Application of Deep Learning on Predicting Prognosis of Acute Myeloid Leukemia with Cytogenetics, Age, and Mutations

Mei Lin, MD1, Vanya Jaitly, MD1, Iris Wang, MD1, Zhihong Hu, MD1, Lei Chen, MD1, Md. Amer Wahed, MD1, Zeyad Kanaan, MD2, Adan Rios, MD2, Andy N.D. Nguyen, MD1*

1Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at Houston, Texas, TX 77030
2Department of Oncology, University of Texas Health Science Center at Houston, Texas, TX 77030

Abstract
We explore how Deep Learning (DL) can be utilized to predict prognosis of acute myeloid leukemia (AML). Out of TCGA (The Cancer Genome Atlas) database, 94 AML cases are used in this study. Input data include age, 10 common cytogenetic and 23 most common mutation results; output is the prognosis (diagnosis to death, DTD). In our DL network, autoencoders are stacked to form a hierarchical DL model from which raw data are compressed and organized and high-level features are extracted. The network is written in R language and is designed to predict prognosis of AML for a given case (DTD of more than or less than 730 days). The DL network achieves an excellent accuracy of 83% in predicting prognosis. As a proof-of-concept study, our preliminary results demonstrate a practical application of DL in future practice of prognostic prediction using next-gen sequencing (NGS) data.

Key Words: AML; Cytogenetics, Age, Mutations; Deep Learning; Neural Network

INTRODUCTION
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 aberrant myeloblasts.1 The highly proliferative cancer cells impede the formation of normal blood cells; leading to death if patients are left untreated. There are about 19,000 estimated new cases and 10,000 estimated deaths from this disease in 2018.2,3

*Corresponding author
Andy N.D. Nguyen, MD
Department of Pathology and Laboratory Medicine
University of Texas Health Science Center at Houston
6431 Fannin Street, MSB 2.292, Houston, TX, 77030
(713) 500-5337; fax (713) 500-0712
Nghia.D.Nguyen@uth.tmc.edu
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. A variety of technologies targeting the gene, mRNA, microRNA and protein level have helped predicting the prognosis of AML patients. Interestingly, most AMLs only have only a few gene mutations, but prognosis of AML patients is quite varied. A possible explanation for this diversity is differences in protein signaling. The genetic aberrations and mutations of myeloid leukemic cells often cause a profound impact on the cellular protein networks.

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. 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. Although risk stratification for AML patients has been improved to a great extent recently, a substantial number of patients still lack 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.

Recent advances in molecular studies, especially NGS, have identified additional recurrent somatic mutations in patients with AML, including mutations in TET2, IDH1 and IDH2, DNMT3A, DNMT3B, DNMT3A, DNMT3B, PHF6, and others. 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. 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 recent application of NGS technique. The TCGA study with 200 AML cases showed that the average number of mutations is 13 per case and there are 23 recurrent mutations. 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 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. Warren McCulloch and Walter Pitts created a computational model for neural networks based on an algorithm called threshold logic in 1943. Neural networks had not shown superior performance compared to other machine learning methods until the introduction of DL in 2006. DL is different 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. Every layer of a deep learning 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.\textsuperscript{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. Deep learning has recently shown impressive results in discovering intricate structures in high-dimensional data and obtained remarkable performances for object detection in images,\textsuperscript{23,34} speech recognition,\textsuperscript{25} natural language understanding\textsuperscript{26} and translation.\textsuperscript{27} Relevant clinical-ready successes have been obtained in health care as well (e.g. identification of metastatic breast cancer on lymph node slides,\textsuperscript{28} aggregating features relevant to specific breast cancer subtypes,\textsuperscript{29} predicting drug therapeutic uses and indications\textsuperscript{30}), initiating the way toward a potential new generation of intelligent tools based on DL for real-world medical care.

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 network where data must be strictly categorized to provide the appropriate label for supervised learning, the unlabeled data in DL can be used in 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\textsuperscript{19} which consist of 200 de novo AML cases and attempt to use DL which incorporates unsupervised feature training to find correlation between cytogenetics, age, mutation and prognosis. To the best of our knowledge, unsupervised feature learning methods has never been applied to predict AML prognosis in this manner.

