MAX-PLANCK-INSTITUT FÜR WISSENSCHAFTSGESCHICHTE

Max Planck Institute for the History of Science

PREPRINT 162

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Abstract: A strong motivation for the human genome project was to relate biological features to the structure and function of small sets of genes, and ideally to individual genes. However, it is now increasingly realized that many problems require a "systems" approach emphasizing the interplay of large numbers of genes, and the involvement of complex networks of gene regulation. New projects of "transcriptomics" and "proteomics" are being conceived along these lines: This implies a new emphasis on integrative, systems theoretical approaches. It may be called 'holistic' , if the term is used without irrational overtones, in the general sense of directing attention to integrated features of organs and organisms. In the history of biology, seemingly conflicting reductionist and holistic notions have alternated, with bottom-up as well as top-down approaches eventually contributing to the solutions to basic problems. By now, there is no doubt that biological features and phenomena are rooted in physico-chemical processes of the molecules involved; and yet, integrated systems aspects are becoming more and more relevant in developmental biology, brain and behavioural science, and sociobiology. Correspondingly, theoretical biology is expected to be increasingly involved in progress in these fields.

1. From genomics to transcriptomics and proteomics

At present, the human genome project aimed at sequencing the entire human genome is not far from completion. The genome is made up of 23 chromosomes with sequences of some three billion nuleotide pairs. They encode perhaps 100 000 proteins, and contain many sequences involved in gene regulation. The project has taken and still is taking up a large number of man- and woman-years; it has been running for more than a decade, and will take perhaps another three years. There are many expectations and hopes vested in this project, ranging from insights into metabolism and its regulation through the mechanisms of development and evolution to the diagnosis and cure of diseases[1,2].

Generally, cloning genes has been almost an obsession in recent years; young scientists were encouraged to extend all sorts of biological studies to include sequence analysis of the genes directly involved wherever possible. However, the realization is now increasingly emerging that there are many interesting questions that cannot be resolved in this manner. Development and evolution, the formation and the function of the neural networks in the brain, are processes that are not easily broken down into elements corresponding to effects of individual genes, individual biochemical components, or even individual cells. A systems approach seems to be required, and this is a challenge for theoretical as well as molecular biologists: in particular, if development as such is to be understood, we need to uncover the - presumably combinatorial - patterns of the activation of different sets of genes in its course.

This, in turn, may benefit strongly from currently discussed large-scale programs of "transcriptomics" and "proteomics."[1] These include systematic studies of the expression of messenger RNA and proteins within cells of one and the same organism under different conditions of development. Further aspects of such post-genomic programs are systematic comparative analysis of structures, modules and functions of proteins, as well as their post-translational modifications and associations. For the understanding of cell differentiation, the regulatory functions of noncoding sequences are of particular importance. Many different interests are connected with such programs, largely medical and pharmacological ones; for the developmental biologist, it is hoped that in this way the internal order of the network of gene regulation, its relation to developmental processes – perhaps including one of their most interesting aspects, namely its indirect relation to the developing neural network in the brain - may be revealed. Comparison of different organisms may allow us to reconstruct pathways of evolution with respect to protein structure and function and to the genomic organization of the regulation of gene activities.

At first glance, such postgenomic programs look as if they just continue and expand the quasi-industrial sort of data collecting of the human genome project. A second look, however, reveals that they imply a substantial change in attitudes: it is the *system* of some hundred thousand genes, and of even more regulatory sequences in the genome, that is to be analyzed in terms of function and features of the whole organism. It is characteristic for such integrative programs that progress does not always come about gradually. There may be phases of data collection without any general insights, until some really challenging ideas elucidate working principles of the system as a whole. After decades of over-emphasis on step-by-step deconstruction of biologically interesting features in terms of the elementary constituent of the genome, the gene and its nucleotide sequences, an age-old attitude to the life sciences is gaining weight in terms of methods, as well as of aims: an emphasis on integrated, top-down approaches. Are holistic thoughts "back on stage"?

