PETUUM

SAILING LAB
Laboratory for Statistical Artificial inteLigence & INtegreative Genomics

PetuumMed: algorithms and system for EHR-based medical decision support

Eric Xing
Petuum Inc.
Carnegie Mellon University

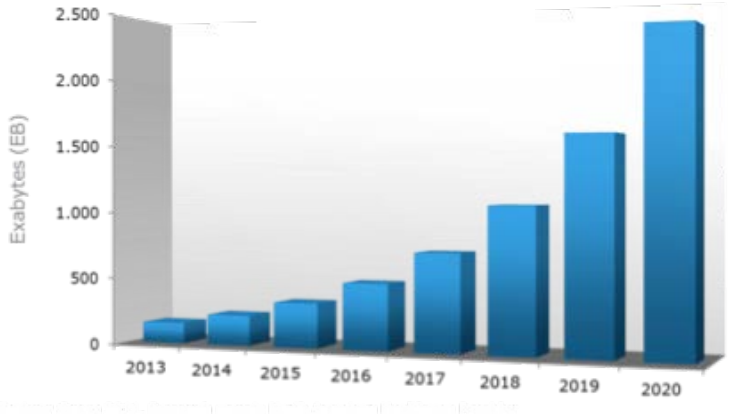
These Data Are …

- Time Constrained
- Mission Critical
- Complex
- Teamwork
- Expensive

The Data Deluge

Data Deluge in Healthcare

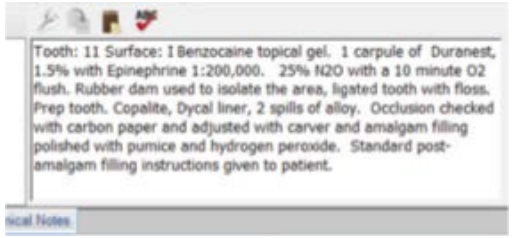
Volume



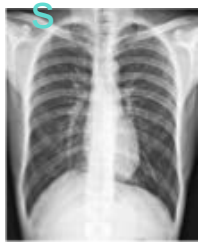
- 153 exabytes (one exabyte = one billion gigabytes) were produced in 2013
- An estimated 2,314 exabytes will be produced in 2020
- An overall rate of increase is at least 48 percent annually

Complexity

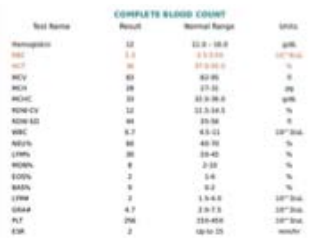
Notes



Images

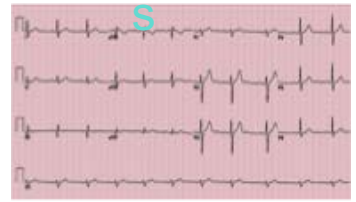


Lab values



Vital signs

Tests



Genomics

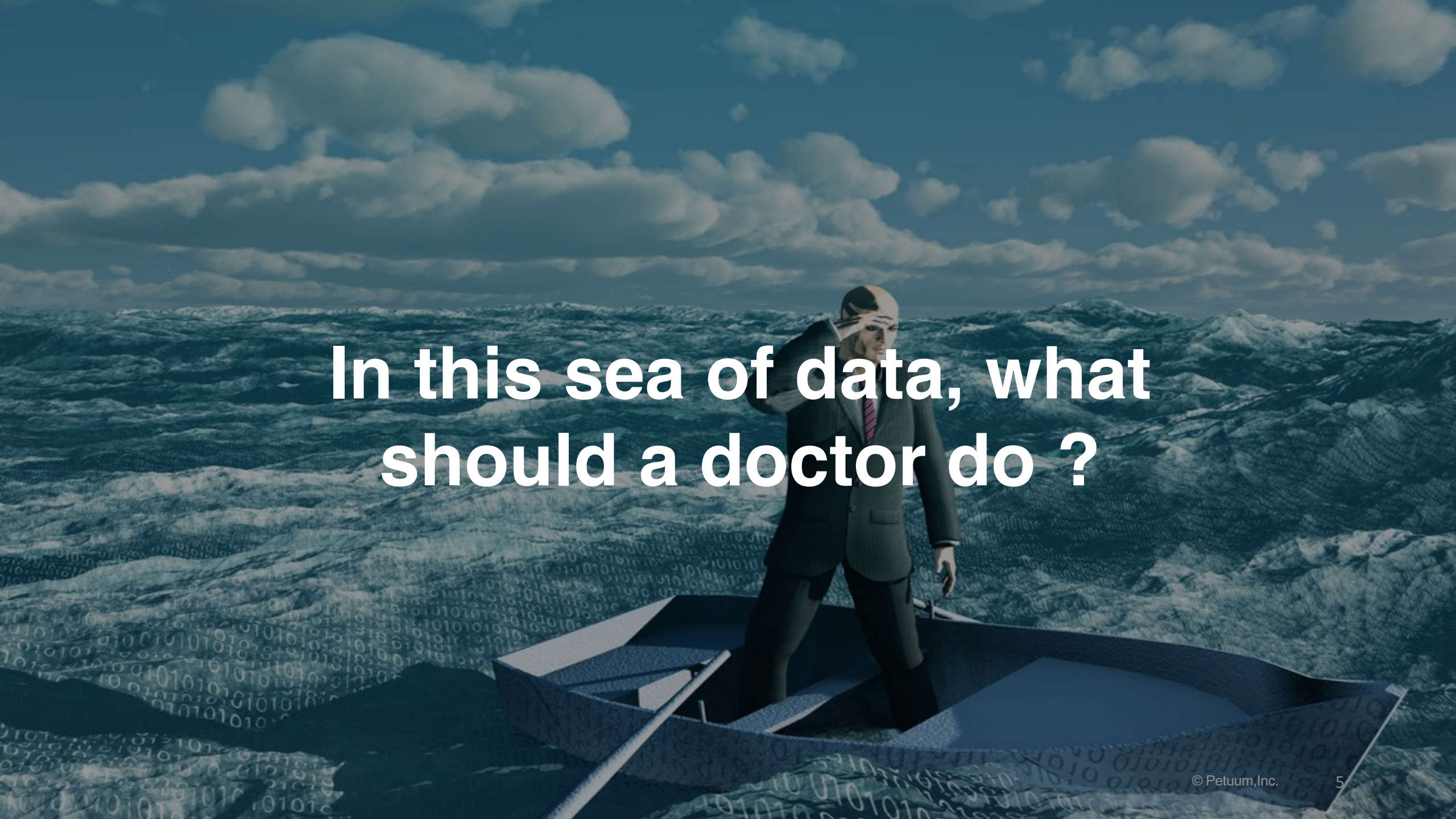
Billing

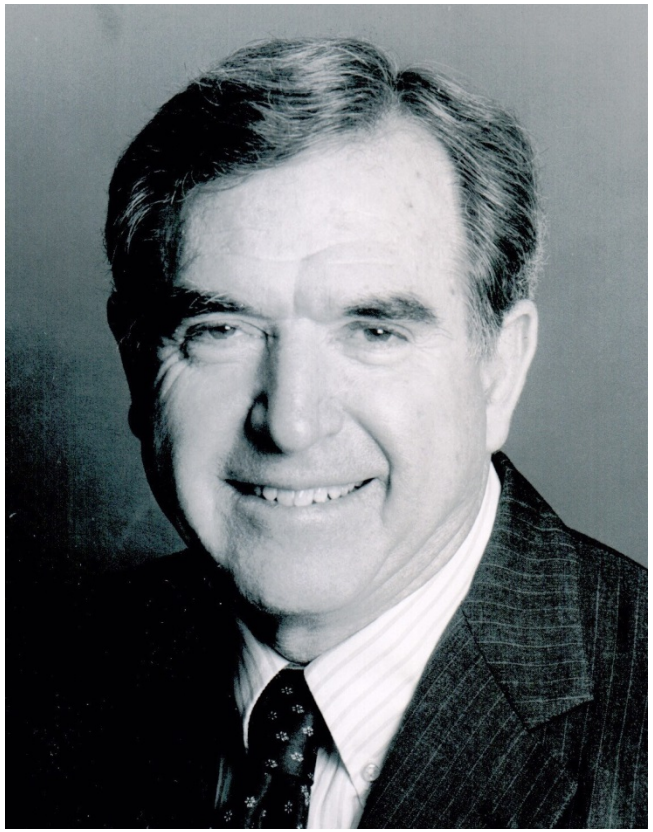
Literature

PubMed
National Library of Medicine
NLM

Social media

patientslikeme
Live better, together.





“Many people think that doctors make their recommendations from a basis of scientific certainty, that the facts are very clear and there’s only one way to diagnose or treat an illness. In reality, that’s not always the case. Many things are a matter of conjecture, tradition, convenience, habit.”

Arnold Relman (1923-2014)

Former Editor-in-Chief, New England Journal of Medicine

Pain Points in Healthcare

Quality

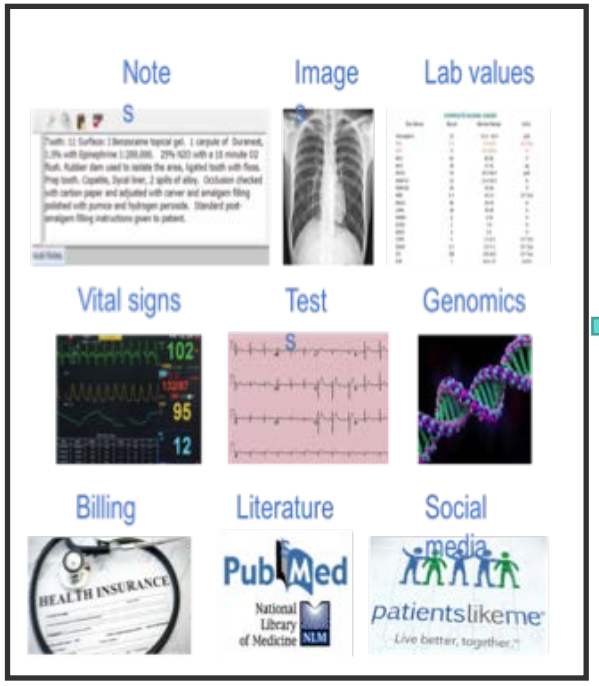
- 250,000 Americans die each year from medical errors (the third leading cause of death in the US).
- 12 million Americans are misdiagnosed each year.
- Preventable medication errors impact more than 7 million patients and cost almost $21 billion annually.
- 15 to 25 percent of patients are readmitted within 30 days and readmissions are costly (e.g., $41.3 billion in 2011).

Efficiency

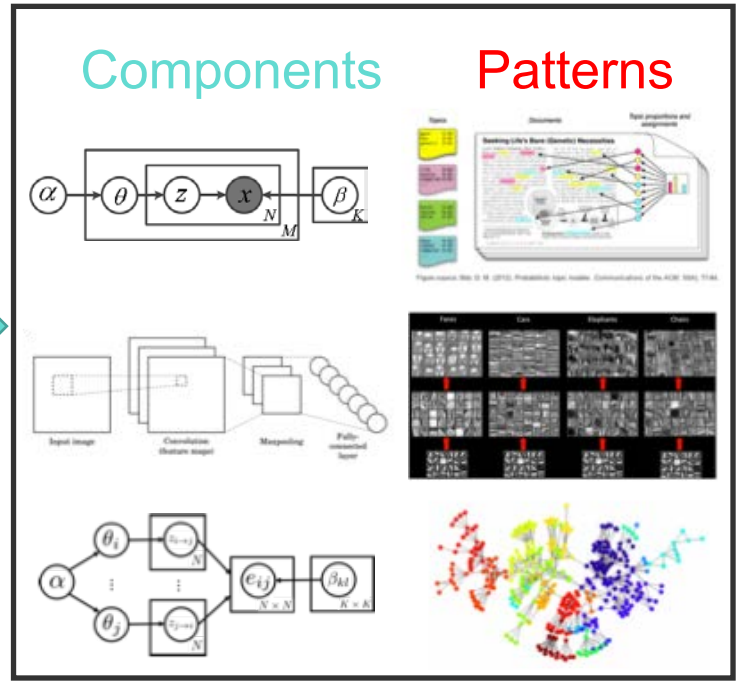
- Patients wait on average 6 hours in emergency rooms. Nearly 400,000 patients wait 24 hours or more.
- Physicians spend only 27 percent of their office day on direct clinical face time with patients.
- The U.S. healthcare system wastes $750 billion annually due to unnecessary services, inefficient care delivery, excess administrative costs, etc.

Machine Learning for Healthcare

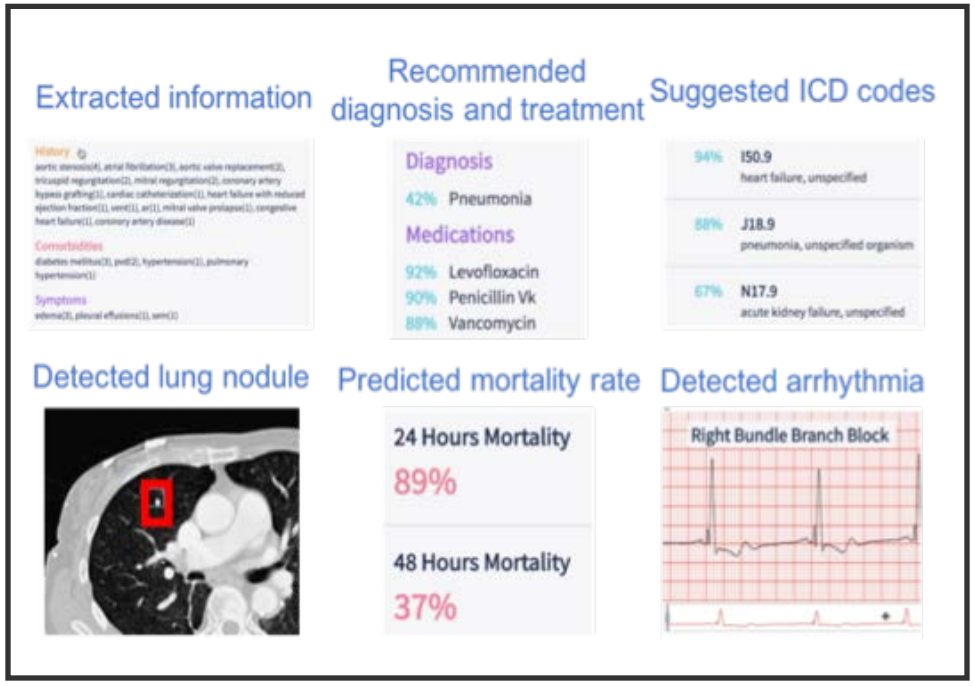
Clinical Data



Machine Learning

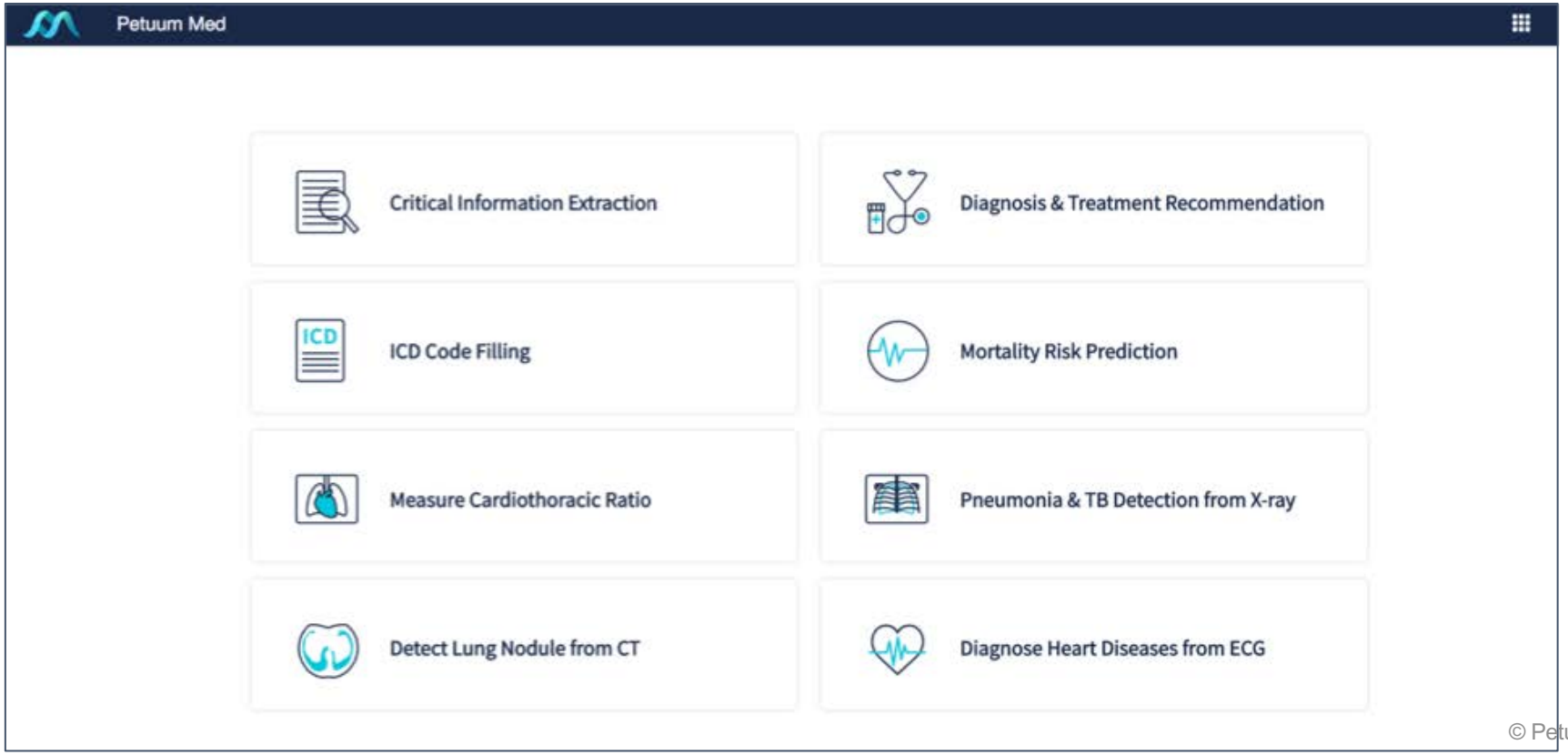


Actionable Insights



Petuum Healthcare Solutions

- **PetuumMed** is a clinical decision support platform powered by artificial intelligence and machine learning (AI/ML). It distills insights from massive and heterogeneous patient data, and empowers medical professionals make accurate and efficient decisions within the clinical flow



Supports clinical decisions at all points of care

Admission → **Diagnosis** → **Treatment** → **Discharge**

- Extracts critical patient medical information to speed up clinical preview

- lists alternative scenarios with probability score and reasoning to reduce error.

