INTERNAL ORIGINATORS OF FUNCTIONS FLUCTUATION IN MULTI-CELLED ORGANISM

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Abstract: To understand general principles that determine fluctuations of integrative functions in multi-celled organism (MO), special theoretical analysis based on mathematical models is done. A complex model includes description of three levels of physiological processes: 1) mechanism of cell adaptation functioning against balance deficit (BD); 2) partial homeostatic systems (HS) and, 3) functional systems. Models and computer simulation allow one to make clear the main causal relations that coming up as step by step generalization of local and independent processes on cellular level. It is shown that the physiological adaptation has a goal (minimization of BD) and special moving forces activating by BD only.

Key words: cellular balance deficit, expanding physiological adaptation, homeostasis.

1. Introduction. Organisms' reactions to each external factor have their specific primary effects and several secondary, mainly non-specific behavior that is a result of internal HS activation aimed to parry these primary changes and to stabilize homeostatic characteristics in general. As far as the external environment is mostly unstable with a random dynamics of characteristics (including electrical and electromagnetic fields), reacting to these factors, organisms appear fluctuations of their internal state. To understand the main principles that determines reliable function of human-operator and fluctuations in physiological state of human organism under its interaction with unstable environment, the relationships between different homeostatic and functional systems were analyzed taking into account local and global effects of cellular adaptation mechanism (CAM).

2. Methods: Systemic analysis was combined with computer simulations. A hypothesis according to which CAM is the only responsible mechanism that determines all local and integral processes of physiological adaptation (PA) was used in model. CAM is presented in model as an "egotistic" mechanism functioning independently and based on a non-symmetric intracellular mechanism tuned against stable trends of the balance deficit (BD) between anabolism and catabolism. An over-threshold level of BD is considered as an originator of special moving forces necessary and enough to activate CAM. To minimize BD, the single cell needs additional energy and structural components. To expand its productiveness by activating of sub-cellular structures that already existed in their passive stage and also by building new such units, the BD-cell try to provide the necessary rate of biosynthesis.

2.1. MODEL OF CAM: Considering that the velocity (V^u) of energy and substrates utilization are depended on external factors with random dynamics ($V^u = R(t)$), while the velocity of synthesis $V^s = \gamma K_m K_r$, where K_m - quantity of currently active mythochndries; K_r - quantity of currently active ribosomes, and assuming that CAM is active when $\Delta^u{}_s = V^u - V^s > \delta$, the adaptation process which will describe the dynamics of K_m and K_r as:

$$T_m \frac{dK_m}{dt} = \alpha \cdot (K^{max}{}_m - K_m) \cdot \Delta^u{}_s; \quad T_r \frac{dK_r}{dt} = \beta \cdot (K^{max}{}_r - K_r) \cdot \Delta^u{}_s$$

where α, β – sensitiveness coefficients and T_m, T_r – time constants of adaptation process.

3.**Results and their discussion**: The model of CAM has shown that using such simple presentation of PA, we able to simulate practically all known local (French, Torkkeli, 1994; Juusola, French, ,1998), and also integral adaptation effects that were observed by researchers on organism level under different changes of external environmental factors (temperature, oxygenation, gravity e. a.), if only we able to present the scheme of causal relations. As shown by Grygoryan (2004), functional diversities that normally are presented even in frame of relevant cells of one single multi-celled organ (cell population), are the main originators of nonlinear relationships. Such a diversity of cells may be caused by four main determinant factors: 1) current phase within the cell's life cycle; 2) reactivity of cell to unstable exogenous factors with random characteristics; 3) concentration of resources in close interstitial environment necessary to provide the needed rate of biosynthesis; 4) the current ability of the cell to provide chemicals transport into the cell and to support appropriate rate of biosynthesis. The

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activation of CAM increases the last ability of BD-cell and thus re-distributes the flows that issued in previous episodes of cell life.

