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Gene Ontology Causal Activity Modeling (GO-CAM) moves beyond GO annotations to structured descriptions of biological functions and systems

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Abstract

To increase the utility of Gene Ontology annotations for interpretation of genome-wide experimental data, we have developed GO-CAM, a structured framework for linking multiple GO annotations into an integrated model of a biological system. We expect that GO-CAM will enable new applications in pathway and network analysis as well as improving standard GO annotations for traditional GO-based applications.

Introduction

The Gene Ontology was created as a computational structure for conceptualizing and describing gene function (1). The broad aims were 1) to create an ontology of gene function, a comprehensive set of terms and relationships between them, and 2)

to support functional annotation of genes. At the time the GO was developed, the first whole genomes were being sequenced, and statements about gene function were conceived of as "annotations" on the "book" of the genome. The goal was to apply a consistent set of concepts describing gene function to a broad range of eukaryotic model organisms (later extended to prokaryotes and viruses). This application would enable the identification of evolutionarily shared genetic programs, with the ultimate goal being to shed light on the functions of human genes based on knowledge about genes in model organisms.

The development of the GO has always been tightly coupled to its use in describing the functions of genes across a wide variety of organisms. New biological concepts, and the revision of existing ones, were and still are driven primarily by requests from expert biocurators, who read published scientific articles reporting discoveries of the functions of gene products and "annotate" the gene with terms selected from the GO. Thus, the GO ontology enumerates the universe of possible functions performed by genes, while GO annotations specify the functions that have been experimentally observed or otherwise inferred for a particular gene. In the initial publication, Ashburner *et al*. (1) emphasized the independence of each of the aspects of the GO. This was an important advance, because it clarified the diverse uses of the word "function" in the biological literature. In the GO, molecular functions (the activities of gene products at the molecular level, such as catalysis of a reaction) are distinct from cellular components (the location, relative to cellular structures, where the gene product is active), and distinct from biological processes (the larger biological "aims" carried out by a series of molecular functions).

At its core, a GO annotation is an association between a single gene and a single GO term (Figure 1a), and a record of the supporting scientific evidence for the association. This association is a statement about some aspect of the function of that gene. However, because it refers to a single GO term, **each GO annotation is necessarily a partial functional description, and there is no representation of how different annotations for the same gene fit together into a more complete description**. As a result, a GO annotation often represents a minimal, discrete piece of biological knowledge that can be determined from one, or at most a few, experiments that appear in a typical scientific paper. The simplicity of the GO annotation structure was a key driver for its success. Over the past 20 years, the GO knowledgebase has become indisputably the largest repository of computational representations of gene functions (2). The ontology currently contains roughly 45,000 terms, and the annotation database has over 750,000 experimental gene annotations, taken from 150,000 distinct scientific publications and contributed by biocurators from around the globe. During this period, we have made many advances in the Gene Ontology itself to facilitate computational analysis (3,4). In contrast, the representation of statements about gene function as separate "annotations" has remained essentially unchanged, until now.

In order to represent more complex statements about biological functions in a way that is scalable and structured, we introduce here a framework we call Gene

Ontology Causal Activity Modeling (GO-CAM). GO-CAM extends the existing annotation paradigm by introducing the concept of a **model**, which is a collection of connected GO annotations (plus contextual information from other ontologies) linked together according to a defined schema. Figure 1 illustrates how multiple GO annotations for the function of NEDD4 in UV-induced transcriptional arrest (5) are linked together in GO-CAM into a more complete, integrated model. If standard GO annotations are analogous to phrases of text, GO-CAM allows us to use these phrases to build sentences, paragraphs and whole documents.

The core structure of GO-CAM

The GO-CAM formalism defines a schema that combines multiple simple GO annotations into an integrated, semantically precise and computable model of biological function. It formalizes the relationships between annotations by integrating different aspects of function, as shown in Figure 2. Each element of GO-CAM refers to terms from an ontology or other standard identifier (Table 1). As originally defined by Ashburner et al. (1) and further elaborated by Thomas (6), a **molecular activity** (GO *molecular function* annotation) of a gene product occurs in a **location** (GO *cellular component* annotation) and is part of a larger **biological program** (GO *biological process* annotation). In GO-CAM, relations to terms from other ontologies can provide additional specificity: for location, a cellular component can be part of a specified cell type, which in turn can be part of a specified anatomical structure; an activity can occur during a specified temporal period (biological phase).

