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Rigid Geometric Constraints for Kappa Models

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Abstract

Rule-based modeling languages such as Kappa [11,7] and BNGL [3,2] allow for a concise description of combinatorially complex biochemical processes as well as efficient simulations of the resulting models [8,7]. A key aspect of the rule-based modeling approach is to partially expose the structure of the chemical species involved. However, the above-mentioned languages do not provide means to directly express the three-dimensional geometry of chemical species. As a consequence models typically capture only the network-topological structure of the species involved. For certain biochemical processes, such as the assembly of molecular complexes, in which steric constraints play a key role, it would seem natural to also model the geometric structure of species. We propose an extension to the Kappa modeling language allowing the annotation of the structure of chemical species with three-dimensional geometric information. This naturally introduces rigidity constraints on the species and reduces the state space of the resulting model by excluding species that are not geometrically sound. We show that models extended in this way can still be simulated efficiently, albeit at the cost of a greater number of null-events occurring during the simulation. The geometric constraints introduced by the extension are inherently non-local in that they may entangle the position and orientation of sub-structures at arbitrary distances in large species such as polymers. We give a formal definition of the notion of locality based on the intuition that local modifications should only affect sub-structures within a finite radius around the point where the modification occurred. We show that there are indeed geometrically enhanced Kappa models that are non-local, and conversely, that every local model can be simulated accurately using a finite classical Kappa model at the expense of a possible combinatorial explosion of its rule set. We also give some sufficient conditions for the locality of a model but show that locality is undecidable in general.

Keywords: rule-based modeling, Kappa, geometric constraints, molecular structure, three-dimensional, rigid body

1 Introduction

Rule-based modeling languages such as Kappa [11,7], or BNGL [3,2], allow for a concise description and the efficient simulation of combinatorially complex biochemical processes, such as cellular signaling pathways. In contrast to reaction-based approaches, rule-based modeling frameworks do not rely on the enumeration of all chemical species involved in a process. The combinatorial complexity of a process can easily make this enumeration intractable or even impossible, for example in the case of polymerization reactions, where the number of possible species involved is infinite in principle.

Due to their stability, molecules such as nucleic acids and proteins can be represented as elementary molecular entities, or *agents* with an interface of *sites* through which they interact. In this context, sites may represent functional groups within molecules that are responsible for the interactions they participate in. Classic examples are binding sites, phosphorylation sites, methylation sites, etc. In particular, agents may form weak inter-molecular *bonds* between sites. These bonds are also called *links* and together with agents they define *site graphs* representing the network-topological structure of molecular complexes.

In rule-based modeling, reactions are replaced by rules. Unlike reactions, rules operate on patterns in the *sub-structure* of chemical species rather than on the species as a whole. A single rule can thereby capture a set of multiple chemical reactions, potentially even infinitely many. However, the above-mentioned rule-based languages do not offer direct support for describing the *geometric structure* of agents and their link structure in *three-dimensional space*. Hence, steric effects that constrain molecular interactions are not easily translated into rule-based languages, and it is not clear if it is always possible to do so.

In this paper we present *geometrically enhanced Kappa*, a minimalistic extension to the Kappa language. As in Kappa, chemical species are represented by *site graphs* and modified through *site graph rewriting rules*. In addition, our extension allows for the annotation of individual agents, sites and links, with radii, positions and orientations, respectively, which introduces implicit rigidity constraints on the corresponding site graphs. Rewrite rules may include updates to the geometric annotations of a site graph in order to capture conformational changes of a molecular complex.

Our extension is only concerned with geometric *realizability* or *soundness* of molecular complexes and not with modeling the evolution of their physical embedding in three-dimensional euclidean space. In particular, we do not track the absolute positions and orientations of agents and therefore can not handle diffusion or collision processes explicitly. Instead we retain the assumption of a well-stirred mixture from classical, geometry-less Kappa. In fact, our framework for geometri-

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cally enhanced site graph rewriting contains geometry-less Kappa as a particular subset, and we show that for our restricted set of geometric annotations, simulations remain tractable, and indeed can be implemented using a slightly modified version of the known efficient Kappa simulation algorithm [8].

Geometric constraints can, in principle, relate and propagate the positions and orientations of agents over arbitrary distances, for example in macro-molecular complexes such as polymer chains. Our extension thereby violates a core principle of classical Kappa, namely that rules can only make local changes to the state of a system. To make this idea more precise, we give a formal definition of *locality* for Kappa models, which captures the intuition that the effects of a locally acting rule on the geometric constraints of a site graph should not extend beyond a fixed, finite radius δ around the substructure modified by the rule. We show that there are indeed geometrically enhanced Kappa models that are non-local, meaning that no such δ exists for these models. We also show that, for purely local models, it is always possible to translate a geometrically enhanced model into a geometry-less model, albeit at the cost of increasing the number of rules of the model exponentially. This further exemplifies the importance of non-locality for our extension. Finally, we show that, in general, it is not decidable whether a model is local, and hence whether the said reduction from a geometrically enhanced model into a geometry-less model is possible.

The principal motivation for developing this extension was to find a basic framework to describe processes such as the self-assembly of protein complexes [12,16,18,15], where agents may be thought of as having a fixed-size volume, sites with fixed sets of possible positions with respect to the center of mass of the agent, and links with fixed orientations relative to the interacting agents. This is the case, for instance, in the assembly of the proteasome, whose structure consists of four stacked heptameric rings (see Figure 1). In this protein complex, interactions between the monomers have a particular geometry that we will revisit later.

Finally, we also expect this work to serve as a formal starting point for the development and implementation of more advanced extensions for modeling spatial aspects such as more generalized steric constraints, diffusion and compartmentalization, or coarse-grained molecular dynamics in rule-based languages, to be explored in future work.

1.1 Related work

In [14] Gruenert et al. introduce an approach to simulating combinatorially complex chemical systems by combining a coarse-grained, particle-based spatial simulation with a rule-based language for triggering association and dissociation events between particles. Unlike in our approach, the simulation not only handles steric constraints, but tracks and updates the positions of individual particles according to a combination of force field and diffusion terms that simulate the interactions between particles and their Brownian motion, respectively.

Another particle-based simulator for biological systems is BioShape [4]. BioShape is a scale-independent simulation environment based on a process algebra

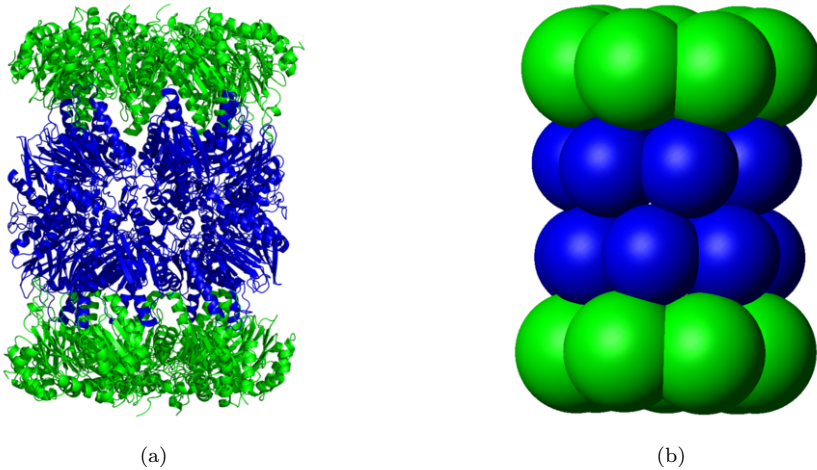


Figure 1. (a) Structure of the yeast proteasome 20S core particle (PDB ID 1RYP). Image created using PyMol. (b) Schematic diagram of the proteasome structure. The catalytic β subunits that comprise the inner two rings are shown in blue and the α subunits making up the two outer rings are shown in green. Image taken from Wikipedia.

for systems biology, the Shape Calculus [1], in which every process is assigned a position, velocity and mass. Processes move according to physical laws and can collide with and bind to other processes depending on their communication on certain channels.

A different approach to describing spatial phenomena using a processes algebra is Cardelli and Gardner’s 3π [5]. 3π is a geometric process algebra that combines the interaction primitives of the π -calculus with geometric transformations. Processes in 3π are localized and move explicitly through frame shift operations. 3π is a powerful process algebra but does not offer any direct support for biological modeling: geometric constraints between processes or laws of motion have to be implemented explicitly. There is also no notion of time-flow, although one could easily be adapted, for example from the stochastic π -calculus.

The rest of this paper is structured as follows: in section 2 we define geometrically enhanced Kappa and its stochastic semantics and outline a basic simulation algorithm. In section 3 we introduce the notion of locality, give examples of local and non-local Kappa models, show that locality is undecidable in general, and finally show how to reduce local models to geometry-less models. Section 4 contains some concluding remarks and outlines future work.

2 Geometrically enhanced Kappa

We will now introduce our extension to Kappa as a simple categorical language. The definitions given below are, for the most part, direct extensions of those given in [17] and [10]. The reader that is somewhat familiar with the Kappa language will recognize many of the concepts introduced here, such as *contact graphs*, *site graphs* and *embeddings*, as variations of those used in classic, geometry-less Kappa.

