КЛЕТОЧНЫЕ МЕМБРАНЫ:
ОТ СТРУКТУРЫ И ДИНАМИКИ – К РАЦИОНАЛЬНОМУ КОНСТРУИРОВАНИЮ НОВЫХ НАНООБЪЕКТОВ

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OUTLINE:

1. Fluid-mosaic membrane model: is it time to revise?

2. Atomic-scale structural/dynamic organization of lipid bilayers:
   - Domains in one- and multi-component lipid bilayers;
   - H-bonding as an important fine-regulator;
   - Stochastic nature of membranes: role of fluctuations;

3. Biological importance of stochastic fluid-mosaic membrane:
   - Self-adaptation of membranes and proteins;
   - Membrane as a communicative medium driving protein-protein interactions;

Fluid—Mosaic Membrane Model

S.J. Singer & G.L. Nicolson, 1972

G.L. Nicolson, 1976

D.M. Engelman, 2005

P.V. Escribá et al., 2008
Limitations of the Singer & Nicolson Fluid—Mosaic membrane model:

“Fluidity”:
- Only macroscopic fluidity is assumed, no atomic-scale dynamic information;
- Microscopic effects of water are not included;

“Mosaicity”:
- Molecular nature of “mosaicity” is not defined:
  dynamic domains (clusters)
  quantitative parameters of mosaicity

Other important aspects:
- Physical nature of intermolecular interactions between membrane components (lipids, proteins, water, ions, etc.) is still not well understood;
- Stochastic nature of membranes (fluctuations!) is not taken into account;

CONCLUSION: Future work is needed, especially on single-molecule level!

A PROMISING WAY TO PROCEED: Atomistic computer simulations (MD, Monte Carlo, etc.)
Point 1:

Atomic-scale structural and dynamic organization of lipid bilayers,

or:

Even simplest membranes are not as “simple” as one can imagine…

Krylov N. et al. (2013) *ACS Nano* 7:9428
A «simple» system: 2-component lipid bilayer:

Similar heads + different (saturated / mono-unsaturated) acyl chains

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Dioleoyl-phosphatidylcholine (DOPC)

Dipalmitoyl-phosphatidylcholine (DPPC)
Another «simple» system: 2-component lipid bilayer:

Different (zwitterionic / anionic) heads + similar acyl chains

Dioleoyl-phosphatidylcholine (DOPC)

n % DOPS + (100-n) % DOPC

10:90
15:85
20:80
30:70
50:50
70:30
85:15

Dioleoyl-phosphatidylserine (DOPS)
Analysis of MD data for hydrated lipid bilayers:

**Macroscopic geometrical parameters:**
- $A_L$ – surface area/lipid;
- $D_{pp}$ - bilayer thickness;
- Density profiles across the membrane;
- Orientation of lipid heads;
- Free volume distribution;

**Dynamic properties:**
- $S_D$ - order parameters of lipid chains;

**Domain organization of lipids:**
- geometrical lipid clusters (lateral & transversal);
- surface mapping and clustering (hydrophobic “defects”, etc.);

**Molecular interactions:**
- H-bonds (lipid-lipid, lipid-water, water-water);
- Coordination of ions, ion-induced clustering of lipids;

**Water dynamics near/inside lipid bilayers:**
- Diffusional velocities;
- Water permeation effects;
Membrane properties nonlinearly depend on lipid composition: results of molecular dynamics simulations:

- Nonlinear change of area per lipid molecule in DPPC/DOPC systems
- Nonlinear change of a number of lipids interacting with ions in DOPS/DOPC systems

Result of non-ideal mixing of lipids in leaflets?
Hydrophobic properties of surfaces of hydrated lipid bilayers in atomistic presentation

Parameters of the systems:

200-500 lipids;

$10^4 – 10^5$ waters;

Cell dimensions: $> 10 \cdot 10 \cdot 10$ nm$^3$.