MATERIALS AND METHODS

Materials:

Data from 200 cases of de novo AML were retrieved from TCGA database (public domain).\textsuperscript{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 (DTD) for each case.\textsuperscript{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.\textsuperscript{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:
- Activated signaling (signal transduction): FLT3-ITD, KIT, KRAS, NRAS, and PTPN11
- Myeloid transcription factors (differentiation): NPM1, CEBPA, and RUNX1
- Epigenetic regulation: DNMT3A, TET2, IDH2, IDH1, EZH2, and HNRNPK
- Tumor suppressors: TP53, WT1, and PHF6
- Spliceosomes: U2AF1
- Cohesins: SMC1A, SMC3, STAG2, and RAD21,
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 number of input parameters was 34 (10 cytogenetics, age, and 23 mutations) and the number of outcome parameter (DTD) was one.

**Methods**

Our main analysis method was a DL neural network with stacked (multi-layered) autoencoder. Training was mostly based on unsupervised feature learning which has been used successfully for image and audio recognition. 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. 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. 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.

The stacked autoencoder neural network, illustrated in Fig. 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 network. During 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 learnt 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 Fig. 1. The sigmoid function is used as activation function in hidden layers. In fine-tuning phase, the back-propagation method minimizes the error with an additional sparsity penalty. 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). For the fine-tuning phase, we used linear function for the classifier.
Fig 1. A Deep Learning Neural Network (Stacked Autoencoder Network) with Unsupervised Training in Pre-training Phase and Supervised Training in the Fine-tuning phase

For the initial analysis, all 34 attributes (10 cytogenetics findings, 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 trained network would be used to predict the prognostic status for each case in the excluded subset (the remaining 84 cases). 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 number 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 > 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 [tr8, 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 DL network is summarized in Table 1. Number of attributes smaller or larger than 14 did not yield better accuracy (data not shown) indicating that 14 is the optimal number of attributes for this study. 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 Validation Set No. | 34 Attribute Set Accuracy | 14 Attribute Set Accuracy |
|---------------------------------|---------------------------|---------------------------|
| 1                               | 90%                       | 90%                       |
| 2                               | 80%                       | 70%                       |
| 3                               | 80%                       | 80%                       |
| 4                               | 90%                       | 90%                       |
| 5                               | 100%                      | 90%                       |
| 6                               | 80%                       | 80%                       |
| 7                               | 70%                       | 70%                       |
| 8                               | 70%                       | 80%                       |
| 9                               | 80%                       | 100%                      |
| 10                              | 75%                       | 80%                       |
| Mean=                           | 81%*                      | Mean=                     | 83% **                     |

Legends:
* 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. 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, 10 nodes, respectively.
The optimal learning parameters for our neural network, obtained through trial and error, were as follows\(^42\): 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 as expected. By separately leaving out cytogenetics, age, or 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,\(^52\)\(^-\)\(^56\) computer vision,\(^47\)\(^,\)\(^48\)\(^,\)\(^57\) and natural language processing.\(^58\)\(^,\)\(^59\)\(^,\)\(^28\) A recent challenge hosted by the International Symposium on Biomedical Imaging (ISBI) in 2016 lead 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,\(^62\) making this an exciting area of data science research.

In the present study, we used DL to predict prognosis of AML. Specifically, we rely 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 are stacked to form hierarchical deep models from which high-level features are 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 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 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 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 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 DL network as a more accurate approach for modeling big data in cancer genomics.

**Acknowledgement:** The data in this study were provided by TCGA database which is available in public domain for research purpose.

**REFERENCES**

1. S. Swerdlow et al (Editors). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. World Health Organization; Revised 4th edition (September 29, 2017)
2. Noone AM, Howlader N, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD
3. Cancer Stat Facts: Leukemia - Acute Myeloid Leukemia (AML). [https://seer.cancer.gov/statfacts/html/amyl.html](https://seer.cancer.gov/statfacts/html/amyl.html) NIH National Cancer Institute. SEER Program. April 2018 (last accessed on 10/30/18)
4. Valk PJ, Verhaak RG, Beijen MA, et al. Prognostically useful gene-expression profiles in acute myeloid leukemia. *N Engl J Med*. 2004;350:1617-28.
5. Byrd JC, Mrózek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood*. 2002;100:4325-36.
6. Bullinger L, Döhner K, Bair E, et al. Use of gene-expression profiling to identify prognostic subclasses in adult acute myeloid leukemia. *N Engl J Med*. 2004;350:1605-16.
7. Ley TJ, Ding L, Walter MJ, et al. DNMT3A mutations in acute myeloid leukemia. *N Engl J Med*. 2010;363:2424-33.
8. Marcucci G, Haferlach T, Döhner H. Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications. *J Clin Oncol*. 2011;29:475-86. [Erratum, J Clin Oncol 2011;29:1798.]
9. Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of pre-remission and post-remission therapy in adult acute myeloid leukemia: A Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood*. 2000;96:4075-83.
10. Schlenk RF, Döhner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358:1909-18.
11. Delhommeau F, Dupont S, Della Valle V, et al. Mutation in TET2 in myeloid cancers. *N Engl J Med*. 2009;360:2289-301.
12. Abdel-Wahab O, Mullally A, Hedvat C, et al. Genetic characterization of TET1, TET2, and TET3 alterations in myeloid malignancies. *Blood*. 2009;114:144-7.
13. Mardis ER, Ding L, Dooling DJ, et al. Recurring mutations found by sequencing an acute myeloid leukemia genome. *N Engl J Med.* 2009;361:1058-66.

