Revista de Saúde Pública
ISSN: 0034-8910
revsp@usp.br
Universidade de São Paulo
Brasil

Almeida-Filho, Naomar
Towards a unified theory of health-disease: II. Holopathogenesis
Revista de Saúde Pública, vol. 48, núm. 2, abril, 2014, pp. 192-205
Universidade de São Paulo
São Paulo, Brasil

Rev Saúde Pública 2014;48(2):192-205

Artigo Especial

DOI:10.1590/S0034-8910.2014048005196

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Towards a unified theory of health-disease: II. Holopathogenesis

Para uma teoria unificada da saúde-doença: II. Holopatogênese

ABSTRACT

This article presents a systematic framework for modeling several classes of illness-sickness-disease named as Holopathogenesis. Holopathogenesis is defined as processes of over-determination of diseases and related conditions taken as a whole, comprising selected facets of the complex object Health. First, a conceptual background of Holopathogenesis is presented as a series of significant interfaces (biomolecular-immunological, physiopathological-clinical, epidemiological-ecosocial). Second, propositions derived from Holopathogenesis are introduced in order to allow drawing the disease-illness-sickness complex as a hierarchical network of networks. Third, a formalization of intra- and inter-level correspondences, over-determination processes, effects and links of Holopathogenesis models is proposed. Finally, the Holopathogenesis frame is evaluated as a comprehensive theoretical pathology taken as a preliminary step towards a unified theory of health-disease.

DESCRIPTORS: Health. Disease. Health-Disease Process. Comprehensive Health Care. Holistic Health.

RESUMO

Este trabalho apresenta uma abordagem sistemática para a modelagem de várias classes de enfermidade-moléstia-doença, designada como Holopatogênese. Holopatogênese é definido como um processo de sobre-determinação de doenças e condições relacionadas, tomadas como um integral, compreendendo facetas selecionadas da saúde enquanto objeto complexo. Em primeiro lugar, o marco conceitual da Holopatogênese é apresentado como uma série de três interfaces significativas: biomolecular-imunológica, fisiopatológico-clínica e epidemiológico-ecossocial. Em segundo lugar, proposições derivadas da Holopatogênese são introduzidas a fim de permitir o desenho do complexo doença-enfermidade como uma rede hierárquica de redes. Em terceiro lugar, propõe-se uma formalização de correspondências intra- e inter-nível, processos de sobredeterminação, efeitos e laços componentes da Holopatogênese. Finalmente, o modelo Holopatogênese é avaliado como uma patologia teórica compreensiva tomada como passo preliminar para uma teoria unificada de saúde-doença.

DESCRITORES: Saúde. Doença. Processo Saúde-Doença. Assistência Integral à Saúde. Saúde Holística.

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Received: 10/19/2013
Approved: 1/7/2014

Article available from: www.scielo.br/rsp

INTRODUCTION

Several authors[1,13-14,41,45,52,68-69,74,82,84] have emphasized the importance of new theoretical models articulated into broader, comprehensive scientific paradigms, needed for understanding concrete health problems and developing efficient technologies to solve them.[18,27,53] Dominant approaches to theory building of health-disease processes and phenomena, such as evolutionary biology[12,20,30] or theoretical pathology,[29,36,44,54,77] still reinforce reductionist, linear models of disease. Indeed, objects of knowledge of health-disease-care have been defined poorly and inadequately, because conventional theoretical frameworks do not take into account holism and complexity.[76]

In this context, subdisciplines of applied human biology have claimed priority to define health-disease as a scientific object. Molecular biology takes genome and proteome as the only valid themes of research, arguing that all other levels of pathological processes flow from basic molecular and biochemical systems.[21,37,81] Histopathology and immunology demand the centrality of tissular or intra-systemic levels in pathogenesis, given that lesions and alterations constitute causes of signs and symptoms that supposedly define what disease is.[27,36] Physiopathology, assigned as the basic clinical science, invoke unbalanced or pathological regulatory mechanisms to explain causality of diseases and, therefore, to dominate the knowledge object.[67,77] In each case, advocates reduce other fields and levels to their respective object and method, advertising their own as the only capable to produce scientifically valid knowledge.[44]

Along these lines, a reductionist concept of disease can be stated as follows:

> Disease is a defect in the molecular structure of cells, producing lesion at tissue level, resulting in alteration of function of organs and systems, which causes pathology, expressed objectively as signs and symptoms in individuals that, as cases accumulate additively in diseased groups, conform morbidity in populations and sickness in societies.

The influence of Cartesian mechanism is evident in this depiction.[41,44] In this approach, society and populations are reduced to the mere sum of individuals, whose bodies are taken as a functional set of systems and organs. Systems and organs are in turn reduced to structures of differentiated tissues formed by cell units, which are treated as biochemical micro-mills of molecules. Indeed, neo-Cartesian theories of disease can subsidize efficient technological solutions of limited scope, as exemplified by linear simulation models of cells and metabolic systems taken as a "virtual lab" to test new molecules with therapeutic purposes.[64,79] But the utility of such models is very restricted due to several reasons. To say the least, pathologies of major social, ecological or population impact surpass the molecular, subindividual and clinical realm and challenge the validity of classical reductionism as an approach to understand the nature of illness[66] and disease.[22,38]

Due to the dependence of these models, theories and approaches upon their own validation patterns, conceptual validity is limited to the respective level of pathogenesis. Indeed, the holistic complex nature of health-related objects such as disease has been dealt with inadequately in scientific practice.[1-5,8,18,31,35,38,46,73] The reduction of complexity of health-disease processes to unidimensional concepts related to molecular and subindividual biological levels – as mutations, lesions, microorganisms, clinical causes and the like – has led to a double drawback. On the one hand, neo-Cartesian reductionism prevents a better understanding of phenomena and processes related to bio-socio-environmental interactions.[25] On the other hand, linear approaches neglect multiple properties that define disease and health as a plural and multidimensional complex that requires rigorous scientific investigation.[1,6,10,19,38]

To overcome reductionism, contemporary epistemologists[16,71] interested in health as a scientific object propose that disease belongs to a set of phenomena defined by non-linear dynamics, interconnected with many different systems, themselves at distinct structural levels.[31,34] As a complex of phenomena related to life, health, cure and care, disease-illness-sickness may be formalized as a system of states.[13,15-17,28,45,47,50,67-69,72-74,78]

As reviewed elsewhere,[5] complexity analysis has often been used in research designed to study hierarchical levels and dynamic interactions in health. In this connection, either in the artificial intelligence domain,[75] in the bio-molecular field[76] or in the ecological sphere,[31,55] new analytical tools and mathematical devices are certainly welcome to model health-disease complexity. Although not yet hegemonic in the health field, this scientific approach is more pertinent for considering complex systems into data analysis of pathogenesis and associated events.