2. Some remarks on the term 'holistic'

Although I could outline much of my argument without refering to the word 'holistic', speaking of systems theory right away, its use may not be inadequate, especially for the comparison with past historical developments, and for discussing research strategies in biology for the immediate future. Then, however, the term requires qualification. It makes sense in relation to current trends in biology, if we take the meaning of 'holistic' at face value: It is defined in the 'Oxford English Dictionary' as a 'tendency to perceive or produce wholes', and in 'Webster's Encyclopedic Unabridged Dictionary of the English Language', as 'the theory that whole entities, as fundamental components of reality, have an existence other than the mere sum of their parts'. Such concepts are in accordance with what modern mathematical systems' theory says. This may be recalled by scientists at crossroads of choices between problems that lend themselves easily to reduction to components, and perhaps more interesting problems, which by the same token, are often more resistant to such resolution.

However, in the literature of the 20th century, the term 'holistic' was also used in rather specialized ways, intended to support specific doctrines and views on the order of nature. In particular, it was often claimed that living systems follow principles not rooted in physical laws and processes; this, of course, gave rise to criticism looking at holism as a somewhat irrational notion. The latter attitude is reflected in an article in the Encyclopedia Britannica (1994) where it says 'in so far as [reductionism] may encourage concentration on those properties of the structure that can be explained as the sum of elementary processes to the detriment of properties that arise only from the operation of the complete structure, the criticism must be considered seriously. The physical scientist is, however, well aware of the existence of the problem. ...What is set up as a contrast to reductionism by its critics is commonly called the holistic approach, whose title confers a semblance of high-mindedness while hiding the poverty of tangible results it has produced'.

In the context of my article, the term 'holistic' is, of course, used in accordance with the wider definition mentioned first, focusing attention on features and processes of organs and organisms as a whole. This applies to, but is not restricted to, lines of thought reaching back far into the history of biology, such as Aristotle's teleological concepts more than 2300 years ago, Stahl's ideas on the organizing role of the 'anima' around 1700, or Driesch's views on vital forces underlying biological development. Current scientific programs aiming at the understanding, in terms of integrative concepts, of the structure, development, behaviour and evolution of organisms are not revivals of past holistic notions, though some of the latter may now appear, in retrospect, in a relatively more sympathetic light as compared to the extremely critical attitude reflected in my quotation from the 'Encyclopedia Britannica'. In fact, they did contribute in their time, to fruitful developments in biology by insisting that *contemporary* reductionist concepts were insufficient for explaining basic processes of life, and by identifying and dealing with neglected but important biological topics, such as homeostasis in the case of Stahl. Later, their wholesale concepts were mostly overcome irreversibly by further scientific advances, especially by expansions of physico-chemical knowledge of cells and molecules. What characterizes integrative and, in this sense, holistic approaches in current sciences is the explicit or implicit relation to systems theory. In contrast to most historical lines of holistic thoughts in the general sense of the term, it is accepted that physical laws are universally valid, applying to the non-living as well as to the living domain; that there are no special forces or determinants operating exclusively in living systems; and that establishing relationships between features of the whole – the organism – and its constituents, say, of molecules, are main aims of biological research.

3. Mechanisms versus organisms: more than two thousand years of debate

In this article, I will first look back into the history of discussions on "the whole and its parts" and on "mechanisms versus organisms"; then, I would like to discuss fields of contemporary research in which holistic notions reappear in the form of systems' theoretical approaches. In a last section I will come back to current issues of "post-genomics"[1,2] in biology.

Looking back far into history, we realize that it was the pre-Socratic philosophers in Ancient Greece who, some two-and-a-half-thousand years ago, postulated that it should be possible to understand nature in theoretical terms with the help of such abstract, nonmythical concepts as "logos," "spirit," "number," "element." Even at the earliest stages, explanations were sought that would encompass both the living and the non-living domains. Democrit claimed that all features and processes could be explained in terms of atoms, their properties and their interactions: a thoroughly materialistic and at the same time bottom-up strategy of thoughts on nature. Aristotle, on the other hand, took an integrative holistic view from the outset. Form, he maintained, must be distinguished from unformed matter. According to Aristotle, events are directed by purposes. Such teleological principles appear plausible in the living world. Inorganic physics would then presumably also follow such principles; for instance, falling bodies fall because they tend to approach their most natural position, which is the lowest possible.

