

Quantitative Microbiology

PHYS 176/276

Instructor: Terry Hwa

Winter 2025

course website:

<https://matisse.ucsd.edu/courses/w25-quant-microb/>

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What is quantitative biology?

→ quantitative biology ≠ biology + numbers/equations

≠ application of quant tools to bio

→ use numbers to gain predictive understanding of living systems

Why quantitative biology?

- because biology *is* quantitative
- needed to formulate and test falsifiable predictions
- demanded by the need to modify (SynBio) and interfere (Medicine)

Role of theory

- formulate expectation and predictions (via quantitative model)
- guide the design of new experiments and technology
- power: the generality of (falsifiable) ideas, not necessarily math [e.g., Copernicus, Darwin, Einstein]
- “cost” : the simplifying assumptions, not necessarily forced by math, but required in order to reveal principles

→ This course: quantitative (molecular) microbiology

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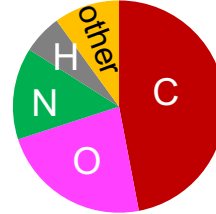
❖ Life of a bacterium:

matter + energy → biomass



TABLE 1. Typical elemental composition of biological specimen

Element	Mass fraction in the following cells	
	Tissue ^a	Bacteria ^b
C	0.50	0.47
N	0.16	0.14
H	0.07	0.06
O	0.25	0.23
P + S + others	0.02	0.10 ^c

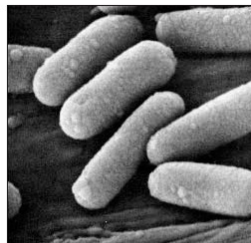


[Heldal et al, 1985]

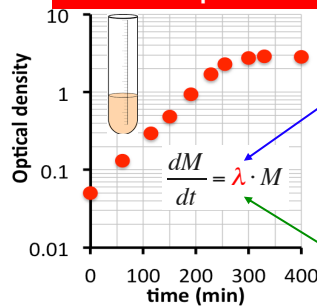
- molar composition: $\text{CH}_{1.5}\text{O}_{0.35}\text{N}_{0.24}$ (+S, P, Mg, Fe, ...)
- algae (photosynthesis):
 $\text{CO}_2 + \text{H}_2\text{O} + \text{N}_2 + \text{photons} \rightarrow \text{biomass} + \text{O}_2$
- *E. coli* (minimal medium):
 $\text{glucose} + \text{NH}_3 \rightarrow \text{biomass} + \text{CO}_2$

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growth of *E. coli*



Can we predict GR & yield?



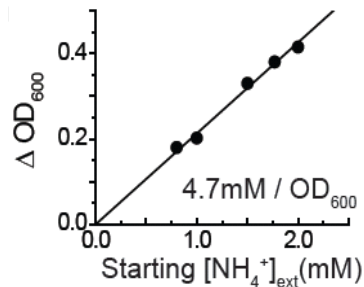
environmental factors:
nutrient types & conc
temperature, pH,
osmolarity, drugs, ...

genetic factors:
enzymes, metabolites,
& regulation

Learning from the growth curve

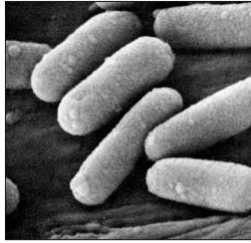
[Monod, Ann Rev Microb. 1949]

- OD_{600} = biomass content
 [1 OD·ml = 0.5mg CDW ~ 10^9 cells]
- saturation OD → yield
- (lag: transition from pre-shift phase)

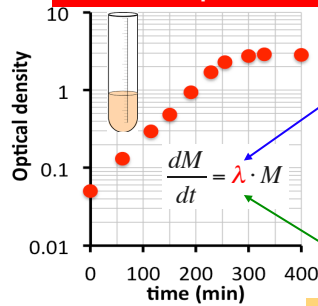


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growth of E. coli



Can we predict GR & yield?

