

# High-Level BioDesign Automation

*Jacob Beal*

SemiSynBio  
February, 2013

**Raytheon**  
**BBN Technologies**

# Overview

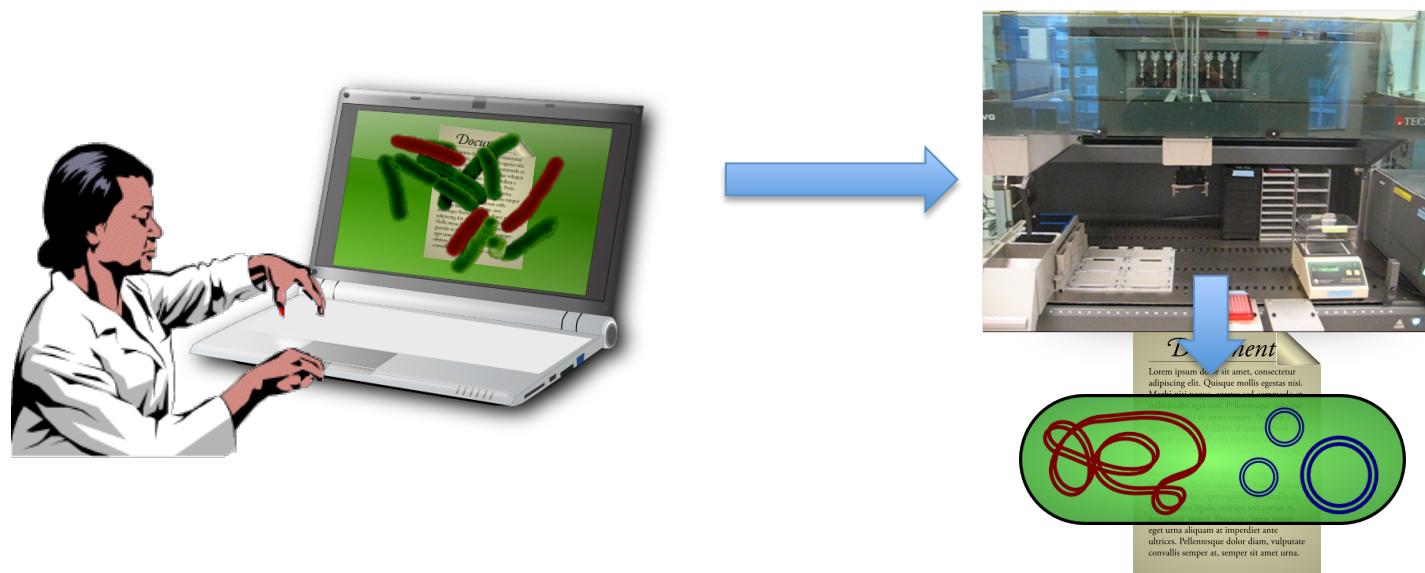
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*Is biology too hard for abstraction?*  
**High-Level BDA is possible *now!***

- Tool-chains for BDA
- Compiling from HLL to biological circuits
- Building computational device libraries

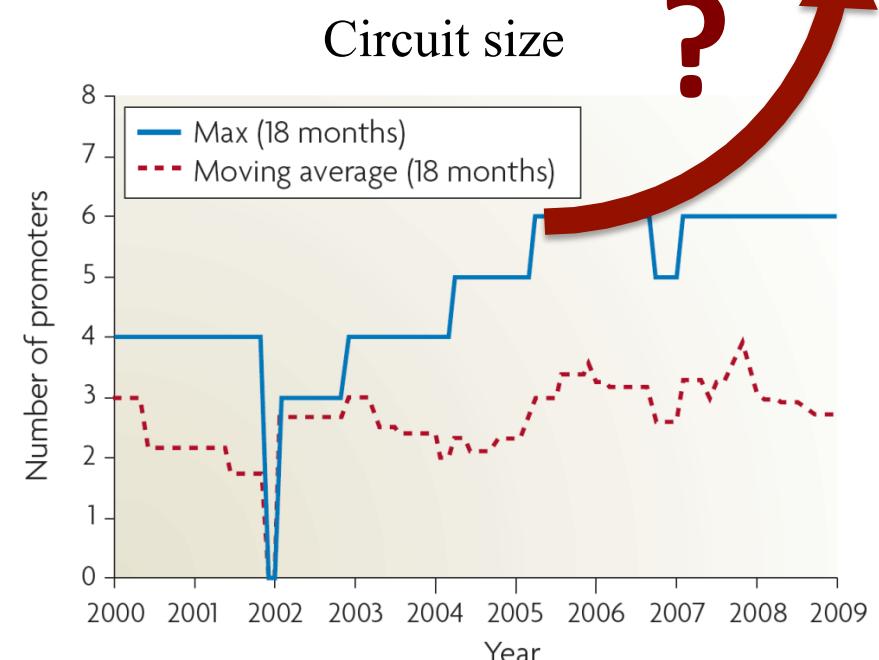
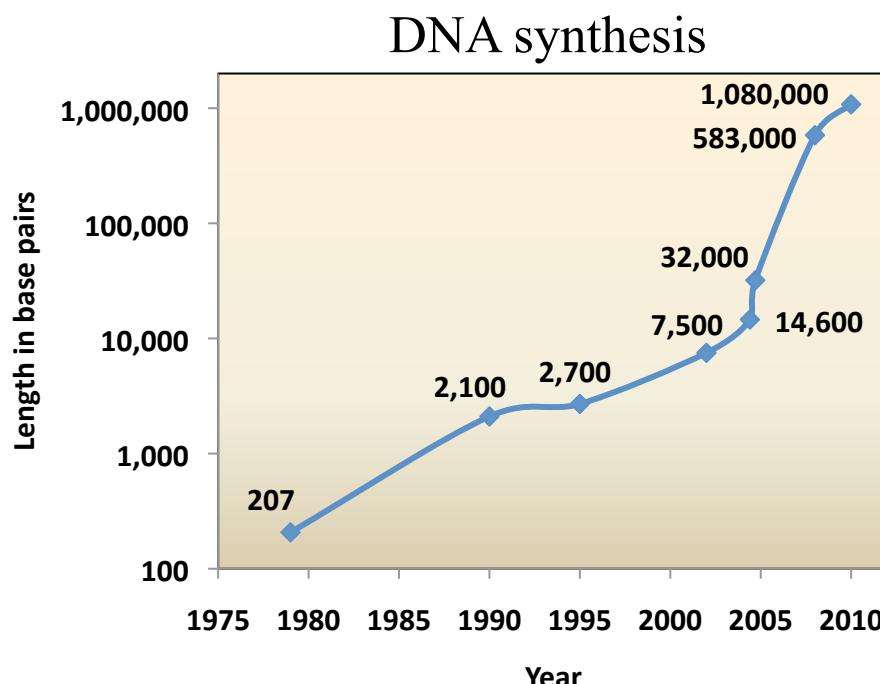
# Vision: WYSIWYG Synthetic Biology

Bioengineering should be like document preparation:



# Why is this important?

- Breaking the complexity barrier:



[Purnick & Weiss, '09]

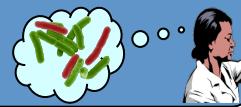
- Multiplication of research impact
- Reduction of barriers to entry

\*Sampling of systems in publications with experimental circuits

# Why a tool-chain?

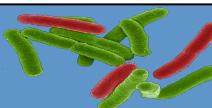
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Organism Level Description

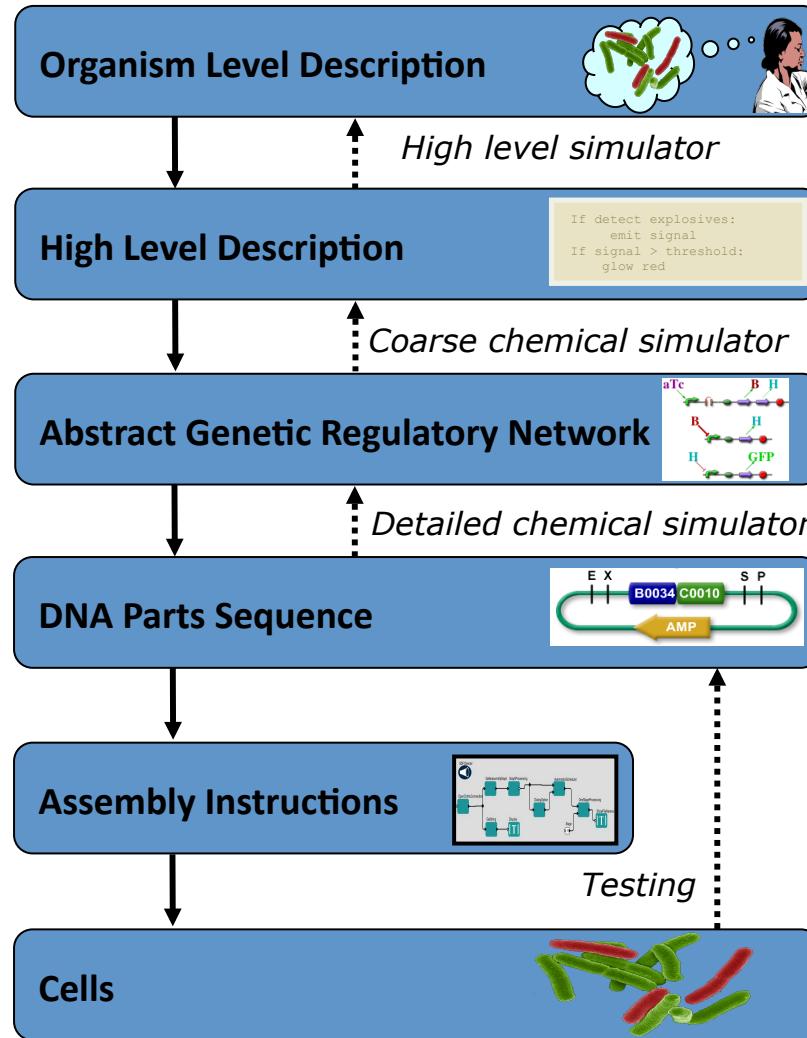


*This gap is too big  
to cross with a  
single method!*

Cells



# The TASBE tool-chain architecture:



Collaborators:



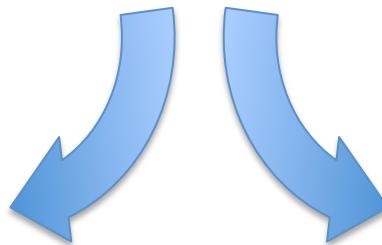
Ron  
Weiss



Douglas  
Densmore

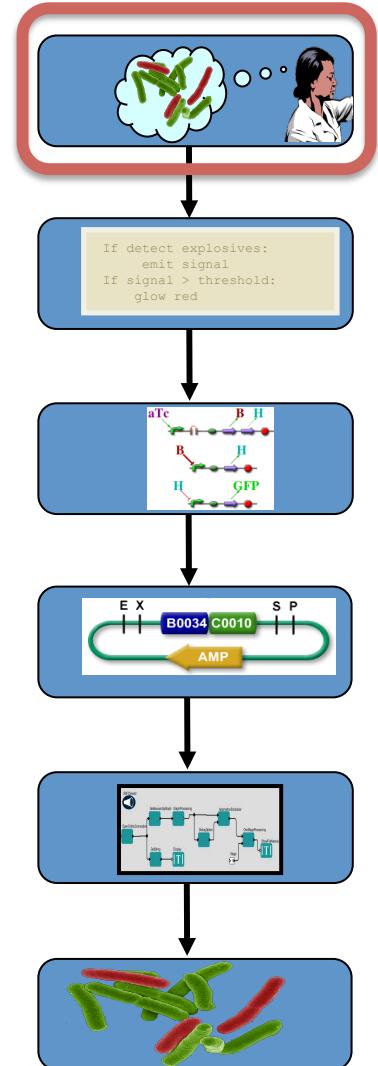
# A Tool-Chain Example

```
(def simple-sensor-actuator ()
  (let ((x (test-sensor)))
    (debug x)
    (debug-2 (not x))))
```



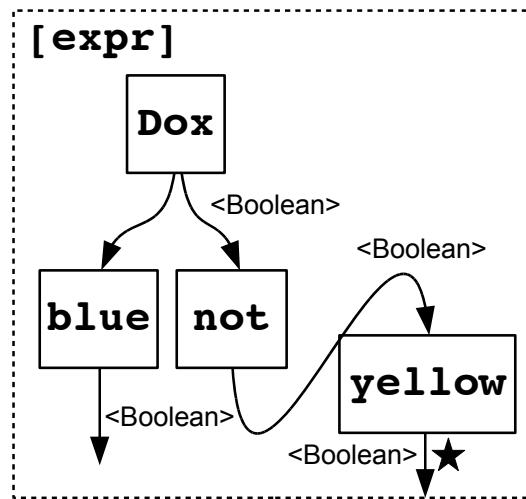
*Mammalian Target*

*E. coli Target*

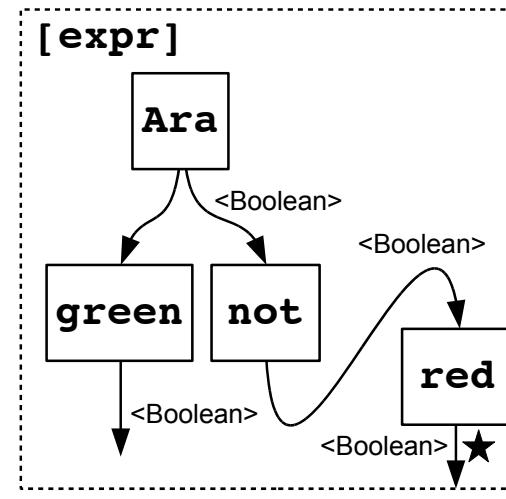


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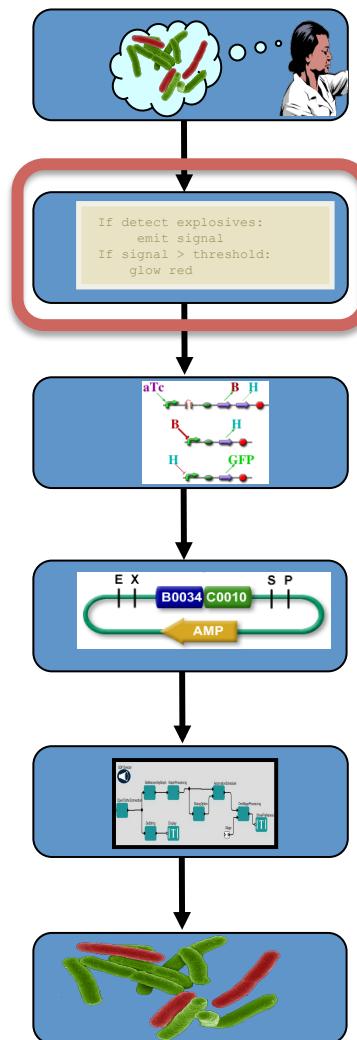
# A Tool-Chain Example



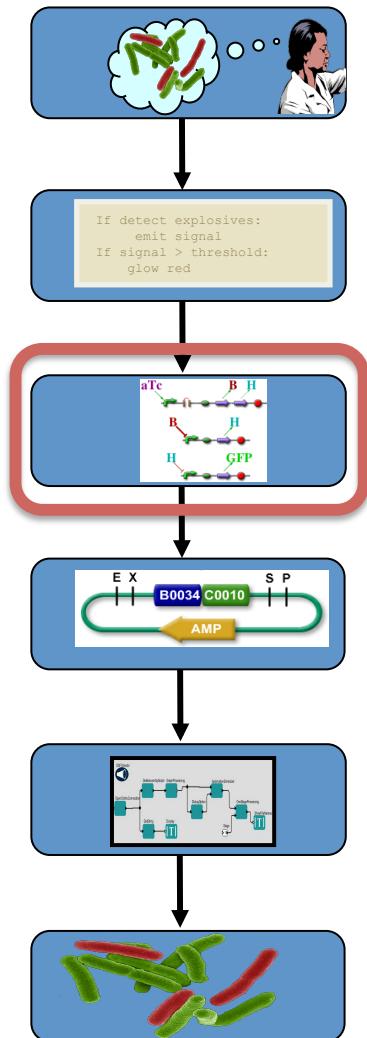
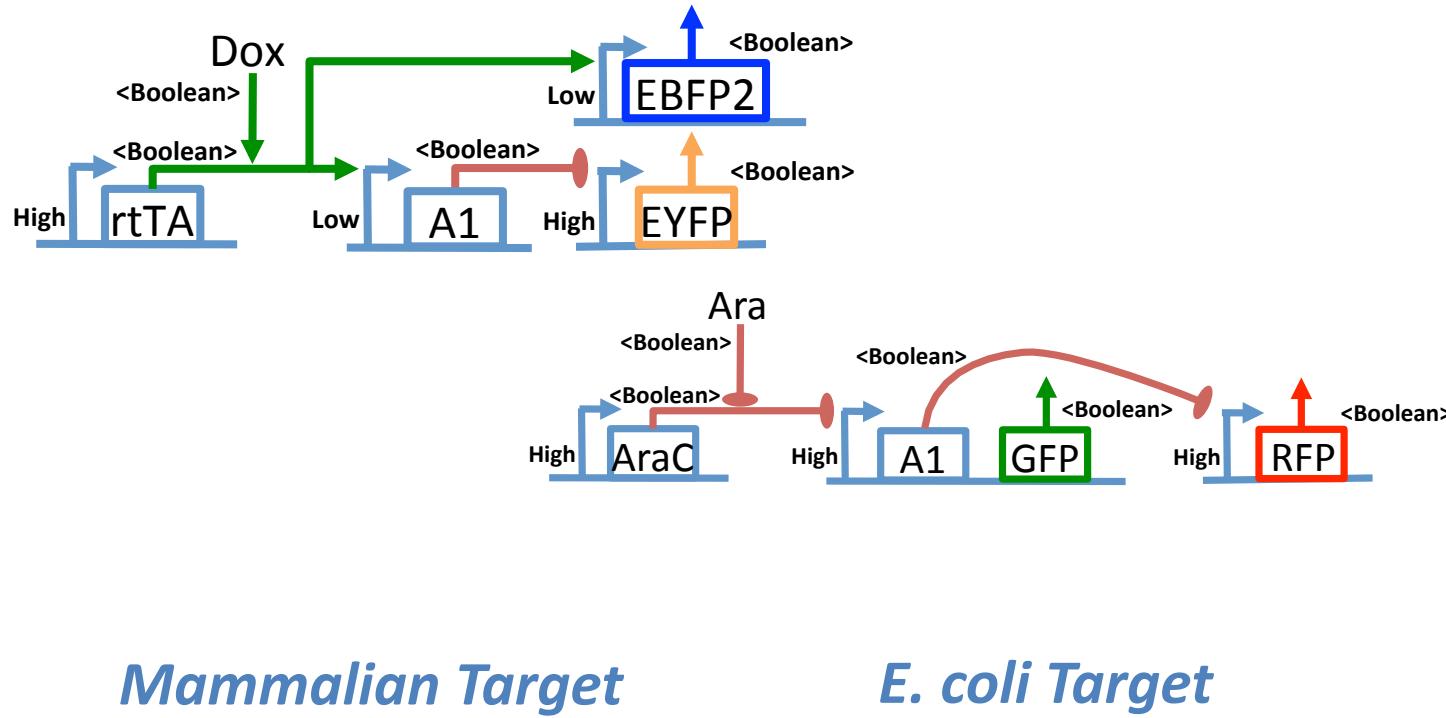
## *Mammalian Target*



