Japan Journal of Research

Short Communication

Structural Characteristics of Ribosome Proteins

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- Received Date: 08 Nov 2024
- Accepted Date: 18 Nov 2024
- Publication Date: 21 Nov 2024

Keywords

ribosome; protein structure; water environment; micelle-like

Abstract

A complete ribosome structure is formed after the 30S and 60S subunits leave the cell nucleus, where all the components of these structures are synthesised. The subunits composed of rRNAs and r-proteins are already constructed in the nucleus. The order of attachment of the r-proteins is already understood. However, the mechanism of the attachment process is not known. The use of a modified fuzzy oil drop model (FOD-M) reveals how hydrophobicity is organised within each protein molecule. This analysis enables an indication of the degree of structural preparation of a given protein for its place within a common structure. The model also assesses the contribution of other, non-aquatic environmental factors to the folding process, which may give rise to speculation about the formation of the 30S unit structure. The 30S structure of the bacterium Thermus thermophilus, available in the Protein Data Bank, which provides data on the composition and three-dimensional structure of this unit, allows the status of the proteins present in the unit to be assessed.

Introduction

The ribosome is an example of macromolecular machines composed of rRNA molecules and proteins in both the 60S and 30S parts of this structure [1]. The role of the ribosome is biological protein synthesis [2,3]. The complex layout of this structure and the complex process of its formation prompts questions about the mechanism of the process of forming this elaborate tool. Both rRNAs and r-proteins synthesised in the cell nucleus build their structures already in the nucleus. The 30S subunit is transported into the cytoplasm, where it combines with the S60 subunit to form a mature structure ready for biological activity in the cytoplasm [4]. The process of ribosome-mediated protein synthesis is satisfactorily understood [5,6]. In contrast, the construction of the macromolecular machinery responsible for this process, despite access to experimentally determined structures, remains a mystery.

The importance of RNA molecules cannot be overestimated, especially in the context of evolutionary studies dating back some 4 billion years, where the organisation of life based on these molecules has been demonstrated [7]. An analysis identifying the predisposition of proteins to complex RNA molecules used an analogy with protein-DNA interactions [8]. The undoubtedly broad functional importance of RNA molecules for many processes is due to the large spectrum of RNA molecules, DNA, proteins, lipids, and metabolites with which RNA molecules interact [9]. The large number of recognised ribosomes, especially in the context of the presence of proteins allows this set to be referred to as a proteform, the analysis of which will allow the generalised term 'ribosome code', for which it will become possible to decode the functional significance of the presence of proteins in the ribosome structure [10]. Research into the structure and function of the robosome is facilitated by access to experimentally identified structures [11-14].

The steps of 30S construction involve the bonding of proteins with the corresponding rRNAs. The sequence of protein attachment and their mutual influence on this process has been uncovered [15]. In this paper, an attempt was made to analyse the status of the proteins comprising the 30S subunit from *Thermus thermophilus*, the structure of which is available in PDB under ID 1HNW [16].

Here, the structural characterisation of the proteins present in this arrangement is analysed with a perspective of the presumed folding process of these proteins, the possible involvement of non-aqueous factors in this process and how the structure of the whole arrangement adapts.

This is because it is assumed that proteins folding in a polar water environment tend to build a structure with centrally placed hydrophobic residues with a polar shell to form a hydrophobic nucleus system. A nucleus with this structure is considered to be a factor

Citation: Roterman I, Stapor K, Dułak D, Konieczny L. Structural Characteristics of Ribosome Proteins. Japan J Res. 2025;6(2):095

in stabilising the tertiary structure alongside disulphide bonds, which are not always present in protein structures. However, the mere finding of an organised, centrally located hydrophobic nucleus is a significant factor in the stabilisation of the structure. In addition to proteins (and domains treated as independent structural units) showing the presence of an organised hydrophobic nucleus (down-hill, fast-folding, and ultra-fast-folding proteins [17]), proteins with a local mismatch to the idealised hydrophobicity distribution are identified. This local mismatch is very often a form of biological activity recording. A local deficit in hydrophobicity indicates the presence of a cavity – a site of interaction with either the ligand or the substrate [18]. Local exposure of hydrophobic residues often provides a site for complexing another protein [19].

Exposure of hydrophobic residues with centralisation of polar residues is identified in membrane proteins acting as a channel for the transport of specific molecules or ions [20].

