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# Medical knowledge integration and "systems medicine": Needs, ambitions, limitations and options

Felix Tretter[a], Henriette Löffler-Stastka[b,*]

[a] Bertalanffy Center for the Study of Systems Science, Vienna, Austria
[b] Dept. of Psychanalysis and Psychotherapy, and Postgraduate Unit, Medical University Vienna, Austria

A R T I C L E I N F O

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A B S T R A C T

Medicine today is an extremely heterogeneous field of knowledge, based on clinical observations and action knowledge and on data from the biological, behavioral and social sciences. We hypothesize at first that medicine suffers from a disciplinary hyper-diversity compared to the level of conceptual interdisciplinary integration. With the claim to "understand" and cure diseases, currently with the label "Systems Medicine" new forms of molecular medicine promise a general new bottom-up directed precise, personalized, predictive, preventive, translational, participatory, etc. medicine. Our second hypothesis rejects this claim because of conceptual, methodological and theoretical weaknesses. In contrary, this is our third hypothesis; we suggest that top-down organismic systems medicine, related to general system theory, opens better options for an integrative scientific understanding of processes of health and disease.

## Preface

In our view, medicine today is confronted with several challenges: economy, lack of personnel, digitalization, etc., but from a scientific perspective "(dissociated) knowledge explosion" is the most urging challenge. Regarding these issues of knowledge analysis, we formulate three complex main hypotheses and sketch possible perspectives:

Our *first main hypothesis* is that the *knowledge domain* of medicine suffers from *hyper-diversity of data* compared to a low level of *conceptual* and *theoretical integration*. This also impairs efficiency of medical practice and education.

Our *second main hypoth*esis claims that even "(molecular) Systems Medicine" cannot bridge several traps and gaps of current *empiricist medical research programs.*

Our *third main hypothesis* s is a proposition for an integrative, but differentiated *multi-level macro-perspective* of a "clinical psycho-social organismal eco-systems medicine" that should essentially integrate qualitative clinical knowledge with molecular systems medicine on the basis of a conceptual multi-level systems framework of the organism-in-the-world.

More detailed empirical *science studies* could test these basically "knowledge philosophical" (epistemological) hypotheses.

## Diversified medical knowledge: more data, observations and actions than theory

Results in *philosophy and history of knowledge and science* show that optimal *knowledge progress* depends on the balanced interplay of empirical observations and theory [1]: thoughts and appearances ("Anschauungen") in the view of Immanuel Kant [2], observations connected by logics [3,4], data (or "empirics") and theory as *constructive realists/empiricists* [5] and protagonists of "Scientific Realism" see it [6,7].

### *Medicine as an empiricistic epistemic project*

In context of these epistemological findings, medical research appears insufficient as the empiricistic approach dominates an only poorly developed field of theoretical medicine, at least compared to physics with its "theoretical physics": For instance, there are no university chairs in Germany devoted to "theoretical medicine". This issue was already discussed in *Medical Hypothesis* [8]. At its best, medical progress in understanding *health, disease* and *treatment* is based on *hypotheses* and driven by *data* that are generated by rapidly developing technologies, for instance in the field of biochemistry and molecular biology.

The main epistemic object of medicine are *disease entities* which are identified by quantified observations that are characterized by

* Corresponding author at: Dept. of Psychoanalysis and Psychotherapy, Währinger Gürtel 18-20, 1090 Vienna, Austria.
*E-mail address:* henriette.loeffler-stastka@meduniwien.ac.at (H. Löffler-Stastka).

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symptom checklists and analyzed by multivariate statistics, thus providing *diagnostic categories* for classification of unhealthy states [9]. It is well known that disease categories are fuzzy concepts, an issue that was counter-balanced by rating scales for severity and by additional categories such as "preclinical" (or "subclinical") states, etc. Also *network medicine* (see below) does not really provide progress by cross correlations of gene expression patterns that are involved in comorbidity and that are expressed by graph theoretical methods of data analysis [10,11].

Regarding *treatment*, in context of the paradigm of *evidence-based medicine* (EbM) probabilistic decisions are made about *treatment effects* that imply the problem of logical decuction [12]. Although EbM prefers evidence which is based on randomized and controlled trials, it also accepts clinical experience, although qualitative knowledge in medicine is challenged [13].

However, at present descriptive-classificatory ICD and evaluative EbM overshadow the relevance of *mechanistic modeling of pathophysiology* as it was common in medical knowledge development until some decades.