14. Ward PS, Patel J, Wise DR, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell.* 2010;17:225-34.

15. Marcucci G, Maharry K, Wu YZ, et al. IDH1 and IDH2 gene mutations identify novel molecular subsets within de novo cytogenetically normal acute myeloid leukemia: A Cancer and Leukemia Group B study. *J Clin Oncol.* 2010;28:2348-55.

16. Yan XJ, Xu J, Gu ZH, et al. Exome sequencing identifies somatic mutations of DNA methyltransferase gene DNMT3A in acute monocytic leukemia. *Nat Genet.* 2011;43:309-15.

17. Van Vlierberghe P, Patel J, Abdel-Wahab O, et al. PHF6 mutations in adult acute myeloid leukemia. *Leukemia.* 2011;25:130-4.

18. Metzeler KH, Maharry K, Radmacher MD, et al. TET2 mutations improve the new European LeukemiaNet risk classification of acute myeloid leukemia: A Cancer and Leukemia Group B study. *J Clin Oncol.* 2011;29:1373-81.

19. The Cancer Genome Atlas (TCGA) Data Portal. <https://portal.gdc.cancer.gov/> (last accessed on 10/30/18)

20. McCulloch WS, Pitts W.. A Logical Calculus of Ideas Immanent in Nervous Activity. *Bulletin of Mathematical Biophysics.* 1943;5(4): 115–133.

21. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature.* 2015;521(7553): 436.

22. Bengio Y. Learning deep architectures for AI. *Foundations and trends® in Machine Learning.* 2009;2(1)1-27.

23. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. *Adv Neural Inf Process Syst.* 2012;1097–1105.

24. Szegedy C, Liu W, Jia Y, et al. Going deeper with convolutions. *IEEE Conference on Computer Vision and Pattern Recognition (CVPR).* 2015;1–9.

25. Hinton G, Deng L, Xu D, et al. Deep neural networks for acoustic modeling in speech recognition. *IEEE Signal Process Mag.* 2012;29:82–97.

26. Collobert R, Weston J, Bottou L, et al. Natural language processing (almost) from scratch. *J Mach Learn Res.* 2011;12:2493–537.

27. Sutskever I, Vinyals O, Le QV. Sequence to sequence learning with neural networks. *Adv Neural Inf Process Syst.* 2014;27:3104–12.

28. Wang D, Khosla A, Gargeya R, et al. Deep learning for identifying metastatic breast cancer. *arXiv preprint arXiv:2016:1606.05718.*

29. Tan J, Ung M, Cheng C, Greene CS. Unsupervised feature construction and knowledge extraction from genome-wide assays of breast cancer with denoising autoencoders. *Pac Symp Biocomput.* 2014;20:132–143.

30. Vidovic D, Koletai A, Schurer SC. Large-scale integration of small-molecule induced genome-wide transcriptional responses, Kinome-wide binding affinities and cell-growth inhibition profiles reveal global trends characterizing systems-level drug action. *Front. Genet.* 2014;5:e77521.

31. Cancer Genome Atlas Research N. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med.* 2013;368(22):2059-74.

32. Lee H, Pham P, Largman Y, et al. Unsupervised feature learning for audio classification using convolutional deep belief networks. *In Advances in neural information processing systems.* 2009;1096-1104.

33. Huang GB, Lee H, and Learned-Miller E. Learning hierarchical representations for face verification with convolutional deep belief networks. *IEEE Conf. on Computer Vision and Pattern Recognition.* 2012;2518-2525.

