Conceptual and theoretical specifications for accuracy in medicine *

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Abstract

Technological developments in genomics and other -omics originated the idea that precise measurements would lead to better therapeutic strategies. However, precision does not entail accuracy. Scientific accuracy requires a theoretical framework to understand the meaning of measurements, the nature of causal relationships, and potential intrinsic limitations of knowledge. For example, a precise measurement of initial positions in classical mechanics is useless without initial velocities; it is not an accurate measurement of the initial condition. Conceptual and theoretical accuracy is required for precision to lead to the progress of knowledge and rationality in action.

In the search for accuracy in medicine, we first outline our results on a theory of organisms. Biology is distinct from physics and requires a specific epistemology. In particular, we develop the meaning of biological measurements and emphasize that variability and historicity are fundamental notions. However, medicine is not just biology; we articulate the historicity of biological norms that stems from evolution and the idea that patients and groups of patients generate new norms to overcome pathological situations. Patients then play an active role, in line with the philosophy of Georges Canguilhem. We argue that taking this dimension of medicine into account is critical for theoretical accuracy.

Keywords: Personalized Medicine, Normativity, Theoretical Biology, Organization, Technology

1 Introduction

Medicine is not a science but an art that builds on sciences (Canguilhem, 1972). It follows that modern medicine always took into account scientific evidence. In this perspective, the name "evidence-based medicine" is somewhat misleading. Moreover, this methodology was never supposed to build on scientific evidence alone. Instead, proponents of evidence-based medicine also acknowledge the physicians' experience (Sackett et al., 1996; Masic et al., 2008). A similar misnaming occurs for personalized and precision medicine. Since Hippocrates, medicine has always been personalized, and hopefully, medicine always aimed for a reasonable level of precision.

"Evidence-based medicine" and the more recent "personalized medicine" and "precision medicine" are notions that are partially misnamed — their name emphasizes a general aspect of medicine that is not specific to them. These names are less appropriate for philosophy and scientific reasoning than for marketing strategies targeting the medical community, patients, managers, and political deciders. They suggest that other approaches are lacking in

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the designated area: nobody defends a medicine that would ignore scientific evidence, would be imprecise, or would not take into account the individuality of patients.

Nevertheless, these different stances concerning medicine correspond to specific strategies for the organization and practice of medical care. These strategies are both epistemological and technological. To an extent, they aim to overcome the shortcomings of previous practices and introduce technological changes in therapeutic work. Thus they are designed to be performative, not descriptive. More precisely, the changes introduced are organological in the sense of Bernard Stiegler (Stiegler and Ross, 2017): they advocate a reorganization of human activities through their technological instruments of publication, measurement, cure, and care. Let us discuss each case briefly.

Evidence-based medicine has two main specificities. First, randomized trials are paradigmatic scientific evidence in this framework. Researchers use statistical tests to analyze the effect of a treatment by comparison with a former treatment or no treatment at all. Randomized trials aim to reduce biases by randomly constituting treatment groups and, when possible, hiding the nature of the treatment given to both patients and caregivers (to correct the placebo effect). In the vocabulary introduced in Montévil (2019a), this method defines symmetrizations, that is to say, the constitution of groups that are similar in a given sense, even though they are never genuinely equivalent biologically. Evidence-based medicine showed that several physiological reasoning leading to widespread prescriptions were actually harmfull. For example, after head injuries, inflammation is a risk factor. However, a clinical trial showed that corticosteroids increased the risk of death and that the standard prescription was detrimental to patients (Edwards et al., 2005). Similarly, myocardial infarction can lead to arrhythmia; however, a clinical trial showed that drugs used to suppress it, encainide and flecainide, actually increase the risk of death (Echt et al., 1991).

Second, evidence-based medicine was proposed in the 80s and emerged in the 90s and 2000s. At this time, biomedical research underwent massification and changed its means of publication progressively, from printed papers to digital media. In this context, it is physically impossible for physicians to follow all the relevant scientific literature even though they are traditionally ethically compelled to do so — physicians are required to provide the best possible care. For research to irrigate clinical works, a methodic approach was necessary. Evidence-based medicine proposes for physicians to catch up with the literature based on the cases encountered. It also organizes the literature by the publication of syntheses: reviews and statistical meta-analyses of randomized trials. Meta-analyses are computational summaries of published results, based on statistical computations (Sackett et al., 1996; Masic et al., 2008; de Leon, 2012).

