A015 · AI-Guided Therapeutic Strategies to Combat Viral Evolution

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Vaccine and binder design relies heavily on the structural stability of target proteins. Predicting mutations or identifying stable regions can help prepare for the inevitability of future pandemics. Since most mutations maintain a protein's overall fold, Inverse Folding (IF), a technique that generates sequences matching a provided structure, could potentially identify stable or highly mutable regions by using positional entropies. This study investigates the SARS-CoV-2 Spike protein using AlphaFold3 to generate a complete 3D model. We used ProteinMPNN to evaluate the minimum number of sequences needed before reaching a point of diminishing returns and observed promising results after only 1000 iterations, with slight improvements from 100 iterations. The positional entropies for each amino acid were calculated using the SoftMax formula. Our analysis identified ~448 very low-entropy positions. Information on positional entropies, combined with information on surface exposure, intrinsic disorder, binding capability, epitope regions, and structure prediction confidence scores, identified 37 target positions for therapeutic targeting. BindCraft shows promise in developing binders specific to these target regions as ZDock and CCharPPI show that the original binder design is either at par or outperforms alternative binding sites/conformations. Targeting stable molecular regions or preparing against a library of possible structures at the start of the pandemic could have saved millions of lives globally and reduced the need for new booster shots to counter newer viral variants.

AI-Guided Therapeutic Strategies to Combat Viral Evolution

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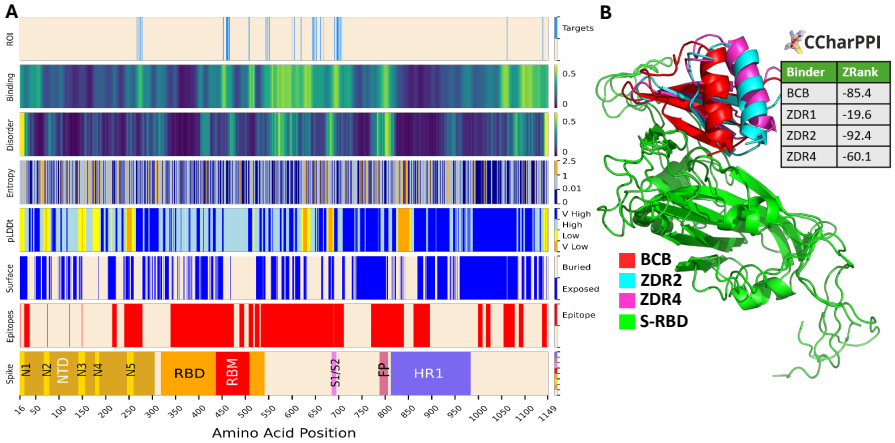

Figure 1. (A) *Using entropy and other filtering metrics to identify stable molecular targets (ROI) along the Spike protein.* ***(B)*** *BindCraft binder (BCB) bound to Spike-Receptor Binding Domain (RBD). Alternative ZDock predictions of BCB (ZDR 1,2&4) bound to S-RBD along with ZRank scores from CCharPPI (lower is better).*

Vaccine and binder design relies heavily on the structural stability of target proteins. Predicting mutations or identifying stable regions can help prepare for the inevitability of future pandemics. Since most mutations maintain a protein's overall fold, Inverse Folding (IF), a technique that generates sequences matching a provided structure, could potentially identify stable or highly mutable regions by using positional entropies. This study investigates the SARS-CoV-2 Spike protein using AlphaFold3 to generate a complete 3D model. We used ProteinMPNN to evaluate the minimum number of sequences needed before reaching a point of diminishing returns and observed promising results after only 1000 iterations, with slight improvements from 100 iterations. The positional entropies (in nats) for each amino acid were calculated using the SoftMax formula. Our analysis identified ~448 very low-entropy positions (0-0.01 nats). Information on positional entropies, combined with information on surface exposure, intrinsic disorder (IUPred scores), binding capability (Anchor scores), epitope regions (combining data from 6 different studies), and structure prediction confidence scores (pLDDt), identified 37 amino acid positions for therapeutic targeting (Figure 1. A). BindCraft shows promise in developing binders specific to these target regions, as seen in Figure 1. B, which shows that one of the original binders (BCB) outperforms alternative docking sites using ZDock and CCharPPI. In Vivo experiments could confirm the stability and specificity of these binders. The pandemic cost US taxpayers 10-39.5 billion USD in vaccine research. Targeting stable molecular regions or preparing against a library of possible structures at the start of the pandemic would help reduce this cost and save millions of lives by enabling the development of therapeutics that remain effective against newer viral variants.