In addition, a molecular activity can have a **causal effect** on another molecular activity. Previously, these were represented as annotations to GO terms from the *regulation of molecular function* branch of the ontology, but in GO-CAM we represent these instead as separate activities linked by a relation from the causal relation branch of the Relations Ontology (7). Note that causal relations can have a positive or negative direction of effect, and encompass many different terms such as *directly regulates*, or *causally upstream of*. By linking together chains of effects, GO-CAM models can specify causal pathways of arbitrary size and branching.

GO-CAM records the evidence for each element of a model

GO-CAM preserves and extends the way in which GO annotations are currently supported by scientific evidence. As described above, each GO-CAM model is composed of "triples" that specify a subject, a relation and an object (e.g. in Figure 1b, ubiquitin-protein transferase activity *enabled by* NEDD4), and each triple must be supported by evidence. As is currently done for all GO annotations, GO-CAM models use the Evidence and Conclusion Ontology (ECO) for specifying the type of evidence (13). An advance in GO-CAM over simple annotations is that a triple can be supported by more than one piece of evidence. Furthermore, like standard GO annotations, GO-CAM triples may not be completely consistent. We recognize that current knowledge of biological systems is incomplete, and in some cases contradictory models may have been proposed. In these cases, multiple alternative models (or different triples in the same GO-CAM model) will co-exist in the GO knowledgebase, and can be revised later in response to additional experimental evidence.

Modeling biological pathways in GO-CAM

As an example of the power of GO-CAM models to represent more complex processes such as signaling pathways, we consider a model of the canonical Wnt signaling pathway (Figure 3). The pathway was constructed by combining standard annotations (one gene to one GO term, e.g. *receptor ligand activity* enabled by WNT3). Causal relations between activities were then added manually using Noctua, the collaborative web curation platform we have developed to support GO-CAM modeling (http://noctua.geneontology.org).

Figure 3 shows the "curator view" of a portion of the GO-CAM model for the initial steps in the canonical Wnt signaling pathway using FZD1 and WNT3 as the receptor-ligand pair. The model comprises multiple molecular activities linked by causal relationships (*directly positively regulates*, *directly negatively regulates*, *positively regulates*, *negatively regulates*); direct relations indicate regulation via direct physical interactions. Each molecular activity is carried out by either a single gene product (*e.g.* WNT3) or a complex of gene products (*e.g.* the beta-catenin destruction complex). A distinct sub-process (regulation of proteasomal protein catabolic process, GO:0010498) represents the use of the relatively general "constitutive" proteasomal degradation process to negatively regulate beta-catenin activity.

As Figures 1b and 3 show graphically, a GO-CAM model has similarities to the "cartoons" published in many molecular biology papers showing how gene product activities causally relate to each other; the primary differences are that, in GO-CAM, 1) the model explicitly represents dynamic **molecular activities** instead of using gene names to stand in for activities, and 2) all entities, activities, processes, locations, and relations are specified from **ontologies** rather than free text or

ambiguous symbols. The GO-CAM schema thus provides a defined, structured representation that makes it computable, i.e. usable in computational analyses, such as complex queries and searches including across causal paths, as well as enrichment analysis tools for analyzing genomics data sets. It utilizes the extensive structure of the Gene Ontology to simplify and abstract away the explicit biochemical details without losing that information; for example, the GO term *protein kinase activity* is already defined in terms of the reaction it catalyzes, including reactants (ATP and a protein substrate) and products (ADP and a phosphorylated protein).

