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

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COMBINE

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Systems Biology Markup Language

- The *Systems Biology Markup Language* (SBML) is a standard for behavioral models of biological systems.
- SBML models biological systems at the molecular level.
- A typical SBML model is composed of a number of chemical *species* (i.e., proteins, genes, etc.) and *reactions* that transform these species.
- SBML is supported by more than 280 tools, enabling researchers to create, annotate, simulate, and visualize models.
- SBML models can also be archived in the BioModels database.

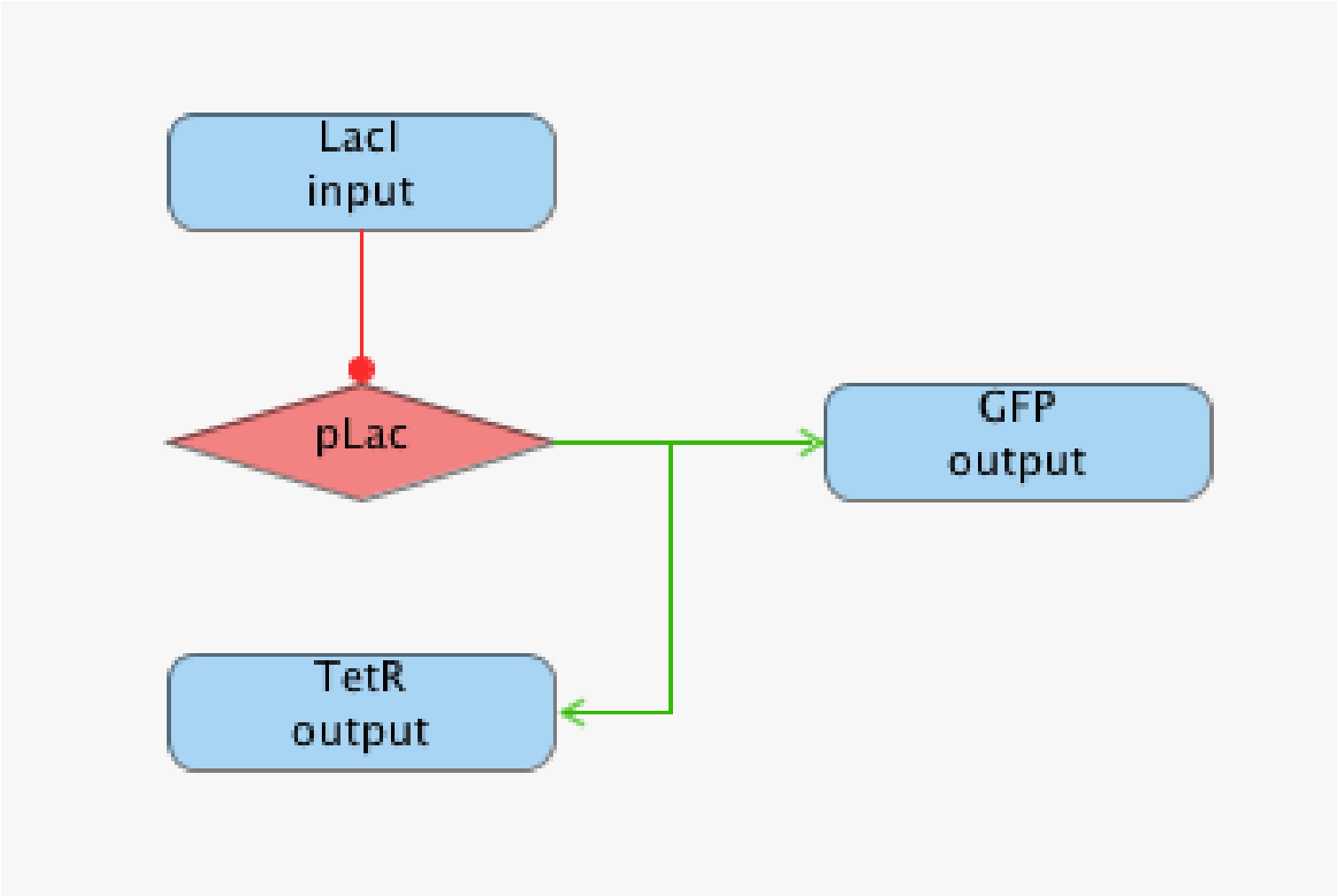
Synthetic Biology Open Language

- The *Synthetic Biology Open Language* (SBOL) describes structural and basic qualitative behavioral aspects of a biological design.
- Version 1.1 specifies the hierarchical composition of *DNA components*.
- Version 2.0 adds generalized *components*, *interactions* between them, and *modules* for hierarchically describing genetic designs.
- SBOL is supported by about 20 tools.
- SBOL data can be archived in several repositories (iGEM, SBPkb, JBEI ICE, SBOL Stack, VirtualParts, etc.).

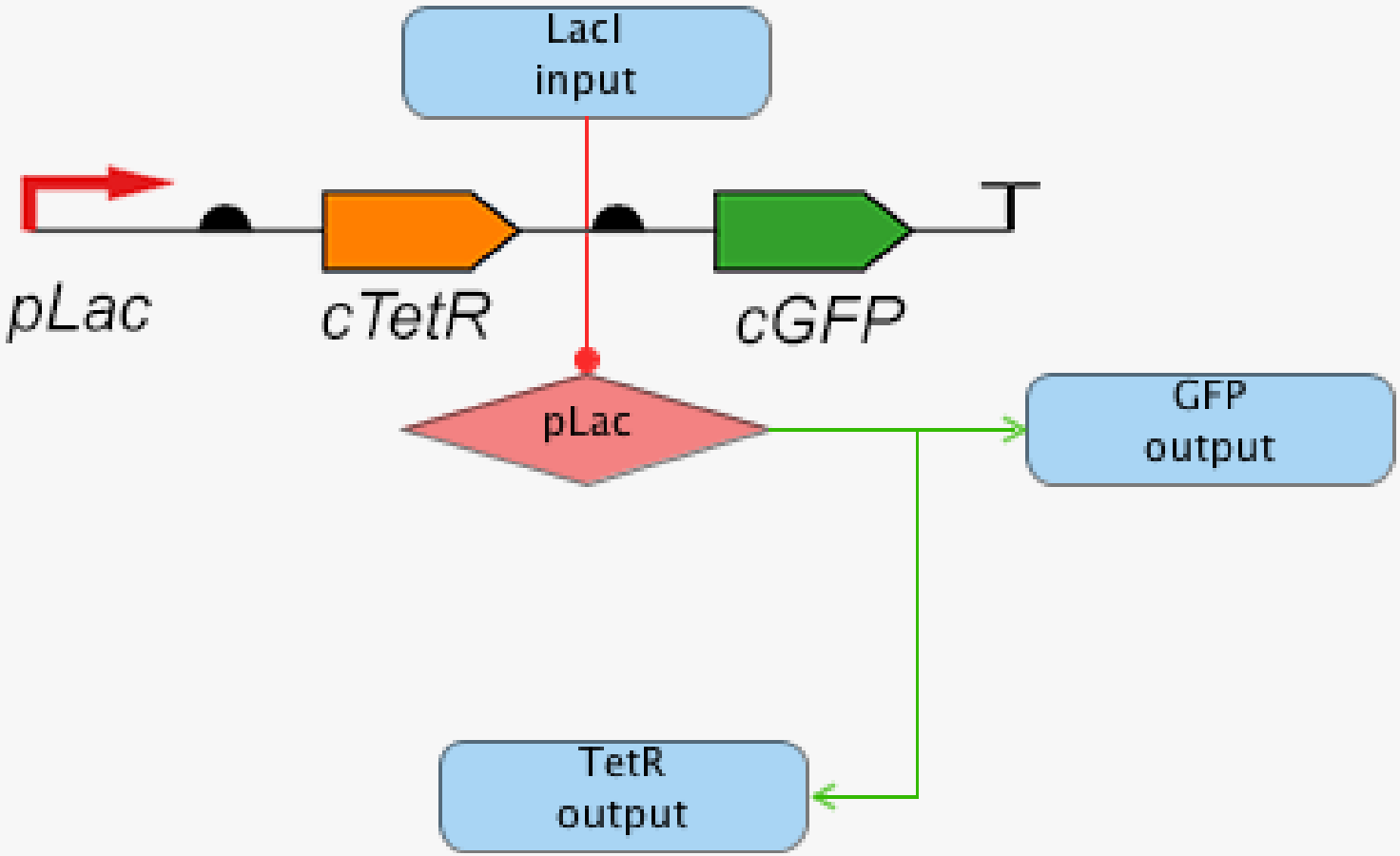
Converter from SBML and SBOL

- Standards are important because they enable exchange and reproducibility of genetic designs.
- Converting SBML to SBOL enables a consistent connection between behavioral and structural information about a biological design.
- Previously, a converter from SBOL to annotated SBML models has been developed (Roehner et al., *ACS Synthetic Biology* 2015).
- This new converter takes an SBML model with annotations using the *Systems Biology Ontology* (SBO), and it infers the structure and qualitative function to produce an SBOL data file.

Example: LacI Inverter



Example: LacI Inverter with SBOL Annotations

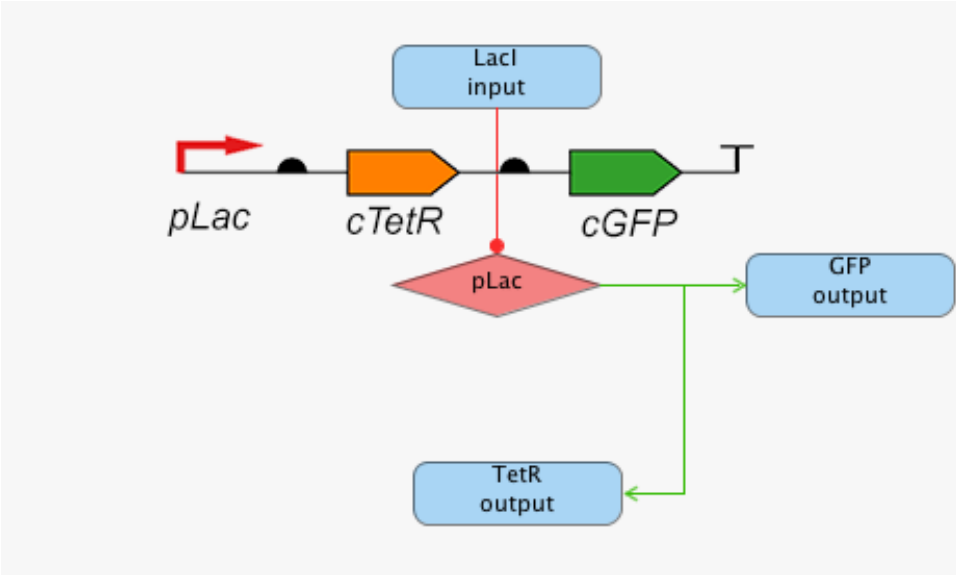


Roehner et al., *ACS Synthetic Biology* 2013

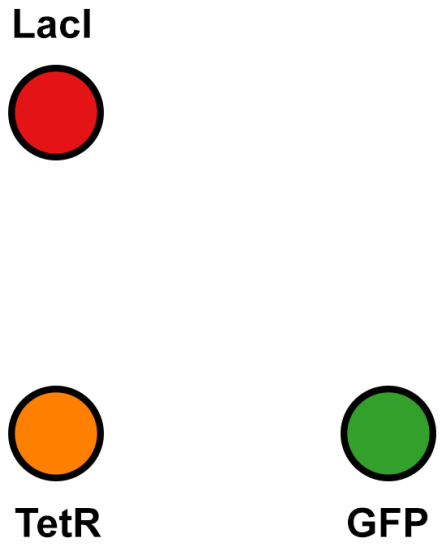
Converting Species to ComponentDefinition

- An SBOL **ComponentDefinition** is created for each **species** which is not already annotated with a **ComponentDefinition**.
- The **type** for the **ComponentDefinition** can be DNA, protein, small molecule, etc. which is inferred from the SBO term associated with the **species**.

