

The Synthetic Biology Open Language (SBOL): recent developments in tools and repositories

Anil Wipat

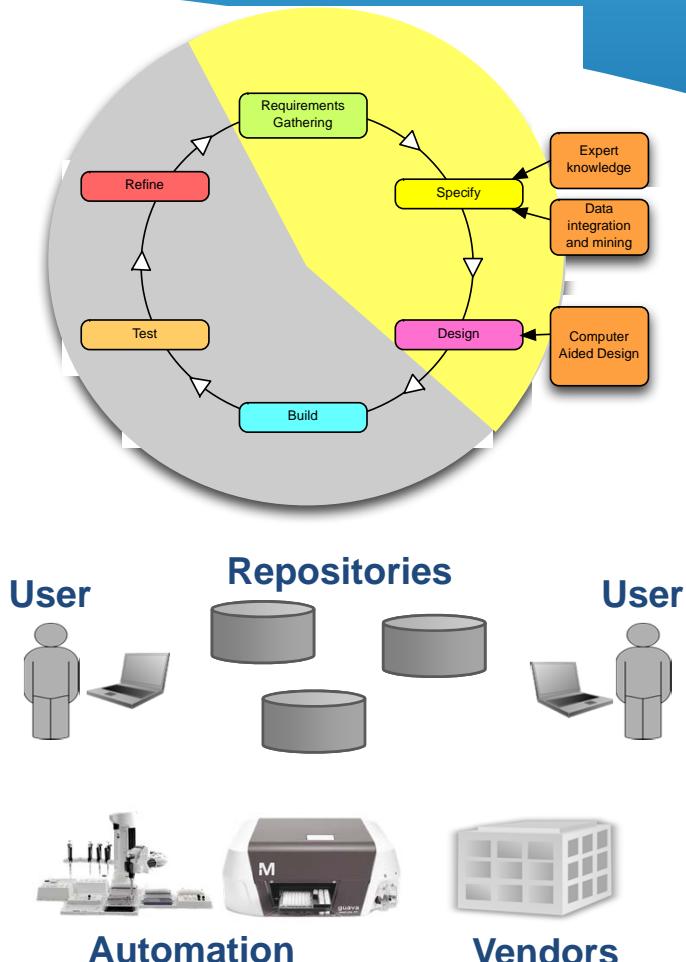
**ICOS, Computing Science & Centre for Synthetic Biology
and the BioEconomy, Newcastle University**

UK

[\(\[ico2s.org\]\(http://ico2s.org\), \[www.csbb.ncl.ac.uk\]\(http://www.csbb.ncl.ac.uk\)\)](http://ico2s.org)

What is SBOL – why is it needed?

- * Synthetic Biology is engineering biology
- * Requires movement of data & information
 - * Between people, software & machines
 - * Across geographic and political boundaries
- * Standards needed to ensure interoperability
- * SBOL - a standard way to represent information about synthetic biology designs



In 2008, a small group of researchers proposed the development of the synthetic biology open language (SBOL), an open-source standard for the exchange of genetic designs

SBOL History

In 2013, the first version of the SBOL Visual standard was released

25+ software tools now support SBOL
Leveraging libSBOLj

In 2011, the first version of the SBOL core data model was released.

SBOL 2 released

Essential information for synthetic DNA sequences

To the Editor:

Following a discussion by the workgroup for Data Standards in Synthetic Biology, which met in June 2010 during the Second Workshop on Biodesign Automation in Anaheim, California, we wish to highlight a problem relating to the reproducibility of the synthetic biology literature. In particular, we have noted the very small number of articles reporting synthetic gene networks that disclose the complete sequence of all the constructs they describe.

To our knowledge, there are only a few examples where full sequences have been released. In 2005, a patent application¹ disclosed the sequences of the toggle switches published four years earlier in a paper by Gardner *et al.*². The same year, Basu *et al.*³ deposited their construct sequences for programmed pattern formation into GenBank³. Examples of synthetic DNA sequences derived from standardized parts that have been made available in GenBank include the refactored genome of the bacteriophage

gaps between key components are almost never reported, presumably because they are not considered crucial to the report. Yet, synthetic biology relies on the premise that synthetic DNA can be engineered with base-level precision.

Missing sequence information in papers hurts reproducibility, limits reuse of past work and incorrectly assumes that we know fully which sequence segments are important. For example, many synthetic biologists are currently realizing that translation initiation rates are dependent on more than the Shine-Dalgarno sequence⁴. Sequences upstream of the

start codon are crucial for translation rates, yet are underreported. Similarly, it has been demonstrated that intron length can affect the dynamics of genetic oscillators⁵. Many more such examples are likely to emerge.

Because full sequence disclosure is critical, we wonder why the common requirement by many journals to provide GenBank entries

for genomes and natural sequences has

and welcome contributions from the greater community.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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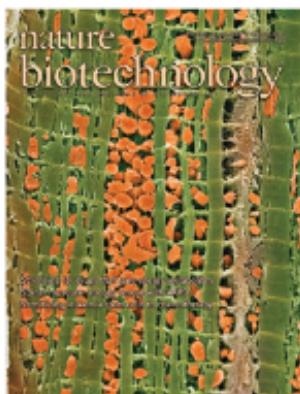
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- Gardner, T.S. & Collins, J.J. US patent 6,841,376 (2005).
- Gardner, T.S., Cantor, C.R. & Collins, J.J. *Nature* **403**, 339–342 (2000).
- Basu, S., Gerchman, Y., Collins, C.H., Arnold, F.H. & Weiss, R. *Nature* **444**, 1190–1194 (2006).

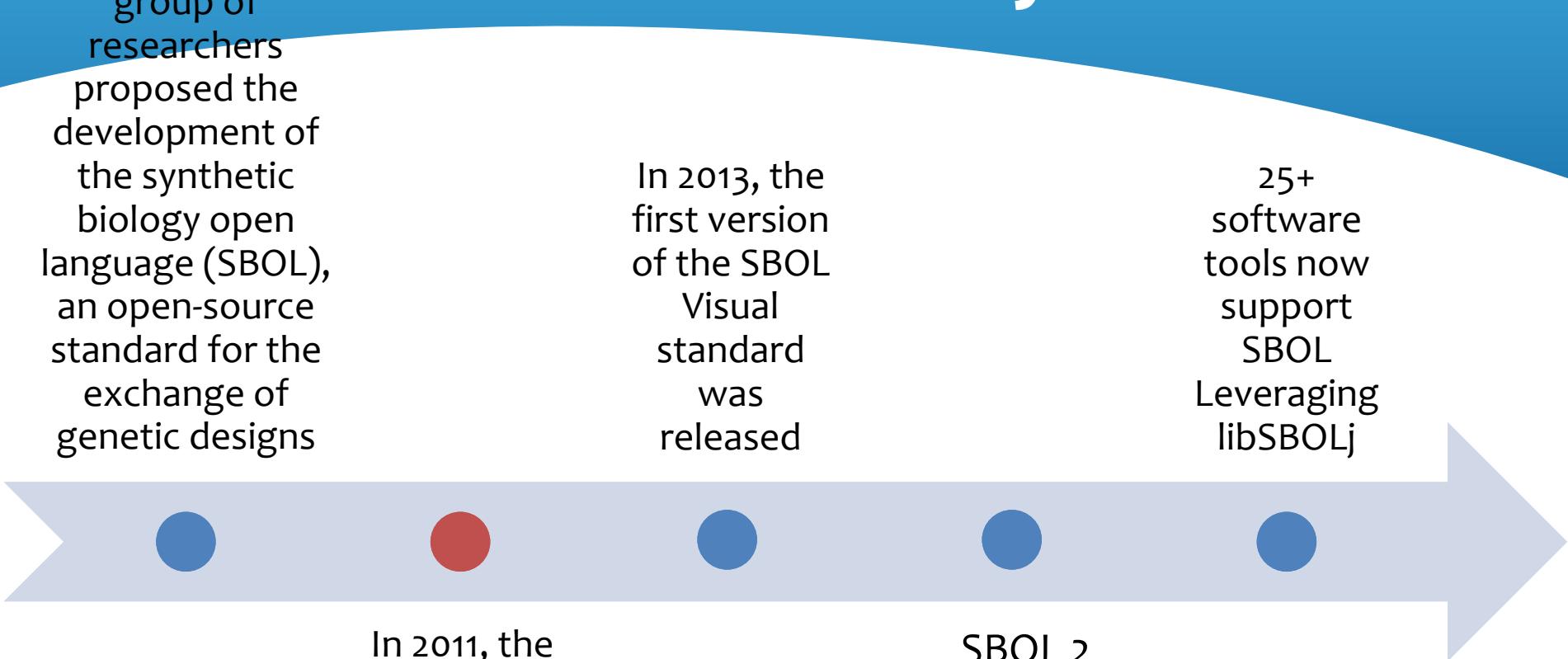


In 2008, a small group of researchers proposed the development of the synthetic biology open language (SBOL), an open-source standard for the exchange of genetic designs

SBOL History

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25+ software tools now support SBOL
Leveraging libSBOLj



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SBOL 2 released

SBOL v 1

nature
biotechnology



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NATURE BIOTECHNOLOGY | COMPUTATIONAL BIOLOGY | PERSPECTIVE



[日本語要約](#)

The Synthetic Biology Open Language (SBOL)
provides a community standard for communicating
designs in synthetic biology

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Cesar A Rodriguez, Nicholas Roehner, Mandy L Wilson, Laura Adam, J Christopher
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Nature Biotechnology **32**, 545–550 (2014) | doi:10.1038/nbt.2891

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SBOL v 1



life
technologies™

Life Technologies

Received design file for
codon optimization
and gene synthesis.



Newcastle
University

Newcastle

Stored design and model
files in repository for
dissemination.

pIKE
pTAK

4x pIKE
4x pTAK

16x pIKE
16x pTAK

Designed four expression
cassettes, leaving RBS and
terminator components
unspecified.

Generated four variant
designs of each cassette
using six RBS and six
terminator components.

Assembled and modeled
sixteen variant designs of
the toggle switch.

jbei
Joint BioEnergy Institute

Joint BioEnergy Institute

Stored design files in
repository for dissemination.

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SBOL visual

BBF RFC 93

SBOL Visual

Synthetic Biology Open Language Visual (SBOL Visual), version 1.0.0

Jacqueline Quinn, Jacob Beal, Swapnil Bhatia, Patrick Cai, Joanna Chen, Kevin Clancy, Nathan Hillson, Michal Galdzicki, Akshay Maheshwari, Umesh P, Matthew Pocock, Cesar Rodriguez, Guy-Bart Stan, Drew Endy

March 21, 2013

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SBOL 2 specification

**BBF RFC 108: Synthetic Biology Open Language
(SBOL) Version 2.0.0**

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Version 2.0.0



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SBOL Community

- * **SBOL Chair** - Herbert Sauro (U. of Washington)
- * **SBOL Editors** - Bryan Bartley (U. of Washington), Jacob Beal (BBN Technologies), Kevin Clancy (Thermo Fisher), Goksel Misirli (Newcastle), and Raik Grunberg (Montreal).
- * **Past SBOL Editors** - Michal Galdzicki (U. of Washington), Ernst Oberortner (JGI/BU), Matthew Pocock (Newcastle), Jacqueline Quinn (Google), Cesar Rodriguez (Autodesk), Nick Roehner (BU) and Mandy Wilson (VBI).

SBOL Community



SBOL Developers Group includes 116 members from more than 30 organizations.

Organisations supporting SBOL

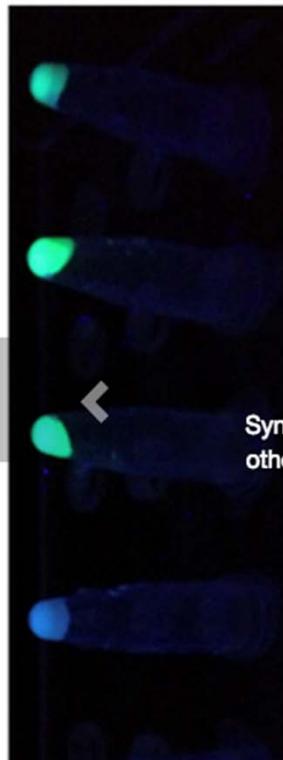
- * Current support for the development of SBOL provided by:
 - * National Science Foundation Grants DBI-1356041 and DBI-1355909
 - * Engineering and Physical Sciences Research Council under Grant Number EP/J02175X/1



A screenshot of a web browser window showing the homepage of sbolstandard.org. The address bar at the top contains the URL "sbolstandard.org". Below the address bar is a horizontal toolbar with various icons and links, including "Apps", "Google", "Biopython Tutorial ar", "Learn Python The Ha", "Nanopore Online", "Welcome to the Min", "ERASynBio: PROJE", "Google Maps", and "Other Bookmarks". The main content area features a large banner with a blue background and a green circular logo containing a DNA helix and a gear. The banner text reads "Curious about Synthetic Biology?" and "Synthetic biology combines the best of biology, engineering, and many other scientific disciplines with the goal of designing and building living systems." A "Learn more" button is visible. To the right of the banner is a sidebar with the SBOL logo, announcements, and discussion archives.

