

Controlled vocabularies in bioinformatics: a case study in the gene ontology

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The automatic integration of information resources in the life sciences is one of the most challenging goals facing biomedical informatics today. Controlled vocabularies have played an important role in realizing this goal, by making it possible to draw together information from heterogeneous sources secure in the knowledge that the same terms will also represent the same entities on all occasions of use. One of the most impressive achievements in this regard is the Gene Ontology (GO), which is rapidly acquiring the status of a de facto standard in the field of gene and gene product annotations, and whose methodology has been much intimated in attempts to develop controlled vocabularies for shared use in different domains of biology. The GO Consortium has recognized, however, that its controlled vocabulary as currently constituted is marked by several problematic features – features which are characteristic of much recent work in bioinformatics and which are destined to raise increasingly serious obstacles to the automatic integration of biomedical information in the future. Here, we survey some of these problematic features, focusing especially on issues of compositionality and syntactic regimentation.

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GO's three ontologies

The Gene Ontology (GO) [1] is an important tool for the representation and processing of gene- and gene-product-related information across all species. It provides a 'controlled vocabulary', designed to support the work of researchers in biomedicine by enabling them to report their results by using a common terminology in annotating genes and gene products.

When a gene is identified, three important types of questions need to be addressed: where is it located in the cell? What functions does it have at the molecular level? And to what biological processes do these functions contribute? GO's controlled vocabulary is correspondingly built out of three terminologies, consisting of cellular component, molecular function and biological process terms, respectively.

As of March 15 2004, GO comprehends 1395 component terms, 7291 function terms and 8479 process terms. These form three separate graphs, the primary purpose of which is to allow researchers annotating genes and gene products to locate the features and attributes they are addressing in their work. Researchers can then either choose corresponding terms already existing within GO's controlled vocabulary or localize corresponding gaps in the existing hierarchies and so recommend new terms that need to be included.

GO's cellular component ontology consists of terms such as flagellum, chromosome, ferritin and virion; terms that (with a few exceptions – above all the term 'cell' itself, as well as 'extracellular matrix' and 'extracellular space') relate to entities properly included within a single cell. All cellular components are, like the cell itself, continuant entities (entities which endure – which means that they preserve their identity over time even while undergoing changes of various sorts). [2] This ontology is the counterpart in the GO environment of what is otherwise called anatomy (though GO also contains a fragmentary ontology of anatomical structures at levels of granularity higher than that of the cell in its treatment of terms such as fat body development, gonad development, thyroid gland development, and so forth, in its biological process ontology). The purpose of the cell component ontology is to allow biologists to register the physical structure with which a gene or gene product is associated.

GO's molecular function (activity) ontology consists of terms such as ice nucleation activity, binding and protein stabilization activity. The GO definition of molecular function is 'activities, such as catalytic or binding

activities, at the molecular level.' This ontology is thus intended to consist of processes, in other words, occurrent entities that do not *endure* but rather *occur*. Where the level of granularity of the entities captured by GO's cellular component ontology is that of the cell, the molecular function ontology comprehends functions/activities of both intracellular and extracellular molecules.

GO's biological process ontology consists of terms such as 'glycolysis', 'death' and 'adult walking behavior' and includes terms referring to entities at both the cellular and the whole organ or organism levels of granularity. A biological process is defined in GO as 'a phenomenon marked by changes that lead to a particular result, mediated by one or more gene products.' Molecular function and biological process terms are thus clearly closely interrelated: both refer to occurrent entities, in other words to entities that unfold themselves in time.

What, now, is the relationship between biological processes and molecular functions in the GO framework? Certainly, there is such a relationship on the side of the corresponding entities in reality. Thus the biological process of anti-apoptosis, for example, clearly stands in some relation to the molecular function labeled apoptosis inhibitor activity. GO's curators attempt to clarify this relationship by stating that 'a biological process is accomplished via one or more ordered assemblies of molecular functions'. This would suggest that molecular functions are constituents of biological processes, so that they would stand to such processes in a part-of relation. The problem is, however, that the authors of GO insist at the same time that the part-of relation can only occur between entities within a single ontology. Thus, although they can capture the relatively unproblematic part-hood relationships that occur between biological processes and their biological process parts they have no means of capturing the relationships between biological processes and the molecular functions that underlie them. Thus receptor binding (a molecular function) and signal transduction (a biological process) are not related in the Gene Ontology, and neither are transcription factor activity and development.

