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Detection and correction of non-conformities and redundancies in complexes of molecules in BioPAX

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Emmanuelle Becker

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Detection and correction of non-conformities and redundancies in complexes of molecules in BioPAX

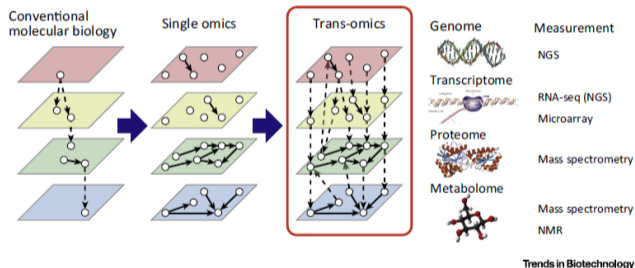
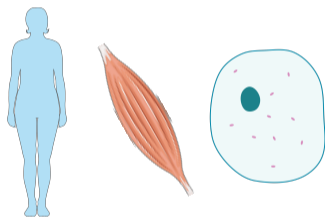
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Florence GONDRET² Emmanuelle BECKER¹

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²PEGASE, INRAE, Institut Agro, 35590, Saint Gilles, France

July 5, 2022

Biological context: understand how biological systems adapt to their environment

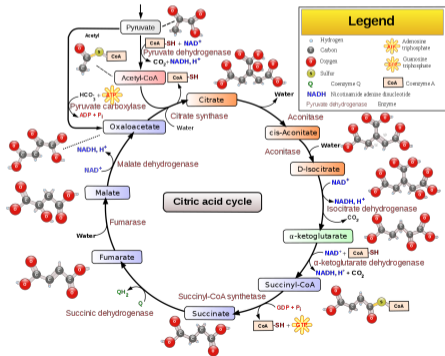


Understand the organization of biological pathways at different scales

Biological context: metabolic pathways and complexes

Biological pathway

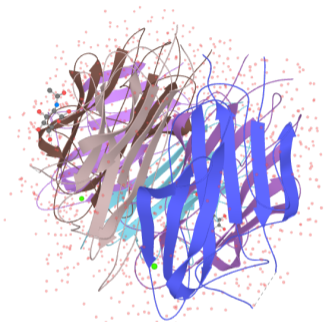
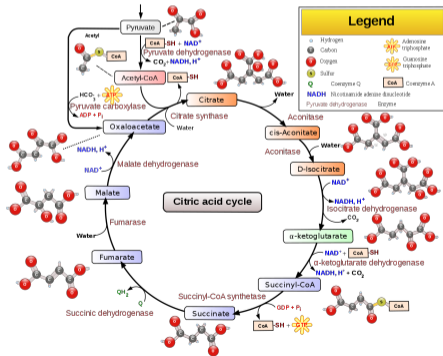
"a series of actions among molecules in a cell that leads to a certain product or a change in the cell" (NIH)



Biological context: metabolic pathways and complexes

Biological pathway

"a series of actions among molecules in a cell that leads to a certain product or a change in the cell" (NIH)



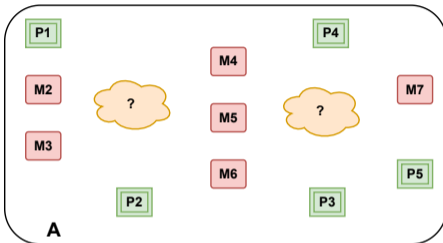
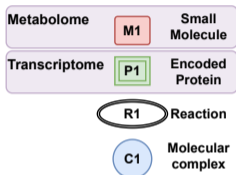
R-HSA-173584

Complexes and interactions in biology

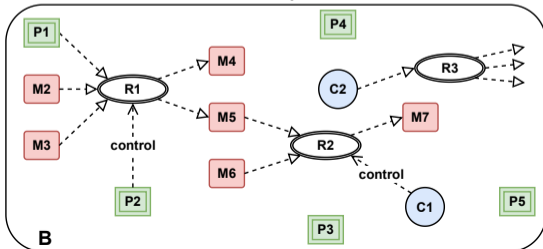
- Chemical assembly of **several molecules**
- Can either **participate in** or **control** interactions

