Moving Forward: Advantages and Challenges of Closed-Loop Control for Cell-Based Therapies

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"In vivo integral feedback control for robust synthetic biology"

CITY UNIVERSITY LONDON

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EPSRC
Pioneering research and skills

Synthetic Biology = (Control) Engineering Biology

Society & Industry

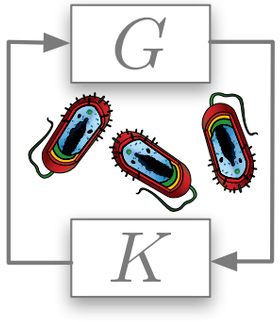
Systems & Control Engineering

Research in my group: "Control Engineering Synthetic Biology"

Synthetic Biology

Academic Research

control
engineering
synthetic
biology

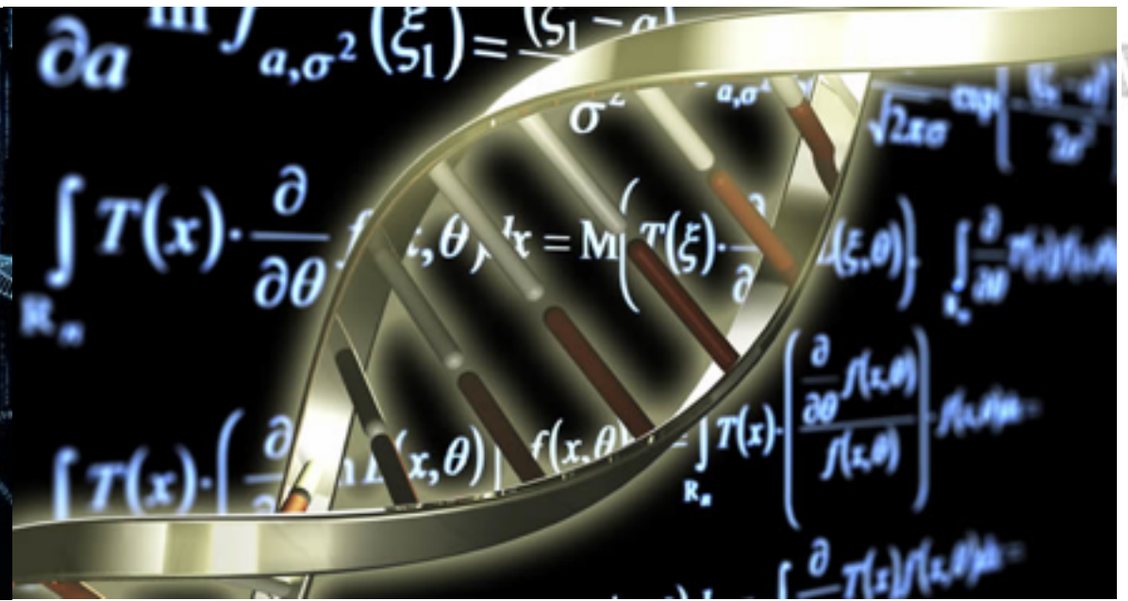


Improving the Robust Performance of Engineered Cells

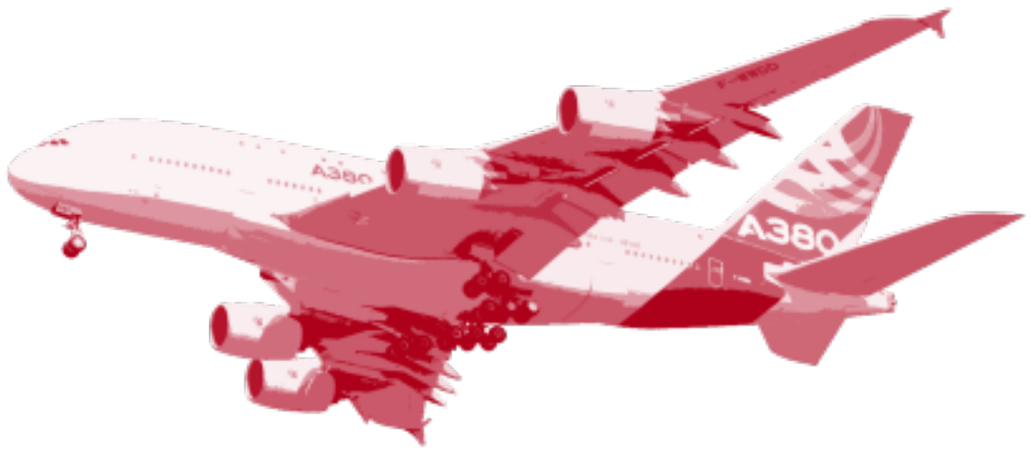
Goal: Engineer cells that *autonomously and reliably* perform useful tasks, with applications to biotechnology and cell-based medicine

