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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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CONTENTS

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

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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 (RBSS) 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
$g(P_1,P_1^*)$ transport function
$k(P),k'(P),k''(P)$ coupling parameters
k_{ij} coupling parameter between both levels of organization (M) and (U)
$(n_\alpha^{(l)})_{\alpha=1,\mu^{(l)}}$ 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
$u_1 \equiv (u_1,u_1^*),u_{k+1} \equiv (u_k,u_1^*)$ associated structural units
E_i enzyme
E_j class of elements in the compartmental theory
Env_j describes input ($E_{nvj}>0$) or outputs ($E_{nvj}<0$) for elements of E_j
F hierarchical system
F^l $(l=1,\ldots,L)$ elementary physiological function: defines the level of organization (L^l)
F_{kj} number of elementary transformations per time unit from a class E_j to a class E_k
F_{ej} number of elementary transformations per time unit towards the environment
$\boldsymbol{G}$ graph of the functional organization
(L^l) level of organization
$\boldsymbol{M}$ matrix of the functional organization
N occupation number of the classes
(N,a) representation
N_j number of elements in a class E_j
P_α, $1 \leqslant \alpha \leqslant \mu$ products in a structural unit
$P_{\alpha,i} \equiv P_{\alpha,u_i}$ denotes an α-product synthesized in the i-unit u_i
P_1,P_2 products in the biochemical pathway: $P_1 \in u_1$, $P_2^* \in u_1^*$
$S^{(l)}$ biological sub-system at level l
S_i substrate
T_0 time coordinate
T^l timescale at level l
U_j population of elements u_j, each containing j units
$X \equiv [mRNA]$ concentration of RNA messenger
$\alpha_X,\alpha_Y,\alpha_i$, $i=1,2,\ldots$, rate constants of the chemical reactions
$\beta(P_1-P_1^*)$ simple passive diffusion factor
Φ,ϕ,ψ transformations that describe the functional interaction
$P_2^* = \Phi(P_1) = \phi o \psi(P_1)$
$\kappa = \gamma/\beta$ allosteric factor
λ dilution factor
v^l degree of functional organization at level l
(ψ,ρ) representation
ψ_{ij}^α functional interaction (α) from the i- to the j-unit
$\psi_{u_1u_1^*}^1$ functional interaction in the epigenetic system between a normal and a pathological unit
ρ geometrical parameter of the biological system; specifically; stoechiometry in the Goodwin model
$\zeta = (\alpha_0\alpha_X\alpha_Y\alpha_1\kappa^{1/\rho})^{1/4}$, $t^* = \zeta t$, $b_1 = \alpha_X/\zeta$, $b_2 = \alpha_Y/\zeta$, $b_{i+2} = \alpha_i/\zeta$, $i=1,2$ 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); Prigogine and

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 (1984*a*,*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 macromolecular 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

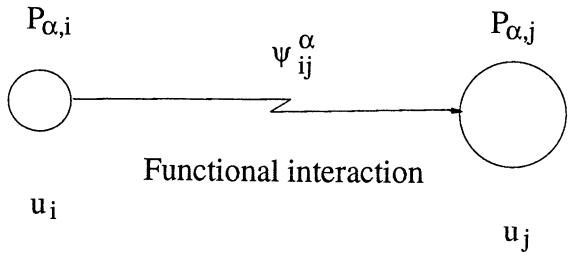

Figure 1. ψ_{ij}^{α} is an interaction between two structural units u_i and u_j, and is called an elementary function. It can be identified by the product $P_{\alpha j} = \psi_{ij}^{\alpha}(P_{\alpha,i})$, which is created after the interaction. In fact, the set of $P_{\alpha,j}$ for all j gives F_{α}^{k} 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 ψ_{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 ψ_{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:

$$d\psi_{ij}/dt = f_{ij}(\psi_{11}, \psi_{12}, \ldots, \psi_{pp}; \rho_1, \rho_2, \ldots, \rho_p) \qquad i,j = 1, \ldots, p, \quad (1)$$

where the ρ_is are specific geometrical or physical parameters. This new representation of a biological system will be denoted by (ψ,ρ).

(*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 extented 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_a, 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 $T_1 = T_0 - d/v_a$ 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 substructures 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

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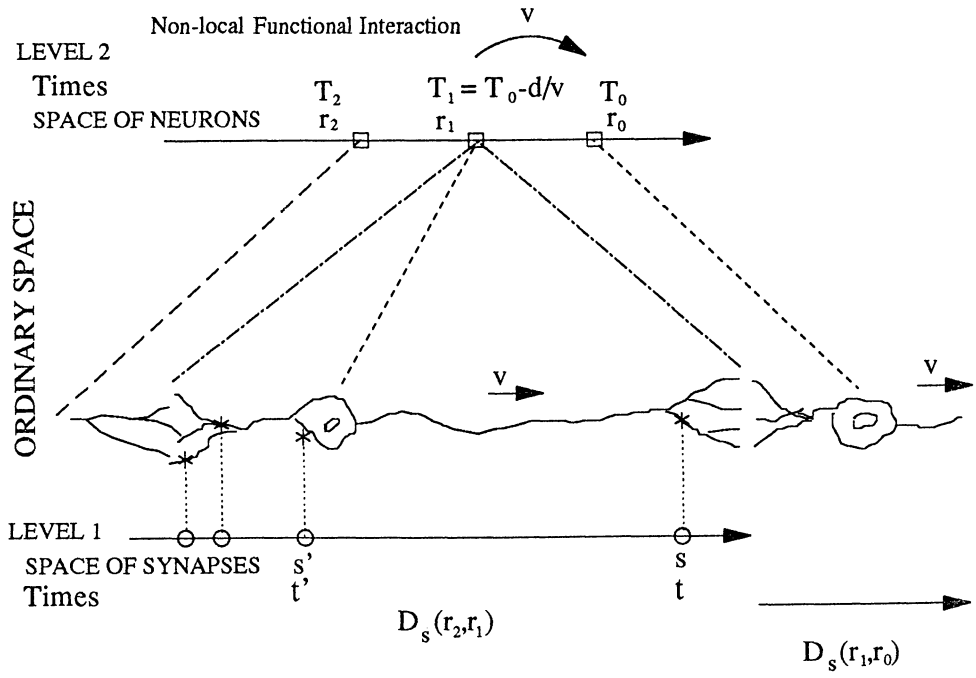

Figure 2. Non-locality due to the existence of several levels of organization. This figure shows the case of nervous tissue where neurons are represented in physical cartesian space with an axis for each level. At level 2, one neuron is represented by one point in the space of neurons. Thus, we have neurons at point r_1 and r_0. At level 1, the space of synapses is $D_s(r_2,r_1)$, i.e. the set of synapses that connect neurons at r_1 and neurons at r_2. The finite extent of the neuron in physical space provides non-local effects in the space of neurons where they are infinitesimally close.

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:

$$S_1 \rightarrow S_2 \ldots \rightarrow S_{i-1} \rightarrow S_i \rightarrow \ldots S_n,$$

where an enzyme E_i, which can be identified as an elementary function, acts sequentially on a product S_{i-1} to create S_i. In this example, S_n 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_i. This kind of substitution is often used at the metabolic level.

(ii) *Functional self-association hypothesis*

The preceding section gives a causal interpretation for the existence of a functional interaction, because, if each structural unit could produce the set of enzymes that are necessary for the life of the system, then there would be no functional interactions. With the functional breaking process, a source is transformed into a sink for a given product: an elementary function is then created from the source to the sink. The following hypothesis constitutes the basis for generating the levels of organization of the biological system.