In a sense, we can regard Aristotle as the founder of biology as a science. It was he who refused to take features of higher organisms, such as breathing, as a basic definition of life; he insisted that the criteria for life as such should apply to all, even the most primitive, organisms (to him, this meant the plants), and he identified these features as reproduction and metabolism (strictly speaking growth and nutrition); higher forms of life then have additional features, animals that of sensibility, humans that of reason.

Aristotle's views on the primary role of purpose in the understanding of nature, and the implication that biologically plausible principles apply to all of physics, rather than physically plausible principles to all of biology, were not the only ones put forward in the time that followed. In fact, Straton "the physicist," who succeeded Aristotle's immediate successor as head of his "peripatetic" school in Athens, claimed that forms arise as a result of the movements and interactions of matter. There are no separate causes, such as those referring to purposes; mechanistic processes of constituents underlie the formation and features of a whole. Basic physical laws and principles apply to all natural phenomena. This is in accordance with modern sciences, but it did not pass into mainstream thinking for a long period of antiquity and the Middle Ages.

After the stagnation of rational inquiries into nature in the first Millenium, they flourished again in late medieval Europe, especially at the newly founded universities. It was the progressive intellectuals who rediscovered and interpreted Aristotle. They were particularly attracted by his beautiful spherical model of the universe. It did not agree with the Bible, where the earth is described as a flat disc; and yet it did lend itself to a Christian interpretation: the earth occupies the lowest part of the universe, a domain susceptible to generation, change and corruption. At its center is hell; in the upper spheres, heaven and the heavenly bodies.

Philosophical views of Aristotle were forbidden, allowed, forbidden again, only to eventually become mainstream lines of thought in Christian medieval Europe. As so often, what is progressive today is reactionary tomorrow: in the Renaissance, Aristotelian philosophy led physics into a dead end. It was revived by an entirely different, revolutionary approach: that of Galilei‘s, Kepler,s, and Newton‘s mathematical mechanics. No holistic principles; no purposes underlying natural phenomena; few forces; just a few simple mathematical laws, valid for all events in space and time. Knowledge of the present state allows for calculating future states. Anything involved in natural phenomena is a mechanical interaction.

It was the consistency and the success of this new line of scientific thought that led to the question "What is life?" in one of ist most radical forms: "How can a physics developed exclusively in the nonliving domain then claim validity for all events in space and time, which do, after all, involve living beings? Are animals just mechanical entities, and humans just machines? Are our actions determined by the laws of mechanics applied to our body rather than programmed by our will? Or is our will itself nothing but an outcome of hidden mechanisms in our brain? What about consciousness, the soul, the emotions?" From this stage on, there were people who claimed that life could be explained in terms of mechanistic principles – based on the mechanical sciences of the time – as well as those who insisted that the organisms could not be understood except in terms of principles or forces that were operative in the living domain only – functions of the soul, for instance.

The first, mechanistic, line of thought is associated to a considerable extent with the philosophy of Descartes. He saw mind and body as separate domains, with body extended in space and subject to mechanical laws. The mind interferes with the body only marginally, this interference being mediated in the brain by a small organ, the pituitary gland. As a proponent of alternative antimechanistic views on life, let me select the physician and chemist Georg Ernst Stahl[3] (1659-1734). He considered, as Aristotle had done before him, that the soul, *anima,* was the guiding principle of organisms. His notions on *anima* are somewhat fuzzy and not very appealing to modern scientists, until it comes to the specific features of life that seemed resistant to explanation by the mechanical sciences of his time, and these features are rather modern topics. One is homoeostasis – the organization of metabolism in such a way that the system of components is self-maintaining, thus sustaining the life of the organism as a whole although individually the components would be subject to rapid decay. The notion of purpose set by the *anima* is to explain, for instance, why an organism may go left instead of right, although its mechanical constituents allow for going in either direction. Stahl insisted on a close interrelation between emotions and actions and found that, according to his medical experience, unconscious emotions often override rational perception of a situation. He explained that voluntary movements are preceded by preparatory internal (psychic) processes. In retrospect, of course, Stahl was not right in claiming that all the structural and behavioral features of living beings as a whole he attributed to the *anima* defied explanation on a physical basis, but the mechanistic notions of his time were certainly inadequate to achieve this. Their reductionist proponents did not usually argue that future extended physics would provide explanations, but rather tended to exclude the problems that were not resolvable by their mechanical insights from consideration: for Descartes, consciousness and the mind were not biological fields of inquiry.

