SBPAX: Turning Bio Knowledge into Math Models, Automated

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Virtual Cell, BioPAX, SBPAX
COMBINE 2011
www.sbpax.org

Qualitative Bio Knowledge on Web

- **Pathway Commons** (BioPAX Level 2):
  - BioGRID, MSKCC Cancer Cell Map, HPRD, HumanCyc, SBCNY, IntAct, MINT, NCI/Nature PID, Reactome
  - 1,623 pathways, 585,000 interactions, 106,000 physical entities, 564 organisms
  - BioPAX Level 3 being tested
- **UniProt**: 531,473 SwissProt, 16,504,022 TrEMBL
- **ChEBI**: 26,091 entries
- **NCBI Taxonomy**: 814,119 taxons
- **Foundational Model of Anatomy**: 120,000+ terms

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Quantitative Bio Knowledge on Web

- **SABIO-RK**: SBML export, rich on SBO; BioPAX L3, SBPAX3 interest;

- **Signaling Gateway Molecule Pages**: 672 curated pages (interactions), large diversity of quantitative values, BioPAX L3 export, SBPAX3 export (test)

- **MetaCyc, EcoCyc**: started to collect enzymatic rate constants recently; SBML, BioPAX L3 export; SBPAX3 plans;

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Bio Knowledge from Web into VCell

- **Virtual Cell (VCell)**: mature, rich modeling platform; visual model editor, simulations, parameter fitting, spatial, stochastic, biomodels.net import, model db, etc; SBML import/export

- **SBPAX at VCell**: Grab Bio Knowledge from Web to build and annotate models

  - **Qualitative**: Queries Pathway Commons, UniProt, ChEBI; imports BioPAX (since years)

  - **Quantitiative**: in process (SGMP) via BioPAX + SBPAX3

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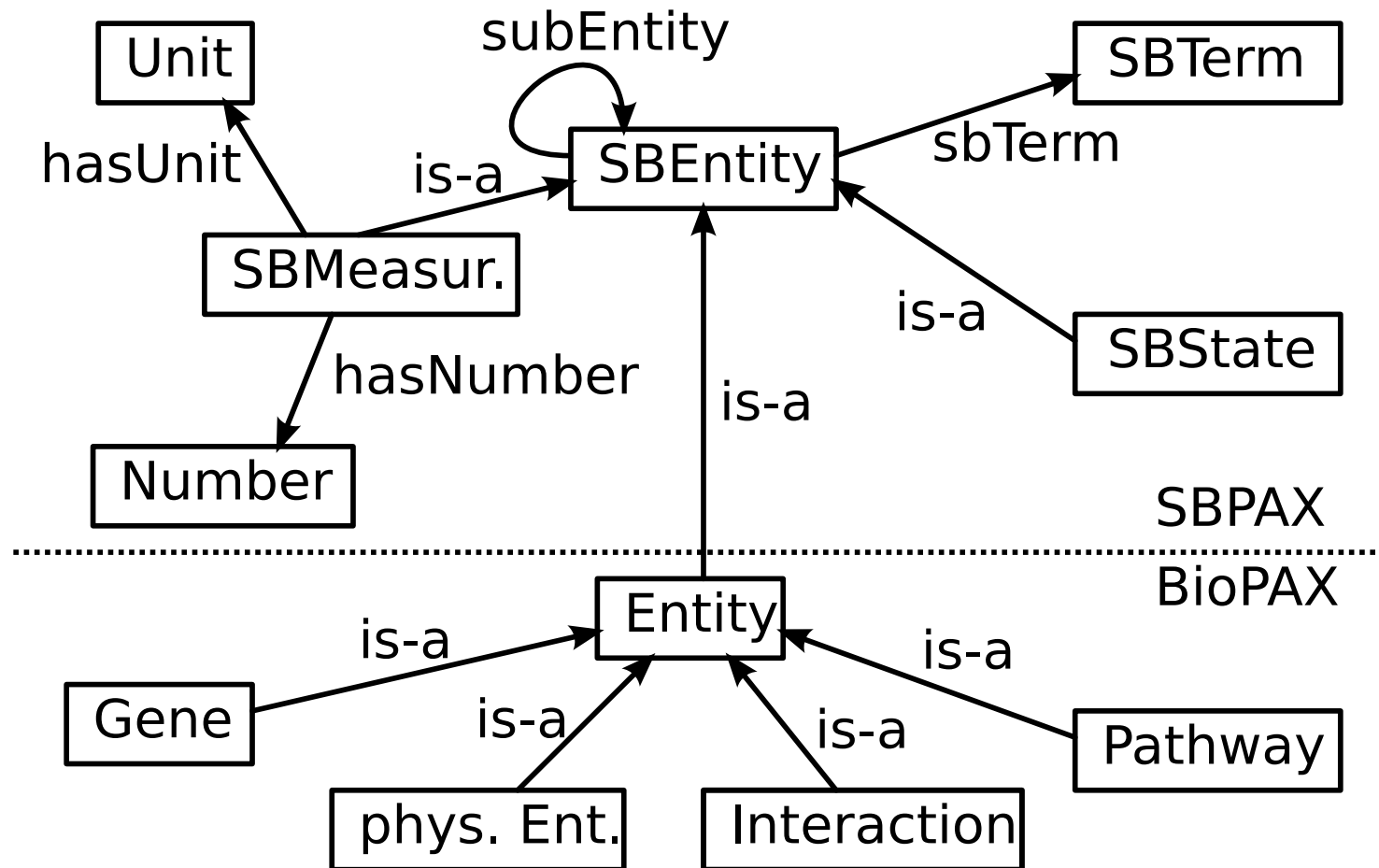
Quantitative Bio versus Modeling

