



# Formalizing complexity in the life sciences: systems, emergence, and metafluxes

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**Abstract** Current plant sciences (as the life sciences in general) tend to follow an empirical rationale focussing on the molecular scale (genes, proteins), which is supposed to causally dominate processes at higher levels of organization (cellular, organismic). This rather simplistic view on the complexity of living systems calls for a more adequate and elaborate theoretical approach, to which I want to contribute three main cornerstones here. *Systems theory* is the first one, mostly referring to Mario Bunge's CESM (Composition, Environment, Structure, Mechanism) approach and its biological application. More than half of this article is dedicated to the philosophical concept of *emergence*, denoting the fact that systems have specific properties not shared or provided by their parts. Different viewpoints on emergence and definitions are contrasted and their potential suitability for the life sciences is discussed. An interesting historical case study is the genesis of the 'ecosystem' concept in plant ecology. Subsequently two widely accepted subtypes, 'weak' and 'strong' emergence are introduced and their quantitative formalization is briefly outlined referring to recent work on this issue. Finally, the *metaflux* concept is presented for the first time. Living systems are characterized by a network

of coupled fluxes of matter, free energy, and entropy, adequately formalized by the thermodynamics of irreversible processes. Dynamical phenomena in organisms emerging from these flux networks which are, in contrast to process philosophy/metaphysics, defined on a scientific (physicochemical) basis will be called 'metafluxes'. Metafluxes and weak and strong emergence are non-exclusive concepts to be employed in a dialectic scientific process.

**Keywords** Emergentism · Ecosystem · Process philosophy · Thermodynamics of irreversible processes · Top-down causation

## 1 Introduction

In previous decades, tremendous progress in biology, including the plant sciences, has been obtained by applying a reductionistic approach, reducing biology largely to its physico-chemical, molecular basis. More bluntly speaking research 'has been inspired by the thesis that organisms are nothing but a bag of chemicals' (Bunge 2003). While this paradigm is still tacitly underlying most of the research strategies in plant physiology being dominated by molecular biology, uneasiness with this line of thinking has been growing in the last two decades, giving rise to systems biology as a new field of research. Systems biology deals with higher levels of organization (the 'macroscopic scale', be it the cell or the intact organism)

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beyond the molecular (or ‘microscopic’) scale. Frequently mathematical modelling is employed for providing an explanatory link to molecular organisation of macroscopic phenomena. The rise of systems biology has been favoured by two trends, which are closely interrelated (i) the rapid expansion of information technology providing the tools to analyse and apply algorithms to large datasets, (ii) the arrival of complexity science—a new, overarching discipline dedicated to identifying common features of complex systems irrespective of the field of science they originate from. In the plant sciences (and biomedical sciences in general) a rather pragmatic approach to systems biology was taken, harnessing whatever mathematical tool was available to arrive at a mechanistic explanation for physiological phenomena inaccessible by mere qualitative reasoning. Little attention was given to more basic considerations such as ‘what is a (biological) system’ or referring to a general systems theory. However, the need for a firmer epistemological basis of our scientific reasoning on plant (and, more generally, biological) systems is recognised beyond the small community dealing with the philosophy of biology and is growing even among experimentally working scientists—the current special issue of ‘Theoretical and Experimental Plant Physiology’ is the best evidence for the perception of this deficit. In view of the spectacular success stories of contemporary molecular biology, we need a convincing reasoning why higher levels of organization do not simply result from processes at the molecular scale, but deserve to be perceived on their own rights as ‘first-hand phenomena’ rather than as epiphenomena (which is the ultimate justification for a separate ‘systems biology’). This necessarily leads us to the old, but still somewhat fuzzy concept of emergence, rooting in Aristotle’s famous dictum that ‘the whole is more than the sum of its parts’.

In this essay, I will start with some basic considerations on systems theory and how it can be made fruitful for biological research, mostly referring to the work of the late philosopher of science Mario Bunge (1919–2020). Subsequently, I will introduce in some detail the concept of emergence, starting with a brief but, in my view, rewarding historical overview and then proceed to more recent attempts to arrive at a mathematical formalization of biological emergence. The next to final section is dedicated to a further extension of these approaches which refers to the

process philosophy of biology in the sense of Dupré and Nicholson (2018), linking it to the thermodynamics of irreversible processes (see also Lüttge (2023), this special issue), followed by concluding remarks.

## 2 The plant as a ‘system’

We may have an intuitive and heuristic understanding of what a system is—in fact it has become a buzzword with little substance used in many contexts. But what does it mean in a scientific sense? An elaborate answer was provided by the Argentinian philosopher Mario Bunge, a quantum physicist by training who spent most of his extremely productive academic life at McGill university in Canada. His memory is still particularly vivid in South America, as I experienced during a conference in Brazil in 2022. Bunge considered himself a ‘systemist’—his mission was to establish systemic thinking in the sciences (not limited to the natural sciences!) to be demarcated from both reductionistic *and* holistic approaches. For the former, understanding means decomposition of the whole into its constituents, precisely studying their properties. Subsequent ‘re-assemblance’ is an intellectual effort entirely based on the knowledge of the properties of the parts. The extreme contrast is provided by holistic thinking: Only the whole matters, with the parts playing only a minor role. According to Bunge (2003), this thinking is frequently opposed to science— but not always, as we will see further below. Bunge advocates a third alternative—the systemic approach. It values the knowledge of the parts and the empirical research it needs to characterize them. However, they are interrelated contributing to a whole which has properties not directly resulting from those of the parts. For providing a simple guideline for treating and analysing systems, he condensed these aspects into his CESM model (Bunge (2003), p. 34ff), with CESM standing for Composition, Environment, Structure, and Mechanism. In the following, Bunge’s explanations are documented unmodified. For a systems we have:

$C(s)$  = *Composition*: Collection of all the parts of  $s$ ;  
 $E(s)$  = *Environment*: Collection of items, other than those of  $s$ , that act on or are acted upon by some or all components of  $s$ ;

$S(s)$ =*Structure*: Collection of relations, in particular bonds, among components of  $s$  or among these and items in the environment ( $e$ ).

$M(s)$ =*Mechanism*: Collection of processes in  $s$  that make it behave as it does.

According to Bunge, biology is prone to systemic analysis since “modern biologists have always studied systems, from cells to organs...to whole multicellular organisms to populations to ecosystems”. He specifies his CESM model for biological systems being “a semi-open material systems, far from thermodynamic equilibrium with its environment, whose boundary is a semi-permeable lipid membrane” (Bunge (2003), p. 46f), a definition focusing on cells and not directly applicable to biological systems of higher order, though. *Components* of the biosystem are obviously various classes of biomolecules (proteins, lipids, nucleotides...), the *environment* provides the building blocks and is characterized by physicochemical parameters such as pH, temperature etc., the *structure* comprises all bonds, covalent or non-covalent, between components plus the ties with the environment, and finally the *mechanism* refers to all processes keeping a system alive. Note that an individual mechanism can be specified for every biological process, whereas the other characteristics of biological systems provide the opportunity for some kind of standardization and classification, which, in turn, allows to identify rules putatively being generally valid for biological systems (see also Hao et al. (2021)). Bunge’s approach is a very useful and pragmatic one, as we will see later. Hence, it is superior for our purposes to other approaches for treating (complex) systems, particularly that of Luhmann (2006), which was rather conceived to meet the needs of the social sciences (see the critical juxtaposition of Bunge’s and Luhmann’s systems theories by Wan (2011)). Both Bunge and Luhmann agree that systems possess properties which cannot be reduced to those of their parts, but only become relevant and meaningful at a given level of organization, which is generally denoted as ‘emergence’. The subsequent section will start with some historical notes on the concept of emergence. A view at past debates will help us to clarify this still somewhat elusive concept. Moreover, we evade the proposition of Garrett (2013) when reviewing earlier discussions on the concept of emergence that “a cursory look at debates of the early

twentieth century offers the impression that little has been learnt and that we have been entertaining arguments rehearsed before world war II” culminating in the diagnosis of “intellectual amnesia”.

