CDS 270-4
BioControl

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BioControl - Week 1, Lecture 1

Goals of this lecture

- Course administration
- Overall structure and objectives of the course

- Principles of feedback control
- Feedback in molecular systems:
  - Central dogma of molecular biology
  - Different layers of control of gene expression
  - Timescales
  - Signal transduction pathways

Course administration

Instructor: Elisa Franco, graduate student, CDS
Email: elisaf@caltech.edu
Office: Steele 9 (basement)
Office hours: TBD

Sponsoring faculty: Richard M. Murray, Professor of Control and Dynamical Systems, CDS.

Lecture Hours: TBD

Website: https://www.cds.caltech.edu/~murray/wiki/CDS_270-4,_2010:_Bio-Control
On the website - Syllabus, Lectures, Code/Software, FAQs

Homework policy:

NO graded homeworks.

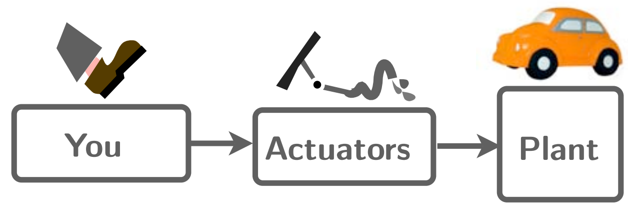
- Class project: pick an existing or synthetic bio-molecular pathway, perform original analysis of properties (e.g. stability, robustness, modularity...)
- Project proposals due at 5PM on April 4th.
- Final project due at 5PM on June 5th.

Feedback control in engineered systems

Example: Vehicle cruise control

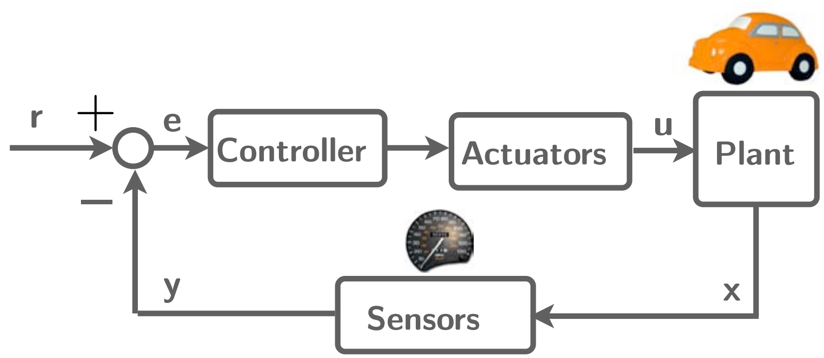
OPEN LOOP

Online operator performs adjustments



CLOSED LOOP

Feedback:
mutual interconnection of two or more systems
Automatic control of system performance.



r reference
y output
x state
e error
u control action

SENSING + COMPUTATION + ACTUATION

Physically decoupled

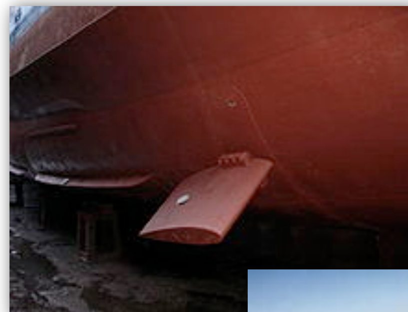
System becomes:

- Modular
- Pliable

Principles of feedback

Design of dynamics

- Stabilization
- Reference following
- Performance optimization...

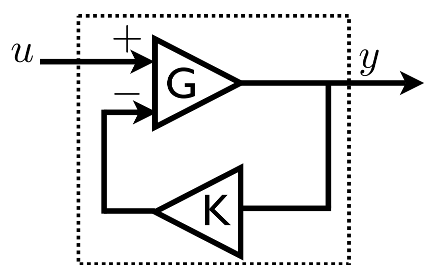


Ship fin stabilizers

Robustness to uncertainty

Example: OPAMP
Gain uncertainty is compensated with
Accurate sensing + closed loop

