Biological Control

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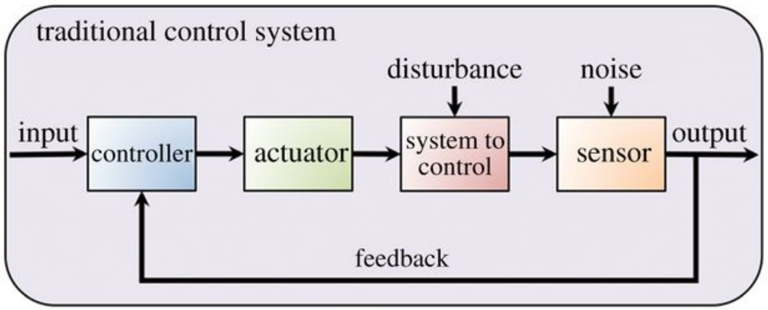
PM, DARPA BTO

Proposers Day

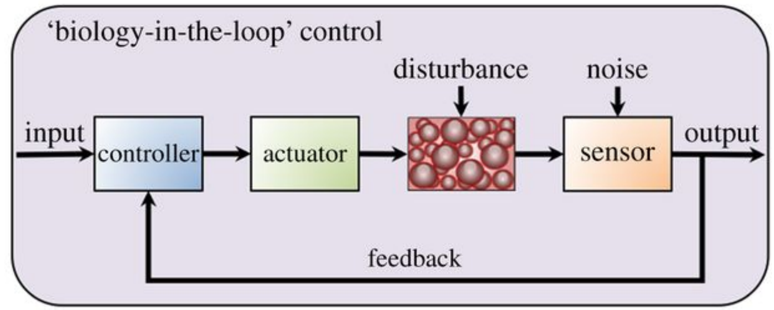
22 February 2016

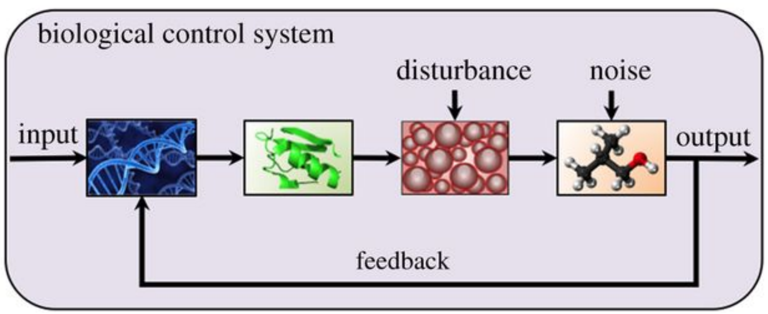
Context: Control systems and biology

Nonbiological control

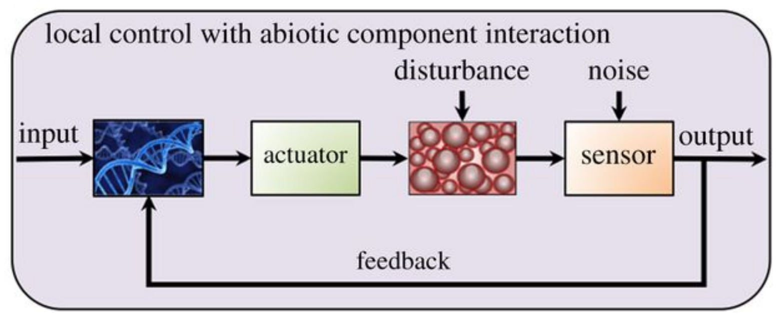


Biology in the control loop





Biological control



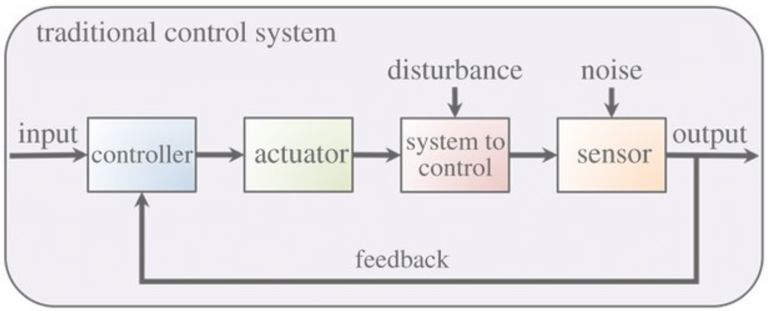
Hybrid control

Adapted from Menezes *et al.* Grand challenges in space synthetic biology. *Interface* (2015)

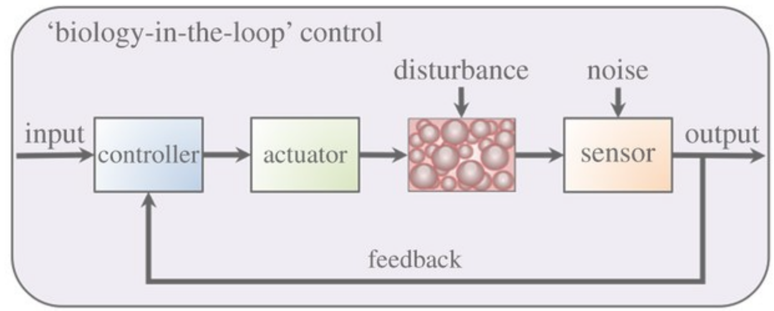
Context: Control systems and biology

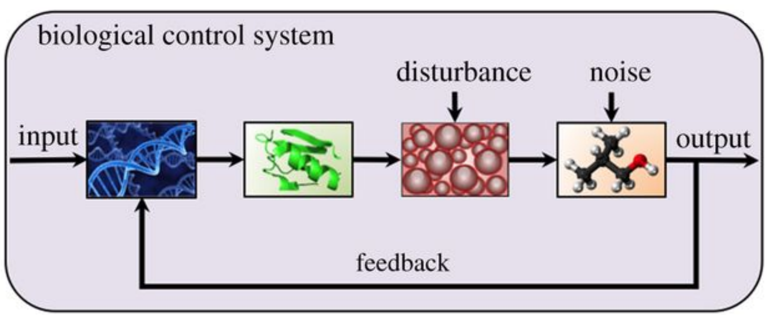
The Biological Control Program is interested only in biological control

Nonbiological control

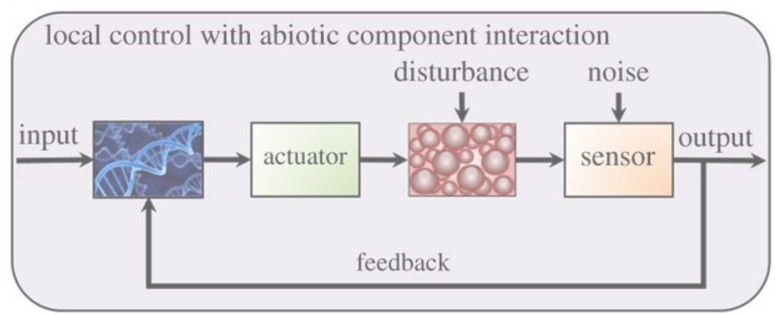


Biology in the control loop





Biological Control



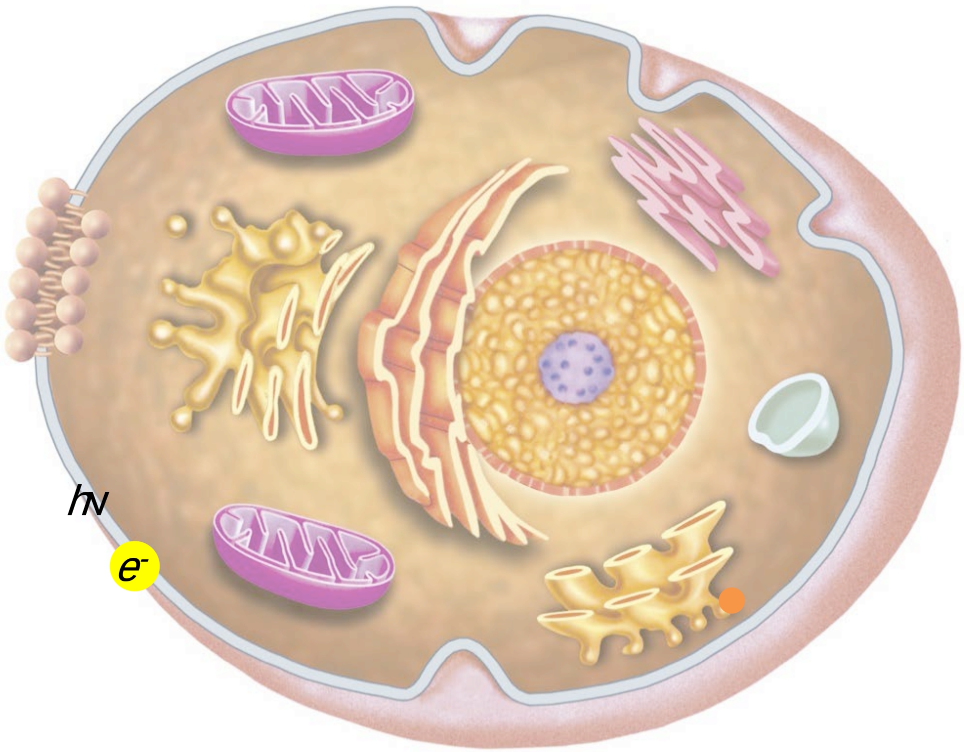
Hybrid control

Adapted from Menezes *et al.* Grand challenges in space synthetic biology. *Interface* (2015)

