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From Mechanistic Biomedicine to Organismal Systems Medicine

De la biomedicina mecanicista a la medicina de sistemas organismales

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Abstract

Biomedicine, the predominant medical model that emerged during the twentieth century, is founded conceptually on mechanism and reductionism, especially in terms of portraying the patient as a machine reducible to its component parts. Systems medicine, in contrast, has emerged during the early part of the twenty-first century to address problems arising from biomedicine's failure to cure diseases such as cancer. In this paper, a conceptual framework is provided for shifting from mechanistic biomedicine to organismal systems medicine. Specifically, organicism and holism provide the necessary foundation for viewing the patient not simply as a diseased or dysfunctional body part but as a whole person embedded within a biological, psychological, social, and environmental framework. Although biomedicine's approach has identified many of the physiological and pathological components of health and disease, a shift to organismal systems medicine promises to deliver the principles and rules by which these components relate and interact with one another in a holistic rather than simply in a reductive mechanistic fashion.

Keywords: holism; mechanism; medicine; organicism; reductionism.

Resumen

La biomedicina, el modelo médico predominante surgido en el siglo XX, se basa conceptualmente en el mecanicismo y el reduccionismo, sobre todo en lo que respecta a la descripción del paciente como una máquina reducible a sus componentes. La medicina sistémica, en cambio, ha surgido a principios del siglo XXI para abordar los problemas derivados de la incapacidad de la biomedicina para curar enfermedades como el cáncer. En este artículo se ofrece un marco conceptual para pasar de la biomedicina mecanicista a la medicina sistémica organismal. En concreto, el organicismo y el holismo proporcionan la base necesaria para considerar al paciente no sólo como poseedor de una parte del cuerpo enferma o disfuncional, sino como una persona completa integrada en un marco biológico, psicológico, social y ambiental. Aunque el planteamiento de la biomedicina ha identificado muchos de los componentes fisiológicos y patológicos de la salud y la enfermedad, el paso a la medicina de sistemas organismales promete ofrecer los principios y reglas por los que estos componentes se relacionan e interactúan entre sí de forma holística y no simplemente de un modo mecanicista reductor.

Palabras clave: holismo; mecanismo; medicina; organicismo; reduccionismo.

1. Introduction

During the twentieth century, biomedicine was the predominant medical model in terms of both basic and clinical research, as well as clinical practice (De Chadarevian and Kamminga, 1998, Lock and Gordon, 1988, Löwy, 2011). Two of the fundamental concepts grounding biomedicine are mechanism and reductionism (Andersen, 2017, Clarke and Russo, 2018, Illari, 2017). According to these concepts, the patient's body is a machine reducible to its individual parts with respect to its functioning and/or malfunctioning. Biomedicine's success depended on mechanical philosophy, which has a rather long history in western medicine (Glennan, 2017, Sheldrake, 1980, Westfall, 1977). And much of that success relied on reducing disease to its mechanistic parts (Darden, et al., 2018). For example, hemophilia and von Willebrand disease are bleeding disorders that were explained and eventually treated through the isolation of clotting factors from human blood (Federici, et al., 2006, Green, 2018). Indeed, as hemostasis or blood coagulation was reduced to various clotting factors, eventually a hemostatic model or cascade was assembled in the second half of the twentieth century and used to investigate and treat other coagulation disorders (Owen, 2001). And this approach to understanding and treating disease led to the prevalent "magic bullet" approach closely associated with the biomedical model (Brandt and Gardner, 2000). Unfortunately, this approach failed to cure complex chronic diseases, like cancer (Cutter, 2018, Keating and Cambrosio, 2012, Mukherjee, 2011), resulting in a situation that resembles a Kuhnian paradigmatic crisis (Kuhn, 1970).

During the first-half of the twentieth century, systems theory and science were used to tackle apparent anomalies in the biological and biomedical sciences in which the traditional mechanistic approach was unable to provide adequate solutions (Bertalanffy, 1974, Hanson, 1995, Skyttner, 2005). Two important fundamental concepts grounding systems theory and science, especially the biological sciences, are organicism and holism (Botz-Bornstein, 2021, Döring, et al., 2015, Capra and Luisi, 2014, Sheldrake, 1981). And these concepts have been incorporated into systems medicine to address problems for treating complex diseases like cancer, diabetes, and cardiovascular diseases (Rosslenbroich, 2016, Tretter, 2019). For example, cancer throughout the twentieth century did not succumb to biomedicine's straightforward "magic bullet" approach to produce a cure; and even then US President Richard Nixon's 1971 "war on cancer," which promised that cancer would be cured by the US 1976 bicentennial, failed to deliver on its promise (Surh, 2021)—although limited success was achieved but it has been costly (Cutler, 2008, Sporn, 1997). Moreover, the military terminology or metaphor of this approach to cancer has been criticized as unproductive and inappropriate (Haines, 2014). In place of the biomedical approach, a systems medicine approach has emerged, especially during the early part of the twenty-first century with the completion of the Human Genome Project, which promises to cure cancer and other complex diseases (Roukos, 2010, Karimi, et al., 2022).

In this paper, the concepts of organicism and holism are used to construct a conceptual framework for the shift from mechanistic biomedicine to organismal systems medicine. Specifically, organicism and holism provide the theoretical foundation for viewing the patient as a whole person, especially in terms of personal health, and not simply as a diseased body part—as is often common in the biomedical sciences. And these concepts are contrasted to the concepts of mechanism and reductionism associated with the traditional biomedical model, as well as with a molecular systems medicine (Tretter, 2019). Although mechanism and reductionism have been instrumental in biomedicine to identify many of the components that compose pathophysiological states, a shift to organismal systems medicine within the twenty-first century promises to deliver the principles and rules by which the components of the organism relate and interact with one another at a holistic level, including the social and environmental levels (Wolkenhauer, et al., 2013, Rosslenbroich, 2016). To that end, the concepts of mechanism and reductionism associated with the biomedical model are examined in the next section, followed in a subsequent section by a discussion of organicism and holism associated with systems medicine. In a concluding section, the relationship between mechanistic biomedicine and organismal systems medicine is explored.

2. Biomedicine: Mechanism and Reductionism

The success of the biomedical model throughout the twentieth century was certainly impressive, especially in terms of the molecularization of physiological and pathological processes (De Chadarevian and Kamminga, 1998, Grote et al., 2021). As already mentioned, hemostasis was reduced to various blood clotting factors that could not only explain the coagulation mechanism but also provide the knowledge and understanding for developing therapeutic agents to treat clotting disorders. In addition, other diseases were explained and treated using knowledge obtained from the biomedical model, such as insulin for type 1 diabetes (Bliss, 1982, Vecchio, et al., 2018), antibiotics for numerous infectious diseases (Hutchings, et al., 2019, Rosen, 2017), and even cancer itself was thought to be explained in terms of reducing it to various molecular entities, especially mutated genes, responsible for regulating the mechanisms responsible for the cell cycle and cellular proliferation (Bertram, 2000, Knowles and Selby, 2005, Pecorino, 2021). Mechanism and reductionism, then, are the underlying concepts of the biomedical model and sciences, and mechanical philosophy in general is the founding metaphysics upon which the medical universe is explained simply in terms of matter and motion. In this section, mechanism is initially examined, followed by reductionism, and then both concepts are illustrated with the examples of hemostasis and carcinogenesis.

2.1 Mechanism

The rise of modern western science reflects the history of mechanism, especially in terms of the analogy between machines or automata and natural phenomena (Berryman, 2003, De Solla Price, 1964). In general, a machine is defined as “a contrivance, with organized parts whose interconnected workings can be easily understood” (Craver and Darden, 2005, 234). The machine analogy was important in the establishment of mechanistic philosophy, since the analogy’s heuristic promise is that natural scientists could control and manipulate natural phenomena qua machines via their component parts. The analogy was also apt because the functions of machines are often deterministic and follow straightforwardly fundamental engineering principles and rules. One of the chief presumptions for the analogy between machines and natural phenomena is the inherent intelligibility of nature itself. A major part of that intelligibility centers on temporally and spatially extended causal processes. In other words, mechanisms are processes that connect within particular locations and between temporal sequences: "a cause (or beginning state) to an effect (or end state)" (Craver and Darden, 2005, 236). Mechanical philosophy, then, had a profound impact historically on both biology and medicine; and its greatest impact was the development of molecular biology in the twentieth century, which was to convert contemporary medicine into a molecular discipline and practice (Bechtel, 2006, Darden, 2006, Tretter, 2019).