Also identified is the mismatch of hydrophobicity distribution towards a micelle-like arrangement encompassing the entire protein molecule, suggesting a different folding strategy aimed at achieving a different distribution associated with the biological function performed. This mismatch to a stable arrangement with a centrally located hydrophobic nucleus introduces a different distribution of the potential flexibility of the structure or even the dynamics of the whole molecule. This may also have to do with the possibility of constructing allosteric forms, which require an appropriate distribution of areas which vary in stability.

This is the characterisation of the protein components of the 30S ribosome presented in this paper. The objective is to indicate the influence of external factors in production of the final, biologically active structural form of the proteins involved in this structure. The interaction of proteins with rRNA, which is based on polar interactions, is expected to use polar residues on the surface of proteins, which will be confirmed by micelle-like structuring in the proteins of interest.

Materials and methods

Data

The object of the analysis was a set of proteins included in the structure of the *Thermus thermophilus* 30s ribosomal subunit (PDB ID 1HNW [16]. Only protein molecules present in 30S were analysed.

Description of the FOD-M model

The fuzzy oil drop model has already been described in numerous works [21]. An abbreviated form is presented here to properly interpret the results presented.

This is based on the assumption that the folding protein strives to reproduce a micelle structure with concentrated hydrophobic residues in the centre of the molecule with exposure of polar residues on the surface. This results from the interpretation of amino acids as bi-polar molecules. The description of the hydrophobicity distribution in a micelle-like arrangement is expressed by a 3D Gaussian function spanning the molecule under analysis:

$$\tilde{Ht}_j = \frac{1}{\tilde{Ht}_{sum}} \exp\left(\frac{-(x_j-\bar{x})^2}{2\sigma_x^2}\right) \exp\left(\frac{-(y_j-\bar{y})^2}{2\sigma_y^2}\right) \exp\left(\frac{-(z_j-\bar{z})^2}{2\sigma_z^2}\right) \quad \text{Eqn 1.}$$

The parameters σx, σy and σz express the size and shape of the molecule under analysis. The arrangement of hydrophobicity conforming to the 3D Gaussian function expresses the presence of a centric hydrophobic nucleus with a polar shell.

The actual hydrophobicity distribution, however, results from the inter-amino acid hydrophobic interaction expressed by a function proposed by M. Levitt [22].

$$\tilde{Ho}_j = \frac{1}{\tilde{Ho}_{sum}} \sum_{i=1}^{N} (H_i^r + H_j^r) \begin{cases} \left[1 - \frac{1}{2}\left(7\left(\frac{r_j}{c}\right)^2 - 9\left(\frac{r_j}{c}\right)^4 + 5\left(\frac{r_j}{c}\right)^6 - \left(\frac{r_j}{c}\right)^8\right)\right] & \text{for } r_j \le c \\ 0 \text{ for } r_j > c \end{cases} \quad \text{Eqn 2.}$$

with c being the cut-off of 9 Å (according to [22]) and rij being the distance between the positions of the effective atoms (the averaged position of the atoms comprising the amino acid). The normalisation of the two distributions allows measuring measure the degree of similarity of the distributions expressed by the divergence entropy proposed by Kullback-Leibler [23].

$$D_{KL}(P \mid Q) = \sum_{i=1}^{N} P_i \log_2 \frac{P_i}{Q_i} \quad \text{Eqn 3.}$$

The difference between the distributions: the analysed Pi (in the FOD-M model, it is the distribution O) compared to the reference distribution Qi (in the FOD-M model it is the distribution T) expressed by $D_{KL}(O|T)$ cannot be interpreted. Therefore, a second reference distribution devoid of hydrophobicity centralisation (uniform distribution of hydrophobicity throughout the molecule) was introduced with Ri = 1/N with N being the number of amino acids in the chain. By comparing the values of $D_{KL}(O|T)$ and $D_{KL}(O|R)$, it is possible to determine the status of the distribution O as being either close to the distribution T or to the distribution R, allowing the degree of presence of a hydrophobic nucleus to be assessed. To assess this status, the parameter RD (Relative Distance) was introduced.

$$RD = \frac{D_{KL}(O \mid T)}{D_{KL}(O \mid T) + D_{KL}(O \mid R)} \quad \text{Eqn 4.}$$

An RD value < 0.5 suggests the presence of a hydrophobic nucleus. Using the RD value, the degree of micelle-like organisation can be assessed. Micelle-like organisation (with low RD values) has been identified in down-hill, fast-folding or antifreeze type II proteins [17].

