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The concept of fitted systems in biology

I. Introduction

Sooner or later the author of a biological work marvelling at the elegant designs of biological systems will compare the exquisite mutual adaptation of ecologies, populations, organisms, organs, tissues, cells, organelles and macromolecules with the fitting of a gigantic jigsaw puzzle whose intricasies exceed human imagination. But, is the `jigsaw puzzle' just a convenient metaphor, or may we trust so much collective wisdom and take it a bit more literally? Often a piece of truth was hidden in a popular metaphor, and in this article, we try to look more seriously at the question what biological systems and jigsaw puzzles may have in common. In particular, we wish to propose, that jigsaw puzzles that flip from one fitting configuration into another may help us develop the concepts to understand how undirected and accidental perturbations might be translated by genomes into seemingly adaptive mutations.

The definition of `fitted systems' and `fitting'. Jigsaw puzzles are special cases of what may be called `fitted systems'. `Fitted systems' by definition consist of parts that are able to interact with each other within the confines of the systems. Each part has one or more functions that require the presence of the others. Once all parts interact, the entire system is able to generate a particular product over and above the products of the isolated parts. In general, only specific configurations of the parts permit their productive interaction. They may be considered as `fitted for the generation of the system product' or simply as `fitted'.

Every fitted system has to solve two problems,

a. to fit the parts according to the rules of fitting (Fitting-problem), and
b. to select among the different fitting configuration of the parts (i. e. the different `solutions') one that supports the production of the desired product of the system (Selection-problem).

Thus, the major conceptual ingredients of fitted systems are `parts', 'interactions', `product of the system', `configuration of the parts' and 'adequacy of a configuration for the generation of the product'.

The term `fitting' is ambiguous because it may mean both a process and an endproduct. *We define as fitting process the successive placement of parts within the confines of the system, that leaves the maximal number of options for the placement of the remaining parts.* The definition describes the fitting process independently of any products of the parts, although `placement' may be understood in a spatial or a functional sense.

II. The Application of the Concept of Fitted Systems to Biological Systems

We wish to consider the existing biological systems as fitted systems in the following sense:

a. In the past times of their variation, these systems changed by applications of fitting strategies of their parts.
b. The various solutions of these fitting strategies were exposed to natural selection.
c. Todays biological systems are the survivors of this procedure, and hence exist in one of the fitting, productive configurations of their parts.

However, before we can compare biological systems with jigsaw puzzles or other fitted systems we must consider in greater detail the requirements that jigsaw puzzles would have to fulfil in order to qualify as candidates for the application to biological systems.

II.1 Demands on jigsaw puzzles as models for biological systems

Biological systems such as ecologies, organisms, cells and even genomes consist of different parts such as different animal populations, different organs, different cells, different organdies etc. Each part may exist in several identical (or almost identical) copies. For example, an ecology may contain several different antnests, an organism may contain two gills or lungs, a liver may contain many hepatocytes etc. Nevertheless, the different copies remain distinguishable, if only by their location. No matter what system we consider, we can at least give identical copies different names. Therefore, we may assume without loss of generality that no two parts of the desired example jigsaw puzzle may be identical. All parts are assumed to be individuals.

The biological systems of our daily experience consist of sometimes large, yet always finite numbers of different parts. The number of populations within an ecology is finite, the number of cells within an organ is fi-

nite and so forth. Yet, in contrast to normal jigsaw puzzles frequently each part consists of a finite number of subparts and each subpart consist of yet other finitely many subparts and so forth. For example, each population within an ecology contains a finite number of organisms, each cell of an organ contains finitely many organelles and so forth. In other words, the parts of the desired example puzzle should be fitted systems of their subparts themselves.

The last conclusion seems to lead to an infinite regress of the structure of parts and subparts eventually turning fitted systems and the desired jigsaw puzzle into fractal objects. In contrast, the hierarchy (or heterarchy) of biological systems seems to lead to a lower limit of structure. For example, we can pursue the hierarchy of fitted organziation of cells from organelles to macromolecules down to the level of amino acids, but we must draw the line somewhere and consider certain subparts as fundamental and no longer decomposable into biologically meaningful sub-subparts. Still, there is no conflict between this property of biological systems and the postulate of the existence of fitted subparts of the parts. At the `lowest' level of the hierarchy of a fitted system the postulate is fulfilled in a trivial sense: Every part is its own single subpart. Therefore, one may maintain the above demand that each part of the desired example puzzle should be a fitted puzzle of subparts, i. e. to be a fractal object.

