Synthetic biology: application of logic synthesis to biological models

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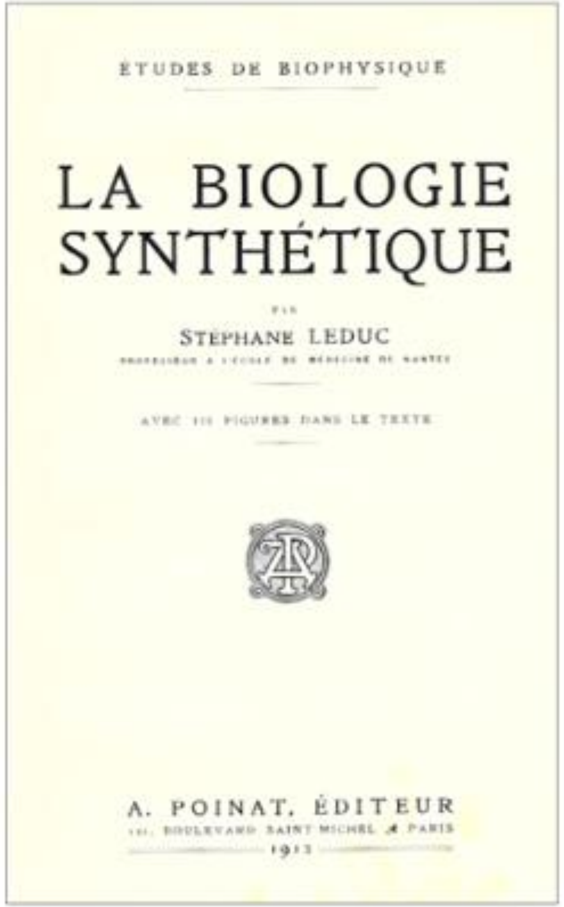
Synthetic biology

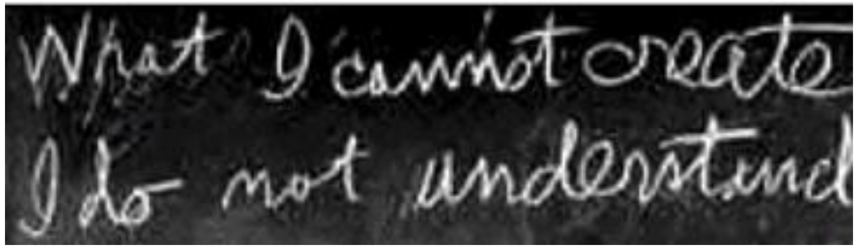

ETUDES DE BIOPHYSIQUE

LA BIOLOGIE
SYNTHÉTIQUE

STÉPHANE LEDUC

A. POINAT, ÉDITEUR


The Nobel Foundation

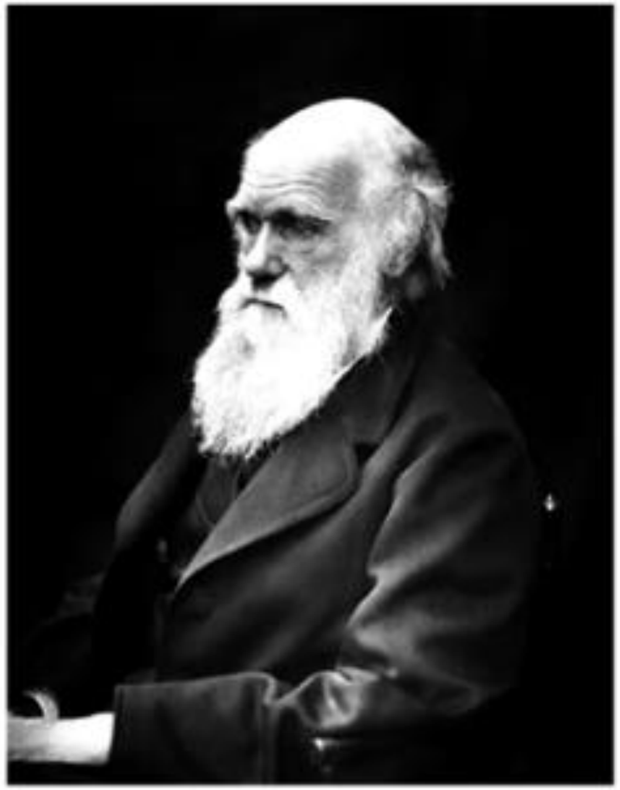


Richard Feynman (1988)

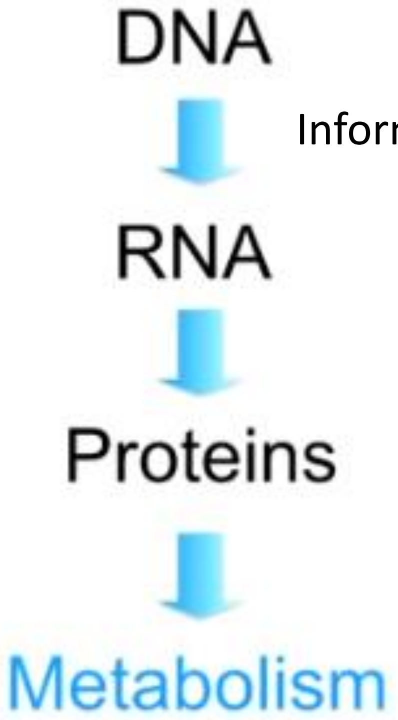
1912: someone proposed the term "synthetic biology" to describe a number of interesting phenomena that perhaps had a different meaning

Pillars of biology

Evolutionary theory



Charles Darwin (1809-1882)



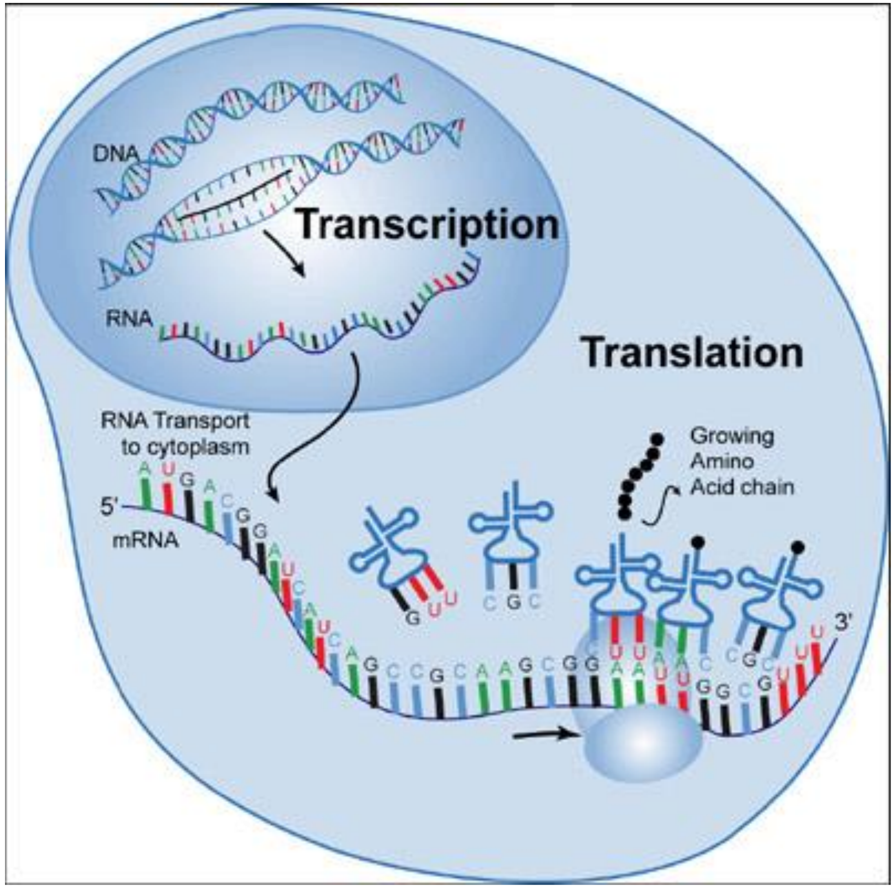
Information transmission

The **central dogma** of Molecular Biology

Central dogma

$$DNA \rightarrow \textit{transcription} \rightarrow RNA \rightarrow \textit{translation} \rightarrow protein.$$

Central dogma: explains how the information in the DNA results in proteins



Questions about (biological) objects

Where do biological systems come from? → evolutionary biology

How do they work?

