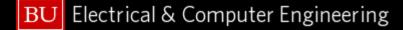
Lecture 8

Design – Overview, Approaches, Challenges

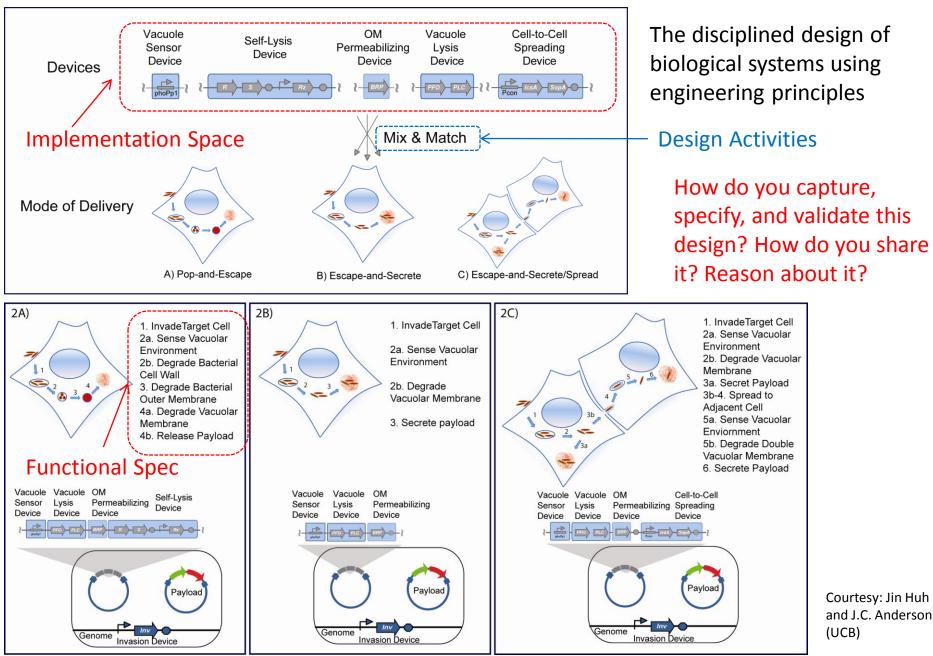
Prof. Douglas Densmore EC/BE552 Computational Synthetic Biology for Engineers



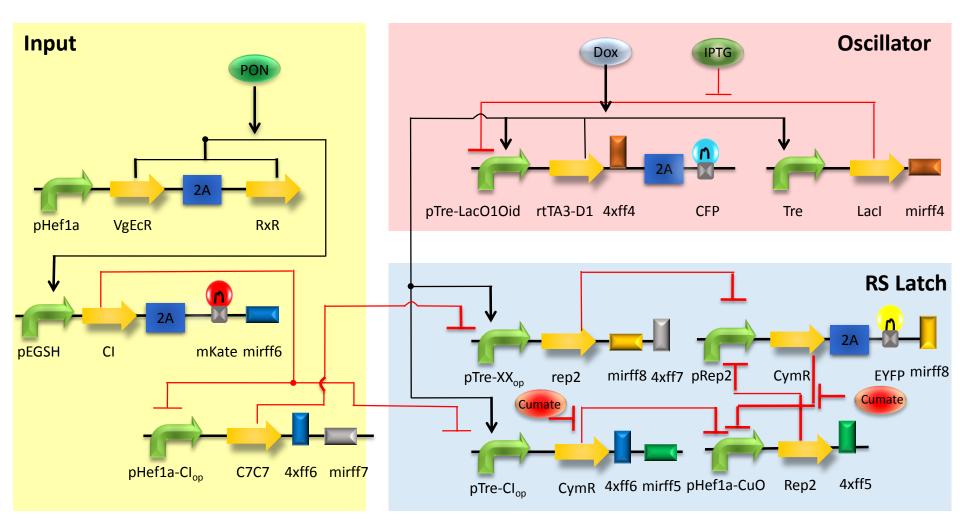


Synthetic Biology:

Tremendous Potential



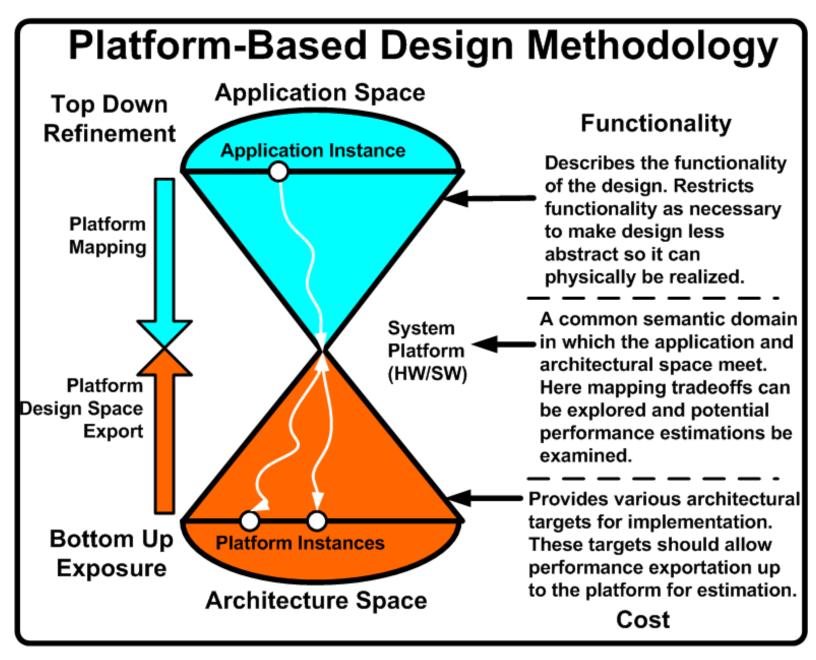
Potential Complexity?



Circuit size: 9 promoters, 13 genes

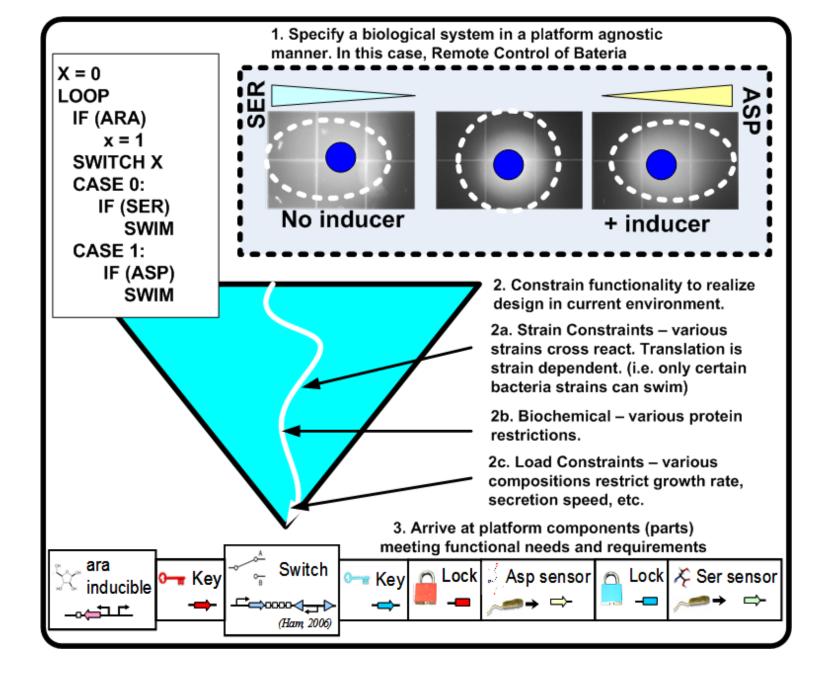
State of the Art??