Given the growing awareness of the role of complexity in nature and in history, key questions are at stake: What is the acceptable scope for contemporary theories of health-disease? Should they be catalogues of risk factors or clinical etiology profiles? Should they afford to be mere letters of intent for just another modeling of agent, host and environment? Would researchers continue insisting in straightforward thin thinking, satisfied with engineering expensive (but unreliable) magic bullets or with manufacturing smart biocards? What should be the role of biomolecular markers

interacting with complex environmental contexts in these explanatory frames? How social determination and cultural diversity could be integrated into these theoretical models?

In this series of articles,[8] we assume that disease-illness-sickness should be studied as a composite, synthetic object that makes sense only in its integrity. In order to pursue alternative theoretical strategies such as complex modeling of health-disease phenomena through non-linear, comprehensive, holistic models, I have proposed mapping disease as a special kind of ontological object that depends on heuristic substrates for its constitution.[4,6] Conceptually and epistemologically, a general theory of health does not stand without "special theories" of disease. Therefore, a restricted theory of disease and related conditions is needed to approach the many facets, manifestations and expressions of such complex object of knowledge.

Following up on such preliminary accounts, in this article, I present in a more systematic fashion a framework for modeling several classes of illness-sickness-disease, named as Holopathogenesis (HPG) theory. First, assumptions, levels and components are discussed as a conceptual background to HPG, needed for supporting definitions of significant interfaces between biomolecular and immunological, physiopathological and clinical, epidemiological and ecosocial realms. Second, a series of propositions derived from HPG is introduced in order to allow drawing the disease-illness-sickness complex as a hierarchical network of networks. Third, a formalization of the intra- and inter-level correspondence, over-determination, effects and links of HPGT models is proposed. Finally, the HPG frame is evaluated as a comprehensive theoretical pathology taken as a preliminary step towards a unified theory of health-disease.

Axiomatic background

Given the baseline scenario, disease is an object ideally construed in its broader configuration, because different facets or angles give access to it, although none of such angles by itself gives access to the object in its entirety.[74] In this regard, disease should be considered as, simultaneously, cluster component of ecosystem structures, chain of sensitive points in a conditioned network, state resulting from a web of determined biological mechanisms, outcome of multiple causes or relationships that generate risk.[26] But disease also has meaning, with a strong symbolic, metaphorical component, being sickness its representation in the realm of social relations and illness its subjective, intimate, personal manifestation.[40,42]

As a conceptual tool, the disease concept can be approached as both an ontological and a heuristic model-object.[24,28,39] In this framework, mutant genes and altered metabolism are ontological models of disease designed to refer to events and phenomena of pathology or disease. In turn, immunogenic models and homeostatic systems comprise heuristic models because they represent explanatory sets of determinants or causal processes.

The phenomenological domain for any given science, defined as an empirical field, may be devised as planes of emergence and corresponding levels of organization (or complexity), following patterns that depend upon the nature of the research object.[49] Such a diversity of levels and planes allows for coupling distinct disciplinary fields, corresponding to hierarchical interfaces, each with particular validation rules and determination models. For the core object of health sciences, Samaja[70] (2000, p. 96) outlines four value-spaces: bio/social, social/cultural, economic/societal, ecological/political. These orders can be condensed into two significant hierarchical orders – bio-individual and socio-cultural, which are composed by levels and interfaces with varied degrees of specificity. The bio-individual hierarchical order (Biho) is a set of levels of occurrence of health-disease phenomena taken as material effects of biological environmental determinants. The ordering of this set, from the least to the most complex level, is as follows:

Biho = molecule>->cell>->tissue>->organ>->system>->organism >->group>->population >->environment

Regarding biological organisms belonging to the human species, primates commonly designated as "human beings" who are capable of creating and operating language, culture and technology, one of the tiers of this order is superimposed to other possible orders, such as the symbolic order. The tier organism-group-population-milieu may be read as subject-family-society-culture, forming a sociocultural hierarchical order (Scho), such as:

Scho = molecule>->cell>->tissue>->organ>->system>->subject >->family>->society>->culture

Figure 1 presents a visual diagram that allows comparison between the two hierarchical orders, composed by contiguous planes. A superimposition of subindividual levels is evident. However, replacing the individual organism by the human subject changes the character of each supra-individual plane of emergence. For example, given the symbolic significance of parental links, a family is more than a group of individuals. Although formed by populations, considering political aspects of social relations, societies should not be reduced to mere demographic aggregates. Finally, there is a fundamental contradiction between environment and culture, as far as nature is radically and continuously transformed by the *praxis* of the human species.