In biological systems each part can exist in several functional modes. For example, a herd within an ecology may be migrating or grasing, lungs within an organism by be aerated or not, and so forth. Therefore, the desired example puzzle must have a similar property.

The different parts of biological systems and their modes are often generated by combinations of a set of basic elements. For example, the basic body designs of different vertebrates of an ecology are variations of different combinations of a few basic shapes of bones, the different organs of an organism are combinations of five basic tissues, and the different parts of DNA are combinations of four basepairs. A related property must be fulfilled to be the desired example puzzle.

A major limitation of the metaphor of the jigsaw puzzle lies in the fact that normal jigsaw puzzles have only one productive configuration (= the configuration of pieces that restore the picture on the puzzle) whereas biological systems such as ecologies, organisms and perhaps even DNA can exist successfully in a multiplicity of configurations. Therefore, the desired sample system must fulfil this property, too. In summary, we obtain the following requirements for a jigsaw puzzle as a model for fitted biological systems.

a. *The jigsaw puzzle should consist of individually different parts.*
b. *The parts should exist in one or more different modes.*
c. *The parts and their modes should be combinations of a simpler set of elements.*
d. *The puzzle should be solvable (i. e. it may be considered as 'productive') in one particular configuration or a multiplicity of different configurations.*
e. *Each part should be a fitted jigsaw puzzle of subparts.*
It is easy to construct model jigsaw puzzles that fulfil these requirements. Therefore, there are jigsaw puzzles that may be taken as more than mere metaphors for biological systems.

II.2 The self-fitting mechanisms

Still, there remains an essential difference between jigsaw puzzles and biological systems. In the case of the jigsaw puzzle the mechanism that fits the pieces together resides in a human brain, i. e. outside the fitted system. In contrast, if we wish to compare biological systems with fitted systems, their putative fitting mechanism must reside within themselves. Therefore, we must examine the minimal requirements of fitting mechanisms and ask whether it is possible to implement them within biological systems. It can be shown that the minimal requirements of a fitted system that enable it to find fitting configurations by itself are the implementations of the following rules.

(A). The system must have a sequential way of trying to fit the next part within its space.

(B). Next, the system needs a detection mechanism to decide whether a piece fits into a partially fitted pattern of the other pieces or not.

(C). Furthermore, the system requires a mechanism to move and replace pieces and change their modes whenever the fitting fails.

(D). Finally, it must choose the replacment pieces and their new modes in a particular, fixed order.

If these four mechanisms are implemented, the system will automatically carry out an effective fitting strategy from within itself.

The possibility to implement an endogenous fitting strategy in biological systems. Is it conceivable that these mechanisms can be implemented in the biological systems that we wish to interpret as fitted systems?

(A). The determination of testlocations. The requirement of a systematic method to select locations within the system in order to test the next pieces does not mean that the system employs some kind of surveillance mechanism to scan the space it occupies. It is sufficient to implement a simple rule to determine the next location where the fitting of a piece is to be tested.

For example, the system fulfils the first requirement if it has a mechanism to make the occupancy of a location the more attractive for its parts, the closer they are to special domains. In this way its parts will sequentially fill up the available space. It seems conceivable to implement such mechanisms in biological systems. For example, in times of variation the special locations of e. g. waterholes in an ecology, blood supply inside an organ, cytoskeletal structures in a cell etc. may provide such graded attraction for the parts of the corresponding biological system.

(B). The detection of fitting. The requirement of a detection mechanism for the fitting of the parts is fulfilled if `non-fitting' i. e. non-productive, detrimental or lethal configurations and actions of parts lead to the paralysis, disassembly, or even elimination of the system directly or indirectly by malfunctioning. Such mechanisms seem to be present in all biological systems.

(C). The remodelling upon a failure to fit. It is more than obvious that biological systems are able to move, replace or change the modes of their parts by endogenous mechanisms at various times. The third requirement, however, demands more than the possibility to move and modify parts. During times of variation the parts must begin to move and become modified if they fail to fit. Or, equivalently, the third requirement demands that the parts are unstable, are continuously exchanged and undergo modifications *until* they fit into an existing larger pattern of parts. Afterwards, they become stabilized by the condition of fitting. For example, the inclusion into a fitting configuration may shelter the parts from the attack of destructive exogenous and endogenous mechanisms. It seems that there are numerous cases of mutual stabilization of the components of biological systems by the formation of fitting configurations. In the case of ecologies, such mutual stabilization and protection seems to exist in symbioses of component populations, in the case of organs and tissues one may think of the trophic and functional interdependence for the differentiation of various tissues, and so forth.

