ONTOX's Physiological Maps Curation Guidelines

Contributors: Luiz Ladeira, Bernard Staumont, Alessio Gamba & Liesbet Geris

Biomechanics Research Unit, GIGA Molecular & Computational Biology, University of Liège, Belgium;

Version: February 2024

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845

Contents

1. Introduction 3
1.1 General Introduction 3
1.2 Physiological maps 3
1.3 This document 4
2. General information 5
2.1. Aims 5
2.2. Communication 5
2.3. Glossary 5
2.4. BioStudies Repository 5
2.5. GitHub Repository 5
3. Documentation 6
3.1. Map plans 6
3.2. Table of contents 6
3.3. Issue reports 6
3.4. Release notes 6
3.5. Checklist 6
3.6. Reference management 6
4. Curation 7
4.1. Curating the maps using the MINERVA platform 7
4.2. Curating the maps using CellDesigner 7
4.2.1. Sharing your results 7
4.2.2. General considerations 8
4.2.3. Entities 8
Color scheme 8
Identifiers 9
4.2.4. Reactions 9
Suggested relations for MIRIAM annotations 10
4.2.5. Protein groups representation 10
4.3. Tutorials 11
4.4. ONTOX PMs Identifiers 12
5. Reading recommendations 13
6. Contact points 14
7. References 14
Annex I 18

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845

1. Introduction

1.1 General Introduction

The ONTOX project (Vinken et al., 2021) focuses on developing mode-of-action ontology frameworks for toxicology, with the goal of developing new approach methodologies (NAMs) in order to predict systemic repeated dose toxicity effects that will enable human-oriented chemical risk assessment.

The Physiological Map (PM) and the mode-of-action Ontology (ON) are frameworks that store and graphically represent mechanistic information about organ physiology (PMs), with the ON also containing pathology, chemical, and kinetic data. PMs and ONs are organized in a comprehensive and structured manner, that is intended to be used and interpreted by humans and computers, as the main data storage formats in the ONTOX project, together with adverse outcome pathways (AOPs) (Vinken et al., 2021). These frameworks are intrinsically linked since PMs serve as the physiological basis for the creation of ONs, which occur with the integration of new domains of knowledge into the PM framework. As a result, certain recommendations might be useful when building and updating these tools to ensure compliance with the machine-readable formats necessary for the use of those data in the project.

To ensure the reusability of these frameworks and the data they include, the PMs and ONs need to fulfill the FAIR Guide Principles (Wilkinson et al., 2016), which state that data must be findable, accessible, interoperable, and reusable. Consequently, the purpose of this guide is also to define the strategy for adhering to the FAIR principles in the construction and curation of PMs and ONs.

1.2 Physiological maps

The PMs' first versions were constructed by adapting the workflow from the Disease Maps Project (Mazein et al., 2018). Briefly, relevant physiological literature (mainly review papers and book chapters) was curated by domain experts (ONTOX WP7 for the liver, WP8 for the kidney, and WP9 for the developing brain case studies). Then, we reviewed the papers and listed the fundamental mechanisms to be mapped and screened in online databases for previously described pathways, including e.g., WikiPathways (Martens et al., 2021), Reactome (Jassal et al., 2019), KEGG (Kanehisa et al., 2021), and other Disease Maps modules (Fujita et al., 2014;

Ostaszewski et al., 2021; Serhan et al., 2020), among others. Finally, we integrated pathways and data from the literature using the Systems Biology Graphical Notation (SBGN) (Novère et al., 2009) to represent the pathways using the CellDesigner software (Funahashi et al., 2006) and saved as an SBML file.

At the end of this process, we have five Physiological Maps:

1. Liver Lipid Metabolism Physiological Map;
2. Liver Bile Secretion Physiological Map;
3. Nephron Physiological Map;
4. Physiological Map of the Developing Brain;
5. Neural Tube Closure Physiological Map.

