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Foundations of metabolic organization: coherence as a basis of computational properties in metabolic networks

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Abstract

Biological organization is based on the coherent energy transfer allowing for macromolecules to operate with high efficiency and realize computation. Computation is executed with virtually 100% efficiency via the coherent operation of molecular machines in which low-energy recognitions trigger energy-driven non-equilibrium dynamic processes. The recognition process is of quantum mechanical nature being a non-demolition measurement. It underlies the enzymatic conversion of a substrate into the product (an elementary metabolic phenomenon); the switching via separation of the direct and reverse routes in futile cycles provides the generation and complication of metabolic networks (coherence within cycles is maintained by the supramolecular organization of enzymes); the genetic level corresponding to the appearance of digital information is based on reflective arrows (catalysts realize their own self-reproduction) and operation of hypercycles. Every metabolic cycle via reciprocal regulation of both its halves can generate rhythms and spatial structures (resulting from the temporally organized depositions from the cycles). Via coherent events which percolate from the elementary submolecular level to organismic entities, self-assembly based on the molecular complementarity is realized and the dynamic informational field operating within the metabolic network is generated.

Keywords: Coherence; Computation; Futile cycle; Information transfer; Metabolic network; Morphogenesis; Non-locality; Switching

1. Introduction

The temporal and the spatial organization of biosystems is essentially determined by their dynamic structure which in turn is based on metabolic organization. The limited energy autonomy of living systems from local, high-energy

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potentials is achieved via their internal metabolic structure by the sensitivity to non-local low-energy fluxes. A certain subsystem (the 'epistemon') is capable of interactions with these low-energy constraints (Barham, 1990, 1996). This explains the adaptive behavior of biological systems and their internal dynamical organization. The interaction between the high-energy (based on the dynamic coherent non-equilibrium energy-driven processes) and the low-energy constraints (based on quantum coherent phenomena) underlies biological organization (Igamberdiev, 1992, 1993). Low-energy recognitions, possibly based on the bosonic fields, trigger energy-driven non-equilibrium dynamic process.

The concept of coherence as an organizing principle of biological structures was introduced by Gurwitsch (1923) who formulated the idea of a low-energetic field determining the biosystem's organization as a total entity. In his views, this field determines the continuous operation of a biosystem, whereas the discrete representation of biosystems is illustrated by the Mendelian, genetic approach. On a quantum level, a coherence via synchronization of phases of the wave functions between different components possessing non-local character is realized. Quantum coherence means that the de Broglie wavelengths of the particles are overlapping, and their trajectories emerge through a dynamical form-generating process. It determines properties at a certain space-time point when they are known at another. Coherent states involving Bose–Einstein condensation (the most ordered form of condensed phase possible when a macroscopic number of particles occupies the same single-particle state) actually bridge the gap between micro and macroscales, realizing the 'prehension' (Whitehead, 1929) of single points into total entities.

The dynamics of enzymes and high-order structures is explained by coherent phenomena (Fröhlich, 1983). The quantum coherent state is limited by the minimum uncertainty condition (Li, 1995), allowing for the provision of computation and information transfer with almost 100% efficiency. The information based on specific recognitions triggering dynamical energy-driven processes appears as non-digital; the transfer of digital information is realized within hypercycles and corresponds to the operation of the genetic code.

In terms of quantum mechanics, Planck's constant determines the condition of the smallest possible time interval that is necessary to transfer the energy of a wave to the ideal detector system (Popp, 1995), and real times of measurement form concrete patterns of interactions leading to the realization of coherent events and formation of spatial structures. Dicke (1959) showed that the ordinary imaging of spontaneous reemission of light from optically dense media (i.e. interference pattern) becomes completely changed as soon as mutual distances of absorbing molecular antennae get much smaller than the wavelength of light. These events based on multiple propagation and diffraction can significantly improve the degree of coherence of light. Sequential quantum measurements generate a time irreversible process organized as a set of multiple coherent events (Dicke, 1989). On macroscales coherence involving energy-driven ordering of processes represents another scale of coherent phenomena. Coherence is a physical representation of the integrative principle coordinating individual events in the organized state.

The goal of this paper is to trace coherent events from the macromolecular to the morphogenetic level, and to define possible ways for theoretical description of metabolism which functions as an interconnecting network for different levels of organization of biosystems. I will discuss how the computable events are formed and maintained by the coherent phenomena. A variety of models have been proposed which may fit together in the framework of coherence. Some of ideas presented here are difficult to examine experimentally at present, however, it is important to introduce them as a basis for further discussion of biological organization.

2. Enzyme operation as a cyclic process with coherent energy transfer

The enzyme molecule is a basic unit of biological organization. Recognition of substrates by

enzymes is connected with the correspondence of the active site of the enzyme to certain molecular coordinates of a substrate (key-lock paradigm). It is an example of molecular complementarity (Root-Bernstein and Dillon, 1997) percolating to different levels of biological organization. In general, the recognition process is quantum–mechanical in nature, being a non-demolition measurement characterized by low energy dissipation and hence by high precision (Igamberdiev, 1993, 1998). During this process, the bosonic fields mediate momentum exchange between the enzyme and the substrate leading to the formation of joint coordinate scale and then to the redistribution of atoms within new coordinates (the conversion of a substrate into product). The joint wave function may collapse whenever the two bosonic fields (of the enzyme and the substrate) overlap and share an identity (or when they cease to do so) (Zohar, 1990).