Each partial HS is a fixed structure that contains populations of specific cells in its structural links. Therefore, every local reaction of these cells to extra-cellular factors will activate their CAM, and thus will change the flows of substrates towards cells both within this HS and in frame of the whole multi-celled organism. The so-called homeostatic constants are sooner variables than really stable characteristics. Their current level reflects general needs of multi-celled organism or its several structural-functional units in substrates and oxygen. No one HS able to set the level of control characteristics. The only function of specialized HS is to minimize the violation of its output variable under random changes of its input loading that able influence functional changes in cells presenting both the external or internal receptors and other links of HS-contour. The complex changes in different indicators of organism's current state reflect the inside of regulator relationships based on nervous and humoral channels involved in providing of organism's integrative reactions.

Internal determinants of state fluctuations are: 1) Genetic predetermined activity of cell; 2) Reaction of cell to the external influences. If the rate of such influences exceeds some threshold level so that the cell is compelled to loss its energy and structural elements, the cell has two alternatives for its behavior: to stop react or to continue its external function (reactivity) but increasing the rate of its biosynthesis. This is a basis of cell physiological adaptation to external environment.

As far as in frame of MO the moving forces that provide substrates distribution between different cells are determined by the rate of cells biosynthesis, every change of the currently rate even it occur in one cell creates another configuration of these forces. But several groups of specialized cells together form specific closed loops that are the basis of different physiological regulator contours including so called homeostatic or functional systems. So, all adaptive reactions of cells aimed to save itself against the exogenous damageable acting factors will obligatory redistribute the previously existing field of moving forces in frame of the MO. Creating new configuration of such forces, this organism transforms its regimes of function in general. The observer fixes these transformations as fluctuations of organism's physiological state. Till now investigators have not any theoretical complete model of this integrative process, and thus, they posses not any approach to the problem allowing them to estimate or to predict these fluctuations. Recently (Grygoryan, 2004) was proposed a general theory and started to create appropriate mathematical models and computer software that aimed to be used by experts-medics and physiologists to make clear the main relationships in human organism under unstable external environment. This presentation illustrates several basic approaches that were used to construct the new research tool. Its basis is a detailed presentation of structural-functional relations in typical partial HS.

The goal of typical HS which is overbuilt on object as structural-functional unit is to minimize the deviations of some output physiological function *Y(t)* in this object. To reach this function, each HS includes the following structural-functional blocks (SFB):

The receptor, which transforms the input analogous influence *Y(t)* into a *R(t)*-variable of another modality (In case of nervous nature of the receptor, the *R(t)* looks like a sequence of afferent impulses.);

1) The interim-element (IN), that does not impart any additional change to the modality of input variable, but has some additional (simulator- *S* and/or inhibitor- *I*) modulator inputs from different structural elements of the MO. Due to these inputs, the interaction between the different functional systems (sometimes containing a lot of partial HS) becomes integrated and almost optimal for the whole MO;
2) The element SE, which changes its state in unison with the changes in the IN. Here may be also some parallel pathways, each with a functional element IE that changes its state in an opposite direction to the change in the IN. (The typical presenter of such doubled pathway is the autonomic nervous system based on sympathetic and parasympathetic nervous subsystems). Such doubled structural-functional organization is able to more precisely optimize the control process.
3) Between the third functional block and the final effector structure, which sometimes may integrate a lot of anatomic elements (for example, heart, systemic and lung vessels), there may be other interim elements as well (for example, the sympathetic nervous ganglions). Usually, they are functioning as if they are the modality transformers only, saving the transformations' direction in unison with their direction in the input function. It is important to mark that the general conservative function of the whole HS requires that the final changes in the parameters of the effector link have to be directed to change the function Y(t) towards direction opposite to its primary changes (negative feed-back).

Below is presented a scheme that illustrates how the physiological adaptation as an expanding reactive process first arose to minimize BD in single cell will step by step involve different partial HS and finally generalized.