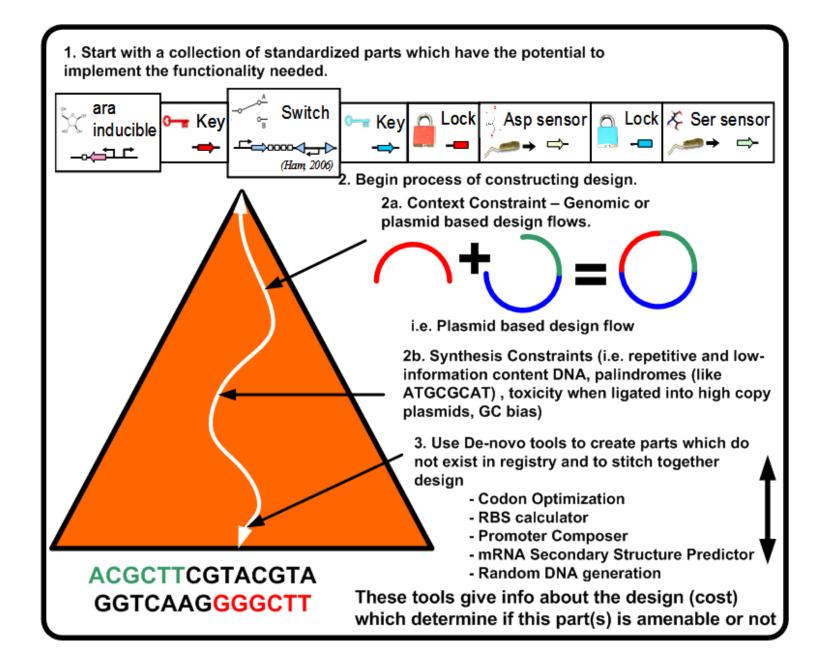
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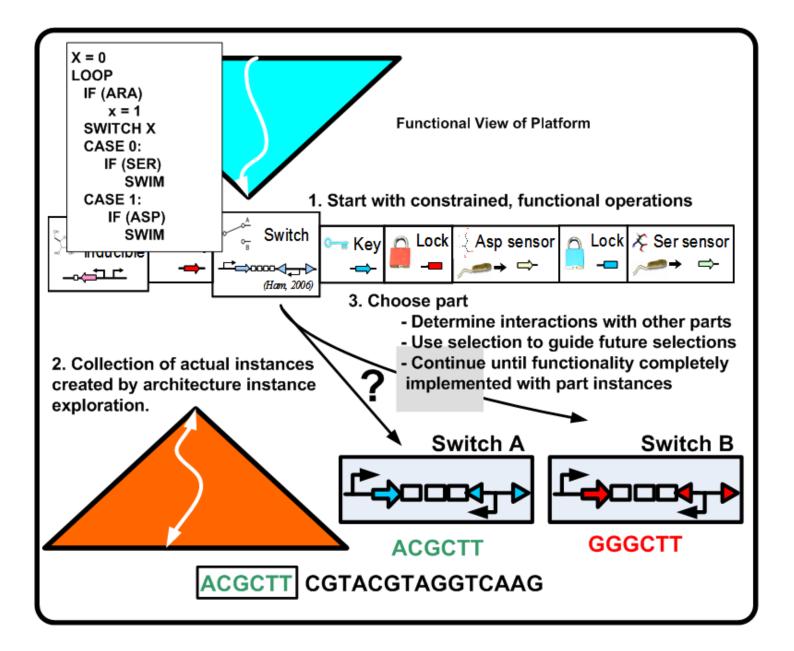




Circa 2008







Clotho 0.0: 2007-2009





A Platform-Based Design Environment for Synthetic Biological Systems

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ABSTRACT

Genomics has reached the stage at which the amount of DNA sequence information in existing databases is quite large. Synthetic biology is now using these databases to catalog sequences according to their functionality thus creating a system of standard biological parts. Flexible tools are needed which both permit access and modification to that data and also allow one to perform meaningful, intelligent manipulation. A Platform-Based Design approach views genetic information as having a particular functionality and assembles platforms (Clections of DNA elements) to perform this functionality. Specifically this paper presents the *Clotho* toolset which uses these concepts to create a complete design environment for standardized biological parts.

Categories and Subject Descriptors

D.2.2 [Software Engineering]: Design Tools and Techniques

General Terms

Design, Management

Keywords

Platform-based Design, Synthetic Biology

1. INTRODUCTION

Synthetic biology is a rapidly growing field in which the techniques of chemistry, biology, and engineering merge. Synhetic biologists look to create new microorganisms by manipulating the basic building blocks of life to create living material which interacts with, manipulates, and responds the environment in which it lives. Synthetic biology is very much a *design science* where a new system is created by researchers in laboratories using a series of design steps along with their understanding of biological processes. Synthetic

Permission to make digital or hard copies of all or part of this work for personal or classroom use is granted without fee provided that copies are not made or distributed for profit or commercial advantage and that copies bear this notice and the full citation on the first page. To copy otherwise, or biology has the potential to greatly impact greater society through the development of new technologies in drug production, biofuels, and drug delivery vessels.

In an attempt to standardize this process, leverage previous design experiences, and begin to create a predictive design environment, registries of standard biological parts are beginning to emerge [14]. Researchers have begun to talk about how to classify these parts, create CAD systems, and establish standards [13], [12], [7], [19], [10]. [18] lays out very nicely an example of how these parts can be used to *program* bacteria and discusses how they can be characterized (e.g. sensors, switch logic, inducers, etc). The fact that these collections of *parts* can be discussed in terms of their functionality along with rules for their composition, raises the interesting question of how the Electronic Design Automation (EDA) community (traditionally in electrical engineering and computer science) possibly can leverage its techniques in the creation of biological systems.

This paper describes the design of a toolset called *Clotho* (named after the Greek fate which spun the thread of life) which uses a methodology called Platform-Based Design (PBD) [16] to approach the problem of designing synthetic biological systems. In particular, we will describe its separation of computation, communication, and coordination, the concept of a "platform" as a common semantic meeting place for designs, and the notion of both "top down" and "bottom up" design styles.

