AL-FARABI KAZAKH NATIONAL UNIVERSITY FACULTY OF BIOLOGY AND BIOTECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY

INTRODUCTION TO BIOLOGICAL ENGINEERING

LECTURE 9.
ENGINEERING ANALYSIS OF BIOLOGICAL SYSTEMS:
CONCEPTUAL ANALYSIS AND SYSTEM-LEVEL REASONING

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Lecture Plan

1. System decomposition
2. Functional architecture
3. Interactions and feedback
4. Constraints
5. Failure modes
6. Robustness
7. Trade-offs
8. Decision matrices
9. Case analyses
10. Synthesis

Learning Outcomes

By the end of this lecture, students should be able to:

LO1 Decompose a biological engineering system into functional subsystems.

LO2 Identify interfaces, feedback loops and dominant constraints.

LO3 Compare design alternatives using explicit criteria.

LO4 Explain trade-offs between performance, safety, cost and complexity.

LO5 Produce a structured conceptual engineering analysis of a biotechnological system.

LO6 Use the concepts to structure a simple biotechnology case analysis.

Conceptual engineering analysis

Conceptual analysis evaluates how a system is organized, what functions each part performs and where constraints or failure modes arise.

It organizes the system into **functions, components, interactions and operating conditions** without requiring a complete mathematical model.

The analysis identifies **critical dependencies, constraints, interfaces and possible failure modes** that may affect overall system performance.

It distinguishes between **normal operation, disturbances and abnormal conditions**, helping engineers understand where the system may become vulnerable.

Conceptual analysis is especially useful during **early design**, when detailed experimental data or reliable parameter estimates may still be limited.

The goal is to identify **leverage points**—parts of the system where a relatively small intervention could produce a large improvement in performance, safety or reliability.

The resulting model provides the basis for deciding **what should be measured, tested, quantified or redesigned next**.

SYSTEM PURPOSE

What must the system achieve?

↓

FUNCTIONS & STRUCTURE

components • interactions • interfaces

↓

CONSTRAINTS & DEPENDENCIES

capacity • resources • operating limits

↓

FAILURE MODES / RISKS

What can go wrong?

↓

LEVERAGE POINTS

Where can intervention have the greatest effect?

↓

ENGINEERING DECISION

measure • test • redesign • control

Functional decomposition

Break the system into subsystems according to function rather than academic discipline.

Begin with the **overall system function** — the main outcome the process must deliver.

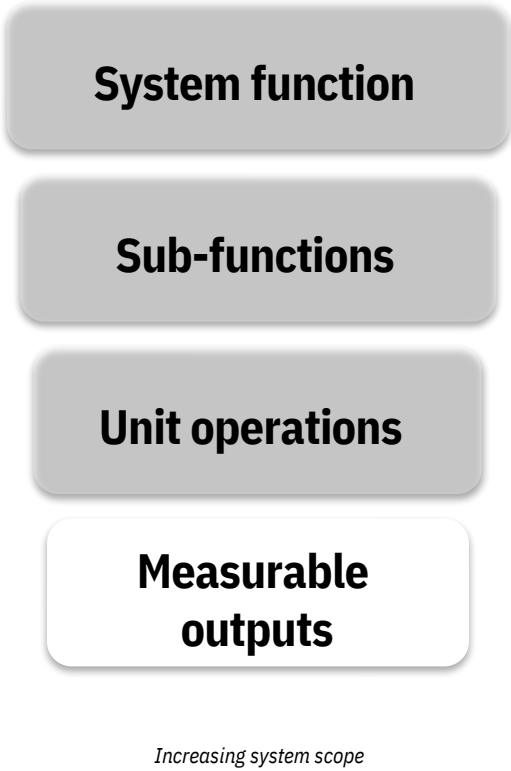
Divide this function into **sub-functions**, such as feed preparation, biological conversion, gas management, product recovery, purification and process control.

Each sub-function can then be linked to specific **unit operations, equipment or biological mechanisms** that perform the required task.

For every subsystem, define its **inputs, outputs, capacity, operating conditions and measurable performance indicators**.

Functional decomposition also reveals important **interfaces and dependencies** between subsystems, where limitations or failures may propagate through the whole process.

The level of detail should be sufficient to identify **bottlenecks, constraints and failure modes** without introducing unnecessary complexity.



Interfaces

An interface is where materials, information, energy or responsibility pass between subsystems. Interfaces connect subsystems that may each work well individually but still perform poorly when they interact.

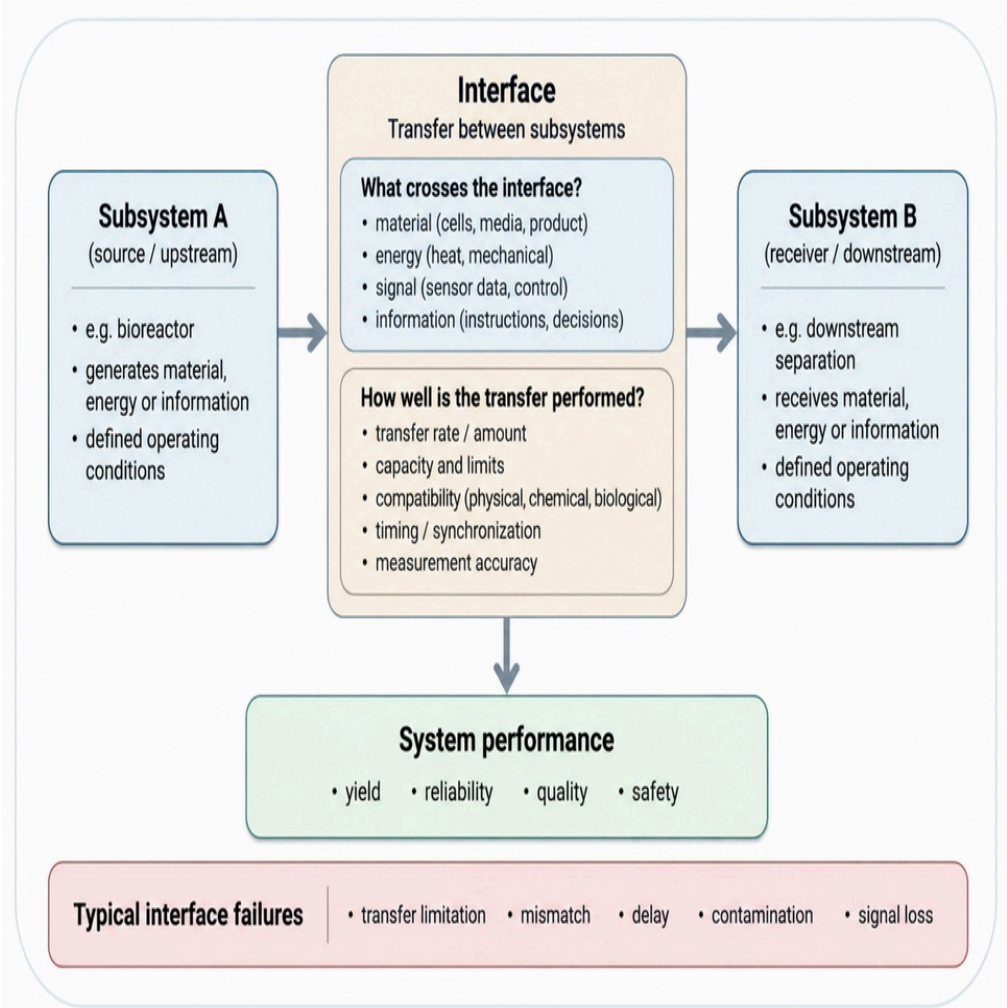
Important interfaces in biological engineering include **cell–medium, gas–liquid, upstream–downstream, tissue–device and sensor–user interfaces**.

