LATERAL HETEROGENEITY AS AN INTRINSIC PROPERTY OF HYDRATED LIPID BILAYERS: A MOLECULAR DYNAMICS STUDY.

Darya V. Pyrkova[a], Natalya K. Tarasova[a,b], Nikolay A. Krylov[a,c], Roman G. Efremov[a,*]

[a] *M.M. Shemyakin & Yu.A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, Moscow, Russia.*
[b] *Department of Bioengineering, Biological Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia.*
[c] *Joint Supercomputer Center of the Russian Academy of Sciences, Moscow, Russia.*

[*] *E-mail: efremov@nmr.ru*

Studies of lateral heterogeneity in cell membranes are important since they help to understand the physical origin of lipid domains and rafts. The simplest membrane mimics are hydrated bilayers composed of saturated and unsaturated lipids. While their atomic structural details resist easy experimental characterization, important insight can be gained *via* computer modeling [1, 2]. We present the results of all-atom molecular dynamics simulations for a series of fluid one- and two-component hydrated lipid bilayers composed of phosphatidylcholines with saturated (dipalmitoylphosphatidylcholine, DPPC) and mono-unsaturated (dioleoylphosphatidylcholine, DOPC) acyl chains slightly differing in length (16 and 18 carbon atoms, respectively). The following conclusions can be drawn:

1) Lateral arrangement of lipids (according to both, geometrical and hydrophobic properties) in all studied systems is not random. Instead, it reveals occurrence of small (most often, 3 lipids) clusters on the surface. Clustering seems to be a feature inherent in the lipid bilayers near the equilibrium state. 2) Lateral heterogeneity is even more pronounced deep in the bilayer – in the hydrophobic core of the membrane (in the region of C=C bonds of DOPC), although not near the termini of acyl chains. Toward the surface, the mosaic-like 2D distribution of lipids becomes much "fuzzy". 3) In mixed bilayers, the clusters are formed both, by alike and unlike lipids. One-component clusters appear only at high concentrations (above 40-50%) of this type of lipid. 4) The observed microheterogeneity picture is highly dynamic – lipid molecules enter and leave clusters with the characteristic lifetimes about 1 ns. 5) Clustering determines to a large extent the structural, dynamic, and hydrophobic properties of bilayers, like area per lipid molecule, bilayer thickness, order parameters of acyl chains, parameters of the mosaic hydrophobicity patterns on the lipid-water interface (Fig. 1), hydration degree of lipid heads, and so forth. 6) Addition of even small (~10%) amount of DPPC to the DOPC bilayer strongly affects the physico-chemical characteristics of the entire system, while the opposite is not true.

By other words, in the two-component system, one (DPPC) may be considered as an "order-preferring" agent, which efficiently modulates behavior of the second one (DOPC).

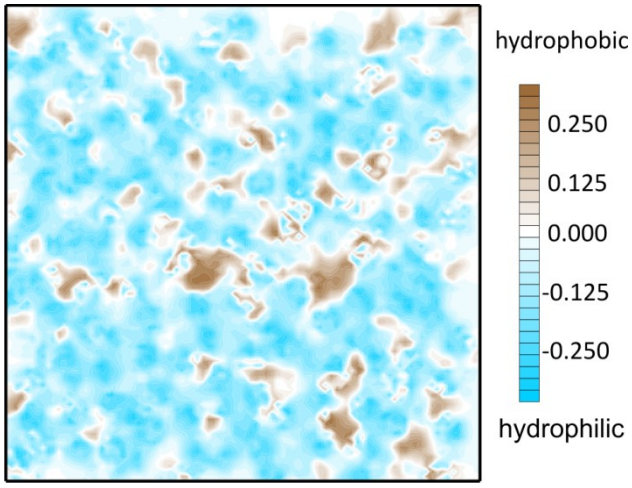

Fig. 1. Hydrophobic/hydrophilic organization of the surface of DOPC/DPPC (50:50) bilayer. In-plane view of the solvent-accessible surface area of the model bilayer (2D-map of the molecular hydrophobicity potential, MHP [3]). MHP values (in octanol-water *logP* units) are calculated in each point of the surface. The map is given for one of the bilayer leaflets. Coloring scheme is shown in the right.

To summarize, bilayer properties are tuned in a wide range by the chemical nature and relative content of lipids. The impact that the micro-heterogeneity may have on formation of lateral domains in response to external signals is discussed. Understanding of such effects creates a basis for rational design of artificial membranes with predefined properties.

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References.

1. Efremov R.G., Nolde D.E., Konshina A.G., Syrtcev N.P., Arseniev A.S. (2004) ***Curr. Med. Chem.***, 11, 2421-2442.
2. Polyansky A.A., Volynsky P.E., Arseniev A.S., Efremov R.G. (2009). ***J. Phys. Chem. B.*** 113, 1120-1126.
3. Efremov R.G., Chugunov A.O., Pyrkov T.V., Priestle J.P., Arseniev A.S., Jacoby E. (2007). ***Curr. Med. Chem.*** 14, 393-415.