Biological context: complexes play a major role in pathways

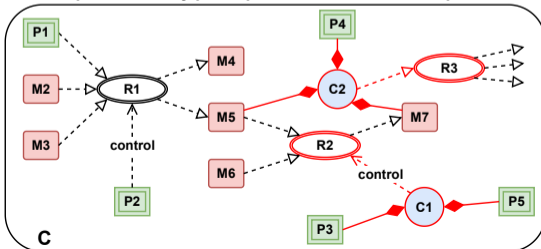
What we consider



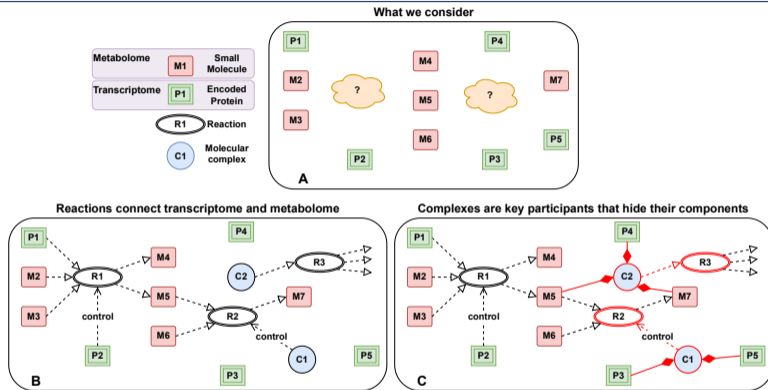
Reactions connect transcriptome and metabolome



Complexes are key participants that hide their components



Impact on the graph topology



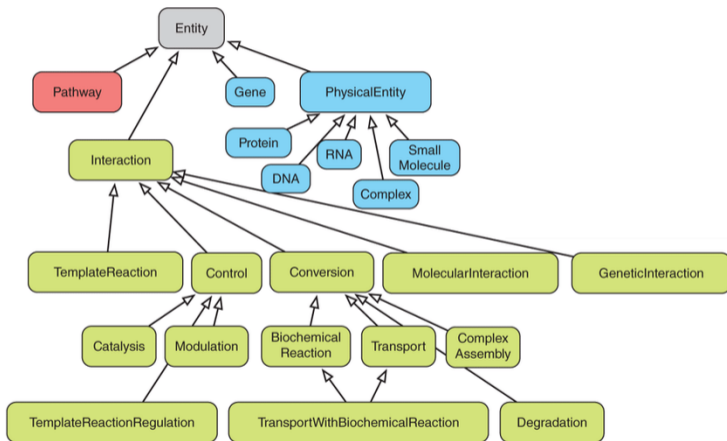
Taking into account (in)valid complexes is required for analyzing:

- Interactions in which a molecule participates
- Molecules participating in an interaction

Computational context: Biological Pathway Exchange format

Database of biological pathways in BioPAX

- **Reactome, KEGG, PathwayCommons...**
- Well established **ontology** to represent pathways at molecular and cellular levels
- Represented in **graphs** (RDF and OWL)
- Can be queried with **SPARQL**

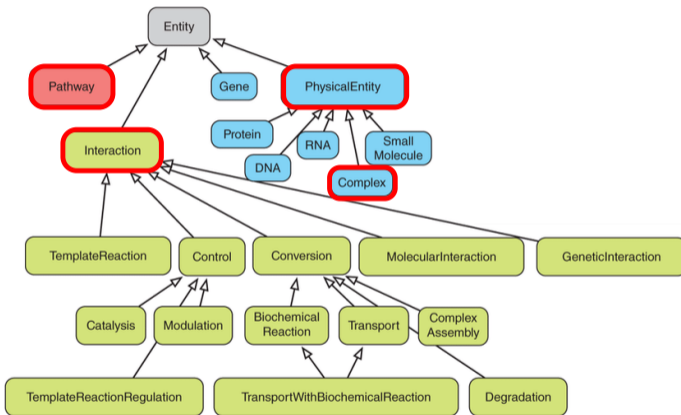


Demir et al. (2010)

Computational context: Biological Pathway Exchange format

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Demir et al. (2010)

In the Reactome database complexes participate to **32%** of the interactions

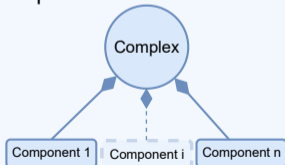
Issue: Complexes composed of other complexes

A complex cannot be composed of other complexes

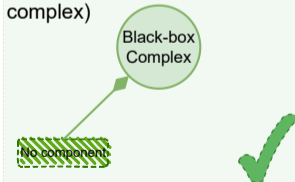
The components of a complex cannot have a component

