Cologne Evolution Colloquium

SFB 680 Molecular Basis of Evolutionary Innovations

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High-order epistasis and its role on the evolution of the capsid of the PhiX-174 bacteriophage family

Viral capsids are structurally constraind by molecular interactions. Therefore, we expect that interactions amongst multiple substitutions result in epistatic effects. The capsid might thus kept close to an energetic minimum, due to frequent mutations and site interactions, resulting on compensatory mutations. To study the nature, distribution and evolution of interactions at variable amino acid sites, we modeled *in silico* the capsid of 19 species of the PhiX-174 family, including the wild-type, as well as all internal and ancestral nodes. The polymorphisms at internal nodes were reconstructed using Bayesian phylogenetic methods, which considered 37 variable amino acid sites of the major capsid protein F. By setting a probability threshold to the Bayesian posteriors, we identified the significant amino acid polymorphisms, whose combinations defined the haplotypes further considered. The ancestral state has 8 variable amino acids (256 possible haplotypes). A molecular model of the capsid was constructed for each haplotype. With it, we studied the distribution of free energies. To estimate epistasis we considered the corresponding single mutants and calculated the difference between the free energies of each species and the sum of the free energy contributions of the constituting single-mutants. We found significant non-additive (epistatic), interactions of high order. There is a positive trend of epistasis against the number of substitutions as well as with free energy. However, free energy is not correlated with number of substitutions. A low dN/dS ratio suggests strong purifying selection. Altogether this indicates that epistasis is important in buffering the phenotype, probably through the action of stabilizing selection during evolution. We also present preliminary experimental results.

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