Personalized medicine and precision medicine stem from a critique of randomized trials, and more specifically of the idea that individuals will exhibit a qualitatively similar response to a given treatment (de Leon, 2012; Cohen and Hersh, 2004). For example, personalized medicine advocates the constitutions of subgroups that may display different responses — a method called stratification. However, by itself, stratification is far from new. For example, the definition of blood groups is a stratification — blood transfusion to a patient may kill or cure her depending on the compatibility of the receiver with the donor. For a large part, the specificity of personalized medicine stems from the introduction of high throughput, relatively low-cost measurement technologies, in particular genomics and sometimes proteomics or microbiome analysis — technics at the molecular and cellular level (The Personalized Medicine Coalition, 2014). From this perspective, "personalized" would just mean adjusted to some genomic or other molecular-level properties — a very reductionist stance that possesses fundamental limitations (Soto et al., 2016b; Bevilacqua, 2019).

However, personalized medicine is also emerging when other technologies are being developed, such as cloud computing, especially the new database and deep learning technologies. The connection between personalized medicine and these technologies is undecided

to no small extent. It remains at the level of prototypes and projects such as IBM Watson (Rhrissorrakrai et al., 2016) — a project that is seemingly not in good shape. The principal, certain applications of personalized medicine remain limited to specific cases of genetic correlations associated with the choice of a few drugs or the adjustment of drug doses (The Personalized Medicine Coalition, 2014). As a result, it is critical to distinguish the real practices, and knowledge from the attempts at performative technological discourses pushed forward by several stakeholders. Let us emphasize that using high throughput methods requires statistical methods. When the latter does not build on the concept of machine learning, they use complex computational models built on classical concepts of statistical analysis.

In this context, the relationship between evidence-based medicine and personalized medicine also remains a matter of debate. For some authors, personalized medicine should be a further development of evidence-based medicine — a logical stance considering that current applications are limited to the use of new observables for the stratification of patient groups (Chow et al., 2018). For others, there is a paradigm shift between the two approaches. Randomized trials assume the homogeneity of the intended population; by contrast, personalized medicine would consider that populations are fundamentally heterogeneous (de Leon, 2012). The latter option culminates in the notion of $n = 1$ experiments, where an experiment is performed repeatedly on a single individual to provide clues on her response and find suitable treatments.

As mentioned above, the core of these approaches is technological, empirical procedures, where statistical computations are central. However, the bare use of statistical methods is a misuse. More than 800 statisticians defend the idea that the categorization of results by statistical significance (p-values) is damaging science and should not be performed anymore (Amrhein et al., 2019). Along the same line, the American Statistical Society felt compelled to produce a statement on the use of p-values, a unique situation since statements by scientific societies usually target non-academic actors, such as decision-makers (Wasserstein and Lazar, 2016). Let us quote this statement:

> Practices that reduce data analysis or scientific inference to mechanical "bright-line" rules (such as "$p < 0.05$") for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision making. [...] Researchers should bring many contextual factors into play to derive scientific inferences, including the design of a study, the quality of the measurements, the external evidence for the phenomenon under study, and the validity of assumptions that underlie the data analysis. [...] The widespread use of "statistical significance" (generally interpreted as "$p < 0.05$") as a license for making a claim of a scientific finding (or implied truth) leads to considerable distortion of the scientific process.

Part of the (intellectual) context of a scientific experiment is the scientific framework in which it takes place, especially its theoretical and epistemological framework. By contrast with the idea that data and statistics could replace the scientific method (Anderson, 2008), statisticians emphasize the role of hypotheses and the underlying scientific reasoning to interpret data and perform statistical analyses. Detailed analyses emphasize this point (Leonelli, 2014; Montévil and Longo, 2018). Evidence-based medicine and personalized medicine are lacking in that regard. Evidence-based medicine focuses on the generic concept of the randomized trial without addressing the theoretical background of such trials, especially the causal analysis of the treatment attempted. Existing personalized medicine builds mostly on genetic determinism, a somewhat outdated perspective; for example, in some cases, overall gene expression does not reflect radical phenotypic changes (Po et al., 2019). Moreover, the genocentric view can only analyze differences between individuals and groups; therefore, it is blind to general trends such as the current pandemics of non-communicable diseases, a

critical topic for current public health (Moodie et al., 2013).

