

Seminari di fisica statistica e teoria della materia condensata

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Connexin 26 structure and function investigated in silico by Molecular Dynamics simulations

About half of all cases of human deafness in countries surrounding the Mediterranean have been linked to mutations in the GJB2 gene, which encodes the gap junction protein connexin 26 (Cx26). We chose a Molecular Dynamics approach aiming to construct a computational environment for the interpretation of experimental results and the prediction of effects not yet observed. Starting from the recently published crystal structure of the Cx26 gap junction channel, we built a fully atomistic model of the Cx26 connexon including plasma membrane phospholipids, water and ions (the whole system contains 206188 atoms) and followed its equilibrium dynamics for about 13 ns. This in silico approach enlivens the "frozen" crystallographic structure of Cx26 and permits us to study the protein in a realistically simulated environment. The analysis of temporal trajectories of each molecule provides critical insight into the interactions that shape the tertiary and quaternary structure of the protein complex. In addition, we can simulate equilibrium thermal fluctuation of the protein and study the dynamics of ions and secondary messenger transit through the pore, which provides invaluable mechanistic insight into channel function and dysfunction, including permeation and gating mechanisms.

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