Peter Machamer, Lindley Darden, and Carl Craver (hereafter MDC) introduced a popular articulation of mechanism in which they stress a mechanism's process-like nature. "Mechanisms," according to MDC, "are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions" (2000, 3). They illustrate the concept as follows: "A->B->C" (2000, 3). The letters A, B, and C, represent entities, while the arrows represent activities. Whereas activities are the processes involved in an orderly change, entities are the agents responsible for that change. MDC claim that their concept of mechanism exhibits ontic, descriptive, and epistemic adequacy. As for ontic adequacy, their concept combines both substantive and process ontologies such that ontology is neither eliminable nor reducible to the other. MDC's concept also exhibits a descriptive adequacy by illuminating the initial and final conditions, as well as the intermediate conditions, for progressive routine change. Finally, their concept of mechanism is epistemically adequate since it renders complex phenomena intelligible in terms of mechanistic explanations.

Although many examples of mechanism are available from the biomedical sciences, such as intermediate metabolism, MDC cite the central dogma of molecular biology as the prime example for their concept of mechanism. The central dogma is the fundamental paradigm of molecular biology, and molecular biologists have used it to guide their research since its introduction in the late 1950s, when Francis Crick (1958) announced the central dogma publicly at a symposium in London. According to Crick's version of the dogma, a polymerase transcribes DNA into RNA, which is then translated into protein, and both DNA and RNA can replicate themselves. In MDC's terms, DNA, RNA, and protein, are entities; while transcription, translation, and duplication are activities which the entities cause and through which predictable change occurs. Importantly, DNA contains the genetic information that shapes living organisms through the production of proteins, i.e., genotype dictates phenotype.

2.2 Reductionism

The central dogma relies not only on mechanism but also on reductionism, which enjoys a privileged position—along with mechanism—in the development of the twentieth-century biomedical sciences (Andersen, 2017, Brigandt and Love, 2017, Jones, 2000, Van Regenmortel and Hull, 2002). The chief idea behind reductionism is that scientists can investigate and explain natural mechanisms with respect to their component parts and properties. And contemporary biological scientists assert that through reductionism "the complete determination of a biological system becomes a concrete, achievable goal" (Selinger, et al., 2003, 254). According to reductionism, then, natural mechanisms can be investigated, described, and explained entirely in terms of their component parts and properties. As John Dupré elucidates, reductionism is "the view that the ultimate scientific understanding of a range of phenomena is to be gained exclusively from looking at the constituents of those phenomena and their properties" (1993, 88). In other words, the whole and its properties are equal to the analysis and sum of its individual parts and their properties.

Reductionism, especially in the biomedical sciences, can be divided into at least three types: ontological, methodological, and epistemological (Boogerd, et al., 2007, Brigandt and Love, 2017). Ontological reductionism claims that material or physical components make up natural mechanisms, in that the material composition of complex mechanisms are reducible to simpler material components. For example, the heart is composed chiefly of cardiac cells, which are the basic unit of the organ (Litviňuková, et al., 2020). Methodological reductionism involves the strategy or method and protocols or techniques by which to investigate and model higher-level mechanisms with respect to lower-level mechanisms. For example, the heart can be investigated in terms of its cellular function such that cardiac cells contract in unison to form a pump (Trayanova, 2011). Epistemological reductionism asserts that higher-level mechanisms can be described and explained in theoretical terms and laws used to describe and explain lower-level mechanisms. For example, the heart and its regulation can be explained theoretically with respect to its contractile proteins (Winegrad, 1984).

Moreover, the relationship among these three types of reductionisms is important. Ontological reductionism espouses that material components make up natural mechanisms. For the biomedical sciences, it is claimed that the body is composed of basic parts, such as macromolecules, cells, and tissues. Based on that claim, biomedical scientists devise and develop methods and technology to investigate these mechanisms in terms of their elemental components. Of course, the development of the microscope was very instrumental in identifying the body's cellular composition (Wilson, 1995). In turn, these scientists then utilize the observations and results obtained from these investigations to reduce theoretical explanations for complex mechanisms to the theoretical explanations for the elemental components constituting complex mechanisms, such as blood coagulation or tumor formation. Finally, these three types of reductionisms are related in the sense that ontological reductionism serves as a guiding principle for conducting biomedical investigations, and the results from those investigations serve to explain higher-level mechanisms with respect to lower-level mechanisms.

2.3 Examples of Mechanistic Biomedicine

The following two examples illustrate the power of the concepts of mechanism and reductionism for advancing the biomedical agenda. The first example is the biochemical mechanism responsible for hemostasis. According to the standard cascade model of blood coagulation, the formation of a fibrin clot begins with the activation of clotting factors associated with either the extrinsic or intrinsic pathway (Davie, 1995, Mann and Lorand, 1993). The extrinsic pathway is activated through tissue factor or factor VII, while the intrinsic pathway through Hageman factor or factor XII. Both pathways converge onto Stuart factor of factor X, which is then activated and results in the activation of prothrombin or factor II to thrombin. Thrombin is responsible for the enzymatic cleavage of fibrinogen or factor I to fibrin, which is finally stabilized to form a fibrin clot. This cascade model for the clotting mechanism has been the foundation for explaining and developing treatment regimens for numerous bleeding disorders (Ratnoff and Forbes, 1996). Although platelets and other blood and tissue cells were known to be important in blood coagulation, their role was not fully appreciated or included into clotting theories until the end of the twentieth and the beginning of the twenty-first centuries (Hoffman, 2003, Riddel et al., 2007, Roberts, et al., 1998). And although the molecular reductive approach to the mechanism of blood coagulation is still critical for understanding and treating hemostatic disorders, it is challenged by several anomalies such as abnormalities of blood clotting in cancer patients (Hamza and Mousa, 2020).

The second example is from oncology and involves the biochemical and genetic mechanisms responsible for tumorigenesis. As for the biological sciences, so the biomedical sciences also adopted the central dogma as its fundamental paradigm for explaining diseases such as cancer, especially as biomedicine became an information science within the postgenomic era (Lenoir, 1999). The cancer phenotype could now be explained reductively in terms of a dysfunctional or mutated genotype. The mechanism of carcinogenesis involves the mutation of genes responsible for regulating the cell cycle, which leads to uncontrolled cell proliferation and growth and ultimately to metastasis (Bertram, 2000, Knowles and Selby, 2005, Pecorino, 2021). Cancer, then, is reduced to mutated genes, such as oncogenes and tumor suppressor genes, that control cellular division and proliferation. But as with blood clotting, theories of carcinogenesis also began to incorporate the role of cells into tumorigenesis. Douglas Hanahan and Robert Weinberg (2000), for example, published probably the most influential article on the mechanism of tumor formation called the somatic mutation theory. The mechanism consisted of six hallmarks or capabilities of tumors, each of which was reduced to biochemical and cellular mechanisms. Hallmarks like sustained angiogenesis or limitless replicative potential represented the outcome of mutated genes that regulate angiogenesis or cellular proliferation. Importantly, Hanahan and Weinberg contrasted their model, which they called heterotypic cell biology, with a model in which cancer cells are uniform or homogenous in that each cancer cell contains a standard set of mutated genes. In sum, a reductive strategy was instrumental in identifying the molecular entities, whether genes or cells, involved in the mechanisms of tumorigenesis and thereby explaining tumor formation, which is comparable in a variety of—if not all—organisms (Marcum, 2005). Thus, during the second half of the twentieth century a method of reductive analysis and synthesis was thought to be adequate for investigating and explaining complex mechanisms like carcinogenesis.

Finally, the biomedical community accepts and promotes mechanism and reductionism, as illustrated by the two examples above, for several reasons. The first is that reductionism is remarkably successful for identifying the mechanisms and their parts underlying biological phenomena (Brigandt and Love, 2017, Robinson, 1992). Part of the success of mechanism and reductionism is their simplification and analysis of complex processes into their constitutive parts and how those parts are structured. By isolating and identifying the various components of complex entities and their properties, biomedical scientists can then piece together or synthesize the underlying mechanisms, especially for diseases. For example, coagulation disorders are the result of dysfunctional or absent clotting factors, while cancer involves mutated genes. Moreover, reductionism provides the opportunity to construct a simple and consistent account for natural mechanisms, which allows biomedical scientists to manipulate and control such mechanisms. In addition, it provides a causal relationship between higher-level mechanisms and their component parts such that “causality entails reductionism” (Dupré, 1993, 99). In other words, lower-level mechanisms and their properties are thought to be causally necessary and sufficient for producing higher-level mechanisms and their properties. So a hemostatic disorder like von Willebrand disease can be explained by the absence of the von Willebrand factor and cured by replacing the factor. In short, reductionistic biomedicine provides universal statements about complex mechanisms constituting physiological and pathological processes.

