

Life After Death:

Techniques for the rapid prognostication of
post-anoxic coma patients.

Mohammad M. Ghassemi
Massachusetts Institute of Technology

Cardiac arrest affects 320K people in the US annually

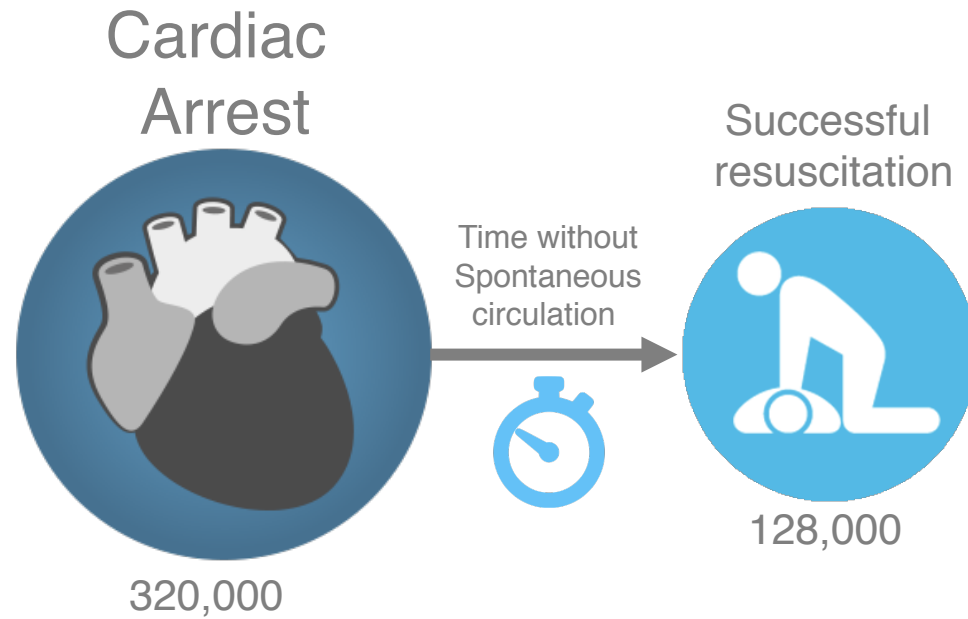
Cardiac
Arrest



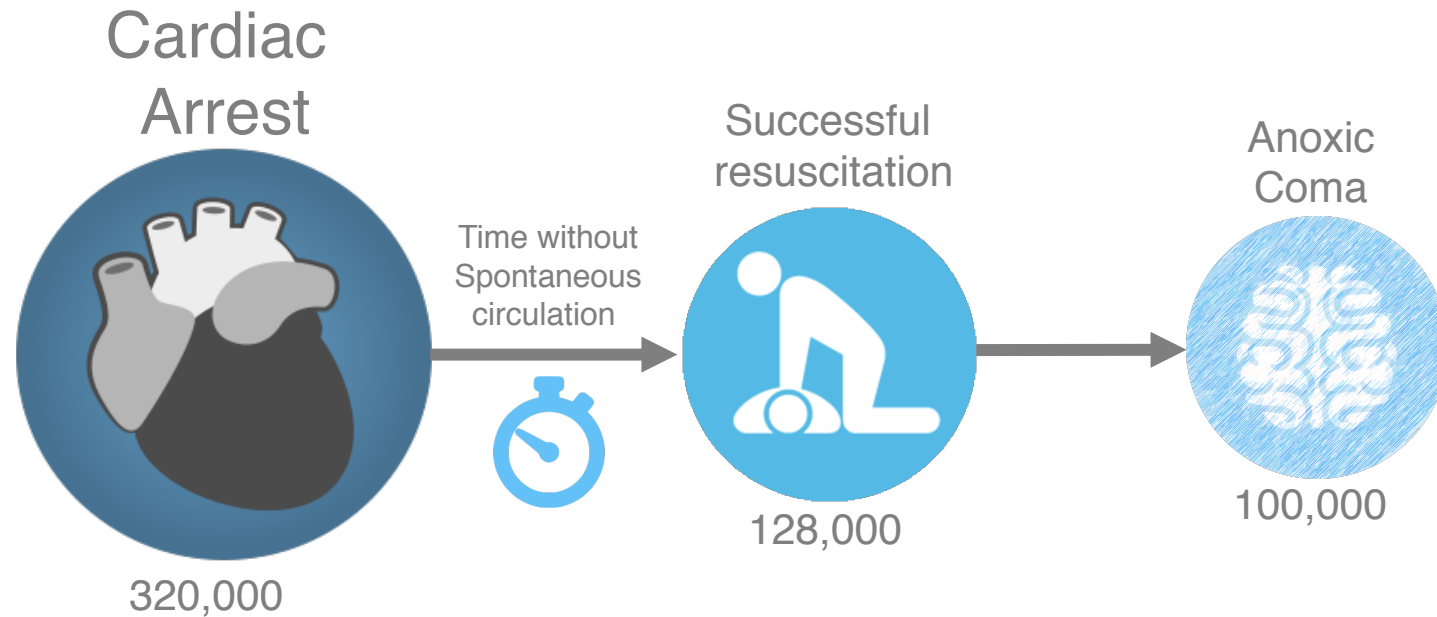
320,000

- [4] G. Citerio, J. Bakker, M. Bassetti, D. Benoit, M. Cecconi, J. Curtis, G. Doig, M. Heridge, S. Jaber, and M. Joannidis, "Year in review in intensive care medicine 2014: I. cardiac dysfunction and cardiac arrest, ultrasound, neurocritical care, icu-acquired weakness, nutrition, acute kidney injury, and miscellaneous," *Intensive Care Medicine*, vol. 41, no. 2, pp. 179–191, 2015.

128K patients are successfully resuscitated

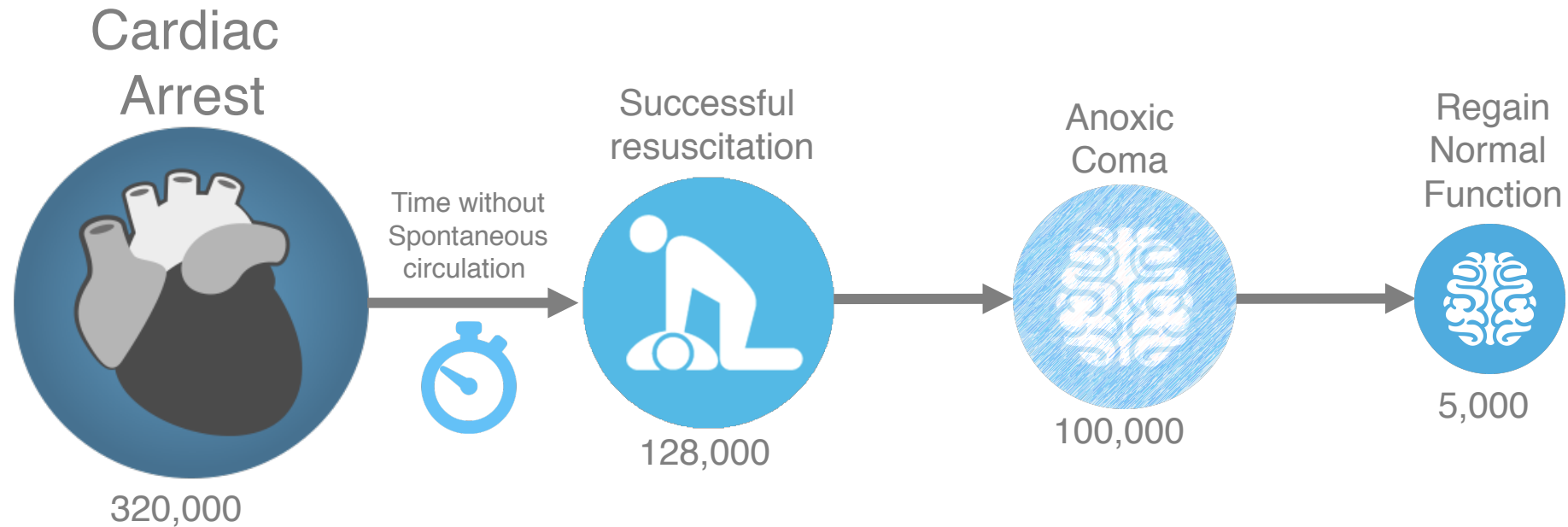


100K enter an indefinite, anoxia-induced coma



[6] R. Deng, M. Koenig, L. Young, and X. Jia, "Early quantitative gamma-band eeg marker is associated with outcomes after cardiac arrest and targeted temperature management," *Neurocritical Care*, vol. 23, no. 2, pp. 262–273, 2015.

10K will survive, but only 5K will regain normal function



[7] P. R. L. I. for Health Policy, "Icu outcomes (mortality and length of stay) methods, data collection tool and data." <http://healthpolicy.ucsf.edu/content/icu-outcomes>, 2016.

Outcome metric

Cerebral Performance Category	Conscious (Y/N)	Cerebral Disability	Consequences
1	Y	Mild	May resume independent activities with minimal complications
2	Y	Moderate	May resume independent activities while requiring some assistance
3	Y	Severe	Will require assistance to perform activities and may involve paralysis, or dementia.
4	N	Vegetative	Requires assistance to survive and will be minimally aware/responsive
5	N	Brain-Death	Requires assistance to survive and will be totally unaware/response

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Good

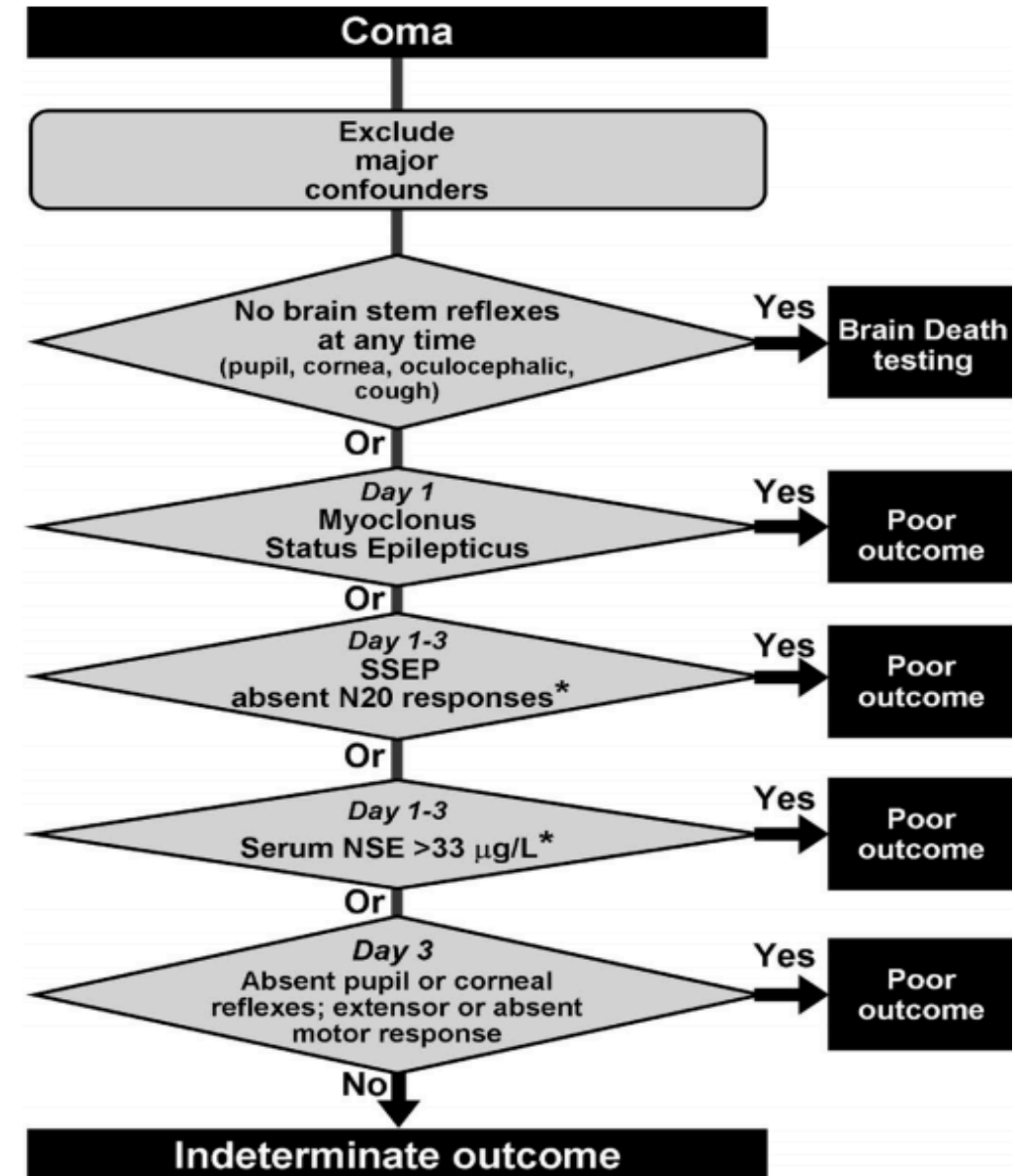
Bad

Goals of prognostication

- **Primary:** Prevent premature withdrawal care
- **Secondary:** Prevent unnecessary care
(up to \$20,000 per day in ICU)

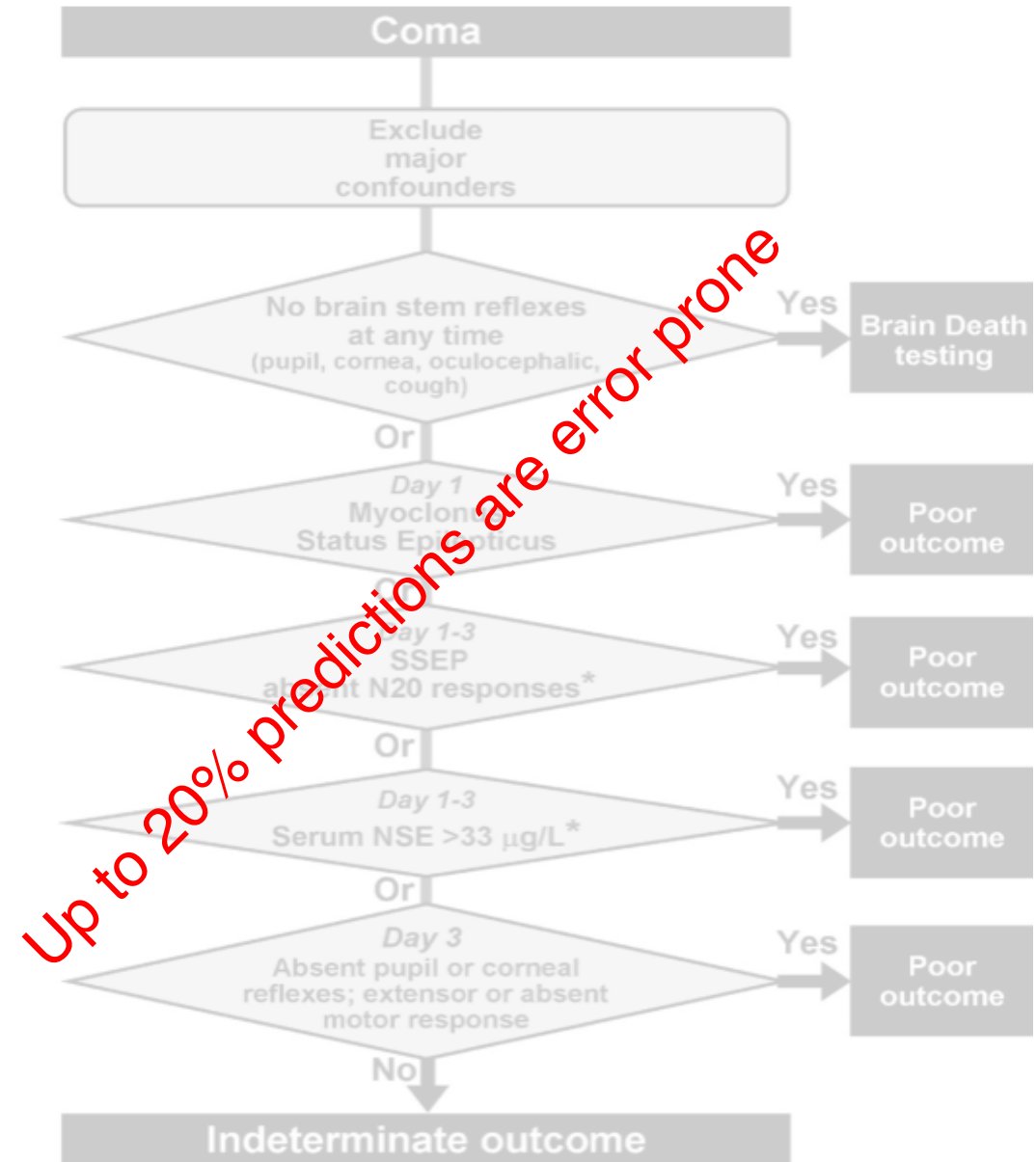
Current Prognostic Guidelines

- A sequence of clinical observations and tests performed following cardiac arrest
- Accurate in predicting poor neurological outcomes when severe deficits are present (FPR < 1%)
- Less guidance in cases where clear-cut signs are lacking, or under varying protocols (e.g. therapeutic hypothermia)



Current Prognostic Guidelines

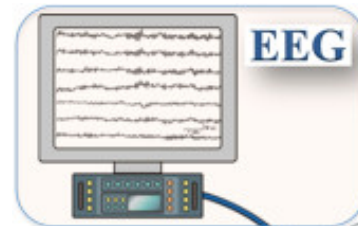
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Review of the Literature

EEG Features

Tjepkema-Cloostermans, 2017
AUC = 0.94 at 24 hours
N = 283



Pain-related SSEP

Zanatta, 2015
AUC = 0.84 at 72 hours
N = 167



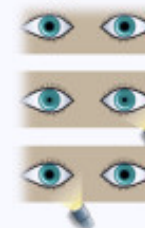
NSE

Dagmar, 2017
AUC = 0.77 at 24 hours
N = 153



Biomarkers

Clinical examination



Quantitative Pupillometry

Suys, 2015
AUC = 0.81 at 24 hours
N = 50

MRI

Jeon, 2017
AUC = 0.89 at 24 hours
N = 47



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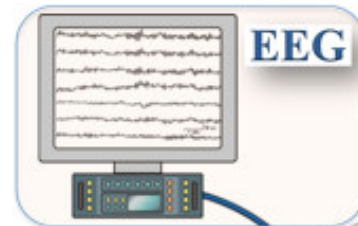
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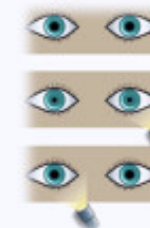


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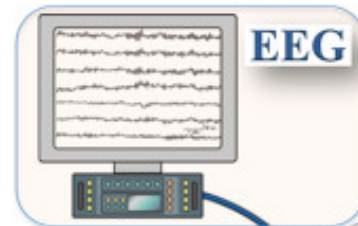
Conclusions

- **Limited Sample Sizes:** larger samples are needed

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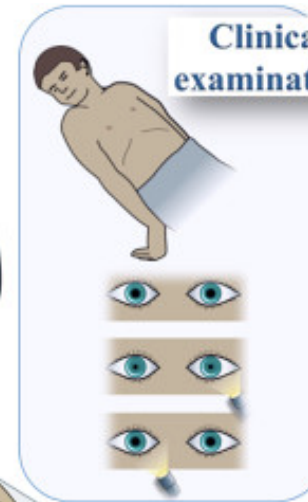
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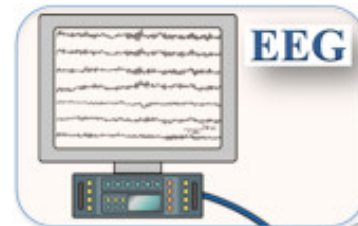
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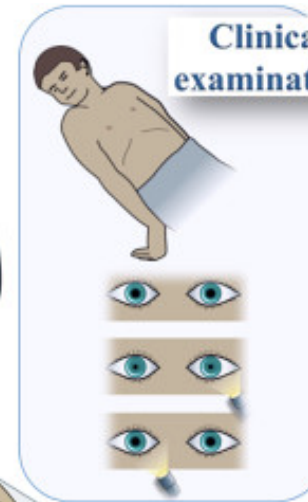
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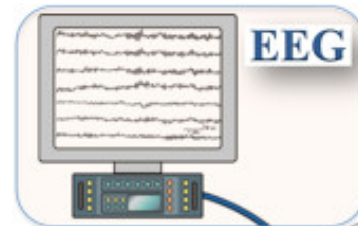
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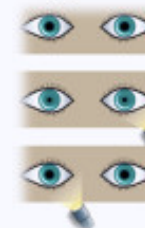


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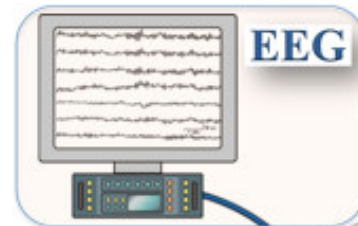
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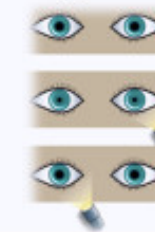
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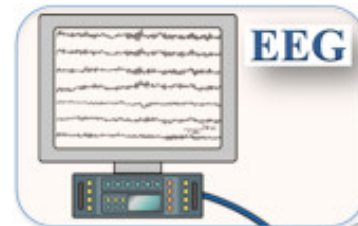
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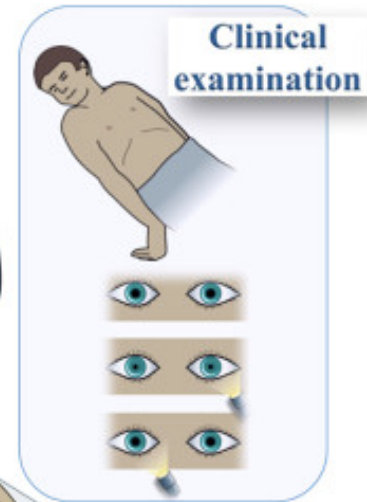


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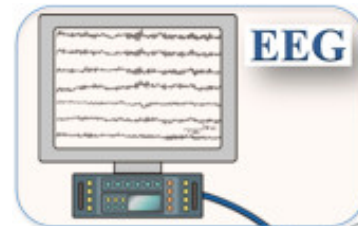
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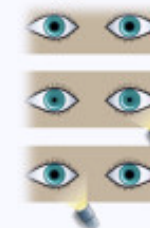


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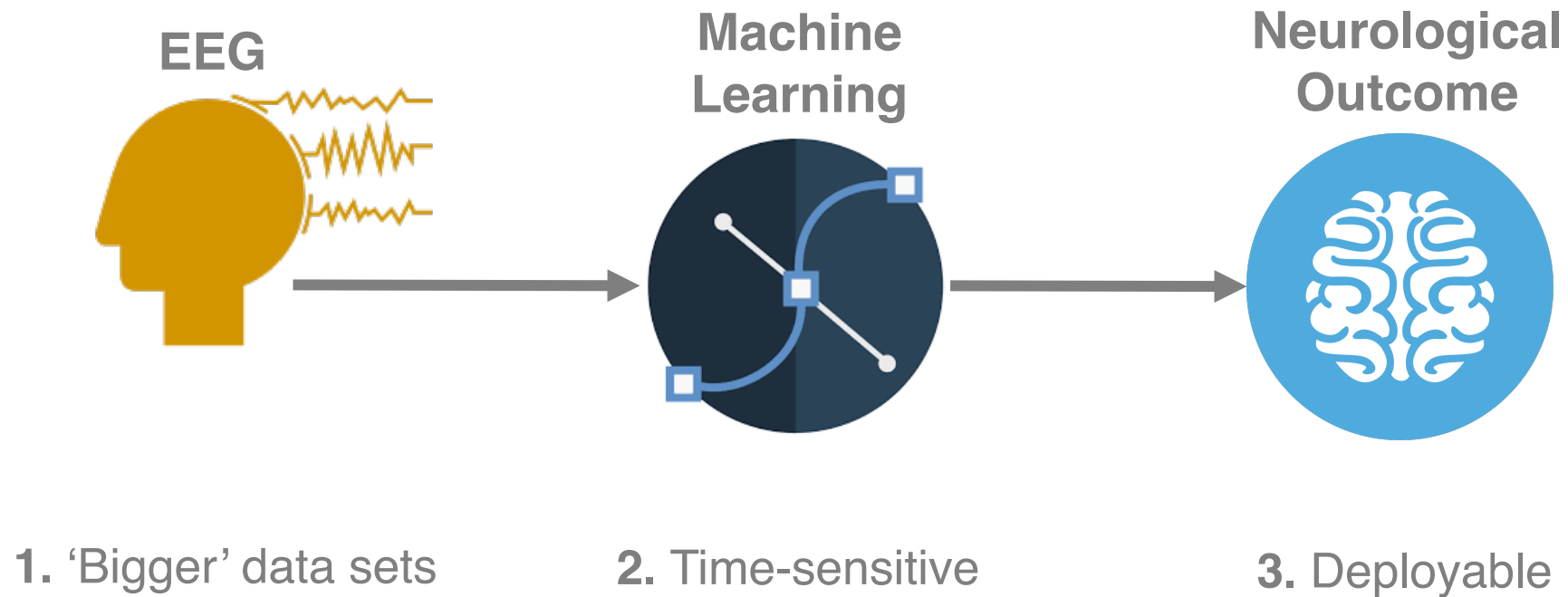
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- **Limited Sample Sizes:** larger samples are needed
- **Time Specific:** prediction should be possible at all points in time
- **Classification focused:** risk scoring may be better
- **EEG alone can provide state-of-the-art performance**

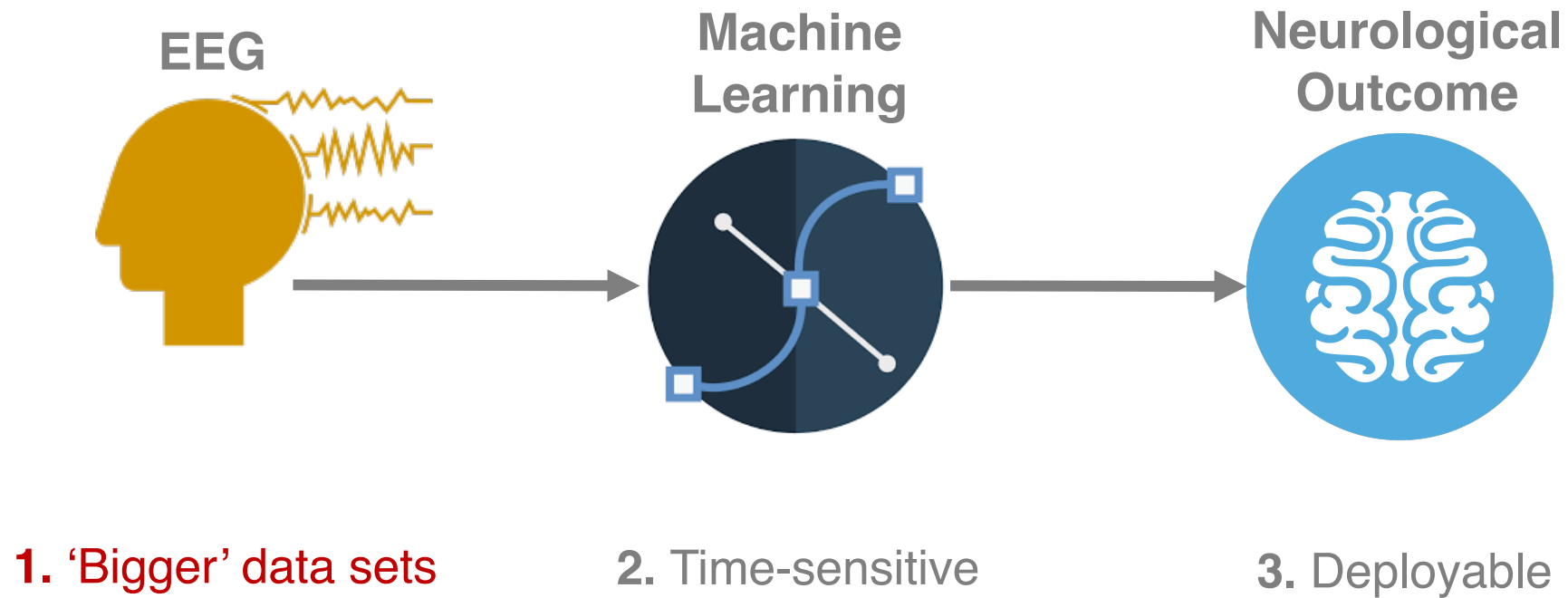
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- **EEG alone can provide state-of-the-art performance**
 - **deep learning could eliminate the need for feature engineering**

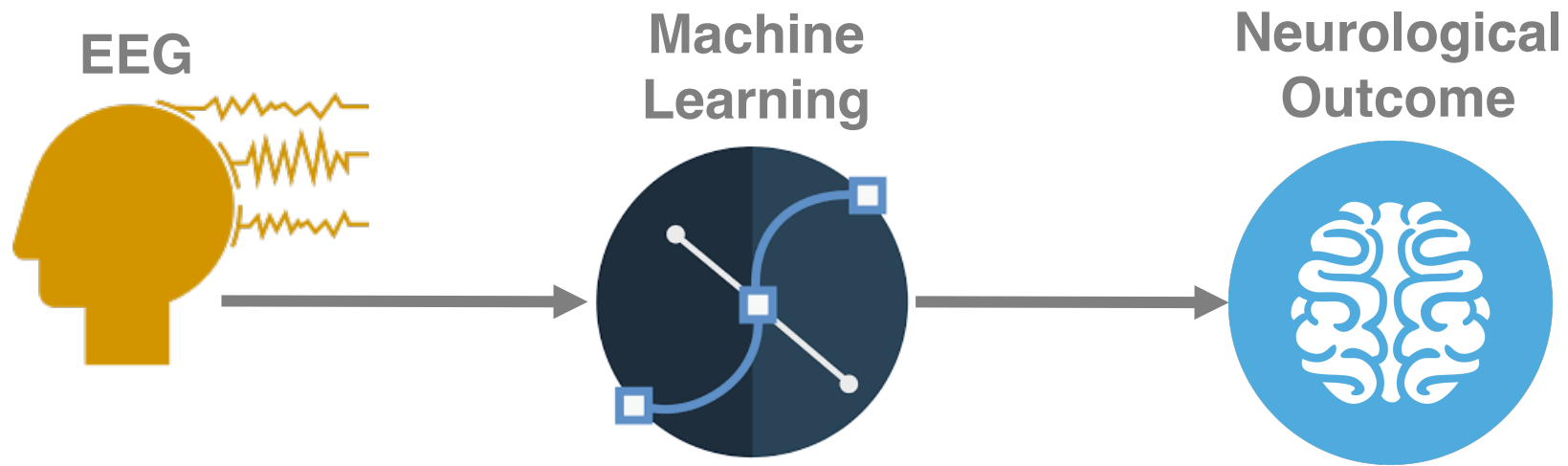
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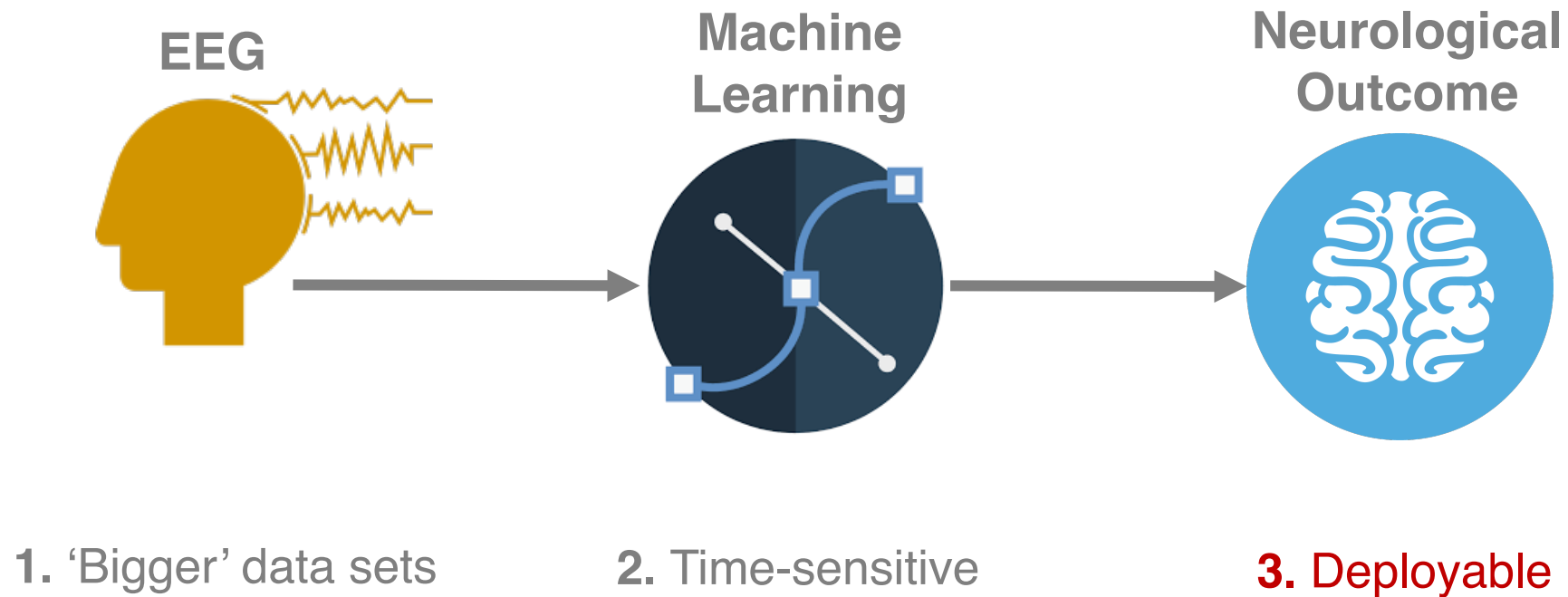


