities, noting that unary, hetero, and homeo reactions are all scaled in different ways. □

4.2–5 Basic examples

The translation $Cont_\gamma$ relates discrete and continuous systems: this connection requires a careful comparison between continuous quantities such as concentrations [X], and the *expected value* <#X> of discrete quantities such as the number of X molecules, #X. It also requires an approximation for homeo reactions, as shown below. What follows is a summary of the argument for Generalized Mass Action from [27], instantiated to three examples; see also the explanation in [10]-IIC. In general, we need to replace continuous concentrations [X]:*M* with discrete expectations <X/V>, for X:*mol* and volume V:*L*, and for a number of molecules #X = X·N_A. That is, we need to replace [X] with <#X>/γ, for γ:M^{-1} = N_AV.

Unary reaction

(C,P): $X \to^r 0,\ P$ where #X(P)=n

$Cont_\gamma$(C,P): $X \to^k 0,\ V$ where k=r, V_X=n/γ, $[X]^\bullet = -k[X]$

Replacing [X] = <#X>/γ in the concentration ODE, $[X]^\bullet = -k[X]$, gives the "particle ODE" $(<\#X>/\gamma)^\bullet = -k(<\#X>/\gamma)$, that is $<\#X>^\bullet = -k<\#X>$. Here, $<R> =_{def} k<\#X>$ is the expected number of reactions occurring in the next time differential (the factor -1 being the number of X molecules removed by each reaction). Stochastically, the expected number of reactions is $<a> =_{def} r<h>$, where r is the stochastic rate of the reaction, and h is the number of distinct combinations of reactant molecules. For X→Q reactions, h = #X. Hence, setting <R> = <a> we obtain $k<\#X> = r<\#X>$, that is r = k. Also, in terms of dimensionality, since [X]:*M* and $[X]^\bullet$:$M{\cdot}s^{-1}$, the ODE implies that k:s^{-1}, which has the same dimension as r:s^{-1}.

Hetero reaction

(C,P): $X+Y \to^r 0,\ P$ where #X(P)=n, #Y(P)=m

$Cont_\gamma$(C,P): $X+Y \to^k 0,\ V$ where k=rγ, V_X=n/γ, V_Y=m/γ, $[X]^\bullet=[Y]^\bullet= -k[X][Y]$

Replacing [X] = <#X>/γ in $[X]^\bullet = -k[X][Y]$, gives $(<\#X>/\gamma)^\bullet = -k(<\#X>/\gamma)(<\#Y>/\gamma)$, that is $<\#X>^\bullet = -(k/\gamma)<\#X><\#Y>$; note that this is a similar ODE, but where k has been replaced by k/γ. Here $<R> =_{def} (k/\gamma)<\#X><\#Y>$ is the expected number of reactions occurring in the next time differential. Stochastically, the expected number of reactions is $<a> =_{def} r<h>$, where h = #X·#Y is the number of distinct combinations of reactant molecules for reactions X+Y→Q. Setting <R> = <a> we obtain $(k/\gamma)<\#X><\#Y> = r<\#X{\cdot}\#Y>$ (assuming $<\#X><\#Y> \cong <\#X{\cdot}\#Y>$), that is r = k/$\gamma$. In terms of dimensionality, since [X][Y]:M^2 and $[X]^\bullet$:$M{\cdot}s^{-1}$, the ODEs imply that k:$M^{-1}{\cdot}s^{-1}$, so that k/γ:s^{-1}, which is the same dimension r:s^{-1}.

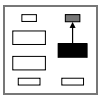
Homeo reaction

(C,P): $X+X \to^r 0,\ P$ where #X(P)=n

$Cont_\gamma$(C,P): $X+X \to^k 0,\ V$ where k=rγ/2, V_X=n/γ, $[X]^\bullet = -2k[X]^2$

Replacing [X] = <#X>/γ in $[X]^\bullet = -2k[X]^2$, gives $(<\#X>/\gamma)^\bullet = -2k(<\#X>/\gamma)^2$, that is $<\#X>^\bullet = -2(k/\gamma)<\#X>^2$; this is a similar ODE, where k has been replaced by k/γ. Here $<R> =_{def} (k/\gamma)<\#X>^2$ is the expected number of reactions occurring in the next time differential (the factor -2 being the number of X molecules removed by each reaction). Stochastically, the expected number of reactions is $<a> =_{def} r<h>$, where r is the stochastic rate, and h is the number of distinct combinations of reactant molecules. For X+X→Q reactions, h = (#X choose 2) = #X·(#X-1)/2, which for large #X can be approximated as $\#X^2/2$. Setting <R> = <a> we obtain $(k/\gamma)<\#X>^2 = r<\#X^2/2>$, that is r = 2k/$\gamma$. Note that, unlike the previous cases, this has been obtained by using a large-number approximation: the law of mass action is *not strictly valid* for low-number homeo reactions. In terms of dimensionality, we have as above that k:$M^{-1}{\cdot}s^{-1}$.

4.3 Continuous-state semantics of processes



We are now ready to define an ODE semantics for processes, moving directly from discrete processes to a continuous framework. For each process state X we consider the *process concentration* [X] of processes in state X. Such a notion is taken as primitive, and formally we simply consider polynomials over quantities [X], [Y], ..., without further elaborating on their nature. Intuitively, it is understood that [X] represents such a large number of processes that changes in this quantity can be considered as essentially continuous.

We consider $[X]^\bullet$ as the rate at which the concentration of processes in state X changes over time, that is, the derivative of [X]; this notion is explicitly defined, and will be compared to the chemical semantics. The fact that $[X]^\bullet$ is *defined* from [X] is analogous to the fact that the law of mass action is normally presented as a *law* based on [X]. Our main task will be to show a certain correspondence between the definition and the law.

The intuitive idea of how to define $[X]^\bullet$ (the so called *rate equation*) is standard: the rate of change in the concentration of X depends on the rate at which processes move to state X from some other state, minus the rate at which processes move from state X to some other state. More precisely, for a set of reagents E, independently of the initial conditions, we define the depletion rate of X in E, $Depl_E(X)$, which is the rate at which X molecules get converted to other molecules by delays or interactions. Similarly, we define, for each Y in E, the accretion rate of X due to Y, $Accr_E(Y,X)$; this is the rate at which X molecules are produced by Y molecules due to Y's delays and interactions. Both $Depl_E(X)$ and $Accr_E(Y,X)$ are polynomials over concentrations of species in E.

Concentration (of processes) must in some way be related to a notion of volume of interaction. To this end, we use the global scaling factor γ (Definition 4.2–2), which has dimension $M^{-1} = mol^{-1}{\cdot}L$. Since the mol^{-1} part is a global constant (N_A), what is important is the L factor, which is a volume. (Similarly, *molarity* $M = mol{\cdot}L^{-1}$ is a concentration L^{-1} scaled by a constant $1/N_A{:}mol$). Then, $r\gamma{:}s^{-1}M^{-1}$ is a rate times a volume of interaction; in other words it is a number of interactions per second times a volume of interaction. Below we use $r\gamma$ in conjunction with the rates of binary reactions, where a factor of dimension $s^{-1}M^{-1}$ is needed.

