Bsys_eval

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

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1 Bsys_eval

1.1 Introduction

Bsys_eval is a tool meant to help study the likelihood of a given scenario in a biological system.

Given a set of *target species*, a set of constraints on the *target species* (constraints which model a scenario that could present, for example, in a disease) and by taking into account all the reactions within a set *target pathways* 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 described scenario.

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: case studies

1.2 Requirements

The basic idea behind the software is to take the description of a scenario (with *target species*, *target pathways*, constraints on the *target species*, and the parameters $\varepsilon, \delta \in (0, 1)$ for the evalation of the constraints), to generate a SBML model with

- the reactions within the *target pathways* that, both directly and indirectly, generate the *target species*
- parameters for the reactions' speeds
- structural constraints on the reactions' speeds (some reactions are faster than others)

  > TODO: I still haven't figured out how to get that information out of Reactome, maybe I just have to search more

- constraints on the quantities of the entities (for which the model needs to be simulated)

Algorithm 1: eval

---

input: S_T, set of `PhysicalEntity`;
input: P_T, set of target `Pathway`;
input: C_T, set of constraints on S_T;
input: $\varepsilon, \delta \in (0, 1)$;
input: seed, random seed;

scenario ← biological_scenario_definition(S_T, P_T, C_T)
(sbml_model, vp_definition, env) ← yield_sbml_model(scenario)

$V = \emptyset$ // set of virtual patients
while ¬ halt requested **do**
  v ← instantiate(vp_definition) // virtual patient
  if (
    v satisfies structural constraints $\wedge$
    APSG(sbml_model, v, env, seed, ε, δ)
) **then**
    $V \leftarrow V \cup \{v\}$;

return V

The bulk of the logic is in the `yield_sbml_model()` function.

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?)

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

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

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

- $\mathbb{N}^+ = \{n \mid n \in \mathbb{N} \land n > 0\}$

Definition 1 (*biological graph*)

A *biological graph* G is a tuple (S, R, E, F) s.t.

- S is a set of species
- R is a set of reactions
- $E : S \times R \to \mathbb{N}^+$
  - $E = E_{\text{reactant}} \cup E_{\text{product}} \cup E_{\text{modifier}}$

Definition 2 (*"produces" relation*)

Given a *biological graph* $G = (S, R, E, F)$ let $\rightsquigarrow$ be a relation s.t.

- $\forall s, r \quad (s, r) \in \operatorname{dom}(E_{\text{reactant}} \cup E_{\text{modifier}}) \Rightarrow s \rightsquigarrow r$
- $\forall s, r \quad (s, r) \in \operatorname{dom}(E_{\text{product}}) \Rightarrow r \rightsquigarrow s$
- $\forall c, c', c'' \quad (c \rightsquigarrow c' \land c' \rightsquigarrow c'') \Rightarrow c \rightsquigarrow c''$

$\rightsquigarrow$ is the *"produces"* relation

Definition 3 (*model??*)

Given a set of target species S_T, a set of target pathways P_T and a biological graph $G = (S, E, R)$ s.t.

- $S_T \subseteq S$

A *model* is a subgraph $G' = (S', E', R')$ s.t.

- $G' \subseteq G$
- $S' = \{s \mid \exists s_t \ s \in S \land s_t \in S_T \land s \rightsquigarrow_G s_t\}$
- $R' = \{r \mid \exists s_t \ r \in R \land s_t \in S_T \land r \rightsquigarrow_G s_t\}$
- $E' = ((s, r, n) \mid (s, r, n) \in E \land s \in S' \land r \in R')$

Definition 4 (*constraint problem on a biological model*)

Given a model G with target species S_T and target pathways P_T let the following be a constraint problem

- $k : R \to \mathbb{R}^{|R|}$

find k subject to

- partial order on k from the structure of the graph
- partial order on the quantities
- constraint on enzymes such that

$$E + S \overset{k_1, k_{-1}}{\leftrightarrow} ES \overset{k_2}{\rightarrow} E + P$$

$$k_1, k_{-1} \gg k_2$$

- for all dynamics of the environment
  - average concentration of species consistent to knowledge

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

Environment: all possible cuts
we can have excluded species!