Each interface should be characterized by what crosses it: **material flow, signal, energy, force or information**.

Interface performance depends on properties such as **transfer rate, compatibility, capacity, timing and measurement accuracy**.

Many failures arise from **mismatch between subsystems**, for example insufficient oxygen transfer, poor product secretion, contamination during transfer or incompatible data formats.

Interface specifications should therefore define **what is transferred, how much, how fast and under which acceptable conditions**.



Dependency structure

Some functions are serial: if an upstream step fails, downstream steps cannot recover performance.
Some dependencies are **serial**: if an upstream step fails or underperforms, downstream operations may be unable to recover the lost performance.

Resource dependencies arise when several functions compete for limited oxygen, nutrients, equipment capacity, energy or operator time.

Information dependencies occur when downstream actions require accurate measurements, control signals or decisions from another subsystem.

Quality dependencies link early process conditions to later product quality; poor upstream control may create defects that cannot be removed during downstream processing.

Parallel pathways, backup equipment and alternative information sources can provide **redundancy and resilience** when critical dependencies fail.

Mapping dependencies helps identify **single points of failure, cascading effects and opportunities for redundancy or additional monitoring**.



Feedback loops

Feedback can stabilize pH, oxygen, gene expression or population size.

A feedback loop requires a **measurable process variable**, a desired **set point**, a comparison step and an actuator capable of changing system behaviour.

In biological engineering, feedback can regulate variables such as **pH, dissolved oxygen, temperature, substrate concentration, gene expression or cell density**.

Negative feedback counteracts deviations and generally stabilizes the system around a target operating condition.

Positive feedback reinforces deviations and can create amplification, switching behaviour or rapid transitions between system states.

Effective control depends on **measurement accuracy, actuator capacity, response time and process delay**; slow feedback may lead to overshoot or oscillations.

Disturbances such as changes in feed composition, biomass concentration or environmental conditions are detected indirectly through their effect on the measured variable.

SET POINT

desired pH / O_2 / temperature

↓

COMPARE

target – measured value

↓

CONTROLLER / ACT

adjust feed • aeration • heating

↓

BIOLOGICAL SYSTEM

process response

↓

MEASURE

sensor output

Constraints taxonomy

Biological constraints: growth, toxicity, resource allocation and evolution.

Biological constraints arise from the living system itself and include growth rate, toxicity, metabolic burden, genetic stability, evolution and cell-to-cell variability.

Physical constraints are imposed by transport and material properties, such as oxygen transfer, diffusion, heat removal, mixing, shear stress and available space.

Process and operational constraints include equipment capacity, cycle time, sterility, sampling frequency, cleaning requirements and operator workload.

External constraints arise outside the process and may include cost, regulation, supply-chain availability, biosafety, ethical requirements and environmental impact.

Constraints may be **hard limits**, which cannot be exceeded, or **soft limits**, where operation is technically possible but leads to poorer cost, quality or reliability.

Identifying constraints early prevents optimization toward operating conditions that are **biologically unrealistic, physically impossible or operationally unacceptable**.

Aspect	Engineering meaning
Biological	Growth, toxicity, stability, variability
Physical	Transport, heat, mixing, mechanics
Process	Equipment, cycle time, sterility Cost, regulation,
External	supply chain, ethics

Hard versus soft constraints

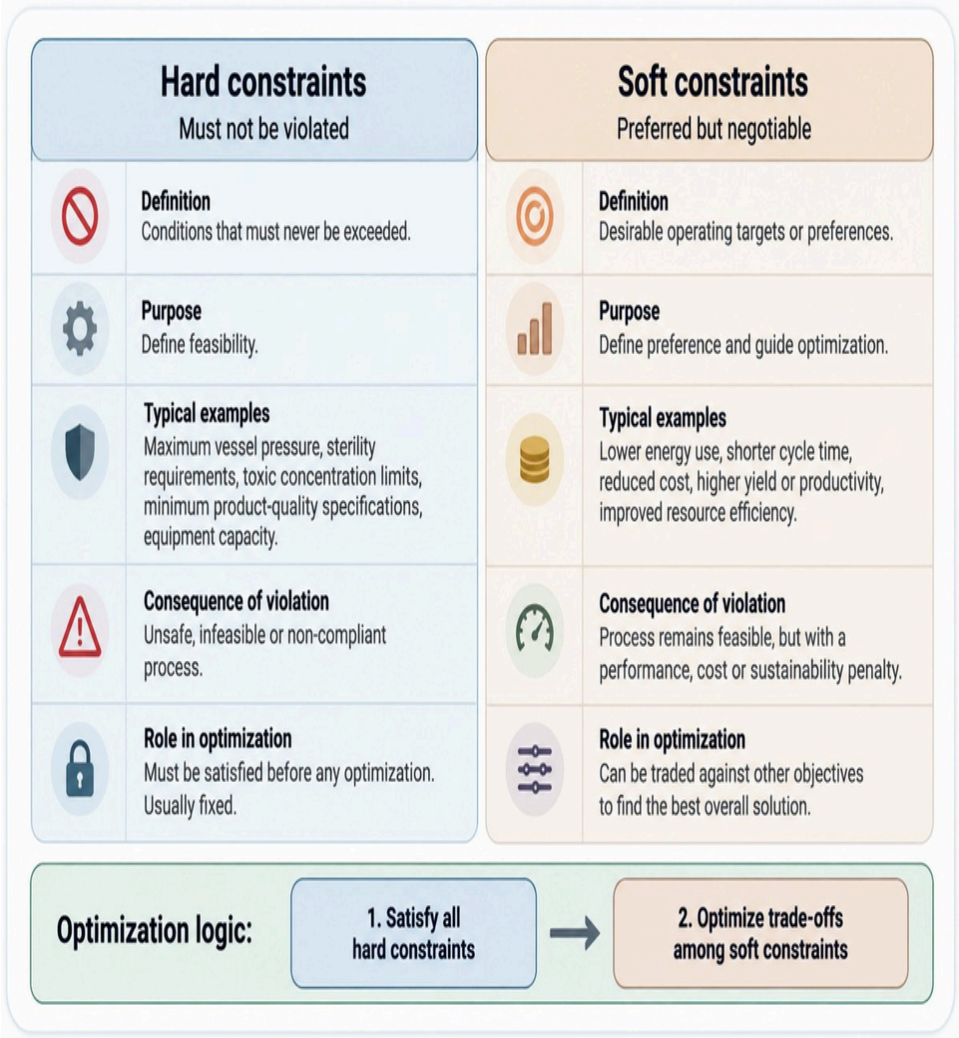
Hard constraints cannot be violated, such as maximum pressure or sterility requirements.

