Description for the general public

With the striking advances in computer technologies in the recent decades, the significance of modeling approaches in science including biology-related disciplines increased dramatically. Before, modeling was seen at best as an almost decorative addition to the experiment or as an abstraction dealing with the ideal systems not really connected with the real world. Nowadays the power of modeling is difficult to overestimate. What are the reasons for using models instead of conducting the experiment? First of all, theoretical studies are usually much faster and cheaper to carry out. However, this would not have been enough to convince the experimentalists to work back-to-back with theoreticians since the quality of the experimental results would have been more decisive than the practical issues of the efforts and expenses. What really makes modeling attractive is that it can provide principally new insights into a scientific problem not achievable by the experiments *per se*. Many experiments deal with the averaged quantities and are not able to provide the details explaining observations. Imagine movements of an earthworm on the ground: by observing them for several minutes and drawing the line connecting the points where the earthworm was observed leads to the conclusion that it moved along a straight line. However, in fact, it never moved straight! In the experiment, we often see the 'straight lines' and not the 'real' nature of the phenomena because feasible time scales of observations and/or the tools used do not allow us to do this providing us with averaged quantities not reflecting the details of the process. Instead, one can model a movement of an earthworm using physics-based characteristics of the ground and the knowledge about the anatomy of the worm. Such a model can explain and predict its movements.

In this project, we aim to use modeling approaches to characterize complex biologically relevant processes going on in the space between cells, which is called as an extracellular matrix (ECM). This space can be seen as a reservoir full of diverse simple organic molecules and biomacromolecules: proteins, carbohydrates, water, ions and so on. Many of the processes occurring there define the behaviour of the cell and, as a consequence, steer the destiny and the health of the full organism. Therefore, understanding of what happens in the ECM is crucial for basic knowledge in biology and for finding the new ways of treating the diseases originated from the disruptions in those processes. In our work, we are particularly interested in the elucidation of the molecular mechanisms where proteins and glycosaminoglycans (GAGs), a special class of carbohydrates, are involved in manifold processes underlying the phenomena of tissue regeneration and involved in severe pathologies as cancer or Alzheimer disease. Whereas many computational approaches are specifically developed to deal with proteins, there are definitely less standard tools to model GAGs, which makes their theoretical analysis indeed more challenging. Previously, we demonstrated success in applying several computation methodologies to these systems: molecular docking and molecular dynamics. Molecular docking predicts mutual disposition of interacting molecules if their structures are not available experimentally. It yields a structure of a molecular complex, a time 'snapshot', showing the interactions between several molecules. This is usually not enough to understand what exactly happens in a system. In contrast, molecular dynamics allows to track atomic movements of the system in time based on the knowledge of their initial coordinates obtained from the experiment or from the molecular docking and knowing which forces are applied between the atoms in the system. We will predominantly use these two methodologies, molecular docking and molecular dynamics, to characterize interactions between GAGs and *i)* particular proteins (such as integrins, anastellin, sclerostin, cathepsin proteases) involved in the processes of tissue regeneration; *ii)* drug molecules, which are scarcely characterized so far and which could have decisive impact on drugs effectivity in the organism; *iii)* ions, which also contribute to the complexity of GAG containing systems attenuating their molecular interactions with proteins/drugs/peptides; *iv)* antimicrobial peptides, substances that by their interaction with the bacterial membrane could be used to destruct the bacterial infection. In addition, we are going to overcome one of the most challenging limitation in theoretical analysis of GAG containing systems originated from their size and time scales needed to be analyzed. This will be done by creating a coarse-grained model: in this model, the approximations are made to track the movements of parts of the molecules as a whole instead of calculating trajectories for all atoms. Such an approach decreases the computational expenses needed to model particularly big systems and allows for investigations at longer time scales. This will provide us the tools to model such processes in the ECM as protein aggregation and formation of multimolecular complexes consisting of diverse interacting partners.

The results we expect in this project planned for 5 years for a new research team will contribute to the general knowledge on how several particular multimolecular systems function in the ECM. The development of new approaches will assist to create a proper methodological pipeline to be more accurate and more effective in modeling these systems. This knowledge and these approaches, in turn, could be of a great importance for the rational molecular level-based studies in the field of regenerative medicine including, in a perspective, creation of innovative ideas for practical medical applications.