Tinkering: biological systems work taking advantage of anything available in order to build a new function.

F. Jacob (1920-2013) Tinkering (*bricolage*)

Exaptation

A biological function, invented by evolution, may be born with a given function and eventually may be recycled into something very different

Feathers Thermal insulation Flight

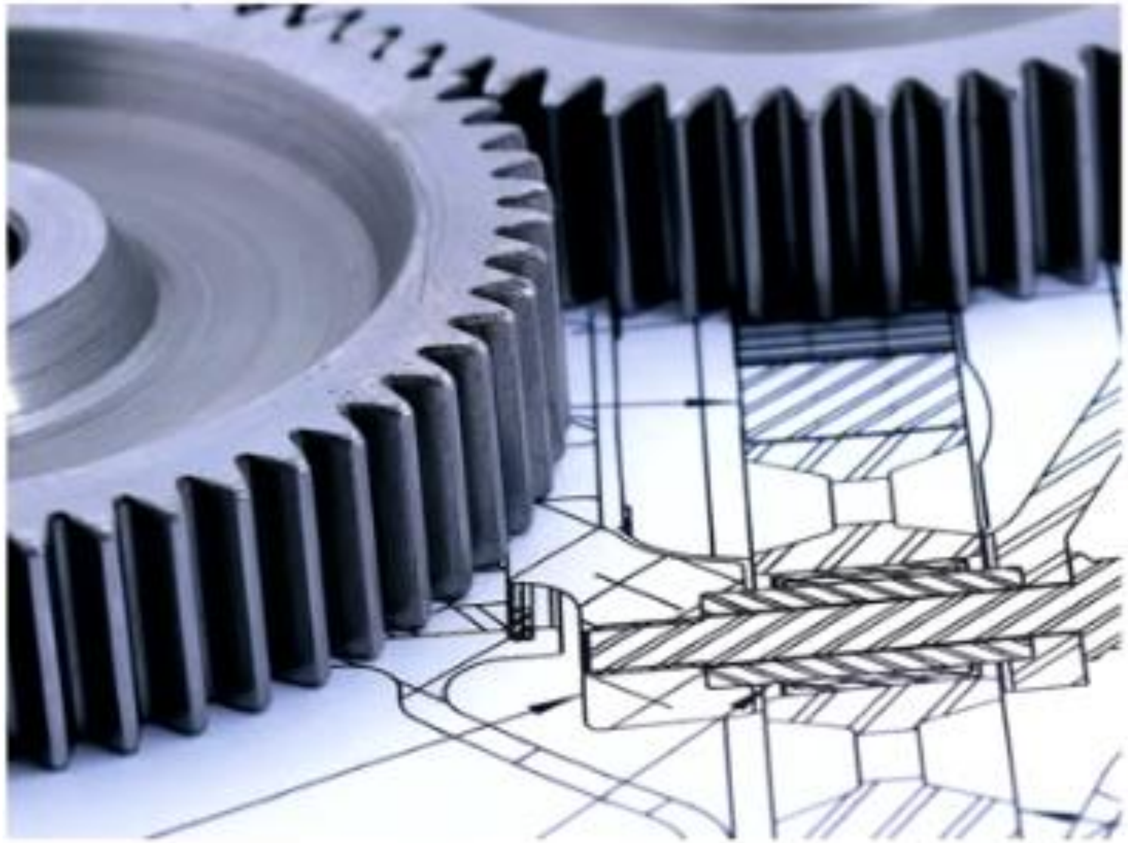
Evolutionary appraches limited to explain how things work

Synthetic biology

Looking at live systems using engineering as a metaphor.

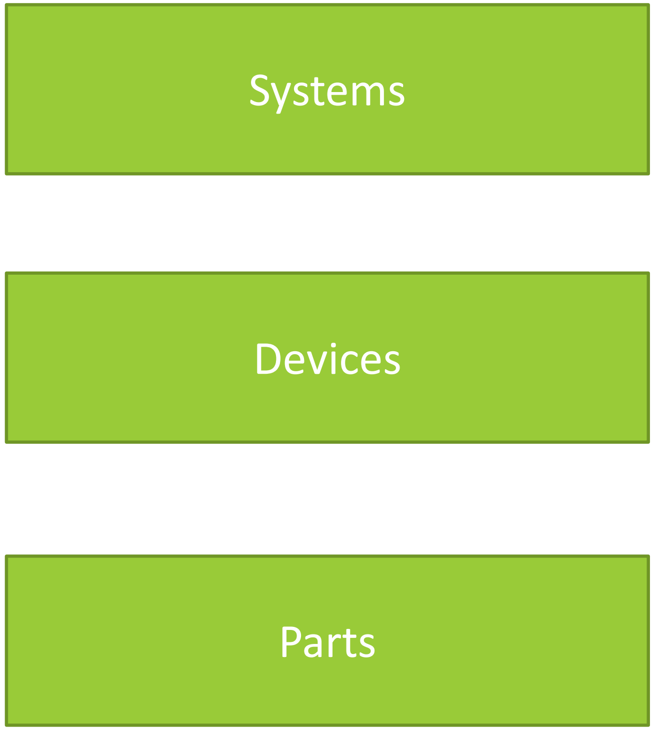
Emphasis on the composition and relational logic…

… not in the evolutionary origin.