(D). The built-in order of remodelling. The really crucial requirement is the fourth. It demands that the system adheres to an arbitrary, but rigid order in the replacement and testing of parts and modes during times of its variation.

Before we try to answer the question whether such a fixed replacement-and-change hierarchy of the parts of a biological system is conceivable, let us reformulate it. One of the properties of fitted systems is, that their parts P_S are fitted systems of subparts p,. Consequently, the mechanisms of the replacement and changes of the parts $P_a, P_b, \ldots, \mathbf{P}_1$ of a fitted system is also a mechanism by which their subparts p, disassemble and reassemble into new, fitting configurations $P_{,n}, P_f, \ldots, \mathbf{P}_Z$. Hence, if the sub-

parts P_t follow a certain hierarchy of replacements, so will the resulting new fitting configurations P_x. More biologically speaking, if the changes and replacements of the parts of a cell's DNA follow a fixed, built-in hierarchy, then this hierarchy automatically creates a certain hierarchy of replacements and changes of parts on all higher levels of biological organization such as macromolecular oligomers, cytoskeletal polymers and organelles, cells, tissues, organs and so forth.

Thus we arrive ultimately at the following formulation of the crucial question: Is there a built-in, fixed hierarchy of replacement and change of the parts of DNA?

At the present time we cannot answer this question because the necessary data are not available. However, there are at least several examples of genomic mechanisms that influence the order of genomic actions such as transpositions in which the order of genes is rearranged as a whole leading to a new functional arrangement, and the existence of clusters of homeotic genes in Drosophila which seem to determine the developmental fate of certain segments of the embryo as a whole leading to a new functional organism.

`Spotty' fitted system. If a fitted system fulfils the four requirements (A) — (D) it may change its functional configurations one after another until all possibilities are exhausted. Most importantly, the system is then able to search for fitting configurations of its parts from within itself.

In the real situation of biological system that undergoes variation there may be no need and no time to generate all possible subsequent configurations. In other words, the four requirements may be too stringent for real applications to biology because they guarantee that the system finds *all* solutions that are not yet tried, whereas it may be quite sufficient in times of variation to find several new and a few old ones and to subject them to natural selection. But which requirements may be relaxed if we no longer require to find systematically all possible solutions of the fitted system? Requirements (B) and (C) are indispensible, i. e. the system must retain a detection system for fitting of parts and remodel itself upon non-fitting conditions. However, requirements (A) and (D) can be relaxed. If we want no more than a few new solutions, there is no need to attach new pieces in a particularly systematic way to the cluster of already fitted ones. As long as the new pieces remain in contact with the already fitted pieces, new solutions can be found. Therefore, requirement (A) can be relaxed. Neither is it necessary to replace non-fitting pieces in a fixed, built-in order, i. e. requirement (D) may be relaxed as well.

In other words, if we give up the demand that the fitting mechanisms of a fitted biological system must find sequentially *all* solutions, we may re-

place the requirements A and D with the less stringent requirements A' and D':

(A'). The system must try to fit a new piece in contact with the already fitted pieces.

(D'). Upon non-fitting conditions, the system must choose a new piece for the next test and not try the same piece in the same place and mode again.

Fitted systems that fulfil the less stringent requirements may be called `spotty' fitted systems because they do not carry out an exhaustive search for all possible solutions. Obviously, it is easier to imagine that biological systems fulfil the less stringent conditions and, thus are spotty fitted systems. Indeed, there may be no rigorously fitted systems among biological systems, and all of them may be more or less `spotty'. This relaxation of the conditions basically increases the number of acceptable solutions of the fitting problem, but by no means turns the system into a random or arbitrary conglomerate of its parts.

II.3 The stability of solutions

Another important aspect of the comparison between fitted systems and biological systems are their mechanisms of stabilisation of the parts. Fitted systems seem to require several different types of stabilizing mechanisms.

