Granularity as a modelling approach to investigate hypothesized emergence in biology*

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Abstract

Informal usage of emergence in biological discourse tends towards being of the epistemic type, but not ontological emergence, primarily due to our lack of knowledge about nature and limitations to how to model it. Philosophy adds clarification to better characterise the fuzzy notion of emergence in biology, but paradoxically it is the methodology of conducting scientific experiments that can give decisive answers. A renewed interest in whole-ism in (molecular) biology and simulations of complex systems does not imply emergent properties exist, but illustrates the realisation that things a more difficult and complex than initially anticipated. Usage of (weak- and epistemological) emergence in bioscience is a shorthand for 'we have a gap in our knowledge about the precise relation(s) between the whole and its parts and possibly missing something about the parts themselves as well', which amounts to absence of emergence in the philosophical sense. Given that the existence of emergent properties is not undisputed, we need better methodologies to investigate such claims. Granularity serves as one of these approaches to investigate postulated emergent properties. Specification of levels of granularity and their contents can provide a methodological modelling framework to enable structured examination of emergence from both a formal ontological modelling approach and the computational angle, and helps elucidating the required level of granularity to explain away emergence. I discuss some modelling considerations for a granularity framework and its relevance for the testability of emergence in computational implementations such as simulations.

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[*] This is an occasionally evolving document that is at times possibly a bit controversial, with the intention to foster some debate about the claims about & usage of emergence. A suggested mode of referencing this document is: *Keet, C.M. Granularity as a modelling approach to investigate hypothesized emergence in biology. Unpublished manuscript v1.0, 3-8-2007. 22 p. http://www.meteck.org/files/Granemergev1.pdf.*

Contents

1 Introduction

To be able to assess the real relevance of emergence in (complex biological) systems, we need to untangle the knot of what an emergent property/behaviour is. A finer-grained, clearer, distinction between the various usages of the term emergence enables the right type of modelling methodology – if and where possible – that is required for developing computational support to investigate emergence within the larger setting of complex systems. I propose here that using granularity can become a useful methodology to make sense of, and disambiguate, the often-mentioned 'levels' of explanation and organisation. Although emergence is claimed in many disciplines, I limit the scope to the biosciences, though the generic approach with levels of granularity can be applied in other domains too.

Emergent properties and emergent behaviour have become buzzwords in biology, in genetics and cell biology in particular whereas ecologists claim this for some time earlier. Several sub-disciplines deal with, or face, emergence, such as systems biology, computational systems biology, and it is contained implicitly in the omics planes, which indicates non-reductionism, systems thinking, or 'whole-ism': the whole is somehow *more* than its parts. If true, this would mean that, depending on the type of granularity [19] and model, content of a higher level (of granularity) is *not deducible* and *not predictable* from its lower level components, and the self-organising characteristics of an entity are absent or not-detectable at the level of its parts. In the debates about emergence, the notion of higher and lower levels is severely underspecified, but as I will put forward here, it is granularity that helps addressing claimed emergent properties. From the point of view of investigating levels of granularity, such emergent properties may provide additional support that granularity is not just a cognitive device of humans to structure their knowledge about the world around us, but that nature is granular. Ontologically, this is different from “natural laws” [38] determining levels of granularity, because if one has laws then it makes the higher level of granularity predictable and deducible, not emergent.

Another motivation to look into emergence has to do with the prospects of computational implementations, where a formal model of granularity that is compatible with emergence acts as a logic layer to provide a data- and knowledge management structure to improve analysis of the subject domain. However, using logics to represent knowledge assumes that not only one can describe the subject domain, but by being captured in logic with computational support, suggests it can demonstrate that seemingly emergent properties can be derived, hence are predictable, and thereby not emergent. Conversely, if it is not possible to model the semantics formally and use it for inferencing, then, first, one may find a proof why it is not computable and, second, manual encoding of the extant knowledge may still be possible. If something is truly emergent, identification and understanding of granular levels, and consequently the software application of a complex system, becomes unstable. Conversely, if a higher-level property seems to be emergent and irreducible, but after modelling the extant knowledge and data manually a successful application of computational reasoning demonstrates derivation of the higher-level property after all, then emergence is refuted. Alternatively, during the manual encoding some ‘gaps’ in the knowledge might be identified that point toward options for specific wet-lab research to identify the problem better and/or find an answer to increase our understanding of reality.

To shed light on the (un)feasibility to model (so-called) emergent properties and its relation with, and effect on, granular levels, I address informal usage of emergence in biology first in §2, subsequently proceed to the philosophical and ontological analysis of emergence in §3, which also contains examples (§3.5), and deal in §4 with the relevance of granular levels and how it is a useful methodological approach for modelling emergence in biology. I draw some conclusions in the last section.

2 Renewed claims of emergence in biology

The recent attention for emergence in genetics and cell biology can be traced back to two major developments. First, during the genomics era, with its height in mapping the human genome, many assumed that all answers for understanding nature could be found in the information encoded in the genes. We now know ‘better’: knowing the sequence of the genome does *not* predict (human) physiology and the phenome in general, like reading assembly code does not tell you how a piece of software behaves at runtime. Hence, there is ‘more’ than can be predicted from the gene sequence alone. This ‘more’ is gradually discovered, such as epigenetics (e.g. the methylation of DNA bases affecting transcription of the gene), signalling pathways involving nuclear hormone receptors, and environmental factors that influence gene regulation and translation. The reductionist belief that genes are everything and are deterministic is being superseded by the notion of 'higher level' molecular mechanisms of regulation, stochasticity, and self-organising characteristics that at the level of its parts are absent or not-detectable. Non-deterministic behaviour include e.g. protein folding, formation of lipid micells, and if an organism is just a bundle of molecules (see [35] [22] for other examples). Stochasticity and non-determinism bring afore the second development: simulations. Simulations require not the abstracted mechanisms depicted in biology textbooks, but comprehensive mathematical models to create an *in silico* representation. Modelling for simulation requires to include as much variables as possible, capturing in formulae the parameters in context and using e.g. hybrid automata [1] or pi calculus [29] to observe the resultant behaviour. In the subject domain of ecology and environmental modelling for simulation, the preferred approach is still to use differential equations that produce more or less acceptable approximations of the chosen aspects observed in nature (e.g. with STELLA modelling software). But that genes were not everything was claimed by cell physiologists long before, and that modelling biological processes satisfactorily appears to be a rather difficult task is not surprising either. Is this sufficient reason to claim irrefutable support for emergent properties and behaviour? What is 'emergence', and what is—or is not—emerging? What aspects are irreducible, and why? Does one refer to emergence and irreducibility due to our gaps in knowledge about nature, or is there an ontological emergence? The next paragraph aims to provide and discuss some of the answers that can be given to these questions.

