Lessons from Current Technologies: Synthetic Biology

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NExTRAC Meeting: Identifying an "emerging" biotechnology
December 5-6, 2019
National Institutes of Health

Antheia

Stanford | Bioengineering
Schools of Engineering & Medicine

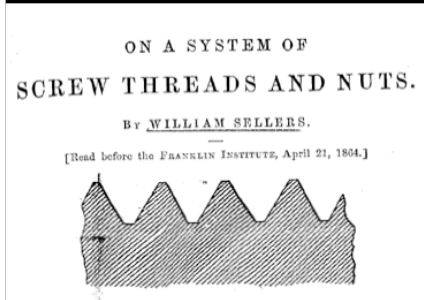
What is Synthetic Biology?

Tools-driven revolution in engineering biology

Synthesis

Decoupling of design & fabrication, leading to CAD and EDA.

Standardization


ON A SYSTEM OF
SCREW THREADS AND NUTS.
BY WILLIAM SELLERS.
[Read before the FRANKLIN INSTITUTE, April 21, 1864.]

Refined genetic components supporting "off the shelf" reuse.

Abstraction

Engineered simplicity enabling many component systems.

Learning-by-building revolution in bioscience

c/o D. Endy (Stanford University)

Tools-driven revolution in engineering biology

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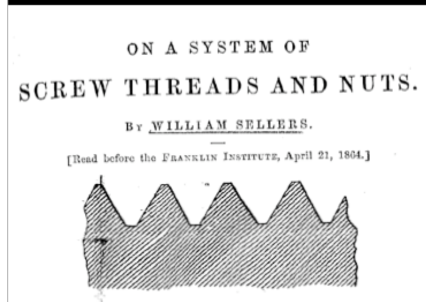

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APPS

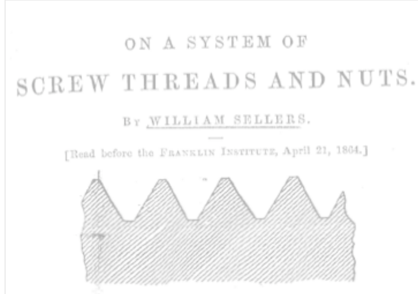
c/o D. Endy (Stanford University)

Synthesis: interconversion of bits and bases

Synthesis

Decoupling of design & fabrication, leading to CAD and EDA.

Standardization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1. Natural lineages

Synthesis: interconversion of bits and bases

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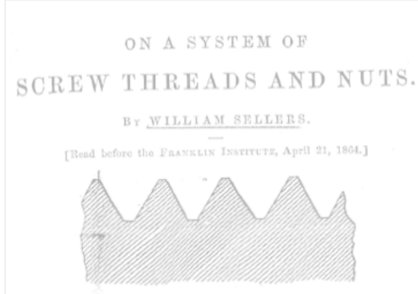
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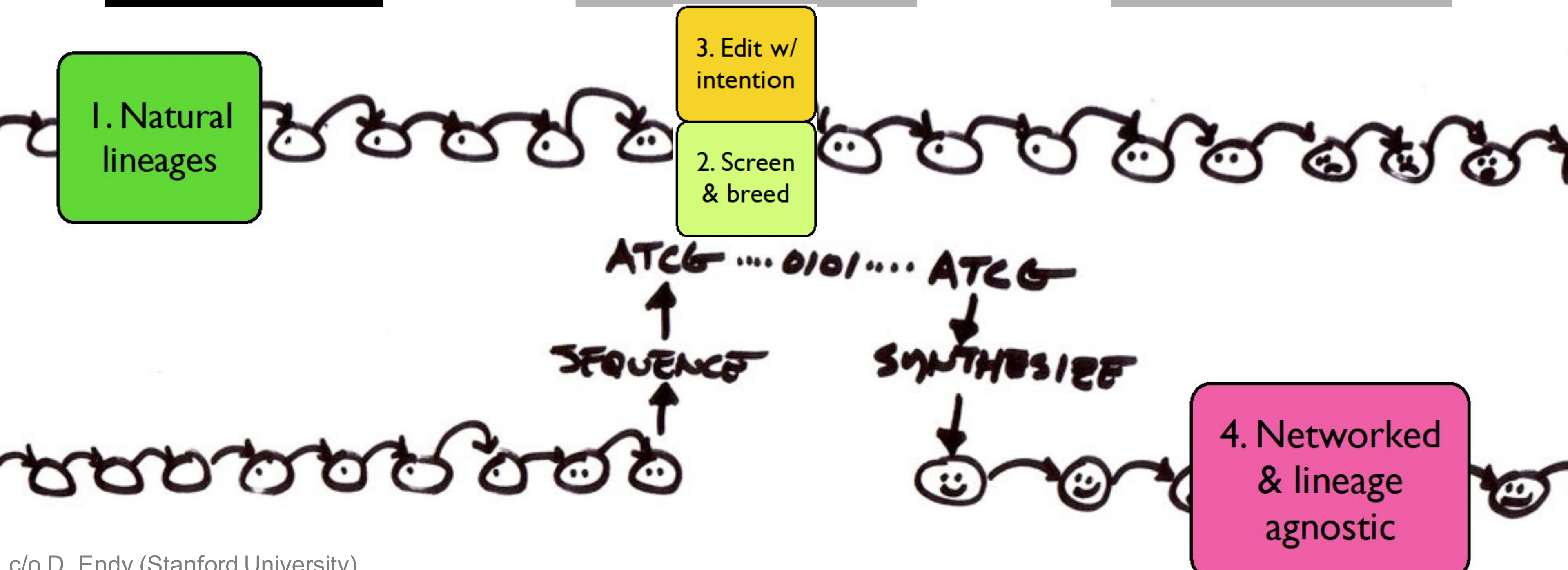

