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Biodynamic Interfaces Are Essential for Human–Environment Interactions

Manish Arora, Alessandro Giuliani, and Paul Curtin*

The environment impacts human health in profound ways, yet few theories define the form of the relationship between human physiology and the environment. It is conjectured that such complex systems cannot interact directly, but rather their interaction requires the formation of an intermediary "interface." This position contrasts with current epidemiological constructs of causation, which implicitly assume that two complex systems transfer information directly while remaining separate entities. Further, it is contended that dynamic, process-based interfaces incorporate components from all the interacting systems but exhibit operational independence. This property has many consequences, the foremost being that characteristics of the interface cannot be fully resolved by only studying the systems involved in the interaction. The interface itself must be the subject of inquiry. Without refocusing the attention on biodynamic interfaces, how the environment impacts health cannot be discerned.

1. Introduction

The interaction between human physiology and the environment is key to deciphering the origins of health and disease. When examining the health consequences of individual agents or mixtures of environmental factors, studies at all levels of organization from human populations to controlled laboratory experiments, are often conceptualized as mono-directional causative occurrences with the environment impacting some physiologically relevant, measurable end point. In **Figure 1**a, we depict the general formulation of such a research thesis. Examples include the impact of the toxic metal, lead, on intelligence quotient (IQ) or stress exposure and cortisol levels in a biological matrix.[1,2] Positive environmental influences are also conceptualized in this manner, for instance access to green space is associated with better measures of cardiovascular function.[3,4]

More recently, with the realization that the relationship between the environment and human physiology is bi-directional, the arrows visualized in Figure 1a can now also point from humans to the environment, as shown in Figure 1b. The scenario depicted in Figure 1b represents a shift from a simple one-directional perturbation to a circular feedback process that emerges within and across multiple levels of organization in each system.[4,5] A simple example of this is the relationship between human activity and air-pollution; our industrial processes release pollutants into the air and the increased environmental air-pollution in turn impacts human health.[6] The nature of this relationship has important consequences in how these systems will evolve over time; in a positive feedback cycle, for instance, increasing exposures to pollution will cause more deleterious health effects, which may in turn lead to increased exposures through, for example, chemical release from medical interventions.[7]

1.1. Interfaces Emerge across Levels and Systems

In both Figures 1a and 1b, the often-overlooked aspect of environmental health is the actual form and physical nature that the interaction between the environment and human physiology can take. Specifically, the underlying assumption in Figures 1a and 1b is that two complex systems (i.e., humans and the environment) can transfer influence directly to one another. In contrast to this, here, we conjecture that complex systems cannot interact directly or exist in isolation. This is because complex systems must, by definition, include the integration of multiple levels of organization, implying several parallel and sequential causal pathways, and as such can neither be seen as discrete entities, nor can any feature of a given system be isolated from the whole. The association between air pollution intensity and IQ, for example, does not imply that air pollution directly modulates cognitive faculties. Instead, because both systems are inherently complex and composed of multiple integrated levels of organization, variability in air pollution will emerge from large-scale population-level factors as well as meso- and micro-scale processes that will ultimately determine the distribution of pollutants and human exposure to

Dr. M. Arora, Dr. P. Curtin
Department of Environmental Medicine and Public Health
Icahn School of Medicine at Mount Sinai
New York 10029, USA
E-mail: manish.arora@mssm.edu
Dr. A. Giuliani
Environment and Health Department
Istituto Superiore di Sanità
Rome 00161, Italy

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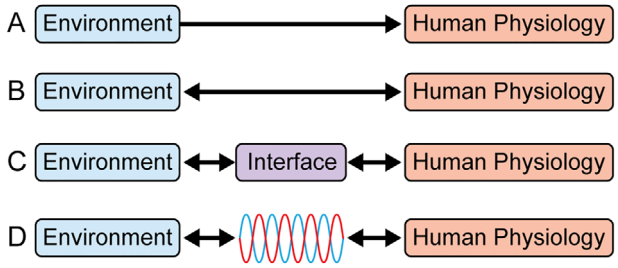

Figure 1. The biodynamic interface conjecture. Interactions between the environment and human physiology have been conceptualized as A) unidirectional and B) bidirectional (B). We conjecture that complex systems cannot interact directly but do so via one or more interfaces that are composed of components from both the environment and human physiology but are C) operationally independent. Such interfaces are D) dynamic.

them. Likewise, at the level of the individual, the pollutants we are exposed to are not passively integrated and directly linked to a biological end-point; rather, they are assimilated as part of ongoing homeodynamic processes, which will be influenced by our biology across multiple levels of organizations, from molecular reactions to metabolic pathways to organs, systems, and neurobehavioral patterns. As such, we propose that the interaction between two or more complex systems requires the formation of an "interface" (as represented in Figure 1c); which, in the context of environmental–physiological interactions, will necessarily include the incorporation of complex processes derived from the host physiology and from the environment. Further, we contend that the interface is dynamic and process-based in nature (Figure 1d); that is, the characteristics and properties of the interface can be assessed through the examination of time-varying patterns.