- Automates ICD coding to simplify reporting
- Predicts ICU patient mortality rate to assist care quality reporting

Information extraction

Diagnosis based on labs

Similar-patient retrieval

CT Lung-nodule detection

X-ray report generation

ECG-based diagnosis

Treatment recommendation

ICD code filling

Mortality prediction

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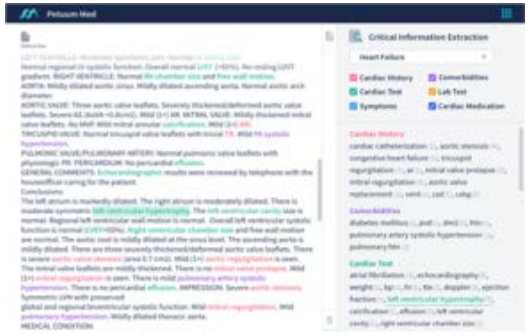
Information extraction



- Automatic construction of disease-specific knowledge graph
- Medical synonym matching
- Named entity extraction
- Relation extraction

Diagnosis based on labs

Similar-patient retrieval

CT Lung-nodule detection

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Mortality prediction

- Attentional matching
- Hierarchical classification
- Domain adaptation
- Isotonic constraints

Supports clinical decisions at all points of care

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Background

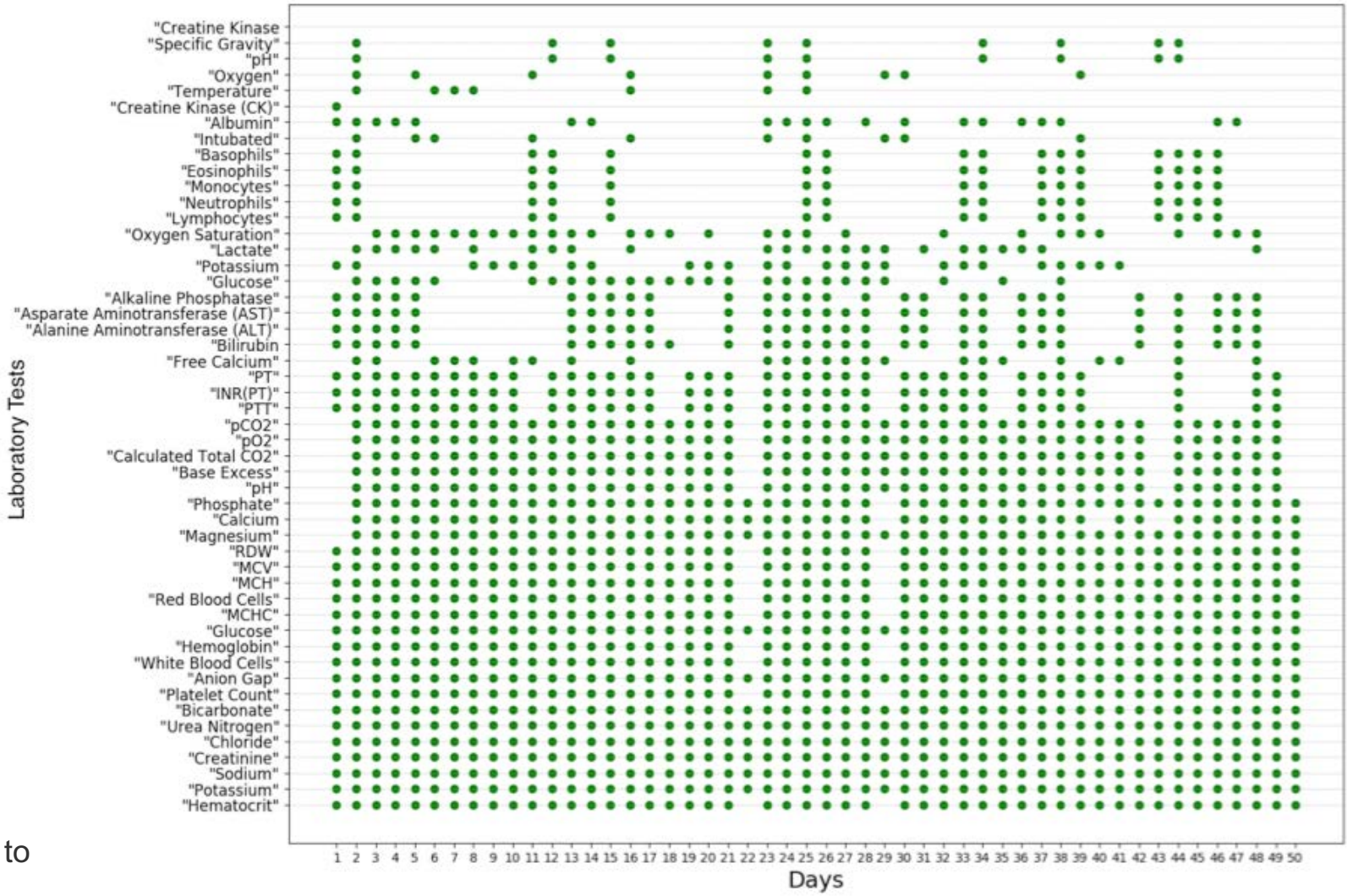
Challenges:

a. **Missing values**

b. **Temporal and multivariate structure**

Problems of existing approaches

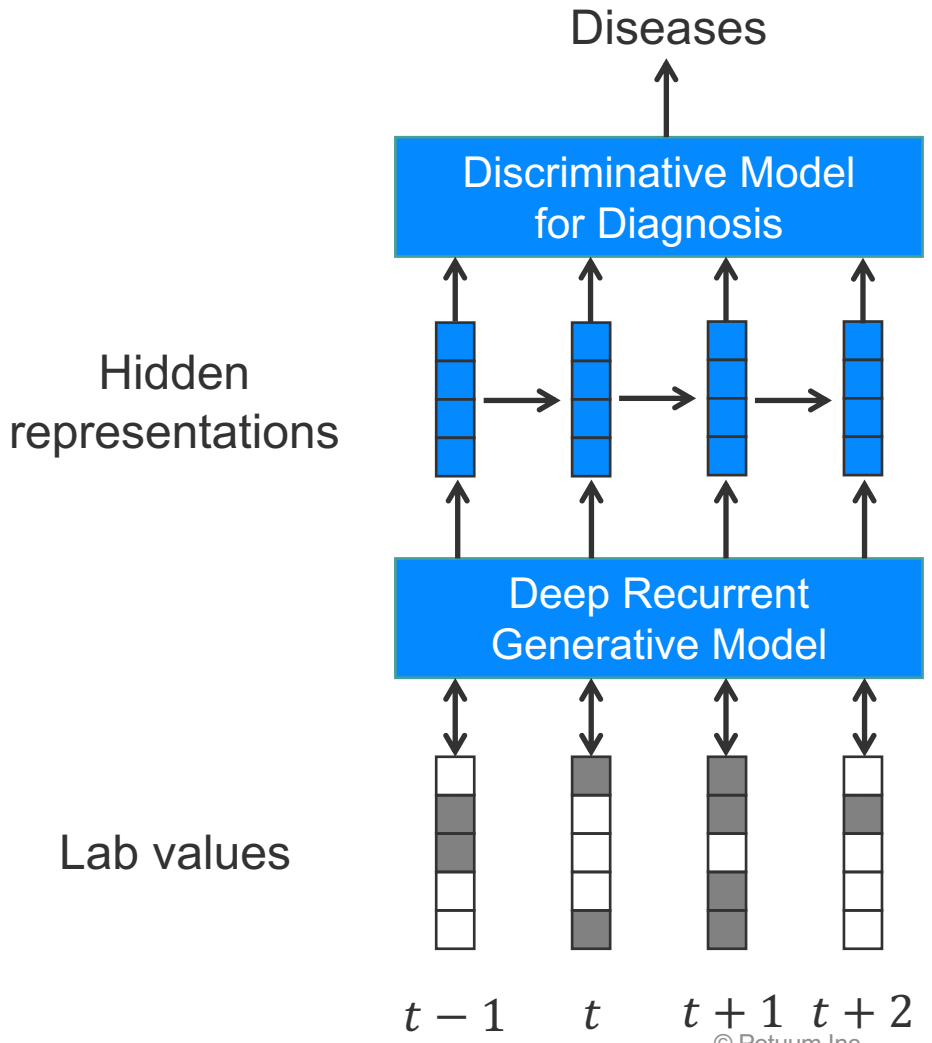
- Missing-value imputation methods (e.g., average filling, forward filling) are:
  - Linear, hence are less-expressive;
  - Heuristic, lacking a principled foundation.
- Missing-value imputation, time-series representation learning, and diagnosis prediction are performed separately, failing to take their inter-relations into account. For example, the imputed missing values may not be specifically good for the prediction task.



An example of a patient's laboratory test records. The green dot means there is a value, otherwise it is missing.

Diagnosis Based on Lab Values

- Solutions
  - Imputing missing values based on deep generative models. The approach is “indirectly supervised” and is able to capture nonlinear patterns in missing values.
  - Capturing time-series structure using recurrent neural networks.
  - Generative modeling and discriminative prediction (for diagnosis) are performed jointly, which is able to explore the correlations among sub-tasks. Missing-value-imputation is tailored to diagnosis prediction.



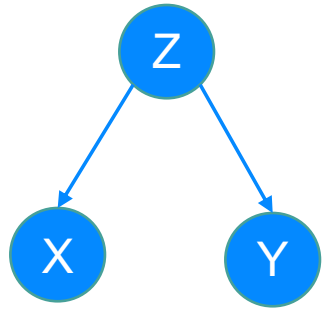
Imputation as Generation: a Probabilistic Approach

- Given the observed values $\mathcal{X}$, impute the missing values $\mathcal{Y}$ by inferring $p(\mathcal{Y}|\mathcal{X})$

$$
\begin{aligned}
&p(\mathcal{Y}|\mathcal{X}) \\
&= \int_{\mathbf{z}} p(\mathcal{Y}, \mathbf{z}|\mathcal{X}) \\
&= \int_{\mathbf{z}} \frac{p(\mathcal{X},\mathcal{Y},\mathbf{z})}{p(\mathcal{X})} \\
&= \int_{\mathbf{z}} \frac{p(\mathcal{X},\mathcal{Y}|\mathbf{z})p(\mathbf{z})}{p(\mathcal{X})} \\
&= \int_{\mathbf{z}} \frac{p(\mathcal{Y}|\mathbf{z})p(\mathcal{X}|\mathbf{z})p(\mathbf{z})}{p(\mathcal{X})} \\
&= \int_{\mathbf{z}} \frac{p(\mathcal{Y}|\mathbf{z})p(\mathcal{X},\mathbf{z})}{p(\mathcal{X})} \\
&= \int_{\mathbf{z}} p(\mathcal{Y}|\mathbf{z})p(\mathbf{z}|\mathcal{X}) \\
&= \mathbb{E}_{p(\mathbf{z}|\mathcal{X})}[p(\mathcal{Y}|\mathbf{z})] \\
&\approx p(\mathcal{Y}|\mathbb{E}[\mathbf{z}|\mathcal{X}])
\end{aligned}
$$

Fixed-point Iteration

$$
\begin{aligned}
&p(\mathbf{z}|\mathcal{X}) \\
&= \int_{\mathcal{Y}} p(\mathbf{z}, \mathcal{Y}|\mathcal{X}) \\
&= \int_{\mathcal{Y}} \frac{p(\mathbf{z},\mathcal{Y},\mathcal{X})}{p(\mathcal{X})} \\
&= \int_{\mathcal{Y}} \frac{p(\mathbf{z}|\mathcal{X},\mathcal{Y})p(\mathcal{X},\mathcal{Y})}{p(\mathcal{X})} \\
&= \int_{\mathcal{Y}} p(\mathbf{z}|\mathcal{X},\mathcal{Y})p(\mathcal{Y}|\mathcal{X}) \\
&= \mathbb{E}_{p(\mathcal{Y}|\mathcal{X})}[p(\mathbf{z}|\mathcal{X},\mathcal{Y})] \\
&\approx p(\mathbf{z}|\mathcal{X},\mathbb{E}[\mathcal{Y}|\mathcal{X}])]
\end{aligned}
$$



where z is a latent variable

Imputation as Generation: a Probabilistic Approach (Cont'd)

- Learning the parameters in $p(\mathcal{Y}|\mathbb{E}[\mathbf{z}|\mathcal{X}])$ anc $p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])]$ by maximizing the likelihood of observed data

$$
\begin{aligned}
&\log p(\mathcal{X}) \\
&= \mathbb{E}_{p(\mathcal{Y}|\mathcal{X})}[\log p(\mathcal{X}, \mathcal{Y})] - \mathbb{E}_{p(\mathcal{Y}|\mathcal{X})}[\log p(\mathcal{Y}|\mathcal{X})] \\
&\approx \log p(\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}]) - \mathbb{E}_{p(\mathcal{Y}|\mathcal{X})}[\log p(\mathcal{Y}|\mathcal{X})] \\
&= \mathbb{E}_{p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])}[\log p(\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}], \mathbf{z})] - \mathbb{E}_{p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])}[\log p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])] - \mathbb{E}_{p(\mathcal{Y}|\mathcal{X})}[\log p(\mathcal{Y}|\mathcal{X})] \\
&= \mathbb{E}_{p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])}[\log p(\mathcal{X}|\mathbf{z}) p(\mathbb{E}[\mathcal{Y}|\mathcal{X}]|\mathbf{z}) p(\mathbf{z})] - \mathbb{E}_{p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])}[\log p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])] - \mathbb{E}_{p(\mathcal{Y}|\mathcal{X})}[\log p(\mathcal{Y}|\mathcal{X})]
\end{aligned}
$$

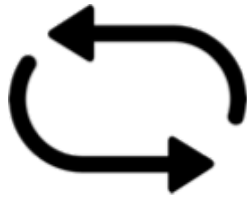
Share the same distribution as $p(\mathcal{Y}|\mathbb{E}[\mathbf{z}|\mathcal{X}])$

- Iteratively perform learning and inference

Fixing the parameters in $p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])]$ and $p(\mathcal{Y}|\mathbb{E}[\mathbf{z}|\mathcal{X}])$ infer $p(\mathcal{Y}|\mathcal{X})$

$$p(\mathcal{Y}|\mathcal{X}) \approx p(\mathcal{Y}|\mathbb{E}[\mathbf{z}|\mathcal{X}])$$

$$p(\mathbf{z}|\mathcal{X}) \approx p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])]$$

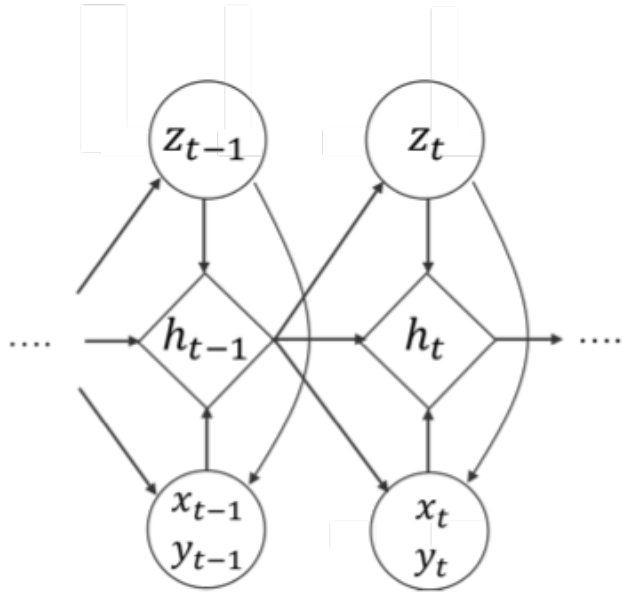


Fixing $p(\mathcal{Y}|\mathcal{X})$ learn the parameters in $p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])]$ and $p(\mathcal{Y}|\mathbb{E}[\mathbf{z}|\mathcal{X}])$ by maximizing

$$
\begin{aligned}
&\mathbb{E}_{p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])}[\log p(\mathcal{X}|\mathbf{z}) p(\mathbb{E}[\mathcal{Y}|\mathcal{X}]|\mathbf{z}) p(\mathbf{z})] \\
&-\mathbb{E}_{p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])}[\log p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])]
\end{aligned}
$$

Imputation as Generation: a Probabilistic Approach (Cont'd)

- Parameterize $p(\mathcal{Y}|\mathbb{E}[\mathbf{z}|\mathcal{X}])$ and. $p(\mathbf{z}|\mathcal{X}, \mathbb{E}[\mathcal{Y}|\mathcal{X}])]$ for time-series missing-value data
- Recurrent neural network with latent variables (Chung et al., 2015)



$$p(z_t|h_{t-1}) = \mathcal{N}(\xi_t, diag(\zeta_t^2)), \text{ where } [\xi_t, \zeta_t] = \phi(h_{t-1})$$

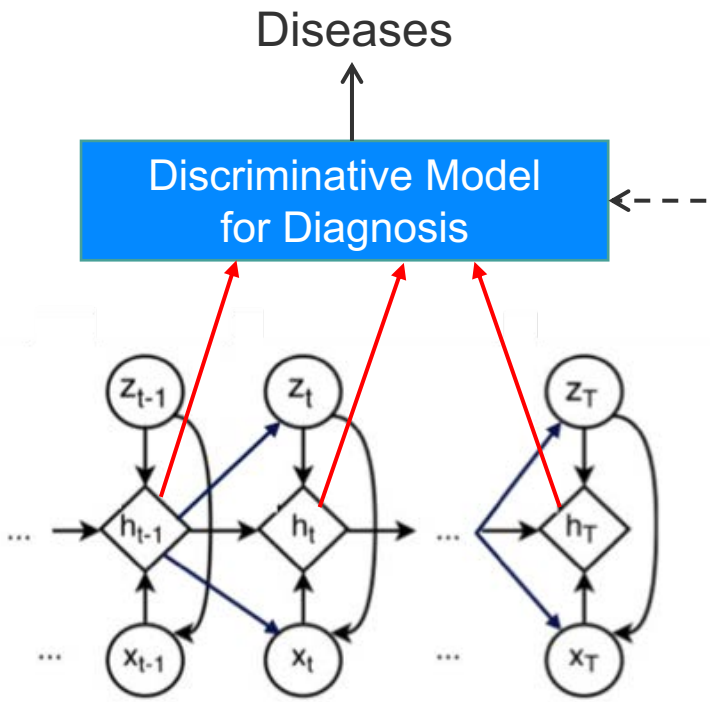
$$p(x_t, y_t|z_t, h_{t-1}) = \mathcal{N}(\mu_t, diag(\sigma_t^2)), \text{ where } [\mu_t, \sigma_t] = \varphi(z_t, h_{t-1})$$

$$h_t = \text{LSTM}(x_t, \mathbb{E}[y_t|x_t], z_t, h_{t-1})$$

$$p(z_t|x_t, \mathbb{E}[y_t|x_t]) = \mathcal{N}(\pi_t, diag(\tau_t^2)), \text{ where } [\pi_t, \tau_t] = \omega(x_t, \mathbb{E}[y_t|x_t])$$

Combine Missing-Value-Imputation with Diagnosis

- Jointly perform generative and discriminative learning



$$\tilde{h}_n = average(h_1, h_2, ..., h_T)$$

$$p(\hat{y}_n) = softmax(\varphi_d(\tilde{h}_n))$$

$$\min\ L_{gen} + \lambda L_{dis}$$

Negative log-likelihood in the generative model

Discriminative loss for diagnosis

MIMIC-III Dataset

- Electronic health records of patients in the intensive care units
- Processing
  - Time stamp is based on days
  - Maximum and minimum sequence length is 100 and 2.
  - Primary diagnosis is used as labels.
- Statistics

Original

# Hospital admissions	58,000
# Unique patients	46,520
# Diseases	2,833
# Lab tests	27.85 million
# Unique lab test items	635

After selection

# Hospital admissions	30,931
# Diseases	50 (most frequent ones)
# Unique lab test items	50 (most frequent ones)

Performance of Diagnosis

Diagnosis performances of different models

Model	Micro-F1	Macro-F1	Macro-F1-w	Micro-AUC	Macro-AUC	Macro-AUC-w
NN	0.376 ± 0.004	0.221 ± 0.003	0.347 ± 0.005	0.939 ± 0.001	0.905 ± 0.001	0.913 ± 0.001
AE+NN	0.366 ± 0.004	0.219 ± 0.002	0.344 ± 0.002	0.938 ± 0.001	0.903 ± 0.002	0.912 ± 0.001
VAE+NN	0.374 ± 0.003	0.226 ± 0.005	0.352 ± 0.004	0.941 ± 0.000	0.908 ± 0.001	0.916 ± 0.001
RNN+NN	0.395 ± 0.004	0.248 ± 0.003	0.373 ± 0.003	0.945 ± 0.003	0.918 ± 0.004	0.923 ± 0.003
VRNN+NN	$\mathbf{0.426 \pm 0.002}$	$\mathbf{0.291 \pm 0.006}$	$\mathbf{0.407 \pm 0.002}$	$\mathbf{0.958 \pm 0.000}$	$\mathbf{0.937 \pm 0.000}$	$\mathbf{0.938 \pm 0.001}$
VRNN+NN (early)	0.422 ± 0.005	0.285 ± 0.006	0.403 ± 0.004	0.957 ± 0.001	0.935 ± 0.001	0.937 ± 0.001
Performance of features derived from different models (with a simple NN classifier)						
E(z_n)(VAE)	0.363 ± 0.004	0.195 ± 0.004	0.326 ± 0.003	0.936 ± 0.001	0.896 ± 0.003	0.906 ± 0.002
E(z_n)(VAE+NN)	0.380 ± 0.004	0.228 ± 0.004	0.353 ± 0.002	0.943 ± 0.001	0.911 ± 0.003	0.918 ± 0.002
$\tilde{h}_n$(VRNN)	0.406 ± 0.003	0.261 ± 0.003	0.381 ± 0.003	0.953 ± 0.000	0.928 ± 0.001	0.930 ± 0.001
$\tilde{h}_n$(VRNN+NN)	$\mathbf{0.427 \pm 0.003}$	$\mathbf{0.297 \pm 0.004}$	$\mathbf{0.410 \pm 0.003}$	$\mathbf{0.958 \pm 0.001}$	$\mathbf{0.936 \pm 0.001}$	$\mathbf{0.937 \pm 0.000}$
Performance with different missing value imputation methods						
RNN+NN(zero)	0.395 ± 0.005	0.248 ± 0.003	0.374 ± 0.002	0.945 ± 0.003	0.918 ± 0.004	0.923 ± 0.003
RNN+NN(last&next)	0.385 ± 0.002	0.233 ± 0.003	0.360 ± 0.002	0.941 ± 0.001	0.912 ± 0.002	0.918 ± 0.001
RNN+NN(row mean)	0.393 ± 0.003	0.243 ± 0.005	0.369 ± 0.001	0.945 ± 0.002	0.917 ± 0.003	0.923 ± 0.002
RNN+NN(NOCB)	0.384 ± 0.003	0.231 ± 0.002	0.359 ± 0.001	0.941 ± 0.002	0.911 ± 0.003	0.917 ± 0.002
VRNN+NN	$\mathbf{0.426 \pm 0.002}$	$\mathbf{0.291 \pm 0.006}$	$\mathbf{0.407 \pm 0.002}$	$\mathbf{0.958 \pm 0.000}$	$\mathbf{0.937 \pm 0.001}$	$\mathbf{0.938 \pm 0.001}$

Performance of Missing Value Imputation

Different imputation methods

Imputation Methods	Imputation Error
Zero	0.909 ± 0.112
Last&next	0.434 ± 0.110
Row mean	0.541 ± 0.114
NOCB	0.547 ± 0.112
VRNN+NN	$\mathbf{0.370 \pm 0.110}$

Supports clinical decisions at all points of care

Admission → **Diagnosis** → **Treatment** → **Discharge**

- Extracts critical patient medical information to speed up clinical preview

- lists alternative scenarios with probability score and reasoning to reduce error.