This is not as yet a fair ground for criticizing GO. The principle according to which its three constituent ontologies should be kept free of relations linking them together is a design choice that has borne considerable practical fruit by allowing the construction of structured terminologies with a wide coverage yet still a high degree of perspicuity. The problems arising through the absence of cross-linkages between GO's three ontologies are also to some degree alleviated externally in virtue of the fact that the terms in question do in any case become unified indirectly, where single gene products are simultaneously annotated via

terms from different GO ontologies. Thus of the 84,833 annotations within the Gene Ontology Annotation from TIGR (GOAT) Database, [3] more than half were simultaneously annotated to terms within two of GO's ontologies, and more than 10% were annotated to terms from all three ontologies. We are currently analyzing these cases as a basis for extending GO by establishing corresponding cross-ontology links between the corresponding terms [4].

GO as a 'controlled vocabulary'

GO's considerable success is testimony to the wisdom of several other crucial choices made by the GO Consortium in the early stages of its development. Above all, the adoption of a relatively simple graph-theoretic architecture (Figure 1) involving just two kinds of edges (labeled '*is_a*' and '*part_of*') meant that work on populating GO could proceed very quickly. Such work does not require the completion of complex protocols, but can be carried out intuitively by the expert biologist, who is subject to few formal constraints when incorporating new terms and definitions.

In a series of recent papers we have attempted to show, however, that there are also certain unintended negative consequences of these choices. The problems turn on certain unanticipated consequences of these choices, above all that they serve as an obstacle to the understanding of Gene Ontology terms on the part of both curators and users of GO, an obstacle that is perhaps most clearly illustrated in the instability in GO's handling of the terms in its function ontology, (almost) all of which were recently relabeled by appending the term 'activity' to each of the original labels, without however any corresponding changes in the accompanying definitions. More precisely, we have argued that the authors of the Gene Ontology have ignored certain benefits which can accrue through the application of formal and syntactic rigor in the formulation of terms and definitions. The upshot is that there are aspects of GO's current architecture that are predestined to cause ever more serious problems as GO increases in size in the future. As the GO Consortium itself accepts, it will 'be increasingly difficult to maintain the semantic consistency we desire without software tools that perform consistency checks and controlled updates' [1]. However, much of the information that GO contains is, under current policies, not capable of being accessed or manipulated by software tools.

For this, adherence to basic principles of logic is required, and such principles are thus destined to play a vital role in GO and similar bio-ontologies in the future as the obstacles of manual inspection and supervision become ever more significant. If formal tools are to be employed for maintenance purposes, however, the information content