Complexes

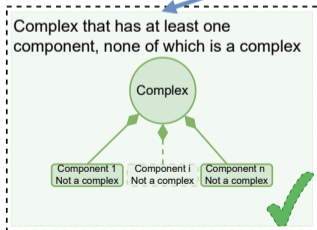
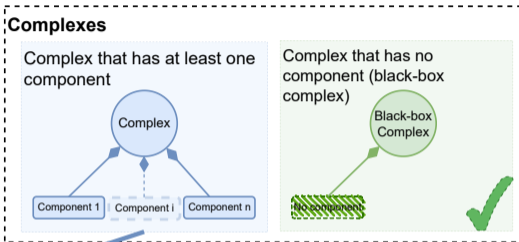
Complex that has at least one component



Complex that has no component (black-box complex)

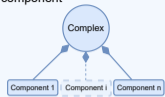


Issue: Complexes composed of other complexes

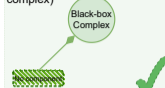


Complexes

Complex that has at least one component



Complex that has no component (black-box complex)

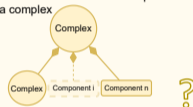


Complex that has at least one component, none of which is a complex



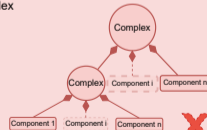
Complex that has at least one component that is a complex

Complex that has at least one component that is a complex

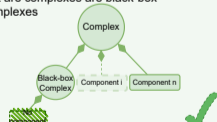


Complex that has at least one component that is another invalid complex

Complex that has at least one component that is a (valid) complex but not a black-box complex



Complex that has at least one component that is a complex, and all its components that are complexes are black-box complexes



We observed some invalid complexes in Reactome (not detected by the BioPAX validator)

Objectives

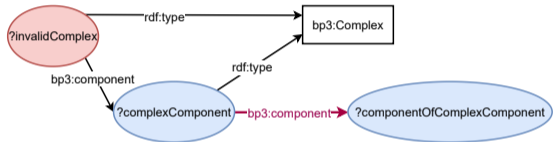
1. Identify invalid complexes
2. Fix invalid complexes
3. Evaluation of the benefits of the procedure

Contrib 1: Identify and quantify invalid complexes

Invalid complexes are composed of ≥ 1 complex with components

```
PREFIX rdf: <http://www.w3.org/1999/02/22-rdf-syntax-ns#>
PREFIX bp3: <http://www.biopax.org/release/biopax-level3.owl#>

SELECT DISTINCT ?invalidComplex
WHERE {
  ?invalidComplex rdf:type bp3:Complex .
  ?invalidComplex bp3:component ?complexComponent .
  ?complexComponent rdf:type bp3:Complex .
  ?complexComponent bp3:component ?componentOfComplexComponent .
}
```

