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Biodynamic Ontology: Applying BFO in the Biomedical Domain

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Abstract. We propose a modular formal ontology of the biomedical domain with two components, one for biological *objects*, corresponding broadly to anatomy, and one for biological *processes*, corresponding broadly to physiology. The result constitutes what might be described as a joint venture between two perspectives – of so-called three-dimensionalism and four-dimensionalism – which are normally regarded as incompatible. We outline an approach which allows them to be combined together, and provide examples of its application in biomedicine.

Introduction

Current approaches to formal representation in biomedicine are characterized by their focus on either the static or the dynamic aspects of biological reality. We here outline a theory that combines both perspectives and at the same time tackles the by no means trivial issue of their coherent integration. Our position is that a good ontology must be capable of accounting for reality both synchronically (as it exists at a time) and diachronically (as it unfolds through time), but that these are two quite different tasks, whose simultaneous realization is by no means trivial.

The paper is structured as follows. We begin by laying out the methodological and philosophical background of our approach. We then summarize the structure and elements of the Basic Formal Ontology on which it rests, in particular the SNAP ontology of objects and the SPAN ontology of processes. Finally, we apply the general framework to the specific domain of biomedicine.

1. Background

1.1 Methodology

The methodology presupposed in what follows and developed in [10, 33] is realist, fallibilist, perspectivalist, and adequatist:

(i) *Realism* holds that reality and its constituents exist independently of our (linguistic, conceptual, theoretical, cultural) representations thereof.

(ii) *Fallibilism* accepts that our theories and classifications can be subject to revision.

(iii) *Perspectivalism* maintains that there exists a plurality of alternative, equally legitimate perspectives on reality.

(iv) *Adequatism* maintains that these alternative views are not reducible to any single basic view. Thus adequatism is opposed to reductionism, i.e. to the thesis that there is some one privileged perspective to which all other representations of reality can be reduced.

These four axes of our methodology are not independent of each other. Thus perspectivalism is constrained by realism, which means that it does not amount to the thesis that just any view of reality is legitimate. To establish which views *are* legitimate we must weigh them against their ability to survive critical tests above all when confronted with reality in scientific experiments.

Those perspectives which survive are deemed in the spirit of realism to be transparent to reality: it is however a fact that apparent scientific certainties are sometimes abandoned over time, and so each given perspective is accepted always in a way which leaves open the possibility of future revision. The biomedical sciences are themselves in considerable flux, a fact that is well illustrated by the recent radical reorganization of science departments in medical schools [21], reflecting an increasing emphasis in the biomedical sciences on subcellular processes and modes of organization.

Perspectivalism and realism combined with adequatism generate the view that we need (and do not merely have as an option) a plurality of alternative theories to reflect the different perspectives which cover complex domains of reality like that of biomedicine. Reality is like cheese: it can be cut in many ways. Our methodology endorses the need for views of entities belonging to different domains (neurology, cardiology, urology) all of which coexist within a single organism. The progress of science often involves appeal to the reductionistic methodology for instrumental reasons: scientific explanations often take the form of a demonstration of how coarse-grained phenomena can be reduced to finer-grained phenomena, for example at the level of microphysical particles. But the purposes of building ontologies are distinct from those of empirical science, and experience has shown that an adequate representation of reality of the sort needed for purposes of biomedical ontology must take account of a plurality of different views, all of which are equally veridical. This is because the central purpose of ontology lies precisely in its ability to assist in the communication between the perspectives associated with different scientific disciplines.

A perspectivalist approach to biomedical ontology with ambitions to remain consistent with science and to cope with its reductionistic tendencies will need to find ways to do justice above all to a plurality of perspectives on different levels of granularity. Granularity is indeed here understood as reflecting those specific ways of carving up domains of reality we associate with different scientific theories. One perspective might focus on whole organisms, another on cellular assemblies. Yet another might seek to do justice to the very same reality in terms of complexes of atoms or molecules. A fourth might talk in terms of changes and invariants in an associated continuum of metabolic pathways, or of behavior (of walking, eating, drinking, sweating) on a whole-organism scale. Our approach allows that all of these views can be tenable within their respective boundaries, and that there need be no privileged approach which could justify the reduction of one to another. It allows us also simultaneously to embrace both commonsensical and scientific perspectives on reality; that is, it allows us to endorse the view that both common sense and science at different levels of detail and granularity can give us genuine knowledge of the world.

1.2 Basic Formal Ontology in Context

Basic Formal Ontology (BFO) is a theory of the basic structures of reality currently being developed at the Institute for Formal Ontology and Medical Information Science (IFOMIS) at the University of Leipzig. BFO is a formal ontology whose construction follows the methodological maxims presented above. The enterprise of building BFO is thus motivated on the one hand by the desire to be faithful to reality, and on the other hand by the need to accept a multiplicity of perspectives upon reality which may be skew to each other.

Such perspectives can be organized along two dimensions, reflecting (i) the opposition between different levels of granularity, from single molecules to whole populations of organisms, and (ii) the opposition between objects and processes. The bacterium in the Petri dish on your desk can be apprehended either as an object in its own right or as a structured group of molecules and either in terms of objects such as the cell and its components, or in terms of processes such as the movements of the cell, the interactions of its components. As to (i), we refer the reader to [4, 35, 37]. Here, we shall concentrate primarily on (ii). Our focus, more precisely, will be the reconciliation of the dynamic approach to biological phenomena with the orientation of biology around objects (molecules, cells, organs, organisms, species). It should be borne in mind throughout that what is said about objects and processes in what follows can be applied, in principle, at all of the different levels of granularity which are relevant to the enterprise of biomedical research. In practice, each material application of BFO will be restricted to some given level of granularity, and each resultant granular ontology will respect the two-component structure here presented.

