Biological Sciences and Physics Unified: Internal Evolution and Urging the Second Scientific Revolution

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Why are there several sciences instead of only one? Are all sciences reducible to the "most fundamental" one, physics? Should we try to do so now that we have the required tools? Why our ancestors could discover effective drugs that we still rely on, thousands of years ago; and we, with incomparably advanced equipment and knowledge, are desperate to do so? Why has biology, e.g., neuroscience and genomics, failed in unraveling the workings of organisms despite spending billions of hours and dollars on gathering data? Why can't we even "reproduce" our results? I show that the current ontological and methodological attitudes toward biological phenomena are flawed. I present emergent bound box theory by following the second law of thermodynamics and selection's simple core: truism-law-of-survival. It explains the evolution of organisms' internal workings and provides the first ab initio scientific framework for biological sciences, including medical, psychological, and social sciences. It is backed up by diverse evidence from Shannon and integrated information theories, computational complexity, decoherence and quantum Darwinism, effective field theories, deep learning, stability of strange attractors, and discovering that despite decades of dominance, the share of reductionist "rational" drug design from all approved drugs is less than 9%. New outlooks appear on long-debated dilemmas: machine metaphor of organisms; the "replication crisis"; Ockham's razor, simplicity, "beauty," and truth; tautology problem and a new synthesis of Darwinism; definition and origin of "life"; Laplace's demon; emergence; "levels of organization"; "downward causation"; "intelligent design"; and skepticism and the post-truth. I demonstrate applying the framework for COVID-19 by a machine learning-based cheminformatics meta-analysis using systematic review and interactome-wide consensually docked 4D-QSAR. I discuss how mistaking products of science for science has led to rote science, useless and even harmful education, intellectual exclusion, and an illusion of progress. I clarify what "philosophy" and "science" are, and explain that contrary to the appearance, our scientific progress, compared to our resources, is at an all-time low in history. This, if not attended to, can soon lead to the extinction of human global civilization.

**** NOTE ****

Here, *biological sciences* also include medical, psychological, and social sciences as they study aspects of some biological organisms. Cited references are opened up only to the point of being contributive to the whole synthesis and should be noted to grasp levels of evidence, counter-arguments, and examples (you can use hyperlinks of the citations and ALT + LEFT (CMD + LEFT in macOS or ALT + P in some Linux distributions to go back and forth between the text and the references). Supplementary data 1 and 2 provide extensive evidence for this manuscript exceeding 500 pages.

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Science started its modern career by taking over ideas derived from the weakest side of the philosophies of Aristotle's successors. In some respects it was a happy choice. It enabled the knowledge of the seventeenth century to be formularised so far as physics and chemistry were concerned, with a completeness which has lasted to the present time. But the progress of biology and psychology has probably been checked by the uncritical assumption of half-truths. If science is not to degenerate into a medley of ad hoc hypothesis, it must become philosophical and must enter upon a thorough criticism of its own foundations.(*1*)
Alfred North Whitehead (emphasis added)

I think the next [21st] century will be the century of complexity. We have already discovered the basic laws that govern matter and understand all the normal situations. We don't know how the laws fit together […] There is no limit to the complexity that we can build using those basic laws.(*2*)
Stephen Hawking in his millennial interview in 2000

Cherishing the monumental creations of Isaac Newton, the great polymath Pierre-Simon Laplace wrote so in his 1814 book, *A Philosophical Essay on Probabilities*:

We ought then to regard the present state of the universe as the effect of its anterior state and as the cause of the one which is to follow. Given for one instant an intelligence [often referred to as Laplace's demon] which could comprehend all the forces by which nature is animated and the respective situation of the beings who compose it—an intelligence sufficiently vast to submit these data to analysis—it would embrace in the same formula the movements of the greatest bodies of the universe and those of the lightest atom; for it, nothing would be uncertain and the future, as the past, would be present to its eyes(*3*)

This model of the universe implies physics is the only necessary science and the reason we have *special sciences* like biology, psychology, and social sciences is that we are currently far from being able to gather and analyze all the lower-scale knowledge we need to build up on to reach higher scales; e.g., to understand and predict the behavior of the human body, we could reduce it to its constituent parts, study them comprehensively, and then put together this lower-scale knowledge(*4*); also see (*5, 6*). For centuries, many, including Aristotle(*7*), Descartes, Kant, Auguste Comte(*8*), Erwin Schrödinger(*9*), Popper, and Putnam(*10*) have had such discussions(*11*): How to unify all sciences(*12-22*)? Is there anything "fundamental" other than the micro parts(*23-26*)? Are wholes the same as the sum of their isolated parts? Can we understand organisms by studying their isolated constituent parts? Many, including John Stuart Mill(*27*), Ludwig von Bertalanffy(*28*), Ernst Mayr(*29*), and Philip Anderson(*30*) have refuted this possibility, contending that new properties *emerge* in such complex systems that are not deducible from the most complete knowledge of the properties of their isolated parts(*31-39*). Despite adhering to *physicalism*(*40-42*), they argue complex systems are *irreducible*. Emergence has always invoked skepticism; it lacks a compelling theory(*43, 44*) and an aura of obscurity and "magic" surrounds it: "It's not magic. But to us humans, with our crude little human brains, it feels like magic(*45*)." Meanwhile, it seems so "obvious" to be ignored; so "obvious" that Aristotle could recognize it over 2400 years ago(*36*):

In the case of all things which have several parts and in which the totality is not, as it were, a mere heap, but the whole is something beside the parts.(*7*)

While this problem is still open, reductionist attitudes and paradigms are disproportionately in reign across most fields of science, despite lack of scientific ground, many appropriate criticisms(*1, 13, 29, 30, 46-58*) and contradiction to established scientific fields like systems and complexity sciences(*45, 59-61*)

Today, assessing emergentism and reductionism is of utmost basic and applied importance. Now, we have begun to obtain the tools and technologies needed to supplant the epistemology and methodology of higher-scale biological sciences with what we may subjectively and baselessly suppose as the superior and more accurate scales of analysis: exceedingly lower scales.

A Medley of Ad Hoc Hypothesis(*1*)
Failures of Reductionism

Actually, I was led to these questions after amazement by the dominant reductionism in biological sciences, especially in drug discovery and neuroscience. Drug discovery and neuroscience epitomize both applied and basic fields coming into crisis in changing and understanding biological systems. Neuroscience aims to understand the most complex known biological system in the universe. Drug discovery aims to change such a complex system. Let us see how hard biological sciences have failed in understanding and changing complex biological systems and how these failures are rooted in reductionism.

Failing to Change Biological Systems
The Machine Mindset

Both in academia and industry(*62, 63*) and reported in hundreds of journals(*64-86*), including *Science*(*87, 88*), *Nature*(*89, 90*), *Cell*(*91*), and *PNAS*(*92*), drug candidates for complex disorders like schizophrenia, Alzheimer's, COVID-19, and cancers are being screened and developed primarily based on their affinity to a single protein hypothesized relevant to the disease, and only terminally filtered based on their effects on humans and non-human animals (hereinafter referred to as animals). These bindings are measured using in vitro biochemical assays and sometimes in silico methods in initial steps. How much do these measurements correlate with the binding of chemicals to proteins inside the human body? Not much(*46, 47, 93*) (for ample experimental evidence, see (*94-103*)). The in silico methods suffer not only from these issues, as they're usually built upon the same in vitro measurements(*104*), they cannot even estimate accurately these themselves-dubious measurements(*105-109*). The more important issue is the relationship between the affinity of chemicals to a "target" protein and their therapeutic effects on, e.g., depression. Does changing the state of a protein to tightly bound free the body from depression? Many of these "targets" are not even relevant to their target phenotypes(*110*). To this date, there is no scientific evidence for the possibility of reducing to single proteins, collections of complex phenotypes like depression whose pathologies are even far from known. This methodology which may only be leniently justified for disorders rooted in a single protein, like monogenetic Mendelian diseases, is ironically called "rational" drug discovery(*111, 112*). Although the initial conception of

"rational" drug discovery around the 1960s by prolific scientists like George Hitchings, Gertrude Elion(*113*) and James Black(*114*) was an applaudable move toward more efficient use of scientific knowledge(*115*), its current deviated implementation could hardly be more oblivious to scientific knowledge.

My amazement was followed by the question that how can such an irrational paradigm be successful. It actually is not. Translating basic science to clinical real-world impact is denigrated as the "valley of death"(*93*). Unproductivity has frustrated drug discovery researchers for years(*116-120*). The number of approved drugs per billion research dollars has halved every 9 years from 1950 to 2010 (denoted as Eroom's Law; Moore's law in reverse)(*118*). Only about 13% of the drug candidates that reach the clinical stage get approval. This is interestingly lower in more complex CNS disorders and cancers, as low as 0.04%(*119, 121*). Estimated research and development costs required to bring a new therapeutic to market have soared up to 6.4 billion dollars with a mean of 1.3 billion dollars(*122*). Many pharmaceutical companies, including Amgen, AstraZeneca, Bristol Myers Squibb, GSK, Merck, and Pfizer have backed off from neuroscience research(*123*), albeit its related disorders are the first cause of disability worldwide and many of its disorders, like Alzheimer's disease, have no cure(*124, 125*). On the other hand, many of the currently approved drugs, that are considered industry's successes, are under question by experts and evidence. A significant portion of them have minimal effectiveness(*126-132*), almost no benefit compared to previously approved similar drugs(*133-137*), or are approved only based on surrogate end points(*131, 132, 138-141*) or flawed and limited evidence(*131-133, 141-146*). Compared to placebo, plenty of them probably offer no benefit and may even lower patients' survival and quality of life(*130, 133, 138, 139, 147-154*). (If you're thinking about the rather-effective drugs we have, I'll discuss them later.)

"Rational" drug discovery is one of the paradigms in possession of *machine mindset*. This reductionist mindset construes systems as machines whose functions or dysfunctions can be traced back and reduced to a single or a few specific parts. It became popular in the Scientific Revolution and culminated in world-changing successes in physics and engineering, including the Industrial Revolution. Machine mindset stems from our own humane approach of designing and building systems. When we aim to design and build a specific system, while designing it, we design each part, having in mind specific roles for that part in the eventual function of the whole system. Because of this, each function or dysfunction of a car or a spaceship can be traced back to specific parts by a *chain of tasks*. The fallacy of machine mindset is its presupposition that this delineated chain of tasks between parts and functions is universal among all systems (see (*155-158*) for examples and (*11, 159-165*) for criticisms and discussions). But biological systems are not the result of the same approach of designing systems. They are the result of evolution by means of selection. Selection does not assign and explicate any role to any part. It only selects among the diverse ultimate outputs and phenotypes of systems created by random variations. All organisms, similar to cities, the internet, and the stock market, are *self-organizing*(*166, 167*) complex systems. Their parts are not *chained* to their behaviors; even though some elements may have accentuated roles in some functions or dysfunctions, there is usually no clear-cut and separable delineation(*168, 169*). This leads to several general distinctive features in complex systems compared to chained systems: extensive multifunctionality of different parts(*170-176*); continuous and spectral, rather than clear-cut and binary-like causal relationships between the states of parts and systems' ultimate behaviors(*177-180*); capability of "self-control" by frequent and extensive feedbacks between parts and the whole system(*181, 182*); therefore, more independence from external agents for control(*183-192*); extensive redundancy(*193-201*); vestigiality(*202-205*); and *degeneracy* or *multiple realizability*, in which several processes yield identical ultimate outputs(*51, 206-215*).

There have been many attempts to define the word "complexity"; yet as it is an arbitrary concept, no "objective" consensus has been and probably will be possible(*216, 217*). Still, I propose that this word will be of far greater use if we unanimously exclude from its applications(*218*), implications of *complicated* chained systems, like airplanes(*156, 219*) and cars(*156*).

Failing to Understand Biological Systems
Foundationalist Materialism

Neuroscience, on the other hand, has been dealing with an epistemic crisis in which despite gathering deluges of data, it has failed to understand how behaviors arise from nervous systems(*49, 51, 220, 221*). We have complete structural knowledge about *C. elegans* genome, connectome, and cell types for several decades now; yet we have remained disproportionately ignorant about the workings of this worm. Still, a dominating portion of all that is being proposed is gathering more of such data, hoping that someday, they would turn into knowledge; e.g., (*222*). Many have argued that the culprit of these failures is the current too-simplistic reductionistic paradigm of neuroscience. It has not been successful even in an "easier" reductionistic task it has set for itself on which plentiful resources have been spent: localizing behaviors to specific parts of brain: "To date, the main achievement of neuroimaging [whose studies are dominated by the reductionistic paradigm] is to have demonstrated that psychiatric disorders involve the brain and not just the 'mind'(*223*)." Such unproductive, yet popular, reductionist endeavors have even been disparagingly likened to the pseudoscience of phrenology(*54, 224-236*); also see (*53, 182, 237-239*) for insightful discussions and (*240-242*) for experimental evidence exposing shortcomings of the current paradigm (the "replication crisis" will be discussed below)).

Reductionist attitudes are in reign across biological sciences. To capture the depth of this reign, let us investigate reductionist presumptions beneath the current forefront of antireductionism in biological sciences: systems biology. It aims to better understand and change organisms by deciphering how their molecular constituents give birth to behaviors by putting more due emphasis on the comprehensiveness of investigated parts and analyzing their interactions using mathematical and computational tools(*156, 243*).

Systems biology confronts many challenges. Sydney Brenner, one of the fathers of molecular biology, contended that systems biology is "bound to fail", explaining that it aims to solve an *inverse problem*: "deriving models of how systems work from observations of their behavior(*244*)." Inverse problems are challenging, and often impossible to solve(*245-247*); e.g., "One cannot hear the shape of a drum(*248*)"(*249-251*). The problem is that observables are only a fraction of the data necessary for reconstructing the system they emanate from(*252-255*). The fact that organisms are not chained systems but complex systems with vast degeneracy and multiple realizability aggravates this inverse problem and reverse engineering of organisms. Because there is no direct linear relationship that would enable deducing the actual workings of the systems based on observations of their behaviors and the correct solution may not be identifiable among several possible solutions(*212, 256-258*). Another challenge is the non-linear and chaotic behavior of biological systems accompanied by our inherently far-from-perfect measurements. This is further aggravated by the common practice of using data that can be traced back to heterogenous measurements from isolated parts of diverse organisms. Chaotic behaviors are not a trivial problem. After his magnificent triumph in mathematizing the laws of motion and gravitation, Isaac Newton, given the initial momenta and coordinates, could exactly depict the future and past states of a system of two mutually gravitating planets. He then went on to a system of three; however, he observed that predicting its future is far more complicated than he had thought(*259*). After about 350 years, we're still trying to solve special restricted forms of this problem in which the weight and thus the gravitation of one body is neglected. Actually, in 1890, Henri Poincaré mathematically proved the impossibility of finding a general analytic solution for three-body problem(*260*). Poincaré discovered that such systems show chaotic behaviors and *sensitive dependence on initial conditions*: Although the

system is completely deterministic, minute variations of the initial conditions can lead to completely different futures after enough time(*261*); e.g., one-millimeter variation in the distance between Mercury and the Sun can shift the solar system from stability to instability in 5 billion years(*262*); failure to consider the flap of a butterfly's wings can in a long time lead to failure in predicting a tornado: *the butterfly effect*(*263*). This last proposition goes back to the observation of Edward Lorenz that rounding up the inputs of his 12-variable deterministic model of atmosphere from six to three decimal points completely changed the results of a 2-month weather simulation(*264, 265*). Such chaotic behaviors abound in nature and biological systems(*266-277*).

Although current systems biology studies are methodologically heterogenous, they are generally guided by a deeply ingrained reductionist bottom-up approach (e.g., (*278, 279*)) which makes them unable to cope with the above challenges(*280, 281*). Possessed by reductionism, current paradigms of systems biology and neuroscience employ a methodology for understanding the workings of organisms that at first seems very natural. They dismantle the systems; inspect each of its parts separately; note how they interact with each other; and finally, reassemble the disconnected information together and try to build again the whole system. The cornerstone of such paradigms is measuring properties not of wholes of organisms, but of their isolated parts: i.e., in vitro and ex vivo measurements. Whole-scale behaviors are only "incorporated as an afterthought(*51*)"(*282*).

Reductionism is the most natural thing in the world to grasp. It's simply the belief that "a whole can be understood completely if you understand its parts, and the nature of their 'sum'". No one in her left brain could reject reductionism.(*283*)

This approach hinges upon a presumption: Behaviors of isolated parts are similar to their behaviors when they are within wholes: *foundationalist materialism*(*284*). This reductionist mindset is another successful relic from the Scientific Revolution, which has continued to dominate the scientific community. Based on this mindset, it is widely, yet tacitly, presupposed that in vitro and ex vivo measurements are intrinsically accurate and ontologically identical with their counterpart processes which are within wholes of organisms and the only problems are that first, little error accompanies them as their settings are not identical with the body and second, it is hard to follow the consequences of these measurements because plenty other processes are added to them inside the body. *Compositionalist* attitude(*13, 285*)(also see (*286*)) of this mindset implies that to understand wholes, it is enough and the best to take their parts apart and analyze them separately: the *analytic method*(*284*).

The analytic method works in physics: to understand what happens in the world, we take things apart into their fundamental pieces; to control a situation we reassemble the pieces, we reorder them so they will work together to make things happen as we will. You carry the pieces from place to place, assembling them together in new ways and new contexts. But you always assume that they will try to behave in new arrangements as they have tried to behave in others. They will, in each case, act in accordance with their nature.(*18*) Nancy Cartwright

Despite their dominance across biological sciences, the suitability of foundationalist materialism and the analytic method for organisms is not backed up by scientific evidence. Indeed, they are contradictory to the convincing evidence and arguments implying the processual nature of biological systems(*287-294*). It has been shown that these are not effective in understanding even chained systems(*50, 51, 254*), let alone the human body which is one of the most complex known systems. Instead of unraveling the workings of organisms, the most notable outcome of studies employing these has been intensifying our awe and humbleness in front of organisms' complexity(*56, 279, 295*).

Repercussions of the uncritical wide adherence to these approaches can be further illuminated by discussing their relevance to Brenner's criticism. Although the problem systems biology tries to solve is indeed an inverse problem, Brenner's conjecture that this problem is not solvable at all is not acceptable. Such problems may be dealt with by constraining the number of possible solutions using ensemble modeling. In ensemble modeling, which is also employed in fields like weather forecasting and ecology, several models that all comply with the available experimental data are constructed(*296-298*). These sets of models can provide an ensemble of probable predictions and also guide the future optimal experimental design to obtain the data which efficiently reduces the uncertainty of future models and predictions(*299, 300*). Ensemble modeling provides a resort for dealing with the challenge of not only the inverse problem but also the uncertainty of measurements and ubiquity of chaotic behaviors in biological systems(*301*). Still, Brenner's criticism is important because efficient ensemble modeling requires that biological systems be primarily investigated from angles where they appear the most informative so that their measurements would constrain the number of possible solutions to the highest degree(e.g., see(*302*)). Currently, there is no general theory on the workings of organisms and their causal structures that would inform us which angles are these. Current reductionist approaches, under the possession of machine mindset, foundationalist materialism, and the analytic method, baselessly presuppose that biological systems must be understood primarily by gaining detailed information about specific lower-scale parts; however, the abundance of features that elicit indeterminism in the relationship between whole-scale behaviors and observed states of a specific part, e.g., multifunctionality(*170-176*), feedback loops(*181, 182*), degeneracy(*206-215*), and robustness(*303, 304*), casts doubt on presuming superior informativeness for lower scales, as they may not specify the most "differences that make a difference(*305*)" within biological systems.

Systems biology has been a laudable move from baseless adherence to reductionism; however, because of the dormancy of theoretical progress in contrast to technological progress, its real-world efficacy has been hindered by hidden uninvestigated reductionist presuppositions and "uncritical assumption of half-truths(*1*)."

The real advance in the application of systems theory to biology will come about only when the biologists start ***asking questions*** *which are based on the systems-theoretic concepts rather than using these concepts to represent in still another way the phenomena which are already explained in terms of biophysical or biochemical principles.*(*306*) Mihajlo Mesarović

Universal Failure in Biological Sciences "Replication Crisis"

The crisis of biological sciences is not restricted to the fields discussed above. In recent years, many have expressed concern for a "replication crisis" in diverse fields, especially psychology and biomedicine(*241, 242, 307-313*). Reproducibility of results, which is claimed by many as a central tenet of science (e.g., (*314-316*); also see (*317, 318*)), is worryingly low for studies published in "high-impact" journals of various fields: 11% in preclinical oncology(*319*)(also see (*316, 320*)), about 20-25% in pharmaceutical "target" identification and validation(*110*), 37% in psychiatry(*321*), 39% in psychology(*314*), 44% in clinical critical care(*322*), and 62% in social science(*323*) (these measures are not comparable; refer to the cited studies). There have been many attempts to identify the causes of the "replication crisis" and propose solutions(*324*). A majority of these revolve around increasing transparency(*325-328*) and refining(*329*) common statistical practices like lowering(*330*) or, even, rising(*331*) the significance-threshold of the *p*-value(*332, 333*). Yet, there is no conclusive prescription and even no consensus on whether we are dealing with a "replication crisis" or not(*334-336*).

Let us inspect a sample case of these "irreproducibility" incidents whose extent has supposedly imposed a huge burden(*337-339*). A researcher investigated the effects of small-molecule drug X on cognitive impairment in mice and concluded that X has a "statistically significant" effect. Another researcher assessed the "results reproducibility(*340*)" of this study in another country by repeating the published procedures as close as she could. However, her conclusion does not confirm that of the original study. As the second researcher tried to "reproduce" the results of the first researcher, she must have had this presumption that the

phenomena they observe are sufficiently similar. I may accept that the drugs both researchers used under the name "X" had sufficiently similar properties for the purpose(*341*) of the study; also see (*342-345*). But were the mice and the environmental conditions also sufficiently similar(*346-348*)?

Perhaps the researcher has an *idealist* preconception toward "mice": that all mice, or all mice of a specific strain, are identical in *essence* as they all belong to the same "kind"(*341, 342, 349, 350*). But is this common, albeit tacit, and deep-seated preconception true? The workings of evolution suggest otherwise(*351*): Behaviors of organisms with even almost-identical genetics differ from each other(*352-358*): After all, variation is a raw material of selection; to the extent that organisms have been selected for their tendency to become diverse(*359-372*). "Mice" or a specific "strain of mice" are all arbitrary concepts for denoting similarity and categorization(*373-375*). To mistakenly concretize arbitrary concepts, like "strain," "race," or "human," is to commit the fallacy of reification, or misplaced concreteness(*1, 376, 377*).

The idealist mindset which reduces, e.g., all mice to an idealized concept of *mouse* is related to foundationalist materialism. We can distinguish them by assigning to foundationalist materialism, the bias to reduce a context-dependent processual phenomenon to a specific cross-section of context and time, and assigning to idealism, the bias to reduce varied members of a similarity group to a single, often imaginary entity, like "average human"(*378, 379*). Having exposed both idealism and foundationalist materialism, we should note not only animals of the two researchers were completely different, but their environments were also different(*315, 380, 381*). We have seen how a little fluctuation in organisms can lead to completely different outcomes as they manifest chaotic behaviors(*266-277*). Subtle "environmental" variations can lead to different measurements(*382-389*). Even "copies" of the "same" enzyme have different catalytic properties(*390-392*). Naturally, the observations of the two researchers were different: they observed different processes.

It may be argued that these individual and environmental variations are not to the extent that would lead to "irreproducibility." We can reject this argument based on the observation that, contrary to the failure of exhaustive standardization in achieving results reproducibility(*382-384*), deliberate heterogenization of study samples may "counterintuitively" improve results reproducibility(*381, 393-401*). When the diversity of organisms and their environments is inevitable and this leads to heterogenous measurements, deliberate heterogenization of study samples increases the base heterogeneity of the measurements and it would be less probable that these already heterogenous measurements would fail to be "reproduced" because of the heterogeneity that "reproducing" adds.

A mature physicist, acquainting himself for the first time with the problems of biology, is puzzled by the circumstance that there are no "absolute phenomena" in biology. Everything is time bound and space bound. […] The physicist has been reared in a different atmosphere. The materials and the phenomena he works with are the same here and now as they were at all times and as they are on the most distant stars. He deals with accurately measured quantities and their causal interrelations.(*402*) Max Delbrück

The "replication crisis" does not boil down to just these two fallacies. Another facet is how records from all these unique individuals and environments turn into single-sentence title-friendly conclusions that currently appear in most scientific journals. Relationships are claimed between pairs of organisms' variables. How organisms have evolved implies that isolated ideal relationships do not exist. What can exist in reality is a general tendency between some observed variables in some specific individuals embedded in specific environments. This tendency is almost always general and rough. So, how do such general and rough tendencies turn into popular single-sentence conclusions?

The object of statistical science is to discover methods of condensing information concerning large groups of allied facts into brief and compendious expressions suitable for discussion.(*403*) Francis Galton

Briefly, and in its most concrete form, the object of statistical methods is the reduction of data. A quantity of data, which usually by its mere bulk is incapable of entering the mind, is to be replaced by relatively few quantities which shall adequately represent the whole.(*404*)
No human mind is capable of grasping in its entirety the meaning of any considerable quantity of numerical data. We want to be able to express all the relevant information contained in the mass by means of comparatively few numerical values. […] It is the object of the statistical processes employed in the reduction of data to exclude this irrelevant information, and to isolate the whole of the relevant information contained in the data.(*405*)
Ronald Fisher, a major pioneer of modern statistical methods

As attested by its pioneers, this condensation is the core aim of the currently used statistical methods. Despite all variations between individuals, by mathematical theories, standardization, and randomization(*405-411*), modern statistical methods provide a logical way to reduce all recorded data from two observed groups and answer this question whether we are justified to claim one group was under the effect of a different causal variable or not(*412*). This is achieved by assuming that the observations are a sample from a larger (mostly infinite(*413*)) hypothetical population, and enabling the application of *long run frequency* property and *law of likelihood* through the theory of testing statistical hypotheses(*404-406, 412, 414-417*).

Although these methods may provide a logical way to answer the above question, they are suitable neither for future predictions in individual organisms nor for unraveling the workings of real organisms (who are individually unique); e.g., (*413, 418-423*). Even a very simple and concrete statement like "Human heart resides on the left side of the chest cavity" is not true for some individuals(*424*); even though it is "statistically significant" and "reproducible." This is because these group-based methods suppose that all the variations between the supposed hypothetical populations are due to differences in the investigated variables. They reduce manifold variables of organisms to the few investigated variables. All the variations due to organisms' uniqueness and their varied environments are washed away as "confounding"(*404, 407*). This attitude can be traced back to fallacies of idealism and foundationalist materialism and an inherent human bias toward simple clear-cut answers for inherently complex problems through binary thinking and digitizing a continuous and spectral world(*425-430*).

All this adherence to group-based statistics is in spite of the fact that it has been known for a long time that individual-level inference from group-level statistics is a mathematical fallacy: ecological fallacy(*431-433*). This fallacy can lead to taking completely wrong decisions for individuals, like in Simpson's paradox(*434-437*).

In a real sense, statistics is the study of populations, or aggregates of individuals, rather than of individuals.(*405*) Ronald Fisher

We must never make average descriptions of experiments, because the true relations of phenomena disappear in the average; when dealing with complex and variable experiments, we must study their various circumstances, […] averages must therefore be rejected, because they confuse, while aiming to unify, and distort while aiming to simplify. […] Certain experimenters published experiments by which they found that the anterior spinal roots are insensitive; other experimenters published experiments by which they found that the same roots were sensitive. These cases seemed as comparable as possible; here was the same operation done by the same method on the same spinal roots. Should we therefore have counted the positive and negative cases and said: the law is that anterior roots are sensitive, for instance, 25 times out of a 100? Or should we have admitted, according to the theory called the law of large numbers, that in an immense number of experiments we should find the roots equally often sensitive and insensitive? Such statistics would be ridiculous, for there is a reason for the roots being insensitive and another reason for their being sensitive; this reason had to be defined; I looked for it, and I found it; so that we can now say: the spinal roots are always sensitive in given conditions, and always insensitive in other equally definite conditions.

I will cite still another example borrowed from surgery. A great surgeon performs operations for stone by a single method; later he makes a statistical summary of deaths and recoveries, and he concludes from these statistics that the mortality law for this operation is two out of five. Well, I say that this ratio means literally nothing scientifically and gives us no certainty in performing the next operation; for we do not know whether the next case will be among the recoveries or the deaths. What really should be done, instead of gathering facts empirically, is to study them more accurately, each in its special determinism. We must study cases of death with great care and try to discover in them the cause of mortal accidents, so as to master the cause and avoid the accidents. Thus, if we accurately know the cause of recovery and the cause of death, we shall always have a recovery in a definite case.(*438*)
Claude Bernard, in his 1865 classic, *An Introduction to the Study of Experimental Medicine*. This major pioneer of modern biomedical sciences was only one of the critics against using group-based statistical methods in biomedicine(*439-441*)

> So, the crisis is not our inability to "reproduce" results. The crisis is that we expect to "reproduce" results despite neglecting most individual and environmental variables(*336, 442-450*). Foundational isolated causal relationships do not exist. One cannot discover "natural laws" by group-based statistical methods.

Uncritically following a system that pioneers set temporarily, without asking if it is suitable for our aims or not, currently, study designs of most biological studies, from psychological and social to pharmacological, neuroimaging, and medical studies, are based on trying to find causal relationships between variables using these group-based statistical methods(*240, 434, 451-469*). E.g., in the dominant paradigm of medical sciences, having neglected almost all individual and environmental variables, researchers try to neutralize their "confounding" effect on the foundationally true causal relationship they seek, by recruiting ever larger samples. They even try to further expand these samples by merging them through meta-analysis. The ecological fallacy occurs as almost all these are performed to decide for individual patients. Ironically, this mathematically fallacious paradigm which neglects most variables is named "evidence-based" medicine(*420, 422, 465-478*).

A likely argument is that we cannot record and use all individual and environmental variables; and therefore, induction and "generalization" from group-based statistics is the only feasible resort. First, great advancement in data gathering and analysis through sensors and machine learning (ML) has made moving toward this aim possible. More importantly, this argument could have been acceptable if the scientific community had been collectively aware of the conceptual fundamentals and deficiencies of the statistical methods they use and had used them only as temporary heuristics to inform interim decisions and inductions while also recording and sharing individual and environmental data. This is not the case. The data that is currently shared is almost always the group-based aggregated data and shockingly, the individual-level data is not usually accessible even through requesting from the original investigator(*479-487*). The scientific community has been searching for years for culprits and solutions of the "replication crisis," failing to notice that its prime culprit has been dismissing most individual and environmental variables(*336, 447-450, 488, 489*). Science has been inflicted by a "statistical crisis"(*447*)"(*426, 490-494*). Current use of statistical methods has been numerously described as "mindless"(*448, 450, 494-497*). Statistical inferences are so pervasively abused that it has been possible to present anything as "significant"(*498, 499*). Abuse of statistics at such a massive scale obliged American Statistical Association (ASA) to release an unprecedentedly alarming "Statement on statistical significance and *p*-values" emphatically reminding basic facts like, "Statistical significance is not equivalent to scientific, human, or economic significance. Smaller p-values do not necessarily imply the presence of larger or more important effects, and larger p-values do not imply a lack of importance or even lack of effect. Any effect, no matter how tiny, can produce a small p-value if the sample size or measurement precision is high enough(*500*)." Statisticians have been urging to "abandon statistical significance(*448*)," emphasizing that "no single index should substitute for scientific reasoning(*500*)," and underlining "the limited role of formal statistical inference in scientific inference(*426*)." Following the alarms, journals from various fields have been trying to restrict these common abusive practices(*501-505*). The important point is perfectly reflected by one title of a recent special issue of an official journal of ASA, dedicated to steering toward this "post $p < 0.05$ era": "Statistical inference enables bad science; statistical thinking enables good science(*506*)." Extent and the real-world impact of "substituting scientific reasoning(*500*)" with "mindless" practice of statistics can be highlighted by reviewing the case of mistaking "clinical significance" with "statistical significance"(*507-509*). For decades, instead of clinical significance, the measure of approving drugs has been whether *p*-values reach the "statistical-significance" threshold or not(*510-513*). Intriguingly, if you look up press announcements of the US Food and Drug Administration (FDA), a globally leading regulatory agency, on approval of drugs (e.g., see (*514*)), you can see a subtle yet immensely impactful(*515*) change of language. The technical term of "statistically significant" is used interchangeably with the common term, "significant." It is very improbable that it comes to the mind of a lay person reading these announcements that this "significant" has nothing to do with the common non-technical meaning of "significant" and actually, conveys a statistical measure that, as ASA has emphasized, can be achieved by "any effect, no matter how tiny(*500*)" and does not denote the magnitude of drugs' effects. So, drugs have been, and are being, approved not only based on flawed and limited data on surrogate end-points(*131, 132, 138-141*), but also based on flawed conclusions from this itself-flawed data.

