About a Mathematical Model of the Psychobiology of Stress Reaction

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Abstract

All biological systems are complex: their behaviour is the result of coordinated action of many elements and it obeys the laws of nonlinearity. In studying such systems, mathematical modelling is a very useful approach, especially because of its predicting abilities, as their dynamics is difficult to foresee intuitively. Mathematical description of biological processes can offer frames of thinking that reconcile opposed points of view in diagnostics or, they can help formulate the key notions in understanding particular processes. In this text, an attempt has been made to acquaint the researchers that were not familiar with mathematical modelling with this kind of approach - its purposes, the principles of constructing, and its applicability to nonlinear dynamical systems. Further, a model of stress response that connects its psychological and biological aspects with accents on individual differences (Savic, Kneževic and Opacic, 2000) is described. The work of Savic and Jelic (2003) is also described. In this work, five versions of models of stress axis are constructed and the origin of time periodicity of its functioning is investigated using the stability analysis.

WHAT IS THE MATHEMATICAL MODEL AND WHAT PURPOSE DOES IT SERVE

Every science begins with observing and describing phenomena. However, the mere description of a phenomenon does not in itself constitute scientific knowledge. When can we say that we have knowledge about a certain phenomenon? Only then when we know the *laws* according to which this phenomenon occurs. These laws are best written down in mathematical language: equations. Mathematics is, as Keith Devlin says in his book "The Mathematical Gene", the science of relations.

The mathematical model is nothing but a proposal of laws written down in mathematical language. Such formulation is precise and straightforward, which gives it multiple advantages over the verbal formulation. Firstly, it avoids misunderstanding arising from differences in subjective interpretations. Secondly, the mathematical script allows a quantitative verification of the hypothesis. Thirdly, maybe the most important, is the *possibility of prediction*. Hans Meinhart (1982), in the foreword to his book on biological morphogenesis, recalls the example of Newton's theory that precisely describes the orbits of inner planets. Deviations found in orbits of outside planets have lead to an assumption about the existence of other planets, which were in fact discovered later. Clearly such prediction could have been possible neither through a non-mathematical formulation, nor by mere observation. Therefore, the mathematical model by way of its predictability provides guidelines for further experimental and empirical research, which makes the combination of these two methods the most effective way towards scientific knowledge. We should not forget that the experiment has the final word, by which the hypothetical mechanism - mathematical model - is improved and supplemented in comparison with the real system.

Basic principles of constructing the mathematical model are the accordance with existing experimental data and the introduction of a minimal number of hypothetical variables, needed for describing the given phenomenon. In the same sense, if we do not know the exact function of dependence of one variable from the other, but rather have a set of points measured, we approximate it by the simplest function corresponding to the measured points. If we know only the rough correlation between two characteristics (rising or decreasing), we begin from the linear dependence. Increasing the complexity of the model is justified only if needed to explain the observed behaviour or if we have good reason to believe that the system acts according to certain laws (e.g. by analogy with something similar).

The model can be incomplete, but must not, however, be in contravention with valid known laws and facts. Another important contribution of the mathematical model is that it singles out values that constitute the essence of the studied process. This is particularly important for biochemical systems, in which regularly involves a large number of compounds. We shall illustrate this by the Hodgkin-Huxley model from the area of neurophysiology, for which these authors have received the Nobel Prize in 1963 and which

is probably well know to psychiatrists. The model relates to ionic canals in the membrane of the irritable nerve cell. In order to explain the conduct of ionic currents and action potential, Hodgkin and Huxley have postulated the existence of certain particles (proteins) in the membrane canals, which must be in the favourable position (of the possible two) in order for the canal to open. Their model perfectly simulates the form of action potential. For every canal they have introduced four particles each - minimum that was required to obtain this type of function. The entire model relates only to sodium and potassium current (and canals). Although it is known today that other ions also participate in these processes, these two ionic types (of various potentials) are sufficient to explain the essence of the phenomenon. This model also explains an entire range of the nervous fibre characteristics (refractiveness, accommodation, etc.)

