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Conciliation of process description and molecular interaction networks using logical properties of ontology

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Background: Systems biology is mostly based on network analysis. Biological networks can be represented in different ways, from molecular interaction networks (MIn; e.g. for genome regulation) to process description networks (PDn; e.g. for systems dynamics). The choice of the representation is a key element to provide consistent answers to an initial hypothesis. Usually, public resources (e.g. the STRING database, KEGG, Reactome...) provide a single network representation that is not necessarily appropriate to the expected analysis. Yet, all types of network representations are intrinsically structured and manageable by logical rules. Thus, it opens perspectives to switch between network representations.

Ontologies are able to manage knowledge and manipulate object properties using logical descriptions and rules. We hypothesize that they are a suitable framework to deal with these perspectives. Here we present an ontology-driven methodology that results in the addition of MIn properties to PDn.

Methods: We designed the Molecular Network Ontology (MNO), which contains 42 classes imported from the Systems Biology Ontology and the Biological Interlocked Process Ontology for a) molecular reactions (e.g. binding, conversion or transcription) and b) molecular participants (e.g. gene, native gene product or converted gene product). Then, process classes were formally defined according to participant classes using the “has input”, “has output”, “positively mediated by” or “negatively mediated by” properties.

The macrophage signal transduction map (MSTM) is a curated PDn that contains 724 molecular reactions involving 1,353 participants. As a use case, the MSTM network was integrated into MNO: reactions and biochemical entities or genes from MSTM became individual instances of process classes and participant classes, respectively. Edges from MSTM were represented by MNO properties. Other information (identifiers, cross-references to the literature or databases) were kept as individual annotations. Then, logical rules were designed to infer molecular interactions from the initial process descriptions.

Finally, in order to validate the consistency of the logical reasoning results, we compared the MIn inferred by MNO and the MIn provided by STRING, after extraction of the set of genes contained in MSTM.

Results: MNO can fully integrate process description information into its classes, then logical rules can automatically enrich the initial PDn properties with consistent MIn properties.

Conclusion: MSTM manipulation by MNO showed that an ontology can integrate different molecular network representations from a single complex one. MNO does not work as a translator but adds new properties between molecular entities and keeps the initial ones. MNO takes advantage of ontology abilities: the integration of knowledge as individual instances of formal classes and the enrichment of relationships thanks to logical reasoning. Ontologies can enrich but cannot create knowledge: MNO is thus able to infer molecular interaction properties from PDn, but is unable to infer process properties from MIn wherein processes are not described. Such a resource opens perspective to expand the choice of appropriate networks for systems biology analysis.