Genetic disorders

A disease caused in whole or in part by a change in the DNA sequence away from the normal sequence.

As we unlock the secrets of the human genome (the complete set of human genes), we are learning that nearly all diseases have a genetic component.

Some diseases are caused by mutations that are inherited from the parents and are present in an individual at birth, like *sickle cell disease*.

Other diseases are caused by acquired mutations in a gene or group of genes that occur during a person's life. Such mutations are not inherited from a parent, but occur either randomly or due to some environmental exposure (such as cigarette smoke). These include many cancers, as well as some forms of neurofibromatosis.

Main causes

mutations in multiple genes

multifactorial inheritance disorder

**mutation in one gene**

monogenic disorder

damage to chromosomes

changes in the number or structure of entire chromosomes, the structures that carry genes

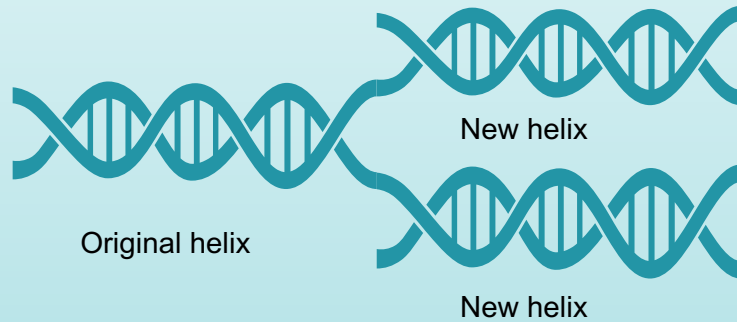**combination of gene mutations and environmental factors**

DNA as a puzzle made of nucleotides

You can think to DNA as a double-helix of puzzle pieces. Each piece represents a nucleotide and can fit only with the complementary one on the other strand.
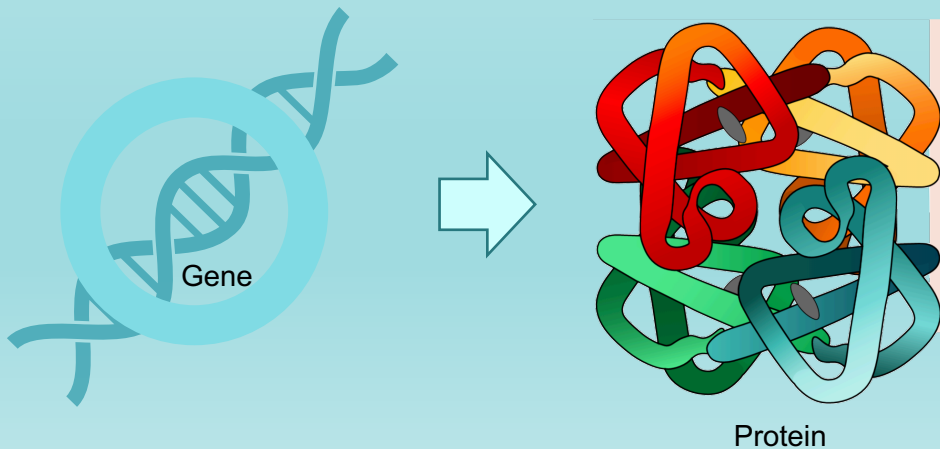
AT

