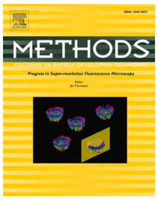
Methods 195 (2021) 113–119

Contents lists available at ScienceDirect

Methods

journal homepage: www.elsevier.com/locate/ymeth



Biologically grounded scientific methods: The challenges ahead for combating epidemics

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ARTICLE INFO

Keywords:
Scientific methods
Method development
Biologically grounded methods
Conceptualization and operationalization
Data structuring

ABSTRACT

The protracted COVID 19 pandemic may indicate failures of scientific methodologies. Hoping to facilitate the evaluation and/or update of methods relevant in Biomedicine, several aspects of scientific processes are here explored.

First, the background is reviewed. In particular, eight topics are analyzed: (i) the history of Higher Education models in reference to the pursuit of science and the type of student cognition pursued, (ii) whether explanatory or actionable knowledge is emphasized depending on the well- or ill-defined nature of problems, (iii) the role of complexity and dynamics, (iv) how differences between Biology and other fields influence methodologies, (v) whether theory, hypotheses or data drive scientific research, (vi) whether Biology is reducible to one or a few factors, (vii) the fact that data, to become actionable knowledge, require structuring, and (viii) the need of *inter-/trans*-disciplinary knowledge integration.

To illustrate how these topics interact, a second section describes four temporal stages of scientific methods: *conceptualization*, *operationalization, validation* and *evaluation*. They refer to the transition from abstract (non-measurable) concepts (such as 'health') to the selection of concrete (measurable) operations (such as 'quantification of anti-virus specific antibody titers'). *Conceptualization* is the process that selects concepts worth investigating, which continues as *operationalization* when data-producing variables viewed to reflect critical features of the concepts are chosen. Because the operations selected are not necessarily valid, informative, and may fail to solve problems, *validations* and *evaluations* are critical stages, which require inter/trans-disciplinary knowledge *integration.*

It is suggested that data structuring can substantially improve scientific methodologies applicable in Biology, provided that other aspects here mentioned are also considered. The creation of independent bodies meant to evaluate biologically oriented scientific methods is recommended.

1. Introduction

The COVID-19 pandemic can be viewed as a global educational experience. Never, before, so much was published so fast on a single topic: +147,000 peer-reviewed papers were generated within 15 months. Yet, the lessons emerging from this experience do not seem to be globally learned: the fact that the pandemic has lasted so long suggests that the scientific methodology has been inadequate.

Even one and a half years after the beginning of this unprecedented problem, no worldwide dialogue on how to face it has been observed [1]. With some exceptions, there is no international process that brings together researchers, politicians, and citizens under the same roof [2]. Not surprisingly, failures have occurred.

Unsuccessful efforts include, although are not limited to (i) the hypothesis that some levels of '*herd immunity*' (a number derived from assumptions on the average number of secondary infections induced by a primary case) can *protect* –a proposition refuted in places where two or more epidemic waves have occurred even with a very high (76%) level of 'herd immunity' [3]; (ii) *predictions on the number of cases and deaths expected to occur at a certain time* point, which have erred by very large amounts [4]; (iii) the *assumption that any vaccine can protect even when new viral mutants emerge* [5]; (iv) exaggerated optimism regarding treatments that did not materialize [6], and (v) the belief *that a pandemic can go away even when there is no explicit policy on diagnostics* [7,8]. The

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https://doi.org/10.1016/j.ymeth.2021.09.001
Received 14 June 2021; Received in revised form 26 August 2021; Accepted 2 September 2021

last assumption relates to the fact that no country knows the number and location of non-symptomatic infections because, given their ‘invisibility’, it would be necessary to test, frequently, 100% of the population with tests designed to diagnose. The previous facts suggest failures involving, partially or totally, the ‘scientific method’ (which, most likely, is a plurality, not a singularity), the individuals or agencies expected to conduct such methods, and/or the procedures that rule these interactions.

This review aims at identifying gaps or opportunities of potential relevance in scientific methodologies applied in Biomedicine. This report is divided into two sections. The first section identifies topics that may be relevant in method development. The second section describes temporal aspects of the scientific process. Together, these sections show a possible template for updating scientific methodologies applicable to Biomedicine.

2. Section 1 – The background

2.1. *The history of the scientific method: From higher education models to science policy*

While partially emphasized by Aristotle, the origin of the scientific method could probably be tracked back to 1597, when Francis Bacon proposed inductivism [9,10]. Originally, scientific research was perceived as a personal activity. Only in the XIX century science started to be institutionalized and, consequently, its professionalization began [11,12].

State-funded scientific research has been associated with new models of Higher Education. While science was ignored in most of the Middle Ages, two models that promoted science emerged a few years after the French Revolution: (i) in France, in 1808, and (ii) in Germany, in 1810 [12,13].

The French model -created by Napoleon- promoted *applied* sciences, separated teaching from research and appointed faculty members appointments based on examinations. The model Wilhelm von Humboldt created in Germany merged research with teaching, promoted *basic* research, protected academic freedom, and validated research through a novel process: peer-reviewed publications [12]. Supported by the massive creation of experimental stations, laboratories, and new scientific journals, the German model was partially imitated in the United States through the ‘Land-Grant’ model created in 1862 [13].

Research results, even after World War II, were viewed as a personal ability, not the consequence of a method. The first academic institutionalization of scientific methodologies took place in 1946, when the London School of Economics created the Department of Philosophy, Logic and Scientific Method, and Karl R. Popper became its first member [14].

Soon after, methodology was emphasized in Psychology [15]. A few years earlier, operationalism emerged in Physics -one pillar of contemporary experimental approaches [16].

While emphasized in Economics, Physics and Psychology, methodological research has not been promoted in all fields. Even today, biomedical institutions lack academic units that promote research on biologically-grounded theory and scientific methods [17].

2.2. *From explaining to solving problems*

In earlier eras, scientific methodologies pursued *explanations*. They were generated either by *inductions* based on observations (as proposed by Aristotle and Bacon) or -as proposed by Popper- hypotheses followed by testing and *deductions* [18]. In contrast, today, *problem-solving* and *problem prevention* tend to be prioritized while -due to the abundance of data- hypothesis testing (and, in general, theory) are less emphasized [19,20].

