Technická univerzita v Košiciach
Fakulta elektrotechniky a informatiky

Moja záverečná práca
(šablóna)

Bakalárska práca

2018 **Bc. Janko Hraško PhD.**

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Fakulta elektrotechniky a informatiky

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Študijný program:	Informatika
Študijný odbor:	9.2.1. Informatika
Školiace pracovisko:	Katedra počítačov a informatiky (KPI)
Školiteľ:	Leslie Lamport
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Košice 2018 **Bc. Janko Hraško PhD.**

Abstrakt v SJ

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Kľúčové slová v SJ

LaTeX, programovanie, sadzba textu

Abstrakt v AJ

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Bibliografická citácia

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Vyhlasujem, že som záverečnú prácu vypracoval(a) samostatne s použitím uvedenej odbornej literatúry.

Košice, 13.5.2018 .....

Vlastnoručný podpis

Poďakovanie

Na tomto mieste by som rád poďakoval svojmu vedúcemu práce za jeho čas a odborné vedenie počas riešenia mojej záverečnej práce.

Rovnako by som sa rád poďakoval svojim rodičom a priateľom za ich podporu a povzbudzovanie počas celého môjho štúdia.

V neposlednom rade by som sa rád poďakoval pánom *Donaldovi E. Knuthovi* a *Leslie Lamportovi* za typografický systém LaTeX, s ktorým som strávil množstvo nezabudnuteľných večerov.

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Úvod

The order of DNA sequence and its variations are the very aspect which dictates the developmental processes of an organism, determines susceptibility to various diseases and uniquely identifies each creature. This area has always been on the periphery of the interests of scientific society, since the discovery in 1869 by Swiss-born biochemist Fredrich Miescher. For instance, The Human Genome Project (HGP) which started on October 1, 1990 and completed in April 2003 was one of the greatest feats of exploration in history of science. It was aimed at reading all the DNA sequences of our species, Homo sapiens. All in all, HGP introduced us the ability to read nature's complete genetic blueprint for building a human being. However, despite the successful completion of the project, a number of unknown DNA properties is still exists and demands the profound studying.

The knowledge of the genome structure has significantly increased in the past few decades thanks to the recent developments in the field of advanced analyzing techniques.[1] The Sanger sequencing technology has been traditionally used to elucidate the DNA sequencing information since it was developed in the 1977th. However, it is capable of obtaining sequences of maximum length of 800 base pairs per one operation, which makes the sequencing process much longer and complicated. In spite of development of new sequencing techniques, some technology limits exist. For instance, the human genome in particular presents a number of major obstacles to correct read alignment, due to its size (3 GB) and complexity (48% repetitive sequences), as do other plant plant and vertebrate genomes.

In addition, it is impossible to assemble the whole genome sequence of species using the data merely of one individual due to occurrence of the single nucleotide polymorphisms and mutations which affect the precise result. Several sequencing algorithms and searching methods were developed to deal with such issues which are the basis of the bioinformatics.[2] To be precise, the science was

[1] Askree, A.H., Yehuda, T., Smolikov, S., Gurevich, R., Hawk, J., Coker, C., Krauskopf, A., Kupiec, M., and McEachern, M.J. 2004. A genome-wide screen for Saccharomyces cerevisiae deletion mutants that affect telomere length. Proc. Natl. Acad. Sci. 101: 8658–8663.

[2] Danilevskaya, O.N., Arkhipova, I.R., Traverse, K.L., and Pardue, M.-L. 1997. Promoting in tan-

developed to deal with the next problems: assembling the complete nucleic acid sequence from the smaller parts, its comparison, analyzing and searching of similarities.

The usual eukaryotic genome consists not only of nuclear DNA, but also of DNA which is isolated from it and belongs to some organelles (mitochondrial mDNA, plastid DNA) that became a part of the cells in the evolution process. To identify key features and determine the exact genes at the complete DNA sequence, to distinguish the segments belonging to particular chromosomes it must visualized in some way. The whole genome might be visualized either as the two dimensional representation of the nucleotide sequence or as the 3D model of the spatial DNA or RNA architecture. The first way allows to analyze each gene and precisely identify each protein that it encodes and to trace the kinship of species, while the second way provides us with the possibility of understanding the inner cellular processes and the very interaction between different enzymes and nucleic acid from the chemical point of view. This work concerns mainly the first method of visualizing sequencing data.

