R E F E R E E   R E P O R T

by

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Institute of Information and Communication Technologies – BAS

Member of Jury for the selection of the academic position "Associate Professor"

Appointed by the Director of IICT-BAS (No. 166/13.07.2021)

<u>Announcement:</u>	*State Gazette, Issue. 21/15.03.2022*
<u>Higher education area:</u>	*4. Natural sciences, mathematics and informatics*
<u>Professional area:</u>	*4.5 Mathematics*
<u>Scientific specialty:</u>	*Mathematical modeling and application of mathematics (applications in computational physics and biology)*
<u>Applicants:</u>	*Dr. Elena Boyanova Lilkova, Senior Assistant Professor (sole candidate)*

1. Brief biographical information

Elena Lilkova graduated from Sofia University "St. Cl. Ohridski" in 2011. Acquired qualification: "Master of Medical Physics". In 2015, he acquired the scientific and educational degree "Doctor". He speaks German and English at an excellent level. In the period 2015 - 2017, he worked as a programmer at IIKT (Development of programs for computer modeling of biological molecules), and from 2017 until now he is the Chief Assistant in the section "Scientific calculations with a Laboratory of 3D digitization and microstructural analysis" (Computer modeling of biological molecules). During that time she worked on a variety of computer architectures, incl. heterogeneous systems with graphics accelerators (GPUS) and co-processors and on some of the most powerful European supercomputers of the TIER-0 class.

During this period, she was the head of two scientific projects under the funding program for young scientists at the BAS and was a participant in 13 other national and international scientific projects. She was a member of the organizing committees of prestigious international conferences.

2. General description of the materials presented

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The materials presented to me by Dr. Elena Lilkova on the announced competition includes: (a) CV in the form; (b) a diploma for the educational and scientific degree "Doctor"; (c) Certificate of position occupied in IIC -BAS and experience in the specialty; (d) a list of scientific publications involving the candidate; (e) a list of scientific publications presented for participation in the competition; (f) copies of the scientific publications presented for participation in the competition; (g) a list of citation; (h) authority; (i) brief summons in Bulgarian and English languages of the scientific publications presented for participation in the competition; (j) a reference to meet the requirements for occupation of the academic position "Associate Professor" and (k) a declaration of lack of established plagiarism.

All the materials provided to me have been carefully prepared and I have no doubt about their veracity.

3. Reflection of the Candidate's Scientific Publications in the Literature (known citations)

I accept the "List of Citations" submitted by the applicant, which is detailed and complete and contains all the necessary information. The lack of numbering, both of the cited publications and of those who cite them, makes it difficult to read and extract the necessary scientometric information. In this list and the accompanying table, 36 citations of 10 publications with her participation are reflected (one publication was cited 13 times, one - 8, one - four times, four - twice, and the remaining three publications once).

4. General characteristics of the applicant's activities

4.1. Scientific and applied scientific activity

I accept the declaration made in the "Reference for original scientific and scientific-applied contributions" by the applicant that "the list of all scientific publications includes a total of 38 titles. I accept the "publications of the candidate for participation in the competition", including 21 titles, of which 19 have already been published and two have been accepted for publication. 16 of the already published scientific articles are visible in SCOPUS/Web of Science, of them four have an impact factor (two are in quartile Q1 and one each in quartiles Q2 and Q3), the rest have SJR. The two papers accepted for print will be published in a series that also has SJR. Five of the publications presented for consideration in the competition are not in journals with SJR or impact factor, but

have gone through a serious review process by leading European specialists in the field of high-performance software and computing within the international association PRACE (Partnership for Advanced Computing in Europe).