It is difficult to understand why statisticians commonly limit their inquiries to Averages, and do not revel in more comprehensive views. Their souls seem dull to the charm of variety […] Whenever [statistics] are not brutalised, but delicately handled by the higher methods, and are warily interpreted, their power of dealing with complicated phenomena is extraordinary.(*516*)
Francis Galton, father of modern statistical methods(*517*)

The Alternative?

Science has explored the microcosmos and the macrocosmos; we have a good sense of the lay of the land. The great unexplored frontier is complexity.(518)

After reviewing fallacies of dominant paradigms of biological sciences, we can better appreciate what Whitehead conjectured a century ago(*1*): biological sciences have degenerated "into a medley of ad hoc hypothesis" due to "uncritical assumption of half-truths."

If the dominant paradigms of biological sciences are so fallacious and ineffective, how have our advances in these sciences been possible? Let us first question a presupposition behind this question: Has any advance taken place in biological sciences?

Our success in understanding and changing biological systems (complex systems) pales beside our world-changing success in engineering and physical sciences (chained systems). We have constructed enormous cities with skyscrapers and bewilderingly complicated plumbing, sewerage and electricity systems while our ancestors had to travel kilometers for water. We can easily meet face-to-face those on the other side of the planet in a few seconds, while it could take several months a few hundred years ago just to transmit written words. The workings of the manufacturing systems we use are awe-inspiring. We are sending spaceships to Mars. Our computers would seem magical and supernatural to our ancestors. Even compared to 1956, they are one trillion (10^{12}) times stronger (Moore's law)(*519*). You may refer to the progress we have had in surgical operations, life expectancy, or molecular biology. Yet even all this progress in confrontations with biological systems is based on our success in engineering and physical sciences. Advanced medical and surgical devices have enabled diagnostic and interventional measures impossible before. Effective plumbing and sewerage systems have immensely improved longevity by improving hygiene(*520*). Advanced chained technologies have enabled dissecting complex systems: from unraveling the structure of DNA in the 1950s(*521-523*) to sequencing

complete genome with $100,000,000 in 2001(*524*), and now, sequencing it with less than $1000 (*525, 526*).

We have had meager progress in understanding and changing biological systems per se. About two decades ago, the data gathered by omics technologies, particularly the Human Genome Project, was thought to spur the introduction of an unprecedented number of effective treatments for various disorders and revolutionize our understanding of human biology. Francis Collins, director of the National Institutes of Health (NIH) stated in 1999 that "This knowledge will dramatically accelerate the development of new strategies for the diagnosis, prevention, and treatment of disease, not just for single-gene disorders but for the host of more common complex diseases(*527*)"(*528*). Such dramatic developments were expected to occur by 2010(*527, 528*). In 2021, almost none has materialized in prevention, diagnosis, and treatment(*529-532*). Even our understanding of the genetic underlying of common complex disorders has not progressed that much(*533*). The medical genetics community has been accused of making empty promises(*529*). Notable progress has been restricted to monogenic Mendelian disorders, which are decipherable by reductionism(*295*). Over decades, accompanied by blaring hype, various technologies have been hoped to bring immense changes: high-throughput screening, combinatorial chemistry, computer-aided drug design, and now artificial intelligence (AI)(*534-537*). Eroom's law suggests that these advancements not only have not fulfilled the promises but we even have regressed in discovering drugs; this is in spite of the fact that many of these advancements are directly used in drug discovery research.

Although this disproportionate disparity between our success in front of chained and complex systems may instill frustration at first, it also suggests that if we develop a satisfactory framework for understanding and changing biological sciences, which would be at least as effective as foundationalist materialism and the analytic method for chained systems, we might enjoy unimaginably immense developments.

Observing an exception to all our failures in front of biological systems led me to such an alternative framework.

A Hypothesis

After amazement by the extent of the irrationality of the dominant reductionism in drug discovery and its catastrophic consequences, I also noticed that still, we have some rather-effective drugs for some complex disorders like schizophrenia and many bacterial, fungal, and parasitic infections. Doubting their origination from the current paradigm, I investigated their discovery origins.

In 1951, Henri Laborit, surgeon of a military hospital, had received a newly introduced antihistamine molecule, chlorpromazine, that was supposed to potentiate anesthesia and reduce the shock after surgery. Yet he observed it caused a calmness and indifference that continued even after surgery. After validating this alongside army psychiatrist on more-agitated patients, he went to Paris and persuaded a healthy psychiatrist to test it intravenously on himself and report its subjective effects. After initially reporting "no effects worthy of mention, save a certain sensation of indifference," the psychiatrist fainted because of the antihypertensive effects of chlorpromazine. Laborit convinced another psychiatrist to test it this time on their psychotic patients. On January 19, 1952, Jacques, a 24-year-old severely agitated schizophrenic, intravenously received 50 mg chlorpromazine, the calming effect was immediate. After three weeks of treatment, Jacques was back to normal life. The first antipsychotic was born(*538-540*). I could trace back the origins of almost all currently available antipsychotics, 27 drugs, to this discovery (figure 3 and supplementary data 1).

Four years after this pivotal event for psychiatry, the quest for chlorpromazine analogue drugs was intense. Roland Kuhn, director of a psychiatric hospital on a tight budget, to both save money and potentially help patients, asked a drug manufacturer if they had any of such investigational antipsychotics they would like to try on their schizophrenic patients. After receiving G22355 and finding it devoid of any antipsychotic activity, he tried it on his depressed patients. After three weeks of administration, most of these patients were drawn out of their suffering by the first antidepressant, imipramine(*538, 541, 542*). Interestingly, at approximately the same time, clinical studies were being conducted to assess the effectiveness and safety of an analogue of the antituberculosis isoniazid, iproniazid, in tuberculosis patients. Apart from its antimicrobial effects, it was observed that iproniazid induced euphoria and enhanced vitality in some patients(*543*). Following this lead culminated in introducing monoamine oxidase inhibitor antidepressants(*544*). Origins of almost all currently available antidepressants, 28 drugs, can be traced back to these two discoveries (figure 3 and supplementary data 1).

But such cases of humble yet impactful discoveries do not end here. A mummified human body dating back to 5300 years ago has was found carrying the fungus *Piptoporus betulinus*. Substances from this fungus have now been shown to have potent antimicrobial and immunomodulatory activities(*545-549*). Further analysis proposed that he was probably using the fungus for his trichuriasis(*550-553*). Other evidence stretches back the possible intentional use of effective drugs further, even to 60,000 years ago and Neanderthals(*554-561*). Even today, some of our most effective drugs can be traced back to the therapeutics our ancestors discovered hundreds of years ago: opioid analgesics (22 drugs), aspirin, digoxin, metformin, and many others (historically used category of figure 3 and supplementary data 1). How is it possible that our ancestors, from about half a century to hundreds of years ago, were so successful in discovering drugs and now, we, with incomparably superior collected knowledge and tools, are so desperate to do so? The onset of the trend captured by Eroom's law may imply that we could look for the onset of a detrimental causal trend in the second half of the previous century. There are several proposals for what this trend is(*46, 47, 116, 118*). I hypothesized that a major reason for the decline in efficiency is that unlike the reductionist "rational" drug design that optimizes structures majorly based on their binding to few hypothetically therapeutic(*110*) "target" proteins and usually uses human and in vivo data only as terminal filters, because of the unavailability of the tools needed for reductionism, traditional drug discovery inevitably had an empirical approach primarily based on observation and optimization according to phenotypical effects on humans and other animals and organisms like fungi and bacteria.

Empirical Evidence
Consequences of Reducing Biology

1. Therapeutic Effects vs Their Micro-Scale "Targets"?

To test my hypothesis, I investigated the discovery origins of all drugs approved by the FDA by the end of 2020. Rather similar to the seminal analysis of Swinney and Anthony who had previously shown that despite the disproportionate dominance of "rational" drug discovery, phenotype-based approaches had contributed more than "target-based" approaches to the discovery of first-in-class drugs approved between 1999 and 2008(*562*), I classified the discovery origins (note the precise definition in methods) to "target-based" and phenotype-based. To more "objectively" identify drug classes, I emphasized verbatim accounts of the original discovery paper and the discoverer(s) themselves and also used feature trees for measuring structural similarities between analogues(*563*).

Figure 1 shows that "target-based" approaches that have tried to reduce the therapeutic effects of molecules to their lower-scale effects on proteins, despite having dominated the field of drug discovery in the last 40-50 years(*111, 112*), have contributed far less than phenotype-based approaches. Supplementary data-1 provides evidence-based insights toward the reality of drug discovery, stripped of all the hype and advertisements; e.g., although some suggest that the increase of FDA drug approvals in recent years seems to have broken the Eroom's law(*564, 565*), a deeper look reveals that the pharmaceutical industry seems to have been adapting to its low research productivity rather than having been able to improve it. It has diverted its focus from complex unaddressed fields like CNS disorders to either more reducible ones like monogenic disorders(*121, 123, 564, 566*) or those fields where expensive revenue-

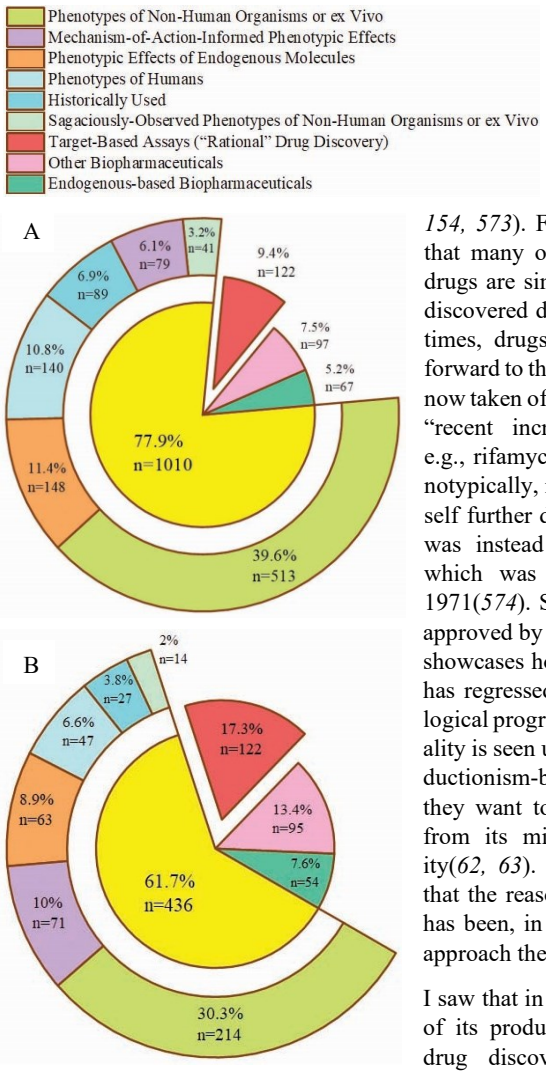

Figure 1. Comparison of shares of different approaches in percentage and count from (**A**) all approved drugs and (**B**) drugs approved after 1995. Details are available in figure 3 and supplementary data 1.

boosting drugs(*137, 154, 567-572*) can get approval regardless of lacking real-world appropriate evidence and efficacy(*131-133, 136-140, 142, 144-146, 154, 573*). Furthermore, we can see that many of the recently approved drugs are simple analogues of drugs discovered decades ago. Even sometimes, drugs that were not brought forward to the market decades ago are now taken off the shelf and lead to the "recent increase of productivity"; e.g., rifamycin was discovered, phenotypically, in 1963 but it was not itself further developed in the US and was instead optimized to rifampin which was approved by FDA in 1971(*574*). Still, rifamycin itself got approved by FDA in 2018(*575*). This showcases how much drug discovery has regressed despite all the technological progress. Interestingly, this reality is seen upside down by many reductionism-based studies: They state they want to rescue drug discovery from its miserably low productivity(*62, 63*). They have not realized that the reason for such productivity has been, in the first place, the very approach they have.

I saw that in parallel with the decline of its productivity from the 1950s, drug discovery methodology has gradually changed in a way that current drug hunters see those days as "otherworldly(*576*)" and "taken place on another planet(*576*)"(*112, 577*). A transition is clear from small teams comprising a few medicinal chemists and pharmacologists without too much specialization and who could directly oversee the relationship between chemical structures and their effects on phenotypes and were trying to answer the same question to current huge teams in which the goal of discovering a drug is reduced and specialized into disconnected tasks: from a seamless two-way translation were observations of the phenotypic effect of molecules back-propagated and informed design and optimization to a one-way translation in which the information of phenotypic observations is not used, but mostly as a filter(*578, 579*).

2. Rationality or Luckiness?

Still, I was suspicious of the role of "rational" drug discovery for even the 9.4% of approved drugs: I hypothesized that many of the drugs discovered by "target-based" approaches, depend on "off-target" mechanisms for their therapeutic effects, like how it was shown recently that "Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials(*580*)." Although "rational" drug discovery designs and screens molecules based on their binding to a specific target, it inevitably uses animal and human results as terminal filters. Even though animal and human data rarely inform the design of molecules, when employed as terminal filters, they may fortuitously lead to selecting drug candidates which benefit from several mechanisms. This possibility is augmented by noticing that many of the approved drugs we currently use have modest origins in which their effects were discovered in humans or in vivo models either serendipitously or out of a few hundreds of initial molecules (see supplementary data 1); and not by systematically screening billions of molecules(*581*).

To assess my hypothesis, I systematically reviewed 30921 articles on the pharmacology of the drugs whose discovery I had identified as "target-based" to find out if they benefitted from therapeutic mechanisms other than their discovery "targets." To rule out the mechanisms that are merely downstream effects of binding to the "target," I excluded from the "off-target" therapeutic mechanisms those that had interactions with the "target" based on STRING v11(*582*).

Table 1 shows the count of these "off-target" therapeutic mechanisms; these mechanisms along with the interaction networks are available in supplementary data 2 detailed and referenced. This shows that the share of "rational" and "target-based" drug discovery from all approved drugs is even far less than 9.4%. If it was solely the reductionist scheme of "rational" drug discovery, none of these "off-target" therapeutic mechanisms would have existed. They have been selected unconsciously and blindly because of the terminal phenotypic filters and do not accompany any molecule selected based on its inhibitory potency on a "target." Noteworthy, these counts are restricted, of course, to mechanisms that have been shown until now; it is fair to expect that the actual "numbers" would be much higher.

Table 1. Counts of "off-target" therapeutic mechanisms of "target-based" drugs. Details are available in supplementary data 2.

DONEPEZIL	41	BORTEZOMIB	69
ACARBOSE	14	CARFILZOMIB	2
ALISKIREN	12	EFAVIRENZ	2
RIVAROXABAN	7	NINTEDANIB	229
SACUBITRILAT	2	GEFITINIB	111
EDOXABAN	1	ERLOTINIB	109
ZANAMIVIR	1	LAPATINIB	16
OSELTAMIVIR	1	VANDETANIB	114
FOMEPIZOLE	2	AFATINIB	41
SITAGLIPTIN	13	OSIMERTINIB	8
SAXAGLIPTIN	20	NERATINIB	4
LINAGLIPTIN	1	SORAFENIB	140
ALOGLIPTIN	1	PAZOPANIB	107
ELTROMBOPAG	1	AXITINIB	102
ARGATROBAN	1	REGORAFENIB	20
DABIGATRAN	2	LENVATINIB	10
MIRABEGRON	2	IMATINIB	78
ORLISTAT	10	DASATINIB	158
RIMEGEPANT	1	NILOTINIB	63
ROFLUMILAST	9	PONATINIB	13
SACUBITRILAT	2	BOSUTINIB	74
TIRBANIBULIN	2	CRIZOTINIB	148
VENETOCLAX	2	CABOZANTINIB	5
SAQUINAVIR	11	CERITINIB	9
RITONAVIR	8	OLAPARIB	4
INDINAVIR	7	RUCAPARIB	17
NELFINAVIR	8	NIRAPARIB	2
LOPINAVIR	2	TALAZOPARIB	3
ATAZANAVIR	1	IBRUTINIB	40
MARAVIROC	3	ACALABRUTINIB	3
ELTROMBOPAG	1	SUNITINIB	270
PALBOCICLIB	38	VEMURAFENIB	18
RIBOCICLIB	14	TOFACITINIB	34
		ABEMACICLIB	17

3. Is Protein Binding Even Relevant?

Now that most drugs have been discovered based on phenotypic observations and even the "target-based" drugs are not that much "target-based," how much is tight binding to "targets", the holy grail of "rational" drug discovery, relevant at all for therapeutic effects? Do approved drugs bind tightly to their "targets"?

According to the scheme of "rational" drug discovery, the relationship between measured binding affinities and drug potencies are rather consistently positive for drugs whose mechanisms of action are based on competitive antagonism and inhibition. As binding affinities should be considered relative to each macromolecule, I investigated the percentile rank of each approved drug's affinity for each of its therapeutic "targets" among all ChEMBL(*583*) ligands of that "target." As figure 2 and supplementary data 3 show, although affinities of a considerable number of approved drugs for their therapeutic "targets" were relatively low, most of them incline toward the highest percentile ranks.

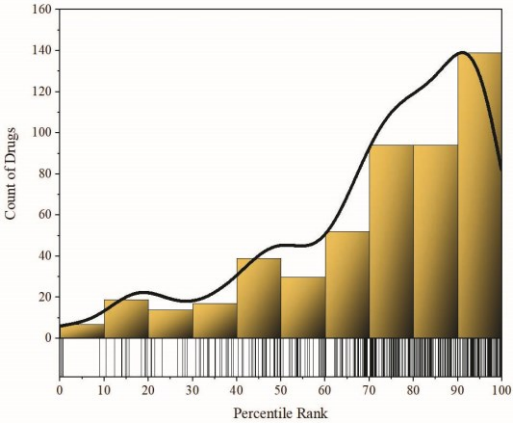

Figure 2. Percentile ranks of the affinity of approved drugs among all ChEMBL ligands of their therapeutic "targets." Details are available in supplementary data 3.

Phenotypes of Non-Human Organisms or ex Vivo

CHLORDIAZEPOXIDE	**FLUOROURACIL**	**CEFALEXIN**	**INDOMETHACIN**	**CAPTOPRIL**	**DIPHENHYDRAMINE**	**PROPRANOLOL**	**MICONAZOLE**	**Standalone Drugs**	**Standalone Drugs**
DIAZEPAM	CYTARABINE	CEFAZOLIN	TOLMETIN	ENALAPRILAT	PHENINDAMINE	TIMOLOL	CLOTRIMAZOLE	KETAMINE	METHYLPHENIDATE
OXAZEPAM	FLOXURIDINE	CEFOXITIN	SULINDAC	LISINOPRIL	PHENIRAMINE	METOPROLOL	KETOCONAZOLE	SPINOSAD	FOSFOMYCIN
FLURAZEPAM	FLUCYTOSINE	CEFADROXIL	DICLOFENAC	RAMIPRILAT	PYRILAMINE	NADOLOL	ECONAZOLE	BEDAQUILINE	TOPIRAMATE
CLORAZEPIC ACID	VIDARABINE	CEFACLOR	ETODOLAC	QUINAPRILAT	THONZYLAMINE	ATENOLOL	TIOCONAZOLE	OMACETAXINE	NATAMYCIN
CLONAZEPAM	TRIFLURIDINE	CEFOTAXIME	BROMFENAC	BENAZEPRILAT	DOXYLAMINE	PINDOLOL	BUTOCONAZOLE	MERTANSINE	ZILEUTON
LORAZEPAM	GEMCITABINE	CEFUROXIME	CELECOXIB	FOSINOPRILAT	CHLORPHENIRAMINE	LABETALOL	SULCONAZOLE	PIRFENIDONE	GLATIRAMER
TEMAZEPAM	5'-DEOXY-5—	CEFTRIAXONE	NEPAFENAC	PERINDOPRILAT	CHLORCYCLIZINE	ACEBUTOLOL	TERCONAZOLE	BRETYLIUM	REPAGLINIDE
ALPRAZOLAM	FLUOROCYTIDINE	CEFOTETAN	**IBUPROFEN**	MOEXIPRILAT	PROMETHAZINE	BETAXOLOL	OXICONAZOLE	DOBUTAMINE	IMIQUIMOD
TRIAZOLAM	CAPECITABINE	CEFTAZIDIME	NAPROXEN	TRANDOLAPRILAT	CARBINOXAMINE	LEVOBUNOLOL	FLUCONAZOLE	DACARBAZINE	FENOLDOPAM
MIDAZOLAM	EMTRICITABINE	CEFIXIME	FENOPROFEN	PERINDOPRIL—	FUMARATE	ESMOLOL	ITRACONAZOLE	DANTROLENE	MODAFINIL
QUAZEPAM	AZACITIDINE	CEFPODOXIME	FLURBIPROFEN	ARGININE	CYCLIZINE	CARTEOLOL	VORICONAZOLE	MITOMYCIN	LEFLUNOMIDE
ESTAZOLAM	CLOFARABINE	CEFEPIME	KETOPROFEN	**RIFAMPIN**	MECLIZINE	SOTALOL	SERTACONAZOLE	DOXAPRAM	CILOSTAZOL
CLOBAZAM	NELARABINE	CEFDINIR	KETOROLAC	RIFABUTIN	HYDROXYZINE	BISOPROLOL	POSACONAZOLE	GUANFACINE	DOCOSANOL
REMIMAZOLAM	DECITABINE	CEFTAROLINE	OXAPROZIN	RIFAPENTINE	BROMPHENIRAMINE	IBUTILIDE	LULICONAZOLE	TRIMETHOPRIM	ZONISAMIDE
MERCAPTOPURINE	REMDESIVIR	CEFTOLOZANE	**STREPTOMYCIN**	RIFAXIMIN	ORPHENADRINE	CARVEDILOL	EFINACONAZOLE	CAPREOMYCIN	NATEGLINIDE
THIOGUANINE	**METRONIDAZOLE**	CEFIDEROCOL	NEOMYCIN	RIFAMYCIN	TRIPROLIDINE	DOFETILIDE	ISAVUCONAZOLE	PYRANTEL	GALANTAMINE
AZATHIOPRINE	TINIDAZOLE	**NAFTIFINE**	GENTAMICIN	**BENZOCAINE**	CHLOPHEDIANOL	NEBIVOLOL	**METOCLOPRAMIDE**	CYCLOSERINE	NITISINONE
PENTOBARBITAL	BENZNIDAZOLE	TERBINAFINE	TOBRAMYCIN	TETRACAINE	CYPROHEPTADINE	**CIMETIDINE**	PRUCALOPRIDE	MITOTANE	NITAZOXANIDE
BUTALBITAL	SECNIDAZOLE	BUTENAFINE	AMIKACIN	BENZONATATE	CLEMASTINE	RANITIDINE	AMISULPRIDE	ETHAMBUTOL	EZETIMIBE
SECOBARBITAL	**CLAVULANIC ACID**	**IMIPENEM**	PLAZOMICIN	**PRAMOXINE**	NALTREXONE	FAMOTIDINE	**Standalone Drugs**	HYDROXYUREA	FULVESTRANT
PRIMIDONE	SULBACTAM	MEROPENEM	**VANCOMYCIN**	DYCLONINE	LORATADINE	NIZATIDINE	WARFARIN	METHYLENE BLUE	DAPTOMYCIN
METHOHEXITAL	TAZOBACTAM	ERTAPENEM	TELAVANCIN	BENOXINATE	ACRIVASTINE	**OMEPRAZOLE**	LITHIUM	DICYCLOMINE	ZICONOTIDE
MEBENDAZOLE	AVIBACTAM	**LOPERAMIDE**	DALBAVANCIN	PROPARACAINE	CETIRIZINE	LANSOPRAZOLE	RESORCINOL	LINDANE	VARENICLINE
ALBENDAZOLE	RELEBACTAM	ELUXADOLINE	ORITAVANCIN	**ZOLPIDEM**	OLOPATADINE	RABEPRAZOLE	PYRITHIONE	PROGUANIL	RANOLAZINE
TRICLABENDAZOLE	VABORBACTAM	**RILUZOLE**	**AMANTADINE**	ZALEPLON	FEXOFENADINE	PANTOPRAZOLE	PYRIMETHAMINE	BUSULFAN	SINECATECHINS
PANCURONIUM	**LEVETIRACETAM**	EDARAVONE	RIMANTADINE	ESZOPICLONE	AZELASTINE	**METHOTREXATE**	GRISEOFULVIN	THIOTEPA	IXABEPILONE
VECURONIUM	BRIVARACETAM	**AMIODARONE**	**LETROZOLE**	**IVERMECTIN**	KETOTIFEN	LEVOLEUCOVORIN	TRIAMTERENE	COPPER UNDECYLE-	RETAPAMULIN
NAPHAZOLINE	**ERYTHROMYCIN**	DRONEDARONE	ANASTROZOLE	MOXIDECTIN	EPINASTINE	PEMETREXED	DACTINOMYCIN	NATE	LACOSAMIDE
TETRAHYDROZOLINE	CLARITHROMYCIN	**TIROFIBAN**	**TOPOTECAN**	**POLYMYXIN B**	BEPOTASTINE	PRALATREXATE	TOLNAFTATE	DALFOPRISTIN-	PLERIXAFOR
XYLOMETAZOLINE	AZITHROMYCIN	EPTIFIBATIDE	IRINOTECAN	COLISTIN	ALCAFTADINE	**LOSARTAN**	VERAPAMIL	QUINUPRISTIN	LUMEFANTRINE
OXYMETAZOLINE	**BELINOSTAT**	**PRAZOSIN**	DERUXTECAN	**LINCOMYCIN**	**CLONIDINE**	VALSARTAN	AMILORIDE	OZOGAMICIN	ERIBULIN
ISONIAZID	PANOBINOSTAT	TERAZOSIN	SN-38	CLINDAMYCIN	APRACLONIDINE	IRBESARTAN	CICLOPIROX	CENOBAMATE	NIFURTIMOX
PYRAZINAMIDE	**METHSUXIMIDE**	DOXAZOSIN	**MEPERIDINE**	**PACLITAXEL**	BRIMONIDINE	TELMISARTAN	PRAZIQUANTEL	AMINOSALICYLATE	FIDAXOMICIN
ETHIONAMIDE	ETHOSUXIMIDE	ALFUZOSIN	METHADONE	DOCETAXEL	TIZANIDINE	CANDESARTAN	POVIDONE-IODINE	CHLORAMPHENICOL	PITOLISANT
ACYCLOVIR	**NIFEDIPINE**	**PIROXICAM**	**ROSIGLITAZONE**	CABAZITAXEL	DEXMEDETOMIDINE	OLMESARTAN	CYCLOSPORINE	MIDOSTAURIN	CHLORHEXIDINE
VALACYCLOVIR	AMLODIPINE	MELOXICAM	PIOGLITAZONE	**TAMOXIFEN**	LOFEXIDINE	AZILSARTAN	BUSPIRONE	NABUMETONE	FOSCARNET
GANCICLOVIR	NIMODIPINE	**LINEZOLID**	**CHLOROQUINE**	TOREMIFENE	**BROMOCRIPTINE**	**DAUNORUBICIN**	MUPIROCIN	INAMRINONE	RUFINAMIDE
VALGANCICLOVIR	NICARDIPINE	TEDIZOLID	PRIMAQUINE	RALOXIFENE	CABERGOLINE	VALRUBICIN	PROPOFOL	BUPROPION	LEFAMULIN
CIDOFOVIR	ISRADIPINE	**PHENYTOIN**	HYDROXYCHLO-	BAZEDOXIFENE	**DIPHENOXYLATE**	MITOXANTRONE	CISATRACURIUM	AURANOFIN	CLIOQUINOL
PENCICLOVIR	FELODIPINE	ETHOTOIN	ROQUINE	OSPEMIFENE	DIFENOXIN	IDARUBICIN	TEMOZOLOMIDE	AZTREONAM	ALLANTOIN
ADEFOVIR	NISOLDIPINE	**DIMETHYL FUMARATE**		**MEFENAMIC ACID**	**TRABECTEDIN**	EPIRUBICIN	PRETOMANID	PERMETHRIN	HALOPROGIN
ENTECAVIR	CLEVIDIPINE	DIROXIMEL FUMARATE		MECLOFENAMIC ACID	LURBINECTEDIN	**ALLOPURINOL**	OSILODROSTAT	ETOPOSIDE	FLAVOXATE
SALBUTAMOL	**FLUTAMIDE**	**MONOMETHYL AURISTATIN E**		**CHLORTETRACYCLINE**		FEBUXOSTAT	ETELCALCETIDE	PENTAMIDINE	ATOVAQUONE
TERBUTALINE	BICALUTAMIDE	MONOMETHYL AURISTATIN-F		OXYTETRACYCLINE	DOXORUBICIN	**LOMUSTINE**	TECOVIRIMAT	TRANEXAMIC ACID	STIRIPENTOL
SALMETEROL	APALUTAMIDE	**PROPYLTHIOURACIL**		TETRACYCLINE	TIGECYCLINE	STREPTOZOCIN	AMIFAMPRIDINE	LIXISENATIDE	TAVABOROLE
FORMOTEROL	NILUTAMIDE	METHIMAZOLE		DEMECLOCYCLINE	ERAVACYCLINE	**ISOFLURANE**	ISTRADEFYLLINE	BACLOFEN	IVABRADINE
VILANTEROL	ENZALUTAMIDE	**PHENTOLAMINE**		DOXYCYCLINE	OMADACYCLINE	DESFLURANE	LAMOTRIGINE	AMPHOTERICIN B	MILTEFOSINE
OLODATEROL	DAROLUTAMIDE	PHENOXYBENZAMINE		MINOCYCLINE	SARECYCLINE	SEVOFLURANE	LETERMOVIR	DAPSONE	DILTIAZEM

Phenotypes of Non-Human Organisms or ex Vivo

- **MECHLORETHAMINE**
- CHLORAMBUCIL
- 4-HYDROXYCYCLO—
- PHOSPHAMIDE
- CYCLOPHOSPHAMIDE
- MELPHALAN
- CARMUSTINE
- ESTRAMUSTINE
- IFOSFAMIDE
- BENDAMUSTINE

- **RIBAVIRIN**
- ZIDOVUDINE
- DIDANOSINE
- FLUDARABINE
- PENTOSTATIN
- CLADRIBINE
- STAVUDINE
- LAMIVUDINE
- ABACAVIR
- SOFOSBUVIR
- DASABUVIR

