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Master2 internship
Building models for organelles with the CellBuilder

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Project description

The next frontier of molecular simulations is simulating entire organelles and eventually entire cells. Simulations of such large systems have the potential to elucidate the details of the interactions among different components of the system, and hence will be extremely useful to interpret experiments on inter-molecular interactions and the functioning of cellular machineries. The first simulation of an organelle has been published a few months ago in the prestigious journal *Cell*: simulations of an entire photosynthetic chromatophore vesicle from a purple bacterium [1]. The effort was heroic, as it required the coordinated work of 7 research teams, 5 years of work, and an extraordinary computational cost. Similar endeavours are difficult to replicate: not only the computational time required is prohibitive, but especially the amount of human effort needed to build an initial structure of the system is out of reach for academic groups. Two bottlenecks exist: (1) the computational cost, and (2) producing a suitable starting configuration of the system. The issue of computational cost can be tackled by the use of coarse-grained models, of which many varieties exist. As for building complex systems, semi-automatic methods already exist, but their usage is far from intuitive – which poses major limitations to their utilization by the vast biological audience. The MOBI team has started to tackle both bottlenecks, through the development of one coarse-grained model, named MARTINI [2, 3], enabling a 1000-fold speed-up of molecular simulations, and the development of a graphical interface to automatically build complex membrane systems (the MArtini Database server, MAD).

Here we propose the development of a graphical user interface (GUI) named the *CellBuilder*, enabling the construction of complex biological systems, including organelles and their content, in terms of coarse-grained models for all the molecules in the system. The *CellBuilder* will produce cartesian coordinates for all molecules in any given systems, a description of their connectivity (i.e., internal bonds, angles, etc.), as well as intra- and inter-molecular forces, within the framework of the well-established MARTINI coarse-grained representation. The engine of the *CellBuilder* will rely on existing, efficient algorithms to convert triangulated surfaces into a coarse-grained representation. A proof-of-concept for these algorithms has

been recently published by our collaborators at the University of Groningen [4]. Moreover, the *CellBuilder* will enable transforming the coarse-grained structures and topologies into all-atom structures and topologies, when it is necessary to provide a more detailed view of the system. The *CellBuilder* will allow real-time visualization of the systems built, and easy access to the options for setting up simulations.
From the technical standpoint, the *CellBuilder* interface will consist in a web client providing access to a database of coarse-grained molecules recently developed in our team (MAD database). Calculations will be performed in Python on the local computer cluster, accessible through a NodeJS back-end server. Depending on the technical level of the applicant, the web interface may use simple (jquery) or more advanced JavaScript libraries (React or vueJS) to manage the input to calculation and the display or results. Single molecule and larger systems will be displayed interactively in 3D in a browser, using JavaScript webGL technology.

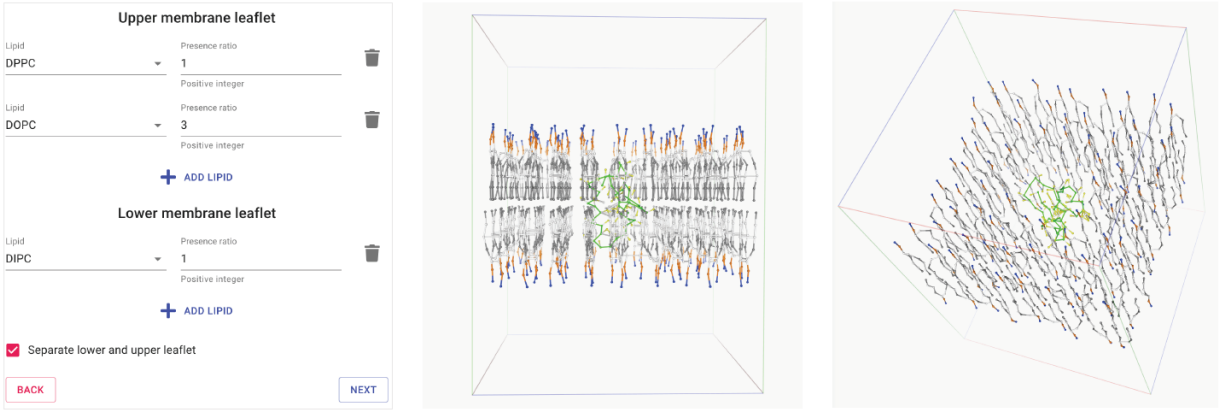

Figure 1. The current web interface for generating lipid membranes around membrane proteins. Lipids and other small molecules are available from the MAD database, while all-atom protein structures are converted on-the-fly into coarse-grained models by the martinize Python script.

The software will allow building entire cells, including bacterial cells and eukaryotic cells, comprising organelles and their content. Such complex models, in turn, will allow studying the interactions (e.g., protein-protein, protein-nucleic acid, etc.) responsible for the functioning of a wide variety of processes within cells and organelles.

References

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4. Pezeshkian W, König M, Wassenaar TA, & Marrink SJ (2020) *Nat Comm* 11(1):2296.