

Parts and wholes, shapes and holes in living beings

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Abstract. All living beings are constituted by molecular entities continuously interacting with each other in the complex patterns through which organic material is created and sustained. From the very small to the very large, such interactions involve three-dimensional objects which fit together by virtue of their complementary shapes. Like the pieces in a jigsaw puzzle, parts of objects fit into holes in other objects as they unite to form wholes, which in turn form the parts that combine to form wholes at increasing levels of granularity. Function follows form, and accurate description of the shapes of such molecular entities entails improved reasoning about their activities in biological systems. However, the dynamic, flexible and multi-granular nature of living material presents several challenges for the notions of shapes and holes, analyses of which have thus far largely focused on the shapes of static objects at the everyday perceptual level of granularity. We focus on two such challenges: describing the shapes of objects that change over time, and extending the definition of holes (and their linings) to one that applies across multiple granularity levels.

Introduction

Accurate ontological description of biological systems is at the heart of novel applications in automated reasoning and sophisticated data mining [16], and in particular facilitates the integrative approaches underlying whole-systems biology [12]. However, such description faces several challenges in application to the dynamic and flexible reality that is biology. The shapes of biological entities are intricately linked to their functions, and providing descriptions of shapes allows for predictions about their behaviour in various contexts, through their interactions with one another. In particular, during these interactions, objects interlock and fit together in a fashion similar to a three-dimensional jigsaw puzzle, with overall shape and the presence of holes of various sorts enabling diverse activities.

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Traditional ontological analyses of part-whole relationships and of shapes and holes have largely been focused on the macro level at which human perception operates – the level of buckets and lakes, tunnels and trains. In these cases, there is a clear distinction between solid material objects and hollow spaces, and the characterization and delineation of shapes can appear rather straightforward. By contrast, accurate description of living systems requires accounting for the perspectives from multiple different granularity levels from the macroscopic right down to the molecular, to which we have limited perceptual access. Moreover, the dynamic nature of such systems means that the shapes of the entities involved are subject to constant change in a way that the shapes of tunnels and buckets typically are not.

In the next section, we describe the ontological and scientific background to this undertaking, before we tackle some of the issues surrounding the ontology of shapes and holes in living systems. We conclude with some remarks on the application of this work to existing bio-ontologies.

1 Background

1.1 Biological reality is dynamic and multifaceted

All matter as we know it is constituted by atoms and molecules. But a distinction can be drawn between organic and inorganic matter in terms of complexity. As a basic building block of organic material, the unique properties of carbon allow the formation of infinitely varied molecular backbones in which specific sites of reactivity and heterogeneous atoms leading to diverse functionality can be located. Water provides the substrate in which weak interactions between biological molecules can unite to create stable but flexible three-dimensional arrangements of these constituents into larger and larger composites. All of this provides the vehicle for the complex and localised processes that sustain life to take place. Living organisms are composed of an extremely wide diversity of parts, which are organised at increasing levels of *granularity* [11] to form a complex whole, as illustrated in Figure 1.

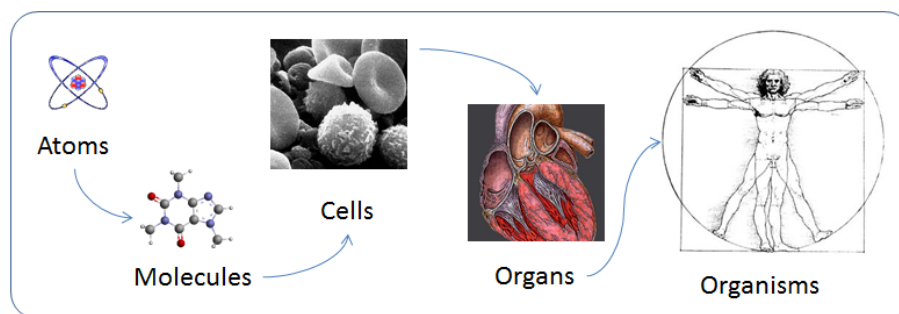


Fig. 1. Granularity of objects in living beings (arrows represent parthood)

Following [8], we distinguish between *continuants*, which are entities that exist through time, such as atoms, cells, and organisms, and *occurrents*, entities that unfold over time, such as chemical reactions, digestions and births. Continuants *participate* in occurrents, and through so doing, they may be changed. Continuants can be further distinguished between those that are *independent* and those which are *dependent*, that is, they cannot exist without a bearer in which they *inhere*, just as colour cannot exist without something that it is the colour of. Dependent continuants can be further subdivided into qualities (categorical properties) and realizable properties such as roles and functions [2]. Dispositions are a special kind of realizable that inhere in their bearers by virtue of what will happen if the bearer comes into the right circumstances [2]. One example of a disposition is the disposition of the stomach to participate in the digestion of food, another is the disposition of carbon atoms to form chemical bonds with each other.

