

Finite Universe of Discourse: The Systems Biology of Walter Elsasser (1904-1991)

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Abstract: Walter Elsasser (1904-1991), an eminent quantum physicist and geophysicist, was also active in theoretical biology over a 35-year period from the early 1950s to the late 1980s. Although increasingly estranged from the biological establishment during the last fifteen years of his life, Elsasser's central concern with complexity has resulted in a revival of interest in his theories over the last decade, particularly among those who see biology from a systems holist rather than a molecular reductionist viewpoint. This article reviews the development of Elsasser's thought from his early opposition to genetic determinism, through the radical epistemology of his middle period, to his later more broadly philosophical ideas. After a summary of existing responses to Elsasser in the literature, a fresh critique and assessment of his work is presented, with particular attention to the implications for systems biology. It is concluded that although Elsasser drew some conclusions from his epistemology that are not justifiable in the light of subsequent research, his insistence on the existence of biotonic phenomena in biology, irreducible (either at present, or in principle) to physics, is correct. Ironically, the most significant biotonic principle is one which Elsasser largely ignored in his own work, that of Natural Selection.

INTRODUCTION

Walter Elsasser (1904-1991) was part of the generation of physicists who turned to biology after the Second World War but, unlike contemporaries such as Maurice Wilkins, Francis Crick and Max Delbrück, who dedicated themselves exclusively to their new field, or those physicists who made only occasional contributions to biology [1-4], Elsasser pursued physics and biology with equal vigour. Although he made a crucial contribution to early quantum mechanics [5] and several major discoveries in geophysics, he eventually came to regard his theoretical biology as his most significant work [6-8].

After a period of neglect, Elsasser is once again receiving attention from experimentalists [8-15] and theoretical/systems biologists [16-21]. Passing mention is also found among cladists [22], ecologists [23-26], semioticists [27, 28] and artificial life researchers [29, 30]. In parallel with this revival of interest, Elsasser has also become a posthumous inspiration to opponents of current research directions in molecular biology [31-33], as well as in less mainstream areas such as so-called 'Intelligent Design'.

During his lifetime, Elsasser's ideas were the subject of considerable comment [4, 34-44], but very little in the way of detailed critique, with one exception [45]. The revival of interest in his work has produced several short introductions [8, 17, 20] but no full reassessment of his ideas. This article attempts to fill this gap, with the emphasis on his relevance to systems biology, a field which Elsasser [46] foresaw. The initial exposition of Elsasser's work will be delivered without immediate criticism, followed by an assessment of Elsasser's influence on current thinking in the various fields in which he is cited.

Then some comments in the literature will be discussed, and a new comprehensive critique presented. The final section is a reassessment of Elsasser's contribution to modern biology.

EXPOSITION OF ELSASSER'S BIOLOGICAL THEORIES

The earlier stages of Elsasser's biological thought were dominated by his development of Bohr's notion of "generalized complementarity" [47, 48], an extension of the concept of complementarity in the quantum world - the dual particle/wave nature of matter, leading for instance to the inability to know precisely a particle's position and velocity - to the macroscopic level. For instance, Bohr [1, 3] argued that a complete set of measurements on a cell or organism carried right down to the quantum level would result in the death of that entity. If such a set of complete measurements were technically feasible - in quantum mechanics, the hypothetical instrument required is picturesquely referred to as a "Heisenberg microscope" [49] - the investigator would have a full description of the state of the organism, but would be unable to extend that description into a series of such over time. Conversely, an investigator planning any time series of measurements on a complex biological entity would have to forego any hope that such measurements could ever be complete right down to the quantum level. It is thus impossible to know both the complete state and complete trajectory of an organism, since these are complementary descriptions.

In parallel with this, Elsasser also carried out some detailed consideration of the nature of automata, comparing the behaviour of electronic and mechanical feedback devices to cellular and physiological processes according to the principles of two theories that were new at that time: cybernetics and the concept of self-reproducing machines [50, 51]. On this basis, Elsasser concluded that there were a large number of biological processes that could reasonably be understood as cybernetic automata, leading to an essentially mechanistic interpretation of biology, provided that one understands that generalized

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complementarity prevents the determinism within such a system from descending to the sub-atomic level [49]. However, a crucial exception was made in the case of the transmission of hereditary information, where Elsasser felt that geneticists had overstated the extent to which developmental programming of the embryo was determined by the germ cells [52].

Elsasser was influenced in this by ideas then current in developmental biology, still at that time rather a separate science to genetics, and based his discussions on the classic embryological dichotomy between *preformation* and *epigenesis*. A hypothetical embryo with complete genetic determination of its developmental program would, Elsasser argued, be equivalent to a preformed system, in that all necessary information would be contained in the fertilized zygote. Rather than the homunculus of 18th century embryologists, this updated notion of preformed content would be encoded in the genome. By contrast, a hypothetical epigenetic embryo would not contain all its developmental information within the fertilised germ cell, and could not be considered as an automaton. Both preformed and epigenetic embryos might look similar, have similar genomes, and indeed perform similar morphogenetic movements during development. The question of the preformed or epigenetic nature of the developmental processes arising in such embryos would hinge on whether or not the processes were entirely encoded in the genome.

Nevertheless, Elsasser emphasised that, apart from such concerns about information storage, he could see no fundamental difference why an organism could not be considered an automaton in the sense described by contemporary cybernetic theory [52]. Throughout his career, Elsasser explicitly rejected any neo-vitalism [6, 7, 20, 46, 49, 52-54, 89]. Rather, he posited that that new “biotonic” principles, compatible with, but not deducible from, quantum mechanics [55], were required to explain the development of an organism in the absence of the complete information storage he regarded as necessary for a *truly* mechanistic embryology to be valid. It is therefore appropriate to consider Elsasser’s early stance as *info-scepticism*: a generalised scepticism about deterministic description of any complex system to the quantum level, coupled with a specific scepticism concerning genetic determination or programming of developmental processes.

A further crucial concept from his early work is “the principle of finite classes” [52, 55], which he frequently illustrated using a state-space or phase-space model [56]. If one represents each theoretical configuration of a complex biological object, for instance a protein, by a point in an abstract state space, then the state space thus constituted is immensely large, and the fraction of that theoretical state space actually occupied in the real world is vanishingly small. Proteins are therefore entities belonging to *finite* or *inhomogeneous classes*. Within a finite class, even if the average conformation could be calculated for all its members in the real world (usually a practical impossibility), there is no guarantee that it will be the same as the average point in the total theoretical phase space. By contrast, a simple gas such as nitrogen has, by virtue of the simplicity of each nitrogen molecule, a limited number of conformational possibilities. The theoretical phase space of nitrogen gas is therefore small and will be fully occupied in the real world. Even with a very small sample of nitrogen gas, the average molecular conformation will be the same as in an infinitely large one. Simple gases, and indeed most subjects of

study in the physico-chemical laboratory, can therefore be considered to be members of infinite or homogeneous classes. Unlike the world of the physico-chemical laboratory, the biological world constitutes a “finite universe of discourse”, meaning a universe where all classes are finite [57].

