

**Presentation by Michael Hucka**  
**at the**  
***Cell Behavior Ontology and***  
***Standards for Multicellular***  
***Modeling Workshop,***  
**16 Oct. 2010,**  
**Edinburgh, UK.**

# SBML fly-by

**Michael Hucka**

*(On behalf of many people)*

*Senior Research Fellow  
California Institute of Technology  
Pasadena, California, USA*

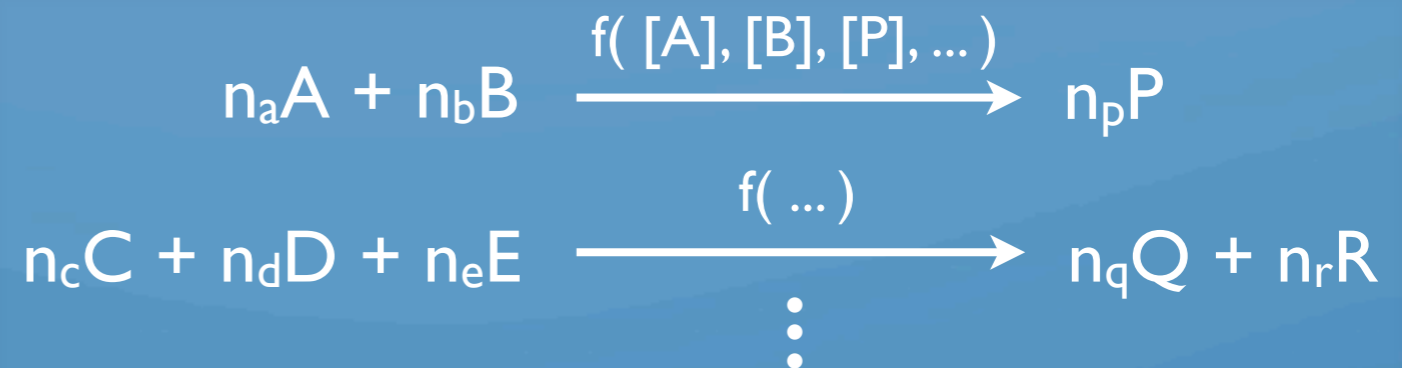


# SBML = Systems Biology Markup Language

- Machine-readable format for representing computational models

- Central concept: **process**

- Literally called **reaction** in SBML, but can be anything similar



- Can include

- Compartments (i.e., where pools of entities are located)
- Mathematical “extras” (e.g., additional assignments, ODEs, etc.)
- Discontinuous events

- A declarative description, not procedural

- Not a script for a simulation

- Not specific to a particular formalism (ODE, stochastic, ...)