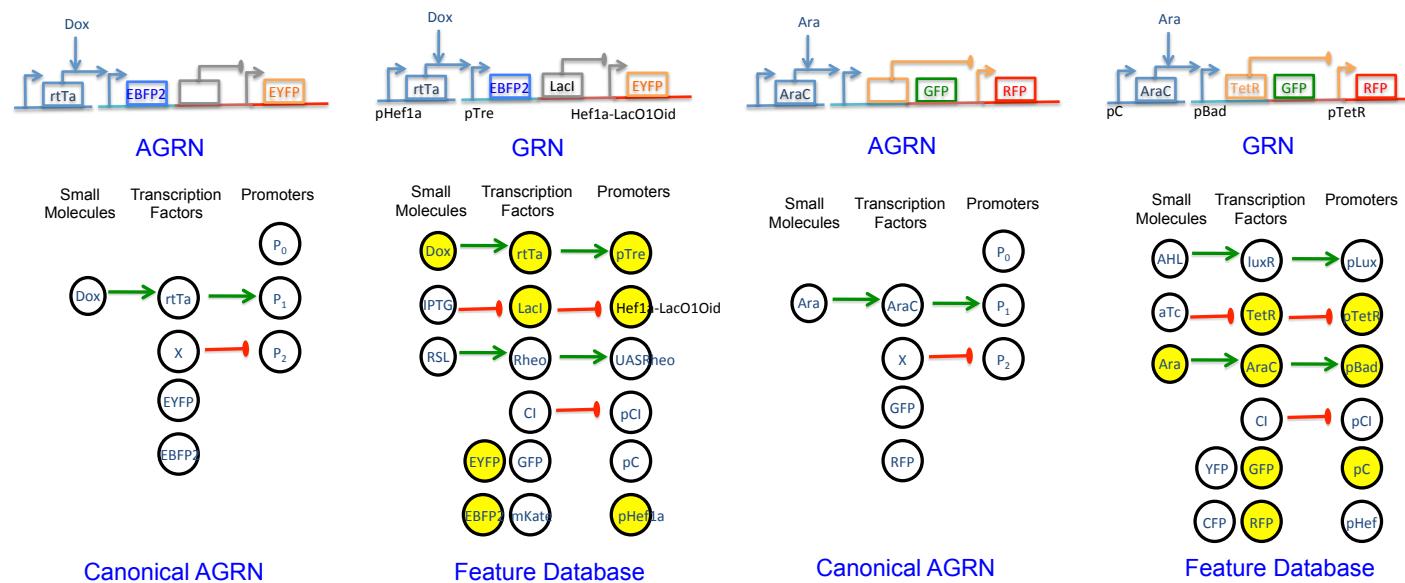
## *E. coli Target*



# A Tool-Chain Example

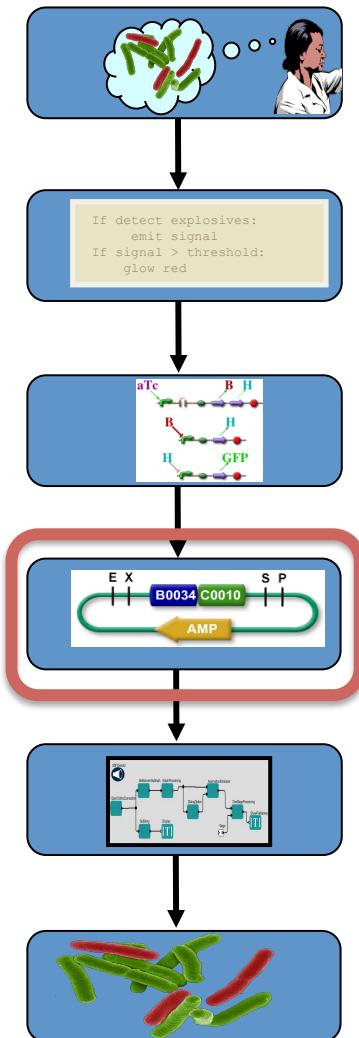


# A Tool-Chain Example

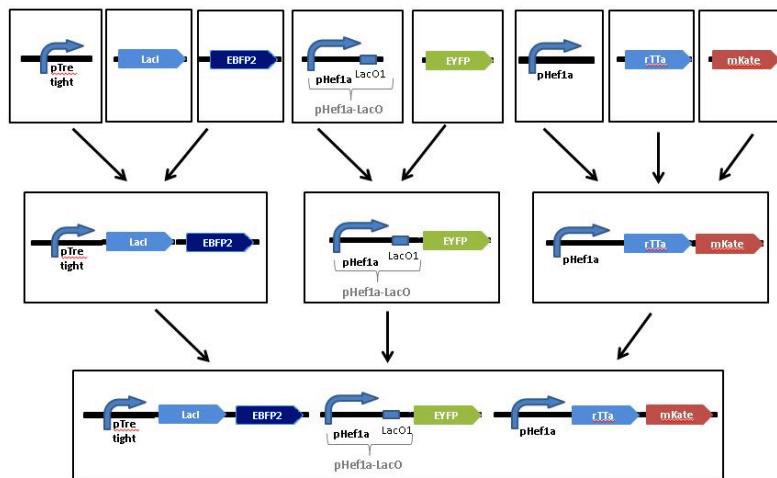


*Mammalian Target*

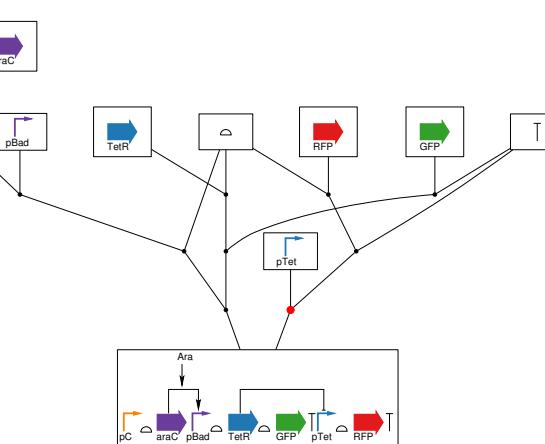
*E. coli Target*



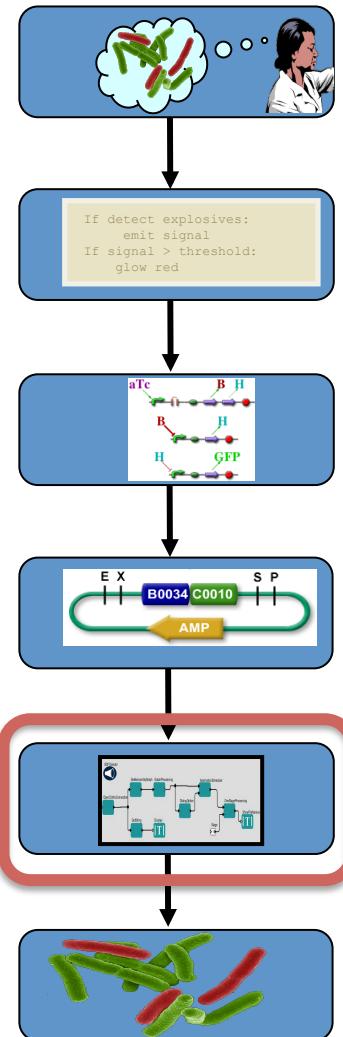
# A Tool-Chain Example



*Mammalian Target*

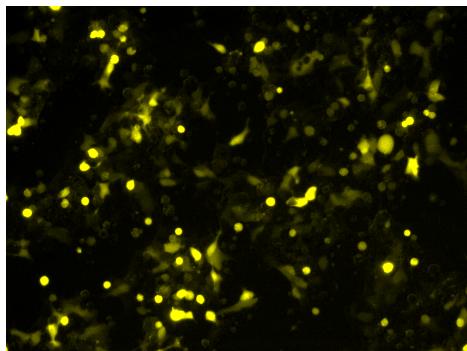