1.3 Continuants and Occurrents

The central dichotomy between objects and processes concerns two distinct *modes of existence in time*. BFO endorses first of all a view according to which there are entities in the world that *endure* through time: entities which persist self-identically even while undergoing changes of various sorts. Such *continuant* or *endurant* entities come in several kinds. Examples are: you, your hippocampus, your kidneys, your chromosomes; but also: your bone mass, your cranial cavity, the surface of your skin. You are, for instance, the same person today as you were yesterday and as you will be tomorrow. In the terms of Zemach [45], continuants are said to be *bound with respect to space*. This means that if we segment the region of space occupied by a continuant, then we segment the continuant also. Continuants are not, however, bound with respect to time. This means that however we segment the interval of time during which a continuant exists, we find this continuant itself in every segment. This is what it means to endure. [19, 20, 25, 41]

BFO endorses in addition a view according to which the world contains *occurrents*, more familiarly referred to as processes, events, activities, changes. Occurrents include: your breathing, her coughing, my drinking, the spreading of an epidemic through a population and the chemical synthesis of proteins. Occurrents have, in addition to their spatial dimensions also a fourth, temporal dimension, and they are, in contradistinction to continuants, bound with respect to time. This means that if we segment the interval of time during which an occurrent occurs then we segment the occurrent also. Occurrents occur in time and they unfold themselves through a period of time in such a way that they can be divided into temporal parts or phases.

Not all entities are segmentable in this way. This is because there are beginnings and endings and other boundaries in the realm of occurrents, which are instantaneous: they are analogous to the edges and surfaces of objects in the realm of continuants. Just as the latter can exist only as the boundaries of three-dimensional spatially extended objects, so the former can exist only as the boundaries of temporally extended processes. Typically, the beginning and ending of an occurrent, as well as everything that takes place between these two points, are parts of the occurrent itself. The beginning and ceasing to exist of a continuant, in contrast, are not parts of the continuant itself, but rather parts of that occurrent which is its life or history.

1.4 Spatiotemporal Ontologies

The challenge is to build a unified framework within which we can do equal justice to the modes of being of both continuants and occurrents. This framework, we shall argue, needs to keep the two corresponding groups of entities clearly separate, since they have ontological features of quite different sorts. Above all, while we can sum of a pair of continuants or a pair of occurrents to produce larger continuant or occurrent entities, continuants and occurrents themselves cannot be summed together in any coherent way. At the same time, however, we have to find a way of bringing them together within the framework of a single theory: continuants are themselves subject to constant change; occurrents, as we shall see, depend in every case on continuants as their bearers: they are changes in continuants.

We distinguish at the outset two main kinds of ontologies, called SNAP and SPAN, the former for continuants, the latter for occurrents. Relations between continuants and occurrents are thus trans-ontological; that is, they are relations between entities that belong to distinct ontologies [10]. The resulting framework is thus a combination, in the spirit of perspectivalism, of the three- and four-dimensionalist perspectives currently predominating in philosophical ontology, positions which are normally seen as mutually incompatible.

Both three-dimensionalists and four-dimensionalists are, in their different ways, reductionists. Each asserts that the entities accepted by the other do not exist. The four-dimensionalist will in effect accept just the SPAN part of the BFO framework, translating all talk about three-dimensional entities into talk which refers exclusively to processes, or to so-called four-dimensional 'spatio-temporal worms' or 'process-things' [24] or to some temporal parts or 'stages' thereof [26]. The three-dimensionalist [29] can take advantage only of the SNAP part of our framework by conceiving processes of change and motion not as entities in their own right but rather in terms of sequences of attributes of continuant objects. In order to account for both things and processes, one needs somehow to combine the two ontologies.

In keeping with our perspectivalist methodology, we shall argue that we need both types of component: SNAP, to do justice to the world of three-dimensional bodies; and SPAN, to do justice to the processes in which such bodies are involved. SNAP and SPAN are constructed in such a way that we can understand in formal terms how, precisely, they are integrated together. This, we believe, gives us the possibility of attaining a new sort of clarity as concerns the relations between anatomy and physiology and, more generally, between all of the structures and processes that constitute biomedical reality.

2. Basic Formal Ontology

The architecture of the SNAP-SPAN theory [11] is one which allows us to talk not only about *entities* but also about the *ontologies* through which entities are apprehended. Entities and ontologies are not however on a par with each other. Entities are denizens of reality. Everything which exists or occurs in the spatio-temporal world is an *entity*. An *ontology* grasps the entities which exist within a given portion of the world at a given level of generality. It includes a taxonomy of the types of entities and relations that exist in that portion of the world seen from within a given perspective.

Each ontology is such that the entities depicted within it fall under certain formal categories, and each type of ontology corresponds to a specific family of categories. In particular, each SNAP ontology corresponds to entities which fall under the categories of continuant entities, and each SPAN ontology corresponds to entities which fall under the categories of occurrent entities. Trans-ontological relations – that is relations between entities which belong to distinct ontologies – involve relations across categories. The distinction between ontologies of the relevant sorts thus allows us to conceive BFO as a multi-categorial ontology [12, 22].

2.1 SNAP and SPAN Ontologies

Each SNAP ontology is *indexed* to some specific instant of time, and being a constituent of a SNAP ontology thus amounts to existing as a continuant at the time of the ontology's index. Each SNAP ontology may thus be conceived as an assay of the continuants existing at some specific temporal instant. Such continuants have of course typically existed already for some time in the past and will typically go on existing into the future. The entities recognized by SNAP ontologies are thus not themselves instantaneous entities, even though SNAP ontologies themselves are indexed by temporal instants. A SNAP ontology is analogous to a snapshot.

Capturing the world as it changes over time involves from the SNAP perspective taking a succession of temporally indexed SNAP ontologies into account. As single SNAP ontologies are akin to snapshots of reality, so a succession of such ontologies is akin to a slide show. Change is then reflected in discrepancies between the successive slides. A SNAP ontological treatment of development would consist, in effect, in a sequence of successive snapshots reflecting the state of the embryo, fetus, and developed organism as these exist at different times. Indices of SNAP ontologies may either be actual instants of time or, more abstractly, they may reflect generic phases of development of an organism.