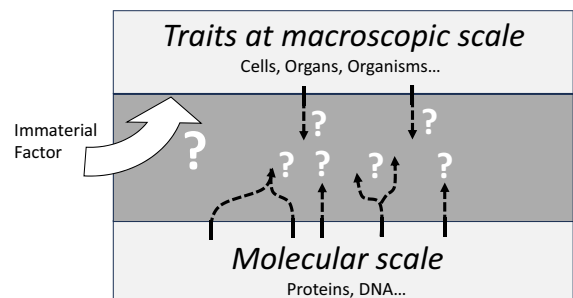
### 3 What can we learn from historical concepts of emergence?

The term “emergence” was coined by the British philosopher G.H. Lewes (1877) referring to J.S. Mills “heteropathic”, or non-additive, effects in nature. Lewes’ wording has caused much confusion for having a second, more common meaning, frequently giving rise to misunderstandings. Numerous attempts were made to replace the terminology, e.g., using the term ‘fulguration’ instead (Lorenz (1973) p. 48), but these were all unsuccessful, so we have to abide by the original wording. Lewes contrasted ‘emergent’ with ‘resultant’ and thus already identified a key problem of the concept of emergence, namely whether it is in accordance with the principle of causality (chain of causation), which is an important principle of science. The theory of emergence became very popular at the begin of the twentieth century when it was promoted by the influential philosophers of science C. Lloyd Morgan, Samuel Alexander, and C.D. Broad, all affiliated with British academic institutions. It was Lloyd Morgan who according to his own retrospective (Morgan 1929) re-discovered Lewes’ work, which had largely been forgotten for some 40 years, and adopted his wording and conception in several publications between 1915 and 1920. His main achievement was to extend the concept of emergence to the life sciences, stating that life and the processes of evolution embody principles of emergence in an ideal way. Lloyd Morgan stressed that emergent phenomena occur in systems with an intrinsic hierarchical order in terms of extension and complexity and that during evolution true ‘unpredictable’ innovations have been borne. They should be considered characteristic manifestations of emergence. Samuel Alexander integrated Lloyd Morgan’s reflections on emergence into his comprehensive philosophical metaphysics unfolded in his main oeuvre “Space, Time, and Deity” (Alexander 1920). He established the chain space–time→matter→life→mind with each of the three last categories emerging from the previous one. Matter is governed by the laws of chemistry

and physics; “Physical and chemical processes of a certain complexity have the quality of life.... The higher quality emerges from the lower level of existence and has its roots therein, but it emerges therefrom, and it does not belong to that lower level, but constitutes its possessor a new order of existence with its special laws of behaviour.” (Alexander (1920), p. 46). This implies that life, being based on matter, follows the laws of physics and chemistry but *additionally* displays unique laws and rules resulting from its emergent status (which, in turn, is also applicable to mind, being emergent to life). The most explicit and elaborate theory of emergence was put forward by the third philosopher of this series, C.D. Broad, then affiliated with Cambridge university. „Put in abstract terms the emergent theory asserts that there are certain wholes, composed say of constituents A, B and C in relation R to each other...*the characteristic properties of the whole cannot, even in theory, be deduced from the most complete knowledge of the properties of A, B and C in isolation or in other wholes which are not of the form R(A,B,C)*“ (Broad (1925), p. 61, italics by the author of this essay). Broad characterized his position as ‘emergent vitalism’. Emergence is considered to be a complex property of matter, which is in stark contrast to ‘substantial vitalism’ invoking the necessity of an immaterial factor to explain life, as advocated by his contemporary Hans Driesch (1908). An update on vitalism in biology has recently been provided by Layer (2022). On the other hand, emergent vitalism is sharply distinguished from reductionistic theories denoted as ‘Biological Mechanism’ by Broad (1925). When elaborating his theory in contrast to the alternatives, Broad explicitly recurs to Lloyd Morgan and to Alexander who states that emergent quality ‘admits no explanation’ and only follows from ‘brute empirical fact’ (Alexander (1920), p. 46f). Actually, this position is characteristic of a scientific school denoted as ‘emergentism’ of which Lloyd Morgan, Alexander, and C.D. Broad are the most prominent representatives in the early twentieth century. However, there are also contemporary philosophers of science rooting in this tradition such as A. Stephan (2007).

It is definitely a merit of the emergentists to have propagated and popularized the theory of emergence. However, it is not without contradictions and does not qualify as a basis for current concepts of emergence to be used in the life sciences. First of all, the

emergentists define themselves as materialists. In fact, they intend to present an alternative to neo-vitalistic positions, which invoked an immaterial factor like Driesch’s entelechy (Driesch 1908) to explain life and gained some popularity in those days; emergentists strongly reject those ideas (e.g., Broad (1925), p. 58; Stephan (2007), p. 14). However, if there is no way *in principle* to find a mechanism explaining the cooperation of the constituents in forming the whole (i.e., how proteins and genes interact to form a complex, multigenic trait; Fig. 1), we cannot exclude that some immaterial factor is *also* constitutive for that trait, unless we can reconstruct life from its organic components (which is certainly far out of reach and, hence, at best a theoretical option). In fact, defining a process as ‘emergent’ in this way may rather reflect our own lack of knowledge and understanding (Hao et al. 2021). This is best illustrated by Broad’s examples of emergent processes in nature taken from chemistry: Chemical reactions were inaccessible for mechanistic explanations then, but can nowadays be deduced, at least in principle, from nuclear physics based, among other things, on the nature of the chemical bond (Pauling 1931). Hence, Stephan (2007), as a more recent proponent of the emergentist’s position, was at a loss finding ‘waterproof’ examples for emergent processes in his sense; he opted for phenomena related to human consciousness, in agreement with Chalmers (Chalmers 2006). Still, the same criticism applies here since we lack a proof that it is unfeasible *in principle* to relate human consciousness to its



