CHAPTER 4

Globular or ribbon-like micelle

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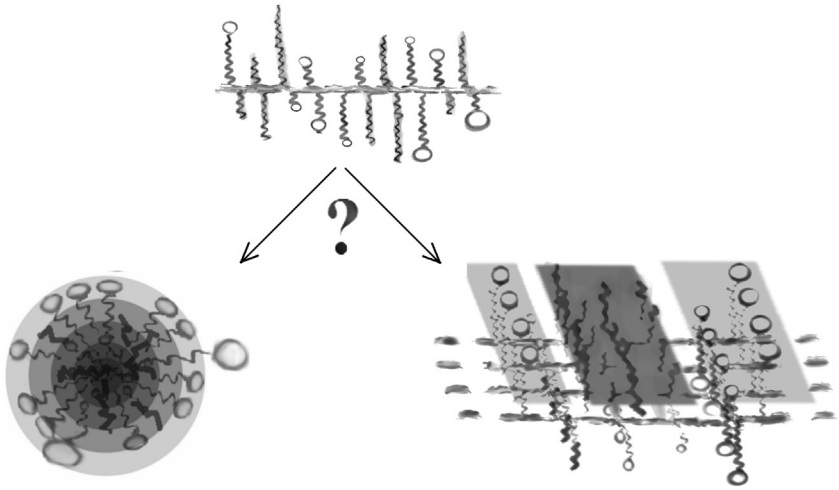

Taking decision: SPHERICAL (globular) or RIBBON-LIKE micelle (fibrilar) ?

As already remarked in the Introduction—in this publication we treat the protein as a specialized tool suited for a particular task. While there are no *useless* proteins in the organism, the role fulfilled by each protein

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may be either simple or complex. For this reason, proteins vary in terms of their information content.

The term "specific" used in biochemistry is equal to saying "information" and in particular "information package" to express the equipment which is able to ensure the appearance of biological activity.

The second assumption used in based on the Heisenberg's uncertainty principle, which excludes equal precision for measurement of two canonically conjugate variables. If the structure of protein is assessed on the level of individual atoms the description of the entire structural unit (for example domain) is impossible—particularly its biological activity is hard to be defined. Function (treated as the aim-oriented local cumulation of information) can be identified using the complete structural unit as a whole.

Particularly hydrophobicity can not be defined using individual atoms as objects for analysis.

It is the characteristics of the set of atoms—like amino acids in particular.

The relation of protein molecule can be expressed solely and exclusively in relation to water. The aim-oriented coding of biological function can be treated in respect to symmetry (order). The higher symmetry the lower information coded. The presence of local discordance in respect to overall order of the object is the form of coding system expression.

Benzene can be taken as an example. As long as all H atoms are linked to C atoms in the aromatic ring any substitution reaction is highly difficult. The consequence of one H atom substituted by for example $-NH_2$ (nitro-benzene) is an easy substitution of the second H atom in ring in a well defined position −meta. The presence of $-NH_2$ is treated as local discordance carrying the information as to the next reactivity position.

Information content is intimately linked with the notion of symmetry. In symmetrical systems, individual components are well ordered and follow a predetermined structural pattern. An example of a (complex) chemical structure characterized by strong symmetry is a spherical micelle. Individual particles with specific chemical properties (polar/nonpolar fragments) self-assemble into a micellar structure when exposed to water. The process is deterministic: given a unit molecule, we may accurately predict the conformation of the resulting micelle. All the required information is encoded in each molecule (note, however, that not all molecules are capable of generating micelles). The driving force, which enables this information to spontaneously manifest itself, is the presence of water.

It is also possible to accurately model the structure of a co-micelle, which comprises more than one type of molecule. The specific nature of each

participating molecule carries information, which, based on intermolecular dynamics and interactions with the water environment, determines the structure of the so-called co-micelle. Given sufficient knowledge of the structural properties of each unit molecule, we may model the resulting co-micelle with high accuracy.

Effect of the aqueous environment on intramolecular processes

The polypeptide chain is a combination of 20 different molecules with different predisposition to generate the spherical micelle. Since amino acids differ in terms of their hydrophobicity profiles, the protein may be treated as a peculiar co-micelle. Nevertheless, it is important to point out a major difference between proteins and surfactant micelles: the presence of covalent bonds between each pair of residues which form the "protein micelle." These bonds severely restrict the conformational freedom of the polypeptide chain—unlike in surfactant micelles where the number of degrees of freedom is much greater.

