Molecular and Cellular Computing

Lecture series at Universidad Politécnica de Madrid

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Day 3: Biological Engineering
1. Biological Background

Some slides from *An Introduction to Bioinformatics Algorithms*, Neil C. Jones and Pavel A. Pevzner (MIT Press), http://www.bioalgorithms.info

Basics of Life

- Cells store all information to replicate themselves
  - Human genome is around 3 billions base pairs long
  - Almost every cell in human body contains same set of genes
  - But not all genes are used or expressed by those cells
- Machinery:
  - Collect and manufacture components
  - Carry out replication
  - Kick-start its new offspring

(A cell is like a car factory)

Basics of Life

- **Nucleus = library**
- **Chromosomes = bookshelves**
- **Genes = books**
- Almost every cell in an organism contains the same libraries and the same sets of books
- Books represent all the information (DNA) that every cell in the body needs so it can grow and carry out its various functions

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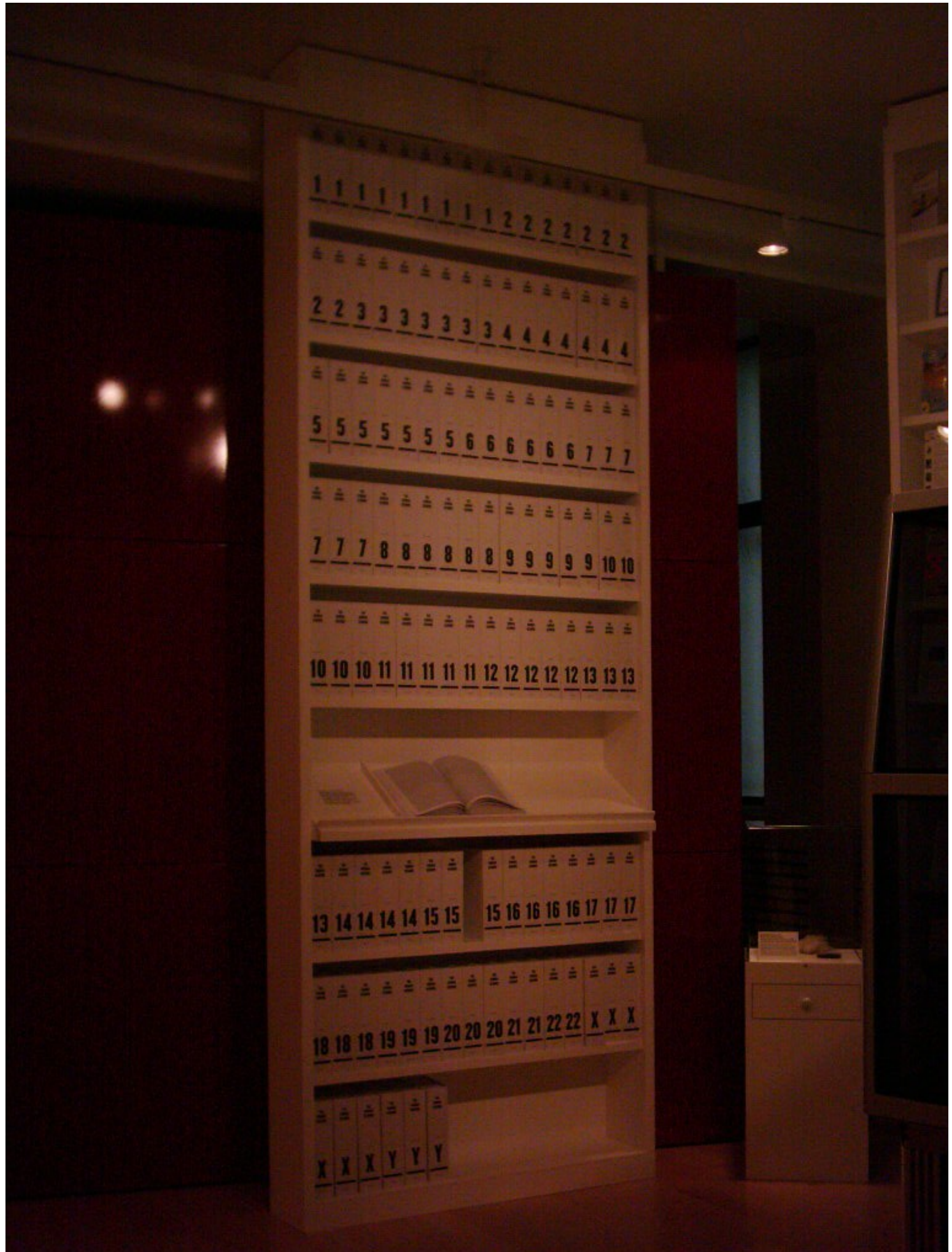