All biologists are aware of the extreme molecular complexity of biological substances relative to those typically studied by an experimental physicist. Therefore, the concept of, for example, ultra-sparse protein phase space might simply be regarded as a formal way of describing what is trivially true. However, Elsasser identified extremely non-trivial implications for the theory connecting quantum mechanics (QM) to the Newtonian universe in which the biological sciences typically operate. This theory, mathematically formulated by John von Neumann in the early 1930s and published in his book *Grundlagen der Quantenmechanik* [58], henceforth referred to as the Grundlagen proof, demonstrates that although quantum indeterminacy rules the world of sub-atomic particles, the statistical averages of such indeterminacies are regular enough for determinism to apply to levels above the quantum. The indeterminate world of QM and the Newtonian deterministic universe are therefore not only compatible, but the latter is a necessary consequence of statistical behaviour within the former.

Based on his concept of finite classes, Elsasser made the radical proposal that this Grundlagen proof included an implicit assumption about the homogeneity of any system in which the quantum indeterminacy averages out to Newtonian determinacy. In a substance with a small theoretical conformational space, such as the nitrogen gas discussed above, the averaging of quantum indeterminacy is easily achieved because nitrogen belongs to an infinite class and its theoretical phase space is fully occupied. There is therefore no reason to believe that nitrogen gas, even in a minuscule sample, would ever behave indeterministically. However, for immensely large conformational spaces such as those of proteins and larger biological objects, the averaging required for the Grundlagen proof to apply, would never occur. This was initially an operational argument against the practicality of reducing biology to physics [52]. However, it later developed into a more direct attack on mechanism within highly complex systems insofar as Elsasser [56, 59-61] gradually began to imply that it meant that proteins and other large organic molecules cannot be expected to behave in the same deterministic way that one would expect of substances of simpler composition [56]. This argument applies equally to any complex system but few non-organic systems would be complex enough for it to become effective [62].

In other words, Elsasser saw the Grundlagen proof of macroscopic determinism as applying to the world normally inhabited by the physicist but ceasing to be reliable in complex biological systems. These are therefore governed by a “non-Gibbsian statistical mechanics” [56], resulting from “non-Neumannian axiomatics” [54]. Consequently, “an organism is a system that is *physically indeterminate*” (Elsasser’s italics) [53, 61]. Biology is therefore not based on physics and chemistry, and its laws are not deducible, “neither derived nor disproved”, from those of physics and chemistry, but rather physics and chemistry are narrower fields of study confined to relatively homogeneous substances belonging to infinite classes. These substances are homogeneous by selection [54] in that

the experiments of physics and chemistry are usually performed on purified materials, often at controlled temperatures and pressures. These considerations led Elsasser to a redefinition of his biotonic principle from his earlier work, and also to some successive name changes: from “biotonic” to “epigenetic” [53], and then later from “epigenetic” to “organismic” [63]. Whereas before, biotonicity pertained to information transmission, an extra principle required to explain the non-automaton nature of the organism with respect to information storage, it had now come to define a property of matter such that: “We call a property of a class organismic if it exists in a finite universe of discourse but becomes lost when one goes to a corresponding infinite universe” [56], and therefore “organisms appear as *primary forms of matter* governed by laws which cannot be established by observations of anything simpler than the organisms themselves” (Elsasser’s italics) [53]. Under such circumstances, biology becomes a purely inductive science [59, 46], and one in which the study of molecular mechanisms is relegated in importance behind the study of whole systems, the study of the “order above inhomogeneity” [60] or “variostability” [62]. These ideas are very similar to those of self-organization within chaotic systems, contemporaneously developed within the computer sciences [64]. Elsasser was the first to present self-organization as a widespread empirical fact based purely on consideration of the nature of biological material.

Elsasser was therefore able to reverse standard scientific logic and state two “conditions for the *lack of adequate prediction*” (italics added) [54]: 1) the calculation of all class averages must be devoid of operational meaning and 2) the microstates must not average out, i.e. local homogeneity must not occur, the entities must be “radically inhomogeneous at all levels of their organization”. If either of these requirements is broken, von Neumann’s Grundlagen proof becomes valid and the system collapses into a mechanistic mode. The second requirement, when broken, would create locally mechanistic areas within an organism, leading to a “biological process as an inextricable mixture of mechanisms with individualities” [62].

To maintain this heterogeneity at the micro-level, Elsasser introduced the concept of ergodizers [55]. An ergodic process is one in which a system at, or near, thermodynamic equilibrium passes through all its possible structural conformations (referred to by physicists as Boltzmann complexions [53]), in other words a process that is not confined to a restricted region of phase space. These ergodizers were hypothesized to be “design features” connecting the microscopic and macroscopic worlds in complex systems, that “subserve the appearance of biotonic regularities” [55]. In its original formulation, metabolism was taken to be “the prime dynamical instrument of ergodization”, but Elsasser soon retracted this view, replacing it with a more difficult but preciser definition: “ergodization is based on geometrically widespread collective interactions with comparatively weaker energies [than chemically specific interactions]” [53]. Elsasser required ergodizers to exist in order to explain why organisms are so highly heterogeneous at all levels. Ergodization is undoubtedly one of the most difficult of Elsasser’s concepts, and never mentioned in modern reviews of his work.

Just as Elsasser came to replace the notion that biology can be reduced to physics – which he terms “logical reductionism”

[53] - with the concept of physics as a limiting case concerned with near-homogeneous infinite classes, so is the theory of logical reductionism itself posited to be a limiting case of a wider theory of logical complexity [54]. This can be understood as meaning that because there are very few absolute binary yes/no answers to biological questions, there is little hope of splitting larger biological problems down into smaller sub-problems that can be solved in isolation and later re-assembled into a view of the whole, the so-called “Cartesian Method”. Just how far Elsasser had come in his rejection of causation in complex systems can be seen by his introduction of the concept of “creative agency” in the formation of “ordered patterns” [57, 60]. Elsasser stressed that the notion of creativity was really just a metaphorical one, especially nothing Bergsonian or vitalistic, but actually a kind of unanswerable question in a Wittgensteinian sense [65].