2.1 Notation

Given a family of sets $(A_i, i \in I)$, we write $\sum_{i \in I} A_i$ for their disjoint union, that is, $\bigcup_{i \in I} \{(x, i) : x \in A_i\}$. We write $A - B$ for the set difference of two sets A and B or the relative complement of B in A , $\mathcal{P}(A)$ for the power set of A , that is, the set of subsets of A , and A_\star for the disjoint union $A + \{\star\}$ that adds a “stub” \star to A .

If $f : A \rightarrow B$ is a map from A to B , we write $f(A) \subseteq B$ for its image (or range). If f is partial, we write $\text{dom}(f) \subseteq A$ for its domain of definition. If $A' \subseteq A$ is a subset of the domain of f , we write $f|_{A'}$ for the restriction of f to A' , that is $f|_{A'} : A' \rightarrow B, x \mapsto f(x)$. We write 1_A for the identity map from A to itself.

If $R \subseteq A \times B$ is a binary relation between two sets A and B , we sometimes treat it as a partial map $R : A \rightarrow \mathcal{P}(B)$ and write $\text{dom}(R) \subseteq A$ for its domain of definition, that is, $\text{dom}(R) = \{a \in A : R(a) \neq \emptyset\}$, and $R(A)$ for its image. Similarly, we often treat partial maps $f : A \rightarrow \mathcal{P}(B)$ and $g : A \rightarrow B$ as relations $f \subseteq A \times B$ and functional relations $g \subseteq A \times B$, respectively.

Definition 2.1 A *partial pairing* on a set A is an irreflexive, symmetric and one-to-one binary relation on A , that is, every element of A is in relation with at most one other element in A and no element in A is in relation with itself.

2.2 Contact graphs and site graphs

Definition 2.2 A *contact graph* is a tuple $C = (\mathcal{A}, \mathcal{S}, \mathcal{I}, \Sigma, \Lambda, I, P, \mathcal{S}, \Omega)$, where

- \mathcal{A}, \mathcal{S} and \mathcal{I} are finite sets of *agent types*, *site names* and *internal state names*, respectively,
- $\Sigma : \mathcal{A} \rightarrow \mathcal{P}(\mathcal{S})$ assigns sets of site names to agent types,
- $\Lambda \subseteq (\Sigma_\star)^2 - \{(\star, \star)\}$ is a symmetric binary relation that represents possible *links* between sites,
- $I : \Sigma \rightarrow \mathcal{P}(\mathcal{I})$ assigns sets of *internal state names* to sites,
- $P : \mathcal{A} \rightarrow \mathcal{P}(\mathbb{R})$ assigns finite sets of *radii* to agent types,
- $\mathcal{S} : \Sigma \rightarrow \mathcal{P}(\mathbb{R}^3)$ assigns finite sets of *positions* to sites, and
- $\Omega : (\Lambda \cap \Sigma^2) \rightarrow \mathcal{P}(\text{SO}(3))$ assigns finite sets of *orientations* to links (A, a, B, b) , such that

$$\mathbf{O} \in \Omega(A, a, B, b) \Leftrightarrow \mathbf{O}^{-1} \in \Omega(B, b, A, a).$$

We refer to $\Sigma(A)$ as the *signature* of an agent type $A \in \mathcal{A}$, and to Σ and Λ as the *collective signature* and *link structure* of the contact graph C , respectively. We often treat the collective signature Σ and the link structure Λ of a contact graph as sets of pairs and quadruples, respectively (that is, as the graphs of the corresponding relations) as in the definitions of Λ, I, \mathcal{S} and Ω above. We call P, \mathcal{S} and Ω the *agent, site and link geometry*, respectively, of C and the combined map (P, \mathcal{S}, Ω) the *geometry* of C .

Definition 2.3 A *site graph* is a tuple $s = (V, C, \Gamma, \lambda, \iota, \rho, \mathbf{s}, \boldsymbol{\omega})$, where

- V is a finite set of *agents*,

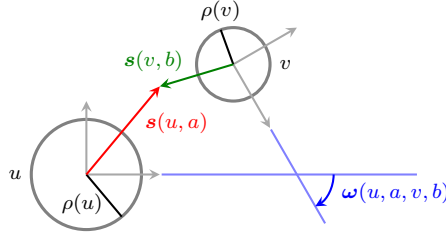


Figure 2. Geometry of a site graph. The circles represent agents $u \in V$ and $v \in V$, the gray arrows represent their frame of reference (or orientation). The sites $a \in \sigma(u)$ and $b \in \sigma(v)$ (and their positions $s(u, a), s(v, b)$) are represented by colored arrows. The presence of a link (u, a, v, b) forces the absolute position of the sites (u, a) and (v, b) to coincide.

- C is a contact graph,
- $\Gamma : V \rightarrow \mathcal{A}$ is map assigning *types* to agents,
- $\sigma = \Sigma \circ \Gamma$ assigns sets of site names to agents,
- $\lambda \subseteq (\sigma_\star)^2 - \{(\star, \star)\}$ is a partial pairing that represents *links* between sites,
- $\iota : \sigma \rightarrow \mathcal{I}$ is a partial map that assigns *internal states names* to sites,
- $\rho : V \rightarrow \mathbb{R}$ is a partial map that assigns *radii* to agents,
- $s : \sigma \rightarrow \mathbb{R}^3$ is a partial map that assigns *positions* to sites,
- $\omega : (\lambda \cap \sigma^2) \rightarrow \text{SO}(3)$ is a partial map that assigns *orientations* $\omega(u, a, v, b)$ to links (u, a, v, b) , such that

$$(u, a, v, b) \in \text{dom}(\omega) \Rightarrow \omega(v, b, u, a) = \omega(u, a, v, b)^{-1}.$$

We call Γ the *contact map* of s . A site graph s with contact map Γ is said to be *well-defined* or *well-typed* if

- (i) Γ preserves links: $(u, a) \lambda (v, b) \Rightarrow (\Gamma(u), a) \Lambda (\Gamma(v), b)$,
- (ii) Γ preserves stubs: $(u, a) \lambda \star \Rightarrow (\Gamma(u), a) \Lambda \star$,
- (iii) Γ preserves internal states: $(u, a) \in \text{dom}(\iota) \Rightarrow \iota(u, a) \in I(\Gamma(u), a)$,
- (iv) Γ preserves agent geometry: $\rho \subseteq P \circ \Gamma$,
- (v) Γ preserves site geometry: $(u, a) \in \text{dom}(s) \Rightarrow s(u, a) \in \mathcal{S}(\Gamma(u), a)$, and
- (vi) Γ preserves link geometry:

$$(u, a, v, b) \in \text{dom}(\omega) \Rightarrow \omega(u, a, v, b) \in \Omega(\Gamma(u), a, \Gamma(v), b).$$

We will only consider well-defined site graphs hereafter.

We refer to σ and λ as the *collective interface* and *link structure* of s , respectively, and we call $\sigma(u)$ the *interface* of an agent u . For an agent u and a site $a \in \sigma(u)$, we say (u, a) is *bound* if $\exists(v, b) : (u, a) \lambda (v, b)$. Conversely, we say that (u, a) is *free* or (u, a) has a *stub* if $(u, a) \lambda \star$. We call ρ, s and ω the *agent, site and link geometry*, respectively, of s and the combined map (ρ, s, ω) the *geometry* of s . The position $s(u, a)$ of a site (u, a) is specified relative to the position and orientation of the agent u . If the orientation $\omega(u, a, v, b)$ of a link $(u, a, v, b) \in \lambda$ is defined, the sites (u, a)

and (v, b) are considered aligned, and $\omega(u, a, v, b)$ corresponds to the orientation of v relative to u . Figure 2 illustrates the various components of the geometry of a site graph.

Two agents u and v of a site graph s are said to be *connected* if there is a *path* $(u, a) \lambda (w_1, c_1), (w_1, c'_1) \lambda (w_2, c_2), \dots, (w_N, c'_N) \lambda (v, b)$ in s connecting u and v . A site graph s is connected if every pair of agents $(u, v) \in V^2$ in s is connected.

Definition 2.4 A site graph $(V, C, \Gamma, \lambda, \iota, \rho, \mathbf{s}, \omega)$ is said to be *complete* if its collective interface, link structure, state map and geometry are all maximal with respect to its contact graph, that is,

- $(\Gamma(u), a) \in \text{dom}(\Lambda) \Rightarrow (u, a) \in \text{dom}(\lambda)$,
- $(\Gamma(u), a) \in \text{dom}(I) \Rightarrow (u, a) \in \text{dom}(\iota)$,
- $\text{dom}(\rho) = \text{dom}(P \circ \Gamma)$,
- $(\Gamma(u), a) \in \text{dom}(\mathbf{S}) \Rightarrow (u, a) \in \text{dom}(\mathbf{s})$,
- $(\Gamma(u), a, \Gamma(v), b) \in \text{dom}(\Omega) \Rightarrow (u, a, v, b) \in \text{dom}(\omega)$.

A site graph that is not complete is said to be *partial*.

Note that the link state $\lambda(u, a)$ or internal state $\iota(u, a)$ of a site (u, a) may be left undefined in a complete site graph as long as the set of possible link states $\Lambda(\Gamma(u), a)$ or internal states $I(\Gamma(u), a)$ of the corresponding site $(\Gamma(u), a)$ in the contact graph are empty. Similarly, a complete geometrically enhanced site graph needs not have all its geometry defined as long as the corresponding piece of geometry is undefined in the contact graph. This allows us to treat ordinary, geometry-less site graphs such as those defined in [8] as just a special case of geometrically enhanced site graphs. It also allows us to model semi-rigid structures, that is, structures where only certain substructures are subject to rigid geometric constraints.