As long as G is sufficiently high,
I/O characteristic is guaranteed by K



$$y = G(u - Ky)$$

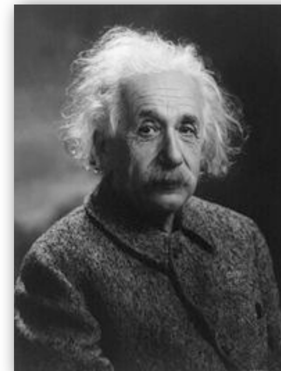
$$y = u\frac{G}{1+KG}$$

$$G \to \infty \Rightarrow y = \frac{1}{K}u$$

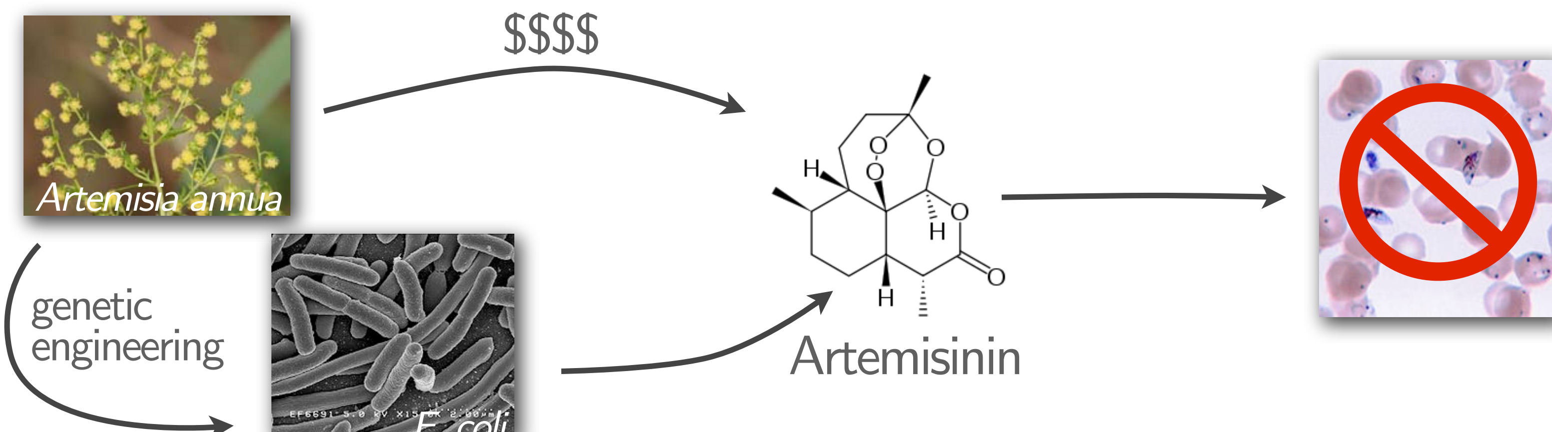
Why a quantitative analysis of feedback in molecular systems?

Example 1: Systems biology. Chimp vs human genome

Genetic divergence only ~ 2%
How do we explain the different outcome?
Feedback

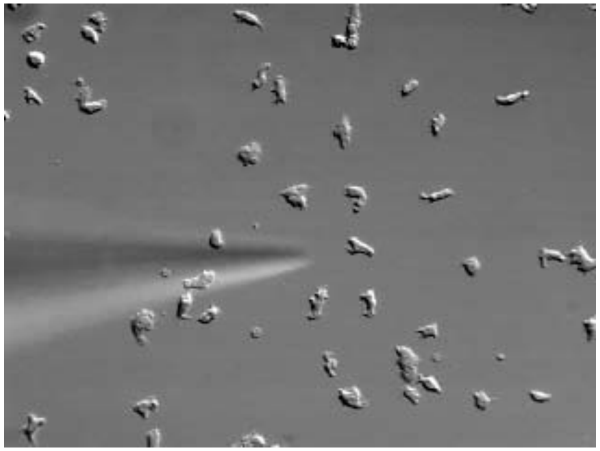


Example 2: Synthetic biology. Optimizing production of anti-malarial drugs in bacteria



Overall objective of the course

Understanding feedback control of bio-molecular systems



Lee S, Firtel Lab, UCSD

Dictyostelium bacteria, chemotaxis triggered by cAMP

- Best ways to **model** this phenomenon?
- **Design** principles?
- **Synthesis** of control loops?

