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**Review of the doctoral dissertation of Ms. Ashmita Bose, M. Sc.**
**„Evolutionary algorithms as a tool for designing chemical computers"**

The doctoral dissertation presented for review was prepared under the supervision of Prof. Dr. Jerzy Górecki and Prof. Dr. Peter Dittrich at the Institute of Physical Chemistry of the Polish Academy of Sciences. Its content is the study of the possibility of using the model of the Belousov-Zhabotinsky oscillatory reaction for information processing, which in the future is to serve the construction of chemical computers. Model chemical oscillators, the dynamics of which, similarly to real systems of this type, are based on competition between species referred to as activators and inhibitors, are coupled in networks in which specific interactions between activators are assumed, and the logical state (0 or 1) is determined on the basis of the number of maxima of values (concentration analogues) of the activator in the selected oscillator. Already this preliminary description proves that the dissertation concerns modern and prospective issues, which also are studied in various research groups around the world. In the Institute of Physical Chemistry of the PAS, both experimental and model studies of chemical information processing have been conducting for years.

The dissertation was prepared in the traditional form, meaning a division in half into a literature part, contained in three chapters, and a part describing own research in four chapters, a total of 132 pages. The final part of the work includes a bibliography, which consists of 123 literature references. The list of own publications related to the doctoral dissertation contains 5 references, including one study of the conference speech, two publications in the journal *Frontiers in Chemistry* (IF = 3.994), and one work in the *International Journal of Unconventional Computing* (IF = 1.379) – a journal specializing in the calculational aspects of nonlinear problems. During the review of the work, the fifth work was still in the stage of submission. It should be emphasized that each of the published 4 works was prepared by only two authors, with Ms. Bose being the first author in 3 cases. Such achievements are undoubtedly a solid justification for efforts to obtain a doctoral degree.

Although the work is assigned to the field of Chemical Sciences, its rather interdisciplinary character should be emphasized. The research described in the dissertation concerns a model of a chemical oscillatory reaction, but treated in a way that requires the ability to perform numerical calculations, with conclusions referring to artificial intelligence, including machine learning, with specific applications, including in medical research.

I would like to emphasize that I am reviewing this dissertation as a chemist, specializing in physical chemistry, while having some knowledge of nonlinear dynamics. Detailed issues

related to computational evolutionary algorithms should therefore be the subject of a separate, professional review.

Below I will briefly describe the main content of individual chapters, at the same time formulating comments and questions.

Chapter 1, referring to artificial intelligence algorithms, describes the scheme of operation of natural neurons, confronted with the typical construction of artificial neural networks and the description of the essence of "unconventional computing" as parallel computing, contrary to sequential computational procedures using conventional computers. The purpose of the work is clearly specified – as the design of a chemical computer that processes information in a non-trivial way. The design of such a computer is based on a network of interacting model chemical oscillators, chemically coupled. According to the doctoral student, such a network better reflects the essence of communication in living organisms than conventional neural networks, based on arbitrarily adopted rules of operation. To achieve the goals, the "top-down design" methodology was used, in opposition to the bottom-up variant. My slight technical remark is that Figures 1.3 and 1.4 should be swapped because they are discussed in the text in reverse order.

From my point of view as a chemist, the content of chapter II is very important, in which the model chemical system is described and the evolutionary computational algorithm used for training the model system is outlined. Undoubtedly, the description of the discovery, course and outline mechanism of the Belousov-Zhabotinsky reaction is needed here. As a chemist, I feel obliged to pay attention to the imprecise definition of the catalyst for this reaction (p. 13): cerium is a metallic element, and the catalyst is the redox couple Ce(IV)/Ce(III), which can be introduced into the system as one of these forms; it is also worth specifying the chemical nature of ferroin as a Fe(II) complex with o-phenathroline.

It is useful that the complex mechanism of BZ process is here reduced to the basic 3 groups of processes, showing how the $Br^-$ ions, crucial for the dynamics of the BZ reaction, are consumed and regenerated. However, I have some reservations about the fact that in the presence of $Ce^{4+}$ ions there is a rapid formation of $Br^-$ ions. It seems to me that this process (Process 3) is relatively slow and thus it takes some time for the system from the dynamics controlled by Process 2 to switch to the ion-demanding $Br^-$ reaction group designated as Process 1. In addition, autocatalysis in Process 2 is directly related not directly to the oxidation of $Ce^{3+}$ to $Ce^{4+}$, but to the autocatalytic role of $HBrO_2$ in this reaction, revealed when the second and double third equations in Process 2 are summed up. However, it is possible that my objections are a consequence of only a condensed description.