Even so, we may assume that the protein during folding process follows the mechanism of micelle-forming, though one incapable of achieving an ideal distribution of hydrophobicity. The consequence of disability to create the idealized spherical micelle proteins contain local deformations, which are due to two factors: the aforementioned limitations imposed by the presence of covalent bonds, and the differing physiochemical properties of amino acids, which represent the building blocks of micellar proteins.

Let's assume for the moment that it is possible to construct a perfect micelle, with an ideal centrally placed hydrophobic core and a regular hydrophilic outer shell. We may ask—what benefit would such a structure bring to the organism? By itself, the micelle carries no information, other than that it is highly soluble and does not interact with other molecules (both properties are in fact closely related). It might be suspected of having no use whatsoever—but, surprisingly, there is a role for such molecules in living organisms (as discussed in Chapter 5). We refer here to type III antifreeze proteins—near-perfect micelles which perform an important function in organisms capable of surviving subzero temperatures. Their solubility is an important factor, since antifreeze proteins must be evenly distributed in the aqueous environment. Exposure of polar groups on their surface alters the structural properties of water in such a way as to prevent formation of ice crystals. Thus, they remain useful—despite carrying almost no information.

If we were to sort proteins by information content, antifreeze proteins type III would need to be placed immediately after the classic surfactant micelle.

In information theory, information may be conflated with the occurrence of an unlikely event. Similarly to surfactant micelles, the structure of a type III antifreeze protein—which carries very little information—may be accurately predicted. The same is true for the so-called fast-folding (or ultra-fast-folding) proteins, which exhibit very strong accordance between the observed (O) and theoretical (T) distribution of hydrophobicity. In some cases, these turn out to be mutated proteins where mutations confer the ability to fold in a very rapid manner.

Moving on to proteins which carry appreciable quantities of information, we note that the structure of such proteins must include elements whose probability of occurrence is low (in structural terms), even though the remainder of the protein may still follow the theoretical (Gaussian) distribution of hydrophobicity with high accuracy. This is a general rule, which results from interaction with the aqueous solvent. As the environment promotes formation of protein micelles, structural deviations which encode specificity must counteract this tendency.

Significant reduction of degrees of freedom of amino acids in chain in relation to freely moving surfactant molecules and determined neighborhood (determined sequence) eliminates the possibility to generate the spherical micelle. The simple one chain enzyme may be the example. The only discordant area in the protein molecule is the active site cavity.

Eliminating residues which comprise such cavities reveals that the remainder of the molecule still resembles a well-ordered micelle and may be generated in a spontaneous manner. Evolution appears to have selected the 20 biogenic amino acids (characterized by differing hydrophobicity profiles) to enable generation of "imperfect" structures, whose imperfections (when compared to surfactant micelles) encode information.

The specific activity of proteins results from the predetermined balance of order and disorder within their micellar structure, and from the associated local deformations.

Along with enzymes, the group of proteins whose information content may be described as modest includes ligand-binding proteins which carry prosthetic groups. Attracting and binding a ligand requires a deformation which corresponds to a binding cavity suitable for the required ligand—however, the effect is localized and does not involve a large quantity of information. Similar considerations apply to proteins which form multichain complexes—in their case, information is encoded in the structure of their

complexation interfaces. Of course, if a protein forms complexes with multiple other proteins, it must contain more information, i.e. a greater number of local deformations. In this case, information is encoded in hydrophobic residues exposed on the surface, where they come in contact with residues belonging to the intended complexation partner.

An even greater quantity of information is present in proteins which require the presence of a ligand (prosthetic group), and are also capable of forming complexes with other (potentially multiple) proteins, nucleic acids or ions. Notably, in the case of ions, complexation does not require deformations in the hydrophobic core structure since it is mediated by polar groups, which are typically exposed on the surface (naturally, there are exceptions: obviously the examples can be found—for example Zn-fingers where the presence of Zn ions is critical) The most complex protein structures in existence—sometimes referred to as biological machines (such as bacterial flagella) [1–7]—are beyond the scope of this study (the work on such objects is currently the object of our analysis); however, it can be safely assumed that their synthesis requires an even greater amount of information, due to their structural complexity and intricate mechanism of action.

The next group comprises proteins which call for the presence of a so-called permanent chaperone. The chaperone is a molecule which temporarily stabilizes a certain structural motif during the folding process, preventing undesirable conformational rearrangements which would result in a misfolded protein [8–10]. In some cases, biologically active proteins may require a permanent chaperone—for example, membrane proteins are only capable of performing their biological activity when attached to a membrane.

