Technologies and Tools For Programming Genetic Systems

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July 9, 2009
Opportunities and Challenges in Synthetic Biology
Tools and Techniques – Enabling Innovation

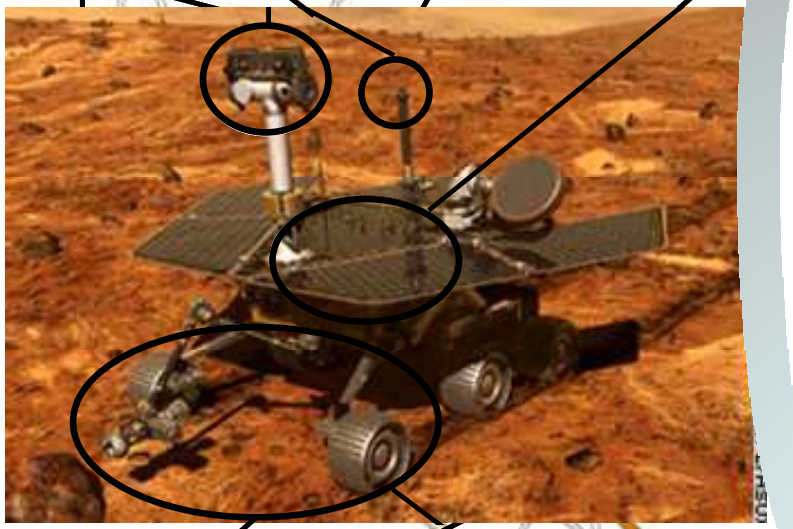
Synthetic biology

Circuitry

signal processing
automated response
dynamic control
remote contro
memory
communicat n

Sensors (Inputs)

chemicals
biomolecules
temperature
light



Actuators (Outputs)

reporting
delivery
motility
phenotype
self-organization
synthesis

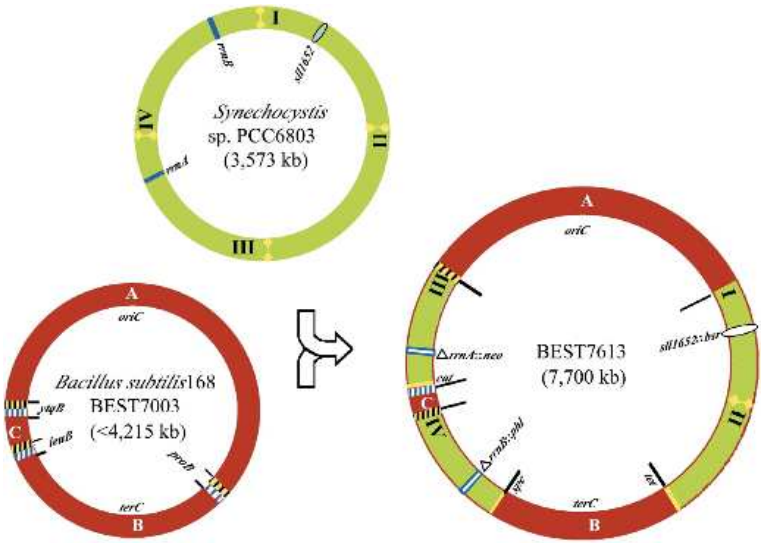
Foundational Technologies
synthesis

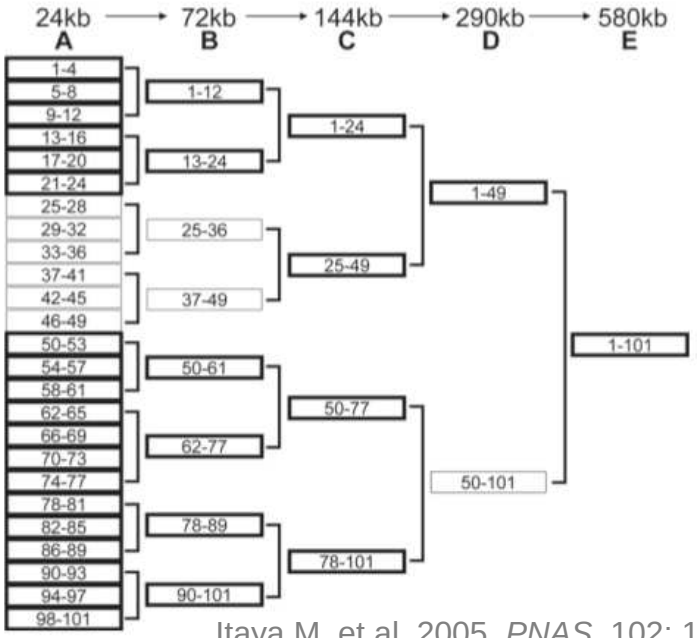
Engineering Frameworks
standardization
composition

Engineered Biological Systems
environment
health and medicine

c/o C. Voigt (UCSF)

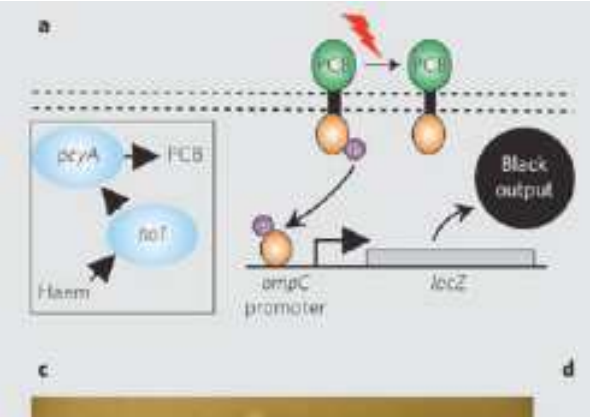
Fabrication tools



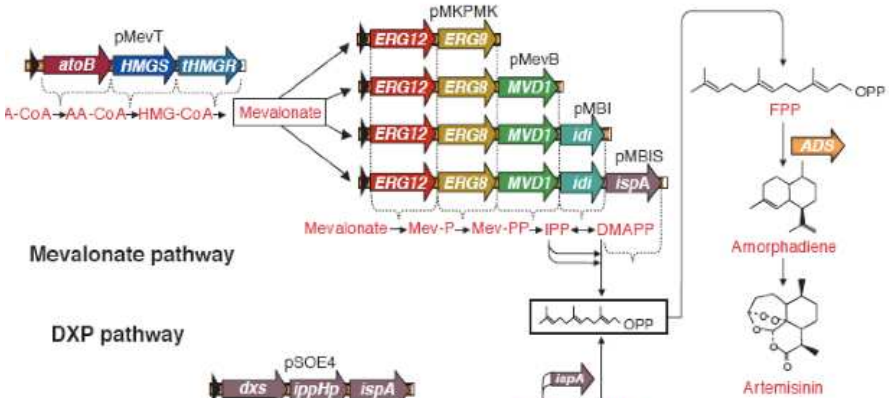


Itaya M, et al. 2005. *PNAS.* 102: 15971-6
Gibson DG. 2008. *Science.* 319: 1215-20