Synthetic Biology Open Language (SBOL)

About Glyphs Software Documents Community FAQ Contact



Curious about Synthetic Biology?

Synthetic biology combines the best of biology, engineering, and many other scientific disciplines with the goal of designing and building living systems.

Learn more



Announcements

- Please join us for the SBOL Community Outreach Meeting at IWBDA!
- SBOL 2.0 Released
- COMBINE 2015: The next SBOL Workshop will take place October 12-16, 2015 concurrent with COMBINE 2015 at the University of Utah in Salt Lake City, USA
- SBOL at SEED 2015
- SBOL 12 Workshop Report
- NIST Synthetic Biology Standards Workshop: March 31

Discussion Archives

[Developer's List](#)
[Visual Working Group](#)

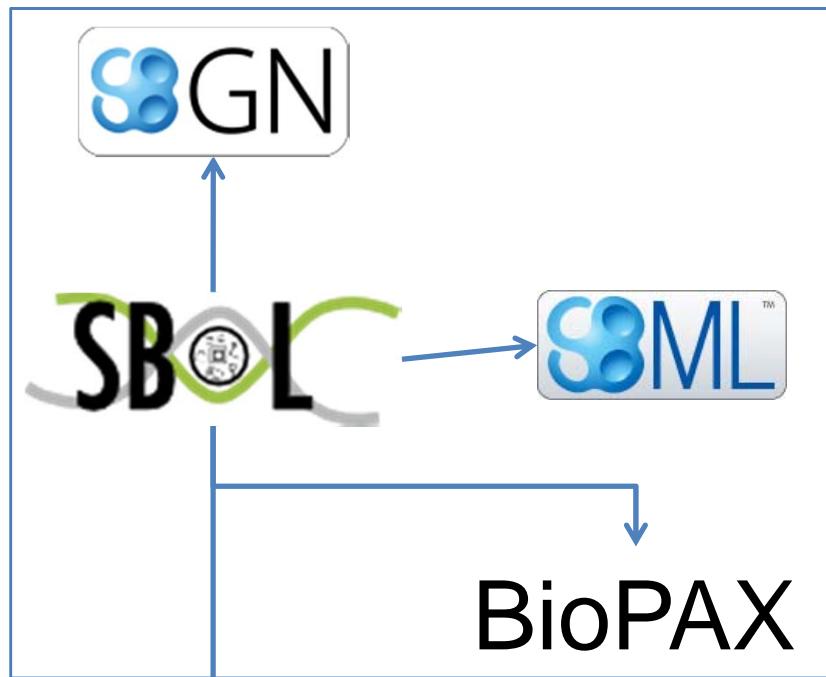
sbolstandard.org

Current support for the development of the SBOL standard is provided by the NSF through Collaborative awards #1355909 and #1356401 and EPSRC grant #EP/J02175X/1. Other sponsorship, support, or endorsements have been provided by the following federal agencies, federal research centers, commercial enterprises, and academic institutions. Please be aware that this list may not be complete, since the number of SBOL supporters is growing rapidly. If your institution supports SBOL, and it is not listed here, please email the [SBOL editors](#).

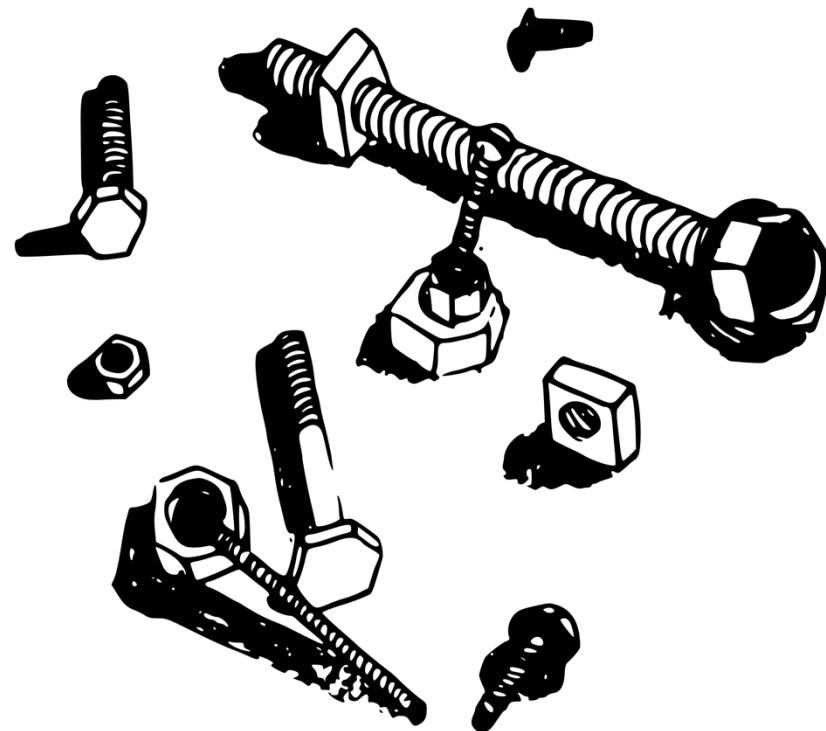
SBOL & COMBINE



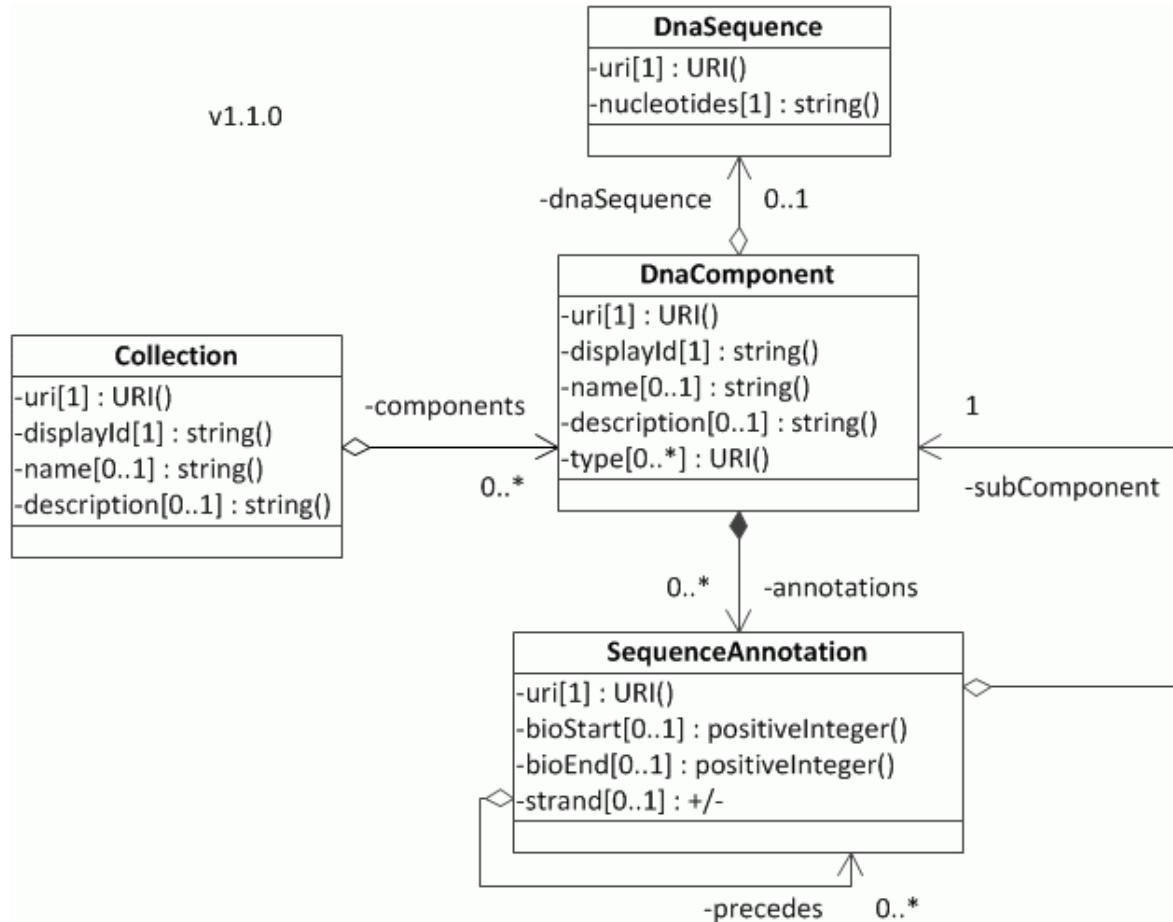
- * SBOL has been a COMBINE member since August 2014
- * Already interacting with communities developing other standards
 - * SBOL Visual/SBGN
 - * SBOL/SBML/SED-ML
 - * SBOL/BioPAX
- * Useful synergies
 - * Specification infrastructure
 - * Metadata and annotations
 - * COMBINE archive
 - * Repositories
 - * Compliance testing