Such ideas were to come to the forefront in Elsasser’s later work, in which he began to develop a wider and more generally philosophical framework, summarized in terms of four principles: 1) ordered heterogeneity, 2) creative selection, 3) holistic memory and 4) operative symbolism [7, 66]. The principle of ordered heterogeneity is simply a reworking of the principle of finite classes, but de-emphasizing the importance of non-Neumannian axiomatics and the conclusions drawn from these [67]. The principle of creative selection is quite close to the metaphorical notion of “choice” that Bohr [1] used to describe the indeterministic transitions of quantum mechanics, expressible only in terms of probabilities. As always, Elsasser squashed any hint of vitalism: “creativity is just a slogan” [66]. The complexity of biological processes means that it is never the case that all the causal chains leading to an event can be traced. Elsasser therefore defines creativity as the formation of ordered patterns under such circumstances [60]. In his earlier work, Elsasser’s info-scepticism took the form of denial that the genome was capable of governing embryonic development. By his final period, he admitted that DNA is an important storage mechanism (although still restricting it to “chemical morphogenesis” and denying it a role in anatomical specification of the embryo [46]), but also postulated a non-stored “holistic memory”. These two elements were proposed to supplement each other in the control of development and other aspects of the phenotype [7]. The role of the mechanistic gene is proposed to be as “a releaser of creative selection” [66] a sort of trigger that somehow channels the complex processes he defined as creativity, engaging cellular holistic memory in appropriate directions. This is what is referred to as the principle of operative symbolism, the gene being a physical “symbol” for a larger creative process working on holistic memory. “Symbol” was defined by Elsasser as “an incomplete message” [7].

As well as introducing this new expanded theoretical framework, Elsasser also attempted to develop some rather less successful direct lines of attack on mechanism at an empirical level, for instance [68, 69] proposing that mutation will gradually increase informational entropy within a genome, in the manner of Muller’s ratchet [70]. Elsasser then went on to argue that increase in genomic entropy would, if one assumes that the genome is the primary controller of the phenotype, result in a corresponding increase in morphological entropy – a kind of phenotypic spread over time. Since such phenotypic change does not appear to occur in the fossil record of any well-studied species, he therefore concluded that the causal

connection between the genome and phenotype is false. This will be dealt with further below.

It is notable that Elsasser at this time in his life expressed his resolve not to be deflected from stating his case through fear of a bad reception from the scientific establishment, as apparently he had been up until about 1975 [6]. Certainly his later work contains more direct philosophical argument about the ultimate origins of mechanistic modes of thought in biology, following the trail back as far as Descartes [46, 7]. For Elsasser, the success of Cartesianism and its mechanistic/reductionistic successors had resulted in a mindset of “mechanistic projection” among scientists, the false attribution of mechanical properties to living things, analogous to the “animistic projection”, the false attribution of human properties to inanimate objects. The net result has been the “dogmatic slumber of reductionist biology”, the “mechanistic overgrowth that has been the bane of biologists for a long, long time” [7]. Against this he posited that his theory was in fact a structural one [46, 71, 66], in the sense of one definition of “structuralism” as that of explanations that do not use reduction, i.e. a structural theory explains or describes something without recourse to any other underlying theory or discipline [72].

ELSASSER’S INFLUENCE ON OTHERS

Much of Elsasser’s influence on current theoretical biology is through the work of Robert Rosen, who might be classed as a friendly critic insofar as he promoted the value of Elsasser’s work but doubted why the principle of finite classes should imply anything about causality [73]. Rosen pointed out that if Elsasser’s interpretation is correct, the implications extend far wider than biology. If physics is a narrow area confined to the homogeneous, then the principle of finite classes has rather profound conclusions for physics, possibly rather more profound than the implication that biology is irreducibly complex. Rather, Rosen felt that there was a need to find some reductionist schema that was not couched in terms of physics [74]. Among Rosen’s followers, Baianu [75] and colleagues [21] claim that living systems are intractable in terms of automata, and they use Elsasser’s concept of heterogeneous classes as part of their argument that they can construct various network topologies, consistent with biological networks, in such a mathematical form as can be demonstrated not to be equivalent to a Turing machine. Baianu [75] also strongly criticises complex systems theory in biology as being just complicated mechanistic model development focussing on digital computation.

Among those who cite Elsasser as part of a criticism of current directions in biological research funding, Mae-Wan Ho [33] made particular use of Elsasser’s concept of variostability as an argument against the Human Genome Project (HGP). A similar but wider line was taken by Strohmman [31, 32] opposing the entire gamut of modern research funding in molecular biology. Strohmman felt that the concepts of the later period Elsasser (complexity, choice, holistic memory) as well as chaos and informational redundancy were more appropriate examples of what should be funded. Elsasser’s complaint that accumulation of sequence information does not “deepen our understanding of the nature of organic life” [7], certainly seems to be a comment against such efforts as the HGP. However, Elsasser’s views on this subject were some-

times contradictory. Whereas in his early period he spoke of “the failure of quantum biophysics” [49], and later looked forward to “a future, more scientific biology” [60], rather than that produced by those who are “making biology resemble too much chemistry” [7], at other times he was prepared to concede that molecular biologists had made some impressive achievements [62].

Elsasser’s theories have found their main empirical expression in the work of Harry Rubin [9-11, 14, 15], who has focussed on the existence of what have elsewhere been referred to as “community effects” [76]. Rubin interprets this in terms of Elsasser’s concept of variostability, as well as Paul Weiss’s “macrodeterminism” [10]. However, there are also possible reductionist explanations (or at least avenues of investigation) of these events. For instance Monk [77] and Furusawa and Kaneko [78] make it clear what a mechanism might be for the community effect in *Xenopus* development [76], and in fact a molecular basis has been partly elucidated [79].

PUBLISHED CRITICISMS OF ELSASSER’S WORK

Francis Crick [35] and Jacob Bronowski [39] both criticised Elsasser’s early work, specifically his first book [52] as an example of neo-vitalism, despite Elsasser’s consistent denials of this charge. Crick’s criticism of Elsasser’s info-scepticism is fairly strong: “a beautiful example of the confusion that can be brought about by ignorance”, obviously feeling that Elsasser had not taken account of the contemporary developments in molecular biology in the early 1950s (the book although published in 1958 was written around 1955 [6]) resulting in a work “clearly conceived in an earlier era” [35]. Crick admitted that the question of how DNA programs development is (or was, in 1966) largely unresolved, but believed that the mechanist viewpoint is the appropriate application of Occam’s Razor. As well as challenging info-scepticism, Crick also expressed doubts about the consequences of the principle of finite classes, seeing this as being more likely to lead to “chance effects” rather than being the source of new biotonic properties [35].

Equally as negative as Crick was Jacques Monod who described Elsasser’s ideas as “oddly lacking in strictness and solidity” [41]. Elsasser later identified Monod as most closely representing the view he wished to oppose [7]. Interestingly, one passage gives the strong impression that Elsasser had not fully grasped Monod’s point concerning the action of natural selection. This will be dealt with further in the critique section below.