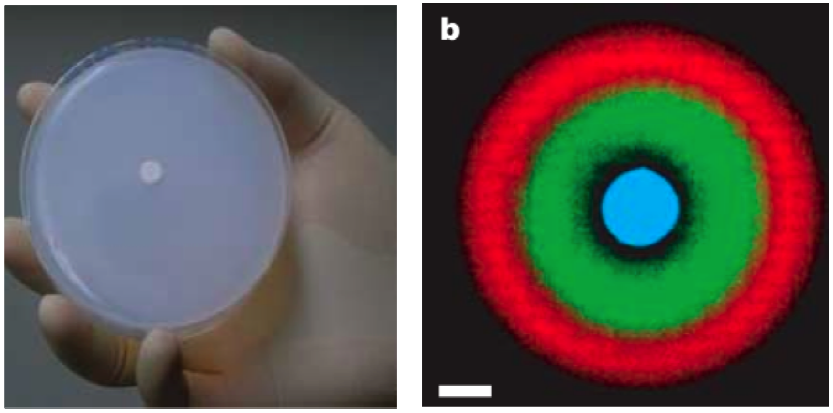
Model circuits



Biosynthesis applications



Why the gap between tools and applications?

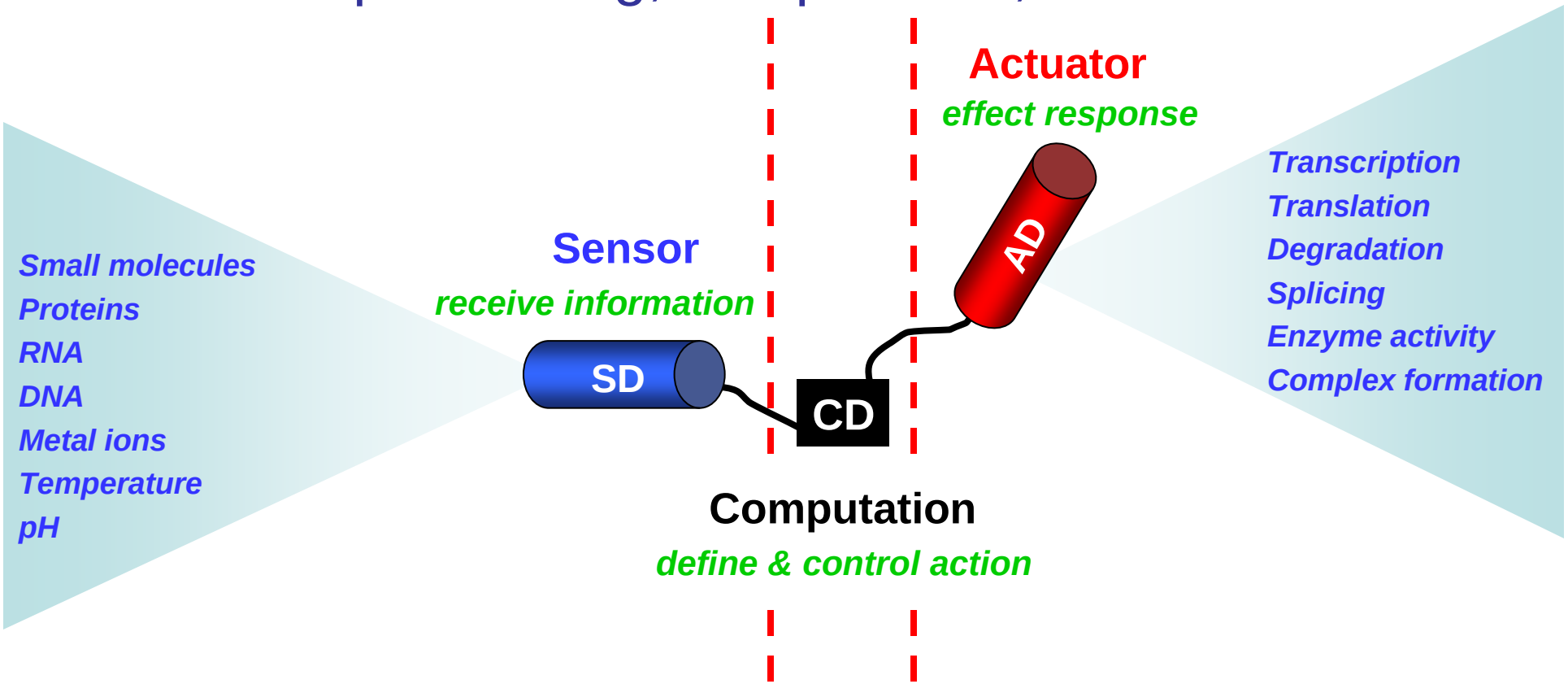


Levskaya A, et al. 2005. *Nature.* 438: 441-2
Basu S, et al. 2005. *Nature.* 434: 1130-4

