

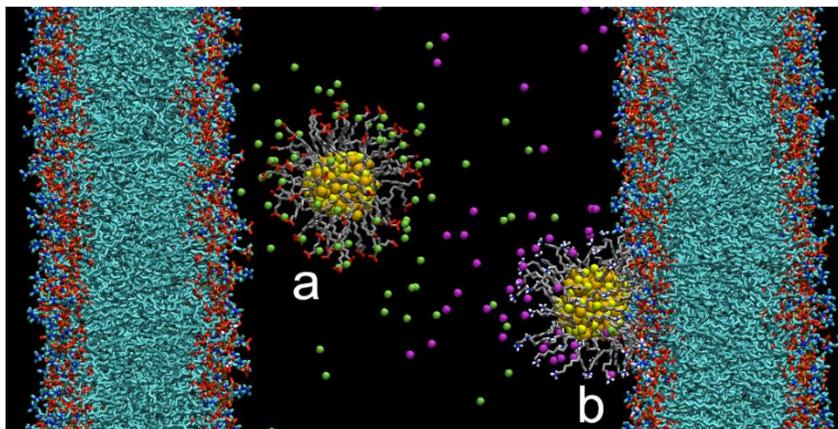


Сучасні комп'ютерні методи дослідження нанорозмірних та біологічних систем



Лекція № 11

Молекулярно-динамічне моделювання взаємодії, транспорту, розподілу та локалізації хімічних сполук, фармацевтичних препаратів та лікарських засобів у біологічних мембранах



План Лекції № 11

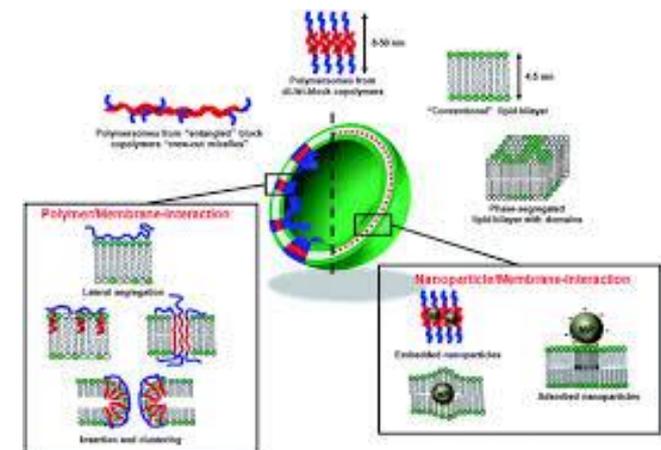
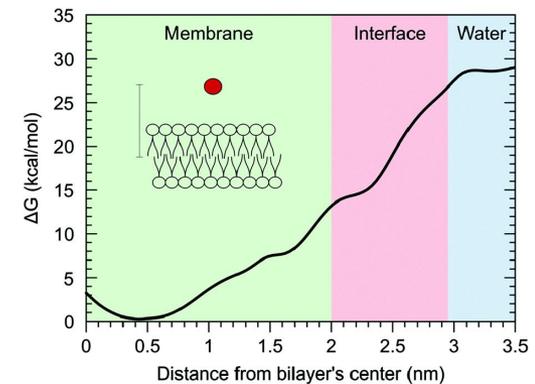
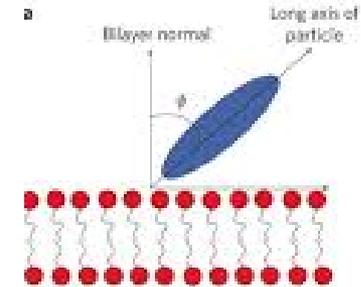
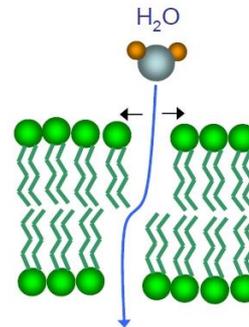
- Процеси взаємодії, транспорту, розподілу та локалізації хімічних сполук з ліпідною мембраною

- Локалізація хімічних сполук у мембрані

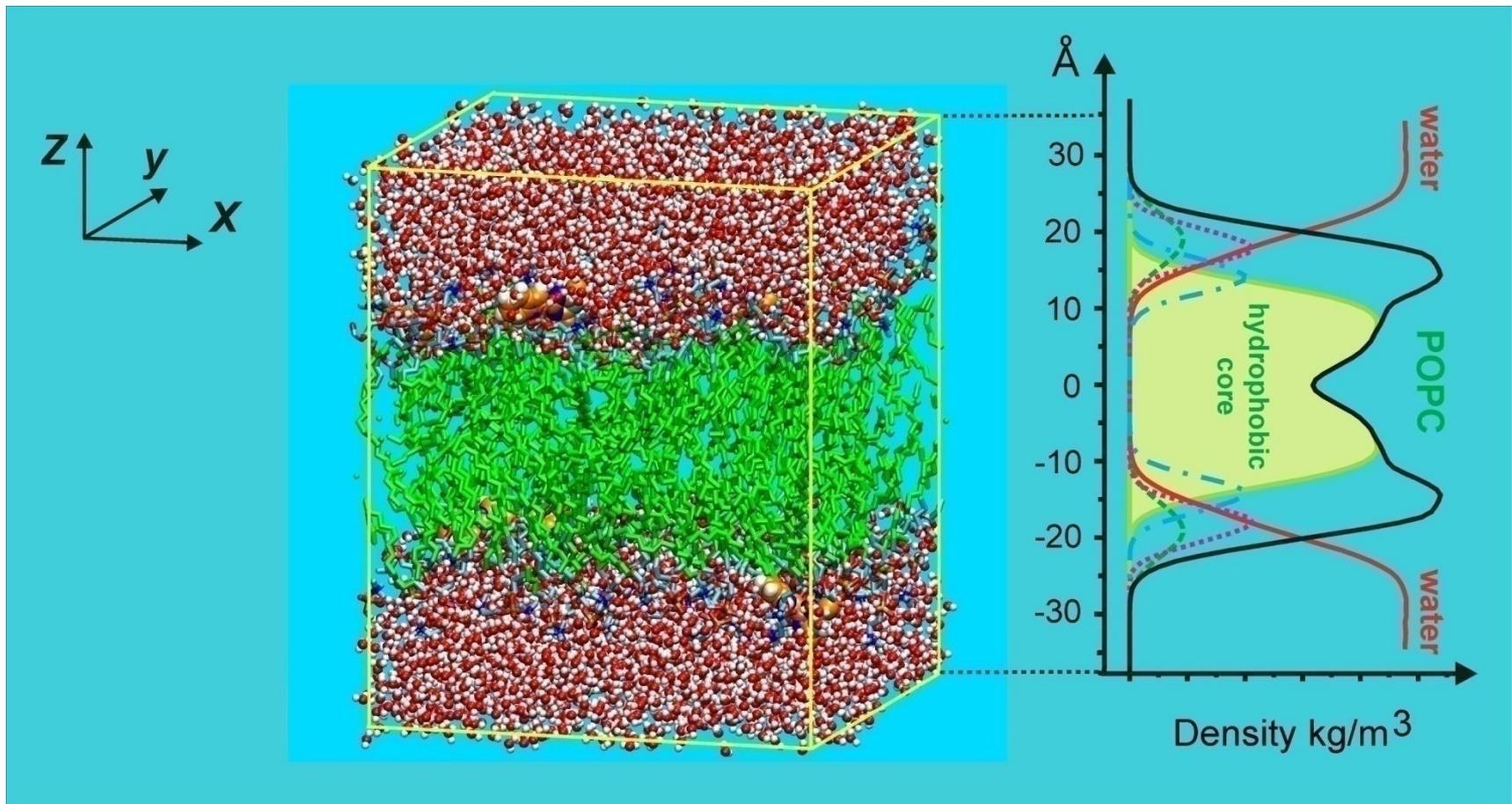
- Цитотоксичність

- Термодинаміка розподілу у системі вода-мембрана

- Комп'ютерне моделювання та пошук нових фармацевтичних препаратів



Молекулярно-динамическое моделирование Метод свободной диффузии



Применение МД моделирования для изучения мембран

- **Связывание химических соединений с мембраной**
- **Проникновение и накопление химических соединений в мембране**
 - **поиск новых фармацевтических препаратов**
 - **влияние анестетиков на мембрану**
 - **воздействие химических соединений на свойства мембраны**
 - **разрушение мембраны под действием химических соединений**
 - **цитотоксичность**
- **Зона локализации химических соединений в мембране**
- **Кинетика и термодинамика мембранных процессов**



КРИОБИОЛОГИЯ – дорога в бессмертие

Потребление кислорода животными при понижении температуры на 10 °С падает в 2-3 раза.

Многие животные способны выживать, переходя в состояние оцепенения, при температуре жидкого воздуха (-190 °С) или даже жидкого гелия (-269 °С). Однако такой сопротивляемостью по отношению к низким температурам обладают далеко не все организмы.

Животные, обитающие в условиях холодного климата, выдерживают длинные холодные зимы, когда их температура может падать гораздо ниже температуры замерзания воды. Одним из способов, который помогает им избегать гибели в таких условиях - **переохлаждение**.



КРИОБИОЛОГИЯ – дорога в бессмертие

переохлаждение

- **Переохлаждение** - снижение температуры жидкости внутри клеток животного ниже температуры ее замерзания без образования кристаллов льда.
- Образование кристаллов внутри клетки приводит к необратимому разрушению и ее гибели.
- Вода или солевой раствор, охлаждённая ниже температуры замерзания, замерзает только при наличии центров кристаллизации.
- При отсутствии чужеродных частиц, служащих, как правило, центрами кристаллизации, чистую воду можно переохладить почти до -40°C . Но, как только появляется первый кристаллик льда, замерзание всей жидкости идет очень быстро.

Cryopreservation and Cryobiology
(Concepts and Applications)



Taniya Lima



Побочные эффекты в криобиологии

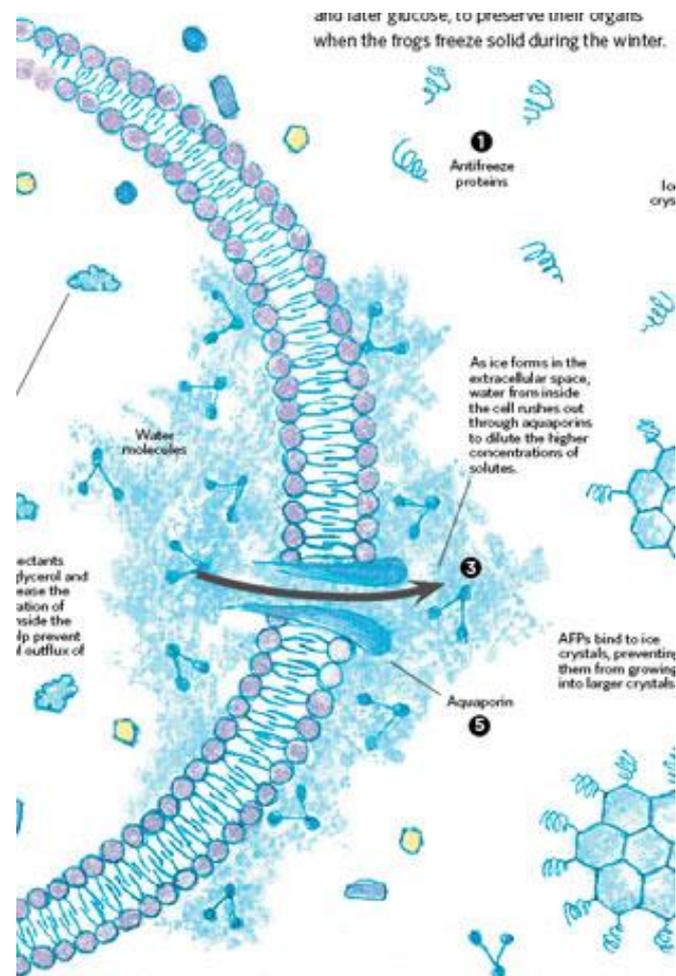





 актуальні проблеми
кріобіології
і кріомедицини Харків 2012

Использование низких температур опасно для живых объектов. Живые клетки погибнут при замораживании, если не осуществят специальные защитные мероприятия.

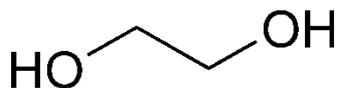
Основными повреждающими факторами при замораживании являются образование внутриклеточного льда и обезвоживание клетки.



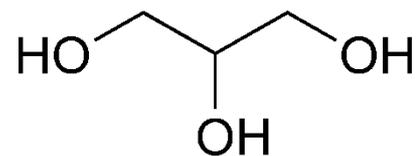
Что такое криопротекторы?

Криопротéкторы — [вещества](#), защищающие живые объекты от повреждающего действия замораживания. Криопротекторы используют при [криоконсервации](#) — низкотемпературном хранении живых объектов (другими словами, при замораживании крови, спермы, эмбрионов, изолированных органов, клеточных культур).

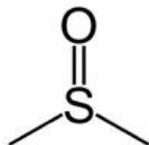
Наиболее распространенные проникающие криопротекторы: [глицерин](#), [этиленгликоль](#), [диметилсульфоксид](#).