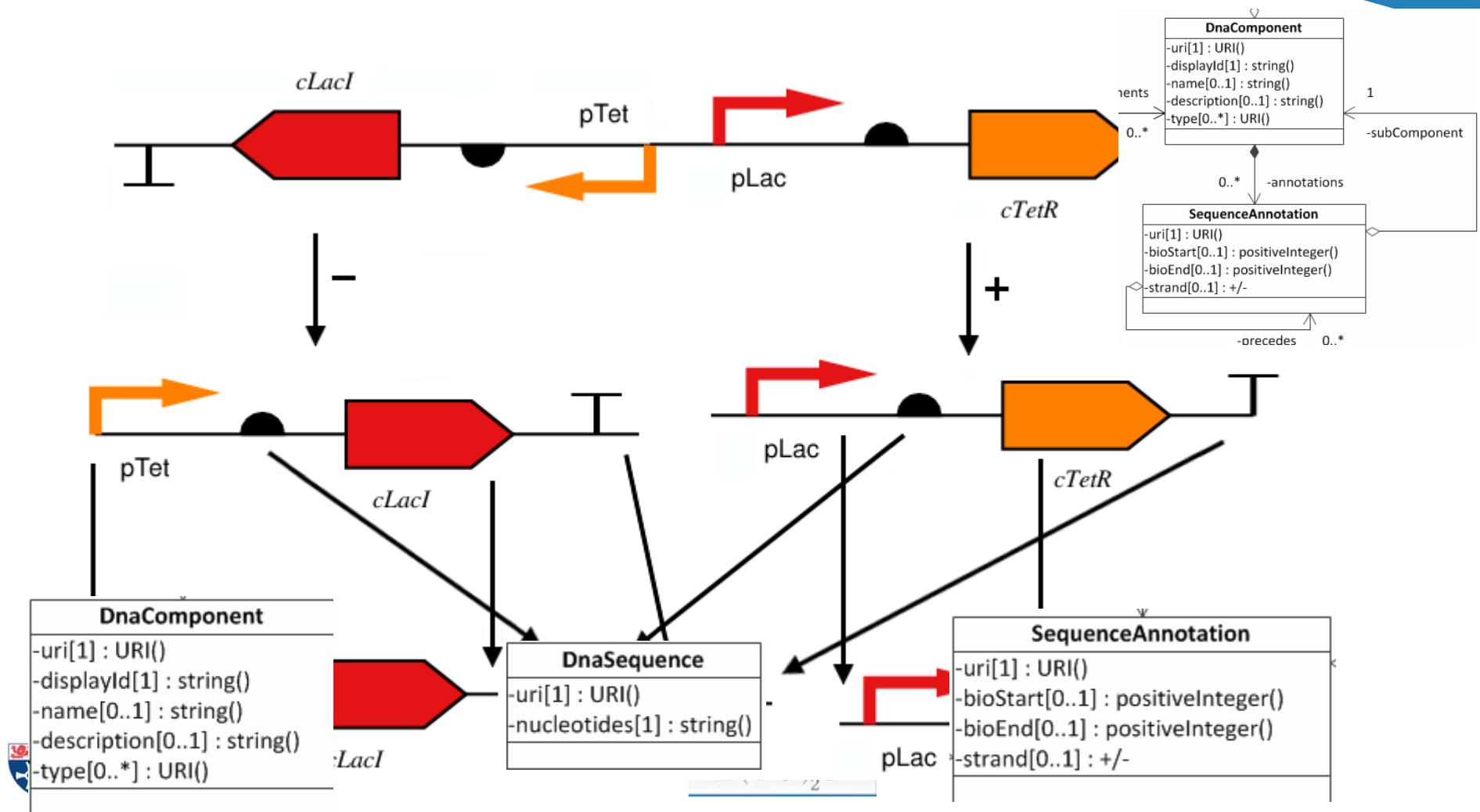
Nuts and bolts of SBOL 1 and 2



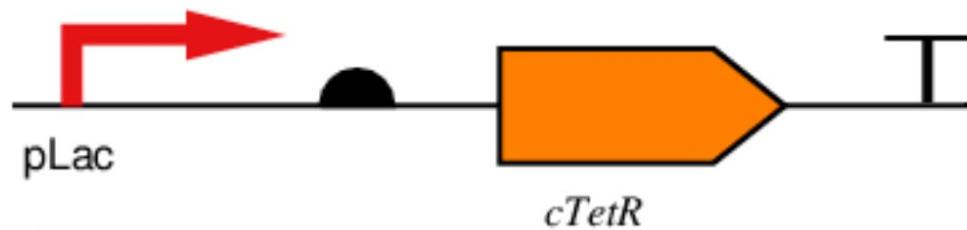
v1.1.0



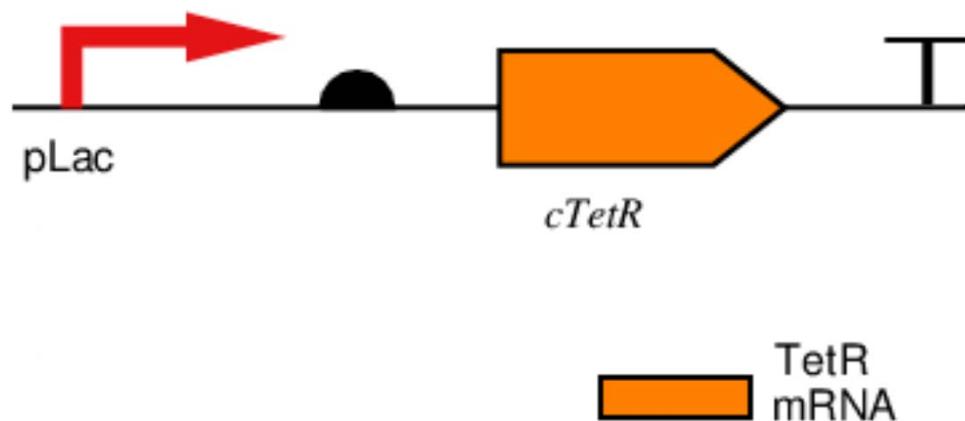
Hierarchical Composition with SBOL v1



SBOL 2.0

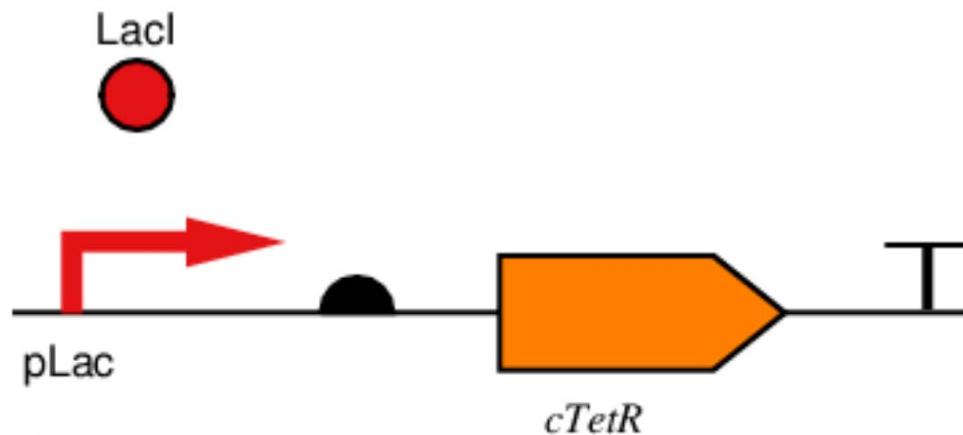


SBOL 2.0



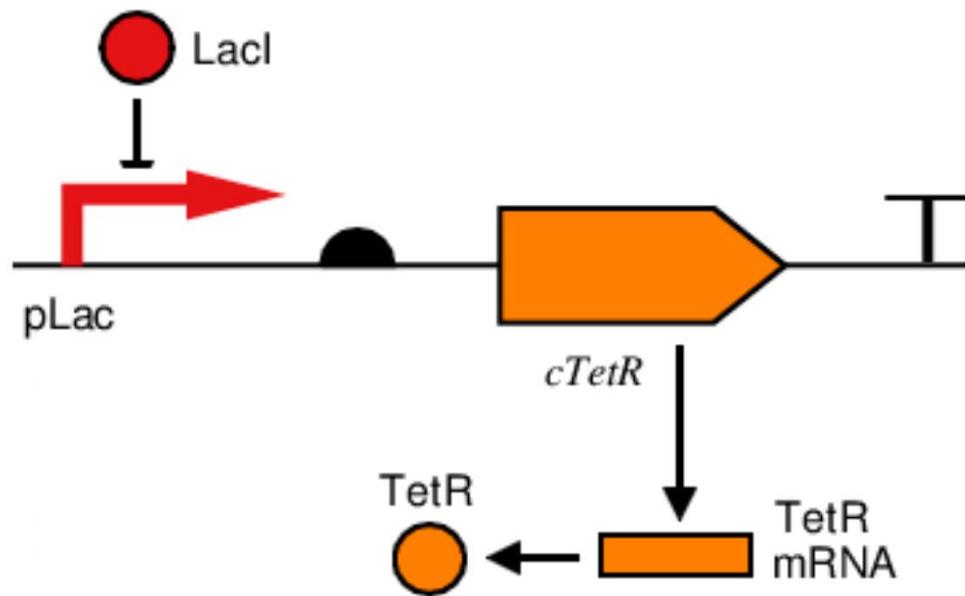
RNA components (mRNA, tRNA, siRNA)

SBOL 2.0



RNA components (mRNA, tRNA, siRNA)
Protein components (TFs, enzymes)

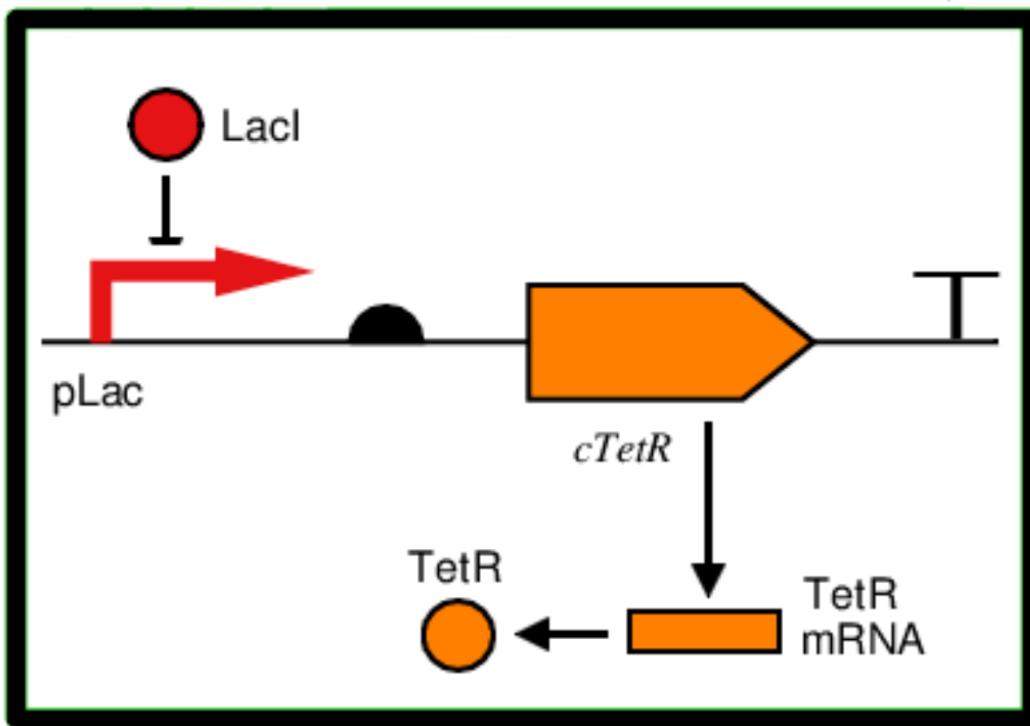
SBOL 2.0



- Interactions (activation, repression, complexation, transcription, translation, phosphorylation)

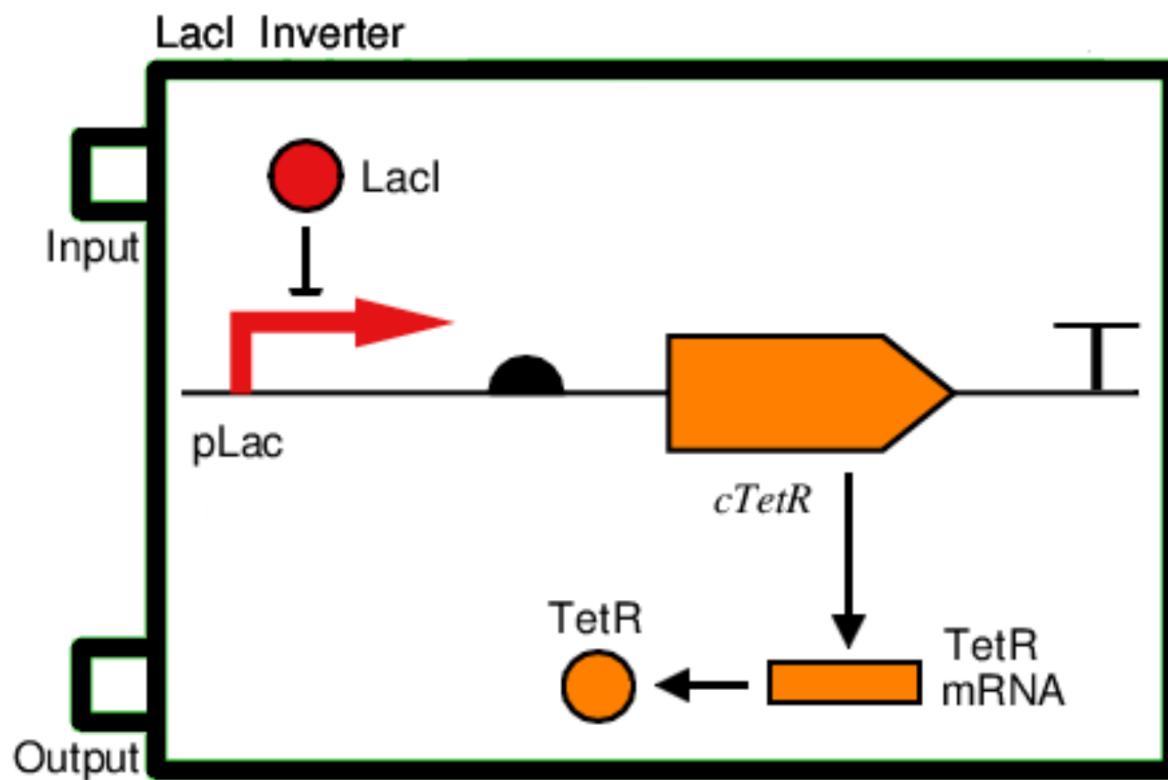
SBOL 2.0

LacI Inverter



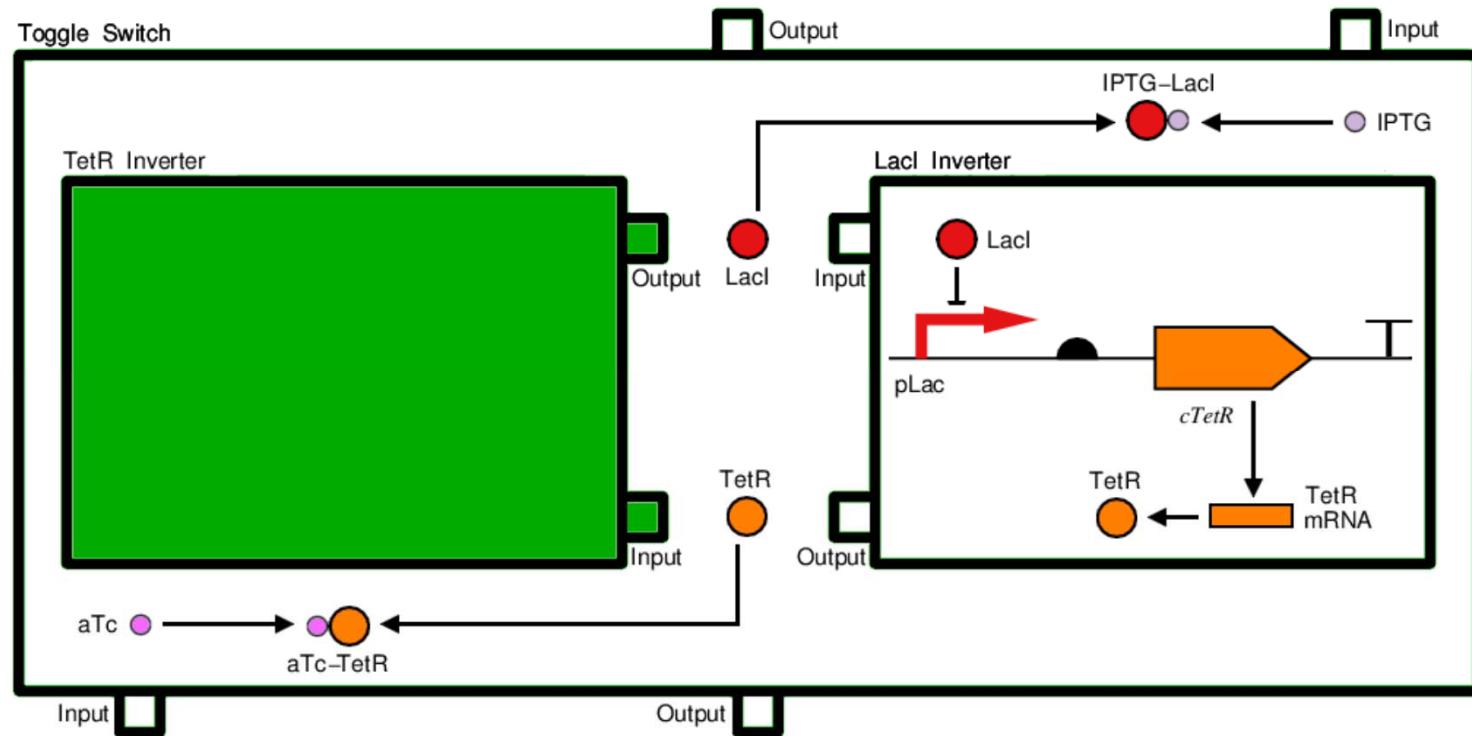
- Interactions
- Modules (logic gates, latches, oscillators, sensors, transducers, pathways, cascades)