**Fig. 1** According to the emergentists’ view on biological systems, it is principally impossible to establish a mechanistic link between the macroscopic and the microscopic (=molecular) scale, even though traits at the macroscopic scale fully rely on the constituents at the lower level and their interactions. This implies that the involvement of some immaterial factor cannot be excluded, unless the biological system is rebuilt from its chemical components (which is only a theoretical option)

biological (and, hence, material) basis. Apparently, the emergentists' position is unsuitable for application to biological phenomena in general. Moreover, from a scientific point of view this position is not as well-defined as it may initially seem—demarcation towards vitalism is rather weak, as we have seen, despite the fervent claim of its proponents that they are materialists (Fig. 1). Hence, we have to search for a more pragmatic definition of emergence to make it a fruitful concept for the life sciences. An interesting and original approach has been advocated by the philosopher of biology William Wimsatt (2000). He contrasts emergence with 'aggregativity' for which he presents four criteria, being (i) inter-substitution (invariance to re-arrangements of parts), (ii) insensitivity to size-scaling, (iii) invariance to decomposition and subsequent reassembly, (iv) no cooperative or inhibitory interactions of parts. Emergence, which is according to Wimsatt not necessarily clashing with reductionism, is rather defined in a negative way as 'non-aggregativity'. Note that the listed criteria are in fact negations themselves supposed to define aggregativity, so it appears a bit clumsy to define emergence, in turn, via a negation of these negations. Some authors have tried to evade the dilemma in defining emergence by using an epistemological approach, i.e., relating it to scientific progress (Hempel and Oppenheim 1948). A phenomenon in nature is considered 'emergent' as long as we cannot explain it in a mechanistic way, making emergence a 'theory of the gaps' and a euphemistic wording for our incomplete knowledge. Therefore, Mahner and Bunge (1997; p. 29) fervently reject this position, stressing that emergence is an ontological quality, i.e., a property of the biological object independent of the process of gaining scientific insight. In terms of emergent processes in evolution they dryly state that "explained novelty is no less novel than unexplained novelty". They come up with a pragmatic definition that goes as follows: "*Let P represent a property of a thing b. P is an emergent property of b if, and only if either (i) b is a complex system no component of which possesses P, or (ii) b is a thing that has acquired P by virtue of becoming a component of a system (i.e., b would not possess P if it were an independent or isolated thing).*" We will see that this is a practically useful definition which, however, needs some concretization and differentiation. Note that it is much broader than the definition favoured by the emergentists, but it does not *exclude*

phenomena potentially resisting a mechanistic interpretation. Hence the definition is not necessarily bound to the 'materialistic emergentism' propagated by Bunge (2003), who insisted that *all* phenomena in nature are accessible by a mechanistic explanation.

The hype of emergentism in the early twentieth century had some echo in animal physiology and in the medical sciences (e.g., Jennings (1927)), but little so in the then still largely descriptive plant sciences—with one remarkable exception that deserves some more attention.

#### 4 The concept of emergence in the plant sciences

Plant ecology had seen considerable conceptual progress in the early twentieth century and had evolved as an independent science, particularly due to the work of the American ecologist F.E. Clements (1916) and his climax theory. Clements postulated that vegetation undergoes a transition of developmental stages, called succession, that ends in a final stationary state, the climax state. Following a holistic approach, he considered vegetation as a kind of super-organism undergoing an ontogenetic process, following intrinsic laws of development. This view was most fervently defended by his follower John Phillips, a South African ecologist, who referred to the concept of emergence and explicitly claimed it to support his and Clement's approach to vegetation ecology (Phillips 1935). The counterpart was taken by another eminent plant scientist, Sir Arthur Tansley. Phillips contended that holism is a driving force integrating both cells into an individual organism and, in turn, individual plants forming vegetation units (or rather, both plants and animals forming biotic communities). Emergent properties arise at each level of organization. Tansley factually agreed with many of Phillip's propositions, including the role of emergence in forming vegetation from individual plants. "What we *observe* is juxtaposition and interaction, with the resulting emergence of what we call (and I agree must call) a "new" entity." (Tansley (1935), p. 297 italics in the original). However, he commented on the claim of 'unpredictability' with some reservation "Unpredictable by us with our present knowledge, yes; but *theoretically* unpredictable, surely not." (P.298). What concerned Tansley most was a concept well founded by empirical data and operational for scientific use. From this



perspective he explicitly rejected the idea of vegetation (or biotic communities) representing a ‘super-organism’ with an intrinsic ontogeny which he considered not well founded and rather philosophical (if not even pseudo-religious, as hinted in his introductory paragraphs). As an alternative to holism, he suggested a *systemic* approach which is retrospectively closely following Bunge’s scheme: Taking account of the constituents of the system (the organisms forming it) *and* their emergent interactions, and including environmental conditions, both biotic *and* abiotic (e.g., edaphic in addition to climatic factors). It was the birth of the ‘ecosystem’ concept, which soon received wide recognition and is generally accepted nowadays.

While vegetation ecology was readily embracing the concept of emergence, that was rather not the case in the other disciplines of plant science. Even on the contrary, it was argued that plants are organized in a modular way, with plants organs (leaves, roots, flowers...) rather operating (semi)autonomously (Haukioja et al. 1991; De Kroon et al. 2005). Hence, it was not before Ulrich Lüttge in a series of publications made a strong case for emergence in plant physiology, starting about a decade ago (Lüttge 2012, 2013, 2019, 2021). Notably, the author of this essay was also first alerted to the particular value of the concept of emergence for understanding physiological processes in plants by Lüttge’s thorough treatise of this issue. Most importantly, Lüttge characterized epistemology of the life sciences (the scientific progress in our understanding of biological processes) as a kind of dialectic process: It starts with identifying and scrutinizing the components or ‘modules’ contributing to a phenomenon associated with a higher level of biological organization (e.g., genes and enzymes contributing to a physiological process like photosynthesis)—this is the reductionistic part of the epistemic process. However, it is insufficient and inadequate to capture the ‘whole picture’ of life—just compiling information as provided by the ‘omics’ approaches will always fall short of providing us with a full understanding of the organism (Lüttge 2013). A holistic aspect must be added to take account of the emergent interdependences of these modules and to arrive at a systemic approach. Systems biology responded to this need by defining modules as ‘knots’ in a network interconnected by ‘edges’ which contain information on their interactions. This principle of

the organization of matter starts at the lowest level, the atom consisting of electrons, protons and neutrons (and some more elemental particles) and ends at Gaia, the entire biosphere on earth emerging from the sum of all biological processes. Lüttge comes up with numerous examples at various levels of organization. Integration at the level of a higher plant is provided by rapidly transmitting information within the plant body by hydraulic or electric signalling (action potentials, variation potentials, systemic potentials). One of the simplest, and at the same time most striking, examples for emergence in the plant field is that of a forest: It is obviously more than just an agglomeration of many trees, but some understanding of tree physiology (usually obtained with a reductionistic approach by working on individual trees in a greenhouse, tissues, or cells) is a prerequisite for adequately studying and understanding it.

## 5 Weak and strong emergence

From the previous historical outline of the concept of emergence it appears that it is of utmost importance for adequately understanding biological systems. At the same time, though, it remains oddly elusive and open to very divergent interpretations. Thus, it constitutes a controversial (and fervently discussed) concept in the philosophy of science. But it seems to be an even more challenging task to (re)define it in such a way that it becomes *operative* and fruitful for *experimental* biology.

Bedau (2002) suggested that “We should not assume that there is just one solution to the problem of emergence”. Part of the problem is obviously that ‘emergence’ has a rather broad meaning covering very different issues (especially if we accept the very broad definition of Mahner and Bunge (1997)), suggesting the need for some differentiation. Bedau (1997, 2002) distinguishes three forms of emergence which received widespread recognition: Nominal, weak and strong emergence, complying with the definition of Mahner and Bunge (see above).