Let us now have a look at some examples of contact and site graphs. Our first example introduces a set of simple, small graphs that we will build upon throughout this section to illustrate the various concepts from the theory of geometrically enhanced site graphs.

Example 2.5 Consider the following definitions of a contact graph C and two site graphs t and s :

$$\begin{aligned}
 C &= \left(\begin{array}{l}
 \mathcal{A} = \{A\}, \mathcal{S} = \{l, r\}, \mathcal{I} = \emptyset, \Sigma = \{A \mapsto l, A \mapsto r\}, \\
 \Lambda = \{(A, l, A, r), (A, r, A, l)\} \cup \Sigma \times \{\star\} \cup \{\star\} \times \Sigma, I = \emptyset, \\
 P = \{A \mapsto 1\}, \mathbf{S} = \{(A, l) \mapsto (-2, 0, 0), (A, r) \mapsto (2, 0, 0)\}, \\
 \Omega = \{(A, l, A, r) \mapsto \{\mathbf{1}, \mathbf{R}_z(\frac{\pi}{2})\}, (A, r, A, l) \mapsto \{\mathbf{1}, \mathbf{R}_z(-\frac{\pi}{2})\}\}
 \end{array} \right), \\
 t &= \left(\begin{array}{l}
 V_t = \{u\}, C, \Gamma_t = \{u \mapsto A\}, \sigma_t = \Sigma \circ \Gamma_t, \\
 \lambda_t = \sigma_t \times \{\star\} \cup \{\star\} \times \sigma_t, \iota_t = \emptyset, \rho_t = \{u \mapsto 1\}, \\
 \mathbf{s}_t = \{(u, l) \mapsto (-2, 0, 0), (u, r) \mapsto (2, 0, 0)\}, \omega_t = \emptyset
 \end{array} \right), \\
 s &= \left(\begin{array}{l}
 V_s = \{u, v\}, C, \Gamma_s = \{u \mapsto A, v \mapsto A\}, \sigma_s = \Sigma \circ \Gamma_s, \\
 \lambda_s = \{(u, l, \star), (v, r, \star), (\star, u, l), (\star, v, r)\}, \\
 \iota_s = \emptyset, \rho_s = \{u \mapsto 1, v \mapsto 1\}, \\
 \mathbf{s}_s = \{(u, l) \mapsto (-2, 0, 0), (v, r) \mapsto (2, 0, 0)\}, \omega_s = \emptyset
 \end{array} \right),
 \end{aligned}$$

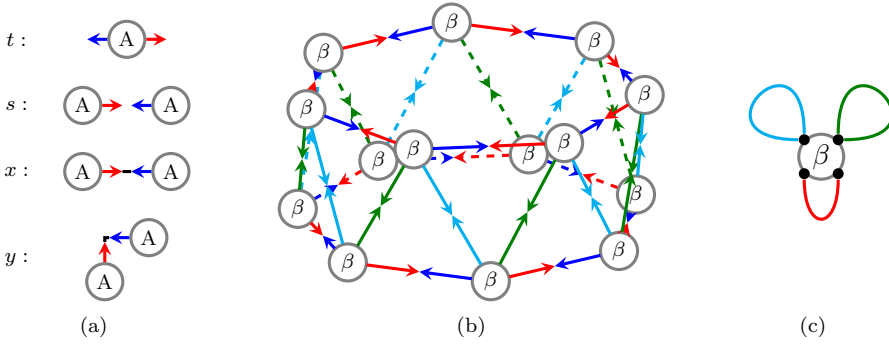


Figure 3. Examples of contact graphs and site graphs.

$$\begin{aligned}
 x &= \left(V_s, C, \Gamma_s, \sigma_s, \lambda_x = \{(u, l, v, r), (v, r, u, l)\}, \iota_s, \rho_s, \mathbf{s}_s \right), \\
 &\quad \omega_x = \{(u, l, v, r) \mapsto \mathbf{1}, (v, l, u, r) \mapsto \mathbf{1}\} \\
 y &= \left(V_s, C, \Gamma_s, \sigma_s, \lambda_y = \{(u, l, v, r), (v, r, u, l)\}, \iota_s, \rho_s, \mathbf{s}_s \right), \\
 &\quad \omega_y = \{(u, l, v, r) \mapsto \mathbf{R}_z(\frac{\pi}{2}), (v, r, u, l) \mapsto \mathbf{R}_z(-\frac{\pi}{2})\}
 \end{aligned}$$

with $\mathbf{1}$ the identity and $\mathbf{R}_z(\theta)$ the rotation of angle θ around the z axis.

Figure 3a illustrates the four site graphs s, t, x and y . Intuitively, the contact graph C enables the construction of linear chains with 90° turns. The site graph t represents a single, unconnected agent, while s represents a pair of agents that could be linked to form a chain of length two. Note that the link state of sites $r \in \sigma(u)$ and $l \in \sigma(v)$ of the agents u and v in s are undefined. The two site graphs x and y are examples of a linear extension and a turn, respectively. t, x and y are all connected, while s is not. t is complete, while s, x and y are not.

Now, let us have a look at a somewhat more involved system, namely the two inner rings of the proteasome. A possible site graph representation of this structure is shown in figure 3b.

Example 2.6 In a model of the assembly of the two inner heptameric rings formed by the β subunits of the proteasome, a geometry-less contact graph like the one shown in figure 3c would be an obvious choice. We extend this contact graph by adding the corresponding geometries as follows:

$$C = \left(\begin{array}{l}
 \mathcal{A} = \{\beta\}, \mathcal{S} = \{l_t, r_t, l_b, r_b\}, \mathcal{I} = \emptyset, \Sigma = \{\beta \mapsto l_t, \beta \mapsto r_t, \beta \mapsto l_b, \beta \mapsto r_b\}, \\
 \Lambda = \{(\beta, l_t, \beta, r_t), (\beta, r_t, \beta, l_t), (\beta, l_b, \beta, l_b), (\beta, r_b, \beta, r_b)\} \cup \Sigma \times \{\star\} \cup \{\star\} \times \Sigma, \\
 \mathcal{I} = \emptyset, P = \{\beta \mapsto 1\}, \\
 \mathcal{S} = \left\{ \begin{array}{l}
 (\beta, l_t) \mapsto (-\cos \frac{\pi}{7}, \sin \frac{\pi}{7}, 0), \quad (\beta, r_t) \mapsto (\cos \frac{\pi}{7}, \sin \frac{\pi}{7}, 0), \\
 (\beta, l_b) \mapsto (-\frac{1}{2}, \frac{1}{2} \tan \frac{\pi}{14}, -1), \quad (\beta, r_b) \mapsto (\frac{1}{2}, \frac{1}{2} \tan \frac{\pi}{14}, -1) \end{array} \right\}, \\
 \Omega = \left\{ \begin{array}{l}
 (\beta, l_t, \beta, r_t) \mapsto \mathbf{R}_z(-\frac{2\pi}{7}), \quad (\beta, r_t, \beta, l_t) \mapsto \mathbf{R}_z(\frac{2\pi}{7}), \\
 (\beta, l_b, \beta, l_b) \mapsto \mathbf{R}_z(-\frac{\pi}{7}) \mathbf{R}_y(\pi), \quad (\beta, r_b, \beta, r_b) \mapsto \mathbf{R}_z(\frac{\pi}{7}) \mathbf{R}_y(\pi) \end{array} \right\}
 \end{array} \right).$$

The contact graph C allows us to build site graphs like the one shown in figure 3b. Indeed, the site graph of figure 3b is the *maximum sound site graph* that has C as its contact graph. We will define what it means for a site graph to be *sound* in section 2.6.

2.3 Embeddings

Definition 2.7 An *embedding* from a site graph x to another site graph y is a map $f : V_x \rightarrow V_y$ such that

- (i) f is injective.
- (ii) f preserves types: $\Gamma_x = \Gamma_y \circ f$,
- (iii) f preserves sites: $\sigma_x \subseteq \sigma_y \circ f$,
- (iv) f preserves links: $(u, a) \lambda_x (v, b) \Rightarrow (f(u), a) \lambda_y (f(v), b)$,
- (v) f preserves stubs: $(u, a) \lambda_x \star \Rightarrow (f(u), a) \lambda_y \star$,
- (vi) f preserves states: $(u, a) \in \text{dom}(\iota_x) \Rightarrow \iota_x(u, a) = \iota_y(f(u), a)$,
- (vii) f preserves agent geometry: $\rho_x \subseteq \rho_y \circ f$,
- (viii) f preserves site geometry: $(u, a) \in \text{dom}(\mathbf{s}_x) \Rightarrow \mathbf{s}_x(u, a) = \mathbf{s}_y(f(u), a)$,
- (ix) f preserves link geometry:

$$(u, a, v, b) \in \text{dom}(\omega_x) \Rightarrow \omega_x(u, a, v, b) = \omega_y(f(u), a, f(v), b).$$

We write $[x; y]$ for the set of embeddings from x to y . When $f \in [x; y]$, we write $x \xrightarrow{f} y$ and say that y embeds x or that x is embedded in y via f . We write $f(x)$ for y , the target site graph of $f \in [x; y]$, not to be confused with the image of f , $f(V_x) \subseteq V_y$.