$$\dot{x} = k_+ \prod_{i=1}^{s} S_i^{k_i} - k_- \prod_{j=1}^{p} P_j^{k_j}$$

$$\dot{x} = \sum_{i=1}^{p} \mathrm{KP}_i - \sum_{j=1}^{n} \mathrm{KN}_j$$

$$\left\{ \sum_{j=1}^{n} \mathrm{KN}_j > \mathrm{KP}_i \mid i \in \{1, ..., p\} \right\} \cup$$
$$\left\{ \sum_{i=1}^{n} \mathrm{KP}_i > \mathrm{KN}_j \mid j \in \{1, ..., n\} \right\}$$

2 Data types specification

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

Math

```
Natural = Integer >= 0
Interval = (lower_bound: Real [0..1], upper_bound: Real [0..1])
MathML = String matching https://www.w3.org/1998/Math/MathML/
MathMLBoolean = String matching MathML returning a boolean
MathMLNumeric = String matching MathML returning a number
Stoichiometry = Natural > 0
```

Reactome

```
ReactomeDbId = Natural [1]
StableIdVersion =
  String matching regex /^R-[A-Z]{3}-\d{1,8}\.\d{1,3}$/ [2]
```

SBML

```
String1 = String matching regex //
SId = String matching regex /^[a-zA-Z_]\w*$/ [3, Section 3.1.7]
UnitSId = String matching regex /^[a-zA-Z_]\w*$/
```

2.1 Interval

The `Interval` type represents an open interval in $\mathbb{R}$ of the type (`lower_bound`, `upper_bound`) s.t.

- when `lower_bound` is not defined, it is interpreted as $-\infty$
- when `upper_bound` is not defined, it is interpreted as $+\infty$

```
[C.Interval.lower_bound_leq_upper_bound]
  ∀ interval, interval_lower_bound, interval_upper_bound
    (
        Interval(interval) ∧
        lower_bound(interval, interval_lower_bound) ∧
        upper_bound(interval, interval_upper_bound)
    ) →
        interval_lower_bound ≤ interval_upper_bound
```

2.2 ReactomeDbId

This is required because not all instances of `DatabaseObject` in Reactome have a `StableIdVersion`, which is the one usually displayed in the Reactome Pathway Browser [4]. Instances of `DatabaseObject` in Reactome can be identified with a `ReactomeDbId`, but its pattern does not match the definition of `SId` used to identify objects in SBML.

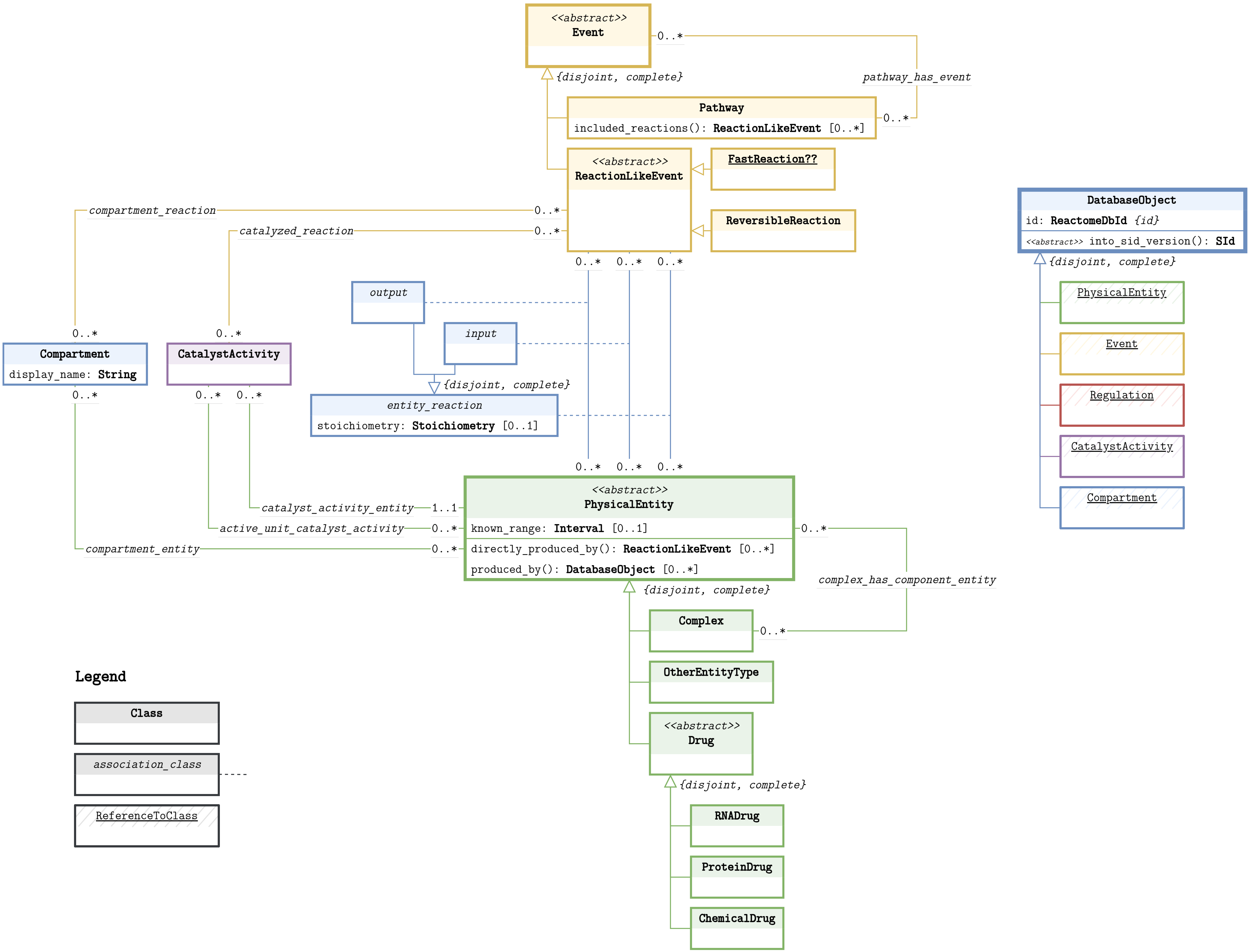
In order to generate a correct `SBMLDocument` the `ReactomeDbId` must be converted into a `SId`.

