QwikMD – Integrative Molecular Dynamics Toolkit for Novices and Experts

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Supplementary Note S1

Using Google Scholar data, plots presented at Figure 1B are based on the number of citations per year of the following manuscripts for each software.

AMBER:

• Case, D. A., Cheatham, T. E., Darden, T., Gohlke, H., Luo, R., Merz, K. M., ... & Woods, R. J. (2005). *The Amber biomolecular simulation programs*. Journal of Computational Chemistry, 26(16), 1668-1688.

• Pearlman, D. A., Case, D. A., Caldwell, J. W., Ross, W. S., Cheatham, T. E., DeBolt, S., ... & Kollman, P. (1995). *AMBER, a package of computer programs for applying molecular mechanics, normal mode analysis, molecular dynamics and free energy calculations to simulate the structural and energetic properties of molecules.* Computer Physics Communications, 91(1), 1-41.

• Weiner, P. K., & Kollman, P. A. (1981). *AMBER: Assisted model building with energy refinement. A general program for modeling molecules and their interactions.* Journal of Computational Chemistry, 2(3), 287-303.

CHARMM:

• Brooks, B. R., Brooks, C. L., MacKerell, A. D., Nilsson, L., Petrella, R. J., Roux, B., ... & Caflisch, A. (2009). *CHARMM: the biomolecular simulation program.* Journal of Computational Chemistry, 30(10), 1545-1614.

• Brooks, B. R., Bruccoleri, R. E., Olafson, B. D., States, D. J., Swaminathan, S., & Karplus, M. (1983). CHARMM: *A program for macromolecular energy, minimization, and dynamics calculations.* Journal of Computational Chemistry,4(2), 187-217.

GROMACS:

• Pronk, S., Páll, S., Schulz, R., Larsson, P., Bjelkmar, P., Apostolov, R., ... & Hess, B. (2013). *GROMACS 4.5: a high-throughput and highly parallel open source molecular simulation toolkit.* Bioinformatics, 29(7), 845-854.

• Hess, B., Kutzner, C., Van Der Spoel, D., & Lindahl, E. (2008). *GROMACS 4: algorithms for highly efficient, load-balanced, and scalable molecular simulation.* Journal of Chemical Theory and Computation, 4(3), 435-447.

• Van Der Spoel, D., Lindahl, E., Hess, B., Groenhof, G., Mark, A. E., & Berendsen, H. J. (2005). *GROMACS: fast, flexible, and free.* Journal of Computational Chemistry, 26(16), 1701-1718.

• Lindahl, E., Hess, B., & Van Der Spoel, D. (2001). *GROMACS 3.0: a package for molecular simulation and trajectory analysis.* Molecular Modeling Annual, 7(8), 306-317.

• Berendsen, H. J., van der Spoel, D., & van Drunen, R. (1995). *GROMACS: a message passing parallel molecular dynamics implementation*. Computer Physics Communications, 91(1), 43-56.

LAMMPS:

• Plimpton, S. (1995). *Fast parallel algorithms for short-range molecular dynamics.* Journal of Computational Physics, 117(1), 1-19.

NAMD:

• Phillips, J. C., Braun, R., Wang, W., Gumbart, J., Tajkhorshid, E., Villa, E., ... & Schulten, K. (2005). *Scalable molecular dynamics with NAMD.* Journal of Computational Chemistry, 26(16), 1781-1802.

• Kalé, L., Skeel, R., Bhandarkar, M., Brunner, R., Gursoy, A., Krawetz, N., ... & Schulten, K. (1999). *NAMD2: greater scalability for parallel molecular dynamics.* Journal of Computational Physics, 151(1), 283-312.

VMD:

• Humphrey, W., Dalke, A., & Schulten, K. (1996). *VMD: visual molecular dynamics.* Journal of Molecular Graphics, 14(1), 33-38.

QwikMD: How to Prepare HIV-Protease's Molecular Dynamics Simulations

1 To perform an MD simulation of the M36I mutant of the HIV-Protease first select "Easy Run".

2 Load the HIV Protease structure by typing the PDB ID: 1KJF and by pressing the "Load" button.

3 A warning message provides information on possible problems found in the structure.

One or more warnings were generated during structure check routines. Please refer to the "Structure Manipulation" window to fix them

4 A visual inspection is always important. Always make a visual check by rotating and looking at details of the molecular system. Molecules not recognized by QwikMD will have their colors throbbing.

5 To facilitate visualizing the complex structure one can turn off the representation of water molecules present in the crystallographic structure. Click in "VDW" representation of water and select "Off".

