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Research Article

Application of Deep Learning in Predicting the Prognosis of Acute Myeloid Leukemia using Cytogenetics, Age, and Mutations

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ARTICLE INFO

Article history:

Received: 20 February, 2020

Accepted: 9 March, 2020

Published: 13 March, 2020

Keywords:

Acute myeloid leukemia

cytogenetics

age

mutations

deep learning

ABSTRACT

Objective: We explored how Deep Learning can be utilized to predict the prognosis of acute myeloid leukemia.

Methods: Out of The Cancer Genome Atlas database, 94 acute myeloid leukemia cases were used in this study. Input data included age, 10 most common cytogenetic and 23 most common mutation results; output was the prognosis (diagnosis to death). In our Deep Learning network, autoencoders were stacked to form a hierarchical Deep Learning model from which raw data were compressed and organized, and high-level features were extracted. The network was written in R language and was designed to predict the prognosis of acute myeloid leukemia for a given case (diagnosis to death of either more or less than 730 days).

Results: The Deep Learning network achieved an excellent accuracy of 83% in predicting prognosis.

Conclusion: As a proof-of-concept study, our preliminary results demonstrated a practical application of Deep Learning in the future practice of prognostic prediction using next-generation sequencing data.

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Introduction

Acute myeloid leukemia (AML) is a neoplasm of the bone marrow that is caused by mutations or cytogenetic (chromosomal) abnormalities in the myeloid stem cells leading to the formation of clonal myeloblasts [1]. The highly proliferative cancer cells impede the formation of normal blood cells, leading to death if patients are left untreated. In the United States, there are about 19,000 estimated new cases and approximately 10,000 deaths from this malignancy in 2018 [2, 3]. There is an urgent need to find better treatments for this type of leukemia as only a quarter of the patients diagnosed with AML survive more than 5 years. AML includes many subtypes that share a common clinical presentation despite different types of mutations and genetic events. These genetic aberrations and mutations of leukemic cells often cause a profound impact on the cellular protein networks. A variety of technologies identifying the gene, mRNA, microRNA, and encoded pathologic protein have helped to predict the prognosis of AML patients. Interestingly, most AMLs only have only a few gene mutations, but the

prognosis of AML patients is quite varied. A possible explanation for this diversity is differences in protein signaling.

Previous studies on the association between prognosis of AML and a small number of cytogenetic abnormalities and mutations highlighted the clinical and biologic heterogeneity of AML [4-8]. The cytogenetic abnormalities with prognostic relevance have led to the adoption of a risk stratification model: three cytogenetically defined risk groups with significant differences in overall survival [9]. Although risk stratification for AML patients has been improved, a substantial number of patients still lack a clear correlation between any specific abnormalities and accurate prognostic prediction. More recently, mutational analysis of FLT3, NPM1, and CEBPA was shown to improve risk stratification for AML patients without karyotypic abnormalities [10].

Recent advances in molecular studies, especially next-generation sequencing (NGS), have identified additional recurrent somatic mutations in patients with AML, including mutations in TET2, IDH1

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and IDH2, DNMT3A, and PHF6, among others [7, 11-17]. Retrospective studies indicate that a subset of these mutations may have prognostic significance in AML, and these mutations may be the “missing” parameters in previous risk stratification models for patients with AML [7, 16, 18]. Whether including these novel mutations in mutational profiling with a larger set of genes would improve prognostication of AML has not been investigated in clinical studies. Numerous mutations in AML have been found with the recent application of NGS technique. The Cancer Genome Atlas (TCGA) study with 200 AML cases showed that the average number of mutations is 13 per case, and there are 23 major recurrent mutations [19]. Such a large number of mutations in AML would certainly present a challenge in predicting prognosis for AML patients using multiple-variable statistical analysis.

In this paper, we propose the use of Deep Learning (DL) methods based on unsupervised feature extraction to address the challenge described above. Most successful DL methods involve artificial neural networks, a family of models inspired by biological neural networks (i.e., the central nervous system, particularly the brain). In such an artificial neural network, artificial nodes (known as “neurons”) are connected to form a network mimicking a biological neural network. In 1943, Warren McCulloch and Walter Pitts created a computational model for neural networks based on an algorithm called threshold logic [20]. Neural networks had not shown superior performance compared to other machine learning methods until the introduction of DL in 2006. DL differs from traditional machine learning in how representations are learned from the raw data. In fact, DL allows computational models that are composed of multiple processing layers based on neural networks to learn representations of data with multiple levels of abstraction [21]. Every layer of a DL system produces a representation of the observed patterns based on the data it receives as inputs from the previous layer, by optimizing a local unsupervised criterion [22].

