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PROTECTED: WE ARE REDUCTIONISTS. SHOULD WE CARE?

We are reductionists. Should we care?

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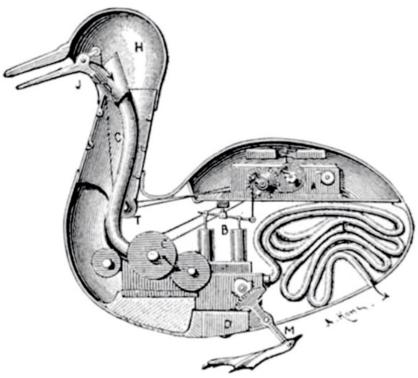

Twenty first century scientists do not have much time for philosophical questions, but one such topic keeps attracting interest, definitely among life scientists [1, 2] but also in physics [3, 4]. This is *reductionism* [5, 6], which for a long time has enjoyed overwhelming dominance in science but seems to be now contested. Certainly, the reductionism *vs* anti-reductionism duscussions have been recurrent in different moments throughout the history of science, but it is interesting to reflect on the reasons why they come back with renewed strength and why they may be relevant to biophysics.

Although reductionism has been tightly bound to science for centuries, it has always found resistance, especially in connection to the study of biological phenomena. From the beginning of the twentieth century, holism (in its different facets) [7, 8] was adopted as the favourite anti-reductionism notion, used mainly to support traditional views in a number of controversies where there was an opposing reductionistic view. This is the case of conflicts like vitalism *vs* mechanicism and intelligent design *vs* Darwinian evolution [9]. Reductionism won a dominant position with the advent of molecular biology (by the mid-20th century), which was seen as a triumph of *physicalism*: Living matter is molecular, i.e., just another type of chemistry, and as such is assumed to respond to the same physical laws as any other matter in the Universe. This view was accepted naturally among the most developed sciences at the time, physics and chemistry, since they had arrived to their *modern* state after a long process (from the 17th century) rooted on reductionist ideas of gigantic characters like Galileo, Descartes and Newton. Molecular biology helped to extend that view towards life sciences, being reinforced by a good number of very successful reductionist methodologies, including techniques for biochemical analysis, gene cloning and molecular structure determination. Francis Crick, in a pick of excitement about this scientific revolution, named it *new biology* [10].

This signalled the starting of a reductionism era of which the landmark was the discovery of the structure of the double helix of DNA. Indeed, structural biology stands as a good example of methodological reductionism, which has also strong epistemological significance through the renowned concept of *structure-function relationship*. By 1966, Crick generalized such a significance by assuring that the "ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry" [10, 11]. The subsequent discovery of the genetic code and the understanding of the replication, transcription and translation processes, named *mechanisms*, consolidated a deterministic view of biology. The reductive mechanicism of life had been introduced three centuries earlier by Descartes [12], although at the anatomical level (the picture heading this article symbolizes that view in the form of an animal *automata*, conceived about 100 years later [13]). Molecular biology, instead, pushed mechanicism down to the more basic level of molecules, from where it was generally accepted to be applicable to all aspects and all forms of life. These ideas extended rapidly and effectively to all branches of biology, although some strong opponents remained, who sporadically fought against what they considered "a sort of taken-for-granted biochemical imperialism" [14, 15]. Biophysics, as one of he main

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inheritors of the molecular/structural biology *momentum*, strongly embraced the new reductionist conceptual framework. Moreover, since reductionism had a long tradition in physics [3, 5], it was also more naturally accepted by biophysicists than by any other life scientists and still today most of the science that we produce is best described as mechanicistic-reductionistic.

Hence, we are reductionists! Should we care about that, to the point that we might consider it a *shame*, or a *sin* (as DAWKINS puts it in "The blind watchmaker") [9]?

After half a century of flourishing development of molecular biology some of its inherent weaknesses started to pop up: *In vitro* biochemical studies in controlled and very well defined conditions, highly resolved structure determinations, super-resolved imaging up to the nanoscale, single molecule manipulation and sophisticated molecular simulations are all able to provide a rich mosaic of astonishing unprecedented observations. But each of them is constrained by still unavoidable limitations imposed by methodological requirements and mandatory scale or solution conditions, all of that hampering extrapolations to relevant biological contexts. Moreover, all these individual studies suffer from some kind of partiality and disregard for many (if not most) possible interactions that define real biological systems, which although unpredictable, happen to be essential.

