Interim Report / Second Phase
(April 2012 – September 2013)

WP10: Supercomputer simulations of biological molecules and systems

1. Main activities and results

Task 10.1.1 ***Studying the structure and stability of human Interferon Gamma C-terminus***

In order to assess the conformations favorability, we performed several free energy perturbation simulations to calculate the relative solvation free energies of the centroids of the biggest clusters of the NAMD+CHARMM22 simulation with respect to the extended starting conformation. The aim was to use the solvation free energies to obtain a rough estimation of the relative free energies and the respective energetic favorability of protein structures. Three independent FEP simulations were performed for each structure using different starting seeds for velocities generation and then the average values were used.

The simulations were performed using the MD package NAMD2.9, whereas the solvation free energy was calculated by decoupling the protein from bulk water, gradually switching off the interactions of the atoms of the protein and the solvent. Due to the soft-core potential, separate simulations were run for the forward and the reverse transformations. The forward and reverse transformation simulations consisted of 67 windows, with a short minimization of 500 steps was first performed, followed by 7000 steps of equilibration and 2000 steps of data collection for ensemble averaging.

The average salvation energies of the centroids of the biggest clusters of the NAMD+CHARMM22 simulation with respect to the extended starting conformation are presented on Fig. 1.

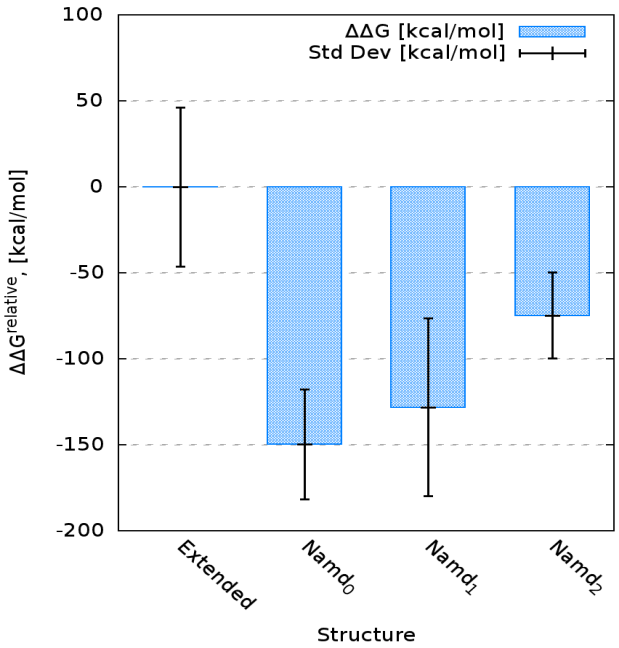

Fig. 1 *Relative solvation free energies of the centroids of the biggest clusters from the NAMD+CHARMM folding simulation with respect to the extended starting structure.*

As expected, the two biggest clusters which encompass about 72 % of the folding simulation are characterized by lower solvation energies than the starting extended structure. These also exhibit the most compact conformations. The solvation free energy decreases with the SASA, the radius of

gyration and the RMS distance between the C-terminal Ca positions from the globular center of mass. This correlation is presented on Fig. 2.

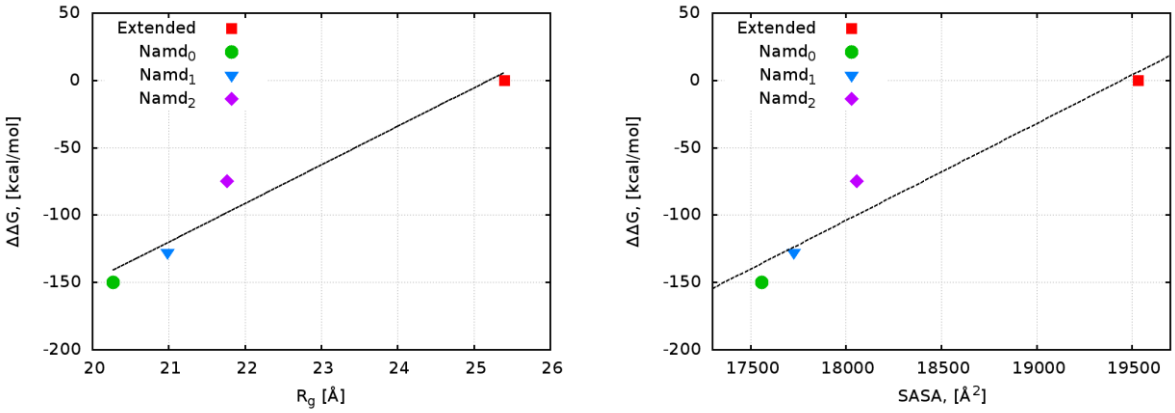

Fig. 2 *Correlation between the relative solvation free energy of the structures and (a) gyration radius, and (b) solvent accessible surface area.*

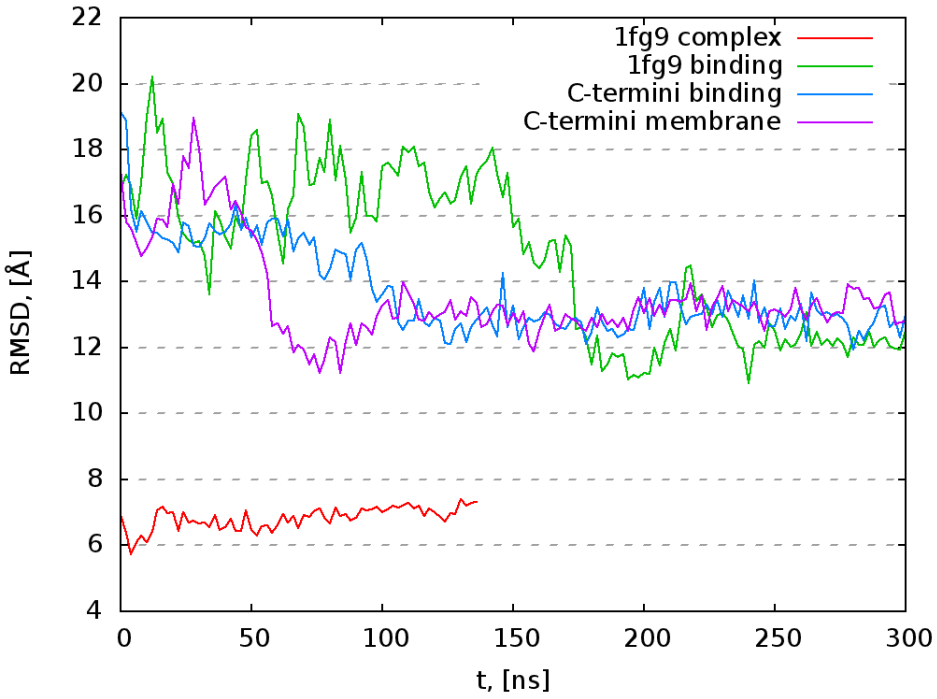

Fig. 3 *Center-of-mass RMS distance of the binding sites in the molecule of hIFNg and of hIFNgRa.*