3 Emergence from a philosophical perspective

Emergentism dates back about 150 years beginning with vitalism and irreducible properties [24] [12], resulting in a "stratification of kinds of substances, with different kinds belonging to different orders, or levels. Each level is characterised by certain fundamental, irreducible properties that emerge from lower-level properties", where the irreducible properties arising from a lower level are somehow 'novel' [24], but also that "emergence describes the passage between levels" [12]. With development of the sciences from the mid 19th century CE, god was gradually removed from the equation to make place for a reductionism where there is no god, no soul, and every phenomenon is reducible to physical-chemical laws with causal determinism [12]. However, this reductionism is not universally supported and investigation into and discussion about emergence continues in various streams. The main topics of discussion in the emergentism debates are (non-)emergence in nature (physics, biology), and then sociology and psychology, and (self-)consciousness and mind, which overlap with philosophy of science discourse on scientific disciplines. The latter, in short, is still concerned with if one is doing either physics or stamp collecting. At least to date, physics cannot explain everything and many attempts in philosophy of science and elsewhere have been made to fill this gap. Depending on how this gap is filled, one observes emergence almost everywhere, occasionally, leaves the door open, or not. Two major distinctions between types of emergence are made: epistemological and ontological emergence, and strong and weak emergence; other variations of emergence can be categorised under these types. These are described and discussed first and then illustrated in examples 1 and 2.

3.1 Epistemological emergence

Epistemological emergence involves the difficulties of describing and explaining complex systems by putting central the limited knowledge we have about such complex systems [24]: with more insight gained from scientific investigations, some emergent property can be explained eventually and thereby ceases to be emergent. Some 'acts of god' in the middle ages are currently scientifically explained [12], therefore what is now considered to be emergent, will be explained, predicted, derived in the (near) future and then is not an emergent property anymore. Variations on this theme follow either the bottom-up *non-predictability* argument that one cannot predict the higher-level property based on its parts alone, or the top-down version of *irreducible-patterns* that the emergent property of a complex system cannot be fully described by a fundamental physical theory [24]. A restricting definition given by Teller is that "a property is emergent if and only if it is not *explicitly definable* in terms of the non-relational properties of any of the object's proper parts" (paraphrased in [24]). One can limit the amount of emergent properties by using token-token reductionism (see [8] for a discussion), which does allow inclusion of the entities *and all their interactions* (relational properties) for describing and explaining systemic features. But extending the explanatory power with token-token reductionism alone does not imply emergence does not exists (see §3.4 on weak emergence and *Example 1* in §3.6).

Cunningham [7] divides epistemological emergence into two different categories: emergence as *multiple realizability* and emergence as *interactive complexity*. With the former, the "higher-level properties of the whole entity have *no theoretically significant relations* to the lower-level properties of its components" (emphasis added), whereas the latter has to do with a highly configurational and holistic property p such that "p's proprietary entity is so interactively complex that it is *difficult (or perhaps impossible)* to track p's relations to the lower-level... components" (emphasis added) [7]. This begs the question what insignificant relations are, because for explaining non-emergence they may be essential, and that something is difficult does not mean one should readily label that property as emergent. Notwithstanding, from a *practical* viewpoint with the recognition that our knowledge about nature is very limited, it may be of use to at least temporarily categorise an as of yet non-deducible and non-predictable property as emergent—pending further research.

Thus, any claim about an epistemologically emergent property ought to be prefixed with a qualified phrase like "given the current state of our knowledge..." or "in the limited model about this piece of reality...". This, however, indicates distinct characteristics of epistemological emergence. The former puts the blame on humans who lack knowledge and have only limited methodologies to investigate nature and suggests a gap that needs to be filled, but does not negate existence of emergent properties in nature. The latter implicitly says that it is neither nature that exhibits emergent properties nor that humans have limited capabilities for understanding nature, but that observation of emergent properties are due to the limitations of our models; this is analysed in some detail by Edmonds [11] and Cariani [4]. This limitation can surface during development of simulation software in particular, examined in §3.5.

3.2 Ontological emergence

With ontological emergence, the emergent properties are fundamental at the level it manifests itself and those emergent properties are irreducible *even if we have perfect complete information* about the entity/system under consideration—ignoring the point *how* we can be sure to have complete information. The whole is not simply the aggregate or sum of its parts, but "[e]ach new layer is a consequence of the appearance of an interacting range of 'novel qualities'." [24] and "entails the failure of part-whole reductionism, as well as the failure of mereological supervenience" [33]. Cunningham specifies it at the level of entities instead, where an "ontologically-emergent property is an ontologically basic property of a *complex* entity" and, in addition, these properties of complex entities are non-physical mythical vital properties, are internal, and are not micro-determined [7]. Unfortunately, Cunningham does not provide examples of this type of ontologically emergent properties. Mythical, vital, non-physical characteristics of such proposed ontological emergent property does not rhyme with bioscience and nature. Three other versions of ontological emergence are summarised.

