

# Deep Learning Models for Health Care: Challenges and Solutions

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College of Computing  
Georgia Institute of Technology

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# Tutorial Slides and Supplementary Materials

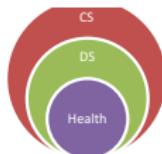
<https://tinyurl.com/y7wuk9xt>



# Why healthcare?



- Healthcare is big
- Healthcare is bad
- Healthcare is challenging



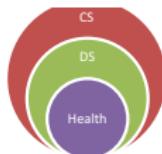
# US healthcare: The COST problem

Overall spending: **3.8 trillion dollars (2014)**



Top 10 most valuable companies combined





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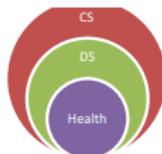
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10x Beijing Olympics





# US healthcare: The COST problem

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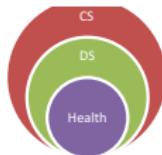
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# US healthcare: The COST problem

Overall spending: **3.8 trillion dollars (2014)**



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+

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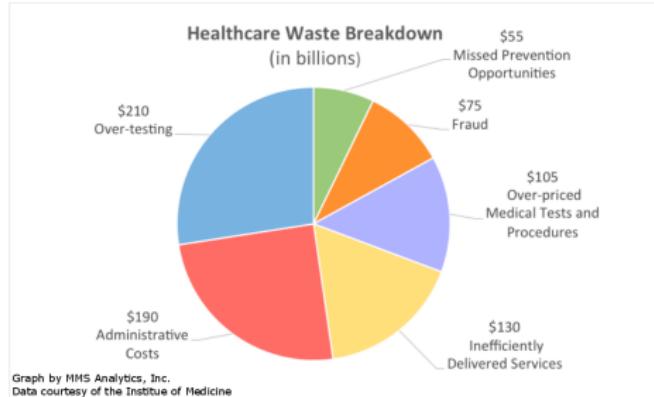
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Net worth of

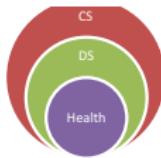




# US Healthcare Waste per year



**\$765 billions**

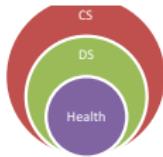


# US Healthcare Waste per year



**\$765 billions** = 50 years budget





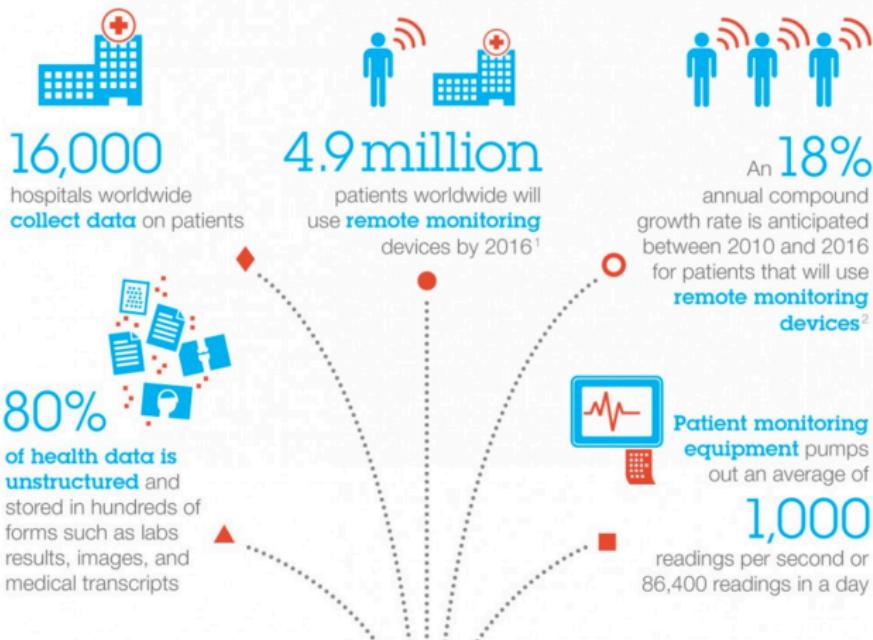
## US Healthcare Quality Issue

- 200K to 400K preventable death per year
  - Over 1000 per day



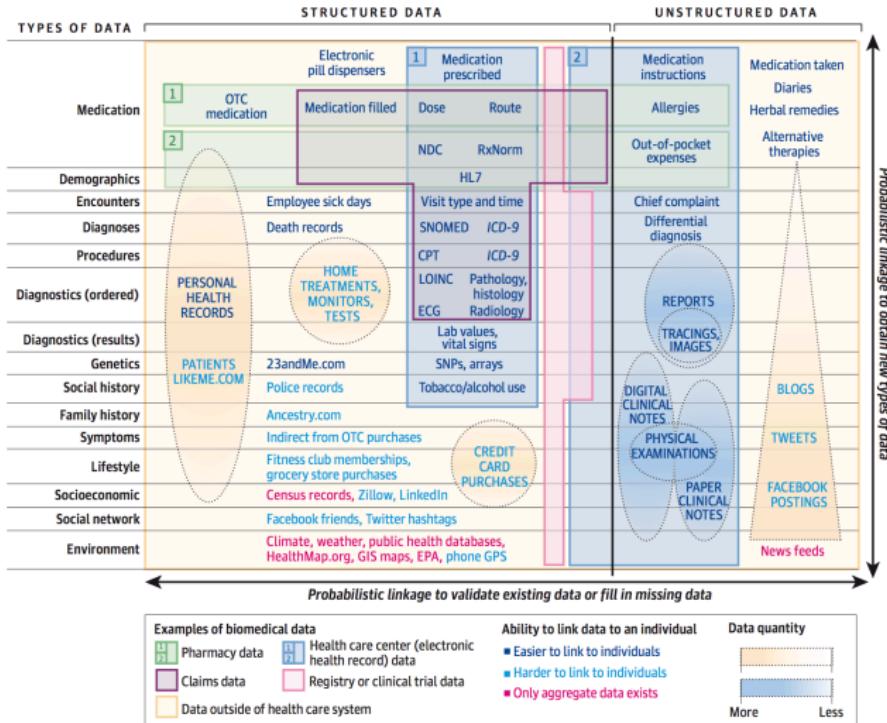
<https://www.documentcloud.org/documents/781687-john-james-a-new-evidence-based-estimate-of.html#document/p1/a117333>

# Healthcare data is everywhere



Source from <http://www.okilab.es/how-big-data-is-changing-healthcare/>

# Healthcare data sources



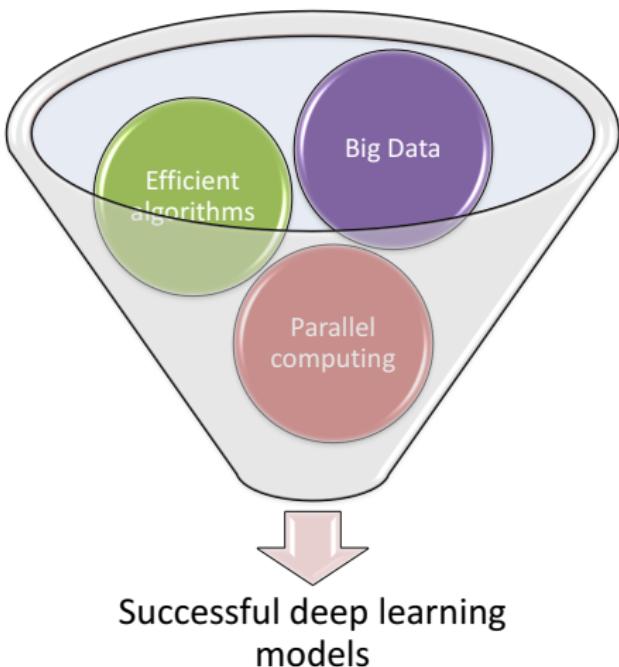
Weber, Griffin M., Kenneth D. Mandl, and Isaac S. Kohane. 2014. "Finding the Missing Link for Big Biomedical Data." *JAMA: The Journal of the American Medical Association* 311 (24): 2479–80.

# Why deep learning?

- *Speech recognition*
- *Computer vision*
  - *Image Classification*
  - *Video analysis*
- *Natural language processing*
  - *Machine translation*



# Recipes for deep learning success



# Early Work on Deep Learning in Health Applications

## Stacked Auto-encoder (SDA)

Computational phenotyping [Lasko et al., 2013; Kale et al., 2014; Che et al., 2015; Kale et al., 2015; Miotto et al., 2016]

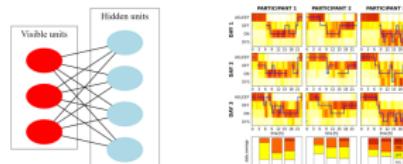


## Deep neural networks (DNNs)

Restricted Boltzmann machine (RBM)

Multi-layer perceptron (MLP)

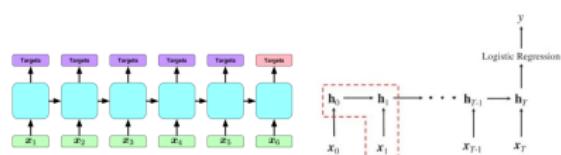
Condition prediction [Dabek and Caban, 2015; Hammerla et al., 2015]



## Recurrent neural networks (RNNs)

Long short-term memory (LSTM) Gated recurrent unit (GRU)

Diagnosis/event prediction Lipton et al. [2015]; Choi et al. [2016]



# Outline

## 1 Lecture 1: Data Sources and Health Care Problems

- EHR and Claims Data
- Medical Imaging Data
- Continuous Time Series (EEG, ECG, ICU monitoring)
- Clinical Notes

## 2 Lecture 2: Challenges and Solutions of DL for Health Care

## 3 Future Directions



## Doctor AI: Predicting Clinical Events via Recurrent Neural Networks



Edward Choi



Taha Bahadori



Andy Schuetz



Buzz Stewart



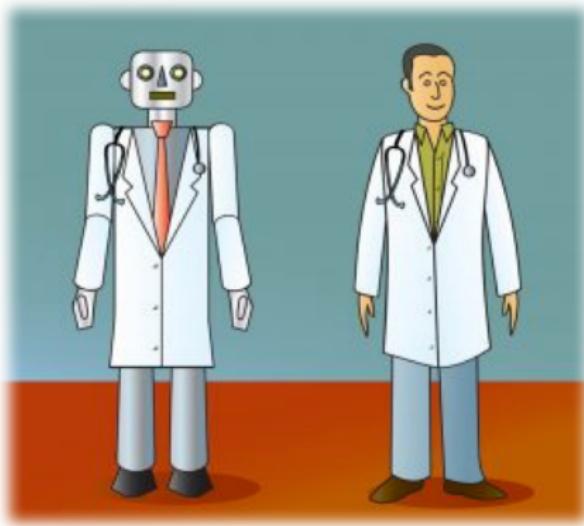
College of  
Computing  
Computational Science and Engineering



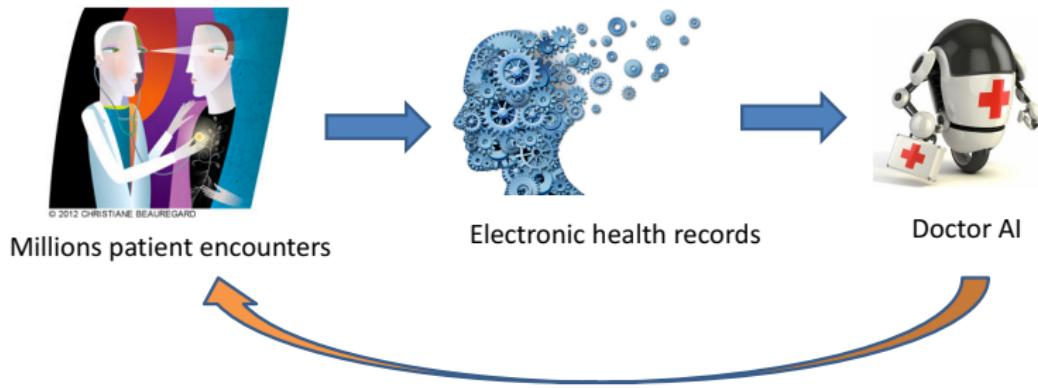
Sutter Health

Choi, Edward, et al. 2016. "Doctor AI: Predicting Clinical Events via Recurrent Neural Networks." In *Machine Learning for Healthcare Conference*, 301–18.

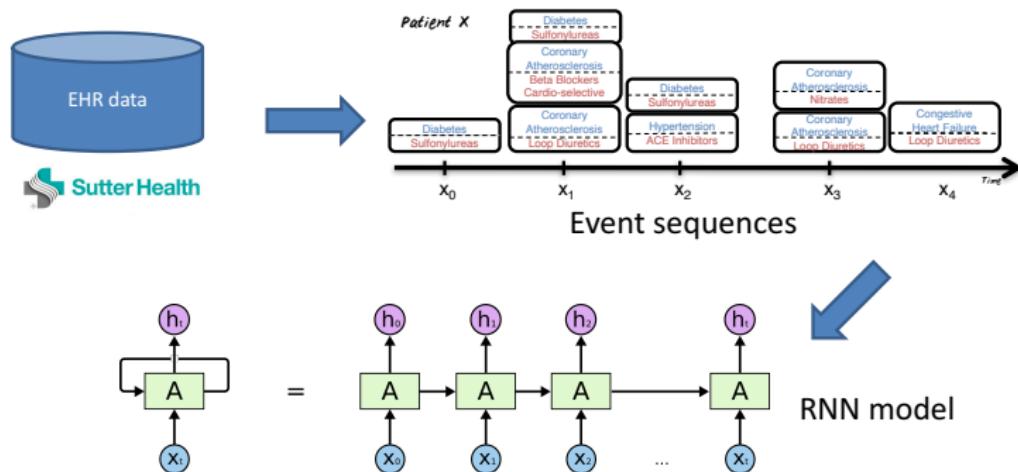
Do you want to be seen by a machine  
or a human for medical care?



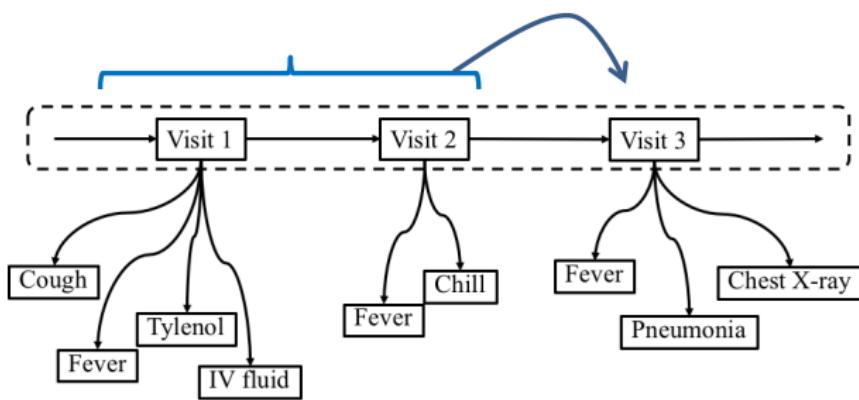
# Can machine perform similarly as doctors in diagnosis?



