Chapter 10.

Modelling versus Realization: Rival Philosophies of Computational Theory in Systems Biology

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Abstract

Systems biology faces a choice between reductionist and holist approaches, but practising systems biologists are often unaware of what the implications of each path will be. Modern neo-holism, as manifested in Robert Rosen's Relational Biology, concludes that the functions of complex systems are irreducible to the functions of their component parts, and also implies that the current foundations of computational theory are inadequate for systems biology. By contrast, modern neo-reductionism replaces classical conceptions of inter-theory reduction with the looser concept of supervenience, in the process reassuring us that we can make progress in systems biology with computational theory as we know it today. However, the price to pay for this is a shift away from modelling to realizational strategies. Either way, the entire field of systems biology may have to change course if it is to accomplish its goals.

FROM BIOCHEMISTRY THROUGH MOLECULAR BIOLOGY TO SYSTEMS BIOLOGY

One rainy spring morning in Glasgow in about 1984, I sat in a lecture theatre and heard my physiology professor tell the class that the problem with biochemists was that they just wanted to put everything in a bucket, blend it to a puree, and then talk about the properties of the resulting sludge. The class laughed, of course, not realising that this was physiology's oldest joke, possibly around 100 years old, and that our professor had been using it for almost as long. About eight years later, by which time I had become a lab research assistant at the University of Warwick, I heard just one of these "bucket biochemists" complain, with somewhat less humorous intent, that it was virtually impossible by then to obtain a grant for doing biochemistry unless some gene-centred molecular biology angle could be found on the project. A quarter century later still, it is now the molecular biologists who are finding it difficult to obtain research funding for single-gene-focussed projects in an age of increasingly "big data" systems biology. In any era, it seems as if a young scientist is unlikely to retire (assuming she survives in the profession to retirement) in the same field in which she began.

Works on systems biology often begin by making some startling claims for its novelty or importance. For instance, one of the commonest generalizations concerning systems biology is that, in the words of the welcome message to the 11th International Systems Biology Conference in Edinburgh in October 2010, it "takes a *holistic* view on biology and aims at elucidating design principles of whole biological systems rather than of individual biomolecules or single events" (italics added). Even more radically, it is sometimes stated that systems biology is a *paradigm shift*, nothing short of a fundamentally new way of doing biological sciences[1].

Certainly, systems biology makes use of a whole raft of new technologies that matured around the millennium and in the decade that followed. Deep sequencing and other high throughput analysis tools spawned a gaggle of data cataloguing capabilities with names all ending in "omics". Genomics, metagenomics, transcriptomics, proteomics, lipidomics and metabolomics, to name just a few, produced data on a scale previously unimaginable in biology. Crucially, this expansion of the traditional molecular biology laboratory into a data generating factory coincided with an explosion in the power and availability of computers. Indeed, omics disciplines would scarcely be possible without some way of handling their often terabyte-sized outputs. With the power to describe whole systems of biomolecules, whole cells, and even whole organisms, at molecular levels of detail, systems biology became an inevitability.

"ORDER AND PROGRESS": AUGUSTE COMTE'S POSITIVISM AND ITS LEGACY

Any discipline so intent on wholes might facetiously be described as "wholist", but does that necessarily imply a genuine *holism*? Although the disruptive technologies of the omics revolution have transformed the practice of biology research, shedding the reductionist legacy of mid-to-late-20th century molecular biology has been difficult[2]. This is scarcely surprising once one considers exactly how deep its roots are, extending back to the *positivism* of the 19th century French visionary Auguste Comte (1798-1857), which by his death had even acquired rituals and a priesthood, the *Religion de l'Humanité*[3]. This cult aspect of positivism was briefly quite successful, especially in Brazil, and its motto, "Order and Progress", can still be found on the Brazilian flag. Positivism also acquired political ambitions, in which the bizarre idea of European unity was stressed. Comte's proposed "Great Western Republic" would include France, the British Isles, Germany, the Low Countries, the Iberian peninsular and Italy and would have its capital, naturally, in Paris. If that were not bad enough, Greece and Poland would also be invited to join in a second phase of "accessory members"[4].

Auguste Comte had a rather unhappy personal life, afflicted with mental illness, unrequited love and at least one unsuccessful suicide attempt. In the words of one unsympathetic modern critic: "Comte was a strange individual. Indeed it would not be stretching language to say he was mad"[5, p.44]. Despite his prickly personality and long-winded prose, or perhaps even because of it, Comte possessed a remarkable ability to influence even those who disliked him personally or had philosophical reservations about the more over-arching aspects of his creed, and positivist ideas spread far beyond his narrow circle of devotees within the *Religion de l'Humanité*[3]. Even in the 21st century it is common to hear scientists, or even the general public, use positivist language, though the vast majority of them have never heard of Comte.

Comte saw all of human thought as classifiable into three modes: Theological, Metaphysical and Positive, and divided up human history on that basis. The thing that characterized science, setting it apart from the religion of the Theologians and the creative philosophizing of the Metaphysicians, was that it was based solely on tangible, demonstrable, common-sense evidence, in other words on what could be *positively* known – science was Positive. However, different sciences were at different stages of the Metaphysical-Positive transition (Fig. 1), and this ordering was the basis for Comte's "law of filiation of the sciences": "Thus we have before us Five fundamental Sciences in successive dependence, – Astronomy, Physics, Chemistry, Physiology, and finally Social Physics"[6, p.28] (irregular capitalization and punctuation in original), and "every science is [rooted] in the one which precedes it". Each successive science had sprung forward from the previous member of the chain, with its transition into Positivity building on the established successes of its predecessor disciplines. Comte considered physics and chemistry as having achieved, by the mid-19th century, the full Positive stage of development, and biology as being nearly there. Sociology was considered to be still wallowing in the Metaphysical morass, and Comte saw it as his own specific scientific task to bring it forward into the Positive phase.