The nature of biodynamic interfaces incorporates components from all the interacting systems but exhibits operational independence of each (see **Box 1** on levels of organization and emergent complexity). This property has many consequences, the foremost being that the characteristics of the interface cannot be fully resolved by studying interacting systems as if they were discrete entities. The interface must itself be the subject of inquiry. This conjecture would require a shift in the practice of environmental health studies that currently use statistical methods to correlate the variance in one or more environmental measures with the variance in some physiological measures, or some comparable form of analysis.

1.2. Interface Dynamics Constrain the Transfer of Information between Interacting Systems

Of importance is the interpretation of direct interaction in the aforementioned conjecture. From a computational perspective, the direct influence of one system on another implies that the variation in the input/exposure measure relates to the variance in the output/health measure, even if it is partitioned through other measured variables. This is the form that many regression models take when studying the relationship of an environmental exposure on a health outcome and adjust for covariates. In observational studies, researchers are generally and appropriately cautious in interpreting such associations through the lens of a causal analysis (see **Box 2**), but the ubiquitous application of this framework nonetheless focuses inquiry at the level of reductionist connections between disparate and disconnected systems. In contrast, we argue that one or more processes, contributing to the interface between systems, serves to constrain (or in more general terms, assign a "meaning" to) what is transmitted to the other interacting system/s. The biodynamic interface, thus, places limits on both what attributes and how much of the signals are transferred between interacting systems. This happens in both directions; from environment to human, and human to environment. The presence and biological relevance of such intermediary processes may be evident in the time-varying dynamics that link environmental and biological systems, which may not be apparent in direct associative studies that seek to link discrete measurements of environmental inputs, often in the form of single measures of concentration and biological responses.

Essentially, an interface emerges wherever the measurement of one system's state intrinsically includes inputs from another system. This is a basic physical phenomenon that can be traced to the generation of molecular orbitals when two atomic species enter into a covalent link. In the same way, at more complex levels of organization, systems can likewise become entangled. For example, in the case of the cardiovascular system when measuring heart rate, we can expect to capture aspects of cardiovascular health; we might notice irregularities in the cardiac rhythm that are indicative of an unhealthy heart. But at the same time our cardiovascular system serves as a common interface for a multitude of other environmental inputs; excitement, anxiety, or arousal due to environmental stimulation of the nervous system will also alter or disrupt the cardiac rhythm. Though the heart produces the rhythm, the physical organ itself is not the interface where the integration of these systems emerges; rather, it is in the functional dynamics of the heart under varying conditions. It is the process of the heart not the structure of the heart that is the interface.

In this essay, we provide supporting evidence for our conjecture and also place our thesis in context of the important work of others that reject homeostasis in favor of homeodynamics,[8] that extend relativistic concepts from physics to biology,[4,5,9,10] that accept the ever-changing nature of our biology and argue for the existence of critical windows of susceptibility,[11] and general systems theory (GST) and Systems Biology that conceptualize human biology as a network of systems.[12]

2. Contrasting the Biodynamic Interface Paradigm with Current Molecular Biology Approaches for Uncovering Mechanisms

Due to the many advances in technology that have allowed us to study human physiology at ever finer scales of analysis, the focus on "mechanism" has often taken a reductionist approach, tunneling deeper to discover molecular markers in the expectation that molecules would explain complex phenomenon at all levels of observation, including at societal levels. As a consequence, in studies examining the interaction of the environment and human physiology, the search for mechanisms has taken the form of identifying molecules that may be up- or down-regulated along a pathway diagram. We provide an analogy here to convey

