Contents

https://sbml.org/documents/specifications/level-3/version-1/qual/
https://github.com/reactome/sbml-exporter?tab=readme-ov-file#known-limitations

1. Identifying the Reactome Compartment containing the Reactome PhysicalEntities that appear as SBML species in the resulting SBML model. It is not always clear from the database which Compartment is appropriate; as some PhysicalEntities list multiple Compartments to account for their possible location in different places. This issue is being addressed by the Reactome curators.
2. There are currently no SBOTerms created for any SBML reaction. The information in the ReactomeDB is not fine-grained enough to categorise types of Reactome ReactionLikeEvents. Work is progressing to provide this information.
3. Reactome creates some PhysicalEntities as a set of possible/probably participants in a Reaction. Currently these get encoded as a single SBML species and added as a reactant/product/modifier. This is inaccurate in terms of the intended meaning of an SBML species. Further thought is being given to how to more accurately portray this information in SBML.

Should inconsistent reactions be discarded from the final model?

1 Kinetic constants estimation in biochemical networks

Let $\mathbb{N}_1 = \mathbb{N} \setminus \{0\}$

1.1 Problem definition

Is it "species" a good name? Reactome uses `PhysicalEntity` because to Reactome `Species` indicates the organism studied (human, rat, etc…). In some papers I read the terms "substrate" (when referring to reactions) and "species" are used (I will stick with it).

Definition 1 (Biochemical network)**.** A biochemical network G is a tuple (S, R, E, ν, C) where

- $S = U \cup X \cup Y$ is the set of **species** of the biochemical network where
  - U is the set of input species of the network
  - X is the set of internal species
  - Y is the set of output species of the network
  - U, X, Y are **non-disjoint** sets
- R is the set of **reactions** in the biochemical network
  - $R_{\text{reversible}} \subseteq R$ is the subset of reversible reactions
- $E \subseteq S \times R \times T$ is the set of **relationships** between the species and reactions, with T as the set of relationship types
- $\nu = \left(\nu_{\text{reactant}}, \nu_{\text{product}}\right)$
  - $\nu_t : E_t \to \mathbb{N}_1$ with $t \in \{\text{reactant}, \text{product}\}$ are the stoichiometry functions for the reactants and products of the reactions
- C is the set of compartments in which the species are located
  - $f_C : S \to C$ is the function that determines the compartment of each species

    not necessary for kinetic laws, necessary for simulation

with

- $T = \{\text{product}, \text{reactant}, \text{enzyme}, \text{activator}, \text{inhibitor}\}$
- $E_t = \{(s, r) \mid (s, r, t) \in E\}$ is the projection of E over $t \in T$

Reactions have at most 1 enzyme

1.1.1 Rate laws

Given a biochemical network $G = (S, R, E, \nu, C)$

Let r be a reaction s.t. $r \in R_{\text{reversible}}$

$$v_r = k_+ \prod_{\substack{(s,r) \\ \in \\ E_{\text{reactant}}}} [s]^{\nu_{\text{reactant}}(s,r)} - k_- \prod_{\substack{(s,r) \\ \in \\ E_{\text{product}}}} [s]^{\nu_{\text{product}}(s,r)} \tag{1}$$

If $r \in R \setminus R_{\text{reversible}}$, then the rate rule can be simplified to

$$v_r = k_+ \prod_{\substack{(s,r) \\ \in \\ E_{\text{reactant}}}} [s]^{\nu_{\text{reactant}}(s,r)} \tag{2}$$

If an enzyme is involved in a reaction, let Equation 3 be the general form of a modular rate law that describes the kinetics of reaction $r \in R$ with $\mathbb{E}$ s.t. $(\mathbb{E}, r) \in E_{\text{enzyme}}$.

$$v_r = [\mathbb{E}] \cdot f_{\text{reg}} \cdot \frac{T}{D + D_{\text{reg}}} \tag{3}$$

where

$$f_{\text{reg}} = \prod_{\substack{(s,r) \\ \in \\ E_{\text{activator}}}} \frac{[s]^{n_s}}{K_s + [s]^{n_s}} \prod_{\substack{(s,r) \\ \in \\ E_{\text{inhibitor}}}} \frac{K_s}{K_s + [s]^{n_s}} \tag{4}$$

$$T = k_{\text{cat}}^{\text{for}} \prod_{\substack{(s,r) \\ \in \\ E_{\text{reactant}}}} \left(\frac{[s]}{K_{m,s}} \right)^{\nu_{\text{reactant}}(s,r)} - k_{\text{cat}}^{\text{back}} \prod_{\substack{(s,r) \\ \in \\ E_{\text{product}}}} \left(\frac{[s]}{K_{m,s}} \right)^{\nu_{\text{product}}(s,r)} \tag{5}$$

