HTGAA Bio Bootcamp Part 1
Genetic Circuits

Dr. Johannes Stein

Group Leader

Max Planck Institute for Molecular Genetics, Berlin (DE)

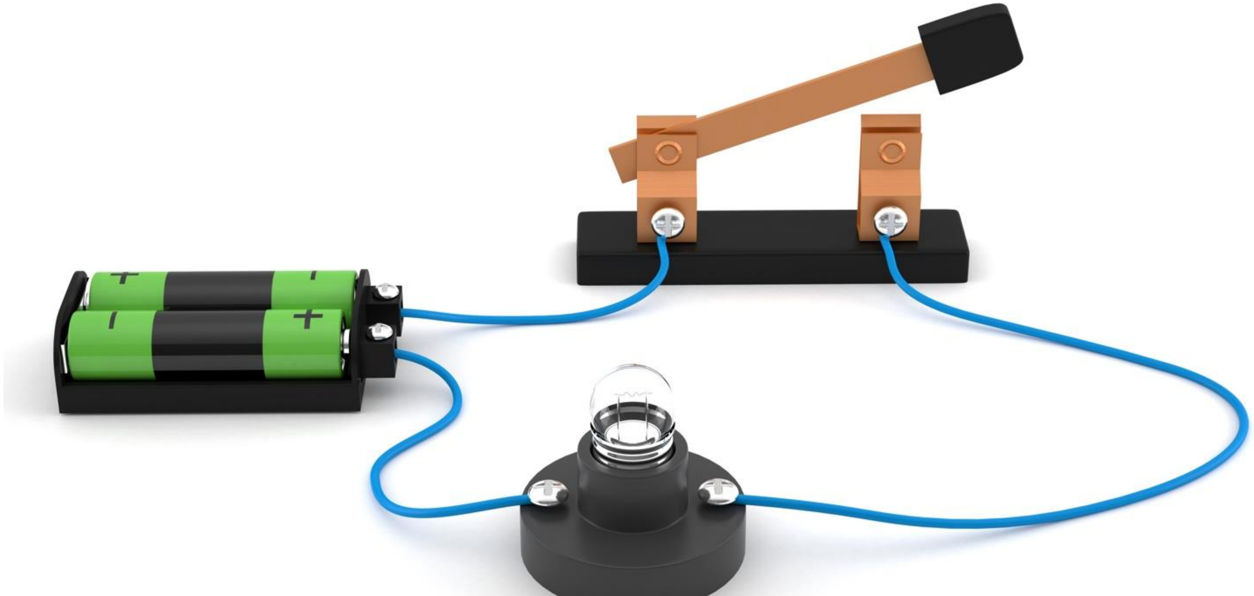
Jan 19th, 2026

Covered in this lecture

- **What is a ”circuit” in biology?**
- **Natural genetic circuits: the lac operon**
- **Synthetic genetic circuits and their building blocks**
- **Applications in biotechnology, medicine, and agriculture**

What is a circuit?

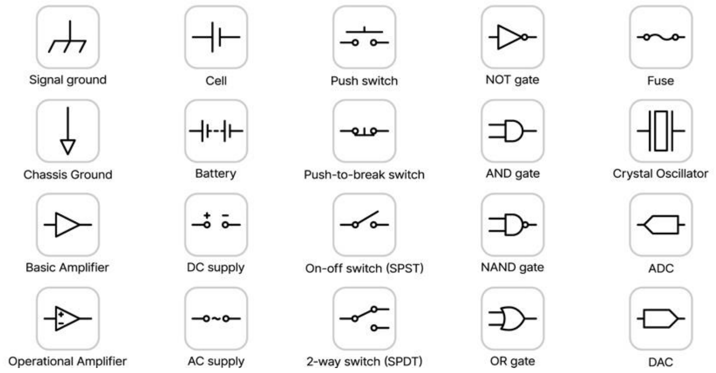
A system that transforms inputs into outputs through connected functional components.

