

# **New approaches to understanding of heavy metals role in pathogeneses of chronic respiratory diseases**

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## INTRODUCTION

It is proved that environmental pollution is one of the major risk factors of occurrence and/or exacerbation of such chronic respiratory diseases (CRD) as bronchial asthma, obstructive lung disease and cancer of lungs. Heavy metals are the most aggressive pollutants and respiratory system is the most sensitive system to their influence.

There is a plenty of data about influence of heavy metals on human organism, structure and function of respiratory system, pathogenesis and exacerbation of chronic respiratory diseases. However this data is not formalized and spread among many literature and biological databases. Thus reasons and pathogenesis of chronic noninfectious lung diseases are not entirely clear and their treatment is not optimal.

Sydney Brenner, 2002 Nobel Prize Winner in Medicine said:

*"We now have unprecedented ability to collect data about nature but there is now a crisis developing in biology, in that completely unstructured information does not enhance understanding. We need a framework to put all of this knowledge and data into — that is going to be the problem in biology. We've reached the stage where we can't talk to each other — we've all become highly specialized. We need a framework, a framework where people can come back to us and say, 'Yes, I understand.' Driving toward that framework is really the big challenge."*

Our work is step in this direction. We are developing Biological Universal Modeling Language (BioUML) that is imagined as a language to write a “book of life” i.e. model of the world in biological terms. Here we demonstrate how it can be applied for comprehensive formalized description of heavy metals influence on pathogenesises of chronic respiratory lung diseases.

## AIM

- Provide comprehensive formalized description of heavy metals influence on human organism and pathogenesis of chronic respiratory diseases.
- Integrate this data with information available in different biological databases.
- Put this data into context of known biological pathways (metabolic pathways, gene networks, signal transduction pathways).

## METHODS

- Information is being extracted from the literature and related biological databases by annotators (fig. 1).
- BioUML technology (fig. 2) is used for formalized description of heavy metals influence on human organism and pathogenesis of chronic respiratory diseases.

## BIOLOGICAL DATABASES USED IN THE WORK (FIG. 1)

- UMLS<sup>®</sup> – Unified Medical Language System<sup>®</sup> - is large-scale knowledge source designed to facilitate retrieval and integration of information from multiple-readable biomedical information resources. <http://www.nlm.nih.gov/research/umls/>
- GO – GeneOntology - contains three structured, controlled vocabularies (ontologies) that describe gene products in terms of their associated biological processes, cellular components and molecular. <http://www.geneontology.org>
- PROMISE – Prosthetic groups and Metal Ions in Protein Active Sites Database. <http://metallo.scripps.edu/PROMISE/>
- GeneNet – database on gene networks. <http://wwwmgs.bionet.nsc.ru/systems/mgl/genenet/>
- KEGG – Kyoto Encyclopedia of Genes and Genomes KEGG – is a suite of databases database on molecular interaction networks in biological processes. <http://www.kegg.com>
- EMBL – is nucleotide sequence database. <http://www.ebi.ac.uk/embl/>
- SWISS-PROT – is protein sequence database. <http://www.ebi.ac.uk/swissprot/>

## BioUML TECHNOLOGY (FIG. 2)

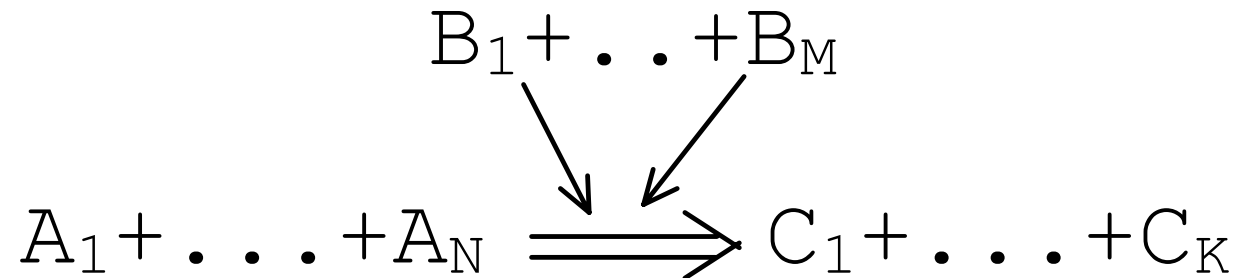
<http://www.biouml.org>

BioUML – Biological Universal Modeling Language – is open source extensible computer program for comprehensive formalized description, visualization and simulation of wide range of biological and other complex systems. It consists from following parts:

- Meta model - provides an abstract layer to present structure of any biological system as a clustered graph.
- Diagram editor - a universal editor to visualize and edit structure of biological system as diagram.
- Search engine - provides searching of components with the specified properties in biological pathway databases. The search result can be presented as graph and further edited by a user in BioUML editor.
- Modeler - allows a user to model/simulate dynamics of biological systems using block diagrams.
- Standard diagram and data types - an attempt to standardize data types and graphic notations for biological pathways.
- Database modules - provides incorporation of different databases biological pathways into BioUML framework.

## PRINCIPLES OF FORMALISED DESCRIPTION OF BIOLOGICAL SYSTEMS (FIG. 3)

A chemical formalism was employed as a basis for describing the events occurring in biological pathways. Thus, any event is described as follows:



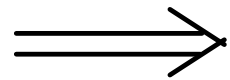
A, B, C – entities (protein, gene, RNA or chemical substance)

A – input (reactants)

B – modifiers (catalysts or inhibitors)

C – output (products)

2 types of relationships between entities:



**reaction** - the interaction between the entities that leads to the appearance of a new entity



**regulatory event** - the effect of an entity on a certain reaction

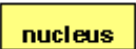

















EXAMPLE OF FORMALIZED PROTEIN DESCRIPTION (FIG. 4)

<b>Field</b>	<b>Value</b>	<b>Field description</b>
<b>ID</b>	<b>Hs:NF-kappaB</b>	<b>Protein identifier</b>
<b>OS</b>	<b>Homo sapiens (human).</b>	<b>Specie</b>
<b>SN</b>	<b>NF-kappaB</b>	<b>Protein short name</b>
<b>NM</b>	<b>nuclear factor-kappaB p65/p50 heterodimer</b>	<b>Protein complete name</b>
<b>SY</b>	<b>p65/p50, NF-kB</b>	<b>Synonyms</b>
<b>FN</b>	<b>Active</b>	<b>functional state (active or inactive)</b>
<b>MM</b>	<b>Heterodimer</b>	<b>Multimirezation level (monomer, homodimer, heterodimer or multimer)</b>
<b>MD</b>	<b>no data</b>	<b>modifications (phosphorylated, non phosphorylated or no data)</b>
<b>SO</b>	<b>Hs:B-cell; Hs:HeLa; Hs:T-cell; Hs:colon carcinoma; Hs:fibroblast; Hs:macrophage</b>	<b>Cell types wher from which protein was isolated</b>
<b>RE</b>	<b>LPS; IFN-gamma; PMA; TNF-alpha</b>	<b>Factors that induce the protein expression</b>
<b>DR</b>	<b>SWISS-PROT; P19838; EMBL; M58603;</b>	<b>References to other databases</b>
<b>RF</b>	<b>Bayon Y. et al., 1998 Chen F. et al., 1995</b>	<b>Literature references</b>
<b>CC</b>	<b>Activated NF-kB regulates transcription of many cytokines, chemokines, nitric oxide synthase, cell adhesion molecules.</b>	<b>Comment</b>

## IMAGES OF BIOLOGICAL PATHWAY COMPONENTS (FIG. 5)

Each object type has its own image in the diagram, representing the features of the object. The shape of the protein indicates the level of its multimerization; color, its functional state (active or inactive); and an additional red ball, its modification resulting from phosphorylation.

The arrows, which represent the relations between the objects, differ depending on their type: reaction is indicated by a green arrow. The color indicates type of the regulatory event: red, switch on of the reaction; pink, positive effect on the reaction; and blue, negative effect on the reaction.