# Approach: Recurrent Neural Network (RNN)

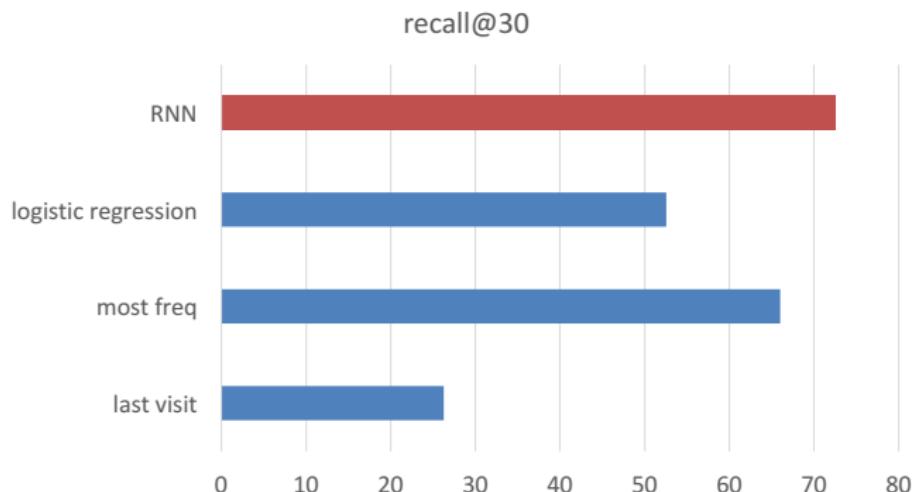


# Disease Progression Modeling

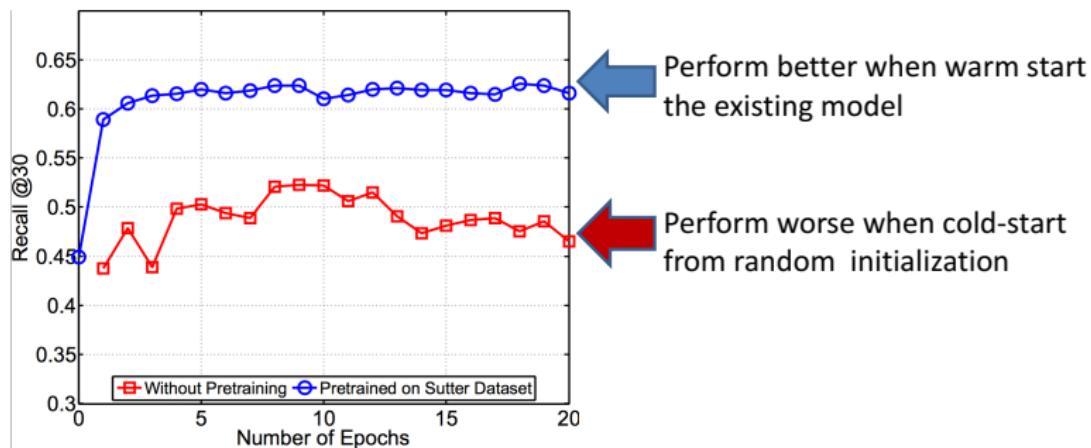


**Accuracy:** top- $k$  recall = 
$$\frac{\text{\# of true positives in the top } k \text{ predictions}}{\text{\# of true positives}}$$

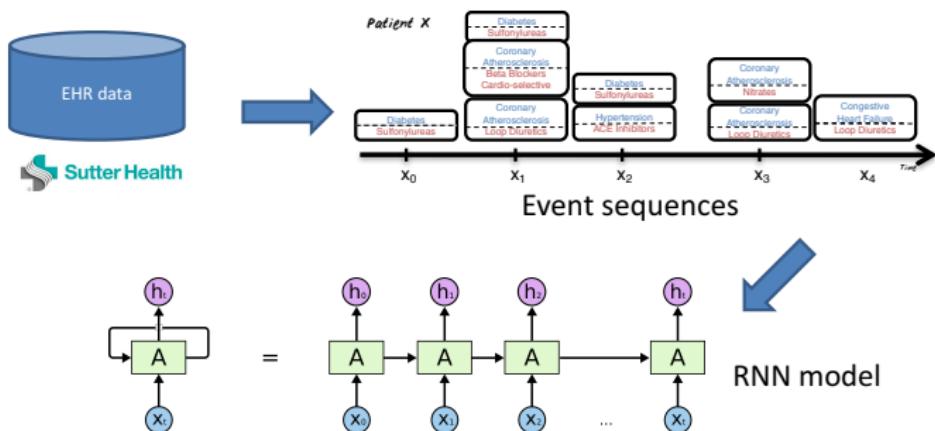
# RNN on predicting diagnoses in next visit



# Generalize RNN model from one institution to another



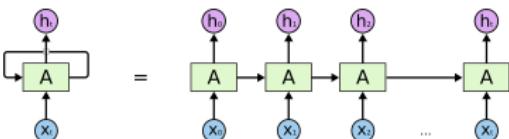
# Summary: Doctor AI



- general & accurate model for many prediction tasks
- Can handle sequences of variable lengths

Choi, Edward, et al. 2016. "Doctor AI: Predicting Clinical Events via Recurrent Neural Networks." In *Machine Learning for Healthcare Conference*, 301–18.

<https://github.com/mp2893/doctorai>



## USING RECURRENT NEURAL NETWORK MODELS FOR EARLY DETECTION OF HEART FAILURE ONSET

How to model temporal relations in the EHR data



Edward Choi



Andy Schuetz



Buzz Stewart



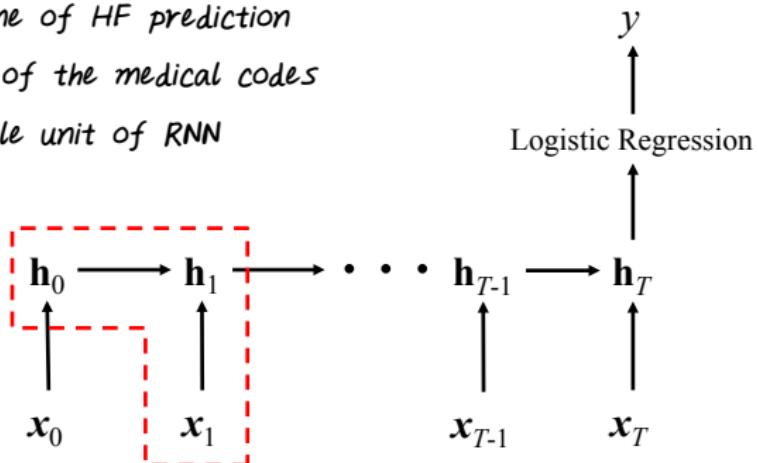
Edward Choi, Andy Schuetz, Walter Stewart, Jimeng Sun. Using Recursive Neural Network Models for Early Detection of Heart Failure Onset, JAMIA 2016

# MOTIVATIONS FOR EARLY DETECTION OF HEART FAILURE

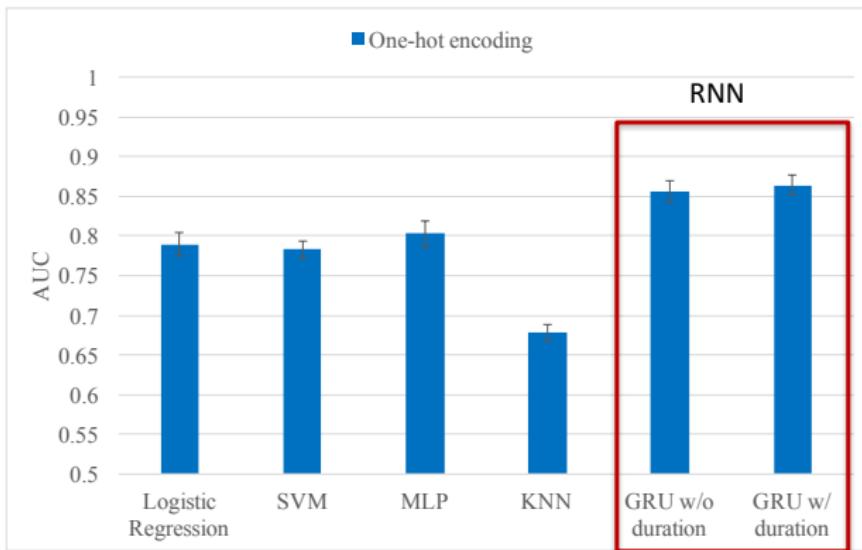


# Temporal model: RNN

- $x_t$ : one-hot coded Dx, Rx, Proc at time  $t$
- $h_t$ : hidden state at time  $t$
- $y$ : binary outcome of HF prediction
- $T$ : total length of the medical codes
- Red box: a single unit of RNN

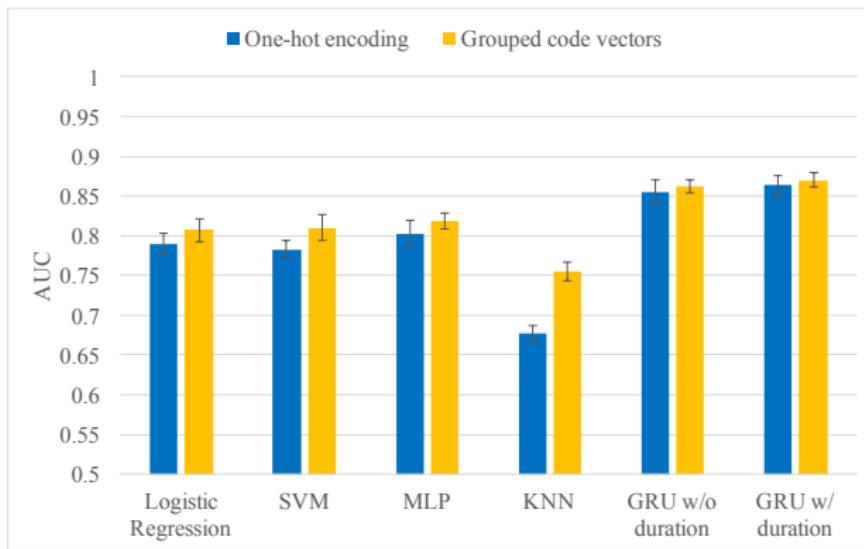


## PREDICTION PERFORMANCE OF RNN



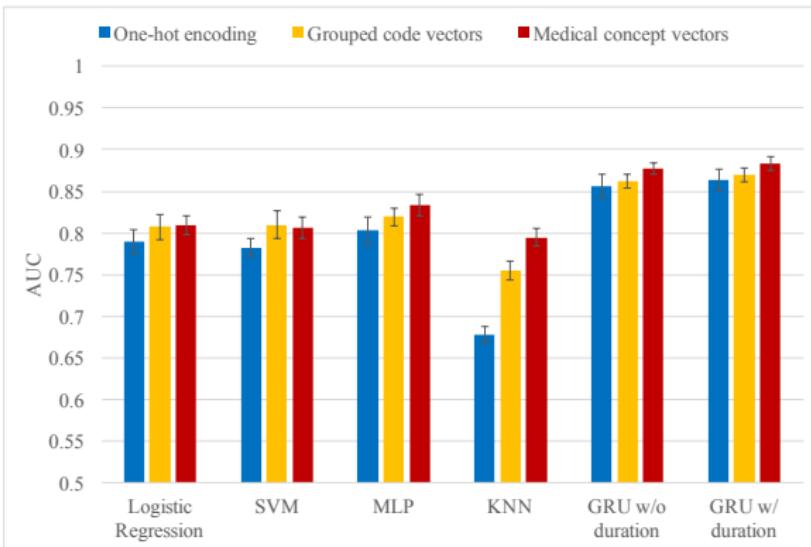
- *RNN model achieves over 10% improvement on AUC*

# PREDICTION PERFORMANCE OF RNN



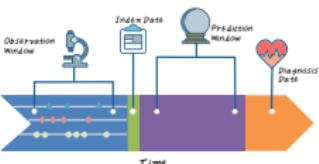
- RNN model achieves over 10% improvement on AUC
- ***Representation matters***

# PREDICTION PERFORMANCE OF RNN

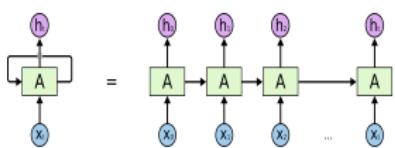


- RNN model achieves over 10% improvement on AUC
- *Data rep. (word2vec) > knowledge rep. (medical groupers)*

# Summary: Recurrent Neural Network (RNN) for heart failure onset prediction



Heart failure onset can be predicted using EHR data



Temporal information matters for  
HF onset prediction



Data driven representation matters



Edward Choi, Andy Schuetz, Walter Stewart, Jimeng Sun. Using Recursive Neural Network Models for Early Detection of Heart Failure Onset, JAMIA 2016

# DEEP LEARNING SOLUTIONS FOR CLASSIFYING PATIENTS ON OPIOID USE



Zhengping Che



Jennifer St. Sauver



Hongfang Liu

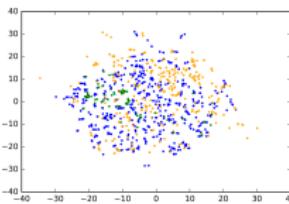
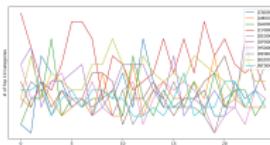


Che et al, Deep Learning Solutions for Classifying Patients on Opioid Use  
Zhengping Che, Jennifer St. Sauver, Hongfang Liu, and Yan Liu. American Medical Informatics Association Annual Symposium (AMIA), 2017

# Deep Learning for Opioid Use Analysis

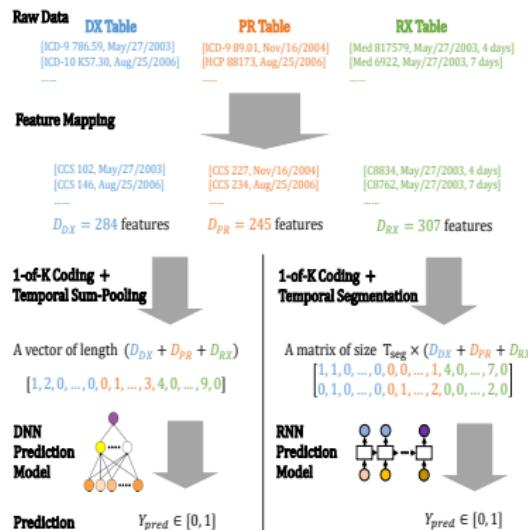
Opioid use study on datasets from the Rochester Epidemiology Project (REP)<sup>1</sup> with more than 140k people

- To extract and understand risk factors and indicators for adverse opioid and opioid-related events
- To predict new opioid users and dependence and recognize misuse on opioid analgesics
- To provide health care providers with better suggestions on pain medication prescriptions



# Our Framework

- Cohort selection and group identification
  - More than 110 millions of medical records in 2013-2016 are used
  - Patients are grouped into *short-term*, *long-term*, and *opioid-dependent* users
- Temporal feature processing
  - Records of *diagnoses*, *procedures*, and *prescriptions* are mapped into different coding systems via one-hot encoding
  - Sum-pooling and segmentation along the temporal dimension is applied to build the input matrix for each patient
- Multilayer DNNs and LSTMs with ReLU function are used for prediction.



