Pushing the boundaries of computational biology with interdisciplinary approaches

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INTRODUCTION

Computational biology greatly benefits from approaches such as **molecular dynamics simulations**. This field is literally exploding with the advent of a continually growing body of large experimental structures and more and more powerful computers. Here I present examples pushing either the time scales or system sizes, reaching microsecond long simulations for systems comprising between hundreds of thousands and five million particles. Handling such complex structures calls for new tools and I highlight the potential of **interactive** approaches for hypothesis generation and circumventing issues of conventional approaches.

A related issue concerns the ever-increasing amount of data generated by such simulations, which calls for new tools to analyze and **visualize** them.

I illustrate these aspects with several **biological systems** of direct medical interest such as the bacterial pentameric ligand-gated ion channel GLIC, a promising model for improving our understanding of neurotransmission and anesthesia. Other examples concern a full-fledged model of an entire influenza virion, membrane fusion mediated by the SNARE complex and a range of enzymatic systems.

Fig. 1 Word-cloud summarizing my research themes

BIO-MEMBRANES and PROTEINS

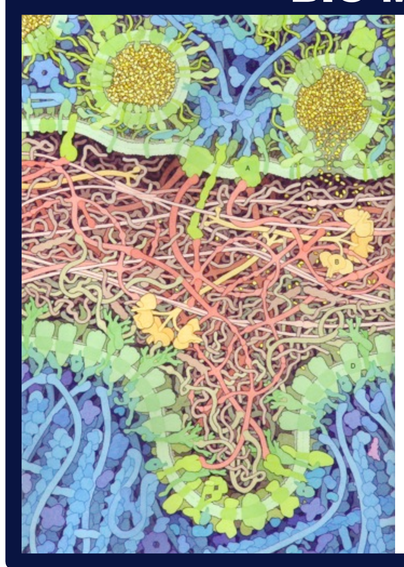
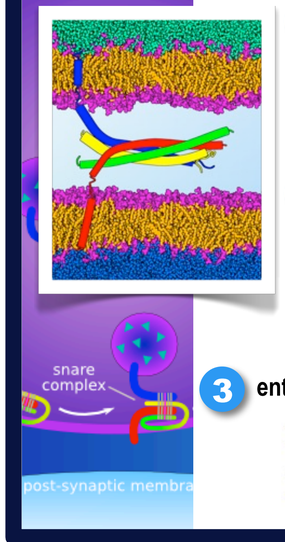


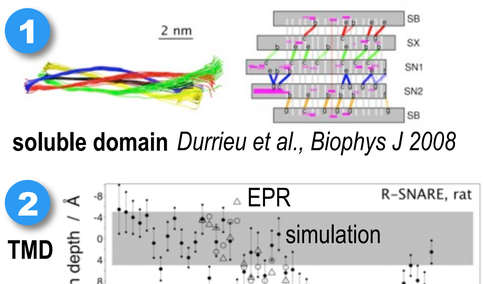
Fig. 2 The synapse painted by David Goodsell. SNARE-mediated vesicle fusion shown in the upper part leads to neurotransmitter release. SNARE proteins form bundles that are anchored within the vesicle and synaptic membranes. Neurotransmitter diffuses across the synaptic cleft activating receptors on the post-synaptic membrane, leading to ion flux. The nicotinic acetylcholine receptor is an example belonging to the Cys-loop family. GLIC is a prokaryotic homolog of these pentameric ligand-gated ion channels.

Biological membranes determine many processes of central importance that are governed by membrane proteins, ingenious nano-machines designed to transmit signals, catalyse chemical reactions or carry out mechanical work. They may work alone (for example the **GLIC** ion channel), grouped together in small assemblies (for example the four-helical **SNARE** bundle) or cooperatively (as in **viral** proteins).

1- SNARE PROTEINS and MEMBRANE FUSION

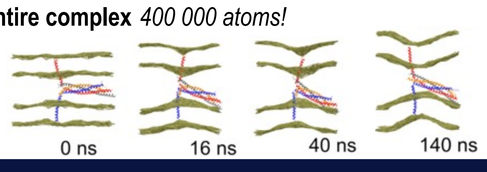


1 **soluble domain** *Durrieu et al., Biophys J 2008*



2 **TMD** *Durrieu et al., ChemPhysChem 2009*

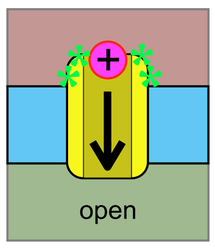
3 **entire complex** *400 000 atoms!*



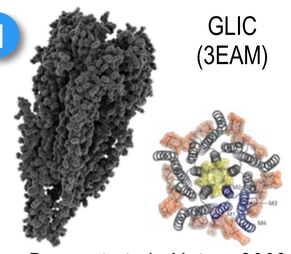
Exocytosis involves transporting molecules stored within lipid vesicles across vesicle and cell boundaries. This process requires **fusion** of the vesicles with the cell membrane mediated by **SNARE** proteins. Their function requires specific properties, possibly to actively pull and hold together both membranes.

