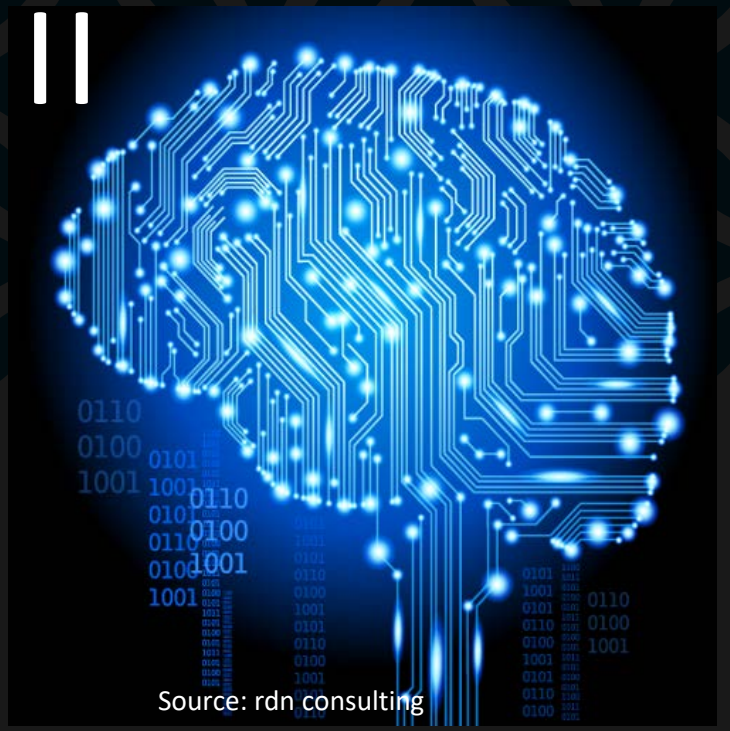
Discovery

Diagnosis

Prognosis

Care

Deep Learning for Biomedical Discovery and Data Mining II



Source: rdn consulting

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goo.gl/3jJ1O0

Melbourne, June 2018

Resources

Slides and references:

- https://truyentran.github.io/pakdd18-tute.html
- Shorten URL: goo.gl/UuZZJ9

Key survey paper (updated frequently):

- **Ching, Travers, et al. "Opportunities And Obstacles For Deep Learning In Biology And Medicine." *bioRxiv* (2018): 142760**

Agenda

Topic 1: Introduction (20 mins)

Topic 2: Brief review of deep learning (30 mins)

- Classic architectures
- Capsules & graphs
- Memory & attention

Topic 3: Genomics (30 mins)

- Nanopore sequencing
- Genomics modelling

QA (10 mins)

Break (30 mins)

Topic 4: Healthcare (40 mins)

- Time series (regular & irregular)
- EMR analysis: Trajectories prediction
- EMR analysis: Sequence generation

Topic 5: Data efficiency (40 mins)

- Few-shot learning
- Generative models
- Unsupervised learning of drugs

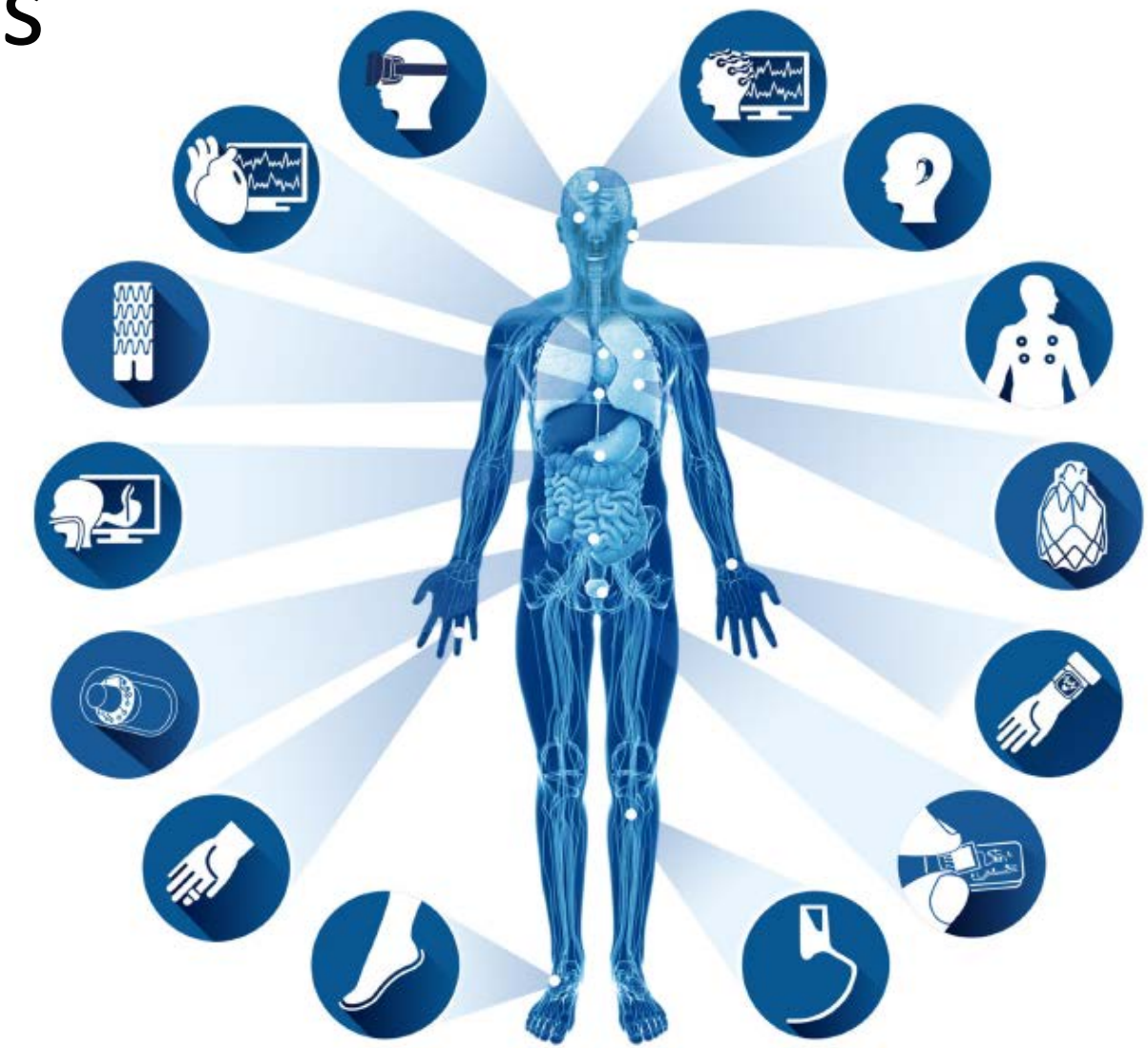
Topic 6: Future outlook

QA (10 mins)

Sensing technologies and data

Raw signals are ideal candidates for deep learning

Speech & vision techniques can be applied with minimal changes

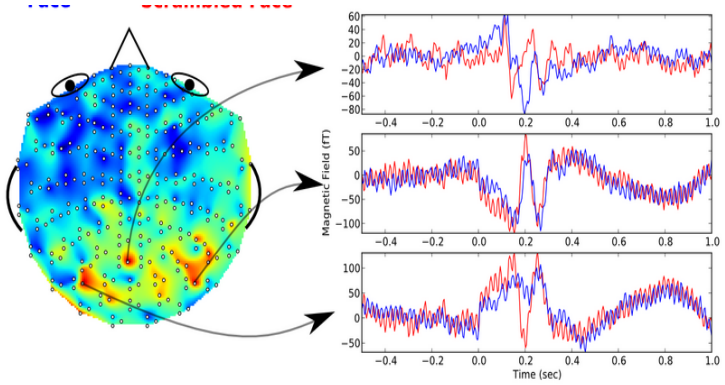


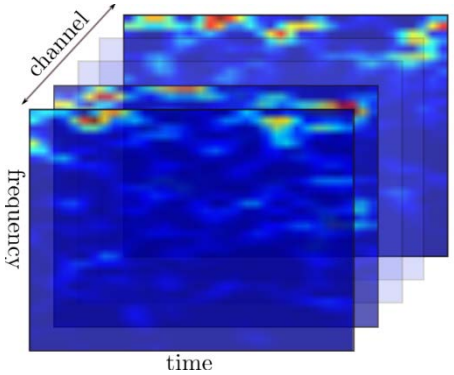
#REF: Ravì, Daniele, et al. "Deep learning for health informatics." *IEEE journal of biomedical and health informatics* 21.1 (2017): 4-21.

EEG → Tensor RBM for alcoholic diagnosis

control

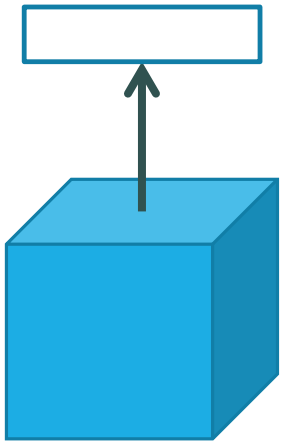
alcoholic





3D Spectrogram

Subject representation



Tensor Restricted Boltzmann Machine

#Ref: Tu D. Nguyen, Truyen Tran, D. Phung, and S. Venkatesh, Tensor-variate Restricted Boltzmann Machines, *AAAI* 2015.

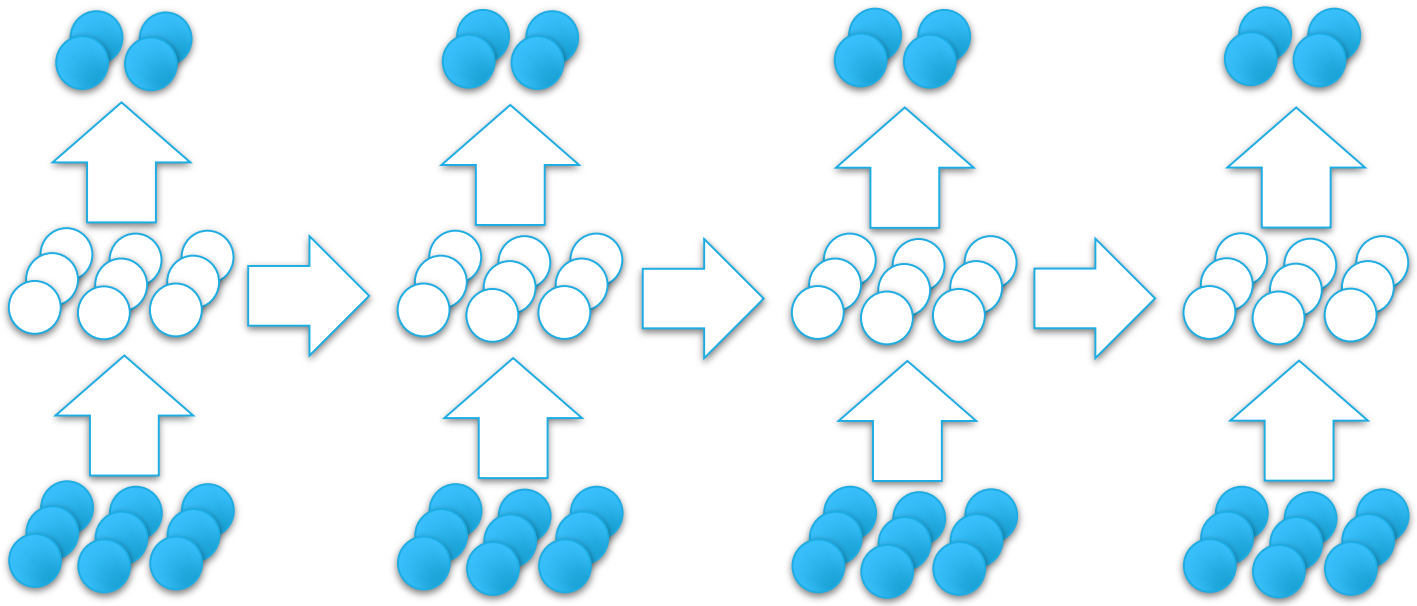
EEG → Matrix LSTM → Classification

EEG segments as matrices

Temporal dynamics as recurrence

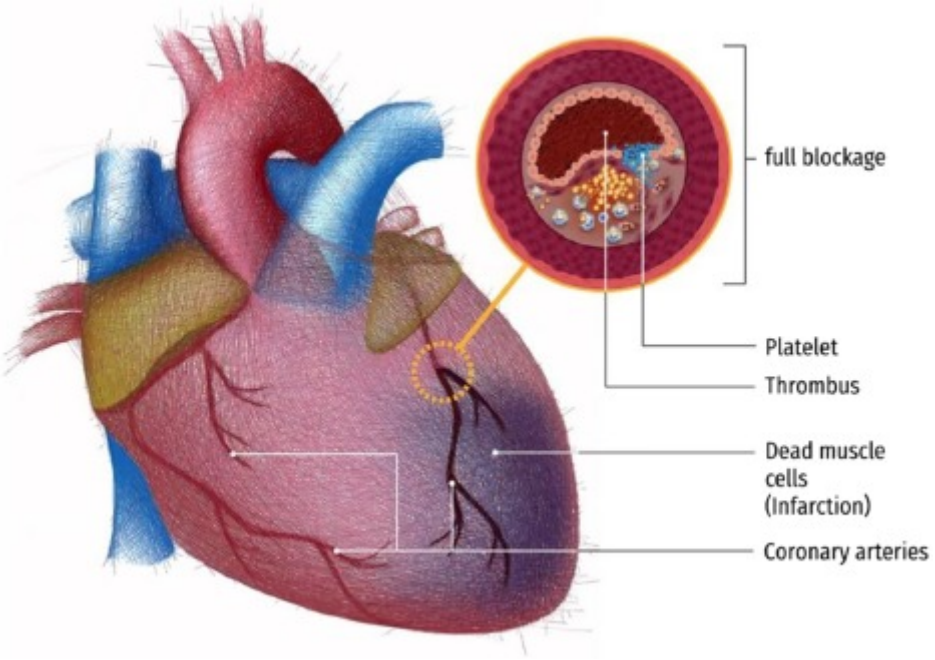
Recurrent dynamics

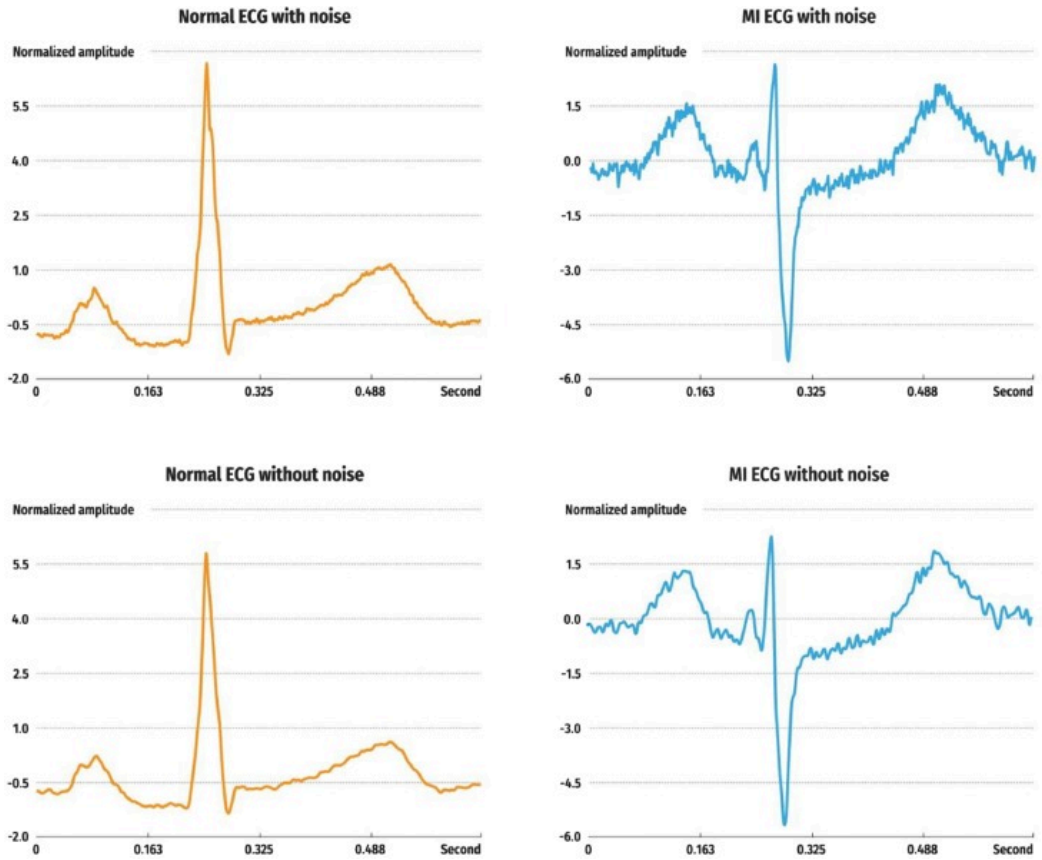
$$H_t = \sigma(U_x^\intercal X_t V_x + U_h^\intercal H_{t-1} V_h + B)$$



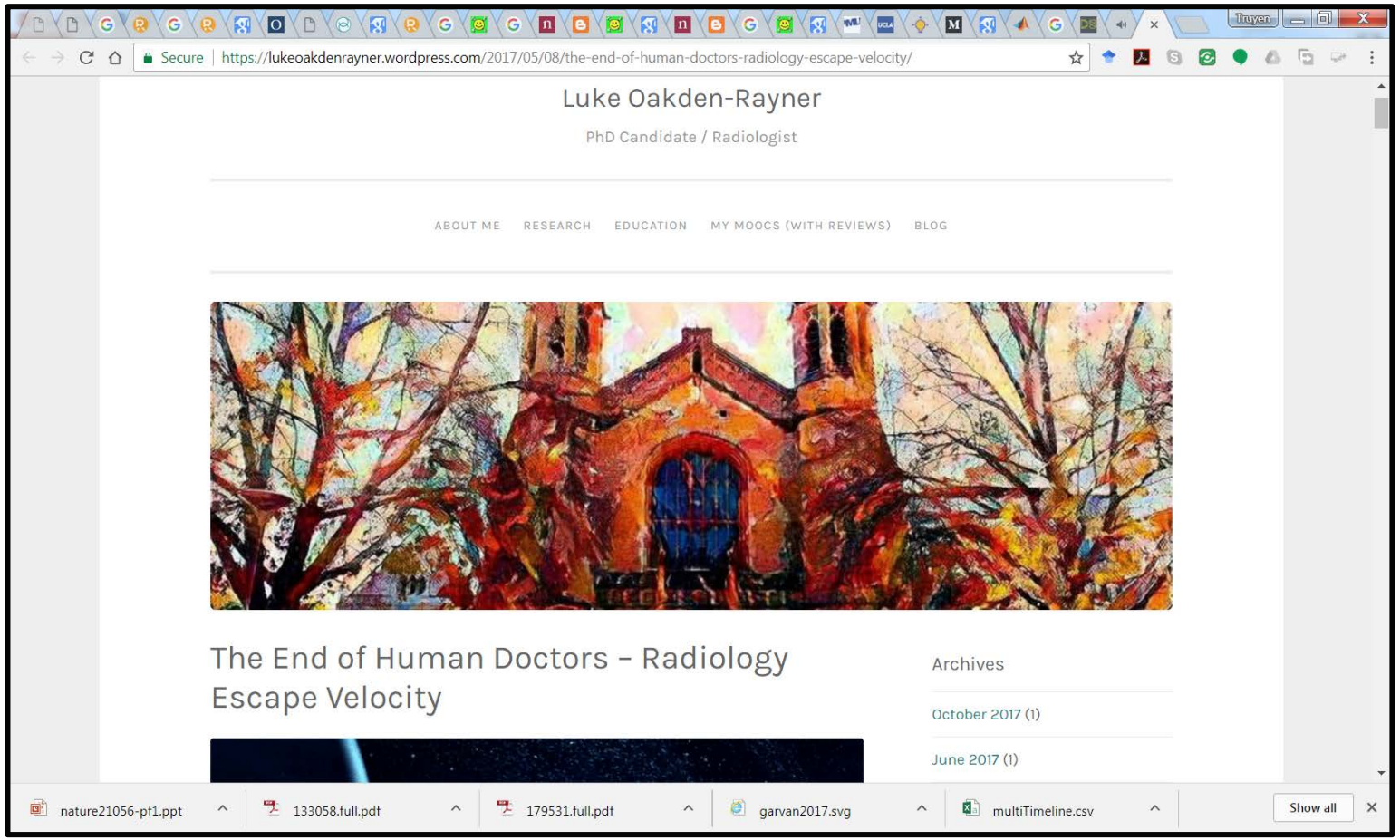
#REF: Kien Do, Truyen Tran, Svetha Venkatesh, "Learning Deep Matrix Representations", *arXiv preprint arXiv:*1703.01454

ECG → CNN for heart attack detection





#REF: Acharya, U. Rajendra, et al. "Application of deep convolutional neural network for automated detection of myocardial infarction using ECG signals." *Information Sciences* 415 (2017): 190-198.



“They should stop training radiologists now.”