A series of SNAP ontologies can reflect a series of findings (in the way in which a temperature chart is used as a basis for inferring changes in a patient's health); but it cannot capture changes (for example the processes involved in growth and developments) themselves. Rather, it is in SPAN ontologies that we find changes as entities in their own right. Where each SNAP ontology relates to what exists in some single instant, a SPAN ontology relates to a whole *span* or interval of time. Here all times within the interval (whether past, present, or future) exist on a par, and these times are themselves constituents of the reality that is captured by the ontology. Occurrents are structured along both the spatial and the temporal dimensions, and they are located in spacetime, which is itself a SPAN entity. A SPAN ontology is obtained by depicting the reality constituted by those occurrent entities that unfold themselves within some determinate interval of time. As ontologies of continuants are analogous to snapshots of reality, so ontologies of occurrents are analogous to videos spanning time. Each SPAN ontology is indexed by some temporal interval.

Both SNAP and SPAN ontologies are indexed not only by times but also by *domain* and by *level of granularity*. An example of a SNAP domain is: *this human organism* or (more abstractly: the typical human organism, of a certain age and gender). An example of a SPAN domain is: *the life of this human organism*.

2.2 Relations in BFO

Our framework comprehends the following types of formal relations:

Intra-Ontological Relations. An intra-ontological relation is a relation between entities all of which are constituents of a single ontology. An example is the relation of topological connectedness between the different parts of an organism. Reflecting the SNAP-SPAN opposition between two main types of ontology is an opposition between two main types of intra-ontological relations. For details, see [11]. Part-whole and topological relations are always intra-ontological, and thus they never cross the SNAP-SPAN divide: an object is never a part of a process and a process is never a part of an object; objects and processes are never topologically connected to each other, nor are they topologically separated: they belong, precisely, to different ontologies.

Trans-Ontological Relations. A relation between entities that are constituents of distinct ontologies is called trans-ontological. Consider the relation of *participation* between an object and a process (as when the fingers of a hand *participate in* the making of a surgical incision). Trans-ontological relations will be needed also to relate entities in distinct ontologies of the same type (for instance the positions of the arm during the incision that are recognized by a succession of SNAP ontologies with distinct time indexes).

Examples of relations between SNAP and SPAN entities include: *dependence*, *participation*, *initiation*, *termination*, *creation*, *destruction*, *sustenance*, *deterioration*, *facilitation*, and *hindrance*. [13, 38] One type of relation is of special importance in integrating the SNAP and SPAN components of our framework. This is the relation between each SNAP entity and that unique SPAN entity which is its *life*. This relation is difficult to define; however it satisfies at least the following conditions: that the life of an organism is *dependent on* this organism (a life cannot exist without its bearer), and that an organism *participates in* its life. Roughly, the life of an organism (a continuant) is the sum of all occurrents in which it participates.

2.3 Taxonomies of Entities in BFO

Biomedical universals are as numerous as are the classes of entities treated of by the different branches of biomedicine, including the sciences of physiology, anatomy, molecular biology, neurology, immunology, psychology, psychiatry, pathology, internal medicine, and so forth. Universals are the real invariants or patterns in the world apprehended by the specific sciences. Universals are multiply instantiated: they wholly exist at different places and different times in the different particulars which instantiate them. [29, 14] The relation between universals and particulars is one of *instantiation*.

Universals are reflected by terms such as *organ*, *cell*, *parthenogenesis*, *death*. Which universals exist in reality is a question for empirical scientists, not for logicians or linguists, to determine. In particular, names for universals cannot be generated via logical composition. Thus while there are organs and cells, there is no universal *organ-or-cell*. We thus accept a sparse theory of universals, as embraced by realist ontologists as such as Armstrong [1] and Lewis [18].

3. The Taxonomy of SNAP Entities

The hierarchy of top-level categories in SNAP is represented in Figure 1, which may be understood as a window on a certain portion of the world. We can look through this window in a way which selects particulars or in a way which selects universals.

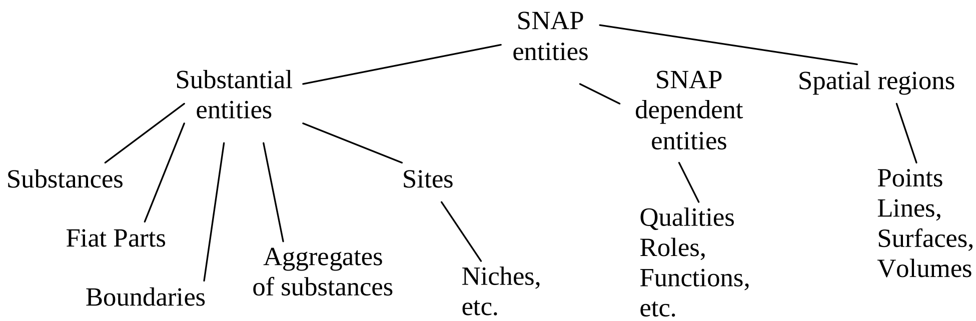

Figure 1. The principal categories of SNAP entities.

3.1 Spatial Regions

BFO embraces a so-called absolutist view of space, sometimes also called a container view. There are spatial regions, which are themselves continuants and which are such that other SNAP entities can be located at or in them. Space itself is the totality of such spatial regions (it is their mereological sum), and space exists – in conformity with the absolutist view – independently of the things which are located at its parts. On the other hand however we need to do justice also to certain intuitions underlying the relational conception of space. [7] On the relational view, spatial regions exist only in virtue of certain relations among objects. We shall see that some varieties of spatial entities – called *sites* below – are of just this sort.

There are spatial relations which obtain between the entities located at spatial regions at any given time in virtue of the relations which exist between the regions themselves. Some of these are topological (see for instance [8]), some are distance and orientation relations. Thus, your brain is located in your brain cavity; a brain tumor may be located in the intermediate gray matter of the left side of the spinal cord between the thoracic levels T3 and T4.