Some responses to these well-known limitations of biochemical and biophysical studies have been to increase their complexity and pluridisciplinarity, and nowadays they are often based on collections of multiple techniques and, if possible, including also *in vivo* observations. Multi scale and multi technique studies under variable conditions increase the relevance of results and the reach of conclusions. However, none of these efforts alone guarantees the comprehension of complex biological phenomena and the reputation of reductionism remains damaged. Even if biophysical studies are directly performed in life cells or organisms, they are still constrained by laboratory conditions and peculiarities of the chosen life-sytem model, which precludes successful extrapolation to *real* life cases, specially if they are of a different, typically more complex, species (like mice being used as models to investigate human pathologies). Problems of this type are consistently being identified among the current challenges of biomedical research. For example, the "impossibility of reducing biology to chemistry" is blamed for the poor success in some drug discovery programs [1].

Modern evolutionary biology takes a holistic path based on the materialistic concept of emergence

Apart from the idea that purely reductionist molecular biology may have reached its limit, some recent literature [1, 2, 16] gives us clues about other concurrent arguments that question the value of reductionism, at least in biology. One of them comes from the impact of epigenetic networks (involving genes, proteins and environmental signals) in shaping the interactive complexity of cellular processes, which escapes the notion of a linear causality, based simply on genes and their products [2]. Instead, life would be ruled by the principle of downward causation, consequence of the complexity of the biological system, which can be enunciated as follows: "The whole determines the behaviour of its parts" [17]. Another criticism to reductionism comes from a renewed view of evolution. Paradoxically, although Darwinian evolution was in the past explained as reductionist [9, 18], in contrast to holistic creationism [7, 8], modern evolutionary biology takes a holistic path that is detached from vitalism and theology and is instead based on the materialistic concept of emergence, that follows from this thesis: "The whole is more than the sum of its parts" [17]. According to this, emergent evolution is a directional, irreversible and progressive source of diversity and complexity that produces unpredictable results [7, 16]. Life (in all its forms, including even protolife) would then be an *emergent* property of complex (biological) systems, since it can neither be predicted from parts of these systems nor explained from combinations of their pre-existent properties.

The latter view is often presented as opposed to the view of physics, although emergentism is in fact one of the central aspects of the physical theory of complex systems (a subset of systems theory), where the emphasis shifts from the parts of a system to their dynamical organization and mutual interactions, as a way to explain the systems behaviour. This theory was also shaped throughout the 20th century and in the mean time the concept of complexity [17] has gained force in different areas, and very specially in biology. Interestingly, modern molecular biology has contributed to consolidate the idea of biological complexity through developments like genomics, proteomics, interactomics and multiple other omics, all accompanied by concomitant production of piles of *big* data that are handled with bioinformatic technologies. The omic studies are already detached from traditional biochemical reductionism since they focus on the collective characterization of a complete pool of a certain type of molecules (genome, proteome, transcriptome, lipidome), or a set of molecules related through metabolic transformations or interactions (metabolome, interactome), occurring in a cell, tissue, organ or organism under certain physiological conditions. Although these *omes* allow to understand particular aspects of the cell function, they are all still partial and thus (alone) cannot capture the emergence of the biological system.

From the need to integrate different omics data and knowledge at the level of a whole system, by the end of the 20th century a new field of study emerged, called systems biology. This new discipline had in fact developed from the 1950s as an application of dynamical systems theory. It came with the promise to provide consistent and seemingly complete (holistic) views about the organism, tissue or cell system [19]. By considering the system as a whole and through extensive computational and mathematical analysis, fed with omics data to build reaction and interaction networks, it aims to model and discover the emergent properties of biological systems. The holistic impulse of systems biology, framed by the new ideas of complexity and emergence, stands today as the most clear contrast with respect to classical biochemical / biophysical / molecular biology reductionism and thus appears as a major contributor to the rise of a new anti-reductionism wave.

