A clinical model IV: The formal version.

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Abstract

Background
An informal clinical model (CM) with a strong empirical basis describes health and disease and the transition between them. Here CM is formalized in category theory.

Results
The healthy human body and its environment are represented by two connected categories. Each object is an ordered triplet consisting of an agent, a carrier and a location. Morphisms between triplets changes the agent, carrier or location. Morphisms that change agents model cell differentiation, mutations, enzyme reactions and electrical activities. Morphisms that change carriers model inheritance, cellular processes such as secretion and endocytosis, and the transfer of microorganisms between species.

Patients are modeled by categories consisting of a list $\tilde{\mathbf{O}}_p$ of objects $\mathbf{O}_p$ and morphisms between them. The etiology **E** is a category with objects called agents **A**. Virulence *V* is a morphism that translocates **A** on a healthy person $\mathbf{P}_H$ from **E** into a healthy primary affected object $\mathbf{O}_p$ and causes disorder $\mathbf{O}_p^D$ according to $V{:}\langle \mathbf{A},\mathbf{P}_H,\mathbf{E}\rangle \rightarrow \langle \mathbf{A},\mathbf{O}_p^D\rangle$. An example is hepatitis A virus infection $V{:}\langle$***HBVA***, $\mathbf{P}_H$, **Water Supply**$\rangle \rightarrow \langle$***HBVA***, **Hepatocyte disorder**$\rangle$. The pathogenesis P_{PS} is a morphism that sends signal **S** from $\mathbf{O}_p^D$ to secondary affected objects $\mathbf{O}_S$ as expressed by $P_{PS}{:}\langle \mathbf{A},\mathbf{O_p^D}\rangle \rightarrow \langle \mathbf{O}_S,\mathbf{S}\rangle$. The response (**PM**) is $P_{SP}{:}\langle \mathbf{O}_S,\mathbf{S}\rangle \rightarrow \langle \mathbf{A},\mathbf{O_p^D},\mathbf{PM}\rangle$ with **PM** in $\mathbf{O}_p^D$. A typical example is $P_{PS}{:}\langle$***HBVA***, **Hepatocyte disorder**$\rangle \rightarrow \langle$***HBVA***, **Hepatocyte disorder**,**IR4**$\rangle$ where IR4 is the immune reaction type 4. More complex pathophysiological processes are modeled by composing individual pathogenetic mechanisms to reach a tertiary affected body part $\mathbf{O}_T$. The composition $P_{SP}\circ P_{PS}\circ V{:}\langle \mathbf{A},\mathbf{P}_H,\mathbf{E}\rangle \rightarrow \langle \mathbf{O}_p^D,\mathbf{PM}\rangle$ defines disease (*D*) and $P_{SP}\circ P_{PS}{:}\langle$'',$\mathbf{O_p^D}\rangle \rightarrow \langle$'',$\mathbf{O_p^D}$,**PM**$\rangle$ a syndrome (*S*). Thus, $D=P_{SP}\circ P_{PS}\circ V$ and $S=P_{SP}\circ P_{PS}$. These two composites transform a healthy person category $\mathbf{P_H}$ into a disordered patient category $\mathbf{P_D}$. The transformation is abbreviated to $D{:}\mathbf{P_H}\rightarrow\mathbf{P_D}$. A

hierarchy of categories capture the size range of objects and agents from the macroscopic level to the submolecular level.

Conclusions

This study shows that a formal CM can be developed in category theory. The etiology category, and healthy and disordered categories contain objects and morphisms between that model the required structures and functions. Composition of virulence and pathogenesis morphisms formalize the concepts of disease and syndrome. The formal CM makes out a coherent clinical theory that corresponds with clinical and laboratory experience.

Background

The biopsychosocial model is hard to formalize and is rarely used in medical research (Alonso 2004, Sulis 2017). Deep causal models in Model-Based Diagnosis (MBD) systems are said to be more efficient than classical rule-based systems, but it is "very difficult to explain a real-world patient evolution using theoretical descriptions of diseases." (Palma 2006) and "…formal representation for automatic classification of cases was out of scope, … ." (Balkanyi 2014). Informal biological categories allow us to recognize similarities between physically distinct systems (Sober 1993). Statistics deliver correlations, but no causal biological networks (Nowak 2017). The description of human beings by heterogeneous terms such as connectomes, metabolomes, and proteomics and genomics makes it hard to construct unified representation but work on this problem is in progress.

Cause-and-effect network models are becoming increasingly popular. More than eighty such models, describing processes involved in cell proliferation, cell fate, cell stress, and inflammation have been published (Martin 2014). Ernst and co-workers have recently built a knowledge base consisting of 13 relations covering genes, organs, diseases, symptoms, treatments, as well as environmental and lifestyle risk factors (Ernst 2015).

Theoretical biology uses standard mathematical constructs derived from mathematical models used in physics (Fagerström 1996, Goodwin 1992). But some maintain that biological objects and their environment are not reducible to contemporary mathematics and physics (Penrose 1991, Casti 1996). Such views are largely based on mathematical paradoxes that involve the infinite, the real line and Gödel's theorem. But biological systems are finite and discrete and such systems do

not attract foundational mathematical problems. We are free to choose tools that are free from paradoxes. Therefore, I opt for a discrete theory built on graph theory.

