Hierarchical functional organization of formal biological systems: a dynamical approach.
I. The increase of complexity by self-association increases the domain of stability of a biological system

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SUMMARY

In this series of papers, a theory of functional organization is proposed for biological systems (formal biological system, FBS), which is based on the concept of 'functional interaction', and on a 'functional self-association hypothesis'. From the specific properties of functional interactions, i.e. non-symmetry, non-locality, and non-instantaneity, it is shown that a biological system can be considered as constituted by two hierarchical systems: (i) the (O-FBS) that describes the topology of the FBS, i.e. the functional organization, with a hierarchical directed graph; (ii) the (D-FBS) that describes the continuous non-linear dynamics of the FBS with a field. In the framework of this theory, the problem of the relation between structure and function is considered to be due to the distinction between structural organization and functional organization.

Some advantages of this approach are: (i) the description of the time evolution, during development, of the organization of an FBS with an optimum principle, which leads to a clear comparison with a
physical system (paper II); (ii) the description of the space–time dynamics as the variation in space and time of field variables in a hierarchical ‘space of structural units’; and, consequently, the relation between topology and geometry, and the existence of non-locality in these hierarchical spaces (paper III).

In this paper, the basic concepts of functional interaction, hierarchical functional organization, and physiological function are discussed from a mathematical viewpoint, and arguments for the validity of the self-association hypothesis are given. Specifically, it is shown that, for a particular class of biological systems that are taken as an example, the domain of stability of the (d-fbs) is increased after functional association. This property, which is specifically due to the nature of the biological system, corresponds to an increase in complexity. It will be shown in the second paper that such a self-organization corresponds also to an optimal principle for the (o-fbs). The case of real biological systems (wbs) is considered in relation with the present theory, which leads to a new hierarchical representation in terms of fields. Such representation could be a base for integrative physiology. As an example, some physiological functions, respiratory and cardio-vascular, are considered and it is shown that the heart shock emerges from the formulation as a cyclic sub-graph.

NOTATIONS AND SYMBOLS

\[ a \] rate constant of the transformations between classes
\[ a_j \] number of elements of \( E_j \)
\[ g(P, P'_1) \] transport function
\[ k(P), k'(P), k''(P) \] coupling parameters
\[ k_0 \] coupling parameter between both levels of organization (M) and (U)
\[ \langle n_i^{(j)} \rangle_{n_i = 1, \mu} \] distribution of functional links between structural units at this level:
defines the functional organization
\[ r_0 \] space coordinate
\[ r \] maximal degree of organization
\[ u, u_i, u_j \] structural units
\[ u^* \] 'pathological' structural unit having a missing product
\[ u_i \equiv (u_1, u_2, \ldots, u_{d_i}) \] associated structural units
\[ E_j \] enzyme
\[ E_{w_j} \] class of elements in the compartmental theory
\[ E_{w_j} \] describes input \( (E_{w_j} > 0) \) or outputs \( (E_{w_j} < 0) \) for elements of \( E_j \)
\[ F \] hierarchical system
\[ F(L) \] elementary physiological function:
defines the level of organization \( (L) \)
\[ F_{ij} \] number of elementary transformations per time unit
from a class \( E_i \) to a class \( E_j \)
\[ F_{ij} \] number of elementary transformations per time unit
between the environment
\[ G \] graph of the functional organization
\[ (L) \] level of organization
\[ M \] matrix of the functional organization
\[ N \] occupation number of the classes
\[ N_{ij} \] representation
\[ P_{a_j} \] number of elements in a class \( E_j \)
\[ P_{a_j} \] products in a structural unit
\[ P_{a_j}^* \] denotes an \( \alpha \) product synthesized in the
\[ i \text{-unit} u_i \]
\[ P_1, P_2 \] products in the biochemical pathway: \( P_1 \in u_1, P_2^* \in u_2^* \)
\[ S^{(l)} \] biological sub-system at level \( l \)
\[ S_i \] substrate
\[ T_0 \] time coordinate
\[ T \] timescale at level 1
\[ U_j \] population of elements \( u_j \) each containing \( j \) units
\[ X \] [mRNA] concentration of RNA messenger
\[ x_i, x_1, x_2, \ldots, x_n \] rate constants of the chemical reactions
\[ \beta(P) - P'_1 \] simple passive diffusion factor
\[ \Phi(\psi, \psi) \] transformations that describe the functional interaction
\[ P_2 = \Phi(P_1) = \phi(\psi(P_1)) \]
\[ \kappa = y / \beta \] allostERIC factor
\[ \lambda \] dilution factor
\[ \nu \] degree of functional organization at level 1
\[ \langle \psi, \rho \rangle \] representation
\[ \psi_{\lambda \nu}^1 \] functional interaction \( \lambda \epsilon \) from the \( i \)- to the
\[ j \text{-unit} \]
\[ \psi_{\lambda \nu}^1 \] functional interaction in the epigenetic system
\[ \lambda \] between a normal and a pathological unit
\[ \rho \] geometrical parameter of the biological system;
specifically: stoichiometry in the Goodwin model
\[ \zeta = (\alpha_{x_2} x_2 x_2)^{1/4}, t^* = \xi, b_1 = \alpha_{x_2} / \zeta, b_2 = \alpha_{x_2} / \zeta, b_{1+2} = \alpha_{x_2} / \zeta, i = 1, 2 \] state variables for the dimensionless problem.

1. INTRODUCTION: SOME REQUISITES FOR AN INTEGRATIVE PHYSIOLOGY

The objective in this series of papers is to introduce some concepts and definitions that will lead to realistic and formalized properties for the functional organization of a physiological system in terms of a new concept, the 'functional interaction'. As a consequence, biological systems are shown to be driven by specific criteria of evolution that are different from those that are found for physical systems.

Many authors have discussed biological organization from various points of view, based on a well-established mathematical or physical theory. Thom (1972), with his catastrophe theory based on qualitative dynamics, conceived a theory of morphogenesis, which was extended by Zeeman (1977); Frigogine and
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associates developed a theory of structural self-organization based on the principles of thermodynamics of irreversible processes (Nicolis & Prigogine 1977; Prigogine 1972); structural pattern forming including the mechanochemical approach to morphogenesis was investigated by Oster et al. (1983) and Murray & Oster (1984a,b); Eigen (Eigen 1971; Eigen & Schuster 1979) applied neo-Darwinian principles to macromolecular self-organization. Other types of formalisms also have been used extensively: transformation systems (Delattre 1971), compartmental analysis (Conrad 1972; Walter 1980, 1983), general and hierarchical systems (Arbib 1972; Pattee 1970), automation theory (Kaufman 1985), graph theory (Rashevsky 1961; Rosen 1958; Levins 1970), graph theory for neural networks (von Foerster 1967; Hopfield 1982), information theory (Atlan 1972), and statistical mechanics (Demetrius 1984).

Although structure and function appear to be non-dissociable, because a biological function cannot be conceived without a structure to support it, the formalization of a functional organization will be shown to involve hierarchical systems that do not necessarily coincide with the corresponding structural systems. Epistemologists have put forth definitions for structure and function that are difficult to formalize within a self-coherent theory. The point of view of mathematical biologists, e.g. Rashevsky (1961), often addresses the topological nature of biological systems. Although the topological description seems near to the idea of a set of relations between elements of a system, the principles that underlie its origin have to be found to answer the following questions: how does a functional organization evolve? Does there exist a minimal number of hypotheses that could explain its behaviour? What is a physiological function?

Physical systems at any level of description are described by their structure, i.e. a combination of structural interactions, the forces, between elements of matter. Physical laws specify how the stability of this set of elements results. Similarly, biological systems are constituted in elements of matter, and therefore, they satisfy those physical laws. But, as physiological systems, they possess specific properties. Because each substructure acts at a distance on another substructure, it is shown that functional interactions exist between any substructures in the physiological system, which play the role of forces in physical systems. Functional interactions have three specific properties, non-symmetry, non-locality, and non-instantaneity, which give their own unique characteristics to biological systems. Because in terms of functional interactions, the observed functional organization has to be a stable combination of these interactions, a first problem is to study the conditions of stability of the functional organization; a second problem is to determine what could be a criterion of organization, and ultimately what could be a general principle of evolution of such a biological system.