A local deficit in hydrophobicity implies the presence of a cavity, often prepared for interaction with a substrate or ligand [17,18]. Local excess hydrophobicity is interpreted as a site of potential coordination of another protein leading to the construction of a complex [19].

The polar water environment directing the folding process towards the formation of a hydrophobic nucleus is not unique to protein function. The membrane environment expects exposure of hydrophobic residues with a concentration of polar residues in the central part (especially for ion channels). This distribution is opposite to the distribution expressed by the Gaussian function. To describe the hydrophobicity distribution for membrane proteins, it was expressed using the function:

$$T_{MAX} - T_i \quad \text{Eqn 5.}$$

However, it turns out that the distribution in membrane proteins can be expressed by a combination of a 3D Gaussian function and a complementary function to the extent expressed by the parameter K:

$$M_i = \left[T_i + K * \left[T_{MAX} - T_i\right]_n\right]_n \quad \text{Eqn 6.}$$

The fit of the function M for a suitable value of the parameter K (the minimum value of DKL(O|M)) determines the extent to which a non-polar water environment affects the structuring of proteins stabilised by the hydrophobic membrane environment [20,21].

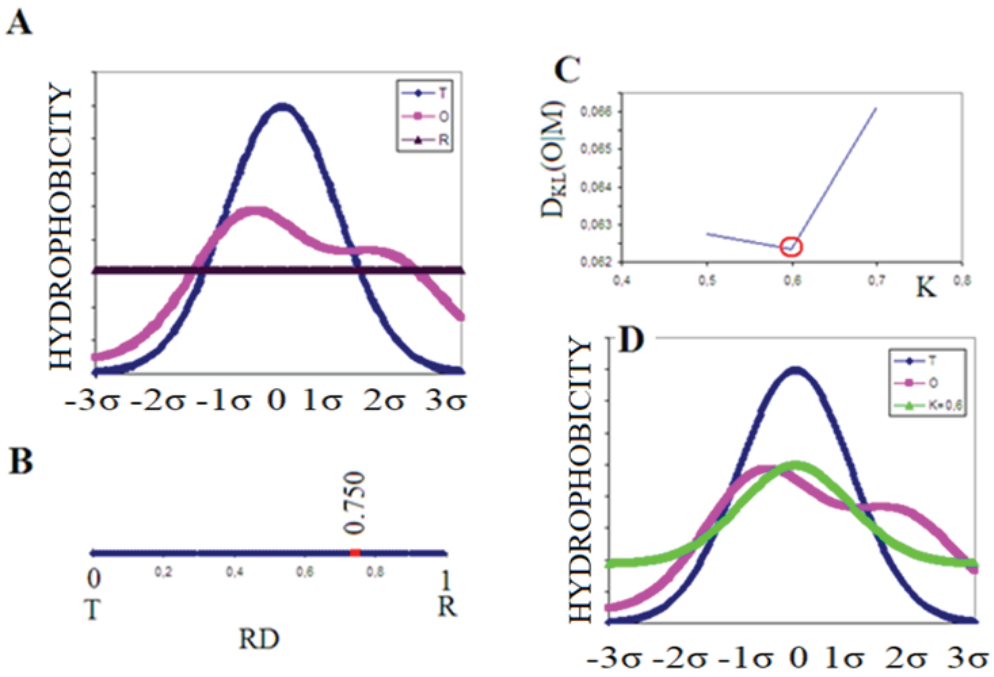


Figure 1. *Visualisation of the FOD-M model*
A – example set of the distribution T (blue), O (red) and R (gray) reduced to a 1D form
B – visualisation of the parameter RD value – for example, the value RD = 0.750 was obtained for A
C – finding the optimum value of the parameter K=0.6 minimum for the given system of distributions O and T for the value DKL(O|M)
D – juxtaposition of the distribution T (blue), O (pink) and M (green) to showcase the example.

The FOD-M model is presented graphically in Fig. 1.

The interpretation of the FOD-M model parameters is as follows:

1. The RD value expresses the degree of dissimilarity of the distribution O from an idealised distribution that fully conforms to the 3D Gaussian distribution. The higher the value of RD, the lower the organisation of the centric hydrophobic nucleus.
2. The value of the parameter K expresses the degree of effect of other non-aqueous factors (including hydrophobic factors in particular) on the folding process, driving the individual amino acid according to the specific environment. The higher the K value, the more reduced the effect of polar water on the protein folding process.
3. The values of the parameters σx, σy and σz parameters reveal the shape of the molecule. The closer the values of these parameters are to the spherical structure of the protein in question.