4.3–1 Definition: Process rate equations $[X]^\bullet_E$

$In(a, M) :Nat = \Sigma(i: M.i=?a_{(r)};P)\ 1$
$Out(a, M) :Nat = \Sigma(i: M.i=!a_{(r)};P)\ 1$

$InsOn_E(a) :M = \Sigma(Y{\in}E)\ In(a, E.Y){\cdot}[Y]$
$OutsOn_E(a) :M = \Sigma(Y{\in}E)\ Out(a, E.Y){\cdot}[Y]$

$Depl_E(X{:}mol) :s^{-1} =$
$\quad \Sigma(i: E.X.i=\tau_{(r)};P)\ r +$
$\quad \Sigma(i: E.X.i=?a_{(r)};P)\ r\gamma{\cdot}OutsOn_E(a) +$
$\quad \Sigma(i: E.X.i=!a_{(r)};P)\ r\gamma{\cdot}InsOn_E(a)$

$Accr_E(Y{:}mol, X{:}mol) :s^{-1} =$
$\quad \Sigma(i: E.Y.i=\tau_{(r)};P)\ \#X(P){\cdot}r +$
$\quad \Sigma(i: E.Y.i=?a_{(r)};P)\ \#X(P){\cdot}r\gamma{\cdot}OutsOn_E(a) +$
$\quad \Sigma(i: E.Y.i=!a_{(r)};P)\ \#X(P){\cdot}r\gamma{\cdot}InsOn_E(a)$

$[X]^\bullet_E = (\Sigma(Y{\in}E)\ Accr_E(Y,X){\cdot}[Y]) - Depl_E(X){\cdot}[X]$

As before, here E.X is the molecule defined by X in E, and M.i is the i-th summand in a molecule of the form $M{=}\pi_1;P_1{\oplus}\ldots{\oplus}\pi_n;P_n$, and #X(P) is the number of occurrences of variable X in a solution P. We use $\Sigma(i: F_i)G_i$ for the sum of the G_i over all i such that F_i (omitting 'i:' when it is obvious).

In(a,M) and *Out*(a,M) simply count the number of inputs and outputs offered by a molecule M.

$OutsOn_E(a)$ is the concentration of outputs !a within E. For each species Y, that number is *Out*(a,E.Y) multiplied by the concentration of Y (see Discussion 4.3–4 below). Similarly, $InsOn_E(a)$ is the concentration of inputs ?a within E.

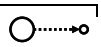
$Depl_E(X)$ is the *depletion rate* of a species X within E. The depletion rate due to a delay $\tau_{(r)}$ that X performs is r. The depletion rate due to an input $?a_{(r)};P$ that X performs, is the rate $r\gamma$ multiplied by the concentration $OutsOn_E(a)$ of outputs !a. A similar case covers depletion due to outputs.

$Accr_E(Y,X)$ is the *accretion rate* of a species X due to the activity of a species Y within E. The accretion of X due to delay $\tau_{(r)}$;P that Y performs, is the rate r multiplied by the number of X molecules produced in P, #X(P). The accretion of X due to an input $?a_{(r)}$;P that Y performs, is the rate rγ multiplied by the concentration $OutsOn_E(a)$ of outputs !a, then multiplied by the number of X molecules produced in P. A similar case covers accretion due to outputs.

Finally, for any variable X, we define the rate of change of [X] in E: $[X]^\bullet_E$. This is the sum for all Y of the accretion rate of X due to Y, multiplied by the concentration of Y, minus the depletion rate of X, multiplied by the concentration of X.

4.3–2 Basic examples

Unary reaction



the system	$X = \tau_{(r)};0$
gives the ODE:	$[X]^\bullet = -Depl(X)\cdot[X] = -r[X]$

Hetero reaction

the system	$X = ?a_{(r)};0,\ \ Y = !a_{(r)};0$
gives the ODEs:	$[X]^\bullet = -Depl(X)\cdot[X] = -(r\gamma\cdot OutsOn_E(a))\cdot[X] = -(r\gamma[Y])\cdot[X] = -r\gamma[X][Y]$
	$[Y]^\bullet = -Depl(Y)\cdot[Y] = -(r\gamma\cdot InsOn_E(a))\cdot[Y] = -(r\gamma[X])\cdot[Y] = -r\gamma[X][Y]$

Homeo reaction

the system	$X = ?a_{(r)};0 \oplus !a_{(r)};0$
gives the ODEs:	$[X]^\bullet = -Depl(X)\cdot[X] = -(r\gamma\cdot OutsOn_E(a) + r\gamma\cdot InsOn_E(a))\cdot[X]$
	$= -(r\gamma[X]+r\gamma[X])\cdot[X] = -2r\gamma[X]^2$

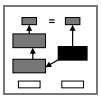
4.3–3 Discussion: Rate doubling

Definition 4.3–1 is remarkable in that, while mapping a discrete framework (stochastic processes) to a continuous framework (differential equations), it does not appear to make any special adjustment beyond the factor γ. In particular, there is no rate-doubling adjustment as in Definition 4.2–3, nor as in Definitions 2.3–1/2.4–1. However, as we shall see in Theorem 4.4–3, this turns out to be the correct definition: the rated-doubling for homeo reactions is brought out explicitly in Lemma 4.4–2. □

4.3–4 Discussion: The presumption of continuity

While processes come in discrete numbers, our "process concentrations" [X] are presumed to represent continuous quantities, since we are taking their derivatives. This presumption is in fact incorporated in a subtle and fundamental way in Definition 4.3–1. There, $OutsOn_E(a)$ is meant to be the *concentration* of outputs !a within E. In the simple case of E = (X=?a.0; Y=!a.0), we have $OutsOn_E(a)$ = [Y], $InsOn_E(a)$ = [X], and $[X]^\bullet$ is proportional to [X][Y]. If we were counting the actual number of interactions per second between X and Y processes, they would be similarly proportional to #X·#Y. But now consider E = (X = ?a;Y ⊕ !a;Z); we have by our definition that $OutsOn_E(a) = InsOn(a)$ = [X], and $[X]^\bullet$ is proportional to $[X]^2$ as in the law of mass action. Instead, if we were counting the *actual number* of possible input-output process interactions, we would count them as #X·(#X-1), because a process cannot output to itself. The definition we adopt effectively rounds #X-1 to #X. This is the one place where we make an approximation and an implicit assumption of continuity, and this is what allows Definition 4.3–1 to match the law of mass action, as shown in Theorem 4.4–3. That approximation is the same one that is implicit in the definition of *Cont* for homeo reactions (see discussion in Examples 4.2–5), as emphasized in [27]. Note that the law of mass action is oblivious as to whether a chemical species interacts with itself or with a different species. □

4.4 Continuous-state equivalence: E ≈ *Cont*(Ch(E))



Our next task is to show that the translations between processes and chemistry are sound with respect to the continuous semantics of each. In the end, since we already know that the translations are stochastically sound, what we obtain is a check of the consistency of the continuous semantics of processes with respect to the law of mass action. In order to compare processes and chemistry at the level of ODEs, we need to following:

4.4–1 Definition: Polynomial equivalence (≈)

1) We say that two systems of ordinary differential equations S_1 and S_2 over the same variables are *polynomially equivalent* ($S_1 \approx S_2$), or simply *equivalent*, iff for every variable Ξ we have that $\Xi^\bullet$ in S_1 and $\Xi^\bullet$ in S_1 are *equivalent polynomials* over the field of real numbers.