ComponentDefinitions for the LacI Inverter



SBML

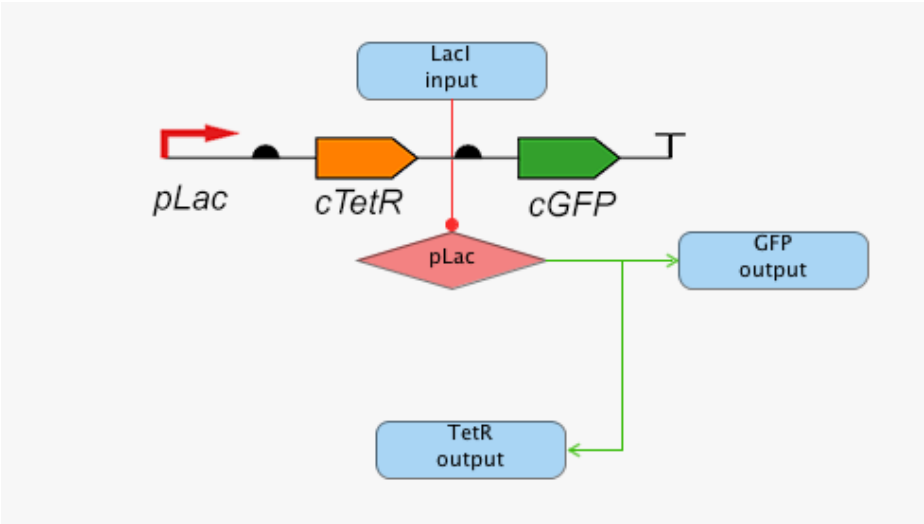


SBOL

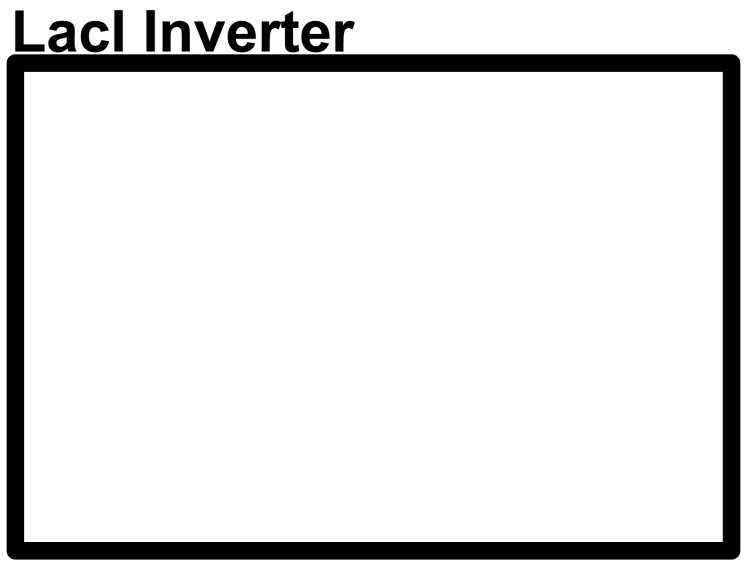
Converting SBML Models to ModuleDefinitions

- All **models** referenced within a top level SBML **model** are converted to an SBOL **ModuleDefinition**.
- For each **ModuleDefinition**, an SBOL **Model** is created that will reference its SBML **model**.

ModuleDefinitions for the LacI Inverter

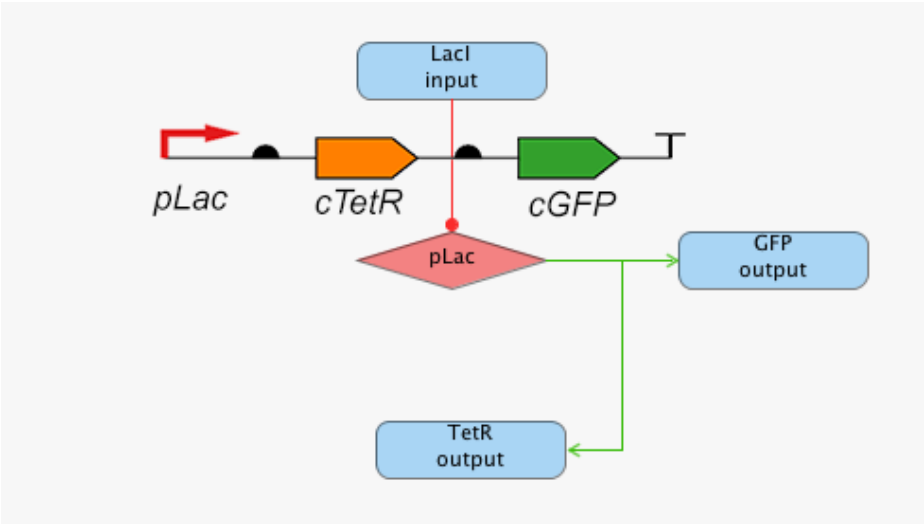


SBML

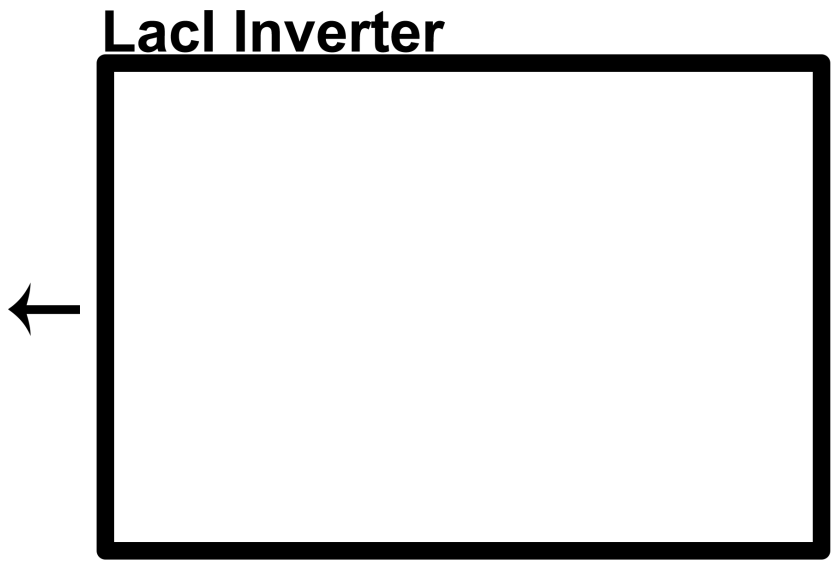


SBOL

Model for the LacI Inverter



SBML

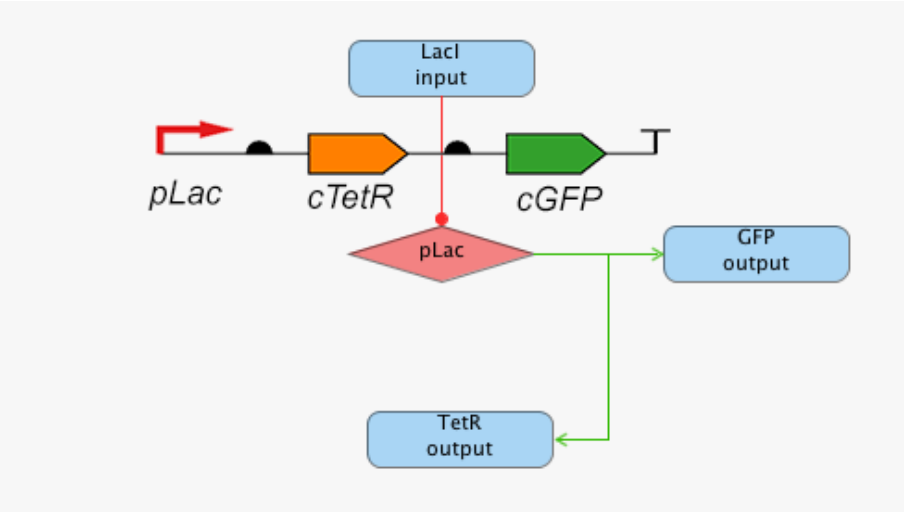


SBOL

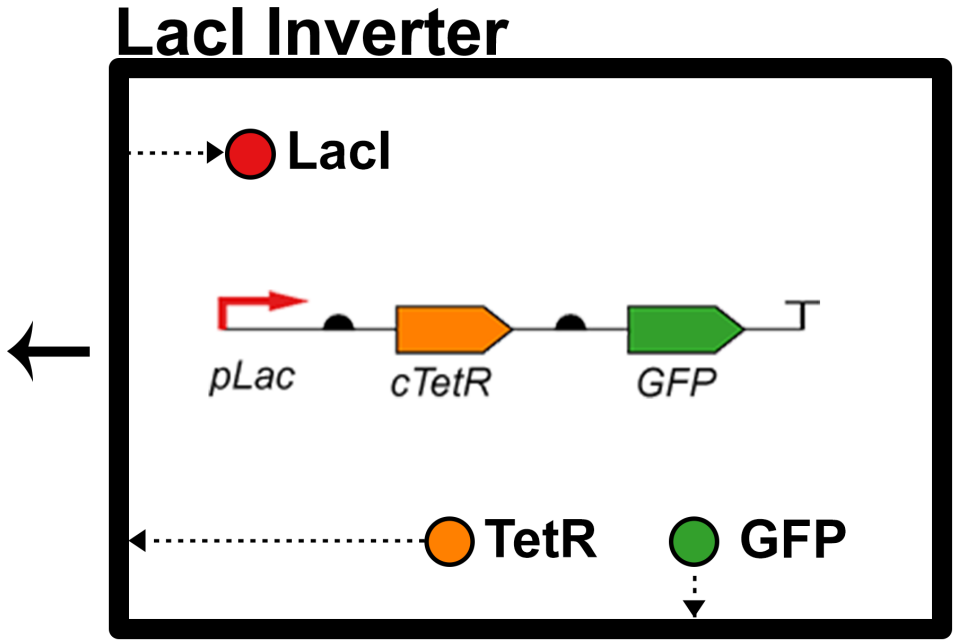
Converting Species to FunctionalComponents

- A **FunctionalComponent** is created within the **ModuleDefinition** for each **species** used in the corresponding SBML **model**.
- A **FunctionalComponent** contains a **definition** that references the corresponding **ComponentDefinition** for the **species**.
- A **FunctionalComponent** is also given a **direction**: an **in**, **out**, or **none**.
- The **direction** is inferred from SBO terms on the SBML **ports** referencing the corresponding species.
- If a **FunctionalComponent** has an **in** or **out direction**, it is given a **public accessType**.