Robert Ackermann [36] questioned Elsasser’s view that biological classes are pervasively finite, finding infinite classes, for instance, in classical genetics where mutant or inbred strains can be considered homogeneous in many, or even all, relevant respects. One could say, if a class is homogeneous with regard to the experiment under consideration, then *ceteris paribus* (the assumption that all other things are equal with regard to the experimental conditions) is invoked. For instance, an inbred strain can, even in a sexually reproducing organism, produce a degree of homogeneity in the genome not normally found in a natural setting. However, Elsasser was always quite willing to concede that it is possible to produce classes that are homogeneous by selection, for instance in the chemistry laboratory. The inbred strain of the geneticist is merely a biological example of such. A slightly different at-

tack on the principle of finite classes was carried out by Kari Lagerspetz [37] who gave the example that rocks are always individual and therefore also a finite class. This has not impeded the reduction of geology to chemistry. Elsasser [62] acknowledged that geological classes can be finite, but denied that complexity was pervasive in mineral mixtures to the same degree as in organic substances.

Ackermann and Nils Roll-Hansen [38] also made the interesting point that an organismic attitude like Elsasser's is justifiable only if it could be made to fit any underlying physics. For the reductionist, if the physics changes, the reductional chain is broken and the biology will need to be re-reduced to the new physics. Conversely, the production of a new physics may allow the reduction of biological phenomena previously regarded as irreducible. One is therefore bound to acknowledge that the denial of reducibility in principle, rather than an admission of its current deficiency in practice, tacitly assumes that current physics is completely correct. Elsasser did seem to be of this opinion, following the line that the Copenhagen Interpretation had survived fifty or more years of attempts to falsify it [46, 66], a position shared by many [5], but which Ackermann believes will sooner or later be undermined. Ackermann also pointed out that indeterminacy does not necessarily preclude mechanism, as for instance seems to occur in mutation or possibly meiosis (in the sense of a random choice of crossover position [36]). For example, a coin tossing machine can be understood in a purely mechanical way, as can a roulette wheel or, at a slightly more sophisticated level, a rand() function in computer programming. Once the nature of the random generator is understood, the randomness may disappear and a more truly deterministic picture appear, but absence of full knowledge of the random generation device does not entail an abandonment of mechanistic explanation of the system in which it is situated.

The longest critique of Elsasser in the literature is by Stuart Kauffman [45], whose first point concerned the variostability argument from which Elsasser postulated an absence of any correspondence between the microstates and macrostates of a complex system. Kauffman pointed out that if one can transition at low energy between two adjacent microstates, and these microstates although adjacent in the notional phase space of the microstate variables, do not correspond to macrostates which are adjacent in the corresponding macrostate phase space, then there is no reason to believe that order would arise above heterogeneity. On the contrary, the more likely outcome of such non-proximity in mappings between micro- and macro-phase spaces would be that disorder would arise above order, the contrary situation to that hypothesized by Elsasser. However, this argument seems to rest on a necessary connection between those micro- and macro-phase spaces. Elsasser argues that there is no reason to assume any such connection, so Kauffman's argument in this respect probably becomes irrelevant.

Kauffman's second criticism was that part of Elsasser's finite class argument is a *non sequitur* [45]. Kauffman gave the following thought experiment: if there were only three oxygen molecules in the universe, they would constitute a finite class, since although the number of potential conformational states of a simple gas is very limited and its phase space is correspondingly tiny, three molecules is not enough to fill it. In this thought experiment universe, oxygen is a finite class in

the way that Elsasser describes protein molecules to be in the real universe. Despite this, one could use still QM to deduce a multitude of predictions concerning oxygen, for instance its spectral lines. One could neither falsify nor verify these predictions since there are only three molecules. However, any regularity that did occur would still be predictable by QM. David Hull [80] made a similar point that events that are unique are not the same as events that are one of a kind. No rules, and therefore no science, could apply to the former, whereas the latter are perfectly addressable scientifically (although perhaps in a strictly *post hoc* fashion).

Kauffman concluded that Elsasser was arguing against what Daniel Dennett [81] later called "greedy reductionism" – the tendency to attempt to reduce a science below the level at which such reduction is useful – after making the false implication that biologists need to be greedy reductionists in order to be mechanists. Kauffman then alluded to "reasonably deterministic class averages, such as an enzyme's activity as a function of the fraction of precursor and product pools in acceptable microstates", as an example of what would be considered as an adequate mechanistic description of a biological function at an appropriate level of reduction. If one knows this, one can meaningfully claim to understand the mechanism of action of the enzyme. However, would such an understanding, good enough for 1972, be regarded as a genuine mechanistic understanding today? The modern biochemist would require to know the sequence and structure of the enzyme and to know how the changes in activity corresponded to occupation of active sites, shifts in allosteric interactions and so on. As we push the question of how things work, we move inexorable down towards the level of QM. This is not greedy reductionism, merely a healthy appetite.

Hull [80] expressed some reservations concerning the importance of generalized complementarity, pointing out that it is quite possible to gain lots of information from an organism without killing it. A similar argument is found in Markowitz [43]. Turning to Elsasser's own work, Hull doubted that there are quite homogeneous classes in physics, since there are isotopes, chiral isomers and so on, even at the atomic level. Similarly, Markowitz [40] shows that superconductors constitute an example of finite classes. Really homogeneous classes are only found at the sub-atomic level. Hull concluded that Elsasser is not merely excluding organisms from reduction to QM, but also objects such as motor cars, and that Elsasser must actually be saying that the only thing that can be reduced to QM is QM itself, or that really there is no science except QM. Hull pointed out that astronomy is a very exact science that studies extremely complex heavenly bodies but does not require all their complexity to be known. Likewise, classical physics is just about mass, motion, energy and so on, and not about colour, shape or chemical composition. Therefore, biology need not refer to every detail of its subject matter. This line of argument, however, could also be construed in support of Elsasser's rather than against it. Hull's insistence that astronomy and classical physics do not need to be reduced to QM to be satisfactorily applicable within their appropriate areas is very similar to Elsasser's arguments for biotonic/organismic emphasis in biology. Both argued that reductionism to QM was inappropriate; Elsasser merely added that for biology, it was also likely to be impossible. Hull also found Elsasser's whole notion of classes in biology rather essentialist in that, classes being defined by a set of properties for each

class member, it does not seem to take into account the possibility that the class will, or indeed can, evolve.