Box 1: Biological Levels of Organization and Emergent Complexity

The consideration of levels in the organization of biological systems is critical to the Biodynamic Interface conjecture, and more broadly to General System Theory (GST) and Systems Biology. The concept of "levels" in biological organization is a long-standing but somewhat loosely defined construct, via which past approaches conceptualized levels as generally related systems, the boundaries of which might be defined on the basis of ontological,[6] mechanistic,[7] temporal[8,10] and/or scalar limits.[11] In essence, these perspectives share the recognition that biological systems involve the integration of multiple mechanisms and processes that span varying temporal and physical scales, and that at each level of organization, different forms of complexity arise. At the smallest level of organization, we are made up of atoms; actually just a few of the elements in the periodic table are the building blocks for life. At the next level, one with higher complexity, we see pathways that regulate proteins, fat, carbohydrates and other molecules. Though these pathways comprise components derived from the first level, their mechanistic interactions at this level yield new biological functions; water, for example, exhibits distinct properties that cannot be derived from studying hydrogen and oxygen ions. At higher levels, where mechanisms and pathways are integrated to form cells and circuits, we start seeing physiological dynamics emerge. These mechanisms are again composed of processes derived from lower levels, but their integration again yields new time-varying functional properties that were not apparent at lower levels. Consider that the integration of synaptic processes will drive neurons to fire at the millisecond scale and, at the other end of the temporal spectrum, we have seasonal changes in our physiology where our biodynamics span several months. This emergent complexity is characteristic of complex physical, biological, and social systems that integrate multiple levels of organization. Of importance here, this complexity also constrains the nature of interactions between one system and another. When humans integrate some environmental exposure in their physiology, that input is processed through multiple stages and levels of complexity as it passes through the processes of ingestion, digestion, metabolism, circulation and excretion. Thus, any observed relationship between exposure biomarkers with health endpoints cannot be assumed to reflect the direct input of the environment upon the body—rather, we must investigate how that input has been assimilated in ongoing physiologic processes, which integrates inputs from the environment and our health. The interface we focus inquiry on is in the dynamics involved in those processes; that is, the nature of complexity in the organization of environmental inputs. This can be done through the application of dynamical phenomenological methods, appropriate for the characterization of stochastic, deterministic, and/or chaotic processes, to time-varying measurements of environmental biodynamics.

why this approach has had limited success in providing consequential understanding of human–environment interactions. In **Figure 2** we show two systems interacting—System A is a human hand that will be transferring information to System B, a piece of paper. Under a reductionist approach, System A would be examined in ever smaller spatial scales, from organ to tissue to cellular to the genetic level and, similarly, System B would be examined down to the molecular and ionic levels. However, neither analysis can predict the style of handwriting; nor, more profoundly, could either approach even begin to elucidate the language or meaning of what is written to a reader. To have an accurate measure of this transfer of information, it is necessary to examine the process-based (and therefore, dynamic) interface that connects the two systems, which in this case is the process of writing. This does not mean that all that is ever written on the piece of paper is necessary. Rather, a small piece of handwriting can be used to deduce the style or pattern of handwriting produced by a person with remarkable detail, as is the case in forensic analysis. This seemingly mundane detail is important because during any scientific experiment examining system-to-system interactions, the whole set of information is never available but rather the wider set is deduced from a small finite collection of data (i.e., the experimental data).

The general premise underlying functional dynamics and constraints is pertinent to ideas that exist in other domains of science. In engineering, during the origins of semi-automated control mechanisms between the 17th and 19th centuries, which saw the advent of proportional–integral–derivative (PID) controllers, the underlying assumptions took a similar form to what we have proposed here.[13] Specifically, the underlying logic of the processes that were developed did not take the form of input → control; rather the general form was input → state → output. Here, the "state" is what decides the transmission of necessary information from the input to the output. Another example is that of a simple mechanical light switch. The action of pressing the button (the input) depends on the current state of the system; if the light is off, then the input would result in it coming on, and vice versa. Although the transmission of the entire variance from one system to another is an idealized scenario, in a more realistic situation that includes the presence of noise, the constraints imposed by the interface do not blur the underlying correlation but impose a discrete tessellation on the state space into "permissive" (where the correlation holds) and "non permissive" (where correlation does not hold) dynamics.

3. Evidence for the Existence of Biodynamic Interfaces across Multiple Levels of Organization and Complexity

Next, we provide examples from human physiology supporting the conjecture we propose in contexts of basic and clinical research, extending from the level of individuals to molecular

Box 2: Biodynamic Interface and Causal Graphs

The use of vector diagrams in epidemiology is quite common, extending from qualitative flow charts and diagrams indicating the directionality of relationships to more refined approaches such as directed acyclic graphs (DAGs). In general terms, these and related methods are typically used toward two goals: first, to aid in the interpretation of direct and indirect causal pathways and, secondly, to provide guidance to the selection of covariates in statistical models. As a tool for the evaluation of hypotheses, DAGs and related vector diagrams typically depict direct and indirect relationships among variables through structural diagrams. In environmental epidemiology, for example, we might hypothesize a direct relationship between the concentration of an exposure biomarker and some health outcome. Through the construction of vectors, we may also identify variables that must be adjusted for or excluded in evaluating relationships between the exposure biomarker and the health measure. Detailed theory on DAGs in health research may be found elsewhere[1–4] as well as more accessible summaries with examples.[5]

Vector diagrams may likewise provide a suitable framework for studying environment-health interactions under the Biodynamic Interface paradigm, with some notable differences. According to our proposition, the edges in a DAG (i.e., the arrows in a DAG, which are also referred by some as "paths") are not passive entities indicating the direction of interaction but rather are complex systems that exhibit operational independence. The interacting systems (the nodes in a DAG) contribute to an emergent interface (the dynamics of an edge) that constrains the action of one system upon the other. As an example, in our study examining the impact of the toxic metal, lead, and an essential nutrient, zinc, on autism spectrum disorder phenotype, we found that it was not the concentration of either lead or zinc that provided the most predictive model but rather the joint dynamics (measures of joint rhythmicity, for example).

