The Unified Medical Language System and the Gene Ontology: Some Critical Reflections

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Published in A. Günter, R. Kruse and B. Neumann (eds.), *KI 2003: Advances in Artificial Intelligence* (Lecture Notes in Artificial Intelligence 2821), Berlin: Springer, 2003, 135–148.

Abstract The Unified Medical Language System and the Gene Ontology are among the most widely used terminology resources in the biomedical domain. However, when we evaluate them in the light of simple principles for well-constructed ontologies we find a number of characteristic inadequacies. Employing the theory of granular partitions, a new approach to the understanding of ontologies and of the relationships ontologies bear to instances in reality, we provide an application of this theory in relation to an example drawn from the context of the pathophysiology of hypertension. This exercise is designed to demonstrate how, by taking ontological principles into account we can create more realistic biomedical ontologies which will also bring advantages in terms of efficiency and robustness of associated software applications.

1. Introduction

1.1 The Unified Medical Language System

The integration of standard terminology systems into a unified knowledge representation system for biomedicine has formed a key area of research in recent years. The Unified Medical Language System (UMLS), designed by the National Library of Medicine in Bethesda MD, is one major effort in this direction, combining a large number of distinct terminologies into a single platform [1,2].

Semantic Networks are one means to find our way around vast terminological edifices such as are represented by UMLS. The January 2003 version of the UMLS Semantic Network consists of 134 Semantic Types together with 54 possible links between these types. These can be arranged in the form of a graph

whose vertices are the Semantic Types and whose edges are the links between them. The result represents a high-level abstraction from the Metathesaurus, which is the total UMLS concept repository. The UMLS Semantic Network is a graph containing more than 6000 edges organized into a double tree structure which divides all items in the UMLS universe into two superclasses of *Entities* and *Events. Entity* is defined as "A broad type for grouping physical and conceptual entities". *Event* is defined as "A broad type for grouping activities, processes and states".

1.2 The Gene Ontology

The Gene Ontology project seeks to provide a hierarchical controlled vocabulary for the description of genes and gene products. Currently, efforts are underway to imcorporate GO into UMLS. GO's compilers have endeavored to develop a standardized cross-species biological vocabulary that can be used by multiple databases to annotate them in a consistent way [3,4,5]. As of June 2003, GO takes the form of a list of some 14,000 common biological terms together with text intended to convey definitions of many of the terms listed. Terms are organized in parent-child hierarchies, indicating that one term is *more general than* another. Additional information is provided where the entity denoted by one term is *part of* the entity denoted by another. Terms are divided into three disjoint trees, with roots: *Cellular Component*, *Molecular Function* and *Biological Process*. The result is meant to facilitate communication among biologists. The GO reference vocabulary is intended to ensure terminological standardization and thus to increase efficiency and reliability, for example in the process of searching for common concepts across large genetic databases.

1.3 Some Basic Formal-Ontological Distinctions

Unfortunately, both UMLS and GO are marked in their top-level categorial organization by certain ontological inadequacies. To see why this is so, we begin by drawing attention to two distinctions drawn by philosophers across the ages: a) between *Continuant* and *Occurrent* entities, and b) between *Dependent* and *Independent* entities [6].

Continuants, as the name implies, are entities which continue to exist through time. Organisms, cells, chromosomes are all continuants: they preserve their identity from one moment to the next even while undergoing a variety of different sorts of changes. Occurrents, in contrast, are never such as to exist in full in any single instant of time. Rather, they are such as to unfold themselves through time, in the way in which, for example, an intravenous drug infusion unfolds itself in successive temporal phases. The continuant/occurrent opposition corresponds in first approximation to the distinction between *Entity* and *Event* drawn by UMLS and to the distinction between *Components* and *Functions*/*Processes* drawn by GO. It corresponds also to the familiar medical distinction between *anatomy* and *physiology*.

