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Getting personal: can systems medicine integrate scientific and humanistic conceptions of the patient?

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Abstract

Rationale, aims and objectives The practicing doctor, and most obviously the primary care clinician who encounters the full complexity of patients, faces several fundamental but intrinsically related theoretical and practical challenges – strongly actualized by so-called medically unexplained symptoms (MUS) and multi-morbidity. Systems medicine, which is the emerging application of systems biology to medicine and a merger of molecular biomedicine, systems theory and mathematical modelling, has recently been proposed as a primary care-centered strategy for medicine that promises to meet these challenges. Significantly, it has been proposed to do so in a way that at first glance may seem compatible with humanistic medicine. More specifically, it is promoted as an integrative, holistic, personalized and patient-centered approach. In this article, we ask whether and to what extent systems medicine can provide a comprehensive conceptual account of and approach to the patient and the root causes of health problems that can be reconciled with the concept of the patient as a person, which is an essential theoretical element in humanistic medicine.
Methods We answer this question through a comparative analysis of the theories of primary care doctor Eric Cassell and systems biologist Denis Noble.
Results and conclusions We argue that, although systems biological concepts, notably Noble's theory of biological relativity and downward causation, are highly relevant for understanding human beings and health problems, they are nevertheless insufficient in fully bridging the gap to humanistic medicine. Systems biologists are currently unable to conceptualize living wholes, and seem unable to account for meaning, value and symbolic interaction, which are central concepts in humanistic medicine, as constraints on human health. Accordingly, systems medicine as currently envisioned cannot be said to be integrative, holistic, personalized or patient-centered in a humanistic medical sense.

Introduction

'Throughout my career, I have been searching for a medicine to which I can belong. For me, medicine will never be a pure and simple place and I will argue that a much more complex but creative and useful place can be defined by the interplay of opposites [1]'
-Iona Heath, Divided we fail: The Harveian Oration 2011.

Systems medicine [2–4] – defined as 'the application of systems biology to medical research and practice' – has recently been proposed as a future and primary care-centred strategy for health care worldwide [5].

Throughout this exploration, we aim to contribute to an understanding of the strengths and limitations of this framework for primary care. More specifically, we investigate whether it can meet the challenge of providing clinicians with a comprehensive

theoretical framework that can integrate the division between scientific and humanistic medicine.

While scientific medicine (or 'biomedicine') is rooted in the traditional world view of the natural sciences and focuses on diseases associated with bodily *parts*, humanistic medicine can be defined as 'medical practice that focuses on the whole person and not solely on the patient's disease' ([6]: p. 10). The key theoretical element in humanistic medicine is the concept of *the patient as a person*. We pursue the following research question:

> Can systems medicine provide a comprehensive conceptual account of and approach to the patient and the root causes of health problems, and – furthermore – can such an account be reconciled with the humanistic concept of and approach to the patient as a person?

In this, we also seek to shed light on the key clinical challenges of medically unexplained symptoms (MUS) and multi-morbidity. We have chosen to approach the research question through a comparative analysis of the relevant thinking of two key theorists. We analyse the conceptual account of and approach to the patient and the root causes of health problems found in the philosophy of systems biologist Denis Noble [7] and whether it can be reconciled with that found in the primary care-oriented and humanistic medical philosophy of Eric Cassell [8,9]. A broad and comprehensive survey of the relevant theoretical literature on systems biology and systems medicine has led us to state the following premise for this investigation: Within the development of systems medicine, Noble's philosophy is the most humanistically inclined [7,10], and thus representative of how close systems medicine can come to humanistic medicine theoretically. Although Noble may not represent mainstream systems biology, he is influential [5,11–13]. He is much quoted in the theoretical development of systems medicine and also involved in the conceptual foundations of fledgling 'systems psychiatry' [14], which makes him directly relevant to a field that obviously faces the challenge of reconciling scientific and humanistic conceptions of patients. Importantly, his philosophy also represents the most comprehensive account of the relevant questions we have found within the current systems biological literature. Cassell's philosophy is chosen as a representation of humanistic medicine more broadly and as the most comprehensive and authoritative philosophy of patients as persons currently found in humanistic medicine. As such, Cassell's philosophy reflects what Noble and systems medicine must account for in order to bridge the sciences–humanities divide.

Background

The challenges of primary care

The practising clinician, and most obviously the primary care doctor who is confronted with the full and uncategorized complexity of human function and dysfunction on a daily basis, experiences several related challenges. These also represent the ultimate real-life trials that systems medicine – no less than humanistic medicine – has to stand up to in order to prove relevant as a strategy for primary care.

One fundamental need and challenge lies at the heart of medical practice: the necessity of providing a comprehensive conceptual account of and approach to the patient as an entity and of the root causes of health problems.

