Formalizing a General Disease Module

Fumiaki TOYOSHIMA[a,1]
[a] *Graduate School of Advanced Science and Technology, JAIST, Japan*

Abstract. Disease is of vital importance in the biomedical domain. A proper understanding of disease would help to provide a general conceptual framework for the integration of biological and biomedical data. This paper aims to elaborate upon the recent view that, on closer examination of existing ontological models of disease, a disease is generally characterized as a dependent continuant of a clinically abnormal causal pattern. This work will constitute a further step towards the development of an ontological module for generic disease representation.

Keywords. disease ontology, causation, pattern, disposition, function

1. Introduction

Biomedicine is nowadays witnessing an unprecedented increasing amount of disease-related data and information. There is accordingly a growing demand for a common semantic framework in which many pieces of biomedical information are sharable among different information systems (e.g., databases) in order to maximize opportunities for medical practitioners to acquire medical knowledge and to improve their clinical decisions. To surmount this difficulty of semantic non-interoperability is nonetheless a considerable challenge, partly owing to the lack of broad consensus among biomedical experts on some key domain concepts: e.g., disease, health, and aging.

The goal of this paper is to seek a general account of disease that can aid in the building of disease ontologies. To do so, we further the project (originally sketched out in [1] and later elaborated in [2]) to harmonize two existing ontological models of disease that have been developed and practically utilized in biomedical ontology research for the last decade: a dispositional model of disease provided by the Ontology for General Medical Science (OGMS) [3] and the River Flow Model (RFM) of diseases [4].[2] More specifically, we expound on the recent finding [2] that a disease can be generally characterized as a dependent continuant of a clinically abnormal causal pattern.

The paper is organized as follows. Section 2 is devoted to preliminaries to our inquiry. To put it more concretely, this part specifies basic ontological assumptions and the scope of our investigation. Section 3 presents the OGMS and the RFM. Section 4 explores the concept of causal pattern which is taken to be the core of disease by both theories of disease and whose sophistication will constitute a further step towards the

[1] Corresponding Author. E-mail: toyo.fumming@gmail.com, fumiakit@buffalo.edu.

[2] For the sake of simplicity, we will sometimes use the term 'the OGMS' to refer specifically to the dispositional model of disease offered by the OGMS.

development of an ontological module for generic disease representation. Section 5 concludes the paper with some remarks on future possible directions of research.

2. Preliminaries

2.1. Basic Ontological Assumptions

For the sake of the anchoring of a general ontological background, we posit some basic categories and relations that are relatively widespread in upper ontologies.[3] Entities fall into two kinds: universals (aka types, classes) and particulars (aka tokens, instances). Particulars (e.g., Mary) bear the instance-of relation to universals (e.g., Human). We speak mainly of particulars in this paper. Particulars fall into two categories: continuants (aka endurants) and occurrents (aka perdurants). Continuants can persist, that is to say, they can exist at one time and also exist at another different time; whereas occurrents (including events and processes) extend through time (typically while having temporal parts).[4] Continuants can be further divided into independent continuants (including objects) and dependent continuants (namely, properties in the broad sense of the term). Independent continuants, or especially objects (e.g., stones) can be bearers of dependent continuants (e.g., hardness) and can participate in occurrents (e.g., a fall of the stone).

2.2. Scope

Our investigation is limited in scope because disease is so intensively researched in various disciplines that we cannot discuss it exhaustively in a single short paper. First, we will put a main focus on a general notion of disease, but not on any specific diseases, viz. cancer, pneumonia, and diabetes. Certainly, discussions on those particular diseases would require fairly specialized knowledge and experience of them, which would reside outside our area of expertise. On the other hand, we can investigate a generic concept of disease relatively independently of disease-related domain knowledge. We rather aim at a theoretical characterization of disease that medical practitioners would have difficulty in providing, but that is general enough to accommodate their clinical viewpoints.

Second, our approach to disease may have a close affinity with, but nonetheless differs considerably from philosophy of medicine, which pivots around the debate over a conceptual analysis of health and disease between the naturalist, normativist, and hybrid accounts of them.[5] Naturalism offers a value-free analysis of disease by taking bodily dysfunction to be a sufficient condition for it [7,8]. Normativism argues for the determination of the harmfulness of disease by social values [9]. Hybridism conceives bodily dysfunction as a necessary, but not sufficient, condition for disease [10,11]. On our view, philosophers of medicine generally examine the nature of clinical abnormality of disease, or what kind of standard disease consists in deviating from. We will proceed,

[3] Borgo and Hitzler [5, p. 3] spell out upper ontologies (aka foundational ontologies) as follows: "(…) while a top-level ontology is a classification system that deals with general domain-independent categories only, a foundational ontology is a top-level (formal) ontology that has been built and motivated by the upfront and explicit choice of its core principles."

[4] As we will see below, formal-ontological discussions on (the sub-classification of) occurrents are complicated by significantly diverse usages of the terms 'event', 'process', and 'state' offered in the literature.

[5] See Lemoine [6] for problems with a conceptual analytical approach to the definition of disease and health.

by contrast, while taking the notion of clinical abnormality as primitive. This is mainly because different criteria for clinical abnormality depend so heavily on different medical fields and professionals that it would be impracticable to seek a single universal definition of clinical abnormality (see e.g., [12] for a similar line of research).