Model = Biology + Method

- **Biology**: biological reality; qualitative + quantitative; general + specific (=> BioPAX, SBPAX)

- **Method**: cropping, filtering, merging, requirements, assumptions, simplifications, omissions, artifacts (=> VCell)

- **Model**: Math (=> SBML, CellML)

Systems Biology Pathway Exchange (SBPAX)

- Integrated with BioPAX classes

  - Extension to BioPAX L3 as SBPAX3

  - Proposal for BioPAX L4

- Arranges Systems Biology terms (e.g. Systems Biology Ontology), numbers and units into hierarchies

- Units based on Units of Measurement Expressions (UOME)

SBPAX3: Classes + Properties

subEntity

Unit

hasUnit

SBMeasur.

is-a → SBEntity

sbTerm → SBTerm

hasNumber

Number

is-a

SBState

is-a

SBPAX
BioPAX

Entity

Gene — is-a → Entity

phys. Ent. — is-a

Interaction — is-a

Pathway — is-a

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SBPAX3 Sub-Elements

Entity type	Sub entity type	Entity example	Sub-entity example
Material object	Component	Hemoglobin	Hb subunit, heme group
Process	Partial process	A → B → C	A → B
Object	Property	Conductor	Conductance
Entity	Mathematical description	Reaction	Rate law
Mathematical expression	Partial expression	Rate law	Rate law parameter
Index-able	Index	Michaelis constant for substrate ATP	ATP

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Systems Biology Ontology (SBO)

- Project by BioModels.net, curator Nick Juty

- Comprehensive collection of SB-relevant terms, hierarchical, open to extensions

- Includes terms for many rate laws, parameters and quantities

- For rate laws, includes math expression and references to SBO terms of the parameters (e.g. term for Michaelis-Menten rate law refers to term for Michaelis constant)

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Units of Measurement Expressions (UOME)

- UOME core: ontology to define units:
  - By scaling, exponentiation, offset, product or quotient of other units
  - By reference to controlled vocabulary (e.g. UO)
- UOME list: long list of predefined units (e.g. micro mole per milligram per minute)
- Can convert UOME to SBML or VCell units