The proteins discussed in this work, which are part of the 30S ribosome, are characterised by the indicated parameters, assessing the degree of differentiation of their structure in geometrical as well as functional terms, assuming the presence of a hydrophobic nucleus as a significant factor in the stabilisation of a given protein molecule.

A high K value is interpreted in relation to membrane proteins as the involvement of a strictly hydrophobic factor. However, it appears that water-soluble structures are sometimes subjected to the persistent presence of a specific 'permanent chaperone', which highly stabilises a structuring far from that which would be formed by the aqueous environment [24].

Programs used

The potential user has two possible access to the program :

The program allowing calculation of RD as well as T and O distribution is accessible upon request on CodeOcean platform: https://codeocean.com/capsule/3084411/tree. Please contact the corresponding author to get access to your private program instance.

The application - implemented in collaboration with the Sano Centre for Computational Medicine (https://sano.science) and running on resources contributed by ACC Cyfronet AGH

(https://www.cyfronet.pl) in the framework of the PL-Grid Infrastructure (https://plgrid.pl) - provides a web wrapper for the abovementioned computational component and is freely available at https://hphob.sano.science.

The VMD program was used to present the 3D structures [25,26]

Results

The analysis presented here is based on the 30S unit construction process model available in [15].

Interpretation of the distribution of hydrophobicity in the analysed proteins and their inter-protein interactions allows the definition of proposed mechanisms leading to the formation of a stable, permanent complex composed of rRNA and proteins.

The status of individual proteins is determined. Proteins showing domain structure are also characterised by treating each domain as a structural unit (the construction of an individual 3D Gaussian function spanning a domain).

The analysis also specifies inter-protein interactions that, in context with the mechanism proposed in [15] may suggest the course of the 30S unit structuring.

Table 1. *Summary of parameters characterising the different protein chains present in the ribosome structure. Identification of chains according to PDB files (first column) and according to the chain ID per the notation introduced by the authors of the structure [27]. The RD and K values for complete chains are specified. The RD values in the next two columns indicate the status of a chain without the residues involved in interactions with other polypeptide chains.*

CHAIN	ID	DOMAIN	RD	K	SS BONDS	P-P	RD No P-P
B	uS2	(10-97)+(154-240) (98-153)	0.529	0.5		7	0.54
			0.463	0.4			
			0.565	0.6			
C	uS3	(17-107) (108-207)	0.588	0.7		27	0.598
			0.477	0.4			
			0.462	0.4			
D	uS4	(2-97)+(195-208) (98-194)	0.544	0.7	SS 9-31	9	0.55
			0.54	0.6			
			0.285	0.1			
E	uS5	(5-68) (69-143)	0.536	0.4		20	0.527
			0.433	0.3			
			0.513	0.5			
F	bS6		0.532	0.5		22	0.475
G	uS7		0.537	0.5		7	0.522
H	uS8	(3-80) (81-139)	0.547	0.3		14	0.477
			0.464	0.3			
			0.474	0.3			
I	uS9		0.404	0.3		7	0.42
J	uS10		0.577	0.6		24	0.473
K	uS11		0.43	0.3		15	0.405
L	uS12		0.589	0.5		5	0.469
M	uS13	(2-72) (73-126)	0.587	0.8		7	0.572
			0.335	0.2			
			0.575	0.8			
N	uS14		0.437	0.4		17	0.402
O	uS15		0.382	0.3		1	
P	uS16		0.415	0.3			
Q	uS17		0.491	0.4		4	0.466
R	uS18		0.397	0.2		5	0.419
S	uS19		0.33	0.1		8	0.338
T	uS20		0.482	0.4			
V	bTHX		0.381	0.1			

The collective determination of the status expressed by parameters RD and K of individual proteins and domains treated as individual structural units is presented in Table. 1 where the number of residues involved in inter-protein interactions is also provided. The status of the part of the protein without the residues involved in interaction with other proteins was also determined. The RD value for such a part of the protein compared to the RD value determined for the complete molecule reveals the status of the residues involved in the interaction. If elimination results in a reduction of RD, it means that the residues involved in the interaction with another protein show a status locally different from the micelle-like arrangement.

The summarised values reveal the varying status of the proteins. The micelle-like organisation of hydrophobicity is interpreted as having been formed in a polar water environment driving hydrophobic residues towards the centre exposing polar residues at the surface. Their role within the ribosome can be considered as organisation centres for the arrangement of rRNA

molecules as the interaction between these molecules is polar.