Critically, in the interpretation of these relationships, the Biodynamic Interface paradigm differs substantially from the traditional vector paradigm in environmental health applications. Whereas DAGs and related approaches are typically interpreted as indicative of a unidirectional causal pathway, such that one system acts directly upon the other, the Biodynamic Interface conjecture posits that the time-varying dynamics that emerge between systems may involve bidirectional processes and operational independence, which in practice may serve to constrain the action of one system upon the other. In other words, through the lens of this conjecture, the edges that connect one system to another are not passive connections between systems but are complex systems unto themselves.

Bidirectional process-based interfaces do not require events to be temporally ordered as in classical epidemiological causal frameworks. This is also true for many natural phenomena—for example, two bodies may exert their gravity on each other simultaneously, and it is not necessary to establish a temporal order to characterize their interactions.

interactions, to show that dynamic interfaces are not limited to any spatial scale or level of observation. At the level of an individual, interfaces emerge in the integration of endogenous organs and systems, and the modulation of these processes by environmental inputs. This is particularly apparent in the interpretation and analysis of human physiology from a clinical perspective.

3.1. Interface Dynamics Regulate the Cardiovascular System

Continuing with our example of cardiovascular disease mentioned earlier, decades of research have aimed at identifying signatures of healthy and dysregulated function. The cardiac rhythm serves as the final common path for multiple neural systems, including both the endogenous pacemakers that mediate and maintain cardiac rhythm as well as the outputs of the sympathetic and para-sympathetic nervous systems.[14,15] These so-called "fight or flight" and "rest and digest" systems, respectively, can be elicited in response to external environmental stimuli, for example the reflexive avoidance of a collision; or, in response to our own activity, as more or less strenuous exercise requires necessary resource recruitment. The confluence of internally and externally generated inputs are superimposed on the common path of the cardiac system where the cardiac rhythm acts as an interface comprising multiple integrated processes. Outside the context of a controlled environment, where various inputs can be isolated, it becomes impossible to determine if a given cardiac rhythm is being driven by the properties of endogenous pacemakers and associated musculature, or by responsiveness to external stimuli. For that reason, assessments of cardiac health are generally conducted under controlled conditions, where a "resting" heart rate can be assessed and contrasted against "stressful" conditions, without intervening activation driven by external inputs.[16] In contrast, in routine non-clinical conditions, where both internally recruited and externally elicited inputs are active, the cardiac rhythm is an interface that constrains the vast amount of information from internal and external environment inputs.

This essential integration in a relatively well-characterized system might appear elementary, but in practice the essential form of this perspective, which follows the configuration outlined in Figure 1d, cannot be routinely incorporated in epidemiological study designs due to a lack of appropriate tools to fully capture the temporal dynamics of our environment or our physiology. Instead, due to the advances in molecular biology, the most common path of inquiry has been towards a reductionist linkage as illustrated in Figure 1a, sometimes with insertions of molecular intermediates: environmental input → molecular marker → clinical measure of health. Fortunately, there is now a momentum in environmental health sciences towards developing tools that will allow further advances in exploring functional linkages between

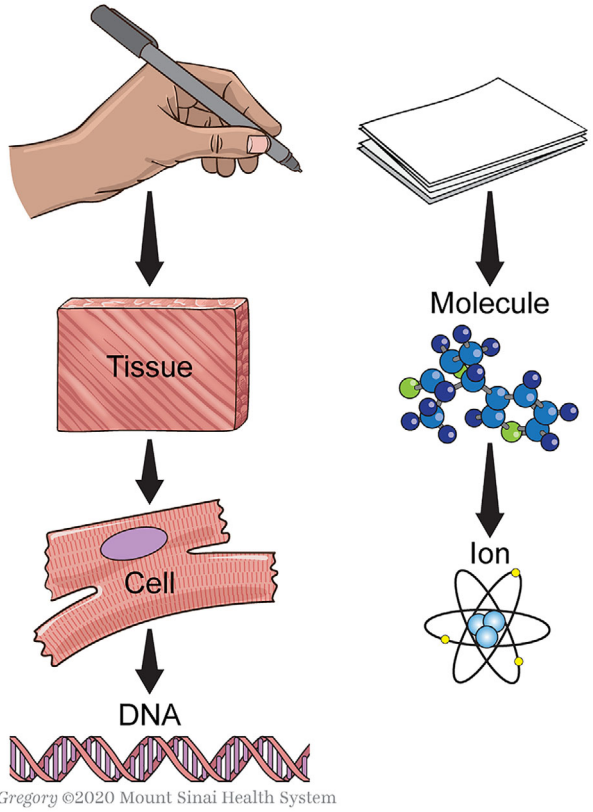

Figure 2. Reductionist approaches that ignore process-based interfaces are unable to uncover key components of system-to-system interactions. Here, analyzing the molecular structure of two systems (hand and paper) cannot reveal the form of the interaction—the handwriting style or the meaning of what is written. Only studying the dynamic interface (the process of writing) can achieve that.