The analysis shows that the conformation of the centroid of the 0-th cluster is the most stable conformation. Therefore, this structure was used for further simulations of the formation of the complex hIFNg-hIFNgRα. The following simulations were performed:

A) Reference simulations of interferon without C-termini and two receptors from the PDB 1FG9. The simulation was 130 ns long and provides reference values of the distances between the active sites in the cytokine and the receptor in bound state.

B) Another reference simulation of hIFNg lacking C-termini and two receptors, however not in complex, but in free state, separated by about 1.8 nm. The purpose of this simulation was to show how the C-termini influence hIFNg binding.

C) Simulation of the binding of interferon with complete C-termini and two receptors. The The conformation of the 0-th cluster of the NAMD+CHARMM22 folding simulation was used as a starting structure of the cytokine.

D) Analogous to C) simulation, but in the presence of a lipid bilayer in order to check if a membrane of polar lipids would influence the hIFNg—hIFNgRa interactions.

The duration of simulations B), C) and D) was 300ns. Unfortunately, it was found that the C-termini of hIFNg do not promote binding to the receptors. The RMS distance of the COM of the binding sites in the molecules of hIFNg anf hIFNgRa for the four simulations are shown on Fig. 3. In none of the binding simulation is complex formation evident. This is probably due to a large energy barrier that should be overcome. In order to estimate how big this barrier is we plan to perform metadynamics simulation, where the hIFNg-hIFNgRα complex will be disrupted.

Task 10.1.2 ***Investigation of the influence of point mutations in the presented peptide on the formation of the pMHC complex and its identification by the T-cell receptors***

Further progress was made in the investigations of one of the key components of the immune system – the major histocompatibility complex MHC. MHC (HLA in humans) presents on the cell surface (fragments of) proteins by forming a pMHC complex to be eventually recognized by the T-cell receptors in which case an immune response might be initiated. The understanding of this process in detail is crucial for the attempted immune modulations both in positive (improved defense against bacterial and virus infections) and negative (when trying to cope with autoimmune diseases) direction.

The possible practical application of the model investigations makes their reliability of primary importance. So far, no method exists to prove that a simulation has converged. We suggest the method of "lagged RMSD-analysis" as a tool to judge if an MD simulation has not yet run long enough. The analysis is based on RMSD values between pairs of configurations separated by variable time intervals Δt. The dependence of the results on the initial conditions, maximal value of the variable step-size and the starting point of the reference interval $t_{offset.}$ was studied. In the case of not yet converged simulations, the shape of RMSD(Δt) strongly depends on $t_{offset.}$. The method combines the smoothing effect of averaging with the specificity of a precise time interval between configurations being compared. Since the "half-saturation time" τ decreases with increasing $t_{offset.}$, by choosing configurations with a large enough $t_{offset.}$ as referent, the RMSD plateau is achieved relatively faster. This might suggest that—regardless of the total simulation length—the fraction of usable (independent) configurations remains the same (final 75% of the trajectory).

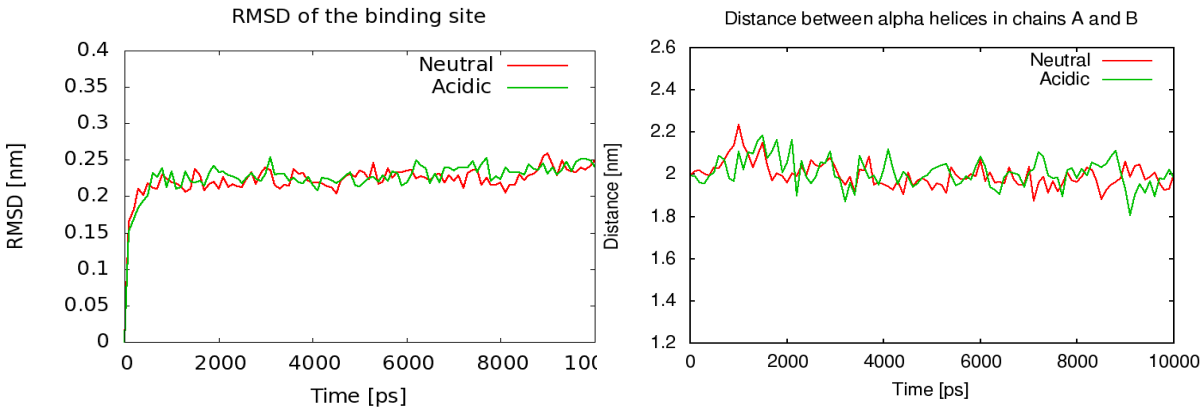

Fig. 4 *a) RMSD of the protein for protein-peptide complexes: neutral in red and acidic in green; b) Distance between alpha-helices of chain A and B is conserved.*

Although the analysis reported in the present work is specific to TCRpMHC complexes, we expect the method of lagged RMSD analysis to be applicable to similar molecular systems, such as membrane proteins comparable in size and structure to assess the degree of convergence of MD simulations and hence the statistical quality of conclusions drawn from such simulations. The results are presented in a journal article.

Based on the above method, a study has been performed on the molecular mimicry as a T-cell allorecognition pattern. Subject of modeling was LC13 T-cell receptor binding both with HLA-B*08 and HLA-B*44 representatives. The contact domain was investigated in detail. A paper based on the obtained results is in process of preparation.

Further, a series of simulations of peptides with one or several point mutations in a complex with HLA-B*0701 were performed in order to develop a MD-based methodology for quantitative estimates of their binding affinity in the context of a specific drug design. The importance of these investigations is in their role as a training example for the analysis of the KIR-HLA:peptide complex, which is attractive with its ability for selecting T-cells, active toward a HLA:peptide complex with a HIV peptide. The prognostic estimate there would be extremely valuable because of the lack of experimental data. The comparison between the predicted and experimentally obtained values (from the Medical Faculty of Imperial College in London) shows 0.68% coincidence, which is comparable with the best prediction software results съвпадение (0.69%). The preparation of an article on these results is forthcoming.