Martin VJ, et al. 2003. *Nat Biotech.* 21: 796-802

1. Refinement and optimization of tools for applications represents a significant challenge

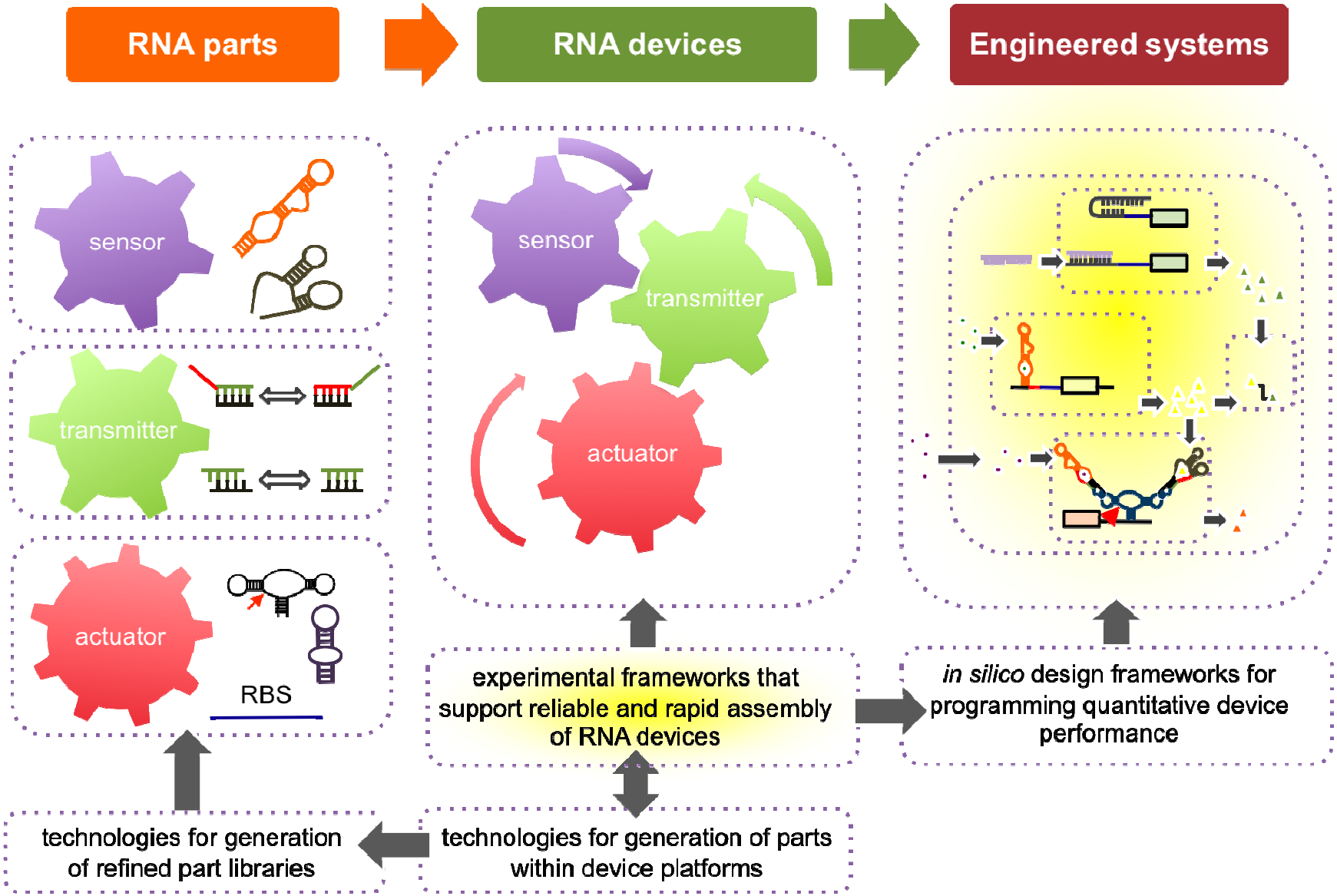
Information processing, computation, and control



Key Engineering Properties

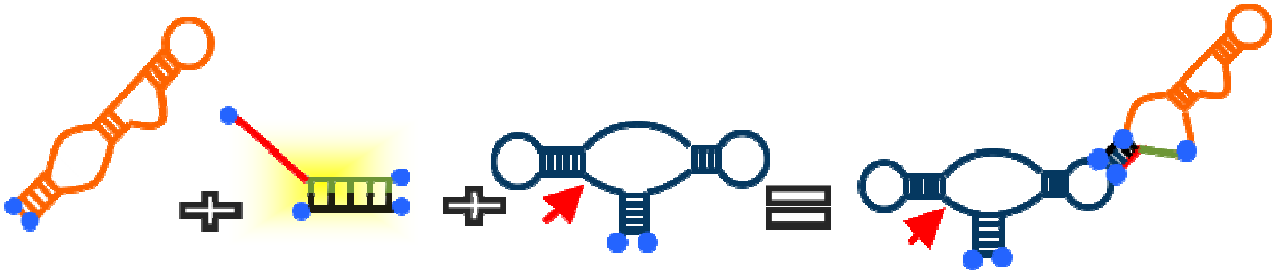
- ✓ scalability
- ✓ portability
- ✓ utility
- ✓ composability
- ✓ reliability

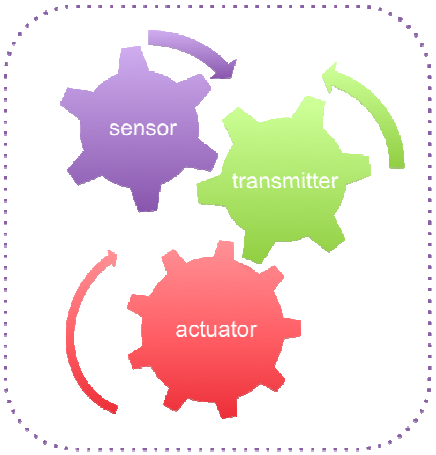
Plan for developing a programmable I/O tool