The GO-CAM model repository

Currently there are over 2,300 GO-CAMs of varying complexity, containing over 11,000 distinct triples, encompassing 16 species and over 1,600 gene products. These are currently available from the GO-CAM public site (http://geneontology.org/go-cam), where they can be browsed and visualized. GO-CAM models are created as part of the existing GO annotation curation process, by trained GO curators from multiple groups that are distributed internationally and meet regularly to ensure a consistent process. Moving forward, all GO annotations will be represented using GO-CAM. We are currently beginning the process of importing legacy standard annotations to the GO-CAM repository, with most existing standard GO annotations initially grouped into a single model per gene product. Ongoing curation will move toward models for the most specific GO biological process terms in the ontology (pathways and other coordinated processes). Formally, the GO-CAM models are expressed in RDF/OWL (14), a semantic web standard that makes them interoperable with a large set of computational tools. To enable use of GO-CAM in Cytoscape and other network analysis tools (15,16), we also provide the causal network in Simple Interaction Format (for more information on conversion and information loss, see http://geneontology.org/go-cam/docs).

GO-CAMs are converted to standard GO annotations

Because GO-CAM links together standard GO annotations, each model can be decomposed into its constituent standard GO annotations. The GO-CAM-derived annotations are integrated into the standard GO annotation releases, and so are already in widespread use. The conversion process inevitably loses some of the information in the full GO-CAM (see http://geneontology.org/go-cam/docs for more detail). Briefly, the conversion involves following chains of multiple relations in the GO-CAM model (e.g. making a GO *biological process* annotation requires following the *enabled by* relation to a molecular activity, then a *part of* relation to a GO *biological process* term, see Figure 2), as well as logical reasoning (e.g. the conversion uses "logical definitions" of GO terms to infer, for example, that if a molecular activity *directly regulates* a *protein kinase activity*, then that activity can be also be classified as a *protein kinase regulator activity*).

We have found that the GO-CAM curation process of specifying an explicit biological model is leading to improved quality and consistency of GO annotations. For *biological process* annotations, GO-CAM modeling aids curators in determining which gene functions are **parts** of a process, which ones **regulate** that process, and which are part of **upstream** processes that otherwise affect the process. For example, Wnt ligands are post-translationally processed and trafficked through the secretory system by enzymes such as acyltransferases and carrier proteins, respectively. In the past, curators had often annotated these upstream gene products to *Wnt signaling pathway*, or *regulation of Wnt signaling pathway*, to capture the idea that they are "in some way related" to Wnt signaling; with GO-CAM upstream causal activities can be represented without losing the distinction between gene products that execute a given biological program versus those that affect that program. Further, a GO-CAM model can be used as a reference, or template, for new curation of homologous or analogous biological systems. As a result, similar processes and pathways can be annotated much more consistently.

Conclusion

GO-CAM provides a computational framework for representing integrated models of the activities of specific genes as well as the larger biological programs to which they contribute. This framework formalizes and extends GO annotations (statements about specific gene functions) analogously to how, starting 20 years ago, the Gene Ontology formalized an ontology of gene function descriptions. GO-CAM explicitly defines the relationships between: 1) different aspects (molecular function, biological process, cellular component) of the function of each gene, 2) the functions of different genes in a larger system, and 3) functions and critical context such as cell type and developmental stage. GO-CAM provides a framework for representing (and answering complex queries about) *qualitative, causal models* of how activities of gene products work together to execute a biological program, but does not represent biochemical details like stoichiometry or reaction kinetics.

By clarifying how a basic, building-block GO annotation relates to a description of overall gene function, GO-CAM leads to increased quality and consistency of GO annotations. As the rate-limiting step in creating GO annotations is reading the primary scientific literature, we do not expect any loss in curation productivity using GO-CAM. Instead, we expect that the ability to link together standard GO annotations into larger models will obviate the need for adding increasingly complex, combinatorial terms (e.g. *Wnt signaling involved in kidney development*, *Wnt signaling involved in heart development*, etc.) to the GO ontology itself, thus simplifying its maintenance and use. Because GO-CAMs are automatically converted (with some loss) into standard GO annotations as part of the GO release pipeline, the new formalism will continue to support the many current applications of GO annotations. The causal networks in GO-CAM models will also enable entirely new applications, such as network-based analysis of genomic data (17-22), and logical modeling of biological systems (23,24). In addition, the models may also prove useful for pathway visualization. For example, the activity-based representation of

GO-CAMs is compatible with the "activity flow" diagrams of the Systems Biology Graphical Notation (SBGN) standard (25). With GO-CAM, the massive knowledgebase of GO annotations collected over the past 20 years can be used as the basis not only for a "genomic biology" representation of gene function, but also for a more expansive "systems biology" representation and its emerging applications to the interpretation of large-scale experimental data.