Such a mechanism for enzyme–substrate interaction is speculative, however, it is indirectly supported by the experiments of Comorosan (1975) who observed the enhancement of enzymic activities which appear only at sharply defined substrate irradiation times at certain wavelengths. The following parameters were introduced: (a) a minimum substrate irradiation time inducing the first effect (t_m) and (b) a fixed time period that delimits two successive effects denoted by the τ parameter (Comorosan et al., 1972). Different enzymes and isozymes reveal higher activities at different irradiation times.

Computational power of enzymes cannot be deduced from their elementary structure: it is essentially unprogrammable (Conrad, 1992). Electronic-conformational interactions during an enzyme's operation constitute a non-classical-classical interface through which percolation to the macro level is realized (Conrad, 1984, 1994). Wave function reduction (collapse of superpositions) must continually occur due to the continual redefinition of forces between particles. Such mediation of forces takes place during enzyme operation (in electronic-conformational interactions). Therefore we can view the visible structures of biological systems as exploiting the unmanifest structures of the vacuum in order to perpetuate themselves (Conrad, 1996).

There is an essential provision and enhancement of computation via coherence. It is possible that this may be based on the emergence of the entangled particles within the enzyme molecules which are involved in the transformation of the initial state (corresponding to interaction with substrate molecule) to the final state (of the releasing of a product molecule) as was shown for the quantum teleportation phenomenon (Bouwmeester et al., 1997). The computation should be executed with virtually 100% efficiency which is realized via the non-demolition coherent operation of molecular machines. Coherent dipole oscillations were for the first time postulated by Fröhlich (1983) for explanation of enzyme operation which should be based on the resonant electromagnetic energy transfer on a frequency specific for each observed interaction. Proteins and their targets may have the same characteristic frequencies. A soliton-like mechanism was proposed to be involved in the resonance recognition process (Ciblis and Cosic, 1997), and excitations produce oscillations of particular frequencies.

The energy released when a substrate is recognized by the enzyme molecule (which corresponds to a new coordinate scale emerged) turns the latter into the different alternate conformation which results in the realization of the actual work of substrate conversion into the product (Blumenfeld, 1983). This conformational movement passes slowly, providing for the transition to a macroscopic time scale. This fact can explain high specificity of enzyme operation in accordance to the quantum non-demolition measurement theory of Braginsky et al. (1980) (Igamberdiev, 1992, 1993). Enzyme operation corresponds to the realization of a 'squeezed' state in quantum measurement, which is considered as a basic event in information transfer and computation (Braginsky and Khalili, 1992). Slow conformation changes in biomolecules allow for a long-lived transition state within which many of energy quanta correlate coherently (Matsuno, 1995).

In the presence of a substrate, the process of conformational movement is connected with the realization of highly effective and specific actual work. The reverse transition in the enzyme–substrate cycle is identical to the transition in the

absence of substrate molecule. During this transition the energy which is not transformed into the actual work is released, and this corresponds to its dissipation. The direct (with substrate) and the reverse (after releasing a product) conformational movements of an enzyme molecule are realized by different routes, and there is an elementary cyclic structure representing the catalytic process. This cycle is characterized by different pathways for the enzyme–substrate complex formation and decomposition. According to Conrad (1979), an enzyme can be considered as a macromolecule which makes possible a cyclic reaction involving an energy loan which is used for barrier removal and which arises from transient pairing.

The enzyme–substrate cycles are characterized by a clear distinction between the catalyst and the substrate and therefore by hierarchical (two-level) structure. In oscillatory chemical reactions, an intermediate serves at a certain stage as a catalyst, whereas in the enzyme–substrate cycle the catalyst is strongly distinguished from the substrate and acts as a molecular machine. The direct and the reverse vectors forming the cycle are found to be quite different: in the presence of a substrate the initially linear structure of the reaction is transformed into the cyclic structure and switching (logical gate) is realized. The absence of distinction between the catalyst and the substrate in biosystems is evident only during the processing of biological macromolecules, e.g. in autocatalytic splicing of RNA-precursors and also during protein folding which is regarded as an autocatalytic process based on intramolecular specific recognitions (Conrad, 1979; Veeraraghavan et al., 1996). We can hypothesize that enzymatic catalysis was built over these autocatalytic processes which themselves were 'improved' via participation of chaperonins filtering out of intramolecular interference so that incorrect associations are avoided. Enzymatic catalysis may have been preceded by the less specific and slower primarily catalytic process realized by molecules now serving as coenzymes (Maden, 1995). Emergence of autocatalysis from the simple chemical reactions of lower amino acids was proposed by Gurwitsch and Gurwitsch (1942).

The energy release after substrate sorbtion in the active site leads to the division of charges inside the enzyme–substrate complex resulting in their deposition in different parts of the protein molecule (Green and Vande Zande, 1981). A similar deposition of charges takes place on the opposite sides of biomembranes during the chemiosmotic process. Here the basic quantum coherence participating in the initial recognition process triggers dynamic energy-driven coherence. Long-range mobile protonic states are the most essential coherent events in organized cellular processes via which interactions of the electronic and the nuclear degrees of freedom are realized. The energy of the divided but non-locally connected charges is used for substrate conversion via breakage and formation of chemical bonds. Therefore the effect of deposition (in this case of charge deposition) is essential during enzyme–substrate interactions. Enzymes serve as intermediary agents in coupling mobile protons to chemical reaction coordinates (Welch and Berry, 1983).

