Lecture 1: Introduction to molecular systems biology

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Overview

(material for the school)

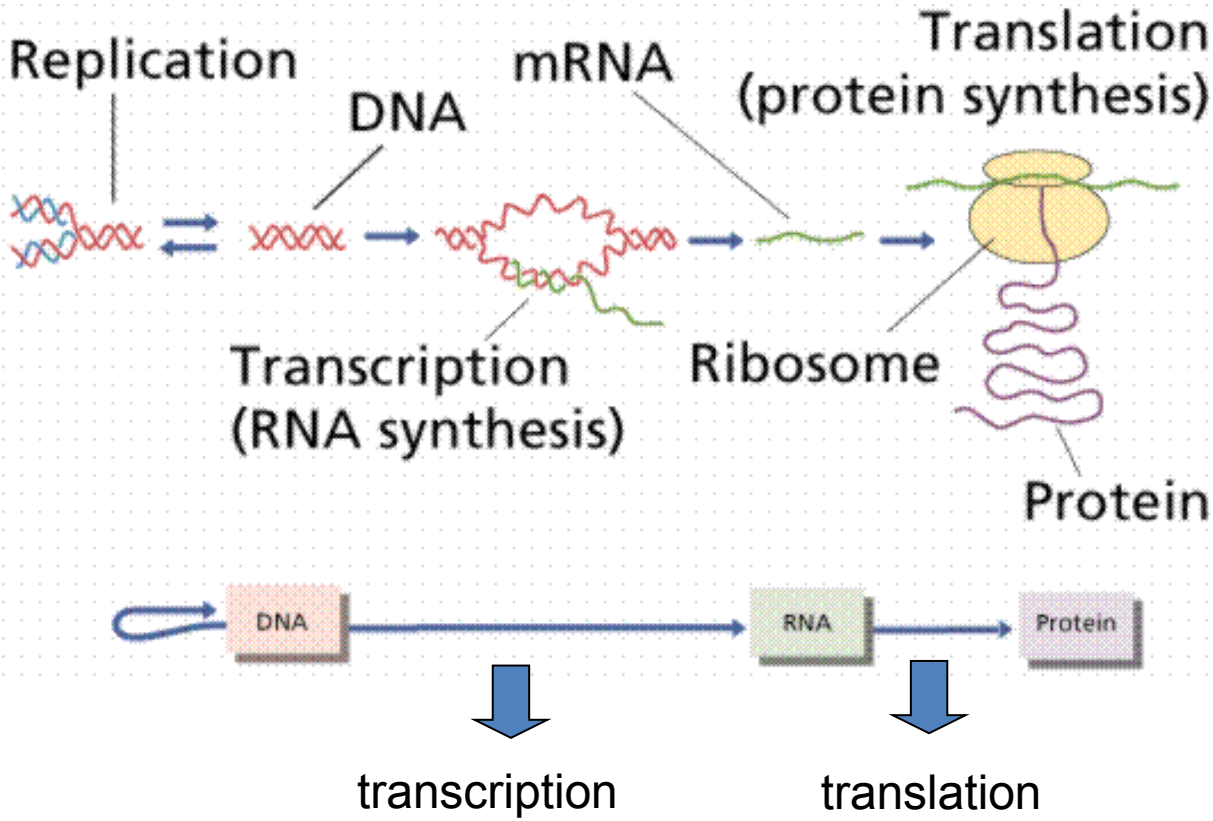
- **Lecture 1 (MD1):** Introduction to computational systems biology
- **Lecture 2 (MD2):** Modeling intracellular dynamics (introduction)
- **Working session 1:** Modeling intracellular dynamics (more advanced): bistability, bifurcations
- **Working session 2:** Biological rhythms (genetic oscillators): delay and relaxation oscillator
- **Lecture 3 (MD3):** Modeling gene expression regulation
- **Working session 3:** Examples of a biophysical approach to bioinformatics

Overview

- **Basic molecular biology (brief introduction)**
- **General discussion: why quantitative biology?**
- **Non-linearity: feedback loops, cooperativity, allostery**

I. Overview of basic molecular biology

Central dogma of molecular biology



DNA -medium for storing information, can be duplicated (during replication).

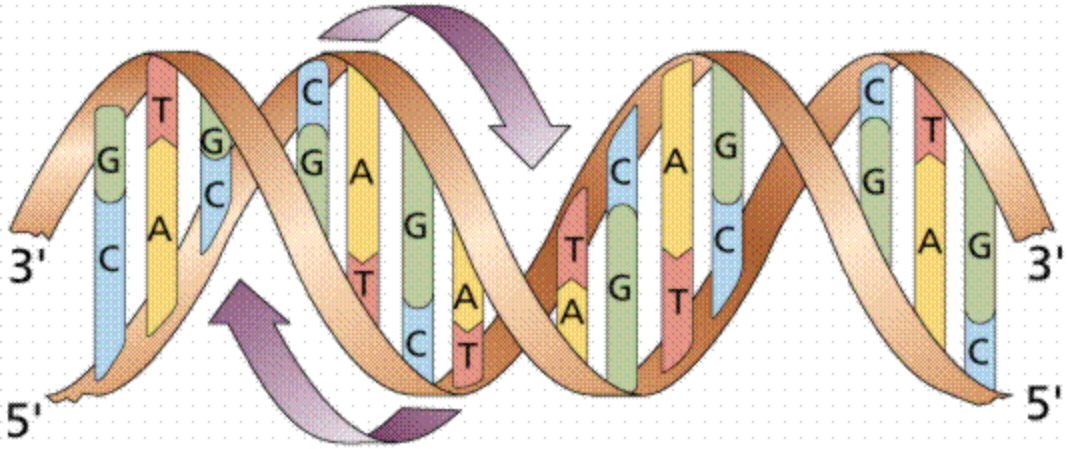
RNA - an intermediate (short lived), synthesized from DNA during transcription.

Proteins – translated from RNA, do all useful work in the cell.