At this point, it is useful to introduce the conceptual difference between precision and accuracy. Let us start with a familiar image: shooting arrows at a target. Precision describes whether arrows hit a specific area of the target consistently, but not necessarily its center, while accuracy represents whether arrows hit the center of the target. In terms of classical measurement[1], precision describes how consistent a measurement method is, while accuracy describes whether measurements correspond to the genuine theoretical target, for example, the right observables without systematic biases. Here, we emphasize that genuine scientific accuracy requires a theoretical framework, whereas precision makes sense in more lenient settings. Let us take a medical example. Heart rate, as defined by EEG patterns, may be measured with very high precision; however, this precision does not make much biological and medical sense since this rate is a non-stationary time series: its average changes over time, at all time scales. It is far more biologically accurate to obtain a reasonably precise measurement of the value of heart rate complemented by an analysis of its variability (West, 2006; Longo and Montévil, 2014). We want to emphasize that an excess of precision in reading instruments is considered bad practice in physics and that measurement reports are limited to significant figures, the digits that are assumed to be accurate accounts of the intended theoretical quantity. By contrast, further digits are noise from the measurement apparatus, and reporting them in publications is a bad practice that mixes significant figures and noise. Let us take a final example. In classical physics, both initial position and velocity measurements are required to make predictions. Without velocity, even extremely precise measurements of the initial position are inadequate to make predictions. Such measurements are insufficient and thus inaccurate for prediction purposes.

In this context, we remark that precision medicine is well-named since it is driven by the precision and ease of use of molecular measurement technologies, and not by a rational understanding of health and disease. By contrast, we contend that it is impossible to progress towards accuracy in medicine without proper theorization. In this chapter, we will first review some aspects of the collective work of theorization that the "organism group" as performed. In 2013, Ana Soto created this transdisciplinary group in the context of her Blaise Pascale Chair in École Normale Supérieure. This group aims to investigate theoretical principles to understand organisms in the postgenomic era. Members are Ana Soto, Giuseppe Longo, Nicole Perret, Maël Montévil, Carlos Sonnenschein, Matteo Mossio, Arnaud Pocheville, and Paul-Antoine Miquel. Then, we will point to several theoretical specificities when addressing human health.

2 Theoretical perspective on organisms

In the introduction, we emphasized that theory seems to be excluded from medical paradigms such as evidence-based or personalized medicine. This lack of theorization has very practical consequences. For example, system thinking could bring about significant progress in biology and medicine (Noble, 2017; Joly and Rondó, 2017). In the NIH (National Institutes of Health) report on systems pharmacology by Sorger et al. (2011), the authors refer to the work of Noble (2002) and consider it a paradigmatic success. However, their scientific recommendations, surprisingly, do not include the central points of Noble's approach. The problem lies in the forceful choice of a molecular ontology to describe phenomena. In heart study, organ geometry and the properties of depolarization waves on this geometry are critical. They are not entailed by generic descriptions at the molecular level of the functioning heart since, among other reasons, these geometric properties are the diachronic results of ontogeny

[1] In classical physics, a system has a state that can be measured with arbitrarily high precision, in principle. However, and again in principle, this precision is never perfect, which is why some systems can be at the same time deterministic and unpredictable.

and not of the processes taking place in the adult beating heart. We think that assimilating the lessons of D. Noble's work is difficult despite its acknowledged success because of the overall lack of theoretical fluency in biology.

