Can we computationally predict the impact of recently proposed ACE2 Designer mutations?

A report by Büşra Savaş, Burcu Özden Yücel, and Ezgi Karaca. The calculations were performed by Karaca Lab.

The angiotensin-converting enzyme (ACE2) is a type I membrane protein found in most of the crucial organs such as lungs, arteries, heart, and kidney. ACE2 is responsible for decreasing the blood pressure through processing angiotensin (1-7), a vasodilator. As widely known, ACE2 is SARS-CoV-2's host cell receptor. At the first step of the infection cycle, SARS-CoV-2 lands on ACE2 via its spike protein's interactions with ACE2's catalytic domain (Figure 1).

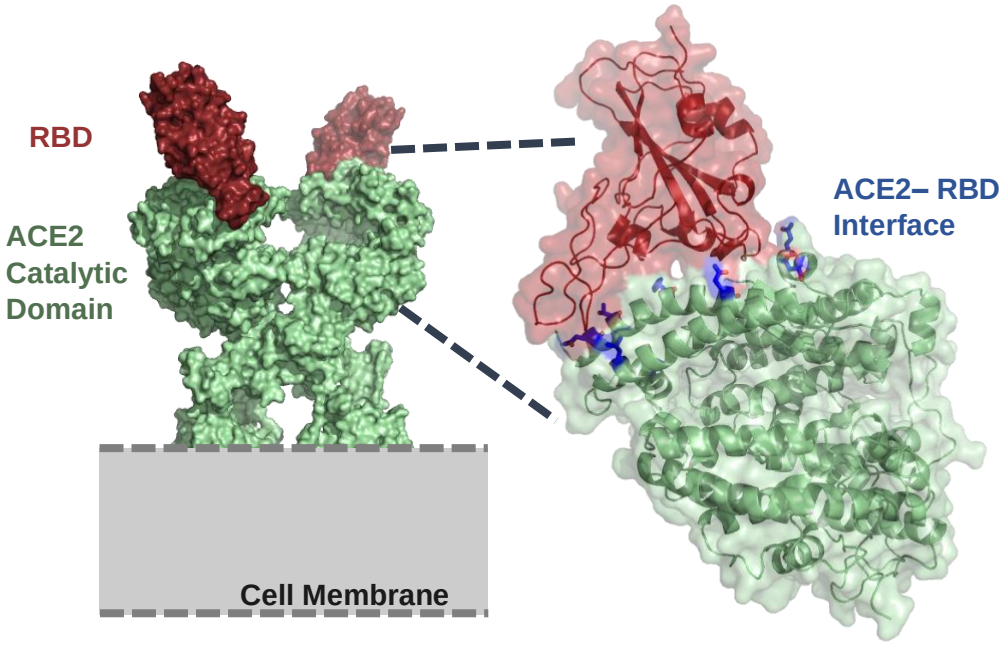

Figure.1 The Receptor Binding Domain (RBD) of SARS-CoV-2's Spike Protein (red) recognizes ACE's Catalytic Domain (green). The probed mutations in this study were shown in blue sticks.

As the coronavirus binds both to membrane-bound ACE2 and soluble ACE2, using a soluble ACE2 variant that can neutralize SARS-CoV-2's spike holds a great potential to halt the infection. Expanding on this, in a recent *bioRxiv* report, Procko experimentally explored the impact of various ACE2 mutations in soluble ACE's spike binding capacity. Among the presented mutations, we concentrated on the most effective ones, as shown in Figure 1-2.