It has been stated that hypotheses should precede data collection because model-driven analyses require data gathered under defined conditions [21] However, the opposite is also possible: data can be assembled before hypotheses are generated [20].

While, in the past, well-defined problems were frequently encountered and usually had simple solutions, in the XXI century problems can be complex, ill-defined, and dynamic [22]. Ill-defined problems may require new cognitive approaches [23].

Earlier versions of scientific methods were oriented to falsify or corroborate prior knowledge. With the current abundance of data, new approaches also focus on discovery [24]. Given that at least 1/3 of all biomedical research publications released over seven decades were generated in the last 5 years [25], it is questionable whether earlier scientific methods - which emerged when most problems were rather simple and the available knowledge was a fraction of the knowledge available today- still apply.

2.3. *Educational models and scientific methods*

The purpose of higher education has influenced the philosophy of science which, in turn, has shaped scientific methods. When preservation of the *status quo* and cultural reproduction were the priority, teaching was separated from research and only applied research was promoted. Because such a model, in education, only pursued the approval of examinations, memorization was the priority (prior knowledge was rewarded, even if invalid or not applicable to solve a specific problem), not knowledge generation and use [12].

When creativity and discovery became the center of economics and national survival, learning how to conduct research has turned into a new priority, even in children education [26]. However, when ill-defined (complex and dynamic) problems predominate, the number of possible solutions may be very large and old techniques may be inadequate. In such situations, visually explicit educational strategies may be helpful [27].

Learning activities that generate research-oriented processes for ill-defined problems (not memorizing solutions for clearly defined, simple problems) is now promoted in many countries [28]. They do not offer pre-established solutions. Instead, they promote self-made construction of processes that, through open-ended evaluations, may shed light on whether the novel knowledge is appropriate or should be reconstructed.

2.4. *Theory/hypothesis-driven methods, data-driven scientific methods, or both ?*

Historically, scientific methods were driven by theories or hypotheses. Now they can also be facilitated by data, technologies, new educational strategies and many other sources of knowledge generation [29–32].

Estimated at 130 exabytes (EB) in 2005, the digital universe was around 40,000 EB in 2020 [33]. While, as societies, we are already in the zettabyte era, medicine and scientific research are suspected to be behind -probably at or before the petabyte era [34,35].

While the abundance of data has been contested as a legitimate scientific methodology [17,36], the combinatorial nature of biologic data is also a source of research and learning opportunities [25]. Instead of reducing all alternatives to just two (while assuming that only one is correct), a not self-limiting paradigm may be more defensible, in which both hypothesis testing and hypothesis generating alternatives coexist [10].

2.5. *From reductionist to pattern recognition-oriented, non-reductionist scientific methods*

Reductionism attempts to explain complexity with only one or a few factor(s) [37]. In addition, a reductionistic method will attempt to fix (or ignore) the environment. Therefore, reductionism does not consider that two or more factors may interact or that time may modify processes and outcomes. While reductionism assumes that the whole is equal to the sum of the parts, non-reductionism also considers interactions with the environment and, therefore, assumes that the whole is different from the sum of the parts. Reductionism has prevented or delayed the advancement of numerous areas in Biology [38]. Non-reductionist methods are needed when *complex* and *dynamic* processes are observed [39,40].

Pattern recognition may provide an alternative to reductionistic methods. The discovery of hidden patterns may reveal critical properties missed by reductionist methods, such as emergence [40,41].

Because the validity of biological methods necessarily depends on the underlying biology, when more than two biological outcomes exist –e.g., no inflammation, early inflammation, late inflammation–, *binary* approaches will necessarily be erroneous because they only consider two alternatives. Hence, methods that emphasize pattern recognition are preferable when the number of possible outcomes is unknown [42–44].

2.6. Beyond falsifiability: Crucial differences between biomedicine and other fields

To develop non-reductionist methods that promote discovery, critical differences between Physics and Biology should be considered. While, in Physics, *order is followed by lack of order*, the *opposite* occurs in Biology: living creatures keep constant their 'order.' Thus, life seems to be an exception to the second law of thermodynamics [45,46].

Biology differs from Physics in many other ways. One example involves *feedback* which, over time, generates circular data patterns [47].

Biological data also tend to show *ambiguity*, i.e., similar values of the same variable may be found at different biological conditions or processes, such as the early and late phases of inflammation. One consequence of biological data ambiguity is *spatial relativity:* data collected over shorter timeframes may occupy larger portions of the space where data are depicted and vice versa [48]. To avoid ambiguity, *redundancy* (the use of several data interactions that yield similar findings or interpretations) may be considered [40].

Biological processes seem to be unpredictable when classic methods are used [49–51]. However, methods that capture one-to-many/many-to-one relationships (which may change over time) may inform beyond the limitations of one-to-one, static methods [52–55].

2.7. From specialized (uni-disciplinary) to multi-, inter- and trans-disciplinary methods

The history of knowledge creation has followed a path that, recently, seemed to reach its limit. After the Humoldtian model of higher education requested published research as a fundamental requirement of new academic appointments, a rapid growth of specialties was observed, which led to a fragmentation process in which many disciplines lacked inter-disciplinary connections [56]. The resulting isolation led to cognitive gaps or unresolved problems that no specialty, alone, appeared to address. While attempts to bridge such gaps have fostered multidisciplinary approaches, such models do not necessarily share the concepts and language required to promote interactions across disciplines.

Inter-disciplinary approaches refer to those that not only foster a dialogue across disciplines but also solutions to ill-defined problems. When not only tangible solutions to complex problems are generated but also individuals not associated with any particular discipline participate, such methods are regarded as *trans*-disciplinary [57].

Therefore, one way to distinguish and evaluate scientific methods is investigating their temporal emphases. When they prioritize the past (prior knowledge), they tend to be unidisciplinary or specialized. Multidisciplinary methods can also be past-oriented when the selection of disciplines invited to solve a problem is pre-established by an authority, as seen in many countries affected by COVID 19 [58].

In contrast, when problem-solving (future-oriented knowledge creation) is pursued, the method is viewed as inter- or *trans*-disciplinary. Unfortunately, academic institutions do not appear to strongly support such methods [59].

2.8. From data to information, knowledge, and beyond

The advent of the *data deluge* brought the concept that research methods could be reduced to *data collection.* In 2008, the intellectual process that also included research questions and explicit formulation of hypotheses seemed superfluous [20].