The Neural Tube Closure PM was a special case, as it was already published (Heusinkveld et al., 2021) and was reviewed, expanded and standardized by the ONTOX University of Liège (UL) team.

After the release of the first versions using the MINERVA platform (Hoksza et al., 2020), the maps were open for revision within the project. A second version for each map was established after nomenclature and annotation standardization. The next versions of the PMs will rely on the following sources:

- Curation and comments of the reviewers;
- New key articles and pathways (from databases) screened manually;
- Exploration of transcriptomics and proteomics data;
- Data from the Sysrev-SBTab-Phymdos-SBML workflow (semi-automated data extraction approach using these different tools). This is currently under development (February 2024).

This last one is the main source of data for the future versions of the map, as it is based on a systematic review approach and is intended to extract data from a myriad of papers.

1.3 This document

In this document, you will find general guidelines (with basic reading recommendations) to design, curate and report updates on PMs in ONTOX. Additional and more detailed information can be found in the recommended readings.

This document was developed based on the Curation Guidelines from the COVID-19 Disease Map (Ostaszewski et al. 2021) and on the "guide for developing comprehensive systems biology maps of disease mechanisms: planning, construction and maintenance" (Mazein et al., 2023).

2. General information

2.1. Aims

We are building and updating Physiological Maps of five different processes relevant to the ONTOX case studies at the molecular interaction level.

2.2. Communication

Our main internal communication channel is via email. Please make sure you are listed in our contributors' mailing lists HERE (this list is closed to the ONTOX consortium for the duration of the project).

If you are not a member of the ONTOX consortium and wish to contact us, please refer to one of the contact points.

2.3. Glossary

A glossary containing all the terms related to the construction and curation of the PMs and ONs is provided HERE.

2.4. BioStudies Repository

All the stable releases of the PMs and ONs, as well as all documentation, will be made available at the BioStudies repository (https://www.ebi.ac.uk/biostudies/). All ONTOX members have access. If you are not an ONTOX member, you will have access to the already public files in the ONTOX collection on BioStudies.

2.5. GitHub Repository

In addition to BioStudies, map files and documentation can be found in our GitHub repositories. These repositories also include pathways under development and interim versions of the PMs.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845

3. Documentation

3.1. Map plans

Each PM has a plan describing the scope of the map, tools and sources used, map content, the development team, contributors, and technical details. They can be found in this FOLDER.

3.2. Table of contents

Each map has its own table of contents listing all the pathways included, sources, and general comments containing the status of curation. You can check which pathways need curation work and send a message to the person responsible for that map to discuss how to help. The table of contents can be found in the map's documentation FOLDER.

3.3. Issue reports

Unsolved issues are listed on the Issue report and described in detail. This document is sent periodically to domain experts to guide specific curation efforts. The Issues reports can be found in the map's documentation FOLDER.

3.4. Release notes

This document is released with the map's stable releases. It lists what was included, removed, and fixed in the newly released version. It can be found in the map's documentation FOLDER.

3.5. Checklist

A checklist is used by the curation team to check if the map or pathway has all the annotations recommended before uploading them to MINERVA. It can also be used as a quality control checklist by the curator when curating a pathway or constructing a new one. You will find it in Annex I.

3.6. Reference management

The literature is organized using this Zotero group. The group is public-by-invitation to allow file sharing. Please apply for access. Instructions on how to use the Zotero group can be found in the "1-START HERE" folder on the group library.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845

4. Curation

4.1. Curating the maps using the MINERVA platform

There is a tutorial on how to use MINERVA to explore and include comments on the maps. You can curate the maps and include comments on the current version, but please keep in mind the following considerations when reviewing a map:

a) The PMs are not homogeneous: this means that different mechanisms described could have very different levels of detail, and this is not necessarily an issue. If you feel that a mechanism could benefit from more detail, please do not hesitate to include a comment.

b) Including a reference in your comment is of great help to the map curators. The PubMed ID (or DOI) of a paper might be sufficient for them to find the information, but the more details you give, the more they benefit from your comments.

c) And of course, you can always send your suggestions and questions by email directly to the contact person for each map.

