BioModels: Quick tour

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- Systems
- Beginner
- 0.5 hour

This quick tour provides a brief introduction to EMBL-EBI's resource of mathematical models of biological/biomedical systems: BioModels [2].

Learning objectives:

- Why mathematical models and how are they used in understanding the mechanism underlying biological systems
- Basic understanding of the content, features, functionality and use of BioModels
- Know where to find out more about BioModels Database

Why use systems modelling?

Mathematical modelling is used to analyse the dynamic interactions between several components of a biological system, with the aim to understand the behaviour of the system as a whole. With high-throughput omics data and network analysis, hypothesis design and the use of predictive models is becoming a necessary component to understand the mechanisms underlying complex biological systems, diseases, and drug action.

- Mathematical models help us to investigate:

1. How complex regulatory processes are connected?
2. How disruption of these processes contribute to the development of pathological conditions?

- Mathematical models help us in decision making
  - Analyse systems perturbations.
  - Assess the suitability of specific molecules as novel therapeutic targets.
  - Develop hypotheses to guide and design new experiments

In Figure 1 you can see an example of a SBGN [4] (Systems Biology Graphical Notation [5]) process diagram of a model that describe the IL13-induced signalling of JAK/STAT pathway in Hodgkin (L1236) and primary mediastinal B-cell lymphoma (MedB-1) cell lines. The model helps us to quantitatively predict possible perturbations, which would allow us to identify potential therapeutic targets.
Figure 1 The SBGN process diagram of lymphoma-derived cell lines MedB-1 and L1236 dynamic signalling network model, consisting of reactions (arrows) with enzymatic, mass action, or custom kinetics. Round-headed arrows indicate reaction catalysis, whereas bar-ended arrows show reaction inhibition. IL13 is used as input function of the system. Reactions and species coloured in grey are omitted in the L1236 model.

View the original model in BioModels Database [6].

What is BioModels?

BioModels [2] is an invaluable core resource for the systems biology/pharmacology community. It stores a vast collection of the literature-based mechanistic models in standard formats, many of which are physiologically and pharmaceutically relevant, and describe a wide range of biological/biomedical processes at different biological scales.

BioModels provides two sets of models:
1. Models described in scientific literature.
2. Models generated automatically from pathway resources (a branch of BioModels called Path2Models [7]).

We have manually validated the model components, as well as the structure and behaviour of a large proportion of literature-based models. This is done to ensure the models correspondence with the original publication. The model elements are also cross-linked to external database resources and ontologies, which enables you to precisely search models from the repository.

BioModels is accessible through a web interface and programmatically through web services [8]. Hosted models are freely available for use, modification and redistribution to all users under the terms of Creative Commons CC0 [9].

![BioModels production pipeline](image)

**Figure 2** BioModels production pipeline. After models are submitted to BioModels they pass through a rigorous curation [10] procedure and are distributed to their respective branches based on the model type, and the curation status.
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What can I do with BioModels?

BioModels can either be used as a comprehensive body of knowledge on existing processes, or alternatively it can be used to building blocks that facilitate the repurposing of a model via further development, refinement or merging.

Figure 4 below shows an example of how you can use BioModels.
**A. How to use models in BioModels?**

1. Search and retrieve the appropriate models from BioModels.
2. Evaluate the suitability of the models’ components for your usage.
3. Modify/extend to accommodate desired input/output.
4. Evaluate with experimental findings (iterative).
5. Application to the problem & Guide to design new experiments.

**B. Example of Model repurposing**

![Diagram](Image)

**Figure 4:** A) Model repurposing: A model in BioModels can be used as a building block for creating extended models. B) An example of model repurposing.

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**Searching and getting data from BioModels**

**Searching BioModels**

**Browse by GO classification**

Allows categorised hierarchical retrieval of models. You can do this by following the GO term classification or tree that is provided on the BioModels homepage. All models are annotated with at least one GO term at the model level to represent the biological process it describes.

**Quick search**

Provides you with a list of models that contain any of your search terms in the model components, annotation [12], or additional information. This option is comprehensive but can return false-positive results. Searches done within quotes (“Search Term”) give more precise results.

**Advanced search**

Allows you to streamline your search. You can combine several elementary searches on the model components, using accession [13] numbers of the data resources used for annotation. For some data resources you can also...
search using text, for example names, synonyms or definitions.

**Downloading models from BioModels**

Models can be retrieved in various formats, in addition to SBML ([Systems Biology Markup Language](https://www.ebi.ac.uk/training/online)) ([14]). The other formats include, BioPAX ([16] and VCML ([17]), but also configuration files for various simulators such as XPPAUT ([18], Octave ([19] and SciLab ([20]). The reaction graphs can be downloaded in SVG and PNG formats (following the SBGN standard, Figure 5). The models can also be viewed as a downloadable PDF format.

![Figure 5: SBGN Process Description map](image)

**Figure 5**: SBGN Process Description map, representing the regulation of mitotic cell division by cyclin and cyclin dependent kinase. From: Tyson (1991).

View the original model in BioModels ([21]).

**Submitting models to BioModels**

We welcome submission of models to BioModels. For your model to be published in the repository, it needs to comply with the MIRIAM guidelines ([22]) (the Minimum Information Required in the Annotation ([12]) of Models).

Once you have submitted your model, you will receive an accession ([13]) number that you can use, for instance, in publications or grant applications. BioModels accepts models submitted in SBML and CellML ([23]) formats.

**Note**: Due to increasing demand for hosting models in other formats, we now accept models in formats other than SBML or CellML. However, our current infrastructure does not support submission of models in other formats. So please contact us at biomodels-cura [at] ebi.ac.uk if you wish to submit using alternative formats. We are working on a new infrastructure for BioModels, which is designed to accept models of any format and type, in addition to various new features.
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Get help and support on BioModels

Support

- For general queries relating to services (e.g. the interface, web services [8], library), which could include feature requests or bug reports, please contact the biomodels-net-support [at] lists.sf.net (BioModels support team).
- For enquiries about the hosted models, please contact the biomodels-cura [at] ebi.ac.uk
- For general (community wide) discussions, please subscribe to: biomodels-net-discuss [25].

Please refer to our contact page. [26]for more information.

References

- Kholodenko et al. (2000). Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. [28]

Collaborators

BioModels is developed by the BioModels team (Part of Molecular Systems Cluster [32] at EMBL-EBI, UK), the Le Novère lab [33] (Babraham Institute [34], UK) and the SBML Team [35] (Caltech [36], USA).

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Contributors

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Vijayalakshmi (Viji) Chelliah has several years of experience in bioinformatics, computational structural/systems biology and modelling. She manages the content of BioModels, and drives the associated projects, which involves systems analysis of certain disease mechanisms.

Prior to joining EMBL-EBI, she did her PhD at the Department of Biochemistry, University of Cambridge, where she investigated and generated an evolutionary analysis of the local structural environment of amino acid [41] and developed a method to predict the functional sites of protein families and applied it in sequence-structure homology recognition and protein-protein docking. During her postdoctoral research at the National Institute for Medical Research (NIMR), London, she worked on de-novo protein structure prediction, refinement and ranking of the predicted protein models based on the functional site potential.

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