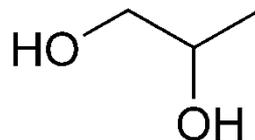
этиленгликоль



глицерин

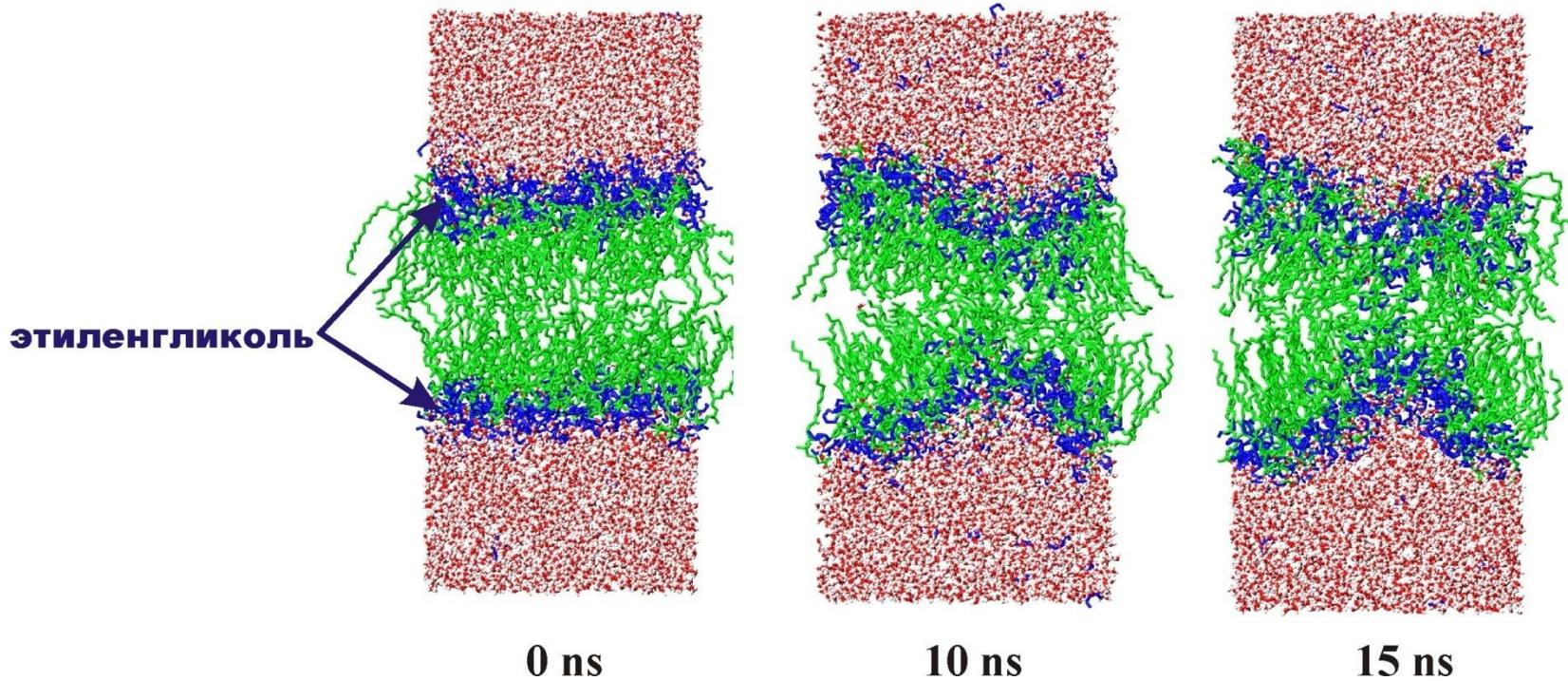


ДМСО



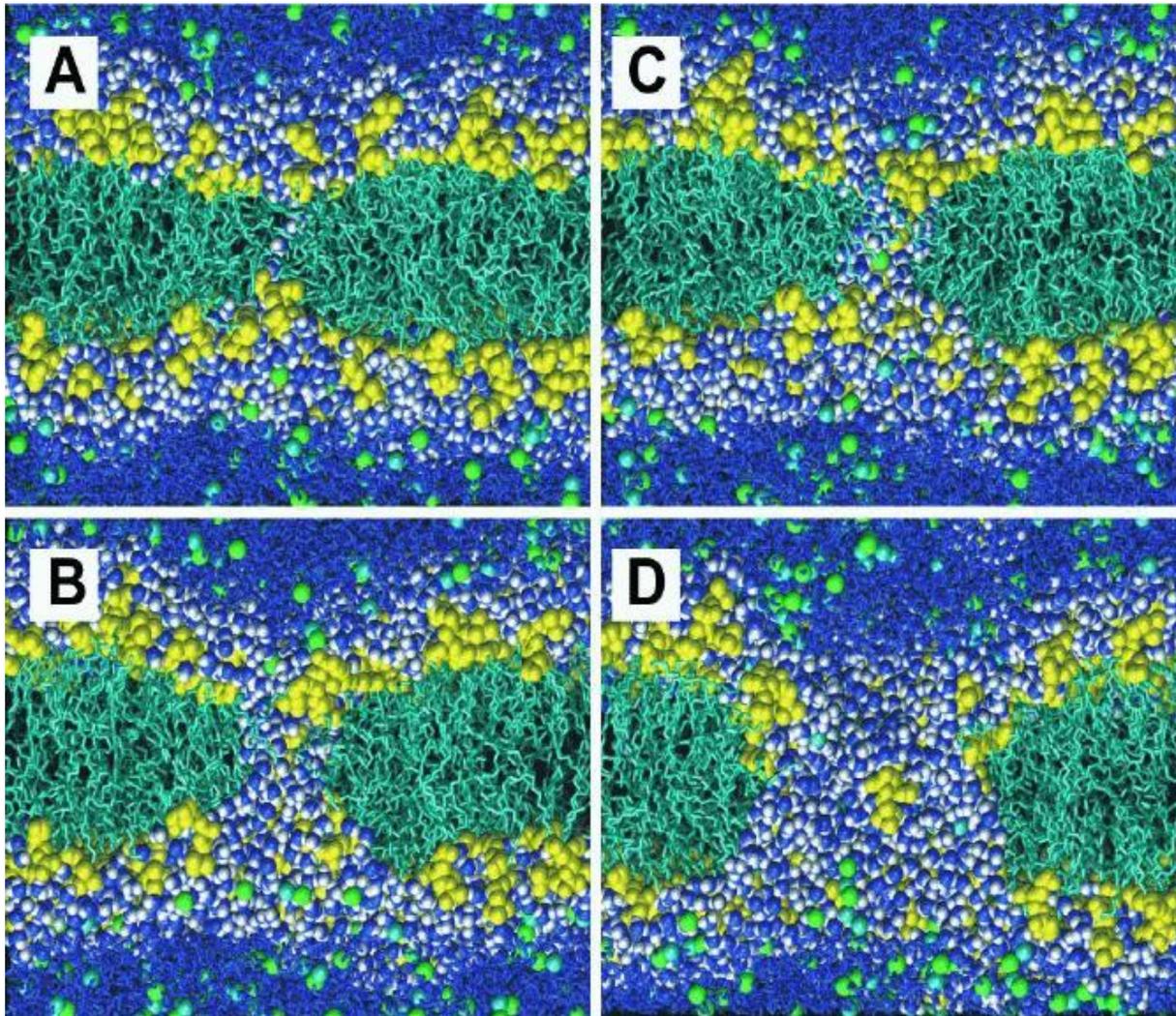
пропиленгликоль

Цитотоксичность

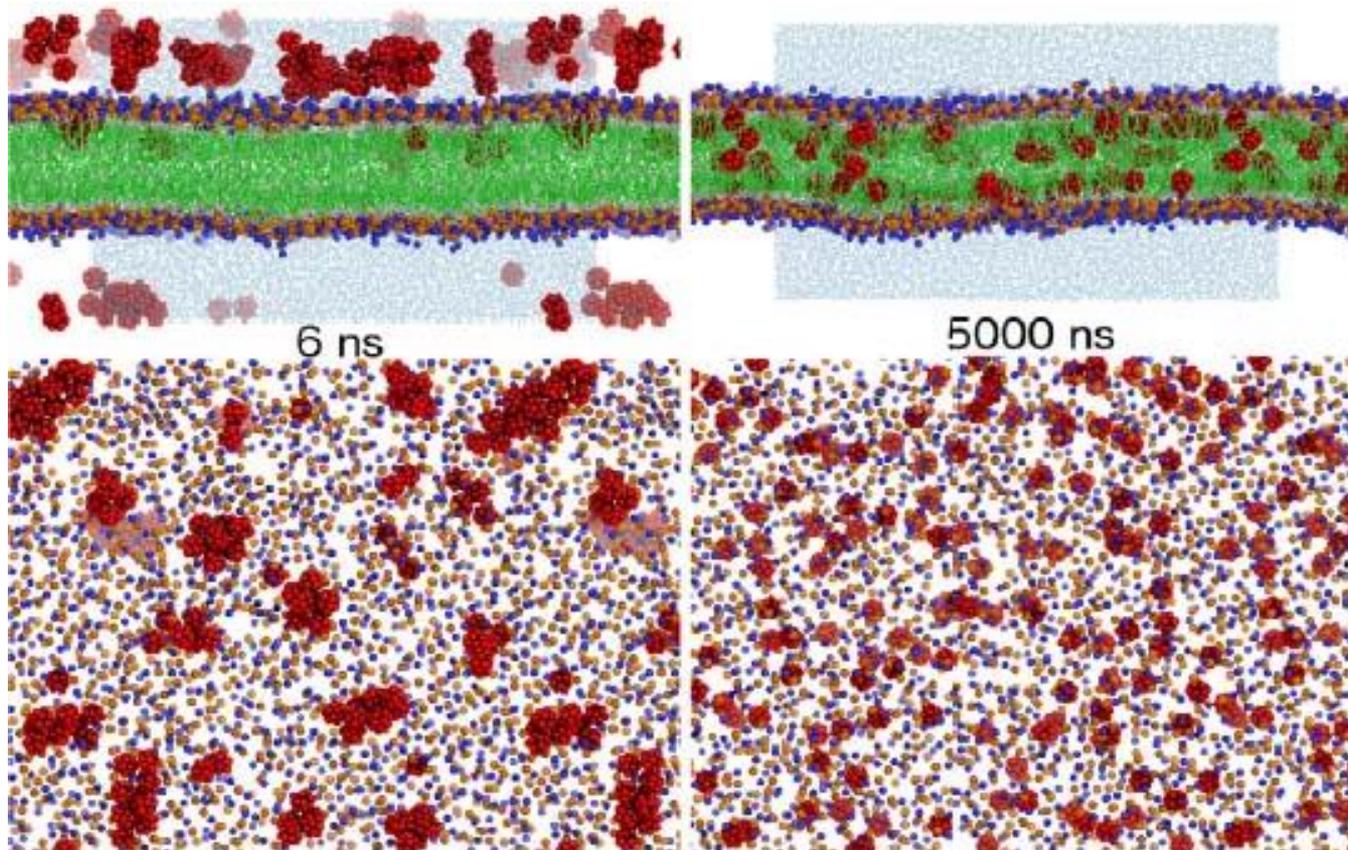


Молекулярно-динамическое моделирование процессов разрушения целостности мембраны при повышении концентрации этиленгликоля

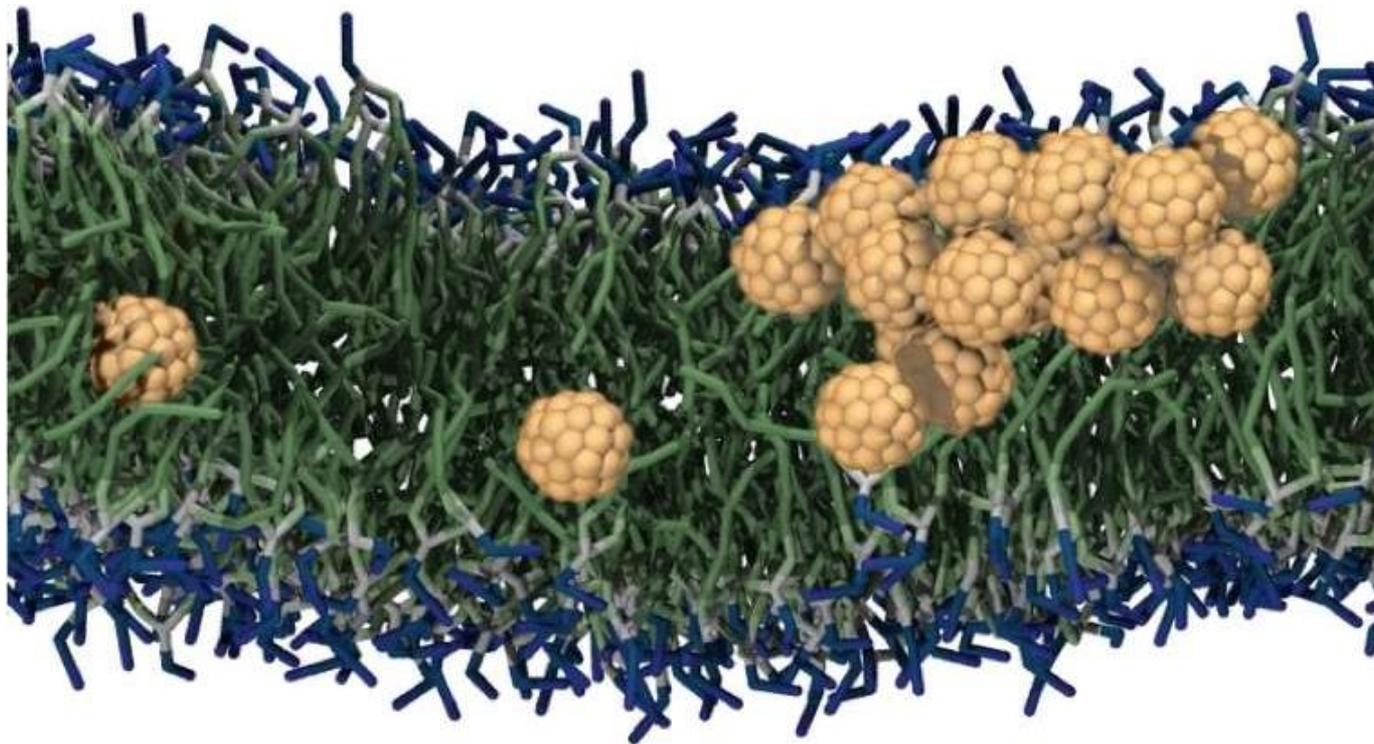
Цитотоксичность: Разрушение целостности мембраны при высокой концентрации ДМСО



