Peer Community In Ecotoxicology & Environmental Chemistry

New features of DRomics workflow for improved analyze of dose-response omics data in ecotoxicology

Claudia Cosio based on peer reviews by Rebecca Beauvais, Beatrice Gagnaire and Jean Armengaud

Marie Laure Delignette-Muller, Aurélie Siberchicot, Floriane Larras, Elise Billoir (2023) DRomics, a workflow to exploit dose-response omics data in ecotoxicology. bioRxiv, ver. 4, peer-reviewed and recommended by Peer Community in Ecotoxicology and Environmental Chemistry. https://doi.org/10.1101/2023.02.09.527852

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Our ability to anticipate and estimate how pollution affects components of ecosystems is of paramount importance in the field of ecotoxicology. Dose-response modeling is instrumental, as it allows deriving sensitivity thresholds used at the basis of regulatory risk assessment. In recent years, omics have highly influenced how the impacts of stressors are understood by revealing molecular changes at all levels of biota biological organization (Ebner et al., 2021). To allow analysis of omics data obtained using a typical dose-response design, DRomics a freely available tool for dose-response was proposed composed of both an R package and a free web application (Larras et al. 2018). Advances in this field depend both on theoretical concepts, technology and data integration.

In this context, Delignette-Muller et al. (2023) address the question of how to better integrate omics information in dose-response questions. The paper lists previous possibilities of DRomics and presents new features. It is now able to handle all types of continuous omic and continuous non-omic data (e.g. growth data). This new version proposes new visualization tools, functional annotation and improved modeling workflow for a better robustness of analysis of data with few replicates. New features are meant to help for biological interpretation at the metabolic pathway level, to compare different measurements, biological materials or experimental settings.

References:

Delignette-Muller, M. L., A. Siberchicot, F. Larras and E. Billoir (2023), DRomics, a workflow to exploit dose-response omics data in ecotoxicology. bioRxiv, 2023.2002.2009.527852, ver. 4 peer-reviewed and

recommended by Peer Community in Ecotoxicology and Environmental Chemistry. https://doi.org/10.1101/2023.02.09.527852

Ebner JN. (2021) Trends in the Application of "Omics" to Ecotoxicology and Stress Ecology. Genes, 12(10):1481. https://doi.org/10.3390/genes12101481

Larras F, Billoir E, Baillard V, Siberchicot A, Scholz S, Wubet T, Tarkka M, Schmitt-Jansen M and Delignette-Muller ML (2018). DRomics: a turnkey tool to support the use of the dose-response framework for omics data in ecological risk assessment. Environmental science & technology, 52(24):14461. https://doi.org/10.1021/acs.est.8b04752

Reviews

Evaluation round #3

Reviewed by Rebecca Beauvais, 27 June 2023

I have no further comments. The publication should be accepted.

Evaluation round #2

DOI or URL of the preprint: https://doi.org/10.1101/2023.02.09.527852
Version of the preprint: 3

Authors' reply, 21 June 2023

Dear Editor,

To take into the last comment from reviewer 3 ("The parts that needed clarification were well rewritten or added. However there is one last point that the authors might consider revising. It concerns the examples they added (lines 54-69) - to illustrate the support of AOPs as requested by the reviewers -which are very convincing but better writing would make it seem less like a list. You might want to combine some examples and give less detail in the text. The reader will jump to the references if interested. »), we rewrote the corresponding paragraph as suggested lines 55-66:

"Studies implementing DR (multi-)omics approaches sometimes aim at a mechanistic understanding of adverse effects (Adverse Outcome Pathway perspective - AOP). They could identify potential Modes of Action of pollutants (MoAs) at the molecular level, that generally need to be validated in a second step using targeted experiments (Andersen et al. 2018). Some authors already used our R package DRomics ("Dose Response for Omics") on transcriptomics and/or metabolomics data on different organisms and pollutants, to help the understanding of the adverse effects, by identifying most sensitive pathways (Larras et al., 2020; Gust et al., 2021; Vokuev et al., 2021). DRomics was also used on community transcriptomics and metabolomics data to provide insights into mechanisms of pollution-induced community tolerance (Lips et al., 2022; Larras et al., 2022). And recently, Song et al. (2023) showed, using DRomics, how DR modelling and estimation of points of departure at several omics and apical levels can be mapped to an AOP network. Those applications of DRomics especially motivated us to develop new R functions and a new shiny application to help the biological interpretation of DR modeling of omics data."

With many thanks,

Sincerely yours,

For the authors,

Marie Laure Delignette-Muller

Decision by Claudia Cosio, posted 01 June 2023, validated 02 June 2023

minor revision

Please consider suggestion made by the reviewer.

Reviewed by Jean Armengaud, 03 May 2023

I very much appreciate the changes proposed by the authors for this version. I found the manuscript to be of interest to a broad scientific community and recommend its publication. I have no doubt about the usefulness of the DRomics tool in ecotoxicology and more generally in toxicology. I look forward to the final print version.