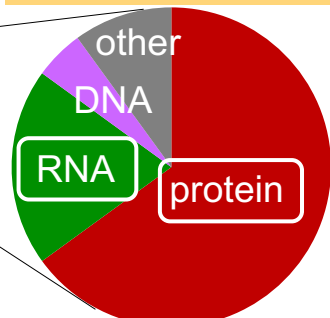
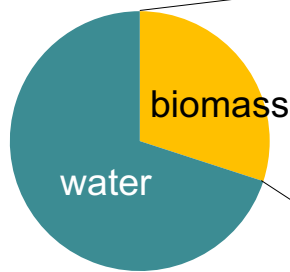
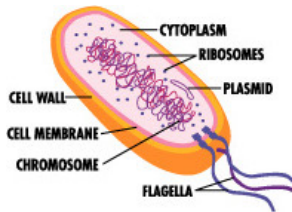


environmental factors:
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temperature, pH,
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(condition-dependent)

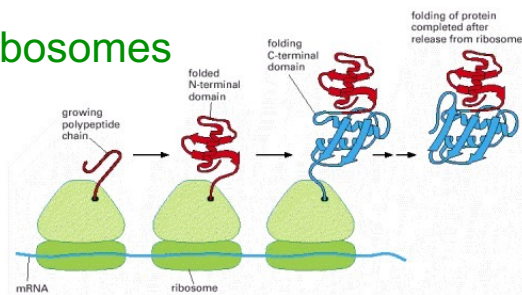
What does it take to replicate a cell?



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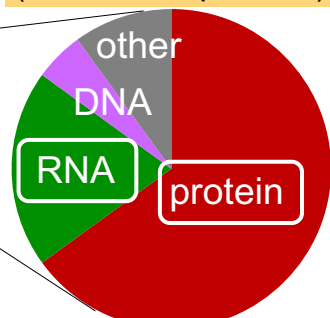
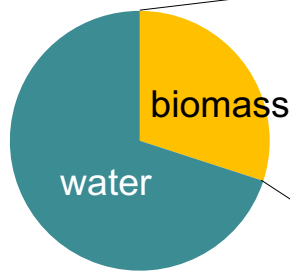
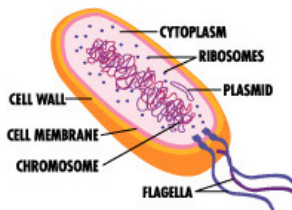
protein = defined sequence of 20 amino acids

protein synthesis: ribosomes



(condition-dependent)

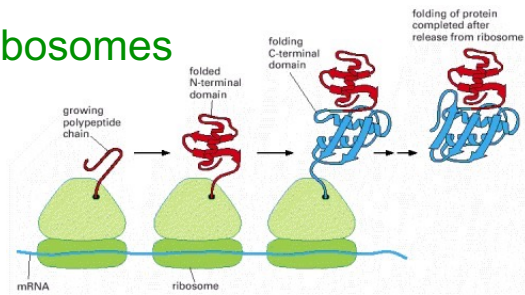
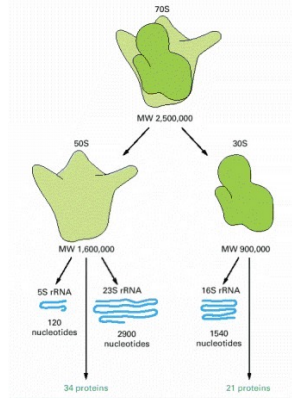
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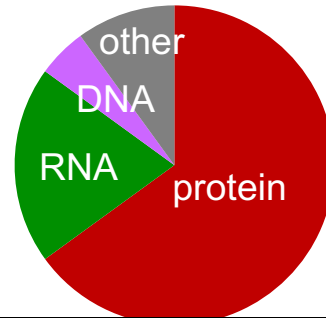
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protein = defined sequence of 20 amino acids

protein synthesis: ribosomes



condition-dependent

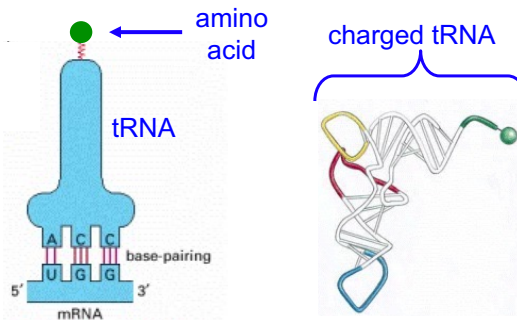
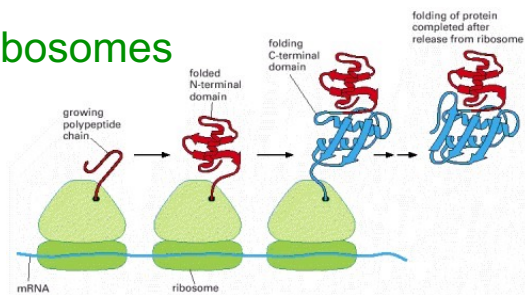
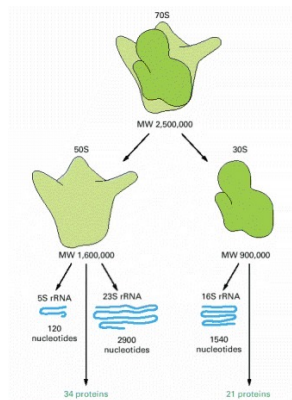