First, supervenience emergentism states that there are layered levels with downward causation where a higher-level property emerges *on* the contents of a lower level [24] [17] and this "newness... entails new primitive causal powers" [24] . O'Connor and Wong [24] assert that this kind of emergent property "is 'non-structural', in that the occurrence of the property is not in any sense constituted by the occurrence of more fundamental properties and relations of the object's parts", whereas Johansson [17] narrows this down to emergent wholes that have a "*base*, on which they are always dependent for their existence and with which they thus always have to exist simultaneously.". Being 'not constituted' and being 'dependent' are not contradictory, but the negative formulation of the former indicates greater independence of the higher-level emergent property than tying the existence of the higher level to the existence of the lower level objects. Put differently, the latter is more reductionist (less holist) than the former. Separate from this, is that causality itself is subject to much debate even without considering emergence.

Second, emergence as fusion [24], where

> Paul Humphreys... favors a metaphysical relation he terms "fusion": "[Emergent properties] result from an essential interaction [i.e. fusion] between their constituent properties, an interaction that is nomologically necessary for the existence of the emergent property." Fused entities lose certain of their causal powers and cease to exist as separate entities, and the emergents generated by fusion are characterized by novel causal powers.

Thus, the property does not supervene on its parts, but the parts somehow physically combine in a particular way such that the combination has novel causal powers.

Curiously, in the formal representation, as given in [24], the parts' properties cease to exist and together make place for the emergent property of the fused entity, *yet* those parts remain their separate identities. This means that the property that each part loses must be a non-sortal property of each object involved in the fusion; else each part cannot remain its identity. Alternatively, the parts continue to exist at the finer-grained level but they are *not identifiable* at the coarser-grained level where the fused entity resides. If possible at all, then fusion will be difficult to detect for we must know the necessary and sufficient properties of the parts for identification, the properties they are supposed to lose, the necessary and sufficient properties of the entity resulting from the fusion, and detect which one of them is the emerging property of the entity.

Third, constraints-based ontological emergence. For Korn [21], hierarchies are central, where the constraints from a higher level constrain the lower level. A top-level without constraints 'from above' has some freedom for emergence to occur, so too has an intermediate level through reassociation of hierarchical constraints "*to give new relationships between the constrainees*" at their level in the hierarchy. Cariani [4] adds an interesting distinction, which clarifies Korn's reassociation of hierarchical constraints: *combinatoric* emergence, which corresponds to Korn's reassociation where no new elements are added but there is a novel resultant, and *creative* emergence, where some new (kind of) element arises. More precisely, creative emergence arises after augmenting the lower level with a new element, a "new primitive" [4], such that at the higher level a "new set of primitives" emerges, hence it "adopts the epistemic perspective of a limited, but expandable observer." [4]. Thus, Cariani's creative emergence is epistemological emergence and his combinatoric emergence is of the type ontological emergence.

3.3 Strong emergence

Explanations of the meaning of both strong and weak emergence do not specifically refer to being either typed as epistemical or ontological emergence. According to Delehanty [8], strong emergence refers to non-reductive materialism and irreducibility of biological systems, where the different levels are ontologically distinct. Along these lines, strong emergence is at least an ontological emergence, but as formulated does not exclude epistemological emergence. Chalmers' [5] interpretation of strong emergence is "when truths concerning [the high-level] phenomenon are not *deducible* even in principle from truths in the lower-level domain". Chalmers restricts that to supervenience emergentism where the emergent phenomenon is systematically determined by the lower level facts (but not deducible), hence also ontological emergence. An interesting addition to the (non)deducibility claim is the distinction between being not deducible from lower level *facts* and/or *laws* [5], with which we can make a finer-grained distinction between simulations. For example, with the Game of Life, the inputs are i) the rules (laws) of birth and death and ii) the initial state (facts); during the game one can observe the self-organising higher-level facts, but not derive a higher-level law from it. In the other direction, when one does not know the initial or homeostatic state, a simulation allows the user to tweak with the values of one or more parameters to try to get the behaviour observed at the higher level, hence trying to establish a relation between facts at different levels (i.e. between the behaviour of the whole and one or more components that partially contribute to the higher level behaviour). This, nevertheless, is an easier task than trying to derive laws governing population dynamics from the laws at the level of individual organisms.

It is important to note that investigating these kind of phenomena faces a plethora of epistemological issues, but in this case of strong emergence you are not supposed to find the (causal) relation! Any claim of existence of strongly emergent properties in nature can always be rebutted by non-emergentists that the emergentist has not looked well enough. (Such claims and counter-claims are not uncommon between reductionist and holists; see e.g. Edmonds [10] for a pragmatic approach.) From the perspective of philosophy of science, strong emergence is most interesting for philosophical inquiry, but if one wants to actually claim existence of strongly emergent properties in nature, one *cannot* avoid epistemological emergence. Even if there is a software program that simulates that what is also observed in nature, this does not imply that that higher-level phenomenon is systematically determined by *only* those lower level parameters encoded in the software. First, because we cannot know if our observation of the phenomenon in nature is complete, i.e. we simulate what we observe, which does not mean that exactly *that* happens in reality: at best, it is with the current state of methods of observation *the best approximation of the truth* (see e.g. [28] [16]). Second, if we know the parameters and their values, this does not mean we know *all* possible combinations of parameters and states that lead to the alleged strongly emergent phenomenon. No matter how one turns around the strong emergence (at least with respect to emergence in biology), one cannot escape epistemological emergence except for the case where one has no desire to investigate a strongly emergent property seriously[1]. From this follows that statements about existence of strongly emergent properties, hence also about ontological emergence, are not testable to prove or refute its existence. Asking the biologist to set aside scientific inquiry to take a leap of faith and believe in strong emergence is doomed to failure; she may get tired trying to find an answer or find it too complicated to investigate with the current tools and methodologies and (temporarily) give up, but this does not mean support in favour of the position for strong emergence in nature.

