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## **PSI-MI XML3.0.0: exchange format for molecular interactions**

### Status of This Document

This document presents PSI-MI XML3.0.0, an update to the existing molecular interaction exchange format. Distribution is unlimited.

### Version of the document

The current version of this document is version 3.0.0, finalized April 2018

### Abstract

The Human Proteome Organization (HUPO) Proteomics Standards Initiative (PSI, <http://www.psidev.info>) defines community standards for data representation in proteomics to facilitate data comparison, exchange and verification. The Molecular Interaction workgroup develop formats for the exchange of molecular interaction data. The existing XML standard (PSI-MI XML2.5) has proven to be, and will continue to be, capable of capturing the vast majority of molecular interaction data, which are generated by techniques such as protein complementation assays, affinity capture, biophysical measurements and enzyme assays. However, use cases have arisen which cannot be adequately described within this XML schema, for example allosteric interactions, abstracted interactions and dynamic interactions. In order to meet these specialist use cases, a new version of the XML format has been developed, PSI-MI XML3.0.0.

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## 1. Introduction

### 1.1 Description of the Need

Version 1.0 of PSI-MI XML was published in 2004 and enabled the description of simple protein interaction data [1]. The format was widely implemented and supported by both, software tool developers and data providers, but was soon found to be too limited in its scope. PSI-MI XML2.5 extended the type of interactor to encompass any molecule or complex of molecules which can be described in the 'interactor type' branch of the accompanying controlled vocabulary (CV) (PSI-MI) [2]. Sequence or positional features on a participant molecule that are relevant for the interaction can be described in a featureList, again using an appropriate CV term (MI:0116 and child terms).

Version 2.5 has proven to be, and will continue to be, capable of capturing the vast majority of molecular interaction data, which are generated by techniques such as protein complementation assays, affinity capture, biophysical measurements and enzyme assays. It successfully describes genetic as well as physical interactions, and can also be used to hold predicted interactions or the results of text-mining exercises, all clearly described as such by appropriate CV terms (MI:1110). As such, this version of the format will continue to be supported by the PSI-MI community for the foreseeable future. However, use cases have arisen which cannot be adequately described within this XML schema, and in 2013 it was decided that the field had advanced sufficiently to justify moving to the next level in this deliberately tiered approach to describing interaction data, and to produce PSI-MI XML3.0.0.

### 1.2 Requirements

The main requirements to be fulfilled are:

- a. The format should be, as much as possible, backwardly compatible with PSI-MI XML2.5. Where this proved not to be possible, changes should be structured to avoid breaking existing parsers.
- b. The format, and other existing formats, should be supported by a software library that can read/write all of the growing numbers of XML and tab-delimited formats available Use cases. The JAMI library has now been developed (<https://github.com/MICommunity/psi-jami>) and will be separately published on.

### 1.3 Use Cases

The following cases of usage have driven the development of the PSI-MI XML3.0.0 data model, and were used to define the scope of the format:

- a. Update to the description of molecule features to enable negative coordinates to be described. This will enable the description of genomic loci in features.
- b. The actual sequence change of a mutation should be systematically captured, and not just the position and effect as is currently the case in PSI-MI XML2.5.
- c. It should be possible to capture multiple feature detection methods in a list, and not be limited to the description of a single methodology.
- d. It should be possible to capture the effect of/requirement for a feature, such as a post-translational modification, which would be described by appropriate CV terms (feature role).
- e. The ability to add kinetic parameters should be possible at the feature level, so that a kinetic value can be directly associated with a specific mutation.
- f. The ability to describe dynamic interactions i.e. interactions measured under identical experimental conditions other than the change of one or more specific variables (for example, increasing concentration of an agonist, or a time course of events) should be available.
- g. The ability to add data which is not directly linked to a single publication but has been abstracted from multiple sources should be available. This change should enable the merge and deprecation of PSI-PAR [3] which is currently separately maintained.