Hard constraints determine whether a design or operating condition is feasible at all and usually arise from safety, physical, biological or regulatory limits. Examples include **maximum vessel pressure, sterility requirements, toxic concentration limits, minimum product-quality specifications and equipment capacity**.

A hard constraint cannot be exceeded without making the process **unsafe, infeasible or non-compliant**. **Soft constraints** describe desirable operating targets such as lower energy use, shorter cycle time, reduced cost or improved resource efficiency.

Soft constraints can be traded against other objectives when the overall system benefits from a different compromise.

Correctly separating hard and soft constraints is essential for realistic optimization because otherwise the model may propose an apparently optimal but **unacceptable operating point**.



Failure-mode analysis

List how each function can fail, what causes the failure and how it affects system outputs.

Begin by asking **what can fail** at each subsystem, interface or operating step.

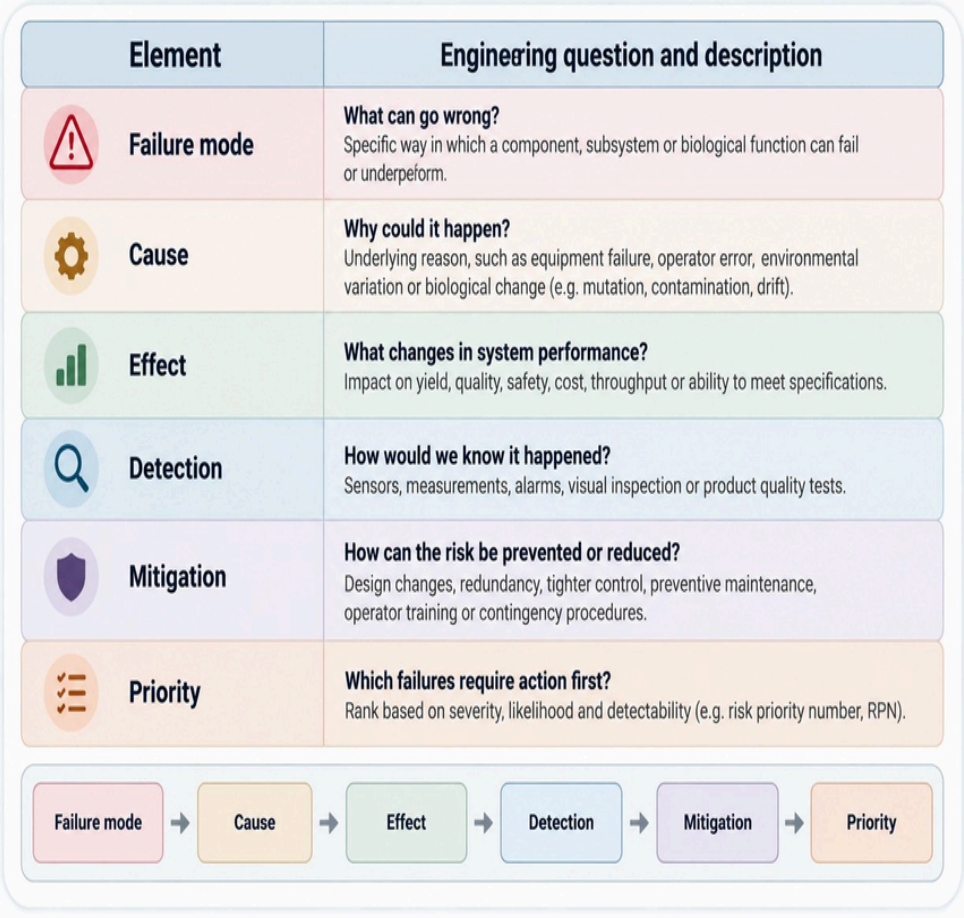
Identify the **cause** of each failure, including equipment malfunction, operator error, environmental disturbance or biological change.

Evaluate the **effect** on system performance, such as reduced yield, contamination, loss of quality, unsafe operation or complete process failure.

Biological systems introduce additional failure modes such as **mutation, phenotype drift, contamination, loss of viability and physiological adaptation**.