5m x 2m,
120 volumes

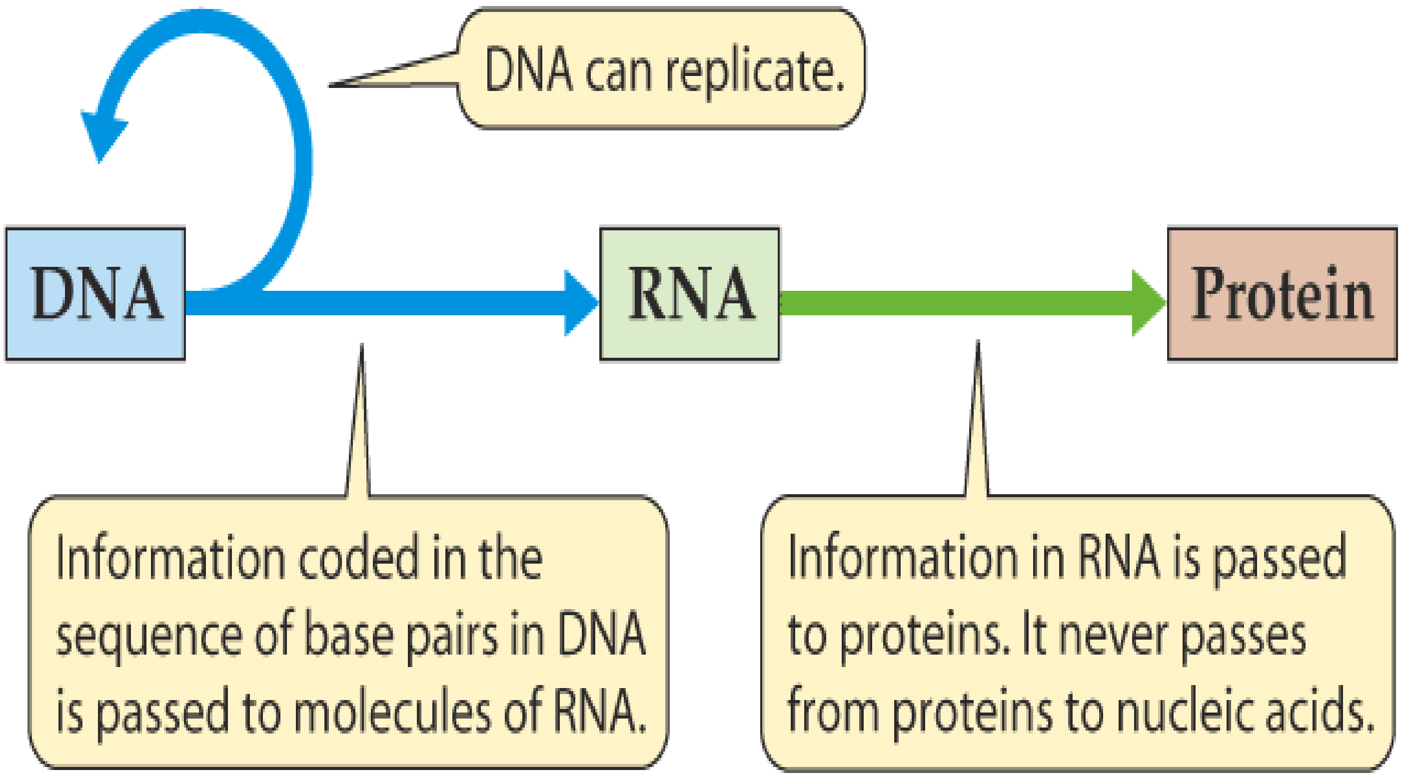
Terminology

- The *genome* is an organism's complete set of DNA.
  - A bacterium contains about 600,000 DNA base pairs
  - Human and mouse genomes have some 3 billion
- Human genome has 24 distinct chromosomes (1-22, X and Y)
  - Each chromosome contains many *genes*
- **Gene**
  - basic physical and functional units of heredity.
  - Specific sequences of DNA bases that encode instructions on how to make *proteins*
- **Proteins**
  - Make up the cellular structure
  - Large, complex molecules made up of smaller subunits called *amino acids*

Three Critical Molecules

- DNAs
  - Hold information on how cell works
- RNAs
  - Act to transfer short pieces of information to different parts of cell
  - Provide templates to synthesize into protein
- Proteins
  - Form enzymes that send signals to other cells and regulate gene activity
  - Form body's major components (e.g. hair, skin, etc.)