A second challenge is that, in providing such a conceptual account and approach, medicine takes on a dual philosophical appearance. The clinician is expected to approach the patient in a way that is not only scientifically valid and evidence based, but also sensitive to the full range of human capacities, including individual experience, needs and values. These two aspects are typically expected to *coexist* or *merge* in the concept of *knowledge-based practice*, but exactly *how* such a merger should come about is far from obvious. On the contrary, the doctor is pulled in two different theoretical and practical directions – towards scientific *and* towards humanistic medicine [6]. This reflects a more general division of Western intellectual life, described by CP Snow in 1959 as 'The two cultures' [15]. In what follows, we will describe the sides of this division (asterisks '*' refer the reader to the definitions in Box 1):

At the heart of *scientific medicine*, the branch of medicine that currently dominates the profession's view of what counts as a medical explanation lies the machine metaphor, which depicts all living entities as machines. In this, scientific medicine is materialist*, reductionist and mechanistic [6,16,17]. The patient is seen as 'nothing but' *parts in interaction* and should, as a corollary, be understood, studied and treated by focusing on those parts [6,18,19]. Associated with this conceptualization is molecular determinism or 'smallism' [20], the belief that entities at the molecular scale or level* are *causally privileged*. Accordingly, patients and their functions and dysfunctions (diseases) are depicted as being caused by interacting parts through 'upward' causation [21]. The lower scales or levels*, especially the genome, hold the necessary information to 'inform' the larger scales or higher levels as through a programme [17]. As a corollary, the emergent phenomena that arise from such interactions of parts are given an inferior ontological* status. They are said to be *epiphenomenal* – that is causally insignificant and not as concrete as parts. The patient is considered as a passive and static *thing* rather than an active and dynamic *process* [22]. As mathematical biologist Stuart Kauffman [23] has pointed out, there are no 'doings' in this world view and, accordingly, patients have no real *agency*. Additionally, a dismissal of teleology and final causes* as non-scientific further downplays any goal-directedness, purpose or will in human action [17,24–26]. Smallism also downplays the patient's environmental, especially social and symbolic relations (including the doctor–patient relationship). Even the personal experiences conveyed by patients, notably in the form of narratives, are being denigrated as private or too complex and uncountable for 'objective' scientific study [6,27]. In sum, scientific medicine attempts to reduce the personal or 'psychosocial' to molecular and cellular mechanisms or programs in the brain. However, as this does not make subjective personal experience go away, ontological mind–body dualism* prevails in practice [28].

As indicated by biological anthropologist Terrence Deacon [25], scientific denial of human agency, goal-directedness, purpose, consciousness, meaning and value renders biological understanding of patients *an unfinished business* and encourages the sciences–humanities divide. Relatedly, this depiction of patients encourages technological intervention directed at body parts rather than personal and social factors [29].

Box 1 Definitions

Epistemology is the study of knowledge, of what can be known and how we know it [49].

Ontology is the part of metaphysics concerned with what exists in the universe and how it is structured [19]. **Materialism/physicalism** is 'The thesis according to which all higher level properties are realized by arrangements of lower level properties. On this view, there are no metaphysically irreducible properties of conscious or other mental states' [63]. **Ontological dualism** is the idea that the universe (including persons) is made of two distinct substances, that is, 'mind' and 'matter' [27].

Complexity: There is no consensus on how to define this key concept, but it can be characterized as a property of systems in which entities at a lower level/smaller scale interact non-linearly and dynamically (through time). These interactions result in emergent (novel) properties in the system (whole) that cannot be found in the parts in isolation. The system is then said to display higher degrees of complexity or **organization**. The emergent whole may or may not be taken to have causal efficacy in itself [19].

Levels and scales: According to Noble, **scale** is the size of a system. Systems of different scale may be nested within each other. Examples of **levels** are molecules, cells, organs and organisms. This hierarchy of levels is metaphorical as these entities are not literally on top or below each other. Levels and scales will in the context of patients be correlated [69]. Molecules are (in reality) nested within cells, within organs, within organisms, within an environment at successively larger scales [64]. These scales and levels also correspond to successively higher levels of complexity or organization [70]. A (multicellular) organism/patient is more complex and highly organized than cells or molecules. Noble conceptually prefers the term scale, but nonetheless uses 'levels' metaphorically in causal explanations.

Intentionality: In a phenomenological sense 'consciousness is intentional, in the sense that it "aims towards" or "intends" something beyond itself'. Intentionality may also refer to the purpose or goal-directedness of acts, which is 'only one kind of intentionality in the phenomenological sense' [81].

Types of causes: Aristotle established four causes: 'Material (substances), efficient (mechanisms), formal (circumstances) and final (needs)'. Material and efficient causes answer questions like 'what is this and how does it work?' while formal and final causes answer questions like 'why did this happen?' [24].

