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FUNDAMENTAL PATTERNS OF BIOCHEMICAL INTEGRATION

Part I – The functional dynamism

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Summary. Two, interdependent, but mutually irreducible kinds of dynamic indivisibility are described and analyzed. Functional indivisibility refers to the structures which carry and transform energy in a selective and efficient way. The essential condition of this efficiency consists in a selective match between the inner properties, shape, number, distance and spatial orientation of the structures involved. The limits of simplification of the above idea are discussed.

Conceptual perspective

Analytical destruction and synthetic reconstruction

Today's biochemistry proceeds in two opposite directions. The analytical, essentially destructive methods are used to fish out those small jig-saw elements of the cell's structure which are still missing in our inventory. At the same time many biochemists and molecular biologists try to put back into the original context the evidence achieved by the destructive analysis of the cell. This reconstruction from the randomized components could not be accomplished, I think, without a proper, nonarbitrary concept of the original whole. Is this concept – one might ask – *prior* or *posterior* to the process of the destructive analysis? If it is **prior,** then the analytical phase of the investigation adds nothing essentially new to the understanding of the object of study. This seems to be unacceptable in the light of the recent and obvious progress in the explanation of biological and biochemical phenomena. If, however, the concept of the whole is **posterior**, then how could the results of the experimental disintegration help us to recreate the original whole from the randomized fragments?

Functional analysis

A third, different methodological approach is essential in the progress of the biological and biochemical investigation. It is the *functional analysis,* that is a process of (a) the gradual elimination of parts and (b) the observation how this elimination affects the original dynamism of the organ. During this cognitive procedure one grasps the idea of interrelation and of interdependence of the parts within the context of the original dynamism. At the same time a clear distinction between a „whole”, a „part”, a set of „wholes”, and a „material” can be formulated.

Energy transfer and the concept of function

To preview the general direction of this consideration let us analyze and discuss two nonbiological, physico-chemical dynamisms. This introductory step will prepare a clearer conceptual ground for a more complex cognitive task.

We are going to analyze two different, dynamic, repetitive patterns, based upon the same physical principle.

Figure 1 illustrates the mechanism of the two recurrent tidal waves on the (E)arth. One is raised by the gravitational influence of the (M)oon, which – on the side of the Earth turned towards the Moon – prevails over the centrifugal force created by the spin of the two bodies. Another wave – on the other side of the Earth – is raised by the centrifugal force, which prevails over the gravitational influence of the Moon.

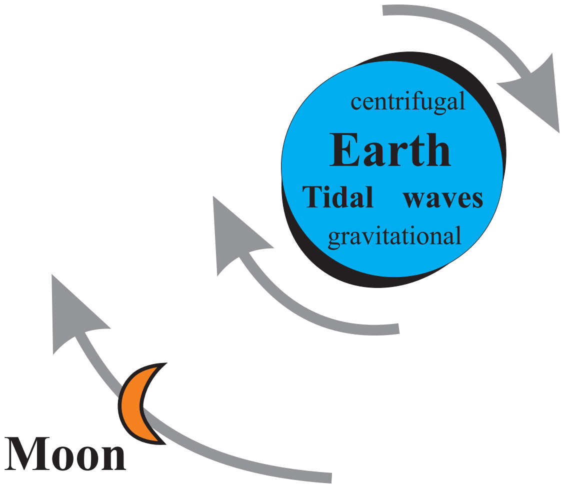

Fig. 1. Simplified mechanism of the tides.

In Figure 2 an imaginary device, Locking Mechanism (LM) is drawn. It periodically closes and opens the door with the (B)olt moved by the (P)endulum. The (W)heels rotate round the (C)enter axles 1 and 2.

In both dynamisms we can distinguish many similarities. The energy of the impetus is stored in the gravitational „system" Moon/Earth, or in the gravitational system Pen-dulum/Earth. In both cases the energy is transferred to a body (the water, the bolt) and moves it periodically. In both cases an inevitable rise in the entropy must lead, sooner or later, to the extinction of the periodical movement.

On the other hand some important differences are visible too. Let us apply the procedure of a functional (biological) analysis. Let us change the selected aspects in both the models[1]. Only a radical change in the shape of the Earth would radically affect the rhythm or eliminate completely the tidal wave. On the other hand a relatively small chan-ge in the shape of the wheels, or cogs of the LM will stop the transfer of the energy from the pendulum to the bolt.

