

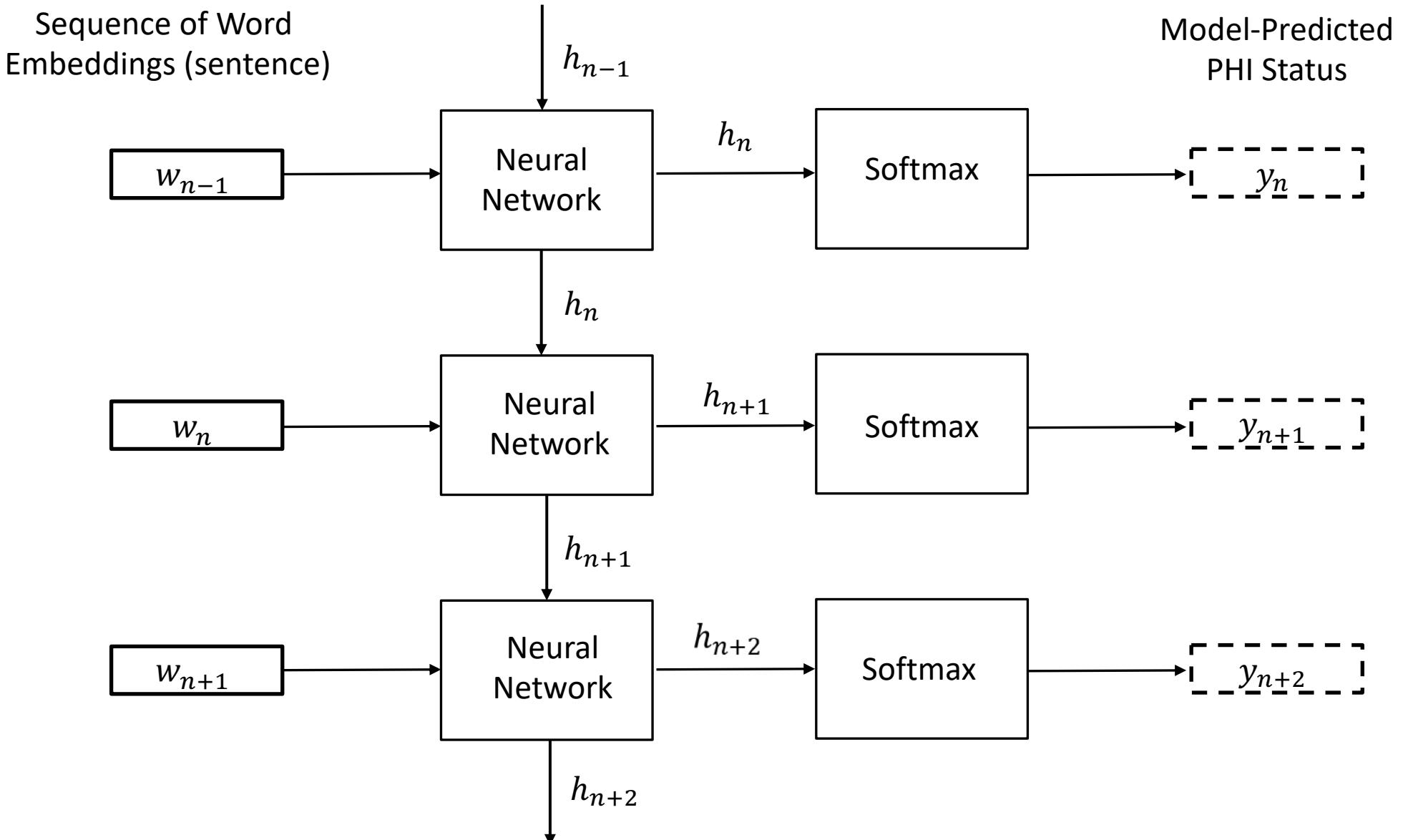
Sequences and Time-Series in Medicine

July 25, 2020

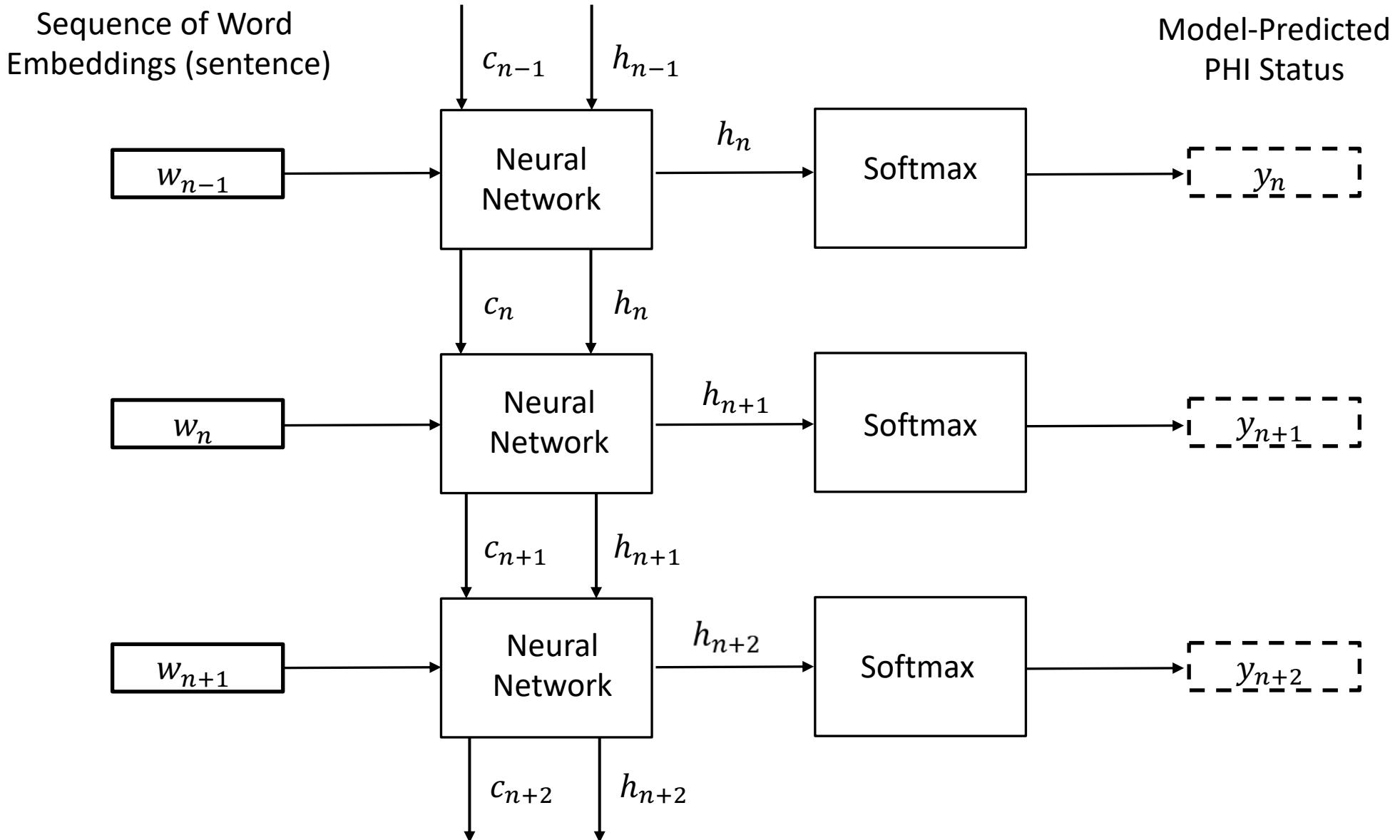
Applied Data Science
MMCi Term 4

Matthew Engelhard

Deidentification via Recurrent Neural Network...

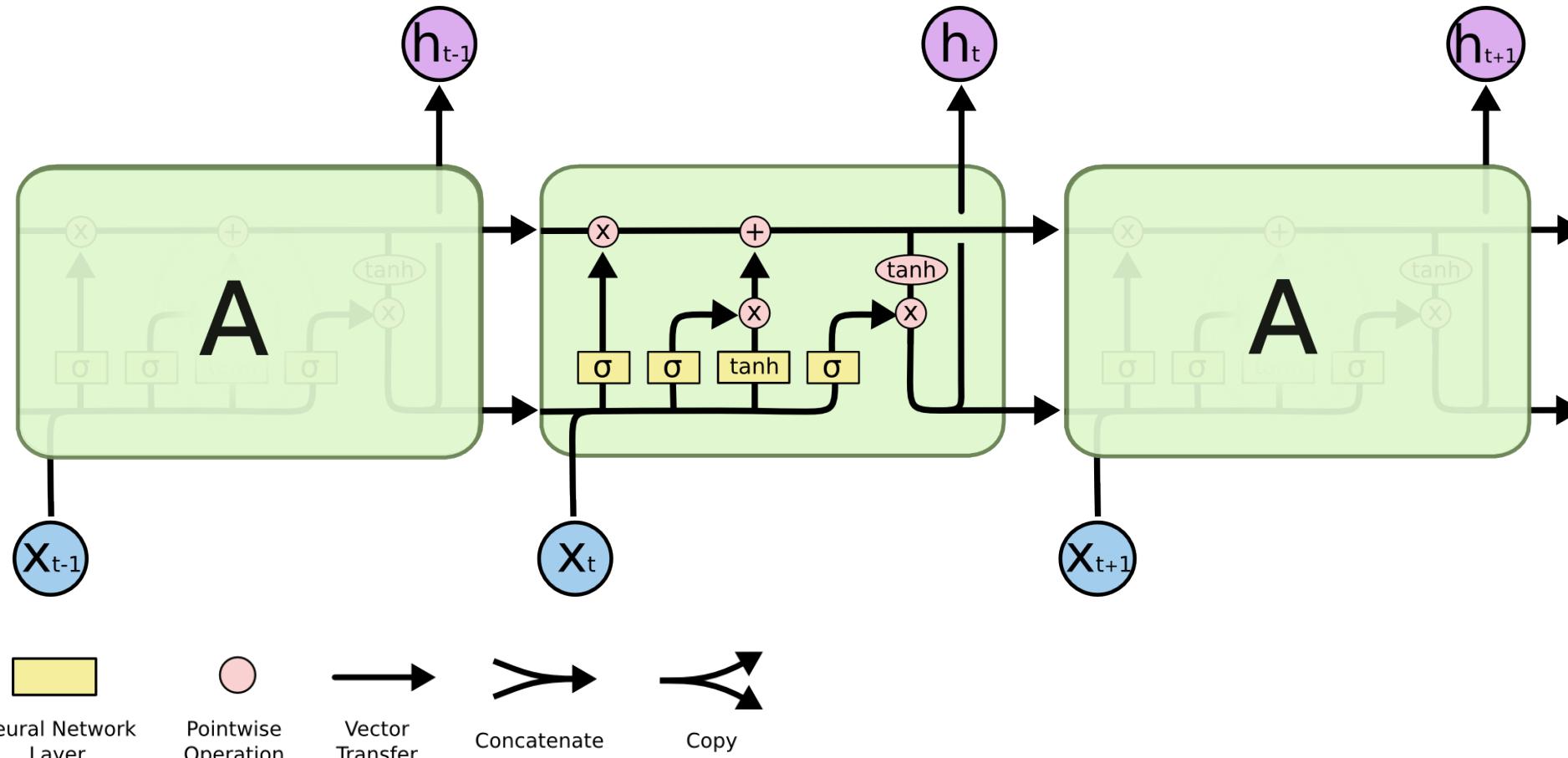


...Specifically, an LSTM



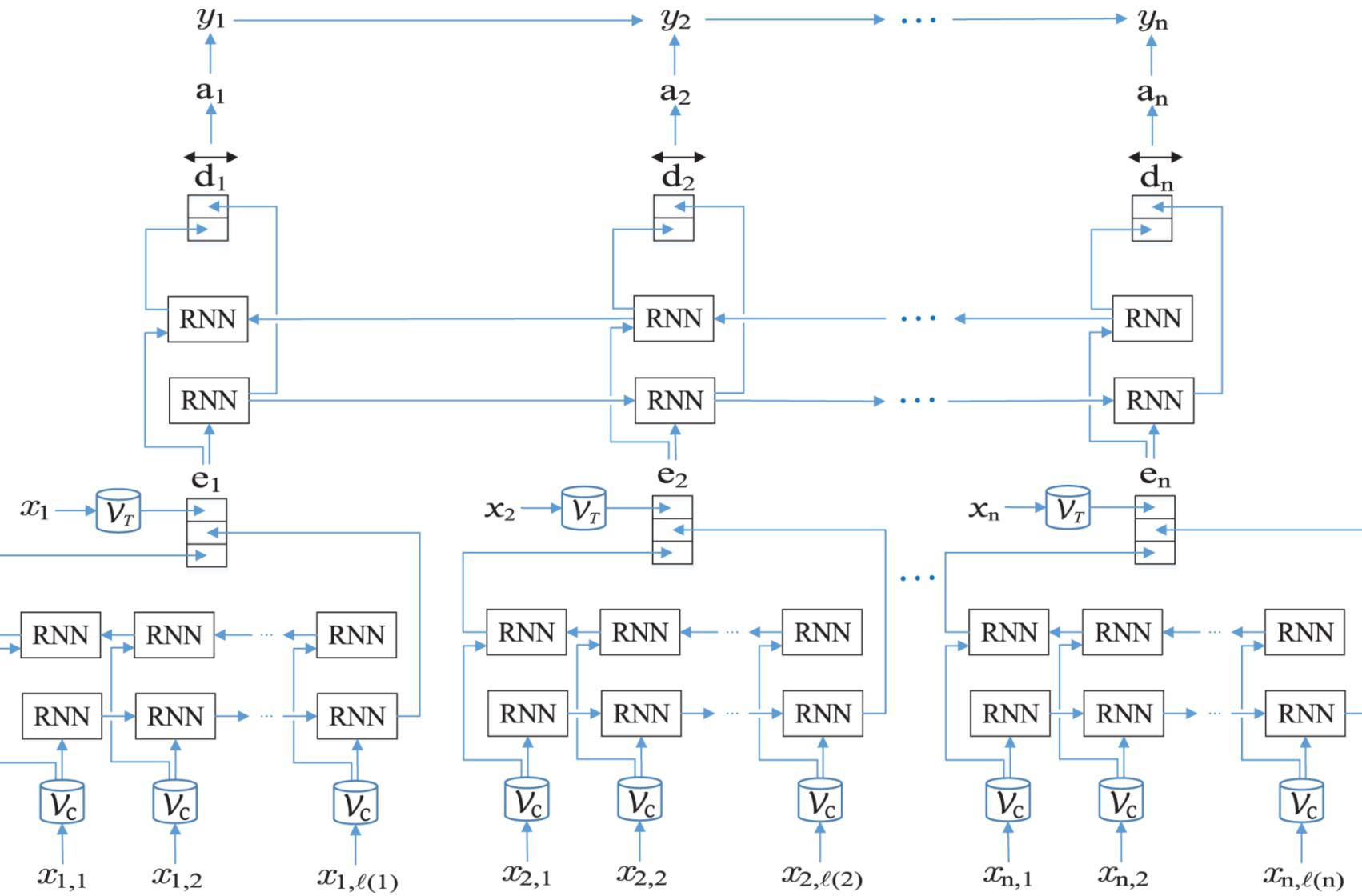
Inside an LSTM

<http://colah.github.io/posts/2015-08-Understanding-LSTMs/>



Modifications to RNN for Deidentification

1. LSTM provides a more flexible representation of previous context
 - output and cell state are both passed to the next block
2. Bidirectional LSTM provides context from subsequent words as well as previous words
3. Character-level RNN allows a non-trivial representation of out-of-dictionary tokens



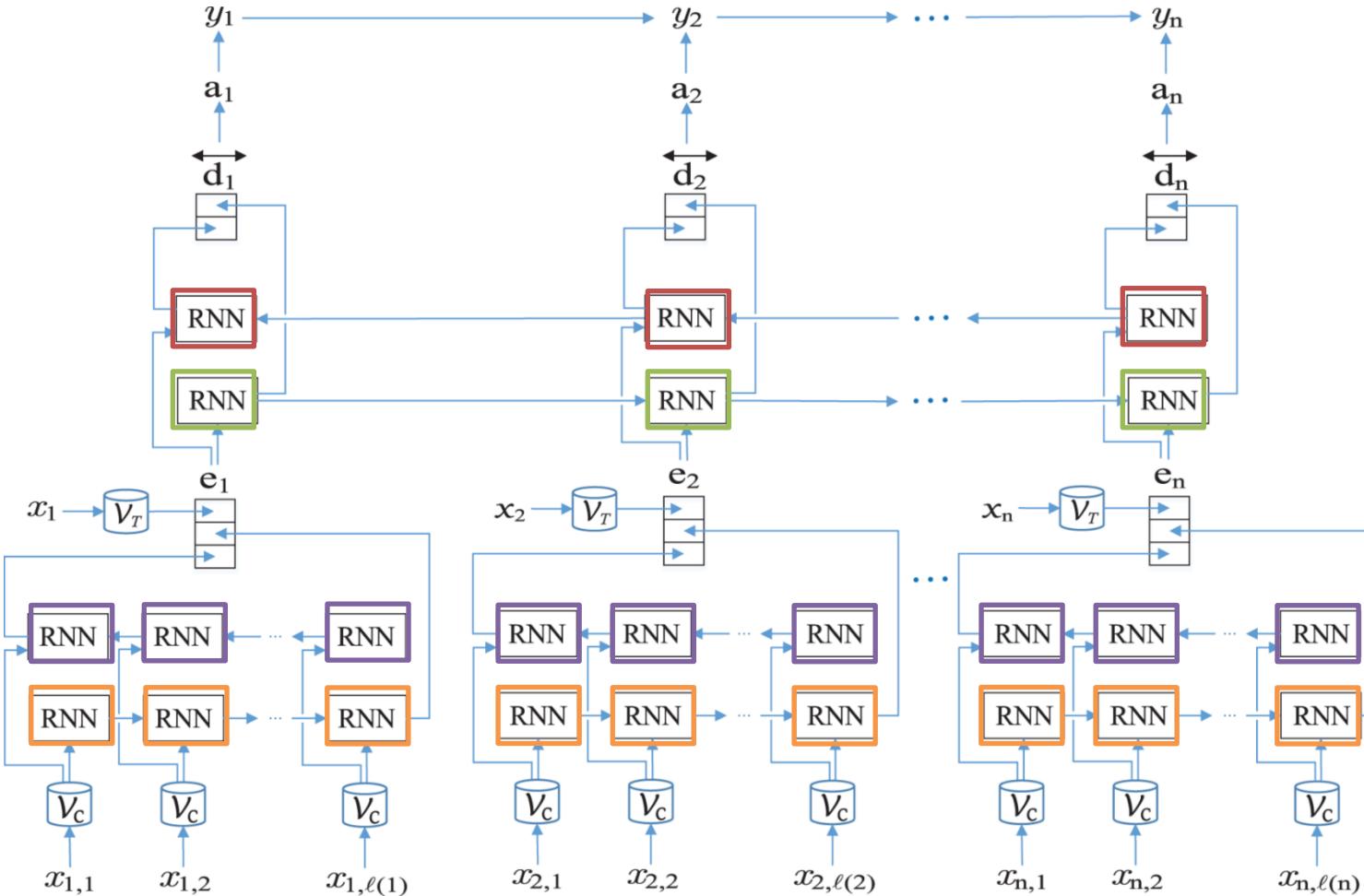
From: De-identification of patient notes with recurrent neural networks

