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REDUCTIONISM AND BIOLOGICAL COMPLEXITY

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"Irreversibility is either true on all levels or on none: it cannot emerge as if out of nothing, on going from one level to another." I. Prigogine & I. Stengers, *Order out of Chaos*, Heineman, 1984.

Molecular biology is widely reputed to have uncovered the secret of life, with DNA being heralded as the quintessential component of biological systems. This reductionistic success has clear limits, however: one cannot recover a chicken from chicken soup, and the problem of "synthesis" remains the stumbling block of the reductionistic programme.

The biologist's problem is the problem of complexity. According to the conventional wisdom, the way to study complex systems is by breaking them down into their parts. In Richard Dawkins's words, "the biologist tries to explain the workings, and coming into existence, of complex things in terms of simpler things. He can regard his task as done when he has arrived at entities so simple that they can be safely handed over to physicists."

This strategy assumes that living systems are arranged hierarchically: molecules make macromolecules, macromolecules make organelles, organelles make cells, cells make tissues, tissues make organisms, and organisms make populations and socio-ecosystems. They can thus be understood by seeking explanations of their properties in terms of behavior at (hierarchically) lower levels of organization. Thus, hydrolysis of energy-rich molecules causes protein filaments to slide, sliding filaments cause muscles to contract, muscle contraction causes the acquisition of food and the escape from predation, and group behavior centered around common defence and protection of food supply causes the formation of social systems. This analytical approach may be termed "hierarchical reductionism". But it is still an open question as to how far this "downward causation" can succeed in any *individual* case; the fact

that it appears to succeed in particular cases constitutes a circular argument, in that the strategy is regarded as successful only *after* it has been shown that it works!

In biology, as in any science, we must distinguish between the "method" and the "philosophy" of reductionism. Methodologically speaking, reductionism is fruitful; it yields much utilitarian detail about observable phenomena. However, reductionism can never be complete; there is always a "residue" which requires new conjectures or hypotheses for its solution. In Sir Karl Popper's words, "Not only is philosophical reductionism a mistake, but the belief that the method of reduction can achieve complete reductions is, it seems, mistaken too. We live, it appears, in a world of emergent evolution; of problems whose solutions, if they are solved, beget new and deeper problems."

Perhaps the greatest concern in the issue of biological reductionism *vs* holism is the transition between the hierarchical levels. We know that we cannot make a lentil out of lentil soup, nor even lentil puree; thus in the analytical approach there must be some point, "the moment between the bud and the rose," at which reductionism fails. We shall argue here that a crucial concept in seeking a more secure philosophical foundation for when we may (or, perhaps, more usually may *not*) adopt even a hierarchically reductionistic method is that of *irreversibility*.

As nicely delineated in Peter Coveney and Roger Highfield's recent book, *The Arrow of Time* (W. H. Allen, 1990), irreversibility remains a philosophical enigma. Newtonian physics is time-reversible; if we watch a film of billiard balls colliding, we cannot tell whether the film is running forwards or backwards. By contrast, if we observe a film of a bull in a china shop, we may be fairly confident that the film is running in one (the "forward") direction; bulls do not normally reassemble broken crockery and emerge smiling from retail stores. As Humpty Dumpty found, there are many ways of breaking things, but only one way of putting them together correctly.

Maxwell, Boltzmann, Gibbs, and others in the 19th century showed that the large-scale, thermodynamic behavior of gases can be understood, statistically, in terms of the properties (like velocity and momentum) of the composite molecules. Central to this statistical-

mechanical approach is the "ergodic hypothesis", in which it is assumed that the time-averaged behavior of an *individual* molecule follows exactly the same distribution as that of a very large number of such molecules.

As exemplified by the bull in the china shop, macroscopic change embodies a direction in time, ascribable to the Second Law of Thermodynamics. In an interesting set of lectures at Oxford in 1985 (*The Nature of Time*, ed. R. Flood & M. Lockwood, Blackwell, 1986), Peter Atkins nicely portrayed time as *geometry*; change, then, is a consequence of the "purposeless exploration" of this geometry. The Second Law says that things tend towards disorder; any *a priori* coherence decays into random thermal motion, with an attendant increase in entropy. Thus, as phrased by Atkins, "Irreversible change arises from purposeless drifting into the available states." Inherent in our analytical understanding of the concept of "non-equilibrium", then, is the idea of *boundary conditions* (constraints), the removal of which allows the given system to relax, thermally, to equilibrium.

Living beings operate as coherent systems by imposing "purpose" onto this geometrical landscape of accessible "particle states"; the activities of the constituent parts, at each level of the biological hierarchy, are constrained to limited regions of the landscape (i.e., a restricted ergodicity). For example, a selectively-permeable membrane envelope (along with various other internal structures) maintains a non-equilibrium internal distribution of chemical constituents vital to cellular function. Likewise, the imposition of legal codes on individual behaviour ensures that human social groups operate for the community good.

