Automated Design of Synthetic Biology Feedback Circuits

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IBE Conference
March, 2012

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Raytheon
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Vision: WYSIWYG Synthetic Biology

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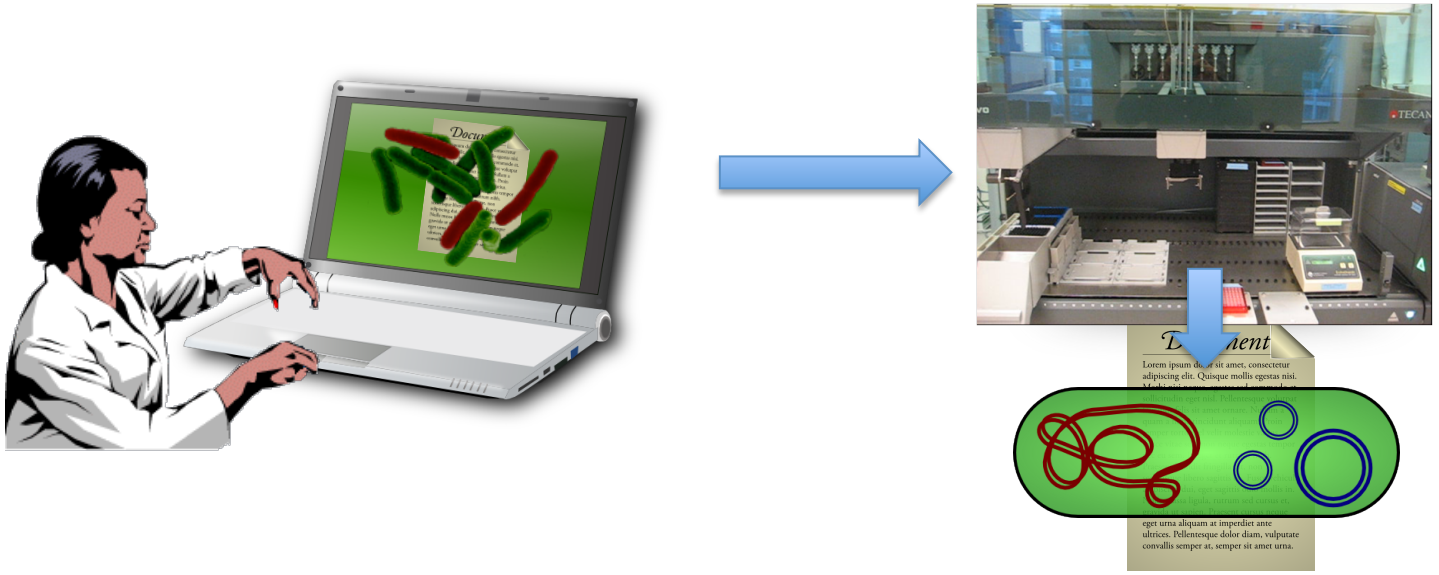
Bioengineering should be like document preparation:



Why is this important?

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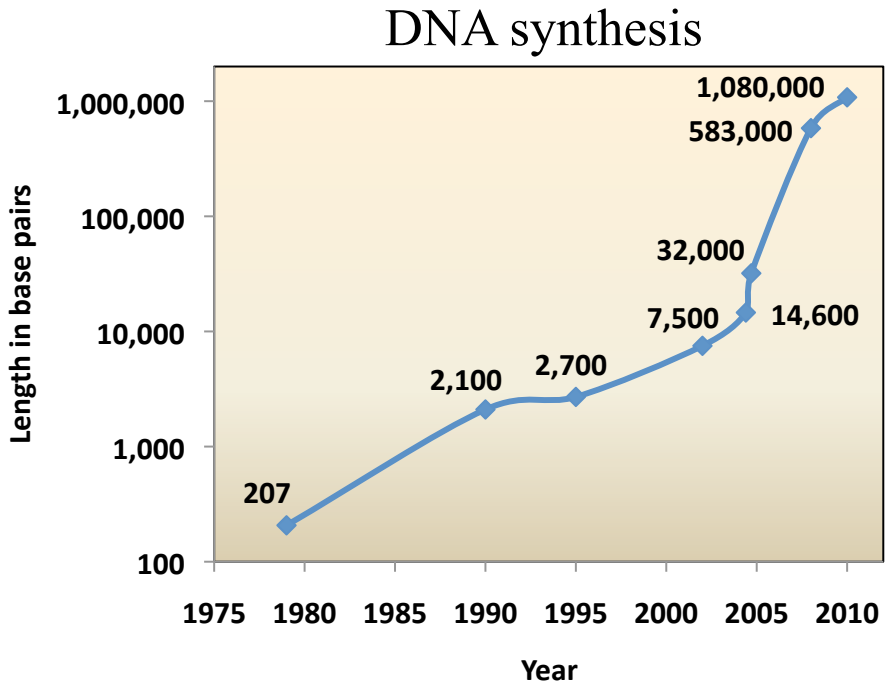
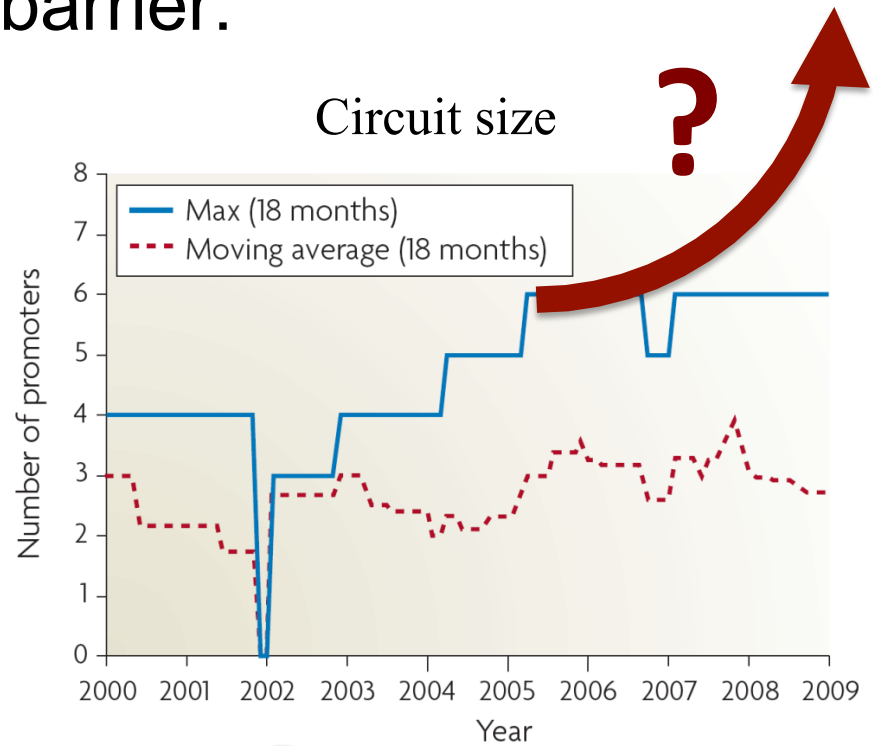
- Breaking the complexity barrier:





[Purnick & Weiss, '09]

- Multiplication of research impact
- Reduction of barriers to entry

*Sampling of systems in publications with experimental circuits

Why a tool-chain?

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Organism Level Description

This gap is too big to cross with a single method!

Cells

The TASBE architecture:

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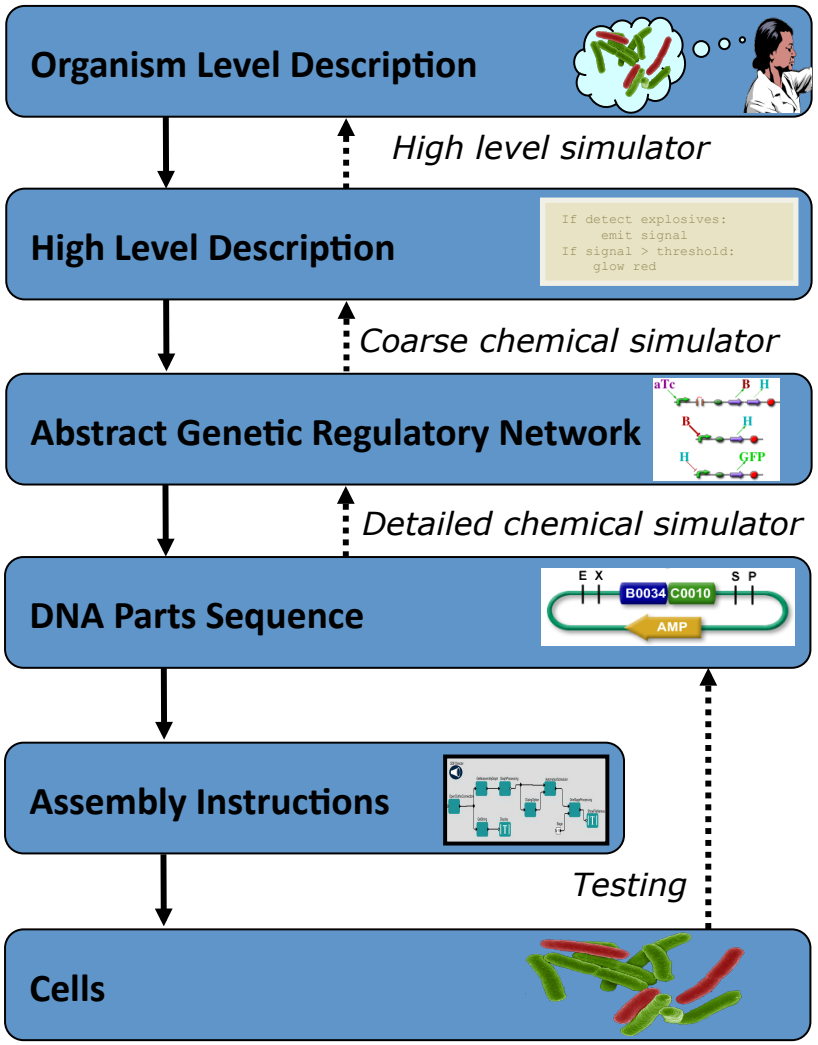

Collaborators:

Ron Weiss

Douglas Densmore

Modular architecture also open for flexible choice of organisms, protocols, methods, …

