Causation and the River Flow Model of Diseases

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ABSTRACT

This paper furthers the River Flow Model (RFM) of diseases based on the functional view of causation that we have elaborated for the sake of formal ontology. The clarification of RFM enables us to offer a clear comparison between RFM and the dispositional model of disease given by the Ontology for General Medical Science (OGMS) and to see the core ideas of disease that RFM and OGMS have in common. This work will be an initial step towards the development of an ontological module for generic disease representation.

1 INTRODUCTION

A disease ontology aims to meet a high demand for a common framework in which an increasing amount of medical information and data are shareable among different information systems. A viable definition of disease is thus indispensable for the robust construction of disease ontologies. Designed to represent the entities that are involved in a clinical encounter in compliance with the framework of the Open Biomedical Ontologies (OBO) Foundry [25] and Basic Formal Ontology (BFO) [26], the Ontology for General Medical Science (OGMS) [24] offers a general model of disease according to which 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. In marked contrast to a naïve conception of disease, e.g., as a state in existing disease ontologies, OGMS's carefully constructed definition of disease as a disposition is nowadays utilized in various application ontologies.

The River Flow Model (RFM) of diseases was initially presented in [18] and further developed in [23] as an alternative model of disease that is built in compliance with Yet Another More Advanced Top-level Ontology (YAMATO) [13]. At the crux of RFM's conception of disease is the idea that a disease is a dependent continuant constituted of causal chains of abnormal states. The effectiveness of RFM is verified through its high competence in enhancing the interoperability and flexibility of disease-related data and information [11, 28-31].[1]

A remaining problem with the RFM of diseases resides in its explicit reference to the notoriously difficult notion to model: causation. RFM will not be articulated clearly until the notion of causation is specified enough, much less RFM's relationship with OGMS's dispositional account of disease. Although it has been long investigated among philosophers, causation still remains an enigma despite its enormous importance for ontological modelling in a wide range of domains. [23]'s argument over causation leaves something to be desired, for instance.

In this paper we provide further development of RFM on the basis of the theory of causation that we have recently tailored for formal ontology, based on YAMATO: the *functional view of causation* [27].[2] The elucidation of RFM with the functional view facilitates the comparison between OGMS's and RFM's definitions of disease, thereby revealing the nature of disease that is conceived in common: disease as a 'causal pattern'. The work done in the paper will be a first step towards the elaboration of an ontological module for representing disease.

The paper is organized as follows. Section 2 presents an overview of YAMATO and the functional view of causation. Section 3 offers a basic idea of RFM, then providing a developed version of RFM's definition of disease. Section 4 compares the RFM of diseases with OGMS's dispositional model of disease from the viewpoint of causation. Section 5 gives concluding remarks and outlines future work.[3]

2 THE FUNCTIONAL VIEW OF CAUSATION

Causation has been explored in formal ontology directly by [7, 12] and indirectly by [2]. There are arguably two primary desiderata for a theory of causation that is well suitable for formal ontology. One is the generality of causation and it requires a philosophically theoretical investigation into causation, especially what grounds causation. The other is the specificity of causation and it demands an ontological framework in which domain experts are able to represent various causal phenomena appropriately.

We have recently developed the functional view of causation [27] against an ontological background of YAMATO (Section 2.1). The functional view aims to meet those two criteria mentioned above. As for the generality of causation, the functional view provides the *functional grounding of*

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[1] The OWL file of the RFM ontology is freely available at the website: http://rfm.hozo.jp/ (Last accessed on July 3, 2017). For a navigation system for the definitions of diseases that is built based on the RFM of diseases (especially on its core notion of causal chains of abnormal states), refer to Disease Compass available at the website: http://lodc.med-ontology.jp/ (Last accessed on July 3, 2017).

[2] In this paper we only give a brief summary of the functional view of causation owing to spatial limitations. We would be happy to send a draft of [27] to those who wish to know more details about the functional view.

[3] For the sake of readability, we will hereinafter use the terms 'OGMS-disease' and 'RFM-disease' to refer to the notion of disease defined by OGMS and RFM, respectively. The same remark applies to the categories defined by BFO and YAMATO: we will employ later the terms 'BFO-process' and 'YAMATO-process', for instance.

causation: function grounds causation (Section 2.2). As for the specificity of causation, the functional view offers the *functional square of causal relations*, according to which there are four kinds of causal relations: *achievement*, *allowing*, *disallowing*, and *prevention* (Section 2.3). Regarding the comparison between an OGMS-disease and an RFM-disease, it is important to see that dispositions as inherently causal properties, if any, are contributors to causation within the framework of the functional view (Section 2.4).