c/o D. Endy (Stanford University)

Synthesis: interconversion of bits and bases

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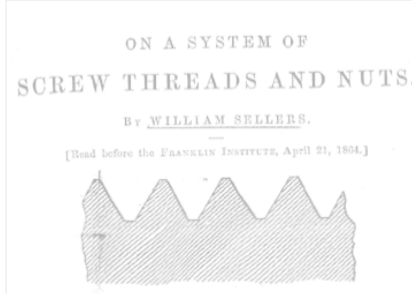
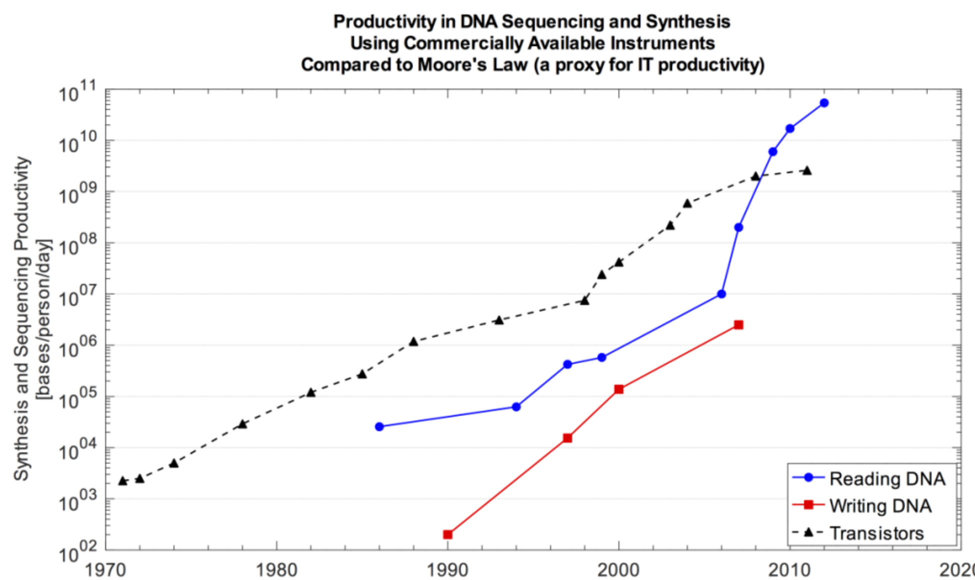


Refined genetic components supporting “off the shelf” reuse.

Abstraction

Engineered simplicity enabling many component systems.

Genetic information & genetic material are increasingly interconvertible



Ex: New function from read-write of bits

Plant hosts

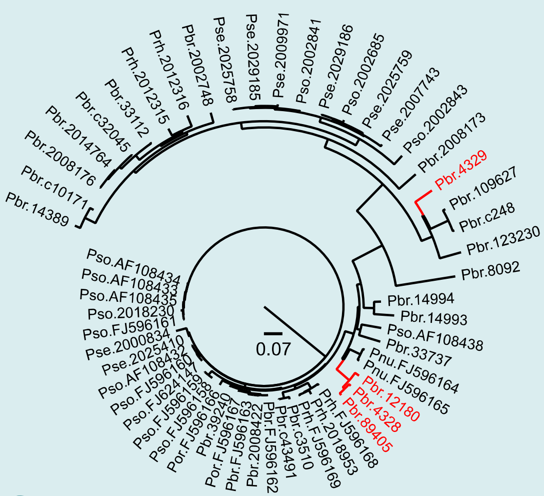
Sequencing

Transcriptome sequences

```
TTGCGATTTGATTAGCTAATGAAACTAAGCAAC
ATAATATCACCACGAATATCTTTTGAAGTAAG
ATTTTTTCTCATTTTCTTTTCTTTTTTG
CCTGGCATCCACTAAATATAATGGAGCCCGGC
TGGAAAAAGCTGAAAAAAAAGGTTGAAACCAGG
```

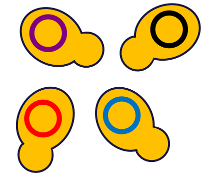
Filters
Biochemical hypothesis
Enzyme class