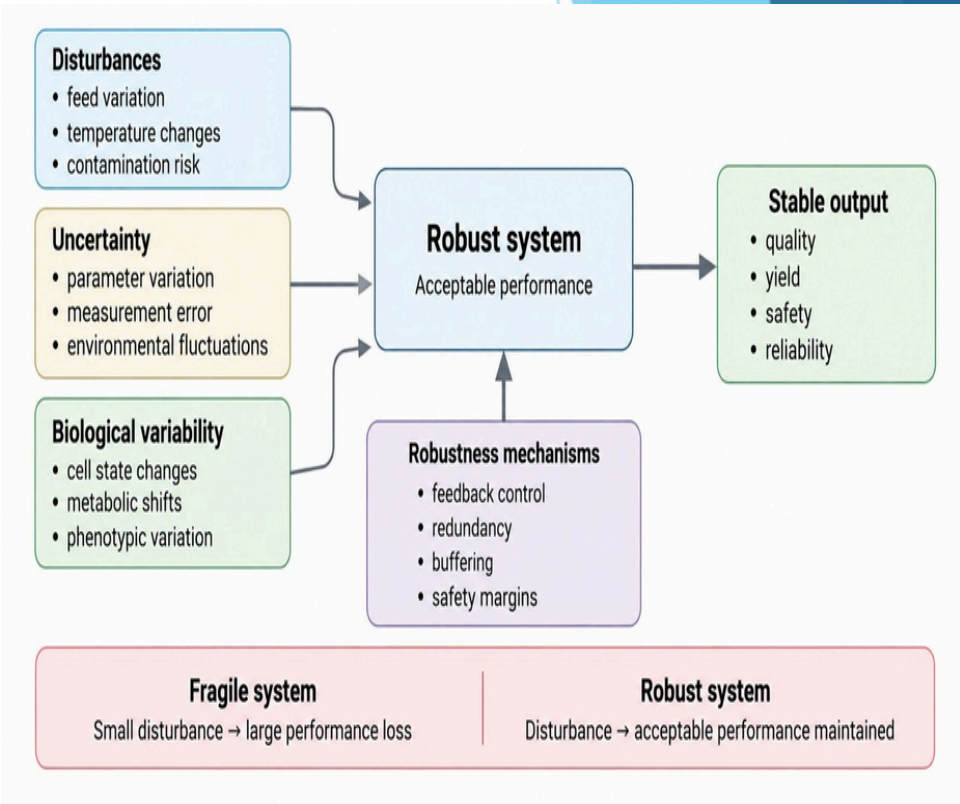
Failure modes should be prioritized according to their **severity, likelihood and detectability**, so engineering effort is focused on the most important risks.

Risk reduction may involve **design changes, redundancy, monitoring, alarms, preventive maintenance or tighter process control**.



Robustness

Robustness is the ability to maintain acceptable function despite disturbances and uncertainty.
A robust system continues to meet its essential performance requirements even when **inputs, environmental conditions or biological states vary**.
Disturbances may include **feed variability, temperature shifts, sensor noise, changes in biomass, raw-material variation or operator error**.
Robustness can be improved through **feedback control, redundancy, buffering, safety margins and conservative operating windows**.
A fragile design may achieve higher peak performance under ideal conditions but lose quality, stability or throughput when conditions change.
Robustness should therefore be evaluated across a **range of plausible operating conditions**, not only at one nominal point.
The engineering goal is to achieve **consistent and acceptable performance**, even if this requires sacrificing some theoretical maximum performance.



Resilience

Resilience emphasizes recovery after disturbance rather than resistance to disturbance.

A resilient system may temporarily lose performance after a disturbance but can **recover, reorganize or adapt** instead of remaining in a failed state.

Resilience differs from robustness: **robustness limits performance loss**, whereas resilience focuses on **recovery after the loss has occurred**.

Biological systems may support resilience through **repair, adaptation, population renewal, metabolic flexibility or regulatory feedback**.

Engineering resilience can also be improved through **redundancy, backup pathways, recovery protocols and flexible operating strategies**.

Important resilience metrics include **maximum performance loss, recovery time, recovery rate and residual performance after recovery**.

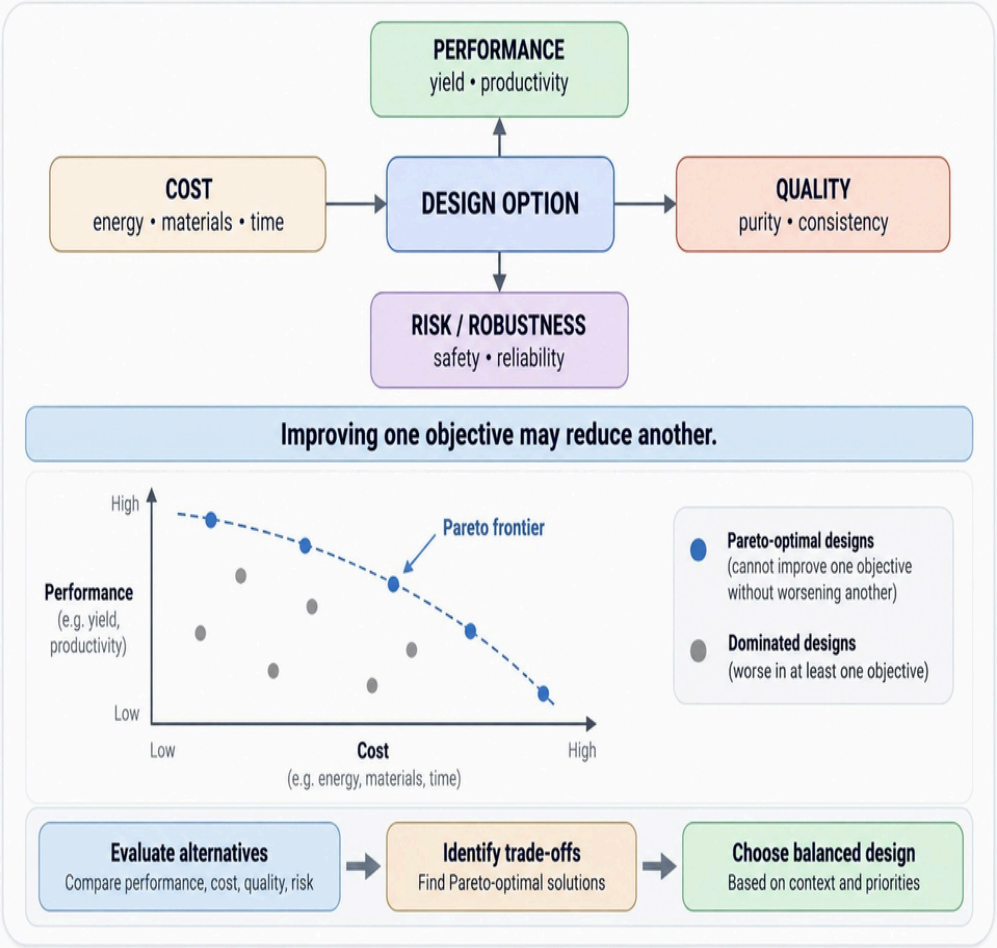
Recovery does not always mean returning to the exact original state; the system may reach a **new stable operating condition** that still satisfies performance requirements.



Trade-offs

Improving productivity may increase metabolic burden; stronger mixing may increase shear; tighter purification may reduce recovery.