1. 'Bigger' data sets

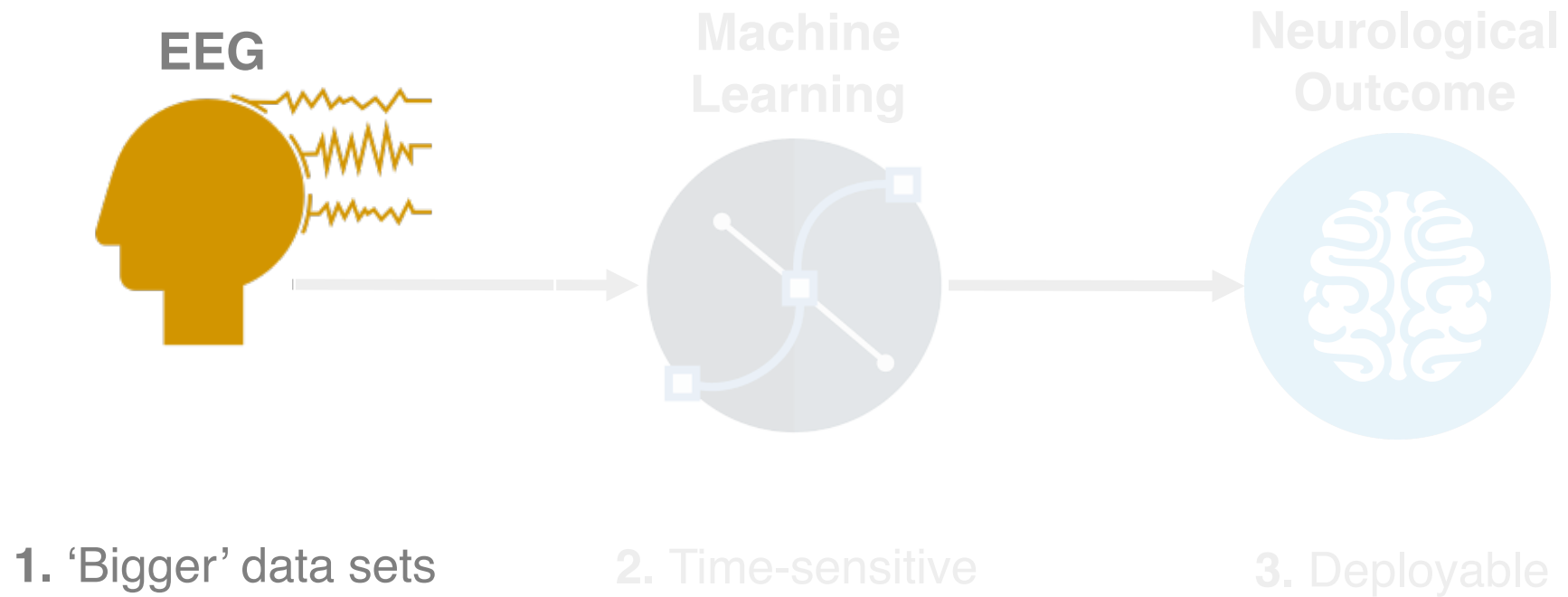
2. Time-sensitive

3. Deployable

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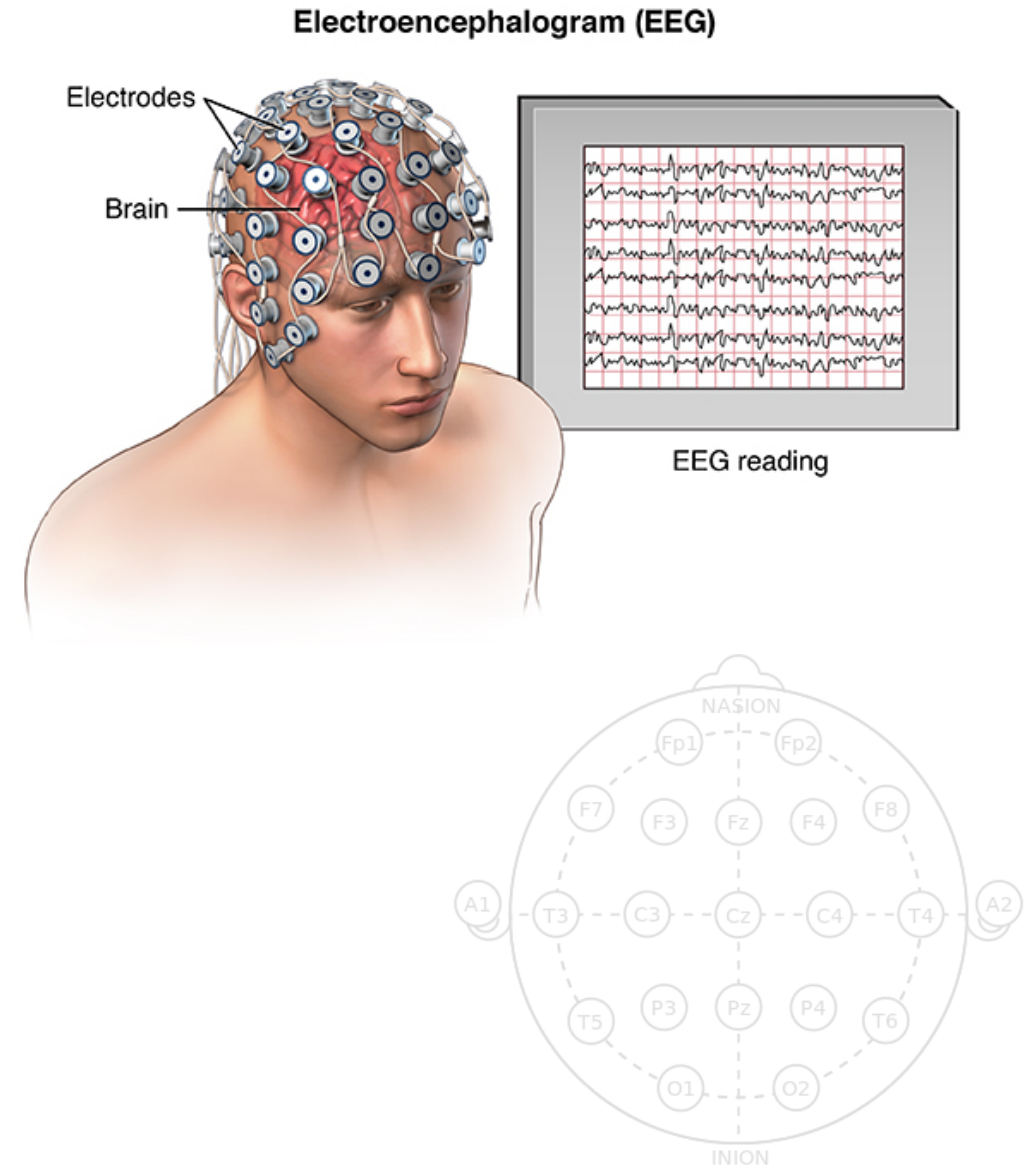


Data collection



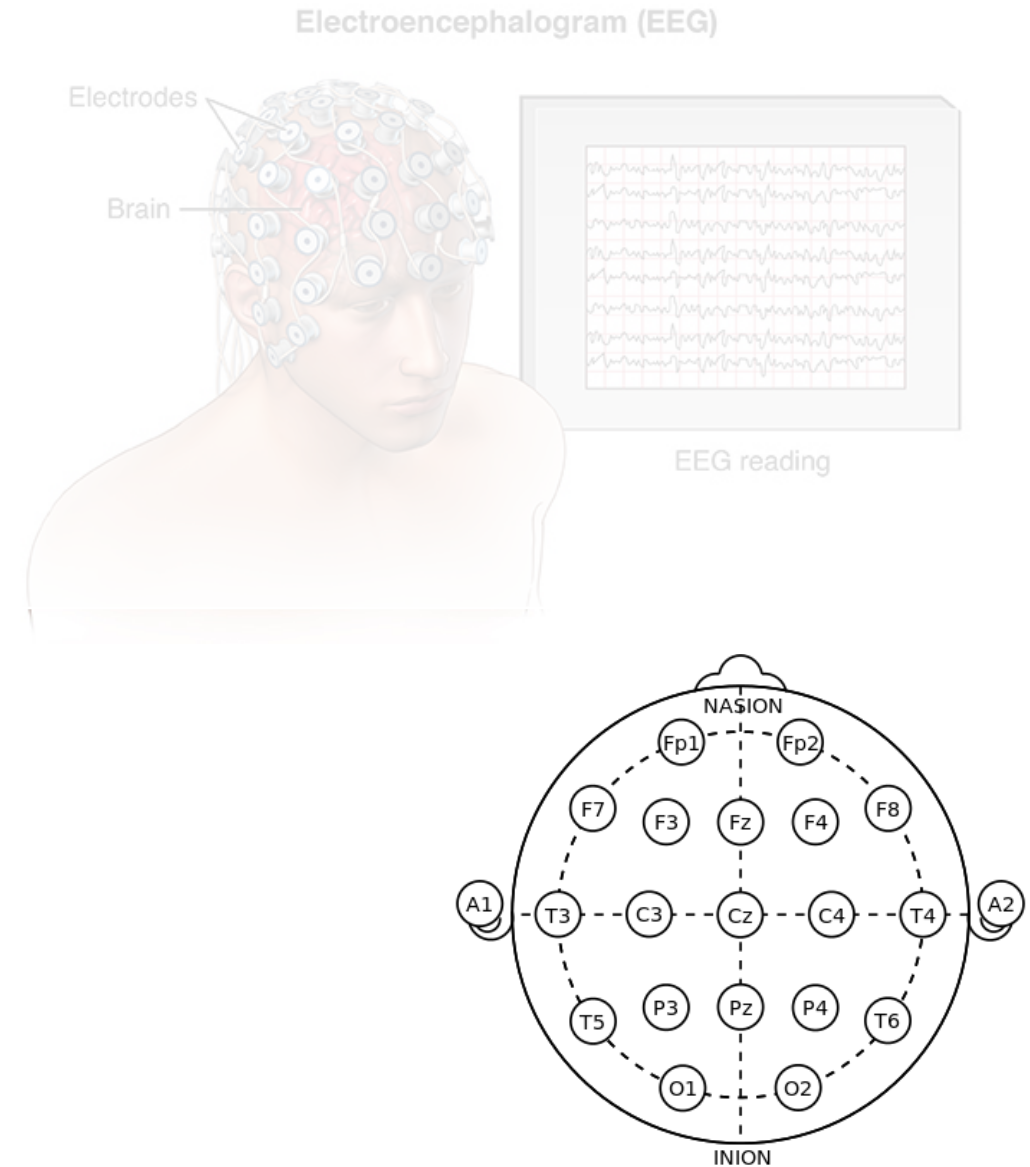
Electroencephalography (EEG)

- Each EEG electrode records an **ensemble** of cellular activity near the location of the electrode
- Electrode Placement was in accordance with the International 10-20 system



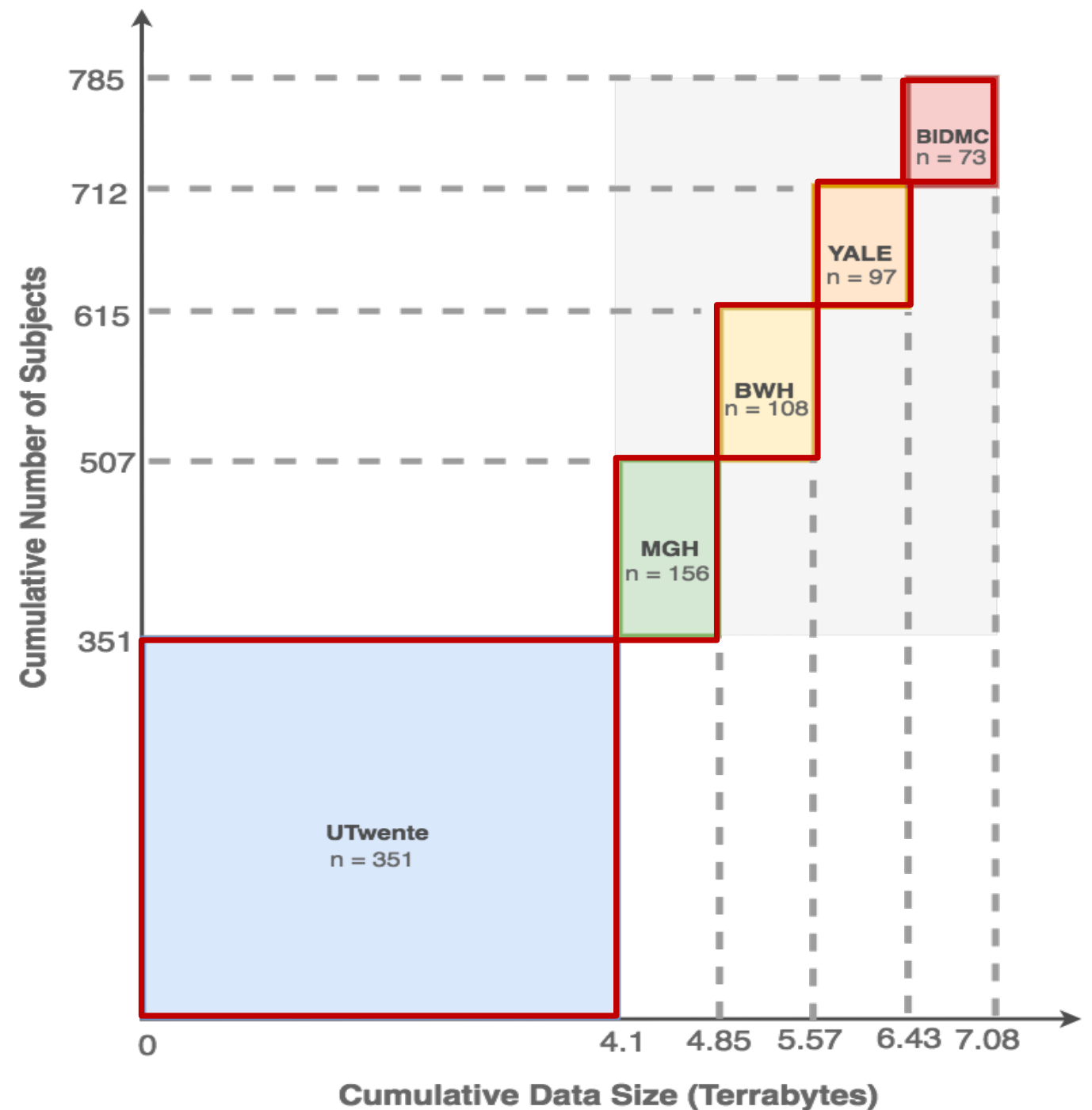
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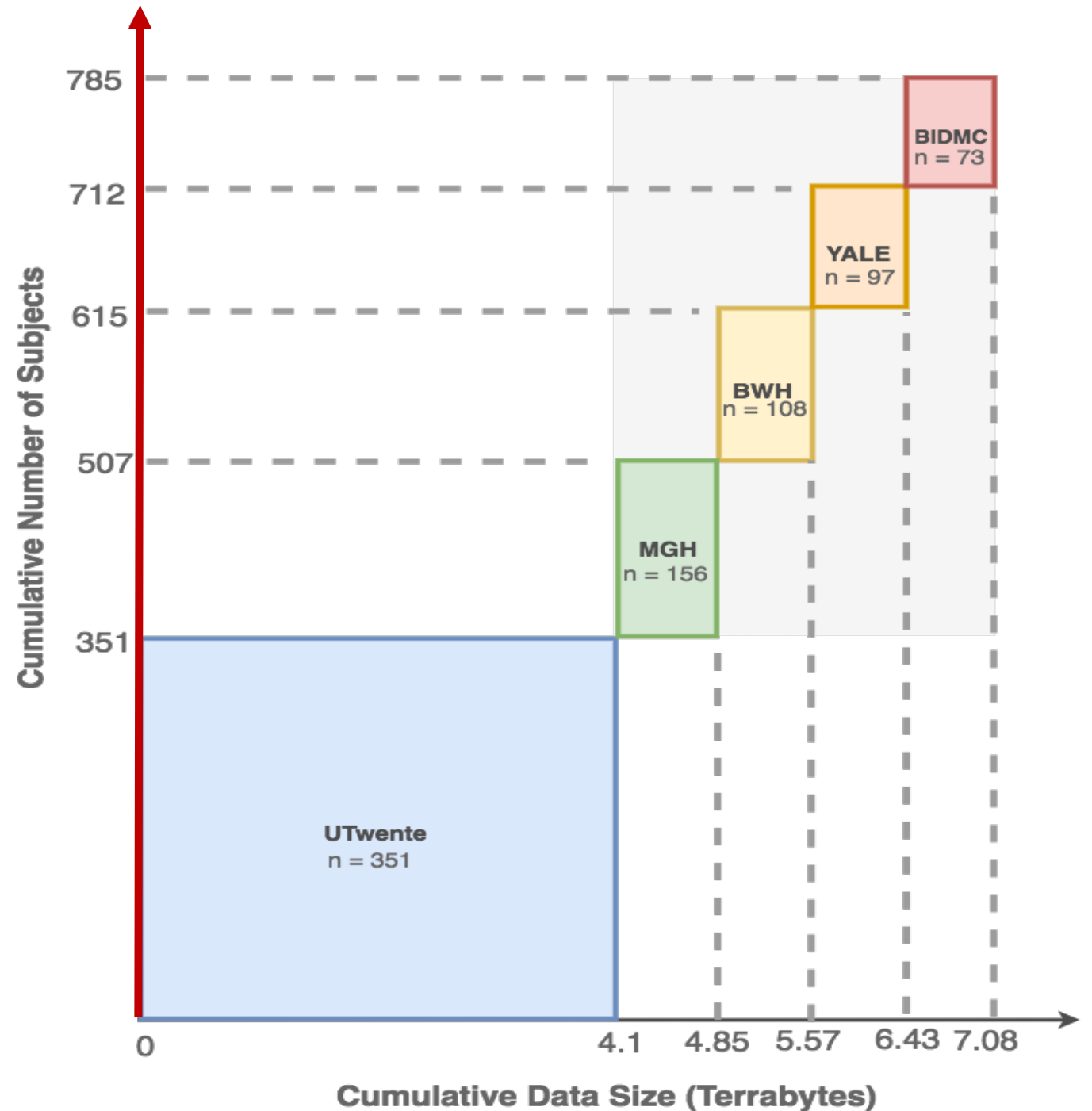
EEG data

- 5 contributing institutions
- 785 unique patients
- 7 terabytes of data



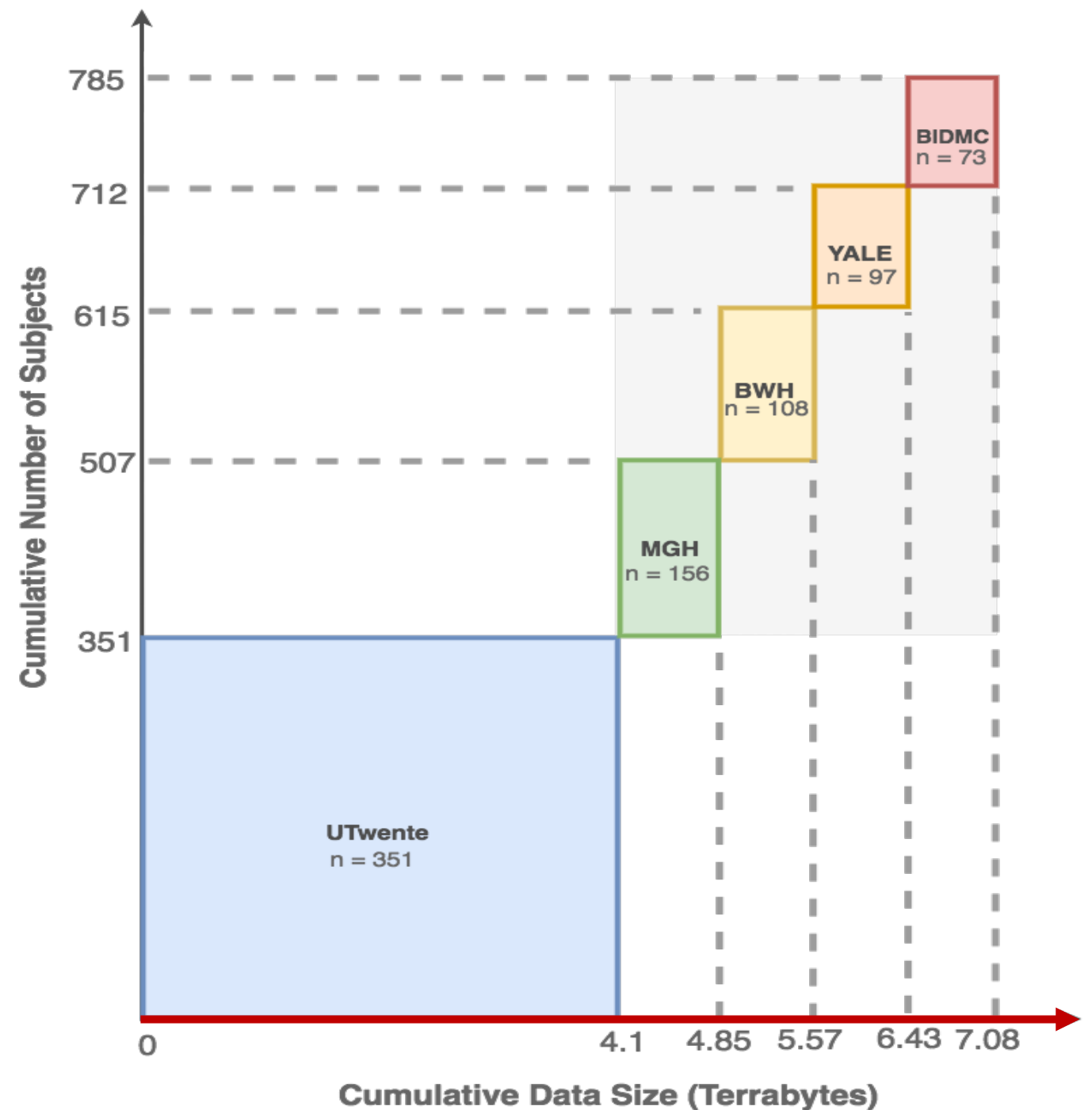
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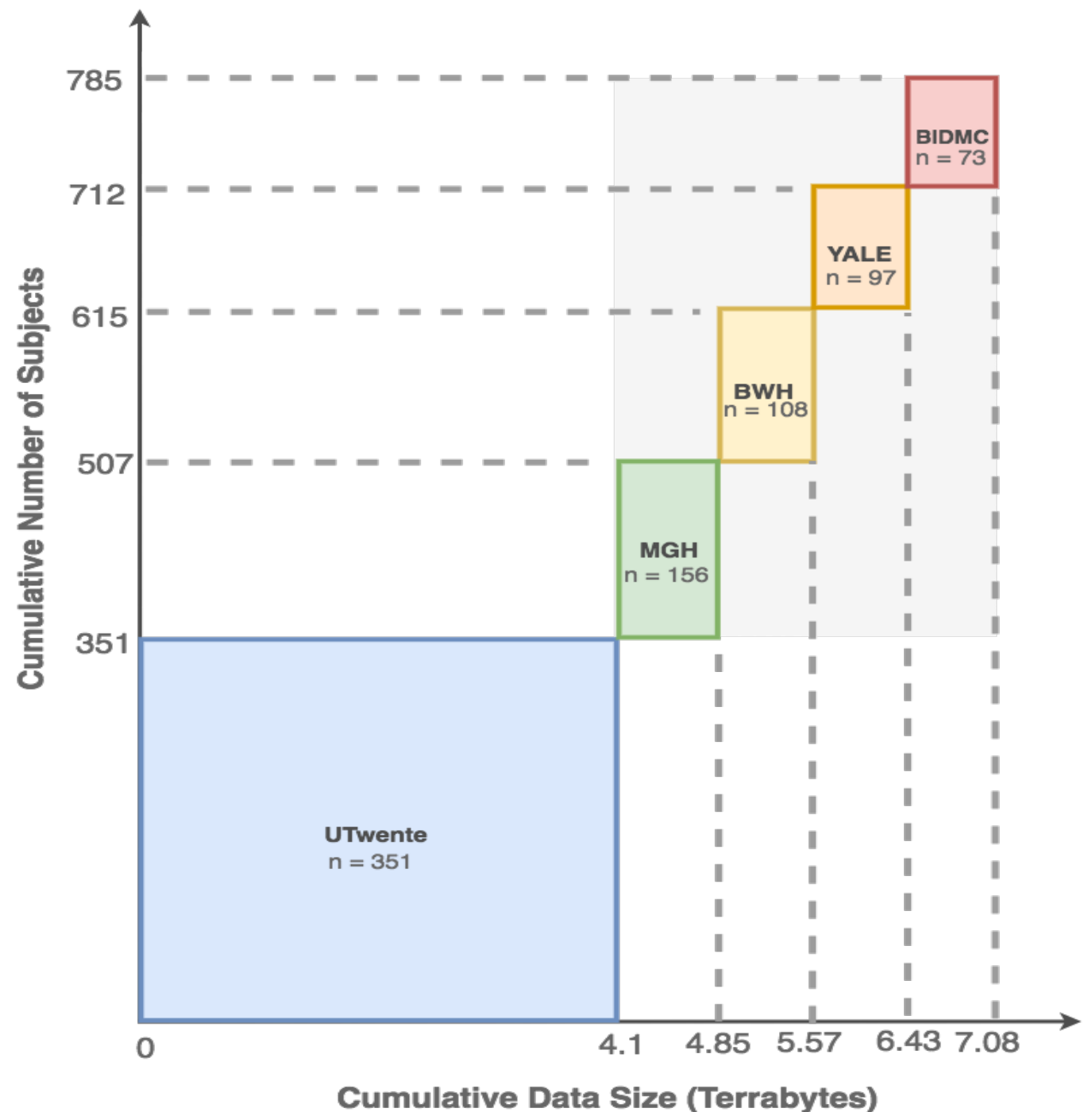
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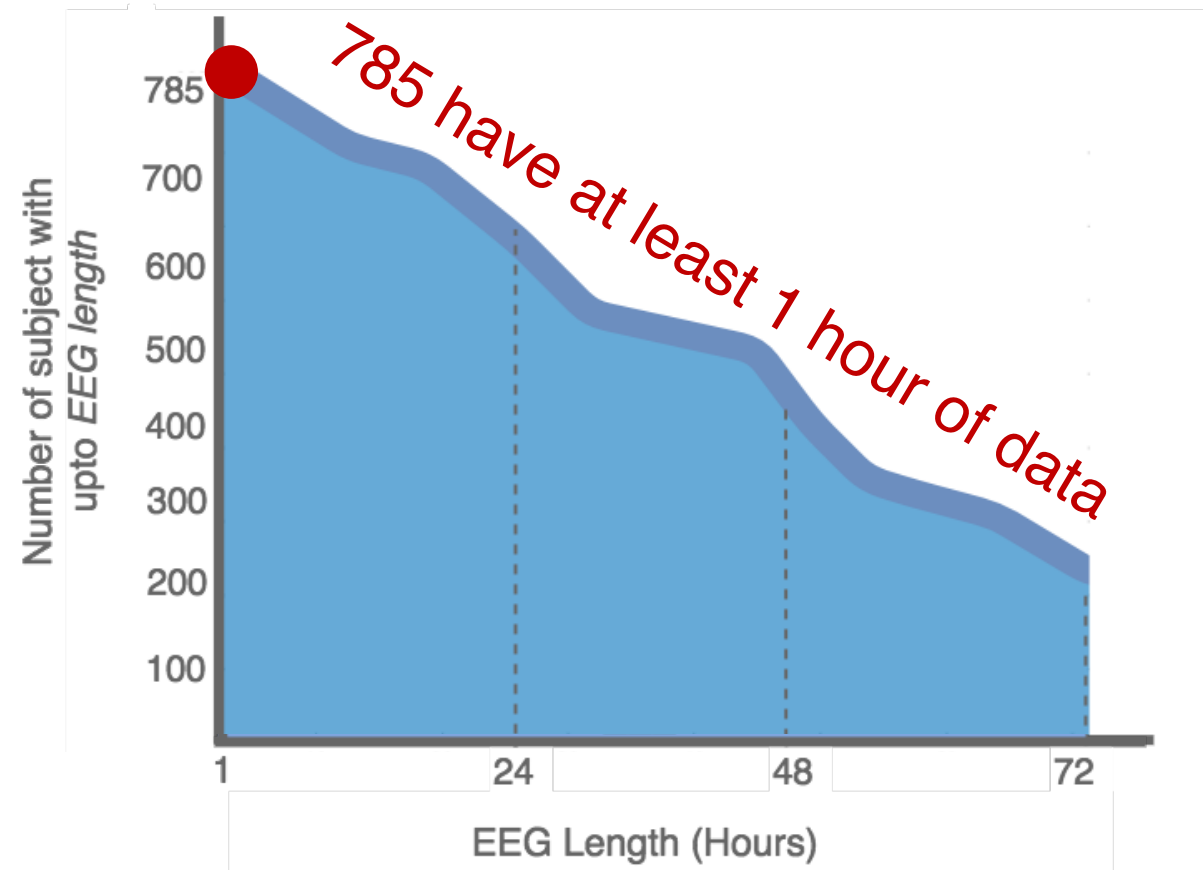
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- 7 terabytes of data
- Over 2x larger than existing archives described in the literature



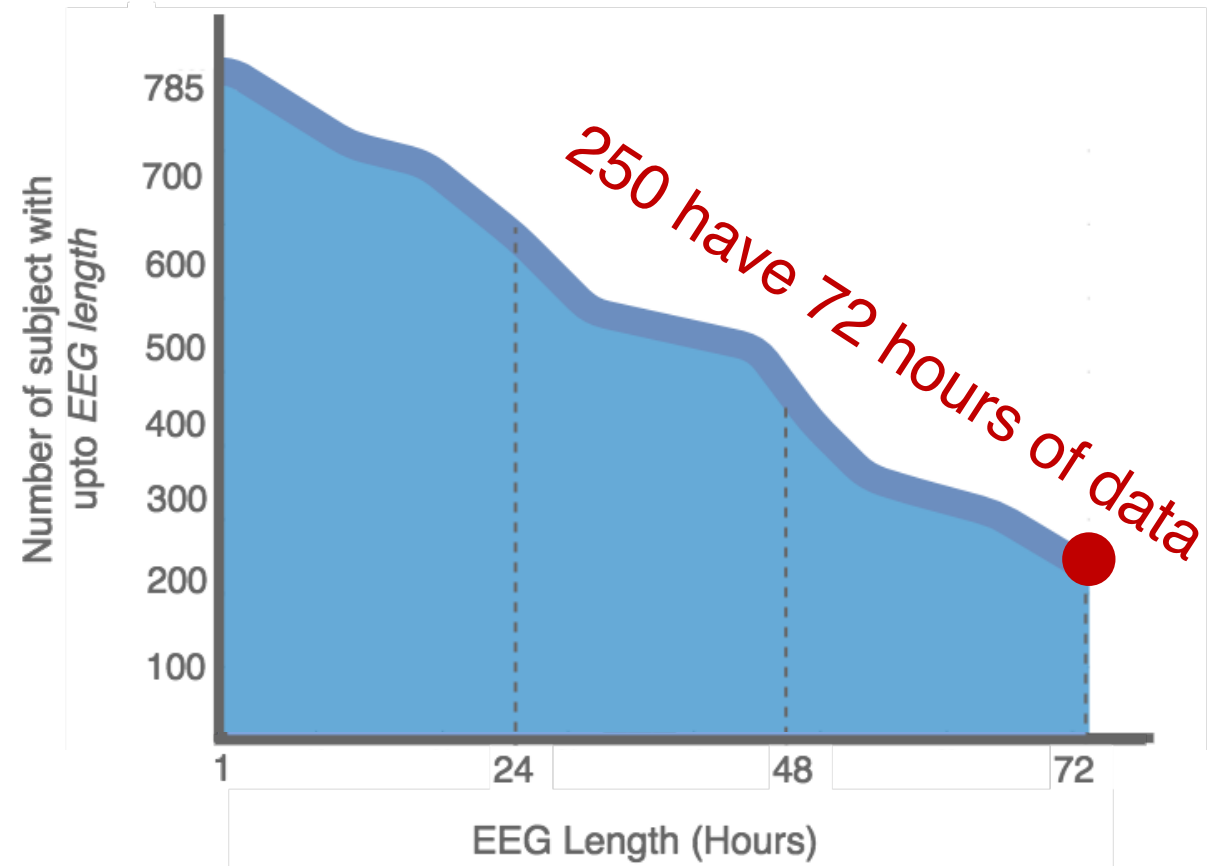
EEG temporal properties

- Data densities linearly decrease over time
- EEG withdrawal is assessed approximately once every 24 hours



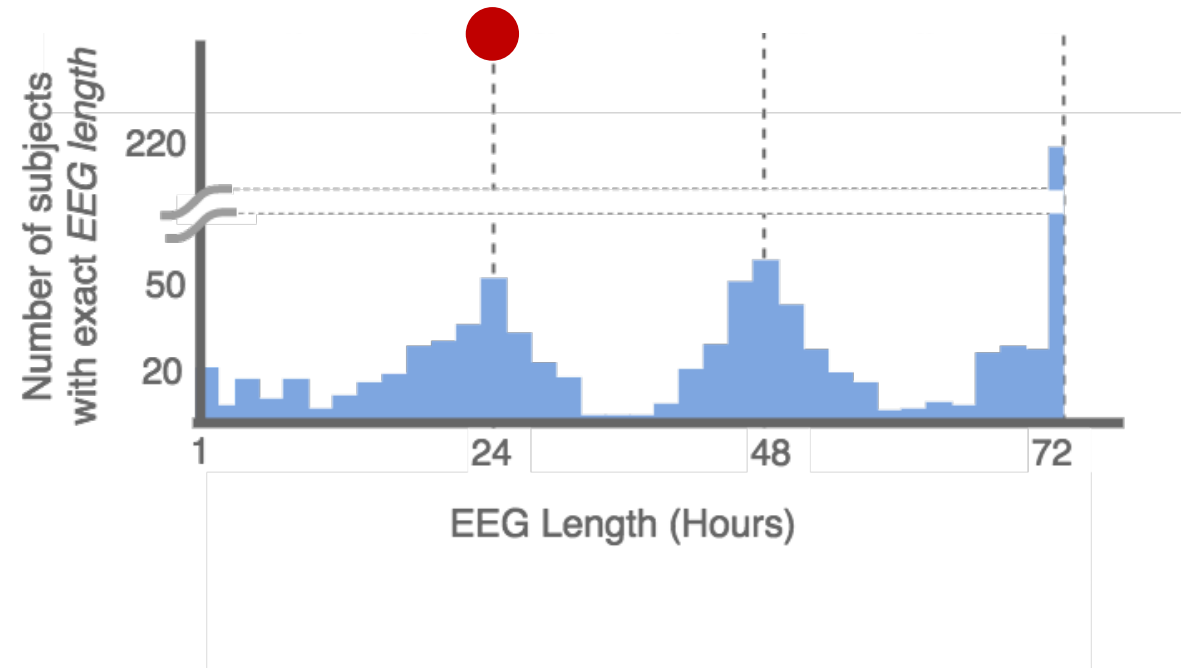
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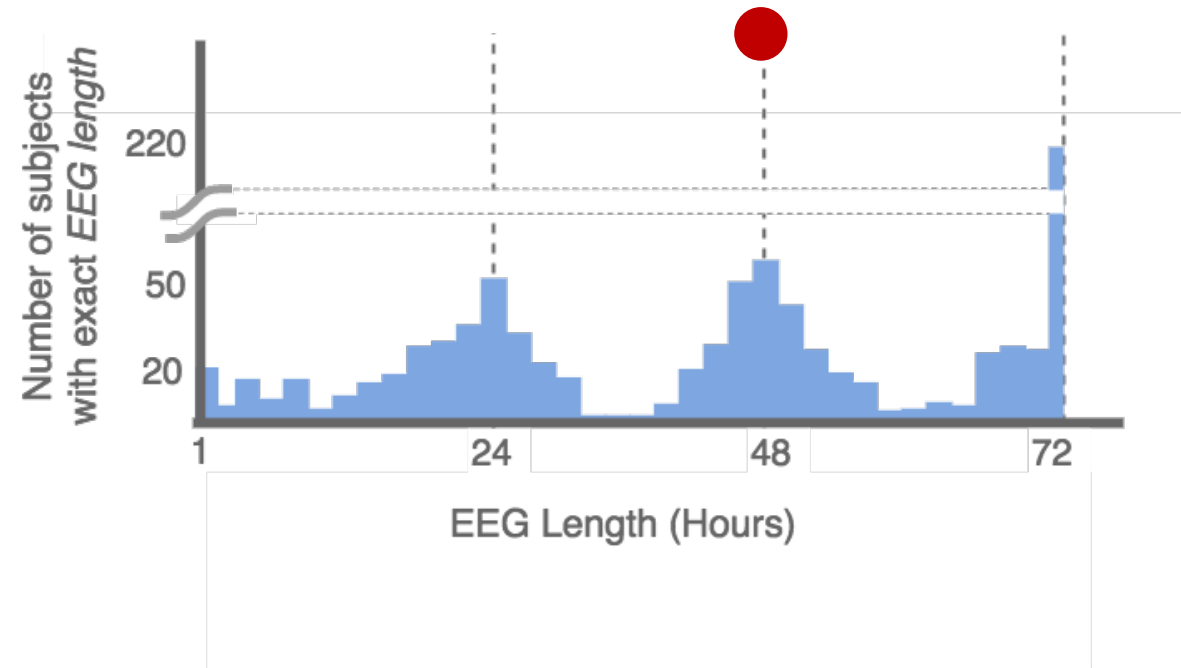
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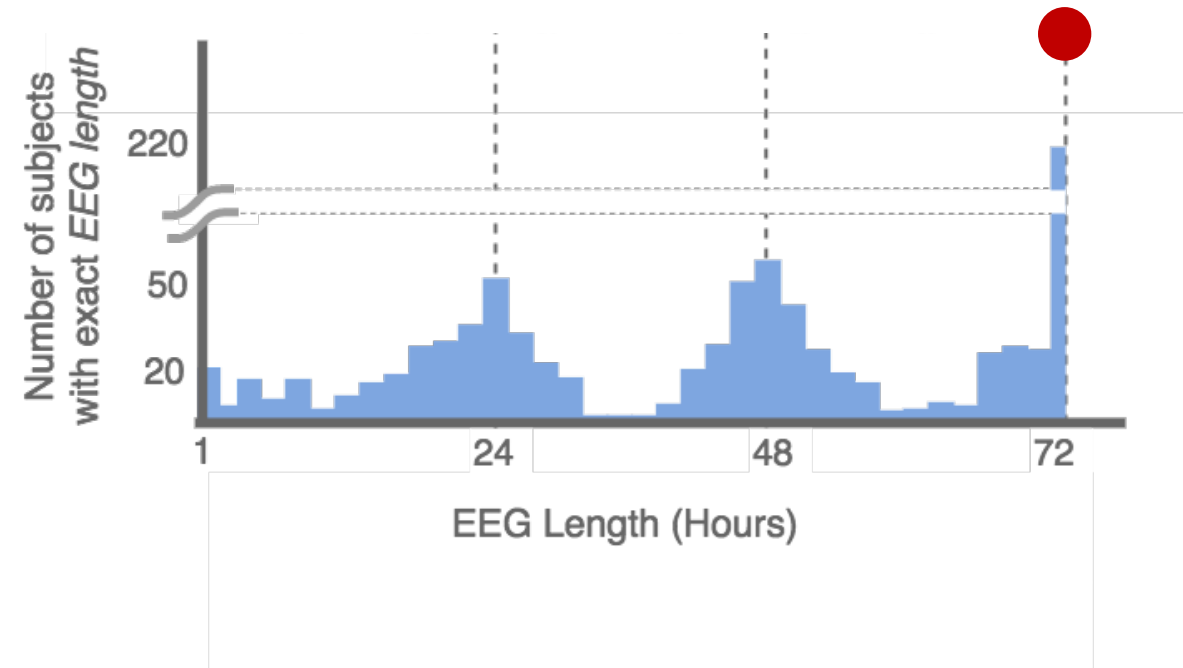
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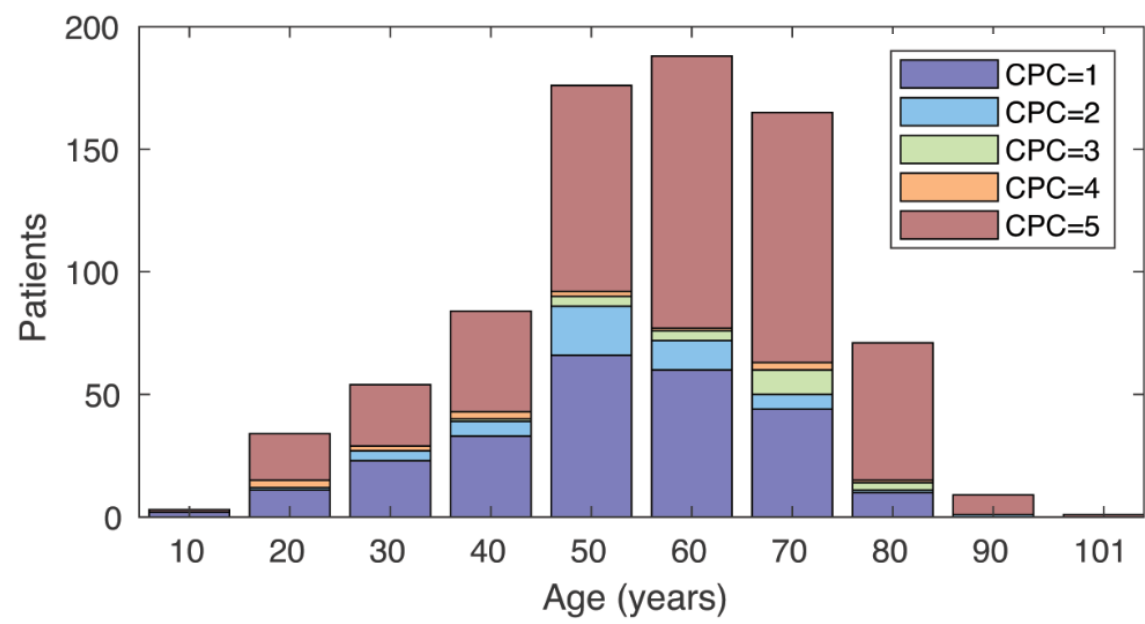