# Some basics of SBML model encoding

- Well-stirred compartments

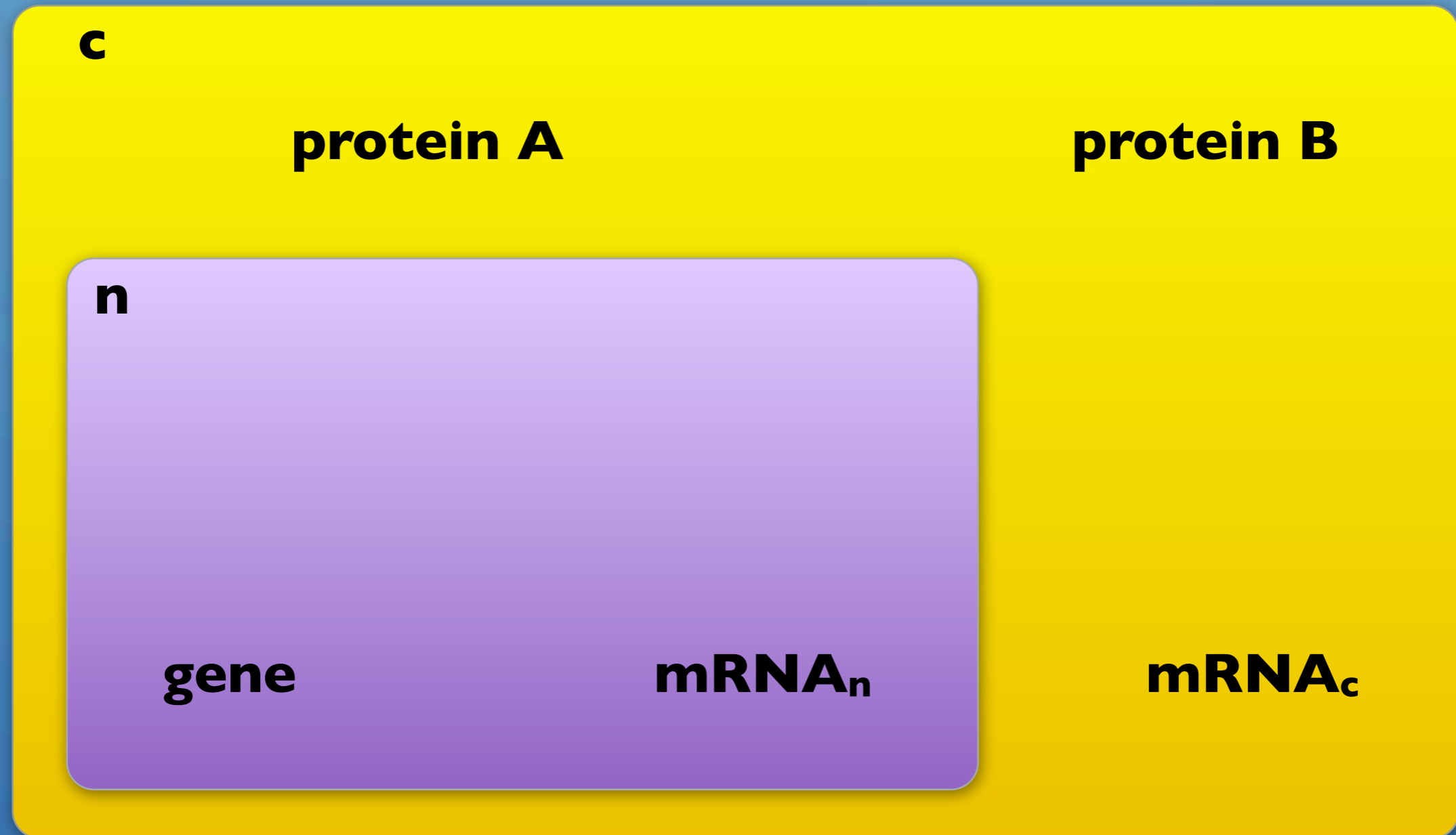
**c**

**n**



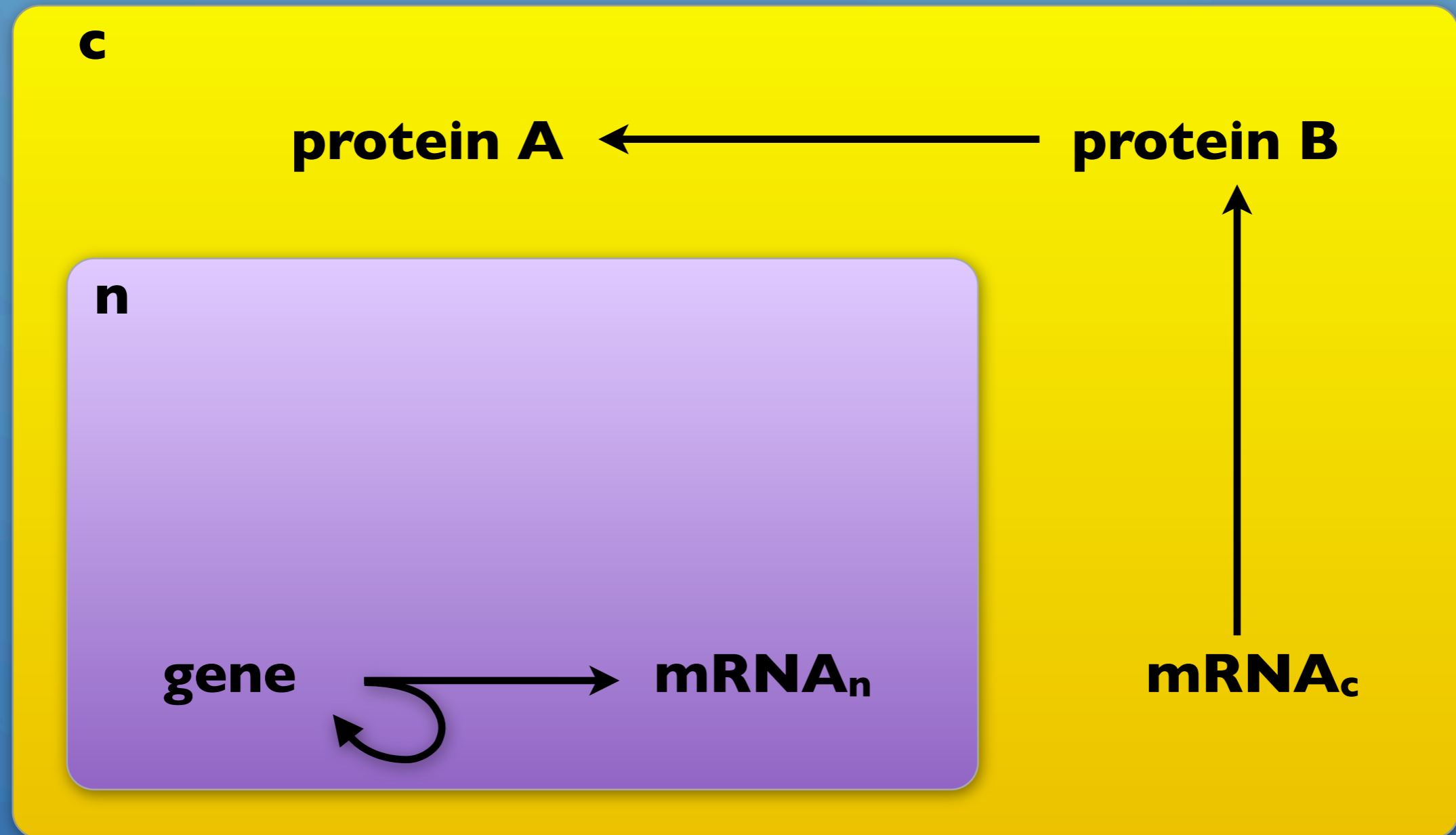
# Some basics of SBML model encoding

- Species pools are located in compartments



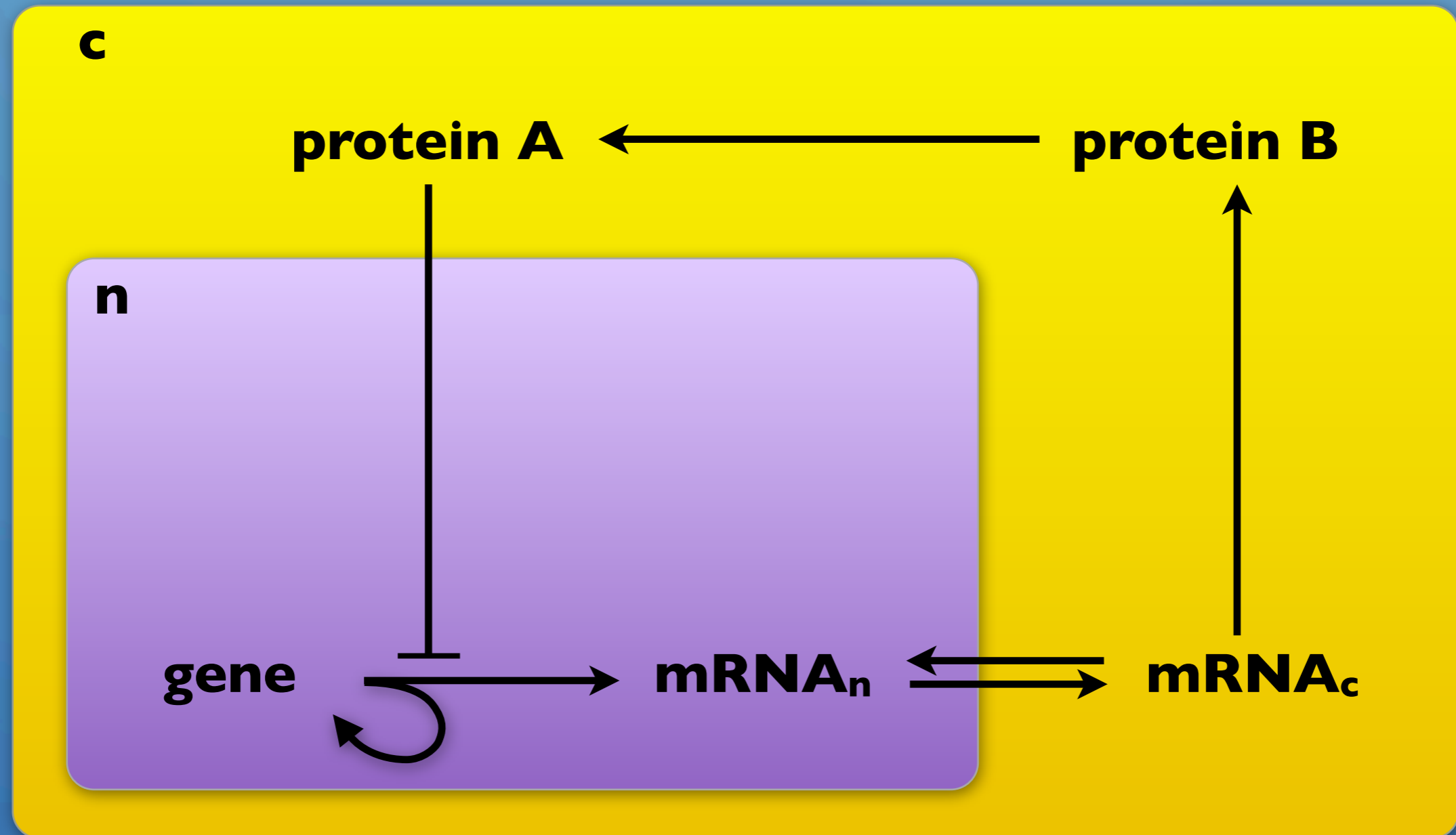
# Some basics of SBML model encoding

- Reactions can involve any species anywhere



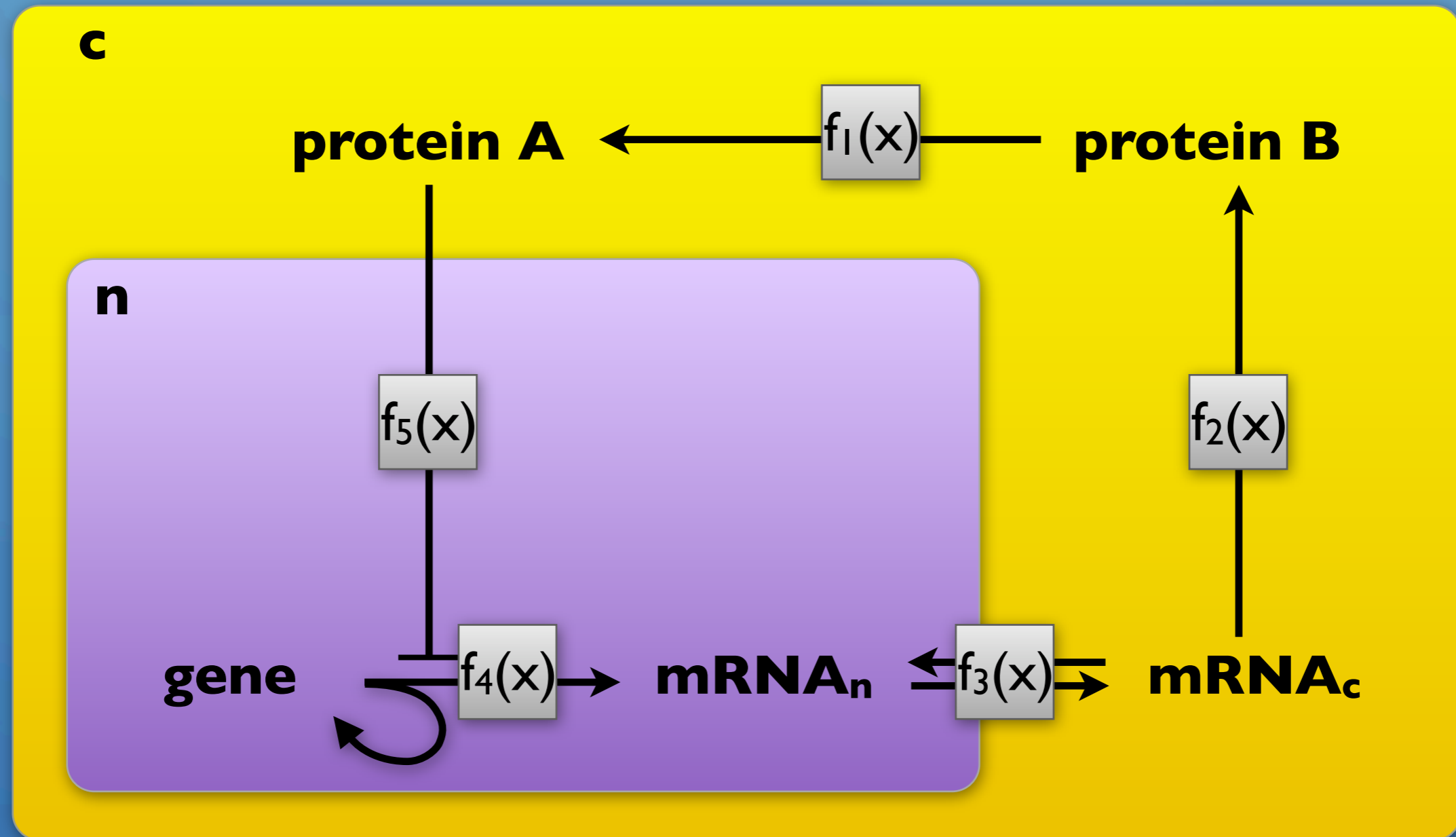
# Some basics of SBML model encoding

- Reactions can cross compartment boundaries



# Some basics of SBML model encoding

- Reaction/process rates can be (almost) arbitrary formulas

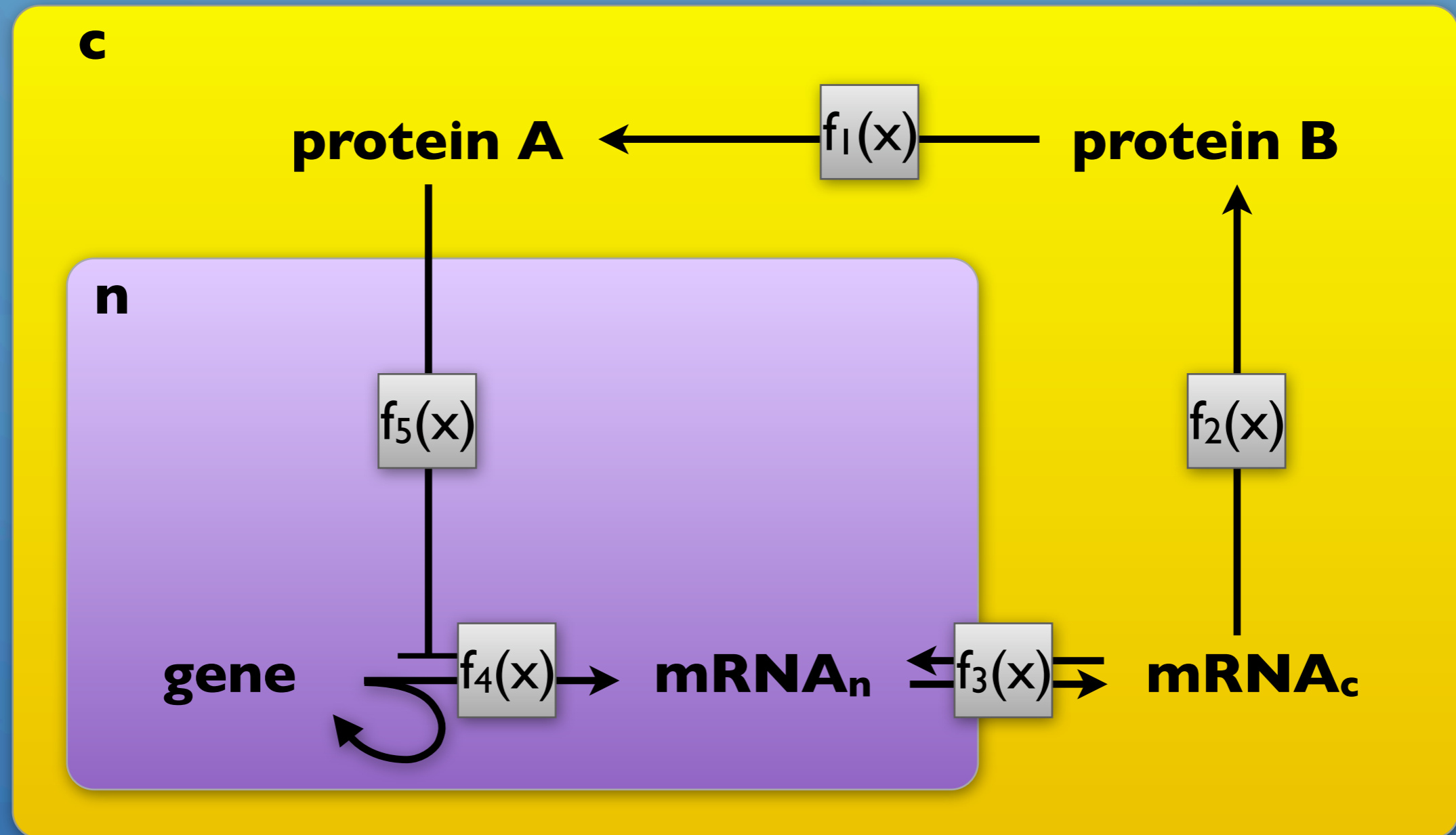


# Some basics of SBML model encoding

- “Rules”: equations expressing relationships in addition to reaction sys.

$g_1(x)$   
 $g_2(x)$

•  
•  
•

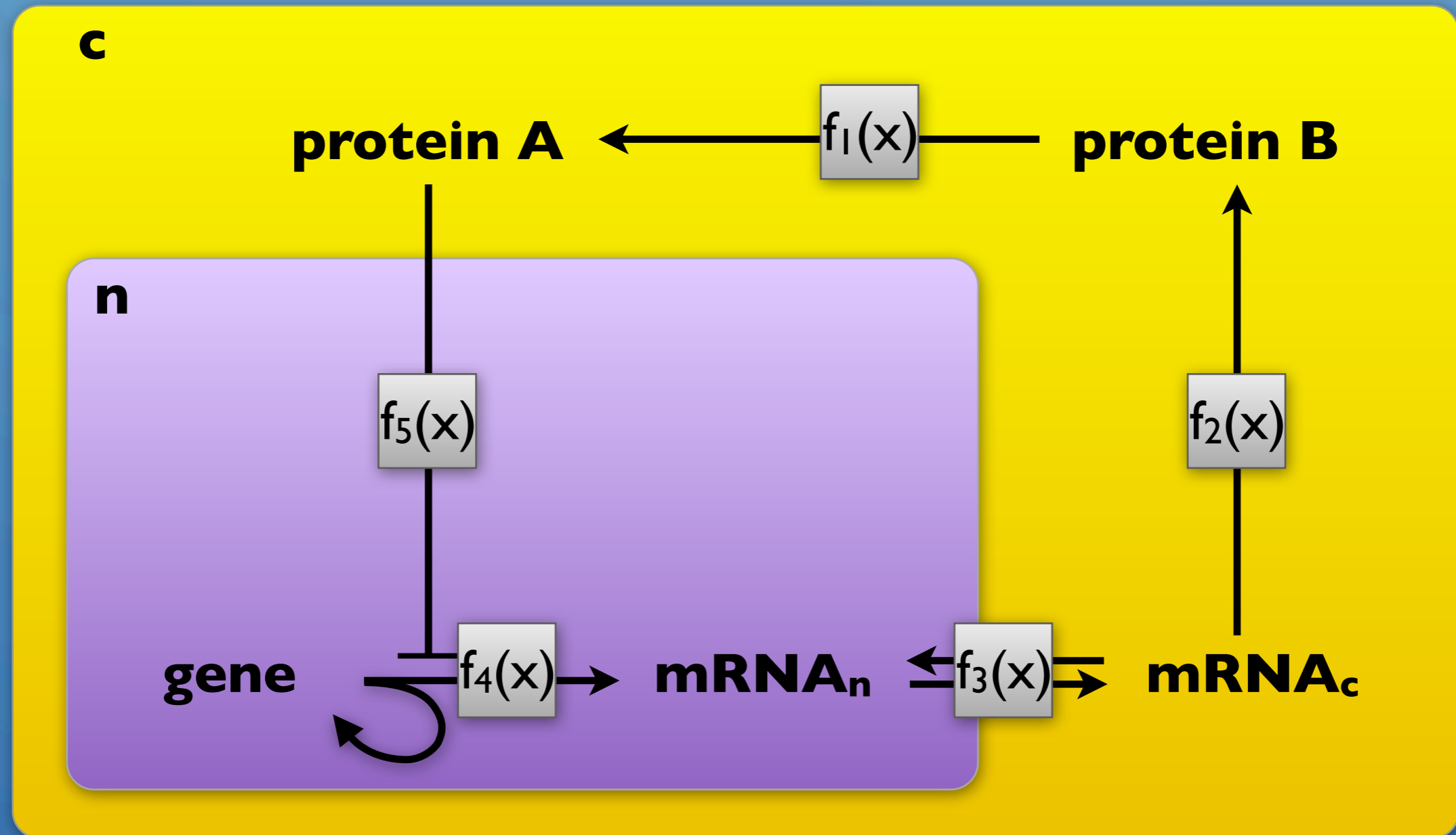


# Some basics of SBML model encoding

- “Events”: discontinuous actions triggered by system conditions

$g_1(x)$   
 $g_2(x)$

•  
•  
•



Event<sub>1</sub>: when (...condition...), do (...assignments...)  
Event<sub>2</sub>: when (...condition...), do (...assignments...)  
...

# Some basics of SBML model encoding

“This is identified by GO id # ...”

“This is an enzymatic reaction with EC # ...”

$g_2(x)$

**protein A**

$f_1(x)$

**protein B**

“This is a transport into the nucleus ...”

“This compartment represents the nucleus ...”

$f_5(x)$

$f_2(x)$

**gene**

$f_4(x)$

**mRNA<sub>n</sub>**

$f_3(x)$

**mRNA<sub>c</sub>**

“This event represents ...”

Event<sub>1</sub>: when (...condition...), do (...assignments...), Event<sub>2</sub>: when (...condition...), ... do (...assignments...)



# SBML is fundamentally an exchange format

- XML-based
- Lingua franca for software exchange of models
  - Not for humans to edit directly
  - Not necessarily a software system's *internal* format
  - Not suited for experimental or numerical results
  - Not a union of all possible features
- Open & free