Third and lastly, we will discuss the ontological notion of causation in biomedicine, rather than epistemic notions of causal inference and causal reasoning. One may be more concerned with causal inference than causation, as in bioinformatics [13] and public health [14]. For instance, Russo and Williamson [15] point out two types of causal evidence in the health sciences: the probabilistic evidence (consisting mainly of observed dependencies in a range of similar studies) and the mechanical evidence (to be used to explain physical phenomena mechanically). They contend that the unification of both the mechanistic and probabilistic aspects of the health sciences can be achieved by the epistemic theory of causation: causal relationships are to be understood in terms of rational beliefs, or the causal beliefs of an (ideally) omniscient rational believer. An ontological analysis of causation should not be neglected in biomedicine, however. To make a substantial contribution to evidence-based practice for healthcare [16], for instance, prevailing epistemic approaches to causation must be supplemented with a deep ontological (e.g., dispositional) understanding of causation [17,18] (see [19] for criticism).

3. Two Existing Ontological Models of Disease

3.1. The Ontology for General Medical Science (OGMS)

One of the most influential ontological models of disease is arguably the one that is provided by the Ontology for General Medical Science (OGMS) [3]. The OGMS is designed to represent the entities that are involved in a clinical encounter in compliance with the Open Biomedical Ontologies (OBO) Foundry [20]: a collaborative project to coordinate ontologies to support biomedical data integration that tends to adopt as a standard upper ontology Basic Formal Ontology (BFO) [21]. Characteristic of BFO is its methodology of ontological realism to view ontologies as representations of the reality that is described by science [22] (see [23,24] for criticism).[6] As the realist methodology goes, for instance, ontologies can represent cells and electrons, but not unicorns.

The OGMS model of disease hinges upon the BFO category of dispositions. A disposition is a dependent continuant which exists because of certain features of the physical make-up (material basis) of the independent continuant (bearer) in which it inheres and whose instances, in response to some stimulus processes (triggers), can be realized in associated processes (realizations) of specific correlated types in which the bearer participates [21, pp. 101-102]. A process therein is a BFO category as well: an occurrent "that exists in time by occurring or happening, has temporal parts, and always depends on at least one independent continuant as participant" [21, p. 183].[7] Classical

---

[6] "The realist methodology is based on the idea that the most effective way to ensure mutual consistency of ontologies over time and to ensure that ontologies are maintained in such a way as to keep pace with advances in empirical research is to view ontologies as representations of the reality that is described by science. This is the *fundamental principle* of ontological realism" [22, p. 139].

[7] To avoid ambiguity in the future, we use the notation 'BFO: process' to refer to processes in the BFO sense of the term.

examples of dispositions include fragility (the disposition to break when pressed with a certain force), solubility (the disposition to dissolve when put in a certain solvent), and flammability (the disposition to ignite when met with a certain heat source). More specifically, fragility of a glass is the disposition of the glass that can be triggered by a BFO: process of pressing with a certain force; that can be realized in a BFO: process of breaking; and that has as its material basis a particular physical molecule structure of the glass. Interestingly, dispositions may exist even if they are not realized or even triggered; e.g., a glass is fragile even if it never breaks or even if it never undergoes any shock.

To introduce the OGMS dispositional account of disease, we present two core terms of the OGMS. A *disorder* refers to a material entity which is clinically abnormal and part of an organism, although its precise definition has been repeatedly changed and seems to be under development [3,25,26]. A *pathological process* is a bodily process that is a manifestation of a disorder, where a bodily process is a BFO: process in which participate one or more material entities within or on the surface of an organism.[8] Pathological process are recognized through symptoms and signs.

For the OGMS, a disease is: "a disposition (i) to undergo pathological processes that (ii) exists in an organism because of one or more disorders in that organism" [3]. As a disposition, a disease has some disorder as its material basis and a disease comes into existence when its corresponding disorder does, i.e., when the organism disposes towards its relevant pathological processes. A disease as a disposition may go unrealized, e.g., when it lies dormant over a long period of time. A related crucial term is a *disease course*: the totality of all BFO: processes through which a given disease instance is realized. A disease course of a disease ranges widely from potentially asymptomatic early stages of the disease to its recognizable, pathological processes. For instance, epilepsy as a disease is a disposition to undergo the occurrence of seizures (pathological processes) that exists owing to some clinically abnormal, neuronal circuitry of the brain (disorder); and the disease course of epilepsy would comprise pathological processes of seizures and BFO: processes of loss of consciousness.

3.2. The River Flow Model (RFM) of Diseases

The River Flow Model (RFM) of diseases [4] was proposed as an alternative that purports to be more friendly to clinicians than the OGMS dispositional account. The RFM is deeply rooted in the 'waterfall worldview' [27] which is most directly reflected, of all the upper ontologies, in Yet Another More Advanced Top-level Ontology (YAMATO) [28]. As Borgo and Hitzler [5, p. 4] report, YAMATO is "vaguely realist in spirit", while it is only indirectly inspired by some philosophical views and prefers a more pragmatic/engineering approach to ontology. We present two subcategories of occurrents in YAMATO: processes and states. Roughly speaking, YAMATO: processes are 'ongoing occurrents' that would correspond approximately to the progressive aspect of the English verb: e.g., "Mary is walking" (see [29] for close examination of YAMATO: processes). Contrariwise, YAMATO: states are time-indexed qualitative occurrents. Examples include being hungry at time t_1, sitting at t_2, and speeding at t_3.