3. Systems Medicine: Organicism and Holism

Just as mechanism and reductionism are the foundational concepts for biomedicine, so are organicism and holism for systems medicine. And so organicism and holism are critical for fully transitioning from mechanistic biomedicine to organismal systems medicine. While mechanism and reductionism focus on lower levels of organization—such as macromolecules and cells—to investigate and explain a patient's pathophysiology, organicism and holism include not only these but also higher levels of organization—such as the tissue, organ, or organism—to examine and explain a patient's pathophysiology while maintaining the patient's integrity as a whole rather than reducing the whole to its isolated parts. Besides the boundaries of mechanistic biomedicine and organismal systems medicine, hybrid models populate the area between these two boundaries, such as molecular systems medicine.[1] However, for these hybrid models the patient is still reduced to individual molecular parts that are generally considered sufficient for investigating and explaining higher levels of functioning. For organismal systems medicine, the patient is treated as a whole in which parts from different levels or sales are interrelated or entangled with one another. Moreover, several systems biologists utilize mechanistic explanations to account for systems phenomena (Brigandt, et al., 2018, Richardson and Stephan, 2007). Although mechanistic systems biology represents a legitimate approach to medical research, some commentators argue that without a holistic context, a system cannot be adequately or sufficiently explained since the isolated parts, especially at lower levels, do not provide sufficient relevant information to explain the system (Soto and Sonnenschein, 2018, Tretter, 2019). In this section, organicism is initially discussed followed by holism, and the section concludes with exploring from an organismal systems medicine perspective the blood clotting and cancer examples discussed in the previous section.

3.1 Organicism

According to organicists, mechanical parts alone, as advocated by mechanists, are insufficient ontologically to investigate adequately or to manipulate effectively living organisms (Botz-Bornstein, 2020, Henning and Scarfe, 2013). What mechanists fail to consider when causally explaining biological or biomedical phenomena from a reductionistic stance is what Daniel Nicholson calls the "*organismic context*" (2012, 159). As Nicholson elaborates, "mechanistic explanations specify

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[1] Felix Tretter (2019) contrasts organismal systems medicine, which he bases on Ludwig von Bertalanffy's organismal biology, to a molecular systems medicine in that the former takes into consideration the patient's developmental stage within an ecological and environmental context, which includes the molecular or omics data, while the latter considers only the molecular data.

only those features of the underlying causal networks that biologists deem *most relevant* for manipulating and controlling the phenomena whilst at the same time presupposing a great deal of the organismic context that makes them possible" (2012, 159, original emphasis). Moreover, mechanism represents a metaphor that, according to Lenny Moss, has "run out of steam" with respect to accounting for living processes (2012, 170), even though during most of the twentieth century, the mechanistic view of life eclipsed the organicist view (Nicholson and Gawne, 2015, Peterson, 2016).

What was problematic for twentieth-century advocates of organicism was an inability to develop the requisite technology and methodology to investigate living organisms as intact entities, and so organicism was eventually obscured by mechanistic biomedicine during the second half of the twentieth century. However, at the beginning of the twenty-first century organicism has had a revival, especially after the completion of the Human Genome Project (Botz-Bornstein, 2020, Nicholson, 2014). An important reason for its revival in the postgenomic era is the development of omics technology, which has permitted clinicians to gather substantial amounts of data on patients, to use these data to treat patients specifically as individuals, and finally to predict diseases to which patients are susceptible based on their omics data (Chen and Snyder, 2013, Loscalzo and Barabasi, 2011, Montévil, 2020).

According to contemporary organicists, a system's properties are independent of its isolated parts and the properties of those isolated parts. For example, Gagliasso contends that for a living organism

> the particular properties are given by the relationships between the parts and the characteristics considered as defining of any living entity (an organ, an organism, an organic and environmental system) and are determined by all the relationships that interconnect the diverse entities and that transform both the entities and the relations. (2003, 344)

As a concept, organicism envisions just a single whole of which all other levels within that whole are interrelated or integrated parts, but the properties of the whole are independent of the parts' properties. For example, Morton Beckner advocates a form of organicism in which "higher level processes…are autonomous with respect to lower levels" (1974, 171). And according to Robert Wilson (2005), the world of organisms is well structured and sufficiently complex to defy reductionistic mechanism.

Contemporary organicism, then, is a relational concept and depends on the organized interactions of the parts that make up the organic whole (Beckner, 2006, Elsassar, 1998). Further, an organism's composition is not necessarily what determines it; rather, an organism depends upon the organization or structure of its components (Brooks, et al., 2021). For the organism's structure is critical for promoting and regulating specific interactions of the components. As Michel Morange observes, the organism's ontological complexities "lay not in the nature of the macromolecular components, but in the way these components associate and interact to generate complex [and ontological distinct] structures and functions" (2006, 357). And Ernst Mayr makes a similar observation:

> The basis for organicism is the fact that living beings have organization. They are not just piles of characters or molecules, because their function depends entirely on their organization, their mutual interrelations, interactions, and interdependencies (1998, 19).

For contemporary organicism, the structure-function relationship—not just its resultant material composition—is what defines the organism. In other words, life can be made of various materials as long as it reflects living processes that are governed by specific principles and rules.[2]

While mechanistic biomedicine is founded on the central dogma of molecular biology and the principles and rules that regulate information flow from genotype to phenotype, organismal systems medicine is founded on the central dogma of systems biology, i.e., "it is system dynamics and organizing principles of complex biological phenomena that give rise to the functioning and function of cells" (Wolkenhauer and Mesarović, 2005, 14). The information flow within organismal systems medicine includes not just the flow dictated by the central dogma of molecular biology but also the flow of information among dynamic modular processes involved in a patient's pathophysiology. In other words, just as genetic information within cells follows particular pathways, so organismic information within biological systems follows certain dynamical pathways. For example, carcinogenesis involves not just the central dogma of molecular biology in terms of information flow between genes and proteins but also the organizational information of the chromosomes in which those genes are located, which includes, for example, epigenetic information (Marcum, 2019).

Just as mechanistic biomedicine's goal is to work out the principles and rules that govern the flow of genetic information within cells, so organismal systems medicine's goal is to work out the general principles and rules that govern information flow within organisms. Mihajlo Mesarović and colleagues, for instance, demarcate between controlling and coordinating principles for organic organization and function (Mesarović, et al., 2004). Controlling principles govern

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[2] Unfortunately, what constitutes the fundamental properties or processes of life or what is life is a highly contested issue (Weber, 2018). Although this might appear problematic for organismal systems medicine, such medicine provides the means for identifying not just the fundamental processes but more importantly the principles and rules by which these processes are regulated.

an organism's fixed behavior, while coordinating principles govern its flexible behavior. Moreover, Ana Soto and Carlos Sonnenschein (2018) identify three principles that center around an organism's agency. The first principle of proliferation involves the rules that regulate organismal growth and reproduction, while the next principle pertains to the rules governing variation within organisms. The final principle includes the rules that are responsible for an organism's organization and function.

Sara Green and colleagues also explore the general characteristics of organismic principles (Green and Wolkenhauer 2013, Green 2015, Green et al. 2018). Their principles are divided into four categories. The first is composed of organizing principles, including the principle of control and adaptation of dynamical systems, the principle of feedback control, the principle of closure to efficient causation, and the coordination principles like bounded autonomy of levels. Design principles composed the next category, including the principle of network motifs, the principle of modularity, the principle of bi-stable switching, and the principle of robustness, along with design principles involved in evolutionary change. The third category includes optimality principles, such as the branching angle principle (as in vasculogenesis) and the demand principle for gene regulation. The last category contains isomorphic principles, which pertain to open systems principles, exponential growth and decay principles, and the principle of allometric scaling relations. And as Green summarizes, these principles represent a need "to understand what generic features characterize pattern-producing systems in biology and beyond, and why we should expect particular organizational patterns in evolution" (2015, p. 649).