- h. The ability to describe cooperative or allosteric binding where a series of events are required to describe an interaction. Again, these may represent data from multiple rather than a single publication (see 1.3g).
- i. The ability to describe molecule sets i.e. cases where a participant may be one of a list of molecules rather than an unambiguous identification of a single molecule.
- j. The systematic capture of the stoichiometry of molecules within an interaction should be added to the format.
- k. The *bibref* section requires update to enable the full description of a publication within a single section.

## Notational Conventions

Only include this section if applicable.

The key words "MUST," "MUST NOT," "REQUIRED," "SHALL," "SHALL NOT," "SHOULD," "SHOULD NOT," "RECOMMENDED," "MAY," and "OPTIONAL" are to be interpreted as described in RFC-2119 (<https://www.ietf.org/rfc/rfc2119.txt>).

## 2. Relationship to Other Specifications

1. *PSI-MI XML* - although PSI-MI XML3.0.0 has been written as a new version of the existing PSI-MI XML standard, it is in fact expected to be complementary to the existing PSI-MI XML2.5, which will remain actively supported by the MI worktrack. It is anticipated that most users will continue to use PSI-MI XML2.5 to exchange experimental-based interaction data, and PSI-MI XML3.0.0 will be required only for specialist use cases. Should the majority of users, in time, move to adopt 3.0.0, the continued support for 2.5 will then be reviewed by the work group.
2. *MITAB* – the use cases supported in PSI-MI XML3.0.0 are too complex to be described in MITAB so no extension to this standard is envisaged as result of this work.
3. *PSI-PAR* – with the acceptance of PSI-MI XML3.0.0 as an official PSI standard, the PSI-PAR format will be formally deprecated and will no longer be supported.

## 3. The PSI-MI Controlled Vocabulary

Terms required to annotate the XML schema are actively maintained in the PSI-MI CV (<http://www.ebi.ac.uk/ols/ontologies/mi>). As recommended by the PSI CV guidelines (<http://www.psudev.info/sites/default/files/CommunityPractice-revised.doc>), a tracker exists (<https://github.com/HUPO-PSI/psi-mi-CV/issues>) for the request of new terms, and major changes to the CV, or to a branch or term within it, are discussed either at the annual workshop or via the mailing list ([psi-mi@ebi.ac.uk](mailto:psi-mi@ebi.ac.uk)).

The following ontologies or CVs are also of use in certain circumstances

- ChEBI (<http://www.ebi.ac.uk/ols/ontologies/chebi>)
- PSI-MOD (<http://www.ebi.ac.uk/ols/ontologies/MOD>)
- Gene Ontology (<http://www.ebi.ac.uk/ols/ontologies/GO>)
- Evidence Ontology (<http://www.ebi.ac.uk/ols/ontologies/ECO>)

## 4. PSI-MI XML3.0.0

### 4.1 The PSI-MI XML Schema

A detailed description of the schema is presented in Appendix 1. It is also available at

MIF300.xsd: <https://raw.githubusercontent.com/HUPO-PSI/miXML/master/3.0/src/MIF300.xsd>

MIF300 schema documentation : <https://rawgit.com/HUPO-PSI/miXML/master/3.0/doc/MIF300.html>

and has been available for community comment through the PSI-MI web pages since 2016.

Example files illustrating how the schema can be used to fill the use cases described in Section 1.3 are available as Appendix 2-11.