Together, site graphs and their embeddings form the *category GS* of *geometrically enhanced site graphs*, with site graphs as objects and embeddings as arrows. In the rest of this document, we will use the terms object and site graph interchangeably, as well as the terms embedding, morphism and arrow.

The notion of an embeddings gives us a straight-forward way to define *subgraphs* in the category **GS**:

Definition 2.8 A site graph t is a *site subgraph* of a site graph s , denoted $t \subseteq s$, if $V_t \subseteq V_s$ and $t \xrightarrow{1_{V_t}} s$. A site subgraph is said to be *minimal* for some property P if, for every other site subgraph $t' \subseteq s$ for which P holds, $t' \subseteq t$ implies $t' = t$, and *maximal* for P if, $t \subseteq t'$ implies $t = t'$. A site subgraph $s[W] \subseteq s$ is said to be *induced* if it is maximal given its agent set $V_{s[W]} = W$. A site graph $t \subseteq s$ is a *connected component* of s if it is a maximal connected site subgraph of s .

At this point it seems appropriate to note that, although many graph-theoretical concepts, such as subgraphs, connected components, paths, etc. extend in an intuitive manner to site graphs, the category of site graphs also has a few somewhat surprising properties due to the restriction of one link per site and the injectivity of morphisms. One such property is *rigidity*:

Lemma 2.9 (rigidity) *Let x and y be site graphs and suppose x is connected, then any non-empty partial injection f from V_x to V_y extends to at most one embedding in $[x; y]$.*

This is a known result from the theory of geometry-less site graphs, which extends unchanged to geometrically enhanced site graphs. We refer the interested reader to [17,10] for the proof. One consequence of lemma 2.9, is that there is a polynomial-time algorithm for computing the number of embeddings $||s; x||$ of a connected site graphs s in a site graph x , that is, to count the number of site subgraphs in x that are *isomorphic* to s . This is at the heart of the efficient simulation algorithm for Kappa models presented in [8].

We denote by \mathbf{GS}_C the subcategory of site graphs with contact graph C . Most of the definitions in the rest of our presentation of geometrically enhanced Kappa will be formulated with respect to a given \mathbf{GS}_C rather than \mathbf{GS} . This restriction reflects the intuition that, in the context of some biochemical process, the active sites of a given type of elementary molecule (represented by the interface $\Sigma(A)$ of some agent type $A \in \mathcal{A}_C$), its set of potential configurations ($I(A)$, $P(A)$, $\mathbf{S}(A)$), as well as its potential interactions with other types of molecules ($\Lambda(A)$, $\Omega(A)$) are all fixed, irrespective of where and how the particular instances of A are embedded in some molecular complex.

2.4 Actions and rules

In order to define rewriting rules on site graphs, we need to be able to relate the site graphs before and after the application of a given rule. One option would be to extend one of the classic semantic approaches from graph rewriting, such as double or single pushout rewriting, which have been defined for geometry-less Kappa [6,10]. Instead, we will adopt the more syntactic concept of an *action script* as a sequence of atomic rewrite instruction, which has been used more extensively in the Kappa literature [8,17].

Definition 2.10 An *atomic action* α on a site graph s in \mathbf{GS}_C is one of the following:

- a subgraph addition $+t$ of a complete site graph t in \mathbf{GS}_C ,
- a subgraph deletion $-t$ of a complete site graph t in \mathbf{GS}_C ,
- a link addition $+(u, a, v, b, \mathbf{Q})$ with orientation $\mathbf{Q} \in \Omega(u, a, v, b)_*$,
- a link deletion $-(u, a, v, b)$,
- a state change $\iota(u, a) \leftarrow p$ to $p \in I(u, a)$,
- a change of radius $\rho(u) \leftarrow r$ to $r \in P(u)$,
- a change of site position $\mathbf{s}(u, a) \leftarrow \mathbf{p}$ to $\mathbf{p} \in \mathbf{S}(u, a)$, or
- a change of link orientation $\omega(u, a, v, b) \leftarrow \mathbf{O}$ to $\mathbf{O} \in \Omega(u, a, v, b)$,

with $u \in V_s$, $v \in V_s$, $a \in \sigma_s(u)$ and $b \in \sigma_s(v)$.

An *action* $\alpha = (\alpha_1, \alpha_2, \dots, \alpha_N)$ is a sequence of atomic actions α_i on $(\alpha_{i-1} \cdot \alpha_{i-2} \cdots \alpha_1 \cdot s)$.

Link additions and deletions are symmetric. We denote by $\alpha \cdot s$ the *result* of an atomic action α on s in \mathbf{GS}_C . An action α on s is well-defined if its result $\alpha \cdot s$ is

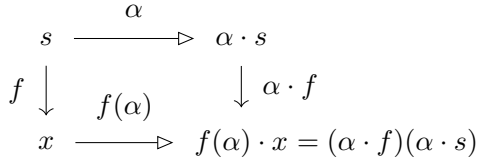


Figure 4. Diagram relating the various objects, arrows and actions defined on s , α , x and f .

a well-defined site graph. The parameter \mathbf{Q} of a well-defined link addition may be $\mathbf{Q} = \star$ iff $\Omega(u, a, v, b) = \emptyset$, in which case $\omega_{\alpha \cdot s}(u, a, v, b)$ remains undefined. Link deletion are only well-defined for complete links. We only consider well-defined actions hereafter. A formal definition of the result of an action can be found in appendix A.1.

Given an embedding $f \in [s; x]$ between two site graphs s and x in \mathbf{GS}_C , we define the *transport* $f(\alpha)$ of an atomic action α along f as the sequence of atomic actions $f(\alpha_i)$, such that every $f(\alpha_i)$ performs the analogue of the action α_i on the corresponding site subgraph of the image of s in x (see appendix A.2 for a formal definition).

If s and x are both site graphs in \mathbf{GS}_C , α is a well-defined action on s , and $f \in [s; x]$, then the above definitions ensure that

- (i) the transport $f(\alpha)$ of α along f is well-defined,
- (ii) there is an *inverse action* α^{-1} such that $\alpha^{-1} \cdot \alpha \cdot s = s$,
- (iii) if x is complete, then so is $f(\alpha) \cdot x$,
- (iv) there is a unique map $(\alpha \cdot f) \in [\alpha \cdot s; f(\alpha) \cdot x]$ called the *result* of the action α on f , such that $(\alpha \cdot f)(\alpha \cdot s) = f(\alpha) \cdot x$ (see A.3 for details).

Figure 4 illustrates the various objects, arrows and actions defined on s , α , x and f . Using the above definitions, we can now define the rules of our site graph rewriting system.

Example 2.11 Let t , s , x and y be as defined in example 2.5, then we can define two actions α_1 and α_2 as follows:

$$\alpha_1 = +(u, l, v, r, \mathbf{1}), \quad \alpha_2 = \left(+ \left(u, l, v, r, \mathbf{R}_z \left(-\frac{\pi}{2} \right) \right), +t \right).$$

Then α_1 is an atomic action defined on s that adds a straight link to s , that is, $\alpha_1 \cdot s = x$. α_2 is a non-atomic action defined on s that first adds a link (a 90° turn) to s and then adds the subgraph t , that is, $\alpha_2 \cdot s = +t \cdot y$.

Definition 2.12 A *rule* is a triple $r = (s, \alpha, k)$, where s is a site graph, α is an action defined on s and $k \in \mathbb{R}_0^+$ is a rate.

Example 2.13 Let t and s be defined as in example 2.5, and α_1 , α_2 as defined in example 2.11, then we can define two rules r_1 and r_2 as follows:

$$r_1 = (s, (\alpha_1, +t), k_1), \quad r_2 = (s, \alpha_2, k_2).$$

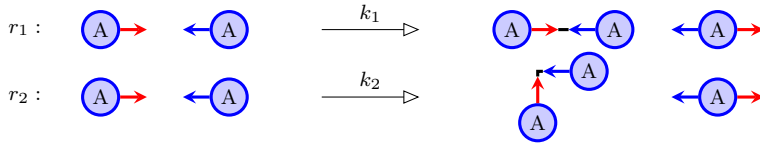


Figure 5. Diagram representing the rule set of example 2.13.

Finally, we are ready to define our notion of a geometrically enhanced Kappa model.

Definition 2.14 A *Kappa model* is a pair $K = (x_0, R)$ with x_0 a complete site graph in \mathbf{GS}_{C_K} called the *initial state* of K , and $R = \{r_1, r_2, \dots, r_N\}$ a finite set of rules $r_i = (s_i, \alpha_i, k_i)$ called the *rule set* of K , with left-hand sides s_i in \mathbf{GS}_{C_K} .

For simplicity, we will write \mathbf{GS}_K instead of \mathbf{GS}_{C_K} hereafter.

Example 2.15 Let C, t, s, r_1 and r_2 be defined as in example 2.13. Then we can define the Kappa model $K = (x_0, R)$ with initial state $x_0 = +t \cdot t$ and rule set $R = \{r_1, r_2\}$.