Geoff Hinton (as of April 2017)

https://www.newyorker.com/magazine/2017/04/03/ai-versus-md

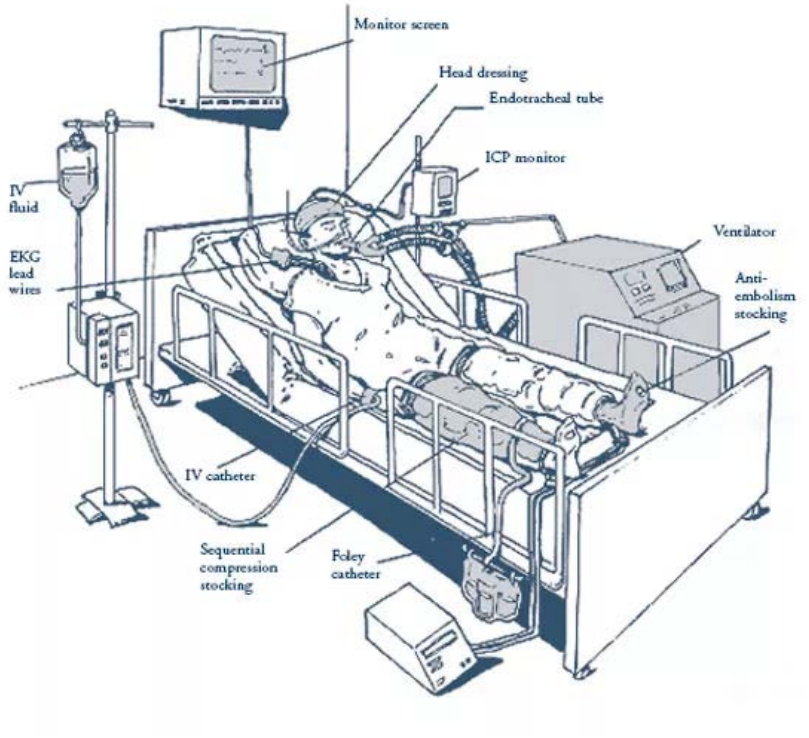
Handling irregular time-series

The needs

- Accuracy
- Interpretability
- As early as possible

The process:

- Irregular time-series → Regular time-steps → Data imputation → Bi-LSTM → **Multiple attentions** → Classification



Source: healthpages.org

#REF: Phuoc Nguyen, Truyen Tran, Svetha Venkatesh, "Deep Learning to Attend to Risk in ICU", *IJCAI'17 Workshop on Knowledge Discovery in Healthcare II: Towards Learning Healthcare Systems* (KDH 2017).

```
Time,Parameter,Value
00:00,RecordID,132539
00:00,Age,54
00:00,Gender,0
00:00,Height,-1
00:00,ICUType,4
00:00,Weight,-1
00:07,GCS,15
00:07,HR,73
00:07,NIDiasABP,65
00:07,NIMAP,92.33
00:07,NISysABP,147
00:07,RespRate,19
00:07,Temp,35.1
00:07,Urine,900
00:37,HR,77
00:37,NIDiasABP,58
00:37,NIMAP,91
00:37,NISysABP,157
00:37,RespRate,19
00:37,Temp,35.6
00:37,Urine,60
```

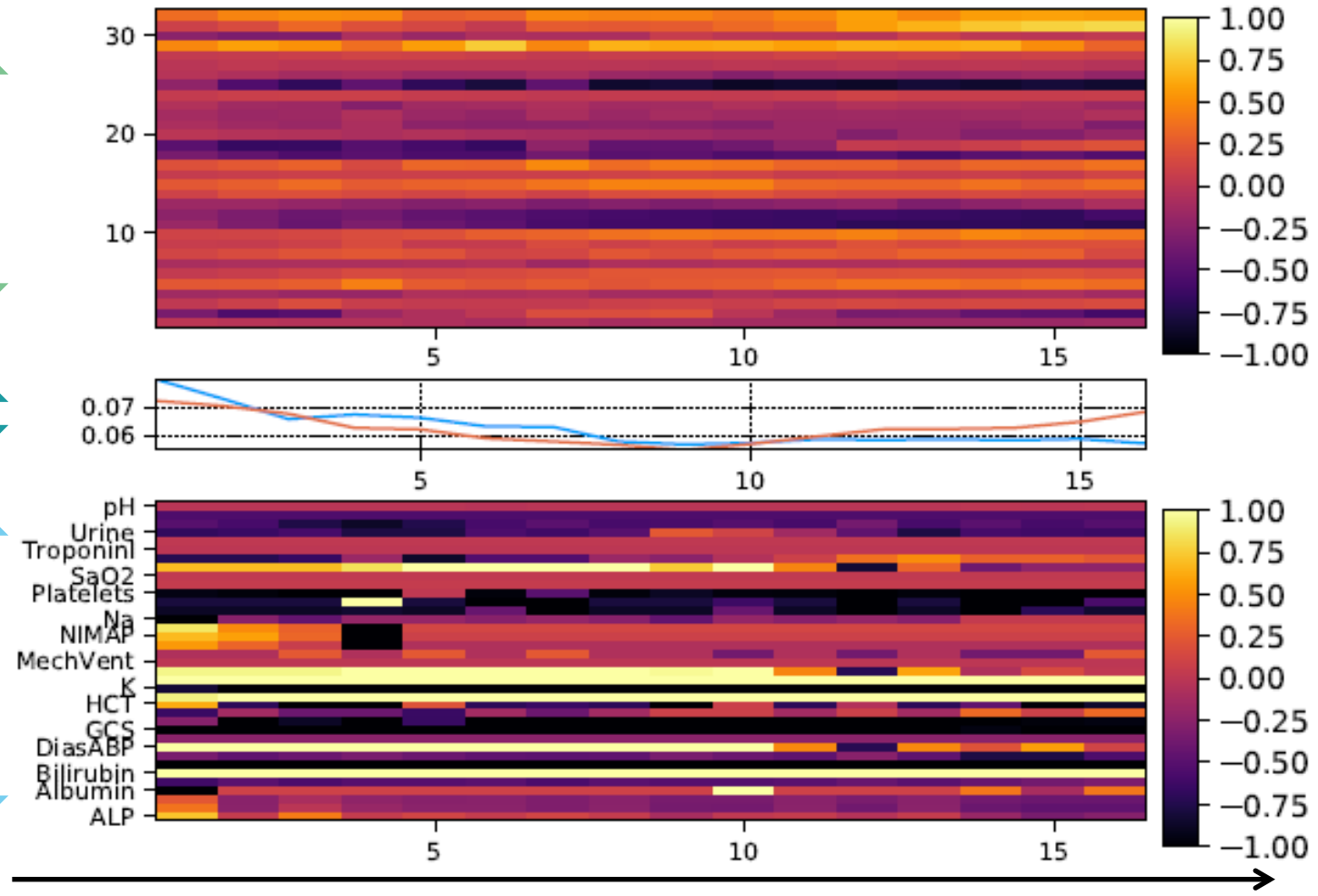
Data: **Physionet 2012**

Result: Attend to risks in ICU

State transition

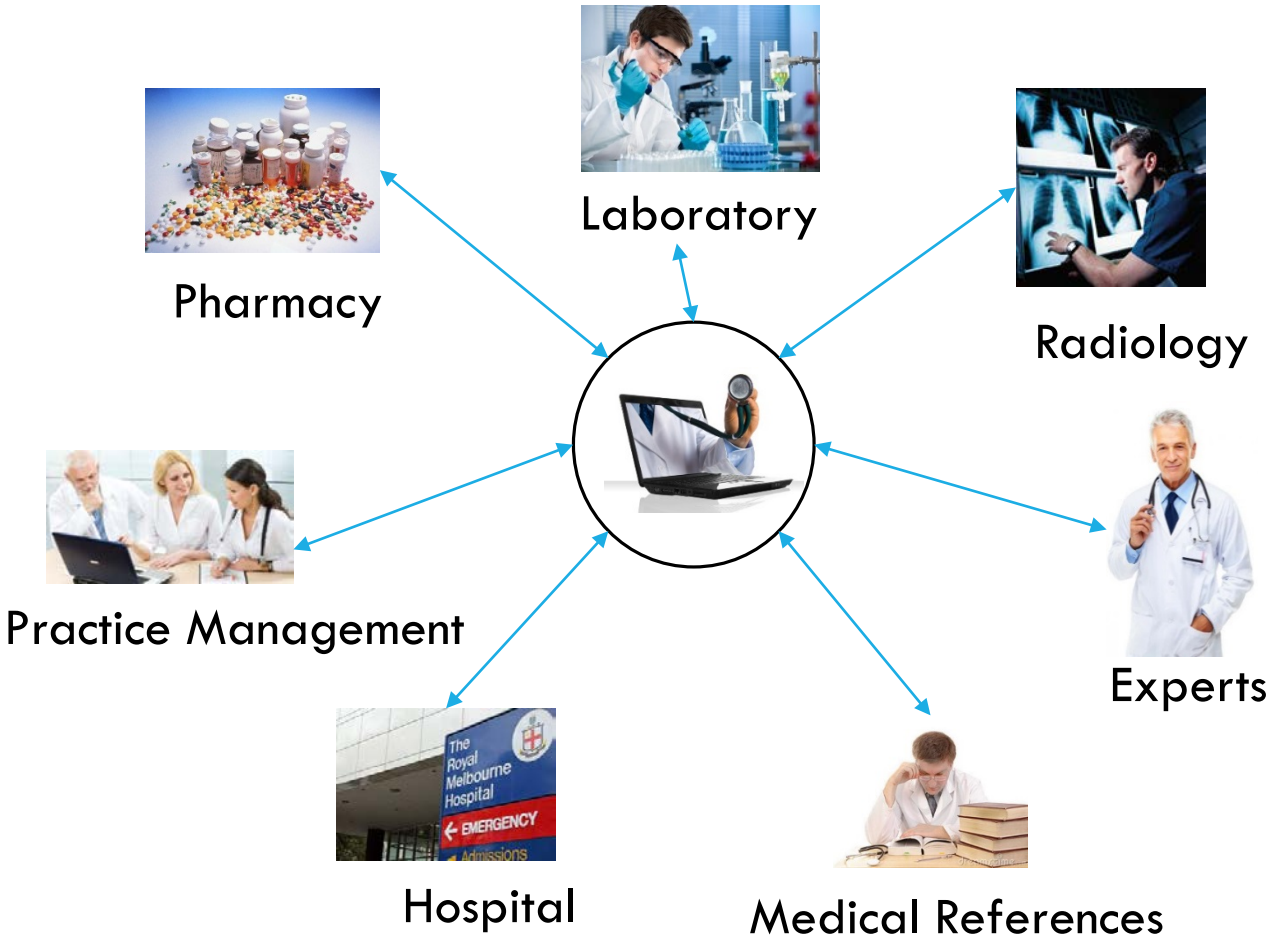
Attention probabilities

Physiological measures



#REF: Phuoc Nguyen, Truyen Tran, Svetha Venkatesh, "Deep Learning to Attend to Risk in ICU", *IJCAI'17 Workshop on Knowledge Discovery in Healthcare II: Towards Learning Healthcare Systems* (KDH 2017).

EMR Connects Services: System of Systems



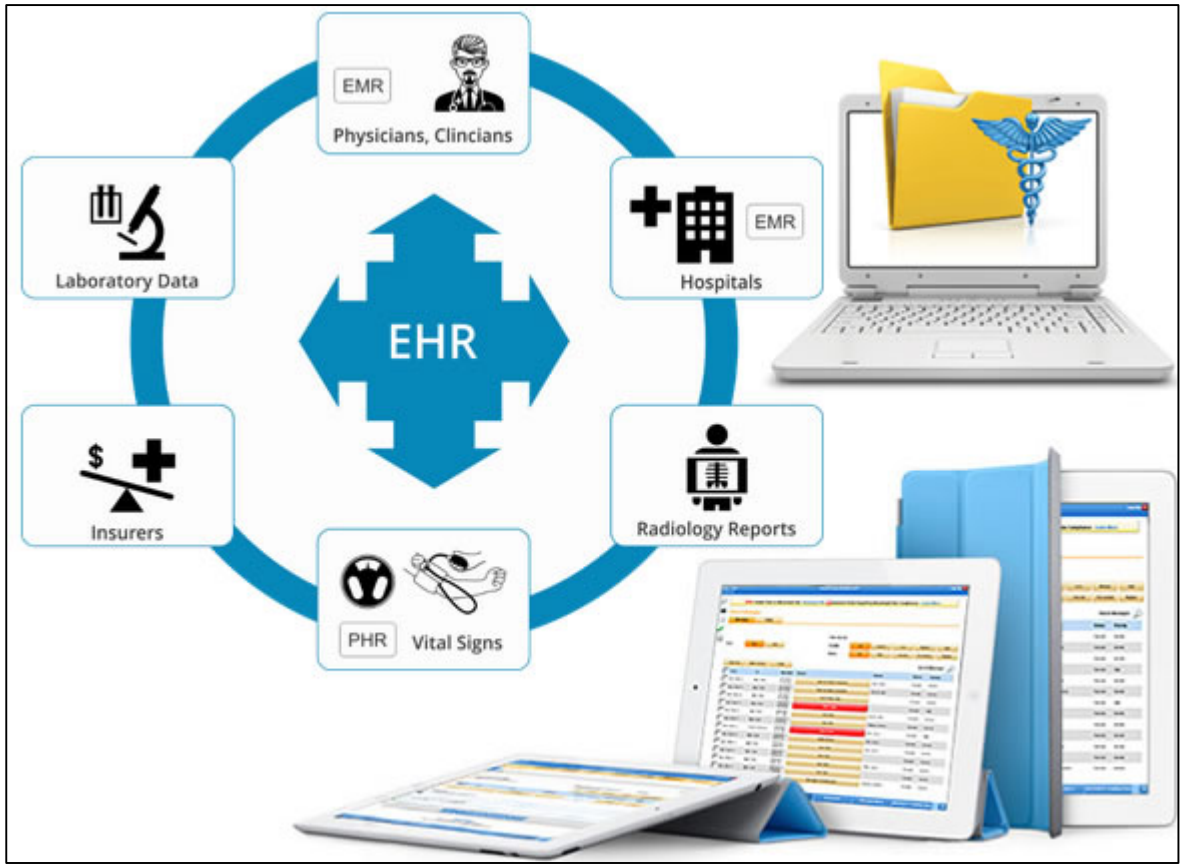
Five main functions

- Integrated view of patient data
- Clinical decision support
- Clinician order entry
- Access to knowledge resources
- Integrated communication and reporting support

Modeling electronic medical records (EMR)

Need to model the healthcare processes, which are interactions of:

- Disease progression
- Interventions & care processes
- Recording processes (Electronic Medical/Health Records)



Source: medicalbillingcodings.org

Clinical Decision Supports

Support protocol/planning of treatment/discharge.

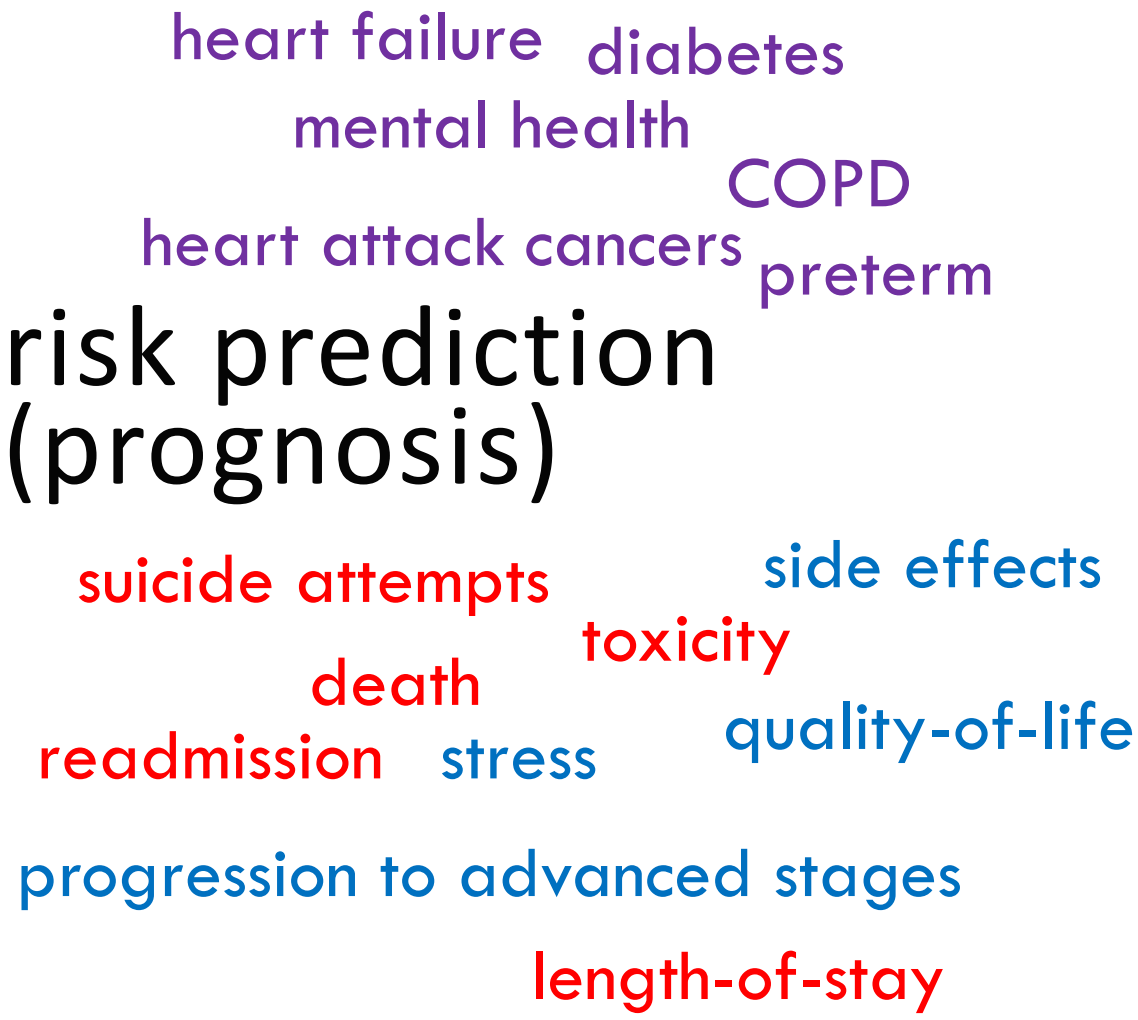
Suggest course of actions:

- E.g., medication/dose/duration.

Estimate risk & predict outcomes.

Alert/reminder.

Support (semi) automated diagnosis.



Warning: leakage!

Make sure the patients are counted AFTER first diagnosis

- Often, we have future data as well
- Retrospective nature

Never use outcomes to do anything, except for training the model

Our early suicide attempt classification from assessments was a form of leakage:

- Any attempt in history is considered as an outcome. BUT:
- Previous attempts were accounted in current assessment already!

Preprocessing: Data normalization & dictionary compression

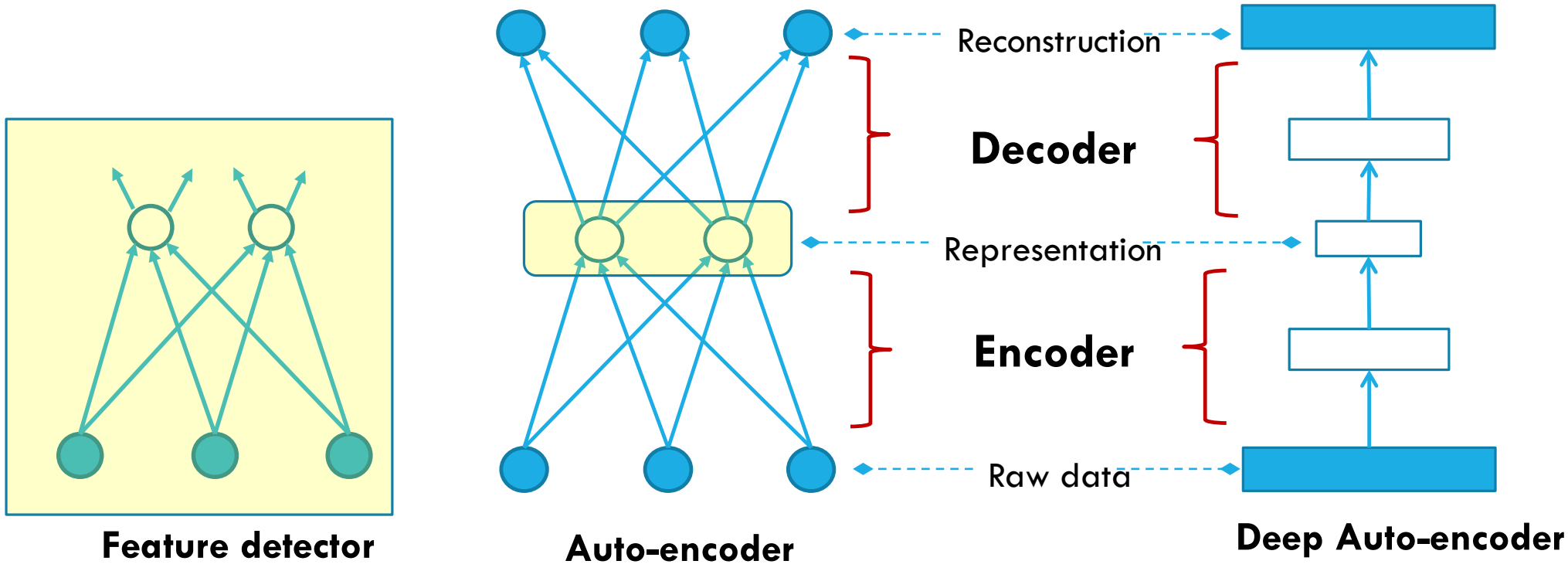
Drugs & tests

- Drug companies offer different brand names of the essentially the same drug
- DDD/ATC is the central register for the medication classes, maintained by WHO
- Several test names may be the same

It may not be robust to use the original “vocabularies”

- Tens of thousands of ICD-codes, thousands of procedures, hundreds of DRGs, thousands of medication classes
- Codes are usually organized in hierarchy
- Choosing the right hierarchy is statistical issue

DeepPatient: Representing medical records with Stacked Denoising Autoencoder



#Ref: Miotto, Riccardo, et al. "Deep patient: An unsupervised representation to predict the future of patients from the electronic health records." *Scientific reports* 6 (2016): 26094.

DeepPatient: Results on disease classification

Time Interval = 1 year (76,214 patients)			
		Classification Threshold = 0.6	
Patient Representation	AUC-ROC	Accuracy	F-Score
RawFeat	0.659	0.805	0.084
PCA	0.696	0.879	0.104
GMM	0.632	0.891	0.072
K-Means	0.672	0.887	0.093
ICA	0.695	0.882	0.101
DeepPatient	**0.773***	**0.929***	**0.181***

Trajectories modeling: Challenges & opportunities

Long-term dependencies

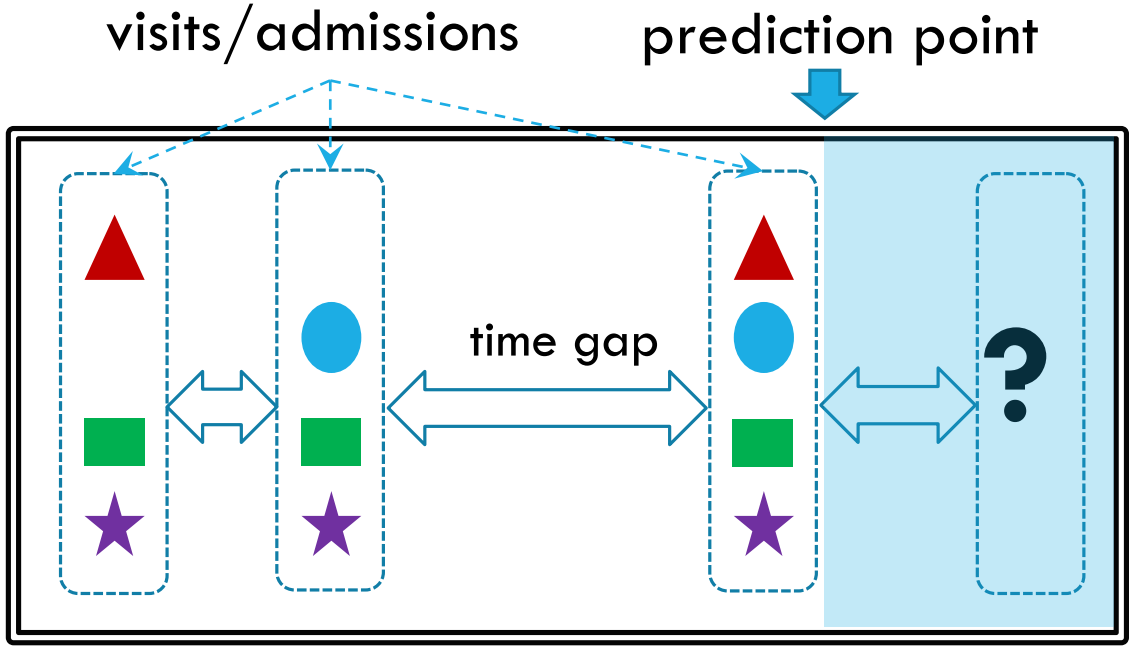
Irregular timing

Mixture of discrete codes and continuous measures

Complex interaction of diseases and care processes

Cohort of interest can be small (e.g., <1K)

Rich domain knowledge & ontologies



Multimodalities: Text, physiological signals (e.g., EEG/ECG), images (e.g., MRI, X-ray, retina), genomics

New modalities: social medial, wearable devices

Explainability!