J Am Med Inform Assoc. 2016;24(3):596-606. doi:10.1093/jamia/ocw156

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□ backward token LSTM
□ forward token LSTM

□ backward character LSTM
□ forward character LSTM



Character
embedding
dimension: **25**

Character-based
token-embedding
LSTM dimension:
25

Token embedding
dimension: **100**

Label prediction
LSTM dimension:
100

Deidentification of Patient Notes

RESULTS

Train, Validation, Test

MIMIC:

80% train/validation

20% test

“All results were computed using the official evaluation script from the i2b2 2014 de-identification challenge.”

i2b2:

60% train/validation

40% test

Table 3. Overview of the i2b2 and MIMIC datasets

Statistics	i2b2	MIMIC
Vocabulary size	46 803	69 525
Number of notes	1304	1635
Number of tokens	984 723	2 945 228
Number of PHI instances	28 867	60 725
Number of PHI tokens	41 355	78 633

Examples of PHI Identified by the RNN

AGE	Father had a stroke at <u>80</u> and died of another stroke at age Personal data and overall health: Now <u>63</u> , despite his FH: Father: Died @ <u>52</u> from EtOH abuse (unclear exact etiology) Tobacco: smoked from age 7 to <u>15</u> , has not smoked since 15.
CONTACT	History of Present Illness <u>86F</u> reports worsening b/l leg pain. by phone, Dr. Ivan Guy. Call w/ questions <u>86383</u> . Keith Gilbert, H/O paroxysmal afib VNA <u>171-311-7974</u> ===== Medications
DATE	During his <u>May</u> hospitalization he had dysphagia Social history: divorced, quit smoking in <u>08</u> , sober x 10 yrs, She is to see him on the <u>29th</u> of this month at 1:00 p.m. He did have a renal biopsy in teh late <u>60s</u> adn thus will look for results, Results <u>02/20/2087</u> NA 135, K 3.2 (L), CL 96 (L), CO2 30.6, BUN 1 Jose Church, M.D. /ray DD: 01/18/20 DT: <u>01/19/0</u> DV: 01/18/20

Evaluation Metrics

Precision, or positive predictive value:

$$\frac{\text{true positives}}{\text{all positive predictions}}$$

Recall, or sensitivity:

$$\frac{\text{true positives}}{\text{all condition positives}}$$

F1-score:

$$\frac{2 * \text{precision} * \text{recall}}{\text{precision} + \text{recall}}$$

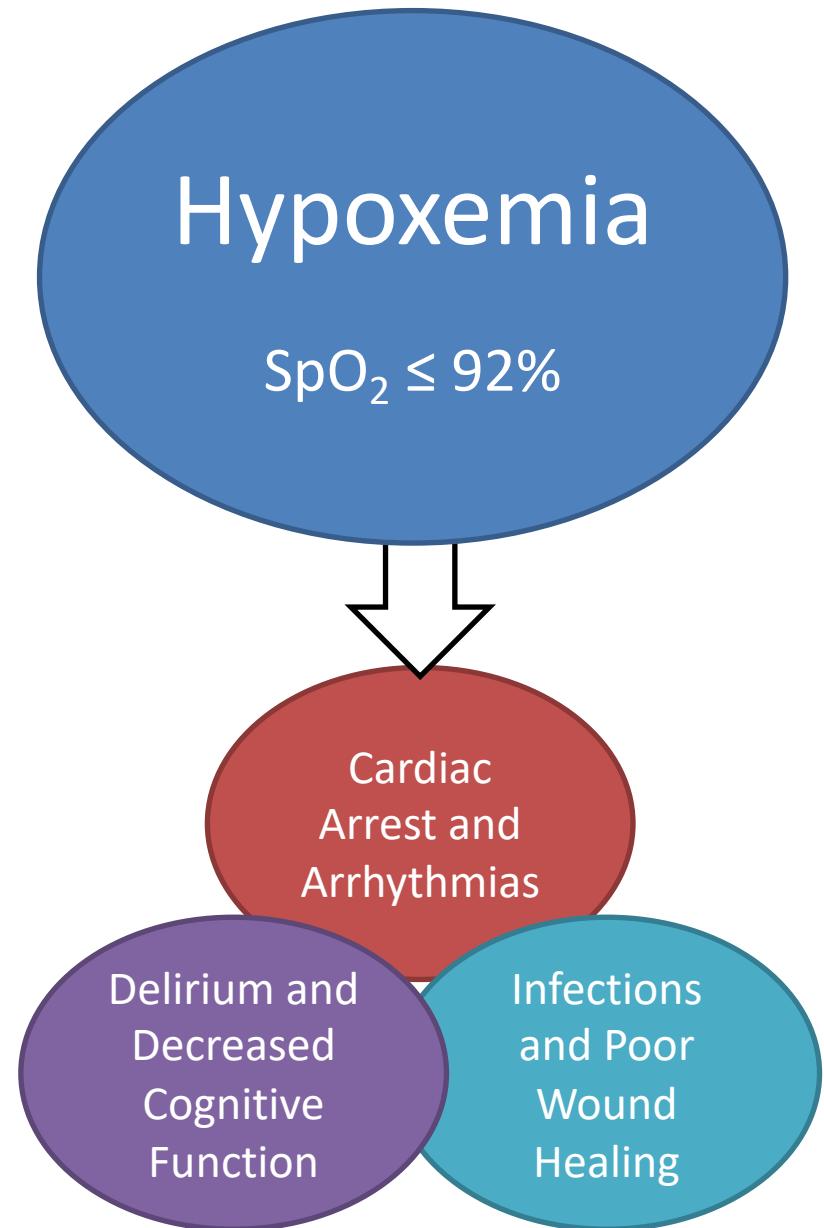
		Condition Positive	Condition Negative
Prediction Positive	True Positive	False Positive	
	False Negative	True Negative	
Prediction Negative			

RNN Model Outperforms Previous Benchmarks

Table 4. Performance (%) on the PHI as defined in HIPAA

Model	i2b2			MIMIC		
	Precision	Recall	F1	Precision	Recall	F1
Nottingham	<u>99.000</u>	96.400	97.680	–	–	–
MIST	91.445	92.745	92.090	95.867	98.346	97.091
CRF	98.560	96.528	97.533	99.060	98.987	99.023
ANN	98.320	97.380	97.848	<u>99.208</u>	99.251	<u>99.229</u>
CRF + ANN	97.920	<u>97.835</u>	<u>97.877</u>	98.820	<u>99.398</u>	99.108

Running Example: Predict Hypoxemia during Surgery



Article | Published: 10 October 2018

Explainable machine-learning predictions for the prevention of hypoxaemia during surgery

Scott M. Lundberg, Bala Nair, Monica S. Vavilala, Mayumi Horibe, Michael J. Eisses, Trevor Adams,
David E. Liston, Daniel King-Wai Low, Shu-Fang Newman, Jerry Kim & Su-In Lee 

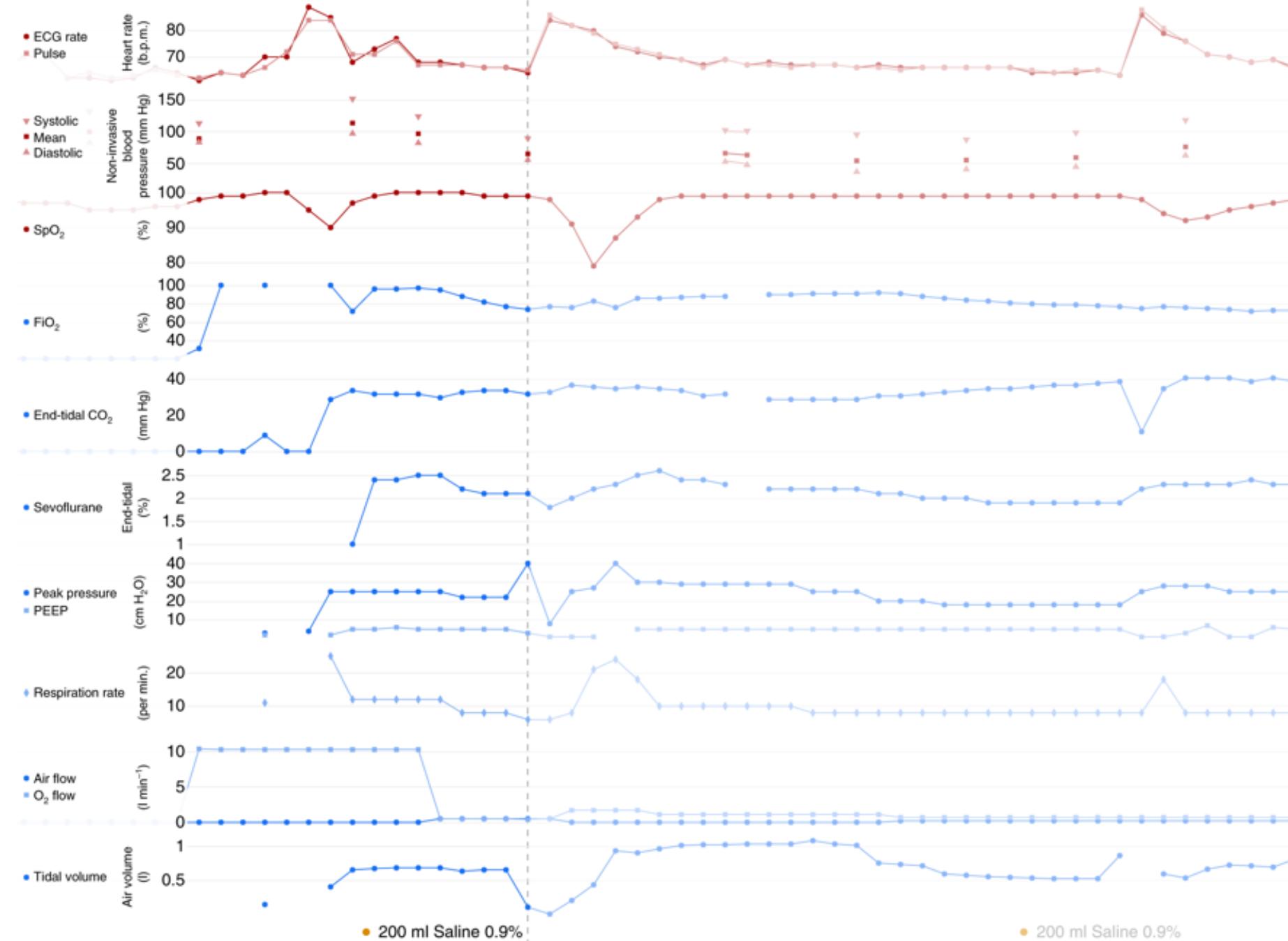
Nature Biomedical Engineering **2**, 749–760 (2018) | Download Citation 

Data: Anesthesia Information Management System (AIMS)

- 3,797 static extracted features for each patient from more than 20 original static sources
- an expanded superset of 3,905 real-time and static extracted features for each time point during anaesthesia care from the more than 20 original static sources as well as 45 different real-time data sources

Element	Description
Patient	
Age	Age of patient
Sex	Sex of patient
ASA Physical Status	ASA physical status of patient before surgery
Height (cm)	Height of patient
Weight (kg)	Weight of patient
Patient class	Inpatient or outpatient
Procedure	
Procedure	Procedure description
Procedure code	Surgical procedure code
Billing codes	Anaesthesia Crosswalk/ procedure codes
Diagnosis	Diagnosis description
Diagnosis codes	ICD-9/10 codes
Location	Operating room location
Facility	Hospital facility
Emergency status	Whether case is an emergency or not - Y/N
Anaesthesia type	Type of anaesthesia
Case Events	
Anaesthesia Start	Time of Anaesthesia Start
In Room	Time of patient in room
Induction	Time of Induction start
Anaesthesia Ready	Time of Induction end or Anaesthesia Ready
Procedure Start	Time of Procedure start (incision)
Closing	Time of Closing
Procedure End	Time of Procedure End
Emergency	Time of start of emergency
Leave OR	Time of leave OR/ Transport to recovery
Anaesthesia End	Time of Anaesthesia End
Patient monitor/Ventilator Data	(Value, Time & Unit of measurement)
Heart Rate	Heart rate from ECG signal (Patient monitor)

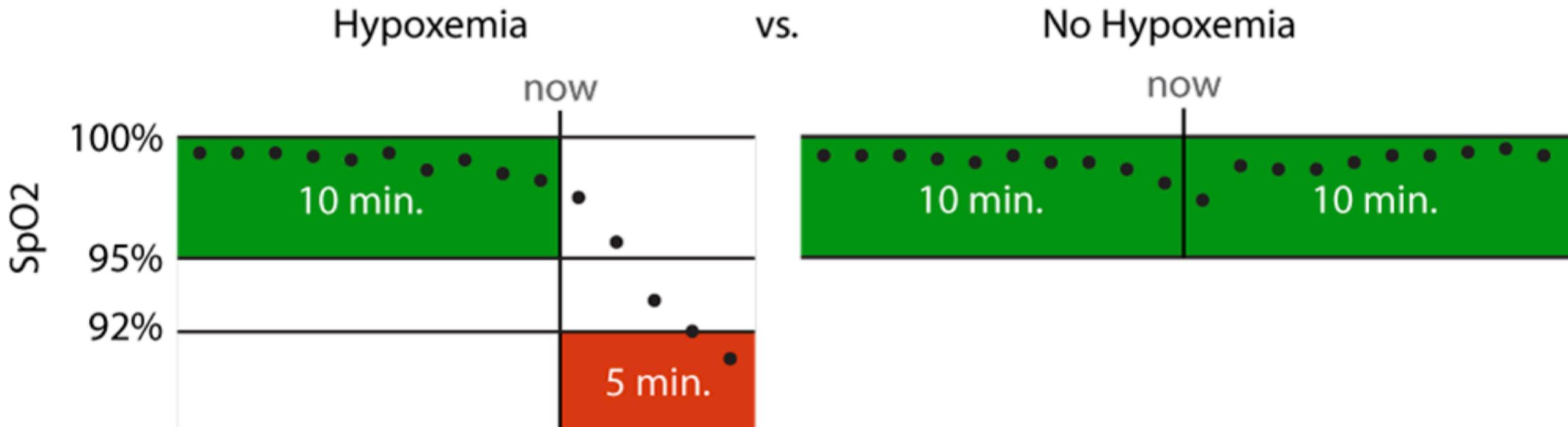
O ₂ Sat	O ₂ saturation from pulse oximetry (Patient Monitor)
Pulse rate	Pulse rate from pulse oximetry (Patient Monitor)
NIBP – Sys	Cuff BP – systolic (Patient monitor)
NIBP – Dia	Cuff BP – diastolic (Patient monitor)
NIBP - Mean	Cuff BP – mean (Patient monitor)
Art BP - Sys	Arterial BP – systolic (Patient monitor)
Art BP - Dia	Arterial BP – diastolic (Patient monitor)
Art BP - Mean	Arterial BP – mean (Patient monitor)
PA - Sys	Pulmonary artery pressure – systolic (Patient monitor)
PA - Dia	Pulmonary artery pressure – diastolic (Patient monitor)
CVP	Central venous line pressure – mean (Patient monitor)
ETCO ₂	End tidal CO ₂ (Capnography) (Patient monitor)
Resp Rate	Measured respiration rate – capnography (Patient monitor)
FiO ₂	Inspired O ₂ (Patient monitor)
ET Sevo	End tidal Sevoflurane anaesthetic agent (Patient monitor)
ET Des	End tidal Desflurane anaesthetic agent (Patient monitor)
ET ISO	End tidal Isoflurane anaesthetic agent (Patient monitor)
ET N2O	End tidal Nitrous oxide (Patient monitor)
BIS	Bispectral Index (Patient/BIS monitor)
SQI	Signal quality index of BIS (Patient/BIS monitor)
TEMP	Temperature (Patient monitor)
SvO ₂	Mixed venous oxygenation (Patient monitor)
CCO	Continuous cardiac output (Patient monitor)
TV	Tidal volume (Patient monitor)
RATE	Ventilator rate setting (Ventilator)
PIP	Peak Inspiratory pressure (Ventilator)
PEEP	Positive End Expiration Pressure (Ventilator)
O ₂ FLOW	O ₂ flow rate (Ventilator)
Air FLOW	Air flow rate (Ventilator)
N ₂ O FLOW	N ₂ O Flow rate (Ventilator)
Cardiac Rhythm	Type of cardiac rhythm
Medications	Delivery information of medications
Time	Delivery time (start / end for infusion medications)
Drug Name	Drug Name
Dose	Drug dose
Dose Unit	Drug dose unit
Route	Drug route
Fluid totals	Fluid totals
Time	Time of fluid input or output
Fluid Name	Fluid name
Volume	Fluid volume recorded
Laboratory results	Intraoperative laboratory results
Time	Time of taking sample or Lab result time
Lab results	Lab result description
Sample type	Sample type – arterial/venous
Lab result	Result value
Unit	Unit of measurement
Notes	Attestations, AIMS Clinical notes, Note option selections
Time	Time associated with the note
Context code	Context code associated with a note or its selections
Note content	Note description field