A Tool-Chain Example

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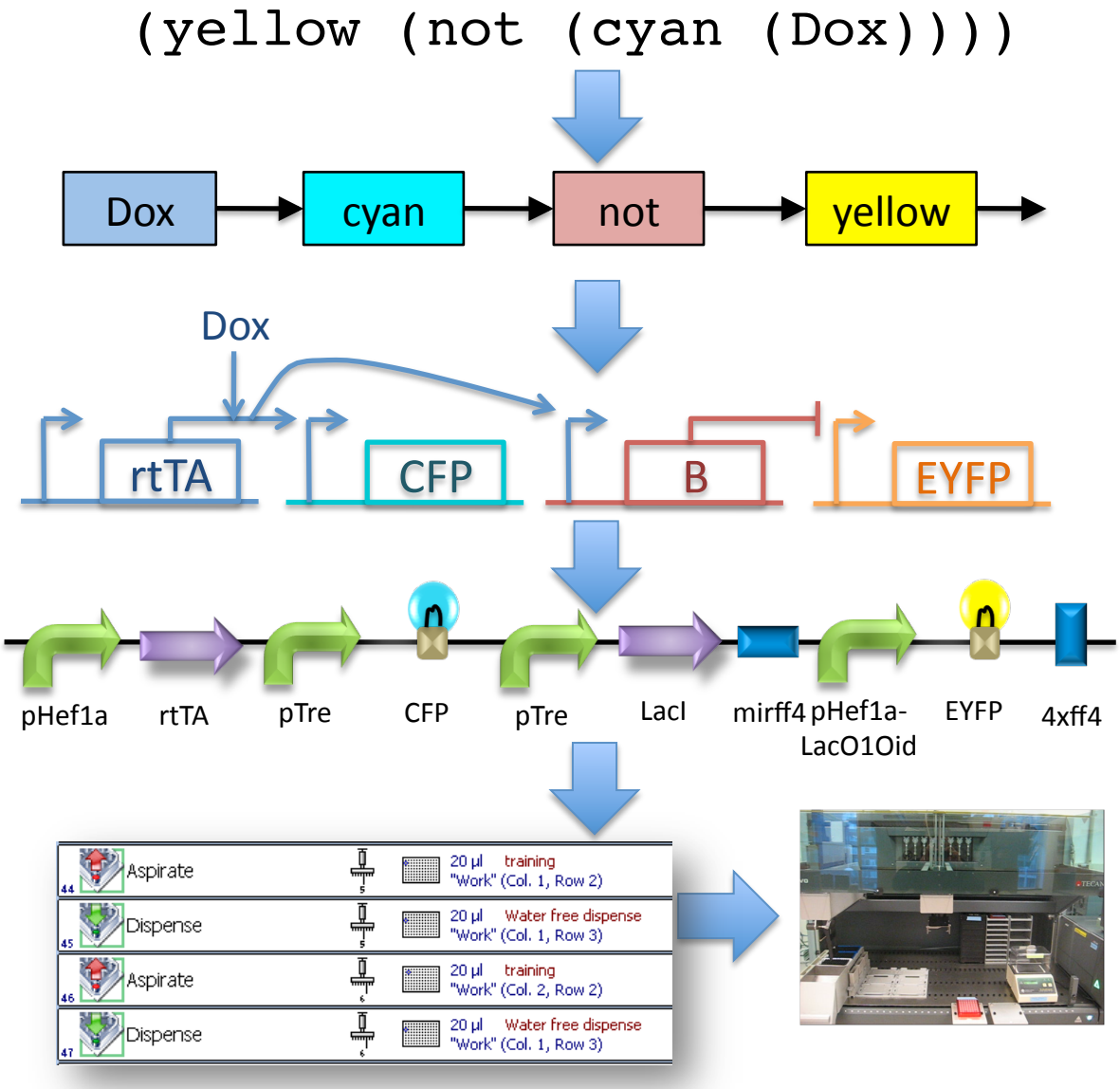

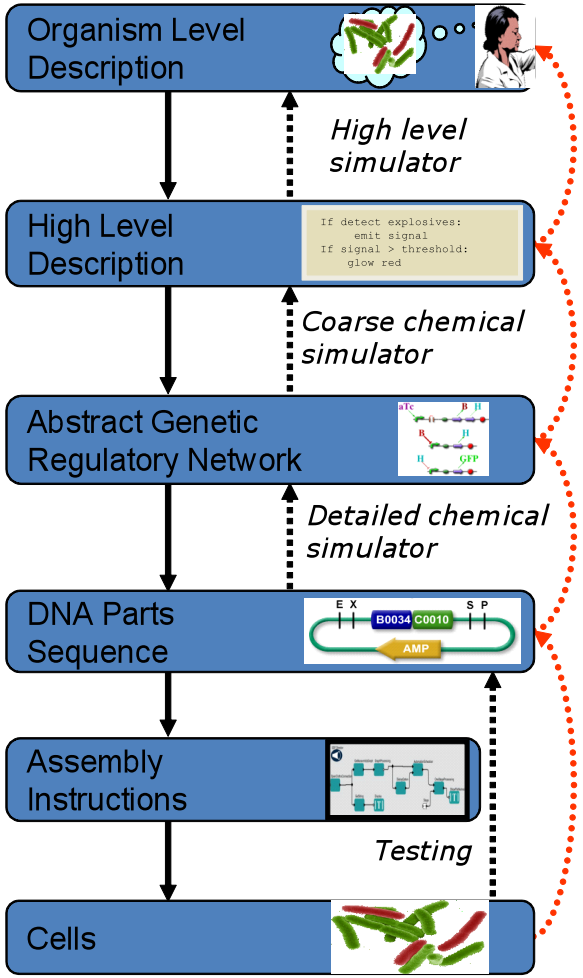

Today's focus: BioCompiler

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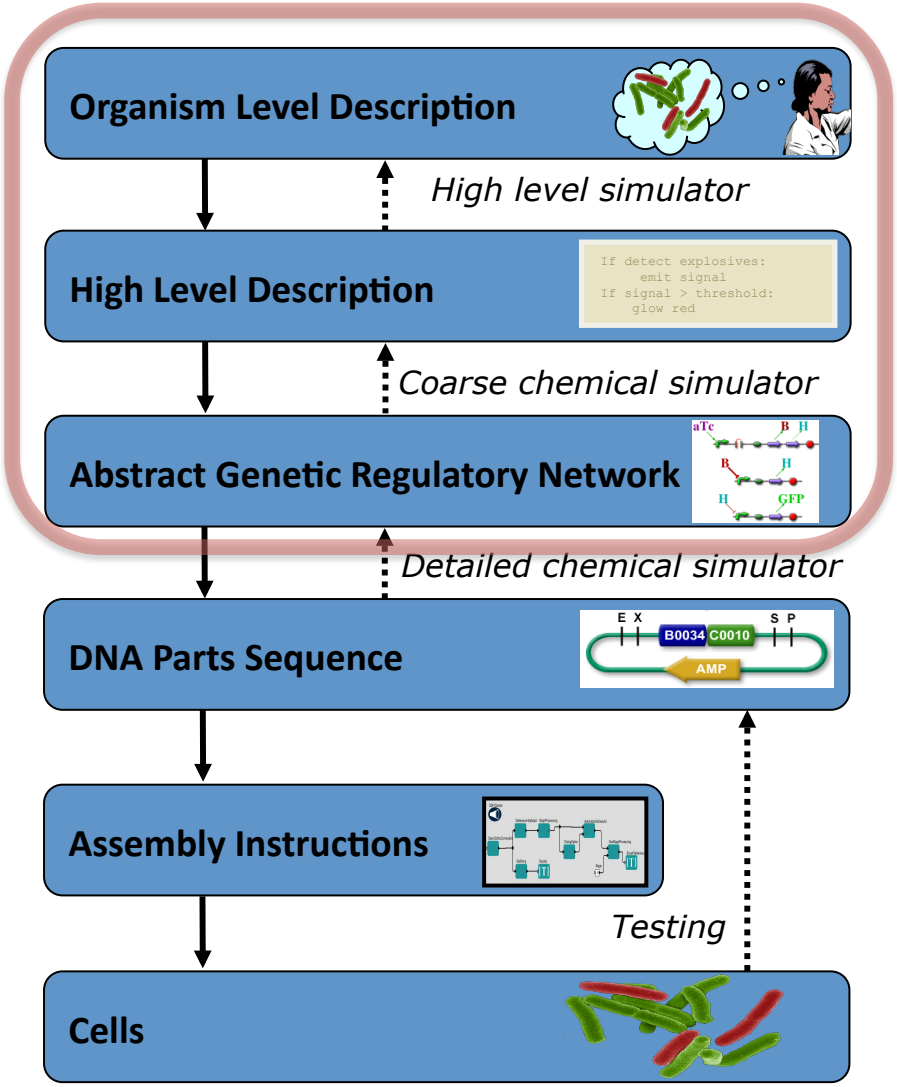
Compilation & Optimization



Transcriptional Logic

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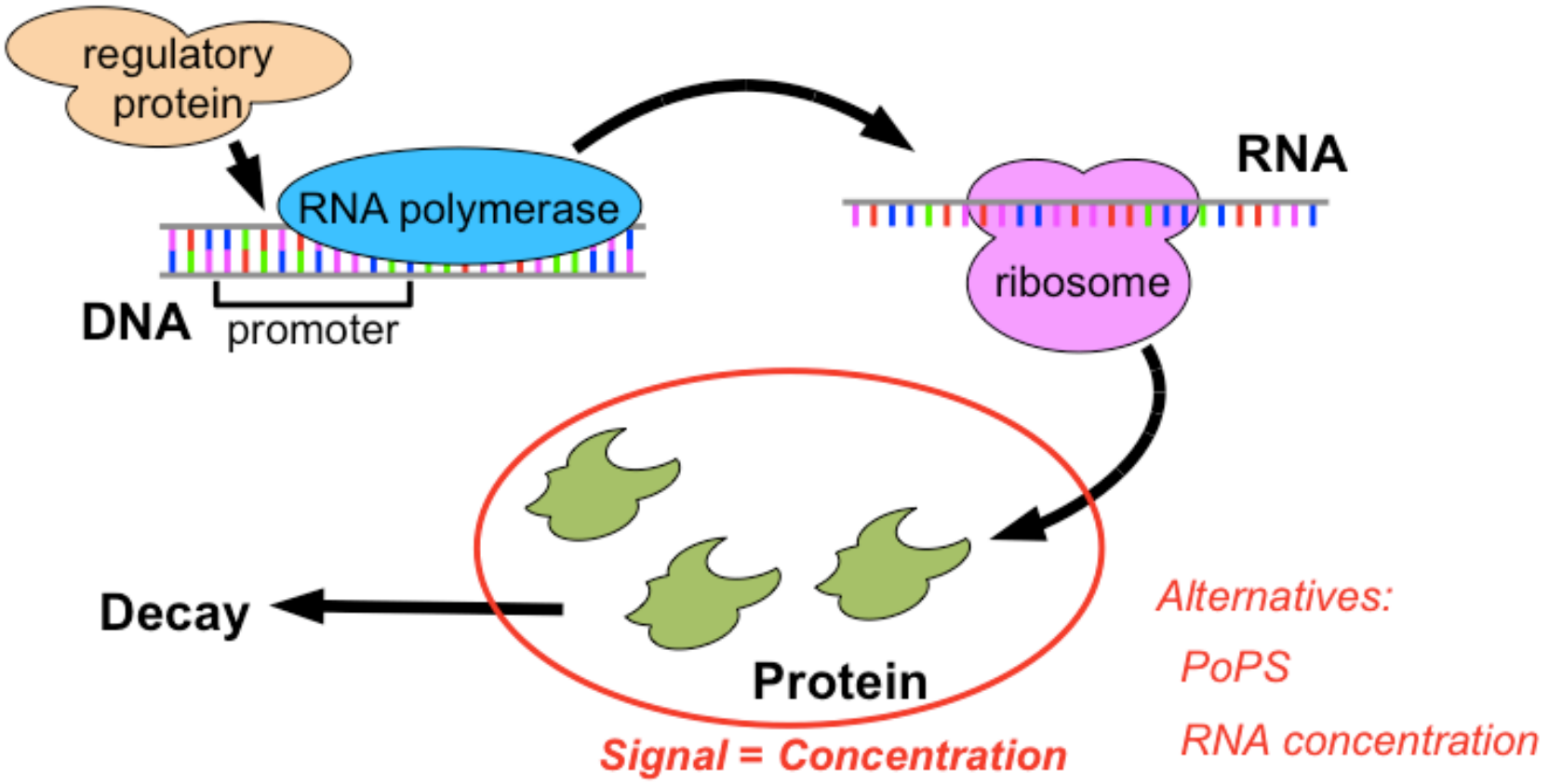

