

## Distill, Distill\_roll

### Distill for CASP10

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Distill has two main components: a fold recognition stage dependent on sets of protein features predicted by machine learning techniques; an optimisation algorithm that searches the space of protein backbones under the guidance of a potential based on templates found in the first stage. The main differences with our CASP9 systems are: the greatly improved fold recognition stage; the fact that we fit structures directly to the distance maps of templates rather than to predicted contact maps. The difference between Distill and Distill\_roll is that for the former we use an improved fold recognition algorithm.

#### Methods

Distill runs 3 rounds of PSI-BLAST against a 90% redundancy reduced UniProt to generate multiple sequence alignments (MSA). The PSSM from the second round is reloaded to search the PDB for templates ( $e=1e-3$ ). MSA and templates are fed to our 1D prediction systems (all based on BRNN): Porter<sup>1,4</sup> (secondary structure), PaleAle<sup>4</sup> (solvent accessibility), BrownAle<sup>4</sup> (contact density), Porter<sup>+2</sup> (structural motifs). All predictors use template information as an input alongside the sequence and MSA.

1D predictions are combined into a structural fingerprint<sup>4</sup> (SAMD) which, alongside the PSSM, is used to find remote homologues in the PDB through 3 searches for Distill\_roll (PSSM and SAMD profile against PDB sequences and SAMD, with 3 different substitution matrices) and 6 searches for Distill (same as above, plus 3 more searches against PDB PSSM rather than sequences).

In the following stage residue contact maps are predicted by a system based on 2D-Recursive Neural Networks (XXstout<sup>5</sup>). We predict binary maps with a contact threshold of 8Å between C $\beta$ , which are submitted to the RR category. Inputs for map prediction are: the sequence; MSA; PSI-BLAST, SAMD and SAMD templates. That is, the maps are template-based whenever suitable templates are found.

The 3D reconstruction, which is only conducted on C $\alpha$  traces, is run as follows: we run a SAMD search for templates with an  $e$ -value of 10,000; for each (overlapping) 9-mer of the protein we gather the structures of the top 50 templates which fully cover it (SAMD\_list); a simulated annealing search of the conformational space is run using crankshaft moves to quickly find a minimum of a potential function which rewards formation of contacts that

appear in a weighed average of the distance maps of templates; from the previous endpoint a simulated annealing search is run by substituting 9-mers from the conformation with 9-mers from the SAMD\_list, and using the same potential function as above.

We run 30 reconstructions for each protein, which we rank by their weighed TM-scores against the template list. For the 5 top-ranked models we reconstruct the backbone with SABBAC, and the full atoms with Scwrl4, then run a brief energy minimisation by gromacs. These are the models submitted to CASP.

It should be noted that everything in our pipeline (except BLAST and the software to blow C $\alpha$  traces into full-atom models) is in house, and that in normal conditions we can provide predictions for a protein in tens of minutes.

#### Results

We await the CASP assessment. On preliminary tests (on the CASP9 set) we have observed a GDT\_TS improvement of over 5% over our CASP9 systems.

#### Availability

<http://distillf.ucd.ie/distill/> (Distill), <http://dbstill.ucd.ie/distill/> (Distill\_roll)

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