NON-LINEARITY

Understanding complex systems - from physical, chemical, biological, meteorological, up to economic and sociological - has advanced greatly by way of using mathematical models. Complex systems are those the behaviour of which is the result of a harmonised activity of many elements (atoms, molecules, cells, individuals) and that obey the non-linear laws. In mathematical modelling of complex systems computers play a significant role - computer simulations supplement the analytical mathematical methods. Precisely because of the non-linear dynamics it is difficult to predict by intuition the behaviour of such systems in the changed conditions. Changing only numeric values of parameters in only one non-linear equation can lead to qualitatively different outcomes. A good model links several seemingly independent phenomena in a joint mechanism. Applied to the field of medicine, or psychiatry, this means that a good mathematical model offers a possible unique neurobiological mechanism that lies in the foundation of various (groups of) symptoms. Medical experience and biochemical analyses can link various illnesses with differences in concentration of one individual compound, but the mathematical model seeks an answer to the question of HOW this happens.

We are frequently faced with the question whether certain phenomena (e.g. characteristics) lie on a rectilinear continuum or belong to different discrete categories. In other words, do these phenomena differ only quantitatively or qualitatively as well? For instance, is the pathological dissociation an extreme demonstration of a normal dissociation (maximal values on the axis) or is this an entirely different category? Experts are fighting over this and other similar issues. Frameworks of thought that could reconcile these two viewpoints may be the following.

Let us assume we have a characteristic x that could linearly grow along one axis. For a certain - *threshold* - value, x_p, it begins to interact with the value y (above its threshold value y_p for the same reaction). What are possible results of this interaction? If the reaction is a positive feedback, we notice a sudden increase (non-linear) of x for values higher than xp.

The other possible outcome is a more complex phenomenon (let us call it the xy complex, which is not a mere sum of the two) in which we recognise the elements of x, but with additional components. In the example of dissociation, normal one is usually reduced to absorption by external or internal contents, that is, on narrowing of attention. With pathological dissociation, besides the narrowed attention, we can notice the dependence of memory and identity from the state (additional component) (Puttnam, 1997). If normal dissociation (absorption) is x, then fear (neuroticism) could be y. Pathological dissociation - xy complex - could be the (non-linear) consequence of synergy between normal dissociation and fear. From such viewpoint, the issue of continuum or discrete states becomes purely the one of terminology.

In principle, phenomenological picture can even be such that either x or y are no longer recognisable, because the mechanism had been diverted in a different direction. It should be mentioned that the threshold for x and y reaction could be a given degree of a third value that affects both of the previous two.

It may become even clearer if we contemplate this on a biochemical level. We know that neurotransmitters and hormones work only through their receptors, and each of them has, as a rule, several kinds of receptors of different affinities. When the concentrations of hormones or transmitters are low, they link only with receptors with the highest affinity. When they are high, enough of them are left for others, with lower affinity, which means that new reactions come into the mechanism - these receptors activate (or inhibit) the production of some other proteins.

To repeat, the non-linear dynamics can give a wide spectrum of outcomes that are difficult to predict by intuition. This means that if we measure the correlations of some values, we must not extrapolate this relationship outside the scope of measuring.

Another example of non-linearity is given by the results of our research on consequences of traumatic events: links between openness and intrusive symptoms. Openness is, according to the "Big Five" personality model a wide and general dimension, which is manifested as "lively imagination, artistic sensitivity, depth of emotions, behavioural flexibility, intellectual curiosity and non-conventional attitudes" (McCrae, 1996) and is measured by NEO PI-R questionnaire (Costa & McCrae, 1992). Intrusive symptoms are intrusive and upsetting memories (images, thoughts, perceptions), dreams, illusions, hallucinations, flashback episodes, all linked to the event and recurring; they are measured by the Impact of Event Scale (IES; Horowitz, Wilner & Alvarez, 1979).

We have anticipated an inverse variation between these values: greater openness - less intrusions and vice versa. This was confirmed on the refugee population: we have obtained small, but nevertheless significant negative correlations (Kneževic, Opacic, Savic & Priebe, 2004) However, in the research on a group of psychology students, we have obtained positive correlations between openness and intrusions (Kneževic, Opacic, Savic & Priebe, 2004) Given that the psychology students are three standard deviations above average in their openness this means that their values are close to a maximum on this axis. Thus it is clear that the dependence of intrusions on openness is a non-linear function (curve), regardless of the cause.