We call theoretical fluency the ability to recognize that any scientific statement depends on theoretical assumptions and an underlying epistemological framework. Theoretical fluency also requires acknowledging that a change of framework may be required either for empirical reasons or as a result of intrinsic contradictions of a theoretical framework or contradictions with other, established, and relevant theoretical perspectives. Of course, one may have a perspective of choice, but the progress of science requires the ability to acknowledge and analyze critically other theoretical perspectives and, when needed, to develop new ones. Otherwise, the adhesion to a perspective becomes a dogma that rational criticism cannot reach. Along this line, the lack of sound theoretical debates on carcinogenesis arguably hinders both scientific research and progress in medical care (Sonnenschein et al., 2014; Sonnenschein and Soto, 2016; Montévil and Pocheville, 2017).

In this situation, paraphrasing Noble (2008), a lot should be done to theorize properly biological organisms. To address current theoretical challenges in the study of organisms, Ana Soto gathered an interdisciplinary group that proposed several new theoretical principles (Soto et al., 2016b). These principles aim to frame and guide both modeling and empirical works in biology. We argue that they also should be useful for medical practice and the critical analysis of scientific evidence — provided that evidence only makes sense in a theoretical framework that defines observables and concept(s) of causality.

The principle of variation posits that invariants underlying the descriptions of biological patterns are ultimately contingent; they have a historical origin and can change over time (Montévil et al., 2016a). This situation is in sharp contrast with theoretical physics' epistemology, where invariants are postulated and explain how objects change over time (Longo and Montévil, 2017). In biology, we posit that there are no such invariants. Without underlying invariants, the nature of biological changes is radically different from the ones in physics, and we need to reassess critically the perspectives inherited from physics epistemology. Biological processes involve the emergence of novelties in a strong sense (Montévil, 2019b). Accordingly, current biological patterns stem from the historical emergence of such novelties at all temporal levels (evolution and ontogenesis). Let us emphasize that the modelization of a system that is the result of history cannot always be performed with the same method as in anhistorical systems, like in physics (Montévil, forthcoming). Moreover, contexts can change biological organizations without an underlying invariant to subsume these changes. The concept of biological context is then different from the concept of boundary conditions in physics. The latter assumes that the changes taking place inside the system follow equations, with their underlying mathematical invariants and invariant preserving transformations (symmetries). Without these theoretical entities, biological contexts have a deeper impact on an object than in physics. In a nutshell, biological objects become fundamentally contextual and historical.

This perspective alone is insufficient, and we need a specific way to account for biological patterns, that is, biological regularities. We call "constraints" the regularities shaping transformation processes. This action of constraints corresponds to a first kind of causation. More precisely, constraints are regularities in the sense that they are conserved at the time scale of the process they affect but can change at other time scales (Montévil and Mossio, 2015). Most of them are far from thermodynamic equilibrium properties: they need to be actively sustained by the use of flows of matter, energy, and entropy from the organism's surroundings. However, organisms are not spontaneous self-organization of flows, unlike flames or cyclones. The latter are the generic result of stable equations once the proper flows are triggered We insist that this is not a side property; instead, it is a fundamental component of physics' method to understand these phenomena. However, the assumptions of this method do not fit the principle of variation. Unlike "physical laws," which are postulated, constraints

are fundamentally historical. As result constraints make possible the appearance of new constraints, a second kind of causation that we called enablement. In the context of the principle of variation, we cannot rely on underlying, postulated invariants. Then, specific reasoning lines are required to justify their theoretical validity and to understand why some constraints last for an extended period. Natural selection explains part of this stability at the level of evolution: variations that do not lead to a viable lineage are selected against. At the level of organisms, we assume that constraints collectively maintain each other, and we have developed a framework to analyze this situation that we called the closure of constraints (Montévil and Mossio, 2015; Mossio et al., 2016). This framework reconnects with principled concepts in Bernard et al. (2015), and the organicist tradition in theoretical biology (see Varela et al., 1974; Rosen, 1991; Kauffman, 1993) where the meaning of parts depends on their relationship with the whole.