Clinical Characteristics

Clinical Feature (Mean)	Good Outcomes	Bad Outcomes
Age (Years)	57	63
Gender (% Male)	68	68
ROSC (Mins)	19.47	25.7
Rhythm at Arrest (%)		
VFib	69	34
Other (PEA / Asystole)	25	61
<i>Unknown</i>	6	5
Cause of Arrest (%)		
Pulmonary	50	34
Anesthesia	3.6	8.5
Neurologic	9.6	13.8
<i>Other/Unknown (%)</i>	<i>36.8</i>	<i>43.7</i>
Arrest Location		
In Hospital (%)	9	11
Out of Hospital (%)	63	56
Unknown (%)	28	33

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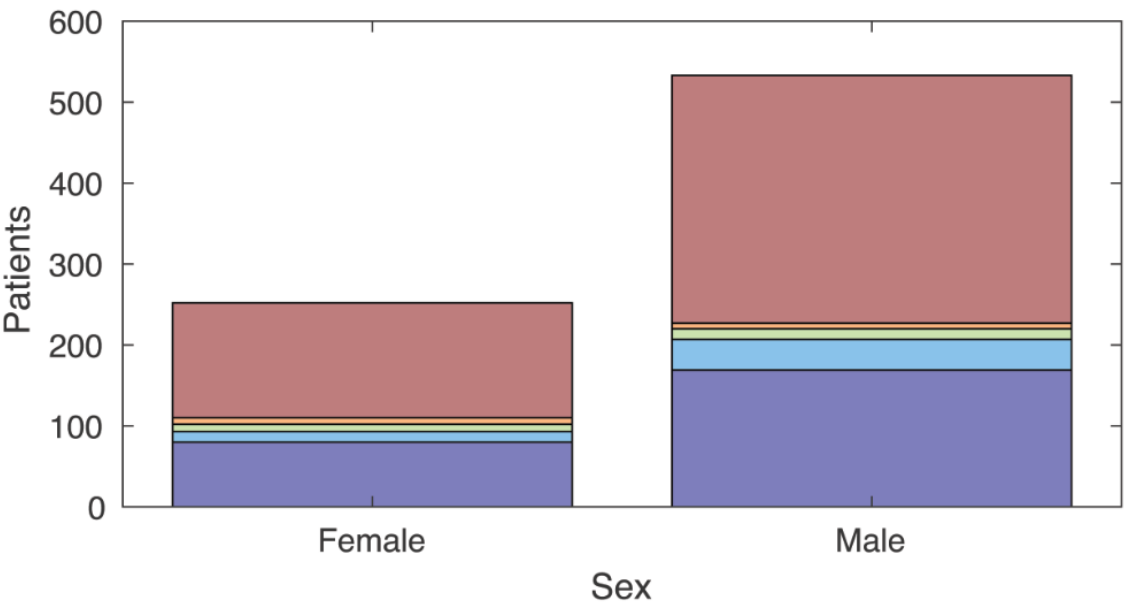
- Average Age: 60
- Older patients do worse



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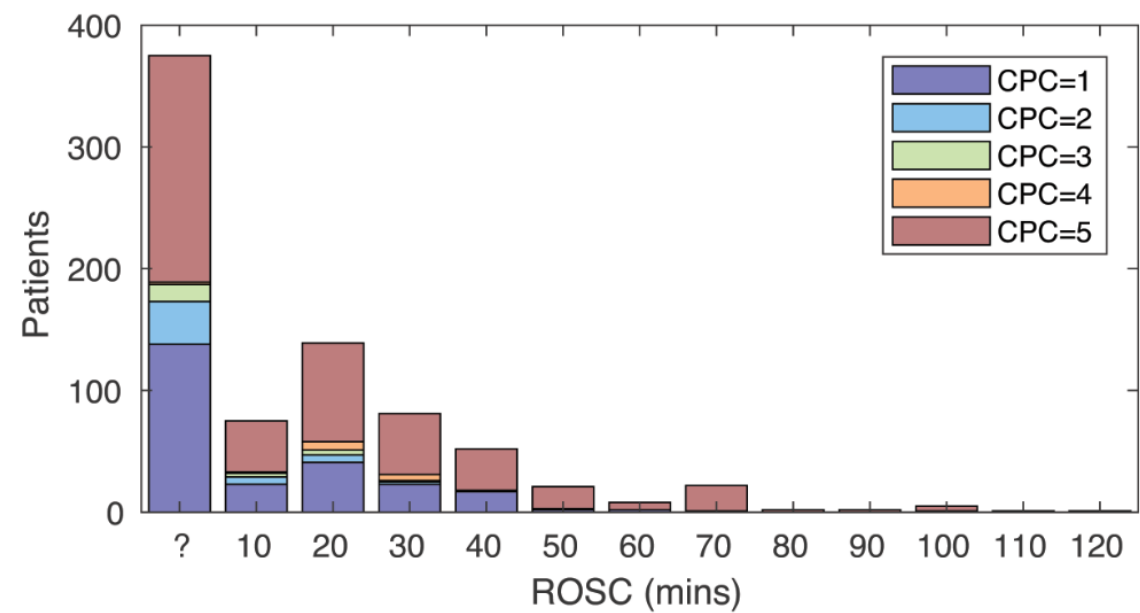
- 68% Male
- No difference w.r.t. outcome



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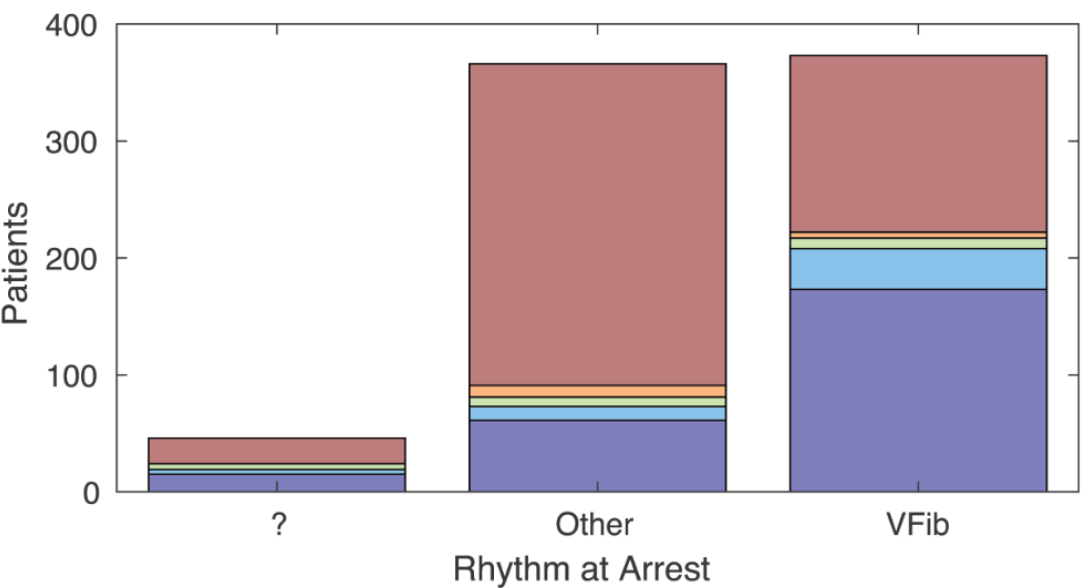
- Average ROSC time: 23 mins
- Longer time to ROSC is bad



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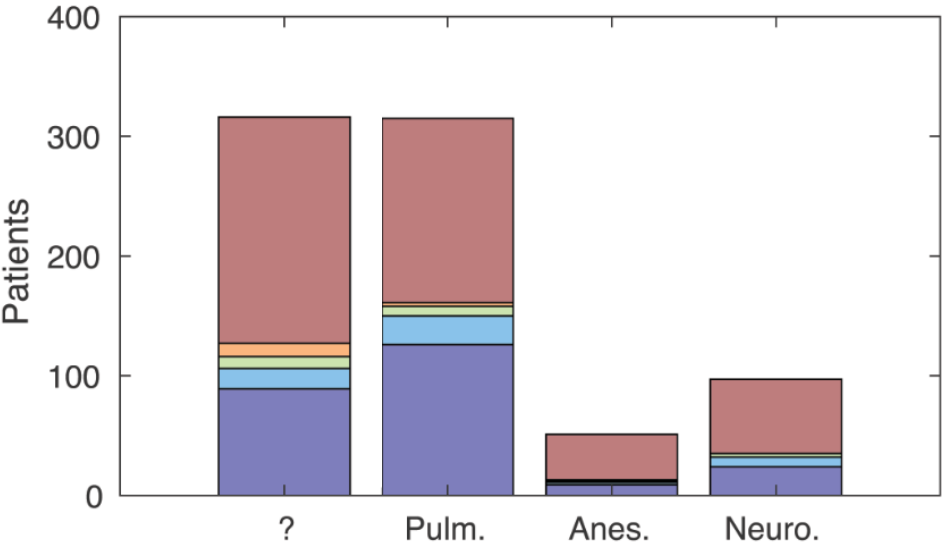
- 50% have Vfib arrest rhythm
- VFib patients do better



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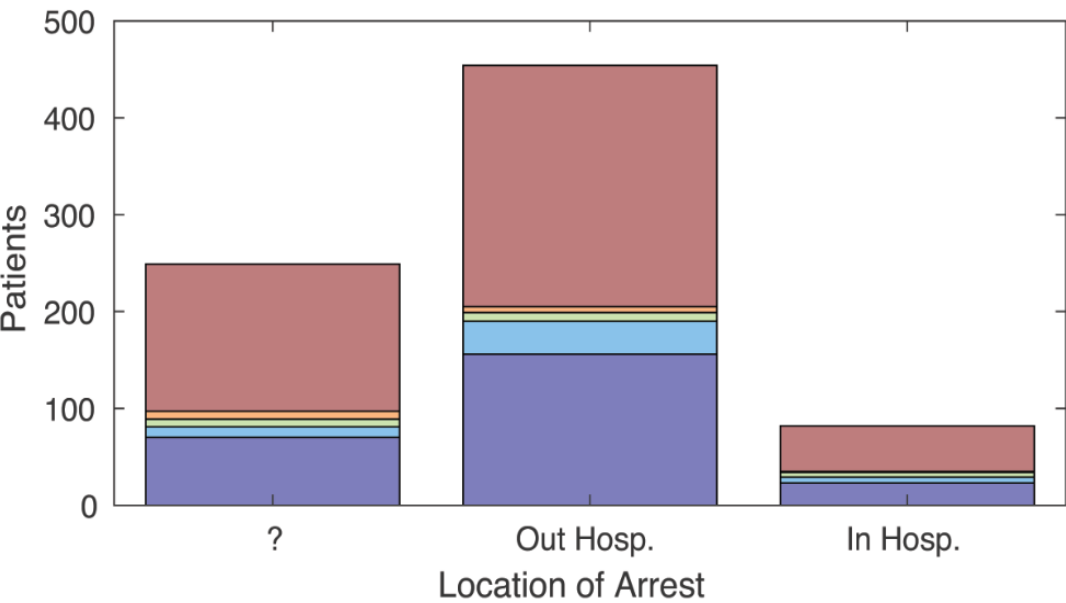
- Causes are often unknown



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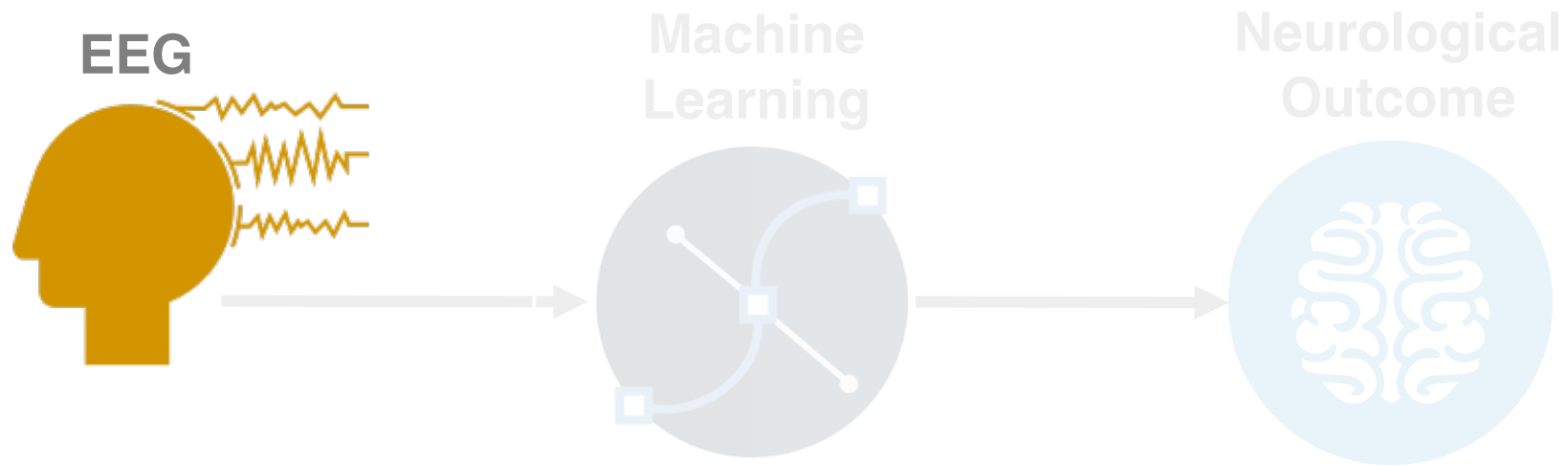
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- Location often unknown
- Most are outside hops.



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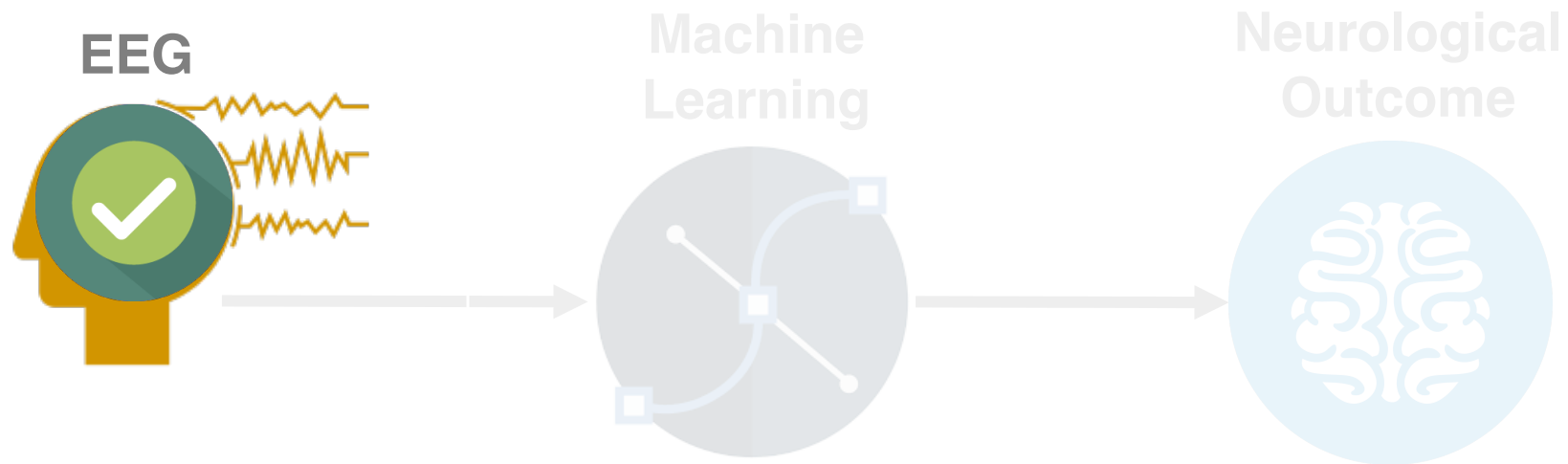


1. 'Bigger' data sets

2. Time-sensitive

3. Deployable

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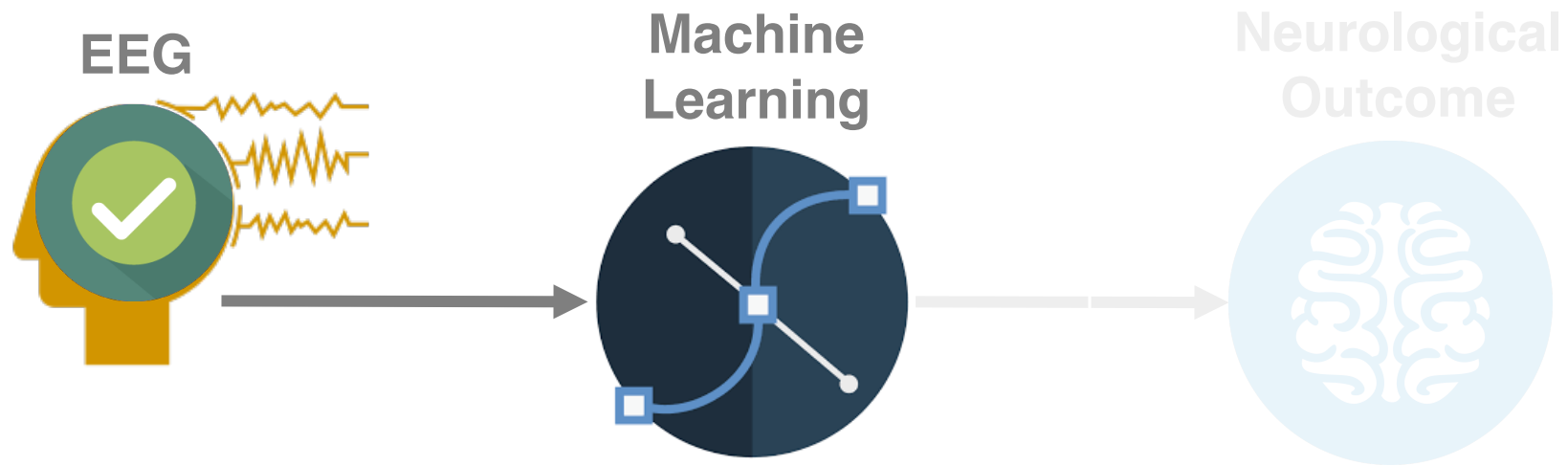


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Develop *time-sensitive* modeling approaches



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Two Feature Based:

- 1. Sequential Logistic Regression with 'Elastic' memories.
- 2. Sequential Logistic Regression with Dynamic Bayesian network constraints

One Data Driven

- 3. Deep neural networks

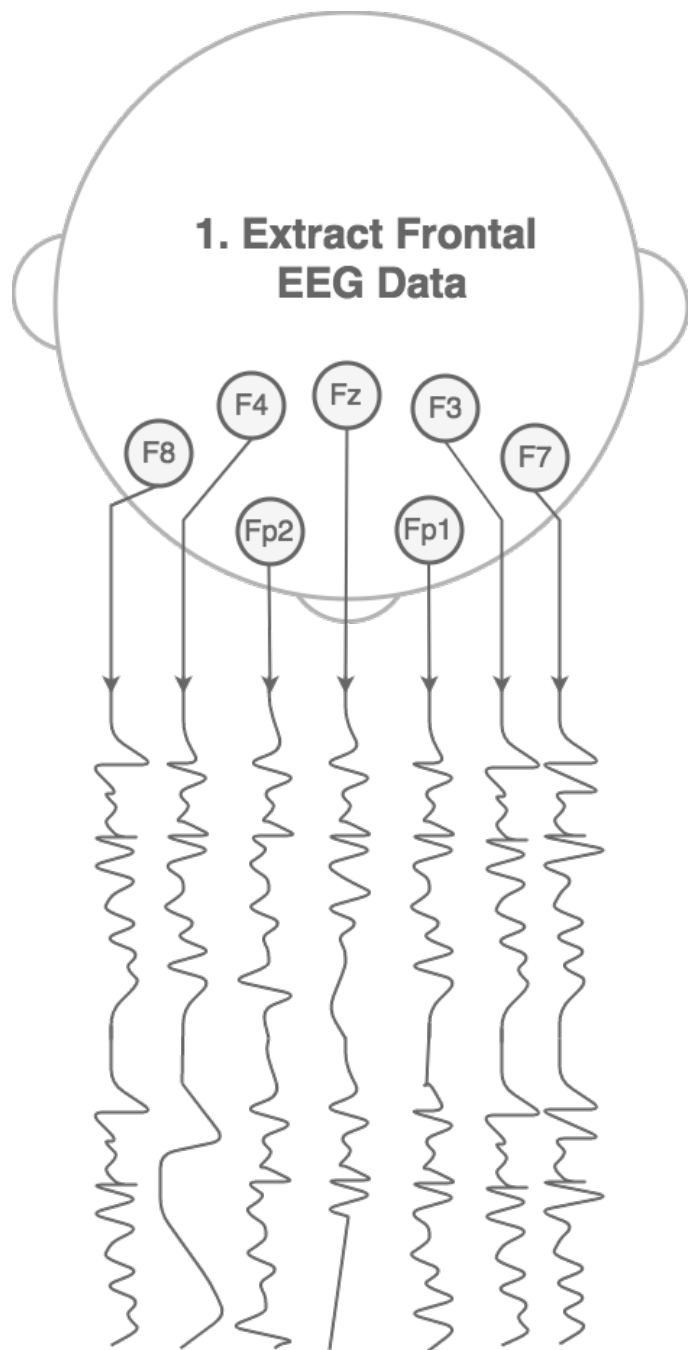
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One Data Driven

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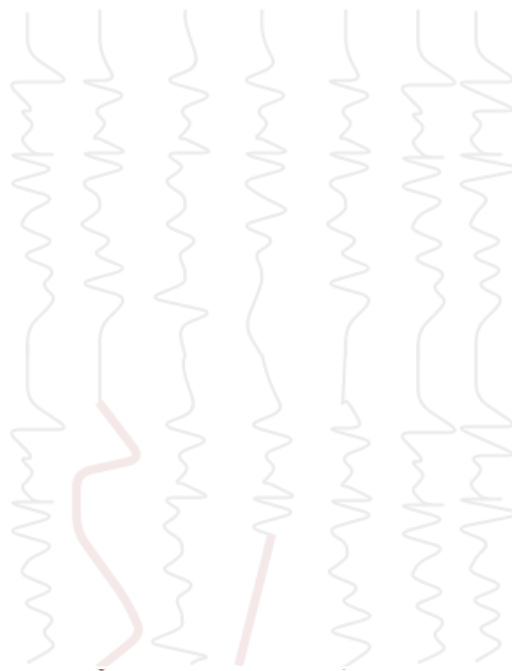


2. Identify **artifacts in five second epochs**

2.1 Disconnects and saturation

2.2 Eye and muscle artifact

2.3 Moment-based artifacts

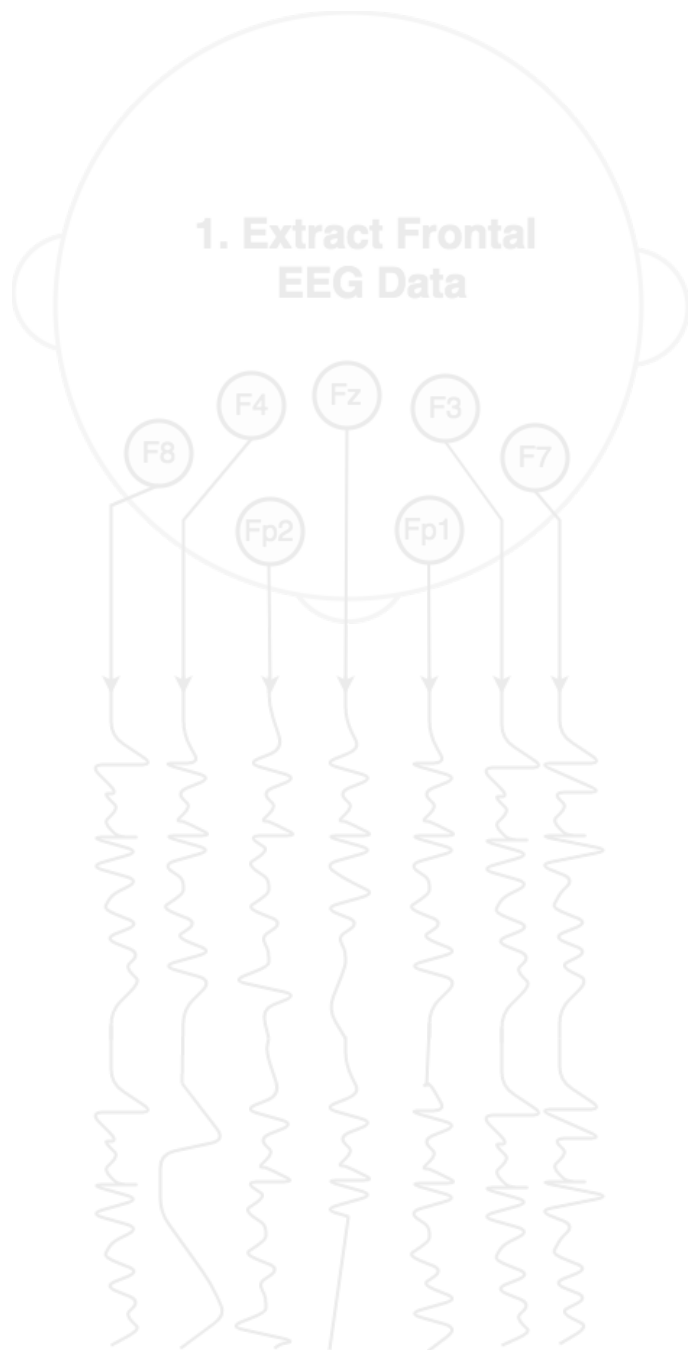


3. Choose five minute epochs with **minimal artifact**

3.1 Generate artifact score

3.2 Identify cleanest epochs in each hour of data



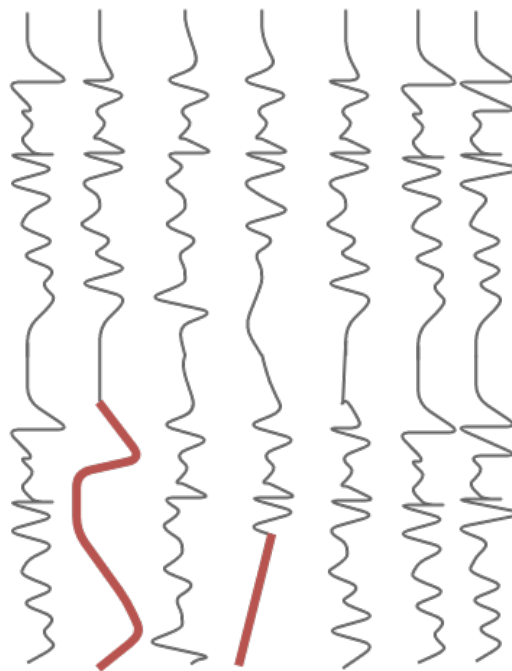


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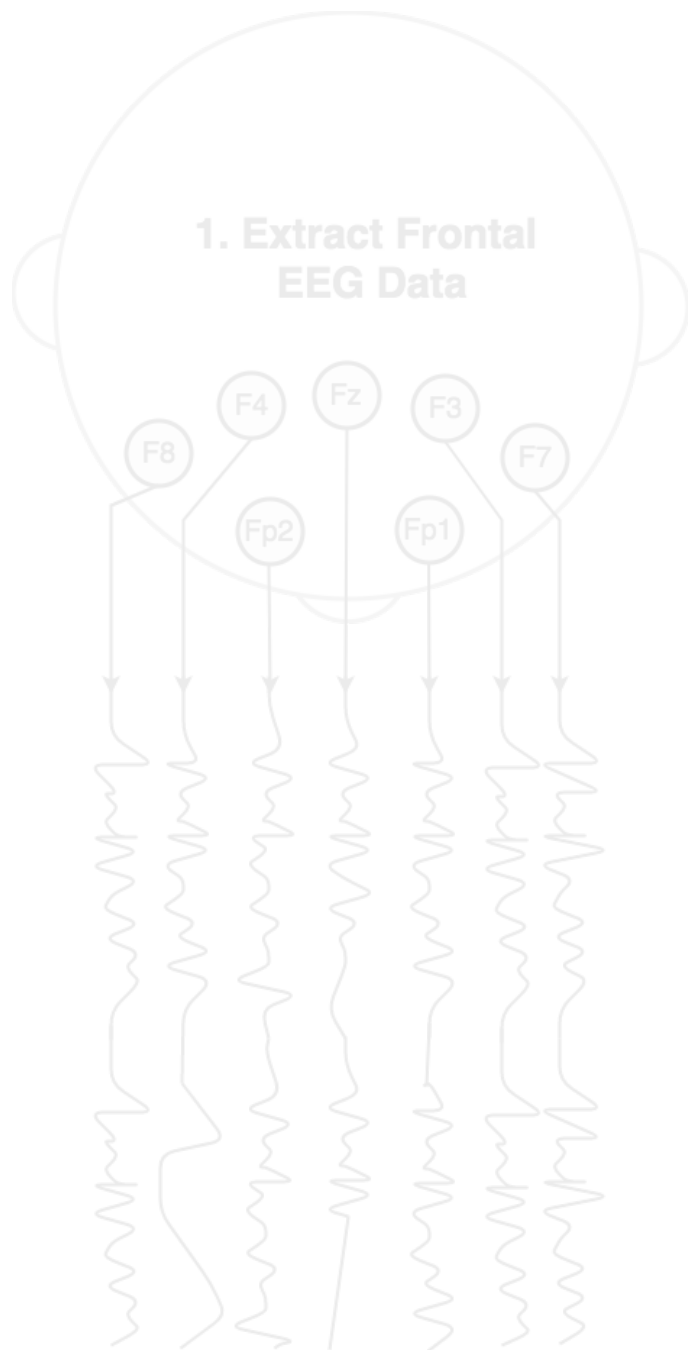


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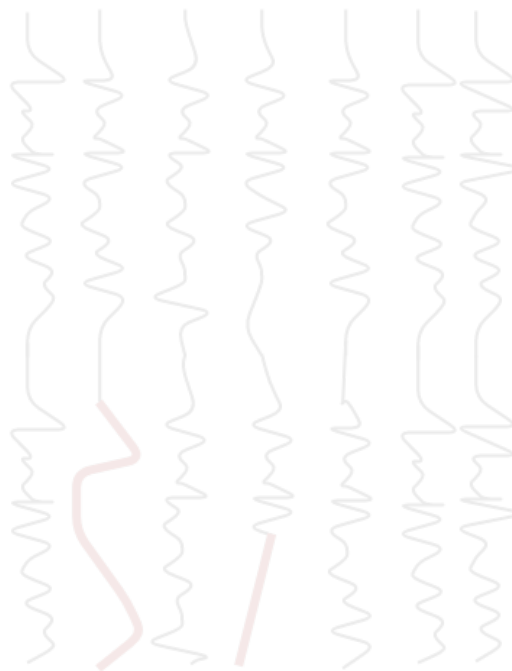


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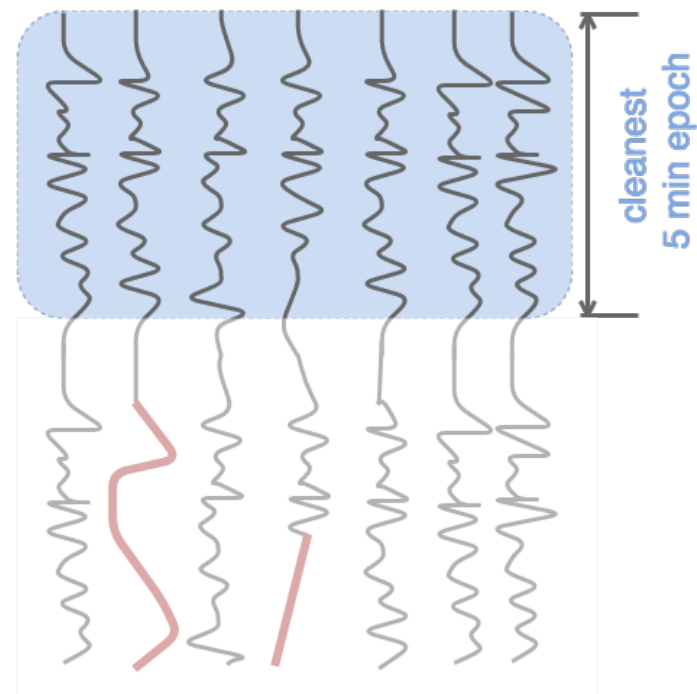
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3. Choose five minute epochs with **minimal artifact**

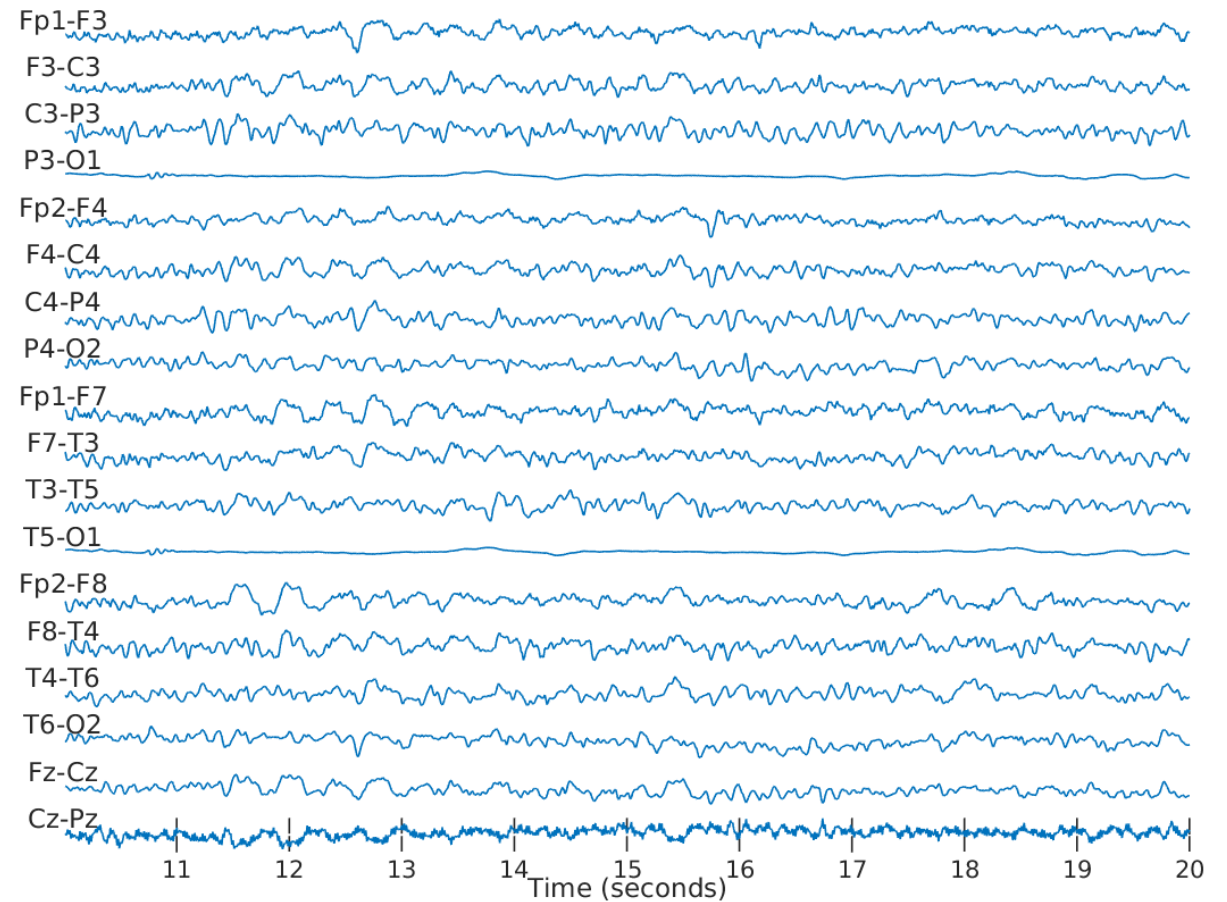
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57 features to describe three signal qualities

