RFERREE REPORT

by Corresponding Member of BAS Svetozar Dimitrov Margenov,
Professor at IICT - BAS,
on materials submitted for competition
to take the academic position "Professor" at IICT - BAS
in professional field 4.5 Mathematics, scientific specialty
"Mathematical Modeling and Application of Mathematics (Applications in
Computational Physics and Biology)"

In accordance with Order № 179/19.07.2019 of the Director of IICT - BAS and Decision of the Scientific Jury, I was appointed as a reviewer of a competition for Professor, announced in the State Gazette (issue 41 of 21.05.2019). Documents for participation in the competition are submitted by Dr. Nevena Petrova Ilieva-Litova, Associate Professor at IICT - BAS.

1. Brief biographical information

Assoc. Prof. Nevena Petrova Ilieva-Litova has graduated in 1985 from the Faculty of Physics at Sofia University "St. Kliment Ohridski" holding a Master's Degree in Physics. In the period 1985 - 1988 she has been a post-graduate student at the Joint Institute for Nuclear Research - Dubna, Russia, where she has defended her dissertation for the PhD degree in Theoretical and Mathematical Physics (кандидат физико-математических наук).

She has worked as a postdoctoral fellow and as a principal researcher in a project funded by the Austrian Science Foundation at the Institute of Theoretical Physics at the University of Vienna (Austria), as well as an invited visiting scientist at the International Institute of Mathematical Physics "Erwin Schrodinger" in Vienna. In 2003 she has been elected as Associate Professor (certificate by the Higher Testimony Commission for Senior Researcher II) in the scientific specialty "Theoretical and Mathematical Physics".

Since April 1, 2015 she is Associate Professor at IICT-BAS.

2. General description of the materials presented

The materials presented by Assoc. Prof. Nevena Ilieva are prepared in accordance with the Development of Academic Staff in the Republic of Bulgaria Act (DASRBA), the Regulations for the Application of DASRBA (RADASRBA), as well as with the specific requirements of the Regulations of BAS and IICT - BAS. They include: European CV; copy of Diploma for the educational and scientific degree "Doctor";

copy of Certificate for Senior Researcher II; a certificate of work experience; list of scientific publications; list of scientific publications for participation in the competition; list of selected indexed citations; abstracts of scientific publications for participation in the competition; a reference from the National Center for Information and Documentation (NCID) website for of the fulfillment of the minimum national requirements under Art. 26, para. 2 and 3 and the requirements of IICT - BAS under Art. 26, para. 5 of DASRBA (for Associate Professor); reference for the fulfillment of the minimum national requirements under Art. 29, para. 2 and 3 and the requirements of IICT - BAS under Art. 29, para. 5 of DASRBA (for Professor); reference and copies of documents by the group of indicators E; reference to original scientific and applied scientific contributions; statement that there is no proven plagiarism. Attached are copies of the scientific publications submitted for participation in the competition.

Assoc. Prof. Nevena Ilieva has presented 23 scientific publications covering the period 2009 – 2019 (23 of them are published during last 5 years). All publications are in English. There are 17 papers in specialized scientific journals with Impact Factor (IF), 4 of which are in Quartile Q1 (Computers and Mathematics with Applications - 1, Phys. Rev. E - 2, Cells - 1). Five of the other articles are in specialized series with SJR. Out of the submitted publications, 6 are with 4 co-authors, 5 with 5, 7 with 6, and 5 with more than 6 co-authors.

The reference for compliance with the minimum national requirements and the requirements of IICT - BAS for the Academic Position "Professor" contains information in separate tables regarding the Data for the groups of indicators В, Г, Д and Е. The points for each of the indicators significantly exceed (between 2 and 3.6 times) the required.

3. General characteristics of the applicant's activities

Assoc. Prof. Nevena Ilieva is an established scientist in the field of Mathematical Modeling and application of Mathematics in Computational Physics and Biology. Analytical and numerical methods, as well as computer (including supercomputer) simulations, are at the heart of the research methodology. Also important in this type of research are the approaches developed for validation and visualization of the obtained results.

