Sequence analysis

The EVcouplings Python framework for coevolutionary sequence analysis

Thomas A. Hopf, Anna G. Green, Benjamin Schubert, Sophia Mersmann, Charlotta P. I. Schärfe, John B. Ingraham, Agnes Toth-Petocz, Kelly Brock, Adam J. Riesselman, Perry Palmedo, Chan Kang, Robert Sheridan, Eli J. Draizen, Christian Dallago, Chris Sander, and Debora S. Marks

1 Department of Systems Biology, 2 Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA, 3 cBio Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA, 4 Center for Bioinformatics, University of Tübingen, 72076 Tübingen, Germany, 5 Applied Bioinformatics, Department of Computer Science, 72076 Tübingen, Germany, 6 Computer Science and Artificial Intelligence Laboratory, MIT, Cambridge, MA 02139, USA, 7 Computational Biology Center, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA, 8 Department of Biomedical Engineering, University of Virginia, Charlottesville, VA 22904, USA, and 9 Department of Informatics, Technische Universität München, 85748 Garching, Germany

*To whom correspondence should be addressed.
†The authors wish it to be known that, in their opinion, the first three authors should be regarded as Joint First Authors.
‡The authors wish it to be known that, in their opinion, the last two authors should be regarded as Joint Senior Authors.

Associate Editor: Alfonso Valencia

Received on May 22, 2018; revised on September 6, 2018; editorial decision on October 3, 2018; accepted on October 8, 2018

Abstract

Summary: Coevolutionary sequence analysis has become a commonly used technique for de novo prediction of the structure and function of proteins, RNA, and protein complexes. We present the EVcouplings framework, a fully integrated open-source application and Python package for coevolutionary analysis. The framework enables generation of sequence alignments, calculation and evaluation of evolutionary couplings (ECs), and de novo prediction of structure and mutation effects. The combination of an easy to use, flexible command line interface and an underlying modular Python package makes the full power of coevolutionary analyses available to entry-level and advanced users.

Availability and implementation: https://github.com/debbiemarkslab/evcouplings

Contact: chris@sanderlab.org or debbie@hms.harvard.edu

1 Introduction

Coevolutionary sequence analysis presents a promising new approach to the long-standing problem of de novo prediction of the 3D structure of proteins and RNAs. In this approach, pairwise graphical models are used to identify evolutionary couplings (ECs) between sites, which frequently correspond to physical contacts in the molecule’s 3D structure. ECs have been used to successfully predict the residue contacts (Balakrishnan et al., 2011; Ekeberg et al., 2013; Marks et al., 2011; Morcos et al., 2011) and full 3D structure of proteins (Hopf et al., 2012; Marks et al., 2011; Ovchinnikov et al., 2015), RNAs (Weinreb et al., 2016), complexes (Hopf et al., 2014; Ovchinnikov et al., 2014; Weigt et al., 2009), as well as effects of mutations (Figliuzzi et al., 2015; Hopf et al., 2017). However, these applications require integrating multiple tools, data sources and extensive data processing. Available software in this field provides high-performance reimplementations of EC inference tools (Kaján et al., 2014; Seemayer et al., 2014; Weinreb et al., 2016), integration of multiple signals to improve prediction...
accuracy (Jones et al., 2015; Skwark et al., 2014), and a library targeted at format conversion between the different approaches (Simkovic et al., 2017). To make these methods accessible to a general biological audience, we present a flexible, open source application and Python package for end-to-end evolutionary coupling analysis. EVcouplings, making use of external tools, covers all necessary functionality, including alignment generation, EC calculation, \textit{de novo} structure and mutation effect prediction, visualization of results, and comparison of predictions to experimental structures.

2 EVcouplings framework

The EVcouplings framework integrates the functionality of the previously published methods EVfold (Hopf et al., 2012; Marks et al., 2011), EVcomplex (Hopf et al., 2014) and EVmutation (Hopf et al., 2017). It provides (i) an easy-to-use command-line application and (ii) a modular Python package containing all functions, data structures and pipelines that comprise the application.