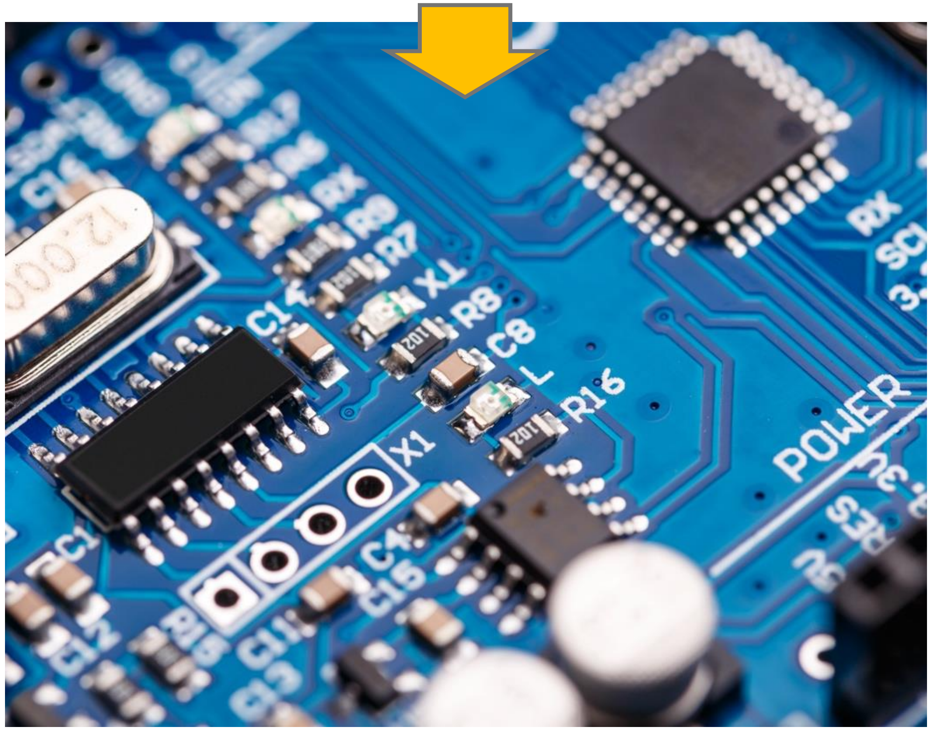


Source: Adobe Stock

Input → Output

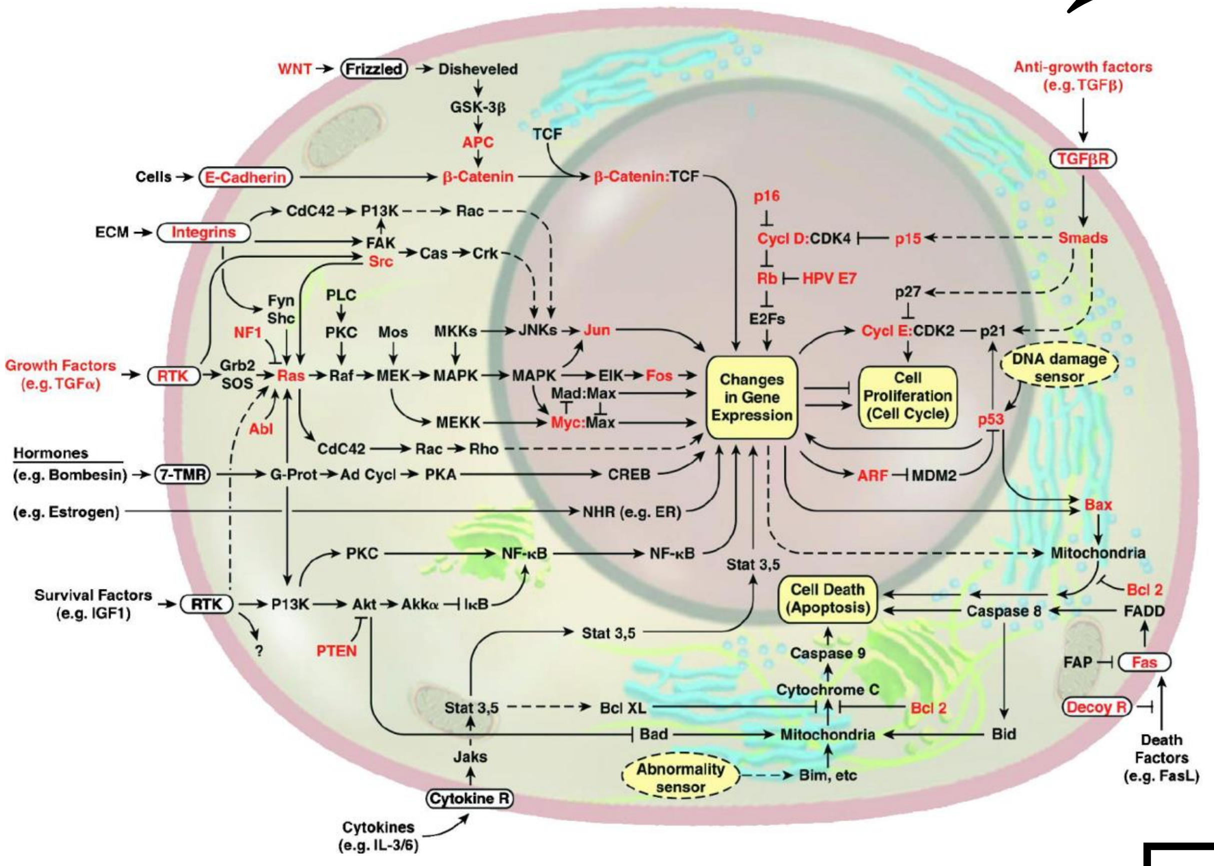
Functional components / building blocks





Source: Adobe Stock

Genetic circuits – from systems biology to synthetic biology



Source: Hanahan & Weinberg, Cell, 2000

Systems biology

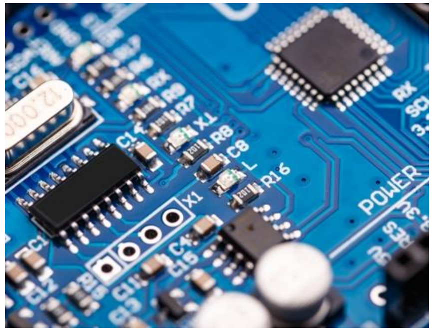
- integrated study of networks of genes, proteins, metabolites; cell or organism level
- omics approaches, high throughput
- studying disease & developing drugs

-> Analysis

Synthetic biology

- repurposing modules of known genetic circuits
- constructing entirely new components
- design synthetic circuits to induce new function