Finally, Bernd Rosslenbroich (2016) incorporates organismal biology into medicine in terms of five principles, especially to define the nature of health.[3] The first principle is that the patient qua organism is organized on different systems levels, while the next two principles are closely related to one another in that each system level is regulated by rules specific for that level and that the various levels are interdependent with respect to causation. The final two principles pertain first to organismic autonomy, i.e., the patient *qua* organism is self-regulatory, robust, independent, and flexible, and secondly to phenotypic plasticity, i.e., changes are in response to perturbations to the patient *qua* system. "Health," as Rosslenbroich concludes, "can be described in medicine and psychology as the

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[3] These principles owe their inspiration to Denis Noble's ten principles of systems biology (Nobel 2006), which both Soto and Sonnenschein (2018) and Tretter (2019) also use to ground their organismal systems medicine.

capacity for dynamically balanced systems autonomy" (2016, 10). And its such health that is one of organismal systems medicine's chief goals rather than simply treating or even preventing disease.

3.2 Holism

Although reductionism is a popular concept among biomedical scientists and clinicians, it has its limits and critics (Brigandt and Love, 2017, Kaiser, 2015); and various holistic concepts have been espoused to replace it (Verschuuren, 2017, Wolfe, 2012). Contemporary versions of holism are explicated in naturalist or physicalist terms and not in a reductionist sense since the parts of the whole are necessary but not sufficient for constituting or determining the whole; and agency, i.e., the capacity to bring about change, is embedded or entangled within the material or matter itself qua whole (Chong and Ray, 2002, Placek, 2004, Woods, 2017). What constitutes holism is unpacked in the remainder of this section by initially defining holism and then by examining it with respect to its metaphysical, methodological, epistemological, and ontological dimensions (Esfeld, 2009). The sequence of these dimensions is important in that holism functions metaphysically by which methodological questions concerning natural phenomena are addressed experimentally and theoretically. Through this process the whole is understood and explained epistemically, and its ontological nature is categorized in terms of integrated levels. Finally, from an organismal systems medicine perspective, the nature of the patient, especially with respect to personal health, is discussed throughout the section in contrast to the biomedical model's reductionist approach.

Holism relies on the notion of wholeness, which entails an irreducible and a dynamical totality that is complete and undivided (Piechocinska, 2004). The main idea behind holism is that the investigation and explanation of natural phenomena or systems and their properties only with respect to their component parts and properties are deficient and incomplete; rather, the whole must be investigated and explained on its own terms. In other words, "the whole is fundamental, not any one [part]" (Jones, 2000, 337). As Denis Noble (2006) claims, no one part is privileged causally. In short, the whole and its properties are greater than the sum of its parts and their properties (McDaniel, 2010). Although the component parts that constitute natural phenomena do provide the basis from which phenomena at higher levels materialize or emerge (Findlay and Thagard, 2012), the component parts do not entirely cause or account for the whole (Boogerd, et al., 2007). Consequently, natural phenomena at lower levels must be investigated and explained with respect to phenomena at higher levels, since phenomena at higher levels regulate or control phenomena at the lower levels.

Philosophically, holism has important metaphysical, methodological, epistemological, and ontological implications for organismal systems medicine. Metaphysically, patients in terms of wholeness are viewed and understood with respect to their totality as holistic agents. To investigate their totality at higher-levels requires a methodology that does not simply reduce or fragment them into isolated component parts, as in the case for reductionist biomedicine, but maintains the integrity of the whole. Epistemically, holism implies that patients as higher-level phenomena are to be understood in terms appropriate for that level and not just in terms for explaining lower-level phenomena. Finally, patients qua higher-level or whole phenomena are ontologically distinct from their lower-level parts. In other words, as higher-level entities they are not just composites of lower-level parts; rather, they are entities in their own right, with their own unique properties. In sum, holism pertains to the integral structure of the material components that make up patients as natural entities and agents; and, consequently, methods and technology must be employed to investigate them with respect to their ontological integrity. However, the observations and results obtained from these investigations must be used to formulate and confirm explanations of complex, higher-level phenomena like health and disease and what they are ontologically.

Conceptually, then, holism is crucial for moving from a mechanistic approach and understanding of patients to an organismal approach and understanding (Sturmberg, 2016, Vogt, et al., 2016). Through holism, the integrity of the patient's personal health from an organismal systems medicine perspective depends on the robustness and interaction of the biological, psychological, social, and environmental factors, composing it. In contrast, reductionistic biomedicine suffers from a myopic and fragmented view of the patient qua machine. And such a view can often result in medical errors, especially in terms of making the wrong diagnosis and then prescribing the wrong medication, that can either harm or even kill the patient (Levins, 2014). Indeed, reductionism can even blind the clinician to obvious clinical facts and prevent an accurate diagnosis. Finally, holism undergirds the healthcare profession by promoting healing as a return to an integral whole or as close to achieving wholeness as possible or even creating a new wholeness. For wholeness denotes a sense of soundness in the body as good health or wellbeing.

3.3 Examples of Organismal Systems Medicine

Both hemostasis and carcinogenesis provide excellent examples for exploring the potential of organismal systems medicine to address the problems arising from mechanistic biomedicine's failure to treat effectively or to cure various pathological conditions and diseases. For blood coagulation, systems theory is used to model clot formation or thrombosis and clot dissolution or fibrinolysis in a test tube or under *in vitro* conditions (Diamond, 2016). Such modeling depends on "bottom-up systems biology" in which blood clotting factors and their rates of interactions are computed to determine clot formation or dissolution (Diamond, 2013). Such models also include the participation of blood cells such as platelets and fluid dynamics, especially under *in vivo* conditions (Chen, et al., 2014, Colace, et al., 2013). However, blood coagulation remains hard to predict "due to nonlinearity, sensitivity to initial conditions, network complexity, feedback regulation, and biorheological/transport influence" (Diamond, 2013, 224). In other words, the future of blood coagulation vis-à-vis organismal systems medicine will require a top-down systems biology in which the integrity of the organism is maintained as clotting parameters are varied. For example, the role of heparan sulfate proteoglycans in the non-thrombogenic properties of the vascular endothelium was determined using a systems biology approach (Marcum and Rosenberg, 1987). However, the question remains as to how this system interacts with other regulatory mechanisms of blood coagulation such as protein C and thrombomodulin (Weiler and Isermann, 2003). Finally, systems medicine is currently being employed to treat, especially with respect to personalized or precision medicine, clotting disorders. For example, studies have been conducted to simulate the impact of low-molecular weight heparin on coagulation pathologies, especially in terms of a patient's blood clotting profile (Pisaryuk, et al., 2022).

For carcinogenesis, Hanahan and Weinberg's original six hallmarks of cancer are expanded and repositioned within a systems biology approach to carcinogenesis, both in terms of basic research and clinical practice (Bertolaso, 2016, Bizzarri et al., 2008, Fouad and Aanei, 2017, Malaterre, 2007, Paul, 2020, Plutynski, 2018). In reflecting on their 2000 article in which they introduced the hallmarks, Hanahan and Weinberg (2011) acknowledge two more hallmarks consisting of reprogramming the cell's energy metabolism and the tumor's evasion of an immune response, as well as the tumor's microenvironment, in tumorigenesis. However, they still advocate a strictly somatic mutation theory for carcinogenesis. In response to Hanahan and Weinberg's original somatic mutation theory, Carlos Sonnenschein and Ana Soto (2000) proposed a tissue organization field theory of carcinogenesis. The theory claims that the default state of normal cells is not quiescence but rather proliferation and that tumorigenesis is the result of changes in the structural organization of the tissue such that cellular proliferation is no longer regulated adequately. Recently, Soto and Sonnenschein (2021) have turned to organicism to advance their theory. Specifically, they argue that besides the bottom-up causation exhibited by mutated genes responsible for many of the hallmarks of cancer, top-down causation, especially in terms of the structural organization of the tissue, is also critical. In support of their theory, they cite studies in which malignant cells when exposed to a normal tissue organization do not express their malignant phenotype. Soto and Sonnenschein conclude that carcinogenesis needs to be situated with respect to the intact organism and not simply reduced to mutated genes.