CRITIQUE OF ELSASSER

Despite the clarity of Elsasser's writing, it is evident that many critics were unable to go beyond a simple intuitive feeling that Elsasser was wrong, outdated or irrelevant. Even the handful of critics who were able or inclined to explore Elsasser's ideas more deeply could often score only glancing blows. It is hoped that the following will go more directly towards eliminating those parts of Elsasser's theory that are untenable, thus revealing the useful parts in more detail.

A. Confusion of Determinism, Mechanism and Reductionism

It is easy to become mired in definitions of terms such as vitalism, mechanism and reductionism, differing as they do to such an extent between writers. This was previously recognised by Hull [80] who goes as far as to suggest that the entire debate is virtually crippled by such problems. It is clear that even within the body of Elsasser's work, a lack of definitional stability seems to undermine some of his arguments.

For instance, in his early writings, Elsasser acknowledges the organism as "determinate", but that this determinism is not "purely mechanical, it must needs be *biological*" (Elsasser's italics) [49]. One may therefore use explanatory terminology of the form 'phenomenon X leads of necessity to phenomenon Y', provided one understands that the organism is not to be seen as *nothing but* a complex mechanical device. This is a 'morethanist' [82] argument against what has been variously called 'nothing buttery' [83, 84] or greedy reductionism [81]. The source of such nothing buttery would appear to be in early natural philosophers such as Descartes, and more fully in slightly later successors such as Julian Offray de La Mettrie (author of *L'Homme Machine* of 1748), for whom the successes of early efforts in the production of clockwork or hydraulic devices provided a powerful analogy for the understanding of organisms [85]. The modern biologist, while recognising this analogy, realizes that organisms are of a complexity and subtlety that exceeds even the most impressive human artefact. The meaning of 'mechanism' in modern biological discourse is therefore more the answer to any question of the form 'how does X work?', and a reply of the form 'X is caused by Y and Z acting together in manner A' would be referred to as 'a mechanism for X', essentially the abstract cybernetic definition given by Ashby [86]. That mechanism could be at the evolutionary, cellular or molecular level. The similarity or dissimilarity of the proposed process to anything seen in contraptions of human devising would certainly be interesting, but nevertheless irrelevant to the question of its status as a mechanism. A salient example of Elsasser's misuse can be found in his representation of Driesch's embryo division experiment, in which a 2-cell sea urchin embryo develops into two different embryos after separation of the cells, as a conclusive experiment against mechanism [7]. Driesch, unlike Elsasser, went even further and took it as evidence for vitalism, but modern developmental biologists simply see it as 'regulative development', another fascinating *mechanism* to be studied. Therefore, Elsasser's distinction between determinism of a mechanical nature and determinism of a biological nature appears at first sight to be rather artificial.

However, for Elsasser, such a reply would probably constitute fudging the issue, since he regarded a truly mechanistic explanation as one that was in principle capable of expression at the quantum level. Nevertheless, in this Elsasser is making several assumptions about the nature of the automata that so captivated the early Cartesian biologists. These would likely have contained many parts of organic origin, made from wood, animal gut, wool, cotton etc. therefore including many parts belonging to finite classes, and so under Elsasser's own terms be quite irreducible. Elsasser does occasionally imply that he takes mechanism and reductionism to be synonymous [7], and also that "physicalism" is synonymous with reductionism [71]. "A prediction is purely *physical* only if it is based on the solution of the differential equations of physics (quantum mechanics)" [55, italics added]. By this criterion, very few objects are mechanisms at all, and certainly not the handcrafted moving dolls that initially inspired the whole machine-organism analogy. Elsasser can only achieve his refutation of mechanism in biology by redefining rather narrowly what a mechanism is, so narrowly in fact that the term becomes meaningless even in contexts outside of biology. More extreme anti-reductionists such as Polanyi have pursued similar lines of investigation even further, resulting for instance in the statement that a motor car is also irreducible to physics, and Hull [80] is of the opinion that Elsasser fails to make a convincing case why his own argument is correct and Polanyi's is wrong. If one rejects Polanyi's argument, as Elsasser did, it casts into doubt the very definition of mechanism that Elsasser uses.

When dealing with embryology, Elsasser also conflates "mechanistic" and "predetermined", stating that a mechanistic view of embryogenesis necessarily entails a view of embryos as predetermined. Again one might appeal to the casual definition of mechanism used by modern biologists, who recognize various degrees of regulative and predetermined processes in embryogenesis without any qualms about referring to them all as *mechanisms of development* (incidentally, the title of one of the main journals in the field). However, there is also a stronger argument against Elsasser's usage. Any automaton capable of if-then decision gating based on environmental conditions will not exhibit predetermined behaviour since the environment is a necessary input to its current state. It is nevertheless entirely mechanistic in a far narrower sense than used in modern biology, and even potentially in the very narrow sense required by Elsasser [87]. It can at least be said that only if one could entirely predict the changes in the environment could one also entirely predict the behaviour of the device. It is interesting in this context that Elsasser changed the name of his purely biological laws from "biotonic" to "epigenetic" [53], reflecting his opinion that the preformation-epigenesis dichotomy was central to his problem. His later change from "epigenetic" to "organismic" may have reflected a realization that his use of the term was non-standard [88], and indeed since the mid-1980s epigenetic has come to have a rather specialised meaning even within developmental biology, referring largely to the process of modification of gene expression *via* methylation of DNA.

This name change issue is interesting, since most modern biologists would see the later "organismic" as pointing towards the organism as a whole. However, it is defined [56] as referring to any property that only exists in finite classes, and therefore could apply to an extensive array of levels of bio-

logical object - one might for instance be led to say that proteins have organismic properties, which although comprehensible to those familiar with Elsasser's entire *œuvre*, may mislead the uninitiated if used casually. Likewise the middle period "epigenetic" seems to point rather narrowly towards the embryo. The earlier "biotonic" could in principle refer to any level, and is therefore the preferred term in the remainder of this article. This avoids the confusion that might result from mixing Elsasser's definitions of epigenetic and organismic with those of more recent terminology. For instance, a non-greedy reductionist could agree that some properties of protein function may be biotonic, but in the standard terminology they could hardly be organismic, and only epigenetic in certain narrow circumstances.

The origin of this confusion seems to originate at some point in the mid-1960s. In his first book [52], it is clear from the extensive analysis of cybernetic models that Elsasser views mechanism as an abstract process. This is quite close to the use of mechanism in the informal way common in modern biology - for instance, various cybernetic processes are analysed by Elsasser [52] and their mechanisms discussed; the reduction of the corresponding physical automata (which in any case never actually exist) to QM is absolutely not the issue. However, Elsasser later moved away from this kind of analysis towards an emphasis on finite classes and reducibility to QM. At this point, mechanism became tied to the molecular structure of the entity under investigation. Whether or not a process could be considered a mechanism, depended largely on its susceptibility to the Grundlagen proof, and therefore on the nature, finite or infinite, of its class membership. Since class membership is defined by molecular structure, mechanism ceased to be abstract at this point. One might even say that it became materialist. For instance, for the early Elsasser electrical conduction in a nerve or in a copper wire was an example of a mechanism implemented in different entities. However, in his later work, the nerve has acquired irreducible complexity by virtue of being composed of membrane lipids, proteins etc, and therefore cannot be analysed in the same way as the copper wire.