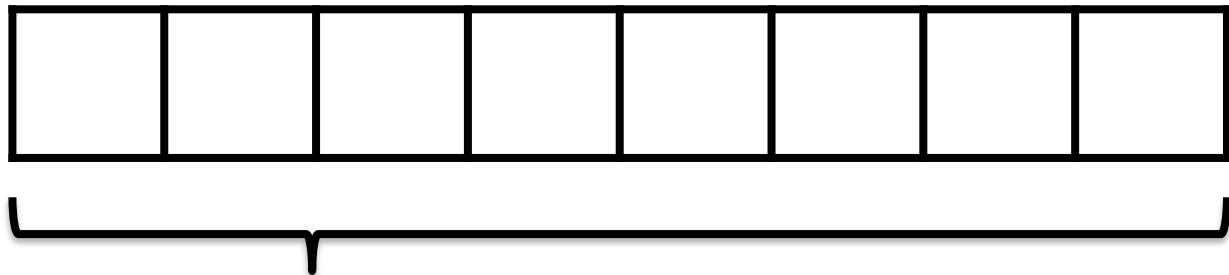
Prediction Tasks:

Initial Prediction: hypoxemia at any time based on static features

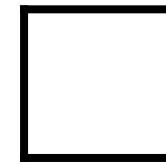
Real-time Prediction: hypoxemia in the next 5 minutes based on static features and real-time features collected up to that time point



Initial Prediction



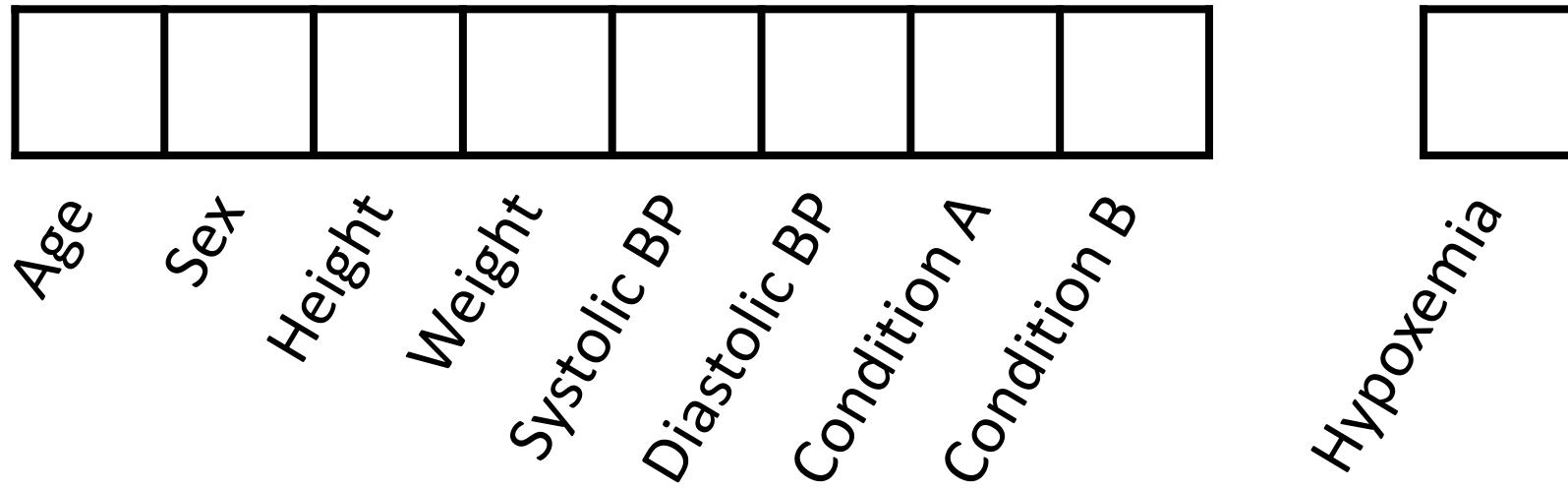
x , data/features for
a subject or patient



y , associated
value or label

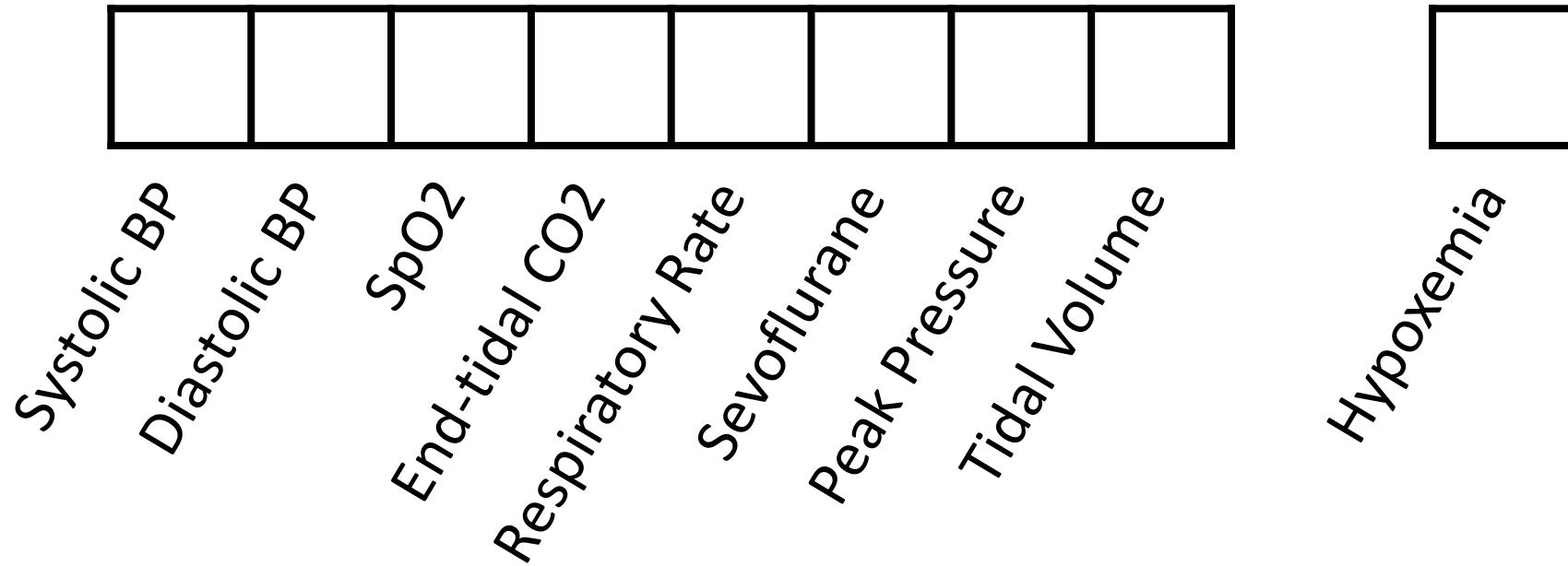
End goal: predict y from x

Initial Prediction



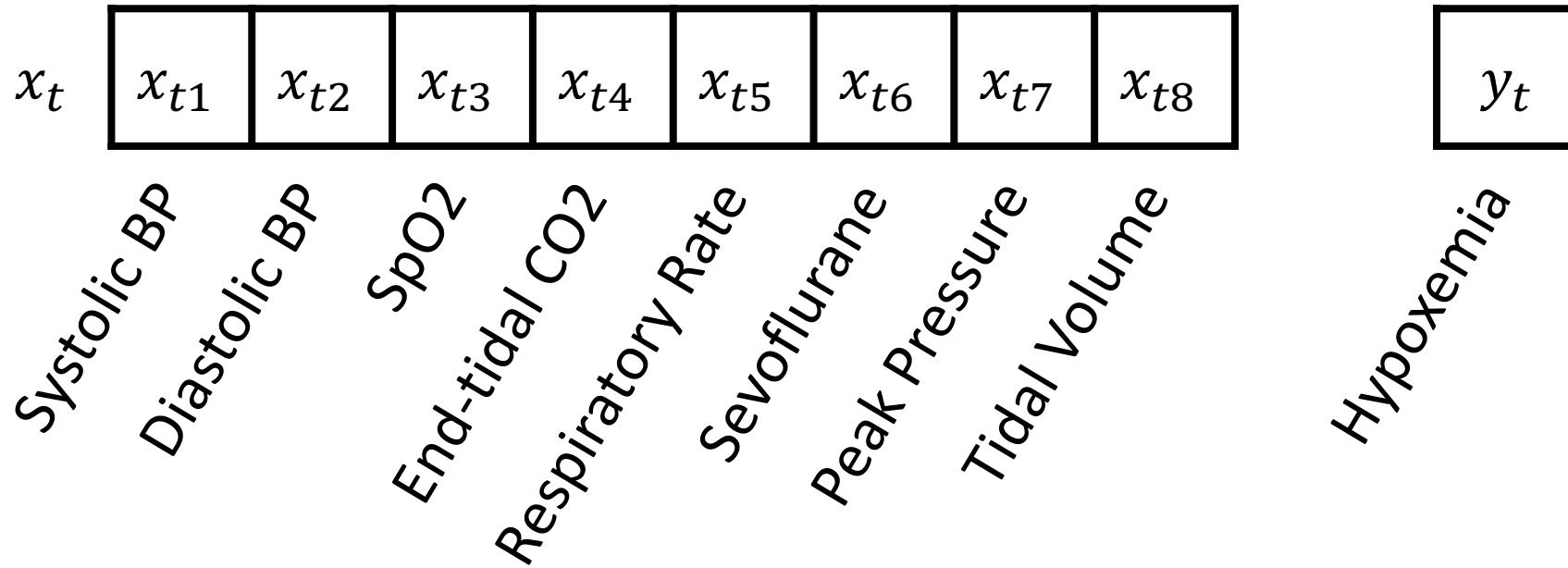
Goal: predict whether pt will become hypoxic at any time during surgery

Real-time Prediction



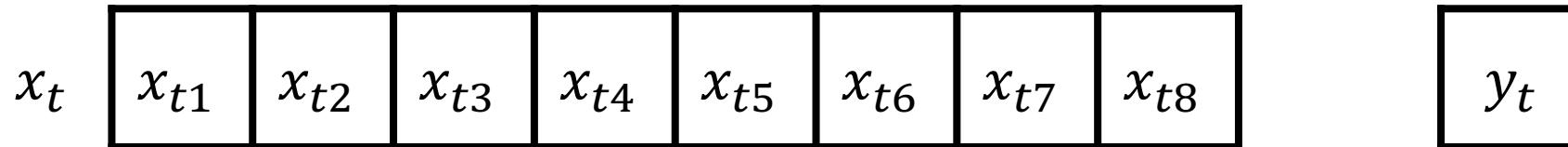
Goal: predict whether pt will become hypoxicemic during the next 5 minutes

Real-time Prediction



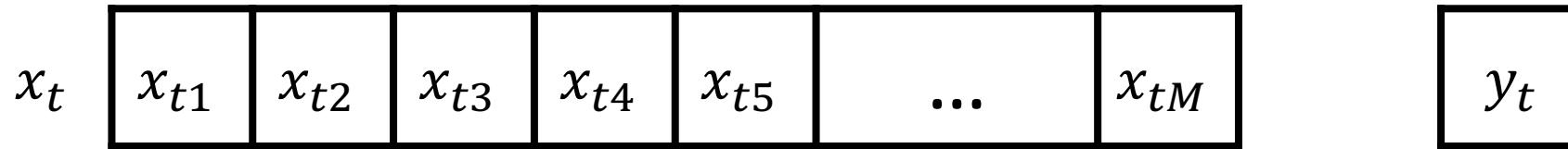
Goal: predict whether pt will become hypoxic during the next 5 minutes

Real-time Prediction



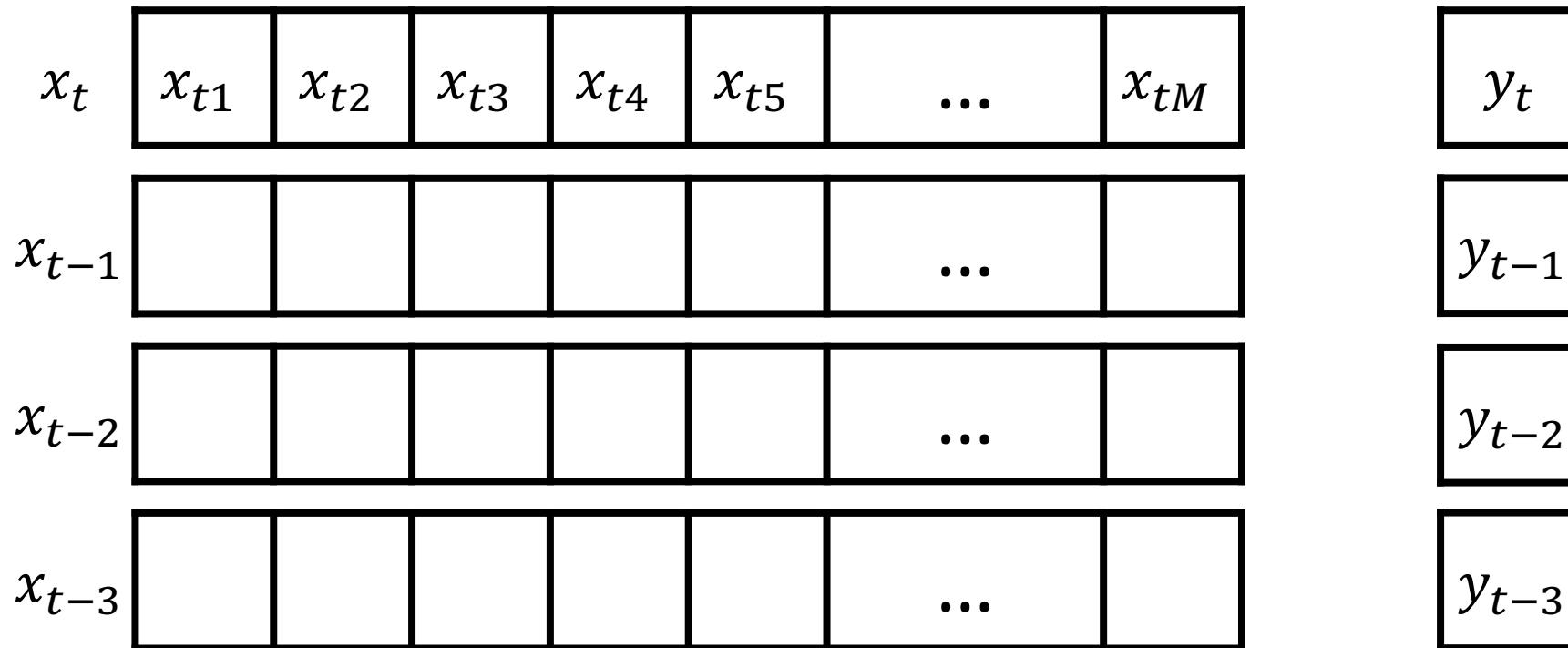
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Real-time Prediction



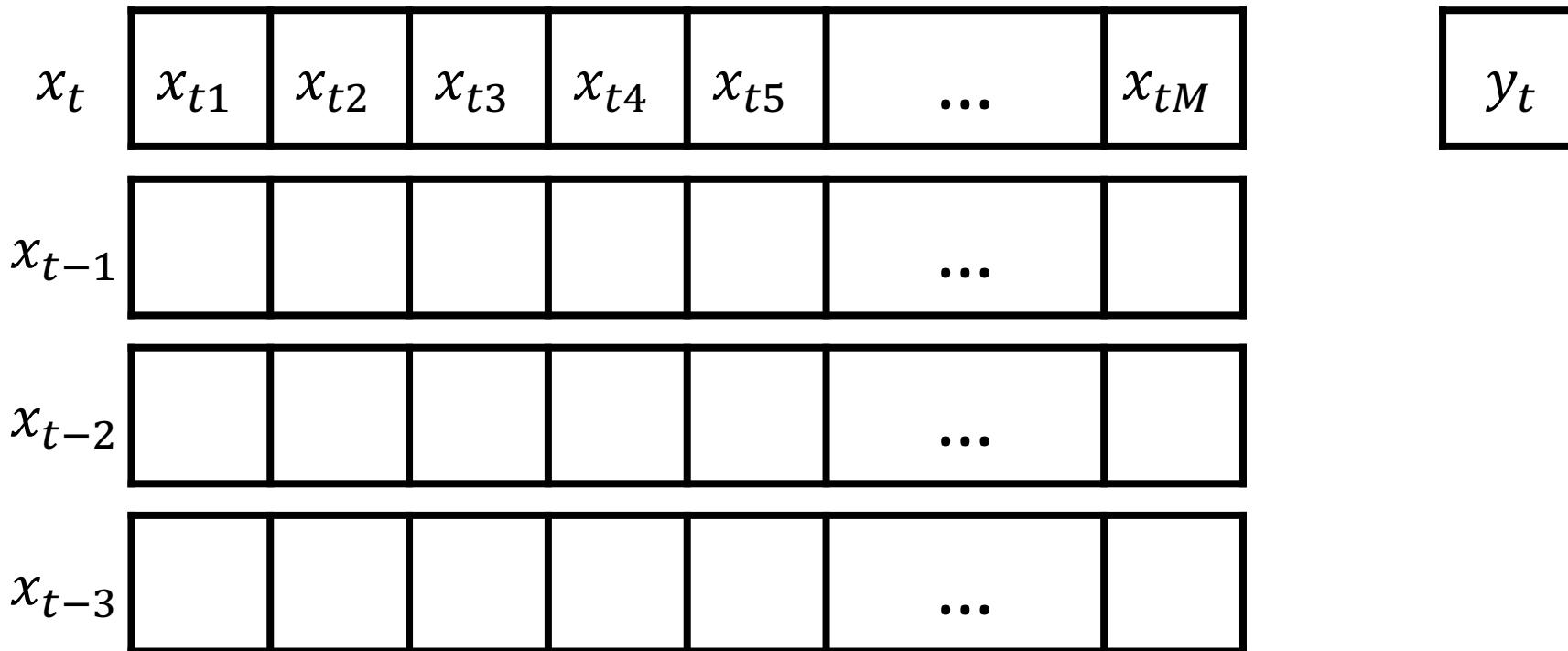
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Real-time Prediction