A similar pattern of a mechanism-organism controversy also arose in connection with biological development. There were thoroughly mechanistic and strongly deterministic biologists, such as Haller and Bonnet, who proposed in the 18th century that all future generations of an organism were contained in the egg, in a manner reminiscent of the Russian dolls within dolls, and that what looks like generation was actually only an unfolding of pre-existing structures. It was Caspar Friedrich Wolff[3,4] who, while studying the development of the chick embryo experimentally, insisted that structures were newly formed in each generation and not already pre-existent in the fertilized egg. And then he assumed that special forces were required to explain such generation of form in the replication cycle, forces that do not operate in the inorganic domain. In the latter point he was wrong, but his insistence on *de novo* generation, the generation of whole, spatially organized, well proportioned organic structures out of initially near-homogeneous tissue – was right; in a creative manner, he opened up the field of experimental developmental biology, which just could not exist in the framework of the dolls-within-dolls concept.

4. Molecular biology and the physical foundations of biology

Now, let us take a big leap forward to modern molecular biology. In the 1930s the substances of life were mostly considered to be proteins, whereas nucleic acids did not receive much attention because they were often assumed to consist of ever-repeating tetra-nucleotides. Then, two paradigmatic changes occurred: proteins, at that time sometimes referred to as colloids, became accepted as molecules in the same way as water (H_20), though a little bigger, and thus susceptible to bottom-up structural and functional analysis. Nucleic acids were more and more recognized as crucially and specifically involved in cell functions. The centennial discovery, in this context, was the finding by Avery et al.[5] that DNA is genetic material of organisms. Nine years later, in 1953, Watson and Crick[6] discovered the structure of the hereditary substance DNA, the double helix. Their DNA-model was based on advances in molecular physics, biochemistry and X-ray diffraction.

This discovery marks the beginning of a decade in which the foundations of molecular biology were laid: sequences of nucleotides encode genetic information. They are copied by a mechanism involving the formation of complementary sequences, as suggested by the double helix. The sequences transferred from a cell to its daughter cells and thus from one generation to the next encode information on building and maintaining the organisms primarily by coding for sequences of amino acids in proteins. Some sequences in the DNA are involved in gene regulation, allowing cells with the same DNA to assume different states of differentiation in the course of an organism's development. Occasional changes in nucleotide sequences, for instance through copying errors and recombination, give rise to variation, selection, and evolution. All this was learned in a single decade, between 1953 and 1963. In the decades that followed techniques were developed which are now the basis of large-scale sequencing, cloning and genetic engineering.

It is perhaps not surprising that this success story was a triumph of bottom-up strategies in biology. Biological processes are now seen to be rooted in the physical laws just as chemical and physical processes proper are, in laws valid for all events in space and time, indicating a hidden unity in all of nature. No extra forces of life are required to explain basic features of life, such as reproduction, metabolism, development, evolution. But soon, this success story became more and more internalized and was often interpreted in a one-sided manner, with insufficient recognition of the fact that the basic laws of physics as such are inadequate to allow *deduction* of features of life from physical principles. In fact, understanding life requires top-down approaches as well, primarily based on *biological* observations and *biological* concepts. In epistemological terms, a hidden but decisive "holistic" aspect must be recognized: the bottom-up approach of molecular biology is essential and constructive, but is not sufficient for biology; if overemphasized, it represents a suboptimal if not uncreative attitude, and such an attitude has been seen in recent decades in different fields, diffusing from the top level of scientific leaders down to young investigators.

