Metal-MACiE: a database of metals involved in biological catalysis
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ABSTRACT
Summary: Metal-MACiE is a new publicly available web-based database, held in MySQL, which aims to organize the available information on the properties and the roles of metals in the context of the catalytic mechanisms of metalloenzymes. Metal-MACiE, which currently covers 75% of metal-dependent enzyme commission (EC) sub-sub-classes and is continuously growing, exploits the existing MACiE database for the annotation of the reaction mechanisms. The two databases constitute complementary sources of information for enzymology, biochemistry and molecular pharmacology studies. Availability: http://www.ebi.ac.uk/thornton-srv/databases/Metal_MACiE/home.html
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Supplementary information: Supplementary data are available at Bioinformatics online.

1 INTRODUCTION
MACiE (http://www.ebi.ac.uk/thornton-srv/databases/MACiE) (Holliday et al., 2005) is a database containing detailed information on enzyme reaction mechanisms. Analysis of MACiE has shown that about half of known enzymatic reactions involve metals. This observation reflects the importance of metals in the chemistry of living systems, which have evolved a wide variety of metalloenzymes acting in almost all biological processes including photosynthesis, respiration and N2 fixation (Bertini et al., 2007), the information giving reaction state, information on the 3D structure of the first coordination sphere of the metal in that state is also reported. Enzymes are retrieved or deduced from the available literature, for which references are provided. When a PDB structure is available for a given reaction state, information on the 3D structure of the first coordination sphere of the metal in that state is also reported.

2 DATABASE DESIGN
Similarly to MACiE, Metal-MACiE entries correspond to enzyme catalytic mechanisms. The identification codes of Metal-MACiE entries are the same as in MACiE (e.g. M0004) to facilitate the communication between the two databases. Each Metal-MACiE entry contains annotation for all the metals involved in the catalysis. Basic information includes the type of center in which the metal is found (e.g. dinuclear, heme) and the identity of the metal in the functional, physiological form of the enzyme. It is reported when the physiological metal is under debate [e.g. for fumarylacetoacetase, M0180 (Bateman et al., 2001) and when protein homologues from different organisms use different metals [e.g. for lactoylglutathione lyase, M0032 (Clugston et al., 1998)].

A detailed description of metal properties (e.g. oxidation state, coordination geometry) and functions (e.g. substrate activation) is given for every step of the enzymatic reaction. These data are retrieved or deduced from the available literature, for which references are provided. When a PDB structure is available for a given reaction state, information on the 3D structure of the first coordination sphere of the metal in that state is also reported.

3 DATABASE CONTENT
Metal-MACiE contains all the metalloenzymes currently annotated in MACiE. This release of Metal-MACiE includes 136 entries spanning 134 enzyme commission (EC) numbers, and contains annotations for 220 metals participating to a total of 605 reaction steps. About 23% of reaction states are associated with a PDB structure describing the metal environment in that state. Enzymes whose EC codes have the same first three digits (defining EC sub-sub-classes) generally share similar overall chemistry. Entries in MACiE and thus in Metal-MACiE are selected so as to cover as many EC sub-sub-classes as possible, i.e. to ensure the largest possible coverage of the EC reaction space. Currently, the PDB covers 188 EC sub-sub-classes, of which 144 include at least one metal-dependent enzyme (Andreini et al., 2008). The 134 EC
numbers spanned by Metal-MACiE entries map to 108 distinct EC sub-sub-classes, so Metal-MACiE now covers 75% of the metal-dependent enzyme reaction space, as represented in the PDB, and is constantly expanding.

4 DATABASE CURATION
The information contained in Metal-MACiE is based on the available primary literature and is manually entered using a web interface that involves data checking and validation. All the terms in Metal-MACiE have been rigorously defined taking as reference the MACiE dictionary (http://www.ebi.ac.uk/thornton-srv/databases/MACiE/glossary.html). The PDB was manually searched for representative protein structures of reaction states. The information on the metal first coordination sphere was automatically extracted from the PDB structure with the highest resolution, and then manually checked.

5 DATABASE ACCESS AND WEB INTERFACE
Metal-MACiE can be queried from the main page and from the advanced query page (Table S1). For enzymes not included in the database, queries based on EC number give information on the reasons of exclusion (e.g. the catalytic mechanism is not defined) and on what is known about their metal-binding capability.

Entry information is organized in four types of page, which share a common design composed of three sections (Boxes A, B and C in Fig. 1). Box A is the same in all page types, and contains links to the other pages of the entry, and to the corresponding entry in MACiE. Box B reports the scheme of the overall enzymatic reaction or of a reaction step. When the scheme exceeds the screen, it can be seen by horizontal scrolling. Box C reports the core data of Metal-MACiE on metals, and differs in each page type (Boxes C1, C2, C3 and C4 in Fig. S1). The four page types are:

- Entry home page: contains general information on the metal(s) involved in the catalysis and on its/their properties in the resting state enzyme.
- Step information page: contains detailed information on the properties and function(s) of the metal(s) in a reaction step. There is one for every reaction step. It can be accessed using the links in Box A (Fig. 1).
- First coordination sphere page: contains detailed information on the first coordination sphere of the metal(s) in a reaction state. There is one for every reaction state for which a representative PDB structure is available. It can be accessed using the links in Box C (Fig. S1). Spatial coordinates of the metal first coordination sphere can be downloaded as a PDB formatted file.
- Metal information page: contains an overview of metal properties and roles during the course of the reaction. There is one for every metal involved in the catalysis. It can be accessed using the links in Box C (Fig. S1).

6 FUTURE DEVELOPMENTS
The main future work will concern the extension of the Metal-MACiE coverage, to include alternative reaction mechanisms, as well as new mechanisms. Due to the intimate link between MACiE and Metal-MACiE, their datasets will grow in parallel. Other work will include adding statistics resulting from several analyses on the database, and creating FTP pages to allow data download.

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