However, predicting the end of both theory and the scientific method has been challenged [17,36]. Data are now viewed as necessary but not sufficient to support informed decision-making. Instead, a process (the *data-information-knowledge-wisdom* or DIKW pyramid) is now regarded as essential to generate actionable knowledge [10,60]. While data, alone, lack meaning, structured *data* may *inform*, produce *knowledge* and, after being interpreted, generate *wisdom* (or understanding) that may be used in decision-making [61].

Yet, there is no consensus on the difference between data and information. While some authors have assigned the difference to functionality [61], other authors have claimed that data structuring is the central distinction between data and information [61]. Because information is, also, an ambiguous concept [62], structuring and functionality are not necessarily opposite to one another −they could be complementary, if not synonymous.

3. Section 2 – looking for concepts, working with variables: Contents and temporal stages of scientific methods

3.1. Connecting the abstract (unmeasurable) with the concrete (measurable) world

Methods are tentative idealizations of phenomena (*abstract* concepts), such as 'health', 'immunity', and 'epidemic control.' Ideally, researchers would like to measure such concepts. Because they are *unmeasurable*, investigators work with *concrete* (*measurable*) operations or variables, which may (or may not) relate to the concept(s) of interest. Fig. 1 shows how methods connect abstract with concrete elements.

The match (or lack of match) between concepts and operations has been a topic discussed for many decades. While operationalism has been abandoned as a philosophy of science, operationalizations subject to open-ended evaluations are still practiced [15]. For example, in control or prevention of epidemics, there is a potential mismatch between the concept '*vaccines prevent infections*' and the operation expressed as '*the*

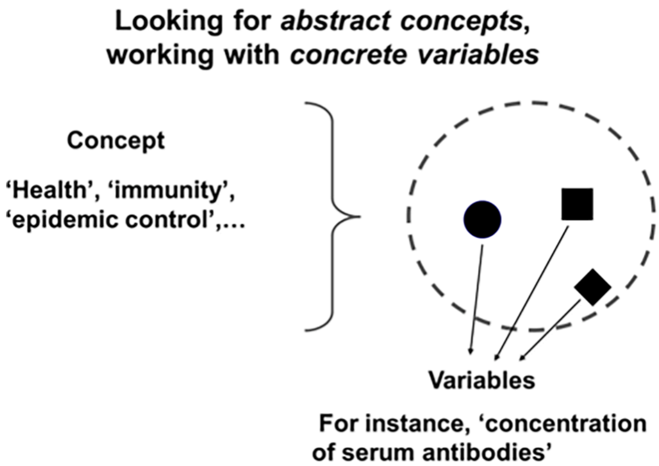

Fig. 1. Four critical elements: concepts, variables, validations, and continuous revisions. Researchers never measure what they want to measure: they only measure a few variables that, at best, partially relate to the concept of interest. Therefore, validations and continuous evaluations are essential.

concentration of neutralizing antibodies indicates whether protection has been achieved or not'. Numerous biological factors may prevent protection even in vaccinated individuals [63].

3.2. The temporal stages -conceptualization, operationalization, validation, and evaluation

The connection between the abstract and the concrete world occurs through a process that includes four stages: *conceptualization*, *operationalization*, *validation*, and *evaluation*. *Conceptualization* is the process that identifies the concept of interest. When two or more of such concepts are selected, *hierarchization* takes place -a process in which concepts are ordered in a way such that the broadest one is located at the top of the hierarchy.

Once the conceptualization is concluded, *operationalization* follows. This is when the variable(s) most likely to capture the nature of the concept(s) of interest are selected, i.e., this is the stage in which *data-generating variables* are chosen.

For example, if a researcher wants to investigate a broad concept (e.g.,'immunity'), *subordinate* concepts may be identified (e.g., 'cell-mediated' and 'humoral immunity'). Then, concepts that facilitate doable operations are chosen, such as 'humoral immunity' (an abstract concept) which may be estimated by 'serum antibodies' (measurable variables).

Operations are often numerical in nature and tend to offer mechanistic answers [64,65]. The operations designed by methods may include many elements, e.g., two or more (i) (subcellular to supra-cellular) *biological levels*, (ii) *time points*, and (iii) *outcomes* [66–68]

The *conceptualization/operationalization* process is followed by *validation* and *evaluation*. These two (sometimes undistinguishable) stages are motivated by the risks associated with selecting insufficient or irrelevant operations.

3.3. Validation

To validate, this question should be answered: *are we measuring what we need to measure or what is easily measured but may be irrelevant?* This implies a double 'trip' that includes (i) the transition between the abstract and the concrete world (from conceptualization to operationalization) and (ii) the reverse process, when the question mentioned above is addressed. When decision-makers initiate these processes, *validations* may be synonymous with *evaluations* (Fig. 2).

To estimate *validity,* at least *five topics* need to be considered: (i) the underlying *theory*, (ii) *hypotheses*, (iii) research *design*, (iv) empirical *observations (data)*, and (v) *revisions* [69]. The underlying theory is expected to be consistent ('coherent') with the specific hypotheses being tested and also yield informative, explanatory, and/or usable data.

For example, if the theory is that *'immunity, when effective, promotes survival*', one hypothesis could be that *'multi-cellularity may be critical to foster survival.'* To test this hypothesis, a research design that explicitly produces multicellular variables would be needed, as previously shown [70]. Hence, future methodologies may be characterized by validations that, at least, pursue three goals: (i) *predict* outcomes; (ii) *prescribe* treatments, and (iii) *understand* or *explain* the underlying processes [71].

3.4. Data structuring and evaluation

Both *validations* and *evaluations* are likely to be influenced by the data. Earlier views on the scientific method did not consider the impact of *data structure* on the 'DIKW' pyramid [61]. When the original data are *unstructured*, they may lack *functionality*.

Gestalt theory-based pattern recognition fosters data structuring. Because it does not depend on numerical properties, Gestalt has solved problems that seemed intractable under mathematical approaches [72]. *Pattern recognition* is a top-down process, in which the overall shape (*gestalt*) is detected even when details are missing -a feature that results in novel information [40,72]. Fig. 3 is an example of a model meant to elicit data *patterns*.