Win MN, Liang JC, Smolke CD. 2009. *Chem Biol.* 16: 298-310

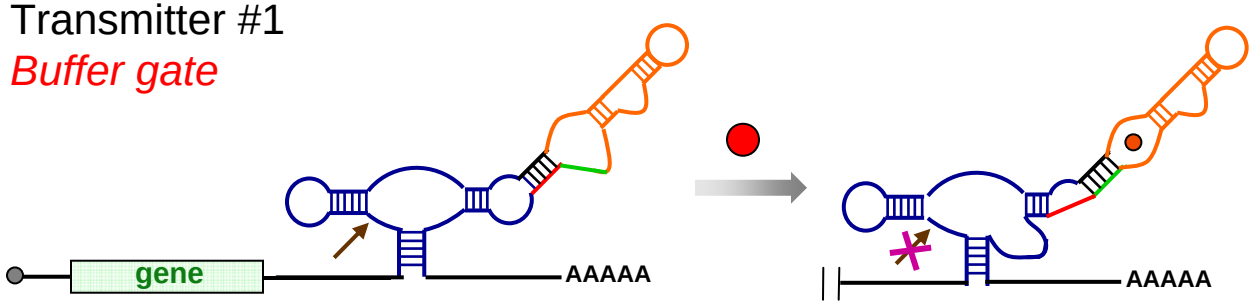
A platform for programming device function

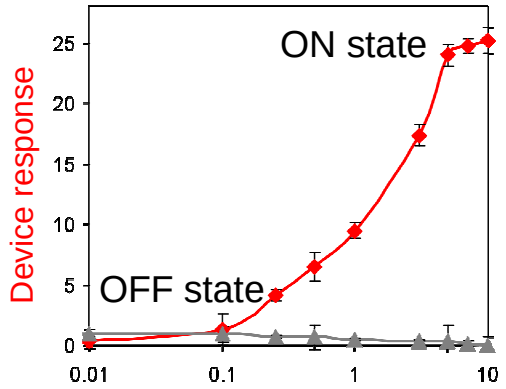




Transmitter #1

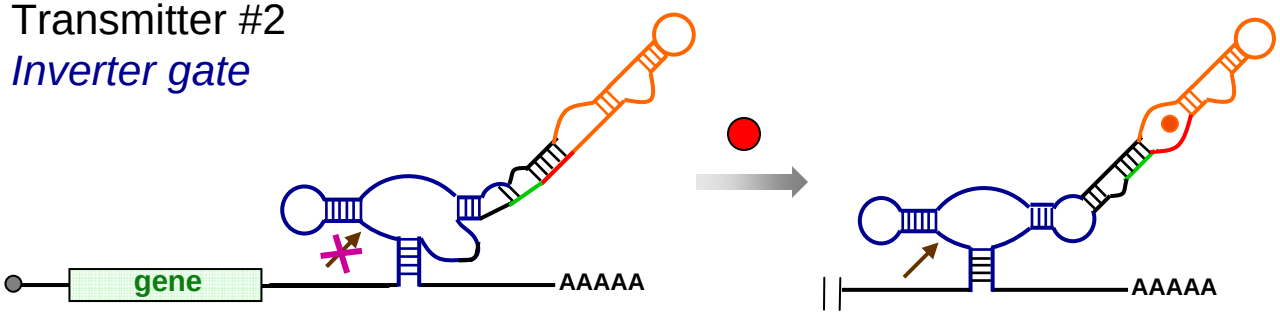
Buffer gate

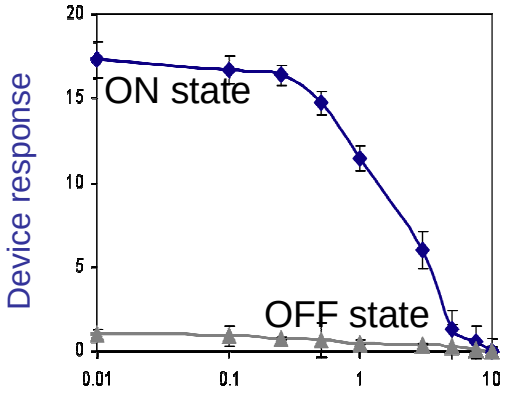




Transmitter #2

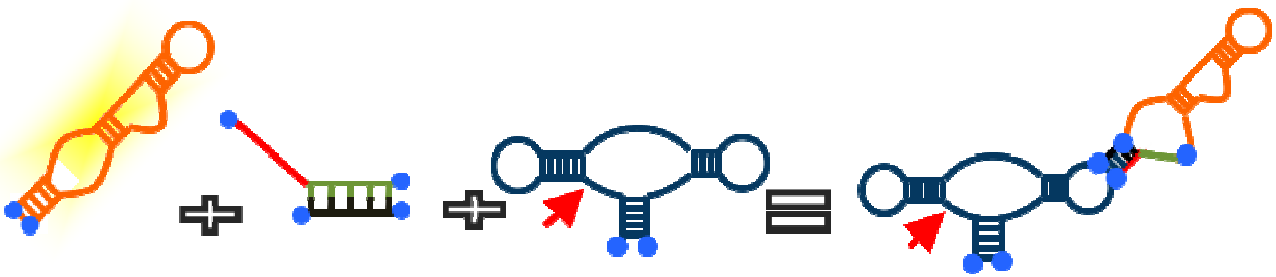
Inverter gate

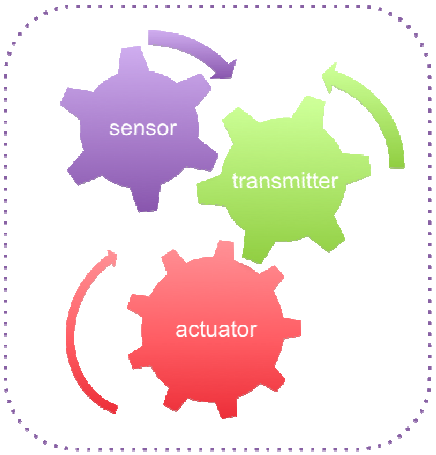




Win MN, Smolke CD. 2007. *PNAS*. 104: 14283-8

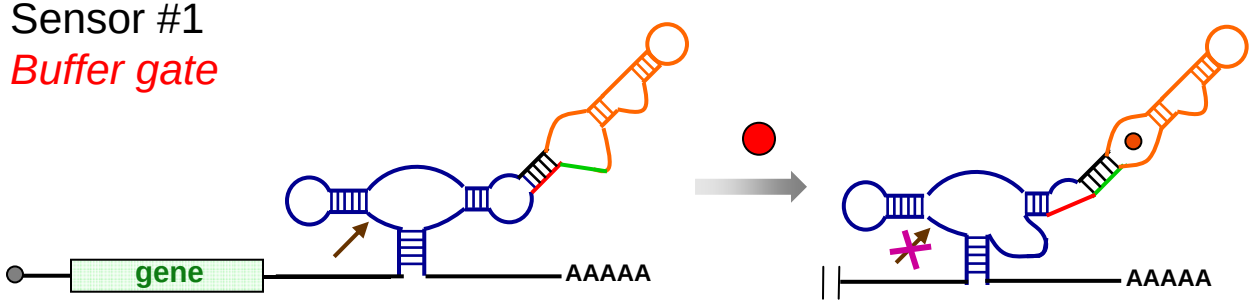
A platform for programming device inputs