6 A visual inspection of the loaded structure shows a few small molecules and ions with their colors throbbing. QwikMD did not identify these molecules and ions as having force field parameters available, at least not with the name they are presented in the PDB file.

7 To investigate the origin of the problems presented in steps 3, 4 and 6 open the Structure Manipulation window. The Structure Manipulation window is the only extra window directly associated with QwikMD. It is responsible mainly for the automatic check of the structure, point mutations, and for changes in protonation states.

8 The structure check shows that topologies and parameters are missing; and that some torsion angles are considered outliers in the Ramachandran plot.

9 Check the molecules and ions that have missing topologies and parameters, which are marked in red. The name ACT for Acetate is not the same as the name in the CHARMM36 force field.

10 To rename the Acetate select "Rename" and click on the name ACT. A list of possible substitutes will become available, select Acetate.

11 QwikMD automatically detects that other molecules have the same name (resname) and asks if they should all be renamed. Click "Yes".

One or more residues can be rename based on the chosen residue name. Do you want to rename all?

12 After renaming ACT to Acetate, check if the problems were fixed by clicking the "Check" button in the Structure Check section.

13 Here, the Ramachandran Outliers can be ignored. To learn how to fix a problem found by QwikMD's Structure Check click on the hyperlink (in blue) when a problem is found.

14 To ignore the outliers in this simulation just click on "Ignore".

15 The mutation M36I is known to influence the flexibility of HIV Protease and its complexed substrats. To prepare this mutation select "Mutate". On the amino acid sequence table click on the Methionine (MET) ResID 36 of the protein chain A, and select Isoleucine (ILE).

16 The M36I mutation is then shown in the amino acid sequence table.

17 Now, as the HIV protease is a homodimer, one needs to make the same mutation M36I for the chain B. To prepare this mutation follow the same steps of "Step 15" and select "Mutate" on the top-right corner of the Structure Manipulation window. On the amino acid sequence table click on the Methionine (MET) ResID 36 of the protein chain B, and select Isoleucine (ILE).

18 Select the "Molecular Dynamics" tab.

19 Select Explicit Solvent.

20 Select 0.15 mol/L of NaCl.

21 Set "Temperature" to 27C and "Simulation Time" to 100ns.

22 Select "Equilibration" and "MD" as the Protocol of the Simulation. In the "Easy Run" mode, QwikMD Equilibration includes Energy Minimization and Annealing steps.

23 To prepare all the files necessary for the simulation click "Prepare". This step can take a few minutes.

24 A visual inspection is always important. Make sure everything looks as expected. QwikMD automatically makes a very simple water box representation, helping the user to better observe the protein and the substrates inside the water box.

25 To start the simulation click on the "Start" button.

Supplementary Figure S3

QwikMD: How to Prepare Glycoside Hydrolase's Molecular Dynamics Simulations
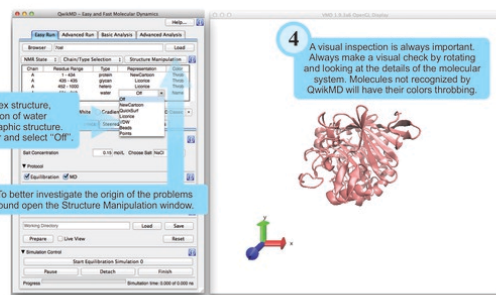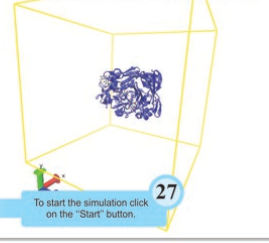

1 To perform an MD simulation of the Cel7A Glycoside Hydrolase first select "Easy Run"
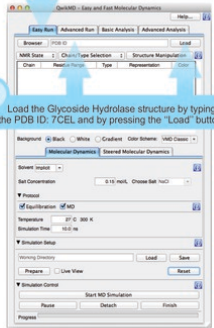
2 Load the Glycoside Hydrolase structure by typing the PDB ID: 7CEL and by pressing the "Load" button.

**3** A warning message provides information on possible problems found in the structure.

4 A visual inspection is always important. Always make a visual check by rotating and looking at the details of the molecular system. Molecules not recognized by QwikMD will have their colors throbbing.

5 To facilitate visualizing the complex structure, one can turn off the representation of water molecules present in the crystallographic structure. Click in "VDW" representation of water and select "Off".

6 To better investigate the origin of the problems found open the Structure Manipulation window.

7 The structure check shows that topologies and parameters are missing; there are sequence Gaps; and some torsion angles are considered outliers in the Ramachandran plot.