FunctionalComponents for the LacI Inverter



SBML



SBOL

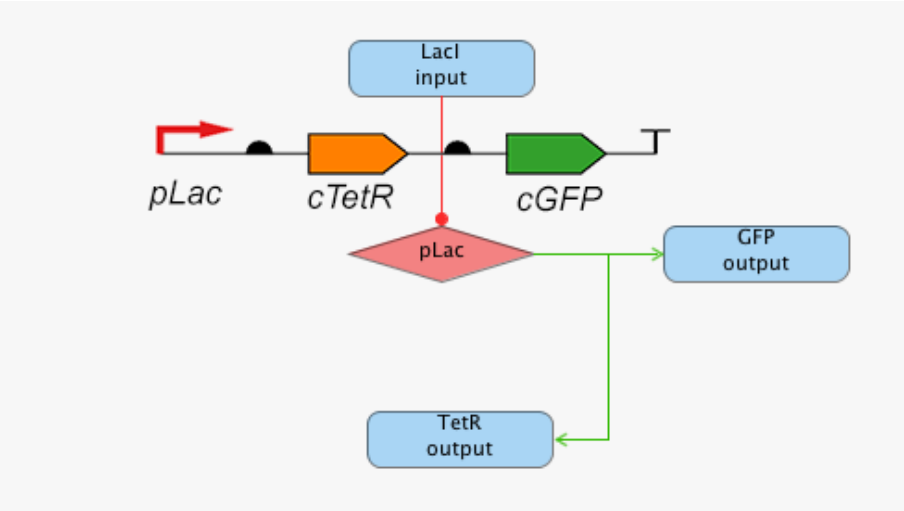
Converting Reactions to Interactions

- Each SBML **reaction** is converted into an SBOL **Interaction(s)**.
- **Interactions** are used for functional relationship between the **reactants**, **products**, and **modifiers** of the **reactions**.
- Depending on what type of SBML **reaction** (inferred by its SBO term), one or more SBOL **Interaction(s)** are created between the corresponding **FunctionalComponents**.

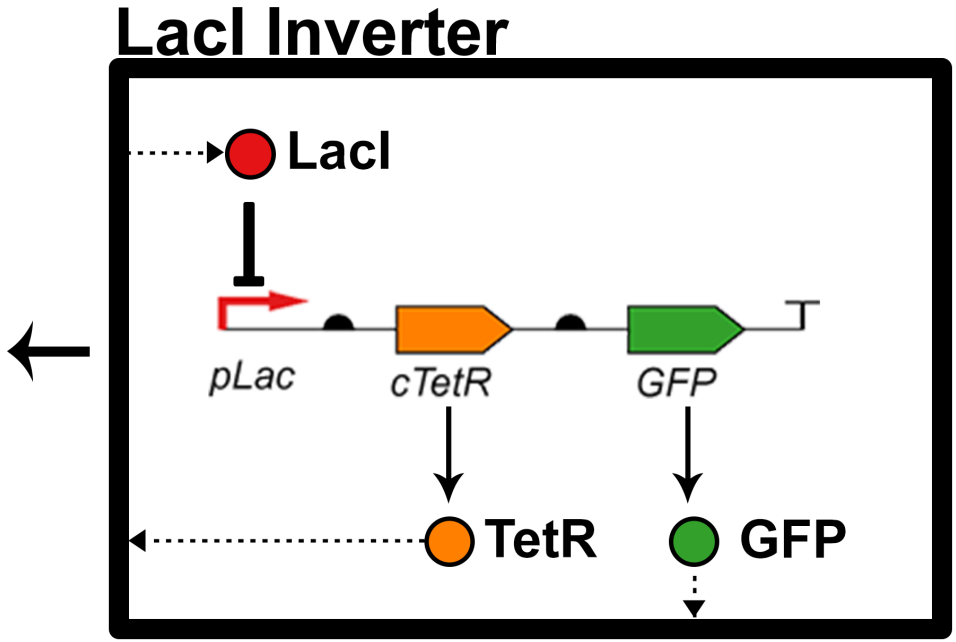
Converting Different Reactions to Interactions

- *Genetic production reaction* creates an **Interaction** for each activator or inhibitor and the promoter, and it creates one production **Interaction** for each promoter with its products.
- *Complex formation reaction* results in an **Interaction** that includes the separate proteins as reactants and the complex as a product.
- A *degradation reaction* includes the degraded protein as a **Participant**.
- For an *ordinary chemical reaction*, an **Interaction** is created that includes all reactants, products, and modifiers as **Participants**.

