Recurrent Neural Network (RNN) based Model to Uncover Temporal Phenotypes for Heart Failure with Preserved Ejection Fraction

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1. Introduction and Motivation

1.1 Heart Failure

Currently, there are about 5.7 million adults in the United States suffering from heart failure (HF). HF has contributed around 1/9 deaths, and about half of patients die within 5 years of diagnosis [Mozaffarian 2016]. Furthermore, HF costs the nation an estimated $30.7 billion each year [Heidenreich 2011]. Targeting HF's high morbidity and mortality, increasing prevalence and escalating healthcare costs, consequently, there is ongoing effort in clinical research to identify high-risk patients, provide more precise prediction and apply customized treatment [Alba 2013].

1.2 Data Mining for Healthcare

In healthcare, data mining has become more and more popular. In the context of complexity and huge volume of healthcare transactions, which usually do not fit traditional analytical methods, modern data mining techniques such as advanced machine learning and the more recent deep-learning methods have particular merits. Through utilizing health information technology (HIT) infrastructure in the form of electronic health records (EHRs), many aspects of care including diagnosis, medication, laboratory results and imaging data would be captured [Jensen 2012]. This so-call phenotyping would boost a finer understanding of genotype-phenotype relationships.

There has been significant amount of research performed on predicting HF. Several models, i.e. Heart Failure Survival Score, the Seattle Heart Failure Model, and the PACE (incorporating peripheral vascular disease, age, creatinine, and ejection fraction) risk score, have been improved and validated continuously [Ross 2008]. More recently, machine learning techniques have been adopted and some results indicate significant improvement in prediction accuracy [Austin 2013].

1.3 Deep Learning for Phenotyping

In recent years, deep learning has gained an unprecedented attention given its state-of-the-art performance in many research domains such as speech recognition and computer vision [LeCun 2015]. Deep learning

utilizes machine learning strategies but with hierarchical deep architectures rather than shallow-structures. Consequently, deep learning is extremely powerful in uncovering the underlying relationships between latent factors and extracting meaningful abstract concepts. This could be particularly suitable for healthcare research. Because human physiology is especially complicated -- modern molecular biology is still far from sufficiency to interpret the detailed physiologic processes -- to this context, deep learning could be potential to drive insight from clinical data, i.e. the EHRs, and discover the hidden nonlinear cause and effect.

Deep learning is distinguished from its more conventional counterparts by the utilization of multiple layers of conventional learning functions [LeCun 2015]. Originally modeled after neurons in the brain, neural networks function by receiving inputs from other "neurons" and once a certain potential or threshold has been reached, they "fire" which propagates the signal onto the next layer of neuronal units. These layers of functionality allow for abstraction from the original data which allows the neural network to "learn" the weights for each neuronal unit.

While in a typical feedforward neural network decision flows in one direction (from the input layer to the output layer), a recurrent neural network (RNN) has some built-in backpropagation mechanisms through time where some outputs will feed back and allow updates to the weights of the nodes further back along the network. This feedback mechanism allows RNNs to be better suited for data with sequential input such as sentence processing (sequential order of words) or, in our case, the time-series of visits/diagnoses/lab results/prescriptions found in EHR. A special subset of RNNs use Long Short-Term Memory (LSTM) hidden units which provide capabilities of finding long range associations and dependencies. Lipton *et al.* were the first to apply RNNs using Long Short-Term Memory (LSTM) hidden units to classify diagnoses in a medical time series dataset (Lipton 2016).

There has been ongoing research of using deep learning for phenotyping. For example, Choi *et al*. has used recurrent neural networks (RNN) to predict clinical events, in which encounter records were inputs and the diagnosis and medication categories for a subsequent visit are the predictions [Choi 2015]. Che *et al*. has trained a collection of neural networks varying sizes and architectures to handle clinical records which are sparse but with temporal order and between-label relationships [Che 2015]. More significantly, early in January 2017, FDA approved the first cloud-based deep learning method for clinical study. This "Arterys imaging platform" helps to diagnose heart problems and passes FDA tests by showing it is able to perform at least as accurate as humans [Marr 2017].