In this series of papers, some advantages of the representation in terms of functional interactions will be shown for various fields of biology. It is my aim to show that one realistic and simple hypothesis, the so-called ‘functional self-association’ hypothesis, leads to some useful properties in physiology and physiopathology. The reason why this hypothesis is useful is because concepts, definitions, and properties once developed on the basis of this hypothesis, lets us express the stability of the physiological function as the stability of the corresponding hierarchical system under the following circumstances: (i) for an n-level biological system, when a condition of conservation of the number of substructures is assumed: in this paper, an example is given in the form of an evolutionary ‘Eigen–Goodwin’ model, which shows that increasing the complexity of its dynamics by self-association of structural units leads to an increase in the domain of stability of the dynamics; (ii) when the variational aspect of the set of functional interactions between the substructures of the biological system is studied as a problem of topological stability, which leads to an optimal principle (paper II); and (iii) when the set of dynamical processes that are associated with the functional interactions are conceived as field variables that evolve under the action of field operators in particular spaces, called ‘spaces of units’ (paper III).

These problems and a possible solution have been presented in preliminary form in Chauvet (1987, 1990), together with various examples. Because the application of these concepts and definitions in the area of general physiology are important to create an integrative physiology, a short discussion for the study of real biological systems will be given in relation to parallel computers, and their simulation as parallel hierarchical systems.

2. CONCEPT OF FUNCTIONAL INTERACTION

(a) Definitions: formal biological systems and functional interaction

Well-defined biological systems, called here ‘formal biological systems’ (FBSs), will be studied first. FBSs are defined as closely as possible to real biological systems. Two basic biological features, referred to as ‘mutational’ and ‘equipotent’, characterize an FBS at its lowest level and determine its construction. Mutational means the possibility of mutation in the macro-molecular apparatus, and equipotent means that the same potentialities of gene expression exist in all cells during their lifetime. The nature of equipotency between units in a level of organization has a particular deep meaning, because systems with such a property are potentially able to elicit a particular functional organization under some biological constraints. Then, as will be shown, the formalized approach for a description of functional organization based on equipotency of lowest structures can lead to variational principles (paper II). The relation between these properties and those observed in ‘real biological systems’ (RBSs) will be discussed in the conclusion. In particular, we will have subsequently to verify whether properties that describe an FBS, correspond to an RBS.

A very common fact in biology is the action of a
Figure 1. $\psi_{ij}^\alpha$ is an interaction between two structural units $u_i$ and $u_j$, and is called an elementary function. It can be identified by the product $P_{ij} = \psi_{ij}^\alpha(P_{\alpha,i},P_{\alpha,j})$, which is created after the interaction. In fact, the set of $P_{\alpha,i}$ for all $j$ gives $P_{\alpha}$ which is the elementary function expressed by $P_{\alpha,j}$ and which defines a level of organization denoted as $k$.

structure on another structure. For example, one neuron emits an action potential which propagates along the axon, releases a presynaptic transmitter, and modifies the soma potential of a postsynaptic neuron, which, in turn, will transform the soma potential of other connected neurons. Endocrine cells synthesize a molecule which is carried through the blood flow, and which acts on another cell. During development, molecular signals are emitted by cells to inform others about their location in the tissue. Communications exist between all the structures in organisms, either in the form of a molecule, a quantity of matter, or even a non-observable parameter. In each case, a functional interaction is described as the transport, with a finite velocity, of an activating or an inhibiting signal between a source, which emits, and a sink, which receives. Then, a combination of these functional interactions constitutes a biological system, and the dynamics of this system can be called a physiological (or biological) function in the given organization. From a mathematical point of view:

1. A functional interaction is defined by two elements, noted $u_i$ and $u_j$, and a signal $\psi_{ij}$. One of the units, the $i$-unit, acts upon the $j$-unit, by emitting 'something', a signal, that reacts with the elements of the $j$-unit. Such a signal will be called an elementary physiological function (more simply, an elementary function) and is represented by $\psi_{ij}$ (figure 1).

2. A structural unit is defined as a structural equivalence class, that contains only elements whose physico-anatomical structural properties are identical.

Then the system is driven by equations such as:

$$d\psi_{ij}/dt = f_{ij}(\psi_{11},\psi_{12}, \ldots, \psi_{ii},\rho_{11},\rho_{12}, \ldots, \rho_k)$$

where the $\rho$s are specific geometrical or physical parameters. This new representation of a biological system will be denoted by $(\psi,\rho)$.

(b) Specific properties of a functional interaction

Three properties of the functional interaction constitute the unique specificity of a biological system: the non-symmetry, non-locality, and non-instantaneity.

Non-symmetry, because an elementary function acts from one structural unit to another, from one source to the sinks, but not from one sink to the sources: the signal is transformed in the source before being emitted. Then, an elementary function represents a non-symmetric, unidirectional action, because the same molecule (or the same signal) will not directly feed back from the sink to the source. Thus, the operator that describes the dynamics of the elementary function will be non-symmetric.

Non-locality, because an elementary function acts at a distance, and creates couplings between distant structures. This property comes from the extension of biological structures in physical space: two sources can be infinitesimally close in the sense of a continuous density, but the corresponding sinks can be very far because of their extended structure in cartesian space. That is the case of a motoneuron, whose cell body is located in the spinal cord, and its axon in the sciatic nerve that acts on the leg muscles. Because the transport of this interaction, neural activity, occurs in the continuous space of one neuron, say with a finite velocity $v_\text{neu}$ and not in the continuous space of neurons reduced to points, what we see at time $T_0$ and at point $r_0$ in the space of the real neurons is what was emitted at time $T_1 = T_0 - d/v_\text{neu}$ by neurons that are located at $r_1$ where $d = ||r_1 - r_0||$ (figure 2). This non-local property, which expresses the coupling of biological substrutures at a distance, is very general, and is the consequence of the division of the system into several levels of organization (Chauvet 1993). To describe this fundamental property of biological systems, the interaction operator that describes the dynamics will have to be non-local.

If the velocity of the transport of an elementary function is finite, then there is non-instantaneity of both emission by the source and reception by the sink, and, as described above, this property implies non-locality. This implies delays in the formulation, as well as non-symmetry and non-locality, and is at the root of important properties for biological systems that will be explored in paper III.

3. FUNCTIONAL INTERACTION BREAKING: CONSEQUENCES ON THE STABILITY OF BIOLOGICAL SYSTEMS

(a) Functional interaction breaking: death or life

(i) The choice

What happens when an interaction in a functional organization is suppressed because of internal constraints, e.g. mutations at the genetic level, or external constraints, e.g. the presence or absence of food at the metabolic level? If the functional interaction under consideration is vital for the system, with the meaning that the product (the elementary function) which is carried from the source to the sink is necessary for the life of the system, then there are two eventualities for the system: either this product comes from another structural unit in the system, or the system dies. The choice depends on what happens at the lower levels.
of organization, i.e. in each source that makes the product.

For example, within the classical scheme of protein biosynthesis, the repressor is emitted by the regulator gene, and acts on structure genes. There is an elementary function from the source, i.e. the regulator, and the sink, i.e. the structure genes, which can be identified to the RNA messenger. The same analysis can be made for the metabolic pathway:

\[ S_1 \rightarrow S_2 \rightarrow \ldots \rightarrow S_{t-1} \rightarrow S_t \rightarrow \ldots \rightarrow S_n, \]

where an enzyme \( E_n \) which can be identified as an elementary function, acts sequentially on a product \( S_{t-1} \) to create \( S_t \). In this example, \( S_t \) can be the final product of a metabolic pathway. If one enzyme in the chain is suppressed, then the survival of the system implies another pathway, i.e. another elementary function that originates in another structure gene, results in \( S_t \). This kind of substitution is often used at the metabolic level.

Hypothesis I:

If, at a given time, a structural unit does not produce the elementary physiological function (i.e. for example \( P_j \) in figure 1) that is necessary for its ‘living’, then for its survival, it must receive this function from another structural unit that possesses it. In that case, a new elementary function is created.

There exist many examples in biology that justify this hypothesis: the passage from one metabolic pathway to another when environmental conditions vary, the grouping of cells when the environmental changes (e.g. *Dictyostelium discoideum*). This hypothesis used for any physiological mechanism constitutes what we have called the ‘principle of vital coherence’ (Chauvet 1990). A later section includes a model for illustrative purposes. First, the concepts introduced in the foregoing sections will be defined more precisely.