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
  <species compartment="cytosol" id="P" initialConcentration="1" />
  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/10/MathML">
        <apply>
          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <apply>
            <times />
            <ci>koff</ci>
            <ci>ES</ci>
          </apply>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
```



# Broad support of SBML

- Supported by 200+ software systems

- Open-source & commercial

- General-purpose environments

- Mathematica, MATLAB, etc.

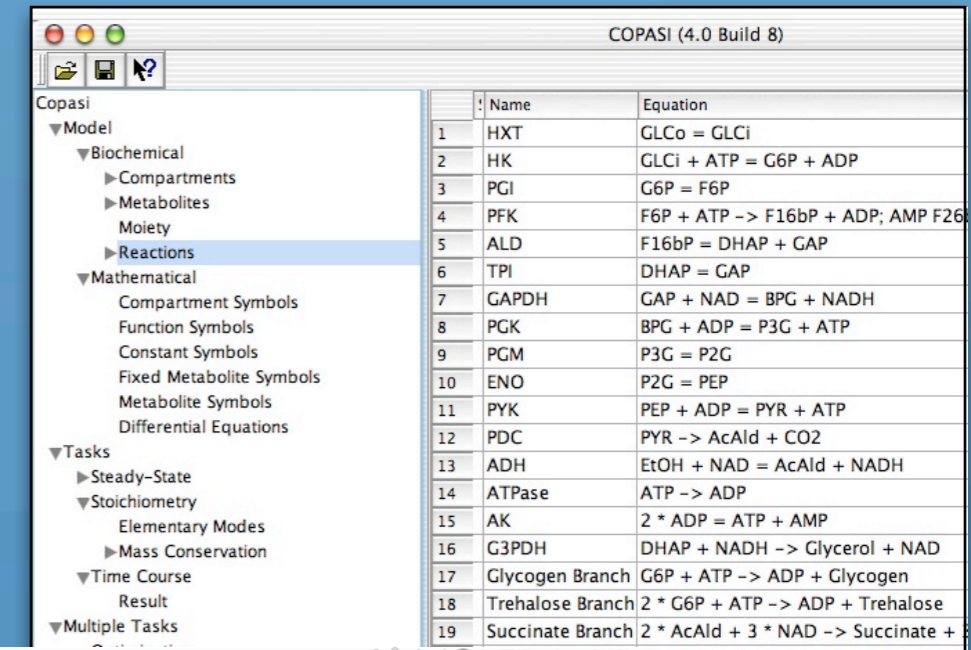
- Special-purpose software

- model editing

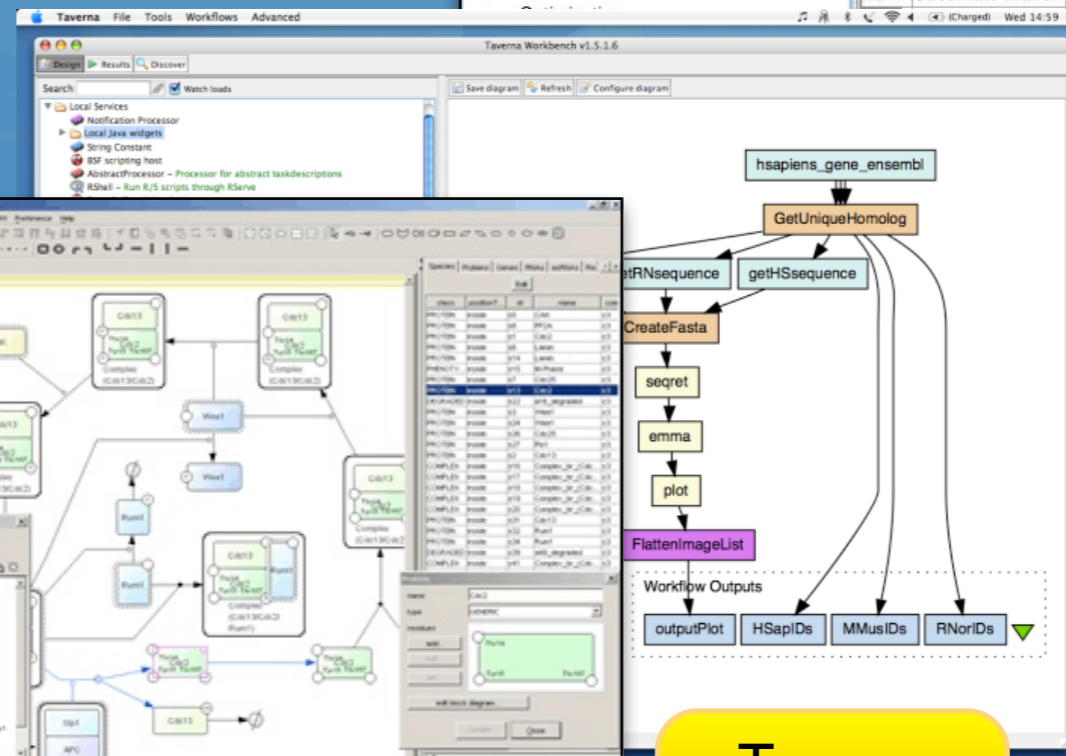
- simulation

- analysis

- visualization



	Name	Equation
1	HXT	$GLCo = GLCi$
2	HK	$GLCi + ATP = G6P + ADP$
3	PGI	$G6P = F6P$
4	PFK	$F6P + ATP \rightarrow F16bp + ADP; AMP F26$
5	ALD	$F16bp = DHAP + GAP$
6	TPI	$DHAP = GAP$
7	GAPDH	$GAP + NAD = BPG + NADH$
8	PGK	$BPG + ADP = P3G + ATP$
9	PGM	$P3G = P2G$
10	ENO	$P2G = PEP$
11	PYK	$PEP + ADP = PYR + ATP$
12	PDC	$PYR \rightarrow AcAld + CO2$
13	ADH	$EtOH + NAD = AcAld + NADH$
14	ATPase	$ATP \rightarrow ADP$
15	AK	$2 * ADP = ATP + AMP$
16	G3PDH	$DHAP + NADH \rightarrow Glycerol + NAD$
17	Glycogen Branch	$G6P + ATP \rightarrow ADP + Glycogen$
18	Trehalose Branch	$2 * G6P + ATP \rightarrow ADP + Trehalose$
19	Succinate Branch	$2 * AcAld + 3 * NAD \rightarrow Succinate +$



COPASI

Taverna

CellDesigner



# SBML Software Guide

The screenshot shows a web browser window with the title "Main Page - SBML.org". The address bar contains "http://sbml.org/Main\_Page". The browser's menu bar includes "1/wos", "2/jrn", "3/uci", "4/saf", "5/time", "6/insta", "7/exif", "8/cite", "9/ig", "money", "sys", "fly", "web", "code", and "data". The website header features the SBML.org logo and the title "The Systems Biology Markup Language". A navigation menu includes "News", "Documents", "Downloads", "Forums", "Facilities", "Community", "Events", and "About". A search bar is labeled "Google Site Search...".

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**Older news ...**

**Community News**

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http://sbml.org/Main\_Page

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# Guide has both matrix and summary views

SBML Software Guide - SBML.org

http://sbml.org/SBML\_Software\_Guide

News Documents Downloads Forums Facilities Community Events About

Parent pages: [SBML.org](#)

## SBML Software Guide

SBML software and projects come in many varieties. Here we summarize all SBML-compatible systems known to us. The *matrix* provides an at-a-glance summary, whereas the *summary* provides longer descriptions of each software or project grouped by themes. Please [use the survey form](#) to notify us about additions and suggestions.

Number of software packages listed in the matrix today: **170**

### SBML Software Matrix

This matrix provides an at-a-glance summary of software known to us to provide some degree of support for reading, writing, or otherwise working with SBML. For an alternate set of larger descriptions grouped into themes, please see our [SBML Software Summary](#) page.

The contents of this table should be read in the following way:

- Capabilities summarizes the features that a package provides by itself (i.e., without invoking another package) for working with SBML. "Capable" = checking/writing models, "Simulation" = performing time-series simulation of most "models" or analyzing models (e.g., sensitivity analysis, flux-response analysis, etc.), "Conversion" = providing a detailed model, and "API" = providing some utility functions (e.g., translating SBML to/from other formats).
- Frameworks summarizes the modeling frameworks supported by a package, regardless of whether the package also supports simulation or analysis using those same frameworks. "ODE" = ordinary differential equations, "ODE2" = ordinary algebraic equations, "ODE" = partial differential equations, "Stochastic" = discrete stochastic simulation, "Events" = discrete events, "Logic" = logic (e.g., Boolean) models, and "Other" = frameworks not listed here.
- API indicates whether a package exposes an application programming interface to other software systems, and if so, the name and the programming languages for which that API is provided. "API" = web services.
- OS indicates dependencies on other software environments. "MAT" = Mathematica, "SB" = BioSPICE.
- Platforms indicates the operating systems for which the software runs. "L" = Linux, "M" = Macintosh, "W" = Windows, "N" = NetBSD, "S" = other BSD-based.
- SBML indicates whether a package allows importing or exporting SBML, or both (read and/or write) of SBML, and is not included because it is impossible to determine this in all cases without exhaustive research.
- Available indicates the availability of the software. "Open source" indicates whether the source code is offered. "Academic user" indicates whether the software is free (F) or for-fee (C) to academic users. "Commercial user" indicates the same for non-academic use.

Software	Capabilities	Frameworks	API	OS	Platform	SBML	Available
CellDesigner	Capable	ODE	API	W	W	Capable	Open source
CellML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source
CellML2SBML	Capable	ODE	API	W	W	Capable	Open source

[Go to the SBML Software Matrix](#)

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# Guide has both matrix and summary views

The screenshot displays the SBML Software Guide website in a browser window. A red speech bubble points to the "Software matrix" link. Below it, two buttons are visible: "Go to the SBML Software Matrix" and "Go to the SBML Software Summary".

**Software matrix**

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 • Available indicates the availability of the software. "Open source" indicates whether the source code is offered. "Academic user" indicates whether the software is free (1) or for sale (2) to academic users. "Commercial user" indicates the same for non-academic users.

Capabilities	Frameworks	API	Dep.	Platforms	SBML	Available
Capable	Framework	API	Dep.	Platform	SBML	Available
Capable	Framework	API	Dep.	Platform	SBML	Available
Capable	Framework	API	Dep.	Platform	SBML	Available
Capable	Framework	API	Dep.	Platform	SBML	Available

**Go to the SBML Software Matrix**

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# SBML Software Matrix

SBML Software Guide/SBML Software Matrix - SBML.org

http://sbml.org/SBML\_Software\_Guide/SBML\_Software\_Matrix

1/WoS 2/Jrn 3/Surv 4/Ibid 5/ebay 6/jkn 7/keep 8/exif 9/cite money fly adm collab X11-UsersFAQ prog

**SBML.org** The Systems Biology Markup Language

News Documents Downloads Forums Facilities Community Events About

Parent pages: [SBML.org](#) / [SBML Software Guide](#)

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	Capabilities					Frameworks							API	Dep.	Platforms	SBML		Availabil.		
	Creation	Simulation	Analysis	Database	Utility	ODE	DAE	PDE	Stochastic	Events	Logical	Other				Import	Export	Open source	Academic use	Commercial use
<a href="#">acslXtreme</a>	•														W	•			\$	\$
<a href="#">AVIS</a>												•		various	L	•		F	F	F
<a href="#">BALSA</a>	•													Sigtran						
<a href="#">BASIS</a>																				
<a href="#">BiNoM</a>	•		•		•							•			L, W, M	•	•	•	F	F
<a href="#">BiNoM Cytoscape Plugin</a>	•		•		•							•		Cytoscape	L, W, M	•	•	•	F	F

# Some particularly full-featured tools for simulation

- ◎ **COPASI**: ODE & stochastic simulation, parameter scanning, powerful plotting capabilities, much more
- ◎ **iBioSim**: special features for genetic circuit models for synthetic bio
- ◎ **CellDesigner**: graphical editing interface, SBGN support, SABIO-RK integration, much more
  - Can use COPASI as computational engine
- ◎ **Virtual Cell**: web-based interface
- ◎ **SBtoolbox2**: MATLAB package
- ◎ **SBW**: collection of interoperating programs (many Windows-only)



# http://sbml.org

The screenshot shows a browser window titled "Main Page - SBML.org" with the address bar containing "http://sbml.org/Main\_Page". The browser's address bar also shows a search engine (Google) and a search bar. Below the browser window, the website's main content is displayed. The header features the SBML.org logo and the title "The Systems Biology Markup Language". A navigation menu includes links for News, Documents, Downloads, Forums, Facilities, Community, Events, and About. A search bar for "Google Site Search..." is also present. The main content area is divided into two columns. The left column contains a descriptive paragraph about SBML and three sections: "For the curious", "For modelers", and "For software developers", each with an icon and a brief description. The right column contains a "SBML News" section with three news items, each with a thumbs-up icon, and a "Community News" section with one news item.

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**RSS & Twitter feeds for news updates**

**SBML.org** Systems Biology Markup Language

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Mailing lists & forums, especially:  
sbml-announce@caltech.edu



# Online SBML Validator

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The main content area is divided into two columns. The left column contains a descriptive paragraph about SBML and three sections with icons: "For the curious" (question mark icon), "For modelers" (bar chart icon), and "For software developers" (laptop icon). The right column contains a "SBML News" section with three news items, each with a thumbs-up icon, and a "Community News" section with one news item.

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**For the curious**  
What *is* SBML? Read our [basic introduction](#) and then perhaps browse the [mailing lists](#) to get a sense for what's currently going on in the world of SBML.

**For modelers**  
Are you looking for ready-to-run software that supports SBML? Take a look at the [SBML Software Guide](#), which lists over **170** software packages. Are you instead looking for ready-to-use models? Visit the [BioModels Database](#), where you can find hundreds!

**For software developers**  
Are you interested in developing SBML support for your software? Read our [basic introduction](#) and then the [SBML specifications](#) to understand how to use SBML. After that, you may want to look at [libSBML](#), an API library supporting many programming languages.

**SBML News**

- SBML Level 3 plans updated** (8 Jul. '09) The SBML Editors have updated the [plans for SBML Level 3 Core](#) and are seeking feedback.
- SBML FAQ updated** (1 Jul. '09) FAQ item #3.6 now features an expanded explanation of SBML Level 2 annotations.
- 5000 visits/month** (26 Jun. '09) Our Google Analytics tracker reports sbml.org gets nearly 5000 visitors/month, 50% of them new.

**Older news ...**

**Community News**

- BioModels Database rel. 14** (16 Jun. '09) [BioModels Database](#), a free database of published models, now contains 216



# Online SBML Validator

Main Page - SBML.org

http://sbml.org/Main\_Page

SBML.org The Systems Biology Markup Language

News Documents Downloads Forums **Facilities** Community Events About

Google Site Search...

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# Online SBML Validator



The screenshot shows a web browser window with the title "Facilities - SBML.org". The address bar contains "http://sbml.org/Facilities". The page header features the SBML.org logo and the text "The Systems Biology Markup Language". A navigation menu includes links for News, Documents, Downloads, Forums, Facilities, Community, Events, and About, along with social media icons and a search box. The main content area is titled "Facilities" and includes a sub-section "Local facilities" with two items: "Validate your SBML file" and "Evaluate SBML support in an application". A "Partner facilities" section is partially visible at the bottom.

Facilities - SBML.org

http://sbml.org/Facilities

Google

**SBML.org** The Systems Biology Markup Language

News Documents Downloads Forums **Facilities** Community Events About

Google Site Search...

Parent pages: [SBML.org](#)

## Facilities

The following online services are offered for the convenience of the SBML community.

### Local facilities

-  **Validate your SBML file**  
The Online SBML Validator checks the validity of an SBML file. It lets you select an SBML file on your computer or provide a URL for an SBML file located on another computer.
-  **Evaluate SBML support in an application**  
The SBML Test Suite allows you to test the degree and correctness of SBML support in an SBML-compatible application.

### Partner facilities

-  **Convert your SBML file to a document**

# Online SBML Validator

The screenshot shows a web browser window with the address bar displaying 'http://sbml.org/Facilities'. The page title is 'Facilities - SBML.org'. The main content area features the SBML.org logo and the text 'The Systems Biology Markup Language'. A navigation menu includes 'News', 'Documents', 'Downloads', 'Forums', 'Facilities', 'Community', 'Events', and 'About'. A search bar is also present. The 'Facilities' section is titled 'Facilities' and contains the text: 'The following online services are offered for the convenience of the SBML community.' Below this, there are three categories of facilities: 'Local facilities', 'Partner facilities', and 'Convert your SBML file to a document'. The 'Local facilities' section includes three items: 'Validate your SBML file', 'Evaluate SBML support in an application', and 'Convert your SBML file to a document'. The 'Validate your SBML file' item is highlighted with a red oval. It features a globe icon with a gear and a document icon, and the text: 'The Online SBML Validator checks the validity of an SBML file. It lets you select an SBML file on your computer or provide a URL for an SBML file located on another computer.'

libSBML

<http://sbml.org/Software/libSBML>



# LibSBML, for programming SBML support

- Reads, writes, validates SBML
    - Hundreds of rules for helping to ensure correct SBML
  - Unit checking & conversion
  - Well-tested
  - Written in portable C++
    - Linux, Mac, Windows, FreeBSD
  - APIs for C, C++, C#, Java, Octave, Perl, Python, Ruby, MATLAB (some via SWIG)
  - Can use Expat, libxml2, or Xerces
  - Open-source under LGPL
  - 110k+ lines of code + 65k lines of XML tests + 18k lines of language interface code
- Latest stable version: 4.2.0  
<http://sbml.org/Software/libSBML>
- Developed by Sarah Keating, Ben Bornstein, Akiya Jouraku, & Mike Hucka, with substantial contributions from many other people



# LibSBML 5 for SBML Level 3 packages

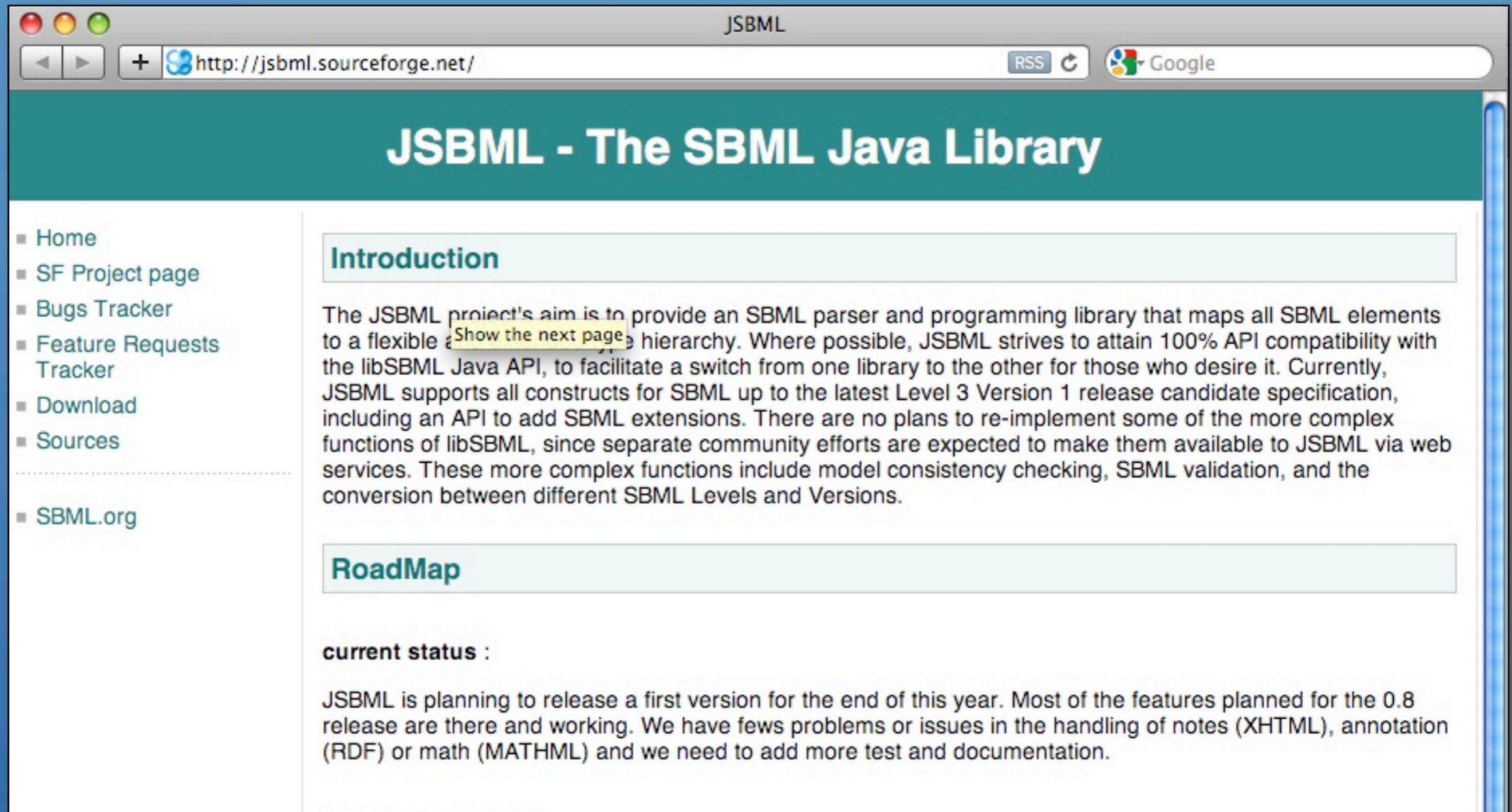
## Relationships between releases:

		libSBML		
		4.0.x	4.2.x	5.x
SBML	Level 2	✓	✓	✓
	Level 3 Core		✓	✓
	Level 3 packages			✓

- libSBML 5 has same API as libSBML 4.2 and adds plug-in mechanism
  - Each plug-in implements one SBML Level 3 package
  - Plug-ins register themselves with libSBML & provide XML namespace
- libSBML 5 is available now as an alpha release

# On the horizon: JSBML

- Pure Java work-alike implementation of portions of libSBML
- Still in development: <http://jsbml.sourceforge.net>



The screenshot shows a web browser window titled "JSBML" with the address bar containing "http://jsbml.sourceforge.net/". The page features a green header with the title "JSBML - The SBML Java Library". On the left, there is a navigation menu with links: Home, SF Project page, Bugs Tracker, Feature Requests Tracker, Download, Sources, and SBML.org. The main content area has two sections: "Introduction" and "RoadMap".

## Introduction

The JSBML project's aim is to provide an SBML parser and programming library that maps all SBML elements to a flexible [Show the next page](#) hierarchy. Where possible, JSBML strives to attain 100% API compatibility with the libSBML Java API, to facilitate a switch from one library to the other for those who desire it. Currently, JSBML supports all constructs for SBML up to the latest Level 3 Version 1 release candidate specification, including an API to add SBML extensions. There are no plans to re-implement some of the more complex functions of libSBML, since separate community efforts are expected to make them available to JSBML via web services. These more complex functions include model consistency checking, SBML validation, and the conversion between different SBML Levels and Versions.

## RoadMap

**current status :**

JSBML is planning to release a first version for the end of this year. Most of the features planned for the 0.8 release are there and working. We have fews problems or issues in the handling of notes (XHTML), annotation (RDF) or math (MATHML) and we need to add more test and documentation.

# BioModels Database

<http://biomodels.net/biomodels>



## BioModels Database - A Database of Annotated Published Models

BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and controlled vocabularies.

BioModels Database also allows users to generate sub-models, provides access to online simulation tools and features programmatic access via Web Services.



[Advanced search](#)

### Browse models

- [Curated models \(269\)](#)
- [Browse models using GO](#)
- [Non-curated models \(361\)](#)

### Simulate in JWS Online

### Submit a model

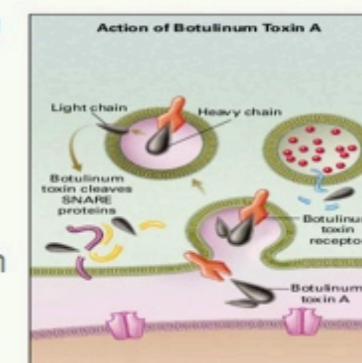
### Model of the month

August, 2010

Botulinum neurotoxin serotype A (BoNT/A) causes flaccid paralysis by a multi-step mechanism.

Two mathematical models that has been developed, to estimate upper limits of the time during which antitoxin and other impermeable inhibitors of BoNT/A can exert an effect, is described here.

[Read more...](#)



### News

30 September 2010 **Eighteenth Release!**  
[Download All Models Under SBML Format](#)

Main instance at European Bioinformatics Institute <http://www.ebi.ac.uk/biomodels/>

Mirror at California Institute of Technology <http://biomodels.caltech.edu>

Display a menu

# BioModels Database

- ◎ Stores & serves quantitative models of biological interest
  - Free, public resource
  - Models must be described in peer-reviewed publication(s)
- ◎ All models are **curated by hand** to reproduce published results
- ◎ Imports & exports models in several formats
  - SBML, CellML, SciLab, XPP, BioPAX
- ◎ Developed by Nicolas Le Novère's group (EBI), funded by EBI & NIH
- ◎ Today: 600+ models



# Curated, annotated models drawn from the literature

BioModels Database

http://biomodels.caltech.edu/BIOMD0000000234

BioModels Home Browse models Support About BioModels Search

## BIOMD0000000234 - Tham2008\_PDmodel\_TumourShrinkage

SBML formats | Other formats | Actions | Submit Model Comment/Bug

**Model** Overview Math Physical entities Parameters Curation

### Reference Publication

Clin Cancer Res 2008 Jul;14(13):4213-8.  
A pharmacodynamic model for the time course of tumour patients.  
Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong W  
Department of Hematology-Oncology, National Unive

Publication ID: [18594002](#)

### Model

Original Model: <a href="#">BIOMD0000000234.xml.origin</a>	bqbiol:occursIn	<a href="#">Taxonomy Homo sapiens</a>
Submitter: <a href="#">Nick Holford</a>	set #1	<a href="#">ICD C34</a> <a href="#">OMIM 211980</a>
Submission ID: MODEL0911120001		
Submission Date: 16 Nov 2009 02:46:45 UTC		
Last Modification Date: 23 Jan 2010 00:08:36 UTC		
Creation Date: 16 Nov 2009 20:37:34 UTC		
Encoders: <a href="#">Vijayalakshmi Chelliah</a> <a href="#">Lai-San Tham</a>		

Notes

### Curation Result

http://biomodels.caltech.edu/simulation-result

2009-11-23T23:49:57+00:00

Comment: The model reproduces figure 1 of the reference publication. The simulation was done using SBML and CellML.

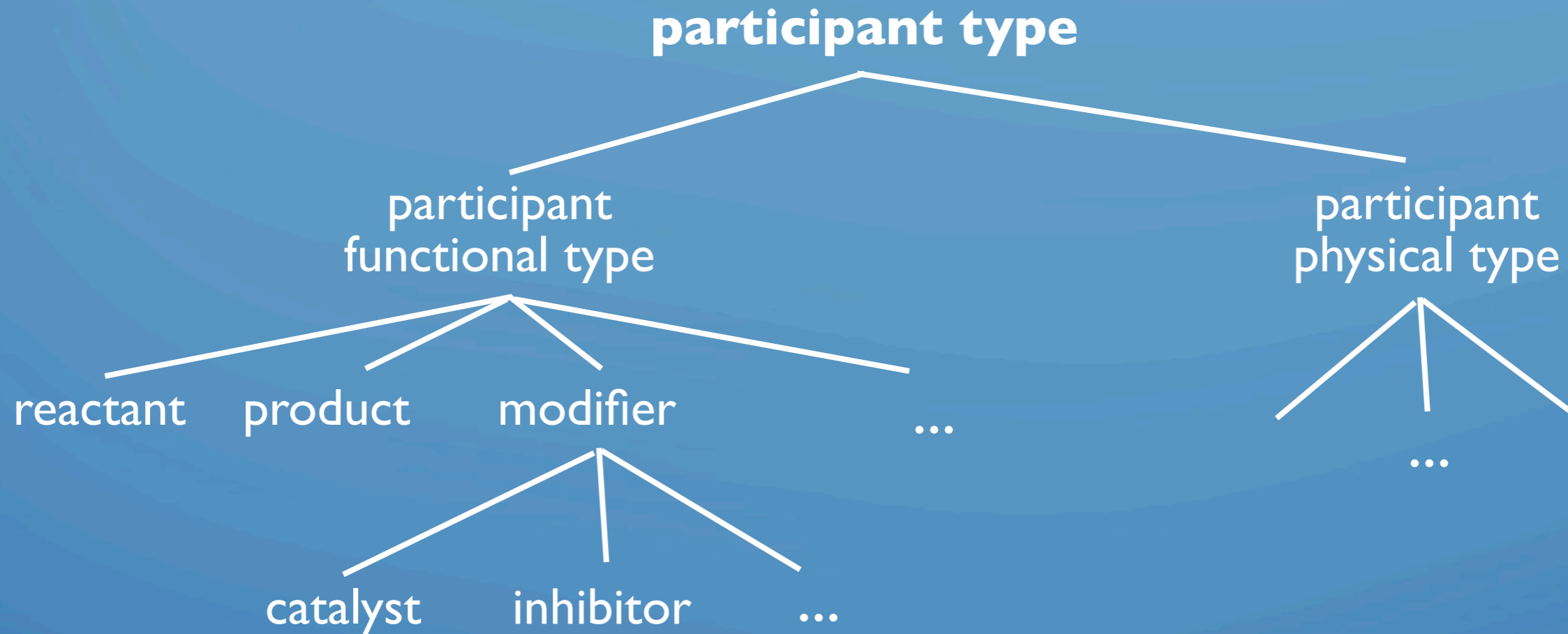
# Ease of model exchange is driving new developments

- ◎ More people are exchanging models and using more software tools
  - Encountering challenges not faced before
    - BioModels Database in particular has uncovered new needs
- ◎ Result: development of additional standardization efforts
  - SBO
  - MIRIAM
  - MIASE
  - Also (but not presented here):
    - SBRML
    - SBGN

SBO



# Set of controlled vocabularies



- ◎ Not for describing the biology, but rather the **math** in a model
  - E.g.: the different pieces of a rate law, the constants, the mathematical framework assumed (e.g., continuous versus discrete)

# SBO browser (for humans) & web services (for s/w)

- <http://www.ebi.ac.uk/sbo>
- Hierarchical organization
- Machine-readable
- **Community input wanted!**
  - Please comment on ontology structure, suggest additions, etc.
- Software developed by Melanie Courtot and Camile Laibe in the Le Novère group @ EBML-EBI

EBI > SBO > Browsing

## SBO::Systems Biology Ontology

+  [Refresh tree](#)

[sbo](#)

+  [quantitative parameter](#)

+  [modelling framework](#)

[mathematical expression](#)

[rate law](#)

[mass action kinetics](#)

+  [irreversible mass action kinetics](#)

+  [reversible mass action kinetics](#)

+  [Hill equation](#)

+  [enzyme kinetics](#)

+  [obsolete mathematical expression](#)

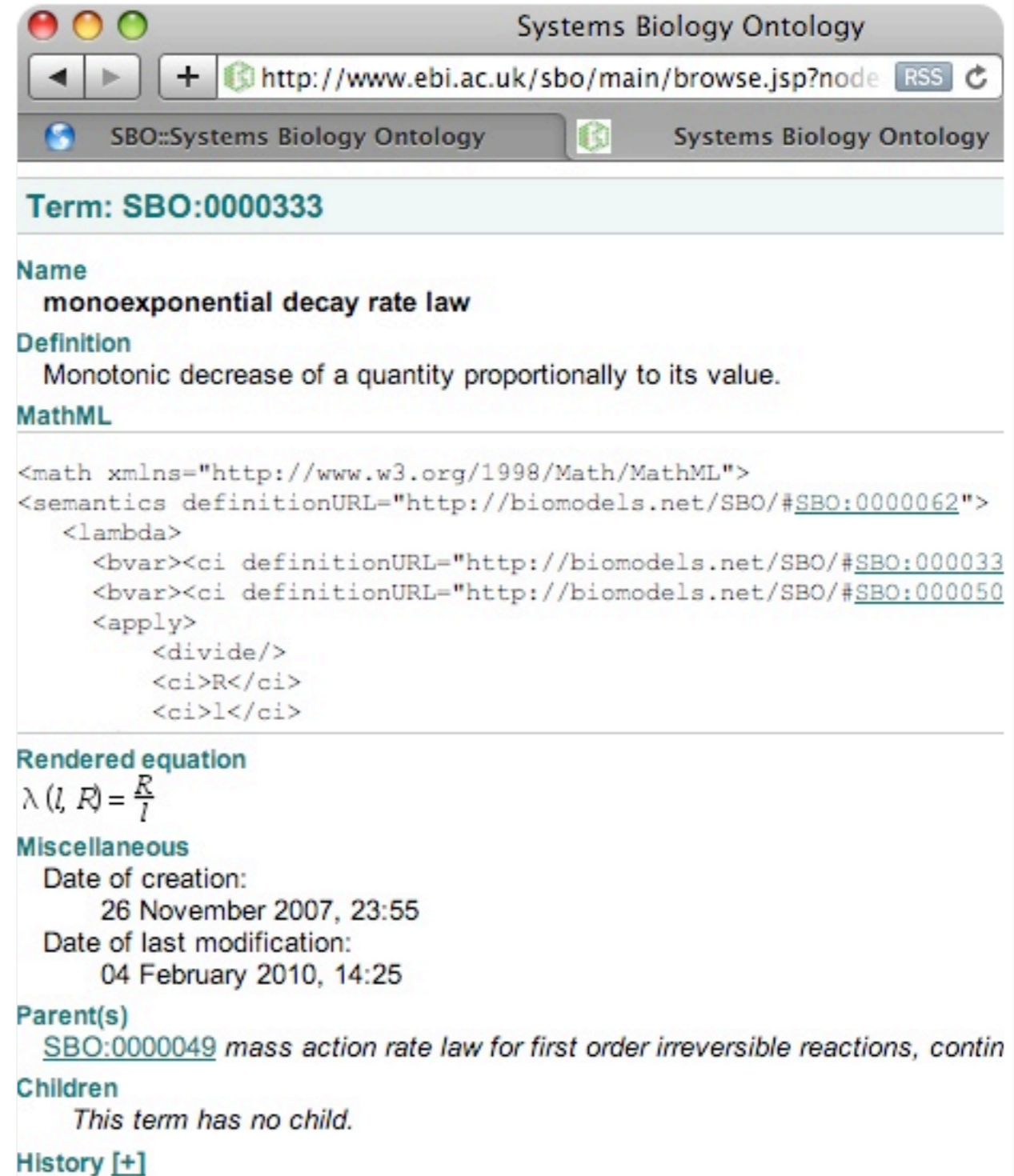
[event](#)

[reaction](#)

[biochemical reaction](#)

# Entries contain retrievable data

- Entries for mathematical expressions contain MathML
- All entries contain cross links



The screenshot shows a web browser window titled "Systems Biology Ontology" with the URL <http://www.ebi.ac.uk/sbo/main/browse.jsp?node>. The page displays the entry for **Term: SBO:0000333**.

**Name**  
monoexponential decay rate law

**Definition**  
Monotonic decrease of a quantity proportionally to its value.

**MathML**

