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REVIEW ARTICLE

REVIEW ON DNA DAMAGE, REPAIR AND DNA SEQUENCING

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ABSTRACT

DNA damage, due to environmental factors and normal metabolic processes inside the cell, occurs at a rate of 10,000 to 1,000,000 molecular lesions per cell per day.[1] While this constitutes only 0.000165% of the human genome's approximately 6 billion bases (3 billion base pairs), unrepaired lesions in critical genes (such as tumor suppressor genes) can impede a cell's ability to carry out its function and appreciably increase the likelihood of tumor formation and contribute to tumour heterogeneity. The vast majority of DNA damage affects the primary structure of the double helix; that is, the bases themselves are chemically modified. These modifications can in turn disrupt the molecules' regular helical structure by introducing non-native chemical bonds or bulky adducts that do not fit in the standard double helix. Unlike proteins and RNA, DNA usually lacks tertiary structure and therefore damage or disturbance does not occur at that level. DNA is, however, super coiled and wound around "packaging" proteins called histones (in eukaryotes), and both superstructures are vulnerable to the effects of DNA damage. Cells annot function if DNA damage corrupts the integrity and accessibility of essential information in the genome (but cells remain superficially functional when so-called "non-essential" genes are missing or damaged). Depending on the type of damage inflicted on the DNA's double helical structure, a variety of repair strategies have evolved to restore lost information. If possible, cells use the unmodified complementary strand of the DNA or the sister chromatid as a template to recover the original information. Without access to a template, cells use an error-prone recovery mechanism known as translesion synthesis as a last resort. Damage to DNA alters the spatial configuration of the helix, and such alterations can be detected by the cell. Once damage is localized, specific DNA repair molecules bind at or near the site of damage, inducing other molecules to bind and form a complex that enables the actual repair to take place. Dynamic programming can be useful in aligning nucleotide to protein sequences, a task complicated by the need to take into account frame shift mutations (usually insertions or deletions). The frame search method produces a series of global or local pair wise alignments between a query nucleotide sequence and a search set of protein sequences, or vice versa. Its ability to evaluate frame shifts offset by an arbitrary number of nucleotides makes the method useful for sequences containing large numbers of indels, which can be very difficult to align with more efficient heuristic methods. In practice, the method requires large amounts of computing power or a system whose architecture is specialized for dynamic programming. The BLAST and EMBOSS suites provide basic tools for creating translated alignments (though some of these approaches take advantage of side-effects of sequence searching capabilities of the tools). More general methods are available from both commercial sources, such as *Frame Search*, distributed as part of the Accelrys GCG package, and Open Source software such as Genewise. The dynamic programming method is guaranteed to find an optimal alignment given a particular scoring function; however, identifying a good scoring function is often an empirical rather than a theoretical matter. Although dynamic programming is extensible to more than two sequences, it is prohibitively slow for large numbers of or extremely long sequences [2]. Sequence alignment is a way of arranging the sequences of DNA, RNA, or protein to identify regions of similarity that may be a consequence of functional, structural, or evolutionary relationships between the sequences [3]. Aligned sequences of nucleotide or amino acid residues are typically represented as rows within a matrix. Gaps are inserted between the residues so that identical or similar characters are aligned in successive columns.

INTRODUCTION

DNA damage, due to environmental factors and normal metabolic processes inside the cell.DNA damage can be subdivided into two main types:

Endogenous damage such as attack by reactive oxygen species produced from normal metabolic by products (spontaneous mutation), especially the process of oxidative deamination, it also includes replication errors. Exogenous damage caused by external agents such as

1. Ultraviolet [UV 200-400 nm] radiation from the sun
2. Other radiation frequencies, including x-rays and gamma rays
3. Hydrolysis or thermal disruption
4. Certain plant toxins
5. Human-made mutagenic chemicals, especially aromatic Compounds that act as DNA intercalating agents
6. Viruses