2) For two systems of chemical reactions C_1,C_2, we say that $\mathbf{C_1 \approx C_2}$ iff they have equivalent ODEs according the continuous semantics of Definition 4.1–1 of $[X]^\bullet_C$ (that is, they are understood as the reactions of continuous chemical systems). Similarly, for two systems of process reagents E_1,E_2, we say that $\mathbf{E_1 \approx E_2}$ iff they have equivalent ODEs according to Definition 4.3–1 of $[X]^\bullet_E$.

3) If C is a system of chemical reactions, and E is a set of process reagents over the same species, we say that $\mathbf{C \approx E}$ iff their ODEs are equivalent, that is iff for each species X we have that $[X]^\bullet_C = [X]^\bullet_E$ (equivalent polynomials).

4.4–2 **Lemma: Tagged summands of *Depl* and *Accr***

(1) $Depl_E(X)$ and $Accr_E(Y, X)$ can be placed in this form with uniquely tagged summands:

$Depl_E(X) =$
$\Sigma(i: E.X.i=\tau_{(r)};P)\ r :\langle X.i\rangle +$
$\Sigma(i: E.X.i=?a_{(s)};P)\ \Sigma(Y\neq X)\ \Sigma(j: E.Y.j=!a_{(s)};Q)\ s\cdot\gamma\cdot[Y] :\langle X.i,Y.j\rangle +$
$\Sigma(i: E.X.i=!b_{(t)};Q)\ \Sigma(Y\neq X)\ \Sigma(j: E.Y.j=?b_{(t)};P)\ t\cdot\gamma\cdot[Y] :\langle Y.j,X.i\rangle +$
$\Sigma(i: E.X.i=?a_{(s)};P)\ \Sigma(j: E.X.j=!a_{(s)};Q)\ 2\cdot s\cdot\gamma\cdot[X] :\langle X.i,X.j\rangle$

$Accr_E(Y, X) =$
$\Sigma(i: E.Y.i=\tau_{(r)};P)\ \#X(P)\cdot r :\langle Y.i\rangle +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \Sigma(Z\neq Y)\ \Sigma(j: E.Z.j=!a_{(r)};Q)\ \#X(P)\cdot s\cdot\gamma\cdot[Z] :\langle Y.i,Z.j\rangle +$
$\Sigma(i: E.Y.i=!b_{(t)};Q)\ \Sigma(Z\neq Y)\ \Sigma(j: E.Z.j=?b_{(t)};P)\ \#X(Q)\cdot t\cdot\gamma\cdot[Z] :\langle Z.j,Y.i\rangle +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \Sigma(j: E.Y.j=!a_{(s)};Q)\ (\#X(P)+\#X(Q))\cdot s\cdot\gamma\cdot[Y] :\langle Y.i,Y.j\rangle$

(2) Ch(E) uses the same tagging for reactions. The tags induce a 1-1 correspondence between the summands of $Depl_E(X)$ and the reactions of Ch(E) that have at least one X on the Lhs.

(3) The tags also induce a 1-1 correspondence between the summands of $Accr_E(Y,X)$ and the reactions of Ch(E) that have at least one Y on the Lhs and one X on the Rhs.

Proof

(1) We begin by manipulating the definitions of depletion and accretion; we recall that:

$Depl_E(X) =$
$\Sigma(i: E.X.i=\tau_{(r)};P)\ r +$
$\Sigma(i: E.X.i=?a_{(s)};P)\ s\cdot\gamma\cdot OutsOn_E(a) +$
$\Sigma(i: E.X.i=!b_{(t)};Q)\ t\cdot\gamma\cdot InsOn_E(b)$

$Accr_E(Y, X) =$
$\Sigma(i: E.Y.i=\tau_{(r)};P)\ \#X(P)\cdot r +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \#X(P)\cdot s\cdot\gamma\cdot OutsOn_E(a) +$
$\Sigma(i: E.Y.i=!b_{(t)};Q)\ \#X(Q)\cdot t\cdot\gamma\cdot InsOn_E(b)$

Expanding *OutsOn* and *InsOn*, and *Out* and *In*, and distributing the sums, we obtain:

$Depl_E(X)$ =

$\Sigma(i: E.X.i=\tau_{(r)};P)\ r +$
$\Sigma(i: E.X.i=?a_{(s)};P)\ \Sigma(Y\in E)\ \Sigma(j: E.Y.j=!a_{(s)};Q)\ s\cdot\gamma\cdot[Y] +$
$\Sigma(i: E.X.i=!b_{(t)};Q)\ \Sigma(Y\in E)\ \Sigma(j: E.Y.j=?b_{(t)};P)\ t\cdot\gamma\cdot[Y]$

$Accr_E(Y, X)$ =

$\Sigma(i: E.Y.i=\tau_{(r)};P)\ \#X(P)\cdot r +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \Sigma(Z\in E)\ \Sigma(j: E.Z.j=!a_{(r)};Q)\ \#X(P)\cdot s\cdot\gamma\cdot[Z] +$
$\Sigma(i: E.Y.i=!b_{(t)};Q)\ \Sigma(Z\in E)\ \Sigma(j: E.Z.j=?b_{(t)};P)\ \#X(Q)\cdot t\cdot\gamma\cdot[Z]$

Now note that in the last two lines of each definition, there are two symmetric copies of each summand (on the same channel and rate, one in input and one in output). We isolate them as follows:

$Depl_E(X)$ =

$\Sigma(i: E.X.i=\tau_{(r)};P)\ r +$
$\Sigma(i: E.X.i=?a_{(s)};P)\ \Sigma(Y\neq X)\ \Sigma(j: E.Y.j=!a_{(s)};Q)\ s\cdot\gamma\cdot[Y] +$
$\Sigma(i: E.X.i=!b_{(t)};Q)\ \Sigma(Y\neq X)\ \Sigma(j: E.Y.j=?b_{(t)};P)\ t\cdot\gamma\cdot[Y] +$
$\Sigma(i: E.X.i=?a_{(s)};P)\ \Sigma(j: E.X.j=!a_{(s)};Q)\ 2\cdot s\cdot\gamma\cdot[X]$

$Accr_E(Y, X)$ =

$\Sigma(i: E.Y.i=\tau_{(r)};P)\ \#X(P)\cdot r +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \Sigma(Z\neq Y)\ \Sigma(j: E.Z.j=!a_{(r)};Q)\ \#X(P)\cdot s\cdot\gamma\cdot[Z] +$
$\Sigma(i: E.Y.i=!b_{(t)};Q)\ \Sigma(Z\neq Y)\ \Sigma(j: E.Z.j=?b_{(t)};P)\ \#X(Q)\cdot t\cdot\gamma\cdot[Z] +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \Sigma(j: E.Y.j=!a_{(s)};Q)\ (\#X(P)+\#X(Q))\cdot s\cdot\gamma\cdot[Y]$

We then add tags $:\langle X.i\rangle$ or $:\langle X.i,Y.j\rangle$ to each summand that are derived from the relevant local indices ($\langle X.i,Y.j\rangle$ is an ordered pair); thus we obtain the statement of the Lemma. The summands are obviously uniquely tagged: in the middle two rows of each summation because of asymmetry of input and output (the left part of a tag is always an input).