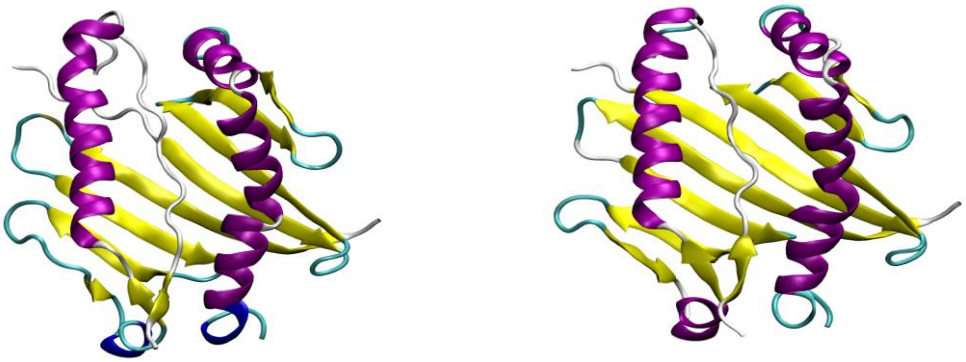

Fig. 5 *Structure of MHC class II — CLIP complex: a) neutral system; b) acidic system. Only the binding center of the protein is shown.*

<u>Task 10.1.3</u> ***Investigation of structural and electrostatic features of the Major Histocompatibility complex class 2 (MHC-II) in different protonation states***

The major histocompatibility complex interacts in environments with different pH. In order to describe our system in a more correct manner and account somehow for the change in pH, a full electrostatic model of the molecule was built that accounts for the protonation of all amino-acid residues in the 7 to 4.5 pH transition. In this way, 4 molecular systems were defined — unbound protein in water in neutral and acidic protonation state and a protein-peptide complex in water in neutral and acidic protonation state. The transition from neutral to acidic form of the system is performed by protonation of all ionogenic amino-acid residues in the protein, which depends not only on pH, but also on protein environment as well. The 7 to 4.5 pH transition demanded a change in the total charge of the protein from -17 to 0.

For the bound systems a peptide that is part of an invariant chain and that binds to all MHC-II analogues, was chosen — CLIP for short.

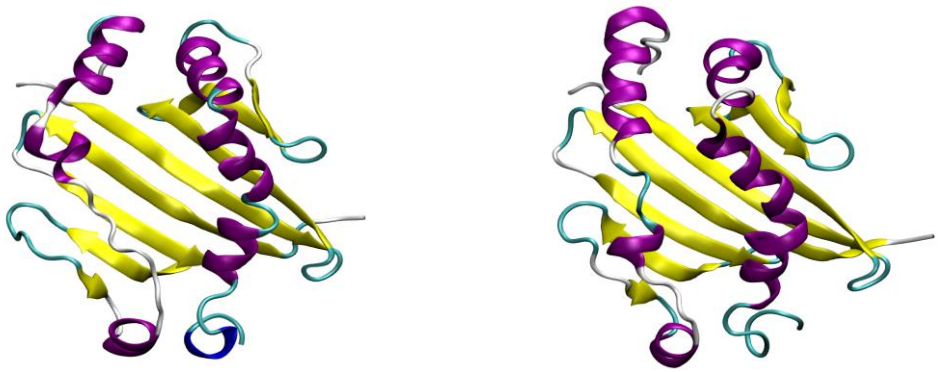

Fig. 6 *Structure of unbound MHC class II: a) neutral system; b) acidic system. Only the binding center of the protein is shown.*

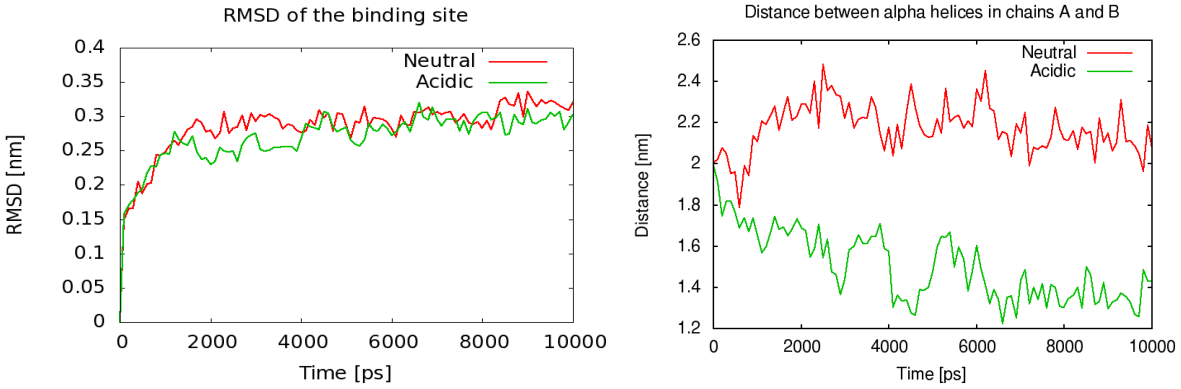

Fig. 7 a) *RMSD of the protein for unbound systems: neutral in red and acidic in green; b) Distance between alpha-helices in chains A and B is preserved for the neutral system, even though the structure is partly unfolded (in red), but it decreases significantly for the acidic system leading to a binding pocket closure (in green).*

Calculations were performed with the GROMACS molecular dynamics package and the Gromos53a6 force field. Each of the systems was simulated for 10 ns in NVT ensemble at 310 K. Unlike previous simulations of MHC-CLIP complex simulations, in this case the structure of the bound protein is preserved and no conformational changes are observed in both the neutral and acidic systems, which is in agreement with the theory of MHC-II function and biologic pathway. In a previous study we have observed a partially unfolding of a bound system due to insufficient size of the simulation box. Simulations are performed with periodic boundary conditions and there was not enough water molecules to exclude selfinteraction with the oposite side of the molecule. Once the distance to the end of the box was increased from 1 to 2 nm, the system remains stable for the whole simulation. Root mean square deviations (RMSD) for neutral and acidic bound systems are represented in Fig. 4a. It is clearly seen that it reaches a constant value — a sign for stability of the current conformation. A parameter — "distance between alpha-helices in chains A and B of the MHC molecule" was defined and stays constant for the entire simulation, shown in Fig. 4b. The obtained structures are represented in Fig. 5.