To say that an entity is *independent* is to assert that it has an inherent ability to exist without reference to other entities – examples are: cells and molecules, organs

and organisms – as contrasted with entities that require a support from other entities in order to exist, for example, in the case of cellular motion, temperature or mass. Cellular motion requires reference to a cell which moves; each case of viral infection, requires reference to some organism which is its subject or carrier. Because occurrents, at least on those levels of granularity which are of concern to us here, are always changes or movements *of* some enduring entity or entities, it follows that occurrents are always dependent entities. Thus of the four abstractly possible combinations yielded by the two divisions of continuants/occurrents and dependence/independence, only three are instantiated:

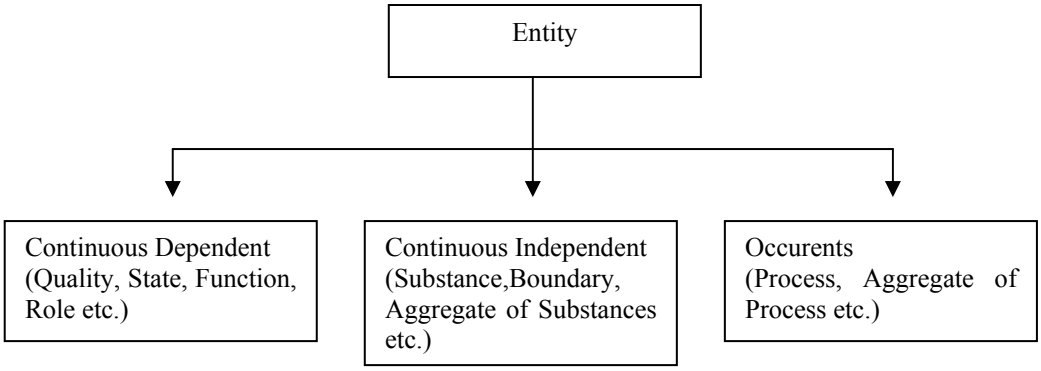

Figure 1. A tripartite taxonomy

We shall use this tripartite ontology in what follows in order to bring to light certain problems and irregularities in the UMLS and GO semantic networks. Note that we have to include under continuants not only substances (such as you and me, this cell, that molecule), but also *qualities* (your height, your skin-color), *states or conditions* (your diabetes, your state of high blood pressure), *roles* (your role as student, as doctor), and *functions* (of a drug, of a machine). This is because, like their bearers, qualities, states, roles and functions endure self-identically through time. The *realizations* of roles and functions, in contrast – for example, the *course* of a disease, the *performance* of a role, the *execution* of a program, are all *processes*, which means that they fall under the heading of occurrents.

1.4 The Theory of Granular Partitions

When human beings classify the entities in the domain of medicine by means of one or other of the standardized terminologies, then they *partition* reality into *cells* of various sorts. The Theory of Granular Partitions (TGP) is a theory of such partitions, which provides a set of simple conditions which partitions must satify together with a set of tools for their manipulation [7,8,9]. TGP deals primarily with transparent (veridical) partitions, that is with partitions which are the products of successfully demarcating some independently existing subject-domain. However, TGP also has the resources to deal with various sorts of partition *failure* and *incompleteness*, and it

provides an elaborate machinery for dealing with the *vagueness* involved in many of our partitions of reality.

Perhaps the most important feature of TGP is that it recognizes that different partitions may represent cuts through the same reality at different levels, and even cuts through reality which are skew to each other. It thus provides a framework within which we can formulate ontologies of a given domain which are at one and the same time realist and also do justice to the existence of a plurality of veridical representations of given domains of reality, as when we partition the human organism successively in terms of molecules, cells or organs.

Each partition consists of cells and subcells (terms which are used here in a formal sense, freed from all connotations of the biological concept of 'cell'), the latter being nested within the former. The simplest type of partition is a mere list. This consists of just one layer of subcells (corresponding to the items on the list), together with one all-inclusive maximal cell (corresponding to the list as a whole). Other partitions are hierarchical: they consist of many layers of cells and subcells (for example, in the animal kingdom, the layers of species, genus, family, order, class, phylum and kingdom). The lowest layer of subcells corresponds to the finest grain of objects recognized by the partition in question.

2 UMLS Semantic Network

As mentioned above, there are certain problems which become apparent when we consider how the two dichotomies of occurrent/continuant and dependent/independent should be applied to the classification presupposed by the UMLS Semantic Network [2].

2.1 UMLS Semantic Tree with root *Entity*

The most problematic sub-class under *Entity* in the UMLS hierarchy is: *Conceptual Entity*. This has subclasses:

Organism Attribute
Idea or Concept
Organization
Group Attribute
Language
Finding
Occupation or Discipline
Group
Intellectual Product

(see Figure 2 below).