Untitled Document | prada1.it.deakin.edu.au:30

prada1.it.deakin.edu.au:3000/view/StrokeMap/000005

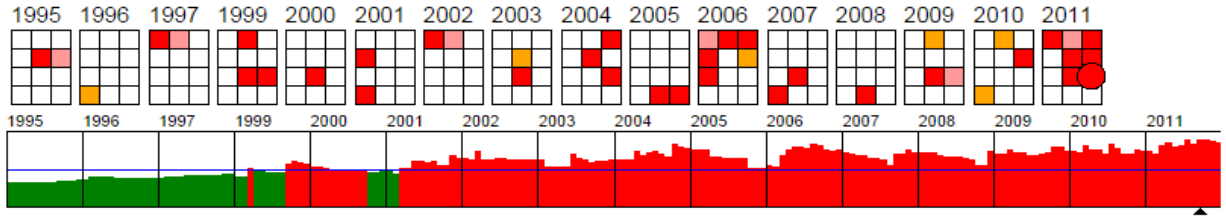
Project name | Home | Page1 | Page2

UR	000005
DOB	1936-01-01
Gender	Female
Occupation	home duties
Marital Status	Married
Risk	0.88 (2011/09/01)

Predictive Factors | All Factors

Disease	Other cataract
	Strep & staph cause dis class oth chptr
	Diverticular disease of intestine
	Oth symptoms signs inv cogn fn awareness
	Chronic kidney disease
	Unspecified urinary incontinence
	Essential (primary) hypertension
	Other disorders of urinary system
	Type 2 diabetes mellitus
	Heart failure
	Abnormalities of gait and mobility
	Pneumonia organism unspecified
	Oth sym signs inv nervous & M/S systems
	Malaise and fatigue
	Disrd lipoprotein metab & oth lipidaemia
	Atrial fibrillation and flutter
Admission	
pastProcNo	
Procedure	Generalised allied health interventions
	Conduction anaesthesia
	Cerebral anaesthesia
Emergency	
Context	Place of occurrence
	Personal history of medical treatment
Comorbidity	hypertension-uncomplicated
	diabetes-complicated
	cardiac-arrhythmias
pastRareProcNo	

History



Events

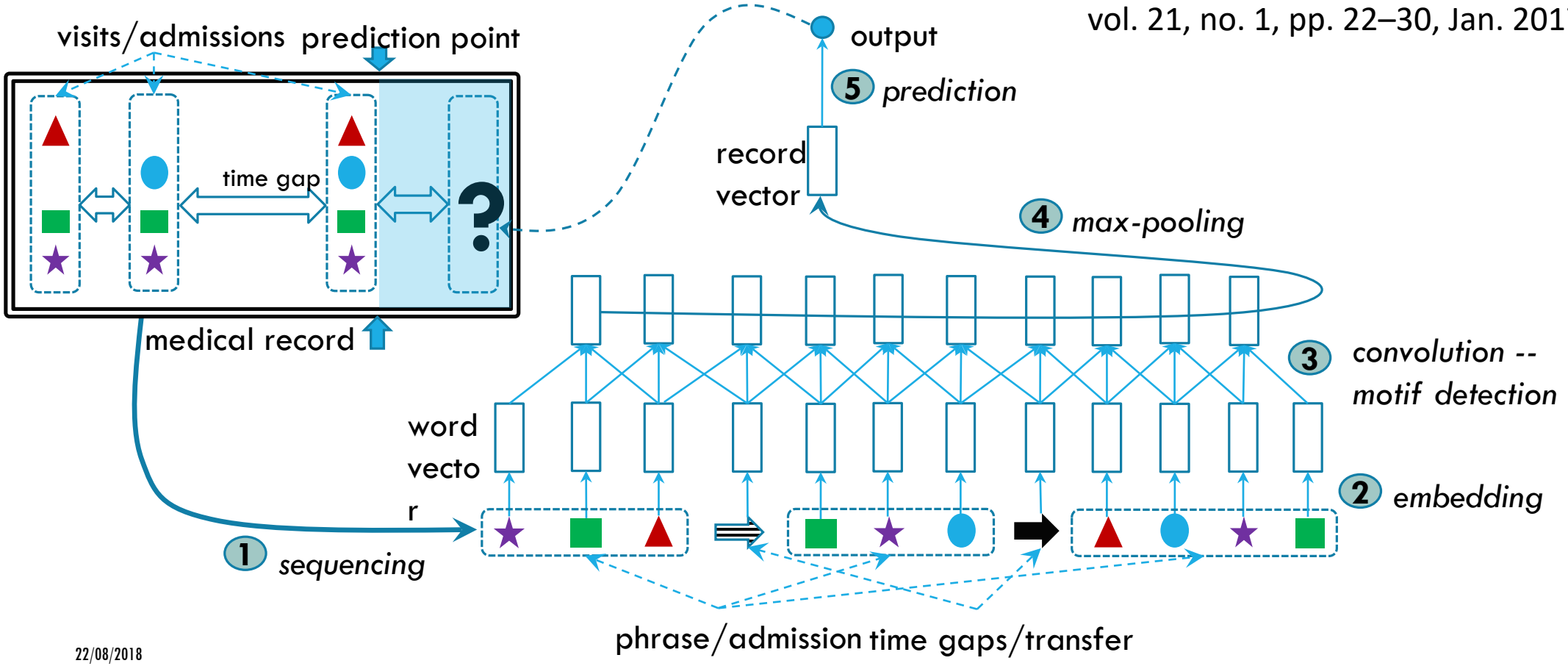
1995/05/24	Emergency Admission (9.8 days)
59010	acute pyelonephritis
03842	septicemia due to other gramnegative or
5929	urinary calculus unspecified
4011	benign essential hypertension
4140	coronary atherosclerosis
8773	intravenous pyelogram

Visualisation and interpretation are keys!

A prototype system developed iHops (our spin-off)

Deepr: CNN for repeated motifs and short sequences

#REF: Phuoc Nguyen et al., Deepr: A Convolutional Net for Medical Records, *IEEE Journal of Biomedical and Health Informatics*, vol. 21, no. 1, pp. 22–30, Jan. 2017



Deepr: Disease embedding & motifs detection

E11 I48 I50

Type 2 diabetes mellitus

Atrial fibrillation and flutter

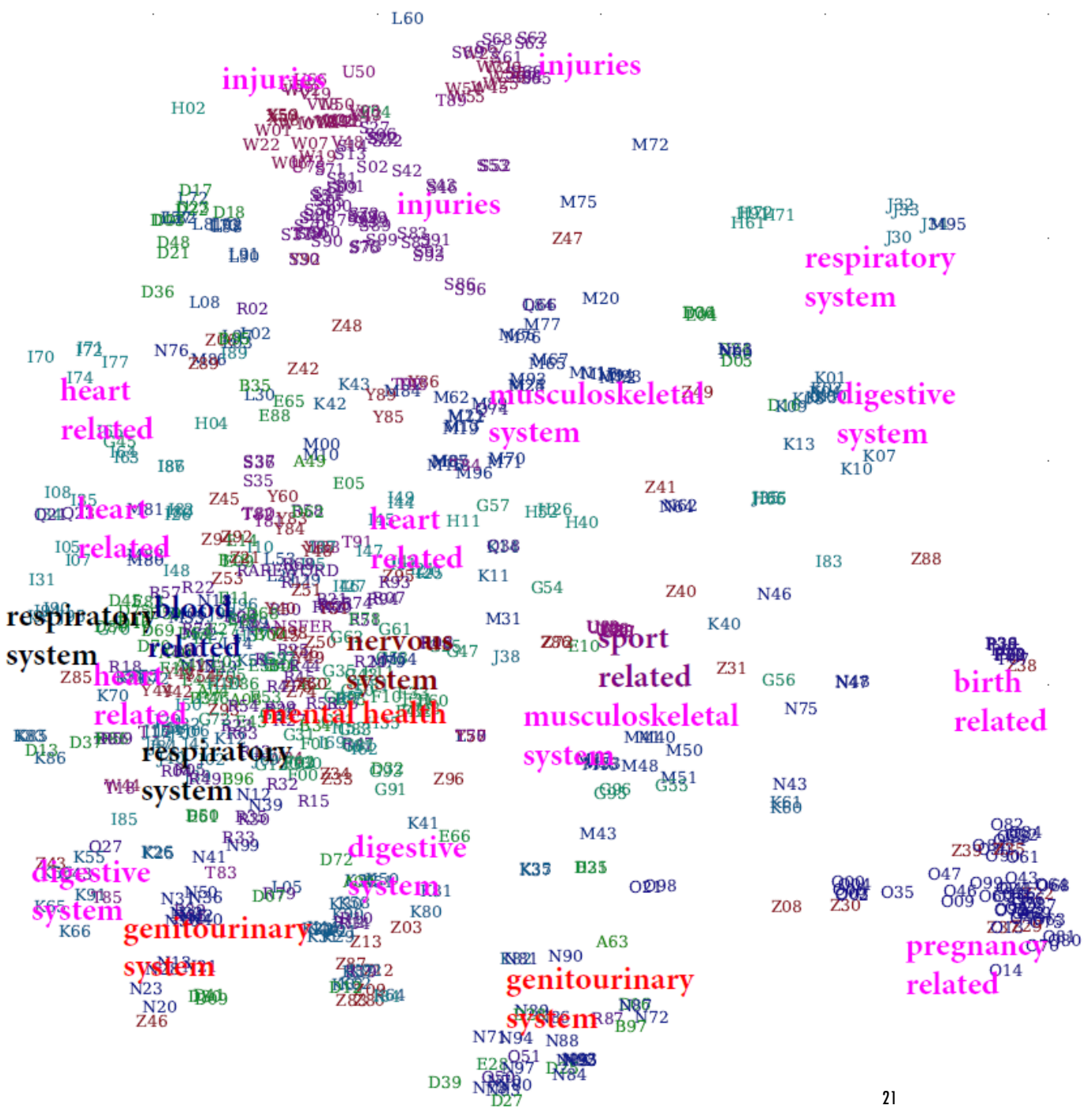
Heart failure

E11 I50 N17

Type 2 diabetes mellitus

Heart failure

Acute kidney failure



DeepCare: intervened long-term memory of health

Illness states are a dynamic memory process → moderated by time and intervention

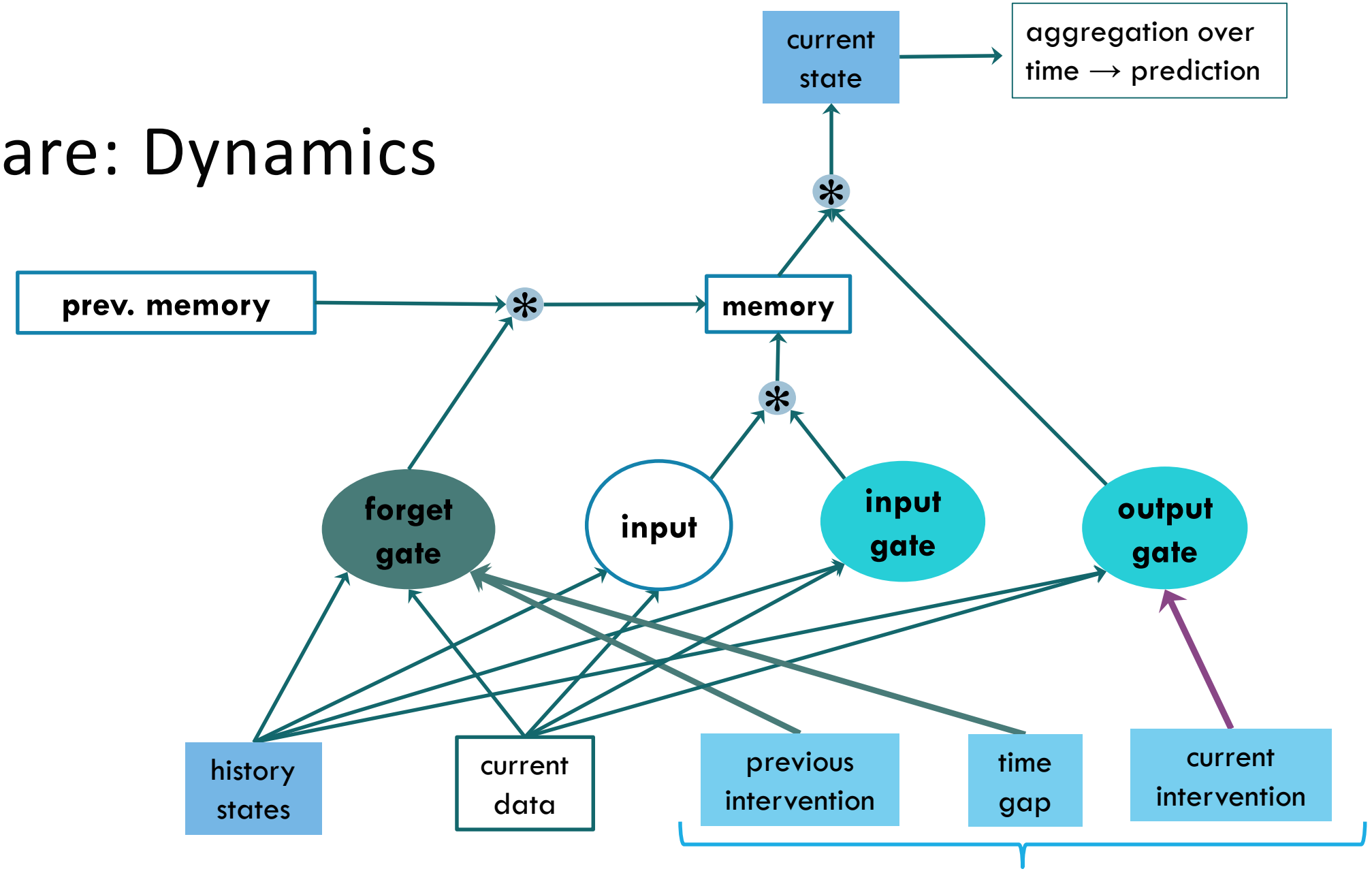
Discrete admission, diagnosis and procedure → vector embedding

Time and previous intervention → "forgetting" of illness

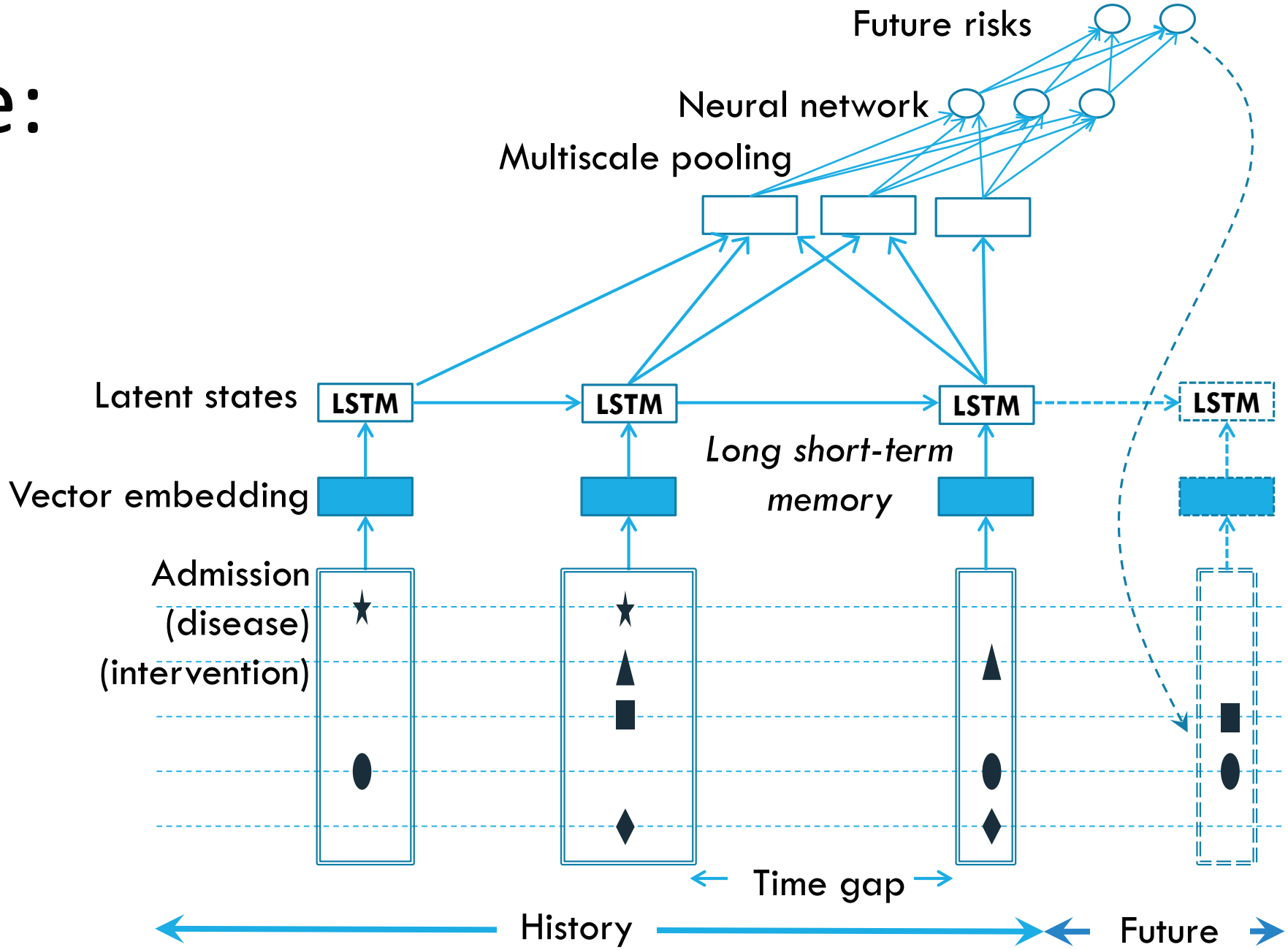
Current intervention → controlling the risk states

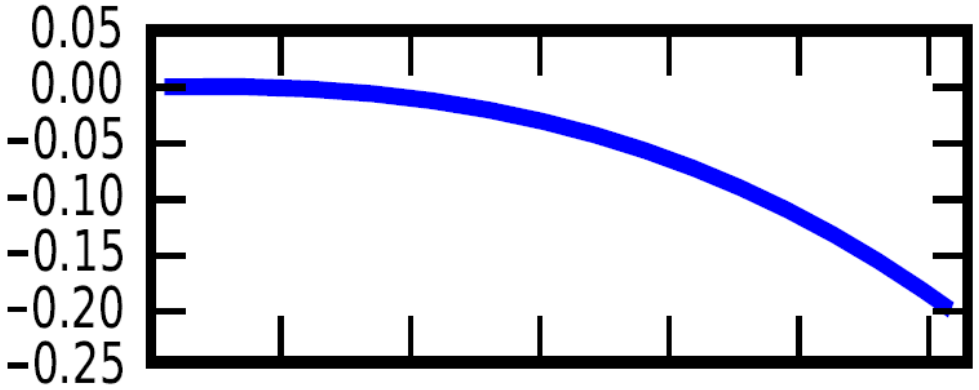
#REF: Trang Pham, et al., Predicting healthcare trajectories from medical records: A deep learning approach, *Journal of Biomedical Informatics*, April 2017, DOI: 10.1016/j.jbi.2017.04.001.