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[1] This is a typical application of J. S. Mill's inductive Method of Difference.

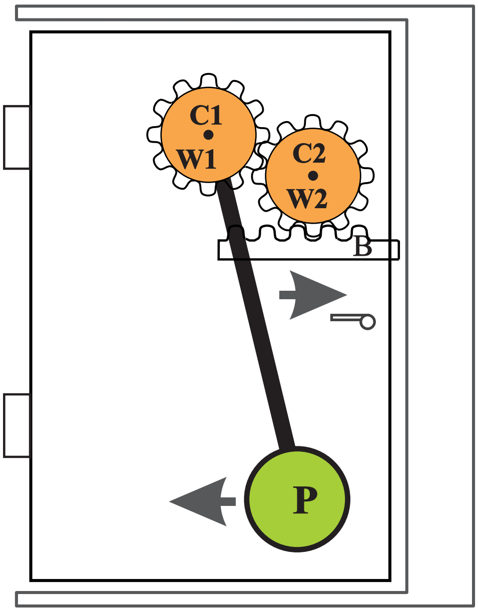

Fig. 2. Locking Mechanism.

We may now change the rigid structure of the Moon into an elastic structure. It would not affect the transfer of the energy from the Moon to the water in the seas and the oceans. It is however easy to imagine that the increased elasticity of the Wheels would ruin the transfer of the energy in the LM.

We may change the distance between the Moon and the Earth. The tidal wave would change in a proportional way. In the LM a relatively small change would necessarily disrupt the link between the pendulum and the bolt, or it will increase the friction, and produce a significant raise in the rate of dissipation of energy.

One might imagine another LM with different number and diameters of the wheels, different spacing of the cogs, and different position of the bolt. This different set of parts would also have to be „interrelated" or matched. Otherwise, the energy of the pendulum would not reach the bolt, or the entropy of the system would rise rapidly.

So, it seems obvious that although both „systems"are purely physical ones, the LM is rather exceptionally vulnerable in its dynamism. The dynamism of a volcano, of a river, of an atmospheric turbulence is much more like the dynamism of the tides. In the case of the tides the gravitational force influences all the objects upon the surface of the Earth (the mountains, rocks, trees, buildings), although only few of them move in a perceivable way. In the case of the LM, however, the energy is **selectively** transferred towards the bolt. The energy seem to flow like in a „channel" determined by a clearly selective set of spatial, qualitative and quantitative properties of the parts. These properties are evidently correlated. I propose to call them **stoichiometry** (a specific number of parts, of a strictly determined category to be sure), **syntopy** (a definite distance and spatial orientation of parts within the whole), **symmorphy** (a determined shape of the parts), **synhexy** (strictly determined, stable physical properties of the material which constitutes the body of a given part). The last condition, **synchrony,** means the absolutely necessary *coexistence* of all the parts.

These conditions are interrelated. The level of that interrelation can be easily measured in terms of the rate of the rise in the entropy of the system upon any attempt of modification. The perfect „functional interrelation" means the lowest physically possible level of increase of the entropy of the system. The efficient transfer of the energy within such a system of physical structures I propose to call **synergy.** Synergy might be defined as *the capacity of a physical system to transfer and transform the energy in a determined, repetitive and efficient way*. The example of the LM shows that synergy is a common property of many technical devices.

Figure 3 explains the idea of synergy. The efficient transport and transformations of energy are made possible, and physically inevitable, because of an *indivisible* („integrated") set of determinations of the parts of the functional system. All the six parameters mentioned on the figure are determinable in a practically infinite number of ways. Synergy appears on the condition that a unique set of determinations is realized simultaneously.

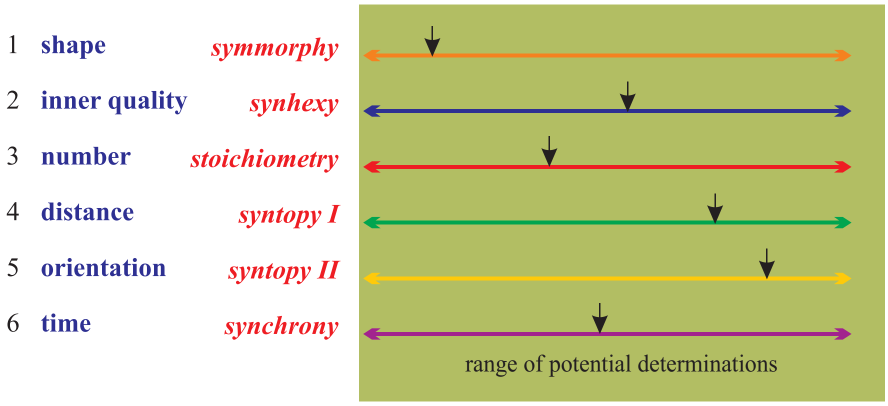

Fig. 3. Synergy as a selective determination of several physical parameters.