- Complexity (21 features)
- Category (31 features)
- Connectivity (7 features)



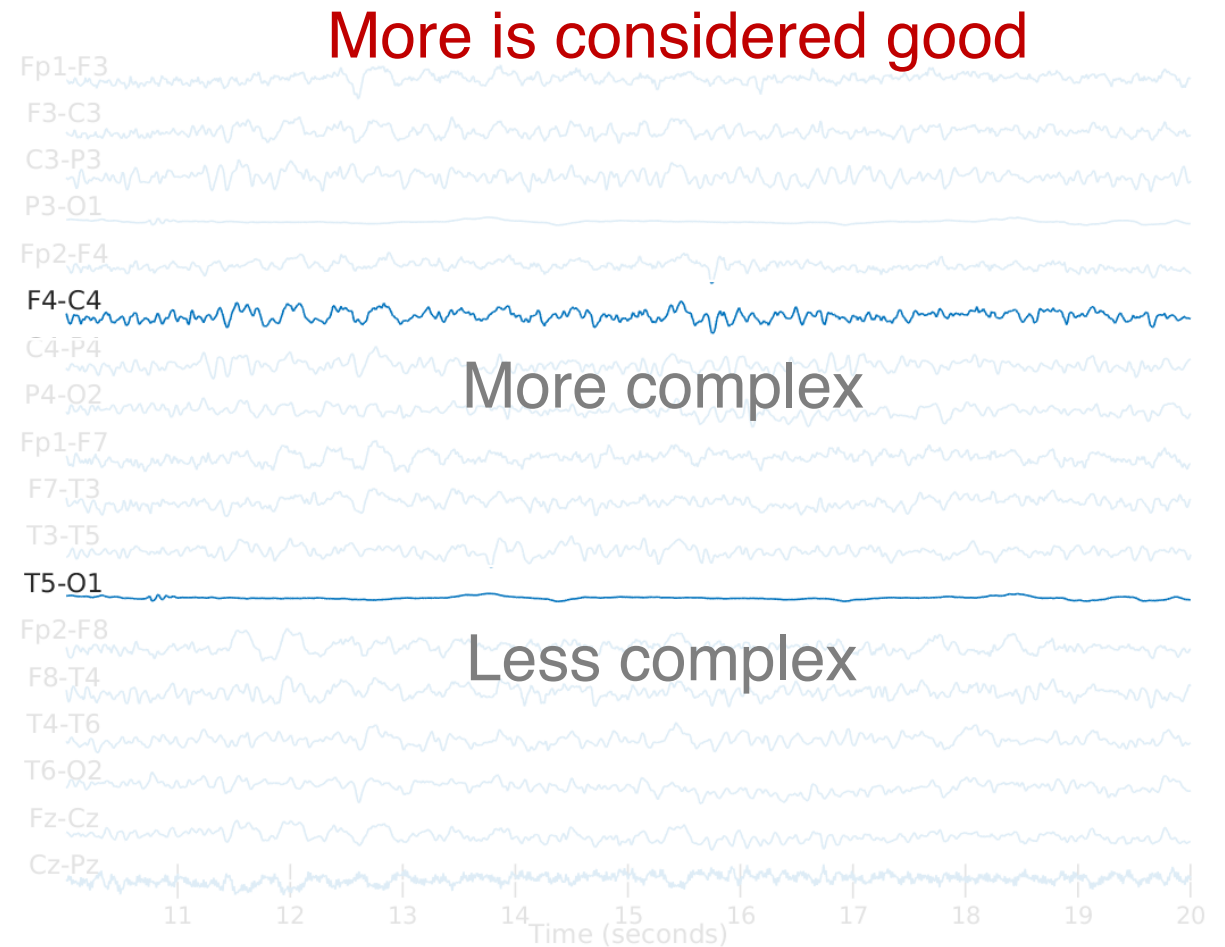
57 features to describe three signal qualities

- Complexity (21 features)

e.g. Shannon Entropy

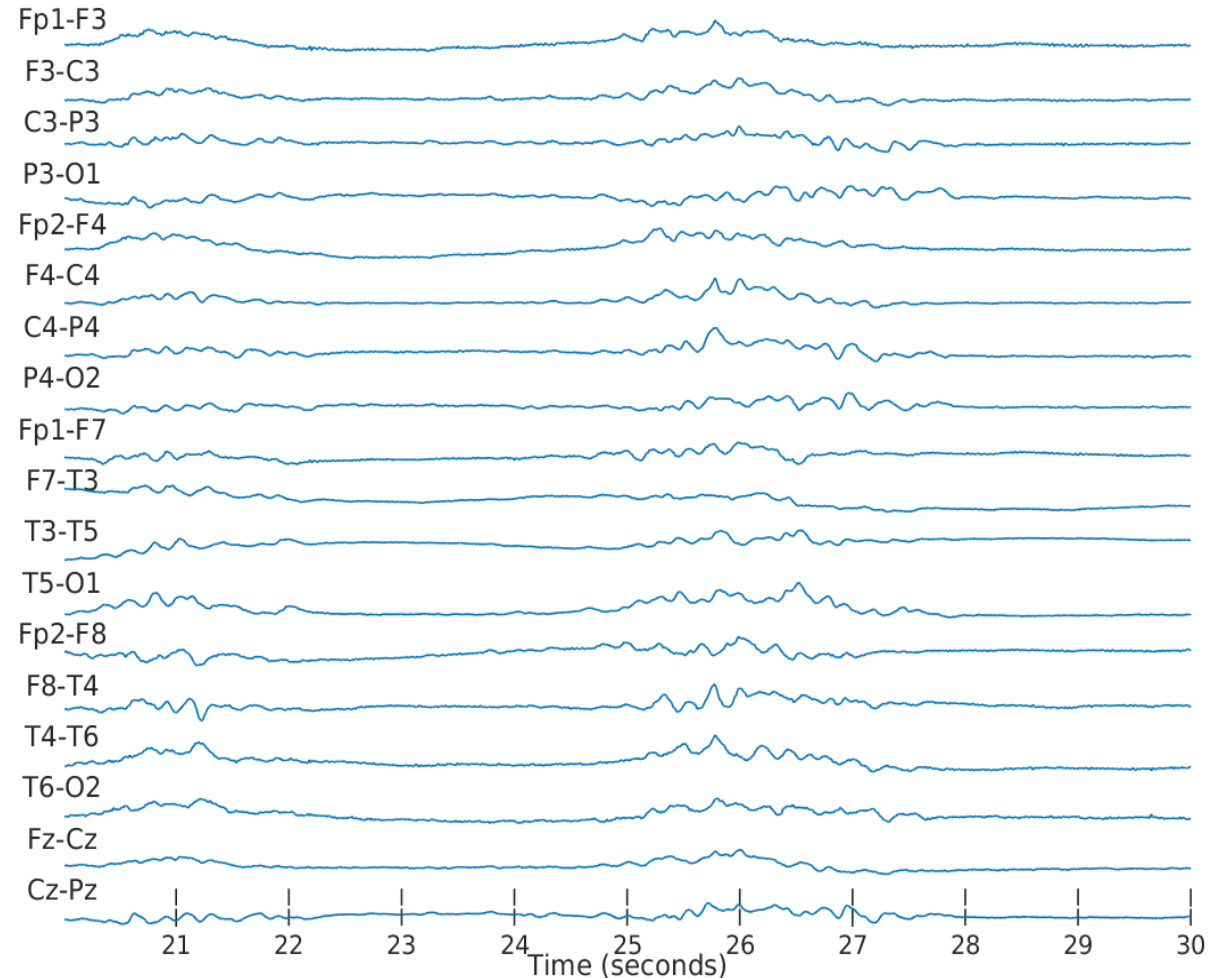
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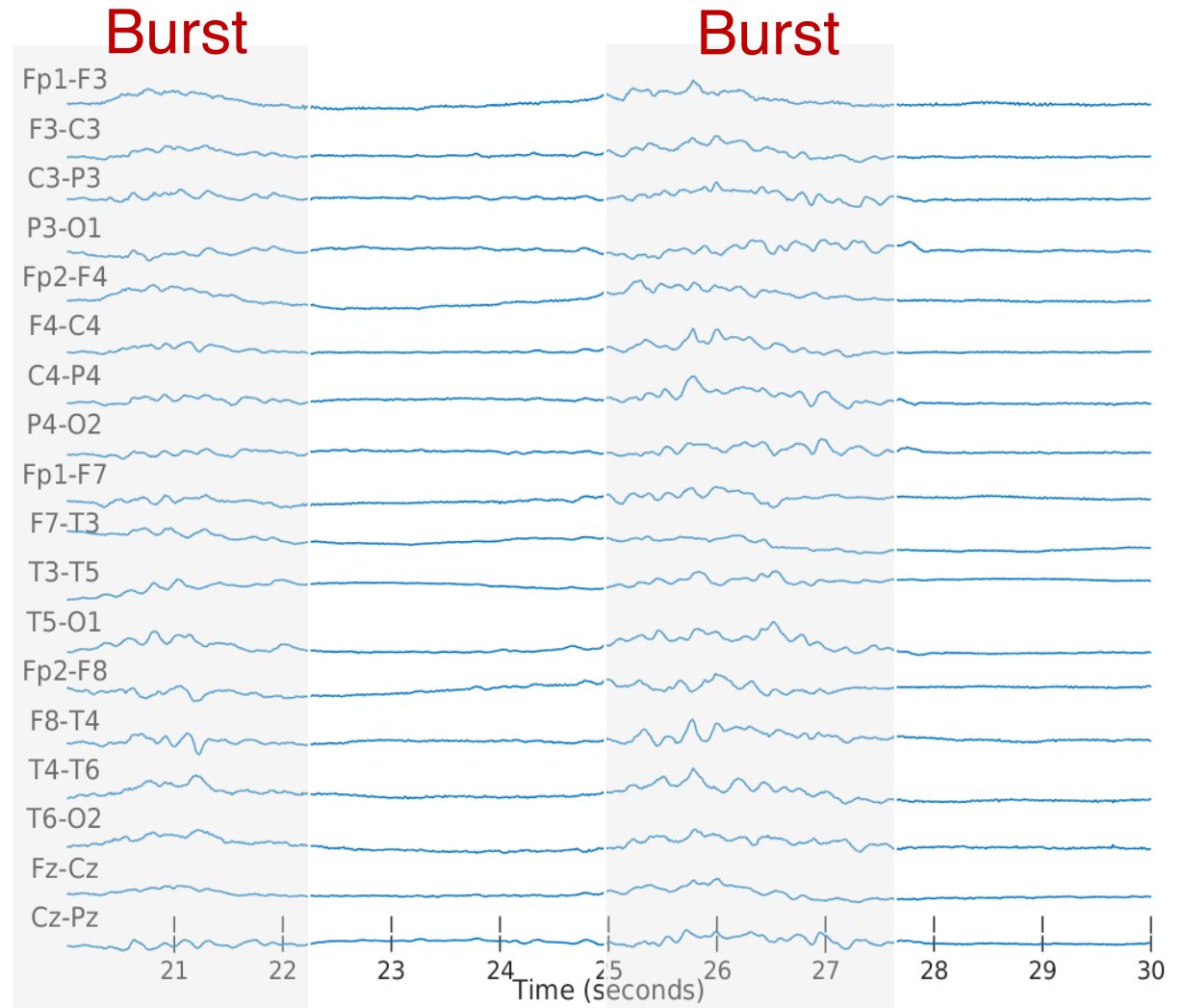
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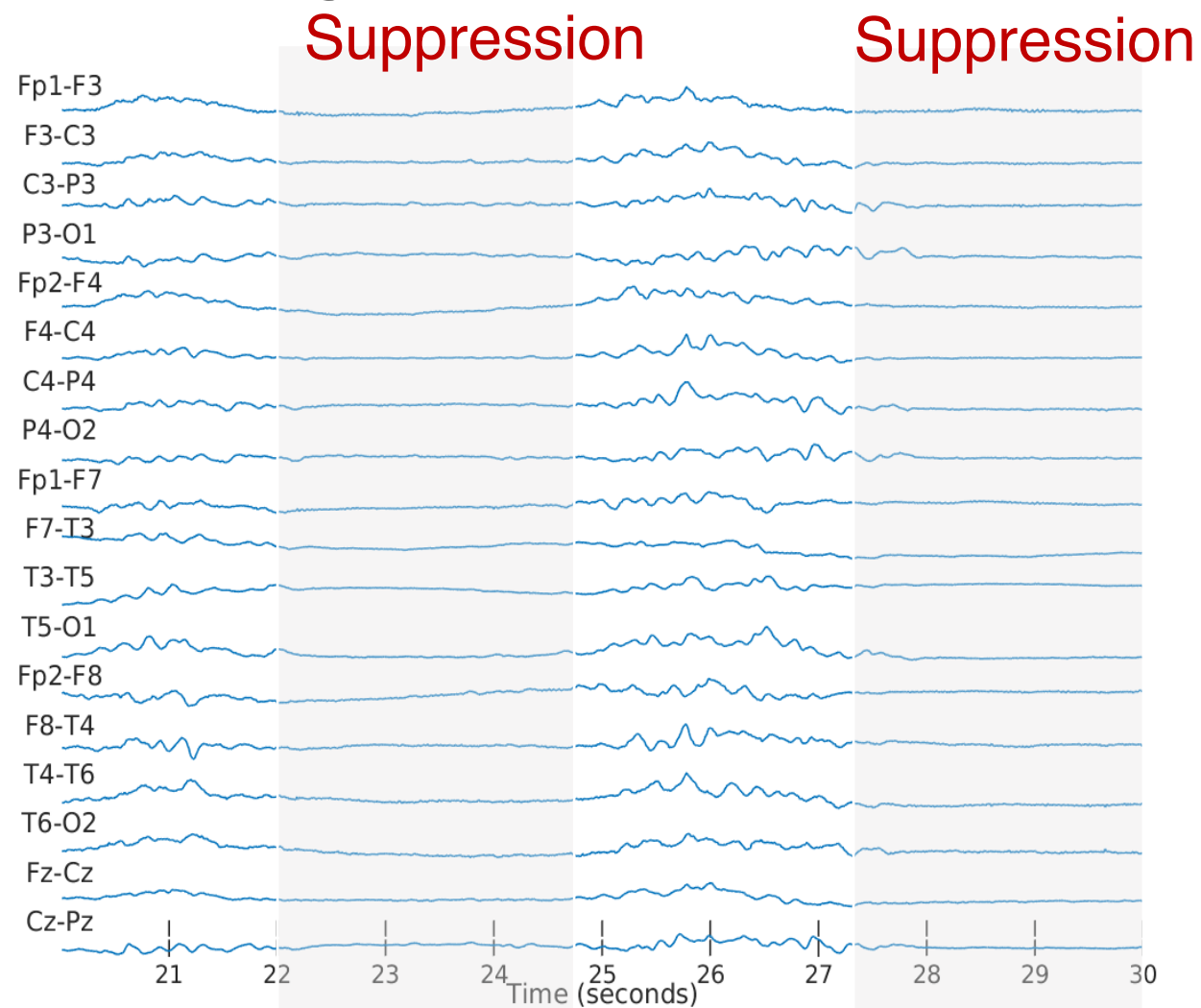
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e.g. **Burst** Suppression
- Connectivity (7 features)



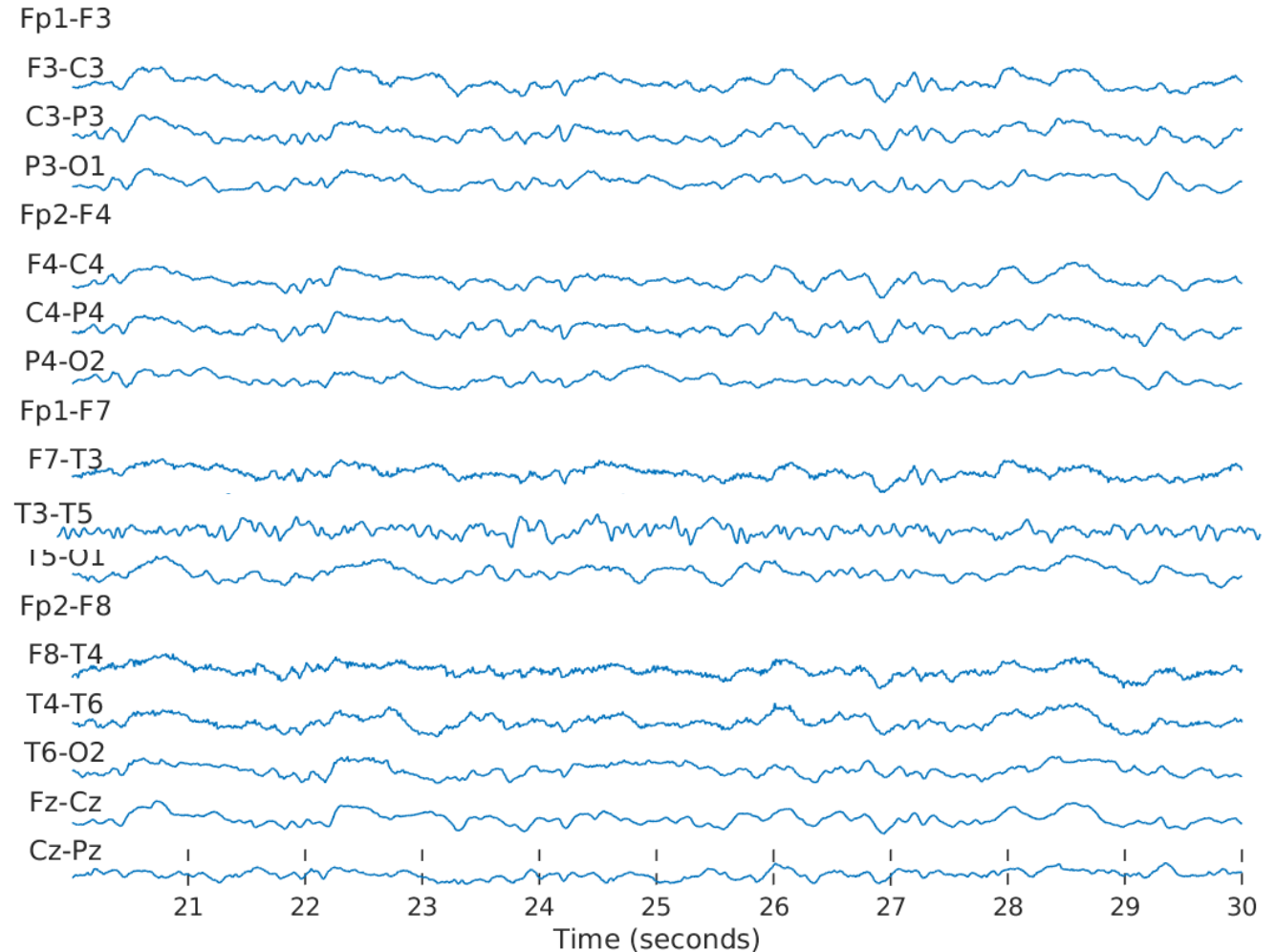
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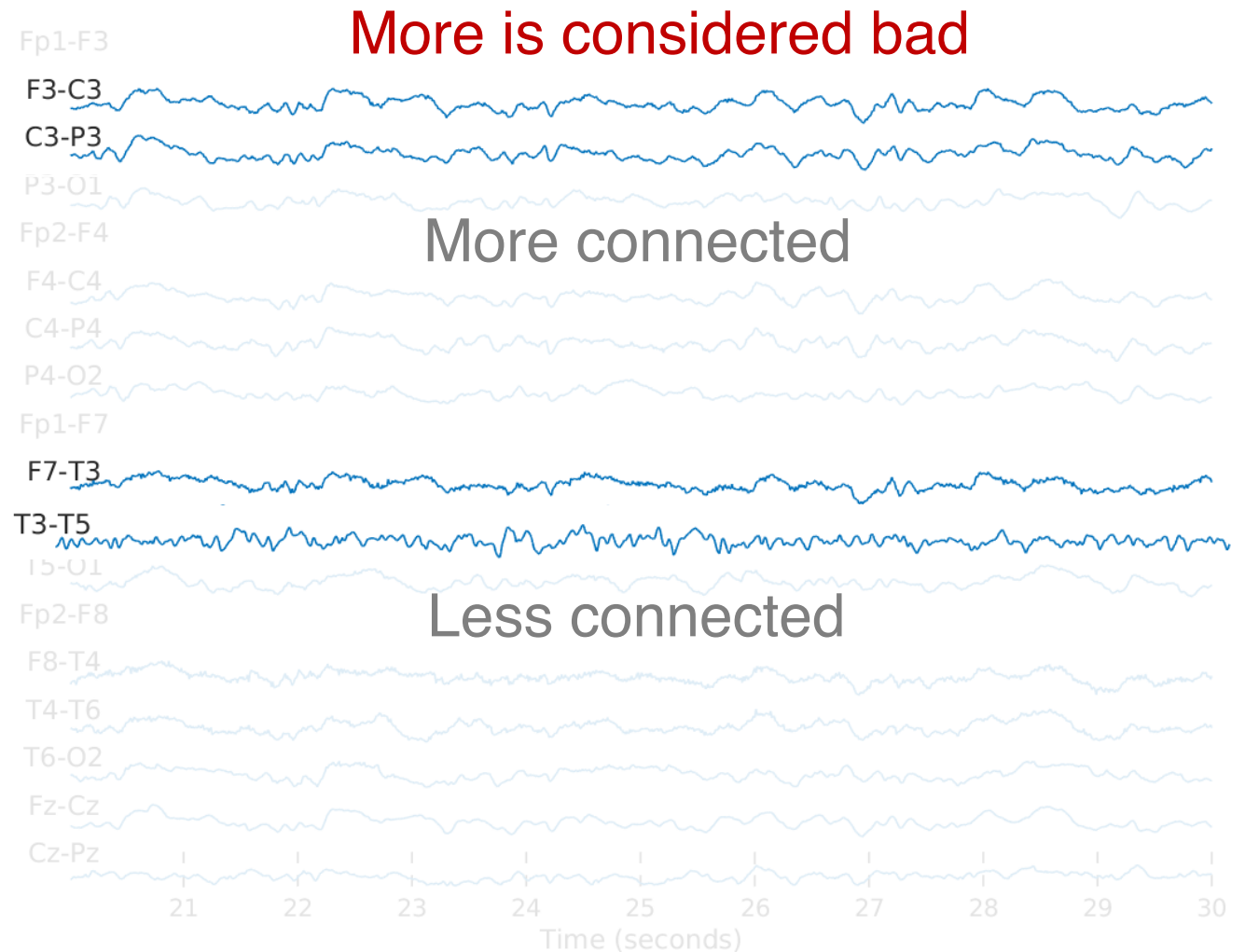
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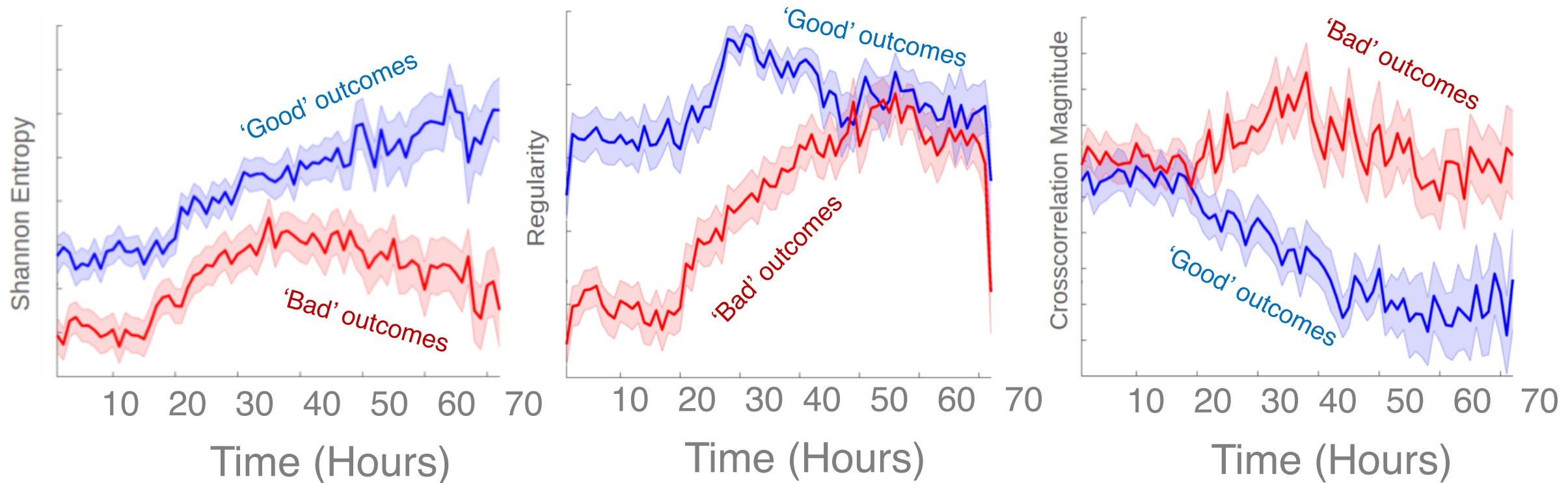
57 features to describe three signal qualities

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- Connectivity (7 features)
e.g. cross correlation



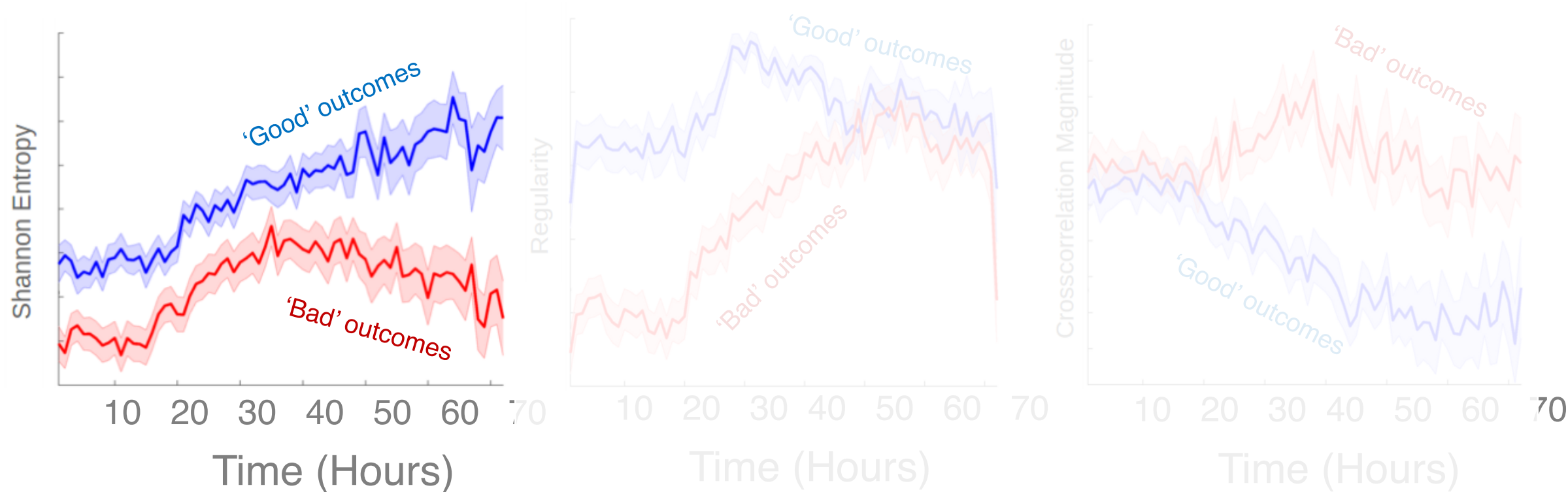
Feature-outcome relationship is time-dependent

The mean and standard error of three features for the study population, partitioned by outcome



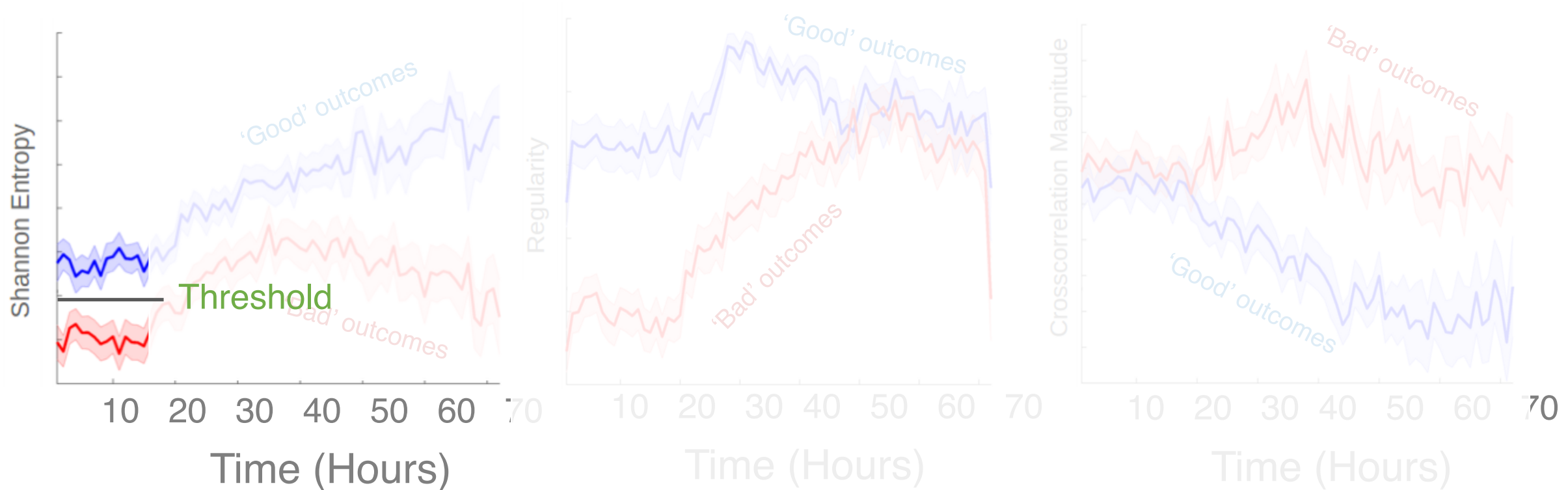
Feature-outcome relationship is time-dependent

Shannon Entropy (a measure of complexity) distinguishes 'Good' and 'Bad' consistently



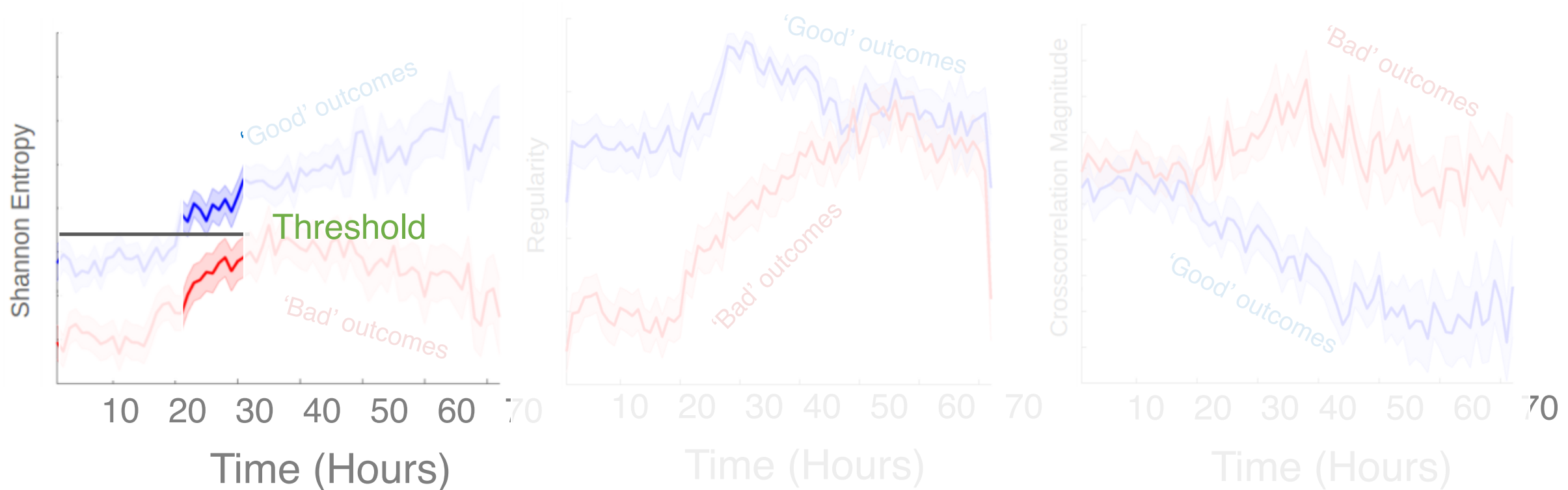
Feature-outcome relationship is time-dependent

But the value that **optimally discriminates** over time, changes.