Control of biological systems using biological parts

Biological Control Program Vision: Enable the rational design of predictive, dynamic, and quantitative control of biological systems

Biological system

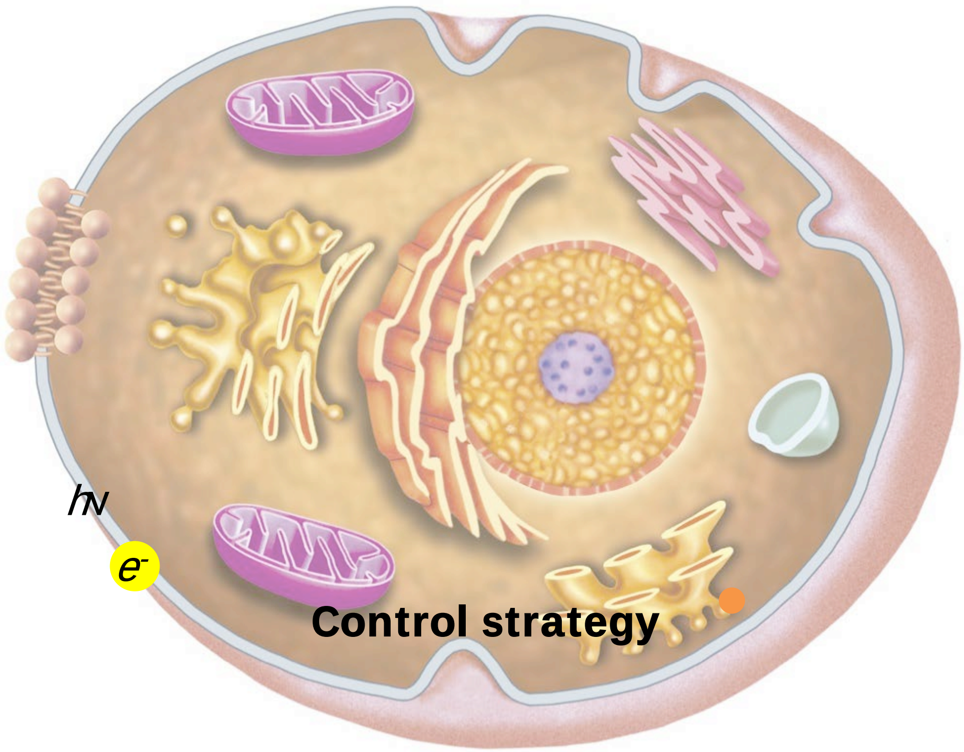


Environmental control

Control of biological systems using biological parts

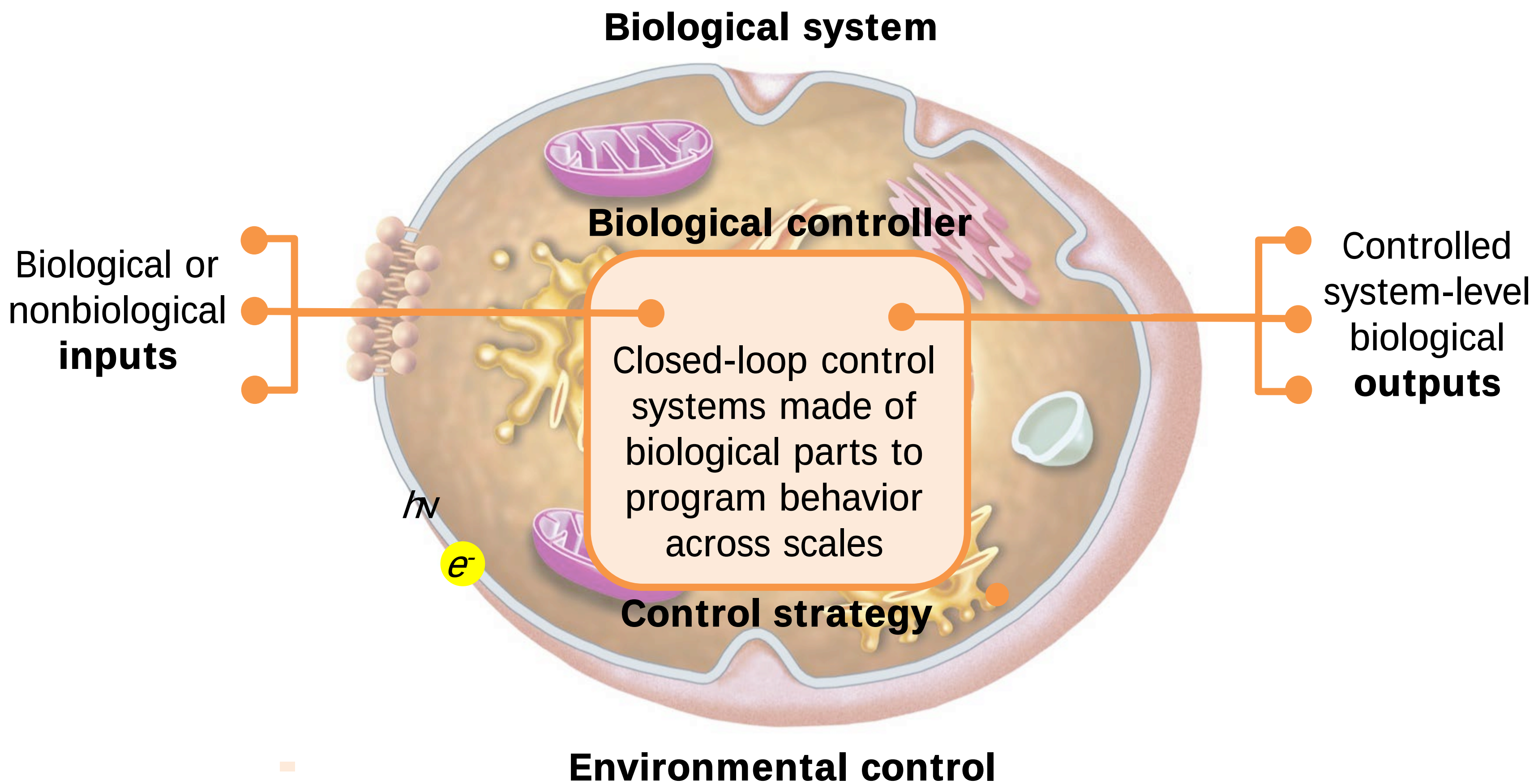
Biological Control Program Vision: Enable the rational design of predictive, dynamic, and quantitative control of biological systems

Biological system



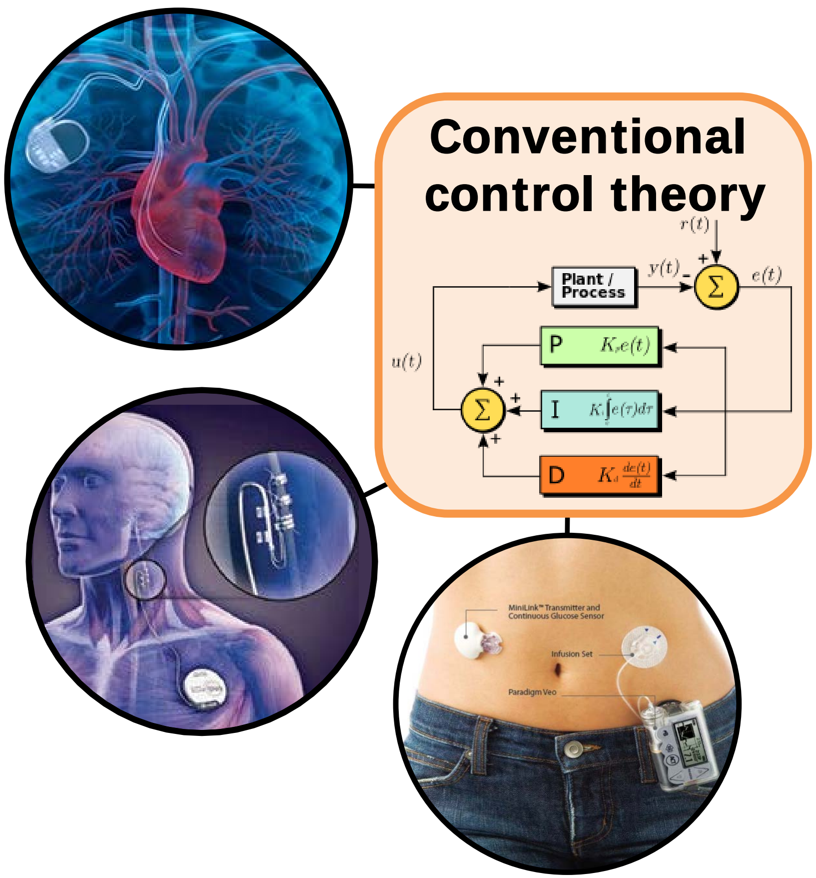
Environmental control

Biological Control Program Vision: Enable the rational design of predictive, dynamic, and quantitative control of biological systems



Control with biology in the control loop today

Control engineering has been used to modulate human physiology through electronic medical devices