Finally, an organismal systems medicine can also be used to combine both hemostasis and carcinogenesis, not only with respect to basic research but also in terms of treating of patients clinically (Buller, et al., 2007, Goubran, et al., 2012, Sharma, et al., 2019, Wang, et al., 2018). Experimentally, for example, "data from basic research indicate that the hemostatic components and the cancer biology are interconnected in multiple ways. Notably, while cancer cells are able to activate the coagulation system, the hemostatic factors play a role in tumor progression" (Falanga, et al., 2013, 223). In terms of the activation of thrombosis, many cancer patients exhibit hypercoagulable states that involve increased levels of clotting factors such as tissue factor or factor VII and suffer from both arterial and venous thrombi (Khorana, 2012, Zwicker, et al., 2007). As for tumor progression, again, clotting factors such as tissue factor are correlated with reshaping the tumor's microenvironment, especially in terms of promoting metastasis (Falanga and Marchetti, 2018, Lima and Monteiro, 2013). Moreover, blood coagulation plays an important role in terms of tumor progression and growth with respect to promoting angiogenesis (Nash, et al., 2001, Tsopanoglou and Maragoudakis, 2004). In sum, organismal systems medicine provides a means and an approach for integrating the various specialties in medicine, as exemplified with hemostasis and carcinogenesis, in order to maintain the patient's integrity and to treat the patient efficaciously and safely.

4. Conclusion

The main conceptual foundation for organismal systems medicine, then, consists of organicism and holism. Organicism, indeed, captures the patient's organic vitality and agency, especially as the biological, psychological, social, and environmental components entangle to give rise to personal health or disease; and it expresses the necessary agency to participate actively in requisite treatment, as well as to promote a healthful lifestyle. In contrast, biomedicine's concept of mechanism can at times imprison and dehumanize the patient as a machine, which when broken is simply fixed by repairing the broken part or by replacing it. The patient's materiality or physicality is often simply passive. Although mechanistic biomedicine can identify important components that constitute the patient, especially as exemplified by hemostasis and carcinogenesis discussed above, organismal systems medicine provides the principles and rules concerning not simply *how* the components interact but also *what*, as Dupré (2020) insists, to expect from those interactions. The interaction of thrombosis and tumorigenesis certainly illustrates the importance of maintaining a system's integrity, particularly in organismal terms. In other words, multimorbidity is an important issue in treating patients given the complexity of many pathophysiological processes (Sturmberg, et al., 2017), as illustrated with hemostasis and carcinogenesis.

Finally, some advocates for a systems approach to the biomedical sciences argue for a paradigm that combines or integrates both reductionism and holism (Latterich, 2005, O'Malley and Dupré, 2005, Woods, 2017). According to Francisco Ayala, for example, the majority of these advocates "agree that the study of problems at a given level of complexity of the living world must proceed by exploring lower as well as higher levels of organization" (1974, ix). In other words, both reductionism and holism represent opposite poles on a continuum in which possible intermediate positions are available between "microscopic 'nothing but' statements" and "macroscopic 'all or nothing' statements" (Boogerd, et al., 2007, 12). And these advocates claim that such intermediate positions provide a comprehensive picture of the natural world. "In order to understand Nature," writes Peter Schuster, "we can neither dispense from the reductionist's program and its results nor can we totally abolish the holistic view" (2007, 12). Moreover, for other advocates of systems medicine, both reductionism and holism are critical concepts for practicing clinical medicine (Berlin, et al., 2017, Federoff and Gostin, 2009). This approach is pluralistic and opportunistic in its nature and takes its cue from the problem at hand. "The consensus view," suggest Marc Van Regenmortel and David Hull, "leads to pluralism: both reductionist methods and a more holistic approach to biological complexity are required, depending on the questions being asked" (2002, 13). But the questions being asked currently in twenty-first century medicine, especially in terms of big-data and discovery science, are outstripping the reductionist approach of mechanistic biomedicine and calling for a holistic approach of organismal systems medicine.

In conclusion, although the proposed organismal systems medicine does appear to rely on integrating its conceptual foundation of organicism with biomedicine's mechanistic approach, still its approach is strictly organismal in the sense that the patient has agency inherent within its embodied and entangled state, especially with respect to participating in the healing process. Certainly, biomedicine's mechanistic approach, with its associated reductionism, is important for a robust organismal systems medicine at the current time, still the concept of organicism drives the conceptual framework for twenty-first century organismal systems medicine. In other words, mechanistic biomedicine with its associated reductionism has provided several of the entities and activities involved in various physiological and pathological processes; but as the examples from hemostasis and carcinogenesis illustrate, organismal integrity is vital for identifying the principles and rules by which those entities and activities are involved in health and disease. Indeed, the power and potential of organismal systems medicine should eclipse the mechanistic biomedicine as the twenty-first century continues to unfold.

References

Andersen, H. K. (2017). Reductionism in the biomedical sciences. In Miriam Solomon, Jeremy R. Simon and Harold Kincaid (eds.), *The Routledge Companion to Philosophy of Medicine* (pp. 81-88). New York: Routledge.

Ayala, F. J. (1974). Introduction. In F. J. Ayala and T. Dobzhansky (eds.), *Studies in the Philosophy of Biology: Reductionism and Related Problems* (pp. vii-xvi). Berkeley, CA: University of California Press.

Bechtel, W. (2006). *Discovering Cell Mechanisms: The Creation of Modern Cell Biology*. New York: Cambridge University Press.

Beckner, M. (1974). Reductionism, hierarchies and organicism. In F. J. Ayala and T. Dobzhansky (eds.), *Studies in the Philosophy of Biology: Reductionism and Related Problems* (pp. 163-177). Berkeley, CA: University of California Press.

Beckner, M. (2006). Organismic biology. En D. M. Borchert (ed.), *Encyclopedia of Philosophy*, 2nd edition, volume 7, (pp. 36-39). Detroit, MI: Thomson Gale.

Berlin, R., Gruen, R., Best, J. (2017). Systems medicine—Complexity within, simplicity without. *Journal of Healthcare Informatics Research*, *1*(1), 119-137.

Berryman, S. (2003). Ancient automata and mechanical explanation. *Phronesis*, *48*(4), 344-369.

Bertalanffy, L. (1974). *General Systems Theory: Foundations, Development, Applications*, revised edition. New York: Braziller.

Bertolaso, M. (2016). *Philosophy of Cancer*. Dordrecht, NL: Springer. https://doi.org/10.1007/978-94-024-0865-2

Bertram, J. S. (2000). The molecular biology of cancer. *Molecular Aspects of Medicine*, *21*(6), 167-223. https://doi.org/10.1016/S0098-2997(00)00007-8

Bizzarri, M., Cucina, A., Conti, F., D'Anselmi, F. (2008). Beyond the oncogene paradigm: Understanding complexity in cancerogenesis. *Acta Biotheoretica*, *56*(3), 173-196. https://doi.org/10.1007/s10441-008-9047-8

Bliss, M. (1982). *The Discovery of Insulin*. Chicago: University of Chicago Press.

Boogerd, F. C., Bruggeman, F. J., Hofmeyr, J-H. S., Westerhoff, H. V. (2007). Towards a philosophical foundation of systems biology: Introduction. In F. C. Boogerd, F. J. Bruggeman, J-H. S. Hofmeyr and H. V. Westerhoff (eds.), *Systems Biology: Philosophical Foundations* (pp. 3-19). Amsterdam, NL: Elsevier.

Botz-Bornstein, T. (2020). *Micro and Macro Philosophy: Organicism in Biology, Philosophy, and Politics*. Leiden, NL: Brill.

Brandt, A. M., Gardner, M. (2020). The golden age of medicine? En Roger Cooter y John Pickstone (eds). *Medicine in the Twentieth Century* (pp. 21-37). London: Taylor & Francis.

Brigandt, I., Love, A. (2017). Reductionism in biology. In Edward N. Zalta (ed.), *Stanford Encyclopedia of Philosophy*. https://plato.stanford.edu/archives/spr2017/entries/reduction-biology/

Brigandt, I., Green, S., O'Malley, M. A. (2018). Systems biology and mechanistic explanation. In S. Glennan and P. Illari (eds.), *The Routledge Handbook of Mechanisms and Mechanical Philosophy* (pp. 362-374). New York: Routledge.

Brooks, D. S., DiFrisco, J., Wimsatt, W. C. (2021). *Levels of Organization in the Biological Sciences*. Cambridge, MA: MIT Press.

Buller, H.R., Van Doormaal, F.F., Van Sluis, G.L., Kamphuisen, P.W. (2007). Cancer and thrombosis: From molecular mechanisms to clinical presentations. *Journal of Thrombosis and Haemostasis*, *5*, 246-254. https://doi.org/10.1111/j.1538-7836.2007.02497.x

Capra, F., Luisi, P. L. (2014). *The Systems View of Life: A Unifying Vision*. New York: Cambridge University Press.

