Chapter 2
Protein Crystals: Molecular to Continuum Level Models Based on Crystal Plasticity Theory

Suvranu De and Amir Reza Zamiri

2.1 Background

Biological materials are extremely well organized in a hierarchical structure from the molecular building blocks at their first level of organization up to the tissue and organ levels with fascinating nonuniform (anisotropic) properties. Nature utilizes hierarchical structures in an intriguing way to self-assemble biomaterials based on molecular building blocks such as amino acids, nucleic acids, polysaccharides, and lipids that are organized into efficient multifunctional structures and systems ranging from the nanoscopic to the macroscopic length scales [1, 2]. The most basic properties and functions of the biomaterials are defined at the very first level of organization. Therefore, it is imperative to incorporate information from the finer scale biological processes, which often govern processes at the coarser scale, to measure the properties and analyze the functions of biological systems.

Proteins are the primary building blocks of biological materials, and are necessary for providing key functions to biological systems, ranging from structural elements to transmitting information between cells, and biological catalysis [1], in particular under mechanical stimulation. Protein materials in a biological system are made up of self-assembled functional protein molecules that are composed of polypeptide sequence of 20 different amino acids, which allows it to fold up into a specific three-dimensional shape, or conformation [1, 2]. This variety in the amino acids leads to a range of different properties in charge, hydrophobicity, interactions, chemical reactivity, and functionality.

The biological function of protein material in the biological systems is connected to the structural deformations whose mechanical actions are coupled to the chemical events that are associated with the conformational changes [1]. While excellent understanding has been gained on the biological function of proteins at the molecular

S. De (✉) · A.R. Zamiri
Department of Mechanical, Aerospace and Nuclear Engineering,
Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, USA
e-mail: des@rpi.edu

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scale, how molecular properties, and range of material scales and hierarchies contribute to the biological function that leads to the unique properties of the specific protein material at the mesoscale, which spans from nanometers to micrometers on length scale and nanoseconds to microseconds on timescale, and what role they play in the physiological and pathological phenomena, remains an active frontier of research. This type of bottom-up hierarchical approach toward understanding behavior of protein material holds great potential for fundamental contributions to biology and medicine as well as for the synthesis of self-assembled engineered materials.

The hierarchical structure of protein in the form of self-assembled three-dimensional molecular crystals enables dissipation of mechanical energy through crystallographic slip, that is sliding of molecules against each other, and, hence, delays the catastrophic failure. For example, the staggered arrangement of protein molecules into fibrils plays a key part in increasing the toughness of various collagen materials such as bone [3–5]. The plastic deformation may also induce refolding of protein into a new three-dimensional folded structure. This unfolding may occur locally and involve only certain domains of the protein that may lead to deformation hotspots. Protein folding is critical to biological functions, and misfolding lead to diseases and disorders such as Alzheimer's disease, Parkinson's disease, Type II diabetes, and several types of cancer [6, 7]. Hence, it may be of interest to relate the response of deformation of distinct domain of the protein to their biological function. This may also be used to advance our understanding of diseases and potentially lead to development of new therapeutic drugs. Further, an improved understanding of how the deformation mechanisms at the multiple scales contributes to the mechanical stability of the protein material in diseases could bring about new strategies for the treatment through selective breakdown of foreign material deposits in diseased tissues in case of Alzheimer's disease, Parkinson's disease, and Type II diabetes [8–11]. Also, detailed understanding of mechanical stability, adhesion properties of the protein crystals due to change in amino acid sequence and solvent effects may help to contribute to advance the understand the molecular origin of sickle cell anemia, or Alzheimer's disease. Aside from therapeutics, it may also help in the development of biomimetic materials and devices for a range of engineering and medical applications including regenerative medicine, electronic materials, biotechnology, nanotechnology, and drug delivery.

However, the mechanical properties and stability of many protein materials under different conditions has not been extensively studied. A little is known about their molecular deformation mechanisms, and influence of the nanoscale processes on the mechanical properties. Therefore, further research is needed to explore the fundamental design principles for the development of such materials with optimal functionality and stability. Goal is to understand the relationship between fine scale primary structure and processes and macroscale response of the protein molecular crystals.