(iii) Functional hierarchical organization: the consequence of the choice

The organization of the system into a hierarchical one is a consequence of the choice made by the system. Let us consider a set of \( v \) structural units which have the same \( \mu \) individual physiological products \( P_n \), \( 1 \leq \alpha \leq \mu \), (i.e. the same potentialities) these products being necessary for the ‘life’ (i.e. the functioning) of this set. If several units, denoted \( u^* \), have lost one or more such physiological products \( P_n^* \), then \( u^* \) dies unless \( P_n \) is given by another unit \( u \) which possesses this \( P_n \). With the present description we say that an elementary function has been created from \( u \) to \( u^* \). This mechanism of functional self-association explains...
why there exist particular functional links in the system. Many such links could be realized that satisfy many combinations between a subset of $U^*$-structural units and a subset of $u$-structural units. This idea will be expressed in the concept of functional complexity (Chauvet 1987) or potential of organization (Chauvet 1990).

According to hypothesis I, either $u_1^*$ will die out or enter into association with another unit $u_1$ to form $u_2 \equiv (u_1^*, u_1)$ which will be the origin of a new population $U_2$. In general, $u_j$ will give rise to a population $U_{j+1}$, with each element possessing a supplementary unit. As shown now, this process, composed of successive associations, creates a hierarchical system (figure 3). It is analogous to the process of tissue specialization and even to the biological concept of organogenesis, in which the micromutation is replaced by a controlled alteration of gene expression.

Let $U_j$ be the population of elements $u_j$, each containing $j$ units. These elements can be obtained in different ways by associations of the type:

$$(u_{j-1}^*, u_j) \ldots \cdot (u_{j-1}^*, u_j, u_{j+1}) \ldots \cdot (u_{j-1}^*, u_j, u_{j+1}, \ldots, u_{j+n-1}).$$

For example, figure 4 contains the units $u_4 \equiv (u_1^*, u_2, u_3) \equiv (u_1^*, (u_2^*, u_3^*), (u_4^*, u_5^*), \ldots) = (u_1^*, u_2^*, u_3^*)$. If, in this description of populations of units, we take into account the physiological functions affected by non-permanent micromutations, we see in particular how tissue specialization may occur (figure 5). In the following, the numbers in parentheses around the arrows of the hierarchical group (such as described in figure 5) show which products have been lost by a unit. Let us suppose for example that $u_1$ 'initially' possesses three physiological functions $P_1, P_2$ and $P_3$; that $P_1, P_2$ are eliminated from the unit $u_1$ (giving $u_1^*$) leading to the creation of $(u_1^*, u_2)$; that $P_2$ is then eliminated from the unit $u_2$ which then associates with $(u_1^*, u_2)$; and that finally $P_3$ is eliminated in a unit $u_3$ (giving $u_3^*$) which then associates with $(u_1^*, u_2^*, u_3)$. Let us now assume that $u_4$ loses $P_1, P_2$ at a given time, then unit $u_4$ will be specialized in the synthesis of $P_3$. The population $U_4$ thus constructed is by definition a specialized tissue. On the contrary, $u_1^*$ obtained from $u_0$ for example by the loss of $P_3$ in $u_1$, would be forced to associate with $u_4$. Finally, a unit of type $u_1^*$, and thus a population $U_7$, obtained by self-reproduction, will be created. This population possesses an important property since $U_7$ is made up of tissues, one being identical to $u_4$, specialized in the synthesis of $P_3$ and the other being identical to $u_5$, specialized in the synthesis of $P_1$ and $P_2$. Thus an organ composed of differentiated tissues is obtained.

This very simple and formal schema constitutes an understandable basis for a definition of a physiological system, considered from the functional viewpoint. The above formal example shows a process that leads to units called $u_4$ specialized in the synthesis of a specific product $P_3$. It appears that the sequence of functional interactions are organized in order to carry out this specific elementary function. They together involve dynamical processes that vary in a common time scale. Thus, units $u_1, u_2, u_3$, which are associated with $u_4$ to produce $P_3$, constitute a level of organization. For reasons that will appear in part III of these papers, timescales are chosen to specify a level of organization.
in the hierarchy of the physiological system. This idea of the structuration of the functional hierarchical system from their dynamics will be developed in the following. They imply a certain ‘order’ in the system which makes simpler a system more complex. In this paper, these concepts are illustrated from a specific model.

(b) Evidence for the existence of self-association: an increase in stability

Let $U_i$ be the population of units $u_i$. We suppose that a given unit $u^*_i \in U_i$ is affected by a micromutation or any perturbation of a physiological mechanism. According to the principle of vital coherence, this unit will survive if and only if it can be associated with another normal unit in $U_i$ which has the same physiological properties. That association between $u_i$ and $u^*_i$ generates a new unit called $u_k \equiv (u_i, u^*_i)$, and increases the complexity of the dynamics at the level of metabolism. Then, the level of organization for $U_{2n}$, the new population of units such that $u_k, j$ is one unity higher that the level of organization for $U_i$. Note that the self-association is bi-unitary, i.e. it can be realized with at most two units at the same time. One way to know if such a self-association may occur between two units, which are two hierarchical systems according to the last section, comes from the study of the stability of the dynamics before association and after association, whatever the nature of that mechanism. An increase in the domain of stability of the new dynamical system obtained by association will be favourable to the existence of that association between units. This hypothesis will be tested below for a particular model that includes two levels of organization: the level of metabolism inside the elements, and the level of replication of these elements.

This process of self-association can be easily generalized: let $u_{k+1} \equiv (u_{k}, u^*_k)$ be a unit in $U_{k+1}$ which is created by an association between a unit in $U_k$ and a perturbed unit $u^*_k$ in $U_k$, or an association between a perturbed unit $u^*_k$ in $U_k$ and a normal unit $u_k$ (e.g. see figure 5). All intermediates give the possibility of self-association (Chauvet 1990). Such a process leads to the construction of recurrent models obtained for $k = 1, 2, \ldots, j$. After a transformation of the corresponding dynamical systems into systems without dimension, the condition of stability of the linearized system around equilibrium points is derived, and the numerical investigations of linear and nonlinear systems are carried out. The stability of the system that corresponds to a higher level of organization is shown to be increased, even if its complexity, i.e. the number of elementary functions, is increasing.

4. A SUGGESTED THEORY FOR THE FUNCTIONAL ORGANIZATION OF AN FBS

(a) Biological system and physiological function

Definition I: system and function

A structural unit is a structural equivalence class constituted by units that are identical with regard to their structure, and independent with regard to their function (for certain criteria). An elementary physiological function is the collective behavior (cooperation in some tasks) of at least one functional interaction.

A physiological function (a biological system) is the collective product of a set of structural units which can be hierarchically classified according to their elementary interactions.

In the following, notations are Latin subscripts $i, j, \ldots$ for units $u_i, u_j, \ldots$, and Greek subscripts for products: $P_{s, i} \equiv P_{s, i, j}$ denotes an $x$-product synthesized in the $i$-unit $u_i$. The functional interaction (a) from the $i$- to the $j$-unit is denoted as $\psi_{ij}$. A level of organization is represented by a Latin superscript. For example, in figure 1 with an elementary di-graph:

1. Each element $u_i$ or $u_j$ (nodes $i$ and $j$) represents a structural unit with an elementary function $\psi_{ij}$. From $u_i$ to $u_j$.

2. However, the result of this interaction is a product which may be either the direct value of the elementary function:

$$ P_{s, i} = \psi_{ij} (P_{s, i}; r), $$

or the transformed value:

$$ P_{s, ij} = \Phi_{ij} (P_{s, i}; r) = \Phi_{ij} \cdot \psi_{ij} (P_{s, i}; r), $$

inside the unit localized in $r$. The variables $P_{s, ij}$ or $P_{s, ij}^{r}$ will be identified as elementary physiological functions. More generally, $\mu$ products $P_{s, i} \, 1 \leq \alpha \leq \mu$ in the $i$-unit could occur in the realization of the elementary physiological function.