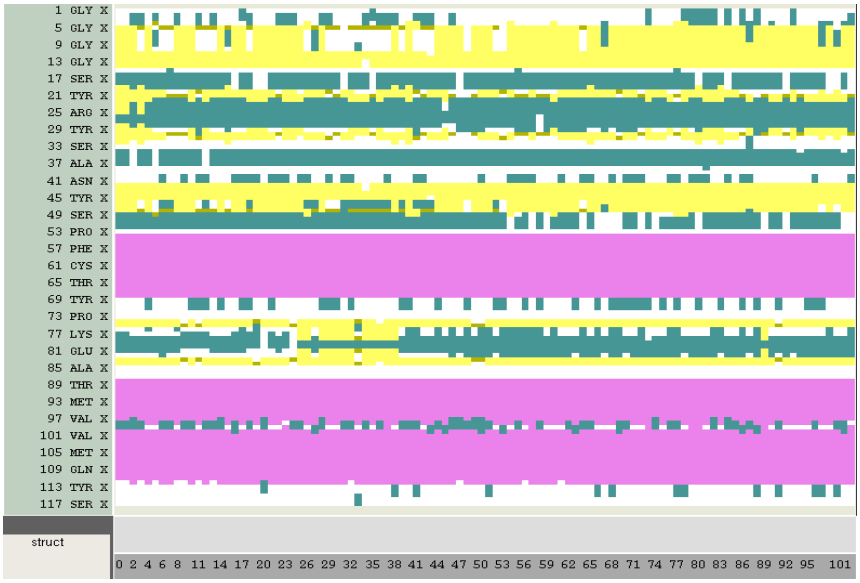

Fig. 8 *Secondary structure of the model of scrapie form of a prion molecule with respect to simulation time. On the Y axis is shown the amino-acid sequence of the prion protein and the color code represents the secondary structure: purple for alpha-helix, yellow for beta-sheet or beta-strand and white and green for unstructured regions of the molecule. It is clearly visible that the amount of beta-structure is preserved through the end of the simulation.*

<u>Task 10.1.4</u> ***Investigation of the conformational space of prion proteins in search of candidates for scrapie form***

Prions are not well studied proteins that are produced in nerve cells, but their function is not fully understood yet. It is known, that they exist in two forms — native and pathogenic (also called scrapie), the latter of which is related to many rare but fatal deseases. Both forms share the same amino-acid sequence, but not a 3D structure, nor any physical characteristics. The native form is soluble, unresistant to proteases and monomeric, while the pathogenic form is insoluble, resistant to proteases, heat, radiation, chemical agents and dissolvents and also tends to aggredate and thus form fibrils. A peculiarity about prions is that the scrapie prion is able to interact with the native one and misfold it to form scrapie again. Investigating this conversion and prions at all is of great fundamental, but also medical importance.

The main problem with investigating prions is that there is no experimental structure of the scrapie form yet. Therefore an investigation of the conformational space of the prion molecule was performed in order to find candidates for scrapie form that contain more than 30% beta-structure, according to experimental data about its secondary structure.

In order to search through conformational space in a fast and efficient way the method of Replica Exchange Molecular Dynamics (REMD) was used. A series of simulations were performed starting with an equilibration run of a native form in water, simulated for 10 ns with standard MD. Two simulations with REMD were performed next in two different temperature regions — 300-318 K and 310-338.5 K for 4.2 ns and 105 ns, respectively. Simulations were performed with the GROMACS MD package and the Gromos53a6 force field in NVT ensemble and applied periodic boundary conditions.

A structure with 28.7 amount of beta-sheets was obtained. Partial unfolding of alpha-helices and formation of beta-sheets in the N-terminus domain of the molecule are observed. In addition a 10 ns standard MD simulation was performed for the evaluation of the stability of the obtained

conformation. Fig. 8 represents the variation of the secondary structure with respect to simulation time for the conformation with maximum amount of beta-sheets, which is preserved during the simulation.

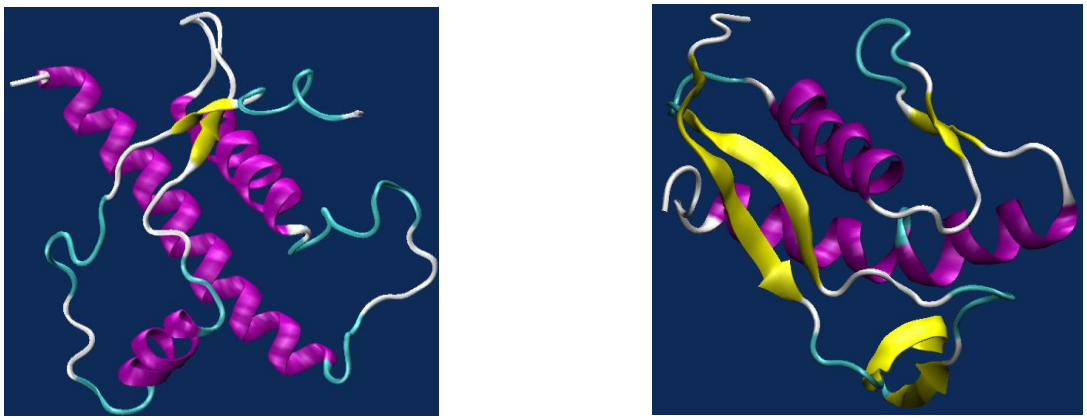

Fig. 9 *Structure of a) native form; b) model of the scrapie form.*

Fig. 9 shows the 3D structure of the native form and the obtained model of the scrapie form.

Task 10.1.5 Profiling of a CPU/GPU version of GROMACS 4.6

A hybrid CPU/GPU version of Gromacs 4.6 with avx vectorization in single precision supported by the CUDA toolkit 5 has been compiled on a local linux machine supplied with a NVIDIA GeForce GTX 680 graphics card.

In the Gromacs programming model, workload is divided between the CPU and the GPU, the latter of which does the real space part of long-range forces calculations. The test system contains around 180000 atoms and is simulated for 10000 steps. The profiling was performed with an NVIDIA tool — the NVIDIA Visual profiler that does not need to instrument the code in advance, unlike other profilers. In this way it is unable to profile the entire application, but only the part of it that takes place on the GPU.