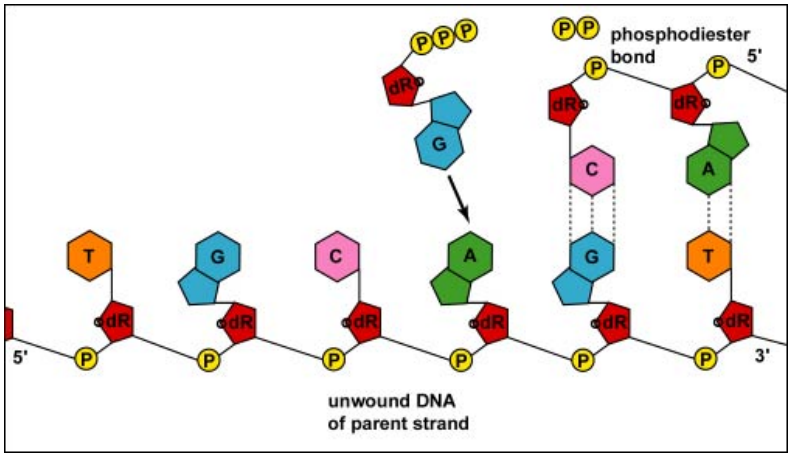
DNA

ATGACCATGATTACGGATTCACTGGCCGTCGTTTTAAACGTCGTGAC

From information point-1 dim sequence of letters



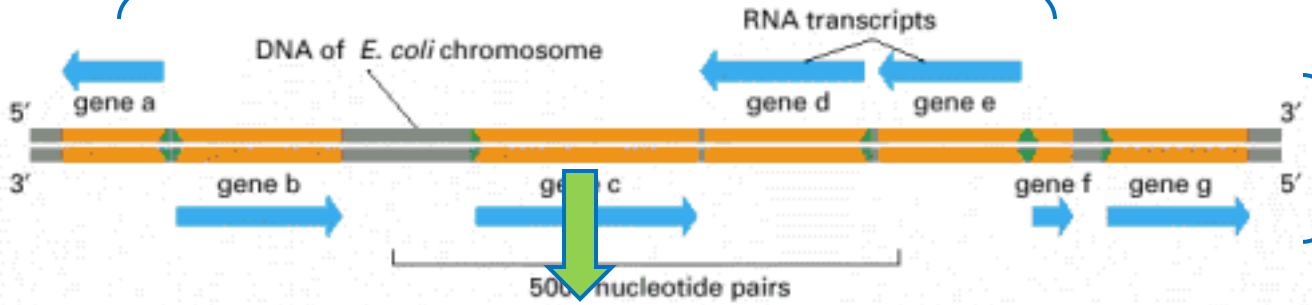
Double helix structure



DNA can be duplicated-replication

RNA

genes + intergenic regions

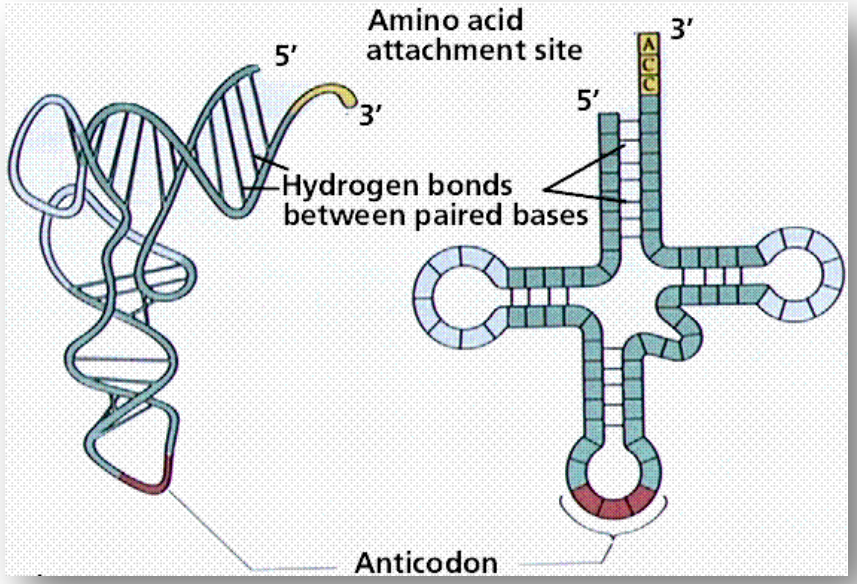


genome consists of DNA

ATGACCATGATTACGGATTCACTGGCCGTCGT → DNA

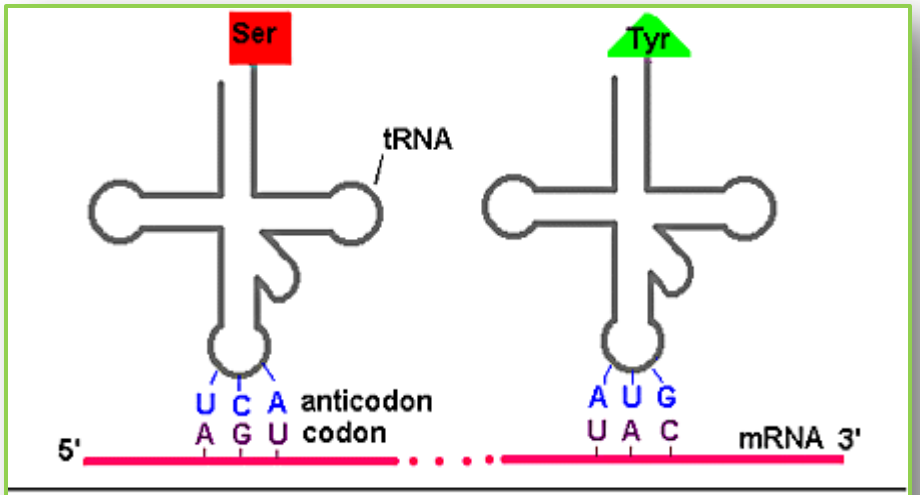
transcription

AUGACCAUGAUUACGGAUUCACUGGCCGUCGU → mRNA



RNA can assume quite complex 3D structure

From RNA to protein



2nd base in codon

1st base in codon	U	C	A	G	3rd base in codon
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