4.2. Curating the maps using CellDesigner

You can skip this section if you don't want to use CellDesigner. But we strongly recommend giving it a try.

You may also want to design a pathway or curate the files using the CellDesigner editor. For this, we have some recommendations:

- A good start is reading the "Mazein et al 2023" paper, as it contains a step-by-step guide for developing and curating mechanistic disease maps (also applies to physiological maps).
- You can check for tutorials in the tutorials section of this document.

4.2.1. Sharing your results

Deposit your work via the GitHub project organization.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845

4.2.2. General considerations

a) The curation should focus on molecular mechanisms described using the Systems Biology Graphical Notation (SBGN) Process Description language, as detailed as possible.
b) The SBGN Activity Flow language is also allowed in cases where the information lacks details for Process Description usage. You can also consider using Activity Flow as a way to enhance the human readability of the map, but this should be discussed with the curation team as to how to best combine both languages, since this may interfere with the applications of the maps for analysis and modeling.
c) Mechanisms should be included in a subcellular localization and cell type/tissue/organ specific. Use the "Compartment" on CellDesigner to delimit the organ/tissue/cell type or organelle.
d) At least one scientific publication or a reference to a pathway database should be annotated for each reaction.
e) The Zotero group contains selected studies organized by key pathways and PMs.

4.2.3. Entities

Color scheme

We recommend using the standard CellDesigner color scheme for developing and submitting your model. A color blind friendly palette will be used in the harmonization phase before uploading the maps to the MINERVA platform. The different color versions do not imply different interpretations of the maps, as colors do not carry meaning in the SBGN standard. The intent of having two different versions is to improve human interpretation of the maps, making them more accessible to everyone.

A table with a suitable color scheme is presented below as a reference for the curators in the release phase and was extracted from Wong (2011).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845

Color	Color name	RGB (1–255)	CMYK (%)	P	D
	Black	0, 0, 0	0, 0, 0, 100		
	Orange	230, 159, 0	0, 50, 100, 0		
	Sky blue	86, 180, 233	80, 0, 0, 0		
	Bluish green	0, 158, 115	97, 0, 75, 0		
	Yellow	240, 228, 66	10, 5, 90, 0		
	Blue	0, 114, 178	100, 50, 0, 0		
	Vermillion	213, 94, 0	0, 80, 100, 0		
	Reddish purple	204, 121, 167	10, 70, 0, 0		

Figure 1. Colors optimized for colorblindness. Protanopia (P) and deuteranopia (D) perceive simulated colors, respectively (Wong, 2011).

Identifiers

To allow automated annotation of biochemical entities using the MINERVA platform, please consider following categories.

- **Genes, RNAs and Proteins identifiers:** use HGNC official symbols as names.
- **Phenotypes describing biological processes:** use the most appropriate Gene Ontology (GO) Biological Process (BP) term; use the GO BP ID for annotation.
- **Complex:** use a regular complex if all complex members are known; if not all members are known, use a hypothetical complex (dashed). Name the protein complex preferentially with a term provided by GO Cellular Component (CC); add an appropriate GO CC ID annotation. If not possible, use "Element A:Element B:Element..." for complexes of multiple elements, or a name suggested by the source article.
- **Compounds, metabolites, drugs and small molecules:** name them preferentially with terms provided by ChEBI or PubChem; for their annotation, use ChEBI identifiers or PubChem CIDs. Short, non-standard names ("ROS" instead of "reactive oxygen species") are allowed as long as the annotation is provided.
- **Compartments:** annotate with the appropriate term from Gene Ontology (preferentially for MINERVA automatic annotation), Cell Ontology, BRENDA, Cellosaurus, or a specific name from literature.

4.2.4. Reactions

- **Reactions should be associated with a PMID and/or a DOI** (in case PMID is not available).

- Use the “Note” field on CellDesigner (next to the MIRIAM annotation tab) to indicate details on the information about the reaction extracted from the literature or databases.