In consequence, medicine suffers not only from *theory-experiment gaps* but also from other knowledge gaps such as the dominance of *experimental research* over *observational clinical medicine* as it was criticized already in 2003 by physiologist David Horrobin, one of the founders of "Medical hypothesis" [14]: For validation of laboratory knowledge, he suggested more integration of clinical knowledge. This view is in line with arguments of the dermatologist Jonathan Rees who highlighted the essential difference between biology and medicine that implicates overestimations of basic research regarding prospective results in clinical issues [15].

In conclusion, medicine has a heterogeneous and complex knowledge status within many taxonomies of the sciences as it is an *applied science*, uses *quantitative laboratory data* and *qualitative clinical data*, is based on *practical knowledge*, intends *rational choices* as well as it has to rely on *intuition*, and is *experience-based* and also oriented towards *consented algorithmic guidelines,* etc. [16–19]. Some authors even suppose medicine to be not only a science but also an *art* [20]. So, if medicine is a science: What is the disciplinary knowledge structure in medicine alike?

### *The disciplinary knowledge structure of academic medicine*

Regarding this critical and complex meta-view on medicine, a short sketch of the academic *disciplinary structure of medicine* should be made ("House of medicine"): the heterogeneous knowledge structure of medicine as the *science of health, disease* and *treatment* consists of medical science as a shell and clinical practice as the core. For example, interpreted in numbers, the famous university clinic Charité (Berlin) has 100 clinics and institutes, a specialization that can be discussed here only roughly [21]. This *complex disciplinary structure of medicine* is represented by a heterogeneously layered and partially hierarchical structure of scientific fields which can be identified by institutes and chairs, with more or less intense interrelations. Its structure, as it is presented here selectively by the sections "basic sciences", "preclinical (auxiliary) sciences" and "clinical sciences", can be experienced by the study of medicine in Germany, even if there are several educational programs established already that practice intersectoral bedside teaching: most university chairs are still characterized according to this structure. Some epistemological aspects are here mentioned too (Fig. 1):

(1). At a *first level* of medical science, like a ground floor, *biology* assisted by *physics* and *chemistry,* constitutes the basis as a *natural science*. Biology should play a central role but increasingly it is transformed into applied physics and – before all - chemistry.

(2). At a *second level*, *anatomy* as a human biological science of the *structures* of the organism and *physiology* as a science of *functional analysis* provide the basic knowledge for clinical medicine on the macro-, meso- and micro-level (e.g. *histology*) of the organism. Also functional, topographic and systematic anatomy is distinguished. Physiology shows an organ-centered diversification (brain, heart, etc.). Interestingly, physiology in the 1960 s and 1970 s had a strong direction towards cyber-systemic thinking but it was substituted increasingly by discoveries of biochemistry [22].

(3). On a *third level*, central preclinical disciplines such as *general* and *special pathology* can be found. Pathology, being composed by pathological anatomy and pathological physiology, also show signs of reduction to molecular biology and medicine – there are only a few (German) textbooks for students providing an integrated view, for instance between physiology and pathophysiology [23].
*Radiology*, based on physics can also be located on this level as it serves mainly for diagnosis and in clinical work it supports to a large extend surgery. Radiology at present is transformed to *imaging technology*, using *big data* and *artificial intelligence* that promise much diagnostic progress by this kind of empiricistic view.
Also *clinical chemistry* and *pharmacology* are important medical subdisciplines of the preclinical field that rely on (bio-)chemistry. They all support mainly *internal medicine* in diagnostic or therapeutic issues.

(4). The *fourth level* is made up by the main fields of clinical medicine, namely *surgery*, *internal medicine* and *neurology.* They constitute basic methods of *exploration* and *physical examination*. They compete also regarding the degree of conservation of integrity of the body (internal medicine) or of dissecting and restituting the body (surgery). These disciplines show also a high degree of organ-related subspecialization (internal medicine: pulmonology, cardiology, gastroenterology, nephrology, endocrinology, immunology, etc.). Other clinical disciplines surround these disciplines. Disease-centered and / or organ-centered clinical departments intend to connect at least surgery and internal medicine as it can be seen in departments for oncology.

(5). On the *fifth level*, *psychology* and *social sciences* provide a roof of knowledge for *psychiatry, epidemiology* and *social medicine*. They are basic sciences for medicine concerned with physician-patient interaction, with the analysis of health care as context of medical action and social factors as risk factors for occurrence of diseases. Also the "structure sciences" *statistics* and *mathematics* (and computer science) are very basic and methodologically important sciences for the whole field of scientific medicine, namely for all stages of data analysis and for formalization of theoretical laws.