SBOL 2.0



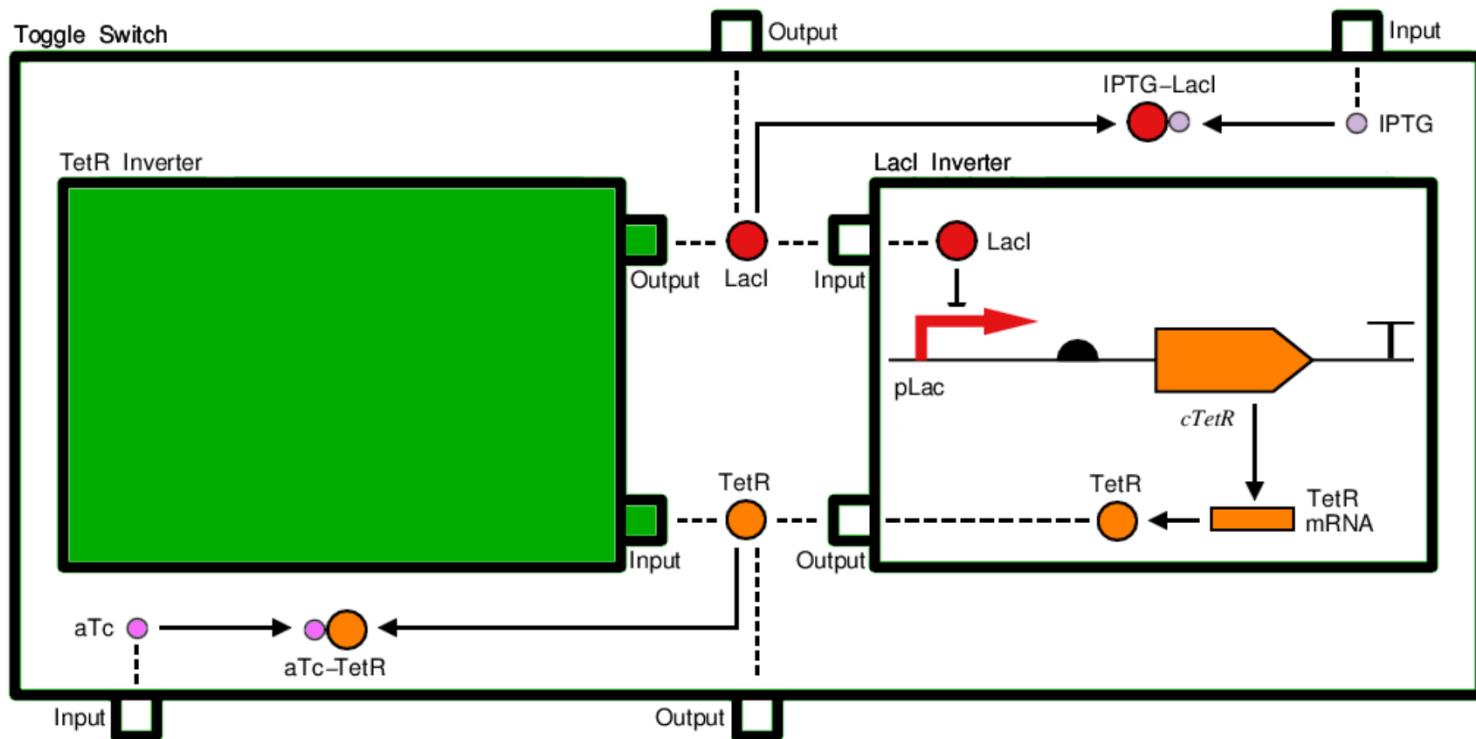
- Ports

SBOL 2.0



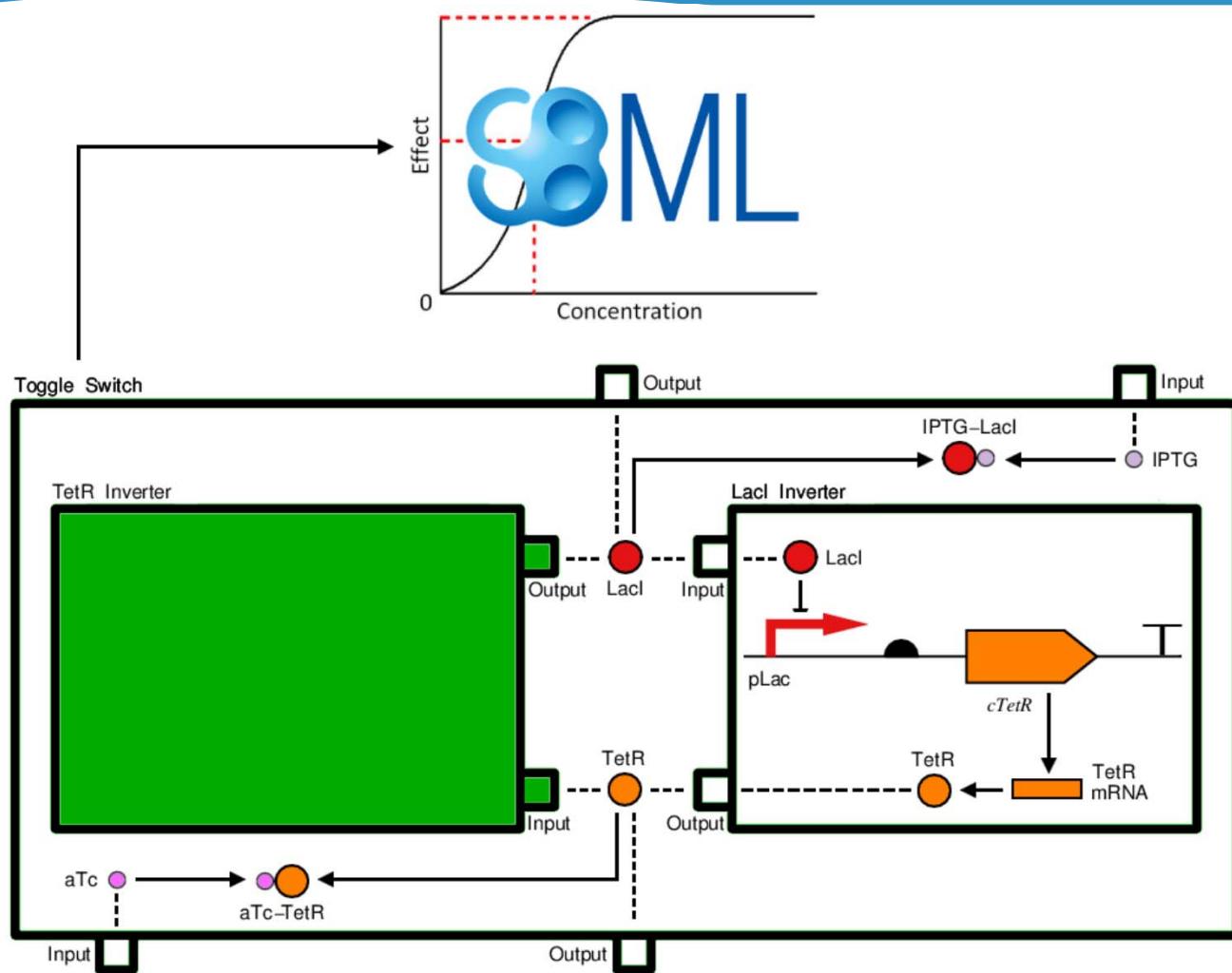
- Ports
- Instantiation

SBOL 2.0

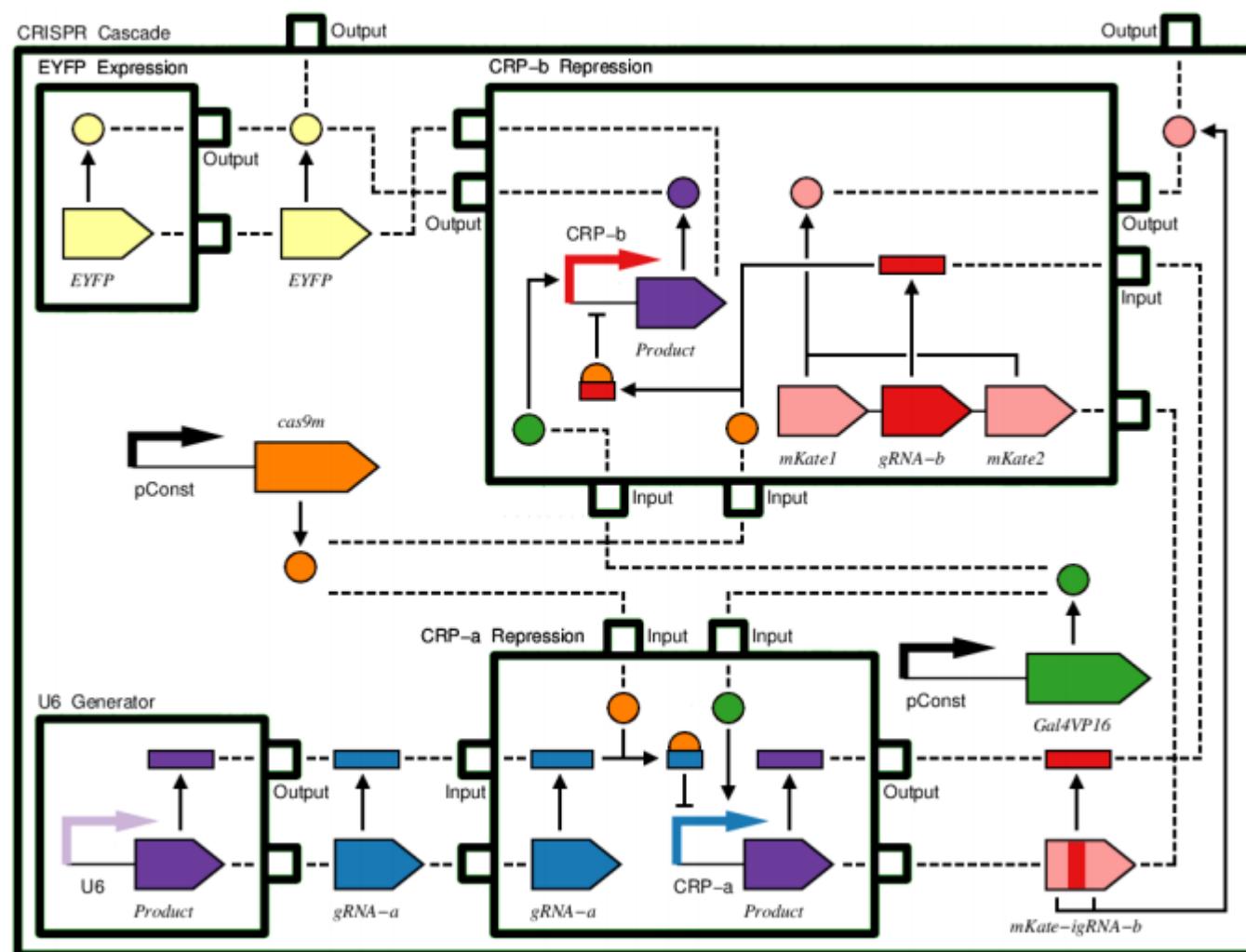


- Instantiation
- Port Mapping

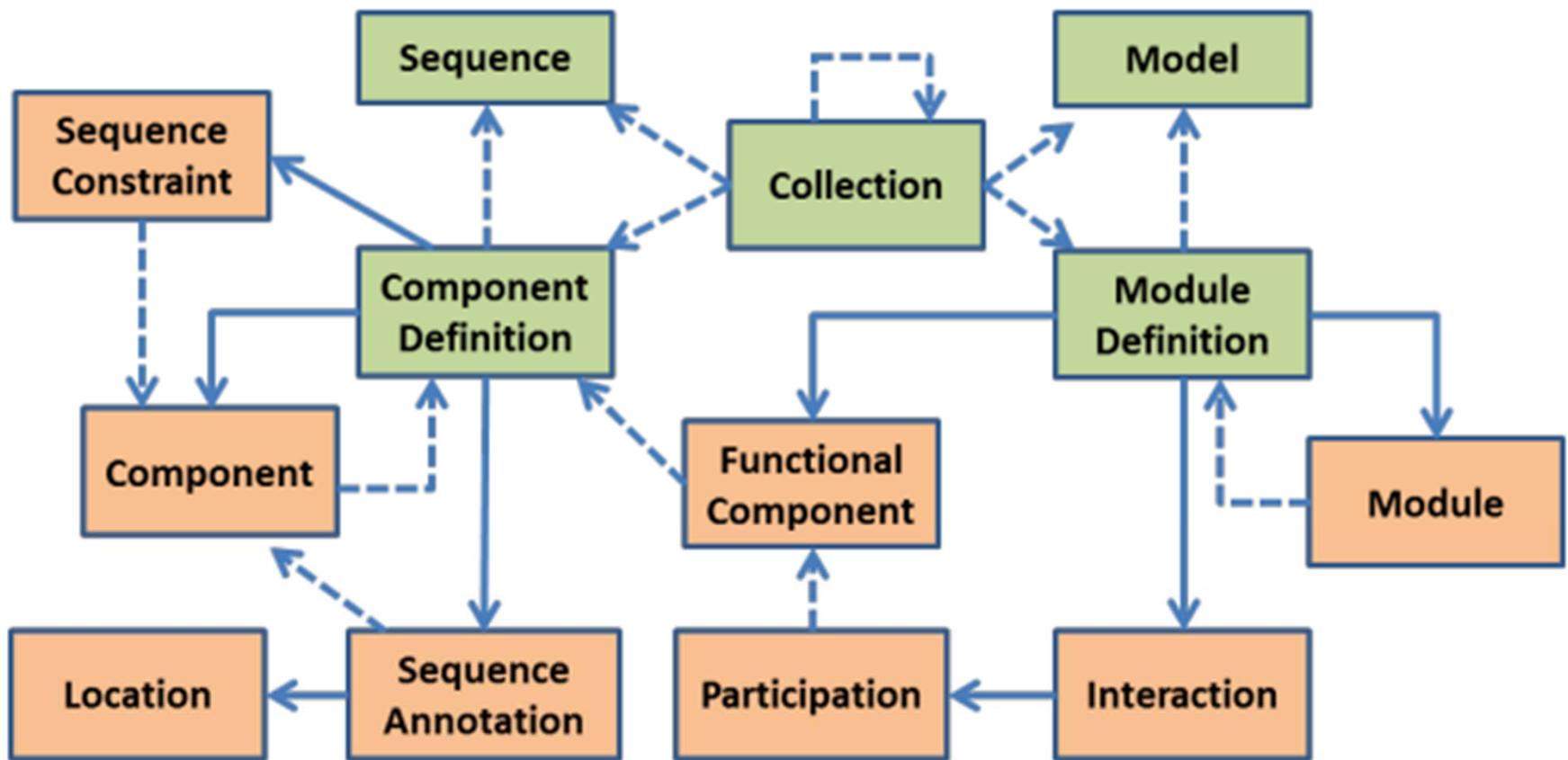
SBOL 2.0



SBOL 2.0 - example



SBOL 2 data model overview



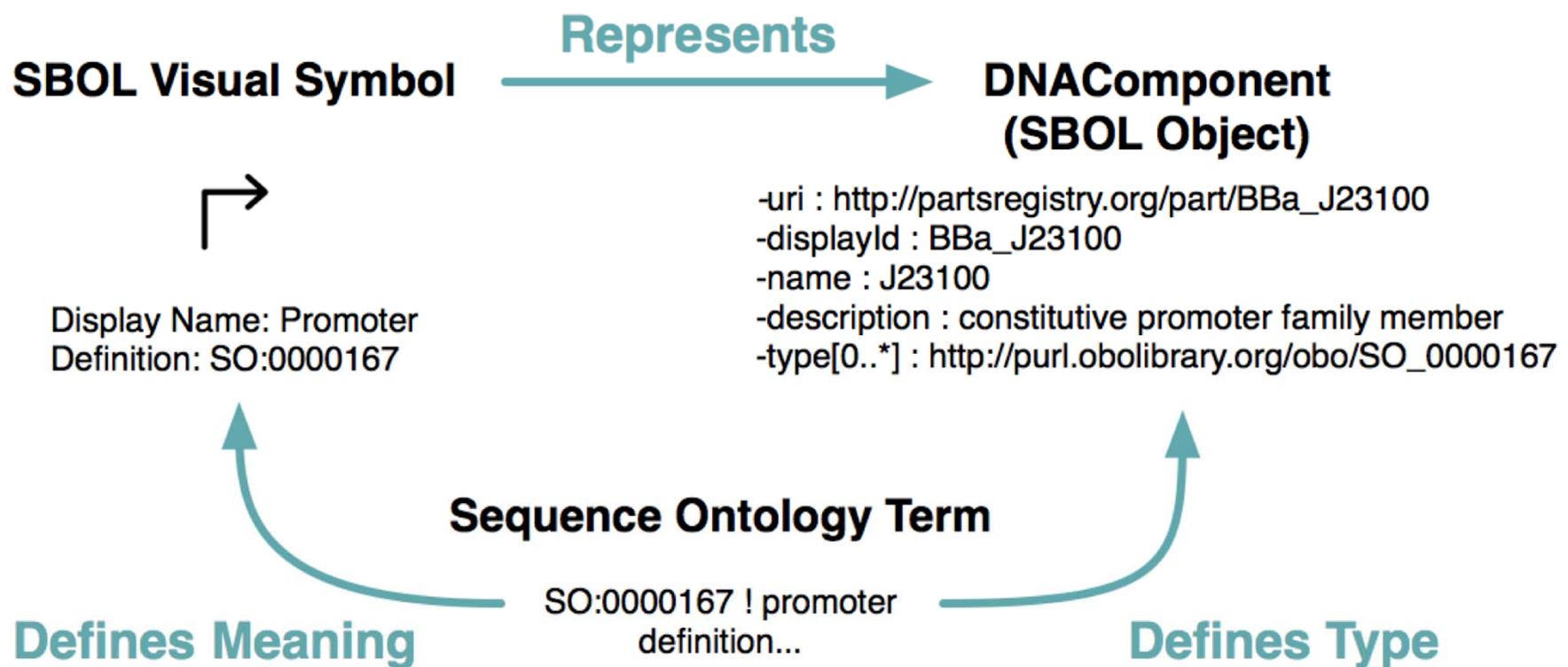
SBOL 2.0 – Current Status

- * Specification document finalised
 - * Available as BBF RFC 108
 - * Available as JIB paper DOI :10.2390/biecoll-jib-2015-272
- * Variety of infrastructure to support SBOL 2.0 tools development
- * 25+ SBOL2.0 tools under already available or under development

SBOL visual

- * Open source graphical notation for SynBio designs
- * SBOL 1 currently, SBOL 2 in progress
- * Spec: DOI 10.1101/1721.1/78349
- * SBOL Visual: A Graphical Language for Genetic Designs. PLOS Biology in press.

↗ promoter	→ primer binding site
□ cds	restriction site
⌇ ribosome entry site] [blunt restriction site
⠑ terminator	⠑⠑ 5' sticky restriction site
□ operator	⠑⠑⠑ 3' sticky restriction site
□ insulator	— 5' overhang
X̄ ribonuclease site	— 3' overhang
Ō rna stability element	= assembly scar
X̄ protease site	⠑⠑ signature
Ō protein stability element	⠑⠑⠑ user defined
○ origin of replication	



Latest developments (selected)



Infrastructure & tools

- * libSBOL
 - * libSBOLJ
 - * libSBOLC
 - * libSBOLScala
 - * sbol.js

 Synthetic Biology Data Exchange
Group
<http://www.sbolstandard.org>

[Filters ▾](#)

libSBOLj Java ★ 12 ⚡ 20
Java Library for Synthetic Biology Open Language (SBOL)
Updated 22 hours ago

libSBOLc C ★ 5 ⚡ 4
Synthetic Biology Open Language (SBOL) C Library
Updated 8 days ago

libSBOLj

- * Facilitates the adoption of SBOL 2.0
