STUDY OF THE INTERACTION BETWEEN GENERAL ANESTHETICS AND A BACTERIAL HOMOLOGUE TO THE HUMAN NICOTINIC RECEPTOR.

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Methods: Extensive Sampling Close To The Crystal Structure

Table 1: Amount of time computed for each system

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>T255A</th>
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<tbody>
<tr>
<td>Desflurane x 5</td>
<td>25 x 8 ns = 200 ns</td>
<td>25 x 8 ns = 200 ns</td>
</tr>
<tr>
<td>Propofol x 5</td>
<td>25 x 8 ns = 200 ns (running)</td>
<td>3 x 25 x 8 ns = 600 ns</td>
</tr>
<tr>
<td>Desflurane x 1</td>
<td>30 x 3 ns = 240 ns (running)</td>
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</tbody>
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Fig. 6 shows sampling of propofol for all subunits for 25 (out of 75) simulations

2 binding sites? 3 sites? more?

- Bacterial homologues of eukaryotic pentameric ligand-gated ion channels (LGICs, Fig. 1) [1,3]
- Structural and functional models of signal transduction in the nervous system.
- Gloeobacter violaceus (GLIC) [1] is gated by protons
- Crystalized at acidic pH [4] with an open pore
- 2 structures of GLIC with general anaesthetics (GA) bound to it: desflurane & propofol [5]

A more detailed contact map

- Hypothesis: «an allosteric effect could prevent GA molecules to go deep inside a cavity once a neighbor cavity is filled»
- Fig. 3 does not show such a behavior, a cooperative effect could even exist (ongoing work).
- Statistical clustering methods can’t discriminate wild-type from mutant channels using MD-based descriptors.

Fig. 5: Normalized number of contacts between the protein and the desflurane. Comparison between WT and T255A mutant. Key residues suggested by crystallography are highlighted in red, contributing residues in blue.

Conclusion - Perspectives

- More statistics is needed to conclude on the potential effect of anesthetic concentration
- More statistics is needed to study the GLIC-propofol interaction (with WT MD simulations)
- Long simulations could provide additional informations on anesthetic induced conformational changes
- Interactive simulations using virtual reality could provide a additional insight in the paths from the solvent to the cavity.

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