Last but not least, cell theory remains fundamental in biology; however, it is insufficient to understand cellular behaviors. As a result, modelers choose hypotheses somewhat randomly (Montévil et al., 2016b). To overcome this situation, building on previous work (Sonnenschein and Soto, 1999), we proposed to reuse a method of theorization existing in physics that starts by defining a "default state." For example, inertia describes what happens when nothing is done to an object in classical mechanics, and the departure from the state of inertia requires a cause by hypothesis; causes are forces in this context. Let us emphasize that, in this method, causation is defined by the departure from the default state. Similarly, the default state of cells is what they do spontaneously. We posited that the default state of cells is proliferation (with variation) and motility, in line with the theory of evolution (Soto et al., 2016a). Like in the case of inertia in physics, a departure from the default state requires causes. In our framework, these causes are constraints. In a developing organism, cells proliferate, mutually constrain each other, and generate other constraints acting on the default state. This perspective transforms the analysis of phenomena such as carcinogenesis or development because the study of constraints and their action on the default state becomes central (Montévil et al., 2016b; Sonnenschein and Soto, 2016; Montévil and Pocheville, 2017).

In this overall framework, we can specify the theoretical nature of the access to empirical objects, that is to say, the theoretical nature of measurement as commonly thematized in physics (Montévil, 2019a). This theoretical question also illustrates the epistemological structure of the theory we are sketching. To fully understand the situation in biology, a critical comparison with physics is necessary due to the historical trickling down of physics views in biology without the corresponding theoretical backbone. In physics, measurement is mostly about getting the position of an object in a theoretically pre-defined space — position and momenta in classical physics. This view is justified by the hypothesis that underlying equations and the corresponding patterns are static. In biology, however, there are changes in constraints and novelties that generate new relevant quantities and relations.Consequently, measurement is firstly about the determination of the relevant constraints, defining an organization. These constraints are never all *explicitly* determined because biological organisms are too complex, and new constraints appear over time. That is to say; constraints are partially unknown both for epistemic and principled reasons. As a result, it is impossible to follow the physics view, which defines objects by static mathematical relations, and the corresponding invariants. An accurate alternative is to refer to historical relationships, for example, defining groups by a common ancestor. We analyze that the practical way to define experimental organisms builds on their historicity, a rational that is theorized in systematics. The phylogenetic classification of living beings, for example, provide the names used ubiquitously in biology. In this method, groups are all the descent from a common ancestor. The same strategy is used to define laboratory strains of cells, animals, and plants, albeit, in some cases, the history of objects can be complex such as in the case of chimera. The growing weight of the microbiome in the analysis of metazoa also entails that we should consider that complex natural histories are

the norm more than an exception.

Let us emphasize that historical definitions do not entail the same kind of practical definition of the object than the definitions of physics. In physics, objects with the same theoretical identity can be obtained *de novo* because it is sufficient for objects to follow the same invariants to be theoretically identical. By contrast, historical definitions require a material connection and a concrete object as reference for a class — all other objects of the group are connected genealogically to this reference specimen by definition.

Defining objects by their past leads to definitions that remain valid whatever variation occurs. At the same time, this kind of definition does not explicitly provide a control on the organization of objects, that is, the properties relevant for experimental biology and medicine. However, it does give a partial control on these properties, due to the limited pace at which novelties appear and the stabilizing processes mentioned above, that is, natural selection and organization sensu closure of constraints (Montévil and Mossio, 2020). By definition, constraints have more or less intrinsic stability (Montévil and Mossio, 2015), and the stabilizations discussed above are more or less intense, depending on the constraints considered. Moreover, the historical dimension of measurement is complemented by direct observation and control of a limited number of constraints, such as the criteria used in tests to enter a randomized trial. Contexts are also critical and can be controlled more or less strictly before and during an experiment. In the case of human experiments, this control is always limited for obvious ethical reasons, whereas experiments on other living beings can control context strictly for generations (Montévil, 2019a).

In this framework, part of the theoretical concept of measurement is a procedure of symmetrization: organisms are considered as equivalent when they have a given shared past, a shared more or less controlled context and some similar constraints that may be directly observed. However, organisms are never genuinely equivalent because variations always occur according to the principle of variation. Depending on the cases, symmetrization can be sufficient to study the structure of one or several related constraints and the structure of the relationship of these constraints with organisms as a whole.