Assoc. Prof. Ilieva is actively involved in research projects, having been: deputy head of the Bulgarian team in the Pan-European projects under Horizon 2020 Program PRACE-4IP, PRACE-5IP, PRACE-6IP; work package leader in the National Scientific Program "Innovative Low-Toxic Biologically Active Agents for Personalized Medicine"; head of the Bulgarian team in two bilateral scientific projects (NSF) in the field of mathematical biology, respectively with Austria (Institute for Biosimulation and Bioinformatics of the Vienna Medical University), and with the People's Republic of

China (Beijing Institute of Technology); project leader/team leader in three national projects in Computational Biomathematics; representative of Bulgaria in the MB of COST Action 17139 EUTOPIA (European Interdisciplinary Topology Action)

During recent years she has been member of the organizing or program committees of the following international scientific conferences: BIOMATH'14, BIOMATH'15, BIOMATH'18; Large Scale Scientific Computations (LSSC'17, LSSC'19); Numerical Methods for Scientific Computing and Advanced Applications (NMSCAA'16, NMSCAA'18); High Performance Computing Bulgaria 2019.

4. Scientific and applied scientific contributions

The presented scientific and applied scientific contributions of Assoc. Prof. Nevena Ilieva are in accordance with the scientific specialty "Mathematical Modeling and Application of Mathematics (Applications in Computational Physics and Biology)".

I accept the candidate's proposed classification of the main results presented in the following four groups:

I. Methods for modeling, investigation and visualization of protein structure and dynamics;
II. *In silico* studies of immunoactive molecules and complexes;
III. Modelling of physical processes;
IV. Tools and techniques for high performance computations.

The number of publications presenting results in the separate groups is 9, 10, 2 and 2, respectively.

I. Methods for modeling, investigation and visualization of protein structure and dynamics

Protein folding is a complex process with many open problems. At the heart of the results presented in [P10, P12, P15, P19] is the synergy of complementary methods of computational biomathematics. Topological techniques have been introduced and developed, in combination with approaches based on the discrete nonlinear Schrödinger equation. The numerical modeling uses three force fields: one with clustered atoms and two (full) atomic ones. The purpose of the studies is to validate the quantification scheme as well as to eliminate the non-physical effects resulting from the applied force field approximations.

The second subset of results (see [P4, P7, P13]) is related to the development of methods and algorithms for obtaining (extracting) macro-level results based on molecular-dynamic simulations. A subject of study is the following two questions: (i) assessment of whether the time of molecular-dynamic simulation is sufficient; (ii) minimizing the dependence of the results on the substitution of the reference structure used in the initial treatment with clusters (sub-domains) where certain constraints on the internal dynamics in the semi-rigid sub-areas are introduced.

Articles [P20, P22] are devoted to the task of visualizing the results of molecular-dynamic simulations. The new method developed is based on the introduced series of orthonormal local coordinate systems along the side chains. The example considered shows that this allows to detect some anomalies in the atomic positions.

II.   *In silico* studies of immunoactive molecules and complexes

The computer simulations (scientific calculations) are being recognized as the third separate branch of the science, complementing the traditional theoretical and experimental studies. For instance, the *in silico* experiments substantially shorten the time in all types of biomolecular studies, and in particular in the process of drug development. Molecular dynamic simulations have been applied in this group of results for studies in two specific cases of immunoactive molecules and complexes (see papers [P2, P3, P14, P16, P18, P21] and [P8, P9, P11, P23], respectively).

A subject of development is the idea for treatment of some currently untreatable autoimmune diseases by regulating the activity of hIFN-Y (human interferon-gamma) through recombinant analogues with preserved affinity for the cellular receptor, which have a reduced biological activity. For example, the structure of the C-ends of the hIFN-Y molecule has been analyzed, showing that the more compact conformations are more energy-efficient. On the basis of an *in silico* study of 100 hIFN-Y mutants, 12 are selected, that most fully meet certain pre-set requirements.

The major histocompatibility complex (MHC) is investigated. Molecular-dynamic simulations of three close MHC complexes are performed and the dynamics of α-helices forming the binding pocket of the MHC molecule are analyzed. A spline approximation is used to determine the geometric characteristics (the surface area stretched along the axes of the two spirals and the distance between them). Such kind of technique is originally developed for analysis of crystallographic structures.