(2) By the tagging of the summands, and the definition of Ch(E) that assigns a unique tag, ρ_j, to reaction j, we can see that in this formulation of $Depl_E(X)$ there is exactly one summand $Depl_E(X).\rho_j$ for each reaction Ch(E).j that involves X on the left-hand side. Each tag X.i corresponds to a reaction $X\rightarrow$, each tag X.i,Y.j to a reaction $X+Y\rightarrow$ (by an X input), each tag Y.j,X.i to a reaction $Y+X\rightarrow$ (by an X output), and each tag X.i,X.j to a reaction $X+X\rightarrow$.

(3) Similarly, we can see that in this formulation of $Accr_E(Y,X)$ there is exactly one summand $Accr_E(Y,X).\rho_j$ for each reaction Ch(E).j that involves Y on the left hand side and X on the right-hand side. Each tag Y.i corresponds to a reaction $Y\rightarrow..X..$, each tag Y.i,Z.j to a reaction $Y+Z\rightarrow..X..$ with at least some X produced by a Y input, each tag Z.j,Y.i to a reaction $Z+Y\rightarrow..X..$ with at least some X produced by a Y output, and each tag Y.i,Y.j to a reaction $Y+Y\rightarrow..X..$. □

As a consequence of Lemma 4.4–2, consider the sum over Y of all $Accr_E(Y,X)$ (each multiplied by [Y], as needed later):

$\Sigma(Y\in E)\ Accr_E(Y, X)\cdot[Y]$ =

$\Sigma(i: E.Y.i=\tau_{(r)};P)\ \#X(P)\cdot r\cdot[Y]\ :\langle Y.i\rangle +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \Sigma(Z\neq Y)\ \Sigma(j: E.Z.j=!a_{(r)};Q)\ \#X(P)\cdot s\cdot\gamma\cdot[Z]\cdot[Y]\ :\langle Y.i,Z.j\rangle +$
$\Sigma(i: E.Y.i=!b_{(t)};Q)\ \Sigma(Z\neq Y)\ \Sigma(j: E.Z.j=?b_{(t)};P)\ \#X(Q)\cdot t\cdot\gamma\cdot[Z]\cdot[Y]\ :\langle Z.j,Y.i\rangle +$
$\Sigma(i: E.Y.i=?a_{(s)};P)\ \Sigma(j: E.Y.j=!a_{(s)};Q)\ (\#X(P)+\#X(Q))\cdot s\cdot\gamma\cdot[Y]\cdot[Y]\ :\langle Y.i,Y.j\rangle$

Since the Y are distinct, the tags on each summand are still distinct, except for those binary reactions where both Y.i and Z.j produce X: then exactly two summands have the tag $\langle Y.i,Z.j\rangle$. This needs to be considered in Theorem 4.4–3.

We now show that a system of chemical reactions Ch(E) is equivalent to E, by comparing the accretions and depletions of each variable X in E.

4.4–3 Theorem: *Cont*(Ch(E)) ≈ E

Let E be process reagents, Ch(E) be the corresponding system of discrete chemical reactions, and *Cont*(Ch(E)) be the related system of continuous chemical reaction. Then we have *Cont*(Ch(E)) ≈ E. That is, for all variables X in E, the process and chemical rates coincide:

$$[X]^{\bullet}_{Cont(Ch(E))} = [X]^{\bullet}_{E} \qquad \text{(for a fixed } \gamma\text{)}$$

Proof

Let *Cont*(Ch(E)) have stoichiometric matrix **N** and vector of rate laws **l**. We need to show that:

$$\begin{aligned} &\mathbf{N}_{X,-} \cdot \mathbf{l} && ([X]^{\bullet} \text{ computed on } Cont(Ch(E))) \\ &= (\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y]) - Depl_E(X) \cdot [X] && ([X]^{\bullet} \text{ computed on E}) \end{aligned}$$

By Definition 4.1–1 we have:

$$\begin{aligned} &\mathbf{N}_{X,-} \cdot \mathbf{l} = \Sigma_{k \in 1..m}\, \mathbf{N}_{X,k} \cdot \mathbf{l}_k = \Sigma_{k \in 1..m}\, (\#X(Rhs_k) - \#X(Lhs_k)) \cdot \mathbf{l}_k \\ &= (\Sigma_{k \in 1..m}\, \#X(Rhs_k) \cdot \mathbf{l}_k) - (\Sigma_{k \in 1..m}\, \#X(Lhs_k) \cdot \mathbf{l}_k). \end{aligned}$$

We derive the result in two parts by showing separately that the depletions are equal ($Depl_E(X) \cdot [X] = \Sigma_{k \in 1..m}\, \#X(Lhs_k) \cdot \mathbf{l}_k$) and that the accretions are equal ($\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y] = \Sigma_{k \in 1..m}\, \#X(Rhs_k) \cdot \mathbf{l}_k$).

Depletion

We show that:

$$Depl_E(X) \cdot [X] = \Sigma_{k \in 1..m}\, \#X(Lhs_k) \cdot \mathbf{l}_k.$$

by showing that for each k such that $\#X(Lhs_k) \neq 0$, we have $Depl_E(X).\rho_k \cdot [X] = \#X(Lhs_k) \cdot \mathbf{l}_k$, where ρ_k is the tag of reaction k in Ch(E) and $Depl_E(X).\rho_k$ is the summand tagged by ρ_k in $Depl_E(X)$. We have shown that those summands are tagged in 1 to 1 correspondence (Lemma 4.4–2) (and that $Depl_E(X).\rho_k$ exists only if $\#X(Lhs_k) \neq 0$).

