

Title

Predicting destabilizing point mutations making full use of the structure in AlphaFold DB

Category

Processing Pipelines And Methods

Challenge

One very exciting use case which AlphaFold 2 sadly fails at is predicting destabilizing point mutations, since it is not sensitive enough to alter its structural prediction based on a single residue change. Can we develop a pipeline that addresses this question, perhaps by extending PolyPhen-2 to make full use of the structures in AlphaFold DB, which cover the entire human proteome? Currently, this predictor only uses structures available in the PDB structure database. Adding AlphaFold structure predictions to this should be an easy improvement to make.

Benefit

This might directly help us assess the effects of missense mutations. It could be released as an “improved” version of a variant effect predictor such as PolyPhen-2, and it could ultimately even be incorporated into the St. Jude Medal Ceremony pipeline (<https://stjudecloud.github.io/docs/guides/pecan/pecan-pie/>).

Helpful Tools, Packages, or Software

AlphaFold 2; AlphaFold DB; Variant effect predictors used in the St. Jude Medal Ceremony (<https://stjudecloud.github.io/docs/guides/pecan/pecan-pie/>): PolyPhen2 (HVAR), SIFT, CADD, REVEL, FATHMM, MutationAssessor, and LRT; Additional variant effect predictor: Ensembl VEP

Test Data

ClinVar, ASHG pathogenicity classification, possibly HGMD