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Author contributions

P.D.T. conceived the framework and supervised its development. C.J.M. developed the OWL representation with contributions from D.O.S and J.P.B, and supervised software implementation. H.M. developed the framework specification and alignment with SBGN. D.O.S., D.P.H. K.v.A., and P.G. refined the Gene Ontology to ensure compatibility with the framework. D.P.H., K.v.A. and P.G. extended the framework to cover multiple types of biological systems, and tested the curation software. S.C. architected the Noctua curation software, and S.C., J.P.B. and B.G. implemented the back-end software and OWL representation. L.-P.A. implemented the public facing interface, and performed QC and developed queries for the GO-CAM repository. S.E.L. helped supervise software implementation. P.D.T. and C.J.M. wrote the paper, with input from all authors.

Competing interests statement

The authors declare no competing interests.

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333

334 Figure legends

335

336 **Figure 1. Standard GO annotations vs. GO-CAM model.** The same biological
337 model (how NEDD4 represses RNA transcription in response to UV-induced DNA

damage as elucidated in (5)) is depicted in **a)** as a set of disconnected GO annotations, each covering a partial description of the overall function; and in **b)** as a GO-CAM model, linking together GO annotations into a structured model of NEDD4 functions, including the effect of NEDD4's activity on the activity of a macromolecular complex, RNA polymerase II. GO molecular functions are shown in white boxes, cellular components in green, and biological processes in light blue. Gene products or complexes are shown in brown if they execute an activity (e.g. NEDD4), and in dark blue if they are acted upon by an activity (e.g. RNA polymerase II in the left part of panel b). The causal relationship representing how the activity of NEDD4 *directly negatively regulates* the activity of RNA polymerase II, which is captured indirectly in the last annotation in panel a, is shown as a red arrow in panel b. Coloring conventions are retained in Figures 2 and 3 below.

Figure 2. An overview of the structured representation defined by GO-CAM. Arrows are relations from the Relations Ontology, and all boxes must refer to a class from an ontology (or other stable object identifier) as described in Table 1. The core of the model is a Molecular Activity, which is carried out (*enabled*) by a specific gene product or macromolecular complex (Active Entity, brown) and may act on a specific Target Entity (dark blue). An activity *occurs in* a specific Location (green), is *part of* a specific Biological Program (light blue), and may *occur during* a specific Biological Phase (gray). In addition, the activity may have *causal effects* on other activities (red arrow). Curved *part of* arrows indicate that smaller processes can be nested as modules inside larger processes (blue), or that an activity is known to occur in a specific cell type or anatomical structure (green, e.g. nucleus *part of* neuron). More detail on the GO-CAM specification can be found at http://geneontology.org/go-cam/docs.