Membrane proteins are a large and diverse family. They usually lack a tertiary structure and cannot be likened to globular micelles—instead, they are embedded in cell membranes (or the surfaces of cellular organelles) and represent collections of secondary folds, such as helices or random coils. The membrane not only acts as a permanent chaperone, but in fact delivers other than water environment (other external force field). Removing this scaffold causes the membrane protein to undergo rearrangements which effectively wipe out its biological activity. Free from the stabilizing influence of the membrane, the protein refolds in a manner dictated by the properties of its environment—it may then be described as "biologically confused" and lacking a well-defined purpose. It turns into an ordinary chemical molecule and becomes a micelle—in this instance, a ribbonlike micelle, which is strongly deterministic and therefore lacks information.

Special object among proteins are amyloids. We treat them here as information-less systems. They appear to not carry any form of information, what can be recognized using the high symmetry criteria. All chains participating in amyloid repeat identical structure generating the ribbon-like micelle.

Experimental studies show that almost any protein may be converted into an amyloid by shaking [11–14]. In trying to explain this peculiar effect we note that shaking causes aeration of the solvent, which greatly increases its interphase (water/air) surface area. A critical property of the aqueous environment now comes into play: water is a fundamental requirement of life. This seemingly simple statement takes on a new meaning in the context of the presented phenomenon. Protein folding invariably occurs in an aqueous environment of which water is an ACTIVE participant. It generates an external force field which guides the folding process, favoring the formation of a micellar structure, which resembles a surfactant micelle. The fuzzy oil drop model acknowledges this effect by introducing a continuous force field, mathematically modeled as a 3D Gaussian. While the field acts upon the polypeptide chain, the chain is not always capable of "obeying" its instructions—simply because it lacks the structural freedom required to align itself with the field with perfect accuracy.

Local deviations from the theoretical hydrophobic core model may emerge in one of two ways:

1. because covalent bonds prevent the chain from reaching perfect (micelar) alignment,
2. as a result of external factors which stabilize certain deviations. Due to the targeted nature of this process (i.e. complexation of a specific ligand) in Ref. [15] we postulate that the ligand itself may be present during folding, and that its presence ensures the generation of a suitable binding cavity. This hypothesis has not been unequivocally validated, but it seems plausible in light of our discussion on the role of information in protein folding.

In subsequent chapters we will try to show that the aqueous environment—rather than being modeled as a collection of molecules—should instead be viewed as a continuous force field. Protein folding is not guided by individual molecules, and modeling atom-atom interactions between the protein and the solvent does not accurately capture the effect of the external force field upon such a large and complex structure as a polypeptide chain. Furthermore, our knowledge regarding the structural properties of water in its liquid phase is very limited. Why do biological

processes call for a very specific concentration of NaCl in water (referred to as physiological or isotonic salinity)? It is likely that these conditions are necessary for the solvent to retain desirable structural properties, facilitating all processes associated with the machinery of life (except for some localized exceptions, such as low pH in the stomach).

Scientific research aimed at determining the structural properties of water (under both standard and altered physiochemical conditions) support the hypothesis that the aqueous environment plays an active role in biological processes. The phenomenon of amyloid transformation caused solely by physical factors (shaking), with no changes in the chemical structure of the solvent, further underscores the need for such research.

Thus far we have established the critical importance of water for protein folding. It is, however, equally interesting to speculate about the effect exerted by proteins upon the surrounding solvent.

The effect of proteins influence on the water structuralization

The active participation of water in protein folding process is expressed by directing the hydrophobic residues toward the center with simultaneous exposition o hydrophilic residues on the surface. Such interpretation is accordant with spontaneous process of micelle generation. On the other hand, the presence of objects like proteins is the source of information for surrounding water. Relatively large surface covered by charge atoms influence the ordering of water molecules in the close neighborhood. The good examples are the antifreeze proteins which alter the structural properties of the surrounding water so as to prevent formation of ice crystals. What tools does a protein have at its disposal in order to achieve this effect? While the properties of the solid state of water (ice) are reasonably well understood, the liquid phase still hides many unresolved questions—for example, it is not clear why the density of water peaks at 4 degrees Celsius, even though this phenomenon plays a critical role in enabling many biological processes.

The protein is able to affect its environment by exposing hydrophobicity and/or hydrophilicity on its surface. Even though—as remarked above—the structural properties of water in contact with various types of surfaces are poorly understood, we may assume that there are major differences in how water interacts with hydrophobic and hydrophilic patches exposed by the solvated molecule. These differences represent a mechanism by which the protein is able to transmit information to its environment.