After the formation of a cycle, the non-equilibrium state is consistently reproduced according to the principle of steady non-equilibrium state formulated by Bauer (1935). Thus, the cycle is represented as an elementary non-equilibrium structure which determines the temporal (rhythmic) and the spatial (morphological) parameters of the biosystem. The first parameters are determined by the periods of cycle turnover, whereas the second are determined by the depositions from the cycles.

Coherence within cycles is maintained by the supramolecular organization of enzymes forming cycles which are assembled in multienzyme complexes (metabolons). Assembly in metabolons is possible because of the specific recognition of molecules of different enzymes, and of specific relation of consequent enzyme to preceding enzyme-product complex (Welch and Berry, 1985). The enzymes constituting metabolons are organized in such a way that the enzymes of the direct and reverse routes are regulated reciprocally in a metabolon structure, e.g. dehydrogenases of the Krebs cycle forming NADH are connected with NADH dehydrogenase of electron transport chain (Srere, 1987) and that organization facilitates

metabolic channeling and maintenance of the NADH/NAD ratio in a homeostatic manner particularly in response to external influences. It has been proposed that the metabolic channeling of NAD(P)H occurs between dehydrogenases differing in stereospecificity (to A- and B-hydrogen atoms of nicotinamide ring) (Srivastava and Bernhardt, 1987).

The macromolecular complexes have configurations which allow coherent energy transduction and machine-like computational properties (Schneider, 1991). They are often associated with the non-equilibrium energy sources (e.g. proton gradients) and realize a conformational cycle coordinated with a corresponding metabolic cycle or process. The direct and the reverse paths are therefore non-locally connected by the proton fluxes (Welch and Berry, 1983). These systems can effectively channel metabolites and are examples of kinetic perfection (Ovádi, 1991).

3. Switching in futile cycles

The enzyme–substrate interaction can be represented as a cyclic structure (enzyme molecule undergoes cyclic conformational transition), whereas substrate conversion into a product is a linear process. The enzyme does not displace chemical equilibrium in triggering the linear route of reaction. In general, this route is reversible, and only transformation of this linear route into the cyclic one can be considered as a precondition to the formation of a branched metabolic network.

The separation between the direct and reverse routes of biochemical reaction, one being linked (coupled), whereas the other non-coupled with the pool of certain (often energy-rich) compounds, results in symmetry-breaking and in ''inequality'' between the direct and reverse pathways. Consequently, separation between the direct and reverse reactions leads to the generation of an elementary metabolic substrate cycle (Igamberdiev, 1994).

Reactions connected with the essential change of free energy, e.g. linked with phosphate transfer or oxidation–reduction, are preferable for the generation of such elementary cycles. The direct reaction can be coupled with ATP utilization and therefore with the reaction of ATP generation, whereas in the reverse reaction only phosphate release takes place. The significant change in free energy makes possible the realization of the direct route only in connection with ATP breakdown whereas the reverse reaction can occur without linkage to pools of adenine nucleotides. The direct and the reverse reactions in this case are catalyzed by two different enzymes, and the initially linear path is transformed into the cyclic one. Its operation leads to energy waste, therefore the cycle is considered as an indirect ATPase or as a futile cycle.

The initial uncoupled structure of futile cycle seems to be very disadvantageous, but transition to a hierarchical organization with strongly coupled reaction networks converts it into a powerful mechanism of reciprocal regulation of the direct and reverse metabolic pathways, i.e. it serves as a metabolic switcher. Allosteric kinetics is effective for the reciprocal regulation of the two enzymes forming the futile cycle. It results in the effective regulation of the direct and reverse routes in such a way that these reactions become separated in time and the energy loss is minimized (Koshland, 1984). The separation between the direct and reverse reactions seems to be the initial precondition for the appearance of networks of increasing lifetime and stability.

Regulation of activity of enzymes also can be achieved via their covalent modifications, which is regulation of the directions of metabolic processes via futile cycles. The enzymes which regulate activity of other enzymes were selected during evolution in the direction of their slower operation which avoids energy loss (Koshland, 1984). The covalent and allosteric regulation generated during the transformation of a futile cycle into the reciprocal regulatory mechanism leads to a new hierarchical level in which the enzyme serves as both catalyst and regulated molecule. Contrary to trivial competitive or non-competitive inhibition, allosteric regulation often needs the complication of enzyme structure via the inclusion of regulatory domain into a molecule. As a result, feedbacks and feedforwards are generated in metabolic structures and the distant points in metabolic pathways become 'stuck together' via the regula-

tory interactions. This can lead to the generation of oscillations and to relaxation periods of up to a minute or more in the system. The integration of many individual reactions into systemic units can be achieved by the mechanisms of allosteric modulations, transport mechanisms, etc. (Marijuán and Westley, 1992).

Reciprocal regulation in futile cycles maintains energy charge and reducing potential of the cell in a homeostatic manner. ATP/ADP/AMP and NAD(P)H/NAD(P) ratios themselves behave as universal switchers for many enzyme systems, acting as their allosteric regulators, and the rate and direction of metabolic flow are determined by the ratios of nucleotides.

