SCALOP: sequence-based antibody canonical loop structure annotation

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Abstract

Motivation: Canonical forms of the antibody complementarity-determining regions (CDRs) were first described in 1987 and have been redefined on multiple occasions since. The canonical forms are often used to approximate the antibody binding site shape as they can be predicted from sequence. A rapid predictor would facilitate the annotation of CDR structures in the large amounts of repertoire data now becoming available from next generation sequencing experiments.

Results: SCALOP annotates CDR canonical forms for antibody sequences, supported by an auto-updating database to capture the latest cluster information. Its accuracy is comparable to that of a standard structural predictor but it is 800 times faster. The auto-updating nature of SCALOP ensures that it always attains the best possible coverage.

Availability and implementation: SCALOP is available as a web application and for download under a GPLv3 license at opig.stats.ox.ac.uk/webapps/scalop.

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Supplementary information: Supplementary data are available at Bioinformatics online.
Here we present SCALOP, which both clusters the H1, H2, L1, L2 and L3 CDRs in an auto-updating database, and creates a canonical form predictor. SCALOP can be used to rapidly approximate an antibody binding site shape from sequence alone (Krawczyk et al., 2018) with a minimum accuracy of 89.47% (Table 1). We evaluated the performance of SCALOP on our training set using a leave-one-out cross-validation protocol (Table 1) and on a blind test set (Supplementary Material). It achieved similar results on both. We also compared to an adapted version of FREAD, an accurate database-search method for loop structure prediction (Deane and Blundell, 2001; Krawczyk et al., 2018) (Supplementary Material). This version does not generate a structural model, but returns the PDB code of its prediction. The prediction coverage and precision of the methods are comparable (Table 1) (Supplementary Material).

To assess the speed and the portion of consistent predictions made by SCALOP and FREAD, we ran both predictors on a next generation sequencing dataset, with ~8 million light chain and ~5 million heavy chain sequences (Krawczyk et al., 2018). About 98% of the predictions are consistent between the two methods (Supplementary Material). On a single core, predicting 100 sequences requires 227s using FREAD, but 0.29s using SCALOP. This rapid prediction suggests the possibility of running SCALOP as a fast and reliable first-screen.

In order to ensure that SCALOP always offers the best possible prediction coverage, it uses an auto-updating database. Figure 1 demonstrates the advantage of this auto-updating approach using L3 as an example. We selected the representative years based on previous publication dates of canonical forms definitions (Al-Lazikani et al., 1997; North et al., 2011; Nowak et al., 2016). Data until the end of the year were used, i.e. for 2016, all structures available on SAbDab deposited before the end of 2016 were used. In 1997, there was only a single L3 cluster; by 2016 there were seven and the portion of non-clustered data had more than halved. Using the 1997 dataset for prediction, we achieve similar precision as with 2017’s data (97.4% in 1997 and 94.0% in 2017), but ~30% less coverage.

### 3 Benchmark

To make a cluster prediction, we only consider the target sequence against clusters of the respective CDR types (i.e. H1 or H2). The PSSM score for a target sequence, $s_c$ for cluster $c$ is:

$$s_c = \sum_{j \in J} M_{kj}$$

where $J$ is the set of positions in the target sequence. Since L2 loop structures are often invariant, we assign L2 loops of the dominant sequence length to a single canonical form; otherwise, it is not clustered.

### 2 Algorithm

SCALOP takes one or a set of amino acid sequences of full antibody chains as input. It then numbers the sequence with ANARCI (Dunbar and Deane, 2016), and scores the extracted CDR sequences against PSSMs of the appropriate clusters. The cluster nomenclature follows that of Nowak et al. (2016) (Supplementary Material). The input CDR sequence is then assigned to the cluster with the maximum score above a scoring threshold (Supplementary Material). SCALOP returns the name of the assigned cluster, and the PDB code and chain identifier of the assigned cluster’s median structure as the result. SCALOP can return a structural model if a structure of the framework is given alongside the CDR sequence (Supplementary Material). The database is updated monthly, previous databases are available from the website.

#### 2.1 Building the PSSM

We adopted the length-independent CDR clustering method developed by Nowak et al. (2016). Structures in SAbDab (Dunbar et al., 2014) available as of July 10, 2017 were used (Supplementary Material). We built PSSMs for each cluster using their unique sequences only:

$$M_{kj} = \log \left( \frac{p_k}{b_k} \right)$$

where $M_{kj}$ is the element score, $p_k$ is the probability of observing an amino acid $k$ at the ANARCI-numbered position $j$ within the cluster and $b_k$ is the background probability of $k$ (Supplementary Material).
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