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Perspectives of (/memorandum for) systems thinking on COVID-19 pandemic and pathology

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Abstract

Is data-driven analysis sufficient for understanding the COVID-19 pandemic and for justifying public health regulations? In this paper, we argue that such analysis is insufficient. Rather what is needed is the identification and implementation of over-arching hypothesis-related and/or theory-based rationales to conduct effective SARS-CoV2/COVID-19 (Corona) research. To that end, we analyse and compare several published recommendations for conceptual and methodological frameworks in medical research (e.g., public health, preventive medicine and health promotion) to current research approaches in medical Corona research. Although there were several efforts published in the literature to develop integrative conceptual frameworks before the COVID-19 pandemic, such as *social ecology* for public health issues and *systems thinking* in health care, only a few attempts to utilize these concepts can be found in medical

Corona research. For this reason, we propose nested and integrative systemic modelling approaches to understand *Corona pandemic* and *Corona pathology*. We conclude that institutional efforts for knowledge integration and systemic thinking, but also for integrated science, are urgently needed to avoid or mitigate future pandemics and to resolve infection pathology.

KEYWORDS

integrative systems pathology of Corona, methodology of systemic modelling, social ecology of pandemics, systems science and thinking

1 | 'INFODEMIC' WITHOUT THEORETICAL FRAMING ACCOMPANIES THE PANDEMIC

> 'In a living system, every part owes its presence to the agency of all the remaining parts, and also exists for the sake of the others'.
>
> Immanuel Kant

The SARS-CoV-2 pandemic has resulted in a large amount and diversity of information about the virus and its distribution throughout the population. This information has been data-driven (inductive) and not theory-driven (deductive) and resulted in an overwhelming multitude and diversity of orientations and behaviour regulations in all societal domains. We propose that a more conclusive management of the Corona pandemic can be achieved in the context of a more concept-driven systemic perspective on the population as on the individual.[1] To this end, adaptive systems thinking could guide the development of scientific models to understand better these behaviours across all system scales.

1.1 | Information deluge and the need for epistemic trust

The COVID-19 pandemic has occasioned a multi-faceted, overwhelming amount of data and observations published in scientific journals or public repositories (e.g., social media, websites, etc.). This deluge of information has resulted in an 'infodemic'.[2] Unfortunately, more data do not necessarily mean more knowledge, as information can be confusing or misleading if it is not embedded in a larger comprehensive conceptual context. To overcome this conundrum, functional organisation of quantitative and qualitative observations by conceptual embedding could be useful in terms of *rule-guided hypotheses* and *explanatory integrative framing* that are to be tested and accompanied by interpretations based on causal models, similar as knowledge growth in physics can be understood by interplay between empirical and experimental observations and theoretical reasoning.[1] This is true for understanding both population health and individual health. For such an integrative understanding of COVID-19, we need not only 'disciplined interdisciplinarity' but also the construction of integrative (systemic) *medical theories*.[3]

1.2 | Heterogeneity, uncertainty and volatility of information

Most reports on new insights into COVID-19 focus on selected and pertinent details. Attempts to depict the entire extent of the disease, which build on the more than 2 years' experience available, are rather underrepresented.[4,5] Statistics regarding the numbers of infected or deceased individuals are dominating the analysis, but the reported incidence numbers fluctuate and have a questionable precision and validity. Other reports describe molecular aspects of the viral infection, but mutations of the virus constantly change the picture. Moreover, human behaviour itself factors into the evidence's capriciousness.

'Big data' are an essential component for the analysis of these highly complex phenomena but are not sufficient without causal, factual interpretations, which in turn require conceptual and dynamic models such as *systemic socio-ecological frameworks*. In other words, the 'big data' approach needs a critical epistemological consideration.[6,7]

Data are of course important, but—even in large quantities—without theory or guiding hypotheses, they are of limited use in health care management,[8,9] public health issues[10] or theoretical immunology.[11] Often pragmatism—whose methods can be easily applied to generate data—rather than fundamental concepts determine the selection and perspective of a research study. The consecutive plurality of essentially unidimensional research in the various research fields associated with the pandemic could be integrated into a multi-dimensional, comprehensive, coherent, abstract but understandable, high-level conceptual framework.[5,12]

1.3 | The utility of system theories and models

Theories (and theoretical models) are essentially a set of generalisations in the form of rules or principles derived from empirical

observations. Thinking of physics, the theory of gravity is an example for a useful theory, in biology evolutionary theory, but in medicine, a comprehensive theory of health and disease is missing.[13] In medicine, the explanations are based on inferences of empirical observations and data. Small-scale mechanistic models provide explanations such as for non-communicable diseases like hypertension, type 2 diabetes, Parkinson's disease and so forth, without taking account of systemic context.

Contrary to this, System Theory provides fundamental concepts for the understanding of complex and dynamic systems, such as theory of self-organisation, feedback loops, nonlinear systems, of chaos, or catastrophes and so forth.[14] The utility of systemic theories and models is that a system is understood as a 'structured whole' that exhibits nonlinear dynamics, complexity and causal connectivity.[15,16] These properties can be explained by concepts of systems theory like adaptive dynamics of homoeostasis generated by fluctuating balancing mechanisms. When these mechanisms fail disease develops.

Interestingly amongst other propositions,[17–19] the Centers for Disease Control (CDC) recently put forward systems thinking as an essential tool in health affairs.[20] Essentially, a systems view could conceptually and methodologically provide several advantages such as an integrated alternation between zooming in to the details and zooming out to the whole. Several modelling strategies based on a set of nested reliable multi-level, multi-layer, multi-compartment, multi-stage and dynamic equilibrium models would clearly advance an integrative view and enrich a causal understanding and management of COVID-19. Basically, the dynamics of the pandemic justifies its conception as a complex adaptive system.[21–23] And in consequence, *forecasting* of dynamics of pandemic might be better if grounded by not only data-driven but also theory-based modelling.[24]

Different conceptualisations of systems—as structured wholes—are used as frameworks, depending on the theoretical and methodological background and they constitute some kind of typology of 'nested' models:

- *Black box-like approaches* with systematic identification of input–output relations by multi-variate analysis based on correlation analysis (regression equation of severity of COVID-19; see below).
- *Network models* focus on the structure of a system based on identified elements, the number of involved components and their interactions from a structure-analytical perspective that enables the identification of 'motifs'.[25,26] For COVID-19, the disease map is one example (see below).
- *Multi-level models*, from the molecular level to the physiological level, represent bottom-up as well as top-down causation.[27]
- *Multi-compartment models* depict flow dynamics between compartments as they are used in epidemiology (SIR models; see below) and in (organism-centred) physiology (respiratory system; see below).
- *Causal loop models* are used in the early stages of modelling in context of system dynamics methodology.[28] Here, we mention the interplay of ACE2 and INF (see below).
- *Dynamic equilibrium-centred models* describe the dynamics within a framework of activators and inhibitors as a homoeostatic and/or an adaptive allostatic process.[15] This was demonstrated for the neurochemistry of the brain, where on a macro-level different neurotransmitter systems show antagonistic operations (glutamate and GABA) and also at the micro-level at the synapse, a dynamic interplay of receptors, autoreceptors, re-uptake mechanisms and so forth, determine mental health and disease.[29] With regard to the immune response, the interplay of the pro-inflammatory and anti-inflammatory subsystems is the focus. In this context, complex pendula models represent complex dynamics of simple systems that will be demonstrated later for the immune system.

It should also be mentioned here that basically systems thinking either is more data-oriented by application of formal analytical tools on data or theory-oriented like the application of theory of dynamic systems: data-centred approaches suffer from conceptual inclusiveness, whereas concept-oriented approaches suffer from lack of data. For this reason, research must use both approaches to combine them and to test them against real-world observations such as clinical courses of the disease. We start here with a top-down, multi-level vision of the COVID-19 pandemic that has to focus on population health, that is, a socio-ecological perspective.

2 | SOCIAL ECOLOGY—BRIDGING GAPS OF KNOWLEDGE BY CONCEPTUAL INTEGRATIVE PERSPECTIVES

Basically, from the public health perspective, the *compartmental segmentation* of the population with regard to the infection—susceptible (S), infected (I) and recovered (R)—are the typical components of epidemiological SIR models.[30] In addition, other compartment models capture additional groups such as carriers, asymptomatic cases, diseased, hospitalized, intensive care patients, and deaths for understanding the gravity of the pandemic. However, a true understanding of a pandemic like COVID-19 would also require the *social sciences*, as the pandemic is clearly affected, if not driven, by the behaviour and interactions among people and their contextual risks, which is usually the subject of studies of *behaviour settings* in the field of *ecopsychology*[31] and can be integrated in a more comprehensive *socio-ecological frame*.[32,33]

The dynamics of the pandemic as represented in the fluctuations of incidence numbers is caused by multiple mechanisms with *pandemic-drivers* such as clusters of infections, travel, night-life, large events and so forth, and in parallel by *pandemic-brakes* such as lockdowns, mask-wearing, vaccinations and so forth. There is obviously no such commonly accepted *general multi-factorial model* of causation of the dynamics. We suggest a *systemic view* for the large picture, essentially assuming that humans are not stimulus-response machines but intentionally planning and acting beings. Consequently, it is necessary to explore whether social class, cultural

issues, and access to health care can help to predict more accurately the course of the pandemic and of the pathology. In addition, the geographical conditions of the respective populations should be considered differentially within a *multi-variate analysis*, that includes climate conditions, seasonal variations, population density and so forth. These approaches need an integrative theoretical socio-ecological framework which justifies comprehensive data collection; unfortunately, there are obviously no effective current trans-disciplinary institutional and/or methodological research co-operations.

2.1 | Population health, society and environment

With regard to a necessary high-level and structured systematic view, the CDC already proposed a multi-level framework referring to 'social-ecology'.[34] Prevention should consider the *individual*, its *relationships*, the *community* and the *society* in their reciprocal causal conditions. Similar framing categories of social ecology[35] were proposed by experts from health promotion, public health, Global health, Planetary health or One health approaches that integrate social and natural dimensions of human ecosystems.[36,37] Interestingly, these propositions seem to be forgotten with regard to the SARS-CoV2 pandemic, although it is evident that there is a need for *multi-dimensional* and *multi-scale considerations*, which bridge the tension between population health, local and global economies and individualized personal health, and individual economy and freedom, which are driven by the 'eigendynamics' of the virus and its mutants (Figure 1). It is important to note, that a socioecological perspective relies on a systemic methodology to develop useful, reliable and valid models that also capture the dynamics of the pandemics.

Thus a comprehensive conceptual multi-level model that integrates environmental conditions and intra-organismic mechanisms top-down over several organisational levels might be useful as a differentiated but integrative theoretical framing (Figure 1).[12,22,38,39] In other words, in addition to the population level of public health, an integrative physiology/pathophysiology is needed at the *individual level*, supported by basic research as well as clinical case studies.

From a fundamental living systems perspective, the basic levels addressed in an integrated multi-level model would—depicting cooperation and competition—extend from culture-related population health down to the molecular level of the cells in both directions[40]: starting with the virus as a molecular structure to cells (in particular, alveolar, endothelial and immune cells), to the cellular environment within tissues (e.g., mucosa), organs (e.g., upper respiratory tract) and organ systems spanning the entire organism

