

OPPONENT OPINION

Competition for holding of academic position “Professor”, gazetted
on 21 May 2019, No 41

One candidate: Assoc. Professor Nevena Petrova Ilieva-Litova PhD

Procedure Notifier: Section of Scientific Computations, Institute of
Computational and Communication Technologies, BAS

Professional direction: 4.5. Mathematics

Scientific Subject: Mathematical Modeling and Application of Mathematics
(Applications in Computational Physics and Biology)

Juri Member: Prof. Michail Todorov, PhD, Department of Applied
Mathematics and Informatics (FAMI) by the Technical University of Sofia,
Section of Numerical Methods and Mathematical Modeling, nominated by the
Director of Institute of Computational and Communication Technologies -
BAS, Sofia, by order 179/19 July 2019.

1. Short biographical record of the applicant

Dr Nevena Ilieva was born in 1957 in Sofia. She graduated Faculty of
Physics by the St. Kliment Ohridski University of Sofia in 1985. Three years
later she took a PhD degree in Physics and Mathematics in JINR – Dubna.
During 1992-95 she holds a postdoc position in the Institute of Theoretical
Physics in Vienna and in 2003 got the academic position Associate Professor
in INRNE-BAS, Sofia. The scientific carrier proceeds with her work as a
visiting researcher in the Schroedinger Institute of Mathematical Physics in
Vienna and European Organization for Nuclear Research (CERN) in Geneva.
Since 2015 Dr Ilieva has been Associate Professor in ICT-BAS, Sofia.

2. General description of the competition documents

The applicant filed following compulsory documents: CV, full list of the works
with their IF and selected indexed citations, thorough author information for
the scientific contributions related to the given competition, summaries of the
works in Bulgarian and English, copies of PhD and Assoc.Professor diplomas,
lists of research projects and scientific conferences where the applicant took
part in, list of supervised and defended PhD students, certificate about length
of scientific service in BG, and affidavit against plagiarism.

3. General characterization of the research, teaching and applied activities

The applicant presents 23 works for the competition, all of them published in
the last 10 years, i.e. after getting her academic position Assoc. Professor.

After the habilitation in 2003 Assoc. Prof. Ilieva has totally 72 publications including 48 reviewed and indexed ones. Twenty four of them are with IF and 12 - with SJR. The interdisciplinary and international research involves the more works to be co-authored – 2, 3 and more authors. Since 2008 the applicant has taken part (including as a scientific leader) in 23 granted projects, half of them international. They are granted by BG Scientific Foundation (FNI), BG Ministry of Education and Science (MON), BAS, 7th Framework Program, Horizon 2020, etc. Along with her research activity the applicant supervises postgraduate students. A contribution is the managing/consulting of two project of BAS for promoting of young scientists (2016, 2017) and joint successful supervision of two PhD students from Beijing Technological Institute – Jin Dai (2016) and Yanzhen Hou (2019). As a teaching activity we can consider the preparation of the manual for the Intel Xeon Phi coprocessor as well as the postgraduated class in the Institute for Experimental Morphology, Pathology, and Anthropology with Museum, BAS.

4. Analysis of the scientific and applied contributions

Assoc. Professor Ilieva presents comprehensive and impressive author information where she claims her scientific and applied contributions. The problems into consideration can be grouped in 4 main directions: 2d models in quantum field theory; theoretical field methods in the condense state of matter; modeling of the structure and dynamics of biomolecules chains; high performance scientific computations.

For the given competition the applicant presents 23 works split into 4 interlaced cycles: methods for modeling, investigation, and visualization of the protein structure and dynamics: 9 works, 3 of them belong to quartile Q1 (*Computers and Mathematics with Applications, Phys. Rev. E, Molecular BioSystems*), other 3 – to quartile Q2, and 2 to quartiles Q3 and Q4; In silico investigations of immune-active molecule complexes: 10 works including 2 works in quartile Q1 (*Phys. Rev. E, Cells*), 1 work in quartile Q2, 4 works in quartile Q3, 1 work in quartile Q4; Modeling of physical processes: 2 works, one of them in quartile Q2; Tools and technics for high performance scientific computations: 2 works. The scientific metrics of these works is impressive: score 748 after National Centre for Information and Documentation (NCID), total IF=37.878, total SJR=0.995.