### *Evaluating disciplinary reduction and integration*

With regards to this description of the diverse disciplinary structure of medicine with its epistemic and operational territories the potential for clinical dysfunctions and conflicts becomes evident. For instance, organ-centered medicine (e.g. neurology, cardiology) as well as method-based medicine (operative versus conservative medicine) are often disconnected in clinical daily routine. Another example is the discussion of internists with surgeons regarding the appropriate treatment of the patient's abdominal problems. Complementary action, for instance, between orthopedic specialists and neurologists, between pulmonologists and otorhinolaryngologists at some anatomical cross sections (e.g. skeletal joints and nerves, upper airways and larynx) is another example of interdisciplinary deficiency. Also the ironical saying "operation succeeded, but the patient is dead" indicates the lack of comprehensive medical understanding of the person to be treated.

These clinical examples should show that the relative hyperdiversity of medicine implicates several conflicts and failures in practice, also in multiprofessional teams [26]. A positive example of institutionalized cooperation between different disciplines is oncology.

However, in our opinion these dysfunctional misunderstandings and conflicts of practical demand a *unifying approach* that integrates the

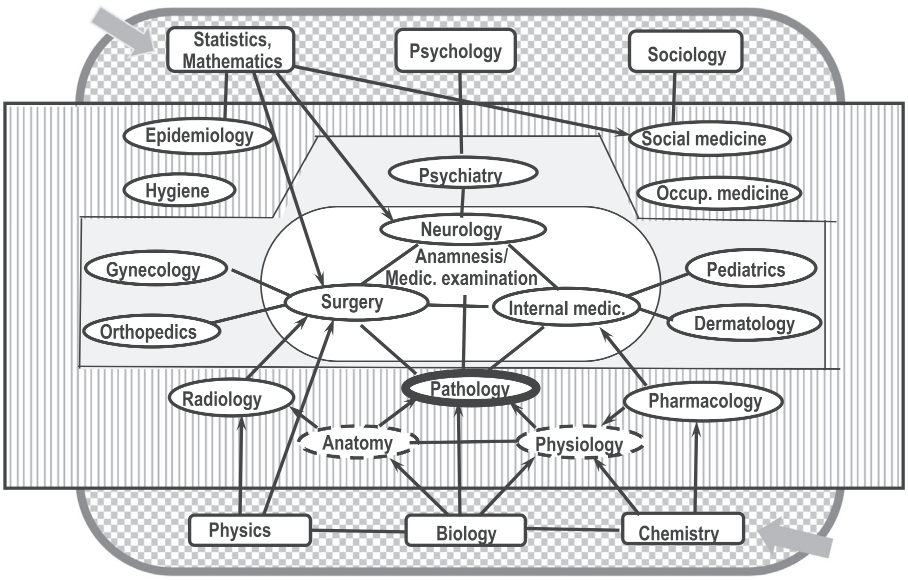


**Fig. 1.** The "House of medicine" [24,25]: The heterogeneous variety of medical disciplines. Basic science (checkerboard pattern), preclinical (auxiliary) sciences (stripes), clinical sciences (white and grey). In systems medicine, the reduction is based on biochemistry and molecular biology, assisted by statistics and mathematics (grey arrows).

diverse mosaic of knowledge by appropriate conceptual frameworks. Interestingly, only a few medical text books still try to communicate a practice-oriented integrated view of pathological anatomy, pathological physiology and clinical fields for medical education [27,28].

But what of the scientific knowledge has to be "integrated" or "connected"? Here we briefly check some scientific gaps:

The main differences between the various medical disciplines can be seen in the *methodological differences* of "explaining" *natural sciences* (physics, chemistry) and "understanding" *social sciences* (psychology, sociology). Additionally, several *interdisciplinary disparities* exist within the natural sciences: For instance, we still miss a sound unifying theory in *physics* yet, especially integrating micro- und macro-physics because of scaling differences [29]. Also *chemistry* is not yet reduced completely to physics of the outer orbits or by explaining thermodynamic properties of substances like water by the properties of its components hydrogen and oxygen [30]. In consequence, also *biology* cannot be reduced to physics and chemistry, it is to be seen as a quite autonomous science [31], although it lacks *nomological explanations* that are specific for traditional natural sciences. In contrast, biology as a science uses *(partially reductive) mechanistic explanations* [32–37]. The most important preclinical field is *pathology* as a biologically based discipline that is also subject to similar restrictions of scientific reduction.

Interestingly, the *clinical fields* use mainly *qualitative observational knowledge*, and of course *praxeological knowledge*, namely the procedural knowledge "how to treat". This implicates the need to integrate quantitative and qualitative knowledge in a complementary way. The social sciences offer an important mode of "understanding" the patient as they focus on socioecological conditions of health, disease and behavior. They also offer a meta-perspective of physician-patient relations and social conditions of salutogenesis.