- * Document centric
- * With methods for creating, updating, accessing, and removing SBOL objects
- * Supports reading/writing data using RDF/XML, Turtle, and JSON formats.
- * Provides data validation
- * Support for application specific data using
 - * Custom objects
 - * Annotations
- * <https://github.com/SynBioDex/libSBOLj>

Infrastructure - applications

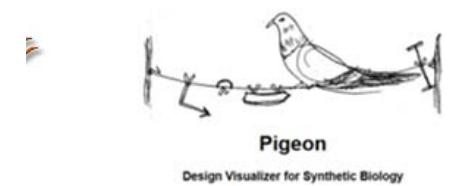


Gene

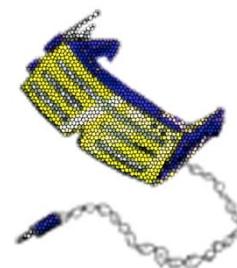
iBio



Software	Type	Visual	Data Model
ICE	Repository	Yes	Yes
SBOL Hub	Repository	No	Yes
GenBank Converter	Helper	No	Yes
MoSeC	Helper	No	Yes
DNAplotlib	Visualization	Yes	Yes
Pigeon	Visualization	Yes	No
VisBOL	Visualization	Yes	Yes
Benchling	DNA Design	No	Yes
DeviceEditor	DNA Design	Yes	Yes
Eugene	DNA Design	Yes	Yes
GeneGenie	DNA Design	No	Yes
GenoCAD	DNA Design	Yes	Yes
SynBad	DNA Design	Yes	Yes
TeselaGen	DNA Design	Yes	Yes
VectorEditor	DNA Design	No	Yes
Cello	Circuit Design	Yes	Yes
iBioSim	Circuit Design	No	Yes
RetroPath	Circuit Design	No	Yes
SBROME	Circuit Design	No	Yes
TinkerCell	Circuit Design	Yes	Yes
BioCompiler	Circuit Design	Yes	Yes
Clotho 3.0	Assembly	Yes	Yes
Raven	Assembly	Yes	No



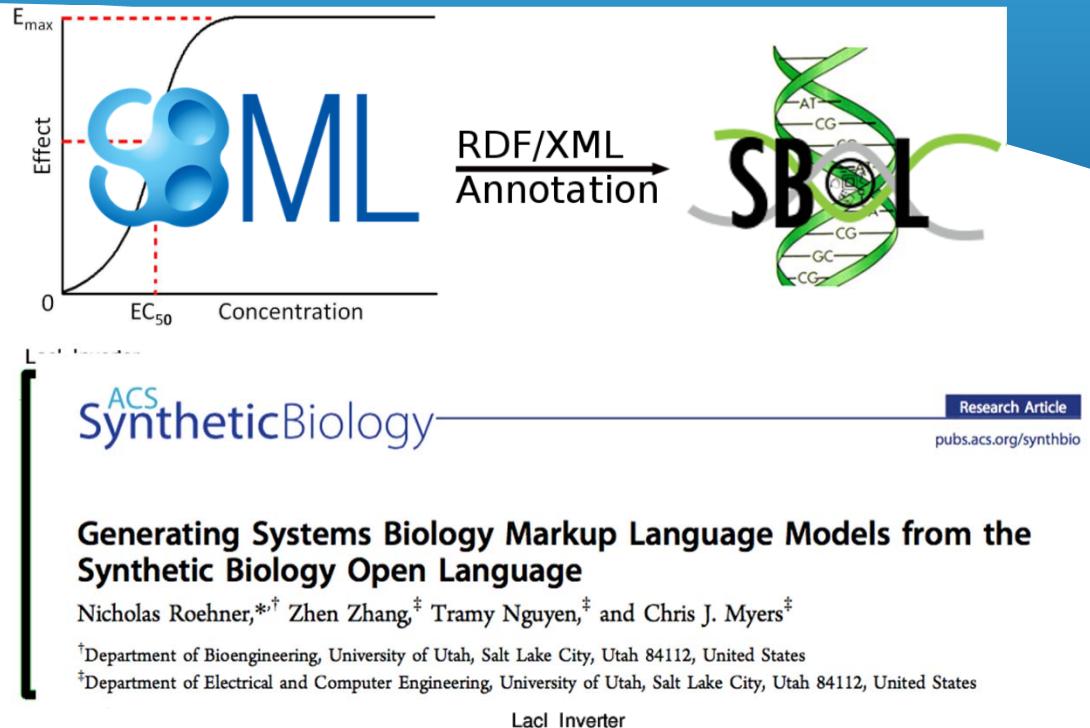
Pigeon
Design Visualizer for Synthetic Biology



DeviceEditor

SBOL and SBML

- * SBOL to SBML and back
- * Misirli et al., (2011)
- * Roehner et al., ACS Synthetic Biology (2013)
- * Roehner et al., ACS Synthetic Biology (2014)
- * Nguyen/Myers, IWBDA (2015)



Generating Systems Biology Markup Language Models from the Synthetic Biology Open Language

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LacI Inverter

A Converter from the Systems Biology Markup Language to the Synthetic Biology Open Language