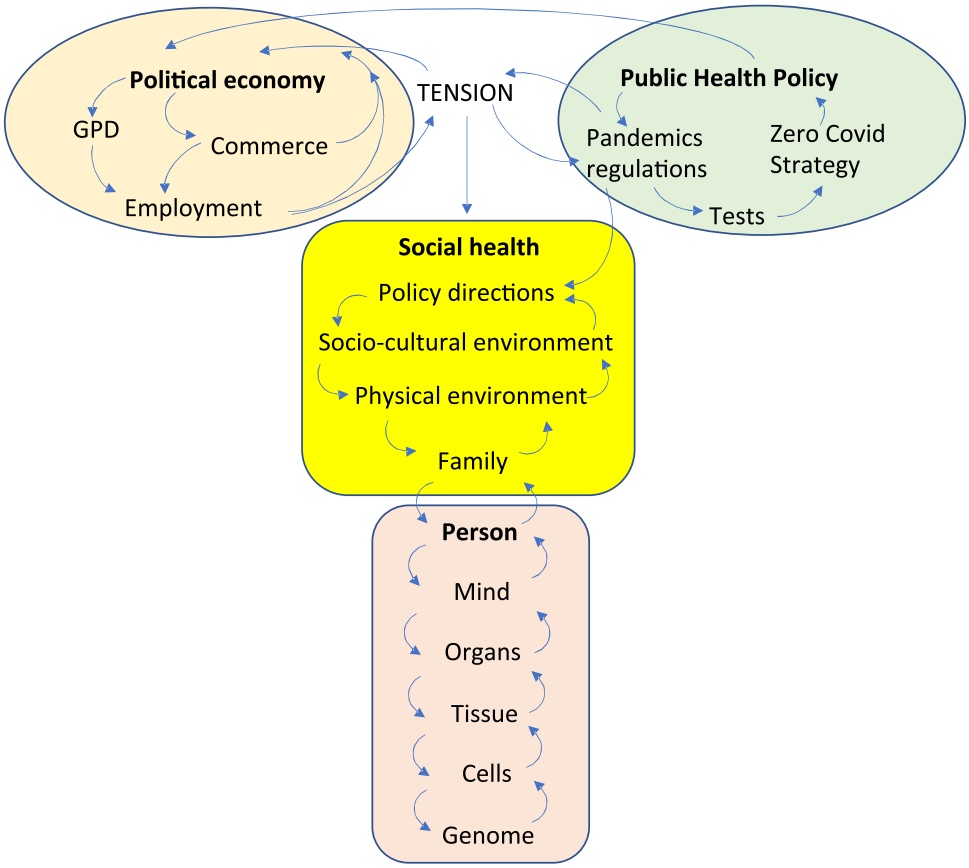

FIGURE 1 A socioecological multi-level systems model—from the whole to the parts and back with particular nested systems models (adopted and modified from Sturmberg and Martin).[21]

(e.g., respiratory system, cardiovascular system, nervous system and endocrine system) and finally to the environment of the person (the disease ecology of a person and the population) within their social contexts (family, community; health care; politics) and the environment of the virus (e.g., air conditions like temperature, humidity, etc.). Especially this framing of an *ecological view of a system* that is embedded in its *environment* is essential for contemporary systemic thinking modelling and intervention: also the cell has its 'cellular environment' within the tissue of the organs with cooperation and competitions.[41,42]

It should be mentioned here that with regard to infectious diseases, an 'ecosystemic immunology' would be more powerful and effective than the usual laboratory-centred molecular immunology. In this view, the evolution of the immune system is not so much devoted to self-/non-self-discrimination but with good or bad agents, for example, exogenous bacteria in the gut.[43,44] In addition, it has been increasingly recognized that lymphocytes and cells of the innate immune system, both individually and collectively, receive, process and deliver biochemical information in ways that suggest a deep functional analogy with (certain aspects of) the operation of the central and peripheral nervous systems.[11] This functional complexity makes an integrative approach to the body interactions with a pathogen even more critical and also more challenging. Here, nested macro- and micro-models should be explored separately.[45] As in context of public health, population health is the focus we started at the macroscopic socio-ecological level and now focus on mesoscopic physiology and pathology.

3 | SYSTEMIC PHYSIOLOGY AND PATHOLOGY

As noted already, it is useful to start any systems analysis on the basis of a multi-variate stimulus-response scheme (Black Box paradigm) but soon—in the context of physiology—one is confronted with feedback and feedforward loops and has to consider homoeostatic and allostatic processes. Referring briefly to various models, we highlight some of these steps toward a more comprehensive picture of the COVID-19 pathology and to understand better the possible pharmaceutical leverage points for the disease.

3.1 | Implicit multi-factorial models of physiological risk factors

The most important finding to be explained (explanandum) is the ratio of healthy infected versus severe cases of COVID-19.[46–48] The individual constellation of vulnerability/risk factors and protective factors could explain the disease courses and the number of Corona-associated deaths as output/outcome variables.

Interestingly, already early in the pandemic, a Pareto-like pattern of disease behaviour was observed—a large proportion of infected people (~80%) had asymptomatic and mild disease, most infected people (~20%) developed moderate and only a small percentage severe life-threatening disease. The latter group was definable in terms of known factors associated with high risk for severe disease,[22] such as male sex, higher age, diabetes, obesity, heart failure, COPD, immune-suppressive cancer treatment, liver cirrhosis, concomitant HIV infection and dementia.[49–51] By contrast, infant health is well protected against Coronavirus by the innate immune system.[52–54]

These risk and protective factors point at the relevance of the immune system with respect to disease vulnerability, as the listed demographic factors and non-communicable diseases are associated with the balance between innate and adaptive immune responses. In addition, pathodynamics with regard to Long-/Post-Covid are unresolved but hint at similar interdependencies but with shifted vulnerabilities such as middle-aged women. Consequently, it is important to note that the most common explanation for Corona-associated death was an implicit *multi-factorial equation*. However, this equation ignores environment, socio-economics, interpersonal communication, and other contributing factors.

3.2 | Integrative multi-level disease models

To identify the essential dimensions of the multiple, complicated conditions resulting in health or disease outcomes during the COVID-19 pandemic, it seems to be useful to develop a framing 'bio-psycho-socio-ecological' model of individual health, indicating by this terminology the roots in Engel's bio-psycho-social model and extending it to the ecological perspective.[55] Such a model could, for instance, also be able to explain the influence of *psychosocial stress* on the course of the emergence of disease in an *individual*.[56] The model should simultaneously address not only individual health but also public health with appropriate stratifications of the population and consider bottom-up and top-down causation in parallel.