CG
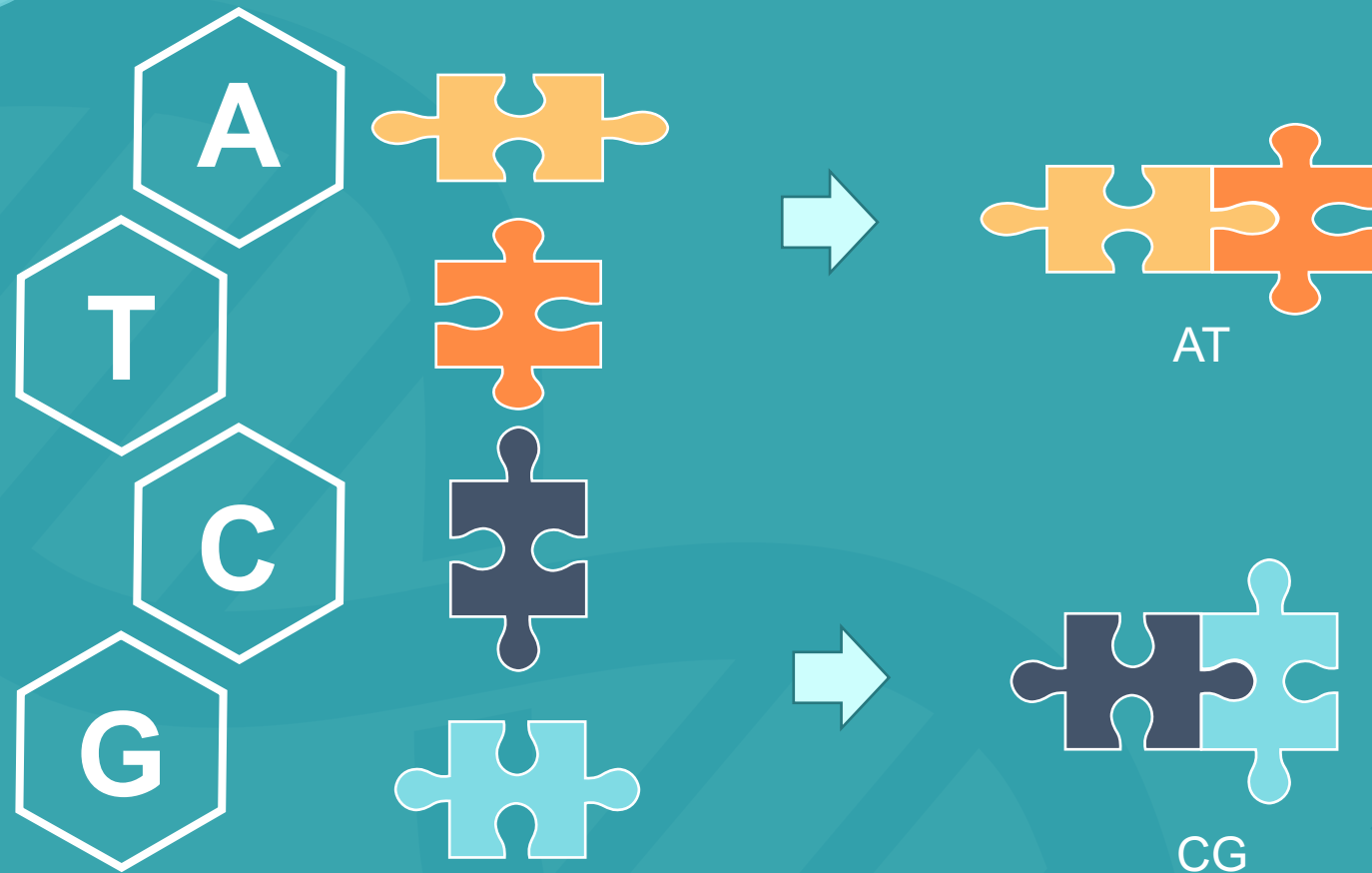
DNA replication and gene expression

DNA replication

New helix

Original helix

New helix

Basing on nucleotides (puzzle pieces) complementarity, the DNA replication generates two new double helices identical to the original one
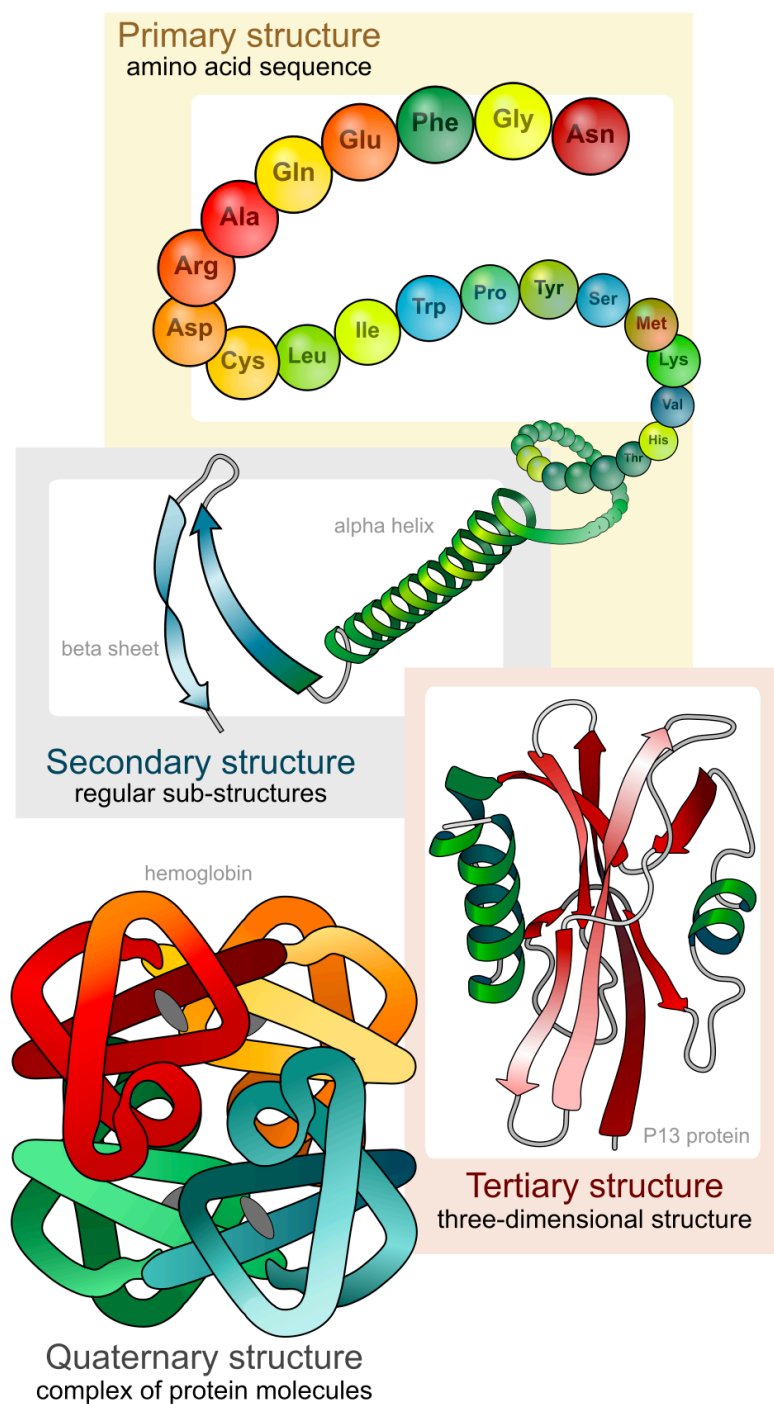
Gene expression

Gene

Protein

A portion of the DNA sequence (a gene) is used as instruction to produce a new protein

Protein folding

Primary structure
amino acid sequence

alpha helix

beta sheet

Secondary structure
regular sub-structures

hemoglobin

Tertiary structure
three-dimensional structure

P13 protein

Quaternary structure
complex of protein molecules

A protein is made by a sequence of amino acids.

Differently from the pieces that compose DNA, amino acids do not have specific complementarities, but the order in which they are connected is determined during the gene expression, basing on the sequence of nucleotides of the related gene.
For that reason we can say that a gene is the instruction for the production of a protein.

Energies of the environment in which the protein is placed and specific properties of each amino acid push the protein to fold into various substructures and eventually reach its final conformation.

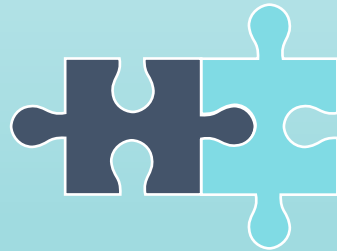# What is a mutation?

A mutation is a change of the correct nucleotide sequence in a gene. It is often transmitted by inheritance or is caused by an error during the gene replication or expression.