Chen, R., Snyder, M. (2013). Promise of personalized omics to precision medicine. *Systems Biology and Medicine*, *5*(1), 73-82.

Chen, Y., Corey, S. J., Kim, O. V., Alber, M. S. (2014). Systems biology of platelet–vessel wall interactions. In S. J. Corey, M. Kimmel and J. N. Leonard (eds.), *A Systems Biology Approach to Blood* (pp. 85-98). New York: Springer. https://doi.org/10.1007/978-1-4939-2095-2_5

Chong, L., Ray, L. B. (2002). Whole-istic biology. *Science*, *295*, 1661. https://www.science.org/doi/10.1126/science.295.5560.1661

Clarke, B., Russo, F. (2018). Mechanisms and biomedicine. In S. Glennan and P. Illari (eds.), *The Routledge Handbook of Mechanisms and Mechanical Philosophy* (pp. 319-331). New York: Routledge.

Colace, T. V., Tormoen, G. W., McCarty, O. J.T., Diamond, S. L. (2013). Microfluidics and coagulation biology. *Annual Review of Biomedical Engineering*, *15*, 283-303. https://doi.org/10.1146/annurev-bioeng-071812-152406

Craver, C.F., Darden, L.(2005). Mechanisms in biology. Introduction. *Studies in the History and Philosophy of Biological and Biomedical Sciences*, *36*, 233-244. https://doi.org/10.1016/j.shpsc.2005.03.001 PMID: 19260190.

Crick, F. (1958). On protein synthesis. *Symposium of the Society of Experimental Biology*, *12*, 138-167.

Cutler, D. M. (2008). Are we finally winning the war on cancer? *Journal of Economic Perspectives, 22*(4), 3-26. https://doi.org/10.1257/jep.22.4.3

Cutter, M. A. G. (2018). *Thinking Through Breast Cancer: A Philosophical Exploration of Diagnosis, Treatment, and Survival.* New York: Oxford University Press.

Darden, L. (2006). *Reasoning in Biological Discoveries: Essays on Mechanisms, Interfiled Relations, and Anomaly Resolution*. New York: Cambridge University Press.

Darden, L., Kundu, K., Pal, L. R., Moult, J. (2018). Harnessing formal concepts of biological mechanism to analyze human disease. *PLoS Computational Biology*, *14*(12), e1006540. https://doi.org/10.1371/journal.pcbi.1006540

Davie, E. W. (1995). Biochemical and molecular aspects of the coagulation cascade. *Thrombosis and Haemostasis*, *74*(7), 1-6. https://dio.org/10.1055/s-0038-1642645

De Chadarevian, S., Kamminga, H. (1998). *Molecularizing Biology and Medicine: New Practices and Alliances, 1920s to 1970s*. London: Taylor & Francis.

De Solla Price, D. J. (1964). Automata and the origins of mechanism and mechanistic philosophy. *Technology and Culture*, *5*, 9-23.

Diamond, S. L. (2013). Systems biology of coagulation. *Journal of Thrombosis and Haemostasis*, *11*, 224-232. https://doi.org/10.1111/jth.12220

Diamond, S. L. (2016). Systems analysis of thrombus formation. *Circulation Research*, *118*(9), 1348-1362. https://doi.org/10.1161/CIRCRESAHA.115.306824

Döring, M., Petersen, I., Brüninghaus, A., Kollek, R. (2015). *Contextualizing Systems Biology: Presuppositions and Implications of a New Approach in Biology*. New York: Springer. https://doi.org/10.1007/978-3-319-17106-7

Dupré, J. (1993). *The Disorder of Things*. Cambridge, MA: Harvard University Press.

Dupré, J. (2020). Life as process. *Epistemology & Philosophy of Science*, *57*(2), 96-113. https://doi.org/10.5840/eps202057224

Elsassar, W. M. (1998). *Reflections on a Theory of Organisms: Holism in Biology*. Baltimore, MD: The Johns Hopkins University Press.

Esfeld, M. (2009). Philosophical holism. In G. H. Hardon (ed.), *Unity of Knowledge in Transdisciplinary Research for Sustainability* (pp. 110-127). Oxford, UK: Eolss Publishers.

Falanga, A., Marchetti, M. (2018). Hemostatic biomarkers in cancer progression. *Thrombosis Research*, *164*, S54-S61. https://doi.org/10.1016/j.thromres.2018.01.017

Falanga, A., Marchetti, M., Vignoli, A. (2013). Coagulation and cancer: Biological and clinical aspects. *Journal of Thrombosis and Haemostasis*, *11*(2), 223-233. https://doi.org/10.1111/jth.12075

Federici, A.B., Berntorp, Erik, Lee, C.A. (2006). The 80th anniversary of von Willebrand's disease: history, management and research. *Haemophilia*, *12*(6), 563-572. https://doi.org/10.1111/j.1365-2516.2006.01393.x

Federoff, H. J., Gostin, L. O. (2009). Evolving from reductionism to holism: Is there a future for systems medicine? *Journal of the American Medical Association*, *302*(9), 994-996. https://doi.org/10.1001/jama.2009.1264

Findlay, S. D., Thagard, P. (2012). How parts make up wholes. *Frontiers in Physiology*, 3. https://doi.org/10.3389/fphys.2012.00455

Fouad, Y. A., Aanei, C. (2017). Revisiting the hallmarks of cancer. *American Journal of Cancer Research*, *7*(5), 1016-1036.

Gagliasso, E. (2003). The metamorphosis of holism. In V. Benci, P. Cerrai, P. Freguglia, G. Israel and C. Pellegrini (eds.), *Determinism, Holism, and Complexity* (pp. 339-348). New York: Plenum.

Glennan, S. (2017). *The New Mechanical Philosophy*. New York: Oxford University Press.

Goubran, H. A., Burnouf, T. P. R. (2012). Platelets, coagulation and cancer: Multifaceted interactions. *American Medical Journal*, *3*, 130-140. https://www.researchgate.net/publication/260471355_Platelets_Coagulation_and_Cancer_Multifaceted_Interactions

Green, D. (2018). *Hemophilia and Von Willebrand Disease: Factor VIII and Von Willebrand Factor*. London: Academic Press. https://doi.org/10.1016/C2016-0-04171-2

Green, S. (2015). Revisiting generality in biology: Systems biology and the quest for design principles. *Biology and Philosophy*, *30*(5), 629-652. https://doi.org/10.1007/s10539-015-9496-9

Green, S., Wolkenhauer, O. (2013). Tracing organizing principles: Learning from the history of systems biology. *History and Philosophy of the Life Sciences*, *35*(4), 553-576. http://www.jstor.org/stable/43862214

Green, S., Şerban, M., Scholl, R., Jones, N., *et al.* (2018). Network analyses in systems biology: New strategies for dealing with biological complexity. *Synthese*, *195*(4), 1751-1777. https://doi.org/10.1007/s11229-016-1307-6

Grote, M., Onaga, L., Creager, A. N.H., de Chadarevian, S., *et al.* (2021). The molecular vista: Current perspectives on molecules and life in the twentieth century. *History and Philosophy of the Life Sciences*, *43*(1), 16. https://doi.org/10.1007/s40656-020-00364-5

Haines, I. (2014). The war on cancer: Time for a new terminology. *The Lancet*, *383*(9932), 1883. https://doi.org/10.1016/S0140-6736(14)60907-7

Hamza, M. S., Mousa, S. A. (2020). Cancer-associated thrombosis: Risk factors, molecular mechanisms, future management. *Clinical and Applied Thrombosis/Hemostasis*, *26*, 1076029620954282. https://doi.org/10.1177/1076029620954282

Hanahan, D., Weinberg, R. A. (2000). The hallmarks of cancer. *Cell*, *100*(1), 57-70. https://doi.org/10.1016/S0092-8674(00)81863-9

Hanahan, D., Weinberg, R. A.(2011). Hallmarks of cancer: The next generation. *Cell*, *144*(5), 646-674. https://doi.org/10.1016/j.cell.2011.02.013

Hanson, B. G. (1995). *General Systems Theory Beginning with Wholes*. New York: Taylor & Francis.

Henning, B. G., Scarfe, A. C. (eds.) (2013). *Beyond Mechanism: Putting Life back into Biology*. Lanham, MD: Rowman & Littlefield.