> **Systems biology appears as a major contributor to the rise of a new anti-reductionism wave**

We may ask ourselves how much we should care about today's reductionism *vs* emergence controversy. Because our reductionist strategies have been, and continue being, quite successful and productive, we may opt for caring little or even caring nothing. However, doing so is equivalent to being satisfied with incomplete solutions to our biological problems, constrained within the limits of our partial objects of study. In most cases that would mean adopting a pure molecule-centric position (characterize the properties and behaviour of the system in an artificial context of study with no concern about its original biological context), which would be more typical of a chemistry approach. There is nothing wrong with that, as it is still a required "piece in the puzzle", but if we stop at that level we will be renouncing to the aim of contributing to understanding biological function, which should be a must for biophysicists. Instead, we may choose to be aware and concerned about the intrinsic limitations of our reductionist studies and at the same time face the challenge of trying to explain biological function; i.e., trying to unravel emergence even from our reductive position. This may sound naive for those who claim intrinsic inconsistency between reductionism and emergence, although such an incompatibility has been rebutted at least for some cases in physics [20]. On the other hand, classifications as emergent or reducible properties are in fact unstable, since for any given system they are both relative to the scientific knowledge of the moment.

> **If we adopt a pure molecule-centric position we will renounce to the aim of understanding biological function**

Perhaps a good commend is to follow the lines of a famous statement by the music composer Roger Sessions [21]: "Everything should be made as simple as it can, but not simpler!", which is believed to be a rewording of an earlier speech by Einstein's [22]:

> *It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience.*
>
> — A. Einstein, 1933

Isn't it true that the composer's *reduction* of the scientist complex thoughts yielded much clearer (and poetic) words?

Indeed, it was Sessions' version (credited to Einstein) which became popular, after being mentioned in a book review accompanied with following text [23]: " – a scientist's defense of art and knowledge – of lightness, completeness and accuracy".

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2. Mazzocchi F. "Complementarity in biology." *EMBO Rep*, **2010**, 11: 339. DOI.
3. Chibbaro S, Rondoni L, Vulpiani A (**2014**). *Reductionism, emergence and levels of reality*, Springer.
4. Jennings B. "Reductionism versus emergence." *Quantum Diaries*, Apr. **2011**. URL.
5. Van Riel R, Van Gulick R. "Scientific reduction". In: *The Stanford Encyclopedia of Philosophy*, Zalta EN (Ed). Stanford University, **2014**. URL.
6. Reductionism in natural sciences may have different meanings, which can be the source of confusion. If taken as opposite of *vitalism* (***ontological*** meaning) it means that living matter does not differ in composition and properties from non-living matter. ***Methodological*** reductionsim claims that composite systems can be understood in terms of the properties of component parts and interactions between these parts. Finally, reductionism is said to be ***epistemological*** when one accepts that general theories that describe phenomena at a higher level can also be used to explain more fundamental phenomena.
7. Weber M, Esfeld M. "Holism in the Sciences". In: *UNESCO – Encyclopedia Life Support Systems (UNESCO-EOLSS)*, Vol. I – Unity of Knowledge (Transdisciplinary Research for Sustainability). UNESCO-EOLSS Publications, **2008**. URL.
8. Although concepts similar to holism can be traced back to Aristotle's ancient Greek philosophy, the term itself was coined at the beginning of the 20th century by J.C. Smuts, referring to complex natural systems as a whole and as a means to capture some special significance (ontological, methodological and epistemological, see [6] for the meaning of this terms in connection to the opposing concept of reductionism) that the parts of the system would lack. Smuts claimed that 'matter, life and mind still remain utterly disparate phenomena' (J.C. Smuts. *Holism and Evolution*. MacMillan & Co., London, **1926**. URL). Contemporary to Smuts' notion and with a similar meaning, early 20th century biologists used the term ***organismal***. Nevertheless, holism may refer to quite different ideas depending on the context or discippline of study [7].
9. Dawkins. *The blind watchmaker*. Pinguin Books **2006**. In this master work, first published in 1986, Dawkins defends the ***Darwinian evolution*** of life against ***intelligent design***. He refers to a hierarchical step-by-step reductionism as an approach towards understanding the mechanism of complex things (Chapter 1, explaining the very improbable), that eventually he uses also to explain how the complex things may have come into existence.
10. Crick F H C (**1966**). *Of molecules and men*, University of Washington Press.
11. In epistemologic reductionism, among the natural sciences ***physics*** lays at the bottom. ***Chemistry*** is said to be reducible to physics while ***biology*** would be reducible to chemistry. At the top of the reductionist chain lays ***psicology***, said to be reducible to biology.
12. Descartes R (**1662**). *De homine*.
13. The picture is a recreating drawing of Vaucanson's automata, known as the ***digesting duck***. This was one of a number of automatons (mechanical devices mimicking biological functions) conceived and built by the French Jacques de Vaucanson (1709-1782). The digesting duck was his masterpiece. It was able to move, drink, eat and seemingly digest grains (and even defecate the residuals of it, although that was a fake). The original automata was destroyed but we know of it from this drawing, published in 1899 in *Scientific American* ("Some curious automata." *Scientific American* Vol. 80 (3): 43, January **1899**. URL: Internet Archive).