Connection between high and low energy constraints is realized via recognition of weak forces by 'epistemons', and this results in the phenomenon of ultrasensitivity (Koshland, 1987). The amplified output which corresponds to ultrasensitivity is possible because of switching, or threshold phenomena. It is achieved either by the functioning of enzymes as switchers and includes allosteric phenomena generating cooperativity, zero-order ultrasensitivity by reversible covalent modifications of enzymes following Michaelis–Menten kinetics, or by the combination of these two factors. The switching phenomenon is multiplied in metabolic sequences by means of multistep ultrasensitivities (an allosteric effector activates or inhibits more than one enzyme in a pathway as in glycogen synthesis and degradation), by branchpoint ultrasensitivity (as in branchpoint combination of the slower rate of formation of a compound and the faster rate of its depletion can cause the step to decrease by a factor of hundreds), or by amplification of sensitivity by a combination of different types of amplified outputs. By this the transition from low-energy non-local input to high-energy response of the system is realized and an exchange of signals loaded by meaning is possible.

The cost of regulation can be very high, e.g. the cost of covalent regulation reaches 20% of energy available in the biosystem, but maintaining of homeostasis is the price of this cost (Koshland, 1987). Nucleotides are molecules which can be specifically acknowledged by enzymes, therefore they can play different roles, all connected with the specific recognition. They can serve as specialized substrates (coenzymes), as switchers between the direct and reverse (e.g. catabolic and anabolic) routes of metabolism, and (via polymerization) as matrices for the reproduction of catalysts themselves. In the last case we see transition from the switching network to information transfer in hypercycles (via encoding). A low-energy recognition process turns on high energy processes connected with charge separation and proton transfer, and dynamic energy homeostasis is achieved within the system.

4. Generation of bifurcations and formation of metabolic cycles

The transformation of a reversible enzymatic reaction into two practically irreversible reactions creating a cycle leads to the possibility of generation of bifurcations and to the formation of metabolic cycles (a possible scenario outlined below). It is common that enzymes catalyzing correspondingly the direct and reverse reactions are distinguished by their specificity. Demolition in enzyme–substrate interactions in one branching of a futile cycle leads to the formation of new mappings and the generation of order (complication of a metabolic informational field). A noncoherent event (bifurcation) after internalization within a metabolic network becomes a coherent event (in the dynamic process). This internalization takes place via a new molecular complementarity provided by the establishment of a new coherent structure. This may take place in the quantum potential field and generate a new appropriate realization from the changed field of possibilities. It cannot be deduced deterministically from the previous structure. The new state vector reduction describes how a previously stable state of the system (corresponding to one of the preferred states) becomes unstable (or metastable) upon a change in environment and has to be resolved to a new stable state. This corresponds to the phenomenon of the establishment of the coherent states via decoherence (Zurek et al., 1993). The system of mappings constructs the classical

dynamical coherence as order generation from chaos.

Oxidase is usually less specific than reductase and operates with a higher turnover number. A splitting is therefore possible in an oxidative reaction with increasing metabolic flow. During evolution, the generation of bifurcations was significantly promoted by the effects of oxygen (Gottlieb, 1989).

In general, a change in relaxation time leads to alteration in specificity of biomacromolecules to certain interactions, and this can result in branching behavior. Irreversible symmetry-breaking emerges from indefinite states provided by quantum measurements. Classical macroscopic bifurcations seem to be a consequence of quantum properties of biosystems, and generation of a metabolic network emerges from quantum phenomena. Quantum uncertainty in molecular interactions is a powerful engine in the formation of complex metabolic structure within biosystems (Matsuno, 1992), and is realized on a quantum-classical interface.

Bifurcations can be generated in the oxidative–reductive futile cycle because of the lower specificity of the enzyme in its oxidative branch. Heat production in dissipative oxidative reactions can also promote generation of bifurcations. The increase of flow via the oxidative path, influenced by environmental inputs, results in changes of pH and of other parameters which also promote alternative conversions of metabolites. There typically will be existing enzymes with some non-specific activity toward newly formed compounds. The genetic redundancy resulting from gene duplications and from other genome reconstructions is a precondition for the further specialization of enzymes. During evolutionary transformations the isozymes acquire specificity to different substrates that are similar in structure. The gradients of dynamic information are generated in metabolic network at the multiple symmetry-breakings within the overall network of 'wet symmetries' (Marijuán, 1996b). Functional voids appearing in the system (in this case they are deviations from normal trajectories) precondition the complication of structure and of informational capacity of the system, and, in systems capable of evolutionary growth, filling in such voids is an emergent self-generating process. We can consider the formation of metabolic networks as spontaneous in complex systems (Kauffman, 1993), but this process is essentially a non-local and non-computable phenomenon of molecular complementarity based on coherence between its different constituents. Proton circuits connecting different metabolic paths may maintain non-locality.

Thus, formation of a biochemical cycle is the result of evolutionary transformation of a certain reaction into different direct and reverse reactions and subsequent 'unfolding' of the initial futile cycle. This corresponds to transition from simple uncoupled processes to the integrated strongly coupled reaction networks. The splitting of oxidative–reductive reactions leads to the generation of bifurcation in one branch and consequently to the appearance of alternative mapping (alternative pathway of metabolic conversion). The latter, after several stages, can result in the formation of a compound identical to the initial substrate. Therefore the futile cycle subsequently unfolds into the complete metabolic cycle.