>85% of all RNA
up to 1/3 of all proteins

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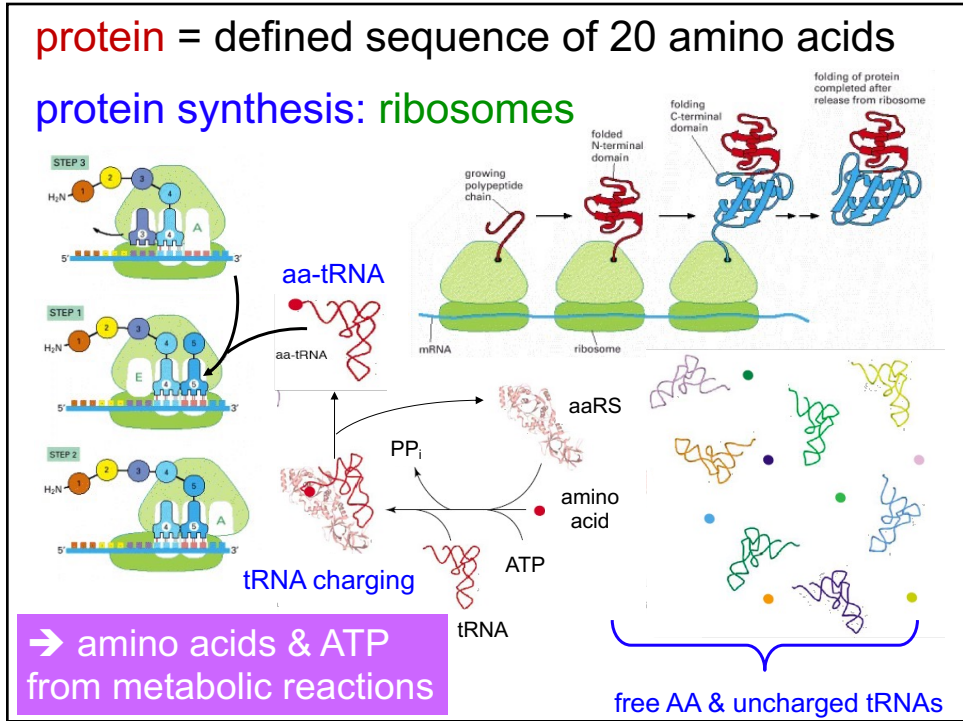
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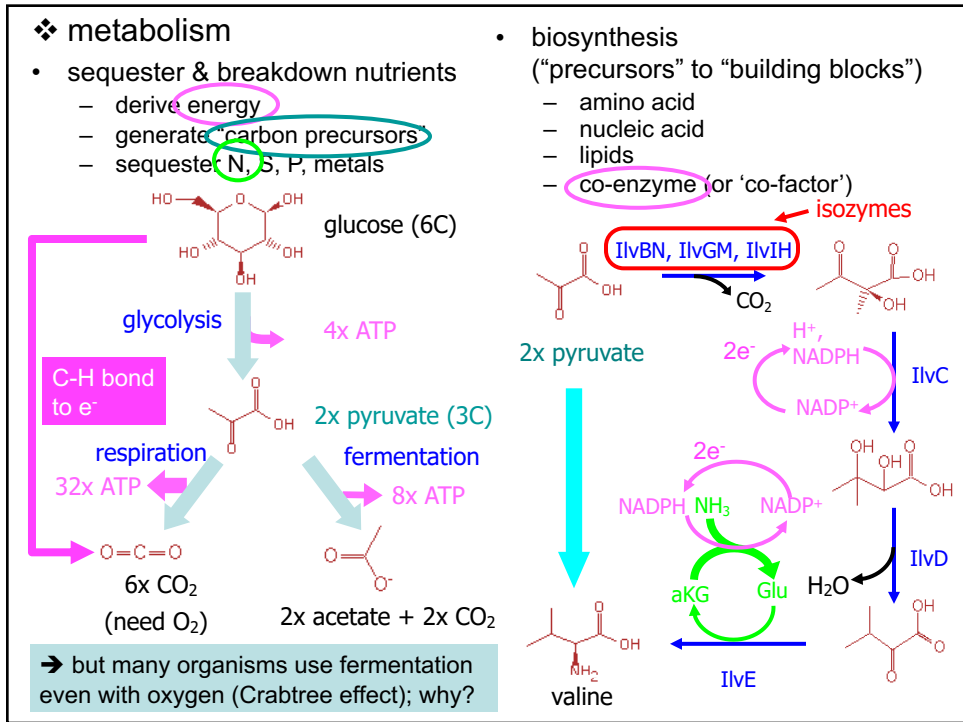