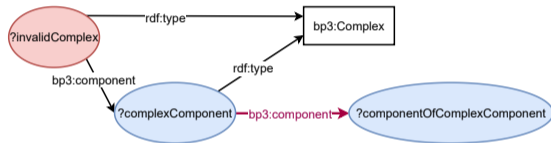


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```
SELECT DISTINCT ?invalidComplex
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  ?invalidComplex rdf:type bp3:Complex .
  ?invalidComplex bp3:component ?complexComponent .
  ?complexComponent rdf:type bp3:Complex .
  ?complexComponent bp3:component ?componentOfComplexComponent .
}
```



Use case



reactome

(v79)

Homo sapiens: 39% complexes are invalid out of 14,840

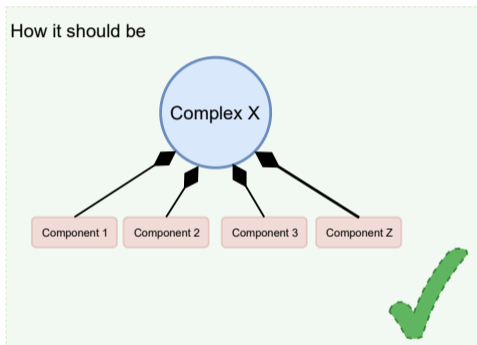
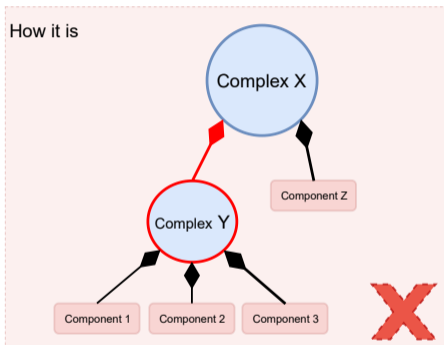
Mus musculus: 39% complexes are invalid out of 10,761

Sus scrofa: 40% complexes are invalid out of 7,769

Complexes represent a large fraction of biological entities

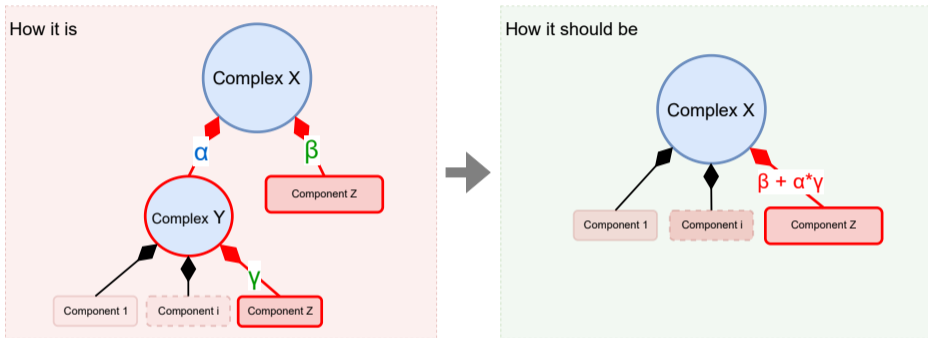
Invalid complexes are present in large quantities in the data sets of different organisms

Contrib 2: Fix the invalid complexes



Collapse as direct components all the (in)direct components that do not have component

Contrib 2: Fix the invalid complexes

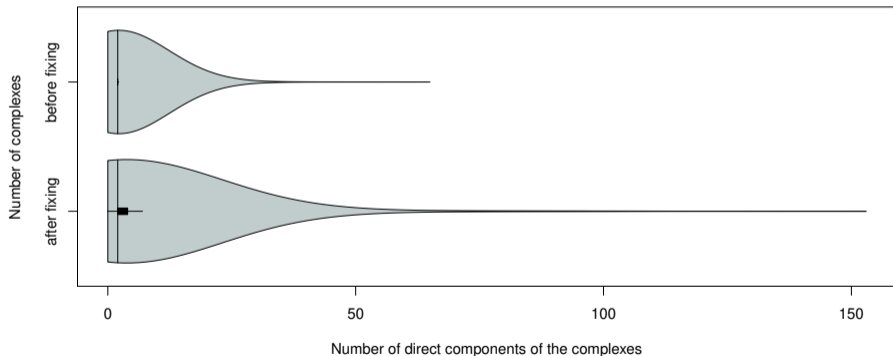


$$S(Z) = \sum_{p \in \text{parent nodes}}^P S_p(Z) * S(p)$$

Stoichiometry has to accommodate the fact that components can occur at several places

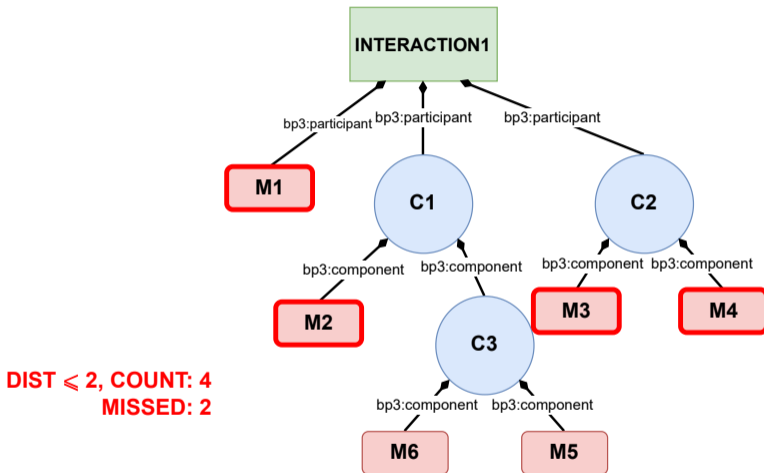
Contrib 3: Homo sapiens Reactome use-case (repair)

All invalid complexes were fixed



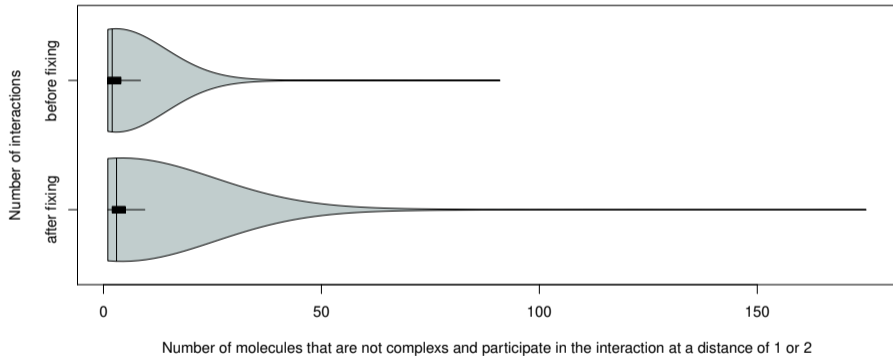
Fixing invalid complexes increases the number of direct components

Number of molecules that are not complexes and participate in interactions at a distance of 1 or 2



2 molecules missed due to invalid complexes

Impact on the graph topology



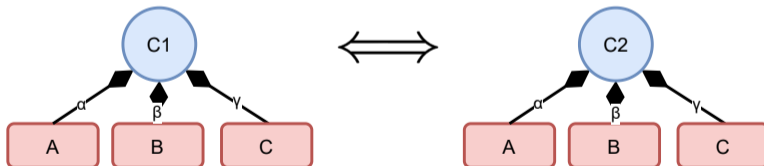
Taking into account invalid complexes has a strong impact on the interaction graph topology

Side effect: detection of artificial redundancy (Homo Sapiens)

