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STRUCTURAL BIOLOGY

Bottom-up de novo protein design

TopoBuilder enables de novo design of proteins bearing complex structural motifs.

Much progress has been made in computational protein design. Proteins can be designed with specific topology and functional features. To design a protein with specific function, typically, the functional motif of interest is grafted onto a functionless but stable scaffold. This works well for contiguous sequence motifs, but complex protein functionality is usually conferred by the three-dimensional (3D) arrangement of non-adjacent elements, which is more difficult to engineer. The research group of Bruno Correia at the École Polytechnique Fédérale de Lausanne has developed a bottom-up de novo protein design strategy to address this challenge.

The approach makes use of TopoBuilder, a computational tool built within the framework of the Rosetta software package. It samples different levels of structural organization to build customized protein topologies to stabilize structural motifs in a specific 3D conformation. "The designed process, starting from the inception of the protein topology, is 'function-aware', potentially biasing the structural and sequence sampling stages towards spaces that are more prone to yield functional sequences in the end of the design process," explains Correia.

The researchers demonstrate the versatility of this approach by designing biosensors that can detect and quantify epitope-specific antibodies from complex samples (Yang et al. 2021). In a separate study, they designed respiratory syncytial virus (RSV) epitope-presenting proteins that were able to induce a neutralizing response against RSV in mice and non-human primates (Sesterhenn et al. 2020).

Challenges remain. TopoBuilder is not fully automated yet and successful design requires screening several protein designs. Correia hopes that in the future "one could perhaps design proteins presenting more complex viral epitopes for vaccine development or even elaborate active sites of enzymes to enable novel catalytic activities."

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Research papers
Yang, C. et al. Bottom-up de novo design of functional proteins with complex structural features. *Nat. Chem. Biol.* https://doi.org/10.1038/s41589-020-00699-x (2021).
Sesterhenn, F. et al. De novo protein design enables the precise induction of RSV-neutralizing antibodies. *Science* **368**, eaay5051 (2020).