```
<math xmlns="http://www.w3.org/1998/Math/MathML">  
<semantics definitionURL="http://biomodels.net/SBO/#SBO:0000062">  
  <lambda>  
    <bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:0000333">  
    <bvar><ci definitionURL="http://biomodels.net/SBO/#SBO:000050">  
    <apply>  
      <divide/>  
      <ci>R</ci>  
      <ci>l</ci>  
    </apply>  
  </lambda>  
</semantics>  
</math>
```

**Rendered equation**  
$$\lambda(l, R) = \frac{R}{l}$$

**Miscellaneous**  
Date of creation:  
26 November 2007, 23:55  
Date of last modification:  
04 February 2010, 14:25

**Parent(s)**  
[SBO:0000049](#) mass action rate law for first order irreversible reactions, contin

**Children**  
This term has no child.

**History** [\[+\]](#)



# Direct SBO support in SBML L2V3

- ◎ **sboTerm** field on all SBML constructs (part of **SBase**)
  - Usage: `sboTerm="SBO:0123456"`
- ◎ Terms must be drawn from appropriate SBO subtrees

Component	SBO vocabulary	Parent SBO id
<b>Parameter</b>	Quantitative parameter	SBO:0000002
<b>KineticLaw</b>	Mathematical expression	SBO:0000064
<b>SpeciesReference</b>	Functional Participant	SBO:0000003
...	...	...

# Example

```
<listOfCompartments>
  <compartment id="cell" size="1e-15" />
</listOfCompartments>
<listOfSpecies>
  <species compartment="cell" id="S1" initialAmount="1000" />
  <species compartment="cell" id="S2" initialAmount="0" />
</listOfSpecies>
<listOfParameters>
  <parameter id="k" value="0.005" sboTerm="SBO:0000339" />
</listOfParameters>
<listOfReactions>
  <reaction id="r1" reversible="false">
    <listOfReactants>
      <speciesReference species="S1" stoichiometry="2" sboTerm="SBO:0000010" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="S1" stoichiometry="2" sboTerm="SBO:0000011" />
    </listOfProducts>
    <kineticLaw sboTerm="SBO:0000052">
      <math>
        \dots
      </math>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

# Example

```
<listOfCompartments>
  <compartment id="cell" size="1e-15" />
</listOfCompartments>
<listOfSpecies>
  <species compartment="cell" id="S1" initialAmount="1000" />
  <species compartment="cell" id="S2" initialAmount="0" />
</listOfSpecies>
<listOfParameters>
  <parameter id="k" value="0.005" sboTerm="SBO:0000339" />
</listOfParameters>
```

**SBO::Systems Biology Ontology**

- +
- 
- SBO:0000000 - sbo
  - P SBO:0000002 - quantitative parameter
    - + I SBO:0000226 - number density
    - + I SBO:0000227 - mass density
    - + I SBO:0000255 - physical characteristic
    - I SBO:0000256 - biochemical parameter
      - I SBO:0000009 - kinetic constant
        - + I SBO:0000016 - unimolecular rate constant
        - I SBO:0000017 - bimolecular rate constant
          - I SBO:0000023 - forward bimolecular rate constant
            - I SBO:0000036 - forward bimolecular rate constant, continuous case
              - I SBO:0000302 - catalytic efficiency
              - I SBO:0000339 - bimolecular association rate constant
            - I SBO:0000067 - forward bimolecular rate constant, discrete case

```
2" sboTerm="SBO:0000010" />
```

```
2" sboTerm="SBO:0000011" />
```



# Example

```
<listOfCompartments>
  <compartment id="cell" size="1e-15" />
</listOfCompartments>
<listOfSpecies>
  <species compartment="cell" id="S1" initialAmount="1000" />
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</listOfSpecies>
<listOfParameters>
  <parameter id="k" value="0.005" sboTerm="SBO:0000339" />
</listOfParameters>
```