- **CIPROFLOXACIN**
- OFLOXACIN
- GATIFLOXACIN
- MOXIFLOXACIN
- GEMIFLOXACIN
- BESIFLOXACIN
- DELAFLOXACIN
- OZENOXACIN

- **SIROLIMUS**
- TACROLIMUS
- PIMECROLIMUS
- TEMSIROLIMUS
- EVEROLIMUS

- **SULFANILAMIDE**
- SULFADIAZINE
- SULFACETAMIDE
- MAFENIDE
- SULFAMETHOXAZOLE

- **CASPOFUNGIN**
- MICAFUNGIN
- ANIDULAFUNGIN

Phenotypes of Humans

- **IMIPRAMINE**
- AMITRIPTYLINE
- DESIPRAMINE
- NORTRIPTYLINE
- PROTRIPTYLINE
- DOXEPIN
- CYCLOBENZAPRINE
- TRIMIPRAMINE
- MAPROTILINE
- AMOXAPINE
- FLUOXETINE
- CLOMIPRAMINE
- SERTRALINE
- PAROXETINE
- VENLAFAXINE
- FLUVOXAMINE
- MIRTAZAPINE
- CITALOPRAM
- DULOXETINE
- DESVENLAFAXINE
- MILNACIPRAN
- VORTIOXETINE

- **ACETAZOLAMIDE**
- DICHLORPHENAMIDE
- METHAZOLAMIDE
- DORZOLAMIDE
- BRINZOLAMIDE

- **TRAZODONE**
- MINOXIDIL
- NEFAZODONE
- VILAZODONE
- FLIBANSERIN

- **FUROSEMIDE**
- ETHACRYNIC ACID
- BUMETANIDE
- TORSEMIDE

- **DAPAGLIFLOZIN**
- CANAGLIFLOZIN
- EMPAGLIFLOZIN
- ERTUGLIFLOZIN

- **QUINIDINE**
- DISOPYRAMIDE

- **CHLOROTHIAZIDE**
- HYDROCHLOROTHIAZIDE
- BENDROFLUMETHIAZIDE
- CHLORTHALIDONE
- METOLAZONE
- INDAPAMIDE

- **CHLORPROMAZINE**
- PROCHLORPERAZINE
- PERPHENAZINE
- FLUPHENAZINE
- TRIFLUOPERAZINE
- THIORIDAZINE
- HALOPERIDOL
- DROPERIDOL
- THIOTHIXENE
- MOLINDONE
- LOXAPINE
- PIMOZIDE
- CLOZAPINE
- RISPERIDONE
- OLANZAPINE
- QUETIAPINE
- ZIPRASIDONE
- ARIPIPRAZOLE
- ATOMOXETINE
- PALIPERIDONE
- ILOPERIDONE
- ASENAPINE
- LURASIDONE
- CARIPRAZINE
- BREXPIPRAZOLE
- PIMAVANSERIN
- LUMATEPERONE

- **THALIDOMIDE**
- LENALIDOMIDE
- POMALIDOMIDE
- APREMILAST

- **ISOCARBOXAZID**
- TRANYLCYPROMINE
- PHENELZINE
- SELEGILINE
- RASAGILINE
- SAFINAMIDE

- **SPIRONOLACTONE**
- DROSPIRENONE
- EPLERENONE

- **QUININE**
- MEFLOQUINE
- TAFENOQUINE

- **CROMOLYN**
- NEDOCROMIL
- LODOXAMIDE

- **NABILONE**
- DRONABINOL

- **Standalone Drugs**
- ACETAMINOPHEN
- NITROUS OXIDE
- MEMANTINE
- BISMUTH
- METHENAMINE
- BENZYL ALCOHOL
- SULFASALAZINE
- PROBENECID
- DISULFIRAM
- HYDRALAZINE
- METHYLDOPA
- BENZOYL PEROXIDE
- ANAGRELIDE
- HYDROQUINONE
- DEACETYLBISACODYL
- BREMELANOTIDE
- DIBUCAINE
- MALATHION

- **LIDOCAINE**
- PROCAINAMIDE
- CHLOROPROCAINE
- MEPIVACAINE
- PRILOCAINE
- BUPIVACAINE
- MEXILETINE
- FLECAINIDE
- PROPAFENONE
- ROPIVACAINE
- ARTICAINE

- **NITROGLYCERIN**
- ISOSORBIDE DINI-
- TRATE
- NITROPRUSSIDE
- ISOSORBIDE MONO—
- NITRATE

- **TOLBUTAMIDE**
- GLYBURIDE
- GLIPIZIDE
- GLIMEPIRIDE

- **GEMFIBROZIL**
- FENOFIBRIC ACID
- FENOFIBRATE

- **SILDENAFIL**
- VARDENAFIL
- TADALAFIL
- AVANAFIL

Phenotypic Effects of Endogenous Molecules

- **CORTISONE**
- HYDROCORTISONE
- PREDNISONE
- PREDNISOLONE
- TRIAMCINOLONE
- NORETHINDRONE
- METHYLPREDNISOLONE
- DEXAMETHASONE
- FLUOROMETHOLONE
- FLUOCINOLONE
- FLURANDRENOLIDE
- BETAMETHASONE
- FLUOCINONIDE
- DESONIDE
- HALCINONIDE
- DIFLORASONE
- CLOCORTOLONE
- DESOXIMETASONE
- AMCINONIDE
- FLUNISOLIDE
- ALCLOMETASONE
- CLOBETASOL
- BECLOMETHASONE
- MOMETASONE
- FLUTICASONE
- HALOBETASOL
- PREDNICARBATE
- BUDESONIDE
- LOTEPREDNOL
- CICLESONIDE
- FLUTICASONE FUROATE
- DIFLUPREDNATE
- 21, DESACETYLDE—
- FLAZACORT

- **DEOXYCHOLIC ACID**
- CHOLIC ACID
- OBETICHOLIC ACID

- **ESTRADIOL**
- ETHINYL ESTRADIOL
- PRASTERONE

- **DINOPROSTONE**
- CARBOPROST
- ALPROSTADIL

- **LATANOPROST**
- BIMATOPROST
- TRAVOPROST
- TAFLUPROST

- **OCTREOTIDE**
- LANREOTIDE
- PASIREOTIDE

- **PROGESTERONE**
- HYDROXYPROGESTERONE
- MEDROXYPROGESTERONE
- ETHYNODIOL
- LEVONORGESTREL
- MEGESTROL
- DANAZOL
- NORGESTIMATE
- DESOGESTREL
- MIFEPRISTONE
- NORELGESTROMIN
- ETONOGESTREL
- DIENOGEST
- ULIPRISTAL
- SEGESTERONE
- BREXANOLONE

- **TESTOSTERONE**
- METHYLTESTOSTERONE
- OXYMETHOLONE
- FLUOXYMESTERONE
- FINASTERIDE
- EXEMESTANE
- DUTASTERIDE
- ABIRATERONE
- CLASCOTERONE

- **EPINEPHRINE**
- PHENYLEPHRINE
- ISOPROTERENOL
- NOREPINEPHRINE
- DROXIDOPA
- METAPROTERENOL
- MIDODRINE
- SOLRIAMFETOL

- **HEPARIN**
- ENOXAPARIN
- DALTEPARIN
- PENTOSAN POLYSULFATE
- FONDAPARINUX

- **GABAPENTIN**
- 4, HYDROXYBUTANOTE
- PREGABALIN
- ACAMPROSATE
- VIGABATRIN

- **ACETYLCHOLINE**
- BETHANECHOL
- CARBAMOYLCHOLINE

- **CARBACHOL**
- CEVIMELINE

- **RAMELTEON**
- TASIMELTEON

- **LEUPROLIDE**
- GOSERELIN
- HISTRELIN
- GANIRELIX
- CETRORELIX
- DEGARELIX
- TESAMORELIN
- NAFARELIN
- TRIPTORELIN

- **Standalone Drugs**
- OXYTOCIN
- GUANIDINE
- UNDECYLENIC ACID
- CORTICOTROPIN
- LEVODOPA
- DOPAMINE
- AMINOCAPROIC ACID
- METYROSINE
- URSODIOL
- PHENYLACETIC ACID
- EFLORNITHINE
- MIGLITOL
- TEGASEROD
- GLUTAMINE
- PRAMLINTIDE
- SAPROPTERIN
- ICATIBANT
- AFAMELANOTIDE
- HEMIN
- MISOPROSTOL
- SETMELANOTIDE
- OXIGLUTATIONE
- SEMAGLUTIDE
- CALCIPOTRIENE

- **TRETINOIN**
- ISOTRETINOIN
- ADAPALENE
- ACITRETIN
- TAZAROTENIC ACID
- BEXAROTENE
- TRIFAROTENE

- **EPOPROSTENOL**
- TREPROSTINIL
- ILOPROST

- **LEVOTHYROXINE**
- LIOTHYRONINE

- **LINACLOTIDE**
- PLECANATIDE

- **VASOPRESSIN**
- DESMOPRESSIN

Historically Used

- **MORPHINE**
- CODEINE
- HYDROCODONE
- OXYCODONE
- LEVORPHANOL
- DEXTROMETHORPHAN
- DIHYDROCODEINE
- HYDROMORPHONE
- OXYMORPHONE
- NALBUPHINE
- FENTANYL
- PENTAZOCINE
- NALOXONE
- BUTORPHANOL
- BUPRENORPHINE
- SUFENTANIL
- ALFENTANIL
- TRAMADOL
- REMIFENTANIL
- ALVIMOPAN
- TAPENTADOL
- OLICERIDINE

- **EPHEDRINE**
- AMPHETAMINE
- METHAMPHETAMINE
- PROPYLHEXEDRINE
- PHENTERMINE
- DIETHYLPROPION
- BENZPHETAMINE
- PHENDIMETRAZINE
- PSEUDOEPHEDRINE
- FENFLURAMINE

- **THEOPHYLLINE**
- PENTOXIFYLLINE
- MILRINONE

- **NEOSTIGMINE**
- PYRIDOSTIGMINE
- RIVASTIGMINE

- **SALICYLIC ACID**
- ASPIRIN
- DIFLUNISAL
- MESALAMINE
- OLSALAZINE

- **METHYLERGONOVINE**
- DIHYDROERGOTAMINE
- ERGOTAMINE

- **SCOPOLAMINE**
- PROPANTHELINE
- CLIDINIUM
- METHSCOPOLAMINE
- IPRATROPIUM
- TROSPIUM
- SOLIFENACIN
- TIOTROPIUM
- DARIFENACIN
- ACLIDINIUM
- UMECLIDINIUM
- REVEFENACIN

- **ATROPINE**
- METHYLHOMATROPINE
- BENZTROPINE
- GLYCOPYRROLATE
- OXYBUTYNIN
- TOLTERODINE
- FESOTERODINE

- **Standalone Drugs**
- ALCOHOL
- COCAINE
- DIGOXIN
- KAOLIN
- CAFFEINE
- COLCHICINE
- MENTHOL
- PILOCARPINE
- APOMORPHINE
- METHOXSALEN
- NICOTINE
- PODOFILOX
- METFORMIN
- SUCCINYLCHOLINE
- TIAGABINE
- BIVALIRUDIN
- INGENOL MEBUTATE
- CAPSAICIN
- CANNABIDIOL

- ARTEMETHER
- ARTESUNATE

- **TETRABENAZINE**
- (+)-α, DIHYDROTETRA—
- BENAZINE
- VALBENAZINE

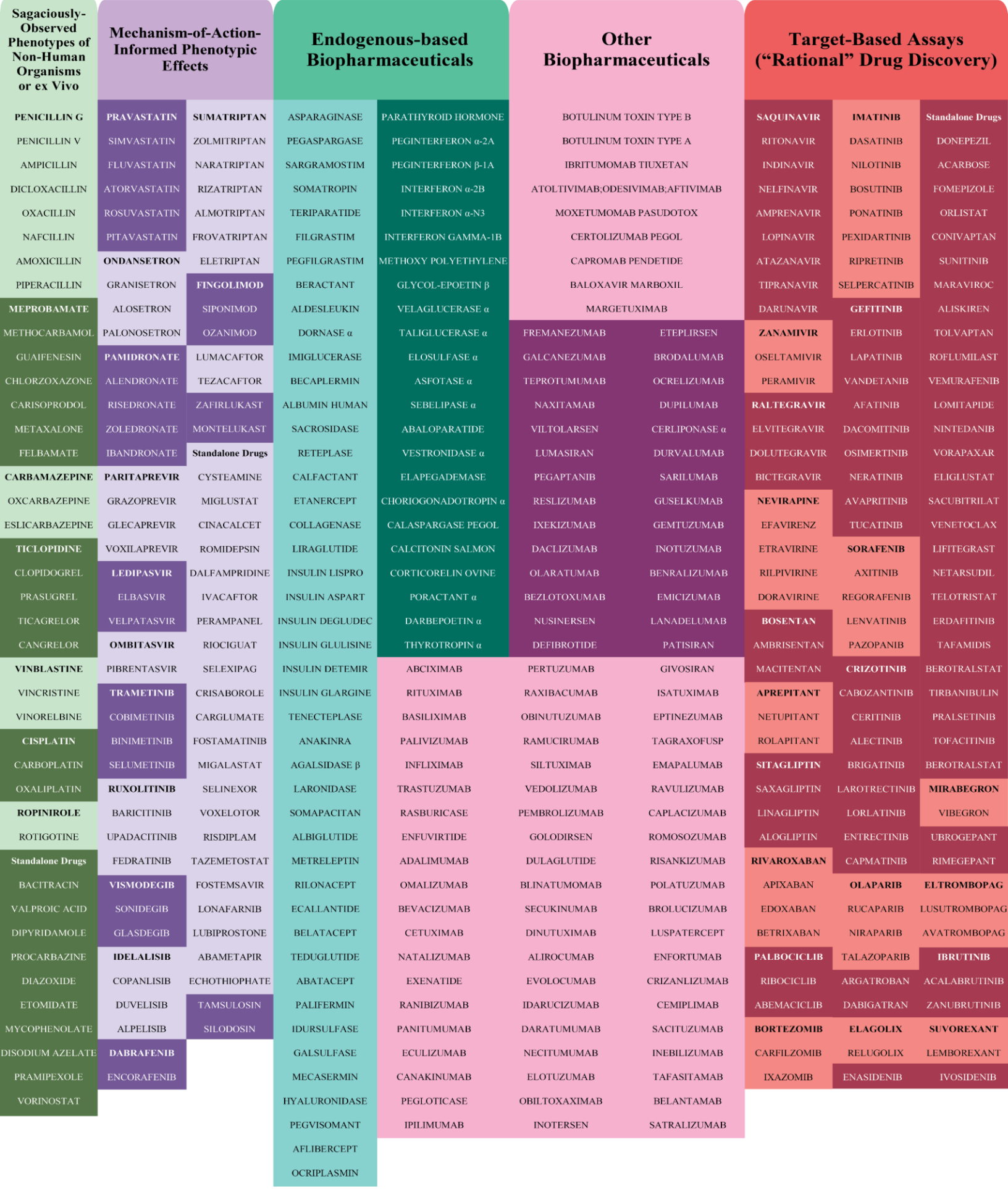

Figure 3. Discovery origins of all approved drugs. Details are available in supplementary data 1.

This suggests that tight-binding of molecules to "targets" is relevant for therapeutic effects. This observation together with the above observations regarding the inefficiency of "rational" drug discovery and the many "off-target" therapeutic mechanisms of "target-based" drugs suggests that binding to therapeutic "targets" with high affinity is only a single aspect of therapeutic effects on phenotypes.

So, the attempt to reduce higher-scale to lower-scale phenomena has decreased the efficacy of drug discovery. Why? Trying to answer this question led me to a theory that can provide a simple and firm framework for biological sciences based on first principles.

Simplicity: The Key of Complexity

Rule V. We shall comply with it exactly if we reduce involved and obscure propositions step by step to those that are simpler, and then starting with the intuitive apprehension of all those that are absolutely simple, attempt to ascend to the knowledge of all others by precisely similar steps.(*584*)
René Descartes, one of the fathers of the Scientific Revolution

To choose those constructions which without straining reduce things to the greatest simplicity. The reason of this is manifest by the precedent Rule. Truth is ever to be found in simplicity, & not in the multiplicity & confusion of things. As the world, which to the naked eye exhibits the greatest variety of objects, appears very simple in its internal constitution when surveyed by a philosophic understanding, & so much the simpler by how much the better it is understood.(585)
Isaac Newton

The only method of preventing such errors from taking place, and of correcting them when formed, is to restrain and simplify our reasoning as much as possible. This depends entirely upon ourselves, and the neglect of it is the only source of our mistakes.(*586*)
Antoine Lavoisier, father of modern chemistry

A physical theory can be satisfactory only if its structures are composed of elementary foundations. […]
The grand aim of all science is to cover the greatest number of empirical facts by logical deduction from the smallest number of hypotheses or axioms.(587)
Albert Einstein

Absence of a general conceptual framework for biological sciences and their failure in contrast to physical sciences have obliged many to pinpoint the importance of developing such a framework and propose such theoretical frameworks(*57, 588-598*). Although these frameworks have underlined important points, they lack a characteristic that is a central tenet of this manuscript: simplicity.

Simplicity has been endorsed by many great philosophers and scientists from Aristotle through Galileo, Newton, Kant, Lavoisier, Poincaré, Einstein, Wittgenstein, and Dirac to contemporary scientists(*599-609*). Although it is noted as a key principle for gaining knowledge, because of lacking a concrete definition(*610*), it has been largely misunderstood for decades, particularly when it is conveyed under the terms of "principle of parsimony" or "Ockham's razor"(*599*). See a parallel thread of misunderstandings regarding the relationship between "beauty," "truth" and simplicity in (*611-616*). You can see a sample of these misunderstandings in this statement of Francis Crick: "While Occam's razor is a useful tool in the physical sciences, it can be a very dangerous implement in biology. It is thus very rash to use simplicity and elegance as a guide in biological research(*617*)."

For nothing ought to be posited without a reason given, unless it is self-evident (literally, known through itself) or known by experience or proved by the authority of Sacred Scripture.(618) William of Ockham

A full philosophical discussion is necessary, yet here I try to mend this misunderstanding briefly. This is required because as I will reiterate, simplicity is indispensable for deciphering complexity. Misunderstandings like that of Crick are due to mistaking ad hoc (for the particular case at hand) simplicity for ab initio (from first principles) simplicity. Ad hoc simplicity, which is implied by most current interpretations of Ockham's razor, like Crick's statement or how "parsimony" is used in phylogenetics(*619-621*), implies being simplistic(*622*): prioritizing those answers and explanations which readily appear simpler at face-value. But have all these great thinkers advised being simplistic and naive? No, by advising simplicity, they, including William of Ockham, meant that we should distill complex questions to their first principles and innermost fundamental causes and cores by examining and pruning, or razoring, all sophistries and unnecessary presumptions and assumptions, rewinding non-fundamental causal iterations and removing all apparent complexities and varieties. This attitude originates from this deep intuition that the universe is eventually unitary: All phenomena of the universe are interconnected(*623*); all phenomena, one way or another, are rooted in "simpler" "fundamental" phenomena of this universe; they are not effects of some other "fundamental"(*624*) "causal agency"(*625*) completely out of this unitary whole(*19, 623, 626*).

What is science? It is before all a classification, a manner of bringing together facts which appearances separate, though they were bound together by some natural and hidden kinship. Science, in other words, is a system of relations.(607)
Henri Poincaré

Science itself, may be regarded as a minimal problem, consisting of the completest possible presentment of facts with the least possible expenditure of thought.(*626*)
Ernst Mach

It's not a matter of bringing all sorts of things together under a single concept but rather of relating each concept to variables that explain its mutations.(627)
Gilles Deleuze

Indeed, attempts at unifying sciences also originate from this conception; e.g., although quantum physics and general relativity, upon which modern physics is grounded, are thoroughly established for their own domains, they are irreconcilable for some questions. And because of the deep intuition that universe is unitary, unifying these two theories has been a major goal in physics for decades. Similarly, phenomena and entities like "living organism," "phenotype," "disease" or "hallucination" do not exist, nor are they currently explainable in the language of some particular science; e.g., physics(*628*). We see no concrete "label" on phenomena that would sort them exclusively to separate theories of quantum physics and general relativity or our arbitrary different scientific disciplines and therefore would necessitate the plurality of sciences. In other words, we have "dappled theories in a uniform world(*19*)"(*18, 20*). Unifying sciences is to dissolve these pluralities and differences by finding the universal fundamentals that give birth to these pluralities. Unification and showing the "natural and hidden kinship" of phenomena has even been noted as the essence of science(*607, 626*). Also, when great scientists stated the value of "beauty" in science, they implied this "sense of the harmony of the cosmos(*607*)," not "that beauty which strikes the senses(*607*)," as has been commonly misunderstood(*611-616*).

There is just one rock which weathers every storm, to which one can always hold fast: the assumption that the fundamental laws of nature correspond to a beautiful mathematical theory. This means a theory based on simple mathematical concepts that fit together in an elegant way.(*629*) P. A. M. Dirac
If, then, it is true that the axiomatic basis of theoretical physics cannot be extracted from experience but must be freely invented, can we ever hope to find the right way? […] I answer without hesitation that there is, in my opinion, a right way, and that we are capable of finding it. Our experience hitherto justifies us in believing that nature is the realisation of the simplest conceivable mathematical ideas. I am convinced that we can discover by means of purely mathematical constructions the concepts and the laws connecting them with each other, which furnish the key to the understanding of natural phenomena. Experience may suggest the appropriate mathematical concepts, but they most certainly cannot be deduced from it. Experience remains, of course, the sole criterion of the physical utility of a mathematical construction. But the creative principle resides in mathematics.(600, 601) Albert Einstein (emphases added)

What real-world advantage does simplicity have? Scientific theories are created constructs that try to explain observed regularities. These

explanations can be based on different angles or scales from which phenomena can be viewed; e.g., Darwinism was conceived based on phenotypic observations and with no knowledge of genetics, while its modern synthesis revolves around genetics and mechanisms of inheritance (see (*606, 630*) for other examples). The question is which scale can provide the most general theories. Generality requires that theories capture not just a pattern contingent on a specific set of observations and data, but could account for future observations. This can be achieved when theories become more independent from data(*630, 631*) and instead, capture "the simplest conceivable mathematical ideas*(600)*" from which all our diverse and complex observations emerge. Do not all empirical observations that lead to theories, finally boil down to some mathematical relationships between some variables? Therefore, theories closer to a priori justifications are more general, durable, and effective than those closer to a posteriori justifications and ad hoc principles(*632-635*); also see (*636, 637*). They are not contingent on the enforcement of those a priori principles on specific mediums and vessels. They capture the innermost fundamental principles themselves.

The proposed frameworks for biological sciences are replete with arbitrary and unnecessary conceptualizations which have been imposed on available observations(*57, 588-598*). Although these arbitrary concepts may provide insights sometimes, their ad hoc and a posteriori nature makes them incapable of guiding future directions. An exception to these not-simple theories is Darwinism: the most central theory of biology presented by Charles Darwin(*638, 639*) and Alfred Wallace(*638, 640*). Alas, its simplicity not only has not been appreciated, it even has put the theory under criticism since a little after the publication of *The Origin*(*641*).

Truism-Law-of-Survival

My theory […] might lead to laws of change, which would then be main object of study, to guide our speculations with respect to past and future.(*642*)
Charles Darwin

My reflection, when I first made myself master of the central idea of the 'Origin,' was, "How extremely stupid not to have thought of that!"(643)
Thomas Henry Huxley

Darwin's theory of natural selection came very late in the history of thought. Was it delayed because it opposed revealed truth, because it was an entirely new subject in the history of science, because it was characteristic only of living things, or because it dealt with purpose and final causes without postulating an act of creation? I think not. Darwin discovered the role of selection, a kind of causality very different from the push-pull mechanisms of science up to that time.(644)
B. F. Skinner (emphasis added)

The core concept of Darwinism is selection. *Survival-of-the-fittest* is another expression for selection which was devised by Herbert Spencer(*645*) and endorsed as "more accurate(*639*)" and used by Darwin(*639, 646*) and Wallace(*647, 648*). It implies a very simple concept: a tautology: a logical truism: survival of those who survive(*649*). Because of this, Darwinism has been claimed to have no explanatory power as tautologies have no explanatory power*(641, 650-653)* as they are circular definitions and always true(*605*)(also see (*654*)).

Intuitively, we see that this claim does not seem compatible with how Darwinism beautifully explains myriad observations. We can see Darwinism even in action in cases like antibiotic resistance(*655*). It even has been extended to theories of universal Darwinism and cosmic evolution to explain the origin of life on this planet((*598, 656-660*); also see (*661*)) and probably anywhere else in the universe(*662*) and the formation of all structures we see in the universe from the big bang(*663-667*). It is also employed in fields like evolutionary computation(*668*) and to explain diverse phenomena in various fields from psychology, neuroscience, and economics(*644, 651, 663, 669-675*) to quantum mechanics(*676, 677*).

Indeed, there have been extensive counter-arguments for the claim against Darwinism(*649, 652, 653, 678-685*); also see (*674, 686*). Yet here, I aim to put the unnecessary intricacies and assumptions aside and embrace this contested simplicity. The problem with the accusations of lack of explanatory power is that they suppose Darwinism's fundamental concept equals Darwinism. Albeit the theory is built upon a truism, its explanatory power results from investigating the consequences of numerous recursions of this truism.

We will see that "life" arises as surviving against the increasing entropy of the universe in the direction of the arrow of time. Survival, in any sense, implies continuing in the next time-step. Survival-of-the-fittest, which I embrace as *truism-law-of-survival*, is a simple law of change(*687*) implying that in a population(*684, 685, 688*) of organisms, the probability of all organisms to continue in the next time-step is not equal. This simplicity not only does not bereave Darwinism of its explanatory power but even endows it with fundamentality and universality. While being maximally simple, to the point of being accused of tautology, and dismissing unnecessary and ad hoc assumptions, Darwinism answers the complex question of evolution. We will see how all various "mechanisms" of evolution emerge from this simple core. Interestingly, truism-law-of-survival is the intersection of Darwin's *natural selection*, Friedrich Nietzsche's *will-to-power*(*689-692*), and two concepts that Darwin was probably influenced by: Arthur Schopenhauer's *will-to-live*(*693-695*) and, at least(*696*) through Schopenhauer(*693*), Benedict Spinoza's *conatus*(*697-700*).

Computational Complexity

But, are the numerous recursions that differentiate truism-law-of-survival and Darwinism, important at all? This question is not unlike asking if Laplace's demon is viable or not. Like how, by knowing all forces and states of all particles, it can shortcut the temporal evolution of the universe and have "the future, as the past, […] present to its eyes(*3*)," it can shortcut the emergence of Darwinism from truism-law-of-survival.

The problem with Laplace's demon and equating Darwinism with its fundamental core is dismissing *computational complexity*(*701-704*). Different steps of the process of evolution have been formalized numerously as mathematical functions(*705-712*) and have kindled the whole fruitful discipline of evolutionary computation(*668*). Such formalized sensitivities of the output of evolution to its initial conditions, merit the evolution of organisms, similar to the temporal evolution of particles in Laplace's model, to be viewed as computation(*713*) based on the behavioral definition of computation(*711, 714-717*), which itself is based on the well-established algorithmic information theory and Solomonoff-Kolmogorov-Chaitin complexity(*718, 719*). Computational complexity deals with practical resources required for carrying out a computation, like space and time. Moreover, the principle of *computational irreducibility* states that the behavior of almost any system whose behavior is not obviously simple, cannot be predicted "except by going through almost as many steps of computation as the evolution of the system itself(*720*)"(*721*); it was further formally defined as "to be unable to compute $f(n)$ without having to compute $f(i)$ for $i = 1$ to $n - 1$ (*722*)"(*723*) and corroborated by more evidence(*724-727*); also see *incompressibility in emergence*(*32, 628, 728-733*).

So, computational processes of the emergence of Darwinism from truism-law-of-survival and the temporal evolution of particles in Laplace's model cannot be circumvented by a shortcut formula, but this question remains if these irreducible computations are physically fundamental. This case is not the first time that the physicality and fundamentality of information and computation have been questioned.

The venerated second law of thermodynamics was under attack for decades by a thought experiment designed by James Clerk Maxwell(*734, 735*): He conceived "a being whose faculties are so sharpened that he can follow every molecule in its course(*734*)." Afterward, he argued that such a being [often referred to as Maxwell's demon] can violate the second law of thermodynamics, because it could use its information to sort the molecules in a closed container into two separate chambers of molecules with high and low energies and therefore, without the expenditure

of work, raise the temperature of one chamber and lower the temperature of the other and ultimately decrease the entropy of a closed system. During years, it has been realized that the aberration of Maxwell's demon is due to ignoring two physical fundamentals: information and computation(*735-748*). The sorting capability of the demon is inevitably compensated by increasing the environment's entropy; therefore, the second law of thermodynamics is not violated.

Computational complexity is a cornerstone of complexity. Usually, we have this preconception that complex phenomena are built on complex rules. Darwinism showcases a completely different approach. "Complex" phenomena are not the result of complex rules; they result from repeating simple rules numerous times. Cases of such emergence of complexity out of simplicity have been experimentally demonstrated by mathematicians like Alan Turing(*749*), John von Neumann(*750*), Stanislaw Ulam(*751, 752*), John Conway(*753-757*), Benoit Mandelbrot(*758, 759*) and Stephen Wolfram(*720, 760-765*). For instance, compare the complexity in figure 4B to the simplicity of its producing rule shown in figure 4A: Rule 30, which is an elementary cellular automaton rule(*720, 760*). This simple rule can give birth to aperiodic(*766*) and chaotic(*720*) behaviors that have even made it suitable(*767*) for random number generation(*768*). Complex patterns which have emerged from simple rules abound in nature, like in figure 4C.

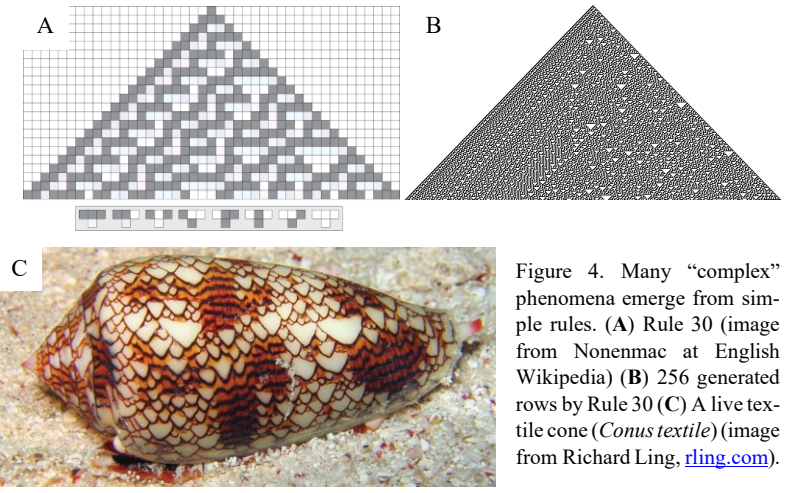

Figure 4. Many "complex" phenomena emerge from simple rules. (**A**) Rule 30 (image from Nonenmac at English Wikipedia) (**B**) 256 generated rows by Rule 30 (**C**) A live textile cone (*Conus textile*) (image from Richard Ling, rling.com).

Fundamental Core of Organisms
What is Life?

To build a general framework for biological sciences, we shall rewind all the complexities of their objects of study, organisms, to their innermost fundamental core. As Darwin conjectured in *The Origin*(*639*), it is established that all organisms share a common ancestor: the last universal common ancestor (LUCA)(*769, 770*). Now we must investigate how we can distill this common point to its innermost fundamental core.

Although universalized versions of Darwinism and selection are often invoked to explain the origin of "life"((*598, 656-660, 662*); also see (*661*)), because of the confinement of Darwinism and even its modern synthesis to already-"alive" organisms, the origin of life has "remained an open debate"(*771, 772*). Here we have synthesized a simpler and more fundamental version of Darwinism that can resolve this problem.