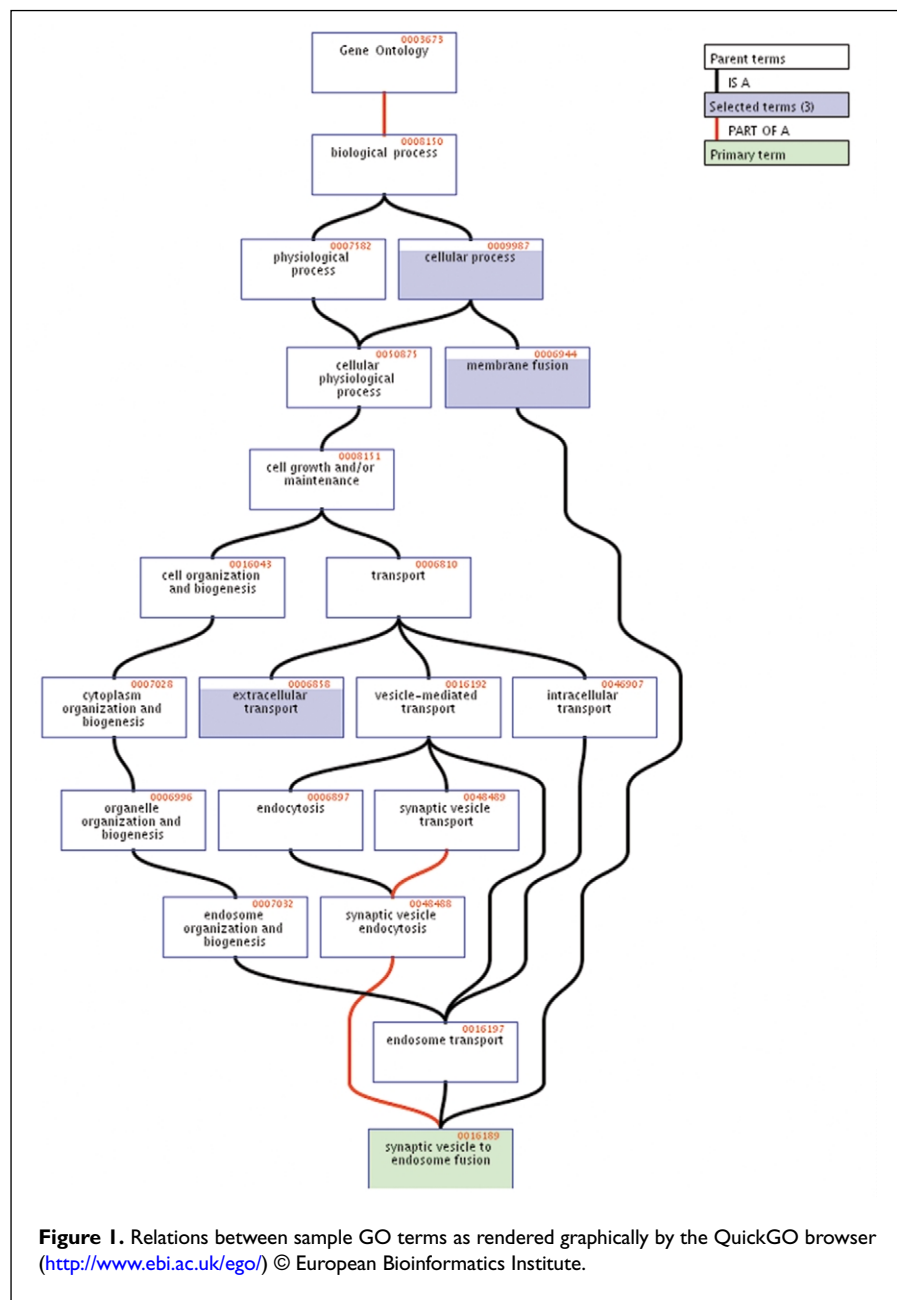


Figure 1. Relations between sample GO terms as rendered graphically by the QuickGO browser (<http://www.ebi.ac.uk/ego/>) © European Bioinformatics Institute.

to its function terms. In [6], we generalized this critique by pointing to certain inadequacies in GO's treatment of the relationships between entities at different levels of granularity. In [7] (see also [8, 9]), we highlighted a series of difficulties and uncertainties in GO's handling of its two foundational relations *is_a* and *part_of*, which constitute the edges of the three graph-theoretic hierarchies from which GO is constituted. In [10], we added discussion of formal inadequacies in GO's definitions, attempting to show how adherence to formal organizing principles drawn from philosophical ontology, principles which represent best practices in classification and definition, can lead to benefits in eliminating certain characteristic types of error by which GO has hitherto been affected.

Here, we turn to those aspects of GO's architecture, which have to do with its status as a 'controlled vocabulary.' We can summarize our argument in the following four points:

- i) With the development of modern formal disciplines (formal logic and the computational disciplines which have arisen in its wake) we have learnt a great deal about the criteria that must be satisfied if a language is to be structured in such a way that the information content expressed by its means can be extracted via automatic procedures that can support logical reasoning tools.
- ii) GO's controlled vocabulary has been developed in large part without concern for these criteria – this applies both to GO's terms and also to the definitions associated therewith. Accordingly GO has been used primarily in support of statistics-based methodologies orientated around string searches and pattern recognition, and much of its information content has therefore not been accessed.
- iii) Aspects of GO's current design, above all the expressive paucity which flows from the absence of relationships between the terms of its three constituent ontologies, have led its curators to bend the rules of term-formation in order, in effect, to simulate such relations by

of GO must be accessible to such tools. The language of GO must therefore come to approximate more closely to a compositional language, that is, a language wherein the meaning of each compound expression is a function of the meanings of its constituent parts. The GO Consortium has acknowledged the significance of this fact and under the auspices of the Open Biological Ontologies umbrella organization it is currently embarking on a program of reform, which is in conformity with the proposals advanced here and in our earlier papers. In [5], we focused especially on inadequacies in GO's specification of the relations between its function and process ontologies, and on associated problems with GO's recent adoption of the suffix 'activity'

constructing artificial terms within which corresponding relational expressions are embedded.