The unfolding of a futile cycle into a metabolic cycle often needs more additional reactions. The initial oxidative reaction of a futile cycle in the formed metabolic cycle becomes only a regulatory reaction making possible a shortened pathway, and it can regulate the redox balance in the cell. The origin of the metabolic cycle from the initial futile cycle determines its essential structure in which it is always possible to distinguish between the two halves (or branchings): the catabolic and the anabolic. The catabolic branch is commonly oxidative, whereas the anabolic branch can include reduction and condensation. The structure of metabolic cycles leads to separate regulation of the two branchings and to differences in their intensity, so that the outflow of compounds from one half of the cycle for alternative conversions can result.

The absence of coupling with an energy store in the oxidative branch, being a precondition of the futile cycle transformation into a metabolic cycle, can be compensated by the arising of new linkages which decrease the initial dissipation of energy. This is the main reason for the promotion of

the futile cycle transformation into a metabolic cycle, can be compensated by the arising of new linkages which decrease the initial dissipation of energy. This is the main reason for the promotion of excessive anabolism by catabolic processes important for biological transformations in ontogenesis and evolution. More rapid passage of certain stages of individual development resulting from the elimination of linkages with energetic pools determines the possibility of neothenic processes. The acceleration resulting from the 'reduction' of certain stages accompanied by higher dissipation of energy can lead to the formation of new metabolic pathways and new morphological structures. These considerations are consistent with the ideas of phylogenetic acceleration and of the 'ontogenetic forestalling of phylogenesis' (Berg, 1977).

Arguably, all essential complications in evolution corresponding to the formation of a new metabolic process are initially energetically disadvantageous. Therefore the evolutionary process is realized more intensively in such environments where the dissipation of energy is not strongly influenced on survival, i.e. in tropical areas (Meyen, 1987).

The increase of number and diversity of links within the biosystem leads to the formation of long-lived and stable homeostatic networks. In this connection, the cyclic structures of metabolism are advantageous in maintaining the stable steady non-equilibrium state of a biosystem. The existence of both cycles and branched pathways in the network of metabolism is conditioned by the parameters of the process of the 'material flow equilibration' (Matsuno, 1992) in which biological systems change their interaction with the exterior endogenously so as to maintain the continuity of their material flow. Metabolic structures include an abundance of both branches and cycles, and the formation of branches resulting from the emergence of initial bifurcation is only a precondition for metabolic cycle formation which can be realized when it leads to the ultimate network stability. Realization of a new cycle is therefore a realization of a new dynamical coherent structure.

5. Rhythms and depositions

The separation between the direct and reverse reactions within the coherent volume of a whole system as its dynamically coherent-linked parts and their reciprocal regulation lead to the subdivision in time of the direct and reverse flows and to the appearance of the internal rhythm within the system fed by the external energy supply. The direct and reverse metabolic pathways become connected with the two depots between which the substances can flow with a certain period. Transport systems between compartments are necessary for providing these oscillations since the depot should be compartmentally separated from the metabolic part.

Every half of the cycle is connected with its own depot, and oscillations between these depots can be provided by the changes in the balance between the rates of the direct and reverse reactions of the cycle. The generation of oscillations can occur only after the emergence of mechanisms of reciprocal regulation of the direct and reverse pathways. Different organizations of rhythms correspond to different morphologies. Sel'kov (1975) showed that two depots (e.g. carbohydrates and lipids in the organism's energetic homeostate), between which periodic oscillatory changes are realized, are necessary for stable dissipative oscillations. Energy rich compounds (ATP), being the 'lateral' outcome of such a pendulum, provide regulation of intensity of the endogenous rhythm. This corresponds to the model of a pendulum with a regulated base. Energy metabolism can be a source of very slow, in particular circadian (of about a 1-day period) oscillations, which may serve as a basis for the temporal organization of the cell.

It is evident that a stoichiometric cycle is neither a necessary nor a sufficient condition for oscillations. For their arising the generator of rhythm is necessary, so that the generation of oscillations can occur only after the emergence of the mechanisms of reciprocal regulation of the direct and reverse reactions which provide coherent modes of oscillations. Such a dynamical non-equilibrium mechanism is important for robust adaptation in signal transduction network which

is a consequence of the network connectivity and does not require the 'fine-tuning' of parameters (Barkal and Leibler, 1997).

6. Isozymes and metabolic channeling

Isozymes can be considered as a result of genetic redundancy and gene duplication. Multiple molecular forms of enzymes can also appear via the alternative splicing or post-translational modifications of enzyme molecules. Isozymes are characterized by different turnover rates and different values of the Michaelis constant. Small alterations in the molecular structure can lead to changes in time intervals of enzyme–substrate interactions and consequently to the alterations of isozyme affinities to the substrates and inhibitors. These changes should be definitely different for the direct and reverse reactions. In the latter case, after the appearance of a new isoform, the previously linear metabolic pathway is split, and this becomes a possible precondition for the formation of new metabolic pathway; the preferential participation of different isozymes in different metabolic pathways is generated. If more specific but slower conversion of a substrate is preferential, the slower isozyme operates in this pathway; if less specific but rapid substrate turnover is important, the faster isozyme operates. It seems to be the case that the appearance of novel isozymes leads to the internalization of bifurcations, i.e. to their genetic fixation.

The presence of different isozymes in biological systems leads to significant consequences for metabolic organization. If a substrate is converted into a product by two (iso)enzymes with different turnover rates, reversible or irreversible transitions are possible after changing of reaction parameters, and non-linearity can arise (Hervagault and Cimino, 1989). It was also shown that the competition for a common substrate can cause oscillations and trigger phenomena in metabolism (Sel'kov and Shevelev, 1989). We can state that the presence of different isozymes with even small differences in kinetic properties generates branchpoints in metabolic network, and represents a possibility for its evolutionary complication.