Refined candidate set

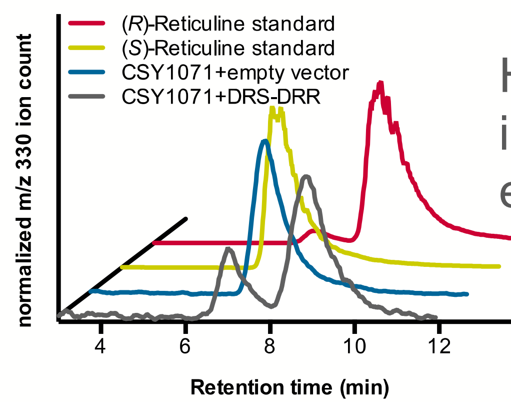


Bits

Recode & Synthesis



Test in yeast



HT assay identifies new enzymes

R/W capabilities advance discovery of unique enzymes from publicly available sequence databases

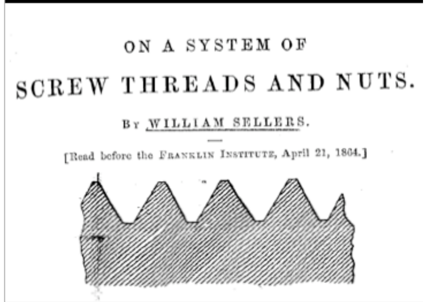
Galanie, et al. 2015. *Science.* 12: 989-94

Standards: coordinating work across locations

Synthesis

Decoupling of design & fabrication, leading to CAD and EDA.

Standardization



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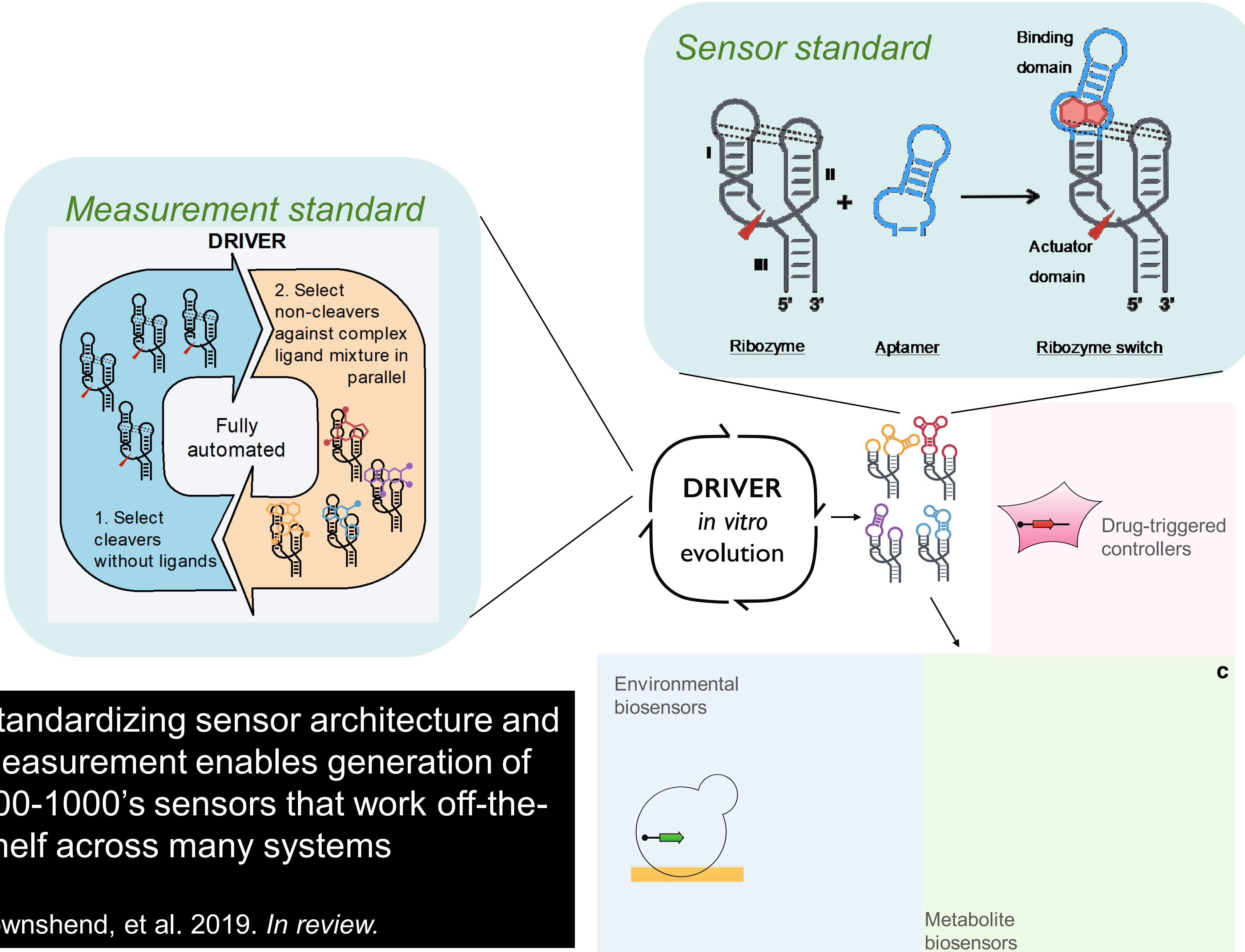
iGEM engages teams of ~6,000 students, across 40+ countries annually