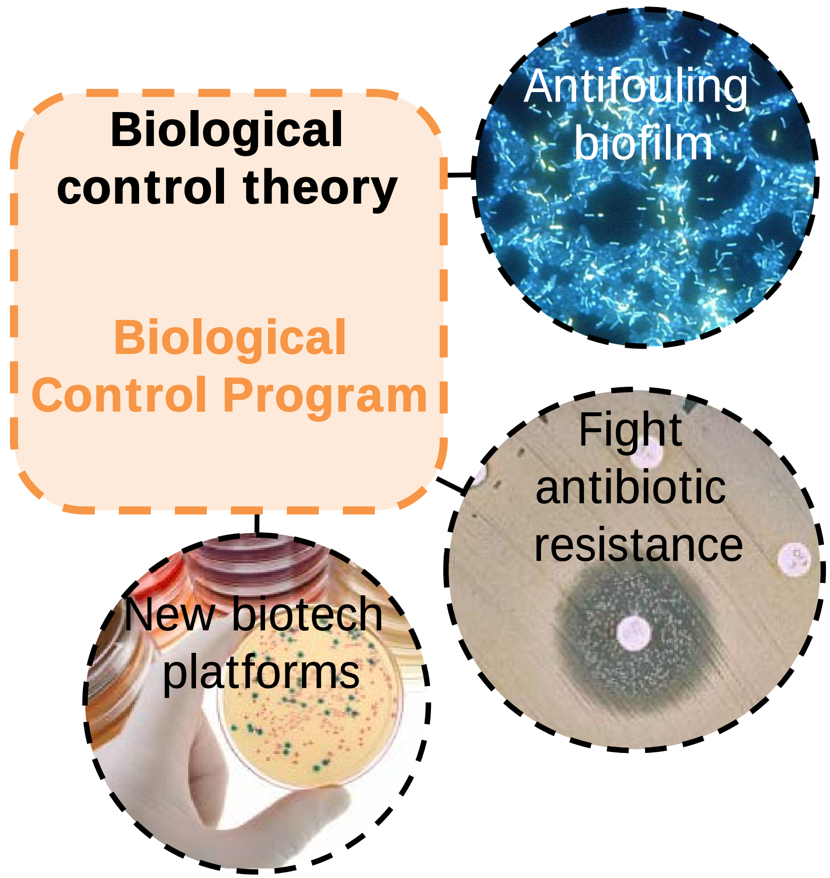
- Built using electrical and mechanical parts
- Designed using conventional control theory
- Embedded surgically
- Controlled at a single scale (*e.g.*, molecular, cell, tissue, organ)
- Limited inputs and outputs
- Limited control of dynamics

DARPA

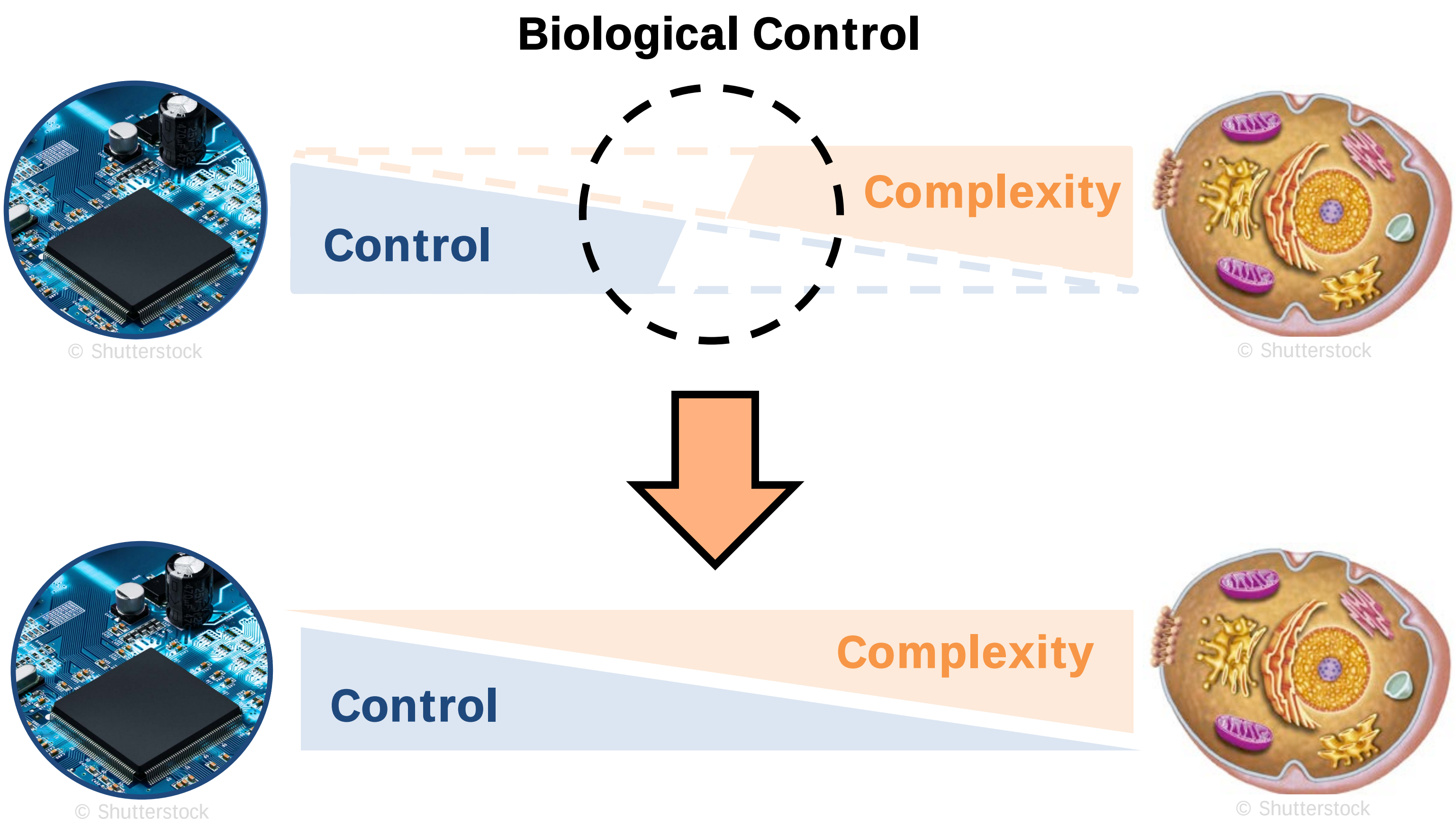
Biological control tomorrow

Apply and advance control engineering to enable the rational design of biological control strategies for a variety of applications

- Build in control of biological systems using biological parts
- Design using a control theory suitable for biological systems
- Embed directly into and move with the biological system
- Operate across scales to control system-level function (*e.g*., genes to cells, cells to population)
- Multiple inputs and outputs
- Dynamic control strategies and outputs to account for environmental change and adaptation
- Leverage innate control in natural biological systems



New possibilities for engineering biology



Terms for Biological Control BAA

Complexity

- Refers to the high degree of interconnectedness of the scales and components of a biological system, in a manner that complicates prediction and control at the state of the art

Generalizable control

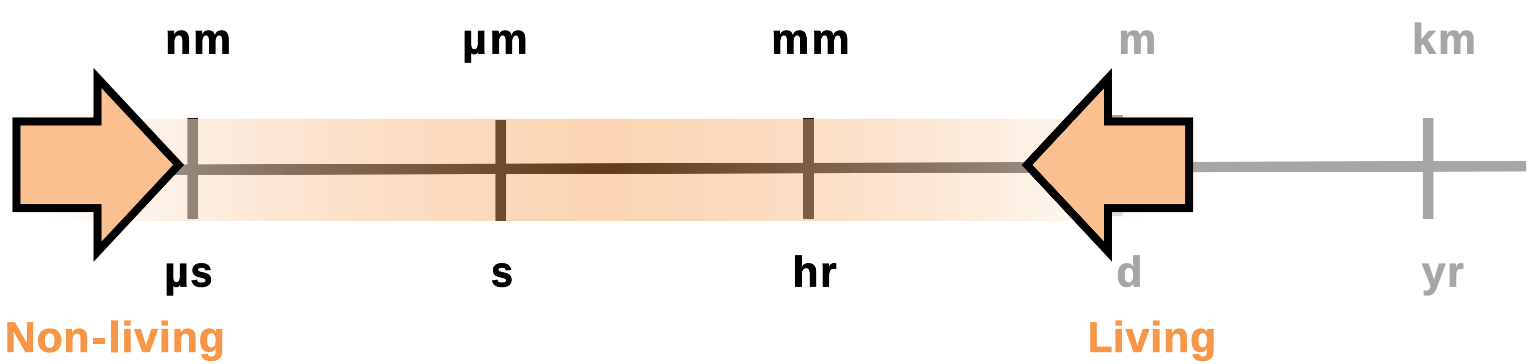
- Control strategies based on system-agnostic theory and modeling that, once well-understood and implemented in one biological system, should be straightforward to adapt for use in other biological systems