B. Biotonic Laws are Commonplace, Including Such Things as Natural Selection

Elsasser sometimes gives the impression that he believes that molecular biologists are opposed to any kind of law that is not rigidly mechanistic in his sense of the word. However, it is clear in practice that modern biology is full of laws, principles, assumptions and working hypotheses that are in no way reducible to QM. The single most outstanding example of this is the theory of Natural Selection, as previously recognised by Olby [42]. As formulated by Darwin and his contemporaries, it operated entirely at the level of the fitness of the individual organism. Even with the advent of population genetics in the 1930s and then molecular evolution in the 1960s, and the consequent shift in emphasis from the whole organism down to single genes, along with far greater understanding of processes such as mutation, there is no serious claim that natural selection would be predictable merely from perusal of the equations of QM. A distinction can be made between "downward" and "upward" analyses in this context [80]. Mutation in DNA can be studied right down to the QM level, and may be said to be explicable in terms that satisfy QM. However, although one can reduce mutation to QM, one cannot deduce mutation from

pure QM. One might be able to deduce the occurrence of a particular mutation if extensive information were given about molecular conformations of nucleotides immediately before the event, and the molecular environment in which they were situated, and one then asked the question: 'given what is known about QM phenomena and given the state of this molecular system, what is likely to happen?', but this deduction upwards is very different in kind from the reduction downwards.

Indeed, the modern tendency in evolutionary theory is towards abstraction of the evolutionary process, creating what has been called a "Universal Darwinism" [89] that could in theory, if not yet in practice, encompass such things as chemical evolution and socio-cultural evolution as well as the phenotypic and molecular evolution more familiar from biological contexts. Attempted explanation of any of these evolutionary processes, whether biological or of another kind, below the level necessary to include the universal tenets of variation, reproduction and selection constitutes greedy reductionism. Universal Darwinism provides explanations of the evolution of abstract entities, some of which correspond to actual biological entities. Even if there were no actual biological entities, Universal Darwinism would still have a logical consistency and explanatory power.

Given the apparent example of Natural Selection as the most successful biotonic theory of them all, it is surprising that Elsasser has so little to say concerning evolution. In his early period he confined himself to comments that adaptation "comes out of the environment" not by "the incorrect Lamarckian" process but by the "well-substantiated neo-Darwinian scheme", although immediately qualified this with the point of view that it "makes little difference" in terms of his theory. His more specific thought is that evolution "over-emphasise[s] the exogenous part of the information content of organisms" but it is not clear if he means by this that adaptation is overemphasized as a mechanism for evolutionary change. Given his opposition to genetic determinism, it does seem a little incongruous to be seeking endogenous information content, unless he implies that it is of a non-genetic nature [52]. Given his later suggestions concerning holistic memory, it perhaps seems that this is a predecessor of that later view, but the treatment is too brief to make this clear. A slightly longer later passage [46] contrasts the external inputs of evolution with the internal inputs Elsasser has in mind, but does little to clarify their nature.

Elsasser produced a single paper specifically dedicated to the question of evolution within his theory [63]. He criticised the use of the term "the theory of evolution" on the grounds that it is not really a theory in the sense that would satisfy a physicist, that it cannot be expressed as "a set of propositions about classes" which are "interrelated" to give "structure" and also be "formalized by means of the logical calculus of classes". Nevertheless, he admitted that there are cases where "adaptations by a single mutation" can be demonstrated but claims these are exceptions "in the nature of limiting cases" from which it is "quite dangerous to extrapolate from there to a general case with its multiple, interrelated parameters". As a result of this "arguments from evolution cannot be used either to support or criticise organismic theory". Despite Elsasser's objections, an attempt to do this will be made below.

Elsasser's later statements on evolution concern mutational pressure and Shannon's Law [68, 69] and therefore do not directly take natural selection into account. His argument concerning entropic spread of phenotype is quite similar to Muller's ratchet, and the same solution is to be found in a combination of purifying selection and recombination. Random mutation under conditions of selective neutrality will increase the informational entropy of the gene pool over time, indeed genetic diversity at well characterised loci is an established method of dating founder effects in populations (for instance in human Y-chromosomes). Elsasser's argument that this will result in an increase in phenotypic entropy identifiable in the fossil record is however a *non sequitur* except in the most extreme cases of neutrality over most of the genome over long period of times. His attempt to use this to disprove any connection between genotype and phenotype is therefore one of his weaker arguments.

C. On Occasions, Elsasser Comes Very Close to Hoyle's Fallacy

'Hoyle's Fallacy' has been most widely disseminated by astrophysicist Fred Hoyle, who claimed that evolutionary processes producing adapted organisms were so unlikely as to be equivalent to a whirlwind passing through an aircraft hanger full of spare parts and assembling a jumbo jet by accident [90, 91]. Other analogies used by less imaginative authors have included a platoon of chimpanzees producing the works of Shakespeare by random typing, and so on. On the basis of this, Darwin's theory is deemed untenable, and other theories are proposed, usually Lamarckian or frankly creationist depending on the background of the writer. Hoyle's Fallacy is a surprisingly easy mistake to make when one has not quite grasped how powerful a force selection can be. Even John von Neumann was sceptical of Darwinism for this reason [92], and Elsasser himself gives a hint along these lines on two occasions [7, 65]. In the second of these passages, it is clear that Elsasser misunderstands Monod's "chance and necessity" motto to imply that Darwinism is a theory of "accidents" acted on by "chemical laws". One passage [7] suggests that Elsasser favoured Goldschmidt's macromutational theories over those of Darwin. Paul Davies [93], also a physicist and one of the modern complexity theorists who cite Elsasser as an influence, gives a fairly sympathetic account of Hoyle's Fallacy, despite the fact that he does seem to understand the principle of natural selection; what he seems to lack is any notion of its power. All evolutionary biologists, however, concur that such reasoning is merely a trivial error [94, 95] and Radner and Radner [96] point out that it is really a residue of views more generally held in the 1920s, prior to the modern evolutionary synthesis.