3.5. Toward overall (inter-trans-disciplinary)knowledge validity

It is suggested that future scientific methodologies may need to explore their *overall knowledge validity*. That is so because what may seem to be adequate within the perspective of one field may reveal gaps when two or more perspectives are simultaneously considered.

One example of the previous concept is the relationship existing between public health and the economy: when one of these areas is neglected, both are deeply affected. In contrast, the benefits of population-level public health expenditure – unlike those of personal healthcare – tend to be long term and induce higher returns on the investment than alternatives [73]. It is now established that the economy requires public health [74]. COVID-19 has shown that both economic and health-related problems require *rational decision-making* [73].

The need for *overall knowledge validity* also applies to vaccine development. This field is not yet a science but a technology that is renovated empirically, i.e., it advances through trial-and-error processes [75]. While the COVID 19 pandemic has demonstrated its relevance, vaccinology has not been emphasized in biomedical curricula [76].

3.6. The twin needs: independent evaluations and biologically grounded methods

While no definition assures that a method is grounded in Biology, biologically grounded methods may be retrospectively validated by their findings. Methods that, analyzing the same data, extract more

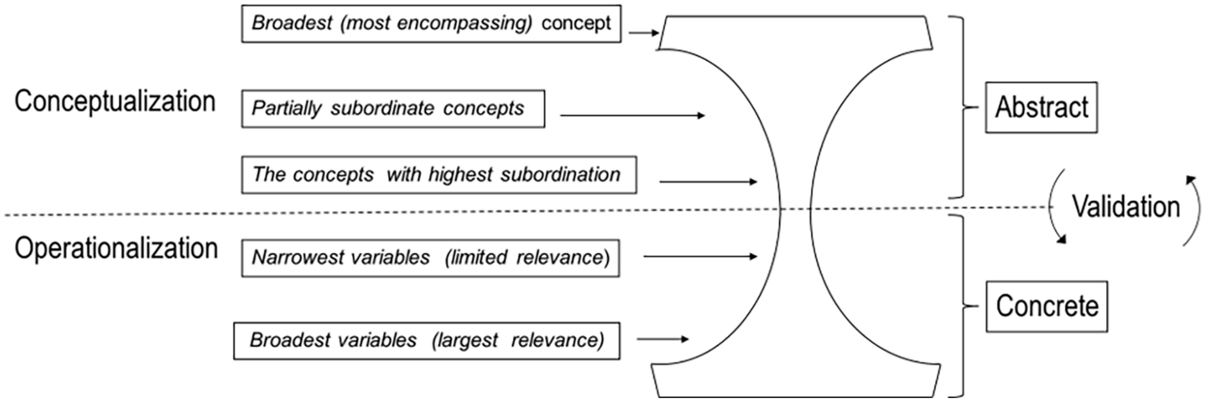

Fig. 2. The double trip: back and forth between abstract concepts to concrete variables. To be valid, research should transition, twice, between the abstract and the concrete world.

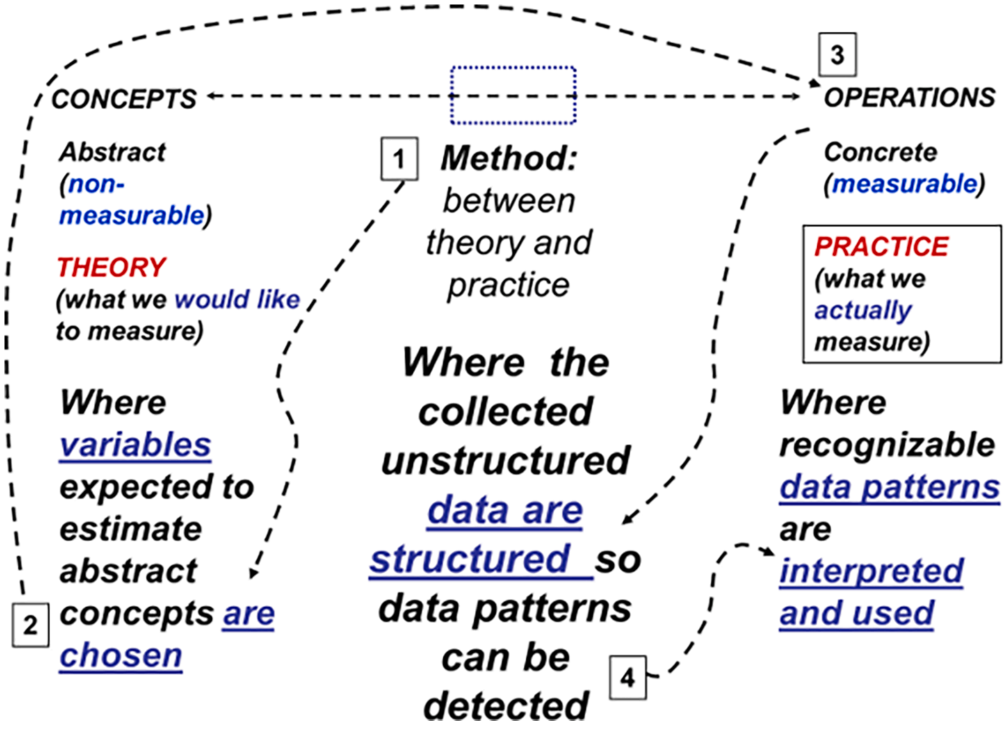

Fig. 3. The method: where abstract concepts become concrete operations and data are structured. If all activities conducted in Biomedicine occurred along a horizontal line, the right end would describe concrete *practices* (operations) while the left end would localize all abstract concepts. Situated between *theory* and *practice*, the *method* helps select or induce: (1) variables that estimate the abstract concept(s), which provide measurable data, (2) data structuring, (3) pattern recognition, and (4) pattern interpretation and use.

information than alternatives and/or provide explanations consistent with Evolutionary theory may be assumed to be grounded in Biology [40].

Once *data are structured following biological concepts* -such as the fact that phagocytes predominate in the early inflammatory response while mononuclear cells show a higher presence in the recovery phase-, *informative patterns tend to emerge*. For instance, experimental and longitudinal data on infections induced in animals show a clear pattern (data circularity) in which the phagocyte/lymphocyte ratio and the neutrophil percentage reveal higher values in the early, post-challenge than the late/recovery stage, while the mononuclear cell/neutrophil ratio reaches its highest values in the recovery phase [Fig. 1 of reference # 47 (https://journals.plos.org/plosone/article?id = https://doi.org/10.1371/journal.pone.0053984)].