Imagine inside the primordial aquatic mixture that eventually gave birth to life, a volume with an arbitrary boundary containing several particles (figure 5) (please forgive my casual use of the word "particle" in this article; the more accurate term is "physical entity"). These particles will not remain inside the initial boundary(*773*). After some time, through random Brownian motion and diffusion, these particles get away from each other to the extent that the initial boundary loses its meaning(*773-776*). Why this happens goes back to the only law of physics which implies the irreversibility of the arrow of time(*777, 778*): Entropy of a closed system, like the whole universe, tends to increase. The second law of thermodynamics is another exemplarily simple scientific construct (especially due to its statistical mechanics interpretation(*779-782*); also see (*783-785*)). This simplicity has garnered it a "supreme position among the laws of nature":

The law that entropy increases—the second law of thermodynamics—holds, I think, the supreme position among the laws of Nature. If someone points out to you that your pet theory of the universe is in disagreement with Maxwell's equations—then so much the worse for Maxwell's equations. If it is found to be contradicted by observation—well, these experimentalists do bungle things sometimes. But if your theory is found to be against the second law of thermodynamics I can give you no hope; there is nothing for it but to collapse in deepest humiliation.(778)
Arthur Eddington

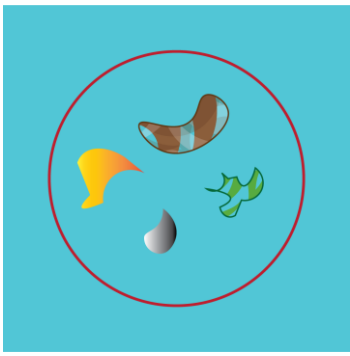

Figure 5. Several particles imagined inside the primordial mixture (the cyan background). By the passing of time, the particles distance from each other and the imaginary boundary encapsulating them (the red circle) gradually gets bigger.

However, the consistent distancing of particles from each other depends on two presumptions: The probability of particles moving in each direction must be equal and the number of particles must be so small that their effects on each other would be negligible(*786*). Surely, in the primordial mixture, particle-containing volumes could be found which did not abide by these conditions. Here, truism-law-of-survival takes place along the second law of thermodynamics. Diverse interactions may take place between particles. Because of the diversity of particles and physical parameters in the primordial mixture(*658, 787*), various volumes may appear whose particles form reciprocal processes and interactions which counter the particles' being carried away by random motion and thus preserve their boundaries longer, to varying degrees(*598, 788*). These surviving volumes are completely in contact with the "environment." They may lose their "distinction" with the "environment" and dissolve into it and become again a part of it, or merge with some other molecules and expand the processes that would enable and further preserve their "distinction" from the "environment." These process-expansions may give their volumes different abilities, like the ability to absorb and employ energy or to replicate(*660, 789-791*). Those groups of particles forming interactions that would delay more their dissolution by the increasing entropy would also have more time to expand their processes and abilities. After further evolution on this path(*657*), we can recognize what might be labeled as "living" cells(*792, 793*): processes that not only survive for much longer by cementing their boundaries with the "environment" and employing the available energy for preserving their inhomogeneities, but also can expand and transform themselves by continuing their flow through materials available in the "environment" and keeping many of their previous process-expansions. Such surviving sets of processes can expand and propagate far more rapidly(*660*). They can be considered as contagious inhomogeneities. Such a process gave birth to all organisms.

So, what is it that we identify as a "living organism"? This question is pertinent to what is purported to be "one of the most frustrating unsolved problems" of biology: definition and nature of "life"(*9, 588, 794-803*). Over 135 definitions have been proposed during decades, yet it has remained "a main fundamental challenge" for biology: "a science in which the most important object has no definition(*802*)." Apart from its purported epistemic importance, solving this problem has been noted to have applied significance; e.g., NASA's latest *Astrobiology Strategy* states that "Recognizing life on other planets depends on how scientists define life(*804*)."

A few have suggested that reaching consensus in defining "life" is inevitably futile((*801, 805-810*); also see (*811*)) and our real problem is that we "lack a general theory of the nature of living systems and their

emergence from the physical world"(*801*)"(*805-807, 812*). These researchers compare the enduring frustration in defining "life" with the frustration in defining water before molecular theory(*801, 807*).

We can see that all organisms that exist today are the continuation and expansion of that surviving process after incomprehensibly numerous recursions of truism-law-of-survival (figure 6). With simplicity and without "feigning hypotheses"(*813, 814*), "life" can be described as a single process surviving against the dissolving tendency of the universe, which has undergone numerous recursions of truism-law of survival and in doing so, has expanded and transformed into all existing organisms. Survival denotes prolonged proximal interaction between a group of physical entities; i.e., staying together against what would be otherwise the distancing of particles from each other according to the tendency of the universe to approach thermodynamic equilibrium and maximum entropy(*55, 815, 816*). "Life" has not survived *despite* the increasing entropy of the universe: "Life" *is* survival against the increasing entropy of the universe. The increasing entropy of the universe not only is not contradictory to "life," but is its ingredient(*817-820*). If the "antagonistic" tendency of the increasing entropy had been absent, survival-against-it would not have existed either. Still, it is important not to subvert this attitude with teleological fallacies like in (*821-829*). There may be found some tendencies regarding why organisms have developed and expanded(*787, 830-832*), yet the supreme and the simplest verdict belongs to truism-law-of-survival.

The effort of a thing to preserve itself is nothing but the very essence of the thing.(*697*) Benedict Spinoza

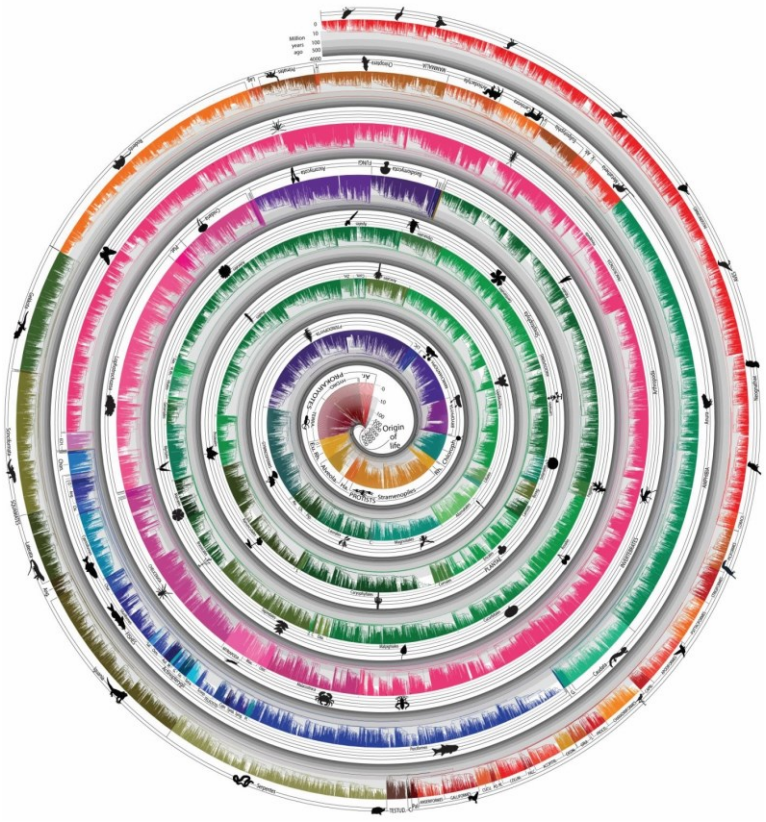

Figure 6. A timetree of 50,632 species synthesized from times of divergence published in 2,274 studies. Time is shown in billions of years on a log scale and indicated throughout by bands of gray. Major taxonomic groups are labeled and the different color ranges correspond to the main taxonomic divisions of the tree; from Reference (*769*).

This conceptualization of "life" also covers cases of virtual or artificial "life" (see video)(*833-839*); and therefore, seems to be a "universal theory of life"(*596, 771, 807*). It also clarifies that organisms are not merely "products of chance and error(*840*)" and lucky flukes. On the contrary, Darwinism is as true and simple as a logical truism. Due to the universality of both the increasing entropy and truism-law-of-survival, "life" and increasing complexity are natural consequences of diverse ingredients and *goldilocks conditions*(e.g., (*655, 841*)): the thin edge between "uninteresting" chaos and "uninteresting" order. In too-high temperatures, the tendency of entropy to increase is so high that it cannot be survived. In too-low temperatures, the tendency of entropy to increase is so low that there is not much to survive against. Yet, once that a suitable condition is provided, "life" is inevitable. That is why "life" seems to have emerged so soon on Earth(*842*).

Processuality
The Increasing Complexity

We are but whirlpools in a river of ever-flowing water. We are not the stuff that abides, but patterns that perpetuate themselves.(843)
Norbert Wiener, one of the fathers of cybernetics

We have sought for firm ground and found none. The deeper we penetrate, the more restless becomes the universe, and the vaguer and cloudier. […] There is no fixed place in the Universe: all is rushing about and vibrating in a wild dance.(844) Max Born

We described "life" as a single process (figure 6); importantly, it is not the particles temporarily staying together, it is the process that flows through different materials and through prolonging their staying together, has survived itself.

This processual attitude(*34, 55, 287-294, 816*) emphasizes the fundamentality of a physical dimension of organisms which has often been neglected because of the dominance of machine mindset and foundationalist materialism: time. Organisms are dynamic *becomings,* rather than static *beings* and material structures. So, criticizing the "materialism" in "foundationalist materialism" is not to advocate for the non-physical and supernatural. On the contrary, it is against sticking to "a momentary cross-section through spatiotemporal pattern(*288*)."

An organism is an event—something happening. It is temporally as well as spatially extended. It has temporal as well as spatial parts. Your pet dog to-day and your pet dog yesterday are two different temporal parts of the same dog, just as his head and his tail are two different spatial parts of the same dog. It is in virtue of the particular kind of continuity of the dog yesterday and the dog to-day that we call it the 'same', and this seems to be the proper sense of the term. But it can no more be taken for granted that today's temporal part is the same as yesterday's than it can be taken for granted that one spatial part, e.g. the head, is the same as another, e.g. the tail. We know, in fact, that they are not the same. Organisms are temporally as well as spatially differentiated.(*287*) Joseph Woodger

This processual perspective is also important for solving another dilemma parallel to the dilemma of defining "life": Why has the complexity of organisms been rising? Why are we more complex than LUCA? Is there an innate tendency or driving force? This was also a problem for Darwin(*845*). Many answers have been proposed(*777, 846-851*); e.g., "zero-force evolutionary law" has been presented which states that the tendency toward more complexity and diversity is the default behavior of evolutionary systems and is independent of any "force" or "constraint" such as selection(*852-856*).

This dilemma can be divided into two questions: Why do constituent elements of "complexity" arise? And Why does a large amount of these elements accumulate in some organisms?

For the second question, all organisms are continuations of that single process that has survived and kept many of the previous process-expansions forged during its survival(*857*). We are more "complex" than our ancestor bacteria which lived two billion years ago because we are later sections of the process of "life" which was previously mediated by "them." Because of this, we have inherited some of the "complexities" that have been added to the process of "life" since two billion years ago; just like how the corpus of knowledge we possess today is more "complex" and diverse than the corpus of knowledge our ancestors possessed. Division of the single process of "life" to separate individuals is arbitrary; the concept of "organism" should not be reified.

But why did not this single process remain "simple"? Imagine that after evolving to the first bacteria, "life" continued in two branches: one where the bacteria remained simple by, e.g., maximizing fidelity and the other where random variations were possible. We know we are the continuation of the second branch and not the first. But not because of some "zero-force evolutionary law" independent from selection. Exactly because of selection or, perhaps better to say, truism-law-of-survival. Increasing entropy of the universe constantly propels "random" shuffling and variation at lower scales. The branch that embraced variability and diversity became able to explore novel interactions and processes which could provide novel capabilities and synergisms(*858-861*) and expand into novel surviving "adjacent possible"(*862-868*) wholes: a random walk(*869*) exploring possibilities based on truism-law-of-survival(*846, 849, 870-872*). Evidence corroborates this: Organisms have been selected and evolved for their capability to become diverse(*359-372*).

Especial Importance of Simplicity in Biology

Biology occupies a position among the sciences at once marginal and central. Marginal because—the living world constituting but a tiny and very "special" part of the universe—it does not seem likely that the study of living beings will ever uncover general laws applicable outside the biosphere.(873)
Jacques Monod

Most of the quotes we reviewed on simplicity were from great physicists; nevertheless, I assert that simplicity is far more important in biological sciences. First, biological phenomena themselves can be traced back to numerous recursions of very simple phenomena. Second, uniqueness is a hallmark of biological phenomena compared to most physical ones(*874, 875*) (a reason for this can be the far larger share of non-ergodicity in biology(*772, 862, 876, 877*)). Third, "life" is itself a unique and "marginal" process in the universe, not prone to universal inductions like what we see in physics*(873)*.

General biological theories must be based on so simple and fundamental justifications that they become independent from data(*630, 631*); and therefore, would inevitably capture behaviors of organisms, despite uniqueness and marginality.

Alas, many general theories presented in biological sciences try to capture all observed phenomena with all their unique intricacies, so that they may a posteriori reach, to some point, the predictability of physical theories. But even physical constructs, like Newton's equations, do not explain the real world with all its intricacies; they provide an ideal general framework that can guide further detailed pragmatic analysis. To be universal, what general biological theories need is exactly the opposite of the current trend: more independence from data. Conflating the aim and nature of general theories and detailed ad hoc theories has been one of the great impediments to the progress of biological sciences.

Darwinism itself is the best place to investigate this assertion. The modern synthesis tried to update Darwinism by incorporating the knowledge (particularly Mendelian and population genetics) that was gathered since its initial conception. This a posteriori synthesis, because of its ad hoc nature, was doomed to be incapable of explaining many phenomena. Now, decades have passed, and we have become much more aware of the phenomena that were not included in the ad hoc principles of the modern synthesis. Consequently, many have been calling for a new postmodern synthesis of Darwinism in which the newly observed phenomena have also been incorporated(*201, 598, 878-898*); on the other hand, also see (*898-905*) and (*906*).

The explanatory power of Darwinism is not due to its empirical observations, but due to its simplicity (albeit, as Einstein remarked, "experience remains, of course, the sole criterion of the physical utility*(600)*"). Although Darwinism cannot provide "accurate" predictions like that of Newton's equations, it has provided illuminating explanations and guidance(*678, 874*). Indeed, principles like computational irreducibility and no-free-lunch theorem(*907*) imply the infeasibility of a formula for evolution that would be predictive like Newton's(*857, 908, 909*).

The correct way to extend Darwinism is not to append ad hoc principles based on a posteriori observations, but to simplify it to the more fundamental principles which underlie not only the observations of Darwin and Wallace, but also the new and future observations. Therefore, I suggest that the calls for a new synthesis are best addressed by truism-law-of-survival. It is based on a priori justification and is much simpler than the original account of Darwinism which was itself based on a posteriori justification of limited phenotypic observations. It accounts for all diverse new observations missed by the modern synthesis. It clarifies why Darwinism is endowed with universality and by decoupling Darwinism from biological inheritance, covers the origin of life. Finally, it is the basis of a theory for the evolution of organisms' internal workings.

Having rewound all the apparent complexities and diversities of organisms to the simple core of truism-law-of-survival and staying together of a group of particles against the increasing entropy of the universe, as Descartes advised, let us derive "absolutely simple(*584*)" laws from this simple fundamental core.

Internal Evolution: Emergent Bound Box Theory

According to the second law of thermodynamics, if there are no interactions among some particles in an aquatic mixture and they be free to show all behaviors they show when they are isolated, they get exceedingly more distant from each other(*773-776, 786*). For a group of particles to stay together, each particle, and consequently the whole, is bound to a subset of all its possible states.

Staying together, i.e., survival, of a group of particles against the increasing entropy of the universe, like the entropy itself, is only relevant for the whole of a group of particles, not individual particles.

Increasing entropy of the universe constantly creates variations at lower scales without restriction.

As survival is only relevant for the whole of a group of particles, truism-law-of-survival is enforced at wholes and higher scales.

This discrepancy of freedom of variability between lower and higher scales creates a bottleneck of variation at higher scales; if several lower scales converge to the same surviving higher scale, they all may survive.

Having evolved to perceive those differences that would make the most difference to their behaviors, organisms create higher-scale descriptions with superior cause-effect power.

Further Elaboration and Evidence

If Darwinism explains the evolution of the diversity and complexity that an outside observer recognizes among organisms, emergent bound box theory explains the evolution of the diversity and complexity among organisms that an observer may recognize from an intrinsic perspective (to accurately grasp what is implied by "intrinsic perspective," see (*910*)): It explains the evolution of organisms' internal workings.

Truism-law-of-survival bounds actuality as it implies that not all survive. It decreases the degrees of freedom(*11, 184, 911-915*) of parts and wholes of the initial unevolved volume to those compatible with surviving. Some associations can be captured between this conceptualization and symmetry-breaking: formation of a priori statistically improbable*(916-918)* patterns from a homogenous background(*30, 55, 787, 816, 919-928*). When parts of organisms get isolated from wholes, they get stripped of the integrated bounds that maintain these enabling states and become ontologically different processes. Thus, foundationalist materialism is unambiguously wrong about the workings of organisms. In vitro and ex vivo measurements may have no contact with the reality of in vivo processes. "In addition to the differential equations you need the initial and boundary conditions," Denis Noble elaborates(*253, 929*). These bounds are imposed by other parts of the human body and cannot

be revealed by investigating isolated parts(*930*). Even the most complete knowledge of the properties of isolated parts does not enable knowing organisms.

Which scales are bounded the most? Lower or higher scales? The increasing entropy "randomly" creates variations at lower scales, like DNA mutations. This "randomness" liberates "lower" scales from being bound to specific variations. Yet such unbounded variations cannot continue surviving at higher scales. Surviving consequent phenotypes of these "free" and "random" variations are bounded by truism-law-of-survival to phenotypes that are compatible with survival.

This has crucial consequences for the internal workings of organisms. Imagine a continuous flow that must inevitably become discrete because of running into some constraining barriers (figure 7) (because of survivability and principles of divergence and competitive exclusion(*639, 931-944*); also see (*945, 946*)). If several varied genotypes and internal workings lead to the same optimal phenotype (degeneracy), selection or truism-law-of-survival does not discriminate between them in an identical environment. Enforcement of truism-law-of-survival at higher scales forces lower-scale variations to converge into optimal phenotypes, during generations. This is why degeneracy abounds in biological systems(*51, 206-215*).

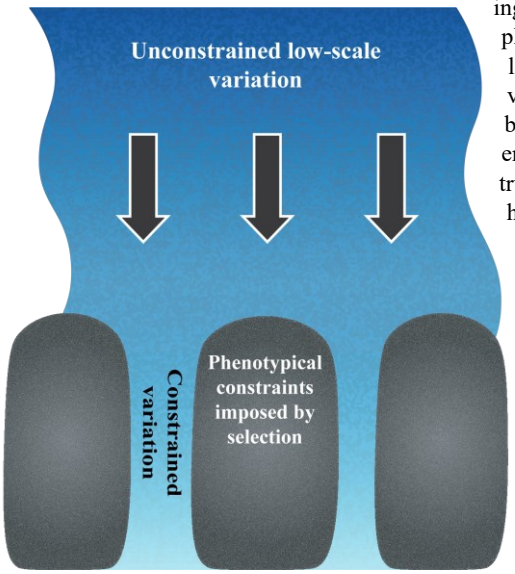

Figure 7. The discrepancy of freedom of variability between lower and higher scales. The unconstrained low-scale variation gets bounded at higher scales by truism-law-of-survival. This creates degeneracy in the internal workings of organisms.

Although these arguments seem simple and logical, and aligned with the observations we had on the discovery origins, promiscuity of "target-based" drugs, and the role of lower-scale states, let us investigate them more rigorously. Fortunately, *integrated information theory* (IIT), developed by Giulio Tononi and his colleagues, provides a mathematical(*947*) framework for this aim(*305*). Although this formalized theory, whose predictions are corroborated by mathematical and empirical evidence(*948-953*), is under investigation and some criticisms for its validity in explaining consciousness(*954-956*), its applicability for investigating *causal structures* of various systems from the "intrinsic perspective" of systems themselves is well-documented(*949, 950, 957-965*); also see (*966, 967*). It adheres to *counterfactual*(*423, 968, 969*) and *interventionist*(*970-973*) accounts of causality(*961*). In summary, IIT investigates "how the parts of the system, by being in a specific state, constrain the potential past and future states of the system itself(*960*)."

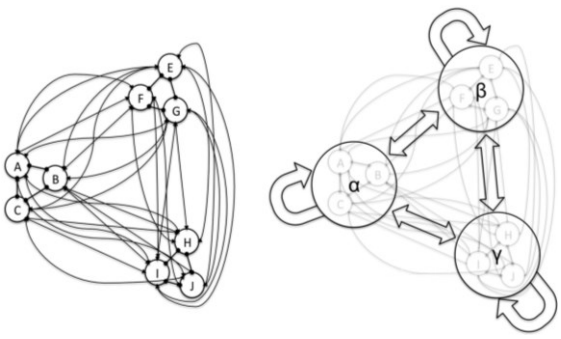

Figure 8. Average-based coarse-graining. A method of converting lower-scale to higher-scale descriptions; from Reference (*959*). ©2013 by National Academy of Sciences

Using the insights and tools provided by IIT, it has been shown that describing systems' states at spatiotemporally *coarse-grained* (figure 8) higher scales can increase information and *intrinsic cause-effect power (Φ)*(*44, 215, 959-961, 974*). This increase is mainly because of increased captured specificity of systems' mechanisms at higher scales, as noisy (indeterministic) and degenerate micro elements are grouped into more deterministic and less degenerate higher-scale descriptions. Later, along with confirmation in a biological model, it was shown that spatiotemporal higher-scale descriptions may provide even more intrinsic cause-effect power through *black-boxing* compared to average-based coarse-graining, especially in systems with heterogenous, integrated specialized parts, epitomized by organisms(*961, 974*). Black-boxing was first proposed in cybernetics to enable modeling highly complicated and complex systems by hiding their inner workings and only preserving their inputs and outputs(*975-978*). Black-boxing increases intrinsic cause-effect power mainly through increasing the system's irreducible integration, joint constraints, and the emergence of higher-scale specific mechanisms(*961*). Mechanisms of how coarse-graining and black-boxing increase cause-effect power, corroborate our arguments regarding the emergence of bottlenecks of variation at higher scales through the enforcement of truism-law-of-survival on these scales.

All these superior cause-effect powers in coarse-graining and black-boxing are achieved despite complete *supervenience*(*979*) of higher scales on lower scales(*959-961*). Nothing extraneous and non-physical is added to physical processes.

It must be noted that concepts of "whole" and "part" in the theory are relative like "higher" and "lower"; these must not be reified. Darwinism extends from the lowest to the highest scales of the temporal evolution of the universe. Truism-law-of-survival simultaneously selects among a multitude of possible futures of the whole universe. This can be vividly seen in *group-level selection*(*980-985*). Still, the far larger share of non-ergodicity in the world of biology(*772, 862, 876, 877*) may imply asymmetries in the significance and application of emergent bound box theory for biological and physical phenomena.

It is fair to look again from distance and ask if these principles we have derived from the fundamental core of organisms, also apply to the behaviors of organisms themselves. All currently established mechanisms of evolution(*986-988*) suggest that evolution of all organisms from LUCA has been, one way(*989-992*) or another(*993-995*), based on gradual tinkering(*996*) and *hill-climbing* toward local or global optima in fitness, i.e., survival, landscapes(*166*). This suggests organisms are, as we expected, extensions of the fundamental core and we may be confident that the principles we have derived apply to behaviors of all organisms.

Biological Sciences and Physics Unified

One of the principal objects of theoretical research in any department of knowledge is to find the point of view from which the subject appears in its greatest simplicity.(997) Josiah Willard Gibbs

Why are there several sciences instead of only one? Now that we have got the technological capabilities, should we try to see all biological phenomena through the supposedly accurate lens of physics? Should we, e.g., see and investigate the effects of candidate antidepressants on humans as changes that they trigger in states and motions of countless atoms of the brain, or should we see this same phenomenon (because of physicalism) as changes that they trigger in mood, behaviors and mental phenotypes of patients? "Rational" drug design has wasted lots of resources and hopes by answering these questions uncritically.

We saw emergence has been proposed as the reason behind the necessity of several sciences, but it has failed to convince most of the scientific community. A problem is that the word *emergence* has been applied for several disparate phenomena. Let us disentangle and investigate these various applications:

A. Are wholes more than the sum of their parts?

Yes, due to the physicality of information. Wholes are the sum of their isolated parts plus their organizing patterns. Emergent bound box theory

reinforces this fundamental and physical difference because isolated parts do not contain information on how they are bounded in wholes. This bears some associations with *fusion emergence* proposed by Paul Humphrey((*37, 998, 999*); however, with important differences toward supervenience(*1000, 1001*) and "downward causation"(*998-1000*); also see (*1001-1004*)) and *transformational emergence*(*37, 1004-1007*).

B. Diachronic or computational emergence

Knowing "all the forces by which nature is animated and the respective situation of the beings who compose it(*3*)" in one instant in 5 billion years ago, could Laplace's demon have "the future, as the past, […] present to its eyes(*3*)" and predict the behaviors of organisms today? As we saw, computational complexity and irreducibility imply the incompressibility of the temporal evolution of an emergent phenomenon by a shortcut formula(*32, 628, 728-733*). This computational irreducibility is multifaceted:

What needs to be computed by Laplace's demon? Evolution can be considered as a computation whose each step's output is the continuation of those of its input processes that survive, along with their "environment." Survivability of processes has meaning only relative to their "environment." There is no concrete demarcation between organisms and the "environment." Thus, the computation cannot be reduced only to organisms. Evolution of the whole universe must be computed. Moreover, the demon cannot surrogate this cumbersome computation by simulating the evolution of simpler models. Properties like chaotic consequences of models' errors(*1008*), historical contingency of evolution(*847, 1009-1011*), and abundance of exaptations suggest that no property can be deemed negligible(*1012, 1013*). Organisms are not deducible from the most complete knowledge of the properties of their isolated parts because their constituting processes are not the only things that have had a role in their formation. Organisms also embody millions of years of irreducible computation. This unambiguously attests autonomy of biological sciences(*29*) and the impossibility of deducing organisms from physics. An illuminating example is group-level selection(*980-985*). All different possible ensembles of societies inevitably adhere to simple rules of physics, yet their collective survivabilities are varied. Only a subset of them have survived recursions of truism-law-of-survival and are now social sciences' objects of study. Bounds that have emerged during these recursions(*11, 184, 911-915*) are not included in physics(*1014*).

The ability to reduce everything to simple fundamental laws does not imply the ability to start from those laws and reconstruct the universe. In fact, the more the elementary particle physicists tell us about the nature of the fundamental laws, the less relevance they seem to have to the very real problems of the rest of science, much less to those of society.(*30*)
Philip Anderson in his classic "More is different"

* Following Mayr(*29*), I propose we restrict the use of *reductionism* only to the fallacious attitude; and instead, use *analysis* to imply investigating lower scales.

C. What is lost in trying to reduce higher-scale descriptions of biological sciences to lower-scale descriptions of physics, like in "rational" drug discovery?

Noteworthy, "rational" drug discovery does not completely reduce higher-scale to lower-scale descriptions. For this, it had to investigate the effects of chemicals on states of <u>all</u>, e.g., molecules upon which a higher-scale state, e.g., hallucination supervenes. As mathematically shown by IIT, even if it could do that, it was reducing the cause-effect power of its descriptions(*44, 215, 959-961, 974*). This is a case of synchronic or combinatorial emergence which emphasizes the irreducibility of higher-scale to lower-scale descriptions(*32, 628, 729-733*).

D. But from where do these higher scales of biological sciences emerge?

This question is behind the aura of obscurity and magic surrounding emergence. How does a unitary universe get dappled into exclusive theories and "levels"(*18-20*)? Phenomena like "disease" or "hallucination" are unexplainable in physics. Did not we completely adhere to physicalism and the unitariness of the universe? Why do not we "see" all phenomena of this one universe with the language of physics? Where do cell, tissue, organ, organism, and society come, i.e., "levels of organization"(*41, 168, 1015-1024*), come from?

These questions can be answered by unifying biological sciences with physics; by dissolving the seeming plurality of ontological novelties of biological sciences and fundamentals of physics in their "natural and hidden kinship(*607*)" and common origin. I conjecture that the emergence of ontological novelties of biological sciences goes back to the previous case of emergence(C): the more cause-effect power endowed by higher-scale descriptions.

Organisms' perception of the universe has evolved according to perceptions' contributions to survival. What to sense and how to perceive it depend on how the perception will guide behaviors and how those behaviors would survive and change in recursions of truism-law-of-survival(*1025*). Organisms do not "see" all phenomena through the "lens of physics," as such lower-scale descriptions of "reality" do not specify the most differences that would make a difference in behaviors of surviving organisms. By converting this lower-scale information to higher scales(*44*), organisms have reached more cause-effect power in their perceptions and pattern recognitions.

This shows that our view of the "objective reality" is completely subjective. A much milder case of such subjective perceptions of reality is wishful seeing(*1026-1030*); also see (*1031*).

So, unlike many who have tried to unify sciences by reducing all of them to physics(*14, 16*), we have dissolved the apparent disunity of sciences while showing that the autonomy of biological sciences from physics is itself based on the physical fundamentality of information(*12, 21, 29*). Any dream for an ultimate "theory of everything"(*1032-1034*) that would "in principle" be able to substitute all other sciences is futile; the mistake has been presupposing that this "in principle" is not something physically fundamental; e.g., (*22, 1032, 1035*).

Indeed, patterns sought for many purposes become *decoupled(43, 1036)* from lower-scale descriptions. We can predict how other people will probably respond to many of our actions based on the pattern we have learned between input actions and output responses of black-boxed humans(*1037*). our ancestors could identify poisonous and therapeutic substances by recognizing patterns between them and the changes they made to states of the black-box of the body. In data analysis, suitable songs and videos are being recommended to us considering nothing about the inner workings of our nervous systems and only based on analyses of the data on responses of humans to input songs and videos.

Black Box theory is, however, even wider in application than these professional studies. The child who tries to open a door has to manipulate the handle (the input) so as to produce the desired movement at the latch (the output); and he has to learn how to control the one by the other without being able to see the internal mechanism that links them. In our daily lives we are confronted at every turn with systems whose internal mechanisms are not fully open to inspection, and which must be treated by the methods appropriate to the Black Box.(*977*)
Ross Ashby, one of the fathers of cybernetics

We may recall that "rational" drug design and reductionist neuroscience, hung up on the technologies that have enabled delving into the black-box of the body, focus almost only on the inner workings of the box and majorly spare the superior cause-effect power of higher-scale descriptions. Interestingly, the ultimate importance of these levels has still kept them in "rational" drug design as terminal filters and validations (human trials) and in neuroscience where "behavior [is] incorporated as an afterthought(*51*)"(*49, 282*). In these paradigms, higher-scale descriptions and investigations not only are not prioritized, they do not even inform primary goals; e.g., structures of designed molecules.

"Downward Causation" Non-Reducibility of The Universe

I too play with symbols […]; but I play in such a way that I do not forget that I am playing. For nothing is proved by symbols […]; things already known are merely fitted [to them].(1038) Johannes Kepler

There are also idols formed by the reciprocal intercourse and society of man with man, which we call idols of the market, from the commerce and association of men with each other; for men converse by means of language, but words are formed at the will of the generality, and there arises from a bad and unapt formation of words a wonderful obstruction to the mind. Nor can the definitions and explanations with which learned men are wont to guard and protect themselves in some instances afford a complete remedy—words still manifestly force the understanding, throw everything into confusion, and lead mankind into vain and innumerable controversies and fallacies.(*1039*) Francis Bacon

Names and attributes must accommodate themselves to the essence of the things, and not the essence to the names, because things come first and names afterward.(1040) Galileo Galilei

What can be said at all can be said clearly, and what we cannot talk about we must pass over in silence.(*605*) Ludwig Wittgenstein

Along with the debates on emergence, there have been unsettled debates around *downward causation* in emergent phenomena. Many argue for it (*32-34, 924, 1041-1046*), while many contend that its existence is in violation of the *causal closure principle* of the physical realm and consequently reject both "downward causation" and emergence(*34, 1047, 1048*), as it is claimed that "downward causation" is a necessary feature of emergence(*34, 929, 1041, 1047, 1048*)(also see (*998-1000*)).