- If $\rho_k = \langle X.i \rangle$, then the reaction k is $X \to^r P$, with $E.X.i = \tau_{(r)};P$. $Cont(X \to^r P) = X \to^r P$, and $\#X(Lhs_k) = 1$, and $\mathbf{l}_k = r[X]$. The summand is $Depl_E(X).\rho_k = r$. Hence $Depl_E(X).\rho_k \cdot [X] = r[X] = \#X(Lhs_k) \cdot \mathbf{l}_k$.
- If $\rho_k = \langle X.i,Y.j \rangle$, $Y \neq X$, then the reaction k is $X+Y \to^s P+Q$, with $E.X.i = ?a_{(s)};P$ and $E.Y.j = !a_{(s)};Q$. $Cont(X+Y \to^s P+Q) = X+Y \to^{s\gamma} P+Q$, and $\#X(Lhs_k) = 1$, and $\mathbf{l}_k = s\gamma[X][Y]$. The summand is $Depl_E(X).\rho_k = s\gamma[Y]$. Hence $Depl_E(X).\rho_k \cdot [X] = s\gamma[X][Y] = \#X(Lhs_k) \cdot \mathbf{l}_k$.
- If $\rho_k = \langle Y.j,X.i \rangle$, $Y \neq X$, then the reaction k is $Y+X \to^t P+Q$ with $E.X.i = !b_{(t)};Q$ and $E.Y.j = ?b_{(t)};P$. $Cont(Y+X \to^t P+Q) = Y+X \to^{t\gamma} P+Q$, and $\#X(Lhs_k) = 1$, and $\mathbf{l}_k = t\gamma[Y][X]$. The summand is $Depl_E(X).\rho_k = t\gamma[Y]$. Hence $Depl_E(X).\rho_k \cdot [X] = t\gamma[Y][X] = \#X(Lhs_k) \cdot \mathbf{l}_k$.
- If $\rho_k = \langle X.i,X.j \rangle$, then The reaction k is $X+X \to^{2s} P+Q$, with $E.X.i = ?a_{(s)};P$ and $E.X.j = !a_{(s)};Q$. $Cont(X+X \to^{2s} P+Q) = X+X \to^{s\gamma} P+Q$, and $\#X(Lhs_k) = 2$, and $\mathbf{l}_k = s\gamma[X]^2$. The summand is $Depl_E(X).\rho_k = 2s\gamma[X]$. Hence $Depl_E(X).\rho_k \cdot [X] = 2s\gamma[X]^2 = \#X(Lhs_k) \cdot \mathbf{l}_k$.

Accretion

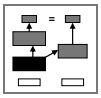
We show that:

$$\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y] = \Sigma_{k \in 1..m}\, \#X(Rhs_k) \cdot \mathbf{l}_k$$

by showing that for each k such that $\#X(Rhs_k) \neq 0$, we have that $(\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y]).\rho_k = \#X(Rhs_k) \cdot \mathbf{l}_k$, where ρ_k is the tag of reaction k in Ch(E), and $(\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y]).\rho_k$ is *the sum of* the summands tagged by ρ_k in $\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y]$, of which there can be 1 or 2.

- If $\rho_k = \langle Z.i \rangle$, then the reaction k is $Z \to^r P$ with $E.Z.i = \tau_{(r)};P$. $Cont(Z \to^r P) = Z \to^r P$, and $\mathbf{l}_k = r[Z]$. The unique summand is $Accr_E(Z,X).\rho_k = \#X(P) \cdot r$. Hence $(\Sigma(Y \in E)\ Accr_E(Y,X) \cdot [Y]).\rho_k = (Accr_E(Z,X) \cdot [Z]).\rho_k = \#X(P) \cdot r \cdot [Z] = \#X(Rhs_k) \cdot \mathbf{l}_k$.

- If ρ_k=‹Z.i,W.j›, W≠Z, then the reaction k is Z+W $\rightarrow^{s}$ P+Q with E.Z.i=?$a_{(s)}$;P and E.W.j=!$a_{(s)}$;Q. *Cont*(Z+W $\rightarrow^{s}$ P+Q) = Z+W $\rightarrow^{s\gamma}$ P+Q, and $\mathbf{l}_k$ = sγ[Z][W]. The two summands with tag ρ_k are $Accr_E(Z,X).\rho_k$ = #X(P)·s·γ·[W], and $Accr_E(W,X).\rho_k$ = #X(Q)·s·γ·[Z]. Hence (Σ(Y∈E) $Accr_E(Y,X)\cdot[Y]).\rho_k$ = $(Accr_E(Z,X)\cdot[Z]).\rho_k$ + $(Accr_E(W,X)\cdot[W]).\rho_k$ = #X(P)·s·γ·[W]·[Z] + #X(Q)·s·γ·[Z]·[W] = (#X(P)+#X(Q))·s·γ·[Z]·[W] = #X(Rhs_k)·$\mathbf{l}_k$.
- If ρ_k=‹Z.i,Z.j›, then the reaction k is Z+Z $\rightarrow^{2s}$ P+Q with E.Z.i=?$a_{(s)}$;P and E.Z.j=!$a_{(s)}$;Q. *Cont*(Z+Z $\rightarrow^{2s}$ P+Q) = Z+Z $\rightarrow^{s\gamma}$ P+Q, and $\mathbf{l}_k$ = sγ$[Z]^2$. The unique summand is $Accr_E(Z,X).\rho_k$ = (#X(P)+#X(Q))·s·γ·[Z]. Hence (Σ(Y∈E) $Accr_E(Y,X)\cdot[Y]).\rho_k$ = $(Accr_E(Z,X)\cdot[Z]).\rho_k$ = (#X(P)+#X(Q))·s·γ·[Z]·[Z] = #X(Rhs_k)·$\mathbf{l}_k$. □



4.5 Continuous-state equivalence: *Cont*(C) ≈ Pi(C)

We show that the Pi(C) is equivalent to the continuous chemical system *Cont*(C), by the fact that Ch(Pi(C)) is essentially identical to C, and by Theorem 4.4–3.

4.5–1 Lemma: *Cont*(Ch(Pi(C))) ≈ *Cont*(C)

Let C be a system of chemical reactions, then *Cont*(Ch(Pi(C))) ≈ *Cont*(C).

Proof

From Proposition 2.4–4 we have Ch(Pi(C)) = C up to reaction labels. These differences, which are preserved by *Cont*(-) do not affect the continuous semantics of chemical reactions (Definition 4.1–1). □

4.5–2 Theorem: *Cont*(C) ≈ Pi(C)

Let C be a system of chemical reactions, and Pi(C) the corresponding process reagents. Then we have Pi(C) ≈ *Cont*(C).

Proof

From Theorem 4.4–3, for any set of reagents E, we have *Cont*(Ch(E)) ≈ E. Hence, for any system of reactions C resulting in a reagents Pi(C), we have that *Cont*(Ch(Pi(C))) ≈ Pi(C). Moreover, from Lemma 4.5–1 we have that *Cont*(Ch(Pi(C))) ≈ *Cont*(C). Therefore, *Cont*(C) ≈ Pi(C). □

Finally, in a very similar way to Proposition 3.5–2, we can use the last two theorems to show that E and Detangle(E) are equivalent:

4.5–3 Proposition: Detangling processes and automata

(1) If E is a set of reagents, then there is an E′ ≈ E that is detangled. (Take E′ = Pi(Ch(E)).)