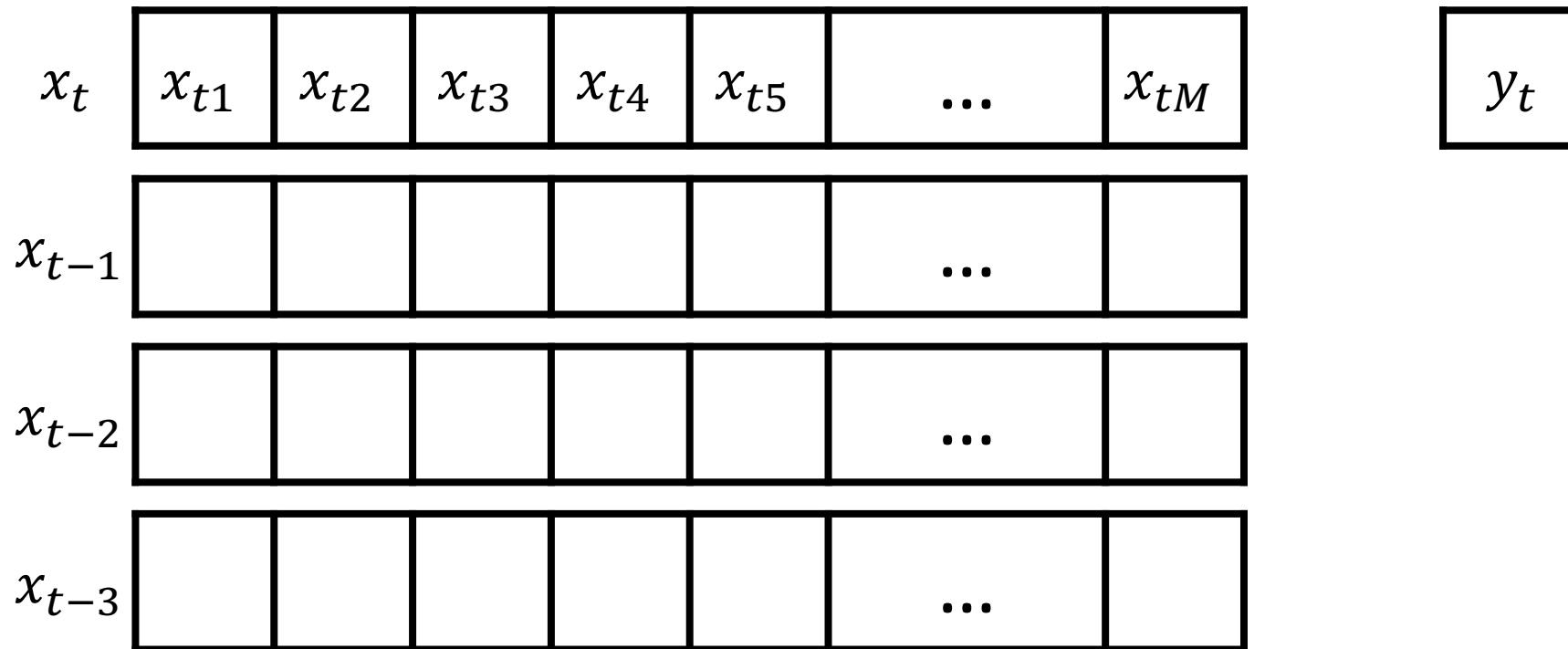
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Real-time Prediction



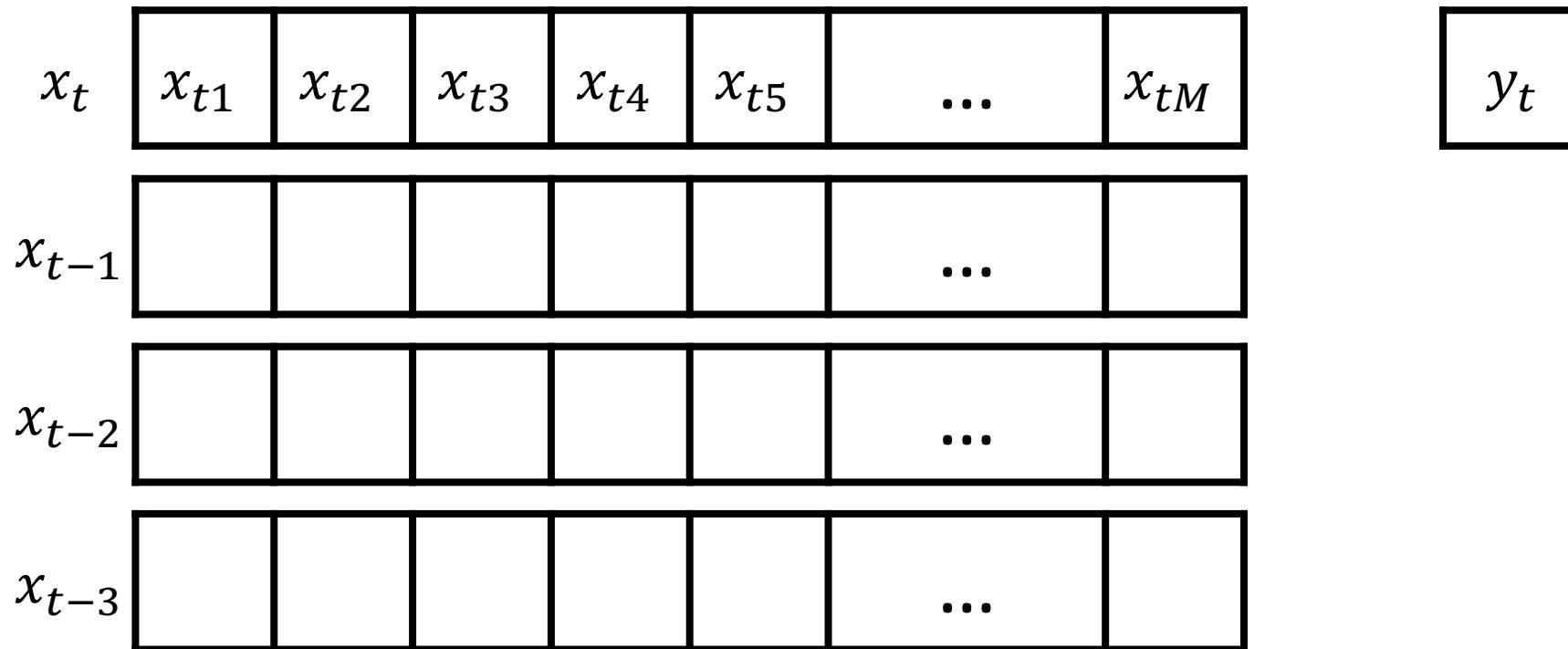
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Goal: combine $x_t, \dots, x_{t-\tau}$ into a fixed-length vector



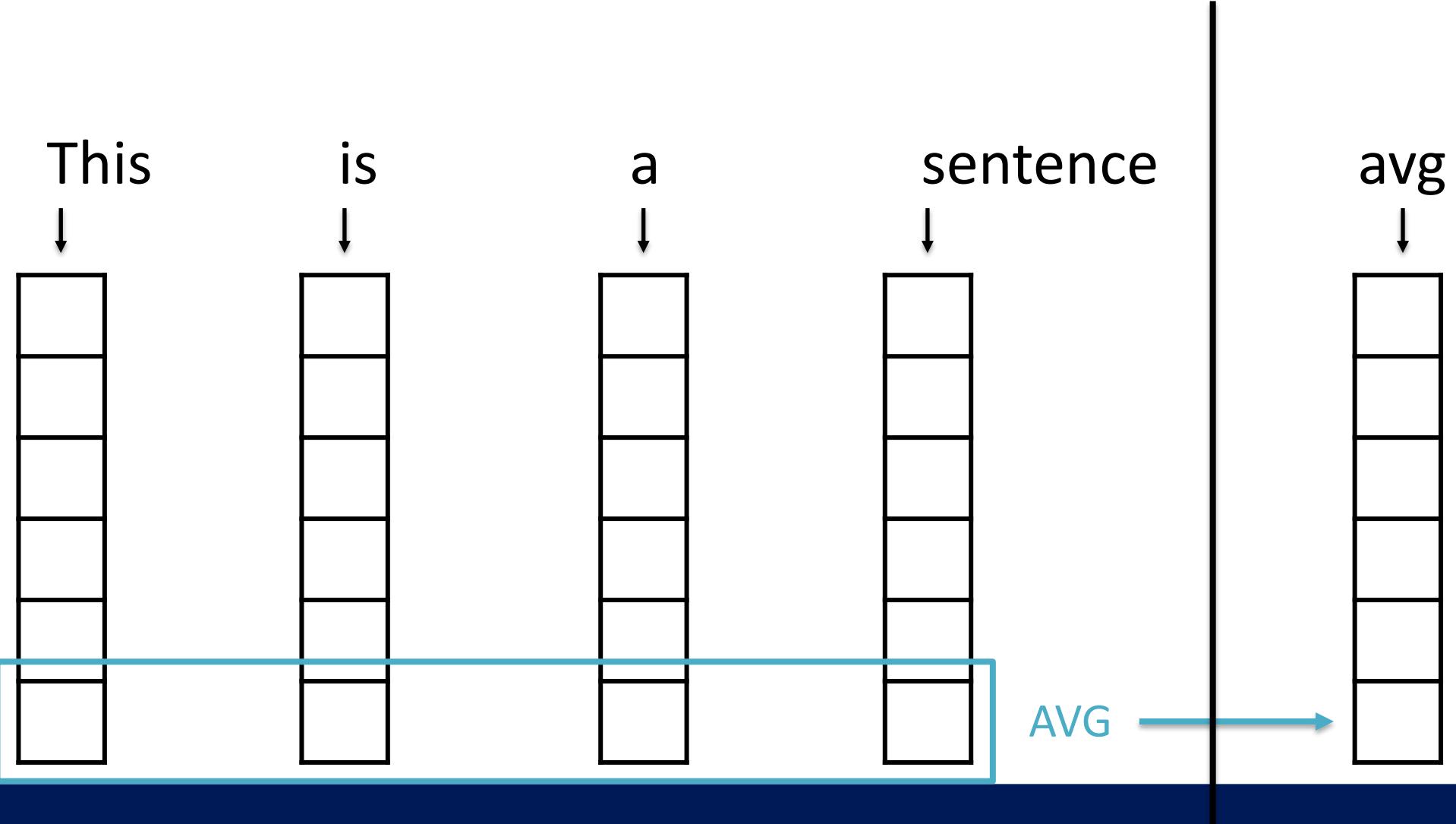
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Goal: combine $x_t, \dots, x_{t-\tau}$ into a fixed-length vector

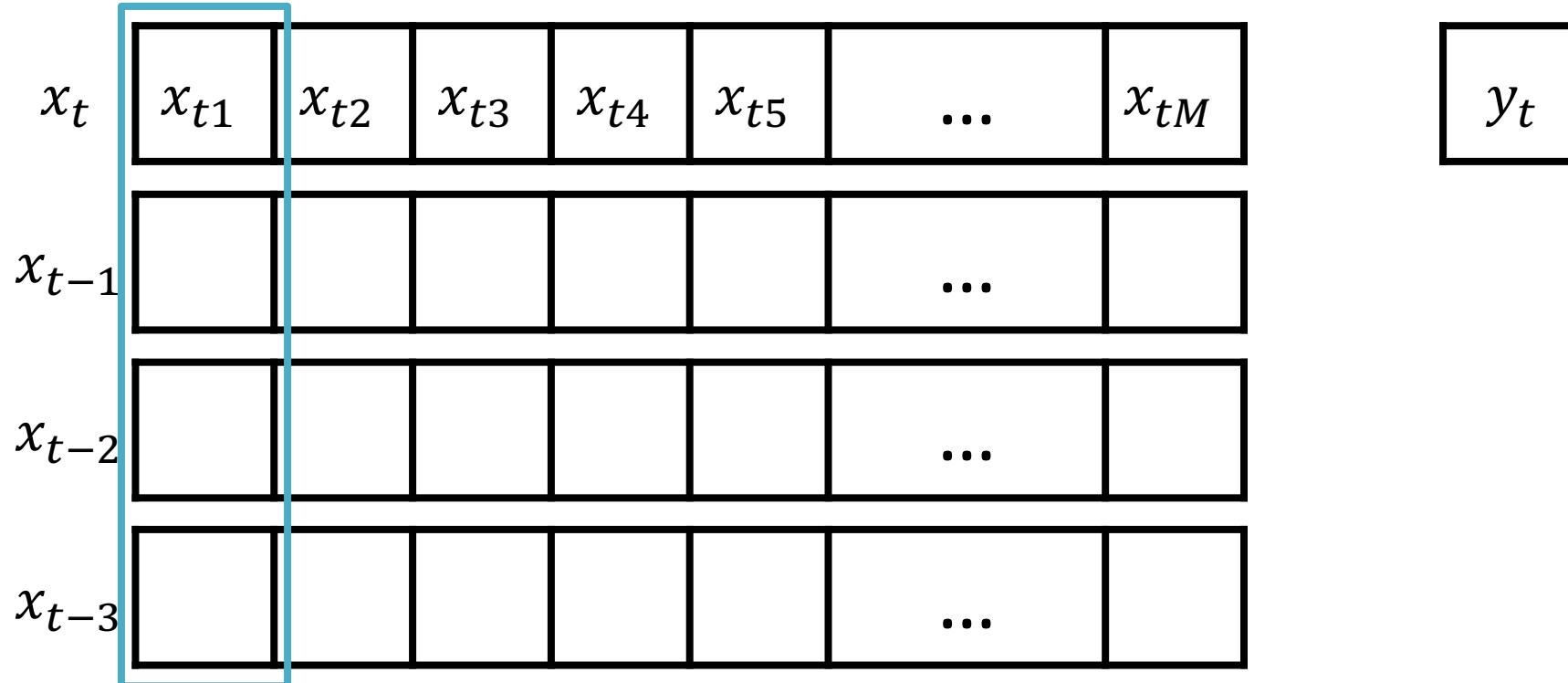


Goal: predict whether pt will become hypoxemic during the next 5 minutes

Recall: Convert variable-length sentence to fixed-length vector with max and average operations



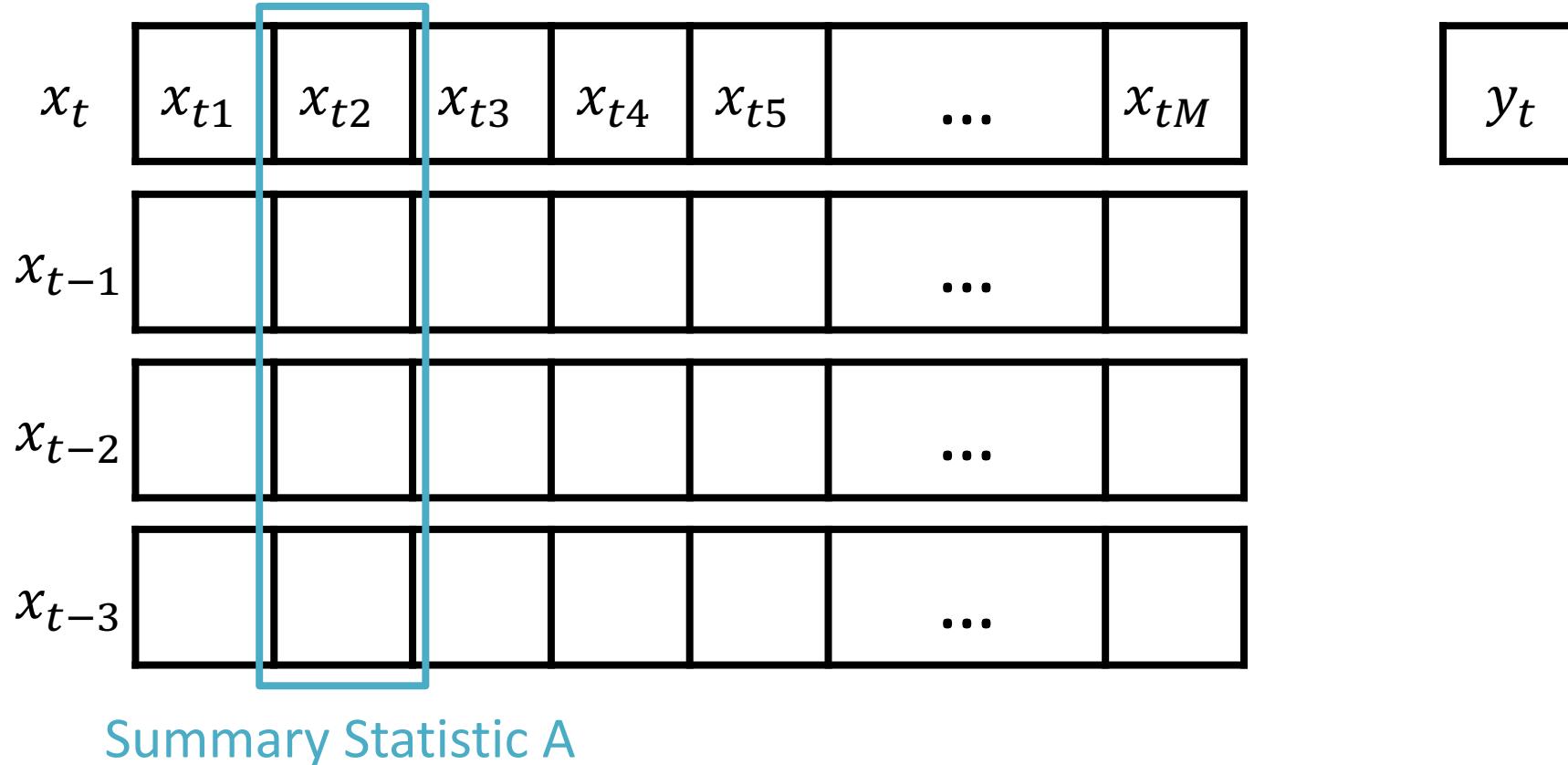
Goal: combine $x_t, \dots, x_{t-\tau}$ into a fixed-length vector