These confusions arise from two fallacies: first, reifying the arbitrary concept of causation; second, imagining a set of phenomena cross-sectioned and isolated from the irreducible temporal and spatial landscape of the universe.

Causation is an arbitrary abstract concept that is formed early in life(*1049-1052*) to denote difference-making, similar to counterfactual(*423, 968, 969*) and interventionist(*970-973*) accounts of causation(*1053*). Due to the fallacy of misplaced concreteness(*1, 376, 377*), it has been reified in some discussions around "downward causation" as a real physical force; e.g., electromagnetic force. This has consequently culminated in many unnecessary debates which ultimately have no contact with reality. Karl Pearson(*1054*), Bertrand Russel(*1055*), and Willard van Orman Quine(*1056*) have already highlighted the pervasiveness of such fallacies and misconceptions around the concept of "causality"; also see (*1057-1059*).

Another fallacy is the presupposition that the entirety of the process of the universe can be reduced to a singleton(*1053*) of isolated parts in vacuo(*1060*); also see(*284, 1061-1063*). This false presupposition has consequently led to reifying the arbitrary concept of *level*; and thereafter, the arbitrary concepts of *downward*, *upward*, *top*, *bottom*, micro, macro, part, and whole*(1064)*. The only truly closed system is the whole universe. These separations are all arbitrary and not physically realistic; therefore, the dilemma of "levels of organization"(*41, 168, 1015-1024*) goes back to conflating the arbitrary and the concrete.

Universality of Emergent Bound Box Theory

A theory is the more impressive the greater the simplicity of its premises, the more different kinds of things it relates, and the more extended its area of applicability.(1065) Albert Einstein

As emergent bound box theory hinges upon simple logical consequences of truism-law-of-survival, we can expect, like Darwinism, its domain would be universal. Let us inspect some patterns from diverse fields that comply with the theory: emergence of more predictable higher scales by bounding of lower-scale variations to those that are compatible with surviving wholes. Analogous patterns from diverse fields can increase our confidence in theory by showing consilience(*1066*) and independence from data and ad hoc principles. However, some of the analogous patterns, like the global stability of strange attractors, are based on an inclusive conception of some principles of the theory.

Decoherence & Quantum Darwinism

Best possible knowledge of a whole does not include best possible knowledge of its parts; and that is what keeps coming back to haunt us […] The whole is in a definite state, the parts taken individually are not.(*1067*) Erwin Schrödinger

Quantum mechanics which has been confirmed to accurately explain the foundations of the universe is replete with fuzziness and uncertainty. The principle of *quantum superposition*, one of its cornerstones, forbids predicting one exact value for a quantum state. All valid values and even all their combinations are valid for a quantum state and a single value cannot be pinned down and predicted. This has been experimentally observed in photons(*1068, 1069*), electrons(*1070, 1071*), atoms(*1072*) and huge molecules(*1073, 1074*). This principle is even central in quantum computing. Objects we see every day are not at the same time at multiple positions. Humans can "objectively" agree on the exact position of an object. It was this "objective" exactness and the ensuing predictability that deluded Laplace. So, how does the unpredictable quantum world give birth to our predictable world and why don't we observe "paradoxical" cases like Schrödinger's cat(*1067*)?

Quantum Darwinism(*676, 677*) which complements the theory of decoherence(*1075, 1076*) and environment-induced superselection (einselection)(*1077, 1078*), currently provides a satisfactory and empirically confirmed(*1079-1082*) explanation (also see (*1083*)). We saw that the behavior of an isolated part is not predictive of its behavior in the body as it gets bound in compliance with a surviving whole. Analogous to this pattern, uncertainty and unpredictability of quantum states are for when quantum systems are isolated from their environment. After interacting and getting *entangled* with the environment, *decoherence* takes place. Superposition reduces by irreversible elimination of the off-diagonal elements of the density matrix and the *environment-induced selection* (einselection) of the set of probabilities that are permissible in the "classical" world. Then, just like how the varying viable sets of processes are further constrained by recursions of truism-law-of-survival according to their interactions with the "environment," among these permissible states, "objective" classical observables emerge(*1034*) through interactions of permissible states with "environment" and selection of "objective" classical observables (see (*1084*) for why even here, there is no concrete demarcation between the system and the "environment," hence why I have it quoted). Quantum states may propagate multiple imprints of themselves(*1085*) and they compete in doing so as the capacity of "environment" is limited for this propagation according to no-cloning theorem(*1086*).

"Objective" classical states are emergent as they "are not deducible from the most complete knowledge of the properties of their isolated parts"(*998, 999, 1002, 1087-1089*).

Effective Field Theories & Renormalization Group

To accurately analyze the diffusion of a gas or the speed of sound in it, we do not need to know all variables of all individual particles of the gas. For gaining accurate insights about many atomic and molecular properties, we do not need to know anything about elementary particles like quarks and leptons. Similarly, Newton presented laws that could predict accurately the mechanics of celestial bodies, that we still use, knowing nothing about quantum mechanics that may explain exactly their microscopic underlying. These higher-scale theories that are decoupled(*43, 1036*) from more "fundamental" distantly lower-scale theories and discard much of their details without sacrificing accuracy are *effective field theories* and are indispensable and ubiquitous in physics(*1036*); e.g., their role in quantum field theory has been crucial, particularly through renormalization theory and the renormalization group(*1090-1093*). Indeed, many physicists consider all current physical theories, including

the Standard Model, to be effective field theories(*1090-1092*) and attribute our capability to explain and predict natural phenomena to such theories(*1094*).

They can be viewed as theories that use higher-scale descriptions by "black-boxing"(*1091, 1095, 1096*). This way, they can capture emergent phenomena better than lower-scale descriptions(*928, 1034, 1090, 1097-1099*) and also may provide additional insights toward mechanisms of observed behaviors(*1095*).

Using Fisher information matrix, it has been quantitatively shown that the reason for the emergence of simpler higher scale descriptions that could be explained by simpler theories is that many spatially or temporally higher-scale behaviors depend only on a few parameters and most of the parameters of lower-scale behaviors bear little importance(*1094, 1100*). This also happens in other fields, particularly biological models(*302, 1094, 1100-1105*). This is because the degrees of freedom of parts get bound through other parts they interact with, to those behaviors that are compatible with survival of their wholes; analogous to how parameter spaces of organisms compress compared to the parameter spaces for the mere aggregation of their isolated parts. The pattern of emergent simplicity at higher scales can be found in many places(*1106-1109*).

Deep Learning

Many are awed by the impressive capabilities of deep learning. As a predictive data analytics tool, it provides more accuracy compared to other ML methods and at the same time, spares the time-consuming task of feature extraction and engineering(*1110*). Let us compare deep learning to other ML methods in building models for the classic example of classifying images of cats and dogs: In non-deep algorithms, we must first convert the input images into a set of informative features that can best provide the needed information for distinguishing images of cats and dogs; e.g., we may notice that head-to-body size ratio may be an informative feature. After converting the input images to such features, whose number may vary from a handful to thousands, the predictive model is trained with these features and their target labels. Although this procedure can also be implemented with deep learning; generally, deep learning is not superior to non-deep methods in these cases where the original input data is first converted to tabular data(*1111-1113*). Deep learning is superior where the model is directly trained with the raw original inputs and their target labels, with no feature extraction in-between.

The point is that in non-deep ML, inputs are first reduced to a set of features but the deep learning algorithm has direct access to raw input data, with no reduction. Various techniques have enabled effective exploitation of information from raw input data in deep learning(*1114*). Hidden layers and deep and convolutional architectures can learn otherwise unrecognizable complex informative higher-scale structures and abstractions(*1110, 1115-1122*) (figure 9). Backpropagation of errors can find out based on output labels, the least-erroneous ways to learn from input data(*1123, 1124*). Long short-term memory can integrate input data even across various time steps to learn temporally higher-scale structures(*1125, 1126*).

Predictive superiority of deep learning is maintained despite the possibility of extracting and engineering thousands of features from inputs to maximize the information provided for non-deep ML and also the capability of non-deep ML algorithms to learn complex and non-linear patterns in input features. Here lies a crucial point: Even exhaustive analyses cannot compensate for the information reductionism wastes, as it dismisses emergent and higher-scale information which can bound possible labels. Mutual information provided by capturing spatial and temporal higher-scale structures, apparently irrelevant local correlations(*1127-1130*), and other informative intricacies endows deep learning with superior accuracy by constraining possibilities and thus the uncertainty of its predictions. Because of the complexity and irreducibility of this captured information, workings of deep learning models are usually incomprehensible and uninterpretable(*1113, 1131*). They are called black-box models. This is inevitable due to the irreducibility and non-localizability(*168, 1132*) of the used information.

Interestingly, deep learning can recognize patterns, using exponentially fewer parameters than what is required in non-deep ML. It is bewilderingly cheap(*1133*). The reason for this is the pattern we have discovered: emergence of more predictable higher scales from lower-scale uncertainty: compression of the parameter space of isolated parts in wholes: feasibility of deriving simpler effective field theories(*1133*). It has been shown that deep learning can capture this "hierarchical generative process" which abounds in nature and consequently in real-world data(*1134*). This is not possible with non-deep ML as the deep networks that can capture hierarchies cannot be "flattened" efficiently(*1133, 1135-1137*). In both deep learning and effective field theories/renormalization group, there is a direct non-reduced bidirectional "flow" and "feedback" between "raw and unreduced data" and our asked question: Because of this, they can use features which "typically correspond to long-wavelength/macroscopic degrees of freedom(*1133*)."

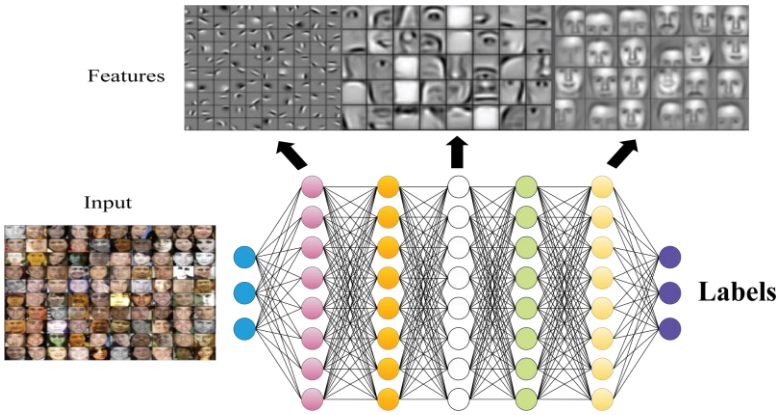

Figure 9. Capturing higher-scale descriptions and abstractions by deep learning.

Strange Attractors

Let us recall the butterfly effect where we saw that chaotic dynamics and sensitive dependence on initial conditions make long-term prediction impossible(*264, 265*). Still, Edward Lorenz himself stated "that over the years, minuscule disturbances neither increase nor decrease the frequency of occurrence of various weather events such as tornados; the most that they may do is to modify the sequence in which these events occur(*264*)."

This insight of Lorenz stems from observing the global structural stability of Lorenz strange attractor(*1138*): Instantaneous states of trajectories starting from extremely close initial conditions get completely away from each other after some time and thus, their prediction becomes impossible. However, all trajectories starting from completely different initial conditions, after enough time, form a similar global higher-scale structure: another adherence to the pattern of the emergence of higher-scale predictability from lower-scale unpredictability(*1139-1141*). Intriguingly, the shape of this global structure which is called Lorenz strange attractor is like a butterfly (figure 10).

What does play the role of truism-law-of-survival here? The motivation of Lorenz to model weather had him constrained to select among the infinite space of all possible systems of differential equations, phase space trajectories with specific global features that would reflect the actual weather. Two features that may readily come to mind are its annual stability and boundedness: We expect specific states for each season every year; also, parameters of the weathers our species has experienced have been in a narrow range of all its possible states: Our species surely has not experienced weathers much like that of Mercury or Neptune.

What does mediate here the emergence of global structural stability and higher-scale predictability? A simple version of Lorenz model in which the existence of Lorenz strange attractor has been proven is a non-linear

system of three differential equations where σ, *r* and *b* are set as 10, 28, and 8/3 respectively(*265, 1142-1144*):

$$\frac{dX}{dt} = -\sigma X + \sigma Y$$
$$\frac{dY}{dt} = -XZ + rX - Y$$
$$\frac{dZ}{dt} = XY - bZ$$

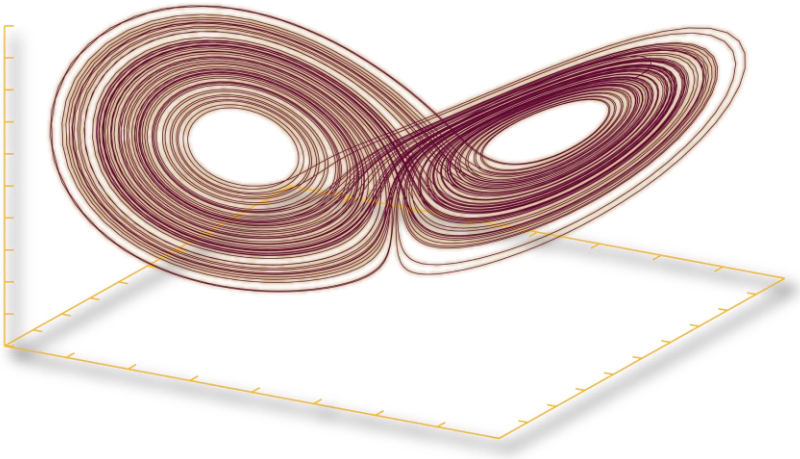

Figure 10. Lorenz strange attractor (based on mizuno.org/c/la/, archived).

Reciprocal interactions between behaviors of *X*, *Y*, and *Z*, function like an effective feedback system to bring about the observed global structural stability which has survived, like the interactions between constituent parts of organisms(*1145*). These equations show well how higher-scale predictability emerges and why many lower-scale parameters can be discarded in studying higher-scale behaviors. You can see that the rate of the change of each variable is completely interdependent and coupled with the state of the other two variables. There is also negative feedback between the absolute value of the rate of change of each variable and the absolute value of each variable: Large absolute value of each variable is followed by a decrease in the absolute value and the direction of the rate of change of that variable. Such complex interactions which constitute self- and cross-couplings in both immediate and distant causal histories sustain and bound the dynamics of complex physical and biological systems(*1145-1150*). When an organism's part is isolated, it is stripped of all these complex interactions and feedbacks.

Lorenz attractor is only an instance of the many cases of the emergence of higher-scale predictability from lower-scale unpredictability that have been investigated for decades by mathematicians, physicists, chemists, and others in fields like chaos theory and synergetics (*55, 1151-1159*).

The 1st Ab Initio Scientific Framework for Biological Sciences

From all we have learnt about the structure of living matter, we must be prepared to find it working in a manner that cannot be reduced to the ordinary laws of physics. And that not on the ground that there is any "new force" or what not, directing the behaviour of the single atoms within a living organism, but because the construction is different from anything we have yet tested in the physical laboratory.(*9*)
Erwin Schrödinger, in his 1944 *What is Life?*, which inspired the inauguration of the era of molecular biology*(1160, 1161)*

We saw that currently, as Whitehead had said, almost all studies in biological sciences are based on "uncritical assumption of half-truths" and "a medley of ad hoc hypothesis." Now that we have been able to construct based on first principles, an ontological attitude toward "life" and organisms and a simple theory that explains the evolution of their internal workings, we may build on these simple grounds a new comprehensive framework that would guide the design, data gathering and analysis of investigations in biological sciences.

Grand schemes of most biological studies boil down to investigating causal relationships between some variables. How can our new ontological attitude and emergent bound box theory help these investigations?

We said that truism-law-of-survival leads to the formation of a priori statistically improbable states. What does a priori statistically improbable mean*(916-918)*? Assuming physicalism(*40-42*), we may describe the state of any system at any moment by specifying the state of all its constituent micro particles, any particle that one may assume is sufficiently "fundamental." These particle-states include properties like element, charge, coordinates (x, y, z) and momenta (p_x, p_y, p_z); e.g., to describe the state of a 1 μm^3 closed volume of helium at the standard temperature and pressure, at least about 27,000,000 variables have to be specified. The volume has 27,000,000 degrees of freedom. It has been shown that, even without knowing their initial coordinates, after some time, the probability that all these atoms accumulate at an instance in one corner is very low. It would be far more likely to observe homogenous distributions. Because the number of "micro-states" that build up such distributions is much greater. Thus, they are much more probable. This lies at the heart of statistical mechanics and microscopic explanation of the second law of thermodynamics(*779, 780*).

In Claude Shannon's information theory, information is defined as the amount of reduction in uncertainty when knowing the specific state of a variable(*1162-1164*). This implies that the amount of information gained is relative and depends on the prior uncertainty about the variable; e.g., more information is needed to know the state of a die than a coin. More information is needed to decode a random sequence of English characters and punctuation than a meaningful English text because the initial uncertainty is higher for the random sequence; the English language constrains all possible states in the random sequence to only those with meaning in English(*916*). *Shannon entropy* of X is the uncertainty about its value and consequently the needed information to specify it and is represented by $H(X)$. Uncertainty about the value of a variable when there is already prior knowledge about it at hand can be formalized as Shannon conditional entropy of X given Y; $H(X \mid Y)$, which equals the uncertainty of X when already knowing Y.

We can assign to X, e.g., the "fundamental" lower-scale state vector of an organism (a vector specifying all variables of all constituent "fundamental" particles of the organism); and to Y, e.g., a variable whose value we know, e.g., if the organism is in the specific environment from which we have previous observations and data about similar organisms.

$$H(X) = -\sum_{x} p(x) \log_2 p(x)$$
$$H(X \mid Y) = -\sum_{y \in Y} p(y) \sum_{x \in X} p(x \mid y) \log p(x \mid y)$$

Mutual information between X and Y, $I(X : Y)$ is the information gained about X by knowing Y. It is always positive and only zero when the two variables are completely independent.

$$I(X : Y) = H(X) - H(X \mid Y)$$
$$= \sum_{x,\, y} p(x, y) \log \frac{p(x, y)}{p(x) p(y)}$$

After accounting that the organism is in the specific environment, uncertainty about the "fundamental" lower-scale state vector of the organism, $H(X \mid Y)$ (which equals the needed information for knowing it), gets less than the uncertainty about the "fundamental" lower-scale state vector of the organism when not accounting that it is in the specific environment, $H(X)$, by the amount of the mutual information between X and Y,

$I(X:Y)$. Based on our new ontological attitude and emergent bound box theory, we know that this is not zero as states of wholes and parts of organisms get bounded by their other parts, "environmental" variables((*212, 382-389, 1165-1175*)) and historical and temporal variables (especially evident in *learning*)(*1176-1183*) to only those that have been surviving(*1184*).

$$H(X \mid Y) = H(X) - I(X:Y)$$

Due to the relationship between Wiener-Granger causality(*1185-1187*) and Shannon information ((*1188-1196*), also see (*1197, 1198*); for the relationship between *transfer entropy* and Shannon information, see (*1199*)), this illuminates that predictions, and interventions(*1200-1203*), would be more accurate by incorporating individual, environmental and temporal variables(*1183, 1204-1206*); contrary to what foundationalist materialism and idealism has inculcated and is practiced now by likes of "evidence-based" medicine and almost all human, animal, psychological and social studies.

"It from bit" symbolizes the idea that every item of the physical world has at bottom, an immaterial source and explanation; that what we call reality arises in the last analysis from the posing of yes-no questions and the registering of equipment-evoked responses; in short, that all things physical are information-theoretic in origin.(1207) John Archibald Wheeler

Information has attracted a lot of attention in recent decades in different sciences, including biology. This word represents several concepts put forth by several theories(*1208*). Many cases of its use in biological sciences depict biological systems as "information processing systems" that inherit and process the "information" in cellular signals or biomolecules like DNA as in (*11, 48, 244, 527, 588, 595, 794, 1163, 1209, 1210*); also see (*1211, 1212*). Our simpler conceptualization, as Wheeler may imply, shares more concrete ground with reality rather than arbitrarily conceptualizing parts of organisms as "information-processors" or "biological Maxwell's demons"; also see (*863, 1213-1218*). Just like how "The actual message is one selected from a set of possible messages(*1162*)," a human is one of the possible states for all constituent "particles" constructing that human. Our conceptualization shares some associations with Schrödinger's *negative entropy* (negentropy)(*9, 1219-1221*) or those formulated for clarification of scientific information(*916-918*).

So, as far as possible, all individual, environmental and temporal variables of observations should be recorded. Technologies like wearable biosensors(*1222*) used in digital health and telemonitoring(*1223*), organoids(*1224, 1225*), high-throughput phenotypic assays(*1226, 1227*) and internet-of-things can facilitate gathering accurate(*1184, 1228*) diverse information in massive scales(*1229*): proteome-wide affinity fingerprints(*1230*), transcriptome, epigenome, metabolome, secretome, radiome, neuroimaging and connectome, behaviors and cognitive responses, social variables(*1231, 1232*), etc. These different observation modalities can be integrated to capture the most information(*1233-1235*). Real-world(*1236, 1237*), patient-centered(*1238*) and pragmatic(*1239, 1240*) observations like electronic health data(*1241, 1242*) should replace the current infatuation with randomization and standardization that try to wash out organisms' uniqueness and contextuality in search for non-existent isolated foundational relationships.

To recognise a class is to throw away information.(*1243*)
Ross Ashby

It is a mark of maturity of a branch of science that the notion of similarity or kind finally dissolves, so far as it is relevant to that branch of science. That is, it ultimately submits to analysis in the special terms of that branch of science.(*374*)
Willard Van Orman Quine

How can relations and patterns be found among all these variables? Fortunately, recognizing patterns among numerous variables is the chief purpose and capability of the currently well-developed technique of ML. It can recognize complex, non-linear, and causal((*1244, 1245*); also see (*1202*)) patterns among thousands of variables in millions of entries and even use these patterns for generating novel entities that would show the desired behaviors(*63, 1246*).

The principle that all variables should be recorded does not seem to be sufficient. "Rational" drug discovery would not become efficient even if it records all variables of its observations. Because its observations have little to do with its ultimate aim, that is changing phenotype (i.e., have little cause-effect power). A crucial point is asking the right question. The asked question is translated in ML to model's target variable: the variable which guides the parameterization of models and for the prediction of which, the information of all variables is used. Here also, emergent bound box theory comes to our help. Higher-scale descriptions of systems tend to have superior cause-effect power. So, target variables should tend toward higher-scale descriptions. However, this depends on the purpose; e.g., affinity for proteins may be an appropriate target variable for developing chemical probes(*1247*).

Whoever condemns the supreme certainty of mathematics feeds on confusion, and can never silence the contradictions of the sophistical sciences, which lead to an eternal quackery.(1248) Leonardo da Vinci
Every possible application of calculation would be excellent if the physiological conditions were quite accurately defined. Physiologists and physicians should therefore concentrate their effort, for the moment, on defining these conditions.(*438*) Claude Bernard
Measure what is measurable and what is not measurable, make measurable.(*1249*)

To complete the compatibility of our framework with the productive mathematically precise methodology of physics(*15, 1250*), we should note if our information truly represents real-world values of their referent phenomena or not(*1249*). Definition of variables must be unambiguous, consistent, "objective" and globally harmonized. Currently, in biological sciences, variables are specified too loosely, ambiguously, and based on foundationalist materialism, e.g., (*350, 375, 1251-1257*) and (*1258-1261*). Any conceivable and apparently negligible difference between phenomena must be specified by translating them to new variables or variable-values, as they may affect phenomena; e.g., "inactive" excipients of drugs(*1262*). ML can reach more accuracy when variables, unlike now(*1263-1268*), are explicated specifically(*1205, 1206*). Metrology, the scientific study of measurement, can help biological sciences in this path(*1269-1273*).

The most important contribution of emergent bound box theory is providing a new ontological framework for biological sciences built up on first principles. Many of the above points had already been pointed out, albeit a posteriori; e.g., the need for considering individual-level variables has been highlighted from more than a thousand years ago(*1274*) to the current "personalized medicine"(*464, 1275, 1276*). Many have also realized the contextuality of observations; e.g., above I cited eleven clinical studies concluding that "lack of blinding leads to statistically-significant bias of effect-size"(*1165-1175*); I also cited two meta-epidemiological finding no "statistically-significant relationship between lack of blinding and effect size"(*1277-1279*). This obliged the authors(*1277*) and editors(*1279*) to suggest that although there had been strong evidence that lack of blinding may lead to bias in effect size, their large sample size implies that this may be confined to "specific settings(*1277*)" and more research is needed to unravel "the relationship between lack of blinding and effect-size." The problem is that they do not have realized that the "causal relationship" they seek between two isolated variables does not exist. Unspoiled by ad hoc principles, our new ontological attitude brings this realization that all effects are "personal" and all settings are "specific settings."

How to Apply the Framework
Demonstrative COVID-19 Cheminformatics Meta-Analysis

The data can be gathered prospectively and/or retrospectively. Unfortunately, ignoring most variables has immensely reduced the value of big

data collections, primary databases, and the primary literature. Regarding the primary literature, even the few recorded individual-level variables are rarely shared publicly or even made accessible by personal request(*479-487*). Only for demonstration, let us apply the framework for COVID-19 drug repurposing. The ultimate scheme is a cheminformatics meta-analysis model for predicting molecules' effect size in improving COVID-19 outcomes. Input data include variables of 2D-structure, assessed outcome, country, size of treatment group, age, gender, race, severity, variation, different aspects of risk of bias, in vitro inhibitory potency against SARS-CoV-2 (pIC50), and affinity fingerprint (for 180 binding pockets across human-SARS-CoV-2 interactome) (supplementary data 4) (see methods). Training data were extracted by systematically reviewing 42916 studies (supplementary data 5). The trained model was used to predict the effect size of repurposable drugs(*1280*). In preparation of the affinity fingerprints, I also used consensually docked 4D-QSAR (four-dimensional quantitative structure-activity relationship) to demonstrate how to integrate various heterogenous modalities and scales of data and also, raw-data deep learning and non-deep learning by a nested design. The 4D-QSAR itself is a demonstration of how different methods can be integrated for synergy and higher efficiency: Docking and QSAR modeling are two different methods of predicting binding affinity: QSAR modeling infers binding affinity from available in vitro data, whereas docking uses simulation and previously developed scoring functions. Consensually docked 4D-QSAR modeling not only synergistically integrates these methods (see methods) but also integrates various, mostly individually insufficient, scoring functions(*1281*) and prediction models(*1282*). To showcase this, I used here all different types of scoring functions(*104*): empirical FlexX(*1283*), PLANTS(*1284*) and X-Score(*1285*); physics-based HYDE(*1286*); ML-based RF-Score-VS(*1287*), and knowledge-based KORP-PL(*1288*).

The framework can be refined and augmented by other techniques; e.g.,

- Multi-output ML can have several target variables(*1289*). These several target variables can represent, e.g., different target phenotypes of a disorder.
- Variable-importance analysis and Shapley value(*1290*) can be used to non-reductively identify the "importance" of variables and understanding mechanisms.
- ML can be integrated with multiscale modeling(*1291*), ensemble modeling(*1292*), and network analysis(*1293*) to enable understanding causal mechanisms of complex behaviors by accounting for the uncertainty of data and chaotic behaviors.
- ML can be integrated with optimization techniques, like reinforcement learning or genetic algorithm(*668*), to enable an optimized search for novel solutions. In such settings, the trained ML model can be used as the fitness function that assesses the novel solutions' fitness. This setting can be accompanied by consecutive experimentations to provide the ML with an acceptable applicability domain. Such settings which include consecutive steps of diversification (e.g., genetic algorithm) and selection (e.g., ML) seem to be very effective for designing new solutions for distinct problems in different disciplines. The target variable of these consecutive diversifications and selections must have the highest cause-effect power.

Some Applications of the Framework

- ✓ **Genetic predictive scores and functional omics.** Even the state-of-the-art approaches for unraveling the genetic basis of phenotypes are confined to investigating isolated crude effects of single, or at most a handful, highly penetrant genes, both in interventional animal studies(*1294-1298*) and in human studies(*531, 1299-1302*). The inability to use the deluges of available omics data inflicts also fields other than biomedicine, like phylogenetics(*1303*). We can redeem these failures and provide predictions of phenotypes for whole genomes and unravel non-reductive genomes-phenome associations and mechanisms. These capabilities along with our current genome editing abilities(*1304*) open the door to untapped possibilities in genetic therapy(*1305, 1306*).
- ✓ **Drug discovery.** Recently, ML found a molecule based on direct patterns between molecular structures and *E. coli* growth inhibition that not only inhibited *E. coli* growth potently but also had efficacy against phylogenetically diverse pathogens in mouse models(*1226*). Employing this rather higher-scale endpoint in ML provides a general proof-of-concept confirmation for the framework; however, here we realized that far higher potencies can be reached by incorporating individual and environmental variables and also assigning the ultimate higher-scale description as the target variable, e.g., therapeutic effects on infected human patients rather than the inhibitory effect on bacteria. Based on the massive presented evidence, I am sanguine that drug discovery's effectiveness will soar so high that we may even supplant current gold-standard drugs(*126-132*) with molecules with far higher efficacy and safety.
- ✓ **Pharmacology and "mechanistic" studies.** Even the state-of-the-art methods for investigating mechanisms of drugs and other interventions are marred by idealism, foundationalist materialism, and organisms' compensatory feedbacks(*1307-1313*). Tools like the biological fingerprint I used in the demonstration (the affinity fingerprint), variable-importance analysis, and Shapley value enable us to non-reductively open the black-boxes of human bodies and peek into their inner workings(*1314*). The discovery of the dopaminergic pathophysiological aspect of schizophrenia and "dopamine receptors" based on phenotypic effects of haloperidol may be considered a classic example of unraveling lower-scale mechanisms from higher-scale description, not the other way around(*1315-1317*).
- ✓ **Herbal and supplement formulations and personalized nutrition.** Especially using tools such as biological fingerprints that enable analyzing mechanisms, we may compound effective combinations(*1318*) and personalized diets(*1319, 1320*).
- ✓ **Toxicological regulation.** Including ecotoxicological and environmental risk assessments(*1321-1323*).
- ✓ **Replacing animal models.** Despite the ubiquity of animal models in biomedicine, they are not reliable and accurate in reflecting behaviors of humans. It has been concluded that "The majority of published effects are most likely measurements of noise(*320*)"(*1324, 1325*). But an alternative has been lacking(*1326*). The framework can help replace(*1327*) animal tests with in silico(*1328*) or non-animal alternatives(*1329, 1330*). And until reaching there, it can be used to reduce(*1327*) animal use by determining what phenotypes in each model should be investigated or ignored(*1331*) or can be used in ethics committees, e.g., to assess based on predicted efficacies and probabilities of proposed molecules, if a drug discovery project is justified to use animals; or to calculate the sample size of animal studies (also human studies) based on better evidence of estimated effect size.
- ✓ **Sustainable development.** E.g., in conservation(*1332, 1333*) of biodiversity(*1334, 1335*), evolutionary forecasting(*1336*) and epidemiological challenges like pandemics.
- ✓ **Medical diagnosis and treatment.** Besides diagnosis, additional cause-effect power can be reached by making seamless and unreduced, the segmented stages of diagnosis and intervention and using AI-based recommender systems. This is because when the purpose is to eventually administer some treatment, response to the received treatment is a higher scale compared to the diagnosis. The real-world impact of this seamlessness can be illuminated by recalling the unreliability of the current best-practice guidelines and recommendations(*453*) provided by "evidence-based" medicine and the rapid shift of medicine toward more automatization and digitalization(*1337*). Intervention is not restricted to pharmacotherapy and extends to psychotherapy, gene therapy, cell therapy,

physiotherapy, rehabilitation, palliative care, neural interfaces(*1338*), food and lifestyle modifications, etc.