Stabilization during assembly. During the fitting process fitted systems are particularly vulnerable to perturbations. As long as not all the parts are connected and interlocking, the fitting mechanism must be able to remove the last fitted piece. Consequently, the pieces must bei connected rather losely' in a mechanical and/or functional sense. On the other hand, the cluster of already fitted parts must not fall apart or self-destruct while the fitting mechanism is trying to complete the configuration. Therefore, the temporary connections between the assembling parts must be rather tight.

The contradiction between these two demands on the strength of connections between parts can only be resolved in special cases and by special tuning of the mechanisms involved. Nevertheless, one can think of numerous possible mechanisms. For example, the stabilizing mechanism may take use of gravity pressing the parts together while fine-tuning the compressing forces by repulsive counterforces. In other cases the system may use a type of scaffold during the disassembly and reorganization of its configuration, i. e. an ephermeral and auxiliary structure or function that maintains the connections between the parts until they are completed. In yet other cases, the system may use a certain fine-tunable affinity between the parts in order to keep them together. Considering that

the fitting mechanism assembles quite different configurations of the parts, the stabilizing mechanisms must not favor certain configurations over others, but support all of them equally well. In particular, any affinity between the parts must bei unspecific (i. e. `promiscuous'), or else it would favour the pairings of certain parts over others.

Stabilization after assembly. The probably most important mechanism of stability in fitted systems is derived from the very concept of the fitting of parts. Once the parts are all fitted together, every perturbation of the system must travel from connection to connection and thus reverberate throughout the system to various degrees until it arrives at the outer boundaries. If they are able to withstand the perturbation, so will consequently the entire system. If there is any affinity between different parts it may support this type of stability by strengthening the interlocking of the parts, but it is not a necessary factor.

A mechanical jigsaw puzzle can easily demonstrate how the tight interlocking of parts can create a network of mutual hindrances which prevents the disruption of the pattern, provided it is held in a mechanically tight frame. This type of stability of the solution does not require that the parts are bound together by any kind of attractive forces. Of course, the jigsaw puzzle can only demonstrate the stabilization by interlocking of parts against mechanical perturbations. Still, it may serve as a model to illustrate the stabilization of fitted systems if the parts are functionally interlocking. In the latter case the system is, of course, not stabilized against mechanical perturbations, but against functional perturbations by noise or other perturbing signals.

Restabilization after disassembly. One can map all the configurations of the parts in an abstract configuration space. In this space, every solution of the puzzle is immersed in an `ocean' of conceivable, although non-fitting configurations of the parts. It is possible to introduce a `distance'-function in this abstract space and subsequently distinguish between solutions that are part of a cluster of close neighbors and others where the distance to the nearest solution is large. In the latter case, the fitted system may have to test a very large number of non-fitting configurations of its parts before it arrives at a new one.

If the fitted system concerned is one of the `spotty' systems, i. e. if it does not test configurations entirely systematically its testing methods of configurations acquires an aspect of random trial-and-error methods. In this case the large distance to the next solutions may cause the system to return time and again to its previous solution because it is too unlikely that it finds one of the distant, i. e. very different ones. In this sense, the distance to the next solution may act as a stabilizing factor for spotty fitted systems.

II.4 The concept of a biological fitted system

The basic idea to compare biological systems with fitted systems is expressed in the following assumptions.

a. The biological system consists of individual parts and generates a certain 'product'(= its function)
b. The shapes or/and interactions of the parts of the biological system must be fitted together in a spatial and functional sense in order to be able to make the product
c. There are multiple ways to fit the parts in a productive way, and
d. There is a certain endogenous mechanism that continuously seeks their fitting.

If biological systems can be shown to fulfil these assumptions they may respond to undirected and accidental perturbations in the following way. The perturbations may at first disassemble the system into its parts. Subsequently, under the influence of the fitting mechanism the system may restructure itself into new, yet again fitting configuration. In other words, such variations of the system would preserve its ability to generate certain products by altering many, if not all components in a concerted action. Subsequent natural selected acting upon a population of systems that were altered in this way would not have to eliminate countless unproductive or poorly productive intermediates that differ in `random', isolated properties before a new and better adapted system has evolved. Instead, it would select among comprehensively altered, yet still productive systems. If any of them is better able to deal with the altered environment, it will emerge so quickly as the survivor of the selection process, that the observer may interpret the mutation as rational and adaptive.