1.1 Requirements

In the world of biology one can roughly separate tool offerings into three broad categories. The first category are those tools which provide computational power to specific biological algorithms. BLAST (Basic Local Alignment and Search Tool) [15] aligns nucleotide and protein sequences to allow for functional prediction and to aid in locating sequences in databases. ORBTT [11], [4] is protein design software which allows the design of an amino acid sequence that folds into a particular 3D structure. Mfold [20] enables the prediction of mRNA secondary structures which aids in predicting mRNA regulation and ribosome binding site strengths. These types of tools require a strong understanding not only of the un-

"A platform-based design environment for synthetic biological systems," in *The Fifth Richard Tapia Celebration of Diversity in Computing Conference: Intellect, Initiatives, Insight, and Innovations,* New York, NY, USA, 2009, pp. 24-29.



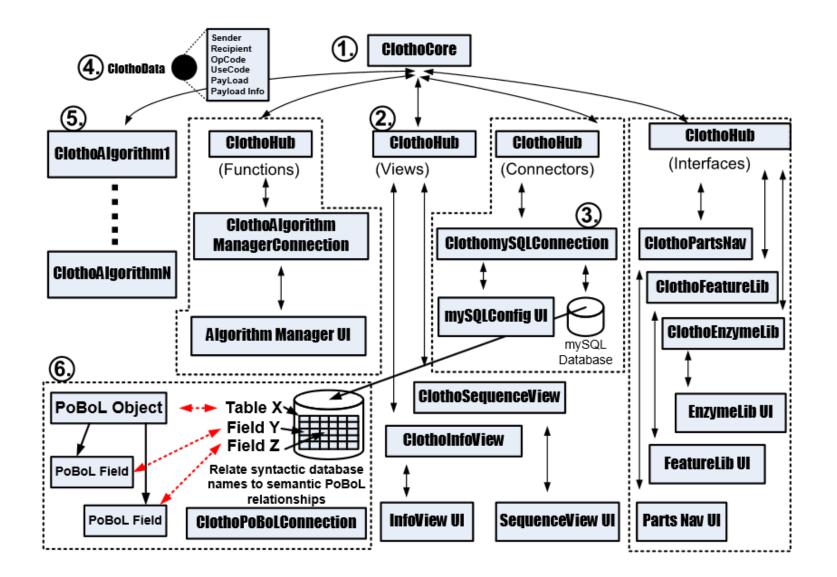






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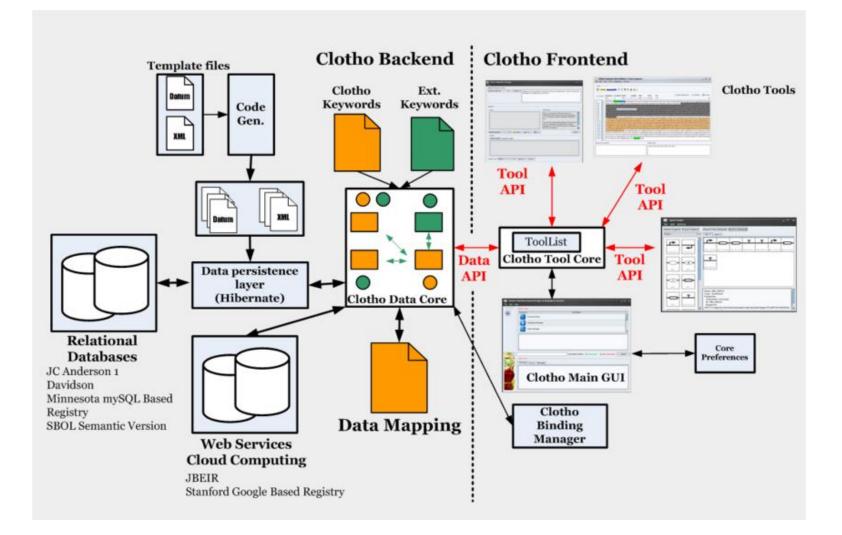






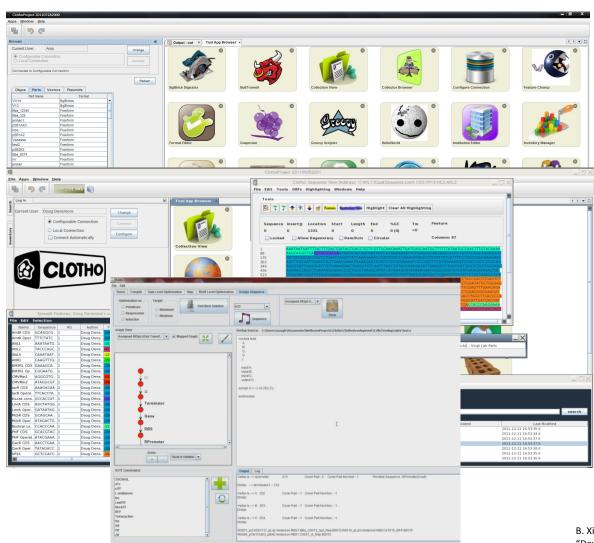


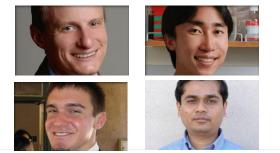
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Clotho 2.0: 2010-2012







CHAPTER FIVE

DEVELOPER'S AND USER'S GUIDE TO CLOTHO V2.0: A SOFTWARE PLATFORM FOR THE CREATION OF SYNTHETIC BIOLOGICAL SYSTEMS

Bing Xia,[†] Swapnil Bhatia,* Ben Bubenheim,[†] Maisam Dadgar,^{*} Douglas Densmore,*.* *and* J. Christopher Anderson^{†, S.}*...