In this context, there are several measurement strategies. Some may aim to obtain organizations that are as close as possible to each other, for example, a population of inbred mice in controlled conditions. However, this somewhat standard strategy bears a cost: it studies a very specific organization which may be far from representative of the population of interest. By contrast, it is also possible to embrace biological diversity in order to obtain results with some general validity. For example, instead of using a single inbred strain, biologists sometimes use several laboratory strains or even wild animals. The cost is a higher variability of the results, and sometimes uncertainty on the nature of what is measured since the underlying constraints may be diverse. It follows that empirical evidence in biology builds on a compromise between stronger symmetrizations that provide very specific results, and more generality that goes together with a more significant diversity of the objects measured. Building on this trade-off seems more accurate than the opposition between evidence-based medicine and personalized medicine.

To synthesize this theoretical view, we have introduced a framework that integrates the two kinds of epistemology required. Constraints correspond to the relational component of organisms' definition, and are epistemologically closer to physics. Constraints are not principled, theoretical invariants. However, they are valid for a time and a group of organisms, with possible variations requiring different definitions — a change of constraints. It follows that they can be investigated both empirically and by modelizations. In particular, disorganizations such as diseases do not involve a change of all constraints. For example, from the perspective of our framework, the heart model of Noble describes many constraints that are common to health and disease, and only some of them are altered in diseases, leading to irregular heartbeat or even a stroke — this is why this model can analyze several diseases

at the organ level.

We also introduced a new symbol, χ, that represents the contextual and historical component of the theoretical and practical definition of organisms, in combination with constraints (Montévil and Mossio, 2020). We contend that this kind of epistemological architecture is required for theoretical accuracy in biology. For example, observing only constraints is insufficient to define objects, and such observations also require historical and contextual specifications. It follows that precision medicine, understood as genomics-based medicine, is inaccurate: it accommodates DNA sequences, which acts as constraints on many processes but are a small part of the organization. However, it does not take into account a significant part of organizations. It does not acknowledge the historical component of biological definitions, for example, life history in the case of medicine. Last but not least, introducing, χ, that is to say, historical definitions, implies that we acknowledge the epistemological limitations of descriptions relying only on explicit constraints, including the ability of organisms to generate functional novelties.

3 Applications and extensions to medicine

Let us discuss the consequences of our framework for medical care. First, we examine these consequences at the strictly biological level, and, accordingly, this part of our discussion applies also to veterinary care. Then, we introduce concepts and questions proper to humans.

According to de Leon (2012), the difference between evidence-based and personalized medicine is that the former assumes homogeneous populations, while the latter does not. This author calls for a perspective that would integrate what these two approaches bring to the table, and we think that our framework meets this specification. On the one side, the constraints of interest may be common to a group of organisms, and their integration to the organism, that is to say, their function, may be generic to an extent. Then, we can justify the assumption that a population is homogeneous for these constraints, and thus support the use of randomized trials. On the other side, populations of organisms as such are ultimately heterogeneous, and this may have more or less impact on the constraints of interest — these constraints may change, or their integration with the rest of the organism may be different (Montévil, 2019b; Montévil and Mossio, 2020).

The analysis of regularities as constraints opens the possibility to integrate different levels and scales, a critical challenge for systems pharmacology and medicine (Sorger et al., 2011; Stéphanou et al., 2018). For example, DNA sequences are constraints on protein production, but the vascular system's geometry is also a constraint, which acts on blood flow. Using this language implies departing from the strictly molecular ontology inherited from the molecular biology revolution, without neglecting its results — the latter can be reinterpreted critically from the organicist perspective. Incidentally, our framework also enables biologists to reinterpret models based on the epistemology of physics. From our theoretical perspective, these models build on constraints and require an explicit articulation with the rest of the organism and the historical dimension of biology.

In our framework, organisms are not objects that follow generic rules. Some aspects of them, constraints, may have restricted genericity; however, the constraints we know at a given time do not entirely and accurately define organisms. It follows that biological norms are not generic; in particular, statistical norms should not be conflated with the organicist norm of a given patient — the norm defined by the analysis of its organization. This idea is emerging in personalized medicine, albeit mostly at the genomic level. When building on this level, norms are somewhat individualized, but they are static and defined at fecundation (except in the case of cancer interpreted with the somatic mutation theory). When faced with diseases or environmental challenges, organisms can generate new norms, at least to an extent. This normativity is central to the conceptualization of medicine by the philosopher and medical

doctor Canguilhem (1972). It is also a question that biologists increasingly take into account (West-Eberhard, 2003).