3.2 Substantial Entities

Apart from spatial regions, SNAP entities can be divided into two broad families of *dependent* and *independent*. Dependent entities, such as qualities or roles, are entities which require other, independent entities in order to exist. The latter serve as the bearers or carriers of the former. The category of *independent SNAP entities*, also called 'substantials', comprehends a number of subcategories, as follows.

3.2.1 Substances

Organisms are the prototypical examples of substances, which are maximal connected substantial entities. [29] They are those substantial entities which enjoy a certain rounded-offness or natural completeness, including not only organisms but also cells, rocks, planets, and a range of self-contained artifacts such as a needle or a plastic bag. Substances have the following main features:

- they do not depend for their being sustained or maintained in existence upon other entities (they are metaphysically independent);
- they are the bearers of qualities and are subject to qualitative change;

– they are enduring entities: they preserve their identity over time and through changes of various sorts;
– they have a location in space;
– they are self-connected wholes with physical boundaries which separate them off from other substances.

The term ‘substance’ is used here as a count noun, in keeping with the philosophical tradition stretching back to Aristotle. For most purposes it can be regarded as synonymous with the term ‘object’ or ‘thing’. In ordinary English, of course, the term ‘substance’ has also a mass sense, according to which water is a substance, iron is a substance, and so on. The treatment of the referents of mass terms involves issues of granularity, which are here left aside.

3.2.2 Fiat Parts

It is possible to carve out zero-, one-, two- and three-dimensional fiat parts of an organism, which is to say parts not demarcated by physical discontinuities. [27, 42, 32] This is what is done when we demarcate upper and lower lobes of the left lung, or the dorsal and ventral surfaces of the body, or when a strip of brain surface is demarcated as the primary motor cortex. Such fiat parts can in some cases be transformed into substances in their own right, as when a certain segment of the kidney is demarcated as cancerous for purposes of surgical removal.

3.2.3 Boundaries

Boundaries in the SNAP ontology are lower-dimensional parts of spatial entities. Examples of two-dimensional boundaries are: the boundary of the organism, the inner surface of the stomach. When dealing with biomedical entities it will prove crucial that we are able to deal with the surfaces of substances and not only with the regions in which such surfaces are located. [6, 30, 42] Boundaries themselves can be divided into two kinds: the fiat, and the physical or bona fide. [42] The boundary between adjacent lobes of the lung is a fiat boundary (it depends upon our fiat demarcations); the surface of the whole organism is a bone fide boundary (it exists independently of any demarcations we may choose to make).

3.2.4 Aggregates

Aggregates of substances are mereological sums comprehending separate substances as parts. In contradistinction to substances, aggregates have non-connected boundaries. Aggregates on one level of granularity (for example a collection of cells) may correspond to substances (for example a whole organism) on another level of granularity, [35, 37].

3.2.5 Sites

Sites are holes, cavities and similar entities [6], for example those holes, formed by aggregates of cells and bony structures together with associated fiat boundaries, which we call sinuses, canals, ventricles, etc. The spinal canal is a site, as are the cranial cavity, the cavernous sinus, and the lumen of the gastrointestinal tract. The tympanic cavity is a site, as also is the interior of your aorta, as also is the room or field in which you are reading these words. Each site is associated at any given time with some specific spatial region – typically with a succession of spatial regions at successive times. In this respect sites are analogous to substances, and like substances they may move through space. Sites are thus not identical with spatial regions. In addition to being located at spatial regions, substances may also, in virtue of their relations to other substances, be located at or in sites.

Niches, Environments: Niches [40] are special sorts of sites, marked out by their capacity to be occupied by organisms. Your nasal cavity may be a site of this kind insofar as it is inhabited by microorganisms. Niches are typically made of a medium (of air, or water) enclosed by a mix of fiat and physical boundaries. It is the medium which enables the niche to sustain the occupant in existence. The media of niches are marked by features such as water pressure and osmolarity, density and chemical constituency of nutrients, which together help to constitute the niches appropriate for given sorts of tenants.

Sites sometimes act as *surrounding spaces* for other entities [42], and they do this in different ways. The oral cavity is a site for the billions of microorganisms which live in it. The addresses where people live and work are labels for certain sites which they characteristically occupy. In the environment surrounding the organism, too, we may carve out fiat portions, for example corresponding to zones of different temperature or toxicity.

The cranial cavity and the eye socket are examples of sites within the human organism. The brain almost completely fills the cranial cavity. If it is significantly displaced by a tumor or internal bleeding its functional capabilities will be destroyed.

Boundary-Free and Physically Bounded Sites: Sites are typically a compound of rigid surroundings and fluid medium. Some sites, however, are defined in whole or in part in terms of fiat boundaries: for instance your lap, the crook in your elbow. Sites whose boundaries are partly or wholly solid we call ‘physically bounded’; others we call ‘boundary-free’. Your nostril is a partly physically bounded site. Your oral cavity, when the lips are closed and the posterior of the tongue is elevated, is a wholly physically bounded site.

3.3 SNAP Dependent Entities

SNAP dependent entities are entities which endure in time and which inhere in substantial entities. *Inherence* is an intra-ontological relation between a SNAP dependent entity and its substantial bearer. The *redness* of the red blood cell inheres in the cell; the *circumference* of a *waist* inheres in the *waist*; the *shape* of a nose inheres in the nose. Such inherence is a form of existential dependence in the sense that the particular colour of the arterial blood would not exist without the arterial blood which it is the colour of. SNAP dependent entities include: particularized *qualities* (the elasticity of the skin, the core temperature of the body), *functions* (the function of the birth canal to transport the fetus), *dispositions* (of the teeth, that they are prone to decaying), *powers* (of tooth brushing, to prevent the decay of teeth), *liabilities* (of the teeth, to be abraded by the tooth brushing function), *disorders* (the headache you have been suffering from for the past two hours), *bodily features* (a smile). Other types of SNAP dependent entity include: *states* or *conditions, plans, norms, tasks, rules, algorithms, procedures,* and *diseases*.

The terminology is hard to fix here, and the types we have distinguished by way of example are themselves not clearly separated from each other and they form a highly heterogeneous family. We avoid the terms ‘property’ and ‘attribute’, not only because they can be applied at best to only some members of this family but also because they ride roughshod over distinctions of importance to us here.