System-level behavior

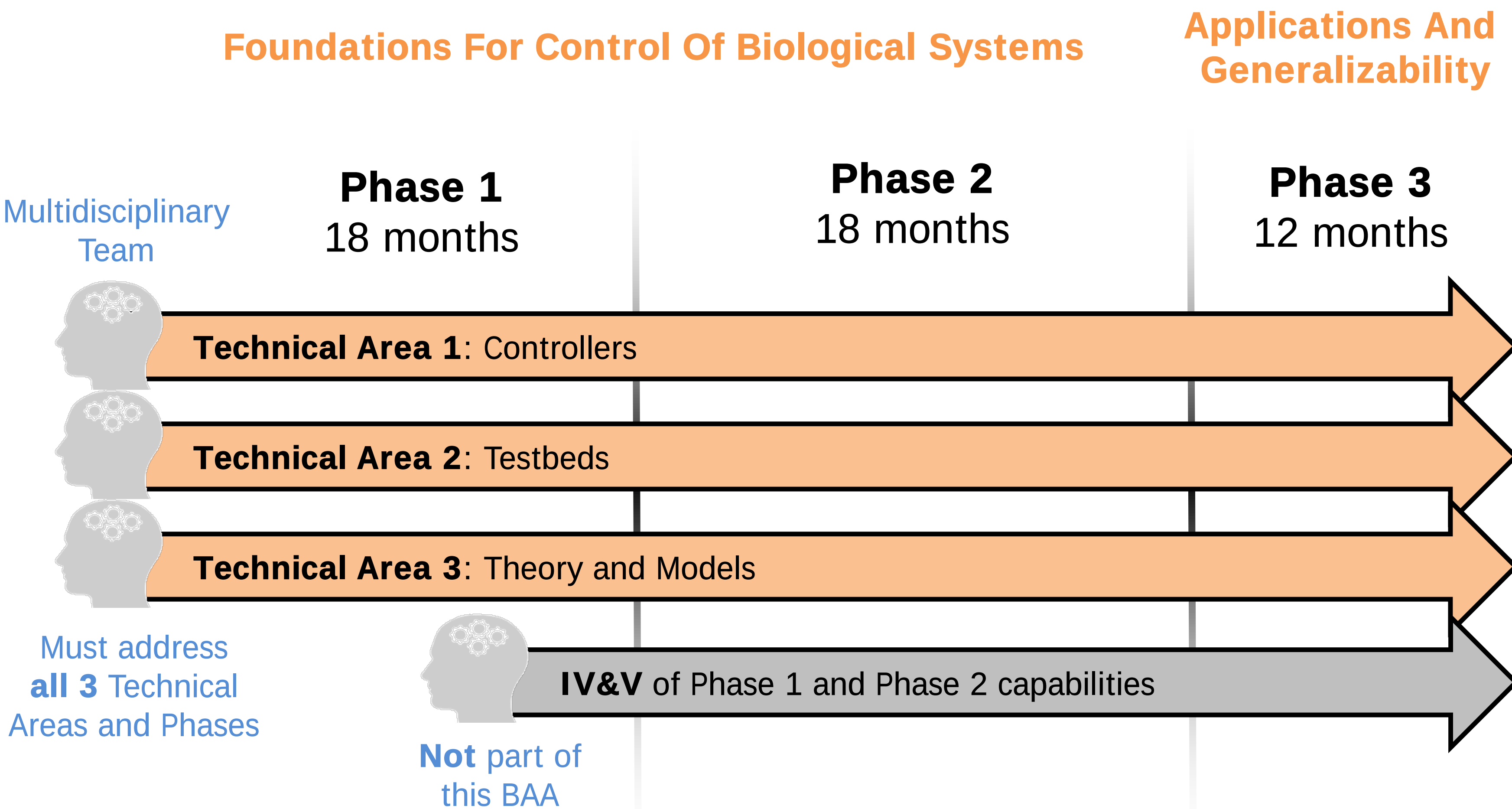
- Complex behaviors targeted for control that manifest at the organizational level of a whole biological system, for example, the unicellular organism, cellular community, multicellular organism, or ecosystem
- Includes, but is not limited to, growth and reproduction, adaptation and evolution, sensing and responding, and metabolism

Scales for Biological Control

- Nanometers to centimeters, seconds to weeks, and biomolecules to populations of organisms



Notional schedule and structure



Technical Area 1 (TA1): Controllers

- Closed-loop control of biological systems built from **biological parts only**
- Based on predictive theory and models, not *ad hoc* empirical screening
- Inputs may be biological and/or nonbiological, while outputs must be biological
- Control of system-level behaviors
- Integrate multiple controllers into testbed individually and in combination

	Phase 1	**Phase 2**	**Phase 3**
Program Goals	Predictable, closed-loop control of system-level behavior using a biological controller	Predictable, closed-loop control of additional system-level behaviors using additional biological controllers	Generalizable, predictable capabilities for biological control for a DoD application
TA1 Goals	Assemble a biological controller described by **TA3** Integrate into testbed in **TA2**	Build additional biological controllers described by **TA3** Integrate into testbed in **TA2**	Work with **TA3** to transfer to a DoD relevant demonstration system in **TA2**

Technical Area 2 (TA2): Testbeds

- Consist of a biological system and hardware for quantitative measurements and dynamic environmental control
- **Use a simple natural or synthetically-simplified biological system**
  - Examples include life-like systems, characterized microbes, and simple multicellular organisms
- Chosen for generalizability to additional biological systems and control strategies
- Time-course measurements are required, and orthogonal measurements are encouraged

	Phase 1	**Phase 2**	**Phase 3**
Program Goals	Predictable, closed-loop control of system-level behavior using a biological controller	Predictable, closed-loop control of additional system-level behaviors using additional biological controllers	Generalizable, predictable capabilities for biological control for a DoD application
TA2 Goals	Build and characterize testbed Evaluate performance of controller from **TA1** Share measurements with **TA3**	Integrate and evaluate additional controllers from **TA1** Share measurements with **TA3**	Build DoD-relevant demonstration system Integrate controllers from **TA1** for practical biological control for a DoD application

Technical Area 3 (TA3): Theory and models

- Provide testable **quantitative predictions** for testbed and controllers
- Provide models and prediction for biological controllers and control strategies, as opposed to merely describing experimental results
- Adaptable and generalizable for modeling control of biological systems beyond the testbed
- Should include the development of new control theory and modeling approaches, as needed

	Phase 1	Phase 2	Phase 3
Program Goals	Predictable, closed-loop control of system-level behavior using a biological controller	Predictable, closed-loop control of additional system-level behaviors using additional biological controllers	Generalizable, predictable capabilities for biological control for a DoD application
TA3 Goals	Develop predictive models for control for **TA1** and **TA2** Exchange domain knowledge with **TA1** and **TA2**	Inform development of additional controllers and control strategies in **TA1** Implement models in a computational environment for rational design of control	Translate control strategies for a DoD application in **TA1** and **TA2** Participate in tests of the models' predictive capabilities

Independent Validation and Verification (IV&V)

Controllers should behave reproducibly, regardless of laboratory, location, operator, *etc*.

- The Biological Control Program will employ IV&V

Proposals must include plans to deliver all necessary materials, protocols, and domain knowledge to the IV&V team(s)

IV&V team(s) will be selected separately from BAA-16-17

If duplication of the testbed presents an unreasonable cost, teams should outline a plan for IV&V team(s) to access the team's laboratory for validation, verification, and testing

Predictive capabilities developed in TA3 will be tested in Phase 3, in a manner to be announced by DARPA no later than the end of Phase 2

Phase 3: DoD relevant application

Candidate Applications

Proposer-defined application

- Proposer-defined applications with impact for national security
- Scientific proof-of-concept for control of biological systems at the laboratory scale
- Based on capabilities from Phase 1 and Phase 2

Demonstrate the utility of biological control in applications of relevance to DoD

Metrics and milestones: Specified and proposer-defined

Few specific metrics and milestones are defined in BAA-16-17, to allow flexibility and creativity

Teams **must fill this gap with clear proposer-defined metrics and milestones**, as appropriate

- Justify these relative to the state of the art
- Explain how these build towards the overall goal of the proposal and program

Clear, concise metrics and milestones demonstrate the strength of your proposal

- Strong preference for quantitative metrics over qualitative metrics
- Meant to quantify and evaluate progress and accomplishments of proposed work
- Central to contracting

BAA timeline and funding overview

Abstracts

- **Strongly encouraged**
- Abstract due date: **March 18, 2016**
- Purpose is to determine if the idea fits within the program before undertaking the effort of a full proposal

Full proposal due date: **April 29, 2016**

Available Biological Control funds

- Up to approximately $38M will be awarded
- Number of teams selected depends on the quality of proposals and availability of funds

Teaming

Teaming is strongly encouraged

- Require deep expertise in both theoretical and experimental science and technology, for example, in fields of biology relevant to the proposed testbed and demonstration system, fields of engineering relevant to the proposed testbed and measurement methods, and control engineering

Equal emphasis on experiment and theory

Address all Phases and TAs

Designated PI or Team Coordinator will be the primary interface with DARPA

The Biological Control program has no bias for teams internal to one institution or across multiple institutions

- Plan for effective communication and collaboration within teams

Communicating research outside the program

Biological Control is funded as basic research

Performers are not expected to be censored

- DARPA does not anticipate a requirement for review of research prior to publication
- Individual contracts will detail review requirements

DARPA will request two-week notice and copies of presentation slides, manuscripts, and other communication prior to distribution

BAA inbox and FAQ

Direct **all** questions and communication to the BAA inbox

- DARPA-BAA-16-17@darpa.mil
- Elizabeth, any member of her team, or any member of the scientific review panel will not communicate directly with a potential proposer regarding BAA-16-17
- All communication will occur through the BAA inbox only
- Elizabeth and the BAA inbox will provide feedback and/or guidance to clarify content of BAA-16-17 only and cannot provide feedback regarding any aspect of a proposal

BAA inbox FAQ

- DARPA will post a consolidated FAQ regularly
- Access the posting at:
    - http://www.darpa.mil/work-with-us/opportunities/Solicitations/BTO_Solicitations
- Submit questions to DARPA-BAA-16-17@darpa.mil at least 15 days prior to the proposal submission deadline

Advice

Read the BAA carefully and thoroughly

Ask for clarification
- FAQs will be updated regularly

Refer to material from Proposers Day, which will be available online

Be bold, take risks, add urgency to forbearance, and have fun

Questions?