Atomistic simulations of the SNARE complex embedded between two lipid bilayers show membrane **bending** compensating for expansion and pressure buildup, while the trans-membrane domains (TMD) remain firmly inserted within the bilayers.

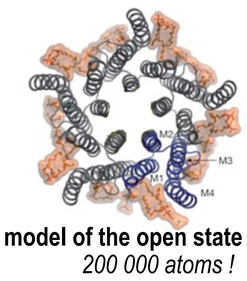
2- NEUROTRANSMISSION and the GLIC ION CHANNEL



1 GLIC (3EAM)



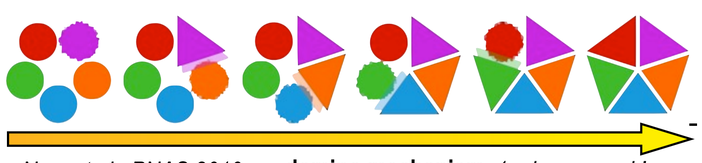
Bocquet et al., Nature 2009



model of the open state *200 000 atoms !*

- model for eukaryotic pLGICs
- Gloeobacter violaceus (GLIC)
- open state at acidic pH (~4.5)
- xtal shows detergent in the pore
- MD simulation in lipid bilayer
- water-filled pore stable (20 ns)

2

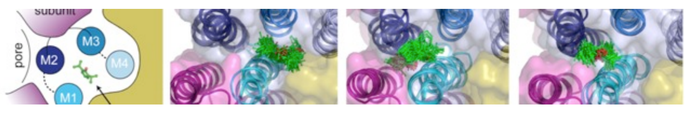


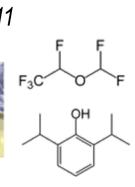
Nury et al., PNAS 2010 **domino mechanism** *1 microsecond !*

- gated by protons
- pH jump: closure
- sequential mechanism
- M2 helices central

3

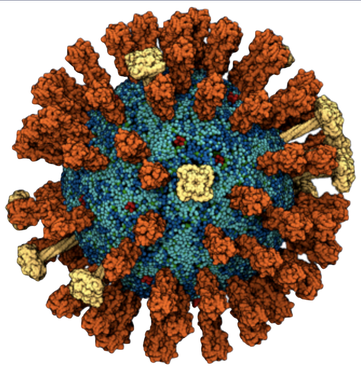
Nury et al., Nature 2011



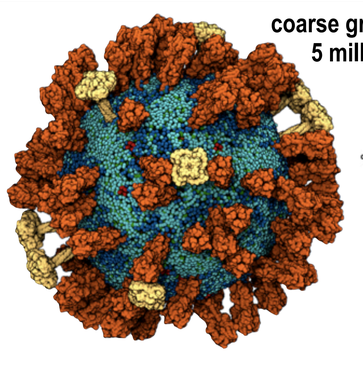


- propofol
- desfluran
- T255A
- V242M

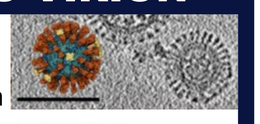
3- MEMBRANE PROPERTIES of an entire FLU VIRION



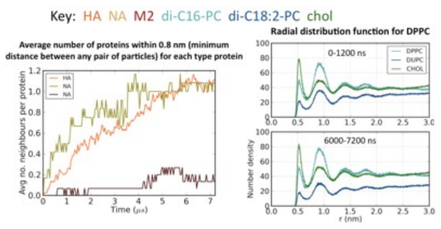
7.2 µs



coarse grained model
5 million particles



100 nm



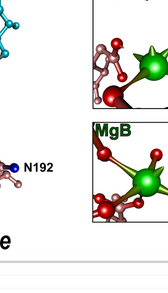
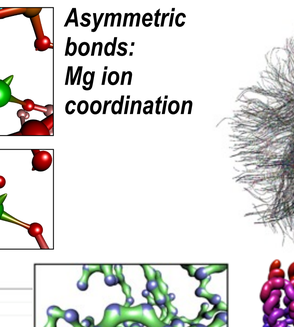
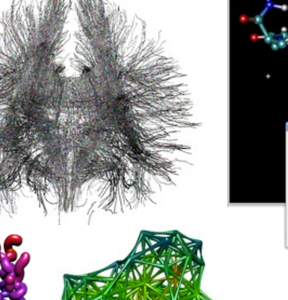
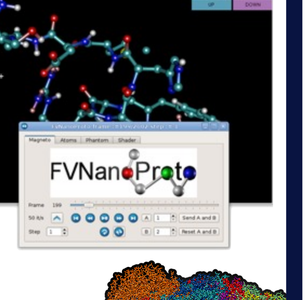
D. Parton, M. Baaden, M. Sansom (Oxford)

To assemble, the influenza virus is thought to utilise lipid rafts. The hemagglutinin and neuraminidase envelope proteins are known to associate with rafts, while the M2 channel may associate at the periphery of rafts.