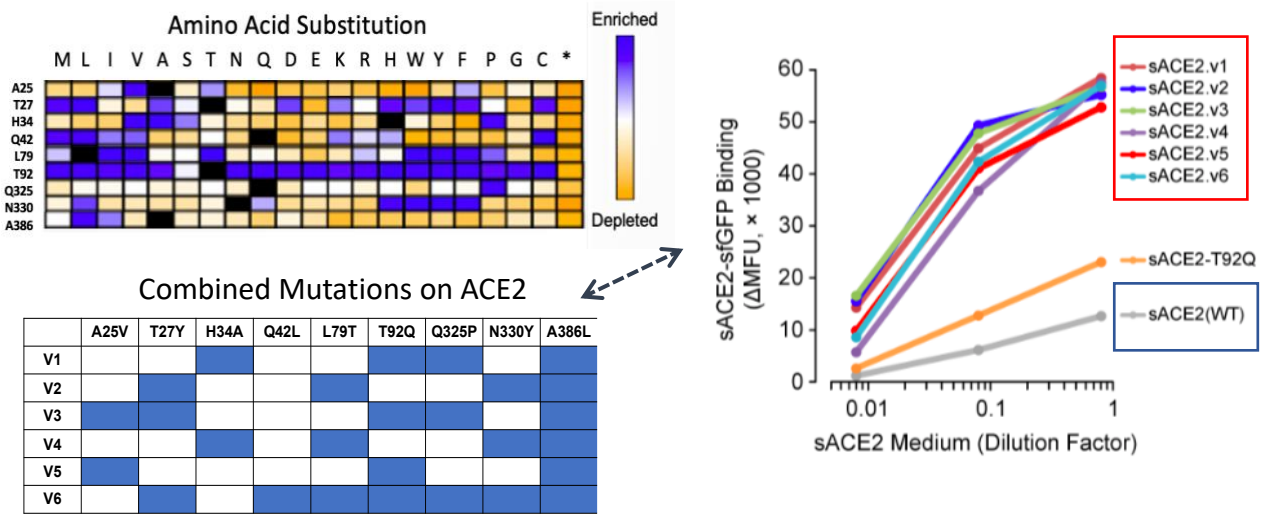

Figure.2 The effect of the proposed ACE2 designer mutations on the ACE2:spike interactions *(Figures adapted from Procko. bioRxiv, 2020).*

In this short report, we probe whether a simple modeling could predict the proposed effect of the documented amino acid substitutions. To that end, we used the molecular modeling platform HADDOCK (https://milou.science.uu.nl/services/HADDOCK2.2/haddock.php) (*Bonvin, J. Mol. Biol, 2016)*. Via HADDOCK, we imposed the selected amino acid substitutions on the crystal structure of ACE2:Spike_RBD (PDB ID: 6M0J) by following http://www.bonvinlab.org/software/haddock2.4/faq/#what-about-point-mutations. The mutant complexes were then optimized with HADDOCK's Refinement Interface (https://milou.science.uu.nl/services/HADDOCK2.2/haddockserver-refinement.html). During the refinement, ACE2 and Spike_RBD glycans were excluded.

Upon obtaining the mutant ACE2:Spike_RBD complexes, we used three common descriptors to calculate the binding score of the generated complexes (i) HADDOCK scoring function (1.0 vdW Energy + 0.2 Electrostatic Energy + 1.0 Desolvation Energy), (ii) Buried Surface Area (BSA), and (ii) PRODIGY score (PROtein binDIng enerGY prediction, https://bianca.science.uu.nl/prodigy/). The scoring results are presented in Table 1 and Figure 3.

As presented in Table 1 and Figure 3, the HADDOCK score and its van der Waals energy component alone could predict all the mutations as affinity enhancers (as they have a smaller score than WT), except for v1. This means that these descriptors have an 86% success rate in predicting the impact of proposed ACE2 designer mutations! The next best performing

descriptor is BSA with a 71% success rate. PRODIGY, unfortunately, could not predict the impact of most of the proposed mutations.

Table.1 The analysis of the probed ACE2 designer mutations by HADDOCK Score, HADDOCK Score components, BSA, and PRODIGY. The correct predictions are highlighted in green, the mispredictions in red.