(2) If E is a set of reagents in automata form, then there is an E′ ≈ E that is in automata form and is detangled. (Take E′ = Detangle(E).)

Proof

(1) Take E′ = Pi(Ch(E)). E′ is detangled by Proposition 2.4–3, and E′ ≈ E because E ≈ *Cont*(Ch(E)) ≈ Pi(Ch(E)) by Theorems 4.4–3 and 4.5–2.

(2) Let Detangle(E) be the automaton obtained from E by Definition 2.4–5. By Proposition 2.4–6, Ch(Detangle(E)) and Ch(Pi(Ch(E))) have the same chemical reactions, so that *Cont*(Ch(Detangle(E))) is rate equivalent to *Cont*(Ch(Pi(Ch(E)))). Therefore, Detangle(E) ≈ *Cont*(Ch(Detangle(E))) (by Theorem 4.4–3) ≈ *Cont*(Ch(Pi(Ch(E)))) (by above discussion) ≈ *Cont*(Ch(E)) (by Lemma 4.5–1) ≈ E (by Theorem 4.4–3). □

5 Examples

The basic examples discussed in the various sections of the paper are summarized in Figure 7, arranged along the pattern of Figure 6, which we use also in the subsequent figures.

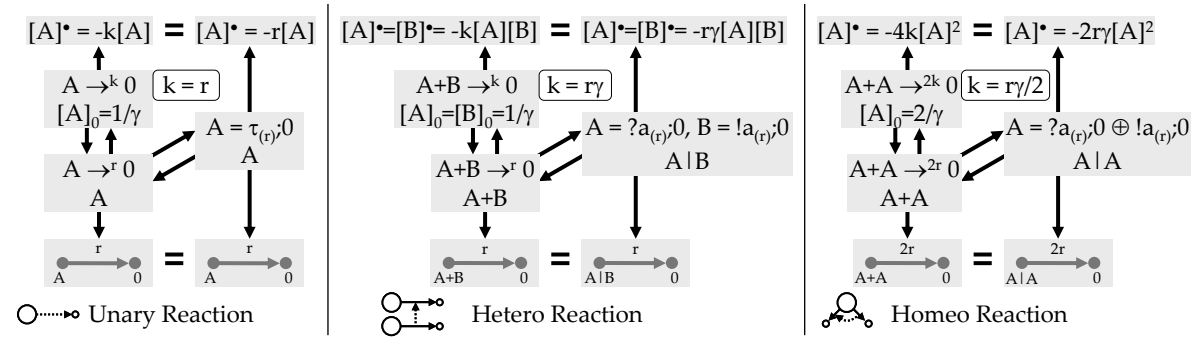


Figure 7 Summary of the Basic Examples

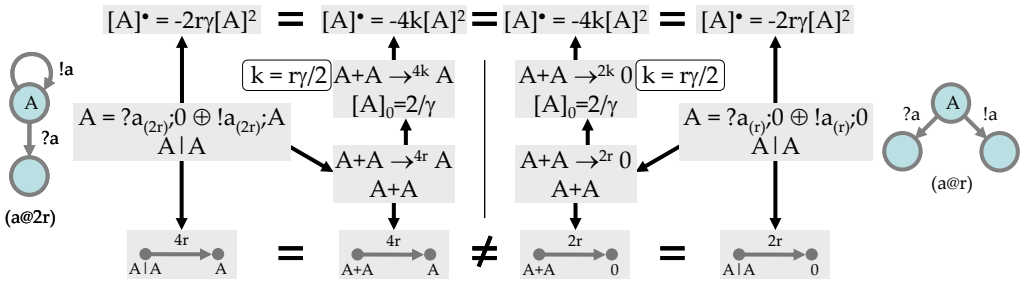


Figure 8 Discrete vs. continuous semantics

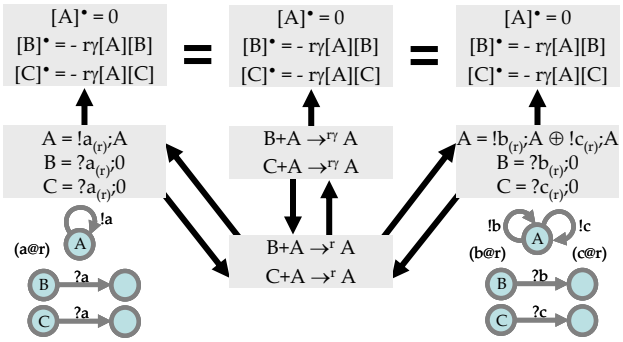


Figure 9 Equivalent automata with the same chemistry

We have shown in Section 3 that the discrete semantics of processes coincides with the discrete semantics of chemical reactions (stochastic chemistry), and similarly in Section 4 that the continuous semantics of processes coincides with the continuous semantics of chemical reactions (law of mass action). However, the discrete and continuous semantics differ, at least at "low numbers". A simple example is given in Figure 8 by alternative ways of expressing self-interacting processes: they produce the same ODEs, but produce different graphs (and CTMCs with different final states) from the same initial population. The same applies to the respective chemical reactions, where the question is whether the reaction A+A $\rightarrow^{s}$ 0 has the same behavior as the reaction A+A $\rightarrow^{2s}$ A: they have the same ODEs but one system stops with zero A, while the other stops with one A, when both start with two A. Another process discretely equivalent to the one on the left in Figure 8 is $A = ?a_{(r)};0 \oplus ?a_{(r)};0 \oplus !a_{(r)};A$.

Next, Figure 9 compares two of the examples from the Introduction that generate the same set of chemical reactions (middle).

Figure 10 compares the other three examples from the Introduction, two of which generate the same set of chemical reactions, while the third does not, but still produces the same set of ODEs.

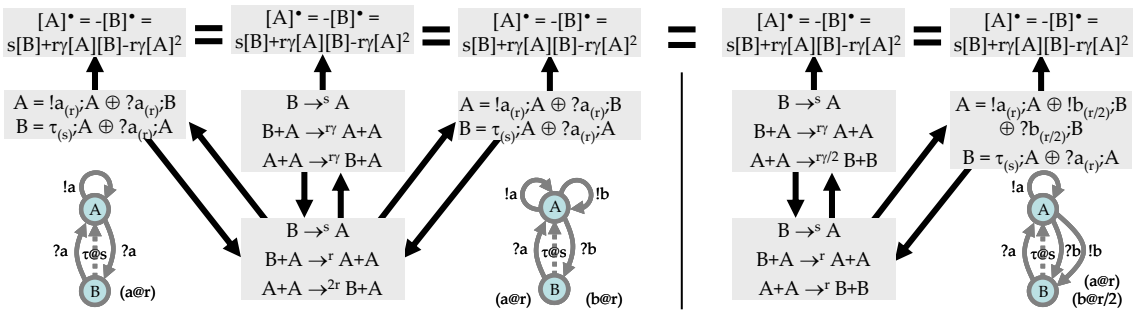


Figure 10 Equivalent automata with different chemistry

As an illustration, we give the detailed computations for the left automaton in Figure 10:

Processes E

$A = !a_{(r)};A \oplus ?a_{(r)};B,$

$B = \tau_{(s)};A \oplus ?a_{(r)};A$

Process ODEs $[\text{-}]^\bullet_E$

$InsOn_E(a) = \Sigma(Y \in E)\ In(a, E.Y)\cdot[Y] = 1\cdot[A] + 1\cdot[B]$

$OutsOn_E(a) = \Sigma(Y \in E)\ Out(a, E.Y)\cdot[Y] = 1\cdot[A]$

$Accr_E(A, A) = 0\cdot r\gamma\cdot OutsOn_E(a) + 1\cdot r\gamma\cdot InsOn_E(a) = r\gamma\cdot([A]+[B])$

$Depl_E(A) = r\gamma\cdot OutsOn_E(a) + r\gamma\cdot InsOn_E(a) = r\gamma\cdot[A] + r\gamma\cdot([A]+[B])$

$Accr_E(B, A) = 1\cdot s + 1\cdot r\gamma\cdot OutsOn_E(a) = s + r\gamma\cdot[A]$

$Depl_E(B) = s + r\gamma\cdot OutsOn_E(a) = s + r\gamma\cdot[A]$

$Accr_E(A, B) = 0\cdot r\gamma\cdot InsOn_E(a) + 1\cdot r\gamma\cdot OutsOn_E(a) = r\gamma\cdot[A]$

$Accr_E(B, B) = 0\cdot s + 0\cdot r\gamma\cdot OutsOn_E(a) = 0$

$[A]^\bullet = Accr_E(A, A)\cdot[A] + Accr_E(B, A)\cdot[B] - Depl_E(A)\cdot[A]$
$= r\gamma\cdot([A]+[B])\cdot[A] + (s + r\gamma\cdot[A])\cdot[B] - (r\gamma\cdot[A] + r\gamma\cdot([A]+[B]))\cdot[A]$
$= r\gamma[A]^2 + r\gamma[A][B] + s[B] + r\gamma[A][B] - r\gamma[A]^2 - r\gamma[A]^2 - r\gamma[A][B]$
$= s[B] + r\gamma[A][B] - r\gamma[A]^2$

$[B]^\bullet = Accr_E(A, B)\cdot[A] + Accr_E(B, B)\cdot[B] - Depl_E(B)\cdot[B]$
$= r\gamma\cdot[A]\cdot[A] + 0 - (s + r\gamma\cdot[A])\cdot[B]$
$= r\gamma[A]^2 - s[B] - r\gamma[A][B]$

Discrete chemistry Ch(E)

‹B.1›: $B \to^s A$

‹B.2, A.1›: $B+A \to^r A+A$

‹A.2, A.1›: $A+A \to^{2r} B+A$

Continuous chemistry $Cont_\gamma$(Ch(E))

‹B.1›: $B \to^s A$ rate law: $s[B]$

‹B.2, A.1›: $B+A \to^{r\gamma} A+A$ rate law: $r\gamma[A][B]$

‹A.2, A.1›: $A+A \to^{r\gamma} B+A$ rate law: $r\gamma[A]^2$ $(r\gamma = (2r)\gamma/2)$

Chemical ODEs $[\text{-}]^\bullet_{Cont(Ch(E))}$

$[A]^\bullet = s[B] + r\gamma[A][B] - r\gamma[A]^2$

$[B]^\bullet = - s[B] - r\gamma[A][B] + r\gamma[A]^2$

6 Conclusions

We conclude that the process semantics and the chemical semantics are in perfect correspondence, and that we can translate back and forth between them without changing the dynamic behavior. Therefore, a process algebra model of a biochemical system is faithful to the chemistry.

Corollaries

$Pi(Ch(E)) \approx E.$ (By Theorems 4.4–3 and 4.5–2)

$Cont(Ch(Pi(C))) \approx Cont(C).$ (By Lemma 4.5–1) □

However, going around the loop of $E \approx Pi(Ch(E))$ is not without effect, as we discuss next.

6.1 Compact representation

The entangled automata from the Introduction can be turned into detangled automata that are equivalent both discretely (Proposition 3.5–2), and continuously (Proposition 4.5–3). However, detangled

automata are not necessarily desirable, because of their size complexity. To see this, consider reagents of the following simple form (see Figure 11 for E_3):

$$E_n = \{X_i = ?a_{(r)};\ X_{(i+1)\bmod_n},\quad Y_i = !a_{(r)};\ Y_{(i+1)\bmod_n} \quad s.t. \quad i \in 0..n\text{-}1\}$$

The automata E_n have 2n variables (nodes) and 2n terms (arcs). $Ch(E_n)$ has 2n species and n^2 reactions of the form $X_i + Y_j \to X_{(i+1)\bmod_n} + Y_{(j+1)\bmod_n}$. The automata Detangle($E_n$), closely corresponding to $Pi(Ch(E_n))$, have 2n variables (nodes) and $2n^2$ summands (arcs). The stoichiometric matrix has size $2n \cdot n^2 = 2n^3$. The ODEs for E_n have 2n variables, and a total of $2n(n+n) = 4n^2$ terms (number of variables times number of accretions plus depletions, when sums are distributed), versus 2n terms for E_n.

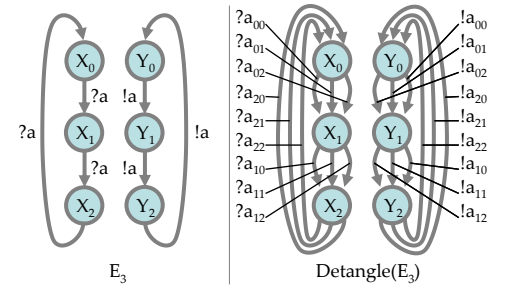


Figure 11 Entangled vs. Detangled

A quadratic explosion arises already in the translation from automata to chemical reactions: from 2n transitions to n^2 reactions. And, as in this example, it arises with ordinary binary reactions between different species. Therefore, even the very restricted process algebra considered in this paper can provide equivalent but more compact *representations* of biochemical systems than chemical or ODE models, at least for those detailed models based on binary reactions. Given such a compact representation, we can compute its continuous dynamics either through chemistry and the law of mass action, or directly from the process rate equation.

6.2 Related work

Stochastic process algebras have been studied in depth for performance analysis. Many of the standard ones (PEPA [15], TIPP [14], MPA [2], Reactive Modules [1] as used in PRISM [18]) are based on CSP-style n-way synchronization, which can help in constructing the Markov chain compositionally over the syntax [6]. We use CCS-style 2-way synchronization, as in other stochastic process algebras [21][22], which is an approach that originated in [23][24] for modeling biochemistry.