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 μ individual physiological products P_α, $1 \leqslant \alpha \leqslant \mu$, (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_α, then u^* dies unless P_α is given by another unit u which possesses this P_α. With the present description we say that an elementary function has been created from u to u^*. This mechanism of functional self-association explains

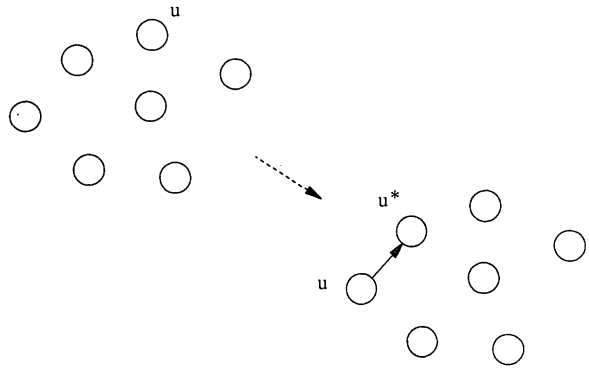

Figure 3. Association between two units. A 'pathological' unit u^*, i.e. a unit u in the space of units which has lost a physiological function (or a product), associates with a 'normal' unit u, in order to retrieve for itself this product.

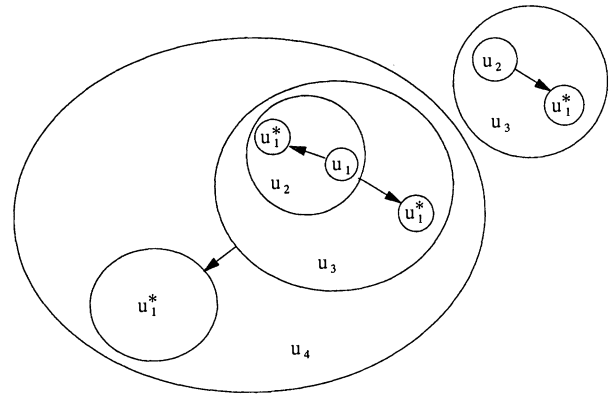

Figure 4. Functional self-association hypothesis. Units u_2,u_3, u_4 are built by association between a modified unit u_1^* and a normal one u_1. For example, units $u_2 \equiv (u_1,u_1^*)$, u_3, . . . are built by association.

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:

$$(u_{j-1},u_1^*), \ldots, (u_{j-p},u_p^*), \ldots, (u_1,u_{j-1}^*).$$

For example, figure 4 contains the units $u_4 \equiv (u_1^*, u_3) \equiv (u_1^*,(u_2,u_1^*)) \equiv (u_1^*,((u_1,u_1^*),u_1^*))$ and $u_3 \equiv (u_2,u_1^*) \equiv ((u_1,u_1^*),u_1^*)$. 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_1); that P_2 is then eliminated from the unit u_1 which then associates with (u_1^*,u_1); and that finally P_1 is eliminated in a unit u_1 (giving u_1^*) which then associates with (u_1^*,u_1). 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_3^* obtained from u_3 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_7, 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, specialised in the synthesis of P_3 and the other being identical to u_3, specialised 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 within 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

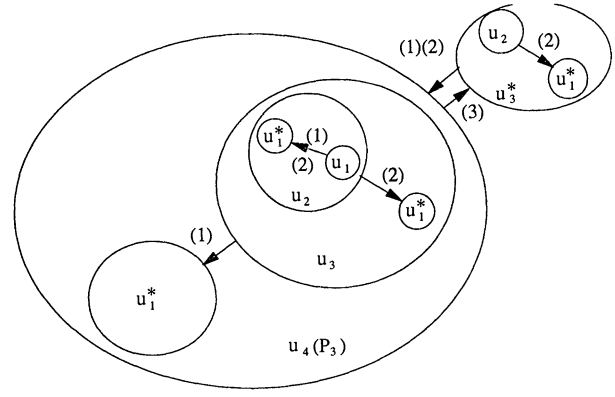

Figure 5. Tissue specialization. Numbers in parentheses represent the product which is transported from the source to the sink. Three such products are assumed to be necessary for the cell living. At a given time, the two products P_1 and P_2 are assumed to be missing. Thus, u_1^* associates with u_1 to create a unit u_2. If P_2 is eliminated from another unit u_1, this unit can associate with u_2 to create u_3, and so on. In the figure, such a set of transformations at successive given times, e.g. u_4 looses P_1 and P_2, leads to a unit u_4 that is finally specialized in the synthesis of P_3.

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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_1 be the population of units u_1. We suppose that a given unit $u_1^* \in U_1$ 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_1, which has the same physiological properties. That association between u_1 and u_1^* generates a new unit called $u_2 \equiv (u_1,u_1^*)$, and increases the complexity of the dynamics at the level of metabolism. Then, the level of organization for U_2, the new population of units such that u_2, is one unity higher that the level of organization for U_1. 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 $u_{k+1} \equiv (u_k,u_1^*)$ be a unit in U_{k+1}, which is created by an association between a unit in U_k and a perturbed unit u_1^* in U_1, or an association between a perturbed unit u_k^* in U_k and a normal unit u_1 (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: $P_{\alpha,i} \equiv P_{\alpha,u_i}$ denotes an α-product synthesized in the i-unit u_i. The functional interaction (α) from the i- to the j-unit is denoted as ψ_{ij}^{α}. 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 ψ_{ij}^{α} 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:

$$P_{\alpha,j} = \psi_{ij}^{\alpha}(P_{\alpha,i}; r), \tag{2}$$

or the transformed value:

$$P'_{\alpha,j} = \Phi_{ij}^{\alpha}(P_{\alpha,i}; r) = \phi_j^{\alpha} \cdot \psi_{ij}^{\alpha}(P_{\alpha,i}; r), \tag{3}$$

inside the unit localized in r. The variables $P_{\alpha,j}$ or $P'_{\alpha,j}$ will be identified as elementary physiological functions. More generally, μ products $P_{\alpha,i}$, $1 \leqslant \alpha \leqslant \mu$ 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:

$$F = f(F^1,F^2, \ldots, F^n), \tag{4}$$

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^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^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^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

at level l is the number v^l 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 FBS: $S^{(l)}(\boldsymbol{G}, T)$

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

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

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

$$a_{\alpha j} = 1 \Leftrightarrow P_{\alpha,j} \in u_j, \tag{5.1}$$

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

$$a_{\alpha j} = 0 \Leftrightarrow P_{\alpha,j} \notin u_j. \tag{5.2}$$

In the first case, the structural unit u_j is called a source. All structural units that do not possess P_α are called sinks. An elementary function is created from a source to a sink:

$$\psi^\alpha_{jk} \neq 0 \Leftrightarrow P_{\alpha,j} \in u_j \qquad P_{\alpha,k} \notin u_k. \tag{6}$$

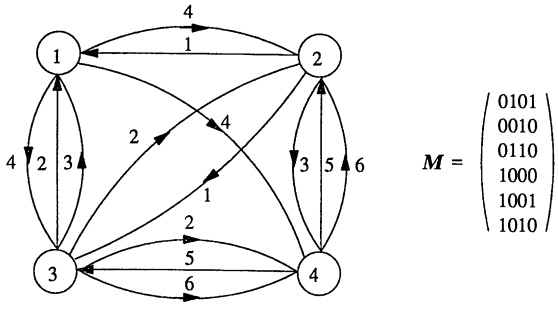

Figure 6. An example of a graph and its incidence matrix to describe, together, an organization whose degree equals 4. Numbers inside nodes of the graph represent the structural unit, i.e. the column of the matrix (on the right). Numbers along the arrows represent the product which is acting from the source to the sink, i.e. the rows of the matrix. Therefore, a row α is constituted by a zero in column j if the structural unit u_j is a sink for the product $P_{\alpha,j}$.