Problem: Depending on the target application, engineered cells must operate in changing and uncertain conditions/contexts

Solution: Design of biomolecular feedback control mechanisms that enable robust performance of engineered cells



Examples of Man-Made Systems with Robust Performance



Fly-by-wire planes

autonomous robots

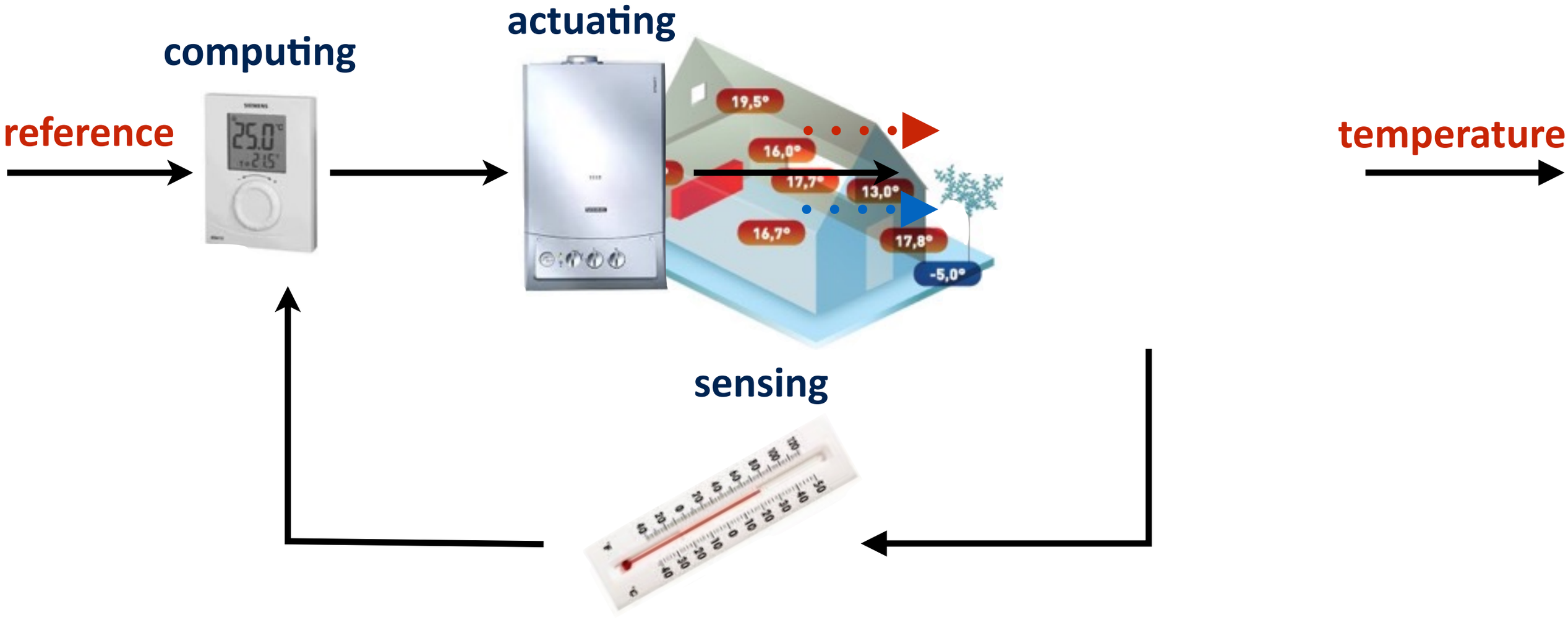
How is this achieved?