Altogether, these issues show difficulties of "reduction" and imply "multiperspectivity" as a strategy for connecting knowledge by complementarity and overlap. This is in line with results of philosophy and history of science, which show that those gaps can only be bridged by a *hybrid or even multidimensional view* that is applied specifically depending on the context. But the *addition of focal views* alone does not lead to an integrative view. There is a need of a bridging conceptual framework as it is partially provided since the late 1970s by the *conceptual extension* of the biomedical perspective by George L. Engel and his "bio-psycho-social model", that allows a macroscopic but integrative orientation for understanding health, disease and treatment [38]. In addition, Engel saw in the systems theory of Ludwig von Bertalanffy the "supradisciplinary" bridging concepts such as the multi-level view, the relevance of dynamic equilibrium, identification of control loops, etc. However at present, the hype of molecular medicine overwhelms this broader view. With the label of "Systems Medicine" it is claimed that current *molecular medicine* could enable integration by identification of pathological chemical structures and processes, combining reduction and holism in one approach [39]. In contrast, we will show now that this issue is more complicated [40]. It even might be necessary to find a "supradisciplinary" level of formal description like *systems science* that allows a more abstract integration of functional and structural knowledge in medicine on different levels of organismic organization as will be shown in the last chapter.

*Summarizing* these issues, the *first main hypothesis* can be formulated that medicine exhibits an *overdiversification of knowledge* in relation to the *poorly developed integrative perspectives*. It was shown that in spite of the communality of the epistemic object, the plurality of concepts and the diversity of methods of sub-disciplines of medicine hamper knowledge integration, even at the level of natural sciences. Such an integrative medical theory on health, disease and effective treatment might reduce several intra-disciplinary as well as "(pseudo-)inter-disciplinary" conflicts.

## Some options and limits of molecular "system medicine"!

In context of the diversity of medical knowledge, currently molecular "systems medicine" and similar new technology-driven medicines promise a comprehensive revolution in health care. These approaches are also often called "Omics"-medicine that targets some holistic vision of different molecular subsystems of the cell (and organism) such as the genome, epigenome, transcriptome, proteome, metabolome, etc. They can be understood as the application of molecular *systems biology* to human health and disease, neglecting however the psychosocial dimension of humans.

The common methodological profile of these approaches is constituted by

(i) high-throughput technology-based approaches that use the method of micro-arrays to record the molecular structure of the genome, transcriptome, proteome, metabolome, etc. together with
(ii) bioinformatics, statistics and mathematics which provide data analysis. This big data-producing approach supposes to be able to fully understand and control human health.

Initially, since around 2005 two main labels were proposed:

- *(Molecular) Systems Medicine* [41–45]. MSM can be conceived as a continuation of (molecular) system biology [46,47].
- "Network Medicine" [48] has similar claims, but it is based on mathematical network science [49]. It appears as some kind of extension of multivariate statistical analysis using topological proximity measures instead of and / or in addition to statistical correlations.

For simplicity, here we assume that both approaches have the common goal to search for functional connections between molecules and they are equipped with a common methodological trunk that follows in some analogy to Immanuel Kant: "data without mathematics are blind, and mathematics without data is empty"- progress is obtained by analytical biotechnology and by mathematical tools assisted by super-computation (e.g., large computer networks).

*Claims of systems medicine*

The specific research program of MSM is generally proposed by the label "*System medicine*" with various differentiations that seem to be expressed by several attractive attributes like "precision", "personalization", "prediction", etc. For instance, "P4 medicine" offers personalization, participation, prediction and prevention [50]. P4 medicine integrates also *behavioral data* in its research program. Special approaches are proposed such as "Personalized medicine" [51] or "Precision medicine" [52]

Especially the P4 systems medicine is a very influential and popular version of MSM in science policy [53]. It stands for the optimism to understand and cure successfully most somatic diseases of men and also their mental disorders by omics-methodology: cancer, diabetes, lung disease, Alzheimer's disease, depression, etc. in a personalized way. MSM, or more precisely: "translational medicine", should also pave the way from the lab bench to the bedside [54]. MSM basically claims to be the medicine of the 21st century. It will also change significantly the entire health care system.