The denominator can be one of the following

1. Power-law modular rate law: $D = 1$ (such as mass action kinetics)
2. Common modular rate law

$$D = \prod_{\substack{(s,r) \\ \in \\ E_{\text{reactant}}}} \left(1 + \sum_{n=1}^{\nu_{\text{reactant}}(s,r)} \left(\frac{[s]}{K_{m,s}} \right)^n \right) + \prod_{\substack{(s,r) \\ \in \\ E_{\text{product}}}} \left(1 + \sum_{n=1}^{\nu_{\text{product}}(s,r)} \left(\frac{[s]}{K_{m,s}} \right)^n \right) - 1$$

3. Simultaneous binding modular rate law

$$D = \prod_{\substack{(s,r) \\ \in \\ E_{\text{reactant}}}} \left(1 + \frac{[s]}{K_{m,s}} \right)^{\nu_{\text{reactant}}(s,r)} \prod_{\substack{(s,r) \\ \in \\ E_{\text{product}}}} \left(1 + \frac{[s]}{K_{m,s}} \right)^{\nu_{\text{product}}(s,r)} \tag{6}$$

4. Direct binding modular rate law:

$$D_4 = 1 + \prod_{(s,r)\in E_{\text{reactant}}} \left(\frac{[s]}{K_{m,s}}\right)^{\nu_{\text{reactant}}(s,r)} + \prod_{(s,r)\in E_{\text{product}}} \left(\frac{[s]}{K_{m,s}}\right)^{\nu_{\text{product}}(s,r)} \tag{7}$$

5. Force-dependent modular rate law:

$$D_5 = \sqrt{\prod_{\substack{(s,r)\\ \in \\ E_{\text{reactant}}}} \left(1 + \frac{[s]}{K_{m,s}}\right)^{\nu_{\text{reactant}}(s,r)} \prod_{\substack{(s,r)\\ \in \\ E_{\text{product}}}} \left(1 + \frac{[s]}{K_{m,s}}\right)^{\nu_{\text{product}}(s,r)}} \tag{8}$$

The section below needs to be revisited, constants are not the same for all reactions! And better names should be given in order to describe the behaviour

Definition 2 (Dynamic biological model)**.** Given a biochemical network $G = (S, R, E, \nu)$ let $B = (G', \mathcal{K})$ be the biological model derived from G with added modular law kinetics, with $G' = (S, R', E', \nu')$ where

- $R' = R \cup R_{\text{input}} \cup R_{\text{output}}$ with
  - $R_{\text{input}} = \{r_s \mid s \in U - Y\}$
  - $R_{\text{output}} = \{r_s \mid s \in Y - U\}$
- $E' = E \cup \{(s, r, \text{product}) \mid r_s \in R_{\text{input}}\} \cup \{(s, r, \text{reactant}) \mid r_s \in R_{\text{output}}\}$
- $\nu' = (\nu'_{\text{reactant}}, \nu'_{\text{product}})$
  - $$\nu'_{\text{reactant}(s,r)} = \begin{cases} 1 & \text{if } (s,r) \in R_{\text{input}} \\ \nu_{\text{reactant}}(s,r) & \text{otherwise} \end{cases} \tag{9}$$
  - $$\nu'_{\text{product}(s,r)} = \begin{cases} 1 & \text{if } (s,r) \in R_{\text{output}} \\ \nu_{\text{product}}(s,r) & \text{otherwise} \end{cases} \tag{10}$$