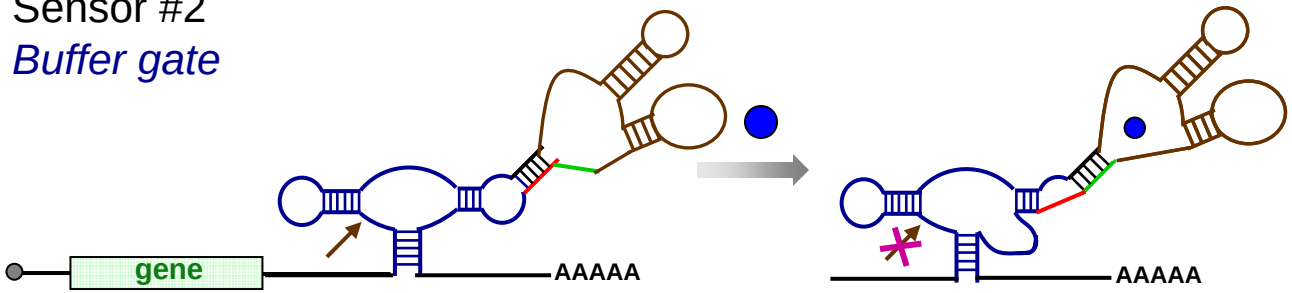
Sensor #1

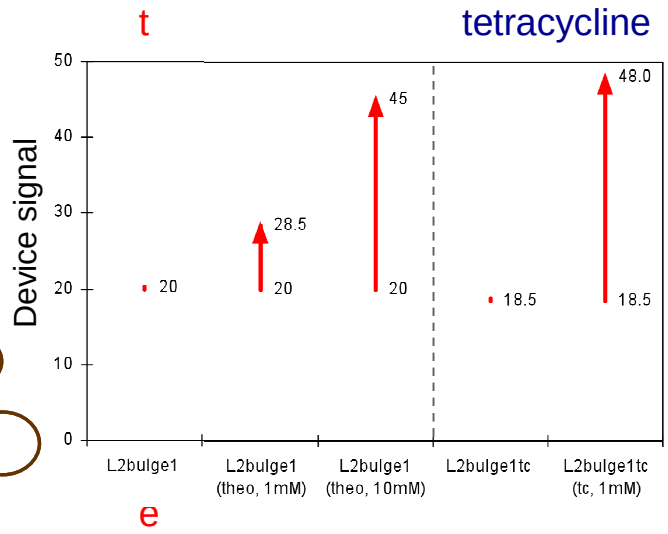
Buffer gate



Sensor #2

Buffer gate



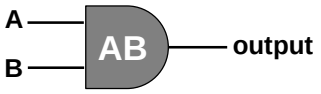


Win MN, Smolke CD. 2007. *PNAS*. 104: 14283-8

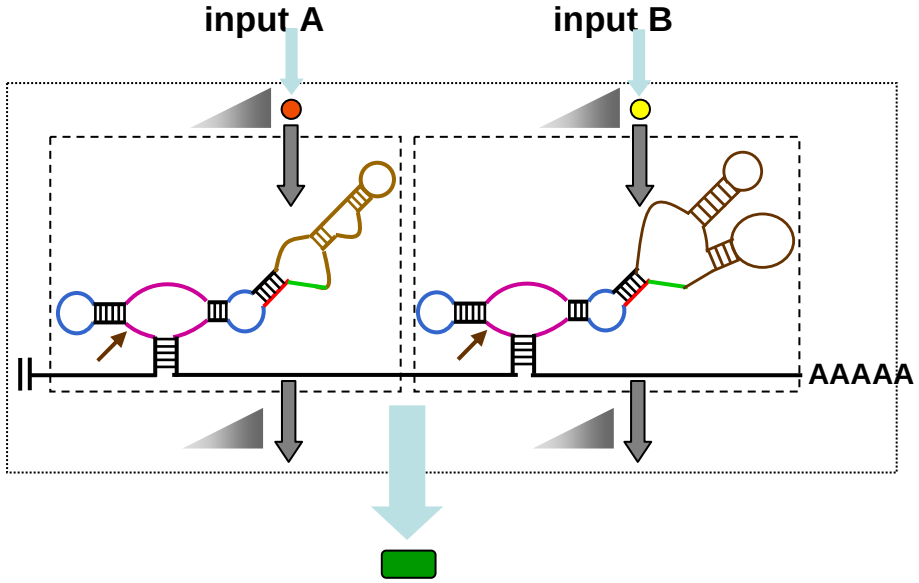
Win MN, Smolke CD. 2008. *Science.* 322: 456-60

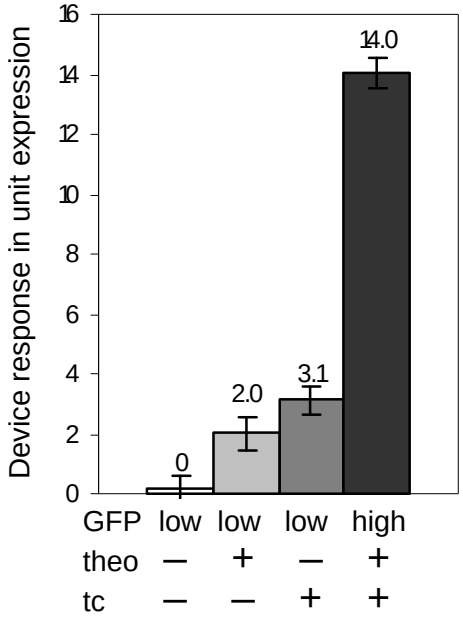
Higher-order computation - logic gate devices