Interactions for the LacI Inverter

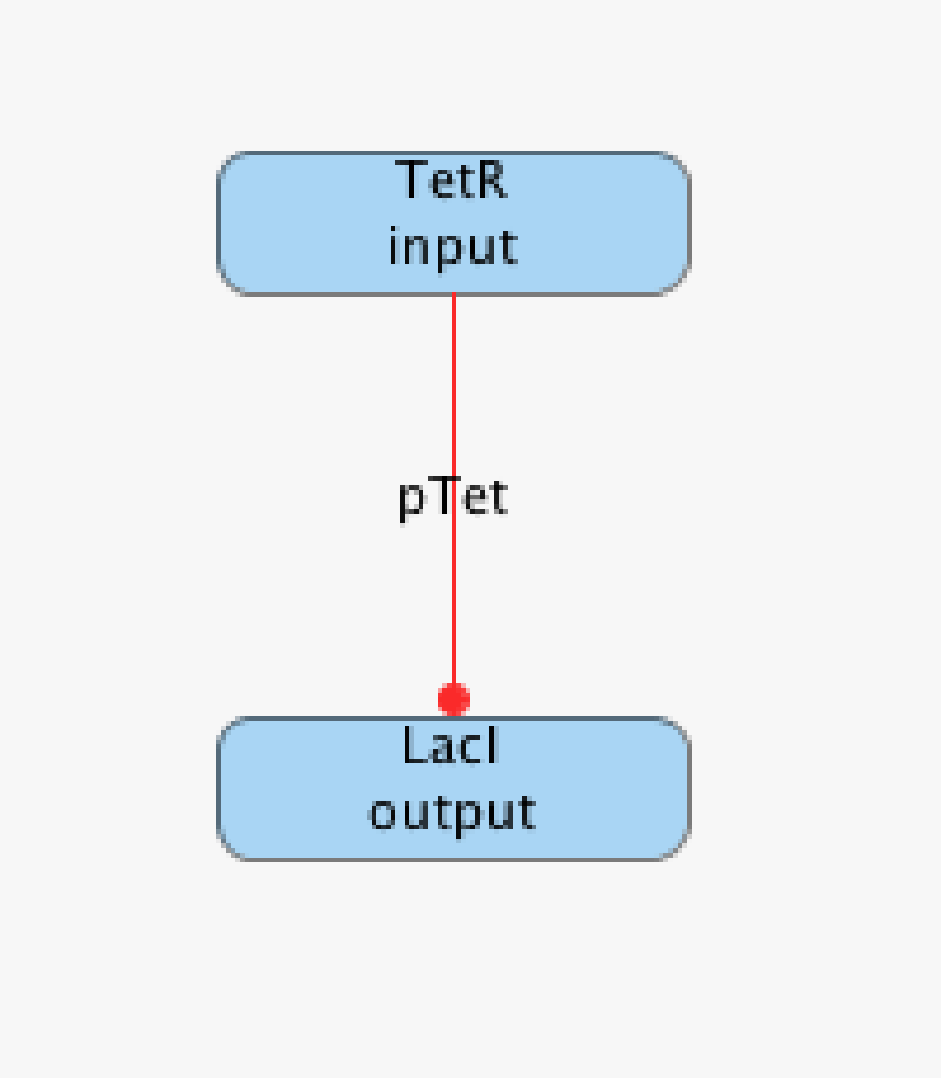


SBML

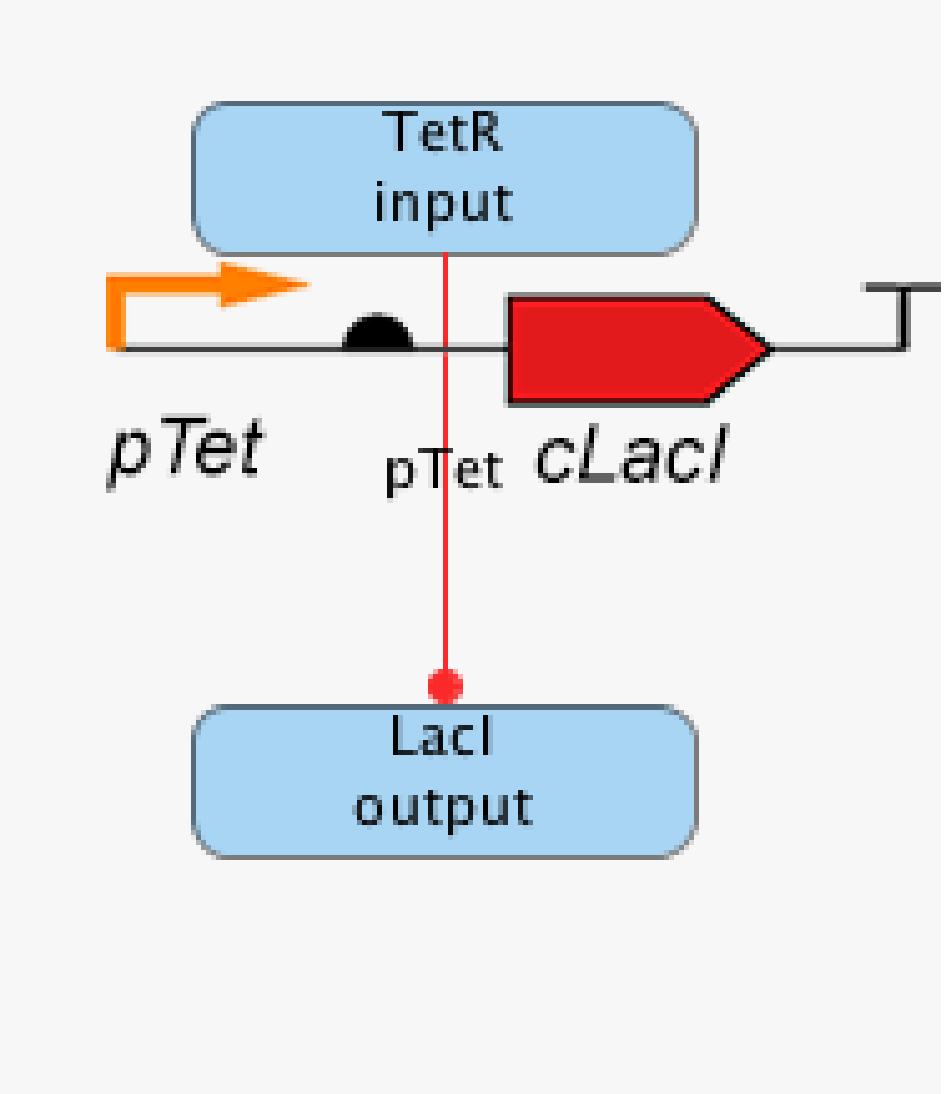


SBOL

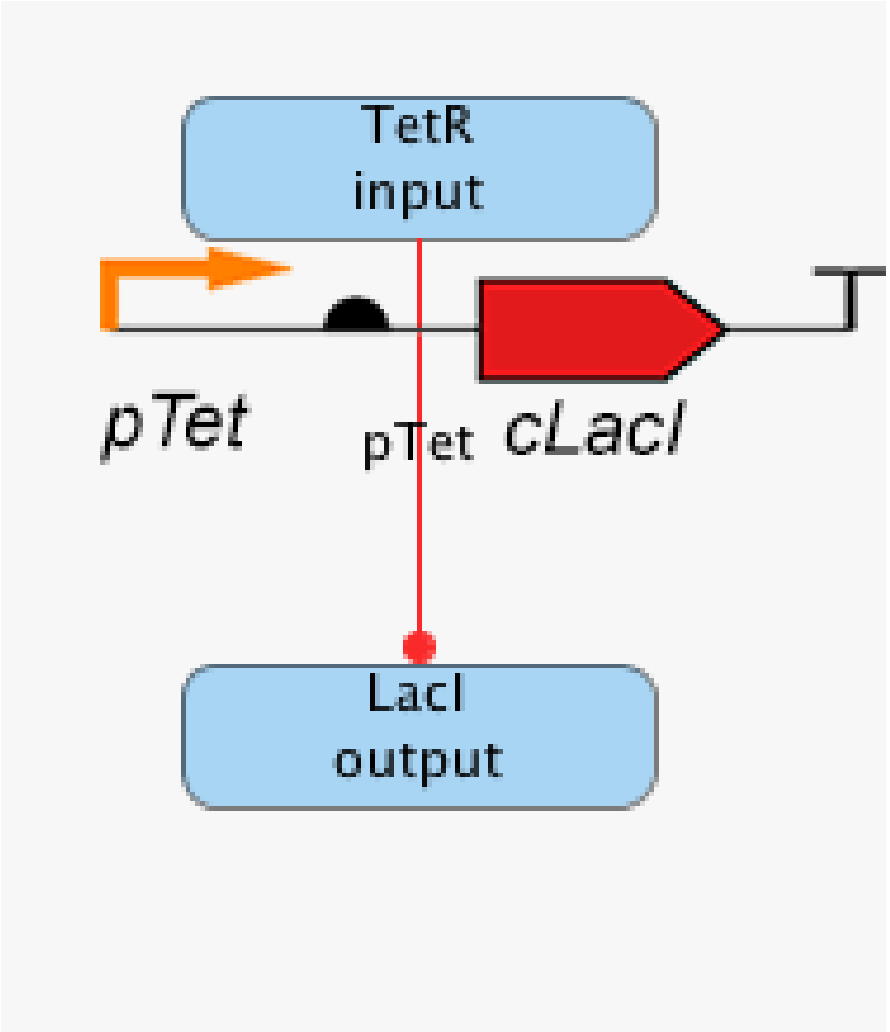
Example: TetR Inverter



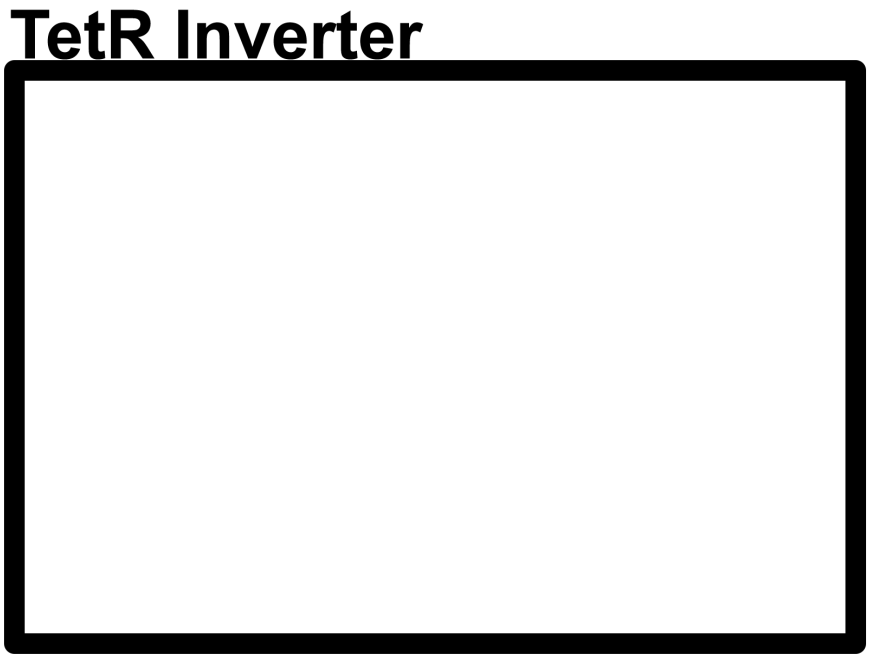
Example: TetR Inverter with SBOL Annotations