DNA, RNA and Information Flow



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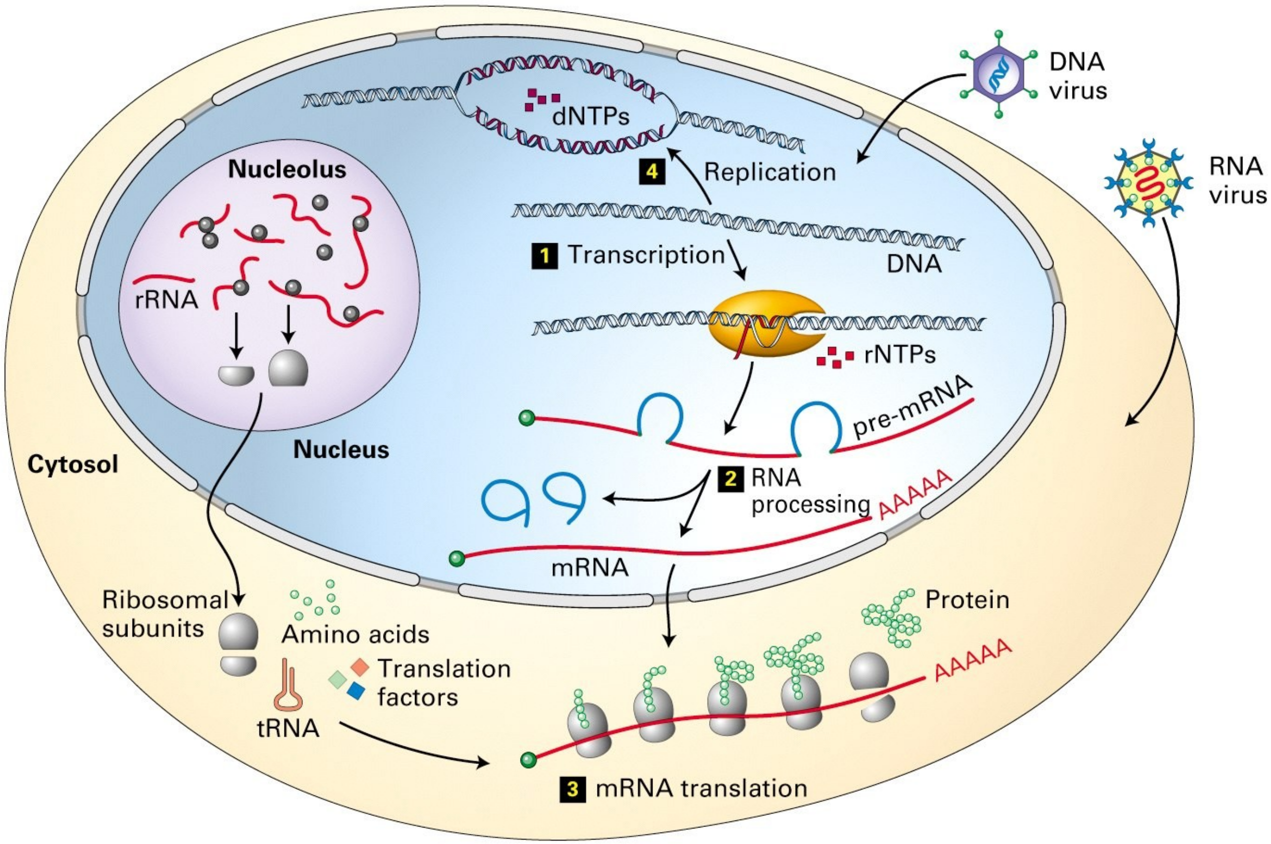
Overview of DNA to RNA to Protein



- A gene is expressed in two steps
  1) *Transcription*: RNA synthesis
  2) *Translation*: Protein synthesis

Proteins: Workhorses of the Cell

- 20 different *amino acids*
  - Different chemical properties cause the protein chains to fold up into specific three-dimensional structures that define their particular functions in the cell
- Proteins do all essential work for the cell
  - Build cellular structures
  - Digest nutrients
  - Execute metabolic functions
  - *Mediate information flow within a cell and among cellular communities*
- Proteins work together with other proteins or nucleic acids as "molecular machines"
  - Structures that fit together and function in highly specific, lock-and-key ways

