Intrinsic Dynamics of the Aminoacyl tRNA Synthetases

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Abstract

The 20 Aminacyl tRNA Synthetases (AARSs) are grouped into two broad classes (class I and II) based on their structure and their interactions with the tRNA molecule. We explored the role of internal protein dynamics in the catalytic function of these enzymes. Specifically, we investigated if the subclasses (class Ia-c and IIa-c) of AARS enzymes exhibit any distinct patterns of motion. Protein dynamics were studied by conducting computer simulations of protein 3-dimensional movement. We compared the movement of protein domains of 20 AARSs and related that movement to the existing classification of AARSs based on 3D structure. In general, the classification based on dynamics was found to be similar to that obtained based on sequence/structural homology for most of the enzymes. However, seryl-tRNA synthetase (SerRS) is an exception; the data suggest that SerRS is more similar to the class IIb AARSs instead of the IIa AARSs. We have also identified other general patterns including that all CP domains are generally anti-correlated to catalytic domains, class I tRNA binding domains are partly correlated and partly anti-correlated to other domains while class II tRNA binding domains are predominately anti-correlated to catalytic domains and correlated to CP domains.

Background

- AARSs catalyze the addition of amino acids to tRNAs[1]
- This is crucial for the accurate translation of the genetic code[1]
- Current classification is based on structural homology and reaction mechanism (Table 1)

Table 1. The differences in structure and catalysis between Class I and Class II AARSs.[1,2]

Property	Class I	Class II
Substrate Binding Motif	HIGH, KMSKS	Motif 2/3
Active Site Character	Parallel β-sheet of Rossmann fold	Antiparallel β-sheet
ATP Conformation	Extended	Bent
Aminoacylation Site	2'OH of tRNA	3'OH of tRNA
tRNA Binding	Minor Groove	Major Groove

- The two classes of AARS can be further divided into 6 subclasses (Table 2)

Table 2. The class/subclass of each amino acid and the multimeric composition of each enzyme in *E. coli* (e.g. α_2/β_2 signifies 2 alpha subunits and 2 beta subunits).[1,3]

	a	b	c
Class I	Leu (α)	Tyr (α_2)	Arg (α)
	Ile (α)	Trp (α_2)	Gln (α)
	Val (α)		Glu (α)
	Cys (α_2)		
	Met (α_2)		
Class II	His (α_2)	Asp (α_2)	Gly (α_2/β_2)
	Pro (α_2)	Asn (α_2)	Ala (α_4)
	Ser (α_2)	Lys (α_2)	Phe (α_2/β_2)
	Thr (α_2)		

- The 3D structure of a protein is known to be encoded by the primary structure[4]
- The movement of a protein could also be encoded by the primary structure
- Proteins with significant homology should have similar protein dynamics.
- Normal Mode Analysis (NMA) can be used to study the dynamics of a protein[5]
- NMA calculates the motion of amino acid residues in relation to each other[5]
- To simplify the calculations only the alpha carbons of amino acids are used[5]

Class I AARSs

Class Ia

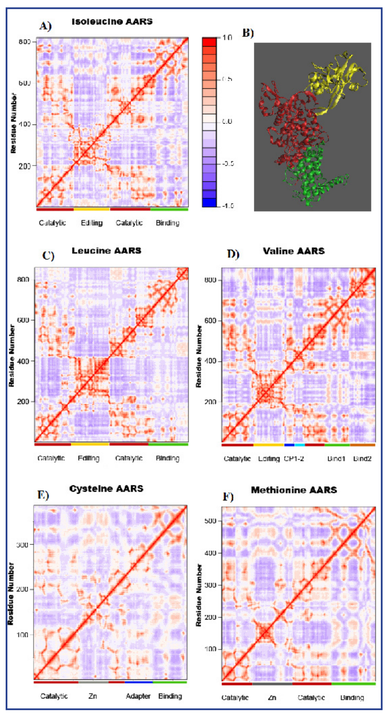

Figure 1. a) Cross-Correlation Matrix of IleRS. Y-axis indicates residue number. Red colors indicate correlated motion between the two residues, while blue indicates anti-correlated motion. X-axis is a color coded label for each domain along the amino acid sequence. The catalytic domain is interrupted in primary structure, but not in tertiary structure. **b)** The corresponding 3D protein structure for IleRS, with domains colored in the same manner as the correlation matrix. **c) – f)** The cross-correlation matrices of LeuRS, ValRS, CysRS and MetRS.[5,7]

Class Ib

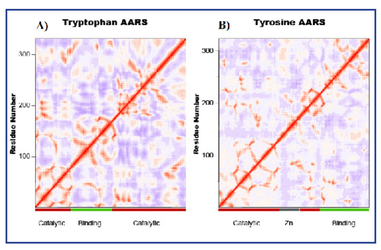

Figure 2. a) The cross-correlation matrix of TrpRS. b) The cross-correlation matrix of TyrRS.[5]

Class Ic

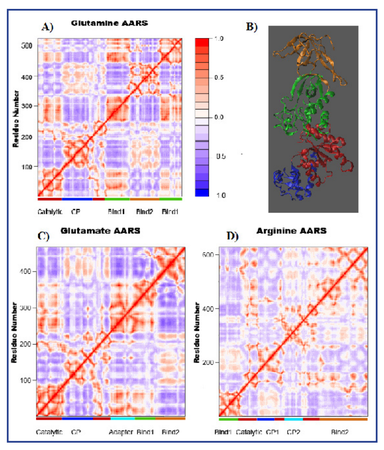

Figure 3. a) Cross-Correlation matrix of GlnRS. The catalytic domain is interrupted in primary structure by a CP domain along with the first tRNA binding domain being interrupted by the second tRNA binding domain. **b)** The corresponding 3D protein structure for GlnRS, with domains colored in the same manner as the correlation matrix. **c) – d)** Cross-correlation matrices for GluRS and ArgRS.[5,7]