- iv) Such artificial terms, however – for example ‘unlocalized’ (with the meaning: localization not yet known) – do not correspond to biological natural kinds: they are, precisely, artifacts of the Gene Ontology itself; and because they are constructed by stretching the rules for term-formation they create difficulties for curators who apply GO in ways that often go hand in hand with characteristic types of coding errors.

GO terms

The problem of expressive paucity created by GO's limited repertoire of relationships between its terms is to some extent counteracted through the policy of constructing special terms that simulate representations of the missing relationships within the very terms themselves. This is achieved by means of special operators such as *with*, *within*, *without*, *in*, *site of*, *acting on*, or *resulting in*. For example, the term ‘electron transporter, transferring electrons *within* the noncyclic electron transport pathway of photosynthesis activity’; or ‘oxidoreductase activity, *acting on* diphenols and related substances as donors, oxygen as acceptor’; or ‘oxidoreductase activity, *acting on* paired donors, *with* oxidation of a pair of donors *resulting in* the reduction of molecular oxygen to two molecules of water’.

Some of these operators – for example ‘involved and involving’ – were sometimes initially used to simulate the presence of *part_of* and similar relations crossing boundaries between distinct ontologies. Others – for example ‘during’ – are used to simulate the presence of a vocabulary for representing temporal relations. And yet others – for example ‘within’ or ‘site of’ – are used to simulate spatial relations and to compensate for the fact that GO has no means of expressing the relation *is_located_at* – in spite of the importance of the specification of cell locations to its general mission.

Such construction of special terms on the part of GO's authors and curators has thus far been uncontrolled. The result is that the operators in question are used in inconsistent ways. This in turn means that the information they express remains opaque to software tools.

Consider GO's use of ‘involved in’ in assertions such as: i) hydrolase activity, acting on acid anhydrides, **involved in** cellular and subcellular movement *is_a* hydrolase activity, acting on acid anhydrides; ii) asymmetric protein localization **involved in** cell fate commitment *is_a* cell fate commitment; iii) cell-cell signaling **involved in** cell fate commitment *is_a* cell fate commitment and iv) protein secretion **involved in** cell fate commitment *synonym_of* protein secretion

The first assertion is correct to the degree that there are indeed two subtypes of hydrolase activity acting on anhydrides: those that are and those that are not involved in cellular and subcellular movement. However, GO has itself declared the term at issue, ‘hydrolase activity, acting on acid anhydrides, involved in cellular and subcellular movement hydrolase activity’, which was taken over from the Enzyme Commission, to be obsolete. This is because it is a function term which also contains reference to biological processes (cellular and subcellular movement), and this opposes GO's principle that disallows links between its three constituent ontologies.

The relationships at issue in the second and third assertions are erroneously classified as *is_a* relations, as inspection reveals that we have to deal here rather with relations of *part_of*. Thus, the instances of asymmetric protein localization, which are involved in instances of cell fate commitment in fact form parts of the corresponding instances of cell fate commitment. The problem with the second and third assertions is that they have the same form as ‘breathing involved in running *is_a* running’.

The fourth assertion equates the class of instances of protein secretion that are involved in instances of cell fate commitment with the class of instances of protein secretion. This, again, is an example of erroneous coding, as there are also instances of protein secretion that are not involved in cell fate commitment. The error flows in part from GO's idiosyncratic understanding of ‘synonym’ (<http://www.geneontology.org/GO.synonyms.html>).

Similar problems arise also in connection with the expression ‘site of’, another example of an operator that is used by GO in its efforts to compensate for the expressive paucity of its repertoire of relations via the construction of artificial terms. Use of ‘site of’ effectively converts the relation *is_located_at* into an *is_a* relation between specially constructed terms. Unfortunately this device, too, proves to be a source of errors – reinforcing our general point that to bend the rules of term-formation involves paying a price of unsure coding on the part of those who are then left with no clear rules to follow.