Mutation ID	Mutations	Haddock score (a.u.)	VDW E. (kcal/mol)	Electrostatic E. (kcal/mol)	Desolvation E. (empirical)	BSA (A^2)	Prodigy Score (kcal/mol)
v0	WT	-138.4	-59.4	-233.3	-32.3	1791.4	-12.5
T92Q	T92Q	-149.5	-62.7	-230.6	-40.6	1787.3	-11.5
v1	H34A,T92Q,Q325P,A386L	-132.9	-58.9	-232.2	-27.6	1774.2	-11.5
v2	T27Y, L79T, N330Y, A386L	-164.6	-66.6	-244.9	-49.0	1926.5	-11.4
v3	A25V, T27Y, T92Q, Q325P, A386L	-156.8	-64.0	-213.5	-50.2	1873.4	-9.9
v4	H34A, L79T, N330Y, A386L	-143.3	-61.3	-243.5	-33.3	1800.8	-12.9
v5	A25V, T92Q, A386L	-150.6	-64.7	-238.7	-38.2	1818.8	-11.8
v6	T27Y, Q42L, L79T, T92Q, Q325P, N330Y, A386L	-165.8	-66.4	-209.1	-57.5	1893.9	-11.2

It seems that the apparent van der Waals enhancers could be correctly predicted as better binders. This could explain why v1 could not be predicted by any scoring term: H34A leads to a decrease in the interaction surface area, which could not be properly modeled with a simple modeling scenario. The same effect also holds for v4, which has the worst HADDOCK score among all mutation combinations.

All in all, here we demonstrate that the recently proposed ACE2 designer mutations and their impact could be rapidly and accurately predicted with HADDOCK. We hope that these findings will aid the therapeutics development to fight COVID19.

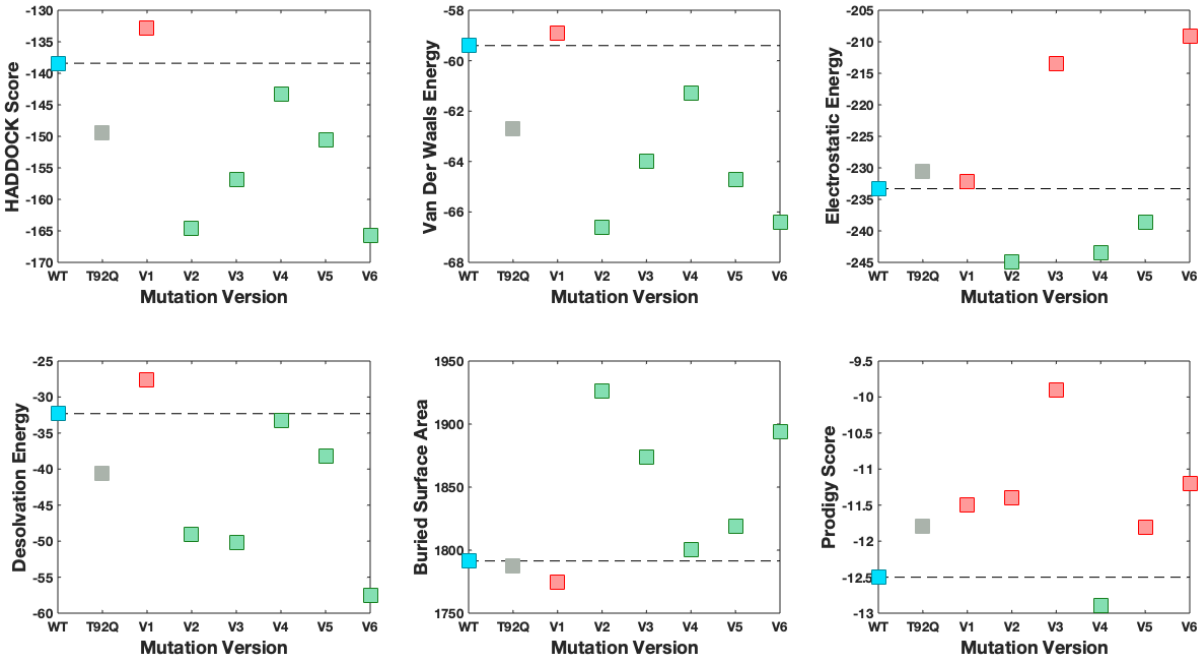

Figure.3 The depicted distributions of ACE2 mutations regarding each scoring term. The WT complex is depicted in blue, the correct predictions in green, and the incorrect ones in red. The T92Q point mutation is colored in gray.

References:

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