Stablizes at *decay* = *production*

Motif-Based Compilation

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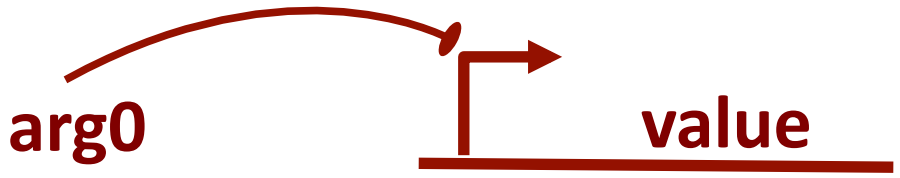
- High-level primitives map to GRN design motifs
  - e.g. logical operators:

```
(primitive not (boolean) boolean
        :grn-motif ((P high R- arg0 value T)))
```



Motif-Based Compilation

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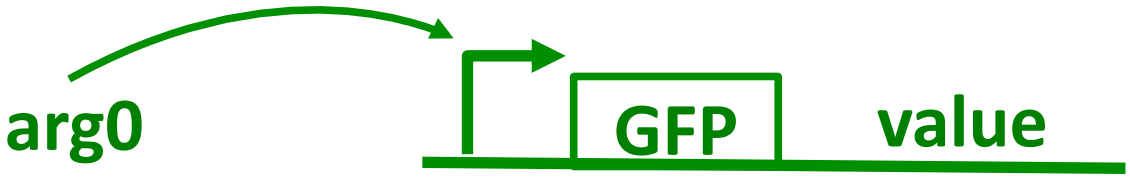
- High-level primitives map to GRN design motifs
  - e.g. logical operators, **actuators**:

```
(primitive green (boolean) boolean :side-effect
  :type-constraints ((= value arg0))
  :grn-motif ((P R+ arg0 GFP|arg0 value T)))
```



Motif-Based Compilation

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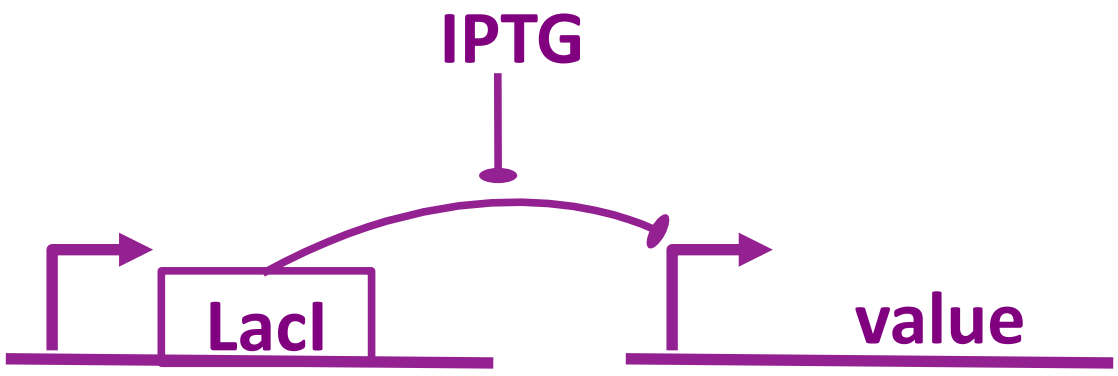
- High-level primitives map to GRN design motifs
  - e.g. logical operators, actuators, **sensors**:

```
(primitive IPTG () boolean
  :grn-motif ((P high LacI|boolean T)
              (RXN (IPTG|boolean) represses LacI)
              (P high R- LacI value T)))
```



Motif-Based Compilation

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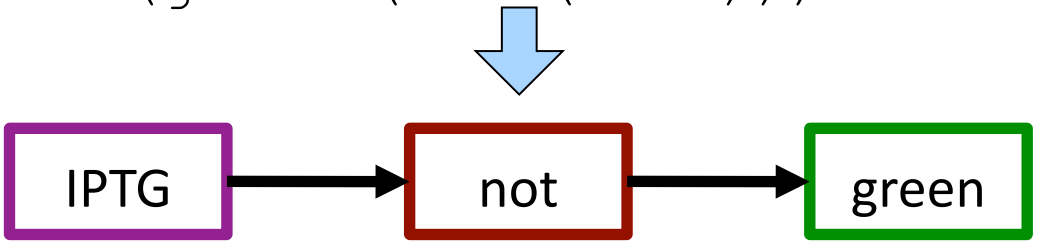
- Functional program gives dataflow computation:

```
(green (not (IPTG)))
```



Motif-Based Compilation

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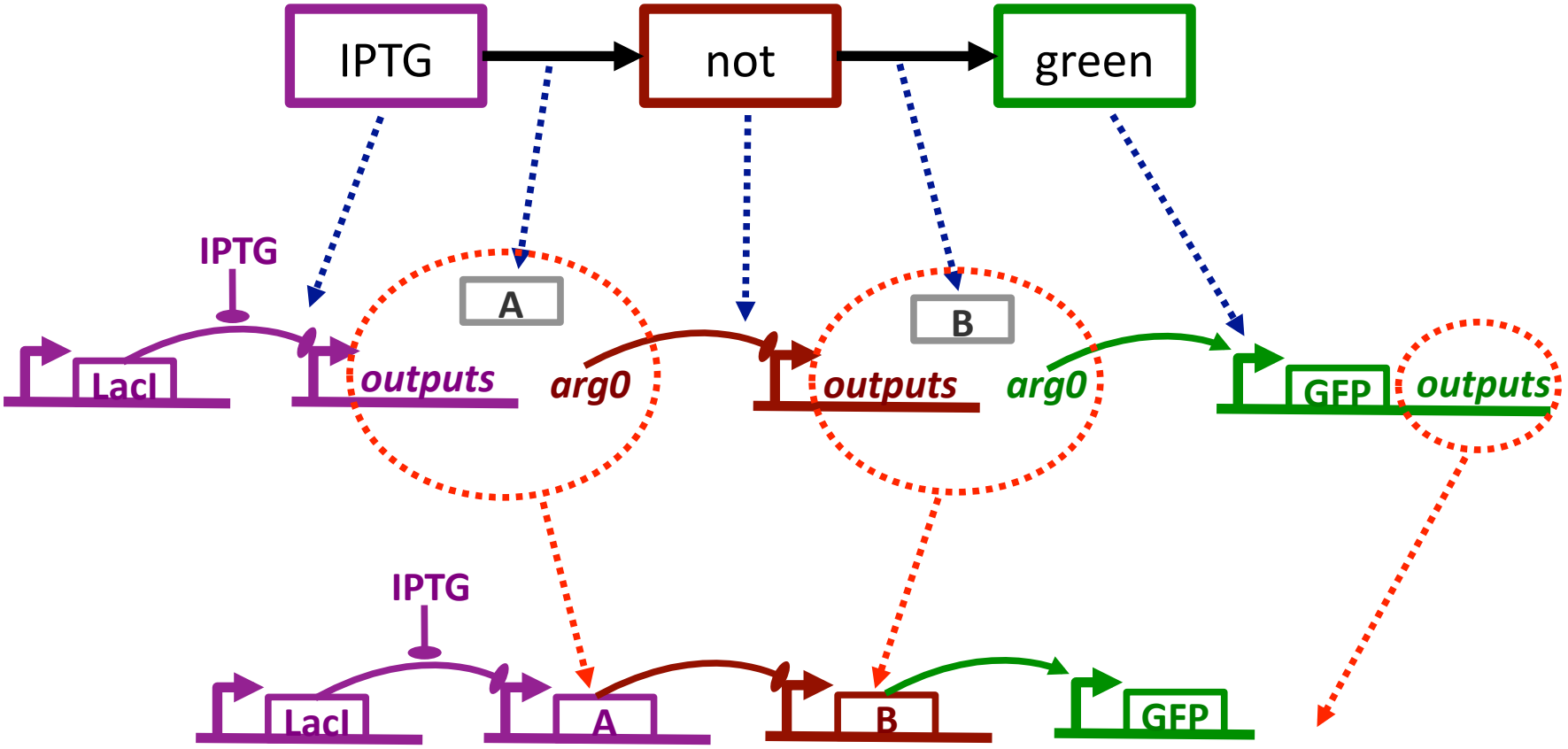
- Operators translated to motifs:



Optimization

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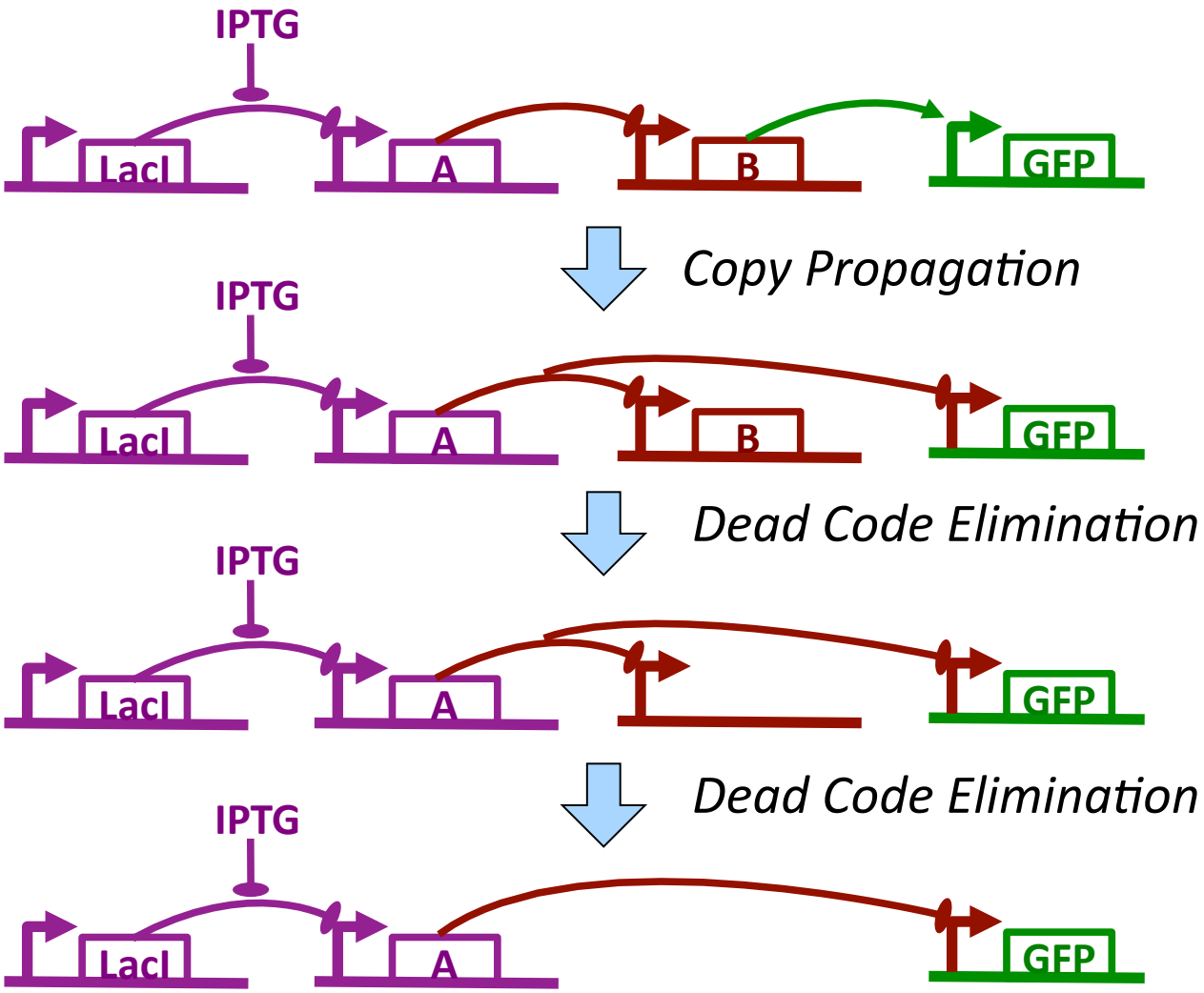

GRN Optimization Library

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- Copy Propagation
- Dead Code Elimination
- Double-Negative Elimination
- Constant Eliminator
- CSE: Output Consolidation
- CSE: Merge Duplicate Inputs
- NOR Compression

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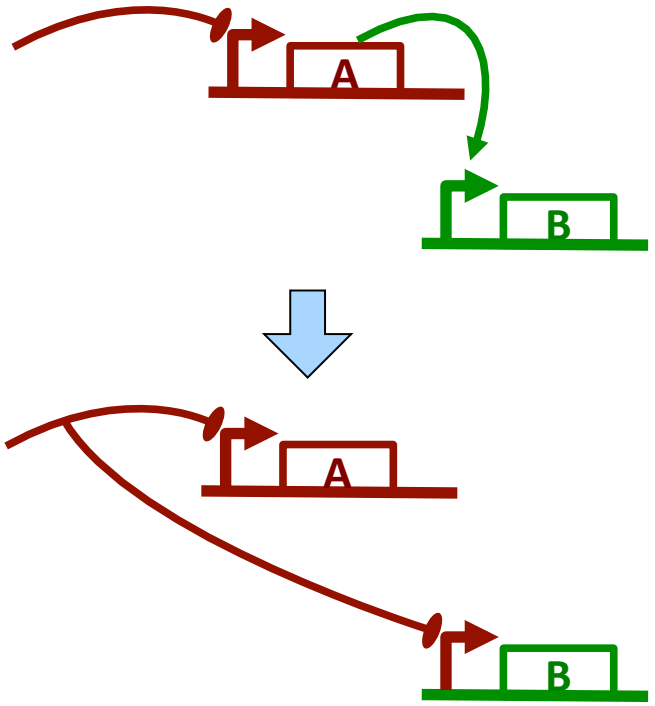

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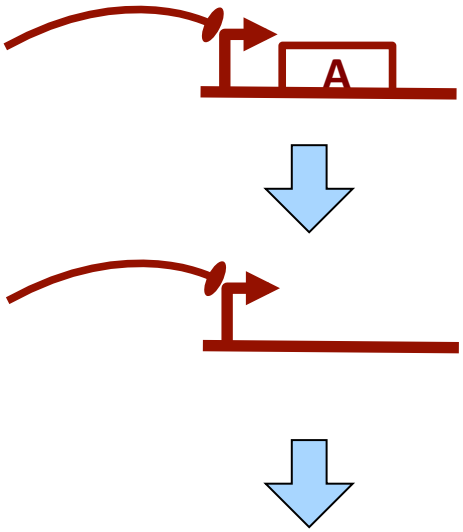

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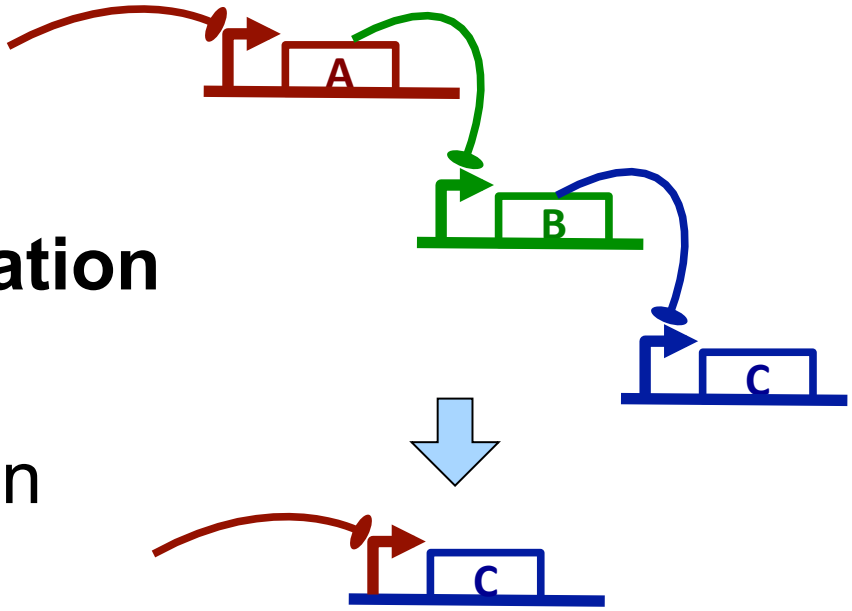

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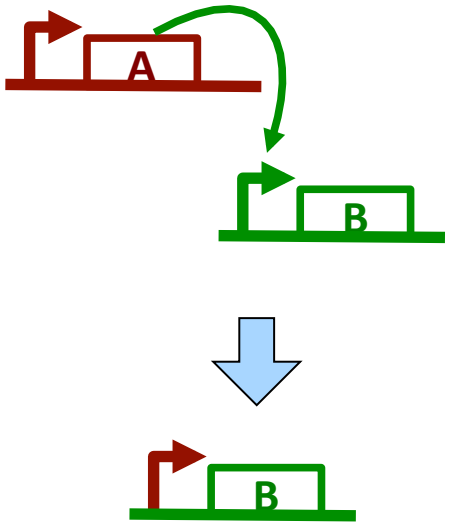

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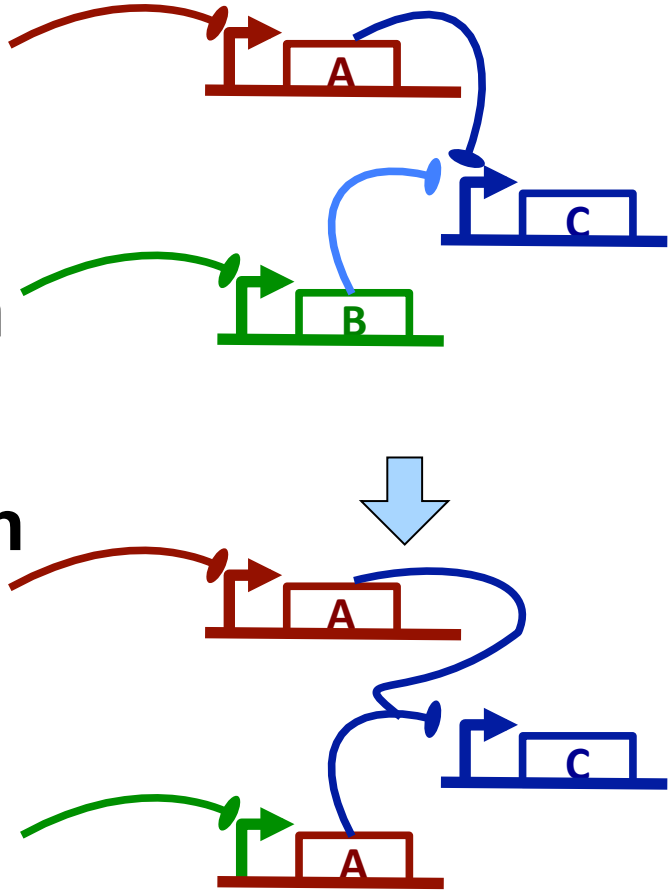

GRN-specific

GRN Optimization Library

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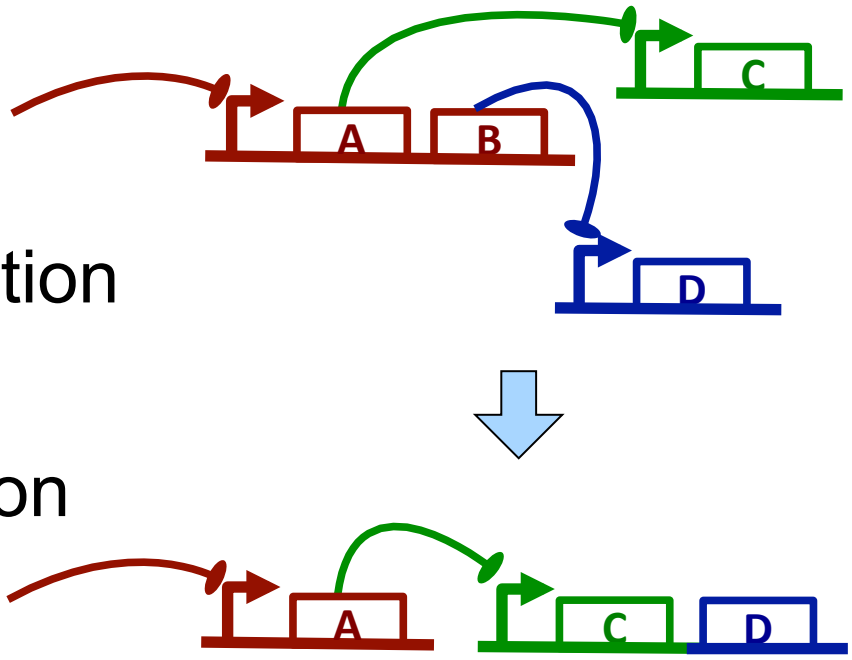