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B. Xia, S. Bhatia, B. Bubenheim, M. Dadgar, D. Densmore, and J. C. Anderson, "Developer's and user's guide to Clotho v2.0 A software platform for the creation of synthetic biological systems," *Meth. Enzymol.*, vol. 498, pp. 97-135, 2011.



What was wrong?

What could be right?

In 2.0

- Rich client physically had to install Clotho; Java/Swing/Hibernate
 - Updates to code base not globally propagated
 - Non-uniform development platforms
 - Code bloat/registry reminants/etc
- Hard-coded bio objects
 - Provided guideline but field still immature
 - Meta-data lost
- 22+ GUIs
 - What about the 23rd? "Can you make that button green?"
- Fragmented documentation
 - No centralized body to maintain this

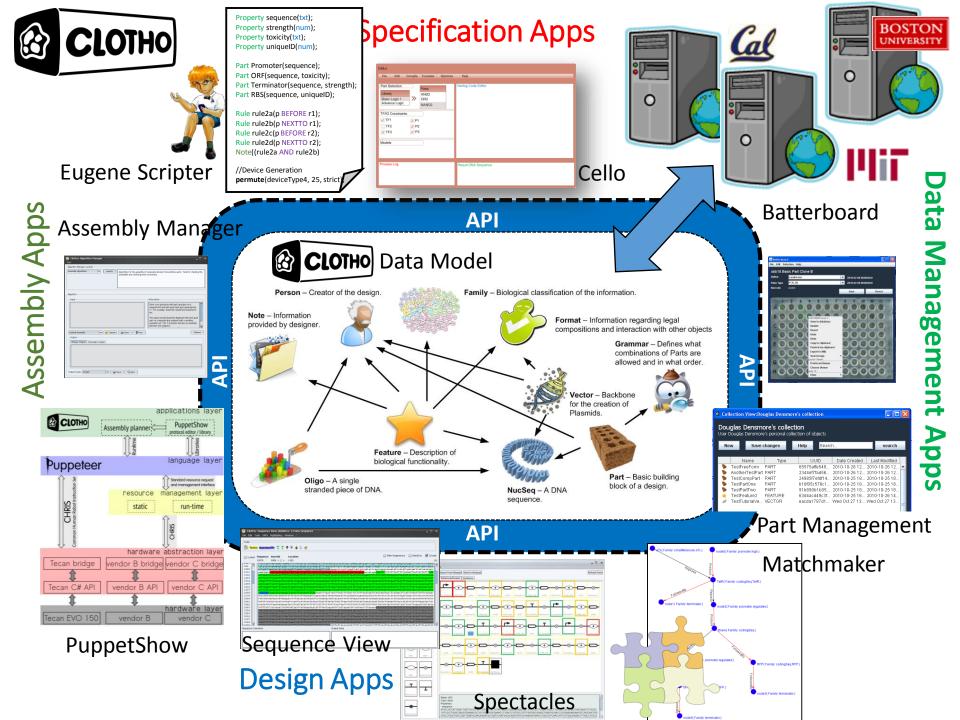


In 3.0

- Web-based "only" need a browser
 - Centralized updating
 - Fewer development platforms
 - More inline with current software development practices
- Abstracted API and Datamodel
 - Comes with 2.0esque model standard
 - Can be modified by the user(s)
 - Multiple UI environment API support
- Just one editor
 - Simplify the Clotho workflow
- Embedded interactive training
 - Clotho actually stores its own documentation
 - Create organization to maintain documentation going forward

Clotho...there's an app for that!



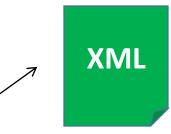


Raytheon **BBN Technologies** Dataflow IPTG not green Network **IPTG** Α В Mapped outputs arg0 Lacl outputs_arg0 GFP outputs Motifs **IPTG** Abstract Lacl Ā GFP GRN **IPTG** GFP Lacl В Α Copy Propagation **IPTG** GFP Lacl В Α Dead Code Elimination **XML IPTG** GFP Lacl Α Dead Code Elimination **IPTG** GFP Lacl