#### New features

- 4.1.1 Representation of a negative feature range: The position attribute type and interval attribute type for *featureRange* have been updated. In PSI-MI XML2.5 these are of the type '*unsignedLong*' which means that features described in this version can only have positive range positions. This has been updated to '*long*' in PSI-MI XML2.5 to enable negative positions, for example designated gene promoter regions, to be captured.
- 4.1.2 Representation of the sequence change caused by introduction of a mutation: The position and effect of a mutation can be systematically captured using the *featureRange* positions and the *featureType* element. However, in PSI-MI XML2.5 there is no defined way to capture the actual sequence change. In PSI-MI XML3.0, a new element named *resultingSequence* has been added at the level of the *featureRange* element. The *resultingSequence* element contains an *originalSequence* element to describe the original sequence, a *newSequence* element which contains the mutated sequence and an *xref* element which would be optional and could be used to add external cross references such as Ensembl cross references to single nucleotide polymorphisms (SNPs). The *newSequence* and *originalSequence* are not required if an *xref* element is provided.
- 4.1.3 It is now possible to add several feature detection methods in the feature element by making the *featureDetectionMethod* element repeatable in the feature element. This will allow users to describe cases in which a feature has been described by more than one method, for example a post-translational modification (PTM) being identified by both a specific antibody and by mass spectrometry. The change was made to maintain backwards compatibility with earlier version of the schema, a goal that was set by the work group when version 1.0 was published. When several feature detection methods are described in a file, most existing parsers will simply use the last feature detection method they have parsed.  
The feature element has been extended in PSI-MI XML3.0 to capture the dependency of an interaction on a particular feature, for example the presence of a specific PTM and also the effect of an interaction, such as the phosphorylation of a tyrosine residue by a protein kinase. In PSI-XML2.5 this information is stored as an attribute of a feature. An optional *featureRole* element has been added to the feature element, which can be used to describe PTMs existing in/resulting from the context of the interaction. This element would be populated from a list of new controlled vocabulary terms added to the PSI-MI ontology, such as 'prerequisite-PTM (MI:0638)' or 'observed-PTM (MI:0925)'.  
The feature element has been extended in PSI-MI XML3.0 to capture the dependency of an interaction on a particular feature, for example the presence of a specific PTM and also the effect of an interaction, such as the phosphorylation of a tyrosine residue by a protein kinase. In PSI-XML2.5 this information is stored as an attribute of a feature. An optional *featureRole* element has been added to the feature element, which can be used to describe PTMs existing in/resulting from the context of the interaction. This element would be populated from a list of new controlled vocabulary terms added to the PSI-MI ontology, such as 'prerequisite-PTM (MI:0638)' or 'observed-PTM (MI:0925)'.
- 4.1.4 The equilibrium dissociation constant or parameters, such as *kon* or *koff* can be added at the interaction level in PSI-MI XML2.5; however, this does not enable the systematic

capture of changes in this parameter when a sequence is mutated at the feature level. The kinetic parameters that are linked to a specific mutation have been moved from interaction *parameterList* to the feature *parameterList*. The kinetic parameter associated with the wild type protein will still be at the interaction level.

- 4.1.5 Representation of variable conditions (dynamic interactions) in an experiment: interaction sub-networks may be rewired in response to changes in the environmental conditions in which the experiment is performed. Examples of such changes include applying increasing concentration of an agonist onto a cell or a single concentration for an increasing amount of time, or merely sampling the interactome at different stages of the cell cycle. An optional *variableParameterList* element has been added to the experiment element, which contains one to many *variableParameter* elements. Each *variableParameter* element contains the required description element to define the variable condition, an optional unit element to describe the unit of the different parameters in the *variableValueList* and a required *variableValueList* element to list all the existing variable parameter values used in the experiment. A *variableValueList* contains one to many *variableValue* elements, which may themselves contain an optional order attribute, an integer defining the position of the given *variableValue* within its containing *variableValueList* parent element. The format can also handle multiple changes in condition, such as parallel time courses of an increasing concentration of an agonist.
- 4.1.6 Representation of an abstracted interaction: The PSI-XML2.5 schema was designed to represent experimental interactions, therefore an experiment description is required for each interaction. However, increasingly groups are looking to capture and exchange data which may have been collated from several publications. Examples of these include reference protein complexes described in the Complex Portal ([www.ebi.ac.uk/complexportal](http://www.ebi.ac.uk/complexportal)) and the descriptions of cooperative binding when distinct molecular interactions influence each other either positively or negatively. In order to describe such cases, the '*interactionDetectionMethod*' element within an '*experimentDescription*' element does not have a specific method assigned as a value in entries in the PSI-XML 2.5 format. Instead the CV terms 'inferred by author' (MI:0363) or 'inferred by curator' (MI:0364) are used to indicate that the interaction was inferred from multiple experiments or from several publications, respectively. Within the '*experimentDescription*' element, the '*bibref*' element refers to a related publication. In PSI-MI XML3.0, a new optional *abstractInteraction* element has been added within the *interactionList*. This element can now be used to describe 'abstract' or 'modelled' interactions such as stable complexes or allosteric interactions. This element contains many optional elements, for example a *participantList*, *bindingFeaturesList*, an *interactorType* element to describe the type, such as a protein complex, a protein-RNA or an antibody-antigen complex and an *interactionType* element to differentiate between a stable or transient complex, a cooperative interaction, or an enzymatic reaction.
- 4.1.7 Representation of a cooperative interaction: In a cellular context, interactions between biomolecules are rarely independent. Instead, distinct molecular binding events affect each other positively or negatively, i.e. they are cooperative. The two main mechanisms underlying cooperative binding are allostery and pre-assembly. Allostery involves a change in binding or catalytic properties of a biomolecule polymer at one site of the molecule by an event at a different distinct site of the same molecule. Pre-assembly involves the generation or abrogation of a binding site through an interaction or enzymatic modification. This includes (i) complex assembly resulting in the formation of a continuous binding site spanning multiple subunits; (ii) competitive binding to overlapping or adjacent, mutually exclusive binding sites; (iii) enzymatic modification that changes the physicochemical compatibility for a binding partner; or (iv) configurational pre-organization involving multivalent ligands that engage in multiple discrete interactions with one or more binding partners for high-avidity binding.