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

$$P_{\alpha,k} = \psi^\alpha_{jk}(P_{\alpha,j}),$$

$$F^k_\alpha = \Phi^\alpha_{jk}(P_{\alpha,j}) = \phi^\alpha_k \cdot \psi^\alpha_{jk}(P_{\alpha,j}). \tag{7}$$

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 $(n^{(l)}_\alpha)_{\alpha=1,\mu^{(l)}}$, of functional links between structural units at this level. Then $n^{(l)}_\alpha$ is also the number of zeros in the row α of the matrix $\boldsymbol{M}$, i.e. the number of sinks for the function P_α 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^ks. Its relation to equation (1) is clear: F^k represents the collective product created by the elementary functions ψ^α_{ij} 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):

$$\psi^{\alpha,kl}_{ij} = f^{\alpha,kl}_{ij}(\psi^{\alpha,11}_{11}, \ldots, \psi^{\alpha,nn}_{pp})$$

each of which describes the dynamics of elementary functions between an i-structural unit at level k (L^k) and a j-structural unit at level l (L^l): $i, j = 1, p$, and k, $l = 1, n$. When $\psi^{\alpha,kl}_{ij} \neq 0$ 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

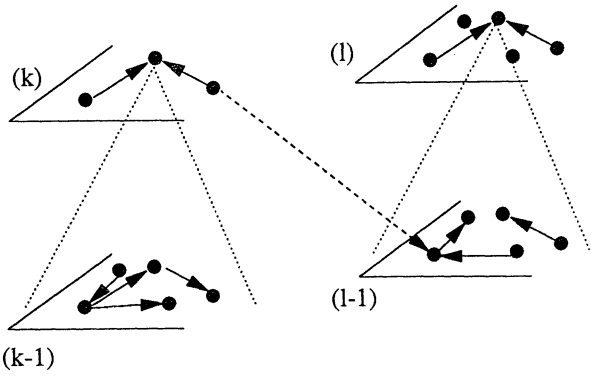

Figure 7. Functional interactions within and between levels of parallel hierarchical systems. In terms of functional interactions, a given unit at a level (k) is composed of a set of units at level ($k-1$), i.e. represents the collective behavior of these units, and is a physiological function. This physiological function is therefore a hierarchical system. The same structural unit can be included in the collective behavior of level ($l-1$) in another hierarchical system. An example is given by a system that controls another system, as shown by nervous system and respiratory system.

of organization. However, due (at least) to the relativism property, it appears to be necessary to distinguish between the structural association of the units involved in a given structure, and the functional association among units involved in a given physiological function. In terms of functional interactions, an organism is identified as a set of parallel hierarchical systems, one for each physiological function, and can be modeled and implemented on a parallel computer. Thus, one major aim will be to investigate the conservation laws applicable to a given interaction and to a set of interactions, i.e. a physiological function (see paper II), to determine which aspects of the related organization of an organism are kept invariant.

All these concepts and definitions are useful to conceive the biological functional organization of some systems. I have studied a particular system of metabolic and self-replicative units with two levels of organization: the so-called 'Eigen–Goodwin' system (Chauvet 1987), which will be considered in the following as an example of an evolutionary process. Such formalized description has additional interesting consequences regarding the concept of potential of functional organization, and the ability to define dynamics in the representation (ψ,ρ) (see paper II).

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 preceeding 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 $P_{\alpha,j}$, 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 $P_{\alpha,j}$.

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

1. The unit dies if $[[P_{\alpha,j}] < P_{\alpha,j}^{(0)}]$ where $P_{\alpha,j}^{(0)}$ is a threshold.
2. An association with other units whose properties are not necessarily identical, but which possess always a $P_{\alpha,i}$ such that $P_{\alpha,j} = \psi_{ij}^{\alpha}(P_{\alpha,i})$. Therefore, an α-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 metabolic system, for example from the product $P_i \equiv P_{i,u_1} \in u_1$ to the product $P_i^* \equiv P_{i,u_1^*} \in u_1^*$, with u_1^* be this unit. If u_1^* needs P_{i+1} for 'living', then, according to hypothesis I, an elementary function from u_1 to any other unit u_1^* has to be created. According to the notations defined in equations (7), let $\psi_{u_1 u_1^*}^{i}$ be this interaction which means that:

$$P_{i,u^*} = \psi_{u_1 u_1^*}^{i}(P_{i,u_1}) \qquad P_{i,u_1^*} \in u_1^* \qquad P_{i,u_1} \in u_1. \tag{9}$$

In the present case, with only one functional interaction represented by the product P_i emitted by u_1 and that acts on u_1^*, we can simplify the notations as follows:

$$P_i^* = \psi(P_i) \qquad P_i^* \in u_1^* \qquad P_i \in u_1. \tag{9'}$$

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_1^*. Therefore, P_{i+1} which is obtained from P_i in this unit disappears,

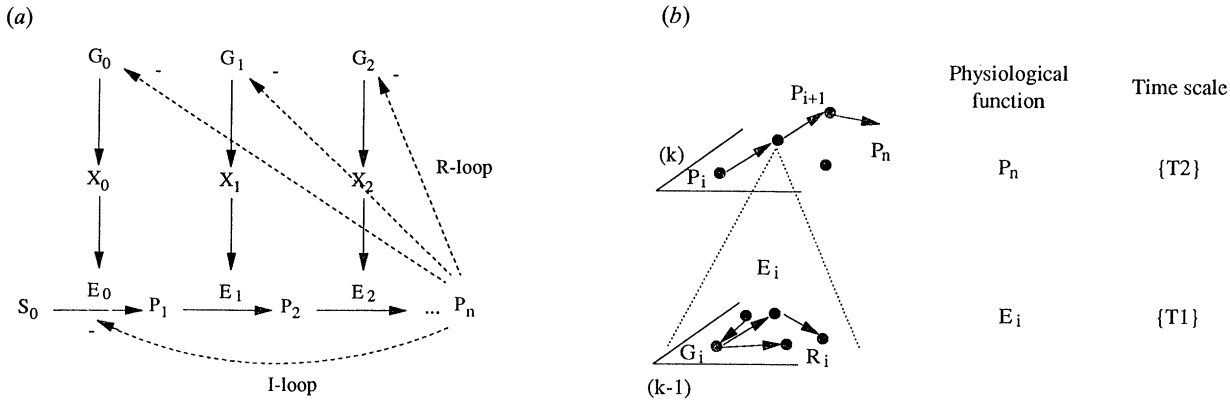

Figure 8. Goodwin model of a regulated enzymic pathway. (*a*) Enzymes E_i, $i = 0$, $n = 1$, result from clusters of structure genes such as G_i and polysomes R_i (top). They enter in a metabolic pathway which leads from substrate S_0 to the terminal product P_n. The synthesis of this product is regulated by an allosteric inhibitory feedback at G_i, and at enzyme E_0. For example, a unit u^* is obtained when enzyme E_1 is modified into E_1^* and disrupts the reaction $P_1 \rightarrow P_2$. (*b*) The same 2-level system where collective functions E_i and P_n are indicated at each level with their timescale.

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, $P_1 \in u_1$ can diffuse passively towards the 'pathological' unit u_1^*, and, when it arrives in u_1^* (we shall then call it, P_1^* 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:

$$\begin{array}{ccc} P_1 & \xrightarrow{\Phi} & P_2^* \\ \psi \searrow & \nearrow \phi, & \\ & P_1^* & \end{array} \qquad (10)$$

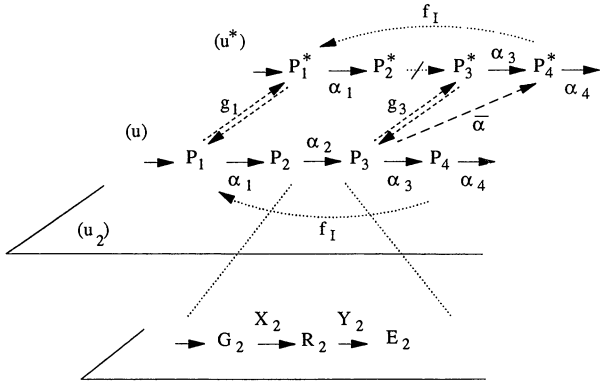

Figure 9. Association of two structural units, the hierarchical system described in figure 8*b*, for which one link is broken before P_3 in the biochemical pathway represented in figure 8*a*, for a unit u^*. The product P_3 in u is assumed to be carried in u^*, and acting (functionally) on P_4^*, in order to maintain the biochemical reactions. As in figure 8*a*, P_4^* feeds back on the first enzyme.