What complicates the picture in psychological measuring in comparison to the exact sciences is the fact that the measured phenomenon x is usually a more complex value or an entire mechanism. In this case, where x is openness, the only possible explanation of the non-linearity is that for medium values of x some components of this characteristic are dominant, whereas in a higher register of x some other components prevail. In our expectations we also had in mind the "behavioural flexibility, intellectual curiosity and non-conventional views" for which it would be logical to assume they help during the processing of information about the traumatic event. It is possible that the dominating element in extreme openness would be "the vivid imagination, artistic sensitivity and depth of emotions", which could become an obstacle to a normal processing of information.

It should be added that, regardless of the differences in openness, the main predictor of intrusions in both populations is neuroticism. This characteristic, defined in the above-mentioned "Big Five" personality model as a general predisposition to "experiencing negative affects such as fear, sorrow, confusion, anger, guilt and disgust" (Costa & McCrae, 1992), always constitutes the core of psychological sensitivity in stress.

MATHEMATICAL MODEL OF STRESS REACTION

Although the existence of close links between somatic and mental processes has long been known, we still ignore the mechanisms that lie in the basis of these interactions in the stress reaction.

Savic, Kneževic and Opacic (2000) have constructed a mathematical model of stress reaction with accents on individual differences, which links psychological and biological aspects of the stress reaction. This model integrates a wide spectrum of results from various research disciplines - psychology, psychiatry, physiology, etc., into a consistent mechanism of feedback between the stress (hypothalamic-pituitary-adrenalin, HPA [1]) axis and the memory system. Prior to the mathematical formulation, we needed to precisely and operationally define values through which the process of stress reaction would be described and postulate their mutual relations (Savic, Kneževic and Opacic, 1999). This model suggests answers to three questions: 1) what is stressful for whom, 2) how much time each person needs to recover and 3) what are the long-term consequences of stress.

To answer the first question, we have introduced the parameter σ (sigma) - *threshold for psychological stressors* that can be defined as a minimal external stimulus (of psychological nature) capable of provoking an increase in HPA axis activity. Or, statistically defined: for any given situation, the threshold of stress is the inverse measure of possibility to experience this situation as stressful. This means that, if there is a large number of situations through which two persons with different thresholds are going

1 A self-regulating system producing a cascade of three hormones in which one stimulates the next, while the third and last one inhibits the production of the first, thereby achieving self-regulation

through, the more sensitive person shall experience more situations as stressful than the resilient person, inversely proportionate to his own σ values. It is important to underline that this definition allows that each individual situation could be stressful for the more resilient person (higher σ) and not stressful for the more vulnerable one (lower σ). In other words, anyone can have *conditioned* stressors that are specific for him/her, even though this person is strong in general. However, the relation between the number of stressful experiences and the overall number of various situations will certainly be higher in the more vulnerable person. In general case there are two groups of factors that determine the threshold of stress: genetic and experience ones. Accumulation of life experience means *learning*, which changes the sensitivity to stress. The core of vulnerability is formed by a personality trait called *neuroticism* (described above).

To answer the second question, we have introduced the time parameter τ (thau), which relates to the speed of processing "emotional" information (those that cause emotional arousal). This parameter is characterised by the time needed to separate factual information from the affective component and to integrate it in the structured memory system. We could say that the stressful information is adopted once the memory of this event no longer provokes an emotional reaction. Hence, at the end of this process there are two long-term inscriptions in the memory that remain: one about the fact related to the event, and one about the emotional reaction. We introduce the assumption that the temporal dependency of the processing of "emotional" information is exponential with the characteristic period τ (thau), so that τ is inversely proportionate to speed. The question arises: is it possible to recognise τ in the behaviour of people and how it could be measured? Our assumption is that τ is directly linked to the other basic personality characteristic - *openness* (described above). Let us assume that the neurophysiologic mechanism that lies in the basis of individual differences in openness plays the key role in processing traumatic information. Higher level of openness means that the person is cognitively more flexible and therefore needs less time (less τ) to assimilate new information that has caused emotional arousal. Low level of openness is characteristic of the rigid cognitive system, to which we ascribe a high τ (slow processing). Direct prediction of this hypothetical relation is that persons suffering from the posttraumatic stress disorder (PTSD) have low score on the scale of openness. Empirical results have been discussed in the section on non-linearity.

