Modeling the lateral aggregation of membrane proteins
ESF - Short Visit Grant - Final Report

Marianna Yiannourakou*

Molecular Thermodynamics and Modeling of Materials Laboratory,

Institute of Physical Chemistry, Demokritos,

GR-153 10, Aghia Paraskevi Attikis, Greece

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The study of biological membranes has drawn much attention during the past years, in the effort to relate their physical properties to the regulatory processes of vital importance for cell life that they accomplish. The difficulty of studying these systems is twofold, since membranes are complex cooperative structures and one needs to take into account a broad range of sizes and timescales.

To overcome these difficulties, it is essential to study reconstituted systems: lipid bilayers composed of one or two lipid species, together with embedded proteins, provide a good model for membranes, which recently have been widely studied with mesoscopic modeling and atomistic simulations [1, 2].

However, due to the large time and length scales involved in peptide aggre- gation within the membrane, such studies need to be limited to few peptides and model membranes of small sizes. Coarse-graining techniques allow to bridge the gap between atomistic and phenomenological description and can thus be used for an integrated study on the activity of transmembrane peptides, with the technique of Dissipative Particle Dynamics (DPD), as recently done by F. De Meyer, M. Venturoli and B. Smit [3]. Although such a mesoscopic model re- produces some properties of real systems [4, 5], simulations of big systems with many embedded proteins for long timescales are computationally prohibitive, due to the large number of degrees of freedom involved.

PREVIOUS WORK

During my collaboration with the group of Prof. Smit at CECAM (Lyon) we have moved to a higher level of coarse-graining, in order to study the properties of larger protein aggregates, using a two-dimensional representation of lipid bi- layers with embedded proteins: the lipid medium disappears, since its presence is taken into account implicitly by the Potential of Mean Force

* e-mail: yiannourakou@chem.demokritos.gr

(PMF) computed within proteins interacting in the mesoscopic model, used as the potential energy in our Monte Carlo simulations. For the cases of negative hydrophobic mismatch, we were able to observe a comparable behavior of peptides in exper- imental reconstituted bilayers with embedded Gramicidin A, in the low density limit [6, 7].

AIM OF THE SHORT VISIT

During my staying at CECAM I extended the application of the model developed in collaboration with Dr. Marsella to the study of big systems of lipid bilayers with a large number of embedded proteins: in particular, we focused on proteins aggregation for the case of positive hydrophobic mismatch [3].

RESULTS AND CONCLUSIONS

Using the two-dimensional model, which we have developed for the cases of negative hydrophobic mismatch, for cases of positive mismatch, we observed significant descrepancies compared to the three-dimensional model. The qualitative features remain the same in both models (two- and three- dimensional), however, quantitativaly there are differences. The reason why systems exhibit a different behavior depending on the presence of positive or negative mismatch, is the presence or absence of the tilting of the proteins respectively. In the case of negative hydrophobic mismatch, the basic way for the hydrophobic lenghts of the bilayer and the proteins to match is by the compression of the hydrocarbon tails of the lipids and so, by the deformation of the bilayer. However, in the case of positive hydrophobic mismatch, the proteins (depending on their size) also accomodate in such a way that the mismatch is minimized, that is by tilting or even bending [1].

Exactly this difference is what does not allow us to use exactly the same model in the cases of positive mismatch, where there is tilting of the proteins. However, the model that we have developed allows us to "tune" the interaction of the proteins, in a way that renders possible the utilization of the model in the cases of positive mismatch.

Our results for all cases of mismatch that have been studied, will be included in a paper that we are preparing and might be used as a guide for new simulations and experiments that will look into the conformational properties of clusters and the effects that their formation might produce on the bilayer.

FUTURE WORK

What would be of great interest to be done in the future, is to develop a systematic way, in which the kind of mismatch (positive-negative) as well as the strength of the mismatch (small, big) can be incorporated in our model and accounted for.

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