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

$$P_2^* = \Phi(P_1) = \phi \, o \, \psi(P_1),$$

i.e. equation (7). It is possible to consider various types of systems to describe these transformations by considering different mechanisms for Φ,ϕ,ψ:

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:

$$P_1 \xrightarrow{\Phi} P_2^*, \qquad (11)$$

where the direct transformation is denoted as Φ. 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 $\bar{\alpha}$.

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

$$\begin{array}{ccc} P_1 & \rightarrow & P_2^* \\ g_1 \searrow & & \nearrow \alpha_1, \\ & P_1^* & \end{array} \qquad (12)$$

where ψ and ϕ are replaced by linear transformations: (i) $g_1(P_1,P_1^*) = \beta(P_1 - P_1^*)$ to describe a simple passive diffusion with coefficient β, and (ii) $\phi(P_1^*) = P_2^*$ given by the kinetic equation:

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

to describe the chemical transformations with the rate constants α_1,α_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 {T2}, results from the collective behavior, i.e. the dynamics, of the epigenetic system at the lower level in a time scale {T1}. The control between the two levels is given by the feedback loop (R) from the end-product P_n that acts on $X_i \equiv [mRNA]$, the concentration of messenger RNA. The allosteric inhibitory interaction is described by the term:

$$f(P_n;\tilde{\omega},\kappa,\alpha_0) = \alpha/(\beta + \gamma P_n^{\tilde{\omega}}) = \alpha_0/(1 + \kappa P_n^{\tilde{\omega}}), \qquad (13)$$

with $\alpha_0 = \alpha/\beta$, and $\kappa = \gamma/\beta$. In this equation, $\tilde{\omega}$ is the stoechiometry of the interaction, i.e. $\tilde{\omega}$ molecules of the end-product P_n 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:

$$\begin{aligned} dX_i/dt^1 &= -\gamma_{X_i}X_i + f_{R,i}(P_n;\tilde{\omega}_R^i,\kappa_R^i,\alpha_{R,0}^i),\\ dE_i/dt^1 &= -\gamma_i E_i + \gamma'_{X_i}X_i,\\ t^1 &\in \{TI\}. \end{aligned} \qquad (14.1)$$

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:

$$\begin{aligned} dP_1/dt^2 &= -\alpha_1 P_1 + f_1(P_n;\ \tilde{\omega},\ \kappa,\ \alpha_0),\\ &\ldots\\ dP_i/dt^2 &= -\alpha_i P_i + \alpha_{i-1}P_{i-1},\\ dP_{i+1}/dt^2 &= -\alpha_{i+1}P_{i+1} + \alpha_i P_i,\\ t^2 &\in \{T2\}, \end{aligned} \qquad (14.2)$$

where $\gamma_{X_i},\gamma'_{X_i},\gamma_i,\alpha_i$, $i = 1,2,\ldots$, are the rate constants of the chemical reactions. The allosteric inhibition feedback term f_I is similar to that in equations (14.1), with different values of the parameters. This metabolic system is composed of enzymic reactions such as $P_i \rightarrow P_{i+1}$ with velocity $v_i = k_{3i}E_iP_i/(K_{M_i} + P_i)$, where $K_{M,i},k_{3i}$ are the Michaelis constants of enzyme E_i, and the rate constant of the reaction: $E_iP_i \rightarrow E_i + P_{i+1}$. If $P_i \ll K_{M,i}$ then $v_i = (k_{3i}/K_{M,i})\ E_iP_i = \alpha_iP_i$.

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_n. Therefore, because of the functional hierarchy, α_i is a constant in the system (14.2).

(ii) *Dynamics of the metabolic pathway in a u_2-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):

$$\begin{array}{ccccccccc} & & \overset{\alpha_1}{\rightarrow} & & \overset{\alpha_2}{\rightarrow} & & \overset{\alpha_3}{\rightarrow} & & \overset{\alpha_4}{\rightarrow}\ldots\\ & & P_1^* & & P_2^* & & P_3^* & & P_4^*\\ & g_1\uparrow\downarrow & & g_2\uparrow\downarrow & & g_3\uparrow\downarrow & & g_4\uparrow\downarrow & \\ & & P_1 & & P_2 & & P_3 & & P_4\\ & & \underset{\alpha_1}{\rightarrow} & & \underset{\alpha_2}{\rightarrow} & & \underset{\alpha_3}{\rightarrow} & & \underset{\alpha_4}{\rightarrow}\ldots, \end{array} \qquad (15)$$

where each product can diffuse from one unit to the other according to the transport function $g_i(P_i,P_i^*)$. The corresponding dynamical system is:

$$\begin{aligned} dP_i/dt &= \alpha_{i-1}P_{i-1} - \alpha_iP_i - g_i(P_i,P_i^*),\\ dP_i^*/dt &= \alpha_{i-1}P_{i-1}^* - \alpha_iP_i^* + g_i(P_i,P_i^*),\\ i &= 2,3,\ldots. \end{aligned} \qquad (16)$$

In the present case of association between the metabolic systems (14.2) where $n = 4$, let us assume, for example, that α_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_1^* can also diffuse towards u_1, the following schema, deduced from (15), will be obtained:

$$\begin{array}{ccccccccc} \downarrow & & & & & & & & \uparrow\\ & & \overset{\alpha_1}{\rightarrow} & & \overset{\alpha_2}{\rightarrow} & & \overset{\alpha_3}{\rightarrow} & & \overset{\alpha_4}{\rightarrow}\\ & & P_1^* & & P_2^* & & P_3^* & & P_4^* & \rightarrow\\ g_1\uparrow\downarrow & & & & g_2\uparrow\downarrow & & & & & .\\ & & P_1 & & P_2 & & P_3 & & P_4 & \rightarrow\\ & & \underset{\alpha_1}{\rightarrow} & & \underset{\alpha_2}{\rightarrow} & & \underset{\alpha_3}{\rightarrow} & & \underset{\alpha_4}{\rightarrow} & \\ \uparrow & & & & & & & & \downarrow & \end{array} \qquad (17)$$

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

$$\begin{aligned} dP_1/dt &= -\alpha_1P_1 + f_{I,4}(P_4;\ \tilde{\omega},\kappa,\alpha_0) - g_1(P_1,P_1^*),\\ dP_2/dt &= -\alpha_2P_2 + \alpha_1P_1,\\ dP_3/dt &= -\alpha_3P_3 + \alpha_2P_2 - g_3(P_3,P_3^*),\\ dP_4/dt &= -\alpha_4P_4 + \alpha_3P_3,\\ dP_1^*/dt &= -\alpha_1P_1^* + f_{I,4}(P_4^*;\ \tilde{\omega},\kappa,\alpha_0) + g_1(P_1,P_1^*),\\ dP_2^*/dt &= \alpha_1P_1^*,\\ dP_3^*/dt &= -\alpha_3P_3^* + g_3(P_3,P_3^*),\\ dP_4^*/dt &= -\alpha_4P_4^* + \alpha_3P_3^*. \end{aligned} \qquad (18)$$