The most straightforward case is *nominal* emergence: It refers to those cases where the mere number of components makes a fundamental difference; new properties arise from the sheer number or by the extension of the system (Anderson 1972): A single tree cannot constitute a forest, but many of them can;

many water molecules are required to form a fluid phase. This is an intuitively obvious, though non-trivial observation.

A more intricate case is provided by what Bedau denoted as *weak emergence*. In this case properties of a complex system are, in principle, deducible from the features of its components and their interactions (in fact being dominated by the latter), thus failing to meet the criteria suggested by C.D. Broad. However, assessment of system properties is only possible by a tedious iterative approach, i.e., by simulating the interactions in a computer model. Bedau insists that this is an objective, ontological feature of the system independent of scientific methodology that he denotes as ‘computationally irreducible’, following Wolfram (1984). Bedau’s concept of weak emergence, that was well received in the scientific community, clearly focusses on *quantitative* aspects of emergence. It is obvious that this approach is well suited to analyse physiological phenomena associated, e.g., with a plant or plant organ, such as extension growth, as a result of multiple processes at the molecular scale (gene expression, metabolism etc.). It only applies to phenomena *principally* accessible by computation, excluding those which are, according to Kauffman (2019), ‘beyond physics’. Another serious limitation may be of an epistemic nature—practical computation may be hampered by our lack of knowledge, or (principal) inaccessibility of certain data. Still the concept of weak emergence appears to be valuable for application in the life sciences.

Both Bedau and Chalmers (2006) concede that there may be a third category, called *strong emergence*, precluding, in principle, any mechanistic deduction from lower levels of organization. Their conception of strong emergence comes close to Broad’s general definition of emergence (see above, Fig. 1). According to Chalmers (2006), consciousness, emerging from the brain as its structural basis, is the only phenomenon qualifying as strongly emergent following this conception—he is convinced that it is virtually impossible to link consciousness to its material, i.e., biochemical and biophysical, basis. Basic problems associated with a separate category defined in this way have already been discussed further above when dealing with the emergentists’ position (Fig. 1). After all we are still unable to provide a *definite proof* for Chalmers’ notion; in fact, it has been openly challenged, e.g., by Seth (2008). However, ‘strong

emergence’ raises an issue which is at the core of the terminology and is somewhat undervalued by the weak emergence concept: The aspect of a completely new quality introduced by an emergent process which is not subject to any scaling (or, in terms of evolutionary nomenclature, represents a true innovation). The ability to convert sunlight into chemical energy, *vulgo* photosynthesis, is an ‘achievement’ by itself, and a historical innovation in evolution, irrespective of any mechanistic details required for simulation of the process, or the amount of CO<sub>2</sub> that is assimilated. However, the most compelling argument against the rather exclusive way Bedau and Chalmers define strong emergence is a pragmatic one: linking macroscopic features of a system to microscopic ones (e.g., a complex process like extension growth to its molecular basis in terms of enzyme activities and gene activity) by *mechanistic* modelling may be hampered, and may even fail, due to our incomplete knowledge of all the mechanisms involved or even the inaccessibility of quantitative parameters like certain concentration profiles of agents. In this case we cannot decide if a trait is weakly or strongly emergent according to Bedau’s definition. Modelling on a (partly) *empirical* basis may still be possible, but is irrelevant to Bedau’s concept of emergence. Note that this pragmatic objection has nothing to do with an epistemic definition of emergence as advocated by Hempel and Oppenheim (1948): Photosynthesis and growth remain emergent features of plants, irrespective of whether we can explain them in a mechanistic way or not!

Still, the above considerations seem to suggest that weak and strong emergence as promoted by Bedau and Chalmers are useful categories for the life sciences, but should rather be used in a modified way: (i) Weak emergence focusses on the interplay of the constituents of a system at a microscopic scale (e.g., enzymes or structural proteins) bringing about a macroscopic, scalable feature such as photosynthesis or extension growth, to be linked and described quantitatively by mechanistic simulation (if available). (ii) By contrast, strong emergence deals with a biological innovation which is basically a question of a binary decision (a species is either endowed with a particular feature like photosynthesis, or it is not). Its fundamental quality is *irreducibility*. This comprises (i) the principle failure to fully reduce a macroscopic trait to its molecular components; this is a criterion which is, arguably, already met when the functional context

of the trait has no equivalent at the molecular scale (Noble 2006); (ii) the strict dependency on a certain set of constitutive proteins (molecular components) which is required to initiate and maintain the trait—insufficient abundance of one of these components, or complete absence would entail a complete loss of the trait. This at first glance straightforward criterion is blurred somewhat by different forms of redundancy (for more details, see the next section and Hao et al. (2021)). Note that weak and strong emergence following this interpretation are non-exclusive, in contrast to the one offered by Bedau (2002). While his definition may be more compelling from a philosophical viewpoint, the one introduced here is more apt for the use in the life sciences, as we will see further below.

Among the frequently discussed criteria of emergence, ‘top-down causation’ has not been addressed in this essay yet, partly because there is some disagreement whether it should be assigned to weak emergence, as argued by Bedau (2002), or rather to strong emergence, as insisted by others, e.g., Baryam (2004). It denotes the fact that a complex system itself may affect, via a systemic property, the parts of which it consists. According to Bedau having genuine causal powers is a key property of emergence making sure that the macroscopic entity is not a mere epiphenomenon. For example the membrane potential, the voltage-drop across a semipermeable biological membrane (e.g., the plasma membrane), may serve as an example which is of relevance for both plants and animals. In fact, it was identified as such by Dennis Noble (retrospectively summarized in Noble (2006, 2012)), who was the first to discover top-down causation as an important phenomenon in biology when he unravelled the mechanism by which pacemaker cells impose the regular rhythm of the heartbeat. He could show that the membrane potential of these cells, which results from the activity of all the electrogenic transporters in the membrane (mainly ion channels), in turn affects the activity of those voltage-dependent ion channels. The rhythmic signal emerges from a cooperation of *both* bottom-up *and* top-down effects. Other examples of top-down causation are regulation of gene expression by the organism interacting with its environment, and signalling at the cellular level which is under control of the entire organism (Noble 2006). An overview on top-down causation focussing on plants was provided by Souza and do Amaral (2019). The examples given by Noble as well

as Souza and do Amaral also invalidate the concern of Kim (2006) that downward causation comes down to a circular argument, at least in the case of weak emergence, since the systemic property which is in principle deducible from its parts is supposed to act on these parts. Emergence requires, to some extent, an autonomy of the system from its parts, implying that it can be a genuine source of causation (see also Bedau (2002)).

## 6 Quantitative approaches to emergence

The reader having followed the essay up to this point may wonder why the concept(s) of emergence, despite being of so high relevance to all aspects of the life sciences (see, e.g., the collection of essays in Wegner and Lüttge (2019), Wegner (2019), have so little impact in practical (plant) science. The author of this essay noticed that many biologists working experimentally are not even aware of this concept, the powerful it may potentially be. The reason for this obvious discrepancy is not surprising: empirical scientists are not interested in philosophical speculations but rather look out for concepts helping them to plan their experiments, or to facilitate interpretation of their data. Neither is provided by what we have heard about emergence so far. What we obviously need is a quantitative treatment of the issue with a potential for practical applications, in other words: we need *algorithms*.