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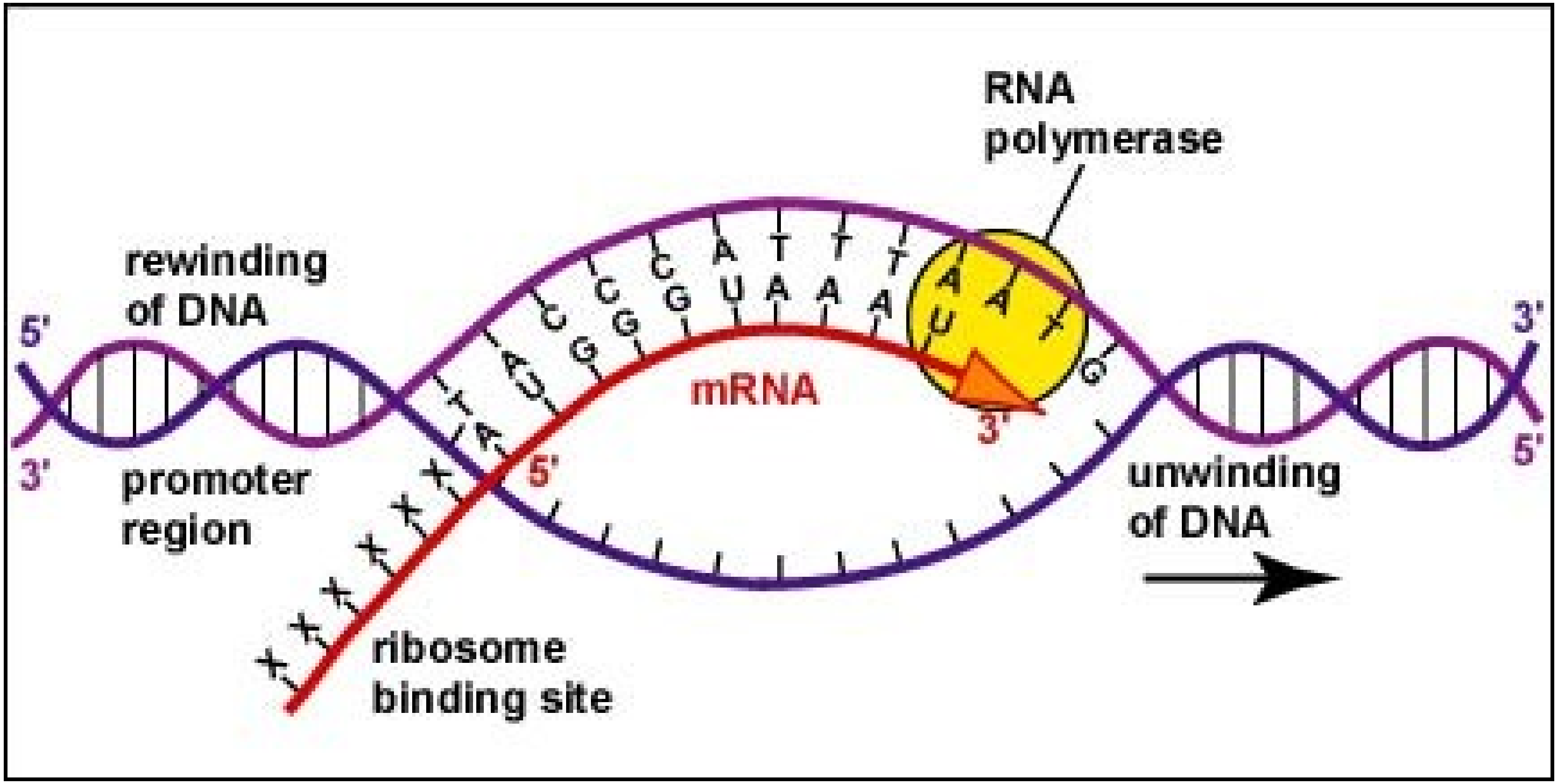
DNA to RNA: Transcription

- DNA gets transcribed by a protein known as *RNA-polymerase*
- This process builds a chain of bases that will become mRNA
- RNA and DNA are similar, except that RNA is single stranded and thus less stable than DNA
  - Also, in RNA, the base uracil (U) is used instead of thymine (T), the DNA counterpart

Transcription

- To begin transcription requires a *promoter*, a small specific sequence of DNA to which polymerase can bind (~40 base pairs “upstream” of gene)
- There can also be *repressors* and *inhibitors* acting in various ways to stop transcription
- This makes regulation of gene transcription *complex* to understand (as we shall see)

Transcription



The Genetic Code

- Scientists conjectured that proteins came from DNA; but how did DNA code for proteins?
- If one nucleotide coded for one amino acid, then there'd be 4^1 amino acids
- However, there are 20 amino acids, so at least 3 bases code for one amino acid, since $4^2 = 16$ and $4^3 = 64$
  - This triplet of bases is called a "codon"
  - 64 different codons and only 20 amino acids means that the coding is *degenerate*: more than one codon sequence code for the same amino acid

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RNA to Protein: Translation

- Ribosomes and *transfer-RNAs* (tRNA) run along the length of the newly synthesized mRNA, decoding one codon at a time to build a growing chain of amino acids (“peptide”)
- Three base pairs of RNA (called a codon) correspond to one amino acid based on a fixed table