5. Top-down and integrative approaches in contemporary biology

Let me now discuss why in some fields of present-day biology increasing emphasis on top-down approaches appears to be required. One of these fields is developmental biology. We have seen that in its early phase, in the 18^{th} century, bottom-up Cartesian-type mechanistic lines of thought tended to deny that there is real development, that is, *de novo* pattern formation in each generation. It is to the credit of adherents of holistic concepts that they revived attention to the fundamental processes of the generation cycle. From their time up to that of Driesch and Spemann, the fascination of developmental biology lay in the regulatory features of the organism as a whole. For example, half an early sea urchin embryo gives rise to a complete organism, with adaptations of the parts to the size of the whole. An inductive kick may initiate the formation of a complete organic structure within originally near-homogenous tissue.

With the advent of molecular biology and its application to development many projects were first strongly biased towards rather narrow molecular aspects. At this stage, only a small sector of the scientific community was involved in a strategy, aiming primarily at understanding morphogenesis proper by an integration of rock-bottom molecular biology with the analysis of the structure of the developing organism as a whole. It was work such as that of Lewis,[7] and, with far-reaching consequences, that of Nüsslein-Volhard and Wieschhaus,[8] on *Drosophila* mutants that caused a breakthrough: mutants affecting the body plan at large in a specific manner, showing, even at early stages of development, spatial coordinates encoded in the distribution of molecules, and the involvement of combinatorial principles. As another example, research on neural development demonstrates that it is controlled by genes in a highly complex and yet specific manner: thus, individual mutations affecting the retinotectal connection were found to result neither in a single effect nor in diffuse consequences, but rather give rise to a distinct set of changes in the nervous system at large.[9]

Integrative aspects are also characteristic for a theoretical approach,[10,11] emphasizing that crucial problems of development are *de novo* pattern formation and its striking self-regulatory features. It would indeed be unwise to hide this central feature of developing organisms as a whole like a needle in a haystack of cloned and sequenced genes. One principle underlying pattern formation appears to be the interplay of activating autocatalytic reactions and inhibiting effects extending across many cell diameters:[11] in a sense, an integrative feature of the development of spatial order of the organism. Graded distributions of molecules specifying positional information for morphogenesis can be newly formed in this manner. Regeneration is possible. Sizes of parts may adapt to the size of the whole. Small inductive stimuli can initiate major morphogenetic processes. Spacing of structures and substructures is regulated. These concepts are based on systems analysis beyond the study of the components involved. Explanations depend on *both* molecules and mathematics. And yet, it remains a matter of philosophical taste whether one is ultimately intrigued more by the material or by the formal aspects, by Democritean or by Pythagorean lines of thought - an age-old issue.

In brain research and neurobiology the relations between bottom-up and top-down approaches were more complex than in developmental biology. Historically, early attempts at localizing functions within the brain can be counted as "bottom-up." The recognition that there are features and capabilities, such as memory and attention, pain and sleep, that do not lend themselves easily to localization encouraged "top-down" ideas. On the other hand, detailed investigations of the biology of the neuron and of neural connections as well as the modular basis of brain functions led again to attempts at primarily "bottom-up" explanations of neural functions. It was often assumed that even human faculties, such as language, mind, and consciousness are within reach of essentially reductionist explanations in terms of neurons and their interactions.

Side by side with these overly reductionist views, there have been and still are overly holistic ones. For instance, quite a few anthropologists sympathize with concepts on the evolution of the human brain and its capabilities, saying that it grew bigger and bigger and thus allowed for more and more self-organization, say of the cerebral cortex, and that all this made it possible for integrating capabilities, language, mind, and consciousness to "emerge". However, such terms as emergence,[12] which are often used in an ambiguous manner, and an overemphasis on self-organization do not really lead to an explanation of what we want to know about the biological basis of the human mind. Actually, the cortex is anything but a homogeneous uncommitted area; specific patterns of connections within the human brain which are genetically encoded do matter. One can hardly expect to understand "higher" brain capabilities without understanding different subunits of the neural network and their interconnections and specific functional interrelations; and yet, the other extreme, namely attempts to explain network capabilities more or less directly in terms of their elementary components, the neurons and their response to defined signals, are bound to fail; a more integrative approach is also required.