34. R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/ (last accessed on 10/30/18)

35. Tippmann S. Programming tools: Adventures with R. *Nature News.* 2015;517(7532):109.
36. The Comprehensive R Archive Network https://cran.r-project.org/
(last accessed on 10/30/18)
37. Coates A, Ng A, Lee H. An analysis of single-layer networks in unsupervised feature learning. In Proceedings of the fourteenth international conference on artificial intelligence and statistics. 2011;215-223.
38. Bengio Y, Lamblin P, Popovici D, et al. Greedy layer-wise training of deep networks. In Advances in neural information processing systems. 2007;153-160.
39. Raina R, Battle A, Lee H, Packer B, Ng AY. Self-taught learning: transfer learning from unlabeled data. In Proceedings of the 24th international conference on Machine learning. 2007;759-766.
40. Pereira F, Mitchell T, Botvi M. Machine learning classifiers and fMRI: a tutorial overview. NeuroImage. 2009;199-209.
41. Snoek J, Larochelle H, Adams RP. Practical Bayesian optimization of machine learning algorithms. Advances in Neural Information Processing Systems. 2012;25:2960-2968.
42. R Package Deepnet. CRAN R Project https://cran.r-project.org/web/packages/deepnet/index.html
(last accessed on 10/30/18)
43. MIT Technology Review https://www.technologyreview.com/s/513696/deep-learning/
(last accessed on 10/30/18)
44. Bengio Y, LeCun Y. Scaling learning algorithms towards AI. Large Scale Kernel Machines. 2007;34:321–360.
45. Bengio Y, Courville A, Vincent P. Representation learning: A review and new perspectives. IEEE transactions on Pattern Analysis and Machine Intelligence. 2013;35(8):1798–1828.
46. Arel I, Rose DC, Karnowski TP. Deep machine learning-a new frontier in artificial intelligence research. IEEE computational intelligence magazine. 2010;5:13–18.
47. Hinton GE, Osindero S, Teh YW. A fast learning algorithm for deep belief nets. Neural computation. 2006;18(7):1527-54.
48. Bengio Y, Lamblin P, Popovici D, Larochelle H. Greedy layer-wise training of deep networks. In Advances in neural information processing systems. 2007;153-160.
49. Larochelle H, Bengio Y, Louradour J, Lamblin P. Exploring strategies for training deep neural networks. Journal of machine learning research. 2009;10:1-40.
50. Salakhutdinov R, Hinton GE. Deep Boltzmann machines. International Conference on, Artificial Intelligence and Statistics. 2009;448–455.
51. Goodfellow I, Lee H, Le QV, et al. Measuring invariances in deep networks. Advances in Neural Information Processing Systems. 2009;646–654.
52. Dahl G, Ranzato M, Mohamed AR, et al. Phone recognition with the mean-covariance restricted Boltzmann machine. Advances in Neural Information Processing Systems. 2010;469–477.
53. Hinton G, Deng L, Yu D, et al. Deep neural networks for acoustic modeling in speech recognition: The shared views of four research groups. IEEE Signal Process Mag. 2012;29(6):82–97.
54. Seide F, Li G, Yu D. Conversational speech transcription using context-dependent deep neural networks. INTERSPEECH. ISCA. 2011;437–440.
55. Dahl GE, Yu D, Deng L, et al. Context-dependent pre-trained deep neural networks for large-vocabulary speech recognition. IEEE Trans. Audio, Speech & Language Processing. 2012;20(1):30–42.
56. Mohamed AR, Dahl GE, Hinton G. Acoustic modeling using deep belief networks. IEEE Trans. Audio, Speech & Language Processing. 2012;20(1):14-22.
57. Krizhevsky A, Sutskever I, Hinton G. ImageNet classification with deep convolutional neural networks. Advances in Neural Information Processing Systems. 2012;25:1106–1114.
58. Mikolov T, Deoras A, Kombrink S, et al. Empirical evaluation and combination of advanced language modeling techniques. INTERSPEECH. ISCA. 2011;605–608.
59. Socher R, Huang EH, Pennin J, et al. Dynamic pooling and unfolding recursive autoencoders for paraphrase detection. In Advances in neural information processing systems. 2011;801-809.
60. Bordes A, Glorot X, Weston J, et al. Joint learning of words and meaning representations for open-text semantic parsing. In Artificial Intelligence and Statistics. 2012;127-135.
61. National Research Council (2013) Frontiers in Massive Data Analysis. The National Academies Press, Washington, DC. http://www.nap.edu/openbook.php?record_id=18374
(last accessed on 10/30/18)

62. Dumbill E. What Is Big Data? An Introduction to the Big Data Landscape. In: Strata 2012: Making Data Work. O’Reilly, Santa Clara, CA O’Reilly.