The Genetic Code

Translation scheme

AUGACCAUGAUUACGGAUUCACUGC

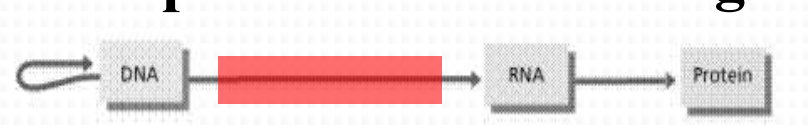
Read mRNA three bases at time

Polypeptide sequence

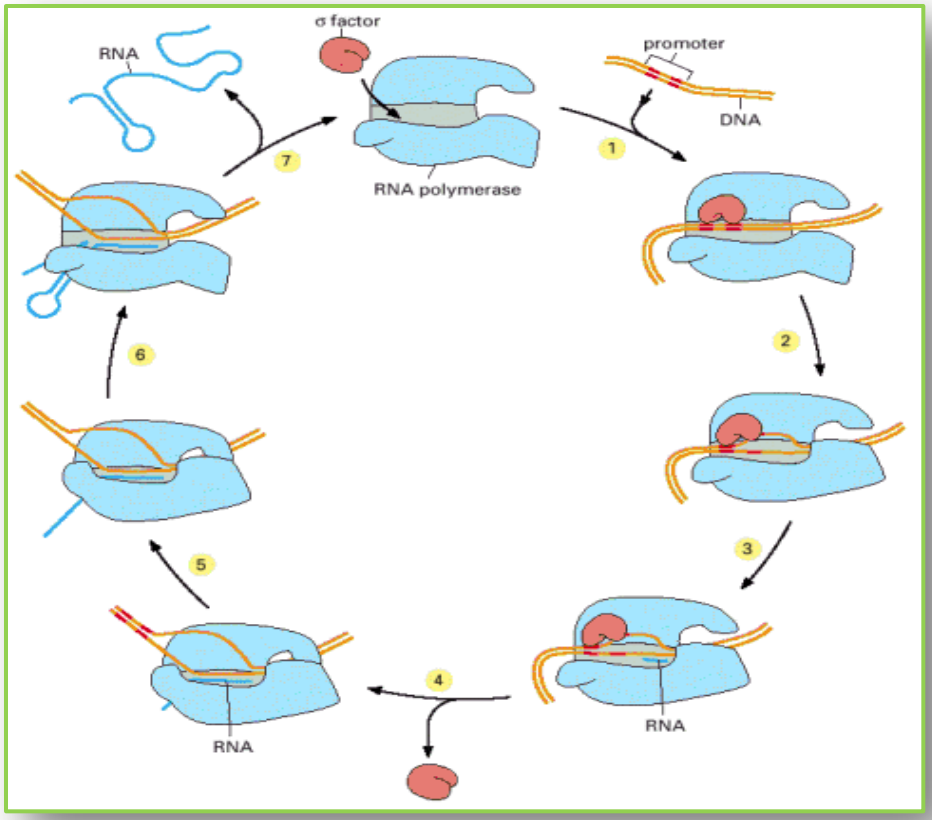
Folds into protein

Regulation of gene expression

Pattern of gene expression has to change-i.e. it has to be regulated

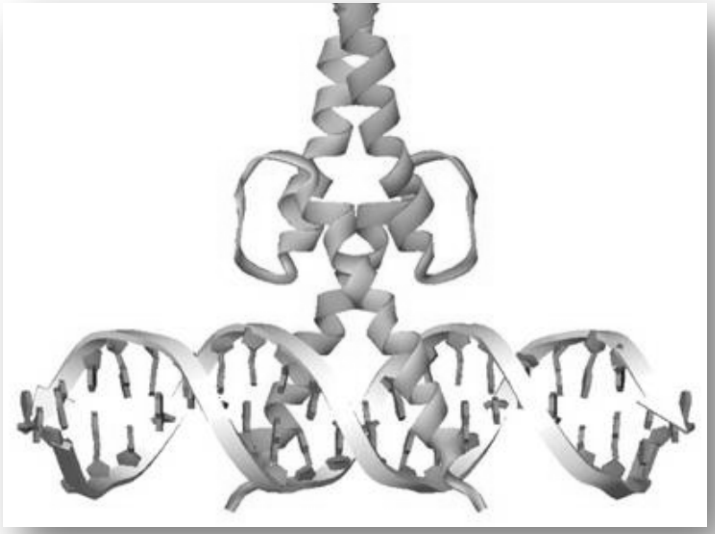


In most cases transcription is regulated

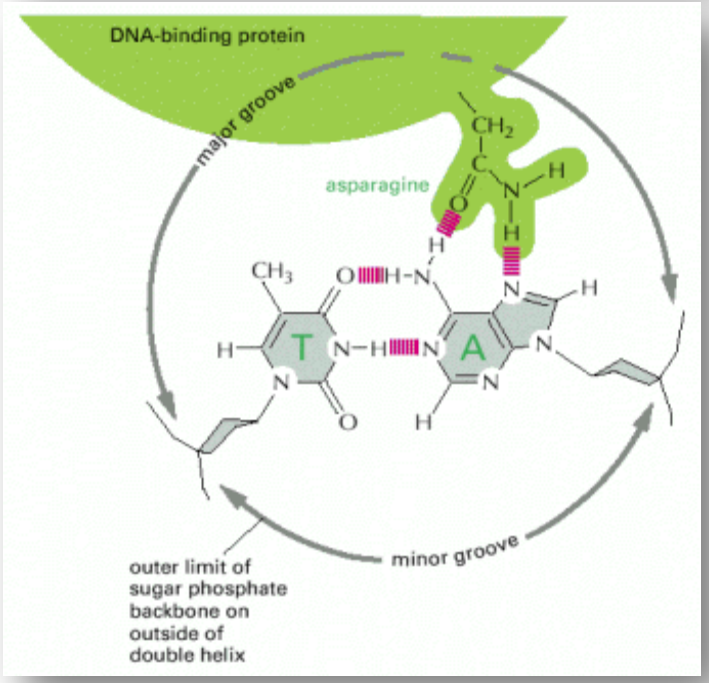


Transcription process

Transcription factors (TFs)