This kind of integrative perspective was also aimed over the last several years by *molecular systems biology/medicine*[57–62] and *network biology/medicine*.[63,64] These approaches are biotechnologically and data analytically driven and raised the hope to treat diseases in a personalized way. However, the results of this *bottom-up approach* with regard to COVID-19, even with high technical input,[65,66] are still aspirational and need additional epistemology- and methodology-oriented philosophical considerations.[67–70] It is important that knowledge of physiology is included to develop an organism-focused medicine (organismal systems medicine).[71]

3.3 | A multi-compartment model

A preliminary systemic conceptual reference framework, in the form of a multi-compartment, multi-level and multi-layer model for the bio-medical perspective that can actually serve to guide practical clinical research was already proposed elsewhere.[4] In line with this and with respect to compartments, it is important to understand the

diversity of organismic topographical resistance factors (e.g., mucosa, immune cells and nerve terminals) since the virus enters the body mainly through the upper respiratory tract. Also, the involvement of the nervous system is not yet fully understood. Furthermore, the understanding of the distribution of the virus to other organs and of the development of Long-/Post-Covid could benefit from such a multi-compartment model. It should be mentioned here that thermodynamically oriented approaches as components of system theories could, for example, improve the understanding of receptor affinity for the virus in different compartments and stimulate novel developments of medications (Figure 2).[72]

3.4 | Dynamic equilibrium models

The traditional principles of homoeostasis[73] and allostasis[74]—as notions on dynamic balances and imbalances of several coupled function systems and their regulations—provide an instructive framework to be re-considered. A crucial framework for this holistic perspective is a foremost needed systems physiology[75] or at least a new emerging network physiology/pathology.[76–78]

One useful translation of the homoeostatic principle is the concept of *coupled pendula* or the *dynamic balances of activators and inhibitors* of a physiological process that constitute health and disease. This metaphorical model can help to understand that COVID-19 depends on differential kinetics of change of activity of several organismic subsystems.

With regard to adaptive dynamics and to the multi-factorial risk equation discussed earlier, it is also important to note that most of the identified risk indicators are closely associated with social dysfunctions (type 2 allostatic load), either as causal factors for their development or as health-related endpoints resulting from chronic stress. The concept of chronic distress thereby addresses any bio-psycho-social cause of continuous and lasting activation of the neuroendocrine stress response systems and how this translates into molecular and cellular toxic effects. Distress thereby disrupts key bodily functions, such as the immune response, energy metabolism, cardiovascular, and metabolic function, as well as oxidative stress regulation. While type 1 allostasis describes how these bodily functions are maintained in a homoeostatic state, type 2 allostasis addresses conflict and social dysfunction as cause for chronic distress. In this concept, distress results in a loss of the capacity to maintain homoeostasis and instead causes allostatic overload due to the incapacity to cope. The potential relationship between chronic distress or type 2 allostasis and the severity of COVID-19 is still understudied, and methodological problems hamper scientific progress in this intersection. It is, however, well understood that elevated sympathetic activity (and para-sympathetic hypoactivity), hyperglycaemia and immune-dysregulation are markers of a poor outcome; and potential pathophysiological mechanisms underlying this relationship have been identified.[79–84] If confirmed by carefully-planned prospective studies, these insights may help to prevent an unfavourable outcome of the disease; and they may also explain the conundrum of bio-social disparities in the prognosis of COVID-19.[85–87]

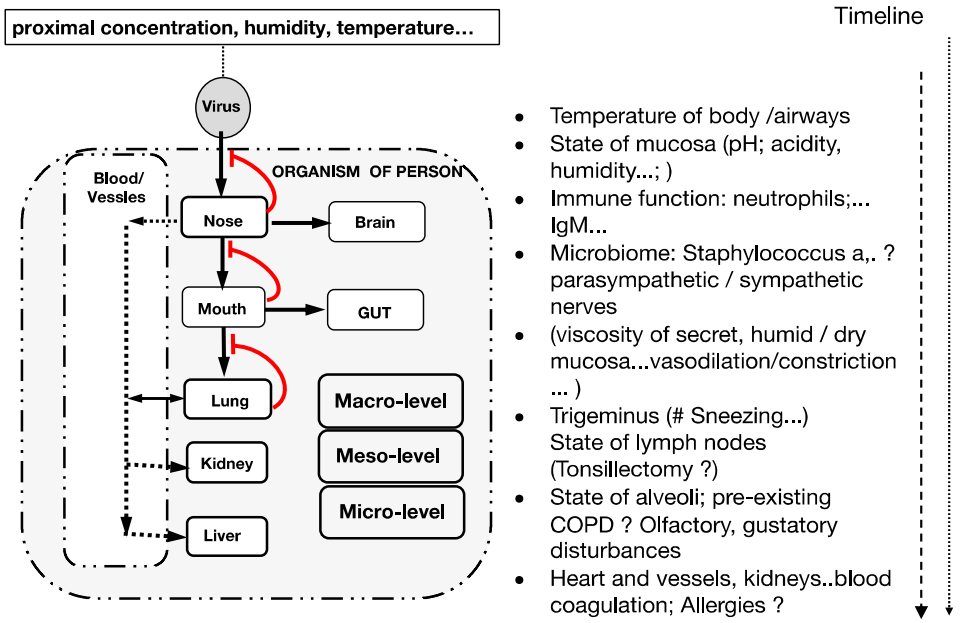

FIGURE 2 Physiological macroscopic multi-compartment and multi-level model of the organismic response to respiratory virus infection, along with stages of the viral invasion process, with conditions and reactions associated with affected compartments (modified from Tretter et al.).[4]

3.4.1 | Imbalance in a qualitative *network model*—the hyperinflammation syndrome

COVID-19 is currently characterized as a hyperinflammatory syndrome (Figure 3). Hyperinflammation is based on interactions within the Renin–Angiotensin–Aldosterone System (RAAS) resulting in an intra-systemic imbalance between pro- and anti-inflammatory mechanisms. Binding of the virus to the angiotensin-converting enzyme 2 (ACE2) results in the blockade of the cleavage of the pro-inflammatory angiotensin into the anti-inflammatory angiotensin 1–7, one driver of the so-called ACE2-angiotensin-(1–7)-Mas receptor axis.[88,89] It is the result of high affinity of SARS-CoV2 to critical components of the ACE2 axis compared to the AT1 receptor axis, resulting in a hyperinflammatory state of RAAS.[90–93] Physiologically, it should be noted that the RAAS belongs to the blood pressure controlling part of the endocrine system; but it also has these effects on inflammation. Integrating RAAS into the conceptualisation of the immune system with its pro- and anti-inflammatory functions and its innate and adaptive cellular components in the view of a systemic functional analysis leads to a network model with imbalanced interactions, resulting in a hyper-inflammatory state of the cellular matrix (Figure 3). Interestingly, it should be mentioned here that there has not been enough research conducted with regard to the experiences with AT receptor blockers/ACE inhibitors and their effects on the progression of COVID-19.[94–97]

3.4.2 | An integrative equilibrium model—multiple coupled pendula and antivirus defence functions

The simple network model presented above shows the inter-dependence of the *immune system*, the *endocrine system*, and the (autonomic) *nervous system* being involved in *defence functions*. A crucial role plays the well-known hypothalamus pituitary adrenal axis.

