Modeling the dystrophin-glycoprotein complex of the muscle cell

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The dystrophin-glycoprotein complex (DGC) is a very large transmembrane protein complex of the muscle cell. The DGC binds on one side through actin to the sarcomeres, that are the contractile units of the muscle fiber, and on the other side to the extracellular matrix. The DGC plays a role in maintaining the structural and functional integrity of muscle fibers. Moreover, some mutations in genes coding for DGC components are responsible for muscular dystrophies. Therefore, studying structure and dynamics of the DGC remains crucial. DGC structures from rabbit and mouse have very recently been resolved by cryo-EM [1][2]. However, these structures are incomplete and no human structure is available. In this context, the objective of this work is to build a model of the human DGC inserted into a membrane. To model the membrane, lipid ratios from experimental data have been integrated into the membrane composition. For the DGC, machine learning methods for structure prediction [3][4] were used to build missing chains, and sequence alignments between human and rabbit/mouse were performed to highlight the residues that had to be mutated to retrieve the human sequence and structure. The human DGC was built into an all-atom model and converted to a coarse-grained model. Membrane was added to the system and we obtained a full human transmembrane DGC. This system will be studied in molecular dynamics simulations to get its behavior and further evaluate the impact of the muscle contraction or of the introduction of known mutations.

Bibliography :

[1] Liu S.; Su T.; Xia X.; Zhou Z.H. Native DGC structure rationalizes muscular dystrophy-causing mutations. Nature, 2025, 637, 1261-1271.
[2] Wan L.; Ge X.; Xu Q.; Huang G.; Yang T.; Campbell K.P.; Yan Z.; Wu J. Structure and assembly of the dystrophin glycoprotein complex. Nature, 2025, 637, 1252-1260.
[3] Jumper J.; Evans R.; Pritzel A.; Green T.; Figurnov M.; Ronneberger O.; Tunyasuvunakool K.; Bates R.; Zidek A.; Potapenko A.; Bridgland A.; Meyer C.; Kohl S.A.A.; Ballard A.J.; Cowie A.; Romera-Paredes B.; Nikolov S.; Jain R.; Adler J.; Back T.; Petersen S.; Reiman D.; Clancy E.; Zielinski M.; Steinegger M.; Pacholska M.; Berghammer T.; Bodenstein S.; Silver D.; Vinyals O.; Senior A.W.; Kavukcuoglu K.; Kohli P.; Hassabis D. Highly accurate protein structure prediction with AlphaFold. Nature, 2021, 596, 583-589.
[4] Passaro S.; Corso G.; Wohlwend J.; Reveiz M.; Thaler S.; Somnath V.R.; Getz N.; Portnoi T.; Roy J.; Strak H.; Kwabi-Addo D.; Beaini D.; Jaakkola T.; Barzilay R. Boltz-2: Towards Accurate and Efficient Binding Affinity Prediction. 2025, https://doi.org/10.1101/2025.06.14.659707.