*E. coli Target*

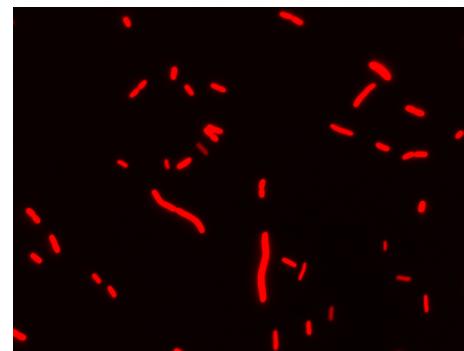


# A Tool-Chain Example

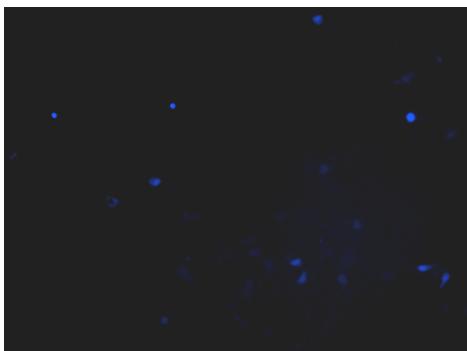
*Uninduced*



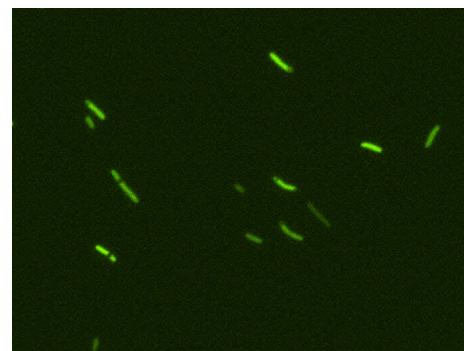
*Uninduced*



*Induced*

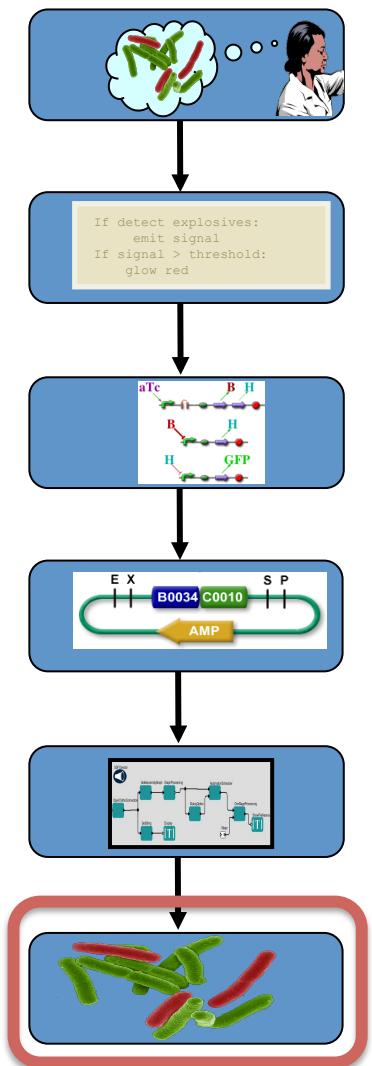


*Induced*



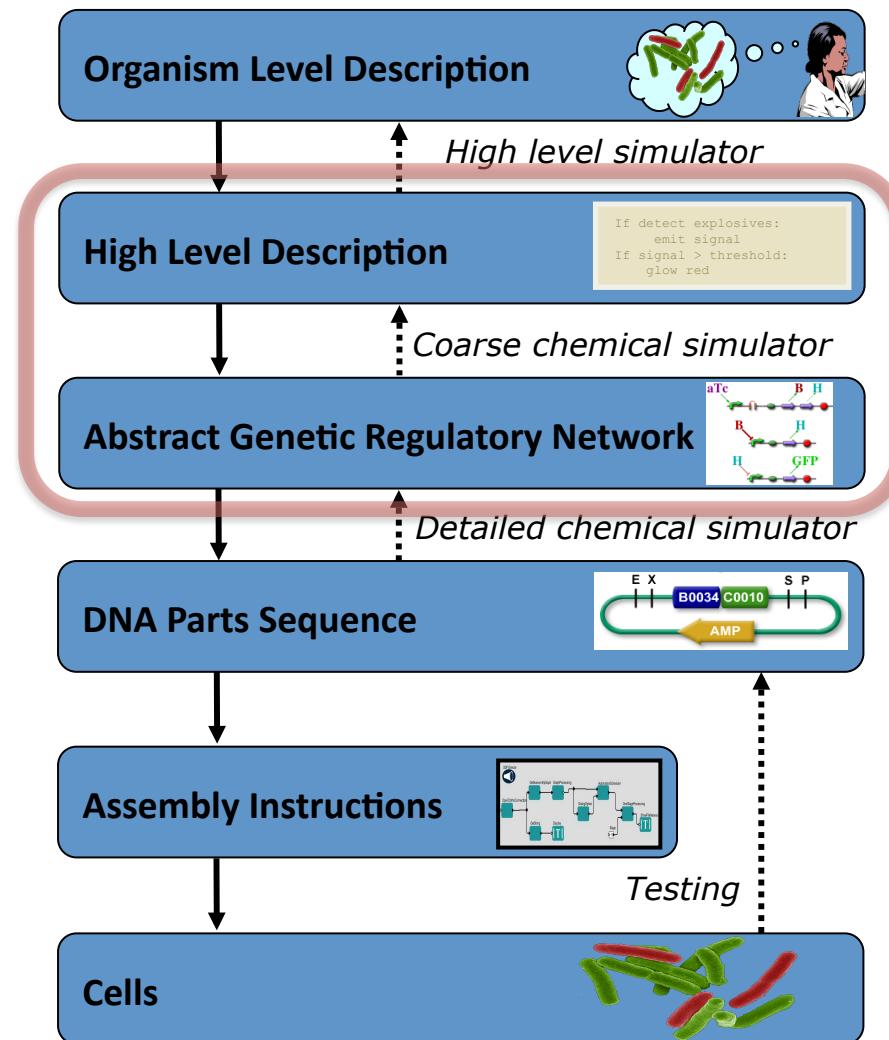
*Mammalian Target*

*E. coli Target*



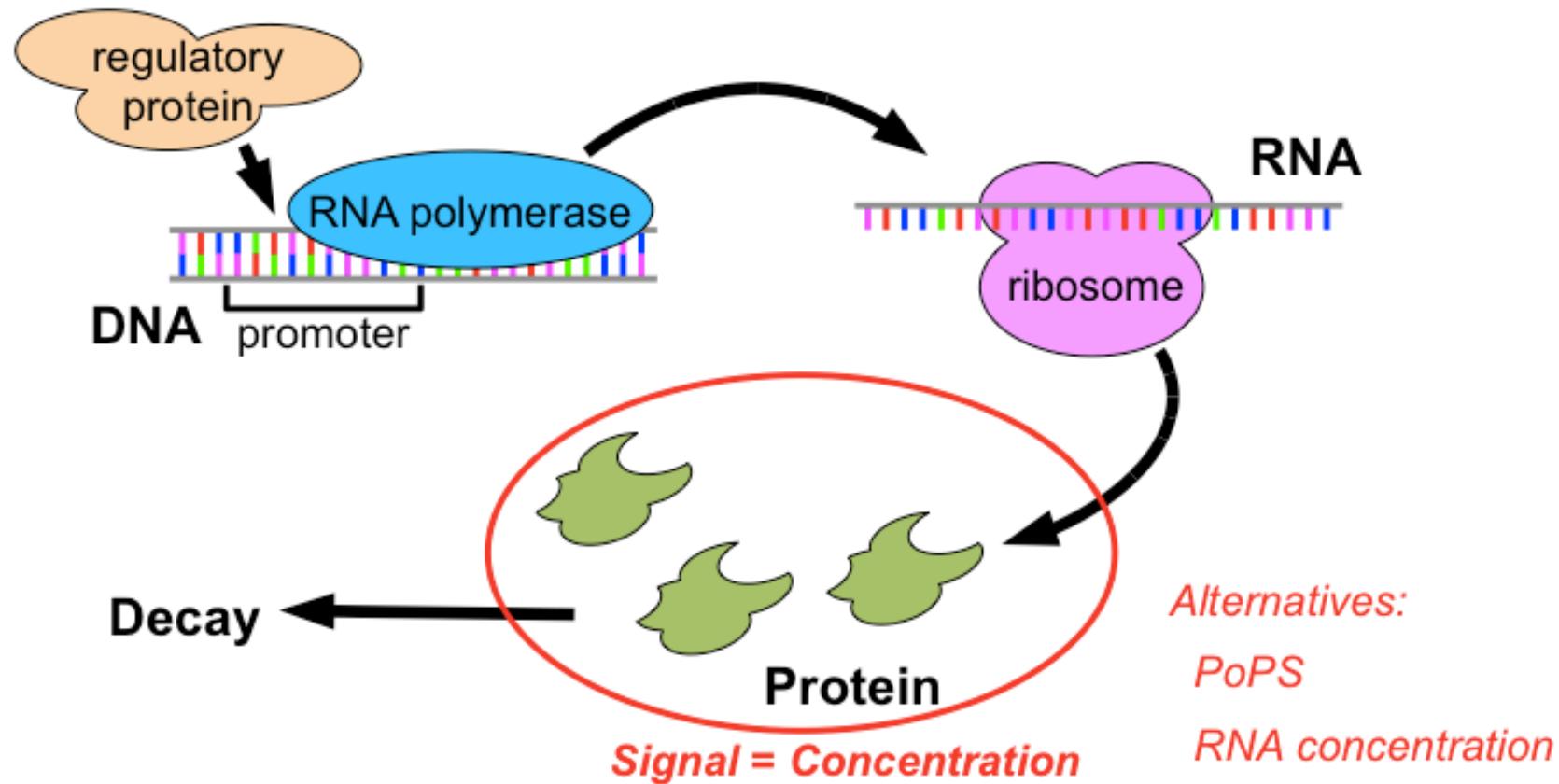