There are several types of damage to DNA due to endogenous cellular processes: Oxidation of bases [e.g. 8-oxo-7,8-dihydroguanine (8-oxoG)] and generation of DNA strand interruptions from reactive oxygen species, Alkylation of bases (usually methylation), such as formation of 7-methylguanine,

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1-methyladenine, 6-O-Methylguanine Hydrolysis of bases, such as deamination, depurination, and depyrimidination. "bulky adduct formation" (i.e., benzo [a] pyrene diol epoxide-dG adduct, aristolactam I-dA adduct) Mismatch of bases, due to errors in DNA replication, in which the wrong DNA base is stitched into place in a newly forming DNA strand, or a DNA base is skipped over or mistakenly inserted. Monoadduct damage cause by change in single nitrogenous base of DNA Diadduct damage Damage caused by exogenous agents comes in many forms. Some examples are:

UV-B light causes cross linking between adjacent cytosine and thymine bases creating pyrimidine dimers. This is called direct DNA damage.

UV-A light creates mostly free radicals. The damage caused by free radicals is called indirect DNA damage.

Ionizing radiation such as that created by radioactive decay or in cosmic rays causes breaks in DNA strands. Low-level ionizing radiation may induce irreparable DNA damage (leading to replicational and transcriptional errors needed for neoplasia or may trigger viral interactions) leading to pre-mature aging and cancer.[4][5][6]

Thermal disruption at elevated temperature increases the rate of depurination (loss of purine bases from the DNA backbone) and single-strand breaks. For example, hydrolytic depurination is seen in the thermophilic bacteria, which grow in hot springs at 40-80 °C.[7][18] The rate of depurination (300 purine residues per genome per generation) is too high in these species to be repaired by normal repair machinery, hence a possibility of an adaptive response cannot be ruled out.

Industrial chemicals such as vinyl chloride and hydrogen peroxide, and environmental chemicals such as polycyclic aromatic hydrocarbons found in smoke, soot and tar create a huge diversity of DNA adducts- ethenobases, oxidized bases, alkylated phosphotriesters and cross linking of DNA, just to name a few.

UV damage, alkylation/methylation, X-ray damage and oxidative damage are examples of induced damage. Spontaneous damage can include the loss of a base, deamination, sugar ring puckering and tautomeric shift.[11] In human cells, and eukaryotic cells in general, DNA is found in two cellular locations — inside the nucleus and inside the mitochondria. Nuclear DNA (nDNA) exists as chromatin during non-explicative stages of the cell cycle and is condensed into aggregate structures known as chromosomes during cell division. In either state the DNA is highly compacted and wound up around bead-like proteins called histones. Whenever a cell needs to express the genetic information encoded in its nDNA the required chromosomal region is unravelled, genes located therein are expressed, and then the region is condensed back to its resting conformation. Mitochondrial DNA (mtDNA) is located inside mitochondria organelles. Inside mitochondria, reactive oxygen species (ROS), or free radicals, by products of the constant production of adenosine triphosphate (ATP) via oxidative phosphorylation, create a highly oxidative environment that is known to damage mtDNA. A critical enzyme in counteracting the toxicity of these species is superoxide dismutase, which is present in both the mitochondria and cytoplasm of eukaryotic cells.

Senescence and apoptosis

The telomeres are long regions of repetitive non coding DNA that cap chromosomes and undergo partial degradation each time a cell undergoes division (see Hayflick limit).[9] In contrast, quiescence is a reversible state of cellular dormancy that is unrelated to genome damage. Unregulated cell division can lead to the formation of a tumor (see cancer), which is potentially lethal to an organism. Therefore, the induction of senescence and apoptosis is considered to be part of a strategy of protection against cancer.[14]

DNA damage and mutation

Damages are physical abnormalities in the DNA, such as single- and double-strand breaks, 8-hydroxydeoxy guanosine residues, and polycyclic aromatic hydrocarbon adducts. DNA damages can be recognized by enzymes. Replication may also be blocked or the cell may die. In contrast to DNA damage, a mutation is a change in the base sequence of the DNA. A mutation cannot be recognized by enzymes once the base change is present in both DNA strands, and, thus, a mutation cannot be repaired. At the cellular level, mutations can cause alterations in protein function and regulation. Mutations are replicated when the cell replicates. DNA damages and mutations are related because DNA damages often cause errors of DNA synthesis during replication or repair; these errors are a major source of mutation.

DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In human cells, both normal metabolic activities and environmental factors such as UV light and radiation can cause DNA damage, Many of these lesions cause structural damage to the DNA molecule and can alter or eliminate the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis. As a consequence, the DNA repair process is constantly active as it responds to damage in the DNA structure. When normal repair processes fail, and when cellular apoptosis does not occur, irreparable DNA damage may occur, including double-strand breaks and DNA cross linkages. The rate of DNA repair is dependent on many factors, including the cell type, the age of the cell, and the extracellular environment. A cell that has accumulated a large amount of DNA damage, or one that no longer effectively repairs damage incurred to its DNA, can enter one of three possible states:

a. an irreversible state of dormancy, known as senescence
b. cell suicide, also known as apoptosis or programmed cell death
c. Unregulated cell division, which can lead to the formation of a tumor that is cancerous

The DNA repair ability of a cell is vital to the integrity of its genome and thus to the normal functionality of that organism. Many genes that were initially shown to influence life span have turned out to be involved in DNA damage repair and protection.[4]

DNA repair and cancer

There are at least 34 inherited human DNA repair gene mutations that increase cancer risk.

Epigenetic DNA repair defects in cancer

Classically, cancer has been viewed as a set of diseases that are driven by progressive genetic abnormalities that include mutations in tumour-suppressor genes and oncogenes, and chromosomal aberrations. However, it has become apparent that cancer is also driven by epigenetic alterations.[10] Epigenetic alterations refer to functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence. Examples of such modifications are changes in DNA methylation (hypermethylation and hypomethylation) and histone modification,[11] changes in chromosomal architecture (caused by inappropriate expression of proteins such as HMGA2 or HMGA1)[12] and changes caused by microRNAs. Each of these epigenetic alterations serves to regulate gene expression without altering the underlying DNA sequence. These changes usually remain through cell divisions, last for multiple cell generations, and can be considered to be epimutations (equivalent to mutations). While large numbers of epigenetic alterations are found in cancers, the epigenetic alterations in DNA repair genes, causing reduced expression of DNA repair proteins, appear to be particularly important. Such alterations are thought to occur early in progression to cancer and to be a likely cause of the genetic instability characteristic of cancers.[13][14][15][16] Reduced expression of DNA repair genes causes deficient DNA repair. When DNA repair is deficient DNA damages remain in cells at a higher than usual level and these excess damages cause increased frequencies of mutation or epimutation. Mutation rates increase substantially in cells defective in DNA mismatch repair [17][18] or in homologous recombinational repair (HRR).[19] Chromosomal rearrangements and aneuploidy also increase in HRR defective cells.[20] Higher levels of DNA damage not only cause increased mutation, but also cause increased epimutation. During repair of DNA double strand breaks, or repair of other DNA damages, incompletely cleared sites of repair can cause epigenetic gene silencing.[21][22] At least 169 enzymes are either directly employed in DNA repair or influence DNA repair processes.[23] Of these, 83 are directly employed in the 5 types of DNA repair processes illustrated

Base excision repair (BER):
Nucleotide excision repair (NER):
Recombination repair :
Mismatch repair (MMR):
Direct reversal repair :

Cancer therapy procedures such as chemotherapy and radiotherapy work by overwhelming the capacity of the cell to repair DNA damage, resulting in cell death.

