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Title	Editorial: computational epitranscriptomics: bioinformatic approaches for the analysis of RNA modifications
Authors	Dassi, Erik;Baranov, Pavel V.;Pelizzola, Mattia
Publication date	2020-12-01
Original Citation	Dassi, E., Baranov, P. V. and Pelizzola, M. (2020) 'Editorial: computational epitranscriptomics: bioinformatic approaches for the analysis of RNA modifications', Frontiers in Genetics, 11, 630360 (2pp). doi: 10.3389/fgene.2020.630360
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.3389/fgene.2020.630360
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Download date	2026-11-08 02:09:43
Item downloaded from	https://hdl.handle.net/10468/13374

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frontiers in Genetics

EDITORIAL
published: 11 December 2020
doi: 10.3389/fgene.2020.630360

Editorial: Computational Epitranscriptomics: Bioinformatic Approaches for the Analysis of RNA Modifications

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Keywords: RNA modification, bioinformatics and computational biology, RNA methylation, RNA editing, pseudouridine (Ψ), nanopore

Editorial on the Research Topic

Computational Epitranscriptomics: Bioinformatic Approaches for the Analysis of RNA Modifications

RNA modifications were discovered decades ago, and more than 150 different marks have been found decorating various RNA species, including coding and non-coding transcripts (Boccaletto et al., 2018). Yet, only in the last decade this research field rapidly expanded, due to the development of simple and effective methods for the genome-wide identification of some of these marks, such as MeRIP-seq for the profiling of N6-methyladenosine (m6A) (Dominissini et al., 2012; Meyer et al., 2012). The renowned interest in the field led to the identification of key effectors—writers, erasers, and readers—that establish and decode the patterning of specific marks. This suggested that RNA modifications have the potential to be dynamically controlled, similarly to their genomic counterparts, the modifications of DNA and chromatin. Indeed, in analogy to the epigenome, the collective set of RNA modifications was named epitranscriptome. Altogether, the epitranscriptome is considered an important determinant of RNA fate, and specific marks were found to be involved in various steps of the RNA life cycle including, while not limited to, transcription, processing, decay, and translation (Roundtree et al., 2017).

As often occurs, following the birth of a new omics, the development of computational methods that are tailored to the analysis of those high-throughput datasets started to flourish. In analogy to the development of computational epigenomics (Bock and Lengauer, 2008), this research field could be referred to as computational epitranscriptomics.

This Research Topic collects a number of contributions in this field. Few manuscripts focused on the development of novel methods for the prediction of RNA modifications. A Galaxy-based user friendly graphical workflow was developed that cover the preprocessing of omics data, the quantification of mismatch and arrest rates with single-nucleotide resolution, and the subsequent machine learning, modification calling and visualization (Schmidt et al.). A computational workflow dedicated to 2′-O-methylation marks was optimized, allowing a more accurate detection of these marks and a more precise quantification of their level variations (Pichot et al.). A novel tool (LITOPHONE) was developed that adopts an ensemble predictor relying on sequence features to predict m6A sites in long non-coding RNAs (Liu L. et al.). A web server (PIANO) was implemented that relies on various genomic features, including sequence information, for the prediction and

OPEN ACCESS

Edited and reviewed by:
Richard D. Emes, University of Nottingham, United Kingdom

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Specialty section:
This article was submitted to Computational Genomics, a section of the journal Frontiers in Genetics

Received: *17 November 2020*
Accepted: *24 November 2020*
Published: *11 December 2020*

Citation:
Dassi E, Baranov PV and Pelizzola M (2020) Editorial: Computational Epitranscriptomics: Bioinformatic Approaches for the Analysis of RNA Modifications. Front. Genet. 11:630360. doi: 10.3389/fgene.2020.630360

functional annotation of pseudouridine sites (Song et al.). Finally, a bioinformatic pipeline (tRFs-Galaxy) was developed for the study of small non-coding RNAs derived from tRNAs (tRFs), allowing the study of tRFs biogenesis in *Drosophila melanogaster* (Molla-Herman et al.).

Two additional contributions discussed pitfalls in the analysis of specific marks. A first study discussed the impact of different bioinformatics steps on the detection of RNA editing events, describing key metrics for the quantification of their level of activity (Giudice et al.). A second contribution compared m6A genome-wide maps generated in various studies based on eight different methods, discussing the agreement of the data and the challenges in their comparative analysis, revealing an expression bias in the detected genes (Capitanchik et al.).

Two contributions were focused on the use of direct RNA sequencing through the Nanopore platform that enables long-reads sequencing of native transcripts. A perspective discussed how these data could allow quantifying the dynamics of modified RNAs at the level of individual isoforms (Furlan et al.). A second study introduced MasterOfPores, a NextFlow workflow that facilitates the analysis of these data, allowing the prediction of RNA modifications and the estimation of polyA tail lengths (Cozzuto et al.).

Finally, three different studies introduced bioinformatics workflows for studying the impact of RNA modifications in various tumor types. In the first study, a workflow based on consensus clustering and gene set enrichment analysis was presented that allowed the subsequent construction of a prognostic risk model suggesting the involvement of three m6A-related genes in liver cancer (Wang et al.). In the second study, bioinformatics analyses revealed a risk signature based on three m6A regulators, proposing candidate prognostic markers predictor of the clinicopathological features in hepatocellular carcinoma (Liu W. et al.). In the third study, integrated bioinformatics analyses led to the identification of differentially expressed transcripts with aberrant methylation patterns in malignant pheochromocytoma (Lin et al.).

Despite the rapid advance of the field, which allowed expanding the set of known marks, profiling their pattern, and disclosing their functional roles, a number of open questions remain (Frye et al., 2016). Most modifications remain poorly characterized, it is unclear whether different marks crosstalk and whether an epitranscriptional code exists. We are only starting to understand how, where and when these modifications are altered and whether they represent potential therapeutic targets in diseases. Key for answering these and other questions will be the continuous development of methods to map and analyze these marks. This research would benefit from the establishment of large scale collaborative and networking efforts such as the European Epitranscriptomics Network (www.epitran.eu) (Jantsch et al., 2018).

AUTHOR CONTRIBUTIONS

All authors contributed writing this Editorial and managing the corresponding Research Topic.

FUNDING

This work was supported by the EPITRAN COST Action (CA16120).

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