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# CREATION OF MIXED LIPID BILAYER: A FORCE FIELD DEVELOPMENT

**A.H. POGHOSYAN, N. M. AYVAZYAN**

*The International Scientific – Educational Center of NAS RA,*
*L.Orbeli Institute of Physiology of NAS RA*
*poghosyan@gmail.com*

A mixed bilayer with 64 various lipid molecules were built and tested by the GROMACS software package modules. The force fields of mentioned 64 lipid molecules were generated using PRODRG and ATB servers and partially changed taking into account the features of lipid molecules. Simultaneously, we have created a mixed bilayer using CHARMM-GUI online generator server, which is aimed to create lipid bilayers with different lipid molecules. Note that the latter provide force fields for CHARMM input. The resulting mixed bilayer was minimized and equilibrated for long run simulation.

*Computer simulations – force field development*

GROMACS ծրագրային փաթեթի մոդուլներով կառուցվել և թեստավորվել է 64 տարբեր լիպիդային մոլեկուլներով խառը երկշերտ: Վերը նշված 64 լիպիդային մոլեկուլների ուժային դաշտը ստացվել են PRODRG և ATB սերվերներով և մասամբ փոփոխվել են հաշվի առնելով լիպիդային մոլեկուլների առանձնահատկությունները: Միաժամանակ, կառուցվել է խառը երկշերտ, օգտագործելով CHARMM-GUI առցանց գեներատոր սերվերը, որը նախատեսված է տարբեր լիպիդային մոլեկուլներով լիպիդային երկշերտերի կառուցման համար: Նշենք, որ վերջինս ապահովում է CHARMM ուժային դաշտերը: Արդյունքում խառը երկշերտը մինիմիզացվել է և հավասարակշռվել երկարաժամկետ մոդելավորման ընթացքում:

*Համակարգչային ուսումնասիրություն – ուժային դաշտերի մշակում*

Смешанный бислой 64 разными липидными молекулами были построены и протестированы с помощью модулей программного обеспечения пакета GROMACS. Силовые поля упомянутых 64 липидных молекул были получены с использованием серверов PRODRG и ATB и частично изменены с учетом особенностей липидных молекул. Одновременно мы построили смешанный бислой, используя CHARMM-GUI онлайн генератор сервер, который предназначен для создания липидных бислоев с различными липидными молекулами. Отметим, что последний обеспечивает силовые поля для пакета CHARMM. В результате смешанный бислой минимизировался и уравновешивался в течение длительного моделирования.

*Компьютерная симуляция – разработка силового поля*

Biological membranes are complicated multi-component formations and their futures, such as fusion, ionic transport and interaction with low- and high-molecular compounds strongly depend on the physical properties and state of main constitutes – lipids [1]. It is well known, that lipid components are mixtures of various types of lipids, which have dual chemistry by differing of the polar part and hydrocarbon chains.

Recently, the molecular dynamics (MD) study of mixed lipid bilayer has been attracted much attention and a number of papers are available [2-4], studying cationic, anionic and zwitterionic mixed bilayers. With the increase of computational power, the atomic-level and coarse grained computer simulations have been mainly used to study such systems.

The aim of this paper was the creation of mixed bilayer and force field development following lipid molecules – phosphatidic acid – PA, phosphatidylcholine – PC, phosphatidylethanolamine – PE, phosphatidylglycerole – PG, phosphatidylserine – PS and cholesterol (CL) based on experimental findings [5, 6]. The energy minimization by steepest gradient method was done, after which the system was modeled by normal canonic and isothermal-isobaric ensembles.

***Materials and methods***. The calculations to derive force fields for some lipids were carried out using Hyperchem 7.5 for Windows (Hypercube Inc.). The $MM^{+}$ and CHARMM force fields were used to optimize the geometry of some lipids and extract the parameters. The MNDO and PM3 semi-empirical methods were used to obtain the partial charges lipids. Simultaneously, the CHARMM-GUI online generator server [7, 8] was used to obtain the force fields for lipids.

The GROMACS software package editconf, genbox and solvate modules were used to contruct the final system.

The parallel MD simulation was performed on ArmGrid sites (http://www.grid.am).

***Results and Discussion.*** The GROMACS and NAMD software packages were installed on multicore clusters from ArmGrid[1] environment for further benchmark testing. As an appropriate package the GROMACS software package have been chosen. It is northworthy to mention that the hardware and software optimization from parallelization point of view has been also done, taking into account some characteristic specifics of a cluster. A 64 various lipid molecules were built and tested by the GROMACS software package modules. It should be noted that the lipid molecules were compared with lipid molecules from other database, in particularly those of available from http://www.bioinfromatics/downloads/. Initially, the force fields of lipid molecules were generated using PRODRG2[2] and ATB3[3] servers and was partially changed taking into account some features of lipid molecules.

The mixed lipid monolayer was built using GROMACS software package editconf and genbox modules. The asymmetric bilayer was built according to experimental data [7, 9], after which the system was inserted into water bulk using GROMACS software package genbox module. Additionally, we use the VMD software package solvate module. After the creation of mixed bilayers, the sensitivity analysis of cut-off variation, time step changing and testing water models: SPCE and TIP3P and variation of system size have been performed. The final mixed bilayer snapshot is monitored in fig. 1.

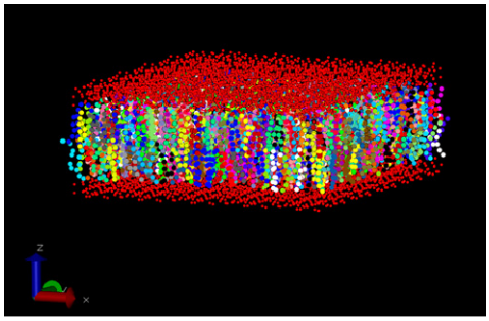

**Fig. 1.** The cross-sectional view perpendicular to the mixed bilayer plane.

[1] Available at http://www.grid.am
[2] Available at http://davapc1.bioch.dundee.ac.uk/prodrg/
[3] Available at http://compbio.biosci.uq.edu.au/atb/

After construction the whole simulation cell, the energy is minimized using steepest descent method for more than 5000 steps in order to remove high-energy contacts that might have formed during the construction process. The obtained mixed bilayer model was tested in ArmGrid environment clusters in order to check their performance. After minimization the system was modeled by normal canonic ensembles.

We are planning to start simulations as mentioned in project, and to determine fundamental parameters with further comparison to real experiment. Currently, the second stage also involves the molecular dynamics study of multicomponent system at $K^+$ and $Na^+$ ionic environment. The MD simulations are planning to carry out on ArmCluster high performance cluster available from ArmGrid environment using 16-32 processors. .

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