2.5 Events and probabilities

Every Kappa model K has an associated Weighted Labeled Transition System (WLTS) [13] on complete site graphs:

Definition 2.16 Let $r = (s, \alpha, k)$ be a rule, R be a set of rules and x be a complete site graph. We define

- the set of events in x associated with r as $\mathcal{E}(x, r) = [s; x]$,
- the set of events in x associated with R as $\mathcal{E}_R(x) = \sum_{r \in R} \mathcal{E}(x, r)$,
- the activity of r in x as $\mathbf{a}(x, r) = k |[s; x]|$, and
- the activity of R in x as $\mathbf{a}_R(x) = \sum_{r \in R} \mathbf{a}(x, r)$.

This defines a WLTS $\mathcal{W}_K = (\mathcal{K}_K, \mathcal{E}_R, w, \pi_0)$ for every Kappa model $K = (x_0, R)$, with

- *state space* $\mathcal{K}_K \subseteq \mathbf{GS}_K$, the class of complete site graphs in \mathbf{GS}_K ,
- *labels* $\mathcal{E}_R = \sum_{x \in \mathcal{K}_K} \mathcal{E}_R(x)$, the set of events in \mathcal{K}_K associated with R ,
- *weight function* $w : \mathcal{E}_R \times \mathcal{K}_K \rightarrow \mathbb{R}_0^+$ defined as

$$w(x, e, x') = \begin{cases} k & \text{if } e = ((s, \alpha, k), f) \in \mathcal{E}_R(x) \text{ and } x' = f(\alpha) \cdot x, \\ 0 & \text{otherwise,} \end{cases}$$

- *initial probability distribution* $\pi_0 = \mathbf{1}_{\{x=x_0\}}$.

A transitions $x \xrightarrow{e} x'$, in \mathcal{W}_K has probability $\mathbf{P}\{x \xrightarrow{e} x'\} = \frac{w(x,e,x')}{\mathbf{a}_R(x)}$ if $\mathbf{a}_R(x) > 0$, and the subsequent time advance is an exponential random variable $\delta t(x)$ such that

$$\mathbf{P}\{\delta t(x) > t\} = e^{-\mathbf{a}_R(x)t}.$$

We write $x_1 \rightarrow^* x_N$ if there is a sequence of transitions

$$x_1 \xrightarrow{e_1} x_2 \xrightarrow{e_2} x_3 \xrightarrow{e_3} \dots \xrightarrow{e_{N-1}} x_N$$

in \mathcal{W}_K with $w(x_i, e_i, x_{i+1}) > 0$, and denote by $\text{reach}(K) \subseteq \mathcal{K}_K$ the set of *reachable states* of K : $\text{reach}(K) = \{x : x_0 \rightarrow^* x\}$.

2.6 Realizations and constraints

Definition 2.17 A *realization* $\pi : V \rightarrow \mathbb{R}^3 \times \text{SO}(3)$ of a geometrically enhanced site graph s is an embedding of s in three-dimensional euclidean space, that is, a map $u \mapsto (\mathbf{r}(u), \mathbf{R}(u))$ that assigns positions $\mathbf{r}(u)$ and orientations $\mathbf{R}(u)$ to agents $u \in V$.

Given a realization $\pi = (\mathbf{r}, \mathbf{R})$ of a site graph s , we call \mathbf{r} and \mathbf{R} the position map and orientation map of s , respectively. We can now define *geometric soundness constraints* for site graphs and Kappa models:

Definition 2.18 A site graph s with associated geometry $(\rho, \mathbf{s}, \boldsymbol{\omega})$ is said to be *sound* if and only if there is a realization $\pi = (\mathbf{r}, \mathbf{R})$ of s , such that

- for every link $(u, a, v, b) \in \lambda$ in the link structure of s , the geometry of $(u, a), (v, b)$ and (u, a, v, b) is consistent, that is,

$$\begin{aligned} \forall (u, a, v, b) \in (\text{dom}(\boldsymbol{\omega}) \cap \text{dom}(\mathbf{s})^2) : \\ \mathbf{R}(v) = \boldsymbol{\omega}(u, a, v, b)\mathbf{R}(u) \\ \mathbf{r}(v) + \mathbf{R}(v)\mathbf{s}(v, b) = \mathbf{r}(u) + \mathbf{R}(u)\mathbf{s}(u, a) \end{aligned}$$

and

- there are no collisions in s , that is,

$$\forall (u, v) \in \text{dom}(\rho)^2 : u \neq v \Rightarrow \|\mathbf{r}(u) - \mathbf{r}(v)\| \geq \rho(u) + \rho(v).$$

We denote by \mathbb{G} the set of site graphs that are geometrically sound and write $s \in \mathbb{G}$ if the site graph s is sound. We say that a Kappa model $K = (x_0, R)$ is geometrically sound, if its initial state x_0 is geometrically sound.

We say that a pair of agents (u, v) in a site graph s are *geometrically connected* if u and v are connected by a path composed of links (w, a, w', b) with completely specified geometries: $(w, a, w', b) \in (\text{dom}(\boldsymbol{\omega}) \cap \text{dom}(\mathbf{s})^2)$. We say s is geometrically connected if every pair $(u, v) \in V^2$ in s is geometrically connected. Let s be a site graph with geometrically connected components $\{c_1, c_2, \dots, c_N\}$, then we have

$$s \in \mathbb{G} \Leftrightarrow \forall i \leq N : c_i \in \mathbb{G},$$

because any agents that are not geometrically connected may be located arbitrarily far apart without violating any of the soundness constraints. It is easy to see that the system of equations in definition 2.18 becomes over-constrained if one fixes the position $\mathbf{r}(u_i)$ and orientation $\mathbf{R}(u_i)$ of an arbitrary agent u_i in every geometrically connected component c_i of s . This suggests a simple $O(n^2)$ algorithm (with $n = |\lambda_i|$) for computing the soundness $s \in \mathbb{G}$ of a site graph s : for every $c_i \subseteq s$

- (i) set $\mathbf{r}(u_i) = \mathbf{0}$ and $\mathbf{R}(u_i) = \mathbf{1}$ for an arbitrary agent $u_i \in V_i$,
- (ii) solve and check the soundness equations for the rest of $(\mathbf{r}, \mathbf{R})|_{V_i}$ by traversing c_i starting from u_i (in $O(|\lambda_i|)$ time),
- (iii) check for potential collisions in c_i (in $O(|V_i|^2)$ time).

See algorithm B.1 in appendix B for details.

Definition 2.19 Let $\mathcal{W}_K = (\mathcal{K}_K, \mathcal{E}_R, w, \pi_0)$ be the WLTS associated with the geometrically sound Kappa model $K = (x_0, R)$, then the *geometrically sound transition system* $\widehat{\mathcal{W}}_K$ is defined as the WLTS $\widehat{\mathcal{W}}_K = (\mathcal{K}_K, \mathcal{E}_R, w', \pi_0)$ with weight function $w' : \mathcal{E}'_R \times \mathcal{K}_K \rightarrow \mathbb{R}_0^+$ defined as

$$w(x, e, x') = \begin{cases} k & \text{if } e = ((s, \alpha, k), f) \in \mathcal{E}_R(x) \text{ and } x' = f(\alpha) \cdot x \text{ and } x' \in \mathbb{G}, \\ 0 & \text{otherwise.} \end{cases}$$

In other words, $\widehat{\mathcal{W}}_K$ is the WLTS with transitions $x \xrightarrow{(r,f)} f(\alpha_r) \cdot x$ restricted to those transitions in \mathcal{W}_K for which $f(\alpha_r) \cdot x$ is sound.

Provided we start out from a geometrically sound initial state x_0 , a geometrically sound transition system $\widehat{\mathcal{W}}_K$ will only evolve along trajectories whose states $x_0 \rightarrow^* x$ are also geometrically sound.

Using algorithm B.1 we can modify the well known simulation algorithm for Kappa systems [8] to efficiently simulate the $\widehat{\mathcal{W}}_K$ of any geometrically sound model K by generating a null-event (that is, time advance without a transition) whenever algorithm B.1 returns $f(\alpha_r) \cdot x \notin \mathbb{G}$ for some event (r, f) in state x .

3 Locality

In this section we will introduce the notion of *locality* of a Kappa model. The core idea behind locality is the following: a Kappa model $K = (x_0, R)$ is said to be *local* if it is possible to decide whether or not any event $((s, \alpha, k), f) \in \mathcal{E}_R(x)$ will produce a sound site graph $f(\alpha) \cdot x$ by inspecting only a finite amount of *context* around the image of the right-hand side $\alpha \cdot s$ in $f(\alpha) \cdot x$. Note that the distinction of local vs. non-local models only makes sense for geometrically enhanced Kappa, as all geometry-less site graphs are geometrically sound by definition, and hence events in geometry-less Kappa models can never produce geometrically unsound graphs. Indeed, the existence of non-local Kappa models is one of the fundamental differences between geometrically enhanced and geometry-less Kappa.