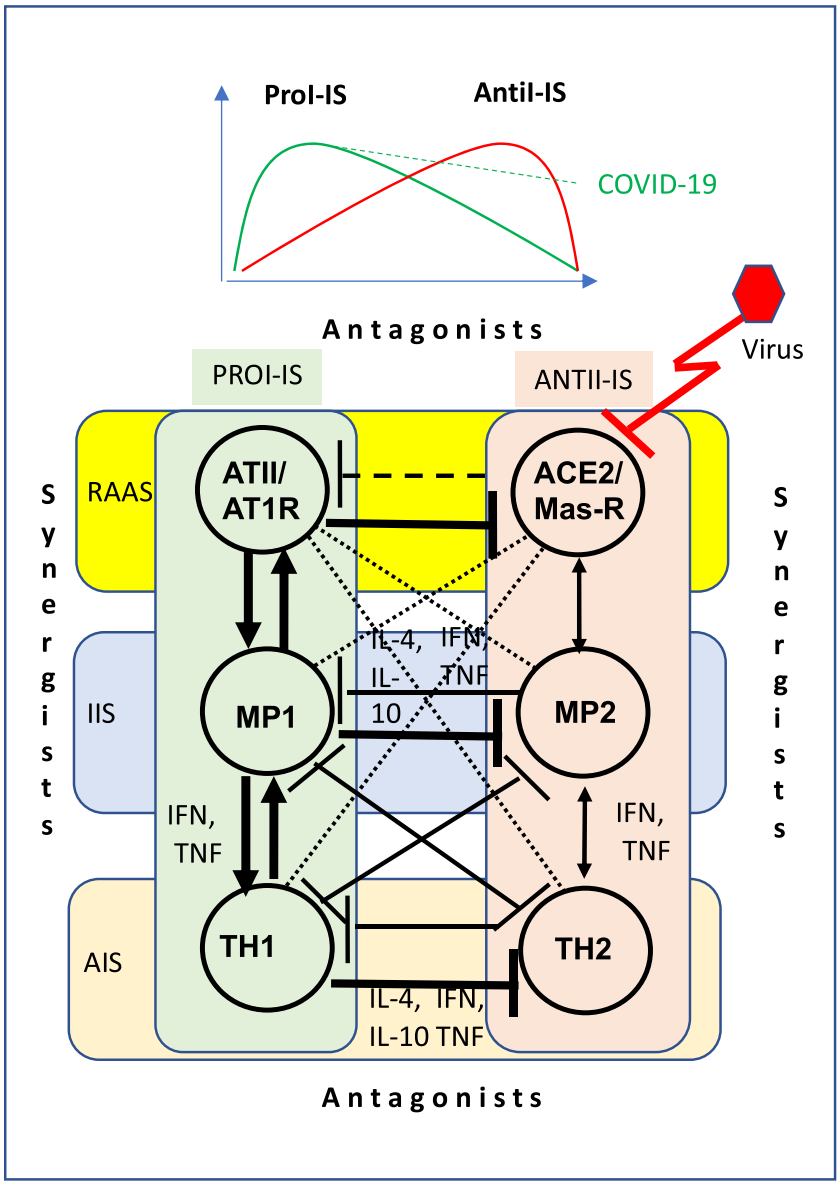

FIGURE 3 Hypothetical qualitative model of the basic cellular network guiding the host's defence to SARS-CoV2 infection, possibly leading to a persistent hyperinflammatory state. The cause may be a pernicious cycle of (1) ongoing asymmetric reciprocal inhibition (antagonism) between pro-inflammatory and anti-inflammatory immune responses to the virus (top panel) and (2) reciprocal synergistic actions within the affected systems. ACE, angiotensin-converting enzyme 2; AntiI-IS, anti-inflammatory immune system; ATII angiotensin II, AT1R, angiotensin 1 receptor; Mas-R, MAS (G-protein-coupled) receptor, MP1, macrophage 1, MP2, macrophage 2; ProI-IS, pro-inflammatory immune system; RAAS, renin–angiotensin/aldosterone system; TH1, T-helper cell 1, TH2, T-helper cell 12, Il-4, IFN, TNF, IL-10, cytokines.

However, a coherent data-based picture is lacking because most available data are collected—as mentioned above—by methods and not by concepts, hypotheses, (exploratory) models, or theories much akin to 'big data' science that believes data speak for themselves. To dynamize this concept of a *network*, a conceptual transformation to a *metaphorical model of coupled pendula* is proposed. This stepwise procedure of modelling was already demonstrated for a function model of neurotransmission in mental disorders, such as alcohol addiction or depression (Figure 4A).[29,98] As the immune system is also a complex adaptive system,[11] this modelling strategy can also be applied to the immune system to capture the pathogenetic persistent dominance of the pro-inflammatory subsystem that determines the picture (Figure 4B). Accepting that the (autonomic) nervous system, the endocrine system and the immune system collaborate within the organism and contribute to defence reactions against the virus, a more complex conceptual model can be designed (Figure 4C). With this complex model in mind, one could collect data and also conduct specific empirical studies to modify the model, formalize it by mathematical equations, test it through computer experiments, and differentiate the model. In general, we think that understanding the interaction of drivers and the brakes of the pathodynamics could help in developing tools for treatment as well as for prevention.