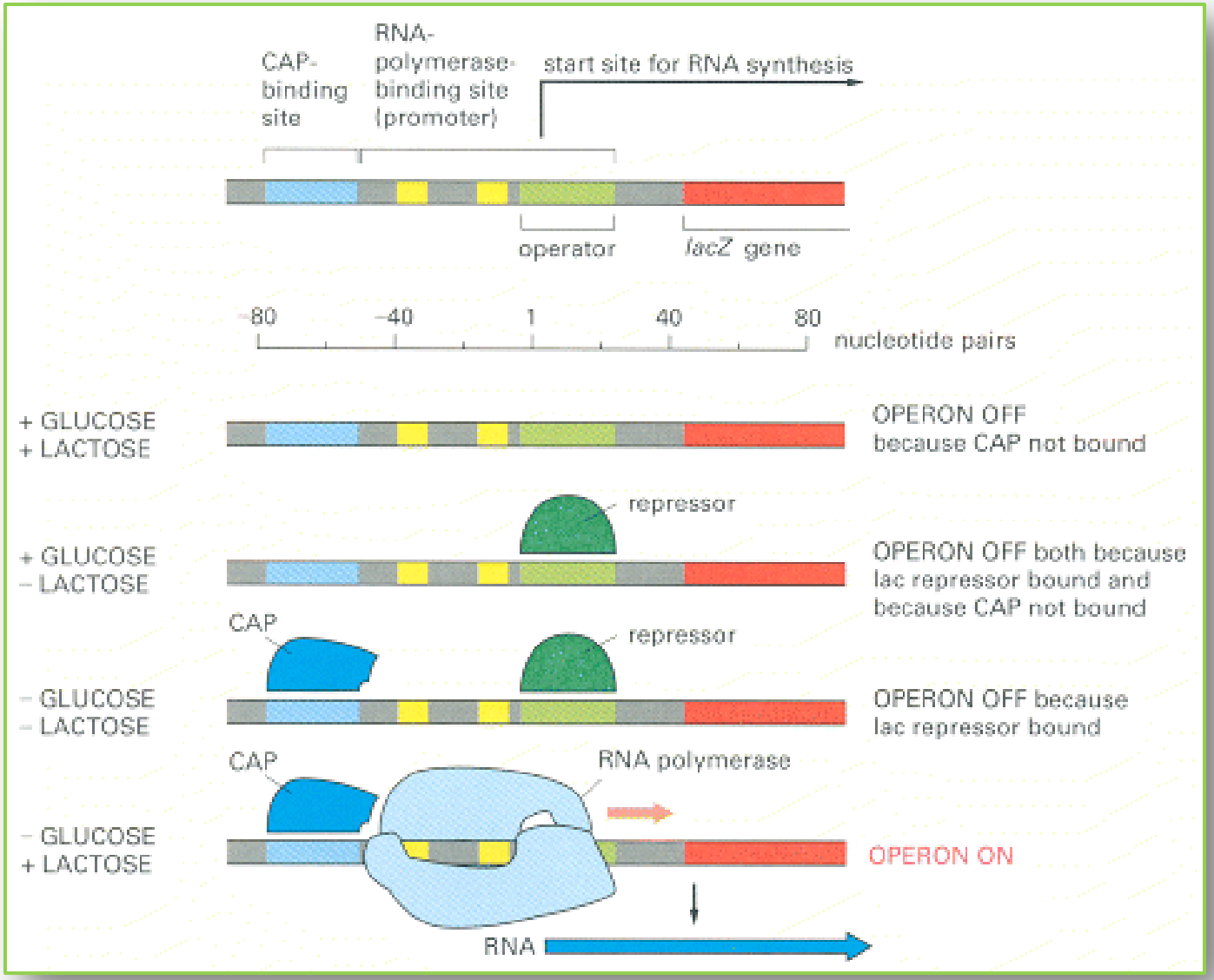


TFs interact with DNA

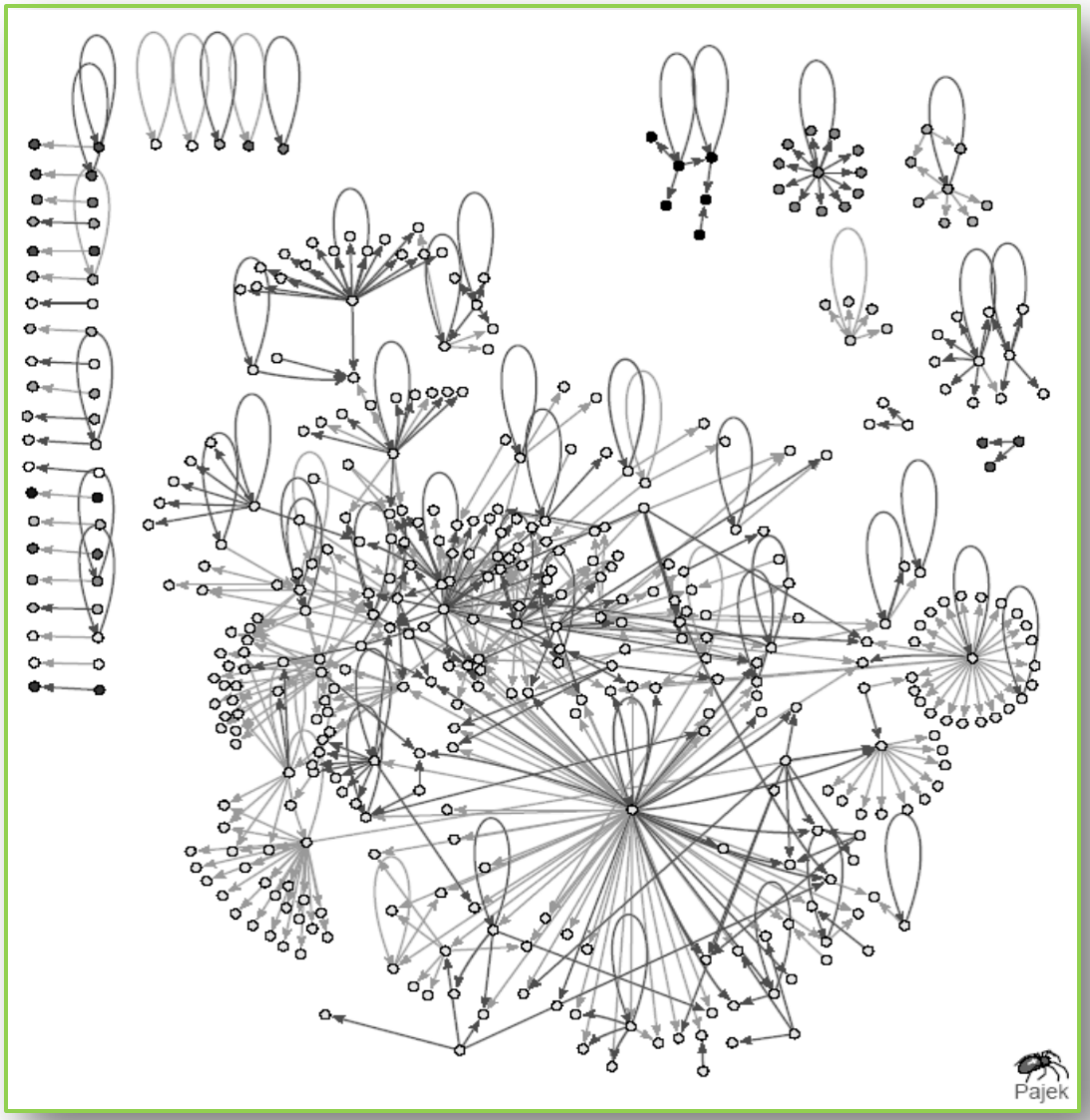


a single amino-acid nucleotide interaction

Transcription regulation



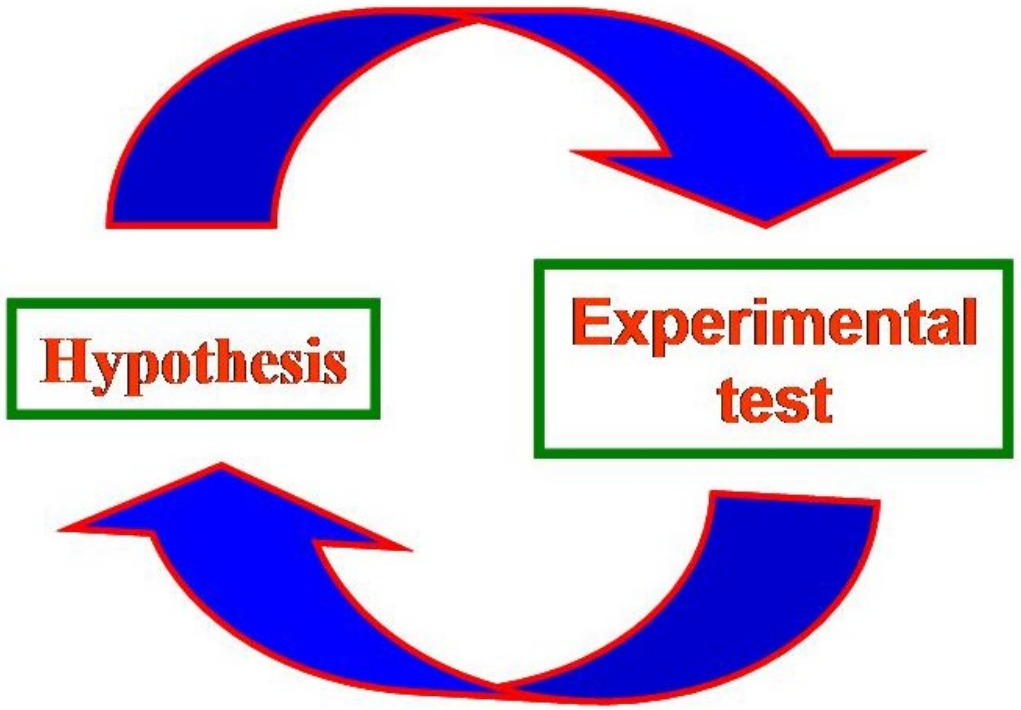
Gene networks



***E. Coli* gene network**

II. Modeling in biology: why quantitative biology?

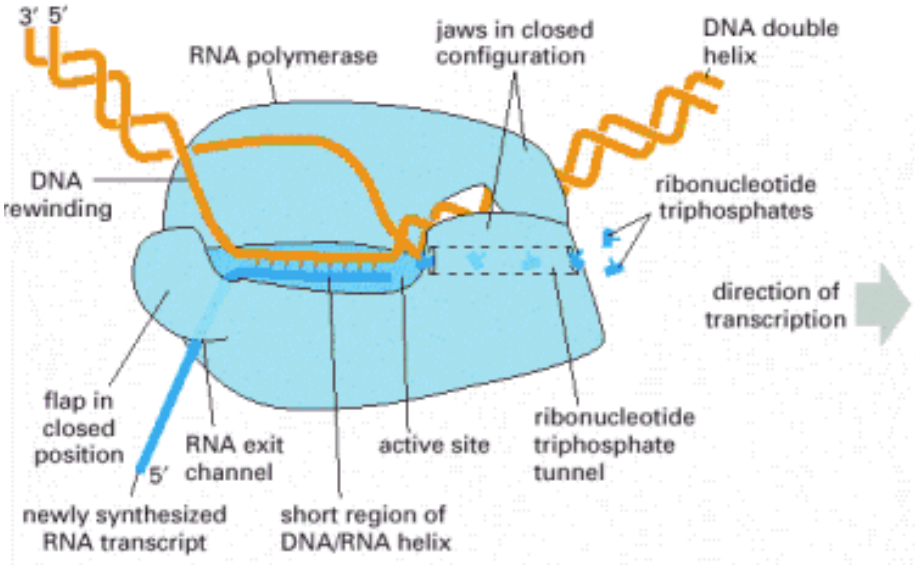
Traditional modeling

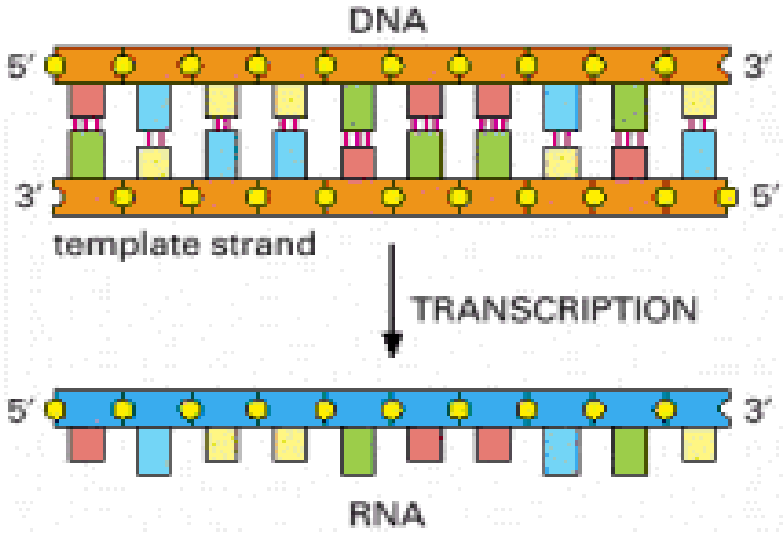


No clear separation between theory and experiment

Scheme of traditional research in biology

Scheme vs. model





Alberts *et al,* Molecular Biology of the cell.