# Empirical Evaluations

Deep learning models outperforms other baselines with similar model size

- Classification comparisons on AUC score ( $auc$ ) and kappa coefficient ( $\kappa$ )

	Short-term / Long-term						Long-term / Opioid-dependent				
	LR	SVM	RF	DNN	RNN		LR	SVM	RF	DNN	RNN
$auc$	0.7323	0.7327	0.6936	0.7340	<b>0.7536</b>		0.6512	0.6429	0.6999	<b>0.7279</b>	0.7144
$\kappa$	0.1090	0.0885	0.1289	$0.0756 \pm 0.004$	<b>0.2076</b>		0.1906	0.1821	0.2342	<b>0.3006</b>	0.2542

Most important features are selected by DNN models

- Feature importance  $\mathcal{I}$  are calculated from weights in all the layers in DNN

$$\mathcal{I} = \mathbf{W}^{[L]} BN^{[L]} \left( \dots \mathbf{W}^{[2]} BN^{[2]} \left( \mathbf{W}^{[1]} BN^{[1]}(\mathbf{1}) \right) \right) \in R^{1 \times D}$$

- Top related feature categories and their corresponding scores

Short-term / Long-term				Long-term / Opioid-dependent			
Table	Code	Feature Name	$\mathcal{I}$	Table	Code	Feature Name	$\mathcal{I}$
RX	C8834	Opioid Analgesics	0.2287	RX	C8834	Opioid Analgesics	0.7784
RX	C8890	Amphetamine-like Stimulants	-0.0843	DX	CCS 661	Substance-related Disorders	0.6186
RX	C8838	Non-opioid Analgesics	0.0802	PR	CCS 182	Mammography	-0.3481

# Outline

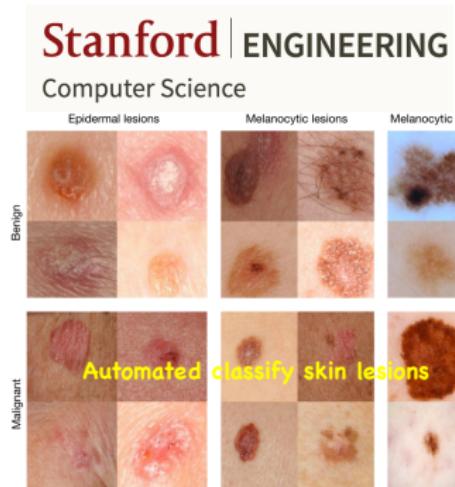
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- EHR and Claims Data
- **Medical Imaging Data**
- Continuous Time Series (EEG, ECG, ICU monitoring)
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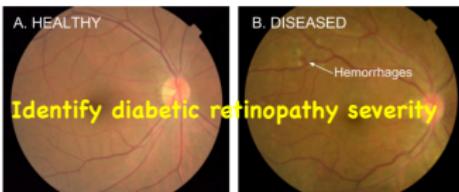
## 2 Lecture 2: Challenges and Solutions of DL for Health Care

## 3 Future Directions

## Unstructured Imaging Data: Data

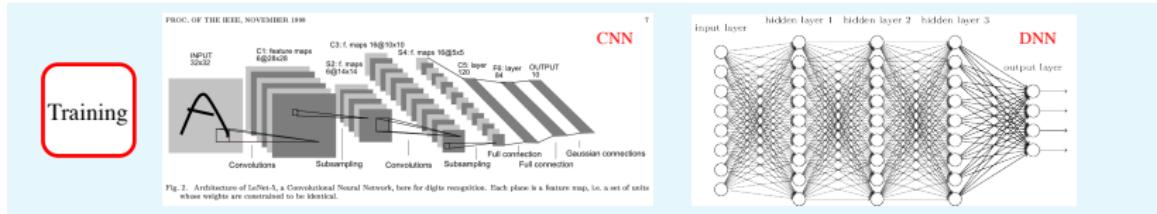


Research at Google



1. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, Venugopalan S, Widner K, Madams T, Cuadros J, Kim R, Raman R, Nelson PC, Mega JL, Webster DR. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. *JAMA*. 2016;316(22):2402-2410
2. Esteva A, Kuprel B, Saligrama V, Yeung A, Tsodikov A, Bergman A, Cestnick I, McMillan A, Kuprel B, Saligrama V, Yeung A, Bergman A, Cestnick I, McMillan A, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542:115–118 (2017)
3. Liu Y, Krishna Gadepalli M, Norouzi M, Dahl GE, Kohlberger T, Boyko A, Venugopalan S, et al. 2017. "Detecting Cancer Metastases on Gigapixel Pathology Images." *arXiv [cs.CV]*. arXiv. <http://arxiv.org/abs/1703.02442>.

## Unstructured Imaging Data: Task



## DNN for detecting diabetic retinopathy

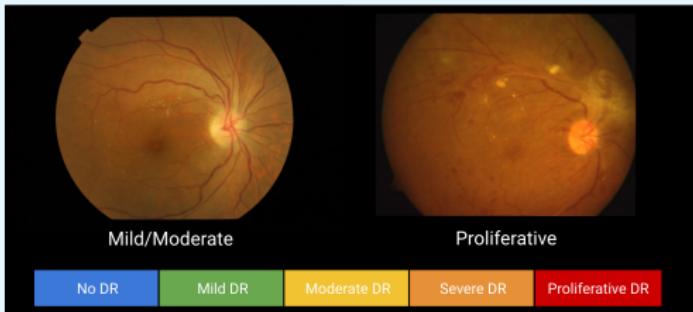
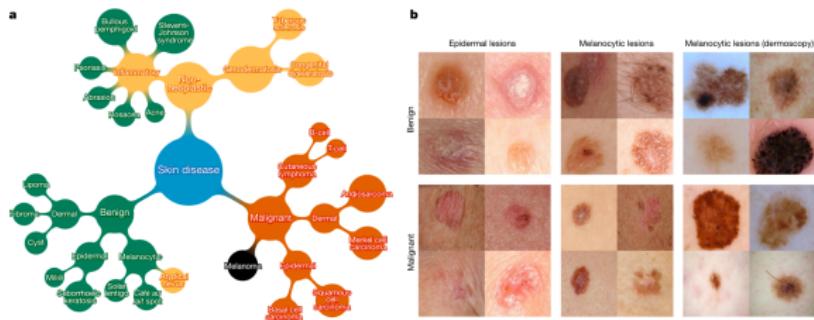


Image based detection of diabetic retinopathy (JAMA 2016)

- Train deep neural networks to find diabetic retinopathy severity from the intensities of the pixels in a fundus image.
- Received testing AUC of 0.991 on EyePACS-1 data, and testing AUC of 0.990 on Messidor-2 data.

1. Gulshan V, Peng L, Coram M, Stumpe MC, Wu D, Narayanaswamy A, Venugopalan S, Widner K, Madams T, Cuadros J, Kim R, Raman R, Nelson PC, Mega JL, Webster DR. Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs. *JAMA*. 2016;316(22):2402-2410

## Unstructured Imaging Data: skin lesion (Nature 2017)



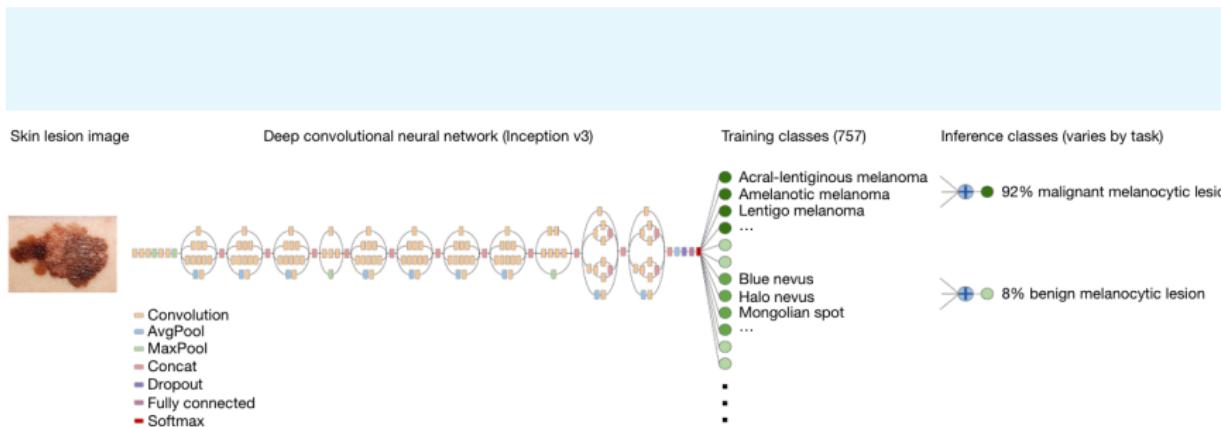
**Figure 2 | A schematic illustration of the taxonomy and example test set images.** a, A subset of the top of the tree-structured taxonomy of skin disease. The full taxonomy contains 2,032 diseases and is organized based on visual and clinical similarity of diseases. Red indicates malignant, green indicates benign, and orange indicates conditions that can be either. Black indicates melanoma. The first two levels of the taxonomy are used in validation. Testing is restricted to the tasks of b. b, Malignant and benign

example images from two disease classes. These test images highlight the difficulty of malignant versus benign discernment for the three medically critical classification tasks we consider: epidermal lesions, melanocytic lesions and melanocytic lesions visualized with a dermoscope. Example images reprinted with permission from the Edinburgh Dermofit Library (<https://licensing.eri.ed.ac.uk/i/software/dermofit-image-library.html>).

- Deep convolutional neural networks to perform binary classification for two use cases:
  - keratinocyte carcinomas versus benign seborrheic keratosis; and
  - malignant melanomas versus benign nevi.
- Achieved better-than-human expert accuracy (0.7210 vs. 0.6556)

1. A. Esteva, B. Kuprel, R.A. Novoa, J. Ko, S.M. Swetter, H.M. Blau , S. Thrun. Dermatologist-level classification of skin cancer with deep neural networks. *Nature* 542, 115–118 (2017)

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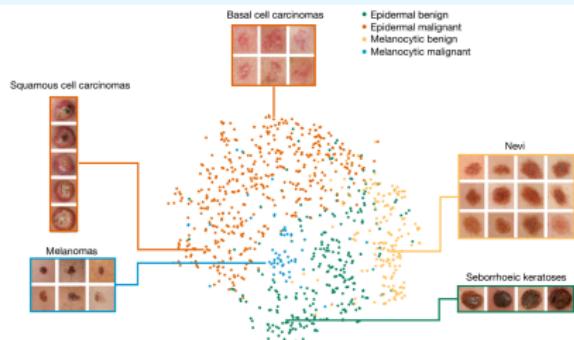


Figure 4 | t-SNE visualization of the last hidden layer representations in the CNN for four disease classes. Here we show the CNN's internal representation of four important disease classes by applying t-SNE, a method for visualizing high-dimensional data, to the last hidden layer representation in the CNN of the biopsy-proven photographic test sets

(932 images). Coloured point clouds represent the different disease categories, showing how the algorithm clusters the diseases. Insets show images corresponding to various points. Images reprinted with permission from the Edinburgh Dermofit Library (<https://licensing.eri.ed.ac.uk/i/software/dermofit-image-library.html>).

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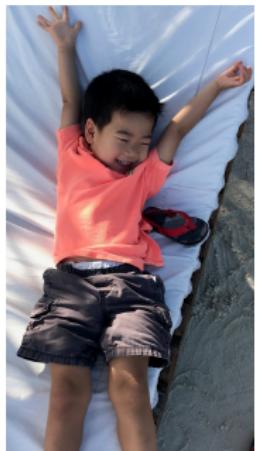
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- Continuous Time Series (EEG, ECG, ICU monitoring)
  - EEG Data
  - ICU Data
  - Clinical Notes

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## SLEEPNET: Automated Sleep Medicine via Deep Learning

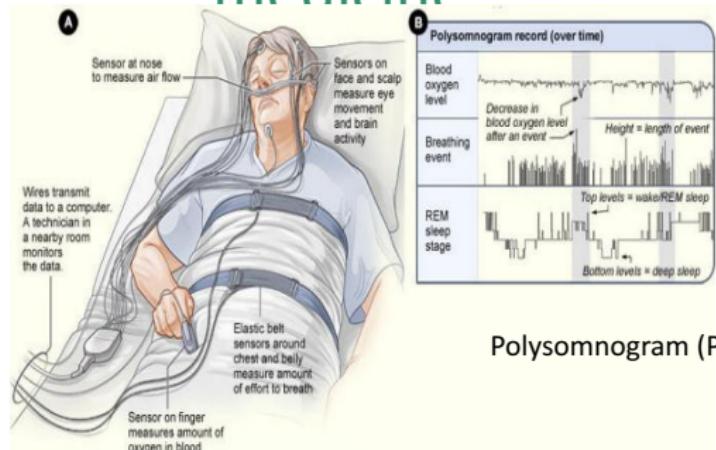
*Siddharth Biswal, Joshua Kulas, Haoqi Sun, Balaji Goparaju, M Brandon Westover, Matt T Bianchi,  
Jimeng Sun*



MASSACHUSETTS  
GENERAL HOSPITAL

<https://arxiv.org/abs/1707.08262>

# Motivation: Automated sleep medicine

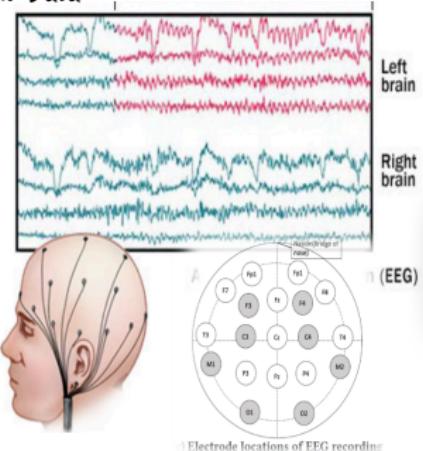


Polysomnogram (PSG) recording

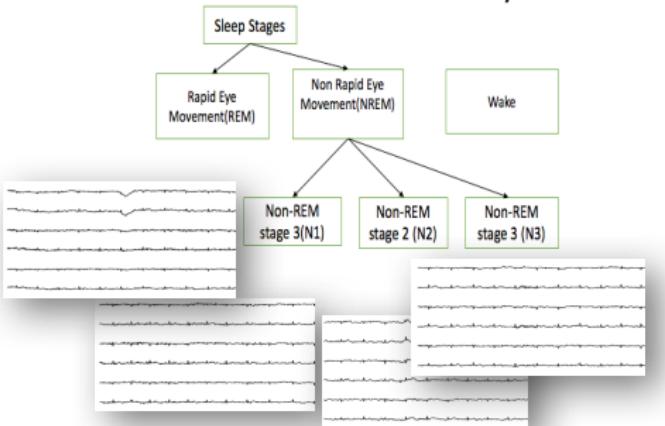
- ~50-70 million people in US currently suffer sleep disorders
- Central diagnostic tool is the overnight sleep study, Polysomnogram (PSG)
- Labor intensive effort to annotating PSG
  - Automation of these could alleviate these concerns

# Sleep staging

## Input Data

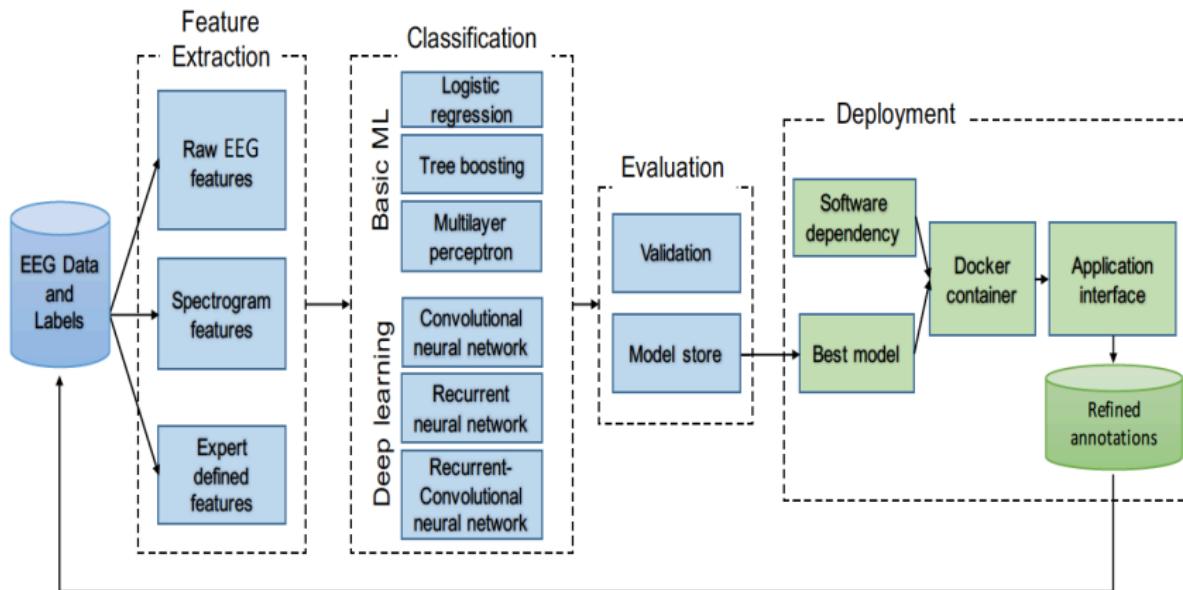


## Output



- EEG data in PSG consists of data from 6 different channels
- Every 30 second of EEG were annotated into one of 5 stages
  - Sleep stages are important for many sleep quality metrics
- Annotation is nontrivial even for experienced technologists
  - Inter rater agreement rate about 70%

## Analytic pipeline of SLEEPNET



(d) Analytic pipeline of SLEEPNET. The blue color components correspond to model training module. The green color components belongs to the model deployment module.