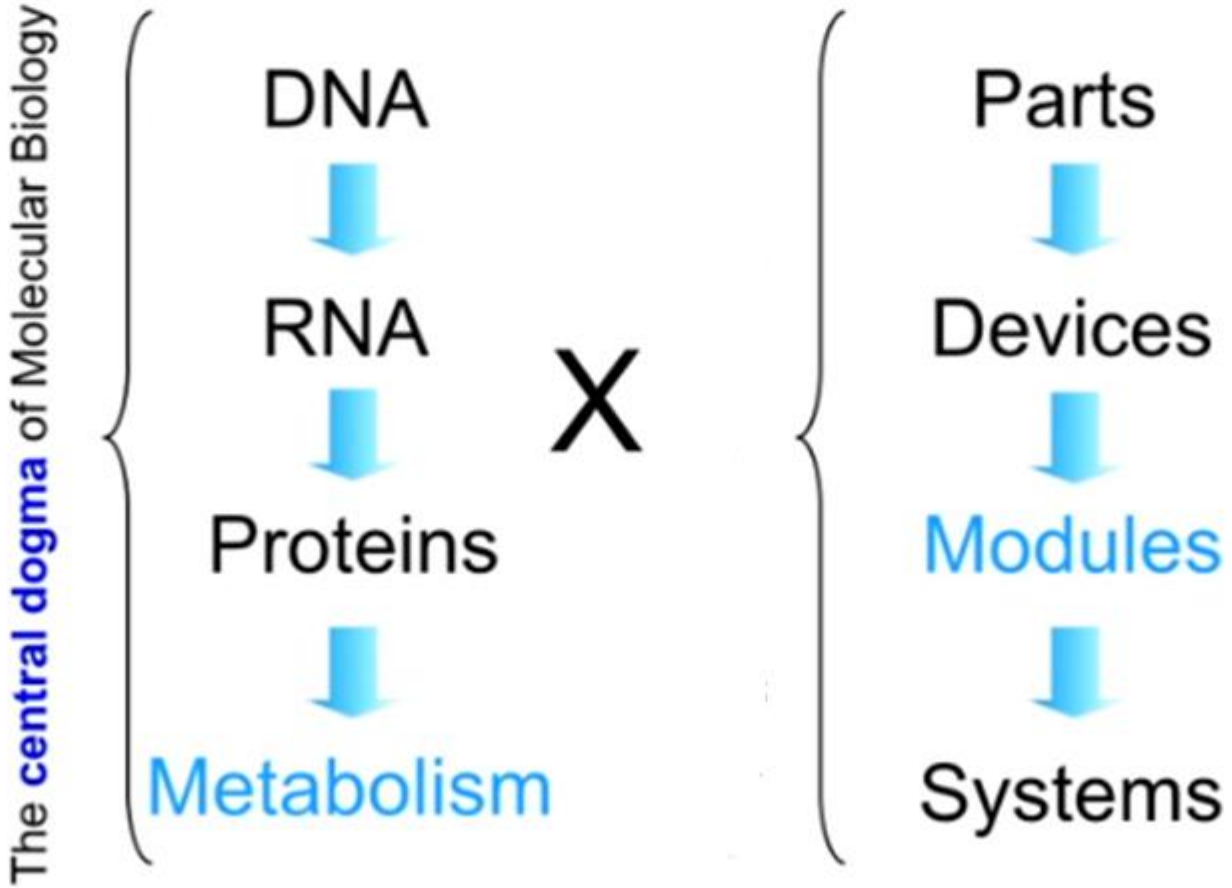


Abstraction hierarchy

Abstract hierarchy very common in engineering!



Molecular biology vs synthetic biology



Definitions of synthetic biology

- 2000 – *Chemical & Engineering News* (Apr 24th)
  - "using the synthetic capability of organic and biological chemistry to design *nonnatural, synthetic molecules* that nevertheless function in biological systems"
- the design and construction of new biological "parts," "devices," and "systems"
- the re-design of existing, *natural biological systems* for useful purposes (www.syntheticbiology.org)

Practical definition of synthetic biology

- "making biology easier to engineer" -- Synthetic Biology Engineering Research Center (SynBERC)

- Applying engineering principles to biological systems
  - Design

    build a machine with specific function
  - Modeling

    equation that support my design
  - Abstraction

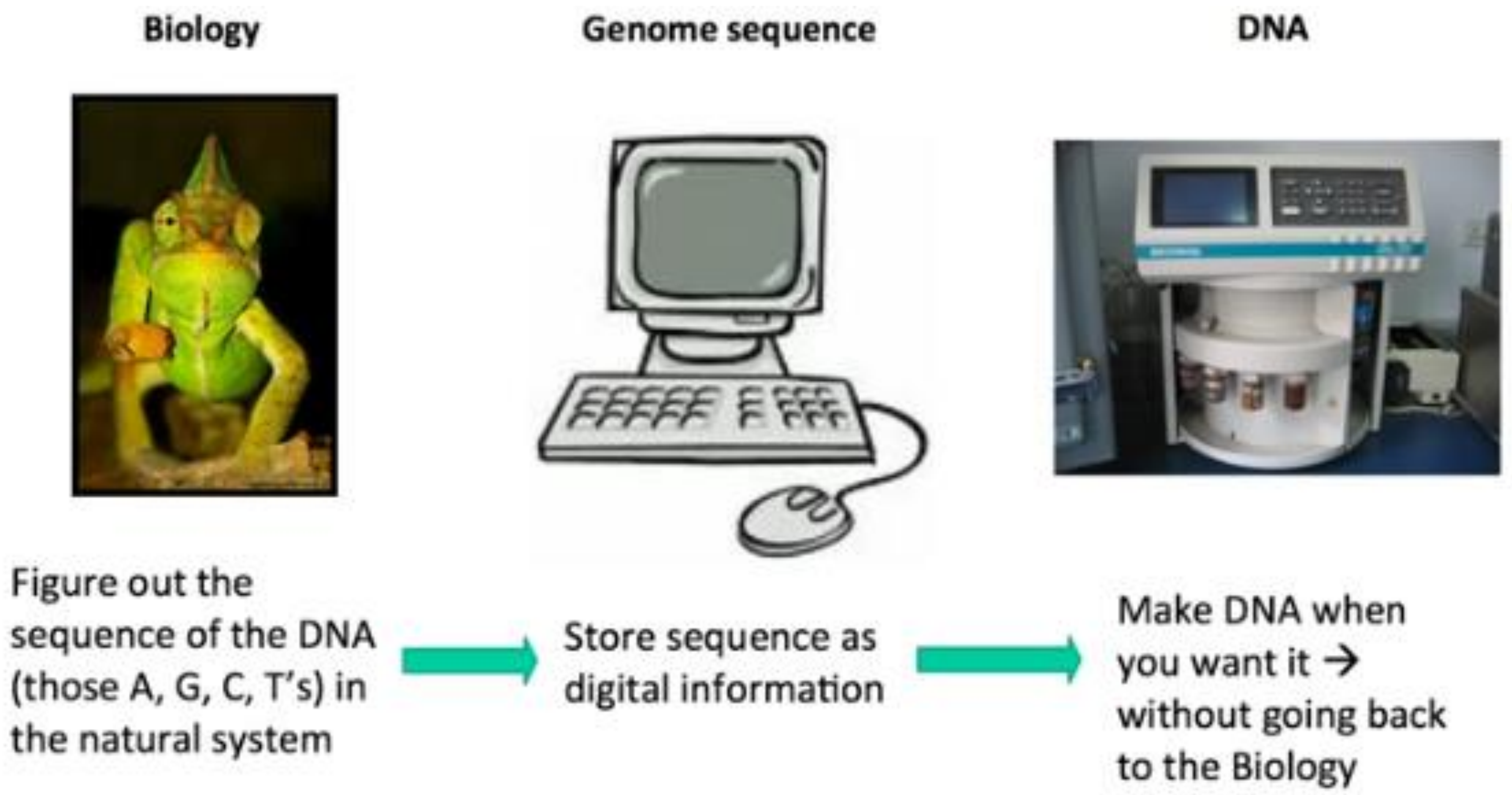
    semplification of some details

Key enabling technology:

DNA synthesis

Having biological function, but removing real biology from that process

DNA synthesis



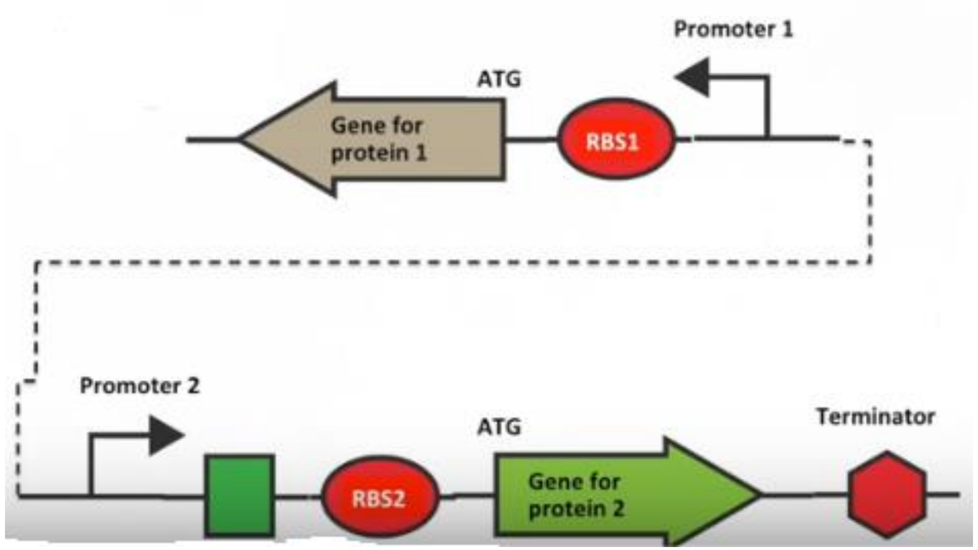
A given sequence for a specified function

New sequence for a new function

Synthetic biology

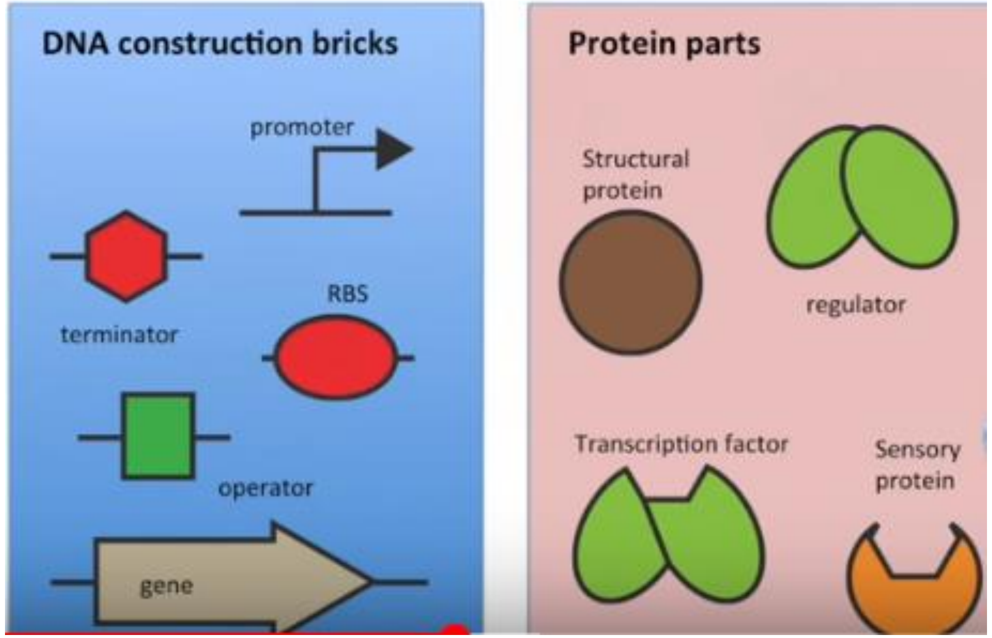
Concept 1: divide DNA in biological parts.

Parts assembled to build proteins



Study parts and move them to create a new sequence with a new function

CIRCUIT PARTS



Synthetic biology

Concept 2: rules and models

Rules: what does the DNA circuit do?

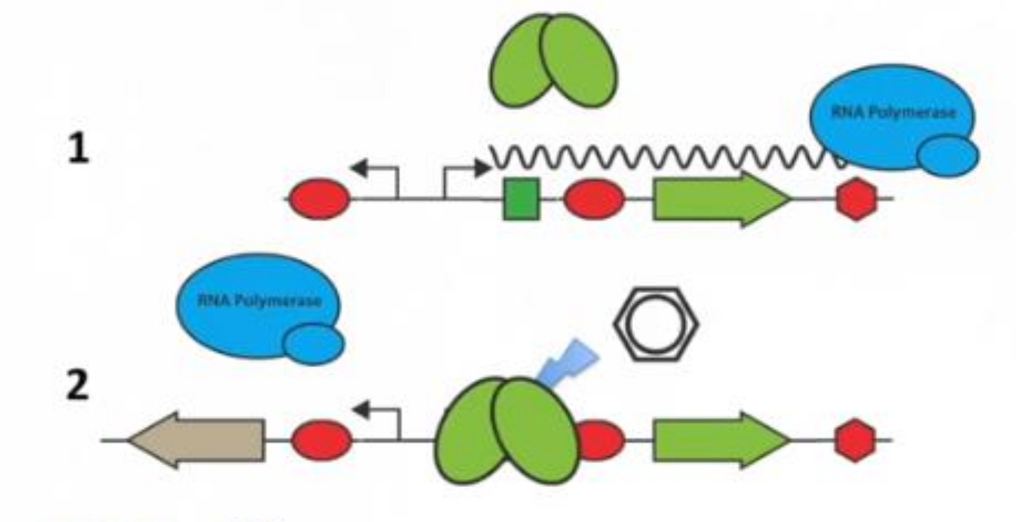
Models: predict as an element

try to work

Concept 3: standards

- Standards for electricity
- Standards for gene expression

What does this DNA circuit do?