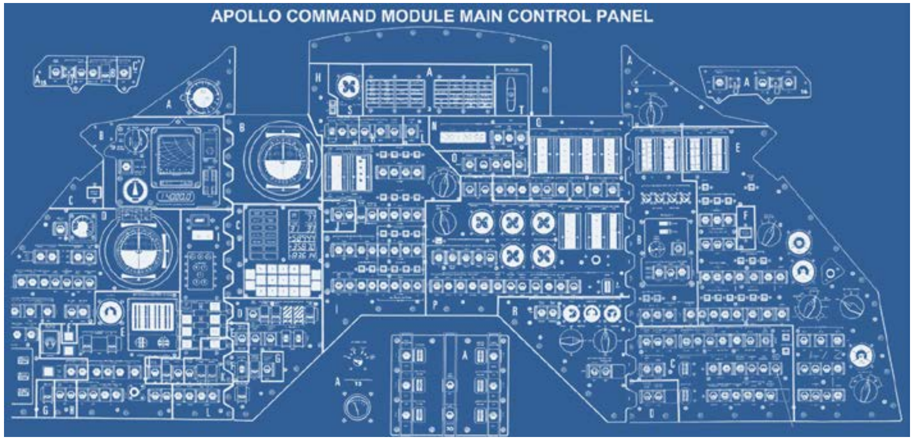
www.darpa.mil

Additional Slides

Biological control ≠ electrical, mechanical control

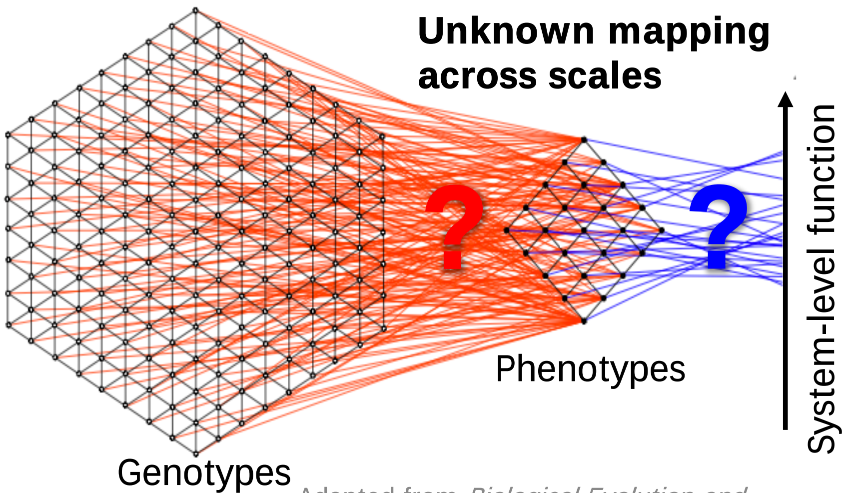
A mechanical or electrical system is designed using conventional control theory to program and maintain a desired, predictable state

- Rational “blueprint” from theory to system implementation for a conventional control system made from electrical and mechanical parts



A natural biological system maintains its state, but the control theory and mechanisms to program control across scales are largely unknown

- Incomplete “blueprint” connecting genotype to system-level function is largely unknown for a biological system made from biological parts



Adapted from *Biological Evolution and Statistical Physics,* Peter Stadler (2002)

Biological systems as control systems

Conventional control theory provides a foundation for the rational design of predictable biological control

All control systems, including natural biological systems

- **Measure** internal state
- **Compare** against a desired state
- **Adjust** state accordingly

Conventionally-controlled system

- Models for prediction
- Clear causality
- Full knowledge of parts
- Full knowledge of organization

Biological system

- Stochasticity and complexity
- Unknown causal relationships
- Unknown/Undefined parts
- Unknown/Undefined interactions

Example of control: Negative feedback

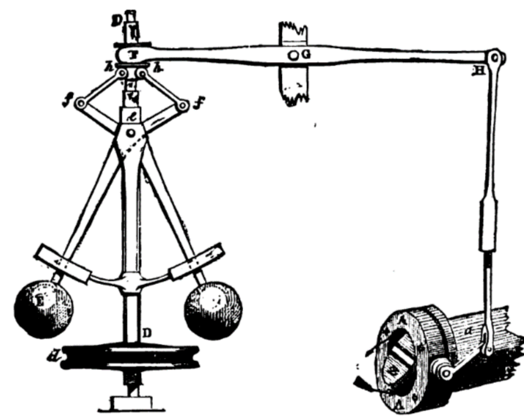
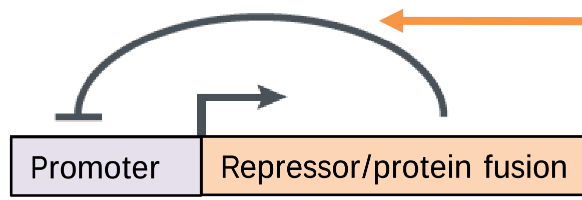


FIG. 4.—*Governor and Throttle-Valve.*

Centrifugal governor: Mechanical control system that uses negative feedback to regulate rotational speed

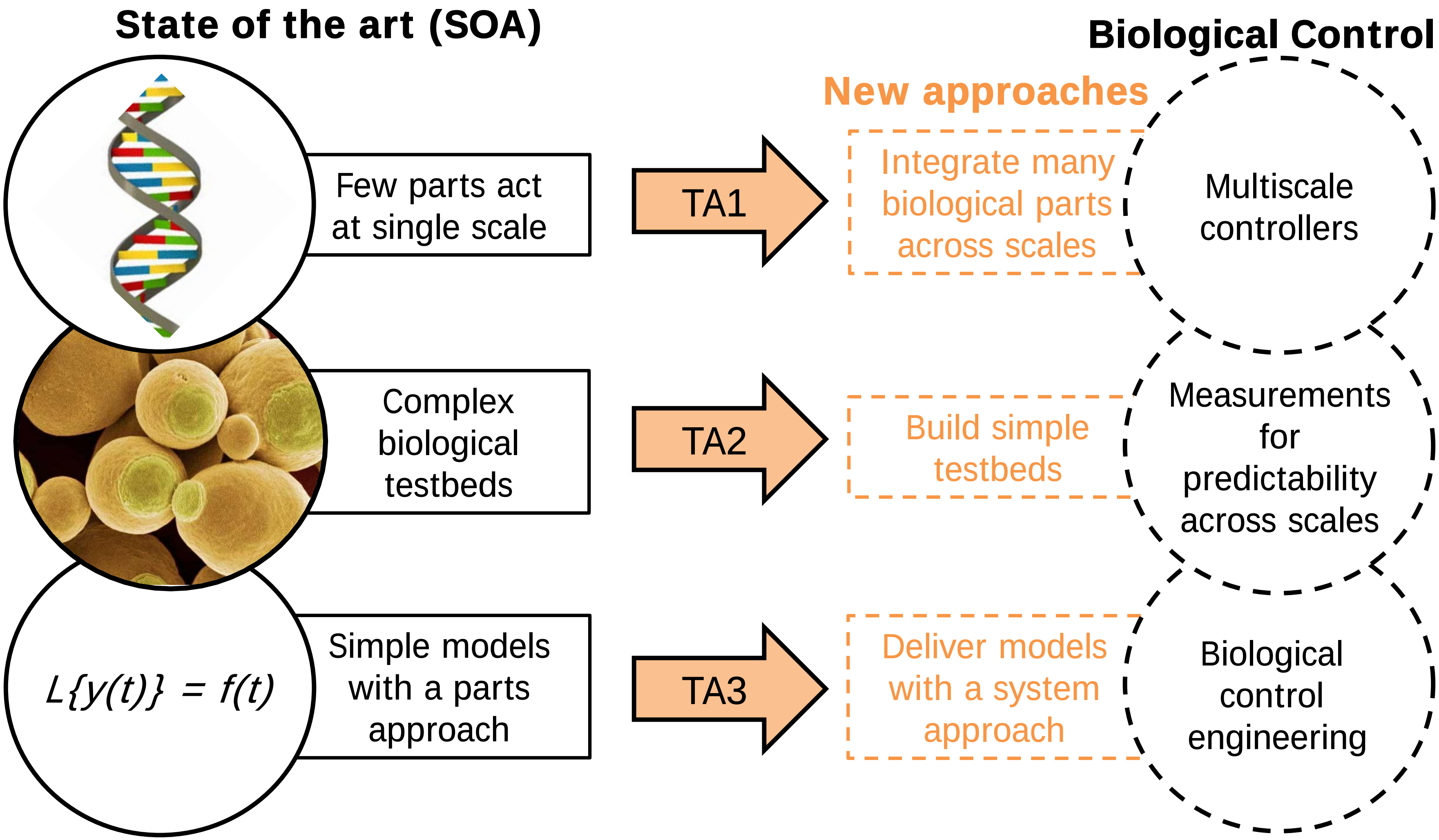


Adapted from Hasty *et al.* (2001)

Repressor: Autoregulating gene circuit that uses negative feedback to regulate rate of protein production