Consider behavior, for example: classical behaviorism tended to reduce behavior and learning to stimulus-response relationships, but this approach turned out to be inadequate. It underrates the important role of internal processes in wider areas of the brain that take time and may involve extensive processing within neural networks even while no external stimuli occur. An example is the evaluation of possible future actions according to the emotional desirability of the results. Of particular interest in this context is the neurobiology of imagination and of attention, which is studied by noninvasive spatiotemporal analysis of brain activities. Most higher brain functions involve different parts of the brain, to be integrated functionally in a given context.[13,14,15] Probably, time codes of electro-physiological signalling in the brain contribute to such integration. Currently, thousands of neural imaging studies of the brain dealing with increasingly complex cognitive and emotional activities are published each year, and many other lines of neurobiological research contribute to our understanding of the brain. Generally, a holistic approach paying attention to the integration of dispersed processes is a necessary ingredient in the explanation of complex higher level behavior, from the preparation of voluntary movements to the development of rather general future-oriented strategic dispositions. Stimulus–response models would not do justice to these capabilities because often there is no direct unmediated relation between stimuli and responses as far as the behaviour of higher organisms is concerned.

Another example of the importance of integrative aspects is the discussion of the biological basis of cooperation and altruistic behavior. How is altruism in animal and man to be reconciled with the fact that evolution favors dispositions toward egoistic behavior which supports survival and reproduction? Lorenz[16] answered that altruistic behavior could evolve to some extent because it serves not the individual but the group, or even the species. It was criticized because, in terms of causal analysis, selection primarily affects individual carriers of genes, not groups or even species. In a cooperative group mutants causing an individual to defect would endow this individual with selective advantages for reproduction; therefore, it is the genetic disposition for defection rather than that for cooperation that is selected for by evolutionary mechanisms. Nevertheless, there are some forms of cooperation and altruism that can be explained without reference to group selection. This applies to cooperation among relatives[17,18] as well as to „reciprocal altruism„[19] with cooperation at one time being reciprocated by cooperation in the future.

Subsequently, however, these valuable concepts became dogmatized and extended by some in an rather extreme manner, particularly by the notion of the "selfish gene".[20] It was claimed that it was generally not individuals but individual genes favoring reproductive success that were selected for. The argument does indeed hold in cases in which an individual gene actually has one distinct effect on which selection operates. However, most genes serve several functions and most functions depend on several genes, their interaction usually not being additive; the explanation then requires more integrative approaches than are allowed for by the reductionist versions of the selfish gene hypothesis, eventually paying attention to gene complexes, the genome as a whole, and even populations as a whole.

In these and other respects, we are experiencing a refreshing de-dogmatization of sociobiological issues. Even group selection is no longer dogmatically excluded, and there is by now an increasing emphasis on central behavioral dispositions, on motives applying to wide ranges of situations.[21,22] In accordance with evolutionary principles, they are thought to have evolved in the direction of sustaining reproductive success. However, since these psychic dispositions are fairly general, they allow for a much wider spectrum of cooperative behavior than previously suspected, even if they do not actually increase reproductive success of the individual carrier of the genes under all circumstances.[21,22] In particular, such general dispositions are consistent with "friendly" traits of cooperativity within the group, including reconciliation following quarrels and fights, not only in groups of humans but also among nonhuman primates.[23]

An even greater challenge for systems theoretical approaches is the interaction between genetics and culture as it was, most likely, an important factor in late stages of human evolution that led to the emergence of modern man some 100 000 years ago. Thereafter, since at least 40 000 years, accelerated cultural dynamics prevailed over genetic change, leading to elaborated features of differentiated human societies that are still based on, but no longer reducible to principles of sociobiology.

