Modeling 3D rotation of polarizable, dynamic proteins in a time-dependent electric field for imaging purposes.

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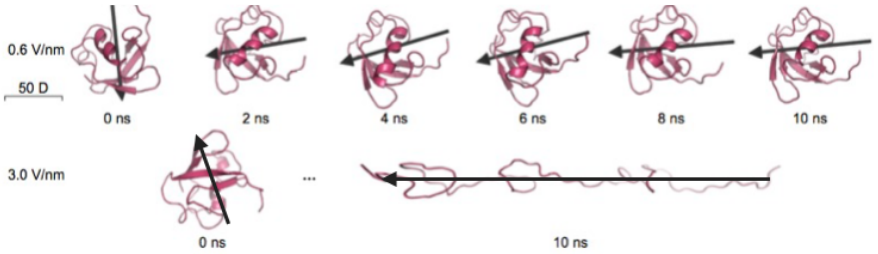

Background. Traditional structural biology techniques require that all molecules are trapped in the same state or, alternatively they report ensemble averages, that obscure the rich variety of molecular states in a sample. Gas-phase approaches to structural biology can bypass some of these constraints and inform about individual states and systems that are problematic for X-ray crystallography or Nuclear Magnetic Resonance. For example, mass spectrometric (MS) techniques have provided much insight into the structure of macromolecules and their interactions and dynamics. In MS techniques samples are transported using electric fields, and a recently presented idea is to use electric fields to orient proteins in the gas-phase based on their natural dipole. The ability to orient molecules would benefit X-ray imaging of biological samples, for example Small Angle X-ray Scattering (SAXS) and Single particle Imaging (SPI) using X-ray Free-electron lasers. It could also develop ion-mobility (IM) techniques, where the average size of the proteins are determined by measuring the time it takes to transport a protein through a gas. If we were able to introduce orientation in IM, more information about the structure could be extracted and this would be beneficial for the gas-phase structural biology community.

Biophysical considerations. Exposing proteins to electric fields affects the structure of the molecules as the distribution of the electrons is changed. This can be simulated by using a combination of classical molecular dynamics (MD) and quantum mechanics (QM). The dipole in the macromolecule and the inertia tensor of a protein in an electric field is affected by the field itself, which in turn affects the dynamics of the protein. The dynamics of a protein in an external electric field has been simulated earlier using MD[1,2], showing that it is possible to orient a protein using an electric field. The oscillating motion induced by the torque caused by a dipole in an electric field, is eventually absorbed into internal vibrations in the protein. Both the QM and MD simulations are computationally very expensive, and are limiting both in terms of protein size and simulation time. A mathematical model that could treat the 3D rotation of a protein caused by an external electric field, would allow us to investigate longer time scales, larger proteins and fields that vary in time. Using such a model we reach time

scales in simulated systems more relevant to experimental conditions, which are too long to reach using conventional simulation tools.

Mathematical motivation: i) Rigid body model. We assume the protein to be rigid, in the sense that all atoms are at fixed positions with respect to the center of mass of the protein. The rotational motion of the rigid body about a fixed point and under the influence of a torque is then described by the *Euler rigid body equations of motion* [3]

$$I\dot{\omega} + \omega \times (I\omega) = M, \qquad (1)$$

where I is the moment of inertia tensor, ω is the angular velocity and M the acting torque. The torque M exerted by an explicitly time-dependent, external electrical field $\epsilon(t)$ on a protein with a dipole moment μ is given by

$$M = \epsilon(t) \times \mu. \qquad (2)$$

We split the dipole moment into an intrinsic μ_0 and an induced component μ_{ind}. For the rigid body, the intrinsic dipole is assumed constant in the body frame, however, the induced dipole moment (which can be obtained from quantum density functional simulations in e.g. SIESTA) is a function of the relative orientation of the intrinsic dipole with respect to the field, which gives

$$M = \epsilon(t) \times (\mu_0 + \mu_{ind}(\epsilon(t), \mu_0)). \qquad (3)$$

In the body frame, this becomes

$$\begin{aligned} I_1\dot{\omega}_1 + (I_3 - I_2)\omega_2\omega_3 &= M_1, \\ I_2\dot{\omega}_2 + (I_1 - I_3)\omega_3\omega_1 &= M_2, \\ I_3\dot{\omega}_3 + (I_3 - I_3)\omega_1\omega_2 &= M_3. \end{aligned} \qquad (4)$$

Introducing Euler angles (φ, θ, ψ) to transform between the lab frame and the body frame produces a differential-algebraic system of equations in the Euler angles (EOM). Closed form solutions are known for some cases [3], including free rotation of spherical or axially symmetric bodies and spinning heavy tops with gravity induced torque but not for general inertia tensors, with explicit time and orientation dependent torques and arbitrary initial conditions.

The EOM can in principle be integrated numerically, however stability issues, sensitivity to initial conditions and singularities in the Euler angles are problematic [4]. Formulations with quaternions based on Euler parameters instead of Euler angles avoid the singularities [5,6]. A number of integrator methods and algorithms are being proposed to accurately numerically integrate the kinematic equations [7–9].

An outline of possible steps could include:

1. compare existing integrators based on literature, select, adapt and implement
2. test against known solutions (trajectory level comparison for relevant observation times)

3. stability analysis (e.g. Lyapunov exponents)
4. energy considerations/conservation analysis

ii) Non-rigid body protein model. In the experiment, proteins are not rigid but vibrate, resulting in non-constant inertia tensors, thus the rigid body equations are no longer applicable. Moreover, also the intrinsic dipole moment varies as a result of the vibrations and MD simulations show that inner degrees of freedom absorb at least part of the rotational energy.

An extended model could account for that by:

1. generalizing rigid body equations of motion to non-rigid bodies
2. developing/including physically meaningful model of inertia and dipole variations (starting from MD simulations)
3. account for absorption (possibly by including a friction term in the equations of motion)

In the specific experimental setup[10] that is planned, the orientation of the proteins when exposure to the external electric field commences, i.e. the initial conditions for the equations of motion, are known at best as rotation and orientation distributions. A complete simulation pipeline could take this into account by considering trajectory bundles (assuming some degree of stability) to predict expected orientation for ensembles.

Main goal. We aim to create a simulation toolbox that can simulate how a protein rotates in an electric field. The model should be dynamic in the sense that it should include the energy transfer from rotation energy to vibrational energy (heat), and the dynamics of the total dipole, due to the intrinsic dipole and the dipole induced by the electric field.

Interdisciplinary aspects. With this proposal we hope to apply mathematics to solve a problem within biophysics. The motivation originates from structural biology, and the problem is physics based, which we intend to solve using mathematics. The student will be employed at the Department of Physics and Astronomy with an assistant supervisor at Chemistry - BMC. The work will be done within the Biophysics network at Uppsala University (www.teknat.uu.se/research/biophysics-network), which spans over four departments (Physics and Astronomy, Chemistry - BMC, Applied Mechanics, Cell- and Molecular Biology), and includes expertise in gas-phase biology, computer modeling (MD and QM) and theoretical physics.

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