The group of proteins described by high values of the parameter K is structured with the involvement of non-aqueous factors including hydrophobic factors in particular. This means that the structure of these proteins can be interpreted as being stabilised by the environment to which the protein adapts its conformation. Here, the environment acts as a permanent chaperon preventing water-adapted folding.

Proteins were selected to visualise the examples discussed in detail:

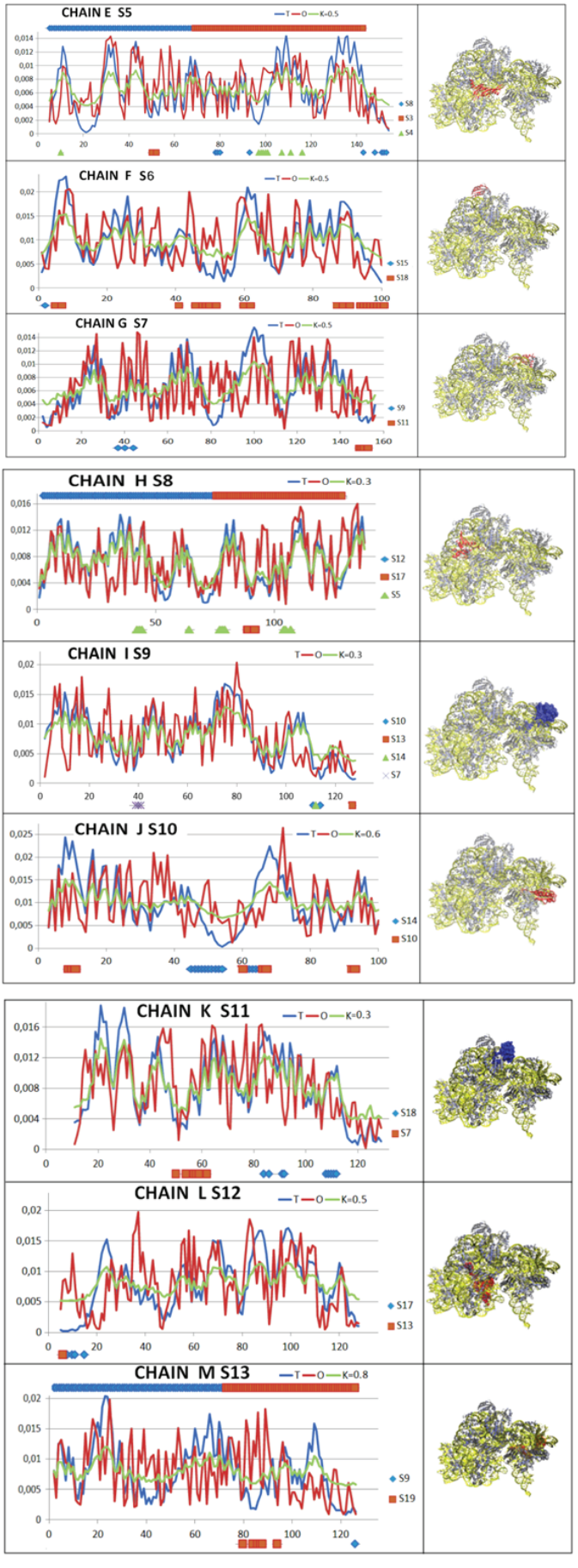
1. With the lowest RD and K values — proteins that can be assumed to have folded in an aqueous environment
2. With the highest RD and K values — proteins that have adapted to the conditions imposed by the corresponding parts of the ribosome, as interpreted using the FOD-M model, the protein in contact with the permanent chaperone, being rRNA molecules in this instance.

The criteria listed above appear to be consistent with the geometric criteria. Low RD and K values are accompanied by globular structuring (the sigma parameter values are comparable) while high RD and K values occur in cases of irregular structures (high discrepancy between sigma parameter values).

The alignment of the distribution O with the distribution T with a minimal correction in the form of the distribution M (for K=0.1) proves the presence of a hydrophobic nucleus with a polar surface. This polar surface in contact with the surrounding aqueous environment on the one hand and with the polar rRNA groups on the other turns out to be optimal for both contact with water and with the polar rRNA groups.

Figure 2. presents a summary of profiles T, O and M for the respective parameter K values of all the proteins of interest. Domain partitioning and the location of residues involved in the inter-protein interaction are also provided. The proteins in red have a status with RD>0.5; the proteins in blue have a status with RD<0.5.

The interpretation of the graphs presented is provided above.