The meaning of `fitting' in biological systems

a. The fitting configuration of genomes. We do not know as yet, whether there are conditions of the fitting of genomic configurations. Fitting of genomes would mean that there are criteria that distinguish between legitimate, i. e. functional orders of genomic sequences and non-functional ones. Some of the present knowledge about preferential sites and directions of integration of plasmids and viruses may be interpreted as distinctions between genomes that are fitted or unfitted for the expression of the integrated genes. A further meaning of the term `fitting genome' may be the genomic conditions for the proper selection of genes

that may be active at the same time without inhibiting transcription or replication of others or even damaging the genome.

b. The fitting of a genomic configuration. In the absence of firm criteria for the requirements of fitting genomes, it is even harder to speculate about genomic mechanisms that establish the properly fitting sequences and orders of genes. One may suspect, though, that the mechanisms of deletion, inversion, crossing over, transposition, integration, attachment of centromers and telomeres and similar mechanisms will be part of the set of fitting mechanisms. Consequently, one may view the fitting of genomes as the operation of these and similar mechanisms.

c. The hierarchy and heterarchy of biological organization.

For the sake of illustration let us distinguish between the following levels of biological organization ordered crudely by the ascending average number N_m of macromolecules involved.

Level	N_m
1. DNA	2 (assuming 1 chromosome)
2. macromolecular oligomers	2-100
3. cytoskeletal polymers and organelles	$100\text{-}10^6$
4. cells	10^{13}
5. tissues	10^{20}_{23}
6. organs	10_{26}
7. organisms	10_{29}
8. populations	10_{32}
9. ecologies	10

Each of these levels contains one or several heterarchies of interacting parts that belong to the same level. For example, each tissue is a heterarchy of cells, each organ a heterarchy of tissues, each ecology a heterarchy of populations.

d. The principle mechanisms of fitting on supragenomic levels. Assume that a perturbation of the DNA triggers its built-in fitting mechanism to find new and functional configurations of its parts such as genes, control elements, DNA structuring protein complexes etc. If the individuals carrying these new configurations of DNA parts are able to proliferate they will be subjected to the process of natural selection.

It is possible that the new genomic configurations have no effect beyond the level of the DNA, i. e. they are neutral for the selection process and merely add to the diversity of the gene pool. Alternatively, some or all of the new genomic configurations may have a disruptive impact on

another level of biological organization. Assume, that they have their primary impact on the level of the macromolecular oligomers of the affected cells. Thus a refitting of the functional parts of this level is required which is another way of saying that dysfunctions occur on various levels of biological organization that have their origin in a dysfunction on the level of macromolecular oligomers. They will lead to the destruction of the affected systems, unless a new fitting of parts on the level of macromolecular oligomers is found.

At this point we have to examine closer the mechanisms that determine the oligomeric conformation of cellular macromolecules. They may involve special transcriptional time sequences, ionic co-factors, special amino-acid sequences to ensure certain tertiary structures to generate intermolecular binding surfaces and special affinities and so forth. Some, like the amino-acid sequences, correspond to directly fixed instructions on the genome. Others, like the ionic cofactors, are very indirect consequences of complex genomic determinations involving membrane structures, ionic pumps, etc.

As a consequence, the requirement of a new fitting configuration of macromolecules on the level of macromolecular oligomers becomes an additional requirement for those parts of the genome that are directly or indirectly involved in the formation of the oligomers. In other words, it is no longer enough for the genomic fitting mechanism to find any new configuration that work on the genomic level. The new configuration must also involve suitable changes in those parts of the genome that determine directly or indirectly the fitting of macromolecular oligomers.

The necessary changes can be achieved in two ways. The mentioned dysfunctions may cause a `genome shock' such as chromosome breakage, heat shock etc. (The term `genome shock' was coined by Barabara McClintock (1984) in her acceptance speech for the Nobel-prize `The Significance of Responses of the Genome to Challenge' Science 226:792). In this case the genome may enter a new round of disruptions followed by new refittings. Alternatively, the genome may remain in one of several previously refitted configurations. Either way, natural selection is given the opportunity to eliminate all the previously or newly refitted genomic configurations that do not generate, in addition to mere fulfilment of the genomic fitting requirements, a new fitting configuration on the level of macromolecular oligomers.