The formal model of oscillations connected with the operation of two isozymes has been developed (Li and Goldbeter, 1989). It shows how the kinetic differences between the two enzymes give rise to complex oscillatory phenomena. In this model the coexistence of two simultaneously stable oscillatory regimes (birhythmicity) is observed, and bifurcations can arise leading to the formation of a stable small-amplitude limit cycle which coexists with the stable, large-amplitude cycle.

The other aspect, non-studied yet, is the coherent correspondence of different isozymes to different metabolons. Some indication of that can be the data of Comorosan (1976) showing that the isozymes related to different metabolic pathways are characterized by the different time periods of activation during illumination of substrates, but they reveal a similar mode of substrate activation with other enzymes of the same metabolic pathway. This may be connected with the induction of particular characteristic frequencies resulting in resonant electromagnetic energy transfer (Ciblis and Cosic, 1997).

The presence of isozymes is a very important precondition of complex spatial and temporal organization of metabolic network. The formation of complexes between the certain isozymes localized in one tissue and participating in the same metabolic pathway was shown by MacGregor et al. (1980). This is based on the specific isozyme–isozyme interactions and excludes the shuttle of common intermediates between opposing pathways. It may be very important for the kinetic perfection of the system and for realization of computation.

An important role of isozymes in metabolic channeling is elucidated (Ureta, 1991). Metabolic channeling is an important integrative factor for maintaining whole dynamic organization (Welch and Easterby, 1994) and it can be considered as a basis for coherent ('dissipation less') events in metabolic networks, and simultaneously it reduces the number of spurious 'outputs' in the system, thereby expanding the configurational domain of the useful 'computation' part of metabolic machinery (Welch, 1996). Diffusion is a dissipative phenomenon, whereas channeling prevents dissi-

pation of energy and provides efficient informational transfer within the whole network. Isozymes provide the conditions in which multiple pools of intermediates may be kept in functional compartments. Thus they maintain branching structure of metabolism in which common intermediates do not shuttle between the opposing pathways.

The presence of isoforms in biosystems is not a result of an adaptive evolutionary process. It itself promotes the complication of metabolic structure and the generation of new metabolic flows which can lead to the appearance of new properties possessing the adaptive significance and to the formation of new ecological niches.

7. Hypercycles and the dynamics of information

When a certain subset of a substrate set of a catalytic system realizes the function of a matrix which determines the formation and reproduction of this catalytic system, a self-reproducing metabolic system arises defined as a hypercycle. Different nucleotides serve as cosubstrates (coenzymes) of many enzymes, and their association into nucleic acids generates matrices for the reproduction of enzymes themselves. When cosubstrates serve as allosteric effectors, they form reflective arrows in metabolic networks leading to the formation of a switching network possessing an internal intrinsic logic. Polymerization of cosubstrates into nucleic acids generates a self-referential set of arrows for the set of catalysts, resulting in the appearance of the digital information of the genetic code forming the internal programmable structure of biosystem.

The hypercycle structure seems to be the main or even the sole condition for the internalization of metabolic bifurcations which is preconditioned by the autonomic recombination between symbols based on the mobility and redundancy of genetic systems consisting of the possibility of gene duplication, amplification and horizontal transfer. The changes in regulative systems during evolution as promoted by the epigenetic reconstructions, makes possible the novel readings of previously existing genetic texts. The other important property of a genome essential for its reconstruction may be its uncertainty (Ogryzko, 1997) which can be based on quantum non-local superpositions.

Uncertainty on a genetic level may be provided by base tautomery, transitions of a proton from one place of nucleotide to another, etc. (Topal and Fresco, 1976). But the main uncertainty which is reduced in the irreversible process is connected with combinatorial transformations using molecular addresses at all levels of informational transfer (mobility of genome, splicing, posttranslational processing). During this process, coherent events corresponding to realization of interacting individual programs form a percolating network, and this leads to a concrete spatial (morphogenetic) pattern. This pattern should correspond to the condition of optimality, i.e. should be constructed using an optimal coordinate scale which is built mostly by non-local transfer (percolating coherent events, fluctuons, mobile proton states, etc.). Coordinate scale is a manifestation of dynamics which generates different forms in different coordinate systems (Thompson d'Arcy, 1917). The transition of a biosystem in a new condition allows some of the components of the superposition to amplify irreversibility, and this is a basis for the selection in the potential field in addition to the common Darwinian selection of actual forms. The directed mutations phenomenon may be explained by this consideration (Ogryzko, 1997).

The 'central dogma' of molecular biology is based on the irreversible expense of price of action on realization of programs by means of optimal molecular devices (Liberman and Minina, 1996). The quantum superpositions in the genome may be reversible, and during the reduction corresponding to the internal measurement they enter into an irreversible process. Coherent events at the genetic level return us to the ideas of Gurwitsch (Gurwitsch, 1923) who considered the non-equilibrium macromolecular constellations as a possible source of biological informational space (Gurwitsch and Gurwitsch, 1959). DNA itself may be a source of coherent photon storage, and besides the genetic information it can be a carrier of the information for 'pattern recognition' (Popp, 1989). This may be a not quite different

property of DNA: the specific recognition and molecular complementarity being the basis of biological information processing, according to the ideas discussed above, can be based on condensed coherent bosonic fields. DNA itself can be a vehicle for the self-assembly model of computing, since even here the conformational dynamics can change in distinctly different ways in response to different input signals (Conrad and Zauner, 1998).