With regard to a tissue-centred view, other systemic perspectives can also be considered. According to this view, the major drivers of a successful or pathogenic inflammatory response are the adaptable and context-dependent interactions of infected cells with their cellular environment in the tissue of the affected organ, particularly with resident and recruited immune cells and neurons, rather than a diversion of systemic controls by the virus. An alternative to probing the impact of infection on the systemic physiological mechanisms is the conceptualisation of actual strategies whereby the system deals with the pathogen and with restoring functional homoeostasis (allostasis), based on broad observations by researchers. For example, a 'rinse and replace' mechanism has been proposed to operate in the context of HIV infection and in the early stages of the development of certain tumours.[99] Accordingly, when

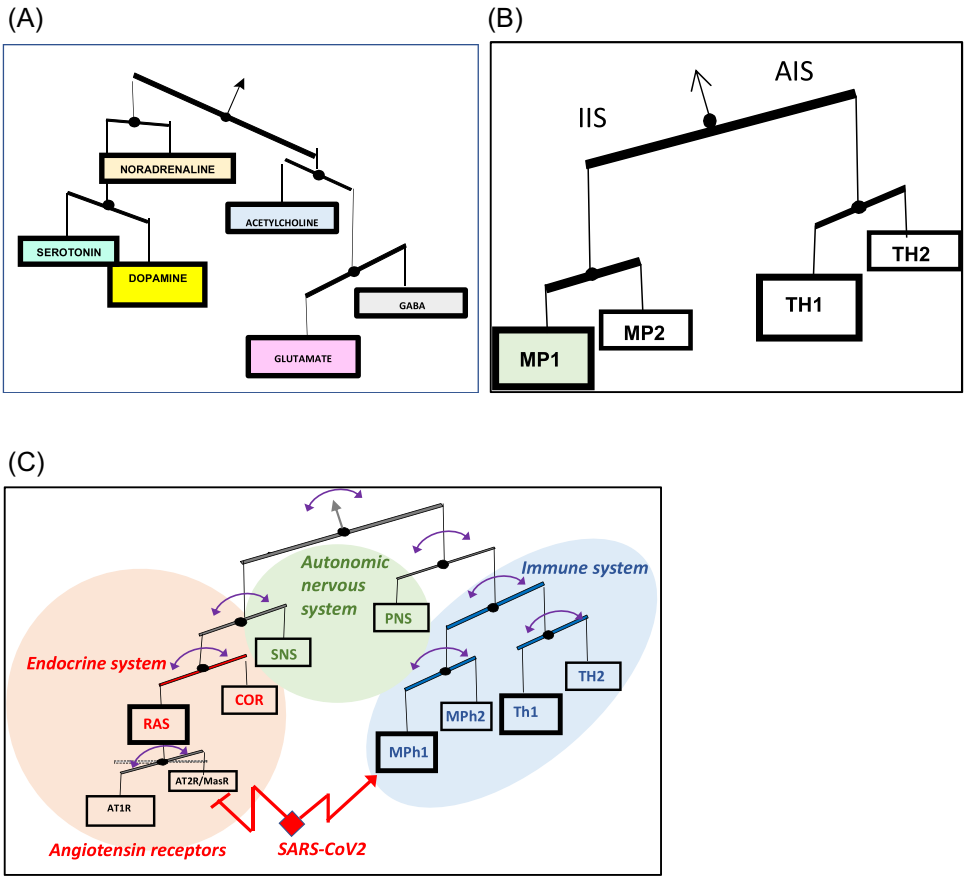

FIGURE 4 Heuristic models of disease in the format of coupled pendula that focus on the relative functional dominance of a subsystem. (A) CNS functions and mental disorders (e.g., depression, schizophrenia and alcoholism) as consequences of different neurotransmitter imbalances with relative hypofunction of biogenic amines and relative hyperfunction of other transmitter systems. (B) The immune system in a pro-inflammatory state that is characterized by dominance of macrophages with MP1 over MP2 and T-helper cells with TH1 over TH2. (C) Integrative pendulum model of the nervous system, the endocrine system and the immune system. For Figure 2; COR, Cortisol; SNS, sympathetic nervous system; PNS, parasympathetic nervous system.

conventional immune elimination is not effective, acceleration of the normal flux of proliferating and differentiating tissue cells can result in effective replacement of infected cells, and of lost and damaged cells, by their uninfected precursors. Biomarkers of such a process might be identified in a top-down approach. Once established, a detailed low-level description might be constructed based on existing and new data.

3.5 | A molecular multi-causal loop model—The ACE2 and INF interaction

A causal loop view of the initial step of the infection sheds light on an interesting feedback mechanism, namely that the virus attachment to ACE2 causes induction of INF gene expression, which stimulates ACE2 production, and this, in turn, further facilitates the invasion of the virus.[100,101] This motif of self-enhancing circular causality could be one of the disease-supporting malicious cycles. In a more integrative view, however, positive and negative feedback loops compete in the individual evolution of COVID-19 (Figure 5). Multiple factors, including the speed of immune responses, basal expression of ACE2 and TMPRSS2, and the initial virus load, determine the fate of affected patients. Computer simulations of the processing structure outlined in Figure 6 show that some of these conditions, for example, higher TMPRSS2 expression, result in oscillatory virus load, which has been observed in severe cases of COVID-19.[102–104] This model also explains, why the prognosis of COVID-19 is worse in males, where TMPRSS2 expression is higher,[105] and why biomarkers of the inflammatory response show a higher dispersion in critical cases of COVID-19.[106,107]

4 | SYSTEMS THINKING AS THOUGHT CULTURE

Recently, it has been demonstrated that several eco-systemic modelling perspectives could improve the understanding of the pandemic. Here, we provide several suggestions for the methodology of systems modelling, starting with one systemic view on health.

4.1 | Poor health as impaired resilience of a complex dynamic multi-level system

The developments in molecular and cell biology, over the last three decades, have often been driven by the desire to understand disease phenotypes through the lens of molecular interaction networks. It is now widely accepted that to understand the role or function of a molecule/cell, we need to study these system components through their interactions in networks.

The number and variety of components, the fact that their interactions evolve and adapt over time, have necessitated mathematical modelling and computational simulations but at the same time have also exposed limitations of this approach. Acquisition of quantitative, sufficiently rich time-course data remains a major challenge for the application of systems theoretical approaches in data-driven modelling. This challenge, however, also motivates more abstract approaches (e.g., balance/imbalance concepts), where systems theory provides a conceptual framework

