Towards programming languages for synthetic biology

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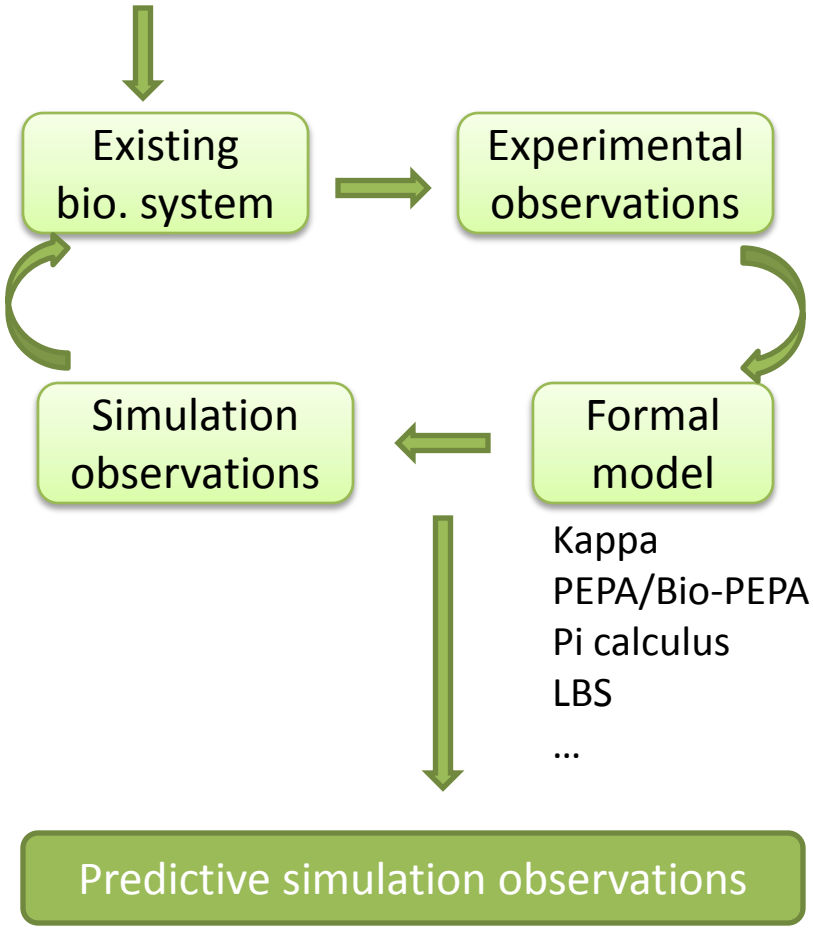
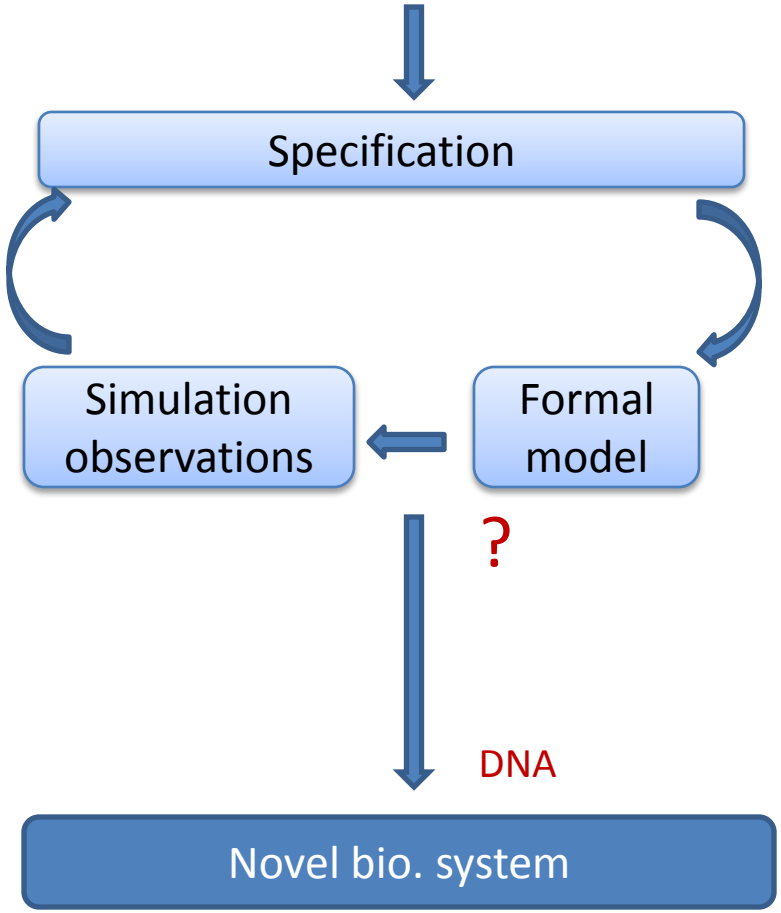
Synthetic biology

- *The design and construction of new biological systems for useful purposes*.
- Applications: medicine, energy, materials …
- Why now? Large-scale DNA synthesis possible.
- Problem: lack of structured engineering techniques.
- Our aim: a language for programming systems at the logical level of interactions between (potentially undetermined) genes and proteins.