RNA polymerase (RNAP) transcription scheme

↓

This scheme is a model!

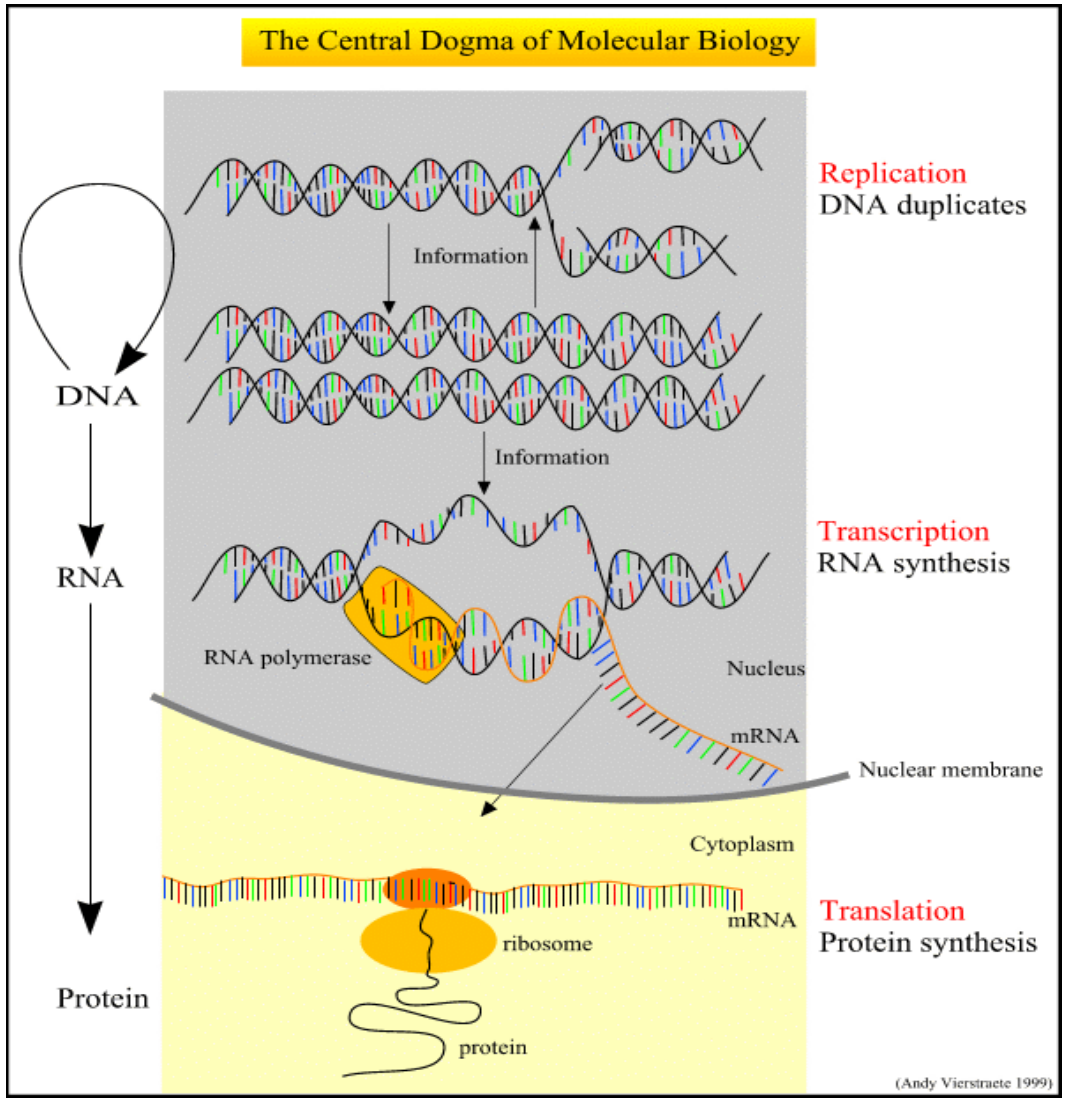
↓

Can be described by even simpler conceptual model

↓

General principle is complementarity

Information flow model



Central dogma of molecular biology

Emphases that information flows from DNA to RNA to proteins

Biological sequences

- **Large amount of data is sequenced**

  ~ 80000 sequenced genomes

  - **Bacteriophage (genome ~50000 bps)**
  - **Bacteria (genome ~5 000 000 bps)**
  - **Human (chromosome ~50 000 000 bps)**

