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A MOLECULAR VIEW OF SARS-COV-2, THE NOVEL CORONAVIRUS

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

Spike detail: A spike (shown enlarged on the right) consists of three intertwined molecules of the spike protein, and the E484 amino acid is highlighted in red. | Photo Credit: Sushil Chandani

Our happy memories of school often include chemistry practicals – test tubes and Bunsen burners. Chemistry is the study of the properties of molecules. Everything living and non-living, is made of molecules. The simple chemicals that were learnt in school, such as hydrochloric acid (which has two atoms, one hydrogen; one chlorine), are dwarfed by the complexities of biological chemistry. A protein molecule can have thousands of atoms.

With increasing knowledge of chemical principles, it has been possible to move from the ‘test tube’ to theoretical studies of molecules, their structure and their interactions with other molecules. Just as there are games that let you simulate the landing of an aircraft on your computer screen, one can simulate the interactions between complex biological molecules with reasonable accuracy. Whether in simulating flight, or a molecule, mathematical methods are being linked to fundamental laws of physics. After all a protein is only a linear chain of linked amino acids (of which there are 20, each made up of between 10 and 27 atoms), neatly folded into a unique shape. Amino acids vary in their charge (positive, negative, neutral) or stickiness. Some regions of the chain of amino acids are buried in the core of the molecule. Others are on the surface. Surface amino acids determine interactions between proteins - important for assembling a structure, for binding to receptors, to antibodies and so on.

Back in the real world, many of us have anxiously followed the progress of the covid-19 pandemic, looking for signs of it slowing down. We have learnt new jargon, got accustomed to scary images of a ball-like virus particle studded with “spikes”. Now, we are confronted with new and worrying variants, each of which is described either with a geographical moniker, or with a WHO classification (Greek alphabets alpha, beta, etc.) or more accurately, with a code such as E484K, D614G. The numbers take us back to our linear chain of amino acids in a protein, which in this case is the spike protein on the surface of the virus. The spike protein initiates infection – it is attracted to and binds to a receptor molecule that lies on the surface of cells in your lung and other tissues. This protein molecule is a chain of 1,273 amino acids, and three individual molecules lock together to form the familiar ‘spike’ shape. The 484 is the position in the chain. It lies within the crucial motif that binds to the host receptor E is shorthand for Glutamate, an amino acid with a negative charge, which is now mutated to K (Lysine) – an amino acid with a positive charge. This mutation is found in the Beta and Gamma variants.

Notice that the mutation has replaced a negatively charged Glutamate with a positively charged Lysine. Will this bode well for us humans? Available data from the field suggest that infectivity of this particular variant of the virus seems to be enhanced. It also appears to make this variant less recognisable to some antibodies generated against the virus.

The Delta variant, much in the news, has a E484Q mutation, Q standing for Glutamine – which is not very different from Glutamate (E), but is neutral in charge and polar. The second mutation is L452R, which also lies within the receptor-binding motif of spike. L is Leucine, an uncharged, ’sticky’ amino acid and R the positively charged Arginine.

An important point to be made here is that the numerous variants of concern do not just have

the one or two amino acid changes in the receptor-binding domain of the spike protein described above. The Alpha variant first seen in the U.K. has a total of 23 mutations. Nine of these are in other parts of the spike protein, some more are in other constituents of the virus, and are not well understood.

It is apparent that changes of this sort – a replacement or two in a macromolecule - can be modeled in a computational environment quite efficiently and with reasonable confidence. Such modelling would give us quick approximations of what to expect whenever a new variant of a viral protein arises. Going further, modelling could help design and refine drug molecules that would bind tightly to a target protein. For example, the coronavirus has an enzyme, a protease that trims the spike protein to its correct size before a new virus particle is assembled. A drug molecule that would bind tightly to this enzyme would inhibit the trimming action and curtail the growth of the virus. Molecular modelling allows you to try out thousands of potential candidates for narrowing down to a few best-fit candidates that could then be tested in real laboratory experiments.

(This article has been co-authored by Sushil Chandani who is an independent consultant in computer modelling of complex molecules.)

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The study was carried out by researchers from National Institute of Virology, ICMR and Bharat Biotech.

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