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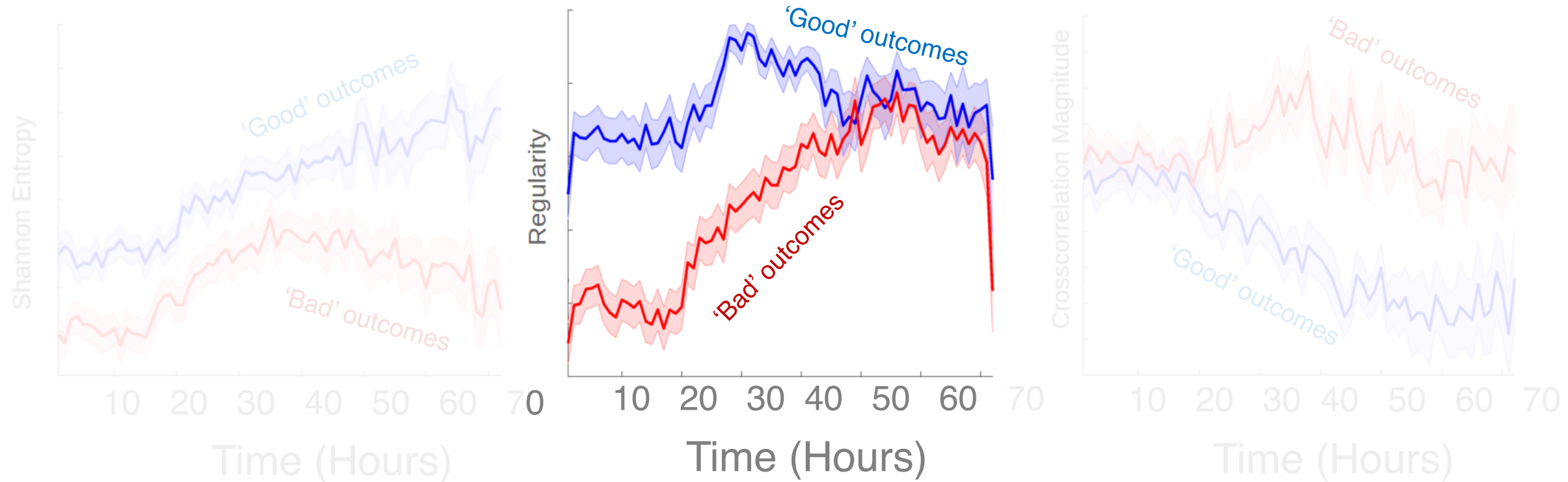
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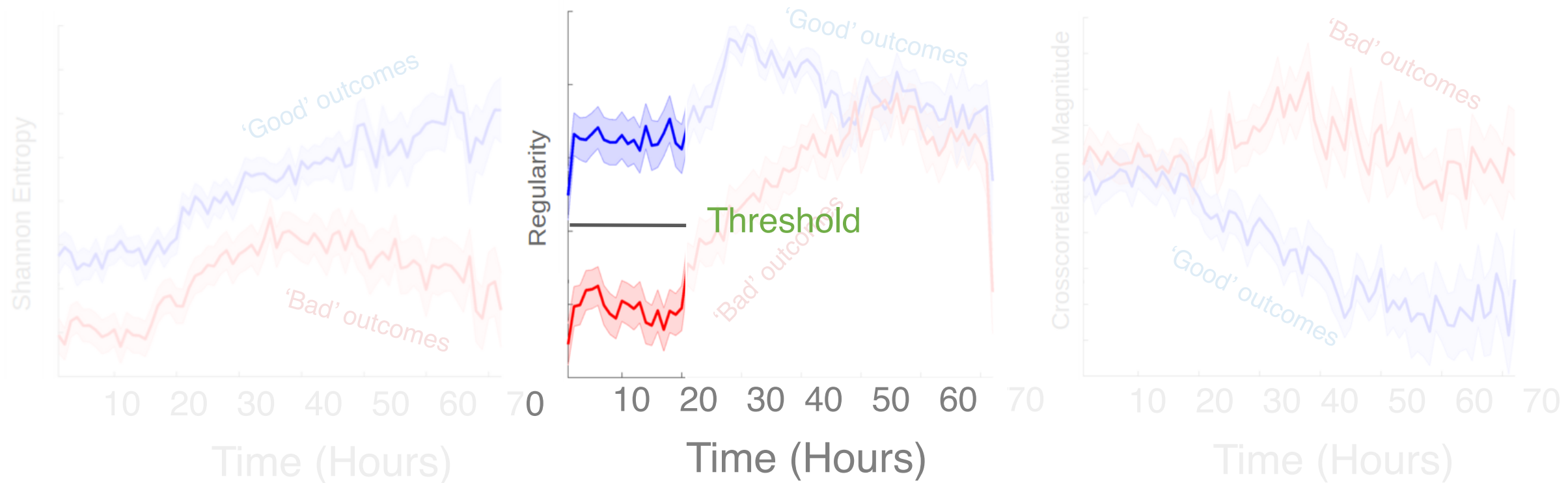
Feature-outcome relationship is time-dependent

Regularity (a measure of burst-suppression) distinguishes 'Good' and 'Bad' earlier



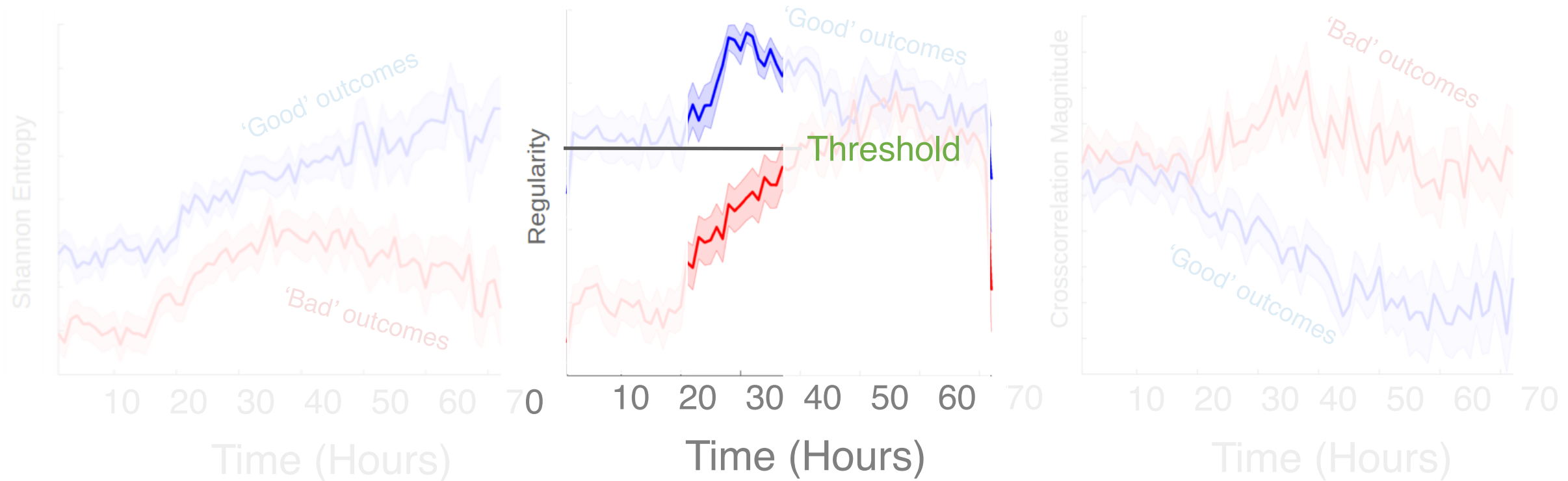
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But the value that **optimally discriminates** over time, changes.



Feature-outcome relationship is time-dependent

But the value that **optimally discriminates** over time, changes.



Feature-outcome relationship is time-dependent

Cross correlation (a measure of complexity) distinguishes 'Good' and 'Bad' later



Conclusion

- The features-outcome relationship changes over time
- Needs modelling approach where coefficients evolve over time

Three Approaches

Two Feature Based:

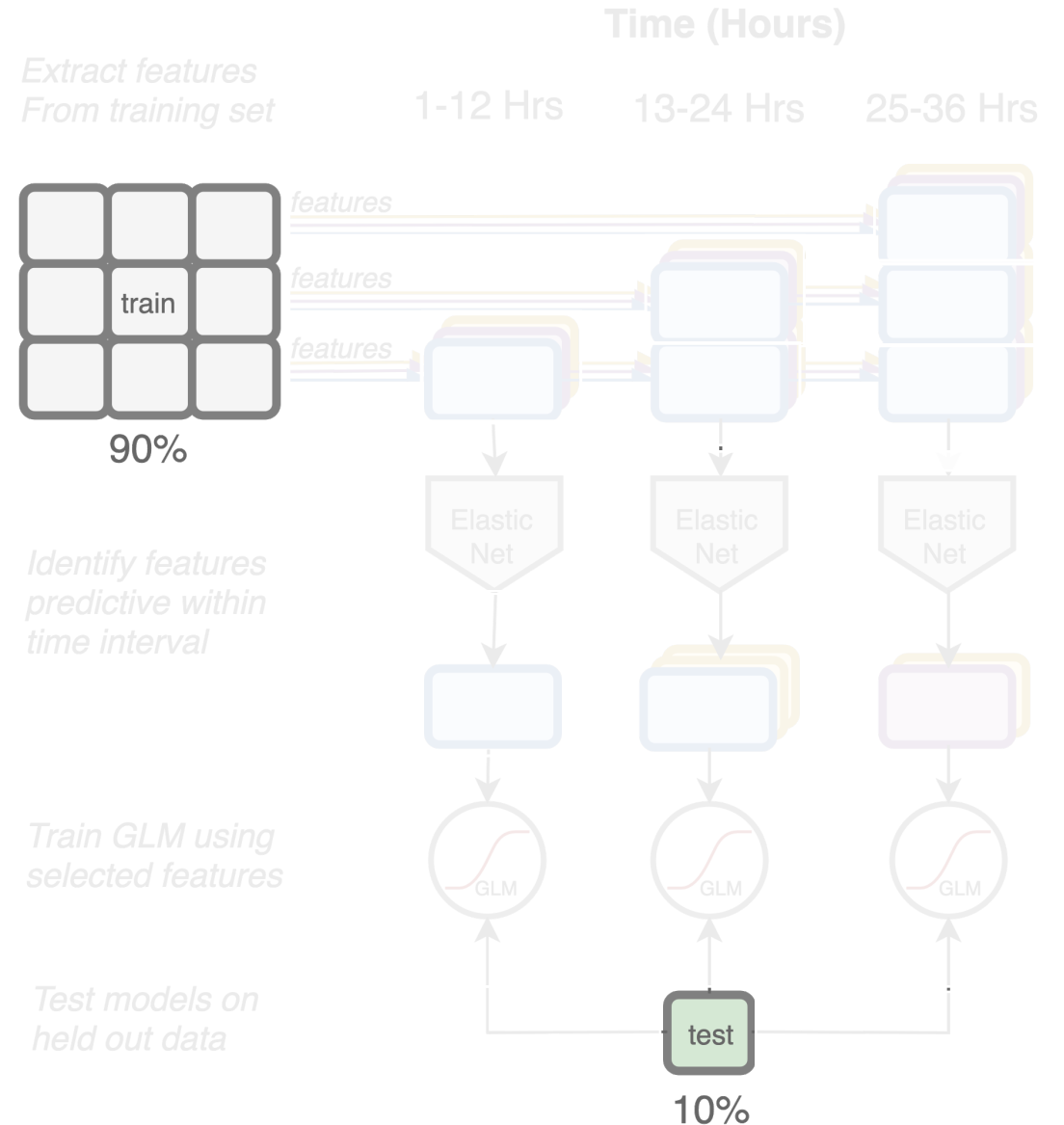
- 1. Sequential Logistic Regression with 'Elastic' memories
- 2. Sequential Logistic Regression with Dynamic Bayesian network constraints

One Data Driven

- 3. Deep neural networks

Logistic Regression with *Elastic Memories*

- $n = 438$ patients
- We used 52/57 features
- Validation: 10-fold



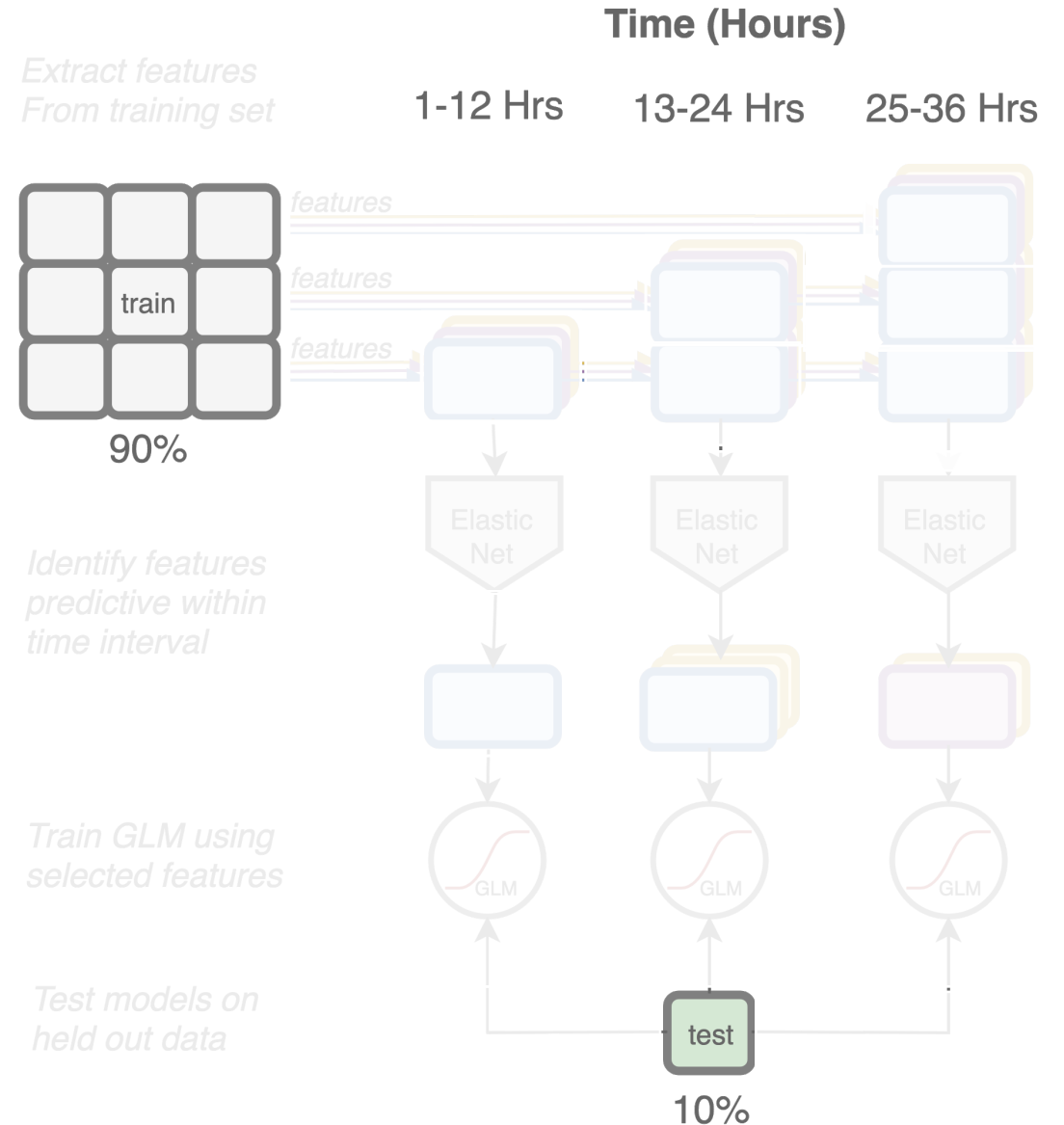
Logistic Regression with *Elastic Memories*

- We train a series of models that classify patient outcomes, in particular time intervals:

1-12 hours

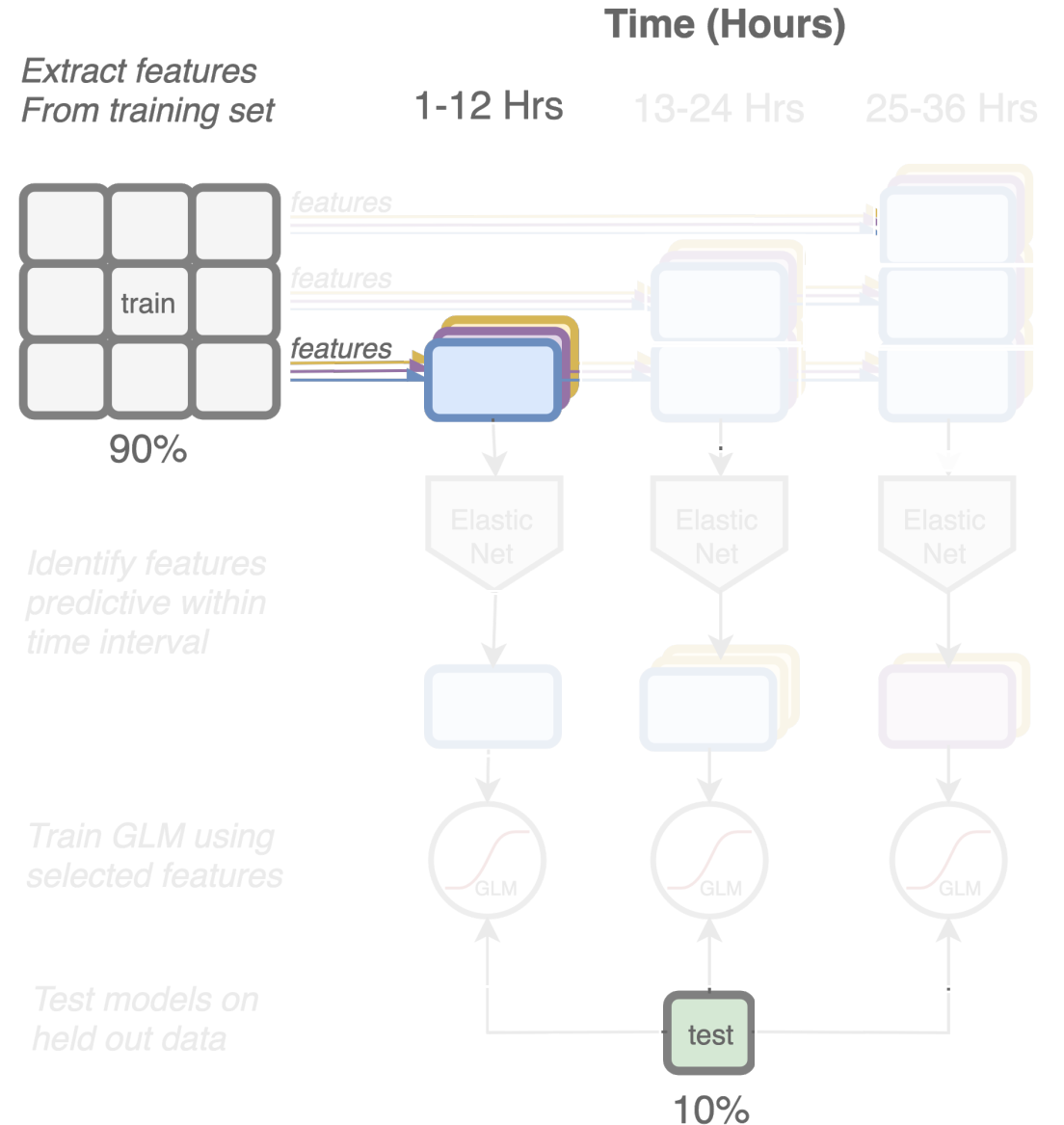
13-24 hours

25-36 hours etc.



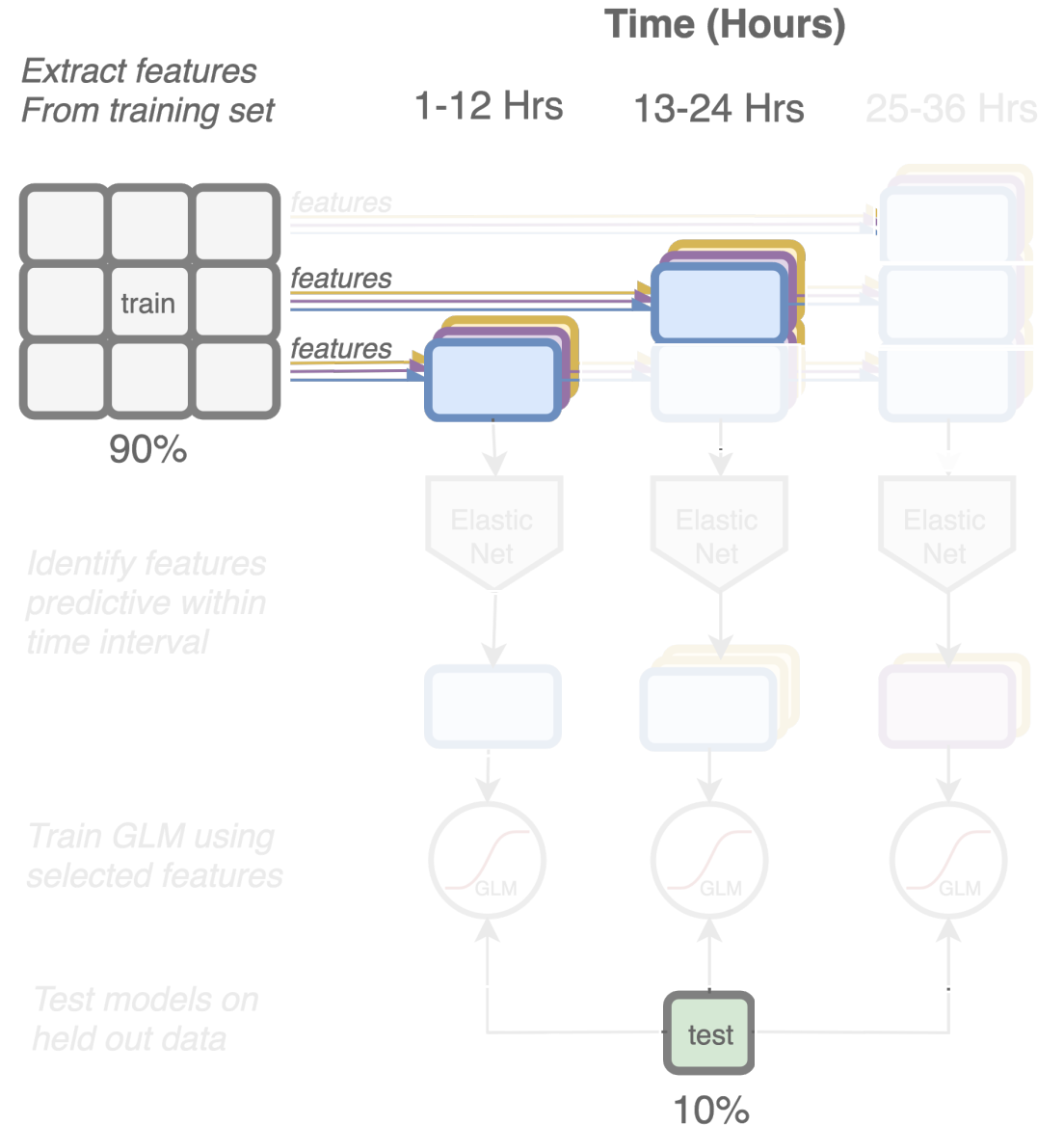
Logistic Regression with *Elastic Memories*

- Features are extracted at particular time intervals
- 1-12 hours



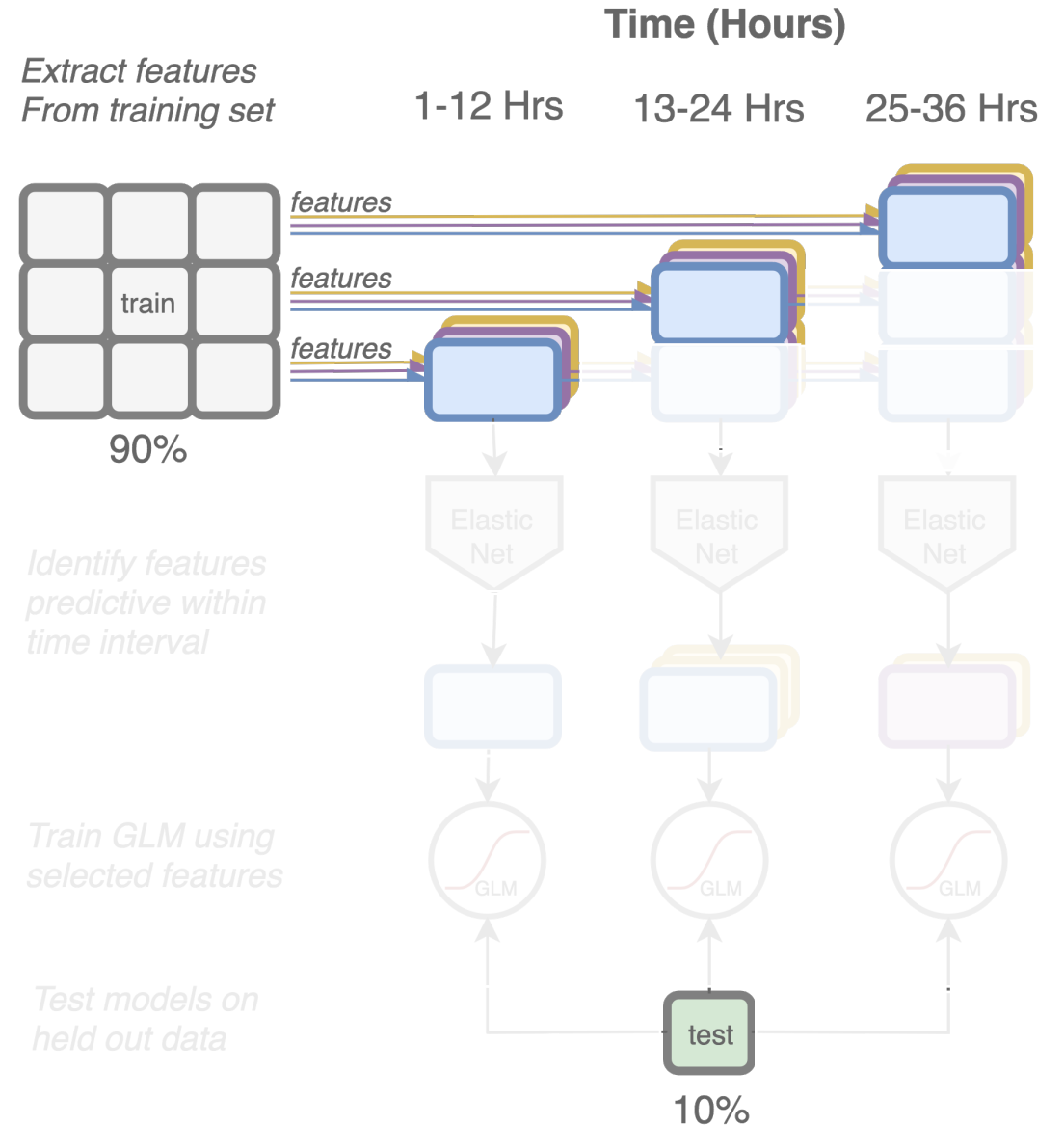
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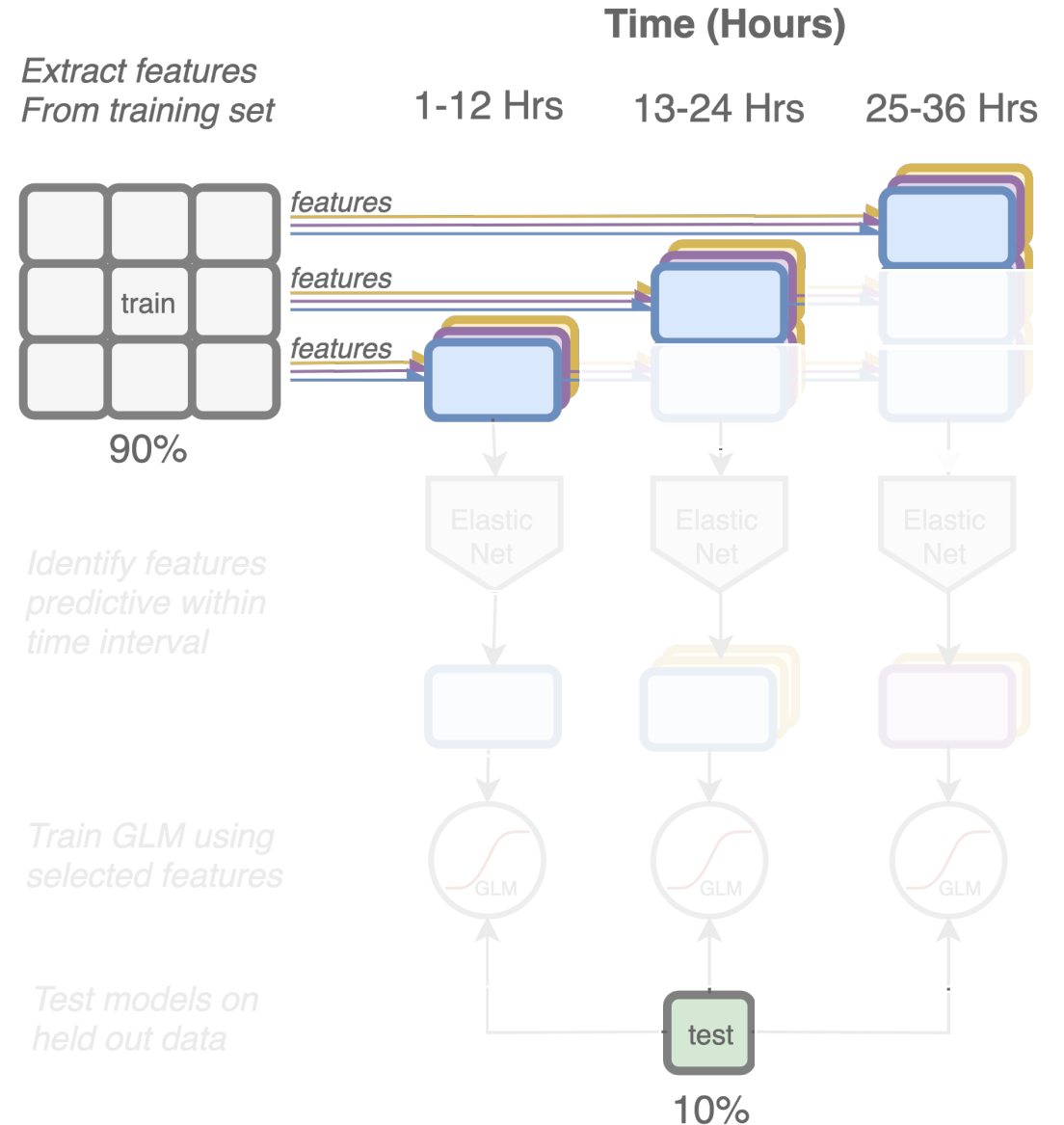
Logistic Regression with *Elastic Memories*

- Features are extracted at particular time intervals
- 25-36 hours, and so on...



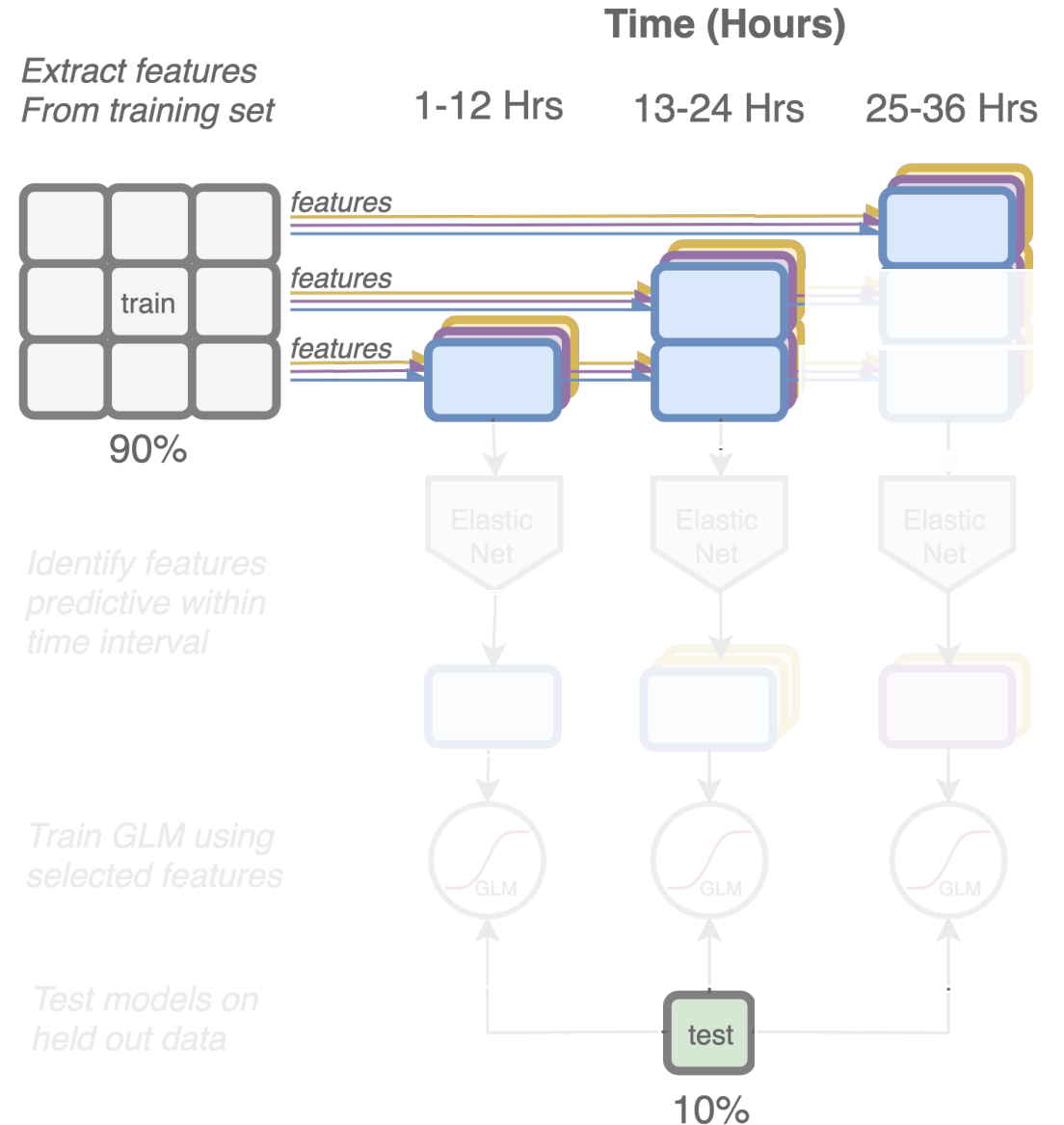
Logistic Regression with *Elastic Memories*

- Features used by models in earlier time intervals are passed forward as ‘**memories**’ for models in future time intervals



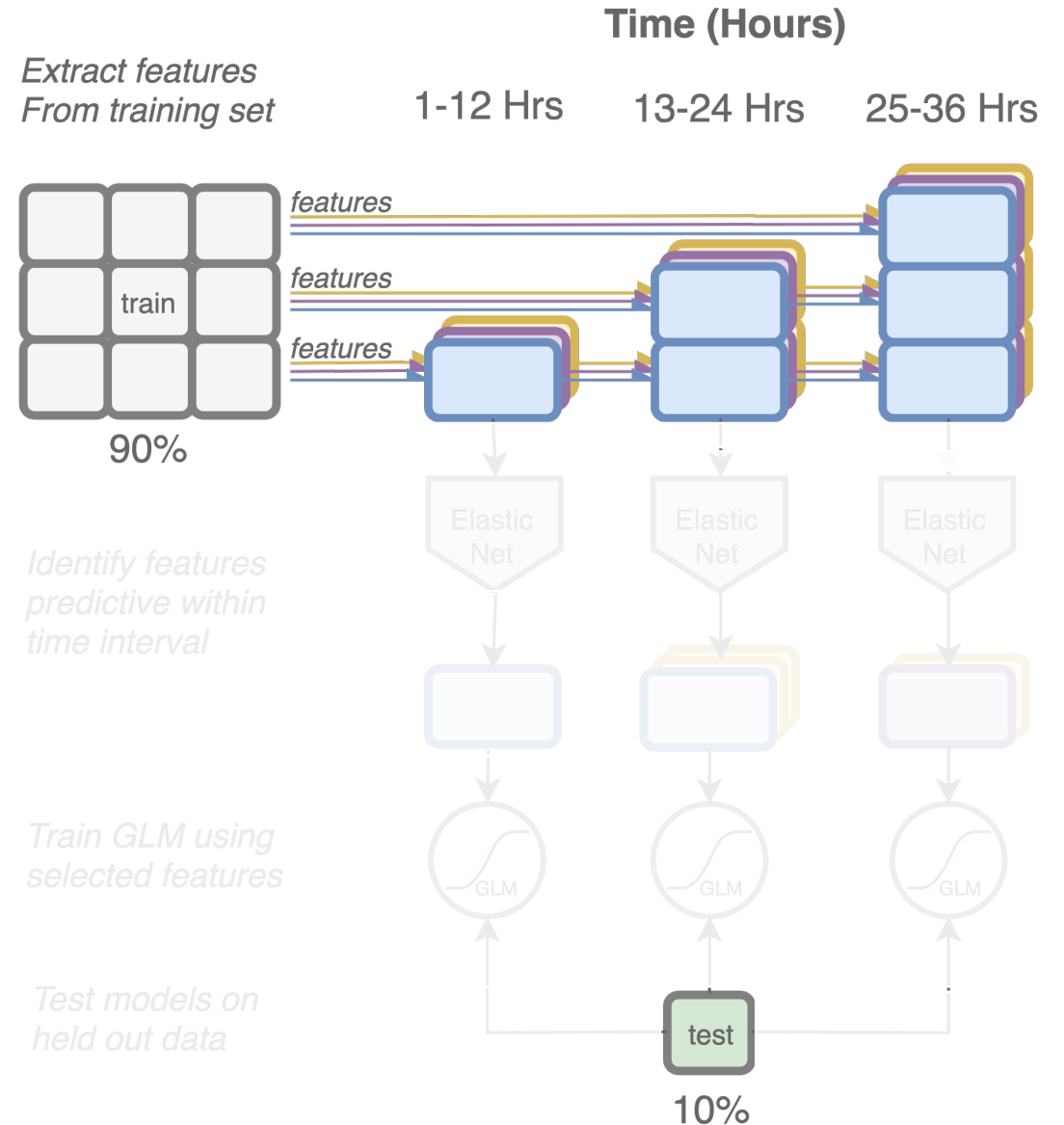
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Logistic Regression with *Elastic Memories*