The RFM is based on the YAMATO theory of objects according to which an object is a unity that *enacts* its *external process* or an 'interface' between its *internal process*

[8] Strictly speaking, a material entity is a BFO category, although the reader can understand it intuitively in our discussion: "An independent continuant that has some portion of matter as part, is spatially extended in three dimensions, and that continues to exist through some interval of time, however short." [21, p. 180].

and external process (see [27] for details). As an object, for instance, a river has as its external process changing its course of water flowing (but not water flowing, which is its internal process). The basic tenet of the RFM is an analogy between a river and a disease. Just as a river enacts changing the course of the flow of water as its external process, a disease enacts as its external process a YAMATO: process of, e.g., spreading and disappearing. While a river is an independent continuant, however, a disease is a dependent continuant: it depends on an organism as its bearer. Moreover, just as a river has as its internal process the flowing of water (a YAMATO: process that occurs inside the river), a disease has as its internal process a number of chains of causal phenomena. A disease is in this respect *constituted of* causal chains of phenomena that are detrimental to the organism from a medical standpoint.

The RFM defines a disease as "a dependent continuant constituted of one or more causal chains of clinical disorders appearing in a human body and initiated by at least one disorder" [4]. The term 'clinical disorder' initially shared its meaning with the OGMS conception of disorder. Since its active practical application, however, the RFM has regarded disease primarily as a dependent continuant constituted of causal chains of *abnormal states* [30,31]. At first, the term 'state' therein referred to a time-indexed property [30,31]; but later it is interpreted as a YAMATO: state through theoretical sophistication of the RFM [1,2]. For instance, diabetes is a dependent continuant whose causal chains have as part the causal relation between a YAMATO: state of the deficiency of insulin and a YAMATO: state of the elevated level of glucose in the blood.

4. Towards a General Disease Module

4.1. Causation

Toyoshima et al. [2] propose, through a comparison between the OGMS and the RFM, that the ontological core of disease be a dependent continuant of a clinically abnormal causal pattern. We will devote the rest of the paper to further sophistication of this basic idea. Let us begin by saying that it is a non-trivial point, on which both models of disease agree, that a disease is a (dependent) continuant, but not an occurrent. A disease is an entity with which a patient is affected and which medical practitioners identify, diagnose, and cure. It is something that comes into existence, grows, and finally disappears in the patient's body. A disease is therefore an entity that persists in time, i.e., a continuant. More specifically, a disease is a dependent continuant that inheres in an organism, since a disease would cease to exist if the organism (i.e., the bearer of the disease) did.[9]

A chief obstacle to an ontological module for generic disease representation is the concept of causal pattern, which remains nebulous notwithstanding some previous endeavors [1,2] to clarify it. First and foremost, causation is notoriously difficult to analyze, although it has been recently investigated from the perspective of 'natural necessity' [33]. Toyoshima et al. [2] attempt to elucidate the causal character of diseases in the RFM in light of a functional account [34] of causation that builds upon a unifying

[9] A full-fledged defense of the conceptualization of disease as a continuant (rather than a sequence of occurrents) may require considering two competing foundational approaches to biological reality: substantialism (which says that objects are more fundamental than occurrents) and processualism (which says that occurrents are more fundamental than objects). This issue lies outside the scope of this paper, though; see Toyoshima [32] for details.

formal-ontological theory [35] of function. Given the fact that a disposition is usually said to be a ‘causal property’, they also argue that the difference between the OGMS and the RFM is due in part to the one between dispositional and functional approaches to causation.

Here we will scrutinize causation *vis-à-vis* a general disease module by providing a more meticulous analysis of the causal difference between those two accounts of disease. To do so, we will examine dispositions, or in particular what kind of outlooks both models have on the causal role of dispositions. We start by disambiguating the highly polysemous term ‘disposition’. Bird [36] distinguishes between *dispositions* as ‘predicatory properties’ and *(causal) powers* as ‘ontic properties’. We will hereafter follow his usage of the terms ‘disposition’ and ‘(causal) powers’. Predicatory properties are properties that are defined by almost any predicate; and the predicatory usage of the term ‘property’ is an ontologically uncommitted, mere *façon de parler*. As predicatory properties, for instance, dispositions may be thus grounded in laws of nature (see e.g., [37]). Ontic properties are, by contrast, properties with a distinctive ontological role; and powers are (ontic) properties with dispositional *essence*. In stating that a glass *is disposed to break* if pressed with a certain force, for example, one is speaking of the fragility disposition of the glass, but not necessarily its fragility power.[10]

Let us also introduce a few more technical terms regarding dispositions. It has been recently suggested that the material basis of a disposition be replaced by the more fine-grained notion of *categorical basis* of the disposition: the sum of *categorical* (non-dispositional) *properties* of the disposition bearer [38,39]. For instance, the fragility disposition and the electrical resistivity disposition of a glass should be grounded in different (sums of) categorical properties of the glass, even though they have as their material basis the same, whole glass.