The problem pertains first of all to the wide formal-ontological diversity of the items included in this list. It turns secondly on the fact that concepts, as we understand them, are dependent on minds, and thus, we assume that the same holds also for Conceptual Entities, too, are dependent entities. This explains why *Finding*, *Idea or Concept*, *Language* and *Intellectual Product* are listed as subclasses of *Conceptual Entity*. But what of *Organism Attributes*? These can however exist without a mind: there were organism attributes before there were concepts, not least the attributes of

all those organisms which evolved before concept-using organisms existed. Hence, *Organism Attribute* cannot be a *Conceptual Entity*. A similar problem arises also in relation to *Group* (for example groups of macac monkeys), and to geographical regions (for example, Hambug), which are classified under *Idea or Concept* in the UMLS Semantic Network.

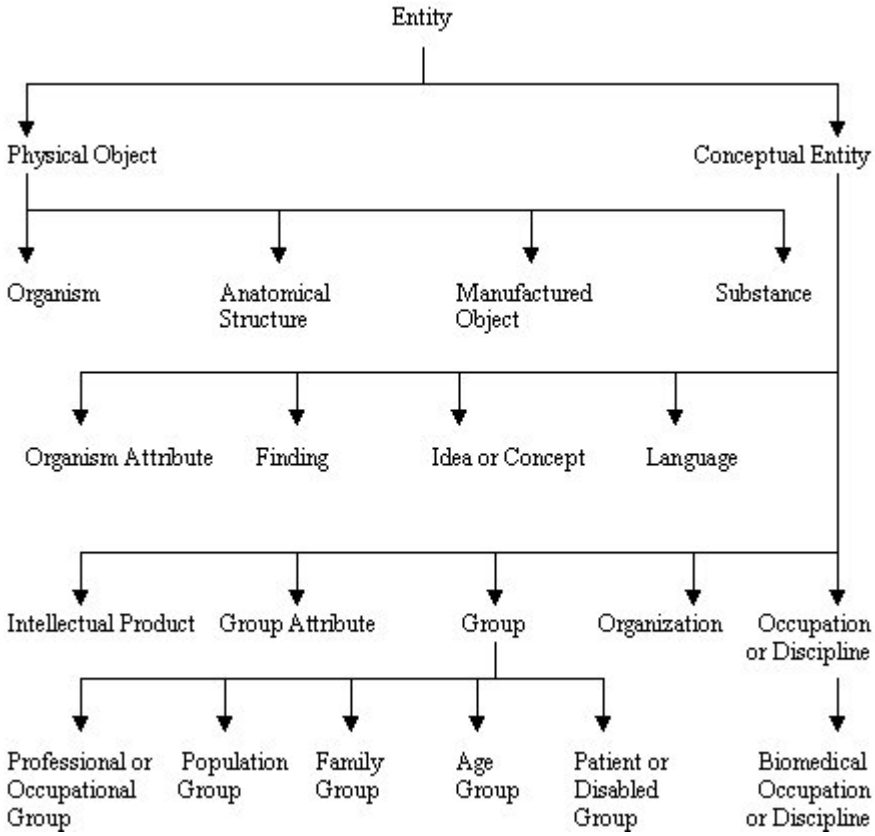

Figure 2. A portion of the subsumption hierarchy of UMLS Semantic Types with root Entity *(for the sake of clarity, not all nodes have been expanded)*

2.2 UMLS Semantic Tree with root *Event*

The tree starting from *Event* has subclasses, *Activity* and *Phenomenon or Process*.