AND gate

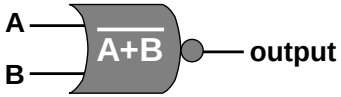


A theo	B tc	output GFP
0	0	0
0	1	0
1	0	0
1	1	1

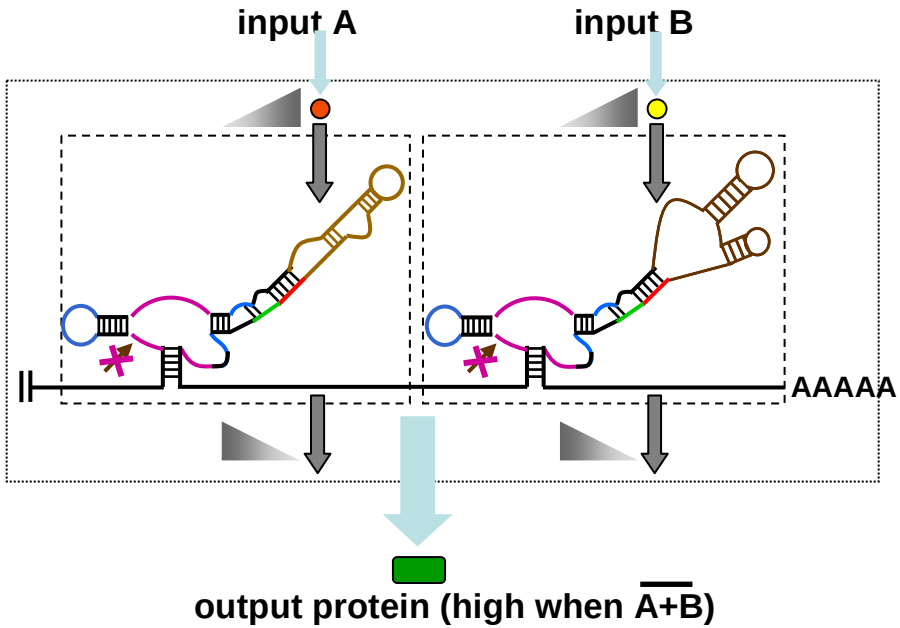


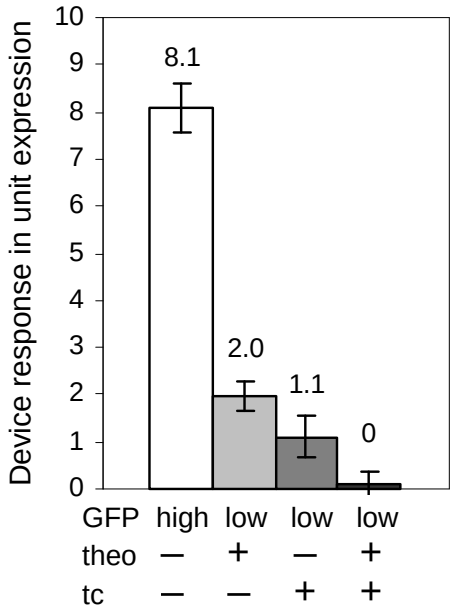


NOR gate

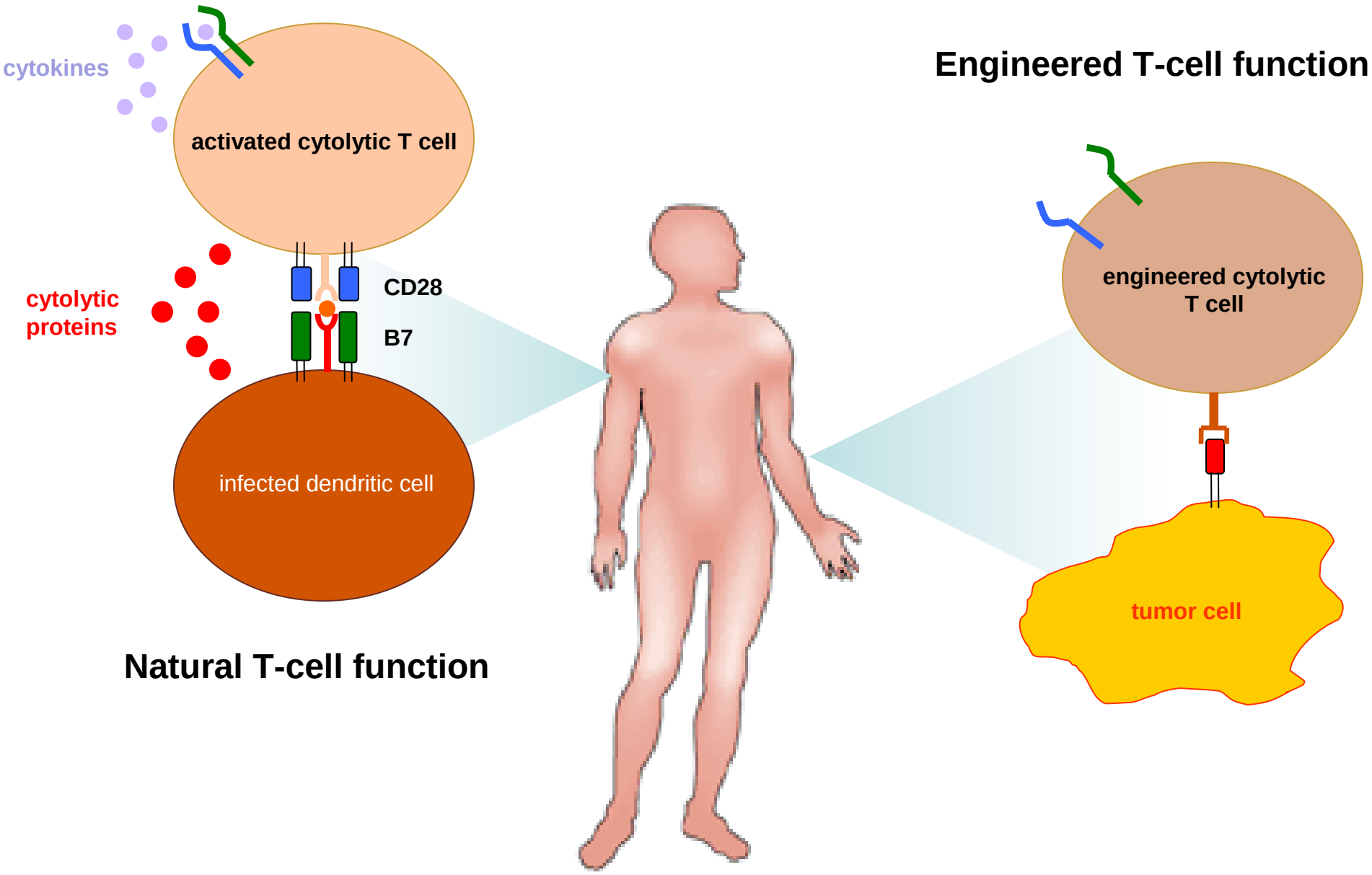


A theo	B tc	output GFP
0	0	1
0	1	0
1	0	0
1	1	0

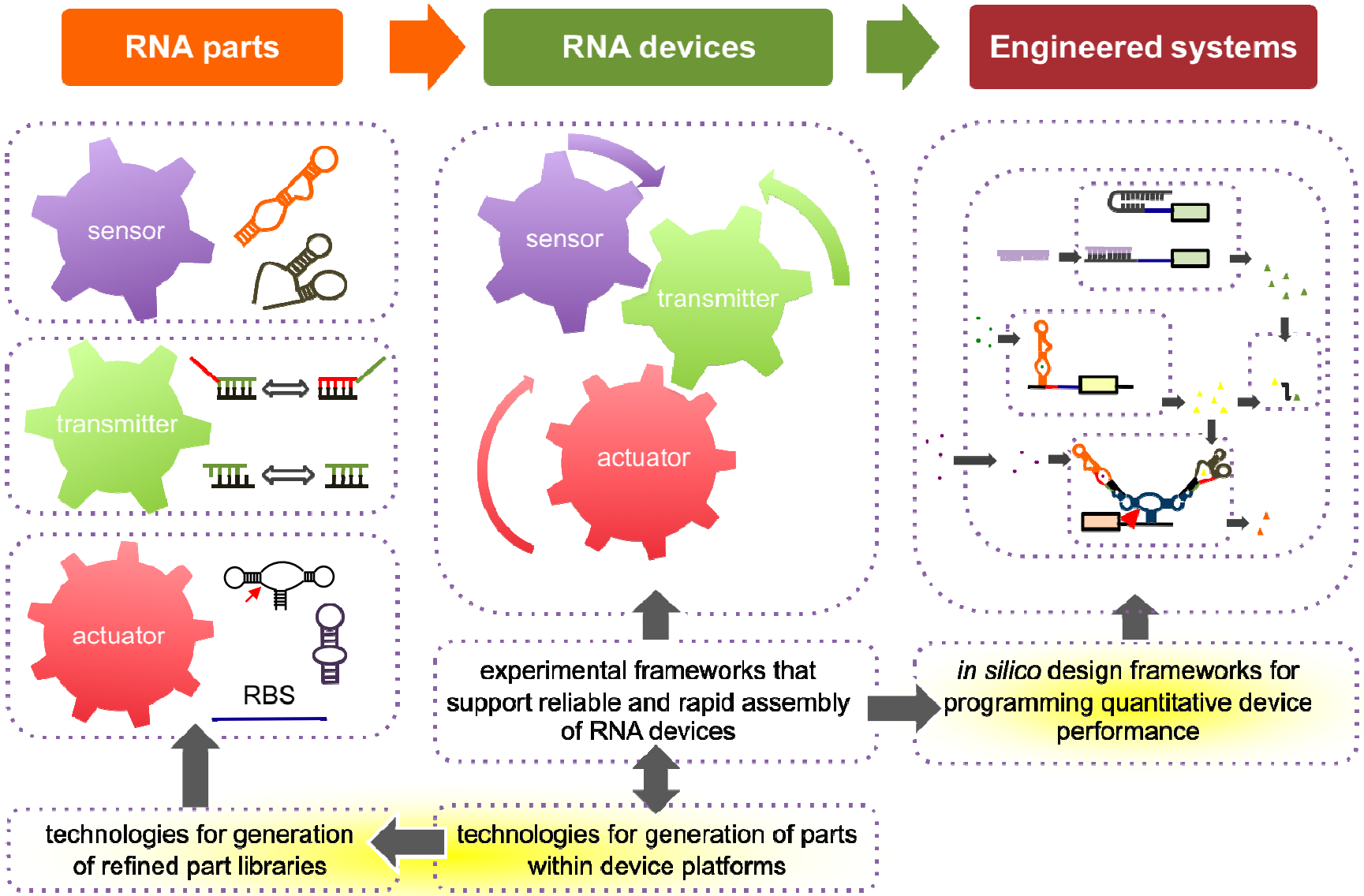




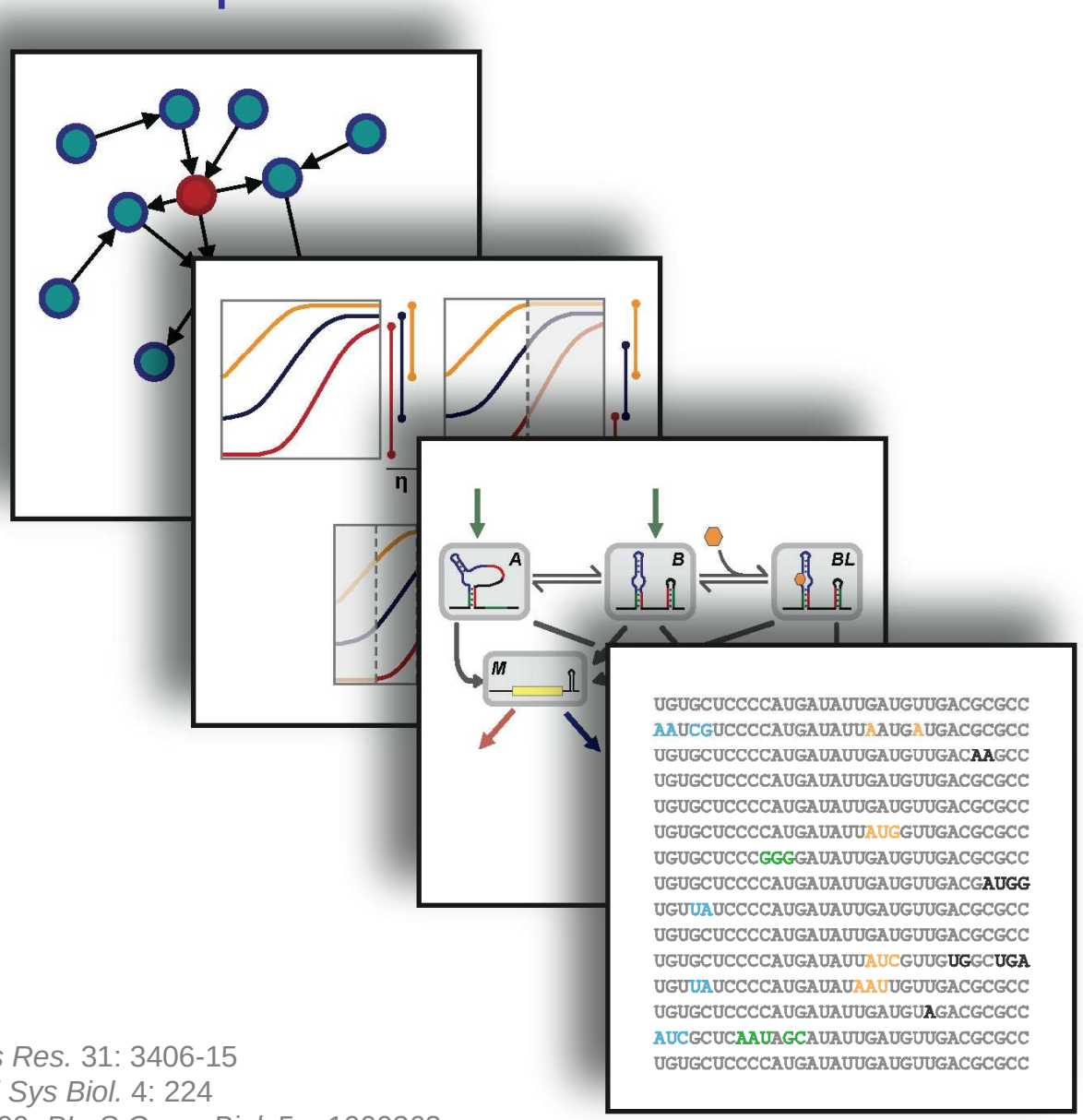
Applications: Cellular therapeutics



Challenges to I/O tool development



Design challenge: CAD tools that predict device function from sequence

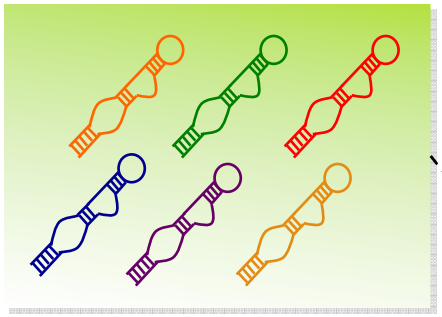