*Limitations of "systems medicine"*

Several shortcomings of MSM are evident by meta-theoretical analysis. This view is already developed in context of "Philosophy of Systems Biology" [55,56] and in our program "Systems Biology of the brain" [57–59]. Unfortunately, we know no comparable "Philosophy of Systems Medicine" yet. Our view is related to analytical philosophy of science and science studies that emphasize quality of terminology, definitions, concepts, empirical arguments, logics of argumentation and theoretical assumptions:

(i) The *terminology*, especially of P4 medicine, is misleading:

- "Precision" devaluates other medical fields of action like surgery that itself aims a maximum of precision as any other handcraft and field of science.
- "Prevention" is one of the main targets of behavioral medicine and public health.
- "Prediction" is already a target at any medical action.
- "Participatory" medicine is practiced since a long while by "informed consent" and "shared decision making" as the necessary basis of a fair treatment contract.
- "Personalized" is also a fundamental goal of practical medicine. On contrary, thus meant individualization of the patient has significant practical limits, when it is considered that only 8 features (4 × 2) are used for the characterization of blood groups that enable very successful acute blood transfusions for the whole world population: medicine is interested in both, *generalizations* and *individualizations*.

Altogether, this P4-medicine related terminology seems to be designed for marketing strategies by non-clinical molecular biologists and/or informatics-experts. These terms are not a product of a thoughtful scientific taxonomy but appear as marketing wordings.

(ii) MSM shows considerable *conceptual vagueness*, and thus also *theoretical weaknesses* occur. For example, it is rarely distinguished between the terms "system" as a bounded set of elements and its relations and "network" as a connectivity of nodes. This is due to the "Methodism" of MSM, as it operates "data-driven", "method-driven", "technology-driven", and "theory-free", specific epistemic features that are significant for "big data" epistemology [60]. However, relating all obtainable biological, psychological and sociological variables by a mathematical formalism has only descriptive but not explanatory power - Big data without theory is blind, it needs big theories to really work sufficiently [61]!

(iii) MSM represents a *reductionist research program* although it proposes the systems perspective: Chemistry should replace biology, biology should replace psychology and psychology should replace sociology. Finally, every epistemic medical object should be seen as chemistry [62]. Also, clinical knowledge should be replaced by "big data". This is not a "systems perspective" regarding systems theory or systems science (see below) as it ignores emergence in multi-level systems: emergence of life from abiotic matter, emergence of consciousness from biotic matter, and emergence of culture from conscious systems [63,64]. Additionally, abottom-up causation is assumed, but there is no Archimedic point in *biological causation* as systems biologist Denis Noble convincingly has shown by pointing on the electrophysiology of the membrane that modulates intracellular molecular processes [65].

(iv) MSM does not consider *explanatory gaps* which exist between physical and mental states and processes of the organism. This *mind-brain problem* was discussed in philosophy of mind since the 1970 s [66–71]. Currently the National Institute of Mental Health proposes a biology-based new *psychiatric taxonomy* of the mental states and processes that is called Research Domain Criteria [72]. Also new developments in *psychopathology* are neglected in context of MSM [73,74]. But even this new network-based approach should be connected with an organismic systems psychology [75,76]. But in principle, there is much doubt that a reduction of the mind to the brain is sufficient [77,59].

(v) Additionally, the distinction between the *organism* and the *environment* is drawn too simple compared to the biological field of "ecology" that has a long tradition with this concept: "environment", from the objective point of view [78] is different to the subjective point of view [79] and only partially congruent [80]. Even the bottom-up reconstruction of the functional organization of the organism from the molecular omics-view is theoretically not consistent. These explanatory gaps are well known in philosophy of Systems biology but ignored by most above mentioned protagonists of MSM.

(vi) MSM is too much *structure-oriented* and ignores several physiological facts: MSM has no detailed and integrative theoretical model of the organism that refers explicitly for instance to the *dynamics* of molecular mechanisms of the membrane, such as the receptor dynamics by sensitivity changes and up- and down-regulation, the adaptive transport processes, as they are known in neurobiology of the synapse [81–83].

(vii) Biochemically driven MSM fundamentally ignores *electrical phenomena*, in particular the electrophysiology of the membrane that exhibits a dynamic that is puffered from processes that are determined by the genome. This was already discussed in systems biology of the brain regarding the electrochemical processing at the synapse [81].

(viii) The importance of the *form of organization* of the organismic structures for the functioning organism is not explicitly considered. An approach that is pioneering here in the field of molecular biology searches for *canonical process structures* across all levels of organismic organization, the "Motifs" [84].

(ix) The value of *knowledge* of MSM regarding *communication with patients* is low as still there is no good conceptual up-scaling of complex graph theoretical presentations of any interesting omics-result to an understandable simplicity.