Then $\mathcal{K}$, the set of constants, can be defined on G' as

$$\begin{aligned} \mathcal{K} = &\{k^{\text{for}}_{\text{cat},r} \mid r \in R'\} \cup \\ &\{k^{\text{back}}_{\text{cat},r} \mid r \in R'\} \cup \\ &\{K^r_{m,s} \mid (s,r) \in E'_{\text{reactant}} \cup E'_{\text{product}}\} \cup \\ &\{K^s_r \mid r \in R' \wedge (s,r) \in E_{\text{modifier}}\} \cup \\ &\{n^s_r \mid r \in R' \wedge (s,r) \in E_{\text{modifier}}\} \end{aligned} \tag{11}$$

where

- k_r is the kinetic constant of reaction r
- K^s_r is the apparent dissociation constant of modifier s in reaction r
- n^r_s the hill coefficient of modifier s in reaction r

Definition 3 (Biological model satisfiability problem)**.** Given a biological model $B = (G, \mathcal{K})$ and a let $\mathcal{S}$ be the set of concentrations of species of the species in the network, $\mathcal{S} = \{s \mid s \in S\}$ and $S_{\text{avg}} = \{s_{\text{avg}} \mid s \in S\}$ the set of average concentrations of the species, $T \in \mathbb{R}^+$ the time horizon, $\varphi \in [0, 1]$ the following constraints must hold:

$$\forall s \in \mathcal{S} \quad 0 \leq [s] \leq 1 \tag{12}$$

$$\begin{aligned} &\forall k_{r_1}, k_{r_2} \in \mathcal{K}, s \in S \\ &\quad (s, r_1, i) \in E \wedge (s, r_2) \in (E_{m^+} \cup E_{m^-}) \wedge r_1 \neq r_2 \rightarrow k_{r_1} < k_{r_2} \end{aligned} \tag{13}$$

$$\forall s \in \mathcal{S}_{\text{avg}} \quad s(\varphi \cdot T) - s(T) = 0 \tag{14}$$

Definition 4 (Optimization problem)**.**

2 Reactome modeling quirks

2.1 Species with multiple compartments

Because the functions of biologic molecules critically depend on their subcellular locations, chemically identical entities located in different compartments are represented as distinct physical entities. (Reactome paper)

```
MATCH (physicalEntity:PhysicalEntity)
WHERE EXISTS {
    MATCH
        (physicalEntity)--(compartment1:Compartment),
        (physicalEntity)--(compartment2:Compartment)
    WHERE
        compartment1 <> compartment2
}
RETURN COUNT(DISTINCT physicalEntity) // 6347
```

Listing 1: Entities connected to multiple compartments

```
MATCH (:PhysicalEntity)-[relation]-(:Compartment)
RETURN DISTINCT type(relation)
```

Listing 2: Types of relation between physical entities and compartments: `["compartment", "includedLocation", "goCellularComponent"]`

Complexes with components that span multiple cellular locations should specify one primary location as the compartment and the location of the other components will be automatically filled into the "includedLocation" attribute during the database release process. For example, a transmembrane complex with components in the extracellular space, plasma membrane, and cytosol would have plasma membrane specified as the compartment.

```
MATCH (physicalEntity:PhysicalEntity)
WHERE EXISTS {
    MATCH
        (physicalEntity)-[:compartment]-(compartment1:Compartment),
        (physicalEntity)-[:compartment]-(compartment2:Compartment)
    WHERE
        compartment1 <> compartment2
}
RETURN COUNT(DISTINCT physicalEntity) // 656
```

Listing 3: Entities with multiple compartments only using the `[:compartment]` relation

```
MATCH (physicalEntity:PhysicalEntity)
WHERE EXISTS {
    MATCH
        (physicalEntity)-[:compartment]-(compartment1:Compartment),
        (physicalEntity)-[:compartment]-(compartment2:Compartment)
    WHERE
        compartment1 <> compartment2
        AND NOT EXISTS {
            MATCH (compartment1)-[:surroundedBy]-(compartment2)
        }
}
RETURN COUNT(DISTINCT physicalEntity) // 491
```

Listing 4: Entities with multiple compartments where one compartment is not `[:surroundedBy]` the other

```
MATCH (physicalEntity:PhysicalEntity)
WHERE
    EXISTS {
        MATCH
            (physicalEntity)-[:compartment]-(compartment1:Compartment),
            (physicalEntity)-[:compartment]-(compartment2:Compartment)
        WHERE
            compartment1 <> compartment2
            AND NOT EXISTS {
                MATCH (compartment1)-[:surroundedBy]-(compartment2)
            }
    }
    AND "EntitySet" IN labels(physicalEntity)
RETURN COUNT(DISTINCT physicalEntity) // 491
```

Listing 5: Entities with multiple unrelated compartments which are entity-sets (how do I treat these?)