# Dataset Description

Dataset Property	Number
Number of Patients	10,000
Hours of EEG data	80,000
Raw data storage	3.2 TB
Number of labeled samples	>9 million

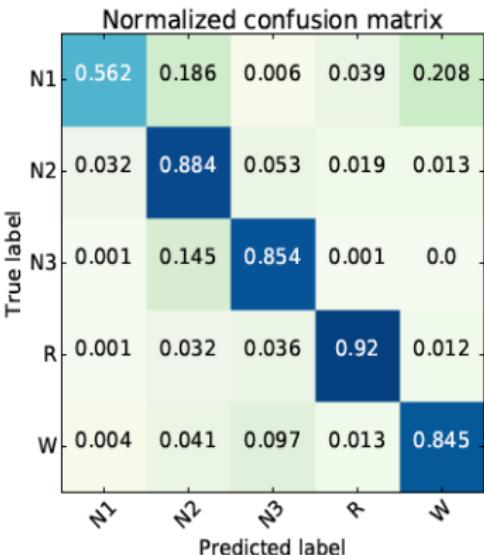
# Results

Model	Expert Defined Features		Spectrogram Features		Waveform Features	
	Accuracy	Kappa	Accuracy	Kappa	Accuracy	Kappa
LR	68.54	63.88	66.54	66.61	67.43	62.71
TB	75.67	69.47	71.61	65.37	72.36	66.37
MLP	72.23	68.41	70.23	66.71	69.56	64.21
CNN	79.45	72.63	77.83	71.45	77.31	71.47
RNN	<b>85.76</b>	<b>79.46</b>	79.21	73.83	79.46	72.46
RCNN	81.67	76.38	81.47	74.37	79.81	73.52

Table 4: Performance of different feature representations with model combinations

RNN + expert defined features perform the best

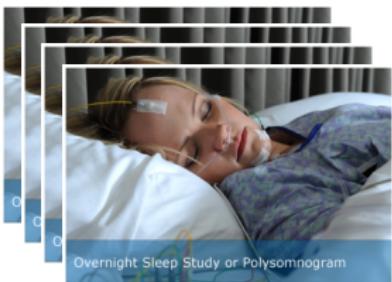
*Algorithm achieves expert-level performance (avg. accuracy > 85%)*



Confusion matrix for the best performing model (RNN+expert)



Automated Sleep Staging  
based on deep learning



Large dataset of 10,000  
polysomnogram studies



Deployed for  
research

<https://arxiv.org/abs/1707.08262>

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# INTERPRETABLE DEEP MODELS FOR ICU OUTCOME PREDICTION



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Che et al, Interpretable Deep Models for ICU Outcome Prediction. of the American Medical Informatics Association Annual Symposium (AMIA), 2016.

# Time Series in Critical Care Unit (ICU)

**Critical care is among the most important areas of medicine.**

- >5 million patients admitted to US ICUs annually.<sup>2</sup>
- Cost: \$81.7 billion in US in 2005: 13.4% hospital costs, ~1% GDP.<sup>1</sup>
- Mortality rates up to 30%, depending on condition, care, age.<sup>1</sup>
- Long-term impact: physical impairment, pain, depression.



Society of Critical Care Medicine website, Statistics page.

# Datasets and Tasks

## Children's Hospital Los Angeles (CHLA)

398 patients stay > 3 days

Static features (age, weight, etc.): 27 variables

Temporal features (Blood gas, ventilator signals, injury markers, etc.): 21 variables

## MIMIC III Dataset

19714 patients stay for 2 days

All temporal features (input fluids, output fluids, lab tests, prescription): 99 variables

## PhysioNet Challenge

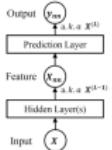
Part of MIMIC II dataset

**Task** Prediction task (mortality, ventilator free days, and disease code), computational phenotyping, anomaly detection, disease subtyping

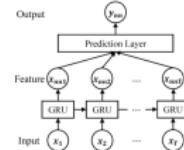
## Deep learning model: DNN + GRU



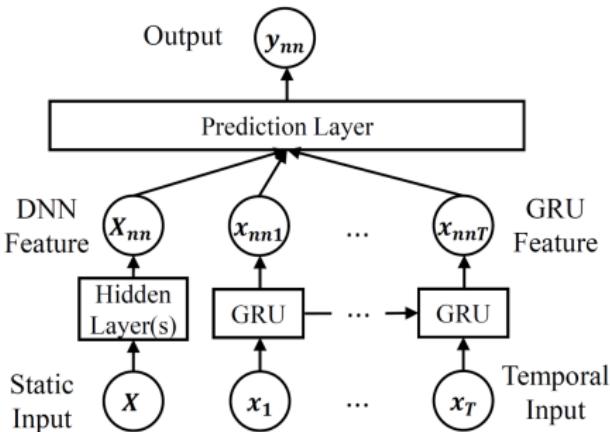
- *Static + (flattened) temporal features*
    - DNN



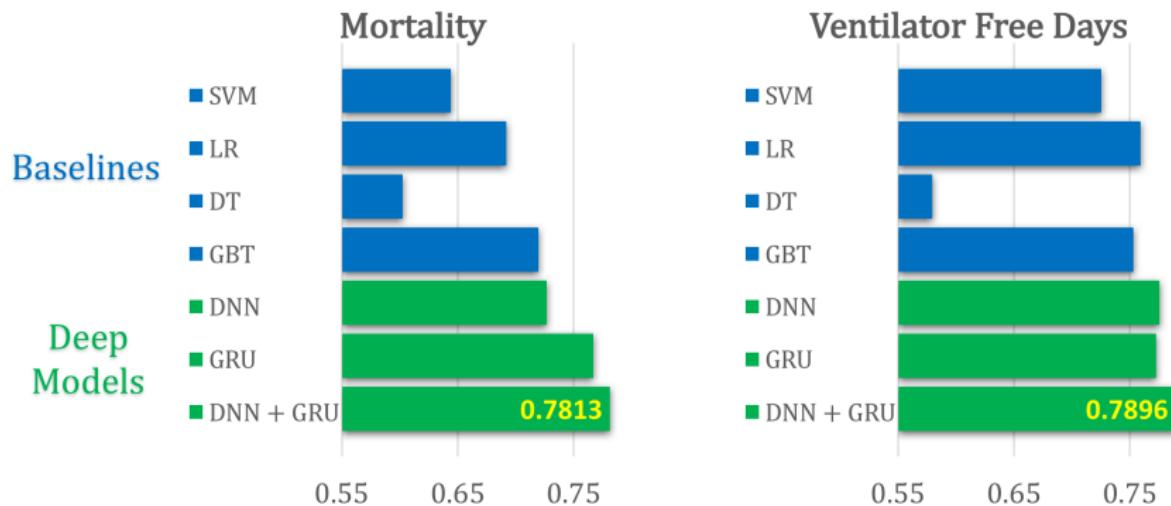
- *Temporal features only*
    - GRU



- Static + temporal features
    - **DNN + GRU** (combination)



# Experiment Results



SVM: support vector machine;

DT: decision tree;

Results are based on 5-fold cross-validation.

LR: logistic regression;

GBT: gradient boosting tree.

# Outline

## 1 Lecture 1: Data Sources and Health Care Problems

- EHR and Claims Data
- Medical Imaging Data
- Continuous Time Series (EEG, ECG, ICU monitoring)
- Clinical Notes

## 2 Lecture 2: Challenges and Solutions of DL for Health Care

## 3 Future Directions

# Deep Neural Networks for Analyzing Clinical Notes

Examples of some recent development:

- LSTM for i2b2/VA relation classification challenge [Luo, 2017]
- Convolutional neural networks for medical text classification [Hughes et al., 2017]
- Bidirectional RNN for medical event detection [Jagannatha and Yu, 2016]
- RNN with attention for adverse drug reaction [Pandey et al., 2017]
- Condensed memory networks for clinical diagnostic Inferencing [Prakash et al., 2016]
- Neural attention models for classification of radiology reports [Shin et al., 2017]

# Outline

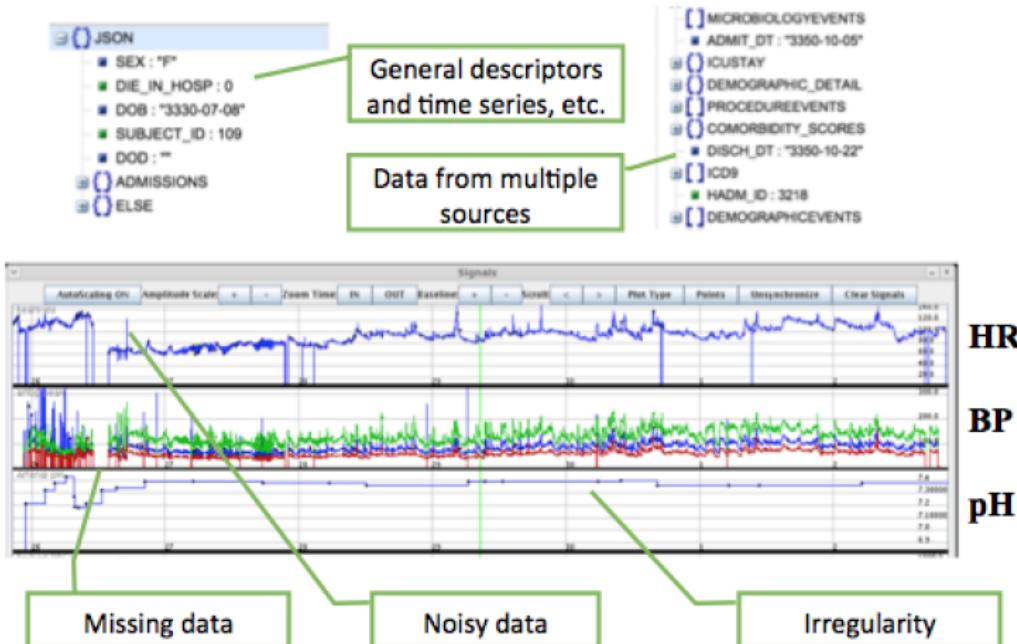
1 Lecture 1: Data Sources and Health Care Problems

2 Lecture 2: Challenges and Solutions of DL for Health Care

- Deep Dive of Health Care Data
  - Challenge 1 - Big Small Data
  - Challenge 2 - Missing Data
  - Challenge 3 - Incorporation of Domain Knowledge
  - Challenge 4 - Interpretable Machine Learning

3 Future Directions

# Example of Health Care Data



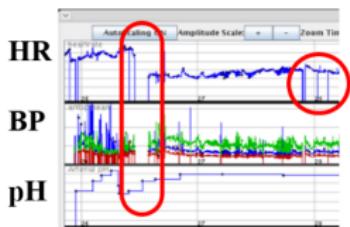
# Machine learning challenges for health applications

## *Small sample size*

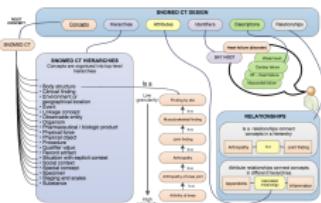


- Rare diseases
- Small clinics

## *Missing value*

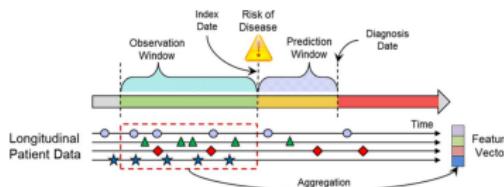


## *Medical domain knowledge*



- Medical ontology

## *Interpretation*



- Explain the prediction

# Outline

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3 Future Directions

# VARIATIONAL RECURRENT ADVERSARIAL DEEP DOMAIN ADAPTATION



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Purushotham et al, Variational Recurrent Adversarial Deep Domain Adaptation.  
International Conference on Learning Representations (ICLR 2017)

# Motivation - Big Small Data

**Limited amount of data available to train age-specific or disease-specific models**

- A toy example: predicting mortality across adults and children in ICU

Target	Model Trained on Adults	Model trained on Children
Children	0.56	0.70

- Training models for each age group independently is not ideal due to limited amount of data

Question: How do we adapt models from Adults (source domain) to Children (target domain)?

# Problem Formulation

Case study: mortality prediction for patients across different age groups



- Input: N multivariate time series example:  $x^i = (x_t^i)_{t=1}^{T^i}$
- Source domain (e.g. adult):  $\{x^i, y_i\}_{i=1}^n$ , target domain (e.g., child):  $\{x^j\}_{j=n+1}^N$
- Output: mapping function  $f^{target}(x^i) \approx y_i$

**Problem definition: unsupervised domain adaptation for multivariate time series**

# Related Work

## Domain adaption for non-time series data

- Domain discrepancy reduction [Ben-David et al., 2007]
- Instance re-weighting [Jiang and Zhai, 2007]
- Subspace alignment [Fernando et al., 2013]
- Deep learning approaches [Ganin and Lempitsky, 2014; Tzeng et al., 2015], domain adversarial neural networks (DANN) [Ganin et al., 2016]

## Domain adaption for sequence or time series data

- Dynamic Bayes networks [Huang and Yates, 2009]
- Recurrent neural networks [Socher et al., 2011]

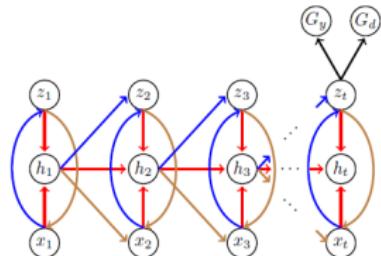
## Our solution:

Deep learning model with adversarial training and variational methods for domain invariant representation while transferring temporal dependencies

# Variational Adversarial Deep Domain Adaptation (VADDA) [ICLR 2017]

VRNN objective function [Chung et al, 2016]

$$\mathcal{L}_r(x_t^i; \theta_e, \theta_g) = E_{q_{\theta_e}(z_{\leq T^i}^i | x_{\leq T^i}^i)} \sum_{t=1}^{T^i} (-D(q_{\theta_e}(z_t^i | x_{\leq t}^i, z_{<t}^i) || p(z_t^i | x_{\leq t}^i, z_{<t}^i)) + \log p_{\theta_g}(x_t^i | z_{\leq t}^i, x_{<t}^i))$$



Inference:  $z_t^i \sim q(z_t^i | x_{\leq t}^i, z_{<t}^i)$

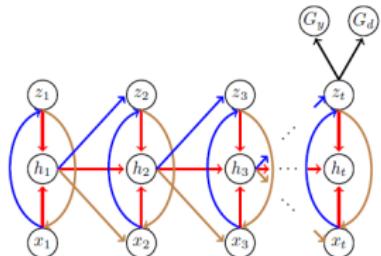
Generation:  $x_t^i \sim p(x_t^i | z_{\leq t}^i, x_{<t}^i)$

Recurrence:  $h_t = RNN(x_t, z_t, h_{t-1})$

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Source classification loss with regularizer

$$\min_{\theta_e, \theta_g, \theta_y} \frac{1}{n} \sum_{i=1}^n \frac{1}{T^i} \mathcal{L}_r(\mathbf{x}^i; \theta_e, \theta_g) + \frac{1}{n} \sum_{i=1}^n \mathcal{L}_y(\mathbf{x}^i; \theta_y, \theta_e) + \lambda \mathcal{R}(\theta_e)$$

Inference:  $z_t^i \sim q(z_t^i | x_{\leq t}^i, z_{<t}^i)$

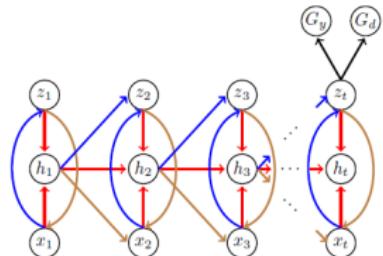
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Recurrence:  $h_t = RNN(x_t, z_t, h_{t-1})$

Source classification loss with regularizer

$$\min_{\theta_e, \theta_g, \theta_y} \frac{1}{n} \sum_{i=1}^n \frac{1}{T^i} \mathcal{L}_r(\mathbf{x}^i; \theta_e, \theta_g) + \frac{1}{n} \sum_{i=1}^n \mathcal{L}_y(\mathbf{x}^i; \theta_y, \theta_e) + \lambda \mathcal{R}(\theta_e)$$

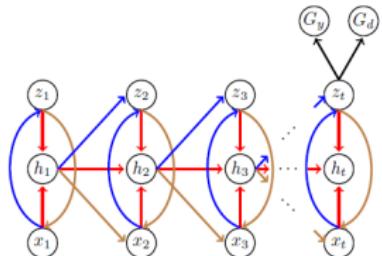
Domain regularizer [Ganin et al, 2016]

$$\mathcal{R}(\theta_e) = \max_{\theta_d} \left[ -\frac{1}{n} \sum_{i=1}^n \mathcal{L}_d(\mathbf{x}^i; \theta_d, \theta_e) - \frac{1}{n'} \sum_{i=n+1}^N \mathcal{L}_d(\mathbf{x}^i; \theta_d, \theta_e) \right]$$