3. A physiological function will result from a set of elements that are hierarchically organized and functionally interacting. The physiological function will be identified with the collective behaviour of the elements whose product (in equation (4)) is denoted by $F$:

$$ F = f(F^1, F^2, \ldots, F^n), $$

where $F^l (l = 1, \ldots, L)$ is an elementary physiological function. A system in which $F=0$, or a constant, is self-controlled.

Definition II: level of organization

A level of organization (L), as an elementary physiological function $F^l$, is identified by the collective behavior, i.e. the dynamics, of a given set of $L$ elementary functions between structural units.

Therefore, a physiological function is the collective product of a set of elementary physiological functions such as $F^l$, and because $(L)$ uniquely defines one level of organization and an elementary physiological function, then a physiological function is a set of $L$ levels such as $(L)$, i.e. a hierarchical system that produces $F$.

Most often, the dynamics is specified for a given time scale of the process, which therefore defines the level of organization.

Definition III: degree of organization

The degree of the functional organization of an FBS

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at level \( l \) is the number \( v' \) of structural units (structural equivalence classes) that constitute the subsystem at this level.

So, the creation of a functional link between one structural unit and the sub-system is the consequence of the association of this structural unit with the sub-system. The association increases its degree of functional organization.

(b) Functional organization

Definition IV: graph and matrix of the functional organization of a RBS: \( S^{(l)}(G,T) \)

A biological sub-system \( S^{(l)} \) at level \( l \) is described by two elements (figure 6): the graph \( G \) of the functional interactions, and some parameters characteristic of the dynamics of the system:

1. The graph \( G \) specifies the elementary functions (edges) between structural units (vertices). A matrix \( M \) of elements 0 and 1 is associated with this graph (incidence matrix of \( G \)).

2. The parameters (e.g. timescale \( T^l \)) for level \( l \), are defined by the dynamical processes that describe the collective behaviour at this level.

\( M \) has \( \mu \) rows, i.e. the number of elementary functions like \( P_{\alpha,j}^l \) (\( \alpha = 1, \ldots, \mu \)), and \( v' \) columns, i.e. the number of structural units \( u_j \) (\( j = 1, \ldots, v' \)) that are included in the collective function at level \( l \):

\[
a_{\alpha j} = 1 \Leftrightarrow P_{\alpha j}^l \in u_j, \quad (5.1)
\]

\( M = (a_{\alpha j}) \),

\[
a_{\alpha 0} = 0 \Leftrightarrow P_{\alpha 0}^l \notin u_j, \quad (5.2)
\]

In the first case, the structural unit \( u_j \) is called a source. All structural units that do not possess \( P_{\alpha j} \) are called sinks. An elementary function is created from a source to a sink:

\[
\psi_{\alpha j}^l \neq 0 \Leftrightarrow P_{\alpha j}^l \in u_j \quad P_{\alpha 0}^l \notin u_j. \quad (6)
\]

![Figure 6](http://rstb.royalsocietypublishing.org/Downloaded from http://rstb.royalsocietypublishing.org/)

Relations (2) and (3) are now written, more generally:

\[
P_{\alpha 0} = \psi_{\alpha 0}^l(P_{\alpha 0}), \quad P_{\alpha 0}^l = \phi_{\alpha 0}^l(P_{\alpha 0}). \quad (7)
\]

Data (1) gives a description of the topology of the system, i.e. the relational aspect between its elements, and their properties will be studied in paper II. Data (2) is associated with the dynamical process for the considered level, and their properties will be studied in paper III. The timescale will be shown to be important for the construction of the functional organization. Moreover, it implies a close connection between structure and function.

Definition V

The functional organization at level \( l \) is defined by the distribution \( (n_{\alpha j}^l)_{\alpha - 1, \mu, j} \), of functional links between structural units at this level. Then \( n_{\alpha j}^l \) is also the number of zeros in the row \( \alpha \) of the matrix \( M \), i.e. the number of sinks for the function \( P_{\alpha 0} \) of the system.

(c) Functional and structural organizations

When \( n \) levels of organization are realized within one physiological function, i.e. when a set of elementary physiological functions \( F^k, k = 1, n \), constitute a physiological function \( F \), we have the relation \( F = f(F^1, F^2, \ldots, F^n) \). This equation expresses an implicit control, or an intrinsic regulation, between the individual \( F^k \)’s. Its relation to equation (1) is clear: \( F^k \) represents the collective product created by the elementary functions \( \psi_{\alpha j}^l \) at level \( k \), and \( F \) is the collective product of all levels that constitute the hierarchical biological system. Of course, this relation is a condensed form of several equations such as (1):

\[
\psi_{\alpha j}^l = f_{\alpha j}^l(\psi_{\alpha j}^{11}, \ldots, \psi_{\alpha j}^{kn})
\]

each of which describes the dynamics of elementary functions between an i-structural unit at level \( k \) (\( L^i \)) and a j-structural unit at level \( (L')^j \), \( j = 1, p, k \), and \( l = 1, n \). When \( \psi_{\alpha j}^l \neq 0 \) with \( k \neq l \), the corresponding link is called an inter-levels link, because it implies equation (4). When two physiological functions having an interaction among them (such as the respiratory and the cardiovascular functions, represented by airflow and cardiac flow respectively) are considered, two parallel hierarchical systems are obtained (figure 7). An important property as regards the practical consequences, is the `relativism’ of levels in that functional organization. Relativism is involved when one variable, at level \( l \) for the first system, is at level \( k \) for the second one. For example, a group of neurons, which are organized in a hierarchical system, can be connected with a group of neurons organized in several subgroups of neurons, where the groups, and then the levels of organization, are defined by their collective behaviour.

Although it may be easy to think of a biological system in terms of structural levels, due to its anatomical description and organization (from cellular to organismic structure), it is considerably more difficult to describe an organism in terms of its functional levels.
5. THE STABILITY OF A 2-LEVEL METABOLIC FBS IS INCREASED BY THE BREAKING OF FUNCTIONAL INTERACTIONS

(a) Description of the FBS

(i) Definition of the ‘Eigen–Goodwin system’

The FBS that we call the ‘Eigen–Goodwin system’ includes three levels of organization: the two lowest (noted 1 and 2) constitute a ‘Goodwin system’, i.e. a hierarchical system of regulated enzymes (second level) and genetical biochemical reactions (first level), both defining the metabolical unit (M) (figure 8); the highest (noted 3) is a ‘Eigen system’, i.e. a set of self-replicating units, e.g. cells, with ecological-like constraints that define the population level (U) by the association of metabolical units. Thus, an ‘Eigen–Goodwin system’ is a 3-level hierarchical system.

Such a system is defined by: two neo-Darwinian postulates (P1) and (P2), the preceding hypothesis (I), and a second hypothesis (I’) which establishes the kinetic mechanism of the association, as follows:

P1: a metabolic network (M) synthesizes a protein $P_{a,j}$, which is responsible for a physiological function involved in the functioning of a self-replicating unit $u \in U$.

P2: such a network is submitted to gene micromutations that can stop the synthesis of $P_{a,j}$.

Hypothesis I: three possibilities exist for the units that underwent a disadvantageous micromutation:

1. The unit dies if $|P_{a,j}| < P_{a,j}^{(0)}$ where $P_{a,j}^{(0)}$ is a threshold.
2. An association with other units whose properties are not necessarily identical, but which possess always a $P_{a,j}$ such that $P_{a,j} = \psi_{a,j}^{(0)} (P_{a,j})$. Therefore, an $\alpha$-functional interaction has been created from the $i$-unit to the $j$-unit.
3. A substitution from a parallel pathway in the metabolical network. However, this possibility is similar to the second one from a formal point of view.

Hypothesis I’: the mechanism of inter-units association is similar to a chemical reaction process. It is justified by the common observation that a random meeting between more than two units at the same time is very unlikely.

These properties allow us to write the dynamical systems that describe the phenomenon of self-association in both levels of organization.