Structure of the course

Part 1: Modeling

- Options for model construction:
    - Deterministic models and CDS tools
    - Stochastic models
- Chemical Reaction Networks
- Monotone systems

Part 2: Synthesis

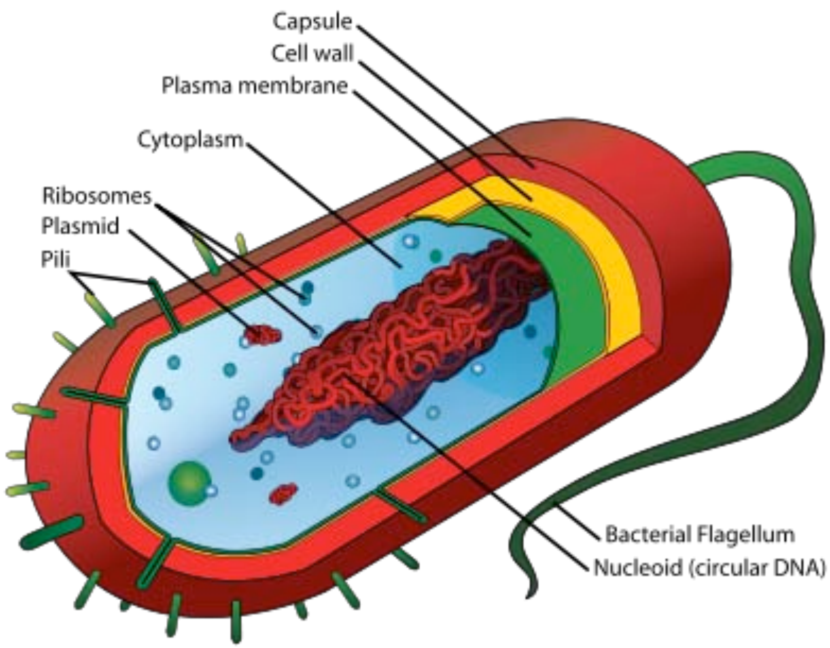
- Design principles
- Robustness
- Modularity

General reference books

• Feedback Systems: An Introduction for Scientists and Engineers. K. Åström and R. Murray.
• An introduction to Systems Biology, U. Alon, Chapman & Hall
• Nonlinear systems. H. Khalil, Prentice Hall, 3rd edition
• Physical Biology of the Cell, R. Phillips, J. Kondev and J. Theriot, 2008.
• Molecular Biology of the Cell, B. Albert et al, Garland Science, 2008

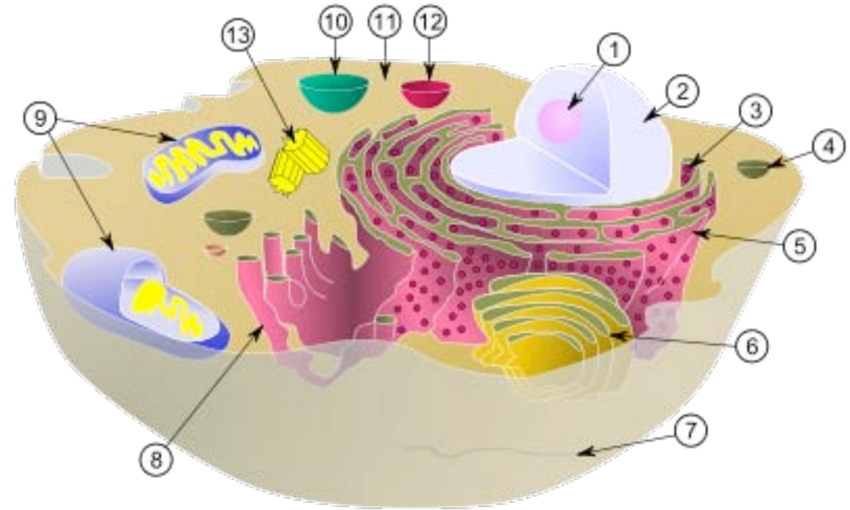
Feedback in Molecular biology: basics

Prokaryotic cell



http://en.wikipedia.org/wiki/Cell_(biology)