>85% of all RNA
up to 1/3 of all proteins

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❖ metabolism

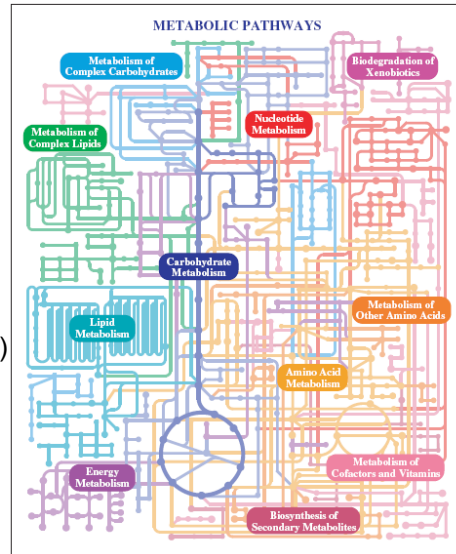
- sequester & breakdown nutrients
 - derive energy
 - generate carbon
 - sequester N, metals
- biosynthesis of building blocks
 - amino acid
 - nucleic acid
 - lipids
 - co-enzymes
- degradation/recycling (e.g., mRNA)
- typical biochemical reaction:

$$S + C \cdot b \rightleftharpoons S \cdot b + C$$

S: substrate
b: component (e.g., CH₃, NH₂, e⁻)
C: co-enzyme
(needed for difficult reactions)

catabolism

anabolism



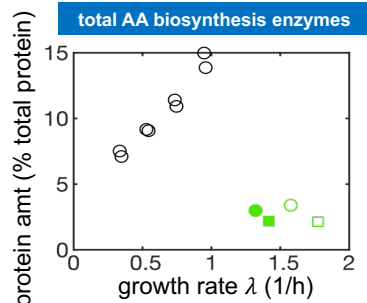
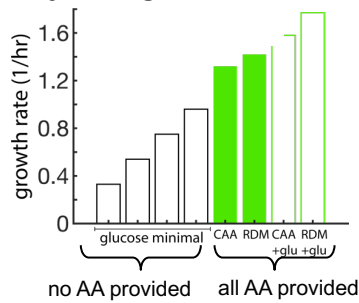
- ➔ most reactions catalyzed by enzymes (proteins)
- ➔ flux of the products and “by-products” need to be balanced

metabolic control via coordinated regulation of enzyme abundance/activity

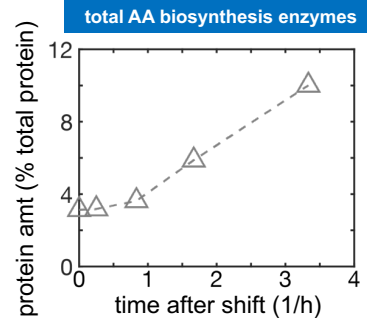
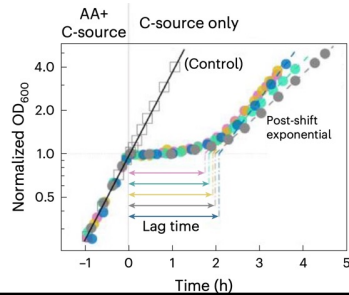
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Coordination of AA biosynthesis with growth need