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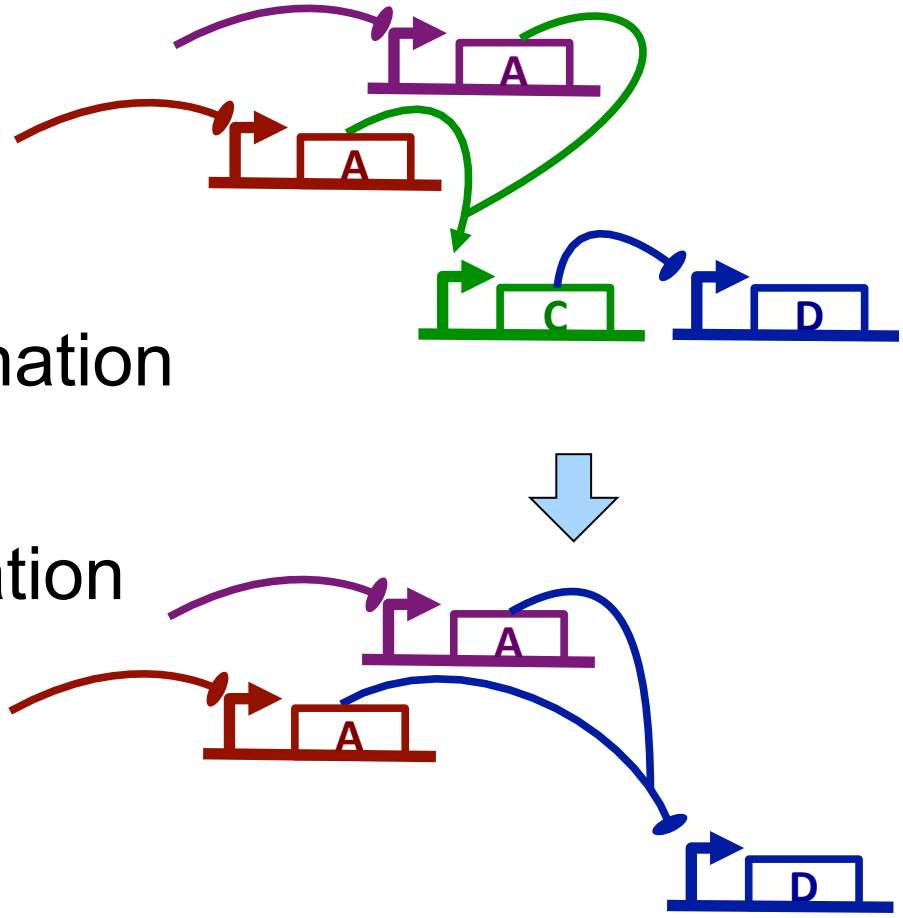

GRN-specific

Feedback System: SR-Latch

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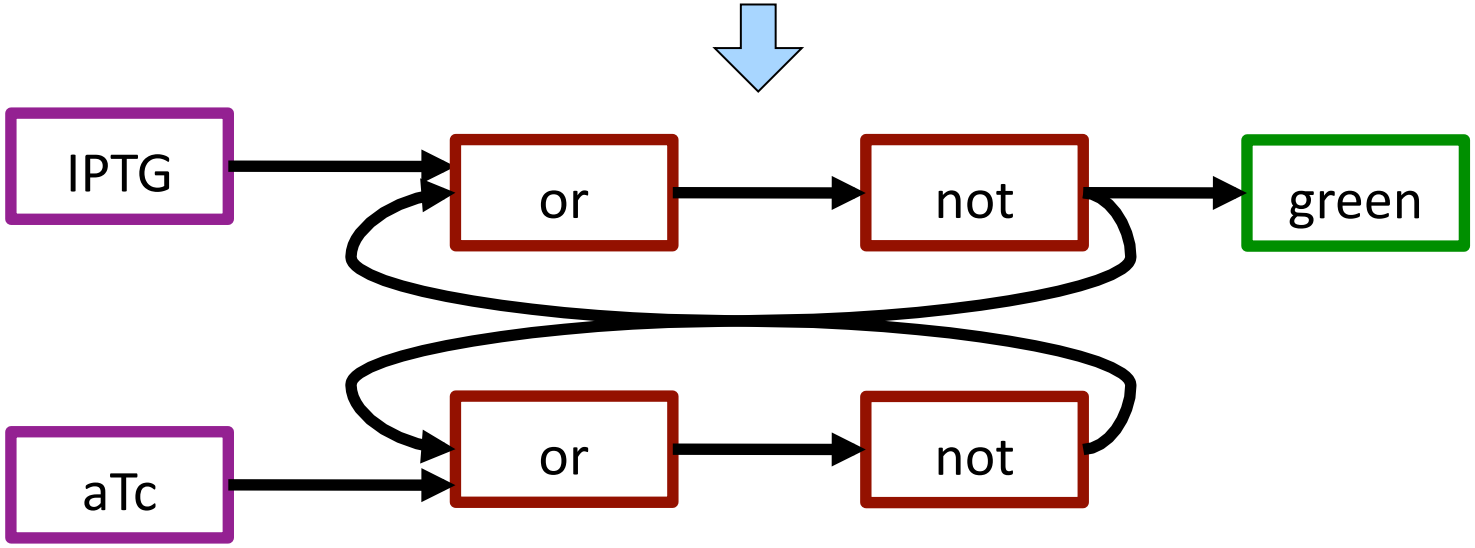
```
(def sr-latch (s r)
  (letfed+ ((o boolean (not (or r o-bar)))
            (o-bar boolean (not (or s o))))
    o))

(green (sr-latch (aTc) (IPTG)))
```



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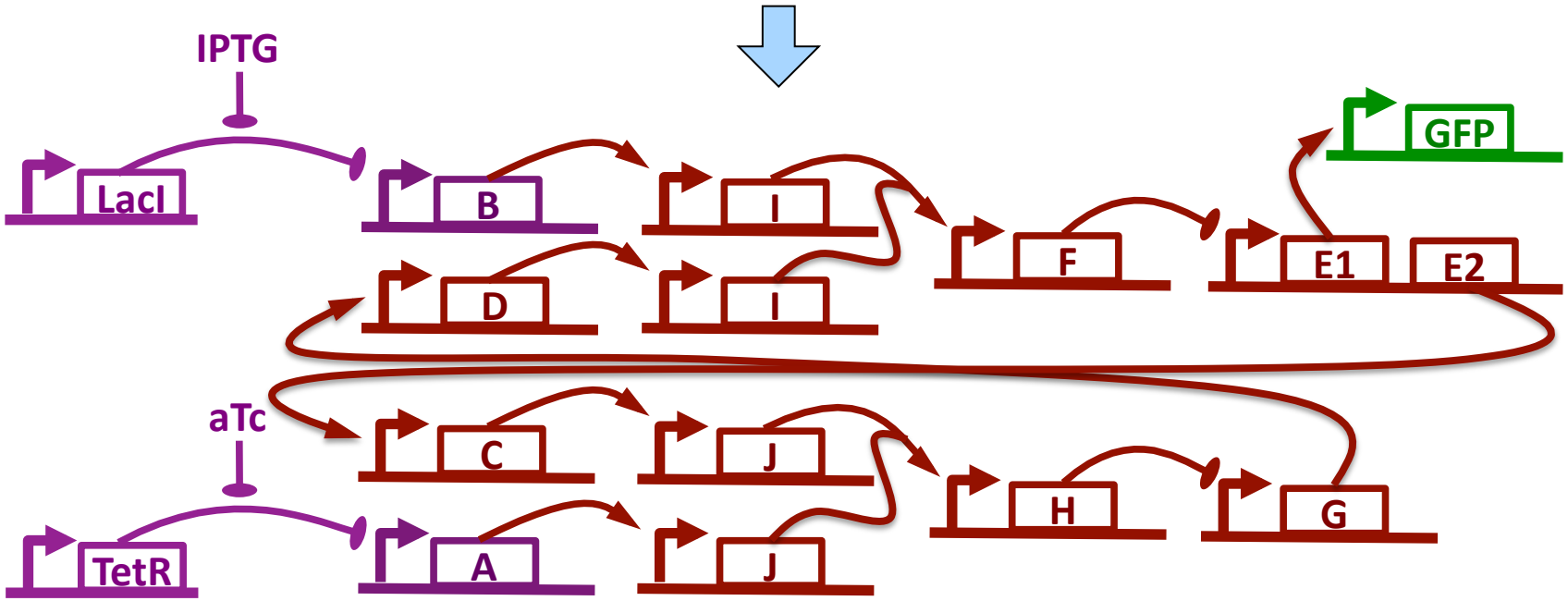

Unoptimized: 15 functional units, 13 transcription factors

Optimization of Complex Designs

Raytheon
BBN Technologies

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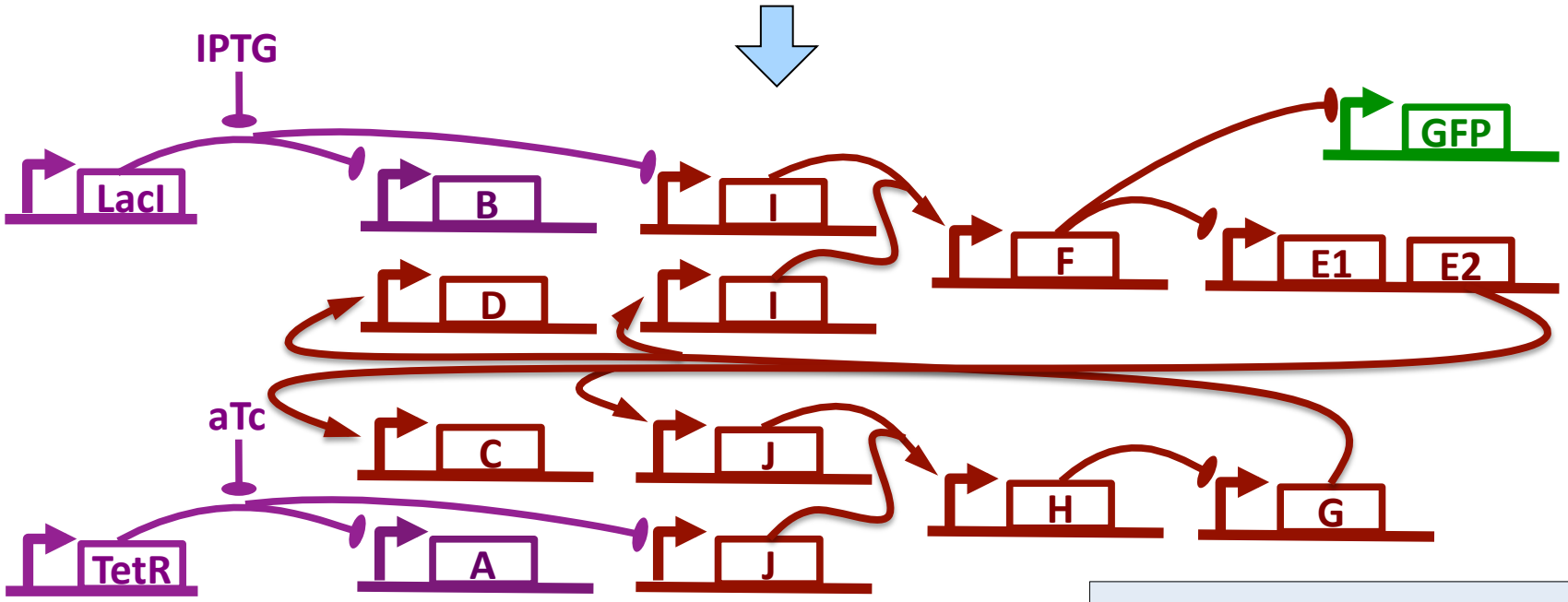

