Bsys_eval

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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: ε, δ ∈ (0,1);
input: seed, random seed;

F ← fixed_point(S_T, P_I)
model ← (S_T, S(F), R(F), E(F))
env ← define env for model
V = ∅ // set of virtual patients

while ¬ halt requested do
   v ← parameter assignement for model // virtual patient
   if ¬ v satisfies structural constraints then
     continue;
   if APSG(model, v, env, seed, ε, δ) then
     V ← V ∪ {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

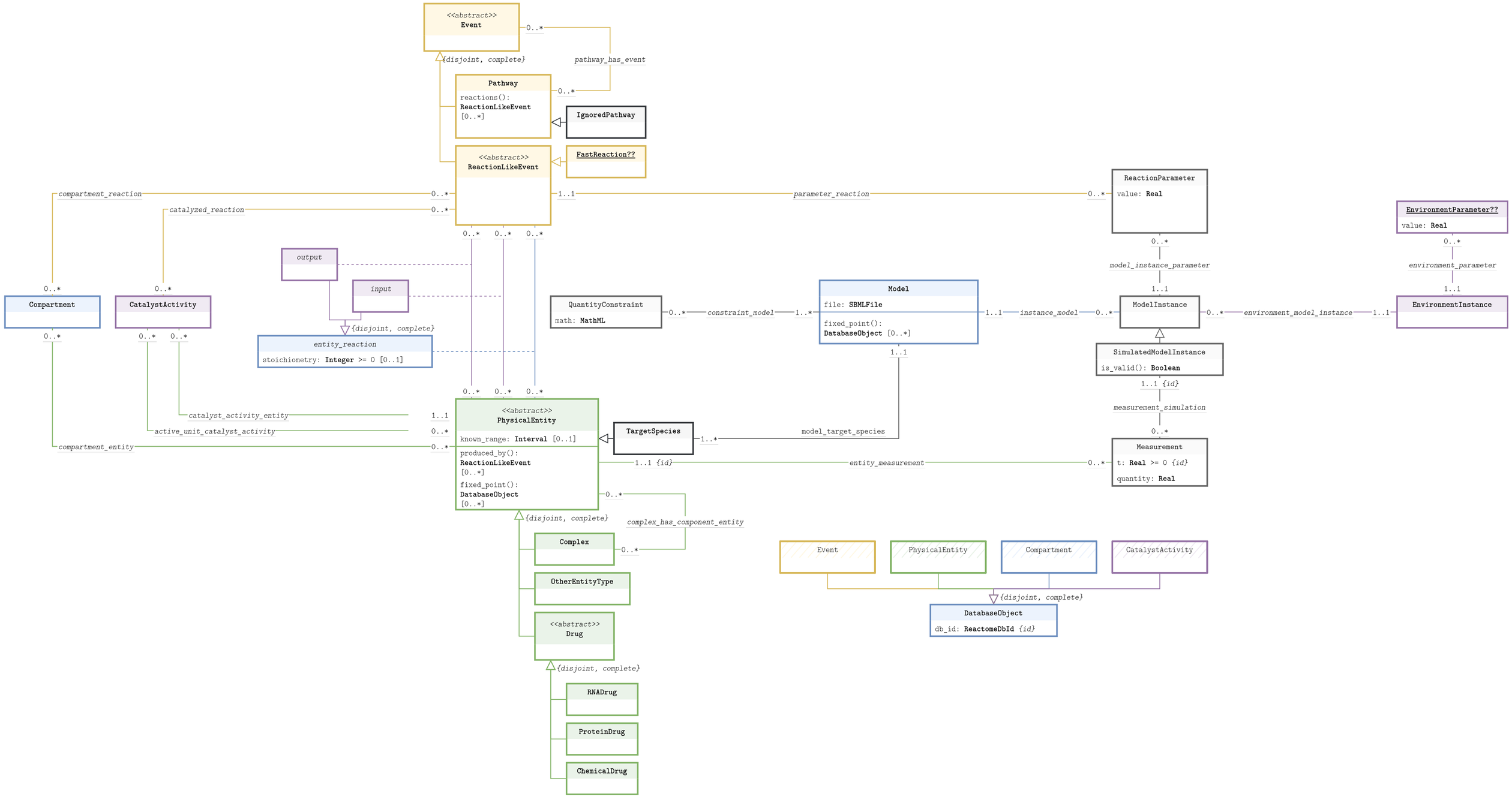
- $S' = S \cup \{S_{\text{avg}} \mid s \in S\}$
- $S' = G(S')$
- $K : R \to \mathbb{R}_+^{|R|} = [10^{-6}, 10^6]^{|R|}$
- find k
- subject to
  - structural constraints
    - partial order on k due to
      - fast/non fast reactions (TODO: as given by Reactome, but how?)

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

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

$$\exists t_0 \ \forall t \ \forall s$$
$$\left(t > t_0 \wedge s \in S_{\text{avg}}\right) \to s(t) \in [\text{known range}]$$

2 UML class diagram



3 Data types specification

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

```
ReactomeDbId = Integer [1]
StableIdVersion (Reactome) =
   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 (min, max).

`C.Interval.min_leq_max`

$$
\begin{aligned}
&\forall\ \text{interval},\ \text{interval\_min},\ \text{interval\_max} \\
&\quad (\\
&\qquad \text{Interval}(\text{interval}) \land \\
&\qquad \text{min}(\text{interval},\ \text{interval\_min}) \land \\
&\qquad \text{max}(\text{interval},\ \text{interval\_max}) \\
&\quad) \rightarrow \\
&\qquad \text{interval\_min} \leq \text{interval\_max}
\end{aligned}
$$

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

TODO: move this information to the *compartment_entity* association, or to PreferredCompartmentForSimulation

The Compartment class has some quirks. In Reactome, the Compartment's role in the *compartment_entity* association has multiplicity 0..*. The problem is that the SBML model requires 1..1 multiplicity for this association to be simulated.

In Reactome there are currently (TODO: version??) 19 physical entities which don't have a compartment (see queries/helper.cypher), so this can be easily solved by just adding a **default compartment** to the SBML model to which these entities map to.

On the other hand there are 14046 entities which have multiple compartments (TODO: how many compartments has each exactly?), so the easiest choice right now is to just pick any of them. For this reason the

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