There are both monadic or single-bearer and polyadic or relational (multiple-bearer) SNAP dependent entities. Examples of monadic SNAP dependent entities include qualities dependent on one substance only, such as the mass of your kidney. In what follows we shall sometimes use the term 'quality' as a convenient shorthand for 'monadic SNAP dependent entity'. Relational SNAP dependent entities are entities which depend upon a multiplicity of substances, which they serve to relate together. Examples include relations of connection, by which motoneurons in the spinal cord and brainstem innervate a particular number of muscle fibers to form together a single motor unit. Each motor unit is composed of a motoneuron and the muscle fibers it innervates.

3.4 SNAP Universals

Universals form taxonomies of various sorts. Each taxonomy is a tree in the mathematical sense, whose nodes correspond to universals of greater and lesser generality. We introduce the terms 'genus' and 'species' to refer informally to universals at higher and lower positions within such trees. [3, 34] A biological taxonomy recognizes the genus *cell* and the species *pyramidal cell, red blood cell, smooth muscle cell*, *retinal ganglia cell*, and so on. Each of the latter is a sub-species of the single genus *cell*. (Similarly in a SPAN ontology, another biomedical taxonomy recognizes the genus *biological synthesis* and a variety of subspecies of this genus.)

There are two main kinds of SNAP universals: *substantial universals* and *universals instantiated by SNAP dependent entities*. The former include substance universals such as *cell*, *limb*, *body*; site universals such as *cavity*, *groove*, *sinus*; universals under which fiat parts of substances fall, such as *leg*, *small intestine, spinal cord*; universals instantiated by aggregates of substances such as *family*, *nursing staff, population.* Universals instantiated by SNAP dependent entities include role universals such as *parent* or *doctor*; function universals such as *to pump blood*, *to transport air*; and quality universals such as *colour* or *shape*, instantiated by the colour and the shape of this specific kidney. The universal *red* is a determinate of the determinable universal *colour*. [17]

By combining substantial and quality universals (or their associated defined predicates), we may build further constructed predicates *a volo*. [14] Take for instance 'is a grey hair'. This predicate does not correspond to any universal, but it nonetheless applies by definition to all hairs which are grey, i.e., to all hairs in whose surface there inheres an instance of the quality universal *grey*.

4. Taxonomy of SPAN Entities

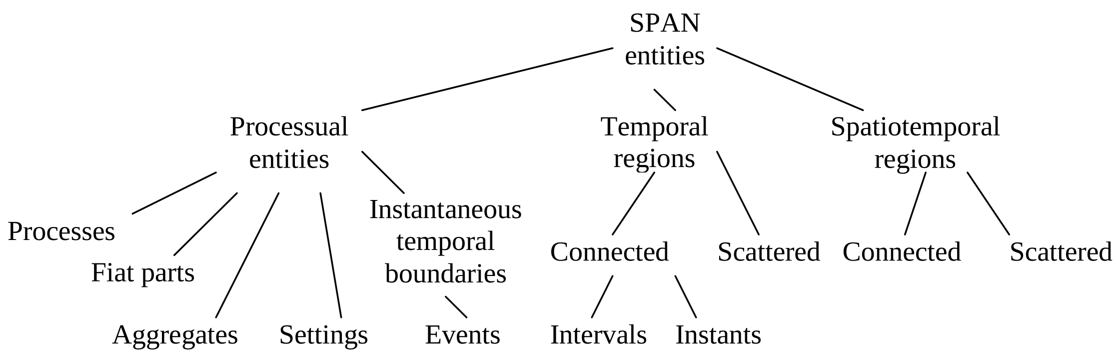

Figure 2. The principal categories of SPAN entities.

4.1 Processual Entities

This family of processual entities stands to processes as the family of substantial entities stands to substances. Processuals are occurrents or happenings; they are entities which exist in time by occurring. Processuals involve participants of a SNAP kind and they are dependent on these participants. A process of drinking cannot exist without some organism and some liquid. Processual entities are located at spatiotemporal regions. They include not only processes (see below) but also arbitrary fiat parts, aggregates and boundaries thereof. Processuals may have more or less complex structures. However, in contradistinction to what is the case in regard to substantial entities, there are few clean joints in the realm of processual entities. This is because the latter merge with each other in a variety of ways to make larger wholes, to the degree that the SPAN realm is in large part a realm of flux (a realm of transitions which are characteristically continuous). When you breathe while your friend talks, these two processual entities become merged together in a way that has few counterparts in the SNAP realm of substances. The gastrointestinal motions in your body likewise became intertwined together with the processuals unleashed by the laxative pill you have taken. In each case, however, the processual entities involved can still be distinguished via the drawing of fiat boundaries, and the products of such fiat demarcations serve to make true propositions for example asserting causal relations between one processual and another.

4.1.1 Processes

Processes are the natural units in the processual realm in that they have bona fide beginnings and endings corresponding to real discontinuities in the processual order. Candidate examples are: the life of an organism, or the process of sleeping (demarcated by the boundary of falling asleep and waking up).

Just as substances in SNAP are defined in such a way as to be maximal spatially connected wholes, so processes in SPAN are required to be maximal spatiotemporally connected wholes. [16, 5] This means first of all that processes involve no temporal gaps. A given process may not be occurring at two distinct times without occurring also at every time in the interval between them. Similarly, a process may not occupy two spatiotemporal regions separated along the spatial dimension without occupying also a continuous sequence of spatiotemporal regions forming a bridge between them. In case a given processual entity is affected by gaps of this sort, we are dealing not with one single process but rather with a process-aggregate – of the sort which is involved, for example, in the production of a series of vowels and consonants that form a spoken sentence in articulated speech, or in the epidemic transmission of diseases across a scattered population. The line between processes and processuals of other sorts is however clearly difficult to draw, [11]. What is classified as process and what as aggregate of processes often depends on the chosen level of granularity.

