Oncogene Protein Annotation assisted with Machine-learning pipelines

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Abstract Breast cancer is one of the major causes of death in females of all ages. It has been studied that the disease is related to a protein called oncogene protein. The protein itself is a result of a mutation in proto-oncogene. By analyzing the structures, properties and functions of the protein pattern then can be determined. During protein structure annotation, various techniques in the analysis are available. One of the assisting techniques used in annotation is the machine learning pipeline as it was known to be applied in many categories such as technologies and not restricted to the health field. Protein annotation tools also play a significant contribution as a part of machine learning pipelines.

Keywords: Oncogene protein, Machine learning, Breast cancer, Protein annotation tools.

Introduction

Breast cancer is the second most dangerous cause of death for women in developed and developing countries [11]. Indonesian Ministry of Health also states that breast cancer is the most dangerous cancer for Indonesian women [10]. Breast cancer that involves multi cell-steps, like ductal hyperproliferation, benign tumor, and metastatic carcinoma. Many factors that may contribute to breast cancer are genetic risk factors, carcinogenic risk factors, environmental risk factors, and hormonal factors [14]. So far, the available therapies to treat breast cancer are radiotherapy, chemotherapy, and surgery. Several approaches were used to treat it, but recurrence occurred in 79% of cases because the underlying mechanism of the protein molecule was not carefully examined [9]. However, the side effects of these remedies are not so good and some even lead to worse effects. Therefore, a better solution is needed to treat breast cancer optimally, namely using Machine Learning methods. Machine learning algorithms aimed to construct a system that accurately differentiates between benign and malignant tumors also provides faster, easier, and accurate in identifying image samples, and early diagnosis can improve the prognosis and the chance of survival [1]. The advantages of the machine learning method for annotating genes or proteins regarding breast cancer far compared the drawbacks, which include its capacity to anticipate fine molecular processes, its extensibility for broad-range-omics research, and the supply of data annotations. Whereas, the disadvantages of machine learning methods is the possibility of defining bias recognition in data annotations, which might result in report redundancy [1].

Materials and methods

The materials needed are papers mentioning the topic of breast cancer, information databases and platforms (NCBI & Makara journal of science). The methods used in choosing the paper is based on a study in which breast cancer is included, such as oncogene protein and its involvement in cancer. In addition, machine learning algorithms are reviewed and chosen specifically in this paper as it's pipeline is used in assisting oncogene protein annotation. Tools that have been included and specifically studied are SUPERFAMILY[2], PFAM[20], RNAfold[16] and MEGA7[21] as each has a different contribution in protein annotation. Proteins that have been targeted for the analyses are BRMS1, BCAR1, BCAR3, BCAR4, and BRCA2. Last, the information gathered in this study must correspond to the keywords: oncogene protein, machine learning, breast cancer and protein annotation.

Results and discussion

Oncogenic protein annotation may be done with a variety of machine learning methods. This table shows how structural annotation information is used for search and analysis by each tool. These tools' URL addresses are listed (see Table 1).

Table 1. List of the structural tools that were chosen for this review. The URLs are supplied and outline the tools' functions.

Tools	Function	URL
SUPERFAMILY[2]	Annotation and structural alignment	https://supfam.org
PFAM[20]	Structural alignment and extended annotation	https://pfam.xfam.org/
RNAfold[16]	Predict secondary structures of single stranded RNA or DNA sequences	http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi
MEGA7[21]	structural alignment and phylogenetic trees	https://www.megasoftware.net/

Phylogenetic tree

The study of the connections between the genomes of various species is known as comparative genomics [5]. This approach is based on the idea that proteins that work together in a metabolic pathway or a structural complex will develop [5]. All functionally related proteins in a new species are likely to be retained or destroyed throughout evolution [5]. Functionally associated proteins belong to one of these categories. For example, If two proteins have homologs in a group of species, they are functionally related [5]. Such functionally related Proteins may be detected via Phylogenetic Profiling.