- ✓ **Biomedical and tissue engineering.** E.g., for process optimization, design, and material tuning in bioreactors, cell culture, 3D-bioprinting (also 3D-printing)(*1339*), etc.
- ✓ **Synthetic biology and genetic engineering.** As a theory of the evolution of organisms' internal workings, it provides insights into how these workings can be changed; e.g., it guides what characteristics to target in selection and optimization of directed evolution and what variables to measure(*1340-1343*). Accompanied by our current genome editing capabilities(*1304*), it can help a lot in managing world hunger(*1344, 1345*) and reducing animal agony through various means from synthesizing non-animal meat to engineering efficacious plants and livestock(*1346*).
- ✓ **Identification of scientific misconducts and bugs.** We will see that a major current challenge in the pursuit of knowledge is the pervasiveness of scientific misconduct(*1347-1368*). By recognizing anomalous patterns, it can help.
- ✓ **Psychological and social sciences.** Unification of physical, biomedical, and social sciences can lead to great synergy and revelations as it complies with the universe's unitariness(*1231, 1232, 1369, 1370*). Psychological and social insights provided by the framework and the tons of available data(*1371*) can help us in fields like political and organizational decision-making(*1372*).

Other Emergent, Collective, Self-Organizing, Critical and Chaotic Behaviors:

Although we developed emergent bound box theory based on organisms, we saw it can capture patterns extending to quantum mechanics. Based on its simplicity and universality, it is wise to expect that it can be of value outside biological sciences in fields that deal with emergent phenomena, to varying degrees. As ML is effective in recognizing patterns in such phenomena(*1373-1375*), the framework may enhance it by guiding the gathering, assignment, engineering, and reduction of variables(*1376, 1377*). Let me elaborate on such applications through an example. There has been a question of why 2D-QSAR modeling can outperform 3D-QSAR modeling(*1378*). Based on its conformation in three dimensions, a single 2D molecular representation can be converted into various 3D representations. 3D representations may be considered "lower-scale" representations of molecules. Now, based on emergent bound box theory, we must see which is closer to our target measurement, the binding affinity of molecules to macromolecules. Because several poses and conformers of ligands may contribute to binding affinity(*1379, 1380*), 2D representations are closer. Thus, they are both cheaper and generally more informative. In designing the consensually docked 4D-QSAR, I used such insights and used features based on 2D structures and docking scores of up to four different poses. This way, I also added information about targets and the different tautomers, protomers, and poses of the molecule. Based on the framework, this can be further expanded by adding environmental and experimental variables of binding affinity measurements, like the used assays and solutions.

- ✓ **Earthquake prediction, geoscience, oil and gas industries**(*1381-1384*). Extracting and engineering higher-scale descriptions may help(*1385*).
- ✓ **Materials science and engineering**(*1386, 1387*)**.**
- ✓ **Self-assembling materials and swarm robotics.** It can guide how to build desired pre-defined structures and also how to guide their collective behaviors toward addressing the eventual purpose itself without reducing it to an intermediary purpose(*1388-1391*).
- ✓ **Trading and finance.**
- ✓ **Weather prediction.** We still cannot accurately predict instantaneous weather for 20 days later(*1392*).

"Intelligent Design"

Darwinism does not explain how organisms' internal workings have changed during evolution. This void can be regarded as a major cause of the discussed stagnation of biological sciences. Another implication of this void has been making room for "intelligent design." This creationist(*1393-1396*) argument has attracted a lot of attention and been unfairly presented to the public, including schools(*1397-1403*); also see (*1404*). Although convincing counter-arguments and evidence have been presented((*199, 1394, 1405-1413*); also see (*1414, 1415*)), proponents of this pseudoscientific((*1416*); also see (*1417*)) idea keep proclaiming the "end of Darwinism"(*1418, 1419*). Although probably no amount of evidence suffices to compel all to prioritize knowledge and truth(*1393-1396, 1420*), emergent bound box theory provides us with two strong counter-arguments against two core arguments of "intelligent design."

"Intelligent design" rests on this claim that as "the purposeful arrangement of parts of a system reliably indicates deliberate design(*1418*)," and as we observe such "purposeful arrangement of parts" in organisms, organisms are "intelligently designed." The appearance of design in organisms has been noted for hundreds of years and even by many scientists(*155, 1421-1423*). It even had initially convinced Darwin of an "intelligent designer"(*1424, 1425*). As we discussed in rebutting machine mindset, deliberate and "intelligent" design results in systems whose parts are chained to systems' functions by a chain of tasks. Then, we counted properties of complex systems whose extent and ubiquity contradict such clear-cut chain of tasks, to varying degrees: whole-part feedbacks(*182-192*), continuous and spectral rather than binary-like causal structures(*177-180*), multifunctionality(*170-176*), redundancies(*193-201*) and vestigialities(*202-205*), degeneracy or multiple realizability(*51, 206-215*). Contrary to "intelligent design," Darwinism is compatible with these empirical observations as, according to emergent bound box theory, selection or truism-law-of-survival is primarily enforced at higher scales; e.g., phenotypes, not genotypes. Biased by machine mindset, "intelligent design" has fallaciously extended our own approach of building systems to organisms. The influence of machine mindset on "intelligent design" is evident from the frequent use of machine metaphor for organisms and their parts by its proponents(*1418, 1419, 1426*). Observations of organisms actually testify that they are not "intelligently" designed. The core argument of "intelligent design" is turned on its head.

Truism-law-of-survival also refutes another argument often used by creationists: "It is hard to believe organisms are mere flukes and 'products of chance and error(*840*).'" As we saw, they are not merely so. The emergence of "life" and complexity is as inevitable and simple as a logical truism, hence their quick emergence on Earth(*655, 841, 842*).

Starting the 2nd Scientific Revolution

Nullius in verba; Take nobody's word for it
Motto of the Royal Society, the first modern scientific society, as
"an expression of the determination of Fellows to withstand the domination of authority.*(1427)*"

Aspired early on to become a scientist, I entered university with this preconception that I would join a thousands-years-old pursuit of knowledge by philosophers and scientists who are in awe of nature and everything we see; who are constantly questioning and doubting established ideas and their own ideas to illuminate the vast seas of unknowns and possibilities before us.

What I observed completely contradicted this preconception: I observed professors that, despite having authored hundreds of "peer-reviewed" biomedical articles and reminding to be among "the top 1% scientists of the world," did not know the very basics of the most fundamental theory of biology: Darwinism. Some even asserted that "science cannot be trusted, because scientific results have been disproven numerously." "Do not they know that science is primarily a set of methods, a perennial pursuit, not an edifice of dictated results; and indeed, falsifiability of scientific theories has been proposed as a distinction and virtue of science(*1428*)?," I asked myself. Afterward, this question occurred to me that how is it possible to be ignorant of the most basic tenets of science and still "reach the top" of the scientific community.

Science justifies itself in its methods, quite apart from any serviceable knowledge it may convey. […] That form of popular science which merely recites the results of investigations, which merely communicates useful knowledge, is from this standpoint, bad science, or no science at all.(*1054*)
Karl Pearson, a major pioneer of modern statistical methods (emphasis added)

It is the activity of the […] not-too-critical professional: of the science student who accepts the ruling dogma of the day; who does not wish to challenge it; and who accepts a new revolutionary theory only if almost everybody else is ready to accept it. I believe, and so do many others, that all teaching on the University level (and if possible below) should be training and encouragement in critical thinking. [He] has been badly taught. He has been taught in a dogmatic spirit: he is a victim of indoctrination. He has learned a technique which can be applied without asking for the reason why. […] I see a very great danger in it and in the possibility of its becoming normal (just as I see a great danger in the increase of specialization, which also is an undeniable historical fact): a danger to science and, indeed, to our civilization.(*1429*) Karl Popper (emphases added)

Positive results […] come from doubting that the lessons are all true. You must here distinguish the science from the forms or procedures that are sometimes used in developing science. It is easy to say, "We write, experiment, and observe, and do this or that." You can copy that form exactly. But great religions are dissipated by following form […]. In the same way it is possible to follow form and call it science but it is pseudoscience.(*1430*) Richard Feynman (emphases added)

I saw that most studies, whether in journals with the lowest or the highest "impact factors," are not, as I had thought, results of hours of questioning, doubting established methods, and curiously exploring and debating new perspectives. Although many of them claim novelty and originality(*1431, 1432*), they are merely rote permutations of previous works, without considerably questioning their methodologies and presumptions: *rote science*: like how a clerk or a technician merely follows prespecified protocols and tasks. This is why the fallacies we discussed, have not been corrected in decades, but cemented (a quick look at the latest issues of journals with the highest "impact factors" can empirically confirm this.).

Let alone questioning presuppositions of widely accepted paradigms; I saw that a majority of studies published in "peer-reviewed ISI-indexed" journals were unaware, or maybe indifferent, toward elementary widely known published scientific facts. Let me bring an example I came across while preparing the demonstrative cheminformatics meta-analysis I presented. Hundreds of "peer-reviewed ISI-indexed" articles have introduced potential drugs for COVID-19 by docking against a single protein a handful to a few thousand chemicals(e.g., (*1433-1443*)). Let alone questioning reductionism and "rational" drug design; accuracy of selecting candidates for inhibiting a random protein among this number of molecules is not unlike reporting results with nanometer precision from a tape measure(*105, 106*). This has been known for years(*105-109*). I was so amazed by this rote science that I assessed the accuracy of the widely used AutoDock Vina(*1444*) and the scoring functions I used in the consensually docked 4D-QSAR, for SARS-CoV-2 main protease and COVID-19 targets, respectively. Results confirmed what has already been known. For AutoDock Vina, Spearman's rank correlation coefficient was 0.178 and Pearson correlation coefficient was 0.12; average Spearman's rank correlation coefficient for all proteins and all the scoring functions was 0.107 (supplementary data 6; also see (*1445*)).

Why Here?

But how are these concerns relevant to our first subject, unifying biological sciences and physics? Why am I expressing them here? First, I assert that for the Second Scientific Revolution, we must cling to what we clung to in our framework and theory: simplicity. Second, I observed that a deeply ingrained presupposition has always hindered my aim to instill change in others by criticizing the scientific community's current awful state: We are living in the pinnacle of scientific progress as is evident from the highly advanced technologies we have; how can my criticisms be relevant when the same science has culminated in all this progress? Here, I have presented massive evidence to the contrary which I will elaborate on and expand further.

Simplicity: Cornerstone of the Second Scientific Revolution

Every science must pass through three periods of development. The first is that of presentiment, or of faith; the second is that of sophistry; and the third is that of sober research.(*997*)
Justus von Liebig

Those who know that they are profound strive for clarity. Those who would like to seem profound to the crowd strive for obscurity. For the crowd believes that if it cannot see to the bottom of something it must be profound.(*1446*)
Friedrich Nietzsche

The problems are solved, not by giving new information, but by arranging what we have always known. Philosophy is a battle against the bewitchment of our intelligence by means of language.(*1447*)
Ludwig Wittgenstein (emphasis added)

We solved the enduring dilemmas of simplicity, "beauty" and Ockham's razor; machine metaphor; foundationalist materialism; "replication crisis"; Darwinism's tautology; definition of life; increasing complexity; and "downward causation" not by providing new empirical results, but by seeking simplicity and clearing ambiguities. As Newton remarked, "Truth is ever to be found in simplicity, & not in the multiplicity & confusion of things*(585)*."

This simplicity is especially important now. In Justus von Liebig's words, we are currently in the age of sophistry: a period in the development of science when layers of misunderstandings have been stacked, cemented, and eventually concealed by a mesmerizing and commercializing facade. Many of our current fallacies are not the results of outright-wrong hypotheses like "Earth is the center of the universe". They are results of "uncritical assumption of half-truths" and the *snowball effect* (computational complexity) following these "half-truths." "Evidence-based" medicine and "rational" drug discovery, e.g., were initially based on sound attitudes: more efficacious use of the available knowledge(*113-115, 1448-1452*). The problem is that instead of clinging to the simplest form of their ultimate purpose, they clung to some ad hoc surrogate purpose. "Rational" drug discovery mistook binding to a single protein for *rationality* and clung to this mistake. "Evidence-based" medicine mistook results of group-based "mindless" statistical rituals for *evidence* and clung to this mistake.

We shall overgrow the age of sophistry similar to how we could disentangle the excessive complexity of biology: more emphasis on simplicity. Lavoisier confirms this by saying that "The only method of preventing such errors from taking place, and of correcting them when formed, is to restrain and simplify our reasoning as much as possible(*586*)." From a perspective, more emphasis on *simplicity* compared to previous philosophies is what propelled the scientific revolution. Therefore, here I aim to clarify what science is and present some necessary concepts for the Second Scientific Revolution with utmost simplicity and independence from data(*630-635*). Noteworthy, although the conceptualizations may seem not to thoroughly reflect our experiences, as Einstein emphasized*(600)*, they do not contradict them either. They are based on the simplest and only the most necessary assumptions.

What is Science?

In order to seek truth, it is necessary once in the course of our life, to doubt, as far as possible, of all things.(1453) René Descartes

Science never imposes anything, science states. Science aims at nothing but making true and adequate statements about its object. The scientist only imposes two things, namely truth and sincerity.(*9*) Erwin Schrödinger

> After the development of agriculture and settlement of our hunter-gatherer ancestors and then the development and expansion of cities, efficiency in providing food soared so high that many could spare much more of their time for other than the spontaneous struggle for survival and reproduction. Many who had been captivated by questions like "what are we?" "where are we?" and "what should we do?" set up and adhered to several frameworks in which they could try to quench their curiosities and wonders in various ways: religions, cults, myths, and philosophy. Among all frameworks which proposed answers for these questions, philosophy was unique in one fundamental way: It was empty; it imposed no answer; not a single presupposition, assumption, or dogma. Literally meaning love [*philo*-] of knowledge and wisdom [*sophia*], it only imposed a single *direction*: striving to move toward knowledge.
>
> Philosophy later discovered something important which culminated in the Scientific Revolution. Although some philosophers, like Aristotle, had previously emphasized empirical observations rather than mere theorization(*1454-1456*), observing our manifold indelible biases, philosophers like Francis Bacon and Robert Boyle discovered that in pursuit of knowledge, we must excessively increase the emphasis on *simple*, concrete, and unambiguous observations and exclusively prioritize it, both for ideation and validation(*1454, 1457-1462*). This discovery proved to be extremely crucial and philosophy gained a revolutionary momentum where such observations were possible: where behaviors of nature could be observed and recorded unambiguously: natural philosophy; e.g., "Is our planet the center of the universe?" "How do things move?" "How do we get sick?" and "what are organisms made of?."

I believe strongly that philosophy has nothing to do with specialists.(*1463*)
Gilles Deleuze

A system such as classical mechanics may be 'scientific' to any degree you like; but those who uphold it dogmatically, believing, perhaps, that it is their business to defend such a successful system against criticism as long as it is not conclusively disproved—are adopting the very reverse of that critical attitude which in my view is the proper one for the scientist. In point of fact, no conclusive disproof of a theory can ever be produced; for it is always possible to say that the experimental results are not reliable, or that the discrepancies which are asserted to exist between the experimental results and the theory are only apparent and that they will disappear with the advance of our understanding.(*1428*)
Karl Popper

> Yet along with immense success, this discovery brought natural philosophy also a challenge. The growing corpus of the knowledge and technologies produced by natural philosophy implied that natural philosophers could no longer pursue knowledge without restriction. Either the breadth or the depth of objects of the study had to be restricted. So, natural philosophers started getting confined to the arbitrary boundaries of their previously defined questions(*1464-1466*). Along with this, the word *scientist* replaced *natural philosopher*(*1467*). As the received corpus of knowledge accumulated and grew larger, such divisions and specialization got narrower to the point that nowadays, many scientists do not question any of the frameworks and methodologies they are taught. What distinguished philosophy was that it imposed nothing but moving toward knowledge. We may say that science (natural philosophy) also imposes concrete observations; but apart from that, its success goes back to it not exempting any dogma and framework from questioning and doubt. How come have scientists abandoned science's cornerstone and key to success?

Mistaking Products of Science for Science

Rule I. *The end of study should be to direct the mind toward the enunciation of sound and correct judgments on all matters that come before it. […] Since the sciences taken all together are identical with human wisdom, which always remains one and the same, however, applied to different subjects, and suffers no more differentiation proceeding from them than the light of the sun experiences from the variety of things which it illumines. […] We are justified in bringing forward this as the first rule of all, since there is nothing more prone to turn us aside from the correct way of seeking out truth than this directing of our inquiries, not toward their general end, but toward certain special investigations. […] We must believe that all the sciences are so inter-connected, that it is much easier to study them all together than to isolate one from all the others. If, therefore, anyone wishes to search out the truth of things in serious earnest, he ought not to select one special science; for all the sciences are conjoined with each other and interdependent: he ought rather to think how to increase the natural light of reason, not for the purpose of resolving this or that difficulty of scholastic type, but in order that his understanding may light his will to its proper choice in all the contingencies of life. In a short time he will see with amazement that he has made much more progress than those who are eager about particular ends, and that he has not only obtained all that they desire, but even higher results than fall within his expectation.*(*584*) René Descartes (emphases added)

It is not the facts themselves which form science, but the method in which they are dealt with.(1054) Karl Pearson

It is only scientific thinking, the method that leads to new knowledge, the insight into possible sources of error, the care in preparing a line of argument, whose study and practice are seen as the true task of the university. […] the capacity for critical thinking in science will in one way or another play a more important part than copious knowledge.(*1468*) Werner Heisenberg

Scientists abandoned the core of science because they did not realize that science is a method. They got hung up on the achievements of this method and dismissed the method itself: from demonstrations for popularizing science where instead of showing the importance of "the natural light of reason(*584*)," attention is directed toward visual spectacles(*1469*)(e.g., (*1470*)), to schools and universities where, following the routine of times before the advent of publishing when the only way to maintain a reliable source for the taught material was to transcribe(*1471*), teachers and professors forgo arguments and discussions to read the materials of books and lecture-notes for students (as if they cannot read them themselves)(*1472-1477*). Instead of teaching how philosophical and scientific method has led to achievements, we are obsessed with equations, definitions, numbers, names, processes, etc.; this is like memorizing all the information I have brought in the supplementary files, without caring why those were sought in the first place (and all along this, it seems to be forgotten that humans' memory is not like that of computers). Therefore, despite spending immense resources(*1478*), including a huge portion of more than a decade of almost everyone's life, our education system has failed in all its goals: preparation for professions revolving around products of science, like health care professions(*1479-1502*); instilling in the public the necessary civic skills (hence the pervasiveness of misinformation and unsubstantiated assertions, even among the educated(*1503-1512*)); eventually, the current education system has hindered the progress of philosophy and science.

When it came time for me to give my talk on the subject, I started off by drawing an outline of the cat and began to name the various muscles. The other students in the class interrupt me. 'We know all that!' 'Oh,' I say, 'you do? Then no wonder I can catch up with you so fast after you've had four years of biology.' They had wasted all their time memorizing stuff like that, when it could be looked up in fifteen minutes.[…]
It's not science, but memorizing, in every circumstance […] I couldn't see how anyone could be educated by this self-propagating system in which people pass exams, and teach others to pass exams, but nobody knows anything.(*1513*)
Richard Feynman

It is not so very important for a person to learn facts. For that he does not really need college. He can learn them from books. […] The aim must be the training of independently acting and thinking individuals
The school should always have as its aim that the young person leave it as a harmonious personality, not as a specialist. […] Otherwise, he—with his specialized knowledge—more closely resembles a well-trained dog than a harmoniously developed person.(*587*) Albert Einstein

> Conformity and obedience are among the few things that have been educated well(*1514-1517*)(also see (*1518-1521*)). But they are antithetical to questioning and doubt: the cornerstone of science(*1522-1529*). Contrary to the motto of the Royal Society*(1427)*, the current attitude of the scientific community "is often no different from the young African villager's […] propounded by one of his elders. In both cases the propounders are deferred to as the accredited agents of tradition.(*1515*)"; also see (*1530-1532*). This polarity to science is evident in how a significant majority of the greatest scientists, to varying extents, saw schools and academia as an adversary, rather than facilitating: Isaac Newton(*1533*), Charles Darwin(*1424*), James Clerk Maxwell(*1534*), Francis Galton(*1535*), Albert Einstein(*1536*), Alan Turing(*1537*), Peter Higgs(*1538*), John Gurdon(*1539, 1540*), etc.(*1538, 1541, 1542*).

Men are born ignorant, not stupid; they are made stupid by education.(*1543*)
Bertrand Russel

During the three years which I spent at Cambridge my time was wasted, as far as the academical studies were concerned, as completely as at Edinburgh [University of Edinburgh] and at school.(*1424*) Charles Darwin

One had to cram all this stuff into one's mind for the examinations, whether one liked it or not. This coercion had such a deterring effect that, after I had passed the final examination, I found the consideration of any scientific problems distasteful to me for an entire year.(*1536*) Albert Einstein

> It is fair to expect that the greatest scientists would flourish in a system that claims to educate science; but the progress has been "happening in spite of the dominant culture of education, not because of it; it is like people are sailing into a headwind all the time(*1544*)." It may be argued that our current education and academic system is better than the times of these giants. On the contrary, I argue it is far worse: far more institutionalized, standardized, commodified, rigid, and rigged for conformity and obedience and against questioning and independent thought. Trained by standardized tests based on passive and docile acceptance and memorization of "facts," instead of philosophy and science (which are methods), many are obsessed with "right" answers(*1473, 1545, 1546*). Whereas half of those with doctoral-level degrees, do not even understand "what it means to study something scientifically"(*1505*), they blame ancient great pioneers like Plato and Aristotle for being "completely wrong"(*1547-1549*). Now, we can confidently guess "Where have all the geniuses gone(*1550, 1551*)?"(*1552-1554*):

Most schooling is just training for stupidity and conformity […] People are filtered out for obedience. If you can guarantee lots of stupidity in the educational system like stupid assignments and thing like that, you know that the only people who'll make it through, are people like me and most of you, I guess, who are willing to do it no matter how stupid it is because we want to go to the next step. So, you may know that this assignment is idiotic and the guy up there couldn't think his way out of a paper bag, but you'll do it anyway, because that's the way you get to the next class and you want to make it. There are people who don't do that. There are people who say they are not going to do it; it's too ridiculous. Those people are called behavioral problems or something like that. They end up in the principal's office or in the streets or selling drugs or whatever. […] and it works right through graduate school. The problem is that you can't have progress this way. […] You can't get anywhere if you just copy what somebody told you. You have to be challenging things all the time, challenging everything. […] a couple of smart guys will decide what the great thoughts are and every student will memorize them and that's education. Well, that's a way to turn people into pure automata: […] I pick them, you memorize them: of course, that's the opposite of education.(*1555*) Noam Chomsky

Without education, we are in a horrible and deadly danger of taking educated people seriously.(*1556*) G. K. Chesterton

Interestingly, many have tried to fill the void created by dismissing philosophy and science by implementing and teaching *critical thinking*(*1472, 1527, 1545, 1557-1559*); still, no consensus has been reached for its definition(*1559-1561*). I argue the void can be best filled by correcting our understanding of philosophy and science.

Reform is no use anymore, because that is simply improving a broken model. <u>What we need is not evolution, but a revolution in education.</u> This has to be transformed into something else. One of the real challenges is to innovate fundamentally in education. Innovation is hard, because it means doing something that people don't find very easy; it means <u>challenging what we take for granted, things that we think are obvious</u>. The great problem for reform or transformation is the tyranny of common sense. Things that people think: "well, they cannot be done any other way, because that is the way it's done." […] <u>Many of our ideas have been formed not to meet the circumstances of this century but to cope with the circumstances of previous centuries, but our minds are still hypnotized by them</u> and we have to disenthrall ourselves of some of them. Now, doing this is easier said than done. <u>It is very hard to know what it is you take for granted and the reason is you take it for granted.</u>(*1562*)
The late Ken Robinson (emphasis added)

Commodification
Where Knowledge and Public Good Is Not Important at All

All too often the main reason for a piece of research seems to be to lengthen a researcher's curriculum vitae.(*1563*)
Doug Altman in his 1994 editorial in *The BMJ*, "The scandal of poor medical research"

Science has taken a turn toward darkness. […] No-one is incentivised to be right(*1564*)
Richard Horton, editor-in-chief of *The Lancet*

The crippling of individuals I consider the worst evil of capitalism. Our whole educational system suffers from this evil. An exaggerated competitive attitude is inculcated in the student, who is trained to worship material success as a preparation for his future career.(*587*) Albert Einstein

Another challenge following science's success was that many started paying attention to science, not primarily for pursuing knowledge, but for making a profit out of this successful method(*1565*). The challenge of prioritizing materialistic whims over knowledge and truth has accompanied the pursuit of knowledge from the beginning. Socrates, Plato(*1566-1568*), and Aristotle(*1569*) were extremely critical of *sophists*. While Socrates refused to take any money for what he did and lived an extremely modest life, sophists taught primarily for money. During centuries, *sophistry* turned into a word for denoting "willingness to prostitute something high, to pursue knowledge or wisdom for low ends(*1570*)"(*1457, 1571-1575*), also see(*1573, 1576-1578*).

The sophist is a man who is unconcerned with the truth, or does not love wisdom, although he knows better than most other men that wisdom or science is the highest excellence of man. […] He is concerned with wisdom, not for its own sake, not because he hates the lie in the soul more than anything else, but for the sake of the honor or the prestige that attends wisdom. He lives or acts on the principle that prestige or superiority to others or having more than others is the highest good.(*1579*) Leo Strauss

Sophistry is well alive today(*473, 1464, 1580-1595*): In several cases, I had provided convincing established scientific evidence that the core of some study was completely wrong; however, I was responded by the investigators that "I only want to improve my CV." Similar notions abound: "Poor methods get results(*1564*)," "I will do anything for another line in my CV. […] [I am] just playing the game, working the system, trying to get ahead. Besides, this is how things work, you either do whatever is necessary or you get left behind(*1580, 1581*)." Focus of a majority of researchers is on how to write articles, how to publish, how to design tempting figures and graphs and where to buy materials, how

to get accepted, etc. I have seen thousands of advertisements for workshops like "how to publish articles," "how to get accepted by writing convincing cover letters," yet I do not remember a single advertisement for a workshop on epistemology or scientific method. Pursuit of knowledge, the public good, and awe in front of nature and possibilities have given their place to concern for publications, citations, metrics, CVs, and paychecks. Thinking, questioning, and doubting are not much important; after all, they do not show up on CVs. They even take the time that could be spent on adding more lines to CVs.

The current system fosters interests conflicting with pursuing knowledge at every step. Students have to focus on making their CVs enticing. Professors have to attract enough funds, lest they would be put under pressure by the business people who run the academia(*1596-1598*), to the point of committing suicide, like the late Stefan Grimm(*1599-1602*). Editors need to fill the pages of everyday-increasing journals. Even the tip of the iceberg(*1347-1351*) of scientific misconduct(*1352-1368*) is skyrocketing. Moreover, scientific misconduct has even been adapting and evolving into more sinister varieties. Some have become organizational business models(*1603-1605*). Like the evolution of camouflage, some have tried to reduce the potential damage by employing low-profile strategies of scientific misconduct and gaming the metrics(*1606-1612*). Overselling and marketing approach has become so pervasive that some may not identify it as misconduct(*1432, 1613-1617*): From 1974 to 2014, the relative frequency of the word *novel* in PubMed abstracts has increased by about 4000% and it is predicted that it will appear in every record by the year 2123(*1431*). Even with the purest of intentions, we face manifold barriers and biases in pursuit of knowledge. What hope is left when there is no care for truth(*1618*)?

Natural Philosophy is Meaningless Without Philosophy

Science without epistemology is, insofar as it is thinkable at all, primitive and muddled.(1065)
So many people today—and even professional scientists—seem […] like somebody who has seen thousands of trees but has never seen a forest. A knowledge of the historic and philosophical background gives that kind of independence from prejudices of his generation from which most scientists are suffering. This independence created by philosophical insight is the mark of distinction between a mere artisan or specialist and a real seeker after truth.(*1619*) Albert Einstein

My opinion about the high, majestic task of philosophy is to make things clear.(*1620*) Ludwig Boltzmann

Philosophy aims at the logical clarification of thoughts. Philosophy is not a body of doctrine but an activity. A philosophical work consists essentially of elucidations. Philosophy does not result in 'philosophical propositions', but rather in the clarification of propositions. Without philosophy thoughts are, as it were, cloudy and indistinct: its task is to make them clear and to give them sharp boundaries.(*605*) Ludwig Wittgenstein

But how can specialization and fixation on products of science be remedied while the accumulative growth of the products of science is inevitable? To remedy its too-much specialization, science must not abandon its original unspecialized form, from even before we discovered the importance of concrete observations and introduced it as dogma: *philosophy*. We must clear our understanding of what science is and what it is not and where its power comes from. We must understand that the power of science does not come from its adherence to "evidence." Do not frameworks other than science claim "evidence" for their statements? They surely do. What distinguishes philosophy and science among them is that they do not impose any dogma but moving toward knowledge; thereby, they have exempted no claim of "evidence" from questioning and doubt and have revealed deficiencies of most claims of "evidence." This way, they have also concluded that concrete observations are the most reliable source of "evidence." But this important discovery does not imply that the *philosophy* part of *natural philosophy* is dispensable. As Daniel Dennett put it, "There is no such thing as philosophy-free science; there is only science whose philosophical baggage is taken on board without examination.(*848*)." Observed phenomena are not in a vacuum. They do not hold a label that would unambiguously convey their meaning and interpretation. Scientific observations and conclusions depend on the specific theoretical and value backgrounds and the zeitgeist they get embedded in(*636, 1621-1629*). What counts as a valid observation, how to design studies, what variables should be considered, what data the instruments are actually collecting, and how to infer general patterns; all these require philosophical thought(*1630-1632*). Despite this and the reliance and stress of many scientists, especially the great ones, like Charles Darwin(*674, 686, 695, 1633, 1634*), James Clerk Maxwell(*1635, 1636*), Ludwig Boltzmann(*1620*), Henri Poincaré(*607*), Karl Pearson(*1054*), Albert Einstein(*1065, 1619, 1637-1642*), Niels Bohr(*1643*), Werner Heisenberg(*1644, 1645*), Wolfgang Pauli(*1646*), Erwin Schrödinger(*9, 1647*) and Alan Turing(*1648, 1649*) on philosophy, nowadays, a majority of the scientific community, in ignorance of what philosophy and science are, have drawn a misplaced concrete line between them(*636, 1638, 1650-1652*); e.g.,(*1032, 1653-1659*). Alas, professional academic philosophers themselves are also responsible for this(*1644, 1660-1662*). This has led to the enduring fallacies and wastes of rote science, only a sample of which we have seen in this manuscript: Is the binding of a chemical to an in vitro or in silico model of a protein "sufficient evidence" for it having a specific therapeutic effect? Is it even "sufficient evidence" for its binding to that protein in the body? Is a small p-value in a pharmaceutical clinical trial "sufficient evidence" for using that drug for an individual? Can we neglect most variables and still expect to reach "the same conclusion" from different observations? All this aside, the most important question is what to ask; e.g., is seeking the definition of "life" or the exact historical origin of "life" even rational?