DeepCare: Dynamics



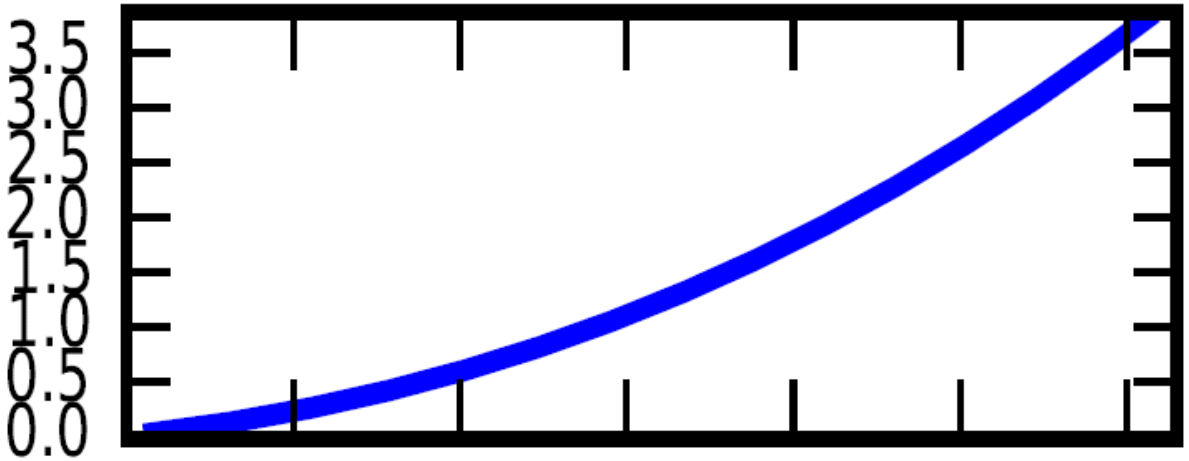
DeepCare: Structure





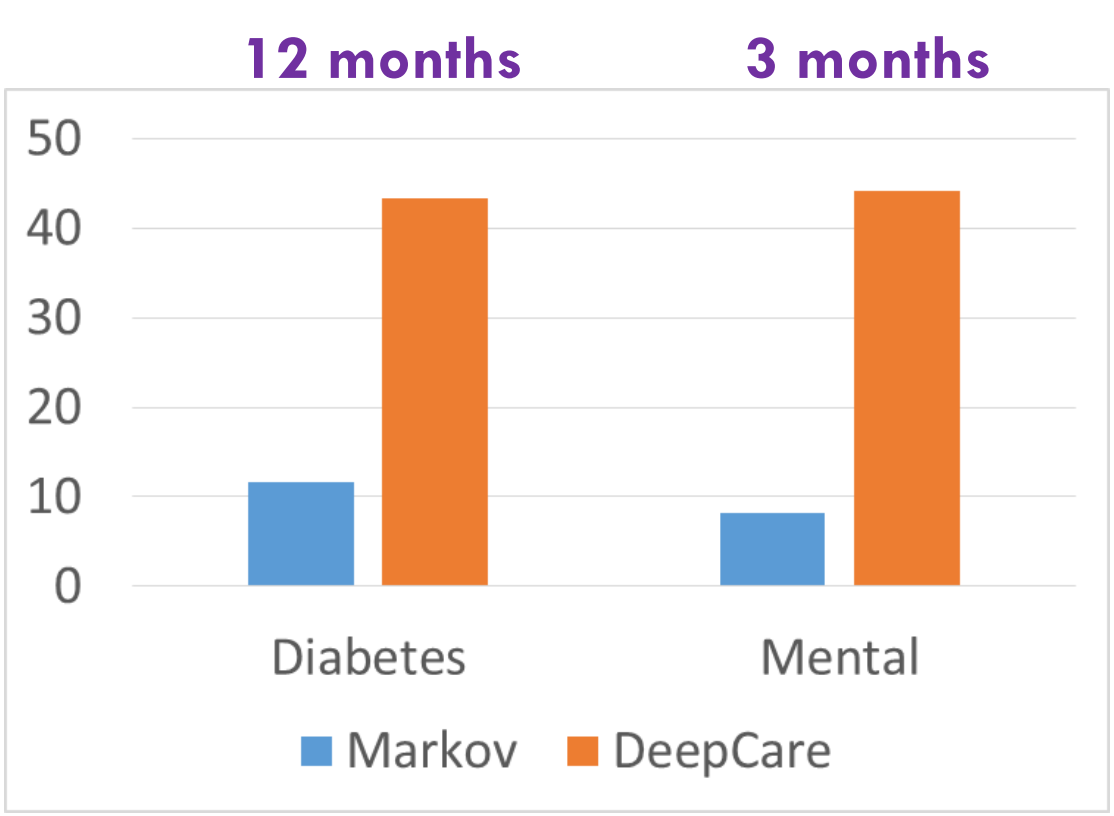
→ decreasing illness

→ Increasing illness

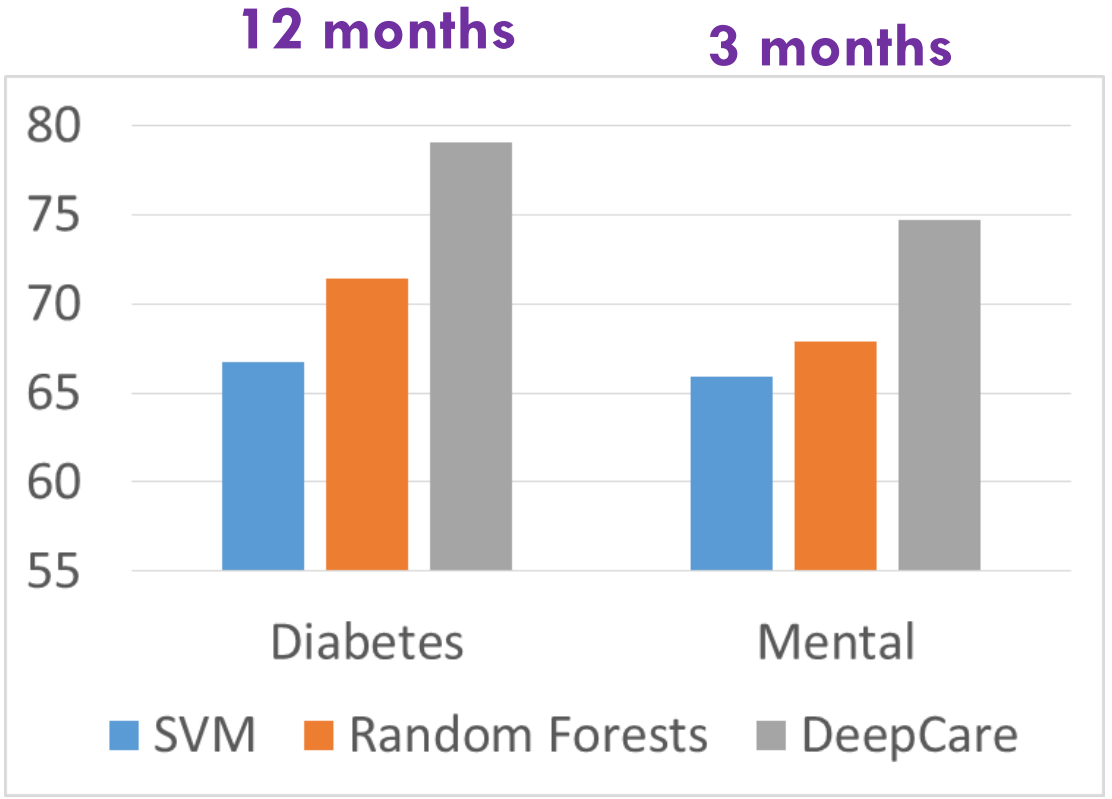


DeepCare: Two modes of forgetting as a function of time

DeepCare: prediction results



Intervention recommendation (precision@3)



Unplanned readmission prediction (F-score)

Modeling multiple disease-treatment interactions over time

Co-morbidity is the norm in modern medicine

Each hospital visit contains a set of diseases and a set of treatments

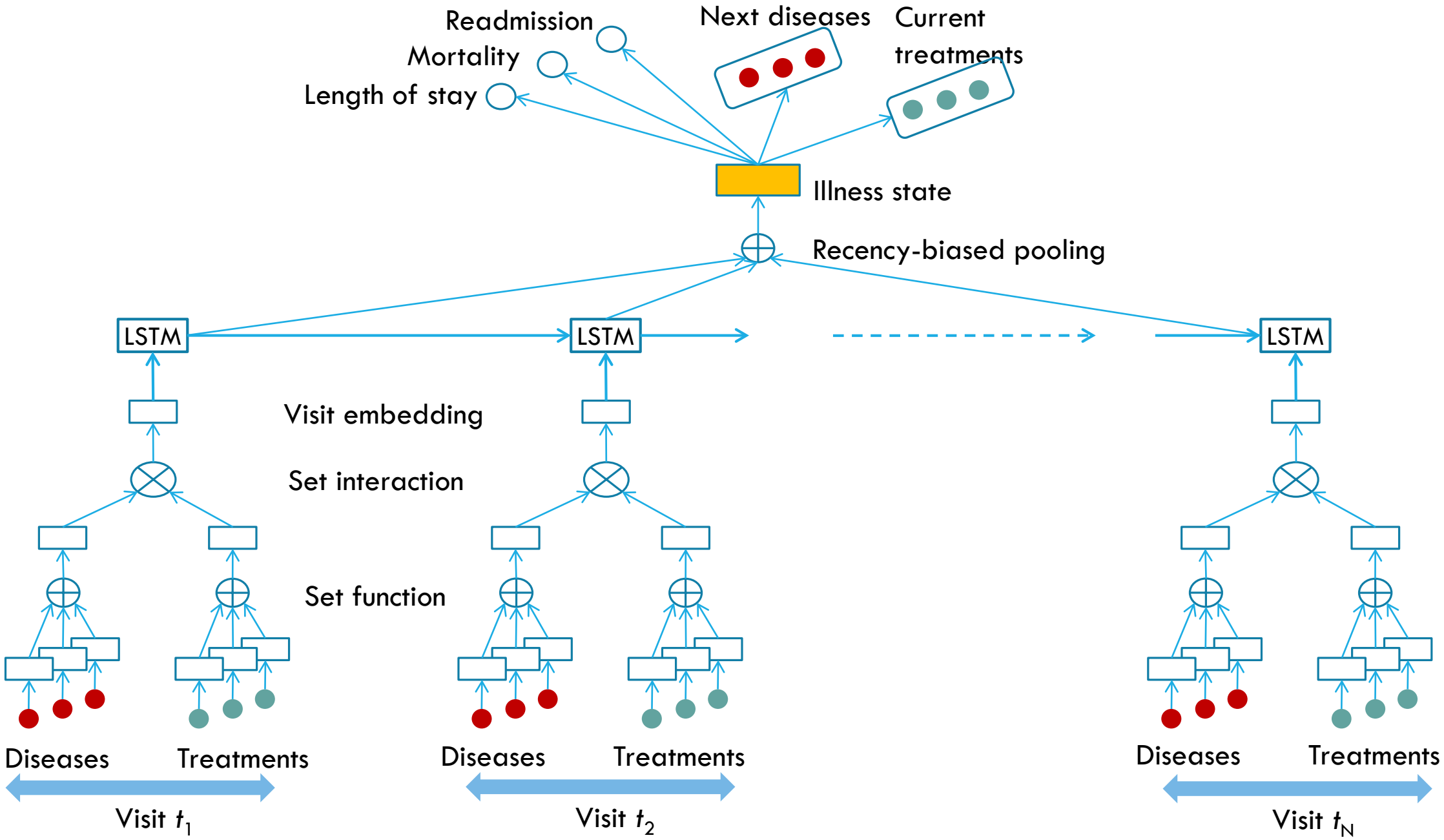
There are interactions between multi-diseases and multiple-treatments

Algebraic view: **Health = *RNN*(Illness – Intervention)**

$$\boldsymbol{v}_t = \rho\left(\Delta\right) \quad \text{where} \quad \Delta = \boldsymbol{d}_t - \boldsymbol{p}_t$$

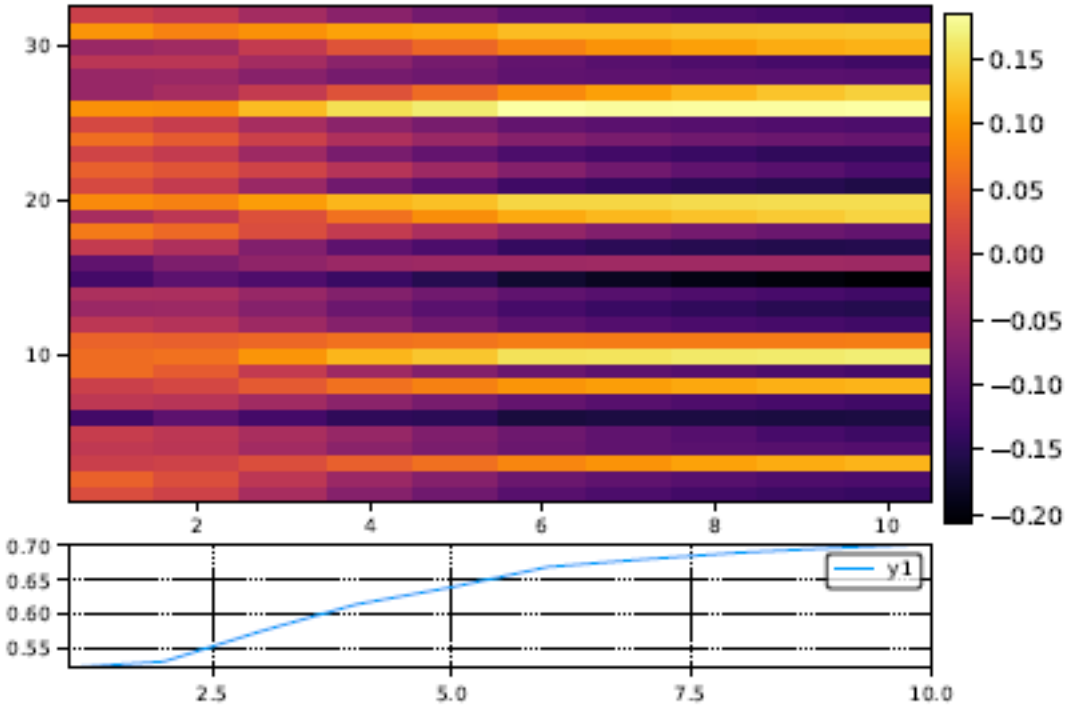
$$f_e(S) \leftarrow \frac{\bar{e}_S}{\epsilon + \|\bar{e}_S\|} \quad \text{where} \quad \bar{e}_S = \max\left(\mathbf{0}, \sum_{i \in S} \boldsymbol{e}_i\right)$$

#REF: Phuoc Nguyen, Truyen Tran, and Svetha Venkatesh. "Resset: A Recurrent Model for Sequence of Sets with Applications to Electronic Medical Records." *IJCNN* (2018).

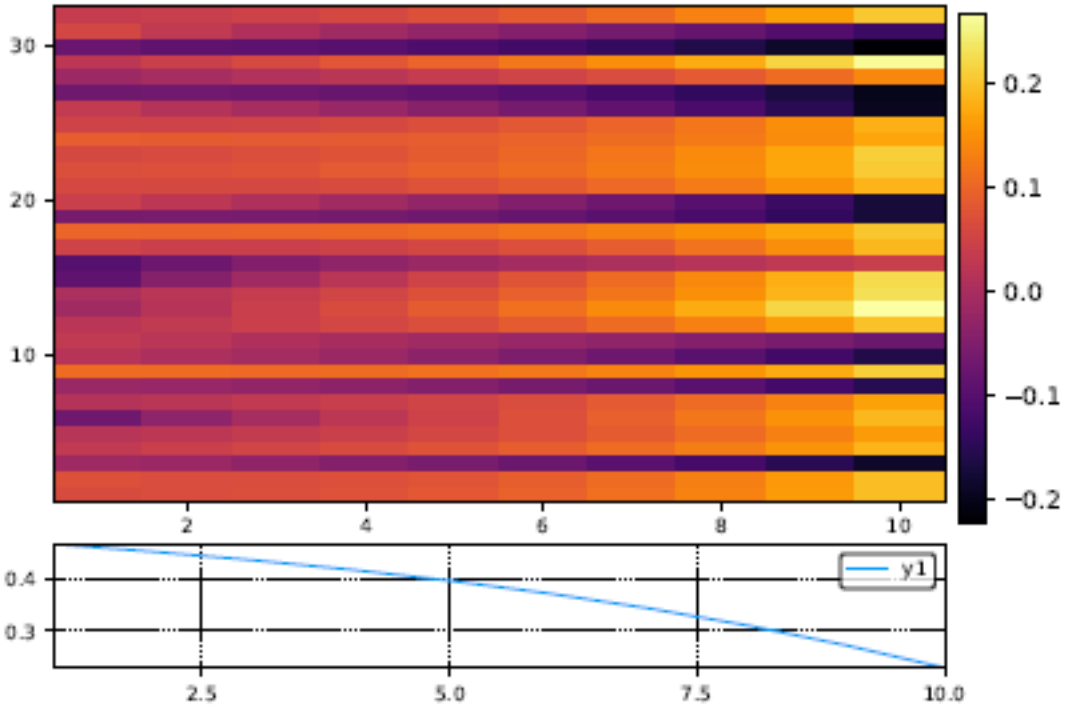

Readmission
Mortality
Length of stay
Next diseases
Current treatments
Illness state
Recency-biased pooling
LSTM
LSTM
LSTM
Visit embedding
Set interaction
Set function
Diseases
Treatments
Diseases
Treatments
Diseases
Treatments
Visit t_1
Visit t_2
Visit t_N

Results (AUC)

Method	*Diabetes*	*Mental health*
BoW+LR	0.673	0.705
Deepr [14]	0.680	0.714
MDMTP+LTSM	**0.718**	**0.726**
MDMT+LSTM	**0.701**	**0.730**



(a) Worsening progression ($P = 0.70$)



(b) Improving progression ($P = 0.23$)

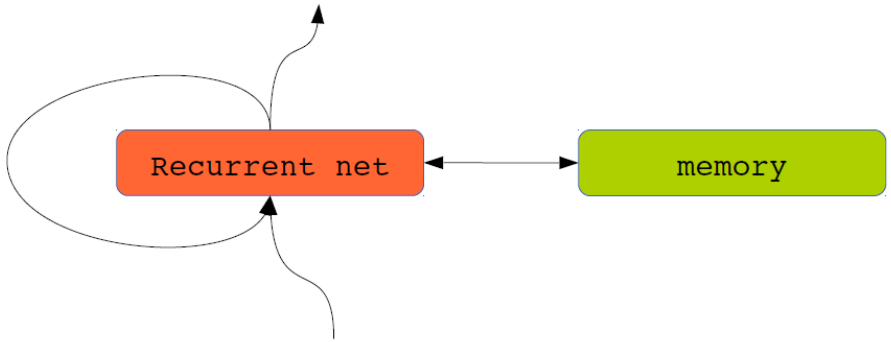
Trajectories prediction

Generating a subset of treatments

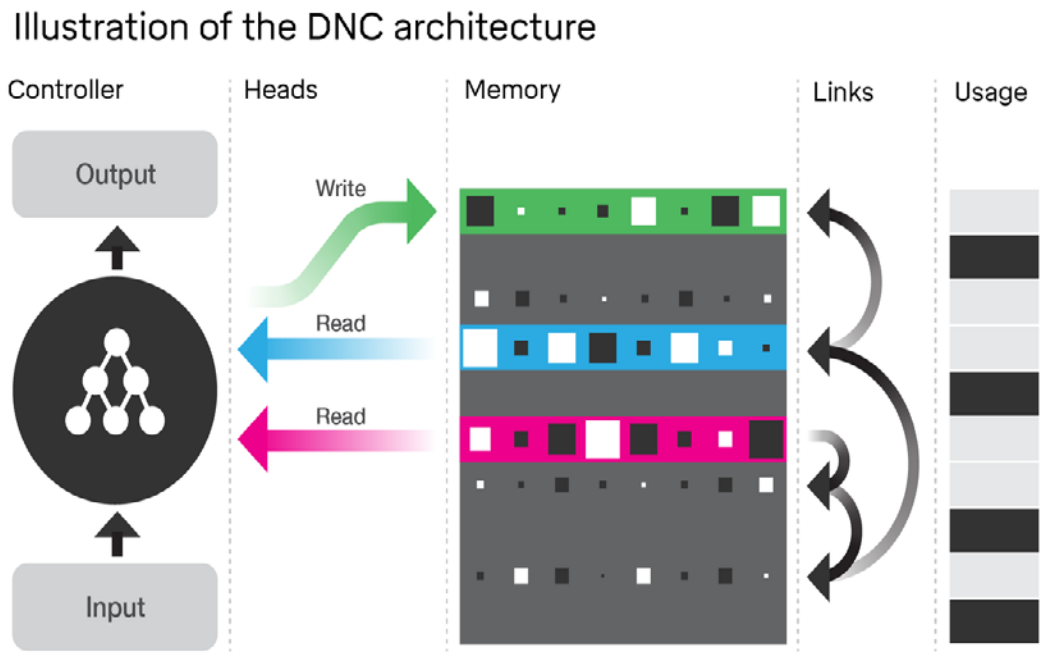
Generating an entire health/care trajectory

Challenges: global loss, meaningful evaluation metrics

A solution: Attention and Memory-augmented neural nets (MANN)



(LeCun, 2015)



Source: deepmind.com

#REF: Graves, Alex, et al. "Hybrid computing using a neural network with dynamic external memory." *Nature* 538.7626 (2016): 471-476.

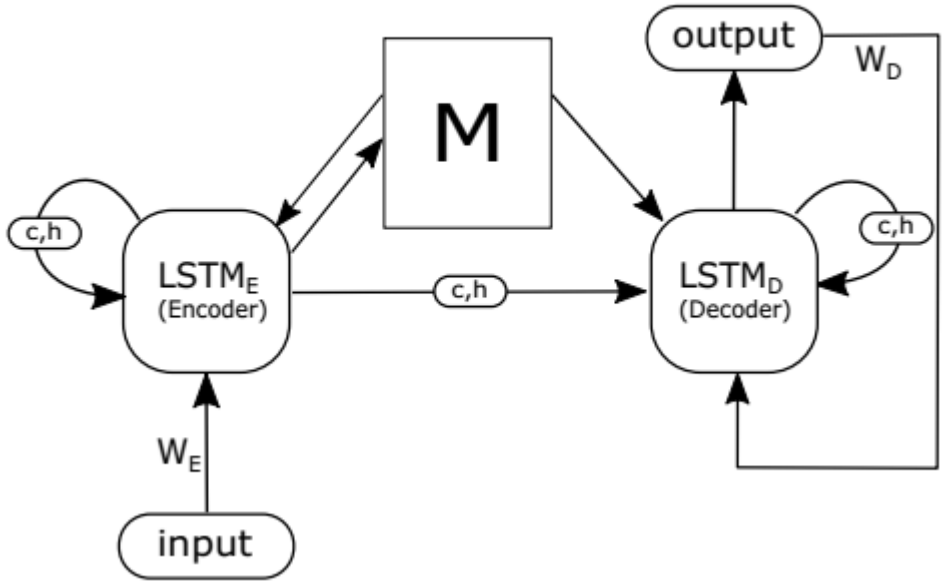
Memory is needed for complex input/output sequences

Diagnoses are encoded to an external memory by the encoder

The decoder reads the memory and produces a sequence of treatment codes. During decoding, the memory is write-protected (DCw-MANN)

Memory captures long-term dependencies inside and amongst admissions

Memory enables skip-connection attentions



#REF: Hung Le, Truyen Tran, and Svetha Venkatesh. "Dual Control Memory Augmented Neural Networks for Treatment Recommendations", PAKDD18.