ModuleDefinitions for TetR Inverter

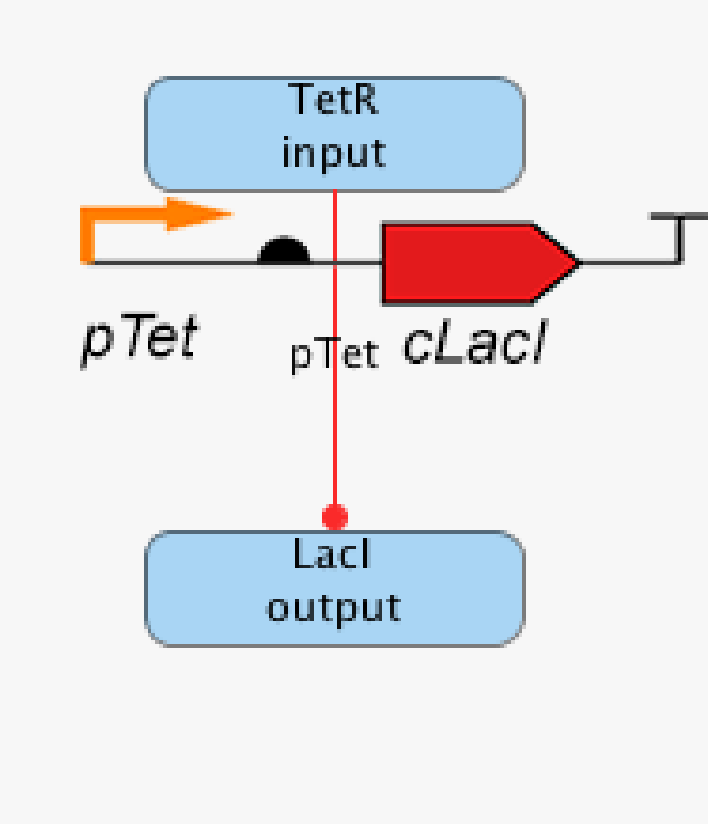


SBML

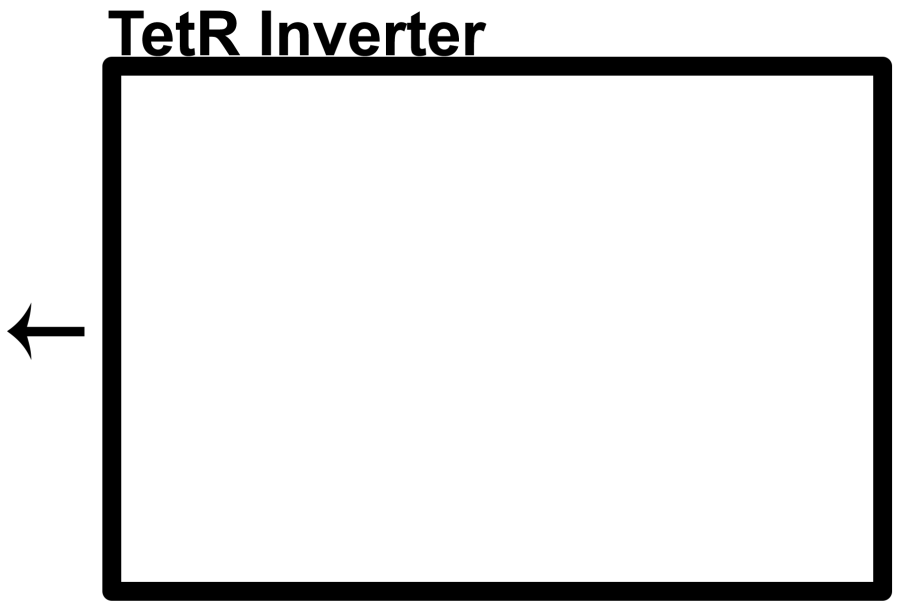


SBOL

Model for TetR Inverter

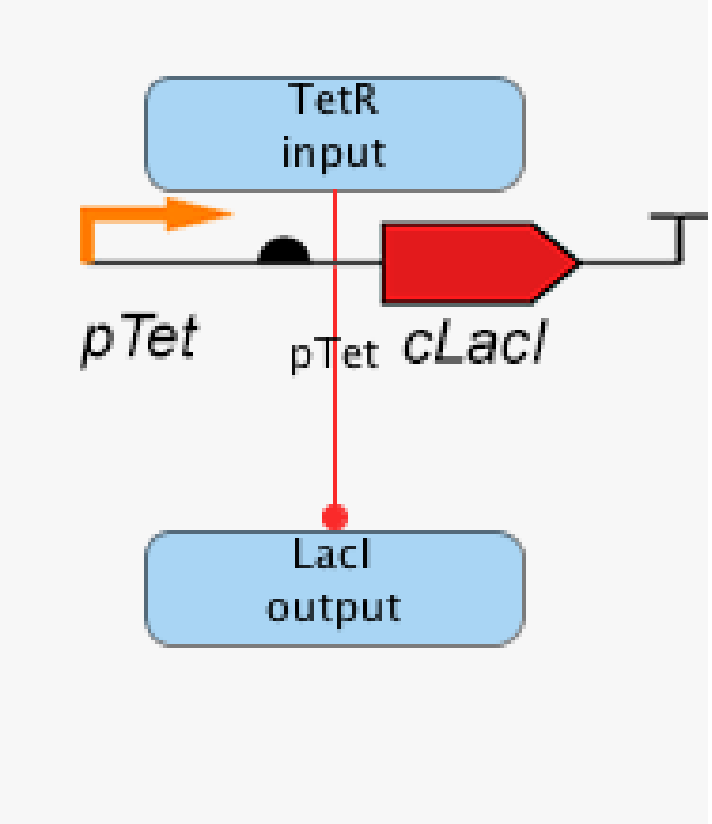


SBML

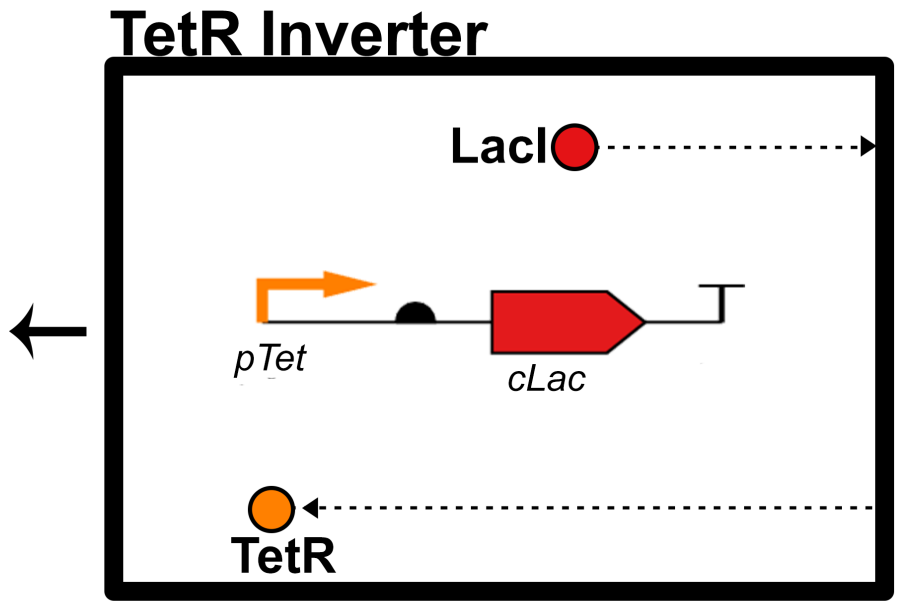


SBOL

FunctionalComponents for the TetR Inverter

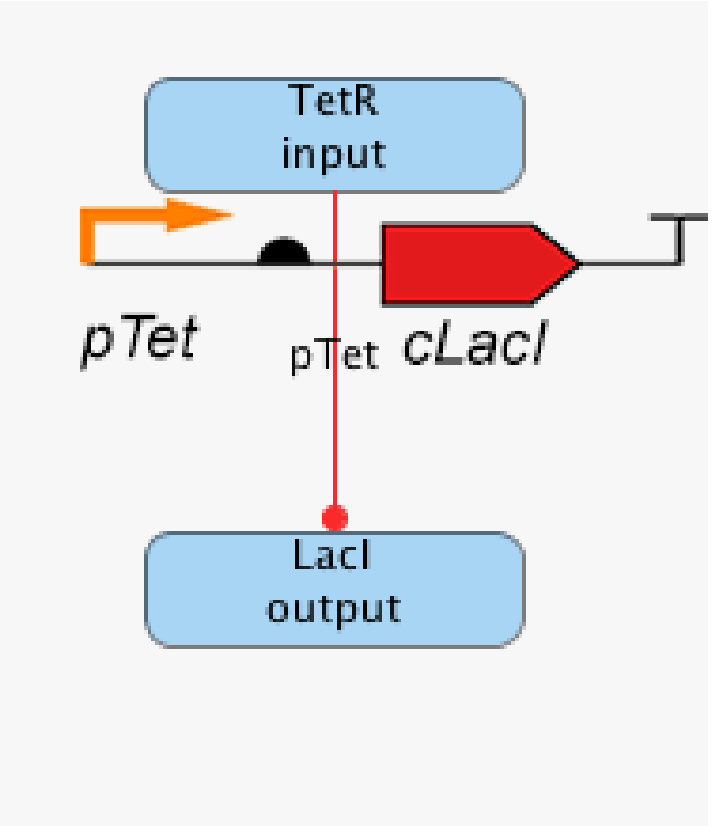


SBML

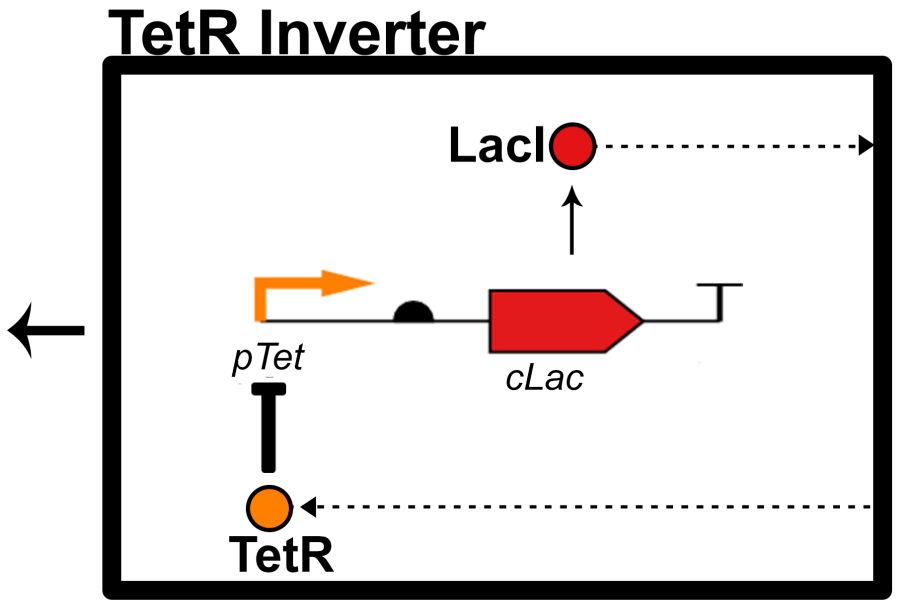


SBOL

Interactions for the TetR Inverter