# Focus: BioCompiler

## Compilation & Optimization



*Other tools aiming at high-level design:  
Cello, Eugene, GEC,  
GenoCAD, etc.*

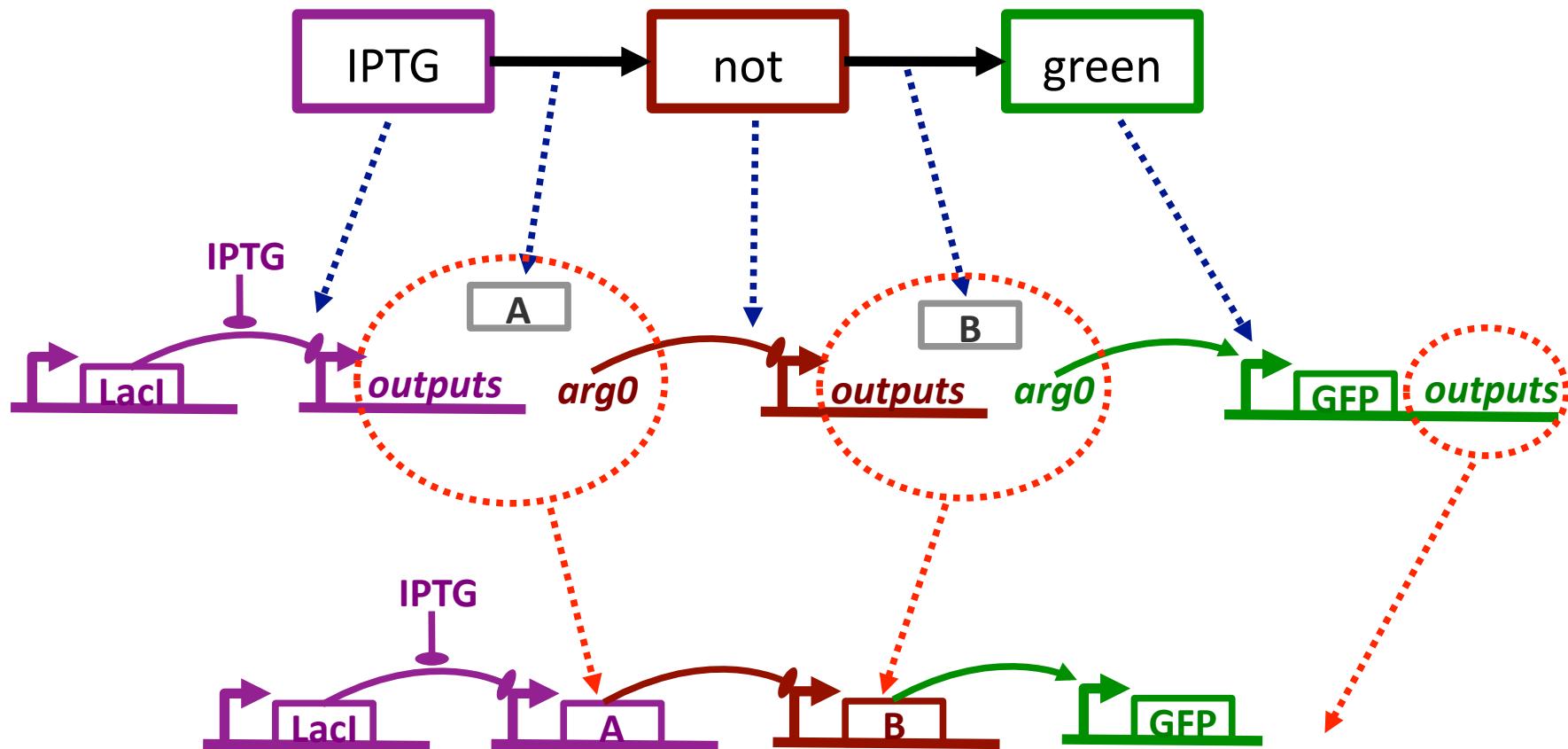
# Transcriptional Logic Computations



Stabilizes at  $\text{decay} = \text{production}$

# Motif-Based Compilation

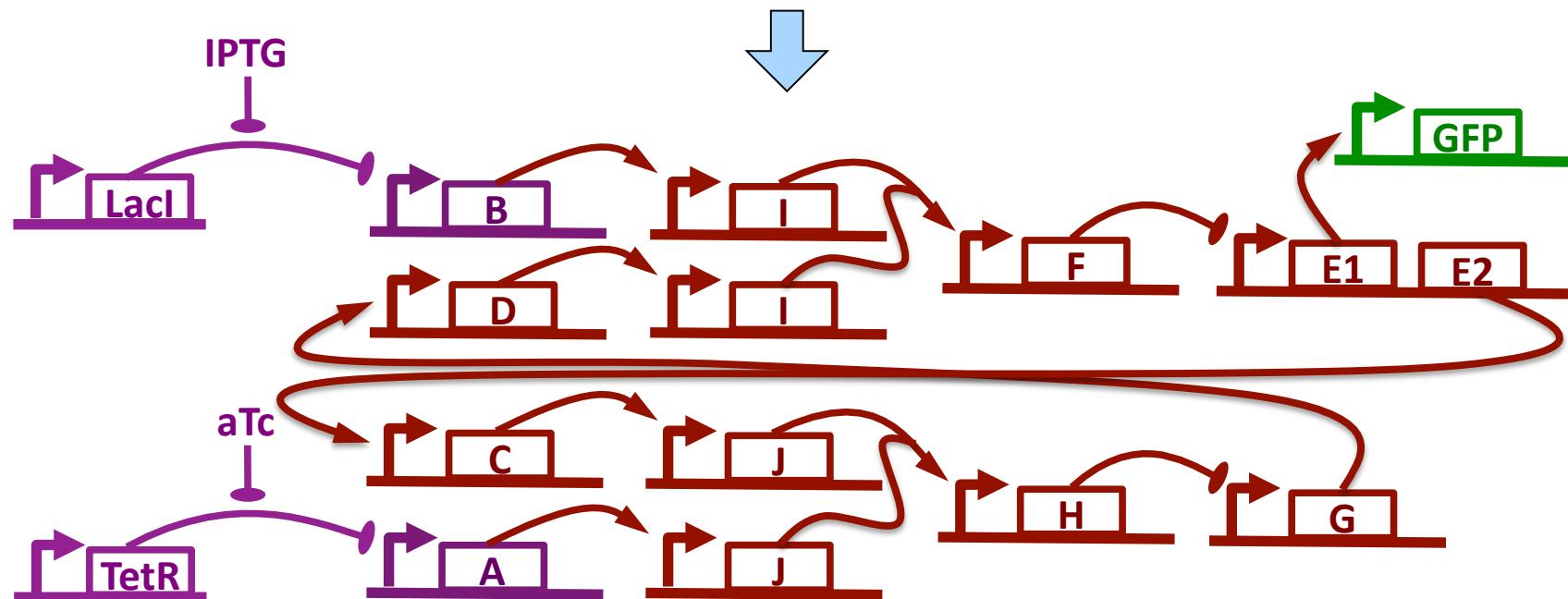
- Operators translated to motifs:



# Design Optimization

```
(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)))
```

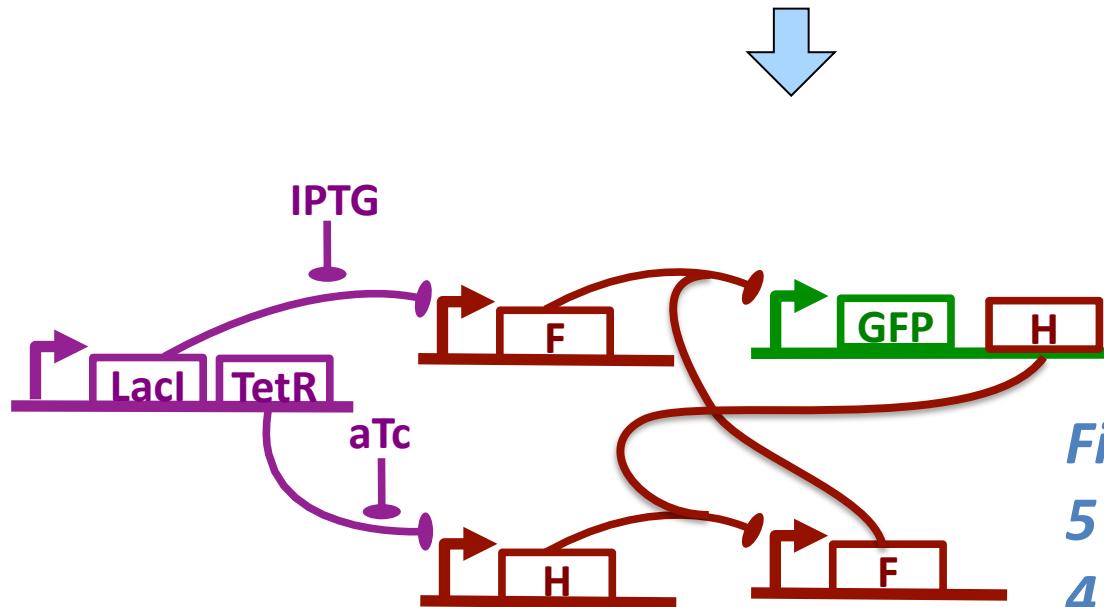


*Unoptimized: 15 functional units, 13 transcription factors*

# Design Optimization

```
(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**)))

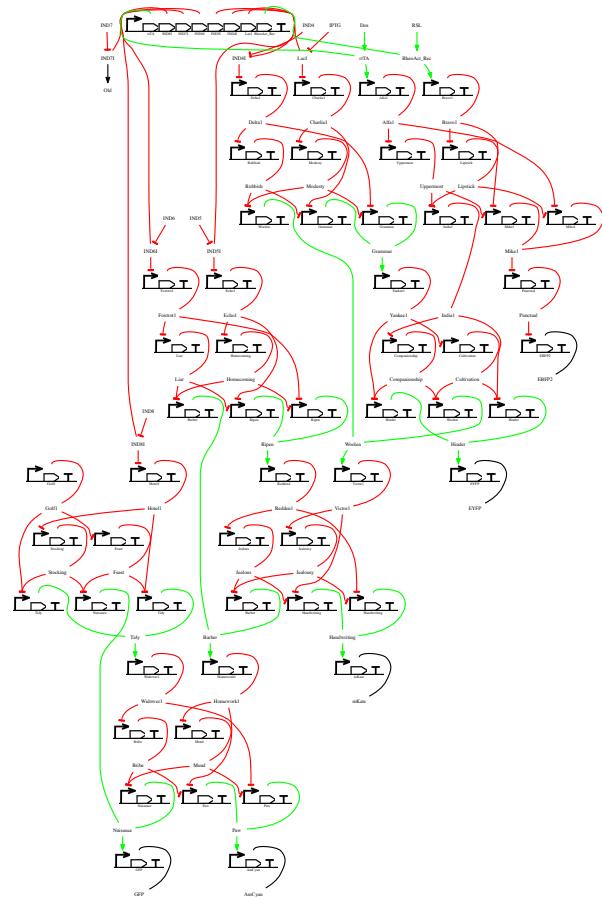


*Final Optimized:  
5 functional units  
4 transcription factors*

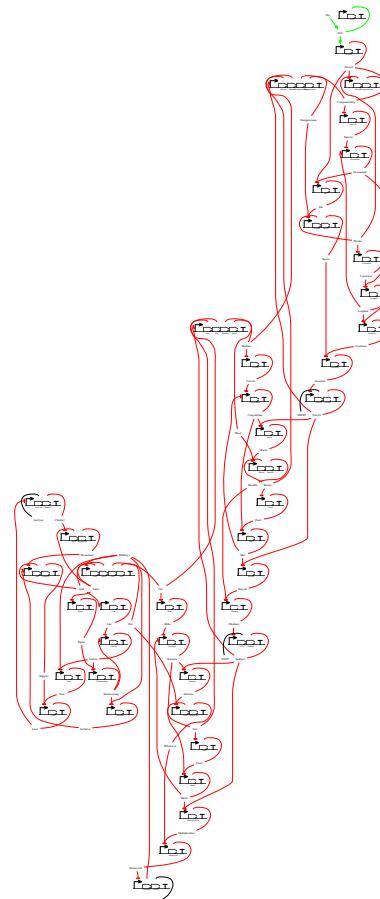
*Unoptimized: 15 functional units, 13 transcription factors*

# Automated Synthesis of Complex Designs

## Example: 4-bit adder



# Example: 4-bit counter



*Optimized compiler already outperforms human designers*

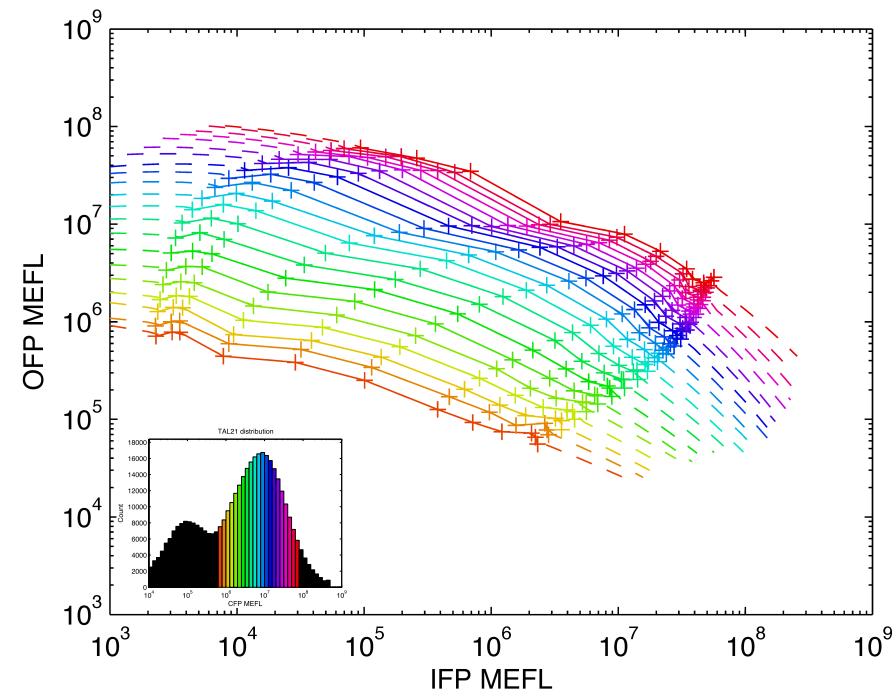
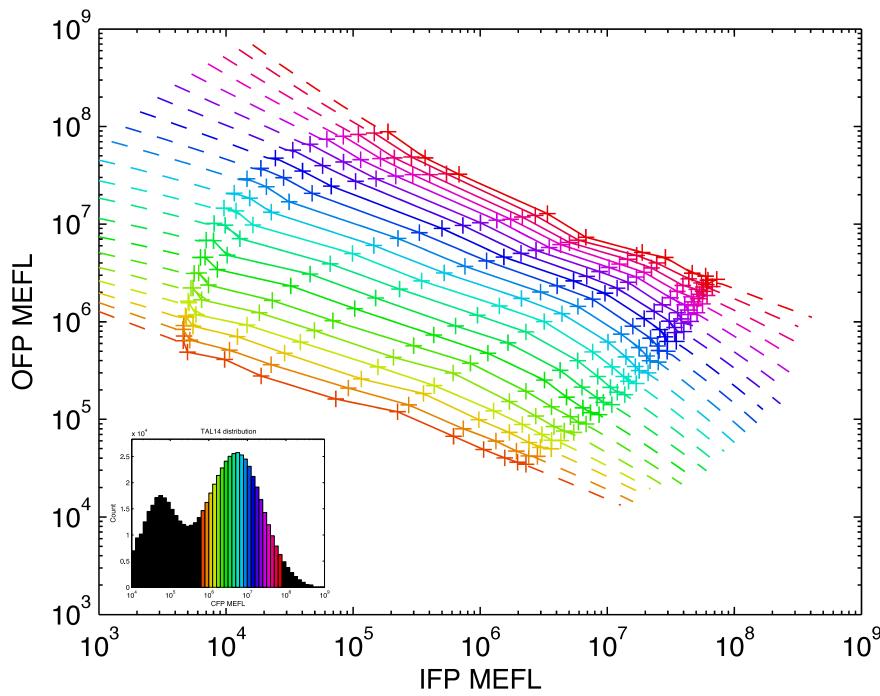
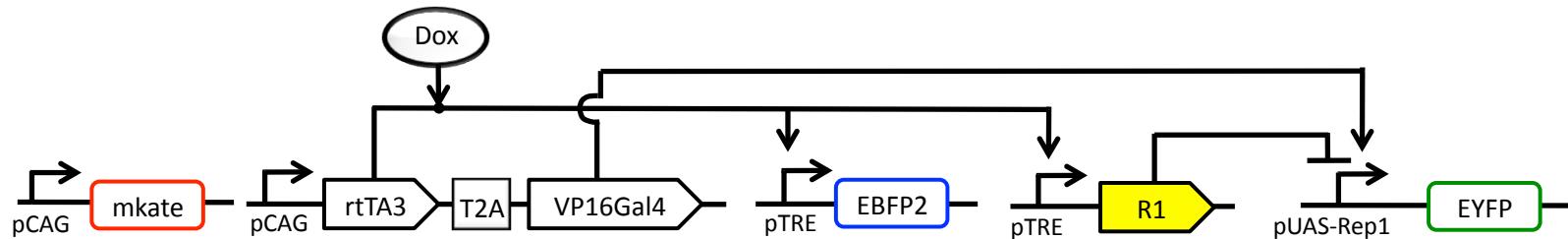
# Barriers & Emerging Solutions:

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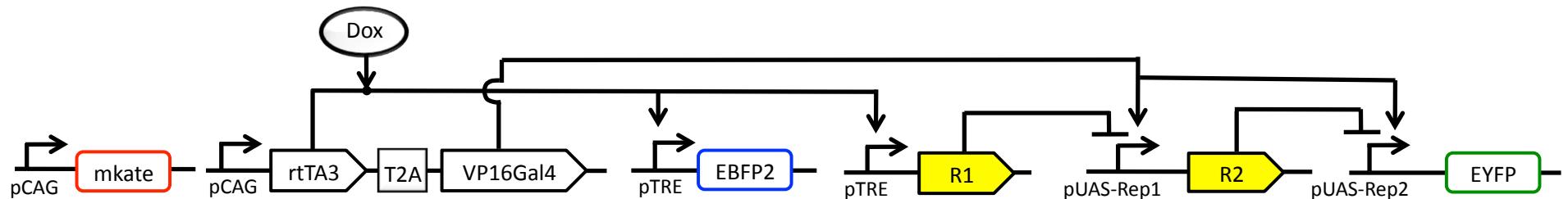
- Barrier: Availability of High-Gain Devices
  - Emerging Solution: combinatorial device libraries based on TALs, ZFs, miRNAs
- Barrier: Characterization of Devices
  - Emerging solution: TASBE characterization method