Graph theory is widely used for modeling in medicine (Newman 2006). Annotated digraphs represent anatomy, and can be coupled with functions, gene expression patterns and phenotype information (Hayamizu 2005). Metabolic and social networks, pedigrees and epidemiological models are built from graphs (Newman 2003). Chemical substances (Wilson 1972) and metabolic pathways (Xia 2003) can be modeled using graph theory. Graphs are also used to describe clinical disorders (Bigras 1996) and clinical work (Smart 1995). In addition, graph theory is applied to the analysis of control systems of the brain (Dosenbach 2008).

Eils and coworkers use dual graphs to study the volumes occupied by chromosomes Eils 1995, Eils 1996, Eils 2003, Eils 2003a). Dual graphs have recently been used to delineate relationships between chemical structures from benzene (Dias 2007) to proteins (Huan 2005, Eargle 2006). Amino acids serve as objects in three-dimensional protein graphs (Huan 2005). Dual graphs are also used to describe both RNA tree- and RNA pseudoknot motifs (Gan 2003). Basic geometric and topological properties of RNA can be utilized in learning algorithms from dual graphs with biologically meaningful labels (Karklin 2005).

Beltrami used a dual graph to identify and differentiate architectural features for the diagnosis of proliferative breast lesions (Beltrami 1995). A prototype was implemented and tested. Some significant graph features validated their approach. That principle is applied here. The edges are simply replaced by Morphisms. The directions of morphisms are determined by biological processes. For example, the direction of blood flow can be modeled by morphisms pointing in the direction of flow. Composing the morphisms' end (target or codomain) to the origin of the next morphism (source or domain) models overall blood flow from the heart to toe and from the heart to the brain. Inputs and outputs to nerve cells determine the direction of information flow, and substrates and products of enzymatic reactions determine the direction of morphisms in metabolic pathways

In an early phase, clinical models were crafted in semantic networks and graphs (Nardi 2007). Graphic duals can represent the anatomy of the human body at all clinically relevant levels of resolution (Bassøe 2007). Transitions from health to disease and back have been captured as formal operations on a digraph (Bassøe

2008). Arrows in digraphs can be thought of as binary relations in a logical model (Hein 1995), but composition is undefined. (Patho)physiological models require composition (Bassøe 2007). Therefore, graph theory lacks sufficient expressivity for a clinical model (CM).

The semantics of network systems were fraught with problems, including vagueness and inconsistency (Nardi 2007). Also, it is difficult to structure graphs and networks appropriately. For these reasons, networks and graphs were abandoned. A precise model-theoretic explanation of the procedure rules is an advantage to clinical models (Baader 2007). Therefore, description logic (DL) gradually took over as core knowledge representation (KR) systems.

Multiple inheritance is usually banned from DL. However, clinical medicine is replete with structures and dynamics that are difficult to model without multiple inheritance. Take for example the venous system. Most veins of the human body receive blood from two or more other vein sources. Likewise, the content of the duodenum is composed of fluids from the stomach, liver and pancreas. Neurons receive multiple inputs and have multiple output connections. Neural networks cannot be modeled without multiple inheritance. The same is true for hormonal and cytokine connections between cell groups, and also for social networks. Thus, the constraints inflicted by DL exclude properties of living systems that are crucial to their performance, and hinder modeling of essential properties.

Description logics has a model-theoretic semantics (Baader 2007a). Recent studies in knowledge representations show that strict requirements of domains and codomains specification of functions such as hasLocation and partOf functions are necessary. In addition, many functions and diagnoses need to obey the associative requirement (Héja 2007, Héja 2008, Bassøe 2007, Bassøe 2019b). These requirements are built into category theory (CT). DL is built on a fragment of first-order logic (Nardi 2007). Since CT covers first-order logic, the properties of DL naturally emerge from CT and it is not necessary to add DL to CT (Lawvere 2003).

CT builds on digraphs. It is a formal mathematical language with high expressive power (Eilenberg 1945, Barr 1990, Walters 1991, Mac Lane 1995, Mac Lane 1996, McLarty 1994, Fiadeiro 2005). CT has been applied to psychology (Halford 1980, Powell 1980) and cognitive development (Bart 1974, Magnan 1994). This may facilitate developing models of the mind and psychiatric disorders. CT is also applied

in medical informatics (Ambler 1996). CT has also been shown to provide a versatile language for general systems theory (Klir 1996, Lin 1995, Ma 1992).

Healy and Caudell propose CT, the mathematical theory of structure, as a vehicle for defining ontologies in an unambiguous language with analytical and constructive features (Healy 2006). In particular, their method allows the incremental analysis of ontologies using an interconnected hierarchy of theories that is rooted in first principles. Krötzsch and coworkers propose category theory as a mathematical foundation for merging ontologies and modeling distributed knowledge (Krötzsch 2007).

Others are not so enthusiastic about CT. Early CT models of biological systems (Rosen 1991, Rosen 2000) are open to interpretation (Letelier 2005). Category theory is still controversial and is claimed to be a too abstract level to generate new understanding (Smoryński 2012, Derbyshire 2006). On the other hand, CT can describe complex phenomena and has generated significant results.

This study has two purposes. We aim for an implementation of CM and a semantics for the universal diagnosis syntax (Bassøe 2019b). First, category theorists hold that computing science programs and datatypes should be specified abstractly before the implementation (Barr 1990:49). Also, the specification should be distinct from the implementation. This can be achieved by a CT. Second, we have an informal clinical model based on empirical clinical facts (Bassøe 2019, Bassøe 2019a), but a formal interpretation of the universal diagnosis syntax requires a formal CM. CT also offers semantics for the diagnosis syntax.

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