Input Specification

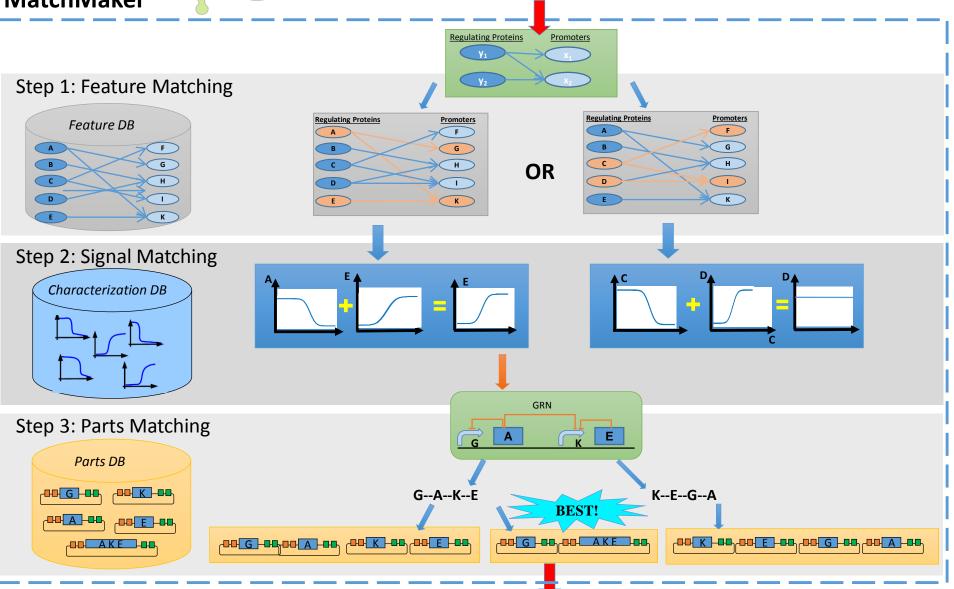




Input to MatchMaker (next step in the tool-chain)



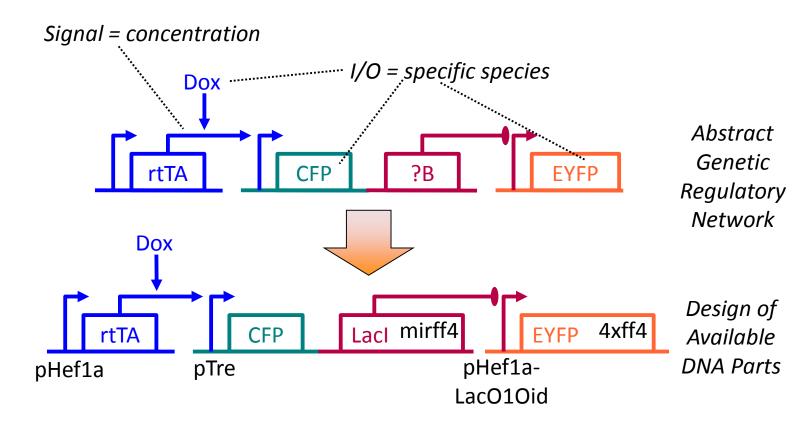
BioCompiler (previous step in tool-chain) output



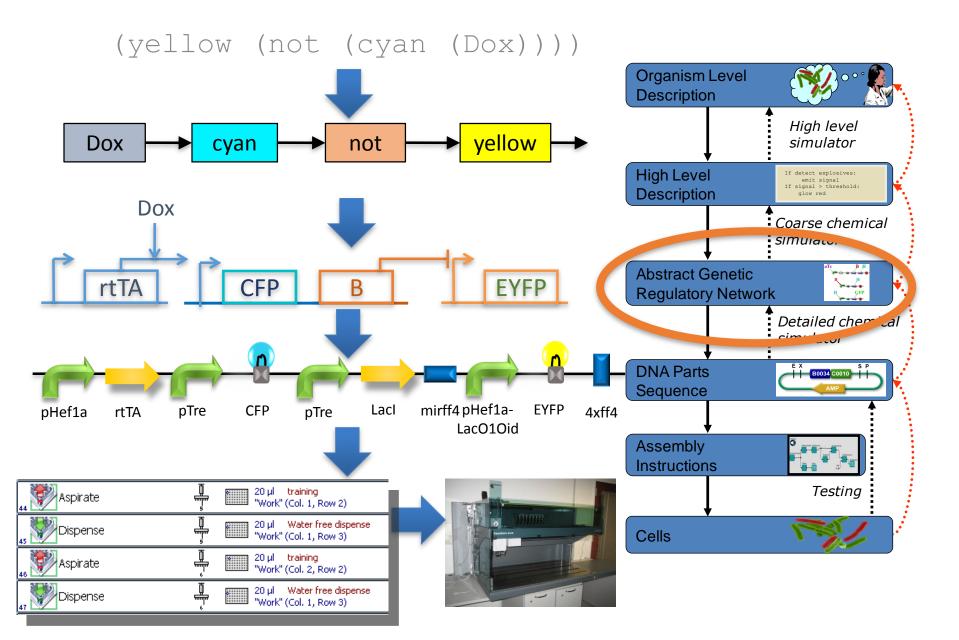
Input to the Assembly Manager (next step in the tool-chain)