Autonomous trains

Self-driving cars

Performance Despite Uncertainties and Perturbations

reference - measured temp

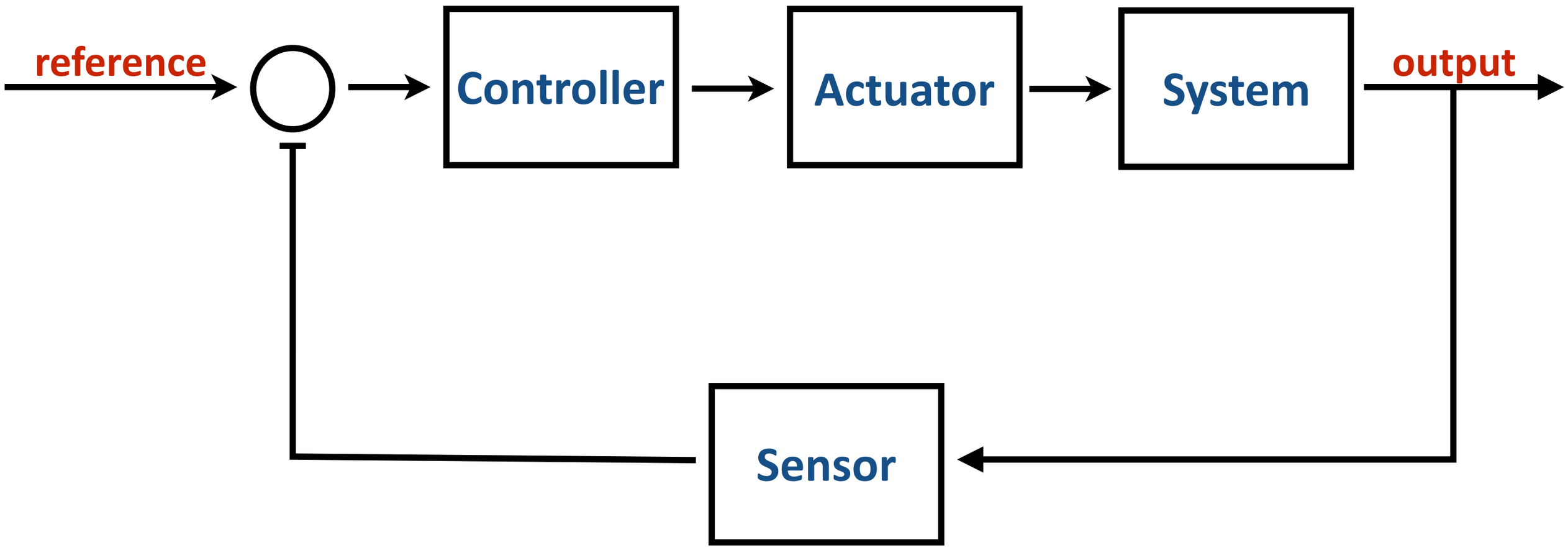


The Feedback (Closed-Loop) Control Paradigm

control error