# Variational Adversarial Deep Domain Adaptation (VADDA) [ICLR 2017]

VRNN objective function [Chung et al, 2016]

$$\mathcal{L}_r(x_t^i; \theta_e, \theta_g) = E_{q_{\theta_e}(z_{\leq T^i}^i | x_{\leq T^i}^i)} \sum_{t=1}^{T^i} (-D(q_{\theta_e}(z_t^i | x_{\leq t}^i, z_{<t}^i) || p(z_t^i | x_{<t}^i, z_{<t}^i)) + \log p_{\theta_g}(x_t^i | z_{\leq t}^i, x_{<t}^i))$$



Inference:  $z_t^i \sim q(z_t^i | x_{\leq t}^i, z_{<t}^i)$   
 Generation:  $x_t^i \sim p(x_t^i | z_{\leq t}^i, x_{<t}^i)$   
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Source classification loss with regularizer

$$\min_{\theta_e, \theta_g, \theta_y} \frac{1}{n} \sum_{i=1}^n \frac{1}{T^i} \mathcal{L}_r(\mathbf{x}^i; \theta_e, \theta_g) + \frac{1}{n} \sum_{i=1}^n \mathcal{L}_y(\mathbf{x}^i; \theta_y, \theta_e) + \lambda \mathcal{R}(\theta_e)$$

Domain regularizer [Ganin et al, 2016]

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## Overall Objective function

$$E(\theta_e, \theta_g, \theta_y, \theta_d) = \frac{1}{N} \sum_{i=1}^N \frac{1}{T^i} \mathcal{L}_r(\mathbf{x}^i; \theta_e, \theta_g) + \frac{1}{n} \sum_{i=1}^n \mathcal{L}_y(\mathbf{x}^i; \theta_y) - \lambda \left( \frac{1}{n} \sum_{i=1}^n \mathcal{L}_d(\mathbf{x}^i; \theta_d) + \frac{1}{n'} \sum_{i=n+1}^N \mathcal{L}_d(\mathbf{x}^i; \theta_d) \right)$$

# Experiments

## Case Study: Acute Hypoxemic Respiratory Failure

- Datasets
  - Pediatric ICU: Child-AHRF
    - 398 patients at Children's Hospital Los Angeles (CHLA) Group 1: children (0-19 yrs)
  - MIMIC-III : Adult-AHRF
    - 5527 patients Group 2: working-age adult (20 to 45 yrs); Group 3: old working-age adult (46 to 65 yrs, Group 4: elderly (66 to 85 yrs); Group 5: old elderly (> 85 yrs)
- Input features - 21 time series variables (e.g., blood gas, ventilator signals, injury markers, etc.) for 4 days
- Prediction tasks - Mortality label

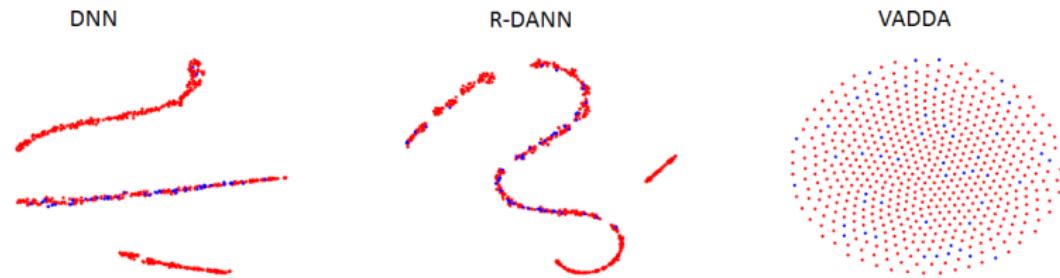
# Classification Accuracy

Baselines:

- Non-domain adaptation: Logistic regression, Adaboost, Deep Neural Networks
- Deep Domain adaptation: DANN, R-DANN, VFAE [Louizos et al, 2015])

Source-Target	LR	Adaboost	DNN	DANN	VFAE	R-DANN	VRDDA
3- 2	0.555	<b>0.562</b>	0.569	0.572	0.615	0.603	<b>0.654</b>
4- 2	0.624	<b>0.645</b>	0.569	0.589	0.635	0.584	<b>0.656</b>
5- 2	0.527	<b>0.554</b>	0.551	0.540	0.588	0.611	<b>0.616</b>
2- 3	<b>0.627</b>	0.621	0.550	0.563	0.585	0.708	<b>0.724</b>
4- 3	<b>0.681</b>	0.636	0.542	0.527	0.722	<b>0.821</b>	0.770
5- 3	0.655	<b>0.706</b>	0.503	0.518	0.608	0.769	<b>0.782</b>
2- 4	0.585	<b>0.591</b>	0.530	0.560	0.582	0.716	<b>0.777</b>
3- 4	<b>0.652</b>	0.629	0.531	0.527	0.697	<b>0.769</b>	0.764
5- 4	0.689	<b>0.699</b>	0.538	0.532	0.614	0.728	<b>0.738</b>
2- 5	<b>0.565</b>	0.543	0.549	0.526	0.555	0.659	<b>0.719</b>
3- 5	0.576	<b>0.587</b>	0.510	0.526	0.533	0.630	<b>0.721</b>
4- 5	<b>0.682</b>	0.587	0.575	0.548	0.712	0.747	<b>0.775</b>
5- 1	0.502	<b>0.573</b>	0.557	0.563	0.618	0.563	<b>0.639</b>
4- 1	<b>0.565</b>	0.533	0.572	0.542	<b>0.668</b>	0.577	0.636
3- 1	0.500	0.500	0.542	0.535	0.570	0.591	<b>0.631</b>
2- 1	<b>0.520</b>	0.500	0.534	0.559	0.578	0.630	<b>0.637</b>

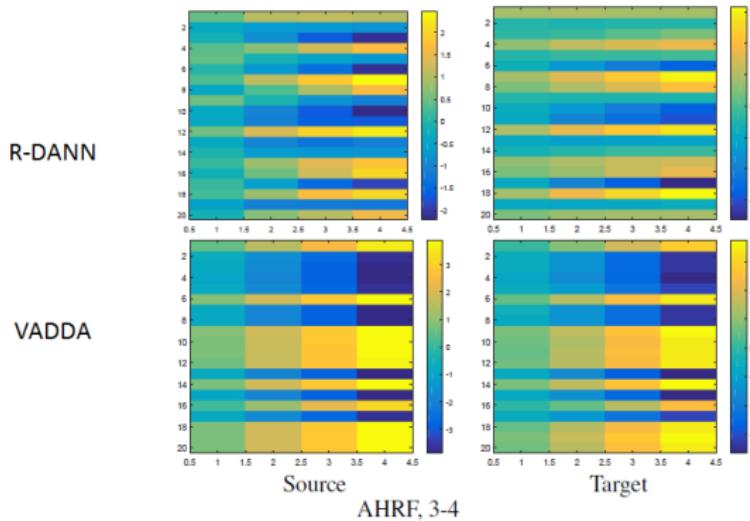
# Domain-invariant Representations



t-SNE projections for the latent representations for domain adaptation from Adult-AHRF to Child-AHRF

VADDA has better distribution mixing than DANN

# Temporal Dependencies across Domains



Memory cell state neuron activations of the R-DANN and VADDA

Activation patterns of VADDA are more consistent across time-steps than for R-DANN

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3 Future Directions

# RECURRENT NEURAL NETWORKS FOR MULTIVARIATE TIME SERIES WITH MISSING VALUES



Zhengping Che



Sanjay Purushotham



Kyunghyun Cho



David Sontag



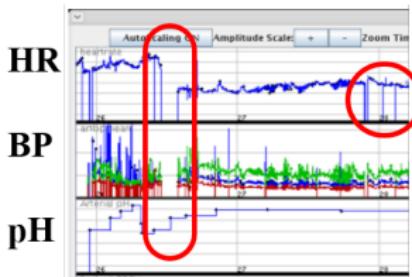
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Che et al, Recurrent Neural Networks for Multivariate Time Series with Missing Values. arXiv:1606.01865

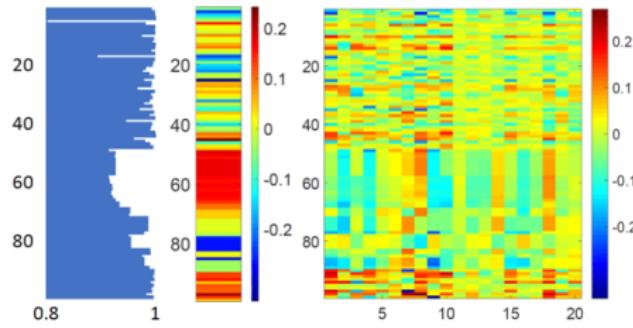
# Missing Values are Useful

Missingness comes from various reasons.



AZ	BA	BB	BC	BD	BE	BF	BG	BH
CRS1	CRS2	CRS3	FI021	FI022	FI023	HCO31	HCO32	HCO33
0.27649;	0.23680;	0.23079;	0.45295;	0.45729;	0.44999;	23.9965;	23.4375;	24.1134;
0.61792;	1.14405;	0.73171;	0.39041;	0.35673;	0.34999;	19.0562;	25.19;	
0.60328;	0.29362;	0.29644;	0.35100;	0.37197;	0.40717;	19.2951;	22.6520;	28.
0.72348;	0.67720;	0.59685;	0.44999;	0.44999;	0.41788;	20.1;	29.6145;	33.6753;
0.40175;			0.41777;			18.6541;	21.5583;	22.
0.27366;	0.15783;	0.24334;	0.97458;	0.69583;	0.60762;	28.1048;	38.5090;	38.4861;
0.9056;			0.35808;			23.3631;	26.9194;	27.
						18.87;		
0.58429;	0.44144;	0.41550;	0.44999;	0.55625;	0.37904;			
0.39599;	0.31453;		0.49458;	0.48620;		21.46875;	20.3508;	
0.22629;	0.20941;	0.28634;	0.40000;	0.40000;	0.40000;	29.1194;	29.0238;	
0.34744;	0.30646;	0.30806;	0.44554;	0.42144;	0.40000;	26.1506;	29.5548;	33.5720;
0.25392;	0.30970;	0.38193;	0.46083;	0.48041;	0.49755;	21.7972;	34.7375;	38.8510;
0.79393;	0.89380;	0.59436;	0.52899;	0.33697;	0.30000;	22.9472;	20.1298;	20.1527;

Missingness provides rich information about patients health condition.



# Time-Series Inputs with Missing Values

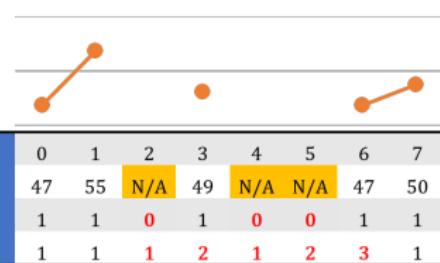
Given time series data with missing values  $\mathbf{X}$ , we have two representations for missingness.

- *Masking M:*

Whether a variable is missing or not.

- *Time Interval  $\Delta$ :*

How long a variable has been missing.



There exist three solutions with no modification on the predictive models.

- Mean imputation of missing values (**Mean**)
- Forward imputation of missing values (**Forward**)
- Simple concatenation of indicators (**Simple**)

# Deep Learning Models for Time-Series with Missing Values

- **Mean:** Replacing each missing observation by the mean of the variable  $\tilde{x}$  across the training examples [Shao et al., 2009].

$$x_t^d \leftarrow m_t^d x_t^d + (1 - m_t^d) \tilde{x}^d$$

Input	47	55	$\tilde{x}$	49	$\tilde{x}$	$\tilde{x}$	47	50
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- **Forward:** Assuming each missing value is the same as its last measurement  $x_{t'}$  and using forward imputation [Unnebrink and Windeler, 2001].

$$x_t^d \leftarrow m_t^d x_t^d + (1 - m_t^d) x_{t'}^d$$

Input	47	55	55	49	49	49	47	50
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- **Simple:** Concatenating the measurement  $x$ , masking  $m$ , and/or time interval  $\delta$ .

- Similar ideas are used in RNN models: [Choi et al., 2015] ( $x$  and time  $t$ ), Pham et al. [2016] ( $x$  and  $\delta$ ), and [Lipton et al., 2016] ( $x$  and  $m$ ).

$$x_t^{(n)} \leftarrow \left[ x_t^{(n)}; m_t^{(n)}; \delta_t^{(n)} \right]$$

Input	47	55	55	49	49	49	47	50
Masking	1	1	0	1	0	0	1	1
Duration	1	1	1	2	1	2	3	1

# GRU-R [Che et al., 2016a]

*Decay Term  $\gamma$ :* A flexible transformation on  $\Delta$  jointly learned with deep model.

$$\gamma_t = \exp\{-ReLU(\mathbf{W}_\gamma \delta_t + \mathbf{b}_\gamma)\}$$

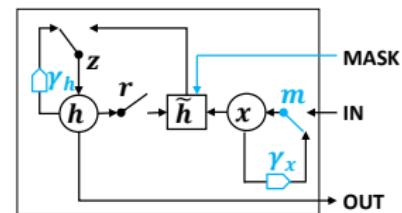
## GRU-D model

- Decay on the last observations:

$$x_t^d \leftarrow m_t^d x_t^d + (1 - m_t^d) \gamma_{x_t}^d x_{t'}^d + (1 - m_t^d)(1 - \gamma_{x_t}^d) \tilde{x}^d$$

- Decay on the hidden states:

$$\mathbf{h}_{t-1} \leftarrow \gamma_{\mathbf{h}_t} \odot \mathbf{h}_{t-1}$$



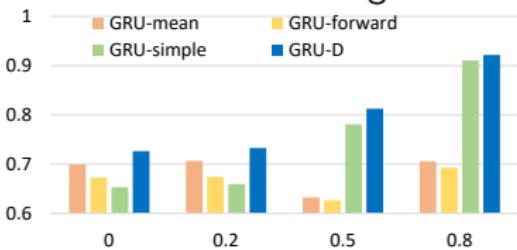
The update functions for GRU are:

$$\mathbf{z}_t = \sigma(\mathbf{W}_z \mathbf{x}_t + \mathbf{U}_z \mathbf{h}_{t-1} + \mathbf{V}_z \mathbf{m}_t + \mathbf{b}_z) \mathbf{r}_t = \sigma(\mathbf{W}_r \mathbf{x}_t + \mathbf{U}_r \mathbf{h}_{t-1} + \mathbf{V}_r \mathbf{m}_t + \mathbf{b}_r)$$

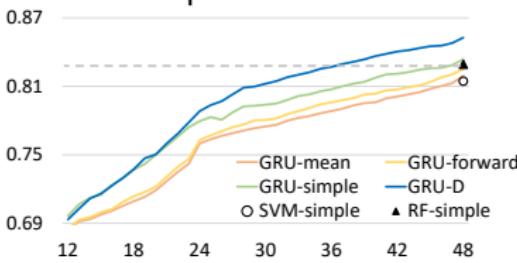
$$\tilde{\mathbf{h}}_t = \tanh(\mathbf{W} \mathbf{x}_t + \mathbf{U} (\mathbf{r}_t \odot \mathbf{h}_{t-1}) + \mathbf{V} \mathbf{m}_t + \mathbf{b}) \mathbf{h}_t = (\mathbf{1} - \mathbf{z}_t) \odot \mathbf{h}_{t-1} + \mathbf{z}_t \odot \tilde{\mathbf{h}}_t$$

# Empirical Evaluation

## Evaluations on synthetic dataset with different missing rates



## Evaluations for mortality early prediction



## AUC score on mortality prediction

Models	MIMIC-III	PhysioNet
Non-RNN	LR-forward	0.7589
	SVM-forward	0.7908
	RF-forward	0.8293
	LR-simple	0.7715
	SVM-simple	0.8146
	RF-simple	0.8294
RNN	LSTM-mean	0.8142
	GRU-mean	0.8192
	GRU-forward	0.8252
	GRU-simple	0.8380
	Ours	<b>0.8527</b>
Ours	GRU-D	<b>0.8424</b>

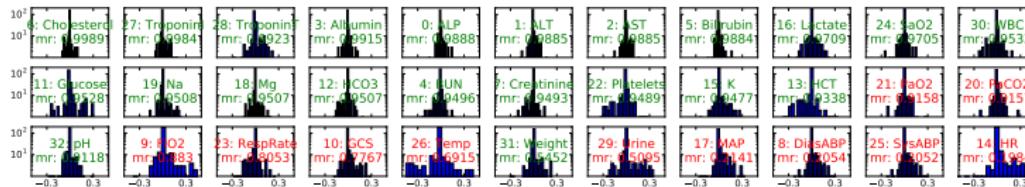
# Empirical Evaluation

Input decay plots of all 33 variables for mortality prediction on PhysioNet dataset



- Get a few important variables, e.g., weight, arterial pH, temperature, and respiration rate, etc.