- Automates ICD coding to simplify reporting
- Predicts ICU patient mortality rate to assist care quality reporting

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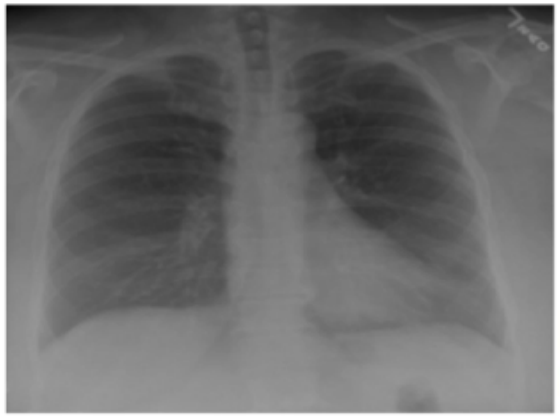
Chest X-ray Report

- A chest x-ray report consists of multiple sections of information.
  - **Findings**: the radiology observations and findings regarding each area of the body examined in the imaging study
  - **Impression**: the radiologist combines the findings, patient clinical history and indication for the imaging study and provides a diagnosis

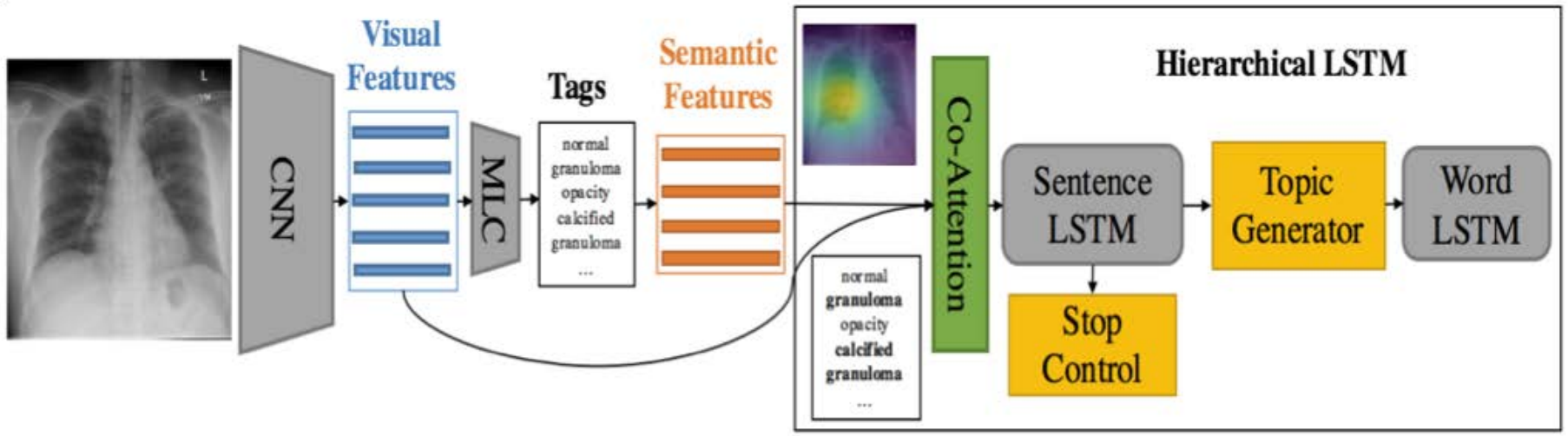


Findings:
There are no focal areas of consolidation.
No suspicious pulmonary opacities.
Heart size within normal limits.
No pleural effusions.
There is no evidence of pneumothorax.
Degenerative changes of the thoracic spine.

Impression:
No acute cardiopulmonary abnormality.

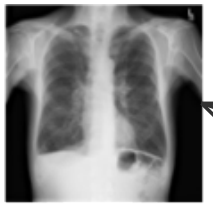
- Abnormal regions in medical images are difficult to identify.
- The reports are typically long, containing multiple sentences.
- Each sentence discusses a specific topic. How to localize the image regions and tags that are relevant to this topic?

Model Architecture



- Semi-supervised learning for lesion tag prediction
- Hierarchical LSTM for long-paragraph generation
- Visual-semantic co-attention to localize the relevant image regions and tags for each sentence to be generated

Hierarchical LSTM for Paragraph Generation



Predicted Tags

- Hyperdistention
- Emphysema
- COPD

h_1 h_2 h_3 …

c_1 c_2 c_3 …

z_1 z_2 z_3 …

o_1 o_2 o_3

w_1 w_2 w_3

Sentence LSTM generates sentence-level hidden vectors: ”meta sentence”

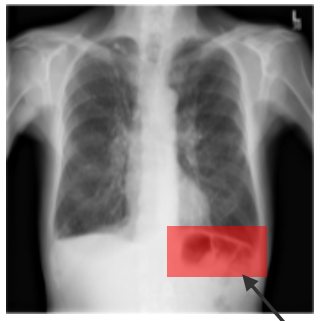
Visual-semantic co-attention module calculates contextual vectors

Calculates topic vectors

Word LSTM generates word-level hidden vectors

Generate words

Visual-Semantic Co-Attention



- Hyperdistention
- Emphysema
- COPD
- Cicatrix

Visual attention

$$a_{tn}^{(v)} \propto \exp(\boldsymbol{U}^{(v)}\tanh(\boldsymbol{V}^{(v)}\boldsymbol{x}_n + \boldsymbol{W}^{(v)}\boldsymbol{h}_{t-1}))$$

Semantic attention

$$a_{tm}^{(s)} \propto \exp(\boldsymbol{U}^{(s)}\tanh(\boldsymbol{V}^{(s)}y_m + \boldsymbol{W}^{(s)}\boldsymbol{h}_{t-1}))$$

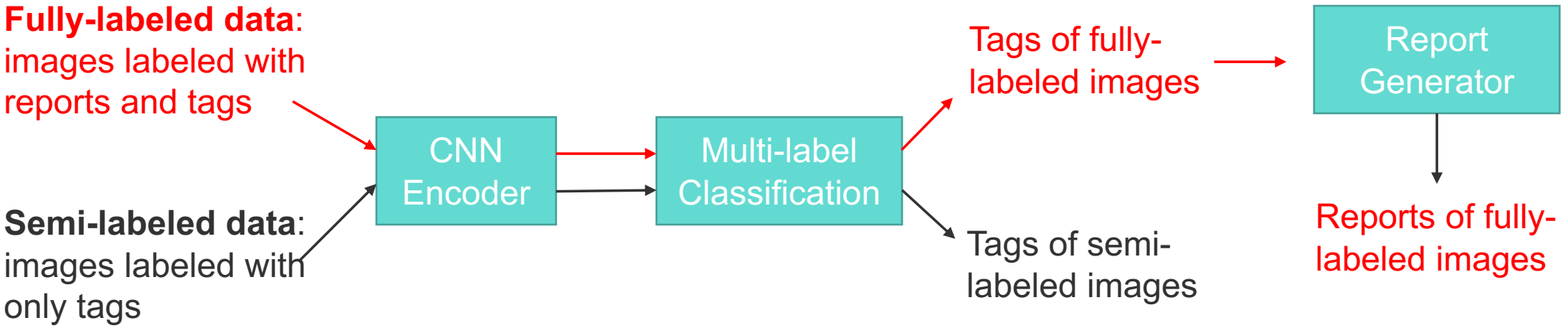
… There is chronic pleural-parenchymal scarring within the lung bases. No lobar consolidation is seen. …

Co-attention

$$\boldsymbol{r}_t^{(v)} = \sum_{n=1}^{N} a_{tn}^{(v)}\boldsymbol{x}_n \quad \boldsymbol{r}_t^{(s)} = \sum_{m=1}^{M} a_{tm}^{(s)}\boldsymbol{y}_m$$

$$\boldsymbol{c}_t = \boldsymbol{Q}[\boldsymbol{r}_t^{(v)}; \boldsymbol{r}_t^{(s)}]$$

Semi-supervised Learning for Lesion Tagging



- The amount of semi-labeled data is large. Their tags can help train a better lesion-tagging model.

Experiments

- Fully-labeled dataset
  - Indiana University Chest X-ray Collection
  - 7,470 pairs of images and reports
  - Each image has a set of tags obtained from Medical Text Indexer
  - 1915 unique words and 572 unique tags
  - On average, each image is associated with 2.2 tags, 5.7 sentences and each sentence contains 6.5 words.
- Semi-labeled dataset
  - NIH Chest X-ray images
  - 108,948 frontal-view X-ray images
  - 14 lesion tags
- Evaluation metrics
  - Language quality: BLEU, METEOR, ROUGE and CIDER
  - Clinical correctness: F1

Evaluation of Language Quality

	Methods	BLEU-1	BLEU-2	BLEU-3	BLEU-4	METEOR	ROUGE	CIDER
Baselines	CNN-RNN [1]	0.316	0.211	0.140	0.095	0.159	0.267	0.111
	LRCN [2]	0.369	0.229	0.149	0.099	0.155	0.278	0.190
	Soft ATT [3]	0.399	0.251	0.168	0.118	0.167	0.323	0.302
	ATT-RK [4]	0.369	0.226	0.151	0.108	0.171	0.323	0.155
Our methods	No-Attention	0.505	0.383	0.290	0.224	0.200	0.420	0.259
	Semantic-Only	0.504	0.371	0.291	0.230	0.207	0.418	0.286
	Visual-Only	0.507	0.373	0.297	0.238	0.211	0.426	0.300
	Co-Attention	**0.517**	**0.386**	**0.306**	**0.247**	**0.217**	**0.447**	**0.327**

- Baselines are the state-of-the-art image captioning methods.

Evaluation of Clinical Correctness

- Whether the presence/absence of 16 major lesions is correctly predicted: atelectasis, calcinosis, consolidation, cardiomegaly, edema, effusion, emphysema, fibrosis, granuloma, hernia, infiltration, mass, nodule, pneumonia, pneumothorax, pleural thickening
- Labeling process: manually read the report and check whether a lesion exists
  - Example

Normal cardiomediastinal silhouette. Interval improvement in lung volumes bilaterally. Improved aeration of the right and left lung bases. Bilateral small pleural effusions and left base atelectatic change, with interval improvement. Visualized XXXX of the chest XXXX are within normal limits.

→

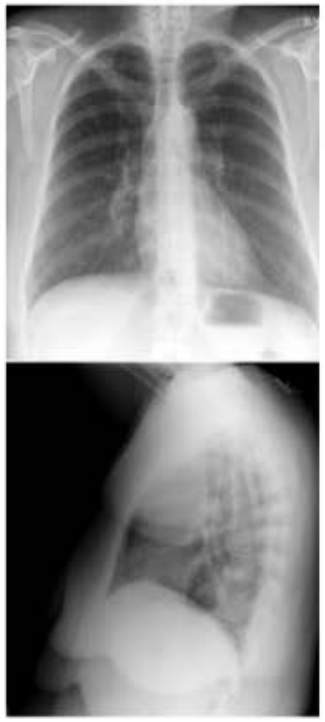
Has effusion and atelectasis.
No other lesions.

Evaluation of Clinical Correctness (Cont'd)

- F1 scores

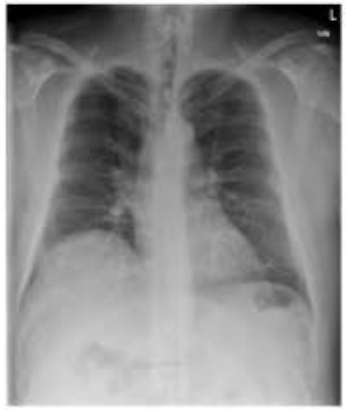
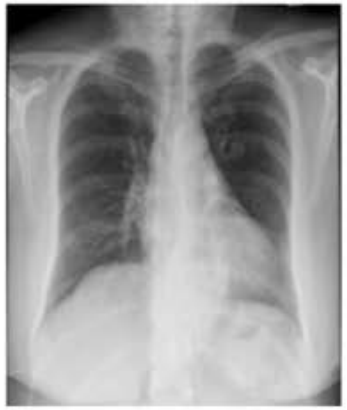
Methods	Our methods			
	No-Attention	Visual-Only	Semantic-Only	Co-Attention
Macro-F1	0.49	0.51	0.75	0.79

Success Cases

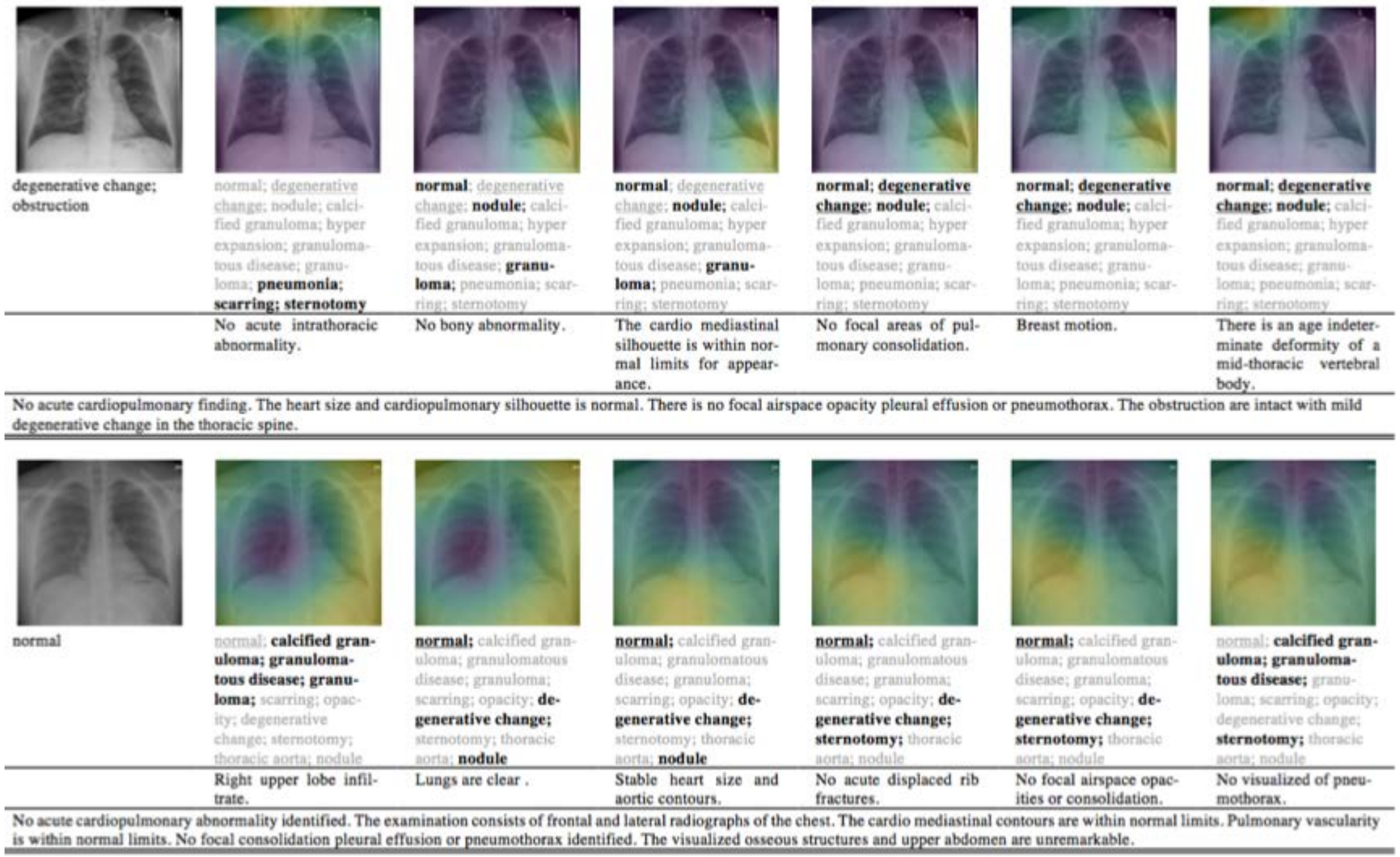
	Ground Truth	Ours-CoAttention	Ours-no-Attention	Soft Attention
	No active disease. The heart and lungs have in the interval. Both lungs are clear and expanded. Heart and mediastinum normal.	No active disease. The heart and lungs have in the interval. Lungs are clear and expanded. Cardiomediastinal silhouette is within normal limits. No pleural effusion or pneumothorax is seen. No pleural effusion. No cavitary or pneumothorax.	The lungs are clear bilaterally. The are grossly normal. No focal lung consolidation. No acute bony abnormality. cm nodule within the right lower lobe on the lateral view. No pneumothorax or pleural effusion. No acute bony abnormality. The heart is not enlarged. The lungs are clear. No acute bony abnormality .	No acute cardiopulmonary abnormality. The lungs are clear bilaterally. Specifically no evidence of focal airspace consolidation pleural effusion or pneumothorax. Cardio mediastinal silhouette is unremarkable. Visualized osseous structures of the thorax are without acute abnormality.
	No evidence of active disease. The lungs are clear. There is no focal airspace consolidation. No pleural effusion or pneumothorax. Heart size and mediastinal contour are within normal limits. There are multilevel degenerative changes of the spine.	No acute cardiopulmonary findings. Heart size is not enlarged. No focal airspace consolidation suspicious pulmonary opacity large pleural effusion or pneumothorax. No focal areas of consolidation. Degenerative changes of the spine. This is moderate exam of the hydropneumothorax. Lungs are clear. There is no focal airspace consolidation pleural effusion or pneumothorax.	The lungs are clear bilaterally. The are grossly normal. No pleural effusion. The heart is normal in size and contour. The lungs are clear. There are no acute bony findings.	No acute cardiopulmonary abnormality. The lungs are clear bilaterally. There is no pleural effusion or pneumothorax. The heart and mediastinum are normal. There is no focal air space opacity to suggest a pneumonia.