[6] A phylogenetic profile for each protein is constructed to show a group of species that possess a homolog. A phylogenetic profile is a one-bit string containing 'n' entries, where n is the number of genomes being considered. If the nth genome includes a homolog for the protein, the phylogenetic profile's nth item is shown as unity. The profiles are grouped together to see which proteins have similar profiles. Functional links exist between proteins with similar or identical characteristics. This technique can find functionally related proteins that have no amino acid sequence similarity, allowing the function of a putative protein to be determined [5]. As discussed by Parikesit et al. [1], the BRMS1 protein is a translational repressor that controls the anti-apoptotic gene and prevents cancer from spreading. The BRCA2 protein regulates homologous recombination, prevents genomic instability, and ensures the fidelity of DNA repair [22]. The BCAR1 protein has two functions: docking for cell adhesion and migration and mediating anti-estrogen resistance [23]. The BCAR3 protein is responsible for regulating the signaling pathway during breast cancer growth. Finally, the BCAR4 protein acts as an oncoprotein in breast cancer, causing tamoxifen resistance. The phylogenetic tree of BRMS1, BCAR1, BCAR3, BCAR4, and BRCA2 shown that the BRCA2 protein in the same cluster as the BCAR4 protein in the phylogenetic study, even though the BCAR1 protein is believed to be a separate and unique cluster that is generally unconnected to other proteins [1]. The phylogenetic analysis identified a domain cluster containing BRCA2 and BCAR4, both of which are the focus of ongoing breast cancer medication research [1]. It's possible that these proteins were grouped together because of their widespread annotations in molecular study, but a shared molecular evolutionary history might also have played a role [1]. It's also possible that the development of diagnostics and therapeutics utilizing these two protein domains are somewhat aligned [1]. Phylogenetic profiling can be used to anticipate the functions of several additional proteins that have similar profiles but no ascribed function [5].

3D structured annotation

3D structure-based function assignment the structures of hypothetical proteins may reveal information about their biochemical or biophysical activities [7]. The attribution of function to uncharacterized proteins can be aided by 3D structure. Because protein folding patterns are frequently maintained during evolution, structure-based comparisons can uncover homologs when sequence-based comparisons are useless [5]. For example, the structure of the annotated domain in the BRCA2 protein shows the helical and beta-hairpin structures that make up the backbone of the BRCA2 protein are similar [1]. As a result, structure-based molecular function assignment is a feasible technique for large-scale biochemical protein assignment and the discovery of novel motifs. Nonetheless, because homologous proteins perform different activities in various instances, predicting protein function from sequence and structure is challenging [5]. Many techniques of function prediction focus on finding sequence and/or structural similarities between an unknown protein and one or more well-known proteins [5].

SUPERFAMILY Annotation

Protein domains in amino acid sequences may be predicted using the SUPERFAMILY database [3]. These domains are categorized using the Structural Classification of Proteins database, which categorizes domains with known structure into classes, folds, superfamilies, and families [4]. SUPERFAMILY is primarily based on the SCOP superfamily level, which puts together the most distantly related domains [2]. SUPERFAMILY uses the hidden Markov model algorithm (HMMs) [12]. HMMs are domain superfamily representation algorithms based on multiple sequence alignments (or family)[13]. Each model includes a web page with a figure depicting its amino acid composition, highly conserved locations, hydrophobicity, and insertion and deletion regions [2]. Using the SUPERFAMILY, Parikesit et al., able to show the domain distribution of the five breast proteins that have been annotated [1].

RNAFold

RNAfold is one of the Vienna RNA package's essential programs. Using the dynamic programming technique introduced by Zuker and Stiegler, it may estimate the minimal free energy (MFE) secondary structure of single sequences [17]. In addition to MFE folding, John McCaskill's partition function (PF) method determines equilibrium base-pairing probabilities [18]. Both ways have recently

been updated to take circular RNA sequences into account [19]. A single RNA or DNA sequence in plain text or FASTA format can be entered into the text box or uploaded as a file as the input. In addition, a second text box can be used to insert structural restrictions (e.g., those generated from structure probing experiments). Both the MFE and PF algorithms are calculated by default [16]. For example, Parikesit et al., were able to predict structure hairpin miR-145 and lincRNA-RoR [14].

Conclusions

All the tools were created with the same objective: to better comprehend the complicated connection between protein sequence, structure, and function. As mentioned earlier in this study, some annotations are determined empirically, while others are generated or inferred from homology. Instead of storing data in storage, all biological databases are beginning to include cross-referenced annotations from other resources to improve the visibility of sequence, structure, and function linkages. The sources of the annotations are occasionally buried in documentation, and annotations that were initially inferred via homology are now considered to be reality. There may also be a time lag between the publication of a new study and its integration into databases or clarifying earlier annotations. Machine learning tools for identifying gene biomarkers for breast cancer survival and the possible drug is a significant step in determining the proper treatment for each patient and will potentially increase survival rates.

Future of Study

Various machine-learning and its implementations on protein annotation must be studied further as it can further improve success rate for the patients in the future. In the paper, few tools have been reviewed and studied based on its function as a part of the machine learning pipeline. In addition, the tools are made to leverage tasks and apprehend complicated analysis. Hopefully in the future, machine learning pipeline will be studied extensively since it can be applied in broad topics or subjects.

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