Цитотоксичность: Разрушение целостности мембраны под действием фуллеренов

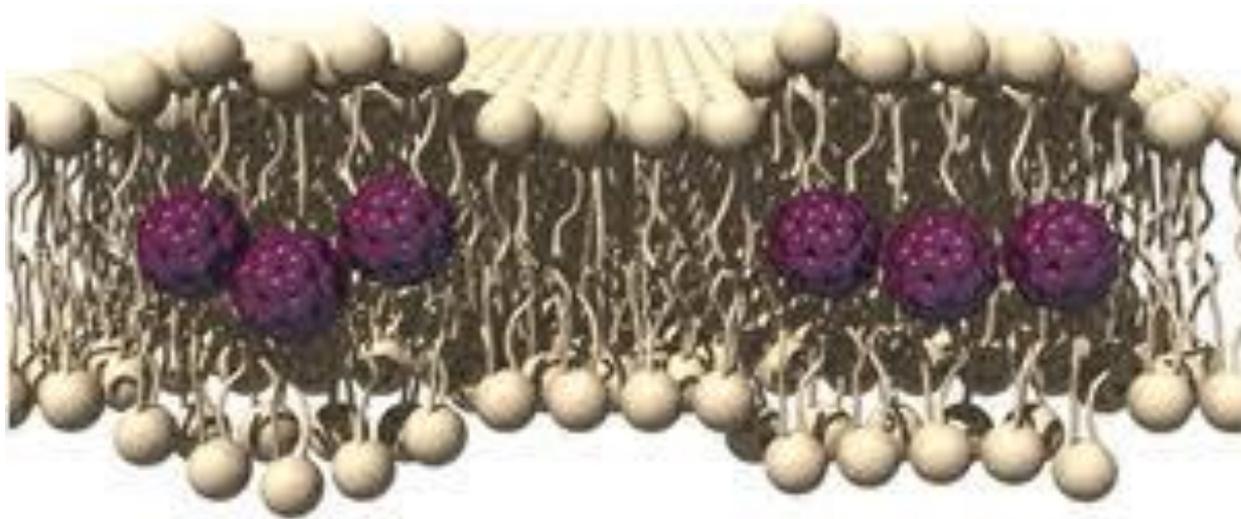


**Цитотоксичность:
Разрушение целостности мембраны под действием
фуллеренов**



**Изменение свойств бислоя при накоплении в нем
молекул фуллеренов**

**Цитотоксичность:
Разрушение целостности мембраны под действием
фуллеренов**



**Нарушение строения бислоя при включении в него
больших молекул фуллеренов**

Цитотоксичность: Разрушение целостности мембраны под действием фуллеренов



Nanoscale

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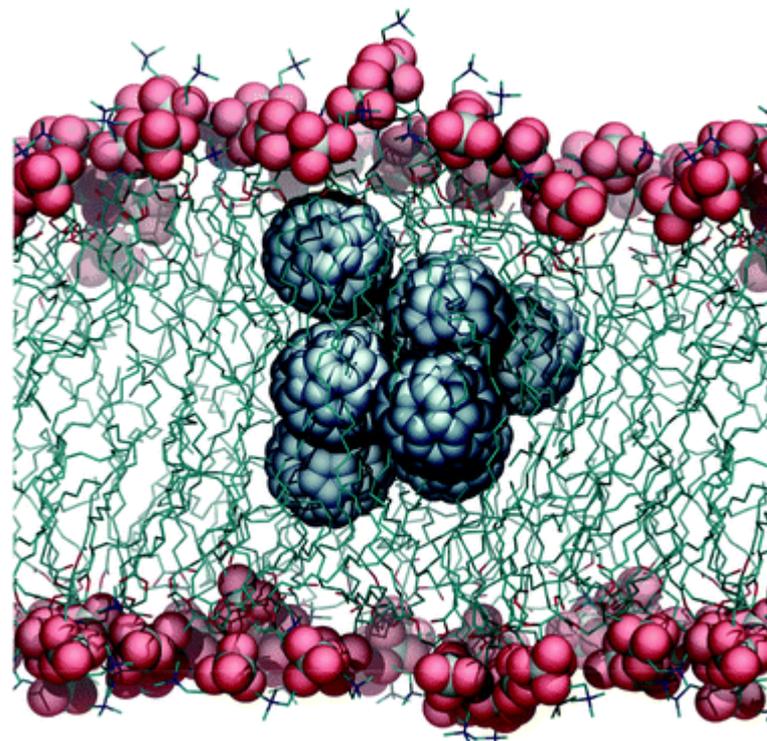
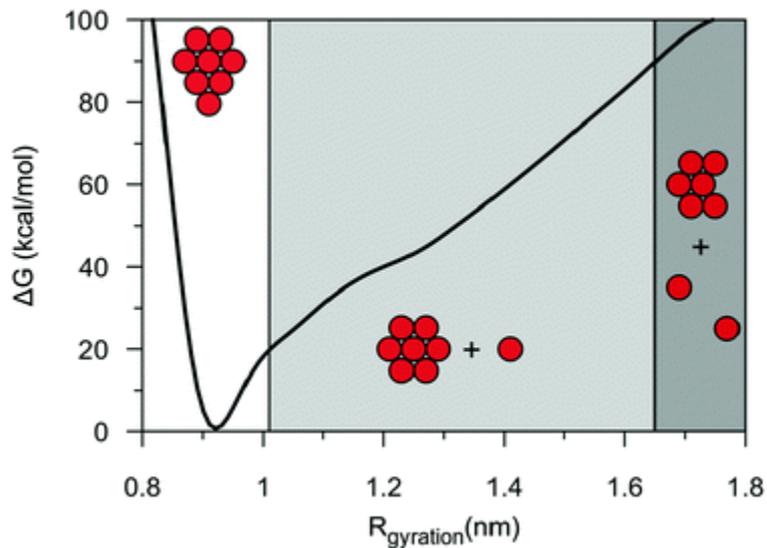


Cite this: *Nanoscale*, 2016, 8, 4134

C₆₀ fullerene localization and membrane interactions in RAW 264.7 immortalized mouse macrophages†

K. A. Russ,^a P. Elvati,^b T. L. Parsonage,^{c,d} A. Dews,^a J. A. Jarvis,^{c,d} M. Ray,^a
B. Schneider,^a P. J. S. Smith,^{c,d} P. T. F. Williamson,^{c,d} A. Violi^{b,e} and M. A. Philbert^a

Nanoscale, 2016, 8, 4134–4144



Цитотоксичность: Разрушение целостности мембраны под действием фуллеренов

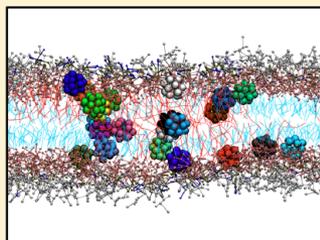
Molecular Dynamics Simulations Predict the Pathways via Which Pristine Fullerenes Penetrate Bacterial Membranes

Pin-Chia Hsu,[†] Damien Jefferies,[†] and Syma Khalid*[‡]

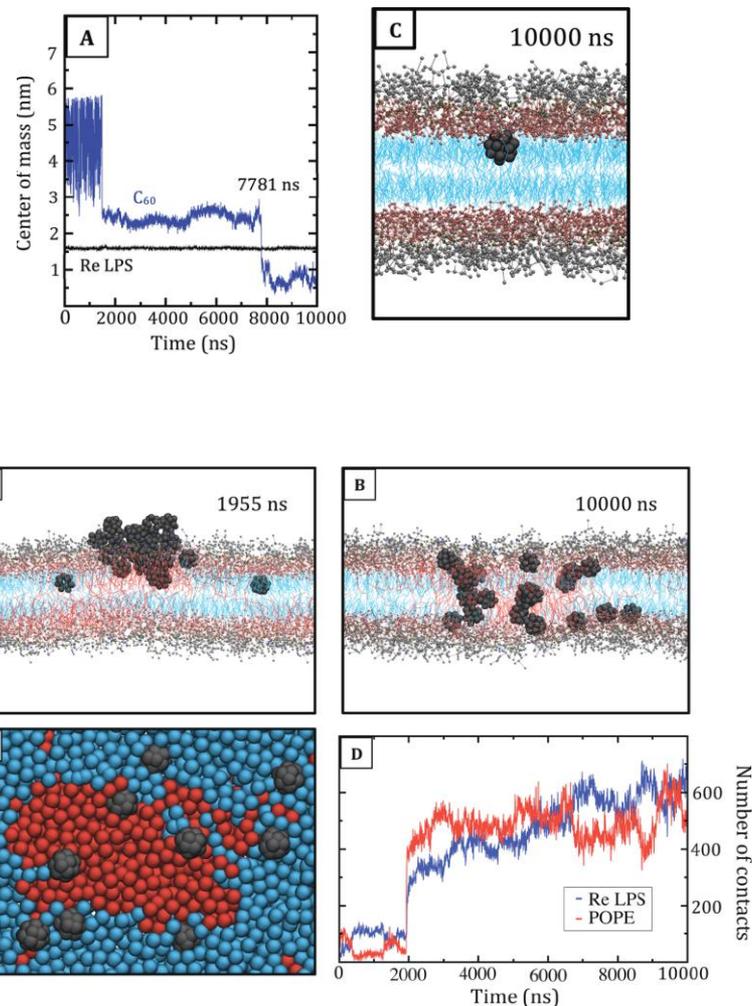
School of Chemistry, University of Southampton, Southampton SO17 1BJ, U.K.

Supporting Information

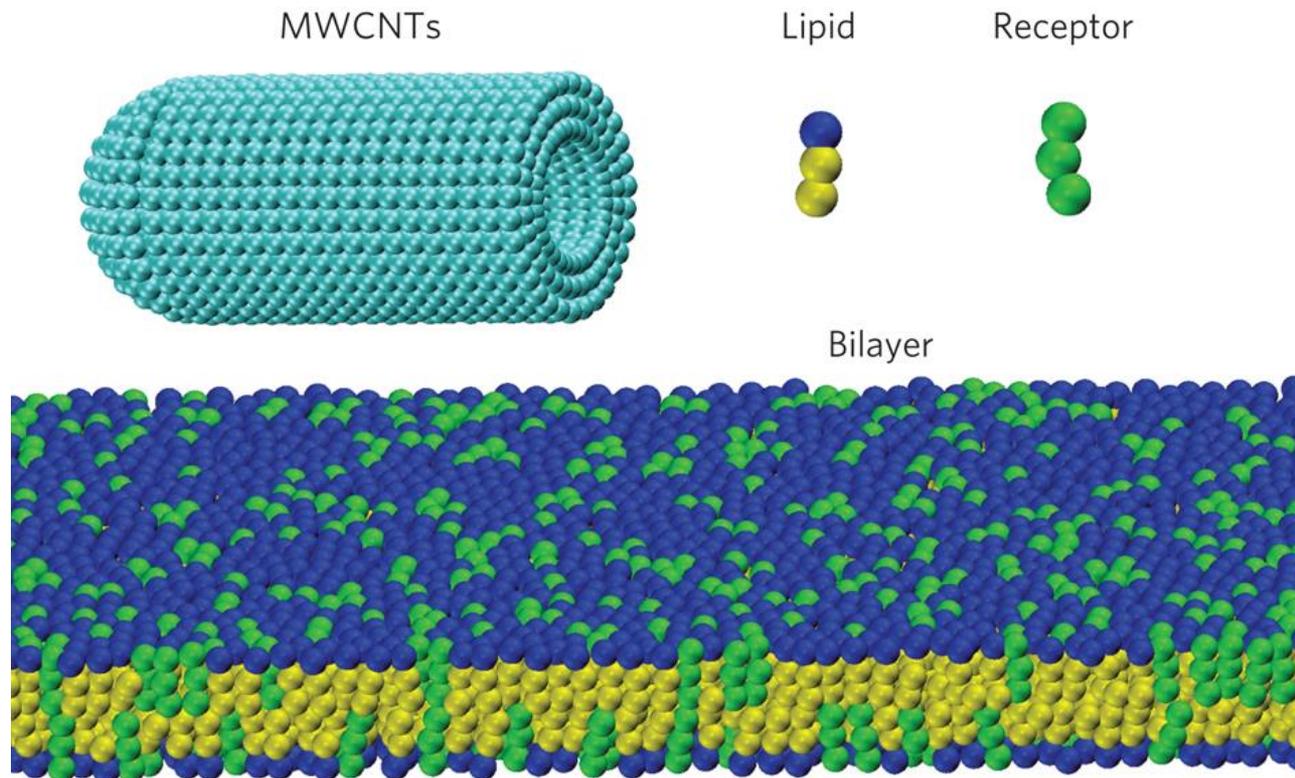
ABSTRACT: Carbon fullerenes are emerging as effective devices for different biomedical applications, including the transportation of nanosized drugs and extraction of harmful oxidants and radicals. It has been proposed that fullerenes could be used as novel antibacterial agents, given the realization that the nanoparticles can kill pathogenic Gram-negative bacteria. To explore this at the molecular level, we simulated C_{60} fullerenes with bacterial membranes using the coarse-grain molecular dynamics Martini force field. We found that pristine C_{60} has a limited tendency to penetrate (incomplete core) Re mutant lipopolysaccharide (LPS) leaflets, but the translocation of C_{60} fullerenes into (complete core) Ra mutant LPS leaflets is not thermodynamically favored. Moreover, we showed that the permeability of the Re LPS bilayers depends sensitively on the system temperature, charge of ambient ions, and prevalence of palmitoyloleoylphosphoethanolamine (POPE) defect domains. The different permeabilities are rationalized in terms of transitory head group pore formation, which underpins the translocation of C_{60} into the lipid core. The Re LPS lipids readily form transient micropores when they are linked with monovalent cations or when they are heated to a high temperature. POPE lipids are shown to be particularly adept at forming these transient surface cavities, and their inclusion into Re LPS membranes facilitates the formation of particularly large pores that are tunneled by C_{60} aggregates of a significant size (~ 5 nm wide). After insertion into the lipid core, the aggregates dissociate, and the disbanded nanoparticles migrate to the interface between separate POPE and LPS domains, where they weaken the boundaries between the coexisting lipid fractions and thereby promote lipid mixing.