A few attempts to formalize emergence have been published previously. Explicitly referring to weak emergence, Seth (2008) developed algorithms based on so-called Granger causality (G causality). The approach relies on a comparison of time series of a trait and its constituents. If the time course of the constituents tends to improve the prediction of a potentially dependent parameter (here, the complex trait) using linear extrapolation, a causal relationship is postulated. By contrast, G autonomy implies that this is not the case, extrapolation from the time course of the complex trait being superior to any cross-correlation. Following a suggestion by Bedau (2002), the complex trait is supposed to be *G emergent* if the complex trait shows some dependence on its constituents, but is *also* dependent on its own history. The approach can be modified to include non-linear effects. A critical point is the use



of correlations for establishing a causal relationship. Seth's concept of emergence also implies that the relationship between the whole and its parts is invariant during the time increment on which the analysis is based. An approach using formal grammar was introduced by Szabo and Teo (2015). Mnif and Müller-Schloer (2006) relate weak emergence to a process of self-organization and quantify emergence as an increase in (statistical) entropy during such a process. Their approach was rather designed for technical systems, though.

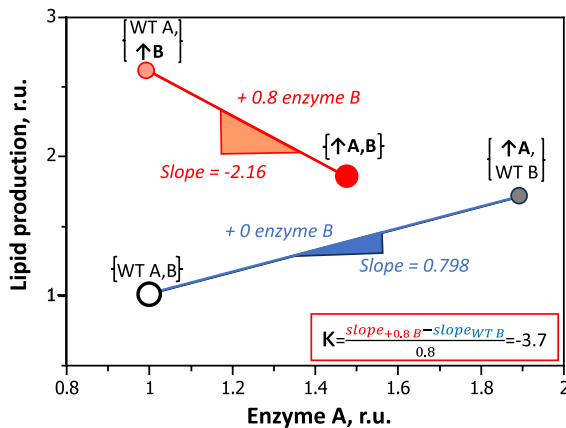
All these approaches have merits of their own, but are of limited use for analysing how complex multi-genic traits at the macroscopic scale emerge from interactions at the molecular scale, particularly referring to proteins, the workhorses of biological function. Wegner (2019) and Wegner and Hao (2021) have suggested a formalism elaborating on metabolic control theory to quantify those interactions, providing a way to formalize weak emergence in biology. According to metabolic control theory, dependence of carbon flow velocity through a metabolic pathway on the concentration of individual enzymes is described by a control coefficient,  $c$  (Here 'concentration' refers to the number of the copies of a certain protein normalized to a parameter expressing the spatial extension of the matrix (volume, membrane area, etc.)). This approach can be modified for application to any complex, scalable trait  $\xi$  and Protein  $Pr_i$

$$c = \left( \frac{\partial \xi}{\partial [Pr_i]} \right)_{[Pr_{n \neq i}]} \quad (1)$$

It is convenient to normalize both  $\xi$  and protein concentration to a reference state, e.g., the wild type. Now consider a second protein  $Pr_k$  also known to affect the trait, which may potentially interact with  $Pr_i$  regarding its effect on  $\xi$ . This is adequately described by a parameter  $\kappa$ , the mixed second derivative of  $\xi$  with respect to incremental concentration changes of both proteins. Formally, each pair of proteins constitutes two identical  $\kappa$  values (with either of the protein serving as the interfering one), which are obtained by moderately changing the concentration of each protein both separately and simultaneously. Again, relative changes are considered by normalizing all variables to a reference value, preferentially the one under wild type conditions.

$$\frac{\partial}{\partial [Pr_k]} \left( \frac{\partial \xi}{\partial [Pr_i]} \right)_{[Pr_{n \neq i,k}]} = \kappa_{ik} \quad (2)$$

If  $Pr_i$  and  $Pr_k$  act on the trait independently,  $\kappa$  will be zero, while the first derivative of the trait with respect to both protein concentrations will be non-zero. In this case both proteins will be said to act on  $\xi$  in a 'modular' way. A non-zero  $\kappa$  value indicates that both proteins mutually interfere, either promoting or attenuating the trait (positive and negative  $\kappa$  values, respectively). This is considered as an indication for weak emergence, literally fulfilling Aristoteles' dictum that "the whole is more than the sum of its parts". Formalized in this way, weak emergence comes close to the more common term 'synergism' in its usual meaning (though, strictly speaking, synergism is broader and includes cases of strong emergence, see also below and Corning (2002), Hao et al. (2021)). An example for assessing  $\kappa$  by overexpressing two proteins (here enzymes playing a role in lipid production in oleaginous microalgae) is shown in Fig. 2; data were obtained from Klaitong et al. (2017); Chungjatupornchai et al. (2019); and Chungjatupornchai and Fa-aroonawat (2021). What is shown here for a single pair of enzymes can be extended to the entire cellular metabolism, provided that a comprehensive quantitative model is available for a cell type. This kind of analysis has recently been undertaken for hepatocytes by making use of the model HEPA-TOKIN I (N. Berndt, H.G. Holzhütter, and L.H. Wegner, manuscript submitted for publication), processing the pairwise interaction of 221 enzymes. Among other things, it turned out to be convenient to nullify  $\kappa$  values close to zero for identifying and separating the most relevant cases of mutual interaction. All  $\kappa$  values for a set of proteins on which the trait (mainly) depends can be summarized in a so-called Hessian matrix, cumulatively representing all protein interactions (Wegner and Hao 2021). From the set of proteins contributing to this matrix we can define a synergy index (SI) allowing us to quantify to what extent a complex trait is shaped by mutual interactions of the proteins contributing to it. To this end, all absolute  $\kappa$  values are added up and divided by the total number of  $\kappa$  values, which is  $(n-1)*n$  for a set of  $n$  proteins.



**Fig. 2** Quantitative assessment of weak emergence in a plant system by calculating the parameter  $\kappa$  (Eq. 2). As an example, triacylglycerol synthesis in the oleaginous microalga *Neochloris oleoabundans* was chosen. Extensive research is undertaken on this species to optimize fatty acid production by overexpressing lipogenic genes. In a series of publications (Klaitong et al. 2017; Chungjatupornchai et al. 2019; Chungjatupornchai and Fa-aroonawat 2021), this approach was applied to plastidial lysophosphatidic acid acyltransferase (LPAAT1) and endoplasmic reticulum-located diacylglycerol acyltransferase 2 (DGAT2). In the figure, they are termed ‘enzyme A’ and ‘enzyme B’, respectively, for simplicity. These endogenous enzymes were overexpressed (indicated by  $\uparrow$ ) both individually (with the other enzyme remaining at wild type (WT) level;  $\{\uparrow A, WT B\}$  and  $\{WT A, \uparrow B\}$ ) and pairwise  $\{\uparrow A, B\}$ . Lipid production was recorded for the 3 transgenic strains and the WT algae. All values are normalized to WT level. Assuming linear relationships, the dependence of lipid production on the concentration of enzyme A is depicted for the WT level of enzyme B (blue line) as well as for a 80% overexpression of this enzyme (red line). From the change in slope with concentration,  $\kappa$  can be calculated as indicated in the figure. Note that co-overexpression has a negative effect on lipid production, inverting the sign of the slope and leading to a negative  $\kappa$  value