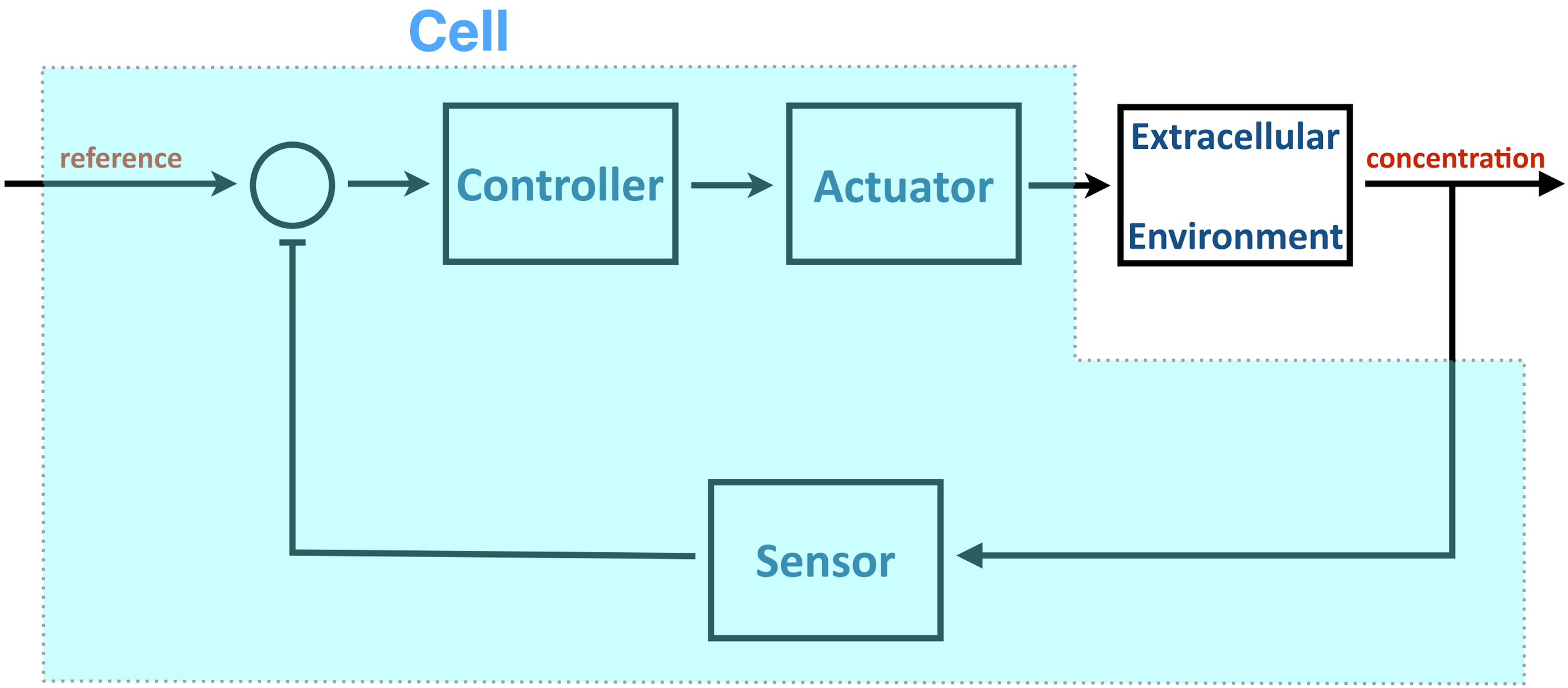
=

reference - measured output



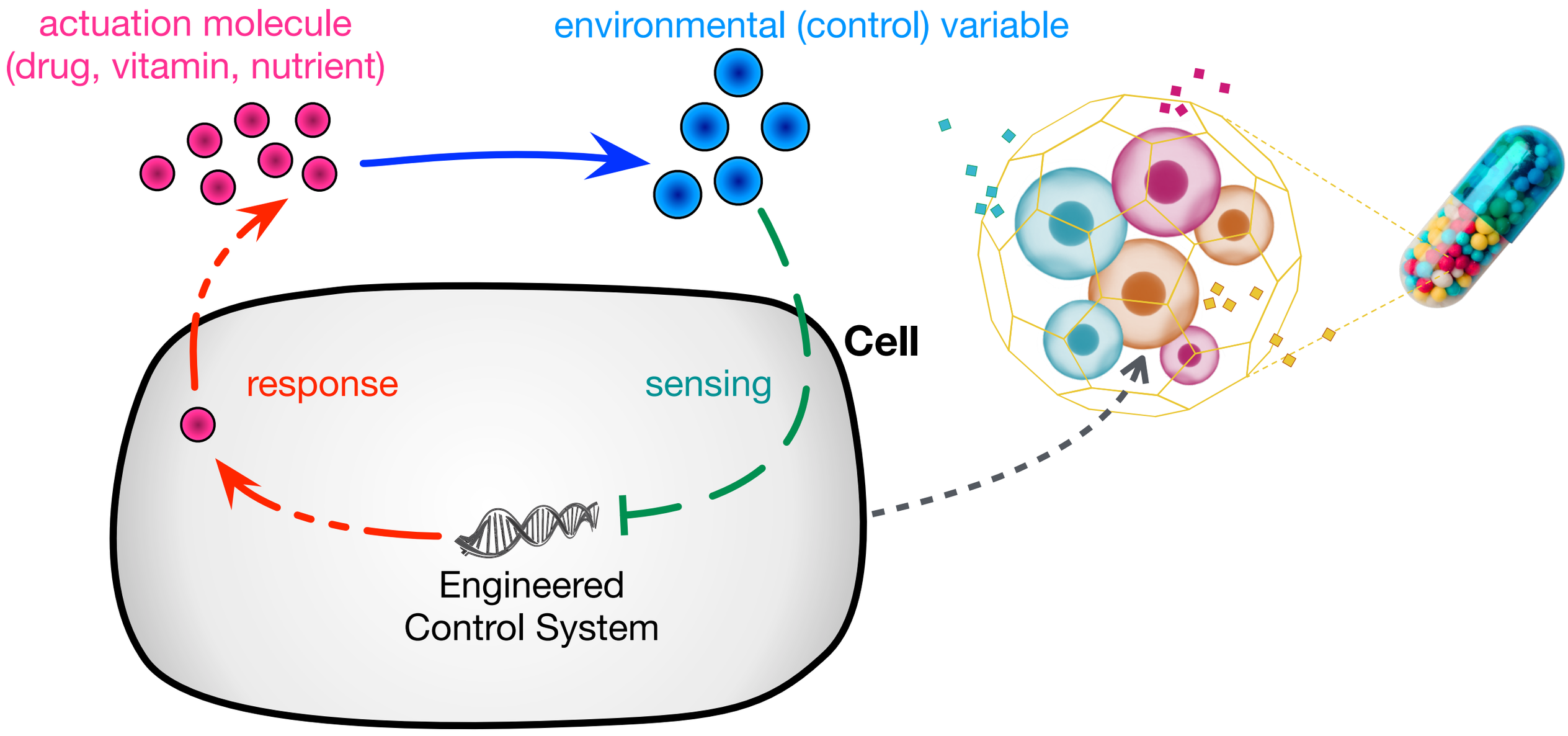
“Feedback Control Paradigm”

The Feedback (Closed-Loop) Control Paradigm



“Feedback Control Paradigm”