It is one of the principal impediments to the advancement of natural philosophy, that men have been so forward to write systems of it. […] the specious and promising titles of these system-writers are apt to persuade the unwary, that all the parts of natural philosophy have already been sufficiently explained; and, consequently, that it were needless for them to be at any farther expence and trouble in making enquiries into nature; the business being done to their hands. […] Such kind of superstructures should be looked upon only as temporary, and preferable, indeed, to others, as being the least imperfect yet not entirely to be acquiesced in, as incapable of farther improvements and useful alterations.(1663)
Robert Boyle, who through his many contributions, including *The Sceptical Chymist* (note the reference to doubt), was pivotal in the Scientific Revolution(*1664*)

Concepts that have proven useful in ordering things easily achieve such authority over us that we forget their earthly origins and accept them as unalterable givens. Thus they come to be stamped as "necessities of thought," "a priori givens," etc. *The path of scientific advance is often made impassable for a long time by such errors.*(*1619*) Albert Einstein

Science can be pictured as a telescope through which we try to see the world with the highest "objectivity." Apart from the fact that this "objectivity" is "relative" as we are all confined to our indelible humane observation point, each theoretical and methodological framework and zeitgeist, e.g., Thomas Kuhn's *paradigm*(*1665*) or Michel Foucault's *episteme*(*1666, 1667*), can be regarded as a specific configuration of this telescope which may provide optimal vision for some points. But they should not be taken as a universally true dogma. For each purpose, the configuration must be calibrated to overcome *epistemological obstacles*(*1668*) and align optimally with "reality." Particular configurations should not be black-boxed and uncritically followed. This is especially important in biological sciences due to organisms' uniqueness(*875*); e.g., in employing the framework presented here, it is imperative to critically think and discuss in each case what variables to include, where to draw the line between different variables and variable-values, what observations can provide the best data for our needs, or if it is wise to follow up an unexpected observation; also see Popper's botany example in (*1429*). The impact of this can be illuminated by recalling that a considerable number of approved drugs have originated from sagacity and critical thinking upon serendipitous observations (figure 3 and supplementary data 1) and dismissal of such careful and critical observations has been

suggested as one culprit of the decline of drug discovery(*1669-1671*). As Louis Pasteur remarked, "In the field of experimentation, chance favors only the prepared mind(*997*)." And at all times, the frameworks themselves should be questioned too. Specialization sweeps all inconsistencies under the rug of technical terms and "norms of the profession" and discourages self-correction based on alternative views and real-world data and creates internally self-consistent(*47*) static bubbles with little contact with reality.

Scientific research, as a way of expanding knowledge, obliges us to overcome classicism. The very process of apprenticeship carries within itself the requirement that it come to an end and yield to independent creation. To study or to learn from a classic ultimately impels us to emulate what its author did: to surpass the previous classical stance, to transform, to extend, and to renew science itself.(*1672*) José Ortega y Gasset

Philosophy is also the root of the social infrastructure of science (it must be remembered that there is no concrete line between philosophy and science(*636*)). If "evidence" and data could talk for themselves, what was the need for peer criticism and discussion? As every human has manifold unexamined presuppositions, by debating and criticizing each other's works, scientists can notice the biases that have remained hidden to themselves. This *intellectual inclusion* in which interlocutors elevate each other is an ancient pillar of philosophy and science, e.g., in Plato's Academy. Let us see how intellectual exclusion has hindered the progress of science.

We recognized foundationalist materialism as one of the major flawed mindsets behind "replication crisis" and "evidence-based" medicine. But what is the root and origin of this mindset? I argue that one of its major roots is the exclusivity of the Judeo-Christian and "Western"(*1673*) worldview among the pioneers and early developers of modern science. Judeo-Christian worldview depicts, at least, humans as foundational entities: "souls" that have come *to* this world. This implies that, first, nature is foundationally alien to and different from us. Second, as we discussed, a foundational "entity" or "material" implies some inherently fixed phenomena which can be captured in a moment (Nietzsche refers to this attitude as soul-atomism(*690*)); in contrast to a flowing process which cannot be captured in a cross-section of time, as it also expands temporally. You can contrast this with the "Eastern" worldview which depicts humans and everything else we see, as processes that come *out of* this world(*1005, 1674-1679*). A *becoming* versus a *being* view(*1680, 1681*). Here, the argument is not on the correctness of these views, the point is that intellectual inclusion and "a bit of blood-transfusion from Eastern thought(*9*)" could have made the scientific community aware that foundationalist materialism is not the only way of looking at the world; that it has employed such a presupposition.

Nowadays, the education system and scientific community, not only do not strive to explore diverse intellectual landscapes, they have turned into extremely rigid and static echo chambers that readily fixate and get hung up on the first publishable framework that they stumble upon(*1541, 1546, 1553, 1554, 1682-1688*).

Illusion of Scientific Progress

The history of Western science confirms the aphorism that the great menace to progress is not ignorance but the illusion of knowledge.(*1689*)

The scientific community, much like the public, is mesmerized by the highly advanced technologies and the immense corpus of knowledge we possess. E.g., a recent *PNAS* article that tries to resolve the "seeming paradox" of "scientific progress despite irreproducibility" states that "No one aware of the present state of science doubts the many important advances that are taking place almost daily. […] Examples are particularly evident in technology and health: computers, cellphones, satellites, GPS, information availability, antibiotics, heart operations, increasing age of mortality, fertilizers, genetically improved crops, minimally invasive joint surgeries and joint replacements, contact lenses and laser surgery, magnetic resonance imaging, robotics, electric vehicles, air bags, solar energy, wind energy, better weather forecasting, and on and on almost without end(*1690*)."

Again, the fallacy here is mistaking products of science for science. Products of science have been extended and accumulated for a long time and we have inherited these products. This does not imply that we are also currently enjoying "the rapidity of scientific progress(*1690*)." You can see in table 2 that the initial seeds of all the innovations exampled to showcase "the translation of the evolving web of scientific advances into applications(*1690*)." can be traced back to before the 1970s. As some scientists including Nobel Laureates(*1686, 1715-1724*) have pointed out, we have been majorly just reaping the innovations of previous generations. Our major role has been linear extension of those innovations; e.g., we have been able to further develop computers, AI, ML, and deep learning which were initially innovated before the 1970s(*1114, 1725*). Innovation of vaccination dates back to ancient times(*1726-1728*): From observing in 420 BCE that "No one was ever attacked a second time" by the plague of Athens(*1729, 1730*) to deliberate prophylactic immunization in China in 300 to 1000 CE and Edward Jenner's safer method in 1798 based on phenotypic observations(*1731*). The scientific community not only has failed to extend the success of previous generations in confronting chained systems to complex systems, it even has not been aware of this failure. Among the examples, antibiotics and anesthetics are the only successes in front of complex systems; interestingly, all antibiotics and anesthetics have been discovered based on phenotypic observations, not "rational" drug design, the currently dominant paradigm (figure 3 and supplementary data 1). We probably could not have discovered these drugs if we had sooner "progressed" to our current "scientifically advanced" state. Even in physics, to which the reign of rote science extends(*1538, 1683, 1684*), there has been an unrequited quest for fundamental progress since the 1970s: We have not been successful, except in experimental validation of previous innovations(*1732*).

Table 2. Examples brought for "the translation of the evolving web of scientific advances into applications" to showcase our current scientific progress.

Technology	Innovation	Refs
Computer	1834 - 1941	(*1691*)
Cellphone	1940 - 1973	(*1692, 1693*)
Fertilizer	c. 5900 BCE	(*1694*)
GPS	1958 - 1978	(*1695, 1696*)
Satellite	1957	(*1697*)
Genetically improved crops	c. 8000 BCE – 1994	(*1698*)
Heart operations	1896	(*1699*)
Minimally invasive surgery	1938	(*1700*)
Joint replacements	1890	(*1701*)
Contact lenses	1508-1887	(*1702*)
Laser surgery	1951-1962	(*1703*)
Magnetic resonance imaging	1938-1974	(*1704-1708*)
Robotics	1961-1972	(*1709*)
Electric vehicles	1832-1870s	(*1710*)
Air bag	1952	(*1711*)
Solar energy	c. 1000 BCE - 1876	(*1712*)
Wind energy	600 - 1887	(*1713, 1714*)

Science becomes dangerous only when it imagines that it has reached its goal. What is wrong with priests and popes is that instead of being apostles and saints, they are nothing but empirics who say 'I know' instead of "I am learning," and pray for credulity and inertia as wise men pray for scepticism and activity.(*1733*) Bernard Shaw

The only way that we will make a mistake is that in the impetuous youth of humanity we will decide we know the answer.(*1734*) Richard Feynman

It may be argued that this is because we have reached the "end of science"(*1552, 1723, 1735*), that we already know all possible fundamental scientific principles and the only thing we are left to do is to uncritically produce more data and fill in the details. This is a delusion imbued by rote science. As it can only see new permutations of previous studies, it is blind to the vast sea of the knowable unknowns and all the possibilities(*772*). Perhaps it is correct that as Dirac pointed out in 1929, "The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known(*1736*)." Still, in other fields like biological sciences, especially psychological and social sciences, we are in infancy(*1033*). And as we saw, these sciences are decoupled(*43, 1036*) from "the underlying

physical laws." "There is no limit to the complexity that we can build using those basic laws(*2*)." An open-ended untrodden landscape lies before us.

Let alone transformative innovation; in many cases, we have even failed to develop and employ the innovations which were handed down to us, and instead, have used them in completely wrong ways. We have failed our milestones in taming infections that are taking millions of lives(*1737, 1738*), by relying on reductionist "rational" vaccine design(*1739-1742*). We have molded X-ray crystallography; nuclear magnetic resonance imaging, rational drug discovery(*113-115*), computers, AI, ML, and deep learning(*1743*) into the wasteful paradigm of "rational" drug discovery.

There's an awful lot of rote learning, and a lot of mistaking knowledge for the right technical words. A guy who says the right words is thought to know something. […] it's not at all impossible to teach a child to say that pi is the ratio of the circumference to the diameter of a circle. It's just as easy to teach him a nursery rhyme. And then to say that pi is numerically equal to 3.14159. That way you can get fooled. You haven't the slightest idea what you're talking about, and you sound just fine.(*1734*) Richard Feynman

Rote science makes fundamental innovation and the full potential of science unreachable as it severs first-hand contact with the real world by censoring it through one-size-fits-all frameworks and reified concepts. Knowledge of a majority of us is like how Feynman depicts above: We may write articulate and highly cited articles; however, what we are looking at is only nature's reflection in previous generations' minds passed to us through the established frameworks and conceptions we have uncritically followed. We do not have close contact with reality.

Those who fall in love with practice without science are like a sailor who enters a ship without helm or compass, and who never can be certain whither he is going.(*1248*) Leonardo da Vinci

Scientists here seem to work hard. In fact, some of them work so hard that there is no time left for serious thinking. They should heed the saying, 'A busy life is a wasted life.'(*617*) Francis Crick

One can watch an object for years and never produce any observation of scientific interest. To produce a valuable observation, one has first to have an idea of what to observe(*996*) François Jacob

Many areas of biology seem stuck with nineteenth-century authoritarian ideology, which favours data production over generating new ideas or questioning stale paradigms. This encourages a kind of 'excellence in mediocrity', which drives off creative minds and attracts researchers who imitate rather than innovate. […] This is not surprising considering that PhD students in the biological sciences receive little or no exposure to the history and philosophy of scientific thought, making the degree a misnomer. Few biologists can distinguish between speculation, demarcated hypotheses and theories. Even fewer appreciate the need for revolutionary hypotheses; and fewer still can generate them.(*1522*) (emphases added)

We may spend billions of hours and dollars(*1744*) and impose agony on millions of animals(*1745*) to produce tons of data and publish incessantly more articles(*1746-1749*). Yet this does not imply that these articles and data have any valuable relation to the real world(*1546, 1750-1753*); recall "replication crisis," the decline of drug discovery, and the far-from-expected output of omics. The evidence I have presented to support the too-week foundations of several paradigms that have been exclusively dominant for decades implies that most of the current conclusions and even the gathered data in biological sciences are of minimal reliability(*453*) and value that they could have had, if the scientific community had upheld, instead of its products, science itself. Even without considering the huge waste of rote science, and also without considering the bias imposed by the ubiquity of scientific misconduct(*1618*), it has been suggested that above 85% of resources spent for scientific research is wasted(*498, 1754-1758*).

So, relative to available resources, our scientific practice is at an all-time low in history. Let us delve into some benefits of science that rote science has deprived humans of.

The Universal Domain of Science: Society's Truth Buffer

Scientific education is fabulously neglected. This is an evil that is inherited, passed on from generation to generation. The majority of educated persons are not interested in science, and are not aware that scientific knowledge forms part of the idealistic background of human life. Many believe—in their complete ignorance of what science really is—that it has mainly the ancillary task of inventing new machinery, or helping to invent it, for improving our conditions of life. They are prepared to leave this task to the specialists, as they leave the repairing of their pipes to the plumber. If persons with this outlook decide upon the curriculum of our children, the result is necessarily such as I have just described it.(*1647*) Erwin Schrödinger

Science claims the whole universe as its field.(*1054*) Karl Pearson

Let us apply to the political and moral sciences the method founded upon observation and upon calculus, the method which has served us so well in the natural sciences. Let us not offer in the least a useless and often dangerous resistance to the inevitable effects of the progress of knowledge; but let us change only with an extreme circumspection our institutions and the usages to which we have already so long conformed.(*3*) Pierre-Simon Laplace

You frequently state that I have developed a completely one-sided outlook and look at everything and think of everything in terms of science. […] But you look at science as some sort of demoralizing invention of man, something apart from real life, and which must be cautiously guarded and kept separate from everyday existence. But science and everyday life cannot and should not be separated.(*1759*) Rosalind Franklin (emphasis added)

Origin of the fallacy of neglecting the subjective and theory-laden nature of observations and "letting data speak for itself" can be traced back to Francis Bacon. He drew a concrete line between humans and nature(*1760*). This fallacy has resulted in dogmatically avoiding first-person pronouns in scientific communications(*1761-1763*); however, considering Bacon's emphasis on being aware of our different biases, e.g., in his four "idols of the human mind"(*1039*), he probably would have been appalled by our current rote science(*1764*).

The human understanding resembles not a dry light, but admits a tincture of the will and passions, which generate their own system accordingly; for man always believes more readily that which he prefers. […] in short, his feelings imbue and corrupt his understanding in innumerable and sometimes imperceptible ways.(*1039*) Francis Bacon

The rigour of science requires, that we distinguish well the undraped figure of nature itself from the gay-coloured vesture with which we clothe it at our pleasure.(*1765*) Heinrich Hertz, translated and quoted by Ludwig Boltzmann

Still, this fallacy of drawing a too-concrete line between humans and nature has had immense repercussions. It has deprived humans of prioritizing science in "all the contingencies of life(*584*)" including governance and management of societies. It is presumed that science "has mainly the ancillary task of inventing new machinery, or helping to invent it, for improving our conditions of life(*1647*)." Because of this, many, in complete ignorance of what philosophy and science are, have no guilt in stating that they have nothing to do with science or do not trust science. "They are prepared to leave this task to the specialists, as they leave the repairing of their pipes to the plumber(*1647*)." This is like saying they have nothing to do with knowledge and truth. Philosophy and science are the supreme approaches toward understanding any phenomena in the unitary whole of the universe. "The whole of science is nothing more than a refinement of every day thinking(*1766*)." By restricting science only to utilitarian applications(*1565*), our current culture deprives us of this refined thinking and turns us into commodity-producing automata. Science is not confined to the arbitrary boundary of some specializations and already-conceived questions. It is "identical with human wisdom, which always remains one and the same, however, applied to different subjects, and suffers no more differentiation proceeding from them than the light of the sun experiences from the variety of things which it

illumines(*584*).” “To say that there are certain fields from which science is excluded, wherein its methods have no application, is merely to say that the rules of methodical observation and the laws of logical thought do not apply to the facts, if any, which lie within such fields(*1054*).” Do behaviors of humans lie outside the universe? Do “politicians” have access to some source of knowledge which is superior to philosophy and science? So, why the scientific community has handed the fate of our species to “politicians” who are known for concealing the truth and lacking the slightest hint of rationality and wisdom(*1767*)?

There is no end to suffering, for our cities, and none, I suspect, for the human race, unless either philosophers become kings in our cities, or the people who are now called kings and rulers become real, true philosophers(*1568*) Socrates

It is of great importance that the general public be given an opportunity to experience—consciously and intelligently—the efforts and results of scientific research. It is not sufficient that each result be taken up, elaborated, and applied by a few specialists in the field. Restricting the body of knowledge to a small group deadens the philosophical spirit of a people and leads to spiritual poverty.(*587*) Albert Einstein

Philosophical thinking has never been more important than it is today, because there's a whole system taking shape, not just in politics but in culture and journalism too, that's an insult to all thinking.(*627*) Gilles Deleuze

It may be argued that science is silent on moral values and thereby, cannot be an alternative. When humans confronted phenomena whose origins, they were ignorant of, like thunders and floods, they invoked untrue causes and agents to justify and respond to these unusual phenomena. In many instances, these illusions resulted in unimaginable unnecessary agony; e.g., countless children and animals have been sacrificed to stop floods(*1768*). Thousands of women have been tortured, murdered, and burned for witchery(*1769-1773*). Many children have been persecuted and murdered for witchery or bringing misfortune(*1774, 1775*). Although some of these atrocities are still taking place(*1771-1775*), many of them are far less prevalent in many societies. Why? Through science, we have come to this *understanding* that, e.g., floods have nothing to do with sacrificing children like how albinism has nothing to do with witchery. Through science, we have understood their natural causes and risen above many of these challenges. We have dissolved our moral conviction and moved toward *amorality* and understanding(*1776-1778*). I assert the two revolutions discussed here, in biological sciences and our conception of science, can dissolve many of our moral convictions that are based on ignorance. Such moral convictions are causing problems extending from those that are threatening the entire human civilization, like fundamentalism, extremism, discrimination, and polarization, to everyday challenges in communication which are due to our ignorance of psychological and social causes of phenomena.

Let me bring an example for the amoralizing effect of science. In recent years, attention toward diversity and inclusion has culminated in large progress(*1779-1781*). However, progress in some aspects has lingered or even stalled(*1781-1787*). Some suggest that resuming progress requires fundamental social and cultural shifts(*1781, 1787, 1788*). A drawback of current discussions promoting inclusion and diversity, even in the scientific community, is that they are only backed up by moral convictions. Moral convictions are subjective(*1789*). Those who oppose inclusion and diversity in many aspects are also propelled by moral convictions(*1790-1794*). And because of the subjectivity of morality, it is probably impossible to convince and convert them based on moral arguments.

Let us employ a completely different perspective: the more “objective” perspective of science. Let us try to see “our” composing processes as outside observers. Now, let us compare the objective trajectories of the preferable scenarios of these two subjective convictions: a human society promoting while the other curtailing diversity and inclusion. We have already compared two similar scenarios: the group of bacteria that embraced variation and diversity versus the group that did not. As we saw, evidence supports this conclusion that embracing variability and diversity enables exploring novel capabilities(*858-860*). Organisms have been selected for embracing diversity and inclusion(*359-372*). This has enabled their expansion and evolution to all the diverse forms we see. Similarly, it is wise to see that a group of humans that actively promote diversity and inclusion among themselves, is “objectively” and naturally far more capable to gain enhanced and new capabilities and opportunities. Empirical evidence corroborates this outlook(*1795, 1796*). Still, in line with our realization that unification of biological sciences and physics does not entail being able to capture everything with a simple physics formula, being able to dissolve psychological and social phenomena by science should not entail too simplistic and naive attitudes; otherwise, upside-down conclusions may ensue(*1790, 1797*). “Although science claims the whole universe as its field, it must not be supposed that it has reached, or ever can reach, complete knowledge in every department. Far from this, it confesses that its ignorance is more widely extended than its knowledge(*1054*)” Even where science does not lead to conclusive dissolution, it brings this important realization that the conviction we choose to employ is not fueled by unequivocal and irrefutable “objective” reasons: this can alone increase our tolerance toward others(*1798*).

Besides dissolving many, not all, moral challenges, “objective” scientific vantage points toward phenomena can reveal broader implications of “objective” principles which are not at all visible when remaining confined to moral convictions: Intellectual inclusion is among such implications of the principle of diversity.

Metacognition

I am wiser than this man, for neither of us really knows anything fine and good, but this man thinks he knows something when he does not, whereas I, as I do not know anything, do not think I do either. I seem, then, in just this little thing to be wiser than this man at any rate, that what I do not know I do not think I know either.(*1799*) Socrates (emphasis added)

Our attempt to employ toward our moral convictions, an “objective” perspective by seeing “ourselves” as outside observers, is an example of trying to achieve metacognition: becoming cognizant of our own cognition. By clearing the line between nature and humans and realizing that we are among the composing processes of this unitary universe, we can better appreciate that our cognition and behaviors are investigable and understandable by philosophy and science. Metacognition is especially important for the second scientific revolution. It makes us aware and helps us manage our manifold biases(*1800*). Let us skim over some metacognitive standpoints.

We Have Not Evolved to Pursue Knowledge and “Truth”:

We must, however, acknowledge that man with all his noble qualities, […] still bears in his bodily frame the indelible stamp of his lowly origin.(*1633*) Charles Darwin

This is the origin of many of our biases.

Incomprehensibility of the Extent of Complexity for Human Cognition:

The complexity that our species evolved to deal with is incomparable to the complexity we may currently face in science and our societies. Our working memories can keep and process only a few objects at a time(*1801-1804*). Thus, similar to how we cannot perceive the extent of the meagerness of the size of Earth compared to the whole universe, we cannot perceive the extent of the difference between a single recursion of truism-law-of-survival and the “number” of recursions from LUCA to ourselves, neither can we perceive the extent of the irrationality and inefficiency of “rational” drug discovery (supplementary data 2).

Binary Thinking: Digitizing a Continuous Spectral Complex World:

One way to cope with such overwhelming amounts of complexity is to reduce them into a few discrete manageable categories and digitize the continuous and spectral reality(*425-430*). This is one reason for the pervasiveness of reducing complex phenomena to a few variables and “substituting scientific reasoning(*500*)” with “mindless statistical rituals.”

Herd Mentality:

Another way to cope with the complexity we have evolved to embrace is to follow peers and take for granted most of what we are told(*1805-1808*). Yet we must remember this is not optimal for pursuing knowledge(*1529, 1809*).

A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.(*1810*) Max Planck

Inflexibility of Developed Structures:

By the time most scientists have reached age thirty they are trapped by their own expertise.(*617*) Francis Crick

In emergent bound box theory, we saw that through recursions of truism-law-of-survival, states of constituents of organisms get bound to a subset of their possible states. Constituents of organisms may get so bound to specific states that they would discourage the emergence of diversity and novelty. This pattern occurs in human organizations too. It has been shown that when they get very large, their creativity diminishes(*1811-1814*) and they show unproductive behaviors which minimize their organizational efficacy(*1815, 1816*). Large organizations become too stable to disrupt and innovate radically. This is why many fundamental and radically disruptive innovations have emerged from solitary individuals rather than large teams. There is a polarity between stability and creativity(*1817, 1818*).

This is a challenge, especially in this era. Organizations have become so large and complex that they may resist any change unless forced to (like in COVID-19 pandemics). This also inflicts the scientific community. A concrete example is the manuscript you are reading: Commending Schrödinger's conception of science, I have strived that the work "aims at nothing but making true and adequate statements about its object(*9*)"; however, I may not be able to share it properly because of not adhering to common size limits that are vestiges of the pre-internet era. Despite environmental impetus, scientific journals still follow established habits and stick to printing in the digital era and thereby, also impose unnecessary pains for both authors and readers(*1819-1824*); also see (*1825*). Remembering this bias and the fact that established habits and bureaucracies are not natural laws cast in stone but are created by us, and that change, flexibility, and inclusion are necessary, can itself make us more tolerant(*1541, 1686, 1688, 1715-1717, 1719-1721*).

Scientific Conviction
It Is Convicted That I am

A doubt that doubted everything would not be a doubt.(*1826*)
Ludwig Wittgenstein

It would be a mistake to suppose that a science consists entirely of strictly proved theses, and it would be unjust to require this. Only a disposition with a passion for authority will raise such a demand, someone with a craving to replace his religious catechism by another, though it is a scientific one. […] It is actually a sign of a scientific mode of thought to find satisfaction in these approximations to certainty and to be able to pursue constructive work further in spite of the absence of final confirmation.(*1827*) Sigmund Freud

The fundamental cause of the trouble is that in the modern world the stupid are cocksure while the intelligent are full of doubt. Even those of the intelligent who believe that they have a nostrum are too individualistic to combine with other intelligent men from whom they differ on minor points. […] Perhaps we shall have to realise that scepticism and intellectual individualism are luxuries which in our tragic age must be forgone, and if intelligence is to be effective, it will have to be combined with a moral fervour which it usually possessed in the past but now usually lacks.(*1828*) Bertrand Russel (emphasis added)

Descartes tried to build his knowledge upon questioning and doubting everything he had taken for granted, including the reliability of his perception from the physical world(*584, 1829, 1830*). He reasoned he could not refute the possibility that some omnipotent demon was deceiving his perception. He supposed that to pursue knowledge, it is necessary to find an initial certain and indubitable firm ground to build upon: "Archimedes, in order that he might draw the terrestrial globe out of its place, and transport it elsewhere, demanded only that one point should be fixed and immovable; in the same way I shall have the right to conceive high hopes if I am happy enough to discover one thing only which is certain and indubitable(*584*)." "After having reflected well and carefully examined all things," he infamously asserted "I think, therefore I am(*584*)."

But this assertion does not seem to be indubitable at all as many have already criticized it(*690, 1446, 1831-1836*); also see (*1837*). Here, I question Descartes' presumption that it is necessary to build knowledge on certain and indubitable grounds. Philosophy and science do not impose certainty, but moving toward knowledge.

We shall seek metacognition toward the most important approach of moving toward knowledge. We said that philosophy and science have been the most successful frameworks for gaining knowledge about the world because they exempt nothing from questioning and doubt. Now, let us doubt doubting itself. Doubt is integral for pursuing knowledge but is not the end itself. As John Dewey put it, "Taken merely as a doubt, an idea would paralyze inquiry. Taken merely as a certainty, it would arrest inquiry. Taken as a doubtful possibility, it affords a standpoint, a platform, a method of inquiry(*1557*)." To build up knowledge, there is no need for our initial ground to be "certainly true." What is needed is awareness toward the extent of the reliability of assumptions we build on; if we are *justified* to employ them or not. From a view, this is what we have been adhering to all along in modern statistical methods: It has never been *proven* that a treatment is effective. It has been shown that we are justified or not to suppose that a treatment is effective (according to the framework of modern statistical methods). Remembering that the aim of philosophy and science is moving toward knowledge, not certainty and that radical skepticism(*1838*) is a choice itself, it should be noted that this justification is relative. We must decide which choice is closer to truth. Absolute truth is not a desideratum. I propose an alternative for Descartes' *cogito*: It is convicted that I am.

Scientific conviction is to open a set of parentheses and inside that parentheses, to fully commit to the implications(*1839*) of that conviction, but always to be willing to abolish the conviction and the whole implicated parentheses if contradicted by more justifying arguments and evidence.

The popular view that scientists proceed inexorably from well-established fact to well-established fact, never being influenced by any unproved conjecture, is quite mistaken. Provided it is made clear which are proved facts and which are conjectures, no harm can result. Conjectures are of great importance since they suggest useful lines of research.(*1840*)
We can only see a short distance ahead, but we can see plenty there that needs to be done.(*1841*) Alan Turing

Science is a way to teach how something gets to be known, what is not known, to what extent things are known (for nothing is known absolutely), how to handle doubt and uncertainty, what the rules of evidence are, how to think about things so that judgments can be made, how to distinguish truth from fraud, and from show.(*1734*) Richard Feynman

The *fallibilist* and *pragmatist* attitude(*377, 1629, 1831, 1842-1846*) of scientific conviction, besides its importance in addressing the ancient challenge of radical skepticism, is especially important in our post-truth era which is rife with impartial and biased use of information, radical relativism and sophistry. Although it may sound that scientific conviction decreases flexibility, I argue that it even increases it and promotes intellectual inclusion. It discourages authoritarianism of some "certainly true" dogma(*1847*) and emphasizes reflective practice(*1848, 1849*). Scientific conviction highlights that pursuit of knowledge is interwoven between building frameworks and destroying them based on observing their real-world implications(*1850*); between the willingness to fail and to reconsider previous convictions while exploring the unknown(*1851,*

1852). Yet it also emphasizes that indecisiveness makes opportunity for those unconcerned with truth. Public education of scientific conviction and how to embrace uncertainty is necessary in our post-truth era(*1853, 1854*); also see (*1855*).

So, my criticisms against "waste" of resources by "rational" drug discovery or "evidence-based" medicine are not aimed at the mistakes per se; mistakes are a part of science(*1852*). The problem is that the dominant rote science cannot self-reflect and self-correct. It not only does not question to enable correcting mistakes but uncritically builds upon whatever it is told and cements mistakes into "a priori givens(*1619*)." The problem is rote science's inherent inability to move toward knowledge.

The sophist, in contradistinction to the philosopher, is not set in motion and kept in motion by the sting of the awareness of the fundamental difference between conviction or belief and genuine insight.(*1579*) Leo Strauss

The way in which knowledge progresses, and especially our scientific knowledge, is by unjustified (and unjustifiable) anticipations, by guesses, by tentative solutions to our problems, by conjectures. These conjectures are controlled by criticism; that is, by attempted refutations, which include severely critical tests. […] As we learn from our mistakes our knowledge grows, even though we may never know-that is, know for certain. Since our knowledge can grow, there can be no reason here for despair of reason. And since we can never know for certain, there can be no authority here for any claim to authority, for conceit over our knowledge, or for smugness.(1856) Karl Popper

The Last Chance

It is no easy matter to root out old prejudices, or to overturn opinions established by time, custom and great authorities. […] Where I have been necessarily led, in this disagreeable part of the work, to criticise the sentiments of eminent and learned authors, I have not done it with a malignant view of depreciating their labours, or their names; but from a regard to truth, and to the good of mankind.(*1857*) James Lind

Here, I have tried to push aside the mesmerizing and deceiving facade of the accumulated products of science and have asserted that our scientific progress, relative to the resources we possess, is the all-time low in history and our scientific practice has minimal relevance to the real world and is a "pseudoscientific imitation(*1430*)" of the scientific method that has changed the world and garnered science, its current credibility and authority. By these, I have not aimed at diminishing the importance of science; on the contrary, I aim to revitalize this most valuable and honorable achievement of "life" on Earth. I have aimed to make the scientific community aware of its condition, so that we may leave behind this all-time low: We cannot improve our reality until we see it. These hopes are based on two convictions: We have to change fast and We can change.

Why Do We Have to Change Fast?

A challenge is that, even with sufficient impetus, massive cultural and social changes generally need decades and centuries; however, the speed at which great dangers are threatening us compels us to accelerate our change.

1. Selection of Bad Science

Some intellectual sits at the typewriter and writes it all out as if the information were really known. The intellectual never says, "I don't know this," or "I'm not really sure." If he were to do so, he couldn't sell his articles because somebody else would come along and say that they have all the answers.(*1734*)
Richard Feynman

The first reason is that our current trajectory naturally leads to exceedingly less room and prospect for positive change in the future.

We saw that currently, questioning, doubting, and real-world value are not crucial in scientific practice. The commodity is the number of articles, citations, "impact factors," etc. The short-term attitude of the business people who run the academia and govern the scientific community does not leave room for science, just numbers(*1596-1602*). Strategies that optimize these numbers survive and propagate far better than those strategies which "waste" time for questioning, adherence to standards(*1263-1268, 1858*), thinking scientifically, and bringing real-world value. We saw how recursions of truism-law-of-survival create organisms highly efficient for what has enabled their survival. Similarly, if the current organizational values of the scientific community survive, the scientific practice will be even more rote, template-based, conformist and unable to solve real-world problems, unless where it could merely permutate previous solutions(*1859, 1860*). Complying with Goodhart's law(*1861, 1862*), "When a measure becomes a target, it ceases to be a good measure(*1859*)," new ways of gaming metrics are being devised constantly(*1606-1612*).