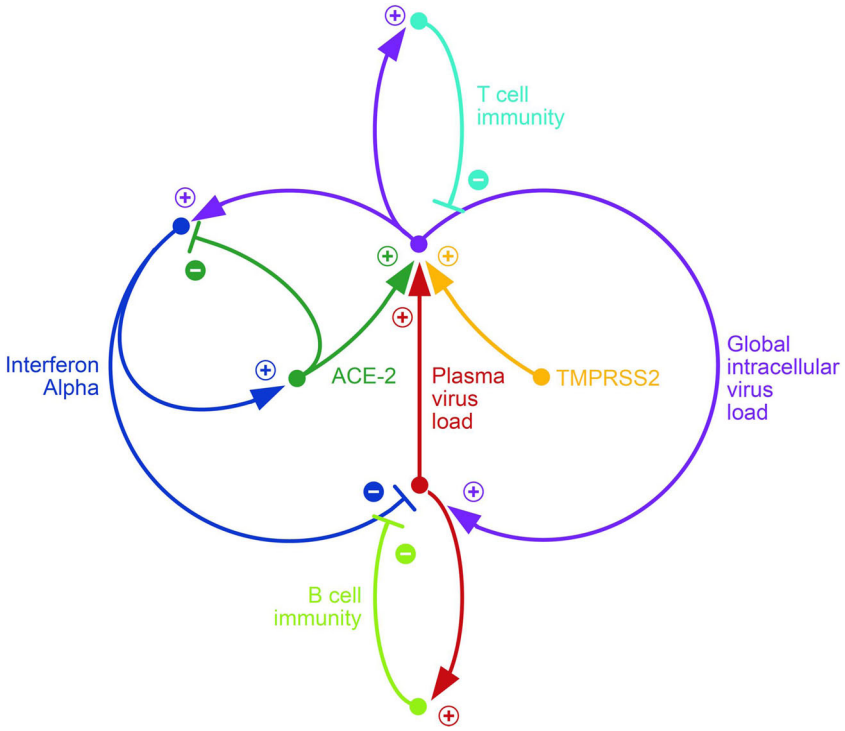

FIGURE 5 The Janus-faced role of interferons and a competition of positive and negative feedback loops determine the course of COVID-19 infection. After binding to ACE-2, SARS-Cov2 is able to enter cells and to replicate. This initiates immune responses via B and T cells and interferon release, thereby reducing the virus load again. However, interferon alpha also stimulates the expression of ACE-2, which facilitates virus entry and implements a positive feedback loop raising the global virus load.

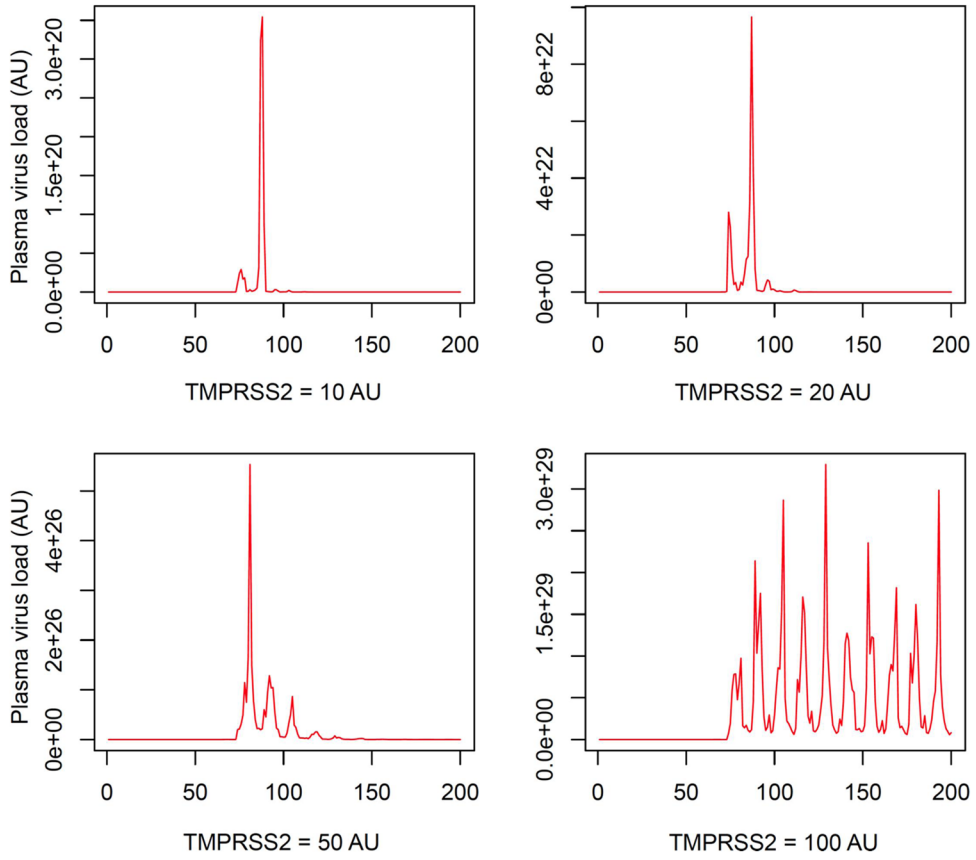

FIGURE 6 Higher expression of the transmembrane serine protease 2 (TMPRSS2), as observed, for example, in males, stimulates the binding of SARS-CoV2 to the ACE receptor and promotes a higher virus load. Simulation of the motif of combined positive and negative feedback loops as outlined in Figure 3 suggests that higher TMPRSS2 expression may also give rise to oscillatory dynamics of the virus load, as previously observed in severe cases of COVID-19.

to formulate hypotheses, and thereby support model-driven experimentation.

Systems medicine and a systems view on epidemiology/public health focus on coherent high functional order of the various subsystems, which are coupled but buffered. In health state, they exhibit a high resilience, whereas in case of a disease, they persist in a dysfunctional state such as allostatic overload.[74]

4.2 | Methodology of systems thinking as a cultural tool

COVID-19 is a truly multi-faceted disease that operates at many different time scales and organisational biological levels. Importantly, it also includes psychological, social, and environmental aspects. In this view, many data are missing. In case data are lacking, in context of systemic modelling, data can be estimated by 'educated guess' and in this situation 'exploratory modelling' can be realized as a starting point.[108,109] A lack of data also justifies 'transdisciplinary methodology' where in addition to scientists other stakeholders of the problem are integrated, as it is practised in sustainability research.[110,111] An immediate consequence is that comprehensive mathematical models of the disease must address multiple levels and scales.[112] Such a task is always a daunting challenge because a 'combinatorial explosion' of state variables and processes makes it infeasible to capture in a higher-level model every single process occurring at a lower level of organisation.