Eukaryotic cell

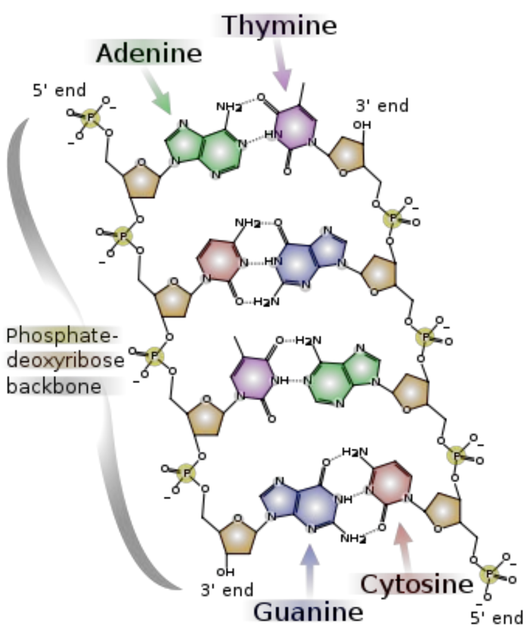


1. Nucleolus (ribosomal RNA)
2. Nucleus
3. Ribosome
4. Vescicle
5. Rough endoplasmatic reticulum
6. Golgi apparatus (protein folding)
7. Cytoskeleton
8. Smooth endoplasmatic reticulum
9. Mitochondria (ATP production)
10. Vacuole (waste, export)
11. Cytoplasm
12. Lysosome (digestion or lysis)
13. Centrioles (organization of mitosis)

Feedback in Molecular biology: Biopolymers

DNA

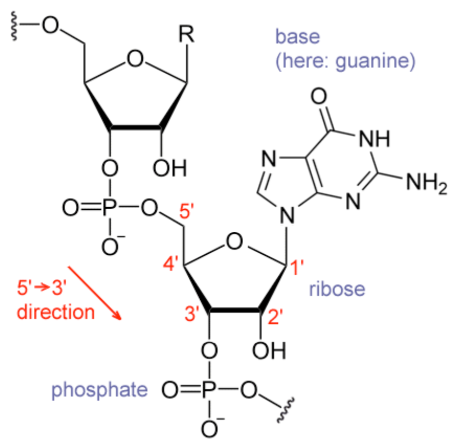
Sugar backbone
Purine and pyrimidine bases



Always double stranded **A-T C-G**

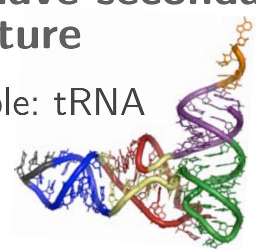
RNA

Different sugar backbone
T -> U



Single stranded, can have secondary structure

Example: tRNA

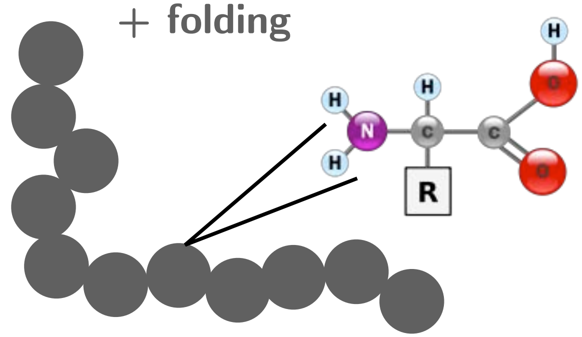


Proteins

3 RNA nucleotides → Amino acid (~20 commonly found in nature)

E.g. UUC/UUG → Phenylalanine

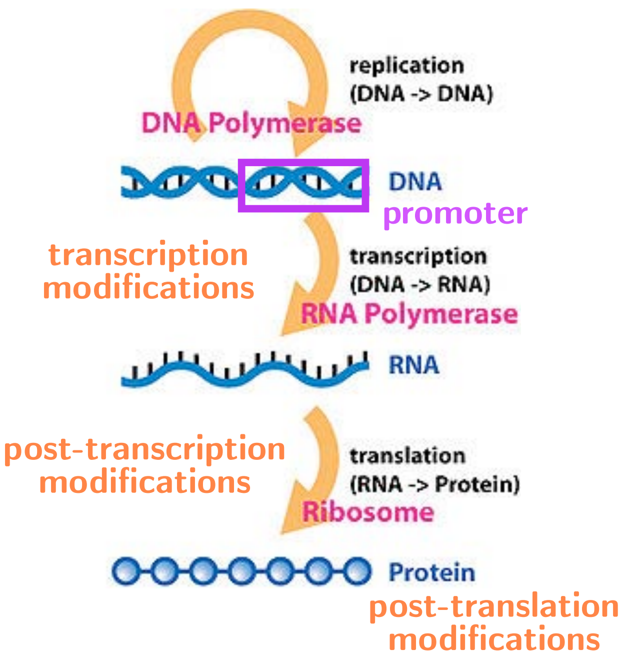
Functional protein = Amino acid chain + folding



Example:
T7 RNA polymerase
α helices
β sheets ...