Treatment prediction results

First drug predictions: precision and Jaccard Score MIMIC3 dataset.		
Models	Precision	Jaccard
Logistic Regression	0.412	0.311
Random Forest	0.491	0.405
LSTM	0.220	0.138
LSTM + attention	0.224	0.142
DNC	0.577	0.529
DCw-MANN	**0.598**	**0.556**

Top Drug predictions: Jaccard Score on top code GPI 1-3 MIMIC3 dataset.		
Models	Jaccard on GPI 1	Jaccard on GPI 3
Basic LEAP	0.510	0.385
LEAP + RL	**0.558**	**0.434**

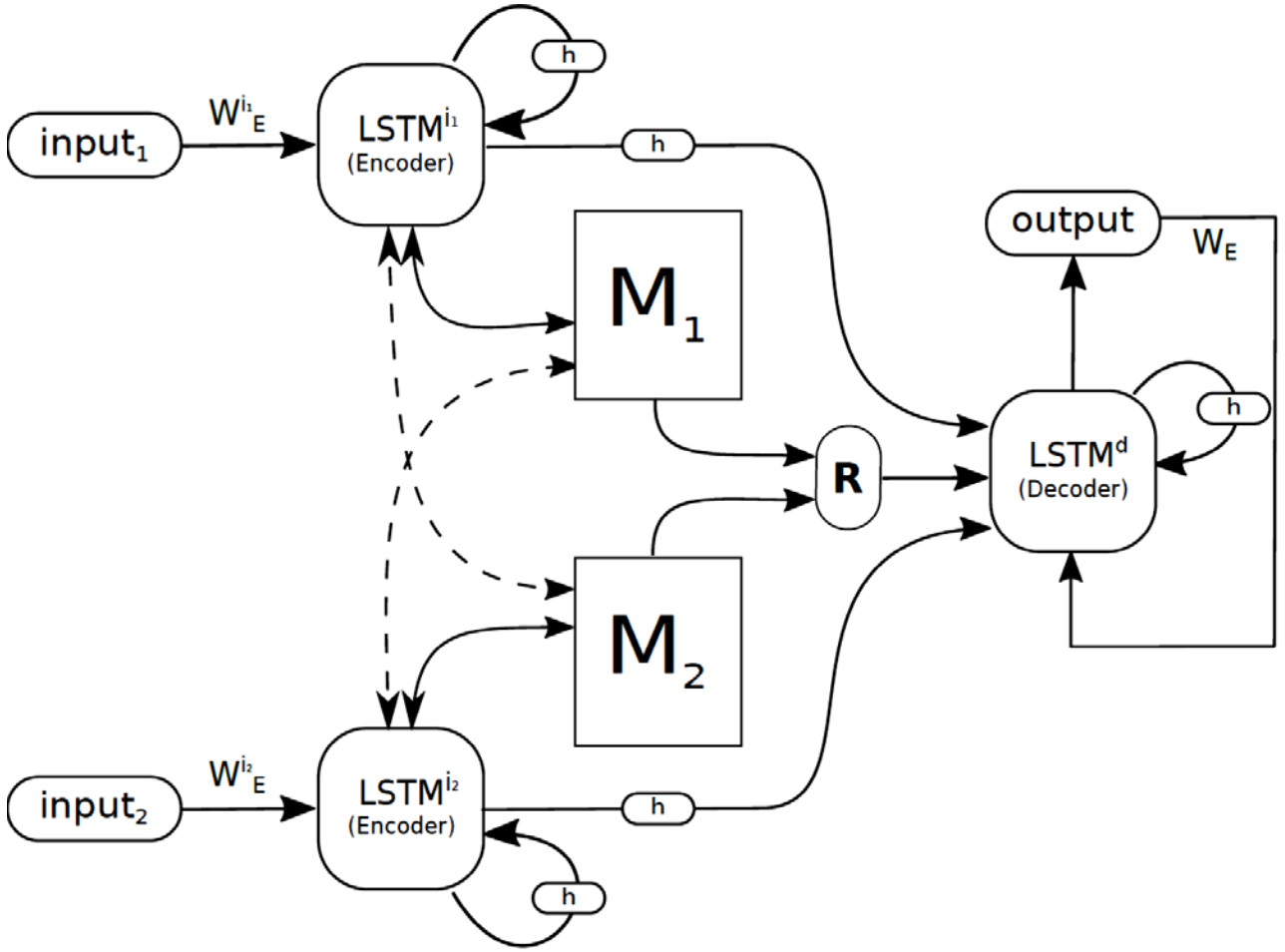
#REF: Zhang et al., "LEAP: Learning to prescribe effective and safe treatment combinations for multimorbidity", KDD'17.

Healthcare has multiple sequential views

Reads multiple EMR channels (disease, procedure, medication)

Memory can be shared or separated.

Generate a sequence of outputs (e.g., medications recommendation, or future disease progression).



#Ref: Le, Hung, Truyen Tran, and Svetha Venkatesh. "Dual Memory Neural Computer for Asynchronous Two-view Sequential Learning." *KDD18*.

DMNC: drug prescription

Two views:

+ Diagnoses

+ Procedures

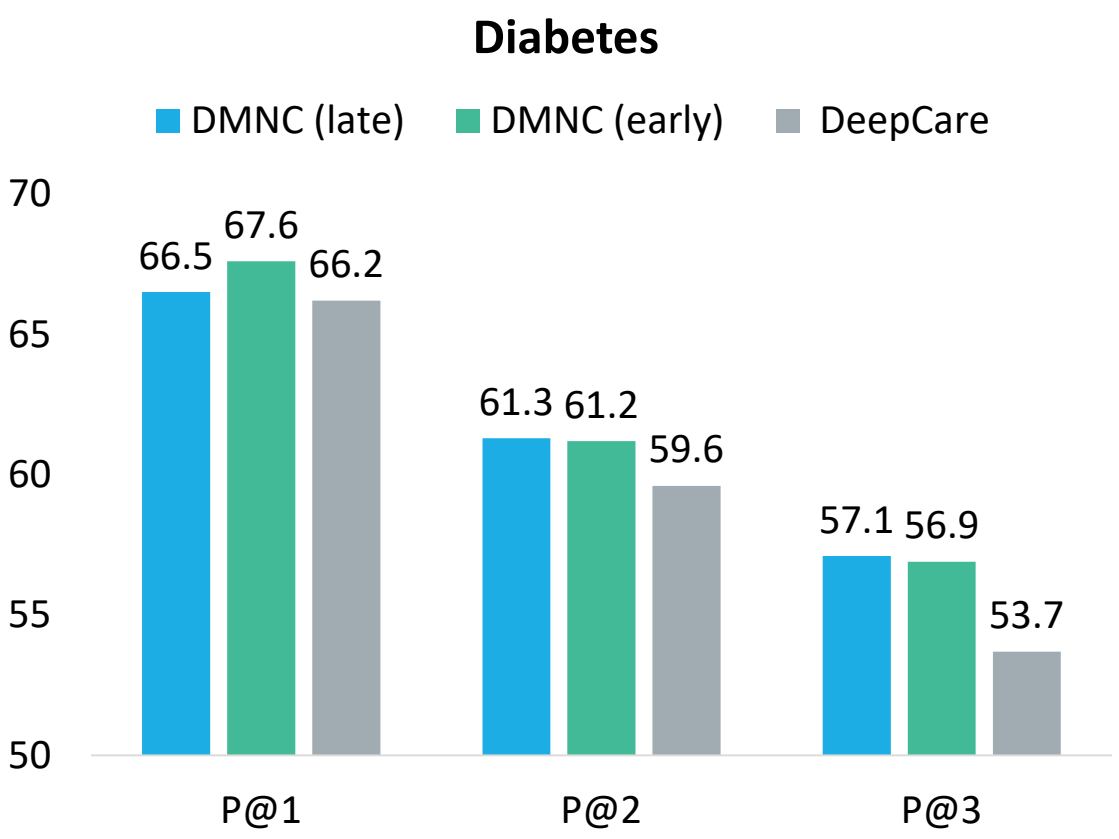
Two modes of memory:

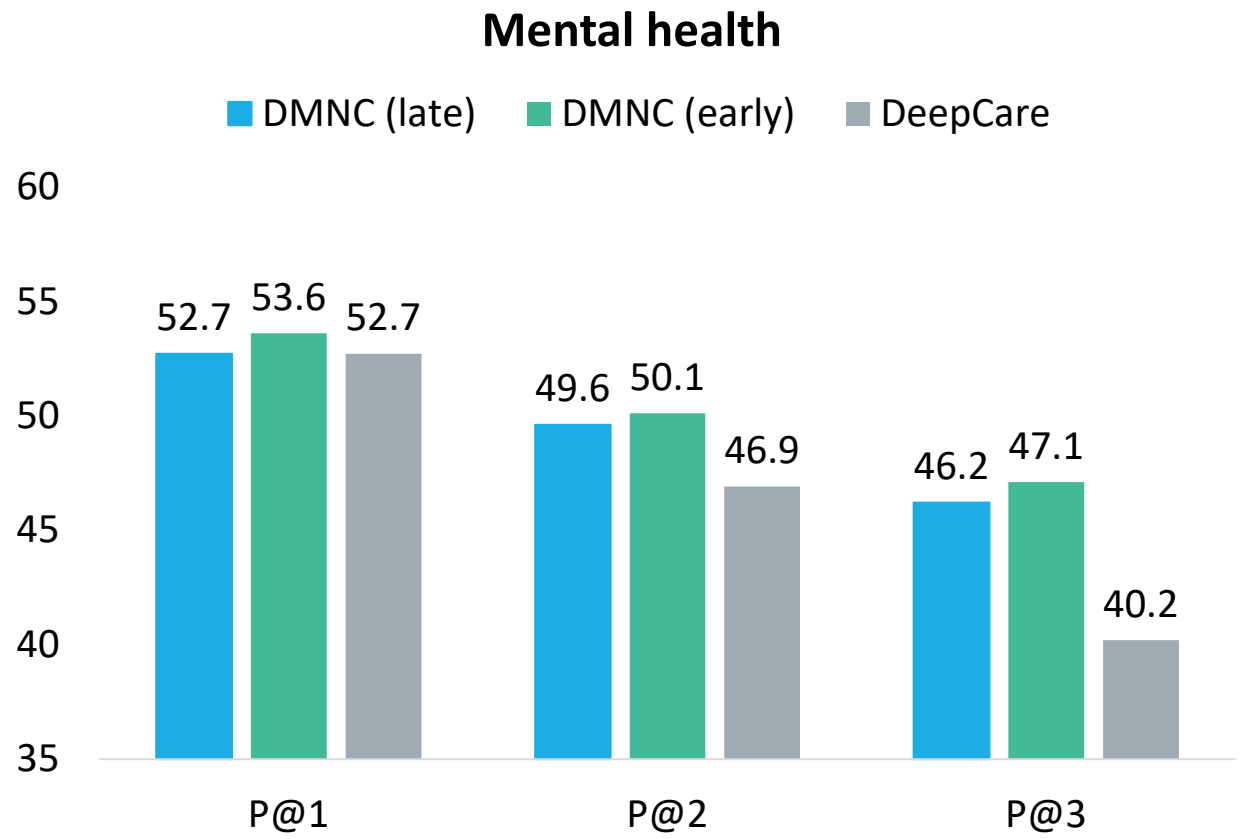
+ Late fusion

+ Early fusion

Model	AUC	F1	P@1	P@2	P@5
Diagnosis Only					
Binary Relevance	82.6	69.1	79.9	77.1	70.3
Classifier Chains	66.8	63.8	68.3	66.8	61.1
LSTM	84.9	70.9	90.8	86.7	79.1
DNC	85.4	71.4	90.0	86.7	79.8
Procedure Only					
Binary Relevance	81.8	69.4	82.6	80.1	73.6
Classifier Chains	63.4	61.7	83.7	80.3	71.9
LSTM	83.9	70.8	88.1	86.0	78.4
DNC	83.2	70.4	88.4	85.8	78.7
Diagnosis and procedure					
Binary Relevance	84.1	70.3	81.0	78.2	72.3
Classifier Chains	64.6	63.0	84.6	81.5	74.2
LSTM	85.8	72.1	91.6	86.8	80.5
DNC	86.4	72.4	90.9	87.4	80.6
Dual LSTM	85.4	71.4	90.6	87.1	80.5
WLAS	86.6	72.5	91.9	88.1	80.9
$DMNC_l$	87.4	73.2	**92.4**	88.9	**82.6**
$DMNC_e$	**87.6**	**73.4**	92.1	**89.9**	82.5

DMNC: disease progression





Big room: Towards personalized healthcare

Medical practice as recommender systems

Personalizing clinical practice guides

Research done on “homogeneous”, healthy subjects

- It is very hard for doctors to “manually” personalize their “recommendations”

Better: on-demand drug design (next)

Agenda

Topic 1: Introduction (20 mins)

Topic 2: Brief review of deep learning (30 mins)

- Classic architectures
- Capsules & graphs
- Memory & attention

Topic 3: Genomics (30 mins)

- Nanopore sequencing
- Genomics modelling

QA (10 mins)

Break (30 mins)

Topic 4: Healthcare (40 mins)

- Time series (regular & irregular)
- EMR analysis: Trajectories prediction
- EMR analysis: Sequence generation

Topic 5: Data efficiency (40 mins)

- Few-shot learning
- Generative models
- Unsupervised learning of drugs

Topic 6: Future outlook

QA (10 mins)

Few-shot deep learning

Lots of biomedical problems are data poor

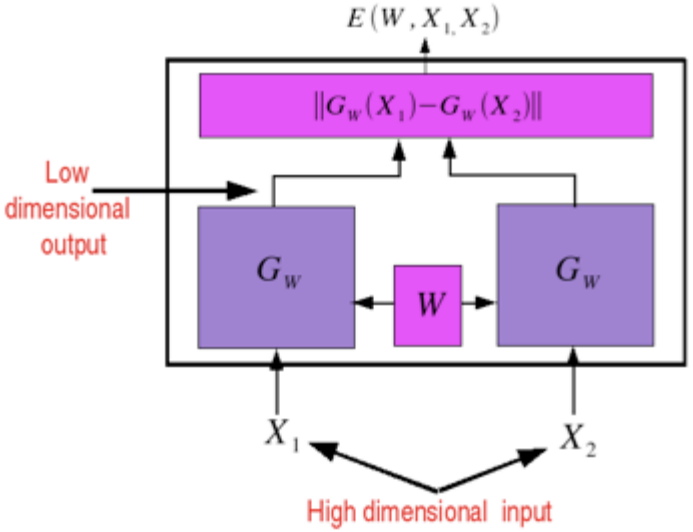
- Rare drugs
- Rare diseases
- Huge cost of data collection (e.g., ask a doctor to label data for you!!!)

Distance metrics learning (DML) methods

- Learn to full any pair of the similar data points, and push the dissimilar
- Well-known methods: Siamese networks

Meta-learning strategies

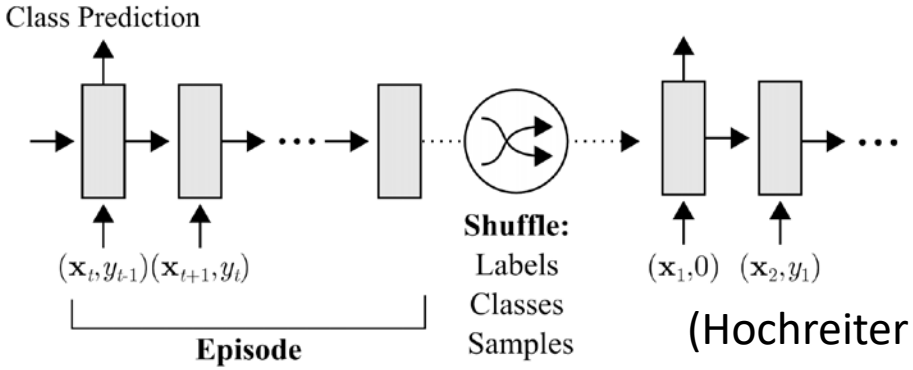
- Tasks are presented in sequence
- New tasks can borrow from similar prior tasks



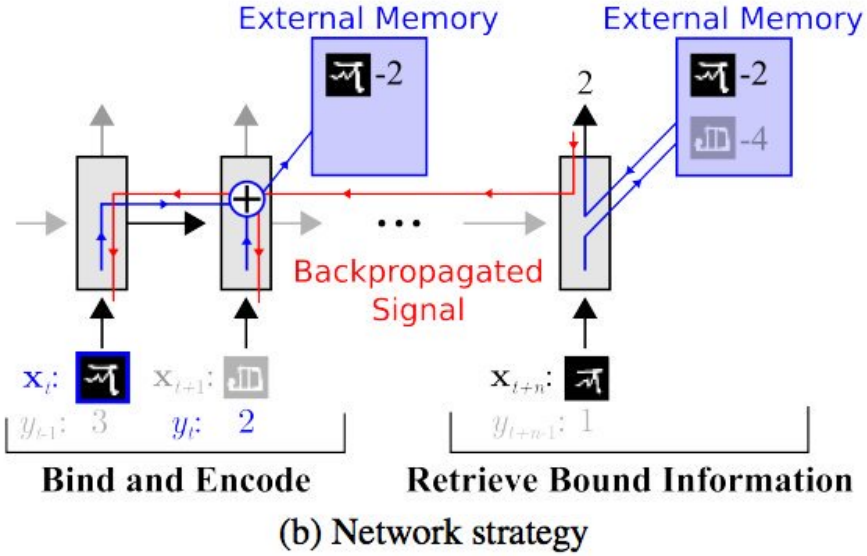
#REF: Chopra, Sumit, Raia Hadsell, and Yann LeCun. "Learning a similarity metric discriminatively, with application to face verification." *Computer Vision and Pattern Recognition, 2005. CVPR 2005. IEEE Computer Society Conference on*. Vol. 1. IEEE, 2005.

Meta-learning strategies

(Santoro et al, 2016)



(Hochreiter et al., 2001)



(b) Network strategy

(Mishra et al, 2017)

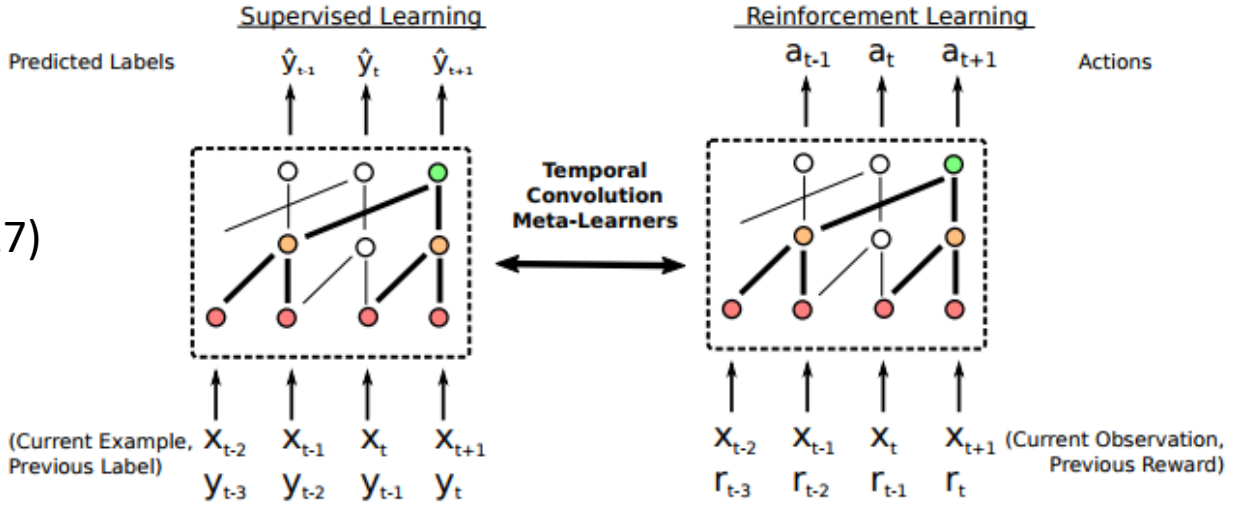
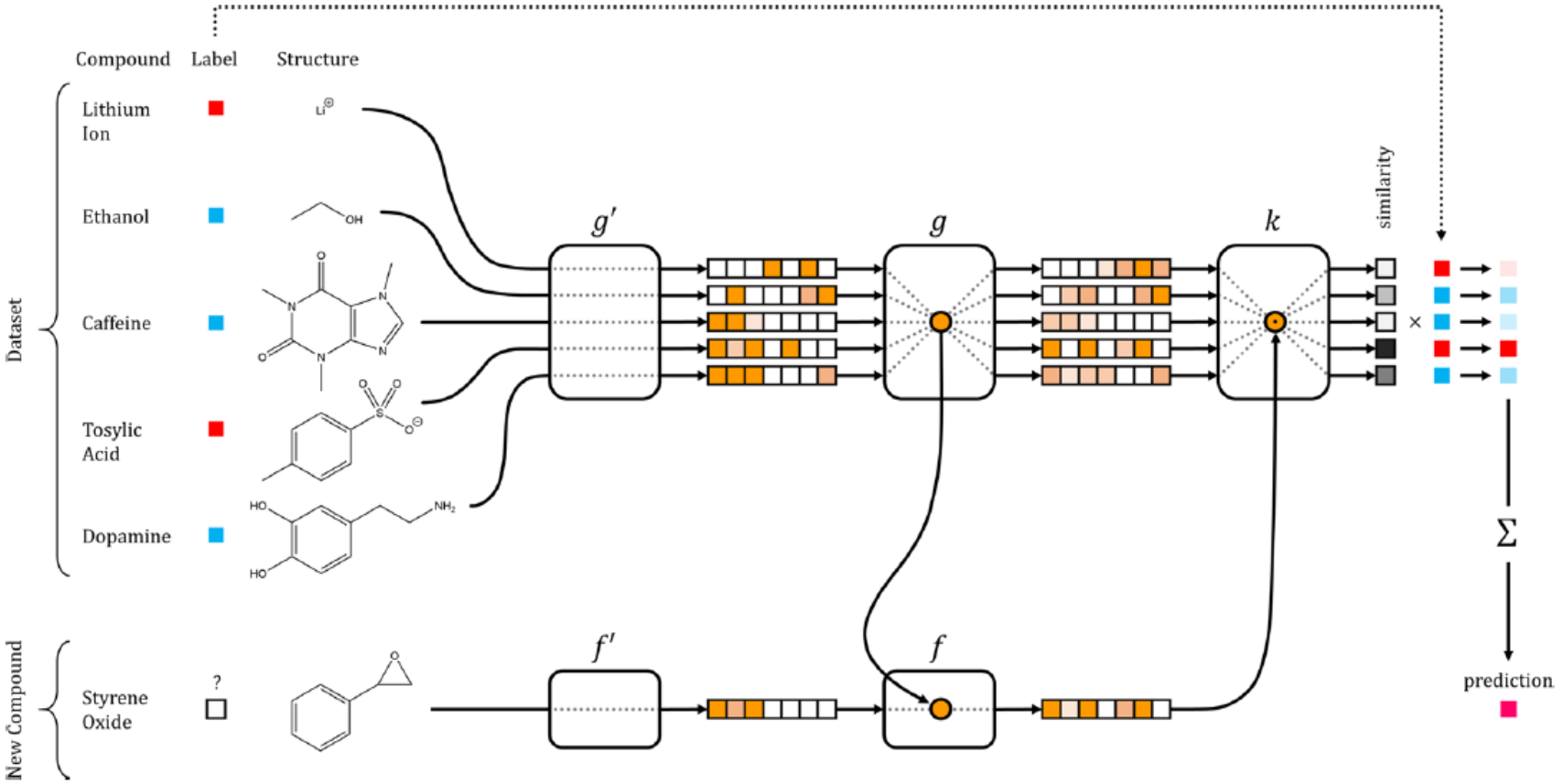


Figure 1: Overview of our temporal-convolution-based meta-learner (TCML). The same class of model architectures can be applied to both supervised and reinforcement learning.