There are nowadays several theoretical positions on (the causal role of) dispositions, among which we present three major ones for the sake of our argumentation:

- **Powerism** [40]. The powerist is committed to ontology of powers, i.e., properties that have their own causal potency, to the manifestation of which she attributes causation. Dispositions play a substantial causal role in this world.
- **Functionalism** [41, Chapter 9]. The functionalist takes dispositions to be functional properties such that they have some first-order property (e.g., their categorical basis) that plays a causal role with respect to their inputs (triggers) and their outputs (realizations). She reduces the alleged causal role of dispositions to the one of properties to which they are functionally related.
- **Categoricalism** [42]. The categoricalist regards dispositions as mere reflections of their categorical basis that acts in accordance with laws of nature. In other words, the purported causal role of dispositions would be eliminatable because it boils down to lawful dynamics of their causally inert, categorical properties.

Reinterpreted from this point of view, the causal difference between the OGMS and the RFM would be concordant with the difference between the powerist and functionalist theories of the causal role of dispositions. The OGMS espousal of powerism can be

[10] In this paper we use the term ‘property’ to refer to ontic properties. For instance, the property of being green or not green is outside the scope of our ontological study because it is merely predicatory (e.g., “This apple *is green or not green*.”) but it is not ontic.

observed by the BFO explicit commitment to the causal potential of dispositions.[11] The RFM endorsement of functionalism is also vindicated by the aforementioned functional clarification of the causal feature of diseases in the RFM [2].

Quite importantly, the functionalist understanding of dispositions may be vital for effective applications of ontology of dispositions. For a general and theoretical reason, Barton et al. [39] maintain that two dispositions are identical if and only if they have the same categorical basis, the same class of minimal triggers, and the same class of maximal realizations, where the class of minimal triggers of a disposition *d* is the class of triggers of *d* for which no proper part is a trigger of *d*; and the class of maximal realizations of *d* is the class of realizations of *d* which are not proper parts of another realization of *d*. Intuitively, to identify a disposition, one needs to understand the relevant aggregate of categorical properties, the 'smallest causal factor' which exceeds the threshold value for causation, and the resulting whole causal chain of BFO: processes (which would correspond, e.g., to the disease course of a disease disposition in the OGMS). This identity condition of dispositions is closely intertwined with the functionalist's focus on the input-output relationship that she takes to be inherent in dispositions.

For a domain-specific and practical reason, the builders of an OBO ontology the Cardiovascular Disease Ontology (CVDO) [43] suggest that the OGMS be supplemented by an informal methodological rule (which they call 'First-Disorder Rule') to determine the material basis of the disease disposition: "The material basis of a disease D is the first disorder in the causal chain of disorders in which D appears (or the first disorder that immediately follows the last material basis of any disease preceding D in this causal chain, in case such diseases exist)" [43, p. 413]. To take their example, the First-Disorder Rule says that the material basis of a restrictive cardiomyopathy may be a genetic mutation (for a genetic restrictive cardiomyopathy) or iron overload in the ventricles (for a restrictive cardiomyopathy due to hemochromatosis). This proposal can be construed as a kind of functionalist emphasis on the practical relevance of the causal role of some first-order entity that pertains to (second-order) dispositions. It is well worth remarking that, since it conceptualizes disease mainly as *causal chains* of abnormal states, the supposedly clinician-friendly RFM can be seen as a functionalist variant of the supplementation of the OGMS with the First-Disorder Rule.

All those considerations would lead us to propose that a causal foundation for a general disease module be provided through some practical harmonization between powerism and functionalism, granted that the OGMS and the RFM both respect the causal role of dispositions, whether in the powerist's direct way or in the functionalist's indirect way. Notice that categoricalism is off the table presumably because causation should be better characterized dispositionally than lawfully in the biomedical domain. For one thing, the disposition concept is central to medical information sciences [44]. For another, dispositions serve as such a useful conceptual tool for the analysis of the explanatory practice in the biological sciences [45] that a dispositional theory of causation captures well the dynamicity, continuity, and context-sensitivity of biological phenomena [46]. Finally, it is interesting to note that the OGMS powerist and the RFM functionalist views of dispositions might come down to the BFO 'robust realist' and the YAMATO 'pragmatic realist' approaches to ontology, respectively.

---

[11] "Incorporation of dispositions into the BFO ontology provides a means to deal with those aspects of reality that involve possibility or *potentiality* without the need for complicated appeals to modal logics or possible worlds" [21, p. 102, our italicization added].

4.2. Pattern: Temporal, Causal, and Dispositional

Careful investigation into patterns is necessary in order to develop a general disease module [1,2], although they remain an elusive ontological category [47]. Here we leverage Galton's [48] analysis of processes as alleged 'ongoing occurrents' (i.e., YAMATO: processes) based on his valuable insights into patterns. For the sake of consistency between his terminology and ours, we will employ the term 'process' to refer to YAMATO: processes and the term 'event' to refer to occurrents in general. For instance, BFO: processes would correspond approximately to events in our terminology.