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

$$\begin{aligned} g_1(P_1,P_1^*) &= \beta_1(P_1 - P_1^*),\\ g_3(P_3,P_3^*) &= \beta_3(P_3 - P_3^*). \end{aligned}$$

We can simplify this kinetic system by using the schema (11) rather than (10), i.e. by introducing the constant $\bar{\alpha}$. With the non direct feed-back of P_4^* on P_1, the following system of equations is obtained:

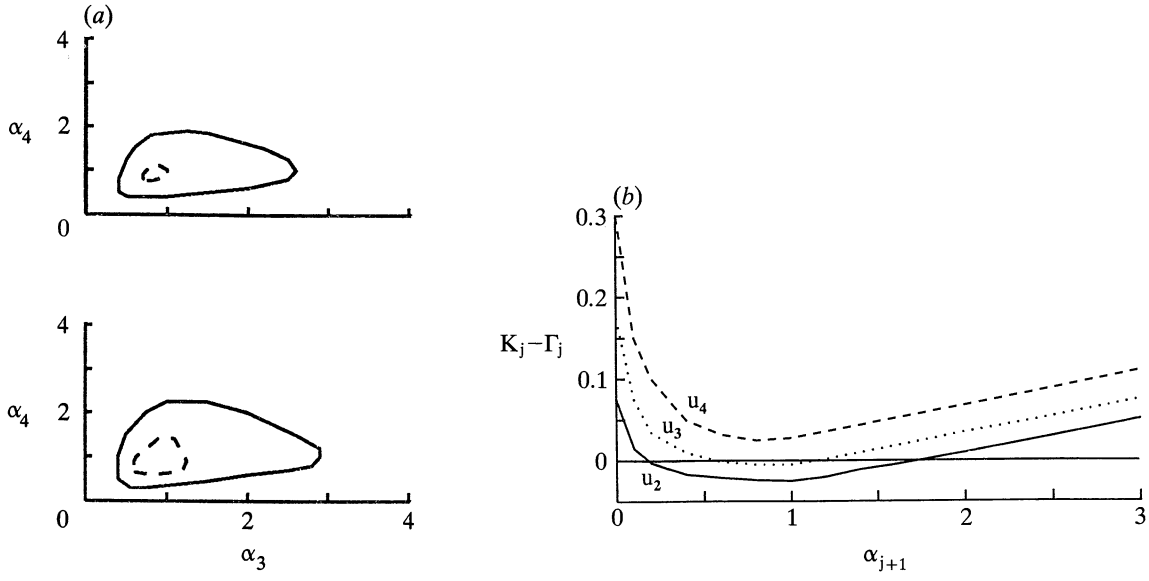

Figure 10. (*a*) Stability area is increasing when the system (10) (full lines) is complexified into system (12) (dotted lines). For each system, i.e. each closed curve, the corresponding domain of stability is outside the internal space: expression of the condition of stability in plane $\bar{\alpha} = 1$, for two values of κ ($\kappa = 0.1$, 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_1. 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 α_{j+1} for $j = 1,2,3$ (Machbub *et al.* 1992).

$$\begin{aligned}
dP_1/dt &= -\alpha_1 P_1 + f_{I,4}(P_4;\, \tilde{\omega},\kappa,\alpha_0) + f_{I,4}(P_4^*;\, \tilde{\omega},\kappa,\alpha_0),\\
dP_2/dt &= -\alpha_2 P_2 + \alpha_1 P_1,\\
dP_3/dt &= -(\alpha_3 + \bar{\alpha})P_3 + \alpha_2 P_2,\\
dP_4 dt &= -\alpha_4 P_4 + \alpha_3 P_3,\\
dP_4^*/dt &= -\alpha_4 P_4^* + \bar{\alpha} P_3,
\end{aligned} \tag{19}$$

where $\bar{\alpha}$ is a positive constant, included in Φ as explained in paragraph 1 above, which simply describes the non-local contribution of product $P_3 \in u_1$ to the production of $P_4^* \in u_1^*$. It is assumed here that P_4^* can modify the synthesis of P_1 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 $u_2 \equiv (u_1\ u_1^*)$ (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 $u(r_0)$ and in $u^*(r)$ at two points r_0 and r. 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:

$$\zeta = (\alpha_0\alpha_X\alpha_Y\alpha_1\,\kappa^{1/\tilde{\omega}})^{1/4} \qquad t^* = \zeta t \qquad b_1 = \alpha_X/\zeta \qquad b_2 = \alpha_Y/\zeta \qquad b_{i+2} = \alpha_i/\zeta, \qquad i = 1,2. \tag{20}$$

A new system of equations is obtained:

$$\frac{dx_1}{dt} = -b_1 x_1 + \frac{1}{1 + x_4^{\tilde{\omega}}} + \frac{1}{1 + \left(\dfrac{b_5}{b_3}x_5\right)^{\tilde{\omega}}}, \tag{21.1}$$

$$dx_2/dt = -b_2 x_2 + x_1, \tag{21.2}$$

$$dx_3/dt = -(b_3 + b_5)x_3 + x_2, \tag{21.3}$$

$$dx_4/dt = -b_4 x_4 + x_3, \tag{21.4}$$

$$dx_5/dt = -b_4 x_5 + x_3, \tag{21.5}$$

in terms of new state variables:

$$\begin{aligned}
&t^* = a_0 t \quad x_1(t^*) = a_1 X(t) \quad x_2(t^*) = a_2 Y(t),\\
&x_3(t^*) = a_3 P_1(t) \quad x_4(t^*) = a_4 P_2(t) \quad x_5(t^*) = a_5 P_2^*(t),
\end{aligned} \tag{22}$$

now with dimensionless coefficients a_i and b_i in place of dimensional ones α_i, κ and $\tilde{\omega}$. In this example, the functional interaction (9), created by a survival condition (hypothesis I), is mathematically expressed by equation (21.5), 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 (1969*a*,*b*), Viniegra-Gonzalez (1973) and Rapp (1976), have studied the stability of the system

(10), which describes the time evolution of units u_1, and they determined sufficient conditions for the system to be asymptotically stable. Chauvet & Girou (1983) deduced the stability of system (21), which represents $u_2 \equiv (u_1,u_1^*)$, 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 $u_2 \equiv (u_1,u_1^*)$ is larger than the domain of stability of the preceding one (14.2) with $n = 4$ for units u_1, i.e. more stable. Results are shown on figure 10. For a given set $(\alpha_0,\alpha_1,\alpha_2,\tilde{\omega})$ of parameters, the condition of stability of system (14.2) (with $n = 4$) is studied in the plane (α_3,α_4). 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,u^*)) for various values of $\bar{\alpha}$ (only one value of $\bar{\alpha}$ is represented in figure 10*a*), and for increasing values of parameter κ, which both describe the existence of the association. We can see that the area of stability (represented by the space outside the dotted lines) increases when the formal biological system is complexified. In other words, unit $u_2 \equiv (u_1, u_1^*)$ is metabolically 'more stable' than unit u_1. 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 $u_j \equiv (u_{j-1},u_1^*)$ that are obtained with the same self-association process as $u_2 \equiv (u_1,u_1^*)$. The linear part of the system is shown to be exponentially stable. Moreover, the stationary states of u_j are asymptotically stable through a balance between the linear and non-linear terms of the equation that describes the time evolution of u_j. An important result has been obtained for the domains of stability of successive units u_j: locally, unit u_j is more stable than u_{j-1}. All these results are confirmed numerically (Machbub *et al.* 1992): successive associations increase the domain of stability (figure 10*b*). 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_2-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: $\alpha_1 = \alpha_2 = 1.$, $\alpha_0 = 50.$, $\kappa = 1$. Coupling between the two units is realized by simple passive transport: $g_i(P_i,P_i^*) = \beta_i(P_i - P_i^*)\ \forall i$, and the study is made in the plane, α_3,α_4. An increase in stability can be shown even when all the coefficients β_i are assumed to be unequal, and, in this case, the higher the value of β_i, i.e. the 'intensity' of the coupling, the wider is the area of stability.