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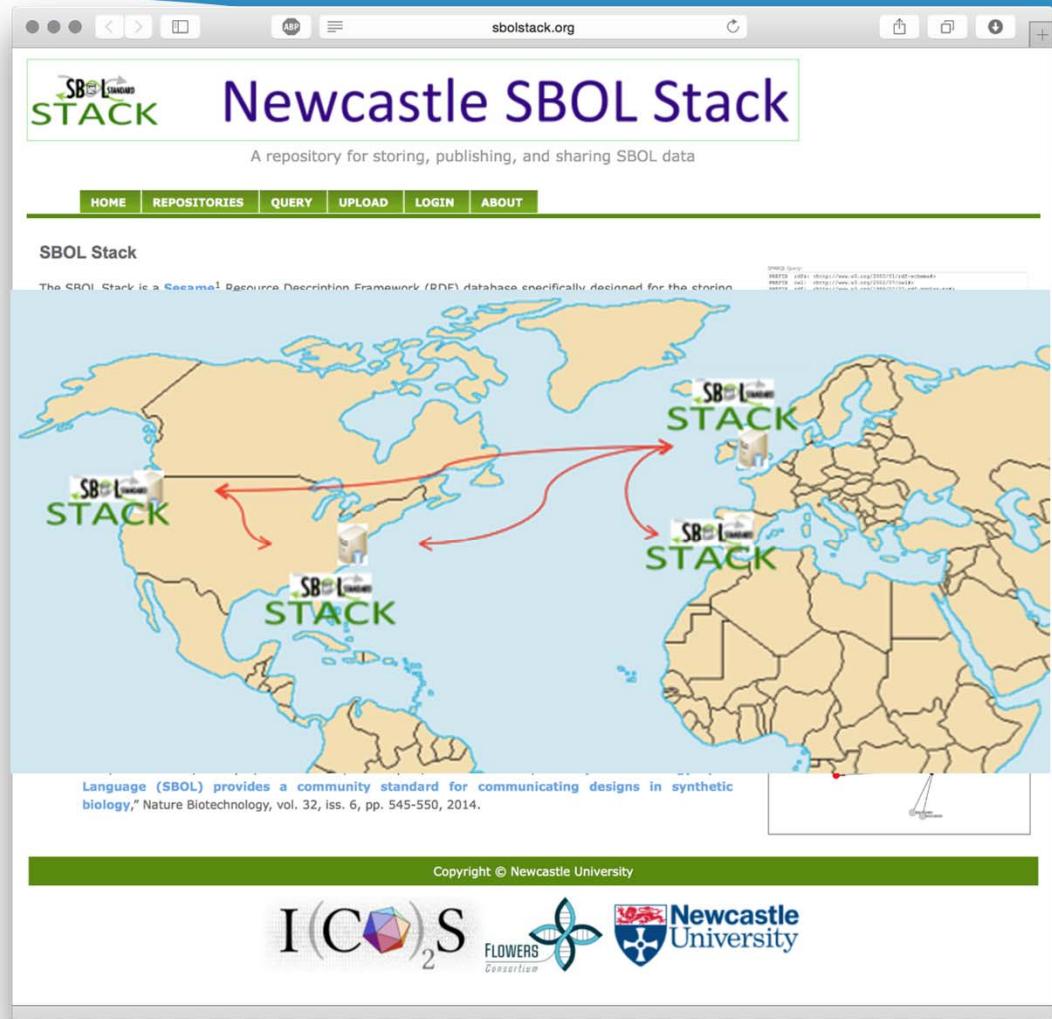


Some Newcastle tools

- * Under development by the ICOS group at Newcastle University
- * See <http://ico2s.org/resources.html>

SBOL Stack

- The SBOL Stack is a RDF database
 - Programmatic access to a warehouse of synthetic parts and designs
 - Sharing SBOL with collaborators
 - Storing designs of biological systems locally
 - Seamless integration across the Internet using Semantic Web
 - sbolstack.org



SBOLhub

- Leverages the data warehouse provided by the SBOL stack to provide a user-facing frontend
- A hub of genetic designs built on open technologies
- Upload, share, visualize, download and fork SBOL designs in the browser
- Launches early November
- To appear at sbolhub.org

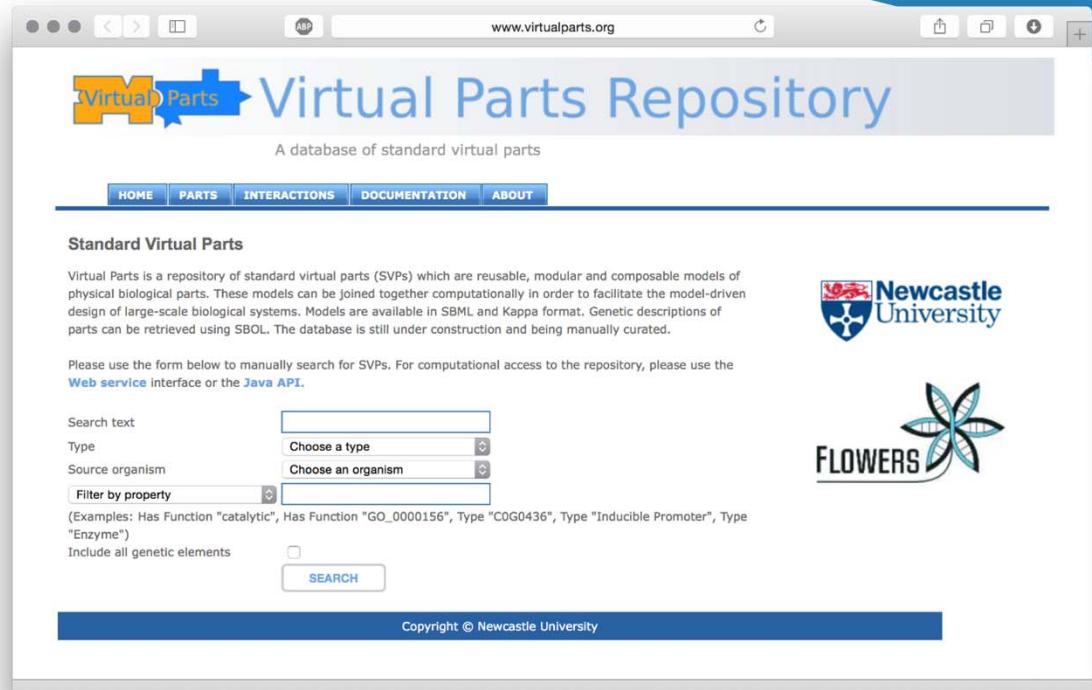
The image displays three separate browser windows showing different parts of the SBOLhub application:

- Top Window:** Shows a "Test Submission" page for a design named "james_test_sbol1_090915121415". The page includes fields for "This is a test" and "test", a note about being applicable to *E. coli*, and buttons for "Download SBOL File", "Edit Record", and "Make Public".
- Middle Window:** Shows a "Design" page for entry T9002. It features a schematic diagram of a genetic circuit with a TetR 1 promoter and a -35 sequence.
- Bottom Window:** Shows a "Private Submissions" page indicating 1 private submission. It lists a "Test Submission" for chassis *E. coli* and provides "Submit to Journal" and "Make Public" options.

All windows have the SBOLhub logo and search bar at the top, and standard browser navigation controls.

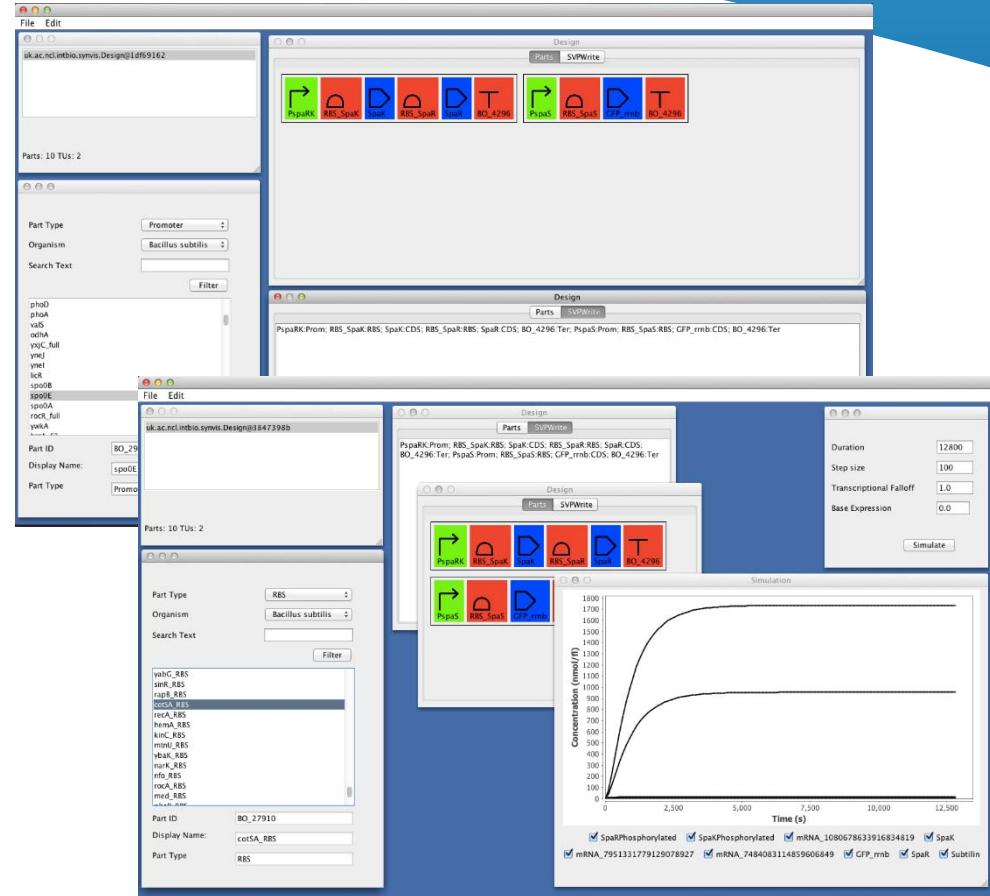
Virtual Parts Repository and SBOL 2.0

- A repository of modular models of genetic parts
 - Allows model based design
 - Simulation
 - API for tool support
 - SBOL2.0 modules with models
 - virtualparts.org



SynBAD

- CAD tool for design of genetic circuits
- Built on standard open source technologies – SVPs, SBML, SBOL2.0, NetBeans Platform
- Manual and automated design
 - Genetic algorithm-based design
- Extensibility through plugins



VisBOL

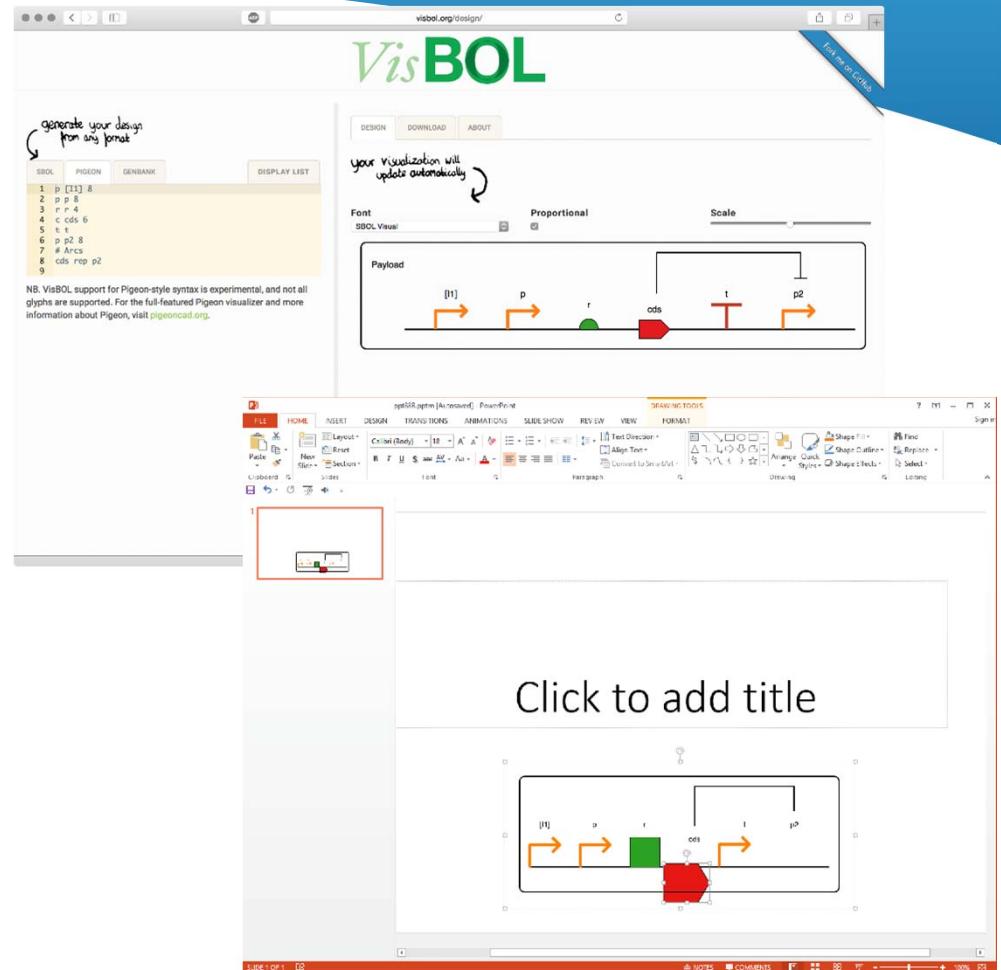
- Open-source Web-based tool for rendering SBOL Visual designs
- Designs can be specified in SBOL2 RDF, Pigeon notation, GenBank, or a JSON display list format
- Rendered live in the Web browser; visualisation updates as you type