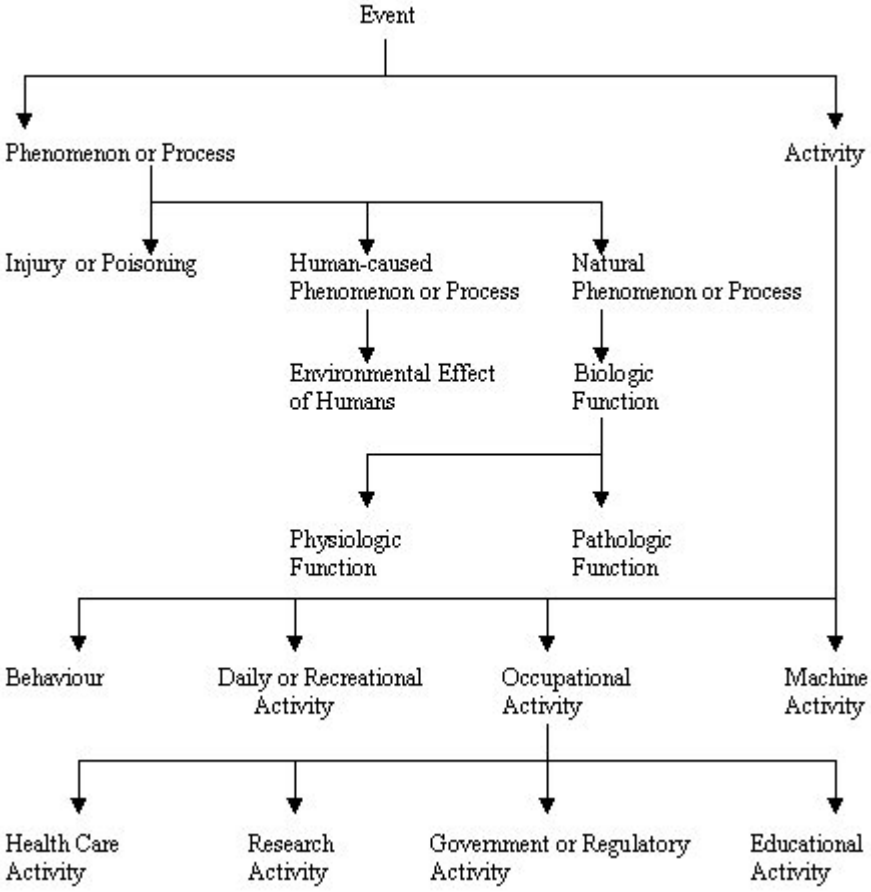

Figure 3. A portion of the subsumption hierarchy of UMLS Semantic Types with root Event

Among the subclasses of *Phenomenon or Process* is *Natual Phenomenon or Process*, with subclass *Biologic Function*, which in turn has *Physiologic Function* and *Pathologic Function* as subclasses.

Here, unfortunately, functions, which are continuants, are run together with processes, which are occurrents. What is almost certainly meant by *Biologic Function* as a sublass of *Natural Phenomenom or Process* is the *exercise* of a function at some given time and place. UMLS hereby runs together *function* with *functioning*; it confuses what exists dispositionally in a thing, a certain power or potential which is the product of evolution or design, with what the thing *does* episodically, which is the product of intentionality or local causal influence. The importance of this distinction becomes clear when we recognise that there are dormant functions and functions which for some other reason do not become expressed in any process.

3 Basic Formal Ontology

Basic Formal Ontology (BFO) is a reference ontology currently being developed in Leipzig for purposes of application in the medical domain. It consists of a series of sub-ontologies, the most important of which are the various SnapBFO and SpanBFO sub-ontologies developed at different levels of granularity within the framework of the Theory of Granular Partitions. SnapBFO is constituted by a series of *snapshot* ontologies indexed by times; SpanBFO is a single videoscopic ontology which apprehends the world in terms of the processes unfolding within it. SNAP is the ontology of continuants in our terminology above; SPAN the ontology of occurrents [10,11,12].

3.1 BFO Hierarchy with Root Continuant Entity

The outline category system of SnapBFO is shown in Figure 4. It consists of *Continuant Entity* as root, under which are the subclasses *Dependent Entity, Independent Entity* and *Spatial Region*. *Dependent Entity* consists of qualities, states, functions, roles, powers, etc. while *Independent Entity* consists of *Substances*, their aggregates, boundaries, fiat parts and so forth.