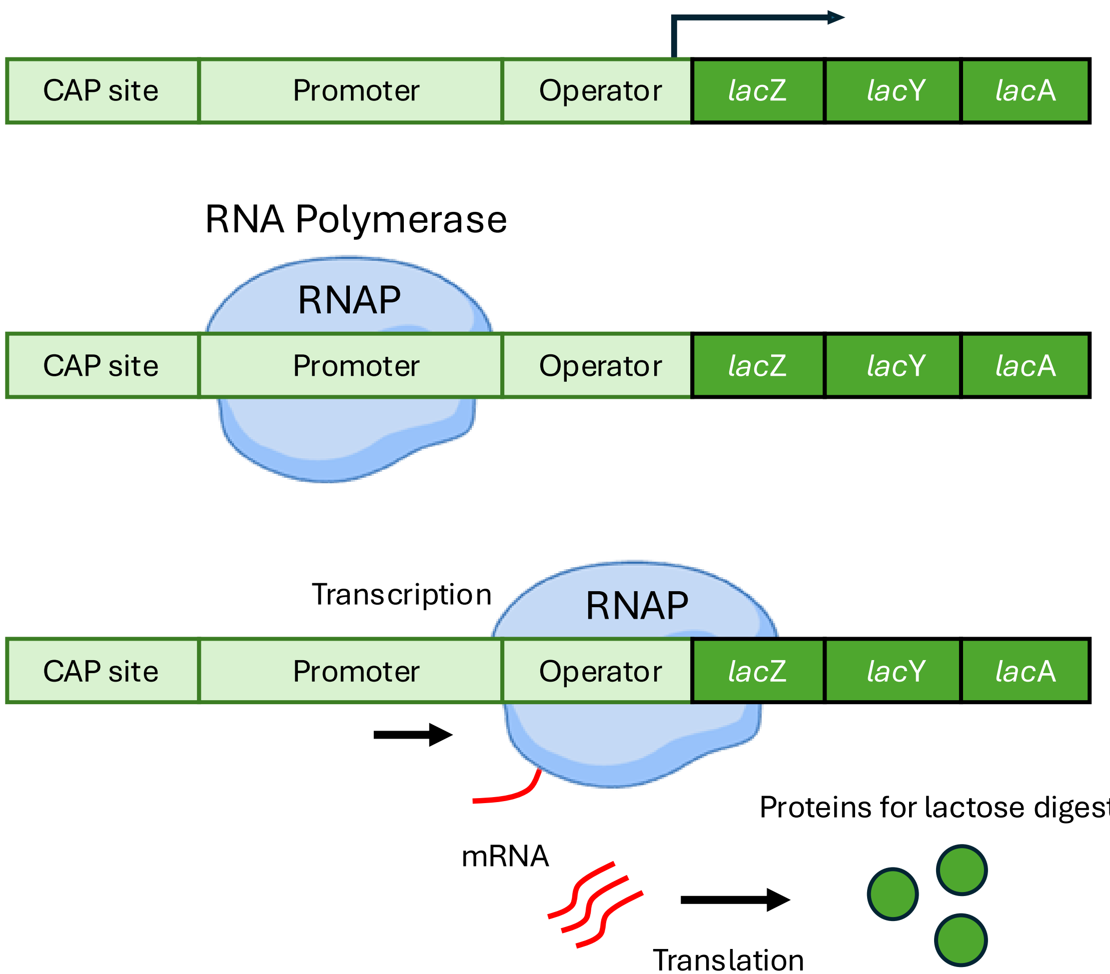
-> Engineering



Source: Adobe Stock

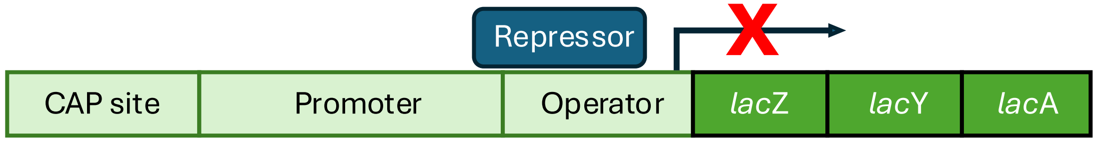
A famous example: the *lac* operon in *E. coli*

Energy source: lactose digestion

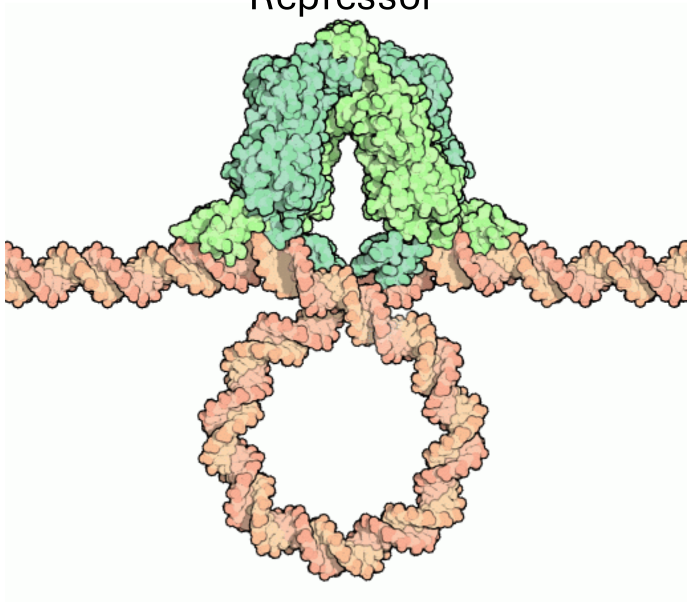


Source: biorender.com

No lactose? No transcription!