Humanistic medicine represents a reaction to this perceived dehumanizing and medicalizing trend. We follow Marcum [6] in broadly categorizing a variety of frameworks and lines of thought as humanistic, including biopsychosocial, patient- or relationship-centred, narrative-based, person-focused and person-centred medicine as well as medical phenomenology [30–37]. Humanistic medicine strives to maintain sensitivity to the full range of human capacities, experiences and needs in medicine, and to integrate what is called 'psychosocial' with biomedicine in the concept of *the patient as a person* [35]. It is currently far from clear, however, just how such an integration can be achieved.

Medically unexplained symptoms and multi-morbidity

The prevailing panorama of health problems represents a *third major challenge* of primary care. Scientific medicine has led to obvious benefits, but a variety of common, complex and costly conditions strongly actualize the challenge of theoretical development. Two key examples are so-called functional disorders or MUS and multi-morbidity. Importantly, systems biological methods are currently starting to be applied to these problems [5,38].

The MUS category encompasses hundreds of diagnostic labels, for example, the chronic fatigue syndrome [39], which represent some of the most common problems in Western medicine [40,41]. The root causes of MUS are poorly understood. However, it is important to note that, when these problems are categorized as *medically unexplained*, they are unexplained in a certain way, namely according to the current ontology and epistemology of scientific medicine. And as they are in fact defined by their very *scientific unexplainedness*, they seem likely to highlight the shortcomings in parts-oriented conceptualizations and explanations of patients and health problems, especially concerning the relations between 'bio', 'psycho' and 'socio' in biopsychosocial thinking [33,39–41].

Multi-morbidity refers to the phenomenon that patients, according to current scientific standards, often satisfy the criteria for many diagnoses. These patients are therefore, by biomedical convention, thought to have many separate diseases, each presumably caused by specific pathogenetic mechanisms related to specific body parts or subsystems, and each correspondingly treated in parts-focused and separate 'silos' of medicine [42]. There is however, emerging evidence, which indicates that many common chronic conditions, which typically cluster and often include MUS, might be produced by pathogenetic life circumstances, sometimes referred to as 'the causes of the causes' [42–44].

The above challenges all trigger fundamental questions relating to *philosophy of science, causality, biology and mind* that involve known dichotomies such as reductionism (parts) vs. holism (wholes), psyche vs. soma, subjectivity vs. objectivity, illness vs. disease and mechanistic explanation vs. meaning [45]. As a consequence, the doctor who professionally seeks to straddle the scientific–humanistic divide, struggles to find a valid reference point [1].

Systems medicine to the challenge

Enter systems medicine. At a first glance, this proposed paradigm intriguingly seems to offer the clinician promises and hope that his/her challenges may soon be catered for by scientific progress. Systems medicine is at once proposed as aiming to tackle *all components of disease complexity** and as being *holistic, integrative*, *personalized* and compatible with *patient-centred medicine* [5]. Systems medicine has also been said to favor a '*novel humanism directed to the management of the patient as individual subject*' [46]. However, the given impression that systems medicine can integrate theoretical elements from 'scientific' and 'humanistic' medicine is not obviously valid and deserves scrutiny.

Broadly conceived, systems biology is a convergence of molecular biology and systems theory [47–53]. Molecular biology

has culminated in 'omics', that is the sequencing of whole bodily 'parts lists', including DNA (genomics), RNA (transcriptomics) and protein (proteomics). The resulting massive amounts of information on parts have not in themselves yielded the sought-after understanding of wholes, predictive power or medical breakthroughs [54]. Rather, it would seem that biology has 'hit the wall of bio-complexity, reductionism's nemesis' [18]. Fundamentally, the connection between parts, especially the genome (genotype), and the whole organism (the phenotype) stands unaccounted for [19,55,56]. The manifest goal of systems biology is precisely to make this connection. Its method is to integrate data on parts, in the context of medicine *'billions of data points'* [5] into explanatory and predictive mathematical (computational) models of patients as wholes (aka 'systems'). Its ambition is no less than to *calculate life* [52].

Importantly, systems biology is not a homogeneous scientific discipline. Although it is clear that systems biology is currently dominated by a highly parts-oriented approach that conceptualizes and investigates patients as networks of molecules [47,48, 51,53,57,58], a minority, exemplified by Noble, seeks a more fundamental philosophical reorientation. Noble also explicitly espouses a humanizing ambition, stating that the focus on lower-level causes in biomedicine may lead to a dehumanizing approach that 'encourages treatment of the disease while ignoring the particular patient who has the disease' [10].

Cassell's humanistic medicine: patients as persons

Such dehumanization is precisely what Eric Cassell and other thinkers who espouse humanistic medicine seek to remedy. Their ambition is to ground medical practice in a comprehensive theory of the patient *as a person*.