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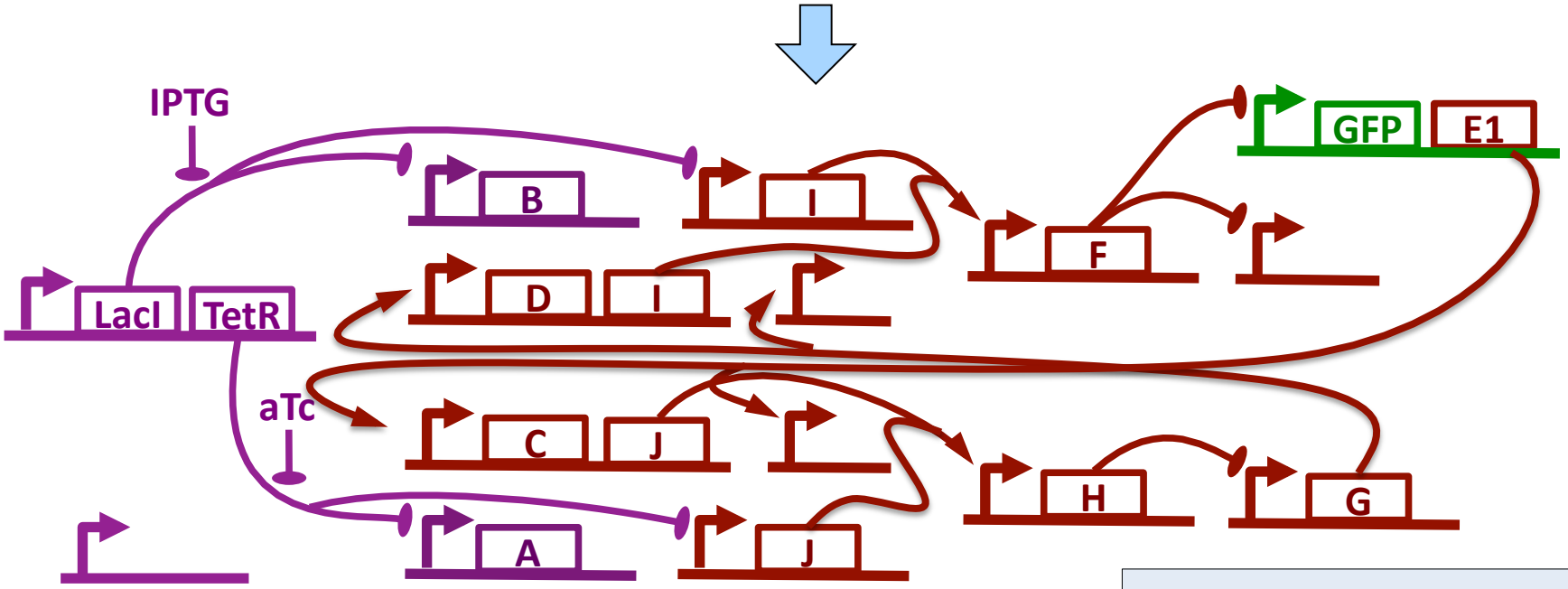

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Common Subexp. Elim.

Optimization of Complex Designs

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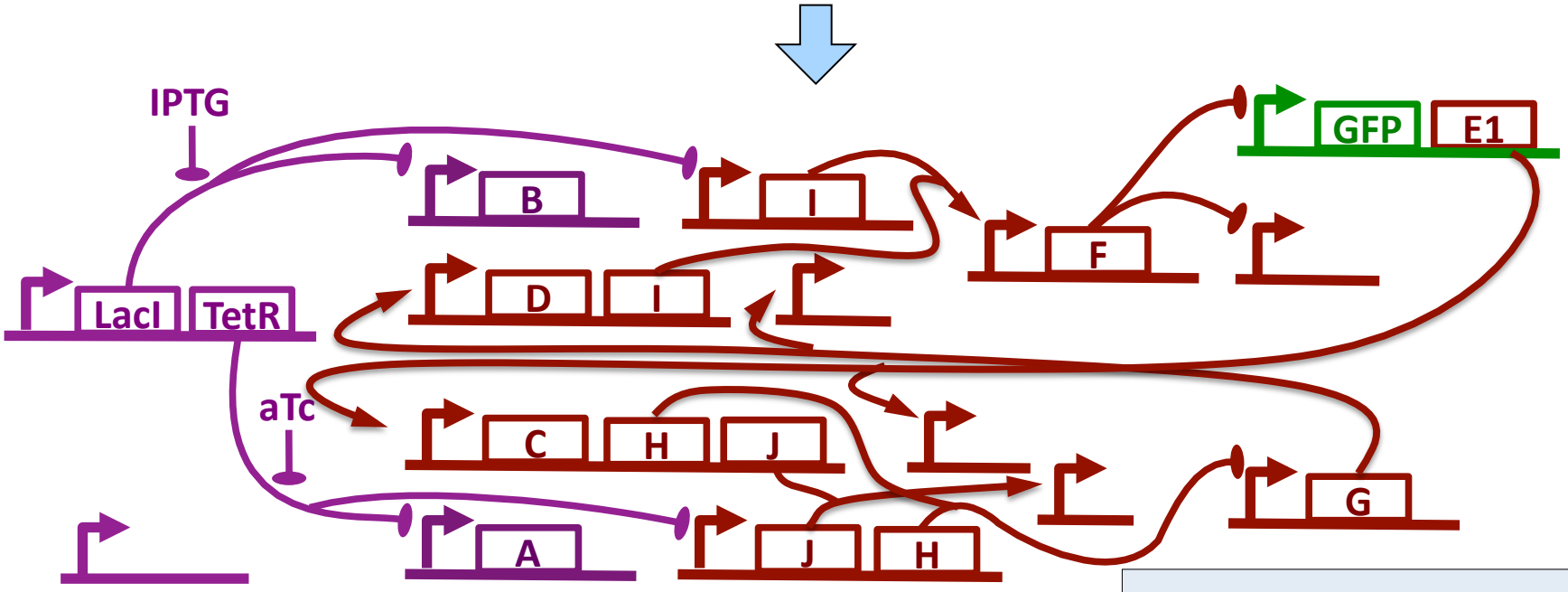

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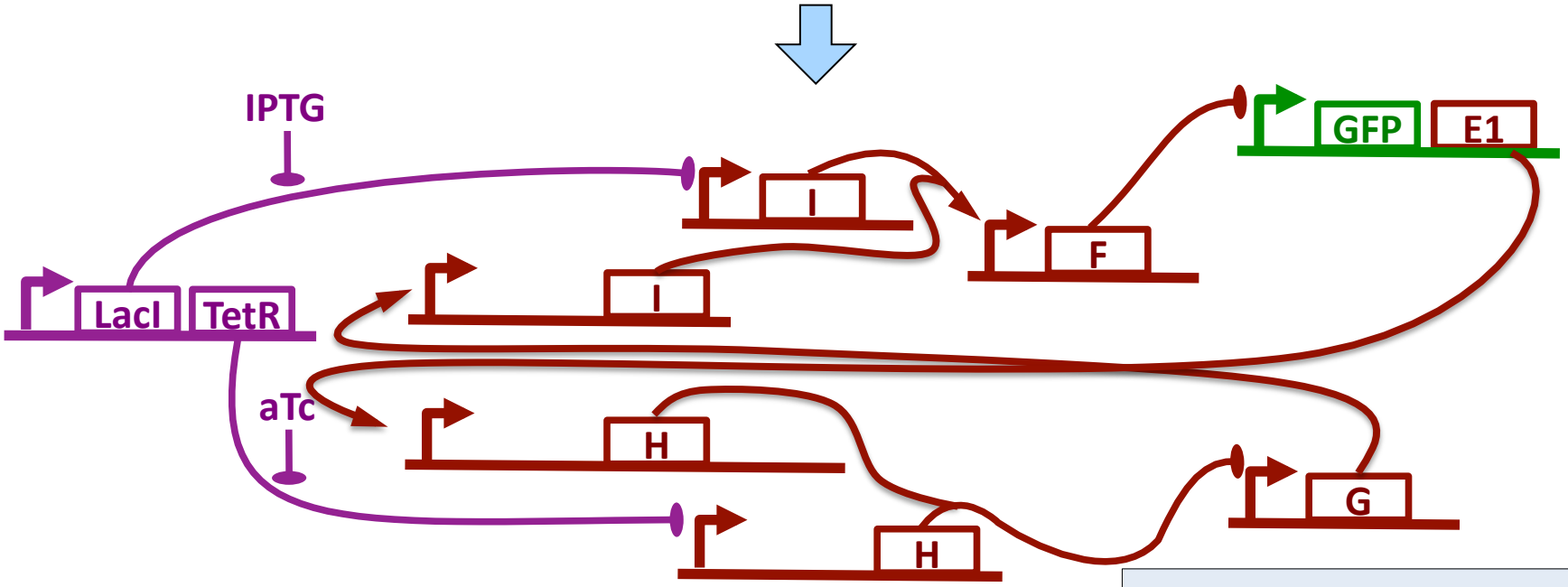