One-shot learning for drug discovery



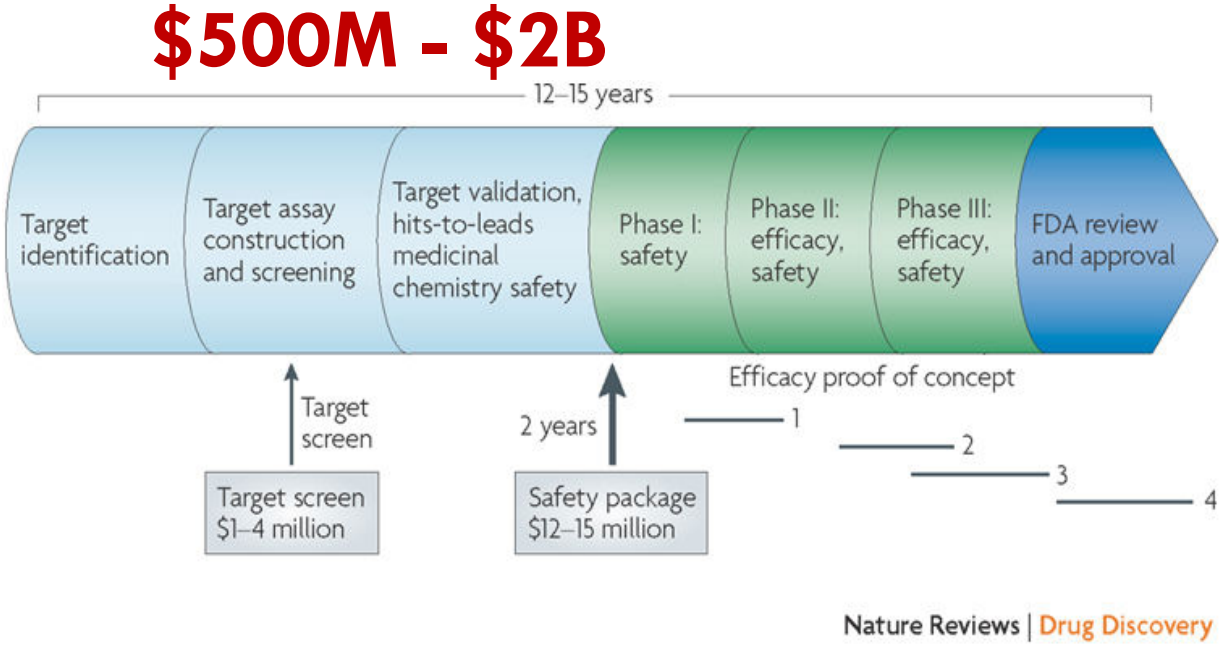
#REF: Altae-Tran, Han, et al. "Low Data Drug Discovery with One-Shot Learning." *ACS central science* 3.4 (2017): 283-293.

Generative deep learning for drug discovery

Predicting bioactivities from molecules

Drug representation, unsupervised learning from graphs

Generate from bioactivities to molecular graphs



#REF: Roses, Allen D. "Pharmacogenetics in drug discovery and development: a translational perspective." *Nature reviews Drug discovery* 7.10 (2008): 807-817.

Traditional method: Combinatorial chemistry

Generate variations on a template

Returns a list of molecules from this template that

- Bind to the pocket with good pharmacodynamics?
- Have good pharmacokinetics?
- Are synthetically accessible?

#REF: Talk by Chloé-Agathe Azencott titled “Machine learning for therapeutic research”, 12/10/2017

First step: Map molecule → drug properties (binding/acting)

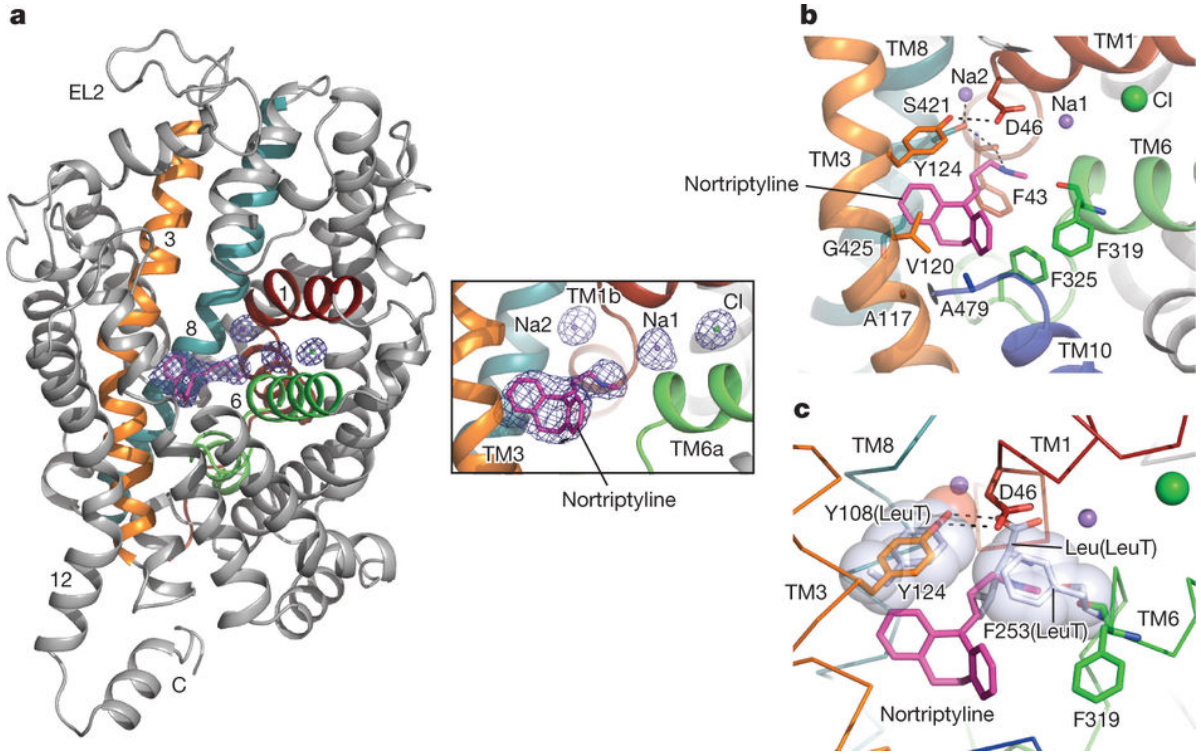
Drugs are small bio-molecules

Traditional techniques:

- Graph kernels (ML)
- Molecular fingerprints (Chemistry)

Modern techniques

- Molecule as graph: atoms as nodes, chemical bonds as edges

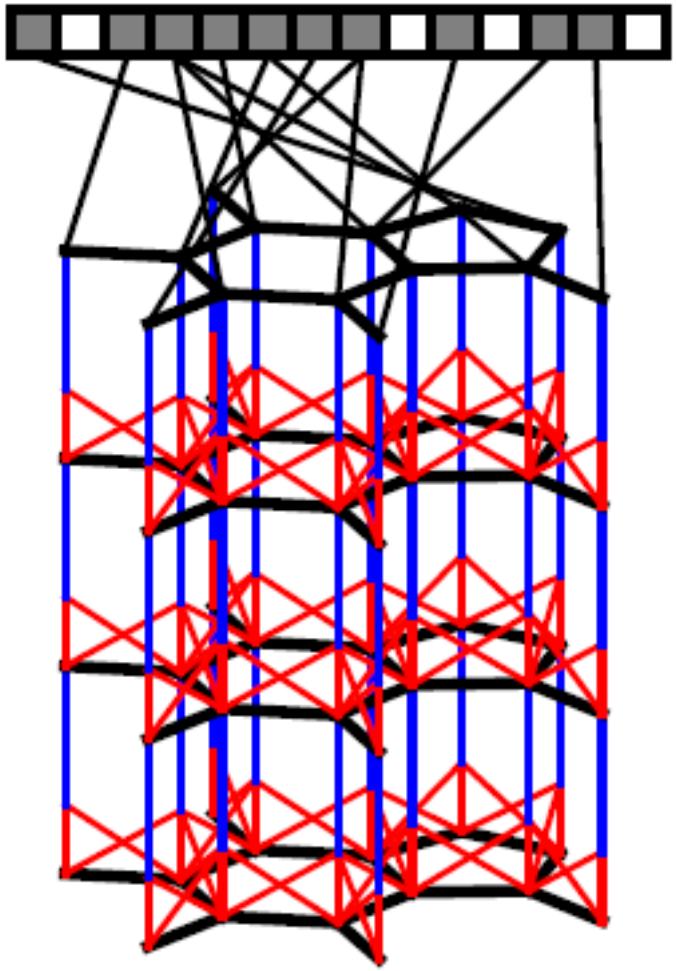


#REF: Penmatsa, Aravind, Kevin H. Wang, and Eric Gouaux. "X-ray structure of dopamine transporter elucidates antidepressant mechanism." *Nature* 503.7474 (2013): 85-90.

Molecular fingerprints

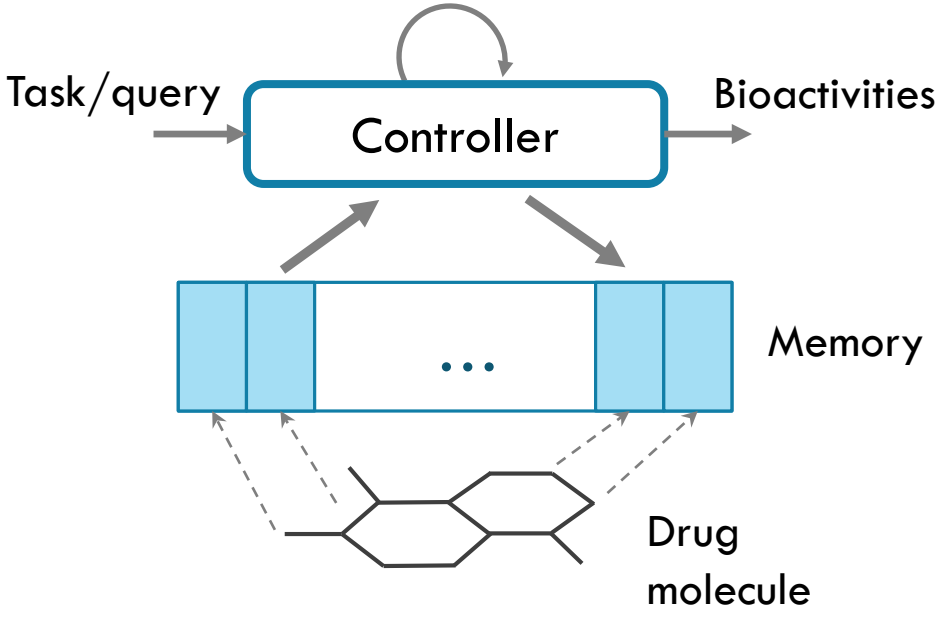
Algorithm 1 Circular fingerprints.

Input: molecule, radius R, fingerprint length S
Initialize: fingerprint vector $\boldsymbol{x} \leftarrow \mathbf{0}_S$
foreach atom a **in** molecule
    $\boldsymbol{r}_a \leftarrow q(a)$ #*extract initial atom features*
for $L = 1$ **to** R #*loop through layers*
    foreach atom a **in** molecule
        $\boldsymbol{r}_1 ... \boldsymbol{r}_N = \text{neighbors}(a)$
        $\boldsymbol{v} \leftarrow [\boldsymbol{r}_a, \boldsymbol{r}_1, ..., \boldsymbol{r}_N]$ #*combine neighbor features*
        $\boldsymbol{r}_a \leftarrow \text{hash}(\boldsymbol{v})$ #*refine atom features*
        $i \leftarrow \text{mod}(\boldsymbol{r}_a, S)$ #*convert to index*
        $x_i \leftarrow 1$ #*Write 1 (indicator) at index*
Return: binary vector $\boldsymbol{x}$.

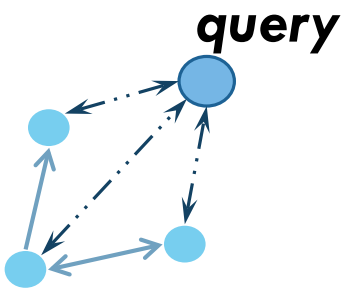


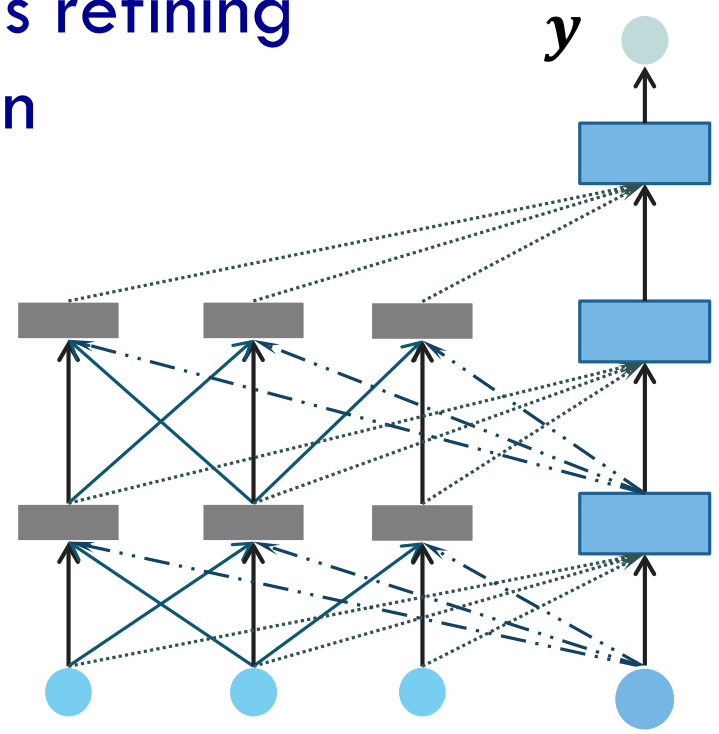
#REF: Duvenaud, David K., et al. "Convolutional networks on graphs for learning molecular fingerprints." *Advances in neural information processing systems*. 2015.

Graph memory networks



Message passing as refining atom representation





#Ref: Pham, Trang, Truyen Tran, and Svetha Venkatesh. "Graph Memory Networks for Molecular Activity Prediction." *ICPR'18*.

Graph memory networks: Results

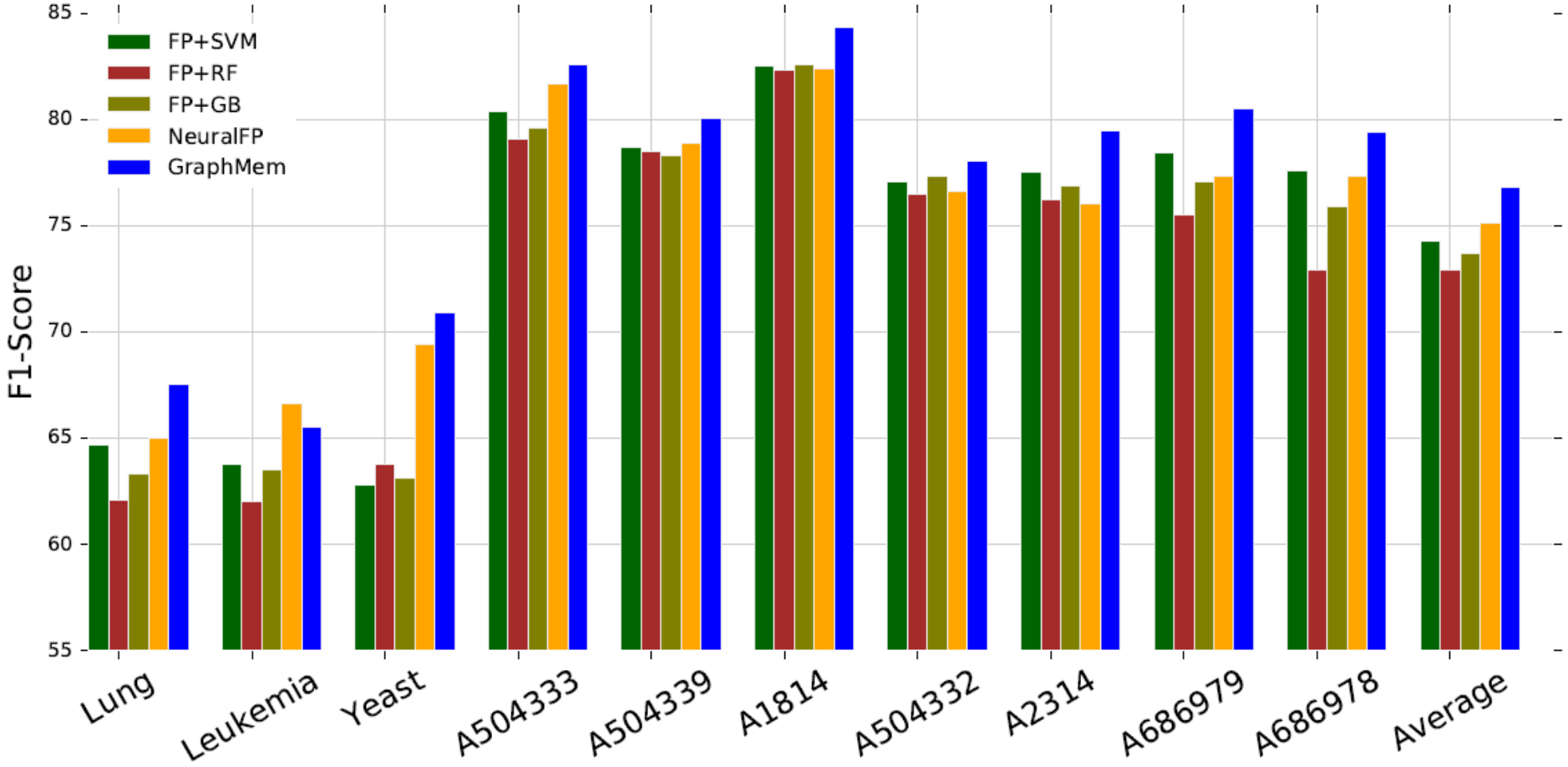


Figure 2: F1-score (%) for NCI datasets. FP = Fingerprint; RF = Random Forests; GBM = Gradient Boosting Machine. Best view in color.

Drug generation

We now have methods for compute bioactivties of a drug molecule

We need a reverse method to generate drug molecules from desirable bioactivities

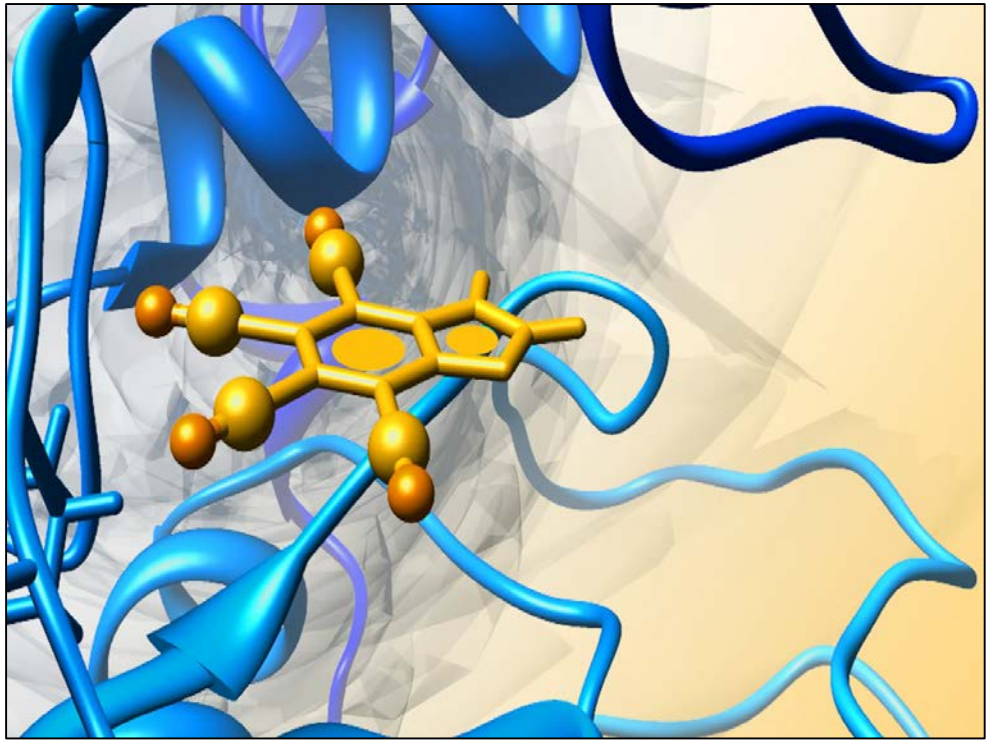
The space of drugs is estimated to be 1e+23 to 1e+60

- Only 1e+8 substances synthesized thus far.

It is impossible to model this space fully.

The current technologies are not mature for graph generations.

But approximate techniques do exist.