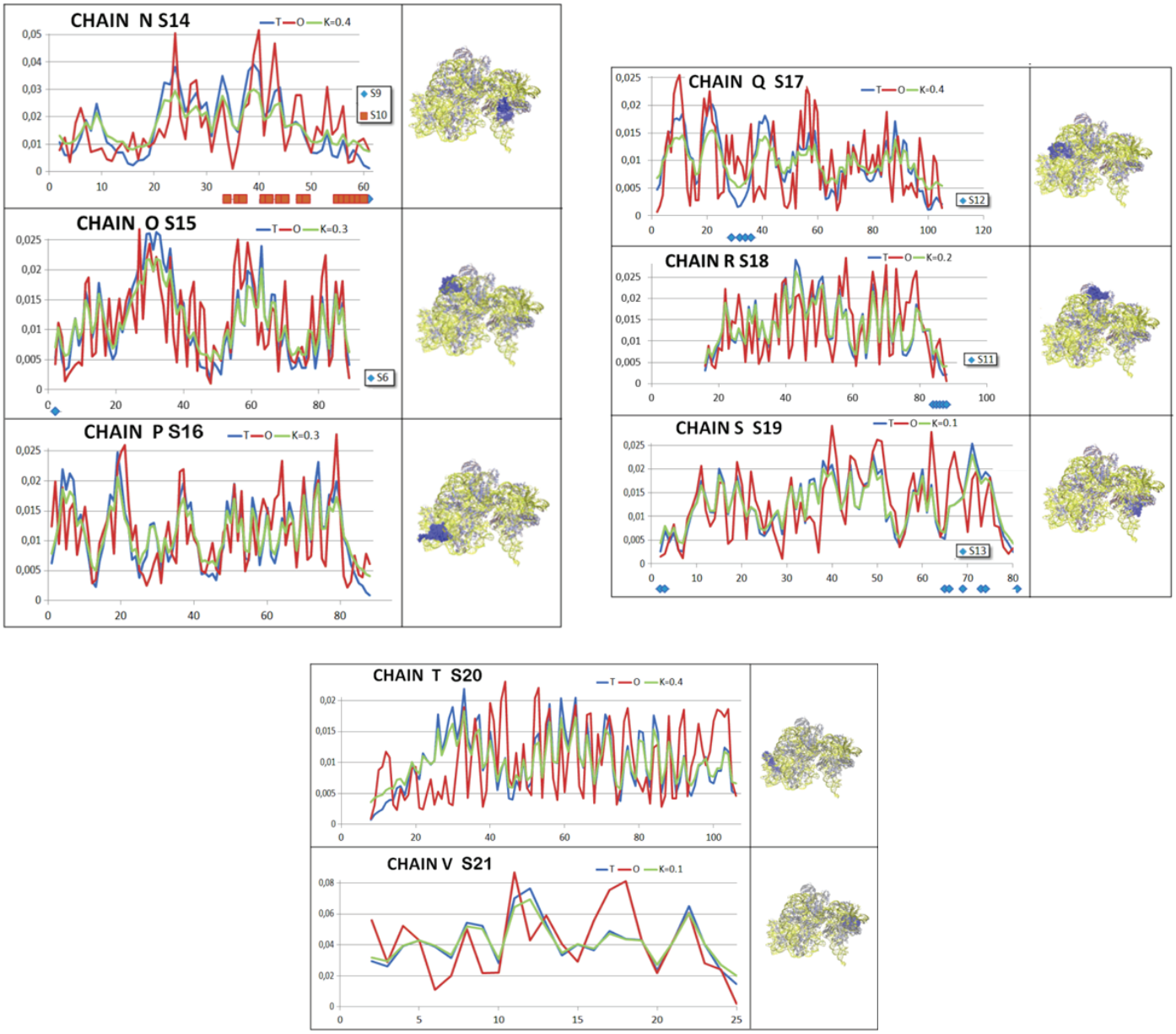


Figure 2. *Summary of profiles T, O and M for the respective parameter K values indicating the status of the 30S proteins present. The location of the proteins within the entire 30S subunit (yellow lines) is shown. A uniform three-dimensional orientation of the entire subunit was adopted to visualise the locations with respect to the other proteins and the subunit surface. Top lines: colour identification of domains, bottom axis positions: the residues involved in interactions with other proteins; the colour variation identifies the protein with which the interaction takes place.*

Inter-chain interaction

Protein complexes (IV-order structure) operating in aqueous environments are often built on the principle of contact of a hydrophobic surface exposed to the surface of the interacting proteins. The elimination of such residues for the calculation of the RD value results in a reduction of the latter. If the elimination of the residues forming the interface results in an increase in the RD value, this means that residues with a status matching the idealised distribution have been eliminated.