Further consideration of the formation of concentric chemical waves in the BZ reaction as a reaction-diffusion system (RD) is valuable. Due to the need to gain control over the oscillatory dynamics of the BZ system, its photosensitive version was then discussed, based on the use of a ruthenium catalyst known from the literature, which in a photochemically excited

form becomes a source of additional $Br^-$ ions, maintaining the system in a non-oscillatory state, defined above as Process 1.

A natural consequence of the experimental characteristics of BZ systems is to discuss simple models of this reaction, necessary to perform calculations in Ms. Bose's own work. The PhD student chose for presentation one of several literary versions of Oregonator, involving three dynamic variables: $U \equiv [HBrO_2]$, $V \equiv [Ce^{4+}]$ and $W \equiv [Br^-]$ and showed how, through transformation to the dimensionless version and elimination of the dynamics of $Br^-$ as "fast variable", to derive the well-known in the literature of the subject the two-dimensional Oregonator. At this point, I would like to ask, again as a chemist, how Ms. Bose understands the term "equilibrium state", which is mentioned on page 18. Mathematicians consider the situation of zero values of all derivatives ($dx_i/dt = 0$) to define an equilibrium state. However, for chemists' equilibrium state means equalization of the rate of forward and backward reactions, and in this version of Oregonator all reactions are unidirectional – irreversible. Hence, the only equilibrium here is the asymptotically achieved state of thermodynamic equilibrium of the system with an environment, in which system there are present only final products and possibly stoichiometrically redundant substrates that no longer have anything to react with, and in which oscillations are no longer possible. For a flow-through system, a state with parameters $dx_i/dt = 0$ can be achieved when all inflows and outflows are exactly balanced, but the chemist will call the resulting state as an non-equilibrium steady state, and not a state of chemical equilibrium, which for them is only a very special case of steady states. I would suggest using the term "non-equilibrium steady state" at this point.

The following outline presentation of the linear stability analysis a two-dimensional dynamical system, together with representative phase trajectories and specific references to the two-dimensional Oregonator, is a very useful part of this chapter, which introduces the basics of the analysis of dynamical systems. This also allows to indicate the role of the stoichiometric coefficient of $Br^-$ ion formation as an important bifurcation parameter. The logical continuation of these considerations is the Oregonator representation in the form of nullclines, taking into account the oscillatory characteristics and a special type of stability, which is excitability. In my opinion, for the excitable regime, it was possible to draw more clearly, how for small disturbances, remaining in the nullcline $du/dt<0$ area, a low-amplitude return of the dynamical system to its original state occurs. A further logical consequence of this description is the presentation of a literature version of the two-dimensional Oregonator, enriched with the production of $Br^-$ resulting from irradiation of the system.

The rest of the chapter is crucial for understanding the concept of applications of oscillatory reactions to information processing. Referring to the work of Showalter et al. [62, 63], Ms. Bose recalls, among others, a pioneering example of modeling logical states "0" and "1" using the spatiotemporal evolution of the BZ system in the capillary. In this approach, logic gates were constructed as arrays from capillary tubes. The interpretation and definition of

entropy from the point of view of information theory (Shannon's definition) is also discussed, as this concept was used in the analysis of the results of Ms. Bose's calculations.

Extremely important for the dissertation is Chapter 2, discussing the essence of evolutionary algorithms used by Ms. Bose, which are a method of optimizing a given problem by steps imitating the evolution of biological systems: from a randomly selected population, through selection, mutation and recombination, which procedure is schematically presented in Figure 2.11. Evolutionary algorithms, the concept of which appeared in the mid-twentieth century, are a method of optimization different from classical deterministic algorithms, and are particularly useful in nonlinear and multidimensional problems. They also allow to solve problems with the discrete search space, which is not implemented by traditional algorithms. Ms. Bose, citing analogies with Darwin's theory of evolution, shows how the ideas of mutation, recombination and selection are transferred to computational procedures in evolutionary algorithms, illustrating this with an example of approximation of a data set by a polynomial function. Of course, such a problem can also be solved by the deterministic method, but its role here is to show a simple example illustrating the evolutionary algorithm, which also allowed to assess the impact of population size and mutation probability on the criterion referred to as fitness value. As can be seen from the above description, Chapter 2 contains a necessary, synthetic description of the basic concepts, definitions and mechanisms of reactions, as well as algorithms needed to capture the content and essence of the research described in the dissertation. These studies were certainly a good preparation for the proper work described in the following chapters.