Reviewed by Beatrice Gagnaire, 03 May 2023

All of my comments have been taken into account, for me the paper is now suitable for publication.

Reviewed by Rebecca Beauvais, 29 May 2023

The authors carefully made the suggested corrections and improved the clarity of some parts that initially seemed imprecise to me.

The parts that needed clarification were well rewritten or added. However there is one last point that the authors might consider revising. It concerns the examples they added (lines 54-69) - to illustrate the support of AOPs as requested by the reviewers - which are very convincing but better writing would make it seem less like a list. You might want to combine some examples and give less detail in the text. The readerwill jump to the references if interested.

With this minor change, the article would be finalized and I would recommend its publication.

Evaluation round #1

DOI or URL of the preprint: https://doi.org/10.1101/2023.02.09.527852
Version of the preprint: 1

Authors' reply, 28 April 2023

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Decision by Claudia Cosio, posted 28 March 2023, validated 29 March 2023

Major revision

Pleasefully address reviewer suggestions and include the missing section in your revision.

Reviewed by Jean Armengaud, 25 March 2023

The manuscript entitled "DRomics, a workflow to model and make sense of dose-response (multi-)omics data in (eco)toxicology" presents the latest version of this tool well suited for the interpretation of dose-response omics experiments, especially for the field of ecotoxicology. The authors have inserted new options in their software and have also developed a new module for biological interpretation. With the new web interface and all these new features, there is no doubt that the DRomics tool will be widely used by the scientific community interested in mono- or multi-omics. I recommend the publication of this interesting manuscript which is well argued and well documented. A few points should be considered by the authors to improve the presentation of the manuscript.

1. I am not sure I understand what the authors mean by "experimental versus in situ data". I assume that the in situ data is also collected experimentally.... Please rephrase by using "in natura" to describe the conditions present in a non-laboratory environment if this is what you mean here.
2. Some of the information in the abstract does not seem very relevant (the fact that an R package was released in its first version in 2019 seems to be a detail).
3. It would make sense to organize Table 1 by first release date (first publication) for each tool.
4. It is important that the link to the web version appears in the abstract.
5. The keywords should be revised. AOP and MoA are mentioned but these two concepts are not really developed in the manuscript. Ditto for toxicogenomics.
6. Last but not least, the title could be much more attractive if it was simplified as "DRomics, a workflow to exploit dose-response omics data in toxicology". Ecotoxicology is part of toxicology, so why try to differentiate the two words. Most users interested in multi-omics might simply be alerted by the introduction of "multi-omics" as a keyword.

Reviewed by Beatrice Gagnaire, 13 March 2023

This paper presents the DRomics tool, an R package designed to analyse multi-omics data obtained in ecotoxicology. The tool was first developed in 2019. The paper presents the new functionalities recently implemented and compare the DRomics tool to other existing tools.

The paper is very easy to read and very clear. I have very few comments. In Table 1, the authors should indicate that DRomics can deal with proteomic and metabolomic data. It is indicated "continuous omics data", but precisions could be added in order to make a clear difference with the other tools compared.

Some illustrations are presented of data explored with the DRomics tool. As it is new, maybe a table presenting an exhaustive list of the data set already analysed by DRomics can be added, in order to see if several type of data (transcriptomics, proteomics etc) have already been analysed.

Reviewed by Rebecca Beauvais, 24 March 2023

First of all, I would like to thank the recommender for giving me the opportunity to review this paper. The topic of the paper fits perfectly with the subject I am currently conducting some experiments on. Even though I knew this tool before I am still enthusiastic about its usefulness and the new possibilities developed and presented here.

I appreciated reading this paper because of two main strengths: the clarity and the conciseness of the text and the overview table, which is quite complete and well designed.

I noticed one major flaw that challenged me. The "in situ data" are not sufficiently explained. One or a few example(s) of applications could illustrate what the authors mean by this. However, this addition is however a nice added value compared to other tools. On the same topic, you mention that the number of doses could be less than 4/5 but what does this mean? Listing the data format requirements in this paper could help

ecotoxicologists to better design their experiment. This means that from my reading, lines 116 to 119 are not clear enough.

I make a few suggestions below that would help to improve the full understanding of all the possibilities offered by the tool.

In the abstract, you mention “understand the mode(s) of action of pollutants”. It sounds too general to me. To solve this, you could give some examples, here or in the introduction.

Regarding the figures, for Figure 2, I would recommend adding “(contigs)” after transcriptomics and “(metabolites)” after metabolomics and a point at the end of the caption; for Figure 3, I suggest to write “dose response (DR)” instead of DR in the caption. Also, many readers may also not fully understand your explanation of “The signal was shifted by...” I would suggest explaining this better in the body text or deleting it is not crucial to the purpose of the figure. In the same figure, have you forgotten to give a name to the x and y axes?

In case of a second run of review, I would be happy to participate.