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The Role of Anionic Protein Residues on the Salt Dependence of the Binding of Aminoacyl-tRNA Synthetases to tRNA: A Poisson-Boltzmann Analysis

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Abstract. Long-range electrostatic interactions in proteins/peptides associating to nucleic acids are reflected in the salt-dependence of the binding process. According to the oligocationic binding model, which is based on counterion condensation theory, only the cationic residues of peptides/proteins near the binding interface are assumed to affect the salt dependence in the association of peptides and proteins to nucleic acids. This model has been used to interpret and predict the binding of oligocationic chains - such as oligoarginines/lysines - to nucleic acids, and does an excellent job in these kinds of systems. This simple relationship, which is used to compare or count the number of ionic interactions in protein-nucleic acid complexes, does not hold when acidic residues, *i.e.* glutamate and aspartate, are incorporated in the protein matrix. Here, we report a combined molecular mechanics (by means of energy-minimization of the structure under the influence of an empirical energy function) and Poisson-Boltzmann (PB) study on the salt-dependence in binding to tRNA of two important enzymes that are involved in the seminal step of peptide formation in the ribosome: Glutamine synthetase (GluRS) and Glutaminyl synthetase (GlnRS) bound to their cognate tRNA. These two proteins are anionic and contain a significant number of acidic residues distributed over the entire protein. Some of these residues are located in the binding interface to tRNA. We computed the salt-dependence in association, SK_{pred}, of these enzyme-tRNA complexes using both the linear and nonlinear solution to the Poisson-Boltzmann Equation (PBE). Our findings demonstrate that the SK_{pred} obtained with the nonlinear PBE is in good agreement with the experimental SK_{obs}, while use of the linear PBE resulted in the SK_{pred} being anomalous. We conclude that electrostatic interactions between the binding partners in these systems are less favorable by means of charge-charge repulsion between negatively charged protein residues and phosphate-oxygens in the tRNA backbone but also play a significant role in the association process

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of proteins to tRNA. Some unfavorable electrostatic interactions are probably compensated by hydrogen-bonds between the carboxylate group of the side chain in the interfacial acidic protein residues and the tRNA backbone. We propose that the low experimentally observed SK_{obs} values for both GlnRS- and GluRS-tRNA depend on the distribution and number of anionic residues that exist in these tRNA synthetases. Our computed electrostatic binding free energies were large and unfavorable due to the Coulombic and de-solvation contribution for the GlnRS-tRNA and GluRS-tRNA complexes, respectively. Thus, low SK_{obs} values may not reflect small contributions from the electrostatic contribution in complex-formation, as is often suggested in the literature. When charges are "turned off" in a computer-experiment, our results indicated that "turning off" acidic residues far from a phosphate group significantly influences SK_{pred}. If cationic residues are "turned off", less impact on SK_{pred} is observed with respect to the distance to the nearest phosphate-group.

AMS subject classifications: 35Q80, 92C05, 92C40, 65N06

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1 Introduction

The association of aminoacyl-tRNA synthetase (aaRS) to transfer RNA (tRNA) is important in various biological events such as the protein biosynthetic machinery, signal transduction and regulation mechanisms [1–3]. Aminoacyl-tRNA synthetases, which are an important class of information-processing enzymes, are highly negatively charged at physiological conditions yet bind to a highly negatively charged partner: tRNA. At first, since both tRNA and aaRS are negatively charged biomolecules and repel each other according to the basic laws of physics, one would not expect that they can form a stable complex. However, some studies suggest that the positive surface potential and the field extending from it, which is created by the cationic enzyme residues, help drive the attraction between the tRNA and aaRS at long distances (*e.g.*, [4]). Different studies have indeed shown that the electrostatic interactions are very important in various aspects of the biological function of this class of tRNA-enzyme complexes [5–7]. For instance, the specificity and strength of the interaction between different natural/cognate substrates/analogs and aminoacyl-tRNA synthetase enzymes can be optimized (in the computer and later on in the lab by site-directed mutagenesis) by changing the charge distribution and thereby adjusting the short-range (hydrogen-bonds and salt bridges) and long-range electrostatic interactions [5–7].

Banerjee and co-workers report tryptophan fluorescence quenching experiments that resulted in a rather low SK_{obs} for the salt dependence in the association of both GluRS and GlnRS to tRNA [8]. The authors rule out that any coupled folding-unfolding events