Sys-bio vs. syn-bio



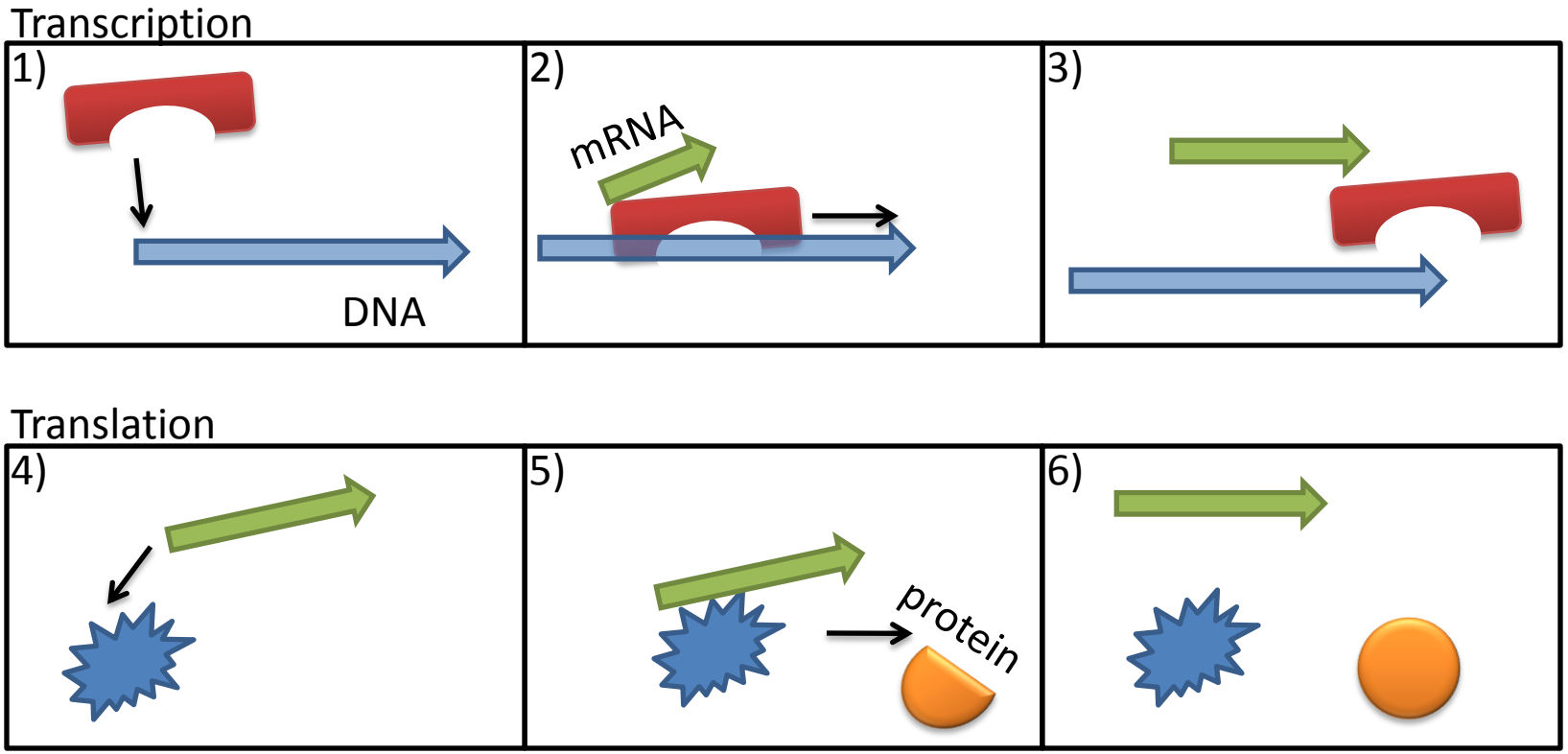


Overview

1. Standard genetic parts.
2. The basics of LSB: a Language for Synthetic Biology .
3. Case study: the predator-prey system.
4. Case study: the repressilator.
5. The syntax and semantics of LSB.
6. Discussion.

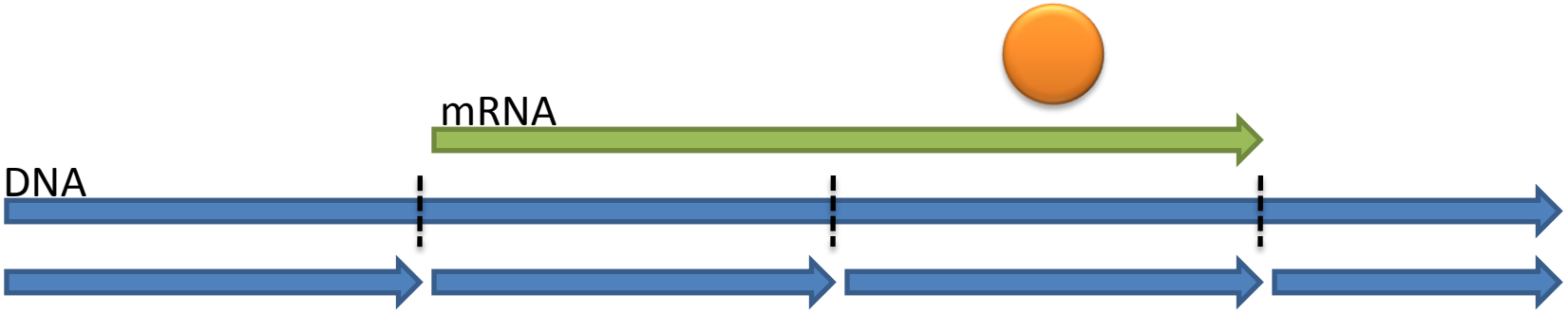
STANDARD GENETIC PARTS

Gene expression basics



DNA parts

- DNA sequences divided into different types of functional *parts* with specific properties.
- Some fundamental part types:



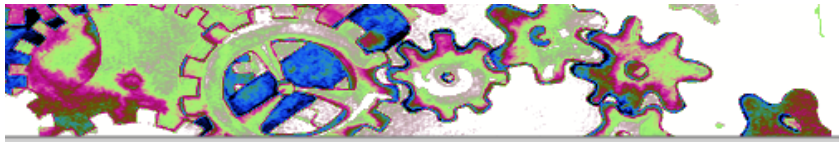
Promoter:
- Rate of transcription.
- Regulated positively or negatively by proteins.

Ribosome binding site:
- Rate of translation.

Protein coding region:
- Codes for specific target protein.

Terminator:
- Signals end of transcription.

Registry of Standard Biological Parts



Regulatory Regions (Promoters)

Available repressible regulators (normally ON) -?- *Show 0 more parts* *Edit*

-?-		Name	Description	Direction	Control -?-	Output Low	Output High	Length
A	W	BBa_I14032	promoter P(Lac) IQ	Forward	lacI			37
A	W	BBa_R0040	TetR repressible promoter	Forward	aTc, tetracyline			54
A	W	BBa_R0051	promoter (lambda cI regulated)	Forward	lambda cI			49

Available inducible regulators (normally OFF) -?- *Show 0 more parts* *Edit*

-?-	Name	Description	Direction	Control -?-	Output Low	Output High	Length
A	BBa_I12007	Modified lambda Prm promoter (OR-3 obliterated)	Forward	cI			82
A	BBa_R0062	Promoter (luxR & HSL regulated -- lux pR)	Forward	luxR, HSL			55
A	BBa_R0079	Promoter (LasR & PAI regulated)	Forward	PAI			157
A	BBa_R0080	Promoter (AraC regulated)	Forward	araC			149

Available other regulators *Show 382 more parts* *Edit*

-?-		Name	Description	Direction	Control -?-	Output Low	Output High	Length
A	W	BBa_I0500	Inducible pBad/araC	Forward	araC, arabinose			1210
A	W	BBa_I13453	Pbad promoter					130
A	W	BBa_I712004	CMV promoter					654
A	W	BBa_I712074	T7 promoter (strong promoter from T7 bacteriophage)					46
A	W	BBa_I714889	OR21 of PR and PRM					101
A	W	BBa_I714924	RecA_DlexO_DLacO1					862
A	W	BBa_I714927	RecA_S_WTlexO_DLacO					862
A	W	BBa_I714929	RecA_S_WTlexO_DLacO3					862
A	W	BBa_I714930	RecA_D_consenLexO_lacO1					862
A	W	BBa_I714933	WT_sulA_Single_LexO_double_LacO1					884
A	W	BBa_I714935	WT_sulA_Single_LexO_double_LacO2					884
A	W	BBa_I714936	WT_sulA_Single_LexO_double_LacO3					884
A	W	BBa_I714937	sluA_double_lexO_LacO1					884
A	W	BBa_I714938	sluA_double_lexO_LacO2					884
A	W	BBa_I714939	sluA_double_lexO_LacO3					884

Assumptions

- A given *parts database* with part identifiers and appropriate logical properties.