- Barrier: Predictability of Biological Circuits
  - Emerging solution: EQuIP prediction method

# TASBE Method: Calibrated, Precise Characterization

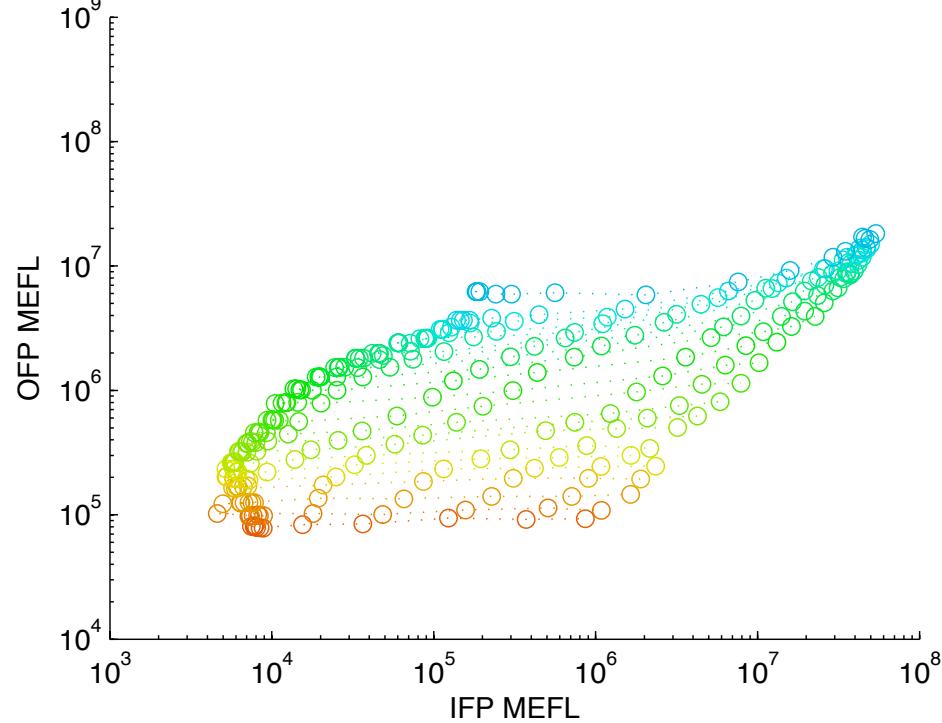
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**BBN Technologies**



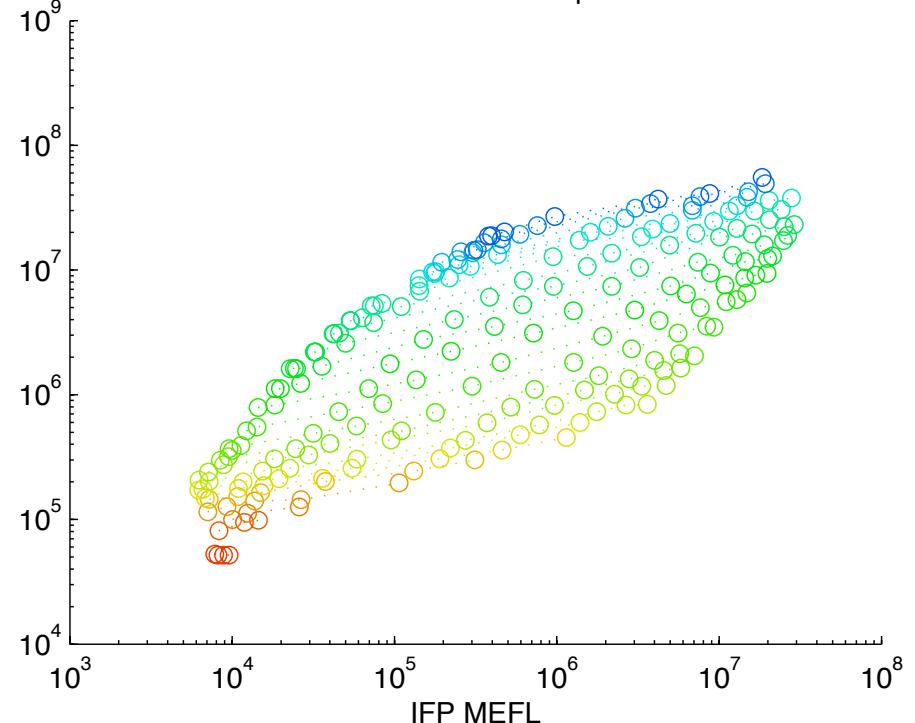
# Characterization → High Quality Predictions



Non-Normalized Cascade–LmrA–TAL14–Interpolated–Prediction transfer q–Normalized Cascade–TAL21–TAL14–Interpolated–Prediction transfer

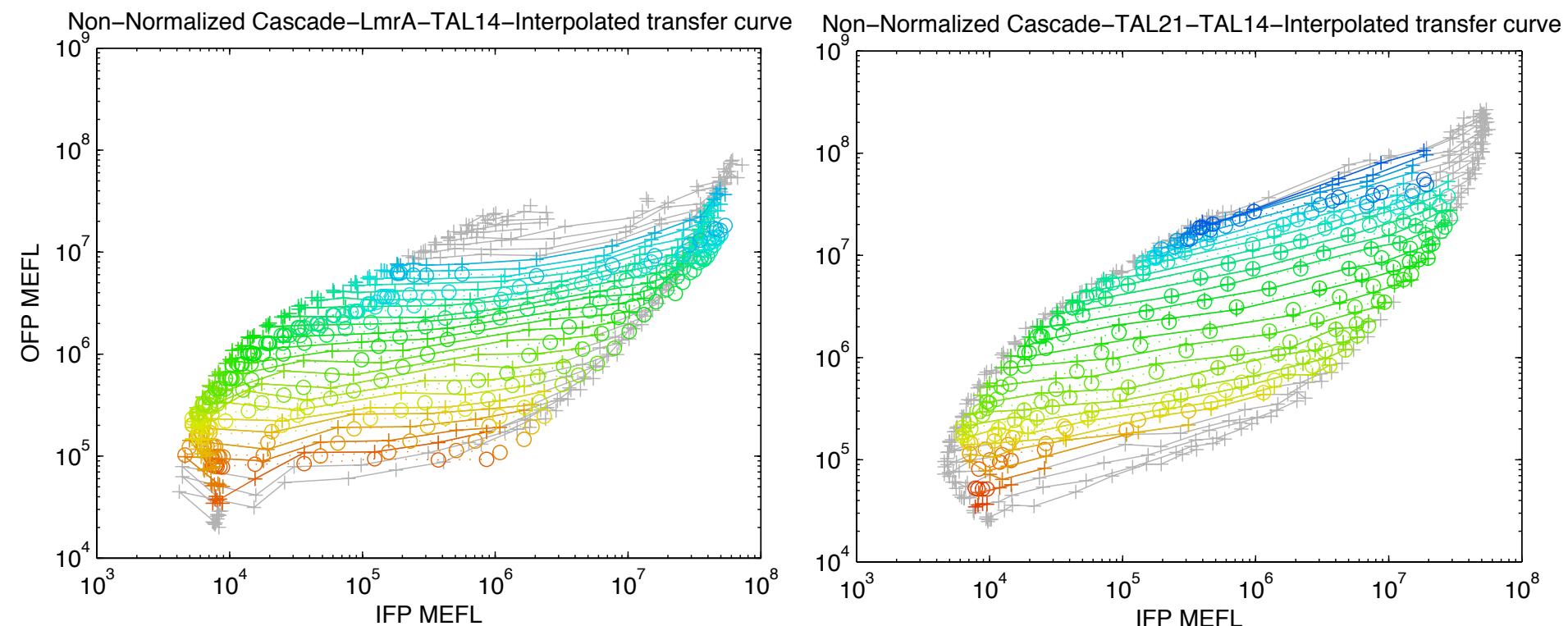
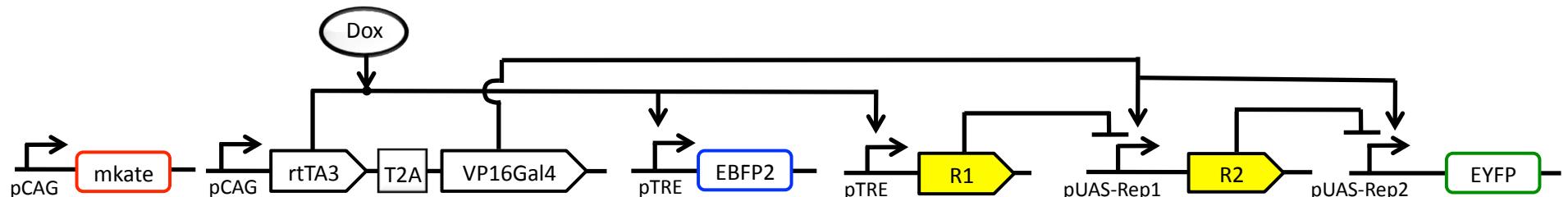


LmrA → TAL14



TAL21 → TAL14

# High Quality Cascade Predictions



LmrA → TAL14

TAL21 → TAL14

**Distribution + dynamics models → good predictions**

# Summary

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## High-Level BDA is possible *now!*

- EDA tool-chain approach works for BDA
- Optimized biological circuits can be generated automatically from high-level specifications
- Emerging solutions for key barriers: device libraries, characterization, prediction
- *Many opportunities for EDA tool adaptation:*