- The underlined sentences are the descriptions of detected abnormalities.

Failure Cases

	Ground Truth	Ours-CoAttention	Ours-no-Attention	Soft Attention
	No acute cardiopulmonary abnormality. Normal heart size mediastinal contours. Eventration of the right hemidiaphragm. No focal airspace consolidation. No pleural effusion or pneumothorax.	No acute cardiopulmonary abnormality. Stable appearance of the thoracic aorta. The right lateral lower lobe is noted in the right lower right midlung. No large pleural effusion or focal airspace disease. Mild interstitial opacities. Atherosclerotic calcifications bony structures bilaterally. There is no pleural effusion or pneumothorax developed in the right lower lobe.	The lungs are clear bilaterally. The are grossly normal. No acute bony abnormality. The lungs are otherwise clear. No acute osseous abnormality. No acute osseous abnormality. The heart and mediastinum are normal. There is no focal air space opacity.	No acute cardiopulmonary abnormality. The lungs are clear bilaterally. There is no focal airspace consolidation. No pleural effusion or pneumothorax. Heart size and pulmonary vascularity appear within normal limits.
	No acute cardiopulmonary abnormality. Heart size appears within normal limits . Pulmonary vasculature appears within normal limits. Overlying the middle cardiac silhouette representing a hiatal hernia. No focal consolidation pleural effusion or pneumothorax. No acute bony abnormality.	No active disease. The heart and lungs have in the interval. Nipple and lateral lucency in the lungs suggestive of focal airspace disease. The lungs are hyperexpanded consistent with emphysema in the left lower lobe. This is most at the upper lobes. This may indicate hypoventilated irregularities or effusions. The lungs are otherwise grossly clear. Resolution of by normal pleural effusion.	No acute cardiopulmonary abnormality. The lungs are clear bilaterally. The are grossly normal. No focal airspace consolidation. No pneumothorax or pleural effusion. Heart size and pulmonary vascularity within normal limits. There is no pneumothorax or pleural effusion.	No acute cardiopulmonary abnormality. There is no focal airspace consolidation. No pneumothorax or pleural effusion. No acute bony abnormality. Heart size is normal .

Visualization of Co-attention



Supports clinical decisions at all points of care

Admission → **Diagnosis** → **Treatment** → **Discharge**

- Extracts critical patient medical information to speed up clinical preview

- lists alternative scenarios with probability score and reasoning to reduce error.

- Automates ICD coding to simplify reporting
- Predicts ICU patient mortality rate to assist care quality reporting

Information extraction

Diagnosis based on labs

Similar-patient retrieval

CT Lung-nodule detection

X-ray report generation

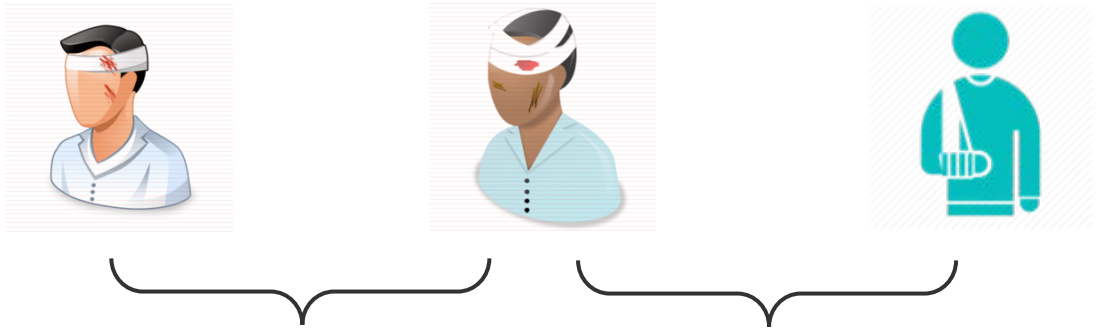
ECG-based diagnosis

Treatment recommendation

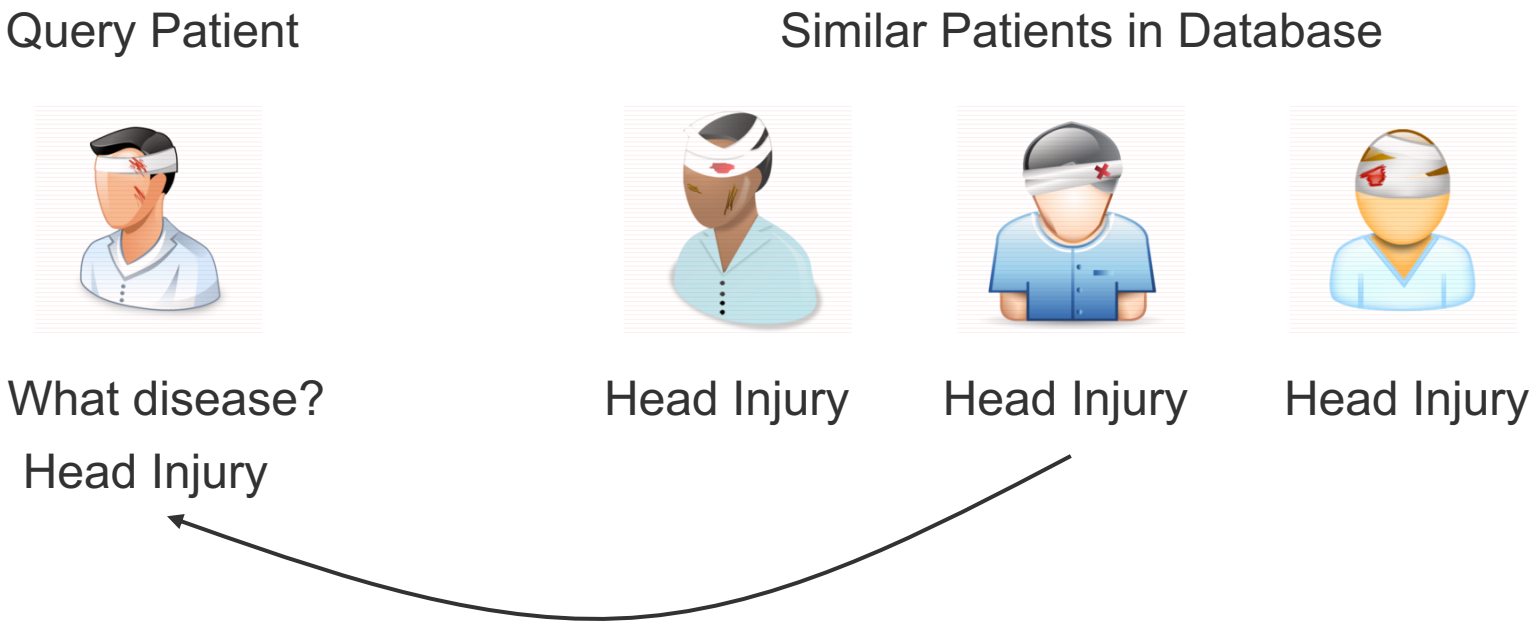
ICD code filling

Mortality prediction

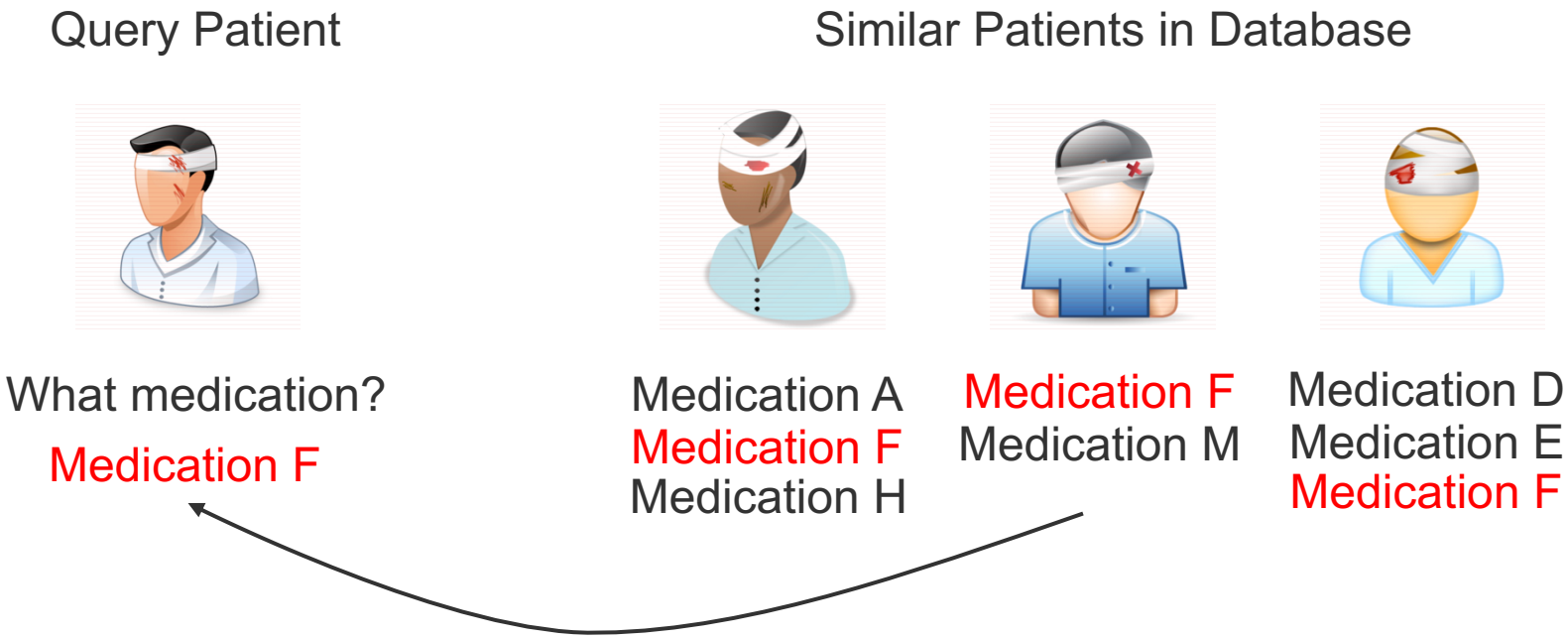
Patient Similarity



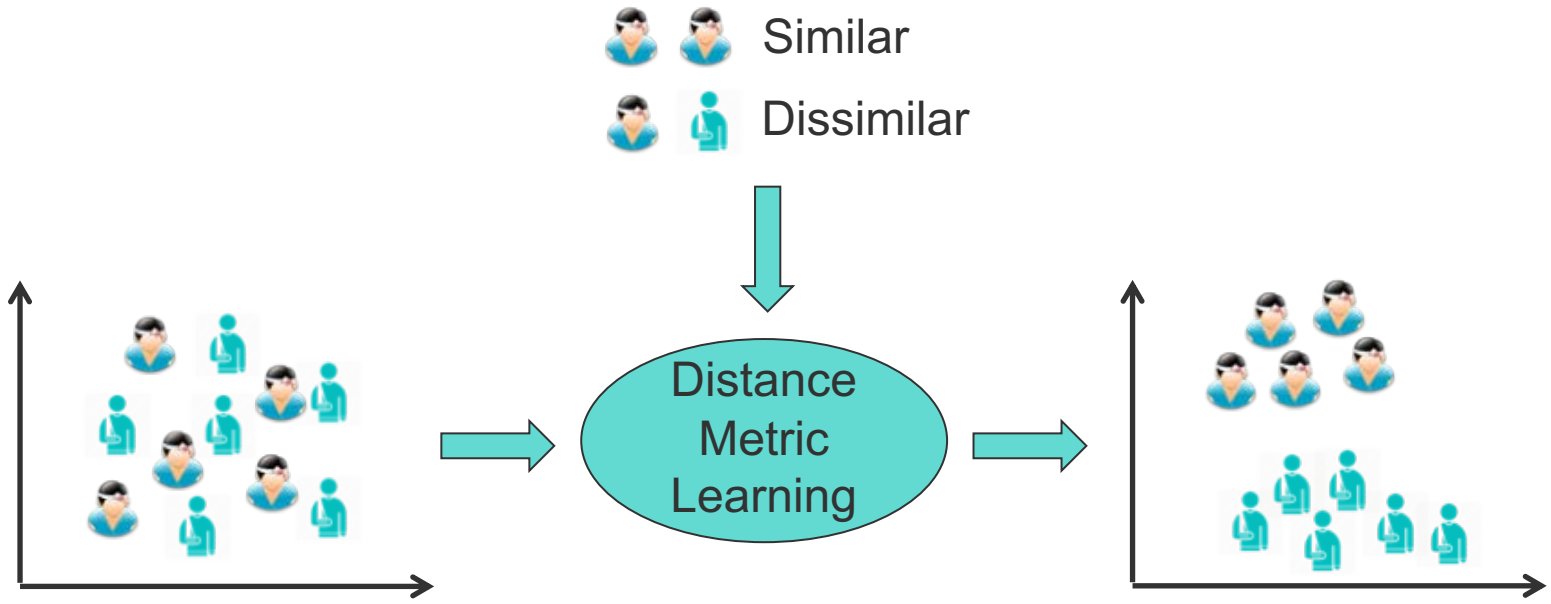
Patient Similarity for Personalized Diagnosis



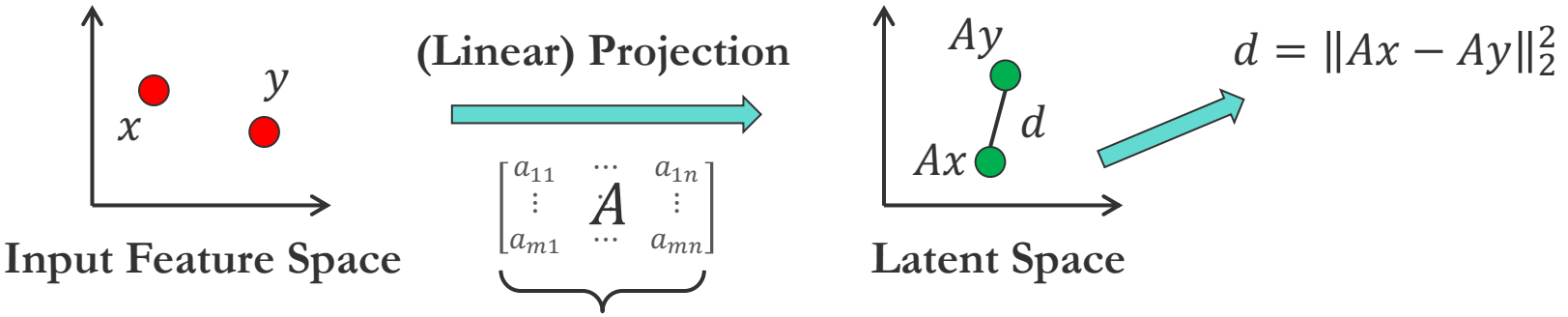
Patient Similarity for Personalized Treatment



Distance Metric Learning (DML)



Distance Metric Learning (Cont'd)



Row vectors of $\boldsymbol{A}$ are called "components", each corresponding to one dimension of the latent space

$$\min_A \sum_{(x,y)\in S} \|Ax - Ay\|^2$$

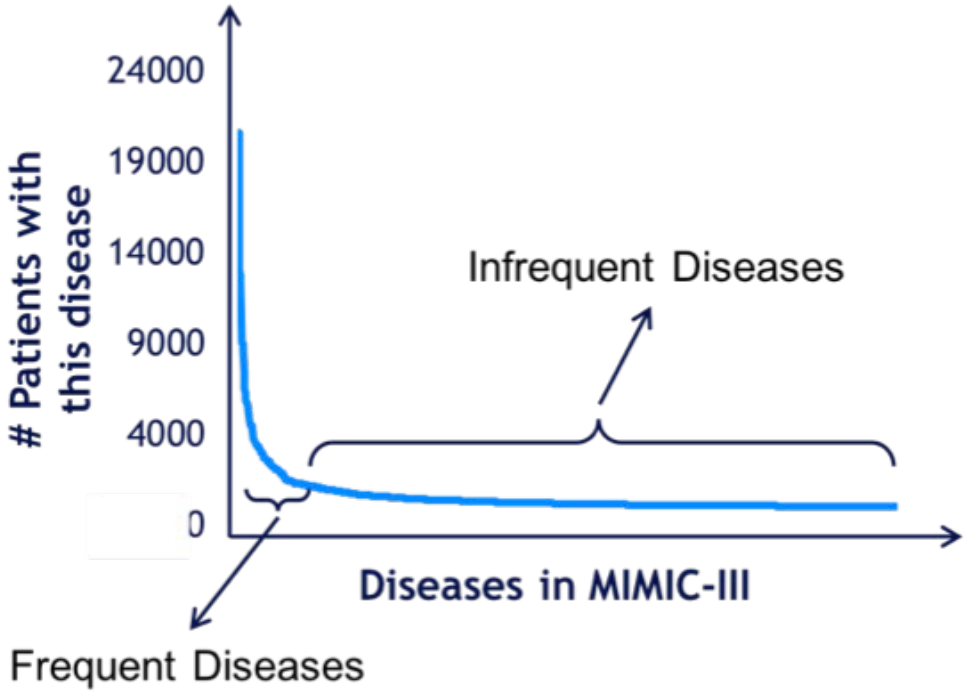
(Xing et al., 2002)

Similar Pairs

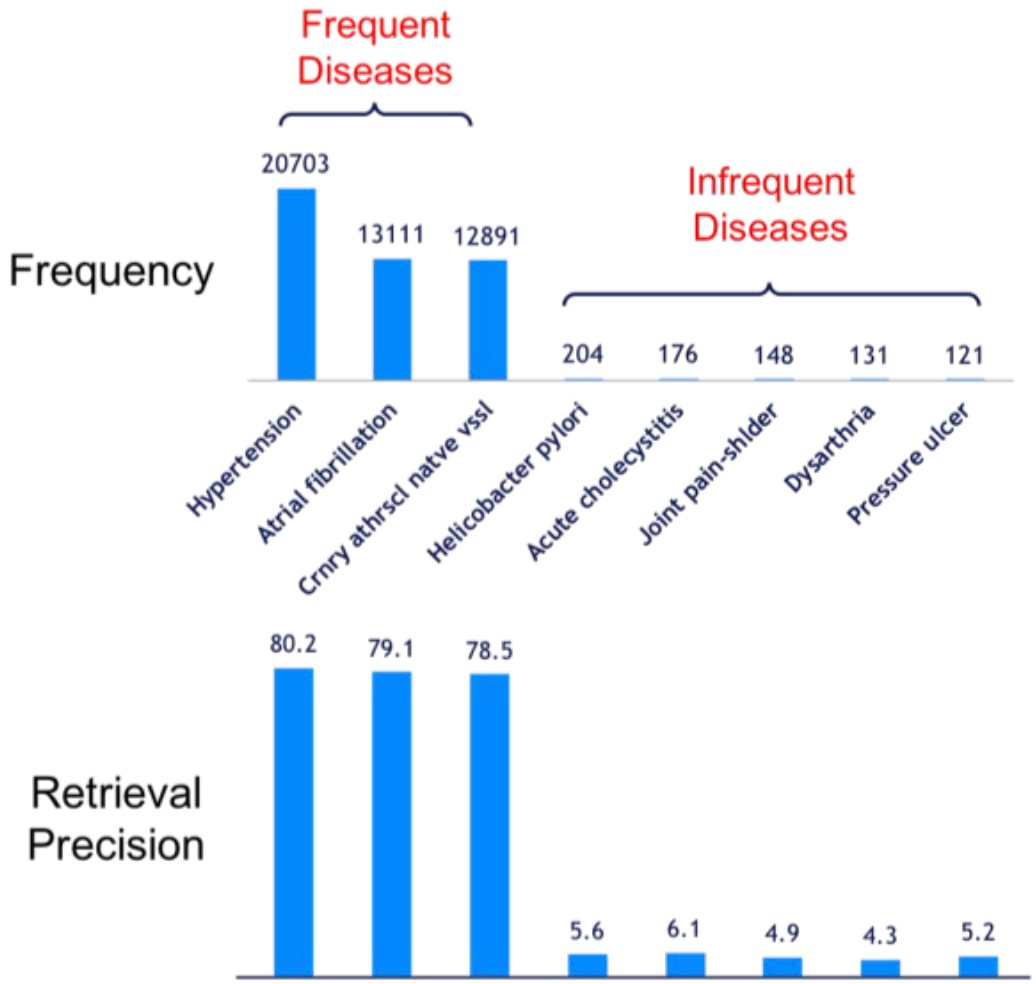
$$s.t. \quad \forall (x,y) \in D, \|Ax - Ay\|^2 \geq 1$$