Suggested relations for MIRIAM annotations

MIRIAM stands for “Minimum Information Requested In the Annotation of biochemical Models” (Laibe & Le Novère, 2007; Novère et al., 2005) and is used to annotate different elements on computational models, including the PMs and ONs. CellDesigner supports MIRIAM annotations, requiring three different elements that compose the annotation, a qualifier (relations), a data type (the type of database you are referring to), and an ID (the identifier of the element on the specific database you are referring). Here we suggest using a generic qualifier (relation) to annotate all data types in the PM and ON, and a specific case for a taxonomy identifier when applicable.

- Generic and preferred annotations: **bqbiolis:Describedby**.
- Taxonomy identifiers (e.g. NCBI Taxonomy) for reactions and bioentities: **bqbiolis:hasVersion** and choose DataType: Taxonomy to use the NCBI Taxonomy IDs (in case the curated information originated from animal experiments). This is particularly interesting for the Neural Tube Closure PM, which incorporates data from animal models along with human-derived data.

4.2.5. Protein groups representation

Sometimes a cell can express several different isoforms of proteins. To avoid misrepresenting proteins, we recommend grouping them using the steps below:

- Use the "Complex" entity to represent a protein group.
- Set the outline as a dotted line to distinguish it from the actual complexes. For that, double-click on the complex and set it as "hypothetical".
- To name a group, use the generic name of the proteins it contains.

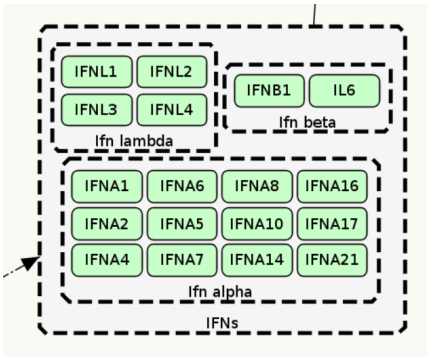

Figure 2. Example from the COVID19 Disease map: https://covid19map.elixir-luxembourg.org/minerva/

You might want to annotate the proteins inside the group; however, CellDesigner does not allow you to do so. For that, you have to drag the protein out of the complex glyph and annotate it using the MIRIAM or Notes resource. After that, you drag it back into the "complex" group. You will notice that you cannot see the annotation in CellDesigner, but it is there, and it will be displayed as "Annotated by curator" on the MINERVA platform.

- If you use the official HGNC name for the proteins, they will be automatically annotated in MINERVA if you choose to do so in the upload process.

4.3. Tutorials

There is a tutorial's summary in our GitHub repository. An introductory video about the Physiological Maps concept in ONTOX can also be found HERE. If you do not know how to use CellDesigner, please take a look at our introductory video tutorial. You will find a tutorial on how to use MINERVA to curate the maps in a dedicated section above. In the meantime, you might find useful the tutorials developed by the Asthma Disease Map project (Mazein et al., 2018), available at https://asthma-map.org/tutorials/, and the user guide from the Parkinson's Disease Map (Fujita et al., 2014), available at https://pdmap.pages.uni.lu/guide/.

4.4. ONTOX PMs Identifiers

Each map and submap must receive a unique identifier and be registered on the "ONTOX PMs Identifiers list". The identifier should comply with the following system.

Prefix:

1. The identifier must start with the prefix "ONTOX" followed by an underscore as "ONTOX_".
2. Organ Code (2 characters): a two-letter code representing the case study.
    a. "LL" for the Liver Lipid Metabolism PM;
    b. "LB" for the Liver Bile Secretion PM;
    c. "NP" for the Nephron Urine Production PM;
    d. "DB" for the PM of the Developing Brain;
    e. "NT" for the Neural Tube Closure PM.
3. Map Number (4 characters): a unique 4-digit number assigned sequentially to each physiological map (example: "0001", "0002", ..., "9999").
4. Version (3 characters): a single value denoting the version of the map. This allows for updates or revisions to be easily tracked. A three digit number should be used in this case (example: 001, 007, 015…).
5. Use an underscore character (" _ ") to separate the version element from the rest of the elements on the identifier.
6. The identifiers must be unique and be linked to a unique file and version.
7. Submaps must follow the same system, differing only in the map number, which must be unique and different from numbers on the main map.