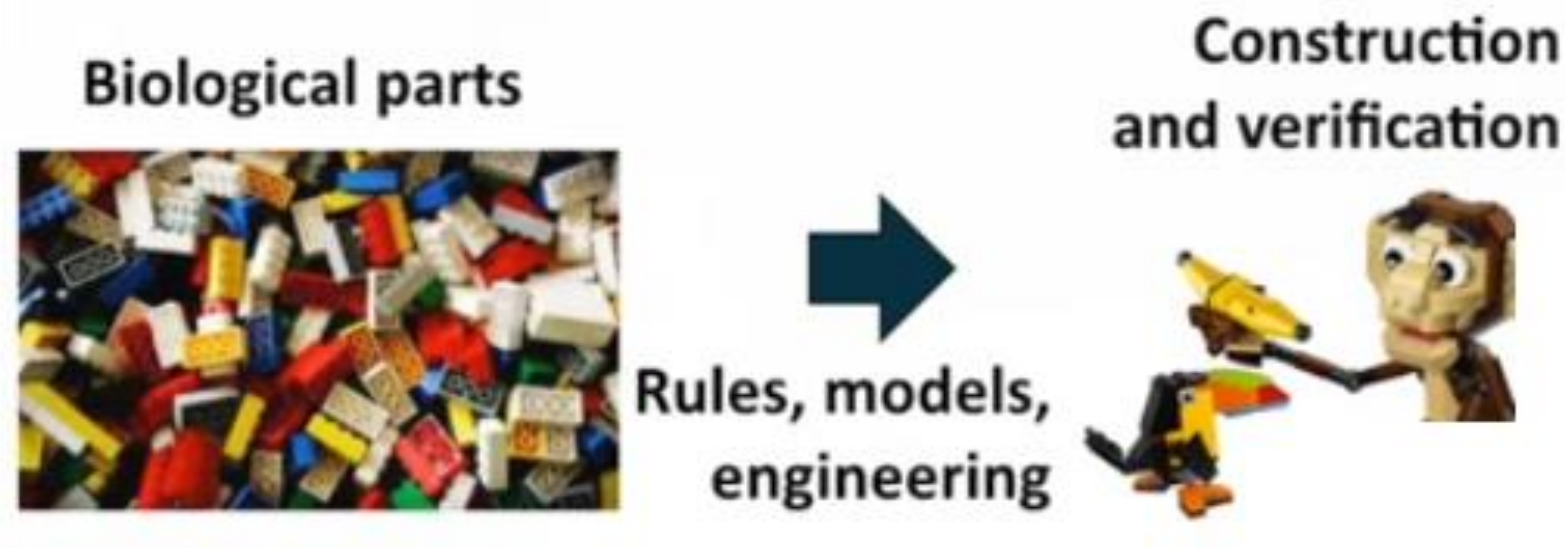


What is synthetic biology hoping to achive?

Understanding biological processes through their reconstruction

Facilitating construction of new biological processes with new functionalities

Engineering idea



Research field

- DNA-encoded set of parts that perform a function
- Biochemical interactions

reliability

Programming language for living cells

Genetic circuits

Genetic parts

Genetic programming

DNA synthesis and assembly

Genome design

Analog synthetic biology

Companies dedicated to DNA synthesis

Circuits in biology similar to circuits in electronics

- Design and program complete genomes
- Convergence of multiple technologie

Potential applications

Agricolture

- Incorporate complex functionalities in plants
- Smart plants programmed to respond to external events
- Engineering bacteria to associate with plants able to obtain nitrogen

Industrial applications

- Chemical factories → pharmaceuticals
- Bioenergy
- Biofuels

Materials

- Materials from natural sources
- Non-carbon nanomaterials (metals, silicates)

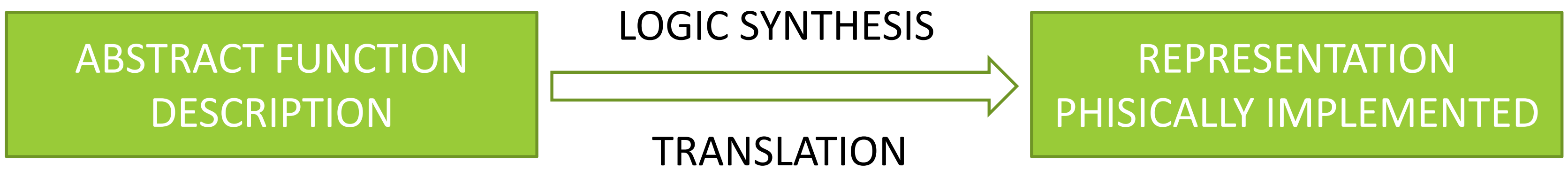
Medical applications

- Stem cells to self-organize and differenziate
- Viruses and bacteria as antibiotics
- Bacteria as drug-delivery devices
- Microbiome: bacteria in symbiotic relation with body

→ Engineering bacteria colonies for the treatment of disease

Which is the role of logic synthesis in synthetic biology???

Genetic logic



Boolean logic functions engineered into living cells

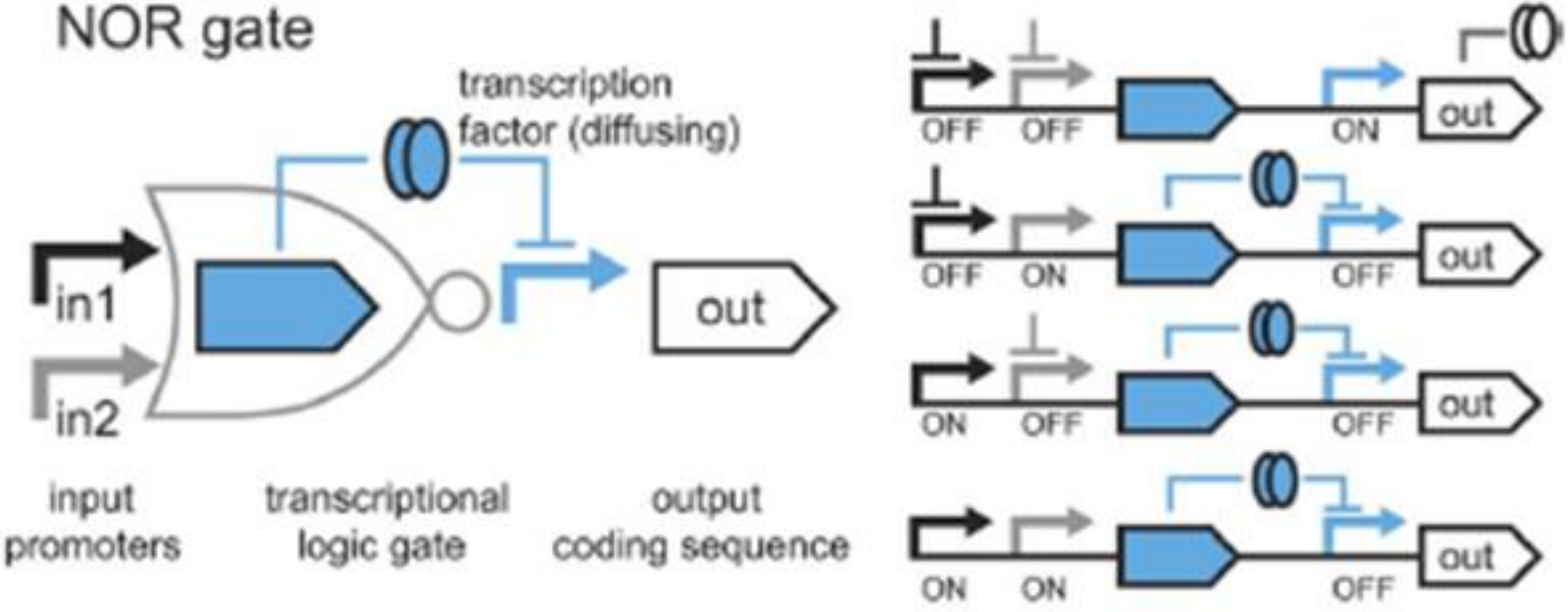
Genetically encoded logic operates within the central dogma of molecular biology.

Genetic logic circuits made up of one or more units.