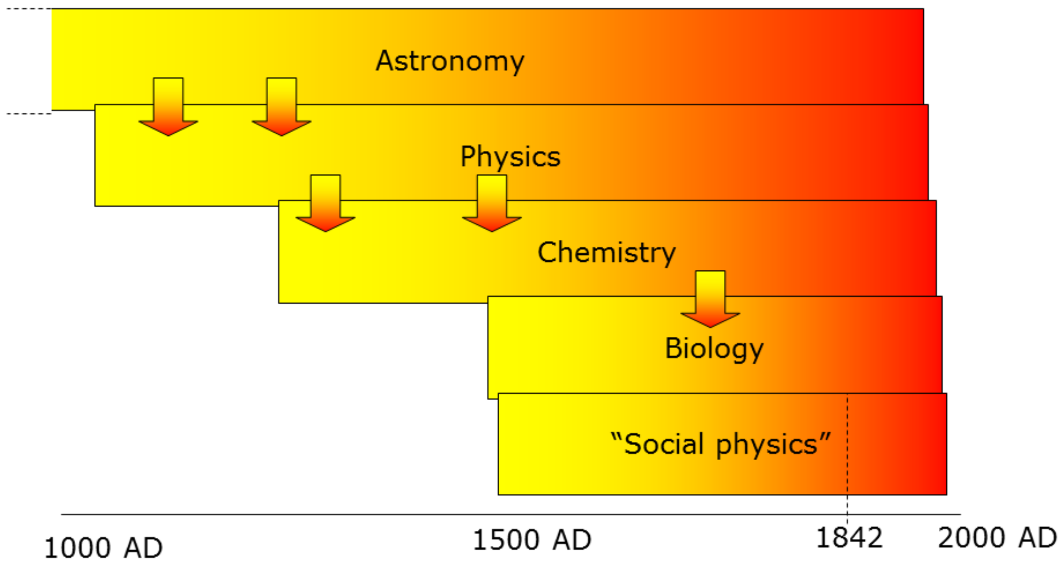

Figure 1: Comte's Law of Filiation of the Sciences

Legend: Each discipline passes progressively through Theological and Metaphysical phases (yellow) before entering the Positive phase (red), at which point it becomes a true science. Comte was vague concerning the exact date of these transitions. Only 1842, the date of the completion of his major work, Cours de philosophie positive, is firmly given as the year in which "social physics" achieves the Positive phase. The transitions are aided by input from the previous discipline in the filial chain.

Comte's eclectic system has often been portrayed by historians as a response to the chaos of the French Revolution and the reactionary regimes that followed it, attempting to restore order and progress, as its motto declared, to a ravaged and disillusioned France. In the following century, this spirit was reawakened in the ruins of the equally devastated Hapsburg Empire in central Europe and, amid the cosmopolitan *Kaffeehaus* culture of Vienna, positivism became *logical positivism*.

THE VIENNA CIRCLE AND CLASSICAL REDUCTIONISM

The Vienna Circle[7] was formally instituted as the Ernst Mach Society on 23rd November 1928. It managed to clean up Comte's positivism, stripping away the religious and political accretions and creating a version of refined purity, and if ever there was a philosophy suited to those of a purist inclination, it is the *logical positivism* of the Vienna Circle. Moritz Schlick (1882-1936) and his Vienna Circle colleagues recast Comte's concept of the unique value of *that which could be positively known*, as a means for creating a boundary criterion between the meaningful and the meaningless. In the new logical positivism, theological and metaphysical statements were not wrong, but merely senseless. The most charitable thing that could be said for them was that they perhaps had some subjective artistic validity, comparable with the meaning to be found in music or literature. The physicist Ernst Mach (1838-1916), after whom they took their official name, had pioneered an extreme form of this neo-positivist attitude in his rejection of the reality of common physical concepts such as atoms, relegating them to the dustbin of metaphysical constructs[8]. In the words of Vienna Circle member Philipp Frank (1884-1966): "physics is nothing but a collection of statements about the connections among sense perceptions, and theories are nothing but economical means of expression for summarizing these conditions"[9, p.220].

Physics, freed from all metaphysical trappings, was the natural foundation stone upon which the rest of science could be constructed. The resulting hierarchy therefore repeated Comte's law of filiation, in essentially the same order but rotating Comte's linear succession into a stacked structure (Fig. 2). Chemistry, depending as it does on the atomic laws of the physicist, is the next level in the structure, sitting on top of physics. This is followed by biology, or possibly biochemistry, then cell biology, physiology and finally things like psychology and the social sciences. This *layered model* is so engrained into our current view of science that it is a little odd to imagine that it is barely 90 years old. The logical positivists' achievement was to begin with a difficult philosophical concept wrung from complex wrangling about meaning and evidence, and turn it into a framework for the explanation of one scientific discipline in terms of another: *inter-theoretic reduction*. By means of the process of inter-theoretic reduction "*the whole of Science becomes Physics* ... every scientific statement can be interpreted, in principle, as a physical statement"[10, pp.98-99] (capitals and italics in original), or as Thomas Nagel has expressed it more recently: "Reductionism is the idea … that physics is the theory of everything"[11, p.3]. Scientific disciplines are mere flags of convenience within a single physics-based *Unified Science*[8].

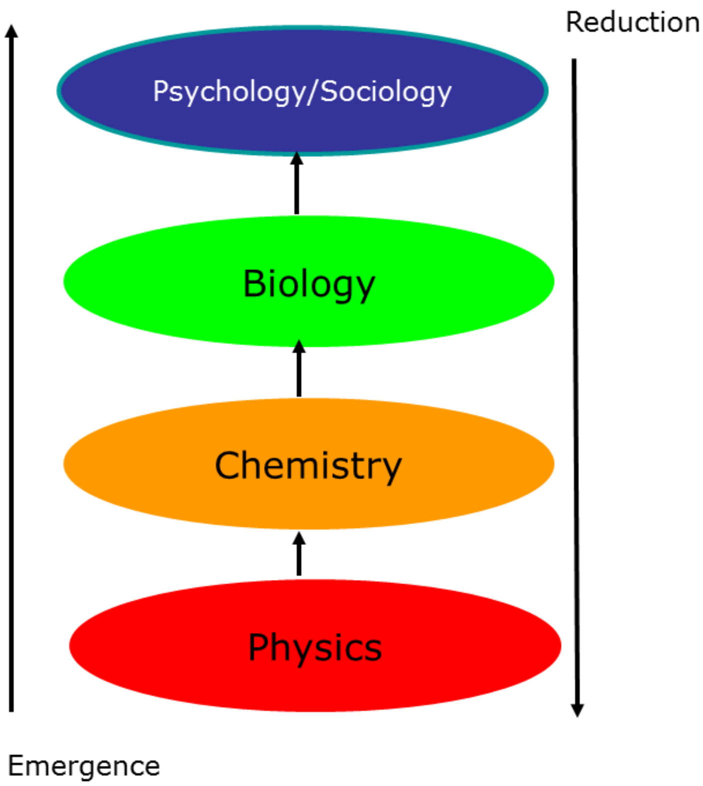

Figure 2: The layered mode of the reductionist hierarchy.

Legend: Statements in each discipline are re-expressible in terms of, or reducible to, statements in the discipline immediately below it.

The Vienna Circle never quite achieved its aims in full. Its leader, Moritz Schlick, was murdered by a student in 1936 and the *Anschlus*s of Austria in 1938 sent many of its main members into exile. However, just in time, the ideas of the Vienna Circle had entered the English-speaking world through the publication of A.J. Ayer's (1910-1989) *Language, Truth and Logic* in 1936, probably the nearest thing to a bestseller that philosophy has ever seen[12]. It is therefore unsurprising that in molecular biology, Francis Crick's (1916-2004) reductionism seems to be sung straight from the logical positivist hymn sheet: "The ultimate aim of the modern movement in biology is in fact to explain *all* biology in terms of physics and chemistry" (italics in original)[13, p.10].

