Synthetic Biology: Motivation?

The advanced form of Biotechnology

Reducing:
Cost
Impact
Time to market
Synthetic Biology: Motivation?

The end of the XIX\textsuperscript{th} Century has witnessed the development of technologies that provided the basis for wealth creation by new industries, \textit{eg} synthetic chemistry. One could also cite computer science / industry for the second half of the XX\textsuperscript{th} Century, or nano-technoscience for the end of the XX\textsuperscript{th} Century.

Synthetic Biology constitutes a wide base of concepts and methods with the same overall potential.
**Interface of Biology to other disciplines**

**Systems Biology:** Science of the systemic analysis of the dynamic and spatial behavior of networks of interactions among bio-molecules.

**Synthetic Biology:** the engineering of biology: the deliberate (re)design and construction of novel biological and biologically based systems to perform new functions for useful purposes, that draws on principles elucidated from biology and engineering (ERASynBio).
Coupling analytics and synthetics
Coupling disciplines

- Biology
- Mathematics
- Computer Science
- Chemistry
- Physics
- Engineering
Emergence

Mathématiques Informatique
- Calcul
- Stockage
- Modélisation
- Simulation
- Intelligence artificielle
- Algorithmes biomimétiques

Chimie
- Synthèse d'ADN
- Nucléotides exotiques

Biologie
- -omicques
- Robotisation
- Fabrication
- Test
- Liposomes

Micro-fluidique Automatique
- Évolution artificielle
- Origine de la Vie
- Cellule unique

Sciences de l'Ingénieur
Perspective

Synthetic Chemistry

Research

Yearly market in 2026

$10^{12}$

Economy

Industry

Development

Synthetic Biology

XX th Century

XXI th Century
Contents

SynBio

Protocells

Biobricks - based Artefacts

Minimal Cell / Genome

3NA (exotic nucleic acids)

Synthetic Chemistry

Genetic Engineering
Design levels

**SYSTEMS**
- Organism; Châssis; Nanomachine

**DEVICES**
- Regulatory circuit; Metabolic pathway

**BIO-BRICKS**
- Protein; RNA
Minimal Cell / Genome: a deconstructivist scheme

CHASSIS
- A miniature factory or a live test tube

EPIGENOME
- A rationale conception

GENOME
- A full synthesis
Artificial Life: a more fundamental slant

**PROTOCELLS**
- Liposomes; Microfluidics; Artificial life

**INNOVATIVE CHEMISTRIES**
- Third-type nucleic acids; New aminoacids; New metabolisms

**INFORMATION RECODING**
- Genetic code; Gene expression code
Keywords

Standardization
Re-utilization
Decoupling conception and fabrication
Orthogonality and modularity
Hierarchy
The improvement spiral in synthetic biology repeats the cycle shown here, until satisfying the initial specifications.
"A bioeconomy is an economic system in which biological resources like forests, agricultural and aquatic ecosystems provide not just food, feed and fibre, but also chemicals, energy and materials as well as environmental benefits such as green gas emission reductions."
The Versant™ diagnostics

Monitors 400 000 patients per annum, afflicted with 1 or 2 viral infections (AIDS and hepatitis)

Siemens®

A good example of collaboration between synthetic chemistry and synthetic biology
The Hydrocortisone drug

Anti-inflammatory drug.
Several hormones.

Sanofi – start production in 2015
The Artemisinin drug

Anti-malaria drug. Synthetic Biology allowed to decrease price and free from variability in quantity and quality. Synthetic chemistry was not an option.

Amyris Technology (US), license to Sanofi – started production of 60 tons per year in 2013
Mosquito Control

**Figure 2 | Synthetic biology for understanding and preventing disease.**

- **a** | A female-specific dominant-lethal gene network for mosquito control. Mosquitoes were engineered to express an intron-containing variant of the tetracycline (TET) transactivator (tTA) under the control of a flight-muscle-specific promoter (P\(_{FM}\)). In male mosquitoes, the intron is not spliced out, which prevents correct tTA translation. In female progeny, however, functional tTA translation is restored by sex-specific mRNA splicing. This results in the activation of the tTA-responsive promoter P\(_{TET}\) and the expression of a toxic gene that triggers a flightless phenotype. If mosquitoes are raised in the presence of tetracycline (TET), tTA is prevented from activating P\(_{TET}\), which results in a normal phenotype. However, following their release into the TET-free environment, engineered males mate with wild-type females. This transmits the female-specific dominant flightless phenotype and should eventually result in the reduction or extinction of the wild-type population.