In this context, it is especially interesting to consider the role of solenoids which are found in some antifreeze proteins. The solenoid is an axial structure, potentially capable of unlimited propagation along its principal axis. For this reason, solenoids used by antifreeze proteins are able to expose a unique type of surface, where alternating bands of high and low hydrophobicity strongly disrupt the natural structure of the surrounding solvent. Interestingly, some studies show that water molecules gain increased mobility when close to antifreeze proteins [16,17]. Clearly, this effect supports the intended function of antifreeze proteins, i.e. disrupting formation of ice crystals by altering the structural properties of water [18].

If solenoids represent a handy way to modulate the structure of the solvent, it might be interesting to search for them in other types of proteins. As it turns out, solenoid fragments are also commonly found in lyases. The difference, however, is that while in an antifreeze protein the sole purpose is to interact with the solvent, an enzyme plays a far more complex role. In addition to remaining soluble, it must also transmit a targeted signal to the intended substrate (i.e. it must be "recognized" by the substrate), and facilitate the intended reaction. The latter tasks requires that at least three distinct structural stages be available to the enzyme: precatalytic, intra-catalytic and post-catalytic. Each stage calls for a mechanism capable of enforcing conformational changes which lead to the following stage, while ensuring high specificity. At all stages, structural rearrangements (including reorganization of water ordering in the close neighborhood) must be subjected to tight control.

Solubility is achieved by creating a suitable "packaging." In enzymes (lyases), solenoids are surrounded by numerous random coil and helical fragments which appear to act as their "guardians." In most cases, these short fragments are well aligned with the Gaussian distribution and therefore promote solubility. Equally important are helices which exist at either end of the solenoid: these "caps" prevent the solenoid fragment from growing indefinitely (or forming a complex with another solenoid), which it would otherwise be capable of. Again, these helices are locally highly consistent with the 3D Gaussian distribution and admit water into close proximity of the protein, thus preventing complexation. The presence of helices along solenoid seems to play a role in mediation with water making the large molecule soluble and protected against uncontrolled complexation.

The structure of lyases is particularly intricate and it seems that their structural complexity acts as a "transmitter," sending out information to the environment. The signal alters the structural properties of water in a

way which can be recognized by the intended ligand. Of course, water plays a key role at each step of this process—by reacting in specific ways to hydrophobic/hydrophilic conditions, it is capable of transmitting information across considerable distances. The same principles are employed in the so-called iceberg model of protein interaction [19].

In summary, the enzyme molecule is not only a tool which facilitates a certain reaction, but also a transmitter, which sends out signals by modulating the properties of its aqueous environment.

Amyloid structures

Where should amyloids be positioned in the presented hierarchy? As already mentioned, an amyloid may be characterized as a nonintelligent ribbonlike micelle, which—from the biological point of view—is generated for no reason, and fulfills no purpose. It is the result of physiochemical processes and carries no information. While their structure, consisting of alternating bands of high and low hydrophobicity, transmits a signal out into the environment, that signal also serves no purpose, other than altering the properties of the solvent. It is akin to transmitting and endless sequence of repeating tones. One may speculate that perhaps the signal is not recognized by any digestive enzyme and while amyloids exists untouched being resistant for degradation processes.

The protein is an intelligent micelle

In conclusion we can state that the protein is a highly intelligent micelle which carries information encoded in its own structure (proper fold), can send signals into the environment (e.g. to recognize its intended substrate or ligand), is capable of specific interaction, and has a specific activity profile, which may also account for its own degradation (interaction with digestive enzymes). While the aforementioned properties may seem difficult to describe using only 20 amino acids, it turns out that nature has managed to accomplish this goal.

If we accept the premise that proteins carry significant (though varied) amount of information, then their overall tendency to adopt micellar conformations (whether spherical or elongated) must be countered by a process which produces deviations from this theoretical model. While the micellar characteristics of proteins may be explained by invoking an external force field (i.e. a 3D Gaussian), it is not quite as obvious how certain targeted

deviations emerge. One conclusion seems inescapable: the native form of a protein represents a compromise between holistic forces (the tendency to generate a micelle) and specific means of encoding information. Models which focus only on optimization of internal force fields cannot accurately capture this property.