Biologically grounded and visually explicit methods may foster problem-solving [27,77]. For example, in epidemiology, the same data may be used to compare several theories (e.g., Network and Neighbor theories). Such approaches determine which theory is more explanatory [78]. Similarly, analyses of the same immunological data under under two (reductionist and non-reductionist) methods can detect the most informative [40]).

When one approach informs more or predicts better, *research becomes indistinguishable from evaluation*. However, to be effective, evaluations should be performed by independent systems [79].

3.7. Directionality matters: top-down and bottom up methods

To further elucidate whether a novel method is grounded in Biology, the directionality (bottom-up and/or top-down) of the process may influence on the detection of emergent biological properties. *Top-down* operations may uncover system-wide interactions. They are data-driven methods that attempt to solve ill-defined problems of unknown causation by focusing on spatial–temporal (toponomic or pattern recognition-based) features [80,81].

Top-down approaches can detect synergies, pleiotropies, and multicellularity –critical features of biological systems [82–85], and identify outcome-related patterns. Because Biomedicine is an indivisible system, top-down approaches help explore the *interdependence* of its elements [71,86].

However, validations may also require bottom-up operations. For instance, evaluations of health-related research utilize both top-down and bottom-procedures [87].

4. Conclusions

Because biomedical knowledge is complex and grows rapidly, biologically grounded scientific methods are needed and they should be frequently evaluated. To that end, the creation of novel, independent, and *inter-/trans*-disciplinary bodies of evaluators is proposed.

5. Author statement

Both authors have read and approved the final version of the manuscript and neither author has conflicts of interest to report. This manuscript has not been submitted to any other journal and it has not been funded by any institution –whether private or public– of any country.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] T.A.C. Raydon, How can science be well-ordered in times of crisis? Learning from the SARS CoV-2 pandemic, HPLS 42 (2020) 53, https://doi.org/10.1007/s40656-020-00348-5.

[2] J. Wise, Covid-19: Global response was too slow and leadership absent, report finds, BMJ 373 (2021).

[3] E.C. Sabino, L.F. Buss, M.P.S. Carvalho, C.A. Prete Jr, M.A.E. Crispim, N.A. Fraiji, R.H.M. Pereira, K.V. Parag, et al., Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence (accessed: Febr 1, 2021), Lancet (2021), https://doi.org/10.1016/S0140-6736(21)00183-5.

[4] J.P.A. Ioannidis, S. Cripps, M.A. Tanner, Forecasting for COVID-19 has failed, Int. J. Forecast. (2020), https://doi.org/10.1016/j.ijforecast.2020.08.004.

[5] A.S. Lauring, E.B. Hodcroft, Genetic variants of SARS-CoV-2—what do they mean? JAMA 325 (2021) 529–531, https://doi.org/10.1001/jama.2020.27124.

[6] A. Bartoli, F. Gabrielli, T. Alicandro, F. Nascimbeni, P. Andreone, COVID-19 treatment options: a difficult journey between failed attempts and experimental drugs, Intern Emerg Med. 16 (2) (2021) 281–308, https://doi.org/10.1007/s11739-020-02569-9.

[7] A.L. Rivas, A.L. Hoogesteijn, J.B. Hittner, M.H.V. van Regenmortel, P. Kempaiah, P. Vogazianos, A. Antoniades, A. Ioannidis, et al. Toward a COVID-19 testing policy: where and how to test when the purpose is to isolate silent spreaders. medRxiv. https://doi.org/10.1101/2020.12.22.20223651.

[8] A.L. Rivas, A.L. Hoogesteyn, J.B. Hittner, F.O. Fasina, M.H.V. Van Regenmortel, Addressing a complicated problem: can COVID-19 asymptomatic cases be detected and epidemics stopped, when testing is limited and the location of such cases unknown? medRxiv. https://doi.org/10.1101/2020.11.10.20223495.

[9] J.M. Rodríguez García, *Scientia potestas est* — knowledge is power: Francis Bacon to Michel Foucault, Neohelicon 28 (2001) 109–121, https://doi.org/10.1023/A:1011901104984.

[10] F. Mazzocchi, Could Big Data be the end of theory in science ? EMBO Rep. 16 (2015) 1250–1255, https://doi.org/10.15252/embr.201541001.

[11] N. Sokolovska, B. Fecher, G.G. Wagner, Communication on the science-policy interface: an overview of conceptual models, Publications 7 (2019) 64, https://doi.org/10.3390/publications7040064.

[12] C. Day, Science, Applied Science and Higher Education in France 1870–1945, an Historiographical Survey since the 1950s, J. Soc. Hist. 26 (1992) 367–384. http://www.jstor.org/stable/3788426.

[13] F.P. Albritton. Humboldt's unity of research and teaching: influence on the philosophy and development of U.S. Higher Education.(SSRN Scholarly Paper No. ID 939811), Rochester, NY, Social Science Research Network, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=939811.

[14] London School of Economics. (https://www.lse.ac.uk/philosophy/, accessed May10, 2021).

[15] E. Vessonen, Respectful operationalism, *Theory Physchol.* 31 (1) (2021) 84–105, https://doi.org/10.1177/0959354320945036.

[16] A.C. Benjamin, P.W. Bridgman, The *Logic of modern physics* by P. W. Bridgman, *J. Philos.* 24 (24) (1927) 663, https://doi.org/10.2307/2014223.

[17] S. Succi, P.V. Coveney, Big data: the end of the scientific method? Phil. Trans. R. Soc. A 377 (2142) (2019) 20180145, https://doi.org/10.1098/rsta.2018.0145.

[18] K.R. Popper. The Logic of Scientific Discovery, Hutchinson: London, UK, 1959, pp. 1–513.

[19] J. Grisemer, Am. Biol. Teeach 47 (1985) 211–215. https://doi-org.libproxy.unm.edu/10.2307/4448021.

[20] C. Anderson, The end of theory: the data deluge makes the scientific method obsolete, Wired Mag 16 (2008) 108–109. https://www.wired.com/2008/06/pb-theory/.

[21] S. Carroll, D. Goodstein, Defining the scientific method, *Nature Meth* 6 (2009) 237, https://doi.org/10.1038/nmeth0409-237.