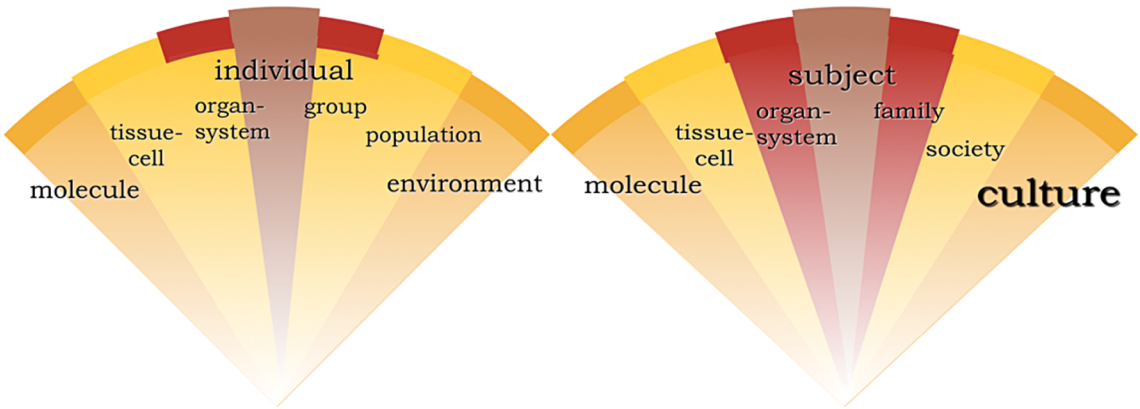

Figure 1. The biodemografical and sociocultural hierarchical orders.

In so-called health sciences, Biho axis is typically overvalued, underestimating the Scho axis in its heuristic function and therefore scientific validity. Respectful of the complexity and wholeness of phenomena of life and health, we ought to integrate levels/facets of both hierarchical orders into a totalizing, integral, hierarchical set of planes of occurrence. Merging Biho and Scho orders generates a 7-uple composite scale of disease-health states:

I. [MSt] *Micro-structural* – molecule to cell

II. [MSy] *Micro-systemic* – metabolism and tissues

III. [SbI] *Subindividual* – body systems

IV. [Cas] *Individual* – clinical cases

V. [PaR] *Epidemiologic* – population at risk

VI. [EcS] *Environmental* – ecosystems

VII. [SoC] *Symbolic* – semeiologic and cultural

The concept of 'health-disease integral' (HDI) was proposed and analyzed previously.[8] To advance further, consider the following set of assumptions:

1. HDI refers to the general set of health-disease-care phenomena and processes affecting human bodies, human subjects and human populations.

2. HDI is concretely expressed as a complex Disease-Illness-Sickness (cDIS) in levels and components because health-disease-care phenomena and processes occur simultaneously at different scales of reality.

3. Health-disease-care phenomena and processes exist if, and only if, they are determined in a given way; therefore, cDIS does not exist *per se*.

4. Holopathogenesis (HPG) engenders cDIS as an integral object-model.

5. HPG is a system of states, ruled by processes of over-determination and emergence, represented by a *net-network* (networks of networks).

Etymologically, the concept of 'holopathogenesis' is herewith defined as a network or a set of processes of over-determination (*genesis*) of diseases, sicknesses and conditions related (*pathos*) taken as an integral, complex, total object (*holos*), comprising distinct facets, manifestations and expressions of such a complex object of knowledge. Built around a class of peculiar heuristic object-models, HPG operates at distinct hierarchical levels of complexity, dependent of its ontological and symbolic subject matter.

Conceptual framework

Axiomatically, no disease is autonomous and discrete in ontological terms; HDI exists only if determined. However, the ways HDI is determined are dependent upon the facet/level of the object-model considered. The representation of distinct facets of a total ontological object demands corresponding but specific heuristic models.[16]

HPG models are polisemic, multifaceted, plural, simultaneously ontological and heuristic objects. As such, they cut across distinct patterns and domains referring to different components and levels of complexity, constructed for (and by) reference to phenomena produced (and referenced) by basic health sciences, simultaneously bioclinical and sociocultural. Biological models of determination have structural or systemic components and processes, operating on different levels (molecule, cell, tissue, organs, and systems).[54,77] Clinical models of disease are based on mechanistic or causal models referred to the individual level.[27,65,67] Epidemiological and ecosocial pseudo-probabilistic models are drawn from population and environmental levels.[19,43,46,60] Linguistic and symbolic models of health-sickness-care are anchored in the realm of language and culture.[40,63]

Following the composite scheme of hierarchical dimensions proposed above, HPG models are formed by a set of seven planes of occurrence, corresponding to different *f*-facets or sub-spaces and levels of pathogenesis. At the microstructural dimension MSt, HPG is expressed concretely as molecular or cellular phenomena. HPG is manifested at a microsystemic MSy dimension, in the metabolism or tissue; at subindividual levels (SbI), as physiopathological processes in organs or body systems; at the clinical dimension in individual "cases" (Cas), at the epidemiological dimension of the population at risk (PaR), in environmental interfaces of ecosystems (EcS), in symbolic or sociocultural grounds (SoC).

Each level of HPG implies components of a given class of determination, with its corresponding HDI-states. In this model, pathological processes, health states and correlates are determined by the set of determinants (causes, factors, determinants, over-determinants or emergent forces) or by the articulate action of different determinant sets, and by the values assumed by those variables *vis à vis* resistance (capabilities, resilience, strength, among others) of the affected dimension (cell, organ, body, group, milieu, among others).

HPG results from "agonistic" dyads formed by the tension between holopathogens and body defenses as components of over-determination networks, which generically can be distributed in two sub-groups, pathogens and resistors. The first group is formed by determinants that promote the occurrence of pathological components, which we name as holopathogens (H), and the second one by determinants that raise resistance to disease spread or avoidance of emergency of non-health states in the system,[51,52] that we designate as resistors (R). Therefore, there is a dynamic tension, expressed as [H*R], between holopathogens and resistors as antagonistic force-mechanisms.