The review of the candidate's publications for participation in the competition shows that the candidate has no independent publications submitted for the competition. The co-authors of Dr. Elena Lilkova are only from Bulgaria. I do not doubt the personal contribution of the candidate in each of the publications. The main results of the candidate are in the field of the announced competition, they are presented in detail, thoroughly and comprehensibly in the author's reference and can be defined in several sub-fields, where I will focus on the most important results achieved in my opinion:

(1) *Молекулно моделиране на човешки интерферон гама. (publications under numbers* В.1–В.4, Г.1, Г.2, Г.4, Г.9– Г.11*)*;

Research in this area is structured and presented in the following four sub-areas:

1.1. *Structure modeling of hIFNγ*

Using molecular modeling and folding simulations, a 3D model of the complete cytokine molecule was constructed with the missing amino acid residues from the C-termini added. The solvation energies of various representative conformations of the cytokine molecule were calculated using the free energy perturbation method. I agree with and support the conclusions drawn by the candidate that, taken as a whole, the results obtained identify the compact conformation, with the C-termini tucked into the cytokine globule, as the most energetically favorable and that, as far as is known, this is the first complete model of the structure of human interferon gamma.

1.2. *Mutant forms*

The structural stability of selected hIFNγ mutants with substitutions at positions 86-88 was investigated. The globule structure stability analysis is based on the multi-step spatio-temporal consensus clustering method. As a result of the research, five domains have been identified that have 4/9 specific functions in the molecule, and the impact of mutations on the composition and conformation of these domains has been analyzed.

1.3. *Glycosylation*

The studies done here have made it possible to show that the pentapeptide recognition site forms about 20 more contacts with the glycosylated tagged proteins than with the non-glycosylated one. The proteolytic resistance of the His6-FLAG tags was shown to be due to interactions of the tags with the entire glycosylated globule of IFNγ, rather than direct contact with the carbohydrate chains.

1.4. *Interaction with glycosaminoglycans*

The results obtained by the candidate in co-authorship show the molecular basis of the protective action of heparin on the integrity of hIFNγ, as well as its inhibitory action regarding the binding of the cytokine to its cellular receptor.

(2) *Modeling of antimicrobial peptides (AMPs) (publications under numbers Г.5 – Г.8, Г.12);*

2.1. *Structure*

Through the studies done, it was shown that in solution, before attacking the target membrane, the native peptide and its mutant mainly occupy the helix-fold-helix conformation, and not the purely helical one. The data obtained from the research show that in the case of the native peptide, conformational changes in the second and third segments do not affect the structure of the first. However, substitution at position 16 is very likely to fully unfold the helices in R2 and R3, and substitution at position 5 destabilizes the helix in the first region.

2.2. *Behavior and self-organization in solution*

The behavior of AMP indolicidin in solution was studied. It is one of the shortest AMPs known, with a very high charge density and unstructured in solution. Indolicidine was shown to aggregate spontaneously almost immediately, with the nanosized clusters formed having a typical globular structure with a central hydrophobic core and surface-exposed positively charged amino acid residues to the solvent.

2.3. *Interaction with membranes*

The activity of AMPs is based on their cationic and amphiphilic nature, which allows them to interact with negatively charged bacterial surfaces and membranes, thus causing disturbances in the structure and integrity of the membrane or changing its metabolic processes. Based on an analysis of the free energy surface of crossing the lipid bilayer, it was found that for only

three of the 10 investigated peptides crossing the membrane from the outer to the inner layer is an energetically advantageous process. In addition, almost all peptides have well-defined deep minima in the hydrophobic layer of the membrane, an indication that they can probably be incorporated into it without translocating.

(3) *Scientific software (publications under numbers Г.3, Г.13 – Г.17)*

The complexity of the studied objects and phenomena, and the expensive and time-consuming experiments is an essential catalyst for using mathematical and computer modeling in this kind of research. In turn, the use of modern high-performance computing systems requires the creation of specific software, which depends on the type of computing technology used - parallel computers with shared or distributed memory, hybrid systems, clusters, etc.

3.1. *Analysis and testing of specialized applications and packages for high-performance computing*

The installation and performance study of one of the most important software packages for the simulation of interactions of ionizing particles with matter - GEANT4 - on the high-performance supercomputer Avitohol@BAS, with a hybrid architecture Intel Xeond - Intel Xeon Phi co-processor, is described. An analysis of the performance dependence of various software parameters of the available MD packages (GROMACS and NAMD) suitable for use on HPC machines has been performed.