The effects of the new fitting configuration on the level of macromolecular oligomers may propagate higher up in the biological hierarchy and cause disruptions on the cellular level. For example, the epithelial cells of a vertebrate may suffer a dysfunction of their attachment to basement

membranes in the kidney. Again, we have to distinguish between dysfunctions that offer a target for natural selection and those which remain neutral. In the latter case, the offspring will carry the genes for a perfectly functional variant of kidney architecture, which may become the phylogenetic branching point for a future species that evolved a new kind of vertebrate organ out of this kidney variant.

Alternatively, the animals may be threatened to die of kidney failure. Similar to the previous case, the selectable dysfunction may cause genome shock bye. g. altering the osmotic conditions in the germinal epithelia. Alternatively, no such effect on the germline may occur. But, either way, natural selection will select among the newly refitted genomic configurations one that is not only fitting on the genomic level and on the level of macromolecular oligomers, but also represents a new fitting configuration of cells at least in the kidney.

In similar ways one can discuss the case of disruptions that begin on the genomic level and propagate to higher and higher level of cells, tissues, organs and organisms. In every case, there is either no requirement for a new fitting configuration on a particular level, or this requirement translates into a selective pressure for newly or previously refitted configurations of the genome.

e. The translation of fitting requirements on higher levels of organization down to the level of the genome. It may appear that the above scheme has the following unrealistic implications. Disruptions on the genome level require a handful of newly fitted genomic configurations for natural selection to find a suitable variant. Disruptions on higher levels require much larger numbers of newly refitted genomic configurations. Otherwise natural selection may not find a suitable variant to deal with the disruption.

This conclusion is misleading because it assumes that all refitted configurations are equally drastic reorderings of the genome. In reality, however, we have to distinguish among the fitting genomic configurations between `substantially different genomic configurations'. The difference will be defined further below in the section on pseudo-phylogenetic trees of fitting configurations. But it is intuitively clear that some fitting configurations differ only by exchanges of a minority of parts, whereas others represent major rearrangements of most of their parts.

In the following, I should like to propose that *natural selection requires a number of substantially new genomic configurations only to 'fix' disruptions on the genomic level. In contrast, disruptions on higher levels of organization can in most cases be fixed by selecting from a number of more or less subtle variants of already refitted configurations.*

Based on simple combinatorics it follows that the number of possible configurations of parts rises with the level of organization. For example, there are more possible configurations of oligomers than there are genes for monomers, and more possible configurations of polymers than there are possible oligomers and so forth. Accordingly, we can expect that by and large the number of fitting configurations rises with the level of organization as well. (At this point the reader might be reminded of the different use of the terms `high level' and low level' in biological organizations and human social organizations. In biology the `commanding' genomic levels are called `low', whereas in human organizations the commanding levels are called `high'.)

What determines the particular choices of parts during the construction of a fitting configuration on each level? We have to postulate the existence of level-specific selector mechanisms and to distinguish between heritable selector mechanisms and non-heritable ones. Heritable selector mechanisms are supposed to be fixed in the genome. In contrast, non-heritable selector mechanisms are invoked if e. g. development accidents determined the particular configuration of the parts on a particular level. In the present context we are only interested in the heritable selector mechanisms.

If a disruption on the genomic level triggers the refitting of the fitted system in heritable ways, a larger number of genetic changes have to occur than in the case of a disruption on a higher level. The reason is that the genetic fixation of refitting on a particular level requires at least the genetic fixation of the new genomic configuration together with the selector choices on all higher levels.

It seems possible, to record genetically the choices of the selector mechanisms by slight variations of the fitted genomic configuration itself.

When it comes to the establishment and genetic fixation of fitting configurations of groups, populations and ecologies we can expect that much more indirect genomic influences will play the decisive roles. Non-fitting configurations on the supraorganismal levels may impose selective pressures on their parts by generating deprivation, stress and similar influences on the individual. The stress, in turn, may trigger the generation of subtle variations of refitted genomic configurations which survive better, if they lead to better fitted supra-organismal configurations of parts and thus reduce selective pressure and stress.

A tacid assumption of the above remarks was that the postulated fitting mechanisms were activated only in response to stress, genome shock or similar influences that can operate on a certain level of organization and on the genomic level as well. It is conceivable, though, that genomes and

parts on other levels are continuously disassembled and refitted by built-in mechanisms. Some of the well-known turn-over mechanisms on various levels of biological organization may be compatible with the latter model of fitting mechanisms. If continuous disassembly-and-refitting were common mechanisms of biological systems their response time to shocks might be shorter than in the case of stress that has to first trigger disassembly mechanisms before a refitting can take place.