Given the predominance of negative expressions in established disease notations, let AR = [1 - R] as anti-resistors. Thus, consider the following classes of vulnerable states related to disease as AR:

(a) alteration – a

(b) debility – d

(c) weakness – w

(d) susceptibility – s

(e) vulnerability – v

(f) fragility – fg

(g) frailty – fr

Concepts of general susceptibility have been widely used in the fields of medicine, epidemiology, biology, ecology, engineering, and toxicology, implying different emphases that relate to the underlying perspectives and methods of each field.[52,58] The same is true for vulnerability and fragility concepts, which already have a recognized theoretical status in ecosystems research[55] and in social determination models of disease.[33,56] On the other hand, for decades already, frailty has been used as an operational tool for studying the relationship of disability related to aging[32] and psychosocial aspects of health inequality.[9]

In addition to these concepts, other designations to particular conditions of vulnerability can be applied to subindividual dimensions of disease-health, such as alteration, debility and weakness, absent from the specialized literature. In this proposal, the term 'alteration' refers to modifications in the microstructure of organic units that, at the molecular and cell levels, lead an anomaly to become abnormal, or a defect. The terms 'debility' and 'weakness' refer to similar processes corresponding respectively to the microsystemic and subindividual HDI dimensions.

Given these definitions, the notion of HPG outcomes may be introduced into the scheme. Consider the following notation for HPG outcomes:

(a) defect – Def

(b) lesion – Les

(c) pathology – Pat

(d) disease (or disorder) – Dis

(e) risk – Rsk

(f) hazard – Haz

(g) sickness – Sik

For the different dimensions of HPG, concepts related to outcomes (O) of typical pathological states, as well as to factors of the sub-groups of HPG forces, respectively H and AR (anti-resistors), are presented in the Table.

This scheme may be useful as a background for a generalized model of the complex Disease-Illness-Sickness (cDIS) as a network of determination processes of phenomena pertaining to health-disease-care in human populations. cDIS is composed by antagonistic relations of pathogenesis and salutogenesis, at distinct subspaces or levels of occurrence, articulated by 'structural coupling',[49] designated as holopathogenesis.[6] This approach supports an primary definition of disease in terms of complexity theory:

> 'disease' is a complex, plural and multifaceted object, being *simultaneously* defect, lesion, alteration, pathology, disease, risk, damage, hazard, illness; ruled by a logic of complexity, subject both

Table. Dimensions and correlates of Holopathogenesis.

Dimension	**O:** outcome	**H:** holopathogen	**AR:** anti-resistor
MSt	**Def** defect	**α** anomaly	**a** alteration
MSy	**Les** lesion	**δ** defect	**d** debility
SbI	**Pat** pathology	**λ** lesion	**w** weakness
Cas	**Dis** disease (disorder)	**κ** cause	**s** susceptibility
PaR	**Rsk** risk	**ϕ** factor	**v** vulnerability
EcS	**Haz** hazard	**χ** condition	$\mathbf{f}_g$ fragility
SoC	**Sik** sickness	**σ** meaning	$\mathbf{f}_r$ frailty

MSt: Micro-structural; MSy: Micro-systemic; SbI: Subindividual; Cas: Individual; PaR: Epidemiologic; EcS: Environmental; SoC: Symbolic.

to the bio-demographical order and to the sociocultural order; structured as a 'network of networks', in distinct levels.

As it is proposed to tackle theoretical and methodological problems normally avoided by linear and fragmented traditional paradigms of pathogenesis, such a conceptual framework requires the integration of several disciplinary approaches into an articulated and interactive research endeavor. These interdisciplinary subspaces, and respective determination rules, may be represented as contiguities or correspondences between object levels, organized as interfaces: biomolecular/ /immunological (molecule to cell), physiopathological/ /clinical (organ/system to body), epidemiological/ /ecosocial (population to species). Certainly, the symbolic order permeates all sets and subspaces.

In this framework, the HPG concept is construed as a special kind of heuristic object-model, operating in different hierarchical levels of complexity, simultaneously dependent of ontological and symbolic substrata.[71] Such a model can be applied to different classes of HDI-states, which have one or more of the facets referred to above more developed than others may. Each of the types or groups of disease may have a more or less "holopathogenic" prototypical format, with their respective semantics and rules of syntax between assumptions, levels and dimensions. Networks of simultaneous processes of 'overdetermination' generate dynamic pathways of pathogenesis. Elsewhere,[7] I and a colleague have proposed the category of overdetermination as useful for helping understanding the chain of multiple components, factors and vectors that conform cDIS as a scientific object of knowledge.

Modeling holopathogenesis

Let 'f' be any given facet of cDIS.

Therefore, cDIS may be partially and provisionally defined as a set of f-facets of pathogenesis, as

$$\text{cDIS: } [f\text{MSt}], [f\text{MSy}], [f\text{SbI}], [f\text{Cas}], [f\text{PaR}], [f\text{EcS}], [f\text{SoC}]... [f]\text{'s}$$

The production of knowledge about pathogenesis regarding only one of the f-facets, assuming its isolation from the other facets, will necessarily be partial and simplistic. Every f-facet combination and its respective outcome compose a partial ontological model of disease, or a pathogenesis submodel of HDI. Therefore, in the light of the framework outlined above, simple, straightforward models are destined to fail as a source of knowledge needed for effective interventions in health situations.

Incomplete definitions of this first HDI ontological model might include the summation of f-facets as if they all pertain to the same class and order, as in

$$\text{DIS} = \Sigma(f)$$

or the simple sum of components of pathogenesis, as in Cartesian modeling of

$$\text{DIS} = (\text{Def} + \text{Les} + \text{Pat} + \text{Dis} + \text{Rsk} + \text{Haz} + \text{Sik})$$

Beyond such partial modeling, let us advance for a second-level definition of disease as a complex model, as cDIS, respectful of the diversity of outcomes and facets and the integrity nature of the model-object disease:

$$\text{cDIS: } [f\text{MSt(Def)}], [f\text{Msy(Les)}], [f\text{SbI(Pat)}], [f\text{Cas(Dis)}], [f\text{PaR(Rsk)}], [f\text{EcS(Haz)}], [f\text{SoC(Sik)}]...$$

from which we derive a first general holopathogenesis (HPG) model:

$$\text{HPG: } [f\text{MSt(a}\rightarrow\text{Def)}], [f\text{Msy(d}\rightarrow\text{Les)}], [f\text{SbI(l}\rightarrow\text{Pat)}], [f\text{Cas(k}\rightarrow\text{Dis)}], [f\text{PaR(f}\rightarrow\text{Rsk)}], [f\text{EcS(c}\rightarrow\text{Haz)}], [f\text{SoC(s}\rightarrow\text{Sik)}]...$$