steady state growth



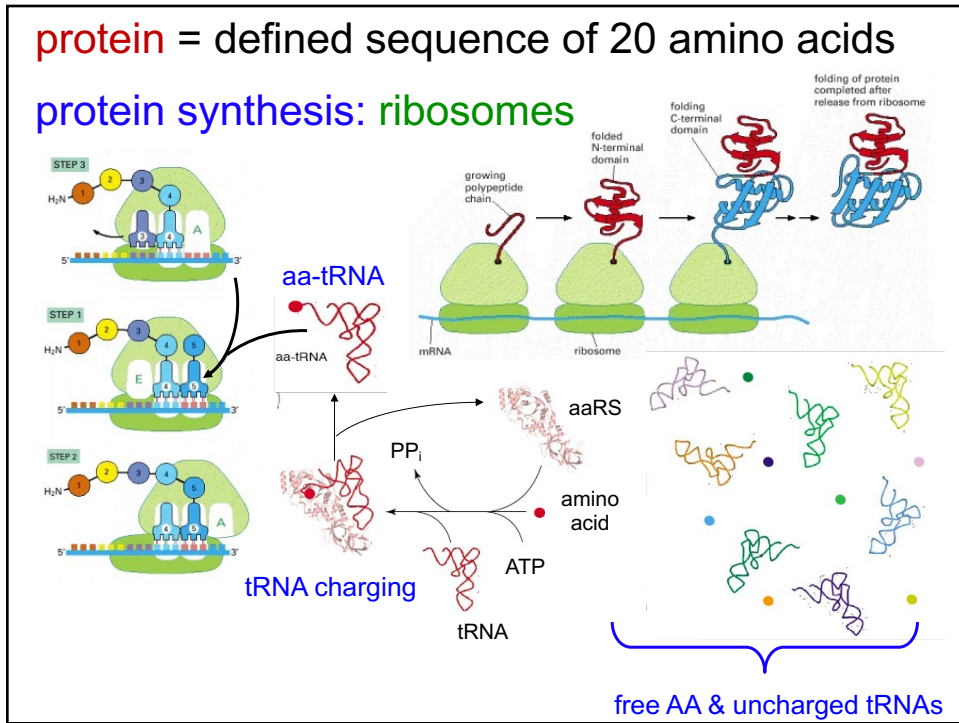
growth downshift



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protein = defined sequence of 20 amino acids

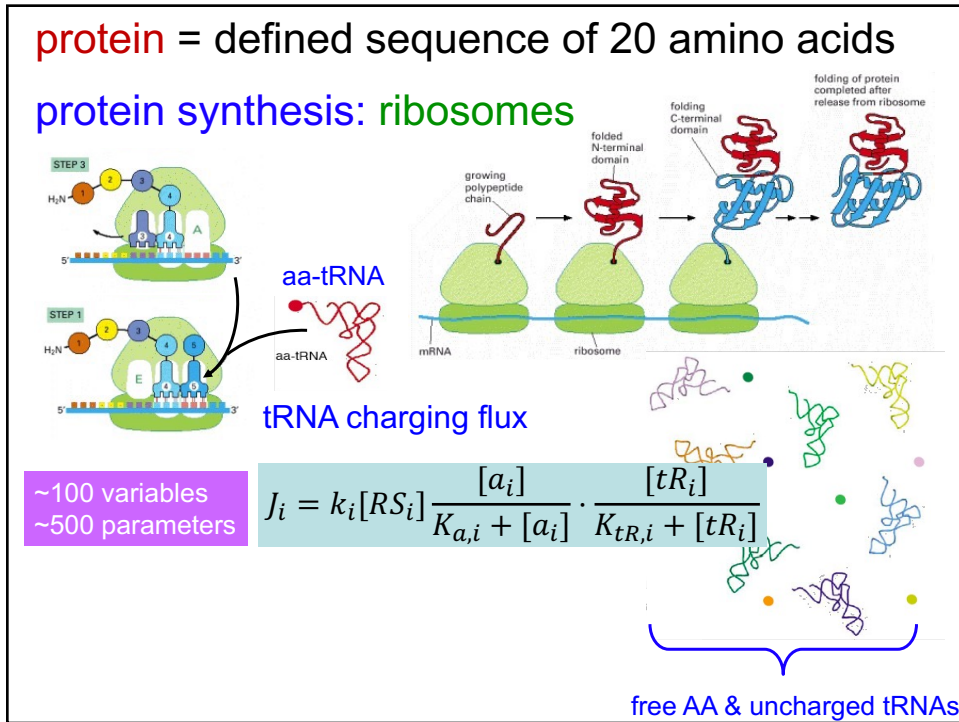
protein synthesis: ribosomes



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protein = defined sequence of 20 amino acids