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Dead Code Elimination

Optimization of Complex Designs

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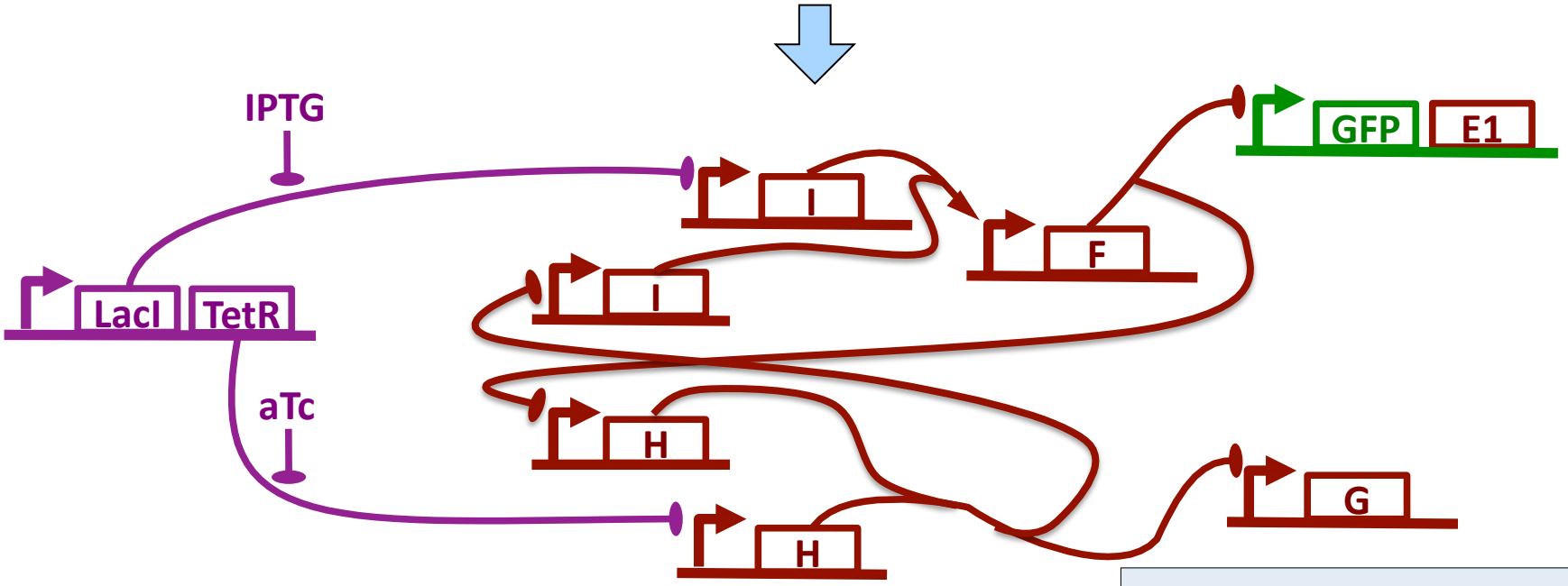

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Copy Propagation

Optimization of Complex Designs

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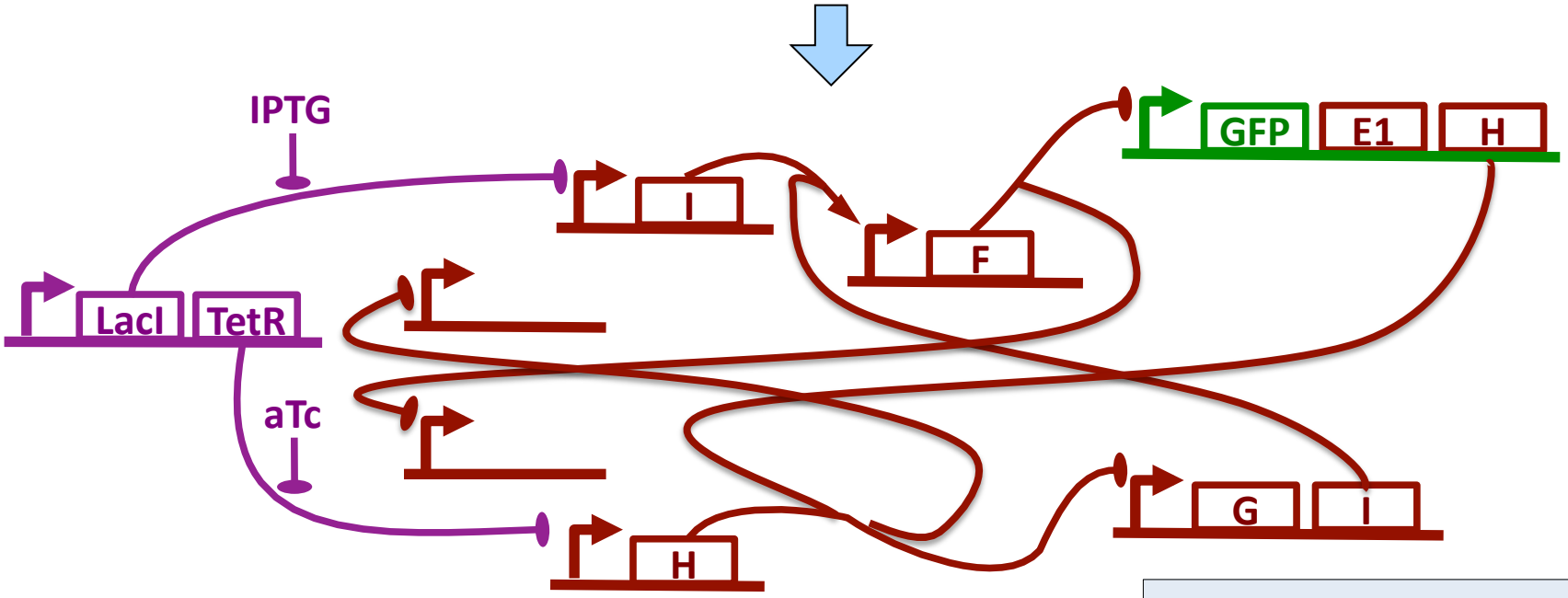

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Optimization of Complex Designs

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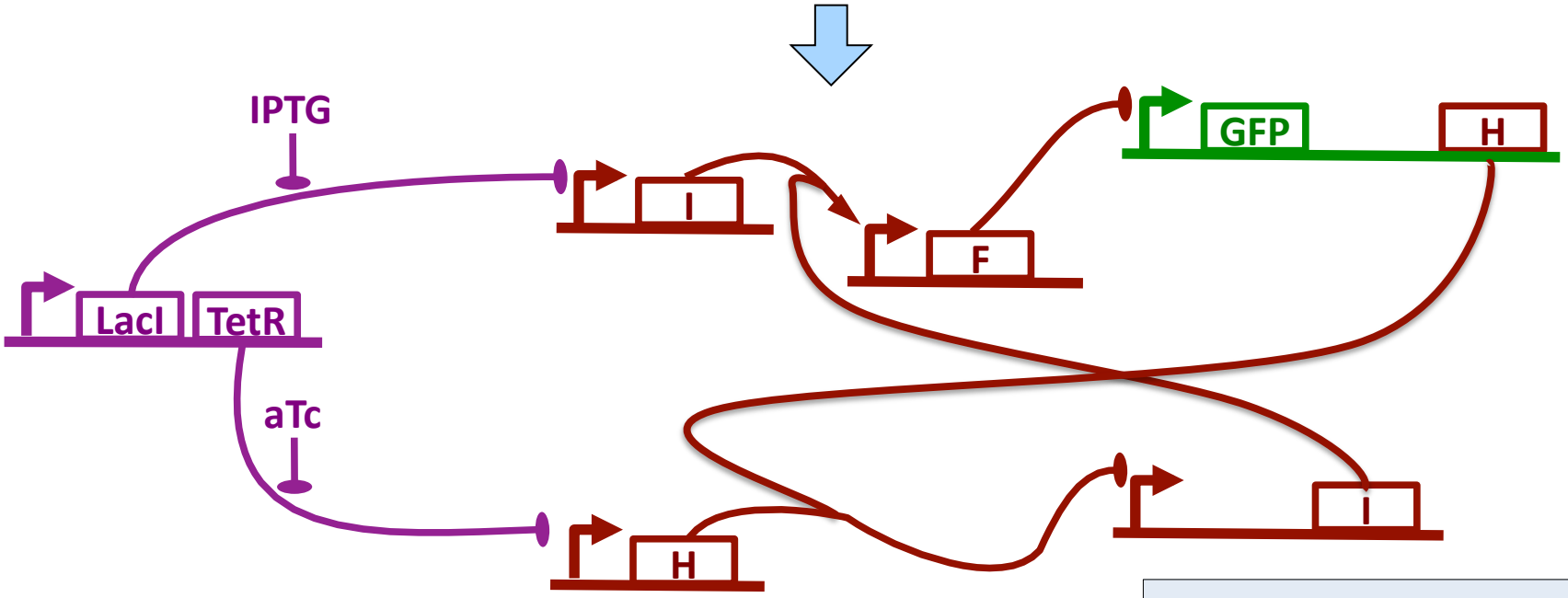

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Optimization of Complex Designs

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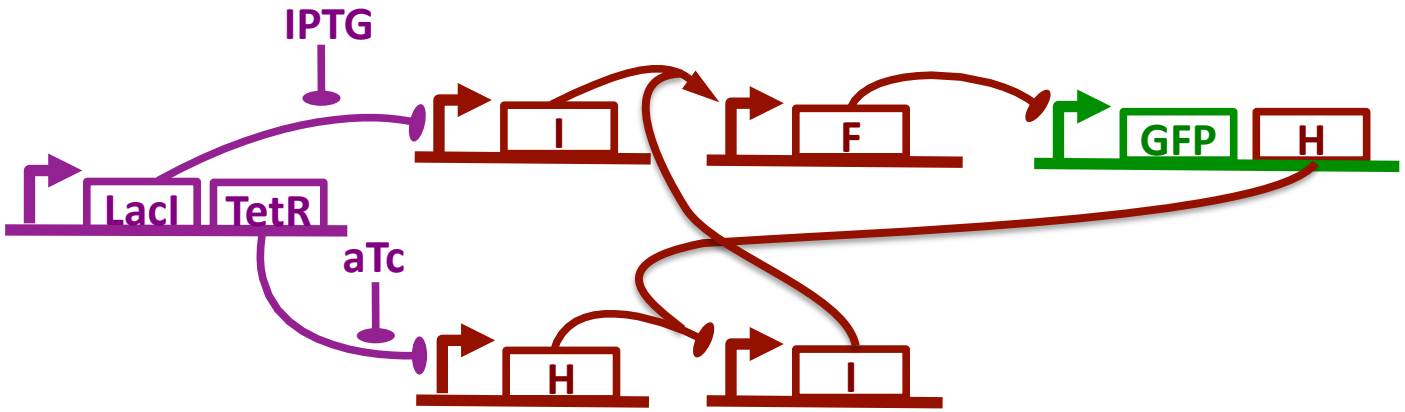

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Optimization of Complex Designs

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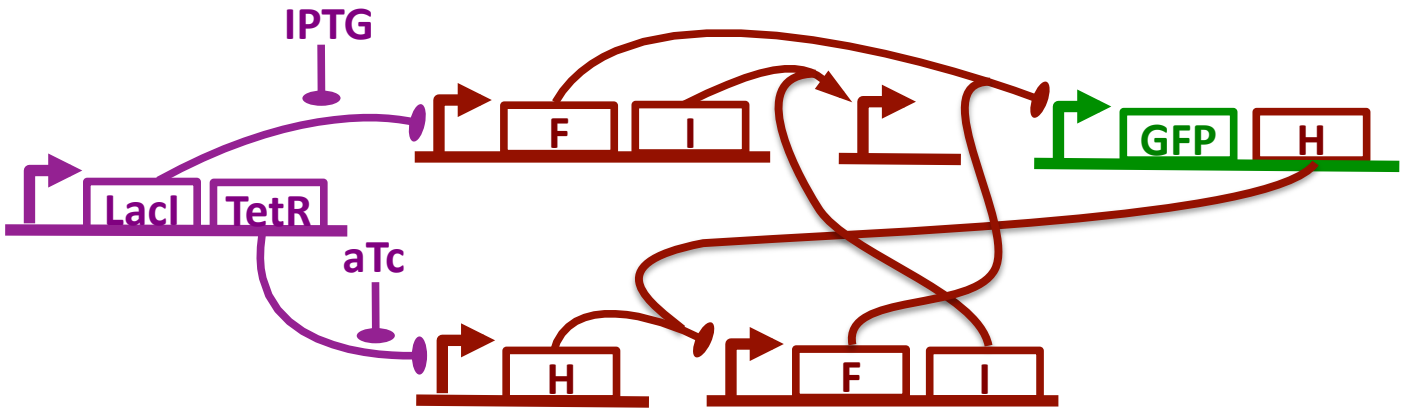