In this model, ($\rightarrow$) is the general notation for links between determinant and outcome at all levels, components and patterns of holopathogenesis, such as:

(a) microstructural genetic models yield molecule or cell anomalies α leading to cell damages Def, or (a→Def);

(b) microsystemic models have metabolic deviations or tissue defects δ producing lesions Les, or (d→Les);

(c) physiopathological models have subindividual processes manifested as lesions λ which are conditions for producing pathologies Pat, or (l→Pat);

(d) clinical models are built based on organ damage or body system failure known as causes κ for cases of diseases (or disorders) Dis, or (k→Dis);

(e) epidemiological models are formed by exposure or risk factors ϕ determining risks Rsk, or (f→Rsk);

(f) ecosystem health models are made of possibility components or conditions χ leading to disbalanced environmental hazards Haz, or (c→Haz);

(g) semiotic models operate as the interplay of signs/meanings/practices σ engendering sickness Sik on symbolic grounds SoC, or (s→Sik).

This possibility of a system of sub-spaces is graphically (and metaphorically) represented in Figure 2 as a patchwork of networks, fitting a descriptive modeling of, say, determination of depression.

If HPG subspaces were strictly orthogonal, the dynamic evolution of each dimensional sub-model would be independent of the others. Yet, we could overwrite a second general holopathogenesis model with the addition of all pathogenesis sub-spaces considered, thus yielding a less incomplete cDIS model, as in:

$$cDIS = MSt \oplus MSy \oplus PPt \oplus Cas \oplus PaR \oplus EcS \oplus SyC,$$

where the symbol $\oplus$ expresses that, in the mathematical formalization of the HPG object, each one of these HPG components should be defined in a different subspace. This symbol is usually employed to indicate an operation of 'direct sum', which acts on elements belonging to orthogonal subspaces, and the result of the operation is defined in the space formed by the Cartesian product of the two sub-spaces.

The corresponding HPG model can be written as follows:

$$HPG: [f\text{MSt}(a\rightarrow\text{Def})] \oplus [f\text{Msy}(d\rightarrow\text{Les})] \oplus [f\text{SbI}(l\rightarrow\text{Pat})] \oplus [f\text{Cas}(k\rightarrow\text{Dis})] \oplus [f\text{PaR}(f\rightarrow\text{Rsk})] \oplus [f\text{EcS}(c\rightarrow\text{Haz})] \oplus [f\text{SoC}(s\rightarrow\text{Sik})]$$

In this notation, the brackets [•] indicate the dynamic evolution within each dimension. Inside the parenthesis, different factors of H*R subsets that alter the complex system of pathological states cDIS are pointed out. The graphical representation of this model as a linear network, superimposed by the composite hierarchical order of dimensions, holopathogens and outcomes, is in Figure 3.

As concerned with the formalism proposed herewith, physiopathological models purely additive imply subspaces necessarily orthogonal for the different dimensions of HPG. None of such incomplete models is representative of complexity because they do not allow inter-articulation of the respective submodels. Models of this kind are a partial and incomplete representation of the complexity of the DIS system of states because they do not allow the articulation among the submodels of each dimension of HPG.

Assembling knowledge generated by decades of research on the determination of each of the pathogenesis submodels, this model is represented in Figure 4 as a network of networks modeling the overdetermination of depression.

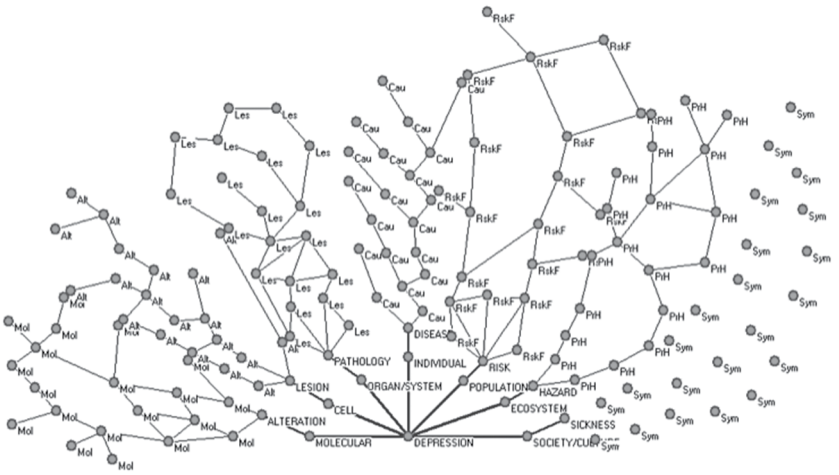

Figure 2. The complex Disease-Illness-Sickness as a patch-network.

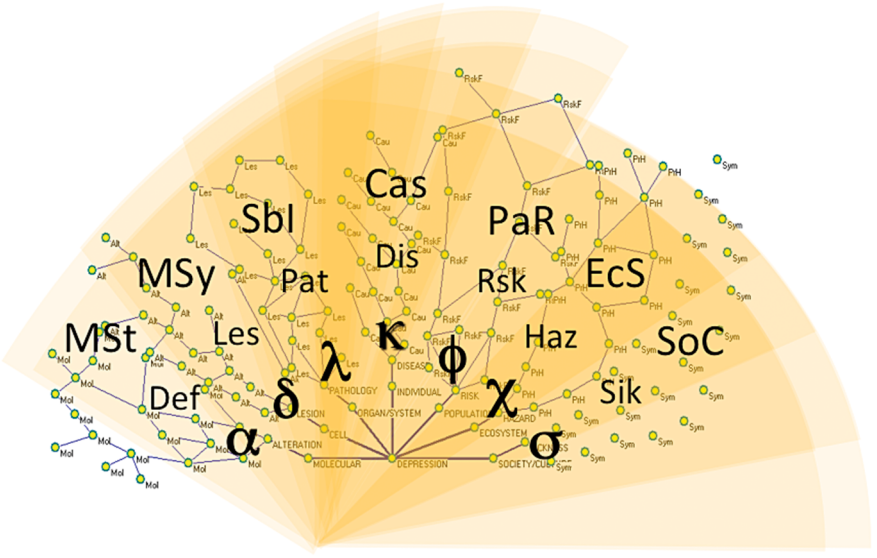

Figure 3. The complex Disease-Illness-Sickness as a hierarchical network.