(x) The current successes of MSM medicine are primarily found in *oncology, as* the genome analysis identifies mutations and according to these findings specific drugs are applied [85]. One canonical example of a solid SB is the computer model of the heart as it was developed by Denis Noble starting with ion channels and ending with the whole organ, the action of which can be simulated in computer experiments [86].

(xi) The explanatory power of mathematics is overestimated. *Mathematical treatment* of phenomena of molecular systems by multivariate correlation analysis, graph theory, differential equations, Markov chains, etc. help to describe quantified structural and process properties of these molecular systems. But mathematics alone is only a language, whereas theories are based on constructs and principles like energy, cell division, metabolic transformation, secretion rate, electrical discharge, etc. [87]. Also it should be minded that "system theory", over the decades, mutated to "systems science" that implicates a methodology of (pre-mathematical) modelling [88].

(xii) The level of abstraction of results of molecular systems medicine and the plenty of new data make it difficult for the clinical practitioner to follow. For this reason in reality of health care systems medicine enhances the division between research and practice.

*Summarizing* this chapter, a lot of these *conceptual,* meta-*theoretical and methodological problems* might limit the *epistemic* and *practical utility* of this kind of systems medicine. In consequence, it would be a great mistake to concentrate all organizational, financial and staff resources to this approach and to deconstruct "traditional" medical knowledge.

## The view of "organismic systems medicine"

Our *third hypothesis* claims that the perspective of an organism-centered systemic view that could be called "organismic systems medicine" (OSM) offer more options for an integrative view. OSM as an expression refers to the conception of an "organismic (or: organismal) system biology" of Ludwig von Bertalanffy in context of the "*General System Theory*" [89]. This perspective was also elaborated, for instance, by other proponents of GST such as James Grier Miller [63] and Mihaeli Mesarovic [90]. This top-down perspective that proposes *general design principles* of functions on different levels of living systems, offers probably more options for an differentiated but integrative multi-level view on humans' health, disease and treatment than MSM. It is also better connected to traditional medicine as it was described in the first chapter.

### *General system theory and systems science*

Ludwig von Bertalanffy suggested a *top-down functional analysis* of the "whole", i.e. the organism or the cell. This claim is based on evidence from an ontogenetic and phylogentic developmental perspective ("Evo-Devo"; compare [91]). It is based on developmental biology as it was established in the 1930 s in Vienna by von Bertalanffy and Paul Weiss [92]. By this school of theoretical biology in Vienna, a balance of theoretical reasoning and experimental research was demonstrated. Experimentally, this research approach concentrated on the development of amphibians focusing the structural realization of diverse functions of the cell and the growing organism during early stages of the embryo (e.g., organogenesis). In line with this approach, the epistemic strategy is characterized by the fact, that discovering *possible structures of known functions* is preferred to identification of functions of discovered structures – there is usually a *multiple structural realization of function* and also a *multifunctionality of structures* in biology that constitutes the puzzle of understanding biosystems. It should be mentioned here already, that for a necessary *integrative systems medicine*, the organism-centered view of OSM must be complemented with the molecule-centered view of MSM.

Several features of GST, and currently of "Systems Science", are important:

(i) Epistemic aspects

Systemic methodology integrates, but distinguishes also, the outside view and the inside view, the micro-perspective (zooming-in) and the contextual macro-perspective (zooming-out). In addition it is assumed that emergence occurs between different organizational levels of biosystems, such as molecules, brain and mind [93].

(ii) Terminology and concepts

GST uses categories, constructs and concepts like "system", "element", "network", "structure", "function", "process", "equilibrium", "self-organization", etc. in a mathematically oriented definition and understanding of the properties of living systems. For instance, the crucial term *growth function* in mathematical context means the formal relation of increase of any quantity (e.g., size, weight) that is related with the increase of another quantity (e.g., time, calories), but in biology it could mean cell division, tissue properties, etc.

On a more formal level, the conceptual pool of GST is focused on a differentiated *equilibrium concept*, regarding flows (dynamics), feedbacks, regulations, adaptations and especially self-organization as basic constructs. The concept of "flow equilibrium" that was invented by von Bertalanffy implies conceptually referring *inputs* (or: inflows) to *outputs* (or: outflows). This functionalistic view integrates process structures (dynamics) over different levels of organization of the organism, such as the molecules, cells, tissues, or organs. But also, the *(convergent) relation of activities of agonists* and *antagonists* which control a state or process or "functions" (e.g., movements, blood fluidity/ coagulation, etc.) is of central importance.

In this context, the question arises, what kind of *functions* an organism has to realize or how the term "functions" can be used to explain biological phenomena [94]. A distinction of two, three and many more main functions are possible, but there is no accepted *taxonomy of functions of biosystems* available.