Type	ID	Properties
pcr	c0051	codes(clR)
pcr	c0040	codes(tetR)
pcr	c0080	codes(araC)
pcr	c0012	codes(lacI)
pcr	c0061	codes(luxI)
pcr	c0062	codes(luxR)
pcr	c0079	codes(lasR)
pcr	c0078	codes(lasI)
pcr	cunknown3	codes(ccdB)
pcr	cunknown4	codes(ccdA)
prom	r0051	neg(clR)
prom	r0040	neg(tetR)
prom	i0500	neg(araC)
prom	r0011	neg(lacI)
prom	runknown2	pos(lasR-m3OC12HSL)
		pos(luxR-m3OC6HSL)
rbs	b0034	
ter	b0015	

- A given *reaction database.*

$$\text{toluene} + \text{xylR} \rightarrow \text{toluene-xylR}$$
$$\text{phzM} \sim \text{pca} \rightarrow \text{metPCA}, \quad \text{phzS} \sim \text{metPCA} \rightarrow \text{pyo}$$
$$\text{luxR} + \text{m3OC6HSL} \rightarrow \text{luxR-m3OC6HSL}$$
$$\text{lasR} + \text{m3OC12HSL} \rightarrow \text{lasR-m3OC12HSL}$$
$$\text{luxI} \sim \rightarrow \text{m3OC6HSL}, \quad \text{lasI} \sim \rightarrow \text{m3OC12HSL}$$
$$\text{ccdA} + \text{ccdB} \rightarrow \text{ccdA-ccdB}$$
$$\text{m3OC6HSL} \rightarrow [\text{m3OC6HSL}], \quad \text{m3OC12HSL} \rightarrow [\text{m3OC12HSL}]$$
$$[\text{m3OC6HSL}] \rightarrow \text{m3OC6HSL}, \quad [\text{m3OC12HSL}] \rightarrow \text{m3OC12HSL}$$

THE BASICS OF LSB: A LANGUAGE FOR SYNTHETIC BIOLOGY

Basic examples

- Negative feed-back loop, fixed sequence of parts:

```
r0051:prom ; b0030:rbs ; c0051:pcr ; b0014:ter
```

Part ID (name) — Part type — Sequential composition

- Compilation:

```
[r0051; b0030; c0051; b0014]
```

- Negative feed-back loop through properties:

```
X1:prom<neg(tetR)> ; X2:rbs ; X3:pcr<codes(tetR)> ; X4:ter
prom<neg(tetR)> ; rbs ; pcr<codes(tetR)> ; ter
```

Part properties — Part ID (variable)

- *Any* negative feed-back loop:

```
prom<neg(Y)> ; rbs ; pcr<codes(Y)> ; ter
```

Some useful modules

```
module tl(out) {
   rbs  ;  pcr<codes(out)>  ;  ter
};

module gatePos(in, out) {
   prom<pos(in)>  ;  tl(out)
};

module gateNeg(in, out) {
   prom<neg(in)>  ;  tl(out)
};

module gateCon(out) {
   prom:r0051  ;  tl(out)
};
```

Some useful modules

```
module tl2(out1, out2) {
   rbs  ;  pcr<codes(out1)>  ;  rbs  ;  pcr<codes(out2)>  ;  ter
};

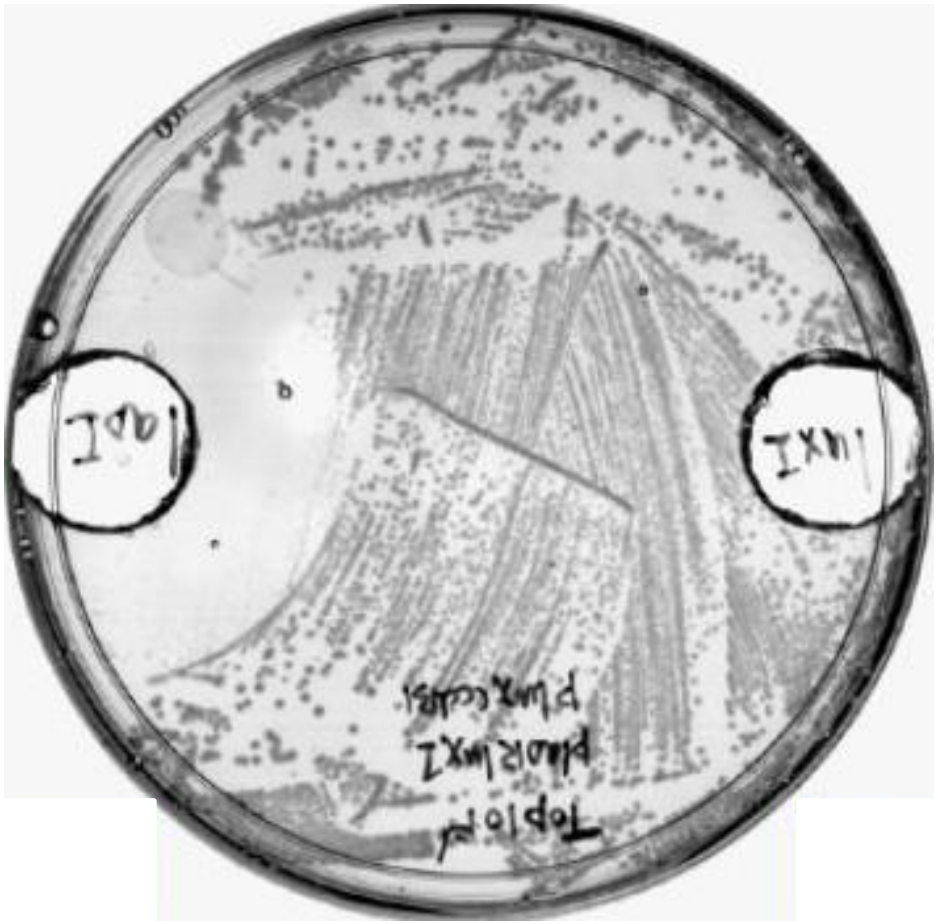
module gatePos2(in, out1, out2) {
   prom<pos(in)>  ;  tl2(out1, out2)
};

module gateNeg2(in, out1, out2) {
   prom<neg(in)>  ;  tl2(out1, out2)
};

module gateCon2(out1, out2) {
   prom:r0051  ;  tl2(out1, out2)
};
```