Identifier examples:

ONTOX_NT0001_001
First version of the Neural Tube Closure PM.

ONTOX_NT0002_001
A submap of the Neural Tube Closure PM.

ONTOX_NT0001_002
Second version of the Neural Tube Closure PM.

Pathways identifiers should be annotated as "model notes" when editing on CellDesigner.

5. Reading recommendations

For a comprehensive guide on how to plan, develop, and maintain a disease map (or physiological map, as the same principles apply), check out the following paper:

> Mazein, Alexander, Marcio Luis Acencio, Irina Balaur, Adrien Rougny, Danielle Welter, Anna Niarakis, Diana Ramirez Ardila, et al. 2023. "A Guide for Developing Comprehensive Systems Biology Maps of Disease Mechanisms: Planning, Construction and Maintenance." *Frontiers in Bioinformatics* 3 (June): 1197310. https://doi.org/10.3389/fbinf.2023.1197310.

Further recommendations and guidelines for pathway curation may be found in the following papers:

> Touré, Vasundra, Nicolas Le Novère, Dagmar Waltemath, and Olaf Wolkenhauer. 2018. "Quick Tips for Creating Effective and Impactful Biological Pathways Using the Systems Biology Graphical Notation." *PLoS Computational Biology* 14 (2): 1–6. https://doi.org/10.1371/journal.pcbi.1005740.

> Hanspers, Kristina, Martina Kutmon, Susan L. Coort, Daniela Digles, Lauren J. Dupuis, Friederike Ehrhart, Finterly Hu, et al. 2021. "Ten Simple Rules for Creating Reusable Pathway Models for Computational Analysis and Visualization." *PLoS Computational Biology* 17 (8): 1–14. https://doi.org/10.1371/journal.pcbi.1009226.

In addition, the following paper contains some tips for general biocuration that are useful in pathway curation as well:

> Tang, Y. Amy, Klemens Pichler, Anja Füllgrabe, Jane Lomax, James Malone, Monica C. Munoz-Torres, Drashtti V. Vasant, Eleanor Williams, and Melissa Haendel. 2019. "Ten Quick Tips for Biocuration." *PLoS Computational Biology* 15 (5): 1–7. https://doi.org/10.1371/journal.pcbi.1006906.

And the following paper provides an overview of the disease maps community and some of the current efforts on mapping biochemical/physiological and pathological mechanisms:

Mazein, Alexander, Marek Ostaszewski, Inna Kuperstein, Steven Watterson, Nicolas Le Novère, Diane Lefaudeux, Bertrand De Meulder, et al. 2018. "Systems Medicine Disease Maps: Community-Driven Comprehensive Representation of Disease Mechanisms." *Npj Systems Biology and Applications* 4 (1). https://doi.org/10.1038/s41540-018-0059-y.

For further reading recommendations, you may check the "Methods" folder in the Zotero group.

6. Contact points

- *Liesbet Geris* (liesbet.geris@uliege.be): task leader for the development of the ONTOX PMs (Task 1.2) and ontologies (Task 5.3).
- *Bernard Staumont* (b.staumont@uliege.be): ULiège team's project manager. Coordinator and supervisor of all activities for PMs and ontologies development.
- *Luiz Ladeira* (lcladeira@uliege.be): developer and curator of the liver maps (lipid metabolism and bile secretion) and the PM of the developing brain.
- *Alessio Gamba* (agamba@uliege.be): developer and curator of the nephron PM and curator of the neural tube closure PM.