- Methods of modeling, investigation, and visualization of the protein structure and dynamics

The protein folding is still an important pending problems of the modern medicine. Its distinguishing feature is the intricacy requiring an interdisciplinary approach. To this end one needs to combine physical methods, computational algorithms, technics, and resources. Basically this is a molecular dynamics (MD) combined with analytical approaches. They originate from the integrability and the structure of the discrete nonlinear Schroedinger equation (DNLSE) admitting kink soliton solutions (topological solitons) and can be present in geometrical variables (angles). MD is a powerful method to investigate biomolecules. Actually it is a tool for computing and locating of equilibria, and tracking of transport processes in

classical dynamical multibody systems. It is rendered into simultaneous numerical integration of huge number of Newton equations with small time stepping. The conducted simulations provide significant results and predictions concerning the dynamics of various kinds of protein chains considered as soliton solutions of the generalized DNLS. MD simulations indicate transitional soliton-like quasi-particle oscillations. Also, they give us reliable macroscopic data for the studied systems based on the synthetic atom level information. The correct and adequate analysis and interpretation of the above information are related to the quality of the MD simulations data. One needs refined methods to extract functional information from the MD data. Such kind of methods are: lagged RMSD analysis as a tool to estimate how long in the time to be a given MD in order to reach a steady-state process; spatio-temporal clusterizing (SMCC), when the distances variations between the atoms are considered as a target function to be minimized. Essential part to give a meaning and interpret of given results especially obtained by *in silico* experiments is their graph visualization. The protein shape can be plotted by using of outer geometry of discrete partially linear curve (outer Ramachandran angles). In a natural frame (Frenet moving frame) is shown the existence of two additional independent geometrical structures. A new method for 3d visualization is developed. Instead of the outer geometry it uses the inner geometry of the lateral chains. The approach grounds on series of orthonormal bases alongside the lateral chains and projecting of atom locations on the unit sphere.

- ***In silico* investigation of immune-active molecules and complexes**

The human interferon-gamma (hIFN- γ) is important immune-modulating signal molecule. The exaggerated production can indicate the etiology of some autoimmune deceases. An innovative idea to treat these uncured troubles consists in regulation the activity of endogene hIFN- γ . The results implementing the realization of the above idea are obtained in collaboration in the Acad. R. Tsanev Institute of Molecular Biology, BAS.

A series of *in silico* investigations based on MD is conducted. It is complemented by metadynamical investigation of given angles measured the protein-spine torsion of 100 arbitrary chosen hIFN- γ mutants and 12 of them are selected. A high degree of correlation between MD simulations and biological (laboratory) data is established. The latter confirms the relevance of the developed methods. By using of MD simulations it is demonstrated the depressing influence of the markers upon forming a compound with the hIFN- γ receptor. The detailed understanding of the developing and dynamics of these processes seems to be crucial for modulation of immune activity in both directions – positive when attack viral and bacterial infections, negative when resist to autoimmune deceases. On mathematical modeling point of view the presented results elucidate some key problems. The geometrical features (the surface area stretched between the spiral axes and the distance between them) are defined by spline-method developed to analyze the crystallographic structure. It is shown that the above features depend on the degree of the interpolation function. They are stable for the inactive complex while they vary for the both alloreactive complexes; It is shown that the curvature of the spiral axes is a sensitive measure, closely related to the

dynamical changes of their form; To specify the relative orientation and domain motions we generate local frames (based on analysis of the main components) and in this way determine the cosine directions and Euler angles. Currently there is no efficient therapy for number of autoimmune deceases even the atherosclerosis and post-transplantation atherosclerosis caused by overproduction of the human interferon-gamma (hIFN- γ). The goal is studying this protein to develop new biotherapeutics depressing the activity of the endogene hIFN- γ combining of two approaches, complementary to one another – rational protein design and *in silico* MD.

- **Modeling of physical processes**

The results of this scientific investigation are applicable direct in modern medicine. To construct a hybrid system for medical imaging combining the positron-emission tomography (PET) and medical resonance imaging (MRI) seems to be a challenge originated by the static magnet field and the gradient magnet field needed MRI to function effectively. The above fields considerably worsen the usual photomultipliers used in PET scanners. Together in research team from Faculty of Physics by the St. Kliment Ohridsky University of Sofia are conducted detailed investigations tracking the full sequence: the positron annihilation, and optimization of the electrons gain in the gas. In order to optimize the detector design are carried out simulations testing the efficiency of photon RPC (resistive plate chambers) detectors by using of package GEANT4 for various materials and geometry. As a result a working prototype of single detector is made.