Feedback in Molecular biology: Central dogma

Information transfer between sequential biopolymers



GENERAL	SPECIAL	UNKNOWN
DNA ->DNA	RNA ->DNA	protein ->DNA
DNA ->RNA	RNA ->RNA	protein ->RNA
RNA ->protein	DNA ->protein [1]	protein ->protein

DNA sequences are expressed when the corresponding proteins are translated and fully functional

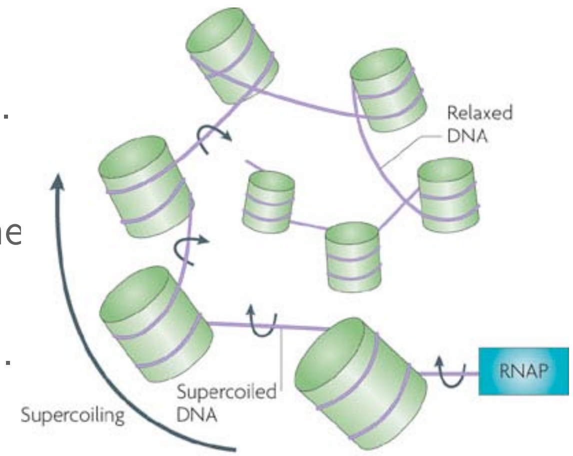
Gene expression can be **controlled** at almost any layer of the dogma. Some of these mechanisms interconnect different genes and introduce **feedback** in the cell environment.

[1] McCarthy BJ and Holland JJ Denatured DNA as a Direct Template for in vitro Protein Synthesis PNAS 54: 880–886.

Layers of control of gene expression

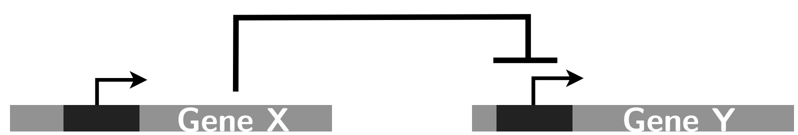
Reference: Molecular Biology of the Cell, B. Albert et al, Garland Science, 2008

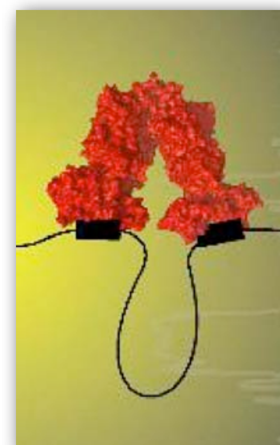
- **DNA Modifications**
  - **Methylation - CH3** Group attached to cytosine. Inheritable. Gene silencing.
  - **Structural modifications** - Supercoiling.
    In relaxed state, the DNA helical strands fully turn around the axis every 10.4-10.5 bases. Genome packing in both prokaryotes and eukaryotes (chromosomes) will cause supercoiling. This modifies the binding affinity for translation.



Brooks & Hurley, 2009 Nature Reviews | Cancer

- **Transcription regulation**
  - **Specificity factors** Alter RNAP promoter specificity (e.g. sigma factors in prokaryotes)
  - **Transcription factors** - Proteins that modulate the likelihood of RNAP binding to the promoter region. TFs can bind to non-coding regions that are close or far from the gene they modulate. Genes are interconnected through the proteins they express!
    Repressors
    Activators
    Enhancers





D. Rutkauskas & F. Vanzi, PNAS 2009

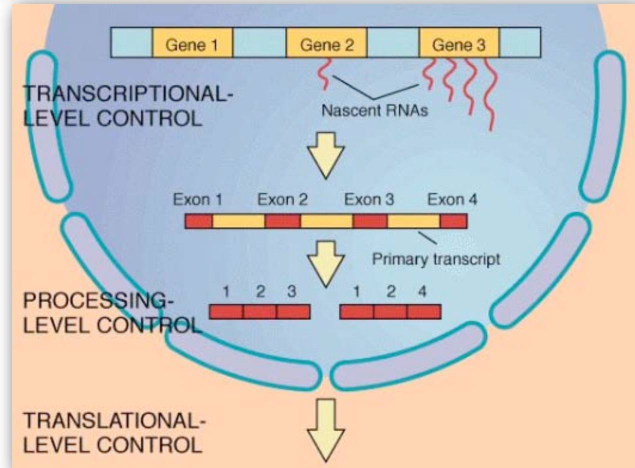
  - **RNA folding**
    Secondary structure of nascent RNA can block transcription