(ii) Functional interaction breaking in the metabolic pathway

Let us assume that a micromutation in the lower level breaks the sequence of reactions in the metabolical system, for example from the product $P_i \equiv P_{i,u_i} \in u_i$ to the product $P_i' \equiv P_{i,u_i'} \in u_i$, with $u_i$ be this unit. If $u_i$ needs $P_{a,j}$ for ‘living’, then, according to hypothesis I, an elementary function from $u_i$ to any other unit $u_i'$ has to be created. According to the notations defined in equations (7), let $\psi_{a,j,u_i'}$ be this interaction which means that:

$$P_{i,u_i'} = \psi_{a,j,u_i'} (P_{i,u_i}) \quad P_{i,u_i'} \in u_i' \quad P_{i,u_i} \in u_i. \quad (9)$$

In the present case, with only one functional interaction represented by the product $P_i$ emitted by $u_i$ and that acts on $u_i'$, we can simplify the notations as follows:

$$P_i' = \psi (P_i) \quad P_i \in u_i' \quad P_i \in u_i. \quad (9')$$

Because of the micromutation that has disrupted the biochemical pathway (the enzyme $E_{i-1}$ is suppressed), the product $P_i$ does no longer exist in $u_i'$. Therefore, $P_{i-1}$ which is obtained from $P_i$ in this unit disappears,
and the unit thereof, except if the product $P_i$ can be captured from another unit that possesses it (principle of vital coherence). In this case, an association between the metabolic pathways, at the higher level, is obtained. We now discuss the general formulation of the possible mechanisms of this association, and then we study the stability of the process.

(ii) Basic mechanisms of the association

Various mechanisms can be assumed for the creation of this association, which lead to a relation such as in equation (9). For example, $P_i \in u_1$ can diffuse passively towards the ‘pathological’ unit $u_1^*$, and, when it arrives in $u_1^*$ (we shall then call it, $P_i^*$ all the metabolites in this pathological unit being denoted with a ‘*’), and assume subscript $i$ to be 1), it can initiate the transformation that leading to $P_2^*$. Such a sequence of transport-transformation can be represented by the diagram:

$$P_1 \xrightarrow{\psi} P_2^* \xrightarrow{\Phi_i} P_1^*$$

where the left part is non-local and the right part is local. Then:

$$P_1^* = \Phi(P_1) = \phi \circ \psi(P_1),$$

i.e. equation (7). It is possible to consider various types of systems to describe these transformations by considering different mechanisms for $\Phi, \phi, \psi$:

1. The simplest mechanism could be a linear transformation from $P_1$ to $P_2^*$ that includes both transport and chemical reaction. It is similar to a classical chemical reaction, i.e. a transfer from the $P_1$-compartment to the $P_2^*$-compartment:

$$P_1 \xrightarrow{\Phi_i} P_2^*,$$

where the direct transformation is denoted as $\Phi$. This case, which is the simplest, is specifically studied here with:

$$P_2^* = \Phi(P_1),$$

and the direct transformation will be expressed below in terms of a rate constant $\tilde{\alpha}$.

2. A passive diffusion of the product $P_1$ can be explicitly included in the previous transformation:

$$P_1 \xrightarrow{\gamma_1} P_2^* \xrightarrow{\alpha_i} P_1^*$$

where $\psi$ and $\phi$ are replaced by linear transformations:

(i) $\gamma_1(P_1, P_1^*) = \beta(P_1 - P_1^*)$ to describe a simple passive diffusion with coefficient $\beta$, and (ii) $\phi(P_1^*) = P_2^*$ given by the kinetic equation:

$$\alpha_2 \frac{dP_2^*}{dt} = -\alpha_2 P_2^* + \alpha_1 P_1^*,$$

to describe the chemical transformations with the rate constants $\alpha_1, \alpha_2$.

(b) Mutations in the metabolic system: Level 2 (M)

(i) Dynamics of the epigenetic and metabolic systems in a $u_1$-unit

We generalize the metabolic system, described by Goodwin (1976) as an epigenetic system (figure 8a) into a metabolic pathway with an allosteric inhibitory
control, and the same kind of feedback interaction with the structural gene. Specifically, it includes two control loops, one is an inhibition with a feedback at a point of the metabolic pathway (I-loop), the other is a repression of structural genes (R-loop).

According to the previous section, because of the very different time scales of these processes in the metabolic pathway and in the epigenetic system, this $u_1$-unit is a hierarchical system with two levels (figure 8b). Each enzyme $E_i$ in the metabolic pathway, which transforms a product $P_i$ into another $P_{i+1}$ in the higher level with the time scale $\{T_2\}$, results from the collective behavior, i.e., the dynamics, of the epigenetic system at the lower level in a time scale $\{T_1\}$. The control between the two levels is given by the feedback loop (R) from the end-product $P_6$ that acts on $X_i [mRNA]$, the concentration of messenger RNA. The allosteric inhibitory interaction is described by the term:

$$f_i(P_6; \omega, \kappa, \omega_0) = \alpha_i(\beta + \gamma P_6^\omega) = \omega_0(1 + \kappa P_6^\omega),$$  \hspace{1cm} \text{(13)}$$

with $\omega_0 = \alpha/\beta$, and $\kappa = \gamma/\beta$. In this equation, $\omega$ is the stoichiometry of the interaction, i.e., $\omega$ molecules of the end-product $P_6$ bind with the aporepressor.

The $u_1$-units function according to the two following dynamical systems with their own time scales:

1. The epigenetic system with a R-loop for the allosteric feedback repression is given by:

$$dX_i/dt^1 = -\gamma X_i f_i(P_6; \omega, \kappa, \omega_0),$$

$$dE_i/dt^1 = -\gamma E_i + \gamma X_i,$$

$$t^1 \in \{T_2\}.$$  \hspace{1cm} \text{(14.1)}$$

It is assumed that the catabolism of $E_i$ is in direct relation with $E_i$, whether $E_i$ is bound or not with $P_i$.

2. The metabolic system with a I-loop for the allosteric feedback inhibition is given by:

$$dP_1/dt^2 = -\alpha_1 P_1 + f_1(P_6; \omega, \kappa, \omega_0),$$

$$dP_j/dt^2 = -\alpha_j P_j + f_j(P_6; \omega, \kappa, \omega_0),$$

$$dP_{i+1}/dt^2 = -\alpha_{i+1} P_{i+1} + \alpha_i P_i,$$

$$t^2 \in \{T_2\}.$$  \hspace{1cm} \text{(14.2)}$$

where $\gamma, \gamma_1, \gamma_2, \ldots$ are the rate constants of the chemical reactions. The allosteric inhibition feedback term $f_j$ is similar to that in equations (14.1), with different values of the parameters. This metabolic system is composed of enzymatic reactions such as $P_i \rightarrow P_{i+1}$ with velocity $v_i = k_{0i} E_i P_i / (K_{M,i} + P_i)$, where $K_{M,i}$ is the Michaelis constant of enzyme $E_i$ and the rate constant of the reaction: $E P_i \rightarrow E_i + P_{i+1}$. If $P_i \ll K_{M,i}$, then $v_i = (k_{0i} K_{M,i}) E P_i \approx 0$.

The two systems (14), which correspond to two distinct levels of organization, are decoupled in time. This means that the value of the concentration of the enzyme $E_i$ is a constant during the dynamics of the metabolic pathway that leads to the end-product $P_6$. Therefore, because of the functional hierarchy, $\alpha_i$ is a constant in the system (14.2).

(ii) Dynamics of the metabolic pathway in a $u_1$-unit: a general and generative schema of the association

On the basis of these simple mechanisms, a more general schema for a metabolic pathway system, corresponding to the dynamics (14.2), can be written in terms of compartments (R. Costalat, personal communication 1991):

$$P_0 \rightarrow P_1 \rightarrow P_2 \rightarrow P_3 \rightarrow P_4 \rightarrow \ldots$$

$$\beta_1 \beta_2 \beta_3 \beta_4 \beta_5 \beta_6 \beta_7$$

$$P_1 \rightarrow P_2 \rightarrow P_3 \rightarrow P_4 \rightarrow \ldots,$$

where each product can diffuse from one unit to the other according to the transport function $g_i(P_6, P_j^*)$.