In the past, censorship worked by blocking the flow of information. In the twenty-first century, censorship works by flooding people with irrelevant information.(*1863*) Yuval Noah Harari

Even if one could persevere against all these systemic adversities(*1864*), and present to the world a scientific work with immense real-world value, there is a good chance that it will be lost among piles of valueless products of rote science(*1747, 1865, 1866*); e.g., look at how this 2007 article, even published by top scientists in a top journal, did not get sufficient attention and consequently, our species suffered the exact future that it had warned: "Coronaviruses are well known to undergo genetic recombination, which may lead to new genotypes and outbreaks. The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb. The possibility of the reemergence of SARS and other novel viruses from animals or laboratories and therefore the need for preparedness should not be ignored(*1867*)."

2. The Anthropocene Crisis

We have made a civilization based on science and technology and then at the same time have arranged things so that almost nobody understands science and technology. That is a clear prescription for disaster: We might get away with it for a while, but sooner or later this combustible mixture of ignorance and power is going to blow up in our faces.(*1868*) Carl Sagan (emphasis added)

Accumulation of products of science has empowered us over the environment to an extent unimaginable for our ancestors. Now, we can inflict damages to the environment that our ancestors were incapable of. Unlike this increasing power, we have regressed science to rote science and article-writing. Our education is also hung up on reciting products of science, rather than science itself. This has led to an unbalance: Currently, our species resembles a child who is given a gun (power). There is a great danger for both the child and others, not because of malevolence or stupidity, but because of ignorance. Our society is like an organism with immense power but without a mind and the ability to think. It lacks the most basic insight into the implications of its actions.

The investigation of the psyche is the science of the future. Psychology is the youngest of the sciences and is only at the beginning of its development. It is, however, the science we need most. Indeed, it is becoming more obvious that it is not famine, not earthquakes, not microbes, not cancer but man himself who is man's greatest danger to man, for the simple reason that there is no adequate protection against psychic epidemics, which are infinitely more devastating than the worst of natural catastrophes.(*1869*) Carl Jung

We are rushing into the extinction of human civilization. Only 100 seconds are left on Doomsday Clock, which is developed by the Bulletin of the Atomic Scientists and whose reaching midnight epitomizes the end of human civilization (thebulletin.org). Challenges like global climate change and other environmental issues like declining biodiversity(*1334, 1335*), antibiotic-resistant bacteria(*1870*), pandemics, food security and hunger(*1344, 1345*), misinformation, and cultural crises(*1571, 1593, 1767, 1871*) are getting bigger and bigger without suitably being attended to(*1872-1874*).

We Can Change

There is only one good, that is, knowledge, and only one evil, that is, ignorance.(1875) Socrates

On applying my mind to politics, I have resolved to demonstrate by a certain and undoubted course of argument, or to deduce from the very condition of human nature, not what is new and unheard of, but only such things as agree best with practice. And that I might investigate the subject-matter of this science with the same freedom of spirit as we generally use in mathematics, I have laboured carefully, not to mock, lament, or execrate, but to understand human actions; and to this end I have looked upon passions, such as love, hatred, anger, envy, ambition, pity, and the other perturbations of the mind, not in the light of vices of human nature, but as properties, just as pertinent to it, as are heat, cold, storm, thunder, and the like to the nature of the atmosphere, which phenomena, though inconvenient, are yet necessary, and have fixed causes, by means of which we endeavour to understand their nature, and the mind has just as much pleasure in viewing them aright, as in knowing such things as flatter the senses.(*1876*)
Benedict Spinoza

Laplace's model that we started this manuscript with implies that all our actions are predetermined. Although we saw that Laplace's model has many mistakes, it is hard to disagree that "our" actions depend, to a large extent, on causes that are out of "our control," like our emotions. But even in such a model, there is one thing that can change "our" "out-of-control" behaviors in response to similar phenomena: *understanding*(*697*). This is confirmed by the fact that today, fewer children are sacrificed to stop floods(*1768*). The understanding provided by science dissolved the emotions provided by blind moral convictions. Similarly, we can overgrow the age of sophistry by trying to understand why we have reached here, the consequences of not overgrowing this age, and why we may be kept in this age. Similar to our discovery in the Scientific Revolution, we can get benefit in our pursuit of understanding from previous observations recorded in history. Indeed, as may have been implied by my frequent use of quotes, many fallacies I criticized here had already been pointed out by scientists living hundreds of years ago. But currently, there is an infatuation with the new. This way we are losing thousands of years of experience and wisdom in pursuit of knowledge and are doomed to repeat the mistakes that have already been observed and recorded. We can infer that just like how the consensus of the intellectual community at Copernicus and Galileo's time did not reverse the fact that Earth goes around the Sun, the high number of our publications, citations, and "impact factors" does not imply that we have moved even an inch forward in pursuit of knowledge. In Feynman's words, "For a successful technology, reality must take precedence over public relations, for nature cannot be fooled(*1877*)."; also see (*1878*). We can recall approaches that have filled millions of pages during hundreds of years, without leading to meager valuable and truthful insight? Isn't rote science among such approaches? We can recall how intellectual communities of different ages gradually grew away from rationality and inclusion of new ideas and failed to optimally pursue knowledge.

In pursuit of understanding, we may confront realities that may seem discomforting at first; e.g., are not we caught up in a giant "rat race" of article-writing and CV-lengthening without any real-world output in spite of all the costs we accept: hundreds of hours of work from millions of researchers, billions of dollars, thousands of institutes and agony of millions of animals(*1745*)? Although many of us may reach our short-term wishes, is not our collective organizational efficacy too miserable? Isn't the honorable pursuit of knowledge molded into just one of the many documented "bullshit jobs(*1879*)" unconcerned with truth (*bullshit* entered the vocabulary of philosophy by Harry Frankfurt to denote unconcern for truth (*1464, 1880, 1881*)? Despite the abundance of scientific journals, institutions and universities, is our scientific output much different from hastily completed school homework and rewriting of previously established concepts and frameworks?

But even at these times, let us dissolve our frustration by understanding that even these phenomena themselves have had natural causes. E.g., as Bacon remarked, science's success leads to many phenomena that are naturally(*1882*) in "contrariety toward true knowledge" as they do not impose pursuing knowledge above everything else.

There is no composition of estate or society, nor order or quality of persons, which have not some point of contrariety toward true knowledge. That monarchies incline wits to profit and pleasure, and commonwealths to glory and vanity. That universities incline wits to sophistry and affectation, cloisters to fables and unprofitable subtilty.(*1883*) Francis Bacon

Also, let us remember this crucial point that all the criticisms and problems I have pointed out do not rid our community of being adherents to science whose ultimate dogma is moving toward knowledge, because many researchers have been unaware of the extent of the dreadfulness of our current state and trajectory. If after becoming aware, we continue our current trajectory, we will then become a disgrace to all great philosophers and scientists.

Our freedom to doubt was born out of a struggle against authority in the early days of science. It was a very deep and strong struggle: permit us to question — to doubt — to not be sure. I think that it is important that we do not forget this struggle and thus perhaps lose what we have gained.(1734) Richard Feynman

Time was when scientists and engineers were among the world's insurgents, daring to question the established order-the church-and to undermine its teachings by their theories and experiments. But the pendulum has swung, as pendulums do, and today the scientific community finds itself on the side of the establishment, in an age when "establishment" has become a "dirty word." Now science once again must take the initiative.(*1884*)

[We are] free to choose not to be conscious, but not free to escape the penalty of unconsciousness: destruction.(*1885*) Ayn Rand

Understanding is not itself sufficient. The current momentum needs massive momentum for change. We must diffuse the understanding we obtain to the whole scientific community. In parallel, we must vehemently strive for changing our immensely inflexible organizational structures. In hardships, let us gain strength by recalling how our forebearers persevered in pursuit of knowledge, in any circumstances and at any cost: From Socrates who chose death over abandoning the pursuit of knowledge (figure 11) to "the determination of Fellows [of the first modern scientific society] to withstand the domination of authority(*1427*)." Despite all my criticisms, the scientific community is, still, far ahead in many aspects from other communities: We form globally inclusive discussions and collaborations. There is much less attention to arbitrary geographical boundaries. And we are tolerant and appreciative to those who criticize us (a characteristic which is non-existent in many places); that I have been criticizing and hoping that my words would be reflected upon is a testament to this. Still, the survival of our global civilization depends on our massive change.

Now, the question is not which way is better to gain knowledge or the "mistakes" and experimentations we naturally commit along pursuing knowledge. The problem is a general unconcern for truth in the scientific community. This is while science is society's truth buffer. We, the scientific community, are responsible for all the misery we see in the world(*1771-1775*): from labor(*1886*) and mutilation(*1887*) of children to agony of animals, domestic violence, discrimination, terrorism, and finally, our imminent extinction. We are society's brain. We could have prevented these sufferings if we had upheld "the natural light of reason(*584*)" itself instead of getting hung up on the things it illuminates. Evidence and our current trajectory do not bode well for the sustainability of our global civilization(*1334, 1335, 1344, 1345, 1571, 1593, 1767, 1870-1874, 1888-1892*). And we, the scientific community, must feel responsible for it. We can keep all these problems under the rug as it may seem more comfortable, for a short while, to stick with the current trend. But one thing is certain: One way or another, our current trajectory will soon end. Either by awareness, self-questioning, and self-doubt of the scientific community or by the extinction of human global civilization.

I say unto you: one must still have chaos in oneself to be able to give birth to a dancing star.
I say unto you: You still have chaos in yourselves. Alas, the time is coming when man will no longer give birth to a star.
Alas, the time of the most despicable man is coming, he that is no longer able to despise himself.
Behold, I show you the last man.(*689*)
Friedrich Nietzsche

The unexamined life is not worth living.(*1799*)
Socrates, after choosing death by hemlock, on the charge of impiety and corrupting the youth,
over abandoning the pursuit of knowledge

Figure 11. The Death of Socrates by Jacques Louis David (1787).

Methods

Discovery origin of all approved drugs

I compiled the list of drugs approved by the FDA by the end of 2020 using three databases: National Center for Advancing Translational Sciences (NCATS) Inxight: Drugs (drugs.ncats.io/), Drugs@FDA (accessdata.fda.gov/scripts/cder/daf/index.cfm) and the Orange Book (fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book). I queried Inxight: Drugs choosing "US Approved OTC" OR "US Approved Rx" for the development status, "Approved" for highest phase, "Principal Form" for substance form, and excluding treatment modalities of "Secondary," "Inactive Ingredient," "Diagnostic." From Drugs@FDA, I retrieved drugs with type 1 (New Molecular Entity) and type 7 ("Previously Marketed but Without an Approved NDA") applications among "Original NDA and Original BLA Approvals" and excluded discontinued. I also checked and added non-discontinued drugs of the orange book if they were not already included. All these retrieved drugs are listed in supplementary data 1; however, I did not investigate the discovery origin of these groups of drugs: diagnostic agents like contrast agents; nutrients vitamins and nutrient inorganic ions; secondary agents which are not therapeutic themselves, like mesna; antidotes; enantiopure or racemic formulations of previously approved drugs; prodrugs of previously approved drugs; excipients; drug whose therapeutic effects depend more on the physical properties of molecules; e.g., surfactants, chelating agents, radiopharmaceuticals, photochemotherapeutics, and osmotic diuretics.

Drug discovery is a multitier process; it is important to settle upon definite and unambiguous criteria for discovery origin so that the decision whether drugs were discovered based on reductionism or not would be most "objective" (compare (*1893*) to (*562*) to see how the same drug has assigned differently to different discovery origins.) I defined *discovery origin* as the first observation that has related a drug class to a therapeutic effect. A *drug class* is a group of analogues (chemical and/or pharmacological(*1894*)) along with their respective lead molecules that

guided their discovery. To identify a set of chemicals as analogues with utmost "objectivity," I cited the literature (e.g., (*1894*)) and calculated feature trees as the molecular similarity measure using FTrees 6.3(*563, 1895, 1896*). I assigned drug classes to *Target-based* for when the discovery origin was observing the effect of the molecule on a "target" protein or *phenotype-based* for when the discovery origin was observing the effect of the molecule on a phenotype; following the seminal study of Swinney and Anthony(*562*), I counted biopharmaceuticals as a separate group, but also further sorted based on whether they are endogenous-based or not. I compared the share of these categories among all the approved drugs and among those approved after 1995, the approval year of the first "target-based" drug, saquinavir. Those drugs whose accurate discovery accounts were not found but were surely discovered based on phenotypical observations according to their discovery year, were put in the category of *therapeutic phenotype in non-human animals and ex vivo*. In investigating the discovery origins, I highly prioritized the accounts of the initially reporting discovery papers and afterward, other narrations from the discoverer(s) themselves.

"Off-Target" Therapeutic Mechanisms of "Target-Based" Drugs

I searched PubMed and Embase to systematically retrieve the studies investigating therapeutic pharmacological mechanisms of the "target-based" drugs I had identified in the previous section, with these queries: "[Drug]/pharmacology"[Majr] for PubMed and 'Drug'/exp/mj/dd_pd for Embase. After deduplicating the retrieved citations from these two databases using Systematic Review Assistant-Deduplication Module (SRA-DM)(*1897*), I reviewed the citations and extracted "off-target" mechanisms that were experimentally shown or suggested to mediate effects related to the therapeutic effect for which the drug was initially approved. To rule out the downstream effects of the binding of drugs to their "target," I excluded from the extracted "off-target" mechanisms, those that were mediated by first shell or second shell interactor proteins; those off-"target" mechanisms that were based on direct binding of the drug to the "off-target" proteins were exempt from this exclusion criterion. I retrieved these interactors from STRING v11(*582*) with these settings: "experiments" or "databases" for active interaction sources; highest confidence (0.900) for minimum required interaction score; 500 for the maximum number of interactors in the first and the second shells. I mostly used IUPHAR/BPS Guide to PHARMACOLOGY(*1898*) or ChEMBL(*583*) for nomenclature.

Percentile Rank of the Affinity of Approved Drugs Among All ChEMBL Ligands of Their Therapeutic Targets

I retrieved the targets of approved drugs from "a comprehensive map of molecular drug targets"(*1899*); this database (supplementary information S2 of (*1899*), archived) has compiled *therapeutic targets* of approved drugs which are defined as "those proteins or other biomolecules (such as DNA, RNA, heparin, and peptides) to which the drug directly binds, and which are responsible for the therapeutic efficacy of the drug(*1899*)." I excluded drug-target pairs with these mechanisms of action: agonists, activators, biopharmaceuticals, channel-openers, modulators, activators, allosteric antagonists, partial agonists, inverse agonists, DNA and RNA inhibitors, "cell membrane inhibitors" and releasing and chelating agents. I retrieved the available binding measurements for the remaining "targets" from ChEMBL27(*583*) with these curations: Measurements lacking pChEMBL value or with pChEMBL values expressed in any relation other than "equal to" like "smaller than" or "bigger than" were excluded; measurements expressed in other than IC_{50} or K_i were excluded; based on (*1900*), 0.30 was added to pChEMBL values of measurements expressed in IC_{50} to make the measurements more comparable; pChEMBLs of molecules with more than one remaining measurement were averaged and one final pCHEMBL was recorded for each ligand. After excluding "targets" with less than 100 remaining ligands, I calculated the percentile rank (inclusive) of the affinity of the approved drugs among the remaining ligands for each target. Percentile ranks of all salt and protonation alternative forms of each drug (available in ChEMBL) were averaged, weighted based on the count of measurements for each form.

Interactome-Wide Affinity Fingerprints of the Drug Repurposing Hub

After retrieving possibly therapeutic proteins across the human-SARS-CoV-2 interactome from the extensive available data(*1901-1906*) and filtering them based on the availability of acceptable structural information and druggability (Tclin or Tchem categories in Pharos(*1907*)), I identified 176 binding sites across these proteins based on the coordination of their co-crystallized ligands, or by using DoGSiteScorer (via SeeSAR 10.0 and proteins.plus) and (*1908*) and PrankWeb(*1909*) for "targets" lacking co-crystallized ligands. After downloading validated(*1910*) 3D structures of the proteins from either PDB-REDO(*1911*) (for experimental structures) or SWISS-MODEL repository(*1912*) (for homology models), I docked the 6676 molecules of the Drug Repurposing Hub(*1280*) by FlexX(*1283*) and HYDE(*1286*) via SeeSAR 10.0. I had prepared structures of the Drug Repurposing Hub (version 2020-03-24) by hydrogenation based on PH= 7.4, deduplication based on the IUPAC international chemical identifier (InChI), removing all but the largest contiguous fragments using Open Babel 3.0(*1913*). Analysis of different states of protonation and tautomerization was performed by Protoss integrated into SeeSAR(*1914*). I used FoldX 5(*1915*) to revert into the wild type, the proteins for which only experimental data for a mutant type was available, e.g., Histone-lysine N-methyltransferase NSD2. To identify putative binding sites across protein-protein interfaces of the interactome, I used the alanine scanning functionality(*1915*) of FoldX 5 and SpotOn(*1916*). I also used 2D-QSAR modeling for predicting the affinities of molecules to druggable targets without acceptable structural information (see next section). Assessed proteins and used binding sites are available in supplementary data 4.

Interactome-Wide Consensually docked 4D-QSAR Affinity Fingerprints for COVID-19 Select Drugs

To enhance accuracy (and demonstrate nested integration of diverse data), I designed consensually docked 4D-QSAR modeling to predict the binding affinity of a select set of compounds with more potential more accurately. After the generation of protomers and tautomers, docking was done with FlexX, allowing the generation of up to 10 poses for each protomer or tautomer. Then, these poses were rescored and optimized by HYDE. After this, the poses were rescored also by these scoring functions: chemplp, plp, plp95 scores of PLANTS(*1284*) (via VEGA ZZ 3.2.1.33(*1917*)); HPScore, HMScore and HSScore of X-Score(*1285*) (via VEGA ZZ 3.2.1.33); RF-Score-VS(*1287*) and KORP-PL 0.1.1(*1288*). For each target, the four best poses were selected for each molecule based on ranking all the docked and rescored poses of its various protomers and tautomers. This ranking was based on calculating a total score by weighted averaging all scores of each pose. This weight was calculated for each target and each scoring function according to Spearman's rank correlation coefficient between the most potent score (variably the highest or lowest according to the specific scoring function) for molecules retrieved from ChEMBL27 and their experimental pChEMBL values. One notable aspect of this 4D-QSAR modeling is that it can cohesively and synergistically integrate various kinds scoring functions and other methods of affinity prediction. The ML part was done using either random forest(*1918*) or XGBoost(*1919*), either one of which was better for each protein in hyper-parametrization and internal validation; I used 10-fold cross-validation in internal validation. I also used 2D-QSAR modeling for predicting the affinities of molecules to druggable targets without acceptable structural information. In both 2D- and 4D-QSARs, these descriptors were used: 1024-bits Morgan fingerprint(*1920*) (radius: 3) and RDKit descriptors (rdkit.org/docs/GettingStartedInPython.html#list-of-available-descriptors (20 September 2020), archived): SlogP, SMR, LabuteASA, TPSA, average molecular weight, exact molecular weight, number of rotatable bonds, number of hydrogen-bond donors, number of hydrogen-bond acceptors, number of amide bonds, number of atoms, number of hetero atoms, number of heavy atoms, number of stereocenters, number of unspecified stereocenters, number of rings, number of aromatic rings, number of saturated rings, number of aliphatic rings, number of aromatic heterocycles, number of saturated heterocycles, number of aliphatic heterocycles, number of aromatic carbocycles, number of saturated carbocycles, number of aliphatic carbocycles, fraction of carbons that are SP^3 hybridized, Chi0v - Chi4v, Chi1n - Chi4n, Hall-Kier alpha value, Kappa1 - Kappa3, SlogP_VSA1 - SlogP_VSA12, SMR_VSA1 - SMR_VSA10, PEOE_VSA1 - PEOE_VSA14, MQN1 – MQN42.

Systematic Review

I retrieved citations related to therapeutic effects of molecules in COVID-19 on 14 March 2020 using these queries:

CINAHL: TI (SARS OR MERS OR "Severe Acute Respiratory Syndrome" OR "Middle East respiratory syndrome" OR "2019 novel coronavirus" OR nCoV OR COVID OR COVID-19 OR "coronavirus disease") OR AB (SARS OR MERS OR "Severe Acute Respiratory Syndrome" OR "Middle East respiratory syndrome" OR "2019 novel coronavirus" OR nCoV OR COVID OR COVID-19 OR "coronavirus disease") Search modes - Boolean/Phrase, Limiters - Exclude MEDLINE records, Expanders - Apply equivalent subjects Narrow by SubjectMajor: - coronavirus infections OR - middle east respiratory syndrome coronavirus OR - middle east respiratory syndrome OR - severe acute respiratory syndrome

Cochrane (via OVID): SARS OR MERS OR "Severe Acute Respiratory Syndrome" OR "Middle East respiratory syndrome" OR "2019 novel coronavirus" OR nCoV OR COVID OR COVID-19 OR "coronavirus disease" [Including Limited Related Terms], deduplicated

Embase: ((('sars-related coronavirus'/exp OR 'middle east respiratory syndrome coronavirus'/exp) AND ('drug development'/exp OR 'drug activity'/exp)) OR (sars:ab,ti OR mers:ab,ti OR 'severe acute respiratory syndrome':ab,ti OR 'middle east respiratory syndrome':ab,ti OR '2019 novel coronavirus':ab,ti OR ncov:ab,ti OR covid:ab,ti OR 'covid 19':ab,ti OR 'coronavirus disease':ab,ti)) AND [abstracts]/lim NOT [medline]/lim

ProQuest: (MAINSUBJECT.EXACT("Drug screening" OR "Drug discovery" OR "Drug development" OR "Drugs" OR "Drug") AND AB,TI(SARS OR MERS OR "Severe Acute Respiratory Syndrome" OR "Middle East respiratory syndrome" OR "2019 novel coronavirus" OR nCoV OR COVID OR COVID-19 OR "coronavirus disease")) NOT bdl(1007527), In: Biological Science Collection, Health & Medical Collection, MEDLINE®, Nursing & Allied Health Database, ProQuest Dissertations & Theses A&I, ProQuest Dissertations & Theses Global

MEDLINE (via PubMed): Search ((SARS[Title/Abstract] OR MERS[Title/Abstract] OR "Severe Acute Respiratory Syndrome"[Title/Abstract] OR "Middle East respiratory syndrome"[Title/Abstract] OR "2019 novel coronavirus"[Title/Abstract] OR nCoV[Title/Abstract] OR COVID[Title/Abstract] OR COVID-19[Title/Abstract] OR "coronavirus disease"[Title/Abstract]) NOT medline[subset]) Filters: Abstract

Scopus: TITLE-ABS (sars OR mers OR "Severe Acute Respiratory Syndrome" OR "Middle East respiratory syndrome") AND SUBJAREA (phar) AND NOT INDEX (medline)

Web of Science: TS=(SARS OR MERS OR "Severe Acute Respiratory Syndrome" OR "Middle East respiratory syndrome" OR "2019 novel coronavirus" OR nCoV OR COVID OR COVID-19 OR "coronavirus disease"), Refined by: [excluding] Databases: (MEDLINE) AND RESEARCH AREAS: (PHARMACOLOGY PHARMACY), Databases= WOS, BCI, DIIDW, KJD, MEDLINE, RSCI, SCIELO Timespan=All years, Search language=Auto

After deduplication with SRA-DM(*1897*) and removing the citations without title or abstract or citations from before 2002 (the advent of the earliest of these epidemics (SARS)), I screened them using abstrackr(*1921*); I used abstrackr AI capability to prioritize relevant citations and continued screening until I became confident that the remaining citations were probably irrelevant. I updated the initially retrieved citations until 27 June 2021 using LitCovid(*1922*) "treatment" citations. Citations of 24 August 2020 onwards were not screened using abstrackr, but entirely manually. I included any assessment of molecules on symptoms and markers of SARS(severe acute respiratory syndrome), MERS (Middle-east respiratory syndrome), or COVID-19 (coronavirus disease 2019) in animals (including humans), irrespective of the severity of the disease, study type, and animal model. I excluded these interventions: macromolecules such as antibodies, vaccines, inorganic compounds; nanomedicines, traditional and herbal medicines. Downloaded citations plus the query file for Reaxys database and the protocol submitted to PROSPERO on 18 March 2020, which was rejected as "It [was] felt that the methods proposed in [the] review are not synonymous with those of systematic review." You can see the PRISMA flowchart(*1923*) in figure 12 (I have brought it in the methods section due to the demonstrative value of the systematic review).

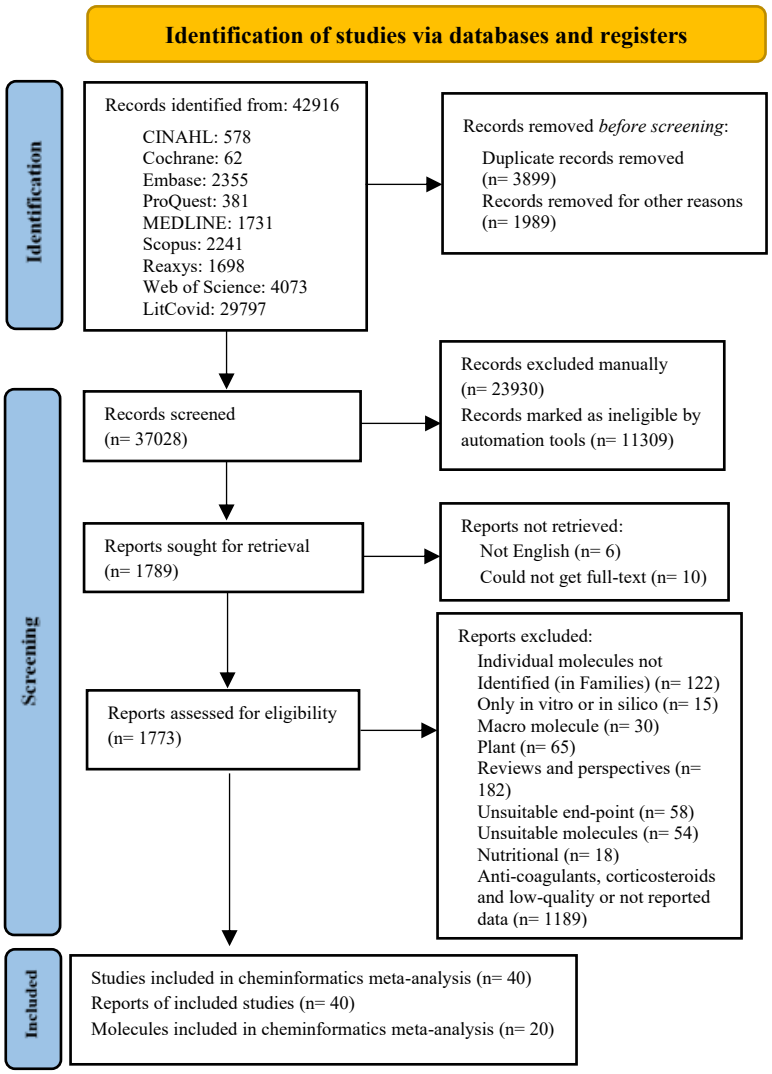

Figure 12. PRISMA(*1923*) flowchart for the systematic review.

Cheminformatics Meta-Analysis

After observing the very low quality of studies, I excluded studies of SARS and MERS, animal studies, and human studies with low quality from the cheminformatics meta-analysis (still, their extracted data is available in supplementary data 5); I also excluded corticosteroids and anticoagulants as their effects on the progression of COVID-19 is not straightforward. For variables of 2D structure, I converted smiles codes of molecules to 1024-bits Morgan fingerprint(*1920*) (radius: 3) and RDKit descriptors (listed above). For pIC_{50}, I used available measurements with this priority for assays: nucleic acid (RT-PCR) > protein (AntiNP) > plaque and others. According to the consensus reported in (*1924*), assessed outcomes included mortality (closest to 90 days), mechanical ventilation (total number of patients, over 90 days), viral clearance (closest to 7 days, 3 days either way), admission to hospital, duration of hospital stay, intensive care unit (ICU) length of stay, duration of mechanical ventilation, time to symptom resolution or clinical improvement and time to viral clearance. For effect size, I used the ratio of means or medians for continuous data and risk ratio or hazard ratio for dichotomous data; I recorded it as a percentage where the effect size of the treatment with better outcome gets larger than 100; adjusted hazard ratios or risk ratios were inverted if necessary. For variation, I used the sum of the coefficient of variation or quartile coefficient of dispersion * 100 for continuous data and 95% confidence interval * 2 * 100 for dichotomous data; where variation was not reported for an outcome, I instead used the variation of another outcome in that study. For risk of bias, I used the OHAT Risk of Bias rating Tool (January 2015) (ntp.niehs.nih.gov/go/riskbias, archived); an answer from 0 to 5 was given to each of its nine questions: 0 for not relevant, 1 for definitely low, 2 for probably low, 3 for not reported, 4 for probably high, 5 for definitely high. Nine questions were these: Was administered dose or exposure level adequately randomized?; was allocation to study groups adequately concealed?; did selection of study participants result in appropriate comparison groups?; did the study design or analysis account for important confounding and modifying variables?; were the research personnel and human subjects blinded to the study group during the study?; were outcome data complete without attrition or exclusion from analysis?; can we be confident in the exposure characterization?; can we be confident in the outcome assessment?; were all measured outcomes reported?. For severity, I used the percentage of patients with scores above 5 on the WHO ordinal scale for clinical improvement (who.int/publications/i/item/covid-19-therapeutic-trial-synopsis, archived). When the aggregate age was not reported, it was estimated by weighted mean or median; when the race was not reported, it was inevitably estimated based on another study from the same country; in case of unreported severity or gender, they were assigned 50. I used random forest(*1918*) and XGBoost(*1919*) for ML with 10-fold cross-validation in internal validation.

Assessing the Accuracy of AutoDock Vina for SARS-CoV-2 Main Protease

I used the data gathered by (*1925*) (ndownloader.figstatic.com/files/26786317, archived) as the reference experimental measurements, which is reported in inhibition-percentage of SARS-CoV-2 main protease in 20 μM. Ligands, which were available in the file as SMILES, were prepared by these procedures using Open Babel 3.1.1: adding hydrogens, removing all but the largest contiguous fragment, calculating Gasteiger partial charges, and removing duplicates by InChI. For the protein, based on the validation data(*1910*), I used chain A of 7JKV from PDB-REDO(*1911*). For docking, I used AutoDock Vina(*1444*) via VEGA ZZ 3.2.1.33(*1917*) with these settings: exhaustiveness = 24, center_x = -19.486, center_x = -19.486, center_y = 63.837, center_z = -0.745, size_x = 28.0, size_y = 36.0, size_z = 28.0. To assess the linear correlation between the calculated Vina Energy and the experimental data, I calculated Pearson correlation coefficient (two-sided *p*-value). To assess the rank correlation, I calculated Spearman's rank correlation coefficient, Kendall's Tau-a and Tau-b rank correlation coefficients and Goodman and Kruskal's gamma.

Limitations

I was not able to find the discovery origins of several drugs. In some cases, I was able to find a discovery-related paper, e.g., in PubMed, but was unable to find its full-text webpage. As feature trees are biology-agnostic, it was not possible to define a static cut-off limit for being an analogue; e.g., although "pharmacophores" of mechlorethamine and chlorambucil are near-identical, as their "auxophores" are very different, their global similarity is rather low. Confirmation bias may have impacted my search for the discovery origins. As discussed before, mechanisms of organisms' behaviors are not necessarily localizable(*168, 169, 1132*). Even the state-of-the-art methods like using si-RNA have many flaws(*1307, 1309, 1926, 1927*); let alone animal studies using pharmacological tool compounds to investigate the mechanisms of drugs. Many studies I used in investigating the "off-target" therapeutic mechanisms of "target-based" drugs were of this kind.

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