The newly generated metabolic pathway or cycle, being induced by environmental inputs, for its conservation should be fixed genetically and this fixation can be realized by different ways, although the number of these ways can not be infinite: in hypercycle formation only a limited number of variants based on mutations and natural selection for providing optimal solutions can be realized, as it was shown for adaptive automata by Kauffman and Smith (1986). It is explained by the fact that the operation of every gene depends on the state of neighboring elements which determines a system's dynamics. Molecular complementarity based on specific correspondence of certain macromolecular structures (Root-Bernstein and Dillon, 1997) may provide a limited number of variants of evolutionary transformations and explain the 'nomothetic' (Berg, 1977) aspect of evolution.

Besides metabolic bifurcations, the processes of protein degradation and apoptosis become informationally determined (programmed) within hypercycles. Appearing functional voids (Marijuán, 1996a) become an important precondition of the development and informational growth within the system. Internalization of a void becomes possible because of the parallel process of genetic recombination. In hypercyclic structure, void becomes a 'creative misunderstanding' (Kampis, 1996) which can be encoded due to a redundance and combinatorial dynamics of the genetic matrices.

The emergence of reflectively autocatalytic sets of peptides and polypeptides is considered by Kauffman (1986) to be an essentially inevitable collective property of any sufficiently complex set of polypeptides. The participation of nucleic acids provides new means to select for peptides with useful properties. It becomes evident that self-replication is an emergent property arising from local interactions in systems that can be much simpler than it generally believed (Reggia et al., 1993). But this property cannot be programmably deduced from the set of system's elements: statements of metalanguage reflecting the ways of configuration change cannot be given independently from the configurations themselves (Kampis and Csányi, 1987; Kampis, 1991).

The origin of the genetic code may be based on the mapping from biosynthetic pathways of amino acids (Di Giulio, 1997). The mode of mapping seems to be explained by some principle of optimality: it is the best compromise that can be achieved between biosynthetic cost and biological return in respect of the rate of protein evolution (Dufton, 1997). It can be provided by minimal price of action during calculation (realization of the program) (Liberman, 1979).

8. Informational field and morphogenesis

The genetic information defines the parameters of morphogenetic processes but it cannot give much for understanding morphogenesis: limits of sequences of computable numbers are generally non-computable (Kak, 1996). The self-assembly of atoms shares non-algorithmic properties: even some crystals grow not in accordance with the classical picture of local adding of atoms, there must be a non-local quantum–mechanical ingredient to their assembly. Many alternative atomic arrangements must coexist in evolving complex linear superposition, and then become singled out as the 'actual' arrangement (quantum reduction) (Penrose, 1989). The selection of an appropriate solution of reduction of a wave function should satisfy certain limit conditions provided by the interfering bosonic fields. Penrose proposes the participation of gravity (curvature units) in this process: superpositioned states each have their own space–time geometries which collapse to a single state when the degree of coherent mass–energy difference reaches a threshold related to quantum gravity. As soon as a 'significant' amount of space–time curvature (equal to one graviton) is introduced, the rules of quantum

linear superposition must fail: one of the alternatives existing potentially actually takes place.

The flow of alternative realizations (of sequential non-demolition measurements) generates dynamic unfolding of morphogenetic structures: time separates contradictory points and creates non-algorithmic phenomena. Coordinate scales in biological space–time are formed therefore by percolating coherent events which generate curvilinear structures according to Thompson d'Arcy (1917). The role of gravity in self-consistency dynamics of biosystems is analyzed by Conrad (1996) who emphasizes that the motions of manifest particles alter curvature and curvature controls the way manifest particles move. Vacuum density structure is isomorphic to the space curvature of general relativity, and decoherence (wave function collapse) depends on that density matrix (space–time curvature).

As we mentioned above, DNA may be a source of coherent photon storage. Besides the genetic information it can be a carrier of the information for 'pattern recognition' (Popp, 1989). This may be based on entangling photons with atoms and realized via coherent interactions in DNA-sequence-specific biophoton transfer. The coherence of biophotons may form 'Gestalt'—information essential for morphogenesis. An ultraweak or even 'non-force' (according to the quantum Aharonov–Bohm effect) three-dimensional field, provided by different topological structures in DNA, is proposed for explanation of structure generation (Zhvirblis, 1993). In morphogenesis the principle of optimal prediction (Liberman and Minina, 1996) in operation of hypercycles works: inequality of different coordinate systems is realized in the selection in the potential field. In non-living systems the reduction is casual (probabilistic), in living systems it is driven by the selection of optimal coordinate scales. The main problem of morphogenesis can be determined as a problem of deterministic actualization based on the optimality principle. Both bosonic fields and dynamical coherence may work together in generation of spatial forms. The participation of bosons in realization of calculations in natural systems was proposed by Liberman and Minina (1996). The biological information processing is possible because the phenomena of the specific recognition and molecular complementarity are of a quantum mechanical nature and based on the condensed coherent bosonic fields.