We will consider *shapes* to be paradigmatic *qualities*, dependent on spatially extended objects. All of the biological objects illustrated in Figure 1 extend in three-dimensional space and have shapes. But unlike the conventional objects referred to in typical analyses of shapes, biological objects in living systems are, by and large, in *constant motion and interaction* within their environments. Their shapes are capable of changing in response to the circumstances of their environments. On one view, all this amounts to is that they simply adopt *several different* shapes over time, the way several different shapes appear in a turning kaleidoscope. This is not incorrect, but it makes it difficult to express the *relationships* between the different shapes which biological objects can adopt, nor the constraints on such shapes (i.e. shapes which they *cannot* adopt).

1.2 The perplexing ontology of holes

Shapes are closely related to *holes*, another class of dependent entities. Holes exist in material objects precisely when those objects are shaped in a certain way. Holes themselves have shapes which are shared by their *ideal fillers*. The shapes of the material objects in which holes are located are further related to the shapes of the holes themselves in a negative, or figure-ground relationship [4]. There are different types of holes [5]: (superficial) hollows, (closed) cavities and (penetrating) tunnels. The philosophical interest in holes is driven by the apparent tension between their appearance in common sense ontology as *bona fide* objects figuring in various relationships and functional roles in the world being described (a hole in my boot is *why* my sock became wet from the snow), and their apparent emptiness or status as *nothings* (the hole is, by definition, precisely where the boot is not) [5]. Different theses have been defended, in some of which holes have been denied existence as entities altogether, and in others they have been equated with the *linings* (minimal surfaces) or shapes of their hosts [5]. Following [5], we allow holes the ontological status of entities in their own rights, located at the surface of material objects (their *hosts*). Some consequences of this view are that holes are *dependent* on their hosts, in the sense that there is no hole without some host, but holes are not *part*

of their hosts, although they may be *contained in* them (as is the case for cavities). This contrasts with the standard biological view of anatomical cavities as holes which *are* part of their anatomical hosts, for example, the cavities of the heart (ventricles, atriums) are considered to be part of the heart [7]. But this distinction can be seen as partly a matter of convention. An uncontroversial spatial relationship between host and hole might refer to location and *external connection*.

2 Shapes of dynamic and flexible objects

Molecules consist of complex arrangements of atoms joined by *covalent bonds* – shared pairs of electrons. The relationship of form to function is no less crucial at the molecular scale than in larger scales, and indeed some classes of molecules are fully definable based on aspects of the shapes of the molecules, e.g. molecular knots (such as trefoil knots), molecular cages and molecular Möbius strips [9]. One characteristic of the chemical bonds from which complex molecular entities are formed is that they can be more or less flexible or rigid. Rigid bonds constrain the overall shape of the molecular entity (or at least a localised part of that entity) to be *just so*, with a particular shape that persists under standard conditions. Flexible bonds, on the other hand, allow for relatively easy movement of parts around the bond such that the overall molecule can adopt different conformations, i.e. different shapes (see Figure 2).

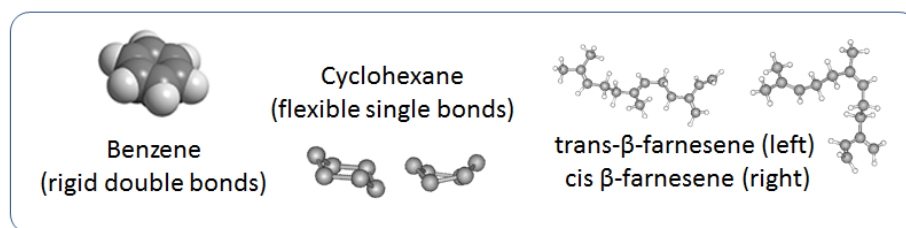


Fig. 2. Shapes of rigid and flexible molecules affect their functions: trans- β -farnesene acts as a pheromone, while cis- β -farnesene, differing in configuration around one single bond, does not.