More accurate and efficient modeling of cDIS implies the projection of determinant networks over subspaces distributed as convergent trajectories of determination on a holospace. As seen above, the ways cDIS is determined are related to the facet/level of the object-model. In this model, distinct facets of a complex ontological object demand corresponding interconnected heuristic models, articulated around a common disease core.[8,57]

Furthermore, HPG should be an expression of complexity for considering the diversity of intraclosure non-linear connections among the submodels Def, Les, Pat, Dis, Rsk, Haz, and Sik, applicable to several well-studied pathological conditions. Indeed, an essential issue for the HPG structure is the interconnection between the different submodels because components that are outcome of one submodel may become determinant for another one. A given pathology (or defect, disorder, lesion, disturbance or abnormality) that provokes damage or failure in a target-organ or body system may act as a cause of clinical disease. The increase of clinical cases and geographical concentration in a given population may represent a risk factor for communicable diseases. This argument is inspired in Samaja's analysis of social reproduction of health situation.[70]

Therefore, the general systemic-dynamic model of HPG has to be reformulated in terms of nature of the structural coupling between sub-models of pathogenesis.

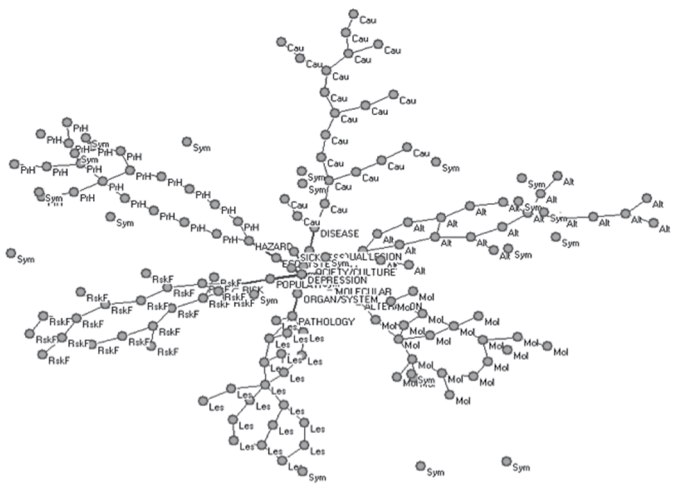

Figure 4. The complex Disease-Illness-Sickness as a net-network.

This can be put forward in two different but complementary procedures.

The first approach is to replace the sign of sums on orthogonal subspaces ⊕ by the sign of interactive connections (⇔) amongst the different dimensions of HPG, resulting in:

$$\text{HPG: } [\text{MSt}(a \rightarrow \text{Def})] \Leftrightarrow [\text{Msy}(d \rightarrow \text{Les})] \Leftrightarrow [\text{SbI}(l \rightarrow \text{Pat})] \Leftrightarrow [\text{Cas}(k \rightarrow \text{Dis})] \Leftrightarrow [\text{PaR}(f \rightarrow \text{Rsk})] \Leftrightarrow [\text{EcS}(c \rightarrow \text{Haz})] \Leftrightarrow [\text{SoC}(s \rightarrow \text{Sik})]$$

In this line, we may also consider the HPG model as composed by *f*-i sub-models that conform specific classes of determinants, as follows:

$$\text{HPG: } [f_1\text{MSt}(a \rightarrow \text{Def})] \Leftrightarrow [f_2\text{Msy}(d \rightarrow \text{Les})] \Leftrightarrow [f_3\text{SbI}(l \rightarrow \text{Pat})] \Leftrightarrow [f_4\text{Cas}(k \rightarrow \text{Dis})] \Leftrightarrow [f_5\text{PaR}(f \rightarrow \text{Rsk})] \Leftrightarrow [f_6\text{EcS}(c \rightarrow \text{Haz})] \Leftrightarrow [f_7\text{SoC}(s \rightarrow \text{Sik})]$$

Figure 5 is a graphical representation of this model, inter-determined by a complex network of networks composed by a non-hierarchical, interconnected order of dimensions, holopathogens and outcomes. Many of the links internal to the sub-models in the sub-spaces belong to or are connected to other chains of determination, in different levels or domains. Such relations are articulated by 'structural coupling', generated by simultaneous processes of 'over-determination' of the different classes of cDIS.

The second approach to this modeling is to recognize that the sub-spaces defined by the different dimensions of HPG are not strictly orthogonal, but share determinants and components of the other sub-spaces. This situation is implicitly recognized in the Table, where concepts as alteration and lesion appear in different HPG spaces, either as a HDI-state characteristic of the cDIS, or as a determinant of disease-health states in the subsequent level. Different symbols are taken as reference for such concepts since that, within the HPG model, they play roles that are also distinct in the dynamic evolution of the system.

Because they are nearly orthogonal, the HPG subspaces are interrelated in such a way that the projection of subspace (i) on the other subspace (j) does not distinguish the individual effects of the subsets H_i and R_i on the pathogenic state of j level. This influence will be then exercised through a projection of the set of these determinants, which can be defined, at a first approach, by the values assumed by the state variable of i level.