4.1.2 Fiat Parts

The parts of processes on a given level of granularity are by definition fiat parts; for if processes are connected entities then any division into parts must of necessity be a fiat division. Examples of parts of processes are: an individual chewing process in the course of a meal, the passage of a bolus of food from the mouth to the stomach. When we move to a lower level of granularity, however, then we often find it possible to recognize bona fide parts (for example, the coordinated contractions of individual muscles in the performance of eating).

4.1.3 Events

Events are the fiat and bona fide instantaneous temporal boundaries of processes. Examples are: the forming of a synapse; the onset of REM sleep; the detaching of a finger in an industrial accident. They are the temporal analogues in SPAN of the spatial boundaries of substances in SNAP. Some extended processual entities are apprehended as event-like changes because they involve sudden qualitative or other jumps which seem to divide temporal reality into two parts. Truly instantaneous events, for example the passage from your 13th to your 14th year, are often created via fiat.

4.1.4 Aggregates of Processes

Examples of aggregates of processes are: the aggregate of all neuronal firings involved in the generation of a thought; the aggregate of all steps taken in the course of running a marathon. Again: aggregates of processes at one level of granularity may appear as processes in their own right at coarser grains.

4.1.5 Settings (Spatiotemporal Environments)

Just as we distinguished sites within SNAP, so we can distinguish settings, their four-dimensional counterparts, within SPAN. [2, 31] Examples of settings are: a surgical operation as a setting for a nosocomial infection, a routine check-up as a setting for the finding of a tumor.

4.2 Spatiotemporal Regions

The totality of spatiotemporal regions reflects the totality of possible fiat demarcations of that maximal region we call *spacetime*. [28] They include in particular those spatiotemporal regions which are the spatiotemporal extensions of processual entities. Processuals then stand to spatiotemporal regions in SPAN ontologies in a way analogous to the way in which substantials stand to spatial regions in SNAP ontologies. Spatiotemporal regions are entities which exist in their own right in the sense that they exist independently of any processuals which may be located at or in them. Partitions of spatiotemporal regions at which processuals are located generate corresponding partitions of the processuals themselves. Spatiotemporal regions have specific sorts of four-dimensional shapes – for example the characteristic shapes of the spread of epidemics – and reference to such shapes may be used in the formulation of taxonomies of their processual occupants.

There are spatiotemporal relations which hold between processuals in virtue of the relations between the regions of spacetime at which they are located. Thus there are mereological and mereotopological relations; relations of coincidence in spacetime (when two entities occupy the same spatiotemporal region), relations of locational overlap (when their respective spatiotemporal regions share parts), and so on.

5. Biodynamic Ontology

A biomedical ontology is a theory of kinds of entities and relations we find in the biomedical realm. Such entities appear at a plurality of distinct levels of granularity (including especially the molecular and cellular levels and the organ/tissue and whole organism levels). Our basic assumption is that reality is made up of substantial entities: molecules, hearts, arms, brainstems, esophagi, bodies, which are involved in a continuous series of processes: of chemical manufacturing and transmission at one level, of reaching out, swallowing, responding to environmental conditions at another level. The processes in biomedical reality are in every case processes involving or taking place within objects. Objects and qualities are apprehended (for example through periodic sampling – as when we measure body-weight or temperature) as they exist at given instants of time; processes are grasped (through extended observation – as when we monitor heart rate on an oscilloscope) as they unfold through some given temporal interval. As should by now be clear, a biomedical ontology cannot be limited to objects and qualities but must make room for processes also.

Each biomedical SNAP ontology has one privileged substance – the organism, which plays a role in biomedical ontology that is analogous to that played by the Earth in geographic ontology [15]. We take the organism as a reference body for the location of entities at or near its surface and in its interior. (Whether the organism is a substance or an aggregate of substances will however depend on the level of granularity of the perspective taken.) There are no precise limits to the scope of a biomedical ontology, which can extend in principle as far as the outer periphery of the organism's environment and down to the biochemical reactions in its core. A biomedical ontology must have the resources to deal with phenomena which causally interact with what exists or takes place in the external and internal environment of the organism even where such phenomena do not fall within the scope of biomedicine as narrowly conceived. The sun, for example, is not a biomedical object, but phenomena such as the heat it generates and the photons it emits are causally connected to the bearers of life.

We will leave aside such considerations here, however, and focus exclusively on the ontology of those objects, qualities, and processes which are located on or near the surface or in the interior of the organism and which are standardly understood as biomedical. (A full account of these matters would however require a detailed treatment of granularity, for this is needed in order to analyze the two concepts of existing or occurring *in relationship to the organism* and of *being of biomedical scale*.)

5.1 Biospatial, Biotemporal, and Biospatiotemporal Regions

We have used 'region' as a generic term embracing regions of *space*, of *time*, and of *spacetime*. The term 'bioregion' will have the same generic character here. It refers to regions that are of a scale relevant to biomedicine and that are located in proximity to the surface or interior of an organism.

We recognize three types of bioregions:

Biospatial Regions: Every organism is located at a biospatial region at any time at which it exists and so are all the parts of every organism. Biospatial regions are regions of space at or in which parts of the organism or its immediate environment are located.

Biotemporal Regions: These are temporal regions with a specific relation to the organism. They are the regions (intervals) of time during which the organism exists. The organism exists at any time at which the process we call its life is occurring, and conversely. The biotemporal regions are then precisely those parts of the region of time occupied by the life of the organism.

Biospatiotemporal Regions: These are spatiotemporal regions with a specific relation to the organism, namely they are those regions of spacetime which are parts of the spatiotemporal location of the life of the organism.

SNAP biomedical entities are characterized, *inter alia*, by the fact that they exist at biotemporal regions. SPAN biomedical entities are characterized by their having a biotemporal and a biospatiotemporal location.

5.2 The SNAP Biomedical Object Ontology

Biomedical objects are all either parts of the human organism or they are located within the human organism or they causally interact with the human organism in specific ways. Examples include proteins, cells, pathogens, limbs, livers, heads, hearts, bladders, brains and entire bodily systems (such as the cardiovascular system). They also include messengers of various sorts with their particular molecular configurations and sets of target cells as well as the media in which cells and organisms live and the aggregate of matter which they consume and excrete.