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[1] This does not mean that I think the research into emergence of consciousness is not done seriously, but that claims of existence of strong emergence of the property of consciousness (e.g. by Chalmers) is premature as, for one, it is debatable if we indeed have systematically fully determined the lower level facts. If we did, we should be able to build an artificial conscious system from the knowledge we have about the lower level facts and/or laws, or *know* why we cannot. If we do not know sufficient, then this means we do not have full knowledge of the lower level system, hence we cannot rightly claim to have a case of strong ontological emergence but one of epistemological emergence at best. Debating about which one it is can go on until we can establish, prove, which one is right, and until then there is no strong emergence there.

3.4 Weak emergence

As discussed in the previous section, strong emergence in biology is problematic, even scientifically irrelevant according to Bedau [2][2], but people seem to like the idea of emergence and use it regularly in scientific communications. If emergence exists in the realms of biology, then it surely belongs to epistemological emergence, but epistemological emergence does not cover all assertions about that type of emergent properties. In particular, by focusing on the fundamental lack of knowledge only, it overlooks the aspect if a property is *irreducible* to its lower level components or if the problem is the other way around where one knows the lower level components but *cannot predict* the higher level property. Weak emergence fills this gap within the reductionist framework. Informally, weak emergence says that the parts *in isolation* do not possess the properties observed a the level of the whole [8] [36], and includes token-token reductionism [8] that takes into account the relations between the lower level parts. Claiming in favour of emergence on the basis that it can exist only if we provide an *incomplete* description of the complex system at the lower level has within this claim its very negation of existence: if one knowingly describes only part of the system then indeed it is no surprise it will not be capable of predicting the higher level property. This does not support that 'therefore' a higher-level property is emergent, but at most it is emergent by one's own making, even being cognizant of that, and most likely even know what is missing in the lower level that, if included, lets the weakly emergent property be explained away. A different and less informal definition of weak emergence by Bedau [2] is:

> Macrostate P of S with microdynamic D is *weakly emergent* iff P can be derived from D and S's external conditions but only by simulation.

where system S is composed of micro-level parts and S has several macro- and micro-level states, the microdynamic "governs the time evolution of S's microstates", and P can be a property, a phenomenon, or a pattern of behaviour. Put differently, the emergent property is both predictable and derivable such that "weak emergence involves *underivability except by simulation*" (emphasis added). Bedau's argument is that simulation is crucial, because it is *undoable in practice* to do the calculations and derivations manually: "this sort of knowledge [of nondeterministic systems] is beyond us, except "in principle;" so, weak emergent macrostates of such systems are predictable *only* "in principle"." [2]. Hence, "in principle we can derive the system's behaviour... on this key issue weak emergence parts company with at least the *letter* of those traditional conceptions of emergence... [but] does share much of the *spirit* of those traditional views that emphasize unpredictability" [2]. But is this weak emergentism still emergence? For if we can derive the higher level property, hence possess sufficient knowledge about the system, there is neither the non-predictability nor the irreducibility of the epistemological emergence. Where does one draw the line to decide what is 'practically undoable' to become weakly emergent? A scientist may

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[2] Note though, that a *hypothesis* for strongly emergent property x can be very useful for directing scientific investigation to unravel the 'mystery' and healthily refute the claim; it is the *belief* in the existence of strongly emergent properties that has no place in science.

lose sight of the higher level property x when being bogged down by a large amount of lower-level objects and states, but then this x may for one person be weakly emergent and for another utterly mundane, thereby making the decision for emergence to be the individual observer's point of view or amount of knowledge about x, rather than independent of the human observer.

3.4.1 Simulations

One avenue to salvage the notion of weak emergence is being more precise about simulations as one of the methodologies to investigate claims about emergence, for which there are two options.

First, to take the approach of Cariani [4], who uses an *operational* definition of emergence: emergence relative to a model, only novel at a level of description (also advocated by [11] [33]) and that "the detection of an emergent event is a joint property of both observer and [measurement-taking] system". When something unexpected, the emergent property/behaviour, pops up during the simulation, one can either 1) change the algorithm, or 2) add more parameters, or 3) make more precise (finer-grained) measurements to resolve the issue. To make the mathematical model manageable, it is practically useful to abstract away smaller details (like modelling population behaviour with organisms but not their constituent molecules), although "Simulation often requires integration of multiple hierarchies of models that are orders of magnitude different in terms of scale and qualitative properties" [20]. In this sense, observation of an unexpected, weakly emergent property amounts to 'we had it too coarse-grained or even wrong the first time round, lets see what happens when we tweak the system a bit'.

The second avenue is of a theoretical nature: not everything can be simulated. In contrast with the first option for simulations, this focuses on the research & software development efforts to create a software application. We may well know how something works, but that does not mean programmers also can develop the corresponding application. Even when we assume perfect programmers' skills, there are some problems for which the computer cannot compute an answer. Here, it is important to make distinctions between complexity theory, computability theory, and intractability: complexity theory studies the cost (resources) to solve a given problem, computability theory deals with if a problem can be solved at all, and intractability looks at things that are solvable in theory but with current computer resources and technology cannot be solved. For instance, the problem of sorting gene sequence inversions is known to be NP-hard, while the complexity of sorting genetic mutations caused by transpositions is still unknown, i.e. at present *no* computer program can solve this other than to develop algorithms that approximate reality [13]. Does this impossibility of perfectly simulating evolution mean evolution is magically (weakly or otherwise) emergent? No. That one cannot simulate everything on the computer does not make it emergent for that reason alone. When a software-simulation-by-approximation-algorithm returns unexpected test results, the likely culprit of the so-called weakly emergent property is already given, but our and the computer's limitations are not sufficient grounds to prove existence of emergence in nature.

Nevertheless, one may fancy using the terms weak- or epistemological emergence as a shorthand to refer to the situation of 'we have a gap in our knowledge about the precise relation(s) between the whole and its parts and possibly missing something about the parts themselves as well', but such reference to 'emergence' seems to cause more confusion than that it solves.