Mind and body

As a point of departure in developing such a theory, Cassell describes how the trauma of 9/11 manifested as health problems in affected New Yorkers [8]. He then asks *how and why** such a perturbation – which would often be described as 'emotional' or 'psychosocial' – could have profound impacts described as 'physical'? In approaching such a conundrum (the mind–body problem), Cassell stresses that our current conceptions of 'mind' and 'body' are inadequate. Asking how the mind *affects* the body, and vice versa are the wrong questions because any fundamental mind–body or person–body duality is false and entities that are not separate cannot affect *each other* in a conventional, mechanistic sense.

Instead, Cassell holds not only that the body and the physical participates in everything a person does, but that what we call physical or biological should be viewed as mental, purposeful and social [8]. Persons are *embodied*, they *have* a body, but if the body were properly understood, it would also incorporate all the capacities attributed to 'the mind'.

Agency

In further explaining the unity of mind and body, Cassell depicts the person more as an unfolding process with a history and a future, 'existing through time in a narrative sense' ([9]: p. 28), rather than as a static object. The concept of agency, the ability to act becomes crucial. Cassell emphasizes an *activating* language when conceptualizing persons: 'Persons do things; they act, think, have emotions, create music, express love, get sick, urinate, see and feel things, and more' ([8]: p. 235). What is called 'mind' and what is called 'body' is blurred and sought unified under the common heading of *activities*: 'The word *mind* is useful as a label for a whole bunch of activities that are characteristic of persons such as thinking, reasoning, assigning meaning, dreaming, imagining, creating, emotions, and others. You will find, that (. . .) you can easily do without the noun *mind*. One merely needs to substitute the word for the activity – thoughts, imagining, reasoning, willing, and so on' ([8]: p. 242).

Consciousness, meaning and value

According to Cassell, even conscious experience and perception are bodily activities, and *meaning*, the active labelling of experience so that it has aboutness and significance, is his core concept. Meanings also have important value-aspects and are always subjective [9].

Meaning is to Cassell what unifies what is usually termed mind and body [8]. Meanings do not *affect* the body as a separate thing, meanings *involve* the body and 'include physical manifestations as an essential and irreducible part of the meaning of things' ([8]: p. 263). Importantly, the activities of the person on every level are based on meanings. The person becomes a meaning-creating, meaning-based process or activity.

Purpose, goal-directedness and will

This also means that the activities of the person are purposeful and goal-directed according to some meaning. In other words, they are intentional* and have a teleological aspect. Some actions are automatic, instinctual or habitual, but some are also volitional or *willed* [59].

Particularity, relationality and narrative

To Cassell, the person is a particular case, an individual different from any other person [8]. At the same time, persons are strongly related to their environments, especially to social processes and activities [8].

Crucially, from an epistemological and methodological standpoint, Cassell's philosophy – like humanistic medicine in general – is characterized by the belief that persons and their complexity can be known not only by studying constituents, but from the information and meaning conveyed and generated through human symbolic interaction, notably *narratives*, and that the doctor–patient relationship is an arena for such knowing [8,9].

Parts and wholes

In explaining the unity of the person, mind and body, Cassell also makes important statements about *parts and wholes*. Concerning persons, 'anything that happens to one part affects the whole; what affects the whole affects every part. All the parts are interdependent and not one functions completely separate from the rest' ([8]:

p. 221). The brain is part of the body, important, but in no way identical to, or exclusive, when it comes to defining the mind or person [8].

However, what Cassell seems to lack is a valid *causal* theory of how the whole person (characterized by the properties often designated as 'mind' or 'psychosocial') can affect the parts like genomes, transcriptomes and proteomes (which in reductionist terms represent 'the body'). This shortcoming also reflects a broader theoretical vacuum in humanistic and biopsychosocial medicine [32,41,60].

Noble's systems biology: persons as integrative processes

In his book 'The Music of Life' [7], systems biologist Denis Noble describes an instant where something makes him cry. He then asks a question, which like Cassell's question regarding the consequences of 9/11, invites an answer of *'how'* and *'why'*. He asks: '*So, what caused me to cry'?* This question also fully reflects the complexity of a primary care patient walking into the clinic. It could be anything.

Parts and wholes

Any systems biologist would agree that such a question could only be answered by considering the patient as a *whole*, that is as a complex system or network [53]. A paraphrased[1] *Nature* editorial reads

> "*What is the difference between a live patient and a dead one? One scientific answer is 'systems biology'. A dead patient is a collection of component parts. A live patient is the emergent behavior of the system incorporating those parts [61].*"

Systems biologists will also acknowledge biological complexity, emphasize the inter-relations of entities at all levels and thus also view the patient as open to the environment. Quote Hofmeyr [62]: 'Nothing in an organism makes sense except in the light of context (. . .) Context captures the essence of the systems approach'.