Distribution of molecular hydrophobicity potential on the membrane surface

- $> 0$ (hydrophobic regions)
- $< 0$ (hydrophilic regions)
Mapping of hydrophobicity on the lipid bilayer surface reveals domain structure of membranes:
DOPC / DOPS case

Evolution of mosaicitv vs PS content

Something is happening here with the membrane organization

Atomic-scale structure & dynamics of biomembranes
Dynamic clustering as an intrinsic property of **ALL** lipid bilayers.

Time evolution of lipid clusters in DOPC bilayer:
Results of MD simulations
DOPC/DOPS membranes: lipid clustering IS NOT RANDOM

**20% DOPS**

**30% DOPS**

**50% DOPS**

**10% DOPS**

random MD
Fluctuations in membranes

Order parameters of lipid acyl chains:

Free volume distribution

Pure DOPC and DPPC

DOPC/DPPC mixture
Why cell membranes are composed of lipids?

Case study: bolalipid (Archaeal-like) membrane

Lipid membranes are much more permeable for water than bolalipids

Lipid membranes are almost “empty” in the middle

Lipid-lipid H-bonding as an important factor for fine-tuning of membrane properties:

CONCLUSION:
Rational design of lipids with proper location of H-bonding donor/acceptor groups is perspective for construction of new membrane-like materials with predefined properties.

H-bonding depends on:
- “vertical” position of donor and acceptor;
- local dielectric permeability ($\epsilon$);
- involvement in H-bonds with water;
- coordination with ions.
Some conclusions about lateral organization of the binary DPPC/DOPC lipid membrane
(in a liquid crystalline state)

- Hydrophobic
- Hydrophilic
- Strongly hydrophilic

- Solvation, H-bonding with water
- Tilt of lipid heads
- Lipid ordering
- Hydrophilicity

Top-view of the water-membrane interface
Biomembrane as a sandwich with “boiling up” stuffing

- Water transition zone
- Polar heads region
- Acyl chains region

Bulk water

Fluctuating hydrophobic core

Buffer polar region

Buffer polar region

Disorder degree

Speed of fluctuations
Point 2:

Biological importance of stochastic fluid - mosaic membrane

Self-adaptation of proteins and membranes:

Lipid-II in bacterial membrane creates a specific hydrophobic/landscape pattern on the bilayer surface – a putative target for lantibiotics

Insertion of antimicrobial peptide *iok* into lipid bilayer:

*Results of molecular dynamics simulation*

**T = 0 ns: Start**

- **Water**
- **Membrane**

**Hydrophobic area**

**Hydrophilic area**

**T = 250 ns**

- **Strong hydrophobic match**

- **Hydrophobicity induced by the membrane**

- **"Own" hydrophobicity (as viewed from the membrane)**

- **No hydrophobic match**

- **Strong hydrophobic match**
Membrane as a communicative medium ("Aether"), which promotes protein-protein interactions

What is a driving force of spontaneous helix-helix association?

**Possible answers:**

- Protein sequence; +
- Membrane; +
- Water; +

CONCLUSIONS TO THIS DATE:

Biomembranes are very heterogeneous and dynamic systems, all whose components (lipids, water, ions, inserted/adsorbed molecules, etc.) effect each other.

Balance of such effects should be carefully assessed in each particular case.

Fundamental intrinsic property of membranes is occurrence of highly fluctuating regions in their nonpolar core, while their interfaces serve as a buffer protecting membranes from external influence.
PERSPECTIVES:

• Development of hybrid models combining advantages of different approximations used to describe biomembranes and protein-membrane interactions (all-atom, coarse-grained, implicit models);

• Multi-level modeling of membranes with complex composition (3 and more components) in order to understand molecular basis of forming rafts and domains in cell membranes;

• Analysis of relationships between properties of mixed bilayers and behavior of membrane and membrane-active peptides and proteins;

• Application of structural, dynamic, and hydrophobic heterogeneity of native membranes to rational design of principally new membrane materials with predefined properties and to design efficient membrane-active compounds (including drugs).