8 The first problem we already see is marked in red in the first residue. Originally a GLU this amino acid was substituted by a cyclic amino acid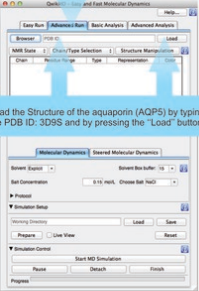 (PCA), that is known to stabilize this enzyme. PCA is not a standard molecule in the CHARMM force field and can be substituted back to a glutamic acid (GLU). To do that, select "Rename" and, clicking on PCA, select to change it to a GLU.

9 Scrolling through the amino acid sequence table, more unrecognized molecules are found. BGC, the glucose chain, is not recognized as such. To change the type of the molecule click on "Type" and clicking on hetero, select to change it to "glycan".

10 QwikMD automatically detects that other molecules have the same type and asks if they should all be renamed. Click "Yes".

11 With the correct type selected you can now rename the BGC to the name known by the CHARMM force field. Select "Rename" and click on BGC and select the molecule name: beta-D-glucose.

12 QwikMD automatically detects that other molecules have the same name (resname) and asks if they should all be renamed. Click "Yes".

13 Cobalt ion (CO) and N-acetyl-D-glucosamine (NAG) are present in the crystal structure, but are only part of the crystallization buffer. To remove CO and NAG molecules, which are not necessary in our simulation, select "Delete", mark the molecules to be removed, and click "Apply".
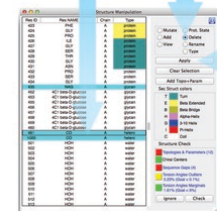
14 After fixing the problems marked in red in the amino acid sequence table check if the problems are fixed. Click the "Check" button in the Structure Check section.

15 Here, the Ramachandran Outliers can be ignored. To learn how to fix a problem found by QwikMD's Structure Check click on the hyperlink (in blue) when a problem is found. The Sequence Gaps can also be ignored as, in this case, they are not real gaps in the protein sequence. To ignore the "warnings" click "Ignore"

16 Make sure no problems or warnings are found before moving to the next steps.

17 To obtain a crystallographic structure of the enzyme with its substrate, a mutation was performed in the catalytic amino acid. In the case of PDB 7CEL the mutation performed was E217Q. This information is found in the protein data bank website (www.pdb.org). To perform this mutation, select "Mutate" and click on the GLN217 to select GLU.

18 Glutamic Acid (GLU) is "active" to start the hydrolysis process only when it is protonated. To protonate GLU217, select "Prot. State", click on the GLU217 and select GLUP.

19 The E217Q mutation, and the change of GLU's protonation state are then shown in the amino acid sequence table.

215	ILE	A	protein
216	TRP	A	protein
217	GLN -> GLU -> GLUP	A	protein
218	ALA	A	protein
219	ASN	A	protein
220	SER	A	protein
221	ILE	A	protein

20 Select the "Molecular Dynamics" tab.
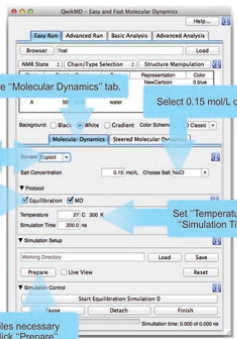
21 Select Explicit Solvent

22 Select 0.15 mol/L of NaCl

23 Select "Equilibration" and "MD" as the Protocol of the Simulation. In the "Easy Run" mode, QwikMD's Equilibration includes Energy Minimization and Annealing steps.

24 Set "Temperature" to 27C and "Simulation Time" to 200ns.

25 To prepare all the files necessary for the simulation click "Prepare". This step can take a few minutes.

26 A visual inspection is always important. Make sure everything looks as expected. QwikMD automatically makes a very simple water box representation, helping the user to better observe the protein and the substrates inside the water box.