The key aspect of deep learning is that these representations are not designed by human engineers, but they are learned from data using a general-purpose learning procedure. DL has recently shown impressive results in discovering intricate structures in high-dimensional data and obtained remarkable performances for object detection in images, speech recognition, natural language understanding and translation [23-27]. Relevant clinical-ready successes have been obtained in health care as well (e.g., identification of metastatic breast cancer on lymph node slides, aggregating features relevant to specific breast cancer subtypes, predicting drug therapeutic uses and indications), initiating the way toward a potential new generation of intelligent tools based on DL for real-world medical care [28-30].

We use stacked autoencoders, which form a deep network capable of achieving unsupervised learning, a type of machine-learning algorithm which draws inferences from the input data and does not use labeled training examples. In contrast to previous methods of conventional neural networks where data must be strictly categorized to provide the appropriate label for supervised learning, the unlabeled data in DL can be used in the unsupervised training phase. The resulting features from all training sets are then used as the basis for constructing the classifier.

In this study, we use data from the TCGA database which consist of 200 de novo AML cases and attempt to use DL which incorporates

unsupervised feature training to find the correlation between cytogenetics, age, mutation, and prognosis [19]. To the best of our knowledge, unsupervised feature learning methods have never been applied to predict AML prognosis in this manner.

Materials and Methods

I Materials

Our study was approved by the Institution Review Board at the University of Texas Health Science Center. Data from 200 cases of de novo AML were retrieved from the TCGA database (public domain) [17]. Demographic information shows: age 55 ± 16.1 , white 89%, black 8%, others 3%; male 54%, female 46%; normal cytogenetics 47%. Molecular testing was performed on multiple platforms: Affymetrix U133 Plus 2, Illumina Infinium Human Methylation 450 BeadChip, and Affymetrix SNP Array 6.0. All karyotypes were analyzed by conventional G-banding in at least 20 metaphases. Results were available for cytogenetics, 260 gene mutations, and survival duration (diagnosis to death, DTD, in days) for each case [31]. As previously reported, in this database, a total of 23 genes were significantly mutated, and another 237 were mutated in two or more samples [31]. Nearly all samples had at least 1 nonsynonymous mutation. To use the most relevant data for analysis, only cases with the following 23 most common mutations (grouped according to categories) were extracted for our study:

- i. Activated signaling (signal transduction): FLT3-ITD, KIT, KRAS, NRAS, and PTPN11
- ii. Myeloid transcription factors (differentiation): NPM1, CEBPA, and RUNX1
- iii. Epigenetic regulation: DNMT3A, TET2, IDH2, IDH1, EZH2, and HNRNP
- iv. Tumor suppressors: TP53, WT1, and PHF6
- v. Spliceosomes: U2AF1
- vi. Cohesins: SMC1A, SMC3, STAG2, and RAD21,
- vii. Non-annotated: FAM5C (BRINP3)

Furthermore, the following 10 common cytogenetic abnormalities were seen in the patient cohort: t(8;21), inv(16), t(15;17), t(9;11), t(9;22), trisomy 8, del (7), del (5), del (20), and complex chromosomal abnormalities. Subsequently, only 94 cases with one or more of the 23 common mutations were selected and included in this study. These include cases with or without cytogenetic abnormalities. DTD was chosen as the prognostic parameter. For the 94 AML cases in this study, the mean DTD was 730 days. In summary, the total number of input parameters was 34, including 10 cytogenetic abnormalities, age, and 23 mutations, whereas the sole outcome parameter was DTD.

II Methods

Our main analysis method was a DL neural network with stacked (multi-layered) auto-encoder. The training was mostly based on unsupervised feature learning, which has been used successfully for image and audio recognition [32, 33]. Our DL neural network was designed with the R language. R is a programming language for statistical computing and graphics supported by the R Foundation for Statistical Computing [34]. R was derived from the S language which was originally developed at

Bell Laboratories by John Chambers and colleagues. R's popularity has increased substantially in recent years with advances in machine learning [35]. The source code for the R software environment is written primarily in Java, C, FORTRAN, and also in R itself. R is freely available under the GNU General Public License, and pre-compiled

binary versions are provided for various operating systems, including UNIX, Windows, and MacOS. In this study, we used many DL functions obtained from various R packages which are available from the Comprehensive R Archive Network [36].