SBO::Systems Biology Ontology

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- SBO:0000000 - sbo
  - SBO:0000002 - quantitative parameter
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            - SBO:0000036 - forward bimolecular rate constant, continuous case
            - SBO:0000039 - bimolecular association rate constant
            - SBO:0000067 - forward bimolecular rate constant, discrete case

```
2" sboTerm="SBO:0000010" />
```

```
2" sboTerm="SBO:0000011" />
```

“forward bimolecular rate constant, continuous case”

MIRIAM

<http://www.biomodels.net/miriam>

# SBML provides syntax

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
  <species compartment="cytosol" id="P" initialConcentration="1" />
  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/10/MathML">
        <apply>
          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <apply>
            <times />
            <ci>koff</ci>
            <ci>ES</ci>
          </apply>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
```



# SBML provides syntax

- ◎ Raw models alone are insufficient
  - SBML only provides syntax

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
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  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
    <kineticLaw>
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          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <apply>
            <times />
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</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
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      <math xmlns="http://www.w3.org/1998/10/MathML">
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          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <apply>
            <times />
            <ci>koff</ci>
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# SBML provides syntax

- Raw models alone are insufficient
  - SBML only provides syntax

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  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="R1" reversible="true" />
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/10/MathML">
        <apply>
          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <times />
          <ci>koff</ci>
          <ci>ES</ci>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
</listOfReactions>
```

Low info content

Unregulated



# SBML provides syntax

- Raw models alone are insufficient
  - SBML only provides syntax
- Need standard schemes for machine-readable annotations
  - For authorship, publication info
  - For links to other data resources
  - For semantics of mathematics

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
  <species compartment="cytosol" id="P" initialConcentration="1" />
  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="R1" />
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/10/MathML">
        <apply>
          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <times />
          <ci>koff</ci>
          <ci>ES</ci>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
</model>
```

Low info content

Unregulated

# SBML provides syntax

- Raw models alone are insufficient
  - SBML only provides syntax
- Need standard schemes for machine-readable annotations
  - For authorship, publication info
  - For links to other data resources
  - For semantics of mathematics
- Need common guidelines for minimal model quality and content

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
  <species compartment="cytosol" id="P" initialConcentration="1" />
  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="R1" reversible="true" />
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/10/MathML">
        <apply>
          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <times />
          <ci>koff</ci>
          <ci>ES</ci>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
</model>
```

Low info content

Unregulated

# SBML provides syntax

- ◎ Raw models alone are insufficient
  - SBML only provides syntax
- ◎ Need standard schemes for machine-readable annotations
  - For authorship, publication info
  - For links to other data resources
  - For semantics of mathematics
- ◎ Need common guidelines for minimal model quality and content

Defined  
by SBML

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
  <species compartment="cytosol" id="P" initialConcentration="1" />
  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E" />
      <speciesReference species="S" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES" />
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/10/MathML">
        <apply>
          <times />
          <ci>cytosol</ci>
          <apply>
            <minus />
            <apply>
              <times />
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
          </apply>
          <apply>
            <times />
            <ci>koff</ci>
            <ci>ES</ci>
          </apply>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
```



# SBML provides syntax

- ◎ Raw models alone are insufficient
  - SBML only provides syntax
- ◎ Need standard schemes for machine-readable annotations
  - For authorship, publication info
  - For links to other data resources
  - For semantics of mathematics
- ◎ Need common guidelines for minimal model quality and content

Defined by SBML

Defined by MIRIAM

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
  <species compartment="cytosol" id="P" initialConcentration="1" />
  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E"/>
      <speciesReference species="S"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES"/>
    </listOfProducts>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/10/MathML">
        <apply>
          <times/>
          <ci>cytosol</ci>
          <apply>
            <minus/>
            <apply>
              <times/>
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
            <apply>
              <times/>
              <ci>koff</ci>
              <ci>ES</ci>
            </apply>
          </apply>
        </math>
      </kineticLaw>
    </reaction>
  </listOfReactions>
```

# SBML provides syntax

- Raw models alone are insufficient
  - SBML only provides syntax
- Need standard schemes for machine-readable annotations
  - For authorship, publication info
  - For links to other data resources
  - For semantics of mathematics
- Need common guidelines for minimal model quality and content

Defined by SBML

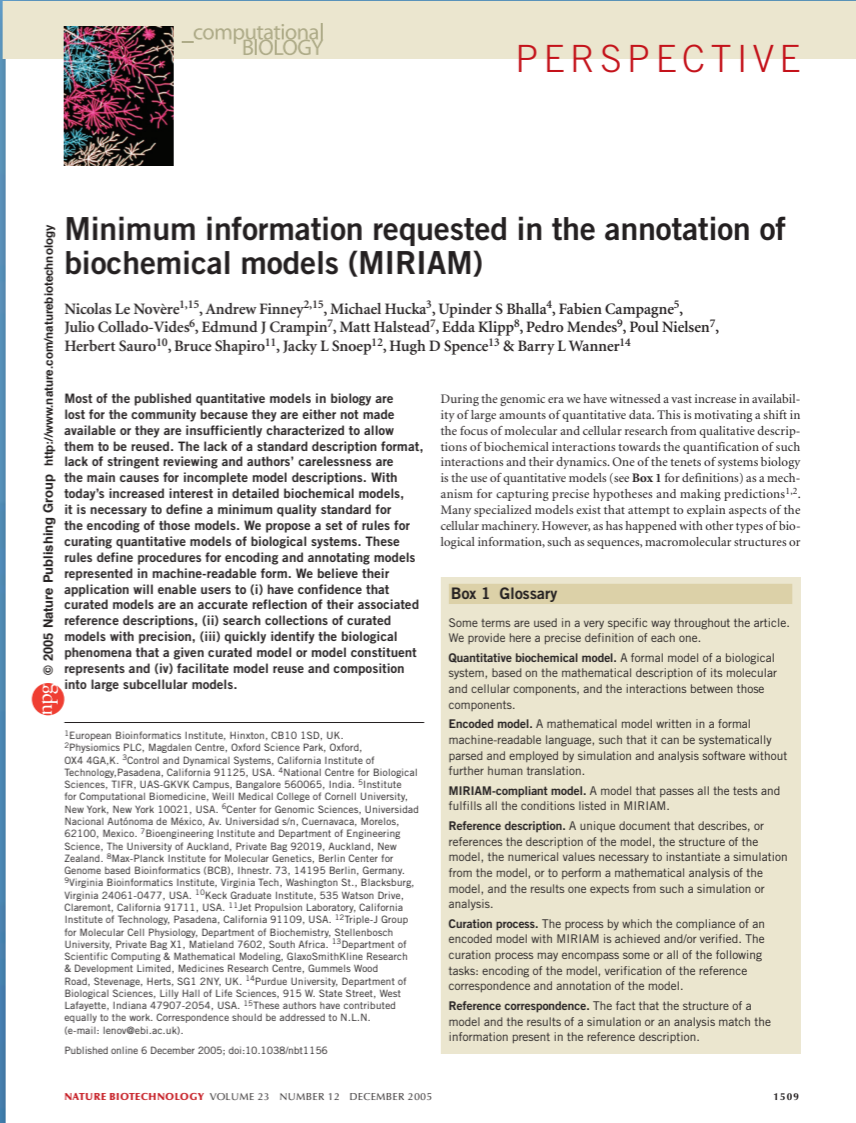
Defined by SBO

Defined by MIRIAM

```
<listOfSpecies>
  <species compartment="cytosol" id="ES" initialConcentration="1" />
  <species compartment="cytosol" id="P" initialConcentration="1" />
  <species compartment="cytosol" id="S" initialConcentration="1" />
  <species compartment="cytosol" id="E" initialConcentration="1" />
</listOfSpecies>
<listOfReactions>
  <reaction id="veq">
    <listOfReactants>
      <speciesReference species="E"/>
      <speciesReference species="S"/>
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="ES"/>
    </listOfProducts>
    <mathLaw>
      <math xmlns="http://www.w3.org/1998/MathML" >
        <apply>
          <times/>
          <ci>cytosol</ci>
          <apply>
            <minus/>
            <apply>
              <times/>
              <ci>kon</ci>
              <ci>E</ci>
              <ci>S</ci>
            </apply>
            <apply>
              <times/>
              <ci>koff</ci>
              <ci>ES</ci>
            </apply>
          </apply>
        </math>
      </mathLaw>
    </reaction>
  </listOfReactions>
```

# Need standardize annotations added to a model

- “Minimum information requested in the annotation of biochemical models”
- Proposed guidelines for annotation and curation of **quantitative** models
  - Specifically about encoding & annotation
  - Limited to models that can be simulated
- **Not** specific to SBML—applicable to any structured model format
- Community effort, originally lead by Andrew Finney and Nicolas Le Novère



**Minimum information requested in the annotation of biochemical models (MIRIAM)**

Nicolas Le Novère<sup>1,15</sup>, Andrew Finney<sup>2,15</sup>, Michael Hucka<sup>3</sup>, Upinder S Bhalla<sup>4</sup>, Fabien Campagne<sup>5</sup>, Julio Collado-Vides<sup>6</sup>, Edmund J Crampin<sup>7</sup>, Matt Halstead<sup>8</sup>, Edda Klipp<sup>8</sup>, Pedro Mendes<sup>9</sup>, Poul Nielsen<sup>7</sup>, Herbert Sauro<sup>10</sup>, Bruce Shapiro<sup>11</sup>, Jacky L Snoep<sup>12</sup>, Hugh D Spence<sup>13</sup> & Barry L Wanner<sup>14</sup>

Most of the published quantitative models in biology are lost for the community because they are either not made available or they are insufficiently characterized to allow them to be reused. The lack of a standard description format, lack of stringent reviewing and authors' carelessness are the main causes for incomplete model descriptions. With today's increased interest in detailed biochemical models, it is necessary to define a minimum quality standard for the encoding of those models. We propose a set of rules for curating quantitative models of biological systems. These rules define procedures for encoding and annotating models represented in machine-readable form. We believe their application will enable users to (i) have confidence that curated models are an accurate reflection of their associated reference descriptions, (ii) search collections of curated models with precision, (iii) quickly identify the biological phenomena that a given curated model or model constituent represents and (iv) facilitate model reuse and composition into large subcellular models.

During the genomic era we have witnessed a vast increase in availability of large amounts of quantitative data. This is motivating a shift in the focus of molecular and cellular research from qualitative descriptions of biochemical interactions towards the quantification of such interactions and their dynamics. One of the tenets of systems biology is the use of quantitative models (see Box 1 for definitions) as a mechanism for capturing precise hypotheses and making predictions<sup>1,2</sup>. Many specialized models exist that attempt to explain aspects of the cellular machinery. However, as has happened with other types of biological information, such as sequences, macromolecular structures or

**Box 1 Glossary**

Some terms are used in a very specific way throughout the article. We provide here a precise definition of each one.

**Quantitative biochemical model.** A formal model of a biological system, based on the mathematical description of its molecular and cellular components, and the interactions between those components.

**Encoded model.** A mathematical model written in a formal machine-readable language, such that it can be systematically parsed and employed by simulation and analysis software without further human translation.

**MIRIAM-compliant model.** A model that passes all the tests and fulfills all the conditions listed in MIRIAM.

**Reference description.** A unique document that describes, or references the description of, the model, the structure of the model, the numerical values necessary to instantiate a simulation from the model, or to perform a mathematical analysis of the model, and the results one expects from such a simulation or analysis.

**Curation process.** The process by which the compliance of an encoded model with MIRIAM is achieved and/or verified. The curation process may encompass some or all of the following tasks: encoding of the model, verification of the reference correspondence and annotation of the model.

**Reference correspondence.** The fact that the structure of a model and the results of a simulation or an analysis match the information present in the reference description.

Published online 6 December 2005; doi:10.1038/nbt1156

NATURE BIOTECHNOLOGY VOLUME 23 NUMBER 12 DECEMBER 2005 1509

Le Novère et al., *Nat. Biotech.* 23 '05



# Example interface in software: COPASI

The screenshot displays the COPASI software interface. The title bar indicates the file path: BIOMD0000000062 - COPASI 4.5.31 (development) /Users/.../curated/BIOMD0000000062.cps. The interface is divided into a left sidebar and a main content area.

**Left Sidebar (Copasi):**

- ▼ Model
  - ▼ Biochemical
    - ▼ Compartments
      - cell
    - ▼ Species
      - "Anthranilate synthase"
      - "Synthesized tryptophan"**
      - "Total tryptophan"
    - Reactions
    - Global Quantities
    - Events
    - Parameter Overview
    - Mathematical
    - Diagrams
    - Tasks
    - Output Specifications
    - Functions

**Main Content Area (Annotation Tab):**

Created at: 2010-07-16 5:04 PM

Authors:

#	▲	Family Name	Given Name	Email	Organization
1					

References:

#	▲	Resource	ID	Description
1		-- select --		

Description:

#	▲	Relationship	Resource	ID
1		is	ChEBI	CHEBI:27897
2		is	KEGG Compound	C00806
3		-- select --	-- select --	

Modified at:

#	▲	Date and Time Modified
1		

Buttons: Delete, Delete All

# Example interface in software: COPASI

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**Left Sidebar (Tree View):**

- Copasi
  - ▼ Model
    - Biochemical
      - ▼ Compartments
        - cell
      - ▼ Species
        - "Anthranilate synthase"
        - "Synthesized tryptophan" (highlighted in green)
        - "Total tryptophan"
      - ▶ Reactions
      - ▶ Global Quantities
      - Events
      - Parameter Overview
    - ▶ Mathematical Diagrams
    - ▶ Tasks
    - ▶ Output Specifications
    - ▶ Functions

**Main Content Area (Annotation View):**

Created at: 2010-07-16 5:04 PM

Authors:

#	▲	Family Name	Given Name	Email	Organization
1					

References:

#	▲	Resource	ID	Description
1		-- select --		

Description:

#	▲	Relationship	Resource	ID
1		is	ChEBI	CHEBI:27897
2		is	KEGG Compound	C00806
3		-- select --	-- select --	

Modified at:

#	▲	Date and Time Modified
1		

Buttons: Delete, Delete All

# Example interface in software: COPASI

The screenshot shows the COPASI software interface. The title bar indicates the file path: BIOMD0000000062 - COPASI 4.5.31 (development) /Users/.../curated/BIOMD0000000062.cps. The main window is titled 'Concentrations' and has three tabs: 'Species', 'Annotation', and 'RDF Browser'. The 'Annotation' tab is currently selected and is circled in red. The left sidebar shows a tree view of the model structure, with 'Synthesized tryptophan' selected under the 'Species' category. The main area displays metadata for the selected species, including a table for authors, a table for references, a table for descriptions, and a table for modification dates. At the bottom, there are 'Delete' and 'Delete All' buttons.

Created at 2010-07-16 5:04 PM

Authors

#	▲	Family Name	Given Name	Email	Organization
1					

References

#	▲	Resource	ID	Description
1		-- select --		

Description

#	▲	Relationship	Resource	ID
1		is	ChEBI	CHEBI:27897
2		is	KEGG Compound	C00806
3		-- select --	-- select --	

Modified at

#	▲	Date and Time Modified
1		

Delete Delete All



# Example interface in software: COPASI

The screenshot shows the COPASI 4.5.31 (development) interface. The left sidebar shows a tree view of the model structure, with "Synthesized tryptophan" selected under the "Species" category. The main window displays the "Annotation" tab for this species. The "Created at" field shows "2010-07-16 5:04 PM". The "Authors" table is empty. The "References" table has one row with "-- select --". The "Description" table is highlighted with a red oval and contains the following data:

#	Relationship	Resource	ID
1	is	ChEBI	CHEBI:27897
2	is	KEGG Compound	C00806
3	-- select --	-- select --	

The "Modified at" table is also empty. At the bottom of the interface, there are "Delete" and "Delete All" buttons.

# Example interface in software: COPASI

The screenshot shows the COPASI software interface. The title bar indicates the file path: BIOMD0000000062 - COPASI 4.5.31 (development) /Users/.../curated/BIOMD0000000062.cps. The interface is divided into a left sidebar and a main content area.