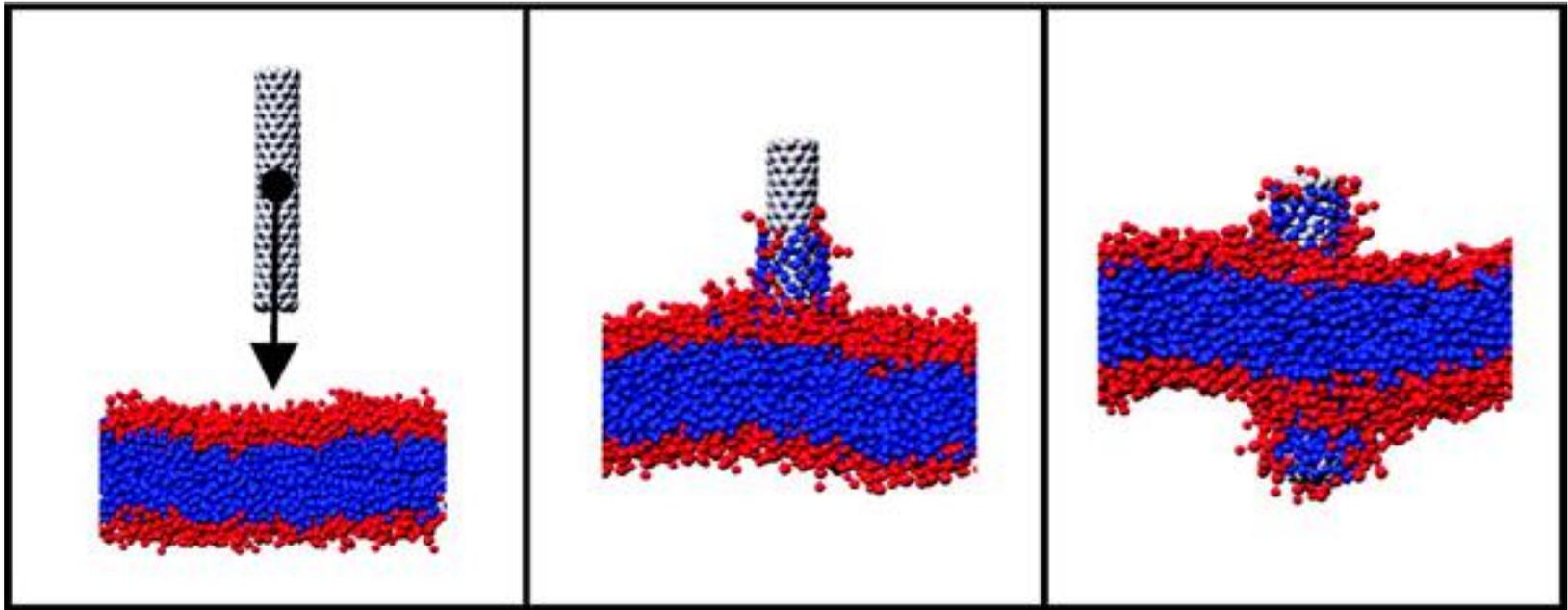
J. Phys. Chem. B 2016, 120, 11170–11179



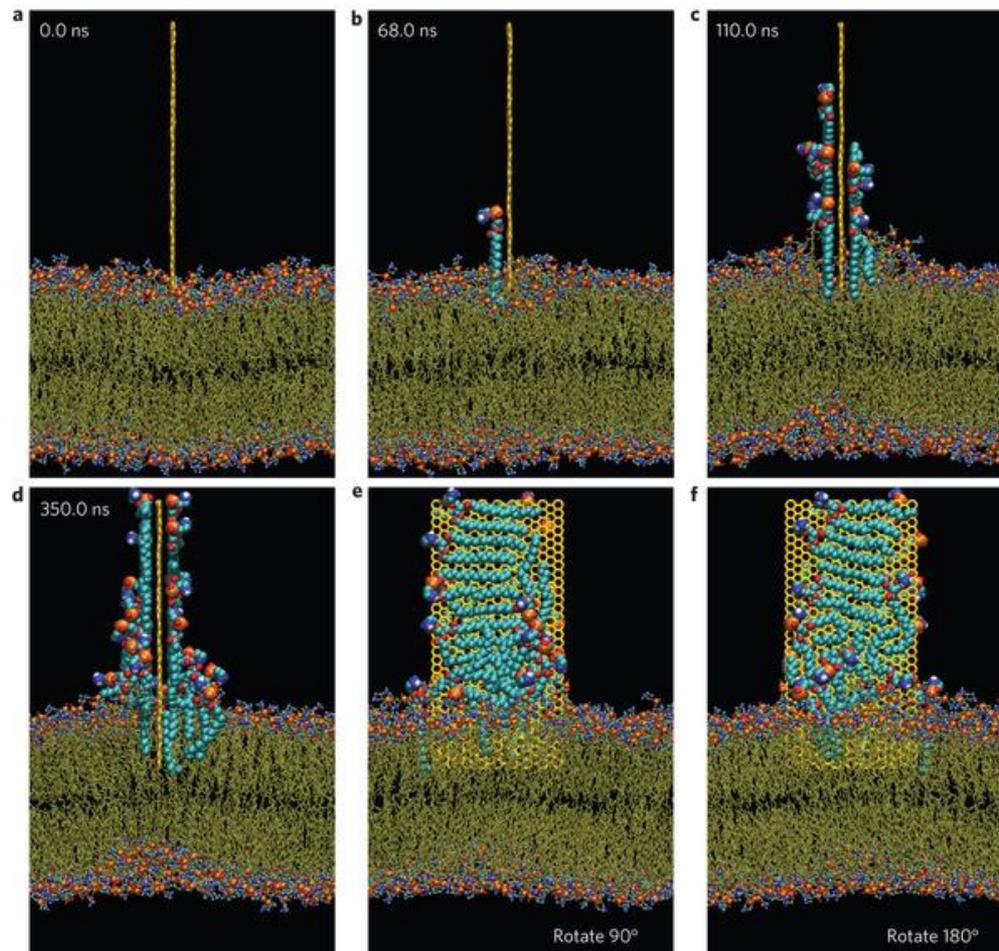
Цитотоксичность: Воздействие наноматериалов на мембрану



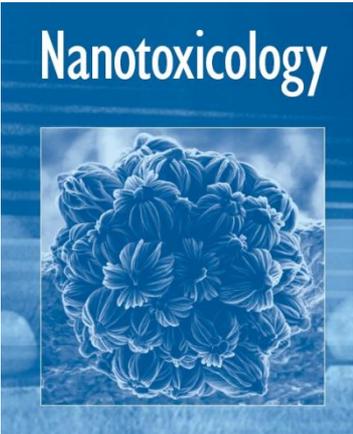
Цитотоксичность: Воздействие наноматериалов на мембрану



Цитотоксичность: Воздействие наноматериалов на мембрану

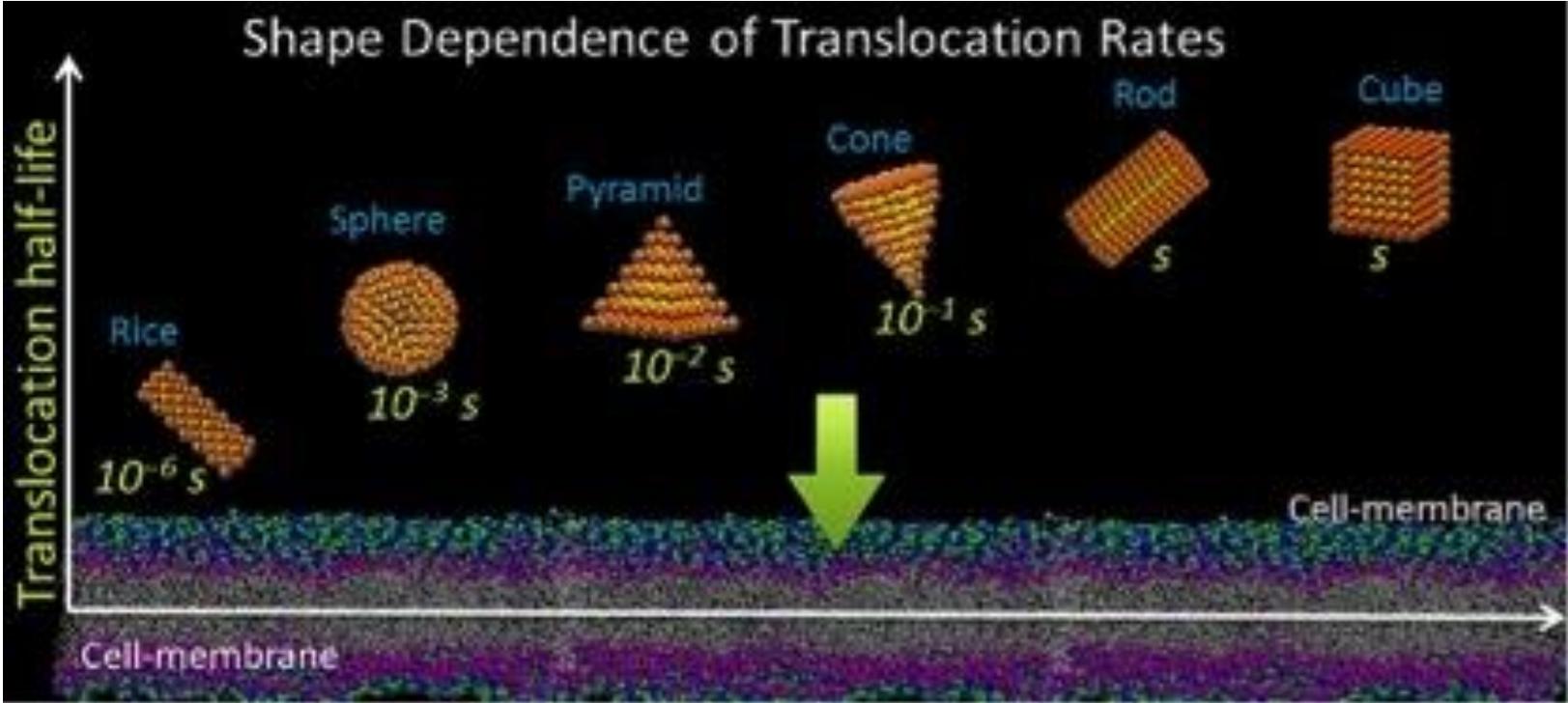


Destructive extraction of phospholipids from *Escherichia coli* membranes by graphene nanosheets. Nature Nanotechnology 8, 594-601 (2013)