Reductionism has achieved possibly its most extreme form in *singularitarianism*. Originating in the work of Raymond Kurzweil[14] and having some affinities with Frank Tipler's "omega point"[15,16], the singularity is a future date at which Moore's Law[17] on the exponential growth of processing power has produced computers of such power that everything can be computed and we will therefore know everything. Kurzweil believes this point will be reached as soon as 2045. Even sooner than that, he claims, computers will be capable of modelling our own cognitive functions, and therefore consciousness, so accurately that we could upload copies of ourselves *in silico* and live immortally in cyberspace. An exact copy of our brain structure, down to the atomic level of every neuron would, the singularitarians believe, exhibit the same thoughts as the real thing, the same emotions, tastes and memories. Its bodily substance would be metal, plastic and silicon chips rather than proteins, lipids and carbohydrates, but those copies would nevertheless be *us* and our disembodied selves would feel our existence as being in the machine – or perhaps spread over several machines in a computing cloud.

Kurzweil's thesis has enormous emotional appeal, promising that all the world's problems will be solved, even our own individual mortalities indefinitely postponed, as long as the inexorable march of Moore's Law continues. But it also requires that reductionism be correct. All biology has to be physics, and all problems have to be computational problems, for the singularitarian vision to be achievable. The world must be merely a sum of atoms, and our understanding of the world no more than a sum of bytes and bits, or else it will fail. Even if this were true, however, there is another problem with the singularitarian project.

Even relatively trivial brute force calculations on computers can require exponentially increasing processing times. Bremerman's Limit[18], the theoretical absolute maximum processing speed, at which every atom of the computer is vapourised as its mass is entirely converted into energy, is insufficient to generate answers to some basic combinatorial problems[19]. Reductionism, and especially its extreme singularitarian variant, breaks down on its epistemology. Even assuming we can solve every scientific problem just by computing it, we would need to wait forever to do so.

FROM CLASSICAL HOLISM TO NEO-HOLISM

Around the time that the Ernst Mach Society was organizing its first formal meetings in Vienna, Jan Smuts (1870-1950) was taking a break after his first stint as South African Prime Minister, to write *Holism and Evolution*[20], coining the word holism from the Greek *ὅλος* (a whole). Like Comte, Smuts had great ambitions for his philosophy: "All the problems of the universe, not only those of matter and life, but also and especially those of mind and personality, which determine human nature and destiny, can in the last resort only be resolved – in so far as they are humanly soluble – by reference to the fundamental concept of Holism". For Smuts, the *vera causa*, an innate tendency for stable wholes to form from parts, occurring at all levels from the atomic through the biological to the psychological, steered the entire universe. The original conception of holism was more metaphysical than scientific, and Smuts did not acquire the same cult following as Comte had done a century previously. Nevertheless, the term holism moved into the world of science and began to be used more generally by opponents of reductionism.

One of the most intriguing critiques of reductionism in biology was supplied by Walter Elsasser (1904-1991), a quantum and geophysicist who, while working in Paris in the 1930s, had been inspired to think about biology by the physiologist Théophile Kahn (1896-1986). Elsasser was by no means the only holist biologist of the post-war era - the names of Paul Weiss (1898-1989) and Conrad Waddington (1905-1975) are often mentioned in this context[21,22] – but Elsasser's holistic vision was more fundamental than any of his contemporaries. Elsasser's biology came to be characterized by a wholesale rejection of the reductionist model of the Vienna Circle as implemented in molecular biology. What makes Elsasser's holism a *neo*-holism rather than a successor to that of Smuts, was that he insisted that it be based on the most fundamental of physical theories, quantum mechanics, and that he rather curiously still described himself as a positivist[23, p.33].

Elsasser only began to publish in biology in the late 1950s, by which time he had decamped to the USA, after some two decades of digesting Theophile Kahn's ideas. Elaboration of his critique of reductionism was to occupy him for most of the 1960s and into the early 1970s. Elsasser does not merely attack the mainstream biological reductionism of the kind popularised by Francis Crick but, rather more radically, attacks the whole notion of molecular determinism in biology, using a difficult argument he named *the Principle of Finite Classes*. Elaboration of this argument would require a chapter in its own right, and has been done elsewhere[24], but in essence it argues that wave function collapse, the phenomenon that produces the deterministic world of observable phenomena from the indeterminate world of quantum mechanics, only applies to simple molecules, such as those studied in the physics and chemistry laboratory. The complex molecules of biology – things like proteins, carbohydrates, lipids and nucleic acids – do not achieve wave function collapse, and therefore are always liable to behave in an indeterminate manner[25, p.169. 26, p.286]. For Elsasser, much of biology was in fact "acausal"[27]. Figure 3 summarises the argument in graphical form.

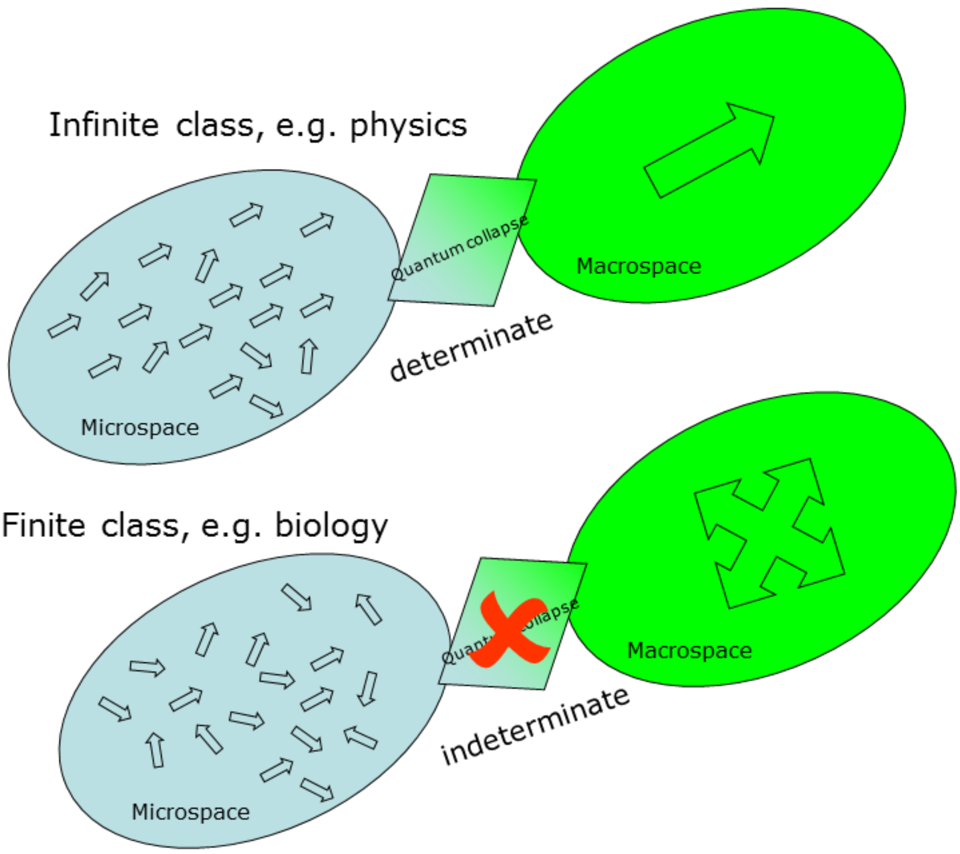

Figure 3: Elsasser's Principle of Finite Classes argument.