In Gromacs 4.6 there are 6 Gpu kernels. The NVIDIA Visual profiler has been used to measure execution times for all kernel calls. Over 86% of the time is consumed in the k_nbnxn_ewald_twin procedure due to the large amount of invocations. Single invocations of any kernel are of similar duration, for example for the k_nbnxn_ewald_twin kernel, all invocations are around 33 to 34 ms. This is a sign for a well balanced procedure and the number of invocations depends on the characteristics of the real molecular system, that is simulated and is not a controlable by the code.

In the current simulation a total amount of 12 GB of data is transferred from the CPU to the GPU and 8 GB in the oposite direction. Again similar duration of single transfer operations is observed, but the total memory bandwidth reaches only 1.9 GB/s, which is substantially less than the maximum achievable memory bandwidth over the PCI express 2.0, consisting of 8 GB/s. It is possible that this limitation is due to a specific algorithm-dependent way that data is transferred.

Task 10.1.6 ***Performance analysis of the GROMACS 4.6.1 package on hybrid CPU/GPU architecture***

A hybrid CPU/GPU version of Gromacs 4.6.1 with SSE4.1 vectorization in single precision supported by the CUDA toolkit 5 has been compiled on a hybrid system, consisting of two 6-core Intel Xeon E5649 processors with hyper-threading, equipped with 6 NVIDIA Tesla M2090 cards with 512 CUDA cores.

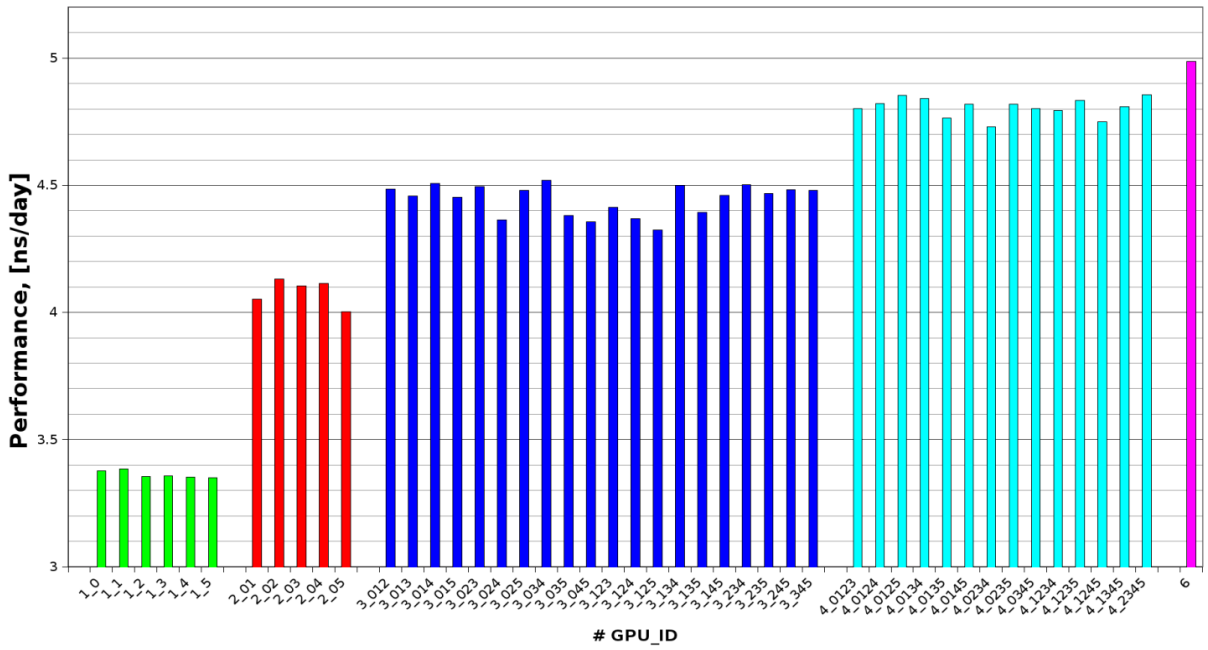

Fig. 10 *Performance of GROMACS 4.6.1 for a test system of about 180 00 atoms with variable GPU number and distribution. On the abscissa are the number of the GPUs used, followed by underscore and the IDs of the respective GPUs.*

The test system is of solvated hIFNg--hIFNgRa complex and consists of about 180 000 atoms (11 382 protein atoms and 169 023 solvent atoms), described by CHARMM 22 force field with the modified TIP3P water model. The simulations had 40 000 steps and were done with expilic solvent under PBC, using PME, V-rescale thermostat, Berendsen barostat, constraints on all bonds and an integration time step of 2fs. The performance counters were reset in the middle of the simulations at 20 000 steps.

The main task was to study the dependence of the performance on the number of GPUs. In addition, we also tested how the performance will vary depending on the specific choice of GPUs. The performance results are summarized on Fig. 10. It was found that the different distribution of the GPUs has negligible effect on the performance (less than 3%).

The highest obtained performance and speed-up are given in Table 1 and shown on Fig, 11. As seen, using all GPUs raises the absolute performance from 3.4 ns/day for 1 GPU to 5 ns/day for 6 GPUs. However, the greatest speed-up, 22 %, is achieved when using 2 GPUs. Adding more GPUs speeds the calculations up by about 10% per GPU, and the package scales worst at 6 GPUs. Therefore, it is inefficient to use more than 2 GPUs.

It was also investigated how the performance depends on the number of OMP threads and the use of hyper-threading. The results are presented on Fig. 12. It was found that in general hyper-threading improves GROMACS 4.6.1 performance.