7. References

Fujita, K. A., Ostaszewski, M., Matsuoka, Y., Ghosh, S., Glaab, E., Trefois, C., Crespo, I., Perumal, T. M., Jurkowski, W., Antony, P. M. A., Diederich, N., Buttini, M., Kodama, A., Satagopam, V. P., Eifes, S., Del Sol, A., Schneider, R., Kitano, H., & Balling, R. (2014). Integrating pathways of Parkinson's disease in a molecular interaction map. *Molecular Neurobiology*, *49*(1), 88–102. https://doi.org/10.1007/s12035-013-8489-4

Funahashi, A., Matsuoka, Y., Jouraku, A., Kitano, H., & Kikuchi, N. (2006). Celldesigner: A Modeling Tool for Biochemical Networks. *Proceedings of the 2006 Winter Simulation Conference*, 1707–1712. https://doi.org/10.1109/WSC.2006.322946

Hanspers, K., Kutmon, M., Coort, S. L., Digles, D., Dupuis, L. J., Ehrhart, F., Hu, F., Lopes, E. N., Martens, M., Pham, N., Shin, W., Slenter, D. N.,

Waagmeester, A., Willighagen, E. L., Winckers, L. A., Evelo, C. T., & Pico, A. R. (2021). Ten simple rules for creating reusable pathway models for computational analysis and visualization. *PLOS Computational Biology*, *17*(8), e1009226. https://doi.org/10.1371/journal.pcbi.1009226

Heusinkveld, H. J., Staal, Y. C. M., Baker, N. C., Daston, G., Knudsen, T. B., & Piersma, A. (2021). An ontology for developmental processes and toxicities of neural tube closure. *Reproductive Toxicology*, *99*, 160–167. https://doi.org/10.1016/j.reprotox.2020.09.002

Hoksza, D., Gawron, P., Ostaszewski, M., Hasenauer, J., & Schneider, R. (2020). Closing the gap between formats for storing layout information in systems biology. *Briefings in Bioinformatics*, *21*(4), 1249–1260. https://doi.org/10.1093/bib/bbz067

Jassal, B., Matthews, L., Viteri, G., Gong, C., Lorente, P., Fabregat, A., Sidiropoulos, K., Cook, J., Gillespie, M., Haw, R., Loney, F., May, B., Milacic, M., Rothfels, K., Sevilla, C., Shamovsky, V., Shorser, S., Varusai, T., Weiser, J., … D'Eustachio, P. (2019). The reactome pathway knowledgebase. *Nucleic Acids Research*, gkz1031. https://doi.org/10.1093/nar/gkz1031

Kanehisa, M., Furumichi, M., Sato, Y., Ishiguro-Watanabe, M., & Tanabe, M. (2021). KEGG: Integrating viruses and cellular organisms. *Nucleic Acids Research*, *49*(D1), D545–D551. https://doi.org/10.1093/nar/gkaa970

Laibe, C., & Le Novère, N. (2007). MIRIAM Resources: Tools to generate and resolve robust cross-references in Systems Biology. *BMC Systems Biology*, *1*(1), 58. https://doi.org/10.1186/1752-0509-1-58

Martens, M., Ammar, A., Riutta, A., Waagmeester, A., Slenter, D. N., Hanspers, K., A. Miller, R., Digles, D., Lopes, E. N., Ehrhart, F., Dupuis, L. J., Winckers, L. A., Coort, S. L., Willighagen, E. L., Evelo, C. T., Pico, A. R., & Kutmon, M. (2021). WikiPathways: Connecting communities. *Nucleic Acids Research*, *49*(D1), D613–D621. https://doi.org/10.1093/nar/gkaa1024

Mazein, A., Acencio, M. L., Balaur, I., Rougny, A., Welter, D., Niarakis, A., Ramirez Ardila, D., Dogrusoz, U., Gawron, P., Satagopam, V., Gu, W., Kremer, A., Schneider, R., & Ostaszewski, M. (2023). A guide for developing comprehensive systems biology maps of disease mechanisms: Planning, construction and maintenance. *Frontiers in Bioinformatics*, *3*, 1197310. https://doi.org/10.3389/fbinf.2023.1197310