Although several DNA processing tools exist, the problem of representing different genome properties which might vary at various species, concerning either the number of particular genes or complete chromosomes (if they are present), remains still actual. Moreover, the processing of the genome and its visualization demand an efficient approach, concerning the size of data and computational capabilities of an average computer. This work aims at representing some key genome properties in such a way.

dem: The promoter for telomere transposon HeT-A and implications for the evolution of retroviral LTRs. Cell 86: 647–655.

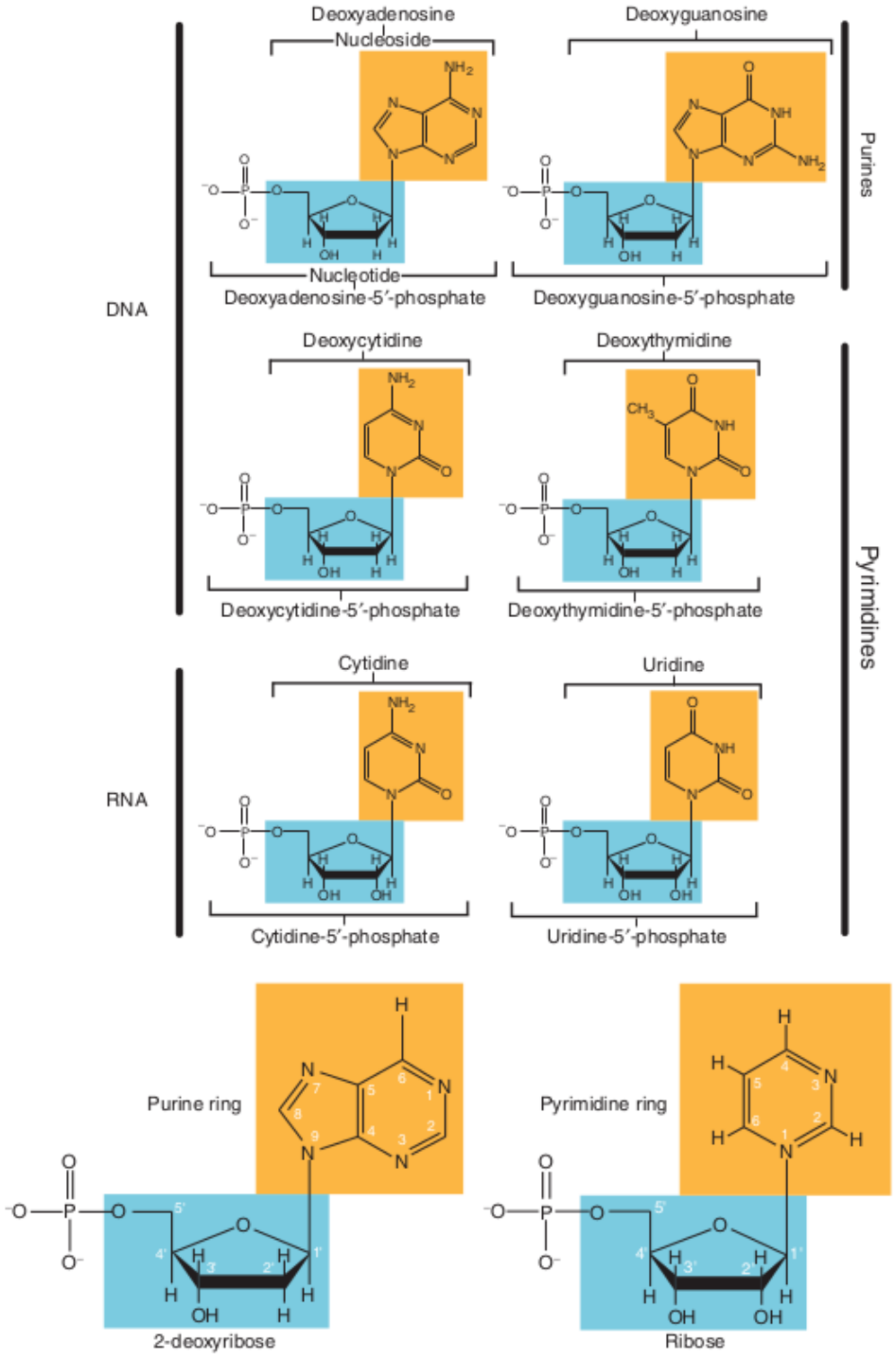
1 Analytická časť

In most eukaryotic and prokaryotic organisms the hereditary material is either linear double-stranded DNA (deoxyribonucleic acid) molecules or a circular double-stranded DNA molecule. However, some extracellular life forms, might use RNA (ribonucleic acid) as the building block for their genome. For instance, viruses have a genome composed of either single-stranded DNA, double-stranded DNA or RNA, depending on the type of a virus. Therefore, a genome itself, is the complete content of genetic information in an organism, or in other words, all the unique DNA or RNA sequences the organism possesses.

