Final report PhD Year 2019/2020
Anna Lucia de Marco
Supervisors: Giulia Rossi, Giovanni M. Pavan

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Overall View.
My Phd consists in a double project between the Giulia Rossi group in Genova and the Giovanni Pavan group in Lugano and Torino, in the field of Computational Physics of Matter. Both groups use Molecular Dynamics (MD) simulations and avanced sampling techniques, e.g. metadynamics and umbrella sampling in order to explore byophysical systems such as lipid membranes when they interact with functionalized gold nanoparticoles and supramolecular polymers design and properties respectively.

Genova Project.

Amphiphilic Gold Nanoparticles Perturb Phase Separation in Multidomain Lipid Membranes.
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.
Despite the important role played by rafts at biological level, the study of the effects of NPs on the phase separation of model lipid bilayers is still in its infancy. We focus on model neuronal membranes - which spontaneously form ordered and disordered lipid domains - and on small, amphiphilic gold NPs, with negative surface functionalization, which are known to passively translocate through cell membranes. Atomic force microscopy, quartz crystal microbalance and our molecular dynamics simulations have shown Au NPs can disrupt the lipid phase separation, potentially altering important membrane functions; moreover Au NPs can form ordered supramolecular aggregates within the lipid membrane core. Our work could have an immediate impact on the biophysics community for the understanding of lipid phase separation driving forces as well as on the material researchers for the future biocompatible NPs and nano-sized systems in general for both medical and new hybrid materials design and application.
These results were collected in the paper “Amphiphilic Gold Nanoparticles Perturb Phase Separation in Multidomain Lipid Membranes”, recently published on Nanoscale.

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. Here we combine coarse-grained modelling, enhanced sampling and machine learning to investigate the factors controlling the molecular mechanisms and kinetics pathways of monomer exchange in a representative family of synthetic supramolecular polymers. We show that the competition between directional and non-directional interactions between the monomers controls the creation/ annihilation of defects in the supramolecular polymers, from which monomer exchange proceeds. This determines the exchange pathway, dictating whether a fibre statistically exchanges monomers from the tips or from all along its surface. The versatility of the models allow us to explore ways to control the exchange pathways in these dynamic assemblies. Our results are almost ready for the submission.

Papers.

- *Amphiphilic Gold Nanoparticles Perturb Phase Separation in Multidomain Lipid Membranes*. E. Canepa, S. Salassi, A.L. de Marco et al., Nanoscale, 2020.

- Controlling the exchange pathways in dynamic supramolecular polymers by controlling defects. Anna L. de Marco, Davide Bochicchio, Andrea Gardin, Giovanni Doni and Giovanni M. Pavan. In submission.