The material, parts, wholes and their assemblage.

The term *material* is ambiguous. It may refer to the specific inner physicochemical properties of the parts of the LM (the processed material). Those specific properties originate by a laborious process of obtaining the ore, by purification, mixing, melting, hammering ... and so on. The same word *material* may refer to the chemical elements constituting the ore (the original material). They were not produced or destroyed during the processing of the ore. So, those chemical substances had a rather unspecified potential to be converted into steel. On the other hand the final, precise determination of the shape was not selected by the inner physico-chemical properties of the steel. In other words one could not predict – just from the inner physico-chemical properties of the elements – which shape will be actually selected.

The parts (the wheels, the pendulum, the bolt, the axles ...) have a determinate shape, determinate dimensions. But their inner properties tell us nothing about their distance and spatial orientation within the LM. If, however, we know *a priori*, that their spatial orientation and distance has to be such, as to create the synergy, then we can relatively easily determine an absolutely unique set of spatial conditions, fulfilling this requirement.

The number of possible, identical copies of the LM usually does not affect the synergy within a single one. So no assemblage of the synergic wholes enters into the definition of the idea of a functional dynamism.

Investigation of biochemical function

The concepts sketched above have to be treated as a help, but never as an intellectual corset. Demonstration in the empirical sciences does not consist, in principle, in deduction, but in such an „illumination" of the object which makes easy to see its most essential properties. Even if the way of our discussion were erroneous – I hope it is not – one could profit from it by formulating one's own, correct or better ideas. I shall not pretend, however, that I am not leading towards the demonstration of the reasons for the recognition of an nonarbitrary, objective idea of a biological whole[2].

Cyclic photophosphorylation – a case study.

We start by looking into the most elementary and most obvious examples of the biological synergy.

Cyclic photophosphorylation is a biochemical process in which the energy of photons is changed into free energy of the ATP (adenosine triphosphate) molecule. The properties of the synergy – the local transfer, the qualitative transformation, the efficiency – are quite pronounced here. The „shower" of differently oriented photons, „carrying" different amounts of energy, is selectively converted into free energy of the identical ATP molecules. The process may be divided into four main stages:

Stage I. Antenna (photon trap, photon funnel) – Transfer of the randomly oriented energy of photons into a narrowly delimited spatial region.

Stage II. Antenna ⟶ photosystem I – Local transfer and transformation of the radiation energy into the energy of a single excited electron.

Stage III. Photosystem I ⟶ proton pump – Local transfer and transformation of the energy of the excited electron into the energy of the chemiosmotic gradient.

Stage IV. Proton pump ⟶ H^+ATPase – Local transfer and transformation of the energy of the chemiosmotic gradient into the chemical energy of the ATP.

Photophosphorylation is the most primitive, the most simple, the most fundamental, and one of the best known processes in biology. The stages enumerated above were found to be necessary for the survival of the overwhelming majority of forms of life on Earth. No simpler way of producing ATP is known.

Let us discuss the above mentioned stages in some detail.

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[2] This may naturally provoke a discussion on the conceptual framework set by Immanuel Kant

Stage I. This stage occurs within the so called antenna (cf. Figure 4). It is composed of the stacked (superimposed) or concentric layers of photoreceptive pigments, chlorophylls or bacteriochlorophyll, depending on the organism under consideration. The outer layer of the pigments is made of pigments selectively absorbing photons of higher energy. Each consecutive, deeper layer of the antenna consists of the pigments capable of absorbing a smaller quantum of radiation energy[3]. The number of pigment molecules in the next, deeper layer is reduced[4]. As the energy of the emitted photon is always smaller than the energy of the photon absorbed (so called Stoke's shift), the trapped photons are constrained to move, like a (playing) ball, bouncing down the steps, in one direction only (cf. Figure 8) – towards the place where the second stage starts[5]. The difference between the emission spectra of the consecutive layers of pigments is usually about 10 nm, which, together with the strictly determined distance (about 12Å) between the single molecules, and the strictly determined angle between their chlorophyllide rings[6] is such that the transfer of radiation energy towards the reac-