(*c*) *Dynamics of the population of units $u_2 \equiv (u_1,u_1^*)$ at level 3 (U): idempotence of the structural units*

The unit u_1 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_n 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_n denotes the set of units like u_n, then the population:

$$U = \bigcup_{n=1}^{r} U_n,$$

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

$$\mathrm{d}u_n/\mathrm{d}t = (a_n - \lambda(u_1,u_2,\ldots,u_n))u_n + \sum_{i+j=n} k_{ij}u_iu_j, \qquad (23.1)$$

$$\sum_n n\,u_n = c \qquad n = 1,2,\ldots,r, \qquad (23.2)$$

where k_{ij} is a coupling parameter between both levels of organization (M) and (U). Here λ is a function that expresses the condition of conservation for the total number of elementary species like u_1. 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:

$$F = f(\Phi(P_3)), \qquad (24)$$

because in this example only one functional interaction Φ exists, which creates the non-symmetry source $\rightarrow$ 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 λ would be the dilution factor Ω. This conservation equation (23.2) leads to:

$$\sum_n n\left(\frac{\mathrm{d}u_n}{\mathrm{d}t}\right) = 0, \qquad (25)$$

and:

$$c\lambda(u_1,u_2,\ldots,u_n) = \sum_n na_nu_n + \sum_n n \sum_{i+j=n} k_{ij}u_iu_j. \qquad (26)$$

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

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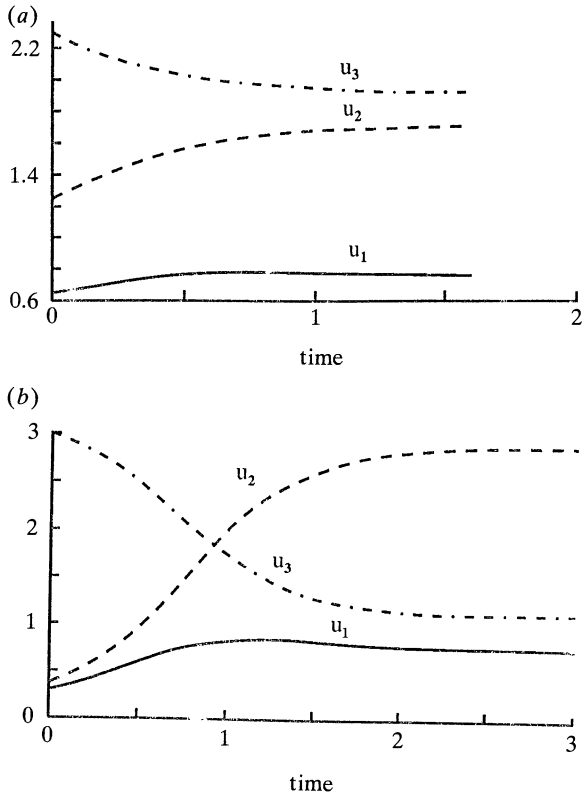

Figure 11. Effect of the self-organization parameter $k \neq k' = k''$ on the selective value for a (u_1,u_2,u_3)-Eigen system: concentrations of units u_1,u_2,u_3 are represented versus time. (*a*) $k = k' = 3$, no selection of units; (*b*) $k = 5$, $k' = 1$, selection of units u_2.

$r = 3$ shows the existence of two stable states for the first system. For $r = 2$, the following Eigen system, where u^* is a constant (an initial condition in this problem), is obtained:

$$du_1/dt = (\alpha - f)u_1,$$

$$du_2/dt = (\beta - f)u_2 + k(P)u_1u_2,$$

$$u_1 + 2u_2 = c, \qquad (27)$$

with the condition:

$$f(u_1,u_2) = (\alpha/c)u_1 + 2(\beta/c)u_2 + 2(k/c)u_1u_2, \qquad (28)$$

and for $r = 3$, an equation has to be added:

$$du_3/dt = (\gamma - f)u_3 + k'u_1u_2 + k''u_2u_1. \qquad (29)$$

This expression shows that the dynamics of units u_1, u_2,u_3 depend on three coupling parameters, denoted by $k(P)$, $k'(P)$, $k''(P)$. A numerical simulation of these systems with $k \neq k' = k''$ leads to a large increase in the population $U_2 = \{u_2;\ u_2 \equiv ((u_1,u_1^*),\ (u_1^*,u_1))\}$, and a selection of u_2-species as a consequence thereof (figure 11).

(*d*) *Stability of the 3-Level Goodwin–Eigen FBS*

Two important properties for the stability of metabolic units that are created by self-association have now been proved (Machbub *et al.* 1992): (i) the nonlinear system of self-associative units is always stable (with their solutions remaining bounded), because the domain of instability of the linearized 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 Φ 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 Γ that replace α_iP_i, and non-local and local diffusion transport terms that replace $g_i(P_i,P_1^*)$. 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 ψ,ρ) 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 ψ satisfies dynamics in the representation (ψ,ρ) where the geometry is given by the density ρ 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 (ψ,ρ).

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_j is given by:

$$dN_j/dt = \left(\sum_k a_{kj}F_{kj} + a_{ej}F_{ej}\right) + \left(\sum_k b_{jk}F_{jk}\right) + Env_j, \qquad (30)$$

where N_j is the number of elements in a class E_j, of states F_{kj} the number of elementary transformations per time unit from a class E_j to a class E_k, and F_{ej} the number of elementary transformations per time unit towards the environment. Generally:

$$F = KN_j^{\alpha_j}N_{j+1}^{\alpha_{j+1}} \ldots N_{j+p}^{\alpha_{j+p}}. \qquad (31)$$

When the transformation involves a_j elements of E_j, . . ., a_{j+p} elements of E_{j+p}, . . ., then Env_j describes inputs $(Env_j > 0)$ or outputs $(Env_j < 0)$ for elements of E_j. Inputs and outputs are independent of the number of elements (say, the occupation number) of E_j. So N represents the occupation number of the classes, and a the rate constant of the transformations between classes. Now, ψ 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 ρ. Then, because ψ and ρ could be deduced, but with difficulty, from N and a, the (ψ,ρ)- 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 (ψ,ρ).

(*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 FBS 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, FBS 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