Legend: In a simple physical system - an infinite class - there are sufficiently few quantum states (small arrows) that they can be averaged (large arrow). In a complex biological system - a finite class - there are so many that no average may be obtained (4-headed "arrow"). There is therefore no causal connection between the microscopic and macroscopic worlds for biological objects.

Elsasser's argument against determinism in biology stimulated some inconclusive critiques in the 1960s, and then faded into obscurity, having been neither conclusively disproved nor having found many adherents. It was, perhaps, a casualty of its own difficulty – few can feel equally comfortable in both the fields of quantum mechanics and biology – and Elsasser's own apparent reluctance to engage directly with his critics. Indeed, by 1969, when Elsasser declared that he was "therefore addressing the present scheme mainly to younger people whose philosophy may not yet have approached a point of condensation"[27,p.503], one can almost hear the electric guitars wailing in the background.

Nevertheless, despite Elsasser's inability, or reluctance, to force his theory into the mainstream, his influence on modern neo-holism remains profound, because even if his anti-deterministic argument was flawed, it produced, as a by-product, an alternative to the layered model of Vienna Circle reductionism. For Elsasser, biology was the science of the complex, and therefore is a superset of all the other sciences which deal with subject matter of greater regularity than the messy stuff of biology. Chemistry and physics are subsets of "biology" (as Elsasser conceived it), activities that commence when we start to refine our area of study down to the molecular and atomic level – they are simply the areas of "biology" where determinism and causality apply.

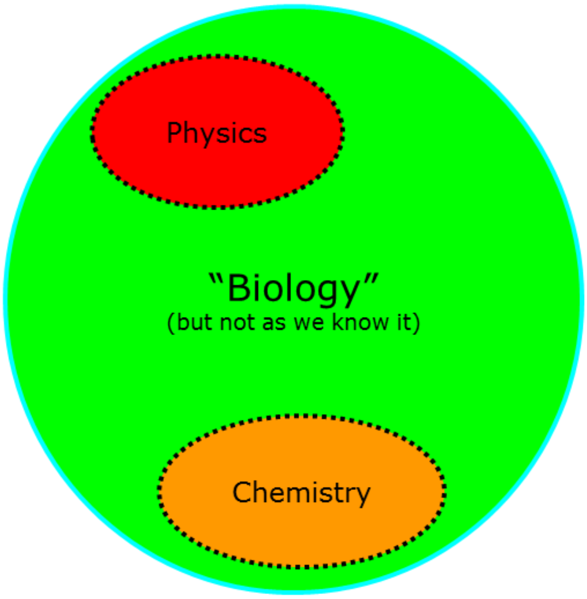

Figure 4: Walter Elsasser's alternative to the layered model (see Figure 2).

Legend: Rather than biology emerging from chemistry or physics, the latter are sub-fields of a new science of complex systems. Physics and chemistry are not more fundamental than biology, but are actually rather specialist areas of biology which deal with infinite classes, i.e. with simple, homogeneous subject matter. See also Fig. 3.

[M,R] – THE IRREDUCIBLE PARADIGM OF RELATIONAL BIOLOGY

Elsasser's influence channels into modern holism through Robert Rosen (1934-1998), whose mathematical work, which he collectively termed *relational biology*, has achieved the status of a Mrs Rochester in systems biology's attic. The centrepiece of Rosen's critique of reductionism is the *[M,R] system* – standing for

Metabolism/Repair. [M,R] is a small self-referential network of four components, three of which act functionally within the network (Fig. 5). It may be interpreted as a biochemical pathway with four moieties and three steps, in which the each of the final three moieties are also catalysts for a unique step. This toy system was the subject of a mathematical demonstration that it was not possible to predict the properties of its entirety through an analysis of the properties of its individual components[28,29]. [M,R] is therefore not reducible to its component parts and can only be understood as a whole. Rosen took pains to give [M,R] as few parts and functions as possible – it is the self-referential nature of its structure, the way that three of the four components are necessary for the production of three other components of the same set of four, that causes the breakdown in the reductionist hierarchy. Irreducible complexity does not require a big and complicated system, but can be present in tiny toy systems like [M,R]. Indeed, Rosen defines complex system as those which cannot be reduced.

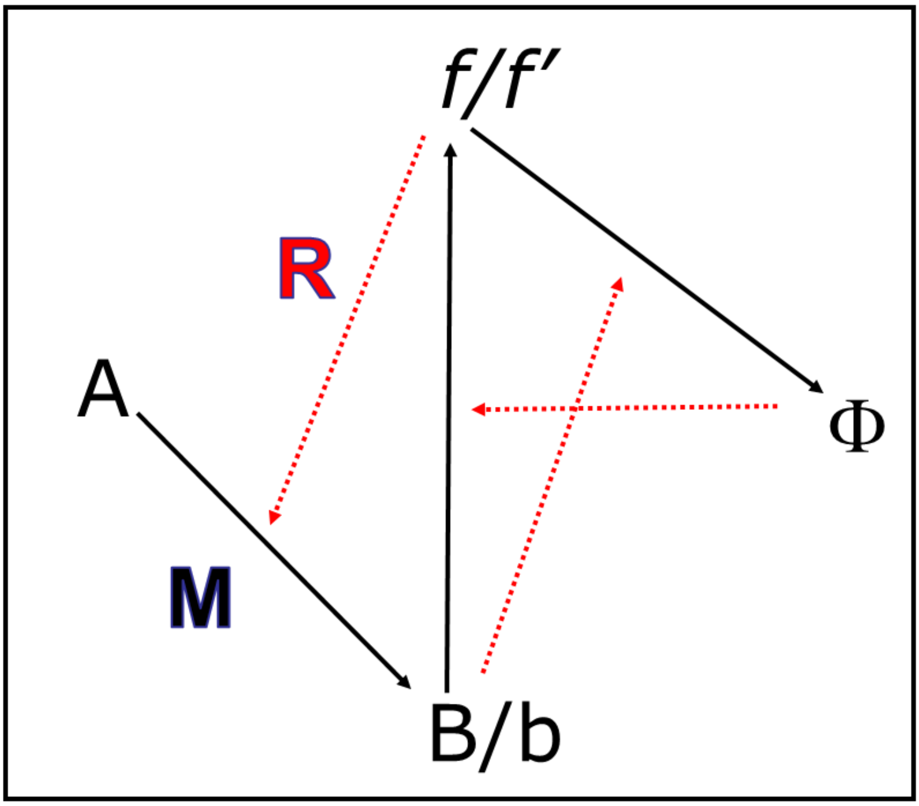

Figure 5: Rosen's allegedly irreducible M-R system

Legend: Full arrows – the M reactions - are chemical transformations: A is converted to B, B to f and f to Φ. Red dotted arrows are the R catalytic steps: f′, the catalytic form of f, catalyses the production of B from A, b, the catalytic form of B, catalyses the production of Φ from f and so on.

