Final Report PhD Year 2018/2019.
Anna Lucia de Marco
Supervisor: Giulia Rossi, Giovanni M. Pavan

Research Activity.
- Overall View
- Genova Project description and next goal.
- Lugano Project description and next goal.
- Papers
- Conferences
- Exams

Overall View.
My PhD consists in a double project between Genova - with the Giulia Rossi group - and Lugano - with the Giovanni Pavan group, in the field of Computational Physics of Matter. Both groups use Molecular Dynamics (MD) simulations and advanced sampling techniques, e.g. metadynamics, in order to explore biophysical systems like lipid membranes when they interact with functionalised gold nanoparticles and supramolecular polymers properties respectively.

Genova Project.
Anionic gold NPs perturb phase separation and form ordered lattices in multi-domain lipid membranes. (In preparation)

Ligand-protected gold nanoparticles (AuNPs) are extensively used for their potential application in nanomedicine, e.g. drug and gene delivery, and imaging. In order to understand how NPs impact on biological systems it is fundamental to clarify the driving forces regulating the interaction between NPs and biologically relevant interfaces, specifically cell membranes. Over the last years, coarse-grained simulations have shown that the NP-membrane interaction mechanism consists of three steps: NP adhesion on the membrane surface, hydrophobic contact with membrane lipid chains and final NP non-reversible embedding via anchoring between NP-ligands and membrane leaflets. For a complete view on NPs behaviour in living systems, it is necessary to investigate the interaction between NPs with lipid rafts. Rafts are liquid-ordered (Lo) phase nanodomains in living cells tipically enriched in cholesterol and saturated lipid species like sphyngolipids and gangliosides embedded in a liquid disordered phase (Ld) mostly consisting of unsaturated lipids; they form phase-separated functional platforms on the cell membrane and there are evidence they are involved in signaling and trafficking cellular processes.
For a deeper understanding of NPs bioactive role, it is meaningful to investigate the interaction between NPs with lipid rafts. To this aim we use coarse-grained molecular simulations to self-assemble heterogeneous membranes. We investigate the interaction of this lipid membrane with an anionic ligand-protected AuNP. As a first result, we find that the same mechanism of NP internalization observed in homogeneous membranes takes place in the Ld phase. The second and more interesting observation is that, as the NP approaches the membrane, the Lo-phase starts to melt until its full disruption after few microseconds. In order to identify the driving forces for this phenomenon, we performed specific analysis on the membrane structural changes by the calculation of the Sz order parameter, lateral diffusion coefficient and density maps showing the long-range effect of the NP-lipid raft interaction; from an energetic point of view we investigate the AuNP adsorption free energy profiles in Lo, Ld e homogeneus phase respectively, finding a clear preference for the latter scenario. This result has been confirmed by our experimental collaborators.

Recently, they also found very interesting AuNP ordered lattices in the homogeneous phase and my next goal is to investigate this phenomenon at molecular resolution.

Lugano Project.
Exploring Exchange Pathways in Dynamic Supramolecular Polymers By Multiscale Molecular Modeling.

Supramolecular polymers, formed via noncovalent self-assembly of elementary monomers, have seen emergence into functional materials for their dynamic and responsive nature. Their rational design requires the study of their intrinsic dynamics - i.e. molecular mechanisms, pathways and kinetics of monomers exchange - at submolecular resolution. The latter task is experimentally prohibitive, but combining all-atom (AA) and coarse-grained (CG) models with advanced simulation approaches we could achieve it. The CG models for the supramolecular polymers we studied were based on the popular MARTINI CG force-field which guarantees a good transferability while preserving the thermodynamic properties of the mapped species. Multiple infrequent WT-MetaD simulations were performed to obtain the average rate of the main exchange steps for 1,3,5-benzenetricarboxamides (BTA) supramolecular polymers in water. Recently, we developed a minimalistic CG model representing a whole family of supramolecular polymers to study the factors controlling their exchange pathways. We found that the defects present in these assemblies are always responsible for their dynamic exchange behavior, their dynamic adaptive properties and dissipative out-of-equilibrium evolution of a supramolecular tubule. Our last important result is that our generic CG model, combined with advanced statistical analysis, has shown how to control the monomer exchange pathways by controlling the amount of defects present in the assemblies. This study provides us a useful platform to understand molecular principles to design supramolecular polymers with programmable and logic dynamic behavior by creating fundamental structure-dynamics-property relationships.
My next goal in Lugano is a further zoom-out of the system studied this year. Instead of a single fiber exchanging monomers with the solvent, I will investigate a larger system made up of multiple fibers exchanging monomers between them and not only with the solvent.

Papers.
Anionic gold NPs perturb phase separation and form ordered lattices in multi-domain lipid membranes. *In preparation*.

Exploring Exchange Pathways in Dynamic Supramolecular Polymers By Multiscale Molecular Modeling. de Marco, A. L., Bochicchio, D. and Pavan, G. M.. *In submission*.

Conferences.
SupraBio 2019. International Symposium on SupraBiomolecular Systems. Barcellona. Poster presentation.
Cecam Workshop. Challenges in modeling and simulations of nanoparticles in complex environments. IIT (Genova). Poster presentation.
IMN 2019. International meeting on nanoalloys. DIFI. Organizing committee and poster presentation.

Exams.
Celle Solari. F. Buatier de Mongeot. 6 CFU. On the next 8th October.