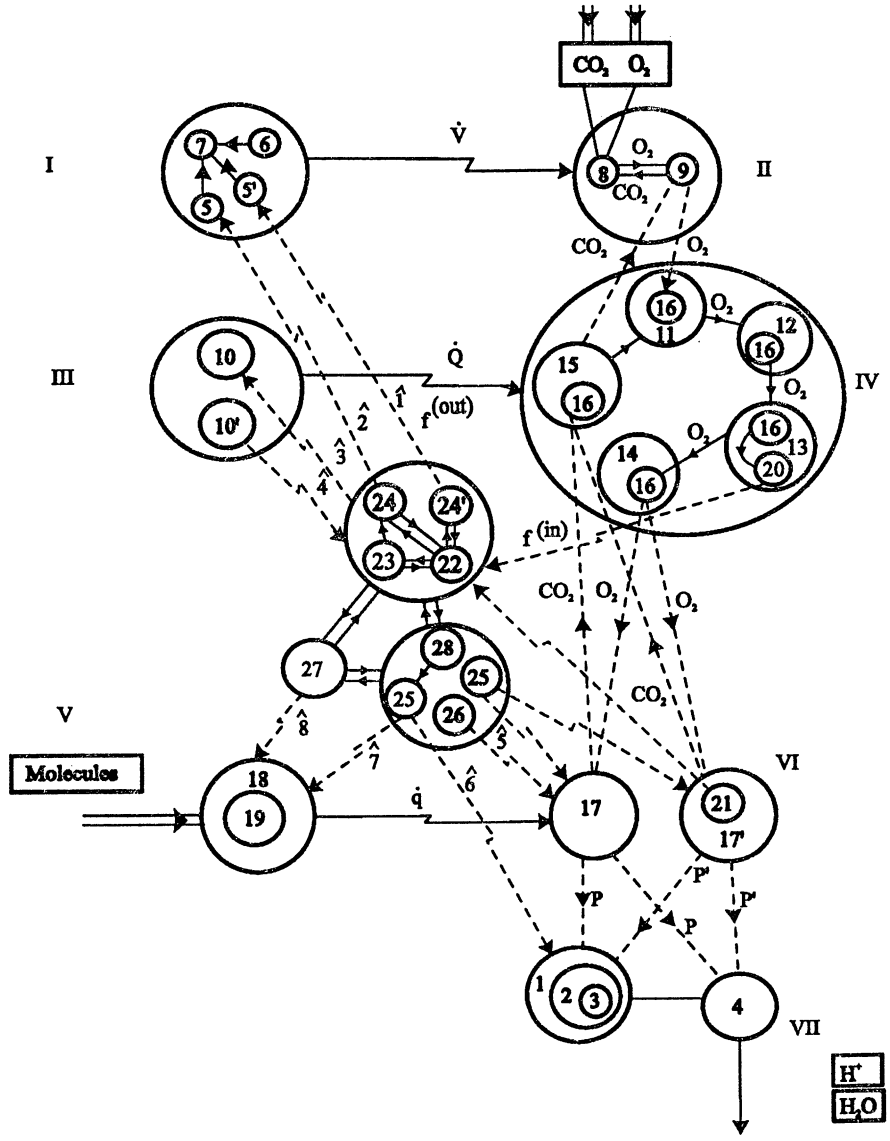

Figure 12. Functional interactions for the respiratory system. $f^{(\,)}$, $\hat{\imath}=1,8$ are control functional interactions; P, P' = hydrostatic pressure; $\dot{Q}$ = fluid flow; $\dot{V}$ = ventilation; $\dot{q}$ = metabolic flow. Inputs: Molecules, O_2, CO_2. Output: H^+, H_2O.

Nomenclature:

- Motor pressure: I
  - Muscles:
    - Inspiratory 5
    - Expiratory 5′
  - Diaphragm 6
  - Pleurum 7
- Ventilatory mechanics: II
  - Bronchii 8
  - Alveolii 9
- Heart: III
  - Myocardium 10
- Vessels: IV
  - Pulmonary vessels:
    - Capillaries 11
    - Veins 12
    - Arteries 13
  - Tissue vessels:
    - Capillaries 14
    - Veins 15
  - Haemoglobin 16
  - Chemo-receptors 20
- Digestive system: V
  - Intestines 18
  - Mitochondria 19
- All cells and receptors: VI
  - All cells 17
  - Mechano-receptors 21
- Kidney: VII
  - Tubules 1
  - Tubular cells 2
  - Membrane 3
  - Collecting tubule 4
- Nervous control
- Respiratory control
  - Neuronal pools 22
  - Pneumotaxic centres 23
  - Bulbus centres:
    - Inspiratory 24
    - Expiratory 24′
- Hormonal control
  - Pancreatic cells 25
  - Thyroid cells 26
  - Post-hypophysis 27
  - Hypothalamus 28

capillaries, arteries and veins and haemoglobin; (iv) metabolical 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

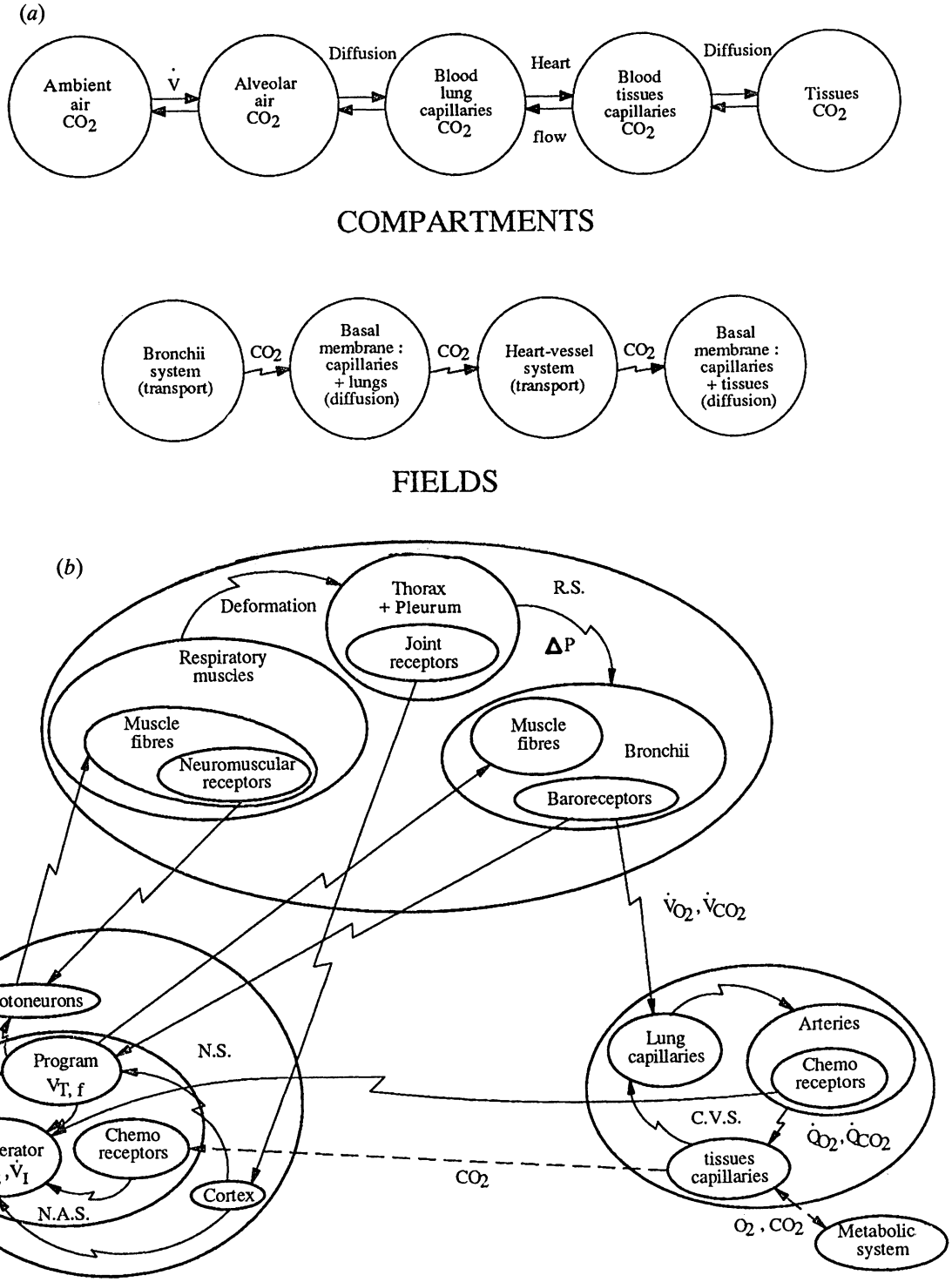

Figure 13. (*a*) Ventilatory function represented (above) in representation (N,a), (below) in representation (ψ,ρ); (*b*) the same function represented as a hierarchical system connected with nervous and cardio-vascular functions according to functional interactions. R.S. = respiratory System; m.f. =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

interactions between the corresponding sub-systems can be viewed as control links (noted $\hat{1}$ to $\hat{4}$ 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 (ψ,ρ) 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 haemoglobina in capillaries) constitutes a compartment. In the dual (N,a)-representation that includes the ψ-space, a hierarchical system of structural units, whose collec-