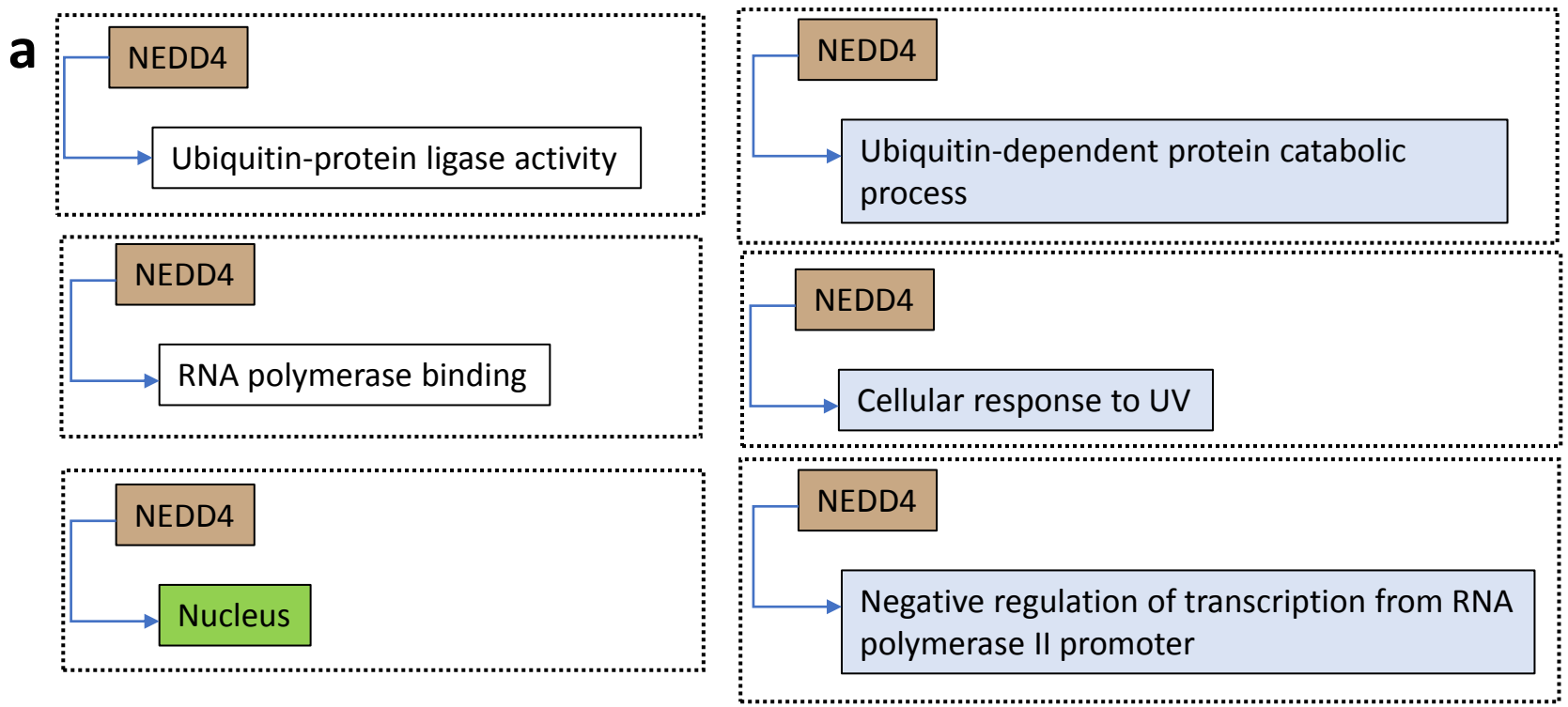
Figure 3. GO-CAM model of initial steps in the canonical Wnt signaling pathway. This diagram is a screenshot of the interface of the web-based curation platform (Noctua) for GO-CAM models. In this view, each molecular activity is represented by a box, and some of the properties in Figure 2 (the active entity, the location and the target entity) are "folded" into that box. The beta-catenin destruction complex is not folded into its activity box, so that the constituent gene products (e.g. AXIN1) are visible. Noctua is available at http://noctua.geneontology.org (the URL for this model is http://model.geneontology.org/596ef51500000088).