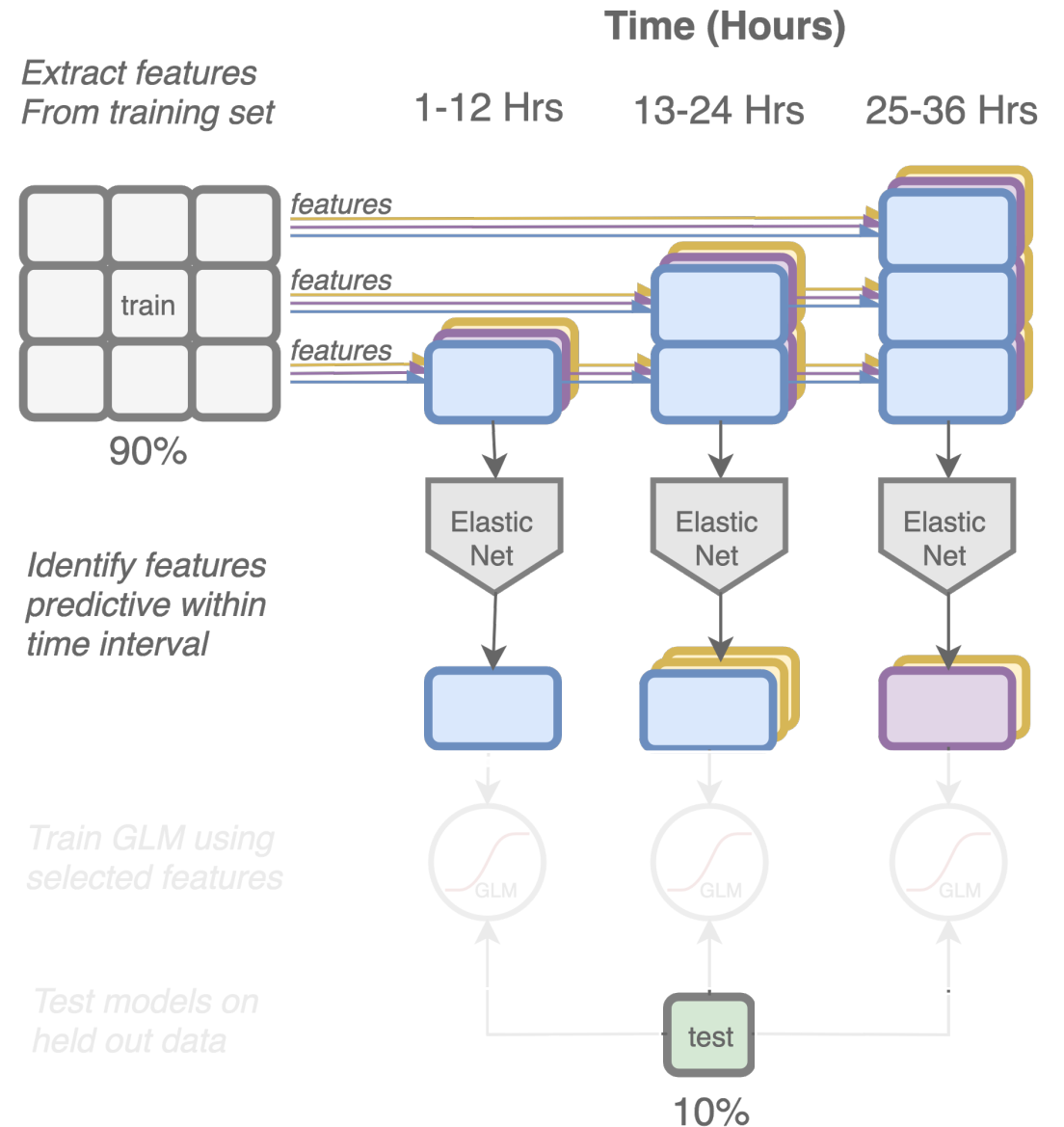
- Features used by models in earlier time intervals are passed forward as ‘**memories**’ for models in future time intervals



Logistic Regression with *Elastic Memories*

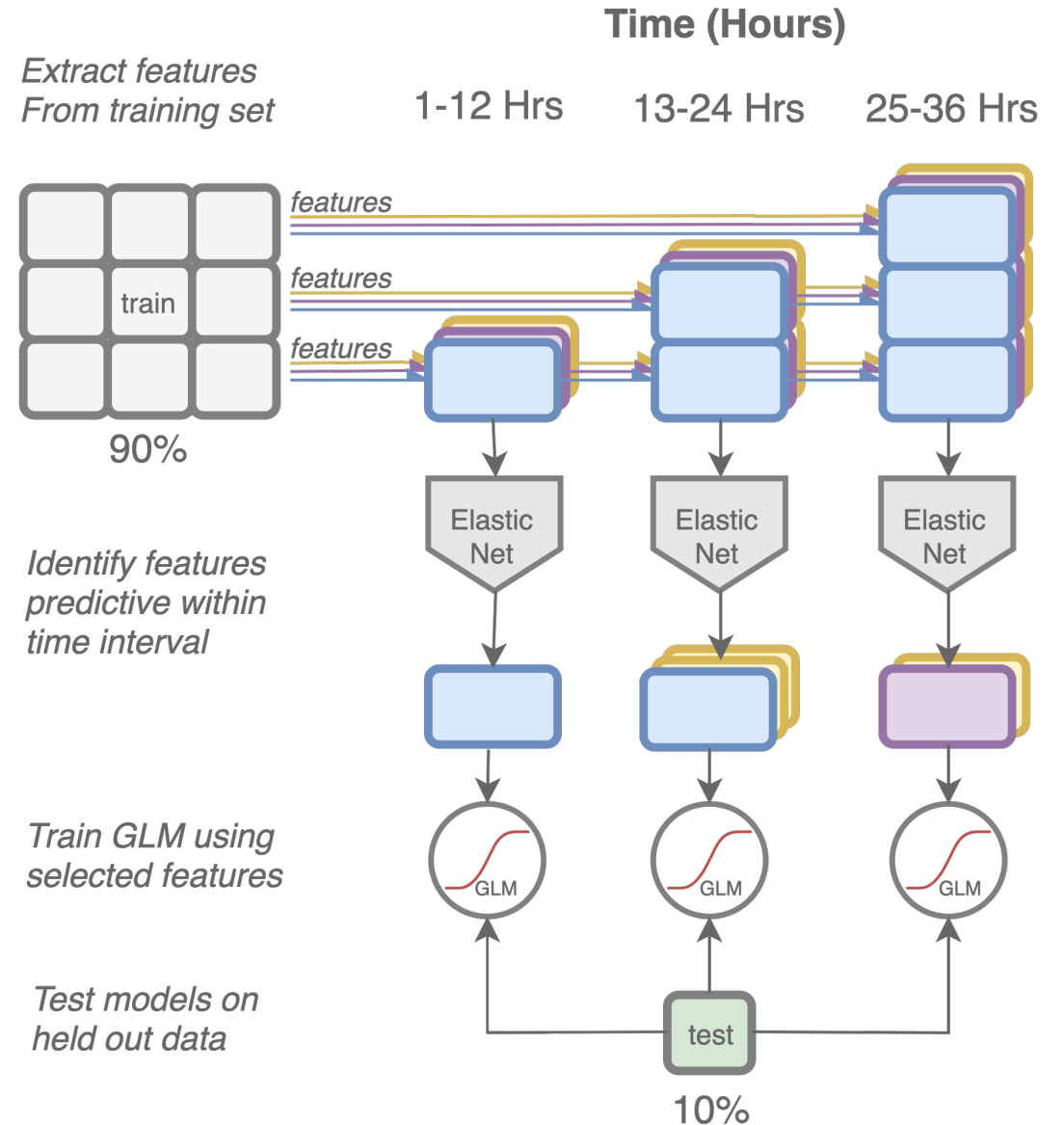
- We retain only the most important features using Elastic Net
- Penalizes the size of the regression coefficients based on both their l^1 norm and their l^2 norm :

$$\operatorname{argmax}_{\beta} \sum_i \log L(y_i; \beta, x_i) - \lambda [\alpha \|\beta\|_1 + \frac{1}{2} (1 - \alpha) \|\beta\|_2^2]$$



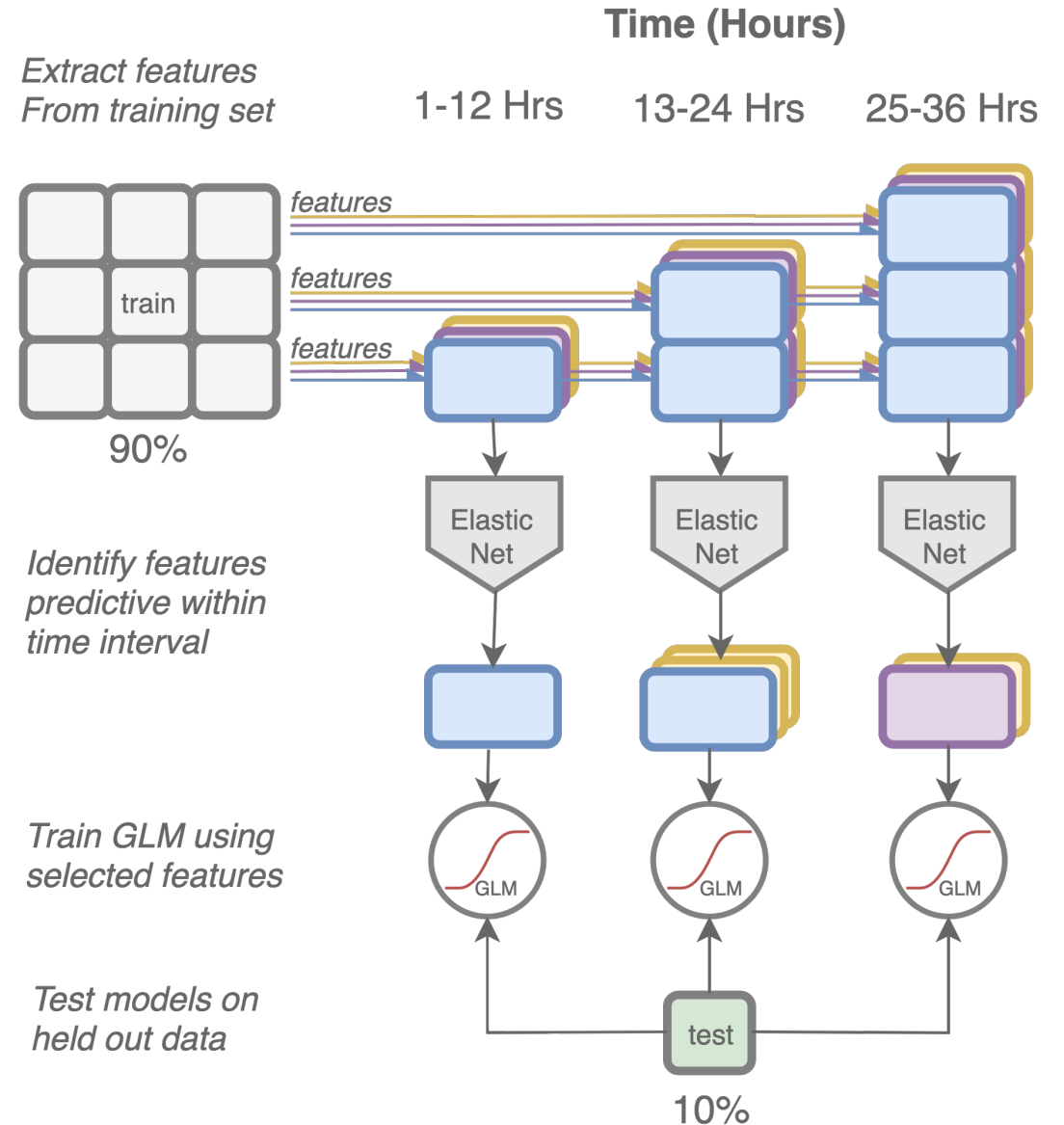
Logistic Regression with *Elastic Memories*

- A logistic regression model with the selected features is used to evaluate performance on the held out test-sets



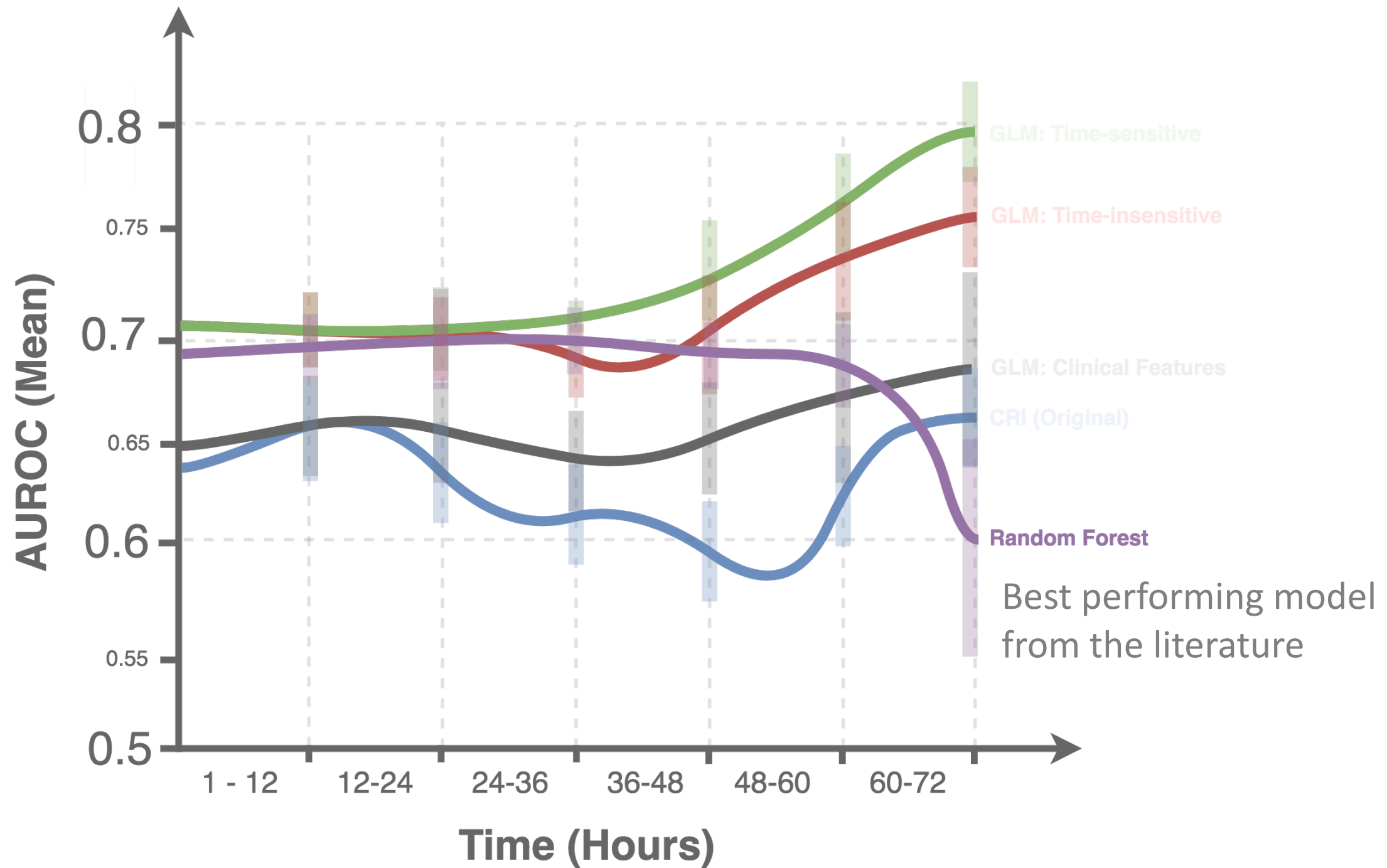
Logistic Regression with *Elastic Memories*

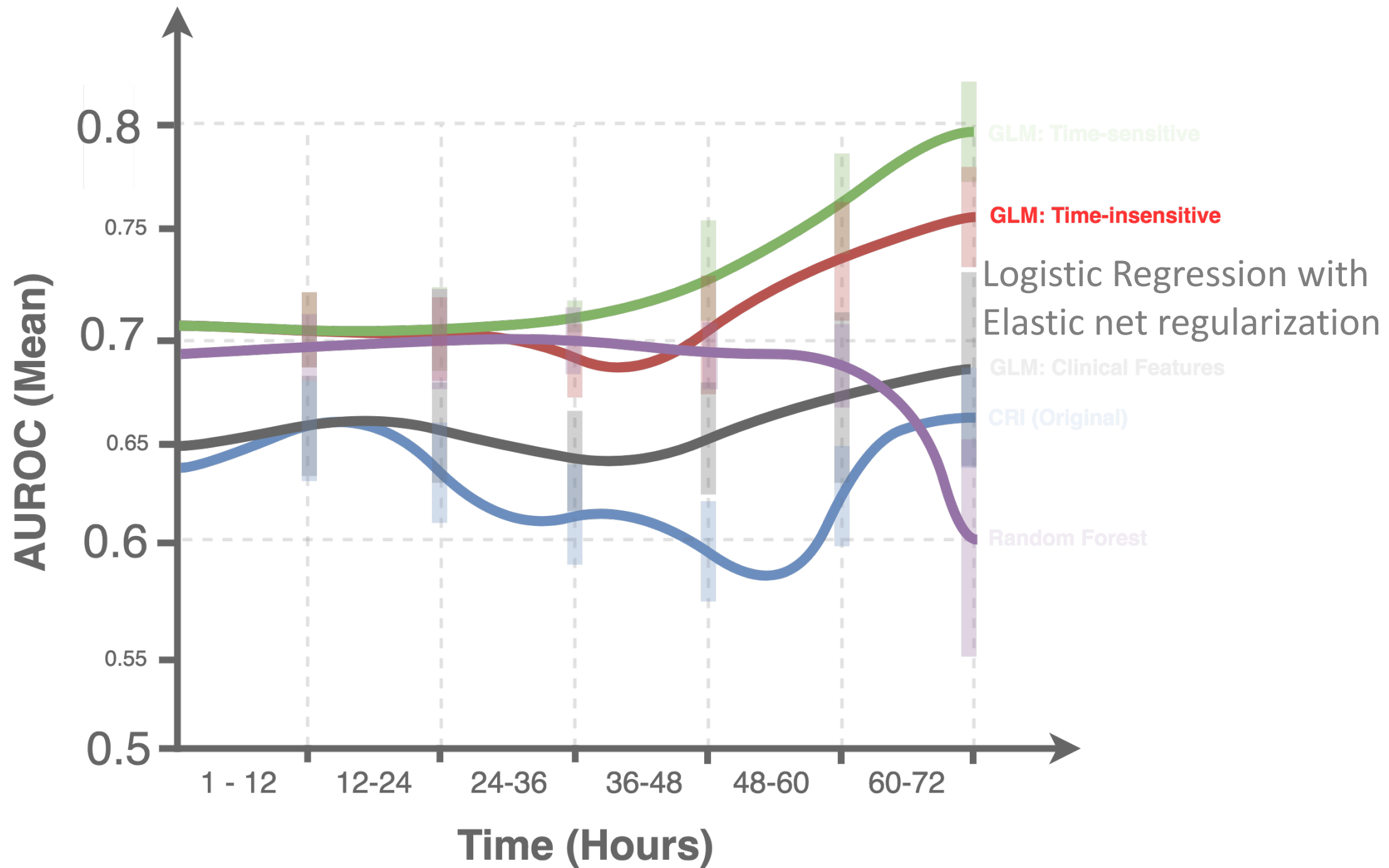
- A logistic regression model with the selected features is used to evaluate performance on the held out test-sets
- This process was designed to imitate how providers might perform prognosis

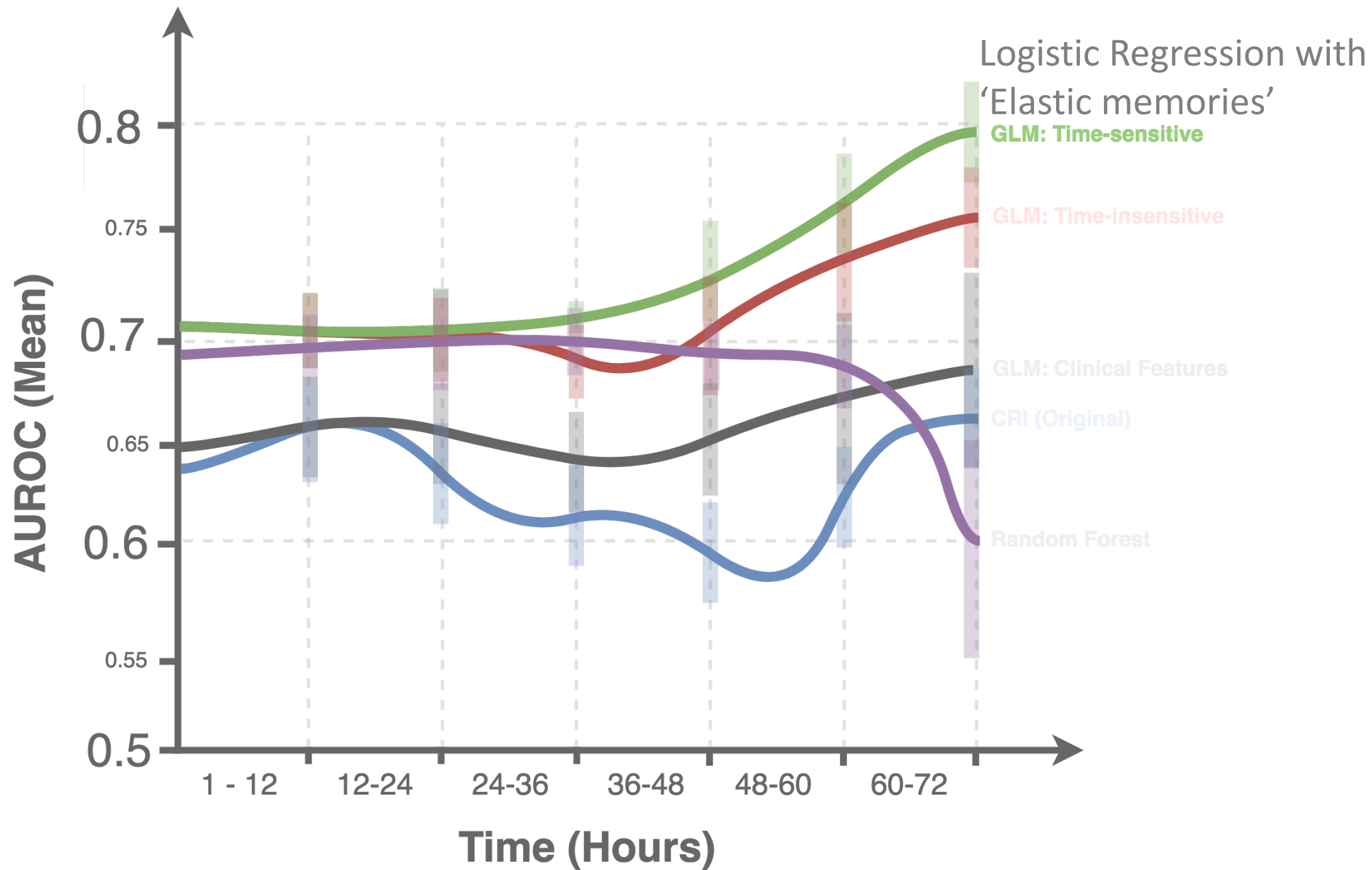


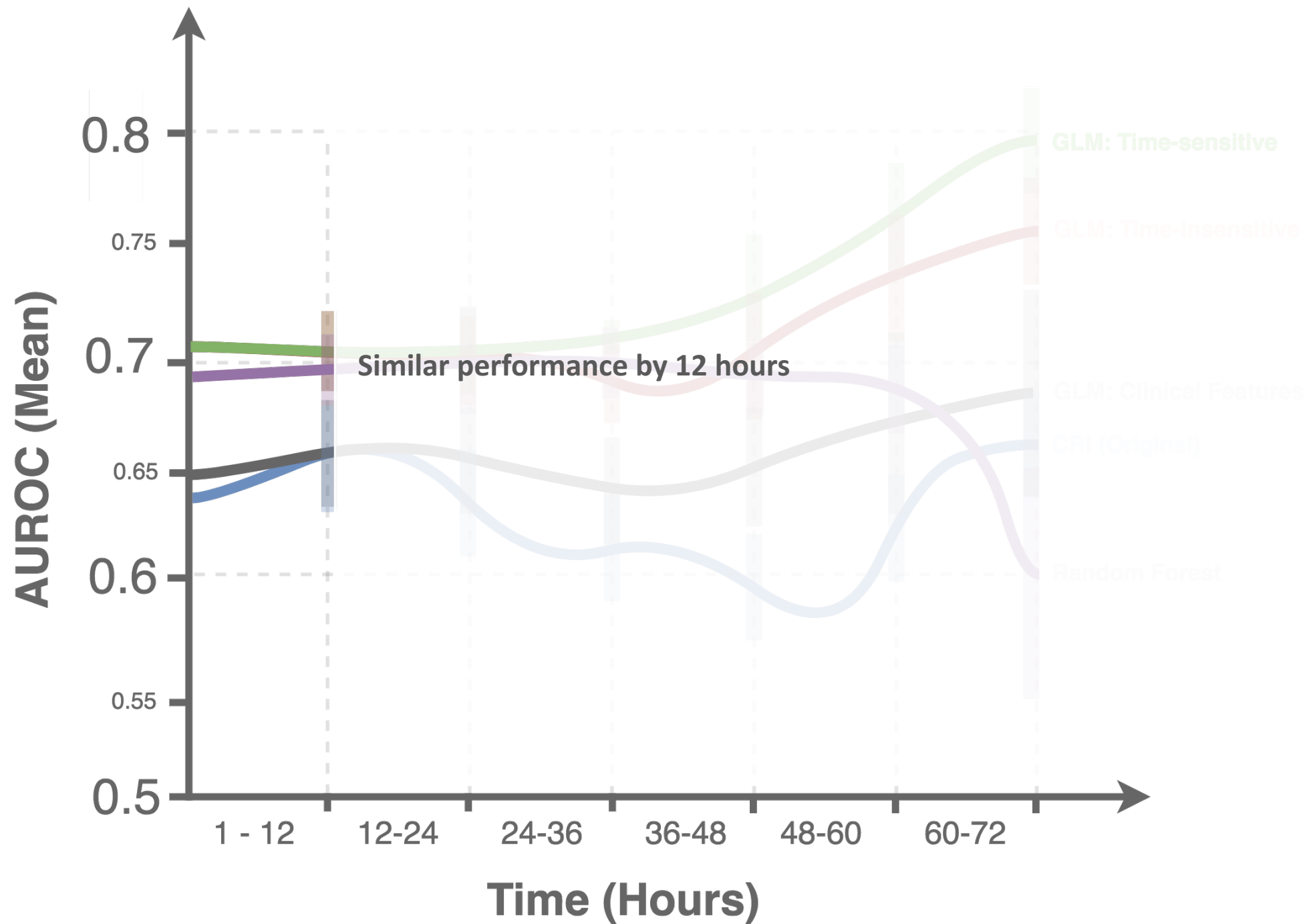
Coefficients Mat Reflect Three Kinds of Relationships

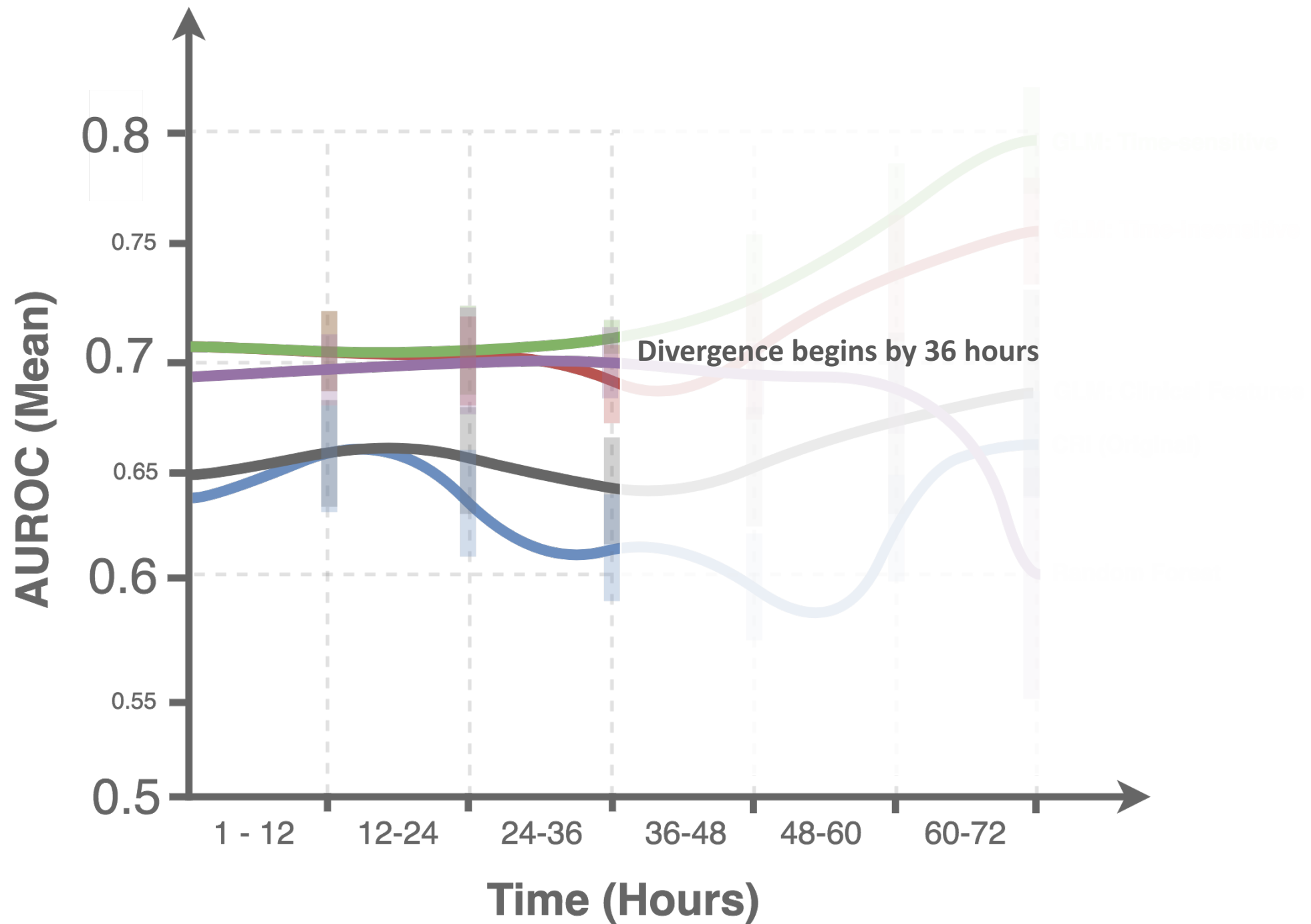
- An **immediate value** is most predictive of outcomes.
- A **prior value** is most predictive of outcomes.
- The **cumulative** value is most predictive of outcomes.

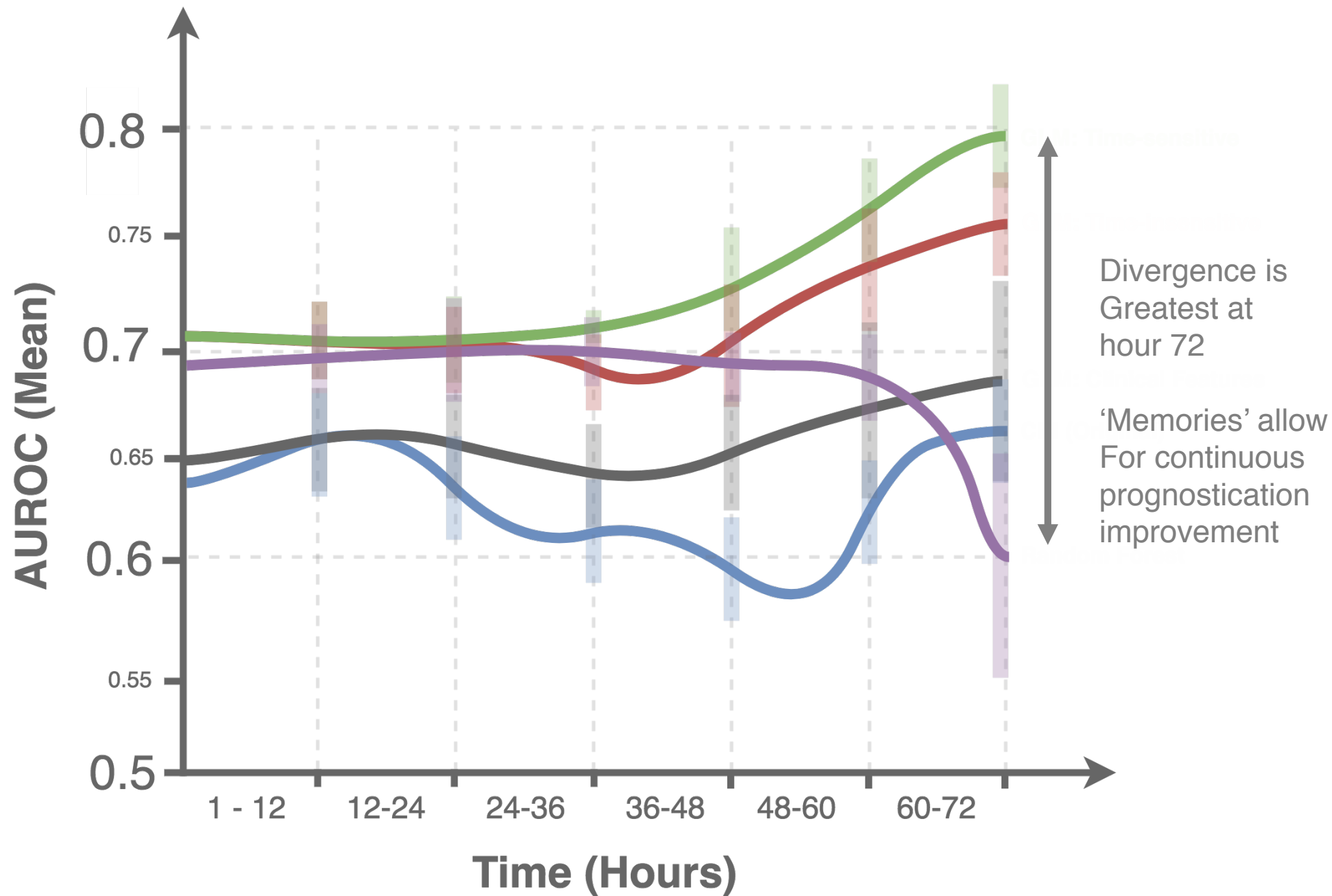






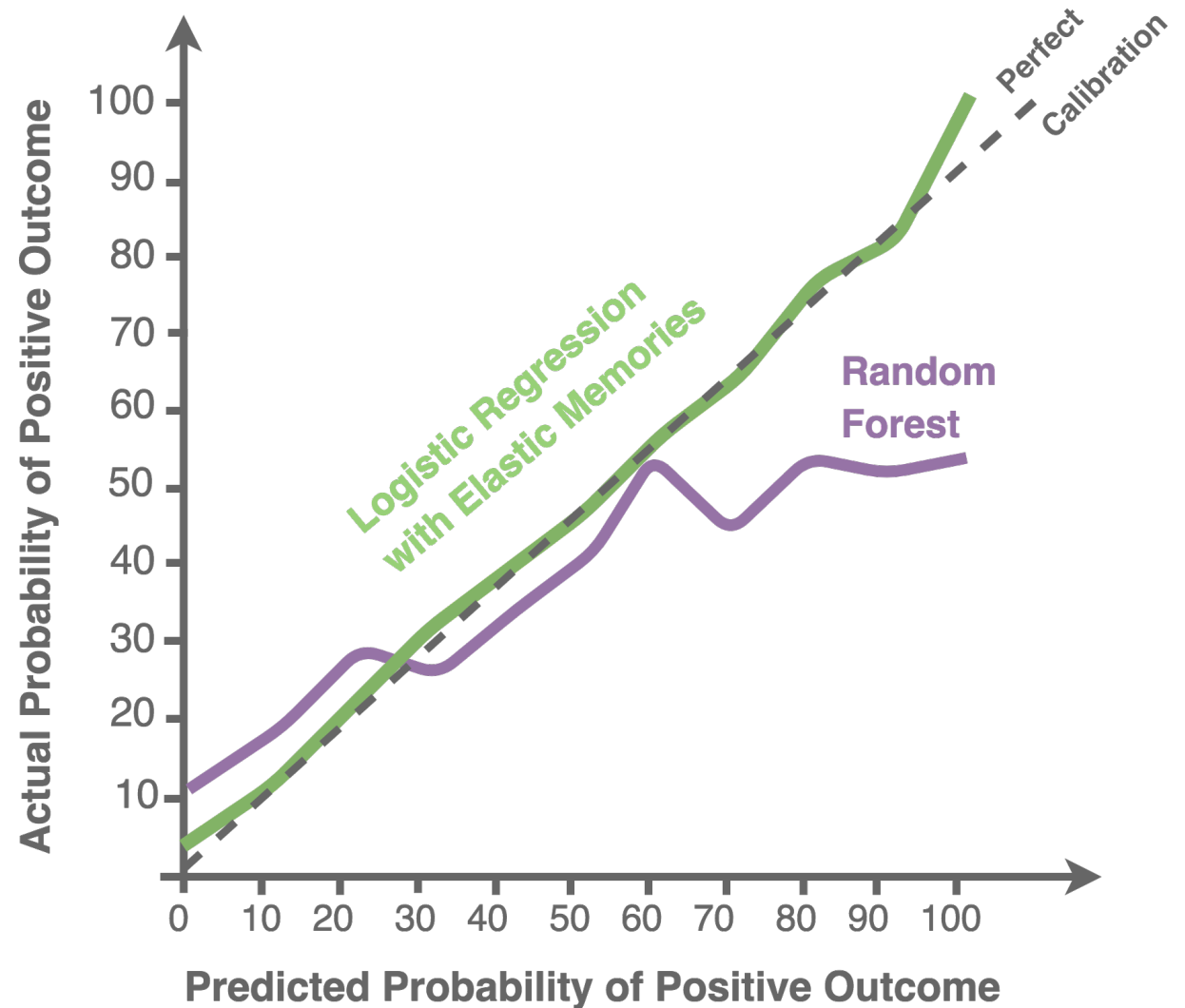






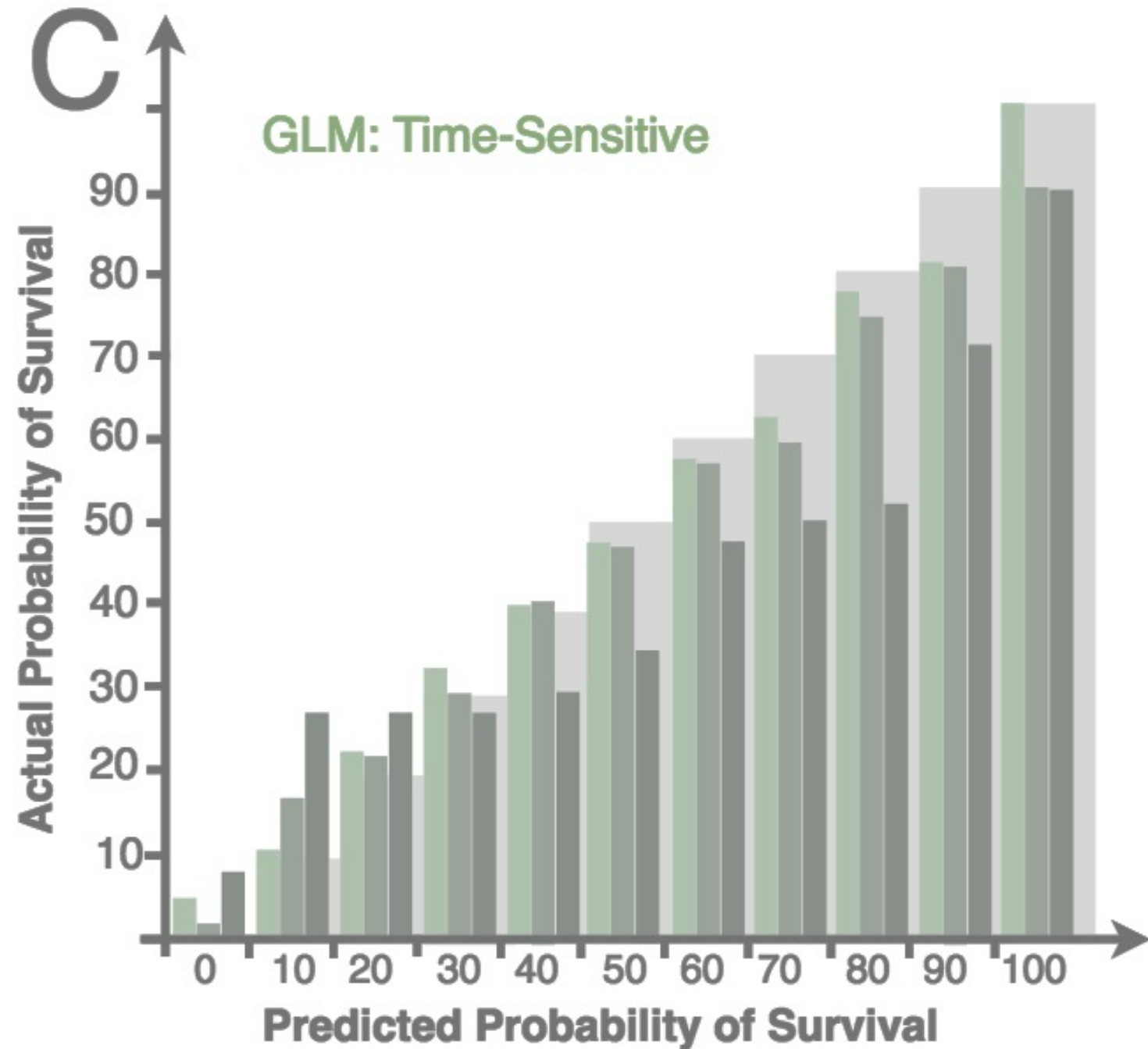
Calibration

- **Our approach** exhibited enhanced calibration compared to the **literature baseline**
- This allows for a more nuanced use of the model, compared to existing approaches