The extensive Chapter 3 is a presentation of Ms. Bose own calculations concerning a single chemical oscillator and a network of such oscillators, along with a teaching strategy applied to such networks. Also for me as a chemist it is undoubtedly a very interesting and educating part of the dissertation. In the introduction, an important sentence is said again that "we think that biological neural computing can be represented more realistically by the network of interacting chemical oscillators compared to the typical artificial neural networks". In my view, the remainder of the thesis constitutes a serious set of arguments for the correctness of that sentence.

The calculations for a single oscillator concerned a two-dimensional Oregonator for a photochemically controlled BZ reaction using one of versions of the Runge-Kutta integration algorithm (Cash-Karp RK45), which is an adaptive time step size method. I understand that the stiffness of the Oregonator system of equations was thus overcome, and the given time step $10^{-4}$ was an a priori declared value that was modified during integration? Also, the form of differential equations in this place (and elsewhere of the dissertation) raises the question of whether it was necessary to use *partial* derivative symbols ($\partial$) in these equations that are essentially *ordinary* differential ones, describing dynamics only as a function of the time coordinate.

At this point, I would also like to ask you to clarify the sense of the threshold value of the activator qualifying the system for oscillatory behavior, to which the logical state 1 is assigned. Was the "threshold value" of 0.05 an inherent feature of the excitable system, above which there was a strengthening of the oscillation, e.g. by the system entering the basin of attraction of an external stable limit cycle, or was it simply an arbitrary choice of Ms. Bose of a value, above which she qualified the amplitude of oscillation as large enough to assign the dynamics of the system a value of 1? Figure 3.2 suggests this last assumption, as the value of 0.05 remains at the base of the activator peaks. At the same time, it should be emphasized that in the slightly simplified procedure adopted by Ms. Bose, the analysis concerned only the dynamics of the activator, omitting the inhibitor. A cleverly defined function $\Phi(t)$ controls the switching of the model system between the illuminated (no oscillation) and dark (oscillating) states. On this basis, the input to the system was programmed by translating them into the illumination time, while the output was measured with the activator maxima. More specifically, the conclusions were based on the amount of activator maxima. An ambitious development of this procedure for more complex problems was the design of a network of chemical oscillators, based on the Oregonator model. The above-mentioned assumption was made that their interaction is carried out by means of activators, and the specific chemical reaction scheme was equivalent to the flow (convective) coupling of the oscillator space in CSTR. If I understand the problem correctly, parameters denoted as $\alpha$ and $\beta$ (together with the respective model process of decay) were necessary to introduce in order to optimize the strength of coupling between the oscillators to the level suitable for successful model calculations. A ring of six coupled oscillators was chosen for test calculations. The next Chapter 3.4 describes the essence of teaching strategy and contains a very important information that "the oscillator with the maximum mutual information will be our output oscillator". In the last chapter 3.5, the calculation scheme for the network of chemical oscillators is given.

The also extensive Chapter 4 contains a very detailed description of two problems solved by the method described by the method – decoding the colors of the Japan flag using the network of (only) three oscillators. According to previous assumptions, the output information was coded in the number of activator maxima observed on one of the oscillators. After proper training of the system, the correct results were obtained with a very satisfactory accuracy of 0.95, and in the modified version – 0.99. The next, classic problem of two intertwined spirals required as many as 6 oscillators and was treated with three networks: linear, hexagonal with interacting neighboring oscillators and pentagonal with a central, sixth oscillator, interacting with each of the other five. The accuracy of the result always exceeded 80%, and the highest was in the case of a linear sequence.