For the third question we have introduced the value named coping factor - κ (kappa), which is also linked to neuroticism. The coping factor also changes by learning from stressful experience, even more directly than the threshold of stress. Despite the fact that the increase of sensitivity is a general reaction arising immediately after the traumatic event, long-term consequences of such event could be different: some individuals are strengthened by this experience, whereas other become even more sensitive. When a person is exposed to a stressor, he/she reacts in a certain way. The latent period (ranging from several hours to several days) between the event and the appearing of sensitivity is the period in which people evaluate their own behaviour. Self-assessment is probably the key determining factor of the "sign" of the ultimate effect of stress: if behaviour in the stressful situation has been assessed as successful, a positive outcome (increased threshold) is more

likely and vice versa. If we take N_+ to mark the number of stressful experiences in the past that a person has assessed as successfully overcome, and N to mark the number of unsuccessful ones, then their relation N_+/N_- shall determine the final change of threshold. The coping factor is a natural logarithm of N_+/N_-. If κ is positive (more successfully than unsuccessfully resolved stressful situations in the past), then the person will be strengthened by the stress; if it is lower, the person will be more vulnerable.

From the definition of the threshold of stress it is evident that this value is a direct link between the HPA axis and the memory system. The mechanism of feedback between these two systems is reflected in the following. Sigma gives the level of stressor that triggers off the "alarm" regime of HPA axis functioning - the influence of memory system on the HPA. Some of the HPA axis hormones (at least one) help the inscription of stressful experience in the memory, where it participates in modifying the threshold of stress - influence of HPA axis on the memory system.

Numeric solution of models simulates three phases of reaction to an individual stressor of short duration: 1) excitation of HPA axis and regulation of primary reaction (minutes - hours); 2) general sensitisation - temporary lowering of the threshold (days) and 3) recovery (months).

Two important implications of this model are: 1) direct correlation between neuroticism and basal cortisol level - above σ (even without stress) and 2) persons with prolonged stress reaction (high τ) have a low level of openness.

STABILITY OF COMPLEX SYSTEMS

Let us go back to complex systems and remind ourselves that each non-trivial form of behaviour requires non-linearity. Their dynamics is described by systems of non-linear differential equations that usually cannot be resolved analytically, that is, without the help of a computer. Nevertheless, the mathematical apparatus of the stability theory is sufficient for an analysis of the general character of such processes (Nicolis & Prigogine, 1977)[2]. It can be used to examine types of behaviour and conditions for their change.

We talk about stability when we deliberate open thermodynamic systems such as the biological ones. Unlike classical thermodynamic systems that reach a state of absolute equilibrium after a sufficiently long period of time, the open ones function far from the point of equilibrium and are constantly exposed to fluctuation. They only have states of temporary dynamic equilibrium - stationary states (which are on relative and not the absolute minimum of free energy). Testing stability means testing whether the system, once brought outside its equilibrium (stationary state) under the influence of fluctuations, would return to the same state or transform into a new one (another local energy minimum). These

2 There are more expert books on the issue of stability analysis, but this book is one of the best for an introduction to non-equilibrium systems, theory and methods of stability analysis, an also includes biological examples.

transformations happen in case of certain relations of parameters called the point of bifurcation and can be determined through analysis of stability.[3]

ANALYSIS OF THE HPA AXIS STABILITY

The HPA axis operates in the basal (homeostatic) regime with characteristic daily rhythm - one maximum and one minimum. In a healthy organism, HPA axis is adjusted in such a way as to increase its activity in stressful conditions and return to the basal level as soon as possible after the removal of external stressor.