Class II AARSs

Class IIa

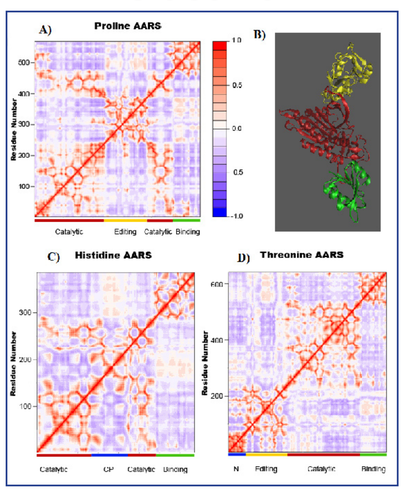

Figure 4. a) The cross-correlation matrix of ProRS. The catalytic domain is interrupted by an editing domain. **b)** The corresponding 3D protein structure for ProRS, with domains colored in the same manner as the correlation matrix. **c) – d)** Cross-correlation matrices for HisRS and ThrRS.[5,7]

Class IIb

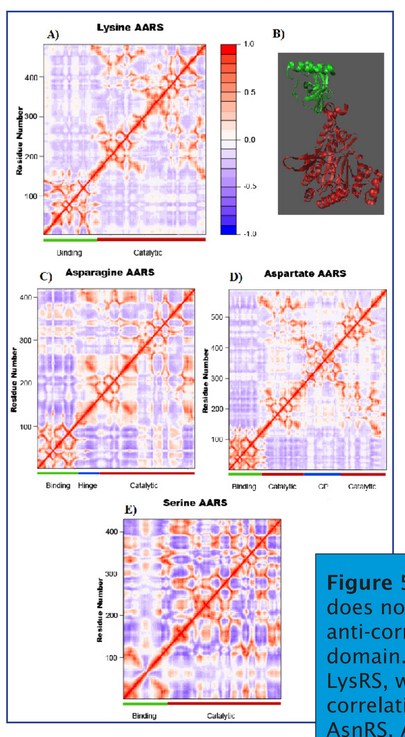

Figure 5. a) Cross-correlation matrix of LysRS. The enzyme does not contain a CP domain, but residues 305-375 show anti-correlated motion compared to the rest of the catalytic domain. **b)** The corresponding 3D protein structure for LysRS, with domains colored in the same manner as the correlation matrix. **c) - e)** Cross-correlation matrices of AsnRS, AspRS, and SerRS. The traditional classification of SerRS is IIa, but the data suggest that the protein dynamics of SerRS are more similar to the IIb AARSs.[5,7]

Class IIc

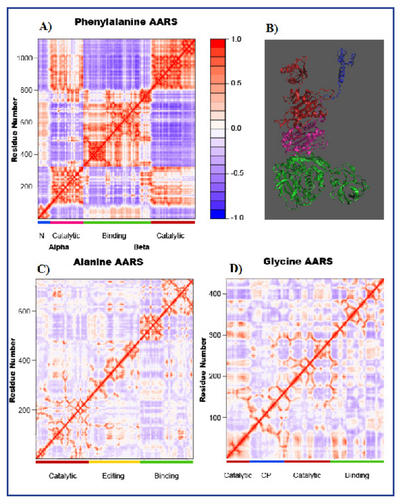

Figure 6. a) Cross-Correlation matrix of PheRS. The two halves of the catalytic domain have a very high level of correlation even though they are on different subunits. **b)** The corresponding 3D protein structure for one alpha and one beta subunit of PheRS. **c) – d)** Cross-correlation matrices of AlaRS and GlyRS.[5,7]

Methodology

- Protein structures were obtained via the Protein Data Bank (PDB) or by homology modeling using the Swiss-Modeling program[6]
- This study attempted to focus on *Escherichia coli (E. coli)* AARSs, but not every structure for E. coli AARSs is known

Table 3. The AARSs protein structure used is listed under its corresponding organism or whether the structure was a homology model. The PDB IDs are in parenthesis. All homology models were done using the PDB ID listed as a template and the sequence for *E. coli* AARS was used as the target.

E. coli		Homology	*P. horikoshii*	*T. thermophilus*
Asp (1EQR)	Lys (1LYL)	Pro (2J3L)	Ala (2ZZF)	Glu (1GLN)
Cys (1LI5)	Met (1P7P)	Ser (2DQ3)	Arg (2ZUF)	Gly (1ATI)
Gln (1NYL)	Phe (3PCO)	Trp (3N9I)	Asn (1X56)	Ile (1ILE)
His (1KMM)	Thr (1QF6)			Val (1GAX)
Leu (4AQ7)	Tyr (1X8X)			

- The vibrations and large scale movements of protein fragments for each AARS were analyzed using Normal Mode Analysis (NMA) and cross-correlation matrices
- NMA was conducted by the WebNM@ webserver
- Only one subunit of each AARS was used for NMA
- For heterodimers, one of each type of subunit was used

Conclusions

- While SerRS has more sequence homology with the class IIa AARSs, this study suggests that the protein dynamics of SerRS are more similar to the IIb AARSs
- All editing domains and catalytic domains are anti-correlated to eachother
- Class I AARS binding domains are partially correlated and partially anti-correlated to the other domains, this mix is accomplished in different ways for each subclass.
- Class II AARS binding domains are mostly correlated to the catalytic domain and anti-correlated to the editing domain

References

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