protein synthesis: ribosomes



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protein = defined sequence of 20 amino acids

protein synthesis: ribosomes

parameter explosion

~100 variables
~500 parameters

~500 enzymes
~500 metabolites
~5000 parameters

~10000 parameters

regulation: when and how much proteins to make
dependence on temp, pH, osmolarity, ...

glucose (6C)

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How to deal with exploding no. of parameters?

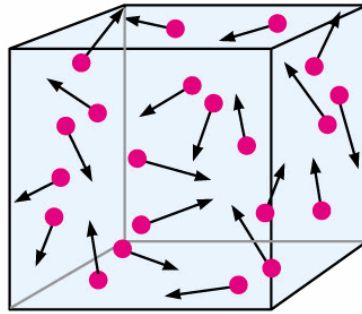
Newtonian Mechanics $\xrightarrow{\text{dimension reduction?}}$ Thermodynamics

$\frac{d^2 \vec{r}_i}{dt^2} = \vec{f}_{ij}(\vec{r}_i - \vec{r}_j)$ $PV = nRT$

Need moles of parameters:
 $\vec{r}_i(t = 0) = \dots$
 $\vec{v}_i(t = 0) = \dots$

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How to deal with exploding no. of parameters?



Newtonian Mechanics



Thermodynamics

dimension
reduction?

Statistical Mechanics

$$\rho(\vec{q}_i, \vec{p}_i; t) \xrightarrow{t \rightarrow \infty} \rho_{eq}(\mathcal{H}(\vec{q}_i, \vec{p}_i))$$