Zuker, M. 2003. *Nuc Acids Res.* 31: 3406-15
Beisel CL, et al. 2008. *Mol Sys Biol.* 4: 224
Beisel CL, Smolke CD. 2009. *PLoS Comp Biol*. 5: e1000363

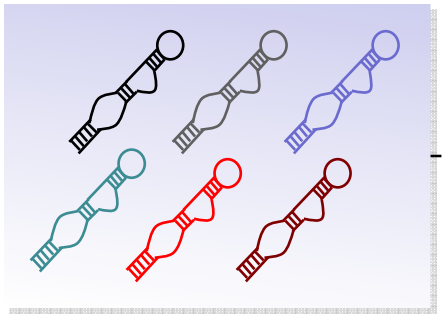
Scalability challenge: libraries of nucleic acid sensors

refined sensor libraries

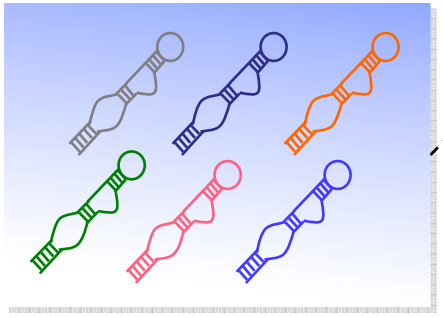
metabolites

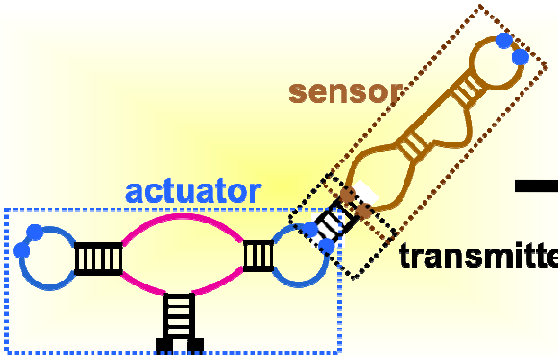


disease biomarkers



exogenous chemicals





noninvasive diagnostics

bioprocessing / biosynthesis

agricultural biotechnology

intelligent therapeutics

Engineering optimization and development needed on selection and characterization strategies

Summary

- The gap between technology/tool development and applications must be bridged
- Invention and implementation of engineering design principles is critical to effective tool development
- Strategies and mindsets supporting the implementation of foundational technologies and tools must be fostered
- Funding and support for new technology and tool development at scales and time frames appropriate for the challenges that must be addressed is critical