In this chapter, we study the bulk mechanical properties of the of protein crystal such that it accounts for the properties of the molecular crystal along with the phenomena occurring at the lower scale. Like most crystalline solids, the mechanical properties of protein materials are strongly influenced by defects such as dislocations through slip-induced plastic deformation [12], which is captured using

continuum-based crystal plasticity model. We apply this model to investigate the temperature- and humidity-dependent mechanical response of tetragonal lysozyme crystals.

2.2 Multiscale Modeling Challenges

A large number of computational methods for modeling protein materials at disparate length- and time-scale have been employed. At the bottom, *ab initio* quantum mechanical simulations can be used to develop potential fields for molecular dynamic (MD) simulations. These coarse-graining approaches are able to reach timescale of the order of 100 ns and length scale of 10 nm [13]. Nonetheless, the computational prediction of the three-dimensional folded structure of proteins directly from the amino acid sequence is still beyond current computational capabilities [14]. Likewise, many questions of practical importance involve system sizes and timescales that significantly exceed what can be treated in classical atomistic simulations.

Larger length scales and timescales can be reached using the results of the classical MD calculation to create parameters for a new simulation capable of exploring length- and time-scales of greater orders of magnitude. These hierarchies of simulation techniques, integrated through multiscale methods are based on the concept of informing coarser scales from finer scales, enabling one to establish direct links between chemical structure and larger scales. The process of systematic coarse graining requires transformation of detailed models to simplified descriptions with less degrees of freedom, effectively averages over some chosen properties of lower scale entities to form larger basic units.

The hierarchical coarse-graining approach seems to be capable of simulating any material regardless of complexity on length scales. However, there is no unique way to perform coarse graining. Besides, purely atomistic-based simulations are computationally expensive and typically limited to very small systems of the order of billions of particles that may be simulated over very short timescales of less than a microsecond. Hence, they are incapable of accounting for defects such as dislocations [15] and other microstrcutural effects in any realistic way, which are assumed to play a fundamental role in determining material properties or functional stability of protein crystals.

Continuum modeling represents a discrete system as a continuous body or fluid, and provides the starting point for multiscale modeling. For example, a continuous system with appropriate material properties and characteristics represents the discrete nanostructures involved with the protein folding process [16]. When the material properties and constitutive relations are developed using data gathered from higher accuracy models of lower scale, the resulting continuum models are hierarchical multiscale model. Continuum models like coarse-grain models greatly reduce the degrees of freedom required modeling the protein of interest. However, the major challenge in the development of continuum multiscale model is to develop a constitutive law and

continuum-level equations of a biological system, whose parameters are computed from finer scale models of the system.

2.3 Methods

A continuum slip theory-based micromechanical constitutive model has been developed to predict the mechanical behavior of the protein molecular crystals, in which crystallographic slip is the predominant deformation mechanism [17]. We now introduce the basic terminology that is necessary to develop a single crystal plasticity model.

Let $\mathbf{m}^{\alpha}$ bea unit normal to the slip-plane and $\mathbf{s}^{\alpha}$ a unit vector denoting the slip-direction of a typical slip-system α in the crystal coordinate system. Then, the slip-system α can be represented by an orientation matrix

$$\mathbf{I}^{\alpha} = \mathbf{s}^{\alpha} \otimes \mathbf{m}^{\alpha} \tag{2.1}$$

with symmetric and antisymmetric parts defined as

$$\mathbf{P}^{\alpha} = \frac{1}{2}\left(\mathbf{I}^{\alpha} + \mathbf{I}^{\alpha T}\right) \tag{2.2}$$

$$\mathbf{w}^{\alpha} = \frac{1}{2}\left(\mathbf{I}^{\alpha} - \mathbf{I}^{\alpha T}\right) \tag{2.3}$$

which defines the plastic rate of deformation $\mathbf{D}^{p}$ and spin rate $\mathbf{\Omega}^{p}$ as

$$\mathbf{D}^{p} = \sum_{\alpha=1}^{N} \dot{\gamma}^{\alpha} \mathbf{P}^{\alpha} \tag{2.4}$$

$$\mathbf{\Omega}^{p} = \sum_{\alpha=1}^{N} \dot{\gamma}^{\alpha} \mathbf{w}^{\alpha} \tag{2.5}$$

where N is the number of slip systems in the crystal and $\dot{\gamma}^{\alpha}$ is the shear slip-rate.