Chl *b* 650 Chl *b* 650 Chl *b* 650 Chl *b* 650 Chl *b* 650 Chl *b* 650 Chl *b* 650
Chl *a* 660 Chl *a* 660 Chl *a* 660 Chl *a* 660 Chl *a* 660 Chl *a* 660
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Chl *a* 678 Chl *a* 678 Chl *a* 678 Chl *a* 678
Chl *a* 680 Chl *a* 680 Chl *a* 680
P- 680

Fig. 4. The scheme of spatial arrangement of the different forms of chlorophyll molecule in the antenna.

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and his followers. It must, however, be postponed not only because of the limited space of this article, but because the analysis presented here should not – in my opinion – be *a priori* limited by the kantian sense of fundamental conceptual categories.

[3] This illustrates the principle of synhexy – the match between the inner properties of the interacting bodies involved in the efficient transfer of energy. „The excited states migrate between pigments by an incoherent Förster mechanism. The efficiency and directionality of excitation transfer reactions depends upon the relative position, orientation, and spectral properties of pigments within the pigment-protein complexes and between interacting complexes in the photosynthetic apparatus" (Owens T. G., Webb S. P., Alberte P. S., Mets L., Fleming G. R., 1988. *Antenna structure and excitation dynamics in photosystem I*. Biophys. J. 53, 733-745).

[4] This stoichiometry is essential in directing the photons into a strictly determined site – namely the reaction center of the photosystem I.

[5] Cfr. Lawlor D. W. (1987) *Photosynthesis: metabolism, control, and physiology*. Longman Scientific & Technical, New York, p. 26-28.

[6] This illustrates the principle of syntopy – the match between the distance and spatial orientation of the bodies involved in the efficient transfer of energy. „The Bchl occupy a space of 45x35x15Å in which the average center to center distance of the porphine rings is

ction center of the antenna may be almost 100% effective[7]. By the end of the first stage the energy trapped is transferred to the double pigment molecule of the

Stage II. In the RC a single electron is excited and sent on a run along a chain of strictly determined, and accurately arranged molecules[8], finally returning back to its own „electron hole", or „gate" which does not accept any new portion of radiation energy („remains closed"), until the electron is back again[9] (cf. Figure 5).

Stage III. The excited electron transfers its energy to a complex molecular device which pumps protons (H^+ions) into a space, confined by a 100Å thick membrane. Across this membrane the so called chemiosmotic gradient ($\boldsymbol{\Delta\bar{\mu}H^+}$) is created[10].

This gradient (ca 200 mV) is the source of the protonmotive force which is used during the final, fourth stage of the photophosphorylation.

Stage IV. Across the same membrane a huge macromolecular system, the so called H^+ATPase is installed. It consists of a channel, and the catalytic unit (see Fig. 6). Through the channel protons may escape the enclosure, on the condition they transfer a part of their energy to the catalytic unit, which uses it to convert the inorganic phosphate (Pi) and the ADP molecule into the ATP high-energy molecule[11]. The term „high-energy" means that the ATP releases – when hydrolyzed to ADP and Pi – a relatively

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12 Å for nearest neighbors, the rings of the Bchl lie between 10° and 40° to one another" (Beddard G. S. and Cogdell R. J., 1982. *Structure and Excitation Dynamics of Light-harvesting Protein Complexes*. In: Fong F. K. (ed), 1982. *Light Reaction Path of Photosynthesis.* Springer Verlag, Berlin, p. 63).

[7] The efficiency is different in different groups of the autotrophs. „Studies done *in vivo* with *Chlorella* demonstrate that the transfer of energy from Chl b to Chl a is nearly 100% efficient. Similarly, the phycobilins can transfer their energy to Chl with efficiencies ranging from 80 to 90%. By contrast, the efficiency of energy transfer from carotenoids to Chl range from 20 - 50%, depending on the particular carotenoid involved" (Fork D. C., 1989. *Photosynthesis*. In: Smith K. C. ed. *The science of photobiology.* Plenum Press, New York, p. 356.