[22] D. Dörner, J. Funke, Complex problem solving: what it is and what it is not, Front. Psychol 8 (2017) 1153, https://doi.org/10.3389/fpsyg.2017.01153.

[23] J. Funke, Complex problem solving: a case for complex cognition? Cogn Process 11 (2) (2010) 133–142, https://doi.org/10.1007/s10339-009-0345-0.

[24] V. Gopalakrishnan, K. Jha, W. Jin, A. Zhang, A survey on literature based discovery approaches in biomedical domain, J. Biomed. Inform. 93 (2019) 103141, https://doi.org/10.1016/j.jbi.2019.103141.

[25] J.B. Hittner, A.L. Hoogesteijn, J.M. Fair, M.H.V. Van Regenmortel, A.L. Rivas, The Third Cognitive Revolution, EMBO Rep. 20 (2019), e47647. https://doi.org/10.15252/embr.201847647.

[26] V. Dagienė, G. Futschek, G. Stupurienė, Creativity in solving short tasks for learning computational thinking, Constructivist Foundations 14 (2019) 382–396. https://constructivist.info/14/3/382.

[27] H. Casakin. Well-defined versus ill-defined design problem solving: the use of Well-defined versus ill-defined design problem solving: the use of visual analogy visual analogy. In: Durling, D. and Shackleton, J. (eds.), Common Ground - DRS International Conference 2002, 5-7 September, London, United Kingdom. https://dl.designresearchsociety.org/drs-conference-papers/drs2002/researchpapers/14.

[28] S. Havu-Nuutinen, S. Kewalramani, N. Veresov, S. Pöntinen, S. Kontkanen, Understanding early childhood science education: comparative analysis of Australian and Finnish curricula, Res. Sci Educ. (2021), https://doi.org/10.1007/s11165-020-09980-4.

[29] T.C. Erren, The quest for questions – on the logical force of science, Med. Hypotheses 62 (4) (2004) 635–640, https://doi.org/10.1016/j.mehy.2003.10.022.

[30] P. Boytchev, Constructionism and deconstructionism. *Constructivist*, Foundations 10 (2015) 355–363. http://constructivist.info/10/3/355.

[31] A. Karpatne, G. Atluri, J.H. Faghmous, M. Steinbach, A. Banerjee, A. Ganguly, S. Shekhar, N. Samatova, V. Kumar, Theory-guided Data Science: A New Paradigm for Scientific Discovery, IEEE Trans. Knowl. Data Eng. 29 (2017) 2318–2331, https://doi.org/10.1109/TKDE.2017.2720168.

[32] E.O. Voit, J.A. Papin, Perspective: dimensions of the scientific method, PLoS Comput. Biol. 15 (9) (2019) e1007279, https://doi.org/10.1371/journal.pcbi.1007279.

[33] S. Dash, S.K. Shakyawar, M. Sharma, S. Kaushik, Big data in healthcare: management, analysis and future prospects, J. Big Data 6 (2019) 54, https://doi.org/10.1186/s40537-019-0217-0.

[34] L. Tavazzi, Big data: is clinical practice changing? Eur. Heart J. Suppl. 21 (2019) B98–B102, https://doi.org/10.1093/eurheartj/suz034.

[35] A.M. Ionescu. Energy efficient computing and sensing in the Zettabyte era: from silicon to the cloud. IEEE International Electron Devices Meeting (IEDM) (2017): 1.2.1-1.2.8. https://doi.org/10.1109/IEDM.2017.8268307.

[36] M. Pigliucci, The end of theory in science? EMBO Rep. 10 (6) (2009) 534, https://doi.org/10.1038/embor.2009.111.

[37] M.H.V. Van Regenmortel, Biological complexity emerges from the ashes of genetic reductionism, J. Mol. Recognit. 17 (3) (2004) 145–148, https://doi.org/10.1002/(ISSN)1099-135210.1002/jmr.v17:310.1002/jmr.674.

[38] M.H.V., van Regenmortel Commentary: Basic research in HIV vaccinology is hampered by reductionist thinking, Front. Immunol. (2016) 7:266, https://doi.org/10.3389/fimmu.2016.00266.

[39] M.H.V. Van Regenmortel, The rational design of biological complexity: a deceptive metaphor, Proteomics 7 (6) (2007) 965–975, https://doi.org/10.1002/(ISSN)1615-986110.1002/pmic.v7:610.1002/pmic.200600407.

[40] A.L. Rivas, G. Leitner, M.D. Jankowski, A.L. Hoogesteijn, M.J. Iandiorio, S. Chatzipanagiotou, A. Ioannidis, S.E. Blum, R. Piccinini, A. Antoniades, J. C. Fazio, Y. Apidianakis, J.M. Fair, M.H.V. Van Regenmortel, Nature and consequences of biological reductionism for the immunological study of infectious diseases, Front. Immunol. 8 (2017), https://doi.org/10.3389/fimmu.2017.00612.

[41] G.B. Fogel, Computational intelligence approaches for pattern discovery in biological systems, Brief Bioinformatics 9 (2008) 307–316, https://doi.org/10.1093/bib/bbn021.

[42] J. Cohen, The cost of dichotomization, Appl. Psychol. Meas 7 (3) (1983) 249–253, https://doi.org/10.1177/014662168300700301.

[43] O.V. Mabikwa, D.C. Greenwood, P.D. Baxter, S.J. Fleming, Assessing the reporting of categorized quantitative variables in observational epidemiological studies, BMC Health Serv. Res. 17 (2017) 201, https://doi.org/10.1186/s12913-017-2137-z\xx.

[44] A. Andreopoulos, J.K. Tsotsos, 50 Years of object recognition: directions forward, Comput Vis Image Understand 117 (8) (2013) 827–891, https://doi.org/10.1016/j.cviu.2013.04.005.

[45] P.T. Macklem, A. Seely, Towards a definition of life, Perspect. Biol. Med. 53 (2010) 330–340, https://doi.org/10.1353/pbm.0.0167.

[46] K. Saetzler, C. Sonnenschein, A.M. Soto, Systems biology beyond networks: Generating order from disorder through self-organization, Sem. Cancer Biol. 21 (3) (2011) 165–174, https://doi.org/10.1016/j.semcancer.2011.04.004.