1.1 Nucleotides

Both of DNA and RNA are polymeric molecules, that are composed of linear chains of various combinations of four different subunits, called nucleotides. The nucleotide itself is the basic unit of the DNA and RNA molecules, the monomer, which, however, could be found in the cell not only as the bearer of the genetic information, but also as a carrier of energy used to power enzymatic reactions. A five-carbon-atom sugar, a phosphate group and a nitrogenous base are three distinct components which, combined together, make up the quite complex nucleotide molecule. The combination of sugar and base is called a nucleoside, while the phosphate-sugar-base is termed a nucleotide. The nucleotide bases can be either a single-ringed pyrimidine or a double-ringed purine. Dinucleotide, trinucleotide and polynucleotide are the terms corresponding to two, three or many nucleotides connected with each other respectively.

A nucleotide can be either a purine or pyrimidine. Guanine (G) and adenine (A) are the common purines for both of DNA and RNA; the pyrimidine called cytosine (C) is also present in both nucleic acids. However, the pyrimidine uracil (U) is limited only to RNA, being replaced with thymine (T) in DNA. There are merely two base-pair combinations that are permissible – A base-paired with T (U) and C base-paired with G. It happens due to the geometries of the nucleotide



Obr. 1.1: The structures of the pyrimidines and purines found in DNA and RNA. The sugar groups are highlighted in blue and the nitrogenous bases are highlighted in orange. The atoms of the sugar are numbered from 1 to 5. The atoms of the purine ring are numbered from 1 to 9, while those of the pyrimidine ring are numbered from 1 to 6.

bases and relative positions of atoms which participate in the connection. This property makes two sequences of polynucleotides in helix complement. Discrete

nucleotides are attached to each other through sugar–phosphate bonds that connect the phosphate group on the 5′ carbon of one nucleotide with the hydroxyl group on the 3′ carbon of another nucleotide. The base pairing between adenine and thymine (uracil) involves two hydrogen bonds, while between cytosine and guanine involves three hydrogen bonds.

1.2 Nucleodic acid spatial stucture

As the three-dimensional structure of a nucleotide is not completely rigid, it is possible for DNA to have various spatial architectures: A-form, B-form, Z-form and the circular one. The position of the base relatively to the five-carbon-atom sugar can be changed by a rotation around the N-glycosidic bond and, in this way, significantly affect the three dimensional configuration of the molecule and helix consequently.

Tabuľka 1.1: DNA double helix

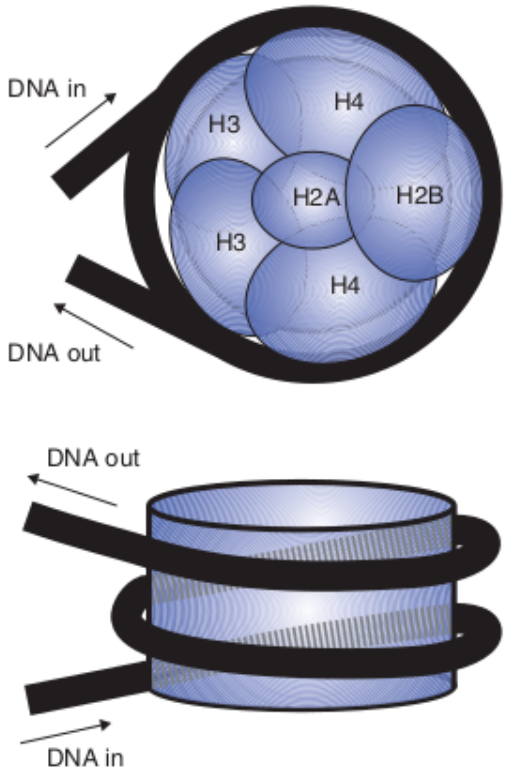
Features of the different conformations of the DNA double helix			
Feature	B-DNA	A-DNA	Z-DNA
Type of helix	Right-handed	Right-handed	Left-handed
Number of base pairs per turn	10	11	12
Distance between base pairs (nm)	0.34	0.29	0.37
Distance per complete turn (nm)	3.4	3.2	4.5
Diameter (nm)	2.37	2.55	1.84
Major groove	Wide, deep	Narrow, deep	Flat
Minor groove	Narrow, shallow	Wide shallow	Narrow, deep

Moreover, although usually single-stranded, some RNA sequences have the ability to form a double helix. However, double helix RNA is rare and has nothing in common with the genome itself, since only the single-stranded RNA molecules appear to participate in some genome related processes in the eukaryotic and prokaryotic organisms. Since circular DNA may exist in several forms inclu-

ding single-stranded c-DNA, intact double-stranded c-DNA (closed circles with both strands covalently linked), nicked ds-c-DNA (only one strand covalently linked) and "concatenated circles" their properties are not described in the following table.