- Engineering analysis makes trade-offs explicit rather than treating them as unexpected side effects.
- Pareto frontier: improving one objective increasingly sacrifices the other
- Pareto thinking identifies alternatives where no objective can be improved without worsening another.
- Decision-makers can then choose based on context and priorities.
- DECISION RULE Decision tools make trade-offs explicit by comparing alternatives against weighted criteria, but the result is only as defensible as the criteria, weights and...



Decision matrices

PRACTICAL INTERPRETATION Decision tools make trade-offs explicit by comparing alternatives against weighted criteria, but the result is only as defensible as the criteria, weights and uncertainty assumptions used to construct the...

Start by defining the **decision alternatives** that are being compared, for example different reactor designs, control strategies or purification methods.

Select a small set of relevant criteria such as **performance, product quality, risk, cost, robustness and implementation complexity**.

Assign each criterion a **weight** according to its importance for the specific engineering decision.

Each alternative is then **scored using the same scale**, and the score is combined with the criterion weight to obtain a weighted result.

The matrix makes trade-offs visible: one option may offer higher performance but also higher **cost, risk or operational complexity**.

The final result should not be treated as automatically correct; conclusions depend on the **criteria, weights, scoring assumptions and uncertainty** used in the analysis.

Aspect	Engineering meaning
Criterion	Example weight / question
Performance	Does the option meet the technical target?
Risk	How vulnerable is it to failure or variability?
Cost / complexity	What resources and infrastructure are required?

Evidence levels

Conceptual analysis should distinguish direct measurements, literature-based assumptions, expert judgment and unknowns.

Mechanistic rationale is based on established biological or physical principles and explains why a relationship is expected to occur.

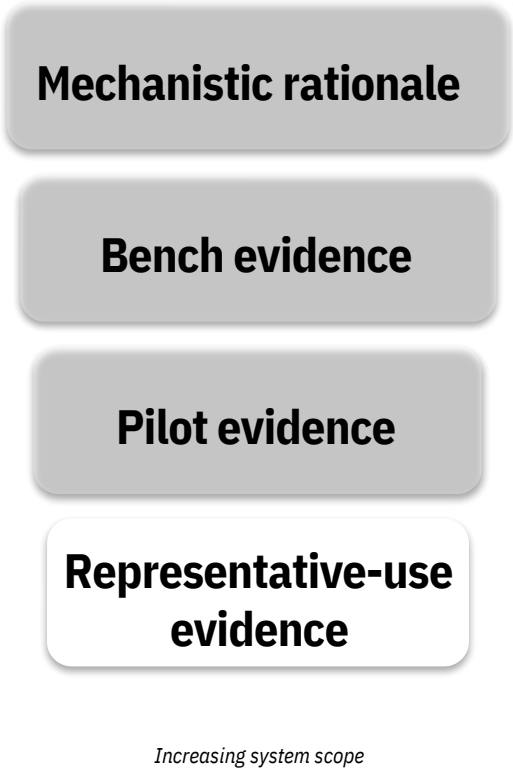
Literature evidence provides previously reported observations or parameter ranges, but its relevance depends on whether the experimental system and conditions are comparable.

Bench-scale evidence directly tests the concept under controlled laboratory conditions and can establish feasibility and basic mechanism.

Pilot-scale evidence evaluates whether performance is maintained when scale, transport limitations, variability and process complexity increase.

Representative-use evidence tests the system under conditions close to its intended real-world application and provides the strongest support for practical performance claims.

Expert judgment and unresolved assumptions should be labelled explicitly, especially when they influence high-impact engineering decisions.



Case: choosing a microbial host

Alternatives can be compared on growth rate, secretion, product modification, substrate use, tolerance and regulatory history.

A suitable host must support the **required product and production pathway**, not simply achieve the highest growth rate.

Growth and robustness determine whether the organism can tolerate substrate concentration, temperature, oxygen limitation, metabolic burden and other process stresses.

Genetic tractability affects how reliably genes, pathways and regulatory systems can be introduced and controlled.

Product requirements may strongly influence host choice because different organisms differ in **protein folding, secretion, post-translational modification and by-product formation**.

Manufacturing factors such as **scale-up behaviour, contamination risk, downstream processing and regulatory history** can be as important as biological productivity.

Therefore, host selection should be based on a **decision matrix or weighted criteria**, rather than a universal ranking of organisms.

Aspect	Engineering meaning
Growth / robustness	Can the host tolerate the intended process?
Genetic tractability	Can the desired pathway be engineered reliably?
Product quality	Can required folding / modification be achieved?
Manufacturing history	Are scale-up and regulation well characterized?

Case: upstream-downstream co-design

Increasing upstream titer may alter impurity profile and make downstream purification more difficult.
Upstream decisions determine not only **product titer**, but also cell density, impurity profile, product localization and broth properties.

Higher expression or biomass may increase product concentration while also increasing **cell debris, host-cell proteins, viscosity or aggregation**.

Product localization strongly affects recovery: **secreted products** may simplify harvest, whereas intracellular products require cell disruption and additional clarification.

Downstream operations must therefore be considered when selecting **host, expression strategy, cultivation conditions and harvest point**.

A process with slightly lower upstream titer may still achieve better overall performance if it provides **higher recovery, simpler purification and lower manufacturing cost**.

Co-design evaluates the **whole process**, rather than optimizing upstream and downstream unit operations independently.

UPSTREAM DESIGN
host • expression • medium • cultivation
↓
affects
BROTH / PRODUCT STATE
titer • localization • impurities • viscosity
↓
HARVEST & CLARIFICATION
cell removal • lysis • debris removal
↓
PURIFICATION
capture • polishing
↓
FINAL PRODUCT
recovery • purity • quality • cost

Case: biosensor deployment

A biosensor is a system, not only a recognition molecule.

Real-world biosensor performance depends not only on the recognition element, but also on **sample collection, preparation, storage and matrix composition**.

Complex samples may contain **interfering compounds, inhibitors or background signals** that reduce sensitivity or specificity compared with controlled laboratory conditions.

The sensor must convert biological recognition into a **stable and calibrated measurable signal** that can be interpreted consistently.

Practical deployment also requires suitable **response time, portability, maintenance, storage stability and ease of use**.

User interpretation is part of the system: an accurate signal can still lead to an incorrect decision if **thresholds, calibration or instructions are unclear**.

Therefore, biosensor performance should be evaluated using **sensitivity, specificity, limit of detection, response time, robustness and decision accuracy under representative-use conditions**.