the environment and human health. These include the development of highly temporally resolved retrospective biomarkers, wearable personal sensors for prospective longitudinal sampling, and localized and remote monitoring for spatial and temporal mapping of the environment.[17–21]

3.2. Behavioral Interfaces Mediate Social Interactions

The constraints on information transfer exerted by dynamic interfaces are also evident in human-to-human interaction. There have been several studies examining the transfer of information between individuals during common tasks that would be encountered in daily routines.[22,23] For example, in observational studies on individuals participating in unscripted conversations, aspects of language, facial expressions, eye gaze, gestures, posture, and many other attributes may be transferred between the participants. However, it has been repeatedly observed, with different measurement tools, that while there is clear synchronization in linguistic and physical expression between participants, it only includes a small subset of the measured parameters.[22] In other words, a set of intervening processes constrain what is transferred and synchronized between individuals.

3.3. Dynamic Interfaces Mediate Environmental Exposures and Elemental Metabolism

In our own work on molecular networks, we have studied exposure to essential nutrient elements and toxic metals during prenatal and early childhood development and risk of autism spectrum disorder (ASD) diagnosis later in life.[24,25] In early studies we investigated these relationships through traditional frameworks, essentially akin to Figure 1a, wherein we created a statistical model to characterize the association between the intensity of metal exposure and the ASD phenotype. From this perspective, we found that the relationship between metal concentrations and ASD phenotype was weak and could not be readily replicated in other populations.[24] More recently, however, we shifted the focus of our studies to examine the dynamics underlying metal assimilation; rather than examine the intensity of exposure alone, we characterized the complexity of cyclical dynamics involved in metal metabolism.[25] Critically, this level of inquiry at the biodynamic interface carries information about both biological and environmental systems; and, as such, possesses emergent properties that may not be evident in either system considered alone. In support of our thesis, of the existence of dynamic interfaces, when we considered the biodynamics of elemental assimilation (rhythmicity, for example), we saw consistent and strong associations between elemental exposure and autism phenotype across markedly different populations in three different countries.[25] These examples support that there exists an intermediary process (or set of processes) between environmental exposures and the aspect of human physiology under study, in this case the neurobehavioral phenotype that is disrupted in autism.

To further illustrate our point, in **Figure 3**, we show a graph based on the well-established dynamics of zinc in human blood (zinc dynamics were consistently related to ASD phenotype in our studies). The blood levels of zinc reach their peak (of approximately 100–110 μg dL^{-1}) in the morning and are lowest in the evening (at round 60–70 μg dL^{-1}).[26] Thus, the interface between environmental (i.e., dietary) zinc exposure and the assimilation of zinc into our biological systems, including the neurological processes impacted in autism spectrum disorder, applies clear constraints on complex environmental inputs during its interaction with human physiology and regulates not only the concentration but also the time-dependent change as it is assimilated into our physiology.

3.4. Biodynamic Interfaces Guide Intermolecular Interactions

The emergence of dynamic interfaces does not appear to be solely a property of high-level interactions among complex systems, such as social groups, whole organisms, or metabolic networks. On the contrary, even at the levels of organization of two molecules, where the structure and function of proteins drive intracellular organization and intercellular signaling, the ubiquity of dynamic processes is equally evident. As aptly stated by Frauenfelder and Wolynes, for example, protein structure is the place where "the physics of complexity and simplicity meet."[27] Typifying this, while the intermolecular forces involved in protein folding are perfectly known, the capacity to predict the actual fold of a protein molecule remains elusive. Similarly, the functional

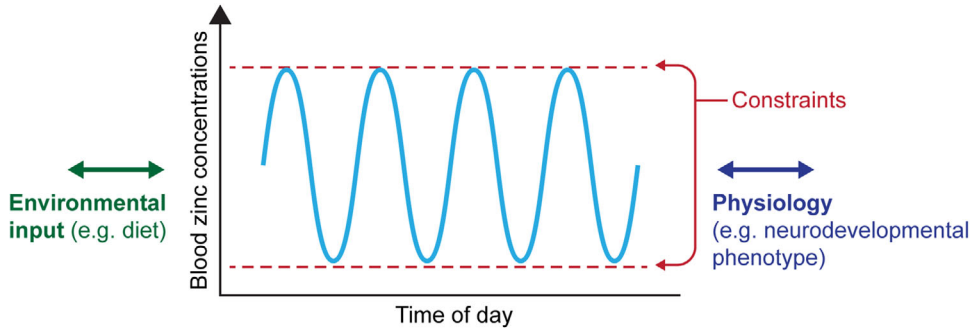

Figure 3. Zinc dynamics over the day as an example of an interface mediating the interaction between environmental inputs (here, zinc from diet) and physiological systems (e.g., neurodevelopment). This biodynamic interface constrains the amount of zinc assimilated from the environment and also how much is made available to the various physiological systems but does so in a time-dependent manner.

efficacy of a given protein is not easily deduced from a purely structural model of either the protein itself or the environmental substrate; rather, one needs to understand as well the dynamics that modulate state-dependent functionality.