With Rosen, we are no longer in the business of the epistemological anti-reductionism which defeats the singularitarian argument. Rosen's antireductionism was *explanatory*. Irreducibility is a property independent of the size of the thing that cannot be reduced. [M,R], he claims, simply cannot be explained using a reductionist approach. Epistemological anti-reductionism is a *holism in practice*, an observation that certain components of the reductionist programme are infeasible. Explanatory anti-reductionism is a *holism in principle*.

Rosen draws comparisons with Elsasser's nested model – as a complex system [M,R] as a whole is situated in the domain of "biology" or the science of complexity whatever name one gives to it. Break [M,R] down into its component individual steps and these are then in the domains of "physics" or "chemistry". However, what we can say mathematically about the behaviour of the component parts, cannot be subjected to any additive process that will allow us a complete mathematical description of the whole. Thus what we can say in the molecular biology laboratory about single proteins or genes does not tell us, *contra* Crick, all that we would wish to know about the whole organism from which they are isolated, even if we have full knowledge of all of the components and how they function in isolation.

Rosen also ventured that [M,R] could have a more general interpretation. As well as representing a single self-referential network, the component parts could be taken to represent sets of reactions in living things. For instance, the first step could represent not just one, but all, metabolic reactions, the second and third steps sets of other reactions necessary to ensure that metabolism can continue – hence the Metabolism/Repair name. Pursuing this set-oriented interpretation of [M,R], Aloisius Louie has described its components in terms of formal set algebra[30]. Louie's central result from this analysis is the identification the presence of an impredicative set within [M,R], meaning a set that is member of itself. Impredicative sets are non-computable on a Turing machine, which remains the basic conceptual architecture of all computers. By implication, no complex system and no biological system can therefore be fully functionally modelled *in silico*.

Biology, if Rosen and Louie are correct, is therefore not only non-reducible in the laboratory but also cannot be modelled on a computer. The seriousness of this conclusion for systems biology as it is currently practiced, has generated a stunned silence punctuated by occasional attempts at refutation. However, the various attempted disproofs[31,32] of Louie and Rosen's work have also proved technically controversial, and the resulting lack of clarity has not served the debate well[33]. Rosen's relational biology has achieved a higher profile than Elsasser's work, insofar as systems biologists are often aware of its existence[34,35], but its technical difficulty for those without the required background has left the adjudication on its validity to a small number of jurors who cannot reach a unanimous verdict.

NEO-REDUCTIONISM: SOFTWARE LAWS, PHYSICS AND STAMP-COLLECTING

Anyone who has been an undergraduate in genetics or molecular biology since the 1970s will be familiar with the workhorse examination question, "What is a gene?" Generations of students are thereby invited to do a little inter-theoretic reduction in the spirit of the Vienna Circle, expressing the higher-level abstract explanations of genetics in terms of the nuts and bolts of molecular biology. Prior to its arrival in the examinations hall, this topic had formed the basis of Kenneth Schaffner and David Hull's (1935-2010) attempts, in the late 1960s and early 1970s, to apply Vienna Circle reductionism to biology[36,37]. It soon became obvious to them that this was not going to be easy.

There is, for instance, no term in molecular biology that can capture everything that is implied by the term *gene* in classical genetics. Molecular biologists know that genes are made of DNA, but each gene is unique in terms of how that DNA is constituted into that particular gene. To reduce processes, such as segregation or gene silencing, the difficulties are even greater. For the process of meiosis - the independent assortment of genes during gamete formation – the abstract genetic explanation is both far easier and far more illuminating than any attempt to be more specific about molecules. Indeed, meiosis can be represented simply in terms of a set of rules for moving objects. Even if those objects are not actual chromosomes but simulations, e.g. beanbags or graphic objects in a computer simulation, the same rules would apply, and that DNA-free explanation would be a fully adequate one[38]. Even if there were no actual biological objects, the theory would still make *logical* sense.

In a systems biology context, one might derive novel rules concerning a set of properties of a gene-regulatory or metabolic network. These rules might turn out to have logical validity in other contexts and different kinds of network, perhaps even in non-biological networks. Of course in the real biological world, Mendelian and Darwinian and metabolic systems phenomena are instantiated in DNA, cells and organisms, but the laws we use to describe their behaviour are often independent of their substrate, what Paul Davies has called *software laws* rather than *hardware laws*[39]. Reductionism does not so much fail here as appear to be an unnecessary complication. Schaffner therefore replaced classic inter-theoretic reduction with a more pragmatic *biological principle of reduction*[36], a commitment to try to reduce wherever possible, to create as many reductive explanations as possible, even in the absence of complete reduction.

Although this softened Crick's vision of explaining *all* of biology in terms of physics and chemistry, it still placed biology within the layered model of the Vienna Circle. The next stage in the evolution of reductionism, taken by Alexander Rosenberg, was to replace that model[40,41]. Rosenberg proposes in its place a two-layer model (Fig. 6) building on the work[42] of J.J.C. Smart (1920-2012). The lower layer is physics and the upper layer is termed "engineering". This is not to be interpreted literally, but to serve as a shorthand for all sciences other than physics. An "engineering" question is one that does not require an answer that includes a full physical explanation, but one for which chemistry, biology, psychology etc., will suffice. Ernest Rutherford (1871-1937) previously made a similar analogy, but replaced "engineering" with "stamp collecting".

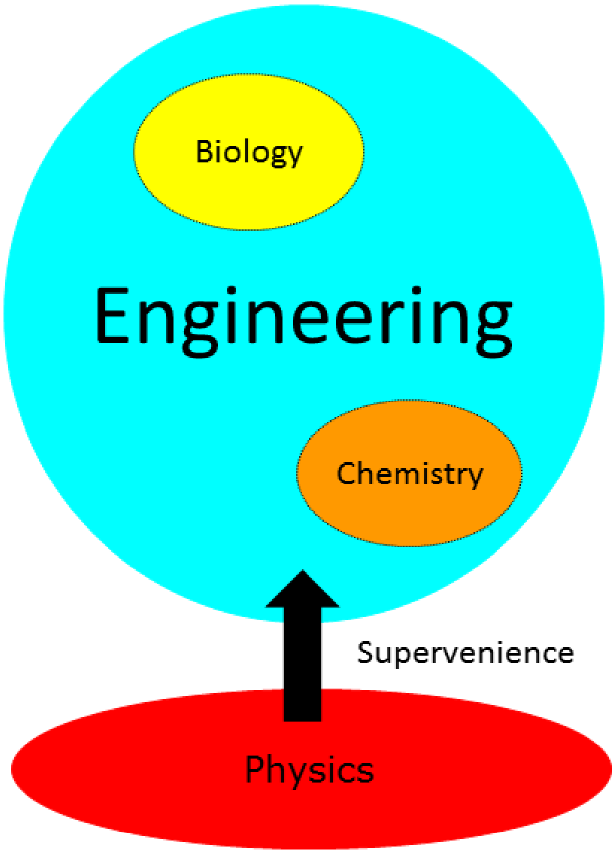

Figure 6: Neo-reductionism's simplification of the layered model

Legend: Neo-reductionism's flat model, an alternative hierarchy to Fig. 1, proposed by J.J.C. Smart but previously implied by Ernest Rutherford: "either physics or stamp collecting".