The first phase of addressing this challenge is the collection of suitable data, which in the case of COVID-19 must include not only biological and clinical factors but also social and environmental factors. Unfortunately, clinical observations of COVID-19 symptomatology, course of disease, response to medications and so forth, are essential but they are difficult to measure since they are only 'qualitative data'. An interesting starting point for the first set of required data is the COVID-19 disease map,[113] which in a repeatedly revised manner organizes what is known about the biology of the disease into functional diagrams. It would be advisable to create corresponding maps of social and environmental aspects and their influences on the progression of the disease. The value of such interaction maps lies in the standardized representation of interactions, which at a sufficiently large scale provides a data set in itself and can be explored with algorithms. The organisation of such maps can, of course, be expert-curated, but the use of tools, for instance from graph theory, uncover patterns, structure and motifs in these networks.

Of course: 'All models are wrong but some are useful', as statistician George Box claims.[114,115] But by reviewing decades of modelling complex dynamic ecological and biological systems, a culture of methodology of modelling emerges that can even be understood by non-mathematicians.[116–118]

As discussed earlier, information regarding isolated facts is insufficient, even if collected in large quantities. The collection of information must be converted into causal knowledge. A conceptual framework for realising this conversion is that of 'templates and anchors', which was developed within the context of locomotion.[119] In the terminology of this approach, a *template* is a high-level model of the entire system of interest. In the case of COVID-19 biology, the variables in this template model might correspond to the larger 'boxes' or headings of the COVID-19 disease map,[110] such as the innate immune system, the adaptive immune system, the circulatory system, or a target cell. The arrows in the disease map are the basis for selecting functions representing the processes among the subsystems. During the course of the infection, these subsystems interact with each other in a dynamic fashion, and the corresponding variables and their interactions can be analysed and simulated at this level. Insights may be gained that pertain just to this high level.

To account for more detail, each variable of the template model is recognized as representing a subsystem, and this subsystem constitutes an *anchor model*. Thus, a variable of the template model like 'target cell' becomes a finer-grained anchor model with variables like 'virus attachment and entry', 'virus replication' and 'cellular metabolism'. In the same spirit, the anchor models themselves may become templates for even more finely grained levels of organisation. For example, the adaptive immune response is captured by an anchor model that may contain as variables CD4 and CD8 cells, B cells and cytokines. The cytokines may in turn become systems at yet a lower level. One may note that this concept of templates and anchors is a natural extension of macro-, meso- and microscopic models that focus on selected temporal, spatial and organisational scales.

The organisation of data, details, processes and subsystems in the manner of a template-and-anchor model has enormous advantages. In particular, it is directly feasible to develop models at any level, depending on how much biological, clinical, or social-environmental information is available. If much is known about a variable in an anchor model, this variable itself may be replaced with a systems model that permits the inclusion of governing details and processes. Our understanding of the workings of this lower-level system can be tested at this level through simulations, sensitivity analysis, and other mathematical and computational diagnostics. Influences from other anchor models are treated as input variables, which may be constant or dynamic.

Now working from the bottom up, by ultimately returning from the lowest-level anchor to the overall template model, the input–output relationships of the anchor models are summarily reflected in the dynamics of the template variables.

This divide-and-conquer strategy permits very detailed modelling at lower levels, which may be validated with methods of the subject area, such as molecular biology, and indicate which processes and variables within a sub-module are directly or indirectly affected by the virus, and how the ultimate outputs of this sub-module are altered in the presence of the infection. It is quite likely that only a small number of variables and processes respond dramatically with respect to the overall output, and only those outputs that are substantially altered in response to particular inputs are retained at higher levels to capture the effects of the virus on this particular sub-module. In the model at the next higher level, the changes in inputs are driven by changes in other anchor models.

The modelling strategy of templates and anchors can be subdivided into distinct although often overlapping conceptual steps. The following steps of systemic conceptualisation of COVID-19 as an epistemic object appear to be useful[106,120]:

- assemble a transdisciplinary group of experts;
- define the boundary structure of the system;
- collect observations and data, ideally within informational contexts;
- establish the organisational levels of analysis;
- for the overall template model, and for each potential anchor, identify the key drivers and their networks of interrelationships;
- perform analyses at each layer, some of which may be detailed and others quite coarse, due to the availability or lack of data;
- assess interactions of anchor models at the same level;
- use input–output relationships of all anchor models of a given level to provide information for the model(s) at next higher level;
- assess reasonableness of the integration of information at the next higher level;
- validate the model, as far as possible, by testing the effects of low-level inputs on the overall responses of the template model;
- replace fixed parameters with ranges of possible values and explore consequences, for instance, through Monte-Carlo simulations;
- test and validate the model with new data, especially from real-world situations (see Section 1.3).

It should be evident that we are far from realising this type of comprehensive modelling of COVID-19 at the present time. Nonetheless, it seems useful to consider data collection, combined with associative and causal modelling within this conceptual framework, and to start developing models of aspects that are sufficiently well known. Such models could focus on any of the contributing levels and include the highest-level template model in a relatively coarse-grained, presumably qualitative or semi-quantitative manner.[121]

Also, the approaches by the Systems Dynamics group are useful insofar as they usually start with conceptual modelling with graphical tools that facilitate cooperation with non-mathematicians but

allow them to proceed further on to formal models and simulations.[28,122,123]

5 | PERSPECTIVES

COVID-19 is such a complex disease that a mindset of the culture of systems thinking appears necessary to yield true progress in understanding the pandemic at a population level as well as the level of individual pathology. An integrated stepwise procedure of modelling, from qualitative models to quantitative models, moving up and down the organisational scale of anchors and templates, will permit computer simulations and scenario analyses that should become 'better' with each iteration. This methodology of modelling—starting with simple networks and ending with the integration of fully regulated systems at different levels of organisation—can begin immediately and will continue throughout the foreseeable future. It will yield insights at technical levels, but also have implications for the clinics and may become an epistemic object of interest for experts and the lay population. Finally, it should be noted that systems theory is not a tool for academics alone but also for laypersons to understand better the connectivity of phenomena in our world.

AUTHOR CONTRIBUTIONS

The paper is the result of several meetings of a working group with different periods of action since Summer 2021. FT and JM initially outlined the manuscript. All authors contributed to all sections. The introductory part and pathology were complemented by JS with former contributions by EP, JD, JB, DF, WW and ZG. The modelling section was formulated by EV and is connected with additional input by OW. Systems perspectives were integrated into several sections by GS. Figure 1 is based on a slide by JS and modified by FT; FT also drew Figures 2–4; Figures 5 and 6 were drawn by JD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

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