  - *Combinatorial device design*
  - *Flexible protocol automation*
  - *Device characterization*
  - *Circuit optimization, verification, safety, debugging*

.. and going from cells to processors...

## *Spatial Computing Process Management*

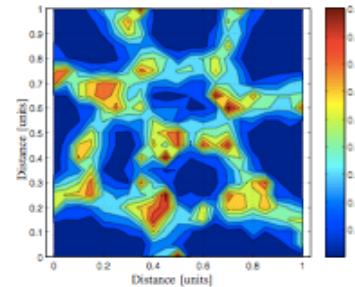
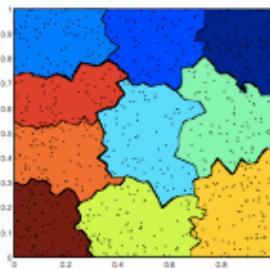
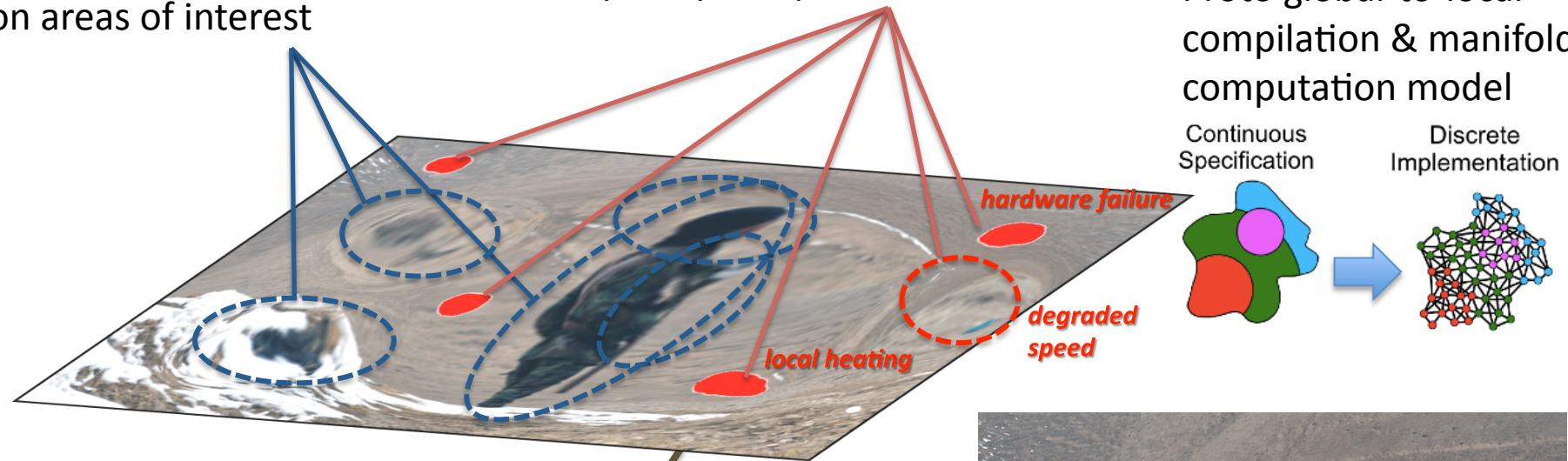
Inference resources  
focused proportionally  
on areas of interest

Distortion of computation around  
temporary and permanent faults

Proto global-to-local  
compilation & manifold  
computation model

Continuous  
Specification

Discrete  
Implementation

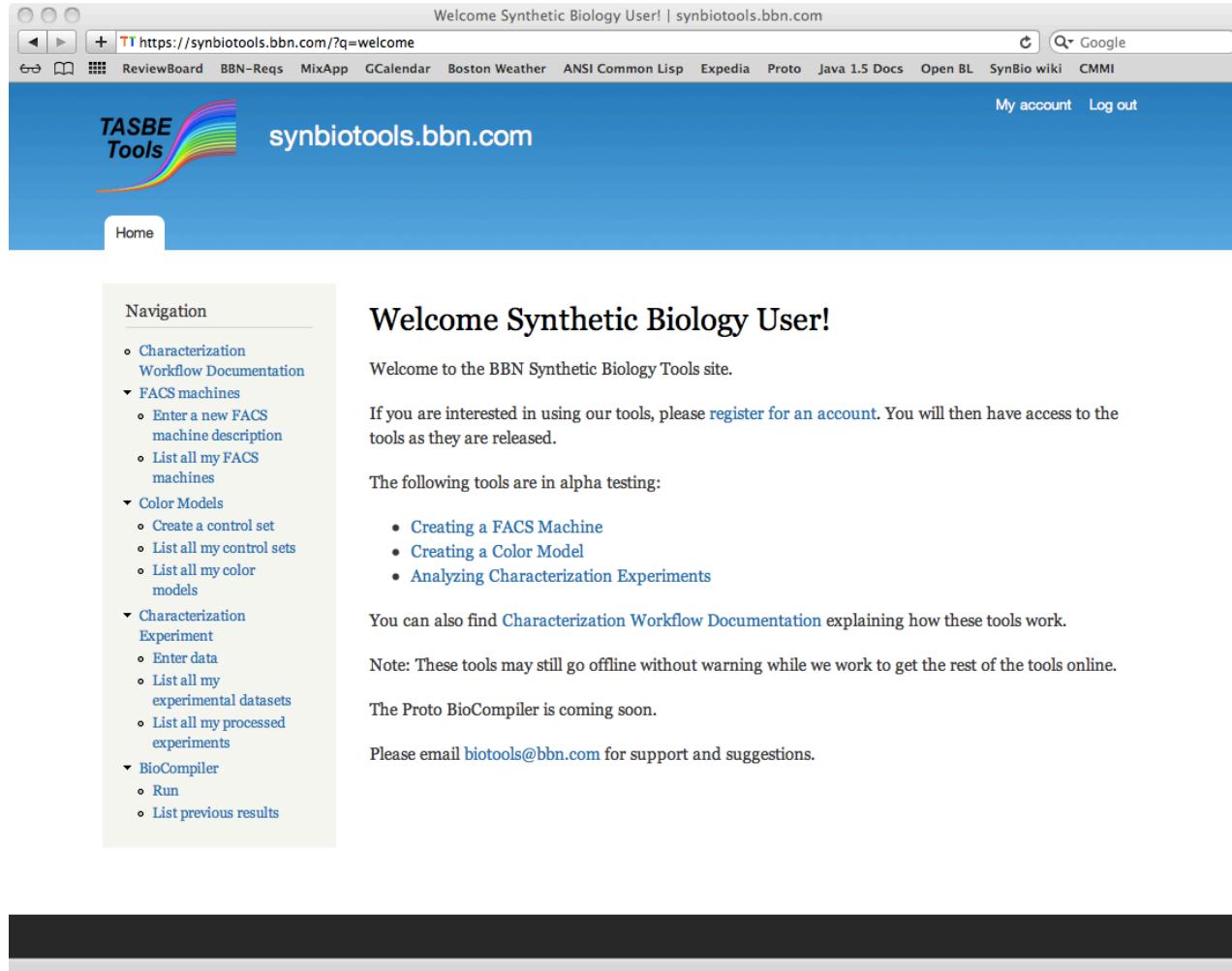


ASH volumetric region management

[Pruteanu, Dulman & Langendoen, '10]



# Characterization & Design Tools Online



**<https://synbiotools.bbn.com/>**

# Acknowledgements:

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**Raytheon**  
**BBN Technologies**

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Ting Lu



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Evan Appleton  
Swapnil Bhatia  
Traci Haddock  
Chenkai Liu  
Viktor Vasilev