Biological macromolecules take particular advantage of such flexible bonds. Macromolecules such as proteins and DNA consist of long chains of repeated amino acids forming a *backbone*, which then, by the flexibility of the bonds of the backbone, are able to fold up into a complex active shape, held together by weak interactions between neighbouring parts of the folded molecule.

Describing the shapes of such molecules – in such a fashion as to enable automated reasoning about their properties, such as extrapolation from *shape* similarity to *functional* similarity – thus requires, on the one hand, describing some rigid aspects that persist fairly invariantly over time, and also describing *flexible* aspects together with their overall range of variability. The standard method for representation of such aspects of shape for chemical entities is visual, and dedicated software tools are available both at the level of small chemical

entities (for which the algorithms involved are fairly performant) and the much larger biological macromolecules (with correspondingly lower performance) to calculate the overall shapes (conformations) that the molecules can adopt based on the known properties of the atoms and bonds, and to display those in visual overlay. Such representation may be the most suitable for humans but does not enable automated reasoning. We thus need to address flexibility, and its relationship to shape, to adequately model shape aspects in chemical ontology.

We can ask, *Is flexibility of the same ontological nature as shape?* The Phenotypic Quality ontology (PATO, [1]) has the answer as yes, flexibility is indeed a quality, as is shape. Flexibility (PATO:0001543) is defined in PATO as “A physical quality inhering in a bearer by virtue of the bearer’s capability of being turned, bowed, or twisted without breaking”. Leaving aside the macroscopic implications of this definition, we wish to focus on the key word *capability*. One of the features of qualities such as shape, size and length is that they are manifested in full at all times that they exist. On the other hand, capabilities seem to be the sorts of things that can be dormant, or un-manifested, yet still exist. We agree that flexibility is *that* sort of entity, but this implies that it is *not* of the same ontological nature as shape. Capabilities are a kind of *realizable* entity within BFO, similar to dispositions. To further avoid the reference to macroscopic notions of twisting and bowing, we offer the following revised definition: “Flexibility is the capability to adopt a different shape without breaking”. Flexibility inheres in a part of a molecule by virtue of the nature of the bond between the atoms within that part and the configuration of the remainder of the molecule. We can thus usefully distinguish not only the shape of the molecule *at a point in time*, but also the overall shape that it can adopt, that is, the sum of all the possibilities for different conformations of the molecule.

3 Binding sites behave as if they were holes in proteins

Much of the functionality of proteins is facilitated or altered by the selective binding of those proteins to small molecular enablers known as ligands. Ligands bind to what are termed *active sites* within proteins. For example, oxygen binds to the active site in the hemoglobin protein which is responsible for the function of red blood cells. Binding sites behave like hollows, in the terminology of [5], in that they can be filled up by, and they have the function of holding onto, their fillers, in much the same way a bucket holds water. However, unlike water in a bucket, it is not gravity that holds the small molecular fillers in their binding sites, but an overall aggregate of weak molecular attractive forces. The small molecule fillers of protein binding sites may be partial, just as a bucket may be half full of water, although arguably they may never be perfect, since the lining of the molecule does not exactly coincide with the lining of the hole. Rational drug design consists in the optimization of a filler for a particular binding site of a protein – optimal filler in this case meaning largest, most specific molecule that binds with the best energetic properties. Just like holes, binding sites remain *the*

same even though the molecular filler changes; it is possible that every atom of the enclosing protein is exchanged without the binding site being affected.

Binding (consisting in weak interactions, not covalent bonds) takes place because of *mutual dispositions* between the atoms of the protein and the atoms of the small molecule [3]. Lock-and-key-type mutual dispositions arise because the disposition of matter to resist combines with the shape of the lock resulting in an additional disposition to only admit objects which themselves have the right shape (the key) (termed ‘actual fillers’ in [5]). Binding is usually modelled as a lock-and-key, but it is a bit more complicated than that for a number of reasons. Firstly, under physiological conditions both the “lock” and the “key” are constantly changing in shape. Secondly, in the lock-key scenario we only have repulsive interactions to take into account, while in the binding scenario there are both repulsive and attractive interactions between the lining of the pocket and the small molecule. Thirdly, driving the air out of a lock by pushing in a key is so easy that we do not recognize we’re doing it, while the same is not true inside the cell, where the “key” has to be more attractive to the “lock” than other molecules floating around in the intracellular medium.