\textbf{Command-line application:} The command-line application allows users to obtain predictions for their proteins and complexes of interest by running the respective EVcouplings pipelines (Fig. 1). Each pipeline is comprised of a series of modular stages that can be configured using a YAML file, which aids reproducibility by documenting all parameters. The pipelines are parallelized and support local multi-process execution as well as commonly used cluster systems, and automatically handles job submission and monitoring. The steps of the prediction pipelines are: \textit{align}, which generates and processes sequence alignments, \textit{concatenate}, which pairs putatively interacting sequences for the protein complex pipeline, \textit{couplings}, which calculates ECs, \textit{compare}, which compares ECs to experimental structures, \textit{mutate}, which predicts the effects of mutations, and \textit{fold}, which generates \textit{de novo} 3D models.

\textbf{EVcouplings Python package:} The command-line application is built on the underlying evcouplings Python package, whose modular architecture and comprehensive documentation facilitate the development of new stages and pipelines. Additionally, the package serves as a toolbox for handling and analyzing EC-related data. Examples for interactive usage are provided in Jupyter notebooks (Kluyver et al., 2016) distributed with the package, and extensive documentation is available on the web (http://evcouplings.readthedocts.io).

3 Conclusion

EVcouplings is an open source, integrated pipeline for evolutionary couplings analyses. The underlying API serves as a modular basis for data analysis and will allow developers to rapidly create new workflows.

\textbf{Acknowledgements}

We thank the members of Marks and Sander labs for helpful comments and testing, and HMS Research Computing for computational resources and support.

\textbf{Funding}

This work has been supported by NSF GRFP DGE1144152 (AGG), DOE CSGF fellowship DE-FG02-97ER25308 (AJR), Pathway Commons U41 HG006623, NRNB P41 GM103504 and R01 GM106303.

\textbf{Conflict of Interest:} none declared.

\textbf{References}

Balakrishnan, S. \textit{et al.} (2011) Learning generative models for protein fold families. \textit{Proteins}, 79, 1061–1078.

Ekeberg, M. \textit{et al.} (2013) Improved contact prediction in proteins: using pseudolikelihoods to infer Ports models. \textit{Phys. Rev. E Stat. Nonlin. Soft Matter. Phys.}, 87, 012707.

Figliuzzi, M. \textit{et al.} (2015) Coevolutionary landscape inference and the context-dependence of mutations in beta-lactamase TEM-1. \textit{Mol. Biol. Evol.}, 33, 268–280.
Hopf, T. A. et al. (2012) Three-dimensional structures of membrane proteins from genomic sequencing. *Cell*, 149, 1607–1621.
Hopf, T. A. et al. (2017) Mutation effects predicted from sequence co-variation. *Nat. Biotechnol.*, 35, 128.
Hopf, T. A. et al. (2014) Sequence co-evolution gives 3D contacts and structures of protein complexes. *Elife*, 3, e03430.
Jones, D. T. et al. (2015) MetaPSICOV: combining coevolution methods for accurate prediction of contacts and long range hydrogen bonding in proteins. *Bioinformatics*, 31, 999–1006.
Kaján, L. et al. (2014) FreeContact: fast and free software for protein contact prediction from residue co-evolution. *BMC Bioinformatics*, 15, 85.
Kluyver, T. et al. (2016) Jupyter Notebooks—a publishing format for reproducible computational workflows. In: *ELPUB*, pp. 87–90.
Marks, D. S. et al. (2011) Protein 3D structure computed from evolutionary sequence variation. *PloS One*, 6, e28766.
Morcos, F. et al. (2011) Direct-coupling analysis of residue coevolution captures native contacts across many protein families. *Proc. Natl. Acad. Sci. USA*, 108, E1293–E1301.
Ovchinnikov, S. et al. (2014) Robust and accurate prediction of residue–residue interactions across protein interfaces using evolutionary information. *Elife*, 3, e02030.
Ovchinnikov, S. et al. (2015) Large-scale determination of previously unsolved protein structures using evolutionary information. *Elife*, 4, e09248.
Seemayer, S. et al. (2014) CCMpred—fast and precise prediction of protein residue-residue contacts from correlated mutations. *Bioinformatics*, 30, 3128–3130.
Simkovic, F. et al. (2017) ConKit: a python interface to contact predictions. *Bioinformatics*, 33, 2209–2211.
Skwark, M. J. et al. (2014) Improved contact predictions using the recognition of protein like contact patterns. *PLoS Comput. Biol.*, 10, e1003889.
Weigt, M. et al. (2009) Identification of direct residue contacts in protein–protein interaction by message passing. *Proc. Natl. Acad. Sci. USA*, 106, 67–72.
Weinreb, C. et al. (2016) 3D RNA and functional interactions from evolutionary couplings. *Cell*, 165, 963–975.