Neo-reductionism proposes that physics provides the description of the molecular order of a system – its *micro-state* - whereas "engineering" explanations refer to supra-molecular configurations of that system – its *macro-state*. All macro-states are *supervenient* on underlying micro-states. Supervenience implies that a given micro-state will always result in the same macro-state. By contrast, a macro-state may have more than one micro-state that will give rise to it (Fig. 7). Micro-states therefore determine macro-states, but macro-states are not reducible to micro-states, or at least not reducible to unique micro-states. Davies' software laws are therefore laws of the macro-state and not reducible to those of the micro-state. The software laws, however, cannot allow behaviour which breaks the laws of the micro-state.

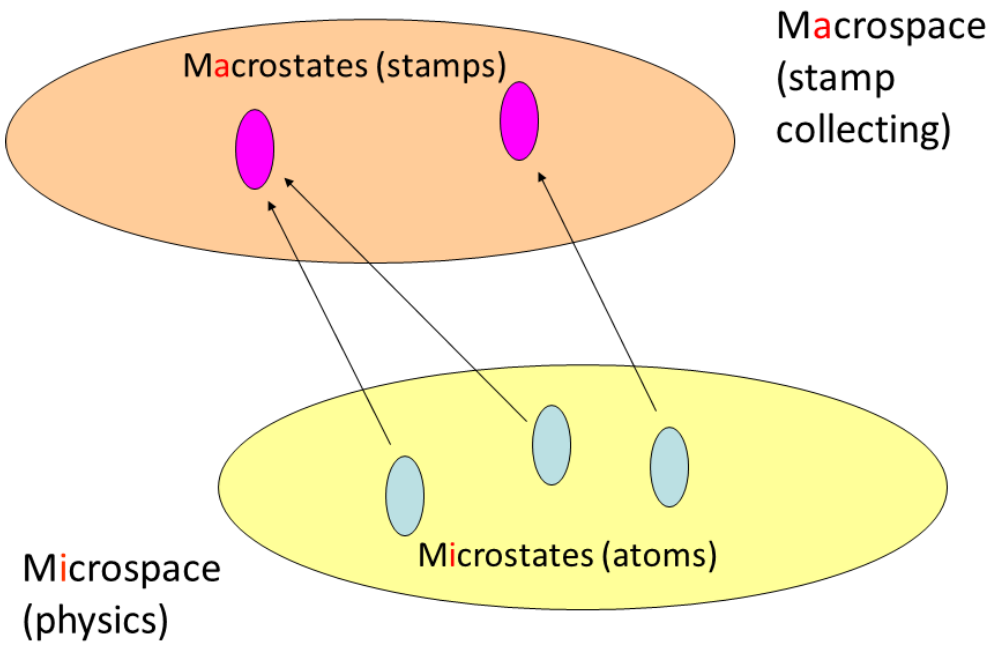

Figure 7: The non-unique dependence of macrostates on microstates

Legend: Classical reductionism has always struggled to determine how macrospace configurations are determined by their underlying microspaces, in other words how to model a macrospace. Neo-reductionism implies that it is more important to understand how microspace variation affects that of macrospace, in other words how macrospace is realized.

Moving outwards beyond individual systems, neo-reductionism sees the universe as consisting of a *micro-space*, its objective atomic/quantum physical reality, and a *macro-space*, which is the configuration of larger order entities studied by all the other sciences, and which is supervenient on the micro-space. Interestingly, Elsasser had already outlined a similar concept as part of his anti-reductionist argument. His concept of *variostability* refers to the tendency of a macro-state of a system to remain coherent in the presence of micro-state variation[43]. Although Elsasser argued that this had not merely anti-reductionist but even anti-determinist implications, his conclusions are dependent on the assumption that reductionism requires a unique micro-state to macro-state binary mapping. Neo-reductionism of the kind advanced by Rosenberg, however, allows for a one-to-many mapping between macro-state and micro-states. This is compatible with variostability.

Another parallel with the work of Elsasser is his concept of *biotonic laws*, which he hypothesized as laws pertaining solely to biological systems, which were not reducible to underlying physical laws[23]. Davies' software laws concept can be made to fit partially with the biotonic laws concept, just as variostability can be made partially congruent with supervenience. Neo-holism and neo-reductionism thus begin to find common ground. Lest we become too enthused over the prospects of synthesis, however, it should be borne in mind that Elsasser drew his conclusions from his controversial quantum mechanical theory of the Principle of Finite Classes, which implied total indeterminacy for biological systems with respect to their physical constitution. Neo-reductionism's concept of supervenience requires a causal relation pointing upwards from micro-state to macro-state and therefore is deterministic in a way that Elsasser would have rejected.

MODELLING VERSUS REALIZATION

Inter-theoretic reduction requires explanations of how one theory can be expressed in terms of a lower level theory in the layered hierarchy. So the macro-space configurations of one discipline must be shown to be determined by the underlying micro-spaces of the theory below. In other words, reductionism requires us to be able to model macro-spaces in terms of a micro-space. Robert Rosen had stern words for reductionists on the subject of modelling, making a distinction between a true model and a mere simulation. Imagine an attempt to build a piece of software to represent a biochemical network. No matter how accurate the representation of the entities of the system may be, they are only in a model *sensu strictu* if the rules that connect them and govern their behaviour are also accurate representations of the laws of the natural world. Otherwise the software is a simulation. The *entailment structure* – the framework of rules that govern how bits of the system interact - of a true model faithfully represents the corresponding entailments of the thing being modelled[28]. Failure to do so will generate a *black box*, a simulation which may be very good at predicting the output given a set of inputs, but which does not represent any true understanding of the system. Simulations are merely *ad hoc* black box predictors of the phenomenological behaviour of whatever they simulate.

This is indeed a tough requirement to satisfy in any field. Simulation, rather than modelling in Rosen's sense, is the norm in most cases. Rosen might be implying that when reductionists often think they have achieved inter-theoretic reduction, the reality may be considerably less conclusive. However, Schaffner's biological principle of reduction acknowledges that this is often the case, at least in biology if not other disciplines, and accurate, if black box, simulation may be a good preparation for the deduction of a true model of the actual entailment structures of the system concerned.