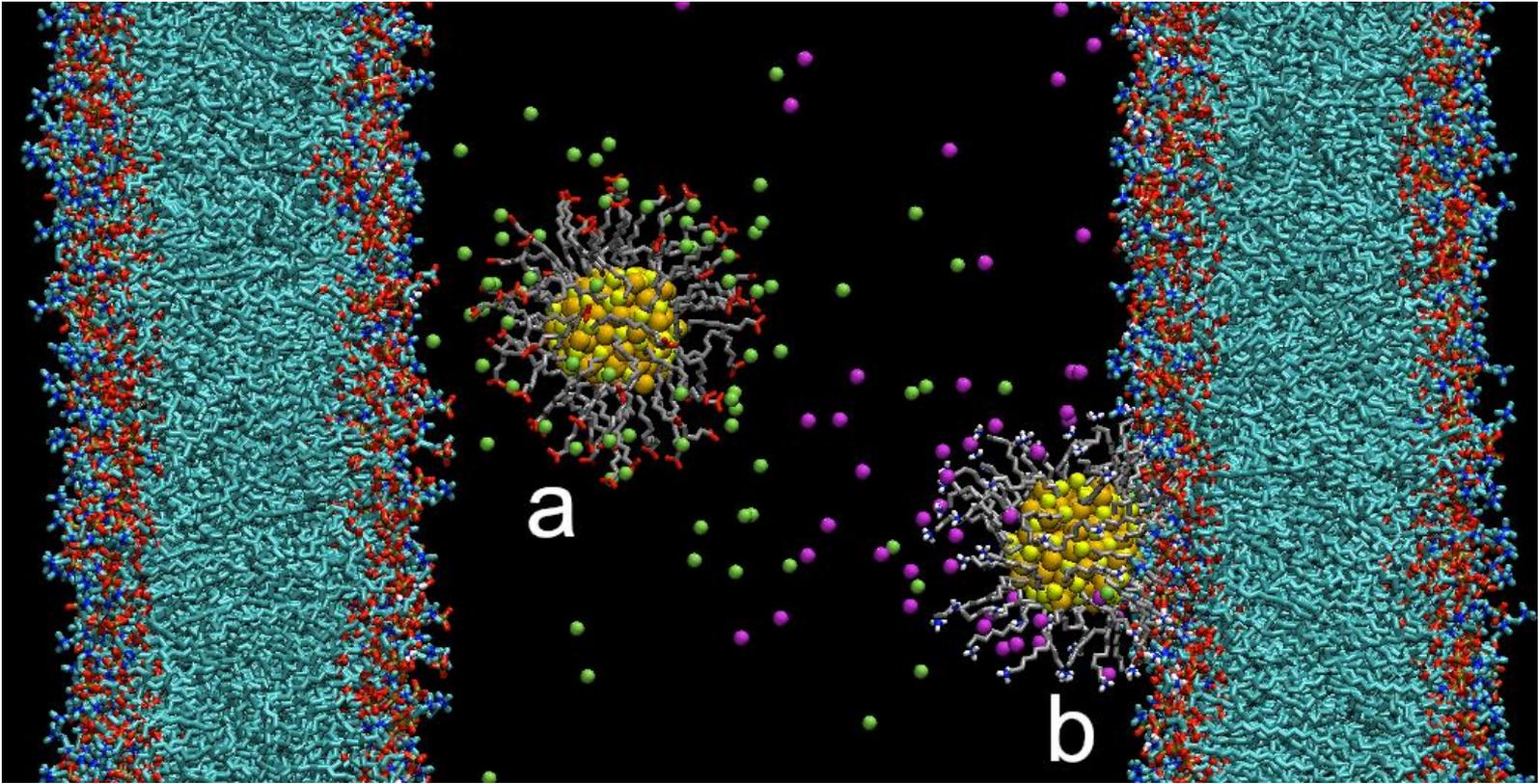


Нанотехнология и нанотоксичность ...

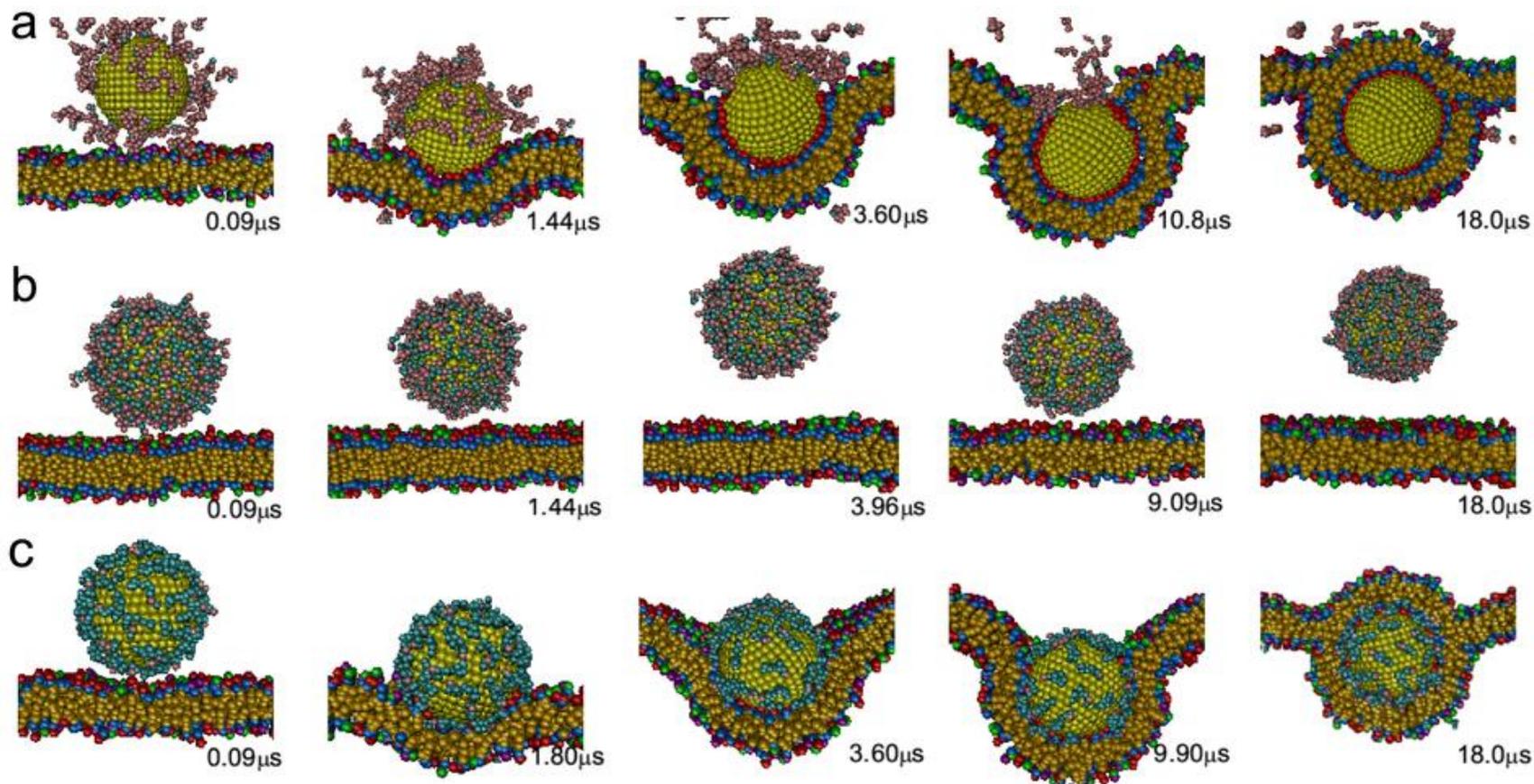
Нанотоксичность - способность безвредных веществ при сильном измельчении становиться опасными для здоровья человека



Цитотоксичность: Воздействие наночастиц золота на мембрану



Цитотоксичность: Воздействие наночастиц золота на мембрану



<http://www.nature.com/srep/2013/130930/srep02804/full/srep02804.html>

Пассивный транспорт незаряженных молекул

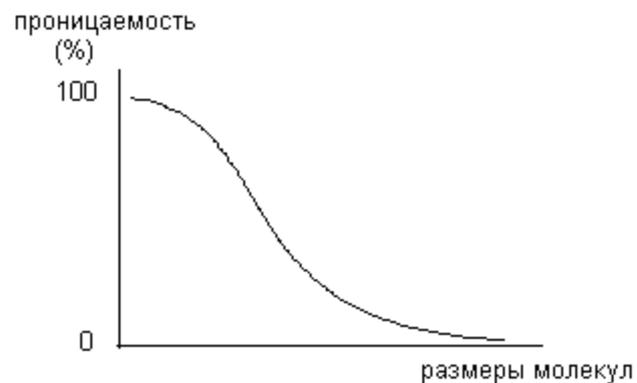
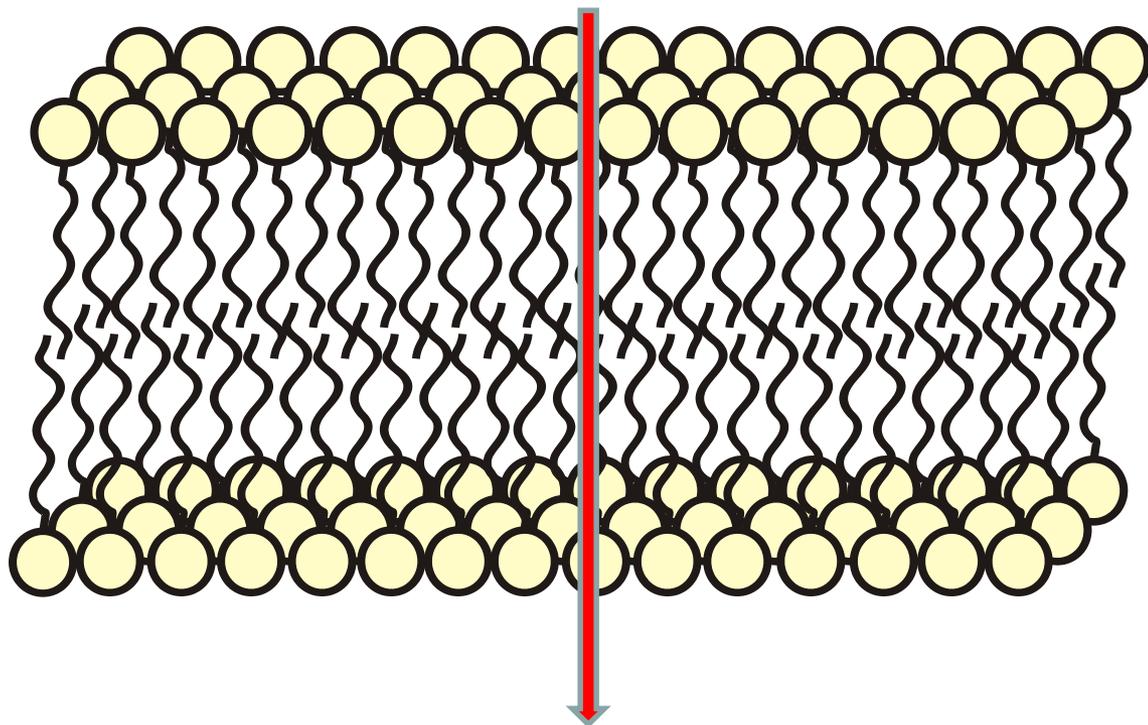
Концентрация частиц на поверхностях мембраны испытывает скачок вследствие различной растворимости вещества в водной фазе и пристеночной слое внутри мембраны. Обычно существует пропорциональное связь:

$$\frac{C_{me}}{C_e} = \frac{C_{mi}}{C_i} = K$$

Где, K - коэффициент распределения вещества между мембраной и водной фазой.

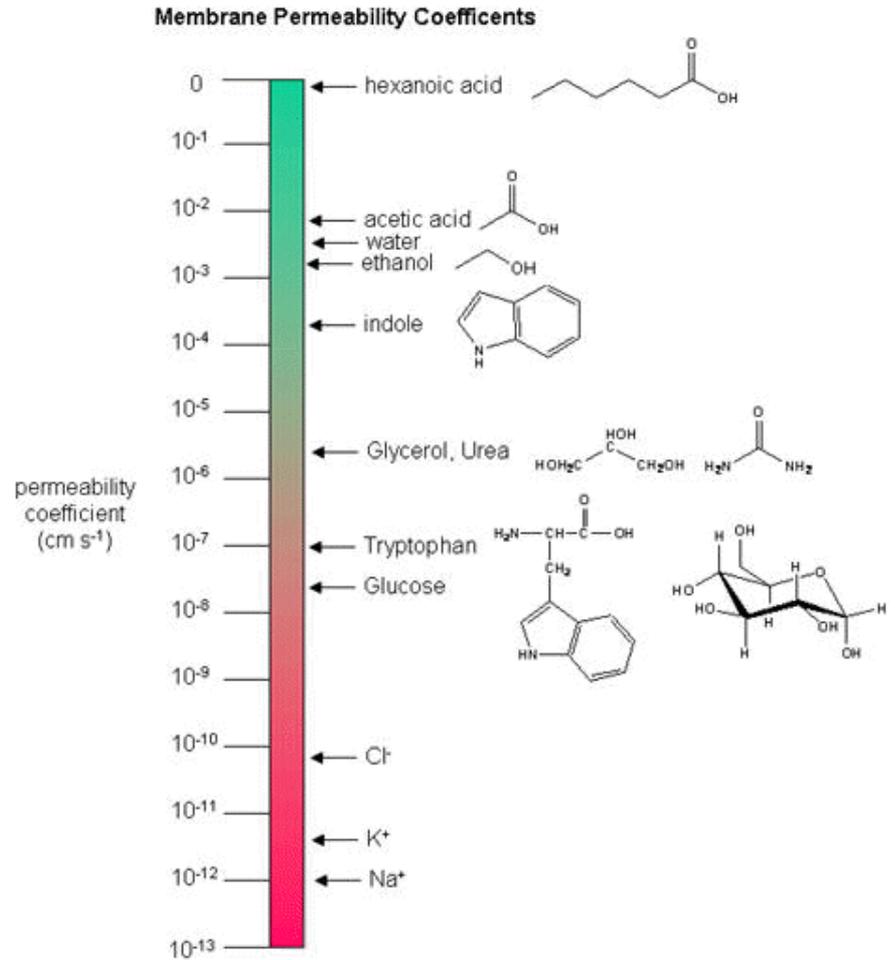
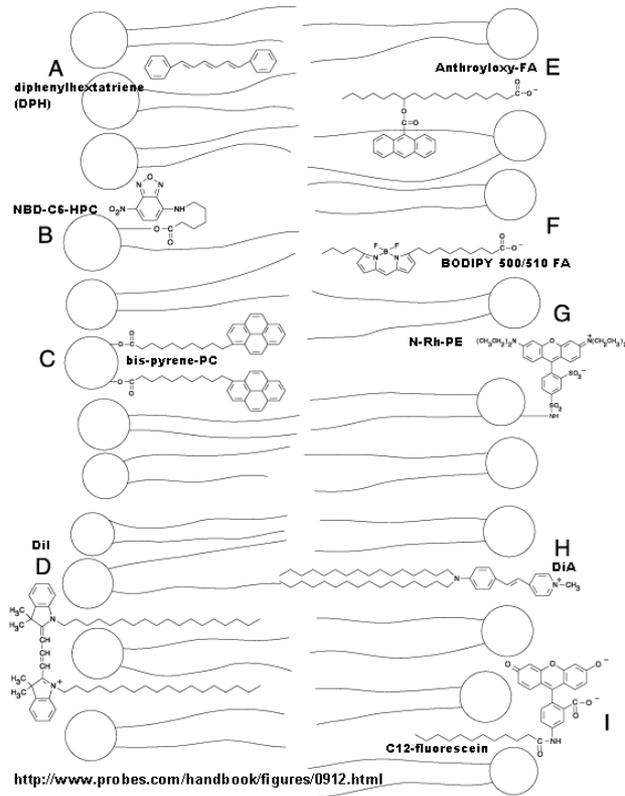
Метод потенциала средней силы