But any agreement among systems biologists in conceptualizing the patient would stop there. For just how systems or wholes and their emergent properties are to be defined ontologically, is a main point of contention [47,48,52]. We may draw a main dividing line between those who emphasize that wholes have some form of causal efficacy over their parts (downward or top-down causation), and those who do not. According to Noble, downward causation is not only what gives living systems their integrity and robustness to stressors and 'distinguishes a functioning organism from a bunch of molecules' [48], it should also be regarded as the main principle of systems biology and a possible 'integrating theme within and across the sciences' [63].

Noble's philosophy is 'anti-smallist'. His theory of biological relativity challenges the reductionist assumption that what is small is causally most important. It is defined by 'the relativistic principle that there is no privileged scale of causality in biology' [64]. This means that what happens at the molecular scale, including the genome, should not be regarded as causally more important than events at the scale of the whole organism, which can also cause events at smaller scales [64,65].

How can this be? Firstly, Noble argues that there is no *a priori* reason to consider molecular scale processes as more important than organism-scale processes. If small were privileged, we should look at even smaller scales than the molecular [64]. Secondly, he supports his theory mathematically: the parts of a system may be represented by a series of differential equations. If only the parts mattered, one would think that the properties of the whole would emerge from these equations. But to model a whole, one needs to reflect the whole and *integrate* the differential equations [66]. Thirdly, Noble refers to physicist Laurent Nottale's theory of scale relativity. This is beyond the scope of this article, but entails a more general principle of relativity of all scales in nature (for details, see [64,65,67,68]). Fourthly, Noble supports his theory with empirical evidence, primarily his own work on the pacemaker rhythm of the heart. Here, the electrical cell potential of the whole heart cell, the rhythm itself, causes the behaviour of the parts 'top-down' [7,22,63,69–71].

How can downward causation be further described? Noble defines it as 'the influence of boundary conditions determined by a higher scale' [64]. Boundary conditions are in turn defined as 'all the structural and environmental conditions that constrain the behaviour of the components' [64]. These *constraints* can also be seen as *feedback* loops. To Noble, the transmission of information goes both ways: from parts to wholes, but also from wholes to parts [11].

Mind and body

According to Noble, the capacities associated with 'the mind' are grounded in matter. However, within these boundaries of materialism* and in line with his theory of biological relativity, Noble does not depict the self, the person or 'mind', as mere epiphenomena [72]. Instead, he asks *'For humans at least, to live is to experience. How can we understand this?'* ([7]: p. 1).

Agency

Time is central in Noble's conceptualization of entities at all scales and levels*, including patients: 'The really significant philosophical difference between systems biology and reductionist biology is that systems biology focuses on processes rather than components' [10]. Whole organisms like patients with their capacities are as important causal agents as lower level processes. The actions of a person in an environment, may just as well serve as a causal explanation as a molecular mechanism. The genome is not 'The book of life' or a programme for the organism. On their own, DNA molecules can do very little. According to Noble, they should more properly be regarded as passive stores of crucial information, a tool that the active, living organism uses [7]. Noble's central argument is that 'the book of life is life itself'([7]: p. 10).

Consciousness, meaning and value

In a similar way, the brain does very little on its own in Noble's view. It is necessary, but not sufficient in explaining consciousness and the other attributes we call 'the mind' [72]. The brain, and its

[1] We have substituted the word 'cat' in the original text with 'patient' to more properly reflect what one is dealing with in medicine.

molecular and cellular mechanisms, is not something that is synonymous with or dictates the self or the person. Even if scientists had been able to reduce the capacities we attribute to 'the mind' to molecules, cells or brains, this is not the level where such phenomena can be seen to exist or be causally explained. Instead, Noble conceptualizes the mind or self, including consciousness, as an integrative, higher level process rather than a thing [72,73]. When Noble uses the word 'meaning', it is in the sense of such higher level processes or wholes giving meaning to DNA by constraining its function: 'The organism itself contains the key to interpreting its DNA, and so to give it meaning' [74].

Purpose, goal-directedness and will

This means that Noble does not use the word meaning in the way Cassell does. However, he does consider intentional action and will to be real [7,71,72]. He accepts teleological explanations at the organismal level, although he underscores that lower level mechanistic explanations may also be sought for the same phenomena [7,71,75]. Although Noble himself does not elaborate on this, biological theorist Stanley Salthe states that 'constraints from the higher level not only help to select the lower level-trajectory but also pull it into its future at the same time' [76]. Noble also mentions one other key concept for systems biology that may play a role in conceptualizing purposes and goals. The constraint of the whole system entails a statistical tendency for it to be drawn towards a certain future behaviour called an *attractor* [64,72,74].