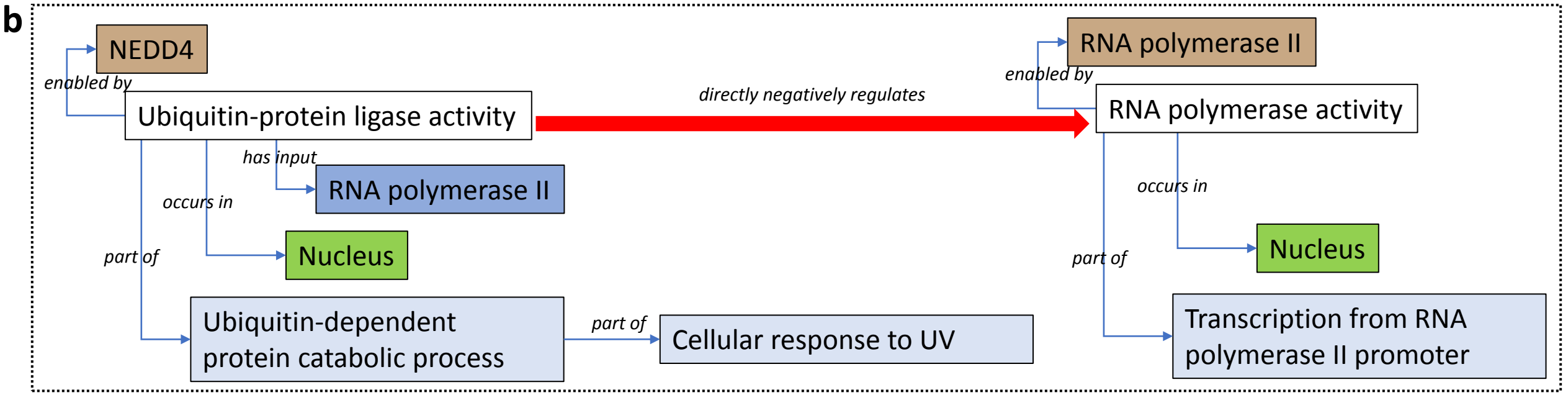
Tables

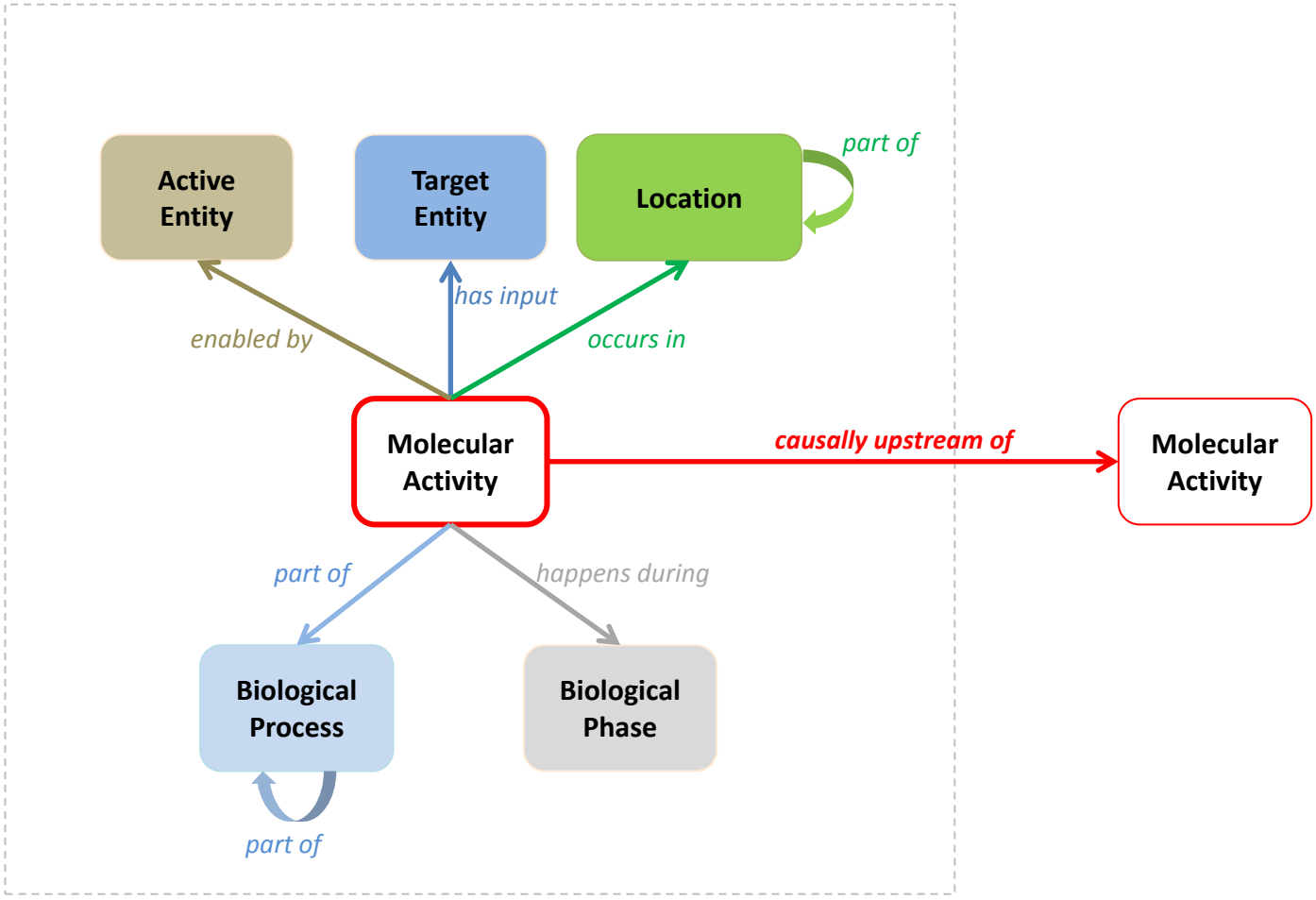
Table 1. GO-CAM elements and ontologies used. Note that the formalism follows GO annotation practice: gene products (or complexes comprising multiple gene products) have molecular activities (GO molecular function), are active in specific locations (GO cellular component) and act as part of larger biological programs (GO