3.2. *Developing tools and methods for molecular modeling of biological systems*

For maximum approach and satisfaction of the peculiarities of the MD, the external library for parallel calculations with the implicit solvent model AGBNP2 (Analytical Generalized Born Plus Non-Polar 2) has been developed. In it, the solution is described as a set of overlapping spheres centered in the atoms of the system and volume calculated according to the formula of Poankare. The 9/9 own volume of each atom is estimated and the two -part dexcrinm scaling coefficients are evaluated to evaluate Bourne's radius. The same algorithm is used to evaluate the surface of the atoms. This library is integrated into one of the popular DL_Poly_4 MD simulations. Poisson algorithm has been developed in the dl_poly_4 package as an alternative to the Ewald sum. This provides the possibility of simulating systems without imposing periodic boundary conditions. The algorithm is based on a 27-point discretization scheme and

uses a stabilized double-spoken gradient.I accept as reliable the information presented regarding participation in international scientific conferences with reports - a list of 66 reports presented at international scientific conferences with author teams with the participation of Dr. Lilkova is presented. However, it is not indicated in which of them the candidate personally participated and presented the relevant report.

I accept as reliable the information presented about the candidate's leadership and participation in research projects - 15 Bulgarian and international, in two of which Elena Lilkova is the leader.

The scientific production of the candidate shows that she is a well-established, highly qualified scientist in the field of the announced competition, both in theoretical and applied aspect.

4.2. Educational activities (work with students, PhD students and postdoctoral)

In the submitted documents for the competition, I do not find the candidate's educational and pedagogical activity, as well as other work with students, specialists and doctoral students, explicitly mentioned.

4.3. Contributions (scientific, scientific, applied)

The applicant's scientific production shows that it is a constructed, highly qualified scientist, with essential scientific and scientific and applied contributions in the field of mathematical and computer modeling and applications in important tasks of computing physics and biology, both in theoretical and attached aspect. Scientific, scientific, applied or applied contributions can be found in any of the publications presented by Dr. Lilk. All such are duly and understandably described by her in the summary of scientific publications for participation in the competition for Associate Professor and a reference to original scientific and scientific and applied contributions, with which I fully agree and do not consider it necessary to recount again. For me personally, the most representative is the results relating to:

> The studies and results obtained in the field of molecular modeling of the human interferon gamma and in particular: (a) The construction of a 3D model of the overall molecule of cytokine with the missing amino acid residues from the C-stories added; (b) The results that show what is the molecular basis of the protective effect of heparin on the integrity of HIFNγ, as well as its inhibitory action with respect to the binding of cytokine to its cell receptor.

> The studies and results obtained in the field of modeling of antimicrobial peptides, and in particular the examination of the behavior of antimicrobial peptide indolicidine in solution.

> Development of an external library for parallel calculations with the AGBNP2 (Analytical Generalized Born Plus Non-Polar 2) model, using a Poisson algorithm application in DL_Poly_4 as an alternative to the Summer method alternative.

5. Assessment of the applicant's personal contribution

I have no doubt about the personal contribution of the candidate in each of the publications presented.

6. Critical notes

I have no critical remarks that would be relevant to determining my position and conclusion on this competition. However, I will mention a few things of a technical nature, some of which have made my work at least difficult in preparing this review: (a) The structuring of the information on the publications and the citations observed by the applicant does not facilitate the extraction of scientometric information, but on the contrary makes it very difficult; (b) The candidate must have some educational activities; (c) Even the field of interest of Dr. Lilkova is too interdisciplinary she need to concentrate on some self publications; (d) The names of the submitted electronic files often do not correspond to their content, which makes it difficult to find the necessary information; (e) There is no clear information regarding the candidate's personal participation in scientific conferences and the reports presented by her.

7. Personal impressions

I know Elena Lilkova from entering the IIKT, in the "Scientific Calculations" section, as well as her work within PRACE (Partnership for Advanced Computing in Europe). I can confidently assert that she has built herself up as an excellent, highly qualified specialist in her field of competence.

8. Conclusion

All the written above forms in me a positive attitude towards the candidate and I suggest **Dr. Elena Boyanova Lilkova TO BE ELECTED for "Assoc. Prof."** in the field of higher education 4.

Natural sciences, mathematics and informatics, professional field: 4.5 Mathematics, scientific specialty: ***"Mathematical modeling and application of mathematics (applications in computational physics and biology)"***

July, 2022

На основание
ЗЗЛД