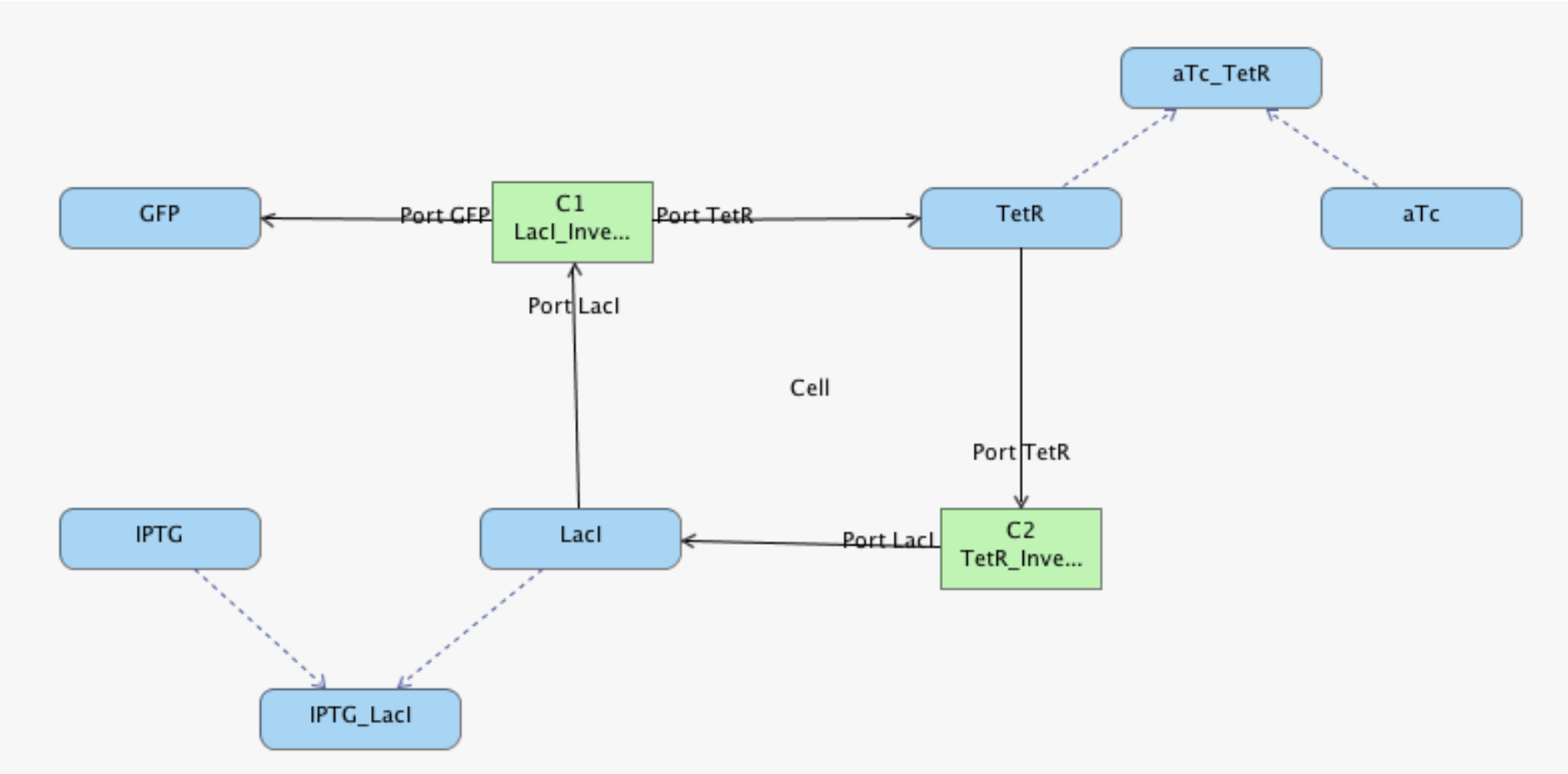


SBML

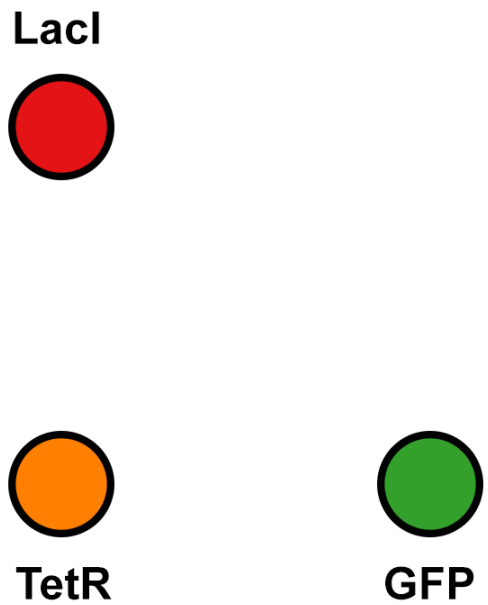


SBOL

Example: Genetic Toggle Switch

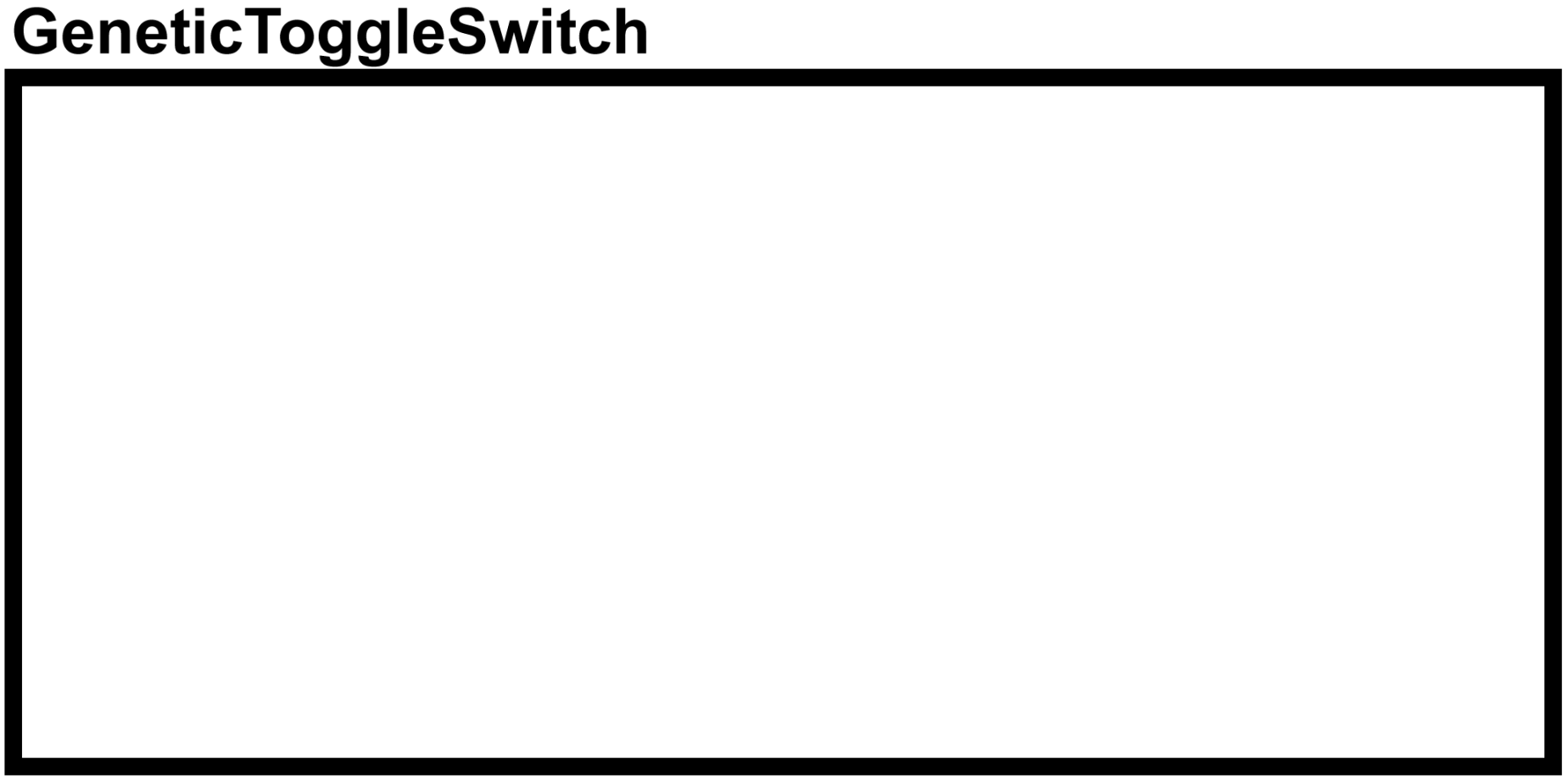


ComponentDefinitions for the Genetic Toggle Switch

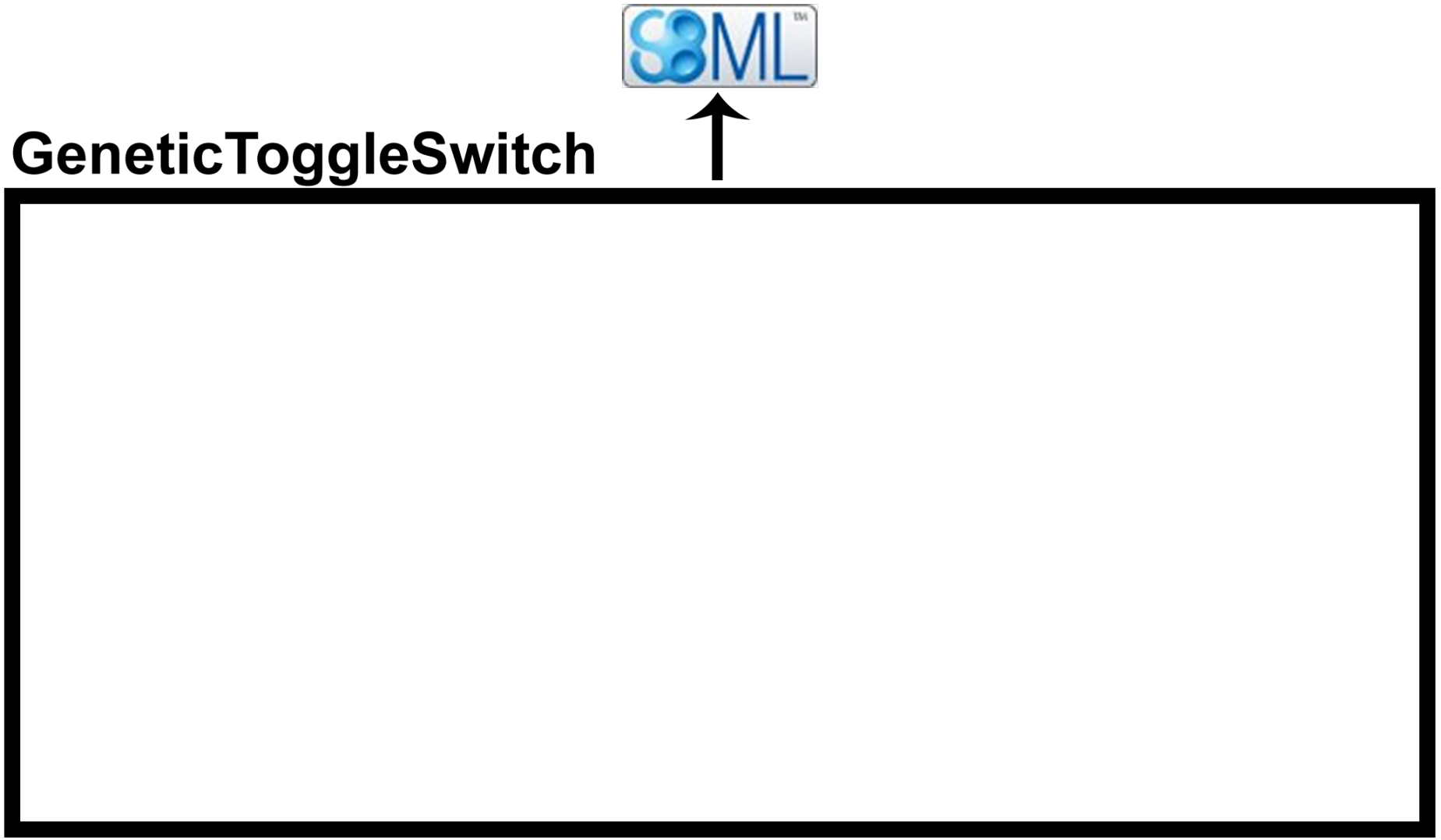


ComponentDefinitions for the Genetic Toggle Switch

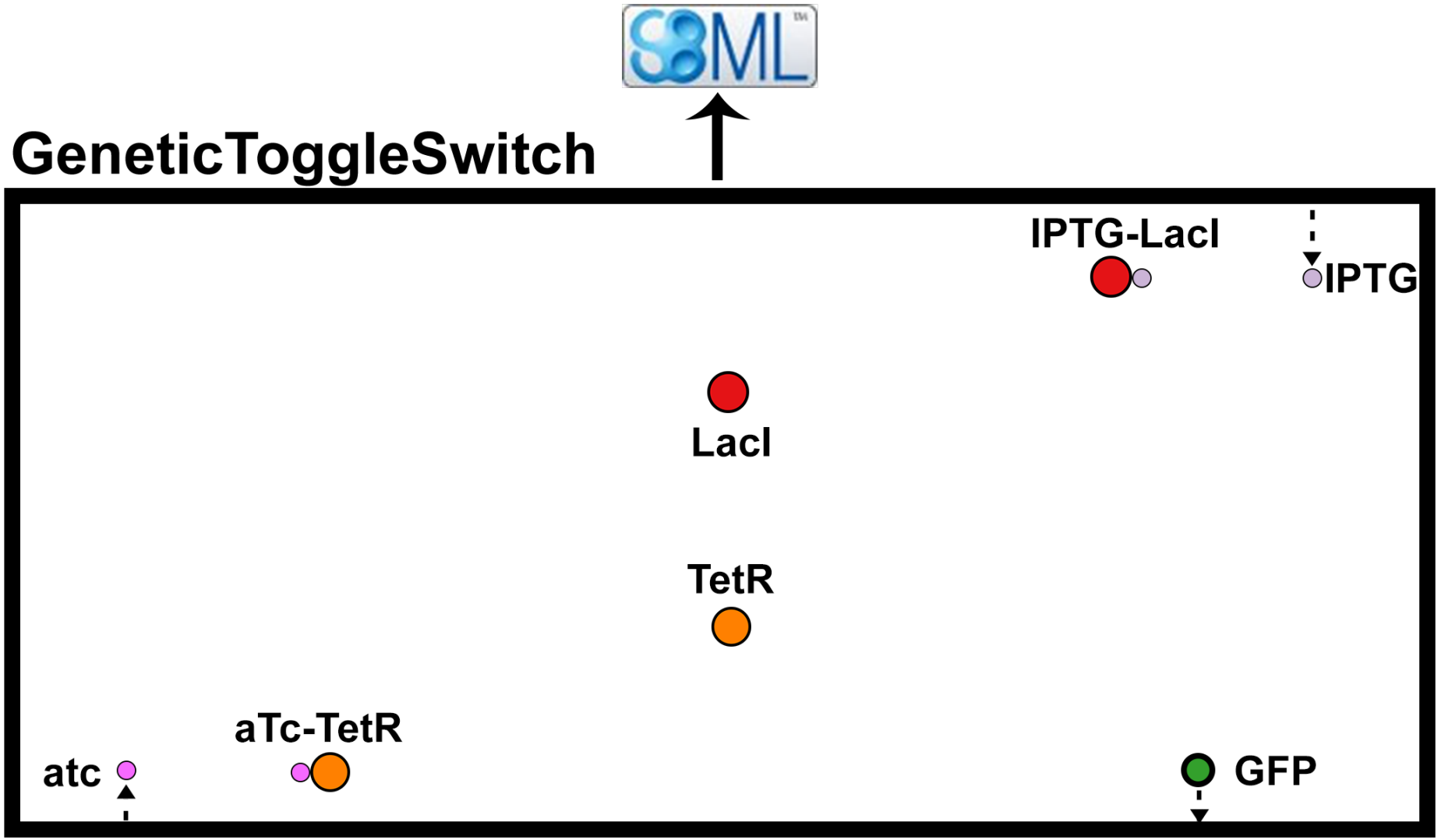
ModuleDefinition for the Genetic Toggle Switch



