Aggregation of Proteins by Polarization

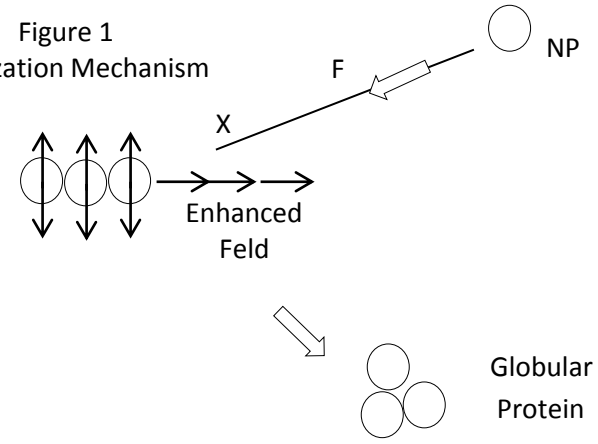
Thomas Prevenslik
Discovery Bay, Hong Kong

Protein therapeutics is used in the treatment of diabetes and various forms of cancer. A major concern is that repeated administration to patients often leads to undesirable antidrug antibodies with a wide range of life threatening consequences that induce immunogenicity or an adverse response of the immune system. The antibodies are generally thought triggered by the tendency of monomer protein molecules to aggregate, although why aggregation occurs is not known. In protein deposition diseases such as Alzheimer and Parkinson, protein aggregates have stronger immunogenicity. Typically, the aggregates known to elicit immunogenicity are globular proteins having molecular weights from 6-100 kDa and diameters from 3–10 nm that are comparable to inanimate natural or manmade nanoparticles NPs that have been linked to damage of deoxyribonucleic acid by the natural emission of low-level UV radiation induced by quantum electrodynamics QED. Similarity suggests the protein aggregates form as monomers cross-link under UV radiation produced by NPs of the aggregates themselves. The possibility that the UV radiation is the source of aggregation is assessed by molecular dynamics.

Theory

The attractive force F between NPs produced by the UV created by the NPs themselves is illustrated in the figure. Once a sequence is initiated, the EM fields superpose to strengthen along the length of the chain causing the NP to be attracted to the end of the chain. A spherical globular protein forms if the NPs are close to each other.

Figure 1
Polarization Mechanism



The force F is given [1] in terms of the polarizability α of the NP in the gradient of the EM energy density U along the distance x to the chain,

$$\mathrm{F} = 4\pi\alpha\frac{\partial \mathrm{U}}{\partial \mathrm{x}} \tag{1}$$

QED creates the UV photons from EM energy Q_C acquired by collisions of water molecules.

$$\mathrm{Q_C} = \frac{\pi}{2\sqrt{3}}\mathrm{pPd}^2\sqrt{\frac{\mathrm{kT}}{\mathrm{m}}} \tag{2}$$

where, p is the probability of inelastic collisions, P is pressure, dis the diameter of the NP, k is Boltzmann's constant, and T is absolute temperature.

The EM energy density U is,

$$U = \frac{Q_C}{\pi d^3/6}\left(\frac{\pi d^2}{4\pi x^2}\right)\int dt = \frac{3}{2\pi d}\frac{Q_C}{x^2}\Delta t \qquad (3)$$

where, Δt is the time increment over which the force is acting.
Combining, the force F is,

$$F = -\frac{12\alpha}{d}\frac{Q_C}{x^3}\Delta t \qquad (4)$$

MD Simulation

The MD simulation of protein aggregation was simulated using a Fortran 95 version of the Allen-Tildesley [2] Leapfrog Verlet Algorithm under periodic boundaries. The initial configuration was taken as the FCC geometry of a crystal with 108 NPs. The NPs having diameter d = 2 nm were assumed to have protein density of 1200 kg/m^3 and dispersed in the computation box of about 20 nm^3 corresponding to density of 100 kg/m^3. Water molecules were excluded. The pressure P = 1 atm and T = 300K. Typical protein polarizability α = 1x10^{-30} m^3 was assumed. The VMD image of natural aggregation of the globular protein is shown in Fig. 2 VMD stands for Visual Molecular Dynamics.

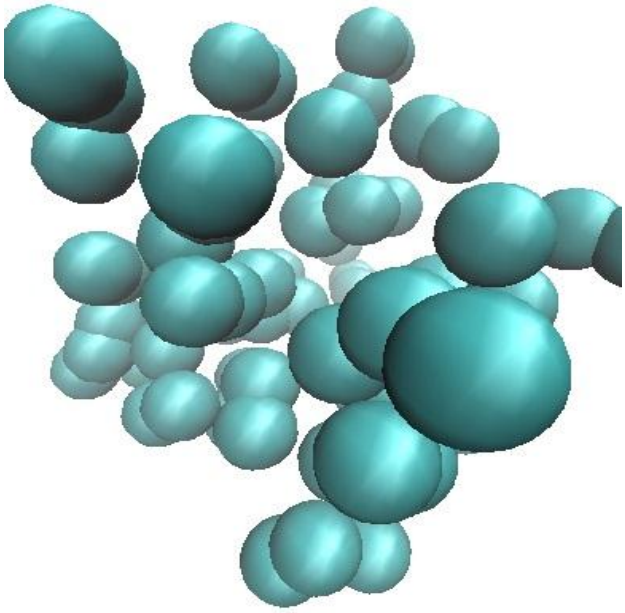


Figure 2

VMD Graphics - Aggregation of Globular Protein

References

[1] M. Antezza, L.P. Pitaevskii, and S. Stringari, "New Asymptotic Behavior of the Surface-Atom Force out of Thermal Equilibrium," PRL, 95, 113202 (2005).

[2] M. P. Allen, D. J. Tildesley, *Computer Simulations of Liquids*, (Oxford: Clarendon Press: 1987).