Relationality, particularity and narrative

In sum, what is a person to Noble? It is the activity of a human organism: 'The activity of the brain and of the rest of the body simply *is* the activity of the person, the self' [69]. Crucially, this self or the person is not a simple or passive thing, but a conscious, integrative process with the causal power to constrain processes at lower levels and scales [7,14,73]. In explaining the overall functioning of persons, their activities must be considered in a social and semantic context [7,72,73]. Noble underscores that '(. . .) when we start to talk about the location of the self, we are talking about a person. Such talk belongs to a context in which it makes sense to refer to persons' ([7]: p. 134). Finally, while searching for general principles that govern human biology, Noble quotes Sulston & Ferry on the particularity of the patient: 'The complexity of control, overlaid by the unique experience of each individual, means that we must continue to treat every human as unique and special, and not imagine that we can predict the course of a human life other than in broad terms' [74].

Analysis and discussion

Could systems medicine, *ad modum Noble*, provide a comprehensive conceptual account of and approach to patients and the root causes of health problems that would enable the building of a bridge towards humanistic medicine *ad modum Cassell*? Would such an account be relevant to primary health care in general and clinical challenges like MUS and multi-morbiditity?

Similarities and integration

Conceptually, the *similarities* between Noble and Cassell are obvious and striking. We would expect Cassell to see the patient as deduced from Noble's philosophy as a more properly understood body or organism than the current depiction found in scientific medicine.

In what we perceive as a mirror image of Cassell's philosophy, time enters the picture in Noble's theorizing and they both seem to lean towards process ontology as opposed to a particle- or thing-oriented ontology and the notion that an integrative theory of human function and dysfunction should have an historical perspective [22,77]. To both, music serves as a metaphor for this process nature of living persons [7,8]. Crucially, Noble, just as Cassell, advocates an *activating* conceptual language based on verbs that convey 'the doing-ness' of living processes rather than nouns [7]. To both, this doing-ness serves to conceptually unify what we call 'mind' and 'body'. As Noble states: 'The significance of this way of expressing things is then best brought out by noting that Descartes' famous philosophical statement 'I think, therefore I am' (*cogito ergo sum*) could be more minimally expressed as 'thinking, therefore being.' 'Thinking' requires that a process exists, just as 'going' does, but it does not require that we should reify that process' [72].

Importantly, Noble seems able to provide a promising theoretical 'bridgehead' towards what Cassell and humanistic medicine are missing: a valid causal theory of how 'bio', 'psycho' and 'socio' actually relate. In Noble's philosophy, the patient at an organismal scale – the self or the person – acts on smaller scale processes by *constraining*, limiting or focusing their interactions and so to determine their functions [64,65,70]. The dynamic organization of the whole *organizes* – or orchestrates – the smaller scale processes. As Noble indicates, downward causation can be depicted as focusing the lower level processes and thus enabling or bringing forth the emergent properties that arise from them and thus serve as a metaphor for agency and intentional action [17,26,70,73]. If information is defined 'as any kind of event that affects the state of a dynamic system' [56], patients continually create novel information through emergence. This information becomes part of the boundary conditions or dynamic organization of the whole and in turn acts as a feedback that makes a difference to functions at smaller scales [12,70]. This makes it possible to consider patients as being their own organizing principles, boundary conditions, feedbacks, constraints and attractors. Noble, like Cassell, also accepts the concept of intentionality and teleological explanations at the level of whole patients. For what kind of cause* is downward causation in terms of constraints? It is not a material or mechanistic (efficient) cause as in parts 'bumping' into each other, which is the standard way of looking at causation in biological science, but more like a formal and perhaps final cause [17,24,25]. As suggested by biologist Jim Shapiro, words like 'downward control' or 'downward regulation' may be more appropriate than 'causation', which connotes mechanisms [11].

Crucially, Noble is also in line with Cassell, when he states that the functioning of the self or person must be understood in a social context.

Relevance to clinical challenges

How may this be relevant to clinical problems like *MUS and multi-morbidity*? Epistemologically and methodologically, the theory of biological relativity implies that, when primary care doctors seek causal explanations for their patients' health problem,