Распределение пробы в мембране



В методе потенциала средней силы проба принудительно перемещается через мембрану под действием дополнительного потенциала

Коэффициент проникновения пробы в мембрану



Обзоры по моделированию коэффициента проникновения пробы в мембрану

CHEMICAL REVIEWS

Cite This: *Chem. Rev.* 2019, 119, 5922–5953

Review

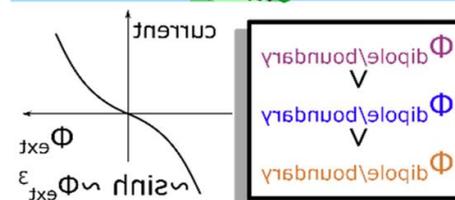
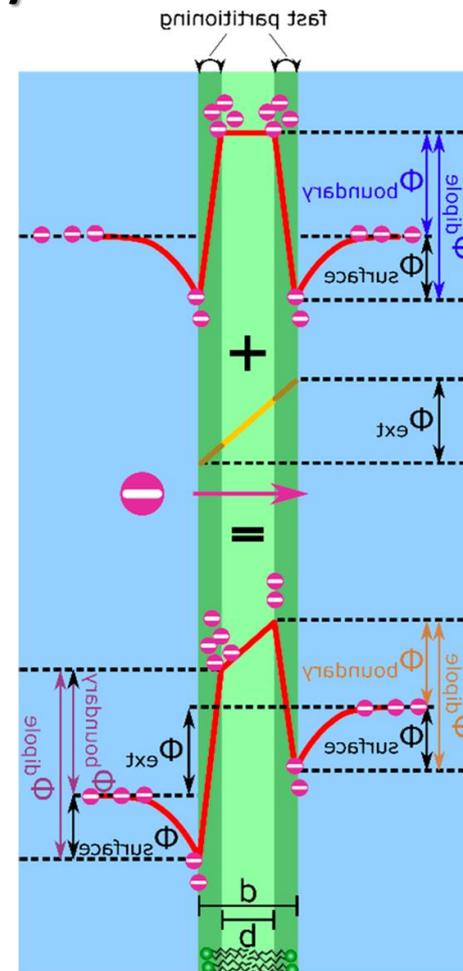
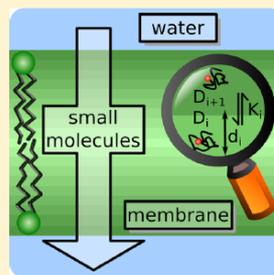
pubs.acs.org/CR

Intrinsic Membrane Permeability to Small Molecules

Christof Hanneschlaeger, Andreas Horner, and Peter Pohl*

From the Institute of Biophysics, Johannes Kepler University Linz, Gruberstrasse 40, 4020 Linz, Austria

ABSTRACT: Spontaneous solute and solvent permeation through membranes is of vital importance to human life, be it gas exchange in red blood cells, metabolite excretion, drug/toxin uptake, or water homeostasis. Knowledge of the underlying molecular mechanisms is the sine qua non of every functional assignment to membrane transporters. The basis of our current solubility diffusion model was laid by Meyer and Overton. It correlates the solubility of a substance in an organic phase with its membrane permeability. Since then, a wide range of studies challenging this rule have appeared. Commonly, the discrepancies have their origin in ill-used measurement approaches, as we demonstrate on the example of membrane CO₂ transport. On the basis of the insight that scanning electrochemical microscopy offered into solute concentration distributions in immediate membrane vicinity of planar membranes, we analyzed the interplay between chemical reactions and diffusion for solvent transport, weak acid permeation, and enzymatic reactions adjacent to membranes. We conclude that buffer reactions must also be considered in spectroscopic investigations of weak acid transport in vesicular suspensions. The evaluation of energetic contributions to membrane translocation of charged species demonstrates the compatibility of the resulting membrane current with the solubility diffusion model. A local partition coefficient that depends on membrane penetration depth governs spontaneous membrane translocation of both charged and uncharged molecules. It is determined not only by the solubility in an organic phase but also by other factors like cholesterol concentration and intrinsic electric membrane potentials.



Chem. Rev. 2019, 119, 5922–5953

Обзоры по моделированию коэффициента проникновения пробы в мембрану

CHEMICAL REVIEWS

Cite This: *Chem. Rev.* 2019, 119, 5954–5997

Review

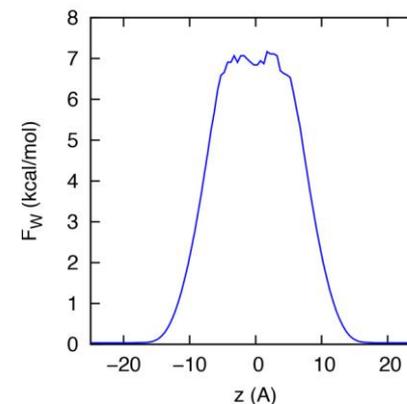
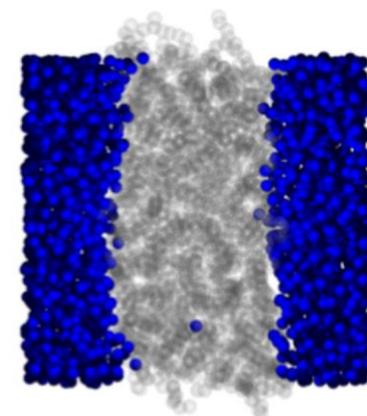
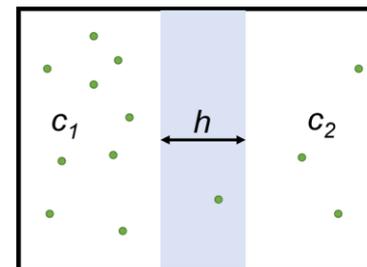
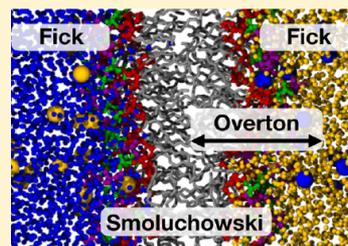
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Molecular Dynamics Simulations of Membrane Permeability

Richard M. Venable, Andreas Krämer,¹ and Richard W. Pastor*¹

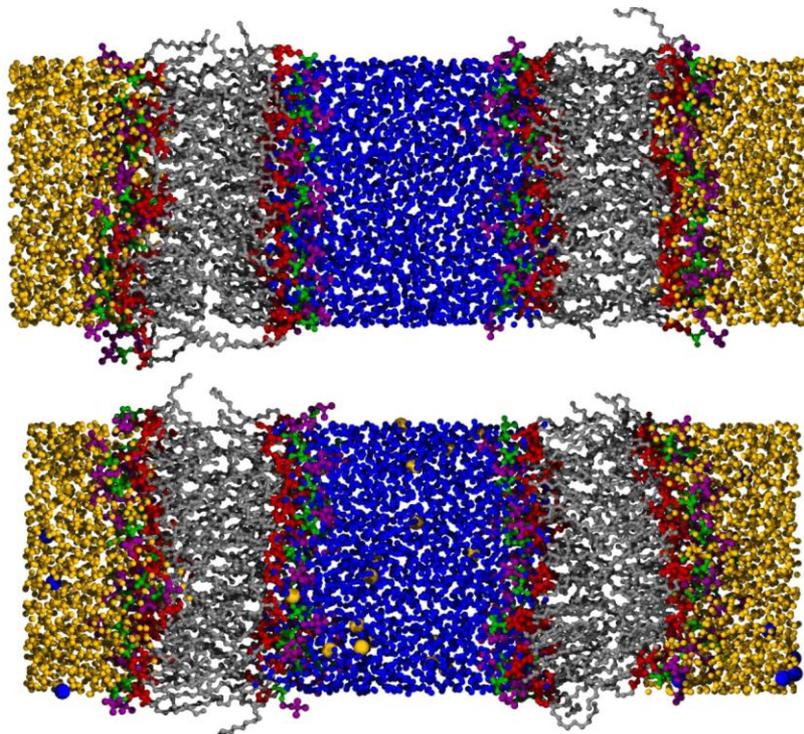
Laboratory of Computational Biology, National Lung, Heart, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, United States

ABSTRACT: This Review illustrates the evaluation of permeability of lipid membranes from molecular dynamics (MD) simulation primarily using water and oxygen as examples. Membrane entrance, translocation, and exit of these simple permeants (one hydrophilic and one hydrophobic) can be simulated by conventional MD, and permeabilities can be evaluated directly by Fick's First Law, transition rates, and a global Bayesian analysis of the inhomogeneous solubility-diffusion model. The assorted results, many of which are applicable to simulations of nonbiological membranes, highlight the limitations of the homogeneous solubility diffusion model; support the utility of inhomogeneous solubility diffusion and compartmental models; underscore the need for comparison with experiment for both simple solvent systems (such as water/hexadecane) and well-characterized membranes; and demonstrate the need for microsecond simulations for even simple permeants like water and oxygen. Undulations, subdiffusion, fractional viscosity dependence, periodic boundary conditions, and recent developments in the field are also discussed. Last, while enhanced sampling methods and increasingly sophisticated treatments of diffusion add substantially to the repertoire of simulation-based approaches, they do not address directly the critical need for force fields with polarizability and multipoles, and constant pH methods.

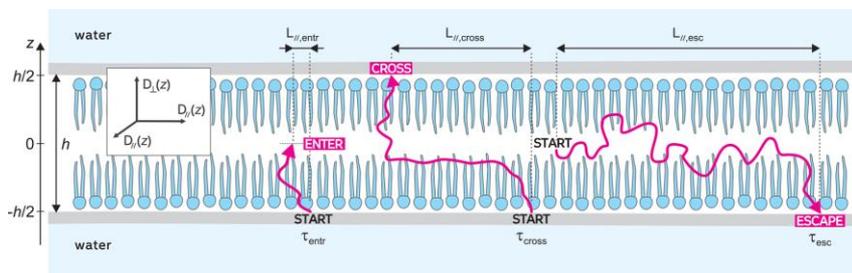


Chem. Rev. 2019, 119, 5954–5997

Обзоры по моделированию коэффициента проникновения пробы в мембрану



Chem. Rev. 2019, 119, 5954–5997



Chemical Reviews

Review

Table 14. Simulations of Permeability of Lipid Bilayers from 2015 to 2018,^a with Citation, Brief Description, Lipids in System, Primary Method, and Last Author