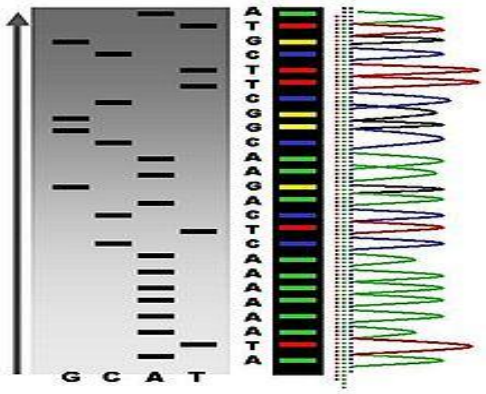
DNA repair and evolution

The basic processes of DNA repair are highly conserved among both prokaryotes and eukaryotes and even among bacteriophage (viruses that infect bacteria); however, more complex organisms with more complex genomes have correspondingly more complex repair mechanisms.[24] The ability of a large number of protein structural motifs to catalyze relevant chemical reactions has played a significant role in the elaboration of repair mechanisms during evolution. For an extremely detailed review of hypotheses relating to the evolution of DNA repair, see.[25]

Rate of evolutionary change

On some occasions, DNA damage is not repaired, or is repaired by an error-prone mechanism that results in a change from the original sequence. When this occurs, mutations may propagate into the genomes of the cell's progeny. Should such an event occur in a germ line cell that will eventually produce a gamete, the mutation has the potential to be passed on to the organism's offspring. The rate of evolution in a particular species (or, in a particular gene) is a function of the rate of mutation. As a consequence, the rate and accuracy of DNA repair mechanisms have an influence over the process of evolutionary change.[26]

Biological method of DNA sequencing is the process of determining the precise order of nucleotides within a DNA molecule. It includes any method or technology that is used to determine the order of the four bases—adenine, guanine, cytosine, and thymine—in a strand of DNA. The advent of rapid DNA sequencing methods has greatly accelerated biological and medical research and discovery.



An example of the results of automated chain-termination DNA sequencing

Knowledge of DNA sequences has become indispensable for basic biological research, and in numerous applied fields such as diagnostic, biotechnology, forensic biology, virology and biological systematics. The rapid speed of sequencing attained with modern DNA sequencing technology has been instrumental in the sequencing of complete DNA sequences, or genomes of numerous types and species of life, including the human genome and other complete DNA sequences of many animal, plant, and microbial species. The first DNA sequences were obtained in the early 1970s by academic

researchers using laborious methods based on two-dimensional chromatography. Following the development of fluorescence-based sequencing methods with automated analysis, [27] DNA sequencing has become easier and orders of magnitude faster [28].

Basic methods of DNA Sequencing

1. Maxam-Gilbert sequencing
2. Chain-termination methods

Advanced methods and de novo sequencing

1. Shotgun sequencing
2. Bridge PCR

Next-generation methods

1. Massively parallel signature sequencing (MPSS)
2. Polony sequencing
3. 454 pyrosequencing
4. Illumina (Solexa) sequencing
5. SOLiD sequencing
6. Ion Torrent semiconductor sequencing
7. DNA nanoball sequencing
8. Heliscope single molecule sequencing
9. Single molecule real time (SMRT) sequencing

Methods in development

1. Nanopore DNA sequencing
2. Tunnelling currents DNA sequencing
3. Sequencing by hybridization
4. Sequencing with mass spectrometry
5. Microfluidic Sanger sequencing
6. Microscopy-based techniques
7. RNAP sequencing
8. In vitro virus high-throughput sequencing

DNA sequencing may be used to determine the sequence of individual genes, larger genetic regions (i.e. clusters of genes or operons), full chromosomes or entire genomes. Sequencing provides the order of individual nucleotides in DNA or RNA (commonly represented as A, C, G, T, and U) isolated from cells of animals, plants, bacteria, archaea, or virtually any other source of genetic information. This is useful for: Molecular biology – studying the genome itself, how proteins are made, what proteins are made, identifying new genes and associations with diseases and phenotypes, and identifying potential drug targets Evolutionary biology – studying how different organisms are related and how they evolved Met genomics – Identifying species present in a body of water, sewage, dirt, debris filtred from the air, or swab samples of organisms. Helpful in ecology, epidemiology, microbiome research, and other fields. Less-precise information is produced by non-sequencing techniques like DNA fingerprinting. This information may be easier to obtain and is useful for: Detect the presence of known genes for medical purposes (see genetic testing) Forensic identification Parental testing.