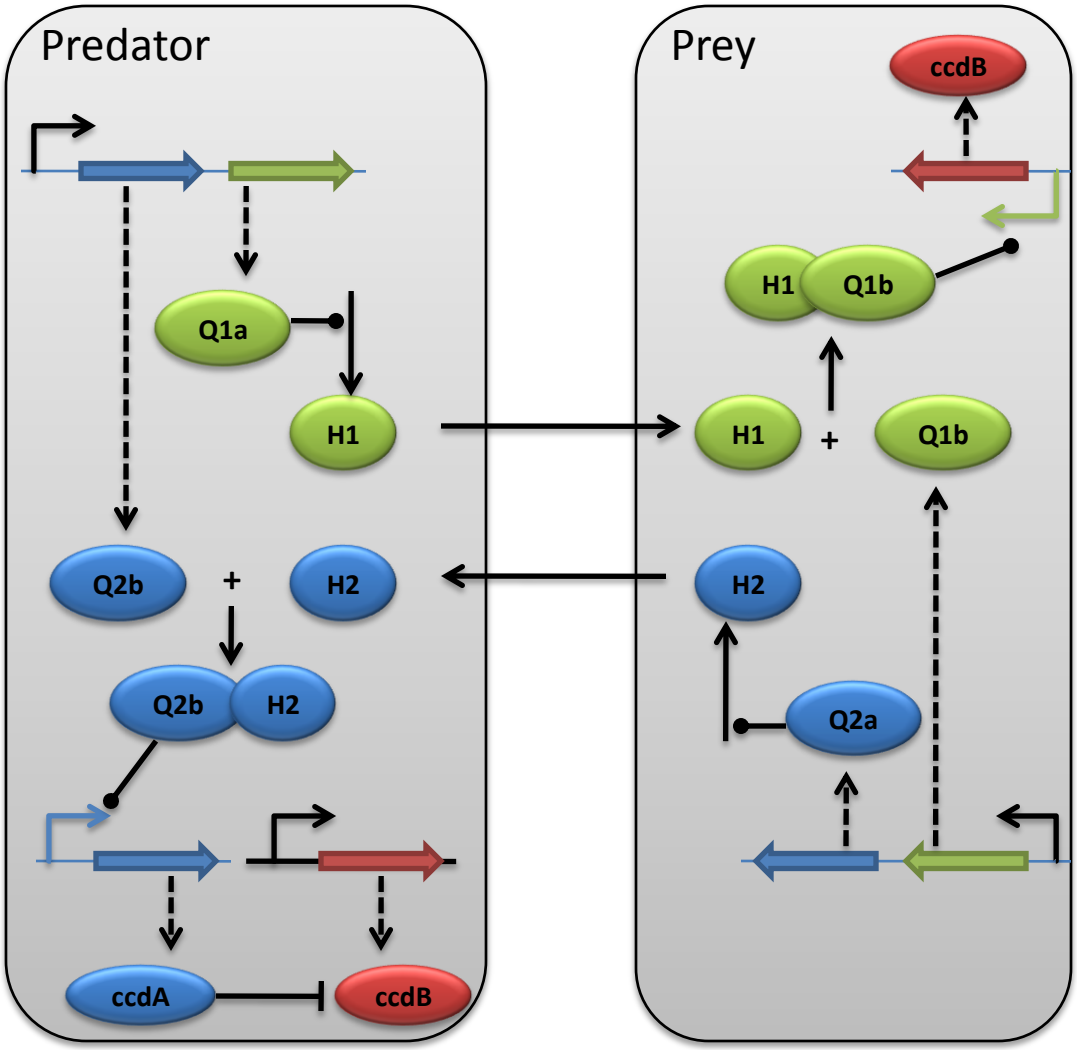
CASE STUDY: THE PREDATOR-PREY SYSTEM

The predator-prey system

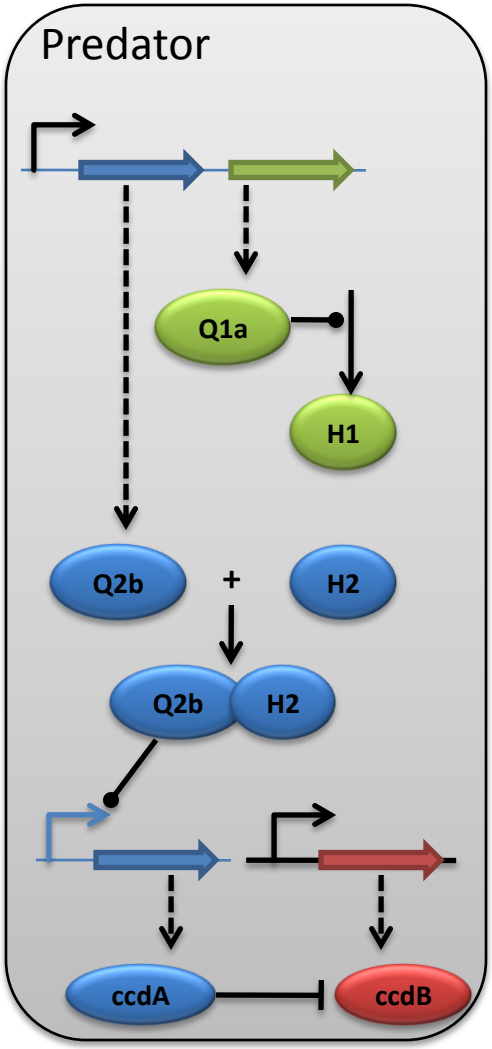


From Balagadde et al:
A synthetic Escherichia coli predator-prey ecosystem. Mol. Sys. Bio. 2008

Predator-prey schematics



The predator module




```
module predator()
{
   gateCon2(Q2b, Q1a) |
   Q1a ~ -> H1  ;

   Q2b + H2 -> Q2b-H2 |
   gatePos(Q2b-H2, ccdA)  ;

   gateCon(ccdB) |
   ccdA + ccdB -> ccdA-ccdB
};
```

