Prediction of pH-dependence in the SARS-CoV-2 spike protein ectodomain.

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Evolution couples differences in ambient pH to biological function through protonatable groups, in particular those that switch from buried to exposed and alter protonation state in doing so. We present a tool focusing on structure-based discovery and display of these groups. Since prediction of buried group pKas is computationally intensive, solvent accessibility of ionisable groups is displayed, from which the user can iteratively select pKa calculation centers. Results are color-coded, with emphasis on buried groups. Utility is demonstrated with coronaviruses, which exhibit variable dependence on the acidic pH of the endocytotic pathway. SARS-CoV-2, causative agent of the COVID-19 pandemic, is thought to release its RNA genome at either the cell surface or within endosomes, the balance being dependent on spike protein stability, and the complement of receptors, co-receptors and proteases. To investigate possible mediators of pH-dependence, pKa calculations have been made on a set of structures for spike protein ectodomain and fragments from SARS-CoV-2 and other coronaviruses. Dominating a heat map of the aggregated predictions, 3 histidine residues in S2 are consistently predicted as destabilising in pre-fusion (all 3) and post-fusion (2 of 3) structures. Other predicted features include the more moderate energetics of surface salt-bridge interactions, and sidechain-mainchain interactions. Two aspartic acid residues in partially buried salt-bridges have pKas that are calculated to be elevated and destabilising. Notably, the degree of destabilisation is predicted to vary between open and closed receptor binding domain conformations. It is therefore suggested that these groups contribute to a pH-dependence of the open/closed equilibrium. These observations are discussed in the context of SARS-CoV-2 infection, mutagenesis studies, and other human coronaviruses.

Availability: Tool available at http://www.protein-sol.manchester.ac.uk/pka/

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