Casati and Varzi [5] state that holes are actual rather than potential objects. Yet what seems to be going on in certain kinds of protein–small molecule binding events appears as though there was a *potential* hole in the protein – which was pushed (by the flexibility of the protein) into an actual hole and then filled by the small molecule. While Casati and Varzi acknowledge that in some cases, fillers can be causally responsible for a hole’s form, in this case, an even stronger conclusion could be that the filler is causally responsible for the hole’s *existence*, since holes that are hosted by such molecules may not only change in shape, they may come into being and disappear depending on the conformation and the local environment.

4 The minimal lining for a hole in a molecule is subatomic

Binding sites depend on both the molecule and the way it is folded, i.e. its shape. An anatomical parallel is the lap or the crook of the elbow or the snuff pocket. Those body sites only exist when you arrange your other body parts in the right way. But there is an important difference. Some theorists have defended a position where holes are identified with hole *linings*, i.e. their hosts, or the minimal part of the host that defines the hole. A good counterargument to this is that the hole lining can be removed in some cases while the hole remains [5]. Similarly, your lap remains if you remove your trousers. However, binding sites are not laps, since if the atoms that line the binding site are taken away, then that destroys the structure of the molecule and, based on what remains, alters the shape and nature of the binding site itself.

A temptation would be to conclude from this that binding sites are not holes in quite the same ontological sense as macroscopic holes. However, this depends on the (implicit) *macroscopic* notion of the “minimal lining” for a hole. Casati and Varzi define hole linings in terms of the surface of the host object, and

surfaces are defined as the minimal part of the host object that is *in contact* with the external world – the outermost part of the object, the part that we can “see and touch”. Under this macroscopic view, the surface of the host – and therefore the lining of the hole – appears to consist in at least a thin layer of atoms. This macroscopic notion of lining, however, breaks down with small enough objects. When the removal of a single atom *fundamentally alters* both the nature of the host and the nature of the hole, a layer of single atoms no longer constitutes a minimal lining in any sense true to the meaning of the term.

But to what should we turn to rescue the concept of minimal lining for molecular scale holes? The intuitive answer is that we should assign the boundary somewhere in the wave of electron density that orbits the relevant atoms. Support for this model is dealt with from the concept of *molecular surfaces* as boundaries of molecules, defined as a spatial position at which the electron density function surrounding the molecule begins to dissipate sharply. It is important to note here that the electron density only *tends* towards zero in the space surrounding the molecule – it never fully reaches it⁶. While Casati and Varzi *deliberately* base their theory of holes on a compact common-sense notion of matter, looking at holes on a molecular scale brings into sharper focus the true underlying nature of physical reality. All matter consists mostly of space with scattered atom nuclei and electrons, glued together by physical forces. Adopting such a physically accurate view of matter could further entail that there were only tunnels, no cavities or hollows, since all matter is essentially ‘holey’; the only purely material bodies are the elementary particles. In a fine-grained perspective all material objects with holes look like the exploded torus in Casati and Varzi. In Figure 3 (left) there are no cavities, only tunnels. Reducing granularity (right) the small spaces are ignored, and therefore the space in the middle becomes a true cavity.



Fig. 3. Cavities and tunnels at different levels of granularity

Since whole-systems modelling requires that our ontology is resilient to such inconsistencies across multiple levels of granularity, we propose a different definition of the minimal surface of the host of the hole, which is that the minimal surface of the host of the hole is just the boundary of the host which suffices to resist intrusion into the host *by other objects at the same level of granularity*.

⁶ See in addition [13], where the Casati and Varzi account of ‘bare space’ is criticised on similar grounds.

Thus, the minimal surface of the bucket for the hole contained in the bucket is the boundary of the bucket that serves to resist intrusion into the material of the bucket with respect to portions of macroscopic substance at the same level of granularity as the bucket itself – such as water. Neutrinos constantly pass through the walls of the bucket unharmed. The minimal surface of a protein molecule, however, is the surrounding wavefunction of electron density at just that level which suffices to repeal the intrusion of other atoms. This constitutes a subatomic part of the protein molecule, but it is characterised by its disposition to resist spatial overlay.

