Issues in Reasoning about Interaction Networks in Cells: Necessity of Event Ordering Knowledge

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Introduction

- The paper discusses several representation issues encountered while modeling molecular interactions in cells of living organisms.
- Modeling molecular interactions in cells is important for predicting side effects of drugs, explaining unusual cellular behavior and for drug and therapy design.

Previous Paper

- **They used an action language approach and modeled molecular interactions in cells as triggered actions.**
- **For that purpose, they introduced action language $\mathcal{A}_T^0$, an extension of $\mathcal{A}$ that allows the specification of triggered and inhibited actions.**

Action Language $\mathcal{A}_T^0$

- **Statements:**

$$a\ \textbf{causes}\ \ l\ \textbf{if}\ \ p \qquad (1)$$

$$p\ \textbf{triggers}\ \ a \qquad (2)$$

$$p\ \textbf{inhibits}\ \ a \qquad (3)$$

- **Triggered actions are assumed to occur immediately unless they are inhibited.**

  Translation to ASP:

$$(2) \quad occurs(a, I) \leftarrow h(p, I), \quad not\ ab(occurs(a, I)).$$

$$(3) \quad ab(occurs(a, I)) \leftarrow h(p, I).$$

Problem in Modeling Interactions in Cells

- **The authors encountered the following problem while refining domain descriptions:**

Sometimes the conclusions produced by a more detailed description were not consistent with the conclusions of the original, less detailed description.

Example

- **We have the domain description:**

$$\mathcal{D} = \{ \; \neg f, \neg g \; \textbf{triggers} \; a; \qquad a \; \textbf{causes} \; f; \\ \neg g \; \textbf{triggers} \; b; \qquad b \; \textbf{causes} \; g; \}$$

- **If the initial situation is $\{\neg f, \neg g\}$, then f is true at the end of the history.**

Example (cont.)

- **Next, we refine the trigger "$\neg f, \neg g$ triggers a":**

$$\begin{aligned} \mathcal{D}' = \{ \ \neg f, \neg f' \textbf{ triggers } a'; &\quad a' \textbf{ causes } f'; \\ f', \neg g \textbf{ triggers } a; &\quad a \textbf{ causes } f; \\ \neg g \textbf{ triggers } b; &\quad b \textbf{ causes } g; \} \end{aligned}$$

- **If the initial situation is $\{\neg f, \neg g\}$ as before, f may be false at the end of the history.**

Reasons

1. **Triggers inside the cell** *do not necessarily fire immediately*.
2. **Sometimes one trigger takes effect** *faster* **than another.**

Attaching a duration to triggers does not work: the duration until a trigger fires is usually unknown and may even be non-deterministic.

Solution: Change the intuition behind triggers and add event ordering.

Solution: Action Language $\mathcal{A}_T^\infty$

- **Syntactically,** $\mathcal{A}_T^\infty$ **extends** $\mathcal{A}_T^0$ **by** *event orderings*, **i.e., statements of the type:**

  $$E \textbf{ restricts } E_1 \textbf{ op } E_2$$

  where E, E_1, **and** E_2 **are** *events* **(sets of fluent literals or sets of actions), and op** $\in \{\prec, ||, \preceq\}$

  ($\prec$ **stands for** *earlier*, $||$ **stands for** *at the same time*).

The Syntax of $\mathcal{A}_T^\infty$

- **The event ordering**

$$E \ \textbf{restricts} \ \ E_1 \ \textbf{op} \ \ E_2$$

is read as:

"If event E happens, then the earliest happening of events E_1 and E_2 after E must obey the ordering op ."

- **A** *theory* **of $\mathcal{A}_T^\infty$ consists of: (1) a domain description, (2) an event ordering specification, and (3) an initial situation.**

The Semantics of $\mathcal{A}_T^\infty$

- **Semantically, triggers are now** *non-immediate***: if an action is triggered then it must occur, but not necessarily immediately.**
- **The** *models* **of a theory are trajectories of the domain that satisfy the event ordering specification (and a minimality condition).**

Example

- **Let's assume that the following two sequences are the** *trajectories* **of a domain description** $\mathcal{D}$**:**

$$\tau_1 \;=\; \langle \{\neg f, \neg f', \neg g\},\; \{a', b\},\; \{\neg f, f', g\} \rangle$$

$$\tau_2 \;=\; \langle \{\neg f, \neg f', \neg g\},\; \{a'\},\; \{\neg f, f', \neg g\},\; \{a, b\},\; \{f, f', g\} \rangle$$

- **Only** τ_2 **will be a** *model* **of a** *theory* **consisting of** $\mathcal{D}$ **and the event ordering specification:**

$$\mathcal{E} = \{\; \{\neg f, \neg g\}\ \textbf{restricts}\ \ a' \prec b\}$$

Discussion

- The paper pointed out an important problem caused by the use of immediate triggers.
- The authors came up with a solution for this problem based on non-immediate triggers and event ordering.

However, these two additions complicate the definition of trajectories and models. As well, there is no known way of reducing the task of finding models of theories of $\mathcal{A}_T^\infty$ to computing answer sets.

Interesting Topics

1. **How could theories of $\mathcal{A}_T^\infty$ be mapped into logic programs?**

2. **Could biological interaction in cells be modeled using a theory of intentions rather than triggers?**