EntitySet [superclass]

- Used to maintain logical integrity of data model, not used for manual annotation. Two or more PhysicalEntities grouped because of a shared molecular feature or function. The superclass for CandidateSet and DefinedSet. While sets are, by default, homogeneous (members having the same subclass of PhysicalEntity), they are not required to be. For example, the defined set platelet alpha granule contents contains, as members, EntitiesWithAccessionedSequences, Complexes and Sets.

```
MATCH (reaction:ReactionLikeEvent)-[:input|output]-(:EntitySet)
RETURN COUNT (DISTINCT reaction) // 22576
```

CandidateSet

- A collection of physical entities that are functionally indistinguishable for the purpose of Reactome annotation, some of which are well-characterized (the "members" of the set) and some of which are incompletely characterized (the "candidates" of the set), as judged by the curator who assembles the set and the outside expert reviewers who evaluate it. Members of a set are related by an "OR" function. That is, either one member OR another member can participate in a reaction.

- Sets may be ordered or unordered as specified in the isOrdered attribute. A specific member of an ordered set has a correspondence with a specific member of another ordered set, as specified by their positions within the sets. For example, consider an ordered set containing substrate1 and substrate2 that reacts to yield an ordered set containing product1 and product2. In this case, substrate1 will yield product1 and substrate2 will yield product2. In the case of unordered sets, any member in an input set can correspond to any member in an output set. Sets in Reactome are considered ordered by default.

DefinedSet

- A collection of well-characterized physical entities that are functionally indistinguishable for the purpose of Reactome annotation, e.g., a collection of isoforms of a protein that all mediate the identical metabolic reaction. A set is formally a list of instances linked by logical ORs. Sets may be ordered or unordered as specified in the isOrdered attribute. A specific member of an ordered set has a correspondence with a specific member of another ordered set, as specified by their positions within the sets. For example, consider an ordered set containing substrate1 and substrate2 that reacts to yield an ordered set containing product1 and product2. In this case, substrate1 will yield only product1 and substrate2 will yield only product2. In the case of unordered sets, any member in an input set can correspond to any member in an output set. Sets in Reactome are considered ordered by default.

```
MATCH (physicalEntity:PhysicalEntity)
WHERE
    EXISTS {
        MATCH
            (physicalEntity)-[:compartment]-(compartment1:Compartment),
            (physicalEntity)-[:compartment]-(compartment2:Compartment)
        WHERE
            compartment1 <> compartment2
            AND NOT EXISTS {
                MATCH (compartment1)-[:surroundedBy]-(compartment2)
            }
    }
    AND EXISTS {
        MATCH (reaction:ReactionLikeEvent)--(physicalEntity)
    }
RETURN COUNT(DISTINCT physicalEntity) // 310
```

Listing 7: Set of entities with multiple compartments connected to at least a reaction

```
MATCH
    path1 = (reaction {dbId: 177941})-[:input|output]-(entity1:PhysicalEntity)
OPTIONAL MATCH path2 = (reaction)--(:CatalystActivity)--(:PhysicalEntity)
OPTIONAL MATCH path3 = (entity1)--(:Compartment)
RETURN path1, path2, path3
```

Listing 8: Example reaction that involves entities with multiple compartments

If a reaction involves entity sets, then create a new reaction for each compartment! Or instantiate the reaction for all the combinations of species in the set!

2.2 Reactions with multiple compartments

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)--(compartment1:Compartment),
        (reaction)--(compartment2:Compartment)
    WHERE
        compartment1 <> compartment2
}
RETURN COUNT (DISTINCT reaction) // 36322 (out of 93672)
```

Listing 9: Reactions connected to multiple compartments

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)--(compartment1:Compartment),
        (reaction)--(compartment2:Compartment)
    WHERE
        compartment1 <> compartment2
        AND NOT EXISTS {
            MATCH (compartment1)-[:surroundedBy]-(compartment2)
        }
}
RETURN COUNT (DISTINCT reaction) // 20974
```

Listing 10: Reactions connected to multiple compartments excluding "surroundedBy"