Last, current drug designs focus on pushing a target variable towards its statistical norm. If this variable plays the role of constraint, then this normalization can be useful to prevent the disorganization of constraints that depend on it — assuming that the statistical norm is appropriate for the organism of interest. This therapeutic strategy fits well with the kind of evidence promoted by evidence-based medicine. Theoretically, it matches the cybernetic paradigm where the existence of a target value is a critical assumption, and homeostasis for this value results from feedback mechanisms. However, we argue that this paradigm is insufficient because it does not accommodate the structure of biological variability (West, 2006) and the articulation between such quantities and the organism (see Bich et al., 2020, for a detailed example and a discussion). As a result, normalizing the value of a quantity tends to hinder more involved strategies where the interdependence between several aspects of the patient is critical, and analyses at different levels are necessary. Some such situations can be relatively generic; however, they may also be specific to an individual. Then, the practitioner aims to respond to the patient's normativity and accompany it instead of enforcing a statistical norm that is inadequate for the patient.

As mentioned, the discussion to this point is not specific to medicine as such; that is to say, the care of humans. Let us now analyze aspects proper to medicine. To address this question, we consider that a characteristic of humans, beyond the physiological and developmental specificities of *Homo sapiens*, is the massive plasticity that stems from the *noesis*, thinking, and the cultures that it generates. Noesis and culture are not just symbolic; they contribute to shaping human bodies, and the world humans live in. In particular, technics generate what can be analyzed as exosomatic organs, leading to a major transition in the process of evolution, that is to say, evolution by producing inorganic organs, typically artifacts (Lotka, 1945). Similarly, culture shapes the non-human organisms living in human worlds, both by the extinction of large predators and the domestication of plants, animals, and even bacteria, for example, to produce fermented food. All the corresponding practices are shaped by knowledge in the broad sense instead of biological evolution alone.

What are the consequences of this theoretical framework on medicine? We discussed above the contextual nature of biological objects: in the absence of principled theoretical invariants, constraints of an organism depends on their past and present contexts. It follows that changes in technics, for example, typically can be associated with changes of organizations even at the strictly biological level. Let us unpack this idea.

A patient's conception shapes the biological level significantly. A patient anticipates her future, and these anticipations impact her medical decisions straightforwardly. In this sense, patient anticipations are a normative force on the biological level of description, via medicine.

Moreover, the way a patient conceptualizes her own body has a profound impact on diseases, as exemplified by the fact that some diseases are specific to a culture (Kuriyama, 1997, 1999). Moreover, a patient's conceptions impact her everyday life, and the latter profoundly influence health and disease, as illustrated by the current pandemic of non-communicable diseases (Moodie et al., 2013).

Technics and technologies shape more or less directly biological norms and diseases. Let us consider dyslexia. This condition only makes sense once writing appeared. To better understand this case, it is critical to recall that writing appeared relatively recently in human history and became a practice of general populations even more recently. As a result, the ability to perform these activities is not stabilized by evolution. Unlike spoken language; reading and writing require exaptations of several brain areas that are facilitated at each generation by pedagogic methods. Moreover, these exaptations differ depending on the writing system and the media — which explains why reading with digital media differs from reading on paper (Wolf and Stoodley, 2008). In this case, technics, culture, and biology become intertwined

to define health and disease, and it stands to reason that norms cannot stem only from the evolutionary past.