Image	Entity types
	<b>Compartment</b>
	<b>Cell</b>
	<b>Substance (nonproteinaceous)</b>
	<b>Gene</b>
	<b>RNA</b>
Proteins	
	<b>Monomer:</b> inactive, nonphosphorylated
	<b>Monomer:</b> inactive, phosphorylated
	<b>Monomer:</b> active, nonphosphorylated
	<b>Homodimer</b>
	<b>Heterodimer</b>
	<b>Multimeric complex</b>
	<b>Phosphorylated protein</b>
Relationships	
	<b>Reaction (binary)</b>
	<b>Reaction (complex)</b>
	<b>Regulatory event: switch on</b>
	<b>Regulatory event: increase</b>
	<b>Regulatory event: decrease</b>
	<b>Regulatory event: switch off</b>

BioUML framework

File

Modules Plugins

metal & CLD : Lung antioxidants

modules

- GeneNet
- SBML model repository
- metal & CLD
  - Data
    - cell
    - compartment
    - constant
    - function
    - gene
    - literature
    - process
    - protein
    - reaction
    - relation
    - rna
    - state
    - substance
  - Diagrams
    - Chronic lung diseases
    - GSH redox cycle
    - Lung antioxidants
    - Lung oxidants
  - test

Diagram illustrating the classification of lung antioxidants:

```

graph TD
    Root["lung antioxidant"]
    Root --> Enzymes["antyoxydant enzymes"]
    Root --> Chelator["metal chelator"]
    Root --> ROS["ROS-scavenging molecules"]
    
    Enzymes --> GPx
    Enzymes --> HO["heam oxygenase"]
    Enzymes --> SOD
    Enzymes --> Catalase
    
    SOD --> CuZn["CuZn-SOD"]
    SOD --> Mn["Mn-SOD"]
    SOD --> Cu["Cu-SOD"]
    
    Chelator --> Ferritin
    Chelator --> Transferrin["trans ferrin"]
    Chelator --> Lactoferrin["lactoferin"]
    Chelator --> Ceruloplasmin
    
    ROS --> GSH
    ROS --> Albumin
    ROS --> Membrane["membrane beta-carotene"]
    ROS --> Alpha["alpa-tocohperol"]
    ROS --> Uric["uric acid"]
    ROS --> Lung["lung lining fluid mucus"]
    ROS --> Ascorbic["ascorbic acid"]
  
```

Node

Title: lung antioxidant

Data:

ID: lung antioxidant

RF: [Ljava.lang.String;@15afd61

[0]: Gilmour et al., 2002

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Preview

## Classification of lung antioxidants

Description Legend JavaScript

BioUML framework

File

Modules Plugins

- modules
  - GeneNet
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    - Data
      - cell
      - compartment
      - constant
      - function
      - gene
      - literature
      - process
      - protein
      - reaction
      - relation
      - rna
      - state
      - substance
    - Diagrams
      - Chronic lung diseases
      - GSH redox cycle
      - Lung antioxidants
      - Lung oxidants
    - test

metal & CLD : Chronic lung diseases

```
graph TD;
    A[air pollution] --> B[metals accumulation];
    C[smoking] --> B;
    D[diet] --> B;
    B --> E[imbalance protease-antiprotease];
    B --> F[Imbalance of microelem ets];
    E --> G[disturbance structure and function respiratory system];
    F --> H[oxidative stress];
    F --> I[disturbance immune system];
    H --> J[imbalance oxidant-antioxidant];
    J --> G;
    I --> K[Development chronic lung diseases];
    G --> K;
```

Title: oxidative stress  
Data:  
ID: oxidative stress  
RF: [Ljava.lang.String;@14d4313  
[0]: Bagchi et al., 2001  
[1]: Buzard and Kasprzak2000  
[2]: Cavallo et al., 2002

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Preview

# Conceptual model of heavy metals influence on pathogenesis of chronic lung diseases

Description Legend JavaScript