2.3 StableIdVersion

The `StableIdVersion` type is useful because is the one usually displayed in the Reactome Pathway Browser [4]. It is useful to accept it in the description of the models.

```
from_stable_id_version(stable_id_version: StableIdVersion):
ReactomeDbId
  postconditions:
    . . .
```

3 *(Reactome)* UML class diagram



4 Classes specification pt. 1

4.1 CatalystActivity

The role of `PhysicalEntity` in `catalyst_activity_entity` has multiplicity `0..*` because *"If a `PhysicalEntity` can enable multiple molecular functions, a separate `CatalystActivity` instance is created for each"* [5, Page 5].

An additional constraint is required for active units, because *"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`."* [5, Page 5]

```
[C.CatalystActivity.active_unit_is_component_of_complex]
  ∀ catalyst_activity, complex, complex_component
      (
          CatalystActivity(catalyst_activity) ∧
          Complex(complex) ∧
          PhysicalEntity(complex_component) ∧
          catalyst_activity_entity(catalyst_activity, complex) ∧
          catalyst_activity_active_unit(
              catalyst_activity,
              complex_component
          )
      ) →
          complex_has_component_entity(complex,
  complex_component)
```

4.2 Compartment

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 Pathway

The instances of `Pathway` are organized hierarchically, i.e. all the signaling pathways are collected under the Signal Transduction top level `Pathway` (`StableIdVersion` R-HSA-162582.13). This allows to easily extract a subset of reactions by specifying the *target pathways* in a model and taking into consideration only the reactions which are included, both directly or indirectly, in that pathway (see the `included_reactions()` operation).

There are about 34 top level pathways.

```
included_reactions(): ReactionLikeEvent [0..*]
  postconditions:
    result =
        { reaction |
            ReactionLikeEvent(reaction) ∧
            pathway_has_event(this, reaction) }
        ∪
        { reaction | ∃ pathway
            Pathway(pathway) ∧
            pathway_has_event(this, pathway) ∧
            included_reactions(pathway, reaction) }
```