Table 1

# GPU	Performance [ns/day]	Speed-up
1	3.386	1
2	4.131	1.22
3	4.526	1.34
4	4.856	1.43
6	4.988	1.47

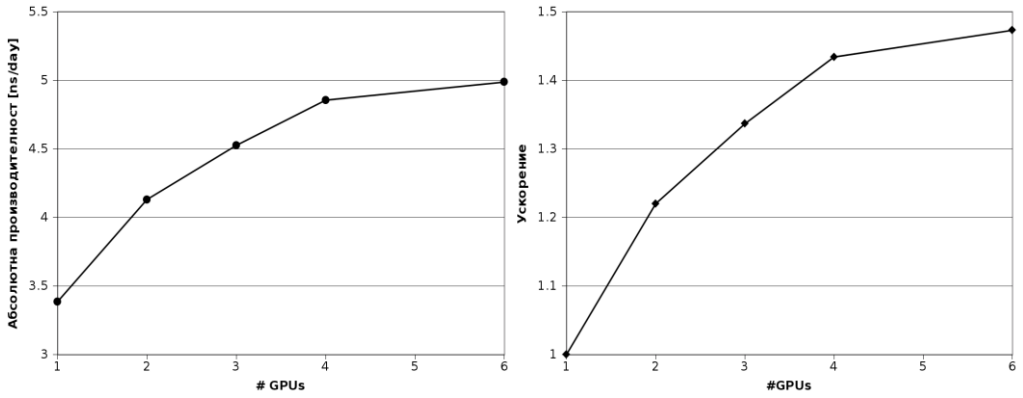

Fig. 11 *Dependence of the maximal performance and speed-up of GROMACS 4.6.1 on the number of GPUs for a test system with 180 000 atoms.*

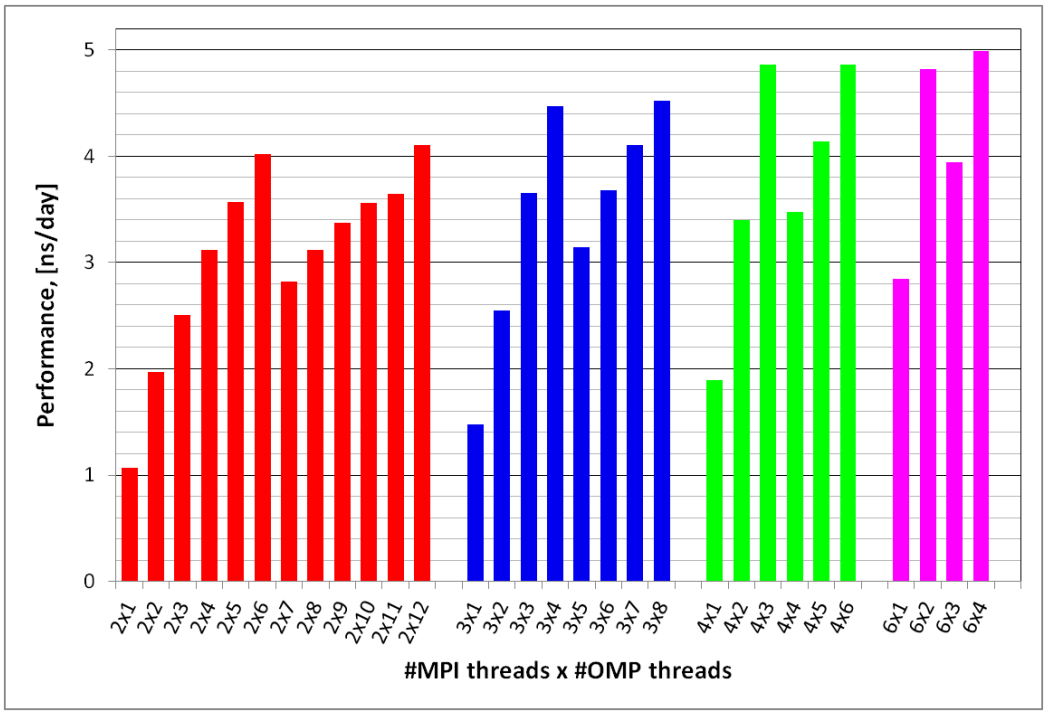

Fig. 12 Dependence of *GROMACS 4.6.1 performance for a test system with 180 000 atoms on the number of OMP threads.*

Task 10.1.7 ***Development of libraries for solving the Poisson equation***

In the reporting period two algorithms for solving the Poisson equation were realized by developing libraries for their application for calculation of the long-range electrostatic interactions in packages for molecular-dynamics simulations. The libraries were written both in C and Fortran 90. The direct solution of the Poisson equation provides a possibility to avoid the use of periodic boundary conditions in these simulations, which is crucial in the cases when they might introduce artifacts or unnecessary complications in them. The algorithms were based on the conjugate gradient method (CG) and on the bi-conjugate stabilized gradient method (BCSG). The platforms on which the realizations have been tested so far are IBM BlueGene/P and NVIDIA CUDA.

Task 10.1.8 ***Development of a program package for calculations within the FMO method***

The molecular orbital method is a computational technique for calculation of the electron density of large molecules by splitting them into fragments. The energy and electron density are then calculated for the individual fragments, pairs of fragments etc. in case higher precision needed. Each fragment and pair of fragments is computed separately and independently of the others. This allows to improve the scalability of the performance due to decreasing the communications as compared to the case when energy and electron density are calculated in a single parallel job. Along the lines of this ides three applications were developed – Fragmen, Gridpot and a modification of the package CP2K so that the computations by the DFT method are being performed in external electrostatic field, defined on a lattice. Fragmen fragmentizes the initial molecule along user-determined criteria and terminates the free valence electrons by adding hydrogen atoms. The program computes the electrostatic field in a predefined domain for each of the fragments while accounting for the electrostatic field in all other fragments. The modified version of the program CP2K takes as input data the coordinates of the atoms in a given fragment, the electrostatic field, generated by all other fragments and defined on a lattice. In that way the number of independent tasks equals the fragment number. In the next step the same procedure is repeated, but for pairs of fragments, constructed so that to compute only nearest-neighbor pairs. The last step provides reconstruction of the full energy of the molecule and its electron density.

Task 10.2 ***Structure and dynamics of the peptidyle transferase center of RNA: ab initio molecular dynamic study of Na and Mg ions at RNA backbone***

The interactions between sodium or magnesium ions and phosphate groups of the RNA backbone in water solution (Fig. 1) have been studied using ab initio Born – Oppenheimer molecular dynamics. All calculations were performed using Density Functional Theory with PBE functional and DZVP basis set. All simulations were carried out in NVT ensemble with a timestep of 1 fs. The studied systems consist of nucleic acid dinucleotide fragment from RNA (with ribose) without the nucleobases, and the metal ions necessary to neutralize the negative charges of the phosphate groups, two Na^+ or one Mg^{2+} ion.