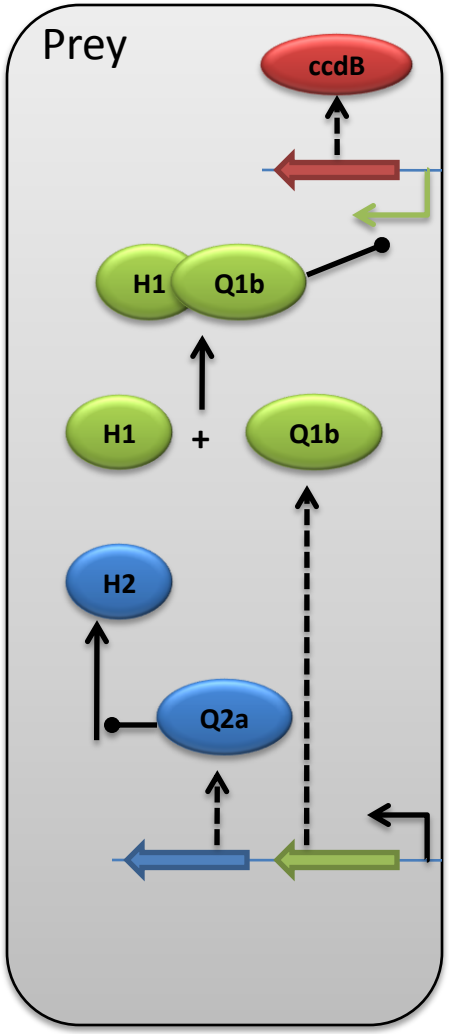
Constraint composition

Reaction constraint

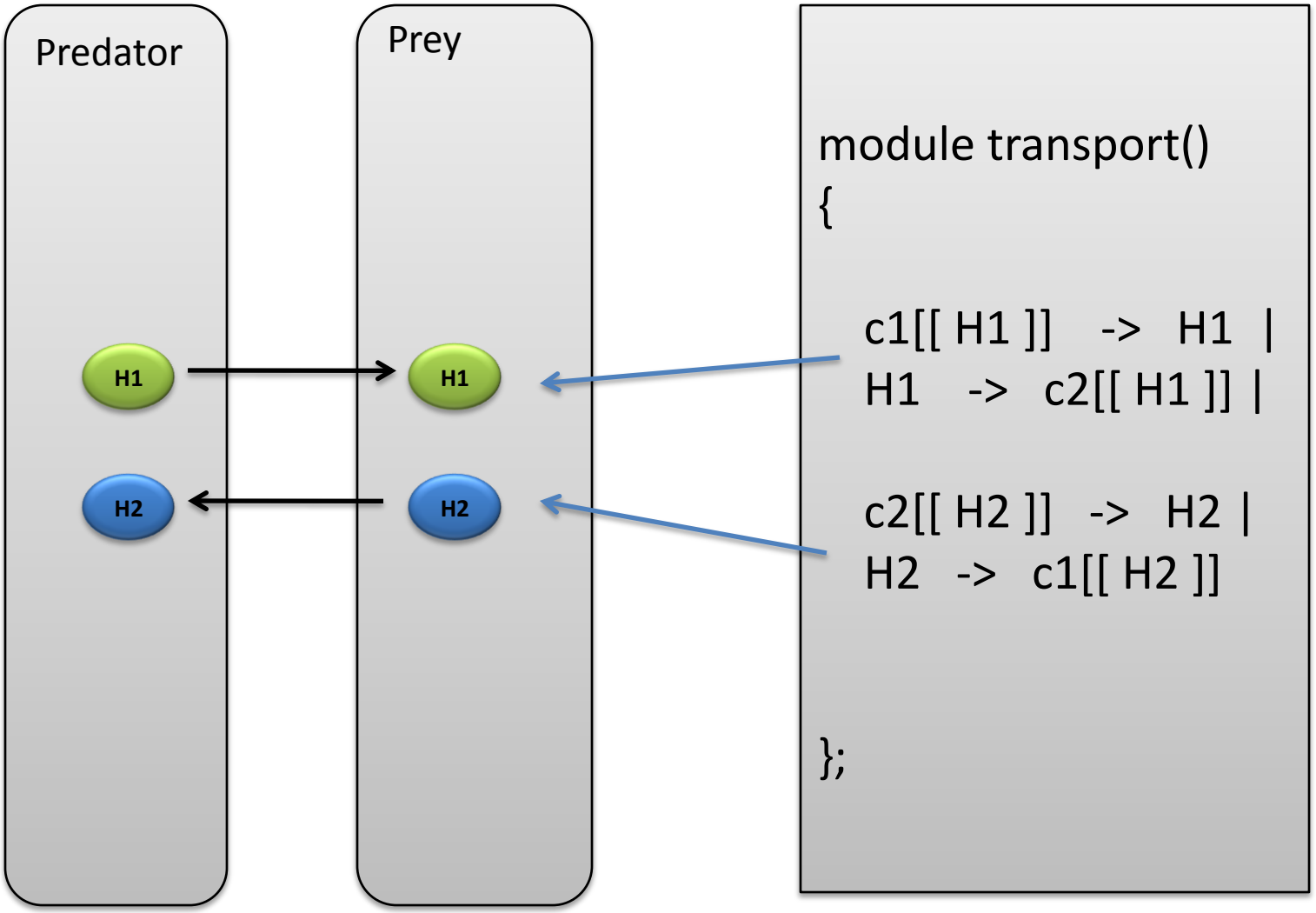
The prey module

```
module prey()
{
   gatePos(H1-Q1b, ccdB) |
   H1 + Q1b -> H1-Q1b ;

   Q2a ~ -> H2 |
   gateCon2(Q2a, Q1b)
};
```

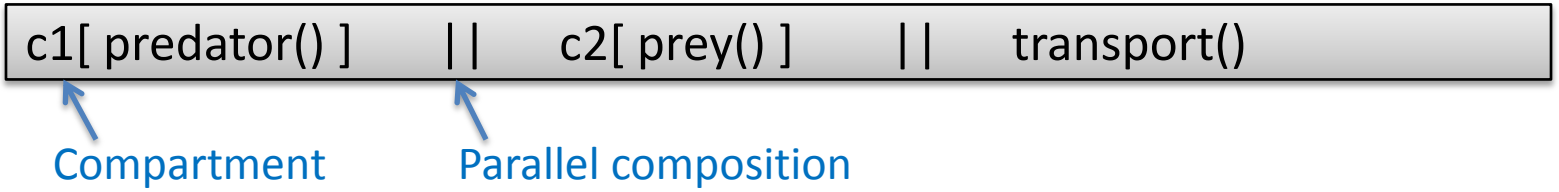


The transport module



The predator-prey program

- The predator-prey program:

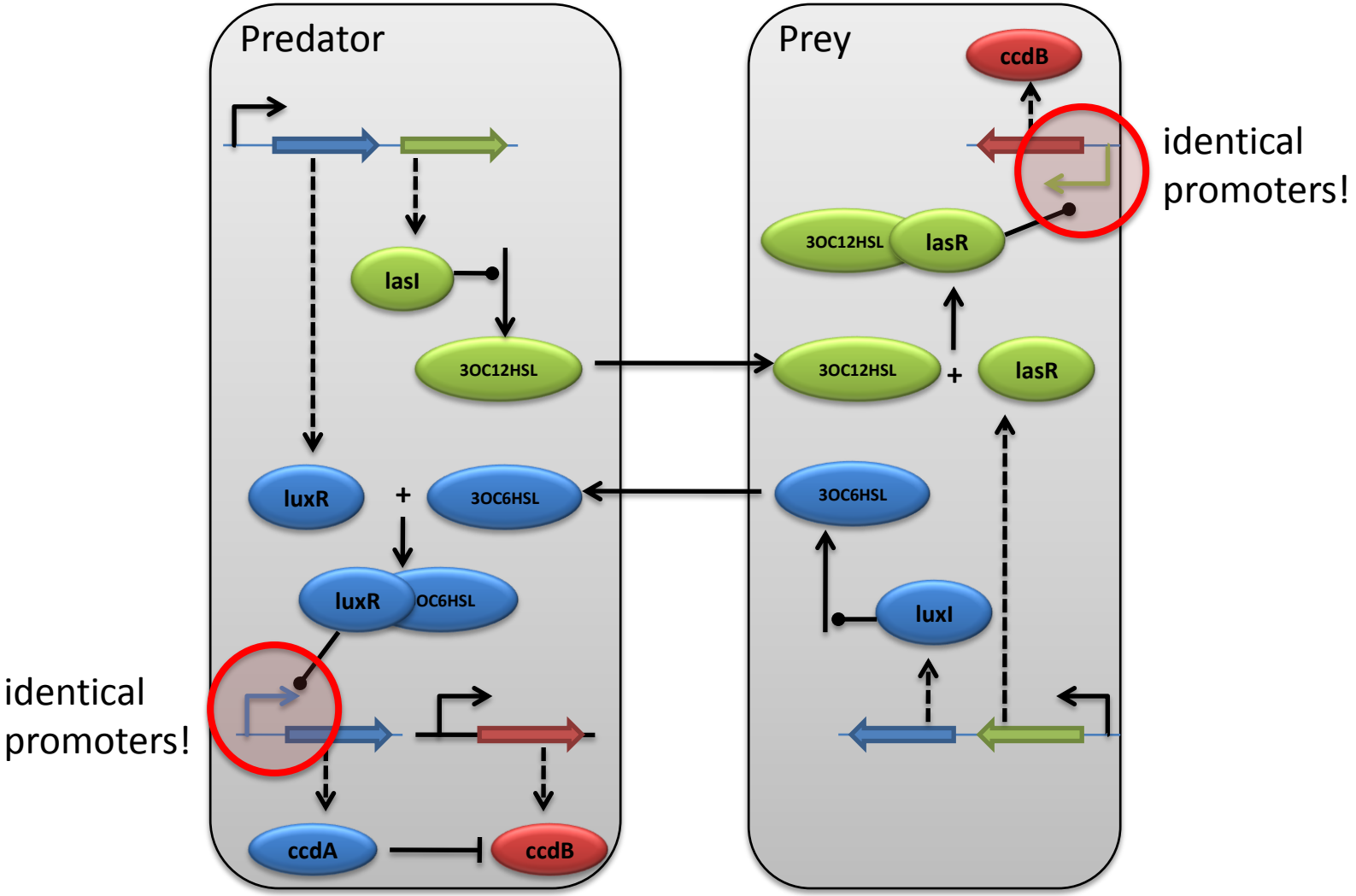


- Compilation yields two solutions, each with two devices, e.g.:

```
[r0051; b0034; c0062; b0034; c0078; b0015; runknown2; b0034;
  cunknown4; b0015; r0051; b0034; cunknown3; b0015]

[runknown2; b0034; cunknown3; b0015; r0051; b0034; c0079; b0034; c0061; b0015]
```