The screenshot shows the VisBOL web application at visbol.org/design/. The interface includes a header with the VisBOL logo and a GitHub fork button. Below the header, there are tabs for DESIGN, DOWNLOAD, and ABOUT. The DESIGN tab is selected, showing a "Font" dropdown set to "SBOL_Visual" and a "Scale" slider. A message says "your visualization will update automatically". The main area displays a DNA construct diagram with labels: pLacI, BBa_J61101 RBS, tetR, BBa_J61101 RBS, gfp, and ECK120033738. Below the diagram are two smaller diagrams: "TetR Inverter" and "Laci/TetR Toggle Switch". At the bottom right are the I(C₂)S and Newcastle University logos.

```
<?xml version="1.0"?>
<rdf:RDF xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#>
<sbol:ModuleDefinition rdf:about="http://sbolstandard.org/2.0.0">
<sbol:persistentIdentity rdf:resource="http://sbolstandard.org/2.0.0">
<sbol:displayId>tetr_inverter</sbol:displayId>
<sbol:portList rdf:resource="http://parts.igem.org/gi/ports">
<sbol:FunctionalComponent>
<sbol:FunctionalComponent rdf:about="http://sbolstandard.org/2.0.0">
<sbol:persistentIdentity rdf:resource="http://sbolstandard.org/2.0.0">
<sbol:displayId>promoter</sbol:displayId>
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<sbol:direction rdf:resource="http://sbols.org/v2#in">
</sbol:FunctionalComponent>
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<sbol:persistentIdentity rdf:resource="http://sbolstandard.org/2.0.0">
<sbol:displayId>LocI_plocI</sbol:displayId>
<sbol:type rdf:resource="http://identifiers.org/biomolecular-interaction">
<sbol:access rdf:resource="http://sbols.org/v2#pull">
<sbol:direction rdf:resource="http://sbols.org/v2#in">
<sbol:Participation rdf:about="http://sbolstandard.org/2.0.0">
<sbol:persistentIdentity rdf:resource="http://sbolstandard.org/2.0.0">
<sbol:displayId>Q00072</sbol:displayId>
<sbol:role rdf:resource="http://identifiers.org/biomolecular-participant">
<sbol:participant rdf:resource="http://sbolstandard.org/2.0.0">
<sbol:participation rdf:about="http://sbolstandard.org/2.0.0">
<sbol:persistentIdentity rdf:resource="http://sbolstandard.org/2.0.0">
<sbol:displayId>BBa_R0040</sbol:displayId>
<sbol:role rdf:resource="http://identifiers.org/biomolecular-role">
<sbol:participant rdf:resource="http://sbolstandard.org/2.0.0">
</sbol:Participation>
</sbol:Interaction>
</sbol:Interaction>
</sbol:FunctionalComponent>
</sbol:FunctionalComponent>
</sbol:ModuleDefinition>
</rdf:RDF>
```

VisBOL

- Modular “font” system enables fast prototyping of new visual depictions
- Export designs as SVG or PNG to embed in presentations and publications
- visbol.org/design
- [See James McLaughlin's talk](#)



In the pipeline....

* Coming soon



SBOL Shorthand

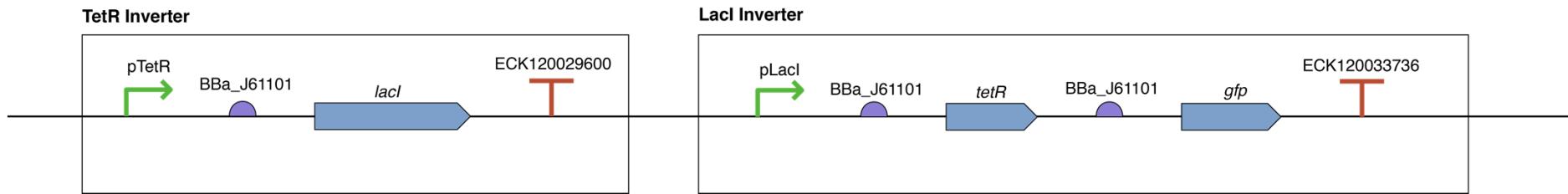
- SBOL RDF/XML is machine language for expressing genetic circuits
- Not easy to read or write for humans
 - Verbose
 - Large footprint
 - Strict syntax
- SBOL Shorthand is a language providing a concise, human-readable way to read and write SBOL documents

```
toggle_switch : ToggleModule
    functionalComponent : public_io
        P03023_protein as LacI
    functionalComponent : public_io
        Q6QR72_protein as TetR

    module
        laci_inverter
            LacI implements TF
    module
        tetr_inverter
            TetR implements TF

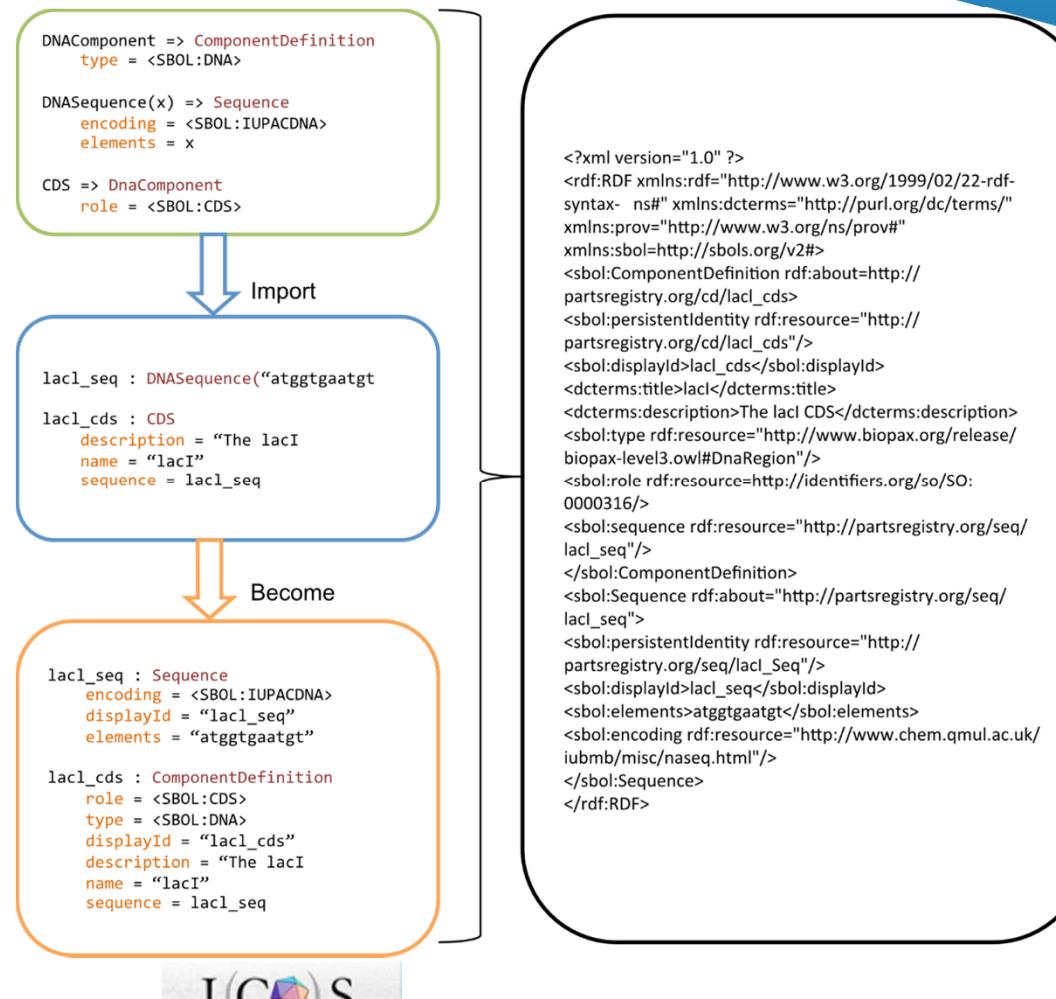
model
    toggleswitch
```

LacI/TetR Toggle Switch



SBOL Shorthand

- Open-source, cross-platform “compiler” produces SBOL RDF/XML from Shorthand files
 - Thus, still readable by machines
- Well-documented, modular, and extensible with new templates



DasBOL

- Access to existing, external data sets as SBOL is important to facilitate data integration in the SBOL ecosystem
- DasBOL canonicalises data into the SBOL standard and provides access through a well-documented RESTful Web API
- ChEBI records, FASTA sequences, Sequence Ontology, and many more to be added
- dasbol.org

The screenshot shows a web browser window with the title 'DasBOL'. The main content area is titled 'ChEBI SBOL' and contains the following text:
The ChEBI dictionary contains thousands of "small" chemicals. This covers all cellular metabolites. We provide a RESTful interface to retrieve SBOL documents for each ChEBI entry. In addition, we provide a number of query methods.
Mapping ChEBI to SBOL
Each ChEBI compound maps to a single ComponentDefinition. A single compound may have any number of associated entities describing the compound's atomic structure, including: formulae, InChI strings, sdf/molfile structures. Any structures or formulae for the compound are mapped to Sequence instances.
The ChEBI mapping makes extensive use of annotations to enrich the SBOL data records. Where ever possible, we have exposed data through annotations using terms from widely-used terminologies. For example, alternative names are attached to the ComponentDefinition for a compound using dcterms:alternative and a reference back to the source ChEBI entry are stored under prov:derivedFrom. If there is data stored in ChEBI that we have not exposed that you would like to use, please let us know and we will modify the export.
RESTful API
The following URL patterns can be accessed through HTTP GET:

http://dasbol.org/chebi/\${number}
The SBOL document exposing the ChEBI compound identified by http://identifiers.org/chebi/CHEBI:\${number}.
Example: <http://dasbol.org/chebi/1606> for 1-methyl-4-imidazoleacetic acid.

http://dasbol.org/chebi?
name=\${string}&exactMatch=\${boolean}&matchCase=\${boolean}
Search for compounds by name.
If exactMatch is true, then only compounds with a name matching the whole of name will be returned. Otherwise, all compounds with name as all or part of any of their names will be returned.
If matchCase is true, then names will be compared in a case-sensitive manner. Otherwise, the compound names will be first converted to lower case and then compared with name.
Example: <http://dasbol.org/chebi?name=1-methyl-4-imidazoleacetic%20acid&exactMatch=true>

ConsBOL

- ConsBOL provides a formal language for constraint-based reasoning about biopolymers
- To formalise description of compositional constraints:
 - Position
 - Length
 - Strand
- Useful addition to the SBOL toolkit
 - Sequence constraints

Index Sequence Constraints
Index Sequence Constraints are built from Allen's interval algebra to describe loci, describe constraints with biopolymer strandedness in mind. To describe constrain

A equals B

This constrains that A and B contain the same start and end positions.

A contains B

Example:

	A	B	Stranded Orientation
A	P	P	A
B	N	N	B
A	P	N	A
B			B

Length Constraints
Length Constraints describe constraints between the lengths of biopolymers.