When submitting this work for publication the authors remarked that, unlike other similar books, this one is prospective in character. To-date publications which the authors have had the opportunity to study adopt a retrospective approach to amyloidosis: they refer to past experiments and entrenched theories. In contrast, the authors prospectively suggest that further research on amyloids should acknowledge the structural properties of the aqueous environment. These properties—which include, among others, on the presence of solvated ions, nonpolar compounds, temperature and aeration—may, in some cases, promote generation of structures capable of unrestricted elongation, and devoid of "caps" (unlike solenoid fragments found in many biologically active proteins). In general terms, understanding the ways in which proteins control and exploit information (e.g. to interact with other molecules) is necessary to explain certain biological processes on the molecular level—including amyloidosis, which should be regarded as a chemical phenomenon rather than a biological one, and therefore not subject to laws which control the behavior of living organisms.

The protein may be compared to an intelligent micelle, while an amyloid represent a nonintelligent ribbonlike micelle. The amyloid transformation process robs the protein of information describing its intended role, and instead produces a repetitive, deterministic structure consisting of multiple identical units (peptides). This repetitive character explains the bandlike distribution of hydrophobicity in amyloid fibrils. Amyloidogenesis (which often depends on external factors, such as shaking) means introducing order among fragments with identical sequences—especially from the point of view of hydrophobicity distribution. A distribution which diverges from the theoretical monocentric Gaussian—for example by introducing a hydrophilic breaker between two local hydrophobicity maxima—may represent a seed for amyloid transformation. This is evident e.g. in the V domain of the immunoglobulin light chain.

In light of the hypothesis presented in this chapter, the process of amyloidogenesis corresponds to forfeiture of information, which produces an information-free structure. The process strips the biological molecule of its purpose-built nature and turns it into a nonintelligent entity, subject only to physiochemical mechanisms. This is the way—as speculated—of transthyretin amyloid transformation (Chapter 12).

The authors are aware that the presented view is controversial. Nevertheless, the ubiquitous presence of water and its effect on polypeptide chains seem to be of key importance in explaining the properties of proteins. If this controversial hypothesis engenders further debate, the authors will consider their work to have been a success. Likewise, we would be very grateful for any critical remarks our readers would care to formulate.

As shown in Fig. 4.1 amyloid transformation may occur spontaneously (*in vivo*), which is considered a pathological process. *In vitro* almost any protein can be converted into an amyloid, as indicated by arrows in the figure.

The presence and role or water environment is discussed in other papers [20,21]. Characteristics and physico-chemical properties of water particularly water in contact with hydrophobic surface are discussed in details in Refs. [22–28].

The list of references given below represents the step-wise development of the model presented here and they can be treated as the base for hypotheses presented in this work [29–43].

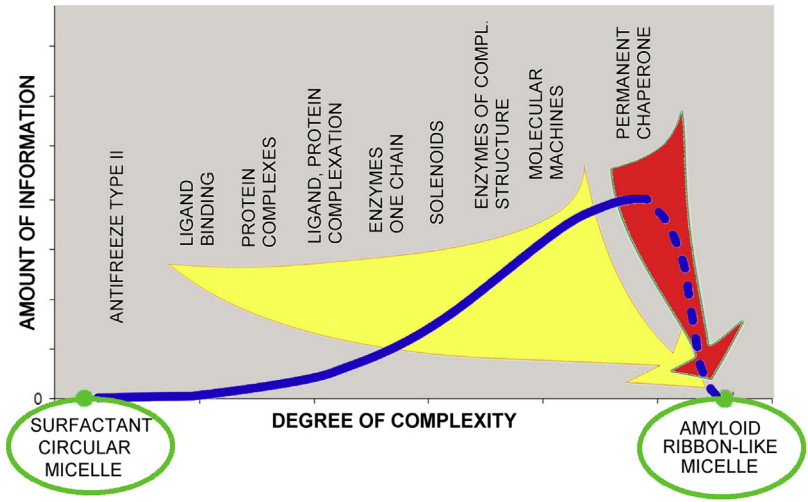

Fig. 4.1 Graphical depiction of the increased quantity of information (arbitrary units) carried by increasingly complex protein structures. Spherical and ribbonlike micelles are regarded carrying low information quantity due to their high degree of deterministic symmetry. Yellow arrow (white in print version)—amyloid transformation as observed *in vitro* (by shaking); red arrow (gray in print version)—spontaneous amyloid transformation *in vivo*, mostly affecting proteins which lose their permanent chaperone and adopt deterministic forms which lead to amyloid structures. Teal frame and dot—zero-information state. Gray frames—single-chain molecules. Dashed line—pathological process.

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