[47] A.L. Rivas, M.D. Jankowski, R. Piccinini, G. Leitner, D. Schwarz, K.L. Anderson, J. M. Fair, A.L. Hoogesteijn, W. Wolter, M. Chaffer, S. Blum, T. Were, S.N. Konah, P. Kempaiah, J.M. Ong'echa, U.S. Diesterbeck, R. Pilla, C.-P. Czerny, J.B. Hittner, J.M. Hyman, D.J. Perkins, L.H. Carvalho, Feedback-based, system-level properties of vertebrate-microbial interactions, PLoS ONE 8 (2) (2013) e53984, https://doi.org/10.1371/journal.pone.0053984.

[48] C. Auffrey, L. Nottale, Scale relativity theory and integrative systems biology 1. Founding principles and scale laws, Prog. Biophys. Mol. Biol. (2008), https://doi.org/10.1016/j.pbiomolbio.2007.09.002.

[49] M.H.V.V. Regenmortel, Reductionism and complexity in molecular biology, EMBO Rep. 5 (11) (2004) 1016–1020, https://doi.org/10.1038/sj.embor.7400284.

[50] F. Mazzocchi, Complexity in biology. Exceeding the limits of reductionism and determinism using complexity theory, EMBO Rep. 9 (1) (2008) 10–14, https://doi.org/10.1038/sj.embor.7401147.

[51] Y.I. Wolf, M.I. Katsnelson, E.V. Koonin, Physical foundations of biological complexity, Proc. Natl. Acad. Sci. U.S.A. 115 (37) (2018) E8678–E8687, https://doi.org/10.1073/pnas.1807890115.

[52] R.A. Quinn, L.F. Nothias, O. Vining, M. Meehan, E. Esquenazi, P.C. Dorrestein, Molecular networking as a drug discovery, drug metabolism, and precision medicine strategy, Trends Pharmacol. Sci. 38 (2017) 143–154, https://doi.org/10.1016/j.tips.2016.10.011.

[53] T. Greenhalgh, Of lamp posts, keys, and fabled drunkards: A perspectival tale of 4 guidelines, J. Eval. Clin. Pract. 24 (2018) 1132–1138, https://doi.org/10.1111/jep.12925.

[54] S.N. Nielsen, S.E. Jørgensen, Goal functions, orientors and indicators (GoFOrIt's) in ecology. Application and functional aspects – strengths and weaknesses, Ecol. Ind. (2013), https://doi.org/10.1016/j.ecolind.2012.12.015.

[55] M.J. Iandiorio, J.M. Fair, S. Chatzipanagiotou, A. Ioannidis, E. Trikka-Graphakos, N. Charalampaki, et al., Preventing data ambiguity in infectious diseases with four-dimensional, earlier, personalized, in vivo evaluations, PLoS ONE 11 (2016), e0159001, https://doi.org/10.1371/journal.pone.0159001.

[56] S. Balietti, M. Mäs, D. Helbing, On disciplinary fragmentation and scientific progress, PLoS ONE 10 (2015), e0118747, https://doi.org/10.1371/journal.pone.0118747.

[57] H. von Wehrden, M.H. Guimarães, O. Bina, M. Varanda, D.J. Lang, B. John, F. Gralla, D. Alexander, D. Raines, A. White, R.J. Lawrence, Interdisciplinary and transdisciplinary research: finding the common ground of multi-faceted concepts, Sustain Sci. 14 (3) (2019) 875–888, https://doi.org/10.1007/s11625-018-0594-x.

[58] D. Rajan, K. Koch, K. Rohrer, C. Bajnoczki, A. Socha, M. Voss, M. Nicod, V. Ridde, J. Koonin, Governance of the Covid-19 response: a call for more inclusive and transparent decision-making, BMJ Global Health 5 (5) (2020) e002655, https://doi.org/10.1136/bmjgh-2020-002655.

[59] M.H. Guimarães, C. Pohl, O. Bina, M. Varanda, Who is doing inter- and transdisciplinary research, and why? An empirical study of motivations, attitudes, skills, and behaviours, Futures 112 (2019) 102441, https://doi.org/10.1016/j.futures.2019.102441.

[60] R. Ackoff, From data to wisdom, J. Appl. Syst. Anal. 15 (1989) 3–9.

[61] J. Rowley, The wisdom hierarchy: representations of the DIKW hierarchy, J. Inf. Sci. 33 (2) (2007) 163–180, https://doi.org/10.1177/0165551506070706.

[62] R. Ridi, La piramide dellĺinformazione: una introduzione, AIB studi: Rivista di biblioteconomia e scienze dell'informazione 60 (2020) 219–267, https://doi.org/10.2426/aibstudi-11903.

[63] A. Telenti, A. Arvin, L. Corey, D. Corti, M.S. Diamond, A. García-Sastre, R.F. Garry, E.C. Holmes, P.S. Pang, H.W. Virgin, After the pandemic: perspectives on the future trajectory of COVID-19, Nature 596 (7873) (2021) 495–504, https://doi.org/10.1038/s41586-021-03792-w.

[64] D.A. Rosenblueth, Editorial: computational methods for understanding complexity: the use of formal methods in Biology, Front. Bioeng. Biotechnol. 4 (2016) 68, https://doi.org/10.3389/fbioe.2016.00068.

[65] K. Peskov, I. Azarov, L. Chu, V. Voronova, Y. Kosinsky, G. Helmlinger, Quantitative mechanistic modeling in support of pharmacological therapeutics development in immuno-oncology, Front. Immunol. 10 (2019) 924, https://doi.org/10.3389/fimmu.2019.00924.

[66] M.A. O'Malley, I. Brigandt, A.C. Love, J.W. Crawford, J.A. Gilbert, R. Knight, S. D. Mitchell, F. Rohwer, Multilevel research strategies and biological systems, Philos. Sci. 81 (5) (2014) 811–828, https://doi.org/10.1086/677889.

[67] V.A. Chereshnev, G. Bocharov, S. Bazhan, B. Bachmetyev, I. Gainova, V. Likhoshvai, J.M. Argilaguet, J.P. Martinez, J.A. Rump, B. Mothe, C. Brander, A. Meyerhans, Pathogenesis and treatment of HIV infection: the Cellular, the immune system and the neuroendocrine systems perspective, Int. Rev. Immunol. 32 (3) (2013) 282–306, https://doi.org/10.3109/08830185.2013.779375.