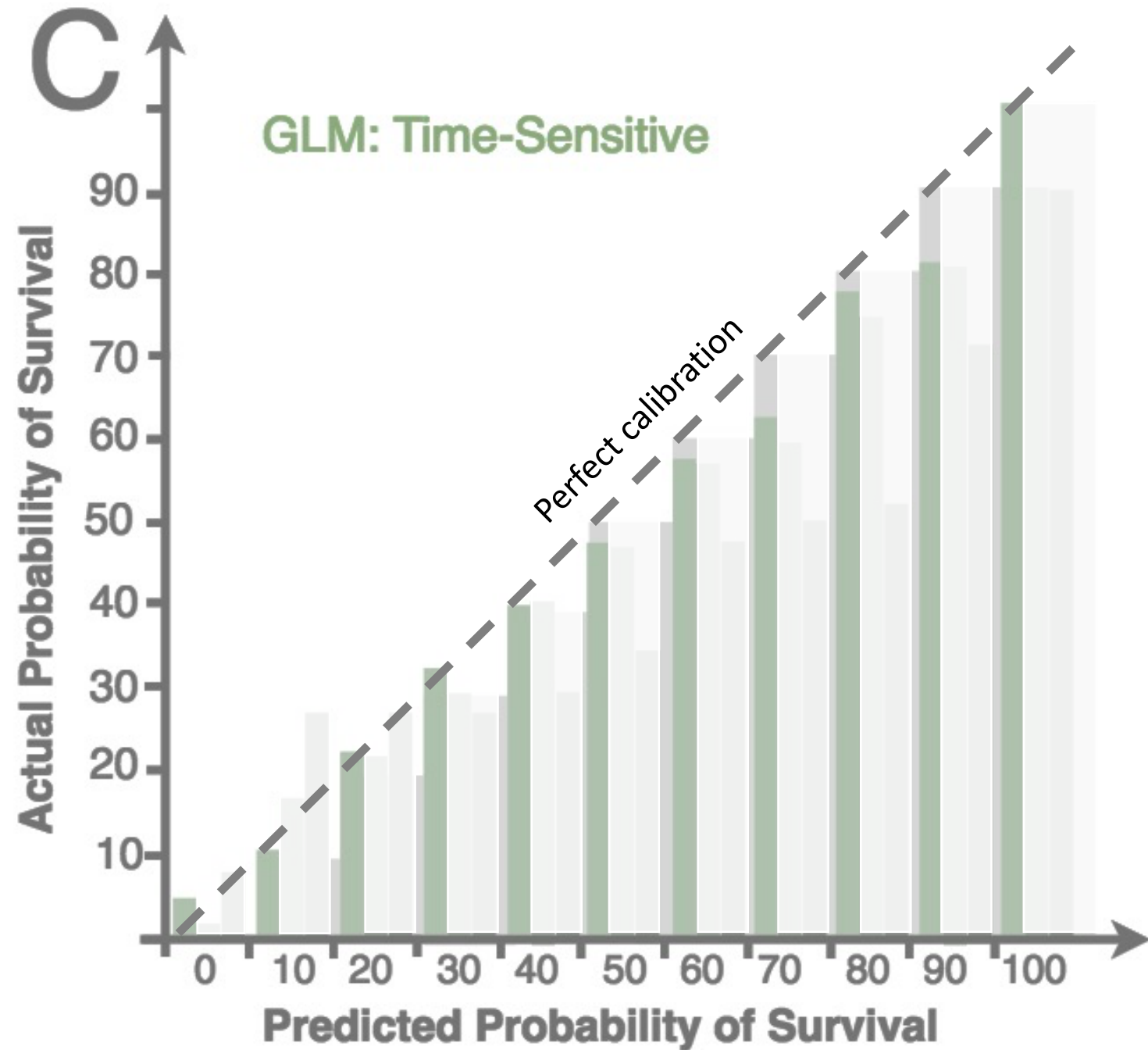
Calibration

- Our approach was also well calibrated over time.



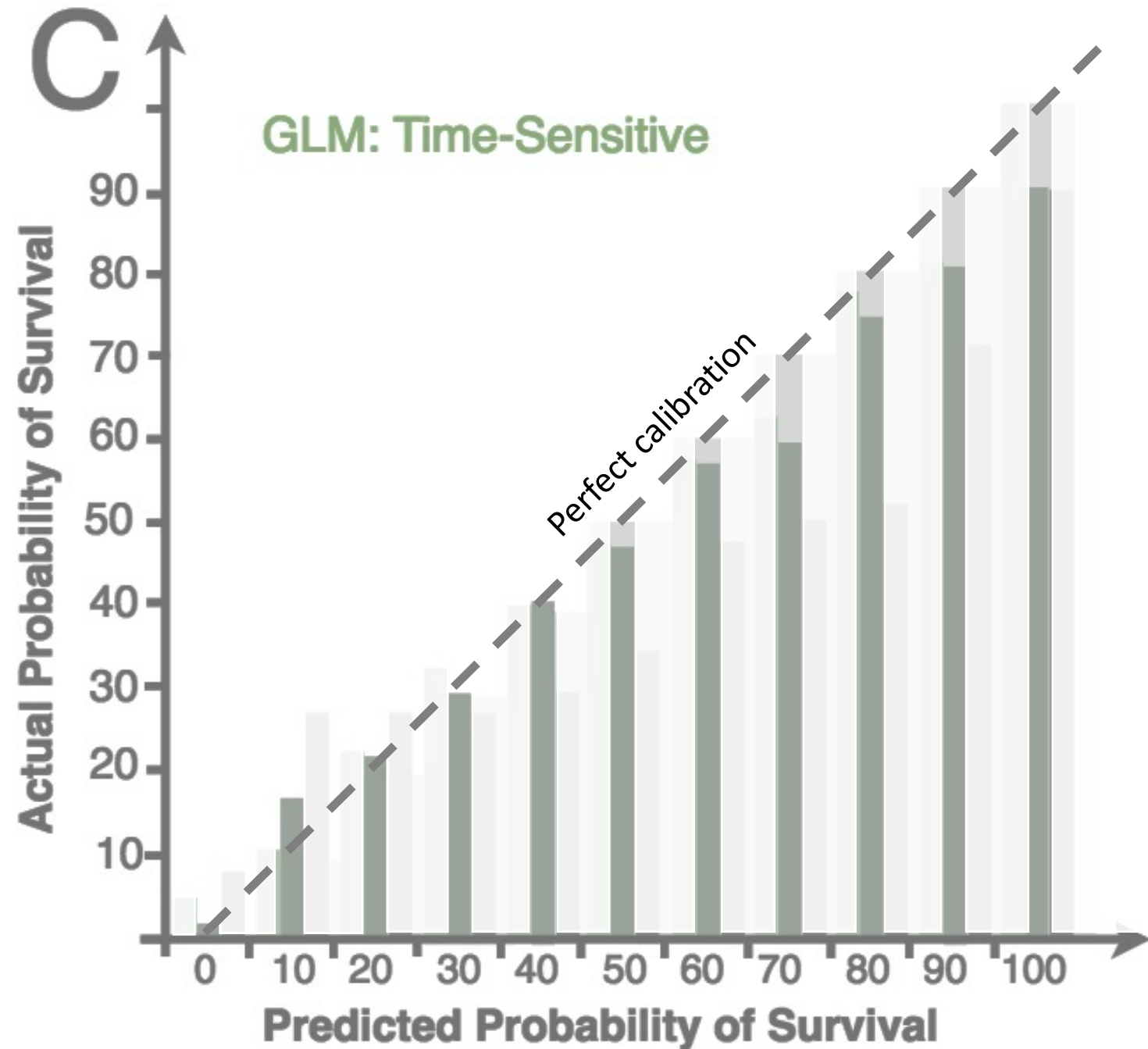
Calibration

- Our approach was also well calibrated over time.
- Day 1



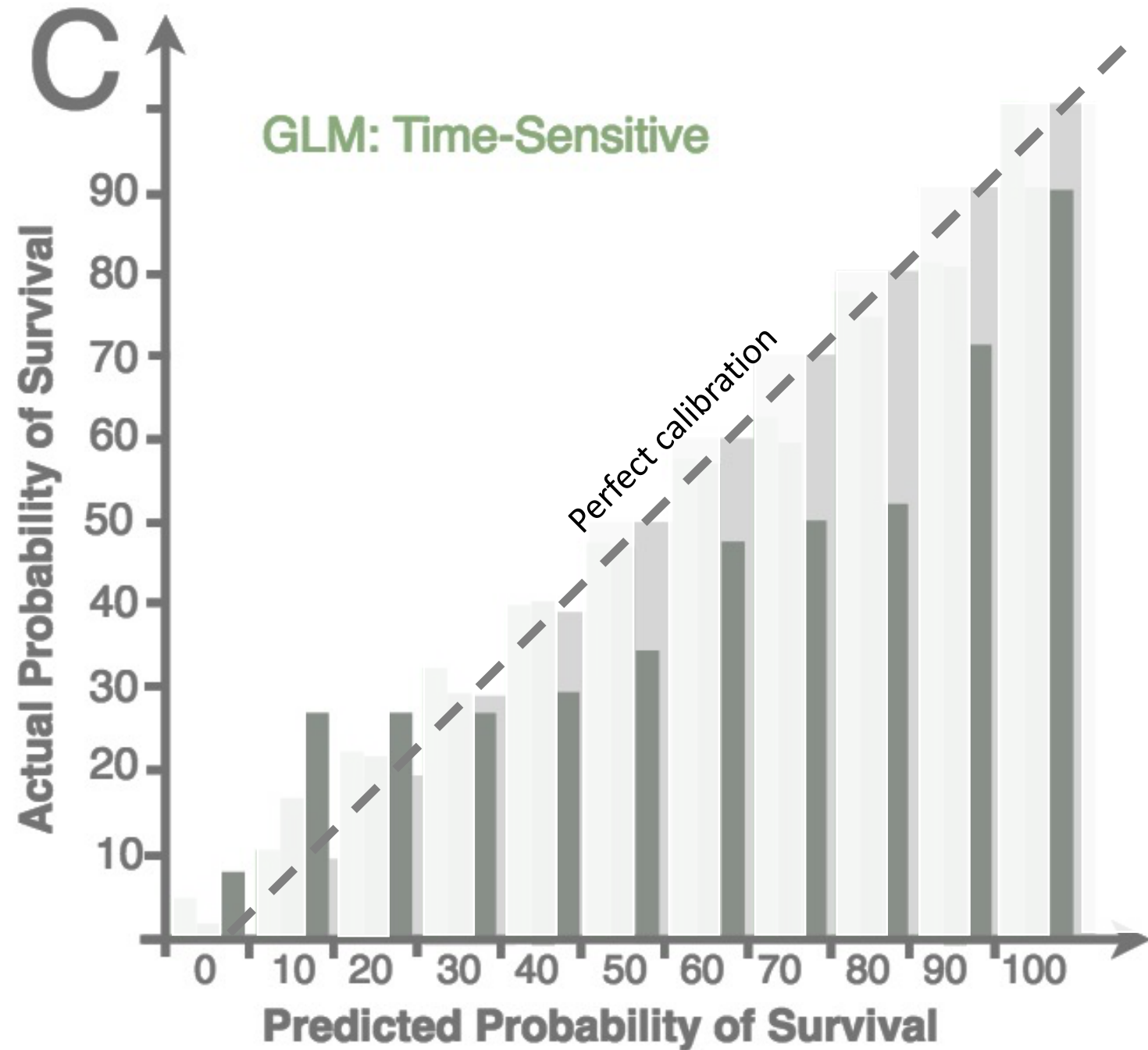
Calibration

- Our approach was also well calibrated over time.
- Day 2



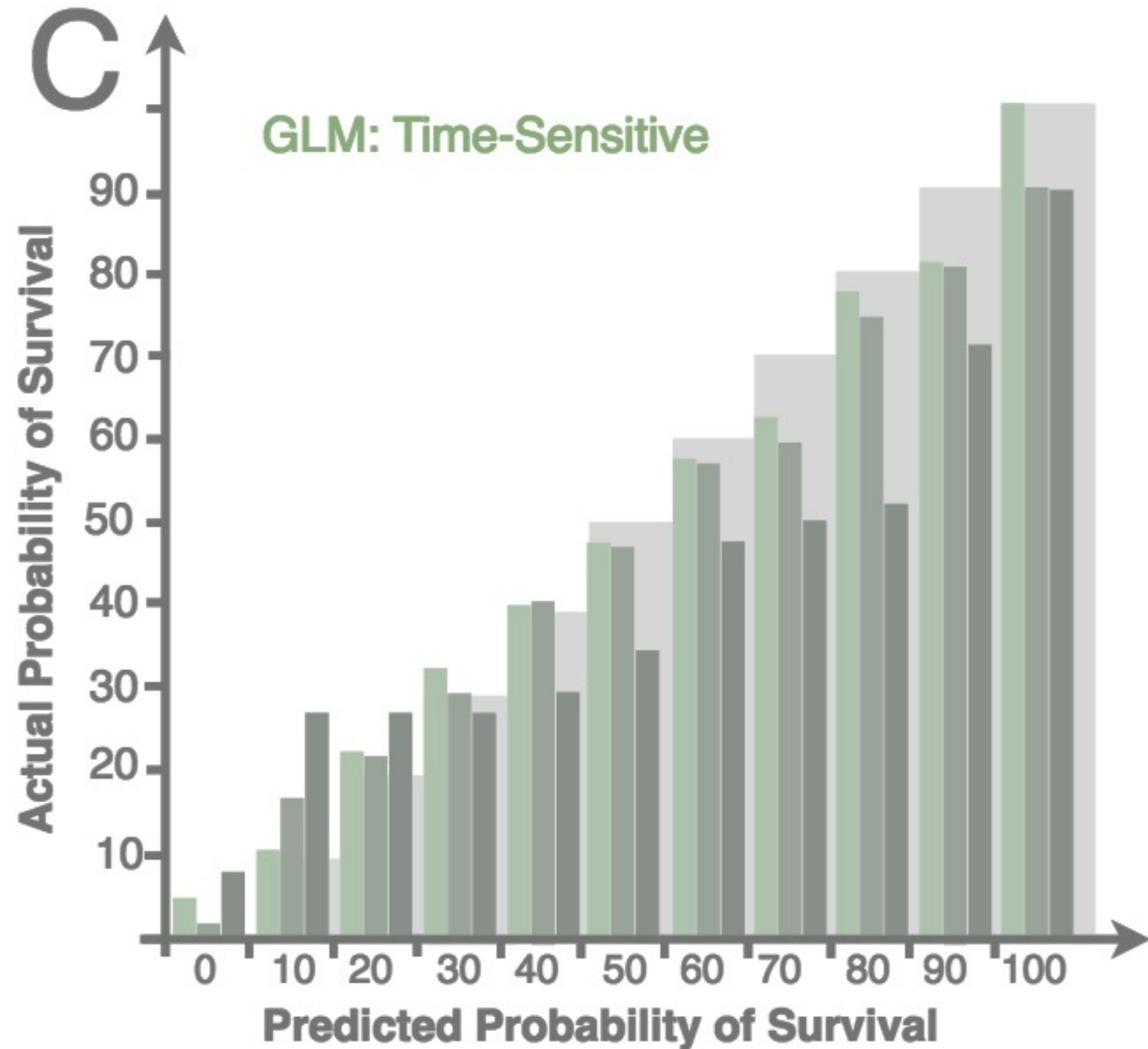
Calibration

- Our approach was also well calibrated over time.
- Day 3

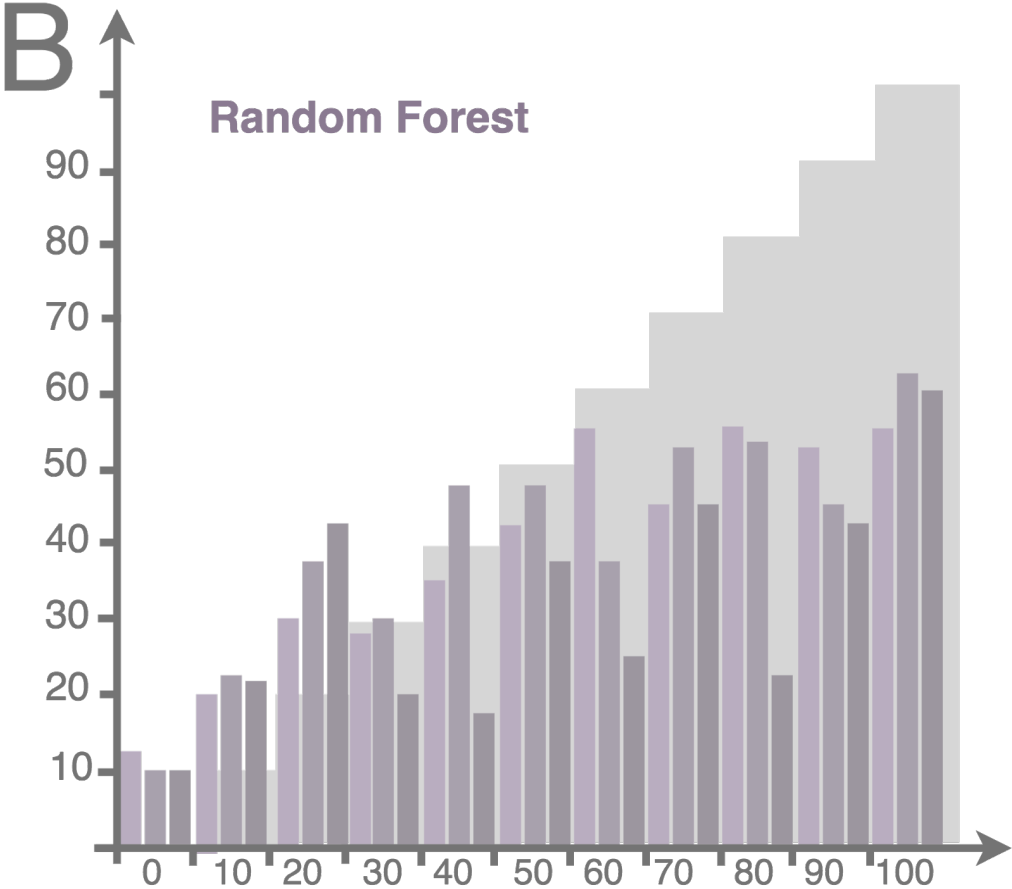
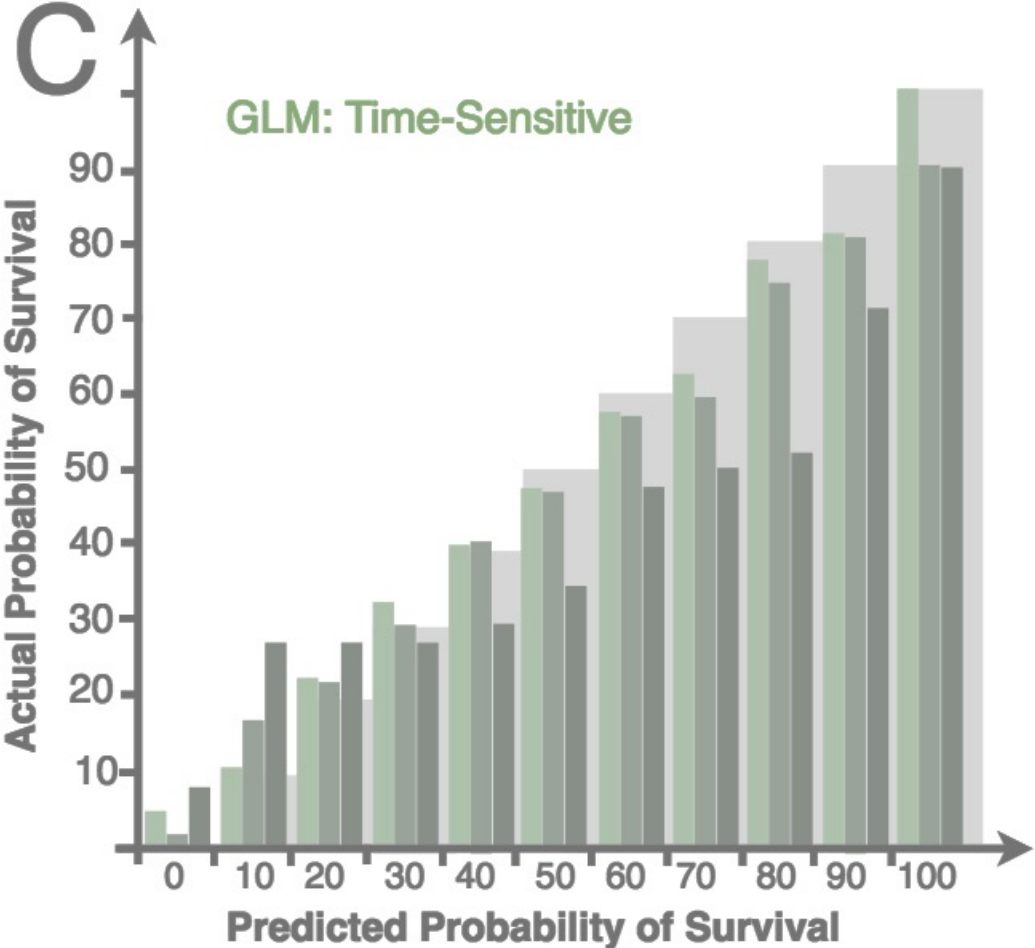
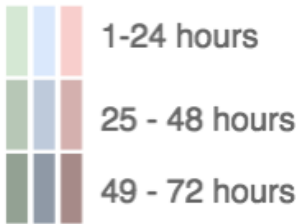


Calibration

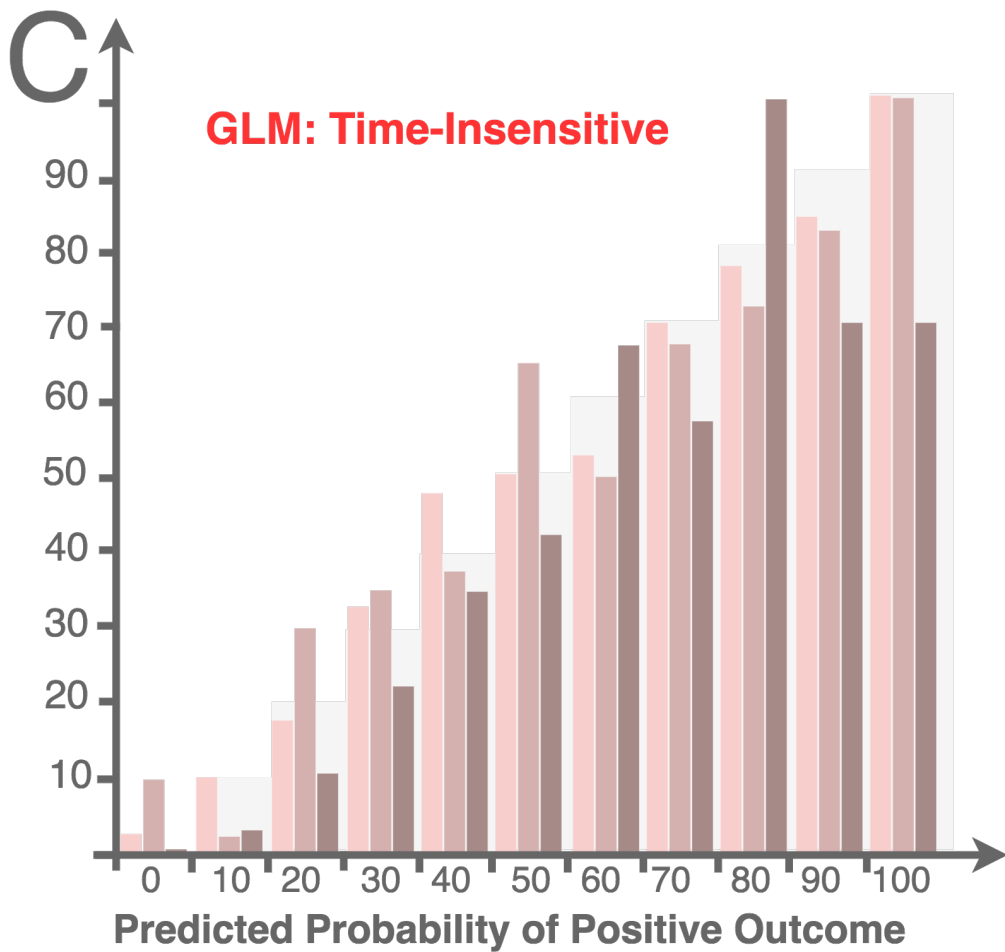
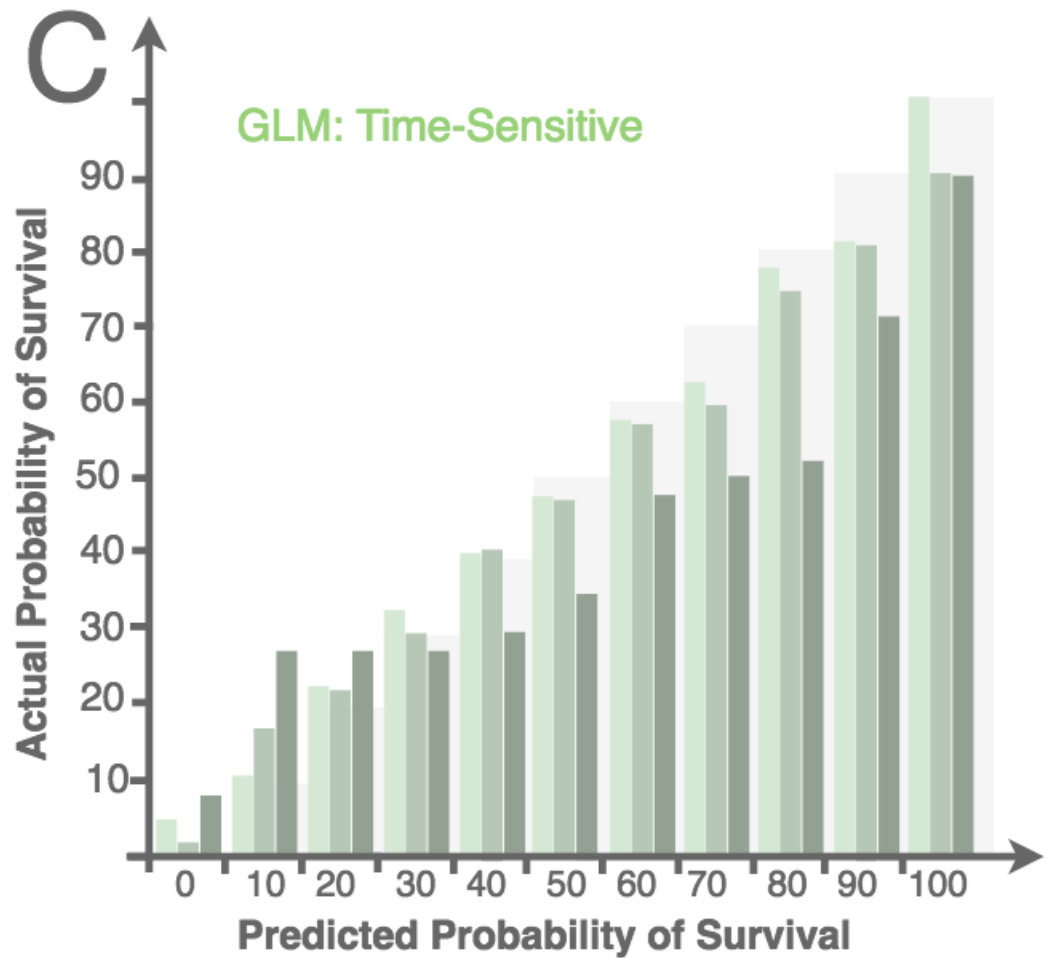
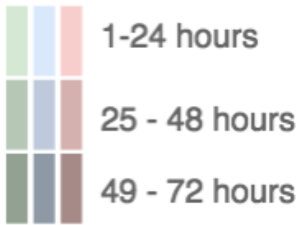
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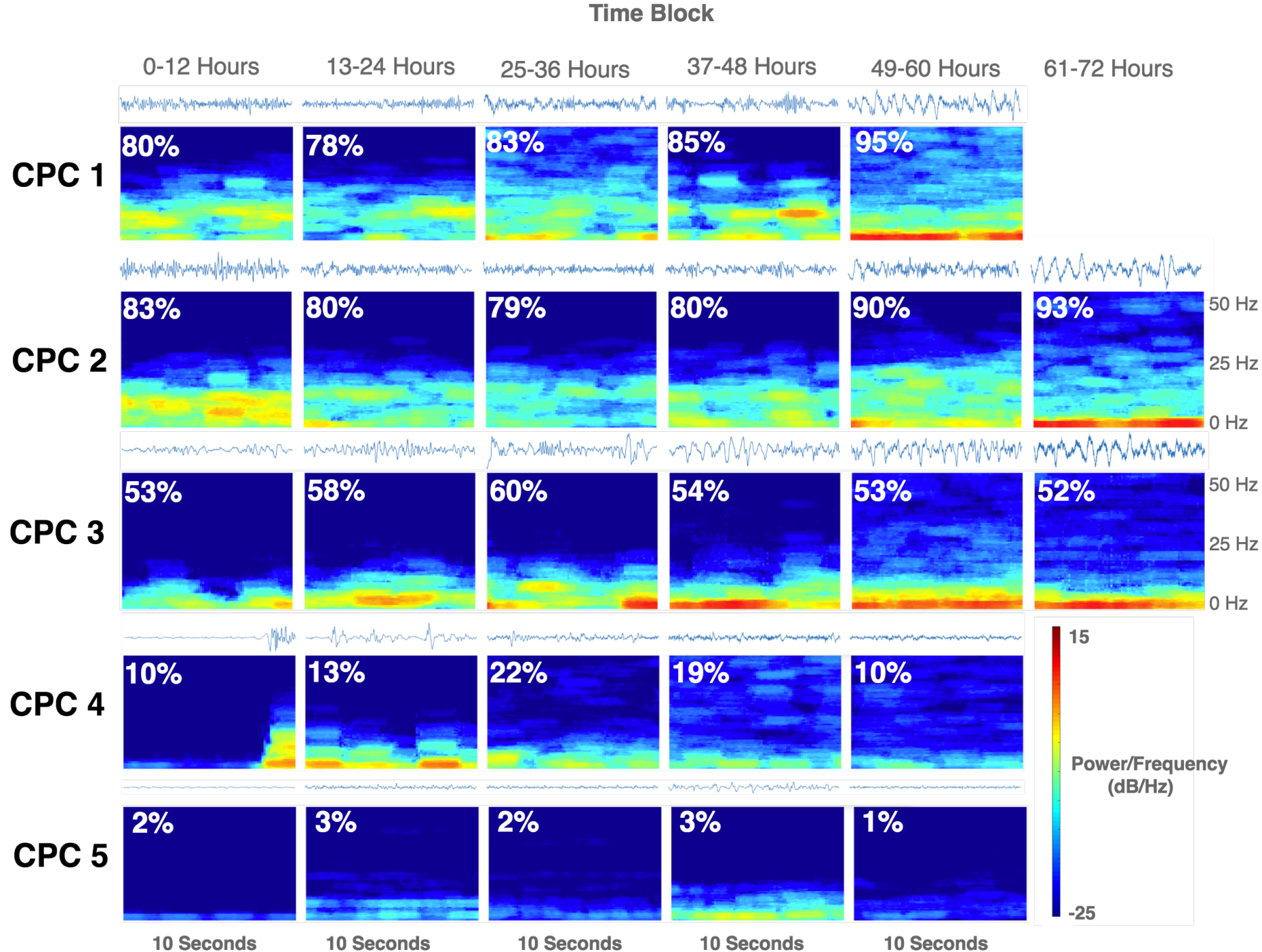
Calibration