Histograms of hidden state decay for mortality prediction on PhysioNet dataset



- Parameters related to variables with smaller missing rate are more spread out.

# Outline

1 Lecture 1: Data Sources and Health Care Problems

2 Lecture 2: Challenges and Solutions of DL for Health Care

- Deep Dive of Health Care Data
- Challenge 1 - Big Small Data
- Challenge 2 - Missing Data
- **Challenge 3 - Incorporation of Domain Knowledge**
- Challenge 4 - Interpretable Machine Learning

3 Future Directions

# DEEP COMPUTATIONAL PHENOTYPING



Zhengping Che



David Kale



Wenzhe Li



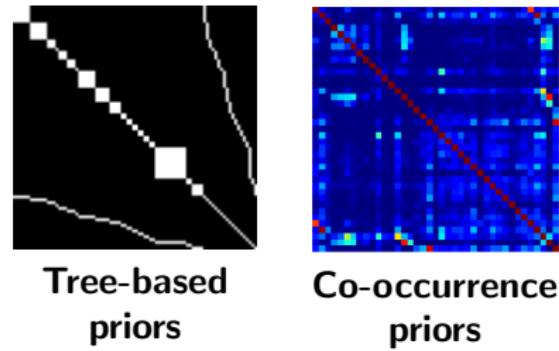
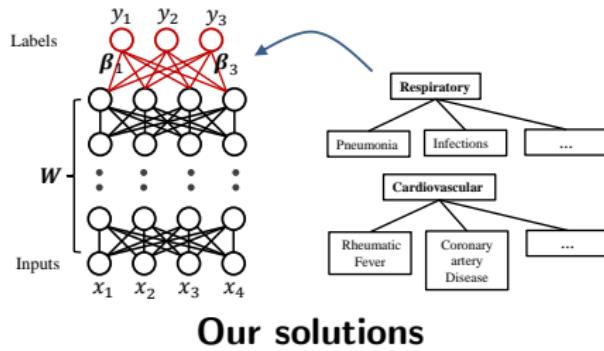
Taha Bahadori



Che et al, Deep Computational Phenotyping. Proceedings of the 21st ACM SIGKDD Conference on Knowledge Discovery and Data Mining (SIGKDD), 2015.

# Label Sparsity and Structured Domain Knowledge

- Many diagnoses occur in < 1% of patients.  
**How do we handle sparsity in our labels?**
- Ontologies (e.g., ICD-9 diagnostic codes) describe relationships between diseases.  
**How can we incorporate (structured) domain knowledge?**
- Solution:** Multi-task net + Graph Laplacian regularization.



# Multi-task Neural Nets + Graph Laplacian Regularization

[Che et al., 2015]

Assume:

- $K$  outputs (labels) with parameters  $\{\beta_k\}_{k=1}^K$ ,  $\beta_k \in \mathbb{R}^{D^{(L)}}$
- Label similarity matrix  $A \in \mathbb{R}^{K \times K}$  where  $A_{ij} \in [0, 1]$ .

Define Graph Laplacian matrix  $L = C - A$  with  $C$  a diagonal matrix  $C_{kk} = \sum_{k'=1}^K A_{kk'}$ , then

$$\text{tr}(\beta^\top L \beta) = \sum_{1 \leq k, k' \leq K} A_{k,k'} \|\beta_k - \beta_{k'}\|_2^2$$

where  $\text{tr}(\cdot)$  represents the *trace* operator.

Regularized loss function for supervised training of multi-task neural network:

$$\mathcal{L} = - \sum_{i=1}^N \sum_{k=1}^K \left[ y_{ik} \log \sigma(\beta_k^\top \mathbf{h}_i) + (1 - y_{ik}) \log (1 - \sigma(\beta_k^\top \mathbf{h}_i)) \right] + \frac{\rho}{2} \text{tr}(\beta^\top L \beta)$$

# Experiment Results

## Impact of priors on phenotype classification

PICU data (AUROC across 67 labels and 19 categories from ICD-9 codes)

	Tasks	No Prior	Co-Occurrence	ICD-9 Tree
Subsequence	All	$0.7079 \pm 0.0089$	<b><math>0.7169 \pm 0.0087</math></b>	$0.7143 \pm 0.0066$
	Categories	$0.6758 \pm 0.0078$	<b><math>0.6804 \pm 0.0109</math></b>	$0.6710 \pm 0.0070$
	Labels	$0.7148 \pm 0.0114$	<b><math>0.7241 \pm 0.0093</math></b>	$0.7237 \pm 0.0081$
Episode	All	$0.7245 \pm 0.0077$	<b><math>0.7348 \pm 0.0064</math></b>	$0.7316 \pm 0.0062$
	Categories	$0.6952 \pm 0.0106$	<b><math>0.7010 \pm 0.0136</math></b>	$0.6902 \pm 0.0118$
	Labels	$0.7308 \pm 0.0099$	<b><math>0.7414 \pm 0.0064</math></b>	$0.7407 \pm 0.0070$

# MED2VEC: MULTI-LAYER REPRESENTATION LEARNING FOR MEDICAL CONCEPTS

E. Choi, M. T. Bahadori, E. Searles, C. Coffey, M. Thompson, J. Bost, J. Tejedor-Sojo, J. Sun, (2016)

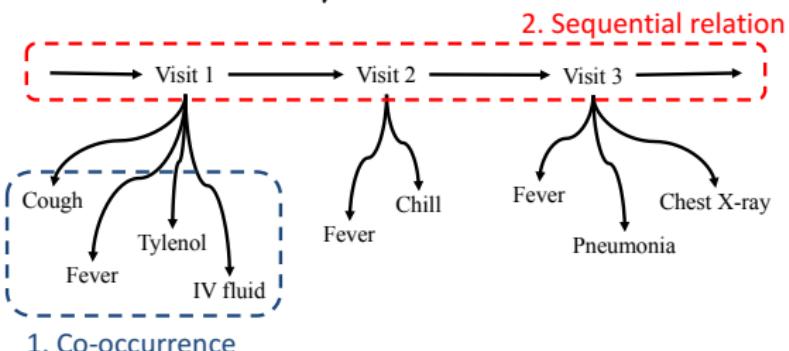
Multi-layer Representation Learning for Medical Concepts



KDD'16

# Med2Vec: two-layered representation learning

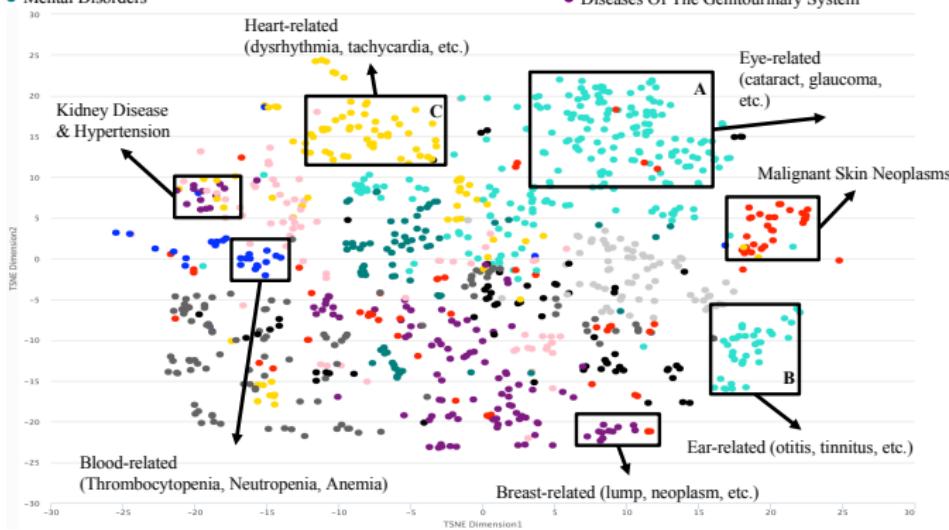
- Abstraction in patient records



- Objective function: the sum of
  1. Negative intra-visit Skip-gram
    - Because Skip-gram objective function is to be maximized
  2. Inter-visit multi-label classification loss

## Med2Vec encoding is well aligned with medical knowledge

- Infectious And Parasitic Diseases
- Neoplasms
- Endocrine, Nutritional And Metabolic Diseases, And Immunity Disorders
- Diseases Of The Blood And Blood-Forming Organs
- Mental Disorders
- Diseases Of The Nervous System And Sense Organs
- Diseases Of The Circulatory System
- Diseases Of The Respiratory System
- Diseases Of The Digestive System
- Diseases Of The Genitourinary System



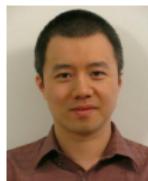
# GRAM: GRAPH-BASED ATTENTION MODEL FOR HEALTHCARE REPRESENTATION LEARNING



Edward Choi



Taha Bahadori



Le Song



Buzz Stewart

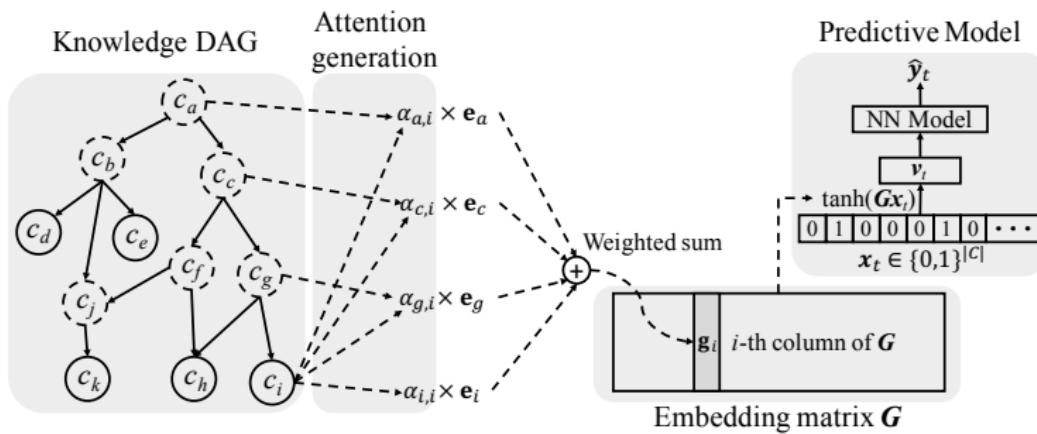


KDD'17

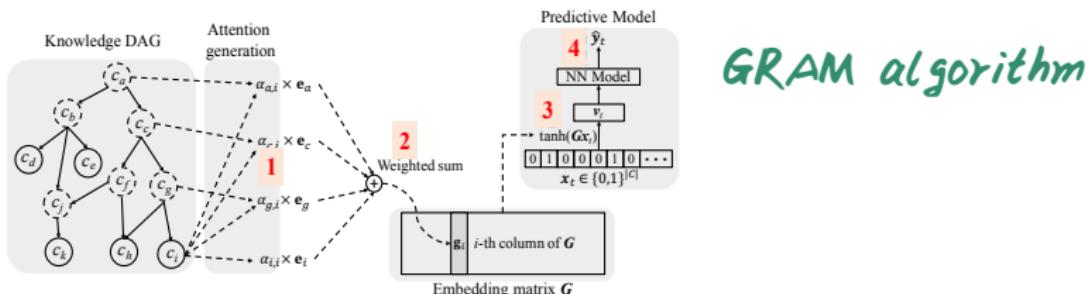
65

## Learned representations of medical codes leveraging medical ontologies

- Method: Generate a medical code representation vector by combining the representation vectors of its ancestors using the attention mechanism



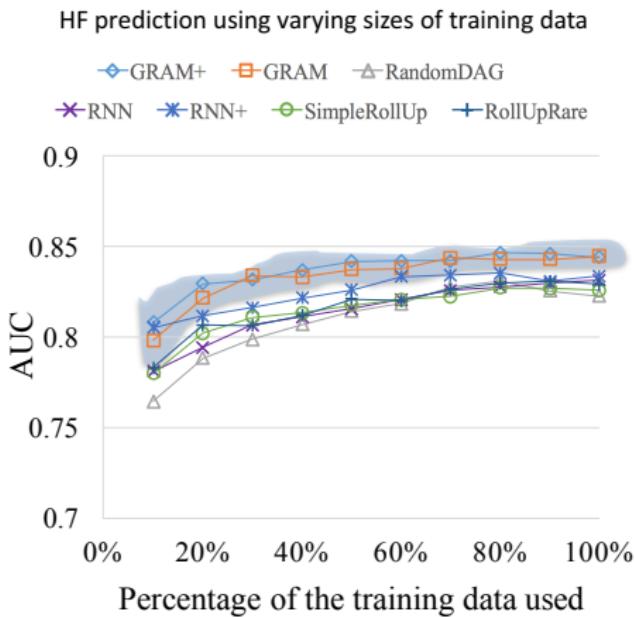
Model structure of GRAM



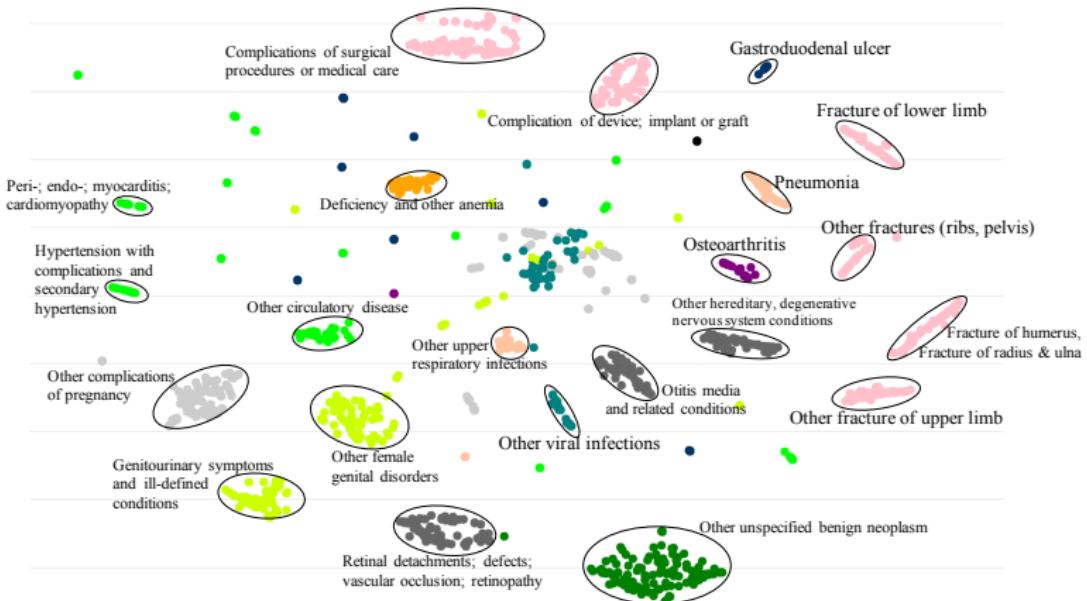
1	$\alpha_{ij} = \frac{\exp(f(\mathbf{e}_i, \mathbf{e}_j))}{\sum_{k \in \mathcal{A}(i)} \exp(f(\mathbf{e}_i, \mathbf{e}_k))}$ where $f(\mathbf{e}_i, \mathbf{e}_j) = \mathbf{u}_a^\top \tanh(\mathbf{W}_a \begin{bmatrix} \mathbf{e}_i \\ \mathbf{e}_j \end{bmatrix} + \mathbf{b}_a)$
2	Attention weights are generated for all pairs of basic embeddings $\mathbf{e}_i$ and its ancestors $\mathbf{e}_j$ .
3	$\mathbf{g}_i = \sum_{j \in \mathcal{A}(i)} \alpha_{ij} \mathbf{e}_j$ ,
4	Final representation $\mathbf{g}_i$ is the weighted sum of attention weights and basic embeddings.
3	$\mathbf{v}_1, \mathbf{v}_2, \dots, \mathbf{v}_t = \tanh(\mathbf{G}[\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_t])$
4	Sequence of visit representations are obtained using the Embedding matrix $\mathbf{G}$ .
4	$\mathbf{h}_1, \mathbf{h}_2, \dots, \mathbf{h}_t = \text{RNN}(\mathbf{v}_1, \mathbf{v}_2, \dots, \mathbf{v}_t, \theta_r),$ $\hat{\mathbf{y}}_t = \hat{\mathbf{x}}_{t+1} = \text{Softmax}(\mathbf{W}\mathbf{h}_t + \mathbf{b}),$
4	Performing sequential diagnoses prediction, outcomes are generated by RNN and Softmax.