Even assuming that both aspects of an inter-theoretic reduction were completed to Rosen's satisfaction, with adequate re-expression of both entities and entailment structures, the completed model of reduction is still vulnerable to change in either, or both, of the reduced and reducing theories. If some aspect of biology is regarded as reduced to physics or at least chemistry, the assumption is made that the underlying chemistry is correct. Should the relevant parts of chemistry be disproved, the reductional chain will be broken, and the biology will require to be re-reduced to the new physics or chemistry. Previous satisfactory reductions may suddenly become invalid in this way, and reduction must always therefore be considered to be provisional. However, just as a previous reductive chain may be broken by changes in the underlying theory, so may reduction become possible where before it was not[44,45]. Anti-reductionist declarations must always be provisional too. Ernest Nagel (1901-1985) points out[46] that chemistry is only reducible to post-1925 physics, and thermodynamics is only reducible to post-1866 statistical mechanics. In both cases it was advances in the lower theory (physics) that enabled the reduction, not any new insight into chemistry or any improvement in reductionist method. The emerging consensus from the mid-1920s onwards that chemistry was finally reducible to physics, was one of the factors that spurred the enthusiasm of the Vienna Circle to apply reductionism everywhere.

Neo-reductionism avoids Rosen's strictures regarding modelling and simulation, not by merely adopting the biological principle of reduction and/or conceding that reductions can remain provisional, but by replacing modelling with *realization*. Neo-reductionism's concept of a non-unique macro-space to micro-space supervenience relationship implies that it is more important to understand how micro-space variation affects that of macro-space than to model the macro-space on the micro-space. In other words, the question becomes how a macro-space is *realized* upwards from its underlying micro-space, rather than how to reduce/model downwards from macro-space to micro-space.

This notion has some considerable implications for scientific method. The inversion required by neo-reductionism would seem to require a kind of *Gestalt*-switch in the way that our brains do science. A plan for what science would look like once we have managed to perform that change in perspective, is not obvious. Nevertheless, some intriguing hints are visible in the work of Stephen Wolfram on *cellular automata*. An automaton is a software entity that performs certain behaviours under a simple set of rules[47]. These may be very clear and straightforward – cellular automata have none of the knotted puzzle nature of [M,R]. However, they may exhibit remarkably rich patterns of activity. Conway's Game of Life is the most famous example of a cellular automaton, where different starting configurations result in radically different shifting outcomes. Crucially, we know that cellular automata are deterministic – we programmers have specified their rules and they always abide by them. We can therefore say that we fully understand the micro-space of the automaton. Wolfram produces a vast variety of such automata showing how complexity can arise from simple starting conditions and conversely how order can emerge from chaotic conditions. According to Wolfram, there are many instances of automaton-like behaviour across a wide range of systems from physics to psychology. Modelling a system is therefore less important than the question of whether the system behaves similarly to a known automaton, i.e. realization.

For neo-reductionism, systems biology is labouring under the weight of the modelling problem, whereas it ought to be recasting itself in terms of the realization problem. The modelling problem founders both on the sheer scale of the data – it cannot counter epistemological anti-reductionist arguments - and also potentially on the hidden problems of self-referential systems – if Rosen is correct, it cannot counter explanatory anti-reductionist arguments either. Even leaving Rosen aside, it is evident that the modelling problem is the problem of data increasing faster than the conclusions we can draw from it – a problem of where to end. The realization problem, by contrast, is one of where to start.

THE SCIENTIFIC UNDERSTANDING OF SCIENCE

The reductionism-holism debate in systems biology sits within a wider context that goes beyond the bounds of daily activity in the research lab. This anthology is on the subject of the public understanding of biology. The public understanding of science in general has become a speciality in its own right with endowed chairs in prestigious universities and "public engagement" high on the priority list of league table-driven British universities. However, this phrase implies that a failure to understand science is largely something "out there" in the public. If only scientists can learn to communicate better, the public will understand better.

Valuable as such evangelical work is – and after all, it is the public who are paying the major portion of the salaries of the scientists, so they are entitled to know where their money is going – it misses a problem rather closer to home: scientists often do not have a very firm conception of their own working methodology, and even less of a comprehension of the methodology of other scientific disciplines. If anybody is looking for another chair to endow, a Professorship in the Scientific Understanding of Science would be both a provocative and valuable contribution.

The origins of this problem lie in the fact that most undergraduate science courses do not teach the philosophy of science. If they do, all that will be included will be an exhortation to perform experiments with careful controls that test hypotheses and seek to falsify rather than confirm them – in other words, most biologists, if they think about scientific method at all, are Popperians[48]. Part of this is due to the advocacy of Karl Popper's (1902-1994) legacy by Richard Dawkins and his predecessor as the UK's favourite popular writer on biology, Peter Medawar (1915-1987), whose best-selling *Advice to a Young Scientist* laid down the Popperian law to many aspiring young molecular biologists of the 1980s and beyond[49].

However, two things are rarely if ever mentioned when Popper is discussed by biologists: his anti-reductionism, which became stronger in his later years[50], and the apparent anti-Darwinism of his late period (although his exact stance on this is still a matter of controversy). Biologists in the 21st century thus usually hold an incompatible mixture of philosophical views on their own subject – a classical reductionism channelled from the Vienna Circle via A.J. Ayer to Francis Crick, rubbing shoulders with the post-Vienna Circle thought of Popper. Often these are held at such an unconscious level that biologists will deny having any philosophical thoughts at all, believing all such things to be irrelevant to science.

Scientists are therefore in a poor position to defend their discipline against those who would cast doubt on its entire existence. To take a few common examples, sociologists of the “science studies” or “science, technology and society (STS)” persuasions seek to represent science as a set of rituals performed by a secular priesthood. Neo-Marxists see it as a bourgeois activity devoted to replicating the existing political structure, and have a particular antipathy to biology as an obstacle to their notions of the infinite malleability of the human social order. Social constructionists wish to deny any discipline that believes an objective view of reality can be achieved. These are caricatures, of course, necessitated by brevity, but these threats to science in its current form are real. In order to defend ourselves, scientists need a clearer idea of who we are, what we are doing and why, that goes deeper than the currently fashionable notions of “impact” and “engagement”. Part of the formation of that clearer idea must come from a deeper understanding of our philosophical underpinnings. Systems biology has an opportunity to lead the way in this endeavour, given that the field sits on the cusp of a profound philosophical decision about its future orientation. Systems biology may make scientists become natural philosophers once more.