Summary Statistic A

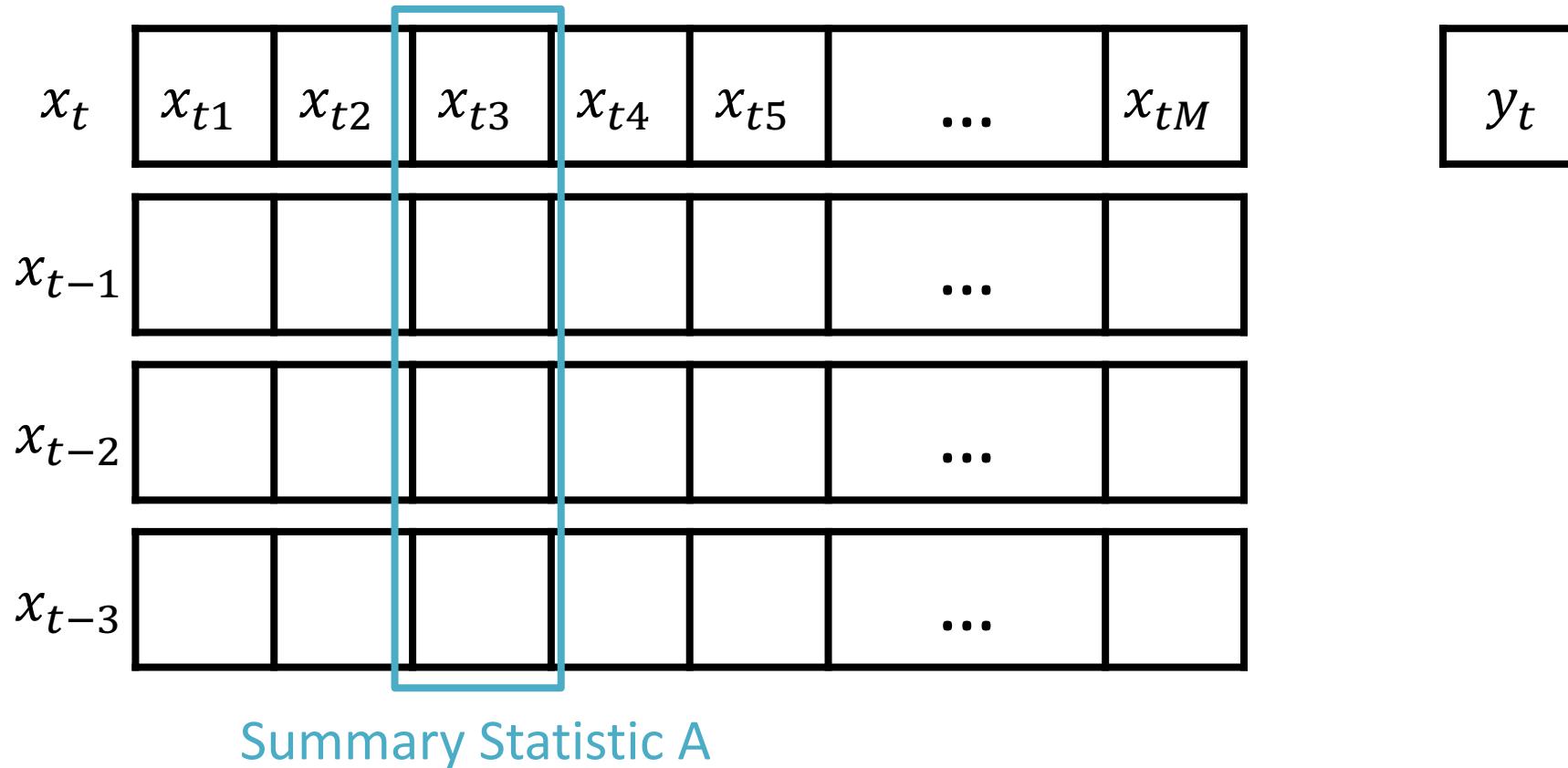
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Goal: combine $x_t, \dots, x_{t-\tau}$ into a fixed-length vector



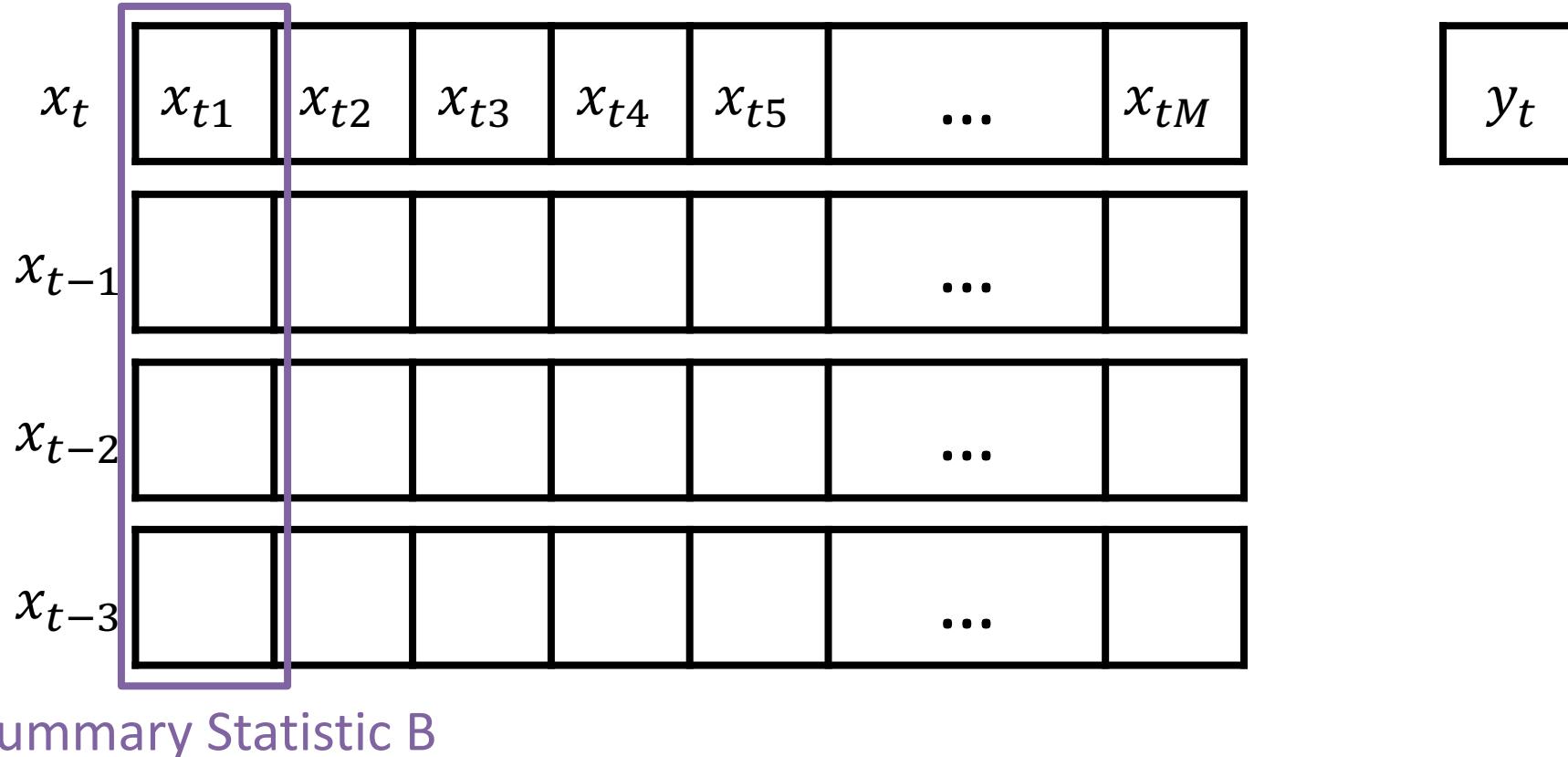
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Goal: combine $x_t, \dots, x_{t-\tau}$ into a fixed-length vector



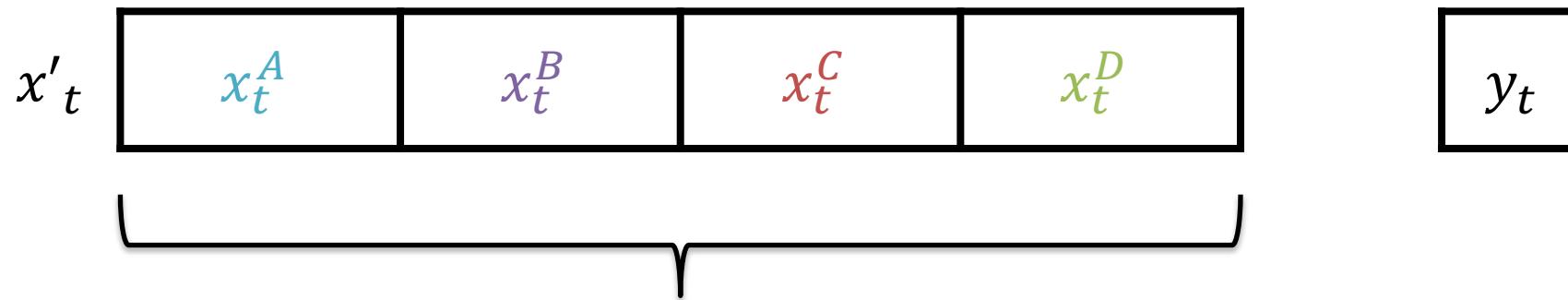
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Goal: combine $x_t, \dots, x_{t-\tau}$ into a fixed-length vector



Goal: predict whether pt will become hypoxemic during the next 5 minutes

Real-time Prediction



Vector of length $4M$ with summary stats A – D at time t

Goal: predict whether pt will become hypoxemic during the next 5 minutes

Summary Statistics

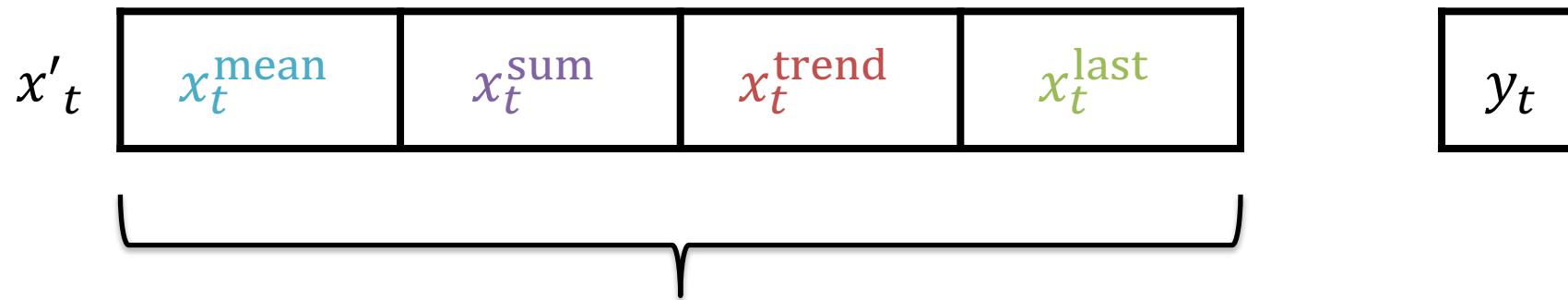
- Current value
- Average and/or extreme values
- Cumulative sums
- Recent trends
- Measurement frequency or time since last measurement

In the Hypoxemia Paper:

We summarized these unevenly sampled time-registered data into a fixed-length feature vector at any point in time using several complementary methods:

- **Last value**, which is zero before any data is recorded and the value of the data afterwards.
- **Exponentially decaying weighted average and variance** estimates using multiple decay rates (6 sec, 1 min, 5 min)
- **Exponentially decaying sum and a time since the last measurement.** For drug dose data (decay rates of 5 min and 1 hour)

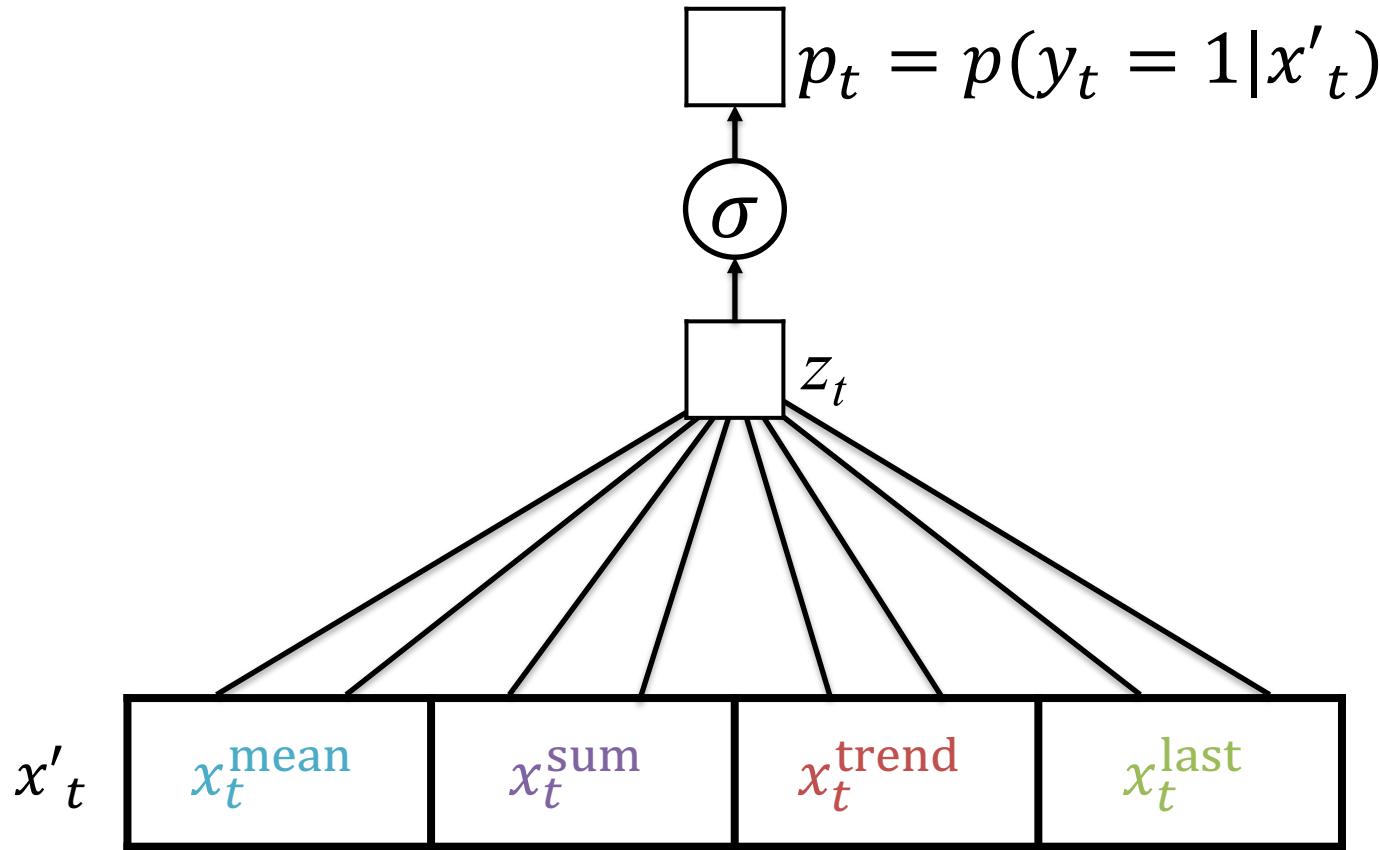
Real-time Prediction



Vector of length $4M$ with summary stats A – D at time t

Goal: predict whether pt will become hypoxemic during the next 5 minutes

Now we can use logistic regression (or any other classifier)