The functional complexity that emerges from the structural properties of the proteome is clearly evident in the so-called "allosteric effect." Allostery is a neologism modeled upon Greek language, which has to do with the ability of proteins to transmit a signal from one site to another in response to environmental stimuli. Of particular relevance to the notion of a dynamic, state-dependent interface, allosteric regulatory mechanisms modulate the efficacy of a given enzyme, either increasing or decreasing the activity associated with a given protein. Although distinct from the effector site at which a given protein directly binds to and acts upon environmental substrates, the activation of allosteric sites can act to alter the functionality of the binding site to modulate the specificity of the enzyme. In this way allosteric modulation provides an essential interface that constrains the functionality of a given protein; one cannot, accordingly, predict the efficacy of a given enzyme according to its structural properties alone, or by its interaction with the environment at its binding site; rather, predicting a given protein's function requires an understanding of its allosteric regulatory state at a given moment.

4. Inclusion of the Biodynamic Interface Paradigm in Current Epidemiological Practices

The concepts we have outlined above are directly transferrable, and will serve to enhance, many standard practices in environmental epidemiology. Furthermore, the application of the Biodynamic Interface paradigm is not limited to molecular or chemical analyses of the environment. In fact, the adoption of dynamical methodologies is already underway in epidemiological fields, particularly those focusing on the role of social and spatial dynamics in disease transmission. Bansai and colleagues for example, reviewed recent innovations that have allowed exploration of the role of time-varying social contacts in the transmission of infectious disease.[28] Though the size and complexity of social networks has long been established as an important determinant of the social transmission of disease, socioeconomic factors continue to be evaluated as static variable in most environmental epidemiological studies.

In our work with ASD, we have likewise illustrated how exposure biology can integrate dynamical perspectives to explore the role of homeodynamics involved in environmental inputs, but this approach is by no means limited to cellular, chemical, or metabolic levels of organization. To the contrary, the investigation of social, behavioral, and cultural dynamics may be a particularly fruitful avenue of investigation for biodynamic interface research. Taking socioeconomic status (SES) as an example, when considered through the standard vectorized paradigm (see Box 2) the most common form of adjustment in statistical models is to assign an individual (or household) an ordinal category, typically assessed through a questionnaire, which is then adjusted for when considering some other exposure–response relationship. This approach treats SES as a static entity, but that is not necessarily true; in fact, for many professions, including those reliant on sales or seasonal revenues, income exhibits dynamics within a year, and thus two households may well have the same annual income on a questionnaire response but have very different income dynamics. The Biodynamic Interface paradigm would reject that static assessment of income magnitude, and measure instead the temporal profile of income. Our investigation of the role of income would then move to uncovering how the attributes of income dynamics are transferred to the other systems being evaluated in the study. This would allow us to assess the interface between income and other processes, including health outcomes using dynamical systems methods.

Inclusion of biodynamic interfaces in epidemiological studies also requires due consideration of current best practices in causal modeling (see Box 2 for additional details). In practical terms, the statistical models our conjecture proposes are compatible with traditional approaches. In both cases, the purpose is to examine the association of exposures of interest with health outcomes, while accounting for covariates. However, consideration of biodynamic interfaces provides a deeper exploration of the processes through which these covariate factors mediate health. Rather than solely consider the unidirectional connections between discrete systems, we propose the examination of dynamics that emerge in the integration of multiple systems and levels of organization.

The importance of bidirectional relationships in integrated systems is a long-recognized but underutilized concept. The German embryologist G. Fankhauser, for example, demonstrated how relevant top-down constraints could be in shaping

organizational structures at lower levels. He considered cell size in salamander larvae, a polyploid triton, while having doubled the cell size with respect to the diploid counterpart, had exactly the same dimension of organs and ducts.[29] In simple terms, relative to the diploid, the polyploid triton used half the number of cells, though each cell was itself double in size, to build up its organs. This is crucial for life—the optimization of the caliber of a biological structure (the duct) is finely tuned to fit with the flow of biological fluids (a top-down constraint) and cannot be established by either its constituent cells or the genome. While this is an intuitive tenet (after all, we do not decide the size of our house based solely on the size of the bricks!), this is a largely overlooked issue in biology that has, in the last fifty years, concentrated almost exclusively on the investigation of bottom-up control. In contrast to a purely reductionist account, which ascribes causality solely to the lowest level of organization, our focus on interface-based dynamics seeks to explore the integration of bidirectional forces that drive the emergence of complexity in biological systems, particularly relating to environmental health.