Second Position

First Position	U		C		A		G		Third Position
U	UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys	U
	UUC		UCC		UAC		UGC		C
	UUA	Leu	UCA		UAA	*Stop*	UGA	*Stop*	A
	UUG		UCG		UAG	*Stop*	UGG	Trp	G
C	CUU	Leu	CCU	Pro	CAU	His	CGU	Arg	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	Gln	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	Lys	AGA	Arg	A
	AUG	Met	ACG		AAG		AGG		G
G	GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	Glu	GGA		A
	GUG		GCG		GAG		GGG		G

Protein Folding

- Proteins are not linear structures, though they are built that way
- The amino acids have very different chemical properties; they interact with each other after the protein is built
  - This causes the protein to start fold and adopting it’s functional structure
  - Proteins may fold in reaction to some ions, and several separate chains of peptides may join together through their hydrophobic and hydrophilic amino acids to form a polymer

Protein Folding

- The structure that a protein adopts is vital to its chemistry
- Its structure determines which of its amino acids are exposed carry out the protein's function
- Its structure also determines what substrates it can react with
- Protein structure prediction is one of the "Holy Grails" of modern biology

Genetic Regulation

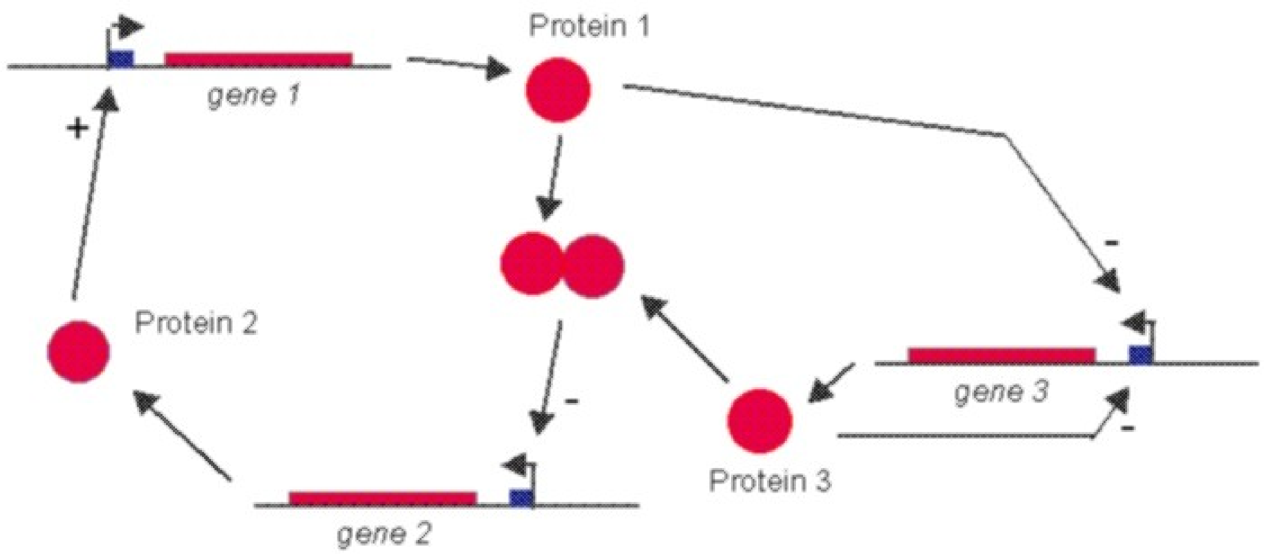
"The punched tape running along the inner seam of the double helix is much more than a repository of enzyme stencils. It packs itself with regulators, suppressors, promoters, case-statements, if-thens".

Richard Powers, *The Gold Bug Variations*, p. 365, HarperPerennial

Genetic Regulation

- DNA contains the potential coding information for a vast range of possible proteins
- Gene expression is not a linear process
- Genes may require the product(s) of other gene(s) to in order to be expressed
- The product of one gene may turn off the expression of another gene
- The product of a gene can even effect its *own* expression (feedback)

Example



Gene 2 codes for a protein that activates the transcription of gene 1, while gene 1 and gene 3 code for proteins that form a complex inhibiting the transcription of gene 2. Activation and inhibition of gene expression are indicated by + and -, respectively.