Source: pharmafactz.com

Theory: Generative models

Many applications:

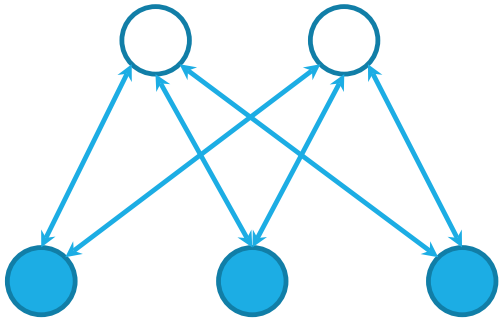
- Text to speech
- **Simulate data that are hard to obtain/share in real life (e.g., healthcare)**
- Generate meaningful sentences conditioned on some input (foreign language, image, video)
- Semi-supervised learning
- Planning

$$\mathbf{v} \sim P_{model}(\mathbf{v})$$
$$P_{model}(\mathbf{v}) \approx P_{data}(\mathbf{v})$$

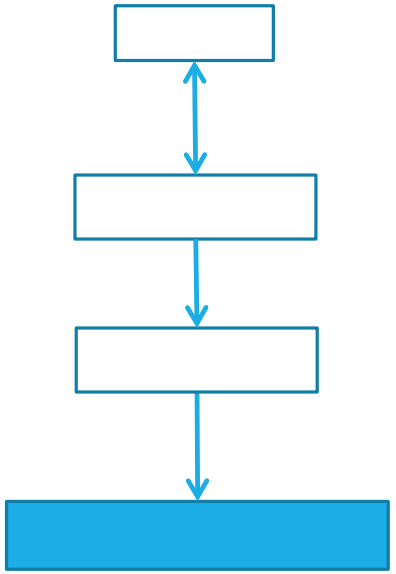
A family: RBM/DAE → DBN/SDAE → DBM

$$p(\mathbf{v}, \mathbf{h}; \psi) \propto \exp\left[-E(\mathbf{v}, \mathbf{h}; \psi)\right]$$

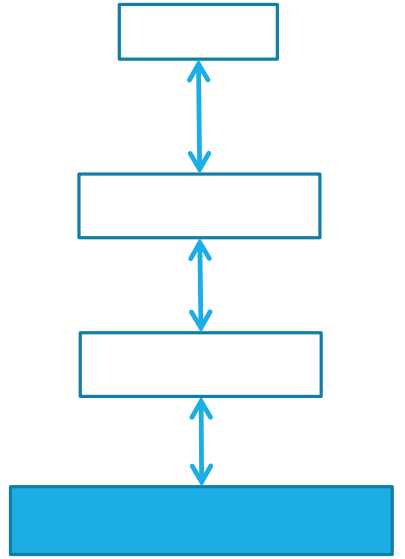
energy



Restricted Boltzmann Machine (~1994, 2001)



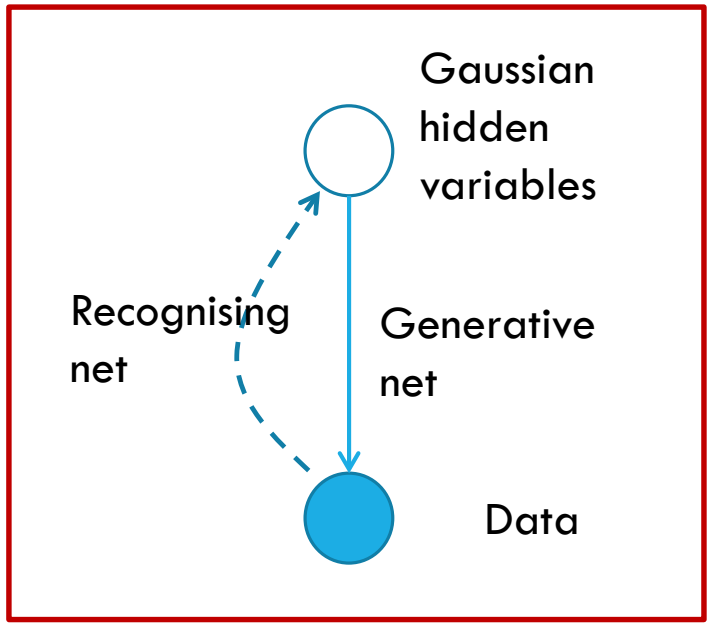
Deep Belief Net (2006)

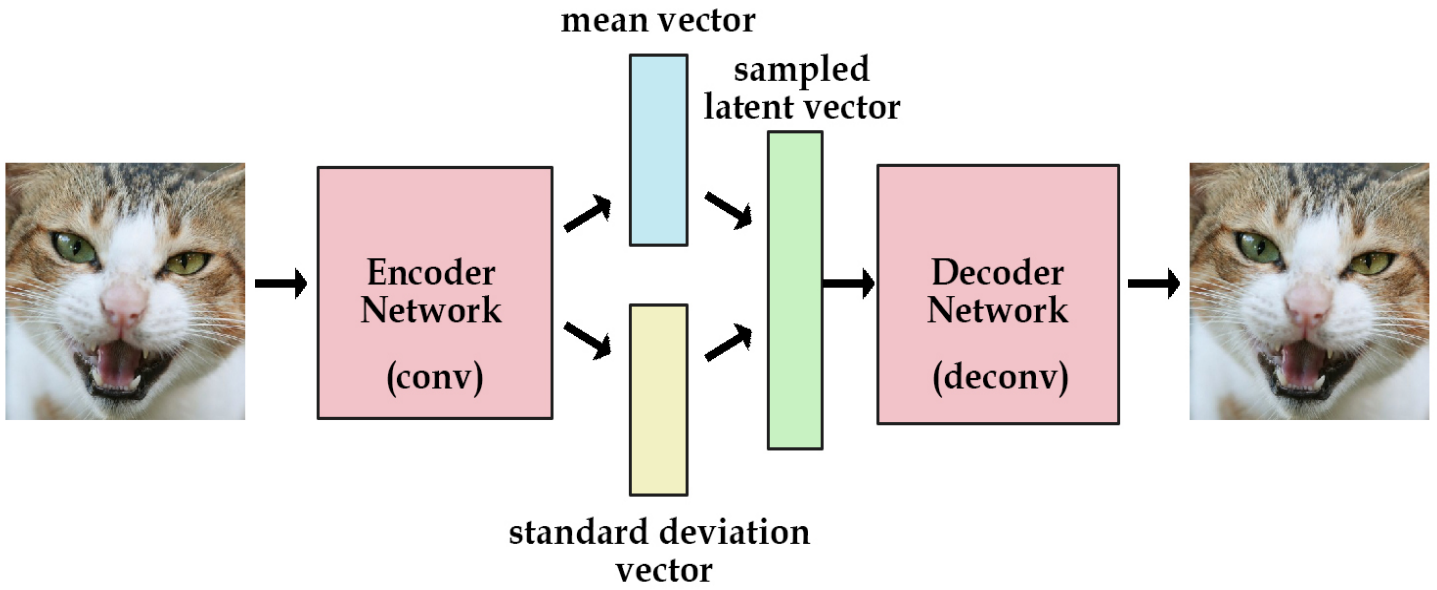


Deep Boltzmann Machine (2009)

Variational Autoencoder
(Kingma & Welling, 2014)

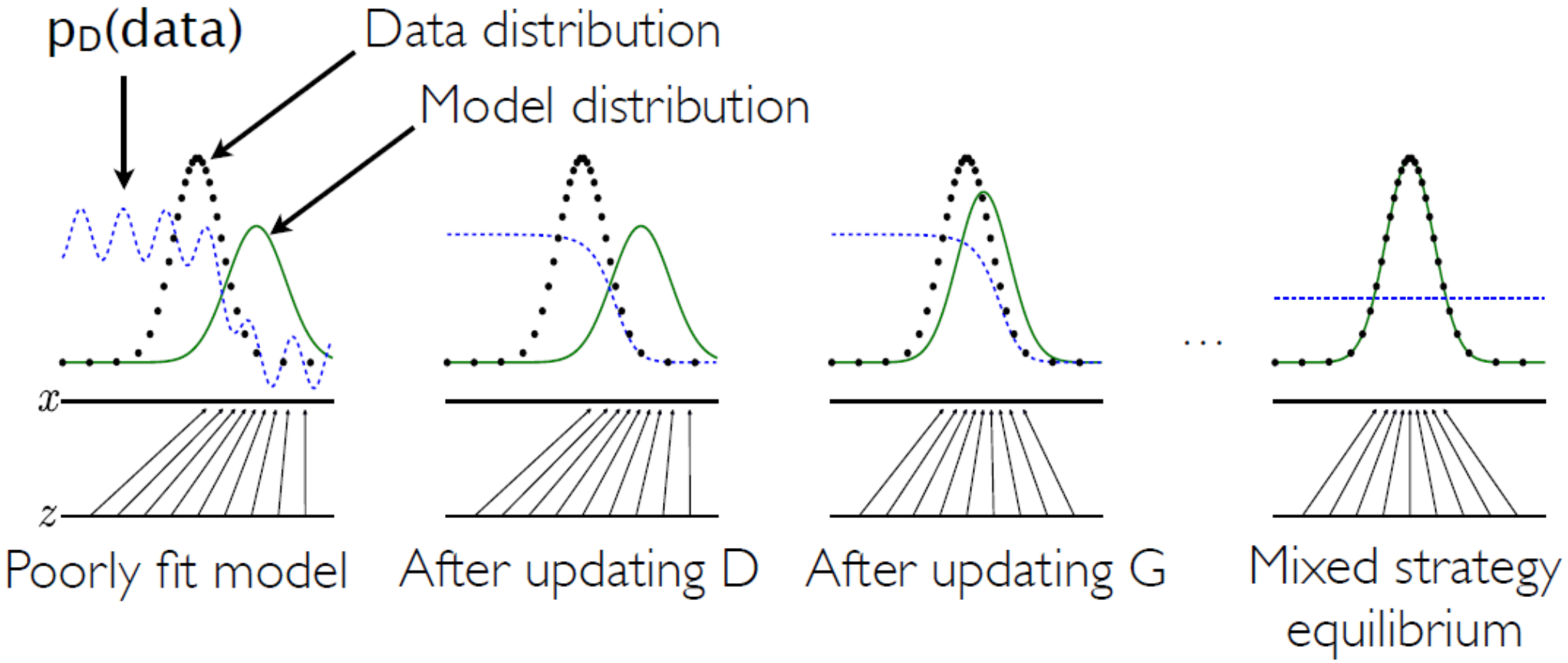
Two separate processes: generative (hidden → visible) versus recognition (visible → hidden)



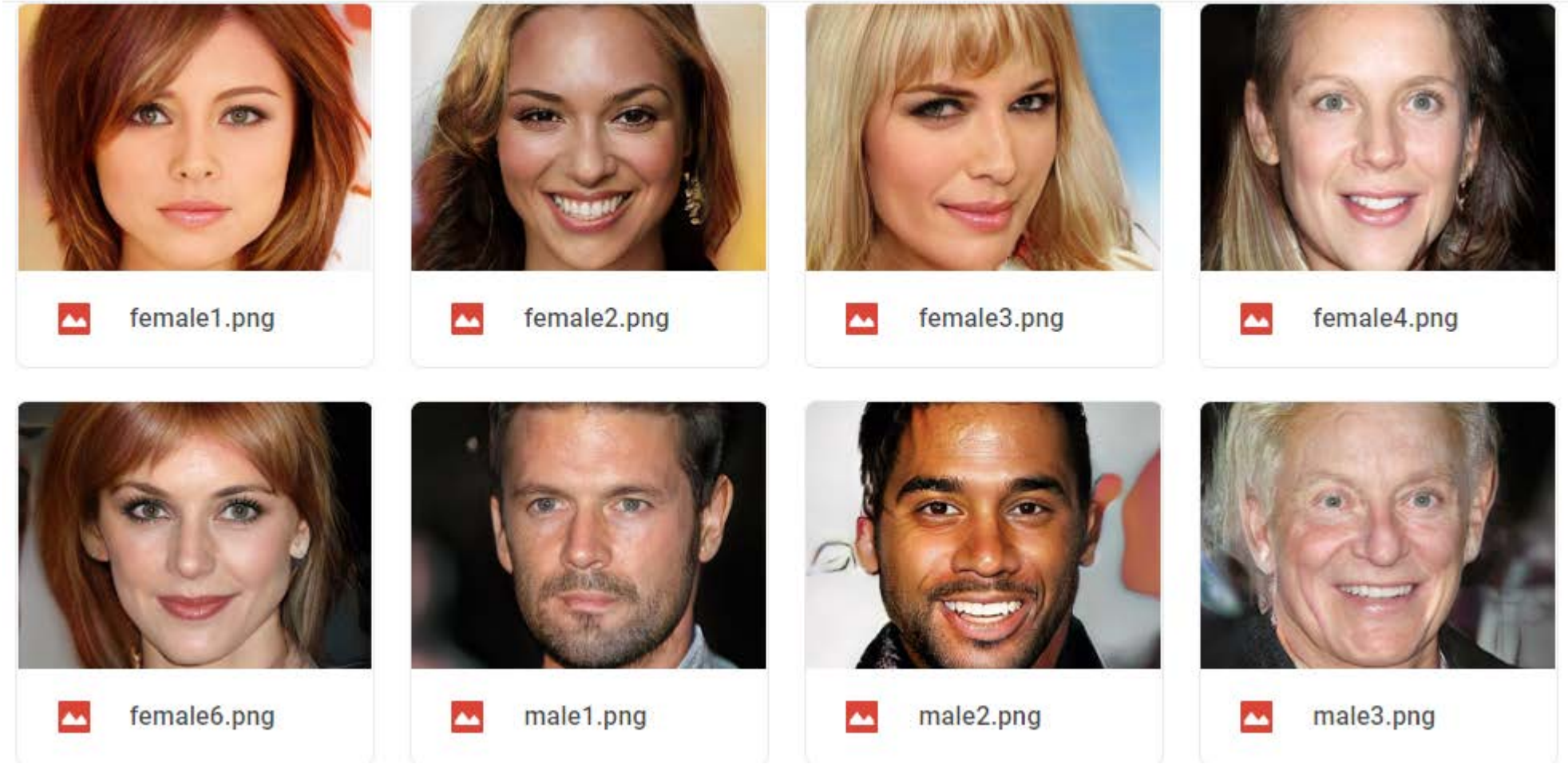


http://kvfrans.com/variational-autoencoders-explained/

GAN: implicit density models
(Adapted from Goodfellow's, NIPS 2014)



Progressive GAN: Generated images



Karras, T., Aila, T., Laine, S., & Lehtinen, J. (2017). Progressive growing of gans for improved quality, stability, and variation. *arXiv preprint arXiv:1710.10196*.

Drug generation approaches

Representing molecules using fingerprints

Representing graph as string, and use sequence VAEs or GANs.

Graph VAE & GAN

- Model nodes & interactions
- Model cliques

Sequences

- Iterative methods

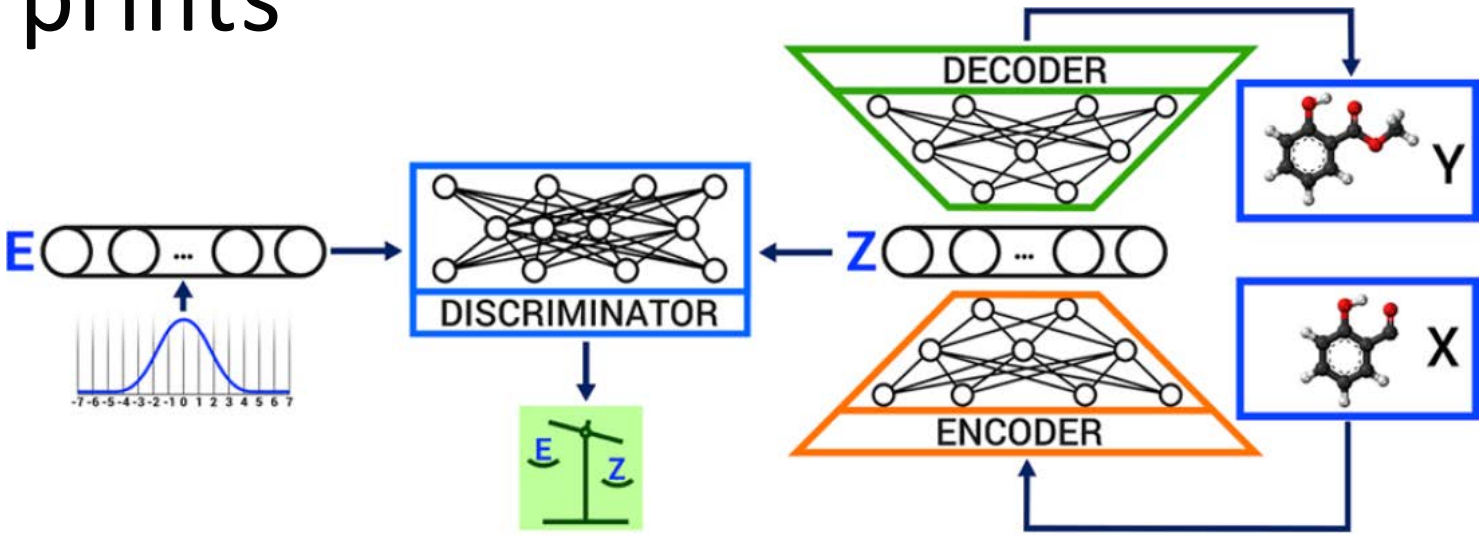
Reinforcement learning

- Discrete objectives

Any combination of these + memory.

Kadurin, Artur, et al. "The cornucopia of meaningful leads: Applying deep adversarial autoencoders for new molecule development in oncology." *Oncotarget* 8.7 (2017): 10883.

Molecule → fingerprints



Input of the encoder : the fingerprint of a molecule

The decoder outputs the predicted fingerprint .

The generative model generates a vector E, which is then discriminated from the latent vector of the real molecule by the discriminator.

Molecule → string

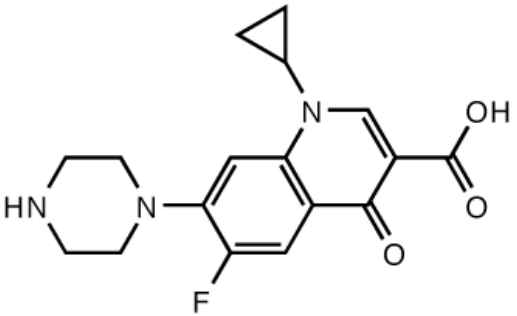
Using SMILES representation of drug, to convert a molecular graph into a string

- SMILES = Simplified Molecular-Input Line-Entry System

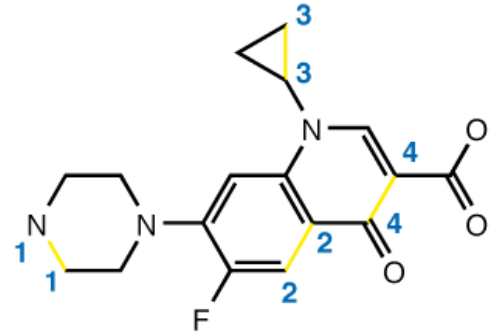
Then using sequence-to-sequence + VAE/GAN to model the continuous space that encodes/decodes SMILES strings

- Allow easy optimization on the continuous space

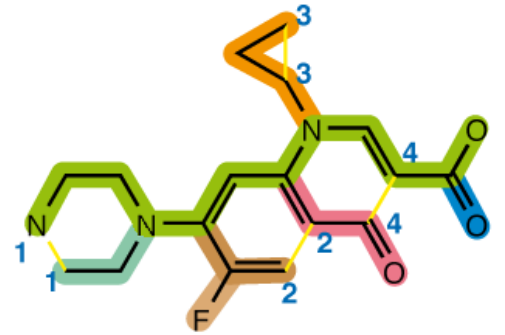
A



B



C



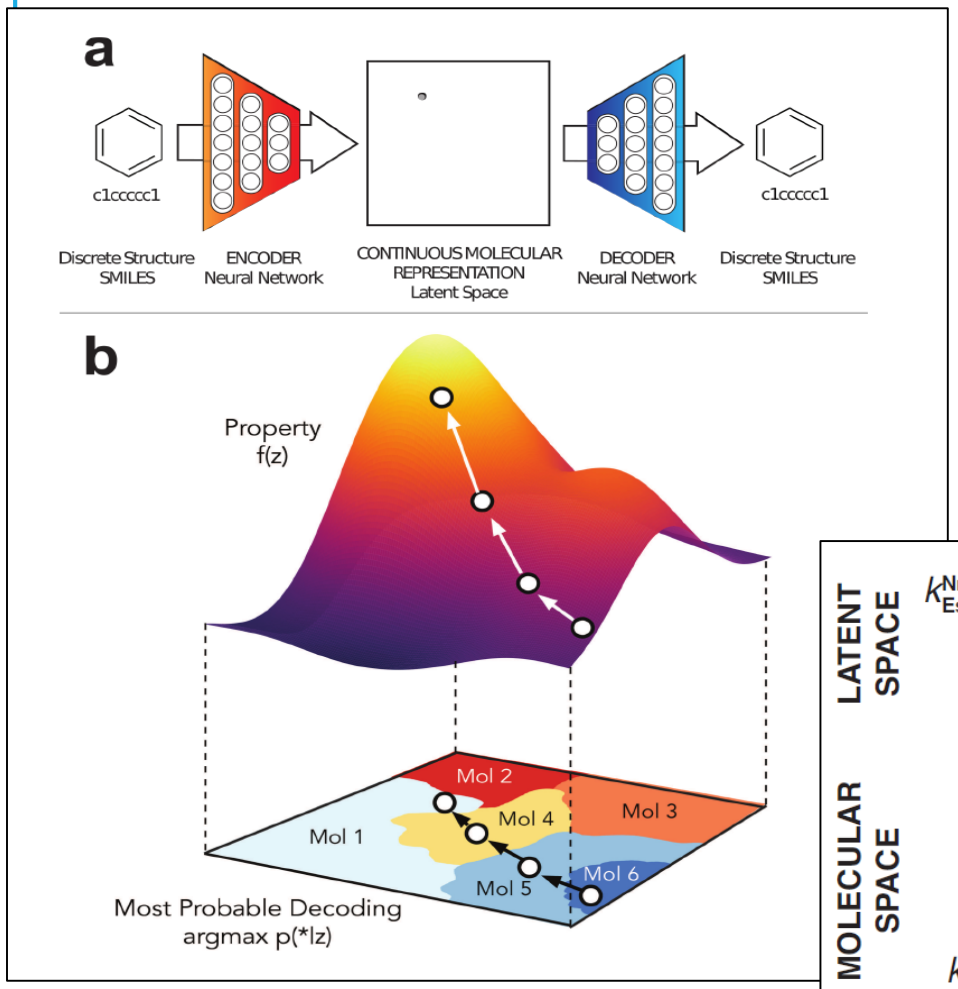
D

N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

Source: wikipedia.org

#REF: Gómez-Bombarelli, Rafael, et al. "Automatic chemical design using a data-driven continuous representation of molecules." *arXiv preprint arXiv:1610.02415* (2016).