4.4 PhysicalEntity

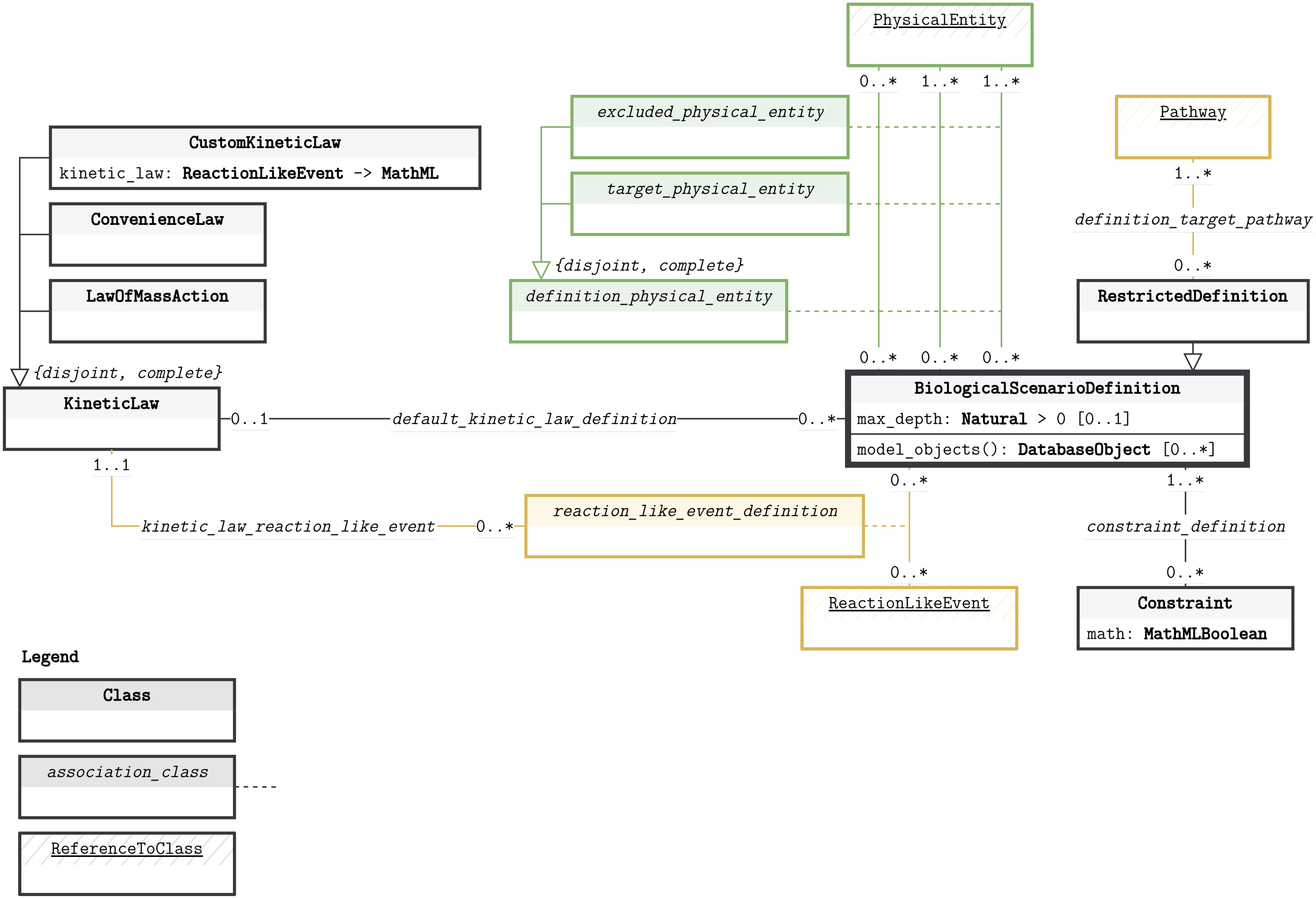
The set of reactions which produce `this` is needed to determine the transitive closure of the *target entities*.

```
directly_produced_by(): ReactionLikeEvent [0..*]
  postconditions:
    result = { reaction |
        ReactionLikeEvent(reaction) ∧ output(this, reaction)
    }
```

The set of instances of `DatabaseObject` which are directly or indirectly involved in the production of `this`.

```
produced_by(): DatabaseObject [0..*]
  postconditions:
    result =
        { this } ∪
        { reaction | directly_produced_by(this, reaction) } ∪
        { object | ∃ reaction, reaction_input
            directly_produced_by(this, reaction) ∧
            (
                input(reaction, reaction_input) ∨
                (∃ catalyst_activity
                    CatalystActivity(catalyst_activity) ∧
                    catalyzed_event(
                        catalyst_activity,
                        reaction
                    ) ∧
                    catalyst_activity_entity(
                        catalyst_activity,
                        reaction_input
                    )
                )
            ) ∧
            produced_by(reaction_input, object)
        }
```