This space-time configuration of biological systems has been rationalized by physicists in various ways, according to such theoretical constructs as "hierarchical constraints", "dissipative structures", and "synergetics". The key point is that the successively higher levels of the hierarchy are dependent, reductionistically, not so much on the *elements* at the lower levels, but on the nature and existence of the boundary constraints. If one removes the constraints at a given level, the systemic (or holistic) properties of all higher levels potentially collapse. Hence, the disruption of the cell membrane causes decomposition not only of the cell *per se*, but also (by the release of enzymes inside the cell) leads to the disorganisation of tissues, organs, and

ultimately a whole organism. Similarly, the removal of civil laws produces social anarchy and, thus, the dissolution of towns, counties and whole nations.

From this point of view, any scientific measurement is an act of reductionism; it entails an irreversible relaxation from some pre-existent constraint. According to a widespread interpretation of the quantum theory, no elementary quantum state *is* a single state until it has been brought to a close by an irreversible act of amplification, from the micro- to the macro-realm. During the measurement process, the mathematical "wave function" -- which is a property of the whole physical system -- is "collapsed" (in the physics vernacular) by an irreversible act of observation, with an accompanying increase of entropy. The observer, who "sees" the system through the eyes of a measurement apparatus which is designed to perturb the system in a certain way, is then left with the daunting challenge of inferring the nature of the intact system (see figure).

In extending these ideas to biological systems, think, for example, of proteins -- the building blocks of the living cell. Every protein is a chain of amino acids, which is folded into a complex three-dimensional structure necessary for some specific function(s). The familiar (and apparently irreversible) process of boiling an egg involves the "denaturation" of egg proteins and may be considered (with some loss in accuracy) simply as the unfolding of the polypeptide chain when it is heated. Denaturation may also be caused by chemicals which disrupt the weak bonds holding the protein in its "native" three-dimensional shape. In a famous experiment, amusingly but incorrectly referred to as "unboiling an egg", Christian Anfinsen exposed the enzyme-protein, ribonuclease, to a mildly denaturing chemical, thereby causing the protein to unfold, and then removed the denaturant. The protein spontaneously refolded to give the catalytically active, native enzyme. Thus, all the information necessary for folding is inherent in the "primary sequence" of amino acids in the chain, and the native state is the most thermodynamically stable one (under defined, laboratory conditions *in vitro*). (It is now known that this is true for many, but not all, proteins, a fact of importance in the production of therapeutic proteins by recombinant organisms.)

This spontaneous refolding is truly remarkable. Suppose a protein has 100 amino acids, and assume that the atoms in each amino acid have 10 possible molecular arrangements or conformations. The protein, then, has 10^{100} possible macromolecular conformations. The time taken for light (and, by the laws of relativity, any information) to cross a protein is some 10^{-16} seconds. The lifetime of the known Universe is 10^{17} seconds; hence, a protein molecule could only explore 10^{33} of the possible conformations during the lifetime of the Universe! The biological solution is, of course, that the protein explores only a very restricted subset of the possible conformations during the actual folding process. Clearly, the individual amino acids lose some of their "individuality" to the system properties of the whole protein; the "geometric landscape" of available particle states is subject to constraints, and these constraints are represented by the sequence of amino acids. The information necessary for refolding is contained within the individual primary sequence of the individual molecule, and this information is not changed upon addition of the denaturant chemical.

Thus, in the example of the protein molecule, something approximating "reversibility" does (or, rather, can be made to) occur. But an individual protein is a far cry from a *living cell*. Despite the trenchant efforts of the last 50 years or so to elucidate the "molecular basis" of life, the goal of reconstructing a viable cell from its molecular parts remains unfulfilled. In the most extreme form of reductionism, one could argue -- based, for example, on the protein-refolding case -- that it is only a matter of time until we know the "hierarchical constraints" which hold the molecules in the form of an intact cell. The fallacy in this contention, however, is that, following the combinatorial logic in the "protein refolding" argument given above, the number of possible ways of reassembling a cell from its components exceeds any realistic experimental time-scale. The information is not explicitly contained simply in the properties of the individual macromolecular components.

As Niels Bohr suggested, the analysis of living systems may involve an analogy to the famous Heisenberg "uncertainty principle" in quantum physics. The act of measurement in biology, Bohr said, requires "collapse" of the living state into a configuration which favors only certain measurable properties of the components. Such an assertion is not an invocation of

"vitalism," but a realization of the significance of *emergent properties* in the hierarchical arrangement of the "parts" when forming the "whole".

We come full circle to the real problem: the nature of the transition between hierarchical levels in biology. Assuredly, the ascent of the hierarchy is not a simple, linear superposition of "particle states." And what of the interface between biology and the other sciences? Following the idea of an "implicate order" propounded by the physicist David Bohm, perhaps it is wrong to "reduce" one science to another; rather, matter and energy in the Universe should be regarded as "enfolded" in a conglomerate "whole", which we, the observers, "unfold" in particular ways when we view Nature.

Our scientific heritage (in the Greek tradition) is to reduce in order to understand; yet physicists have still to come to grips with the synthetic aspect of understanding, and it seems premature for biologists to lay claim to such a lofty achievement. Analysis is not the reverse of synthesis (see Figure). If we "reduce" what is uniquely found in Nature, we cannot expect to put the pieces together correctly -- even with the help of "all the King's horses and all the King's men".

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