Predator-prey implementation

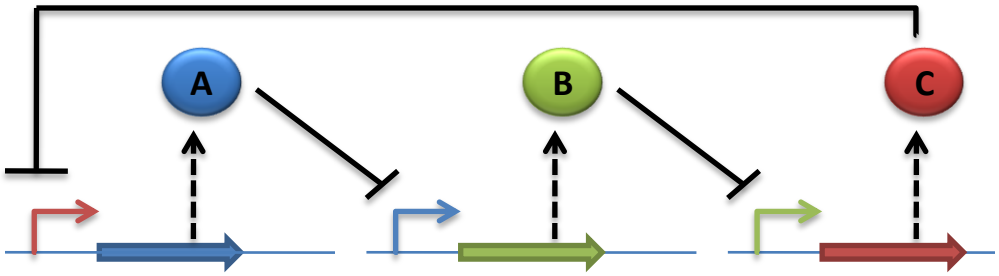


Compartments: 1) avoid cross-talk and 2) distinguish populations.

CASE STUDY: THE REPRESSILATOR

The repressilator

- Informal pictorial diagram:



- LSB program:

```
gateNeg(A, B)  ;  gateNeg(B, C)  ;  gateNeg(C, A)
```

- Compilation yields 24 devices, including e.g.:

```
[r0051; b0034; c0040; b0015; r0040; b0034; c0012; b0015; r0011; b0034; c0051; b0015]
```

```
[r0051; b0034; c0080; b0015; i0500; b0034; c0012; b0015; r0011; b0034; c0051; b0015]
```

- So which do we choose?

From Elowitz and Leibler:
A synthetic oscillatory network of transcriptional regulators. Nature 2000.

Extended databases

Type	ID	Properties
pcr	c0051	codes(clR, 0.001)
pcr	c0040	codes(tetR, 0.001)
pcr	c0080	codes(araC, 0.001)
pcr	c0012	codes(lacI, 0.001)
pcr	c0061	codes(luxI, 0.001)
pcr	c0062	codes(luxR, 0.001)
pcr	c0079	codes(lasR, 0.001)
pcr	c0078	codes(lasI, 0.001)
pcr	cunknown3	codes(ccdB, 0.001)
pcr	cunknown4	codes(ccdA, 0.001)
prom	r0051	neg(clR, 1.0, 0.5, 0.0001)
		con(0.12)
prom	r0040	neg(tetR, 1.0, 0.5, 0.0001)
		con(0.09)
prom	i0500	neg(araC, 1.0, 0.0000001, 0.0001)
		con(1.0)
prom	r0011	neg(lacI, 1.0, 0.5, 0.001)
		con(0.1)
prom	runknown2	pos(lasR-m3OC12HSL, 1.0, 0.5, 0.1)
		pos(luxR-m3OC6HSL, 1.0, 0.5, 0.1)
rbs	b0034	rate(0.1)
ter	b0015	

$$\text{toluene} + \text{xylR} \rightarrow^{1} \text{toluene-xylR}$$
$$\text{phzM} \sim \text{pca} \rightarrow^{1} \text{metPCA}, \quad \text{phzS} \sim \text{metPCA} \rightarrow^{1} \text{pyo}$$
$$\text{luxR} + \text{m3OC6HSL} \rightarrow^{1} \text{luxR-m3OC6HSL}$$
$$\text{lasR} + \text{m3OC12HSL} \rightarrow^{1} \text{lasR-m3OC12HSL}$$
$$\text{luxI} \sim \rightarrow^{1} \text{m3OC6HSL}, \quad \text{lasI} \sim \rightarrow^{1} \text{m3OC12HSL}$$
$$\text{ccdA} + \text{ccdB} \rightarrow^{1} \text{ccdA-ccdB}$$
$$\text{m3OC6HSL} \rightarrow^{1} [\text{m3OC6HSL}]$$
$$\text{m3OC12HSL} \rightarrow^{1} [\text{m3OC12HSL}]$$
$$[\text{m3OC6HSL}] \rightarrow^{1} \text{m3OC6HSL}$$
$$[\text{m3OC12HSL}] \rightarrow^{1} \text{m3OC12HSL}$$

Compilation to reactions

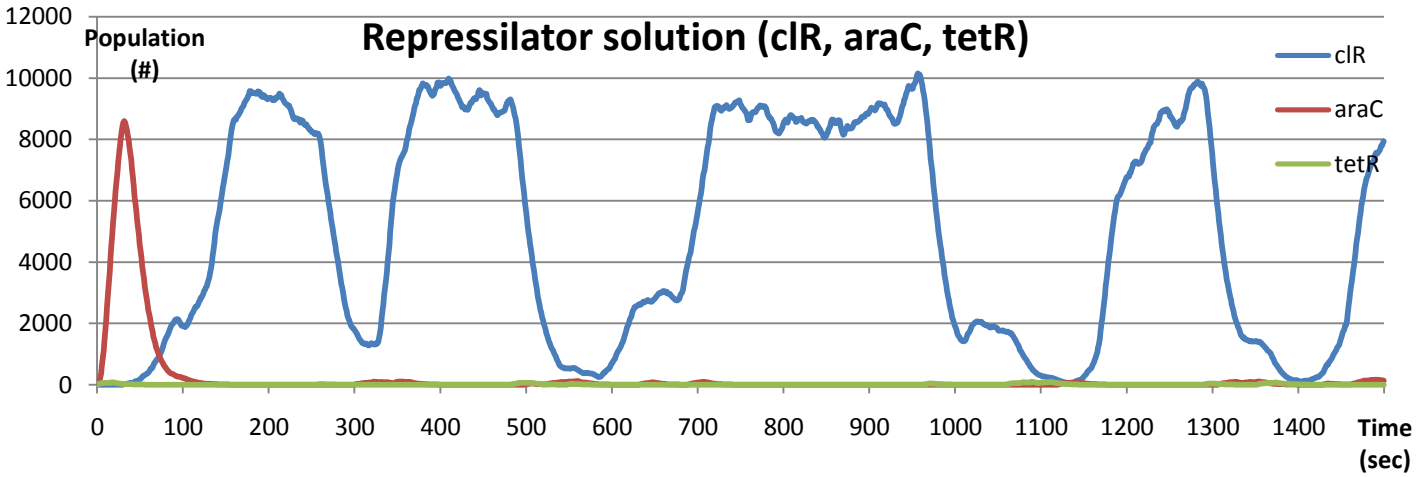
- Promoters:
  - “con” property -> constitutive transcription reaction.
  - “pos” and “neg” properties -> transcription factor binding/unbinding reactions and regulated transcription reactions.
- Ribosome binding sites:
  - “rate” property -> translation reaction.
- Protein coding region:
  - “codes” property -> degradation reaction for coded protein.