Galton begins by distinguishing between *open patterns* and *closed patterns* of spatial patterns and illustrates them with a wallpaper pattern and a dress pattern, respectively. Open patterns can have a potentially infinite repetition (e.g., of some basic *motif* of the wallpaper pattern), while closed patterns must have fully specified demarcations (e.g., a particular arrangement of certain specific planar shapes of the dress pattern). "Both open and closed patterns are abstract specifications of certain possible physical arrangements; they are realized by actual physical structures in the world, arranged according to the specification. However, open and closed patterns are realized in different ways. An open pattern may be thought of as a way of filling space or covering a surface (…). A closed pattern (…) is a way of building a finite structure such as a dress" [48, p. 43].

Galton then characterizes processes as temporal analogues of spatial patterns: "processes are higher-level, abstract patterns that are realized concretely as states or events" [48, p. 42]. Two kinds of spatial patterns naturally yield two kinds of temporal patterns and processes: *open processes* and *closed processes*. "Just as an open spatial pattern specifies a way of covering or filling space, so an open temporal pattern specifies a way of filling (or spending) time. Such a pattern is an open process; if it has an agent, then it may be described as an activity of the agent. (…) A closed spatial pattern specifies the spatial structure of a kind of object. By analogy, a closed temporal pattern specifies the temporal structure of a kind of event. Such a pattern is a closed process; if it has an agent then it may be described as a kind of action" [48, p. 46]. Examples of open and closed processes include walking *simpliciter* and filling in a form, respectively.

To investigate causal patterns in biomedicine, we assume two findings that previous formal-ontological studies on causation generally have in common (see [33] for a general survey). First, causation is (or at least can be represented as) a binary relation between events. When pressing with a certain force caused a glass to be broken, for instance, the event of the pressing the glass with a certain force caused the event of the breaking of the glass. Second, the most paradigmatic kind of causation is arguably what we may call 'canonical causation' [33,49]. Being observable in the macroscopic world (where classical physics holds), canonical causation is so-called 'forward causation' (where the cause occurs earlier than its effect), physical causation (which is roughly entirely explicable in physical terms), and non-probabilistic causation (whose occurrence is necessary, as compared to probabilistic causation such as landing on heads of a coin caused by its toss). For our argumentative purpose, we also postulate simultaneous causation (which biomedical experts usually perceive), although it is philosophically controversial (see e.g., [50]). Simultaneous causation is the same as canonical causation, except that the cause occurs at the same time as its effect. Typical examples comprise the correlation between a sperm and an egg: an egg becomes fertilized only when combined with a sperm and *vice versa*.

We hypothesize that, at least insofar as disease ontology is concerned, simultaneous and canonical causation would be, for the most part, interwoven with open and closed processes, respectively. Consider the fact that a clinically normal organism maintains homeostasis: the state in which the body reacts to changes in order to keep bodily conditions (e.g., temperature) the same.[12] Seen macroscopically, homeostasis is based on highly complex causal interactions between bodily organs and it can be seen as a realization of an open process whose repeating motif consists of coordinated activities of the physiological system. When an organism contracts a disease, however, the development of the disease would be well characterized in terms of causal chains of clinically abnormal events and it would be a realization of a closed process whose specific pattern is determined by the disease in question. This view would contribute to elucidation of the idea of clinical threshold (which the OGMS and the RFM both embrace, according to Toyoshima et al. [2]), namely the level at which a pathological state of affairs begins to develop, in such a way that a clinical threshold can be characterized as an ontological shift from clinically normal simultaneous causation (resp. open process) to clinically abnormal canonical causation (resp. closed process).

Since we argued for the importance of the causal role of dispositions for a general disease module in Section 4.1, let us finally see causation and temporal pattern from a dispositional perspective. We think that the pair of simultaneous causation and open process (resp. canonical causation and closed process) can be well modelled upon mutual realization of reciprocal dispositions (resp. solitary realization of a unilateral disposition) [49].[13] The traditional solitary-realization model [38,39] of dispositions has been effectively deployed in biomedical ontology (see e.g., [52]). The aforementioned dispositions such as fragility, solubility, and flammability are unilateral. Canonical causation is generally explicable in terms of the relation between the trigger and the realization of a disposition: e.g., the event of pressing a glass with a certain force triggered fragility of the glass, which was in turn realized in the event of the breaking of the glass. In formal ontology, by contrast, the idea of reciprocal dispositions was examined under the name of 'complementary dispositions' [53] and it has been recently formalized as an extension of the solitary-realization approach [54].[14] Examples of reciprocal dispositions include the disposition of a key to open a lock and the disposition of the lock to be opened by the key. Simultaneous causation would be explained by the causal interrelationship between reciprocal dispositions, although we do not delve into details owing to spatial limitations (see [49] for details). The main findings to be obtained from this section are briefly summarized in Table 1.