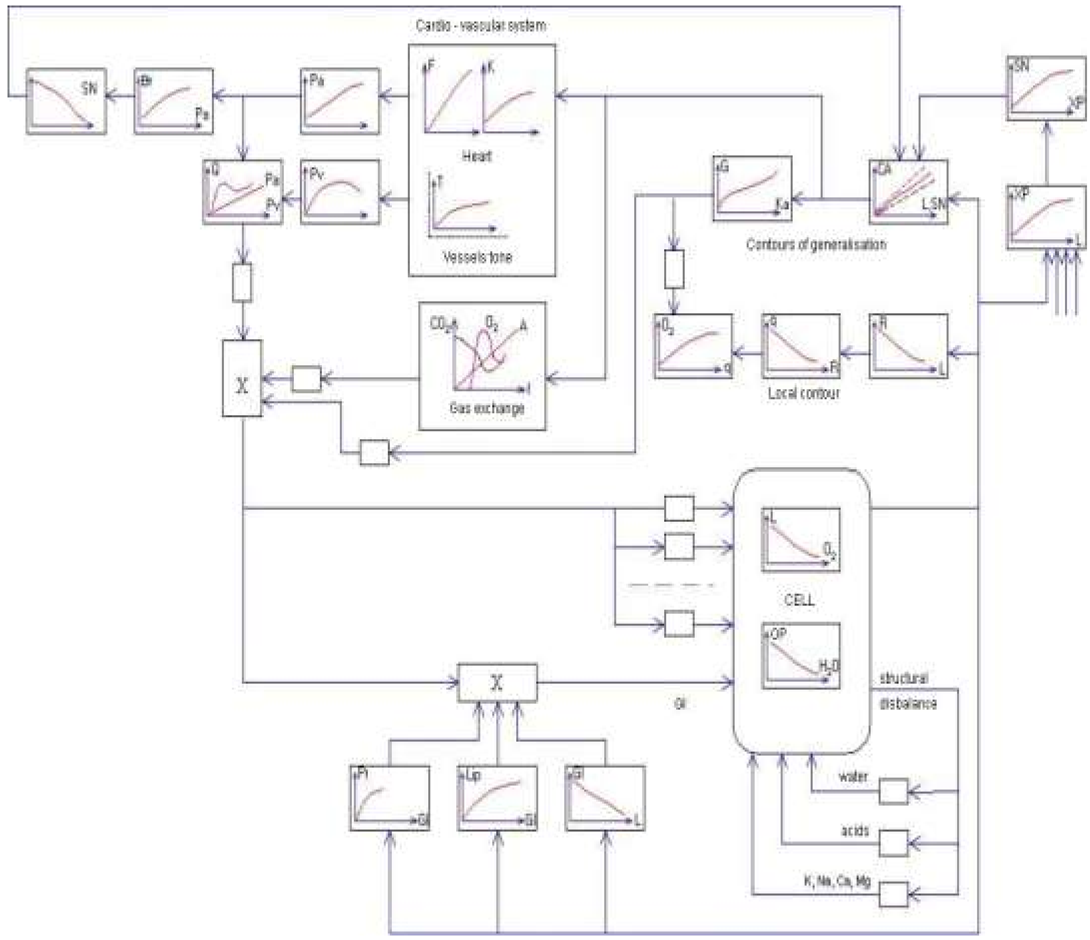

Figure. Schematic presentation of expanding adaptation mechanism. The physiological adaptation starts from the single BD-cell and then, expanding step by step, it may cover BD-cell populations until its generalization. This process involves different local and global regulator contours.
CA- Cathecholamines, SN-Efferent sympathetic nerve, Br- Baroreception, F,k- Rate and power of heart contraction, T,R- Vessels' tonus and resistance, Pa,Pv -Arterial and venous pressures, L-lactate, Gl- Glucose, Lip- Lipids, Pr-Proteins.