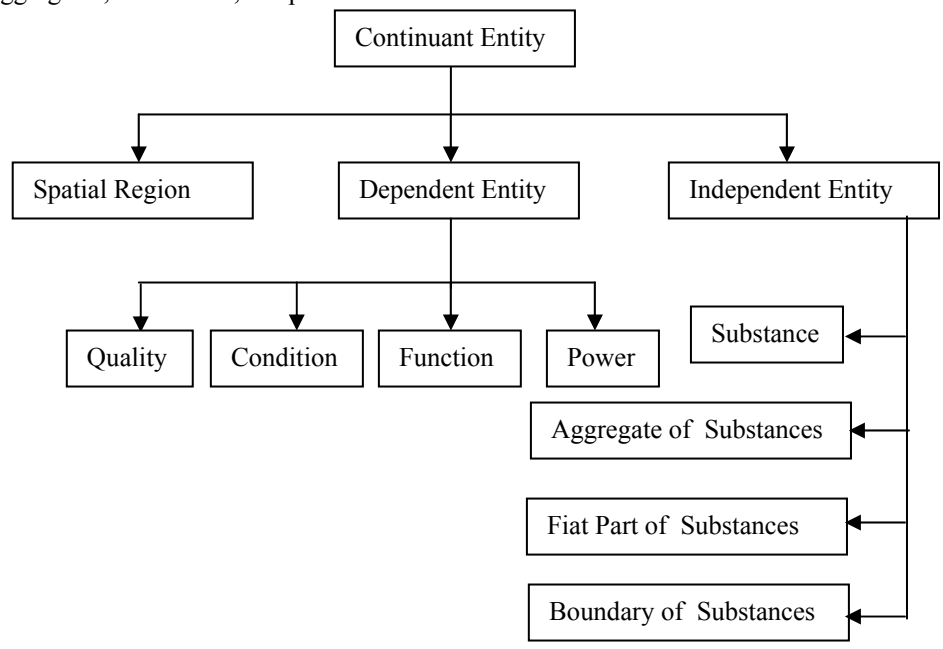

Figure 4. SnapBFO: The Basic Formal Ontology with root Continuant Entity *(for the sake of clarity, not all nodes have been expanded) [10]*

3.2 BFO Hierarchy with Root Occurent Entity

SpanBFO, as shown in Figure 5, consists of *processes*, with *Occurrent Entity* as root. More precisely, it divides occurrent entities into the two sub-categories of *Processual Entities* and *Spatiotemporal Regions*. The category *Processual Entity* is sub-divided into processes, aggregates of processes, fiat parts of processes, and boundaries of processes [11].

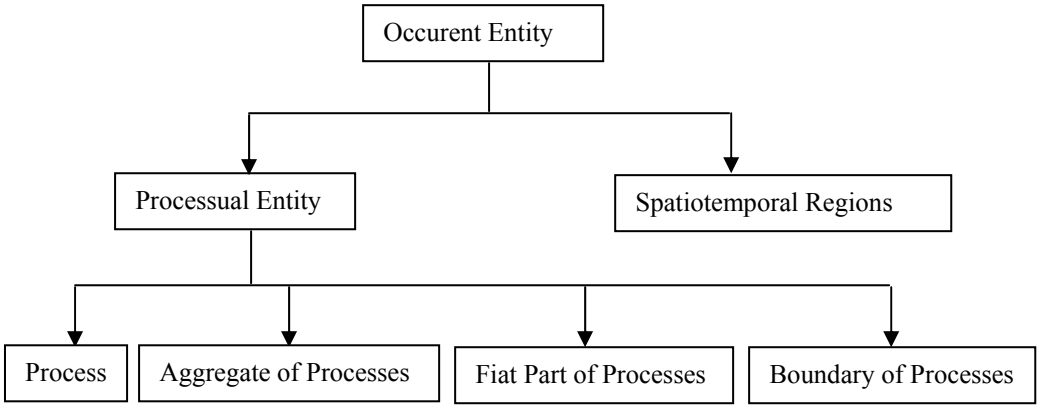

Figure 5. SpanBFO: Basic Formal Ontology with root Occurrent Entity *(for the sake of clarity, not all nodes have been expanded)*

4 Using BFO for Ontological Error-Detection in UMLS

Chen, Perl *et al.* and Geller, Perl *et al.* have provided a method for partitioning the UMLS Semantic Network into a smaller number of more meaningful units, called Semantic Type Collections. In Table 1 we used BFO in order to analyze the classifications incorporated in such collections in order to bring to light what we believe are the classification errors in the Network itself.

We have pointed out that substances are independent entities. Thus the Semantic Types *Biologically Active Substance*, *Enzyme*, *Food* etc. are classified as independent entities. However, there is for each of these types a closely associated dependent entity, which is the corresponding role, for example, the role of a biologically active substance of being precisely biologically active. In Table 1, we have separated these issues based on BFO and categorised substances as *Independent Continuant Entities*, roles and functions are *Dependent Continuants* and the processes of exercising those functions as *Occurrents*.