Table 1. Causation, Temporal Pattern, and Dispositional Modeling (in Disease Ontology)

Causation	**Temporal Pattern**	**Dispositional Modeling**
simultaneous causation (clinically normal)	open process (homeostasis)	mutual realization of reciprocal dispositions
canonical causation (clinically abnormal)	closed process (development of disease)	solitary realization of a unilateral disposition

[12] We are using the term 'state' in its general sense while remaining neutral on whether it designates a YAMATO: state or not. See Section 5 for some preliminary thoughts on states.

[13] We use the phrases 'mutual realization of reciprocal disposition' and 'solitary realization of a unilateral disposition' taking a cue from Williams's [51] terminology, although our argument has no direct bearing on his.

[14] In philosophy of dispositions or powers, Martin [55] originally invented the mutual-realization model of dispositions to *replace* with it the orthodox solitary-realization one, though.

5. Conclusion and Future Work

In summary, we proceeded with the orchestration of two existing ontological models of disease, namely the OGMS and the RFM, to take a further step towards the construction of an ontological module for generic disease representation. In particular, we strove to clarify the idea of (clinically abnormal) causal pattern which had remained unexplored in previous works [1,2] notwithstanding its centrality to a general notion of disease. Consequently, we identified the task of the harmonization between the OGMS powerist and the RFM functionalist approaches to (the causal role of) dispositions. In addition, we specified the relationship (as visualized in Table 1) between causation, its corresponding temporal pattern, and its dispositional modeling with regard to disease ontology.

There remain nonetheless many thorny questions to be answered so that a full-fledged general disease module will finally obtain. We end the paper by hinting at a promising strategy for tackling some future issues. The first thing to note is that, based on our work in Section 4.2, we would be able to connect YAMATO: processes and BFO: processes in such a way that the former are abstract patterns whose concrete realizations are the latter. For this finding to be fully utilized in our inquiry into disease, however, close examination of states is clearly warranted because states (as well as processes) play a key role in the RFM. Galton [48] identifies two kinds of states (which would be concordant with the multiple usages of the term 'state' in a biology textbook [56]):

- *States as continuants*. An 'instantaneous state' of some thing or situation, as given by the values assumed at one time by some of its variable properties. E.g., the position and momentum of a particle in physics.
- *States as occurrents*. A 'state situation', described as unchanging with respect to some selected. property or combination of properties. E.g., the state of the water temperature being 50 degrees Celsius.

As Toyoshima [49] says, continuant-states and occurrent-states can be ontologically analyzed as subtypes of the BFO categories of quality and process, respectively, such that states-as-BFO: qualities are more fundamental than states-as-BFO: processes. On the other hand, states should be conceived centrally as occurrents in YAMATO [1,2]. One of the interesting implications of this observation for our ontological modeling of disease is that a primary clinically abnormal entity is a state. As said, the RFM ascribes clinical abnormality to YAMATO: states. Although the present OGMS says that a disorder (a BFO: material entity) is clinically abnormal, the replacement of the material basis of a disposition by its categorical basis (see Section 4.1) would prompt us to reconceptualize a clinically abnormal entity in the OGMS as some state-as-BFO: quality, although this would require considering carefully mereology of properties (see e.g., [57]). It is generally expected that further foundational investigation into occurrents (processes and states) will facilitate significantly the OGMS-RFM harmonization.

References

[1] R. J. Rovetto and R. Mizoguchi. Causality and the ontology of disease. *Applied Ontology*, 10(2), 79-105, 2015.

[2] F. Toyoshima, R. Mizoguchi and M. Ikeda. Causation and the River Flow Model of diseases. In M. Horridge, P. Lord and J. D. Warrender (Eds.), *Proceedings of the 8th International Conference on Biomedical Ontology (ICBO 2017)*, Newcastle-upon-Tyne, United Kingdom, September 13-15, 2017, CEUR Workshop Proceedings, vol. 2137, 6 pages.

