Building Mutational Signatures in Cancer using Deep Bayesian Neural Nets

A Deep Dive into Cancer Mutational Signatures

Jan Alfonso Busker

*352905 - j.a.busker@st.hanze.nl*

*Hanzehogeschool Groningen*

*Missing in abstract:*

* *Most important results*
* *Conclusion and future vision*

Abstract

Cancer, characterized by uncontrolled cell growth. These mutations accrue due to exposure to DNA-damaging processes, both endogenous and exogenous, throughout life. These genetic variations result in unique "mutational signatures" on the DNA, which offer valuable information on their causes and the degree of cellular exposure to particular mutagenic events. By looking at the direct context of the mutations, we can infer the way these mutations were created.

This project aims to refine the statistical model and the current representation of mutations in building mutational signatures in cancer using deep Bayesian neural nets. Additionally, the representation will be expanded to capture more context, by using latent dirichlet allocation (LDA) to divide mutations further according to DNA annotations, potentially revealing recurring contextual imprints.

The methodology includes curating and quality controlling samples, replicating mutational signatures using non-negative matrix factorization (NMF), and determining priors for the expanded mutation representation.

The project's significance lies in advancing our understanding of cancer mutational signatures, which has implications for cancer diagnosis, treatment, and prevention.

Abbreviations

Latent Dirichlet Allocation (LDA)

Non-negative matrix factorization (NMF)

Organisation

This assignment is given by UMCG. The Department of Epidemiology is a major driving force in initiating and conducting life course research and is instrumental to the clinical research within the UMCG’s main theme of Healthy Ageing. The research group ‘Medical statistics and decision making’ is part of the Department of Epidemiology. They focus on developing methods for statistical modeling in clinical and epidemiological studies and analyzing large cohort data. And develop decision analysis techniques to support benefit-risk assessments of medicines and medical decision-making. External guidance is provided by Prof. G.A. Lunter and Dr. Hylke C. Donker.

Introduction

Cancer is a genetic illness characterized by uncontrolled cell development. Cancer cells develop numerous abilities to support this expansion, mostly through genomic alterations. Throughout life, these mutations accumulate as a result of exposure to DNA-damaging mechanisms from both endogenous and external causes [1-3].

It is becoming increasingly clear that a wide range of mutational pathways contribute to the mutation landscape of cancer. Cancer genomes contain somatic mutations acquired during the normal cell cycle as well as those triggered by cancer-related aberrations of DNA maintenance machinery such as mismatch repair or by carcinogenic exposures such as tobacco smoking, ultraviolet light, and replication stress. Each of these processes frequently results in a particular pattern of changes, known as the mutational signature [4,5].

The study of mutational changes, specifically the modification of a single letter within the surrounding context, has been the focus of numerous scholars. The utilization of this methodology has yielded a meticulously selected collection of mutational signatures as provided by COSMIC [6]. Several approaches have been developed to determine the signatures and infer the attributions.

MutationalPatterns is an R/Bioconductor tool for analyzing single and double base substitutions, as well as small insertions and deletions. It additionally allows the analysis of regional mutation spectra and the discovery of strand asymmetry occurrences [7]. And decompTumor2Sig is a R package that can breakdown a single tumor genome into a series of Alexandrov- or Shiraishi-type signatures. This enables quantification of the contribution of several mutational processes to the somatic mutations found in the tumor [8].

Despite the advancements in understanding mutational signatures and the development of tools to analyze them, there are still several gaps in current knowledge. Most studies have only looked at mutations that include a single letter of context to the left and right. This has hampered the ability to distinguish between other DNA damage sources, such as ABOPEC3A and ABOPEC3B, which require at least one more context letter [9]. Large sets of tumor samples are required for the initial discovery and definition of mutational signatures, which are not always available [8]. Or that some packages show signature overfitting when determining the contribution of known patterns to a sample, resulting in a disproportionate amount of signatures being assigned. It also only allows for the analysis of spectra for mutations in the entire genome, making studying the role of specific genomic elements challenging [7].

Researchers could better distinguish between different mutation origins if they considered additional context around the mutations. This could lead to a better understanding of the mutational processes that contribute to cancer. Improving tools for mutational signature analysis: Addressing current techniques' weaknesses, such as overfitting and the inability to study specific genetic components, could improve their accuracy and usefulness. This could allow for more in-depth and advanced studies of mutational phenomena.

Objective

The primary aim of this study is to improve both the statistical model and the existing representation of mutations in building mutational signatures in cancer through the utilization of deep Bayesian neural networks. The previously stated aim will be accomplished through the process of improving the model in order to evaluate mutational signatures that are hierarchically linked, as well as augmenting the context size by incorporating an additional context letter.

The study will involve the curation and quality control of samples and mutations, the replication of mutational signatures through the utilization of NMF, and the subsequent comparison of the outcomes with signatures derived from Bayesian neural networks consisting of one and two layers.

Furthermore, the study aims to establish prior probabilities for the expanded mutation representation and compare the identified signatures of higher dimensions with the existing 96 feature representation.

Theory

Mutational signatures are a critical aspect of cancer research, providing a physiological readout of a cancer's biological history [10]. They are the imprints left on the genome by numerous endogenous and exogenous mutagenesis events that have happened throughout a human being's lifetime. These processes can lead to base substitutions, insertions and deletions, or structural modifications, each of which leaves a distinct pattern or signature [10]. Mutational signatures have proven to be a valuable resource in understanding cancer treatment and prevention. For instance, they have been instrumental in studying the molecular processes of DNA damage, DNA repair, and DNA replication [11]. Furthermore, several mutational signatures, such as SBS4 and SBS92, are linked to the same etiology, as are SBS1 and SBS5, both clock-like signatures [4].

The context of mutations is crucial in understanding mutational signatures. Increasing the context size is a strategy used to capture complex phenomena. Current single base substitution signatures are based on one flanking nucleotide left and right of the substitution, but this is not enough context to discriminate [9]. This approach can be achieved using LDA.

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