Mazein, A., Knowles, R. G., Adcock, I., Chung, K. F., Wheelock, C. E., Maitland-van Der Zee, A. H., Sterk, P. J., Auffray, C., & AsthmaMap

Project Team. (2018). AsthmaMap: An expert-driven computational representation of disease mechanisms. *Clinical & Experimental Allergy*, *48*(8), 916–918. https://doi.org/10.1111/cea.13211

Novère, N. L., Finney, A., Hucka, M., Bhalla, U. S., Campagne, F., Collado-Vides, J., Crampin, E. J., Halstead, M., Klipp, E., Mendes, P., Nielsen, P., Sauro, H., Shapiro, B., Snoep, J. L., Spence, H. D., & Wanner, B. L. (2005). Minimum information requested in the annotation of biochemical models (MIRIAM). *Nature Biotechnology*, *23*(12), 1509–1515. https://doi.org/10.1038/nbt1156

Novère, N. L., Hucka, M., Mi, H., Moodie, S., Schreiber, F., Sorokin, A., Demir, E., Wegner, K., Aladjem, M. I., Wimalaratne, S. M., Bergman, F. T., Gauges, R., Ghazal, P., Kawaji, H., Li, L., Matsuoka, Y., Villéger, A., Boyd, S. E., Calzone, L., … Kitano, H. (2009). The Systems Biology Graphical Notation. *Nature Biotechnology*, *27*(8), 735–741. https://doi.org/10.1038/nbt.1558

Ostaszewski, M., Niarakis, A., Mazein, A., Kuperstein, I., Phair, R., Orta-Resendiz, A., Singh, V., Aghamiri, S. S., Acencio, M. L., Glaab, E., Ruepp, A., Fobo, G., Montrone, C., Brauner, B., Frishman, G., Monraz Gómez, L. C., Somers, J., Hoch, M., Kumar Gupta, S., … COVID-19 Disease Map Community. (2021). COVID19 Disease Map, a computational knowledge repository of virus-host interaction mechanisms. *Molecular Systems Biology*, *17*(10), e10387. https://doi.org/10.15252/msb.202110387

Serhan, C. N., Gupta, S. K., Perretti, M., Godson, C., Brennan, E., Li, Y., Soehnlein, O., Shimizu, T., Werz, O., Chiurchiù, V., Azzi, A., Dubourdeau, M., Gupta, S. S., Schopohl, P., Hoch, M., Gjorgevikj, D., Khan, F. M., Brauer, D., Tripathi, A., … Wolkenhauer, O. (2020). The Atlas of Inflammation Resolution (AIR). *Molecular Aspects of Medicine*, *74*, 100894. https://doi.org/10.1016/j.mam.2020.100894

Tang, Y. A., Pichler, K., Füllgrabe, A., Lomax, J., Malone, J., Munoz-Torres, M. C., Vasant, D. V., Williams, E., & Haendel, M. (2019). Ten quick tips for biocuration. *PLOS Computational Biology*, *15*(5), e1006906. https://doi.org/10.1371/journal.pcbi.1006906

Touré, V., Le Novère, N., Waltemath, D., & Wolkenhauer, O. (2018). Quick tips for creating effective and impactful biological pathways using the Systems Biology Graphical Notation. *PLOS Computational Biology*, *14*(2), e1005740. https://doi.org/10.1371/journal.pcbi.1005740

Vinken, M., Benfenati, E., Busquet, F., Castell, J., Clevert, D.-A., de Kok, T. M., Dirven, H., Fritsche, E., Geris, L., Gozalbes, R., Hartung, T., Jennen, D., Jover, R., Kandarova, H., Kramer, N., Krul, C., Luechtefeld, T., Masereeuw, R., Roggen, E., … Piersma, A. H. (2021). Safer chemicals

using less animals: Kick-off of the European ONTOX project. *Toxicology*, *458*, 152846. https://doi.org/10.1016/j.tox.2021.152846