We now derive the specific form of plastic slip-rate based on dislocation dynamics models. The average velocities of dislocations on a slip-plane α may be expressed as

$$\bar{v}^{\alpha} = v_0^{\alpha} f_p\left(\tau^{\alpha}, \boldsymbol{\chi}\right) \tag{2.6}$$

where v_0^{α} is the limiting velocity, f_p is a probability function, τ^{α} is the resolved shear stress on slip system α, and $\boldsymbol{\chi}$ is a vector containing state variables such

as temperature. It has been shown that for most materials the probability function satisfies a power type expression

$$f_p\left(\tau^\alpha, \boldsymbol{\chi}\right) = \lambda \mathrm{sgn}(\tau^\alpha)\left(\frac{\tau^\alpha}{\tau_y^\alpha}\right)^{2n-1} \tag{2.7}$$

where λ and n are material constants and τ_y^α is the critical resolved shear stress of the slip-system α. The rate of shear strain on a slip-system α is

$$\dot{\gamma}^\alpha = \varphi^\alpha \rho^\alpha b^\alpha \bar{v}^\alpha \tag{2.8}$$

where φ^α is a material parameter, ρ^α is the dislocation density, and b^α is the Burgers vector. Combining Eqs. (2.6)–(2.8) one obtains:

$$\dot{\gamma}^\alpha = \lambda \mathrm{sgn}(\tau^\alpha)\left(\frac{\tau^\alpha}{\tau_y^\alpha}\right)^{2n-1} \tag{2.9}$$

where the resolved shear stress τ^α on the slip-system can be related to the Cauchy stress tensor $\boldsymbol{\sigma}$ in the fixed coordinate system as:

$$\tau^\alpha = \boldsymbol{\sigma} : \mathbf{P}^{\boldsymbol{\alpha}} \tag{2.10}$$

Using Eq. (2.9), the overall accumulated slip $\bar{\gamma}$ in a the crystal can be obtained by

$$\bar{\gamma} = \sum_{\alpha=1}^{N} \int_0^t \left|\dot{\gamma}^\alpha\right| dt \tag{2.11}$$

The accumulated slip $\bar{\gamma}$ can be used as a good measure for evaluation of the deformation propensity of a crystal having specific orientation with respect to the external load.

According to the normality rule in plasticity, a yield function $f(\sigma, \chi)$ could be defined such that

$$\mathbf{D}^P = \lambda \frac{\partial f(\boldsymbol{\sigma}, \boldsymbol{\chi})}{\partial \boldsymbol{\sigma}} \tag{2.12}$$

where λ is a positive parameter which depends on the type of dislocation barriers. Comparing Eqs. (2.4) and (2.5) and solving the differential Equation (2.12), a yield surface for protein crystals can be defined as:

$$f(\boldsymbol{\sigma}, \boldsymbol{\chi}) = \frac{1}{2n}\left(\sum_{\alpha=1}^{N}\left|\frac{\boldsymbol{\sigma} : \mathbf{P}^\alpha}{\tau_y^\alpha}\right|^{2n} - 1\right) \tag{2.13}$$

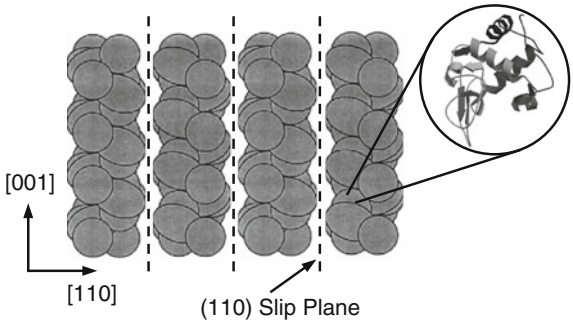

Fig. 2.1 A 3D crystallized structure of a tetragonal lysozyme crystal (protein molecule is from PDB code: 133L [18])