[3] R. H. Scheuermann, W. Ceusters and B. Smith. Toward an ontological treatment of disease and diagnosis. *Summit on Translational Bioinformatics*, 116-120, 2009.
[4] R. Mizoguchi, K. Kozaki, H. Kou, Y. Yamagata, T. Imai, K. Waki and K. Ohe. River Flow Model of diseases. In O. Bodenreider, M. E. Martone and A. Ruttenberg (Eds.), *Proceedings of the 2nd International Conference on Biomedical Ontology (ICBO 2011)*, Buffalo, New York, USA, July 26-30, 2011, CEUR Workshop Proceedings, vol. 833, pp. 63-70.
[5] S. Borgo and P. Hitzler. Some open issues after twenty years of formal ontology. In S. Borgo, P. Hitzler and O. Kutz. (Eds.), *Proceedings of the 10th International Conference on Formal Ontology in Information Systems (FOIS 2018)*, Cape Town, South Africa, September 17-21, 2018, Amsterdam: IOS Press, 1-9.
[6] M. Lemoine. Defining disease beyond conceptual analysis: An analysis of conceptual analysis in Philosophy of Medicine. *Theoretical Medicine and Bioethics*, 34(4), 309-325, 2013.
[7] C. Boorse. On the distinction between disease and illness. *Philosophy and Public Affairs,* 5(1), 49-68, 1975.
[8] C. Boorse. A rebuttal on health. In J. M. Humber and R. F. Almeder (Eds.), *What is Disease?* Totowa, NJ: Humana Press, 3-143, 197.
[9] L. Reznek. *The Nature of Disease*. New York: Routledge, 1987.
[10] J. C. Wakefield. The concept of mental disorder: On the boundary between biological facts and social values. *American Psychologist,* 47(3), 373-388, 1992.
[11] J. C. Wakefield. The biostatistical theory versus the harmful dysfunction analysis, Part 1: Is part-dysfunction a sufficient condition for medical disorder? *Journal of Medicine and Philosophy,* 39(6), 648-682, 2014.
[12] N. Williams. The factory model of disease. *The Monist*, 90(4), 555-584, 2007.
[13] S. Kleinberg and G. Hripcsak. A review of causal inference for biomedical informatics. *Journal of Biomedical Informatics,* 44(6), 1102-1112, 2011.
[14] T. A. Glass, S. N. Goodman, M. A. Hernán and J. M. Samet. Causal inference in public health. *Annual Review of Public Health*, 34, 61-75, 2013.
[15] F. Russo and J. Williamson. Interpreting causality in the health sciences. *International Studies in the Philosophy of Science*, 21(2), 157-170, 2007.
[16] D. L. Sackett, S. E. Straus, W. S. Richardson, W. Rosenberg and R. B. Haynes. *Evidence-Based Medicine: How to Practice and Teach EBM* (Second Edition). Edinburgh: Churchill Livingstone, 2003.
[17] R. Kerry, T. E. Eriksen, S. A. N. Lie, S. Mumford and R. L. Anjum. Causation and evidence-based practice --- An ontological review. *Journal of Evaluation in Clinical Practice*, 18(5), 1006-1012, 2012.
[18] R. L. Anjum, R. Kerry and S. Mumford. Evidence based on what? *Journal of Evaluation in Clinical Practice*, 21(6), E11-E12, 2016.
[19] A. Strand and V. P. Parkkinen. Causal knowledge in evidence-based medicine. In reply to Kerry et al.'s causation and evidence-based practice: an ontological review. *Journal of Evaluation in Clinical Practice*, 20(6), 981-984, 2014.
[20] B. Smith et al. The OBO Foundry: Coordinated evolution of ontologies to support biomedical data integration. *Nature Biotechnology*, 25(11), 1251-1255, 2007.
[21] R. Arp, B. Smith and A. D. Spear. *Building Ontologies with Basic Formal Ontology*. MIT Press, 2015.
[22] B. Smith and W. Ceusters. Ontological realism: A methodology for coordinated evolution of scientific ontologies. *Applied Ontology*, 5(3-4), 139-188, 2010.
[23] G. H. Merrill. Ontological realism: Methodology or misdirection? *Applied Ontology*, 5(2), 79-108, 2010.
[24] G. H. Merrill. Realism and reference ontologies: Considerations, reflections and problems. *Applied Ontology*, 5(3-4), 189-221, 2010.
[25] W. Ceusters and B. Smith. Malaria diagnosis and the plasmodium life cycle: The BFO perspective. In *Proceedings of the 3rd Interdisciplinary Ontology Meeting*, Tokyo, Japan, February 27-28, 2010, Tokyo: Keio University Press, 25-34.
[26] W. Ceusters and B. Smith. Foundations for a realist ontology of mental disease. *Journal of Biomedical Semantics*, 1(1), 10, 2010.
[27] A. Galton and R. Mizoguchi. The water falls but the waterfall does not fall: New perspectives on objects, processes and events. *Applied Ontology*, 4(2), 71-107, 2009.
[28] R. Mizoguchi. YAMATO: Yet Another More Advanced Top-level Ontology. In K. Taylor, T. Meyer and M. Orgun (Eds.), *Proceedings of the Sixth Australasian Ontology Workshop (Advanced in Ontologies)*, Adelaide, Australia, December 7, 2010, University of Adelaide, 1-17.
[29] F. Toyoshima. How do processes work? In *Proceedings of the 5th Joint Ontology Workshops (JOWO 2019)*, Graz, Austria, September 23-25, 2019, accepted.
[30] Y. Yamagata, K. Kozaki, T. Imai, K. Ohe and R. Mizoguchi. An ontological modeling approach for abnormal states and its application in the medical domain. *Journal of Biomedical Semantics*, 5:23, 2014.