Indeed, the challenge of offering an appropriate inter-projection of effects at different scales in modeling health-disease phenomena is a non-trivial demand to the several attempts of approaching complex systems. In general, the inter-level projection can be formally written that:

$$Vt_i = f_i\,(H_i, R_i)$$

where VTi indicates the temporal variation of the pathological state of the i-th HPG dimension, and f_i is a function of the antagonistic subsets H_i and R_i as defined above. The interrelation among different dimensions i and j of HPG is expressed by a projection operation:

$$M_{ij}: (\{H_i\}, \{R_i\}) \rightarrow (\{H_j\}),$$

in such a way that the pathological state of the i-th level over determinates the pathological factors of the j level. The great challenge to the proposed framework relies exactly in the determination of the M_{ij} operations of projection.

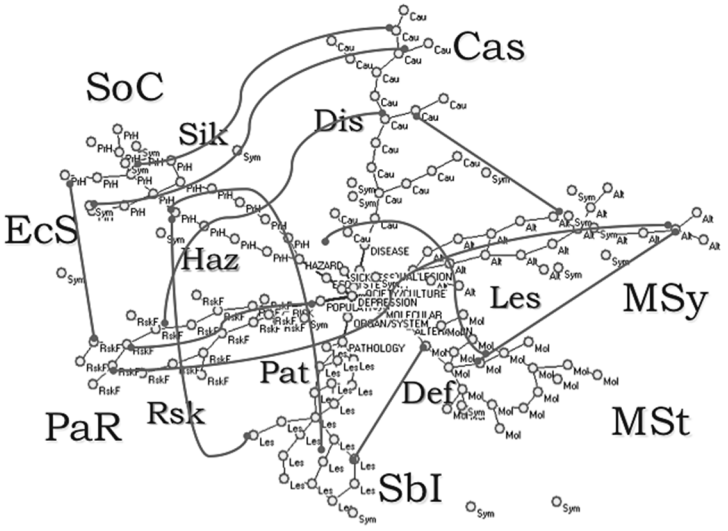

Figure 5. inter-determination among sub-spaces in the complex Disease-Illness-Sickness.

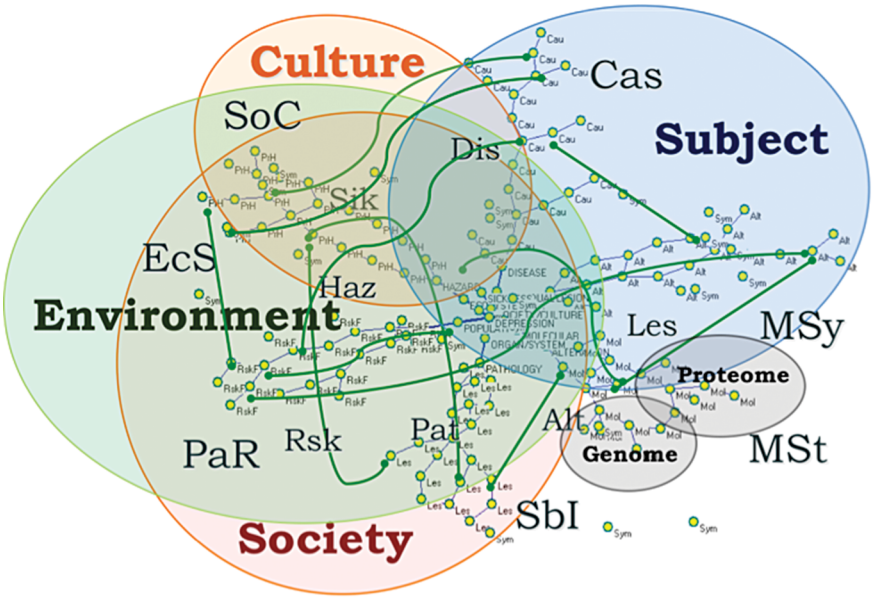

Figure 6. Research areas of interest in the complex Disease-Illness-Sickness.

The concrete forms of these operations will be drawn out of available empirical data in each dimension/level/facet of HPG, as much as from the accuracy with which the different models will be able to reproduce and predict situations observed in concrete health situations. In this regard, HPG mapping also permits the visual representation of the influence of research areas and categories on the cDIS model. This is illustrated in Figure 6, where it is graphically demonstrated how limited in scope and relevance are biomolecular research targets as compared to environmental and sociocultural conditions for the over-determination of health-disease outcomes.

Finally, HPG can be regarded as exemplary of a fractal structure, since each of its components can be explored as an entire whole system in itself. In this model, the *f*-facets can be considered as fractal dimensions of the holopathogenesis concept if we consider that they are each a proper determined model-object.

Considering fractality as reiteration of patterns across levels, by definition the heteronomic nature of the submodels apparently stands against modeling pathogenesis as a fractal phenomenon. Nevertheless, since each dimension is ruled by H*R antagonistic relations, one could identify in this general dynamic pattern a fractal structure in the overdetermined cDIS system.

Toward a new research agenda

In the conclusion of his book Epistemology of Health, Samaja[71] comments that holopathogenesis theory might be considered as a formal ontology of evolution, self-organization, complexity, life, society and culture, needed for a unified theory of health-disease-care. The great advantage of the HPG approach lies on the possibility of allowing a description of special features (for instance, of a tissue, of a peculiar immunological system, of a local population distribution, of a health program or a care system) and an analytical understanding of the whole explanatory model, much richer in functions and details than those obtained by partial differential equations applied to fragmented sections of a piecemeal chain of causation.

Research focusing on complex model-objects generated by unified theoretical frames has transformed important scientific fields of today (such as "the market" for economy, "the environment" for ecology, "cosmos" for astrophysics and "life" for biology). Creative cross-disciplinary efforts aimed at producing synthetic models can be used to construct complex objects of this kind. Particularly with regard to concrete processes of the health reality, better dialogue and articulation across the different health disciplines may be a secondary gain to consider in developing HPG research strategies.