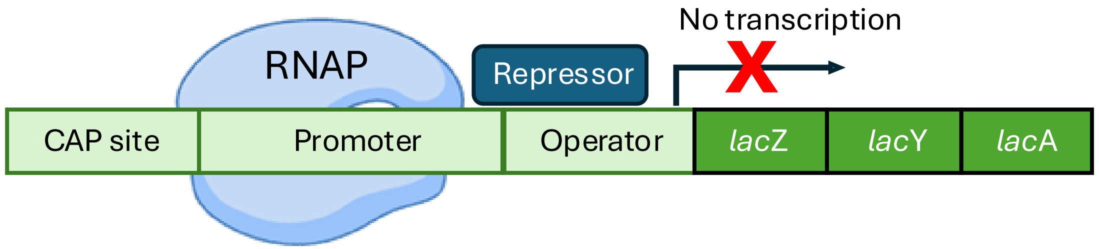
Repressor



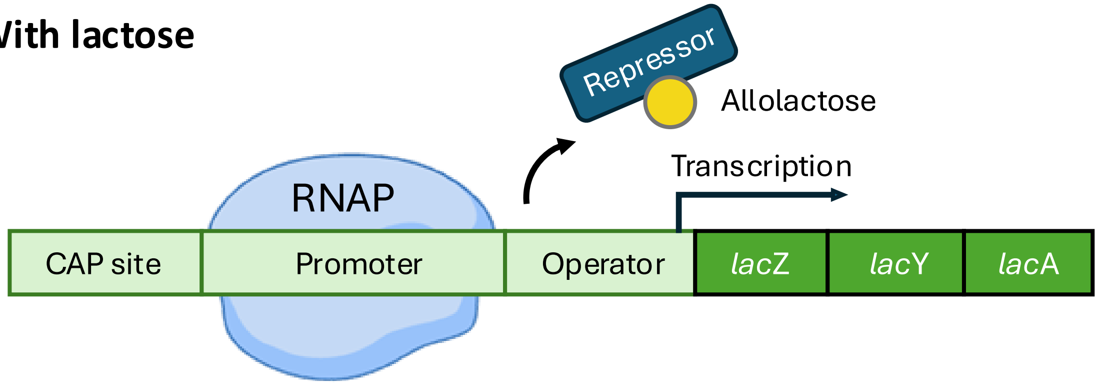
Source: David Goodsell; http://doi.org/10.2210/rcsb_pdb/mom_2003_3

A famous example: the *lac* operon in *E. coli*

No lactose

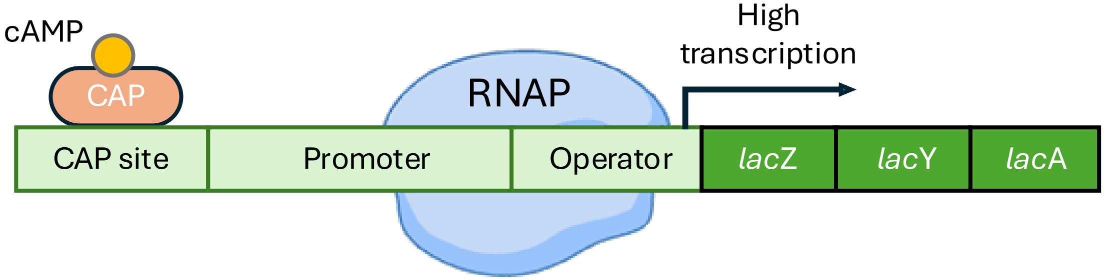


With lactose

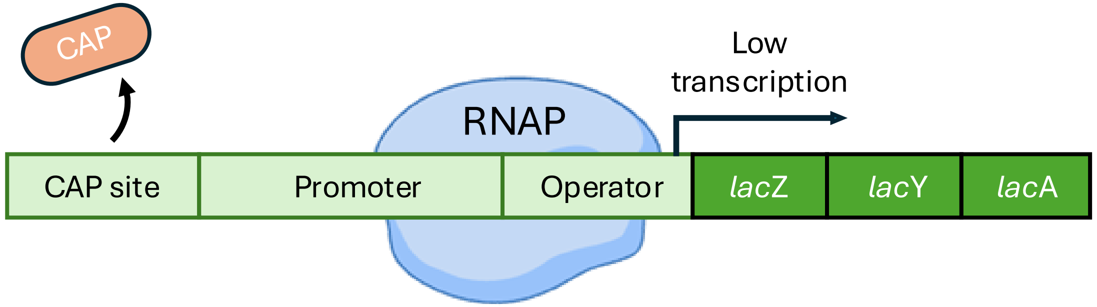


Glucose is E. coli's preferred food choice
What if both glucose and lactose are present?

Low glucose



High glucose

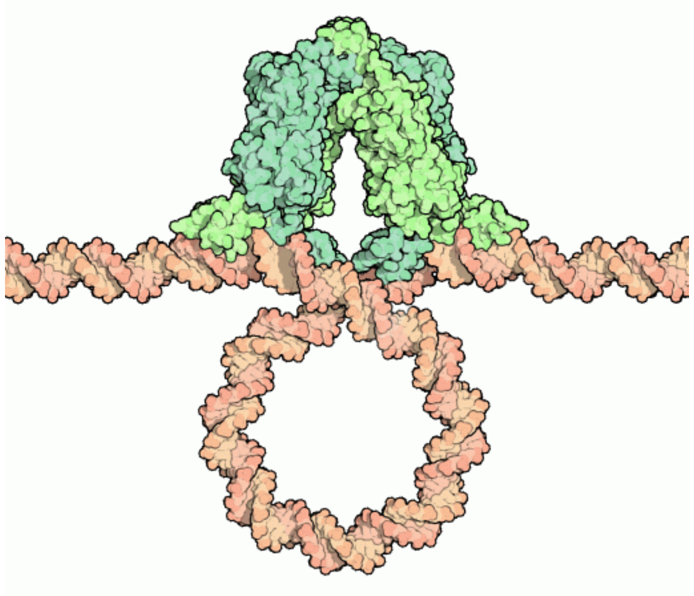


→ Genetic toggle switch

Source: BioRender.com

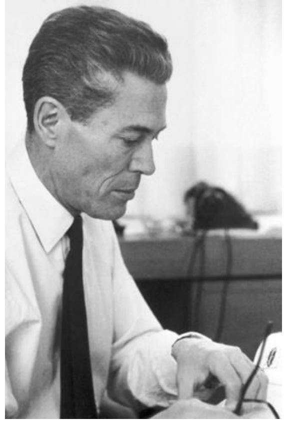
A famous example: the *lac* operon in *E. coli*

First clearly understood genetic regulatory mechanism → Nobel Prize in Medicine 1965