Sodium ions have higher mobility than the magnesium ions and readily change their position with respect to the phosphate groups, from directly bonded to completely solvated state. Within the 104 ps simulation at 300 K the lifetime of bonded Na^+ was about 20 to 30 ps during which the sodium ion binds to only one of the oxygen atoms from the phosphate group at about 235 – 255 pm. One of the studied sodium ions remain completely solvated during the whole simulation and interact with the phosphate groups through one or two water molecules.

Sodium ions coordinate 4 to 7 oxygen atoms from water molecules or phosphate group in their first coordination shell with the most frequently encountered coordination number five (about 80% of the simulation time), followed by coordination number six (about 15% of the time). The coordination number of the sodium ions frequently changes in irregular intervals ranging from several femtoseconds to about 10 ps. The distance between the sodium ion and the oxygen atoms from the

first coordination shell is about 235 pm and does not depend on the origin of the oxygen atom - from water molecule or phosphate group.

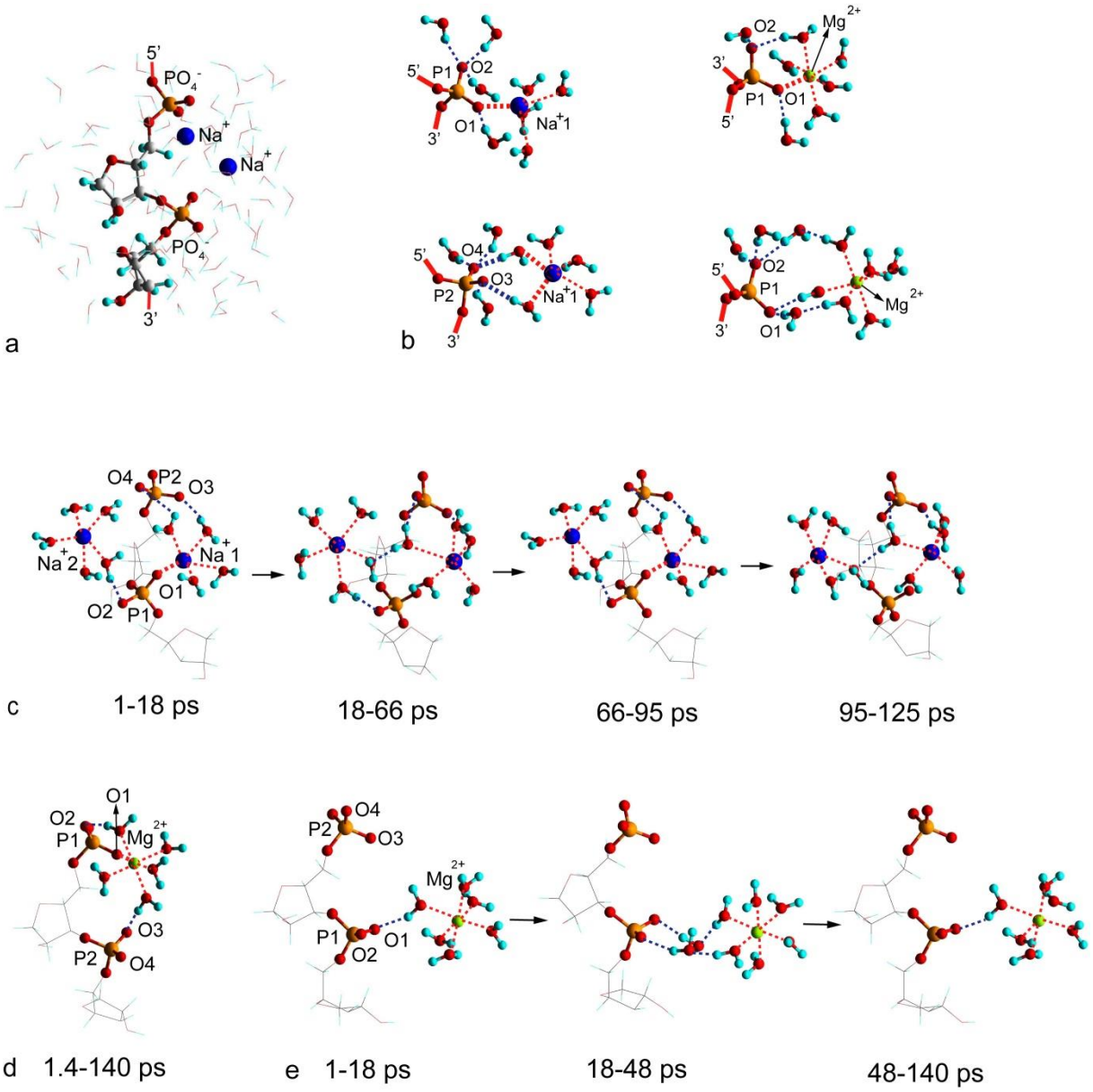

Fig. 13 *Selected snapshots from the simulations: (a) the simulation box with the RNA backbone model and two sodium ions (water molecules are shown only as lines); (b) water molecules solvating P1 or P2 phosphate groups and the counter cations in bonded and solvated state; (c) sodium ions in different time periods; (d) bonded magnesium ion; and (e) solvated magnesium ion in different time periods.*

Two states of the systems containing magnesium ions, with Mg^{2+} directly bonded to the phosphate group and with completely solvated ion, were found stable for 140 ps simulations. The Mg^{2+} binds to one of the oxygen atoms of one of the phosphate group of the selected RNA fragment with optimal Mg^{2+}…O=P distance of about 205 pm. The completely solvated Mg^{2+} interacts with the phosphate groups through one or two water molecules. Both the directly bonded and completely solvated magnesium ions have exactly six oxygen atoms in their first coordination shell. Moreover, during the whole simulation at 300 K and 320 K no exchange of ligand in the first coordination shells

has been observed. The distance between the magnesium ion and the oxygen atoms from the first coordination shell is about 215 pm.

The stability of the system containing sodium ions does not depend strongly on the position of the ions with respect to the phosphate groups, being directly bonded or interacting through a water molecule. The energy difference between the bonded and solvated states of one of the cations is only 6 kJ/mol (simulated at 300 K), negligible for the system, and could be attributed to minimal variations in the arrangement of the water molecules.

The study was performed by S. Kolev and M. Rangelov.

