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Brute Force Orientation of Proteins

Diffractive single-particle imaging (SPI) using X-ray free-electron lasers (XFELs) offers a promising approach for determining protein structures without crystallization (Neutze2000) . For successful reconstruction thousands of diffraction images of individual proteins have to be assembled. It has been shown with molecular dynamics simulations that proteins carrying a dipole moment can be oriented with external electric fields (Marklund2017) and that the computer algorithm that sorts the diffraction images benefits from pre-orientation (Marklund2017, Wollter2024). A general estimate of the required minimum field strengths for sufficient orientation is still unknown.\
Expressions for the distribution of the angle θ between the dipole moment μ and the field ϵ were derived for 1) a theoretical mechanical rigid rotor model (RR) of a single protein in which no energy is transferred to inner degrees of freedom and 2) a theoretical thermodynamic model (TM) that assumes equilibration of all internal degrees of freedom in the protein. Molecular dynamics (MD) simulations show similarity with RR for low fields and good agreement with TM for higher fields, when the simulation duration is sufficiently long for the system to reach equilibration.

Based on RR for a single protein and assuming random orientation as well as Boltzmann-distributed rotational kinetic energy when entering the field region, we estimate the distribution of orientation angles for an ensemble of proteins.

To study the beneficial effect of pre-orientation we performed Enhanced EMC (Marklund2017, Wollter2024) with thousands of simulated diffraction pattens (Hantke2016) of proteins oriented according to the theoretical distributions (RR ensemble, TM).

We estimate the required fields for a given dipole moment to achieve given angular confinements and for EEMC to benefit from pre-orientation and relate them to the dipole moments of a dataset of 60k proteins lankar2016).
We conclude that TM is suitable to describe the distribution of angles even for a single protein and that field strengths required to achieve sufficient orientation for EEMC to benefit are technically feasible for a wide range of proteins.

<!— ![Distribution of θ from MD simulations of Ubiquitin. Theoretical distributions of rigid rotor (RR) and the thermodynamic model (TM) are included. The vertical dotted line indicates the starting angle $(\pi/2)$ in the simulations. The field varies from 1.0 V/nm (leftmost plot) to 0.001 V/nm (rightmost plot).]()fig:MD

![Required field to achieve $F_\theta(\alpha) = 0.68$ (i.e. angular confinement with 68(dotted) and TM (solid) model. The relative frequencies of dipole moments are shown in the background in blue (a.u.). Within the grey band, EEMC benefit from pre-orientation is greatest. Dipole moments of selected proteins are indicated by their pdb identifier.]()fig:req$_f ield - -- >$

Scholarship elegibility

no

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