5.2.1 Biomedical Substantial Entities

In addition to *organism*, there are a number of other kinds of substantial entities which must be recognized by a biomedical ontology: fiat parts such as head and limbs, but also lower-dimensional parts (surfaces, lines and points) and corresponding aggregates, including sites. We can recognize the following subcategories of biomedical substantial entities:

Biomedical Elements: For instance limbs, toes, hairs. Such substantial entities are the most salient biomedical entities for human subjects. In addition, there are biomedical elements distinguished by biomedical science, such as organs, chromosomes, genes, as well as segments of the stomach, regions of the brain, amino acid sequences, and so on. The elements of the body include cells, organs and organ systems, conceived as entities with specific functions rather than as mere aggregates of material substances. [39] The body is structured in a modular hierarchy, with elements appearing on finer levels of granularity contributing to the functioning of elements of coarser grain.

Biomedical Features: These are lower-dimensional entities appearing on those levels of granularity at which elements are given. They are typically boundaries or fiat parts of boundaries of elements. They can also be boundaries between two elements forming an aggregate. They can be internal as well as external. Examples include the face, the cheek, the waist, the palm of your hand.

Biomedical Artefacts: These include prosthetic teeth, hips, heart valves, breast implants, pacemakers, and so on. These, too, are substantial entities. They are not parts of the organism into which they are inserted, but rather exist in the organism's interior and interact with those entities which are its parts. There exist also non-biomedical artifacts, which play a biomedical role because they exist in the interior of an organism (a piece of shrapnel, a swallowed coin) or more generally because they enter in causal relationships with the organism or its parts.

Biomedical Sites: These are first of all the spaces inside the body – the mediastinum, the intestinal tract, the nasal sinus, the brain cavity – in which body parts are located or with which they are associated in some other way. Body sites are organized into hierarchies of increasing size, from those, such as an alveolus of the lung, which can only be seen under the microscope, to those, such as the interior of a hospital bed, a hospital ward, and so on, which are objects of ordinary perception. There are also conduits, such as the interior of the ureter, which is designated to be a part of the urinary system.

Biomedical Boundary Entities: The boundaries of biomedical substantial entities are of two sorts: fiat and bona fide. The former reflect human demarcations, the latter are real physical discontinuities. Often some extended substantial entity will be taken as an indicator of a boundary (a plate of bone called the hard palate, for example, serves to demarcate the oral from the nasal cavity); the central sulcus participates in the physical delineation of the border between the precentral gyrus and the postcentral gyrus of the cerebral cortex. Brain regions are demarcated not just by physical discontinuities but by fiat boundaries drawn for the purposes of obtaining a partition that is coherent and useful for theoretical purposes.

The surface of the organism is the boundary that separates the interior of the organism from the rest of the world.

5.2.2 Biomedical SNAP Dependent Entities

The realm of SNAP dependent entities comprehends qualities such as an organism's mass or shape. We can distinguish, again, between qualities as *determinables* and qualities as *determinates*. The former are universals such as *body temperature* or *blood pressure*. The latter are specific *values* of such universals, such as 39°C or 120 mm Hg. Values of attributes form scales, sometimes demarcated in terms of real numbers, sometimes in terms of other cardinal or ordinal measures. Some attributes, for example blood types, have *qualitative* determinables and determinates.

One distinguished subcategory of SNAP dependent entities in the biomedical domain is that of function. Functions are the ontological foundation for the engagement of parts of the organism in a variety of processes. The structure of the organism is to a certain extent determined by the functions of its parts. The realization of a function is a process: a *functioning*. The life of the organism includes such realizations among its parts: for instance actions of the organism driven by cells which result in delivery to those same cells of the resources which they require for their own survival.

5.3 The SPAN Biomedical Process Ontology

Biomedical processes are those processes which either take place within the human organism or are processes of causal interaction in which the human organism is involved. Examples include: a heart's beating; a heart beating faster when its host organism exerts itself; an arm withdrawing when a finger touches a flame; a human becoming thirsty, fetching a glass of water, experiencing a pain in the abdomen, going to see a doctor; a peristaltic wave proceeding down an esophagus.

A primary division among the processual entities occurring within the biomedical domain can be made according to the kinds of participants they involve. First are *physical processes* – such as cartilage erosion, urination, local infections – whose main participants are organisms or organism parts. Second are *social processes*, which is to say processes involving (aggregates of) human beings, such as the making of diagnoses, clinical trials, the application of therapies, processes of demographic change, the spreading of epidemics. We can distinguish also various families of biomedical *actions*, which are processes involving either human beings or institutional agents on a given level of granularity, and the counterparts of such actions on the side of biomedical *patients*.

Other varieties of SPAN biomedical entities include changes in the qualities inhering in a SNAP entity, locational changes, substantial changes (for example: conception, death), fiat changes (getting older in the sense of calendar years), developmental changes (for example: gastrulation, neurulation), evolutionary changes (the formation and extinction of species).

5.3.1 Changes in the Qualities Inhering in a SNAP Entity

These include:

Changes in determinables. In many cases a SNAP dependent entity will instantiate different *determinates* of the same *determinable* quality at different times. The elasticity of the skin changes over time. Yet still there is something, a token – as opposed to a type – *determinable*, which remains the same and which is the ultimate subject of such change in transitioning through successive token determinates or values. The temperature of your body is a continuant entity despite its variation in values from one moment to the next. [23] This is a common type of qualitative change in the biomedical context: it is illustrated by change in hair color and texture, muscle strength, joint flexibility, memory retrieval capacity and so on. Other sorts of biomedical changes include qualitative, structural and morphological changes: for example a change in temperature in the organism. Note that the latter is at another level of granularity a (non-biomedical) matter of the movement of molecules. This shows the importance of a more general formal apparatus within which macroscopic biomedical phenomena can be related to the microscopic processes by which they are constituted.