$$SI = \frac{\sum_{i,k=1,1}^{n,n} |\kappa_{i,k}^{WT}|}{(n-1)n} \quad (3)$$

The Hesse matrix is very helpful if we want to assess how a change in protein expression patterns, induced, e.g., by environmental stress or infliction by a disease, would affect a scalable complex trait. First-order derivatives (corresponding to the control coefficients for proteins) and the mixed second derivatives (i.e., the  $\kappa$  values) can be extended into a Taylor series for a quantitative estimation. For details, which are beyond the scope of this essay, the reader

is referred to Wegner and Hao (2021). In principle,  $\kappa$  can be addressed in two ways: Empirically, by modifying the expression pattern of proteins using the genetic toolbox (Fig. 2) and measuring the outcome on  $t$ . Ideally  $\kappa$  should be assessed by a ‘mild’ (co-) overexpression for which there are only few examples available in the literature. A more convenient access is provided if a mechanistic model is available (following Bedau’s criterion that a simulation is required for analysing weak emergence) and multiple interactions can be analysed *in silico*. Such an approach is feasible, e.g., for liver metabolism using the comprehensive computer model HEPATOKIN I (Berndt et al. 2018), but unfortunately this is not at reach yet for most plant systems.

The above quantitative treatment does not take account of all aspects of emergence and requires some complementation. In fact, a case frequently occurring in biological systems is not covered by that formalism. Consider a biochemical reaction which is at steady state being invariant to changes in the abundance of the enzyme catalysing that reaction around the wildtype level, and insensitive to interference from other proteins. This does by no means imply that this enzyme is irrelevant for the trait, though, since lowering its concentration below a certain threshold may interrupt the biochemical pathway, with fatal consequences for the trait. The other case still awaiting a quantitative treatment is strong emergence.

Quantifying strong emergence is an even more challenging—if not almost impossible—task, and an apparent paradox. It seems to belong to the realm that is, according to Kauffman, ‘beyond physics’ resisting, in principle, any mathematical formalization (Kauffman 2019). However, agreeing with Bedau (2002) that “we should not assume that there is just one solution to the problem of emergence” we can address certain *aspects* of emergence in a quantitative way rather than reaching out for the one comprehensive algorithm. In the previous section irreducibility had been identified as a key criterion for strong emergence. This leads us to find a quantitative criterion for strong emergence corresponding to its composition, which is a key criterion for any system according to Bunge’s CESM model. A set of constitutive proteins is required to bring about and sustain a certain strongly emergent trait—for this trait to come into being, each of these proteins must

exceed a certain *threshold concentration*,  $[Pr_i]^{th}$ . If the concentrations of all constitutive proteins are at or above the threshold level, a value of ‘1’ is assigned to  $t$ , otherwise it is 0:

$$t([Pr_i]) = \begin{cases} 1, & \text{if } [Pr_i] \geq [Pr_i]^{th} \text{ for all } i = 1, 2 \dots n \\ 0, & \text{otherwise} \end{cases} \quad (4)$$

See also the schematic drawing in Fig. 3. Note that this mathematical approach *does not require* any mechanistic link between a trait and its molecular basis; on the other hand it *does not preclude* the existence of such a link. Note further that this approach provides a mathematical solution for an essential enzyme which is operating under steady state conditions in the wild type but causes its breakdown once the concentration drops below the threshold level (compare the previous paragraph).

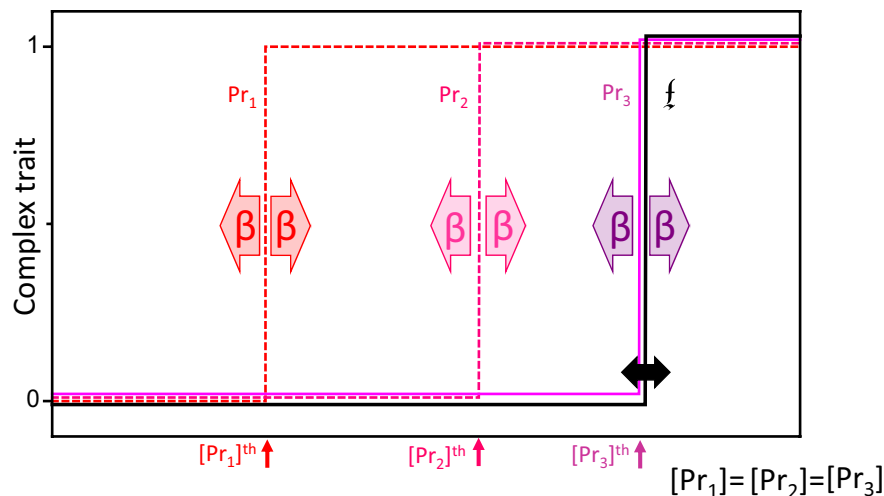
Threshold concentrations are not necessarily constant; rather, each threshold concentration,  $[Pr_i]^{th}$ , is allowed to vary, depending on the concentration of another constitutive protein  $k$  (with other protein

concentrations remaining constant), as expressed by a coefficient  $\beta$

$$\beta_{ik} = \left( \frac{\partial [Pr_i]^{th}}{\partial [Pr_k]} \right)_{[Pr_{n \neq i,k}]} \quad (5)$$

Consider, e.g., the case that an increase in  $[Pr_k]$  can partly compensate for a gradual loss in  $Pr_i$ , implying that  $[Pr_i]^{th}$  decreases with  $[Pr_k]$ . Hence,  $\beta$  will attain a negative value. At high concentrations  $Pr_k$  may even fully replace  $Pr_i$ , with  $[Pr_i]^{th}$  dropping to zero. This case will be called a *partial redundancy*. A separate case is that of *full redundancy*, i.e., among isoenzymes performing the same function with respect to a complex trait. Threshold concentrations of isoenzymes may be treated in an additive way to arrive at a cumulative value—for more details on redundancy in strong emergence and graphical representations, the reader is referred to Hao et al. (2021).

For a set of constitutive proteins, all  $\beta$  values may be summarized in a Jacobian matrix. Among other things, this matrix can be used to decide if a certain trait is sustained at a given combination of protein



**Fig. 3** A complex trait  $t$  is initiated by three constitutive proteins  $Pr_1$ ,  $Pr_2$  and  $Pr_3$ . For the argument they are supposed to occur at equal concentrations in this hypothetical case and supposed to differ with respect to the threshold concentrations as indicated by upward-directed arrows at the x-axis. For the trait  $t$ , the transition from 0 to 1 (i.e., initiation of the trait) is associated with all three concentrations exceeding their individual

threshold (black line). Threshold concentrations can be variable, depending on the concentrations of other (constitutive) proteins, as expressed by the parameter  $\beta$  (Eq. 5). Therefore, the threshold concentration of the complex trait can also shift (black double-headed arrow). After Wegner and Hao (2021), modified

concentrations, as described by Wegner and Hao (2021). Which proteins are constitutive for a complex trait? This key question obviously needs some more attention. Arguably, all proteins required for survival are ‘constitutive’ in this sense, since any physiological trait is bound to the living state, but this is obviously completely impractical. Therefore, unspecific functions are summarized in a ‘biological environment’ that needs to be intact to bring any physiological trait about. Only proteins, which are indispensable for a *particular* trait, are considered as ‘constitutive’ for it.