they should not automatically regard smaller scale processes as the most valid focus of investigation. The scale of the living person, constrained by an environment, might be just as valid in understanding how a given trait is integrated or disintegrated. It may well be that medically unexplained symptoms, for example, those constituting the chronic fatigue syndrome [39], simply do not exist, or cannot be explained, at the level of molecules or cells, and that they reflect clinical scenarios where downward causation is especially important to consider. Biological relativity implies that the relevant physiology may be integrated at the scale of the patient in an environment. As a corollary, it may well be that the *disintegration* experienced and observed in such syndromes must be grasped by considering processes at these scales. At what level such integration or disintegration is to be pinned down is, according to Noble, an empirical question [64]. Meanwhile, we hypothesize that medically unexplained syndromes may be 'functional' in a very simple sense: their causal explanation may be found at the level of the context-dependent functioning of patients as persons, and their automatic, instinctual, habitual or volitional activities, including perception itself. It may well be that the very unexplainedness of these syndromes is related to the way traditional scientific medicine tends to leave larger scales out of the causal picture. They may be 'person-level disorders' left unexplained because persons themselves and their interpersonal relations are not considered to be root causes. Similarly, the effects of the doctor–patient relationship, so-called placebo and nocebo effects [78], as well as context-dependent personal experiences like loneliness [79] and other social conditions may also broadly be seen as integrating or disintegrating constraints. Note that, as Noble has pointed out [65], the traditional use of words like 'root' and 'underlying' to describe the most important causes falsely imply that they should necessarily be found at the bottom of some hierarchy of scales or levels. Metaphorically, constraints (downward causation) may perhaps suitably be described as 'overarching' causes in order to communicate their importance as 'the causes of the causes'.

The theory of biological relativity should also lead to a reconsideration of the concept of multi-morbidity and medical taxonomy. The ontological implications of the concept of downward causation would imply that what is considered separate diseases with separate causes may fruitfully be regarded as different manifestations of 'overarching' constraints. What is considered multimorbidities (e.g. different MUS in one person) may causally cluster at the level of patients as persons or their environment. The theory may also lead to a reconsideration of current efforts in disease categorization and the default premise that health problems are best categorized at the level of parts. One example is mainstream systems medicine itself, which seems to focus mainly on how diseases 'cluster at the genetic, molecular or mechanistic level' [5]. Another example is the genome- and brain-focused Research Domain Criteria developed by the National institutes of Mental Health for psychiatry [80].

Differences and remaining gaps

Although Noble's philosophy may contribute significantly to a bridging between scientific and humanistic medicine, there are certain differences with Cassell's and limitations that need to be considered. The most striking difference between the two is the relative absence of the concepts of meaning and value in Noble's writings. Noble also has trouble in fully accounting for consciousness and intentionality. But so has Cassell and science in general [81]. We believe this illustrates a more fundamental shortcoming, what Deacon calls the *unfinished business of science* [25]. In accordance with this, Noble underscores that there is *no genuine theory of biology*, and that systems biology must learn from other fields in developing its 'musicality' of life [10,69]. This points to a fundamental problem for scientists in general and systems biologists in particular: they do not fully know how to ontologically conceptualize their subject matter: living wholes [23,47,49,69,76,81]. The concepts that influence systems biological thought are currently taken mostly from the engineering sciences and physics, and systems biologists often emphasise the commonalities rather than the differences between man and machine [82,83]. If persons are to be considered their own self-organizers and constraints, it is important to note that these concepts do not as yet explain the difference between living agents and non-living entities [84]. For example, it is difficult to know what kind of agency or will is granted to humans when looking at them as their own *self-constraints*. Concerning the concept of attractors as a metaphor for goal-directedness, one must also note that attractors are rule-governed in a way that human beings may not be [85].

So, why did Denis Noble cry? In his book, he explains that the cause was related to his listening to a musical work: 'We would say that the causes of me crying include: Schubert, because he wrote the music; the piano trio, because they played it with such heart-tugging inspiration; and the beautiful context in which I first heard the music and first cried as a result of it. This, we would say, is in my memory and forms the emotional context' ([7]: p. 2). One could add that the crying could also be seen as an act, as caused by someone actively engaging with the music, and as meaningful symbolic communication unique to humans [86]. Human beings are not like conventional pieces of music. As Noble points out, living humans 'play themselves' [7]. And it is exactly here systems medicine faces its deepest challenge. Systems medicine risks reducing patients to systems, while current concepts of systems may be inadequate in comprehensively mapping human functioning [47,85]. Given such caveats, it is interesting to note that conceptual work is ongoing to further such understanding – with great potential for understanding of patients [17,20,22–26,41,56,57,63,76,77,81,87–92].

In addition to conceptual limitations, it is also important to note that Noble and Cassell differ methodologically. For while systems medicine is all about *calculating human life* in mathematical models, Cassell underscores the patient's narrative and the doctor–patient communication itself as key sources of information about living human systems. To Cassell, dismissing personal experience and meaning as unscientific is the cardinal mistake of medicine, it is like 'deploring the fact that patients are human' ([9]: p. xxiv). The humanistic medical interest in narratives stems from the need to grasp the complexity of human biology comprehensively [36]. However, although Noble may well agree, the concept of narrative plays little or no explicit role in his account. This leads to the question: Can systems medicine, defined as a purely quantitative science, tackle the fullness of human biocomplexity, which inevitably also defines the full complexity of human health and disease?