Because the data required to describe cooperative interactions rarely comes from a single experiment, or even need to be assembled from many distinct publications, they

- are treated as abstract interactions and in PSI-MI XML3.0, captured using the *abstractInteraction* element. Within this element, an optional *cooperativeEffectList* allows listing the cooperative effects a specific interaction has on one or more other interactions. The effect will be described in the allosterity or pre-assembly child element, as appropriate. Within these elements, additional details are captured, including the experimental methods and publications from which the data were inferred, references to the interactions that are affected, and the outcome of the effect.
- 4.1.8 Representation of molecule sets: PSI-MI XML2.5 contains a key element *interactorType*, to describe the type of molecule involved in an interaction. This qualifies an interactor with a term from the PSI-MI controlled vocabulary, for example 'protein' (MI:0326) or 'polysaccharide' (MI:0904). However, there are cases when the exact molecule cannot be described, where it may be one of several possible entities. Examples of such cases include a peptide identified as the result of a mass spectrometry experiment which can be redundantly assigned to any one of a family or closely related molecules, and a non-specific antibody which cannot distinguish between two proteins with a high degree of sequence homology. There are cases when the products of one or more genes cannot be distinguished at the protein level, for example human calmodulin is an identical protein produced by three genes (CALM1, CALM2, CALM3). In these cases it may be necessary to describe a 'set' of molecules. This cannot be a simple addition to the Participant type CV as the ability to add a feature to a specific molecule within that set may be necessary. In PSI-MI XML3.0, the participant element will now contain a choice between *interactor*, *interactorRef*, *interactionRef* and *interactorCandidateList*. The *interactorCandidateList* element would contain a *moleculeSetType* element (*cvType*) followed by one to many *interactorCandidate* elements. The *interactorCandidate* node contains a required *id* attribute, a required *interactor* or *interactorRef* element to describe or reference an interactor and an optional *featureList* element with one to many features to describe binding features for each interactor candidate.
- 4.1.9 Representation of the systematic capture of the stoichiometry of molecules within an interaction: In PSI-MI XML2.5 the stoichiometry of a molecule can only be described as free-text annotation or as an attribute of the participant. In PSI-MI XML3.0 the participant element has been updated to add an optional XML Schema Development (XSD) choice sub-element, which provides a choice between a *stoichiometry* element to describe the mean stoichiometry for this participant and a *stoichiometryRange* element to describe a stoichiometry range for this participant. If the *stoichiometry* element is selected, a *value* attribute is required to describe the stoichiometry as a decimal value. If the *stoichiometryRange* element is chosen, both *minValue* and *maxValue* attributes are required to describe the stoichiometry range as decimal values.
- 4.1.10 Update of the *bibref* element: the *bibref* element refers to a publication. PSI-MI XML 2.5 allows either a cross reference (*xref*) element (to describe PubMed primary reference if it exists) or an *attributeList* element (to describe publication details such as publication title and publication date). To export both PubMed primary reference and publication details, the PubMed primary reference is added in *bibref* and the publication details attributes in the *attributeList* of the *experimentDescription*. In PSI-MI XML3.0 the *bibref* element has been updated to accept both *xref* and *attributeList* so that the publication can be entirely described within *bibref*.