One simple concept of *three connected function systems* in living systems was constructed as a "Chemotron" by the biochemist Tobor Ganti [95], and it was explored analytically by the philosopher of biology William Bechtel [96]: the *metabolism* is one basic function of living systems that take energy and substances like carbon, oxygen, nitrogen, glucose, fatty acids, etc. from the environment and must decompose and compose it, distribute it, store it and extrude metabolic (toxic) products via a metabolic cycle. This metabolic process is controlled by (cyclic) *control mechanisms* and as a third constituent the membrane as a *boundary structure* is to be produced and to be regulated, also in a cyclic mode.

A much more differentiated conception of functions in living systems was published by James Grier Miller who identified 19 basic functions that have to be realized by a living system in order to exist, to develop and to cope with the environment [63]. He distinguished subsystems which process both, matter-energy and information*: Reproducer, Boundary,* and subsystems which only process matter-energy*: Ingestor, Distributor, Converter, Producer, Matter-energy storage, Extruder, Motor, Supporter.* Furthermore he identified subsystems which process information*: Input transducer, Internal transducer, Channel and net, Decoder, Associator, Memory, Decider, Encoder, Output transducer.* This terminology represents results of functional analyses of living systems on various levels of organization, as it was known in the end of the 1970s. It obviously relies on a "deeper semantic" of function analysis in context of systems analysis [97]. Unfortunately this conceptual framework is nearly forgotten nowadays although it could probably be revisited and modified fruitfully in the light of current molecular biology / medicine and informatics.

(iii) Systemic Modeling as an instrument for theory development

An important overlap between MSM and OSM comes up in the field of *mechanistic modelling* that should be distinguished from *formal modelling* - the latter is mainly based on correlations (or contingencies) in context of mul*tivariate statistical analysis* that are used to construct a generic equation that "explains" most of the variance, etc. [98–101]. In contrast and in addition, mechanistic models help to discover, identify and explore organizing principles in biosystems [102,103].

*Systemic modelling* uses graphical tools for system description and several researchers propose canonical (or generic) circuits (or "motifs"; [104]) that can be found on all levels of the organismic organization. These circuits are composed of convergence of activators and inhibitors and of differently acting (fast or slow) feedback loops.

To give an example, a structurally simple *simulation model* was developed for *molecular systems biology of the brain*, with regard to *psychiatric disorders* that depicts the dynamics of various *transmitter systems* in order to describe and explain the dynamics of various clinical syndromes , and their treatment (e.g., alcohol withdrawal, working memory deficiencies, schizophrenia, depression) in an integrative conceptual framework and that also can be communicated to patients in a proper metaphorical way [105,106]. The general construction principle of the functional structure of the model that is metaphorically called "neurochemical mobile" is based on the concept of an *interaction matrix of activators and inhibitors* with different intensity-time profiles that are reciprocally connected and that exhibit a circadian fluctuation of the respective activity. The physical reference model is a *complex of coupled non-linear pendula.* By translation of this concept into differential equations that are expressed numerically by neurobiological data an "exploratory" simulation model can be designed that enables computerized explorations [107,108].

In contrast to data-driven and technology-centered approaches, this approach explicitly uses biological principles. And in this view, such modeling is one property of theoretical medicine that integrates several isles of knowledge that were mentioned in the first section of this paper. In systems thinking, small and soft data are sufficient to build small and smart models that serve as heuristic tools for clinical practice [109,110].

*A holistic integrated multi-level conceptual framework*

Starting from the whole that is conceived as a structured whole, and considering the context and the infrastructure of the respective system, a multi-level perspective of the system and its environment should serve as a reference framework. From the disciplinary point of view, OSM should be within a sandwich structure between biology and social sciences. Regarding biology and current molecular biology some new postulates published from Houck et al. [111] are useful regarding also the criticism of MSM. These postulates say that medicine should recur on laws of Biology considering the following issues: (i) consistency with laws of physics and chemistry, (ii) biosystems can create order, (iii) the cell is the fundamental unit, (iv) the cell must be in homeostasis with its environment, (v) there must be a distinction between self and the environment and (vi) electromagnetic information transfer is necessary for development and regeneration. This is in line with criticism of Denis Noble on molecular biology, where is also criticizes that the heuristic and causal analytical power of the Omics-perspective is overestimated because also top-down causation has to be considered [112].

