Structural bioinformatics

CMV: visualization for RNA and protein family models and their comparisons

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Abstract

Summary: A standard method for the identification of novel RNAs or proteins is homology search via probabilistic models. One approach relies on the definition of families, which can be encoded as covariance models (CMs) or Hidden Markov Models (HMMs). While being powerful tools, their complexity makes it tedious to investigate them in their (default) tabulated form. This specifically applies to the interpretation of comparisons between multiple models as in family clans. The Covariance model visualization tools (CMV) visualize CMs or HMMs to: I) Obtain an easily interpretable representation of HMMs and CMs; II) Put them in context with the structural sequence alignments they have been created from; III) Investigate results of model comparisons and highlight regions of interest.

Availability and implementation: Source code (http://www.github.com/eggzilla/cmv), web-service (http://rna.informatik.uni-freiburg.de/CMVS).

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Probabilistic models are constructed for specific RNA and protein families sharing a common ancestor and a biological function. The most prominent instances are the HMM architecture as used by HMMER3 (Eddy, 2011) and the CMs utilized by INFERNAL (Navrotsky and Eddy, 2013). Currently there are 2686 RNA families available from the Rfam (Burge et al., 2012; Kalvari et al., 2017; Navrotsky et al., 2015) database and 16 712 from Pfam (Finn et al., 2016). Visualization of the models provides an overview over whole regions and allows to directly inspect states, nodes and probabilities. A HMM visualization tool exists as part of SAM (Krogh et al., 1994), while for CMs, as far as we are aware, no automatic solution exists.

2 Approach

Each tool of CMV accepts one or more models (INFERNAL, HMMER3 format) and optionally one or more corresponding alignments (Stockholm format) as input. The tools for comparison visualization require inputs in CMCompare (Eggenhofer et al., 2013; Honer zu Siederdissen and Hofacker, 2010) format. Additional parameters can be set that control the level of detail of the visualization. In the minimal setting only the index for each node is shown, while full details provide states and probabilities. Moreover it is possible to select if emission probabilities should be displayed as numerical values or using a graphical representation. The number of entries in the alignment, the image size and the output format (svg, png, eps, pdf) can also be defined via options.
The tools have been written using the diagrams library with a Cairo back-end for visualization. Processing takes on average, for the first 100 Pfam models, 13 s for a model with detailed output (see Supplementary Table 1).

The tools create one visualization output file per input model. If the Stockholm alignment for the family was provided, then a second output file is generated per alignment.

It is possible to select from three levels of visualization detail (minimal, simple, detailed) for family models and, exclusively for CMs, linear or tree layout. The minimal detail setting shows each node (roughly corresponding to paired nucleotides or single aminoacids or nucleotides) of the model as a box labeled with the index of the node. When the detail level is set to simple, emission probabilities are included in the visualization for each node in case of HMMs and the node type in case of CMs. The detailed level shows the individual states (encoding match, insertion and deletion options) per node, with emission and transition probabilities (see Fig. 1B–G). Emission probabilities are either shown as numerical values (score, probability) or as graphical bars. Transition probabilities are visualized as arrows between states, with probabilities indicated by increasing opacity, as well as text labels. For more information and figures see the Supplementary Material.

Results of model comparison are visualized by labeling nodes with colors encoding the linked models (see Fig. 1A). Since the alignment columns corresponding to a node are known via the column index, the comparison information is also annotated in the alignment visualization (see Fig. 1).

In the case of (structured) RNAs this comparative information can be mapped back to the consensus secondary structure of the family, thus enabling the identification of specific motifs or regions that are linked. This is done via labeling a secondary structure visualization of R2R (Weinberg and Breaker, 2011) or alternatively an input file for forma (Kerpedjiev et al., 2015) (see Fig. 1H and I).

The tool also is available as a web-service, along with documentation and precomputed examples in three detail levels for all available models in the Pfam database and the first 1500 models of the Rfam database.

3 Conclusion

We provide an open-source tool and web-service for the visualization of HMMs, CMs, their alignments and, for RNA, their consensus secondary structure. The visualizations can supplement models in the Pfam and Rfam databases and enable convenient inspection of newly constructed models with RNAliens (Eggenhofer et al., 2016), RNAscClust (Miladi et al., 2017), or the RNA workbench (Backofen et al., 2017; Grüning et al., 2017). Nodes linked by comparison to other models are highlighted in the visualization, which allows to investigate sequence and structure elements shared among family clans. This simplifies the identification of domains, respectively secondary structure elements, with potentially related biological functionality.

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