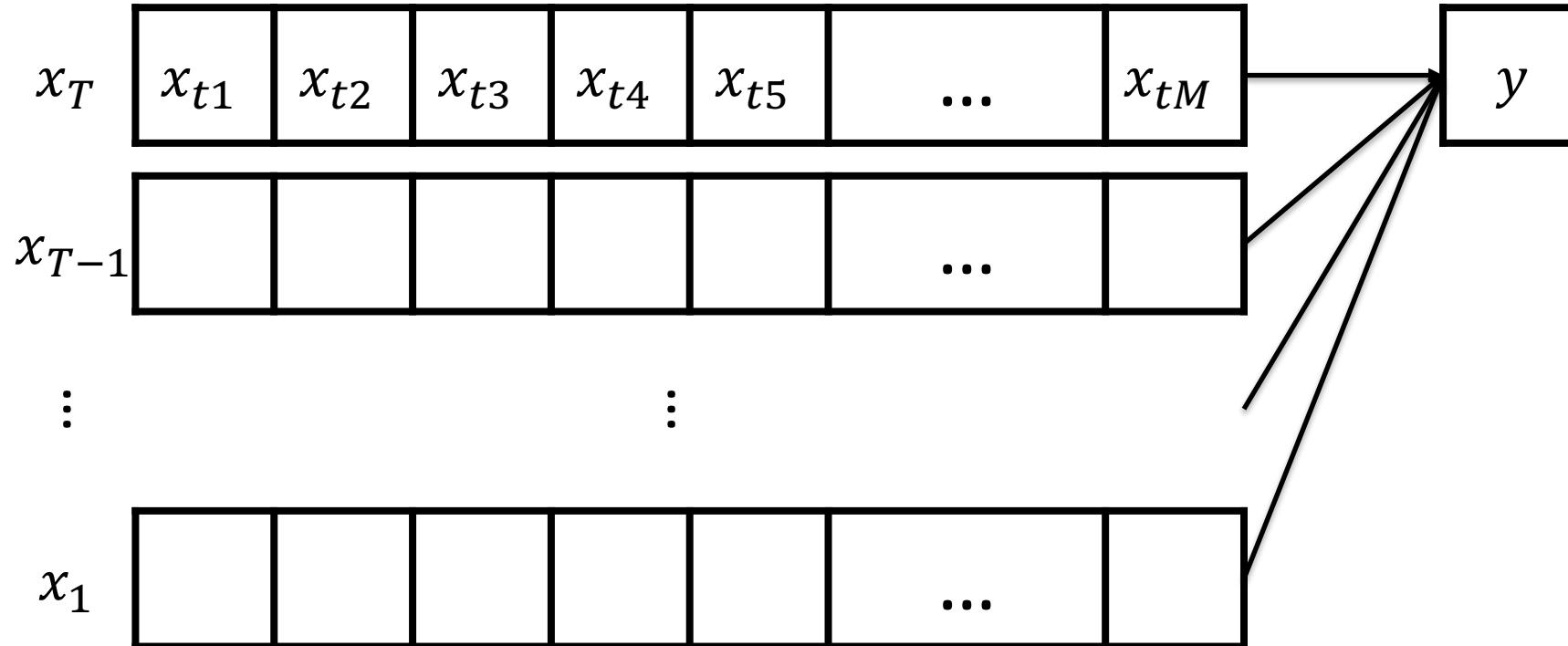
Contrast with text summary stats

- Cannot look at future values
- Window length is fixed

Challenges

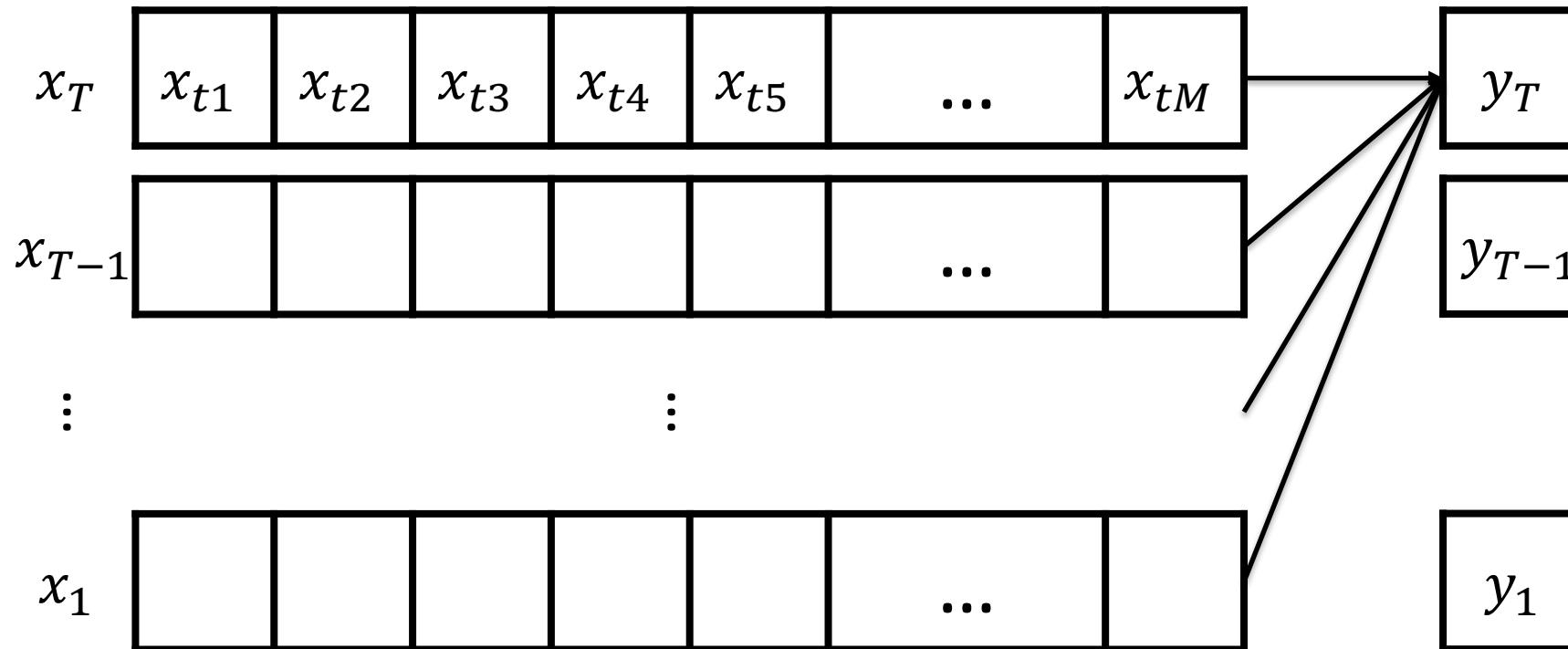
- Missing values
- Inconsistent or unequal measurement intervals
- Appropriate summary stats vary between measurement types

Prediction task A: one label per series



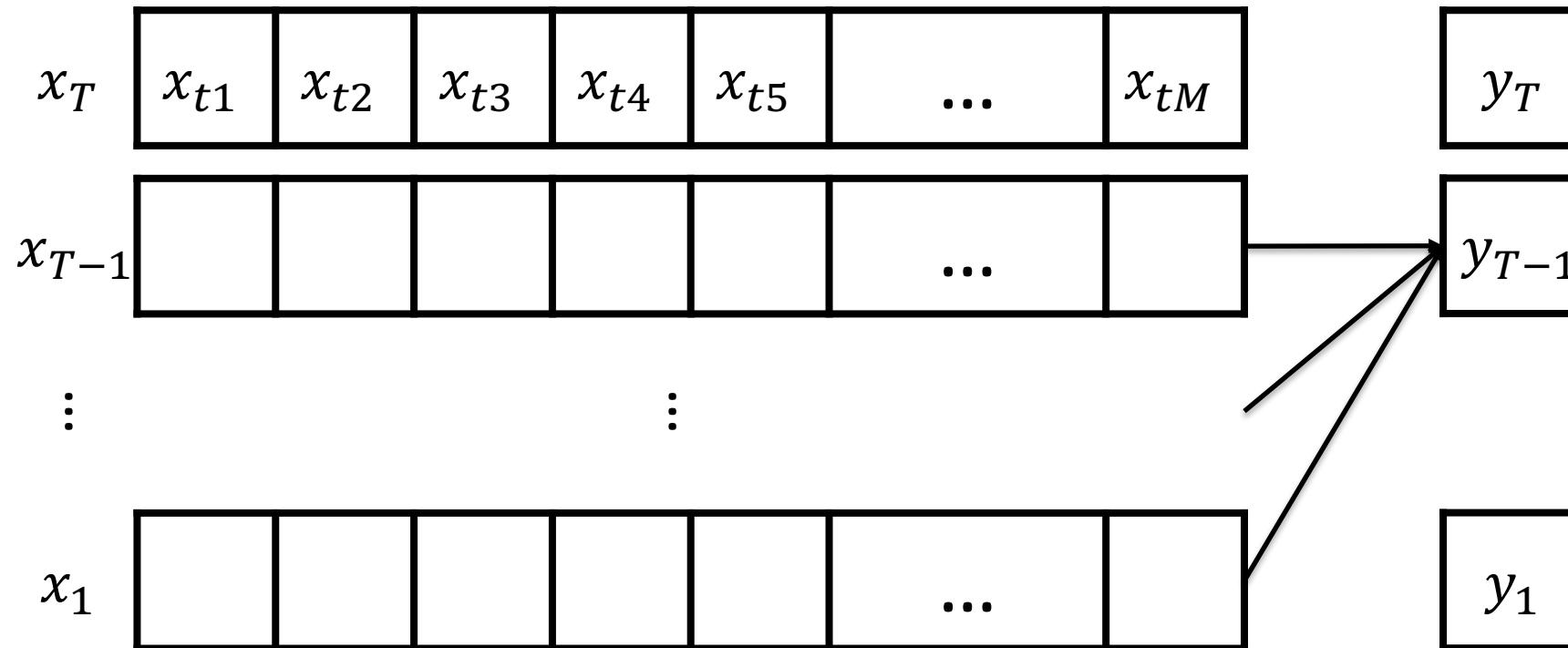
Goal: predict whether pt will become hypoxemic at any time during surgery

Prediction task B: one label per time step



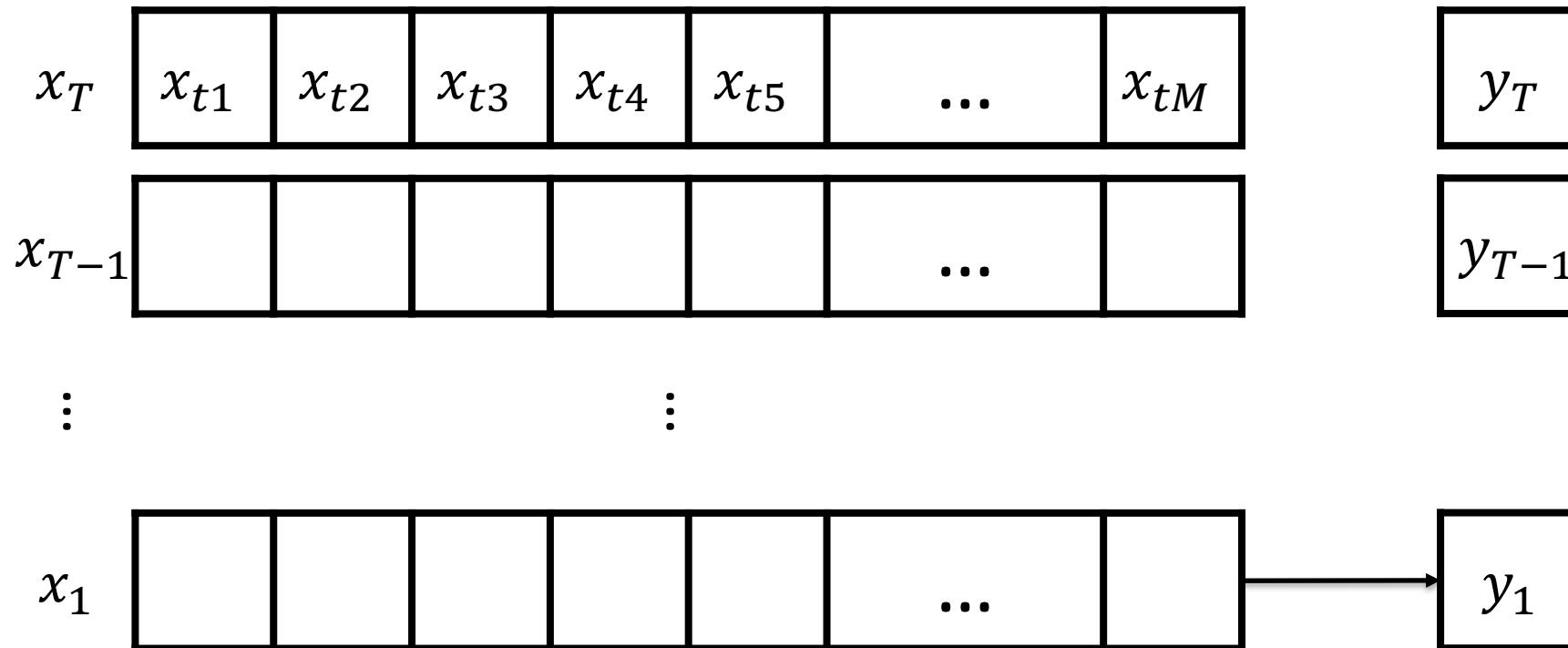
Goal: predict whether pt will become hypoxemic during the next 5 minutes

Prediction task B: one label per time step



Goal: predict whether pt will become hypoxemic during the next 5 minutes

Prediction task B: one label per time step



Goal: predict whether pt will become hypoxemic during the next 5 minutes

Hypoxemia Detection

MODEL DEVELOPMENT & RESULTS

Test / Validation / Train

Initial prediction:

- Training: 42,420 procedures (each a single surgical case)
- Validation: 5,649 procedures
- Test: 5,057 procedures



Real-time prediction:

- Training: 8,087,476 per-minute time points
- Validation: 1,053,629 per-minute time points
- Test: 963,674 per-minute time points

All time points from the same procedure were included in the same sample set and no missing data imputation was performed.

“To ensure that there was no bias towards the final test set, the test data was initially compressed and left compressed until method development was completed.”

Their Classifier: Gradient Boosting Machine

Step 1: Fit initial model

$$y = f_0(x) + \varepsilon_0$$

Step 2: Fit a second model to the residuals
(or pseudo-residuals)

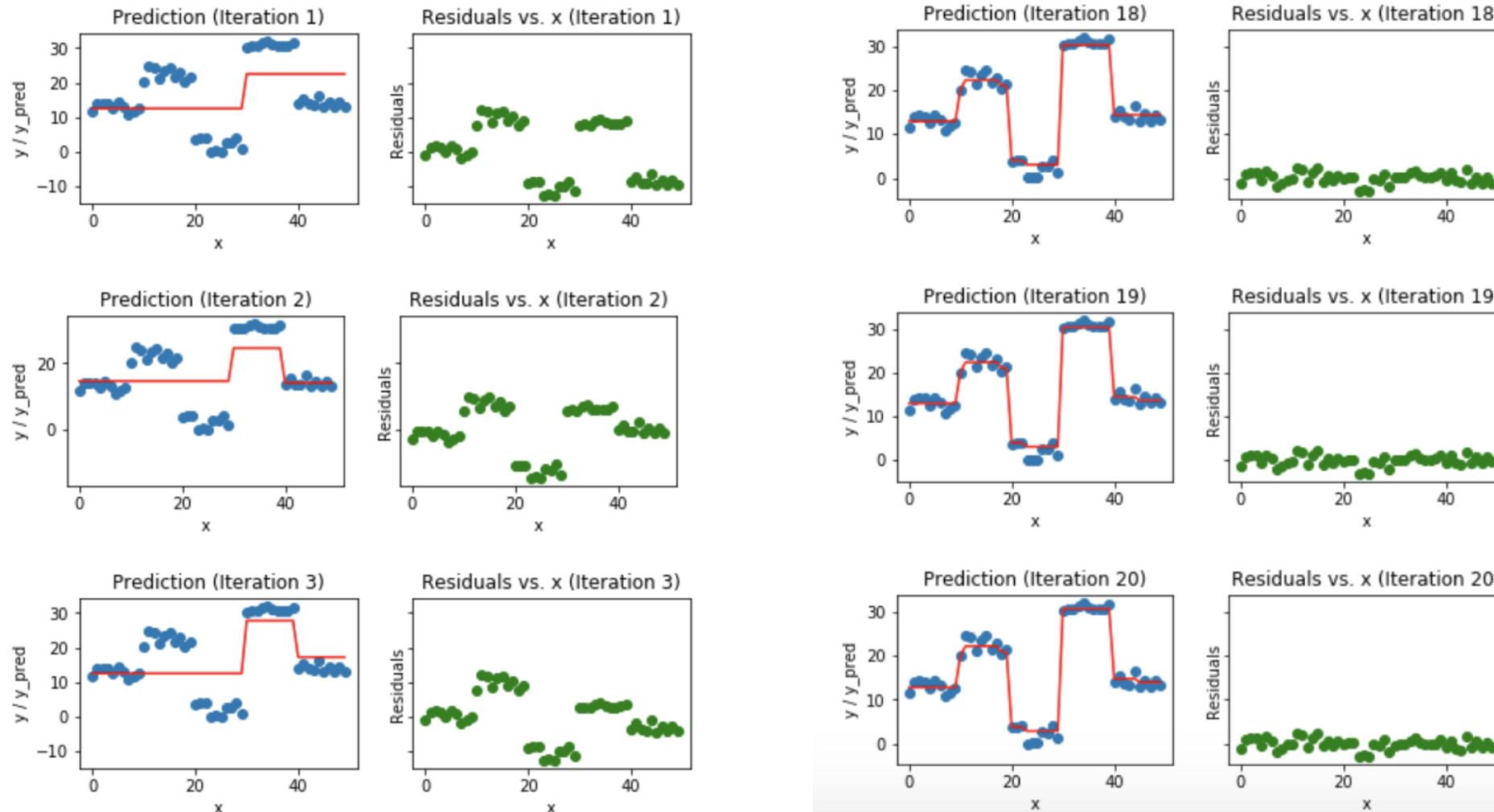
$$\varepsilon_0 = f_1(x) + \varepsilon_1$$

Step 3: Repeat (2)...