Problem: DNA Part Selection

Transcriptional boolean logic networks:

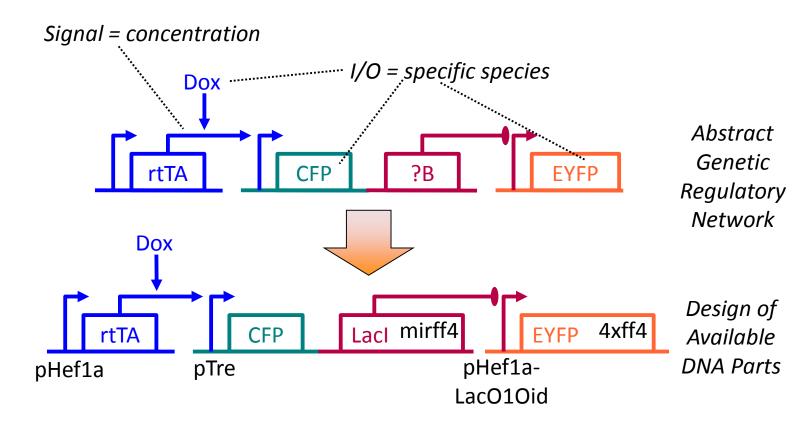


Solution: Feature Mapping + Signal Matching



Problem: DNA Part Selection

Transcriptional boolean logic networks:



Solution: Feature Mapping + Signal Matching

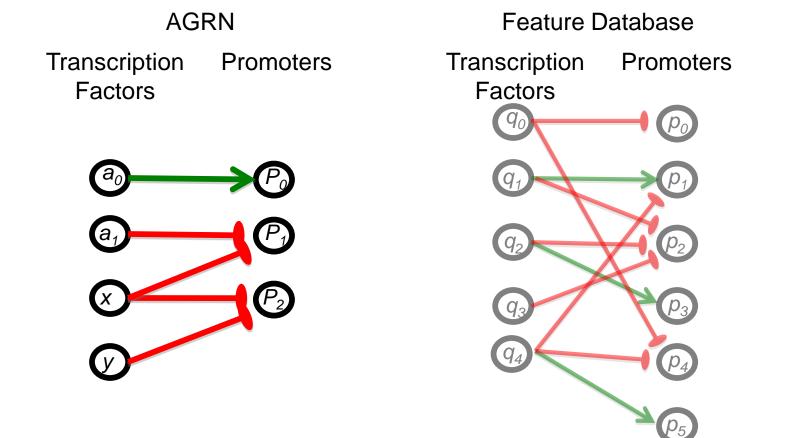
Feature Mapping: assign features to variables

- Feature: a DNA sequence responsible for a specific biochemical behavior
- Feature database: a collection of features and transcription factors with the regulatory relationships between them

TetRO PTet rtTAO PTRE

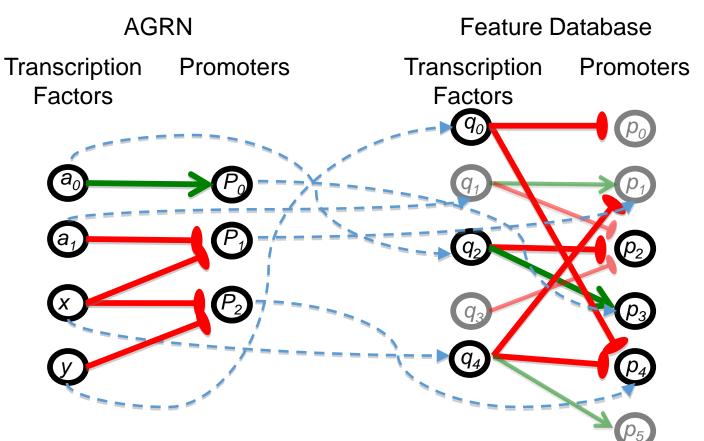
- Feature mapping: Given an AGRN G and a feature database H, find a network of promoters and transcription factors in H that is isomorphic to G.
 - isomorphism: a strict correspondence between arcs in G and the solution

Feature Mapping: assign features to variables



• Feature mapping: Given bipartite graphs G and H, find a subgraph of H that is strictly isomorphic to G.

