picoseconds (2 nanosecond simulation) with frequent sampling (1.0 femtosecond/timestep for >1,000,000 timesteps) time.

For proper perturbation of interaction energy between various residues and a specific RNA sequence, equilibration of a protein *in-aqua* is used as the preliminary step for calculating free energy changes computationally. The protein-RNA complex was solvated in a periodic 3-D box with a 10 Å distance between the edge of the complex and the boundary of the box in each dimension.

Table 1: Binding energy between protein and RNA for a series of mutations at site 95 of SRSF2

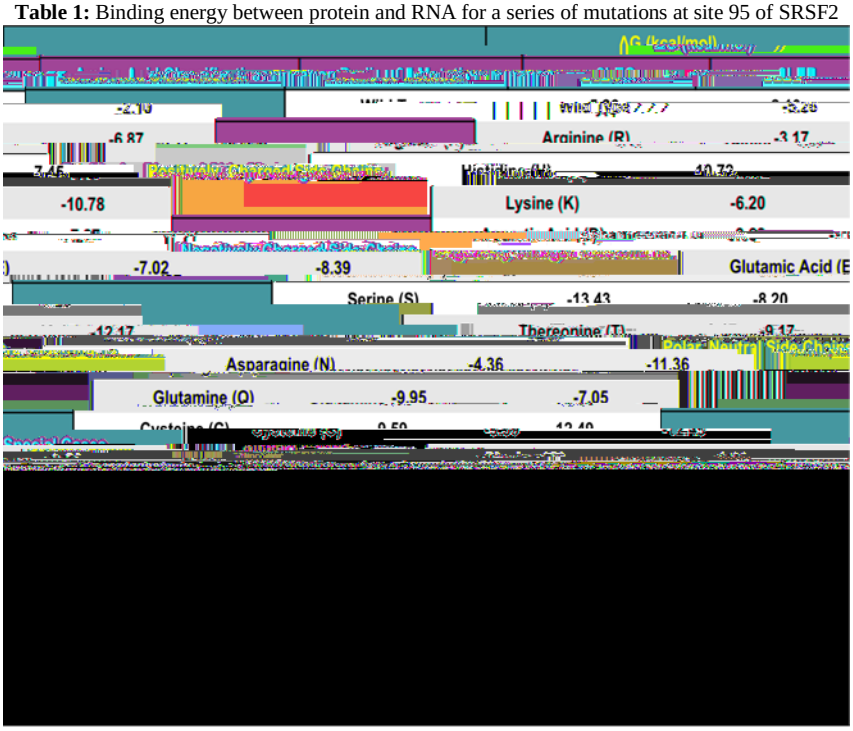

Table 2: Comparison for ΔΔG from the experimental measurement and the FEP calculations

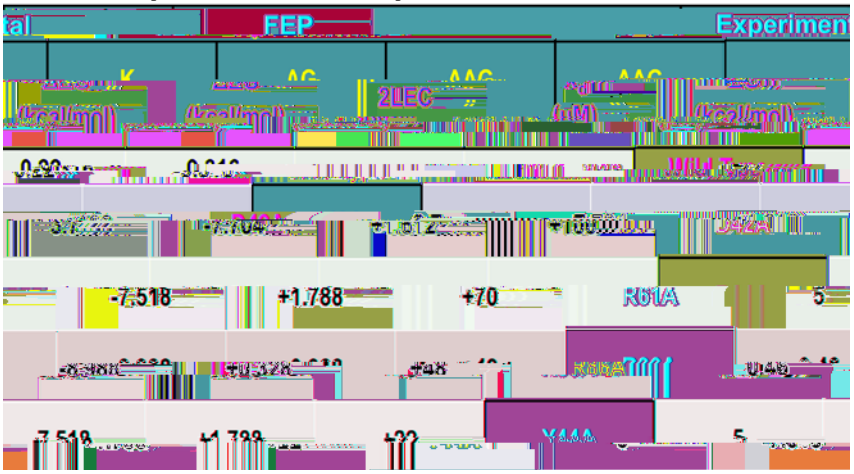

Figure 4: Illustrated interactions between the SRSF2 protein and the RNA sequences at particular mutation sites before (a-f) and after (a'-f') the mutations. The hydrogen bonding interactions are denoted by yellow dashes, the π-π interactions are denoted by red lines, and the hydrophobic interactions are denoted by green lines.

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