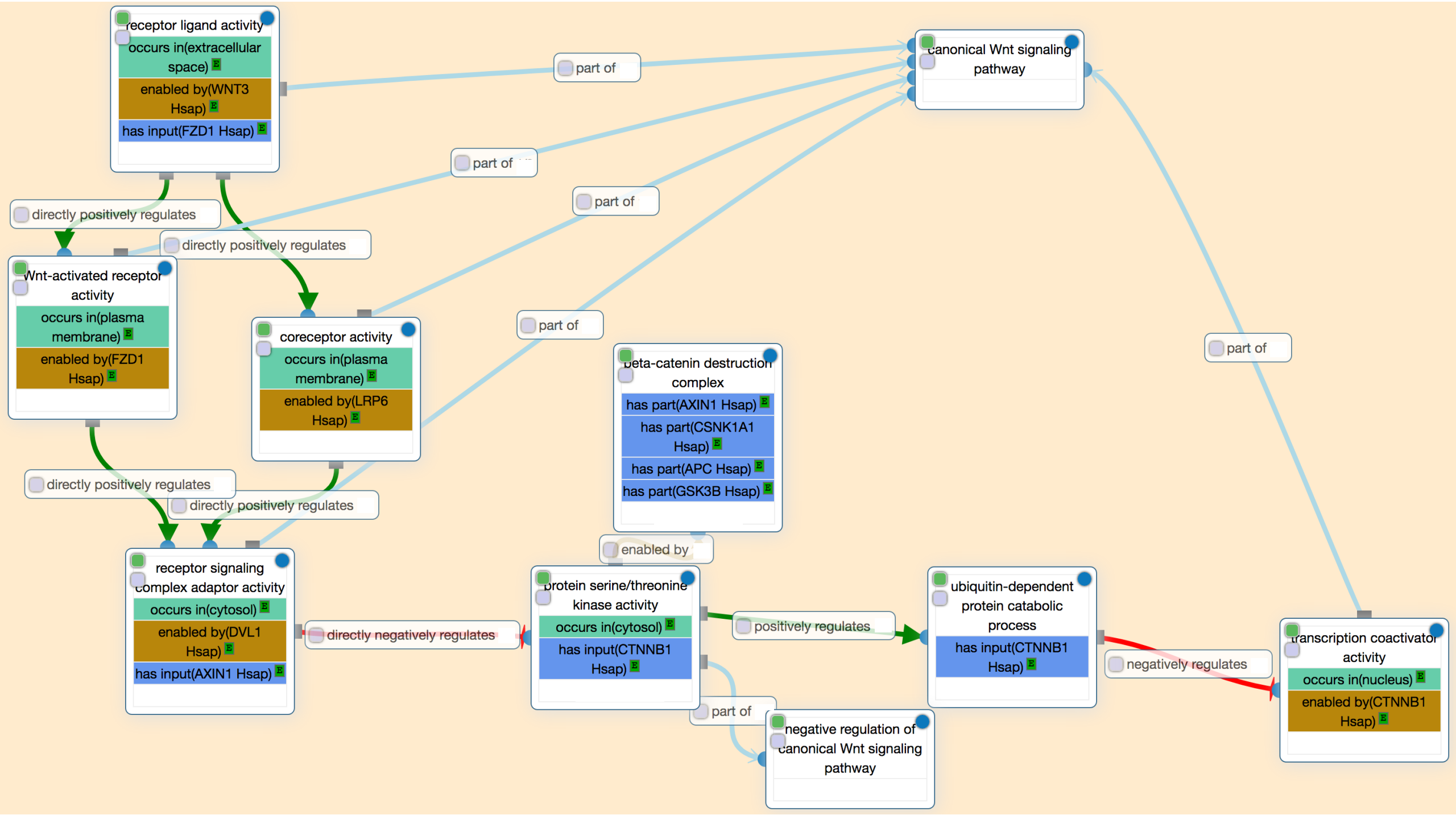
biological process). Other elements of GO-CAM provide further structured extensions of standard GO annotations.