Feature Mapping: assign features to variables

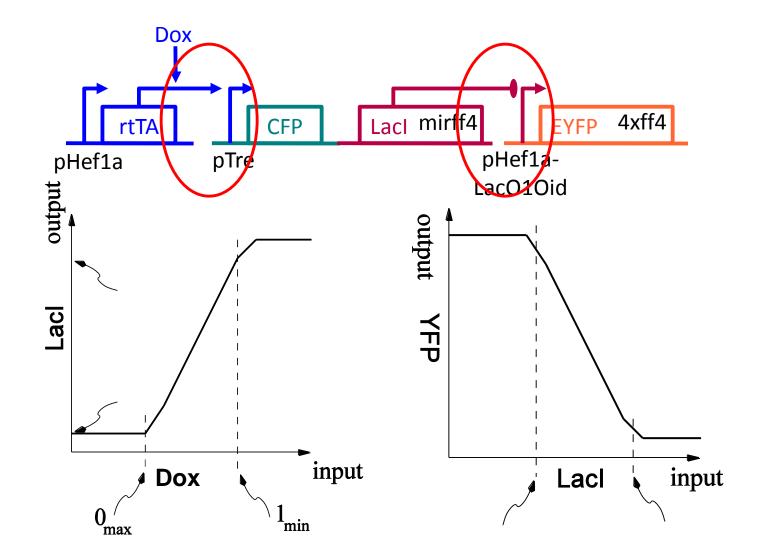


- Feature mapping: Given bipartite graphs G and H, find a subgraph of H that is strictly isomorphic to G.
- This problem is NP-complete: unless an astonishing mathematical hypothesis—P=NP—is true, there is no fast algorithm for solving this problem.

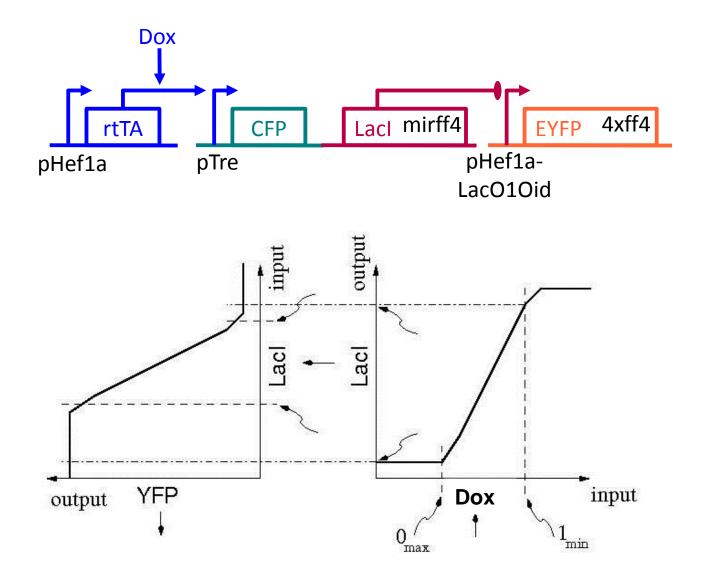
Solution: Feature Mapping with heuristic guided search

- 1: $M \leftarrow m \times n$ zero-one matrix of m rows (variables) and n columns (database)
- $_{2:}$ Choose 1s in M such that one 1 in every row and at most one 1 in every column
- 3: If (i, j) is a chosen 1, and heuristics satisfied, then assign feature j to variable i
- $_{4:}\,\,{\bf if}$ the network induced by the assignment is isomorphic to the given AGRN ${\bf then}$
- 5: return the assignment as a solution
- 6: end if
 - Two heuristics to reduce search space (Ullman, JACM 1976)
 - Number of arcs on the variable ≤ number of arcs on the feature
 - Number of arcs on neighbors
 - (types must match)

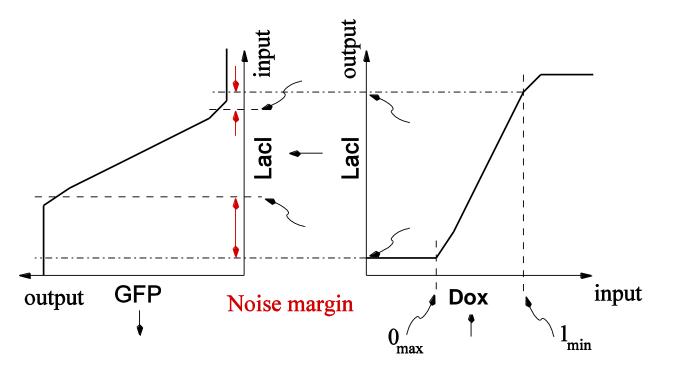
Signal Matching



Signal Matching



Signal Matching



Output 0_{max} of Dox/Lacl \leq input 0_{max} of Lacl/YFP

Output 1_{min} of Dox/Lacl \geq input 1_{min} of Lacl/YFP

Noise margin of a circuit is the minimum noise margin over all junctions Extend earlier algorithm with greedy search for noise margin maximization

"Cross Compilation" Possibilities