- **b** | Propagation of a selfish gene converting a heterozygous into a homozygous host. The homing endonuclease I\(_{-}\)SceI is expressed and cleaves its cognate restriction site (RS) on the homologous chromosome. Following end resection and repair, the I\(_{-}\)SceI expression cassette is inserted into the second chromosome. pA, poly(A) tail.
Disease-relevant metabolites, process off-level concentrations and coordinate adjusted diagnostic, preventive or therapeutic responses in a seamless, automatic and self-sufficient manner.

An example of the use of a prosthetic network is the sensing of metabolites to improve control of urate homeostasis (FIG. 7b). Moderate levels of uric acid, which scavenges radicals, are deemed to be beneficial. However, a transient surge in uric acid that is released by dying cells during cancer therapy leads to tumour lysis syndrome, and chronic hyperuricaemia can result in gout. Humans are particularly sensitive to imbalances of urate homeostasis because they lack uricolytic activity. A prosthetic network that constantly monitors blood urate concentrations and restores urate homeostasis by controlled expression of a urate oxidase — which reduces excessive urate concentration while preserving levels that are suitable for radical scavenging — could represent a treatment strategy for hyperuricaemic disorders.

In brief, human cells that contain such a prosthetic network have recently been designed by combining: the uric acid sensor HucR, which manages oxidative stress protection in Deinococcus radiodurans; the human uric acid transporter URAT1 (also known as SLC22A12), which increases the intracellular uric acid levels and thus the sensitivity of the prosthetic circuit; and a secretion-engineered urate oxidase (smUOX) that is clinically licensed for the treatment of the tumour lysis syndrome.

Figure 7 | Advanced therapeutic and prosthetic networks.

**a** Light-triggered transcription control of blood glucose homeostasis. The synthetic phototransduction cascade consists of rewired melanopsin and nuclear factor of activated T cells (NFAT) control circuits. Photo-isomerization of the 11-cis-retinal chromophore (R) by blue light (~480 nm) activates melanopsin. This sequentially turns on Gaq-type G protein (GAQ), phospholipase C (PLC) and phosphokinase C (PKC) and triggers Ca$_2^+$ ion influx via transient receptor potential channels (TRPCs) and possibly also from the endoplasmic reticulum. This Ca$_2^+$ ion surge activates calmodulin (CaM) to calcineurin (CaN), which dephosphorylates NFAT. NFAT then translocates into the nucleus, where it binds to specific promoters (P$_{NFAT}$) and coordinates transgene transcription. When linked to the glucagon-like peptide (GLP1), this mechanism allowed light-controlled...

**b** Prosthetic network for the treatment of tumour lysis syndrome and gout. Implanted sensor–effector cells are used to monitor serum urate levels constantly: they import urate via a transgenic human uric acid transporter (URAT1). Urate prevents binding of the uric acid-sensitive transsilencer (KRAB–HucR, which is the uricase regulator linked to a KRAB domain) to its operator (hucO$_8$). This operator controls expression of secretion-engineered urate oxidase (smUOX), so smUOX is expressed when urate concentration reaches pathological levels. smUOX mediates conversion of urate into allantoin. Expression of smUOX stops when urate concentration reaches oxidative-stress-protective urate levels. pA, poly(A) tail.

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Other types of interventions in the biomedical domain

- Drug Discovery
- Cancer type classifiers
- Strategies for the control of the expression of mammalian genes (in gene therapy)
iSSB
Genopole®, CNRS, U. Evry
2009: Design
2010: Opening with regional funding
2011: Enlargement

*Partners:*

**Academic:** Genoscope, URGV, …

**Industrial:** Imagene, Isthmus, Biométhodes, …

**Technological:** Genethon BRC, Genopole® Bioproduction Center, …
Laurent Jannière
Mohamed Elati
Laura Adam (co-VirginiaTech)
Thibaut Lepage
Brian Jester
Costas Bouyioukos
Romain Bodinier
Charles Winterhalter
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Rémy El Halaby
Jorgelindo Da Veiga Moreira
Konstantinos Koutroumpas
François Képès

NIDDK / NIH
Ann Dean
Ryan Dale

the MEGAlomaniacs

Collaborations
The problem at hand

Bioproduction of non-proteic molecules

- State of the art: 10-14 enzymes in production pathway (100 person-year, 10 years, 30 M$)
- Long trial-and-error process – not rationalized
- Production triggered by several stimuli
- Production strains not robust for scale-up
The (potential) solution at hand

Bioproduction of non-proteic molecules

• Rational conception of microbial genomes
• Break ceiling of maximal number of co-regulated genes
• Intense, single-stimulus triggering of gene co-regulation
• Work directly on main chromosome, not episomes
Layout, Conformation and Expression
The cofunction-based solenoidal model of chromosomes

Is there a collective transcriptional scheme in cells?
Thank you!