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Rigid Geometric Constraints for Kappa Models

Vincent Danos[a,1] Ricardo Honorato-Zimmer[b,2]
Sebastián Jaramillo-Riveri[c,3] Sandro Stucki[d,4]

[a] *School of Informatics*
University of Edinburgh
Edinburgh, United Kingdom

[b] *Informatics Life-Sciences Institute*
University of Edinburgh
Edinburgh, United Kingdom

[c] *SynthSys*
University of Edinburgh
Edinburgh, United Kingdom

[d] *PPS Laboratory*
Université Paris Diderot – Paris 7
Paris, France

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

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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, phosphorilation 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-

[1] Email: vdanos@inf.ed.ac.uk
[2] Email: s1066652@sms.ed.ac.uk
[3] Email: sjaramil@staffmail.ed.ac.uk
[4] Email: sandro.stucki@epfl.ch