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    - Parameter Overview
    - Mathematical
    - Diagrams
    - Tasks
    - Output Specifications
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**Main Content Area (Annotation Tab):**

Created at: 2010-07-16 5:04 PM

Authors:

#	▲	Family Name	Given Name	Email	Organization
1					

References:

#	▲	Resource	ID	Description
1		-- select --		

Description:

#	▲	Relationship	Resource	ID
1		is	ChEBI	CHEBI:27897
2		is	KEGG Compound	C00806
3		-- select --	-- select --	

Modified at:

#	▲	Date and Time Modified
1		

Buttons: Delete, Delete All

# Example of semantic annotation in SBML

```
<species metaid="metaid_0000009" id="species_3" compartment="c_1">
  <annotation>
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
             xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
             xmlns:bqmodel="http://biomodels.net/model-qualifiers/">
      <rdf:Description rdf:about="#metaid_0000009">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:obo.chebi:CHEBI%3A15996" />
            <rdf:li rdf:resource="urn:miriam:kegg.compound:C00044" />
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```



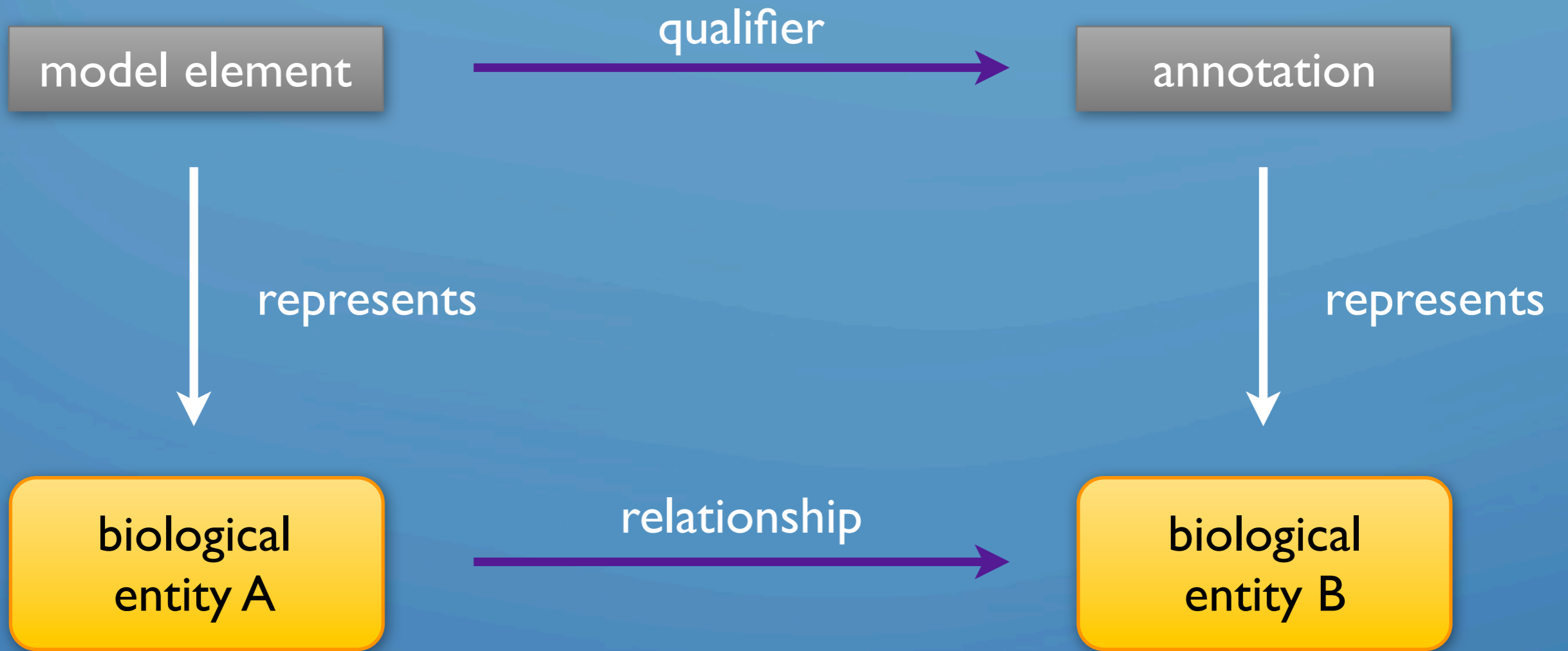
# Example of semantic annotation in SBML