5. What Are the Implications of Biodynamic Interfaces for Environmental Health Sciences?

If this conjecture holds true, the implication for the theory and practice of environmental health sciences are profound. If, as proposed here, the effects of environmental inputs on human physiology are mediated by dynamic interfaces that have to date been unexplored, then their characterization can only propel us towards a better understanding of environmental health. We hope to enculture a new field of inquiry, focusing on the role of environmental biodynamics, that can begin the exploration of these questions. It would shift the current focus from efforts in measuring more and more exposures at lower and lower concentrations to identifying dynamic processes that assimilate exposures into human physiology. It will also require a shift from trying to identify which exposures impact human health to identifying which attributes of the environmental exposures under study are relevant to human health. Alas, we can continue with the current paradigm propelled by a genomic era-driven emphasis of digging deeper to smaller spatial scales, and study the finger and the light bulb down to their molecular constituents, but we will never establish an accurate relationship between the two unless we examine the state of the interface (whether the system is "on" or "off").

To realize the full potential of the biodynamic interface conjecture, environmental health science must refocus the examination of the interaction of environment and health from an emphasis on measuring physiological "moments," (i.e., static measures of environmental factors, infrequent anthropometry, momentary health indicators) to studying dynamic human–environment interfaces, physiologic states and the processes that constrain to those states. To this end, we provide a set of endeavors that must be undertaken to capitalize on and formally test the biodynamic interface paradigm:

1) To focus our scientific inquiry on interfaces that connect biological and environmental systems. An important consequence of the conjecture we propose is that studying the input and output systems will not permit complete characterization of the interface. The interface is not a derivative of either system; it is operationally independent and it must be studied directly. Given that the interface may exhibit complexity independent of the systems contributing to its emergence, we must focus on the characteristic emergent complexity, self-organization, state-dependency, and sensitivity to initial conditions.
2) To develop theoretical frameworks that focus on the identification and interpretation of constraints in biological–environmental interfaces. The constraints acting upon a given interface will ultimately determine the organization of the interface, its response to perturbation and subsequently the phenotypic "output" signal. Analyzing correlations between different measures of the environment and human physiology without characterizing the constrains will not yield a satisfactory explanatory model.
3) To develop laboratory, clinical, and epidemiological methods to relate the complexity characterized at the level of biodynamic interfaces to human health, particularly with regard to the interfaces of processes that unite humans and their environments. We need to measure processes with better characterization of organizational levels and time. Explicitly, this requires the rejection of epidemiologic study designs that ignore processes and measure the environment and human physiology as static entities. At a conceptual level, we must reject a purely structural reductionist perspective. At an operational level, we suggest the adoption of mathematical methods already well-established in other disciplines, particularly systems biology and statistical physics. These include methods appropriate for characterizing the phenomenological nature of a given system, and its dependency on varying inputs and underlying processes. The application of Takens Embedding Theorem,[30,31] recurrence quantification analysis to measure signal periodicity, entropy, and determinism;[32] potential energy analysis to identify transitions in underlying attractors;[33,34] and, the empirical estimation of Lyapunov exponents[35–37] to characterize stochastic, deterministic, and chaotic processes underlying a given system are well-characterized methods suitable to achieve these goals, which should be complemented by the development and application of newer approaches to data analysis.

6. Testing and Falsifiability of the Biodynamic Interface Conjecture

It is important that any new conjecture be formally tested to confirm its legitimacy. Here, we provide the form of research questions that would allow formal testing of the key components of this conjecture. We also provide a wider discussion on formal testing of theories; like many other paradigms, not every facet of the biodynamic interface conjecture is falsifiable in a classical sense but its utility is dependent on the nature of the research question under consideration.

As we have stated earlier, biodynamic interfaces exhibit operational independence, because of which they cannot be derived from measurements on the interacting systems; the interfaces must themselves be the focus of inquiry. The primary questions

to ask then are—What are the process-based interfaces that mediate the interaction between human and environmental systems under investigation? What are the characteristics of the constraints applied by the biodynamic interfaces in the transfer of information between systems? Does the explanatory potential of models quantifying the inter-system interactions increase when biodynamic interfaces are included in the modeling strategy? If, after comprehensive assessment, the answer to the latter question is "no" then the conjecture has failed in that scenario. Of importance here is that the assessment be comprehensive because crude examinations are necessarily biased towards the null and may neither prove nor disprove the conjecture.