1.3 Chromosomes in eukaryotic genomes

In eukaryotic cells nucleic acid is situated in a membrane-bound organelle called the nucleus.[1] The nuclear genome is split into a set of linear double-helix DNA molecules, each contained in a chromosome. No exceptions to this pattern are known: all eukaryotes that have been studied have at least two chromosomes and the DNA molecules are always linear. The only variability at this level of organization of eukaryotic genome is coherent with the number of chromosomes. Moreover, it appears, that biological features of an organism have no dependence on the number of chromosomes.



Obr. 1.2: The nucleosome structure. H2A, H2B, H3 and H4 represent different types of histones.

[1] F RANCA , L. T. – C ARRILHO , E. – K IST , T. B. A review of DNA sequencing techniques. Quarterly reviews of biophysics. 2002, 35, 02, s. 169–200

Despite the size of a nucleus (5-10 um), an overall length of DNA in the human cell is approximately 2.1m and can be packed inside the cell because of the method the nucleic acid is stored. The genetic material in viruses and bacteria consists of strings of DNA or RNA almost devoid of proteins. However, in eukaryotes, a substantial quantity of protein is associated with the DNA to form chromatin. At the lowest level, the DNA is organized by wrapping DNA strands around he proteins called histones, that contain a large amount of positively charged amino acids arginine and lysine. Those amino acids, and histones in general, play the crucial structural role, making it possible to bind the negative charged phosphate groups of the DNA nucleotides.

Averagely, the DNA rolled around the histones consists of 140-150 base pair, dependently on the species. Such a complex of DNA and histones is termed a nucleosome. These nucleosomes can be further coiled into increasingly larger coils up until forming chromosomes[2]. However, tight coiling of DNA limits cells ability to access DNA and to process it.[3] Instead of being constantly coiled, the nucleic acid is usually found in a state called chromatin where some segments of acid are tightly reeled (heterochromatin), while other segments are entirely open (euchromatin). Euchromatin DNA is is highly accessible by the molecular complexes used by the cell and therefore is easier to manipulate with.

The formation of nucleosomes represents the first level of packing, whereby the DNA is reduced to about one-third of its original length. In the nucleus, however, chromatin does not exist in this extended form.[4] Instead, the 10 nm chromatin fibre is further packed into a thicker 30 nm fibre, which was originally called a solenoid. It is not clear whether the transition between the 10 nm fibre and the 30 nm fibre represents a physiological event or whether it merely occurs in vitro as a consequence of altering the salt concentration. The 30 nm fibre does, however, consist of numerous nucleosomes packed closely together, but the precise orientation and details of the structure are not clear.[5]