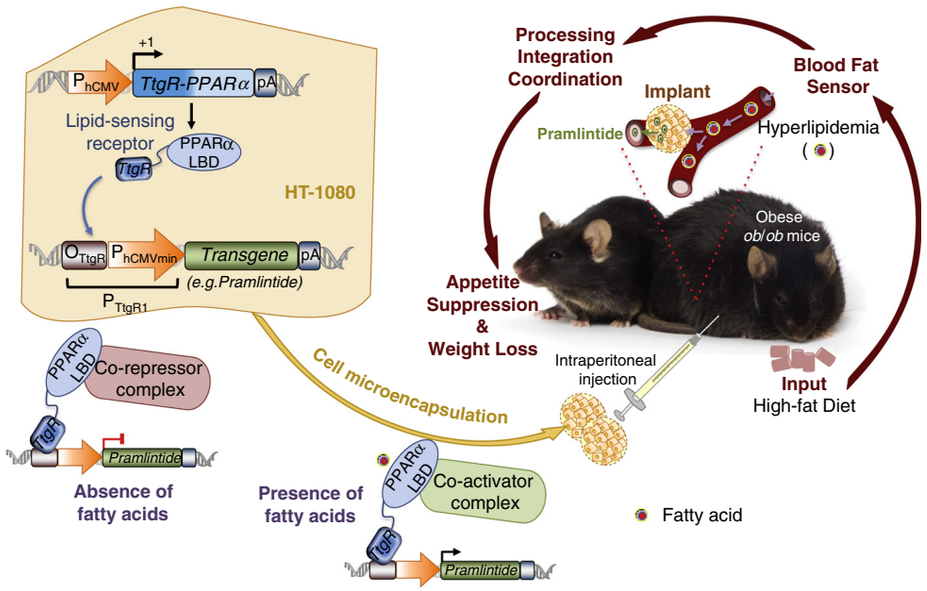
Closed-Loop Control by Engineered Cells
Cells that Maintain Homeostasis



Goal: Engineer (populations of) cells that autonomously, reliably and safely:

- Monitor the status of their surrounding environment (diagnosis)
- Produce, locally and on-demand, specific molecules (treatment)
- Continuously check and adjust the performance of their action (closed-loop) (automatic correction of error between desired and actual values)