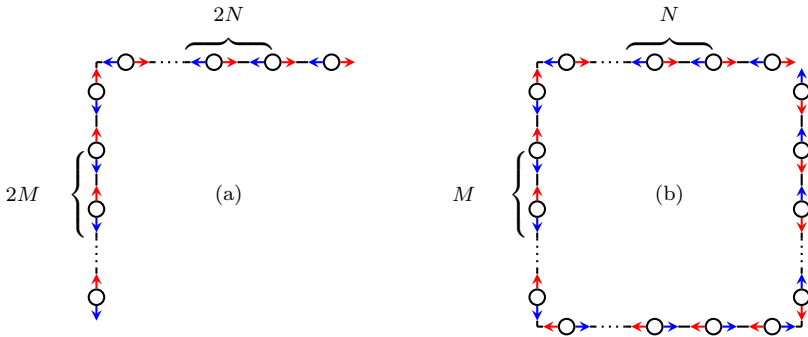


Figure 6. Possible states of the model K from example 2.15: (a) an open chain with $2(N + M) - 1$ links and one turn; (b) an almost closed chain with $2(N + M) - 1$ links but three turns.

In order to make the concept of locality more precise, we first need to define what exactly we mean by context. For this purpose, we will use the concept of a *closed ball* around a subset of agents in a site graph.

Definition 3.1 Given a pair of connected agents $(u, v) \in V^2$ of a site graph s , the *distance* $d(u, v)$ between u and v is defined as the length, that is, the minimum number of links, of the shortest path between u and v .

Definition 3.2 The *closed ball* $B_\delta(u, x)$ of radius δ around an agent $u \in V_x$ of a site graph x is defined as the set of agents $B_\delta(u, x) = \{v \in V_x : d(u, v) \leq \delta\}$ that lie within distance δ of u in x .

The *closed ball* $B_\delta(f)$ of radius δ around an embedding $f \in [s; x]$ is the induced site subgraph

$$B_\delta(f) = x \left[\bigcup_{u \in V_s} B_\delta(f(u), x) \right].$$

Definition 3.3 A Kappa model $K = (x_0, R)$ with initial state x_0 and rule set R is said to be δ -local for a finite radius $\delta \in \mathbb{N}$, if for every state $x \in \text{reach}(K)$ reachable in K , rule $(s, \alpha, k) \in R$ and embedding $f \in [s; x]$, the following holds

$$B_\delta(\alpha \cdot f) \in \mathbb{G} \Rightarrow f(\alpha) \cdot x \in \mathbb{G}.$$

K is called *local* if there exists a finite radius $\delta \in \mathbb{N}$ such that K is δ -local.

We denote by \mathbb{L}_δ the set of δ -local Kappa models and by $\mathbb{L} = \bigcup_i \mathbb{L}_i$ the set of local Kappa models.

Example 3.4 To see that there are indeed non-local Kappa models $K \notin \mathbb{L}$, consider the Kappa model $K = (x_0, R)$, as defined in example 2.15:

After n events, a state $x_n \in \text{reach}(K)$ of this model consists of two or more connected components that are either *free agents* t of type A , *open chains* c_m , $m \leq n$ of $m + 1$ agents w_i of type A with adjacent agents w_i and w_{i+1} linked through m links (w_i, l, w_{i+1}, r) , or *loops*, that is chains that have been closed. A given state x_n can contain many loops, but at most two free agents t , or a single free agent t and a single open chain c_m . Most events will connect the single free

agent t to the existing chain c_m producing a new chain c_{m+1} . Events involving rule r_1 create a straight extension at one of the ends of the existing chain c_m , while rule r_2 creates a left or right turn at the l -end or r -end, respectively, of c_m . Both r_1 and r_2 also create a new free agent t for the further extension of c_{m+1} . Occasionally, the model will produce chains $c_{2N+2M-1}$, such as shown in figure 6b, that can be closed into a *rectangular loop* $r_{N,M}$ of dimensions $N \times M$ by the event $(r_2, f = \{u \mapsto w_{2N+2M-1}, v \mapsto w_0\})$.

Given any $\delta \in \mathbb{N}$, let $x_{2\delta+1} = +t \cdot c_{2\delta+1}$ be a site graph where $c_{2\delta+1}$ is a chain as shown in figure 6a with $N = \delta$ and $M = 1$, and let $f_{2\delta+1} = \{u \mapsto w_{2\delta+1}, v \mapsto w_0\}$ with $w_{2\delta+1}$ and w_0 the agents at the l -end and r -end of $c_{2\delta+1}$, respectively. Clearly, $x_{2\delta+1} \in \text{reach}(K)$ and $f_{2\delta+1} \in \mathcal{E}(x_{2\delta+1}, r_2)$. Assume we apply $f_{2\delta+1}(\alpha_2)$ to $x_{2\delta+1}$, that is, we attempt to close the chain $c_{2\delta+1}$. Then the resulting site graph $f_{2\delta+1}(\alpha_2) \cdot x_{2\delta+1}$ must be unsound, as the chain $c_{2\delta+1}$ has too few turns to be closed (only chains with three or more turns, such as the chain in figure 6b, can be closed). However, the closed ball $B_\delta(\alpha_2 \cdot f_{2\delta+1})$ is sound, as it is *not closed* (the agent w_δ is missing from $B_\delta(\alpha_2 \cdot f_{2\delta+1})$). We conclude that

$$\forall \delta \in \mathbb{N} : B_\delta(\alpha_2 \cdot f_{2\delta+1}) \in \mathbb{G} \wedge f(\alpha_2) \cdot x_{2\delta+1} \notin \mathbb{G},$$

and therefore $K \notin \mathbb{L}$.

3.1 Sufficient conditions for locality

The following are sufficient conditions for the locality of a model K :

- (i) *A model K is local if its contact graph C_K is acyclic.* As we have seen in section 2.6, a site graph x is sound if all its connected components $c \subseteq x$ are sound. If C_K is acyclic, then no connected component c can have more agents than there are agent types in C_K , that is, $|V_c| \leq |\mathcal{A}_K|$. Hence no rule of $(s, \alpha, k) \in R_K$ can affect any agent at a distance greater than $\delta = |\mathcal{A}_K|$ around its left-hand side s , and it follows that K is $|\mathcal{A}_K|$ -local.
- (ii) *K is local if*

$$\begin{aligned} \exists \delta \in \mathbb{N} \forall x \in \mathcal{K}_K \forall (s, \alpha, k) \in R \forall f \in [s; x] : \\ B_\delta(\alpha \cdot f) \in \mathbb{G} \Rightarrow f(\alpha) \cdot x \in \mathbb{G}. \end{aligned}$$

Since $\text{reach}(K) \subseteq \mathcal{K}_K$, the above statement is simply a stronger version of locality. We say that K is *local with respect to its contact graph* if it fulfills the above condition. An example of a model that is local with respect to its contact graph is a modified version K' of the model K from example 3.4, with the rule r_1 and the straight extension in Ω_K removed. The possible connected components of any complete site graphs $x \in \mathcal{K}_{K'}$ are free agents t , chains c_1, c_2, c_3 with one to three turns, respectively, and rectangles $r_{1,1}$. Hence $K' \in \mathbb{L}_4$.

An example of a model that is *not* local with respect to its contact graph but still in \mathbb{L} would be another modified version K'' of the model from example 3.4, where we replace the initial state x_0 by $x_1 = +t \cdot c_1$, with c_1 a chain of two agents

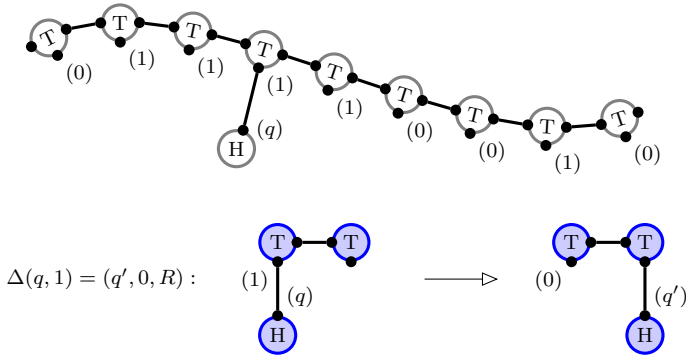


Figure 7. Simulating Turing machines using Kappa models. The configurations of the Turing machine are represented by complete site graphs (the states of the model), while the transition function Δ is represented by the rule set of the model.

connected by a straight link and t a single free agent, and we refine the left-hand side of the rules r_1 and r_2 , such that the new left-hand sides s_1 and s_2 match exactly the two agents at the free end of a chain that are connected by a turn and a straight extension, respectively. The possible connected components of any state $x \in \text{reach}(K'')$ are free agents, chains c_1 to c_7 , with straight extensions and turns interleaved, and rectangles $r_{2,2}$. Thus $K'' \in \mathbb{L}_8$. However, the class $\mathcal{K}_{K''} = \mathcal{K}_K$ is identical to that of the model K from example 3.4, and hence K'' can not be local with respect to its contact graph.

3.2 Undecidability of locality

Proposition 3.5 (undecidability) *The set of local Kappa models \mathbb{L} is undecidable.*

We will not give a full proof of proposition 3.5 here, but rather a proof sketch.

Proof sketch The proof is by many-one reduction from the halting problem. We will assume that we can fix a suitable Gödel numbering for Kappa models such that they can be manipulated by Turing machines.⁵ Conversely, when given a Turing machine M , it is easy to construct a geometry-less Kappa model $(x_0(M, n), R(M))$ that simulates M for input n , with the rule set $R(M)$ implementing the state transition function of M , and $x_0(M, n)$ representing the initial state of M for input n , that is, a site graph representing M with the contents of its tape set to n and the head of M pointing to the first cell of its tape. Figure 7 illustrates this idea.