year	ref	subject	lipid ^b	method ^d	last author	
2015	270	nanoparticle induced water and ion leakage	DPPE (CG)	PMF	Murad	
	276	translocation of amphiphilic copolymers	DPPE-like (CG)	PMF, FPT	Sommer	
	258	position and orientation of amitriptyline and clozapine	assorted PC	PMF	Biggin	
	315	insertion of imidazolium-based cations	POPE, POPG	ISDE	Klahn	
	265	water permeation by collapse of cavitation bubbles	POPC (AA and CG)	density	Chipot	
	275	serine-based surfactants as permeation enhancers	DPPE	density	Vaiga	
	294	menthol effects on the stratum corneum	SC ^c (CG)	density	Qiao	
	293	effect of length of CER on water partition	SC (AA and CG)	density	Berka	
	2016	10	review (background, compilation of sims to 2015)			Rowley
		242	review (sampling errors in PMF)			Pomes
178		review (methods for ISDE)			Gumbart	
240		review (alternatives to ISDE)			Shinoda	
241		review (drug partitioning)			Trouillas	
29		method development: first passage times, milestone	single particles	ISDE+ FPT	Amaro	
152		subdiffusion of methanol	POPC	FSE	Chipot	
247		line tension and permeation	CG DPPC	CT	Kindt	
199		GLE for diffusion constant of O ₂ and H ₂ O	DPPE	ISDE+ GLE	Rowley	
255		bias exchange metadynamics to explore Ca _v 2 assay	POPC	J	Lattanzi	
280		aromatic peptides; expt and sim	DOPC	ISDE	Jas	
299		assorted permeants through stratum corneum	SC	ISDE	Rai	
259		nanotripton forms pore-like structures	POPC	density	Pickholz	
314		small molecules through E. coli outer membrane model	LPS, PG/PE, PG, CL	PMF, D(z)	Khalid	
271		PEGylated gold nanoparticle	DPPE (CG)	density	Murad	
296		transdermal delivery of borneol	SC (CG)	density	Qiao	
272		gold nanoparticles through skin	SC (CG)	ISDE	Rai	
300		effects of ceramide chain lengths	CER12–24	ISDE	Rai	
249		monovalent ions (need collective variables)	POPC	2D-US	Wei	
165		trimethoprim with transition-tempered metadynamics	POPC	ISDE	Voth	
246		accelerating PMFs (including system size)	POPC	US	Hab	
284		biphenol A permeation and pore formation	DPPE	US	Wang	
282		aliphatic amine and carboxylic acid drugs	DPPE	ISDE	Seser	
2017		269	review (focus on nanoparticles)			Murad
		158	short chain alcohols	POPC	FSE	Chipot
		13	Bayesian method to obtain diffusion tensor of O ₂	POPC, mitochondrial	ISDE	Hummer
	31	multiscale modeling of ring systems	POPC	ISDE	Duca	
	228	cholesterol effect on O ₂	POPC + chol	CT	Pias	
	230	comparison with EPR measurements of O ₂	POPC + chol	CT	Pias	
	302	cholesterol effect on reactive oxygen (H ₂ O ₂ + others)	DOPC + chol	US	Bogaerts	
	266	electric fields on permeation of reactive oxygen	DOPC	US	Bogaerts	
	301	in silico skin model; fentanyl, caffeine, naphthol	SC (UA)	multiscale	Rai	
	278	fillerene C ₆₀ through skin	SC (CG)	ISDE	Rai	
	273	effect of size and charge of gold nanoparticles	SC (CG)	ISDE	Rai	
	274	proteins with gold nanoparticles	SC (CG)	US	Rai	
	137	Na ⁺ and Cl ⁻ with E field	POPC	NC(2-layer)	Matthai	
	283	pinacetam	DOPC	US	Fernandes	
	245	boosting method for accelerating PMF estimates	DMPC	PMF	Ramos	
	319	calibrating PMF using experimental permeability assay	DOPC	ISDE	Carpenter	
	254	salt dependence of water flux from vesicles	PA+C ₁₂ trimlyline (CG)	CT	Shi	
	264	sampling stratum corneum using steered MD	SC	ISDE	Pedretti	
	320	effect of hydrophobicity of nanoparticles	DPPE (CG)	CT, PMF	Sommer	
	316	mercury complexes through bacterial membrane	POPE+POPG	ISDE	Parks	
261	high-throughput screening	water/octanol (CG)	PMF	Bereau		
295	menthol effects on the stratum corneum	SC (UA)	density	Ming		
257	effect of protonation state/polarizable models	POPC	PMF	Ma		
317	extraction of fatty acyls from microbial hosts	yeast + dodecane layer		Crowley		
2018	298	lateral domains in stratum corneum hinder diffusion	SC	ISDE	Notman	
	311	effect of charged state of D-sotalol	POPC, POPG	ISDE	Vorobyov	
	303	cholesterol effects in O ₂ transport in eye lens	POPC+chol	density, D	Paenikiewicz-Gierula	
	244	methods for free energy profiles	DOPC	PMF	Malbaum	
	277	nanoparticles for enhanced permeation	SC (CG)	PMF	Rai	

Термодинамика распределения аминокислот в системе вода/мембрана

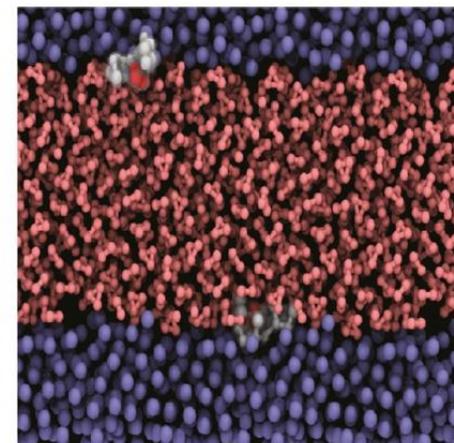
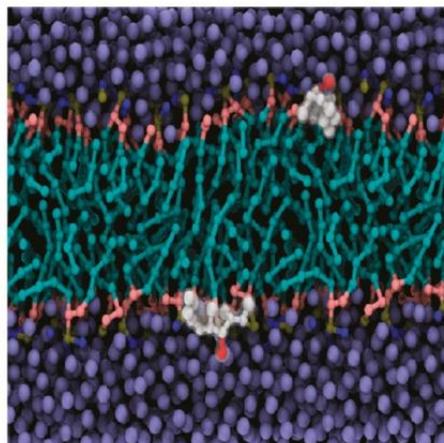
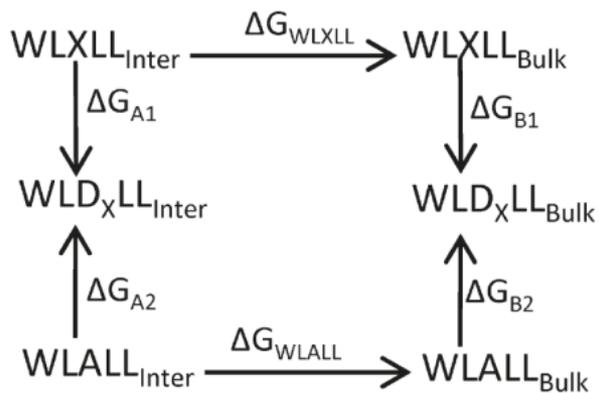
J. Chem. Theory Comput. 2011, 7, 2316–2324

Using the Wimley–White Hydrophobicity Scale as a Direct Quantitative Test of Force Fields: The MARTINI Coarse-Grained Model

Gurpreet Singh[†] and D. Peter Tieleman^{*,†,‡}

[†]Department of Biological Sciences, and [‡]Institute for Biocomplexity and Informatics, 2500 University Drive N.W., University of Calgary, Calgary, Alberta, Canada T2N 1N4

Пример применения фрагментированной модели мембраны и силового поля MARTINI



$$\begin{aligned}
 \Delta\Delta G^{residue} &= \Delta G_{WLXLL} - \Delta G_{WLALL} \\
 &= \Delta G_{A1} - \Delta G_{A2} - (\Delta G_{B1} - \Delta G_{B2}) \\
 &= \Delta G_{A1} - \Delta G_{B1} - (\Delta G_{A2} - \Delta G_{B2}) \\
 &= \Delta G_X - \Delta G_{ALA}
 \end{aligned}$$

Распределение в системе вода/октанол-1

Липофильность (буквально — сродство к жирам) — свойство вещества, означающее его химическое сродство к органическим веществам. И является по сути синонимом гидрофобности.

Экспериментально значение **коэффициента липофильности** определяется при помощи стандартной системы вода/1-октанол. Логарифм коэффициента распределения незаряженных форм субстрата и есть искомая величина, стандартно обозначаемая как $\log P$.

$$\log P_{oct/wat} = \log \left(\frac{[solute]_{octanol}}{[solute]_{water}} \right)$$

Наличие большой экспериментальной базы данных по коэффициентам липофильности различных соединений позволяет применять эти данные для дополнительной термодинамической калибровки сыловых полей для МД расчетов

МД моделирование распределения веществ в системе вода/октанол-1

The MARTINI Force Field

J. Phys. Chem. B, Vol. 111, No. 27, 2007 7817

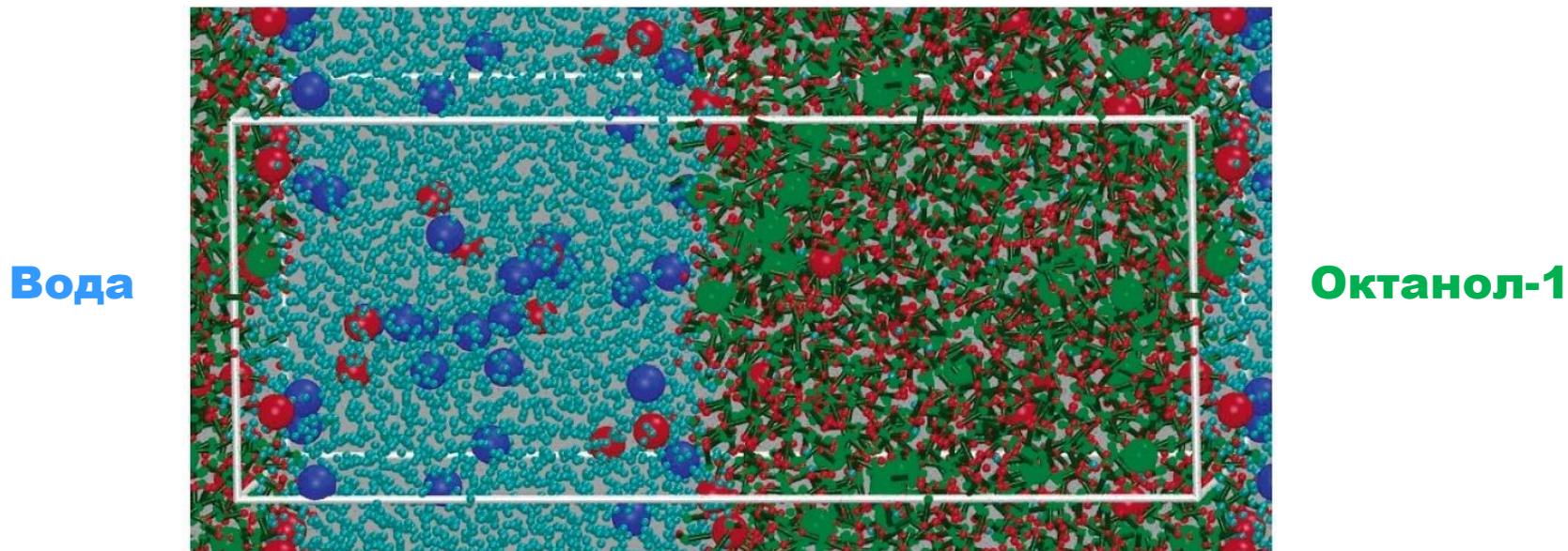
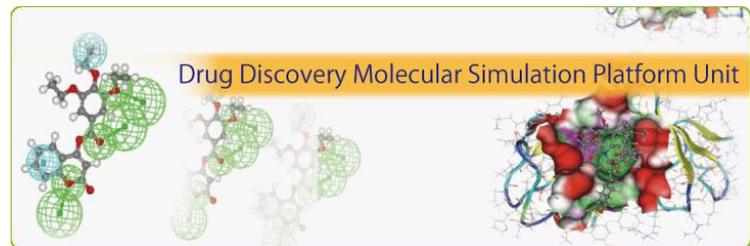


Figure 2. Equilibrium configuration of a water/octanol system used to determine partitioning free energies. Small beads denote the water phase (P_4) in cyan, and the octanol phase consisting of dimers of hydrocarbon (C_1) in green and alcohol (P_1) in red. The larger beads represent solutes: butane (C_1) in green, propanol (P_1) in red, and sodium ions (Q_d) in blue. The simulation box is indicated by thick gray lines.

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Computational Resources for Drug Discovery

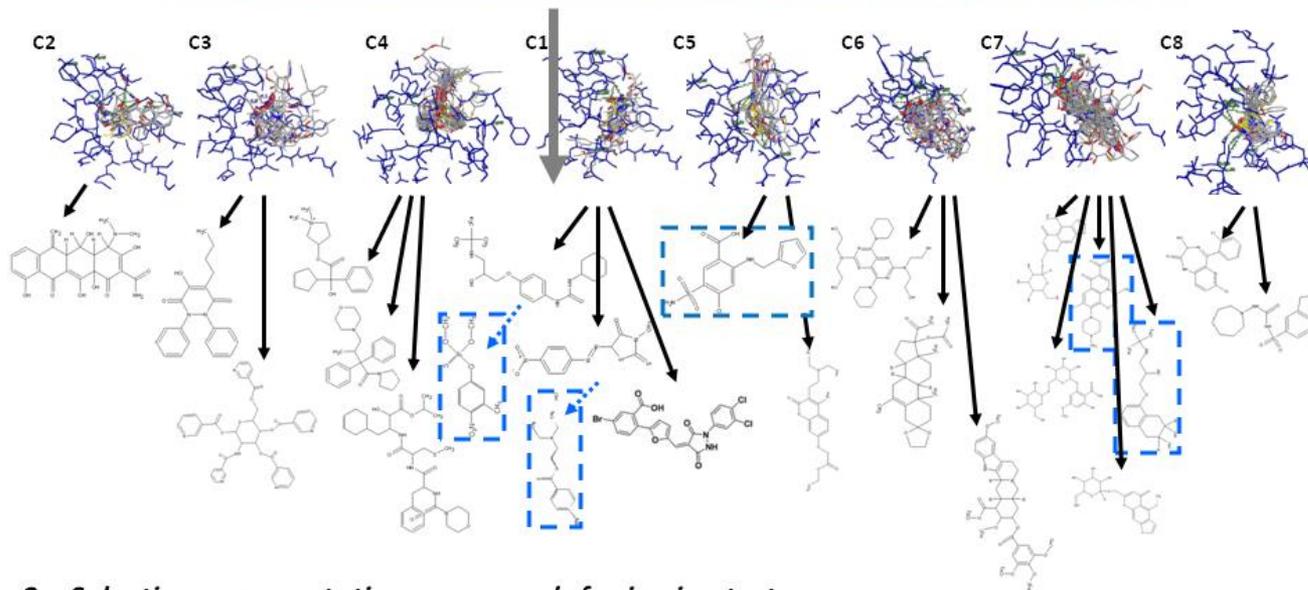
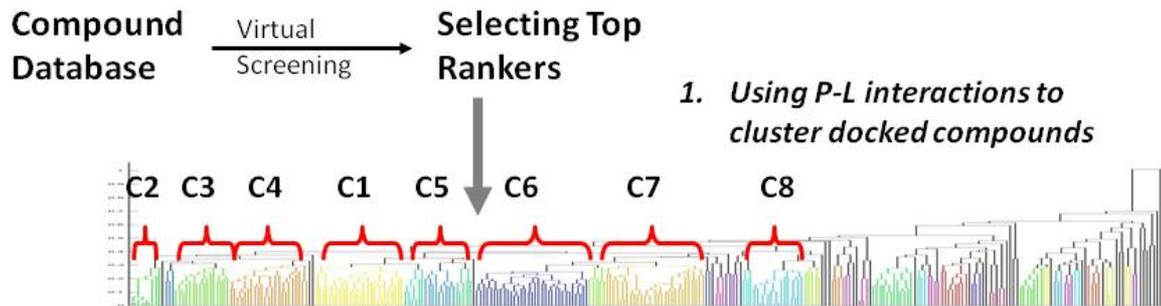
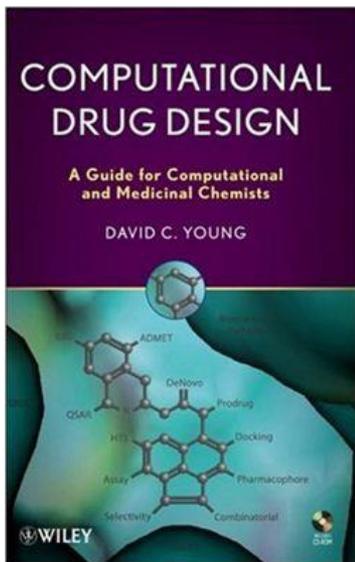
OSDD Forum is an initiative with a vision to provide affordable healthcare to the developing world. The OSDD concept aims to synergize the power of... and facilitate the participation of young and brilliant talent from Universities and industry. It seeks to provide a global platform where the best brains can collaborate on solving problems associated with discovering novel therapies for neglected diseases like Tuberculosis.