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)--(compartment1:Compartment),
        (reaction)--(compartment2:Compartment)
    WHERE
        compartment1 <> compartment2
        AND NOT EXISTS {
            MATCH (compartment1)--(compartment2)
        }
}
RETURN COUNT (DISTINCT reaction) 20833 (if you remove :surroundedBy)
```

Listing 11: https://reactome.org/PathwayBrowser/#/R-HSA-9646399&FLG=R-HSA-9640114&FLGINT

The fact that reactions are connected to multiple compartments is not a problem! In SBML compartments are optional for reactions, as the simulators should be able to deduce the compartment of the reaction based on the compartment of the substrate.

https://sbml.org/documents/faq/

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

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)--(compartment1:Compartment),
        (reaction)--(compartment2:Compartment)
    WHERE
        compartment1 <> compartment2
        AND NOT EXISTS {
            MATCH (compartment1)-[:surroundedBy]-(compartment2)
        }
        AND EXISTS {
            MATCH (compartment1)--(compartment2)
        }
}
RETURN COUNT (DISTINCT reaction) // 189 "componentOf"
```

```
MATCH (:Compartment)-[relation]-(:Compartment)
RETURN DISTINCT type(relation)
```

2.3 Species which are both inputs and outputs of a reaction

```
MATCH (reaction:ReactionLikeEvent)-[:input]->(entity:PhysicalEntity)
WHERE EXISTS {
    MATCH (reaction)-[:output]->(entity)
}
RETURN COUNT(n) // 1062
```

```
MATCH (n:ReactionLikeEvent)-[:input]->(p:PhysicalEntity)
WHERE EXISTS {
    MATCH (n)-[:output]->(p), (m)-[:output]->(p)
    WHERE n <> m
}
RETURN COUNT (n) // 895
```

```
MATCH (n:ReactionLikeEvent)-[:input]->(p:PhysicalEntity)
WHERE EXISTS {
    MATCH (n)-[:output]->(p), (n)-[:output]->(q)
    WHERE p <> q
}
RETURN COUNT (n) // 741
```

```
MATCH (n:ReactionLikeEvent)-[r1:input]->(p:PhysicalEntity)
WHERE EXISTS {
    MATCH (n)-[r2:output]->(p), (n)-[:output]->(q)
    WHERE
        p <> q
        AND r1.stoichiometry <> r2.stoichiometry
}
RETURN COUNT (n) // 36
```

Di queste 36, 24 sono “electron transfer”

```
MATCH (n:ReactionLikeEvent)-[r1:input]->(p:PhysicalEntity)
WHERE EXISTS {
    MATCH (n)-[r2:output]->(p), (n)-[:output]->(q)
    WHERE
        p <> q
        AND r1.stoichiometry <> r2.stoichiometry
}
AND NOT n.displayName STARTS WITH 'Electron transfer'
RETURN COUNT (n) // 12
```

```
MATCH (r:ReactionLikeEvent)
WHERE EXISTS {
    MATCH (r)--(c1:CatalystActivity), (r)--(c2:CatalystActivity)
    WHERE c1 <> c2
}
RETURN COUNT (DISTINCT r) // 17
```

```
MATCH path = ({dbId: 983702})--(:CatalystActivity)
RETURN path
```

Of these 12:

- 11: “CYP19A1 hydroxylates ANDST to E1”
- 1: “Prdm9 Trimethylates Histone H3 (murine, bovine)”

2.4 Modifiers which are both positive and negative regulators

Reactions that are driven by an enzyme are described as requiring a catalyst activity, modeled in Reactome by linking the macromolecule that provides the activity to the GO molecular function term [10,11] that describes the activity. In addition, the Reactome data model allows reactions to be modulated by positive and negative regulatory factors. When a precise regulatory mechanism ('positive allosteric regulation', 'noncompetitive inhibition') is known, this information is captured.