```
<species metaid="metaid_0000009" id="species_3" compartment="c_1">  
  <annotation>  
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"  
      xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"  
      xmlns:bqmodel="http://biomodels.net/model-qualifiers/">  
      <rdf:Description rdf:about="#metaid_0000009">  
        <bqbiol:is>  
          <rdf:Bag>  
            <rdf:li rdf:resource="urn:miriam:obo.chebi:CHEBI%3A15996" />  
            <rdf:li rdf:resource="urn:miriam:kegg.compound:C00044" />  
          </rdf:Bag>  
        </bqbiol:is>  
      </rdf:Description>  
    </rdf:RDF>  
  </annotation>  
</species>
```

# Example of semantic annotation in SBML

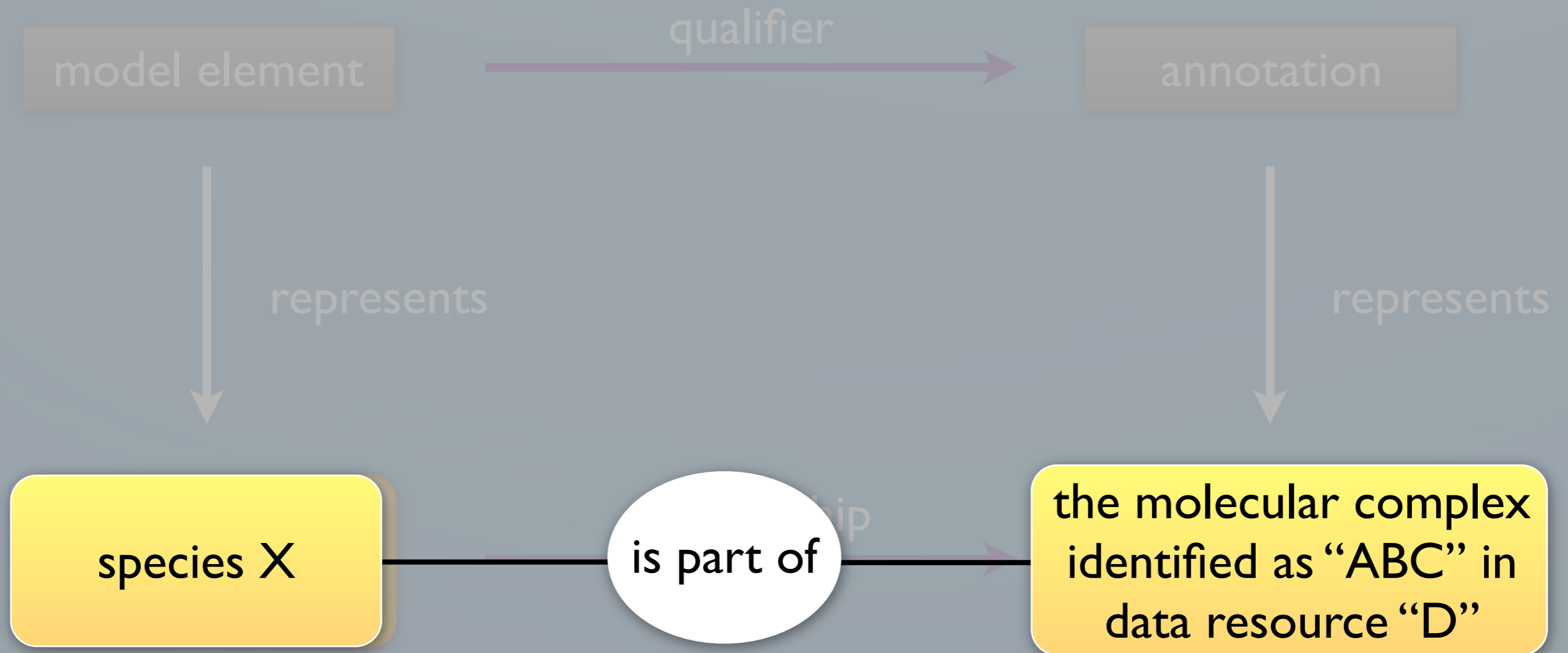
```
<species metaid="metaid_0000009" id="species_3" compartment="c_1">  
  <annotation>  
    <rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"  
      xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"  
      xmlns:bqmodel="http://biomodels.net/model-qualifiers/">  
      <rdf:Description rdf:about="#metaid_0000009">  
        <bqbiol:is>  
          <rdf:Bag>  
            <rdf:li rdf:resource="urn:miriam:obo.chebi:CHEBI%3A15996" />  
            <rdf:li rdf:resource="urn:miriam:kegg.compound:C00044" />  
          </rdf:Bag>  
        </bqbiol:is>  
      </rdf:Description>  
    </rdf:RDF>  
  </annotation>  
</species>
```

# What are the relationships?

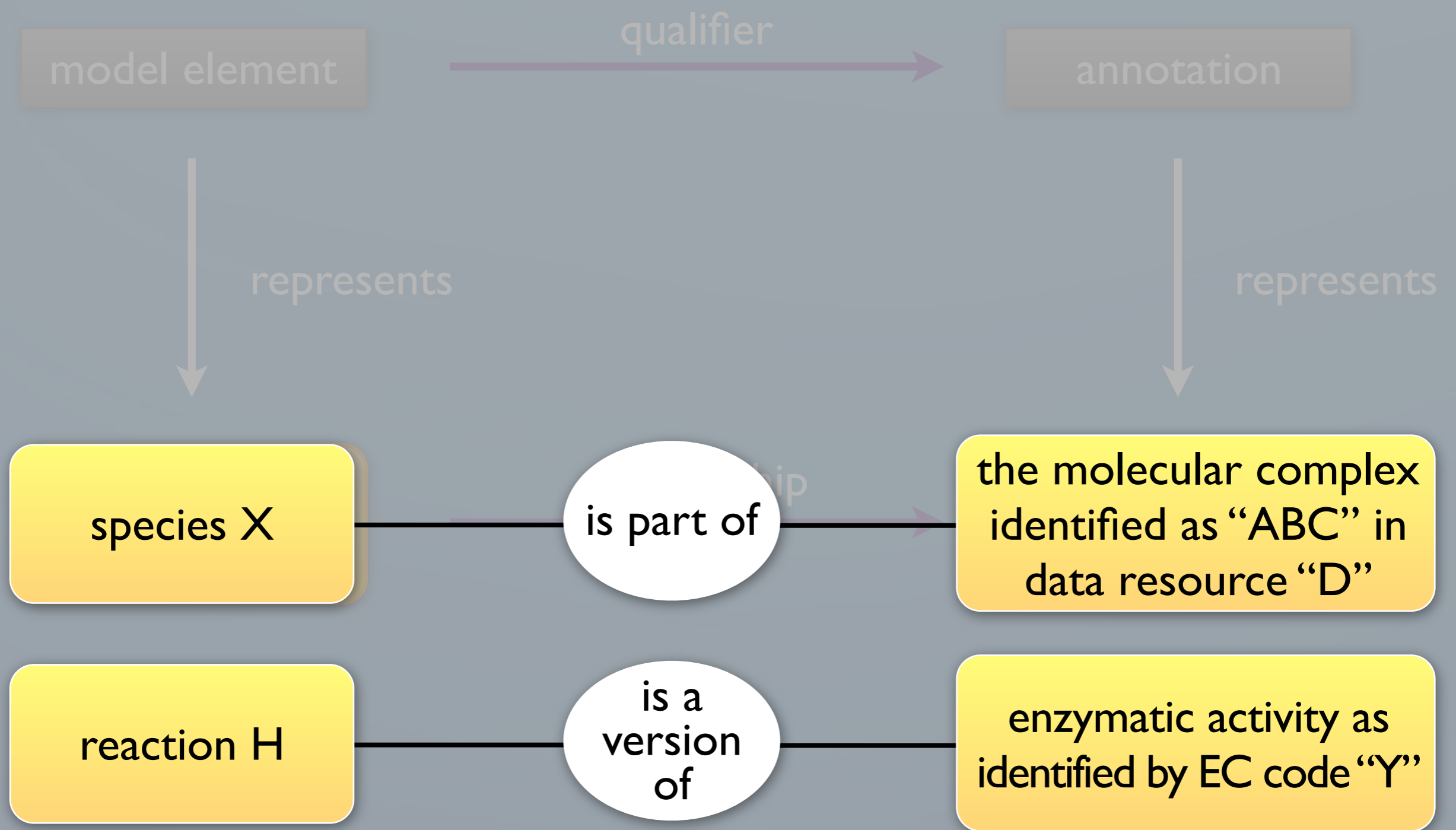




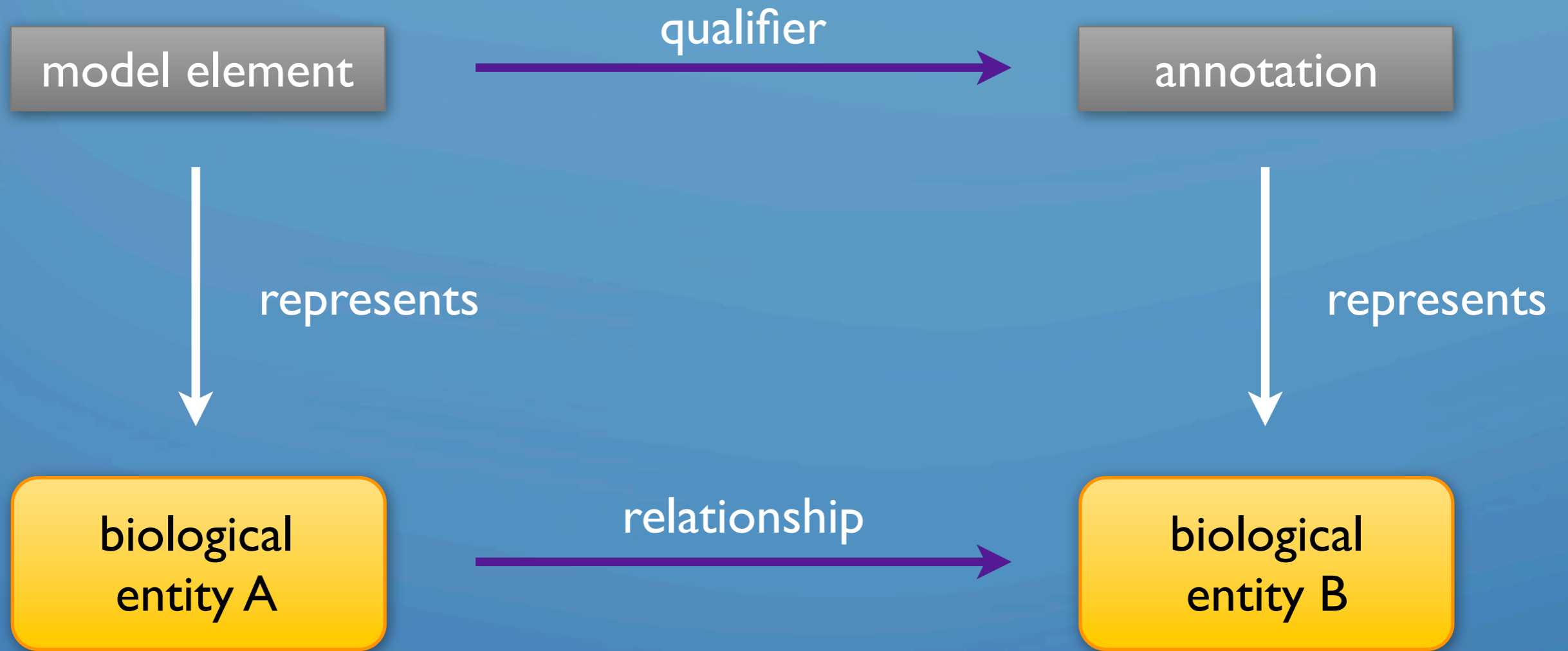
# What are the relationships?



# What are the relationships?

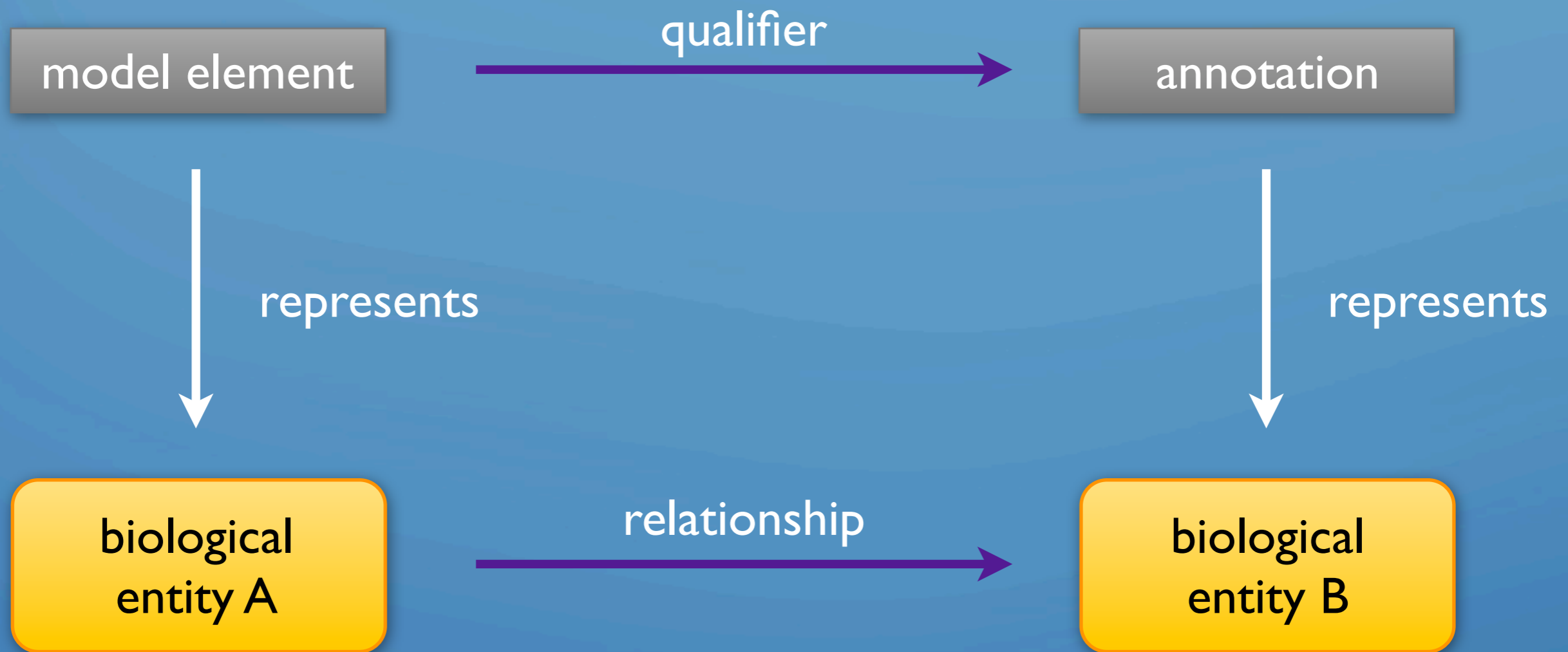


# What are the relationships?





# What are the relationships?



The relationship is rarely “is”, hence the need for a dictionary of qualifiers

# MIRIAM Resources

- Provides 3 key resources:
  - Central catalog of agreed-upon standard URNs for data types
  - Facility for the community to add and update entries
    - People can “own” an entry
  - Resolution services for software via standard protocols (web services)
- Developed by Camille Laibe in Nicolas Le Novère’s group @ EBI
- **biomodels.net/miriam**

EBI > Groups > Computational Neurobiology > Research > MIRIAM

## MIRIAM Resources

### Browse the data types

Brief overview of the different data types stored in *MIRIAM D*

[Next page](#) ➔

Name	URI	
<a href="#">3DMET</a>	urn:miriam:3dmet	3DMET is a
<a href="#">Aclame</a>	urn:miriam:aclame	ACLAME is a d genetic elemer
<a href="#">Anatomical Therapeutic Chemical</a>	urn:miriam:atc	The Anatomical T substances into act and their th classified in gro groups (1st leve 3rd and 4th leve 5th level is the cl classification sy and compari
<a href="#">ArrayExpress</a>	urn:miriam:arrayexpress	ArrayExpress is MIAME-compli
<a href="#">arXiv</a>	urn:miriam:arxiv	arXiv is an e-

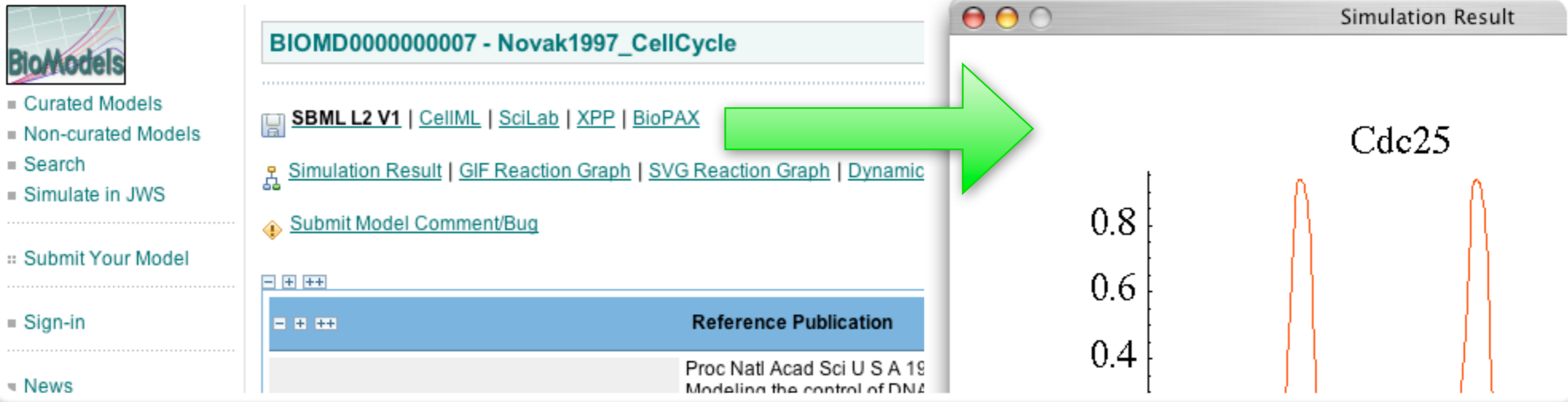
MIASE

<http://biomodels.net/miase/>



# How was a given simulation output obtained?

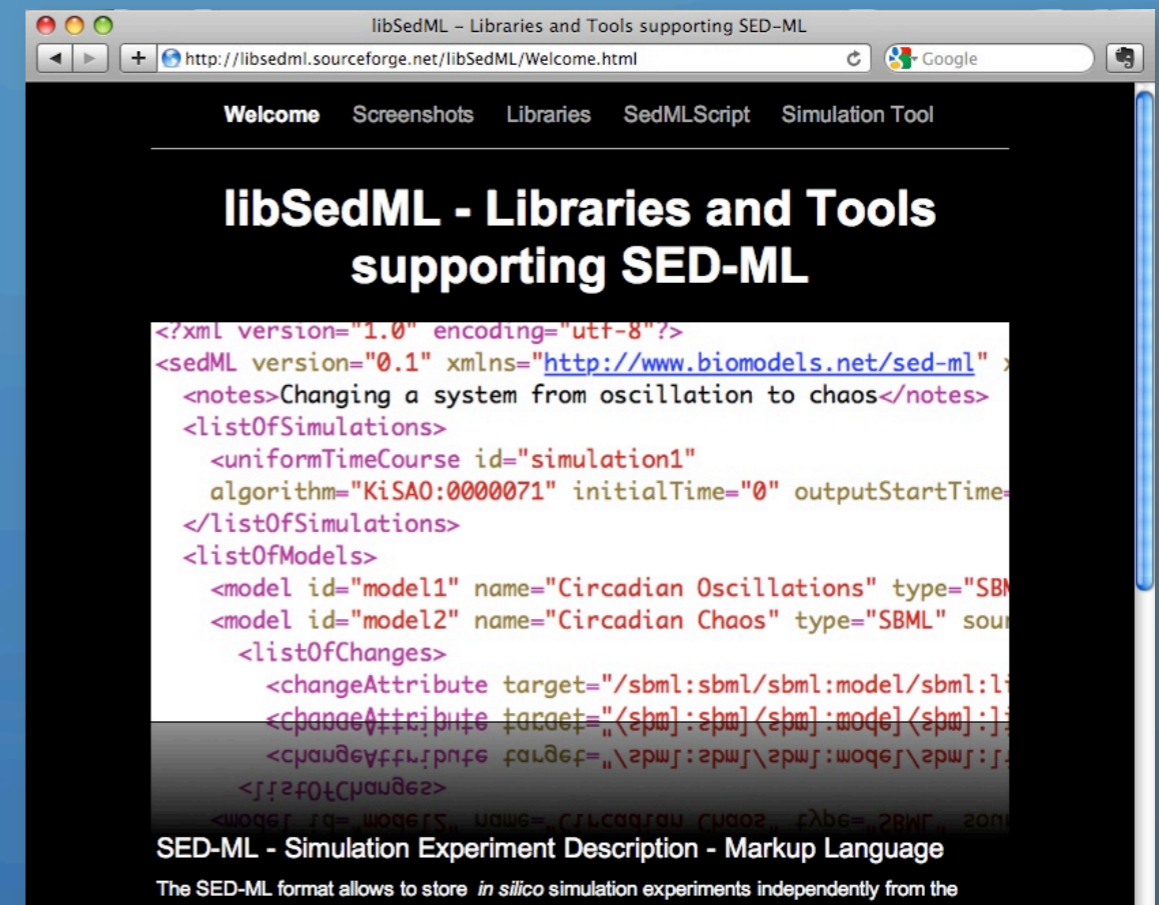
- Procedures are not captured in SBML
  - It's a **model** representation formats, **not a simulation language**
- Want to record essential steps to go from model to output data
  - Essentially explaining how a figure in a paper (or database) was obtained
  - Format must be independent of any particular simulation tool
  - Format must be machine-readable to allow automation



The screenshot displays the BioModels website interface. On the left is a navigation menu with options like 'Curated Models', 'Non-curated Models', 'Search', and 'Simulate in JWS'. The main content area shows the model identifier 'BIOMD0000000007 - Novak1997\_CellCycle'. Below this, there are links for 'SBML L2 V1', 'CellML', 'SciLab', 'XPP', and 'BioPAX'. A large green arrow points from the 'Simulation Result' link to a window titled 'Simulation Result'. This window contains a line graph for the variable 'Cdc25'. The y-axis ranges from 0.4 to 0.8, and the graph shows two distinct peaks, each reaching a value of approximately 0.8.

# MIASE & SED-ML

- ◎ MIASE = “**M**inimum **I**nformation **a**bout a **S**imulation **E**xperiment”
  - Allow person or software to reproduce the results of a simulation
    - E.g.: software used, procedures used, transformations applied, etc.
- ◎ SED-ML = “**S**imulation **E**xperiment **D**escription **M**arkup **L**anguage”
  - Formal representation satisfying the MIASE guidelines
  - The libSedML project:
    - ◎ <http://libsedml.sf.net/>



The screenshot shows a web browser window with the URL <http://libsedml.sourceforge.net/libSedML/Welcome.html>. The page title is "libSedML - Libraries and Tools supporting SED-ML". The main content area displays XML code for a simulation experiment. The code includes a header with version and encoding information, followed by a list of simulations and models. The simulation is a uniform time course with a specific algorithm and initial time. The models are "Circadian Oscillations" and "Circadian Chaos". The code also includes a list of changes to the models.

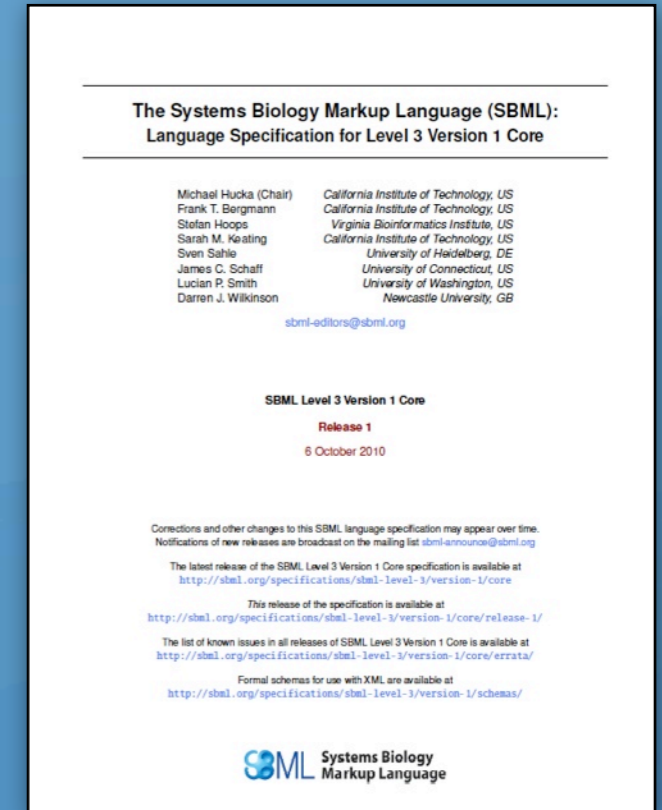
```
<?xml version="1.0" encoding="utf-8"?>
<sedML version="0.1" xmlns="http://www.biomodels.net/sed-ml" >
  <notes>Changing a system from oscillation to chaos</notes>
  <listOfSimulations>
    <uniformTimeCourse id="simulation1"
      algorithm="KiSA0:0000071" initialTime="0" outputStartTime=
    </listOfSimulations>
  <listOfModels>
    <listOfModels>
      <model id="model1" name="Circadian Oscillations" type="SBM
      <model id="model2" name="Circadian Chaos" type="SBML" sou
    </listOfModels>
    <listOfChanges>
      <changeAttribute target="/sbml:sbml/sbml:model/sbml:l
      <changeAttribute target="/sbml:sbml/sbml:model/sbml:l
      <changeAttribute target="/sbml:sbml/sbml:model/sbml:l
    </listOfChanges>
  </sedML>
```

SED-ML - Simulation Experiment Description - Markup Language  
The SED-ML format allows to store *in silico* simulation experiments independently from the

# SBML Level 3

# What are SBML “Levels”?

- Specification document available from <http://sbml.org/Documents>
- Newest: **Level 3 Version 1 Core**
  - Oct. 2010
- About SBML “Levels”:
  - Levels help manage significant restructuring of SBML architecture
  - Levels coexist
    - E.g., Level 2 models will remain valid and exist for a long time
  - A Level is *not* solely a vertical change (i.e., more features)—there is horizontal change too (i.e., changes to existing elements)





# Modularizing SBML

## ◎ The future of SBML

- Major extensions have been requested and are sorely needed
- But SBML is complicated enough
  - Only the largest-scale efforts have implemented most of Level 2

## ◎ Idea (a natural one): modularize

- Layer additional language extensions on top of a core
  - Similar to XML: XML is core, then there's MathML, etc.
- Additional benefits:
  - Can decouple development of individual extensions
  - Software can recognize & work with extensions it needs

# Evolution of features took time & practical experience

Level 1	Level 2	Level 3