- Promoters: start site for transcription
- Coding sequences

One or more promoters preceding a coding sequence enables activation or repression of transcription factor (signal that regulates the transcription at a specific promoter)

Genetic regulatory relationships enable the implementation of transcriptional genetic logic gates

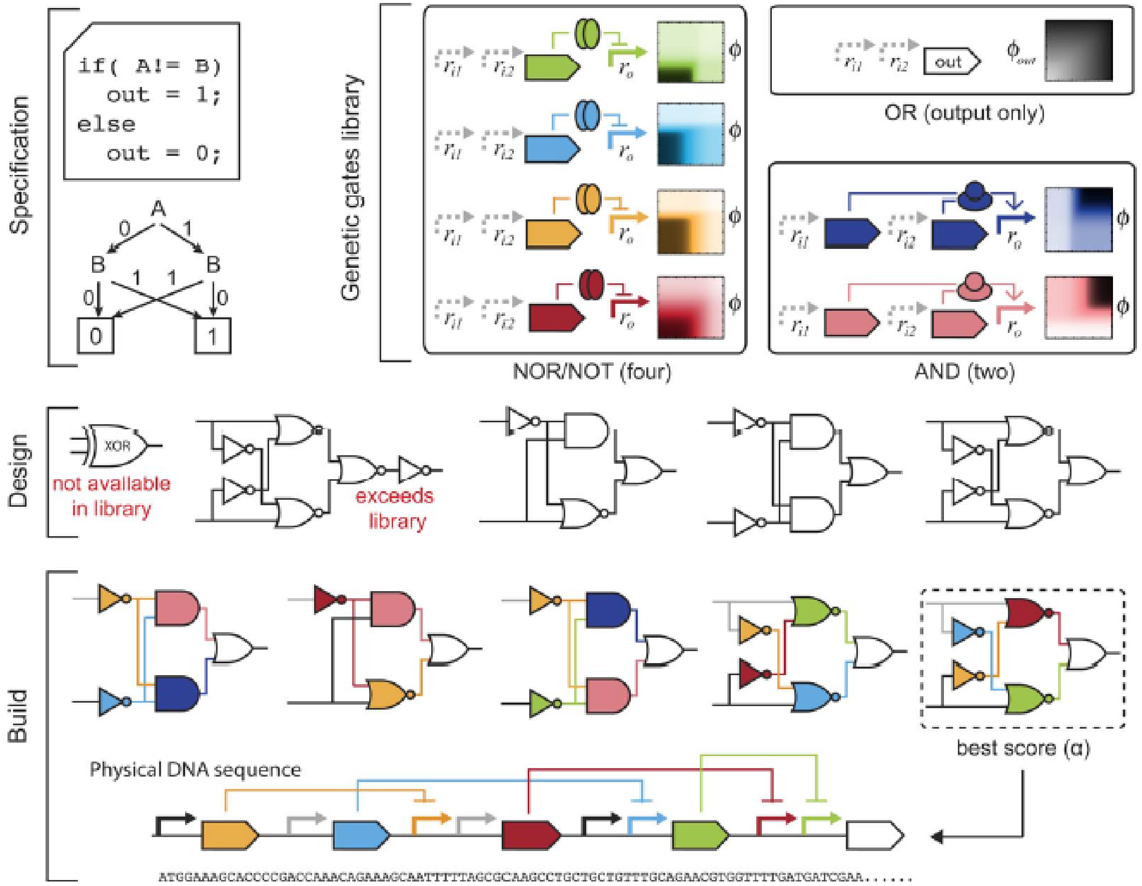


Coding sequence encode transcription factor that can diffuse and regulate promoter state

Logic synthesis workflow

Input: any abstract logic description able to be specified using a description language or description tool

Output: a technology-specific mapping of the input logic

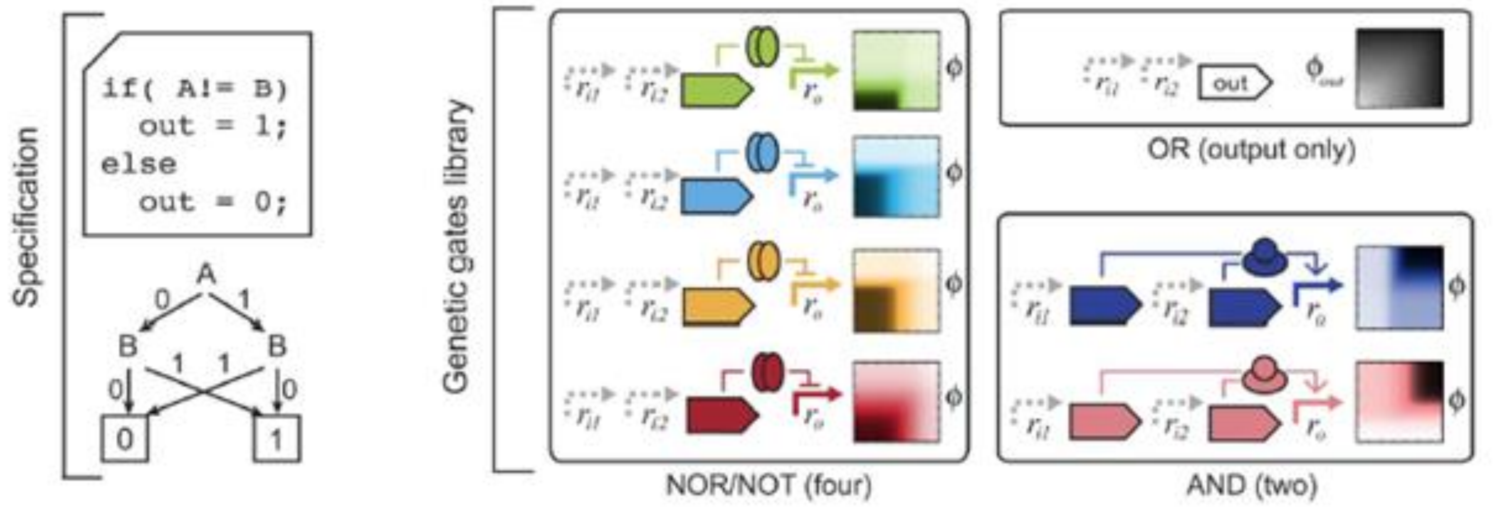


Specification

Process of creating a correct representation of the description that is canonical for optimization (truth table or a reduced ordered binary decision diagram (ROBDD))

Example of specification for electronic circuits: Verilog description

For genetic circuits: Verilog, VHDL, GEC (Genetic Engineering of living Cells), Proto, SBOL (Synthetic Biology Open Language)

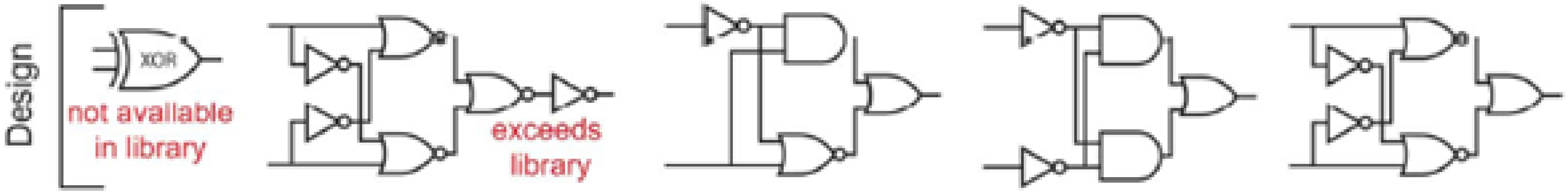


Design

Output of specification translated in an optimized gate level schematic.