Substituting Eqs. (2.9) and (2.10) into Eqs. (2.4) and (2.5) leads to the following expressions for plastic rate of the deformation and spin:

$$\mathbf{D}^p = \lambda \sum_{\alpha=1}^{N} \frac{\text{sgn}(\tau^\alpha)}{\tau_y^\alpha} \left| \frac{\tau^\alpha}{\tau_y^\alpha} \right|^{2n-1} \mathbf{P}^\alpha \tag{2.14}$$

$$\mathbf{\Omega}^p = \lambda \sum_{\alpha=1}^{N} \frac{\text{sgn}(\tau^\alpha)}{\tau_y^\alpha} \left| \frac{\tau^\alpha}{\tau_y^\alpha} \right|^{2n-1} \mathbf{w}^\alpha \tag{2.15}$$

The effects of the temperature, water molecules, and other environmental effects on the deformation behavior of protein crystalsare considered through their influence on the critical resolved shear stress τ_y^α.

2.4 Results

We present a particularly interesting application of the protein model in modeling the effects of deformation mechanisms, temperature, and amounts of intracrystalline water on the stability and mechanical behavior of tetragonal lysozyme crystals. Lysozyme is a well-studied enzyme, which is found in egg white, tear, saliva, mucus, and other body fluids. The main role of these enzymes is to lyse cell walls of gram positive bacteria. Lysozyme can be easily self-assembled into different crystal structures including orthorhombic, tetragonal, and monoclinic. Its well-known and stable crystal structure makes it a good choice for our study. Figure 2.1 shows a self-assembled structure of a tetragonal lysozyme protein crystal. The tetragonal lysozyme crystal belongs to the $P4_32_12$ space group with lattice constants of $a = b = 7.91$ nm, $c = 3.79$ nm, and $Z = 8$ [12]. In these molecular crystals there are specific molecular planes such as (110) which have the greatest separation and therefore, may glide on each other under external loads, see Fig. 2.2. The plastic deformation in the lysozyme protein crystals at the microscale has been established due to crystalline slip [12].

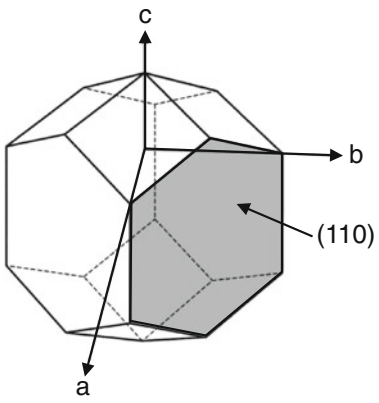

Fig. 2.2 A tetragonal lysozyme single crystal

The indentation and compression analysis of three-dimensional crystallized form of the tetragonal lysozyme protein crystals reveal that they are relatively fragile and soft materials and their mechanical properties are highly sensitive to both environmental conditions and the type of the protein molecule [19], and size dependent [12, 19]. The compression testing of crystal leads to nonlinear elastic deformation leading to fracture, whereas, during microindentation, the microcrystals exhibit elastic-plastic deformation. The temperature and amount of intracrystalline water have significant effects on the elastic and plastic properties of the crystals. At lower temperature and water content, the crystal is more brittle while it is more ductile at higher temperature and humidity [12].

The elastic constants of tetragonal lysozyme crystal are highly sensitive to both temperature and humidity [20–24]. The Young's modulus of lysozyme crystal decreases with increasing temperature according to the following relationship [20]:

$$\Delta E = -C_T E_\circ \Delta T \tag{2.16}$$

where ΔE and ΔT are increments in the Young's modulus and temperature, respectively, $E_\circ$ is the Young's modulus at 300 K and C_T is a constant equal to $2 \times 10^{-3} \mathrm{K}^{-1}$ for lysozyme crystals [20]. The Young's modulus increases with increasing amount of the intracrystalline water molecules [21, 22] as

$$\Delta E = C_w E_\circ \Delta t \tag{2.17}$$

where Δt is the evaporation time and C_w is a constant whose value depends on environmental parameters such as temperature. For natural evaporation of water from lysozyme crystal surface at room temperature, C_w was calculated to be 0.0396 (1/min) [17].