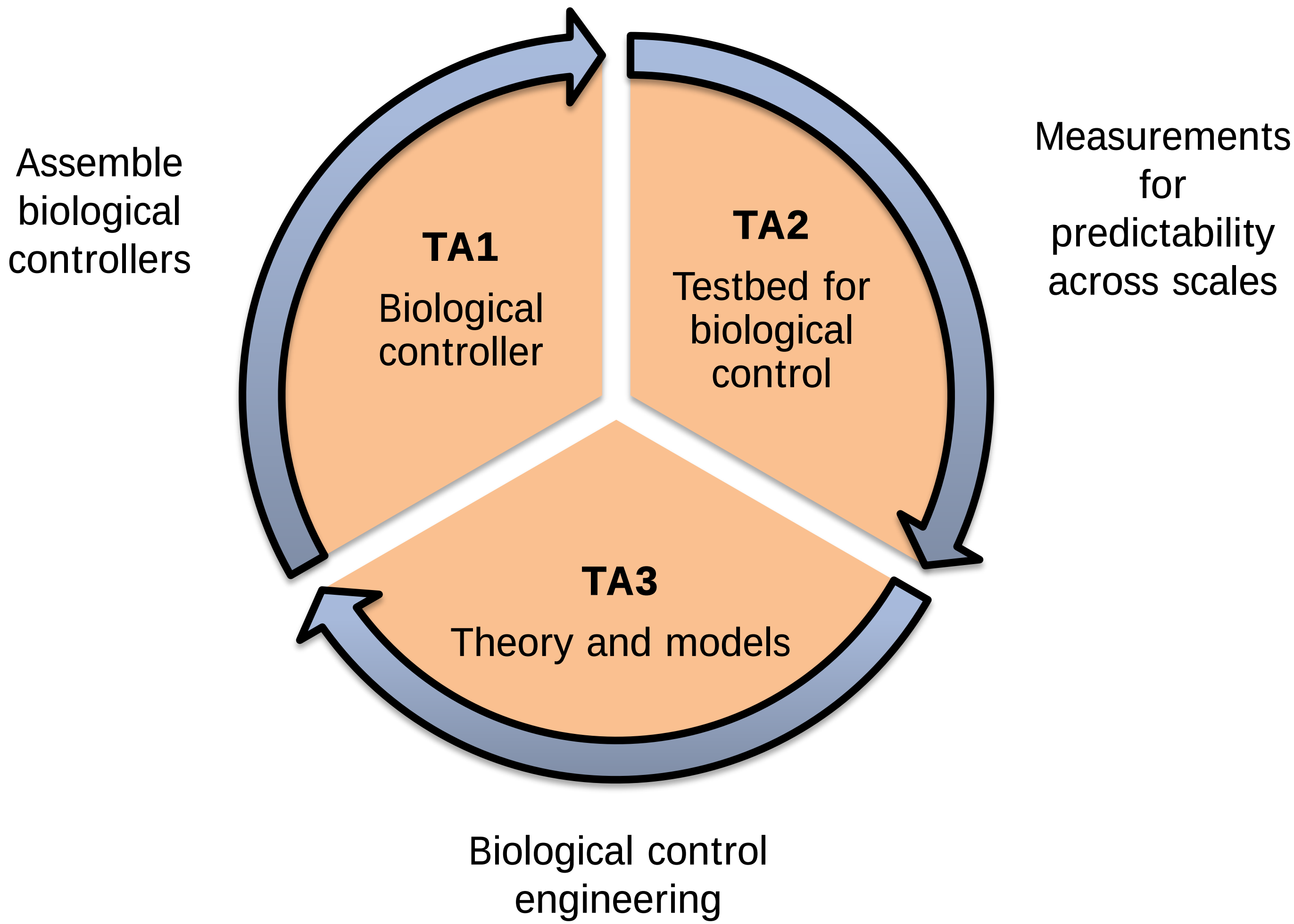
Existing control theory must be advanced to address the unique set of challenges presented by biological systems

Technical Areas

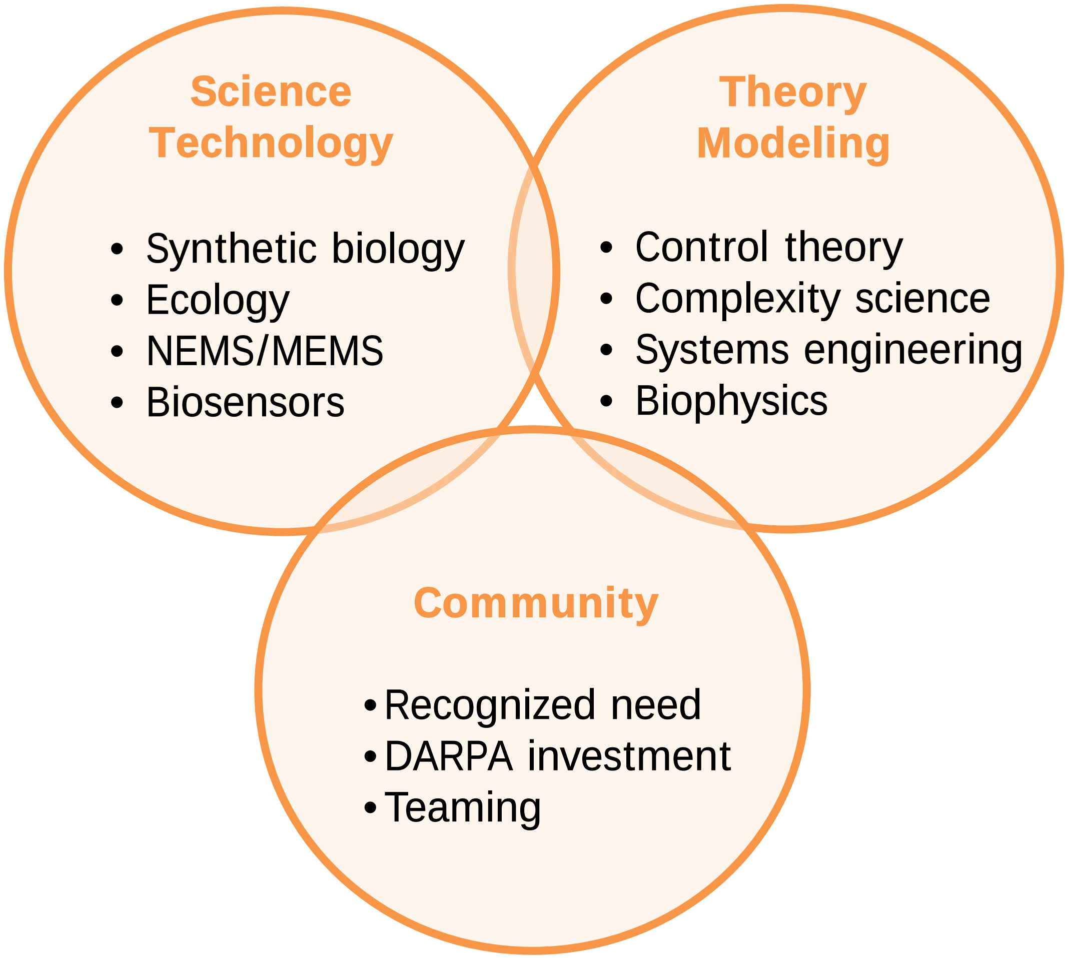


Deliver predictive, embedded biological controllers with tunable, multiscale output for rational design

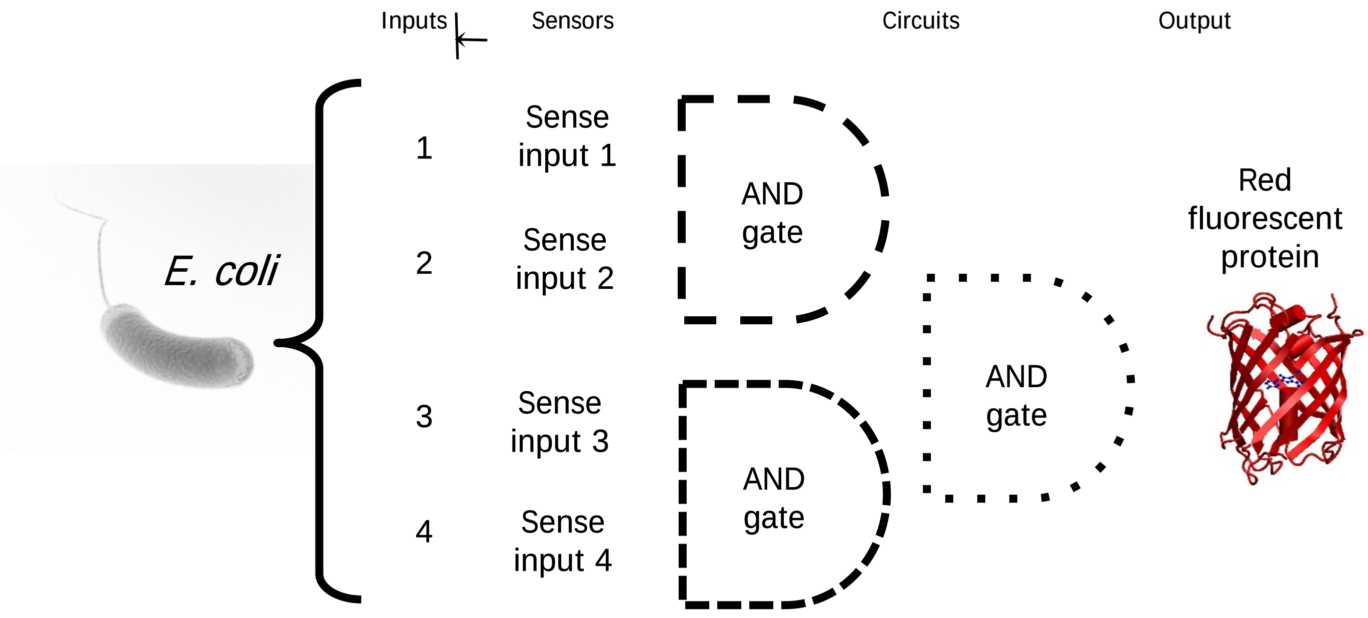
Integrated Technical Areas (TAs)