Thus, as is shown in [7], from bud tip *is_a* site of polarized growth (*sensu* Saccharomyces); and site of polarized growth (*sensu* Saccharomyces) *is_a* site of polarized growth (*sensu* Fungi), we can infer logically either i) that every instance of non-Saccharomyces fungus polarized growth is co-localized with an instance of Saccharomyces polarized growth or (ii) that there is fungus polarized growth only in Saccharomyces. The first example is taken to be biologically false; the second example however, implies that the terms ‘site of polarized growth (*sensu* Saccharomyces)’ and ‘site of polarized growth (*sensu* Fungi)’ in fact refer,

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confusingly, to the same class, and so the latter should be removed from GO's cellular component ontology. The lesson to be learned from this example is that there is a logic to which one becomes committed when using terms like 'site of' – a logic which may stand in conflict with the logic to which one becomes committed when one uses 'is_a' and 'part_of' to form assertions by combining terms.

Problems with 'Sensu'

Part of the problem just referred to derives from GO's use of what is perhaps the most important operator in the formation of new terms, namely *sensu*. *Sensu* terms are introduced to cope with those cases where a word or phrase has different meanings when applied to different organisms, as for example in the case of the cell wall. (Cell walls in bacteria and in fungi have a completely different composition.)

Since it is a primary goal of the GO Consortium to provide an ontology of gene products applying to all species, GO insists that *sensu* terms be introduced sparingly. In consequence, such terms often have non-*sensu* terms as children, as for example in: R7 differentiation *is_a* eye photoreceptor differentiation (*sensu* *Drosophila*).

GO's interpretation of *is_a* sanctions the inference from A *is_a* B to: every instance of A is an instance of B. If this is correct, however, then this statement carries the implication that R7 differentiation occurs only in *Drosophila*, which seems to stand in conflict with the fact that such differentiation also occurs for example in crustaceans. Analogous problems involving *sensu* and non-*sensu* terms also arise in connection with GO's *part_of* relation. Thus we have: larval fat body development *part_of* larval development (*sensu* *Insecta*), which seems to tell us that every instance of larval fat body development occurs in insects, which ignores for example the presence of fat bodies in crustaceans and worms.

GO has responded to these concerns by pointing to special features of its reading of 'sensu'; by adding *sensu* the idea was not to exclude certain taxa from being implied by the use of a given *sensu* term, but rather to give a user an idea of what sense a term should be used in. For example, if another flying insect were to be annotated to GO, we would hope that the '*sensu* *Drosophila*' terms could be used for this new species.

An example where you might want to annotate a gene product from a taxon outside that specified in the *sensu* designation is 'fruiting body formation (*sensu* *Dictyosteliida*)'. If you were annotating a gene from the subclass *Myxogastria* (the true slime moulds, *Dictyosteliida* are the cellular slime moulds) you would still use this term, because the process in both taxa is identical (J Lomax personal communication).

Note that larval fat body development *part_of* larval development (*sensu* *Insecta*) is an example of a *sensu* term that has a non-*sensu* term as child. Such child-parent relations might at first seem counter-intuitive, given that the purpose of '*sensu*' is precisely to allow a non-*sensu* term to be modified in such a way that it can refer to entities marked by special features which precisely do not arise in the entities referred to by the term in its original unmodified form. Closer inspection reveals, however, that there may be disadvantages to including the *sensu* designation in all children of *sensu* terms. Thus the term 'cell wall (*sensu* *Fungi*)' has the *part_of* child 'hyphal cell wall'. Because hyphae are only ever found in fungi it would then be confusing to add the *sensu* qualifier to the term 'hyphal cell wall' as this would suggest precisely that there were hyphal cell walls of other, non-fungal types. However, it is important to note that the current rule, whereby the '*sensu* X' operator can be applied even to terms relating to taxa disjoint from the taxon X creates one more barrier to the automatic retrieval of information. This is because a term like 'Y (*sensu* X)' identifies only indirectly the features shared in common by all the Ys at issue – in a way that requires the intervention of a human biologist with the relevant specialist knowledge. A better solution, therefore, would be to replace such terms with terms of the form 'Y which is Z', where 'Z' would then contain in explicit form the relevant positive information about the peculiar features at issue, rather than providing this information in coded form via a (somewhat indeterminate) linkage to a taxon.

Problems with syntactic operators

GO also employs a series of purely syntactic operators, such as ',', '/', and ':', in ways that seem to contravene the underlying idea of a controlled vocabulary. Many of the terms involving ',' (for example 1,4 lactonase activity) are standard IUPAC designations. Others, however, are problematic. Does the comma in 'hydrolase activity, acting on acid anhydrides' mean 'while' or 'of the type which is'? Here the definition helps to resolve the issue in favor of the latter, although as mentioned previously, the information contained in GO's definitions is not formulated in such a way as to be accessible to software tools.

