AI-driven analysis of molecular pathways

Ionuț Cicio

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

Contents

1 Introduction

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.

2 Problem definition

Definition 1 (*biological network*)

A biological network G is a triple (S, R, E, σ) s.t.

- $S = U \sqcup X \sqcup Y$ is the set of species of the biological network
  - U is the set of input species
  - X is the set of other species in the network
  - Y is the set of output species
- R is the set of reactions in the biological network
- $E \subseteq S \times R = E_{\text{reactant}} \sqcup E_{\text{product}} \sqcup E_{\text{modifier}}$ is a relationship between species and reactions
- $\sigma : E_{\text{reactant}} \cup E_{\text{product}} \to \mathbb{N}^1$

Definition 2 (*constraint problem*)

Given a biological network $G = (S, R, E, \sigma)$ let C be the constraint problem s.t.

Definition 3 (*"produces" relation*)

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

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

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

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

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

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

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

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

Environment: all possible cuts
we can have excluded species!

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

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

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

3 Data types specification

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

Math

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

3.1 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
```

3.2 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.

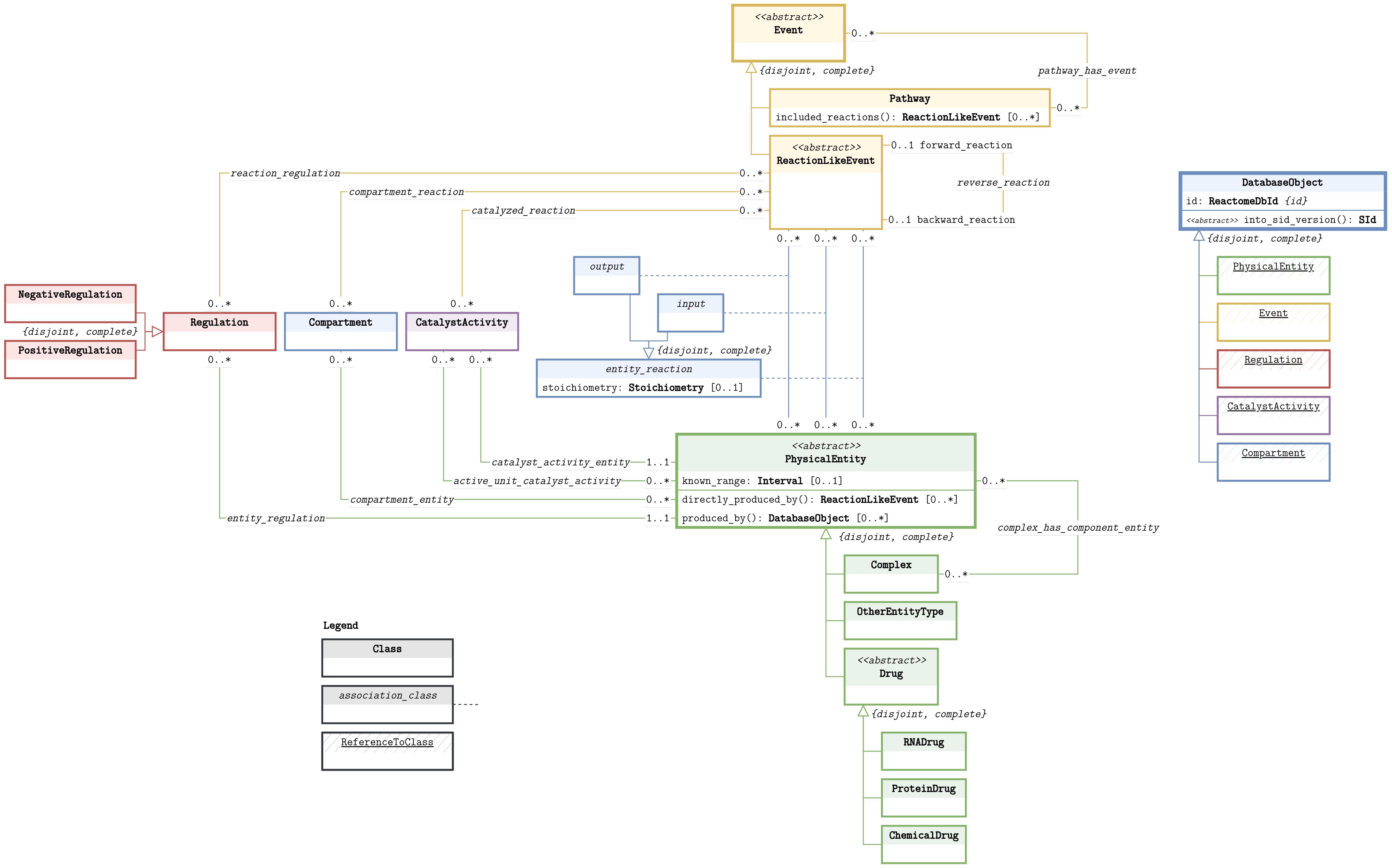
In order to generate a correct SBMLDocument the ReactomeDbId must be converted into a SId.

3.3 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
        ...
```