Cytoskeleton is an important milieu for providing coherent events being the basis for acoustic/phononic transmission and quasiparticle processes, i.e. quantum coherence may be realized within it (Penrose, 1989). This corresponds to the ideas of Gurwitsch about the mitogenetic rays. The position of many multienzyme complexes on cytoskeleton is an important precondition for their self-according operation.

An important role in morphogenetic processes belongs to the heterogeneities which participate in the process of self-organization and realize coherent events as energy-driven self-consistent dynamics. Biomembranes provide the deposition of charges and determine the transport of ions and metabolites which results in the intracellular autoelectrophoresis, i.e. to the polarization of the cell being an important precondition of morphogenetic processes. Electromechanical alterations sensibilized by plasmalemma precede biochemical changes leading to cellulose biosynthesis and cell wall formation. Morphogenesis is not only a chemical, but it is a mechanochemical process in which heterogeneities, phase boundaries and mechanical tensions play an important role (Beloussov, 1998).

The underlying structure can provide operation of bound enzyme systems in which the reversible desorbtion of enzymes takes place. The membrane can be regarded as a device allows for coherent events. The water-membrane interface is considered to be a substrate for a proton superflow based on the pairing of mobile hydrogen bonds by propagating electronic oscillations in polar side groups of the membrane (Conrad, 1987). It was also proposed that the region of water surrounding the cell is a dynamically ordered non-linear coherent optical device (Jibu et al., 1997) which provides that cells can receive electromagnetic signals consisting of evanescent photons tunneling through the dynamically ordered region of water.

Multienzyme systems are formed correspondingly to the symmetry of underlying structure. The organized charged milieu, such as a mem-

brane, plays an important role in generating functional long-distance interactions between bound enzymes. This spatial organization of enzymes can lead to the generation of cooperativity in behavior of enzymes which follow Michaelis–Menten kinetics. Membranes may provide the accommodation of antagonistic enzyme reactions resulting in the avoidance of futile cycles (Ricard et al., 1992). The charged membrane can transform the futile cycle into organized long-distance structure with feedback and feedforward regulations. This is the precondition of morphogenetic events. The model of such a construction of morphology was proposed by Ricard (1987) who described the cyclic structure involved in the ionic regulation and building up the plant cell wall. The fixed negative charges in this model modify the activity of bound multienzyme systems, and the coupling emerges between the diffusion of reactants and enzyme reactions. This coupling between very simple reactions, the joint operation of which in the solution leads to the futile dissipation of energy, after the compartmentalization provided by membrane or cell wall, generates complex dynamic events which are regulated cooperatively and prevent futile recycling. Many enzymes associated with membranes are kinases and dehydrogenases realizing non-local proton transfer. A number of them are regulatory.

Kinetic parameters correspond to spatial geometric effects, and structures can be considered as morphological fixations of dynamical processes. The biochemical cycle being a system of incomes and outcomes of certain compounds can be considered as an axis of symmetry relative to which biological structures are organized (Petukhov, 1986). Even insignificant changes in the parameters of cycles can lead to essential morphological reconstructions. Morphology is formed by the stable trajectories of the formation and deposition of compounds formed in biochemical cycles. The formation of new cycles leads to the overbuilding of new metabolic trajectories, and this corresponds to morphological changes. This process is highly context-dependent generic phenomenon, and it may recall the operation of taking of limits (Rosen, 1991). It cannot be represented algorithmically, as computability itself is non-generic: there is no syntactic operation which takes us from simple systems to complex ones.

Thus, morphology is a result of the temporal and spatial organization of matter and energy flows in biosystems. Morphological transformations occur via changes of organization of these flows, and this results in the transformations of coordinate scales describing biological forms (Thompson d'Arcy, 1917). The degree of curvilinearity of the 'space of biological forms' is determined by the periods of cycles' turnover and by the differences in the rates of reactions providing depositions from cycles. If the deposited compounds can turn in reverse transformations, oscillations are possible, but if they turn into the insoluble form, they participate in the construction of rigid skeletons. The formation of morphological structures is a result of interference among concentration oscillations of compounds participating in structure formation, in this process nonlocal coherent phenomena of non-algorithmic nature are important.

Morphology is a projection from the multi-dimensional space of kinetic equilibria and processes into the three-dimensional space possessing an epimorphic (many-to-one) reflective structure which cannot be modeled programmably, and may only satisfy certain limiting conditions for its realization. Alterations of the time intervals of the cycles can lead to the changes of such projections which results in modifications of morphology. The morphogenetic field operates in the space of physical fields and metabolic cycle being a primary morphological generator providing the conditions of structure formation.

Regulatory products of metabolism, e.g. hormones, affect bifurcations and therefore realize morphological transformations. Most of them are regarded to be mild uncouplers between different processes connected with energy conservation (Skulachev, 1996). It seems evident that regulators of growth and development via influence on bifurcations make it possible for the system to transform into a new state (to undergo a metasystem transition). Under their influence the system becomes more dissipative (consequently less stable) and can more easily be transformed.

Thus, morphogenesis can be understood only in frames of limiting conditions which define possible emergent (self-generating) processes. Functional activity of biosystems emerges during the process of morphogenesis via non-programmable generation of computable events through the coherent phenomena. Coherent events and computing phenomena percolate from elementary submolecular level to organismic entities by generating the dynamic informational field which operates within the metabolic network.

The concept of coherence in biology needs to be further substantiated. Many of the ideas are hard to test experimentally at this point in time. Further progress in this area should significantly contribute to our understanding of the processes underlying biological computation.

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