BIOLOGY & COMPUTING

Franck Delaplace
IBISC – Evry University - Genopole
BERDER 2012
Synthetic Biology in a Nutshell

- Multi disciplinary approach
- design of synthetic bio-systems
- Engineering principles

Design ➔ Assembly of BIOBRICKS

Kwok - Nat. 463 Jan. 2010

FIVE HARD TRUTHS FOR SYNTHETIC BIOLOGY

Can engineering approaches tame the complexity of living biology? Roberta Kwok explores five challenges for the field and how they might be resolved.
What I cannot create, I do not understand.

Know how to read, very little that has been learned.

Why must I sort, please?

Bethe Ansatz Prob.

Kondo 2-D Hall: Next Temp.
Non-linear Channal Higgs

Modeling

Design
What I cannot compute, I cannot understand ...

Computing = Understanding

HOPE SO!
computation \leftrightarrow \text{Biology}

Bio-inspired

Life as model of computation

Computing with Life

Synthetic Biology

Programming Life

computation model as a model of Life

Systems biology
BIO-INSPIRED
ALGORITHMS & MODELS

Life as model of computation
Bio-Inspired algorithms

• Computation Framework
  • For a large class of problems
  • Meta heuristic

• For complex problems
  • Intractable $\Rightarrow$ NP complete
  • IA problems (Design)

• Common Features
  • Population, Society
  • Local operations
  • Global evaluation
  • Randomness

Genetic Algorithm
J. Holland - Goldberg

Swarm algorithm
M. Dorigo, V. Maniezzo, et A. Colorni

Neural networks
Hopfield – Rosenblatt
Genetic algorithm - Bridge Design

Darwinian Paradigm

Mutation

Fitness ranking

Cross over

Selection

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Agent = Genome coding for a bridge
Bio-Inspired models

Turing machine = “common ancestor”

- New computing model
  - Alternative computation medium
  - New computing rules
- Computational power
  - Turing universality: Simulation of a computer (universal Turing machine)
  - Massive parallelism: combinatorial resolution of NP complete problems

Membrane computing
G. Paun

L – Systems
A. Lindenmayer,
P. Prusinkiewicz

Cellular Automata
J. Von Neuman - S. Wolfram

DNA computing
Adleman – G. Paun, G. Rozenberg
Example Membrane computing

- P-System
- Non determinism
- Evolution strategy \(\rightarrow\) maximal parallel
- Application
  - Sorting
  - NP complete problem (TSP)
  - Verification of cryptography protocol
SYSTEMS BIOLOGY

computation as a model of biological processes
computation-inspired framework

« De toute évidence, la cohérence fonctionnelle d'une machine chimique aussi complexe, et en outre autonome, exige l'intervention d'un système cybernétique gouvernant et contrôlant l'activité chimique en de nombreux points. » (p. 59)

- “Cybernétique moléculaire”
- Circuit / Network explanatory framework of biological process
- Logical Network (R. Thomas)
Formal models

- Discrete dynamics
  - State based
- Formal property analysis
  - Safety
  - Reachability / invariance
- Explanatory framework
  - Formalization of Biological process
  - Phenotype = molecular signature $\rightarrow$ equilibria

Automata
Petri net
Process algebra
Game theory
Membrane comp.
Example - Automata based model

Specification

\[ a = \text{NOT} \ c \]
\[ b = a \]
\[ c = \text{NOT} \ b \]

Dynamics

\[ 000 \rightarrow 001 \rightarrow 010 \rightarrow 011 \rightarrow 110 \rightarrow 111 \]
SYNTHETIC BIOLOGY

Programming/designing living organism
Design-manufacturing → compilation

main()
{
    printf("Hello World");
}

Program → Compilation → Execution

Computer

Synthetic Biology → Synthesis → SB function

Franck Delaplace - Berder 2012
CAD Environment (ideal) Overview

Integrated view from the current states of art
Compilation principles in a nutshell
Languages for SB ➔ Structural description

- Program = sequence description
- Usual in language & CAD Env.
- Genocad, GEC, Kera
- Clotho, Eugène, Tinker Cell, ...
- Grammar rules = guide of design
- Structural description
- Low level (DNA sequence)

r0040:prom;b0034:rbs;c0040:prc;X:ter

(GEC [Pedersen, Plotkin])

(Genocad [Peccoud])
Structural vs. behavioral description

- **Structure**
  - Component assembly description
  - Low level of description
  - Back end

- **Behavior/function**
  - Process design
  - Functional => safety
  - High level of description
  - Specification/document

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**Hardware Description Language**

- Verilog
- VHDL

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**Behavioral program**

Generate Oil

Y when X

X

Y

r0040:prom;b0034:rbs;...

ATG|AAA|TTG|...

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**Structural program**

**Synthesis**

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**Toy example**
Compilation ➔

Part assembly = behavior assembly

• Component description = behavior description
• Bio system design = behavior description
  • The program describes the expected “function”
• The issue is to define a compilation method assembling parts such that the behavior of the assembly is “similar” to the behavior of the designed function.
• Problem - Reliability ➔ guaranty on the assembly
  • i.e. formal guaranty that each step is correct w.r.t. to the behavioral “similarity”.

Correct translation (compilation) ?
Behavior compilation for SB - 2 possible ways

**Computational description**
- Behavior = Abstract machine instruction
- Synthesis = Semantic rules

**Logical Specification**
- Behavior = Specification
- Synthesis = Proof rules

State = Situation
Event-driven transition

Dessine moi un canard !

Axioms
Behavior of components

Proof

Theorem
Behavior of the function
Model & theory in logic

Is a formula true?

**Model**

**Theory**

**Completeness**

**Correction**

**Interpretation**

\[ I(b) = 1, I(c) = 1 \]
\[ I(b \lor c) = \max(I(b), I(c)) \]
\[ I(b \land c) = \min(I(b), I(c)) \]

**Deduction system**

\[ c \text{ is proved} \]
\[ \frac{b \lor c \text{ is proved}}{b \text{ is proved}} \]
\[ \frac{b \text{ is proved} \quad c \text{ is proved}}{b \land c \text{ is proved}} \]
Correction of the assembly

Correction of assembly = observational behavior inclusion

Compilation = Proof $\Rightarrow$ find a behavior assembly s.t. the behavior of the designed function is included

Part A

Part B

AATTGGAAGCC

AATGCGTTTATAGCCCCATGG..
Remarks

• Functional/behavioral programming
  • 1 function $\Rightarrow$ n structures – e.g. inhibition -
  • Document function $\Rightarrow$ Safety analysis capability

• Proof framework
  • Safe design $\Rightarrow$ formal method + safety analysis
  • Functional/qualitative description $\Rightarrow$ Specification, resolution principles
  • Quantitative description $\Rightarrow$ Strategy of the resolution, tuning

• Hierarchy of the components $\neq$ Organization for organisms
  • Functionality
  • Inter-operability

• GUBS project - Adrien Basso Blandin – Franck Delaplace
  • Behavioral language
  • Compiler
Synbiotic: Tower of languages

- Population level
- Global programming

- Agent centric
- Elementary behavior

- Interface
  - in-silico / In vivo
  - Regulatory network

Global specification

Local Specification

Implementation

Nature 484: Basu S & al.

IBISC
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Conclusion

- Function
- Process

Behavioral Language for synthetic biology
THANK YOU !