A wrong gene sequence represent an incorrect instruction for the generation of a new protein.
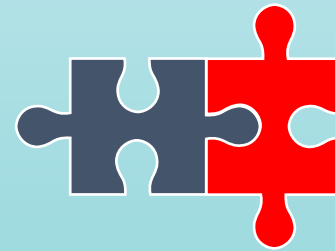
A mutation can affect even a single nucleotide (point mutation).
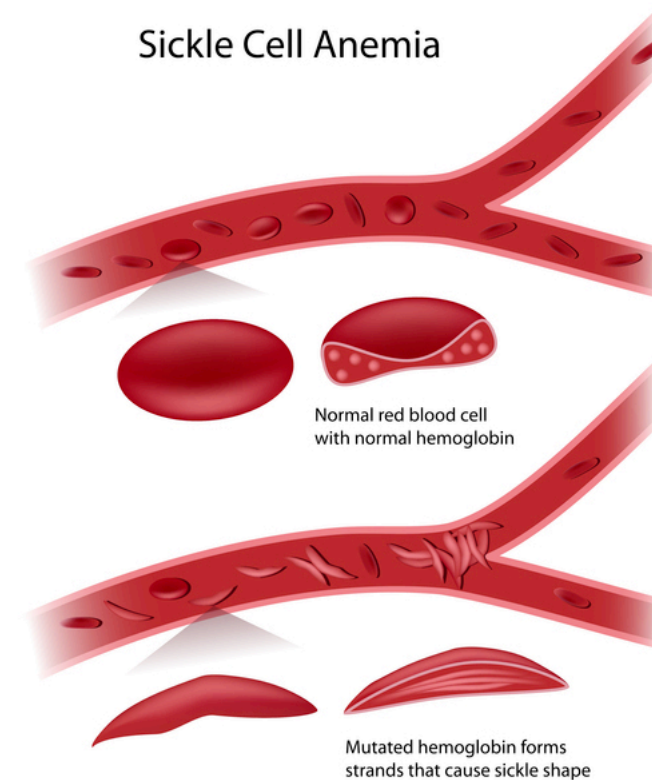
correct pairing   mutation   wrong pairing

Sickle cell disease

Sickle cell disease is a group of disorders that affects hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle, or crescent, shape.

The hemoglobin S is generated by a point mutation of the related gene, which cause change the production of a wrong amino acid in the protein sequence.

The properties of this amino acid cause the molecule to produce a patch that fits into a pocket of another hemoglobin molecule. This process forms fibrous precipitates, which produce the characteristic sickle shape of the affected red blood cells.

Sickle Cell Anemia

Normal red blood cell with normal hemoglobin

Mutated hemoglobin forms strands that cause sickle shape

Information and image courtesy of National Human Genome Research Institute (genome.gov)
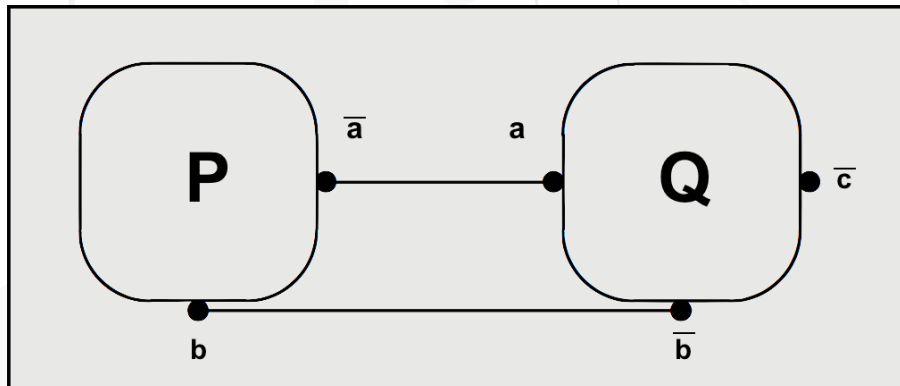
Modeling the gene expression

Theoretical tool: Process algebras

Collection of operations for building a new process description from existing ones.

A process can be viewed as a system that exhibit a behavior, a black box with a name and a set of communication channels.