3.5 Examples

The next two examples, pseudoplasmodium formation by cellular slime moulds and horizontal gene transfer with metagenomics, illustrate and discuss several of the philosophical aspects of (non-)emergence in biology, and introduces informally its connection to levels of biological granularity.

3.5.1 Example 1: pseudoplasmodium formation by cellular slime moulds

One can apply token-token reductionism and "mechanism extension" [8] to incorporate more information in the lower level—a context extension by changing the boundary of the system—such that the higher level becomes explainable within the reductionist framework and refute a proposed emergent property. The context in the lower level that provides the causal explanation observed at the higher level then includes previously excluded parts that, in the light of reductionist explanation, have to be included in the lower level after all. An example Delehanty [8] provides is the extended mechanism of molecular causation of pseudoplasmodium formation by the cellular slime mould ('social amoeba') *Dictyostelium discoideum*, one of the model organisms: the aggregate formation of the individual cells of type *D. discoideum* should not be explained at the *Cell*-level where it is as of yet unexplainable but is fully explainable at the "most basic level" [8] of *Molecule*, i.e. the evolutionary ancient Second Messenger System with cAMP. This ignores the point why neither physics nor *Cell*-level biology can explain the behaviour. For why do we have to 'skip' at least two levels of granularity – at least the *Cell*-level and the *Organelle*-level – to explain the formation of supra-cellular structures and cellular behaviour. Delehanty ignores them in her explanation, but they are not irrelevant – that pseudoplasmodium formation is reductionistically explainable is true, but that 'only molecules matter' is incorrect. *In casu*, for organelles are not unrelated in the overall mechanism: with the changes in gene expression involved in pseudoplasmodium formation, such as the *pkaC* gene, this also means that ribosomes (organelles) are involved for protein synthesis of the corresponding protein kinase PKA; a function of PKA is to regulate cell type specialization after up-regulation of genes related to cAMP synthesis. All this is induced by the YakA protein kinase that is responsible for the cell cycle during growth of the cell. [34]. Talking about genes is taking into account *functional units*—not molecules—and ribosomes are not just two clumps of rRNA, they constitute a unit where both parts are necessary for translation of the mRNA into a protein.

Why are molecules the lowest level and not the atoms and below of physics? Even if we would accept this molecule-approach, does one example justify its extension to the still hoped-for molecular explanation of supra-cellular structures of cocci where sphere-shaped bacteria get together in groupings of two, four, eight, a string or grape-like bunches of cells? And does a molecule-based explanation suffice for the extracellular *matrix* that keeps tissue cells together in shape, distinct from the cocci that have to make do without the matrix? The basic *Molecule*-level to explain all higher-level phenomena then takes the place as most fundamental science of nature that physics enjoyed before; biochemistry-or-stamp-collecting. That Delehanty ignores physics leaves open the question if there may be emergence going from the sub-atomic and atom levels to (macro-)molecules, hence is not convincing against emergence in general, but shows that weak emergence is an unsustainable position. Her approach is useful for the idea of mechanism extension and more clearly using the distinction between strong and weak emergentism, but does not negate ontological and epistemic emergence. If Emmeche [12] is right in his optimism that science will discover the unknown to eliminate an emergent property to a deducible, predictable, reducible property, then epistemic emergence is unsustainable, and therefore strong emergence too. This leaves an unusable ontological emergence, which can be neither proven nor refuted, as discussed in the previous sections.

3.5.2 Example 2: horizontal gene transfer with metagenomics

More recent than systems biology that has brought back the attention of emergence among biologists, is metagenomics, also called 'high-throughput molecular ecology', community genomics, ecogenomics, environmental genomics, or population genomics [9]. It combines molecular biology with ecosystems, which is at present limited for technological constraints to the study of the interactions within microbial communities *in situ*, such as marine microbiology [9] [32], soil microbiology, and biotechnology [23]. It reveals community and population-specific metabolisms, i.e., the interdependent biological behaviour of the organisms in nature that is affected by its micro-climate, hence requiring ecological knowledge to resolve the gaps in understanding of the natural world[3]. Simplified, it tries to answer questions like "what lives in my soil sample?" and "what is the genetic composition and diversity of the microbial community?". At the microscopic scale, it traverses a *Chromosome*-level, *DNA fragment*-level that contains mobile DNA fragments for horizontal gene transfer (HGT) between bacteria of the same and different type (see [25] for an overview), bacteria in turn are entities located in the *Cell*-level and *Organism*-level, depending on criteria used for level specification. These levels indicate involvement of molecules and coordination of molecular processes, such as gene regulation and metabolic pathways, but do not imply that molecules and their behaviour alone can explain everything. Both prevalence and preference for mechanisms of HGT between prokaryotes *in situ* are topics for which the biologists hope to gain insight and answers through metagenomics. Mech-

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[3] Note that micro-climate and micro-environment are ill-defined; it is used to contrast with climate at the customary grander scale, like sea climate, global warming and so forth. A micro-environment can be your lungs where invading bacteria of one type acquire antibiotic resistance from resident bacteria that survived prior treatment, or the rhizosphere with bacteria living close to the roots of plants (between 0 and 3 mm) where there are relatively more nutrients than farther away in the soil.

anisms are known in some detail, such as conjugation, bacteriophages or plasmids as 'transmitters' of a gene or group of genes between bacteria, but they do not provide understanding of the composition and management of the bacterial gene pool, nor about factors that stimulate or inhibit HGT influenced by local environmental conditions. Furthermore, scientists have observed that HGT of operational genes are much more often transferred compared to informational genes, which led to the "complexity hypothesis" for HGT. It postulates that the former is easier because operational genes involve often only one or a few genes, whereas informational genes are part of a large network of interacting genes and proteins and is therefore less likely to transfer and be successfully incorporated in the new host [15]. For instance, the translational machinery of the bacterium *Escherichia coli* involves at least 100 gene products, but there are only two genes involved with the thioxin - thioxin reductase complex [15]. The gene product of a complex gene network has to make more interactions to survive in the new host, hence the probability of success decreases correspondingly.