# GRAM provide accurate prediction

*GRAM shows better predictive performance under data constraints*



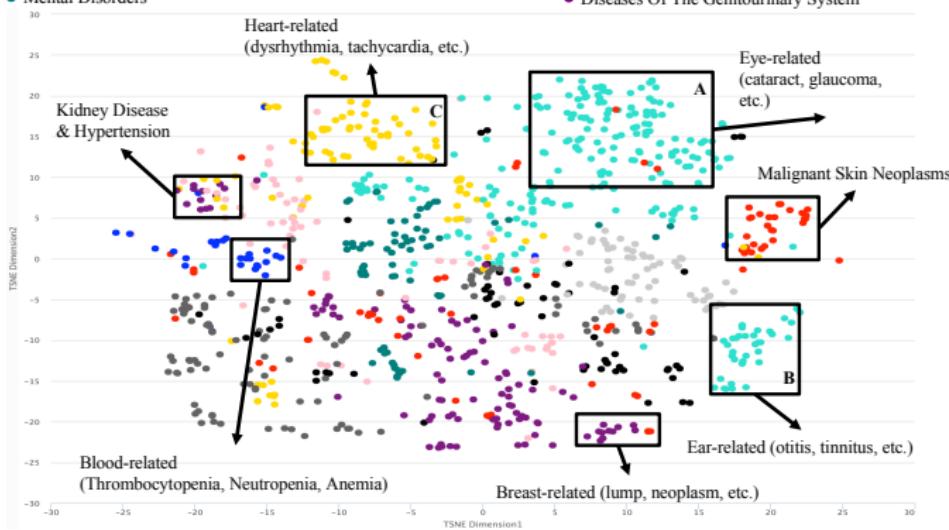
# GRAM learns representations well aligned with knowledge ontology



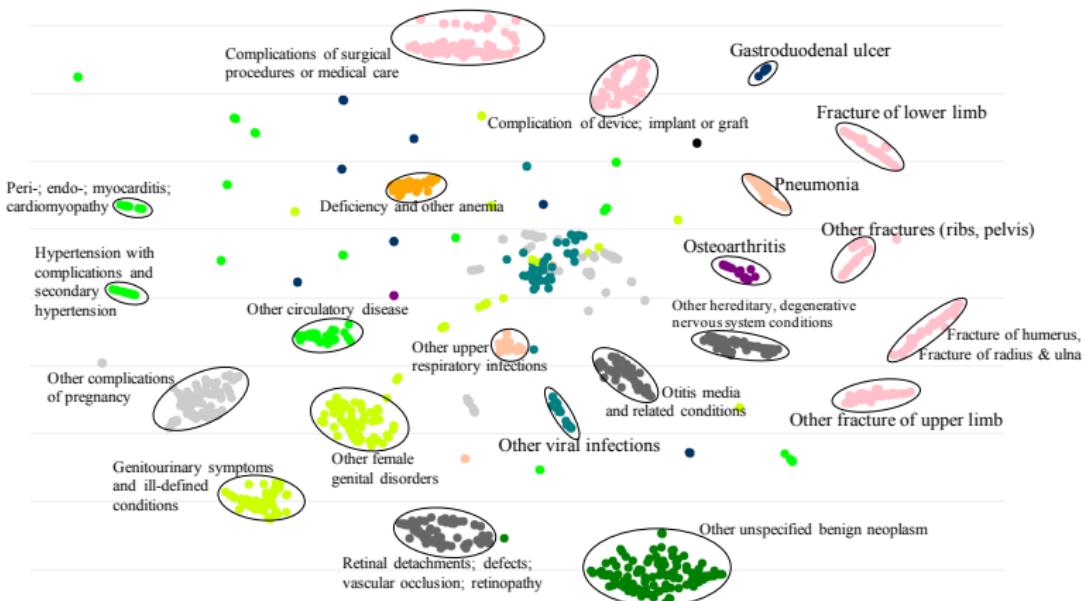
Scatterplot of GRAM representations

# Med2Vec encoding is well aligned with medical knowledge

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- Diseases Of The Genitourinary System



# GRAM learns representations well aligned with knowledge ontology



Scatterplot of GRAM representations

# GRAM: Graph-based Attention Model for Healthcare Representation Learning



- Robust representation against *data insufficiency*
- *Interpretable*: Well aligned with medical knowledge

# Outline

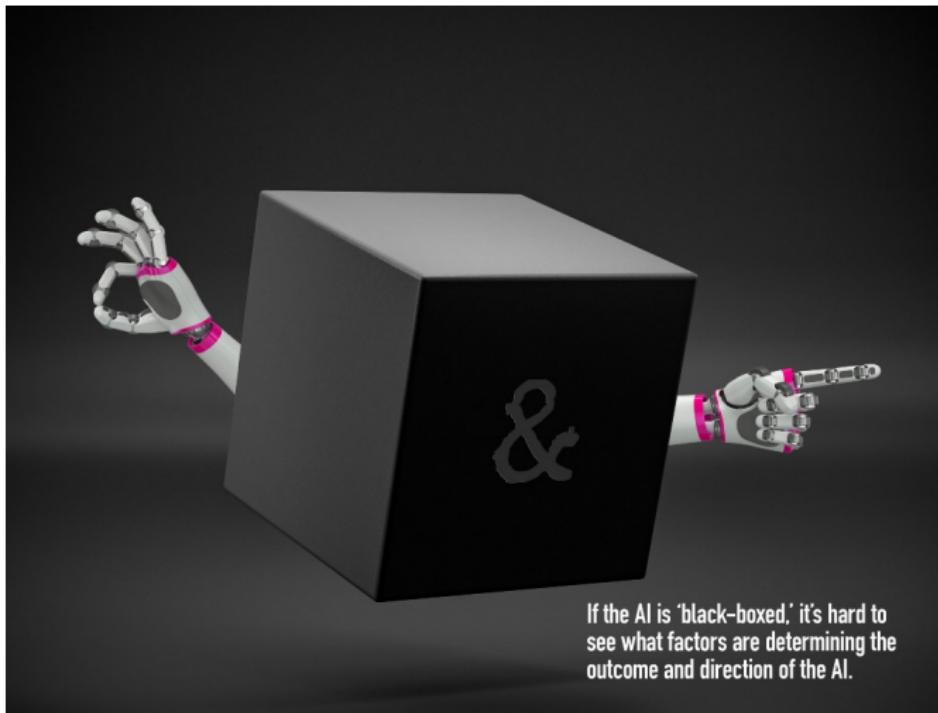
1 Lecture 1: Data Sources and Health Care Problems

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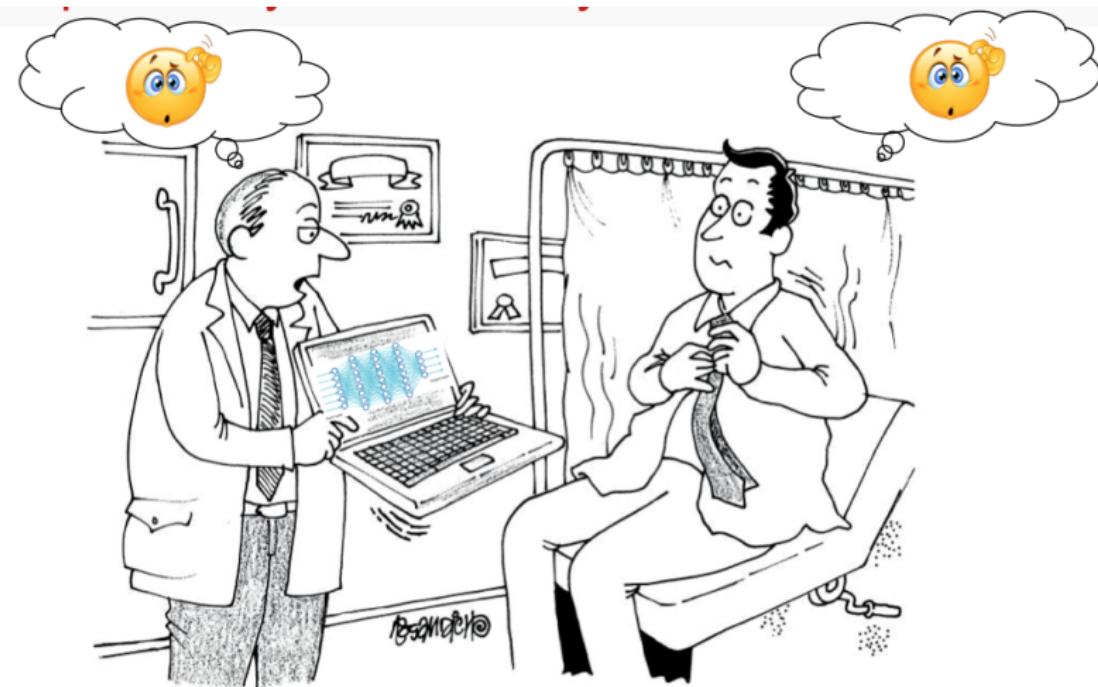
3 Future Directions

# Deep Learning as Blackbox

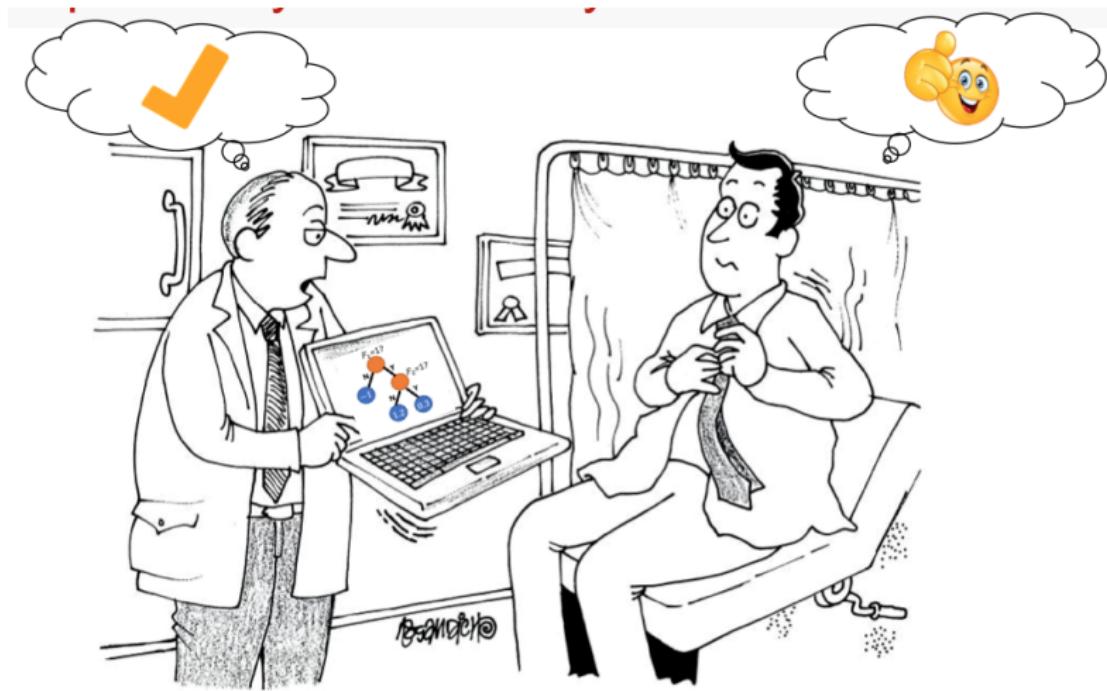


If the AI is 'black-boxed,' it's hard to see what factors are determining the outcome and direction of the AI.

# Importance of Explainable Artificial Intelligence - I

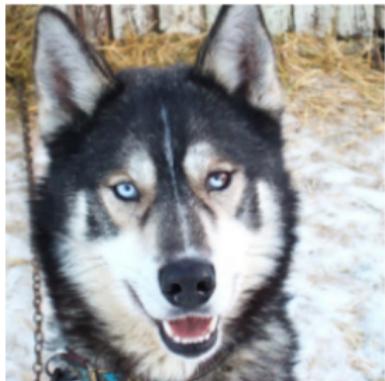


# Importance of Explainable Artificial Intelligence - I

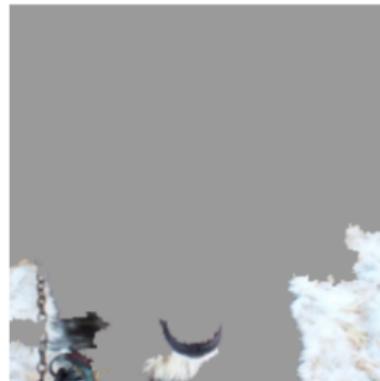


# Importance of Explainable Artificial Intelligence - II

How can I trust any machine learning algorithm? [Ribeiro et al, 2016]



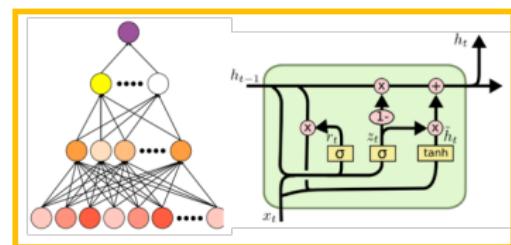
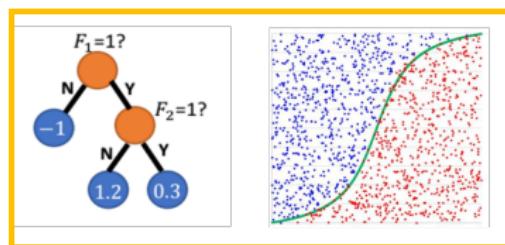
(a) Husky classified as wolf



(b) Explanation

# Interpretable Model is Necessary

Interpretable predictive models are shown to result in faster adoptability of machine learning models.



- Simple and commonly use models
- Easy to interpret, mediocre performance
- Deep learning solutions
- Superior performance, hard to explain

*Can we learn interpretable models with robust prediction performance?*

# Ongoing Work on Explainable Machine Learning Models

## Direct Interpretation

- [Garson, 1991]: estimating feature importance directly from network weight connections
- [Hechtlinger, 2016]: computing output gradients with respect to input features
- [Itti et al., 1998; Mnih et al., 2014; Xu et al., 2015]: attention models

## Indirect Interpretation

- [Provost et al., 1997]: sensitivity analysis of feature contributions to a neural network's output
- [Ribeiro et al., 2016]: local interpretability for black-box models
- [Che et al., 2016b]: mimicking the blackbox through the prediction scores
- [Maaten and Hinton, 2008; Simonyan et al., 2013; Yosinski et al., 2014; LeCun et al., 2015; Mnih et al., 2015; Mahendran and Vedaldi, 2015]: visualizing the hidden units

# INTERPRETABLE DEEP MODELS FOR ICU OUTCOME PREDICTION



Zhengping Che



Sanjay Purushotham



Robinder Khemani



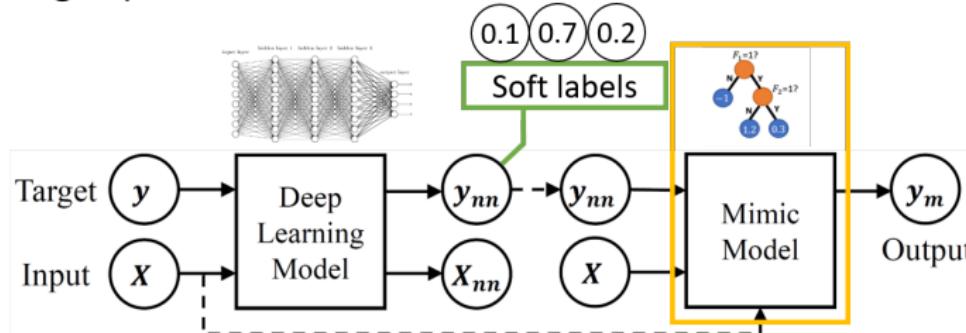
USC



Che et al, Interpretable Deep Models for ICU Outcome Prediction. of the American Medical Informatics Association Annual Symposium (AMIA), 2016.