Chapter 5 describes the application of a network of chemical oscillators to qualitatively different issues – medical problems concerning the diagnosis of schizophrenia and the response to *Bortezomib* treatment of patients with multiple myeloma.

In the first part, the source of the data was the results of EEG tests, and the goal of the analysis was to distinguish, with the best possible accuracy, patients with schizophrenia from healthy people. A system of 6 oscillators (5+1), described as variant 3 in the previous chapter, was used for the diagnosis. By combining the analysis of 3 signals, positive results were obtained with an accuracy of up to 90%. Comparative results for networks with fewer oscillators were also presented, indicating that only a 3-element network gives similar results.

With regard to the analysis of the effects of *Bortezomib* on patients with multiple myeloma, an analysis using a network of only three coupled oscillators was performed on the basis of a rich set of clinical data (gene expression values), which was justified by the above comparative analysis of the different networks. An interesting element is the use of "concilium of optimized networks", where each network is specialized in finding correlations between the expression value of one gene and the success of *Bortezomib* therapy. The accuracy of the results reached 85%. This chapter also raises the important self-critical question of whether drug performance evaluation really requires a procedure based on coupled oscillators – instead of inference based on histograms of single gene expression value? Based on her results, Ms. Bose comes to the conclusion that traditional analysis, based on histograms, offers much less accuracy. Only this part of the research discussed so far remained at the stage of submission of publication.

Relatively short Chapter 6 refers to the experimental implementation of the BZ reaction in interacting lipid droplets. After a synthetic review of previous works on this subject, created, among others, in Prof. Górecki's team, Ms. Bose describes her own preliminary research on the interaction of droplets of different sizes, which particular problem seem to be a novelty. Although these are preliminary results and are rather an addition to the dissertation, they show that Ms. Bose not only can perform advanced numerical calculations, but also conduct experiments.

The last, concise 7th Chapter of the dissertation is a synthetic compilation of conclusions and discussions. These have been discussed by me above. Hence, at this point I will only allow myself to express the conviction that the promising results of numerical modelling will be subjected to experimental verification in the future. Despite the undoubted high value of the results obtained by Ms. Bose, this is needed because the calculations were based on a simplified model of the BZ reaction, showing a slightly simplified dynamics compared to even the three-dimensional Oregonator, let alone the real Belousov-Zhabotinsky reaction. In addition, even for the simplified model, various simplifications and assumptions have been applied. Of course, this does **not** reduce the high value of the dissertation in the slightest, because this is the natural way of solving scientific problems in which modeling precedes experimental verification.

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Concluding, in my opinion, from both the essential and formal point of view, the doctoral dissertation of Ms. Ashmita Bose meets the criteria specified in Article 187 of the Act of July 28, 2018 (Law on Higher Education and Science, Polish Journal of Laws of 2018, item 1668, with amendments). This carefully prepared thesis evidently contains elements of scientific novelty, supported by valuable publications and on this basis, I recommend further stages of the procedure of obtaining by Ms. Ashmita Bose a Ph.D. degree (Doctor of Philosophy) in the field of Chemical Sciences.

**Application for a distinction of the Ph.D. theis**

In addition, I would like to include in my review an application for the distinction of the presented Ph.D. thesis. I believe that the substantive level of work, which required not only the calculations themselves, but also the creation of appropriate theoretical constructions and assumptions for this purpose, combined with a significant number of valuable results and analyzes obtained, justifies the recognition of this work as evidently above average. What's more, the main subject of research – oscillatory reactions and their application – is in itself very valuable, although in the chemists' community it is currently rather little known and even unjustly underestimated. Ms. Bose's dissertation and publications offer hope to change this by showing how chemical dynamical systems can become the basis for modern idea of constructing chemical computers. Such innovative application of oscillatory reactions is worth emphasizing.

Also, I would like to emphasize that I do not believe that the number of publications should be one of the important arguments for distinguishing the Ph.D. theses, since their substantive content should really be decisive. The dissertation is based on couple of publications, which Ms. Bose co-authored mainly or only with the Ph.D. supervisor, and which are a significantly original contribution to the problem of application of chemical dynamical systems, in this case on the way to chemical computers.

My one-sentence justification of the application for distinction is the following:

***For the original, significant computational contribution to the theory of the application of chemical dynamical systems in computer science using evolutionary algorithms.***

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