III. Basic Properties of Fitted Systems

III.1 The disruptive rearrangements of fitted systems

A most fundamental feature of fitted systems is the impossibility to change one fitting configuration gradually into another. The very concept of fitting implies that there is no spare room in the fitted configuration of the system. Consequently, no piece can be moved to another location without initiating a chain-reaction of other pieces pushing yet others out of their places. In that sense, every change of the solutions of fitted systems is not gradual but discontinuous. During the rearrangements of the various pieces, their productive interactions are likely to be disrupted and can only be resumed after a new fitting configuration is reached. Therefore, one may consider the changes of fitted systems as shocks or catastrophes for the function of the system.

Still, the rearrangement of a fitted configuration into a new one does not necessarily involve all parts. One may try to regard transitions between two fitting configurations that need the exchange of only two or three pieces as `gradual'. It would, however, be entirely misleading. Counting all possible configurations of the parts it is easy to show that the fitting ones are almost neglegible minority. In the case of a model system of 12 parts and no more than eight orientations there are some 3×10^{13} possible configurations for each fitting one. In other words, each solution is a completely isolated island in an ocean of non-solutions. Even solutions with many common pieces are separated by many non-fitting configurations and, therefore, not connectable by gradual changes.

III.2 The pseudo-phylogenetic tree of solutions

The varying numbers of pieces that have to be moved in order to turn one solution into another offer a natural possibility to define close or far 'relatives' of a solution: The more pieces two solutions have in the same location and mode, the closer relatives they may be called. Inevitably, therefore, the solutions of a fitted system can be arranged in some kind of a schematic that looks like a phylogenetic tree. To be sure, the construction of such a pseudo-phylogenetic tree is ambiguous because there are several ways of defining communalities between solutions. But, regardless what convention one uses, there will always be solutions that are more similar to a particular one than others. Accordingly, close relatives may be considered as `subtle variations' whereas remote relatives may be regarded as `substantially different configurations' of a given solution.

Yet, despite the similarity of this graph with a phylogenetic tree, we must not conclude that the solutions arose by a mechanism of Darwinian evolution. The result poses a warning to our analysis of the evolution of biological systems. If they represent solutions for fitting configurations of their parts, and we have no proof that they do, the possibility to set up phylogenetic trees by virtue of similarities is not ground enough to argue that they are relatives by virtue of natural selection.

Of course, evolutionary biologists are aware of this danger, because there is the well-known phenomenon of convergence. Convergence may arise quite naturally among the solutions of fitted systems. If the fitting mechanism leaves too few alternatives, then solutions with common features may arise **in** entirely different branches of the pseudo-phylogenetic tree.

Therefore, the concept of fitted systems, if indeed it applies to biological systems, may offer general reasons for caution in the identification of relatives: Several independently evolved organisms may appear related (i. e. they may have similar phenotypes, or stretches of genomic sequences), not because they are related, but because the fitting mechanisms of genomes at the times of their variation did not permit sufficiently different alternative solutions as fitting configuration of the parts.

Fitted systems may also offer another aspect to the famous problem of the `missing links' in the fossil records of several evolutionary trees. Commonly the absence of fossil links between certain known fossils is explained by the assumption that the intermediary forms were too rare to leave enough fossils for us to find. If we consider the concept of fitted systems there may be another reason: There may never have been an intermediary form, because the fitting mechanisms of the genome could not create it, despite our naive expectation that a link should have been possible.

III.3 Absence of general fitting algorithms. A conjecture

In many years of studying fitting problems with the aid of a model system I found one experience more educational than any other. It was my failure to find an algorithm to construct solutions. By algorithm, I mean a set of rules that prescribe the choice and placement of the n + 1" part after having fitted n parts in order to arrive at a solution.

Of course, there is always the trivial algorithm that consists of

1. a list of the completed solutions and
2. the single rule: "After having fitted n parts, look up the next part in the list of solutions."

But is there a non-trivial algorithm to construct solutions? For reasons too elaborate to explain here, I doubt that they exist in general. This result would have important consequences for our understanding of biological systems, provided they can be regarded as fitted systems. It would mean that the mechanisms of variation are fundamentally neither random nor algorithmic.