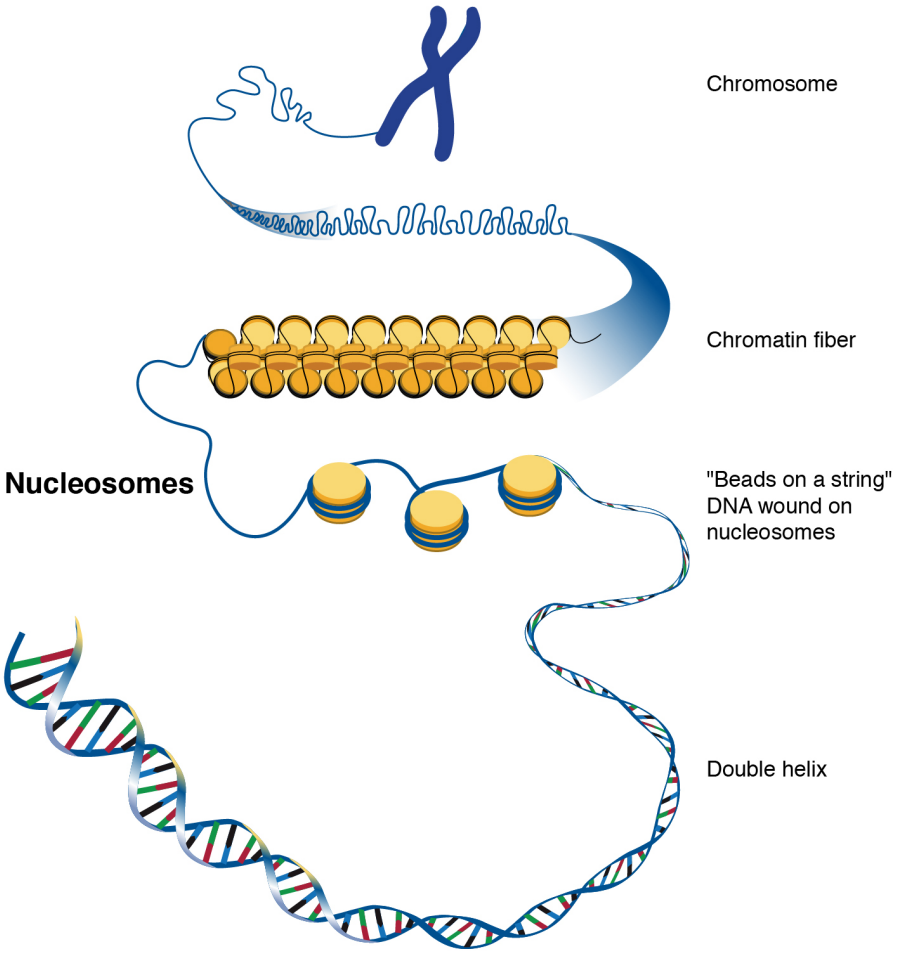
The amount and extent of packing are determined by a sell, to control which sections of the genome can be expressed and which cannot. It affects cellular function and appears to be the predominant cause of differentiating cells type, while having the same DNA.

[2]C HAISSON , M. J. – P EVZNER , P. A. Short read fragment assembly of bacterial genomes. Genome research. 2008, 18, 2, s. 324–330.

[3]Analysis of Genes and Genomes Richard J. Reece University of Manchester, UK

[4]Kipling, D. and Cooke, H.J. 1990. Hypervariable ultra-long telomeres in mice. Nature 374: 400–402

[5]Greider, C.W. 1996. Telomere length regulation. Annu. Rev. Biochem. 65: 337–365.



Obr. 1.3: Ncleosomes as the part of a chromosome.

Transcription is the process by which an RNA copy of one of the strands in the DNA double helix is made. The antisense strand of the DNA directs the synthesis of a complementary RNA molecule. The RNA molecule produced is therefore identical to the sense strand of the DNA – except that it contains U instead of T. There are fundamental differences in the ways in which genes are transcribed in prokaryotes and eukaryotes.[6] Here, it is important to understand the processes involved in each case. Many of the experiments we will look at in later chapters involve the use of eukaryotic cells, but the bacterium E. coli still plays a vital role in almost all genetic engineering experiments. Transcription begins at specific DNA sequences called promoters. Like DNA replication, transcription occurs in three phases – initiation, elongation and termination. Initiation of transcription usually

[6]Smogorzewska, A. and de Lange, T. 2004. Regulation of telomerase by telomeric proteins. Annu. Rev. Biochem. 73: 177–208

occurs to the 3 side of the promoter, and termination occurs at specific sites downstream of the coding sequence of the gene. At first glance, the overall architecture of a typical prokaryotic gene and a typical eukaryotic gene may appear to be similar. However, the controlling region for eukaryotic genes will not function in a prokaryotic cell, and vice versa.[7] Most protein coding genes in prokaryotes are transcriptionally active by default. That is to say, in the absence of other factors, the RNA polymerase can recognize the promoter of a gene, bind to it and produce RNA. Transcriptional control is brought to bear on the gene by repressor proteins that bind to DNA sequences adjacent to the RNA polymerase binding site. DNA binding by the repressor either occludes RNA polymerase binding and/or prevents a bound polymerase from transcribing. The eukaryotic RNA polymerase involved in the production of protein coding genes is unable to recognize promoter sequences on its own. Therefore, eukaryotic genes are transcriptionally inactive in the absence of other factors. In both prokaryotes and eukaryotes, transcription is a highly regulated process. Proper timing and levels of gene expression are essential to almost all cellular processes.

[7] Levis, R.W. 1989. Viable deletions of a telomere from a Drosophila chromosome. Cell 58: 791–801.

2 Syntetická časť

3 Vyhodnotenie

4 Záver