The plastic flow in the lysozyme crystals is induced by the dislocation glide along the preferred slip-systems [25]. The tetragonal lysozyme crystal has two sets of slip

systems [20], a primary {110}<001> system and a secondary {110}<110> system. Depending on the crystal orientation and environmental conditions, the primary slip-systems {110}<001> get activated first followed by the secondary slip systems at higher stresses. We perform computer simulations of microindentation experiments of lysozyme single crystals. The critical resolved shear stresses (CRSS) for these slip systems is then characterized from experimental data as a function of temperature and intracrystalline water molecule [17].

2.4.1 *Temperature Dependence of Plastic Deformation of Lysozyme Crystals*

We first examine the temperature-dependent plastic deformation of the tetragonal lysozyme molecular crystals. Figure 2.3 shows the temperature dependency of the CRSS of tetragonal lysozyme crystals. At normal rates of deformation, thermal fluctuations provide the energy to carry the dislocations over the lattice potential barriers [26, 27]. Hence, the dislocations at higher temperatures have a higher probability of overcoming lattice potential barriers due to higher thermal fluctuations. This leads to decrease in the CRSS for activation of the slip systems with increasing temperature, as shown in Fig. 2.3. At lower temperatures, the CRSS of the {110}<001> slip system is much less than that of the {110}<110> slip system, therefore, the former can be more easily activated. However, at higher temperatures the CRSS of both slip-systems are small and, hence, both can easily get activated. At temperatures below room temperature, the deformation in lysozyme crystals is primarily elastic, whereas, at higher temperatures it is elastic-plastic. Therefore, at lower temperatures, the variation of CRSS is primarily due to the temperature dependence of the elastic constant. However, at higher temperatures, both the elastic constant and dislocation mechanisms are affected by temperature, which results in a higher drop in CRSS with increasing temperature.

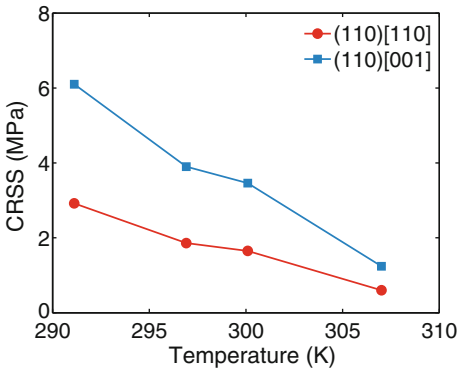

Fig. 2.3 The effect of temperature on critical resolved shear stresses of the tetragonal lysozyme crystal

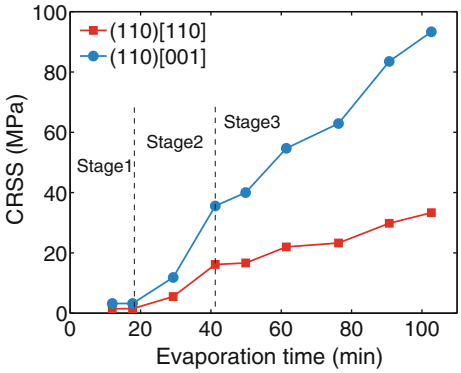

Fig. 2.4 The effect of the amount of intracrystalline water molecule on critical resolved shear stresses of slip systems in tetragonal lysozyme crystal

2.4.2 *Effect of Humidity on the Plastic Deformation of Lysozyme Crystals*

We next study the humidity-dependence of the plastic deformation of the tetragonal lysozyme molecular crystals. Protein crystals in biological systems are usually in a fluid environment and, therefore, have a significant amount of intercrystalline water. In Fig. 2.4, we see that the CRSS for both slip systems increase with evaporation time, that is, with the decreasing amount of intracrystalline water. The decrease in the amount of intracrystalline water leads to an increase in elastic constants and a decrease in the lattice parameters[38]. This increases the self energy of the dislocations significantly and hinders their nucleation and activation, thereby increasing the CRSS of the slip systems.

The decrease in CRSS with increasing temperature may also be related to the water molecules, see Fig. 2.4. Two types of intracrystalline water may be present in the lattice, the mobile water, which can easily traverse through the crystal, and bounded water, which is more strongly bound to the molecules [20, 22]. The mobile water has a high diffusion coefficient at higher temperatures [26] and, therefore, has little interaction with dislocations. However, at lower temperatures, it may interact with dislocations and thereby affect dislocation creation and motion in the lattice [20].