Table 1. UMLS Semantic Types analyzed using BFO classifications.

ICE = Independent Continuant Entities and their parts and aggregates;
PE = Processual Entities;

DCE = Dependent Continuant Entities;
** signifies an ontologically incoherent composite of different classes*

Collection	UMLS Semantic Types in Collection	BFO
Anatomical Abnormality	Anatomical Abnormality; Acquired Abnormality; Congenital Abnormality	DCE (Qualities, etc.)
Anatomical Structure	Anatomical Structure; Embryonic Structure	ICE (Fiat Part/Boundary)
Animal	Animal; Invertebrate; Vertebrate; Amphibian; Bird; Fish; Reptile; Mammal; Human	ICE (Substance)
Behaviour	Behaviour; Social Behaviour; Individual Behaviour	PE
Biologic Function	Biologic Function	DCE (Function)
Biologically Active Substance	Biologically Active Substance; Receptor; Vitamin; Enzyme; Neuroreactive Substance or Biogenic Amine; Hormone; Immunologic Factor	ICE (Substance)
Chemical	Chemical; Chemical Viewed Structurally; Chemical Viewed Functionally; Hazardous or Poisonous Substance; Inorganic Chemical; Biomedical or Dental Material; Element, Ion or Isotope; Indicator, Agent or Diagnostic Aid; Carbohydrate; Organic Chemical; Organophosphorus Compound; Steroid; Eicosanoid; Amino Acid, Peptide or Protein; Lipid; Nucleic Acid, Nucleoside or Nucleotide	ICE (Substance)
Entity	Entity; Physical Object; Conceptual Entity; Group Attribute; Language; Intellectual Product; Classification; Regulation or Law	* (a conglom-erate of ICE and DCE)
Event	Event; Activity; Daily or Recreation Activity; Machine Activity	PE
Finding	Finding; Lab or Test Result; Sign or Symptom	DCE (Quality, Condition)
Fully Formed Anatomical Structure	Fully Formed Anatomical Structure; Cell; Cell Component; Tissue; Gene or Genome; Body Part, Organ or Organ Component	ICE (Substance, Fiat part, Boundary etc.)
Group	Group; Professional or Occupational Group; Population Group; Family Group; Age Group; Patient or Disabled Group	ICE (Aggregate)
Health Care Activity	Health Care Activity; Diagnostic Procedure; Laboratory Procedure; Therapeutic or Preventive Procedure	PE
Idea or Concept	Idea or Concept; Functional Concept; Body System; Temporal Concept; Qualitative Concept; Quantitative Concept; Spatial Concept; Geographic Area; Body Location or Region; Molecular Sequence; Carbohydrate Sequence; Amino Acid Sequence; Body	* (a conglom-erate of ICE, DCE and spatial region)

	Space or Junction; Nucleotide Sequence	
Manufactured Object	Manufactured Object; Medical Device; Research Device; Clinical Drug	ICE (Substance)
Natural Phenomenon or Process	Natural Phenomenon or Process	PE
Occupation or Discipline	Occupation or Discipline; Biomedical Occupation or Discipline	PE
Occupation Activity	Occupation Activity; Educational Activity; Governmental or Regulatory Activity	PE
Organism	Organism; Archaeon; Virus; Bacterium; Fungus; Rickettsia or Chlamydia	ICE (Substance)
Organism Attribute	Organism Attribute; Clinical Attribute	DCE (Quality, Condition)
Organization	Organization; Health Care Related Organization; Professional Society; Self-help or Relief Organization	ICE (Aggregate)
Pathologic Function	Pathologic Function; Experimental Model of Disease; Cell or Molecular Dysfunction; Cell or Molecular Dysfunction; Disease or Syndrome; Mental or Behavioral Dysfunction	* (a conglomerate of DCE, ICE and PE)
Pharmacologic Substance	Pharmacologic Substance; Antibiotic	ICE (Substance)
Phenomenon or Process	Phenomenon or Process; Injury or Poisoning; Human-caused Phenomenon or Process; Environmental Effect of Humans	PE
Physiologic Function	Physiologic Function; Organ or Tissue Function; Mental Process; Molecular Function; Genetic Function; Cell Function	* (a conglomerate of DCE and PE)
Plant	Plant; Alga	ICE (Substance)
Research Activity	Research Activity; Molecular Biology Research Technique	* (a conglomerate of DCE and PE)
Substance	Substance; Body Substance; Food	ICE Substance, Aggregate of Substances)

5 Gene Ontology

The Gene Ontology is an inert hierarchy of terms, that is focused not on reasoning power or on supporting software implementations but rather on providing a robust framework for the annotations that are applied by biologists to organism gene products.