REAL SAMPLE
matrix • contaminants • variability
→
SAMPLE HANDLING
collection • preparation • storage
→
BIOSENSOR
recognition • transduction
→
SIGNAL PROCESSING
amplification • calibration
→
USER / DEVICE
display • threshold • interpretation
→
DECISION
positive / negative / concentration

Case: tissue scaffold

Mechanical properties must be sufficient to support the target tissue, but excessive stiffness or crosslinking can restrict cell spreading and matrix remodeling.

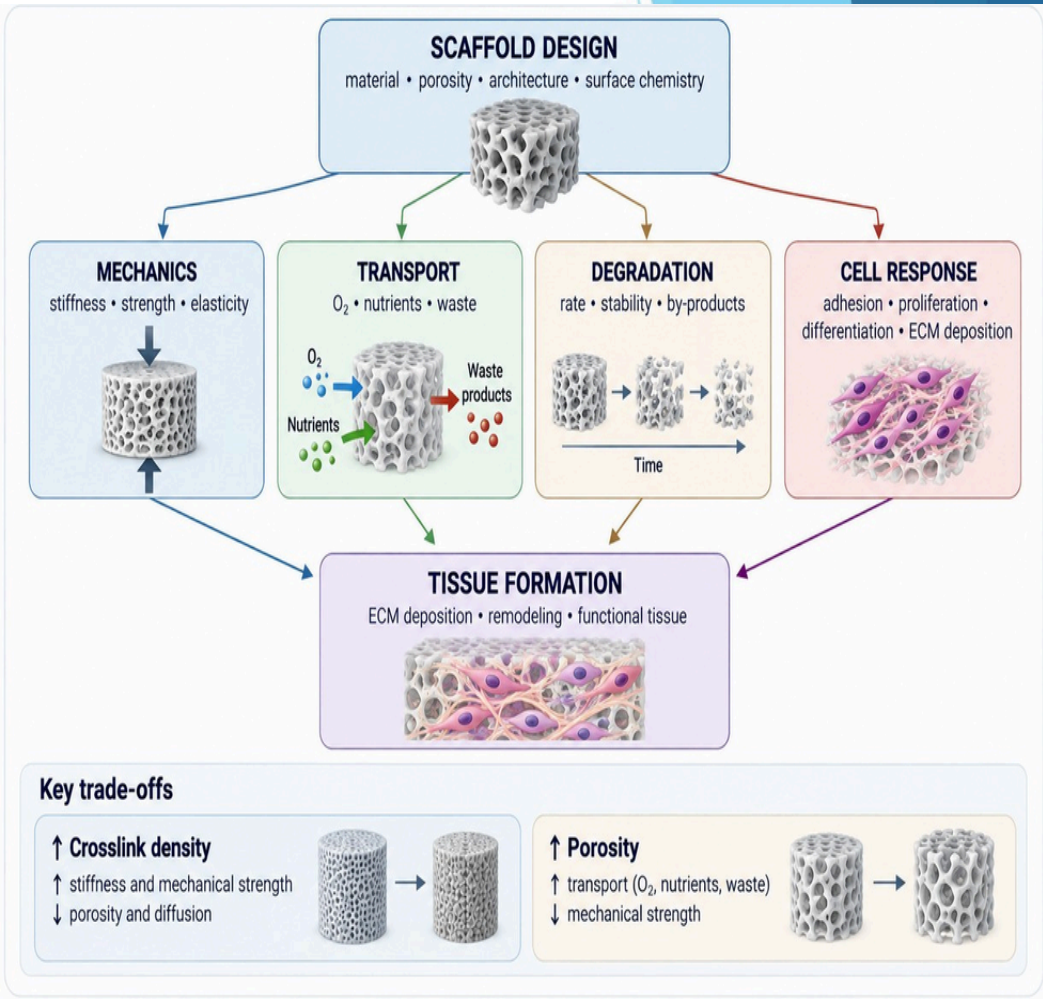
Transport properties determine how efficiently oxygen, nutrients and metabolic waste move through the scaffold.

Scaffold architecture, including **porosity and pore connectivity**, affects both diffusion and cell migration.

Surface chemistry and biological cues influence **cell adhesion, proliferation, differentiation and extracellular-matrix deposition**.

Degradation rate should be coordinated with new tissue formation: degradation that is too fast can cause loss of support, while degradation that is too slow can interfere with remodeling.

Scaffold design therefore requires balancing several competing properties rather than maximizing a single parameter.



Case: environmental release

An engineered microbe may perform well in a laboratory but face competition, predation and environmental variability in the field.

An engineered organism may perform well in the laboratory but behave differently in the field because of **competition, predation, nutrient limitation and environmental variability**.

Risk assessment must consider whether the organism can **survive, persist, multiply or spread beyond the intended site**.

Important concerns include **horizontal gene transfer, unintended ecological interactions and effects on non-target organisms or microbial communities**.

Environmental applications therefore require **monitoring, containment strategies and predefined responses** if the organism behaves outside the intended operating range.

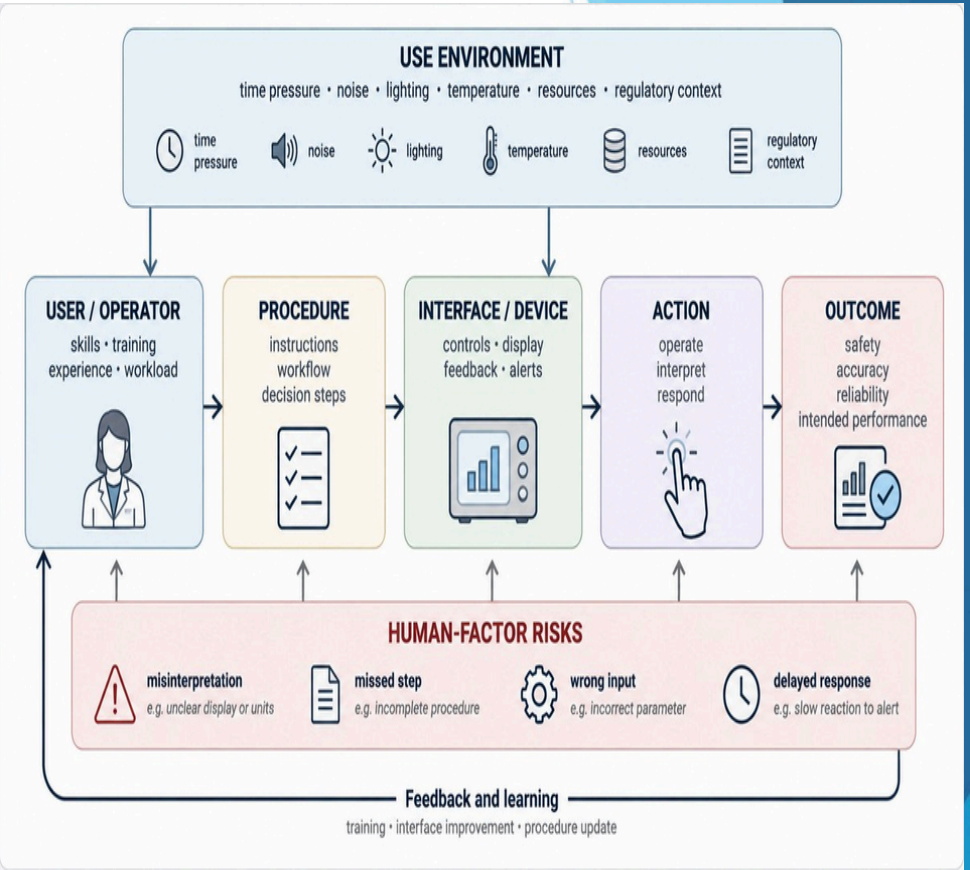
The design should consider **reversibility and controllability**, including whether activity can be reduced, stopped or contained after deployment.