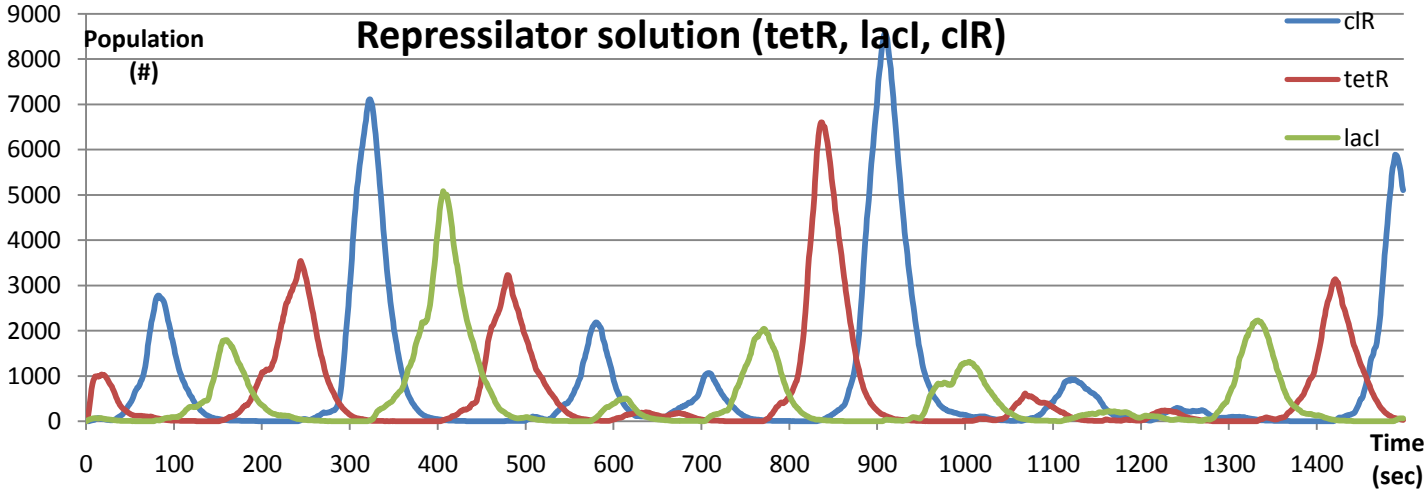
Compilation to reactions

```
rate RMRNADeg = 0.001;

initpop g775 1 |
mrna776 ->{RMRNADeg}   |
g775 ->{0.12} g775 + mrna776  |
g775 + clR ->{1.0} g775-clR  |
g775-clR ->{0.5} g775 + clR  |
g775-clR ->{0.0001} g775-clR + mrna776  |
araC ->{0.001}     |
mrna776 ->{0.1} mrna776 + araC  |
initpop g794 1 |
mrna795 ->{RMRNADeg}   |
g794 ->{0.1} g794 + mrna795  |
g794 + araC ->{1.0} g794-araC  |
g794-araC ->{1e-6} g794 + araC  |
g794-araC ->{0.0001} g794-araC + mrna795  |
tetR ->{0.001}     |
mrna795 ->{0.1} mrna795 + tetR  |
initpop g813 1 |
mrna814 ->{RMRNADeg}   |
g813 ->{0.09} g813 + mrna814  |
g813 + tetR ->{1.0} g813-tetR  |
g813-tetR ->{0.5} g813 + tetR  |
g813-tetR ->{0.0001} g813-tetR + mrna814  |
clR ->{0.001}     |
mrna814 ->{0.1} mrna814 + clR
```

Stochastic simulation





Rates from Blossey, Cardelli and Phillips:
Compositionality, stochasticity and cooperativity in dynamic models of gene regulation. HFSP Journal 2008.

Quantitative constraints

- Oscillating variable ranges via parameter scan.
- Gate module with quantitative constraints:

```
module gateNeg(in, out) {
    new RB. new RUB. new RTB. new RT. new R. new RD.

    prom<con(RT), neg(in, RB, RUB, RTB)>;
    rbs<rate(R)>;
    pcr<codes(out, RD)>; ter |

    0.9 < RB   | RB < 1.1      |    0.4 < RUB | RUB < 0.6 |
    0.05 < RT | RT < 0.15     |    0.05 < R   | R < 0.15   | RTB < 0.01
};
```

New operator

Quantitative constraints

- Compilation of the repressilator now yields 6 solutions.

THE SYNTAX AND SEMANTICS OF LSB

The abstract syntax of LSB

$$P ::= u : t(Q^t) \;\vdots\; \mathbf{0} \;\vdots\; p(\widetilde{A})$$

$$\vdots\; P \mid C \;\vdots\; P \parallel P' \;\vdots\; P \,;\, P' \;\vdots\; c[P] \;\vdots\; \text{new } x.P$$

$$C ::= R \;\vdots\; T \;\vdots\; K \;\vdots\; C \mid C'$$

$$R ::= S \sim \sum m_i \cdot S_i \to \sum m'_j \cdot S'_j$$

$$T ::= S \to c[S'] \;\vdots\; c[S] \to S'$$

The denotational function

Databases

"Device templates"

"Context-sensitive" substitutions

$$[\![P]\!]_{\mathcal{K}} \triangleq (D, \Theta)$$

$$\mathcal{K}_b \subsetneq \{n : t(Q^t) \mid \mathrm{FV}(Q^t) = \emptyset\}$$

$$\mathcal{K}_r \subsetneq \{R \mid \mathrm{FV}(\{R\}) = \emptyset\} \cup \{T^\star \mid \mathrm{FV}(\{T\}) = \emptyset\}$$

$$D = \{d_i\}$$

List of variables/names

$$\Theta = \{(\theta_i, \rho_i, \sigma_i)\}$$

Substitution

Species

Exclusive species

Context-sensitive substitution composition

DEFINITION 1. *Two context-sensitive substitutions* (θ, ρ, σ) *and* $(\theta', \rho', \sigma')$ agree *if*

1. $\forall x \in Dom(\theta) \cap Dom(\theta').\theta(x) = \theta'(x)$
2. $\forall n \in N \cap Im(\theta) \cap Im(\theta').\theta^{-1}(n) = \theta'^{-1}(n)$
3. $\rho \cap \sigma' = \rho' \cap \sigma = \emptyset$

We define the composition of two sets of context-sensitive substitutions thus:

$$\{(\theta_i, \rho_i, \sigma_i)\} \circledcirc \{(\theta'_j, \rho'_j, \sigma'_j)\} \triangleq$$
$$\{(\theta_i \cup \theta'_j, \rho_i \cup \rho'_j, \sigma_i \cup \sigma'_j) \mid (\theta_i, \rho_i, \sigma_i) \textit{ and } (\theta'_j, \rho'_j, \sigma'_j) \textit{ agree.}\}$$