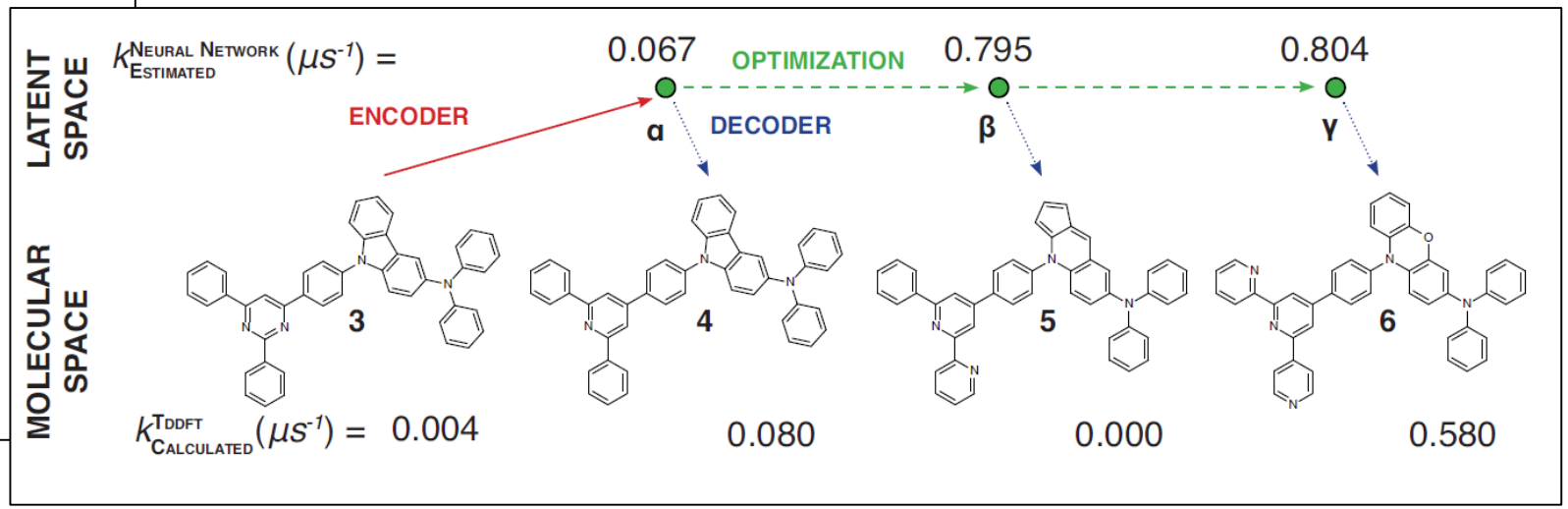
VAE for drug space modelling



Uses VAE for sequence-to-sequence.

#REF: Bowman, Samuel R., et al. "Generating sentences from a continuous space." *arXiv preprint arXiv:1511.06349* (2015).

Gómez-Bombarelli, Rafael, et al. "Automatic chemical design using a data-driven continuous representation of molecules." *ACS Central Science* (2016).



Drawbacks of string representation

String → graphs is not unique!

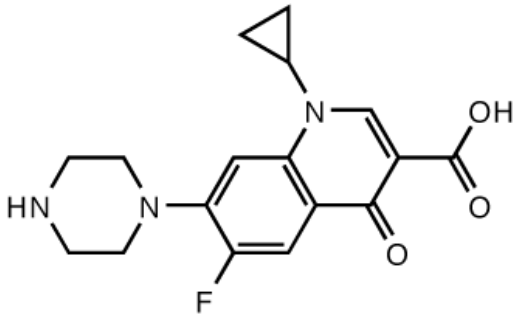
Lots of string are invalid

Precise 3D information is lost

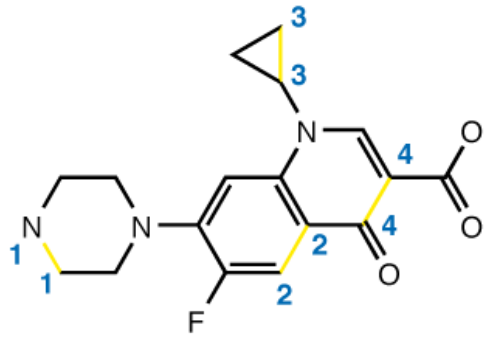
Short range in graph may become long range in string

A better way is to encode/decode graph directly.

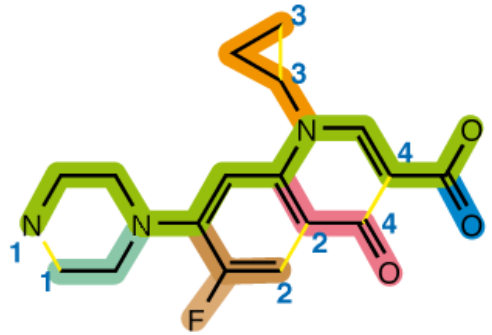
A



B



C



D

N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

Source: wikipedia.org

#REF: Gómez-Bombarelli, Rafael, et al. "Automatic chemical design using a data-driven continuous representation of molecules." *arXiv preprint arXiv:1610.02415* (2016).

Better approach: Generating molecular graphs directly

No regular, fixed-size structures

Graphs are ***permutation invariant***:

- #permutations are exponential function of #nodes
- The probability of a generated graph G need to be marginalized over all possible permutations

Multiple objectives:

- **Diversity** of generated graphs
- **Smoothness** of latent space
- Agreement with or optimization of multiple "**drug-like**" objectives

GraphVAE

Handles irregular structures

- Predict the whole adjacency matrix, node types and edge types

Deals with variable size graph

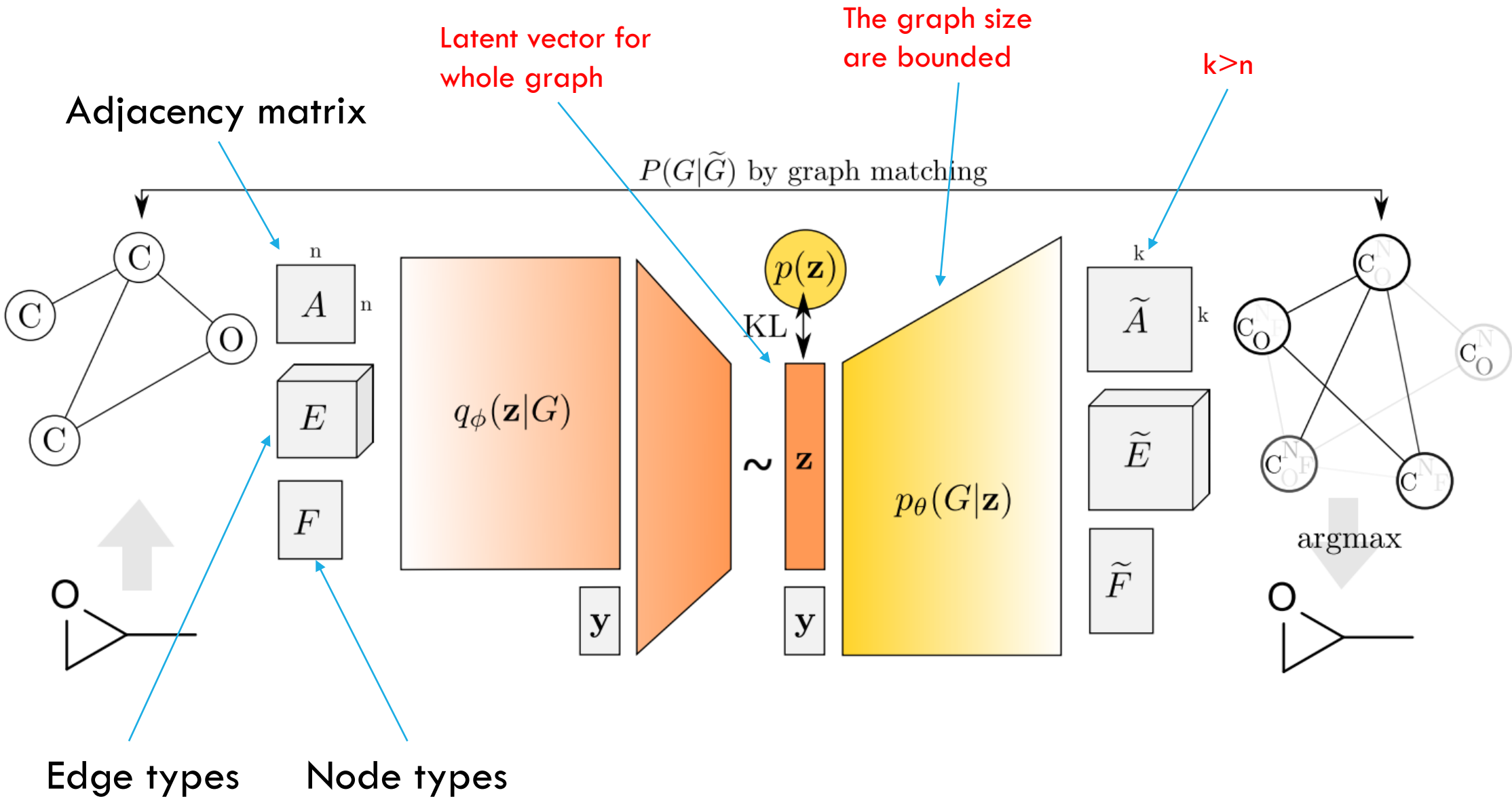
- Bounded by the size of the largest graph in training data.

Handles permutation invariance

- Matching every pair of nodes in 2 graphs

Partially promotes diversity

#REF: Simonovsky, M., & Komodakis, N. (2018). GraphVAE: Towards Generation of Small Graphs Using Variational Autoencoders. *arXiv preprint arXiv:1802.03480*.



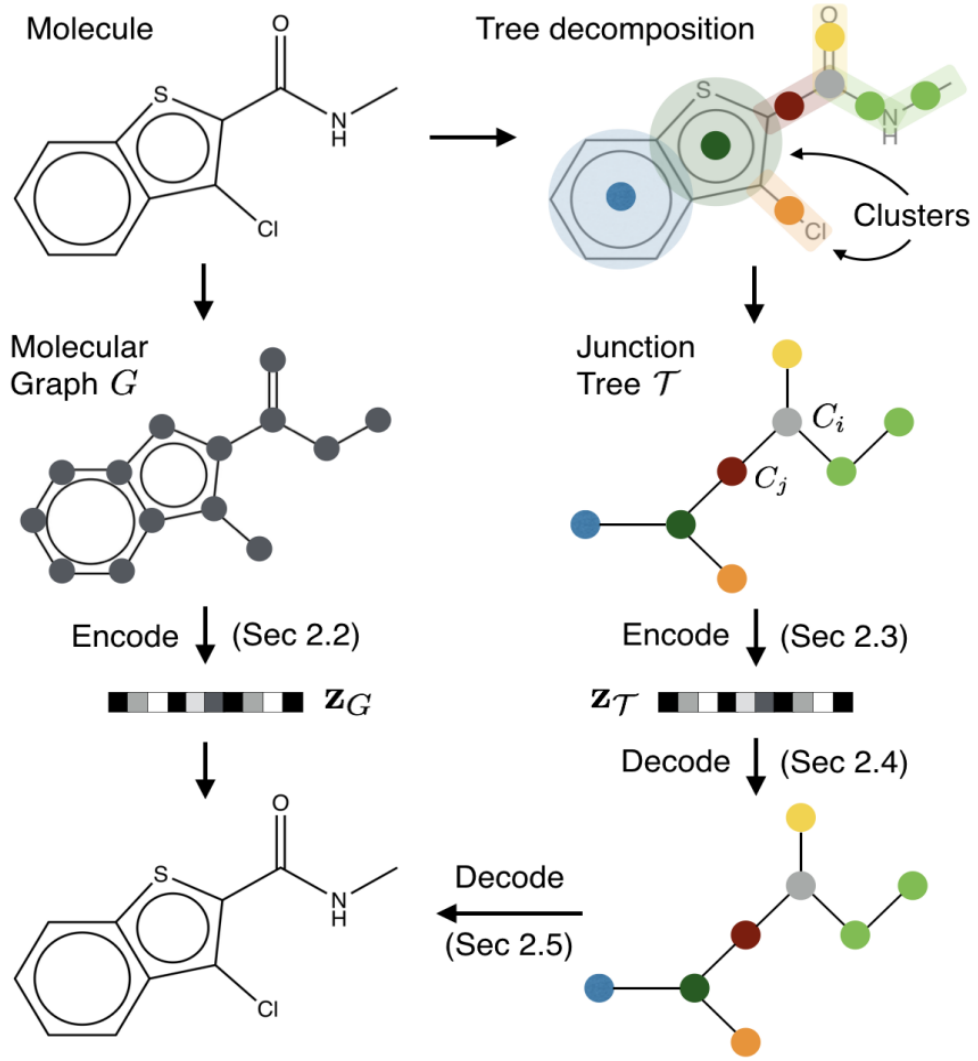
#REF: Simonovsky, M., & Komodakis, N. (2018). GraphVAE: Towards Generation of Small Graphs Using Variational Autoencoders. *arXiv preprint arXiv:1802.03480*.

Junction tree VAE

Junction tree is a way to build a “thick-tree” out of a graph

Cluster vocab:

- rings
- bonds
- atoms



Jin, W., Barzilay, R., & Jaakkola, T. (2018). Junction Tree Variational Autoencoder for Molecular Graph Generation. *ICML'18*.

Algorithm 2 Tree decomposition of molecule $G = (V, E)$

$V_1 \leftarrow$ the set of bonds $(u, v) \in E$ that do not belong to any rings.
$V_2 \leftarrow$ the set of simple rings of G.
for r_1, r_2 **in** V_2 **do**
  Merge rings r_1, r_2 into one ring if they share more than two atoms (bridged rings).
end for
$V_0 \leftarrow$ atoms being the intersection of three or more clusters in $V_1 \cup V_2$.
$\mathcal{V} \leftarrow V_0 \cup V_1 \cup V_2$
$\mathcal{E} \leftarrow \{(i, j, c) \in \mathcal{V} \times \mathcal{V} \times \mathbb{R} \mid |i \cap j| > 0\}$. Set $c = \infty$ if $i \in V_0$ or $j \in V_0$, and $c = 1$ otherwise.
Return The maximum spanning tree over cluster graph $(\mathcal{V}, \mathcal{E})$.

Method	Reconstruction	Validity
CVAE	44.6%	0.7%
GVAE	53.7%	7.2%
SD-VAE[2]	76.2%	43.5%
GraphVAE	-	13.5%
JT-VAE	**76.7%**	**100.0%**

Jin, W., Barzilay, R., & Jaakkola, T. (2018). Junction Tree Variational Autoencoder for Molecular Graph Generation. *ICML'18*.

Agenda

Topic 1: Introduction (20 mins)

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- Capsules & graphs
- Memory & attention

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QA (10 mins)

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- Generative models
- Unsupervised learning of drugs

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QA (10 mins)

Living in the future: AI for health care

We tend to overestimate the short-term and underestimate the long-term.

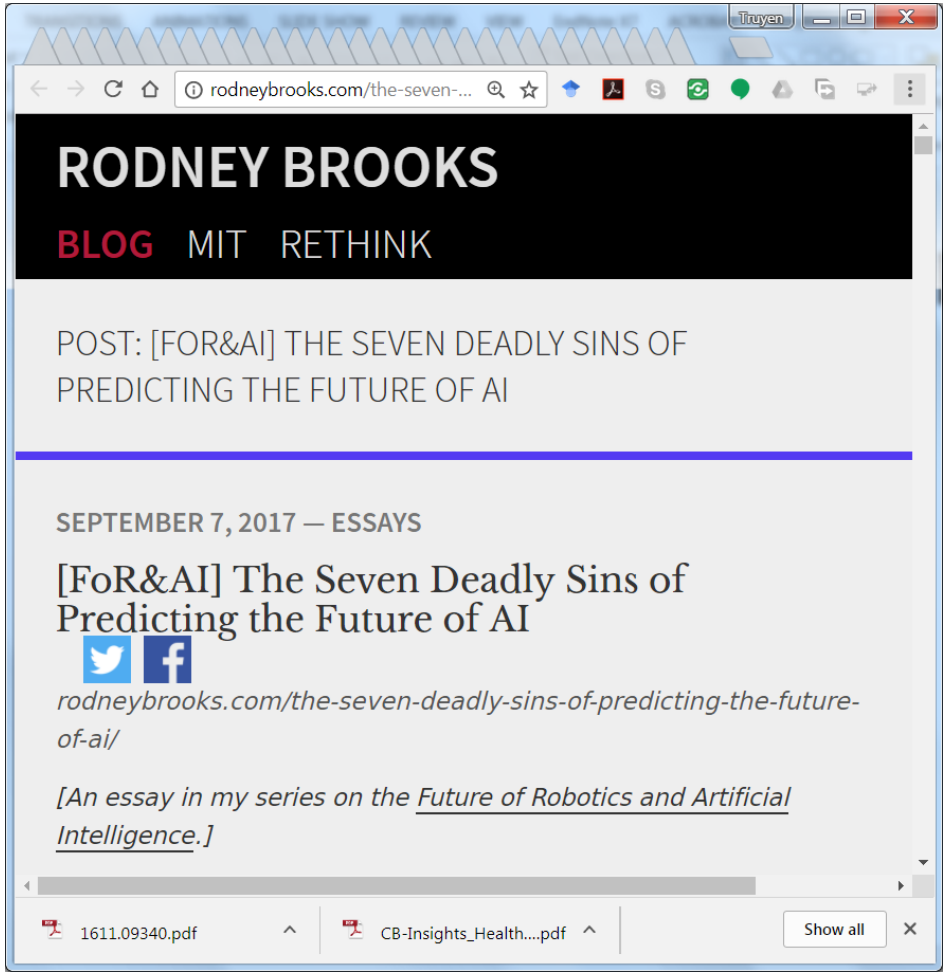
Bear in mind that anything beyond 5 years are nearly impossible to predict!

Let's map Kai-Fu Lee's vision:

- Wave 1: Internet data (→ PubMed, social media)
- **Wave 2: Business data (→EMR)**
- **Wave 3: Digitalize the physical world (→Drugs)**
- Wave 4: Full automation (→ Robot surgeons, GPs)

Some speculations (by me):

- https://letdataspeak.blogspot.com.au/2017/02/living-in-future-deep-learning-for.html



Toward personalized medicine

Will this patient response to that treatment?

Can we find the best treatment for a patient?

Which biomarkers predict the patient's response?

Sound familiar to Recommender Systems (patient = user, treatment = item)?

Can we synthesize a drug for the patient on-demand?

#REF: Talk by Chloé-Agathe Azencott titled "Machine learning for therapeutic research", 12/10/2017

Towards a dialog system → Replace GP?

Leveraging existing knowledge

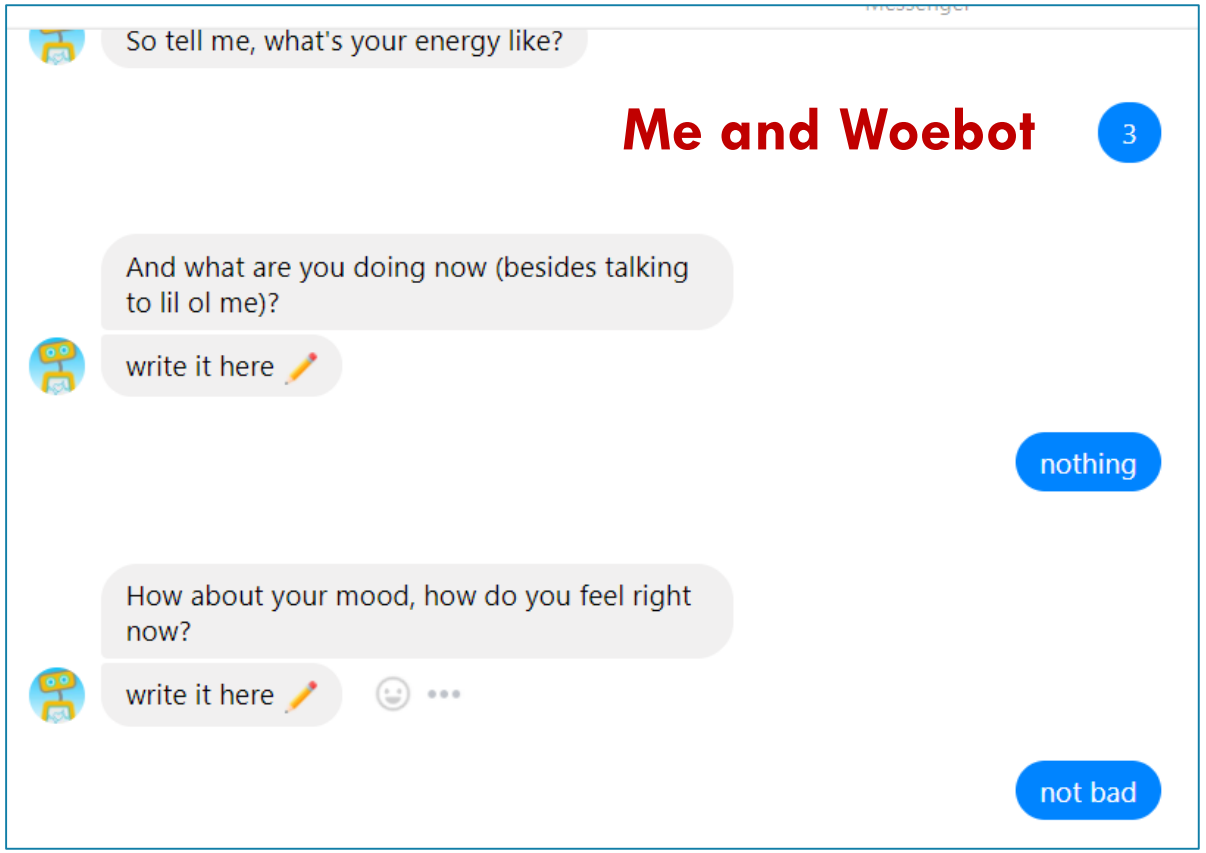
- Medical knowledge bases
- Medical texts
- Probably needs to build knowledge bases from text

Personalizing through EMRs

- Learn from hospitals data

Ask right questions → Finding answers from databases → Generating dialog

Never ending learning (NEL).



Thank you!

We're hiring

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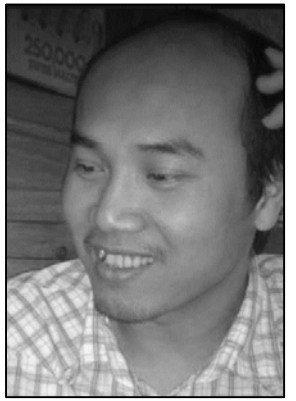
https://truyentran.github.io/scholarship.html

http://ahsanqawl.com/2015/10/qa/

The team that helps with slides







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