The case of dyslexia may be seen as somewhat specific since it corresponds to the mastery of a specific technic (reading and writing). However, we argue that the impact of technics on biological property is deeper. Protsiv et al. (2020) observe a decrease of body temperatures since the industrial revolution. Moreover, the pandemic of non-communicable diseases, such as diabetes and obesity, is a major illustration of the intrication between technics and somatic health. This pandemic stems from the organization of production and the prescription of behaviors by mass media and advertisement. However, the relationship between technics and organic properties is far broader. As pointed out by (Lotka, 1945), technics are a fundamental part of the way humans evolve, i.e., change the way they live, in a process that he called exosomatization; that is to say, the functional use of non-somatic organs. However, this process destabilizes both somatic and social organizations, and, in the philosophy of B. Stiegler, care and knowledge are critical for social and biological reorganizations to incorporate new technics and technologies, mitigate their toxicity and reshape them to this end when needed (Stiegler, 2016; Stiegler and Ross, 2017). The pandemics of non-communicable diseases driven by industrial technologies strongly suggest that much work remains to be done to mitigate the negative impacts of current technologies on the biological level (Moodie et al., 2013). In this context, the theoretical analysis of how technics can disrupt biological organizations remains insufficient (Montévil, submitted). Such disruption range from the chemical level, for example, in the case of endocrine disruptors, to the use of digital media by young children and their parents. Endocrine disruptors are chemicals or mixtures of chemicals that interfere with hormone action and disorganize the development and physiology of exposed organisms (Zoeller et al., 2012). Similarly, digital media, especially smartphones, tend to capture attention by design and disrupt the relationship between children and their parents and between children and their toys, leading to detrimental consequences (Brown and et al, 2011).

Following the broader line of reasoning of Bernard Stiegler and the *Ars Industrialis* group (Stiegler and Kyrou, 2015), we argue that future medical care requires developing popular knowledge. Groups typically generate such knowledge. Examples are groups of patients with a chronic disease, such as diabetes, or patients experiencing addiction such as alcoholism (Kelly et al., 2020). Such knowledge should be generated on the vectors of these non-communicable diseases, and, more generally, on the changes introduced by technics and technologies. Such knowledge should shape technology uses and technological developments towards less toxic paths. In other words, normativity should extend beyond the somatic body including for the heath of the somatic body. For example, knowledge on food, from raw products to cooking has a direct impact on somatic health, including the microbiome and the immune system. Another direct example are prostheses from glasses to artificial limbs with digital technologies. However, the general idea that we defend is that there is no sharp line between prostheses and general technologies. For example, technologies are central to follow sugar levels in the case of diabetes. Knowledge is also relevant for the prevention concerning vectors of communicable diseases that are indirectly affected by technologies, like the tiger mosquito, which migrates in response to climate change. In this perspective, patients and the general public are no longer considered as passive recipients of vulgarized medical knowledge, making informed decisions; instead, they become normative not only for themselves but for technologies as such. Moreover, this normativity does not stem from individuals. Instead, it is the result of collective work, and primarily group works.

This general reasoning also applies to medical care practitioners. Medical practitioners have to tame the technologies that they use to ensure the accuracy of their work. To this end, a critical assessment of the technologies pushed forward as precision or personalized medicine is mandatory. This assessment should include the theoretical points we have developed above; however, it should also include the consequences of these technologies for

the practitioners. For example, relying on automated diagnosis means that knowledge is transferred from the practitioner to the technological apparatus. This transfer entails a loss of practitioner knowledge in a process called proletarianization. By contrast, computers can be used to increase clinicians' capabilities in the sense of Sen (1999). These capabilities should enable medical care practitioners to go beyond the application of standardized protocols and accompany patients' normativity better, both at the individual, biological level, and at the group, noetic level.

Let us wrap our discussion up. Accuracy in medicine requires a well-defined theoretical basis. We argue that this basis should analyze organizations as a whole and in their historicity. Historicity means that organizations are the result of history but also that they produce history by generating new constraints. It follows that statistical norms and biological norms cannot be conflated and that medical practitioners cannot always follow standardized protocols if they are to accompany this normativity. This normativity is not just strictly biological. Instead, patients' ability to generate knowledge is part of this normativity, and this work is typically performed in groups. Groups are then a fundamental level for health care. Let us emphasize that the current period is characterized by rapid changes in technologies or due to technologies, such as climate change. As a result, an accurate account of health care cannot ignore this group level normativity that impacts lifestyles, technics, and biological properties. Last, the same applies to the use of technologies by healthcare practitioners themselves, such as the ones advocated by evidenced-based or precision medicine. Technologies require specific knowledge to mitigate their negative consequences, and specifically, algorithmic methods tend to ignore normativity at all levels.

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