Wilkinson, M. D., Dumontier, M., Aalbersberg, Ij. J., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J.-W., da Silva Santos, L. B., Bourne, P. E., Bouwman, J., Brookes, A. J., Clark, T., Crosas, M., Dillo, I., Dumon, O., Edmunds, S., Evelo, C. T., Finkers, R., … Mons, B. (2016). The FAIR Guiding Principles for scientific data management and stewardship. *Scientific Data*, *3*(1), 160018. https://doi.org/10.1038/sdata.2016.18

Wong, B. (2011). Points of view: Color blindness. *Nature Methods*, *8*(6), 441–441. https://doi.org/10.1038/nmeth.1618

Annex I

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 963845

Checklist for annotation and documentation control:

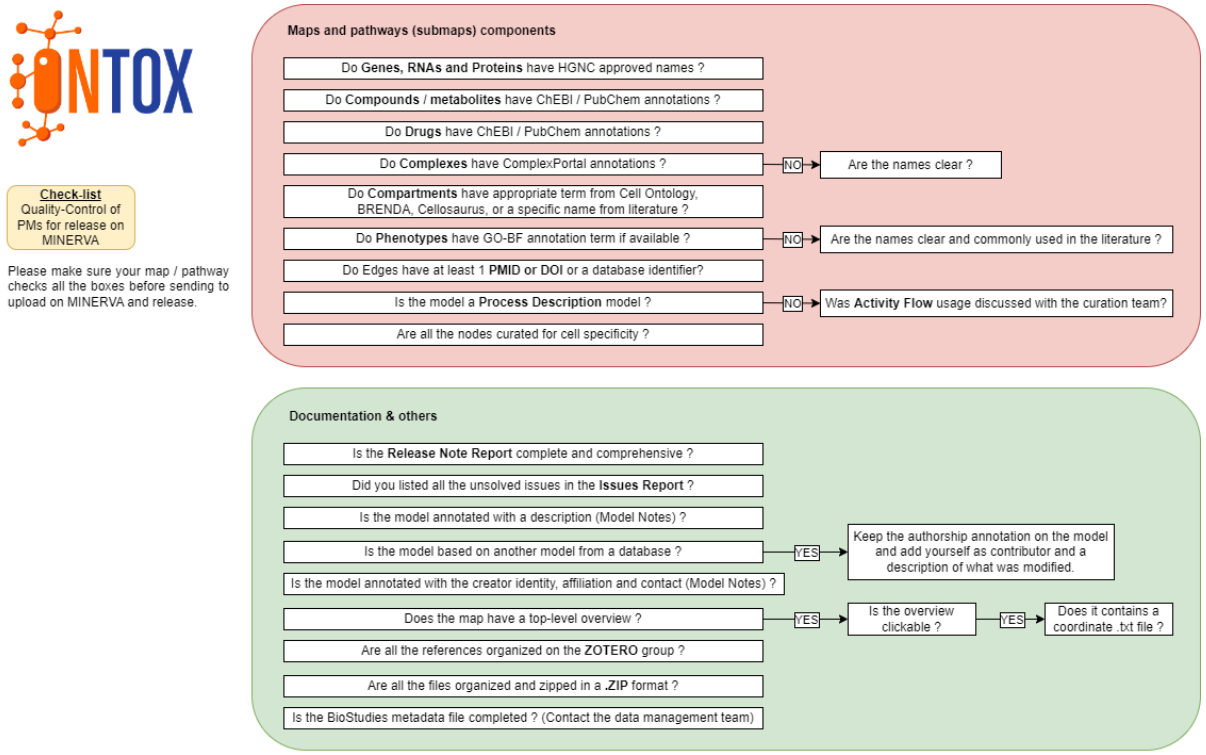

Figure 3. Checklist for annotation and documentation control when submitting a map or pathway for upload into the ONTOX MINERVA Platform instance (https://ontox.elixir-luxembourg.org/minerva/).