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Molecular/Cell Biology

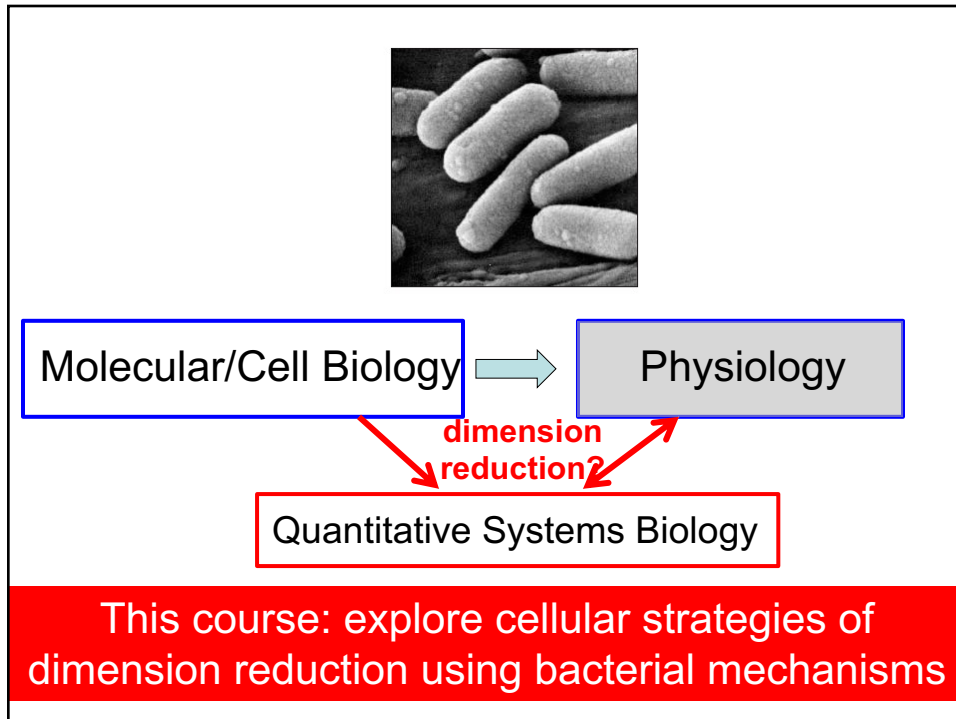


Physiology

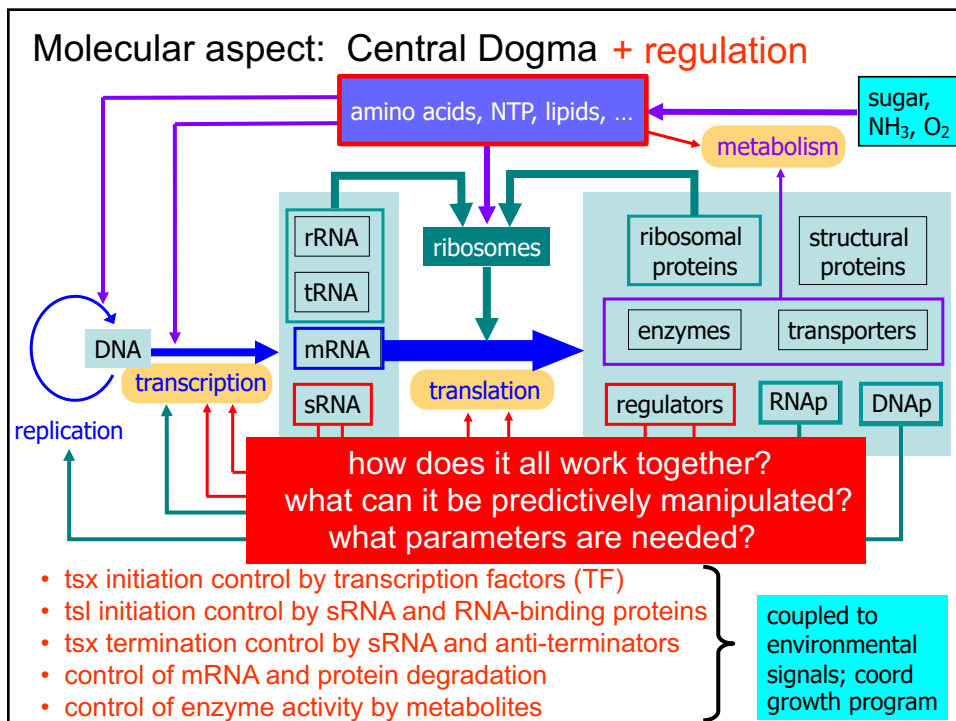
dimension
reduction?

Quantitative Systems Biology

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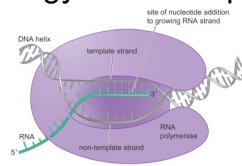


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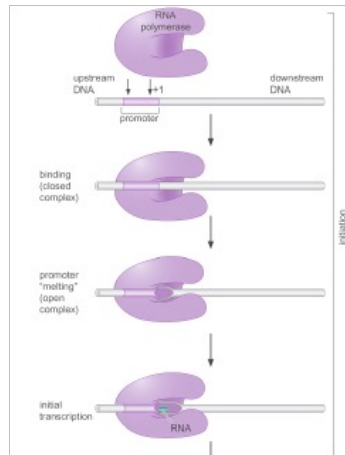


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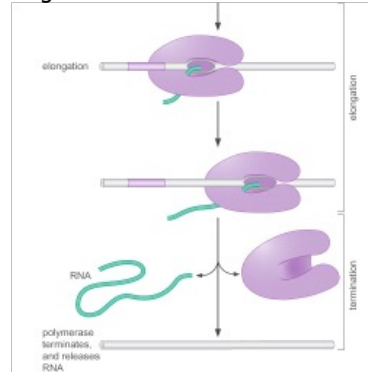
molecular biology of transcription (RNA synthesis)



transcriptional initiation



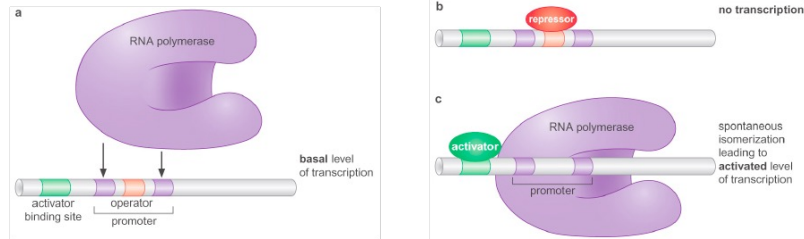
elongation and termination



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transcriptional initiation control