Computational Methods of DNA sequencing by using the programme by Algorithm

The technique of dynamic programming can be applied to produce global alignments via the Needleman-HYPERLINK "http://en.wikipedia.org/wiki/Needleman-Wunsch_algorithm" WunschHYPERLINK "http://en.wikipedia.org/wiki/Needleman-Wunsch_algorithm" algorithm, and local alignments via the Smith-Waterman algorithm. In typical usage, protein alignments use a substitution matrix to assign scores to amino-acid matches or mismatches, and a gap penalty for matching an amino acid in one sequence to a gap in the other. DNA and RNA alignments may use a scoring matrix, but in practice often simply assign a positive match score, a negative mismatch score, and a negative gap penalty. (In standard dynamic programming, the score of each amino acid position is independent of the identity of its neighbors, and therefore base stacking effects are not taken into account. However, it is possible to account for such effects by modifying the algorithm). A common extension to standard linear gap costs, is the usage of two different gap penalties for opening a gap and for extending a gap. Typically the former is much larger than the latter, e.g. -10 for gap open and -2 for gap extension. Thus, the number of gaps in an alignment is usually reduced and residues and gaps are kept together, which typically makes more biological sense. The Gotoh algorithm implements affine gap costs by using three matrices.

Dynamic programming can be useful in aligning nucleotide to protein sequences, a task complicated by the need to take into account frame shift mutations (usually insertions or deletions). The frame search method produces a series of global or local pair wise alignments between a query nucleotide sequence and a search set of protein sequences, or vice versa. Its ability to evaluate frame shifts offset by an arbitrary number of nucleotides makes the method useful for sequences containing large numbers of indels, which can be very difficult to align with more efficient heuristic methods. In practice, the method requires large amounts of computing power or a system whose architecture is specialized for dynamic programming. The BLAST and EMBOSS suites provide basic tools for creating translated alignments (though some of these approaches take advantage of side-effects of sequence searching capabilities of the tools). More general methods are available from both commercial sources, such as Frame Search, distributed as part of the Accelrys GCG package, and Open Source software such as Gene wise. The dynamic programming method is guaranteed to find an optimal alignment given a particular scoring function; however, identifying a good scoring function is often an empirical rather than a theoretical matter. Although dynamic programming is extensible to more than two sequences, it is prohibitively slow for large numbers of or extremely long sequences [29]. Sequence alignment is a way of arranging the sequences of DNA, RNA, or protein to identify regions of similarity that may be a consequence of functional, structural, or evolutionary relationships between the sequences [30]. Aligned sequences of nucleotide or amino acid residues are typically represented as rows within a matrix. Gaps are inserted between the residues so that identical or similar characters are aligned in successive columns.

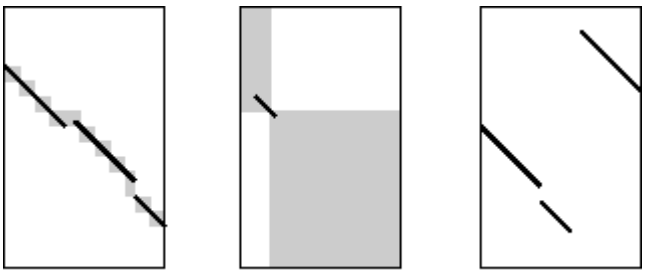
Limitations in DNA sequencing by using the programme by Algorithm

1. Accuracy

Library extension is not performed unlike TCoffee and ProbCons-CONTRAlign, because we think at present that iterative refinement is more efficient than library extension.

2. Scalability

If two unrelated and long genomic DNA sequences are given, FFT-NS-2 tries to make a full-length alignment using rigorous DP and requires large CPU time. For such a case, homology search tools such as FASTA and BLAST are more suitable. The order of alignable blocks or domains are assumed to be conserved for all input sequences.



EXPECTED RESULTS

From the work we are going to develop a new algorithm which can do alignment DNA sequences with better comparison

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