Standards enable reliable reuse of objects, which requires reliable reuse of measurements of performance and models

c/o D. Endy (Stanford University)

Ex: Sensor standardization



Standardizing sensor architecture and measurement enables generation of 100-1000’s sensors that work off-the-shelf across many systems

Townshend, et al. 2019. *In review.*

Abstraction: managing increasing complexity

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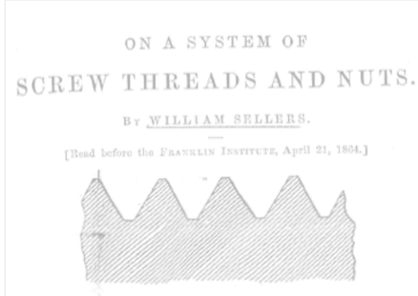
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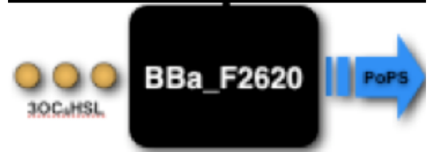
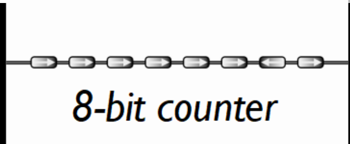


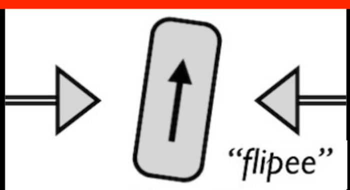
Engineered simplicity enabling many component systems.

An abstraction hierarchy supports 'compiling' down to primary sequence through a series of layers of functional power



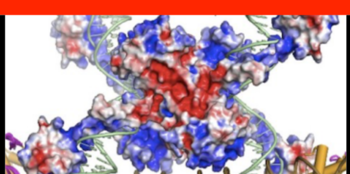
Systems = One or more devices encoding a human defined function(s).

Abstraction barrier! Do not cross!



Devices = One or more parts encoding a human defined function(s).

Abstraction barrier! Do not cross!



Parts = Basic biological functions encoded via molecules.

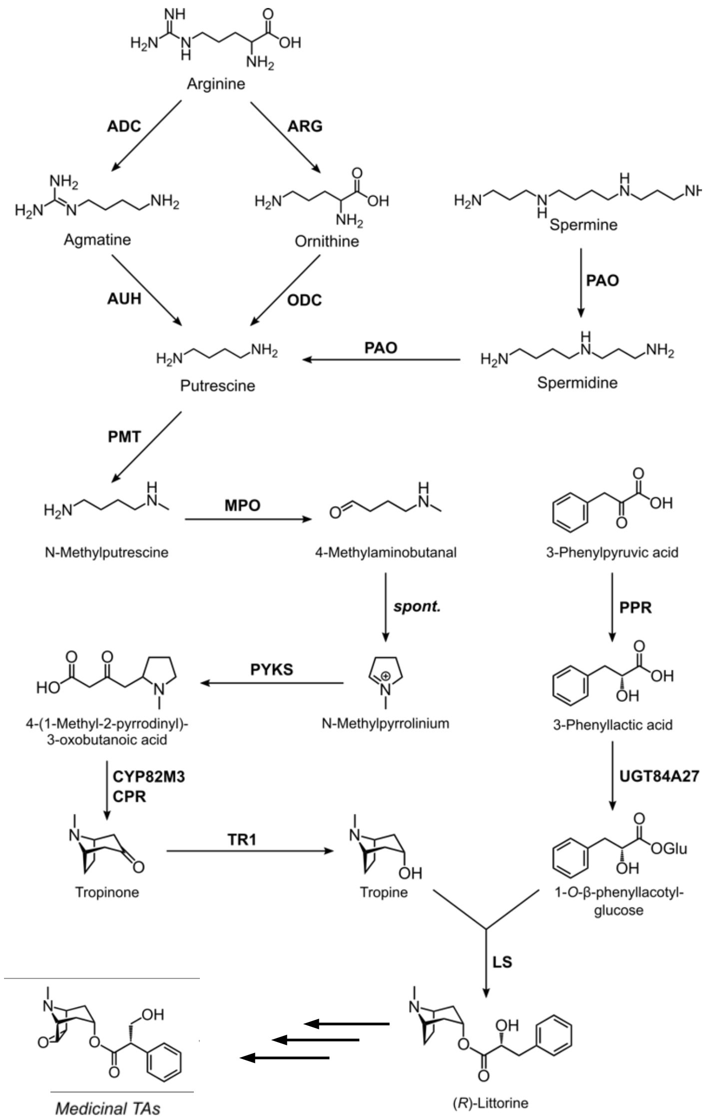
Abstraction barrier! Do not cross!