6. Systems theory: the integration of bottom-up and top-down approaches

The examples refering to development, strategic behavior and social cooperation show a similar historical sequence of prevailing lines of scientific thoughts in various fields of biology: top-down notions starting from biological phenomena are followed by predominantly bottom-up explanations based on elementary components and their interactions. After a phase of success, reductionist ideas tended to exclude problems that did not lend themselves to such reduction; criticism of such exclusion, in turn, elicited a new emphasis on more reflective, integrative approaches. The historical record suggests that scientific explanations eventually require bottom-up *and* top-down directions to meet somewhere for integration. Formerly, in fields of biological developmental biology, it was often thought that such such merging is impossible on the basis of known physical laws, that new forces may have to be added to the framework of existing physics, or that holistic principles, such as purpose or the soul, need to be introduced into biology in a manner that would be inconsistent with physical sciences. However, we now have good reason to think that there is no such inconsistency between component analysis on the basis of physical laws and processes, and scientific explanations of features of biological entities and processes as a whole; this is a fundamental insight of modern systems theory that I would like to explain briefly.

One aim of science is to understand interesting phenomena by means of a chain of explanations – say from organisms to cells, from cells to molecules, from molecules to atoms – a chain eventually anchored in the basic laws of physics. This, however, is an unidirectional process; it would not be possible to start out with the basic physical laws and nothing else, and then deduce the features of the whole just by meditating on, say, Schrödinger's equations. Rather, explanations of the natural structures and phenomena require holistic conceptualization in the first place, with concepts applying to cells, animals, mammals, heredity and evolution, to mention only a few.

The relation between the whole and its parts, between basic laws and overall features, is best reflected and elucidated in an abstract manner by modern systems theory. Systems of components have properties that the components do not have; to be more precise, properties that are not deducible from the basic features of components, say of atoms and from the rules of interactions between these components – say, between one atom and another - in an algorithmic manner. For systems with linear interactions of components it would be possible to derive a set of solutions ("solutions" of equations implying possible states of a system consisting of many components); then, with knowledge of the limited set of solutions, in principle, all of them can be derived because all are linear combinations of the basic set. However, this type of reductionism only holds if interactions are linear; and most interactions, say, of molecules in the cell, are nonlinear. Even if one knows a thousand solutions for such a nonlinear system, corresponding to possible states, one does *not automatically* know whether a one-thousand-and-first solution exists or what it might look like: there is no algorithm for such deduction. The reasons why the detection and elucidation of possible states of a complex system and its features is not a straightforward process that could be automated, then, are just basic epistomological reasons. This is a process that often requires luck and intuition, and – most essential – it requires a conceptual approach starting from features of the whole: phenomena, classifications, empirical rules applying to living systems.

In even more general terms, we realize that there can be no guarantee of an algorithmic solution for any reasonably well-stated problem; this is in accordance with findings of mathematical decision theory showing that there are questions that are undecidable even in principle, and not only in practice, within a given framework, especially if self-referential features are involved. I consider it a fair guess that such limitations might apply to the psychophysical relation, in that a complete scientific theory of the brain-mind-relation may be impossible in principle and not only in practice[24] – even though all brain processes occur according to the laws of physics. This is not a mainstream view and it has not been confirmed; but what can be safely said is that the existence of an algorithm for decoding brain states with respect to conscious states is not self-evident or guaranteed; it is not a straightforward consequence of scientific rationality.

Most of the interesting problems in biology, however, are expected to be eventually resolvable if bottom-up, molecular studies are combined with top-down systems theoretical thought, with increasing contributions of theoretical, mathematical biology. Is it then adequate to say that holistic biology is 'back on stage'? If, by holistic, we mean the introduction of wholesale principles overriding physical laws and if we introduce overtones of irrationality in this manner, the answer would be 'no'; if we take 'holistic' at face value, as paying primary attention to features of the whole, and let this attention be a determining factor in the design of scientific strategies and programs, the answer will be 'yes'.