CRDD (Computational Resources for Drug Discovery) is an important module of the in silico... platform. Following are major features of CRDD:

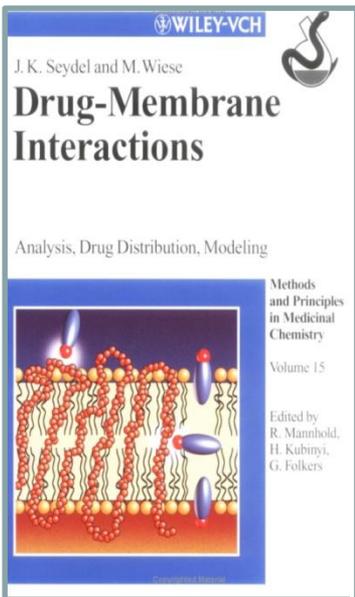
- CRDD provides computational resources for drug discovery.
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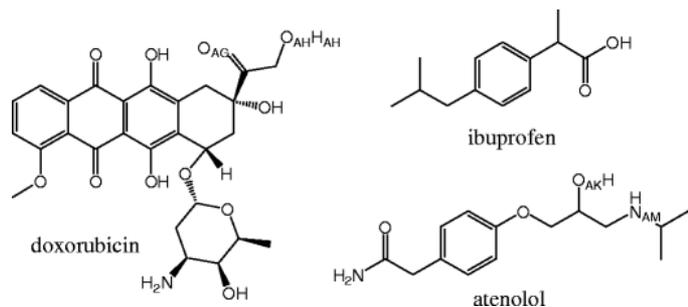
Комбинаторный поиск новых биологически активных соединений



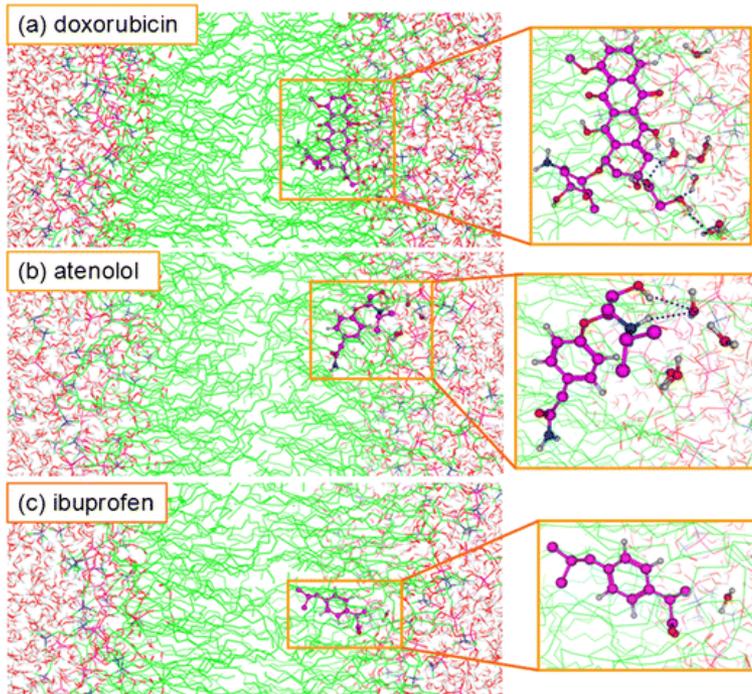
2. *Selecting representative compounds for in vivo test*



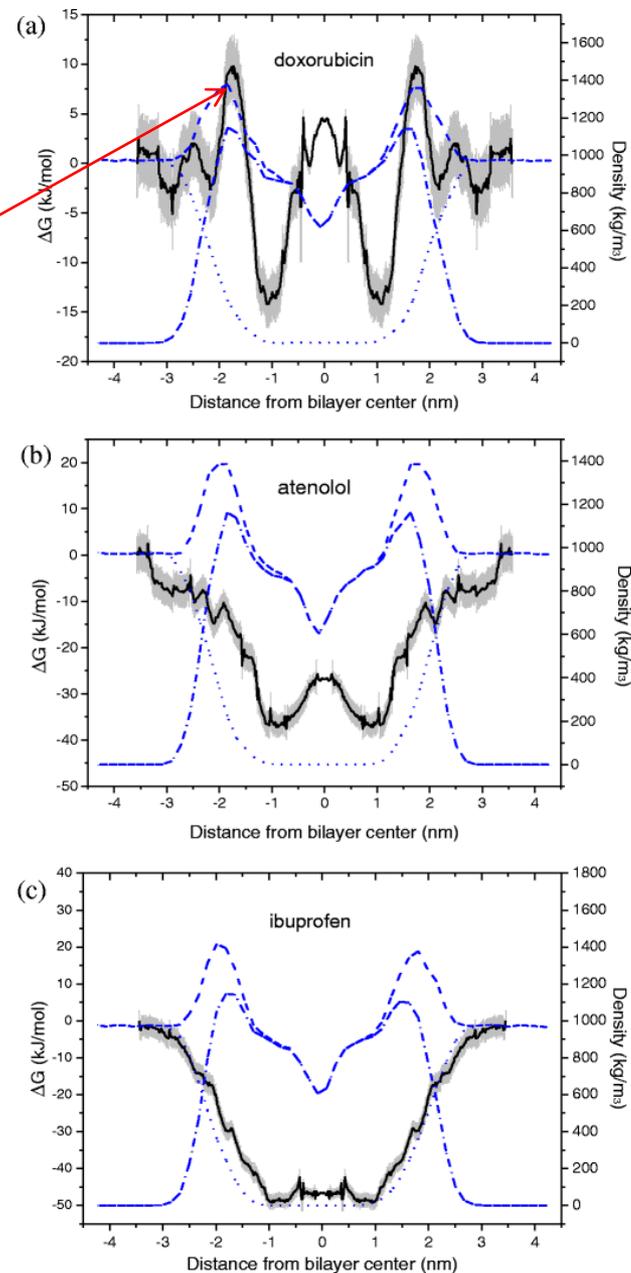
Пример МД моделирования проницаемости лекарственных препаратов через мембрану



**Наличие
Энергетического
Барьера**



Drug
permeability
prediction
using
PMF method,
J. Mol.
Modeling,
2012



Пример МД моделирования проницаемости гидрофобных лекарственных препаратов через мембрану

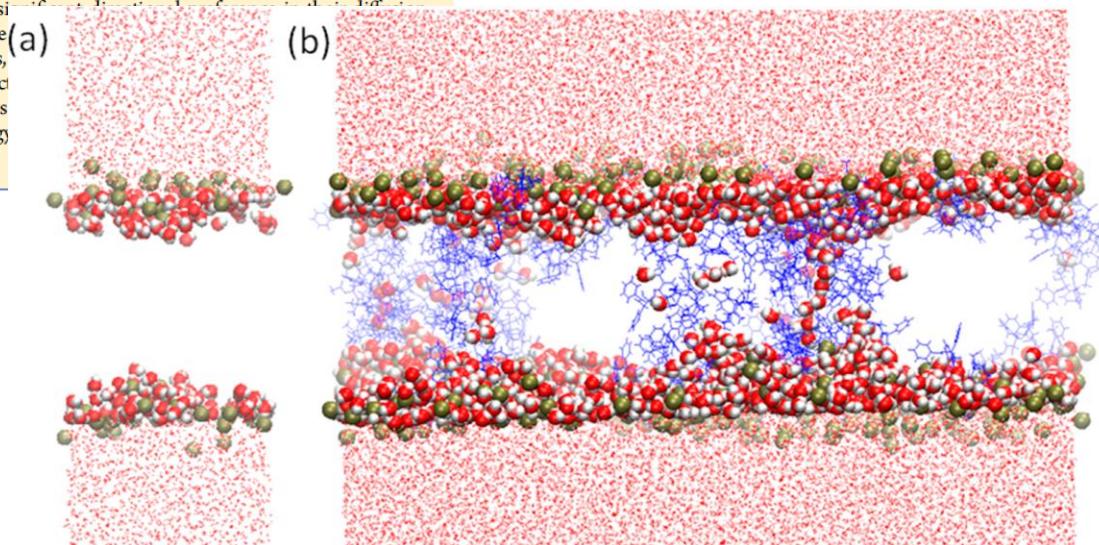
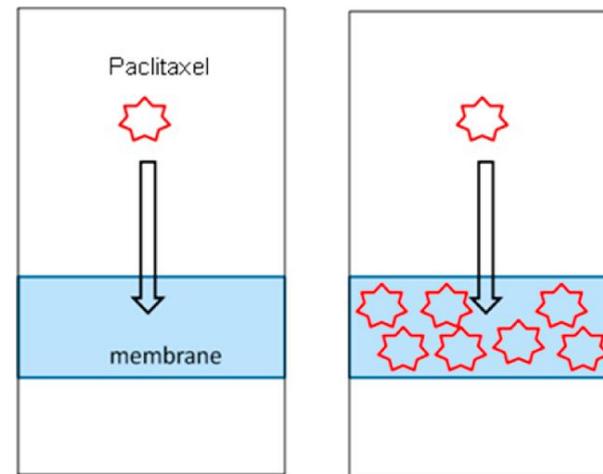
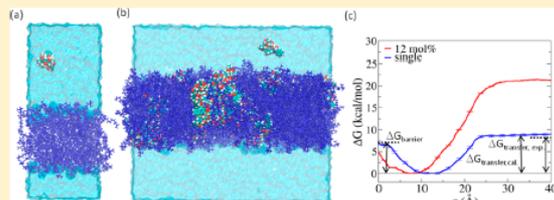
Molecular Simulation of the Concentration-Dependent Interaction of Hydrophobic Drugs with Model Cellular Membranes

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Supporting Information

ABSTRACT: We report here the interactions between a hydrophobic drug and a model cellular membrane at the molecular level using all-atom molecular dynamics simulations of paclitaxel, a hydrophobic cancer drug. The calculated free energy of a single drug across the bilayer interface displays a minimum in the outer hydrophobic zone of the membrane. The transfer free energy shows excellent agreement with reported experimental data. In two sets of long-time simulations of high concentrations of drug in the membrane (12 and 11 mol %), the drugs display substantial clustering and rotation with si... The main taxane ring partitions in the outer hydrophobic zone, while the hydrophobic core of the membrane. The clustering of the drug molecules, penetration suggest that the fluidity and permeability of the membrane are affected. Furthermore, at the high-concentration limit, the free energy minimum shifts barrier to cross the membrane decreases. Moreover, the transfer free energy increasing concentration facilitates drug partitioning into the membrane.



J. Phys. Chem. B 2014, 118, 11965–11972

Рекомендуемая литература

[1] Martinez-Seara H. and Róg T., Molecular dynamics simulations of lipid bilayers: Simple recipe of how to do it, *in Biomolecular simulations*, L. Monticelli and E. Salonen, Editors. 2013, Humana Press. p. 407-429.

[2] Computer simulations of transport through membranes: Passive diffusion, pores, channels and transporters / Tieleman D. Peter // Proc. Australian Physiol. Soc. — 2006. — V. 37, — P. 15-27.

[3] The importance of membrane defects—lessons from simulations / Bennett W. F. D. and Tieleman D. P. // Acc. Chem. Res. — 2014. — V. 47, № 8. — P. 2244-2251.