One of the challenges with the ontology of holes is that they appear to ground dispositions, while nothings or absences cannot ground dispositions. Casati and Varzi argue that the disposition of fillability can inhere in ‘bare’ matter, in order that their immaterial objects ontology can allow for the dispositions of holes. Here, we argue that a more central disposition is the disposition of *displaceability* – the disposition of the electron density in the relevant region of space to resist displacement by other clouds of electron density.

5 From molecules to organisms and back again

Folded proteins group together and form the various complex structures of cells, which in turn group together to form tissue, organs and finally organisms. Cells depend on a highly stabilised inner environment, which needs to be protected to the greatest extent possible from environmental toxins. One of the mechanisms by which cells ensure such protection is with a protective lipid membrane, through which only certain controlled substances are allowed to pass, through special *channels*. Cellular membranes thus behave like containers of cavities that are punctuated by functional tunnels, which allow only certain substances to pass through in a mediated fashion. A similar pattern can be observed in certain intracellular organelles such as the mitochondrion. At a larger scale, tunnels in the form of blood vessels also allow for the circulation of lifegiving oxygen and nutrients.

Anatomical cavities mediate the process by which parts of the environment become parts of the body, and vice versa. Food is taken in via the mouth and broken down in a process of digestion before it enters the bloodstream, travels to the cells where it is needed, and is absorbed across the membrane through a cross-membrane transport. Anatomical cavities of interest include the inside of the stomach, which is the site for digestion processes, and the inside of the lungs, the site for breathing processes. Anatomical cavities and tunnels are seldom the loci for bare space. They are *usually* filled: the heart’s ventricles are filled with blood, the stomach is filled with food, the lungs with air. Indeed, there are cases (certainly at the cellular level of granularity) in which it can be difficult to define where the lining ends and the hole begins. Some anatomical holes *collapse* when they are not filled. Should we conclude that anatomical holes are not holes at all (although there are some rigid anatomical holes, e.g. bone cavities), and that their common-sense classification as such is mistaken? We think not, and

the reason lies with the function of the hole lining – specifically, to resist the penetration of matter of a certain type.

Consider the case of digestion in greater detail. The purpose of the intestine is to facilitate the extraction of nutrients from food. Ingested food, however, contains a great deal besides nutrients, and the function of the intestine is also to ensure to the extent possible that this extraneous matter never passes into the bloodstream of the organism. Thus, part of the processes that take place during digestion function to break down food substances into molecules at a lower level of granularity; which molecules can then be screened and allowed to pass through tunnels in the intestine lining if they are of the right type. This process sheds new light on the question as to when food constituents, originally environmental, becomes *part of* the body, raised in [7]. Food, or rather, the nutrients from food, could be seen to become part of the body at precisely the point that they are allowed to cross the barrier from the cavity of the intestine to the remainder of the body, leaving the protective hole in which foreign matter is quarantined. This protective function of anatomical holes is paralleled at the cellular level [15].

6 Conclusions

Terminology describing biological shapes and holes at different levels of granularity is currently spread throughout the bio-ontologies such as the Gene Ontology (GO, [17]), the Foundational Model of Anatomy (FMA [14]) and various ontologies of bio-molecular entities such as RNA (RNAO, [10]) and small molecules (ChEBI, [6]). However, these entities appear with various different implicit or explicit ontological commitments, such as a division between those who admit cavities as *material parts* (e.g. ‘cavity of stomach’ is part of stomach in the FMA, and is defined as ‘Organ cavity which is bound by the internal surface of the wall of stomach’) and those which ascribe cavity-like entities as *functions* (e.g. ‘ion channel’ in GO is part of the molecular function hierarchy, but not the cellular component hierarchy). Facilitating interoperability between bio-ontologies requires finding a means to unify these diverging views.

We have applied the theory of holes contained in Casati and Varzi to the description of some of the shapes and holes that are of relevance in living beings. In so doing, we have admitted a large role for dispositions in the story. We have raised doubt on the description of holes that takes no consideration of granularity, in the sense that all matter is ultimately full of holes at the lower levels of granularity, but addressed this doubt by allowing for the explicit role of energetic factors – themselves dispositional in nature – in the definition of material boundaries. Finally, we have introduced flexibility as a shape-related disposition of biological objects that is required in order to characterise the changing shapes of such objects over time in their natural environments.

Acknowledgements

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