7. Remarks on some scenarios for postgenomics

After these epistemological remarks on the relation between the whole and the parts, the scope and limits of algorithmic theories, I would like to come back briefly to the current issues of postgenomics in biology. What do we expect from proteomics, transcriptomics and related programs of systematic, semi-industrialized biological studies with respect to developmental biology? Development consists of a cascade of stages generating different types of cells as well as different structures and substructures. With luck, the patterns of gene expression and their sequential changes and differentiations in course of development may reveal key regulatory molecules, regulatory genes, regulatory hierarchies and combinatorial principles underlying these cascades of development and differentiation. The development of the neural networks poses a particular challenge: How to relate the order of neural connections as far as it is genetically specified to the order of gene regulation. This relation is indirect and not easy to disclose, but it is also basic to our understanding of the genetic basis of brain functions and their evolution. The analysis may be facilitated, with luck, if combinatorial and hierarchical principles are involved,[25] and if pragmatic criteria can be found identifying molecules and genes which are relevant for axonal guidance and targeting in establishing the neural network in the first place. Further, comparisons between different organisms may contribute to a reconstruction of evolutionary processes; this is particularly challenging with respect to brain evolution, for which the fossil record can supply only very sparse information. And there is the question that is most relevant for our self-understanding, namely how humans and their brains have evolved and what characterizes, in genetic and in neurobiological terms, the specifically human brain faculties. Will the comparison of man and chimpanzee or bonobo provide key information? Their genomes differ by about one percent, that is some 30 million nucleotide pairs. Most of them may be meaningless, but some of them must be meaningful, in fact very meaningful indeed for the understanding of our species.

Obviously, there are many important medical aspects of genomics and postgenomics. Generally, systematic data collections on the genes of an organism, their expression and the corresponding proteins, once available, will relieve scientists from much boring work in their pursuit of knowledge. And yet, I am far from being uncritically enthusiastic about the new prospects. It is conceivable within a more negative scenario that we may be overwhelmed by information that we cannot understand; that solutions to the main problems I have mentioned are more elusive than we optimistically expect; and that the risks and temptations inherent in the application of knowledge gained in this way may lead us into dubious and dangerous pathways, such as patenting inventions that we owe more to evolution than to inventors, or medical overdiagnosis, giving rise to anxieties and possible discrimination.

Last but not least, the industrialization of a considerable section of science changes the style of research and might in a way turn out to be detrimental to creativity. There is no denying that there are branches of modern science that require, at an advanced stage, large-scale modes of organization and formalized procedures of evaluation. However, such procedures could be strongly inhibitory to new developments involving relatively few scientists in fields of research outside the mainstream. The pioneering phase of research on electricity in the 18th century up to about 1780 was the work of less than a hundred workers, and the foundations of electromechanics laid in the great period between the discoveries of Coulomb's law (1785) and Faraday's law of induction (1831), was the work of only a few hundred scientists. The pioneering phase revealing the role of nucleic acids as genetic material of organisms in the 1940s again involved less than a hundred, and the foundations of molecular biology in the decade between the discovery of the double helix (1953) and breaking of the genetic code (about 1963) were also essentially the work of only a few hundred scientists. Only since then have thousands and thousands of people working in a large number of newly founded research institutes been involved in elaborating these fields. The almost metaphoric „Silicon Valley" story stands for another development of this general type. All of these beginnings led into large-scale development after the foundations were laid, with far reaching effects on economics, technology and society at large.

In the future, a similar pattern may apply for subfields of science which, almost by definition, we are not able to identify at present. Inhibiting pioneering phases would not have immediately obvious effects, but would be the kiss of death for creative science in the long run. Allowing for them, however, requires types of support based more on the intuition of a few rather than on immediate recognition by their mainstream peers and policy makers. It is all too easy to advocate an emphasis on creativity as long as one allows oneself to be unspecific, so let me be a little more specific: I think a substantial part of scientific funding should be earmarked for the support of individuals pursuing off-mainstream lines of thought, and who seem to be creative according to their *record* and not on the basis of continuous outputs or alleged prospects of proposals according to the often short-sighted and not unbiased fashions of the day. Would Avery‘s centennial discovery of DNA as hereditary material or Perutz' determination of the structure of hemoglobin have been possible in any other circumstances? It is not only patience that is required, it is also necessary to overcome initial resistance among peers to unexpected ways of thinking and to unexpected results; there were preconceptions retarding the discovery of the background radiation in the universe, there was resistance to recognizing that there is an ozone "hole" in the Arctic, and that "blind sight" may result from cortical damage in the human brain. Prevailing rules and procedures may be good for some areas of science, but they could be inhibitory, in the long run, if applied to all of science without reflection.

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