Bsys_eval

Ionuţ Cicio

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https://github.com/CuriousCI/bsys-eval

Contents

1 BSYS_EVAL

1.1 Introduction

BSYS_EVAL is a tool meant to help study the likelihood of a given situation in a biological system.

Given a set of *target species*, a set of constraints on the *target species* (constraints which model a situation that could present, for example, in a disease) and by taking into account all the reactions that lead to the production, both directly and indirectly, of the *target species*, the goal is to find a subset of virtual patients for the situation.

TODO: find papers in literature that do similar things; what does this method add compared to other approaches? (i.e. using multiple pathways by generating the fixed point, ensemble of SAs etc…)

TODO: add case study, multiple if possible

1.2 Requirements

The algorithm

TODO: better notation here, write something decent to introduce the algorithm

Algorithm 1: (high level pseudocode)

```
input: $S_T$, set of PhysicalEntity;
input: $C_T$, set of constraints on $S_T$;
input: $P_I$, set of ignored pathways;
input: $\varepsilon, \delta \in (0,1)$;
input: seed, random seed;

$F \leftarrow$ fixed_point($S_T$, $P_I$)
model $\leftarrow$ $(S_T, S(F), R(F), E(F))$
env $\leftarrow$ define env for model
$V$ = $\emptyset$ // set of virtual patients

while $\neg$ halt requested do
   $v$ $\leftarrow$ parameter assignement for model // virtual patient
   if $\neg$ $v$ satisfies structural constraints then
     continue;
   if APSG(model, $v$, env, seed, $\varepsilon$, $\delta$) then
     $V \leftarrow V \cup \{v\}$;
```

The idea is to expand a portion of Reactome

Definition 1 *(… Model).* A … model G is a tuple (S_T, S, R, E) where:

- S_T the set of target species
- S is the finite set of species s.t.
  - $S_T \subseteq S$
  - S is the transitive closure of S_I within the Reactome graph (to be more precise, the closure within the specified bounds, bounds yet to be defined)
  - $S' = S \cup \{s_{\text{avg}} \mid s \in S\}$.
  - $\dot{s} = f(s_1, s_2, s_3, ..., s_n)$
- R is the finite set of reactions
  - $R = R_{\text{fast}} \cup R_{\text{slow}}$
- E is the set edges in the graph (where and edge goes from a species to a reaction, it also has a stoichiometry)
  - $E \subseteq S \times R \times \mathbb{N}^1$
  - $E = E_{\text{reactant}} \cup E_{\text{product}} \cup E_{\text{modifier}}$
  - TODO: account for order (edges also have an "order" attribute, I have to check how it impacts the simulation and if it's optional)