Closed-Loop Control by Engineered Cells Examples



- Cell Therapy to Maintain Uric Acid Homeostasis
- Cell Therapy for Graves' Disease
- Cell Therapies for Obesity Control
- Cell Therapy for Psoriasis

(Martin Fussenegger, ETH Zurich)

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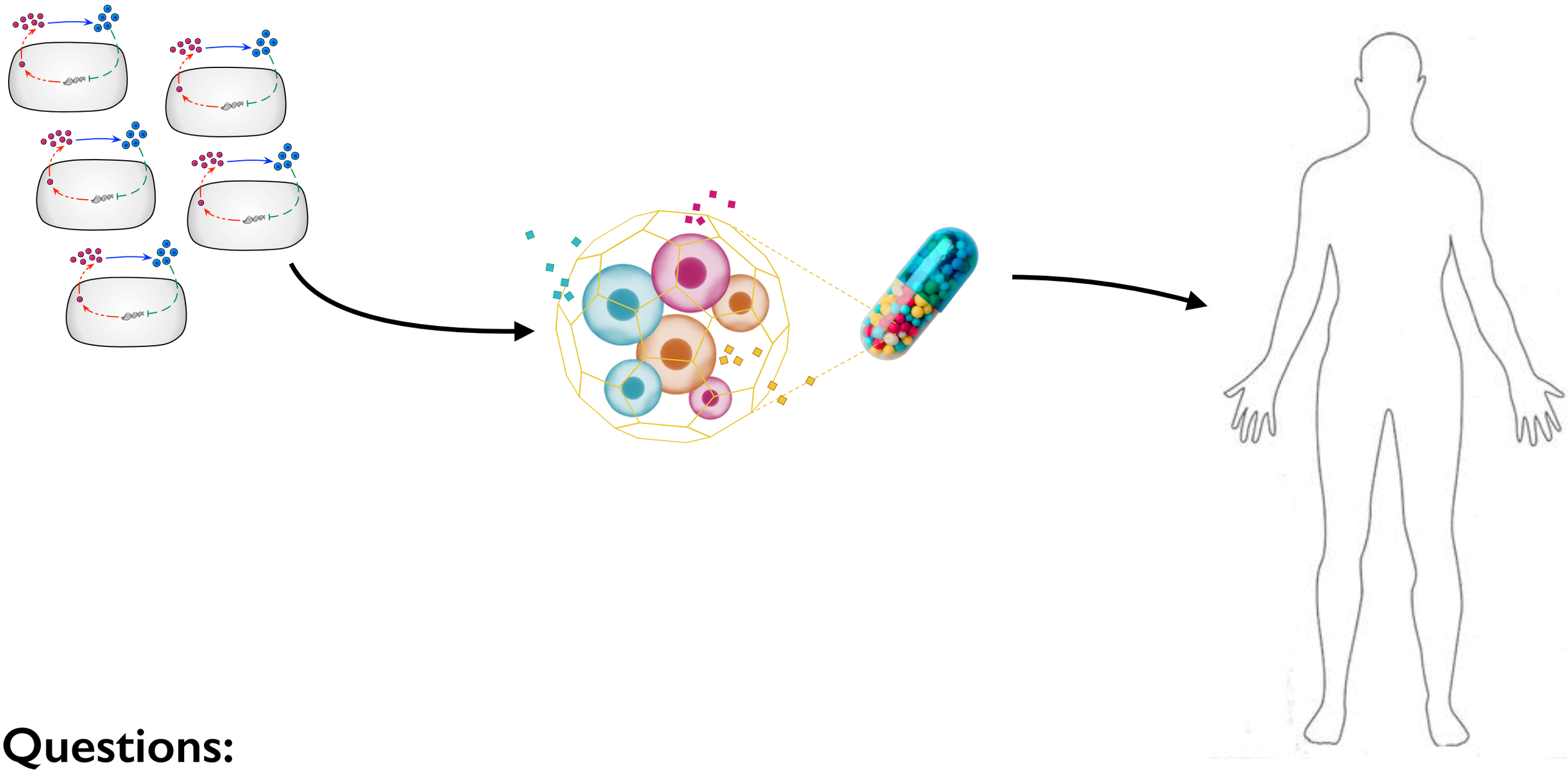
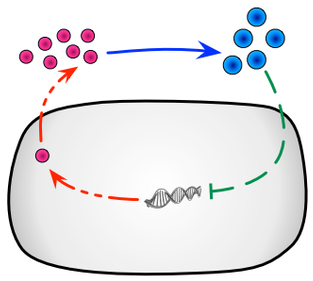
Closed-Loop Cell-Based Therapies: "the Cells Will See You Now"