A classic example of chain complexing leading to the generation of a common hydrophobic nucleus stabilising the complex is utrophine and dystrophine [19]. These molecules, by virtue of their function of tight integration into protein molecules associated with high dynamics and stresses, ensure stabilisation and return to the initial structure after the disappearance of sources of stress.

The arrangement of residues in the interchain interphase within the ribosome does not show this characteristic. The RD values given for the part of the chains without the residues involved in the inter-chain interaction change slightly the RD value determined for the complete chain. For complexes based on hydrophobic interactions, the elimination of interphase residues significantly reduces the RD value by eliminating local mismatch in the form of hydrophobicity exposure on the protein surface. In the examples discussed here, such regularity is not the case (Table 1.)

The complexing of the proteins discussed here involving exposed hydrophobic residues involves chains F, H, J, and L. In

other cases, the change in RD after elimination of the residues forming the interface is negligible. Examples with increased RD after elimination of interface residues demonstrate the involvement of polar residues that are correctly located on the surface.

A detailed presentation of the distributions T, O and M for the respective K values reveals the specificity of each ribosomal protein. The summary also visualises the location within Unit 30S with its fixed three-dimensional orientation. The status of the proteins was differentiated by colour: proteins with RD < 0.5 were shown in blue, while proteins with RD > 0.5 (having no centric hydrophobic nucleus) were shown in red.

Figures showing the profiles T, O and M visualise sections involved in interactions with other proteins.

Discussion

The characterisation of the structure of this macromolecular machinery provided above in the context of the proposed model indicates the involvement of external factors in the formation of individual proteins (Figure 3.). A diagram based on the proposal [15] provides the variation in status resulting from the proposed assessment of the structure of a given protein.

The assembly map visualises the construction sequence of the 30S unit. The base is ribosomal 16S RNA. The immediate contact proteins S4 shown with thick arrows indicate a major facilitating effect. This protein, as interpreted by the FOD-M model, represents a status discordant from a micelle-like one. However, one domain singled out in the structure of this protein shows an organisation that is consistent with the arrangement of the centric hydrophobic nucleus. The S7 interaction identified to be weak in respect to 16S RNA shows an arrangement with a hydrophobicity distribution diverging from a micelle-like one. According to the interpretation of the FOD-M model, the structure of this single-domain protein adapts to the arrangement imposed by 16S RNA, as expressed by K = 0.5. This value means that factors outside the polar water are involved in the formation of the structure, albeit the contribution is not radical.

The assembly map authors' interpretation of the weak influence of S4, S8, S20, S9 and S19 resulting in an enhancement for the bonding of S7 to 16S RNA. The status of this protein as distant to the micelle-like arrangement reveals the effect of the mentioned proteins on its structuring (K=0.5).

The thin line connecting the grey box to S11 suggests proteins present in the grey box to stabilise the S11 protein in the complex.

According to the assembly map authors [15], S2 is bonded late in the construction process of the whole arrangement. The authors suggest stimulation of this bonding by S3. The status of S2 in the light of the FOD-M model shows a deviation and a slight influence of the environment on its structuring (K=0.5), although one domain present in this protein shows an organisation consistent with a micelle-like arrangement (K=0.4) while the other domain shows a significant departure expressed with a value of K=0.6.

The status of S7 deviates from the micelle-like arrangement (K = 0.7) although both domains show the presence of a centric nucleus with a polar shell at K = 0.4.

Analysis of the other proteins present in the S14-S20 complex not discussed by the authors of the assembly map [15] shows an ordering of hydrophobicity highly consistent with a micelle-like arrangement. Based on the FOD-M model, this means that they folded under polar water conditions as an external force field. The central hydrophobic nucleus provides stability. The polar surface coating favours contact with water but also interaction with RNA molecules, where hydrophobic interactions do not take place.

However, the structure of S8 with RD > 0.5 (a micelle-like discordance) is determined by the low K value of 0.3 as well as both domains present in this protein.

Noteworthy is the protein S10, whose status is clearly far from a micelle-like according to the arrangement on the assembly maps, remains under significant influence of S9 and S14.