Source: David Goodsell; http://doi.org/10.2210/rcsb_pdb/mom_2003_3

François Jacob

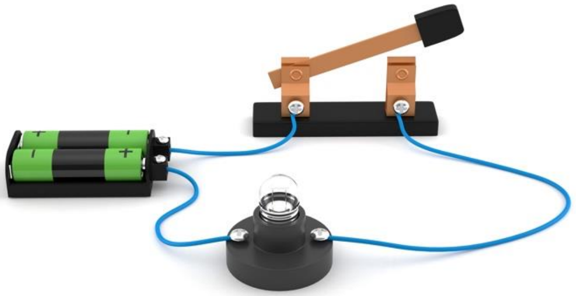


Jacques Monod

Source: https://www.nobelprize.org/prizes/medicine/1965

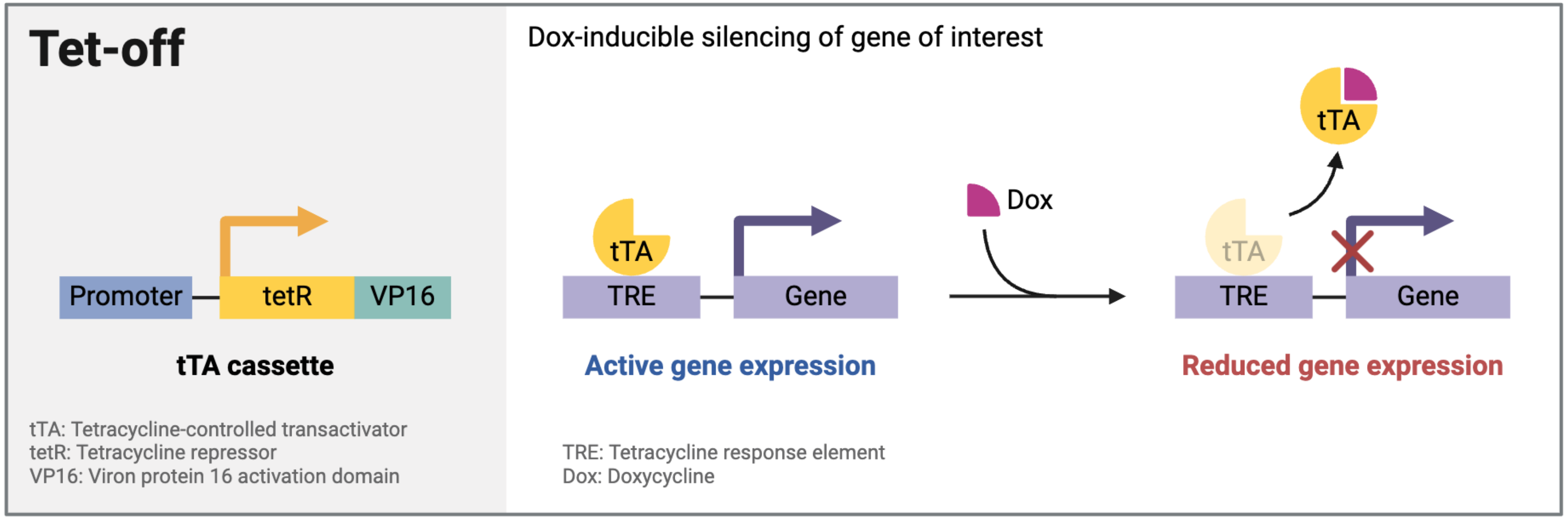
Implications for synthetic biology:

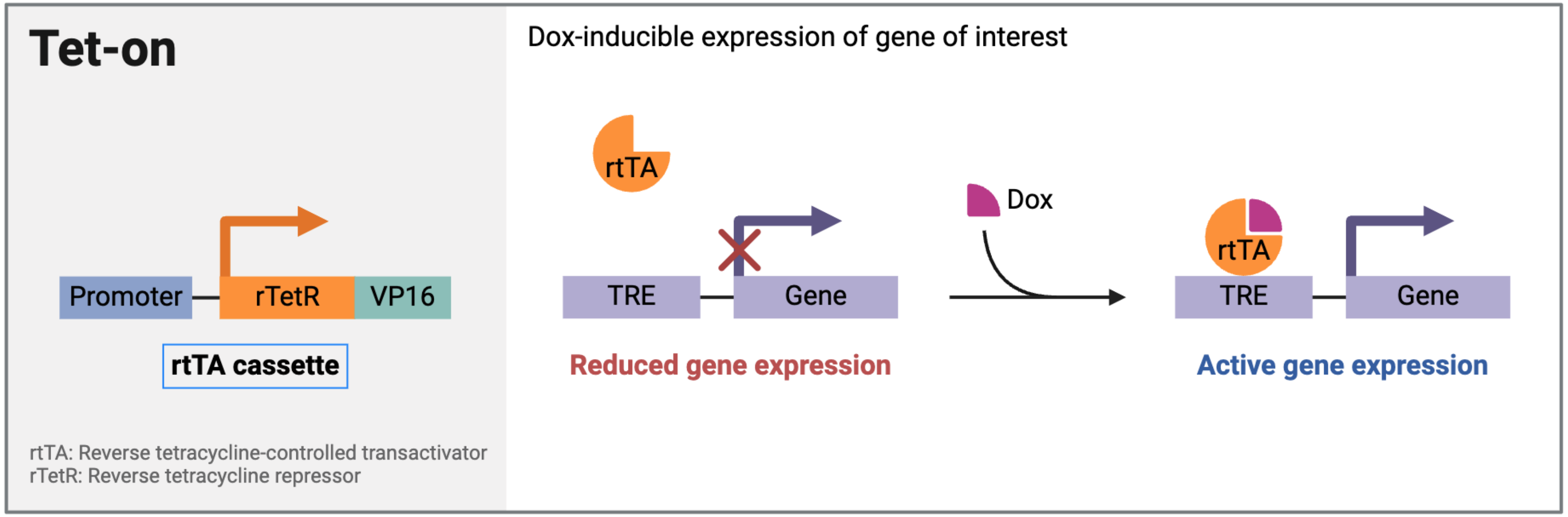
Repressor
Operator + *Any target gene* =