*Organism-in-environment: a human ecological framework*

If *biology* is seen as a basic science for medicine, as it was demonstrated in the first chapter, *ecology* might be the superior reference discipline: any living system is embedded in an environment and can only exist and function in a certain environmental context. For human beings *human ecology* might the appropriate reference discipline [113]; "Ecology of the Person", [114]: The basic systemic assumption is that "man-is-in-the-world". In this view the first function of a new born living system that is separated from the mother organism is to connect again to obtain matter and energy and to experience shelter. Basically, energy is to be generated from collected matter that can be used by the organism in order to generate a *boundary relation* by a structure like the membrane or the skin or a house where the person lives. And then, a control system must be developed to coordinate these processes. This control system could be the *brain and the brain nerves for external relations* [115] and the *autonomous nervous system*, but also the *endocrine system* and the *immune system* for *internal relations*.

But functional analysis cannot be that static as the developmental perspective shows: after fertilization of the human cell in the uterus, cell division and structuring of the blastula takes place, processes that are controlled by intrinsic molecular signaling systems that, by the way, are explored by organismic systems biology/medicine. In this view, after the first division, the cell is not alone anymore and has other cells as a *homotypic environment* - the cell lives in a tissue. Soon cellular specializations occur, configurating the *epidermic tissue*, the *endodermic tissue* and the *mesodermic tissue*, which are the mother tissues for furthermore developed (connected) organ systems and organs. By these mechanisms, in mammals already around the 4th embryonal week, the basis of the nervous system for *coordination*, the cardio-vascular system for *circulation* and the gastrointestinal system for *metabolic processes* like ingestion and extrusion are developed. Also the *respiratory system* is implemented, even if it is not operating in utero. Furthermore, other organic structures, for instance the pancreas, the liver etc., are generated. Interestingly, these function-oriented macro-anatomic morphological structurations can be found analogously on the cellular level. Also *dynamic equilibrium* of *growth* and *death of the cell* is important, and both processes depend on their situation within the tissue. Any cancer theory that does not reflect the influence of the microenvironment of cancer cells would be insufficient [116].

*An integral issue of "systemic pathology" - stress*

One of the most fruitful stimulus–response constructs in medicine has been Hans Selye's concept of stress that helps to understand pathogenesis of most diseases on organismic, organ and cellular level [117,118]: mainly the organismic level as a conceptual framework that is important in the clinical context depicts the role of environmental stimuli and the adaptive reaction mode of the brain and its autonomous system, the endocrine system and the immune system [119]. In this context it is important to note that these three systems represent interconnected organismic subsystems that can operate in a stress mode, under acute and chronic conditions with different reactions such as *homeostasis* and adaptative *allostasis* [120,121]. Probably because of persistent elevated cortisol and adaptation of receptors and fatigue of the adrenal gland in accordance to the sympathetic nervous system all organ and tissue functions are dysregulated. These empirical findings very early were integrated in a complex organismic feedback loop model consisting of several subloops. As feedback loop systems are hard to be studied empirically also computational modelling served as a tool to gain evidence about the dynamics. But even simple endocrine feedback structures as they are organized between the brain and the thyreoidea exert complex behavior patterns of regulation as computer simulations show [122].

*Summarizing this final chapter*, organismal systems medicine might be a more appropriate approach to target a holistic (or better: holocentric) approach in medicine that starts with conventional physiology and current psycho-social medicine and that integrates molecular medicine. It could be one basis of a theoretical field in medicine that even can provide explanations and that can even be understood by and communicated to patients.

## Conclusions

It was shown that the reflection of the current methodological orientations of medicine exhibit a *diverse mosaic of knowledge in "the house of medicine"* with severe gaps between different approaches. This finding is a good reason to claim for a "theoretical medicine". The claim of the currently expanding MSM to provide an integrative and holistic view of health and disease and to "revolutionize" medicine in science and practice has some severe limitations – the knowledge islands cannot be integrated by MSM by explanatory reduction to molecular mechanisms. Especially clinical phenomena cannot be reduced to molecular mechanisms alone. This critical proposition can be explored on a *meta*-scientific level in context of the raising "philosophy of systems biology" because a living *philosophy of systems medicine* seems not to exist yet. Additionally, investments into theoretical medicine that searches for principles in context of theoretical biology as it was proposed and worked out by the Viennese school of "theoretical biology" according to Ludwig von Bertalanffy and his OSM might be a solid supplement to MSM. Finally, by theory-based development of disease-specific "simpler", but "smart" *conceptual system models* it seems to be possible that mechanisms of health and disease could be more understandable than results of big data analytics alone. Epistemologically speaking, this results in a medicine that is based neither on empiricism nor constructivism alone but on integration of data and theory. It could be an example of modern scientific realism.

## Conflict of interest

The authors, Felix Tretter and Henriette Löffler-Stastka, declare, that they have no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109386.

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