To what extent the capacity for HGT is encoded in prokaryotic DNA is underspecified at present, but even if it is fully encoded and eventually the precise processes known, having a *capacity* for HGT is insufficient as it is only by virtue of the bacterial community and its surrounding environment that HGT occurs. Thus, HGT *seems* to be irreducible to molecules alone because it requires interaction at the *Cell*-level and has *Cell*-level effects. For instance, a bacterium has a sex factor F^- or F^+, where an F^+ bacterium has sex pili on its cell surface and an F^- bacterium has compatible receptors. The genes for pili development are on a plasmid in the F^+ bacterium. Pilus and receptor 'mate' whereby genes from the F^+ bacterium are transferred through the pilus into the F^- bacterium, which thereby becomes an F^+ bacterium.

Conversely, the genes and molecules do not seem to direct transfers at the level of the community in the sense of being predictable and deducible from (initial) states of the system. Is there a full causal explanation at the DNA or *Molecule*-level for 'emergence' of multi-antibiotic resistant bacteria like the MRSA? Does HGT *supervene on* the participating organisms and/or their DNA, or is the occurrence of HGT *not* constituted by the occurrence of more fundamental properties and relations of the objects parts? What fused and what should then be designated as the new primitive causal power of HGT? The supervenience argument requires the parts HGT is dependent on and, because it acts out at a community level, it would make HGT a property of the bacterial community, but there is no *unique* base on which it emerges because there are entities of *several levels* required to provide a basis on which it is dependent. There are occurrences of fundamental properties such as the plasmid and pili that do not cease to exist upon 'fusion'. Emergentists might claim HGT is an example of epistemological emergence—pending further research—and a biologist might talk about it as a weakly emergent property that at present can be explained only partially within the reductionist framework, but this does not match philosophical requirements for qualifying as an emergent property as the scope and interactions of the properties involved are insufficiently defined.

4 Emergence and levels of granularity

If one assumes emergent properties exist or uses it as a working hypothesis, then what effect, if any, does it have on identification of levels of granularity and on the granular perspective? And if so, which type of granularity? Emergentism itself does not deal with granularity and levels of granularity explicitly, but does use the un(der)specified notion of 'level' in general. With this usage, emergence essentially says that there are at least two levels (as opposed to Salthe's three [31]): a level of focus and a level 'below' to which it is irreducible, or in the other direction one has the focal level and the emerging property at a higher level that is unpredictable or not derivable. After some preliminaries about granularity, I will address the impact of the irreducibility argument first, then the non-predictability & non-derivability. §4.4 discusses the modelling considerations how and where emergence influences a domain-independent characterisation of a granular level and how it is a useful methodological approach to investigate claims of emergence.

4.1 Preliminaries of granularity

Granularity involves modelling something according to certain criteria, the granular perspective, where a lower level within a perspective contains knowledge (i.e. entities, concepts, relations, constraints) or data (measurements, laboratory experiments etc.) that is more detailed than the adjacent higher level. Conversely, a higher level simplifies or makes indistinguishable finer-grained details. A granular level contains one or more entities and/or instances.

Differences between types of granularity are based on: i) arbitrary scale, such as those of the Système International d'Unités, versus non-scale-dependent granularity, which involves partitioning one entity (/instance) according to one or more criteria versus applying granularity to multiple entities (/instances) and simple arithmetic aggregation versus more complex folding operations; ii) how levels and its contents in a perspective relate to each other; and iii) the (mathematical) representation (e.g. set theory, mereology). [19]. With relation to emergence, non-scale-dependent types of granularity are of interest; scales are not unimportant, see e.g. Wimsatt's list of considerations [36], but a scale does not generate emergence. Observe the difference where it might be that *at* a certain level of granularity of the measurement scale something seems to emerge, but there is an important difference if, for instance, one takes units of *Year* versus observing processes one *Second* at a time (like offspring does not magically emerge), the rounding off for grouping measurements with rough set theory or fuzzy logic (e.g. [27]), and the precision of a measurement device. This is distinct from a non-scale-dependent granularity with a structural perspective and its levels (1), the (preliminary) genomic information units perspective (2), or granularity in modes of transmission of infectious diseases (3), where the connective "$\prec$" denotes proper-part-of between the levels of granularity.

$$Atom \prec MoleculePart \prec Molecule \prec OrganellePart \prec Organelle \prec Cell \quad (1)$$

$$Gene \prec GeneComplex \prec OrganismalGenome \prec PopulationGenome \quad (2)$$

$$SexualIntercourse \prec Person\text{-}to\text{-}PersonTransmission \prec DirectContact \quad (3)$$

Keet [19] has constructed a taxonomy of types of granularity and contains a basic formalisation of domain, perspective, level, their relation, and how contents of levels can relate to each other within that level. Relations between entities residing in granular levels in one perspective can be (at least) either of the type *is-a*, or *part-of*, or *involved-in* for processes and part of processes, or *contained-in* for spatial containment. In order to construct a domain-independent theory of granularity for developing a sound methodology for investigating emergence, we need to know if, and if so where, hypothesized emergent properties affect the domain-independent definitions of and constraints on the components of granularity—such as the minimum amount of levels in a perspective and type(s) of relation(s) between levels or their respective entities residing in the levels.

4.2 The irreducibility argument

Irreducibility at best complicates identification of, and assigning content to, a granular level because not all component endurants and perdurants are known with epistemic emergence; hence, the lower level is *under*specified or *incomplete* by definition. As such, one may be inclined to state that there are not at least two levels, but one: there is no 'proper' lower level of granularity because the content in the higher level is not fully devisable into component parts. However, the only way to prove there is no such lower level is to assume there is one, try to describe it, fill it with data and/or knowledge and test its explanatory power with respect to the hypothesized irreducible emergent property. Thus, the focal granular level with the assumed emergent property exists by virtue of the lower level that supposedly has insufficient explanatory power.