[8] A variation of 20Å in the distance between donor and acceptor [protein molecules] changes the electron-transfer rate by 10^{12} fold. (Cfr. Moser Ch. C., Keske J. M., Warncke K., Farid R. S., Dutton P. L., 1992. *Nature of biological electron transfer*. Nature 355, 796-802).

[9] If the energy from the antenna were injected into the RC before the „electron hole" is filled, the efficiency of the process would be considerably diminished. So, a mechanism which keeps the „gate" closed provides a *synchrony* between the flow of the energy in antenna and the electron's migration in the photosystem I. This sense of the term synchrony is different from the sense defined earlier.

[10] „In chloroplasts the pH difference between the stroma and the thylakoid interior can amount to up to 4 pH units, which corresponds to a H+ concentration difference of 1:10,000" (Häder D.-P. & Tevini M., 1987. *General photobiology.* Pergamon Press, Oxford, p. 144.)

[11] „In chloroplasts the stoichiometry has been determined experimentally as one ATP per three protons; bacteria seem to need only two protons" (Häder D.- P. & Tevini M., 1987. *General photobiology.* Pergamon Press, Oxford, p. 144).

high amount of free energy, which is used by the living cell to drive its energy-consuming activities[12].

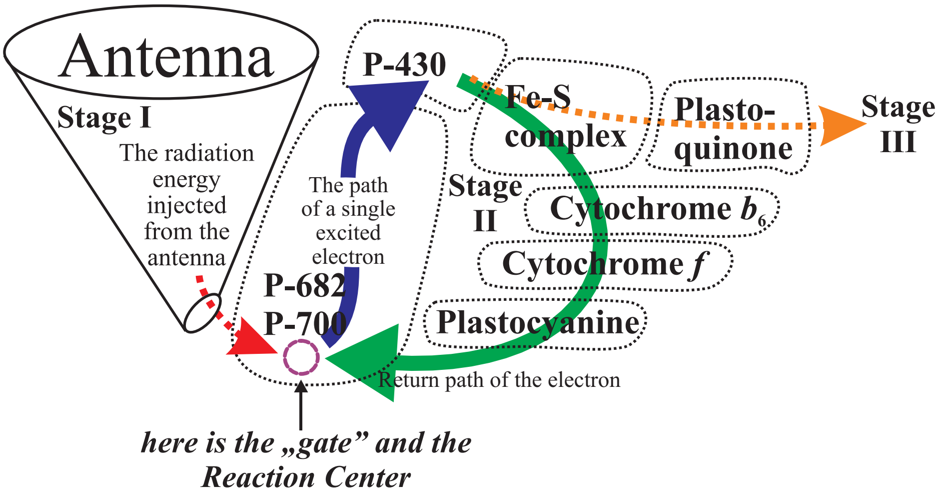

Fig. 5. Schematic representation of the photosystem I.

Efficient energy transfer and transformation.

Summing up, during photophosphorylation the energy of chaotic photons becomes ordered in space, selectively transferred to a specialized molecular system, which transforms this energy to the energy of the excited electron, then converts it to chemiosmotic gradient, which drives the catalytic activity of ATPase. In this way a chemical, relatively stable form of energy is produced, ready to be used when needed.

The idea of synergy, i.e. the parsimonious transport and transformation of energy, explains the almost isothermal execution of work in the living organisms on the one hand, and the contrast between the apparent fragility of chemical gear of the cell and the amount of work done by it on the another. The overall efficiency of this multi-stage process is estimated to be some 30% of the energy trapped by the antenna. The number of intermediate dynamisms of the separate structures involved cannot be less than 15. Some stages are more, some are less efficient. However, the average efficiency of a single stage cannot be less than 92%, which is close to the physically possible maximum for an irreversible process. Any significant decrease of this efficiency within a given stage could hardly be compensated by the remaining stages, as they operate close to the physically possible maximal efficiency.

The idea of the „whole”.

This efficiency quite evidently depends upon a set of physico-chemical, spatial and temporal parameters. Each single constituent of the set is to be narrowly determined,

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[12] The ATP hydrolyzation within the living cell is controlled enzymatically, so that the released energy is applied in the proper site and in the proper moment of time.

otherwise the efficiency of the whole process collapses dramatically. This set of determinations is *intrinsically heterogenous.* It cannot be simplified, or reduced to a single parameter. The above necessity in turn, refers not to the *structures,* but to the *dynamism* of the energy transfer. The heterogeneity and necessity constitutes the essence of the idea of the dynamic indivisibility (or integration) of biochemical (and biological) function.