4 *(Reactome)* UML class diagram



5 Classes specification pt. 1

5.1 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)
```

5.2 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

5.3 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) }
```

5.4 PhysicalEntity

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

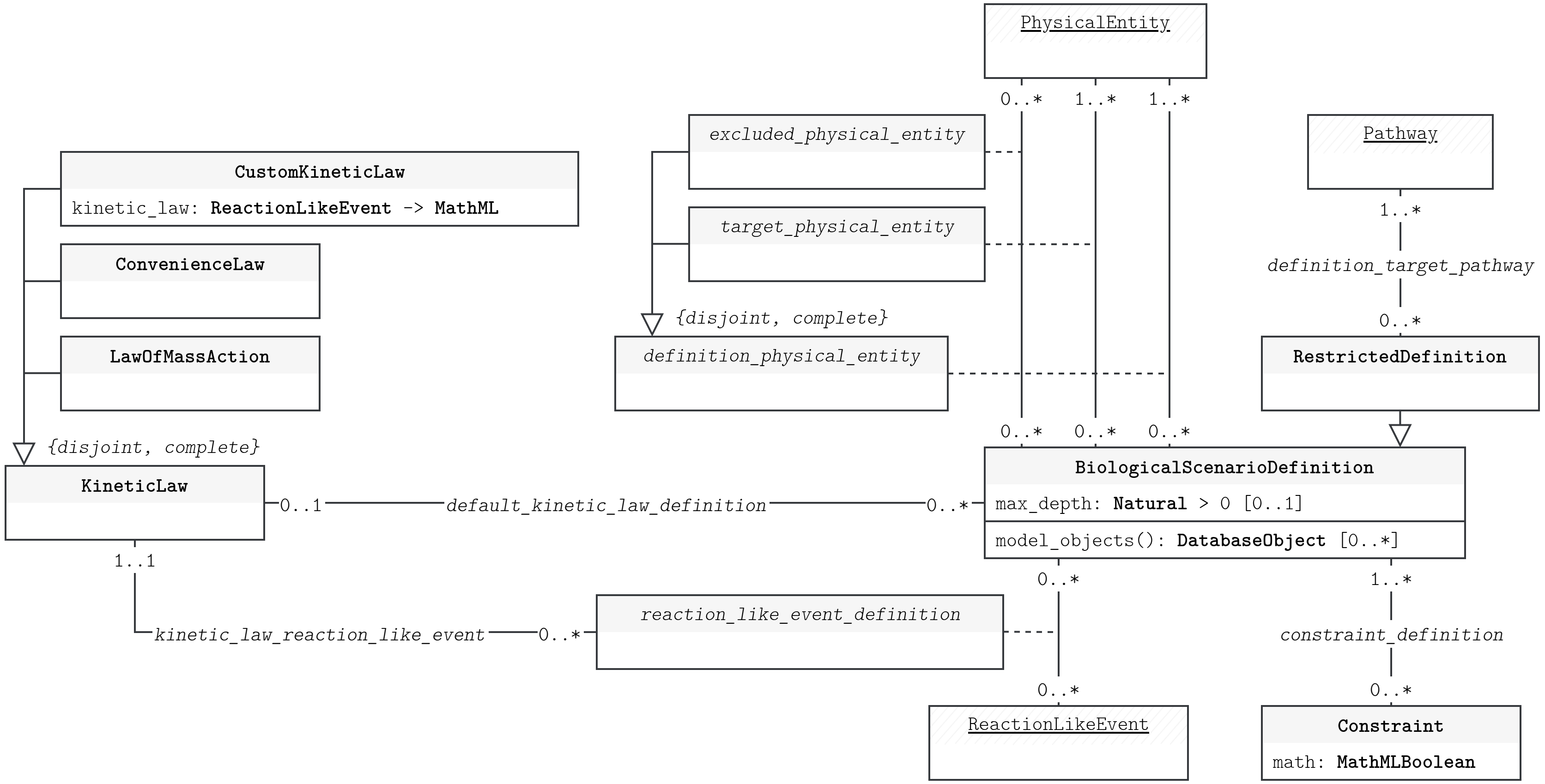
directly_produced_by() : ReactionLikeEvent [0..*]

```
    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)
            }
```