- Example: ABC uses AND-inverter graph library to heuristically optimize the logic operation

Optimization weighs several cost functions, such as reducing the total number of components in the schematic or the total amount of component fan-in

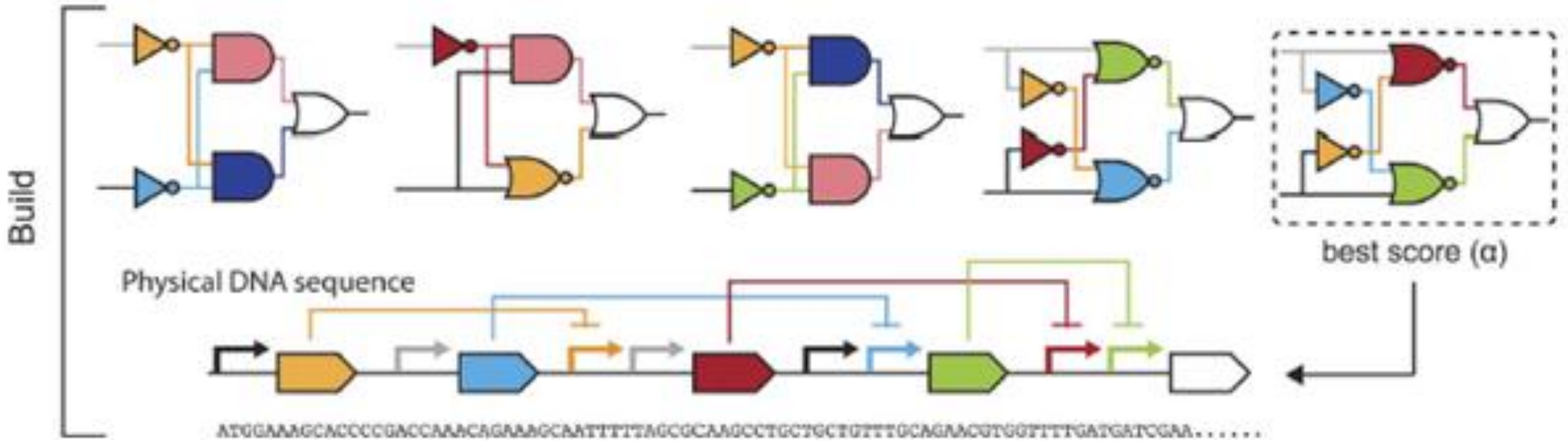


Cost functions

- Wires
  - Electronic circuits: wires cheap → two level synthesis (SOP forms) → higher fun-in
  - Genetic circuits: wires expensive → multilevel synthesis
- Circuit size: circuits run by living cells with limited resources
- Number of genetic modules
- Number of transcription factor
- Total amount of component fan-in

Build

Final step in the process of converting an abstract design into a realizable form.
Translation of the optimized gate-level schematic into structures that can be found in a specific target technology



Example of circuit optimization

Chun-Ning Lai, Jie-Hong Jiang, François Fages. Recombinase-Based Genetic Circuit Optimization. BioCAS 2017 - 13th IEEE Biomedical Circuits and Systems Conference, Oct 2017, Turin, Italy. pp.1-4, 2017, <http://biocas2017.org/>. <hal-01659183>

Goal: reduction on the DNA sequence length

Minimizing the total DNA sequence length is important because a shorter DNA sequence is more likely to succeed in insertion into the host cell for the intended computation.

Library

TABLE I. SOME SIMPLE GATES AND THEIR DNA SEQUENCES

Gate	Function	DNA Sequence	Cost
CONST0	0	G	1
CONST1	1	PG	2
BUF(a)	a	dG	2
NOT(a)	$\neg a$	P_aG	2
AND2(a,b)	$a \cdot b$	d_aT_bG	3
OR2(a,b)	$a \vee b$	d_ad_bG	3
NAND2(a,b)	$\neg a \vee \neg b$	P_aP_bG	3
NOR2(a,b)	$\neg a \cdot \neg b$	P_aL_bG	3
XOR2(a,b)	$\neg a \cdot b \vee a \cdot \neg b$	$d_{ab}G$	2
XNOR2(a,b)	$a \cdot b \vee \neg a \cdot \neg b$	$P_{ab}G$	2
IMPLY(a,b)	$\neg a \vee b$	d_bP_aG	2
NOTIMPLY(a,b)	$a \cdot \neg b$	d_aL_bG	2
AND$k(v_1,\ldots,v_k)$	$v_1 \wedge \cdots \wedge v_k$	$d_{v_1}T_{v_2}\ldots T_{v_k}G$	$k+1$
OR$k(v_1,\ldots,v_k)$	$v_1 \vee \cdots \vee v_k$	$d_{v_1}d_{v_2}\ldots d_{v_k}G$	$k+1$

Gate Merging for Circuit Optimization

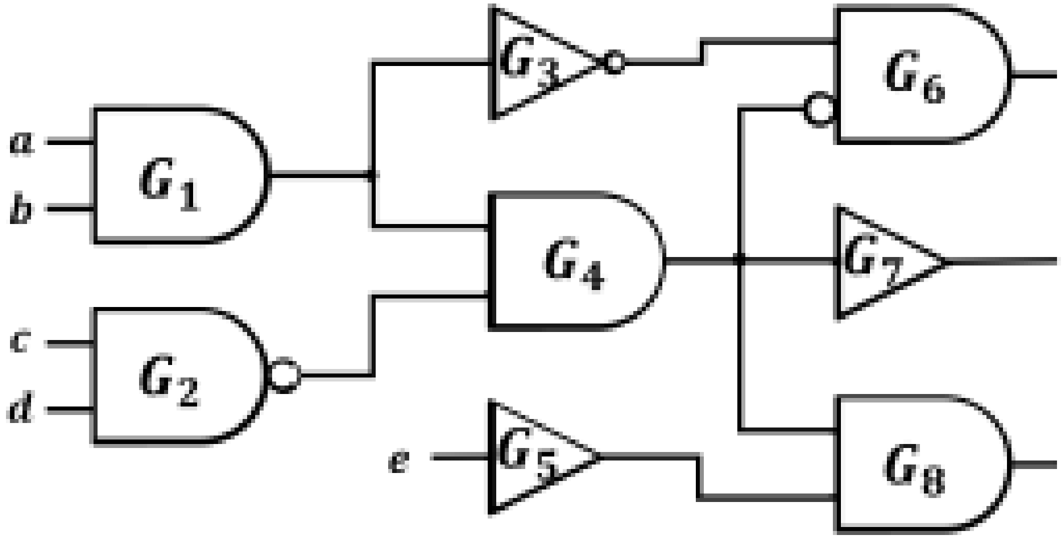
Example of optimization rule

$$\underbrace{P_aP_bX\overbrace{T}^{\text{drop}}}_{X=\text{NAND2}(a,b)}\ \underbrace{\overbrace{d_x}^{\text{drop}}T_cYT}_{Y=\text{AND2}(x,c)} \xrightarrow{\text{merge}} P_aP_bXT_cYT$$

NAND2's output gene X corresponds to the inducer x of AND2

Problem Statement 1: Given a logic circuit $G(V, E)$, find a well-formed sequence implementation for each logic gate of V, and merge gates u and v with $(u, v) \in E$ such that the total DNA sequence length and the depth of protein-production cascade are minimized.