The semantics of LSB

- Selected cases:
  - $[\![u : t(Q^t)]\!]_{\mathcal{K}} \triangleq (\{(u)\}, \Theta)$ where
    $\Theta \triangleq \{(\theta, \mathrm{FS}(Q^t\theta), \mathrm{FS}(Q' \setminus Q\theta)) \mid u\theta : t(Q') \in \mathcal{K}_b \wedge Q^t\theta \subset Q'\}$
  - $[\![P_1 \ ; \ P_2]\!]_{\mathcal{K}} \triangleq (\{d_{1_i} d_{2_j}\}_{I \times J}, \Theta_1 \circledcirc \Theta_2)$ where
    $(\{d_{1_i}\}_I, \Theta_1) \triangleq [\![P_1]\!]_{\mathcal{K}}$ and $(\{d_{2_j}\}_J, \Theta_2) = [\![P_2]\!]_{\mathcal{K}}$
  - $[\![P_1 \parallel P_2]\!]_{\mathcal{K}} \triangleq (D_1 \cup D_2, \Theta_1 \circledcirc \Theta_2)$ where
    $(D_1, \Theta_1) \triangleq [\![P_1]\!]_{\mathcal{K}}$ and $(D_2, \Theta_2) = [\![P_2]\!]_{\mathcal{K}}$
  - $[\![c[P]]\!]_{\mathcal{K}} \triangleq (D, \{(\theta, \emptyset, \emptyset) \mid (\theta, \rho, \sigma) \in \Theta\})$ where
    $(D, \Theta) \triangleq [\![P]\!]$

TOOLS

PROTOTYPE WEB INTERFACE TO THE LSB COMPILER

LSB EDITOR

```
sim-rate RMRNADeg 0.001 |
//sim-initpop A 200.0 |


// Translation unit + termination modules:
module transl(out) { rbs; pcr<codes(out)>; ter };
module transl2(out1, out2) { rbs; pcr<codes(out1)>; rbs; pcr<codes(out2)>; ter  };

// Positively regulated gene modules:
module gatePos(in, out) { prom<pos(in)>; transl(out)  };
module gatePos2(in, out1, out2) { prom<pos(in)>; transl(out1, out2)  };

// Negatively regulated gene modules:
module gateNeg(in, out) { prom<neg(in)>; transl(out)  };
module gateNeg2(in, out1, out2) { prom<neg(in)>; transl(out1, out2)  };
```

Load sample program: programs-rates2.lsb

Compilation flags: ☐ Simulation-only reactions

Compile

COMPILATION RESULTS

Messages:

```
Compilation successful.
```

Number of solutions: 2

Select solution: Solution 1

Species:

```
[("H1", "m3OC12HSL"); ("H2", "m3OC6HSL"); ("Q1a", "lasI"); ("Q1b", "lasR");
 ("Q2a", "luxI"); ("Q2b", "luxR")]
```

Parts implementation:

```
[["r0051"; "b0034"; "c0062"; "b0034"; "c0078"; "b0015"; "runknown2"; "b0034";
  "cunknown4"; "b0015"; "r0051"; "b0034"; "cunknown3"; "b0015"];
 ["runknown2"; "b0034"; "cunknown3"; "b0015"; "r0051"; "b0034"; "c0061"; "b0034";
  "c0079"; "b0015"]]
```

```
<?xml version="1.0" encoding="UTF-8" ?>
<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1">
  <model>
    <listOfCompartments>
      <compartment id="W" name="W" size="1" />
      <compartment id="c1" name="c1" size="1" outside="W" />
      <compartment id="c2" name="c2" size="1" outside="W" />
    </listOfCompartments>
    <listOfSpecies>
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DISCUSSION

Contributions

- First dedicated “high-level” language for synthetic biology.
  - Existing “low-level” language - Cai et al:

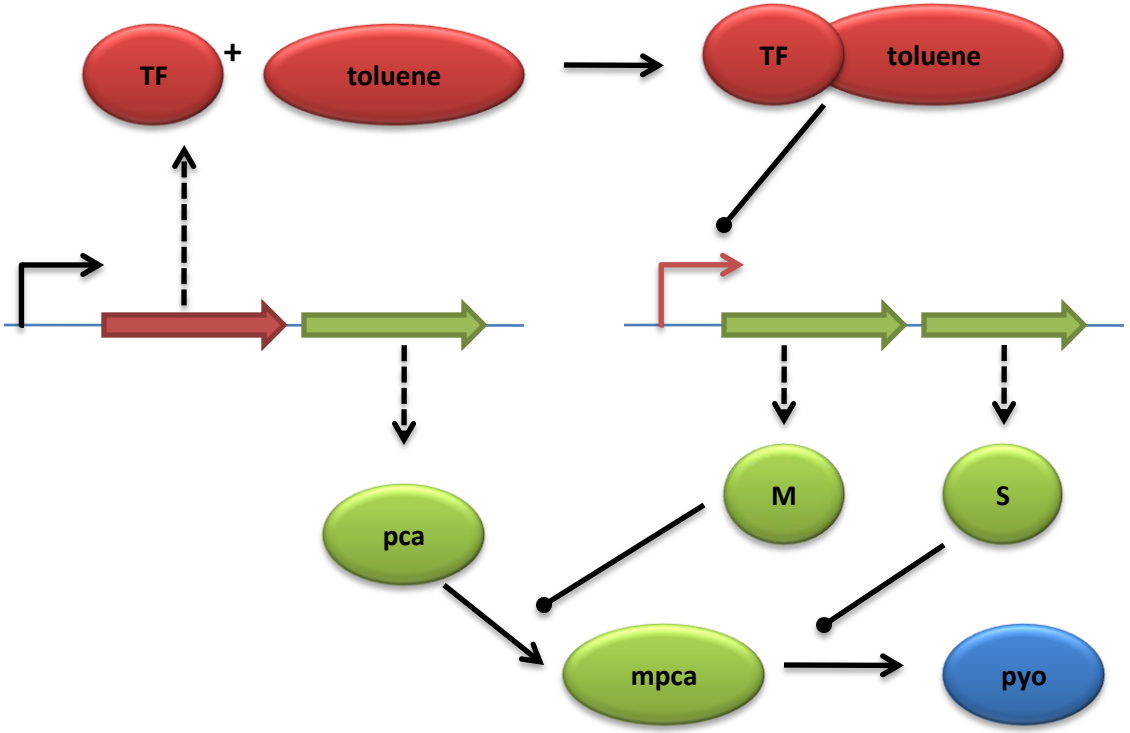
    A syntactic model to design and verify synthetic genetic constructs derived from standard biological parts. Bioinformatics, 2007.
- Allows formal representation of synthetic designs, simulation, and exploration of possible solutions.
- Provides a framework for prototyping parts standardisation proposals.

Future directions

- Ensuring that compiled programs work when implemented *in vivo*.
- Further levels of deductive reasoning.
  - Shrager et al: *Deductive biocomputing*. PLoS ONE, 2007.
- Large-scale reaction databases at the “right” level of abstraction.
- Performance: Prolog implementation will not scale. Use dedicated constraint solvers?
- Better quantitative constraint framework.
  - Marchisio and Stelling: *Computational design of synthetic gene circuits with composiable parts.* Bioinformatics, 2008.
- Integration with other languages.

APPENDIX

The environmental pollutant detector



Heiner et al: *A case study in model-driven synthetic biology*. BICC, IFIP WCC, 2008