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)-[:catalystActivity]->
            (:CatalystActivity)-[:physicalEntity]->(enzyme),
        (reaction)-[:regulatedBy]->
            (:NegativeRegulation)-[:regulator]->(inhibitor)
    WHERE enzyme = inhibitor
}
RETURN COUNT(DISTINCT reaction) // 4
```

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)-[:regulatedBy]->
            (:PositiveRegulation)-[:regulator]->(enzyme),
        (reaction)-[:regulatedBy]->
            (:NegativeRegulation)-[:regulator]->(inhibitor)
    WHERE enzyme = inhibitor
}
RETURN COUNT(DISTINCT reaction) // 4
```

```
MATCH
    (reaction:ReactionLikeEvent),
    path1 = (reaction)-[:catalystActivity]->
            (:CatalystActivity)-[:physicalEntity]->(),
    path2 = (reaction)-[:regulatedBy]->
        (:NegativeRegulation)-[:regulator]->()
WHERE
    reaction.dbId IN [164341, 164087, 164136, 164055]
RETURN path1, path2
UNION
MATCH
    (reaction:ReactionLikeEvent),
    path1 = (reaction)-[:regulatedBy]->
        (:PositiveRegulation)-[:regulator]->(),
    path2 = (reaction)-[:regulatedBy]->
        (:NegativeRegulation)-[:regulator]->()
WHERE
    reaction.dbId IN [8950347, 10181912, 10290972, 10761215]
RETURN path1, path2
```

- top ones are all in either *"Mus musculus"* or in *"Rattus norvegicus"*

- bottom ones are basically the same reaction, but inferred to multiple species

2.5 Enzymes which are substrate too

```
MATCH (reaction:ReactionLikeEvent)
WHERE
    EXISTS {
        MATCH
            (reaction)--(:CatalystActivity)--(entity:PhysicalEntity),
            (reaction)--(entity)
    }
RETURN COUNT(DISTINCT reaction) // 10650
```

Listing 14: Enzymes which are also involved in the reaction

```
MATCH (reaction:ReactionLikeEvent)
WHERE
    EXISTS {
        MATCH
            (reaction)--(:CatalystActivity)--(entity:PhysicalEntity),
            (reaction)-[:input|output]-(entity)
    }
RETURN COUNT(DISTINCT reaction) // 10639
```

Listing 15: Enzymes which are either inputs or outputs of the reaction

2.6 Reactions with multiple enzymes

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)--(:CatalystActivity)--(entity1:PhysicalEntity),
        (reaction)--(:CatalystActivity)--(entity2:PhysicalEntity)
    WHERE
        entity1 <> entity2
}
RETURN COUNT(DISTINCT reaction) // 10916
```

Listing 16: Reations with multiple enzymes (this is given by complexes, I have to consider only the active unit!)

```
MATCH (reaction:ReactionLikeEvent)
WHERE EXISTS {
    MATCH
        (reaction)--(activity1:CatalystActivity),
        (reaction)--(activity2:CatalystActivity)
    WHERE
        activity1 <> activity2
}
RETURN COUNT(DISTINCT reaction) // 17
```

Listing 17: Reactions with multiple CatalystActivity

For this one can just create a new reaction for each different enzyme!

2.7 On the reversibility of reactions

```
MATCH
    path = (r1 {dbId: 1482894})-[:reverseReaction]-(r2),
    path2 = (r1)--(:PhysicalEntity),
    path3 = (r2)--(:PhysicalEntity)
RETURN path, path2, path3
```

Listing 18: On the reversibility of reactions

```
MATCH (:ReactionLikeEvent)-[relation]-(:ReactionLikeEvent)
RETURN DISTINCT type(relation)
```

Listing 19: List of relations between `ReactionLikeEvents` `["precedingEvent", "inferredTo", "normalReaction" "reverseReaction"]`

FailedReaction

- A FailedReaction instance is a step in a disease process that is directly affected by a loss-of-function (LoF) mutation (germline or somatic). This type of disease event has its normal ReactionLikeEvent counterpart (the reaction mediated by the un-mutated gene product) specified at its normalReaction attribute and is represented as having inputs (an abnormal physicalEntity plus any wild-type entities that are inputs in the normal reaction), but no outputs. FailedReaction instances are labeled with disease term(s) that are used to populate the disease attribute of the associated abnormal PhysicalEntity (GenomeEncodedEntitiy, Complex or EntitySet).

inferredFrom

- Points to the event or entity in another species that this event/entity has been inferred from. If the inference is based on computation only, this is indicated under evidenceType (= IEA).

```
MATCH (reaction:ReactionLikeEvent)-[:reverseReaction]-(:ReactionLikeEvent)
RETURN COUNT(DISTINCT reaction) // 224
```