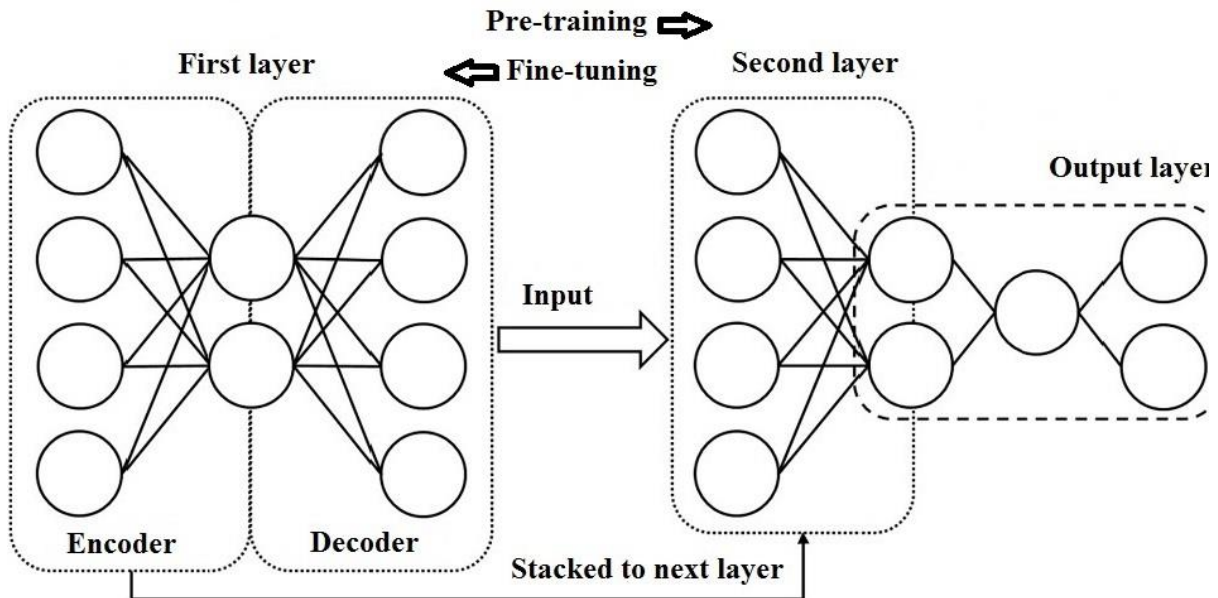


Figure 1: A Deep Learning Neural Network (Stacked Autoencoder Network) with Unsupervised Training in Pre-training Phase and Supervised Training in the Fine-tuning phase.

The stacked autoencoder neural network illustrated in (Figure 1), incorporates two training phases: pre-training with unsupervised learning method, and fine-tuning, which is similar to the supervised back-propagation in conventional neural networks [37, 38]. During the pre-training phase, the output from one layer is subsequently used as the input for the next output layer. The output from each layer essentially represents an approximation of the input data constructed from a limited number of features learned by the hidden units of the network. The stacked autoencoder is constructed by multiple layers in the neural network (i.e., input layer, hidden layers, and output layer). For simplicity, only 2 layers are illustrated in (Figure 1). The sigmoid function is used as an activation function in hidden layers. In the fine-tuning phase, the back-propagation method minimizes the error with an additional sparsity penalty [39]. The features learned in the pre-training phase are subsequently used with a set of labeled data for specific status (positive or negative) to train a classifier. A classifier can be defined as a function that receives values of various features from training examples (cytogenetics, age, and mutations as independent variables) and provides an output, which predicts the category that each training example belongs to (prognosis or DTD as dependent variable) [40]. For the fine-tuning phase, we used the linear function for the classifier.

For the initial analysis, all 34 attributes (10 cytogenetic abnormalities, age, and 23 mutations) were used to train the network to predict prognosis (good prognosis vs. poor prognosis, i.e., DTD is either more than or less than 730 days). A tenfold cross-validation method was used to obtain comprehensive validation results due to the small number of samples (94 cases). In this validation, a small subset of data (10 out of

94 cases) was excluded each time for training; the resultant network (trained on the remaining 84 cases) would be used to predict the prognostic status for each case in the excluded subset. The process was repeated until all 94 cases in the data set had been validated. The overall accuracy of the neural network is the mean of those for all the validated subsets. Subsequent analyses, using trial and error with different numbers of input parameters, are expected to show the optimal input for the most accurate prediction.

Results

The initial use of the full attribute set (10 common cytogenetic abnormalities, age, and 23 common mutations) yielded 81% accuracy for predicting good prognosis of an AML case (day-to-death \geq 730 days). This accuracy corresponded to a sensitivity of 74% and a specificity of 86% in predicting good prognosis of an AML case. The initial analysis showed that the following 14 attributes rank highest in term of predicting power among the 34 attributes: age, 7 cytogenetic abnormalities [tri8, del5, del7, complex chromosomal abnormalities, t(8;21), inv(16), t(15; 17)], and 6 mutations [FLT3, NPM1, TP53, DNMT3, KIT, CEBPA]. Using these top-ranked 14 attributes, the DL network subsequently achieved a slightly better accuracy of 83%, with a sensitivity of 80% and a specificity of 85%. The accuracy in predicting prognostic status with different attribute sets by the DL network is summarized in (Table 1). The optimal number of attributes for this study was 14. It appeared that fewer than 14 attributes contain insufficient data for prediction. Conversely, more than 14 attributes introduced background noise, compromising accuracy.