Without loss of generality, assume that every Turing machine M has exactly one dedicated final state q_\downarrow . The rule set $R(M)$ of any Kappa model $K_M = (x_0(M, n), R(M))$ simulating a Turing machine M , can easily be extended with the rule set R^* of some canonical non-local model $K^* = (x_0^*, R^*)$, such as the one given in example 3.4, and one additional rule $r_\downarrow = (s_\downarrow, +x_0^*, k_\downarrow)$ with $k_\downarrow > 0$

⁵ When we want to reason about the decidability of sets of Kappa models, we are forced to limit ourselves to the class of Kappa models that can be encoded as natural numbers or finite bit strings, that is, models with rate constants and geometries consisting of computable numbers.

some non-zero rate constant, x_0^* the initial state of K^* , and s_\downarrow a site graph that embeds into exactly those states of K_M that represent M being in its final state q_\downarrow . Since K_M is geometry-less and completely deterministic, the extended model $K'_M = (x_0(M, n), R(M) + R^* + \{r_\downarrow\})$ can reach a “non-local state” if and only if there is a state $x \in \text{reach}(K'_M)$, in which r_\downarrow becomes active, that is, $\mathcal{E}(x, r_\downarrow) \neq \emptyset$. But this implies that x represents M being in a final state, and therefore K'_M is a non-local model if and only if M halts. We conclude that the halting problem many-one-reduces to the decidability of \mathbb{L} . \square

3.3 Reducing local models to geometry-less models

The definition of locality tells us that, for any rule $(s, \alpha, k) \in R$ of a δ -local model $K = (x_0, R)$, inspecting a finite amount of context (represented by the closed ball of radius δ) around the image of the right-hand side $\alpha \cdot s$ of the rule in the result $f(\alpha) \cdot x$ of an event $((s, \alpha, k), f)$ is sufficient to determine whether $f(\alpha) \cdot x$ is sound or not. It therefore seems natural to think that, by extending the left-hand side s of the rule with a corresponding (finite) amount of additional context, one might be able to decide whether the result $f'(\alpha) \cdot x$ of the extended event $((s', \alpha, k), f')$, $f' \in [s'; x]$ is sound, simply by checking whether the right-hand side $\alpha \cdot s'$ of the extended rule itself is sound. If so, one could statically compute the “soundness” of all such extended rules $(s', \alpha, k) \in R'$ and then *flatten* the model K' to obtain a *geometry-less counterpart* \bar{K} that “behaves” the same as K . This intuition turns out to be correct.

Proposition 3.6 (reducibility) *For every local Kappa model $K \in \mathbb{L}$, there is a geometry-less Kappa model \bar{K} that is strongly bisimilar to K .*

For lack of space, we will not give a formal proof of proposition 3.6 here, but instead sketch the *reduction* from a δ -local model K to its geometry-less counterpart \bar{K} . The reduction consists of three steps:

- (i) *refine* the rule set R of K up to radius δ to obtain $K' = (x_0, R')$;
- (ii) *prune* the resulting rule set R' , by removing unsound rules, that is rules (s, α, k) for which $\alpha \cdot s \notin \mathbb{G}$, to obtain $K'' = (x_0, R'')$;
- (iii) *flatten* the resulting model K'' , that is, replace geometry with internal state in all site graphs and actions of K' , to obtain $\bar{K} = (\bar{x}_0, \bar{R})$.

Each of the Kappa models K' , K'' and \bar{K} resulting, respectively, from one of the above three steps can be shown to be bisimilar to its predecessor. The first step is based on the theory of *rule refinement* [17]. Every rule $r \in R$ is replaced by a finite set $B_{\delta, K}(r)$ of mutually exclusive, refined rules. Given a site graph s in \mathbf{GS}_K , one may build a set $B_{\delta, K}(s)$ inductively, starting from the set $B_{0, K}(s) = \{s\}$, and extending sites $(u, a) \in \sigma_t$ of site graphs $t \in B_{i, K}(s)$ that are neither bound nor stubs according to $\Lambda(\Gamma(u), a)$ in order to obtain $B_{i+1, K}(s)$. This process is guaranteed to terminate for all i since $\Lambda(A, a)$ is finite for any site $(A, a) \in \Sigma$. The theory of refinement guarantees, that every event in $(r, f) \in \mathcal{E}_R(x)$ maps to exactly one event $(r', f') \in \mathcal{E}_{R'}(x)$ of the refined rule set $R' = \sum_{r \in R} B_{\delta, K}(r)$, and thereby ensures the

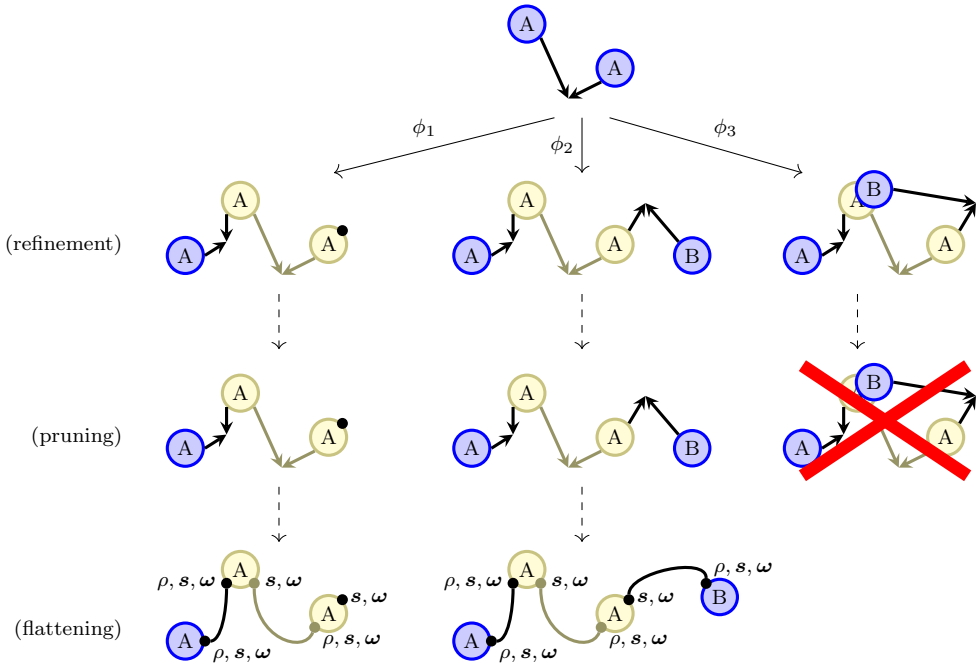


Figure 8. The three-step process of reducing a site graph x in a 1-local Kappa model K to its geometry-less counterpart \bar{x} in the geometry-less model \bar{K} .

correctness of this step. However, for large and highly connected contact graphs C_K , the set $B_{\delta,K}(r)$ may suffer a combinatorial explosion in the number of rules and the size of the corresponding site graphs even for moderate values of δ , making the computation of $B_{\delta,K}(r)$ intractable in practice.

The correctness of the second step follows from the definition of a geometrically sound WLTS: no transition in $\widehat{\mathcal{W}}_{K'}$ results from an unsound rule.

The last step can be achieved by first adding a set of dedicated sites (A, s_ρ) , $(A, (s_s, a))$ and $(A, (s_\omega, a, B, b))$, for every agent type A , site (A, a) and link (A, a, B, b) of the contact graph C'_K of K' , and then replacing every site graph x and atomic action α in K' by a geometry-less counterpart \bar{x} and $\bar{\alpha}$, respectively, in which the geometries of every agent u , site (u, a) and link (u, a, v, b) have been replaced by appropriate internal states of (u, s_ρ) , $(u, (s_s, a))$ and $(u, (s_\omega, a, \Gamma(v), b))$, respectively. The correctness of this step is by construction of the flattening function $\bar{\cdot}$ and locality itself: the transports of any action in K'' can no longer result in unsound site graphs (all left-hand sides contain the necessary context and have passed pruning), and hence their geometry has become redundant.

Figure 8 illustrates the reduction of a concrete site graph x in a 1-local model K to its geometry-less counterpart \bar{x} in the geometry-less model \bar{K} .

4 Conclusion and future work

We presented geometrically enhanced Kappa, a framework for geometrically enhanced site graph rewriting and sketched an algorithm for tractable simulation.

We also showed that the geometric constraints introduced by the framework allows for the definition of non-local models and that all local models can be reduced to geometry-less Kappa models without changing the dynamics of the associated transition system, if one is willing to accept a combinatorial increase in the number of rules of the model. Finally, we showed that locality is undecidable in general.

A principal limitation of our framework is that it is restricted to rigid geometric constraints, while the chemical species of some systems, such as polymer chains, enjoy a certain amount of *flexibility* in their structure. A possible solution to this limitation would be to allow geometric annotations to occupy *continuous intervals* in the corresponding vector spaces, rather than a finite set of fixed points. A further generalization would be to allow *distributions* over such intervals. However, this might increase the complexity of checking the soundness of the resulting site graphs, possibly making it intractable.

Another current limitation is that, while the possible realizations of site graphs may be computed in order to check their soundness, they remain inaccessible to the modeler. Indeed, they are not even kept track of in the current framework. Extending the dynamics of the system to take the realization of its state into account might provide a way of modeling processes such as *diffusion* and *compartmentalization*, which play a key role in certain biochemical processes. Combinations of the above are of course possible, and in general there is a spectrum of possible *spatial extensions* to Kappa, with geometry-less Kappa at one end, and coarse-grained molecular dynamics approaches, such as [14], at the other.