Layers of control of gene expression

- **Post-transcriptional regulation: Eukaryotes**

  mRNA **Capping**
  Polyadenylation
  Splicing (message editing)
  Transport (Outside Nucleus)
  Degradation

  NOTE: prokaryotic Txn and Tsl coupled



- **Regulation of translation**

  General idea: RNA secondary structure can be affected by endogenous or exogenous factors, altering the translation pattern.
  Ex: Riboswitches: Domain of RNA binds to a small molecule, changes conformation and ligand may activate or repress translation (and transcription)

Prokaryotes (polycistronic RNA)		Eukaryotes (monocistronic RNA)
Riboswitches (cis-acting)		Antisense (trans-acting)
Small non-coding RNAs (trans-acting)	Ribozymes (self cleaving RNA)	RNAi

- **Regulation of protein activity/stability**

  Folding, Phosphorylation...

Timescales - Numbers from the literature

	Prokaryotes	Eukaryotes
mRNA production	30-90 bases/s or ~ 18 codons/s [1] depending on the growth medium	~ 25 bases/s [2] (*S. cerevisiae*)
mRNA half life	~ 100 s [3]	Hours [4]
mRNA folding/editing	Seconds	Splicing: 4-7min [6] Transport: ~ 4min [6] (mammalian)
Protein production	20-40 amino acids/s [5]	Slower
Protein half-life	~ 5x10^4 seconds [3]	Minutes-hours [7]
Protein folding - homework	?	?

Timescales - References

1. Vogel U, Jensen KF. The RNA chain elongation rate in Escherichia coli depends on the growth rate. J Bacteriol. 1994 May176(10):2807-13

2. Edwards AM, Kane CM, Young RA and Kornberg RD, Two dissociable subunits of yeast RNA polymerase II stimulate the initiation of transcription at a promoter in vitro, J. Biol. Chem. 266 (1991), pp. 71–75

3. Yildirim, N., M. Santillán, D. Horike, and M. C. Mackey. Dynamics and bistability in a reduced model of the lac operon. Chaos (2004). 14:279–292

4. G Brawerman Annual Review of Biochemistry, July 1974, Vol. 43, Pages 621-642

5. Physical Biology of the Cell, R. Phillips, J. Kondev and J. Theriot, 2008

6. Audibert, A., D. Weil, and F. Dautry. 2002. In vivo kinetics of mRNA splicing and transport in mammalian cells. Mol. Cell. Biol. 22:6706-67018

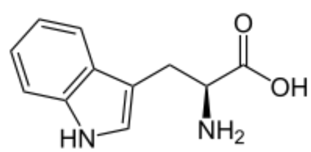
7. Bachmair, A., Finley, D. and Varshavsky, A. (1986) In vivo half-life of a protein is a function of its amino-terminal residue. Science 234, 179-186.

Statistics on *E. coli* - http://gchelpdesk.ualberta.ca/CCDB/cgi-bin/STAT_NEW.cgi

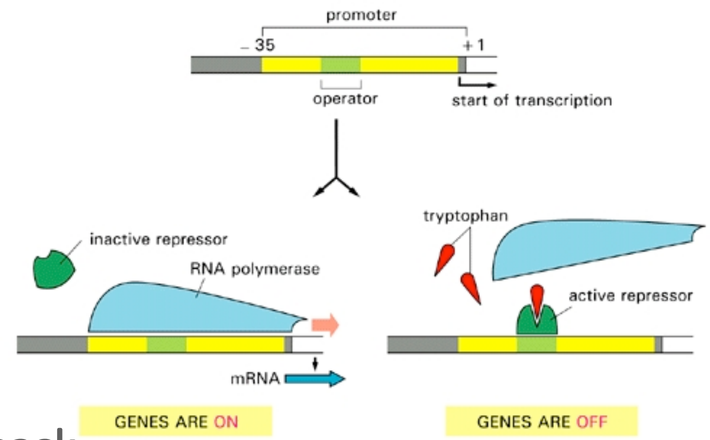
Transcriptional regulation: Example

- The most studied, since the Jacob and Monod experiments on the lac and trp operons
- Model organisms are often *E. coli*, *B. subtilis* and *S. cerevisiae*
- Classical examples: lac operon and trp operon...