## 7 Processes, fluxes and metafluxes

The previous sections insinuate that proteins, and in turn, genes encoding for them are the basis of life. They are generally assumed to be the firm material ground on which life in form of complex multigenic traits unfolds in an emergent way. This view seems to be the current steadfast paradigm of biological research. But does it tell the whole story? Or does it reflect a fundamental conceptual flaw in the way we look at nature and particularly at life?—a strong feeling of uneasiness remains, as Lüttge articulated in the introduction to his 2012 essay on emergence. This is the viewpoint of a process philosophy (or ontology) approach to biology, stating that *processes* are fundamental to life rather than biological structures (i.e., the functional arrangement of *matter*). A process philosophy of biology (and the natural sciences in general) was inspired by the British-American philosopher Alfred North Whitehead, as outlined in his main oeuvre “process and reality” first published in 1929. Only recently, process philosophy has seen a revival (or rather resurge of attention) particularly in the philosophy of biology, sometimes also at an explicit critical distance to Whitehead’s extensive metaphysical system (Nicholson and Dupré 2018; Dupré and Nicholson 2018). Starting with historical proponents of process philosophy, notably Heraclitus and his famous dictum ‘panta rhei’ (everything flows), Dupré and Nicholson published ‘a manifesto for a processual philosophy of biology’ which ‘defends the thesis that the right way to understand the living world at all levels is a hierarchy of processes rather than of things’. Compellingly, they underpin this statement with a number of facts and observations: (i) sustainment of

life relies on a constant uptake of energy and matter to be processed by metabolism, so the very existence of all living is manifest as a process (in contrast to, e.g., a rock which is just undergoing long-term processes like erosion. (ii) Another striking point is that organisms are subjected to a rapid turnover of matter encountered at any level of their existence, particularly at the molecular and cellular level. Metabolically most active cells in the stomach, e.g., are replaced every 5 days, while the liver is completely renewed every year, implying that all atoms have been replaced during this time, so there is no continuity at all in terms of matter. Shape is also subjected to a constant change, e.g., for a plant from the moment of germination to flowering and fruiting. In fact, the dazzling diversity of life forms makes ‘biological identity’ an intricate problem, and the ability to perform a life cycle (a process!) on its own has been identified as a more or less sound criterion for an individual (Pradeu 2018). (iii) Often organisms live in close functional association with others, such that their survival relies on an interactive *process*. Mycorrhiza forming symbiotic relationships with higher plants are an example. Different organisms forming a unity, i.e., with respect to natural selection, are denoted as holobionts (e.g., biofilms; Lüttge 2012, 2022; Dupré 2021)). It has been proposed that the whole biosphere should be considered a holobiont-like system (zu Castell et al. 2019) reminiscent of the Gaia hypothesis. Focussing on processes would allow us to circumvent the challenging—and sometimes unsolvable—problem of defining individuality to some extent, and would not require to impose a rigid classification on beings. In the case of lichens we have factually surrendered to this problem and classify consortia of individuals (namely algae *plus* fungi), rather than these individuals separately. There are other phenomena we tacitly or conventionally handle as ‘things’, such as hurricanes, even though in reality they are processes. (iv) A processual view would cure us from any undue analogy of living objects to machines, since machines are lacking all the properties like ontogeny and self-organization as listed above. (v) A final point added here is not explicitly raised by Dupré and Nicholson (but is repeatedly alluded to in Dupré (2021)): A processual approach to life would rescue us from an extremely genocentric view which is currently dominating the life sciences (Layer 2022), a burden we

are owing to Dawkins' metaphor of the 'selfish gene' (Dawkins 1976).

Dupré and Nicholson (2018) claim that a processual view on biological systems would profoundly affect the way we do, e.g., physiology, genetics and the medical research. But the problem seems to be that their approach receives considerable recognition in the philosophy of biology, but has little impact on the way biological science is actually *done* (with maybe few exceptions). This is reminiscent of the concept of emergence that appears to be compelling in itself, but is largely neglected by the experimentally working community, which is de facto defining the directions the life sciences are taking (see above). And again we end up with a similar diagnosis: To my knowledge, no attempt has been made to conceptually link process philosophy (which is eventually of a metaphysical nature; Dupré (2021)) to the well-established physicochemical basis of the life sciences. Such a conceptual link would allow biologists to develop strategies for modelling biological processes inspired by process ontology. The second part of this section will be dedicated to filling this gap. Here I can only provide a preliminary sketch of how this link could possibly be provided. More, and more in-depth conceptual work needs to be performed to come up with a viable theory.

When talking about the "well-established physicochemical basis of the life sciences", I refer to the thermodynamics of irreversible processes, mainly developed by the physico-chemists Lars Onsager (Onsager 1931a, b) and Ilya Prigogine (1978) (which both earned them the Nobel Prize in 1968 and 1977, respectively) and was applied to biology (where it turned out to be most powerful) by Kedem and Katchalsky (1958) and, in the plant sciences, by Jack Dainty (1963). Although derivation of this relatively new field from *equilibrium* thermodynamics is sophisticated theoretical work (which is beyond the scope of this essay), the basic structure of the equations is rather simple: A flux  $J$ , being a displacement of matter, or processing of free energy/entropy with time, is elicited when there is a driving force  $\Delta F$ , implying that the particular component is not at its thermodynamic equilibrium. Flux and driving force are linked by a scaling factor  $L$  which formally corresponds to the flux at some standard condition. Note that the formalism is applicable to solute fluxes across biological membranes (for which it became famous), but also, e.g., to biochemical reactions being part of metabolism:

$$J = L * \Delta F \quad (6)$$

Note that the particular gradient driving this flux itself results from several preceding fluxes, forming an interactive network. Of course, this network of fluxes can only operate away from thermodynamic equilibrium. Hence it eventually relies on two fluxes which are governing the others and are prevailing throughout the process: The system we are dealing with, e.g., a cell, continuously needs to take up free energy, and to export entropy.