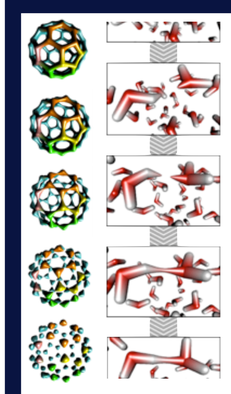
We hope to investigate the effect of high protein concentration on membrane organization and dynamics using a realistic model of an entire influenza A virus envelope. First results add to our understanding of lateral membrane sorting.

INTERACTIVE SIMULATIONS and VIRTUAL REALITY

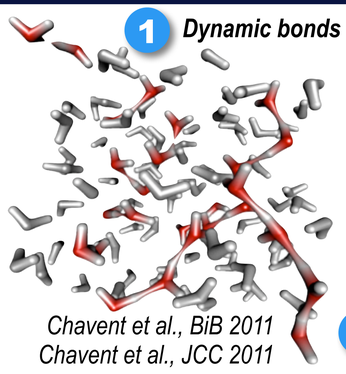
Interactive simulations are precious in exploring and generating **hypotheses**. They introduce **human expertise** and benefit from the user's experience and insight. Using a 3D **haptic** device, molecules can be manipulated with great precision and interactions can be felt in real time *via* tactile feedback. Below, interactive approaches to study macromolecular structure, flexibility and interactions are shown using interactive molecular dynamics or elastic networks with our own BioSpring tool. The latter has been tested in a recent CAPRI round to guide and constrain docking. Macromolecular interactions can be refined *via* a user-guided set of **constraints**, interactive **deformations** and manual **assembly** steps. Such methods enable expert guided modelling experiments. For the purpose of these simulations, we have developed a **freely available software library** called MDDriver. It facilitates the implementation and application of interactive simulations such that it becomes very easy to render any particle-based molecular simulation or docking engine interactive.

Tools	***Steering, deformation, ..***	***BioSpring software** (OpenMP, OpenCL..)* ***Ion binding***	***Interactive docking***	***(Re)Construction***
MDDriver *mddriver.sourceforge.net*				
FVNano *www.baaden.ibpc.fr/projects/fvnano/*	*J Comput Chem '09*	*PSB 2010*	*CAPRI 2009*	*NAR 2010*
bioSPRING *InTech Book chapter (in press)*				

MOLECULAR VISUALIZATION

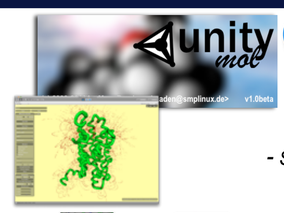


1 ***Dynamic bonds***

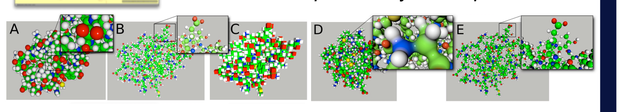


Chavent et al., BiB 2011
Chavent et al., JCC 2011

4 ***UnityMol, a game-engine implementation***



- *optimized performance*
- *webplayer as browser plugin*
- *standalone MacOSX & Windows*
- *particle system optimizations*



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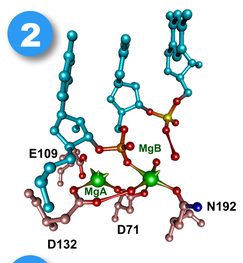
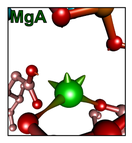


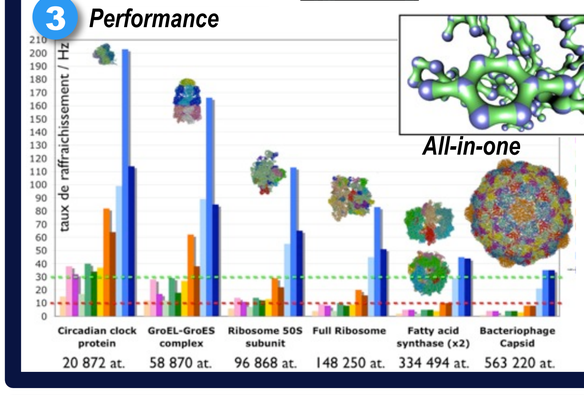


Asymmetric bonds: Mg ion coordination

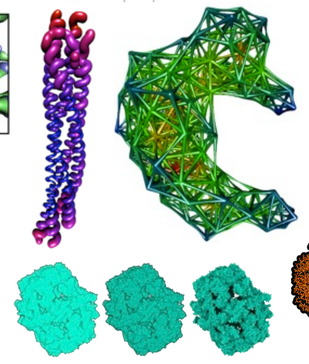
6 ***Many Examples***

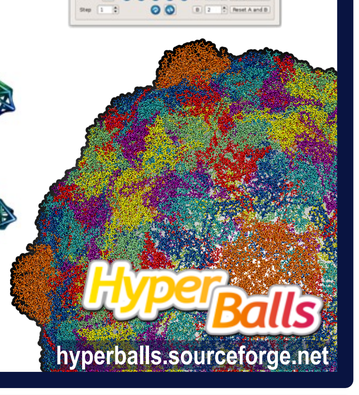
5 ***FvNano-based molecular dynamics trajectory viewer***

3 ***Performance***



All-in-one





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