PhysicalEntity
0..*
1..*
1..*
excluded_physical_entity
target_physical_entity
{disjoint, complete}
definition_physical_entity
0..*
0..*
0..*
Pathway
1..*
definition_target_pathway
0..*
RestrictedDefinition
CustomKineticLaw
kinetic_law: ReactionLikeEvent -> MathML
ConvenienceLaw
LawOfMassAction
{disjoint, complete}
KineticLaw
0..1
default_kinetic_law_definition
0..*
BiologicalScenarioDefinition
max_depth: Natural > 0 [0..1]
model_objects(): DatabaseObject [0..*]
1..1
kinetic_law_reaction_like_event
0..*
reaction_like_event_definition
0..*
0..*
ReactionLikeEvent
1..*
constraint_definition
0..*
Constraint
math: MathMLBoolean

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

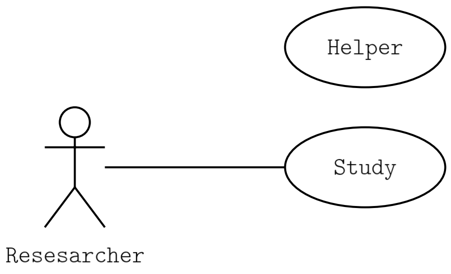
```
    ∀ measurement, model_instance, model, species
        (
            Model(model) ∧
            SimulatedModelInstance(model_instance) ∧
            Measurement(measurement) ∧
            Species(species) ∧
            *measurement_species*(measurement, species) ∧
            *measurement_simulation*(measurement,
    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 $\vee$ 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

8 OpenBox on the Slurm Workload Manager

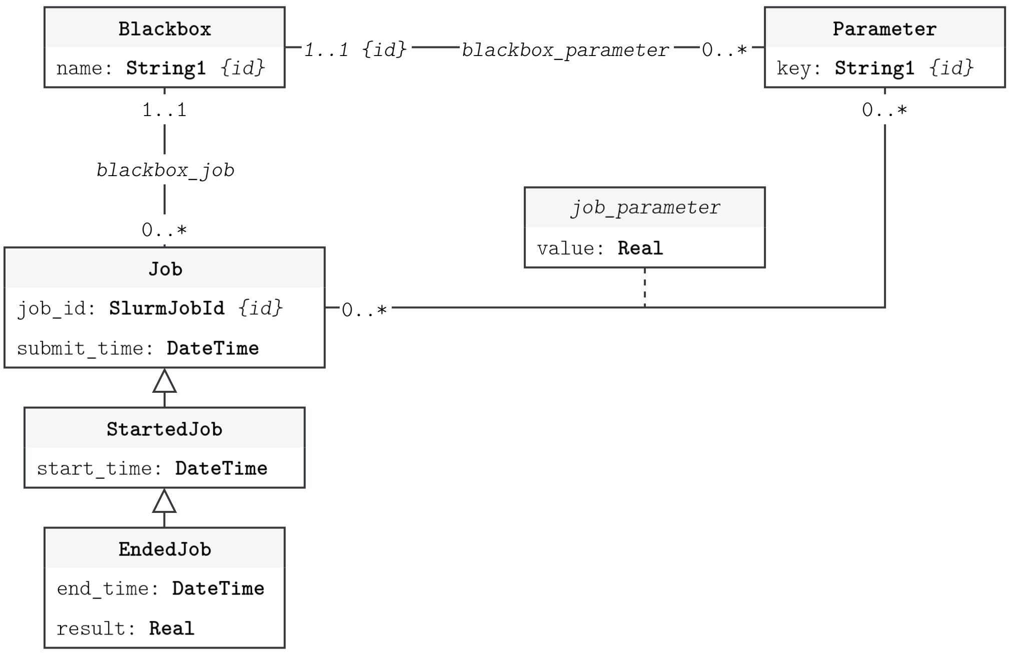
The HPC cluster at the Computer Science Department has some restrictions in place, as it's used by many different teams / students and no single user can request the indefinite usage of the whole cluster for a single job (jobs have a time limit of 6, 24 or 72 hours based on permissions and resoruces required).

The goals of this section are to

- be able to run an OpenBox throught **multiple sessions**
- run **multiple smaller jobs** to increase **fairness** among users, instead of running a single big job for the whole simulation
- provide a simple framework that can be used **locally to simulate** executions on the cluster

8.1 Analysis

In order to use OpenBox on the cluster in different sessions, it's a good idea to store the results of the simulations in a database (i.e. PostgreSQL) to retrieve the data of different session for an overall analysis.



8.1.1 Data types specification

`SlurmJobId` = `Integer` ≥ 1

`String1` = `String` matching regex `/^\S$|^\S.*\S$/`

8.1.2 Classes specification

8.1.2.1 Job

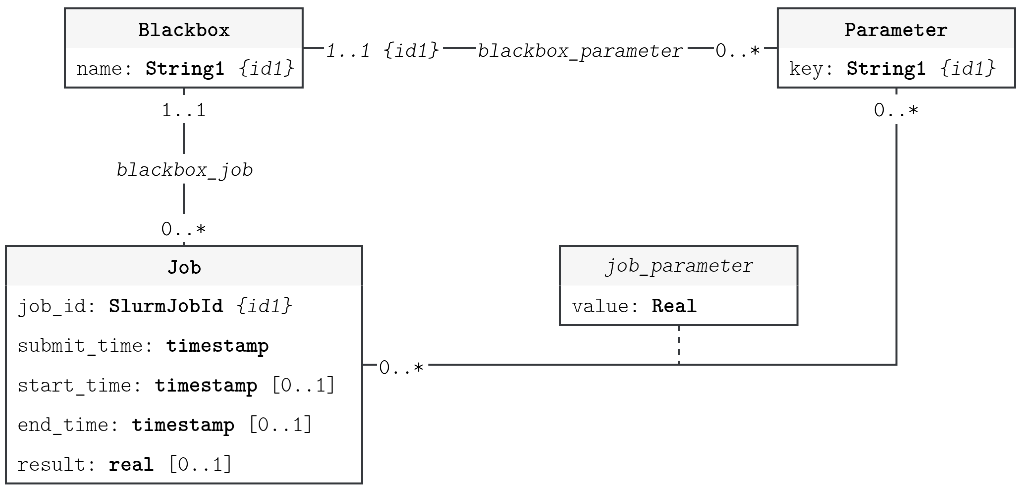
```
C.Job.all_parameters_are_instantiated
     ∀ job, blackbox, parameter
       (
         Job(job) ∧
         Blackbox(blackbox) ∧
         Parameter(parameter) ∧
         blackbox_job(blackbox, job) ∧
         blackbox_parameter(blackbox, parameter)
       ) →
         job_parameter(job, parameter)
```