The vocabulary is divided into three parts, called the cellular component ontology, the molecular function ontology, and the biological process ontology (Figure 6). This corresponds, superficially at least, to the tripartite structure of independent continuants, dependent continuants (functions), and occurrents (processes) underlying BFO.

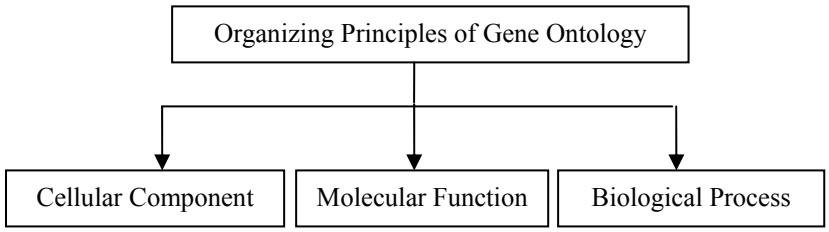

Figure 6. The Tripartite Organization of the Gene Ontology

5.1 The Cellular Component Ontology

The GO definition for the term "Cell Component" is: "subcellular structures, locations, and macromolecular complexes; examples include nucleus, telomere, and origin recognition complex".

Cellular components are physical objects, or the *substances* or parts or aggregates of substances in the BFO terminology: thus they are instances of *Independent Continuant Entity*. Cells themselves are subsumed by GO under *cellular component*.

5.2 The Molecular Function Ontology

The GO definition of the term "Molecular Function" is: "the tasks performed by individual gene products; examples are transcription factor and DNA helicase." The term 'task' is unfortunately ambiguous and GO, like the UMLS Semantic Types, correspondingly incorporate some confusions in the distinction between *functions* and their *functioning*. Until recently this confusion was compunded by the fact that the molecular function hierarchy includes terms such as *anti-coagulant* (defined as: "a substance that retards or prevents coagulation") and *enzyme* (defined as: "a substance & that catalyzes") which refer neither to functions nor to actions but rather to substances. This problem was remedied by a policy change effective as of March 1, 2003 whereby GO molecular function term names are to be appended with the word "activity". Because, however, the change was *not* applied to the parent term "Molecular Function", and because associated defintions were not overhauled in the light of the new policy, some confusion as between "function" and "activity" still remains.

5.3 The Biological Process Ontology

A "Biological Process" is defined in GO, somewhat unclearly, as: "A phenomenon marked by changes that lead to a particular result, mediated by one or more gene products". Biological process terms include *glycolysis*. As far as one can tell, *biological processes* are compounds or aggregates of molecular functions, the latter being identified as tasks (actions) performed by individual gene products together with the processes set in motion in their wake. However, this means that there is a parthood relationship between functions and processes, which contradicts GO's sections to the effect that its three term hierarchies are strictly disjoint from each other.

6 A Biomedical Example

In order to show the relevance of the above, we will discuss the use of the BFO ontology in giving a realistic analysis of a specific biomedical example drawn from the pathophysiology of hypertension and of antihypertensive treatment [13,14].

6.1 Regulation of Blood Pressure

The diagnosis of hypertension depends primarily on the measurement of blood pressure. According to the UMLS Metathesaurus, hypertension is a *Disease or Syndrome* or a *Sign or Symptom* and blood pressure is an *Organism Function*. All of these Semantic Types correspond to *Dependent Continuant Entities* according to BFO. That is, they endure identically for a certain period of time and they depend for their existence on the organism which is their bearer.

According to the hydraulic equation: BP = CO*PVR, arterial blood pressure is directly proportional to the product of blood flow (cardiac output, CO) and peripheral vascular resistance (PVR).