14. Rose S. “Reflections on reductionism.” *Trends Biochem Sci*, **1988**, 13: 160. DOI.
15. Biochemist and neurobiologist, Steven Russell Rose is a fervent defender of a special quality of life systems which makes them irreducible to chemistry. In his TIBS paper [**14**] he recalls a discussion between Karl Popper, who criticised reductionism through a discussion about evolution during a lecture at the Royal Society of London, and Max Perutz, who contested him with an article in the *New Scientist* (Perutz M. *New Sci*. **1986**, 1528: 36,), using arguments based on the explanation of the physiology of oxygen transport by haemoglobin on the basis of the structure of this protein. Rose opposes vigorously to Dawkins reductionist view of evolution [**9**] as well as to any attempt to explain human nature only on genetic basis. He also denounces abuses of reductionism when it comes to explanations of complex behavioural and social phenomena in terms of molecular (genetic) disorders, thus turning into ***ideological reductionism*** (Rose S. “What is wrong with reductionist explanations of behaviour?” *Novartis Found Symp*. **1998**, 213: 176. DOI).
16. Rull V. “Time, evolution and physical reductionism. The arrow of evolutionary time challenges an eventual physical theory of everything.” *EMBO Rep*, **2012**, 13: 181. DOI.
17. Kuppers BO. “Understanding complexity”. In: *Emergence or reduction?: Essays on the prospects of non-reductive physicalism*, Flohr ABH (Ed). De Gruyter, **1992**, p. 241. URL.
18. Rosenberg A (**2008**). *Darwinian reductionism: Or, how to stop worrying and love molecular biology*, University of Chicago Press.
19. Wanjek C. “Systems biology as defined by NIH. An Intellectual resource for integrative biology.” *The NIH Cathalyst Blog*, Nov. **2011**. URL.
20. Butterfield J. “Less is different: Emergence and reduction reconciled.” *Found Phys*, **2011**, 41: 1065. DOI.
21. Sessions R. “How a ‘difficult’ composer gets that way; harpsichordist.” *The New York Times*, Jan. **1950**. URL.
22. According to Alice Calaprice (“The Ultimate Quotable Einstein” Princeton University Press, **2011**), Einstein’s original words, which may have inspired Sessions’, were pronounced in the “Herbert Spencer Lecture”, delivered at Oxford in June 10th **1933** (published in *Philosophy of Science*, **1934** Vol. 1, No. 2, pp. 163-169).
23. Louis Zukofsky. *Poetry Magazine*, **1950**. Zukofsky also used Einstein’s (Sessons’) aphorism in his poem named “A”, section A-12: “Had he asked me to say Kadish / I believe I would have said it for him. / How fathom his will / Who had taught himself to be simple. / Everything should be as simple as it can be, / Says Einstein, / But not simpler” (Details from Garson O’Toole, Everything Should Be Made as Simple as Possible, But Not Simpler (*Quote Investigator*, May **2011**. URL).

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