[31] K. Kozaki, Y. Yamagata, R. Mizoguchi, T. Imai and K. Ohe. Disease Compass: A navigation system for disease knowledge based on ontology and linked data techniques. *Journal of Biomedical Informatics,* 8: 22, 2017.
[32] F. Toyoshima. Linking temporal parts in processual biological ontology. In *Proceedings of the 5th Joint Ontology Workshops (JOWO 2019)*, Graz, Austria, September 23-25, 2019, accepted.
[33] F. Toyoshima. Natural necessity: An introductory guide for ontologists. *Applied Ontology*, accepted.
[34] F. Toyoshima, R. Mizoguchi and M. Ikeda. Causation: A functional perspective. *Applied Ontology*, 14(1), 43-78, 2019.
[35] R. Mizoguchi, Y. Kitamura and S. Borgo. A unifying definition for artifact and biological functions. *Applied Ontology*, 11(2), 129-154, 2016.
[36] A. Bird. Overpowering: How the powers ontology has overreached itself. *Mind*, 125(498), 341-383, 2016.
[37] N. Guarino. BFO and DOLCE: So far, so close.... *Cosmos + Taxis*, 4(4), 10-18, 2016.
[38] J. Röhl and L. Jansen. Representing dispositions. *Journal of Biomedical Semantics*, 2(Suppl 4), S4, 2011.
[39] A. Barton, O. Grenier, L. Jansen and J.-F. Ethier. The identity of dispositions. In S. Borgo, P. Hitzler and O. Kutz (Eds.), *Proceedings of the 10th International Conference of Formal Ontology in Information Systems (FOIS 2018)*, Cape Town, South Africa, September 17-21, 2018, Amsterdam: IOS Press, 113-126.
[40] S. Mumford and R. L. Anjum. *Getting Causes From Powers*. Oxford: Oxford University Press, 2011.
[41] S. Mumford. *Dispositions*. Oxford: Oxford University Press, 1998.
[42] D. Lewis. *On the Plurality of Worlds*. Oxford: Blackwell, 1986.
[43] A. Barton, A. Rosier, A. Burgun and J. F. Ethier. The Cardiovascular Disease Ontology. In P. Garbacz and O. Kutz (Eds.), *Proceedings of the 8th International Conference of Formal Ontology in Information Systems (FOIS 2014)*, Rio de Janerio, Brazil, September 22-25, 2014, Amsterdam: IOS Press, 409-414.
[44] L. Jansen. Tendencies and other realizables in medical information sciences. *The Monist,* 90(4), 534–554, 2007.
[45] A. Hüttemann and M. I. Kaiser. Potentiality in biology. In K. Engelhard and M. Quante (Eds.), *Handbook of Potentiality*, Netherlands: Springer, 401-428, 2018.
[46] R. L. Anjum and S. Mumford. Dispositionalism: A dynamic theory of causation. In D. A. Nicholson and J. Dupré. (Eds.), *Everything Flows: Towards a Processual Philosophy of Biology*, Oxford: Oxford University Press, 61-75, 2018.
[47] I. Johansson. Patterns an ontological category. In N. Guarino (Ed.), *Proceedings of the 1st International Conference on Formal Ontology in Information Systems (FOIS 1998)*, Trento, Italy, June 6-8, 1998, Amsterdam: IOS Press, 86-94.
[48] A. Galton. Processes as patterns of occurrence. In R. Stout. (Ed.), *Process, Action, and Experience*, Oxford: Oxford University Press, 41-57, 2018.
[49] F. Toyoshima. Representing causation: A dispositional perspective. In *Proceedings of the 10th International Conference on Biomedical Ontology (ICBO 2019)*, Buffalo, NY, USA, July 30 - August 2, 2019, accepted.
[50] R. Taylor. *Action and Purpose*. Upper Saddle River: Prentice Hall, 1966.
[51] N. Williams. Powerful perdurance: Linking parts with powers. In J. D. Jacobs (Ed.), *Causal Powers*, Oxford University Press, 139-164, 2017.
[52] A. Barton, O. Grenier and J.-F. Ethier. The identity and mereology of pathological dispositions. In L. Cooper and P. Jaiswal (Eds.), *Proceedings of the 9th International Conference on Biological Ontology (ICBO 2018)*, Corvallis, Oregon, USA, August 7-10, 2018, CEUR Workshop Proceedings, vol. 2285, 6 pages.
[53] A. Goldfain, B. Smith and L. G. Cowell. Dispositions and the Infectious Disease Ontology. In A. Galton and R. Mizoguchi (Eds.), *Proceedings of the 6th International Conference of Formal Ontology in Information Systems (FOIS 2010)*, Toronto, Canada, May 11-14, 2010, Amsterdam: IOS Press, 400-413.
[54] F. Toyoshima and A. Barton. A formal representation of affordances as reciprocal dispositions. In O. Kutz and M. M. Hedblom (Eds.), *Proceedings of TriCoLore 2018 - Creativity | Cognition | Computation*, Bozen-Bolzano, Italy, December 13-14, 2018, CEUR Workshop Proceedings, vol. 2347, 14 pages.
[55] C. B. Martin. *The Mind in Nature*. Oxford University Press, 2007.
[56] V. K. Chaudhri and D. Inclezan. Representing states in a biology textbook. In *Proceedings of the 12th International Symposium on Logical Formalizations of Commonsense Reasoning 2015 (Commonsense 2015)*, part of the AAAI Spring 2015 Symposia series, Palo Alto California, March 23-25, 2015, AAAI Press, 46-52.
[57] C. Masolo and L. Vieu. Graph-based approaches to structural universals and complex states of affairs. In S. Borgo, P. Hitzler and O. Kutz (Eds.), *Proceedings of the 10th International Conference of Formal Ontology in Information Systems (FOIS 2018)*, Cape Town, South Africa, September 17-21, 2018, Amsterdam: IOS Press, 83-96.