Problems arise also with GO's inconsistent use of '/'. In some cases GO's '/' means 'and', for example in GO:0005954 calcium/calmodulin-dependent protein kinase complex. In others it means 'or', as in GO:0001539 ciliary/flagellar motility. In yet other cases it means 'and/or', as in GO:0045798 negative regulation of chromatin assembly/disassembly. In GO:0008608 microtubule/kinetochore interaction, it means 'between'. In GO:0000082 G1/S transition

Table 1.

Operator	Examples	Component ontology	Function ontology	Process ontology
With	GO: 0010483 conjugation with cellular fusion	1	17	36
Within	GO: 0045153 electron transporter, transferring electrons within CoQH2-cytochrome c reductase complex activity	1	5	8
Without	GO: 0000748 conjugation without cellular fusion	0	0	10
From	GO: 0019285 betaine biosynthesis from choline	0	2	139
During	GO: 0042074 cell migration during gastrulation	0	0	73
And	GO: 0016743 carboxyl- and carbamoyltransferase activity	2	42	136
In	GO: 000014 G1-specific transcription in mitotic cell cycle	0	18	32
Acting on	GO: 0016684 oxidoreductase activity, acting on peroxide as acceptor	0	145	1
Resulting in	GO: 0000077 DNA damage response, signal transduction resulting in cell cycle arrest	0	1	7
Regulator;	GO: 0042754 negative regulation of circadian rhythm	0	66	1260
Regulatory;	GO:0045055 regulated secretory pathway			
Regulated;				
Regulation				
Dependent	GO: 0004692 cGMP- dependent protein kinase activity	14	90	78
Constituent, Constitutive	GO: 0030280 structural constituent of epidermis	0	28	1
Response	GO: 0000751 cell cycle arrest in response to pheromone	0	5	261
Sensu	GO: 0000143 actin cap (sensu <i>Saccharomyces</i>)	140	14	315
Site of	GO: 0016366 site of polarized growth	3	0	1
Complex	GO: 0015667 proteasome activator complex	518	11	34
: (colon)	GO: 0015296 anion:cation symporter activity	3	170	4
/ (slash)	GO: 0000871 pilin / fibrilin exporter activity	12	112	162
, (comma)	GO: 0002279 cyclin-dependent protein kinase, intrinsic regulator activity	71	724	411

of mitotic cell cycle '/' it means 'from ... to ...'. And in GO:0001559 interpretation of nuclear/cytoplasmic to regulate cell growth it means 'with respect to'. It may be that human biologists find no difficulty in keeping control over these and a range of other different meanings of a single piece of syntax. What is certain, however, is that the information that is currently coded by means of such operators is to a large degree masked to automatic tools for information extraction. We are thus gratified to see that reforms are currently under way by virtue of which the treatment of syntactical and other operators will be standardized through the imposition of a set of rules governing the use of these operators in different ontologies within the OBO framework.

In Table 1, we provide a list (which complements the discussion in [11]) of the more important syntactic operators in GO, to give some idea of the scale of the problems at issue – problems which are currently being addressed by the GO consortium under the auspices of its OBOL project. In the left-hand column are the terms or syntactic operators

that contribute to the compositional character of GO – they are, as it were, standard linking expressions in terms of which complex terms are built up out of simpler parts. Examples in the next column are selected to illustrate how these linking expressions are characteristically used. The remaining columns give information as to the number of uses of the expressions in question in GO's three ontologies.

Conclusions

As the GO consortium has recognized (Mungall, C. *et al.* The OBOL Ontology Language, unpublished), many of the problems connected with GO's departure from compositionality can be resolved by preparing a canonical list of admissible operators and providing strict usage rules for each. The terms involving such operators currently receive a significantly lower number of annotations than do other terms in GO. This, we believe, provides some indication that the meanings conveyed by the terms in question are not only inaccessible to software tools but also to human biologists who find them difficult to understand. These

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examples highlight general concerns about the development and maintenance of systems like GO in the future. Terminologies are likely to be less susceptible to error and also more susceptible to integration with other terminologies if they are subjected to robust principles for handling syntax and for formulating terms and definitions.

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