GO-CAM element (Figure 2)	Ontology or identifier source(s)	Example
Molecular activity	GO molecular function	ubiquitin-protein transferase activity (GO:0004842)
Biological process	GO biological process	cellular response to UV (GO:0034644)
Location	GO cellular component	nucleus (GO:0005634)
	Cell Type Ontology (CL) (8)	retinal cell (CL: 0009004)
	anatomy ontologies, e.g. UBERON (9), *C. elegans* gross anatomy (10), EMAPA (11)	eye (UBERON: 0000970)
Active entity	Gene, protein, RNA or complex identifier from a standard source, e.g. HGNC for a human gene	NEDD4 (HGNC:7727)
Target entity	Same as active entity, or chemical from ChEBI (12)	MAP2K1 (HGNC:6840)
Biological phase	GO biological phase (GO:0044848)	mitotic G1 phase (GO:0000080)
	Developmental phase ontology, e.g. Mouse Developmental Stage	Theiler stage 02 (MmusDv:0000005)
Relations (arrows in Figure 2)	Relations Ontology	*occurs in* (BFO:0000066)


a
NEDD4
Ubiquitin-protein ligase activity
NEDD4
Ubiquitin-dependent protein catabolic process
NEDD4
RNA polymerase binding
NEDD4
Cellular response to UV
NEDD4
Nucleus
NEDD4
Negative regulation of transcription from RNA polymerase II promoter


b
NEDD4
enabled by
Ubiquitin-protein ligase activity
has input
RNA polymerase II
occurs in
Nucleus
part of
Ubiquitin-dependent protein catabolic process
part of
Cellular response to UV
directly negatively regulates
RNA polymerase II
enabled by
RNA polymerase activity
occurs in
Nucleus
part of
Transcription from RNA polymerase II promoter


Active Entity
Target Entity
Location
part of
has input
enabled by
occurs in
Molecular Activity
causally upstream of
Molecular Activity
part of
happens during
Biological Process
Biological Phase
part of


receptor ligand activity
occurs in(extracellular space)
enabled by(WNT3 Hsap)
has input(FZD1 Hsap)
part of
canonical Wnt signaling pathway
part of
part of
part of
directly positively regulates
directly positively regulates
Wnt-activated receptor activity
occurs in(plasma membrane)
enabled by(FZD1 Hsap)
coreceptor activity
occurs in(plasma membrane)
enabled by(LRP6 Hsap)
beta-catenin destruction complex
has part(AXIN1 Hsap)
has part(CSNK1A1 Hsap)
has part(APC Hsap)
has part(GSK3B Hsap)
part of
directly positively regulates
directly positively regulates
enabled by
receptor signaling complex adaptor activity
occurs in(cytosol)
enabled by(DVL1 Hsap)
has input(AXIN1 Hsap)
directly negatively regulates
protein serine/threonine kinase activity
occurs in(cytosol)
has input(CTNNB1 Hsap)
positively regulates
ubiquitin-dependent protein catabolic process
has input(CTNNB1 Hsap)
negatively regulates
transcription coactivator activity
occurs in(nucleus)
enabled by(CTNNB1 Hsap)
part of
part of
negative regulation of canonical Wnt signaling pathway