That would leave us rather unprepared to deal with fitted systems because our experience with normal physical systems is quite the opposite. In their case, it is precisely the local interactions of the parts and the external boundary conditions that determine uniquely the solutions of their describing equations.

One of the reasons for the discrepancy between ordinary physical systems and fitted systems may be the fact, that the solutions of fitted systems seem to depend predominantly but not exclusively on the configurations of many parts that do not necessarily contact each other. Perhaps, one may call this configuration the `context' which each part has to accept from all the others. Therefore, fitted systems may challenge us to face again and in a new way the problem of `context' that is still unsolved in many areas of the natural sciences and the humanities.

Another reason that we seem relatively unprepared to deal with fitted systems may be our tendency to think of structures and functions as the result of certain generative processes. In contrast, a small group of three or four already fitted parts do not produce anything to promote the solution, but rather pose increasing steric hindrances for the subsequent parts. In this sense, the solutions of fitted systems are not the results of a production process but the survivors of an exclusion and elimination process of options for others for which we have little scientific experience.

IV Conclusions

IV.1 Advantages of the concept of fitted systems for the analysis of biological systems

In summary, one may say that the major attraction that fitted systems may offer to the analysis of biological systems is the possibility to unify under one concept such diverse features of biological systems as the following.

a. The exquisite fitting of their parts, subparts, sub-subparts, and so forth down to the level of small molecules.
b. The existence of phylogenetic trees.
c. The apparent `leaps' within an evolutionary chain from one perfectly functional system to another.
d. The existence of convergence despite an apparent abundancy of alternate paths of evolution.
e. The continuous replacement of parts (turn-over) within every level of the system, even if wear and degenerations are not apparent.
f. The self-stabilization of parts in a functional configuration which may decay rapidly after their isolation from the system.
g. The possibility that catastrophe-like perturbations of a system do not necessarily destroy it, but may lead to an evolutionary change in essential ways. In contrast, sufficiently small perturbations of the system always seem to be ineffective for evolutionary changes, because they are neutralized by built-in homoeostatic mechanisms.
h. The generation of highly specific configurations of the parts despite a frequently observed unspecific and `promiscuous' interaction between any pair of parts.

IV.2 Which experiments can test whether genomes are fitted systems?

Using the above lines of reasoning we can conclude that if biological systems are fitted systems, then the genomes of evolutionarily related organisms represent essentially different configurations of basic genes or groups of genes, and subtle variations of postulated `selector' genes, and that genome shock induces a change of fitting configurations of distinct genomic parts to generate new individuals for the subsequent process of natural selection. Therefore, the experimental test of the concept has to examine the following questions.

1. Do selector-genes exist, i. e. genes that decide on the genome level which of several possible variants which differ on some high level of organization a system will express?

2. Is there a classification method for genome parts, including a method to distinguish between essential and unessential parts by which the genomes of evolutionary related species can be interpreted as different configurations of representatives of the different classes?
3. Are there fitting requirements for the configurations of members from these classes? In other words, when mechanisms such as crossing over, transposition or integration of plasmids and viruses generate new orders of genome parts, is it possible to characterize sets of orders that lead to lethal mutations and others that survive even before exogenous selective pressures can act?
4. Is it possible to show that genome shock initiates the re-ordering of the genome parts? If one could monitor over time the genomic configurations of all systems which responded to a shock (including the mutations that will turn out later to be lethal), would it be possible to observe one or several waves of reorderings of genome parts until survival or extinction of the variants is decided?
5. Are functional genomes undergoing continuous changes of configurations of their parts particularly during development regardless of the absence or presence of shocks?
6. Is it possible to demonstrate that genome parts derive stability from membership in a certain configuration, whereas they are disassembled and destroyed in other configurations or in isolation?
7. The perhaps most important test would be a test whether and to what extent the rules (A) — (D) are implemented in genomes. In particular one would have to test.
   a. whether the manipulation of the order of genes which is likely to produce non-fitting configurations leads automatically to a self-reordering of the affected genome,
   b. whether there is a sequential order in which shocked genomes exchange parts,
   c. whether there are preferential domains of the genome which seem to be the nucleation center of changes of genomic configurations.

Depending on the outcome of these tests, the concept of fitted systems may deserve further development into greater details.