As stated in the Introduction, the present proposal is a theoretical research endeavor that, nevertheless, is intended to produce a systematic approach with immediate practical outcomes. Beyond validity of HPG as a theoretical construct, dimensions and components must be translated into descriptors to allow assessment of its operational validity as a complex modeling device. In this regard, the definition of holopathogens across the planes of occurrence (subindividual, individual and supraindividual), as presented in the Table, may

be completed by the equivalent descriptors, as follows (Holopathogens/Descriptors): anomaly/state; defect/condition; lesion/sign or symptom; cause/status; factor/indicator; condition/situation; meaning/metaphor.

The development of HPG-based strategies may pave the way for the adoption of measures much more effective for the control of disease and therefore for the promotion and protection of health than the use of straightforward sequencing of molecules or bio-information particles, naïve narrative therapies or conventional techniques of strategic planning. Conventional proposals of modeling disease-health states have typically used formal logic and linear equation systems, which can vary from a standard deterministic approach to a modified conditional stochastic formulation.[11,19,62]

Given the scheme sketched above, a prospective research agenda can be proposed. First, we need to advance by formalizing intra- and inter-level correspondences, effects and links of HPG models and submodels of prototypical classes of cDIS. Treatment of the following questions may be considered as intermediate goals: How to prepare the submodels for coupling into the general HPG models? How to conduct inter-level transduction within HPG models? How to operate the inter-correspondence of HPG models between distinct groups of pathology?

Second, we have to face the challenge of developing more refined diagnostic criteria and efficient tools for different classes of cDIS.[59,75] This implies tackling the following regional heuristics: What kind of syntax of inter-model articulation should be more feasible and efficient heuristically and of better fit *vis à vis* the HPG theory? Which HPG-derived nosological devices should be prompted for the analysis of co-occurrence of different classes of pathology known as comorbidity? Indeed, to conceptualize 'disease' in a way that respects its integrity and complexity, as possibly achieved by HPG modeling, may become one of the essential tasks for the health sciences in the near future.[18,26,31,35,73,76]

The third step is to elaborate, test and standardize HPG-oriented research protocols, applicable to distinct components and pathogenesis levels. In such a research program, every formal advance and instrumental development can be validated and tested for application regarding distinct classes of pathology. This includes graphical tools to visualize HPG conceptual mapping as well as computational tools that will be needed to operate HPG/FSTD research protocols, applied to the different groups of pathology. Eventually, methodological strategies and technological devices generated from HPG approaches are planned to be used for inter-sectorial and transdisciplinary research aimed at a more comprehensive, deeper understanding of health problems.[5,18,44]

Final comments

No doubt, it is time to ask fundamental questions such as "what is health?"[3,28] and "what is disease?".[65,83] These questions are in parallel to the problem of what life is, why it is organized the way it is and how and why entropic and interactive processes and agents threaten bio-processes and survival functions. Nevertheless, the rewards in terms of technological advancement for disease control strategies should be equivalent to the degrees of difficulty found in modeling complexity in health research.[11,19,23,35,43,46,60,62,73] Disease control in this sense is not the mere reduction of prevalence or incidence in exposed populations, or cure, healing and recovery in persons. It rather implies considering all known sets of sensitive points of the etiologic network bound to change towards becoming healthier. This will be crucial for developing more effective computer simulations in each case, and for engineering a new generation of knowledge-based technologies applied to the control of diseases and promotion of health.[26,76] To some extent, this means to design, apply and test technological solutions for HPG simulations, designing virtual models of Artificial Pathogenesis analogous to Artificial Life approaches.

In sum, this paper is about theory-building on health-disease-care, pursuing a comprehensive approach to death, dysfunction, pathology and suffering. However, the logic that rules complex, prospective objects such as cDIS is a multiple, non-linear and plural logic that cannot be expressed in simple coded form. Therefore, a regional epistemology, in Piagetian terms,[61] will be needed to build an applied theory of knowledge using maps as an essential device for HPG research. Generalized and unified theories such as HPG may be of vital importance as a source of heuristics and of semantic operators needed for understanding organization, evolution and determination of diverse groups of pathology.

Axiomatically, HPG includes assumptions formalized in logical-mathematical terms, allowing a multidimensional holodynamics of causation, determination and overdetermination of hierarchical structures. As a theoretical outline, HPG is translated by net-networks of overdetermination processes of health-disease phenomena, composed by antagonistic, non-linear relations of pathogenesis and salutogenesis, at distinct levels or subspaces. To be interpretable in biological, clinical and psychosocial terms, it may be formulated as an integral system of model-objects, including dimensions that are still absent although necessary for a rigorous understanding of the complexity of disease objects. That this understanding is feasible through HPG theory is our preliminary answer.

A generalized or unified theory of pathogenesis is indeed necessary for providing a valuable and justified frame of reference for a unified comprehensive theory

of health and of the living.[71] The broad understanding of pathogenesis pursued by HPG theory implies the possibility of studying and projecting the balance of both local and global dynamics in order to achieve different levels and definitions of health. Although not totally anew in applied theoretical biology, these questions are at present especially urgent in connection with the problems of development of bioinformatics and dynamic systems approaches applied to non-discrete, un-limited, fuzzy objects of knowledge such as the complex object of disease-health-care.

In the biomedical and social health fields, potential uses of fuzzy set logic have been proposed for clinical medicine[59,75] and for epidemiologic research.[48,80] Only recently, Sadegh-Zadeh and collaborators[68,69,75] have proposed a Fuzzy Set Theory of Health, as an approach critical to the notions of boundary and precision of formal set theory, which has been the logical ground to linear, categorical systems still prevailing in the analytics of modern science. Further explorations on this line of enquiry (forthcoming) will be needed to review, adjust and apply a unified theory of health and non-health objects based on fuzzy set logic.

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This study was supported by the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq – Process 302.600/2008-6 – Productivity grant).
The author declares that there is no conflict of interest.