2.1 YAMATO: an overview

YAMATO is fundamentally based on [8]'s view of reality: *continuants* and *occurrents* are existentially interdependent. Continuants are the entities that persist in time while undergoing various changes (e.g., a person, a river, a statue, and an amount of clay). Occurrents are the entities that are temporally extended (e.g., walking, a walk, and the flowing of water). The major subcategory of continuants is *objects* (e.g., a person, a river, and a statue, but not an amount of clay).

Two prominent subcategories of occurrents are *processes* (e.g., walking and the flowing of water) and *events* (e.g., a walk). Most importantly, processes are intrinsically 'ongoing', whereas events are in nature 'completed'. Among subcategories of occurrents are *states*: time-indexed qualitative occurrents (e.g., being hungry at time t_1, sitting at time t_2, and speeding at time t_3).

Concerning relations in YAMATO, an object *participates in* a process, an event, or a state. A process is *enacted* by (made possible by) an object that participates in that process. Any process *constitutes* a (unique) event. For instance, John enacts a walking process, which constitutes the walk event.

Finally, YAMATO exploits the model of *roles* (a subtype of dependent continuants) [14, 19] the basic tenet of which is understood through the schema: an entity (*potential player*) plays a *role* as a *role-holder* in a *context*. For instance, Mary plays a student role as a particular student in the school context. The notion of context is too complex to formulate easily, but it can be elucidated through some examples. For instance, an object can be seen as a context in which other objects play part roles as part and an occurrent can be considered as a context in which continuants play participant roles as participants, for example.

2.2 The functional grounding of causation

The functional grounding of causation is based on the device ontology view of reality. The *device ontology* [15], whose initial purpose was to analyze technical artifacts, refers to a specific way of assigning roles to objects in general (whether natural or artificial). A *device* in the device ontology refers to a role-holder that processes something (i.e. receives something to produce something). The device ontology enables us to analyze as devices a full range of objects (including the human heart and an electron).

According to the device ontology, an object O plays an agent role as a device O_d in a given context and a *behavior* B of O_d is the change from one state S_1 to the other state S_2 of the operand OP that is processed by O_d. For instance, a behavior of the human heart (as a device) is the process of pressuring blood: the process of change from the low state to the high state of the pressure (operand) of the blood that has travelled through the human heart.

Given the intimate relationship between change and causal connections, there must be a causal connection behind B as a change in the operand OP.[4] Aiming to explain causation in terms of an inherently causal entity, the functional view of causation consists in saying that B of O_d is an inherently causal process *in virtue of its own functional nature* whose combination of *how to achieve* and *what to achieve* [10] concretizes into the causal relation between what occurs *inside* O_d and S_2 in which OP participates (see [27] for details).

To illustrate this, suppose for instance that a cutting machine cuts a fish into pieces. A cutting machine plays an agent role as a cutting device in the fish-cutting context and a behavior of the cutting device is the change from the state of being one piece to the state of some pieces of the fish that is processed by the cutting machine. The causal connection behind the behavior of the cutting device is the relation between what occurs inside the cutting device (say the cutting motion with a knife) and the state of being some pieces in which the fish participates.

Consider the function of a cutting machine. Analyzed in terms of [10], the function of a cutting machine is to divide something (what to achieve) and using a sharp knife refers to a specific 'way' of performing the function to divide (how to achieve). Cutting is in this respect a conceptual mixture of what to achieve (to divide) and how to achieve (to use a knife).

This conception of function justifies the idea that a cutting behavior of a cutting device is inherently causal primarily because cutting involves both to divide something to some pieces (what to achieve) and to use a sharp object in order to divide something (how to achieve). The state of being some pieces in which the fish participates and the cutting motion with a knife inside the cutting device are concretizations of what to achieve and how to achieve of a cutting behavior of a cutting device, respectively.

Suppose for another example that, when emitted by a nuclear reactor, an electron e_1 impacts another electron e_2. E_1 plays an agent role as a device (say $Device_1$) in the context of a quantum jump of e_2 and a behavior of $Device_1$ is the process of exciting e_2: the change from the lower state to the higher state of the energy (operand).[5] Being of a functional nature, the behavior of exciting e_2 by $Device_1$ involves both to bring e_2 to the higher energy level (what to achieve) and to use the motion of e_1 (how to achieve).

[4] Consider for instance that an object travels at a constant velocity. A behavior of the object in constant motion is the change in the position (operand) corresponding to the transition between two places which the particle occupies. The causal connection behind this behavior is the relation between the motion of the object and the position change behavior of the object.