Average quantities

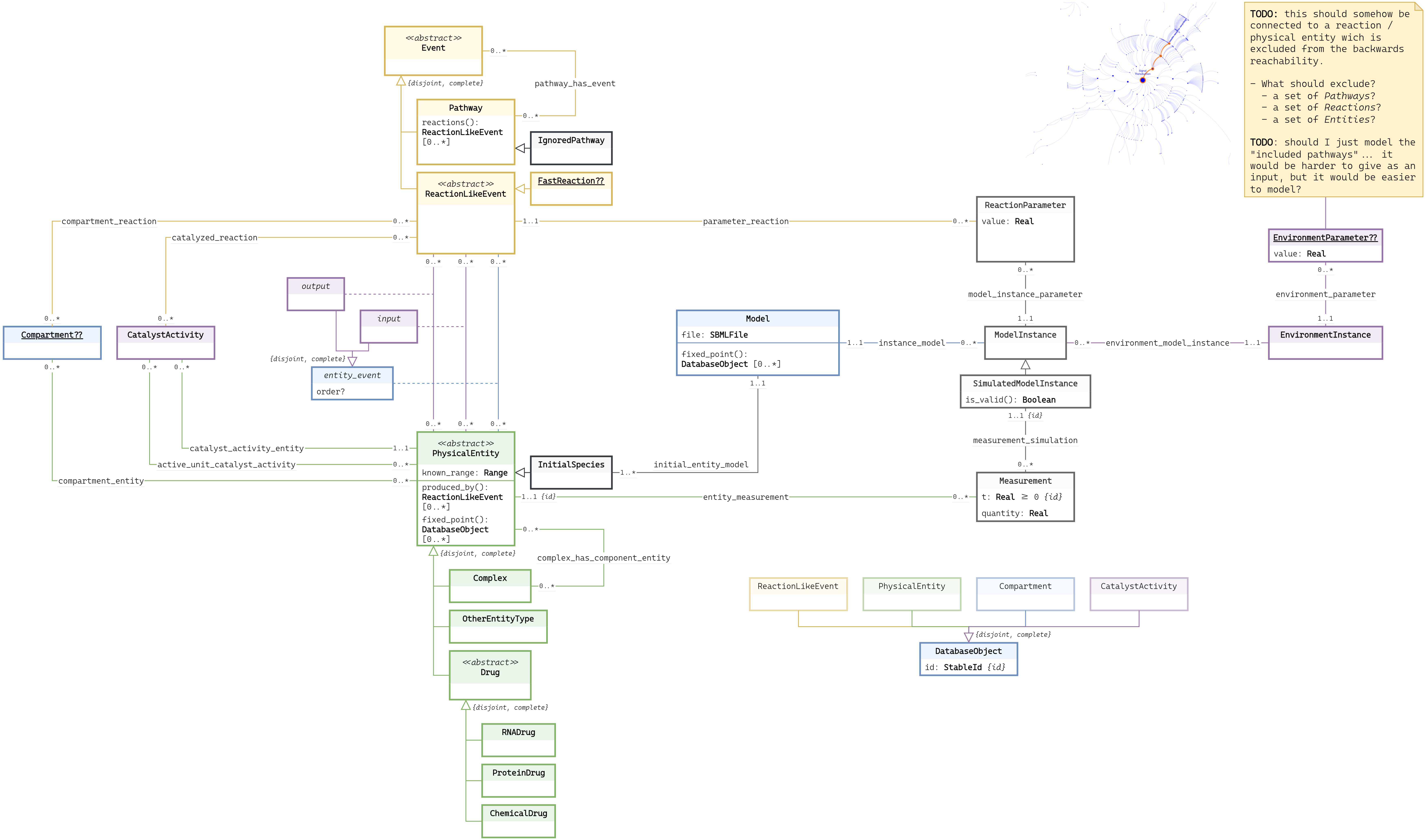
- $S' = S \cup \{S_{\text{avg}} \mid s \in S\}$
- $S' = G(S')$
- $K : R \to \mathbb{R}_+^{|R|} = [10^{-6}, 10^6]^{|R|}$
- find k
- subject to
  - structural constraints
    - partial order on k due to
      - fast/non fast reactions (TODO: as given by Reactome, but how?)

        $$\forall r_f, r_s \ \left(r_f \in R_{\text{fast}} \land r_s \in R_{\text{slow}}\right) \to r_f > r_s$$

      - reaction modifiers (like above?)
  - for all dynamics of environment
    - avg concentration of species consistent to knowledge

      $$\begin{aligned} &\exists t_0 \ \ \forall t \ \ \forall s \\ &\quad \left(t > t_0 \land s \in S_{\text{avg}}\right) \to s(t) \in [\text{known range}] \end{aligned}$$

2 UML class diagram



TODO: this should somehow be connected to a reaction / physical entity wich is excluded from the backwards reachability.

- What should exclude?
  - a set of *Pathways*?
  - a set of *Reactions*?
  - a set of *Entities*?

TODO: should I just model the "included pathways"... it would be harder to give as an input, but it would be easier to model?

3 Data types specification

- `\d = /[0-9]/`
- `\w = /[A-Za-z0-9_]/`

ReactomeDbId = Integer [1]
StableId = String matching regex `/^R-[A-Z]{3}-\d{8}\.\d{2,3}$/` [2]
SId = String matching regex `/^[a-zA-Z_]\w*$/` [3, Section 3.1.7]
Interval = (min: Real [0..1], max: Real [0..1])
MathML = String according to https://www.w3.org/1998/Math/MathML/

3.1 Interval

The Interval type represents a real open interval of the type $(\mathrm{min}, \mathrm{max})$.

```
C.Interval.min_leq_max
```

```
∀ interval, interval_min, interval_max
    (
        Interval(interval) ∧
        min(interval, interval_min) ∧
        max(interval, interval_max)
    ) →
        interval_min ≤ interval_max
```