TATAGGGAGA

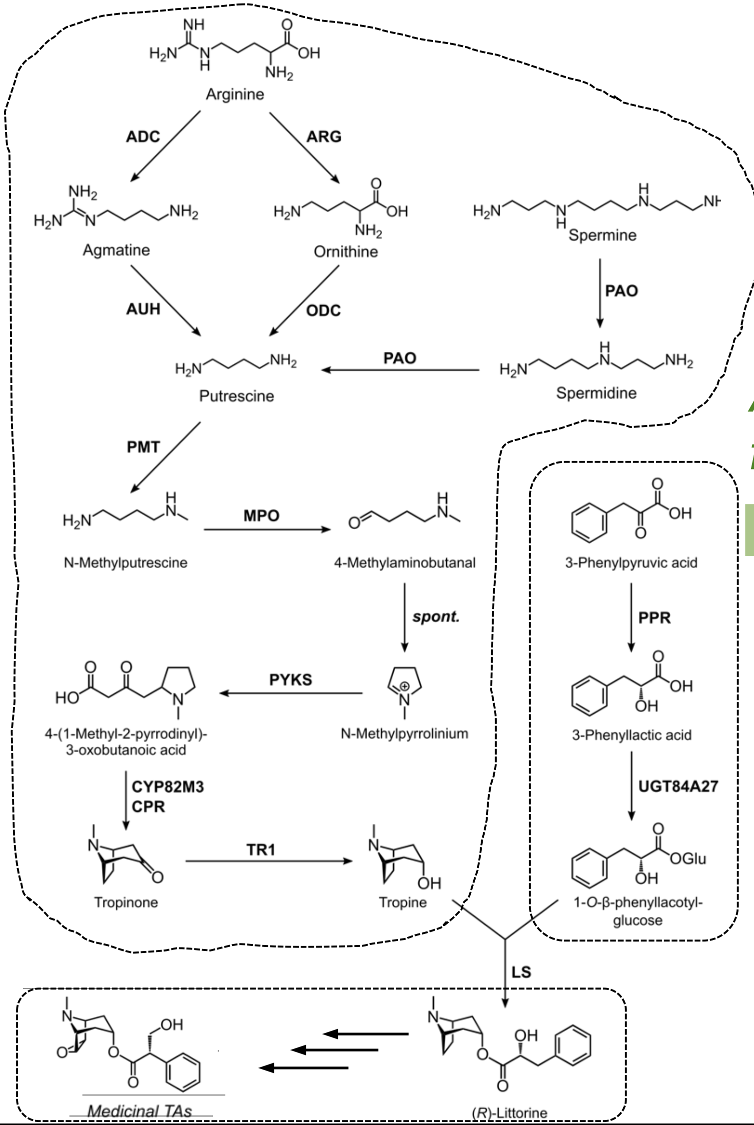
DNA = Material encoding molecules

c/o D. Endy (Stanford University)