Succession of genes in the DNA molecule	**2**	**5**	**6**	**8**	**1**	**7**	**4**	**3**
Symbols of polypeptide subunits	χ	ω	ψ	δ	α	γ	β	ϵ
Molecular weight	**30276**	**8288**	**17265**	**19582**	**5564**	**31387**	**50157**	**14914**
Number of subunits	**1**	**10**	**2**	**1**	**3**	**1**	**3**	**1**
Function	**channel**			**catalytic part**				

Fig. 6. The table represents the complex stoichiometry of different protein molecules (polypeptides) constituting a single H^+ATPase macromolecule.

Aspects of the functional indivisibility

There are many questions concerning the inner logic of the biochemical functional processes. One set of questions concerns the limits of *simplification* of those dynamisms. It is a crucial question, as it can decide about the legitimacy or, to the contrary, about inappropriateness of many abstract, formal models used in the description of biochemical phenomena. Another question concerns the problem of *indivisibility.* Synergy, as we have seen, embraces the idea of the intrinsically complex, heterogenous set of interrelated bodies and properties, which manifest the familiar physiological *„all or none"* property. Is synergy a manifestation of a deeper, more fundamental, positive property, namely a whole? Is it necessary to admit that a dynamic whole does exist independently of our theoretical procedures and that it is recognizable in the purely physico-chemical phenomena? If this were true, it would put into question the fashionable, kantian, subjective interpretation of category of the „whole". This in turn would necessarily imply a reconsideration of the developmental dynamisms and the nature of the genetic information. But this problem will be discussed in the second part of this essay.

Limits of simplification.

Now let us try to reduce – in our mind – the idea of a functional (synergic) system (sS) without, however, obliterating its characteristic properties. We may ask first: How many separate parts has such a system to include? As the idea of the transfer and transformation is crucial, it seems nonsensical to suggest that a single part might do. So at least two parts seem to be the lower limit of the sS complexity.

The second question is this: How different do those parts have to be? Again, the idea of synergy rules out two identical parts. They have to be different.