2.4.3 *Anisotropic Plastic Yielding of Lysozyme Crystals*

Figure 2.5, shows two-dimensional plots of the yield function, as given in Eq. (2.13), for three different crystal orientations of tetragonal lysozyme crystals at 285 and 307 K. From the yield surface plot in the Fig. 2.5, it is evident that the tetragonal lysozyme crystal is highly anisotropic and the shape of its yield surface changes with both temperature and crystal orientation. As discussed in the previous sections, at higher temperatures both {110}<110> and {110}<001> slip systems are activate during the deformation, therefore, the material is softer while at low temperature

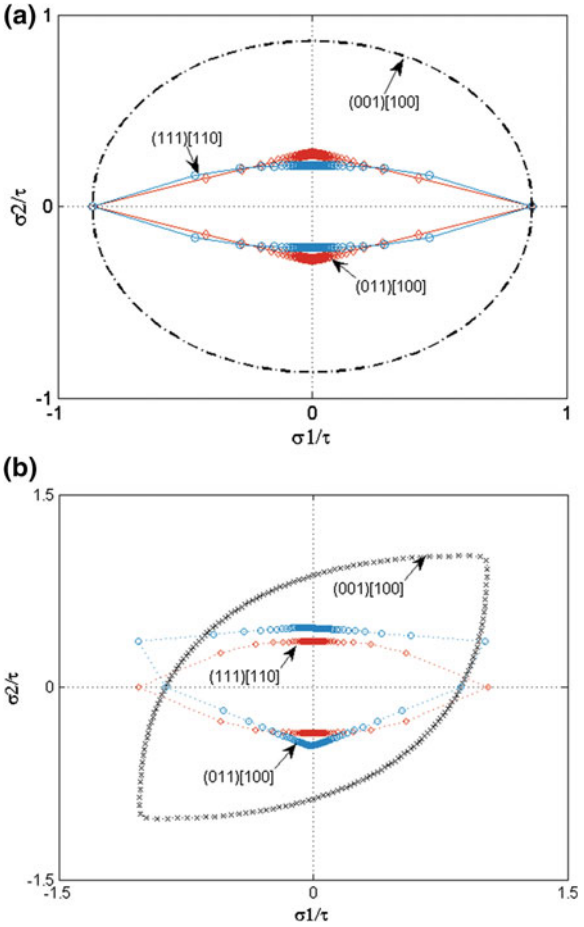

Fig. 2.5 The yield surface of the tetragonal lysozyme crystals for three different crystallographic orientations of (001)[100], (011)[100], and (111)[110] at two temperature of **a** 285 K and **b** 307 K

only the {110}<001> slip system can get activated and, hence, materials is more rigid. At room temperature, for the lysozyme crystals that have high amount of intracrystalline water both {110}<110> and {110}<001> slip systems are getting activated, however, at the lower amounts of intracrystalline water only {110}<001> slip system is getting activated (Figs. 2.6, 2.7 and 2.8).

2.5 Discussion and Future Work

In this work, we analyze the mechanical properties and deformation behavior of three-dimensional crystallized proteins such as tetragonal lysozyme crystal using continuum-slip theory based on micromechanical model that accounts for the

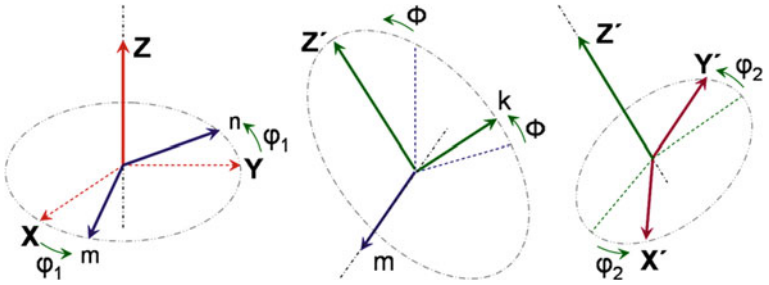

Fig. 2.6 Orientation of a crystal (X', Y', Z') with respect to the fixed coordinate system (X, Y, Z) based on Bunge Euler angles [28]