We have avoided giving a structural operational semantics for our stochastic algebra, which is the focus of much of the early work in the area (see, e.g., [2],[21]; a shade of those "auxiliary label" techniques remains in our labeled transition graphs). Instead, we give directly the Markov generator matrix (non-compositionally, by unfolding the reductions, and without lumping), via a graph representation, which is all we need in proofs. In producing the graph representation, we are helped by the fact that the states of our Chemical Ground Form are not arbitrary terms, as common in process algebras, but just multisets of variables (molecules). Our Markov semantics is aimed mostly at justifying the translations between chemistry and processes, and for comparison with the continuous semantics; a deeper connection to the theory of Markov chains is investigated in [7].

We allow the Markov chains to be infinite, because simple stochastic systems with unbounded number of states are common in chemistry and biology, for example whenever there is a dynamic balance between production and degradation [3]. Current tools based on stochastic π-calculus allow the simulation of unbounded-state systems [20] and, although we have treated here only a small fragment of π-calculus, we have preserved the unbounded splitting of processes that is necessary to represent chemical reactions of the general form $A \to^r B + C$. This unbounded-state property is shared also by CSP-style algebras and their stochastic versions, in their general formulation. Historically, those algebras have been aimed at performance evaluation, and have introduced restrictions that are useful in that context for the analysis of the underlying finite Markov chain. PEPA [15] is based on the composition of sequential processes (automata) to enable analysis by linear algebra, and therefore supports parallel composition only at the top level. Early stochastic process algebras like TIPP [14] have similar restrictions to a finite number of states, again for deliberate practical reasons.

A direct translation from a stochastic process algebra (PEPA) to ODEs is presented in [8][16]; it is not based on the law of mass action, but rather on a law of interaction aimed at computer network analysis. Other connections between stochastic languages and continuous semantics are being developed, some aiming at the full Generalized Mass Action [4]. We have provided a direct continuous semantics of stochastic processes consistent the law of mass action, a translation of processes to chemistry, and a proof of correspondence of the process semantics to the chemical rate equations. The critical link between stochastic and continuous systems is given as in [10][27].

The correspondence between *ground* processes and chemistry presented here can be generalized to *parametric* processes, which are useful for modularizing biochemical models, and therefore for achieving even more compact representations. That generalization can be carried out by purely syntactic means; the present paper establishes the necessary foundations.

6.3 Acknowledgments

Thanks to Pierpaolo Degano, Michael Huth, Cosimo Laneve, and Andrew Phillips for comments on early drafts and discussions.

References

[1] R. Alur, T.A. Henzinger. Reactive Modules. Formal Methods in System Design 15(1), 1-48, Kluwer 1999.

[2] M. Bernardo, L. Donatiello, R. Gorrieri. MPA: a Stochastic Process Algebra. Technical Report UBLCS-94-10, University of Bologna, Laboratory of Computer Science. 1994

[3] R.Blossey, L.Cardelli, A.Phillips: A Compositional Approach to the Stochastic Dynamics of Gene Networks. Transactions on Computational Systems Biology IV, LNCS 3939, 99-122. Springer 2006.

[4] L. Bortolussi, A. Policriti. Stochastic Concurrent Constraint Programming and Differential Equations. Proc. QAPL'07 Quantitative Aspects of Programming Languages, 41-54, 2007.

[5] W.E. Boyce, R.C. DiPrima. Elementary Differential Equations and Boundary Value Problems, 5th ed. New York: Wiley, 1992.

[6] P. Buchholz. Markovian Process Algebra: Composition and Equivalence. Proc. PAPM '94, Erlangen (Germany), 11-30, 1994.

[7] L. Cardelli: A Process Algebra Master Equation. Proc. Fourth International Conference on the Quantitative Evaluation of Systems, QEST 2007.

[8] M. Calder, S. Gilmore, J. Hillston: Automatically Deriving ODEs from Process Algebra Models of Signalling Pathways. Proc. Computational Methods in Systems Biology 2005, 204-215.

[9] M. Dam. On the Decidability of Process Equivalences for the pi-Calculus. Theoretical Computer Science 183, 215-228, 1997.

[10] D.T. Gillespie. Exact Stochastic Simulation of Coupled Chemical Reactions. Journal of Physical Chemistry 81, 2340–2361. 1977.

[11] D.T. Gillespie. The chemical Langevin equation. Journal of Chemical Physics 113(1), 297-306, 2000.

[12] H. Hermanns. Interactive Markov Chains. Springer LNCS, vol 2428, 2002.

[13] H. Hermanns, M. Rettelbach. Syntax, Semantics, Equivalences, and Axioms for MTIPP. Proc. of PAPM '94, Erlangen (Germany), pp 71-87. 1994.

[14] N. Götz, H. Hermanns, U. Herzog, V. Mertsiotakis, M. Rettelbach. Stochastic Process Algebras: Constructive Specification Techniques Integrating Functional, Performance and Dependability. In Baccelli and Mitrani (eds): Quantitative Modelling in Parallel Systems. Chapter 1, Springer 1995.

[15] J. Hillston. A compositional approach to performance modelling. Cambridge University Press, 1996.
[16] J. Hillston. Fluid flow approximation of PEPA models. Proc. Second International Conference on the Quantitative Evaluation of Systems, 33-43. IEEE Press, 2005.
[17] F. Horn, R. Jackson. General mass action kinetics. Arch. Rational Mech. Anal. 47, 81–116, 1972.
[18] M.Z. Kwiatkowska, G. Norman, D. Parker. Probabilistic Symbolic Model Checking with PRISM: A Hybrid Approach. Proc. Tools and Algorithms for Construction and Analysis of Systems (TACAS), 52-66, 2002.
[19] R. Milner. Communicating and Mobile Systems: The π-Calculus. Cambridge University Press, 1999.
[20] A. Phillips, L. Cardelli. A Correct Abstract Machine for the Stochastic Pi-calculus. Proc. Concurrent Models in Molecular Biology (Bioconcur'04), affiliated with CONCUR'04. 2004.
[21] C. Priami. Stochastic π-calculus. The Computer Journal, 38, 578–589, 1995.
[22] C. Priami, A. Regev, E. Shapiro, W. Silverman. Application of a stochastic name-passing calculus to representation and simulation of molecular processes. Information Processing Letters 80, 25-31. 2001.
[23] A. Regev. Computational Systems Biology: A Calculus for Biomolecular knowledge. Ph.D. Thesis, Tel Aviv University. 2002.
[24] A. Regev, E. Shapiro. Cellular abstractions: Cells as computation. Nature 419 343. 2002.
[25] M. Ullah, O. Wolkenhauer. A general derivation of the differential Chapman-Kolmogorov equation. http://www.citebase.org/abstract?id=oai:arXiv.org:q-bio/0610003. 2006.
[26] M. Ullah, H. Schmidt, K-H. Cho, O. Wolkenhauer: Deterministic Modelling and Stochastic Simulation of Pathways using MATLAB. IEE Proc Systems Biology, 153(2), 53-60, 2006.
[27] O. Wolkenhauer, M. Ullah, W. Kolch, K. Cho. Modelling and simulation of intracellular dynamics: Choosing an appropriate framework. IEEE Transactions on NanoBioscience 3, 200-207. 2004.