- **Informatics resources are necessary for repository and systematization**
- **Mathematical methods are necessary for sequence analysis**

} **bioinformatics**

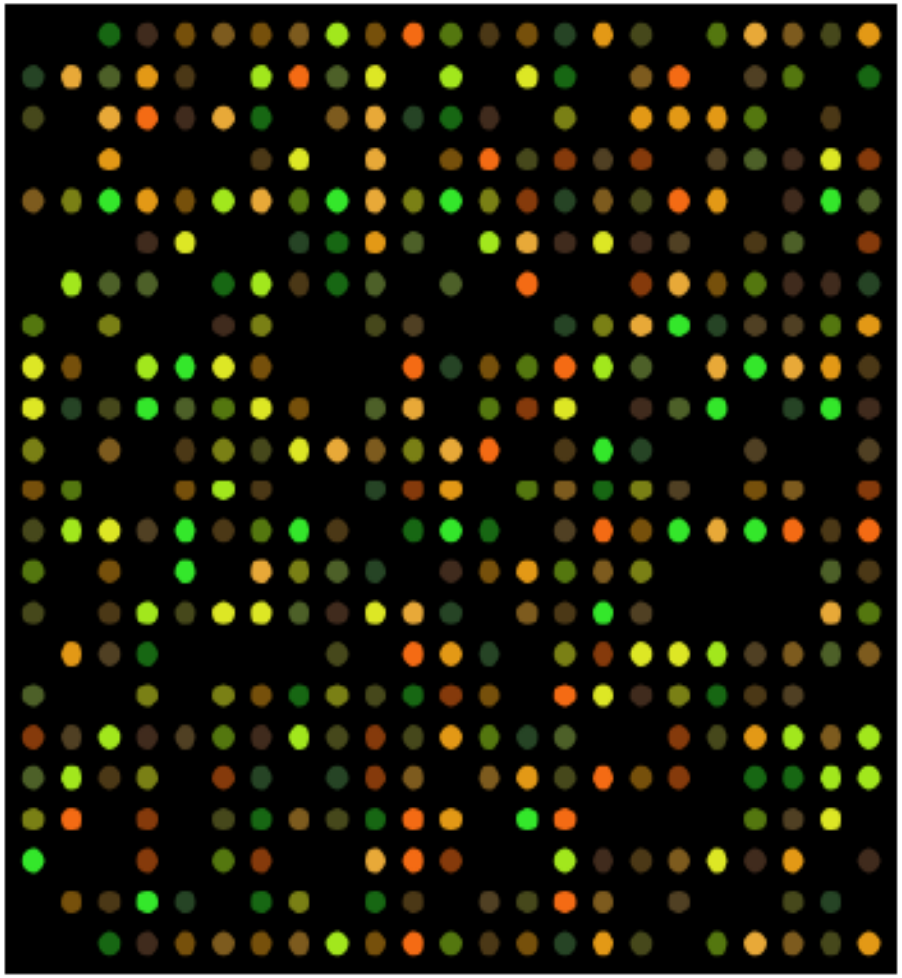
Can have a close connection between biophysical modeling and bioinformatics

Quantitative (biophysical) understanding of biological processes

Improved bioinformatics methods

Specific examples in working session 3!

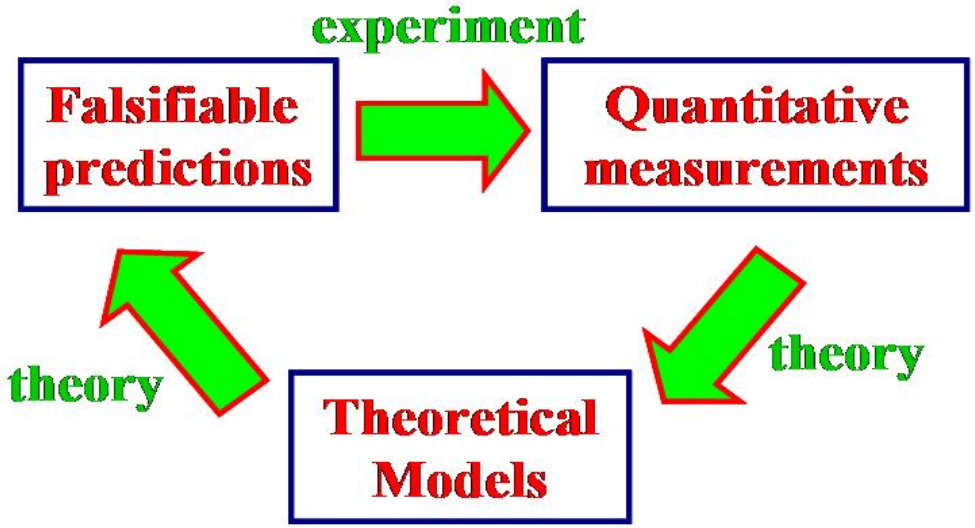
Measuring expression of all genes in genome



DNA microarray measurements

Mathematical modeling necessary for testing the hypothesis.

Research scheme in modern biology



Separation between theory and experiment

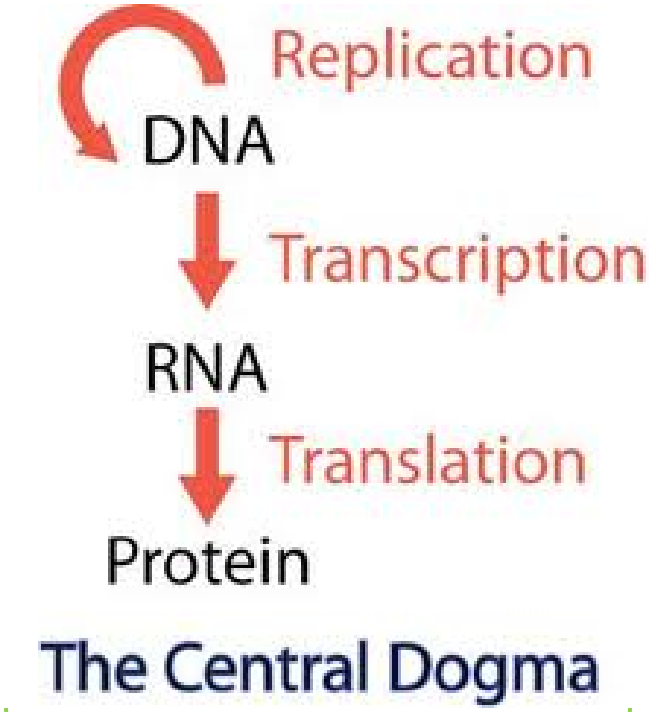
Scheme reminds to physics

Understanding dynamics (complicated)