Open-system applications require a broader system boundary than closed bioreactors because the surrounding ecosystem becomes part of the engineering context.

ENGINEERED ORGANISM
designed function
→
ENVIRONMENTAL EXPOSURE
soil / water / field conditions
→
SURVIVAL & PERSISTENCE
growth • adaptation • competition
→
SPREAD / INTERACTIONS
dispersal • gene transfer • non-target effects
→
MONITORING & RISK MANAGEMENT
containment • detection • response

Human factors

Operators, clinicians, farmers or end users are part of many biological engineering systems.
Operators, clinicians, technicians, farmers and end users may directly affect **system performance, safety and decision quality**.
Complex workflows increase **training requirements, cognitive load and the probability of operational error**.
Interface design should support clear actions, understandable feedback and appropriate **decision thresholds**.
Human-factor analysis considers **usability, training, maintenance, communication, workload and error recovery**.
A technically strong device or process may still fail in practice if instructions are unclear, controls are confusing or the workflow is too complex.
The intended user and use environment should therefore be included in **system design, validation and risk assessment from the beginning**.



Economic structure

Cost drivers may include raw materials, capital, labor, utilities, failure rate, purification and quality control.

Major cost drivers may include **raw materials, media, utilities, labor, equipment, quality control, purification and waste handling**.

Some costs are mainly **fixed**, such as capital equipment and facility infrastructure, while others increase with production volume or batch number.

Poor yield or recovery can increase cost because more **raw material, reactor time and downstream processing** are required per unit of final product.

Batch failure, contamination or reprocessing can strongly increase cost because they consume materials, labor and equipment capacity without producing saleable product.

Downstream purification may become a major economic burden when the product is dilute, unstable or mixed with many impurities.

Economic optimization should therefore focus on variables with the greatest effect on **total cost of goods**, rather than maximizing biological yield alone.

Sustainability structure

Environmental burden can shift between subsystems-for example from lower feedstock impact to higher purification energy.

Sustainability assessment considers **materials, energy, water, emissions, waste and resource efficiency** across the entire process.

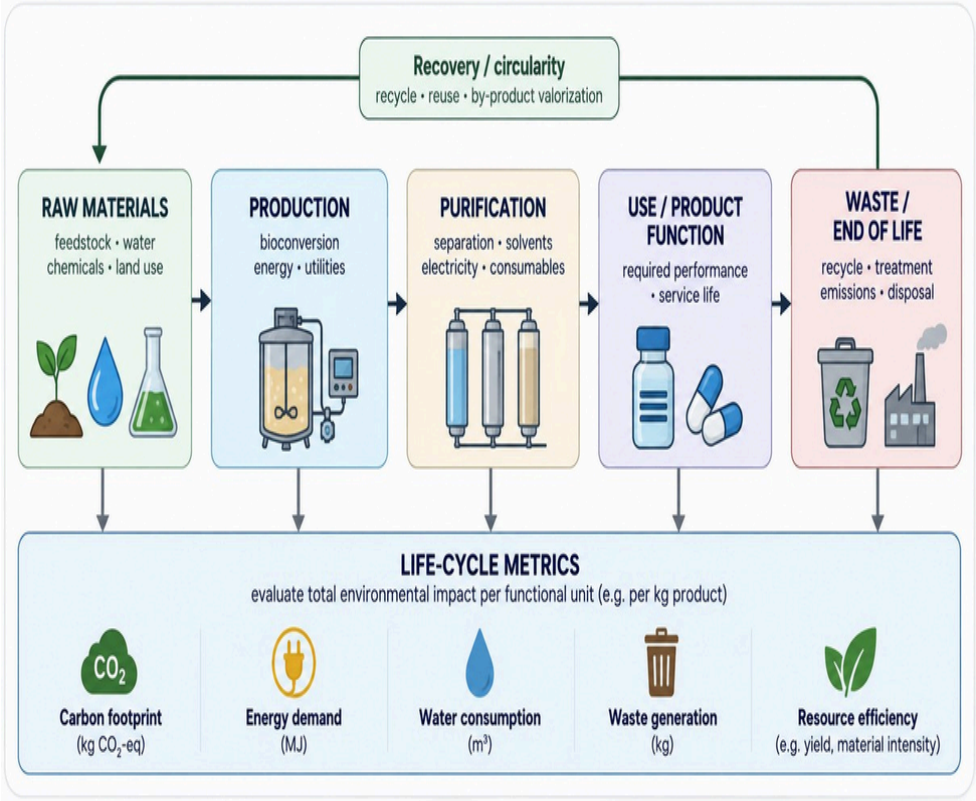
A biological route is not automatically more sustainable than a conventional one; the result depends on **feedstock production, processing, purification, utilities and waste treatment**.

Improving one stage may shift the environmental burden elsewhere—for example, a lower-impact feedstock may require **more energy-intensive purification**.

Meaningful comparison requires a clearly defined **system boundary and functional unit**, such as impact per kilogram of final product.

Key indicators may include **carbon footprint, energy demand, water consumption, waste generation and material efficiency**.

Sustainability should therefore be treated as a **system-level design criterion** alongside performance, cost and product quality.



Safety architecture

Hazard prevention is stronger than relying only on downstream detection.

Intrinsic safety reduces the hazard at the source through safer biological design, lower-risk materials or less hazardous operating conditions.

Containment limits the spread of cells, biological material or hazardous substances through physical and, where appropriate, biological barriers.