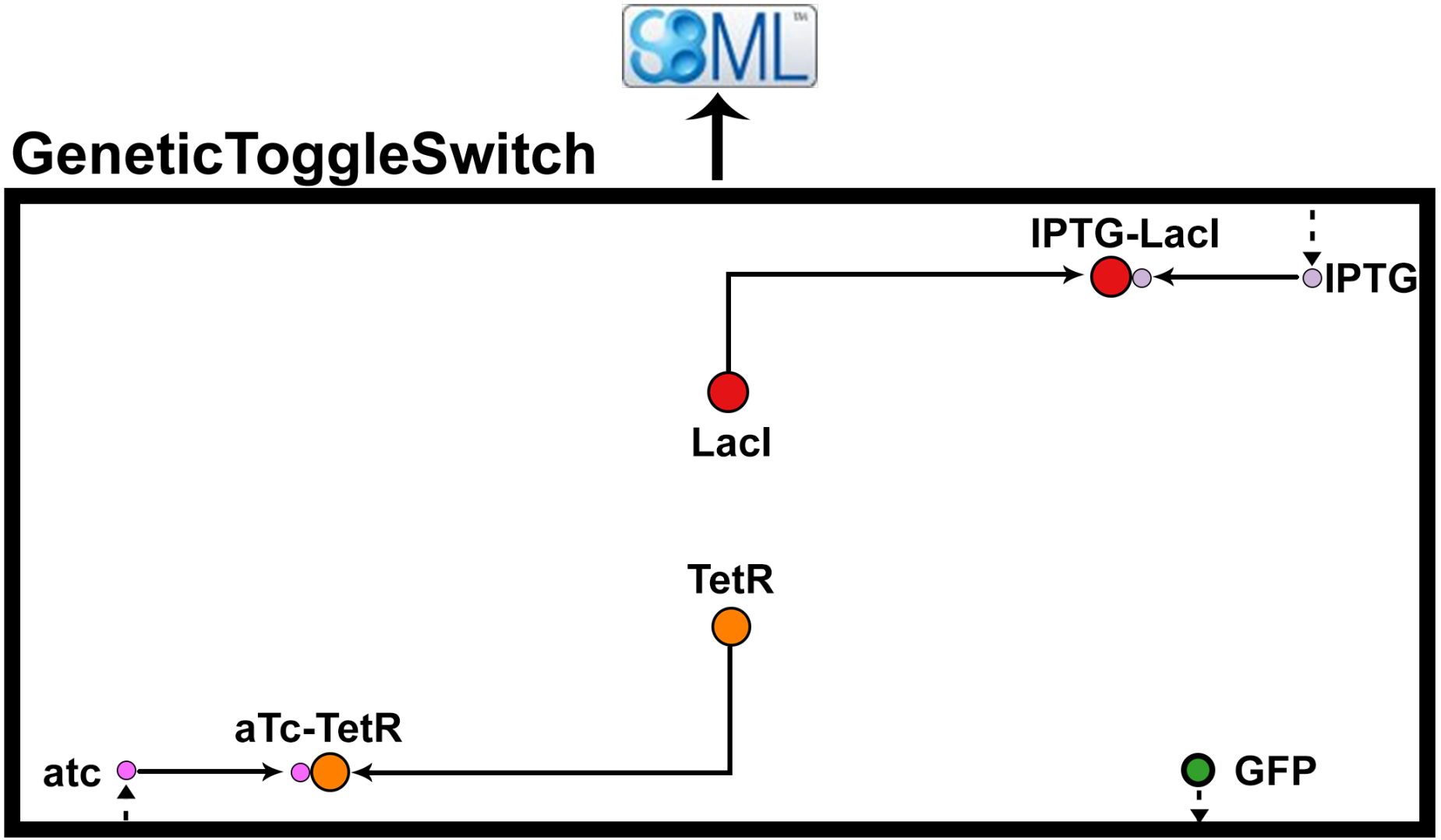
Model for the Genetic Toggle Switch



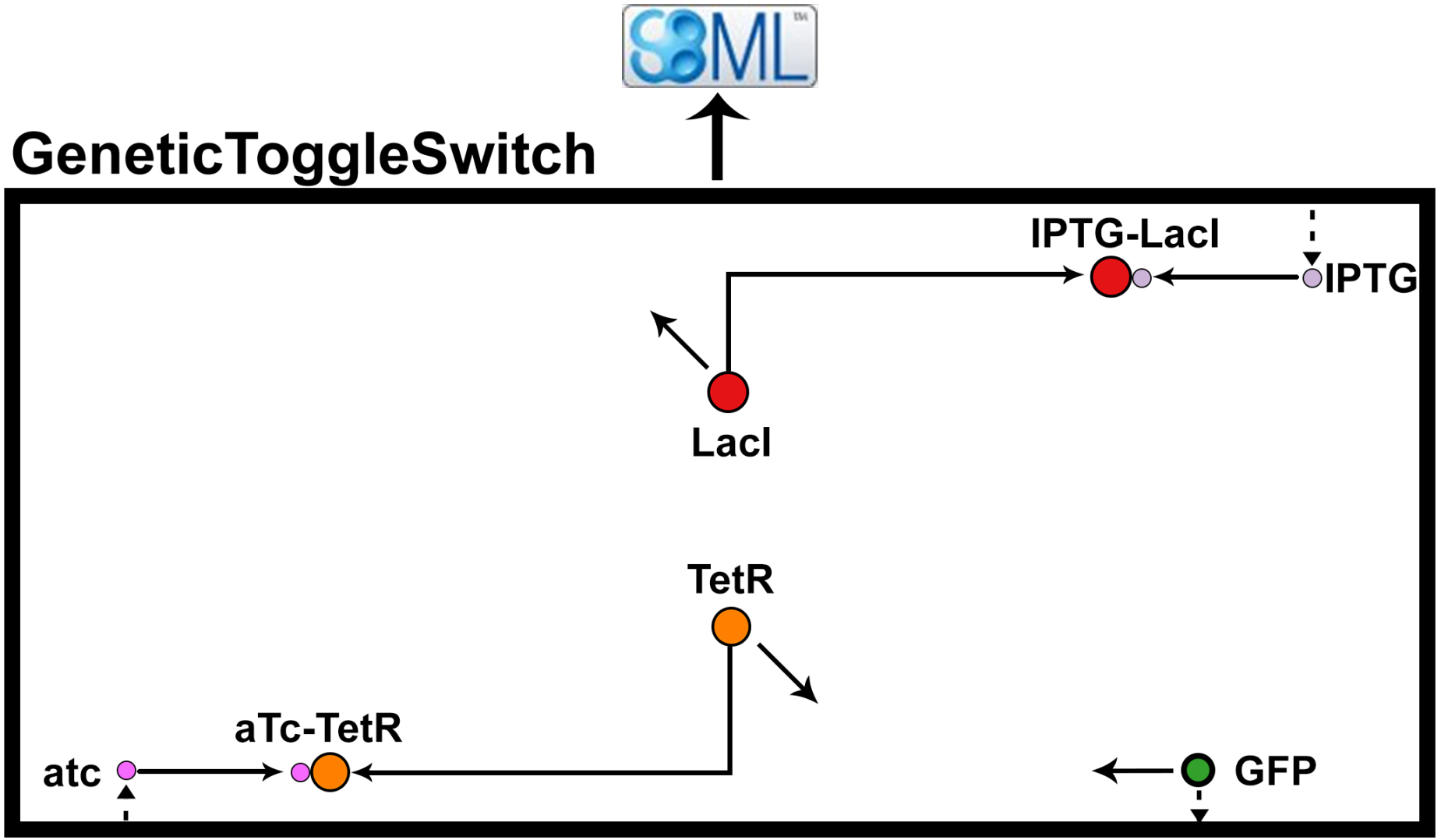
FunctionalComponents for the Genetic Toggle Switch



Complex Formation Interactions



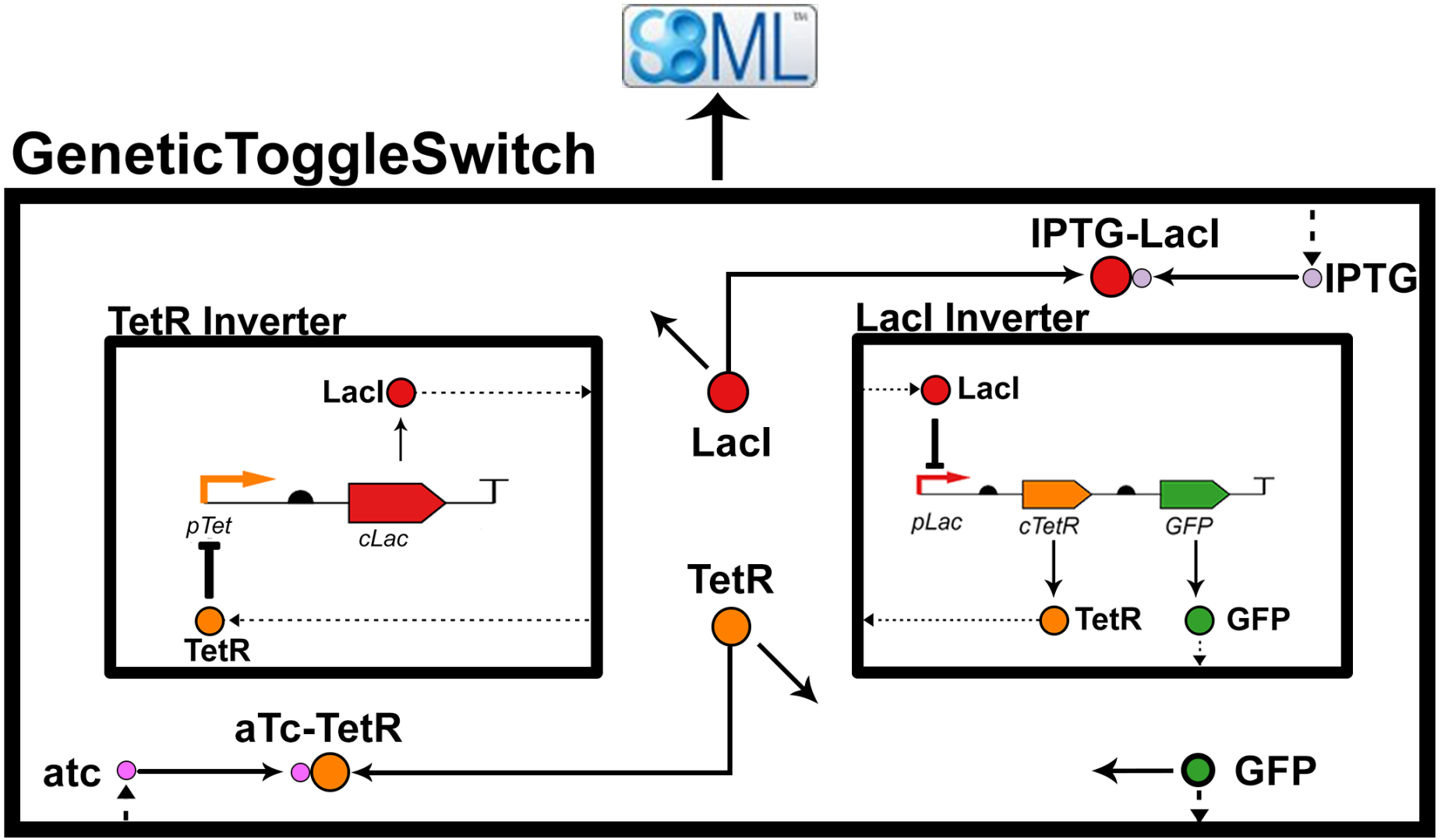
Degradation Interactions



Modules from SBML subModels

- A **Module** is created within the **ModuleDefinition** for each **subModel** used in the corresponding SBML **model**.
- A **Module** contains a **definition** that references the corresponding **ModuleDefinition** for the **subModel**.