Another direction for future work is to explore approaches to answer the question of whether a given Kappa model is local or not approximately. Techniques such as [9] for computing overapproximations of the set $\text{reach}(K)$ of reachable states of a model K based on *abstract interpretation* could help to find subsets of \mathbb{L} if it turns out that locality is decidable with respect to the corresponding supersets of $\text{reach}(K)$.

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A Additional definitions

To simplify some of the definition below, we will first give a formal definition for two basic operations for composing or dividing site graphs, namely the disjoint union and the difference of two site graphs.

Definition A.1 The *disjoint union* $x_1 + x_2$ of two site graphs x_1 and x_2 in \mathbf{GS}_C is defined as the site graph in \mathbf{GS}_C with agent set $V_{1+2} = V_1 + V_2$, and with Γ_{1+2} , λ_{1+2} , ι_{1+2} , ρ_{1+2} , \mathbf{s}_{1+2} and ω_{1+2} the disjoint unions, with respect to V_{1+2} , of the corresponding components of x_1 and x_2 .

Given two site graphs x_1 and $x = (x_1 + x_2)$, we call $x - x_1 = x_2$ the *relative complement* of x_1 in x or simply the *difference* of x and x_1 . Given a site graph x we say that $\{x_1, x_2, \dots, x_N\}$ is a *partition* of x if $x = \sum_{i=1}^N x_i$.

A.1 Result of an action on a site graph

The *result* $\alpha \cdot s$ of an atomic action α on a site graph s in \mathbf{GS}_C is defined as

- $+t \cdot s = s + t$,
- $-t \cdot s = s - t$,
- $\lambda_{+(u,a,v,b) \cdot s} = \lambda_s - \lambda_{-(u,a,v,b)} \cup \lambda_{+(u,a,v,b)}$,
- $\omega_{+(u,a,v,b) \cdot s} = \omega_s \cup \omega_{+(u,a,v,b)}$,
- $\lambda_{-(u,a,v,b) \cdot s} = \lambda_s - \lambda_{+(u,a,v,b)} \cup \lambda_{-(u,a,v,b)}$,
- $\omega_{-(u,a,v,b) \cdot s} = \omega_s - \omega_{-(u,a,v,b)}$,
- $\iota_{(\iota(u,a) \leftarrow p) \cdot s} = \iota_s[(u, a) \mapsto \iota_s(u, a)/(u, a) \mapsto p]$,
- $\rho_{(\rho(u) \leftarrow r) \cdot s} = \rho_s[u \mapsto \rho_s(u)/u \mapsto r]$,
- $\mathbf{s}_{(\mathbf{s}(u,a) \leftarrow \mathbf{p}) \cdot s} = \mathbf{s}_s[(u, a) \mapsto \mathbf{s}_s(u, a)/(u, a) \mapsto \mathbf{p}]$, and
- $\omega_{(\omega(u,a,v,b) \leftarrow \mathbf{O}) \cdot s} = \omega_s[(u, a, v, b) \mapsto \omega_s(u, a)/(u, a, v, b) \mapsto \mathbf{p}]$,

with

$$\begin{aligned}
 A[a/b] &= A - \{a\} \cup \{b\}, \\
 \lambda_{+(u,a,v,b)} &= \{(u, a, v, b)\} \cup \{(v, b, u, a)\}, \\
 \lambda_{-(u,a,v,b)} &= \{(u, a), (v, b)\} \times \{\star\} \cup \{\star\} \times \{(u, a), (v, b)\}, \\
 \omega_{+(u,a,v,b)} &= \begin{cases} \left\{ \begin{array}{l} (u, a, v, b) \mapsto \mathbf{Q} \\ (v, b, u, a) \mapsto \mathbf{Q} \end{array} \right\} & \text{if } \Omega(u, a, v, b) \neq \emptyset, \\ \emptyset & \text{otherwise,} \end{cases} \\
 \omega_{-(u,a,v,b)} &= \begin{cases} \left\{ \begin{array}{l} (u, a, v, b) \mapsto \omega_s(u, a, v, b) \\ (v, b, u, a) \mapsto \omega_s(v, b, u, a) \end{array} \right\} & \text{if } \Omega(u, a, v, b) \neq \emptyset, \\ \emptyset & \text{otherwise,} \end{cases}
 \end{aligned}$$

where we only mention the components of $\alpha \cdot s$ that differ from those in s . The result of a non-atomic action $\alpha = (\alpha_1, \alpha_2, \dots, \alpha_N)$ is defined as

$$\alpha \cdot s = \alpha_N \cdot \alpha_{N-1} \cdots \alpha_1 \cdot s.$$

A.2 Transport of an action along an embedding

Definition A.2 Given an embedding $f \in [s; x]$ between two site graphs s and x in \mathbf{GS}_C , the *transport* $f(\alpha)$ of an atomic action α along f is defined as

- $f(+t) = +t$,
- $f(-t) = -x[f|_{V_t}(V_t)]$,
- $f(+ (u, a, v, b, \mathbf{Q})) = + (f(u), a, f(v), b, \mathbf{Q})$,
- $f(- (u, a, v, b)) = - (f(u), a, f(v), b)$,
- $f(\iota(u, a) \leftarrow p) = (\iota(f(u), a) \leftarrow p)$,

- $f(\rho(u) \leftarrow r) = (\rho(f(u)) \leftarrow r)$,
- $f(\mathbf{s}(u, a) \leftarrow \mathbf{p}) = (\mathbf{s}(f(u), a) \leftarrow \mathbf{p})$, and
- $f(\boldsymbol{\omega}(u, a, v, b) \leftarrow \mathbf{O}) = (\boldsymbol{\omega}(f(u), a, f(v), b) \leftarrow \mathbf{O})$.

The transport $f(\alpha)$ of a non-atomic action $\alpha = (\alpha_1, \alpha_2, \dots, \alpha_N)$ along f is defined as $f(\alpha) = (f(\alpha_1), f(\alpha_2), \dots, f(\alpha_N))$.

A.3 Result of an action on an embedding

Definition A.3 Given two site graphs s and x in \mathbf{GS}_C , a well-defined action α on s and $f \in [s; x]$, there is a unique map $(\alpha \cdot f) \in [\alpha \cdot s; f(\alpha) \cdot x]$ called the *result* of the action α on f with

- $+t \cdot f = f + 1_{V_t}$,
- $-t \cdot f = f|_{V_s - V_t}$,
- $\alpha \cdot f = f$ for any other atomic action α , and
- $(\alpha_1, \alpha_2, \dots, \alpha_N) \cdot f = \alpha_N \cdot \alpha_{N-1} \cdots \alpha_1 \cdot f$ for non-atomic actions.

B Algorithms

B.1 Checking soundness of a site graph

Input: A site graph $s = (V, C, \lambda, \iota, \rho, \mathbf{s}, \boldsymbol{\omega}, \Gamma)$.

Output: **true** if $s \in \mathbb{G}$, **false** otherwise.

```

1: checked  $\leftarrow \emptyset$ ;
2: while  $V - \text{checked} \neq \emptyset$  do
3:   Pick an arbitrary agent  $i \in (V - \text{checked})$ ;
4:    $\mathbf{r}(i) \leftarrow \mathbf{0}$ ;  $\mathbf{R}(i) \leftarrow \mathbf{1}$ ;
5:   next  $\leftarrow \{i\}$ ; checked'  $\leftarrow \emptyset$ ;
6:   while next  $\neq \emptyset$  do ▷ Check consistency.
7:     Pick an arbitrary agent  $u \in \text{next}$ ;
8:     for all  $(v, b, u, a) \in (\text{dom}(\boldsymbol{\omega}) \cap \text{dom}(s)^2)$  do
9:       if  $v \notin (\text{checked} \cup \text{checked}')$  then
10:         $\mathbf{R}' \leftarrow \boldsymbol{\omega}(v, b, u, a)\mathbf{R}(u)$ ;
11:         $\mathbf{r}' \leftarrow \mathbf{r}(u) + \mathbf{R}(u)\mathbf{s}(u, a) - \mathbf{R}'\mathbf{s}(v, b)$ ;
12:        if  $v \in \text{next}$  then
13:          if  $\mathbf{r}' \neq \mathbf{r}(v) \vee \mathbf{R}' \neq \mathbf{R}(v)$  then
14:            return false; ▷  $s \notin \mathbb{G}$ 
15:          end if
16:        else
17:           $\mathbf{r}(v) \leftarrow \mathbf{r}'$ ;  $\mathbf{R}(v) \leftarrow \mathbf{R}'$ ;
18:          next  $\leftarrow \text{next} \cup \{v\}$ ;
19:        end if

```



```

20:     end if
21:   end for
22:   next ← next - {u};
23:   checked' ← checked' ∪ {u};
24: end while
25: for all (u, v) ∈ checked' × checked' : v ≠ u do      ▷ Check for collisions.
26:   if ||r(u) - r(v)|| ≤ ρ(u) + ρ(v) then
27:     return false;                                     ▷ s ∉ G
28:   end if
29: end for
30: checked ← checked ∪ checked';
31: end while
32: return true;                                         ▷ s ∈ G

```