- **Tools and technics for high performance scientific computations**

MD being the most ambitious computational approach for the structure and interaction of biomolecules actually can be a source of *in silico* information hard of access for the modern experimental equipment. Therefore the MD simulations are mainly *in silico* experiments. The size of the investigated object and the duration of the processes and phenomena require considerable computational resources (supercomputers). Some obtained results are as follows: Installation and activation of GEANT4 – the basic software package for interaction between the ionizing particles and the matter. It is installed on the supercomputer Avitohol @ BAS, which is a heavy duty (HPC) hybrid architecture of kind Intel Xeon & co-processor Intel Xeon Phi and testing of its performance; Preparation in team of a manual (Best Practice Guide) for Intel Xeon Phi co-processor containing information about MIC architecture on Intel and the coding models for Intel Xeon Phi co-processor.

The applicant presented and reported the results of her investigations many times at the conferences, seminars, colloquia all over world – Europe, Asia, Africa. She was invited plenary and keynote lecturer of top-notch events.

In my opinion, Assoc. Prof. Ilieva holds and can use professionally the respective mathematical methods and tools in order to study successfully both qualitatively and quantitatively this complicated interdisciplinary matter.

5. Importance and contribution to the science and practice.

Citations by other authors

The total number of citations is about 170. The applicant filtered the 100 celebrated citations. They cite 32 her works. Most cited are: work [21] (*Eur. Phys. J. C*) – 11 cites, work [26] (*Theor. Math. Phys.(Russian)*) – 15 cites, work [53] (*Computational and Mathematical Methods in Medicine*) – 9 cites, work [54] (*Journal of Instrumentation*) – 10 cites, work [56] (*Best Practice Guide Intel Xeon Phi*) – 13 cites. It is unduly to mention that the cites are in top journals with high IF and belongs to quartiles. The unequivocal conclusion is that the achievements of the applicant are well known and rated highly from the international scientific community. Looking up the information in NCID and comparing clearly states that the Assoc. Prof. Ilieva contributions and activities several times exceed the threshold values required for academic position “Professor”.

6. Critical remarks and recommendations

Besides the NCID criteria Assoc.Prof. Ilieva covered and exceeded the national laws, BAS and IICT regulations and administrative provisions in order to apply for academic position “Professor”, namely: number of works 23 (totally 104) – all of them published in reviewed journals and issues; number of citations – 170 all of them in foreign ones; and 23 participations in research projects in BG and abroad. The actuality of the developed topics and scientific directions as well as the unflagging work of the applicant presuppose an attracting of more young people to this direction and training and supervising of more postgraduate students including from BG. All needed resources to do that are available. The active scientific and research activity, the big number talks and reports in national and foreign events, sharing by invitation of scientific and program committees being a reviewer as well the big number of citations (170 against 40 required) – all that demonstrates the readiness of Assoc. Prof. Ilieva to hold the academic position of Professor.

7. Personal impression

I have known Nevena Ilieva since 2012. I had few discussions with her in INRNE, BAS and later she became regular visitor and contributor of AMiTaNS conferences in Albena (since 2015) and BG SIAM where she took part very actively and attracted few more participants from IICT and Beijing Technological Institute, China. Also, I know her and appreciate as an independent and rigorous referee of AMiTaNS manuscripts. She strikes me as a high level professional deeply penetrated in an extremely complicated field of study. The results obtained in this field are substantial for the modern medicine and biochemistry.

Conclusion

Gaining an impression for the all-round scientific and research activity of the applicant and having in mind the legal rules and criteria (LDASRB and its regulations in BAS) as well as the specific rules in IICT I **rate positively** the

entire activity. On the strength of virtue of the law **I propose Assoc. Professor Nevena Petrova Ilieva-Litova** for academic position Professor in IICT, Professional Direction 4.5. Mathematics, Scientific Subject: Mathematical Modeling and Application of Mathematics (Applications in Computational Physics and Biology).

JURI MEMBER:

**NOT FOR
PUBLIC RELEASE**

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Mathematical Modeling
FAMI by TU of Sofia

September 12, 2019
Sofia