Profile Comparer: a program for scoring and aligning profile hidden Markov models

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ABSTRACT

Summary: Profile Comparer (PRC) is a stand-alone program for scoring and aligning profile hidden Markov models (HMMs) of protein families. PRC can read models produced by SAM and HMMER, two popular profile HMM packages, as well as PSI-BLAST checkpoint files. This application note provides a brief description of the profile–profile algorithm used by PRC.

Availability: The C source code licensed under the GNU General Public Licence and Linux and Mac OS X binaries can be downloaded from http://supfam.org/PRC.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 INTRODUCTION

Profile Comparer (PRC) is a program for scoring and aligning a profile hidden Markov model (HMM) of a protein family against other profile HMMs.

Profiles are tables that give a score for a particular amino acid to be found at a particular position in an alignment of a protein family. The best known profile method is probably PSI-BLAST (Altschul et al., 1997). Profile HMMs are similar to profiles, but replace scores with probabilities, and introduce additional probabilities for insertions and deletions at each position in the profile (Durbin et al., 1998; Eddy, 1998). All probabilities are placed within a single statistical framework, an HMM. In this note, we shall count profile HMMs among profile methods.

It is now well established that profile–profile methods detect more distant homologies than profile–sequence methods, which in turn are more powerful than sequence–sequence methods (see e.g. Sadreyev and Grishin, 2008; Soding, 2005). Profile–profile methods also generate the most accurate alignments; in fact, profile–profile methods are more powerful than sequence–sequence methods (see e.g. Eddy, 1998). All probabilities are placed within a single statistical framework, an HMM. In this note, we shall count profile HMMs among profile methods.

When scoring a profile HMM against a library of profile HMMs, PRC reports E-values, which give an estimate of how significant the matches are. In order to calculate E-values, PRC first calculates three other scores: co-emission, simple and reverse. Each score builds upon the previous one, until finally reverse scores are converted into E-values.

The co-emission score $S_{co-em}$ is a generalization of the log-odds score $S_{log-odds}$ calculated by SAM and HMMER,

$$S_{log-odds} = \log \frac{P(\sigma | HMM)}{P(\sigma | null)},$$

(1)

to the HMM–HMM case:

$$S_{co-em}(1,2) = \log \sum_{\sigma} \frac{P(\sigma | HMM1)P(\sigma | HMM2)}{P(\sigma | null)}.$$ 

(2)

The sum is over all possible amino acid sequences $\sigma$, and the probability $P(\sigma | HMM)$ that the profile HMM emits a sequence $\sigma$ is calculated using the forward algorithm (Durbin et al., 1998). When one of the HMMs is extremely 'narrow', e.g. it only emits a single sequence $\tau$ with a non-zero probability ($P(\sigma | HMM) = 1$ if $\sigma = \tau$, 0 otherwise), the co-emission score tends to the profile HMM log-odds score for $\tau$. The null model emits random sequences with background amino acid frequencies and a geometric distribution of lengths.

The simple score $S_{simple}$ is the same as the co-emission score $S_{co-em}$, but both profile HMMs are restricted to regions of significant similarity. The regions are found by an iterative procedure that picks a new end point as the maximum of the forward score in the dynamic programming matrix, and a start point as the maximum of the backward score.
The reverse score better than of reverse scores:

E reverse sequence null model used by SAM (Karplus et al., 2005).

Finally, for library runs the reverse score $S_{rev}$ is turned into an E-value by fitting the following function to the observed distribution of reverse scores:

$$E(S_{rev} > x) = \frac{n_{unrel}}{1 + \exp(\lambda x + \kappa)}.$$  (5)

The E-value $E$ is the expected number of random matches with a reverse score better than $x$, and $n_{unrel}$ is the number of profile HMMs in the library that are unrelated to the query. The formula is a slight generalization of the function used by SAM (Karplus et al., 2005).

Optimal values of the two parameters $\lambda$ and $\kappa$ for each run are found using a censored Maximum Likelihood fitting procedure.

HMM–HMM alignments are computed by finding the Viterbi path that maximizes the sum of forward–backward odds scores (Durbin et al., 1998).

### 3 USING PRC

PRC can read SAM3 (ASCII and binary) and HMMER2 model files, and PSI-BLAST checkpoint files. The same internal profile HMM is used for scoring all three. For PSI-BLAST checkpoint files, the profile part is taken from the checkpoint file and the insertion and deletion probabilities are set to default values, constant throughout the model. For best performance, users should build a full profile HMM using the SAM w0.5 script.

For accurate $E$-values, the library should contain at least 1000 profile HMMs. For libraries of sufficient size, $E < 0.003$ can be taken as indicative of homology and $E < 10^{-5}$ as a strong match. When a large library is not available, Equation (5) with $\lambda = 0.8$, $\kappa = 0$ can be used as a conservative guide.

Starting with version 1.5.5, the PRC source code also includes a simple Perl script, merge_aligns.pl. Given two HMM–sequence alignments in the SAM a2m format, and a PRC alignment between the two HMMs, the script will output a pairwise alignment between the two sequences. Users who would like to visualize their HMM–HMM alignments are referred to the pairwise HMM logos server (Schuster-Bockler and Bateman, 2005).

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