```
C.Job.continuity_1
     ∀ job, submit_time, start_time
       (
         Job(job) ∧
         submit_time(job, submit_time) ∧
         start_time(job, start_time)
       ) →
         submit_time ≤ start_time
```

```
C.Job.continuity_2
     ∀ job, start_time, end_time
       (
         Job(job) ∧
         start_time(job, start_time) ∧
         end_time(job, end_time)
       ) →
         start_time ≤ end_time
```

8.2 Implementation

Diagram restructuration for PostgreSQL. The SQL code is available in the `migration.sql` file.



8.2.1 Data types definitions

```sql
CREATE DOMAIN String1 AS varchar CHECK(value ~ '^\S$|^\S.*\S$');
CREATE DOMAIN SlurmJobId AS integer CHECK(value >= 1);
```

8.2.2 Additional constraints

8.2.2.1 Job

```
C.Job.end_implies_job_was_scheduled
     $\forall\ job,\ end\_time$
       $(\mathrm{Job}(job) \land end\_time(job,\ end\_time)) \rightarrow$
         $\exists\ start\_time\ start\_time(job,\ start\_time)$
```

A result is present if and only if the job ended

```
C.Job.result_only_on_end_time
     $\forall\ job,\ job\_result$
       $(\mathrm{Job}(job) \land result(job,\ job\_result)) \rightarrow$
         $\exists\ end\_time\ end\_time(job,\ end\_time)$
```

```
C.Job.end_time_only_on_result
     $\forall\ job,\ end\_time$
       $(\mathrm{Job}(job) \land end\_time(job,\ end\_time)) \rightarrow$
         $\exists\ job\_result\ result(job,\ job\_result)$
```

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