The root of Hoyle's Fallacy is the assumption that large state spaces are somehow fatal to deterministic processes. For Hoyle, the immensity of protein state space forces him to the mistaken conclusion that it is impossible that any process could find optimal configurations in it within limited geological time. For Elsasser, the immensity of all biological state spaces leads to an even more radical conclusion concerning the Grundlagen proof and determinism. A more recent example of the use of a state space argument in a systems biology context, is given by Harry Rubin [7]. The number of genes involved in sporulation in *Bacillus subtilis* was initially estimated by classical genetic methods to be around 800 [97] and

recent molecular techniques give a slightly more conservative figure of 193 [98]. There is nevertheless by either estimate an immense state space of genotypes relevant to sporulation. Even if each gene can be either on or off, a gross simplification, there are still at least 2^{193} , or around 10^{58} , possible states in this system (c.f. the 10^{80} atoms in the universe – [66]). At face value, this is a sobering thought to any systems biologist where networks of only a dozen or so elements present considerable computational strain in a simulation.

Quantitative genetics, however, suggests that in most polygenic situations, the heritability of any trait can be substantially attributed to handfuls rather than hundreds or thousands of genes. Therefore, no systems biologist would need information on the state of all genes in order to make a high precision prediction of the bacterium's biosynthetic state. Although full state space for the genetic network in *Bacillus* sporulation is a near-astronomical 2^{193} , relevant state space may be as small as 2^{25} and thus well within the reach of modern computing power. A simpler analogy concerning this kind of reasoning is provided by the solar system, the archetypal Newtonian mechanistic system. Here, the interactions between all the bodies make for a bewilderingly complex set of simultaneous equations that defy full solution by even the most powerful computers. Nevertheless, cosmologists can make predictions about the future state of the solar system to a degree of accuracy sufficient to send probes accurately to other planets with projected arrival times many years in the future. The reason for this is that the future state of each planet is overwhelmingly dominated by its interaction with the sun, making the calculation of the effects of all other planets dispensable in practice [80].

This tendency, to imply the necessity of impossible searches of immense state space, is the root of Hoyle's Fallacy, and also seems to be the central weakness of the application of the principle of finite classes. It should be recalled that Elsasser applied it in two ways: initially as an operational constraint on the practicalities of reducing complex systems to underlying simpler systems, and later as a metaphysical basis for the inapplicability of the Grundlagen proof, and therefore the inapplicability of Newtonian determinism, to biological objects. Elsasser only contrasted two kinds of situation in state space: the astronomically large theoretical space and its vanishingly small proportion constituting actual occupied state space in the real world. However, natural selection may seriously limit the proportion of state space within which the resulting organism will be viable. Full theoretical phase space therefore contains a sub-space here termed 'accessible state space'. This is the portion of full state space that could be occupied in the real world.

In other words, Elsasser simply assumes that, for state space:

possible >>> real,

However, if we allow:

possible >>> accessible > real,

or:

possible >>> accessible \approx real,

then the implications for Elsasser's application of the principle of finite classes are serious. In effect, the situation he describes of sub-spaces within infinite state space which exhibit determinism owing to their local restrictiveness [56], may actually be nearly the whole picture rather than a local exception. If real configurations of biological objects are strongly constrained by their environment, or by internal structural factors, or by natural selection, then the Grundlagen proof may well apply in more cases than Elsasser is willing to concede. By failing to consider the implications of natural selection on state spaces, Elsasser commits essentially the same error as proponents of Hoyle's Fallacy.

D. Quantum Decoherence Means that Proteins do Exhibit Newtonian Mechanics

Recent explorations of the interface between the quantum and macroscopic worlds suggest that the interaction of neighbouring atomic particles causes the local collapse of indeterminacy [99]. Although it remains possible that QM effects can leak out into the macroscopic world, laboratory studies have so far only managed to demonstrate wave behaviour in molecules as large as porphyrins or fullerenes [100]. These are considerably smaller than proteins. Where QM effects are manifested in protein action, it is at the level of individual atoms rather than the protein as a whole [101, 102]. In short, there is simply a lack of empirical evidence for the indeterminacy predicted by the principle of finite classes.

E. Elsasser Decided on his Conclusions and then Sought Supporting Evidence

Several aspects of his writing style suggest that Elsasser started out from the premise that biology is not mechanistic and sought evidence to support what he had already decided to believe. Some of the inspiration for this came from his experience of being psychoanalysed as a young man [6, 157, 158]. A considerable proportion of his later energies seemed to be taken up with maintaining that his intuition of inscrutability of life, which came to him during his psychoanalysis, was scientifically valid even after molecular biologists had provided many satisfactory answers.

At one point Elsasser [46, 54, 55] explicitly lays out a series of logical steps which appear to show how he worked backwards from his intuitive conclusion towards his proposed justification:

1. the theory of means (meaning the Grundlagen proof) is inescapable
2. therefore biology must ultimately conform to it
3. therefore we must fall back into reductionism, but we do not want to
4. therefore we must look for evidence that the theory of means does not apply in organisms
5. but we cannot contradict QM, so the evidence we collect cannot lead to new laws in the strict sense [55].

This would seem to imply that Elsasser's application of the principle of finite classes was very close to a logical sleight of hand. As a Jungian, he wished to derive an anti-mechanistic proof, but as a physicist and follower of von Neumann, he could not. The solution lay in stepping back and contravening the axioms of physics while leaving the laws intact. Elsasser's

honesty in laying out the way his theory developed is, of course, to be applauded. However, it does not inspire confidence in its cogency. If one considers Elsasser's central idea to be an opposition to what he saw as anachronistic manifestations of the Cartesian reductionist, and by implication crudely mechanist, program in biology, it is possible to see how it evolved as the scientific background changed. In the 1950s, the tentative nature of early molecular biology made it possible to create an info-sceptic case for the failure of genetic deterministic models in development. As the 1960s progressed and the understanding of gene regulation and the genetic code increased, it became apparent that such a stance was untenable, and Elsasser shifted to more fundamental arguments against determinism in protein function. By the late 1970s, protein structure-function relationships were far clearer and there was no empirical evidence for the predicted consequences of the principle of finite classes. Elsasser's final position followed a retreat from specific arguments about proteins or other molecules and into the question of overall systems complexity.

SUMMARY AND REASSESSMENT OF ELSASSER'S BIOLOGY

Until recently, it seemed that Elsasser's biological work might vanish into obscurity, with references to it in the literature becoming increasingly rare from the mid-70s onwards, even though Elsasser remained scientifically active in biology until the late 1980s. Under such circumstances, the present article would scarcely be required, but his star is once again on the ascendant, with the realisation that Elsasser's themes are important to modern biology in a way that they were not in an era of simpler model systems studied using simpler methods. Now that the technical difficulties of systems biology have become apparent, anyone with original thoughts on the meaning of complexity is well worth a reassessment. It is mildly shocking that, amid the plethora of recent books, both popular and academic, devoted to complexity theory, barely a single one mentions Elsasser [93]. In fact, many of the current contexts in which Elsasser is cited appear to be only tangential to his actual theories, and are often either misunderstandings, misrepresentations or selective readings of his work. Many enthusiasts are clearly excited more by his reputation as an unorthodox thinker than by any specific idea. If Elsasser's theories are to be of value to modern biology, it is important that they be clearly and fully exhibited and their strengths and weaknesses exposed.