[68] S. Green, Revisiting generality in biology: systems biology and the quest for design principles, Biol. Philos. 30 (5) (2015) 629–652, https://doi.org/10.1007/s10539-015-9496-9.

[69] G.T. Smith, On construct validity: issues of method and measurement, *Psychol.* Assess 17 (2005) 396–408, https://doi.org/10.1037/1040-3590.17.4.396.

[70] A.L. Rivas, A.L. Hoogesteijn, A. Antoniades, M. Tomazou, T. Buranda, D.J. Perkins, J.M. Fair, R. Durvasula, F.O. Fasina, G.P. Tegos, M.H.V. van Regenmortel, Assessing the dynamics and complexity of disease pathogenicity using 4-dimensional immunological data, Front Immunol 10 (2019), https://doi.org/10.3389/fimmu.2019.01258.

[71] A. Trevawas. A brief history of systems biology. "Every object that biology studies is a system of systems." Francois Jacob (1974). The Plant cell (2006). 18: 2420–2430. https://doi.org/10.1105/tpc.106.042267.

[72] S. Guberman, V.V. Maximov, A. Pashintsev, Gestalt and image understanding, *Gestalt Theory* 34 (2012) 143–166. https://web.archive.org/web/20141228205728/http://gth.krammerbuch.at/sites/default/files/articles/AHAH%20callback/01_Guberman_KORR.pdf.

[73] R. Masters, E. Anwar, B. Collins, R. Cookson, S. Capewell, Return on investment of public health interventions: a systematic review, J. Epidemiol. Community Health 71 (8) (2017) 827–834, https://doi.org/10.1136/jech-2016-208141.

[74] M. Anderson, E. Pitchforth, M. Asaria, C. Brayne, B. Casadei, A. Charlesworth, A. Coulter, B.D. Franklin, C. Donaldson, M. Drummond, K. Dunnell, M. Foster, R. Hussey, P. Johnson, C. Johnston-Webber, M. Knapp, G. Lavery, M. Longley, J. M. Clark, A. Majeed, M. McKee, J.N. Newton, C. O'Neill, R. Raine, M. Richards, A. Sheikh, P. Smith, A. Street, D. Taylor, R.G. Watt, M. Whyte, M. Woods, A. McGuire, E. Mossialos, LSE-Lancet Commission on the future of the NHS: re-laying the foundations for an equitable and efficient health and care service after COVID-19, Lancet 397 (10288) (2021) 1915–1978, https://doi.org/10.1016/S0140-6736(21)00232-4.

[75] J.A. Plante, B.M. Mitchell, K.S. Plante, K. Debbink, S.C. Weaver, V.D. Menachery, The variant gambit: COVID-19's next move, Cell Host Microbe 29 (4) (2021) 508–515, https://doi.org/10.1016/j.chom.2021.02.020.

[76] P.-H. Lambert, A. Podda, Education in vaccinology: an important tool for strengthening Global Health, Front. Immunol. 9 (2018) 1134, https://doi.org/10.3389/fimmu.2018.01134.

[77] J.M. Griffin, Constructionism and de-constructionism: opposite yet complementary pedagogies, Constructivist Foundations 14 (2019) 234–243. https://constructivist.info/14/3/234.

[78] A.L. Rivas, F.O. Fasina, A.L. Hoogesteyn, S.N. Konah, José.L. Febles, D.J. Perkins, J. M. Hyman, J.M. Fair, J.B. Hittner, S.D. Smith, A. Vespignani, Connecting network properties of rapidly disseminating epizoonotics, PLoS ONE 7 (6) (2012) e39778, https://doi.org/10.1371/journal.pone.0039778.

[79] A. García-Basteiro, C. Alvarez-Dardet, A. Arenas, R. Bengoa, C. Borrell, M. Del Val, M. Franco, M. Gea-Sánchez, J.J.G. Otero, B.G.L. Valcárcel, I. Hernández, J. C. March, J.M. Martin-Moreno, C. Menéndez, S. Minué, C. Muntaner, M. Porta, D. Prieto-Alhambra, C. Vives-Cases, H. Legido-Quigley, The need for an independent evaluation of the COVID-19 response in Spain, Lancet 396 (10250) (2020) 529–530, https://doi.org/10.1016/S0140-6736(20)31713-X.

[80] M.H.V. Van Regenmortel, Development of a preventive HIV vaccine requires solving inverse problems which is unattainable by rational vaccine design, Front. Immunol. (2018) 82009, https://doi.org/10.3389/fimmu.2017.02009.

[81] R. Berlin, R. Gruen, J. Best, Systems Medicine—complexity within, simplicity without, J. Healthc Inform Res. 1 (1) (2017) 119–137, https://doi.org/10.1007/s41666-017-0002-9.

[82] G. Pezzulo, M. Levin, Top-down models in biology: explanation and control of complex living systems above the molecular level, J. R. Soc. Interface 13 (124) (2016) 20160555, https://doi.org/10.1098/rsif.2016.0555.

[83] Z. Wang, B.-Y. Liao, J. Zhang, Genomic patterns of pleiotropy and the evolution of complexity, Proc. Natl. Acad. Sci. U.S.A. 107 (42) (2010) 18034–18039, https://doi.org/10.1073/pnas.1004666107.

[84] L.W. McGee, A.M. Sackman, A.J. Morrison, J. Pierce, J. Anisman, D.R. Rokyta, Synergistic pleiotropy overrides the costs of complexity in viral adaptation, Genetics 202 (2016) 285–295, https://doi.org/10.1534/genetics.115.181628.

[85] K. Chesmore, J. Bartlett, S.M. Williams, The ubiquity of pleiotropy in human disease, Hum. Genet. 137 (1) (2018) 39–44, https://doi.org/10.1007/s00439-017-1854-z.

[86] E. Holroyd, R.D. Simari, Interdependent biological systems, multi-functional molecules: the evolving role of tissue factor pathway inhibitor beyond anticoagulation, Thromb Res. 125 (Suppl 1) (2010) S57–S59, https://doi.org/10.1016/j.thromres.2010.01.039.

[87] H.T. Chen, The bottom-up approach to integrative validity: A new perspective for program evaluation, Eval. Prog. Plan 33 (3) (2010) 205–214, https://doi.org/10.1016/j.evalprogplan.2009.10.002.