5 *(Biological scenario definition)* UML class diagram



6 Classes specification pt. 2

6.1 BiologicalScenarioDefinition

The following operation finds the transitive closure of the *target entities* specified in the scenario, by including only reactions within the *target pathways* if necessary.

```
model_objects(): DatabaseObject [1..*]
  postconditions:
    result = { object | ∃ entity
        PhysicalEntity(entity) ∧
        DatabaseObject(object) ∧
        target_physical_entity(this, entity) ∧
        produced_by(entity, object) ∧
        (
            ¬ RestrictedDefinition(this) ∨
            ∃ pathway, reaction
                Pathway(pathway) ∧
                ReactionLikeEvent(reaction) ∧
                included_reactions(pathway, reaction) ∧
                (
                    object = reaction ∨
                    entity_reaction(object, reaction) ∨
                    catalyzed_reaction(object, reaction)
                )
        )
    }
```

6.2 ModelInstance

```
[C.ModelInstance.no_local_parameters_without_value]
  ∀ model_instance, model, reaction, kinetic_law,
  local_parameter
      (
          ModelInstance(model_instance) ∧
          Model(model) ∧
          ReactionDefinition(reaction) ∧
          KineticLaw(kinetic_law) ∧
          LocalParameter(local_parameter) ∧
          instance_model(model_instance, model) ∧
          model_definition(model, reaction) ∧
          kinetic_law_reaction(kinetic_law, reaction) ∧
          kinetic_law_local_parameter(kinetic_law,
  local_parameter) ∧
          ¬ ∃ value
              value(local_parameter, value)
      ) →
          ∃ local_parameter_assignment

  LocalParameterAssignment(local_parameter_assignment) ∧
              model_instance_paramenter(
                  model_instance,
                  local_parameter_assignment
              ) ∧
              assignment_local_paramenter(
                  local_parameter_assignment,
                  local_parameter
              )
```

6.3 SimulatedModelInstance

```
is_valid()
  postconditions:
    . . .
```

6.4 Measurement

```
[C.Measurement.species_in_model]
```

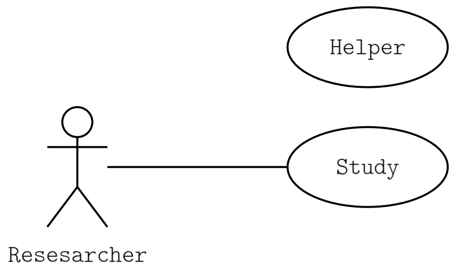
```
∀ measurement, model_instance, model, species
    (
        Model(model) ∧
        SimulatedModelInstance(model_instance) ∧
        Measurement(measurement) ∧
        Species(species) ∧
        measurement_species(measurement, species) ∧
        measurement_simulation(measurement, model_instance) ∧
        instance_model(model_instance, model)
    ) →
        model_definition(model, species)
```

6.5 UnitDefinition

[3, page 45]

TODO: better description

7 Use-case diagram



7.1 "Helper" use-case

```
yield_sbml_model(description: BiologicalScenarioDefinition):
(SBMLDocument, )
  postconditions:
    TODO:
      • create necessary units (TODO: which? how?)
      • create default CompartmentDefinition
      • create CompartmentDefinition from Compartment
          ▸ convert id to SId
      • create SpeciesDefinition from PhysicalEntity
          ▸ convert id to SId
          ▸ add one of the compartments if the entity has any
          ▸ otherwise assign to default
      • create ReactionDefinition
          ▸ convert id to SId
          ▸ connect products (inputs)
          ▸ connect reactants (outputs)
          ▸ connect modifiers (catalysts)
          ▸ add kinetic law (either manually specified ∨
            automatic, like LawOfMassAction)
          ▸ add local parameters
      • create constraints
          ▸ i.e. from known_range attribute
      •

instantiate_model(model: SBMLDocument): ModelInstance
  postconditions:
    TODO:
      • add LocalParameterAssignment for undefined
        LocalParameters
      • add environment parameters to model (Parameter)

simulate_model(instance: ModelInstance): SimulatedModelInstance
  postconditions:
    TODO:
      • generate measurements
```

Bibliography

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

[2] "Reactome." [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://reactome.org/PathwayBrowser/

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