Dissimilar Pairs

Power Law Distribution of Diseases



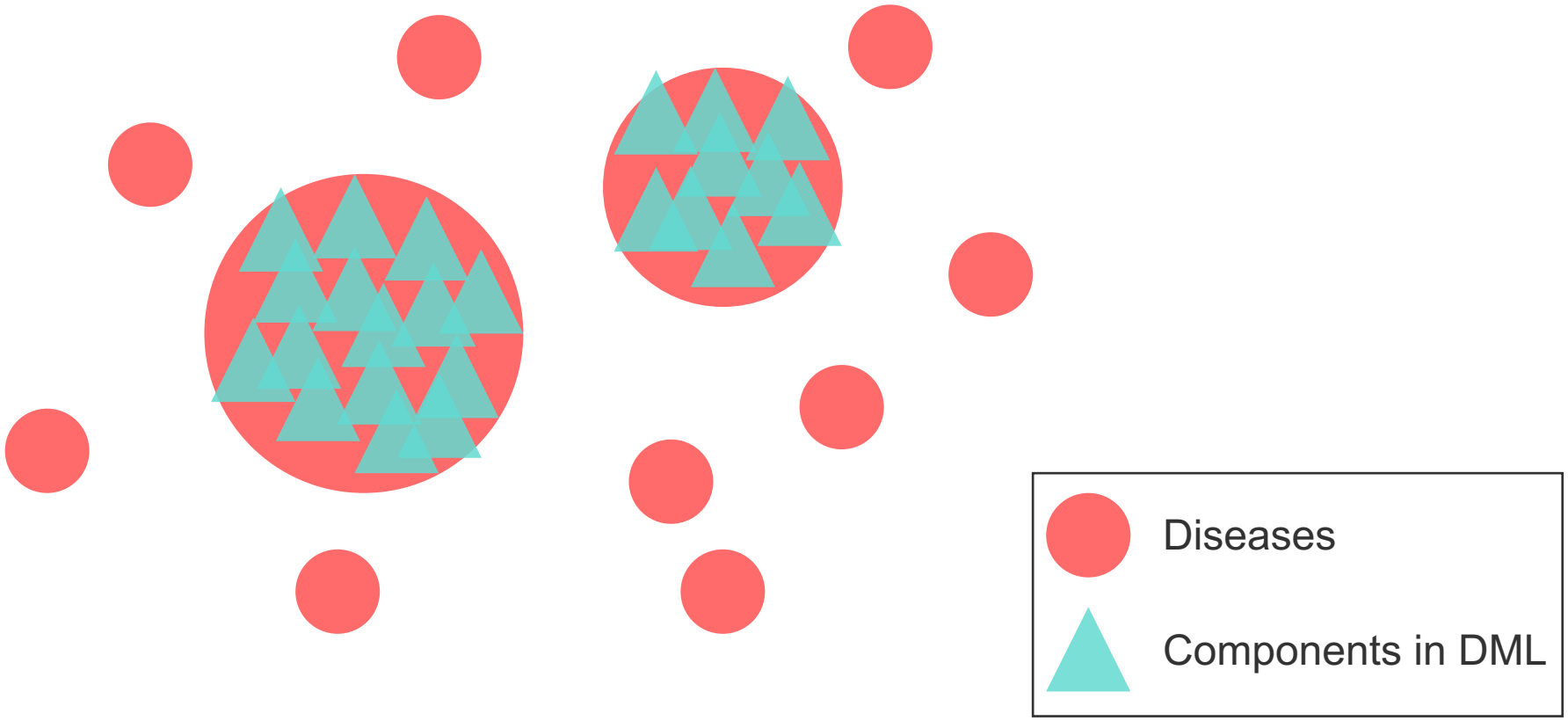
DML is Biased to Frequent Diseases



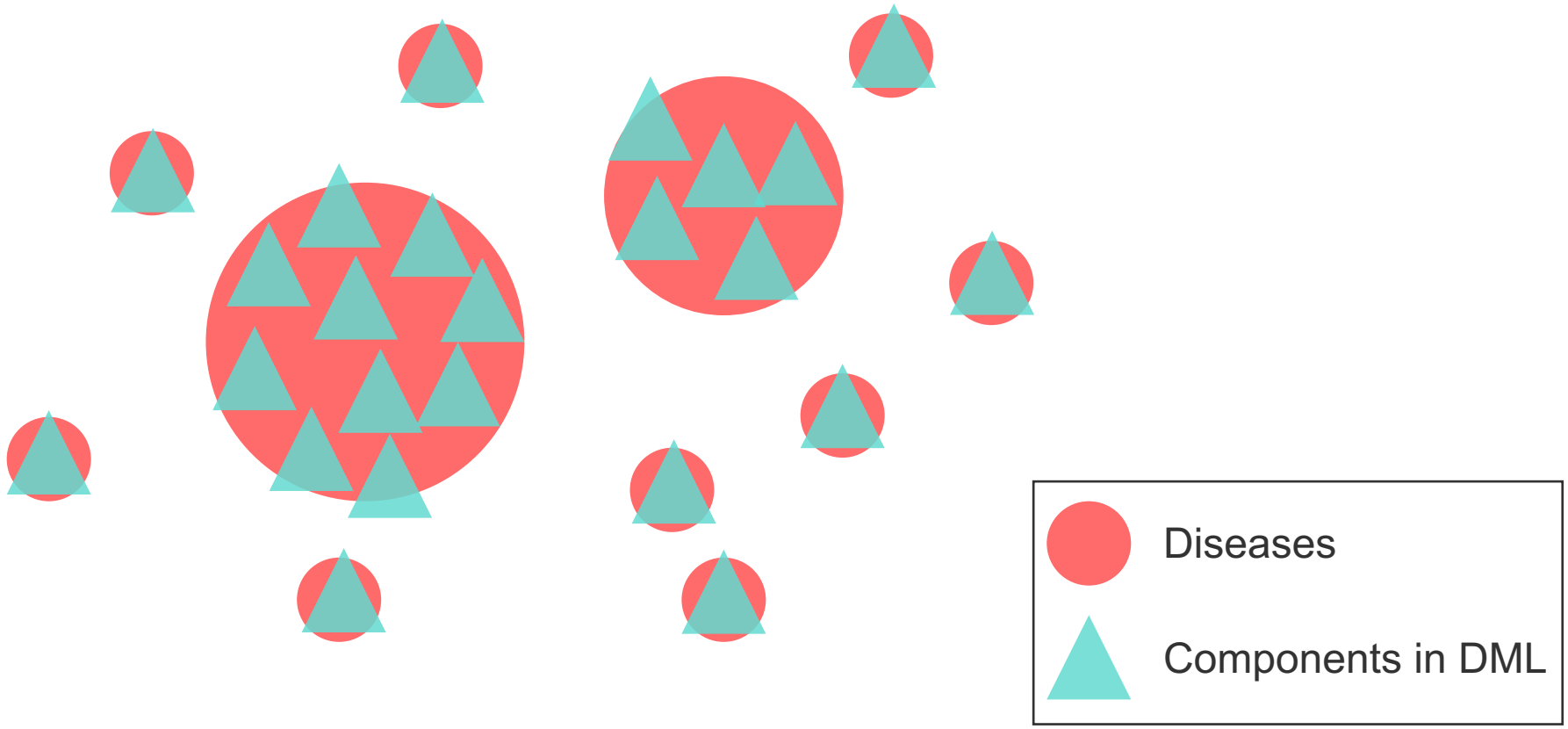
Infrequent Diseases Are Not Neglectable

- Many infrequent diseases are life-threatening
  - “Flail chest is a life-threatening medical condition that occurs when a segment of the rib cage breaks due to trauma and becomes detached from the rest of the chest wall.”
  - Flail chest is infrequent, occurring only in 0.1% MIMIC-III patients
- The total amount of infrequent disease is very large
  - In MIMIC-III, the number of infrequent diseases (with < 200 patients) is 2458, accounting for 86.8% of all diseases
  - The number of patients with infrequent diseases are 36278, accounting for 78.0% of all patients

Why DML is Biased to Frequent Diseases



“Diversify” Components to Capture Infrequent Diseases



Encourage Near-Orthogonality among Components

- Vector a_i and a_j are near-orthogonal if $a_i \cdot a_j \approx 0$, $\|a_i\|_2 \approx 1$, $\|a_j\|_2 \approx 1$
- A set of vectors are near-orthogonal if the Gram matrix is near to the identity matrix

$$\begin{bmatrix} a_1 \cdot a_1 & a_1 \cdot a_2 & a_1 \cdot a_3 \\ a_2 \cdot a_1 & a_2 \cdot a_2 & a_2 \cdot a_3 \\ a_3 \cdot a_1 & a_3 \cdot a_2 & a_3 \cdot a_3 \end{bmatrix} \approx \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

- How to measure the nearness between two matrices?

Diversity-Promoting DML

$$\min_A \sum_{(x,y)\in S} \|Ax - Ay\|^2 + \lambda R(A)$$

$$s.t. \quad \forall (x,y) \in D, \|Ax - Ay\|^2 \geq 1$$

- Bregman divergence between Gram matrix G and identity matrix I:

$$R(A) = D_\phi\left(AA^{\mathrm{T}}, I\right)$$

  - Under von Neumann divergence

$$R_{vn}(A) = \mathrm{tr}\left((AA^{\mathrm{T}})\log(AA^{\mathrm{T}}) - AA^{\mathrm{T}}\right) + k$$

  - Under Log-Det divergence

$$R_{ld}(A) = \mathrm{tr}\left(AA^{\mathrm{T}}\right) - \mathrm{logdet}\left(AA^{\mathrm{T}}\right) - k$$

Summary of Algorithm

- Convex relaxation
  - Using semidefinite programming relaxation to convexify the data-dependent loss
  - Using the properties of eigenvalues to convexify the regularizers
- Proximal gradient descent
  - Eliminating constraints on “dissimilar” pairs
  - Deriving proximal operators of the von Neumann and LogDet regularizers

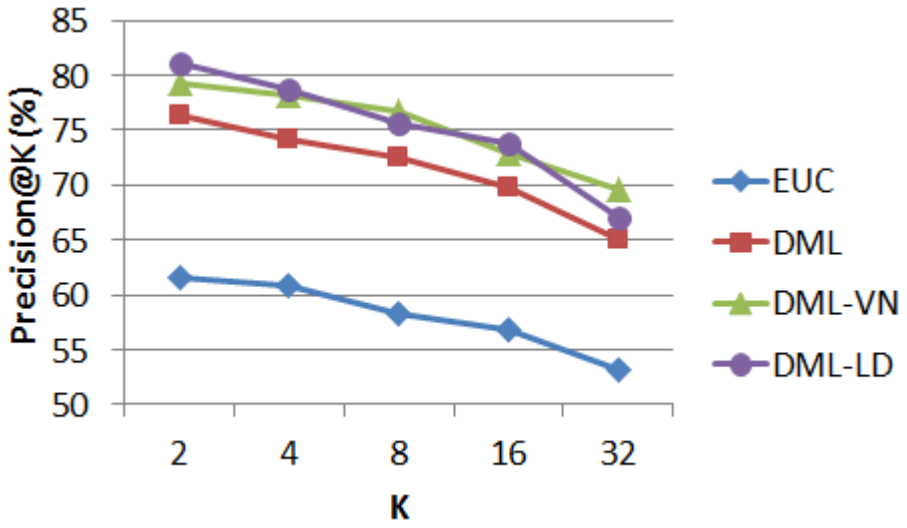
Experiments: Feature Extraction

- Demographics
  - Gender, age
- Clinical notes
  - 5000-dimensional bag-of-words representation
  - 300-dimensional Word2Vec representation
- Lab tests
  - 635 test items
  - Zero-order, first-order, second–order time series features
- Dimensionality reduction
  - Reduce the feature dimension from 7207 to 1000 using principle component analysis

Experimental Setup

- Determine whether two patients are similar or dissimilar based on their diagnostic results (a set of diseases)
  - Given the disease set S_i and S_j of patient i and j, measure their overlap score $o(S_i, S_j)$
  - Determine similarity/dissimilarity label: if $o(S_i, S_j)$ is greater than a threshold c, then patient i and j are regarded as similar; otherwise, dissimilar
  - Training data: 0.1 million similar pairs and 0.1 million dissimilar pairs
- Application of the learned distance metric: similar-patient retrieval
  - Given the query patient, compute its distance with patients in the database using the learned distance metric
  - Use precision@K to evaluate the retrieval performance: among the top K retrieved patients, how many are similar to the query patient

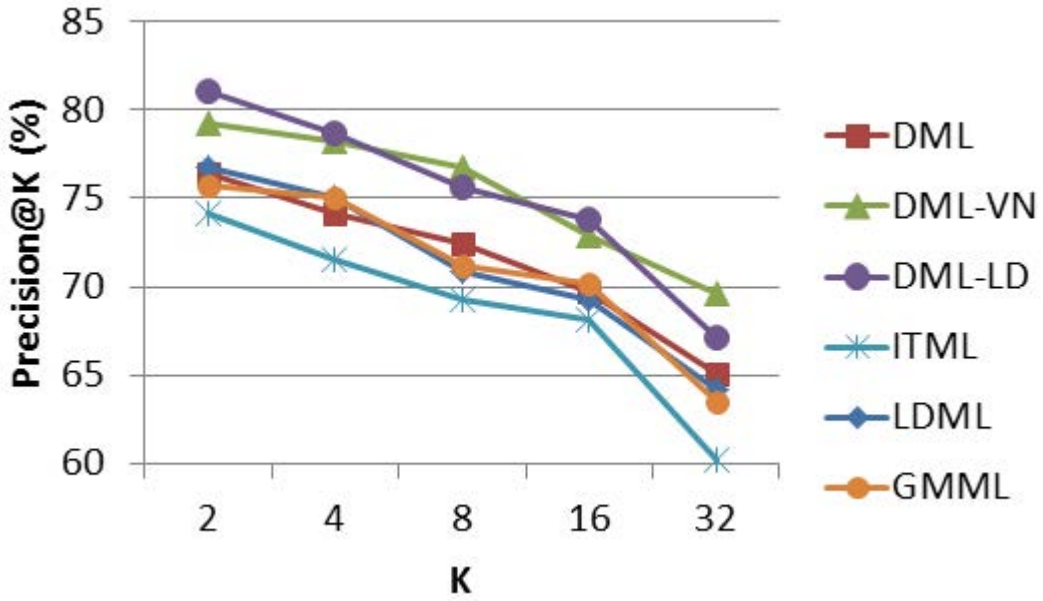
Similar-Patient Retrieval Results



- EUC: Euclidean distance
- DML: Distance metric learning
- DML-VN: DML with von Neumann divergence regularization
- DML-LD: DML with Log-Det divergence regularization

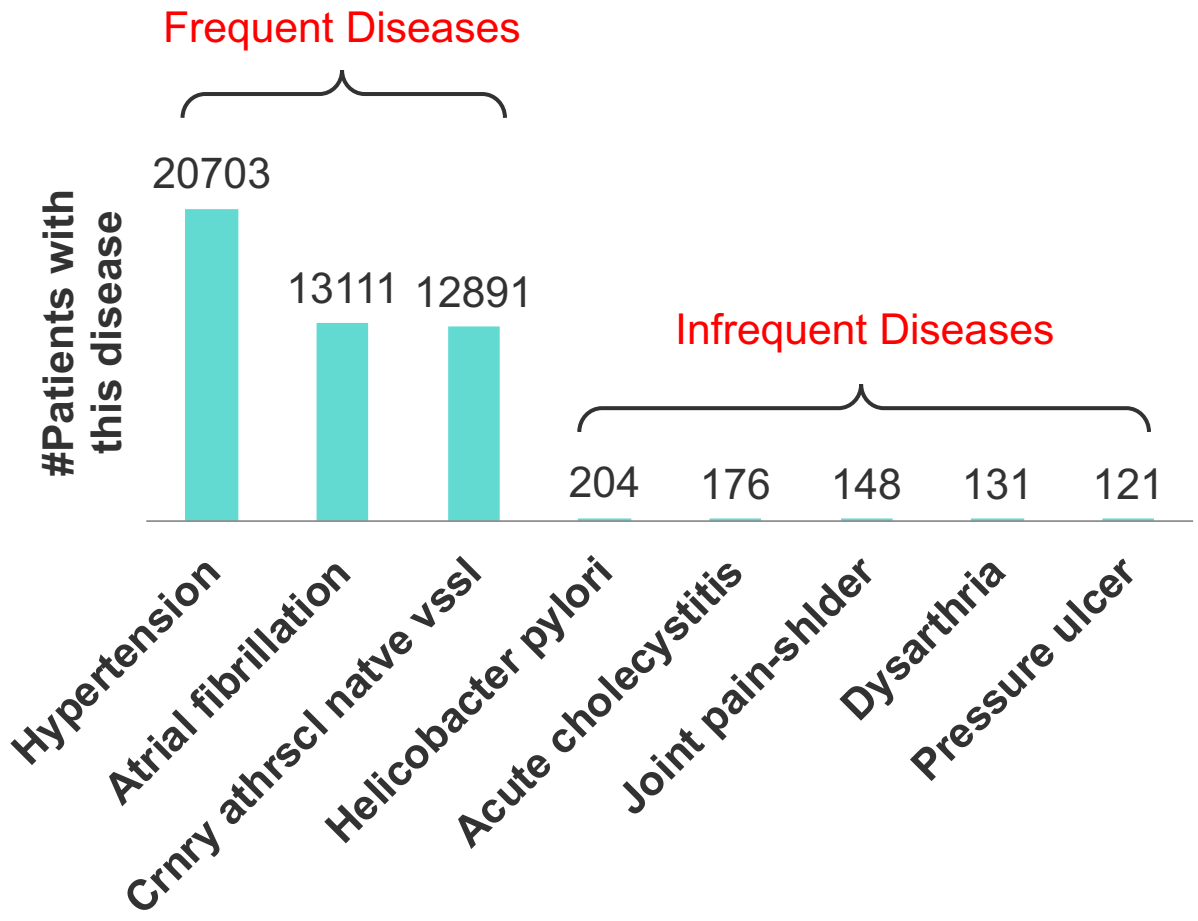
- Compared with the vanilla Euclidean distance, DML dramatically improves retrieval precision.
- Adding diversity-promoting regularization significantly improves the performance of DML.