As we have noted, most of systems medicine has a strongly molecularized concept of and approach to patients. It is no coincidence that the website of the influential Institute of Systems Biology is called 'Molecular Me' [58]. However, systems medicine has also been characterized – and must be taken seriously – as *the medical science that aims to study the way wholes constrain their components* [93]. From an epistemological and methodological standpoint, this must mean that, in order to get a comprehensive understanding of *human health*, one must ultimately also consider specifically *human constraints*. In this regard, it is vital to remember that the evolutionarily derived and *key defining features of human biology* are in fact our cultural capacities of symbolic interaction and creation of narratives [94,95]. The theory of biological relativity implies that these human activities should, *a priori*, be considered as important when considering human health as lower-level functions.

This poses a fundamental challenge to systems medical projects: if systems medicine aims to bridge the genotype–phenotype gap, it needs mathematically usable representations not only of parts (genomes, transcriptomes, proteomes, etc.), but also of wholes, so-called *phenomes*. A phenome is a 'characterization of the full set of phenotypes of an individual' [96]. Intriguingly, human 'phenomics' and a Human Phenome Programme have been called for [55]. Taking the integrative perspective of general practice, we support the development of an organismic, wholes-oriented systems medicine [57]. However, no matter how detailed human phenomes may become, it is still difficult to see how systems biologists can mathematically represent human agency, intentionality and values which are linked to the defining human features of symbolic interaction and narrative. Considering that it is unclear how systems biologists are to quantify a human brain or a living human organism with symbolic behaviour and other social relations, an account of *all components of disease complexity*, as promised by Bousquet *et al*. [5], seems outside the scope of quantitative systems medicine. For example, if human agency, including symbolic activities, are causally influential constraints in medically unexplained syndromes, it is difficult to see how systems medicine can faithfully model these very common and costly health problems mathematically as is currently being proposed [38].

This is also important in considering systems medicine as 'personalized'. Systems biologists Wolkenhauer, Mesarovic and Wellstead state that 'personalized medicine (. . .) requires us to know the parameters that define the individuality of the particular patient' [97]. However, given that the constraints of human symbolic interaction and personal narrative are important in defining human particulars, and that these biological features cannot be meaningfully parameterized or otherwise mathematically described, systems medicine as a fully personalizing science also seems beyond reach even in theory. In practice, systems medicine also has the need to develop 'parameters that define the average, idealized, healthy individual' [3].

Significantly, founding father of systems biology, Ludwig von Bertalanffy [98], who originally also inspired George Engel's biopsychosocial model [30], was aware of such caveats. He regarded symbolism as a defining feature of humankind, noted that there are aspects of human biology one cannot expect to formulate mathematically and advocated complementary models formulated in ordinary language. In a way that seems fundamentally relevant today as systems biology is finally set to define medicine, Bertalanffy also cautioned against the dehumanizing potentials of a science that disregards such humanistic concerns:

> *'(. . .) to the new utopians of systems engineering (. . .) it is the "human element" which is precisely the unreliable component of their creations. It either has to be eliminated altogether and replaced by the hardware of computers, self-regulating machinery and the like, or it has to be made as reliable as possible, that is mechanized, conformist, controlled and standardized'* ([98]: p. 10).

Conclusion

We conclude that systems medicine *ad modum Noble* can contribute significantly in reinstating the person in human biology and medicine. But while Noble's theoretical effort within the field of systems biology is a significant step towards bridging the sciences–humanities gap, systems medicine seems likely to remain *incomplete* as a foundation for clinical understanding and practice. Considering also that most of today's systems medicine seems more molecularly focused than Noble, the image of systems medicine as 'holistic', 'personalized', 'patient-centred' or 'humanistic' in the sense being directed towards the 'patient as individual subject' lacks an adequate theoretical foundation at this time. As Noble also makes crystal clear: 'On the one hand, it seems sensible to deal only with what we can observe, measure and understand. This is the pragmatic approach of science. (. . .) On the other hand, it is laughably presumptous to suppose that this resolves all questions about life. Clearly, it can't' ([75]: p. 120).

Systems medicine must therefore be complemented with other methods. Again, Noble seems to recognize this: 'The point is that in practice we *know* when we act intentionally. We don't need to study our brain states to know that' ([7]: p. 125). Narrative-based medicine and phenomenology are examples of candidates for such complementary fields of knowing, and efforts are ongoing in linking human biology to phenomenology [17,36,37,39,40,81].

Hunter and co-workers have stated that systems biological models should be integrated with 'wisdom produced in the research laboratories and in clinical practice' [4]. We suggest that the wisdom of experienced general practitioners [1] and core challenges like multi-morbidity and medically unexplained symptoms should serve as reference points of primary care complexity in the development of systems medicine. The similarities and differences between Cassell and Noble may also serve as one fruitful point of departure for further work in developing a future unifying theory of medicine. Ultimately, systems medicine may also have to recognize that, to faithfully model a human being, it is necessary to be a human being.

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