SBPAX3: Dissociation Constant

SBEntity: C5a receptor-ligand binding

SB Term: SBO 526: protein complex formation

BioPAX Class: complex formation

SBMeasurable: Dissociation constant

SB Term: SBO 282: dissociation constant

Number: 0.001   **Unit:** micro molar

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SBPAX3: Multi-Ion Channel

SBEntity: Polycystein 2 Ion Channel

SB Term: SBO 252: polypeptide chain

BioPAX Class: protein

> **SBMeasurable: Conductance for Calcium**
>
> **SB Term:** SBO 257: conductance
>
> **Number:** 88.0   **Unit:** pico Siemens
>
> > **SBEntity: Calcium**
> >
> > **SB Term:** SBO 327: non-macromolecular ion
> >
> > **BioPAX Class:** small molecule

> **SBMeasurable: Conductance for Sodium**
>
> **SB Term:** SBO 257: conductance
>
> **Number:** 18.0   **Unit:** pico Siemens
>
> > **SBEntity: Sodium**
> >
> > **SB Term:** SBO 327: non-macromolecular ion
> >
> > **BioPAX Class:** small molecule

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SBPAX3: Multi-Substrate Enzyme

SBEntity: Phosphatidylinositol-4-kinase type III beta

SB Term: SBO 216: phosphorylation

BioPAX Class: catalysis

> **SBEntity: Michaelis-Menten kinetics 3**
>
> **SB Term:** SBO 432: Michaelis-Menten kinetics for two substrates
>
> > **SBMeasurable: Michaelis constant 3a**
> >
> > **SB Term:** SBO 322: Michaelis constant for substrate
> >
> > **Number:** 400.0   **Unit:** micro molar
> >
> > > **SBEntity: ATP**
> > >
> > > **SB Term:** SBO 247: simple chemical
> > >
> > > **BioPAX Class:** small molecule
> >
> > **SBMeasurable: Michaelis constant 3b**
> >
> > **SB Term:** SBO 322: Michaelis constant for substrate
> >
> > **Number:** 1000.0 **Unit:** micro molar
> >
> > > **SBEntity: phosphatidylinositol**
> > >
> > > **SB Term:** SBO 247: polypeptide chain
> > >
> > > **BioPAX Class:** protein

> **SBMeasurable: maximal velocity 3**
>
> **SB Term:** SBO 324: maximal velocity
>
> **Number:** 0.6   **Unit:** micro mole per minute per milligram

> **SBMeasurable: catalytic rate constant 3**
>
> **SB Term:** SBO 320: catalytic rate constant
>
> **Number:** 0.9   **Unit:** per second

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Outlook I: Adding kinetics

- **VCell can do**:
  - Keyword query, select, filter, merge results
  - Turn pathway into annotated model, keep links to go back to sources
  - After user adds numbers and equations, simulate
- **Coming soon**:
  - Include numbers and equations automatically (e.g. kinetic laws, diffusion coefficient, conductance, molecular weight, etc.)

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Outlook II: Modeling Expert System

- Linking SBO terms with UnitProt keywords, ChEBI classes etc (e.g. phosphorylation (SBO) needs a kinase (UniProt), acid-base reaction (SBO) needs acid and base (ChEBI), etc)

- Expert system:
  - VCell: "Is it enzymatic? Reversible? Multiple substrates? ..."
  - User: "Yes. Yes. No. ..."
  - VCell: "Then it is SBO term ..."

Outlook III: Curing Cancer

- User: "My patient has leukemia."

- VCell: "Looking up leukemia … mitosis in leukocytes … mitosis pathways … key genes/ proteins … targets … interactions with small molecules … select candidates … simulate oral intake … simulate side effects … select best small molecule … drug X … optimize dosage"

- VCell: "Your patient should take 570mg of X every morning before breakfast."

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