Hoffman, M. (2003). Remodeling the blood coagulation cascade. *Journal of Thrombosis and Thrombolysis*, *16*(1), 17-20. https://doi.org/10.1023/B:THRO.0000014588.95061.28

Hutchings, M. I., Truman, A. W., Wilkinson, B.(2019). Antibiotics: Past, present and future. Current Opinion in Microbiology, *51*, 72-80. https://doi.org/10.1016/j.mib.2019.10.008

Illari, P. (2017). Mechanisms in medicine. In M. Solomon, J.R. Simon and H. Kincaid (eds.), *The Routledge Companion to Philosophy of Medicine* (pp. 62-71). New York: Routledge.

Jones, R. H. (2000). *Reductionism: Analysis and the Fullness of Reality*. Lewisburg, PA: Bucknell University Press.

Kaiser, M. I. (2015). *Reductive Explanation in the Biological Sciences*. Cham: CH: Springer. https://doi.org/10.1007/978-3-319-25310-7

Karimi, M. R., Karimi, A. H., Abolmaali, S., Sadeghi, M., Schmitz, U. (2022). Prospects and challenges of cancer systems medicine: From genes to disease networks. *Briefings in Bioinformatics*, *23*(1), bbab343. https://doi.org/10.1093/bib/bbab343

Keating, P., Cambrosio, A. (2012). *Cancer on Trial: Oncology as a New Style of Practice*. Chicago: University of Chicago Press.

Khorana, A. A. (2012). Cancer and coagulation. *American journal of hematology*, *87*(S1), S82-S87. https://doi.org/10.1002/ajh.23143

Knowles, M. A., Selby, P. (eds.) (2005). *Introduction to the Cellular and Molecular Biology of Cancer*, 5th edition. New York: Oxford University Press.

Kuhn, T. S. (1970). *The Structure of Scientific Revolutions*, 2nd edition. Chicago: University of Chicago Press.

Latterich, M. (2005). Molecular systems biology at the crossroads: To know less about more, or to know more about less? *Proteome Science*, *3*, 8. https://doi.org/10.1186/1477-5956-3-8

Lenoir, T. (1999). Shaping biomedicine as an information science. In M. E. Bowden, T. B. Hahn and R. V. Williams (eds.), *Science Information Systems* (pp. 27-45). Medford, MJ: Information Today, Inc.

Levins, R. (2014). The road to wholeness in medicine and public health. *International Critical Thought*, *4*(2), 221-240. https://doi.org/10.1080/21598282.2014.906807

Lima, L. G., Monteiro, R. Q. (2013). Activation of blood coagulation in cancer: Implications for tumour progression. *Bioscience Reports*, *33*(5), e00064. https://doi.org/10.1042/BSR20130057

Litviňuková, M., Talavera-López, C., Maatz, H., Reichart, D., *et al.* (2020). Cells of the adult human heart. *Nature*, 588, 466-472. https://doi.org/10.1038/s41586-020-2797-4

Lock, M., Gordon, D. (eds.) (1988). *Biomedicine Examined*. Dordrecht, NL: Kluwer.

Loscalzo, J., Barabasi, A-L.(2011). Systems biology and the future of medicine. *Systems Biology and Medicine*, *3*(6), 619-627. https://doi.org/10.1002/wsbm.144

Löwy, I. (2011). Historiography of biomedicine: "Bio," "medicine," and in between. *Isis*, *102*(1), 116-122. https://doi.org/10.1086/658661

Machamer, P. Darden, L., Craver, C. F. (2000). Thinking about mechanisms. *Philosophy of Science*, *67*, 1-25. http://www.jstor.org/stable/188611

Malaterre, C. (2007). Organicism and reductionism in cancer research: Towards a systemic approach. *International Studies in the Philosophy of Science*, *21*(1), 57-73. https://doi.org/10.1080/02698590701305792

Mann, K. G., Lorand, L. (1993). Introduction: Blood coagulation. *Methods in Enzymology*, *222*, 1-10. https://doi.org/10.1016/0076-6879(93)22003-x

Marcum, J. A. (2005). Metaphysical presuppositions and scientific practices: Reductionism and organicism in cancer research. *International Studies in the Philosophy of Science*, *19*(1), 31-45. https://doi.org/10.1080/02698590500051076

Marcum, J. A. (2019). The cancer epigenome: A review. *Journal of Biotechnology and Biomedicine*, *3*, 67-83. https://doi.org/10.26502/jbb.2642-91280011

Marcum, J. A., Rosenberg, R. D. (1987). Anticoagulantly active heparan sulfate proteoglycan and the vascular endothelium. *Seminars in Thrombosis and Hemostasis*, *13*, 464-474. https://doi.org/10.1055/s-2007-1003523

Mayr, E. (1998). *This is Biology: Science of the Living World*. Cambridge, MA: Harvard University Press.

McDaniel, K. (2010). Parts and wholes. *Philosophy Compass*, *5*(5), 412-425. https://doi.org/10.1111/j.1747-9991.2009.00238.x

Mesarović, M., D., Sreenath, S.N., Keene, J.D. (2004). Search for organising principles: Understanding in systems biology. *Systems Biology*, *1*(1), 19-27. https://doi.org/10.1049/sb:20045010

Montévil, M.(2020). Conceptual and theoretical specifications for accuracy in medicine. In C. Beneduce and M. Bertoloso (eds.), *Personalized Medicine in the Making: Philosophical Perspectives from Biology to Healthcare* (pp. 47-62). Cham: Springer. https://doi.org/10.1007/978-3-030-74804-3_3

Morange, M. (2006). Post-genomics, between reduction and emergence. *Synthese*, *151*, 355-360.

Moss, L. (2012). Is the philosophy of mechanism philosophy enough? *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, *43*(1), 164-172.

Mukherjee, S. (2011). *The Emperor of All Maladies: A Biography of Cancer*. New York: Simon and Schuster.

Nash, G.F., Walsh, D.C., Kakkar, A.K. (2001). The role of the coagulation system in tumour angiogenesis. *The Lancet Oncology*, *2*(10), 608-613. https://doi.org/10.1016/S1470-2045(01)00518-6

Nicholson, D. J. (2012). The concept of mechanism in biology. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, *43*(1), 152-163. https://doi.org/10.1016/j.shpsc.2011.05.014

Nicholson, D. J. (2014). The return of the organism as a fundamental explanatory concept in biology. *Philosophy Compass*, *9*(5), 347-359. https://doi.org/10.1111/phc3.12128

Nicholson, D. J., Gawne, R. (2015). Neither logical empiricism nor vitalism, but organicism: What the philosophy of biology was. *History and Philosophy of the Life Sciences*, *37*(4), 345-381. https://doi.org/10.1007/s40656-015-0085-7

Noble, D. (2006). *The Music of Life: Biology Beyond Genes*. New York: Oxford University Press.

O'Malley, M. A., Dupré, J. (2005). Fundamental issues in systems biology. *BioEssays*, *27*, 1270-1276. https://doi.org/10.1002/bies.20323

Owen, C. A. (2001). *A History of Blood Coagulation*. Rochester, MN: Mayo Foundation for Medical Education and Research.

Paul, D. (2020). The systemic hallmarks of cancer. *Journal of Cancer Metastasis and Treatment*, *6*, 29. http://dx.doi.org/10.20517/2394-4722.2020.63

Pecorino, L. (2021). *Molecular Biology of Cancer: Mechanisms, Targets, and Therapeutics*, 5th edition. New York: Oxford University Press.

Peterson, E. L. (2016). *The Life Organic: The Theoretical Biology Club and the Roots of Epigenetics*. Pittsburgh, PA: University of Pittsburgh Press.

Piechocinska, B. (2004). Wholeness as a conceptual foundation of physical theories. *Physics Essays*, *17*(4), 505-517. https://doi.org/10.48550/arXiv.physics/0409092

Pisaryuk, A. S., Povalyaev, N. M., Poletaev, A.V., Shibeko, A. M. (2022). Systems biology approach for personalized hemostasis correction. *Journal of Personalized Medicine*, *12*(11), 1903. https://doi.org/10.3390/jpm12111903

Placek, T. (2004). Quantum state holism: A case for holistic causation. *Studies in the History and Philosophy of Modern Physics*, *35*, 671-692. https://doi.org/10.1016/j.shpsb.2004.06.001

Plutynski, A. (2018). *Explaining Cancer: Finding Order in Disorder*. New York: Oxford University Press.