Questions:

- How useful might bacterial cell-based therapies that involve feedback regulation be? For what purposes?
- How could they be translated into commercially viable medical products that deliver real benefits to patients?



Closed-Loop Cell-based Therapies: Suggested Questions for Discussion

1. How useful might bacterial cell-based therapies that involve feedback regulation be? For what purposes?

- What are the advantages? What are the disadvantages?
- Which medical/health conditions might they be most useful for? Why?
- How does this therapeutic approach compare to other existing or potential approaches?
- Who should decide and on what basis?

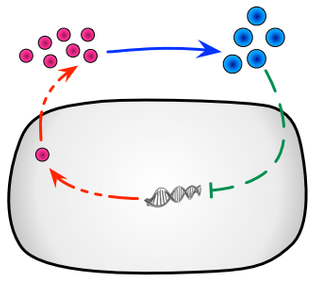
2. How could they be translated into commercially viable medical products that deliver real benefits to patients?

Consider:

- **Technical aspects;**
- **Regulatory aspects; and**
- **Social & economic aspects (including Health Technology Assessments)**

In each case:

- What is the current status? What are the hurdles? How could they be addressed? By whom?
- What is the timescale from prototyping in the lab, to clinical trials, to access to therapies for people who need them?



Closed-Loop Cell-based Therapies: Questions for Clinical Use

- What are the best indications for the first clinical applications, balancing risk / benefit?
- How to do preclinical modelling of closed-loop therapies in vitro and animals?
- How to characterise the pharmacodynamics / pharmacokinetics of closed-loop therapies?
- How to quality-control the manufacturing of closed-loop therapies?
- How to monitor the in vivo performance of closed-loop therapies when introduced into patients?
- How to measure the long-term durability of closed-loop therapies?
- How to incorporate safeguards or external control over closed-loop therapies?
- How does this fit into existing regulatory frameworks? Do these make sense?
  - When in the process does environmental risk assessment come into play?
  - How are fecal transplants regulated?