The corresponding dynamical system is:

$$dP_i/dt = \alpha_{i-1} P_{i-1} - \alpha_i P_i - g_i(P_6, P_j^*),$$

$$dP_j^*/dt = \alpha_{j-1} P_{j-1}^* - \alpha_i P_i^* + g_i(P_6, P_j^*),$$

$$i = 2, 3, \ldots$$  \hspace{1cm} \text{(15)}$$

In the present case of association between the metabolic systems (14.2) where $n = 4$, let us assume, for example, that $\alpha_2$ becomes null in a given unit $u_1$, leading to a 'pathological' unit $u_1^*$. If $u_1^*$ receives $P_3$ from $u_1$, and if $P_i^*$ can also diffuse towards $u_1$, the following schema, deduced from (15), will be obtained:

$$P_1 \rightarrow P_2 \rightarrow P_3 \rightarrow P_4 \rightarrow \ldots$$

$$\beta_1 \beta_2 \beta_3 \beta_4 \beta_5 \beta_6 \beta_7$$

$$P_1 \rightarrow P_2 \rightarrow P_3 \rightarrow P_4 \rightarrow \ldots$$  \hspace{1cm} \text{(16)}$$

This schema is shown in figure 9. Similarly to obtain the dynamical system (14), it can be written as:

$$dP_1/dt = -\alpha_1 P_1 + f_{1A}(P_6; \omega, \kappa, \omega_0) - g_1(P_1, P_1^*),$$

$$dP_2/dt = -\alpha_2 P_2 + \alpha_1 P_1,$$

$$dP_3/dt = -\alpha_3 P_3 + \alpha_2 P_2 - g_2(P_3, P_3^*),$$

$$dP_4/dt = -\alpha_4 P_4 + \alpha_3 P_3,$$

$$dP_1^*/dt = -\alpha_1 P_1^* + f_{1A}(P_6; \omega, \kappa, \omega_0) + g_1(P_1, P_1^*),$$

$$dP_2^*/dt = \alpha_1 P_1^*,$$

$$dP_3^*/dt = -\alpha_2 P_2^* + g_2(P_3, P_3^*),$$

$$dP_4^*/dt = -\alpha_3 P_4^* + g_3(P_3, P_3^*).$$  \hspace{1cm} \text{(18)}$$

The case of a simple passive diffusion for $P_1$ and $P_2$ is obtained as described above by putting:

$$g_1(P_1, P_1^*) = \beta_1 (P_1 - P_1^*),$$

$$g_2(P_3, P_3^*) = \beta_2 (P_3 - P_3^*).$$

We can simplify this kinetic system by using the schema (11) rather than (10), i.e., by introducing the constant $\overline{\alpha}$. With the non direct feed-back of $P_i^*$ on $P_i$, the following system of equations is obtained:
Figure 10. (a) Stability area is increasing when the system (10) (full lines) is complexified into system (12) (dotted lines). For each system, i.e. each closed curve, the corresponding domain of stability is outside the internal space: expression of the condition of stability in plane $\alpha = 1$, for two values of $\kappa$ ($\kappa = 0.1$, figure at the top; $\kappa = 0.01$, figure below) that expresses the 'intensity' of the molecular linking. (b) Extension of the preceding results regarding the stability for an association between a unit $u_{j+1}$ with degree $j - 1$ and a unit $u_j$. Such an association is represented by the factor $K_j - \Gamma_j$ (where each term comes respectively from the linear and the nonlinear parts of the generalized dynamical system (14) in the derived characteristic equation) as a function of the added parameter $u_{j+1}$ for $j = 1, 2, 3$ (Machhub et al. 1992).

\[ \frac{dP_1}{dt} = -\alpha_1 P_1 + f_{1,4}(P_4; \partial, \kappa, \alpha_0) + f_{1,4}(P^*_4; \partial, \kappa, \alpha_0), \]
\[ \frac{dP_2}{dt} = -\alpha_2 P_2 + \alpha_3 P_1, \]
\[ \frac{dP_3}{dt} = -(\alpha_3 + \bar{\alpha})P_3 + \alpha_2 P_2, \]
\[ \frac{dP_4}{dt} = -\alpha_4 P_4 + \alpha_5 P_3, \]
\[ \frac{dP^*_4}{dt} = -\alpha_4 P^*_4 + \bar{\alpha} P_4, \tag{19} \]
where $\bar{\alpha}$ is a positive constant, included in $\Phi$ as explained in paragraph 1 above, which simply describes the non-local contribution of product $P_5 \in u_j$ to the production of $P^*_4 \in u_j^*$. It is assumed here that $P^*_4$ can modify the synthesis of $P_4$ in an additive manner, in the same way as $P_4$, and that the coefficients for the degradation of $P_4$ and $P^*_4$ are the same. Such a system represents the dynamics of a new unit noted $u_2 \equiv (u_i, u_{i+1})$ (figure 9).

In reality, structural units are located at different points in the physical space. Thus, the variation in time of the product satisfies partial differential equations that describe the dynamics in $u(t)$ and in $u^*(r)$ at two points $r_0$ and $r_1$. The present study will be extended to these cases in the third part of this work.

(iii) Mathematical study of the dynamics in a $u_2$-unit: specific system (19)

The system (19) is made dimensionless by using a transformation given by Walter (see Rapp 1976) where:

\[ \zeta = (\alpha_0 \sigma_2 \sigma_1 \gamma_1)^{1/4} \]
\[ t^* = \zeta t \]
\[ b_1 = \alpha_1 \zeta \]
\[ b_2 = \alpha_2 \zeta \]
\[ b_{i+2} = \alpha_i \zeta, \quad \sigma_i = 1, 2. \tag{20} \]

A new system of equations is obtained:

\[ \frac{dx_1}{dt} = -b_1 x_1 + \frac{1}{1 + x_4^a} + \frac{1}{1 + \left(\frac{b_5}{b_3} x_5\right)^a} \tag{21.1} \]
\[ \frac{dx_2}{dt} = -b_2 x_2 + x_1, \tag{21.2} \]
\[ \frac{dx_3}{dt} = -(b_3 + b_5) x_3 + x_2, \tag{21.3} \]
\[ \frac{dx_4}{dt} = -b_4 x_4 + x_3, \tag{21.4} \]
\[ \frac{dx_5}{dt} = -b_5 x_5 + x_3, \tag{21.5} \]
in terms of new state variables:

\[ t^* = a_0 \eta \]
\[ x_1(t^*) = a_1 x(t), \]
\[ x_2(t^*) = a_2 P_4(t), \]
\[ x_3(t^*) = a_3 P_4(t), \]
\[ x_4(t^*) = a_4 P_4(t), \]
\[ x_5(t^*) = a_5 P_4(t), \tag{22} \]

now with dimensionless coefficients $a_i$ and $b_i$ in place of dimensional ones $\gamma_i$, $\kappa$ and $\sigma_i$. In this example, the functional interaction (9), created by a survival condition (hypothesis I), is mathematically expressed by equation (21.3), and corresponds to equation (8), where $k = l_i = j$. This is a very simple case of an organic link in a given level of organization, here the metabolical level (M).

Walter (1969a,b), Viniegra–Gonzalez (1973) and Rapp (1976), have studied the stability of the system
(10), which describes the time evolution of units \( u_i \), and they determined sufficient conditions for the system to be asymptotically stable. Chauvet & Girou (1983) deduced the stability of system (21), which represents \( u_i \equiv (u_i, u_i^\#) \), from an analysis of the linearized systems. It was possible to show numerically that, around steady states, the domain of stability of the new system (21) of units \( u_i \equiv (u_i, u_i^\#) \) is larger than the domain of stability of the preceding one (14.2) with \( n = 4 \) for units \( u_i \), i.e. more stable. Results are shown on figure 10. For a given set \((x_i, a_i, x_i, x_j)\), the condition of stability of system (14.2) (with \( n = 4 \)) is studied in the plane \((x_i, a_i)\). The domain of stability of the 1-unit metabolic system is outside the solid line. The same study is repeated with the system (19) (corresponding to the 2-unit metabolic system \((u_i, u_i^\#)\)) for various values of \( x_i \) (only one value of \( x_i \) is represented in figure 10a), and for increasing values of parameter \( k_i \), which both describe the existence of the association. We can see that the area of stability (represented by the space outside the dotted line) increases when the formal biological system is complicated. In other words, unit \( u_i \equiv (u_i, u_i^\#) \) is metabolically 'more stable' than unit \( u_i \). With this expression, I want to postulate that a more complex system is more likely to exist.