Returning to the example from our own work on ASD, we firstly undertook a purely structural study, that ignored dynamic interfaces, to analyze environmental exposure to essential nutritive elements and toxic metals and their relationship to a neurodevelopmental phenotype, autism spectrum disorder.[25] While this provided a statistically significant correlation it could not be leveraged to predict the risk of an autism diagnosis. In a subsequent analysis, we focused our attention on the interface between the two systems in the form of dynamic processes that are involved in environmental elemental assimilation into human metabolism. Rather than modeling the exposure variables as one structural entity (that is, as the concentration of each metal), we considered specific components of the interface (specifically, the entropy, temporal duration, determinism, regularity, and time to recurrence of dynamic processes underlying elemental assimilation). We found that the interface constrained the specific set of dynamic properties to a few,[25] and by focusing on those we were able to achieve a high level of predictability between the two interacting systems (over 90% accuracy in a classification model).

It is important to recognize that the Biodynamic Interface conjecture, as with all scientific approaches, cannot ascertain with complete certainty if an important variable has been "missed." We can certainly evaluate the sufficiency of the variables we do observe in relation to biological questions. For example, in the case we offer with autism spectrum disorder, we show that some interfaces, particularly those characterized in zinc and copper metabolism, are related to the emergence of disease, whereas other elemental pathways were not related to disease. As such the "right" relationship is the interface that relates to the biological question at hand. This can be established through the application of standard analytical approaches—that is, we characterize aspects of interface dynamics then relate these measurements to the health outcome. In that sense, the evaluation of interface dynamics can be conducted under standard scientific and statistical hypothesis testing paradigms.

Second, although a variety of methodologies might be used to characterize interfaces, we have advocated for the use of phenomenological methods such as the application of Takens Embedding Theorem. The appeal of this framework is that it allows the reconstruction of the underlying attractor system that governs a given time-series simply through the observation of that sequence, even though the underlying dimensionality and causal pathways involved in that process are unknown. This might be considered analogous to the use of gaussian probability distributions in cross-sectional measurements; we might measure height in a given population, for example, and characterize its mean, variance, and standard deviation even though we do not know the many complex relationships that ultimately determine a person's height. In the same sense, the application of Takens Embedding Theorem and related methods such as recurrence quantification analysis allow us to characterize the dynamics involved in a time series even when our understanding of that process is incomplete.

6.1. Beyond the Conjecture to a New Field of Inquiry—Environmental Biodynamics

Lastly, although we have provided a path for testing specific core aspects of the biodynamic interface conjecture, there are other facets that cannot be subjected to formal testing as would be the case when dealing with a hypothesis with a narrow focus. Consider, for example, Nobel laureate Nico Tinbergen, who with the publication of the seminal "On aims and methods of Ethology" in 1963,[38] introduced an exploratory paradigm that ultimately defined ethological studies, but was not classically falsifiable. In the same vein, our biodynamic interface perspective seeks to refine and guide inquiry in human environmental health studies to focus on a new set of questions, and by doing so our inherent aim is to foster inquiry, rather than limit ourselves to making specific predictions. Similarly, and of direct relevance to biological sciences, the introduction of GST,[39] and subsequent development of Systems Biology,[40] had profound implications for the scientific exploration of complex systems, which contradicted reductionist paradigms that sought to accomplish the same goals; yet, at the same time, neither GST nor its descendent frameworks can be considered falsifiable. The validity of an interface-based approach to studies of human–environment interactions is consequently in the utility of the outcome, rather than the accuracy of its prediction. That is, an interface approach is valid and appropriate where it leads to new insights of the interdependence between human health and the environment. It is because of this insight, that we propose the establishment of a new field of inquiry—environmental biodynamics—that places time and dynamic interfaces at its core.

7. Conclusions and Outlook

The focus of the conjecture presented here is in the exploration of functional dynamics that emerge in the interdependence of complex systems which span multiple levels of organization. We propose this can be achieved through the exploration of dynamics measured at the level of the interface between systems; that is, aspects of either system which include inputs from the other. We provide examples of how this has been explored in the examination of systems at molecular, system, and behavioral levels of organization, and provide examples from our own work linking the concept of biodynamic interfaces to the assimilation of essential and non-essential elemental exposures. Future studies can similarly utilize this concept through the implementation and exploration of the steps outlined here, which include similar applications of dynamical analytical methods, as well as expansions of traditional methodologies to focus on the investigation of time-varying dynamics.

Many scientific theories and methods rely on the existence of levels, scales and states defined by their properties, and

compartments defined by their structures and/or functions. Because of this, the direction of interaction across levels has been, and rightly so, the focus of much scientific debate.[4,5] These levels, scales, and compartments are necessary, but let us not forget that equally necessary is what exists between them. Here, we have turned our gaze to this seemingly empty and undefined space, and in doing so, we have presented an argument, not about the direction of interaction between systems and their components, but where the interaction between systems exists, and what makes causal linkages possible—biodynamic interfaces.

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Conflict of Interest

The authors declare no conflict of interest.

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