# Interpretable Mimic Learning Framework [Che et al., 2016b]

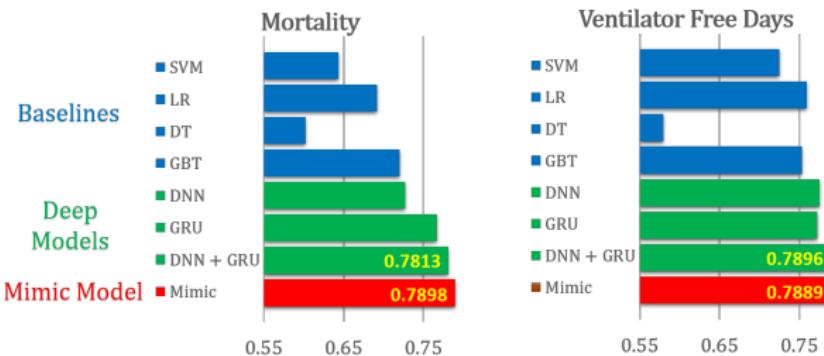
- Main ideas:
  - Borrow the ideas from knowledge distillation [Hinton, et al., 2015] and mimic learning [Ba, Caruana, 2014].
  - Use **Gradient Boosting Trees (GBTs)** to mimic deep learning models.
- Training Pipeline:



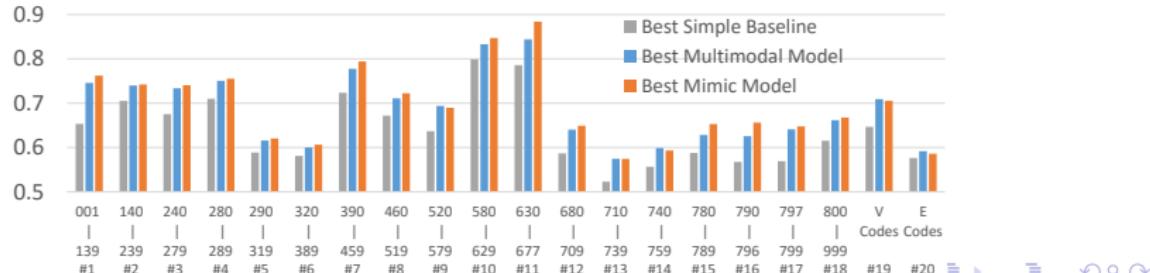
- Benefits: Good performance, less overfitting, interpretations.

# Quantitative Evaluation

AUROC score of prediction on patients with acute hypoxemic respiratory failure.

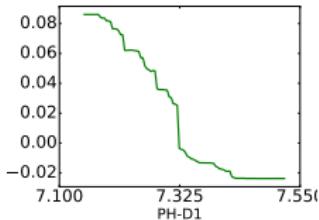


AUROC score of 20 ICD-9 diagnosis category prediction tasks on MIMIC-III dataset.



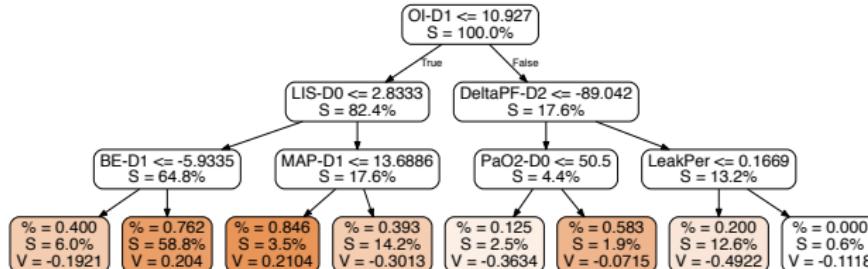
# Model/Feature Interpretation

**Partial dependency plot** for mortality prediction on patients with acute hypoxic respiratory failure.



- pH value in blood should stay in a normal range around **7.35-7.45**.
- Our model predicts a higher mortality change when the patient pH value **below 7.325**.

**Most Useful Decision Trees** for ventilator free days prediction.



Useful features:

- Lung injury score
- Oxygenation index
- PF ratio change

# RETAIN: INTERPRETABLE DEEP LEARNING MODEL



Edward Choi



Taha Bahadori



Andy Schuetz



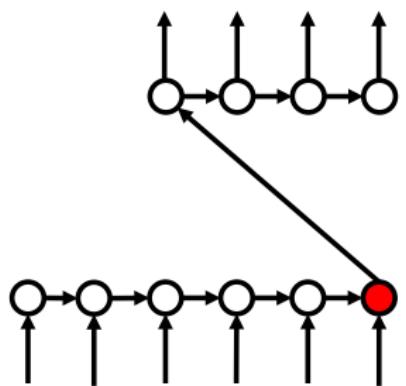
Buzz Stewart



Choi, Edward, et al. 2016. "RETAIN: An Interpretable Predictive Model for Healthcare Using Reverse Time Attention Mechanism." In *NIPS*

## Regular Machine Translation

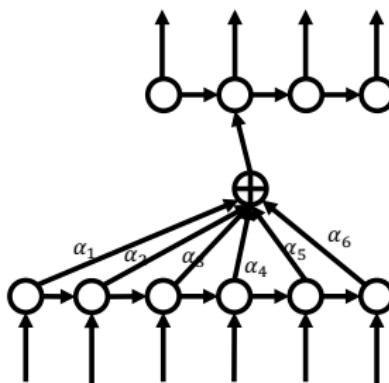
如果你不在乎谁获得了荣誉，  
你所能完成的事情是**惊人的**。



It is amazing what you can accomplish if you do not care who gets the credit

## Neural Attention Mechanism

如果你不在乎谁获得了荣誉，  
你所能完成的事情是惊人的。

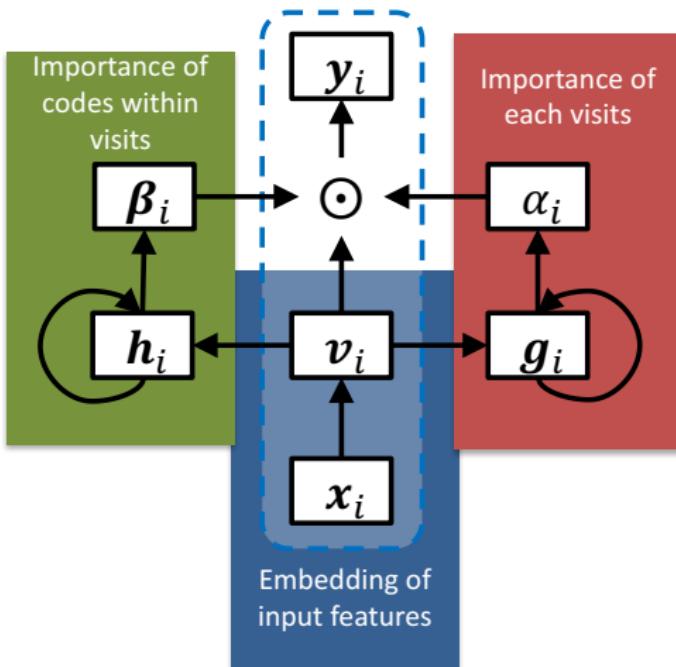


It is **amazing** what you can accomplish if you do not care who gets the credit

Bahdanau, Dzmitry, Kyunghyun Cho, and Yoshua Bengio. 2014.

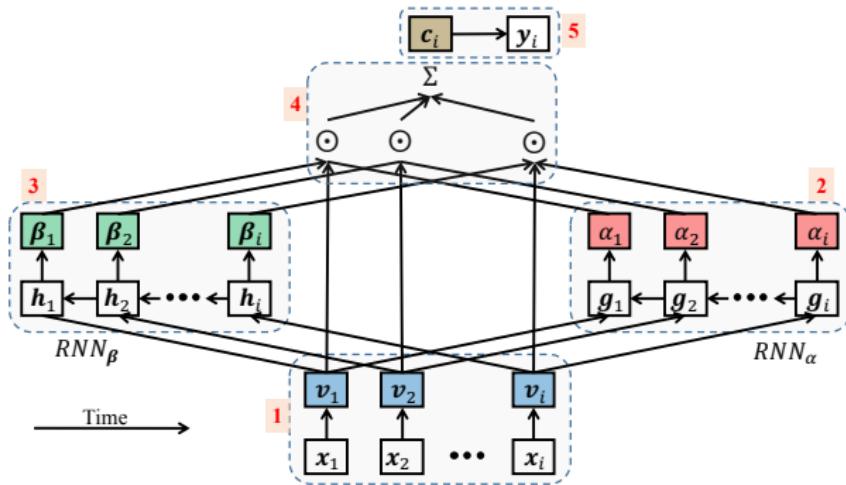
"Neural Machine Translation by Jointly Learning to Align and Translate." *arXiv [cs.CL]*. arXiv. <http://arxiv.org/abs/1409.0473>.

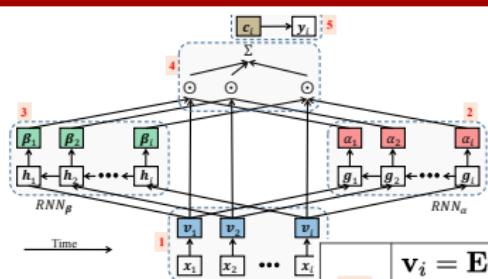
# RETAIN: REverse Time AttentIoN model



Choi, Edward, et al. 2016. "RETAIN: An Interpretable Predictive Model for Healthcare Using Reverse Time Attention Mechanism." In *NIPS*

# Details of RETAIN

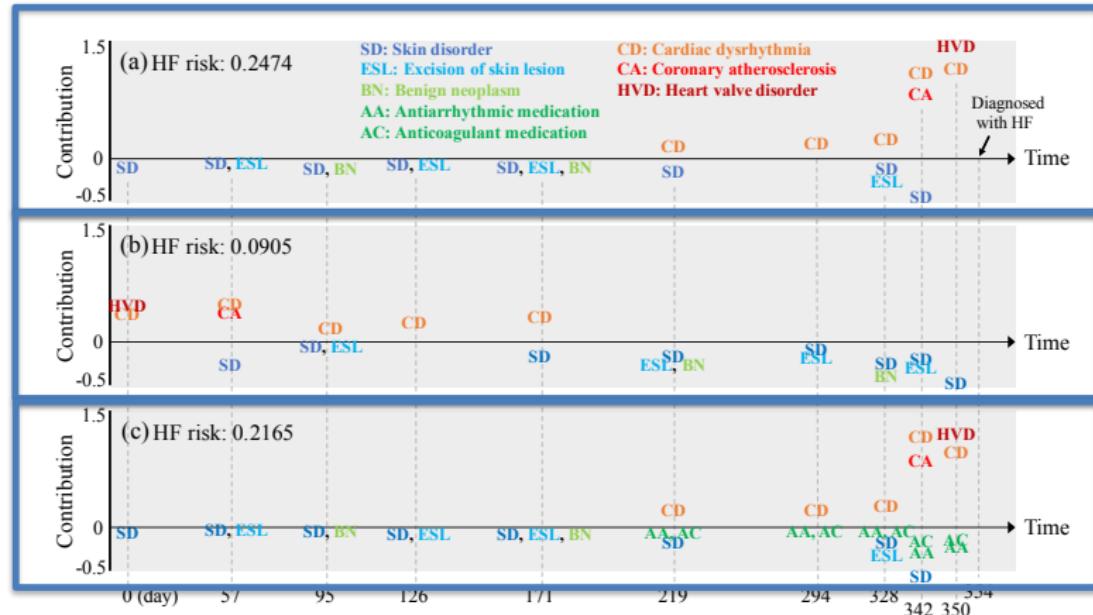




# RETAIN Algorithm

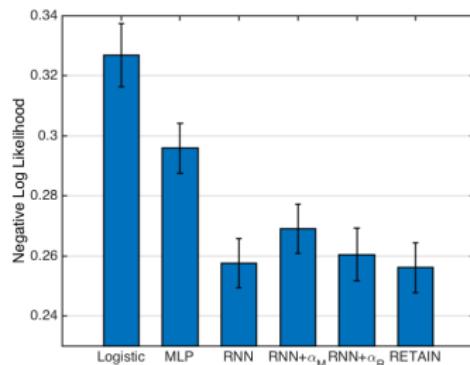
<b>1</b> $v_i = \mathbf{E}x_i$ Multi-hot representation of the visit is linearly projected by the embedding matrix $\mathbf{E}$ .
<b>2</b> $\mathbf{g}_i, \mathbf{g}_{i-1}, \dots, \mathbf{g}_1 = RNN_{\alpha}(v_i, v_{i-1}, \dots, v_1),$ $\alpha_1, \alpha_2, \dots, \alpha_i = \text{Softmax}(\mathbf{w}_{\alpha}^T [\mathbf{g}_1, \mathbf{g}_2, \dots, \mathbf{g}_i] + b_{\alpha})$
<b>3</b> $\mathbf{h}_i, \mathbf{h}_{i-1}, \dots, \mathbf{h}_1 = RNN_{\beta}(v_i, v_{i-1}, \dots, v_1)$ $\beta_j = \tanh(\mathbf{W}_{\beta} \mathbf{h}_j + \mathbf{b}_{\beta}) \quad \text{for } j = 1, \dots, i$
<b>4</b> $\mathbf{c}_i = \sum_{j=1}^i \alpha_j \beta_j \odot \mathbf{v}_j$ The attention weights $\alpha_i$ and $\beta_i$ are combined with the visit representation $\mathbf{v}_i$ to obtain the context vector $\mathbf{c}_i$ .
<b>5</b> $\hat{y}_i = \text{Softmax}(\mathbf{W}\mathbf{c}_i + \mathbf{b})$ Using the context vector $\mathbf{c}_i$ , we make the final prediction.

# Interpretation of RETAIN model

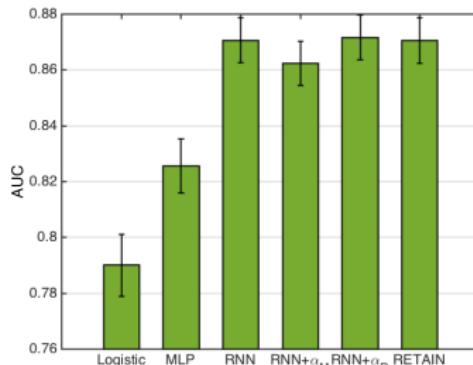


# Heart Failure Results

Negative Log Likelihood on Test Set



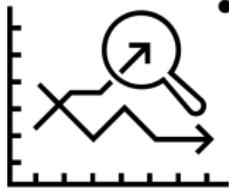
Classification AUC



## Retain: Interpretable Deep learning model



- Challenge: Deep learning models are often difficult to interpret



- RETAIN is a temporal attention model on electronic health records
  - Great predictive power
  - Good interpretation

Choi, Edward, et al. 2016. "RETAIN: An Interpretable Predictive Model for Healthcare Using Reverse Time Attention Mechanism." In *NIPS*

# What's next?

Modeling heterogeneous data sources



Clinical notes



-Omic data



sensor



Medical imaging

Model interpretation



More complex output



Clinical  
question & answer

# Acknowledgment

Yan Liu © USC

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## Collaborators:



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(MIT)



Kyunghyun Cho  
(NYU)



# Jimeng Sun @ Georgia Tech Healthcare Analytics



## Collaborators & Sponsors



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Government

Provider

University

Company

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**Tutorial websites:** <https://tinyurl.com/y7wuk9xt>

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