Unoptimized: 15 functional units, 13 transcription factors

NOR Compression

Optimization of Complex Designs

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BBN Technologies

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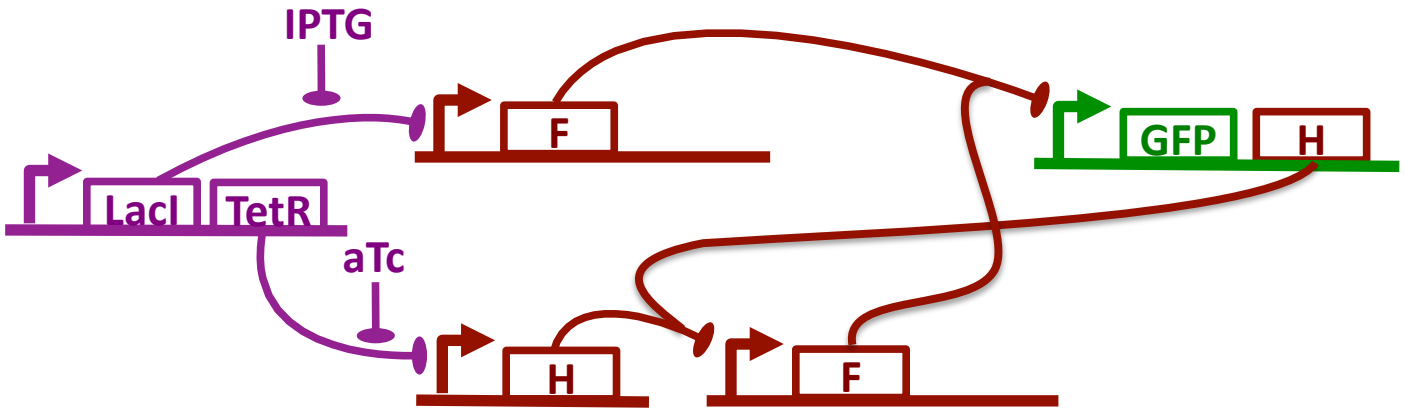

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Dead Code Elimination

Optimization of Complex Designs

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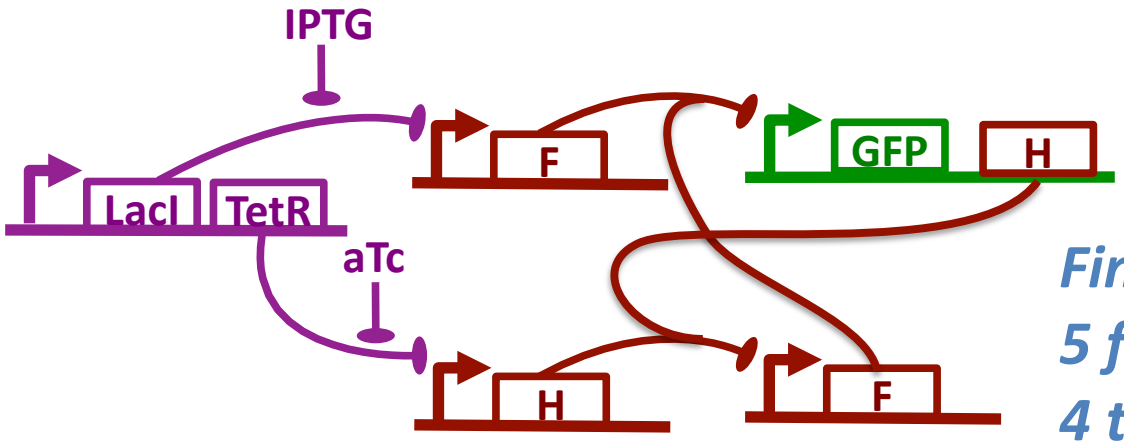

Final Optimized:
5 functional units
4 transcription factors

Unoptimized: 15 functional units, 13 transcription factors

Compilation & Optimization Results:

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- Automated GRN design for arbitrary boolean logic and feedback systems
  - Verification in ODE simulation
- Optimization competitive with human experts:
  - Test systems have 25% to 71% complexity reduction
  - Optimized systems are often homologous with hand designed networks
- Routine use within team

Onward Through the Tool-Chain…

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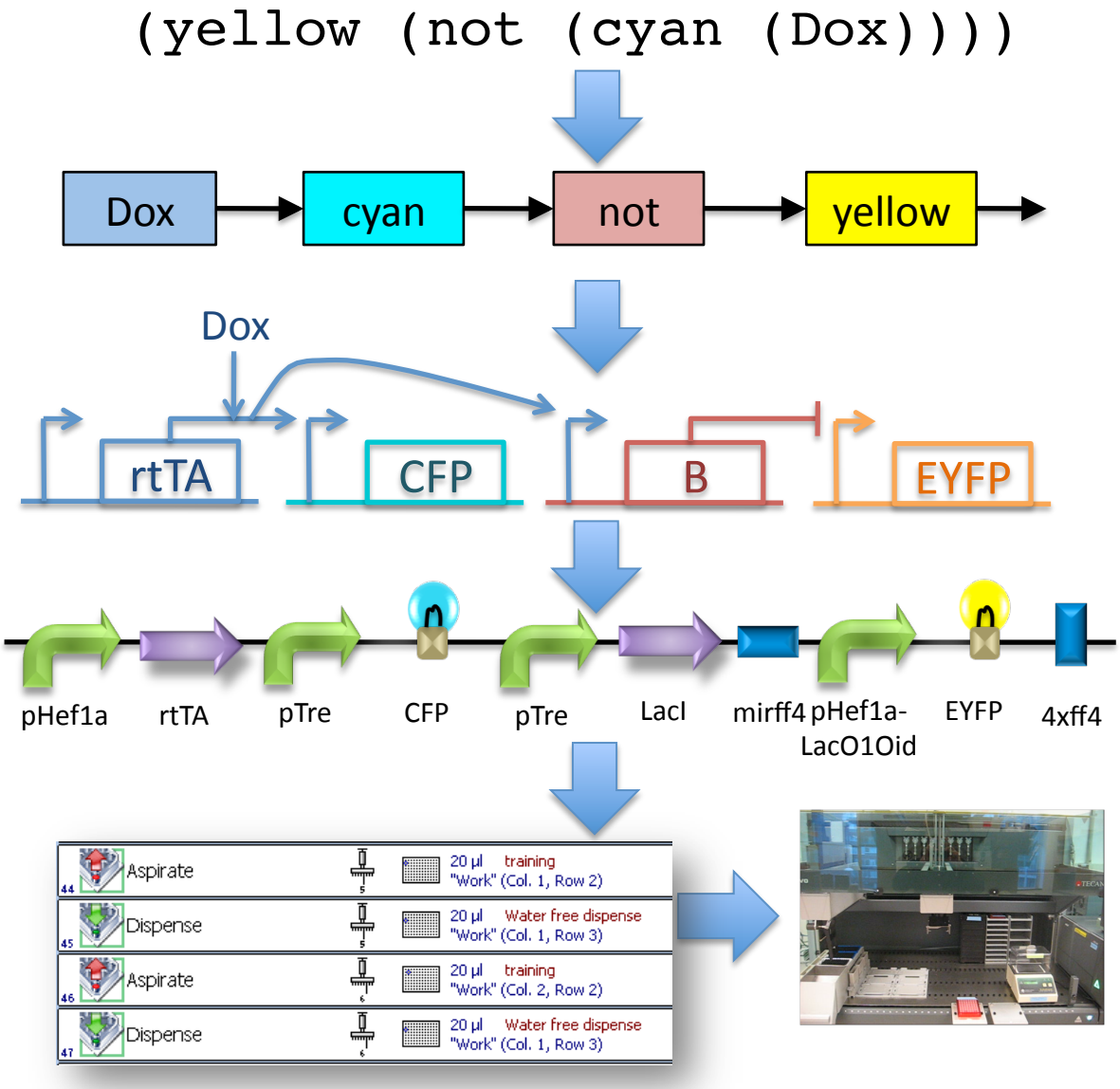

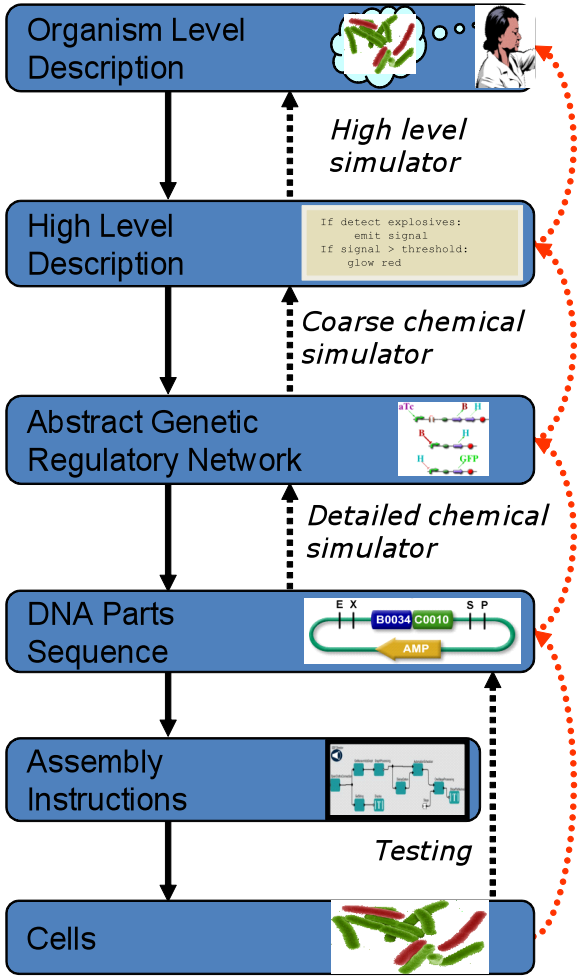

Contributions

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- Boolean & feedback logic circuits can be expressed in high-level language.
- GRN-specific optimizations allow dramatic optimization of circuit size.
- Automatically generated circuits are competitive with hand-designs created by experts.

Next steps: automatic verification, numerical computation, intercellular communication