Ratnoff, O. D., Forbes, C.D. (1996). *Disorders of Hemostasis*, 3rd edition. Philadelphia: W.B. Saunders.

Richardson, R. C., Stephan, A. (2007). Mechanism and mechanical philosophy in systems biology. In F. C. Boogerd, F. J. Bruggeman, J-H. S. Hofmeyr and H. V. Westerhoff (eds.), *Systems Biology: Philosophical Foundations* (pp. 123-144). Amsterdam, NL: Elsevier.

Riddel, Jr., James P., Aouizerat, Bradley E., Miaskowski, Christine, Lillicrap, David P. (2007). Theories of blood coagulation. *Journal of Pediatric Oncology Nursing*, *24*(3), 123-131. https://doi.org/10.1177/1043454206298693

Roberts, H.R., Monroe, D.M., Oliver, J.A., Chang, J.Y., Hoffman, M. (1998). Newer concepts of blood coagulation. *Haemophilia*, *4*(4), 331-334. https://doi.org/10.1046/j.1365-2516.1998.440331.x

Robinson, J. D. (1992). Aims and achievements of the reductionist approach in biochemistry/molecular biology/cell biology: A response to Kincaid. *Philosophy of Science*, *59*, 465-470. http://www.jstor.org/stable/188161

Rosen, W. (2017). *Miracle Cure: The Creation of Antibiotics and the Birth of Modern Medicine*. New York: Penguin Books.

Rosslenbroich, B. (2016). The significance of an enhanced concept of the organism for medicine. *Evidence-Based Complementary and Alternative Medicine*, *2016*, 1587652. https://doi.org/10.1155/2016/1587652

Roukos, D. H. (2010). Systems medicine: A real approach for future personalized oncology? *Pharmacogenomics*, *11*(3), 283-287. https://doi.org/10.2217/pgs.10.36

Selinger, D. W., Wright, Matthew A., Church, G. M. (2003). On the complete determination of biological systems. *TRENDS in Biotechnology*, *21*, 251-254. https://doi.org/10.1016/S0167-7799(03)00113-6

Sharma, B. K., Flick, M. J., Palumbo, J. S. (2019). Cancer-associated thrombosis: A two-way street. En *Seminars in Thrombosis and Hemostasis*, *45*(6), 559-568. https://doi.org/10.1055/s-0039-1693472

Sheldrake, R. (1980). Three approaches to biology. Part I. The mechanistic theory of life. *Theoria to Theory*, *14*, 125-144.

Sheldrake, R. (1981). Three approaches to biology. Part III. Organicism. *Theoria to Theory*, *14*, 301-311.

Skyttner, L. (2005). *General Systems Theory: Problems, Perspectives, Practice*, 2nd edition. Singapore: World Scientific Publishing.

Sonnenschein, C., Soto, A. M. (2000). Somatic mutation theory of carcinogenesis: why it should be dropped and replaced. *Molecular Carcinogenesis*, *29*(4), 205-211. https://doi.org/10.1002/1098-2744(200012)29:4<205::AID-MC1002>3.0.CO;2-W

Soto, A.M., Sonnenschein, C. (2018). Reductionism, organicism, and causality in the biomedical sciences: A critique. *Perspectives in Biology and Medicine*, *61*(4), 489-502. https://doi.org/10.1353/pbm.2018.0059

Soto, A. M., Sonnenschein, C. (2021). The cancer puzzle: Welcome to organicism. *Progress in Biophysics and Molecular Biology*, *165*, 114-119. https://doi.org/10.1016/j.pbiomolbio.2021.07.001

Sporn, M. B. (1997). The war on cancer: A review. *Annals of the New York Academy of Science*, *833*(1), 137-146. https://doi.org/10.1016/s0140-6736(96)91015-6

Sturmberg, J. P. (2016). "Returning to holism": An imperative for the twenty-first century. In J. P. Sturmberg (ed.), *The Value of Systems and Complexity Sciences for Healthcare* (pp. 3-19). Cham, CH: Springer.

Sturmberg, J. P., Bennett, J. M., Martin, C. M., Picard, M. (2017). 'Multimorbidity' as the manifestation of network disturbances. *Journal of Evaluation in Clinical Practice*, *23*(1), 199-208. https://doi.org/10.1111/jep.12587

Surh, Y-J. (2021). The 50-year war on cancer revisited: Should we continue to fight the enemy within? *Journal of Cancer Prevention*, *26*(4), 219-223. https://doi.org/10.15430/JCP.2021.26.4.219

Trayanova, N. A. (2011). Whole-heart modeling: Applications to cardiac electrophysiology and electromechanics. *Circulation Research*, *108*(1), 113-128. https://doi.org/10.1161/CIRCRESAHA.110.223610

Tretter, F. (2019). "Systems medicine" in the view of von Bertalanffy's "organismic biology" and systems theory. *Systems Research and Behavioral Science*, *36*(3), 346-362. https://doi.org/10.1002/sres.2588

Tsopanoglou, N. E., Maragoudakis, M. E. (2004). Role of thrombin in angiogenesis and tumor progression. *Seminars in Thrombosis and Hemostasis*, *30*(1), 63-69. https://doi.org/10.1055/s-2004-822971

Van Regenmortel, M. H.V., Hull, D. L. (eds.) (2002). *Promises and Limits of Reductionism in the Biomedical Sciences*. West Sussex, UK: John Wiley.

Vecchio, I., Tornali, C., Bragazzi, N. L., Martini, M. (2018). The discovery of insulin: An important milestone in the history of medicine. *Frontiers in Endocrinology*, *9*, 613. https://doi.org/10.3389/fendo.2018.00613

Verschuuren, G. M. (2017). *Holism-Redcutionism Debate: In Physics, Genetics, Biology, Neuroscience, Ecology, and Sociology*. Virginia Beach, VA: Createspace Publishing.

Vogt, H., Hofmann, B. y Getz, L. (2016). The new holism: P4 systems medicine and the medicalization of health and life itself. *Medicine, Health Care and Philosophy*, *19*(2), 307-323. https://doi.org/10.1007/s11019-016-9683-8

Wang, T-F., Li, A., Garcia, D. (2018). Managing thrombosis in cancer patients. *Research and Practice in Thrombosis and Haemostasis*, *2*(3), 429-438. https://doi.org/10.1002/rth2.12102

Weber, B. (2018). Life. In Edward N. Zalta (ed.), *The Stanford Encyclopedia of Philosophy*. https://plato.stanford.edu/entries/life

Weiler, H., Isermann, B.H. (2003). Thrombomodulin. *Journal of Thrombosis and Haemostasis*, *1*(7), 1515-1524. https://doi.org/10.1046/j.1538-7836.2003.00306.x

Westfall, R. S. (1977). *The Construction of Modern Science: Mechanisms and Mechanics*. New York: Cambridge University Press.

Wilson, C. (1995). *The Invisible World: Early Modern Philosophy and the Invention of the Microscope*. Princeton, NJ Princeton University Press.

Wilson, R. A. (2005). *Genes and the Agents of Life: The Individual in the Fragile Sciences*. New York: Cambridge University Press.

Winegrad, S.(1984). Regulation of cardiac contractile proteins. Correlations between physiology and biochemistry. *Circulation Research*, *55*(5), 565-574. https://doi.org/10.1161/01.RES.55.5.565

Wolfe, C. T. (2012). Chance between holism and reductionism: Tensions in the conceptualisation of life. *Progress in Biophysics and Molecular Biology*, *110*(1), 113-120.

Wolkenhauer, O., Mesarović, M. (2005). Feedback dynamics and cell function: Why systems biology is called systems biology. *Molecular BioSystems*, *1*(1), 14-16. https://doi.org/10.1039/B502088N

Wolkenhauer, O., Auffray, C., Jaster, R., Steinhoff, G., *et al.* (2013). The road from systems biology to systems medicine. *Pediatric Research*, *73*(2), 502-507. https://doi.org/10.1038/pr.2013.4

Woods, S. (2017). Holism in healthcare: Patient as person. In T. Schramme and S. Edwards (eds.), *Handbook of the Philosophy of Medicine* (pp. 411-427). Dordrecht, NL: Springer.

Zwicker, J. I., Furie, B. C., Furie, B.(2007). Cancer-associated thrombosis. *Critical Reviews in Oncology/Hematology*, *62*(2), 126-136. https://doi.org/10.1016/j.critrevonc.2007.01.001