Most of the existing mathematical models of HPA axis (quoted in Savic and Jelic, 2003) were made for pharmaceutical purposes, i.e. with the aim of predicting the level of cortisol (glucocorticoid, the final product of this hormone cascade) after administering certain medication, so that these models are phenomenological. Temporal periodicity in them is most often modelled by a trigonometric function that best fits the measurements and the origin of which is not explained. The shortcoming of phenomenological models is that they only describe and do not explain the observed behaviour.

Savic and Jelic (2003) have constructed five variants of the model of basal HPA axis activity. All five versions have been constructed according to principles of chemical kinetics in which every element has an essential physical-chemical explanation. The base is formed by a system of three differential equations describing the production and consumption of hormones with inhibiting feedback created by cortisol. The model has gradually been rendered more complex to ensure the smallest possible loss of potentially important information by approximation, and each modification introduced has an empirical justification. Subsequently we have tested the dynamics of these models through the analysis of linearised stability in order to determine the source of temporal periodicity evident in reality.

Why is the issue of the origin of temporal periodicity so important?

Glucocorticoids are global regulators of many other hormonal and metabolical processes. Regular rhythm of their secretion is therefore of crucial importance for the body. If it should be disturbed, the synchronisation of many vital processes would be disrupted and effects of this could be lethal. There is a large difference in the general dynamics between two possible cases: 1) pacemakers that give the rhythm are independent of the hormone dynamics and 2) dynamics of the HPA axis system (successive production of hormones with self-regulatory cortisol) generates oscillations.

3 One of possible forms from the wide spectrum of behaviour of non-linear systems is a deterministic chaos, which is being largely discussed and should not be equated with non-linear dynamics, which has been observed in some papers.

The second case - intrinsic oscillations of the HPA axis - could lead to rather complex temporal schemes, especially if external stimuli are superposed on them. In that case it is possible that a multiple periodical, quasi-periodical or even chaotic dynamics might occur.

The analysis of all five variants of the model shows that the HPA axis does not generate oscillations, which represents counter-intuitive results from the methodological point of view. This is especially relevant for the model with delay, since in these systems of equations oscillations usually occur (Baker, et al, 1999). Therefore, the HPA axis system is asymptotically stable and does not oscillate at all. What we see - regular daily variations of cortisol concentration p are exclusively the consequence of the response of this system to the temporally periodical signal coming from another part of the brain (for which we empirically know it exists). Numerical solution of even the simplest version of the proposed model, once an independent periodic activator is introduced, simulates well the real picture.

The fact that circadian rhythm is also maintained in most stress induced disorders speaks in favour of the results obtained, in other words, in favour of the stability of the HPA axis.

REFERENCES [4]

Baker, C.T.H. , Bocharov, G.A. and Rihan, F.A. (1999) A report on the use of delay differential equations in numerical modelling in the Biosciences. *Numerical Analyses Report No 343.* University of Manchester, Department of Mathematics.

Costa, P.T. and McCrae, R.R. (1992) NEO PI-R Professional Manual, Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI). Odessa: Psychological Assessment Resources, Inc.

McCrae, R.R. (1996) Social consequences of experiental openness. *Psychological Bulletin* **120**, 323-337.

Meinhardt, H. (1982) Models of Biological Pattern Formation. London: Academic Press.

Nicolis, G. and Prigogine, I. (1977) Self-Organization in Nonequilibrium Systems: From Dissipative Structures to Order through Fluctuations. New York: John Wiley & Sons, Inc.

Putnam, F.W. (1997) Dissociation in Children and Adolescents. New York: The Guildford Press.

Savic, D. and Jelic, S. (In preparation) A theoretical study of the hypothalamo-pituitary-adrenocortical axis dynamics. *Journal of Theoretical Biology.*

Savic, D., Kneževic, G. and Opacic, G. (1999) Individualne razlike u stresnom odgovoru - uvod u matematicki model, [Individual differences in stress response - Introduction to mathematical model]. *Psihijatrija Danas* **31**, 339-361.

Savic, D., Knezevic, G. and Opacic, G. (2000) Mathematical Model of Stress Reaction: Individual Differences in Threshold and Duration. *Psychobiology* **28**, 581-592.

4 The list of literature in our quoted papers is quite extensive, therefore interested readers are invited to consult it.