Comparison with More Baseline Methods

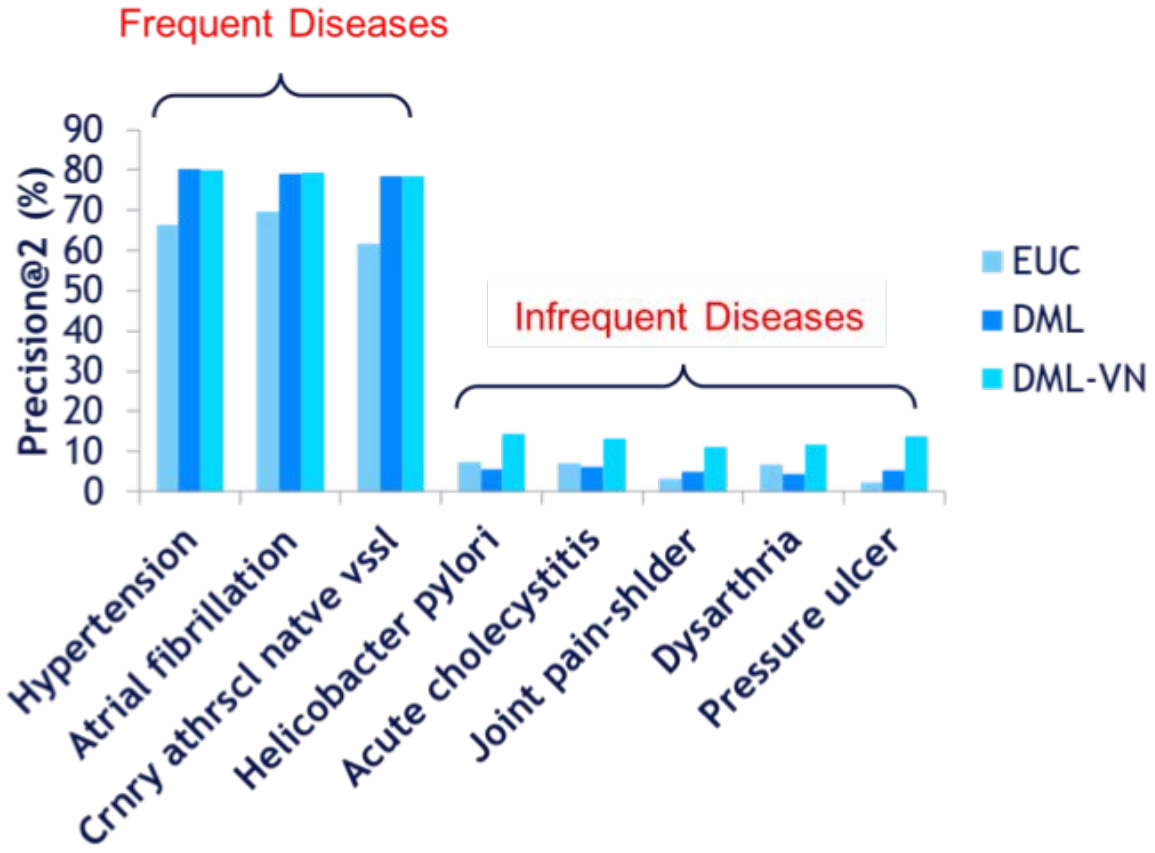


- ITML: Information theoretical metric learning (David et al., 2007)
- LDML: Logistic discriminant metric learning (Guillaumin et al., 2009)
- GMML: Geometric mean metric learning (Zadeh et al., 2016)

Performance on Infrequent Diseases



Performance on Infrequent Diseases (Cont'd)



- DML-VN (promoting diversity) significantly improves the precision on infrequent diseases without sacrificing the performance on frequent diseases

Supports clinical decisions at all points of care

Admission → **Diagnosis** → **Treatment** → **Discharge**

- Extracts critical patient medical information to speed up clinical preview

- lists alternative scenarios with probability score and reasoning to reduce error.

- Automates ICD coding to simplify reporting
- Predicts ICU patient mortality rate to assist care quality reporting

Information extraction

Diagnosis based on labs

Similar-patient retrieval

CT Lung-nodule detection

X-ray report generation

ECG-based diagnosis

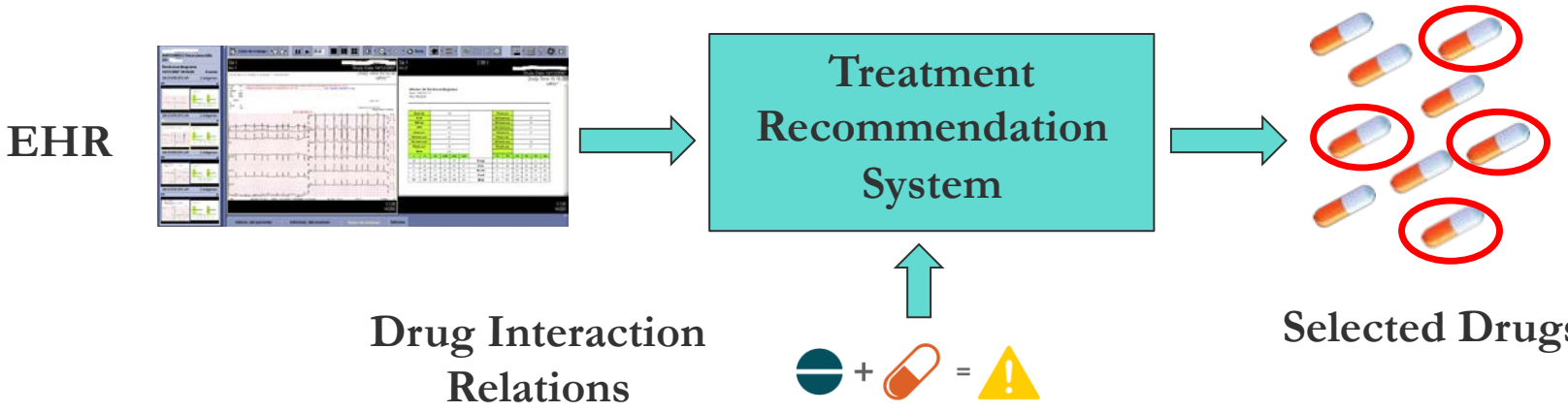
Treatment recommendation

ICD code filling

Mortality prediction

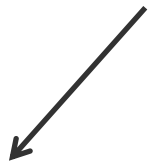
Treatment Recommendation

- Based on the EHR of a patient, select a subset of drugs that
  - Can effectively treat the conditions/ diseases of the patient
  - Discourage adverse interactions
  - Encourage beneficial interactions



Multiple Diagnosis for Each Patient

PATIENT_ID	DISEASE CODE
109	33829
109	78900
109	79092
112	53100
112	41071
112	2859
112	41401
112	725
113	1915
113	3314
113	53081
114	41401
114	4111
114	48283
114	2859
114	2720
114	3051
115	1940
115	1977
115	2553
115	4240
115	5845



Each patient is diagnosed with multiple diseases/conditions

Multiple Drug Prescriptions for Each Patient

Each patient is prescribed with multiple drugs

PATIENT_ID	DRUG	DOSE_VAL_RX	DOSE_UNIT_RX	PROD_STRENGTH	STARTDATE	ENDDATE
6	Tacrolimus	2	mg	1mg Capsule	6/11/2175 0:00	6/12/2175 0:00
6	Warfarin	5	mg	5mg Tablet	6/11/2175 0:00	6/12/2175 0:00
6	Heparin Sodium	25,000	UNIT	25,000 unit Premix Bag	6/11/2175 0:00	6/12/2175 0:00
6	D5W	250	ml	HEPARIN BASE	6/11/2175 0:00	6/12/2175 0:00
6	Furosemide	20	mg	20mg Tablet	6/11/2175 0:00	6/12/2175 0:00
6	Warfarin	1	dose	Check with MD for Dose	6/11/2175 0:00	6/15/2175 0:00
6	Heparin Sodium	25,000	UNIT	25,000 unit Premix Bag	6/12/2175 0:00	6/12/2175 0:00
6	D5W	250	ml	HEPARIN BASE	6/12/2175 0:00	6/12/2175 0:00
6	Heparin Sodium	25,000	UNIT	25,000 unit Premix Bag	6/12/2175 0:00	6/13/2175 0:00
6	Warfarin	2	mg	2mg Tab	6/12/2175 0:00	6/13/2175 0:00
6	D5W	250	ml	HEPARIN BASE	6/12/2175 0:00	6/13/2175 0:00
6	Tacrolimus	5	mg	5mg Capsule	6/12/2175 0:00	6/13/2175 0:00
6	Tacrolimus	2	mg	1mg Capsule	6/12/2175 0:00	6/13/2175 0:00
13	Heparin Sodium	25000	UNIT	25,000 unit Premix Bag	1/8/2167 0:00	1/9/2167 0:00
13	Nitroglycerin	100	mg	100MG/250 PM	1/8/2167 0:00	1/9/2167 0:00
13	Docusate Sodium	100	mg	100MG CAP	1/8/2167 0:00	1/9/2167 0:00
13	Atropine Sulfate	0.5	mg	1MG/10ML SYRINGE	1/8/2167 0:00	1/9/2167 0:00
13	Zolpidem Tartrate	5	mg	5mg Tab	1/8/2167 0:00	1/12/2167 0:00
13	Midazolam HCl	2	mg	2MG/2ML VIAL	1/9/2167 0:00	1/9/2167 0:00
13	Nitroglycerin SL	0.3	mg	0.3MG SL TAB	1/9/2167 0:00	1/9/2167 0:00
13	Lorazepam	1	mg	2MG/ML SYR	1/9/2167 0:00	1/9/2167 0:00
13	Magnesium Sulfate	2	gm	1gm/2ml vial	1/9/2167 0:00	1/9/2167 0:00

Treatment Recommendation as a Combinatorial Subset Selection Problem

- Formulation: a combinatorial subset selection problem with relational constraints

$$f: x \rightarrow S \qquad S \subseteq T = \{1, \cdots, t\}$$

EHR — Recommended drugs — Number of candidate drugs

- Probabilistic modeling
  - Modeling: define conditional probability $p(S|x)$
  - Training: maximize the conditional likelihood
  - Inference: $f(x) = \text{argmin}_S\, p(S|x)$

Determinantal Point Process (DPP)

- The DPP defines a probability distribution over subsets, with tractable partition function (Kulesza and Taskar, 2012)
- Given a set of items $\{y_i\}_{i=1}^{t}$, DPP defines the probability over a subset $S \subseteq T = \{1, \cdots, t\}$ as

$$p(S|x) = \frac{\det(L_S)}{\det(L + I)}$$

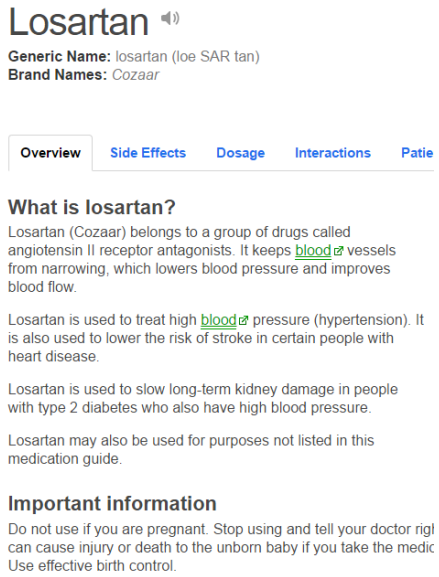
  - L is a $t \times t$ matrix where $L_{ij} = k(y_i, y_j)$
  - L_S is a sub-matrix of L indexed by elements in S
  - The partition function $\det(L + I)$ is computable in polynomial time

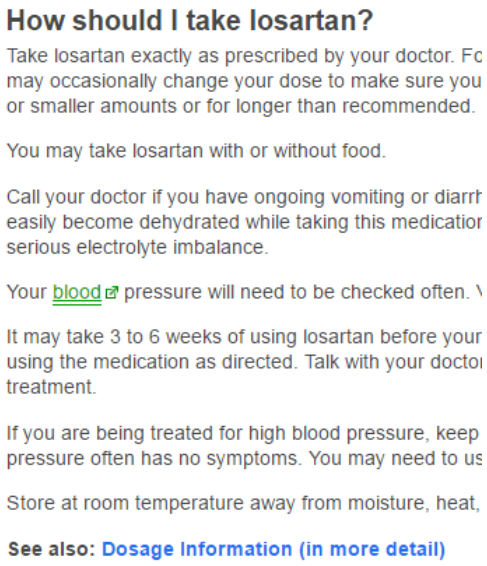
Treatment Recommendation based on Conditional DPP

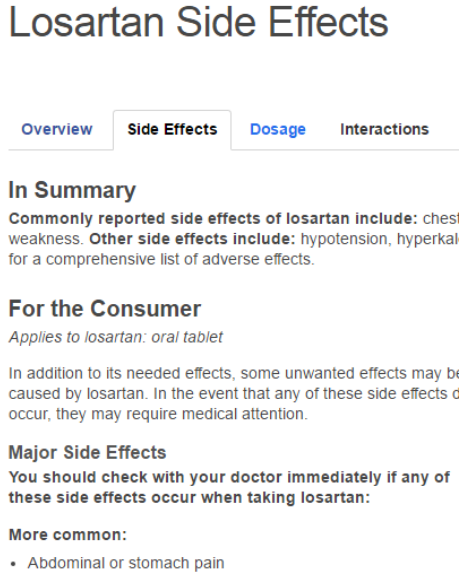
- Use DPP to define $p(S|x)$
- Model the correlation between drugs
  - Represent drugs
  - Define kernel function over the representations of drugs
- Model the dependency between drug and EHR
  - Define a dependency score function
  - Build the score function into drug-drug kernel function

Drug Representation

- Many web articles contain rich information of drugs







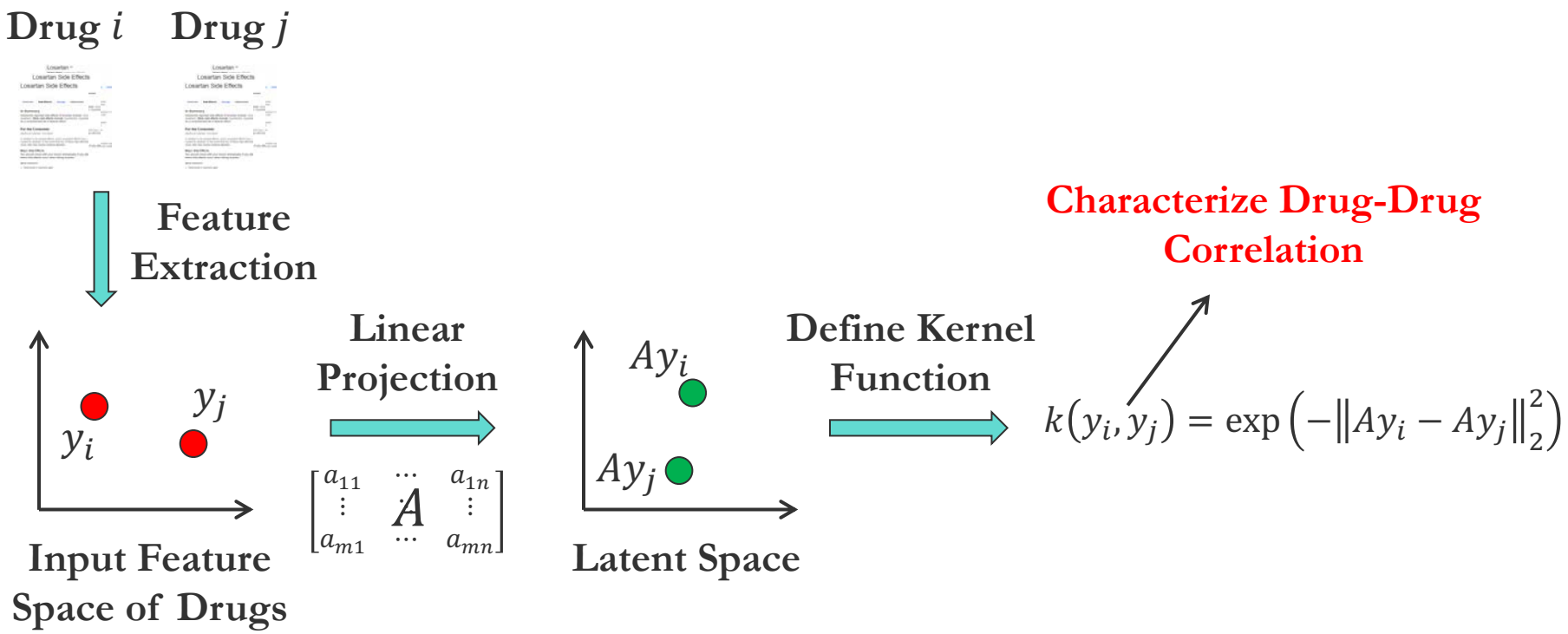
What conditions/diseases the drug can treat

How to take the drug

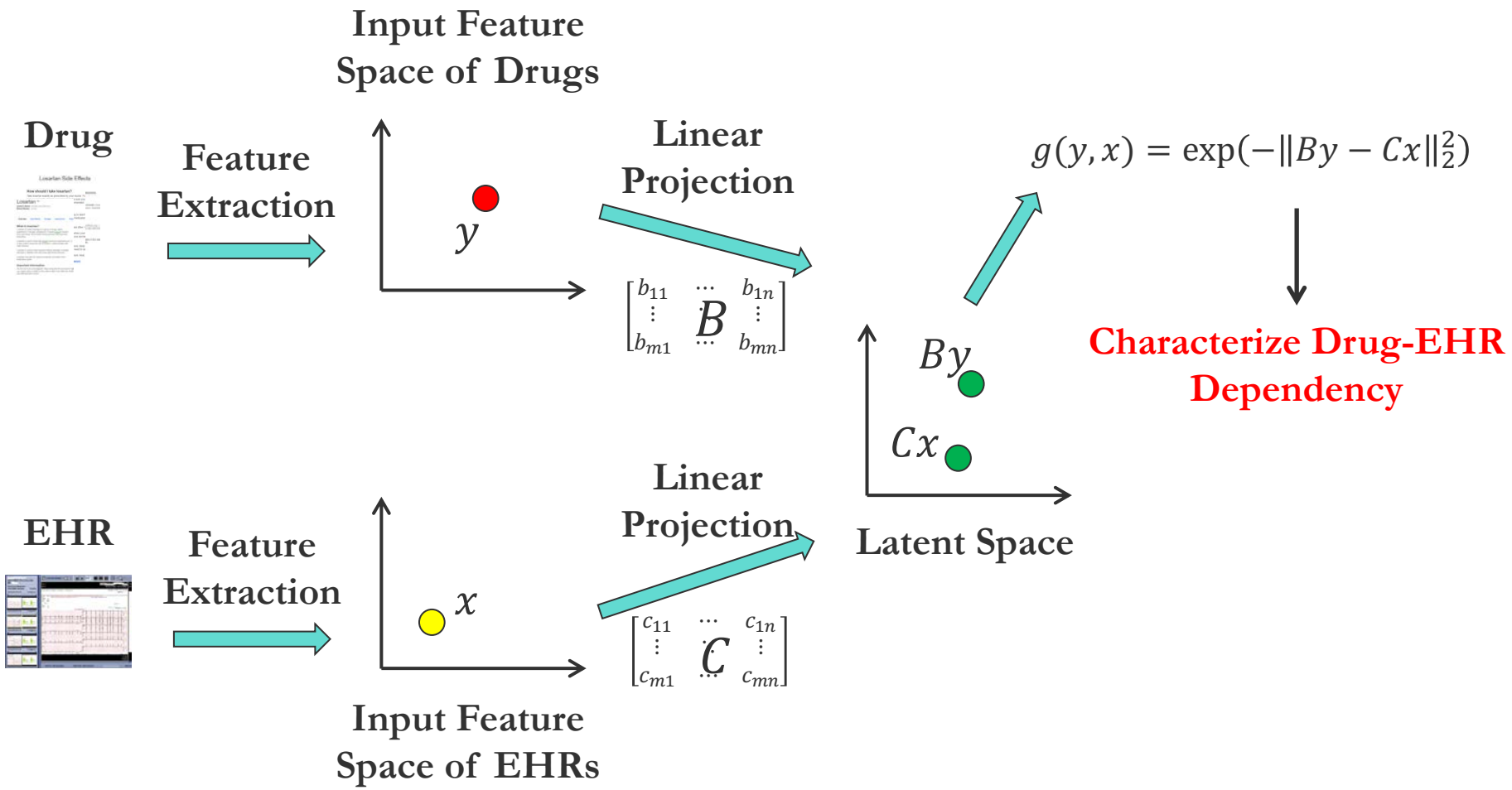
Side Effect

- Use these articles to represent drugs

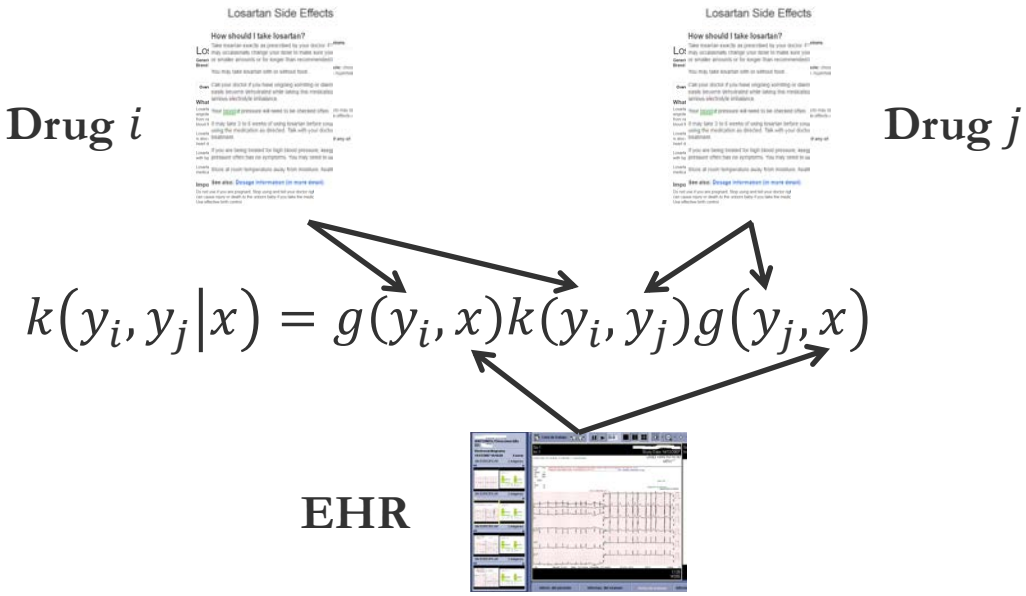
Characterize Correlation between Drugs



Characterize Dependency between Drug and EHR



Simultaneously Characterize Drug-Drug Correlation and Drug-EHR Dependency



A conditional DPP: $p(S|x) = \frac{\det(L_S(x; A, B, C))}{\det(L(x; A, B, C) + I)}$

where $L_{ij}(x) = g(y_i, x)k(y_i, y_j)g(y_j, x) = \exp\left(-\|By_i - Cx\|_2^2 - \|Ay_i - Ay_j\|_2^2 - \|By_j - Cx\|_2^2\right)$