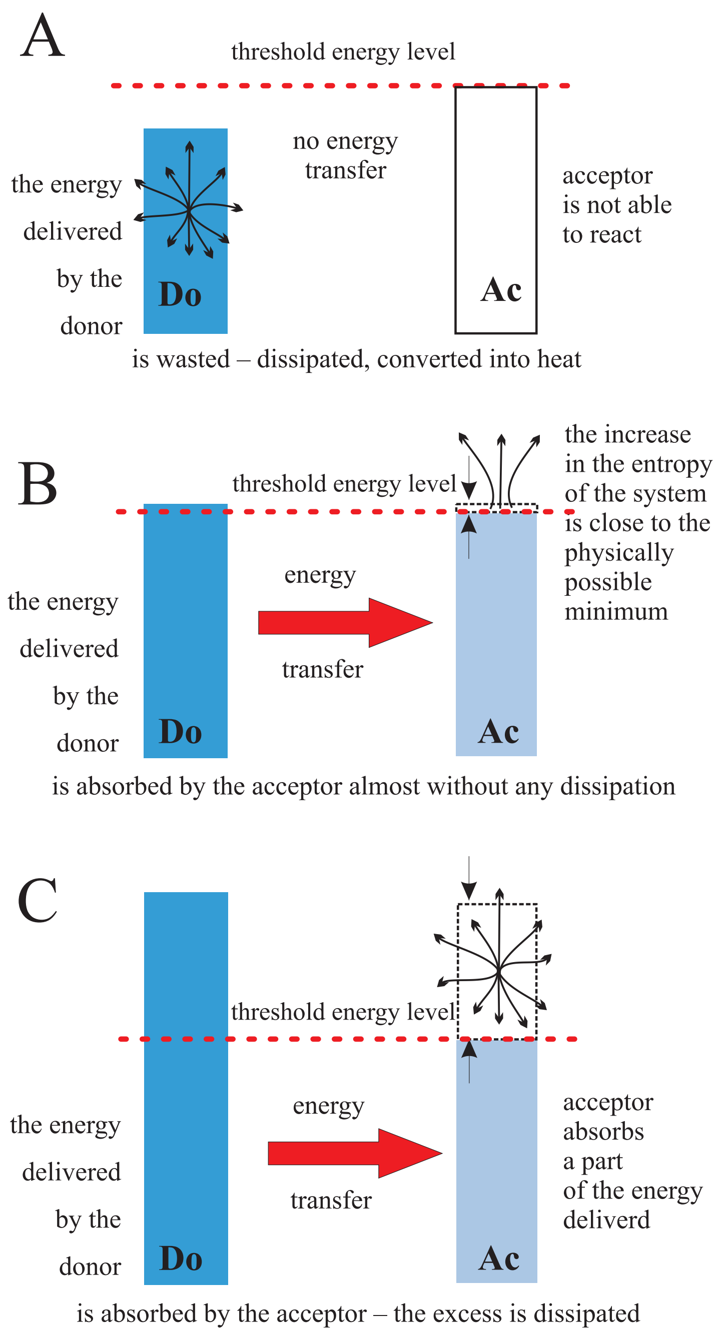

Fig. 7. The scheme illustrating the idea of a subthreshold (A), threshold (B), and excessive (C) amount of energy.

To put it more explicitly, we may reflect upon some elementary properties of the mechanism of the energy transfer. The most convenient model of a body capable of absorbing energy and transferring it, is a pigment molecule. It absorbs a portion (a quantum) of the radiation energy if its value exceeds a certain threshold (Eth). Any amount of the energy lower than Eth would not be absorbed, but wasted, i.e. dispersed in the environment in the form of heat. If the energy absorbed is higher than the Eth, the excess would also be wasted in the form of heat. The reason is this. No matter how big the energy absorbed was, the amount of energy released in the form of radiation (emitted) is always the same. Only this form of energy is useful. The energy converted into heat and dissipated in the environment is useless.

Another important necessity has also to be taken into account. The radiation energy released (emitted) by a pigment is always a bit smaller than the energy previously absorbed. A necessary loss of radiation energy (in the form of heat energy) is inevitable (see Figure 8). So the efficiency of the energy transfer between two pigment molecules never reaches 100%[13].

In Figure 7 C an amount of free energy (shadowed area on the left side) is transferred from a pigment molecule. One has to accept that the donor molecule was different from the acceptor molecule depicted on the right side of the scheme.

Why it must be so? The acceptor molecule will never emit the full amount of the absorbed radiation energy (see Figure 8). If the donor was identical with the acceptor, than the energy released by it would never be absorbed by the acceptor. So, if the amount of energy released by the donor was sufficient to excite the acceptor, then the donor was not identical with the acceptor. Its threshold absorption energy was certainly higher than the threshold absorption energy of the acceptor.

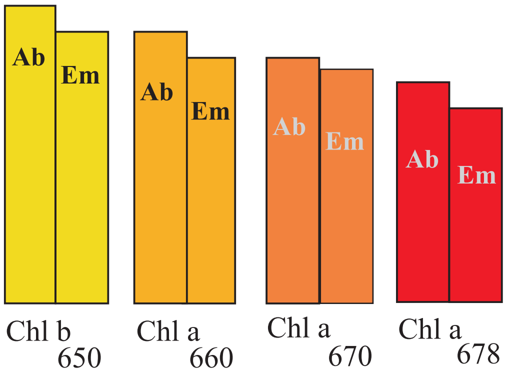

Fig. 8. Scheme of the relation between the absorbed (Ab) and emitted (Em) energy of the chlorophyll molecules in the photon trap.

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[13] Cfr. Grossweiner L. I. (1989) *Photophysics*. In: Smith K. C. (ed.) *The science of photobiology.* Plenum Press, New York, p. 33, fig. 1-17.

We may then conclude, that the idea of a minimal sS necessarily implies two different parts. One of them is an energy donor, another accepts the energy donated. The elementary condition for the transfer of energy is satisfied. But synergy implies something more than this. It requires the utmost economy of this transfer. So the idea of the minimal sS postulates not just any, but precisely matched difference between the donor and the acceptor.

This last requirement may be conveniently described by the above mentioned concepts of symmorphy, synchrony, stoichiometry, syntopy and synhexy (cf. Figure 3). The vocabulary of those concepts is not essential. Any other set of sufficiently strange words might do. But the concepts themselves are far from being new. They may be recognized in any experimental or observational record which reaches the level of the inner, genuine biomolecular mechanisms of the energy transfer.

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