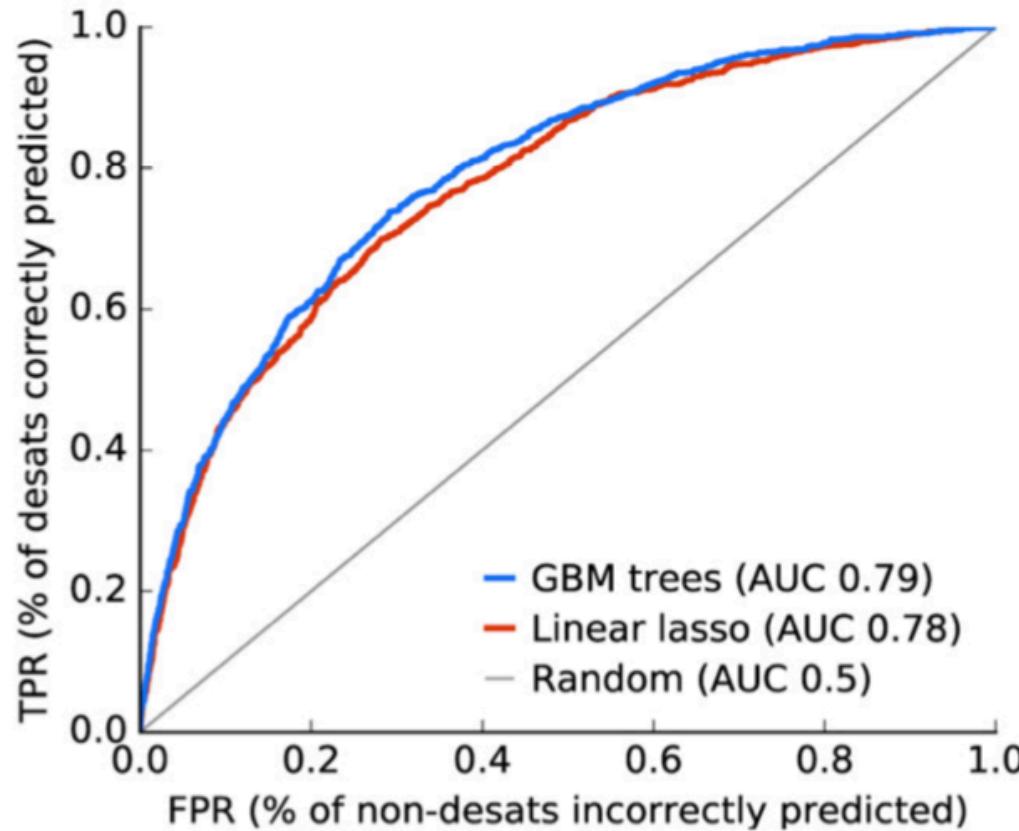
$$\hat{y} = \sum_{i=1}^M f_i(x)$$

GBM for least squares regression

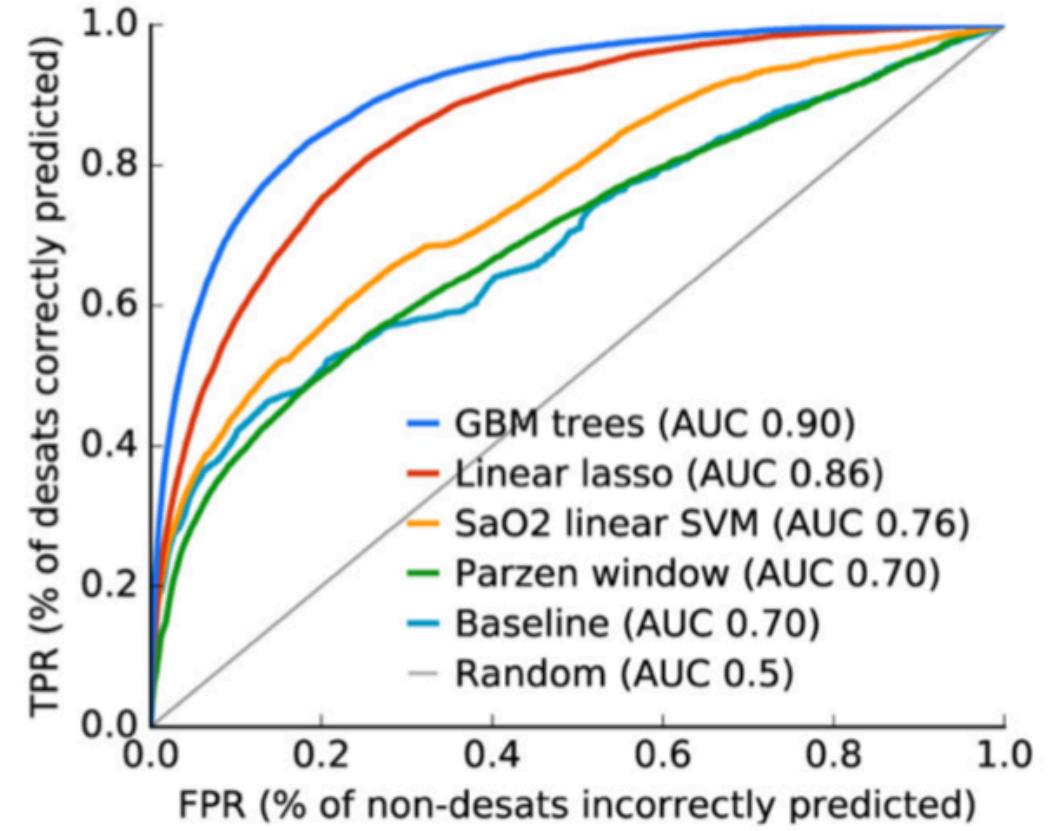
Their Model: Gradient Boosting Machine



Comparison to Alternatives

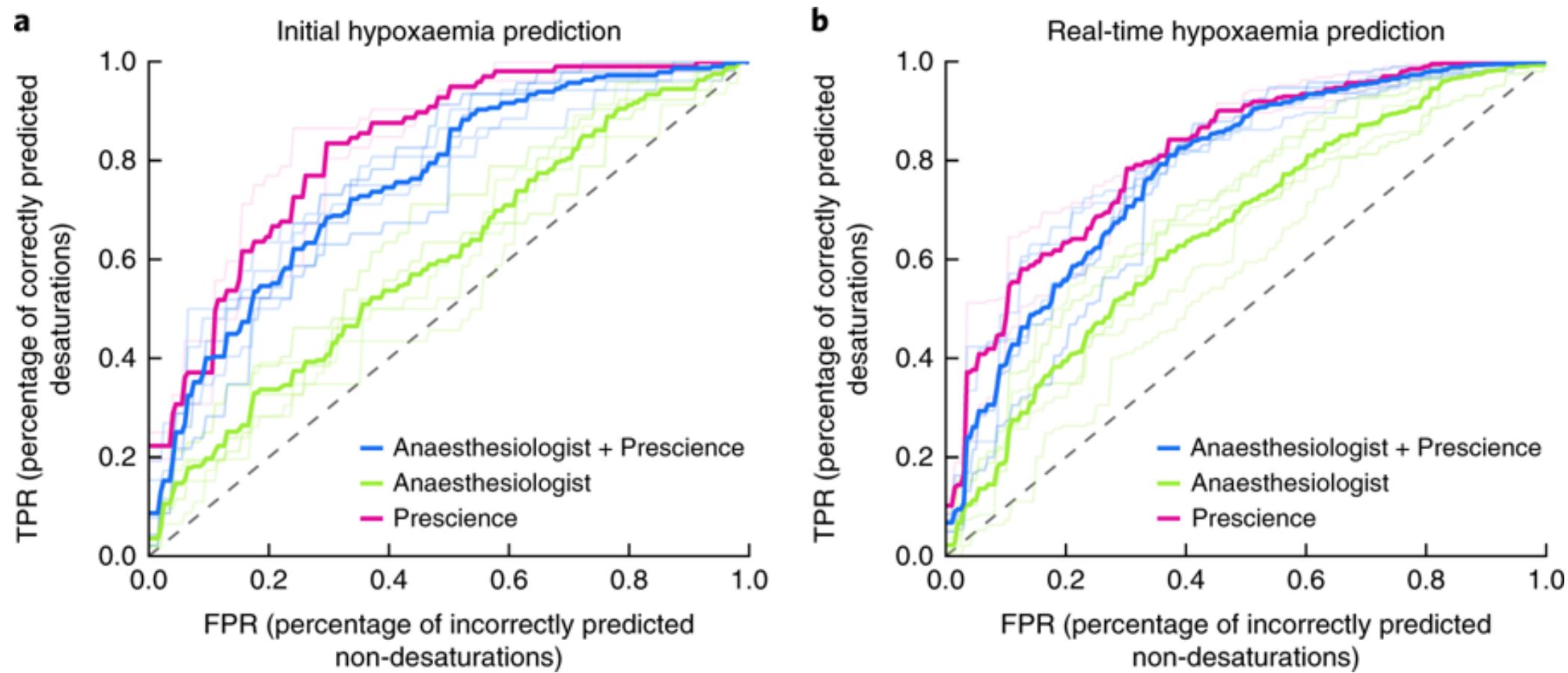


Initial Prediction



Real-time Prediction

Comparison to Experts



For initial risk prediction:

- Anaesthesiologists performed significantly better with Prescience ($AUC = 0.76$ versus 0.60 ; $P < 0.0001$)
- Prescience performed better in a direct comparison with anaesthesiologists ($AUC = 0.83$; $P < 0.0001$)

For intraoperative real-time (next 5 min) risk prediction:

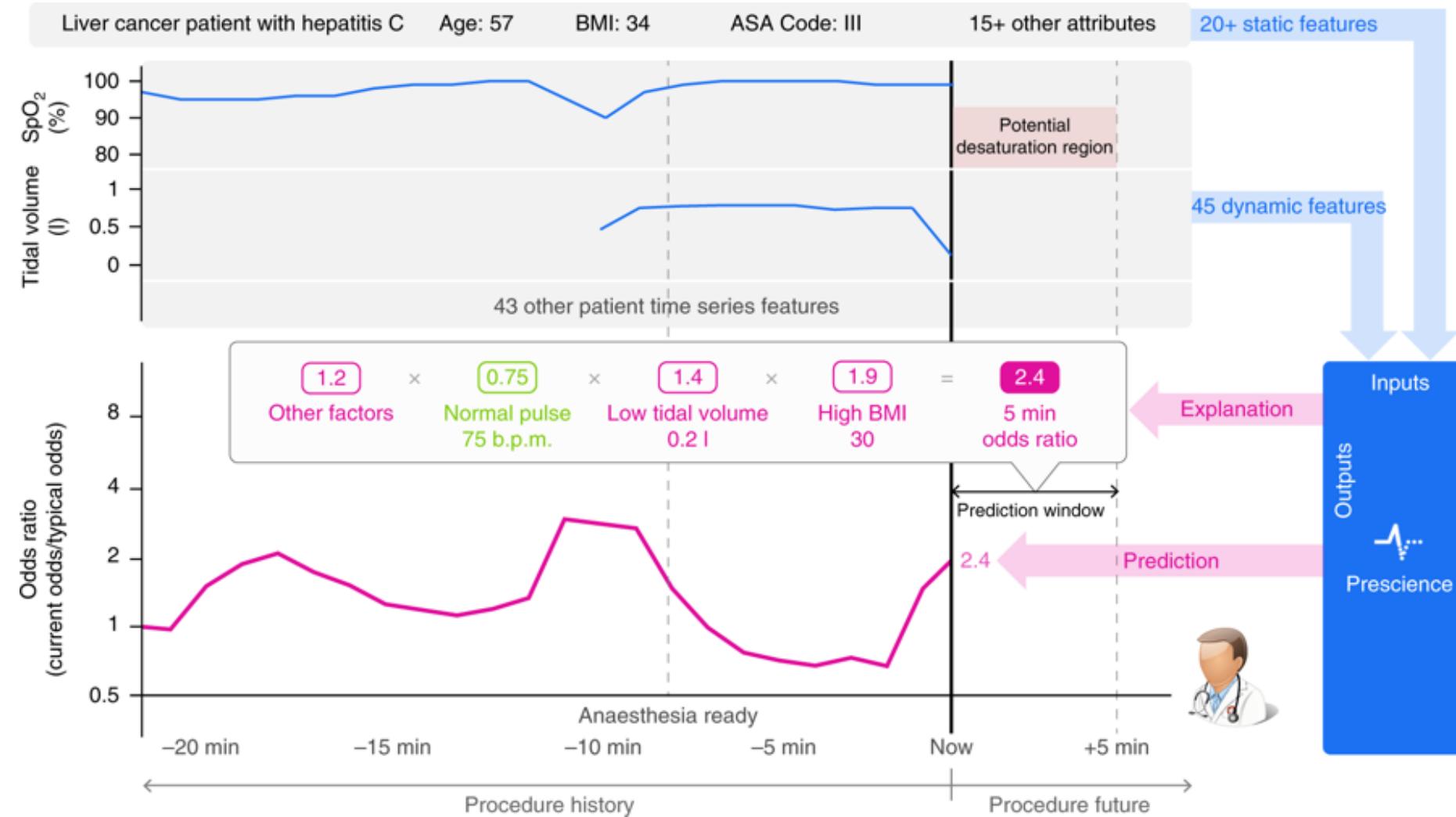
- Anaesthesiologists ($AUC = 0.66$) again performed better with Prescience ($AUC = 0.78$; $P < 0.0001$)
- Prescience alone outperformed anaesthesiologists predictions ($AUC = 0.81$; $P < 0.0001$)

Is this a fair comparison?

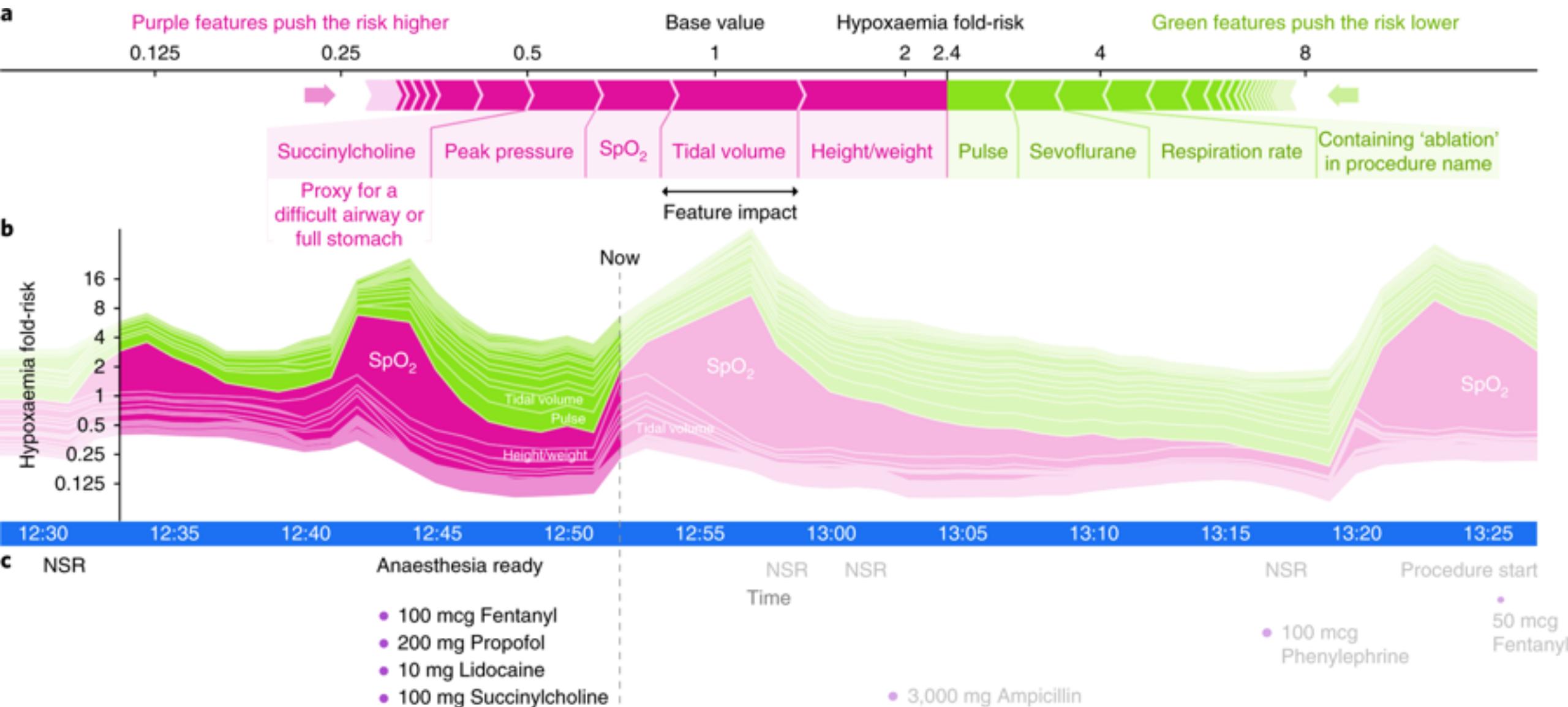
- Training examples are episodes of hypoxemia that were not prevented during surgery
- Expert comparison:
 - the expert is predicting likelihood hypoxic episodes, some of which were prevented
 - the model has learned to predict hypoxic episodes that couldn't be avoided