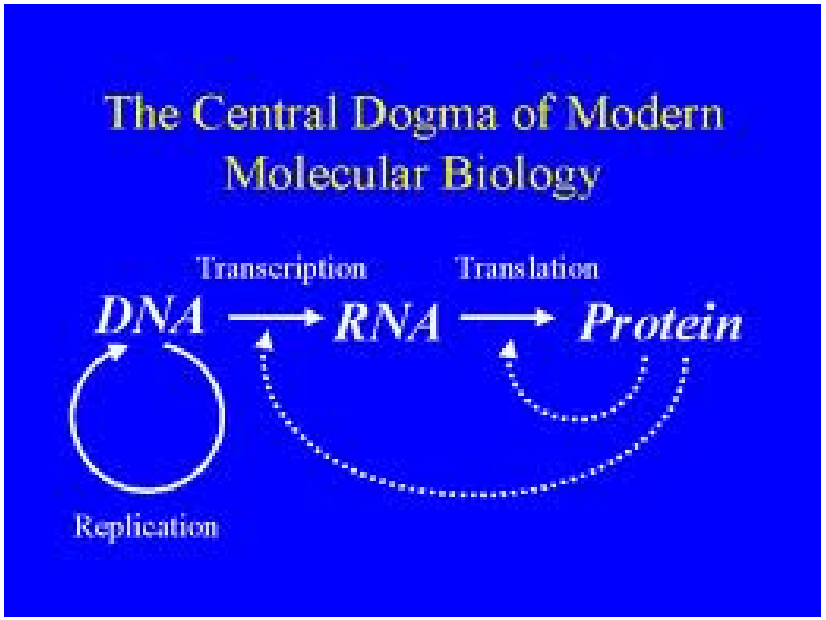
- **Relatively easy to measure dynamics for macroscopic systems.**
- **Hard to measure dynamics of molecules "in-vivo" (but recent advances are making it possible).**
- **Systems typically employ a large number of components (degrees of freedom) with interactions that are highly non-linear.**
- **Advanced biophysical techniques from theoretical biophysics are necessary (statistical physics, nonlinear dynamics, stochastic modeling)**

III. Role of non-linearity: Feedback loops, allostery and cooperativity

Central dogma of molecular biology



Classical formulation: Information flows from DNA to RNA to proteins



For (computational) systems biology feedback loops are crucial.

Intracellular regulation – general properties

- **Nonlinear realationship of output vs. input quantity – linear relationship is generally not a good approximation.**
- **Allostery and cooperativity often have a crucial role.**

Input-output relationship

***A* and *B* are arbitrary molecules, *AB* is their complex:**

$$A + B \rightleftarrows AB$$

Examples:

A	–	**Transcription factor**
B	–	**DNA**
AB	–	**Complex which activates or represses transcription**

A	–	**Small molecule (e.g. oxigen)**
B	–	**Receptor (e.g. hemoglobin)**
AB	–	**Ligand bound за рецептор**

A	–	**Antibody**
B	–	**Antigene**
AB	–	**Complex antibody-antigene**

Input (ligand concentration) to output (binding probability) relationship

$$K_D = \frac{[A][B]}{[AB]} - dissociation\ const.$$

$$\text{"input"} = [B]$$

$$\text{"output"} = \frac{[AB]}{[B]+[AB]} = \frac{[A]}{[A]+K_D}$$

Receptor occupancy

(Fraction of the total receptors bound by ligand)

Nonlinear relationship

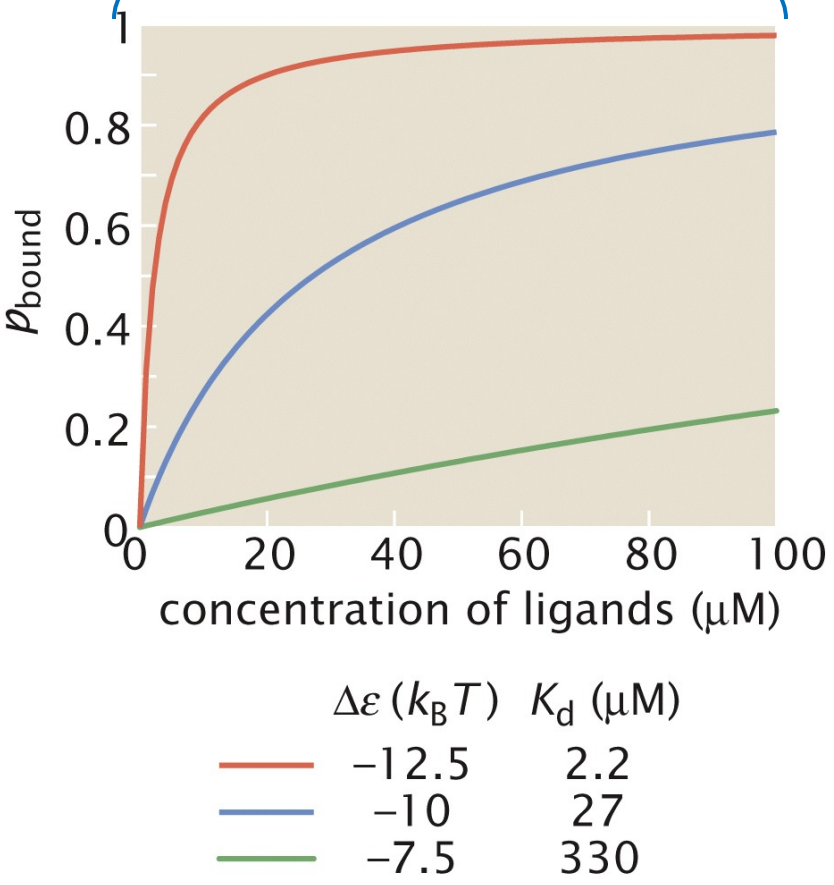


Figure 6.6 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Cooperativity and allostery

Hemoglobin as a model system:

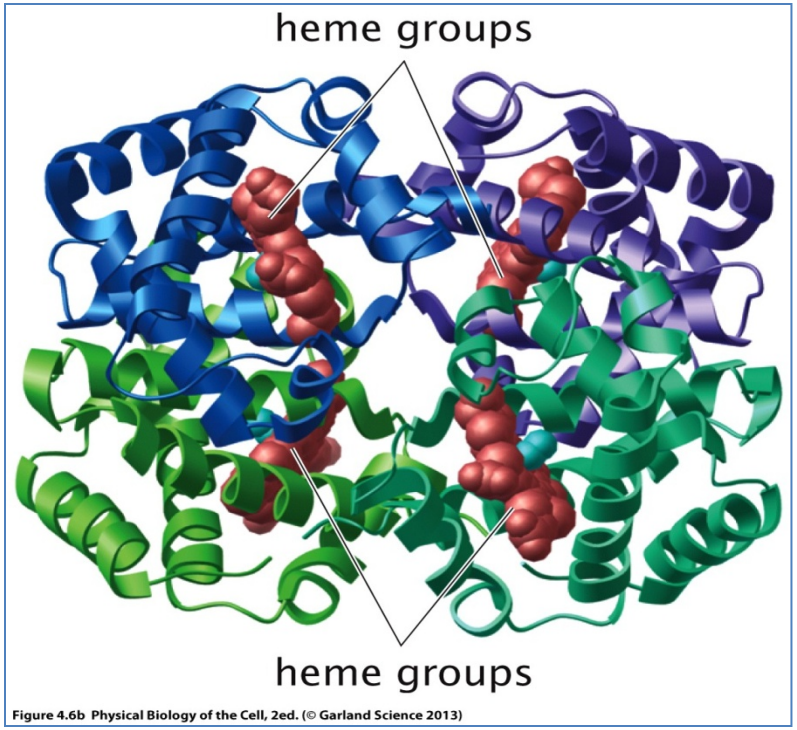
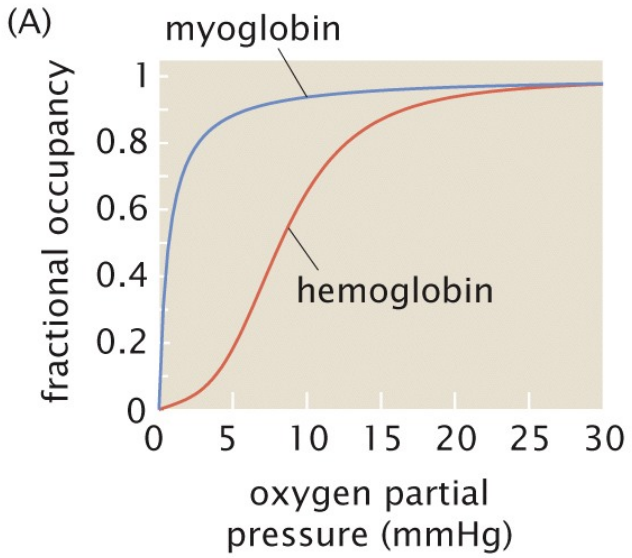