Source: Adobe Stock

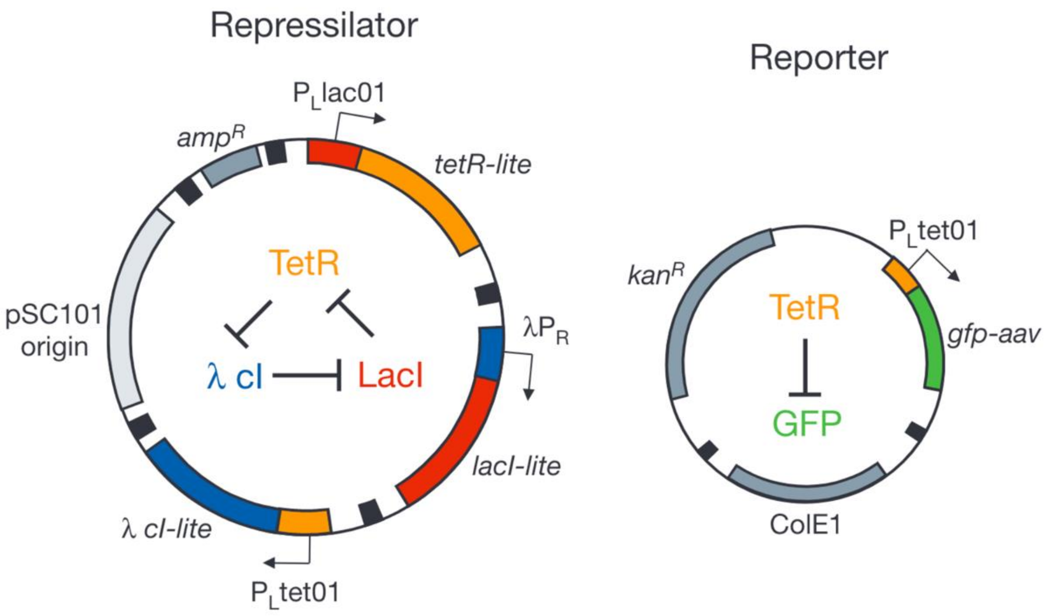
Are there more genetic switches for modulating transcription?