[5] An electron that receives the amount of energy exceeding the threshold value is said to make a *quantum jump* or to be *excited* from the lower-energy state to the higher-energy state.

It is interesting to note that, given the device ontology, the example of a quantum jump of an electron bears a close similarity to the scenario in which, when shot by a billiard cue, a billiard ball collides with another billiard ball. As this shows, the device ontology view of reality is versatile enough to be applicable to different granularity levels of reality.

2.3 The functional square of causal relations

The functional square of causal relations is the fourfold distinction of causal relations that are in nature functional: achievement, allowing, disallowing, and prevention (see **Table 1**). The functional square claims to be an all-encompassing table of causal relations, thereby meshing well with a counterfactual theory of causation [6, 21].

Table 1 The functional square of causal relations

	Indirect	Direct
Positive	**Allowing**	**Achievement**
Negative	**Disallowing**	**Prevention**

2.3.1 Achievement

Achievement is a direct and positive causal relation: a relation between occurrents (not only events but also processes and states) that we ordinarily take to be causal. The functional view of causation [27] deduces achievement from an inherently causal behavior of a device (Section 2.2) and a recent work on a unifying definition for artifact and biological functions [3, 16, 17].

Example: regarding thrombosis, the growing process of a blood clot in a blood vessel *achieves* the state of being small of the cross-sectional area of the blood vessel, which in turn *achieves* the state of being in short supply of oxygen. Note that thrombosis is cured only when the cross-sectional area of the blood vessel is of a clinically normal size.

2.3.2 Allowing

Allowing holds between an occurrent and the state of being a necessary condition for achievement. In this respect, allowing is indirect with respect to achievement. It is also positive because its holds both between actual occurrents both ontologically and linguistically. Example: ATP production *allows* active calcium transport (by achieving the state of being in operation of transporters as a necessary condition for active calcium transport).

2.3.3 Prevention

Prevention is direct because it is ontologically the same as achievement but it is nonetheless negative because, linguistically speaking, it has as relatum a non-actual occurrent (see [27] for details). Example: a tendon *prevents* the separation between muscle and bone. Note that this is essentially the same as the achievement by a tendon of the connection between muscle and bone.

2.3.4 Disallowing

Disallowing consists in 'preventing' some sufficient condition for a phenomenon, thereby preventing the phenomenon. It is therefore indirect with respect to prevention and it is also negative, just as prevention is. Example: ras inactivation *disallows* signal amplification of MAP kinease cascade (by 'preventing' the activation of kinease molecules such as MAPKK in the following MAP kinease cascades).

2.4 Dispositions as contributors to causation

Dispositions are of high utility in overall ontological modelling, especially in the biomedical domain [22]. For the sake of future argument, we will hereafter use BFO's notion of disposition, which relies on a BFO-*process* (but not a YAMATO-process): an occurrent that has temporal parts and always depends on some material entity (an independent continuant that has some portion of matter as part).

A disposition is a dependent continuant (*bearer*) that exists because certain features of the physical make-up (*material basis*) of the independent continuant in which it inheres and whose instances can be *realized in* associated BFO-processes of specific correlated types in which the bearer participates. For instance, fragility is the disposition of a glass (bearer) to break (realization) that depends on a particular physical molecule structure (material basis) of the glass.

In philosophy, there is a growing interest in a dispositional theory of causation according to which, roughly, causation occurs when a disposition realizes itself [20]. The functional view of causation says that a realization of a disposition is a *contributor* to causation. Recall the example of a cutting machine. A cutting device may possess the disposition of a knife whose realization is the cutting motion as a concretization of how to achieve of cutting. In this way, a realization of a disposition serves as a basic ingredient of an inherently causal behavior of a device. Functional causal power is nonetheless irreducible to dispositional causal power, as the functional view says.

3 THE RIVER FLOW MODEL OF DISEASES

3.1 A basic idea

We said in Section 2.1 that a river is an object (continuant) and the flowing of water is a process (occurrent). According to YAMATO or rather [8], an object is a unity that enacts its *external process* or the 'interface' between its *internal process* and external process. The basic tenet of RFM is the 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 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 the flowing of water as its internal process (a 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 harmful to the organism from a medical viewpoint. This *constituted-of* relation has a close affinity with the constitution relation of a process to the event (see Section 2.1).

All these considerations lead to the above-mentioned main idea of the RFM of diseases: a disease is a dependent continuant constituted of causal chains of abnormal states. Type I diabetes, for instance, may have inside it the causal relation between the state of being broken of pancreatic beta cells and the state of being little of insulin in the blood.