The *lac* Operon

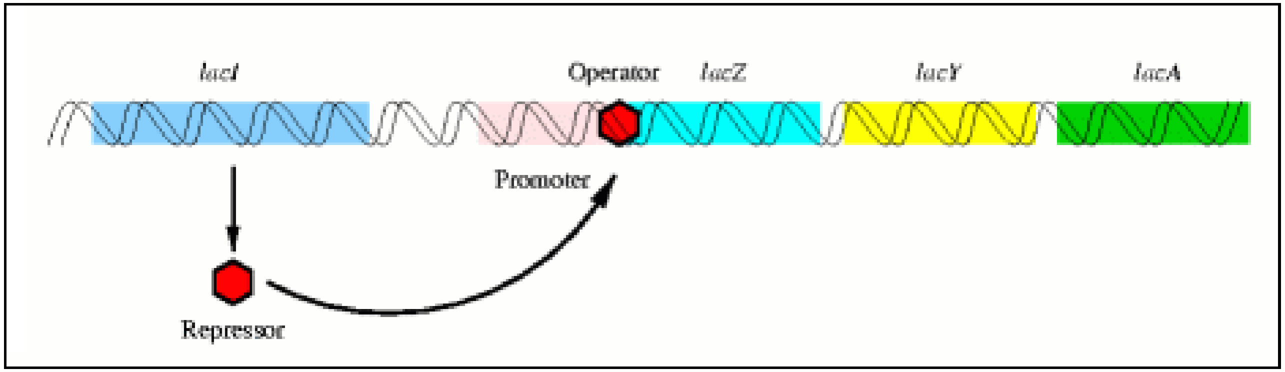
- *Operon* - set of functionally related genes with common promoter
- *lac* operon contains three structural genes that allow *E. coli* to utilise lactose
- When bacteria grown in glucose, product of *lacI* gene *represses* transcription of *lac*
- When grown in glucose *and* lactose, lactose by-product inhibits repressor, and the genes are expressed
- *lac* operon controlled by two sugars (inputs)

Jacob F; Monod J (1961). Genetic regulatory mechanisms in the synthesis of proteins. *J Mol Biol*. **3**: 318-56

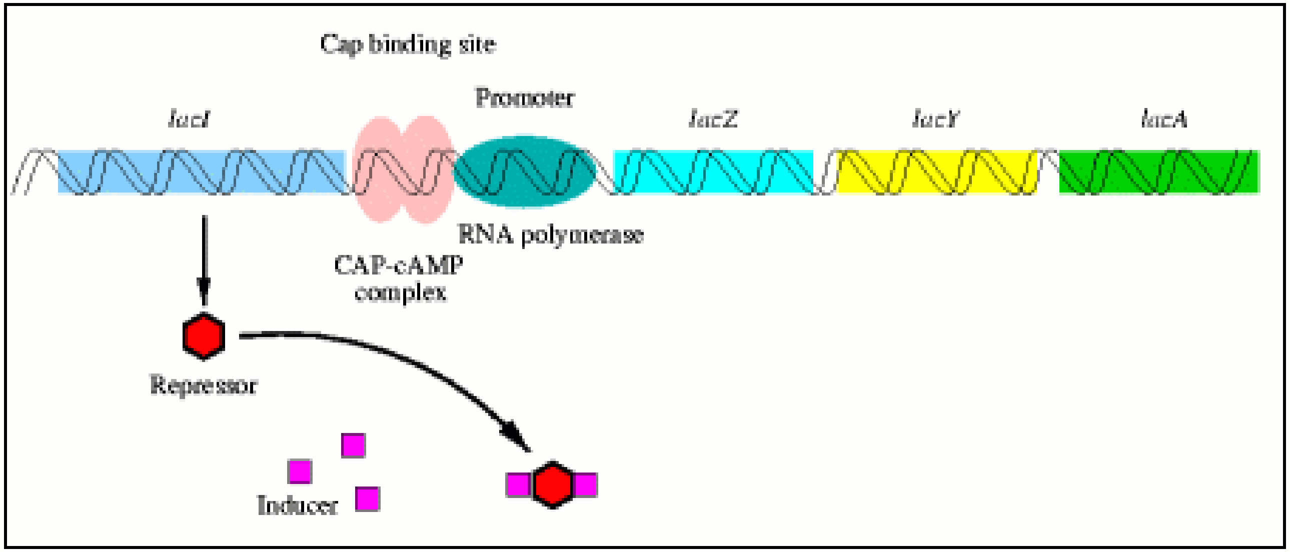
The *lac* operon

- The *lac* genes are so-called because, in the E. coli bacterium, they combine to produce a variety of proteins that allow the cell to metabolise the sugar lactose
- For reasons of efficiency, these proteins should only be produced (i.e., the genes be turned on) when lactose is present in the cell's environment
- Making these proteins when lactose is absent would be a waste of the cell's resources
- However, a different sugar – glucose – will always be preferable to lactose, if the cell can get it, since glucose is an "easier" form of sugar to metabolise