References

1. Marcum, JA (2008). Does systems biology represent a Kuhnian paradigm shift? *New Phytologist* **179**(3): 587-589.
2. Gatherer, D (2010). So what do we really mean when we say that systems biology is holistic? *BMC Systems Biology* **4**(1): 22.
3. W. Simon (1963). *European Positivism in the Nineteenth Century. An Essay in Intellectual History.* Cornell University Press, Ithaca.
4. A. Comte (1880 [1851]). *A General View of Positivism. 2nd ed.* Reeves and Turner, London.
5. A. Wilson (2000). *God's Funeral.* Abacus, London.
6. A. Comte (1853). *The Positive Philosophy of Auguste Comte*. John Chapman, London.
7. Stadler F (1992). The 'Verein Ernst Mach' - What was it really? In: J Blackmore (ed.), *Ernst Mach - A Deeper Look.* Boston Studies in the Philosophy of Science. Vol. 143, pp. 363-378. Kluwer, Dordrecht.
8. Frank P (1970). Ernst Mach and the Unity of Science. In: SR Cohen and Seeger RJ (eds.), *Ernst Mach: Physicist and Philosopher*. Boston Studies in the Philosophy of Science. Vol. 6, pp. 235-244. D. Reidel, Dordrecht.
9. Frank P (1970). The importance of Ernst Mach's philosophy of science for our times. In: SR Cohen and Seeger RJ (eds.), *Ernst Mach: Physicist and Philosopher*. Boston Studies in the Philosophy of Science. Vol. 6, pp. 219-34. D. Reidel, Dordrecht.
10. R. Carnap (1995) *The Unity of Science*. Thoemmes Press, Bristol.
11. Nagel T (1998). Reductionism and antireductionism. In: GR Bock and JA Goode, (eds.), *The Limits of Reductionism in Biology.* Novartis Foundation Symposium Vol. 213, pp 3-14. John Wiley and Sons, Chichester.
12. A.J. Ayer (1936). *Language, Truth and Logic*. V. Gollancz, Ltd., London.
13. F. Crick (1966). *Of Molecules and Men*. University of Washington Press, Seattle.
14. R. Kurzweil (2005). *The Singularity is Near. When Humans Transcend Biology.* Viking/Penguin, London.
15. F.J. Tipler (1994). *The Physics of Immortality: Modern Cosmology, God and the Resurrection of the Dead*. Doubleday, New York.
16. F.J. Tipler and J.D. Barrow (1986). *The Anthropic Cosmological Principle*. Oxford University Press, Oxford.
17. Moore G. (1965). Cramming more components onto integrated circuits. *Electronics Magazine.* 19 April 1965.

18. Bremermann H (1982). Minimum energy requirements of information transfer and computing. *International Journal of Theoretical Physics* **21**: 203-217.
19. Gatherer D (2007). Less is more: the battle of Moore's Law against Bremermann's Limit on the field of systems biology. *BMC Systems Biology* **1** supp.1:53.
20. J.C. Smuts (1926) *Holism and Evolution*. Macmillan and Co., London.
21. Drack M and Apfalter W (2006). Is Paul Weiss' and Ludwig von Bertalannfy's System Thinking still valid today? *50th Annual Meeting of the International Society for the Systems Sciences*.
22. Gatherer D (1996). A stroll across the epigenetic landscape: bringing Waddington's ideas into molecular biology. *Early Pregnancy: Biology and Medicine* **2**(4): 241-243.
23. Elsasser WM (1961). Quanta and the concept of organismic law. *Journal of Theoretical Biology* **1**: 27-58.
24. Gatherer D (2008). Finite universe of discourse. The systems biology of Walter Elsasser (1904-1991). *The Open Biology Journal* **1**: 9-20.
25. Elsasser WM (1962). Physical aspects of non-mechanistic biological theory. *Journal of Theoretical Biology* **3**: 164-91.
26. Elsasser WM (1969). The mathematical expression of generalized complementarity. *Journal of Theoretical Biology* **25**(2): 276-96.
27. Elsasser WM (1969). Acausal phenomena in physics and biology: a case for reconstruction. *American Scientist* **57**(4): 502-516.
28. R. Rosen (1991). *Life Itself: A Comprehensive Inquiry into the Nature, Origin, and Fabrication of Life*. TFH Allen and DW Roberts (eds.), Columbia University Press, New York.
29. R. Rosen (2000). *Essays on Life Itself*. TFH Allen and DW Roberts (eds.), Columbia University Press, New York.
30. A.H. Louie (2009) *More than Life Itself. A Synthetic Continuation in Relational Biology.* Ontos Verlag, Frankfurt.
31. Chu D and Ho WK (2006). A category theoretical argument against the possibility of artificial life: Robert Rosen's central proof revisited. *Artificial Life* **12**: 117-134.
32. Landauer C and Bellman K (2002). Theoretical biology: organisms and mechanisms. *AIP Conference Proceedings* **627**(1): 59-70.
33. Louie AH (2011). Essays on More Than Life Itself. *Axiomathes*. **21**: 473-489.
34. Cornish-Bowden A (2015). Tibor Ganti and Robert Rosen: Contrasting approaches to the same problem. *Journal of Theoretical Biology* **381**: 6-10.
35. Cornish-Bowden A and Cardenas ML (2007). Organizational invariance in (M,R)-systems. *Chemistry and Biodiversity* **4**(10): 2396-2406.
36. Schaffner KF (1976). The Watson-Crick model and reductionism. In: M Grene and E Mendelsohn (eds.), *Topics in the Philosophy of Biology*, pp. 101-27. Boston Studies in the Philosophy of Science. D. Reidel, Dordrecht.
37. D.L. Hull (1974). *Philosophy of Biological Science*. E Beardsley and M Beardsley (eds.), Prentice-Hall, Englewood Cliffs, NJ.
38. Kitcher P (1984). 1953 and all that: a tale of two sciences. *Philosophical Review* **93**: 335-373.
39. P. Davies (1987). *The Cosmic Blueprint*. Heinemann, London.

40. A. Rosenberg (1985). *The Structure of Biological Science.* Cambridge University Press, Cambridge.
41. Rosenberg A (2007). Reductionism (and antireductionism) in biology. In: DL Hull and M Ruse (eds), *The Cambridge Companion to the Philosophy of Biology,* pp. 120-138. Cambridge University Press, Cambridge.
42. J.J.C. Smart (1963). *Philosophy and Scientific Realism*. Routledge & Kegan Paul, London.
43. W.M. Elsasser (1998). *Reflections on a Theory of Organisms. Holism in Biology.* The Johns Hopkins University Press, Baltimore.
44. Roll-Hansen N (1969). On the reduction of biology to physical science. *Synthese* **20**(2): 277-289.
45. Ackermann R (1969). Mechanism, methodology, and biological theory. *Synthese* **20**(2): 219-229.
46. Nagel E (1960). The meaning of reductionism in the natural sciences. In: A Danto and S Morgenbesser (eds.), *Philosophy of Science*, pp. 288-312. Cleveland: Meridian.
47. S. Wolfram (2002). *A New Kind of Science*. Wolfram Media, Champaign, IL.
48. K.R. Popper (1963). *Conjectures and Refutations*. Routledge and Kegan Paul, London.
49. P.B. Medawar (1979). *Advice to a Young Scientist*. Harper & Row, New York.
50. Popper KR (1974). Evolution and World 3. In: PA Schlipp (ed.), *The Philosophy of Karl Popper*, pp. 1048-1080. Open Court, La Salle, IL.