A same_length_as B

This constrains that the length of A is equal to the length of B

A shorter_than B

length A < length B

A not_longer_than B

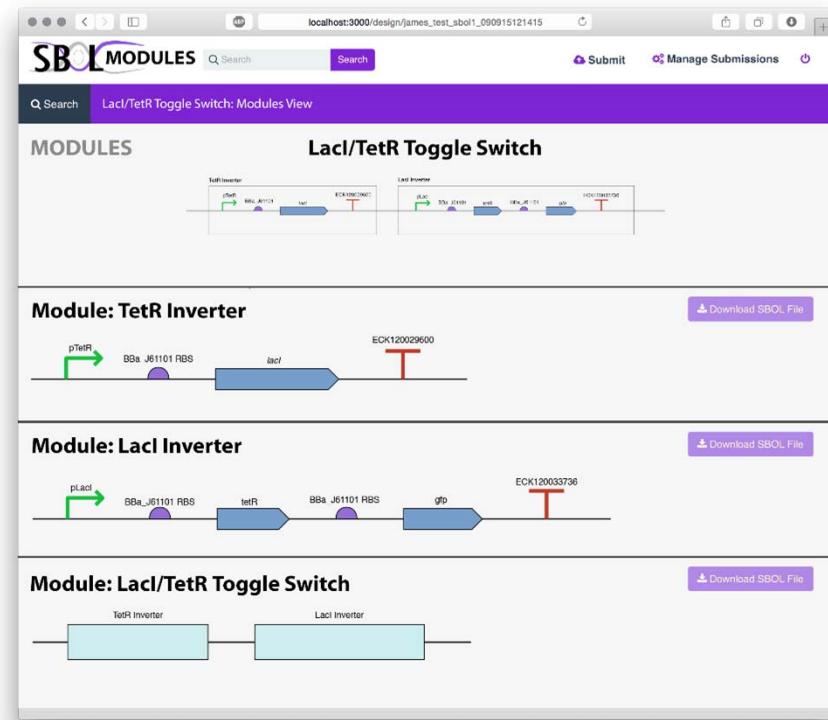
GGTCTTATTTCGA or CGATCATGGTCGC CTT

Topological Sequence Constraints

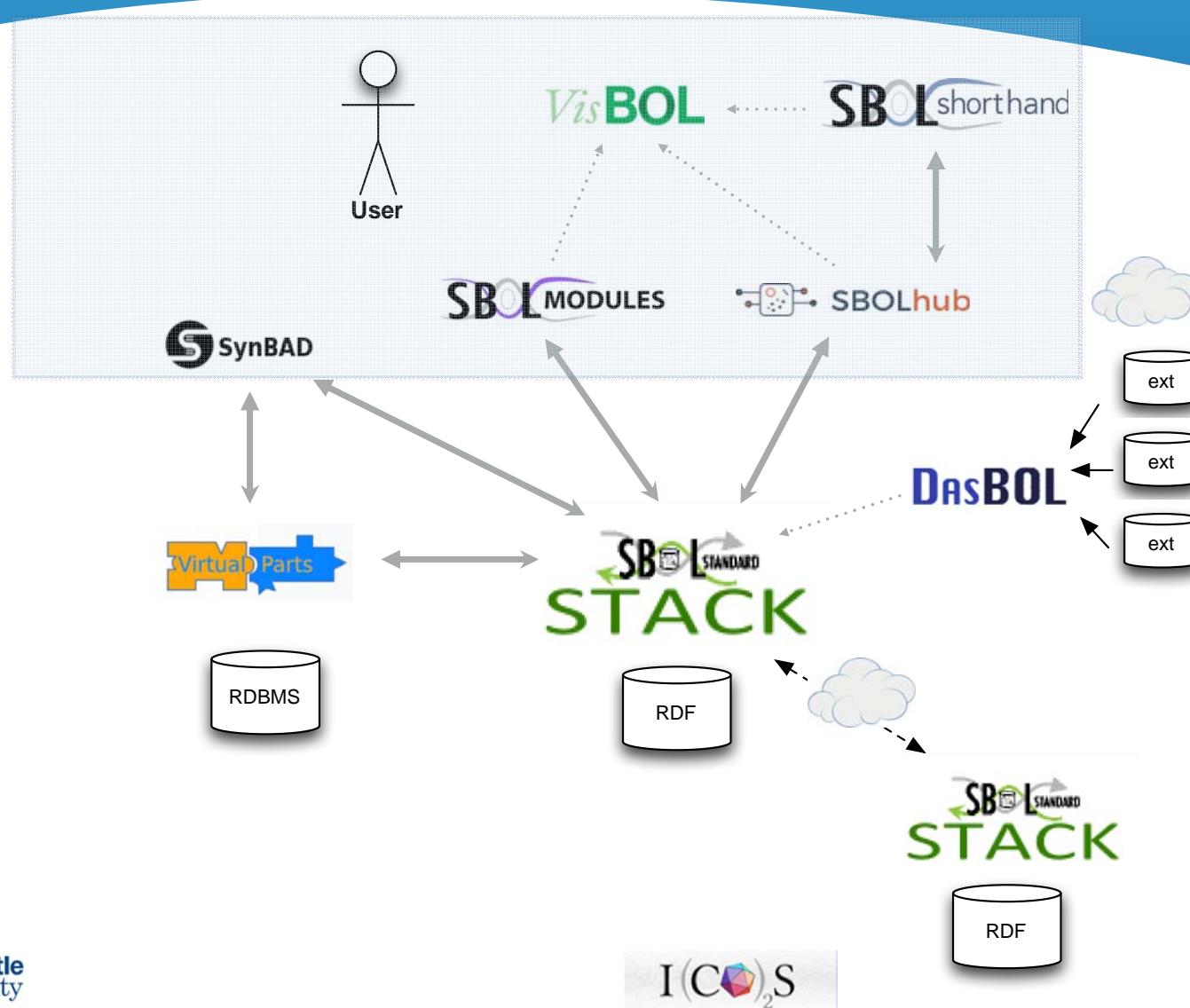
contains
within
equals
contains_suffix
contains_prefix
joins_directly
joins_with_gap

SynBioMod

- * A database of SBOL modules
- * A view over the SBOL stack and the VPR
- * SBOL 2.0 modules can be composed
- * Attached models can also be composed

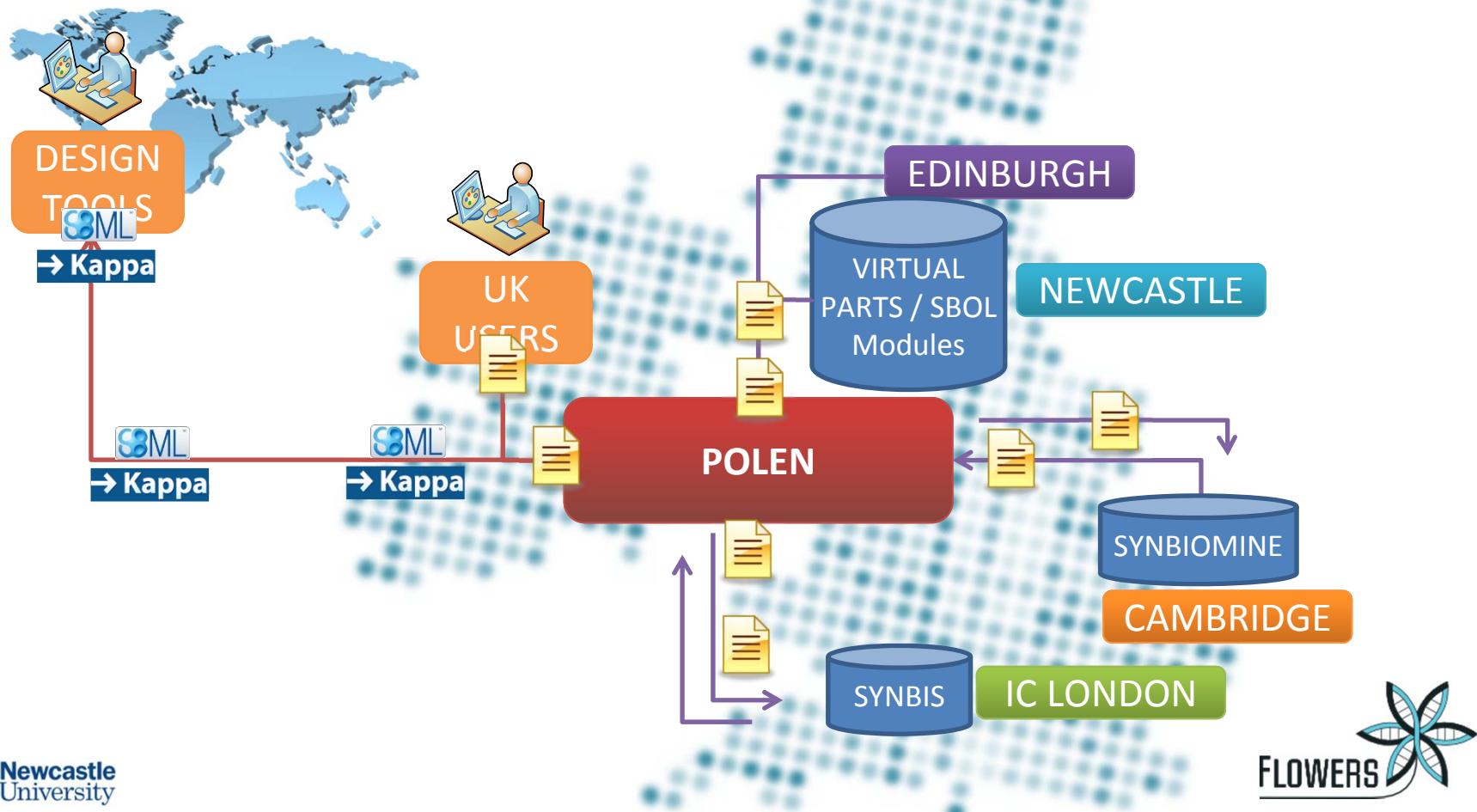


Inter-Relationship between NCL tools



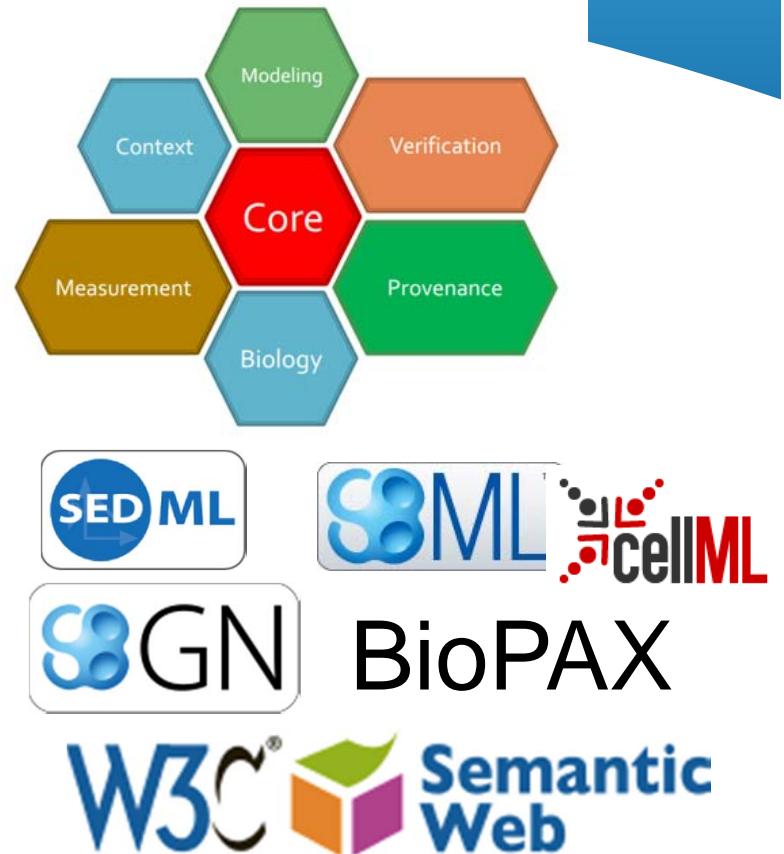
Synthetic Biology Workflows in the Cloud

Microbase
<http://www.microbasecloud.com/>



SBOL Research challenges

- * Development of extensions using annotations
- * Interface to other standards
- * Data integration and mining
- * Visualisation
- * Exploiting modularity and hierarchical composition
- * Genetic design automation
- * Model-based design
- * Distributed Workflows
- *



Conclusions

- * SBOL 2.0 finalised, Spec and papers out
- * SBOL 2.0 offers support for generalized components, interactions and modular design
- * Supportive infrastructure under development
 - * libSBOLj etc.
- * SBOL aims to support the entire SynBio workflow
- * SBOL connects to other relevant standards via Combine

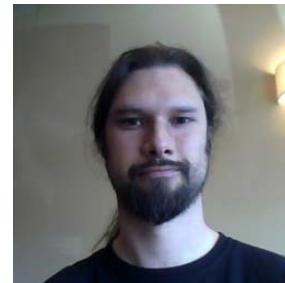
Acknowledgements - NCL



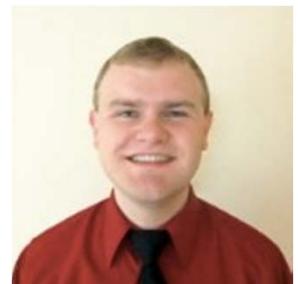
Dr Jennifer Hallinan



James McLaughlin



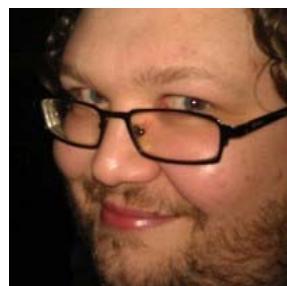
Dr Matthew Pocock



Dr Curtis Madsen



Laurence Orr



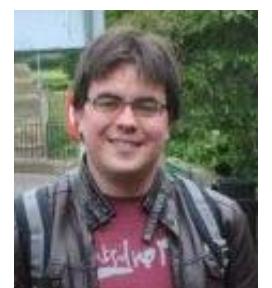
Owen Gilfellon



Goksel Misirli



Chris Taylor

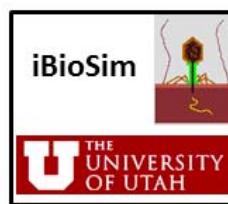
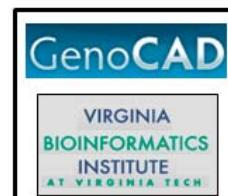


Dr Keith Flanagan

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BBN Technologies



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