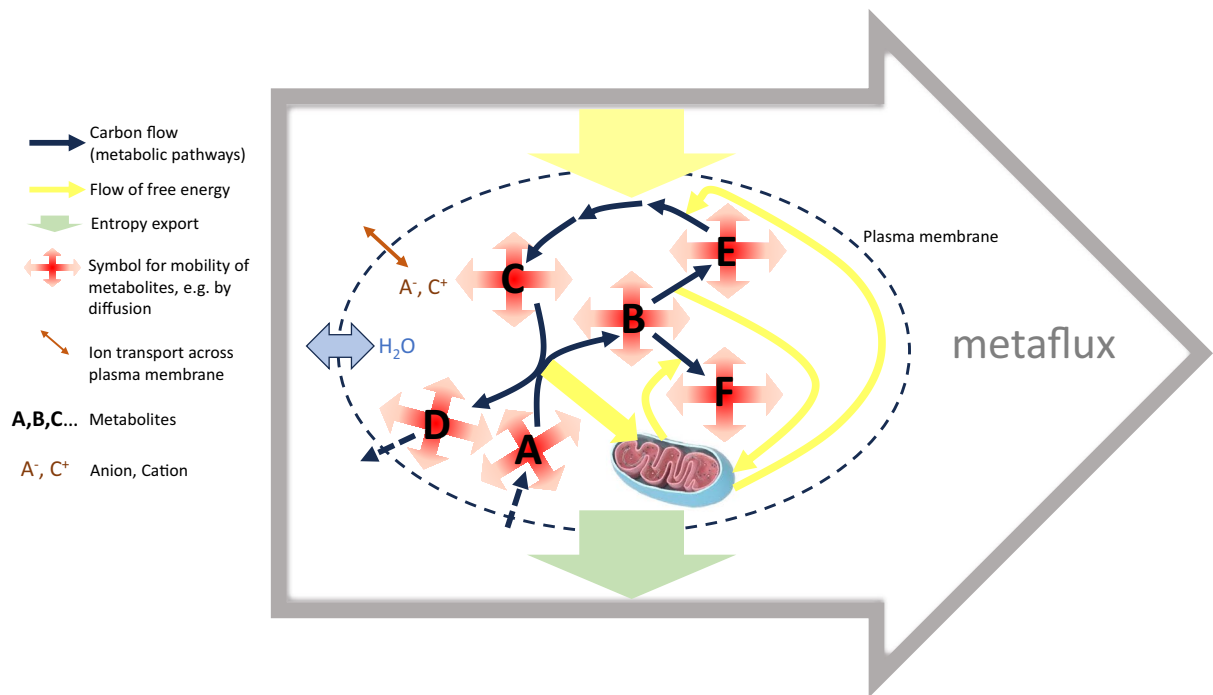
Now it is evident that the network of fluxes in question should have a function within the organism which is likely to be subject to intrinsic dynamics. This could be the output of a metabolic network, e.g., synthesis of a hormone, which is readily perceived as (being part of) a dynamic process. However it could also be the maintenance of a biological structure, e.g., a membrane. The latter is static at first glance, but actually results from a continuous process of decomposition and rebuilding. Functional networks of fluxes will be called a '*metaflux*' (Fig. 4). Primarily, metafluxes are postulated to result from the underlying fluxes, but there is no point in being dogmatic here: Complex biological structures also qualify for an inclusion.

**Definition:** Metafluxes are complex dynamical processes operating in living systems. They result from arrays of fluxes of matter, energy and entropy as formalized according to the thermodynamics of irreversible processes, and involve biological structures.

This definition encompasses, e.g., membrane transport and metabolism, but also still more complex dynamic biological phenomena related to ontogeny and development. Note further that metafluxes are largely equivalent to 'processes' as invoked by Dupré and Nicholson (2018) and Dupré (2021). But instead of being philosophical (metaphysical) categories they root in physical chemistry.

Metafluxes are *emergent* with respect to the fluxes they originate from, much as complex multi-genic traits are with respect to their molecular components (see above and Fig. 4). The analogy holds: We encounter multiple cases of flux coupling which scale the metafluxes and serve as examples for weak emergence. Flux coupling at biological membranes should be mentioned here, first identified and studied





**Fig. 4** Schematic diagram visualizing the metaflux concept. Metafluxes are complex processes rooting in fluxes at the microscopic, mostly cellular and subcellular, level. These include carbon fluxes in metabolic networks and related conversions of free energy in the cell, and exchange of metabolites

and ions across the plasma membrane. Two fluxes are constitutive, a continuous influx of free energy into the cell as well as an export of entropy. Metafluxes rely on microscopic fluxes in an emergent way. For more details, see text

experimentally by Hans Ussing (Larsen 2002). Flux coupling is a key mechanism of energizing membrane transport, which, in turn, plays a key role in metafluxes like extension growth. Recently Wegner and Shabala (2020) and Wegner et al. (2021) described direct coupling of membrane transport to metabolism in plant cells.

More complex cases of metafluxes operating on the organismal level as related, e.g., to their ontogeny display symptoms of strong emergence. At a higher level of organization, fluxes contribute to novel (in an evolutionary sense) and irreducible processes. A set of fluxes and structures is indispensable for these metafluxes to come about, but there can be multiple variants of redundancy, both partial and full (see above). This has been demonstrated convincingly by Layer (2019) in his many-ways-to-Rome approach to developmental biology. At this stage of the project we have to abide with these rather general remarks—a more detailed analysis will have to follow revealing the potential of this concept.

It may be argued that metafluxes are just process philosophy in disguise, new wording with no factual progress. However, implementing the thermodynamics of irreversible processes does make a difference—it introduces the demarcations set by thermodynamics, thus reducing the degrees of freedom, e.g., related to the energy and entropy balance of the processes to be described. Another obvious restriction includes the conservation of matter and energy. Moreover, it paves the way to a mathematical formalization of process philosophy, at least partially, opening new avenues for modelling approaches.

We may tentatively reach out here for the application of the metaflux concept beyond organismic physiology. It may as well apply to ecology, which is governed by multiple dynamical processes. At a still higher level with respect to time scale and spatial extension, evolution may be considered as the ultimate metaflux in this sense.

It is important to note that the metaflux concept outlined here in coarse lines is non-exclusive to other

quantitative approaches which are rather emanating from the conventional ‘substance ontology’. Rather than furthering a competition for the most appropriate approach to life sciences, they are intended for a mutual complementation. Their application is seen as forming part of a dialectic process in extending our knowledge and understanding of life.

## 8 Concluding remarks

In his contribution to this special issue, Lüttge (2023) pleads for an integration of science and philosophy (though keeping in mind that both are separate fields); this requires the ‘casting of bridges’. He responds to Dupré’s statement that ‘metaphysics is continuous with science’ (Dupré 2021). The present essay dealing with issues in-between science and philosophy reinforces their view, though with an important corollary. Again citing Lüttge (2023), ‘Science forces metaphysics into fights of retreat when unexpected advancements in development of methods allow empirical progress’. Indeed this has been the mission of science ever since it arose as a separate realm of human activity, tentatively to be followed back to Aristotle. We may add here that besides empirical progress, scientific theory going hand-in-hand with mathematical formalization is a sharp sword in this fight, too. This affirmation goes with a note of caution, though, to make use of it in a due way and keep in mind limitations of mathematical approaches (Kauffman 2019; Hao et al. 2021), thus evading, as Whitehead famously put it, the ‘fallacy of the misplaced concreteness’ (Whitehead 1925).

Obviously, we are still far behind a comprehensive theory of biology ready to serve the needs of the experimental life sciences for designing new experimental strategies, and quantitative models allowing us to make a true difference in the interpretation of our datasets. Algorithms for weak and strong emergence are currently tested on liver and erythrocyte metabolism, rendering promising results. The metaflux concepts awaits further elaboration, designated to cast a bridge from process philosophy to life science in the future.

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## Declarations

**Conflict of interest** The corresponding author states that there is no conflict of interest.

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