Table 1: Accuracy in Predicting Prognostic Status with Different Attribute Sets by the Deep Learning Network.

Conventional	34 Attribute Set		14 Attribute Set	
	Validation Set No.	Accuracy	Validation Set No.	Accuracy
	1	90%	1	90%
	2	80%	2	70%
	3	80%	3	80%
	4	90%	4	90%
	5	100%	5	90%
	6	80%	6	80%
	7	70%	7	70%
	8	70%	8	80%
	9	80%	9	100%
	10	75%	10	80%
	Mean=	81%*	Mean=	83%**

* corresponding to sensitivity of 74%, and specificity of 86%.

** corresponding to sensitivity of 80%, and specificity of 85%.

The use of machine learning algorithms frequently involves careful tuning of network configuration and learning parameters. This tuning often requires experience, and sometimes brute-force search [41]. During network training, we have tried various configurations for the neural network to achieve optimal accuracy and noted that our DL network performed best with 3 hidden layers consisting of 20, 15, and 10 nodes, respectively. The optimal learning parameters for our neural network, obtained through trial and error, were as following [42]. Learning rate: 1.0, Momentum: 1.0, batch size=10, sigmoid function for activation and output.

We also noted that the 3 general types of attributes (cytogenetics, age, or mutations) are almost equally important in predicting prognosis. By separately excluding cytogenetics, age, and mutations in the analysis, the accuracy for prognosis prediction degraded significantly to 67%, 61%, and 74%, respectively.

Discussion

DL algorithms are new and innovative tools of research in machine learning to extract complex data representations at high levels of abstraction. In fact, DL has been cited as one of the 10 breakthrough technologies in 2013 by MIT Technology Review [43]. The most important contribution of DL algorithms is to develop a hierarchical architecture of data, where higher-level features are defined in terms of lower-level features. The hierarchical learning architecture of DL algorithms is motivated by the biological structure of the primary sensorial areas of the neocortex in the human brain, which automatically extracts abstract features from the underlying data [44-46]. DL algorithms rely on large amounts of unsupervised data, and typically learn data representations in a greedy layer-wise fashion [47, 48]. Studies have shown that data representations obtained from stacking up nonlinear feature extractors (such as autoencoders used in our study) often yield better machine classification results [49-51].

DL applications have produced outstanding results in several areas, including speech recognition, computer vision, and natural language

processing [28, 47, 48, 52-59]. A recent challenge hosted by the International Symposium on Biomedical Imaging (ISBI) in 2016 led to a successful DL system for automated detection of metastatic cancer from whole slide images of sentinel lymph nodes [60]. Data-intensive technologies as well as improved computational and data storage resources have contributed to Big Data science [61]. Technology-based companies such as Microsoft, Google, Yahoo, and Amazon have maintained databases that are measured in exabyte proportions or larger. Various private and public organizations have invested in Big Data Analytics to address their needs in business and research, making this an exciting area of data science research [62].

In the present study, we used DL to predict the prognosis of AML. Specifically, we relied on a set of attributes (cytogenetics, age, and mutations) to predict prognostic status in newly diagnosed AML patients. We implemented a DL network consisting of autoencoders that were stacked to form hierarchical deep models from which high-level features were compressed, organized, and extracted, without labeled training data. We showed how DL, which incorporates unsupervised feature training, can be used to predict prognosis using cytogenetics, age, and mutations with excellent results (accuracy of 83%, sensitivity of 80%, and specificity of 85%).

The main limitation of our preliminary study was the relatively small size of cohorts (94 cases out of 200 from the TCGA database). Nevertheless, this study provided excellent preliminary results for future studies that may include many more cases, more cytogenetics and mutation data, and other clinical data such as co-morbidity index. With more data, it is expected that the accuracy would be even higher than that from this preliminary study.

Conclusion

DL method, a disruptive technology, is predicted to be an integrated part of future practice in molecular diagnosis and prognostic prediction using NGS data. Our preliminary study demonstrated a practical application in this area. The successful validation of this DL software is of tremendous value to the personalized treatment of AML patients, i.e., stratifying treatment, especially bone marrow/stem cell transplant for each patient based on predicted prognosis. The software's database can be continually kept up to date by adding new patients' data (with more patients, with additional tests, etc.) to improve its predicting ability. Furthermore, input ranking techniques in the neural net can detect critical parameters which impact prognosis, and this helps to identify sets of important data to predict prognosis (novel patterns). While the amount of data used here was relatively modest, this study provided a proof-of-concept for using the DL network as a more accurate approach for modeling big data in cancer genomics.

Acknowledgements

The data in this study were provided by the TCGA database which is available in the public domain for research purposes.

Conflicts of Interest

None.

Funding

None.

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