Parameter Learning

- Maximum Likelihood Estimator
  - N patients, each has an EHR x and a set of prescribed drugs S_i

$$\max_{A,B,C} \quad L(\{(x_i, S_i)\}_{i=1}^{N})$$

$$L\left(\{(x_i, S_i)\}_{i=1}^{N}\right) = \prod_{i=1}^{N} p(S_i|x_i) = \prod_{i=1}^{N} \frac{\det(L_{S_i}(x_i; A, B, C))}{\det(L(x_i; A, B, C) + I)}$$

Rich Interactions between Drugs

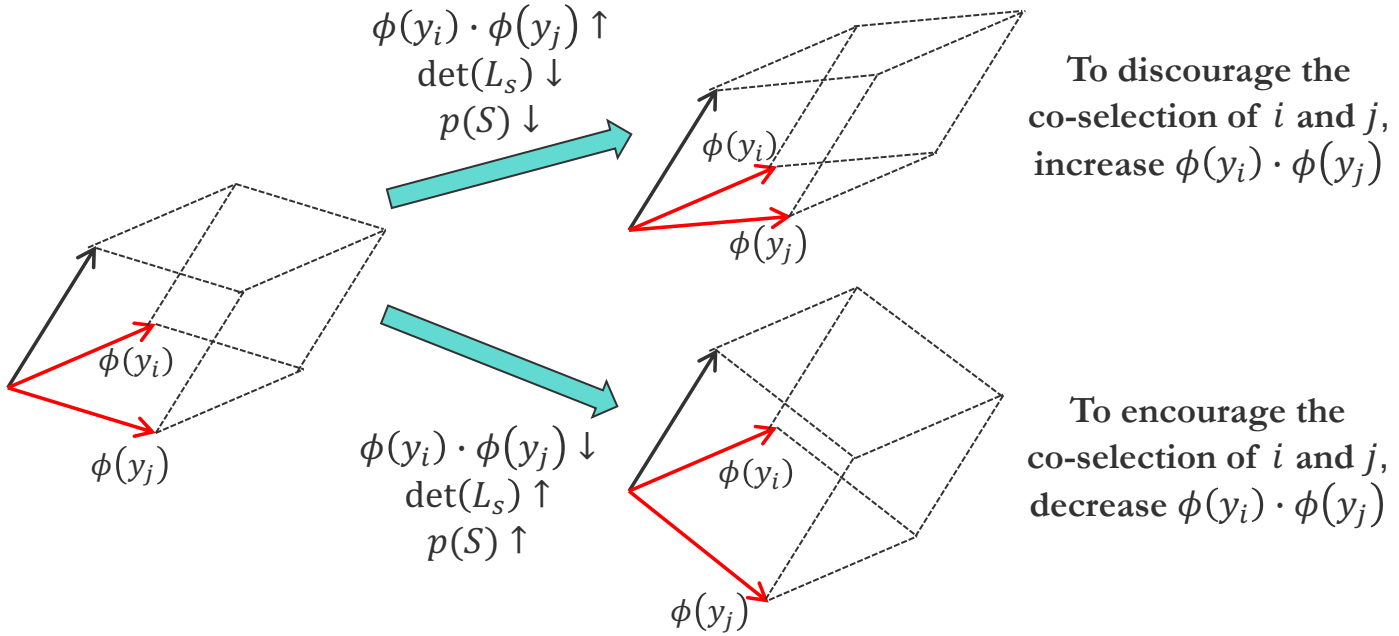
- When used together, one drug can affect the activity of another in different ways:
  - Antagonism (adverse interaction): two drugs may lead to a decrease in the beneficial effects and bring in adverse effects
    - E.g. *Antacids* can prevent *antibiotics* from being absorbed into the blood stream
    - Antagonistic drugs are discouraged to be used together
  - Synergy (beneficial interaction): two drugs work together to cause a positive effect greater than the sum of its parts
    - E.g. When mixed with *ibuprofen*, *codeine* is more effective in relieving pain
    - Synergic drugs are preferred to be used together

En-/Dis-couraging Co-selection

$$p(S) \propto \det(L_s) = \begin{vmatrix} \phi(y_1)\cdot\phi(y_1) & \cdots & \phi(y_1)\cdot\phi(y_S) \\ \vdots & \ddots & \vdots \\ \phi(y_S)\cdot\phi(y_1) & \cdots & \phi(y_S)\cdot\phi(y_S) \end{vmatrix}$$

↑

Volume of the parallelepiped formed by $\{\phi(y_i)\}_{i=1}^{|S|}$



$$\max_{A,B,C} \quad L(\{(x_i, S_i)\}_{i=1}^{N}) + \lambda\left(\sum_{(i,j)\in AR} k(y_i, y_j) + \sum_{(i,j)\in SR} -k(y_i, y_j)\right)$$

↑ Antagonism Relation ↑ Synergy Relation

Algorithm for Parameter Learning

- Stochastic gradient descent
  - Log-likelihood $\log L\left(\{(x_i, S_i)\}_{i=1}^N\right) = \sum_{i=1}^N \left(\text{logdet}(L_{S_i}(x_i; A, B, C)) - \text{logdet}(L(x_i; A, B, C) + I)\right)$
  - Major bottleneck of computing gradient

$$\frac{\partial \text{logdet}(L(x_i; A, B, C) + I)}{\partial L(x_i; A, B, C)} = (L(x_i; A, B, C) + I)^{-1} \longleftarrow \textbf{Matrix inverse, cubic complexity}$$

- Method of inducing points (Silverman, 1985)
  - Introduce a set of inducing point $\{(u_k)\}_{k=1}^r$ where $(r \ll t)$
  - Reparameterize the drug-drug kernel

$$k(y_i, y_j) = v_i^T U v_j$$

where $v_i \in \mathrm{R}^r$ and $v_{ik} = \exp(-\|Ay_i - Au_k\|_2^2)$; $U \in \mathrm{R}^{r \times r}$ and $U_{kl} = \exp(-\|Au_k - Au_l\|_2^2)$

  - Compute the low-rank kernel matrix $L(x; A, B, C) = V^T U V$

where $V \in \mathrm{R}^{r \times t}$ and the ith column of V is $g(y_i, x)v_i$ with $g(y_i, x) = \exp(-\|By_i - Cx\|_2^2)$

Drug Recommendation: Mode Inference

- Given the input features x, the recommended drug set is:

$$S^* = \text{argmax}_{S \subseteq T} \ \text{logdet}(L_S(x))$$

- Exponentially many subsets; NP hard
- Approximate inference (Gillenwater el al., 2012)
  - Continuous relaxation

$$F(\boldsymbol{x}) = \log \sum_{S \subseteq T} \prod_{i \in S} x_i \prod_{i \notin S} (1 - x_i) \det(L_S(x)) = \text{logdet}(\text{diag}(\boldsymbol{x})(L - I) + I) \ \text{ where } x \in [0,1]^t$$

  - Find the optimal solution $\boldsymbol{x}^*$ of $F(\boldsymbol{x})$ using gradient method

$$\frac{\partial F(x)}{\partial x_i} = \text{tr}((\text{diag}(\boldsymbol{x})(L - I) + I)^{-1}(L - I)_i)$$

    - $(\text{diag}(\boldsymbol{x})(L - I) + I)^{-1}$ can be efficiently computed using the Sherman–Morrison–Woodbury formula since L is low-rank
    - $(L - I)_i$ denotes the matrix obtained by zeroing all except the i-th row of $L - I$
  - Rounding: Drug i is selected if $\text{round}(x_i) = 1$ and is not selected if $\text{round}(x_i) = 0$

Summary of Algorithm

- Training
  - Using the inducing point method to perform low-rank re-parameterization of the kernel matrix
  - Using Sherman–Morrison–Woodbury formula to compute matrix inverse
  - Using stochastic gradient method to learn model parameters
- Inference
  - Relaxing the 0-1 programming problem into a continuous one
  - Finding the optimal solution of the relaxed problem
  - Rounding the continuous solution to $\{0,1\}$

Feature Extraction from MIMIC-III

- Diagnostic results
  - 2833 diseases
- Demographics
  - Gender, age
- Clinical notes
  - 5000-dimensional bag-of-words representation
  - 300-dimensional Word2Vec representation
- Lab tests
  - 635 test items
  - Zero, first, second – order time series features
- Total feature dimension: 7207
- 57461 EHRs, 40000 for training, 17461 for testing

Drug Representation and Relations

- 1687 drugs
- Drug representation
  - For each drug, crawl its “profile” articles from Drugs.com, including *overview, side effects, dosage, professional*
  - 5000-dimensional bag-of-words representation
    - Words are filtered using Unified Medical Language System (UMLS)
    - Weighted using TF-IDF
  - 300-dimensional Word2Vec representation
- Drug relation
  - 8106 antagonism relations obtained from Drugs.com
  - 1372 synergy relations obtained from Drugs.com

Summary of Experimental Settings

$$\max_{A,B,C} \; L\left(\{(x_i, S_i)\}_{i=1}^{N}\right) + \lambda\left(\sum_{(i,j)\in AR} k(y_i, y_j) \; + \sum_{(i,j)\in SR} -k(y_i, y_j)\right)$$

$$p(S|x) = \frac{|L_S(x; A, B, C)|}{|L(x; A, B, C) + I|} \qquad L_{ij}(x) = \exp\left(-\frac{1}{\gamma_2}\|By_i - Cx\|_2^2 - \frac{1}{\gamma_1}\left\|Ay_i - Ay_j\right\|_2^2 - \frac{1}{\gamma_2}\left\|By_j - Cx\right\|_2^2\right)$$

N	# Training data	40,000
|AR|	# Antagonism relations	8,106
|SR|	# Synergy relations	1,372
Dim(x)	Dim. of EHR features	10,040
Dim(y)	Dim. of drug features	5,300
Size(L)	Size of kernel matrix	1687 x 1687 (# Drugs)
Size(A)	Size of projection matrix	500 x 5300
Size(B)	Size of projection matrix	500 x 5300
Size(C)	Size of projection matrix	500 x 10040

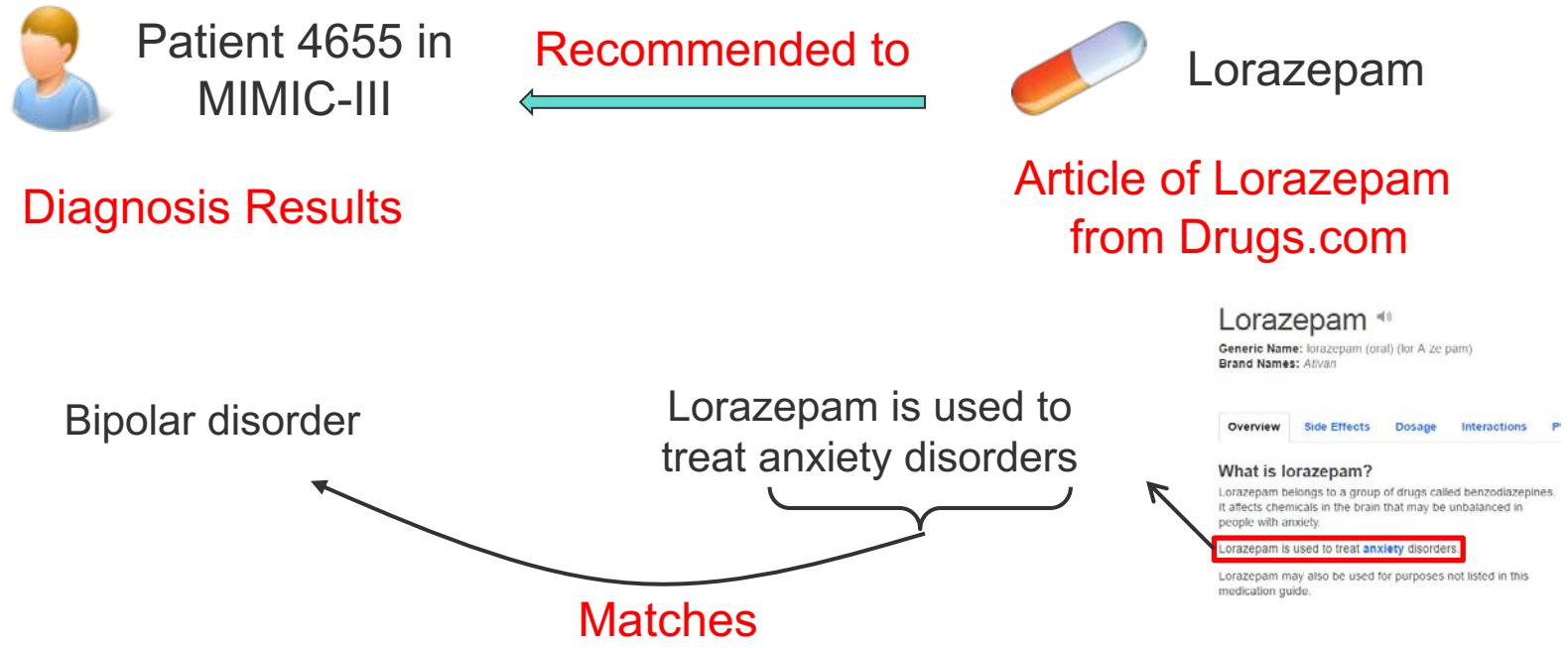
Dim. of latent space

Recommendation Performance

Methods			F1(%)
Baselines	Logistic Regression		55.8
	Neural Network		57.2
	Structured Energy Network (Belanger and McCallum, 2016)		59.1
Ours	Using Drug Documents	Using Drug Interactions	
1	No	No	62.9
2	Yes	No	67.5
3	Yes	Yes	71.4

- Compare baselines and 1: Conditional DPP performs better than other subset selection methods
- Compare 1 and 2: it is very helpful to incorporate external medical articles to enrich the representation of drugs
- Compare 2 and 3: leveraging drug interaction relations can greatly improve the quality of recommendation

Example: Effect of Incorporating Medical Articles for Drug Representation



- Without incorporating external articles, the system didn't recommend Lorazepam to this patient.

Example: Effect of Incorporating Drug Interaction Relations

Patient 3026 in MIMIC-III

Recommended drugs before incorporating interaction relations

Haloperidol

Ketoconazole

Recommended drugs after incorporating interaction relations

Haloperidol

Adverse interaction between Haloperidol and Ketoconazole

Using haloperidol together with ketoconazole can increase the risk of an irregular heart rhythm that may be serious and potentially life-threatening

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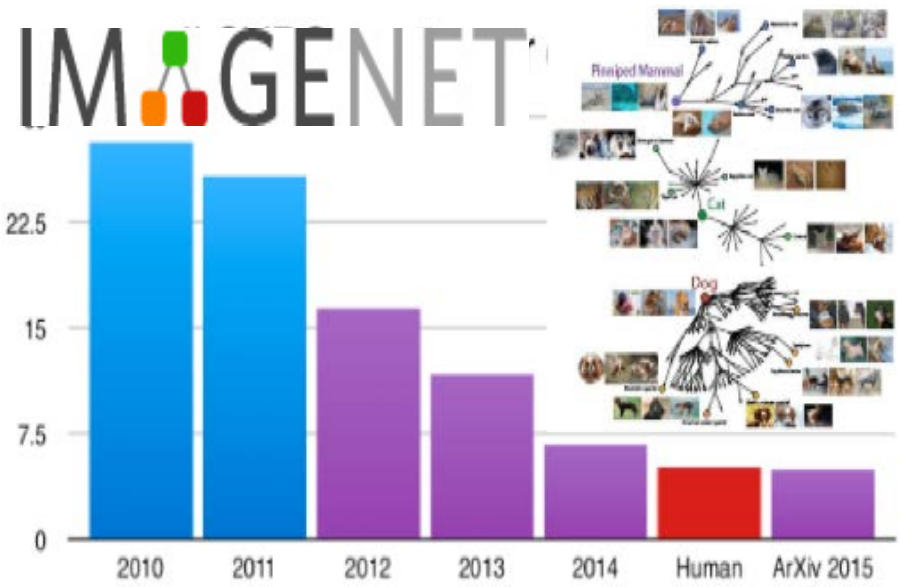
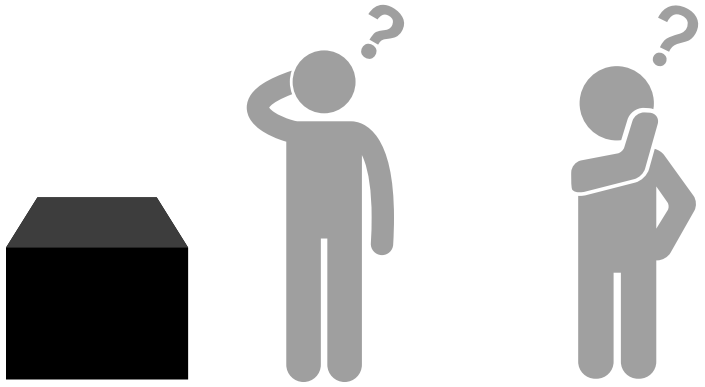
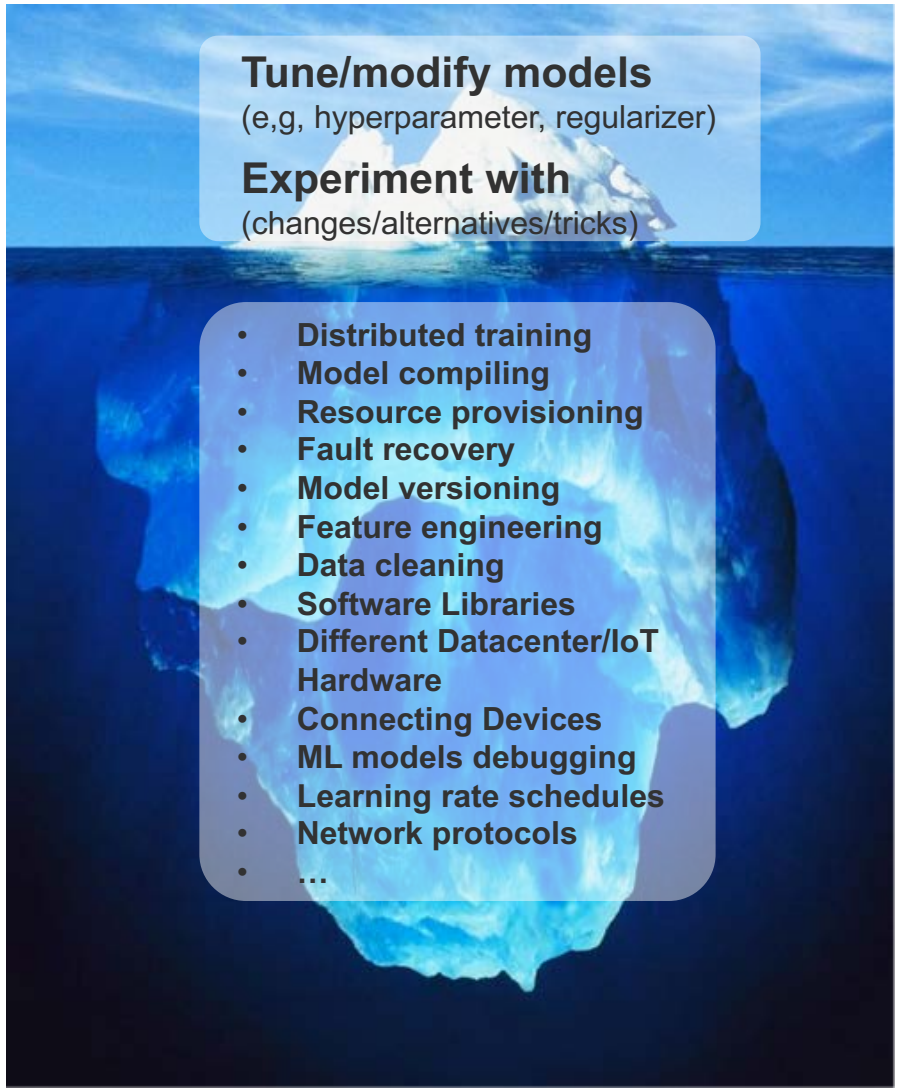
Toward New System for Automatic ML