3.2 ReactomeDbId

Other Reactome entities can be identified with a ReactomeDbId, but it's pattern does not match the definition of SId used to identify objects in SBML. In order to generate a correct SBML Model the ReactomeDbId must be converted.

```
into(db_id: ReactomeDbId): SId
```

```
POSTCONDITIONS:
  . . .
```

3.3 StableId

The StableId type is used to identify a PhysicalEntity or an Event in Reactome, but it's pattern does not match the definition of SId used to identify objects in SBML. In order to generate a correct SBML Model the StableId must be converted.

```
into(st_id: StableId): SId
```

```
POSTCONDITIONS:
  . . .
```

4 Classes specification

4.1 CatalystActivity

The one above is the reason why a PhysicalEntity's role in *catalyst_entity* has multiplicity 0..*.

"If a PhysicalEntity can enable multiple molecular functions, a separate CatalystActivity instance is created for each" [4, Page 5]

"If the PhysicalEntity is a Complex and a component of the complex mediates the molecular function, that component should be identified as the active unit of the CatalystActivity." [4, Page 5]

```
C.CatalystActivity.active_unit_is_in_complex

  ∀ catalyst_activity, complex, complex_component
      (
          CatalystActivity(catalyst_activity) ∧
          Complex(complex) ∧
          PhysicalEntity(complex_component) ∧
          catalyst_entity(catalyst_activity, complex) ∧
          catalyst_active_unit(catalyst_activity, complex_component)
      ) →
          complex_has_component_entity(complex, complex_component)
```

4.2 Compartment

4.3 Event

4.4 FastReaction

4.5 Model

```
fixed_point(): DatabaseObject [1..*]

  POSTCONDITIONS:
    result = { object | ∃ entity
        initial_entity_model(this, entity) ∧
        fixed_point(entity, object)
    }
```

4.6 ModelInstance

```
C.ModelInstance.every_reaction_has_a_parameter
```

```
C.ModelInstance.reaction_parameters_are_structurally_valid
```

4.7 SimulatedModelInstance

```
is_valid()
```

```
  POSTCONDITIONS:
```

4.8 Pathway

```
reactions(): ReactionLikeEvent [0..*]
```

```
  POSTCONDITIONS:
    result =
        { reaction |
            ReactionLikeEvent(reaction) ∧
            pathway_has_event(this, reaction) }
        ∪
        { reaction | ∃ pathway
            Pathway(pathway) ∧
            pathway_has_event(this, pathway) ∧
            reactions(pathway, reaction) }
```

4.9 PhysicalEntity

TODO: how should I handle complexes here?

```
produced_by(): ReactionLikeEvent [0..*]
```

```
  POSTCONDITIONS:
    result = { reaction |
        ReactionLikeEvent(reaction) ∧
        output(this, reaction) ∧
        ¬ ∃ pathway
            IgnoredPathway(pathway) ∧
            reactions(pathway, reaction)
    }
```

TODO: union with CatalystActivity

```
fixed_point(): DatabaseObject [0..*]
```

```
POSTCONDITIONS:
  result =
      { this } ∪
      produced_by(this) ∪
      { object | ∃ reaction, reaction_input
          produced_by(this, reaction) ∧
          (
              input(reaction, reaction_input) ∨
              (∃ catalyst_activity
                  CatalystActivity(catalyst_activity) ∧
                  catalyzed_event(catalyst_activity, reaction)) ∧
                  catalyst_entity(catalyst_activity,
  reaction_input)
          ) ∧
          fixed_point(reaction_input, object)
      }
```

4.10 ReactionLikeEvent

4.11 ReactionParameter??

- it must satisfy structural constraints

Bibliography

[1] [Online]. Available: https://reactome.org/content/schema/DatabaseObject

[2] [Online]. Available: https://reactome.org/documentation/faq/37-general-website/201-identifiers

[3] [Online]. Available: https://raw.githubusercontent.com/combine-org/combine-specifications/main/specifications/files/sbml.level-3.version-2.core.release-2.pdf

[4] [Online]. Available: https://download.reactome.org/documentation/DataModelGlossary_V90.pdf