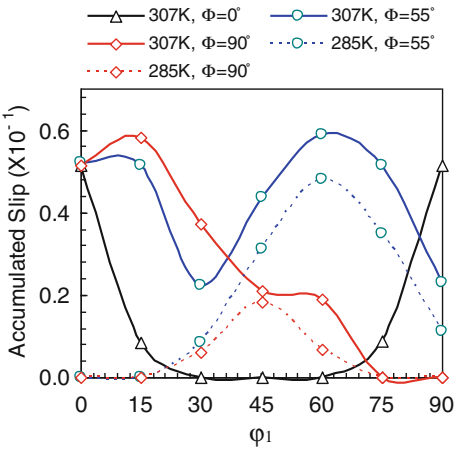

Fig. 2.7 The orientation-dependent accumulated slip $\bar{\gamma}$ obtained for 3D lysozyme crystals loaded up to 0.01 strain at two different temperatures of 285 K and 307 K and Euler angle $\phi = 0°$, 55°, and 90°. In all these analyses, Euler angles $\varphi_2 = 0°$

molecular and crystal properties, and defects such as dislocations through slip-induced plastic deformation. The results of our investigation show that the propensity to plastic deformation for all slips systems increases with increasing temperature and the quantity of intracrystalline water molecules. Further analysis of the deformation along different crystallographic directions shows that the mechanical properties of the lysozyme crystals are highly anisotropic and the degree of anisotropy is a function of temperature and intracrystalline water molecules. We also observe that at higher temperatures the crystals are very ductile while they are more rigid at lower temperatures. These observations may provide valuable information regarding design of the structures, devices and systems using three-dimensional crystallized protein materials. The analysis present here could be easily extended to explore the mechanical behavior of the any three-dimensional self-assembled protein crystal under different loading conditions. However, further work is necessary, especially in experimental characterization of protein crystals, to develop sophisticated models for post yield behavior, hardening, damage, and softening under different environmental conditions.

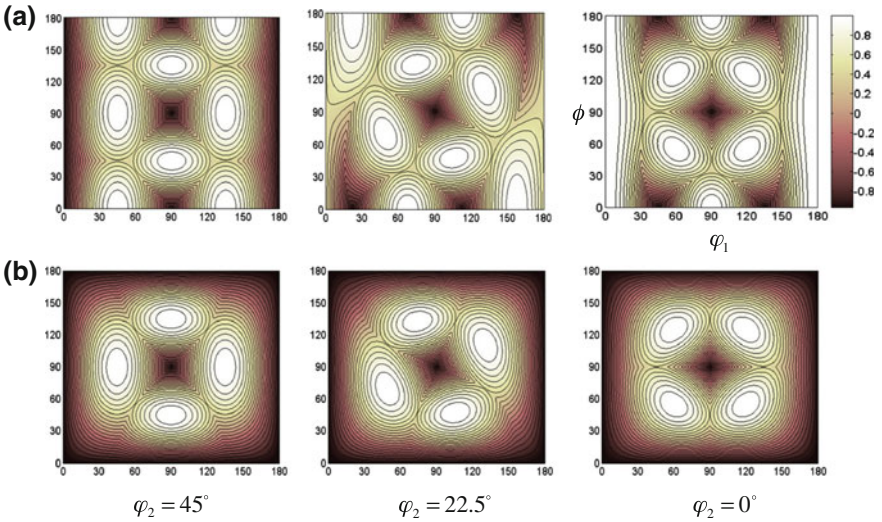

Fig. 2.8 The deformation distribution maps of the 3D assembled lysozyme crystal at two different temperatures of **a** 307 K and **b** 285 K, and for different values of φ_2. For all orientations the uniaxial compression is along the X-axis of the lab coordinate system with compression up to 1 % strain. At any φ_2 section, the maps show the crystal orientations that have the highest and the lowest values of the yield function (Eq. (2.13)) and, therefore, the greatest tendency for plastic deformation and elastic deformation, respectively

Many challenges associated with the characterization of protein crystals including stability, remain an open field of research. The functionality and stability of protein molecules are largely dependent on the environmental working conditions such as temperature, pH and the surrounding fluid. However, the mechanical stability of protein crystals under different conditions has not been extensively studies. Therefore, further research is needed to explore the fundamental design principles for the development of such materials with optimal functionality and stability.

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