What we call redundant complexes:

Complexes that share the **same components** with the **same stoichiometric coefficients** and have the **same cellular location**

Before fixing, we identified **241** of these complexes

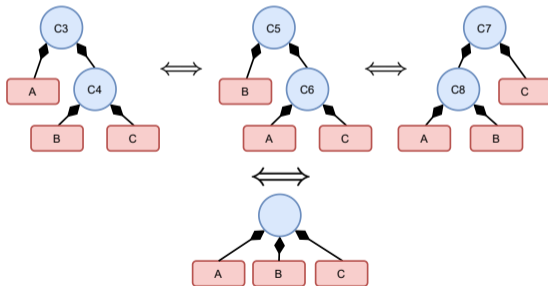


Side effect: detection of artificial redundancy (Homo Sapiens)

What we call redundant complexes:

Complexes that share the **same components** with the **same stoichiometric coefficients** and have the **same cellular location**

Before fixing, we identified **241** of these complexes



Fixing invalid complexes allowed to identify **92** additional redundant complexes (+38%)

Conclusion

- Semantically-rich queries for identifying and fixing invalid complexes that are **reproducible** on other databases
- Improves the conformity and the analysis of the graph by repairing the **topology**
- Will allow to **apply reasoning methods on better quality data**
- Will allow a better understanding of the **regulation of complex phenotypes**
- Side effect of **allowing the detection of complex redundancies**
- Essential methodology to **analyse and advance in the knowledge of biological processes**

Acknowledgments



Team Croissance



camille.juigne@irisa.fr

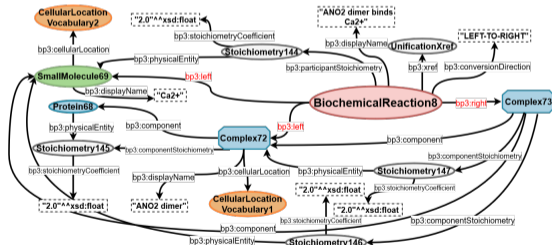
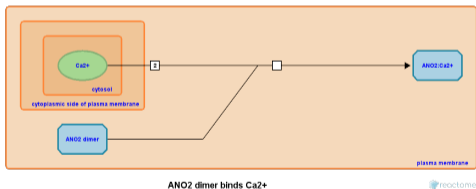
Appendix

Issue: Complexes composed of other complexes

Complex component: defines the subunits of a complex (BioPAX v3 spec)

"This property should not contain other complexes, i.e. it should always be a flat representation of the complex. [...]"

Exceptions are black-box complexes (i.e. complexes in which the component property is empty), which may be used as component's of other complexes because their parts are unknown."



We observed some invalid complexes in Reactome (not detected by the BioPAX validator)