More recently (Machbub et al. 1992), we have studied, in the same way, the stability of units \( u_i \equiv (u_i-1, u_i^\#) \) that are obtained with the same self-association process as \( u_i \equiv (u_i, u_i^\#) \). The linear part of the system is shown to be exponentially stable. Moreover, the stationary states of \( u_i \) are asymptotically stable through a balance between the linear and nonlinear terms of the equation that describes the time evolution of \( u_i \). An important result has been obtained for the domains of stability of successive units \( u_i \): locally, unit \( u_i \) is more stable than \( u_{i-1} \). All these results are confirmed numerically (Machbub et al. 1992): successive associations increase the domain of stability (figure 10b). So, building an association by creating a functional interaction appears to lead to greater stability for the level (M). It is possible that this mathematical property could be generalized to a class of dynamical systems such as (18).

**(iv) Numerical study of the dynamics in a \( u_i \)-unit: general dynamical system (16)**

The same method has been used to study the general dynamical system (16), not mathematically equivalent to the specific system (19). Numerical simulations have shown that, in this case too, association increases the domain of stability. The values of parameters are: \( a_1 = a_2 = 1 \), \( x_0 = 50 \), \( k = 1 \). Coupling between the two units is realized by simple passive transport: \( g_i(P_i, P_i^\#) = \beta_i(P_i - P_i^\#) \) \( V_i \), and the study is made in the plane \((x_i, a_i)\). An increase in stability can be shown even when all the coefficients \( \beta_i \) are assumed to be unequal, and, in this case, the higher the value of \( \beta_i \), i.e. the 'intensity' of the coupling, the wider is the area of stability.

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**(e) Dynamics of the population of units \( u_i \equiv (u_i, u_i^\#) \) at level (3) (U): idempotence of the structural units**

The unit \( u_i \) is also a self-replicative unit which can reproduce itself following above neo-Darwinian properties (P1) and (P2) from Eigen (1971). A constant overall organizational constraint is imposed to the system, which has the meaning of a constant overall flux constraint, requiring the conservation of the number of elementary units.

Let \( u_i \) be the number of units, i.e. the 'density', obtained by a bi-unitary process in which \( i \in [1,n-1] \) and \( j \in [1,n-1] \) units are being associated. If \( U_i \) denotes the set of units like \( u_i \), then the population:

\[
U = \bigcup_{n-1}^r U_n
\]

where \( r \) is the maximal degree of organization, evolves according to the dynamical system:

\[
\frac{d u_i}{d t} = (a_i - \lambda(u_i, u_{i-1}, \ldots, u_i)) u_i + \sum_{i+j=n} k_{ij} u_i u_j
\]

(23.1)

\[
\sum_i n u_i = c \quad n = 1, 2, \ldots, r,
\]

(23.2)

where \( k_{ij} \) is a coupling parameter between both levels of organization (M) and (U). Here \( \lambda \) is a function that expresses the condition of conservation for the total number of elementary species like \( u_i \). In fact, this condition is similar to the control equation (4) for the system (23): let \( F \) be the assumed physiological function realized by all units. Then \( F \) is a function of the \( u_i \)’s that themselves depend on the \( P_j \)’s, in particular on \( P_3 \):

\[
F = f(\Phi(P_3)),
\]

(24)

because in this example only one functional interaction \( \Phi \) exists, which creates the non-symmetry source → sink between the units, and this interaction is the elementary physiological function \( P_3 \) carried out at level (M).

A simplified form of equations (23) was assumed by Eigen (1971) in his model of macromolecular evolution where \( \lambda \) would be the dilution factor \( \Omega \). This conservation equation (23.2) leads to:

\[
\sum_i n \frac{d u_i}{d t} = 0,
\]

(25)

and:

\[
c \lambda(u_i, u_{i-1}, \ldots, u_i) = \sum_i n a_i u_i + \sum_i n \sum_{i+j=n} k_{ij} u_i u_j
\]

(26)

According to Hypothesis I, the coupling parameter between both levels of organization (M) and (U) \( k_{ij} \) is a function of the concentration \( P \) of the product which is synthesized at level (M). These functions \( k_{ij} \), generally antisymmetrical, describe the self-organization process between the two levels of organization (M) and (U), for structural units whose functional degrees of organization are \( i \) and \( j \). Therefore, \( k_{ij} \) will be called a self-organization parameter.

A mathematical study of systems (26) for \( r = 2 \) and
system corresponds to the domain of stability for the nonlinear model with periodic solutions; (ii) the admissible domain for the added supplementary parameter that results from an association of degree \( j \) is larger than the one that corresponds to an association of degree \( j-1 \).

Clearly, the coupling of the three levels of functional organization introduces parameters which have a different meaning from that of Eigen’s selective value, and it contributes strongly to the time variation of the system. This result is a consequence of the fundamental hypothesis of self-association. Because the Eigen–Goodwin system studied here includes three levels of organization, organic links like \( \Phi \) defined by (11): \( P^*_2 \Phi(P_1) \) at metabolical level (M), and an implicit control link expressed by equation (23.2) at the third level (U), it constitutes a good basis for the mathematical study of functional self-organization and theoretical related problems.

6. DISCUSSION AND CONCLUSION: REAL BIOLOGICAL SYSTEMS?

(a) About the generality of the self-association hypothesis: creation of functional interactions during development

This paper is an attempt to give a formalized description of biological functional organization that is based on a hypothesis called the ‘self-association hypothesis’. The consequences of this hypothesis are analysed for a specific example, the Eigen–Goodwin system, which is defined as a population of structural units the behavior of which is (i) analogous to macromolecular species, and (ii) ecological-like. Each structural unit consists of a general metabolic system with two coupled metabolic and epigenetic networks. It is proved, at least for this particular case, that the self-association hypothesis, applied to functional interactions, is compatible with the nature of the biological processes. Moreover, from this example, I have found the same property for a general schema of two coupled biochemical pathways (15) described by the general dynamical system (16). Such a dynamical system originates in the description of several biological systems (Chauvet 1987), in molecular biology and biochemistry, as well as for larger ones such as the cardiovascular and respiratory systems. It will be shown in paper III that the same results are valid for structural units distributed in space. Partial derivative equations can be derived from general equations (16) with specific source terms \( \Gamma \) that replace \( \alpha_p P_0 \) and non-local and local diffusion transport terms that replace \( g(P,P^*) \). For example, in the nervous system, the non-local transport is due to the connectivity between neurons, and the local transport occurs in the extracellular space.

Of course, we do not know yet if such a self-association property is really general, but the problem could be presented in another form: because this property of an increase of stability with complexity is observed in the living world, we can structure the functional organization, i.e. determine how the levels
of functional organization are built during development, in order to obtain this property. I have chosen the timescale of the dynamics as a parameter to specify the levels, but the fundamental property of an increase in stability has to be considered together with that of self-association in order to define the functional organization. In the specific example considered here, the self-association is between two hierarchical systems, the normal metabolic pathway and the ‘pathological’ one. The entire hierarchical system has three levels of organization, the first level is the epigenetic system which provides the specific enzyme that is needed at each step of the metabolic pathway, i.e. the biochemical reaction, and the second level is the metabolic pathway in which the association is generated. The much larger timescale required for the epigenetic system than for the metabolic pathway justifies the existence of these two levels, and is the cause of the increase in stability by association. The hierarchy between timescales and the self-association between the corresponding hierarchical systems can be used to determine the unique functional organization of the system.

(b) Comparison with compartmental systems: \((N, a)\) and \((\psi, \rho)\) representations

The existence of the functional interaction is due to the fact that some localized substructure acts on another. I have found that the hypothesis of self-association leads to a structuring of the biological system into levels of organization, and that the domain of stability of the related dynamics is increased. The elementary function represented by the variable \(\psi\) satisfies dynamics in the representation \((\psi, \rho)\) where the geometry is given by the density \(\rho\) of structural units. The phenomena that can be described with such a formalism are those which evolve with a certain finite velocity between structural units. Because chemical kinetic phenomena exhibit a strict reaction-diffusion process, i.e. a thermodynamical spread in space due to the statistical brownian motion, it is clear that they cannot be incorporated in the representation \((\psi, \rho)\).