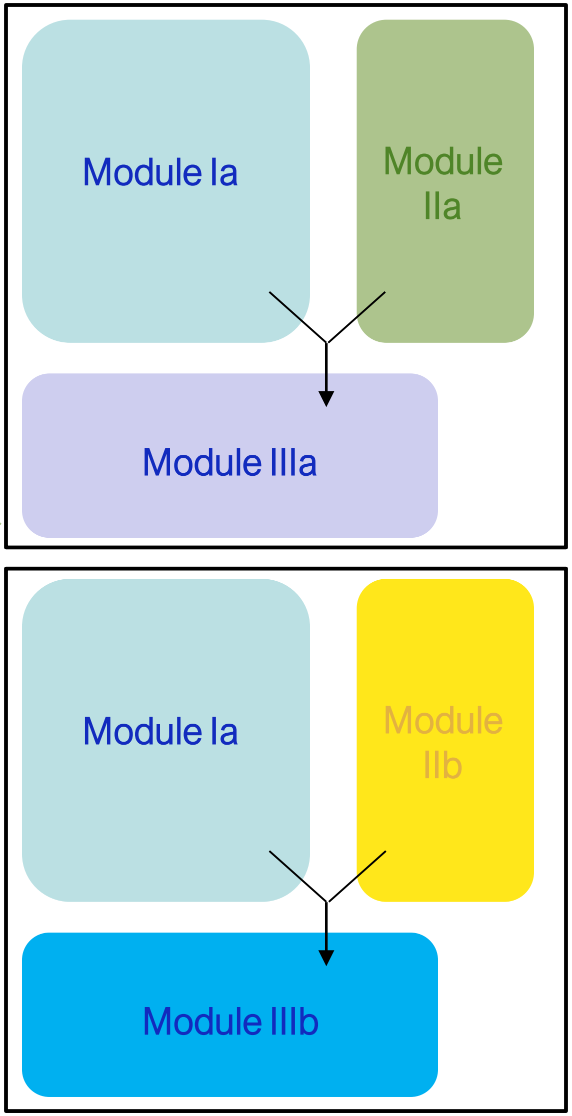
Ex: Abstraction of metabolism



Ex: Abstraction of metabolism



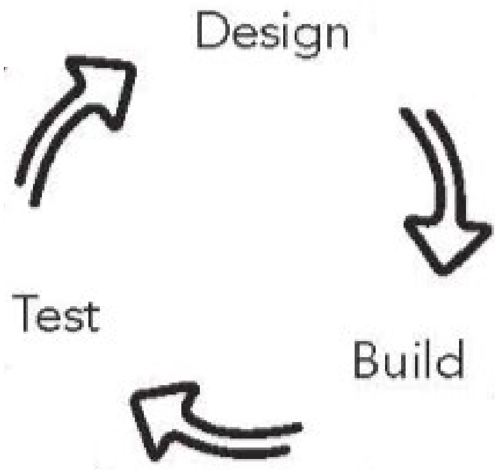
Abstract to functional modules



Defining functional metabolic modules enables rapid mix & match of complex biosynthetic pathway assembly and diversification of accessible chemistry

Srinivasan, et al. 2019. *Nat Comms.* 10: 3634

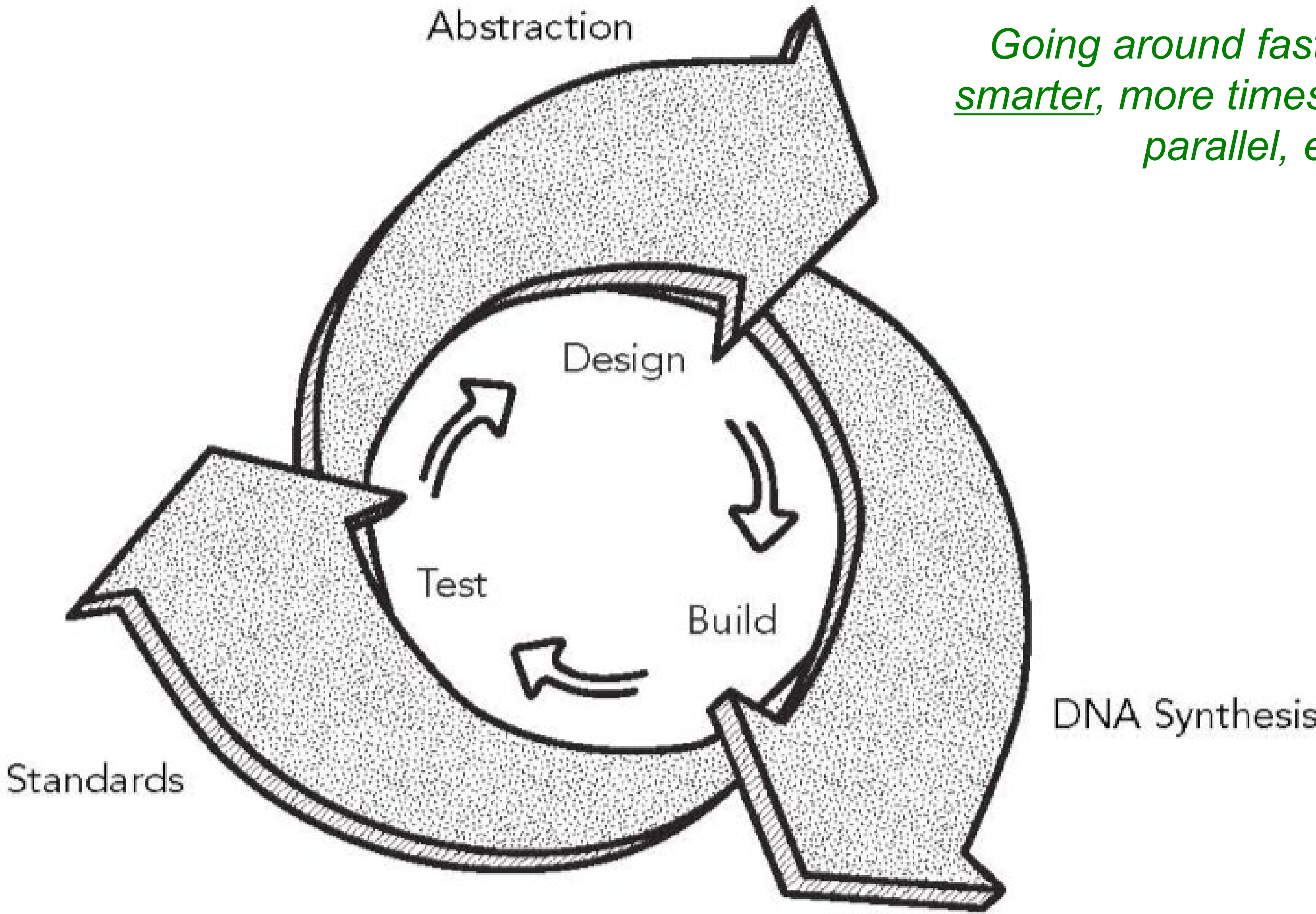
Improving the engineering cycle (for biology)



Graphic from "Synthetic Aesthetics" MIT Press (2014)

Improving the engineering cycle (for biology)

Going around faster, smarter, more times in parallel, etc.