3.2 The imbalance model

The imbalance model, initially presented in [18], is a key element of RFM in the sense of supplementing and generalizing a simple conception of a disease as causal chains of abnormal states. According to the imbalance model, a clinically normal organism maintains homeostasis (by which we basically mean a disposition of an organism to regulate its body in close with [24]) when the 'supply' and the 'demand' are well-balanced as regards all the parameters that are relevant to the organism's living condition. In a clinically abnormal organism, however, the supply and the demand for some (if not every) parameter that relates to the organism's life are so different from each other that the difference between them lies outside the clinically permissible range for the maintenance of the organism's homeostasis.

To illustrate the imbalance model, consider diabetes in general. In a patient with diabetes (whether Type I diabetes or steroid diabetes), the required amount of insulin (demand) exceeds to a clinically abnormal degree the amount available for working insulin (supply) and this imbalance state causes the state of being at an elevated level of glucose in the blood, which may result in the loss of sight of the patient over a long period of time. The difference between Type I diabetes and steroid diabetes resides partly in the fact that, in the case of Type I diabetes and steroid diabetes, causal chains that lead to the imbalance state described above include the state of having depleted pancreatic beta cells and the state of having large quantity of steroids, respectively.

We have the following definition of a clinical imbalance state:

Clinical imbalance state $_{=\mathrm{def.}}$ a state of an organism such that, given a parameter *p* that is relevant to the organism, the mismatch between the supply and the demand that are specified with respect to *p* falls outside a clinically normal range for the organism's homeostasis.

3.3 The RFM definition of disease

An existing RFM definition of disease [18, 23] involves the term ‘causal chain’. Based on the functional square of causal relations presented in Section 2.3, we have the following revised and developed RFM definition of disease:

Disease (revised) $_{=\mathrm{def.}}$ a dependent continuant that is constituted of abnormal states occurring in an organism that are connected by achievement, allowing, disallowing, or prevention, either of which is initiated by at least one abnormal state.

Note also that an RFM-disease has at least one clinical imbalance state (see Section 3.2).

The reader should keep in mind that RFM's notion of clinical abnormality is virtually primitive. This is justified through the sharp distinction between the domain-neutral notion of clinical abnormality and the domain-specific task of the identification of clinical abnormality. What counts as clinically abnormal would vary from clinical to clinician in a broad biomedical field. RFM purports to be an ontological (domain-neutral) model of diseases and RFM's notion of clinical abnormality refers to the *existence* (rather than the content) of criteria for observing a state from a clinical perspective. For an application of RFM's notion of abnormal states, see [11, 28-31].

4 DISCUSSION

4.1 OGMS's dispositional model of disease

To investigate the commonalities and differences between RFM and OGMS's dispositional model of disease, we briefly present some core terms of OGMS. A *disorder* basically refers to a material entity which is clinically abnormal and part of an organism, although the precise definition of a disorder has been repeatedly changed and seems to be under development (see [4, 5, 24]). 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. Pathological process are recognized through symptoms and signs.

An OGMS-*disease* is a disposition (i) to undergo pathological processes that (ii) exists in an organism because of one or more disorders in that organism. The material basis of a disease as a disposition is a disorder of the disease 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 *disease course* is 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).

4.2 Disease as a 'causal pattern'

RFM and OGMS share some common views on disease. First of all, an RFM-disease and an OGMS-disease both say that a disease is in nature a 'causal pattern'. An RFM-disease is characterized by the regular way in which abnormal states are causally connected and the pattern nature of an RFM-disease may be represented in terms of a directed graph in graph theory [9].

Similarly, an OGMS-disease reasonably qualifies as a causal pattern. For one thing, an OGMS-disease is causal, since a disposition is an inherently causal property. For another, an OGMS-disease is of a pattern nature because a disposition which has a 'specific' material basis realizes its 'corresponding' BFO-processes when exercised under some 'appropriate' circumstances.

It is important to emphasize that a disease is a dependent continuant, but not an occurrent, although some existing ontologies classify a disease a subtype of occurrent. A disease is some entity with which a patient is affected and which medical practitioners identify, diagnose, and cure. A disease is something that comes into existence, grows, and finally disappears in the patient's body. All these observations imply that a disease is an entity that persists in time, i.e. a continuant. Additionally, a disease is a dependent continuant that inheres in an organism.