The FOD-M model assumes a significant environmental contribution to the protein folding process. The polar water environment directs structuring towards generating a centrally located hydrophobic nucleus with a polar surface. Local deviations from micelle-like structuring provide insights about the location of the cavity – a local deficit of hydrophobicity and a local excess – the exposure of high hydrophobicity levels on the surface suggests a potential site for complexing another protein. The cell membrane environment – where membrane proteins are also active – expects the exposure of hydrophobic residues with polar residues in the centre.

The environment within the ribosome is different from the two mentioned. Given the characteristics of rRNA molecules, an analysis of phenomena based on hydrophobicity is not reasonable. However, the question arises as to how the proteins within it adapt to this unusual environment.

The demonstrated variation in their status in the form of very high RD values alongside examples with very low RD values may suggest a different involvement in the construction of the complex system that is the ribosome.

Proteins with low RD values can be thought of as coordinating centres of the environment through the imposed orientation of polar groups of rRNA molecules.

Proteins with very high RD values are proteins that have adapted to the backbone imposed by the arrangement of rRNA molecules.

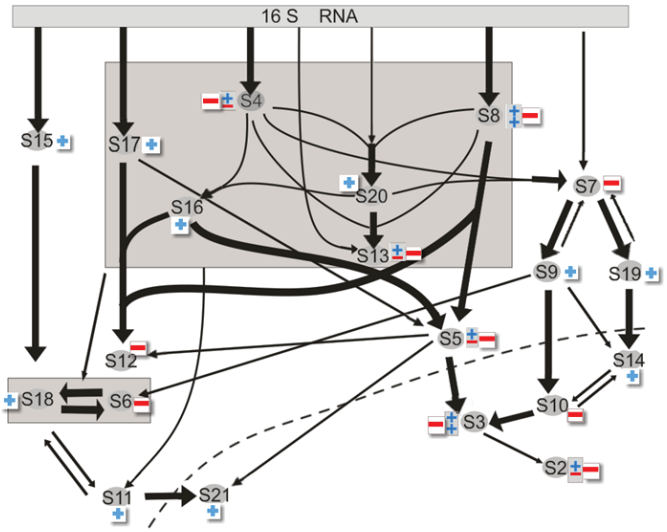


Figure 3. *Assembly map of 30S according to [15]. Red horizontal lines – status of the structural unit – discordant versus the micelle-like; blue + – status accordant in respect to micelle-like hydrophobicity distribution. Two symbols in vertical orientation – status of domains treated as individual structural units in the protein of interest.*

The significance of the K value in the proteins in question is somewhat different from that applied to proteins operating in a polar water environment and a hydrophobic membrane. According to the FOD-M model, the value of the parameter K is interpreted as the contribution of non-polar water to protein structuring. Here, the magnitude of this parameter can only be used to assess the degree of deformation towards the globular system. It can be assumed that this value expresses a degree of structuring orientation different from the structuring present in the aquatic environment. Here, the arrangement of the protein may result from an imposed distribution of polar groups that is different from the water environment.

The reference proteins present in the analysis presented here aim to show the difference and structural specificity but also the different mechanism leading to the biologically active form. In reference proteins, it is the pursuit of stability resulting from the construction of a common hydrophobic nucleus that is the mechanism for ensuring stability under the varying operating conditions of a given protein.

Conclusion

The specificity of the proteins that make up the ribosome illustrates their differentiated structure from the point of view of hydrophobic nucleus construction. In addition to proteins showing a near-perfect micelle-like structure to relatively high RD and K values suggesting the need to adapt their structures to external conditions. The relation of the assessment of the degree of deviation from a micelle-like organisation to the role in the macromolecular machine structure indicated in [21] indicates the need for differential structural adaptation to the conditions under which individual proteins perform within a common structure. Most of these occupying positions on the surface of the 6S unit show structuring with very low RD and K values providing a favourable contact with the polar water environment. The contact in rRNA is also based on the principles of non-bonding electrostatic and vdW-type interactions, which means exposure of polar groups. .

Funding details

This work was supported by the Jagiellonian University – Medical College under Grant N41/DBS/001127.

This research was partially supported by the European Union's Horizon 2020 Program under grant no. 857533 and the Sano project carried out within the International Research Agendas Program of the Foundation for Polish Science and was co-financed by the European Union under the European Regional Development Fund.

We also gratefully acknowledge Polish high-performance computing infrastructure PLGrid (HPC Center: ACK Cyfronet AGH) for providing computer facilities and support within computational grant no. PLG/2024/01739.

Disclosure statement

The authors report there are no competing interests to declare.

Data availability statement

All presented results can be recreated using the programs available in open access in the chapter : Materials and Methods.

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