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Current Challenges

Although DNA synthesis has gotten 100-fold cheaper, it is high latency, length limited & ROW is starting to lead

Although read-write (sequencing-synthesis) capacities are in place, composition (what & how) lags far behind

Synthesis is more advanced than Standards & Abstractions

It is difficult to make fundamental advances in workflow, because everyone emphasizes applications

Applications are still expensive and risky… who will control / own the technology and access to it

Those leading technology development, historically lead governance… who will be world leading in syn bio?

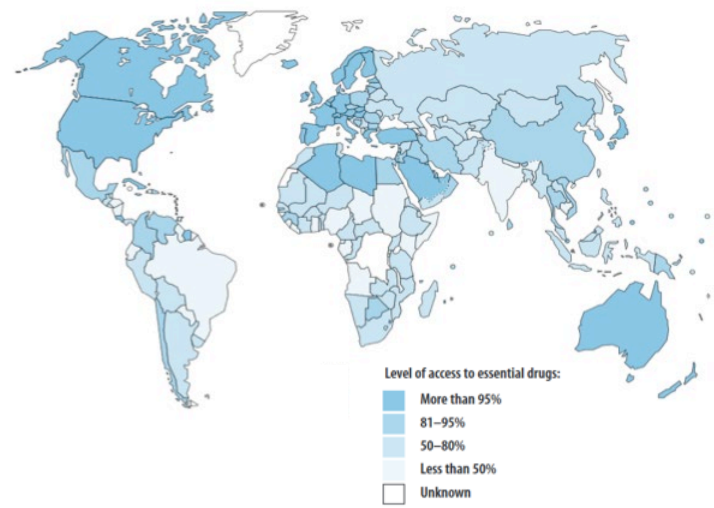
What emerging applications are enabled by Synthetic Biology?

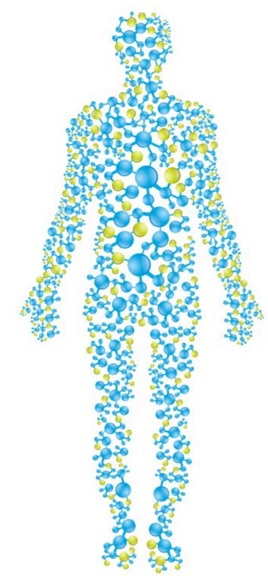
Cracking the code on building molecules

Current: reliance on & limited by the natural world

Near future: access to full chemical space

Future: on demand, distributed and/or in situ manufacturing





Editing genetic information

Matter

Sequencing →

Information / Analysis

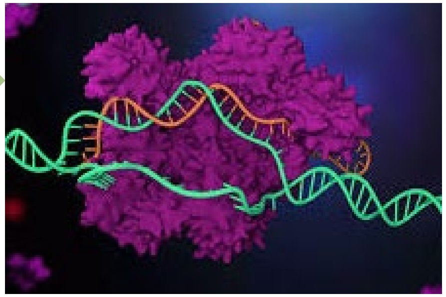
TTAGCCAAGCAGATGGTAGCTTTTGCT
CTTGCAAGTATGGTCAACGAATTCAAA
TGGGGTACGCCATTCATCACGATCCAA
ATGTTTTTCCAGCTCCATACAAGTTCAT
GCCTGAAAGATTTTTGAAGGGTGTTAA
CTCCGATGGTAGATACGGTGATATTAA
CACCATGGAATCCTCATTGATTCCATTT
GGTGCTGGTATGAGAATTTGCGGTGGT
GTTGAATTGGCAAAACAAATGGCTACC
ATGTATTCCGCTGCCGTTGAAGTTATT
TCTAAAGAAACCATTAAGCCAAAGACC
CCAACCTTGTACCATTTCAAGAATTTCA
ACTTGTCCTTGTTGGACCAATATTACC
CACCATTCGTCCCATTGTCCCAATTATT
GCCATCTGAAGTTGTTTCTGCTTGCGT
TGCTAAAGAAGCTCATGATTTGGATGT
CCGTTATGAAGTCTACTTTGGCTGGTT
TTTTGCCAGTTGTTAACCATGCTGTTAA
CTTGAGAAAGAAGATGTACCCACCATT
GCAAGATGTTTCTTTCGGTAACTTGTC
TTTGTCTGTTACTGCTTTGTTGCCTAAG
TTTGAATTGCACTTGTCCGAAATCTTG
GAATTGATTTGATTCTATTCATATATAT
ATATATATATATATGTGGATATATATATA
TGTGGTTTCTGCTGATTCATAGTTAGAA
TTTGAGTTATGCAAATTAGAAACTATGT
AATGTAACTCTATTTAGGTTCAGCAGCT
ATTTTAGGCTTAGCTTACTCTCACCAAT
GTTTTATACTGATGAACTTATGTGCTTA
CCTCCGGAAATTTTACAGAGGACATAT
GTCATCTGCAGACTTGAGTACAAGGGT
GATGATGCGGACATTCTATCTGCTTAT
GCAATAGATCCCACCTCCATACAAGTA

