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

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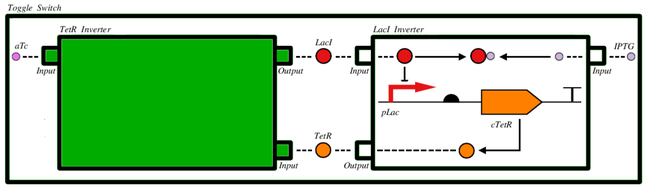
1 Introduction

- A recent proposal [4] for the next version of SBOL [1] enables its qualitative genetic designs to refer to mathematical models written in other standards such as SBML [2].
- To facilitate interdisciplinary collaboration, software tools are needed to help automate the process of creating quantitative models based on qualitative designs.



$$\frac{d[LacI]}{dt} = \frac{n_p k_o n_g K_o n_r}{1 + K_o n_r + K_r[TetR]^{n_c}} - k_d[LacI] - k_{c_f}[LacI][IPTG] + k_{c_r}[LacI:IPTG]$$

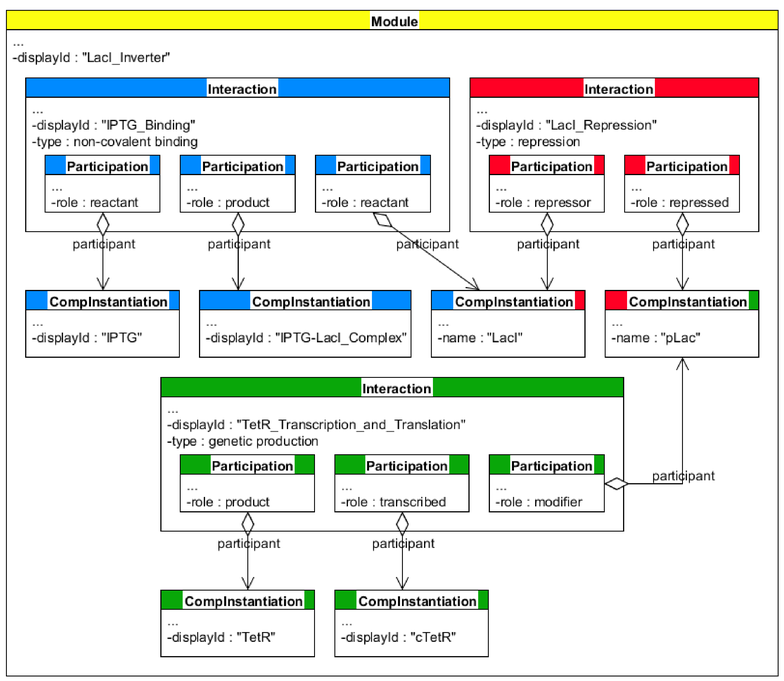
$$\frac{d[TetR]}{dt} = \frac{n_p k_o n_g K_o n_r}{1 + K_o n_r + K_r[LacI]^{n_c}} - k_d[TetR] - k_{c_f}[TetR][aTc] + k_{c_r}[TetR:aTc]$$

- The methodology presented here is implemented in the software tool `iBioSim` and enables generation of quantitative SBML models from qualitative SBOL modules.

2 SBOL for LacI Inverter

Under the proposed SBOL data model, the function of the LacI inverter can be described using a SBOL module that:

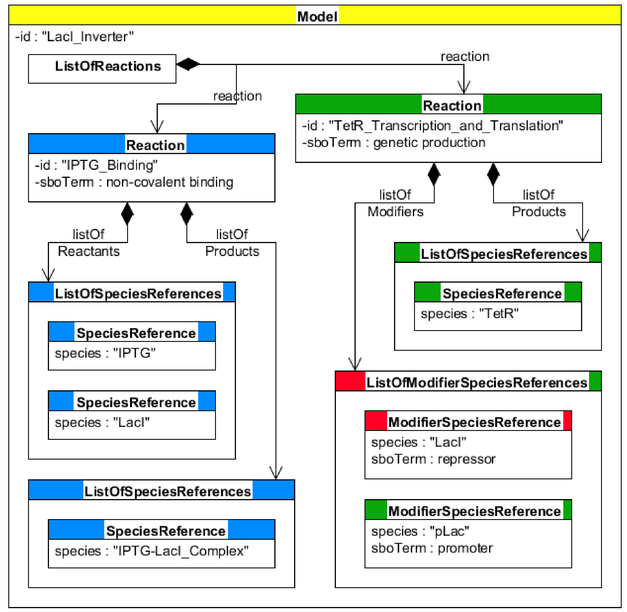
- Instantiates the DNA, protein, and small molecule components of the LacI inverter.
- Asserts the regulatory, gene expression, and general binding interactions between the component instantiations of the LacI inverter.