Monitoring and detection identify deviations such as contamination, loss of containment, abnormal growth or process failure before they escalate.

Operational controls include validated procedures, access control, maintenance, training and clearly defined responsibilities.

Emergency response provides predefined actions for isolation, shutdown, decontamination and recovery when normal controls fail.

Biological systems require additional attention because **mutation, adaptation, contamination and phenotype drift**can change system behaviour over time.

1. PREVENT

intrinsic safety • safer design

↓

2. CONTAIN

physical barriers • biological containment

↓

3. DETECT & CONTROL

monitoring • alarms • procedures

↓

4. RESPOND & RECOVER

shutdown • isolation • decontamination

System review questions

Where are the critical interfaces and single points of failure?

Purpose: What must the system accomplish, and which performance metric defines success?
Boundary: What is included in the analysis, and which external influences may still affect the result?
Critical variables: Which inputs, states or operating conditions have the greatest influence on performance?
Interfaces and dependencies: Where does material, energy, information or responsibility pass between subsystems?
Constraints: Which limits are hard requirements, and which can be traded against cost, performance or time?
Failure and uncertainty: What can fail, what evidence supports the assumptions, and which missing data could change the decision most?

Aspect	Engineering meaning
Purpose	What must the system accomplish?
Boundary	What is included and excluded?
Critical variables	What most strongly controls performance?
Failure / uncertainty	Where can the conclusion break down?

Structured analysis output

A professional conceptual analysis should include a system diagram, subsystem table, metrics, constraints, failure modes and proposed improvements.

Start with a **system map** showing the main subsystems, interfaces, inputs, outputs and important dependencies.

Summarize the **evidence and assumptions** used in the analysis, clearly distinguishing measured data, literature values and uncertain estimates.

Define the key **performance metrics** used to evaluate whether the system meets its intended function.

Identify major **constraints, bottlenecks and failure modes** that limit performance, safety, reliability or manufacturability.

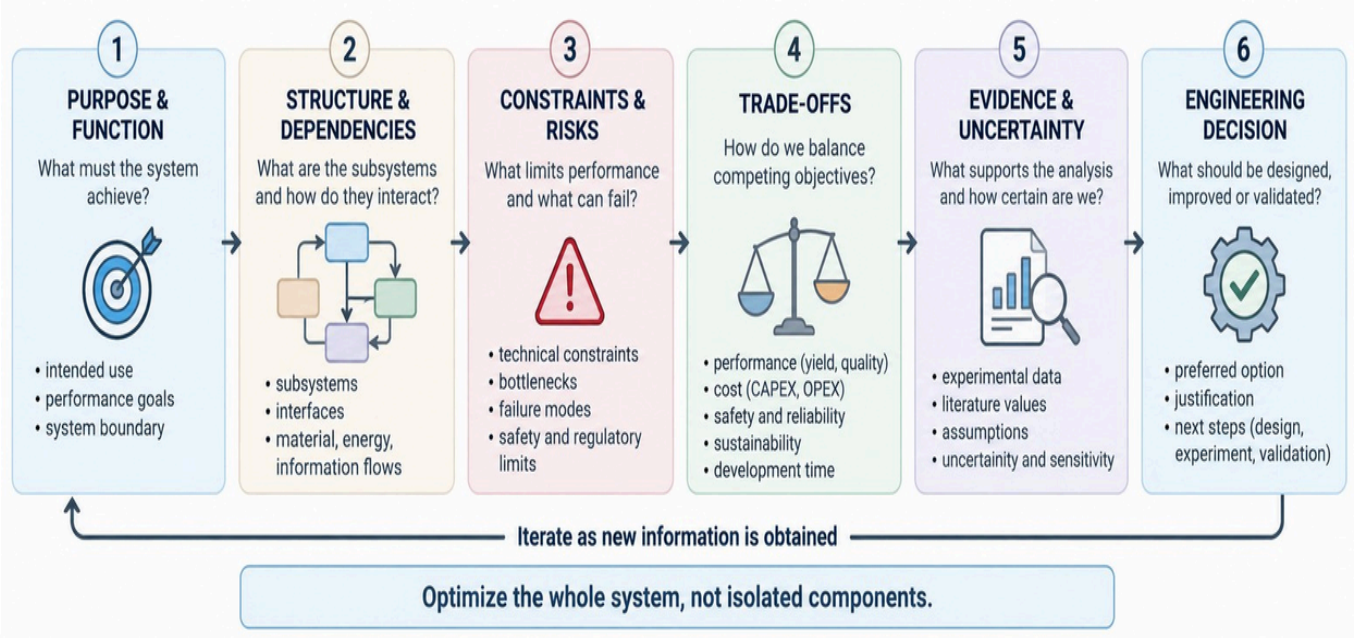
Each proposed improvement should be linked to a **specific identified limitation**, with its expected benefit and possible side effects stated explicitly.

Finish with a **decision recommendation** and the next experiment, measurement or design action needed to reduce remaining uncertainty.

SYSTEM MAP
subsystems • interfaces • flows
→
EVIDENCE & ASSUMPTIONS
data • literature • uncertainty
→
PERFORMANCE METRICS
yield • quality • reliability
→
CONSTRAINTS & FAILURE MODES
limits • bottlenecks • risks
→
IMPROVEMENT OPTIONS
redesign • control • monitoring
→
DECISION / RECOMMENDATION
preferred action + justification

Take-home synthesis

System-level reasoning connects biological detail to engineering decisions.
Begin with the **system purpose and boundary**: define what the system must achieve and what is included in the analysis.
Decompose the system into **functions, subsystems, interfaces and dependencies** to understand how performance emerges from their interaction.
Identify **critical variables, constraints, bottlenecks and failure modes** rather than optimizing components independently.
Evaluate **trade-offs** among performance, quality, cost, robustness, safety and sustainability.
Use the available **evidence and uncertainty** to decide which assumptions are reliable and which require further testing.
The final goal is not the “best” individual component, but a **whole system that delivers the intended function reliably under realistic conditions**.



Student Tasks and Discussion

1. Define one system boundary relevant to this lecture and explain what is deliberately excluded from the analysis.

2. Identify the three most important measurable variables for judging performance; state their units and why they matter.

3. Draw one conceptual diagram (process, causal loop, balance, or decision map) using the notation introduced in the lecture.

4. Describe one realistic failure mode or limitation and propose an engineering control, design change or monitoring strategy.

5. Locate one peer-reviewed article from the last five years that extends the lecture topic and summarize its engineering contribution, evidence and remaining

Selected References and Further Reading

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