INTERPRETABLE PREDICTIONS

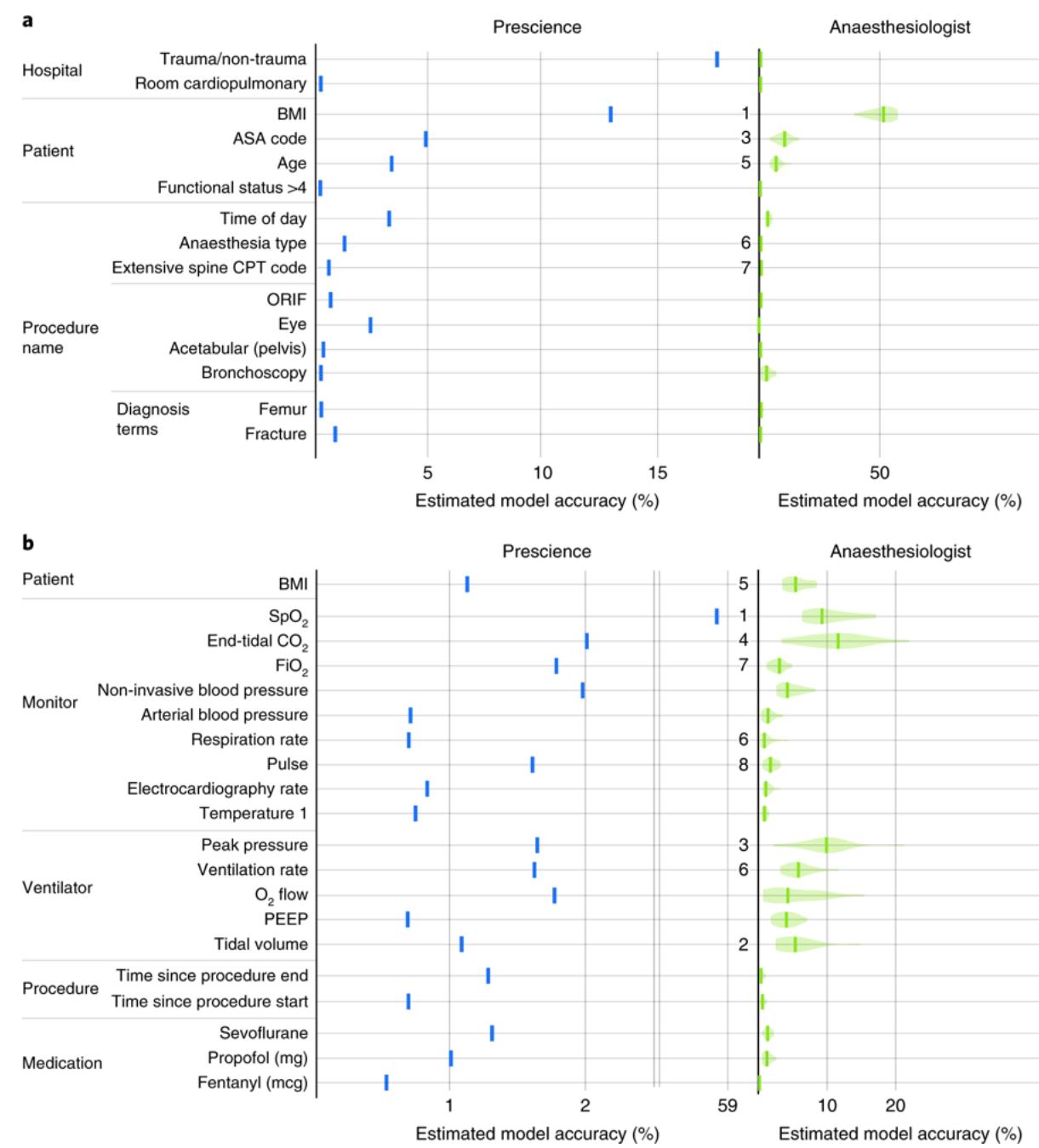
Highlight Feature Importance



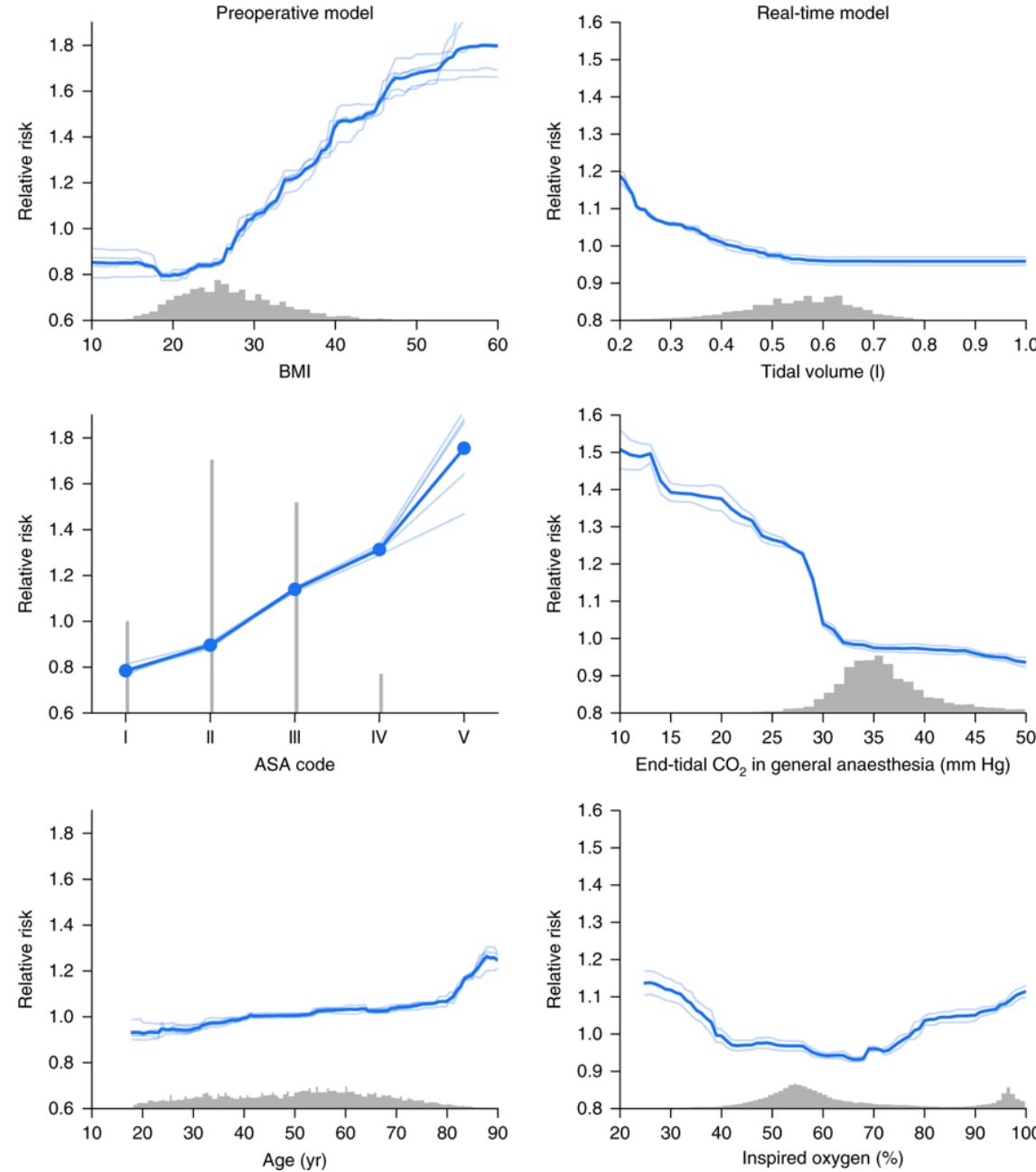
Cumulative Effect of Features



Model Predictions vs Physician Predictions



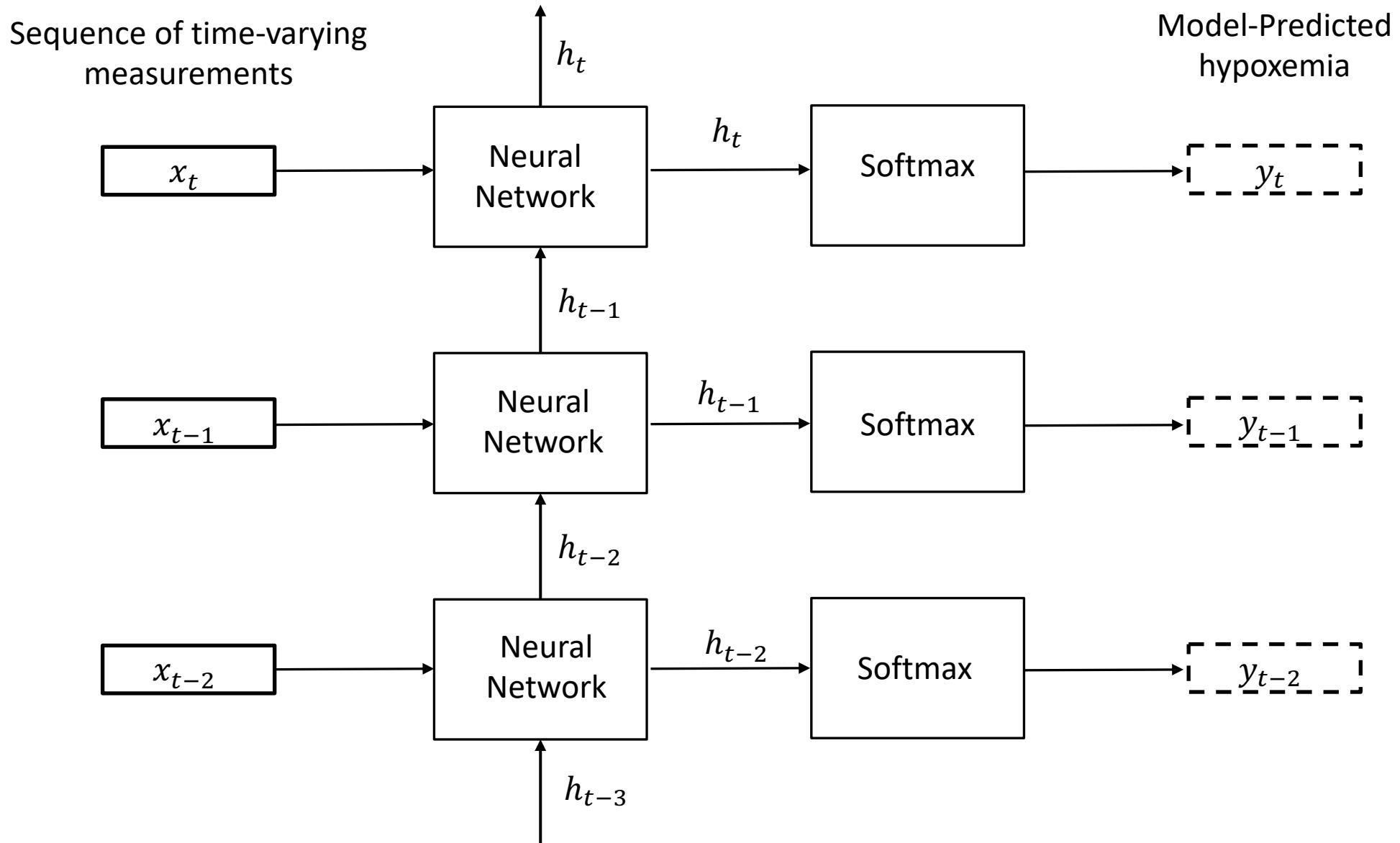
Sensitivity Analysis



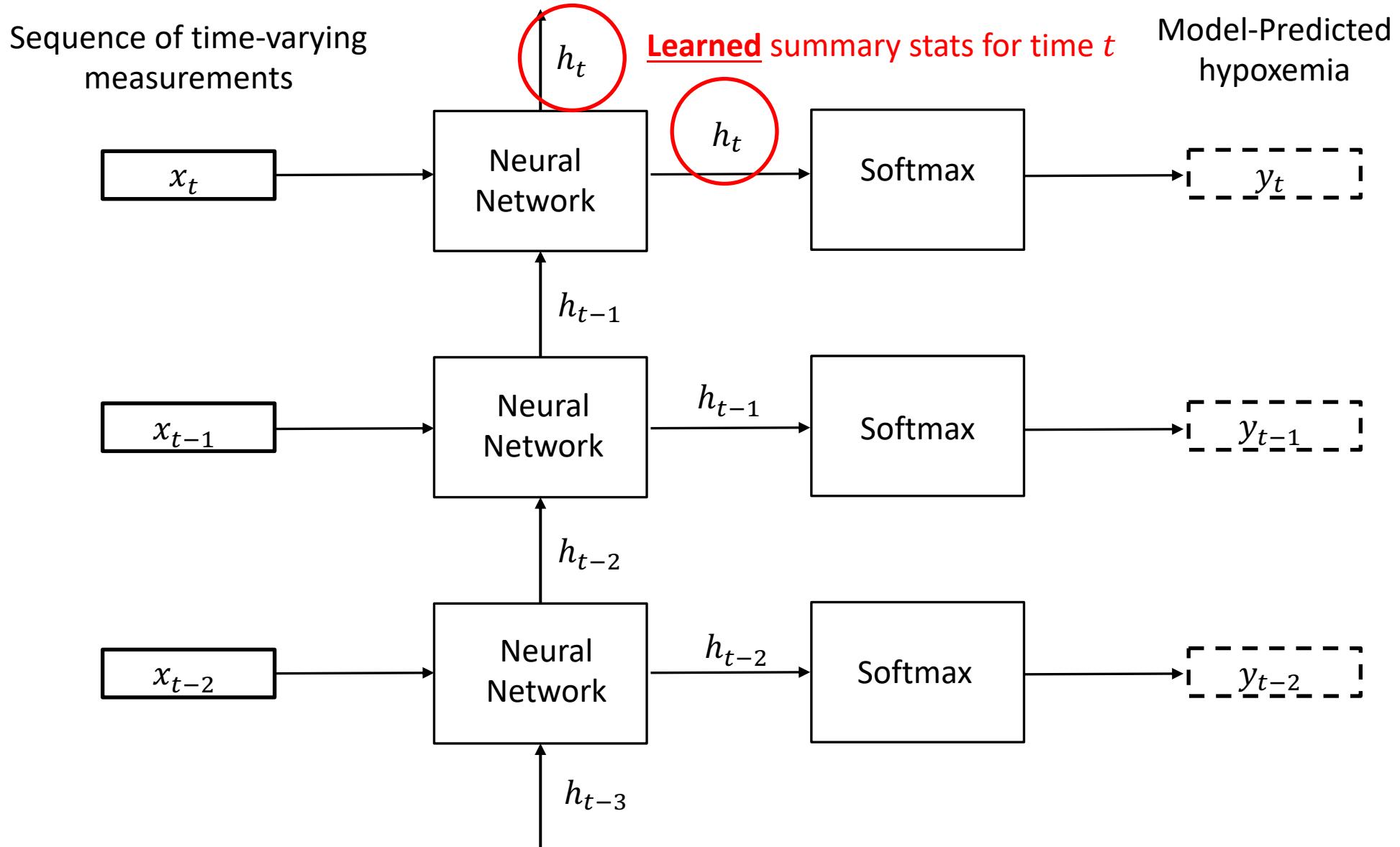
These partial dependence plots show the change in hypoxemia risk for all values of a given feature. The grey histograms on each plot show the distribution of values for that feature in the validation dataset. The lighter coloured lines represent model variability from bootstrap resampling of the training data, the dark lines represent the average of the bootstrap runs.

ALTERNATIVE APPROACH: RNN

Recurrent Neural Network



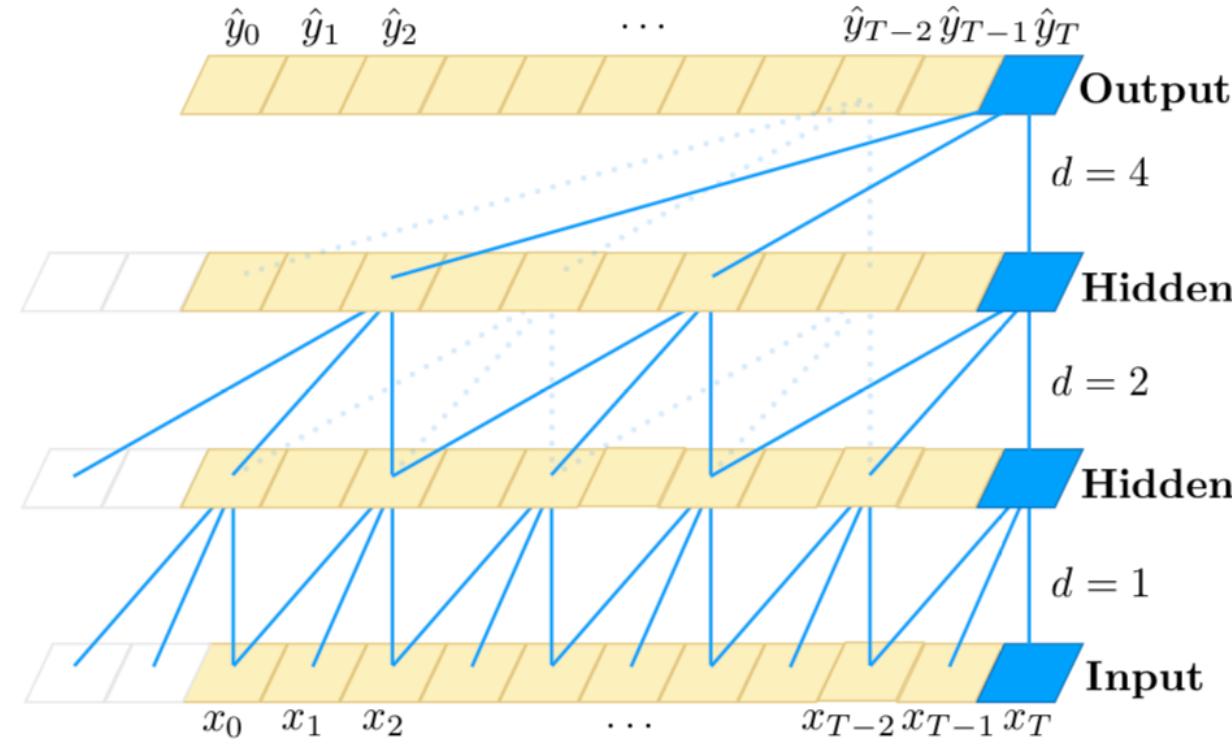
Recurrent Neural Network



RNN or CNN?

- Key advantage of RNN: able to handle variable-length sequences
- Key disadvantage of RNN: difficulty with long-term dependencies
- Recent work: CNNs that can handle variable-length sequences

Convolutional Architecture for Time Series (uses “dilated” convolutions)



(a)

A dilated causal convolution with dilation factors $d = 1, 2, 4$ and filter size $k = 3$.
The receptive field is able to cover all values from the input sequence.

CNNs for Sequences: (Bai et al, 2018)

An Empirical Evaluation of Generic Convolutional and Recurrent Networks for Sequence Modeling

Table 1. Evaluation of TCNs and recurrent architectures on synthetic stress tests, polyphonic music modeling, character-level language modeling, and word-level language modeling. The generic TCN architecture outperforms canonical recurrent networks across a comprehensive suite of tasks and datasets. Current state-of-the-art results are listed in the supplement. h means that higher is better. $^\ell$ means that lower is better.

Sequence Modeling Task	Model Size (\approx)	Models			
		LSTM	GRU	RNN	TCN
Seq. MNIST (accuracy h)	70K	87.2	96.2	21.5	99.0
Permuted MNIST (accuracy)	70K	85.7	87.3	25.3	97.2
Adding problem $T=600$ (loss $^\ell$)	70K	0.164	5.3e-5	0.177	5.8e-5
Copy memory $T=1000$ (loss)	16K	0.0204	0.0197	0.0202	3.5e-5
Music JSB Chorales (loss)	300K	8.45	8.43	8.91	8.10
Music Nottingham (loss)	1M	3.29	3.46	4.05	3.07
Word-level PTB (perplexity $^\ell$)	13M	78.93	92.48	114.50	88.68
Word-level Wiki-103 (perplexity)	-	48.4	-	-	45.19
Word-level LAMBADA (perplexity)	-	4186	-	14725	1279
Char-level PTB (bpcl $^\ell$)	3M	1.36	1.37	1.48	1.31

Stacked RNN & Transformer

- Hierarchical architectures
- The latter is based on “self-attention”: determine which words modify a given word, and how