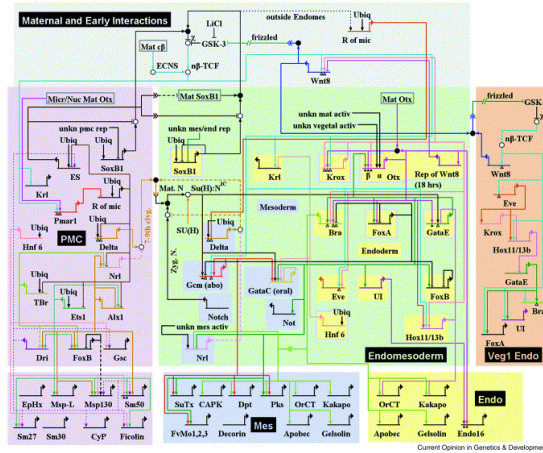
- modulation of RNAP-promoter affinity via activators and repressors



→ net result: rate of transcriptional initiation dependent on cellular conc of activators and repressors controlled by metabolites and signaling molecules

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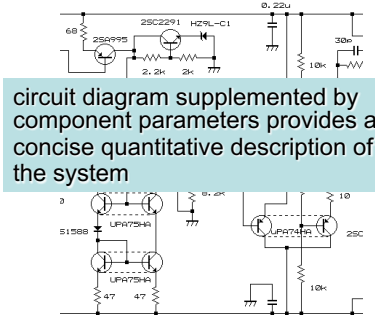
Gene regulatory networks



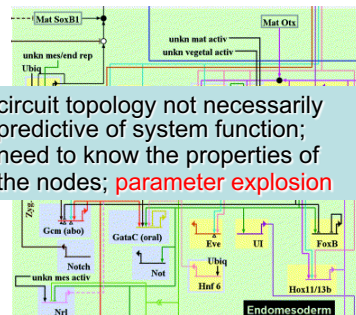
- A grand challenge of Systems Biology
 - map out the complete wiring diagram of the cell
 - predictive computational model of the cell

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Circuit diagram as system-level descriptor ?



circuit diagram supplemented by component parameters provides a concise quantitative description of the system

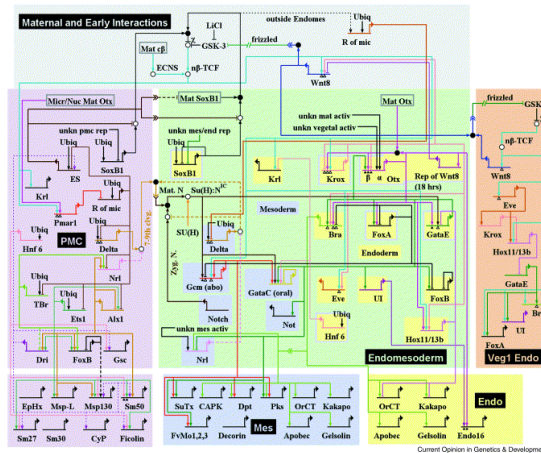


circuit topology not necessarily predictive of system function; need to know the properties of the nodes; **parameter explosion**

	electronic circuits	genetic circuits
components	simple & well-characterized; many (~10 ⁹); fast (10 ⁻⁹ sec)	heterogeneous, most rates unknown; few (~1000); slow (> 10 min)
connectivity	physical interconnect between well-insulated components (1~2 inputs per node)	multiply-connected (1~10 inputs per node); regulation at all stages
network complexity	iterated cascades from complex network wiring	combinatorial signal integration from complex molecular control

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Gene regulatory networks



- ~~A grand challenge of Systems Biology~~
 - ~~– map out the complete wiring diagram of the cell~~
 - ~~– predictive computational model of the cell~~

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scope of this course

- focus on simple systems (bacterial gene regulation)
- role of theory, modeling, and computation
- coarse-grained description at multiple scales (telescoped description)
- **quantitative connections between molecular mechanisms and physiological (functional or behavioral) characteristics**
- **power of functional and mechanistic constraints**

Course content

- molecular interactions: ligand-protein, protein-DNA, and protein-protein
- transcriptional control: activation, repression, and combinatorial
- modeling genetic circuits: bi-stability, oscillation, and stochasticity
- post-transcriptional control and functional enhancement
- from molecular interaction to cell physiology

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