27 To start the simulation click on the "Start" button.
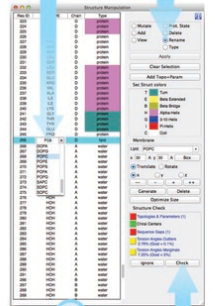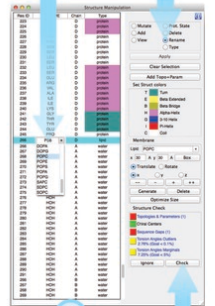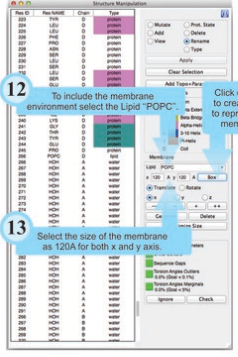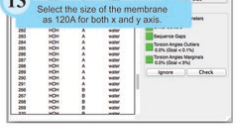
QwikMD: How to Prepare Molecular Dynamics Simulations of a Peptide + Membrane

1. To perform an MD simulation of a membrane system first select "Advanced Run"

2. Load the Structure of the West Nile Virus envelope glycoprotein by typing the PDB ID: 2HG0 and by pressing the "Load" button.

3. A warning message provides information on possible problems found in the structure.

One or more warnings were generated during structure check routines. Please refer to the "Structure Manipulation" window to fix them

4. A visual inspection is always important. Always make a visual check by rotating and looking at the details of the molecular system. Molecules not recognized by QwikMD will have their colors throbbing.

5. Since we are only interested in a small portion of the protein structure, deselect the molecules that we are not interested (A and hetero; A and water) by clicking on "Chain/Type Selection".

6. To better investigate the origin of the problems found when loading the Strucutre, to select the region of interest of the protein and create a membrane, open the Structure Manipulation window.
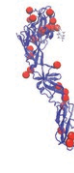
7. Our interest here is to study how a small peptide affects a membrane. The peptide is a part of the of the West Nile Virus envelope glycoprotein. We are interested in the region between amino acids 98 and 110. So, to remove the rest of the protein, select "Delete" and mark the region from ResID 1 to 97 and click "Apply". Repeat this step for the region starting at ResID 111 to the end of the protein.
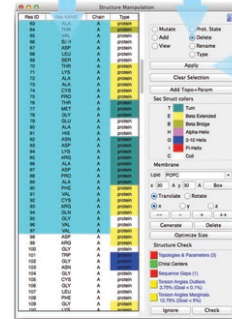
8. After removing most of the protein click on "Check" to verify if problems are found in the peptide structure of interest. Here, the Ramachandran Outliers can be ignored. To learn more about how to fix a problem found by QwikMD's Structure Check click on the hyperlink (in blue) when a problem is found. To ignore the "warnings" click "Ignore"

9. To include the membrane environment, select the Lipid "POPC".

10. Select the size of the membrane, as 50A for both x and y axis.
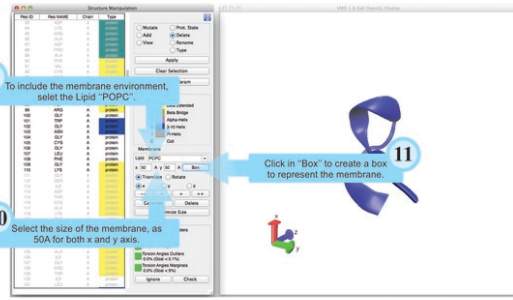
11. Click in "Box" to create a box to represent the membrane.
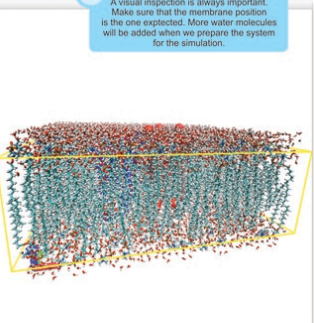
12. Move the box representing the membrane to the desired position by selecting: "Translate"; x, y or z; and by clicking on "–" to move fast in the oposity direction of axis arrow and "-" to move slow in the axis arrow direction. Click on "+" to move fast in the axis arrow direction and "+" to move slow in the same direction. The option "Rotate" alows for a rotation of the box around the axis (x, y or z) selected.
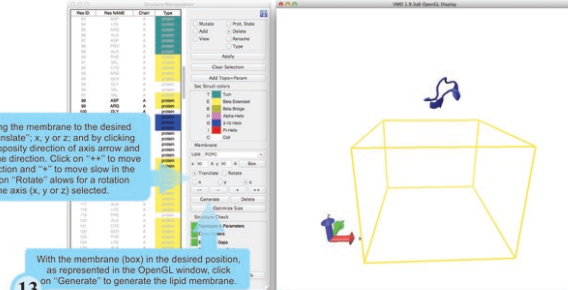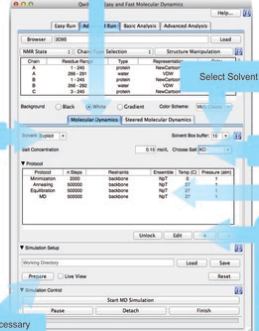
13. With the membrane (box) in the desired position, as represented in the OpenGL window, click on "Generate" to generate the lipid membrane.