Figure 4.6b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

- Interaction of ligand with receptor
- Protein structure
- Molecular model of desease
- Allostery and cooperativity



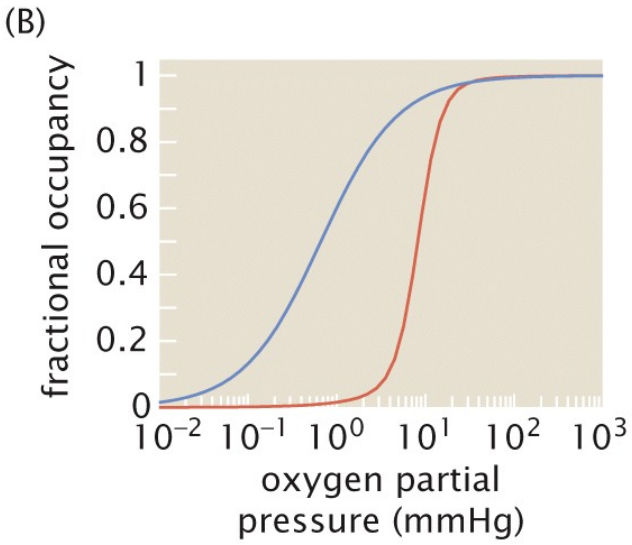


Figure 4.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Myoglobin – only one oxygen bound
Hemoglobin – four oxygens bound

Hemoglobin has much more rapid transition from "OFF" to "ON" state.

OFF state– small oxygen amount bound to receptors

ON state – almost all receptors bound by oxygen

Consequence of coooperativity in interactions (binding of oxygen).

Cooperativity in interactions is related with allostery – Ligand binding at one place in protein, influences binding properties at some other place.

Hill function

n molecules *A* are cooperatively (together) bound to molecule *B*

$$n\,A + B \rightleftarrows nAB$$

$$K_d{}^n = \frac{[A]^n [B]}{[nAB]}$$

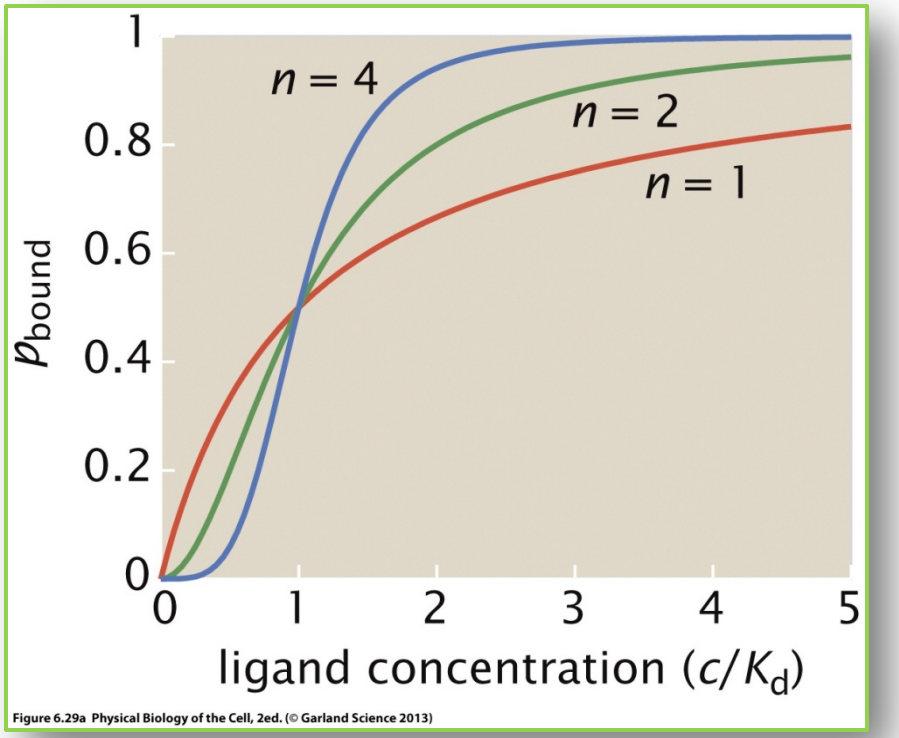


Figure 6.29a Physical Biology of the Cell, 2ed. (© Garland Science 2013)

$$\text{"output"} = \frac{[nAB]}{[B]+[nAB]} = \frac{([A]/K_d)^n}{1+([A]/K_d)^n}$$

Hill constant

Hill function - cooperative binding of ligand to receptor

Problem: hemoglobin vs. myoglobin binding

data from Imai, K. (1990). Biophys Chem 37(1-3): 197-210.

Hill curve, hemoglobin

Experimental data for fractional occupancy of hemoglobin receptors by oxigen are provided in the Excel file.

a) **Show that Hills function fits well this data**
b) **What is the Hill constant value?**
c) **What is biophysical interpretation of the second parameter in the fit?**

Note1: The first column in Excel file is oxygen pressure (proportional to ligand concentration), the second column is fractional receptor occupancy.

Note2: You can do this in any software of your choice, where non-linear regression is available.

Hill curve, myoglobin

The same as for hemoglobin, but now data for mioglobin are provided.

a) Show that Hills function again fits well this data.

b) What is now the value of the Hill constant?

c) Based on this, discuss what is crucial difference between hemoglobin and mioglobin with respect to receptor binding?

Literature:

General:

- **Phillips, R., Kondev, J., Theriot, J., & Garcia, H. (2012). *Physical biology of the cell*. Garland Science.**
- **Ingalls, B. P. (2013). *Mathematical modeling in systems biology: an introduction*. MIT press.**
- **Sneppen, K., & Zocchi, G. (2005). *Physics in molecular biology*. Cambridge University Press.**
- **Strogatz, S. (2001). Nonlinear dynamics and chaos: with applications to physics, biology, chemistry, and engineering.**

Specific:

- **Bruce Alberts et. al. (2014). *Molecular Biology of the Cell*. W. W. Norton & Company**
- **Djordjevic, M., Rodic, A., & Graovac, S. (2019). From biophysics to 'omics and systems biology. *European Biophysics Journal*, 1-12.**