Core idea

Entire molecules, their substructures or even their elementary units as well as their interactions can be modelled as processes. In this way it is also possible to identify similarities among different classes of molecules and in the functions they carry out.
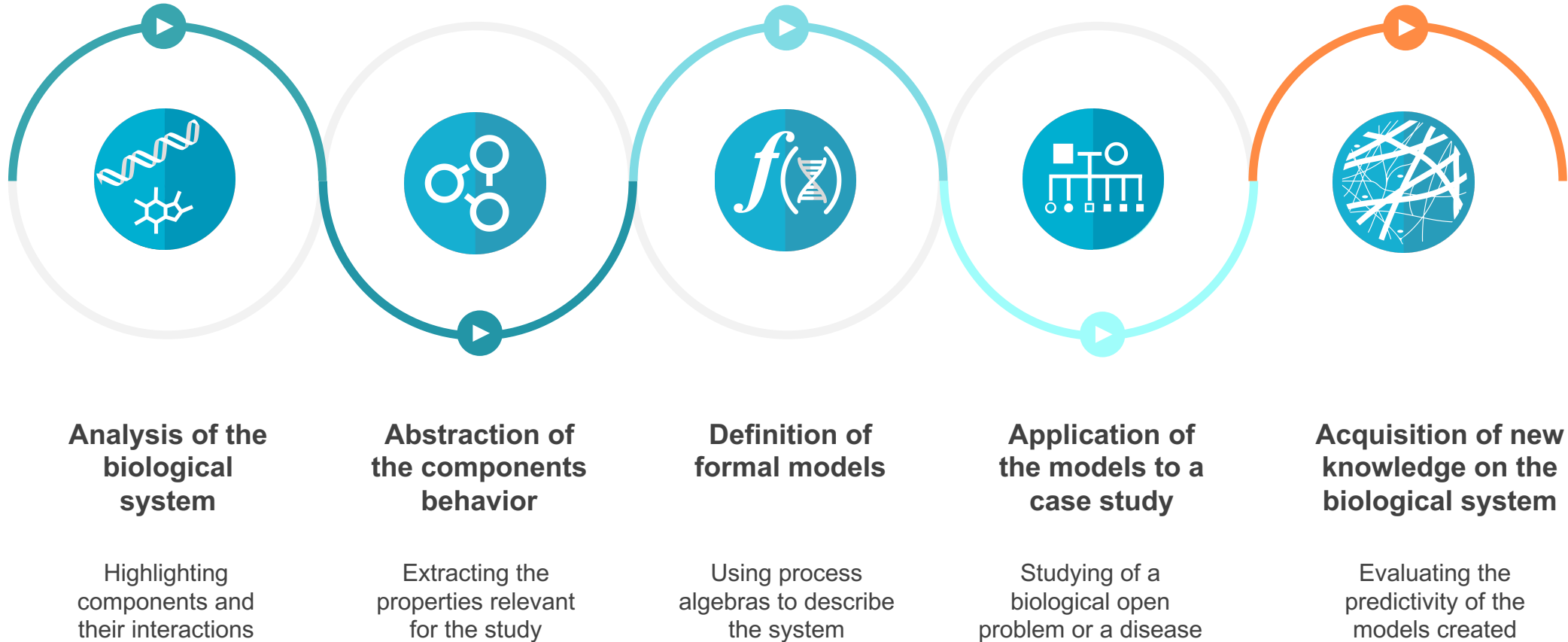
P and Q are processes that communicate with the channels labeled *a* and *b*; Q may communicate with a third process via the channel labelled *c*

Modeling Phases

Analysis of the biological system

Highlighting components and their interactions

Abstraction of the components behavior

Extracting the properties relevant for the study

Definition of formal models

Using process algebras to describe the system

Application of the models to a case study

Studying of a biological open problem or a disease

Acquisition of new knowledge on the biological system

Evaluating the predictivity of the models created

Results and aims of our approach

Formal models of the gene expression

We modeled through process algebras the entire gene expression, so we are already able to predict the effect of a mutation on the folding process of a protein in sickle cell anemia

Basis for the development of computational tools for further studies on the gene expression

Better understanding of the effect of mutation in genetic disorders

Study of rare genetic disease