Bits

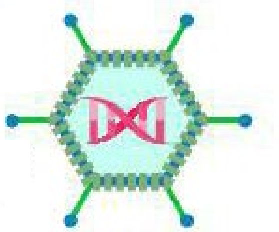
Synthesis →

Editors

RNA silencing



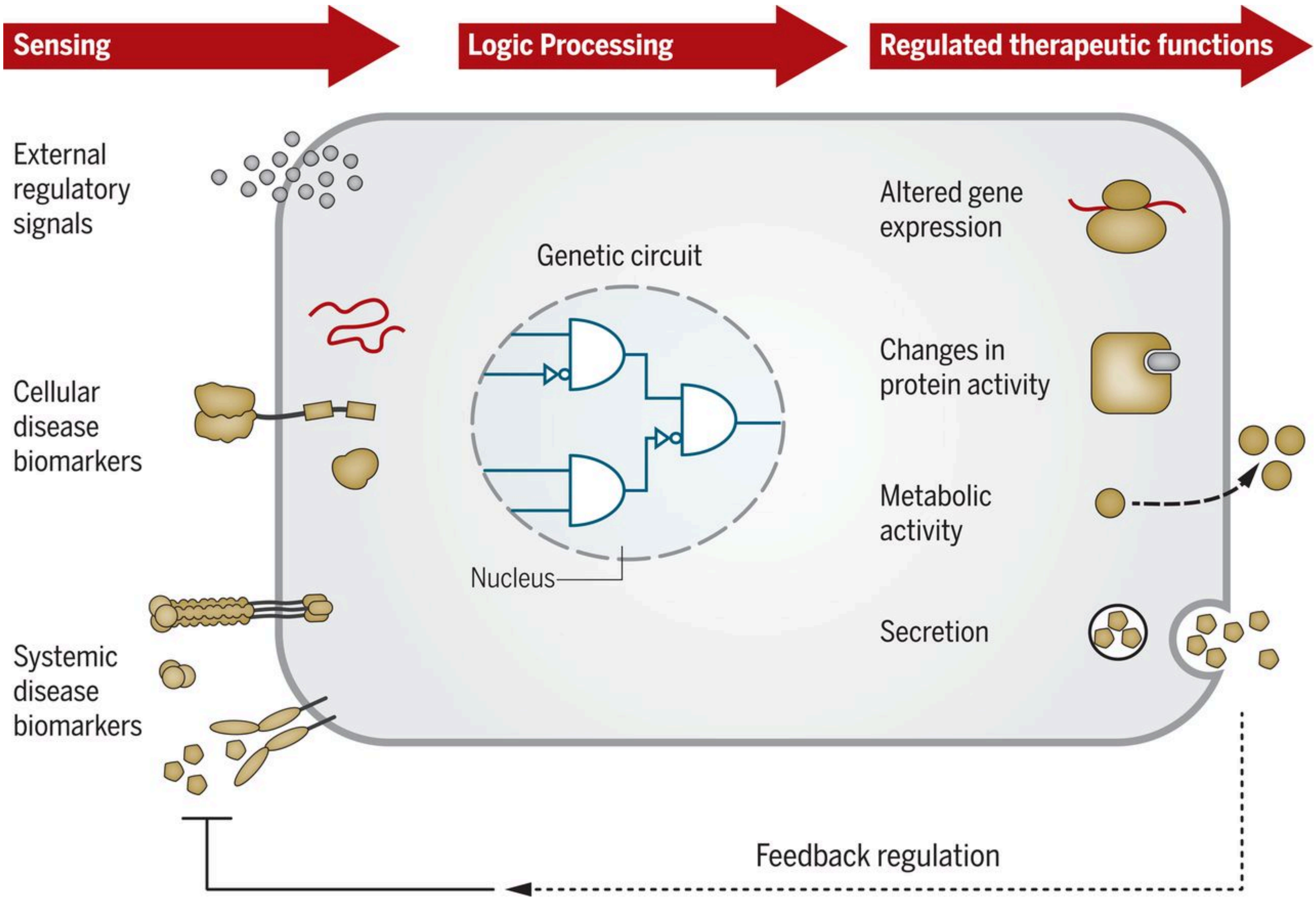
CRISPR/Cas



Gene therapy

Programming living therapies

R/W -> Composition | Standardization | Abstraction



Kitada, et al. 2018. *Science*. 359: 6376

Questions & Discussion