Example



Starting DNA sequence: 29 DNA units

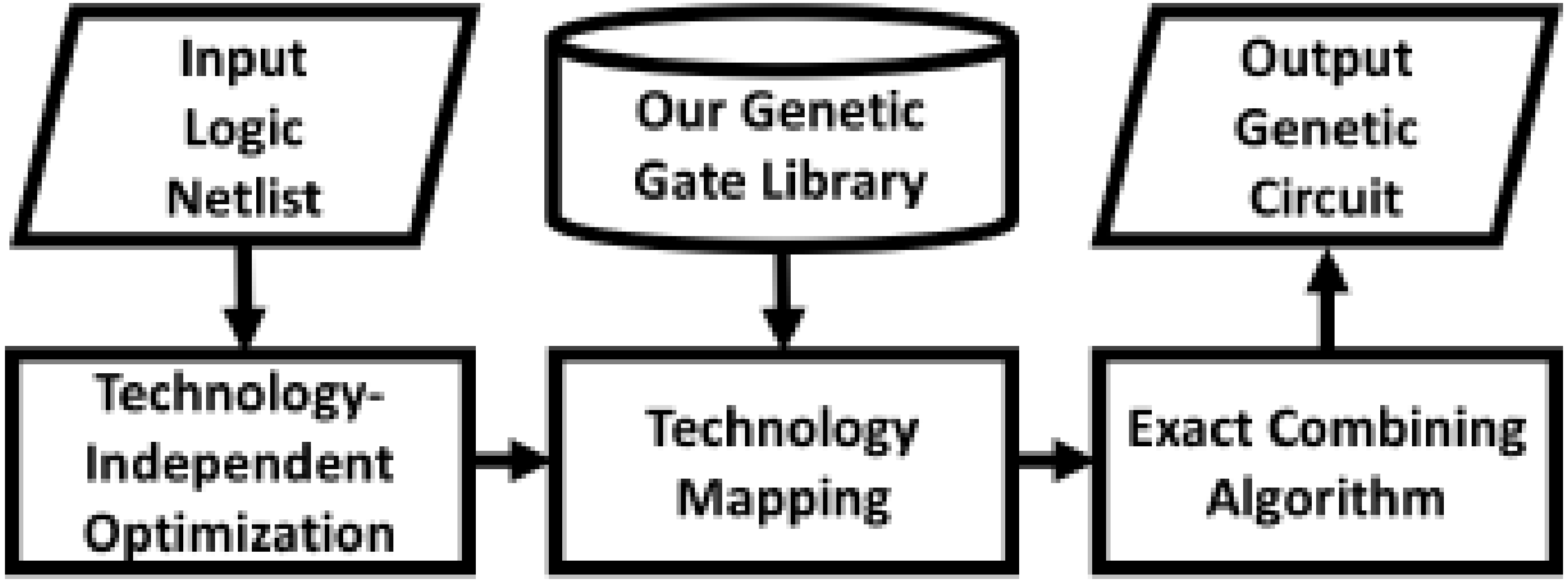
$$\underbrace{d_a T_b G_1 T}_{G_1}\underbrace{d_c d_d G_2 T}_{G_2}\underbrace{P_{g_1} G_3 T}_{G_3}\underbrace{d_{g_1} T_{g_2} G_4 T}_{G_4}\underbrace{d_e G_5 T}_{G_5}$$

$$\underbrace{d_{g_3} L_{g_4} G_6 T}_{G_6}\underbrace{d_{g_4} G_7 T}_{G_7}\underbrace{d_{g_4} T_{g_5} G_8 T}_{G_8}$$

Optimized DNA sequence: 18 DNA units

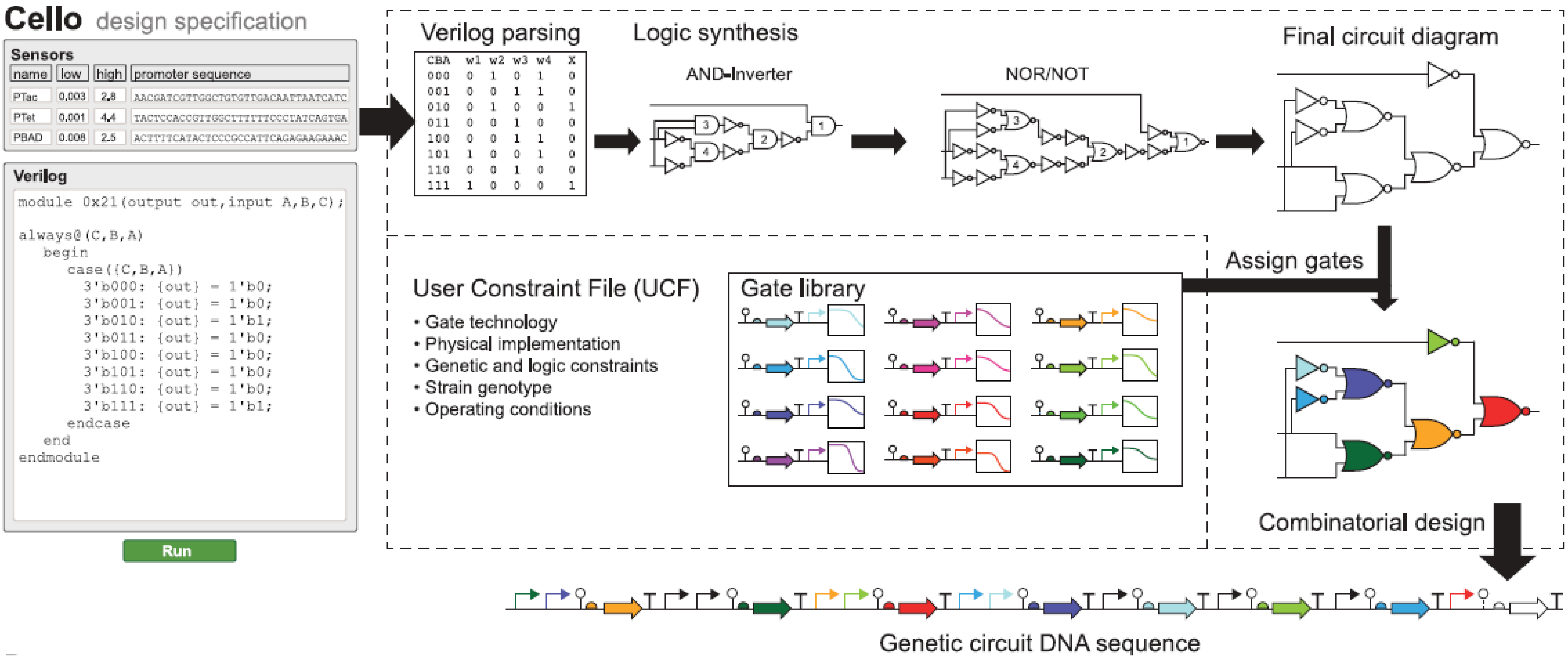
$$\underbrace{d_a T_b G_1 T}_{G_1}\underbrace{P_c P_d T_{g_1} G_4 G_7 T}_{G_2, G_4, G_7}\underbrace{P_{g_1} L_{g_4} G_6 T}_{G_3, G_6}\underbrace{d_e T_{g_4} G_8 T}_{G_5, G_8}$$

Synthesis flow



Genetic circuit design automation

Alec A. K. Nielsen, Bryan S. Der, Jonghyeon Shin, Prashant Vaidyanathan,
Vanya Paralanov, Elizabeth A. Strychalski, David Ross,
Douglas Densmore, Christopher A. Voigt*



SUMMARY

- WHAT IS SYNTHETIC BIOLOGY
- APPLICATIONS AND RESEARCH FIELD
- ROLE OF LOGIC SYNTHESIS IN SYNTHETIC BIOLOGY

Thanks for your attention!