Community for biological control



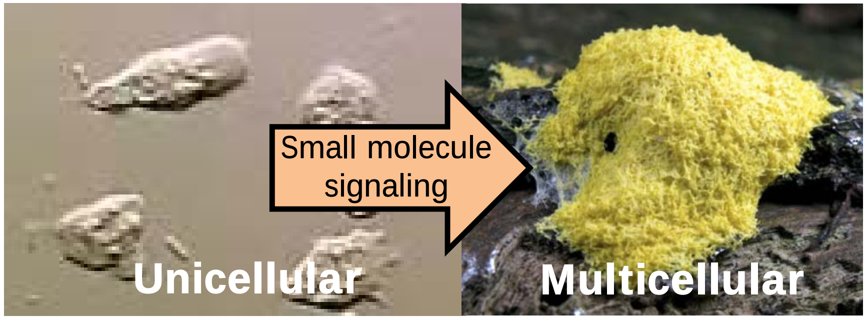
Integrated biological parts and multiscale signaling



Must sense all 4 inputs to generate response

Adapted from Moon *et al.* (2012)

Slime mold
Dictyostelium



Thomas Gregor

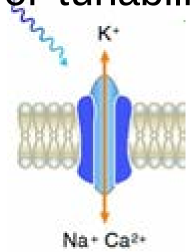
Integration exists to combine engineered signals but not coupled across scales to control system-level function

TA1 solution: Biological controllers

Example: Assemble controller for biofilm growth through selective cell death

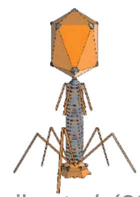
Genetic circuit for programmability

Optogenetics for tunability



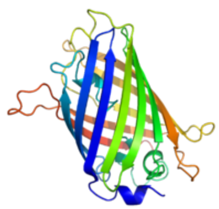
Rein & Deussing (2012)

Synthetic virus for intercellular signaling



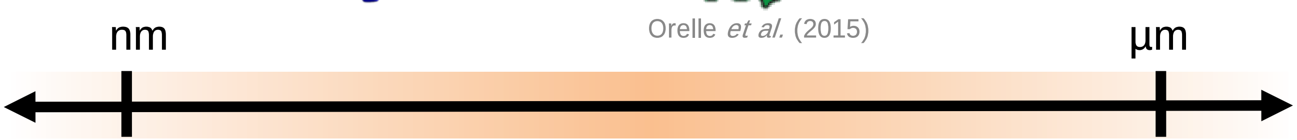
Citorik *et al.* (2014)

Fluorescent protein readout



Synthetic ribosome for modularity

Orelle *et al.* (2015)

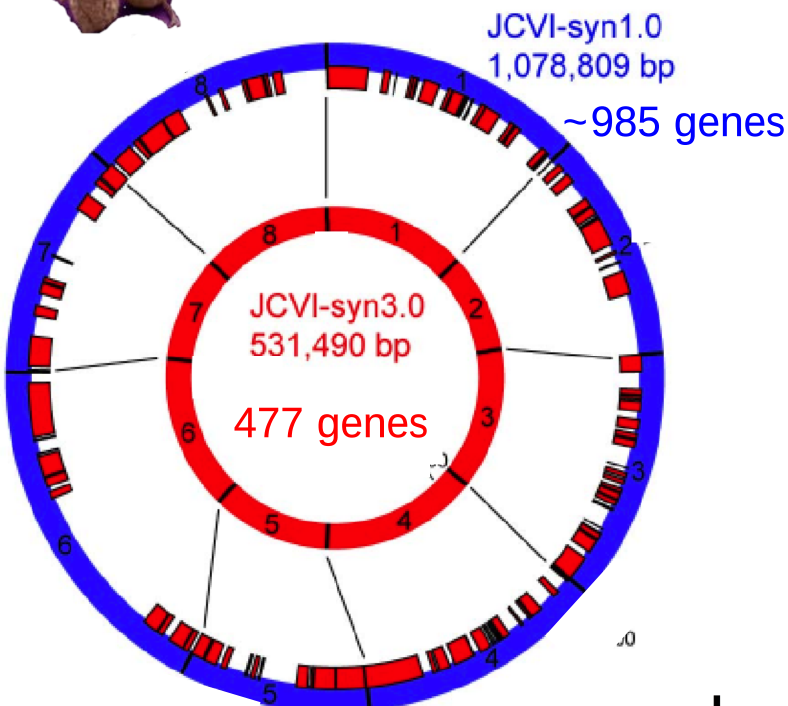


Integrate

Combine biological parts rationally for controlled function across scales

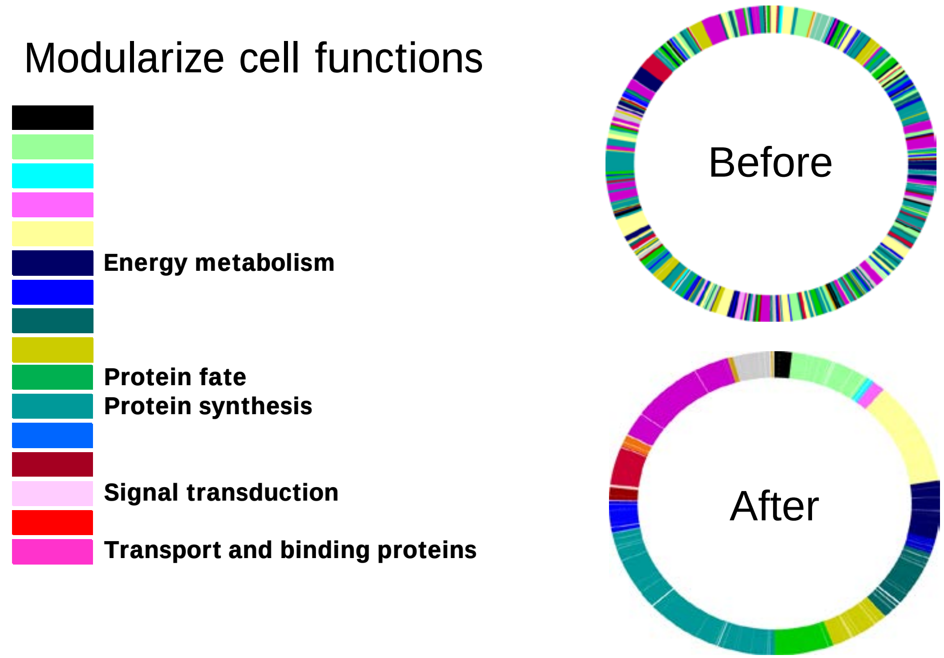
TA2 SOA: Genetically minimized cell testbed

M. mycoides



Genome reduced by half

Modularize cell functions



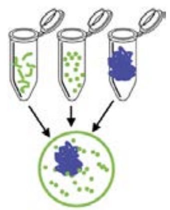
Minimized cell is simplest living testbed but does not allow study of larger-scale, multicellular functions

TA2 solution: Testbeds to measure biological control

Integrate

Example testbeds

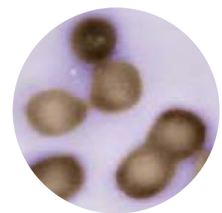
Cell-free system



Gibson (2014)

- Molecular scale
- Gain mechanistic understanding

Genetically minimized cell



© JCVI (2015)

- Cellular scale
- Connect genotype to phenotype

Hydra

© Yuste (2015)

- Organism scale
- Connect molecular to multicellular scales

Predict

Building tractable testbeds

- Experimental protocols
- Theoretical understanding
- Simplify to essential functions

Develop tractable lab-scale testbeds with controlled environments for high-quality measurements of controller function

TA3 SOA: Theory for rational design of control

Unbuffered: Load-dependent output

Signaling protein production

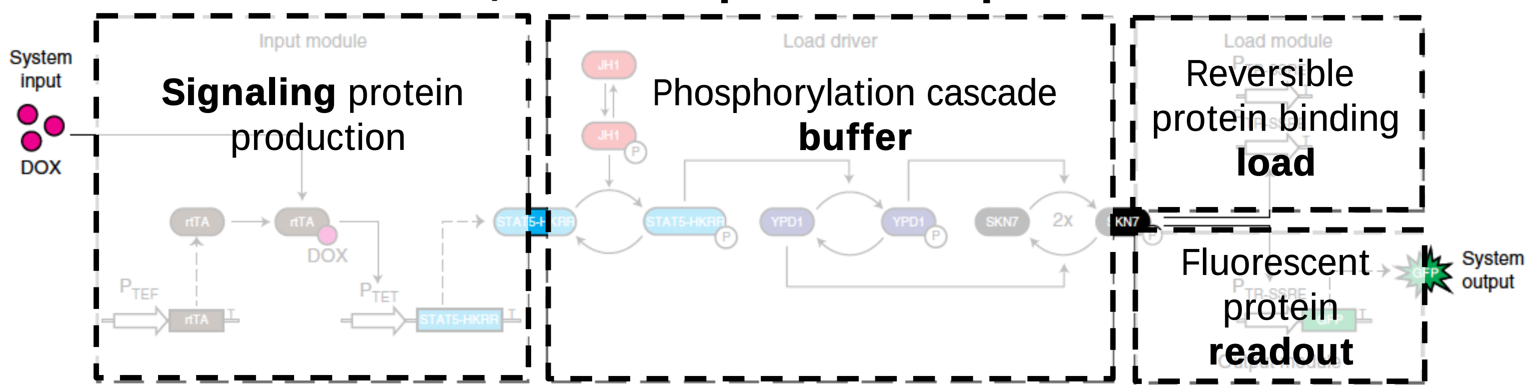
Reversible protein binding **load**

Fluorescent protein **readout**

Yeast

≤ 75 % lag in response time

Buffered: Predictable, load-independent output



Performance restored

Slow dynamics | **Fast dynamics** | **Slow dynamics**

Adapted from Mishra *et al.* (2014)