3 SBML for LacI Inverter

Under the data model for Level 3 Version 1 of SBML, the function of the LacI inverter can described using a SBML model that:

- Includes the chemical species and reactions of the LacI inverter.
- Supplies kinetic rate laws for these reactions to facilitate simulation and mathematical analysis of the LacI inverter.



4 Model Generation

1. For each protein, small molecule, and complex instantiated by the SBOL module:
   (a) Add a species, s, to the SBML model.
   (b) Add a degradation reaction, r_s, with a mass-action rate law of the form below to the SBML model.

$$\text{rate}(r_s) = k_d s$$

2. For each genetic production interaction with promoter p in the SBOL module:
   (a) Add a promoter species, p, to the SBML model.
   (b) Add a genetic production reaction, r_p, to the SBML model and p to the list of modifiers for r_p.
   (c) If the promoter is repressed or activated in a repression or activation interaction, add the corresponding set of repressor species, $\text{Rep}(p)$, and the corresponding set of activator species, $\text{Act}(p)$, to the list of modifiers for r_p.
   (d) If one or more proteins participate as products in the interaction, add the corrsponding species to the list of products for r_p.
   (e) Add a Hill function rate law of the form below to r_p.

$$\text{rate}(r_p) = \begin{cases} \dfrac{n_p k_o n_g K_o n_r}{1 + K_o n_r + \sum_{s_r \in \text{Rep}(p)} (K_r s_r)^{n_c}} & \text{if } |\text{Act}(p)| = 0 \\ \dfrac{n_p k_b n_g K_o n_r + n_p k_a n_g K_{oa} n_r \sum_{s_a \in \text{Act}(p)} (K_a s_a)^{n_c}}{1 + K_o n_r + \sum_{s_r \in \text{Rep}(p)} (K_r s_r)^{n_c} + K_{oa} n_r \sum_{s_a \in \text{Act}(p)} (K_a s_a)^{n_c}} & \text{otherwise} \end{cases}$$

3. For each non-covalent binding interaction with product s in the SBOL module:
   (a) Add a reversible non-covalent binding reaction, r_s, with product species s to the SBML model.
   (b) Add the reactants of the interaction, $\text{React}(s)$, to the list of reactants for r_s.
   (c) Add a mass-action rate law of the form below to r_s.

$$\text{rate}(r_s) = k_{c_f} K_c^{|\text{React}(s)|-2} \prod_{s' \in \text{React}(s)} s' - k_{c_r} s$$

The SBML models generated by this methodology are similar to the genetic circuit models generated in [3].

Default Parameters for SBML Kinetic Laws

Parameter	Symbol	Value	Units
Rate of degradation	k_d	0.0075	$\frac{1}{sec}$
Stoichiometry of production	n_p	10	$unitless$
Open complex production rate	k_o	0.05	$\frac{1}{sec}$
Basal production rate	k_b	0.0001	$\frac{1}{sec}$
Activated production rate	k_a	0.25	$\frac{1}{sec}$
Promoter count	n_g	2	$molecule$
RNApol binding equilibrium	K_o	0.033	$\frac{1}{molecule}$
Activated RNApol binding equilibrium	K_{oa}	1	$\frac{1}{molecule}$
RNApol count	n_r	30	$molecule$
Repression binding equilibrium	K_r	0.5	$\frac{1}{molecule}$
Activation binding equilibrium	K_a	0.0033	$\frac{1}{molecule}$
Stoichiometry of binding	n_c	2	$unitless$
Forward non-covalent binding rate	k_{c_f}	0.05	$\frac{1}{molecule*sec}$
Non-covalent binding equilibrium	K_c	0.05	$\frac{1}{molecule}$
Reverse non-covalent binding rate	k_{c_r}	1	$\frac{1}{sec}$

5 Discussion

- Other rule sets can be developed for generating a variety of models in different standards for different design tasks.
- SBML kinetic laws generated by this methodology are populated with default parameters—in the future, SBOL could store these parameters.

6 Acknowledgements

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References

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