AI as we see it now …

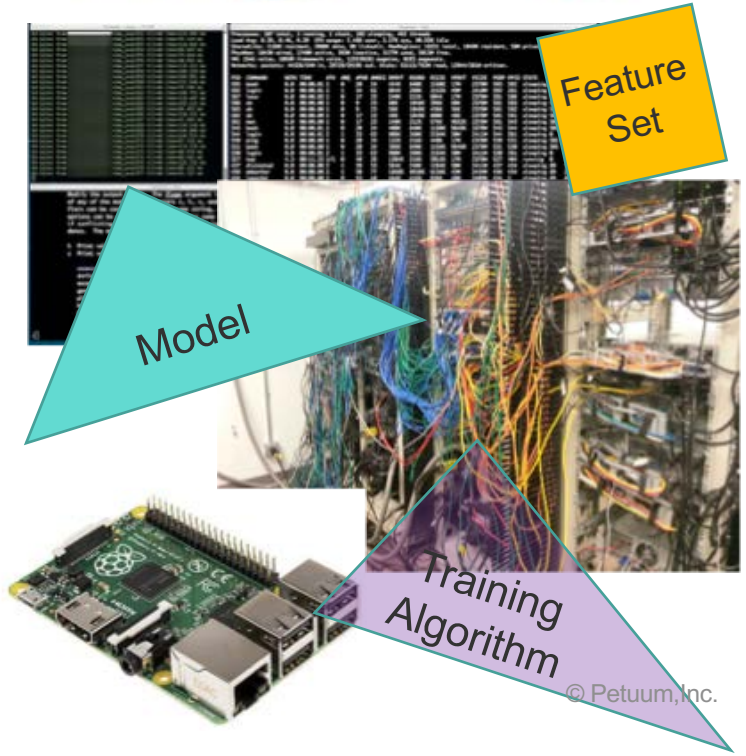




Petuum Simplifies Model/Algorithm Development



DIY "tuning"
("tuning" AND all else)



Petuum Simplifies Model/Algorithm Development

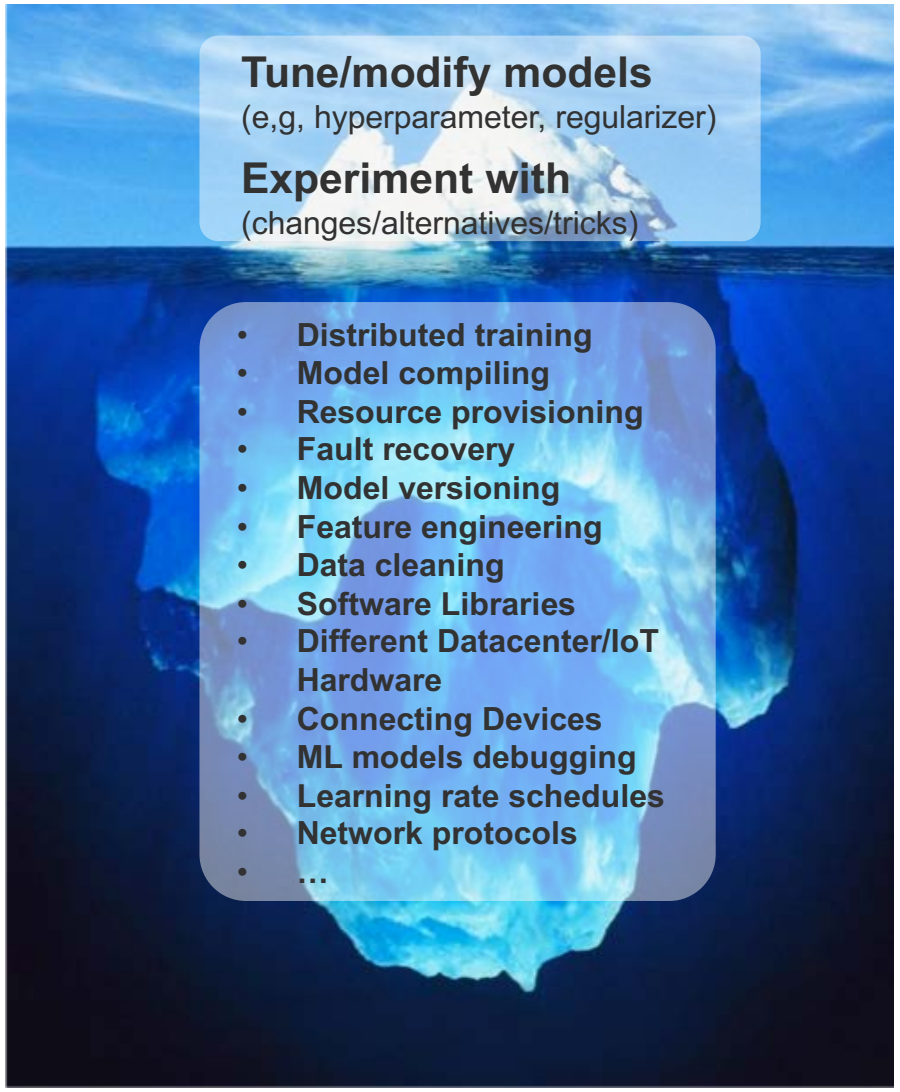
Petuum dev
(nothing but, e.g., tuning)

ML Building Blocks

ML Engine

Data Machine

PetuumOS



DIY "tuning"
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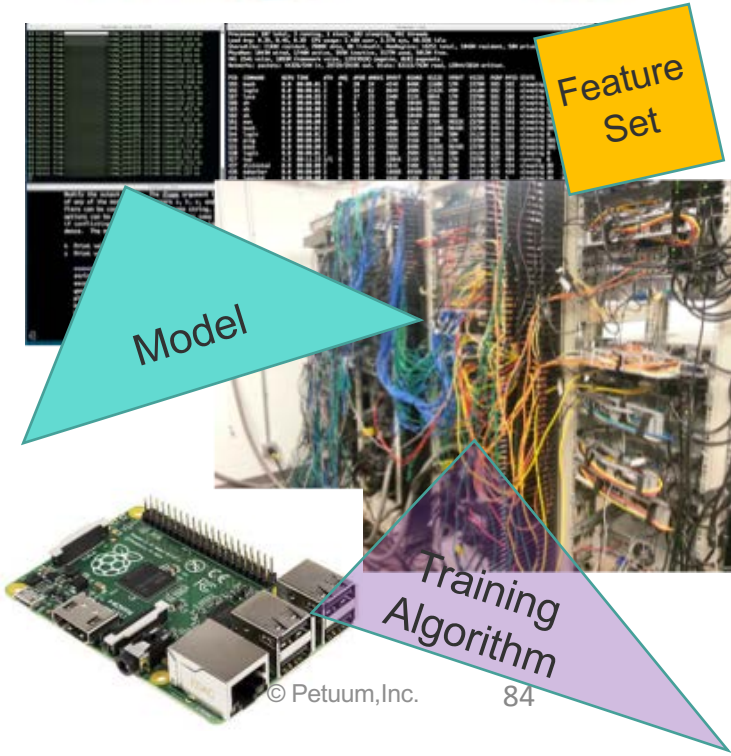
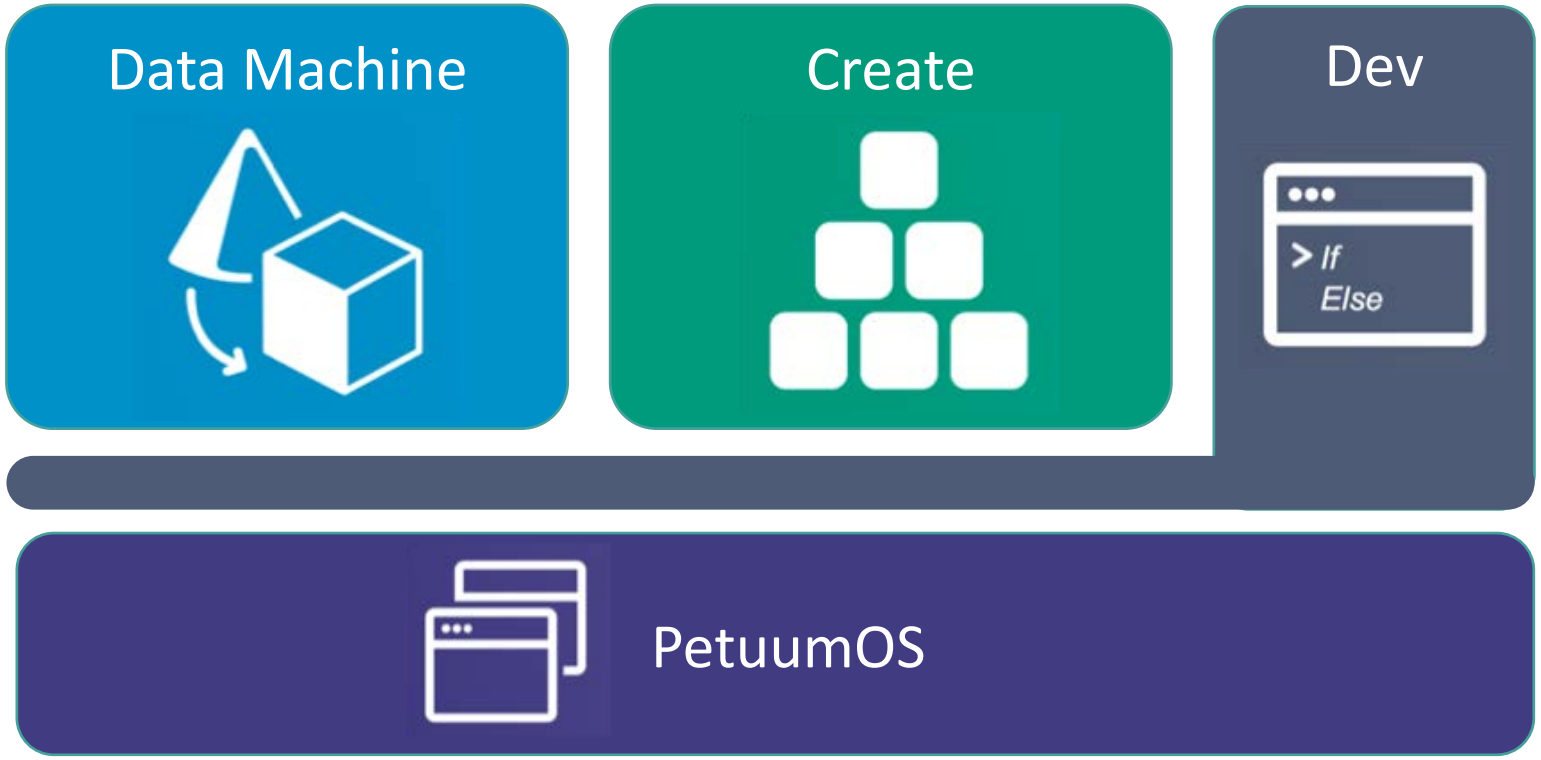
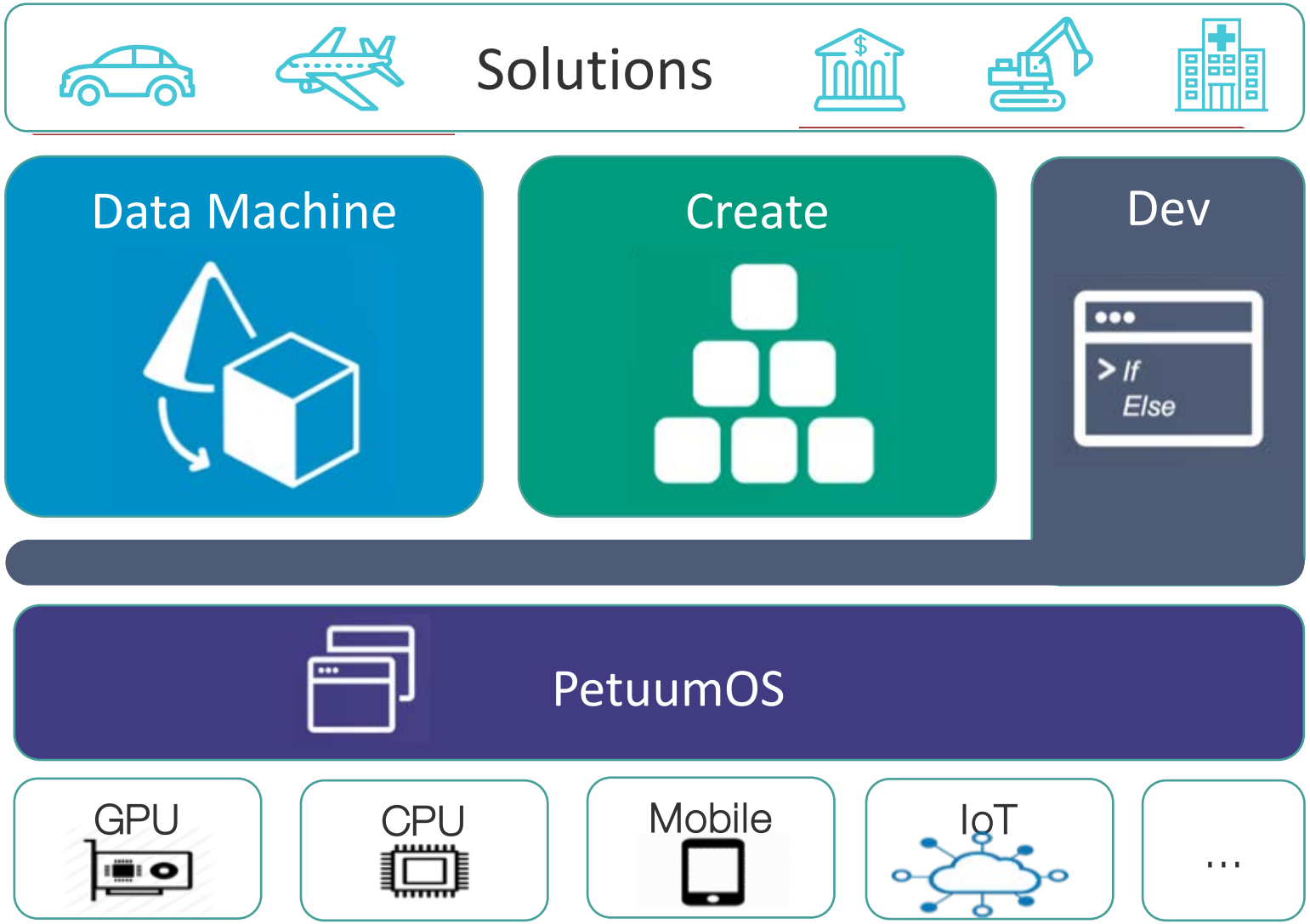


Petuum Symphony



Petuum Symphony



Stack Building Blocks to Create Complex Applications

- Implementing a state-of-the-art ML solutions as simple as stacking available components
  - Traditionally: thousands of lines of code
- Emphasize modularization and abstraction
- Clean and simple interfaces for users to assemble models
- Broad coverage of both common and cutting-edge models

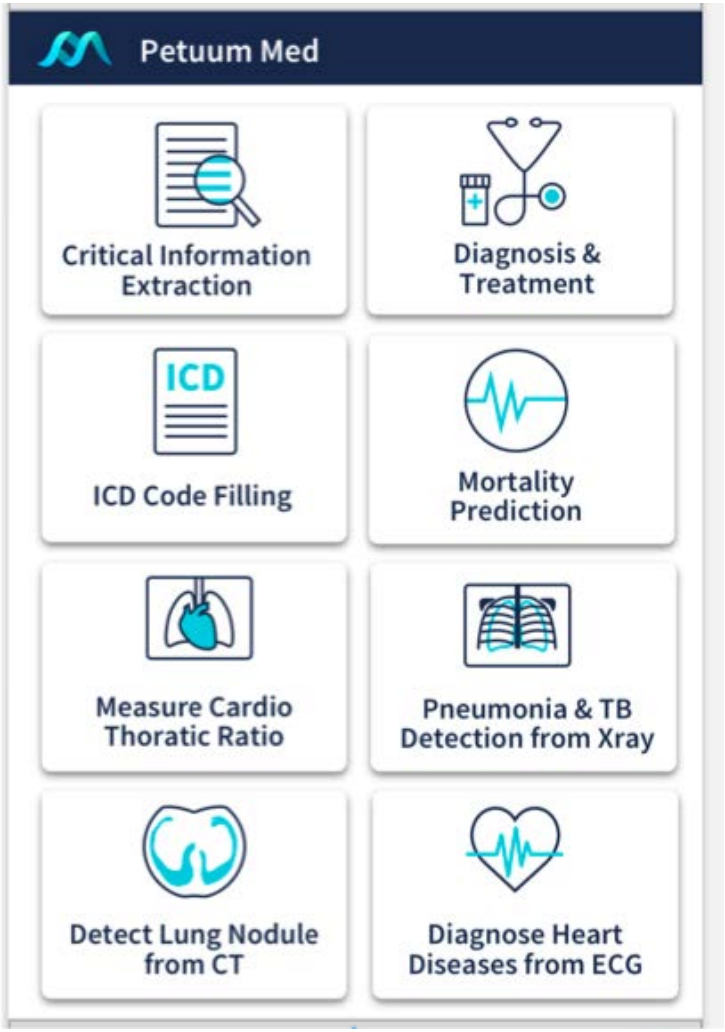
Hundreds of thousands of lines of code

With the toolbox

PetuumMed: AI-aided Healthcare

- State-of-the-art healthcare AI embedded in existing clinical workflows
- Leverage all available clinical inputs: medical notes, images, vitals, lab tests, genomic data, and more
- Productivity: offers distilled patient info & second opinion at practitioners' fingertip
- Deploys & scales with

  Petuum Symphony



AI Meets Applications At Fingertips

– Experiencing & Using AI at Any Scale Like Never Before with Petuum UI

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Thank You!