Combining weak and epistemological emergence with the modelling considerations of granular perspective and token-token reductionism & mechanism extension, the following observations can be made. With a granular perspective, we do not intend to capture the complete entity but only those properties of interest within the perspective. When we model human anatomy (e.g. [30] [6]), cell physiology or gene products as in the Gene Ontology [http://www.geneontology.org], we separate the structural entities from their involvement in processes and the functions they are capable of performing, like a short chain of amino acids is structurally a peptide and functionally a hormone (e.g. insulin). With such non-scale-dependent levels of granularity, it is no surprise when a lower level cannot fully explain a higher-level property because it is within a granular perspective only partially defined. To be able to test a hypothetical emergent property, contents of levels of different perspectives have to be combined by availing of the whole database, knowledge base or through ontology integration. Although the latter is not an easy task, testable it is.

The irreducibility argument is particularly interesting for non-scale-dependent biological granularity, as opposed to scale-dependent types of granularity, and fits with epistemic emergence and mechanism extension, where more research results allows a more comprehensive theory to be added to the lower level in the human-constructed model to fully explain, hence refute, the higher-level emergent property.

4.3 Non-predictability and non-derivability

In the other direction, a lower level of granularity can be fully specified but either the higher level or the relation between the two granular levels cannot be identified. Concerning the former that assumes a fully specified lower level, then the emergent property would be an ontologically truly novel property. Korn's [21] thesis of rearranging constraints at the higher level suggests an 'insufficient' specification of either the lower level or the higher level. This also implicitly claims a minimum of two levels of granularity. Accepting Korn's emergence at the top-most level that is free from constraints from above, amounts to accepting that domain granularity cannot be properly characterised at the top-most level, and possibly neither at an intermediate level where emergence occurs though rearrangement of constraints. The second case, where the relation between levels cannot be fully specified, faces a similar problem, as one cannot predict that what emerges at a higher level, hence one cannot pre-encode the relation between the entities in the two levels—but note it requires two levels. Are we left to encode 'the future' where a novel property emerges? No, by virtue of being novel, this cannot be done. Once when there is a novel property, we can reposition the problem as one of irreducibility, encode the extant knowledge manually and take the same approach of investigation as described above to confirm or eliminate the emergence. Thus, even when one is an emergentist, granular levels can be defined, hence emergence tested.

Non-predictability and non-derivability do not emphasise properties as an important aspect of the essence of a granular level, but, for instance, Korn's constrains can be modelled as properties and Johansson's [17] and O'Connor and Wong's [24] supervenience emergence allows straightforward specification of the finer-grained level and loading of entities in that granular level. Moreover, granularity provides a methodology to add structure to the knowledge by disambiguating what supposedly supervenes on which lower-level entities. When one has a formalised granularity framework, then (non-)derivability can be relatively easy determined with extant automated reasoners (e.g. RACER or FaCT for Description Logics and OWL files). Even if it is not derivable, declaring the conjectured relation helps further in understanding the system, where inconsistencies and unsatisfiability indicate a modelling error or a wrong assumption of the knowledge that is represented. This, of course, has the issue that not everything can be expressed in logic and can have an additional complication that the modeller may not be proficient enough to express the knowledge in the formal representation language. The latter is quite common in bio-ontologies development where biologists try to construct (in)formal ontologies and adding constructors for modelling granularity may exacerbate this challenge. Nevertheless, in both cases we are well on the topic of user & model limitations, certainly not non-derivability due to emergence in nature. The same argument holds for modelling for simulations to examine (non-)predictability. Hence, the non-predictability and non-derivability claim has no effect on what a granular level is.

4.4 Characterisation of granular level from the viewpoint of emergence

Following from the compatibility of levels of granularity with the various interpretations of emergence, then how can one characterise the domain-independent granular level? Given that the existence of emergent properties is not undisputed, it is exactly granularity that serves as one of the methodologies of investigation of such claimed emergent properties. Representing the data, information, and knowledge formally in a proper and clear structure enables more precise specification and description of the entities involved, which facilitates highlighting and narrowing down the 'gaps' in the system that makes the higher-level property difficult or at the time impossible to explain. Difficulties of modelling the (hypothesized) emergent property arise with the specification of the domain granularity framework, allocating the content into the levels, and inferencing but not by definition at the domain-independent specification of what a granular level is. However, methods like token-token reductionism and mechanism extension affect that what resides in a granular level, in particular that it may not be one type of entity. To provide a formal framework that can cope with hypothesized emergent properties, there are two principle options:

1. **Systems approach**, where a finer-grained level contains *all* types of entities and their relations together. For instance, one has the coarse-grained level with biological signalling pathways (see e.g. the KEGG pathway repository [http://www.genome.jp/kegg/]) containing, among others, *SecondMessengerSystem* and *MAPKSignallingPathway*, and the *immediate* finer-grained level that expands the *SecondMessengerSystem* contains its parts, such as *cAMP*, G_s *protein*, *GTP-GDP exchange*, *GTPase*, *involvedIn(GTPase, GTP-GDP exchange)* and so forth. Although this may be a preferred option for one-off models, it is difficult to store, is not scalable[4], let alone be amenable to reasoning over the information. One-off models may be useful for simulation software, but a modular structure (more easily achieved with the next option) lends itself better for creating simulations of larger subject domains like a virtual cell or artificial life (e.g. E-cell [http://www.ndsu.nodak.edu/instruct/mcclean/vc], PACE [http://134.147.93.66/bmcmyp/Data/PACE/Public], and COSMIC [26], where crucial hub-like components such as P43 and ubiquitous molecules like ATP can reoccur in an interconnected mode instead of added to each model separately.