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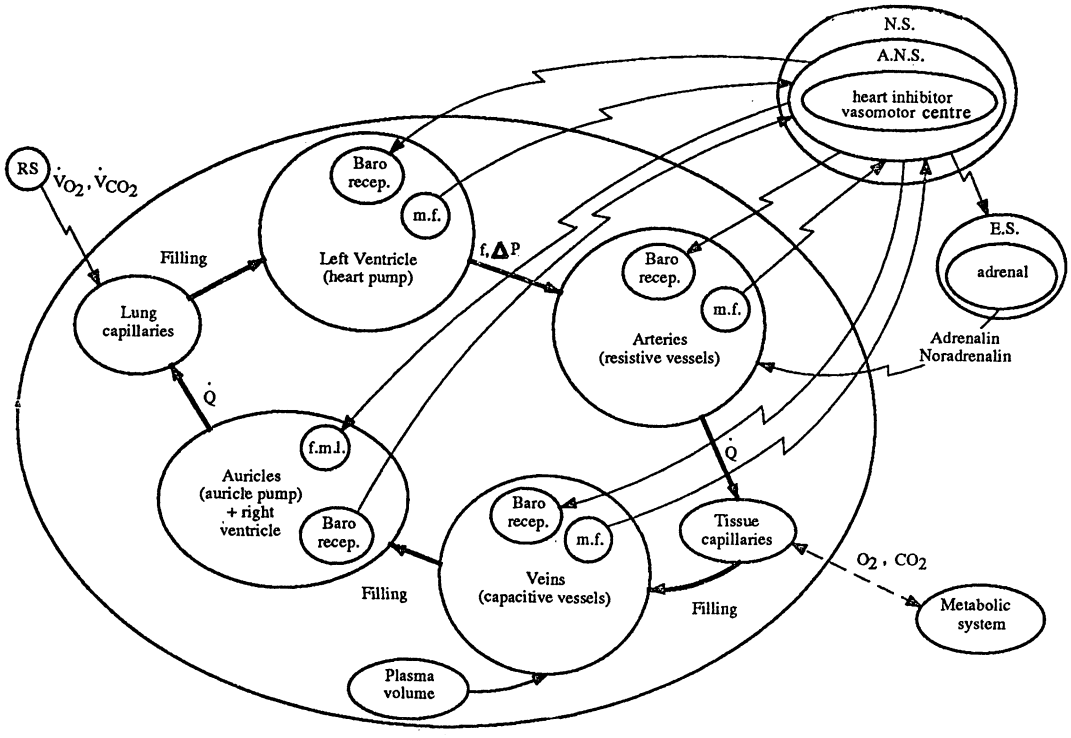

Figure 14. Hierarchical graph of the heart-vascular function with the heart shock sub-graph represented in bold arrows. R.S. = respiratory system; m.f. = muscle fibers; E.S. = endocrine system; N.S. = nervous system; A.N.S. = autonomous nervous system; f = frequency; ΔP = pressure gradient.

tive behaviour is a physiological function, corresponds to bilateral exchanges between compartments (figure 13*a*). By choosing a specific representation, actions and substrates are not mixed. Figure 13*b* 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

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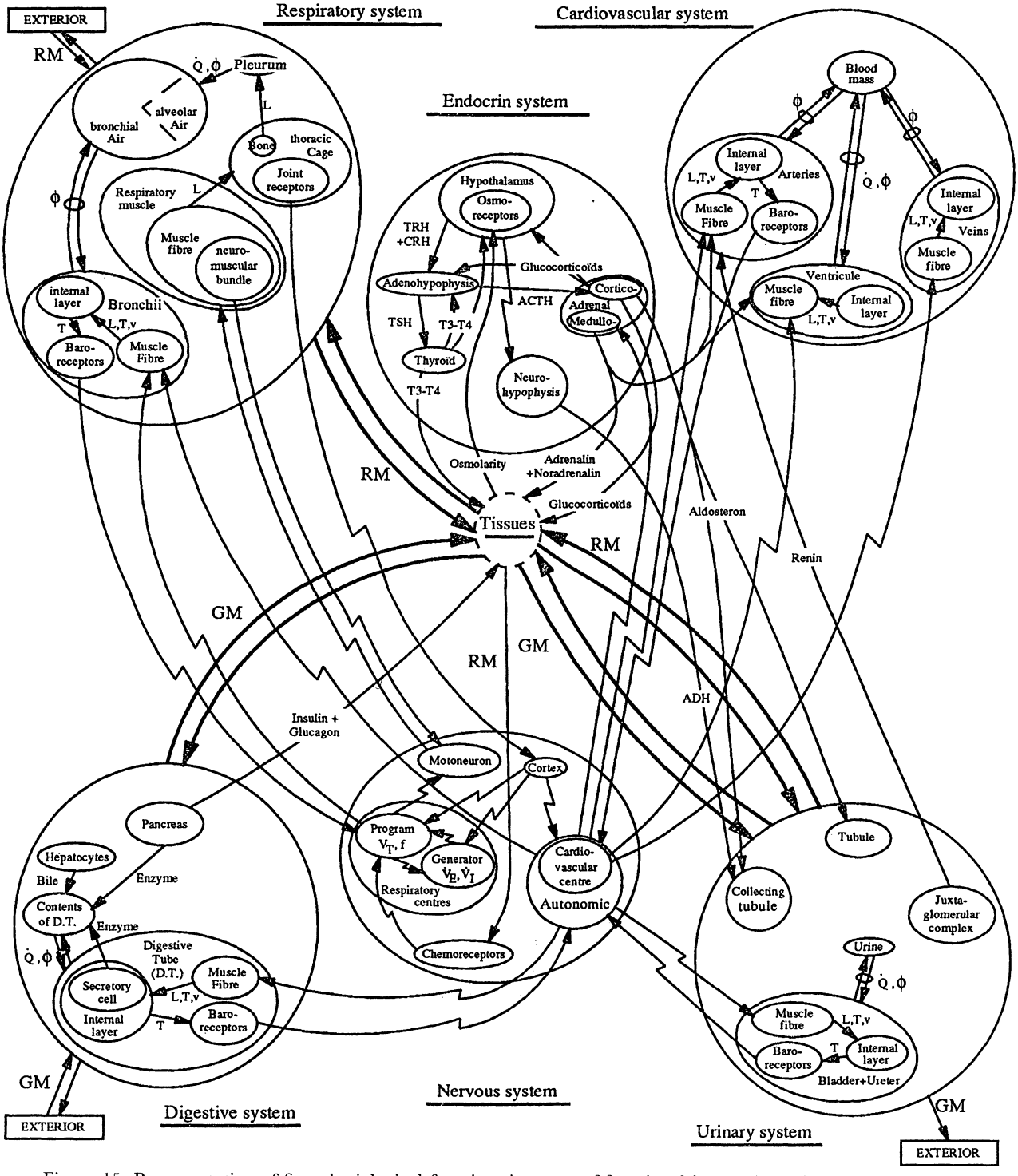

Figure 15. Representation of five physiological functions in terms of functional interactions. An illustration of the relationships between the physiological functions previously described. The complexity is such that a computer is required to reconstruct the corresponding hierarchical systems. The 'balloons' describe the various hierarchized levels. d = diameter; $\dot{Q}$ = fluid flow; $\dot{V}$ = ventilation; RM = respiratory metabolites; GM = general metabolites (see text for other symbols).

existence of the interactions, then the existence of the elementary physiological function. The distribution $(n_\alpha)_{\alpha=1,\mu}$ 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 $(n_\alpha^l)_{\alpha=1,\mu}$ 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

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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