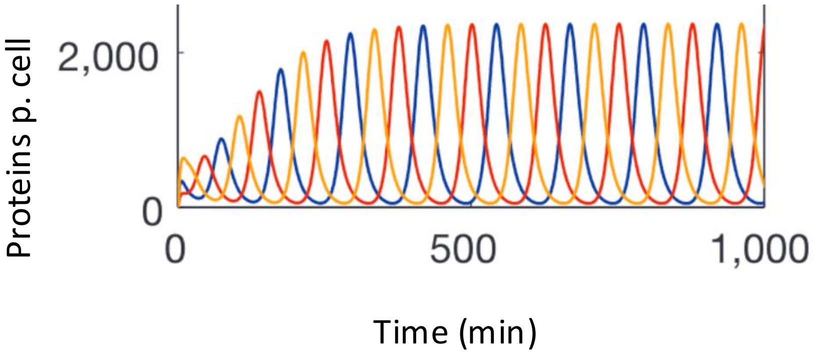


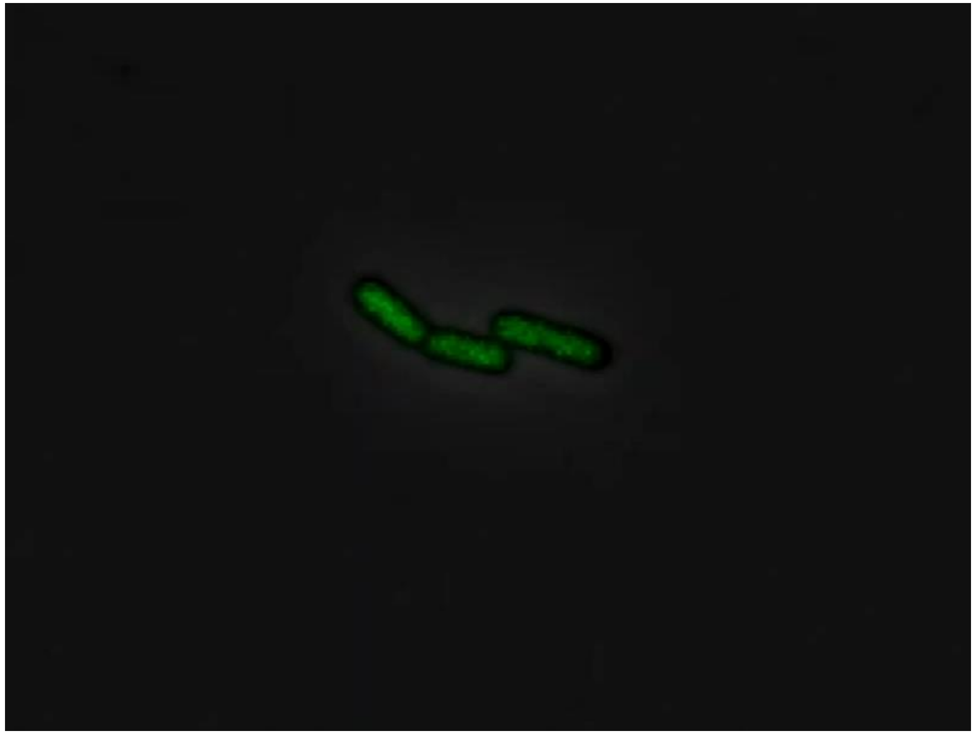
Source: BioRender.com

The Repressilator – a synthetic genetic oscillator of three repressors

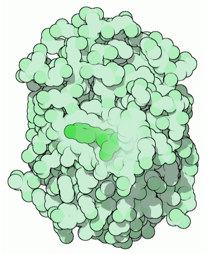


Source: Elowitz & Leibler, Nature, 2000





Green fluorescent protein



Source: David Goodsell;
https://pdb101.rcsb.org/motm/42

Source: Gao et al., Science, 2018

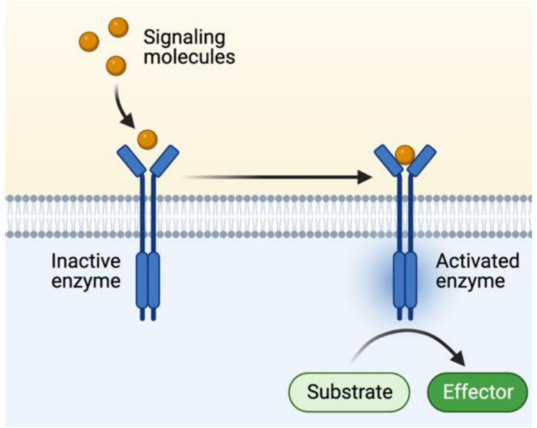
What are the available building blocks of genetic circuits?

Source: Adobe Stock

Important building blocks of genetic circuits – non-exhaustive list

1. Input Modules
Function: detect and process environmental or cellular signals.
Examples:

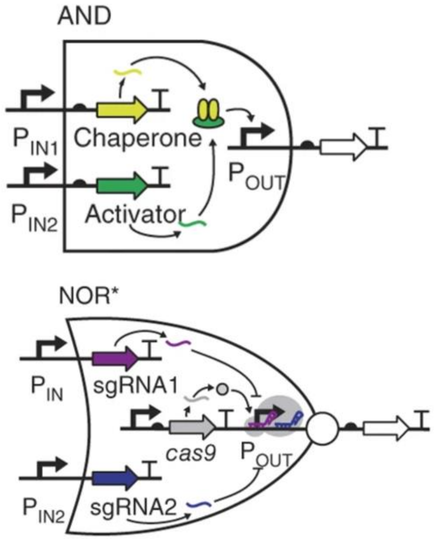
- **Sensors:** proteins or RNA molecules that detect specific molecules (e.g., small molecules, light, temperature, pH).
- **Receptors:** transmembrane or intracellular proteins that respond to external stimuli.
- **Promoters:** inducible or constitutive promoters controlling the transcription of downstream genes.



Source: BioRender.com

2. Logic Modules
Function: perform computational operations like AND, OR, NOT, or NOR based on inputs.
Examples:

- **Transcriptional Regulators:** repressors (e.g., LacI, TetR) and activators.
- **CRISPR-Cas Systems:** for programmable logic gates through guide RNA design.
- **Protein-Protein Interactions:** designed scaffolds or split proteins to perform logical operations.



Source: Brophy & Voigt, Nature Methods, 2014

Key building blocks of genetic circuits

3. Memory Modules
Function: store information about past inputs or events.
Examples:

- **Genetic toggle switches:** flip between two stable states (e.g., LacI-TetR circuits).
- **Recombinase systems:** site-specific DNA modifications (e.g., Cre/LoxP or Bxb1 systems).
- **CRISPR-based recorders:** write inputs into genomic DNA using Cas enzymes.

Source: Adobe Stock

4. Processing Modules
Function: amplify, delay, or modulate signals within the circuit.
Examples:

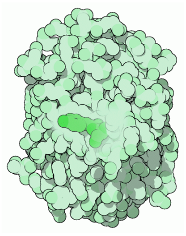
- **Feedback loops:** Positive or negative loops to enhance or suppress output.
- **Synthetic transcription factors:** tunable activation or repression.
- **RNA switches:** riboswitches or toehold switches for post-transcriptional regulation.

Key building blocks of genetic circuits

5. Output modules
Function: generate the desired cellular response or readout.
Examples:

- **Reporter genes:** Fluorescent proteins (e.g., GFP) or luminescent proteins (e.g., luciferase)
- **Therapeutic outputs:** Expression of proteins for cell signaling, apoptosis, or drug delivery.
- **Metabolic outputs:** Production of small molecules or metabolites (e.g., biofuels or pharmaceuticals).

Green fluorescent protein



Source: David Goodsell; https://pdb101.rcsb.org/motm/42

6. Communication Modules
Function: enable information transfer between cells or systems.
Examples:

- **Quorum sensing:** systems like LuxR/LuxI in *Vibrio fischeri* for population-wide signaling.
- **Secreted molecules:** enable physical or chemical intercellular communication.

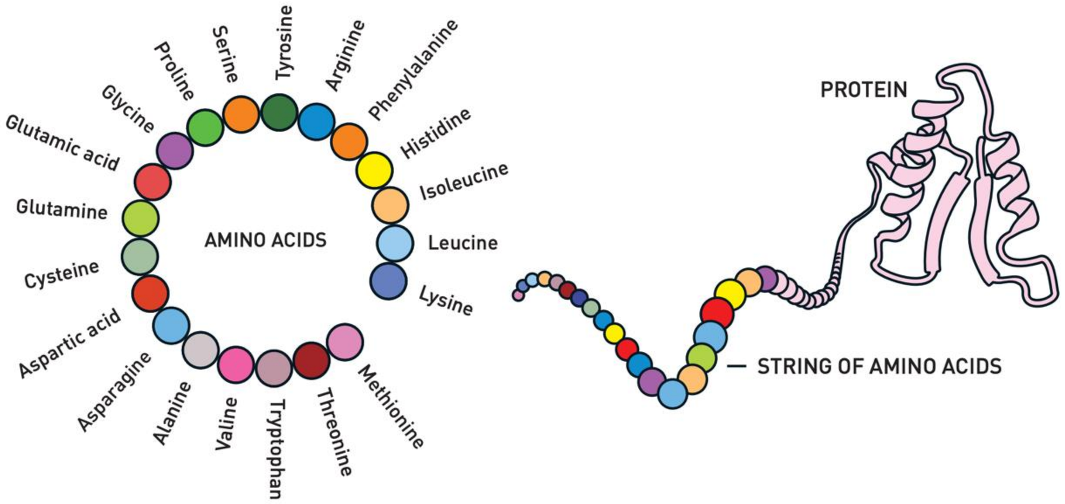
Key building blocks of genetic circuits

7. Degradation Modules
Function: control the decay or turnover of proteins, RNA, or metabolites.
Examples:

- **Degron tags:** directed protein degradation.
- **RNA destabilizing elements:** reduce RNA stability for temporal control.
- **Enzymatic systems:** pathways to degrade specific metabolites.