## 4.2 Implementation and tools

All data resources using the IntAct database as their data storage repository, i.e. members of the IMEx Consortium including IntAct, IID, InnateDB, MINT, DIP, MatrixDB, HPIDB [4], now make their data available in PSI-MI XML3.0.0, in addition to the existing PSI-MI XML 2.5 and MITAB 2.7 formats (<http://psicquic.github.io/MITAB27Format.html>). Manually curated protein complexes from the Complex Portal ([www.ebi.ac.uk/complexportal](http://www.ebi.ac.uk/complexportal)) are also made available in PSI-MI XML3.0.0.

The PSI validator [5], a tool, that not only checks the XML syntax but also enforces rules regarding the use of an ontology class or CV terms by checking that the terms exist in the resource and that they are used in the correct location of a document, is currently being updated to validate PSI-MI XML3.0.0 files. The PSI-MI maker software (<https://github.com/MICCommunity/psimi-maker-flattener>), a desktop application that helps users to both create PSI-MI XML documents and to extract data from them, has been updated to support PSI-MI XML3.0.0. In addition, the new features included in PSI-MI XML3.0.0 are being used to extend an existing tool suite that integrates molecular, structural and genomics data and that already relies on the PSI-MI standard [6].

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## 9. Glossary

PSI-MI Proteomics Standards Initiative – Molecular Interactions

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## 11. Appendices

Example files showing how the schema meets each of the use cases listed in section 1.3. Due to file size, all files have been made available at <https://github.com/HUPO-PSI/miXML/tree/master/3.0/pub> Note, all examples are available in the IntAct database ([www.ebi.ac.uk/intact](http://www.ebi.ac.uk/intact)) unless otherwise stated, and may also be accessed from there.

- 11.1 Appendix 1. Schema documentation for MIF300.xsd.  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%201.pdf>)
- 11.2 Appendix 2. Example file showing the representation of all molecular interaction data from a single publication (PMID: 26919541) in PSI-MI XML3.0.0 – note, includes use case 1.3k, rewrite of bibliography section.  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%202.docx>)

- 11.3 Appendix 3. Representation of a negative feature range (use case 1.3a).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%203.docx>)
- 11.4 Appendix 4. Representation of the sequence change caused by introduction of a mutation (use case 1.3b).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%204.docx>)
- 11.5 Appendix 5. Representation of multiple feature detection methods and feature roles (use case 1.3c, use case 1.3d).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%205.docx>)
- 11.6 Appendix 6. Representation of kinetic parameters added at feature level (use case 1.3e).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%206.docx>)
- 11.7 Appendix 7. Representation of variable conditions (dynamic interactions) in an experiment (use case 1.3f).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%207.docx>)
- 11.8 Appendix 8. Representation of an abstracted interaction, a manually curated protein complex, in PSI-MI XML3.0.0 (use case 1.3g).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%208.docx>)
- 11.9 Appendix 9. Representation of a cooperative interaction in PSI-MI XML3.0.0 (Use case 1.3h).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%209.docx>)
- 11.10 Appendix 10. Representation of molecule sets i.e. cases where a participant may be one of a list of molecules (use case 1.3i).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%2010.docx>)
- 11.11 Appendix 11. Representation of the systematic capture of the stoichiometry of molecules within an interaction (use case 1.3j).  
(<https://github.com/HUPO-PSI/miXML/blob/master/3.0/pub/Appendix%2011.docx>)