Repression and Inhibition



Just glucose

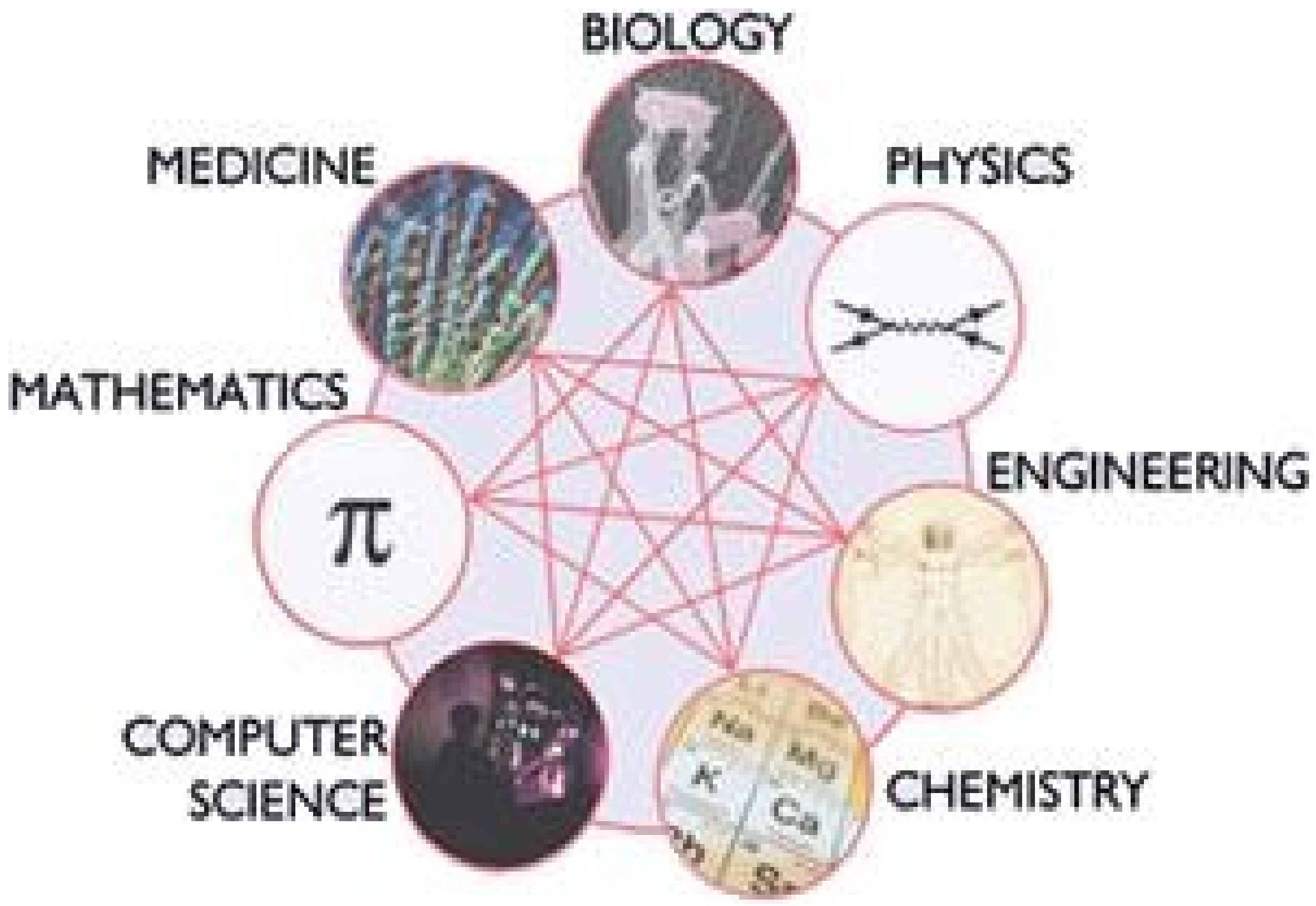


Glucose and lactose

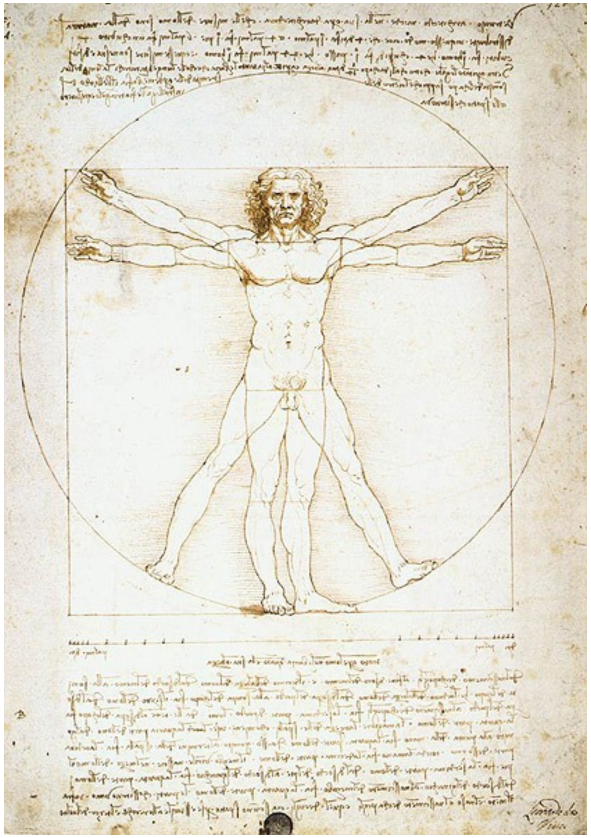
Sugar Logic

- "The logic of biological regulatory systems abides...like the workings of computers, by the propositional logic of George Boole." F. Jacob
- *lac* operon may be thought of as a genetic circuit that computes the function
  - L AND (NOT G)
- Car seat belt circuit
- By showing how one gene could affect the expression of another, Jacob and Monod laid the foundations for a *systems* level understanding of the genome