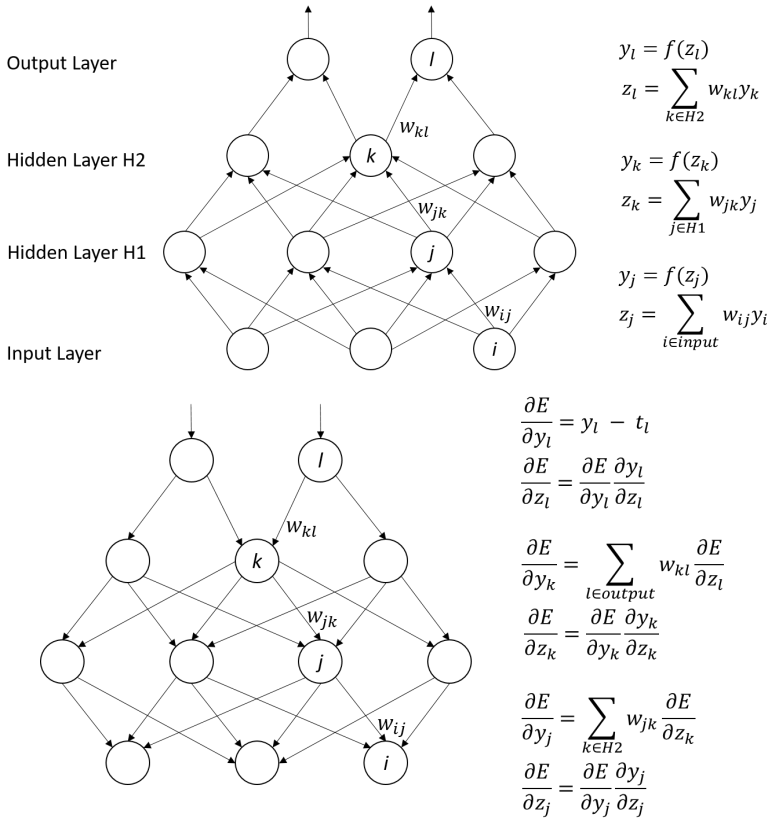

Figure 1. Training a neural network **(top)** showing the feedforward mechanism which propagates in one direction from input layer through the hidden layers to the output layer. **(bottom)** Once an output is obtained, it is compared with the actual label and the error is calculated and backpropagated through the nodes to adjust the weights ***w***.

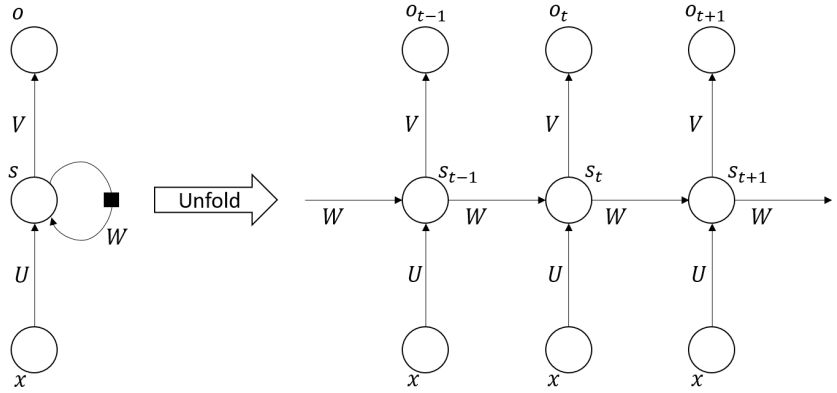

Figure 2. A recurrent neural network (RNN) unfolded through time showing the how the states of node *s* interacts with previous time steps *t*. Matrices U, V, and W which contain the parameters are unchanged at each time step and are used at each time step.