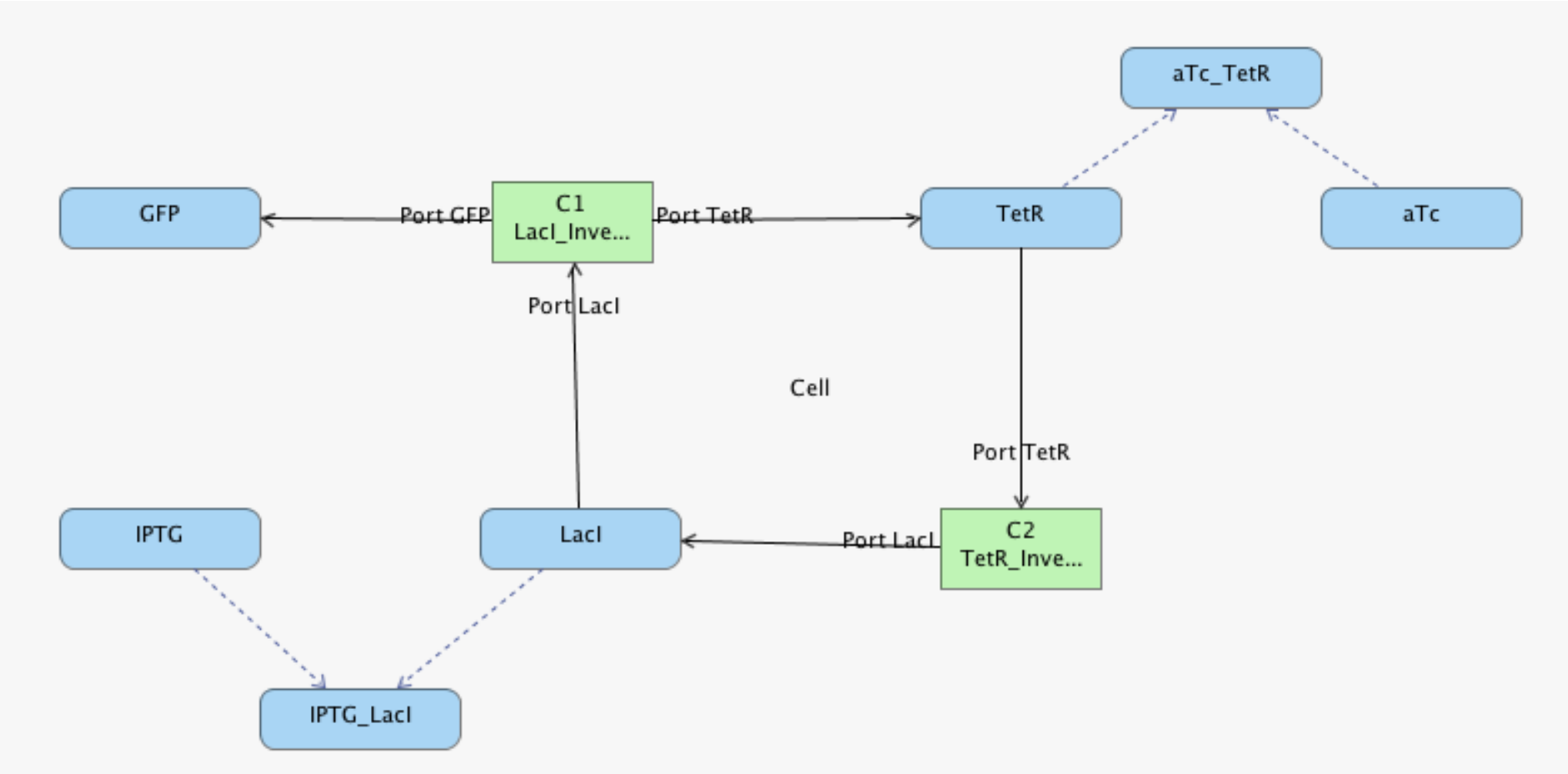
Modules for Genetic Toggle Switch



Converting SBML Replacements/ReplacedBys to MapsTos

- The SBML **replacements** and **replacedBy** objects are used when the same **species** are used at different levels of hierarchy.
- A **replacement** in an SBML model indicates all **species** instances within the **subModel** should be replaced with the top level **species**.
- A **replacedBy** object indicates a **species** in the top-level **model** should be replaced by a **species** in the corresponding **subModel**.
- The **replacements** and **replacedBy** elements are converted to **MapsTo** in SBOL.

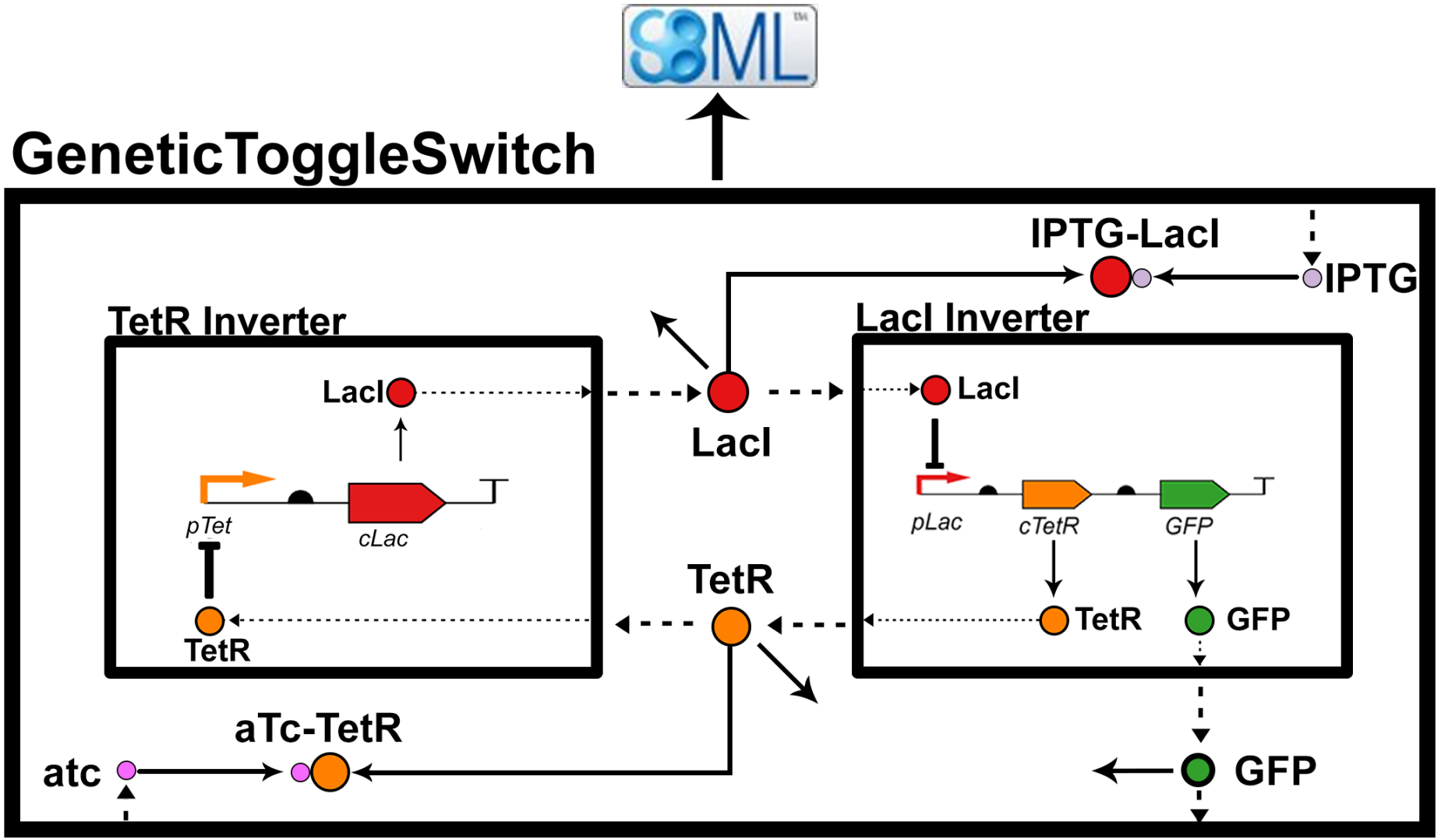
Example: Genetic Toggle Switch



Creating MapsTo

- **MapsTo** objects map a local **FunctionalComponent** to a remote **FunctionalComponent**.
- For a **replacement**, **MapsTo** object has a **RefinementType** of **useLocal** indicating that the properties of this object should be taken from the **FunctionalComponent** in the top level object.
- For a **replacedBy**, the **MapsTo** object has a **RefinementType** of **useRemote** indicating that the properties of this object should be taken from the referenced object.

MapsTos for the Genetic Toggle Switch



Discussion

- SBML is used to create models for simulation.
- SBOL is used for the structural design of genetic circuits.
- Conversion of annotated SBML to SBOL is capable of representing structural and qualitative behavioral information.
- Converting an SBOL file back to SBML has limitations.
- The conversion is not able to represent quantitative information (i.e., reaction rate constants, **species** initial amounts, stoichiometry, etc.).
- Expand conversion by expressing quantitative information through SBOL **GenericTopLevel** objects and **Annotations**.
- Current converter can convert a single SBML element to SBOL element.
- Future goal is to create a converter for different level of abstractions.

Acknowledgements

- National Science Foundation under Grant Number DBI-1356041.