Systems Biology



Systems Insight



30,000 genes (approx.)

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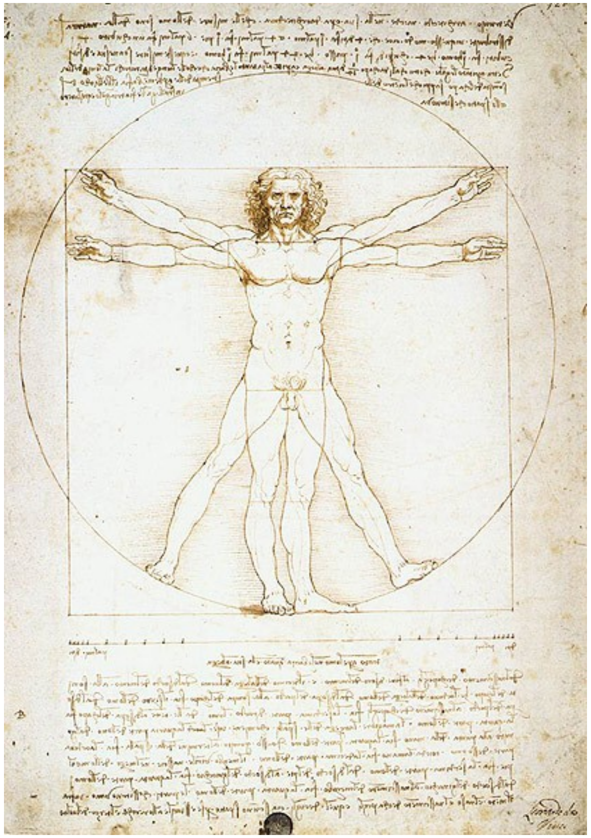
Systems Insight



30,000 genes (approx.)

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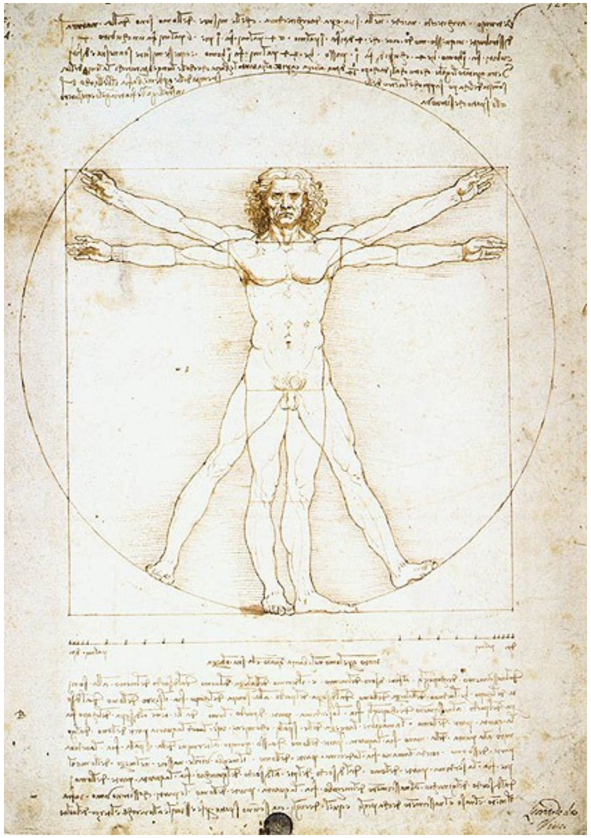
Systems Insight



30,000 genes (approx.)

20,000 genes!

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$2^{10,000}$ =

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