2. Objective

In this project, our goal is to use EHR data to uncover feature representations of patients with heart failure (HF). As mentioned, previous literatures had successfully applied deep learning models such as RNN in prediction and computational phenotyping tasks. The advantage of deep learning models like RNN is that they can easily learn temporal relations in raw patient event in a scalable fashion, a task that is very difficult for classic machine learning models. In our project, we will incorporate RNN and other variations of deep learning models to extract meaningful temporal feature representations for patients with HF and compute phenotypes using the extracted features.

3. Proposed Methods

Our approach will be conducted in two steps:

1. Train a neural network model (e.g. RNN/LSTM/GRU) with some objective functions (e.g softmax). The objective can be maximizing probabilities of codes appeared in subsequent events as in disease progression modeling or simply maximizing the probability of labels as in prediction tasks.
2. After the neural network is trained, we will use learned weights from some of the intermediate neurons as a new encoding of features that incorporates temporal information of medical events for each patients. We will cluster those features to identify new sub-groups of patients with HF.

We will validate our new feature representation by testing its performance on some prediction tasks. One challenge of our project is that the weights from recurrent neural networks are hard to interpret. Choi *et al.* developed a variation of Attention model (RETAIN) that achieved similar prediction results with much more interpretable weights. Developing upon the RETAIN model can be one way to get more interpretable phenotyping results. Another challenge is the dimension and sparsity of the raw patient event sequences. To cope with this, we can utilize Med2Vec model [Choi 2016] to do feature learning before the main neural-network is trained.

4. References

1. Alba AC, Agoritsas T, Jankowski M, Courvoisier D, Walter SD, Guyatt GH, Ross HJ. “Risk Prediction Models for Mortality in Ambulatory Patients With Heart Failure. A Systematic Review.” *Circ Heart Failure*. 2013. **6**(5):881–9.

2. Austin PC, Tu JV, Ho JE, Levy D, Lee DS. “Using methods from the data-mining and machine-learning literature for disease classification and prediction: a case study examining classification of heart failure subtypes.” *Journal of clinical epidemiology*. 2013. **66**(4):398-407.

3. Che Z, Dale D, Li W, Bahadori MT, Liu Y. “Deep Computational Phenotyping.” *KDD*. 2015.

4. Choi E, Bahadori MT, Kulas JA, Schuetz A, Steward WF, Sun J. “RETAIN: An Interpretable Predictive Model for Healthcare using Reverse Time Attention Mechanism.” *NIPS*. 2016.

5. Choi E, Bahadori MT, Schuetz A, Stewart WF, Sun J. “Doctor AI: Predicting Clinical Events via Recurrent Neural Networks.” *Proceedings of Machine Learning for Healthcare*. arXiv preprint arXiv:1511.05942, 2015.

6. Choi E, Bahadori MT, Searles E, Coffey C, Sun J. “Multi-layer Representation Learning for Medical Concepts.” arXiv preprint arXiv:1602.05568, 2016.

7. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD. “Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011. **123**(8):933–44.

8. Jensen PB, Jensen LJ, Brunak S. “Mining electronic health records: towards better research applications and clinical care.” *Nature Reviews Genetics*, 2012. **13**(6):395-405.

9. LeCun Y, Bengio Y, Hinton G. “Deep learning.” *Nature*. **521**. (2015)

10. Lipton ZC, Kale DC, Elkan C, Wetzel R. “Learning to Diagnose with LSTM Recurrent Neural Networks.” *ICLR*. 2016.

11. Marr B. “First FDA Approval For Clinical Cloud-Based Deep Learning In Healthcare.” *Forbes*. 20 Jan 2017. Web.

12. Mozaffarian D, Benjamin EJ, Go AS. on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. Circulation. 2016. **133**:e38-e360.

13. Ross JS, Mulvey GK, Stauffer B, Patlolla V, Bernheim SM, Keenan PS, Krumholz HM. “Statistical models and patient predictors of readmission for heart failure: a systematic review.” *Archives of internal medicine*. 2008. **168**(13):1371-1386.