Qualitative Creation. A SNAP dependent entity that is not present in one ontology appears in later ontologies. This is what happens when sex hormones are secreted in adolescents and the body thereby acquires new dispositional qualities with the emergence of secondary sex characteristics.

Qualitative Destruction. A substance has a certain SNAP dependent entity for a certain interval of time but not at later times. This is what happens when a substance loses powers or functions, as when an older person loses the power of sight or is deemed not eligible for a needed liver transplant.

5.3.2 Spatial and Locational Change

In one SNAP ontology the testes are in the abdomen, in a later SNAP ontology they are in the scrotal sacs. In one SNAP ontology the saphenous vein is in the leg; in a later SNAP ontology a part of it is in the heart. The two types of location – sites and regions – correspond to two types of locational change. Some biomedical objects are tied to specific sites; this holds especially of biomedical elements such as the brain and heart. Other biomedical objects move through space – this applies for example to red blood cells and limbs. Yet others may change their relative positions within the organism over time – this applies for example to hairlines and waistlines and to the curvature of the spine. Such biomedical motions are locational changes on a biomedical scale.

5.3.3 Substantial Change and Substantial Formation

Substantial changes are always instantaneous (the conclusion of the process of gastrulation; the moment of the final heart beat) [36]; clearly however they are in every case associated with extended processes which proceed or follow them. Substantial changes occur when substances are created or destroyed, as when a substance is divided up in such a way as to produce a plurality of substances or when a plurality of substances is fused or merged. At some precursor stage in the life of each human organism there was a single, fertilized egg; at every stage in the life of the mature organism it is a complex of billions of cells and houses a wide variety of substances and sites of various shapes and relationships. This complex, the organism, is a continuant; it remains the same even while constantly gaining and losing parts.

We can distinguish in this connection the following simple types of *substance formation*.

Budding: a part of a substance becomes detached, forming a new substance while the original substance goes on existing; joint cartilage erosions form an example here, as also does the formation of cancerous tumors, or the build-up of plaque in the coronary arteries, or of new veins emanating from existing ones in the formation of corollary circulation.

Absorption: one substance ceases to exist after becoming absorbed into a second substance; as when osteoclasts remodel bone or in the formation of confluences of streams of afferent input at various parts of the central nervous system in the formation of memory traces.

Separation: parts of a substance are transformed into entities in their own right, as when a zygote splits into two cells.

Unification: separate substances join to form a new substance, as when separate plates of membranous bone fuse to form the cranial vault.

5.3.4 Functions and Functionings

Biological functions in general seem paradigmatically to be such that they are associated with parts of an organism and to be such that their realization brings benefits to the including organism which are relevant to the latter's survival. Functions relate more specifically to the need for energy of the organism and its parts. Functions, like the functionings which are their realizations, exist at every level of granularity relevant to the organism. Functions are continuants (SNAP entities): functionings are processes and thus belong to the SPAN ontology.

The organism is incessantly dynamic and in most cases this activity appears functional to the biomedical scientist. This is true for primitive prokaryotes as well as for human beings and other complex mammals. In normal circumstances, the organism serves itself oxygen, water and food in sufficient quantity to meet its needs for energy and matter to maintain its structure. These sources of energy and matter (which are themselves a matter of SNAP entities) are the fuel for the realization of the functions of the various parts of the organism. In turn these processes are precisely what enables the organism and its parts to endure. A case of normal functioning results in outcomes that, all things being equal, are beneficial to the organism. This is what 'functioning' (as opposed to engaging in the many different types of processes which are not realizations of functions) means. [39]

5.3.5 Patterns of Change

In all regions of the organism there are processes which occur with greater or lesser regularity, defining for example biomedical rhythms and other processes. Such patterns of change may be correlated with one another via complex relations of causality and dependence – for example in the way in which sleep-wake rhythms are correlated with day-night cycles. In order to describe such SPAN patterns we have to build a framework for describing the characteristic attributes of processes. Biomedical processes have participants, they occur in places, and they typically amount to changes in SNAP biomedical entities participating more or less actively or passively in them. There are patterns of change of intensity or rate of a process, which are second-order processes (changes in changes). Other process-characteristics include: alternating (day-night variations), instantaneous, continuous, discrete, regular, zigzagging, cyclical, seasonal, gradual (aging), transitional (adolescence), transient (moods), and so on. There are also patterns of changes in spatial extent: spreading (of an infection), remission (of a tumor), migration (bacteremia), and so on. These patterns define subcategories of processual entities (extra nodes extending the taxonomies depicted in Figure 2 above) which are crucial for the understanding of the dynamism in the biomedical domain.

6. Conclusion

We have presented the main features of BFO, showing how it may be applied to the biomedical domain and focusing on BFO's ability to capture in a perspicuous way the essentially dynamic nature of reality. The SNAP/SPAN distinction allows us to do justice to both sides of biospatial dynamics by allowing us to focus alternately and in a non-reductionistic manner on both processes as occurrent entities and the substantial entities which they involve as agents and patients. In addition, our framework is conceived in such a way as to readily allow the formulation of relations between different ontologies, in particular between the SNAP and SPAN ontologies. [13, 38]

The framework can be readily extended to the treatment of families of ontologies of other types, above all to the treatment of relations between ontologies of different levels of granularity, from genes to species and from a single patient to epidemics at a geographical scale (combining an application of BFO to the medical and to the geographical domain). The framework may also be used as a tool for dealing with the relations between distinct perspectives on the biomedical domain including culturally-generated perspectives of the sort which are studied by linguists and anthropologists. [37]

We emphasize that our approach, which draws on [15] and applies the ideas of geospatial dynamics worked out in that paper to the domain of biomedical ontology, consists in devising a formal (domain neutral) ontology which can then be applied in successively more restricted domains. In this way, we secure clear foundations for a unified treatment of reality. We have laid what we believe is a firm ground for the specification of adequate ontologies of the biomedical domain. It remains to provide a more detailed (and formal) treatment of the categories and relations here surveyed.[1]

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