The first regulator contour looks like a local auto-regulatory mechanism that come active as negative feed-back channel to BD in cell. This contour usually reacting to soils in close environment, tries to liquidate these soils by local vasodilatation and increasing of capillary flows. If local auto-regulatory mechanisms is not able to liquidate (or minimize) BD, and it continues to increase, step by step other contours come active. This is a generalization of adaptation.

Important is to underline that this process needs not any central organization. In fact, when the concentration of soils continue to increase, all the next regulator contours come active using a common principle: the contour which has higher activation threshold level will be involved later. Theoretically, the final of such process will be such a power of cells' metabolism that provides minimum of the BD for the whole organism. It means that the quantity of currently active sub-structures of cells involved in this adaptation process, will increase. So, each such cell will provide a higher metabolism than it was before BD appears. Generalization of adaptive reactions means that the MO uses all its opportunities to provide an optimal interstitial space. Therefore, cardiovascular system (CVS) has to provide higher arterial pressure that brings to increasing of blood flows. This intensification of circulation could be reached using both reflector mechanisms of CVS and higher production of cathecholamines. At the same time, to provide the arose level of metabolism, respiratory system will support a more active gases' exchange. If these mechanisms together are not able yet to liquidate soils inactivating of cell metabolism in weak links of MO, thanks to activation other synergetic processes (increasing of hemoglobin concentration, quantity and power of heart and vessel muscles), the mechanism of PA tries to reach its general aim – minimization of summary concentration of negative factors compelling cells to loss energy and structural elements with a rate exceeding the rate of their bio-synthesis.

These regulator trends may have different final results for different scenarios of external influences. In case these influences have not stable trends but are changing wit a random dynamics, we will see several random fluctuations of functions only. In versus case, different HS will slowly change their parameters and the whole organism will come to new steady-state functional regimes.

To understand the basis of rapid adaptation in cells, including receptors, important is to turn attention on components that determine the velocity of synthesis $V^s = \gamma K_m K_r$. In fact, power limits that will characterize the ability of each BD-cell to increase its productiveness and to minimize the level of current BD are determined by value of coefficients K_m, K_r. Perhaps, the values of time constants in differential equations describing mechanism of CAM, also are variables depending on biochemical activity of cell. So, we have to take in mind that inside parameters of cellular homeostasis are the optimal to provide adequate rate of biosynthetic processes. This key idea allows us to understand why fluctuations of such integral functions of MO as blood pressure, body temperature e. a. Under unstable external environment go to be more essential in aged humans. Parameters that determine cell ability to maximal rapidly and with a maximal extensive increase its productiveness are slowly but stable decreased with a age. It is likely that the aged cell will have less quantity of its active mithochondries and ribosomes. Therefore, under essential changes of such damageable for cells factors as external magnetic, electromagnetic fields, the cellular homeostasis will feel dramatic changes that could not adequately recovered even in case normal function of upper integrative regulator contours shown on figure above.

To model physiological processes in human organism, there is necessary to develop both models describing local processes on organ level and models that describe the main relationships between these organs. This publication mainly covers two sub-systems: cardiovascular system (hemodynamic function), kidneys. Although kidneys are not shown on scheme, it consists of contours on its bottom part that have to turn readers attention to a mineral exchange as very important component of systemic homeostasis.

Thanks to original presentation of organs as populations of cells functioning parallel but asynchronously, and also taking into account energetic and structural balance on cellular level, we already able to cover several regimes of these sub-systems interaction.

4. Conclusion: Fluctuations of functional activity usually indicated by rapid changes of homeostatic constants of MO will be considered as its normal reactions to sensitive changes of both external and internal environments. Under essential and relatively long-term stable shifts of environmental characteristics the adaptive responses of MO are mostly determined by egotistic and independent functioning CAM. Therefore, these responses will have stable trends and could be mainly forecasted if only we can find adequate measurement methods. However, experts cannot understand the moving forces of functions fluctuations trying to find (Dodel, Herrmann, 2001) spatially or temporally correlated activity between different brain structures only. Important is also to understand function of internal local and integrative regulator mechanisms.

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