High-Level BioDesign Automation

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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:
  - Multiplication of research impact
  - Reduction of barriers to entry

*Sampling of systems in publications with experimental circuits*
This gap is too big to cross with a single method!
The TASBE tool-chain architecture:

Organism Level Description

- **High level simulator**
- If detect explosives: emit signal
- If signal > threshold: glow red

High Level Description

- Coarse chemical simulator

Abstract Genetic Regulatory Network

- Detailed chemical simulator

DNA Parts Sequence

- Assembly Instructions

Cells

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

Collaborators:

- Ron Weiss
- Douglas Densmore
A Tool-Chain Example

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

If detect explosives:
emit signal
If signal > threshold:
glow red

Mammalian Target

E. coli Target
A Tool-Chain Example

If detect explosives:
emit signal
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Mammalian Target  E. coli Target
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Mammalian Target  E. coli Target
A Tool-Chain Example

If detect explosives:
emit signal
If signal > threshold:
glow red

Mammalian Target

Uninduced

Induced

E. coli Target

Uninduced

Induced
Focus: BioCompiler

Compilation & Optimization

High Level Description

If detect explosives: emit signal
If signal > threshold: glow red

Coarse chemical simulator

Abstract Genetic Regulatory Network

Detailed chemical simulator

DNA Parts Sequence

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

Assembly Instructions

Testing

Cells

Organism Level Description

High level simulator
Transcriptional Logic Computations

Decay

Protein

Signal = Concentration

RNA polymerase

RNA

Ribosome

DNA

promoter

regulatory protein

Alternatives:
PoPS
RNA concentration

Stabilizes at \( \text{decay} = \text{production} \)
Motif-Based Compilation

- Operators translated to motifs:

```
  IPTG → not → green
  ▼   ▼   ▼
  A    B    GFP
```

The diagram illustrates the flow of information, with IPTG activating LacI and then participating in a series of boolean operations (not, arg0) leading to the final output (green). The motif-based compilation approach leverages these operations to achieve the desired biological outcomes.
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:

• 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

TAL14

TAL21
Characterization → High Quality Predictions

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

Normalized Cascade–TAL21–TAL14–Interpolated–Prediction transfer

LmrA → TAL14

TAL21 → TAL14
High Quality Cascade Predictions

Non-Normalized Cascade–LmrA–TAL14–Interpolated transfer curve

Non-Normalized Cascade–TAL21–TAL14–Interpolated transfer curve

LmrA $\rightarrow$ TAL14

Distribution + dynamics models $\rightarrow$ good predictions
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

ASH volumetric region management

[Pruteanu, Dulman & Langendoen, ‘10]
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