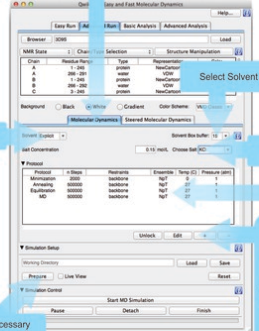14. A visual inspection is always important. Make sure that the membrane position is the one expected. More water molecules will be added, above and below the membrane surface, when preparing the simulation.
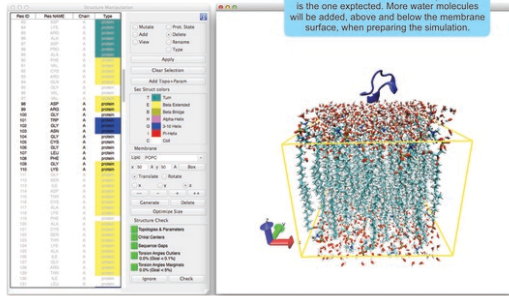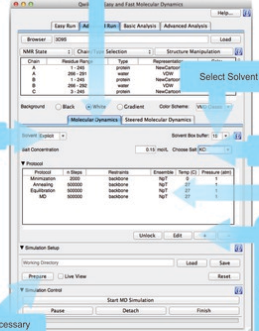
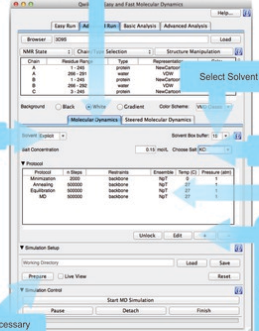15. Select the "Molecular Dynamics" tab.
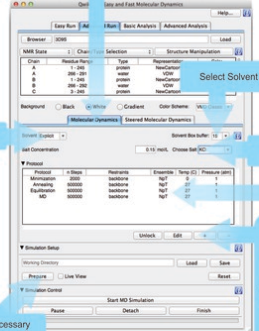
16. Select Explicit Solvent
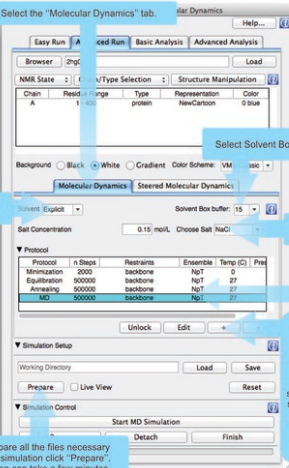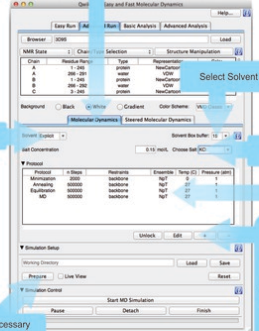
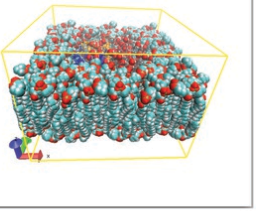17. Select Solvent Box buffer 15Å

18. Select 0.15 mol/L of NaCl

19. Add all the necessary Protocols by clicking on "+" and selecting the Protocol, n Steps, Restraints, Ensemble, Temperature and Pressure, as shown in the Protocol table list. The last step, the MD step, will need repetitions of the same protocol, as more steps will be necessary than the 500,000 steps selected. To repeat the same protocol from the previous simulation select the MD line in the Protocol table and click on "+". Here, it will be necessary to have several repetitions of the MD protocol.
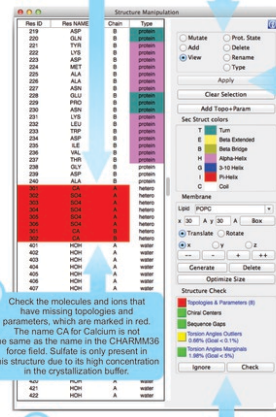
20. To prepare all the files necessary for the simulation click "Prepare". This step can take a few minutes.

21. A visual inspection is always important. Make sure everything looks as expected. QwikMD automatically makes a very simple water box representation, helping the user to better observe the protein and the membrane inside the water box.

22. To start the simulation click on the "Start" button.

QwikMD: How to Prepare Aquaporin's Molecular Dynamics Simulations

Supplementary Figure S6

QwikMD: How to Prepare Cohesin-Dockerin's Steered Molecular Dynamics Simulations