Experimenting with Reaction Systems using Graph Transformation and GROOVE

Graph transformations (GT) are a formal rule-based framework for modelling changes to graph structures. The paper shows how this framework can be applied to analysis of reaction systems (RS) by encoding a given reaction system as a single graph and describing rules that transform that graph according to the semantics of reaction systems.

Strengths

The paper has several strong points:

- Contributes to the research on verification of RS by showing how it can be reduced to GT and it demonstrates how an existing GT tool can be applied to the analysis of RS
- It provides an extensive and well-documented experimental evaluation
- It includes a helpful overview of existing tools relevant to the problem domain
- It uses interesting case studies, including:
  - Comorbidity treatment analysis
  - Protein signalling networks

Major remarks

The paper adopts a process algebra approach to introduce RS, but it is unclear what advantages this offers over the standard definition in this paper. The introduced notation is not used much across the contribution, raising the question of whether this formalism is necessary or beneficial. Moreover, no meaningful effort is made to relate the process-algebraic perspective to the later use of GT. The two approaches are presented in isolation, without a semantic link, which leaves the overall methodology disjointed. The paper should clearly articulate how they interact, ideally grounded in a consistent formal basis. The translation from RS to GT is presented in an overly informal manner. The lack of precise definitions or formal semantics makes it difficult to assess the correctness or generality of the proposed approach. The authors write:

> To mimic the BioResolve semantics as closely as possible…

However, it is unclear what specific semantics this translation is intended to match. If the goal is to encode RS using GT, then the semantics being preserved should be those of RS themselves. If the translation adheres to different semantics then either the intended correspondence is not properly explained, or the translation does not faithfully represent RS. This ambiguity needs to be addressed explicitly.

The review of related work is limited. A search for "model checking" in the publicly available Zotero group on reaction systems [1] reveals several related papers that are not cited. Some notable examples are [2] and [3], which addresses foundational questions that seem relevant to the paper's scope. This leads to another problem. The authors claim that their results are encouraging

and that their approach yields an order-of-magnitude improvement for large state spaces compared to other available tools. However, this claim is difficult to fully assess, as the paper does not consider some existing tools specifically designed for model checking of RS. For instance, ReactICS [4] (a dedicated model checker for RS) is not discussed. This omission limits the completeness of the evaluation and is potentially problematic, as one would reasonably expect ReactICS to be optimised for this domain.

[1] https://www.zotero.org/groups/5802518/reactionsystems
[2] S. Azimi, C. Gratie, S. Ivanov, L. Manzoni, I. Petre, A. E. Porreca, "Complexity of model checking for reaction systems", Theoretical Computer Science, Volume 623, 2016, Pages 103-113
[3] A. Meski, W. Penczek, G. Rozenberg, "Model checking temporal properties of reaction systems", Information Sciences, Volume 313, 2015, Pages 22-42
[4] A. Meski, M. Koutny, W. Penczek, "Reaction mining for reaction systems", Natural Computing, Volume 23, 2024, Pages 323-343

Minor remarks

The plural of "Entity" should be "Entities" (L099(L)). The use of "Entitys" is grammatically incorrect and visually jarring, even if "Entity" is being typeset in bold. More generally, this may stem from the paragraph's overall lack of clarity. As it stands, the explanation of Figure 1 is vague and uninformative, and would benefit from a clearer, more structured description of what the figure is intended to illustrate. This would most likely lead to a proper introduction of what is a "Reaction" and what is an "Entity". Currently, the description is caught in an awkward middle ground: either too detailed for an introduction, or not detailed enough to be truly informative.

- L036(R): "less" -> "fewer"
- There are inconsistencies between uses of AmE and BrE spelling. Just to list a few examples:
  - L043(R): analyze (AmE)
  - L044(R): modeled (AmE)
  - L060(L): modelling (BrE)
  - L071(L): visualized (AmE)
  - L076(R): controlled (BrE)
  - L230(R): visualisation (BrE)
  - L249(L): labelled (BrE)
  - L287(R): analyze (AmE)
  - L912(R): generalizes (AmE)
- Inconsistencies in how "T cell" ("T-cell") is written: L761(R), L763(R), L778(R), L781(R).
- L813(R): "An trace" -> "A trace"
- L825(R): "yield a counterexamples": remove "a"
- L293(L): Instead of "bang" it might be more appropriate to just say "hit" or "slam" (?)
- L887(R): "Many capabilities … has been discussed" -> have

Recommendation

The paper proposes an interesting application of the graph transformation framework to reaction systems and presents a set of compelling case studies supported by experimental analysis. However, the current version lacks some formal clarity and methodological coherence that should be expected of this type of contribution. The translation from reaction systems to the graph transformation framework is presented informally, without a clear semantic foundation, which makes it difficult to assess correctness and generality. In addition, the paper introduces multiple formalisms without integrating them, which leaves the overall approach somewhat fragmented. The related work section is also lacking and overlooks several relevant contributions in the area. While I do not believe the paper is ready for publication in its current form, I see clear potential in the approach and would be glad to see it accepted following a revision that addresses the major issues identified.