The trp operon



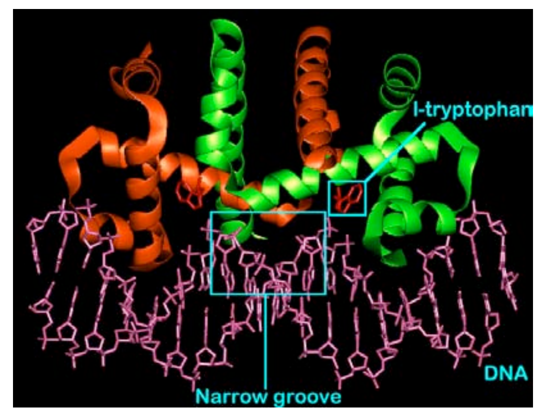
tryptophan
one of the standard 20 amino acids
codon: UGG (not all organisms can synthesize it)



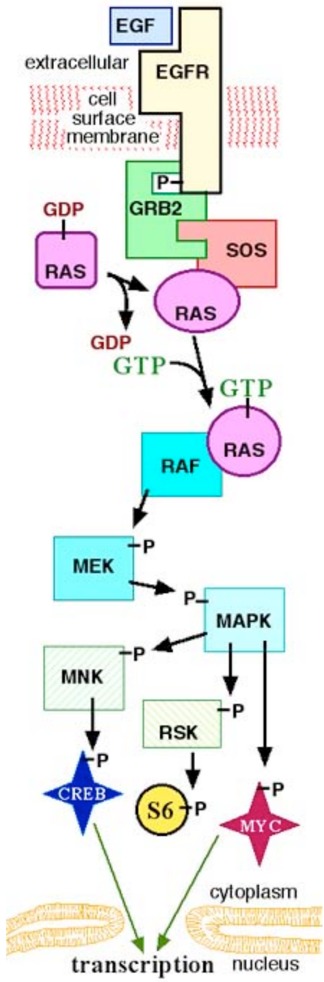
Molecular Biology of the Cell,
B. Albert et al, Garland Science, 2008

Bacteria that synthesize trp present a **negative-feedback** based regulation mechanism:
- **High** cellular levels of trp activate a **repressor** protein, which binds to the trp operon
- Binding of the repressor to the operon blocks transcription of enzymes involved in the trp synthesis
- **Low** levels of intracellular trp decrease the repressor amount, so the operon becomes **active**

Timescales: 60-80 min (Santillán & Mackey, 2001)



Signal Transduction pathways



MAPK

epidermal growth factor receptors

Kinase cascade
Phosphorylation

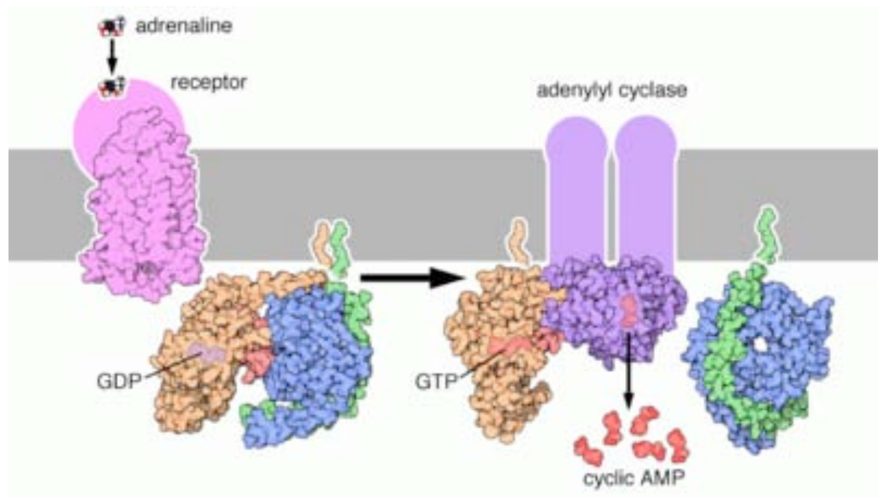
Downstream phosphorylation of many different proteins