III.   Modelling of physical processes

In this group are presented results, identified by the applicant as scientific applied. They are published in [P1, P5]. Subject of the study is a hybrid scanning system that combines positron emission tomography (PET) with nuclear magnetic resonance (MRI). Complex investigations have been performed covering the cycle: annihilation of the positron in the tissue; conversion of generated photons into electrons; optimization of the yield of electrons in the gas.

A detector prototype is created. Computer simulations with the GEANT4 (GEometry ANd Tracking) software package has been carried out for its optimization. The PET-MRI scanning is characterized by less radiation exposure in a combination with a higher tissue resolution, which is a prerequisite for significant benefits in imaging diagnostics in oncology, neurology, cardiology, and diseases of the musculoskeletal system.

IV.   Tools and techniques for high performance computations

This group of studies is dedicated to the efficient use of modern high-performance computing systems - supercomputers. The results obtained are published in [P6, P17]. The topic has an integrated importance for the overall work of the applicant. Additional results related to the optimization of models and parameters of software tools (packages) for supercomputer simulations have been included in a number of publications reported in the previous three groups.

Here, the results devoted to the work with high-performance computing systems with heterogeneous architecture deserve a high mark. The presented numerical experiments are performed at IICT-BAS on the Avitohol supercomputer. The supercomputer architecture is based on Intel Xeon processors & Intel Xeon Phi coprocessor.

In conclusion, it is important to note that the scientific and applied results of Assoc. Prof. Nevena Ilieva are aimed at solving problems of high scientific value and of great public importance. They are highly interdisciplinary in nature. They have an innovative potential for high-tech breakthroughs.

5. Impact of the applicant's scientific publications

A total number of 170 citations are noticed by the applicant. According to Scopus, the h-index of Assoc. Prof. Ilieva is equal to 5. In the framework of the present procedure, the citations are presented in a separate table of Data related to the group of indicators E. When 140 points are required, the evaluation of the listed citations is 279 points. All citations in the table are in works of foreign authors, including in papers in some of the most highly ranked specialized international journals and series.

6. Evaluation of the applicant's personal contribution

I accept as a general assessment, that in the joint works, Assoc. Prof. Nevena Ilieva has at least an equal role.

7. Critical remarks

I don't have any substantial critical remarks about the materials of Assoc. Prof. Nevena Ilieva, presented within the present procedure. They fully comply with the requirements of the DASRBA, RADASRBA, the regulations of BAS and the specific requirements of IICT – BAS.

I will note two inaccuracies. In the list of scientific publications for participation in the competition, the paper [P13] is considered as belonging to quartile Q1. The check

WoS ranking revealed that the journal is in quartile Q2. This leads to a decrease of 10 points in the Table with Data by the Indicators in Group C. Thus, the points become 534 when the required ones are 260. Also, in the Table with Data by the Indicators in Group E, there is one citation for whish "?" is written instead of a number of the related points.

8. Personal impressions

I have known Dr. Nevena Ilieva since 2008, as a member of the scientific team of the Center for Excellence "Supercomputing Applications" project, funded by the Bulgarian NSF, of which I was the coordinator. She became very active and successful in the work on WP10: Supercomputer simulations of biological molecules and systems. The successful collaboration was at the heart of her transition to the Scientific Computing Department of IICT - BAS in 2015.

I highly value the scientific and professional level of the applicant, determining Assoc. Prof. Nevena Ilieva as a qualified, correct and responsible scientist and colleague with proven ability to work in a team.

I will especially note the contribution of Assoc. Prof. Ilieva to the validation and development of biomodeling, as an important integral part of the research thematic of Scientific Computing Department.

9. Conclusion

After getting acquainted with the materials of the competition, the complex evaluation of the applicant's qualities, including the scientific and scientific applied contributions, **I strongly recommend Assoc. Prof. Dr. Nevena Petrova Ilieva-Litova to be elected to the academic position of "Professor"** at IICT - BAS in professional field 4.5 Mathematics, scientific specialty "Mathematical Modeling and Application of Mathematics (applications in Computational Physics and Biology)".

26.08.2019

Sofia

Reviewer:

/Prof. Svetozar Margenov
Corresponding Member of BAS /