4.3 Clinical threshold

Furthermore, both an RFM-disease and an OGMS-disease involve what we may call a 'clinical threshold': the level at which symptoms of a disease begin to develop. RFM characterizes a clinical threshold employing the imbalance model. Symptoms of a disease show themselves when the clinical imbalance state that is relevant to the disease has occurred. Likewise, OGMS explicates a clinical threshold in terms of the emergence of a disease as a disposition (and of its corresponding disorder as a material basis of the disposition). Having reached a clinical threshold, an organism disposes towards pathological processes, which are recognizable through symptoms.

It is nonetheless vital to clarify the difference between an RFM-disease and an OGMS-disease from the viewpoint of a clinical threshold. In the case of an RFM-disease, a clinical imbalance state of a disease is not always an initial state of the disease. As said in Section 3.2, the imbalance model abstracts from a disease its generality and eliminates its specificity. For instance, Type I diabetes and steroid diabetes fall into a group of diabetes, since they have the same kind of clinical imbalance state (i.e. the deficiency of insulin), but those two diseases still differ from each other because they have different causal chains of abnormal states.

By comparison, it is clear that the emergence of an OGMS-disease as a disposition is always at the beginning of the disease. To do justice to the specificity as well as the generality of disease, OGMS covers a *predisposition to disease of type X*: a disposition in an organism that constitutes an increased risk of the organism's subsequently developing the disease X [5, 24]. A predisposition is a disposition to acquire a further disposition and some diseases as dispositions (e.g., osteoporosis) are predispositions to further diseases as dispositions (e.g., fracture).

Roughly speaking, the generality and the specificity of an OGMS-disease are to be captured by a disease as a disposition and a predisposition to disease of type X, respectively. For instance, Type I diabetes and steroid diabetes belong to the same diabetes category because they are essentially the 'diabetes disposition'. These two diseases are nevertheless different because a predisposition to have diabetes that is involved in Type I diabetes is of a different nature from that involved in steroid diabetes. A realization of the former predisposition, but not of the latter predisposition, may have as part the BFO-process of destruction of pancreatic beta cells; conversely, a realization of the latter predisposition, but not of the former predisposition, may have as part the BFO-process of the increase of steroids.

4.4 Causation: dispositional vs. functional

Though conceived as a causal pattern in common, an OGMS-disease and an RFM-disease are significantly difference in the sense that OGMS's basic "unit of thought" is a disposition (dependent continuant) but RFM's is a state (occurrent). This fundamental difference between an OGMS-disease and an RFM-disease is largely, if not totally, explicable in terms of causation.

For OGMS, causation is dispositional: causation occurs when a disposition as an inherently causal property realizes itself. The dispositional conception of causation leads directly to an OGMS-disease as a disposition. For RFM, causation is functional: causation occurs when an inherently causal behavior of an object (a device) achieves some occurrent. An RFM-disease inherits its causal nature from the linkages, brought about by functional causal power, among abnormal states.

4.5 Clinically abnormal: continuant vs. occurrent

Another indicator of the contrast between OGMS's and RFM's conceptions of causation is the difference in what is clinically abnormal between OGMS and RFM. Clinically abnormal are a disorder (continuant) in OGMS and a state (occurrent) in RFM. In OGMS, a disease as a disposition inherits its clinical abnormality from a disorder as its material basis; and therefore, a disorder (a material entity) is defined as clinically abnormal. In contrast, RFM's notion of clinically abnormal state reflects well the idea of an inherently causal occurrent (process) embraced by the functional view of causation.

Consider for instance inflammation as a disease. OGMS would say that inflammation as a disposition is clinically abnormal primarily because so is its material basis, e.g., the cells in the relevant part of the organism. RFM says however that the clinical abnormality of the cells there, if any, is a contributor to that of states that inflammation has inside it. This marks a close analogy with the argument for the functional view of causation: a realization of a disposition contributes to functional causation (see Section 2.4).

5 CONCLUDING REMARKS

We have furthered the River Flow Model (RFM) of diseases employing the functional view of causation. By so doing, we have offered a clear comparison between an RFM-disease and an OGMS-disease in terms of causation, in particular the contrast between functional causation and dispositional causation. The work done here will contribute to the formalization of a general disease module for foundational ontologies (whether BFO, YAMATO, or others) and also to the methodological supplementation of OGMS [1].

Future work includes further development of RFM using the functional view of causation. For instance, the exploration of the formal relationships among the causal relations in the functional square would enable us to have a closer examination of the nature of causal chains of abnormal states in a disease. Along another line of research lies the question of whether RFM can be extended to mental disease, just as OGMS's disease model was in [4]. To address this question would demand the task of investigating mental causation, which is currently outside the scope of the functional view.

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