2. **Components approach**, which both conforms to the reductionist framework and Ontology by separating types of entities into different structures such as taxonomies and partonomies. This facilitates constructing a model by more precisely categorising its components by type, such as structural components,

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[4] One can think of desiring to compare the second messenger systems across species to gain an understanding of its evolution and how complexity of the system was gradually built up. One-off models do not lend themselves for such task other than conducting a laborious manual comparison. To automatically find if part of the second messenger sysem, say, the G_s *protein*, has dual or even multiple use is nigh impossible except for literature research; with more signalling pathways, some degree of automation can greatly facilitate the analysis.

> processes, and location, aids representing specialisation and generalisation to enable to include more knowledge in the representation, and make it possible to have an explanation refuting emergence by traversing several finer-grained levels instead of only a *Molecule*-level or only the direct adjacent finer-grained level. For instance, using a taxonomic representation, one would include that *GTPase* is an *Enzyme* and in another taxonomy of location that *GTPase* is located in the *Cytoplasma*. Provided there is a relation between the structure-based taxonomy and spatial location taxonomy, it can be derived that enzymes are located in the cytoplasm (see [18] for more elaborate examples for infectious diseases). However, this also indicates the potential weakness of the components approach: how should one link the separate structures? If this is represented in a machine-readable version of an ontology or conceptual model, these type of relations are manually created or discovered by using automated heuristics for ontology integration and schema matching. Alternatively, 'fact-finding' in database systems can be an effective method by using joins between tables.

Both options conform to the reductionist approach, with the components approach more so than the systems approach. The components approach is more time consuming in the initial stages, but in the end will be more powerful than the systems approach as it allows the user to retrieve more, and more detailed, information from the model in an easier and more flexible manner. The disambiguation required for the components approach entails distinguishing entities based on the properties they have, whereas this is of no particular importance for the systems approach. To be able to analyse and test an emergent property, it is indispensable to know what properties both the whole and its parts have. For these reasons, the second option is preferred over the first to be taken into account at the domain-independent specification of granularity.

Allowing modelling of (weak) emergence in a domain granularity framework freely, favours the modelling consideration that within each granular perspective, one neither has one type of relation connecting the entities residing in granular levels in the hierarchy nor a single property or criterion to identify and distinguish granular levels (as in option 1 above). The former is highly undesirable for a) testing derivability and reasoning in general because it invalidates transitive closure and b) stimulates ontological sloppiness instead of ontological rigour required for good modelling practices. The latter can be adequately addressed with the components approach, because e.g. with a taxonomic classification one adds one property (or more) at a time for each node traversed downwards in the tree via the $\subseteq$ (subsumes) relation. So, the possibility of emergence does not contradict the usage of properties for identification of levels; in fact, it adds a challenging notion concerning the criterion (combination of properties) for biological granularity. In addition, it provides an argument for distinguishing between scale- and non-scale-dependent types of granularity [19]: the latter may be faced with accommodating (hypothesized) emergent properties, but not the former as it is not the scale by itself that makes a property emergent.

Framing an explanation of a phenomenon at a particular level of granularity helps making explicit the mechanisms of explanation and clarifies what is, or is not, directly used to assert emergence, or to explain it away. For instance, given one has only the *Cell*-level at one's disposal to elucidate the mechanism of pseudomplasmodium formation, then the contents of this level is indeed insufficient to give a full account of the process. It being insufficient then strongly suggests taking into account other levels to 'search' for the right level(s) that do provide the required explanatory power. This is not simply mechanism extension to just add entities as one pleases, as proposed by Delehanty, but a structured approach that equips one with a tool to also find an answer *why* another level is indispensable. Moreover, one can 'ignore', set aside, lower levels for some software implementation and relatively minimize getting bogged down in detailed encoding of low-level parameters by taking either a modular approach with input/output points for each granular level or noting where and why approximations suffice, without having to attribute the resultant to 'magic' emergence.

Thus, levels of granularity can be a useful modelling approach for investigating (hypothesized) emergent properties. However, granularity is more than this and before defining what a granular level is, other facets, such as similarity and indistinguishability [14], have to be taken into account to represent its meaning comprehensively. A basic theory of granular partitions limited to mereology [3] and the more comprehensive characterisation of types of granularity [19] provide several modelling guidelines for experimentation.

5 Concluding remarks

Summarising the philosophical points on emergence combined with informal usage of emergence in biology, then this informal usage tends towards epistemic emergence due to our lack of knowledge about nature, but philosophically this is an unsustainable position. Philosophy adds clarification to better characterise the fuzzy notion of emergence, with e.g. the untenable strong and weak emergence, but paradoxically it is exactly the methodology of conducting scientific experiments that can give decisive answers. A renewed interest in whole-ism does not imply emergent properties exist, but illustrates the realisation that things a more difficult and complex than initially anticipated. Against this backdrop, weak- or epistemological emergence is a shorthand for 'we have a gap in our knowledge about the precise relation(s) between the whole and its parts and possibly missing something about the parts themselves as well', which amounts to absence of emergence in the philosophical sense.

Besides more wet-lab experimentation, computer science with both simulations and, more importantly, the conceptual and ontological modelling that precedes software development, are essential methodologies for investigation. Granularity as a structured modelling framework is a useful approach to facilitate research into hypothesized emergent properties. Both irreducibility and unpredictability & underivability confirm that within a granular perspective at least two granular levels are required. Although separating the entities based on types of properties, such as location or function, will not by itself directly explain a higher-level property, focussing on the properties of the constituents of the whole is essential for understanding what exactly is the relation between the entities in the two levels. Separating them before linking, or merging, the hierarchies of granular levels of the different granular perspectives amounts to admitting to a reductionist approach that superficially seems to go against emergentism, but actually serves it because ontologically sound categorisations of the entities involved relies on an improved understanding of the properties of the entities in a level, and therefore, by extension, the characteristic property of a level that provides the desideratum for allocating entities in one level or the other.

Granular levels and their contents provide a methodological modelling framework to enable structured examination of claims of emergence both from a formal ontological modelling as computational angle. It makes the complex at least less complex, and aids understanding which levels are essential for explanation of some property of observed behaviour, hence that are more, or less, relevant for e.g. developing simulation software.

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