Stimulate/repress gene expression

http://en.wikipedia.org/wiki/MAPK/ERK_pathway

cAMP

http://en.wikipedia.org/wiki/CAMP-dependent_pathway

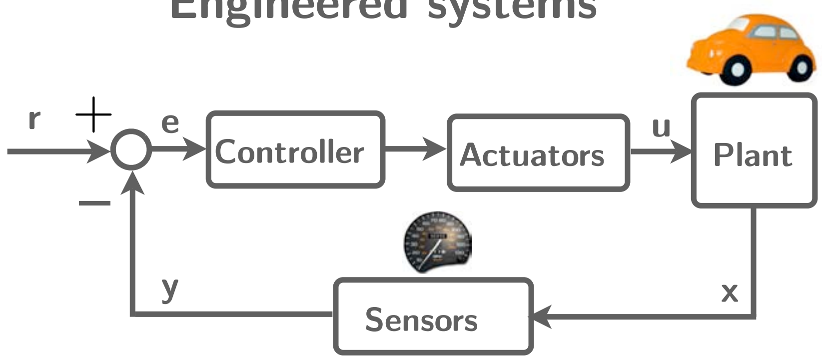


Can activate or repress gene expression

Responses: heart rate, cortisol secretion, and breakdown of glycogen and fat

Feedback in engineering and in biology

Engineered systems



- **Sensors:**

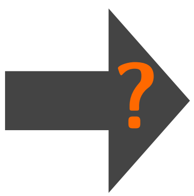
  Signal conversion/transduction
  Dynamics are neglected (fast timescale)
  No influence on the measured signal

- **Controller:**

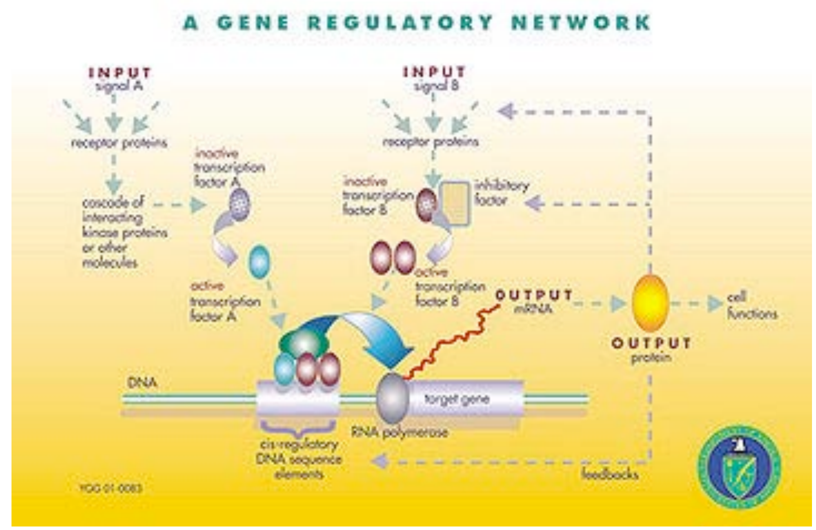
  Tunable computation
  Can add dynamics

- **Actuators:**

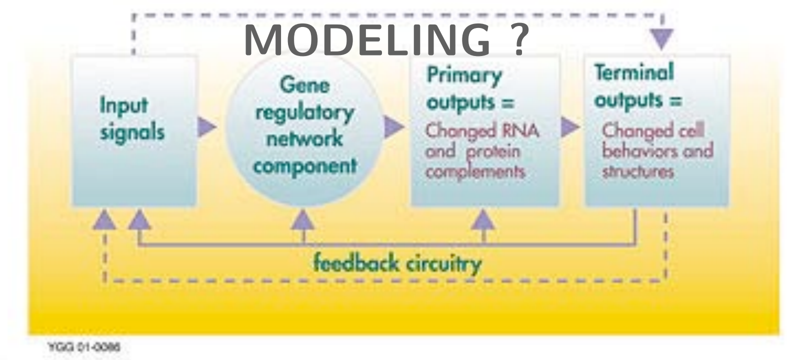
  Signal conversion/transduction
  Dynamics should be negligible
  Can saturate



Biology
Evolution-engineered



http://en.wikipedia.org/wiki/Gene_regulatory_network



Next lecture

How do we build models?

Questions to be asked

Tools available

-> Ordinary differential equations