8. De novo engineering of new modules?

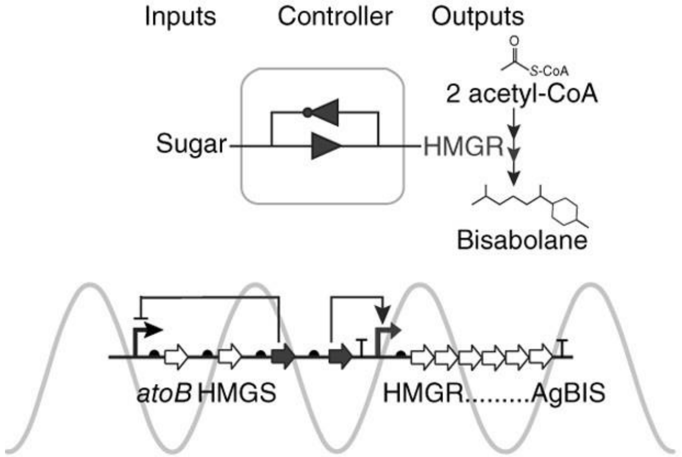
→ Protein design



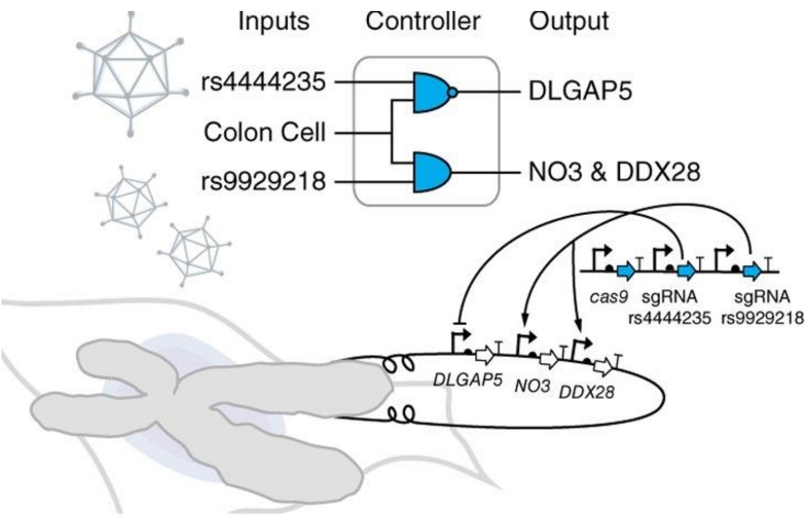
Source: https://www.nobelprize.org

Impact of genetic circuits – examples from bioproduction to therapeutics

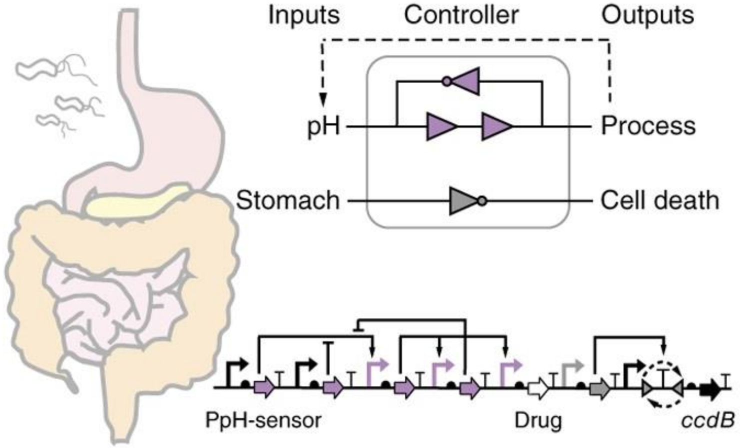
Chemical production



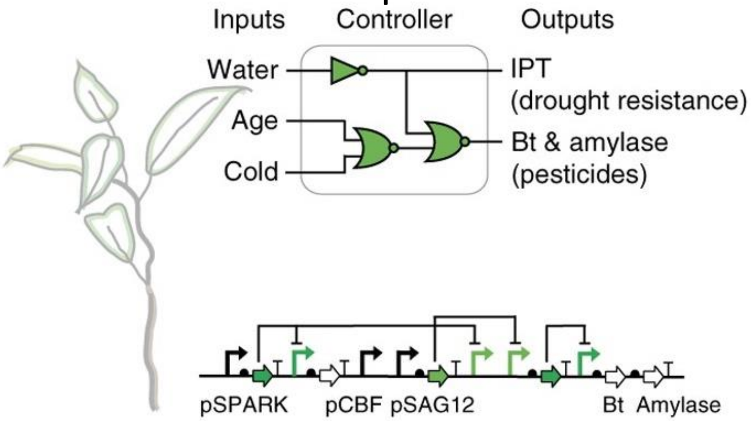
Gene therapy



Microbiome therapeutic bacteria



Smart plants



Source: Brophy & Voigt, Nature Methods, 2014

Key take aways

- Gene regulation can be understood as genetic circuits that process information
- The lac operon is a natural genetic switch controlling lactose metabolism in E. coli
- Modular genetic components can be repurposed and recombined to engineer new circuits
- Synthetic genetic circuits enable programmable control of cellular behavior across many applications