Elsasser's early info-scepticism has been largely rendered obsolete by advances in molecular biology. It is true that there is still extensive doubt concerning the extent to which biological processes are genetically determined, for instance the debate concerning human intelligence or culture [103]. However, progress in molecular embryology in particular has demonstrated that it is possible to see the genome as a program for development without any implication of a resurrected pre-determinism. Nevertheless, Elsasser provides a salutary warning against the inappropriate adoption of genetic determinist models where direct evidence is lacking.

There is no doubt that the distinction between finite and infinite classes, first developed during Elsasser's middle period, is a logically valid one, and that finite classes are common in biology. One example of an area where finiteness has

recently reared its head, is found in standard sequence analysis. Based on the nucleotide content ($k=1$, where k is a character string length) of a completely sequenced genome, it is possible to produce prior probabilities for the occurrence of the dinucleotides ($k=2$), with either a random expectation or a bias of choice defined by a Markov transition table. Since there are only 16 dinucleotides - and 10 once self-complementary dinucleotides are accounted for [104] - the human genome is large enough to make a comparison between predicted and actual dinucleotide frequencies statistically valid. This is the basis of the technique of genome signatures that has found application in clinical microbiology as well as basic comparative genomics [105]. The same is the case for trinucleotides ($k=3$) and larger, but as k increases the number of potential oligonucleotides - i.e. the theoretical state space of k -mers - increases exponentially. Any given 10-mer string, assuming a zero-order Markov transition table and equal frequency of nucleotides, will only be expected to occur every 4^{10} , or one million or so, bases. Likewise any given 15-mer can only be expected every 10^9 bases, or roughly three times in the entire human genome. Statistical assessment of the significance of its actual occurrence in any genome is therefore problematic. The problem is exacerbated when smaller genomes are used or when one studies the frequencies of strings in protein rather than DNA sequences (in proteins the theoretical state space has dimensions of the order 20^k rather than the 4^k of DNA). Future studies in other areas will no doubt throw up further examples of the principle of finite classes in unexpected locations. Elsasser was undoubtedly correct that individuality and finiteness do present problems for any quantitative biological analysis.

Nevertheless, although the principle of finite classes seems solid in itself, Elsasser's more radical conclusions concerning this principle are implausible in the light of more recent research. Extensive studies on protein structure and function have yielded no examples of the indeterminacy predicted by Elsasser's non-Neumannian axiomatics. In the light of several decades of empirical structural biochemistry of proteins, there is simply no compelling reason not to apply Newtonian models to proteins. Various catalytic processes and interactions do depend on quantum effects, but these are confined to the sub-atomic level. Decoherence mops up quantum indeterminacy at the level required for doing structural-functional biochemistry on proteins.

Despite the fact the Elsasser failed to prove the necessity of biotonic laws by argument from von Neumann and the principle of finite classes, there is no denying that biological discourse is filled with biotonic phenomena, in the looser sense of processes that are not necessarily reducible to QM. The most important of all is evolution by natural selection, ironically never identified as such by Elsasser. The importation of concepts into biology from the theories of chaos, catastrophes and self-organizing systems, as well as the tendency of biology to become a compute-intensive data-driven science will mean that increasing numbers of new principles discovered will be relational, applying in general to systems like biological ones rather than being laws that act only in biological substances. Davies [93] makes the distinction between "software" laws and "hardware" laws. Systems biology is almost entirely concerned with software laws; it is a totally biotonic science.

Where does this leave reductionism? Modern biologists, aware of the perils of greedy reductionism, are only inclined to reduce phenomena to a level where explanatory power is maximised. For instance, molecular evolutionists study patterns of mutational events in great detail, but it is the event positions and frequencies that are important, not the chemical means by which they occur. It is the abstract pattern that maximises explanatory power in a molecular evolutionary question. Conversely, a nucleic acid biochemist may be interested in the actual mutational event itself and its causes in terms of mutagenic agents, without any reference to the position of the event on a chromosome, its occurrence through evolutionary time, or its phenotypic effect. At an even lower level a quantum chemist may be interested in the behaviour of the electrons in pair clouds in nucleotide side chains, without any reference to the gross molecular structure of any mutation that might occur as a result. There is no doubt that all of these levels are connected. However, a full understanding of the entire process may be a case of diminishing returns for the practical scientist. Each has to choose the level at which the question in hand needs to be answered. This process has been described [94] as hierarchical reductionism.

Just as we need to choose the appropriate level of the hierarchy of explanations and beware of greedy reductionism, Elsasser's work provides a lesson in the avoidance of the opposite vice, greedy holism. Elsasser's intuitive feeling that life was more than could be explained by science led him on a long search for reasons why reductionism would not work. An inflation in the scope of this anti-reductionist agenda can be seen from the info-scepticism of his early work to the molecular anti-determinism of his middle period and finally the more nebulous concepts of his final work that have secured his position among counter-cultural theorists. Systems biologists, dealing with software laws rather than with the raw material are in little danger of succumbing to greedy reductionism, but difficulties with the complexity of networks should not lead to a greedy holism. Just as a transition down a level of the explanatory hierarchy requires justification, so does a transition upwards. For instance the current debate about the scale-free nature of biological networks [106] depends very much on the details of the networks themselves. It is essentially an empirical question using empirical data, although approached entirely using computers and mathematics. Levels above the network, e.g. the cell or organism, or below it, e.g. the structure of the transcription factors regulating it are, for the present, only background information. If systems biology remains focussed on achieving explanation, then it matters little whether the approach is 'top-down' or 'bottom-up'; indeed it should be both: "inclusive" [107], or "multi-scale" [108, 109]. A pragmatic holism and a pragmatic reductionism are really the same approach [110]. Contrary to Elsasser, a mechanism does not need to be reduced to the quantum level, or be fully determinate, or to qualify as a mechanism. All it needs to do is to answer the question of how something works, in a way that can be seen as a logical consequence of the way other things are known to work [86]. Insofar as these postulated mechanisms are pragmatically situated, they are likely to be biotonic explanations, in Elsasser's sense. Perhaps that is his most important lesson - that systems biologists should remember to be biologists. On the other hand, when Elsasser claimed that biology was in need of an all-encompassing non-reductionist

theory, he overlooked the fact that we have had one for nearly 150 years. Its name is Darwinism.

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