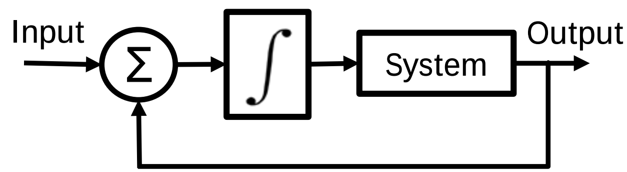
Adapting strategies from control theory aids predictability for rational design of control but has not been scaled-up

TA3 solution: Adapt existing control theory for controlled biological solutions to technological problems

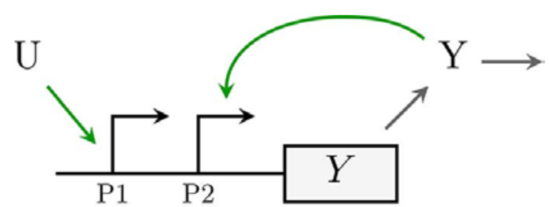
Predict

Example: Biological integrator for ideal adaptation to environmental change

Abstract control description



Biological description



Adapted from Harris *et al.* (2015)

Control

Translate variety of control strategies, *e.g.*
- Open-loop
- Closed-loop
- Feedback
- Feedforward

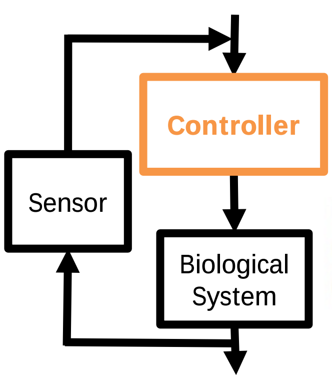
Control analysis
- Performance
- Stability
- Robustness

Develop theory and models to design a variety of biological controllers and evaluate controller function

Biological control using biological parts

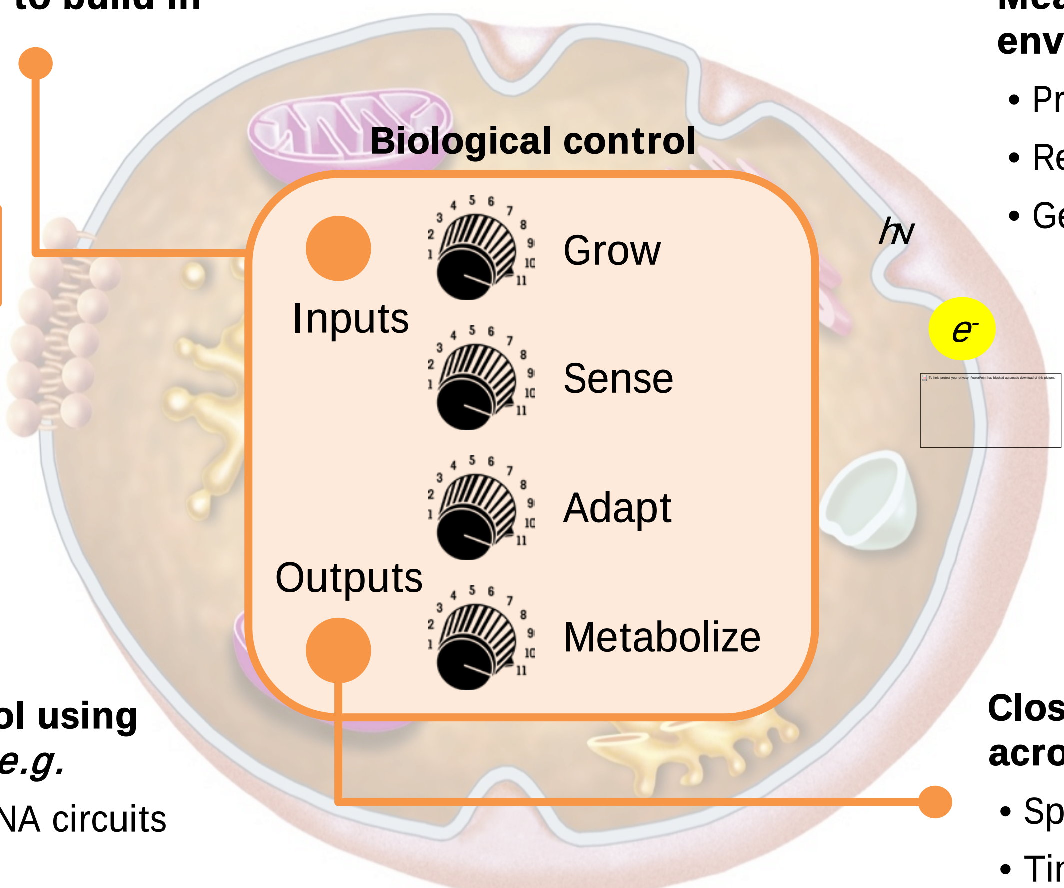
Enable the rational design of predictable, dynamic, and quantitative control for biological systems

Predictive theory to build in tunable control



Measurements and environmental control

- Predictability
- Reproducibility
- Generalizability



Biological or nonbiological inputs

Embedded control using biological parts, *e.g.*

- Synthetic DNA/RNA circuits
- Proteins
- Synthetic organelles/cells

Closed-loop control across scales

- Space
- Time
- Biological organization

Control Biological Systems Using Biological Parts

Foundations for multiscale control of biological systems

Inspired by conventional control engineering

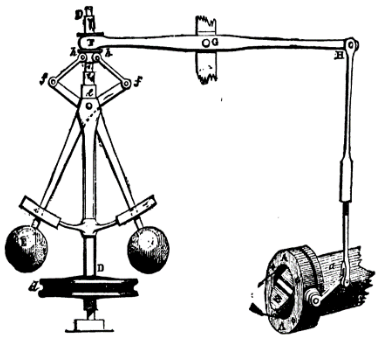
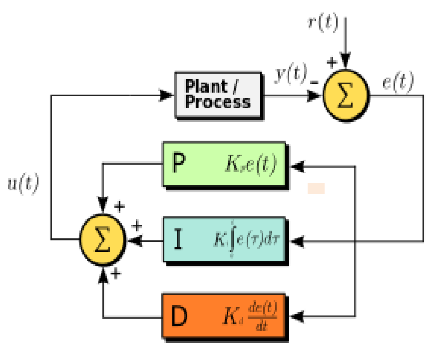
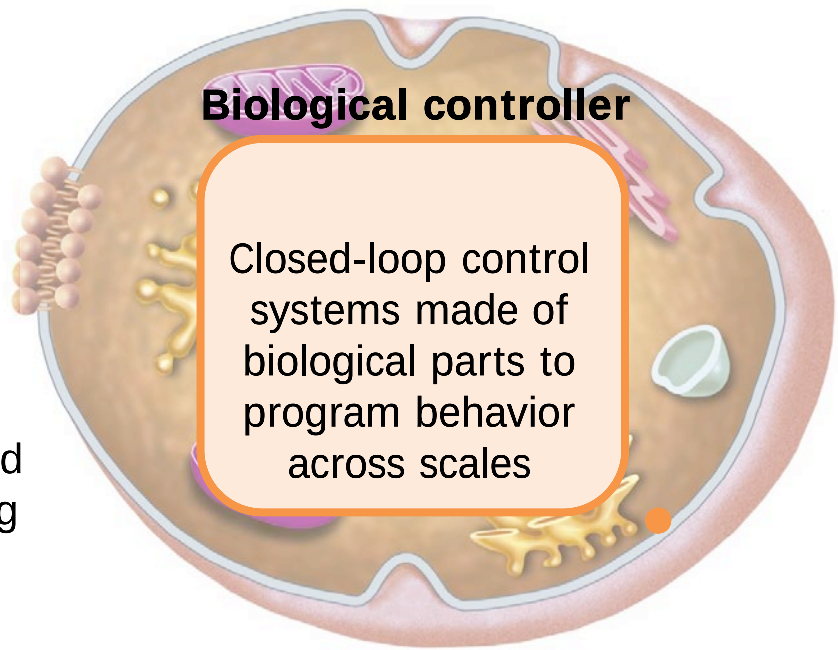


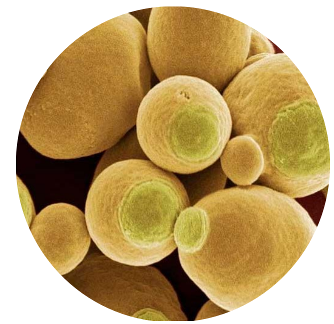
FIG. 4.—Governor and Throttle-Valve.

Grounded in theory and mathematical modeling





Characterized rigorously in simplified testbeds



Constructed from biological parts