According to the UMLS Metathesaurus, blood flow is an *Organism Function*, cardiac output is a *Laboratory or Test Result* or *Diagnostic Procedure*. In BFO, *Organism Function* and *Laboratory or Test Result* are *Dependent Continuant Entities*, a *Diagnostic Procedure* is an *Occurrent*, or in other words it is a process that unfolds itself through time. This leads to a conflict because the same term "cardiac output" embraces both continuant and occurrent entities. It harbors confusion also since it implies that blood pressure is proportional either to a laboratory or test result or to a diagnostic procedure, where in fact of course the relationship of proportionality applies to the underlying biomedical phenomena of which the latter are measures.

UMLS, as we might say, confuses epistemology with ontology; that is, it runs together the results of our attempts to gain knowledge about specific phenomena of the organism (functions, attributes, processes) with those phenomena themselves. This is seen already in the classification of cardiac output and of peripheral vascular resistance as *Findings*.

6.2 The Ontology of Antihypertensives and the Theory of Granular Partitions

Antihypertensives are a class of drugs used in the treatment of acute or chronic hypertension via a range of pharmacological mechanisms. These include diuretics, adrenergic Beta-antagonists, adrenergic alpha-antagonists, angiotensin converting-enzyme inhibitors, calcium channel blockers, ganglionic blockers and vasodilator agents.

We can classify such a family from a range of different perspectives. Our concerns might be biochemical, pharmacological, clinical, physiological etc., and even within each of these perspectives there can be subdivisions. For example, an antihypertensive could have a clinical role in relation not only to hypertension but also to cardiac failure, diabetes, and so on. The Theory of Granular Partitions is designed, now, to provide a framework within which precisely such differences of perspective on the same subject-matter can be comprehended within a single framework.

Beta receptor antagonists (or beta blockers) are one of the major drug families used in the management of hypertension. In Table 2 we take one prototypical example from this drug family – Propranolol – to show the different partitions being applied.

Table 2. Partitions of Antihypertensive Agents with propranolol as example

Partition	Explanation of Classification	Illustration: Propranolol
General Therapeutic Partition	Actions of the drug which are significant at a symptomatic clinical level.	Management of hypertension; management of angina; management of life-threatening arrhythmia.
Causative Clinical Partition	Roles played by the drug in a specific pathological state, for example, based on a clinical practice guideline.	For the treatment of hypertension, the initial oral dose of propranolol is generally 40 to 80 mg per day.
Collateral Clinical Partition	Other effects the drug can have while being used in relation to a specific clinical condition.	Adverse effects (including effects of overdose). For example, dizziness, decreased heart rate, nausea.
Pharmaco-kinetic Partition	Effects of the different body systems on the drug, for example its absorption, metabolism, excretion, etc.	Complete oral absorption, 75% metabolism in first passage through the portal circulation, large volume of distribution, etc.
Pharmaco-dynamic Partition	Effects of the drug on different body systems from the pathophysiological point of view, with a granularity lower than that of the clinical level.	Slowing of the heart rate, decrease in myocardial contractility, decrease in cardiac output, increase in peripheral resistance, etc.
Biochemical Partition	Chemical attributes of the drug (according to its chemical family, chemical structure, etc.)	A benzene ring with an ethylam-ide side chain. Substitution of an isopropyl group favours inter-

		action with beta-adrenergic receptors.
Product Partition	Commercially available products containing the drug as active principle (reflecting differences in physical form, mode of administration, etc.)	Propranolol HCl available as 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration and as a 1 mg/ml sterile injectible solution for intravenous administration.

There is no doubt that these partitions are related to each other. Each provides a different window onto the same reality. Only a framework which can do justice to the existence of such distinct views on reality can allow us to formulate an adequate ontology of the domain in hand.

7 Conclusion

The vast amounts of knowledge currently being accumulated in the biomedical domain demand ontological resources based on clear and tested principles. The semantic types underlying UMLS and the organizing principles of the Gene Ontology both manifest a number of significant problems in this respect. We have apply the principles underlying Basic Formal Ontology and the Theory of Granular Partitions which brings not clarity to such terminology-based classifications and could provide a framework within which divergent classifications can be unified in a robust and realistic fashion.

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Acknowledgement: Work on this paper was supported by the Wolfgang Paul Program of the Alexander von Humboldt Foundation.