predefined math functions	user-defined functions	user-defined functions
text-string math notation	MathML subset	MathML subset
reserved namespaces for annotations	no reserved namespaces for annotations	no reserved namespaces for annotations
no controlled annotation scheme	RDF-based controlled annotation scheme	RDF-based controlled annotation scheme
no discrete events	discrete events	discrete events
default values defined	default values defined	no default values
monolithic	monolithic	modular

# SBML Level 3

- ◎ *SBML Level 3* is modular:
  - “Core” defines common aspects
  - “Packages” add optional features
    - Models declare which packages they use
    - Tools can tell their users which packages they support



# SBML Level 3 packages in development

Package	Specification status
Diagram layout	Finalized & updated for L3; needs review
Diagram rendering	Finalized & updated for L3; needs review
Multi* species	Finalized & updated for L3; needs review
Hierarchical composition	New L3 specification now under discussion
Qualitative models	Draft specification proposed
Groups	Draft specification proposed
Steady-state models	Draft specification proposed
Spatial geometry	Draft specification proposed
Annotations	Specification in development
Distribution & ranges	Past spec. proposed; needs update for final L3
Arrays & sets	Past spec. proposed; needs significant update
Spatial diffusion	No specification yet
Dynamic structures	No specification yet



# Hierarchical Model Composition

# Composition as it is currently envisioned

- ◎ Goals of model composition extension is to support the following:
  - Models containing/including other models (“hierarchical models”)
    - Arbitrary nesting depths
    - Models may be defined internally or externally (in separate files)
  - Allow linking entities (species, compartments, reactions) between models
    - Support links between internal and external models
  - Allow definition of explicit interfaces (“ports”)
    - But make use of ports optional

# Models & submodels

Current SBML

Model "A"

Compartments ...

Species ...

Parameters ...

Reactions ...

# Models & submodels

## Current SBML

### Model "A"

Compartments ...

Species ...

Parameters ...

Reactions ...

## With model composition

### Model "A"

Compartments ...

Species ...

Parameters ...

Reactions ...

### Model "B"

Compartments ...

Species ...

Parameters ...

Reactions ...

### Model "C"

Compartments ...

Species ...

Parameters ...

Reactions ...



# More scenarios

## Model "A"

Compartments ...

Species ...

Parameters ...

Reactions ...

## Model "B"

Compartments ...

Species ...

Parameters ...

Reactions ...

## Model "B"

Compartments ...

Species ...

Parameters ...

Reactions ...

## Model "B"

Compartments ...

Species ...

Parameters ...

Reactions ...

...

# More scenarios

## Model "A"

Compartments ...

Species ...

Parameters ...

Reactions ...

## Model "B"

Compartments ...

Species ...

Parameters ...

Reactions ...

## Model "C"

Compartments ...

Species ...

Parameters ...

Reactions ...

## Model "D"

Compartments ...

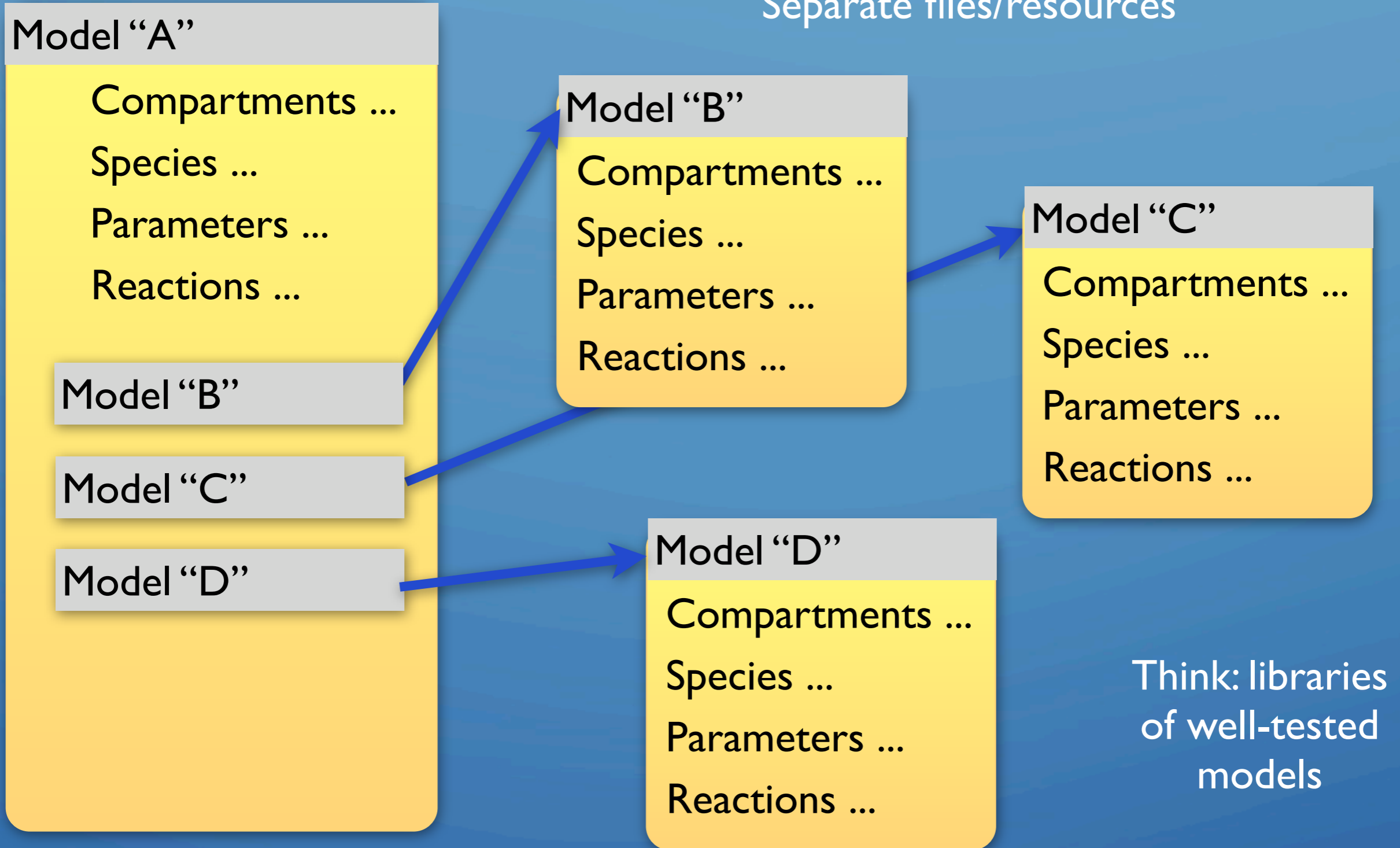
Species ...

Parameters ...

Reactions ...

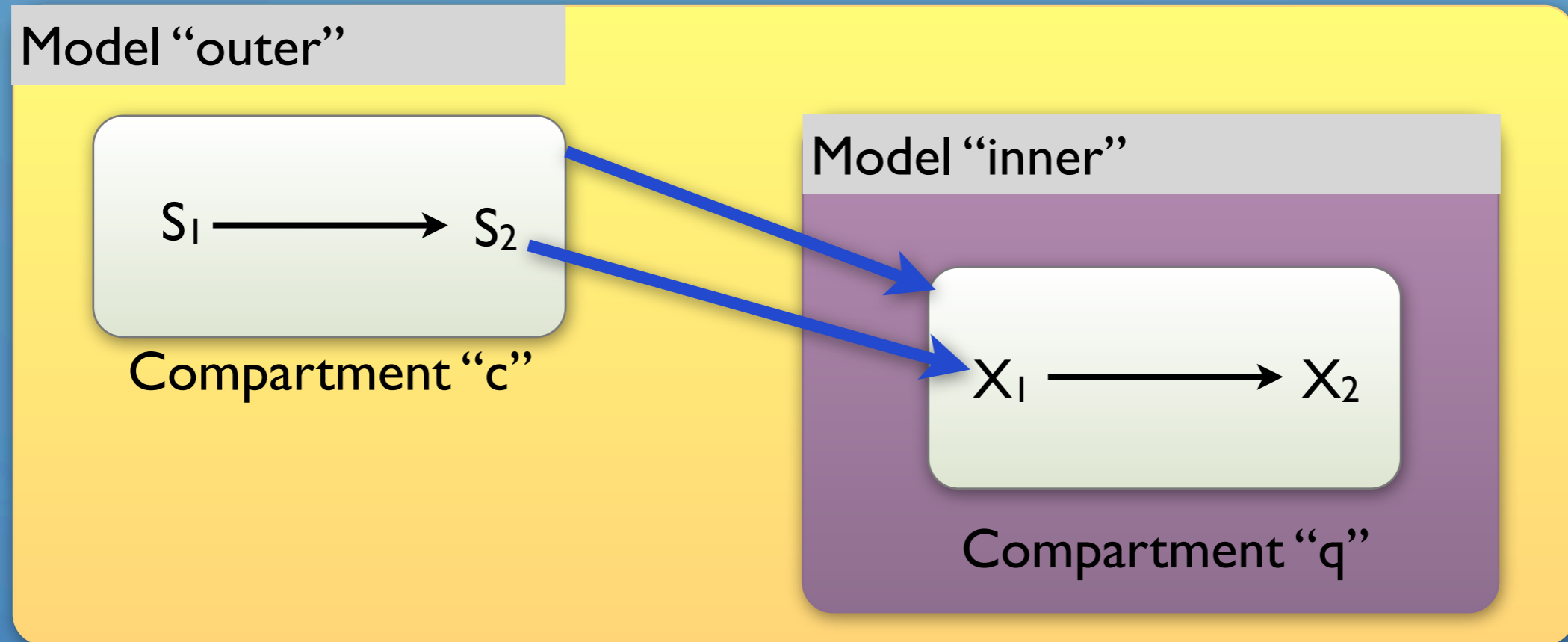
# More scenarios

Separate files/resources



Think: libraries  
of well-tested  
models

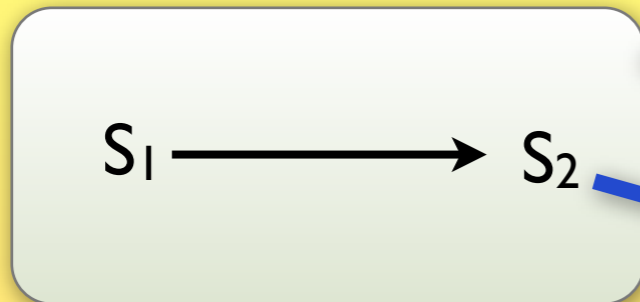
# Links/references/replacements





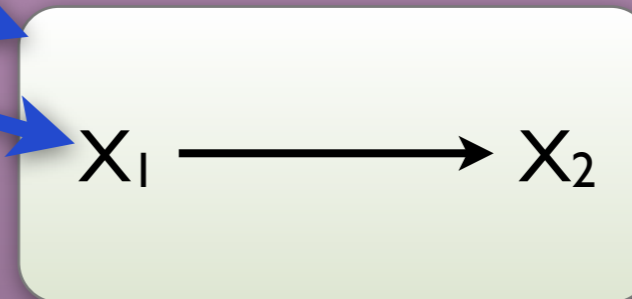
# Links/references/replacements

Model "outer"



Compartment "c"

Model "inner"



Compartment "q"

Implied model

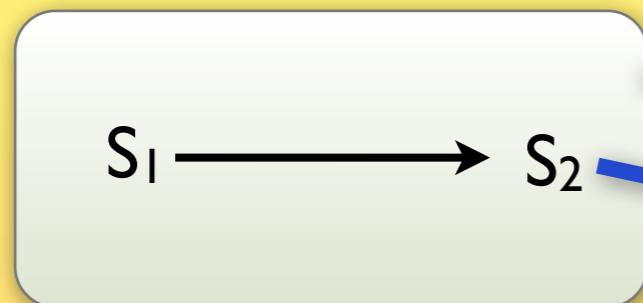
Model "outer"



Compartment "c"

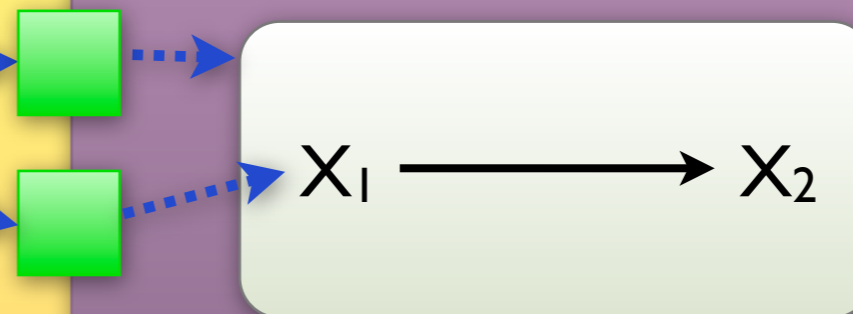
# Interfaces/ports

Model “outer”



Compartment “c”

Model “inner”



Compartment “q”

- ◎ Defined interfaces act as “contracts”
  - Promote designed encapsulation & reuse of components

# Gory bits

## ◎ Unit conversions

- Need to specify how base units of one model are related to the base units of another model
- For each entity link (species, compartment parameter), need to allow conversion factors
  - E.g.:  $X$  amount of glucose-6-phosphate in model M1 should be considered equal to  $Y$  amount in model M2

# Acknowledgements: SBML



Sarah Keating



Frank Bergmann



Lucian Smith

## SBML Team

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**James Schaff**

**Lucian Smith**

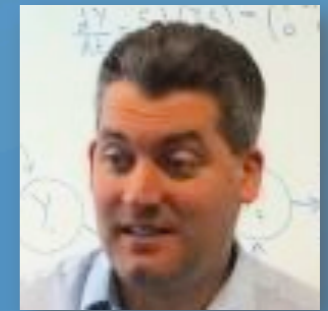
**Darren Wilkinson**

## SBML community

**Dozens of contributors**



Sven Sahle



Darren Wilkinson



Jim Schaff



# Acknowledgements: BioModels Database

## ■ EBI

- Nicolas Le Novère
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## ■ Journals supporting BioModels Database

- Molecular Systems Biology
- All PLoS Journals
- All BioMedCentral Journals

## ■ Programs used for curation

- CellDesigner/SBMLodeSolver
- COPASI
- Jarnac/JDesigner
- MathSBML
- RoadRunner
- SBMLeditor
- XPP-Aut

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(Slide from Nicolas Le Novère)

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NIH/NIGMS



EMBL-EBI



Caltech

# Thanks for listening!

- ◎ How to keep informed about SBML and learn more:
  - Join **sbml-announce@caltech.edu** (low-volume, broadcast-only)
  - See **<http://sbml.org/Forums>**
- ◎ SBML: <http://sbml.org>
- ◎ MIRIAM: <http://biomodels.net/miriam>
- ◎ MIASE: <http://sourceforge.net/projects/miase>
- ◎ SBO: <http://biomodels.net/sbo>
- ◎ BioModels Database: <http://biomodels.net/biomodels>





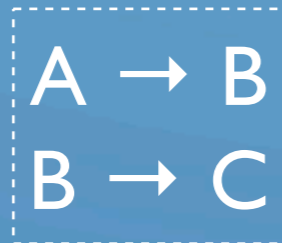
# SBML's *Model*

## model

- list of function definitions
- list of unit definitions
- list of compartment types (*Level 2 only*)
- list of species types (*Level 2 only*)
- list of compartments
- list of species
- list of parameters
- list of initial assignments
- list of rules
- list of constraints
- list of reactions
- list of events

# SBML example

2 simple reactions:



Reaction r1 rate =  $k_1[A]$

Reaction r2 rate =  $k_2[B]$

1 compartment of volume 0.5 L

A, B, C in concentrations

$$A(0) = 3 \text{ M}$$

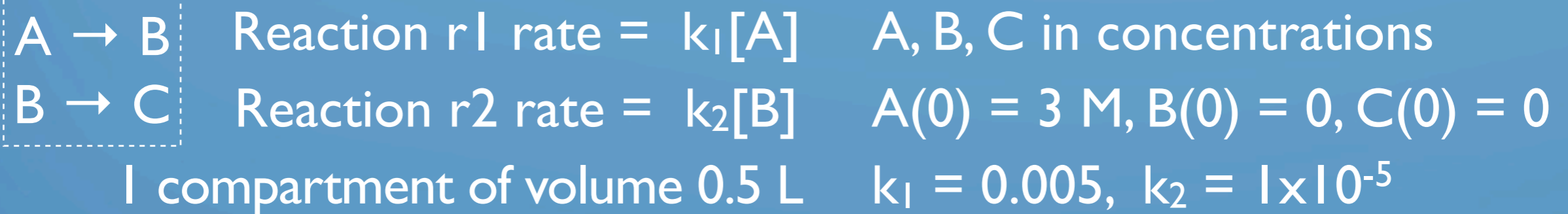
$$B(0) = 0$$

$$C(0) = 0$$

$$k_1 = 0.005$$

$$k_2 = 1 \times 10^{-5}$$

# Structure of SBML representation of the example



model

list of compartments

compartment id = "comp", initial volume = 0.5

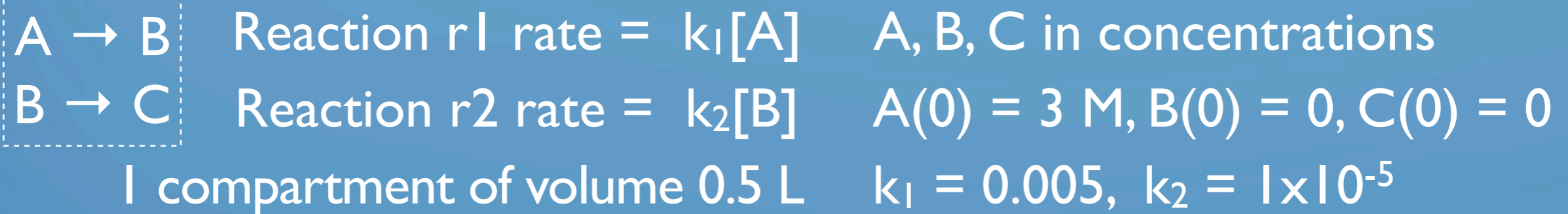
list of species

species id = "A", initial concentration = 3

species id = "B", initial concentration = 0

species id = "C", initial concentration = 0

# Structure of SBML representation of the example



## list of reactions

reaction id = "r1"

list of reactants

species reference to "A"

list of products

species reference to "B"

kinetic law

math = " $k_1 \cdot A \cdot \text{comp}$ "

list of parameters

parameter id = "k1",  
value = 0.005

reaction id = "r2"

list of reactants

species reference to "B"

list of products

species reference to "C"

kinetic law

math = " $k_2 \cdot B \cdot \text{comp}$ "

list of parameters

parameter id = "k2",  
value =  $1 \times 10^{-5}$