Delattre (1971) developed an axiomatic theory of molecular transformations, including external effects such as radiation, which was a generalization of compartmental analysis. He showed that the evolution of \(N_f\) is given by:

\[
dN_f/dt = \left( \sum_k a_{k}F_{k} + a_{0}F_{0} \right) + \left( \sum_k b_{k}F_{k} \right) + E_{nf}\rho
\]

where \(N_f\) is the number of elements in a class \(E_f\), of states \(F_k\) the number of elementary transformations per time unit from a class \(E_j\) to a class \(E_{0}\), and \(E_{nf}\) the number of elementary transformations per time unit towards the environment. Generally:

\[
F = KN_{f}^{a}N_{f}^{a_{0}} \cdots N_{f}^{a_{0}}N_{f}^{a_{0}}
\]

When the transformation involves \(a\) elements of \(E_{0}\), \(a_{0}\), elements of \(E_{0}^{+}\), then \(E_{nf}\) describes inputs \((E_{nf} > 0)\) or outputs \((E_{nf} < 0)\) for elements of \(E_{0}\). Inputs and outputs are independent of the number of elements (say, the occupation number) of \(E_{0}\). So \(N\) represents the occupation number of the classes, and \(a\) the rate constant of the transformations between classes. Now, \(\psi\) denotes an elementary function link between two structural units which are equivalence classes from a structural, i.e. anatomical or histological point of view, and whose geometrical density is \(\rho\). Then, because \(\psi\) and \(\rho\) could be deduced, but with difficulty, from \(N\) and \(a\), the \((\psi, \rho)\) and \((N, a)\) representations could be called ‘dual’ representations.

Methods of compartmental analysis (see, for example, Jacquez (1985)), and more generally, formalisms like transformation systems (Delattre 1971), and statistical mechanics (Demetrius 1983), are appropriate when the number of elements is large enough to justify statistical laws. This classical representation \((N, a)\) is currently used in ecology, epidemiology, biochemical kinetics and population dynamics. However, at upper levels of organization, such as those observed in physiological systems, one way to study the process based on functional interactions, will be to choose the representation \((\psi, \rho)\).

(c) From formal to real biological systems

Although the study of complex real biological systems can be more easily deduced from related formal biological systems, when moving from this simple but useful rbs toward a real biological system (RBS) as, for example, the respiratory system, many complications appear in the description of its dynamics. In fact, the preliminary identification of functional interactions, elementary physiological functions, and levels of organization, have to be accounted for in building the global system. Because of the self-association hypothesis, and because the concept of level of functional organization corresponding to an elementary physiological function has been defined as the collective behaviour of a set of structural units, rbs as well as rbs can be structured according to their physiological functions. With this framework in mind, a physiological function corresponds to the collective behaviour of a hierarchical system. Therefore, a physiological system will be described as a set of parallel hierarchical subsystems, and corresponds to the definition of a real biological system.

This method is useful in simulations, since it is possible to establish a one-to-one correspondence between each subsystem and one numerical processor. The connections between subsystems are the control or organic functional links as defined above. Thus, the connectivity between parallel processors appears to be a consequence of the parallel structure of biological systems. One problem is to preserve the synchronization between all subsystems.

Let us consider the respiratory function as an example. At least seven physiological functions constitute the respiratory function: (i) homeostatic function (kidney); the structural units are the sets of nephrons, and some parts of tubules for the homeostasis of \(H^+\) and other electrolytes; (ii) ventilatory function (lung); structural units are muscles and bronchi; (iii) circulatory function (vessels and heart); structural units are
capillaries, arteries and veins and haemoglobin; (iv) metabolic function: structural units are tissues, muscles and digestive tracts; (v) sensory function: structural units are mechano-receptors, chemo-receptors; (vi) neuronal regulation function; structural units are pools of neurons; (vii) hormonal regulation function: structural units are the endocrine glands, such as hypophysis, thyroid, and pancreas. The functional

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interactions between the corresponding sub-systems can be viewed as control links (noted 1 to 4 in figure 12) that are, from a physical point of view, modifications of the neural activity (defined as a frequency of action potentials) and organic links.

Because of the complexity of the functional organization, transitive order relations between constitutive functional interactions are often hidden. Thus, in the same representation \((\psi, \rho)\) of the physiological functions, at least for the upper levels of organization, and according to the definitions given in §4, a functional order could appear. For example, in figure 12 the respiratory function is drawn in terms of its functional interactions. In the \((N, a)\) representation, the \(CO_2\) molecule (free in the alveoli or bound with haemoglobin in capillaries) constitutes a compartment. In the dual \((N, a)\)-representation that includes the \(\psi\)-space, a hierarchical system of structural units, whose collec-

Figure 13. (a) Ventilatory function represented (above) in representation \((N, a)\), (below) in representation \((\psi, \rho)\); (b) the same function represented as a hierarchical system connected with nervous and cardio-vascular functions according to functional interactions. R.S. = respiratory System; m.f. = muscle fibres; E.S. = endocrine system; N.S. = nervous system; A.N.S. = autonomic nervous system; f = frequency; \(\Delta P\) = pressure gradient.

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tive behaviour is a physiological function, corresponds to bilateral exchanges between compartments (figure 13a). By choosing a specific representation, actions and substrates are not mixed. Figure 13b shows the hierarchical graphs that are obtained for some physiological systems of the organism. Because the graph is generated from the set of functional interactions following the self-association hypothesis, some particular properties of the graph could be elicited. This is so with the graph which represents the cardio-vascular function (figure 14). A cyclic subgraph can be identified, which corresponds to the heart shock: the cyclic sequence of events can be decomposed into elementary steps.

Based on the self-association hypothesis of functional interactions, this approach leads to new results: (i) hierarchical physiological systems are classified so as to generate the functional organization of the whole system (an example is given in figure 15); (ii) structural and functional organizations are clearly separated; (iii) particular cyclic subgraphs can be identified; (iv) the consequence of a perturbation inside a source at a given level of the functional organization is thought of as the path that corresponds to the modified dynamics; (iv) the functional map of the combination of functional interactions can lead to a better understanding of the system.

(d) Self-association as a principle of vital coherence. Coupling between topology and geometry

Results obtained for an Eigen–Goodwin system lead to some interesting conclusions and conjectures: (i) when a new functional interaction is created as a consequence of the self-association hypothesis, a new functioning mode is obtained and an increase in stability (considered as the area of stability in the space of parameters) is found; (ii) a new functional order is created in the population of structural units following a selection of units that have increased their degree of organization through association; (iii) there exist self-organization parameters (k) that couple both levels of functional organization, and modify the selective value introduced by Eigen (1971).

Could these results be generalized to a class of dynamical systems whose interpretation in terms of biological functions is possible? If the answer is positive, then there would exist a more general principle that could constitute the basis of stable functioning of formal biological systems. In this abstract and formal approach, ‘something’ is conserved during the ‘life’ of the system, and this property of invariance is described by the self-association hypothesis applied to the set of functional interactions. Given its basic importance for the present theory, we have called this invariance of the physiological function the ‘principle of vital coherence’. Applied to the set of functional interactions, that principle describes the fact that the system during development has to reorganize the distribution of sources and sinks in order to continue to live.

Specifically, the principle of vital coherence included in this approach will be applied to two different and complementary aspects of a biological system. First, the topological aspect that describes the
existence of the interactions, then the existence of the elementary physiological function. The distribution \((h_k)_{k=1,...,N}\) of functional links between structural units has to be re-organized according to a new distribution after perturbation of an element of the representative graph (equation 5). The related system will be called \((o-FBS)\), and the \((h_k)_{k=1,...,N}\) constitute the state variables. Second, the dynamical aspect that describes time evolution of the set of elementary functions \(\psi(t)\) (equation 8), i.e. the intensity of the interaction. The related system will be called \((d-FBS)\). Finally, the biological system is composed of two systems describing respectively the topology and the dynamics, i.e. the existence and the intensity of the functional interactions. Therefore, the stability of the system which is subjected to a perturbation results from the
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stability of the two subsystems (o-FBS) and (d-FBS). Subsequently, the problem is to determine how could the system stay o- and d-stable, while it grows and reproduces by re-structuring both the levels of organization and the distribution of functional interactions? The second and the third papers will focus on this problem, namely the (o-FBS) and the (d-FBS) respectively.

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