2. Publications related to the topic of the project, where the project is acknowledged

a) published

1. G. Nacheva, E. Lilkova, P. Petkov, P.St. Petkov, N. Ilieva, S. Markov, S. Petrov, I. Ivanov, and L. Litov, *In silico studies on the stability of human interferon-gamma mutants.* Biotechnology and Biotechnol. Eq. **26** (2012) 200–204; doi: 10.5504/50YRTIMB.2011.0036 (IF 0.760, ISSN 1310-2818);
2. D. Grancharov, E. Lilkova, N. Ilieva, P. Petkov, L. Litov, *Open problems in High-Performance Molecular-Dynamics Simulations*. Information Technologies and Control **2** (2012) 23–29 (John Atanasoff Society of Automatics and Informatics, Sofia, 2012; ISSN: 1312-2622);
3. L. Litov, I. Ivanov, P. Petkov, P. Petkov, E. Lilkova, S. Markov, N. Ilieva, G. Nacheva, S. Petrov, *A new approach to cope with autoimmune diseases: computer simulations and laboratory tests*. Radiotherapy and Oncology **102** (Suppl. 1) (2012) S134–S135; http://www.sciencedirect.com/science/article/pii/S0167814012702256 (IF 5.58, ISSN: 0167-8140);
4. W. Schreiner, R. Karch, B. Knapp and N. Ilieva, *Relaxation Estimation of RMSD in Molecular Dynamics Immunosimulations*. Computational and Mathematical Methods in Medicine, Volume 2012, Article ID 173521, 9 p.; doi:10.1155/2012/173521 (IF 0.814, ISSN: 1748-6718);
5. S. Kolev, P. St. Petkov, M. Rangelov, G. N. Vayssilov, *Ab Initio Molecular Dynamics of Na^+ and Mg^{2+} Countercations at the Backbone of RNA in Water Solution.* ACS Chemical Biology, 8, 1576-1589 (2013). (IF=5.44);
6. Elena Lilkova, Peicho Petkov, Nevena Ilieva, Damyan Grancharov, Leandar Litov, Petko Petkov, *Molecular Dynamics Simulations of Human Interferon Gamma.* 2nd Congress on Physical Sciences, Sofia, 25-29.09.2013. Book of abstracts, p. … (Sofia Univ. Press, 2013; ISBN 978-954-07-3600-6);
7. Peicho Petkov, Elena Lilkova, Damyan Grancharov, Nevena Ilieva, Leandar Litov, *Replica exchange MD investigation of conformational space of prion proteins.* nd Congress on Physical Sciences, Sofia, 25-29.09.2013. Book of abstracts, p. … (Sofia Univ. Press, 2013; ISBN 978-954-07-3600-6).

b) accepted

1. Peicho Petkov, Elena Lilkova, Damyan Grancharov, Petko S. Petkov, Nevena Ilieva, Leandar Litov, *Calculating Binding Free Energies of Variants of hIFN-g and their Extracellular Receptor*. Biomath (ISSN: 1314-7218/online. ISSN: 1314-684X/print) *(to appear);*
2. Peicho Petkov, Elena Lilkova, Damyan Grancharov, Nevena Ilieva, Leandar Litov, *MD construction of chicken prion protein candidate by replica exchange.(???Title).* Biomath (ISSN: 1314-7218/online. ISSN: 1314-684X/print) *(to appear).*

c) submitted

d) in preparation

- P. Petkov, E. Lilkova, G. Nacheva, P.St. Petkov, I. Ivanov, N. Ilieva, S. Markov, and L. Litov, *Human Interferon Gamma C-Termini Modeling*.
- Nevena Ilieva, Antti Niemi, Xubiao Peng, Peicho Petkov, *On the phase transitions in protein folding.*

3. Presentations

International Conference on Bioinformatics and Computational Biology, BIOCOMP 2012 (20 – 21 Sept. 2012, Varna, Bulgaria)

- Peicho Petkov, Elena Lilkova, Nevena Ilieva, and Leandar Litov, *Modeling the Structure of Human Interferon Gamma C-Termini*
- Peicho Petkov, Elena Lilkova, Damyan Grancharov, Petko St. Petkov, Nevena Ilieva, and Leandar Litov, *Calculating binding free energies of hIFN-gamma variants and its extracellular receptor (poster presentation)*.

International conference on Bio-IT World Europe (October 2012, Vienna, Austria)

- M. Rangelov, P. Petkov, P. Petkov, S. Markov, L. Litov, G. Vayssilov
  Insights on the mobility of the ribosome and the mechanism of protein biosynthesis in it from large scale classical molecular dynamics and quantum chemical modeling

Seminar in the Academia Sinica (January 2013, Taipei, Taiwan)

- G. N. Vayssilov, S. Kolev, P. Petkov, M. Rangelov
  Computational modelling of the ribosome and the mechanism of the peptide bond formation

International Conference on Mathematical Methods and Models in Biosciences, BIOMATH 2013 (16 – 21 June 2013, Sofia, Bulgaria)

- Peicho Petkov, Elena Lilkova, Damyan Grancharov, Petko S. Petkov, Nevena Ilieva, Leandar Litov, *Calculating Binding Free Energies of Variants of hIFN-g and their Extracellular Receptor;*
- Peicho Petkov, Elena Lilkova, Damyan Grancharov, Nevena Ilieva, Leandar Litov, *Replica exchange MD investigation of conformational space of prion proteins.*

Second National Congress on Physical Sciences (Sept. 25─29, 2013, Sofia, Bulgaria)

- Elena Lilkova, Peicho Petkov, Nevena Ilieva, Damyan Grancharov, Leandar Litov, Petko Petkov, *Molecular Dynamics Simulations of Human Interferon Gamma;*
- Peicho Petkov, Elena Lilkova, Damyan Grancharov, Nevena Ilieva, Leandar Litov, *Replica exchange MD investigation of conformational space of prion proteins.*

Seminar at Beijing Computational Science Research Center (September 2013, Beijing, China)

- G. N. Vayssilov, S. Kolev, P. Petkov, M. Rangelov
  Ab initio and molecular mechnical modeling of RNA fragments and the ribosome

<u>Active international collaboration that were initiated and are being developed based on SuperCA++ project</u>

- Section for Biosimulation and Bioinformatics, CeMSIIS, Vienna Medical University (Austria)
- Laboratory for Mathematical and Theoretical Physics, CNRS, Tours (France)
- Department of Physics and Astronomy (Theoretical Physics), Uppsala University (Sweden)
- Faculty of Medicine, Imperial College, London (Great Britain)

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