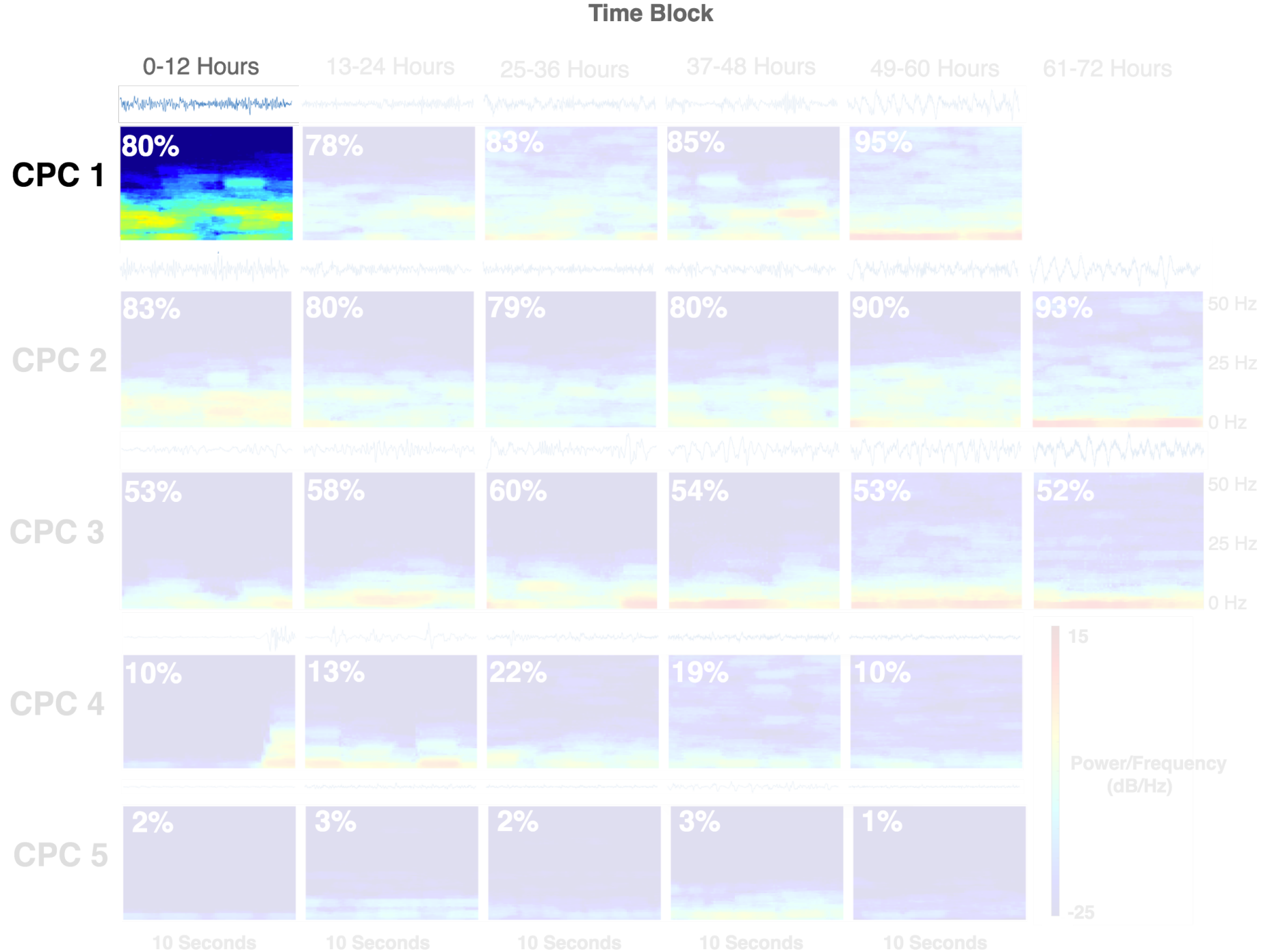
Calibration



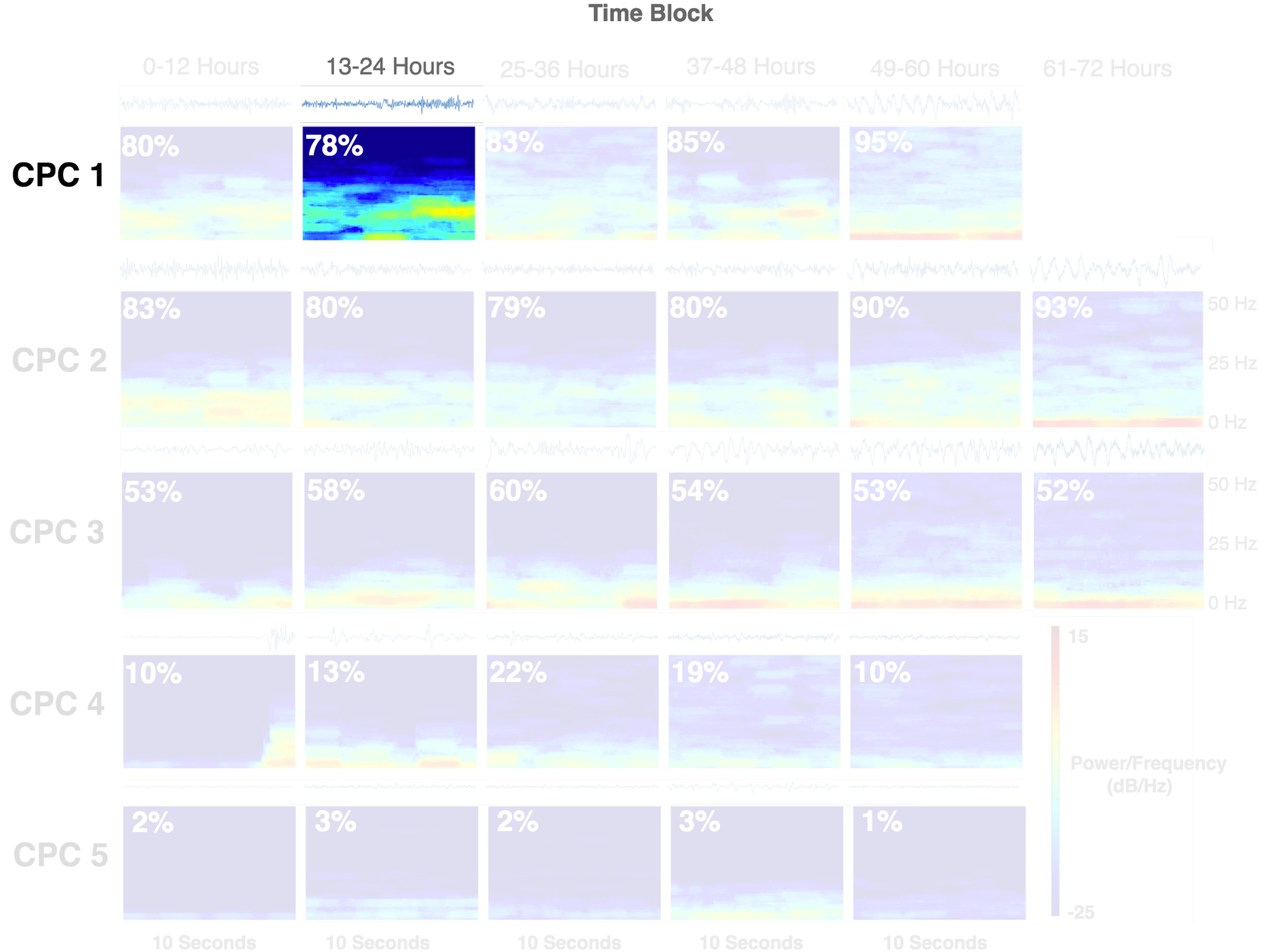
Exemplary Patients



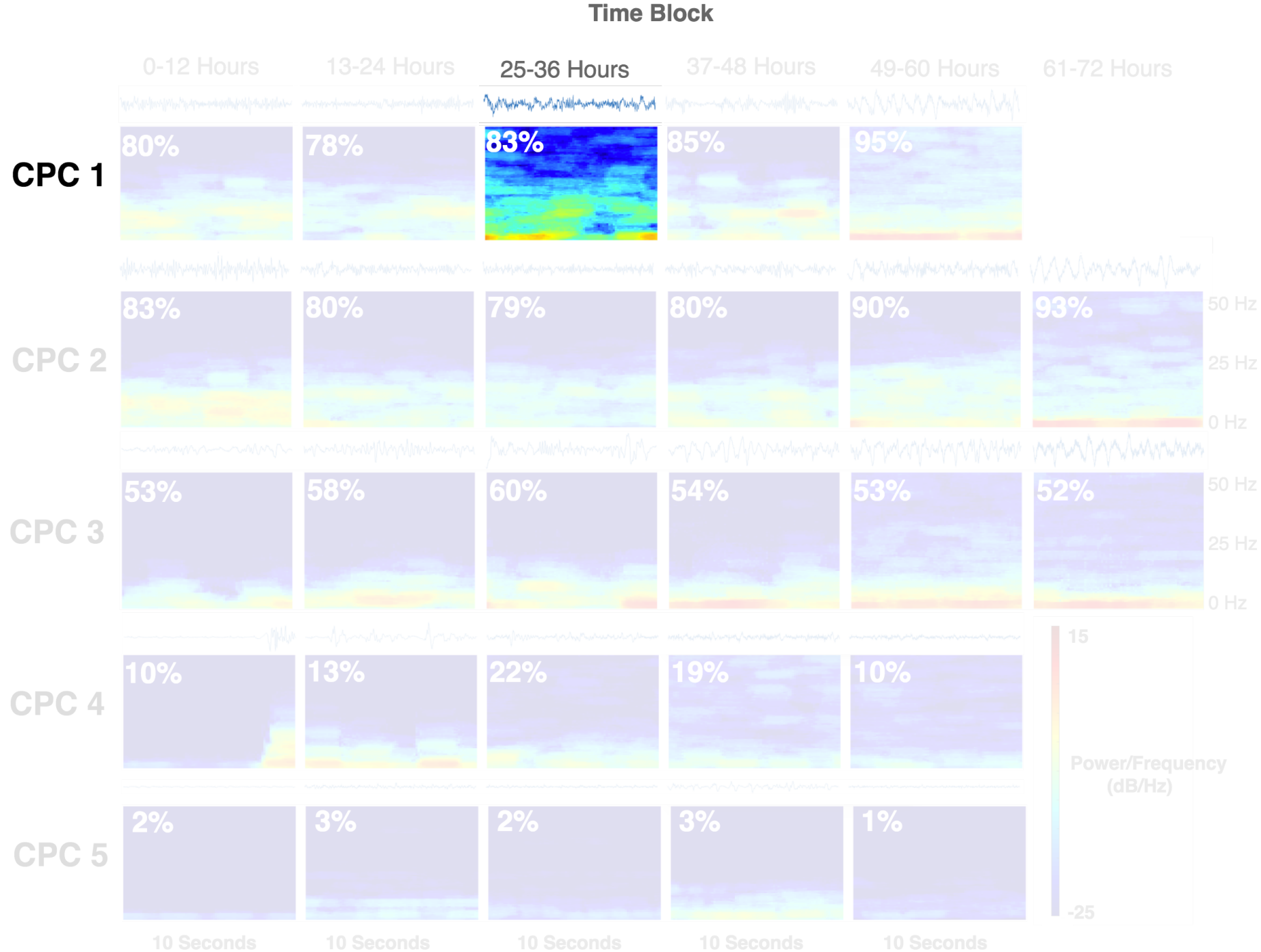
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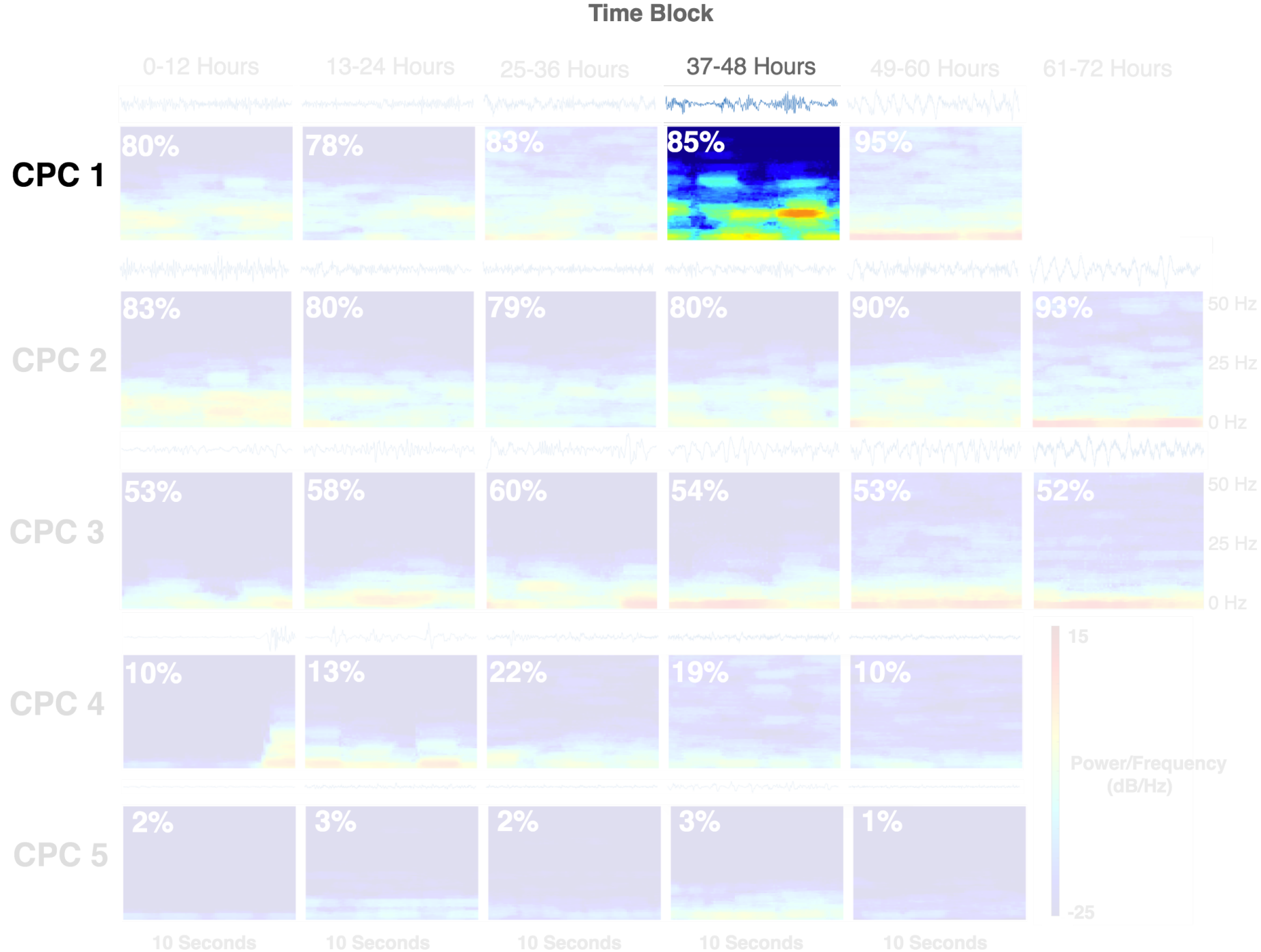
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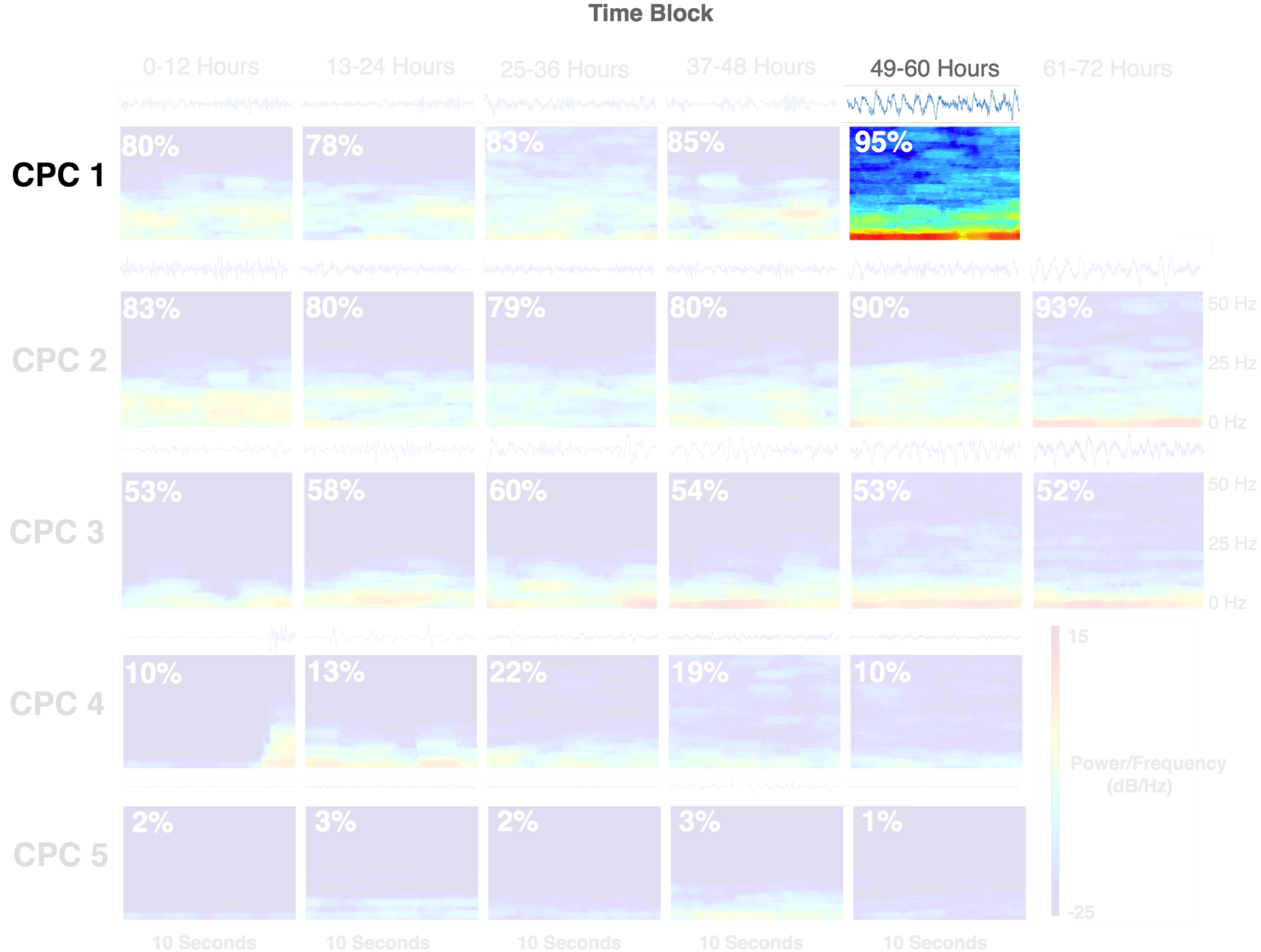
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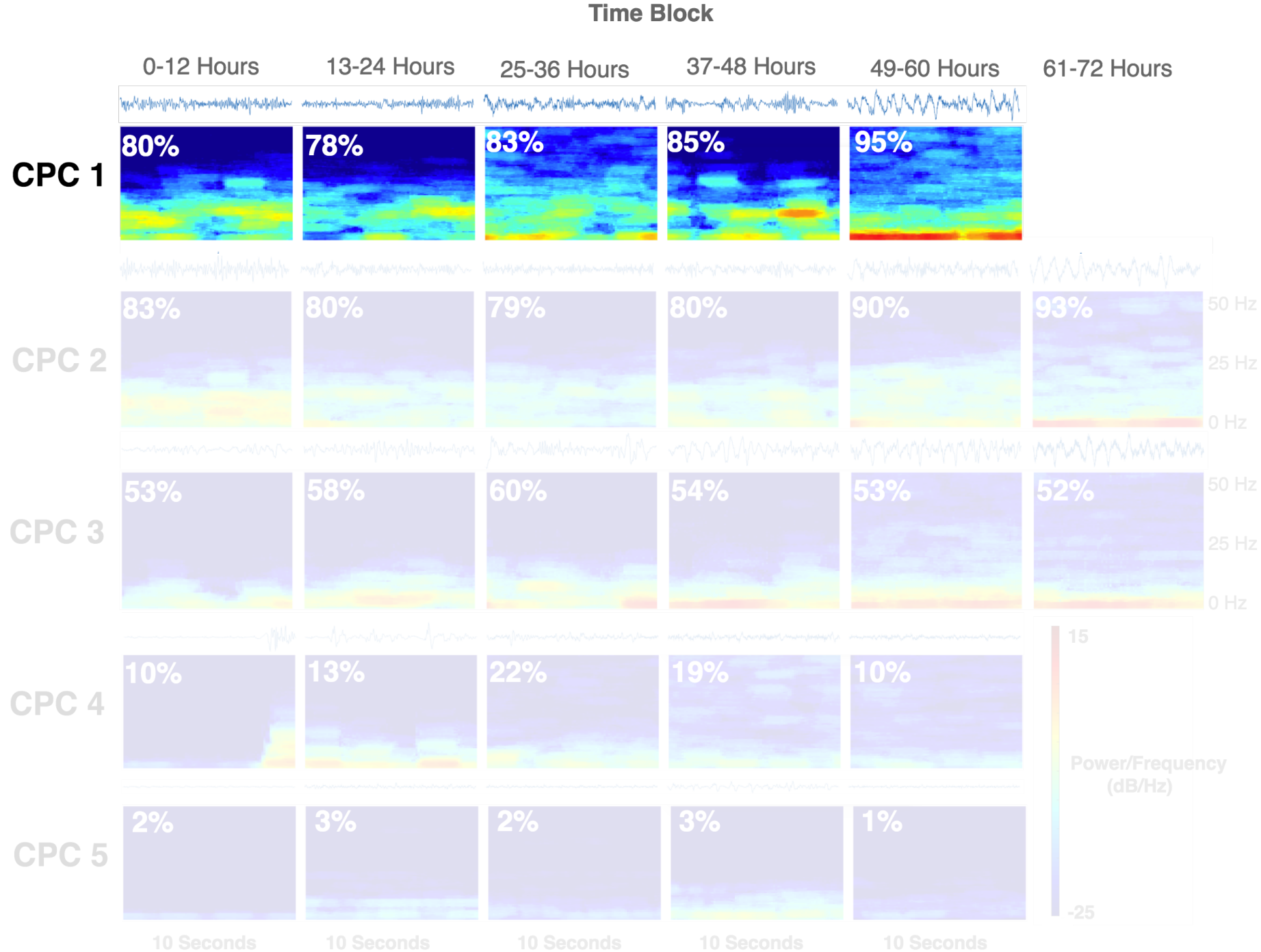
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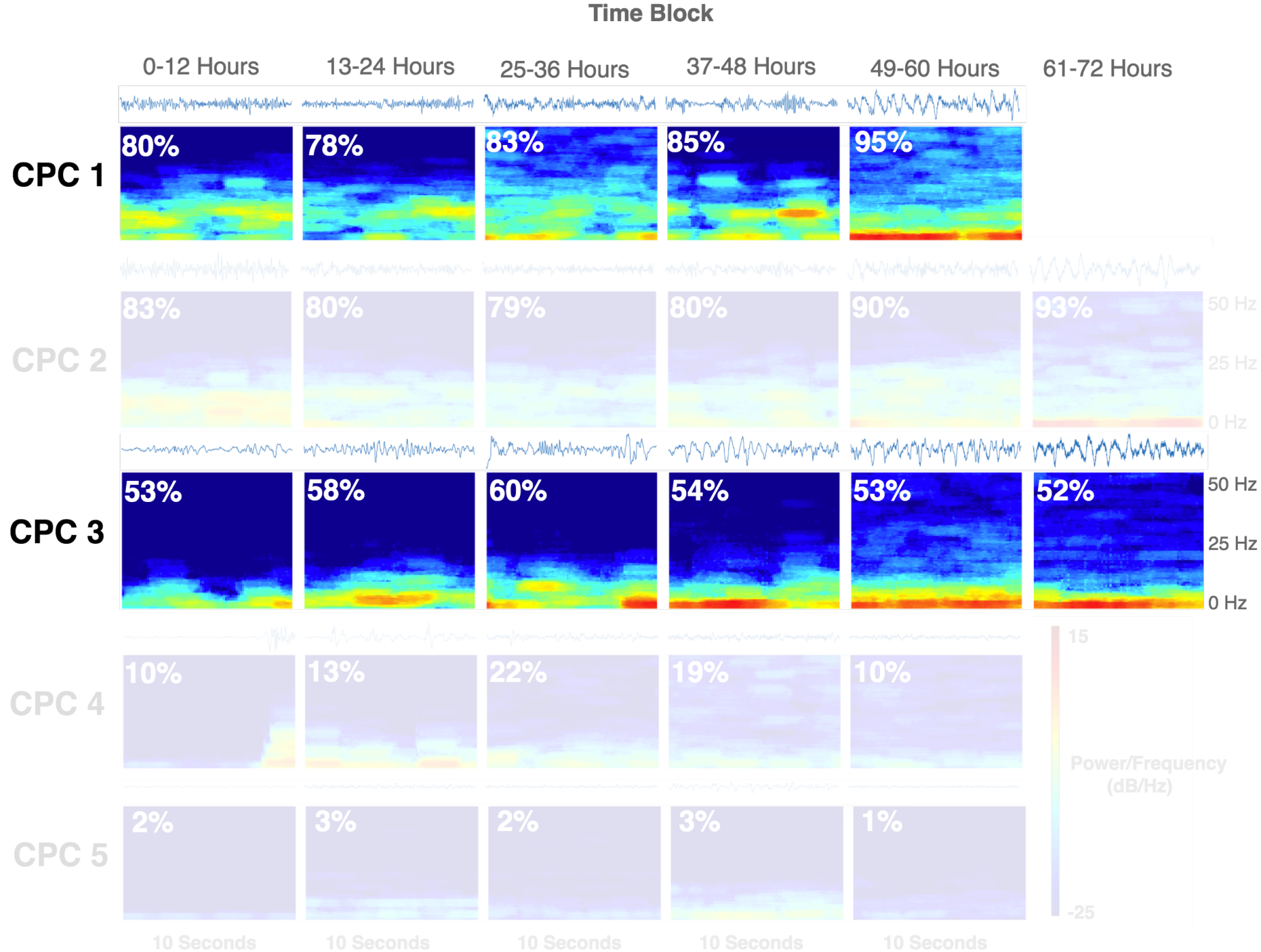
Exemplary Patients



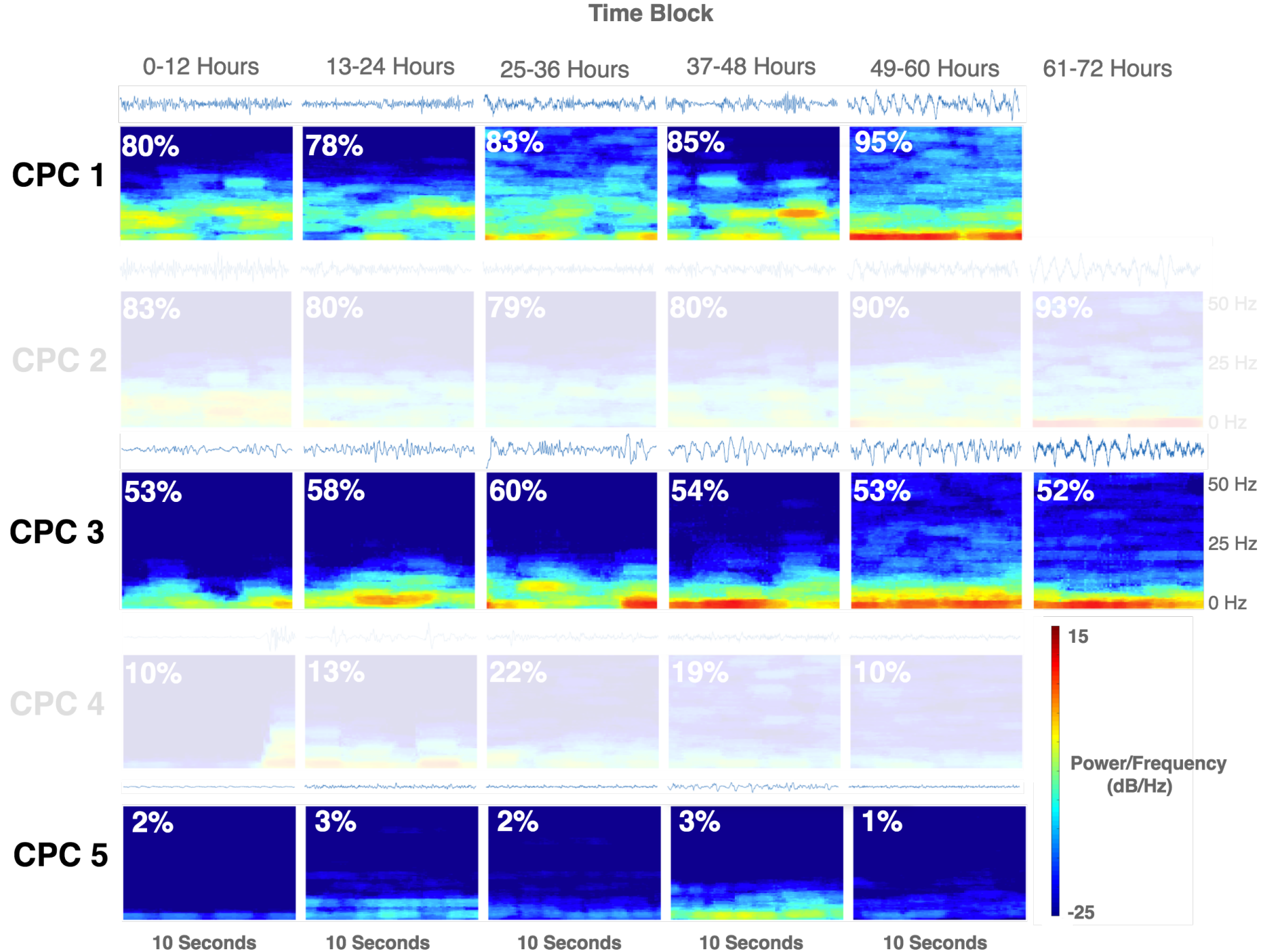
Exemplary Patients



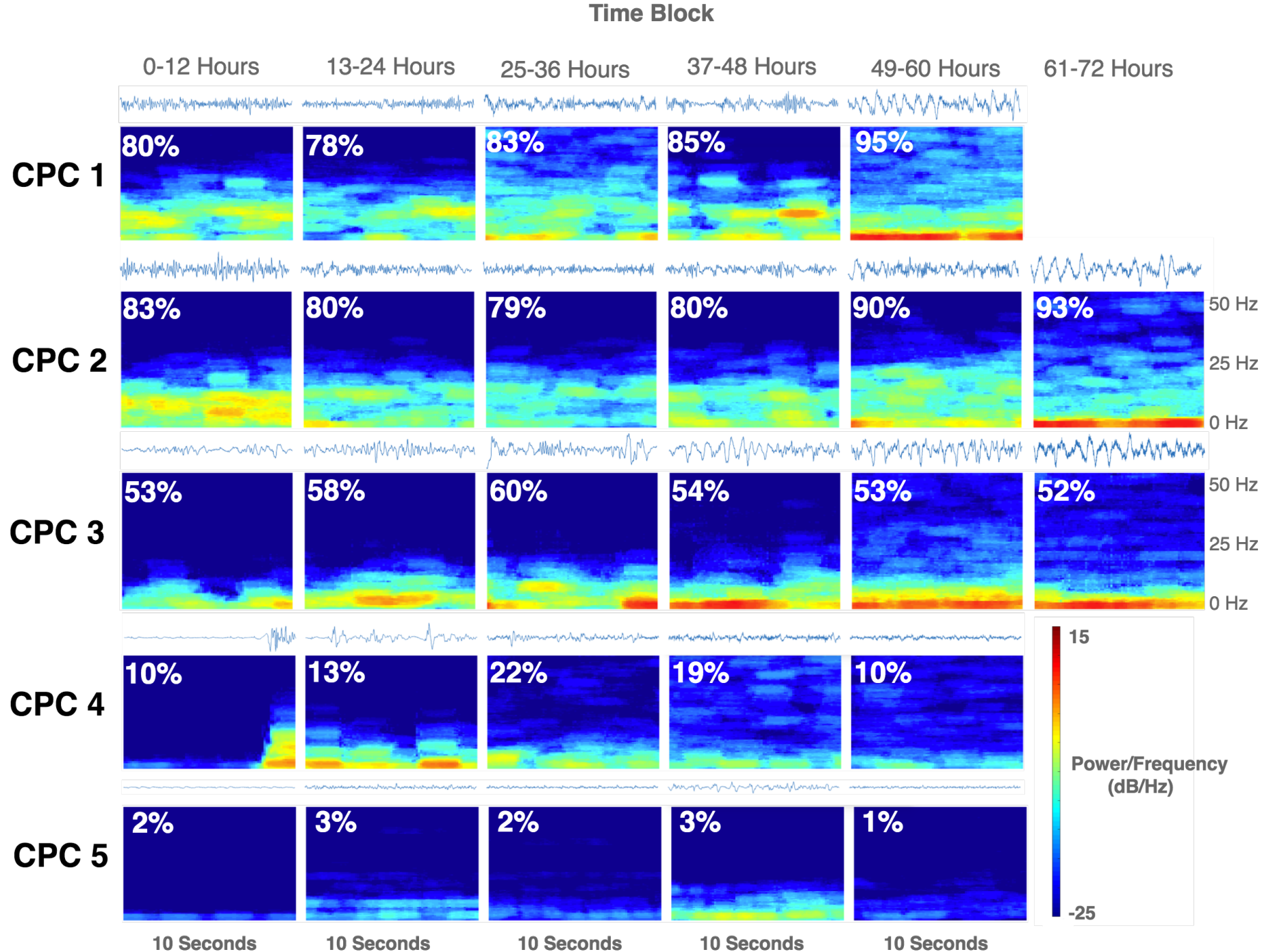
Exemplary Patients



Exemplary Patients



Exemplary Patients



Pros/Cons of the Approach

- Advantages

- Does not require time of arrest
- Prognostic performance improves over time using 'memories'
- Well calibrated

- Disadvantages

- Alignment with respect to EEG initiation harm physiological interpretations
- Assumes that feature coefficients in neighboring intervals are independent
- Does not account for spatial information

Three Approaches

Two Feature Based:

- ~~1. Sequential Logistic Regression with 'Elastic' memories.~~
- 2. Sequential Logistic Regression with Dynamic Bayesian network constraints

One Data Driven

- 3. Deep neural networks

Logistic Regression with *DBN*

- $n = 785$ patients
- 10 EEG, 5 clinical features
- Validation:
- Leave-one-subject-out

Logistic Regression with *DBN*

- n = 785 patients
- **10 EEG, 5 clinical features**
- Validation:
- Leave-one-subject-out

Signal Feature

Complexity

Shannon Entropy
Hjorth Complexity
False Nearest Neighbor

Category

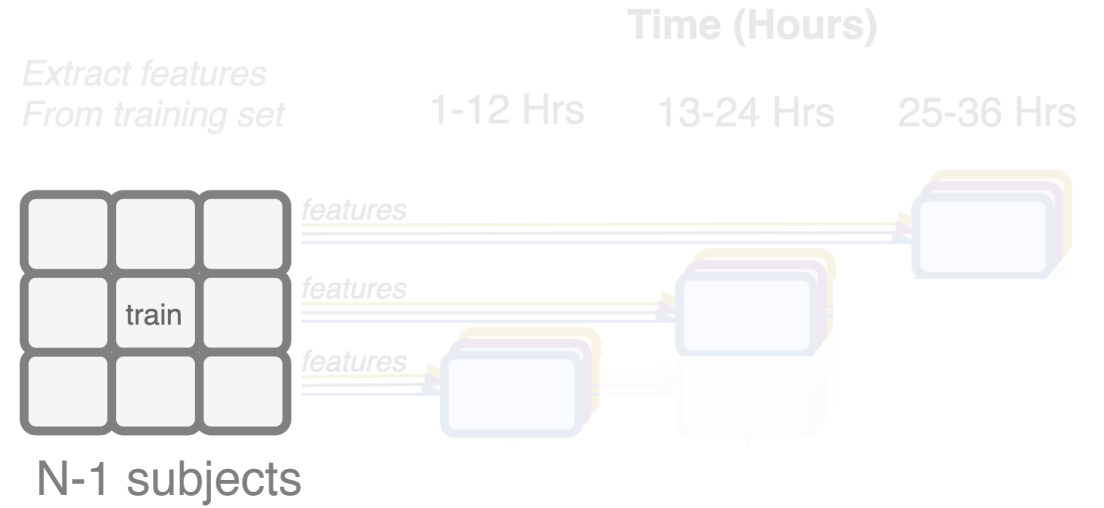
Standard Deviation
Regularity (burst-suppression)
Diffuse Slowing
Spikes

Connectivity

Coherence - delta
Phase Lag Index
Cross-correlation Magnitude

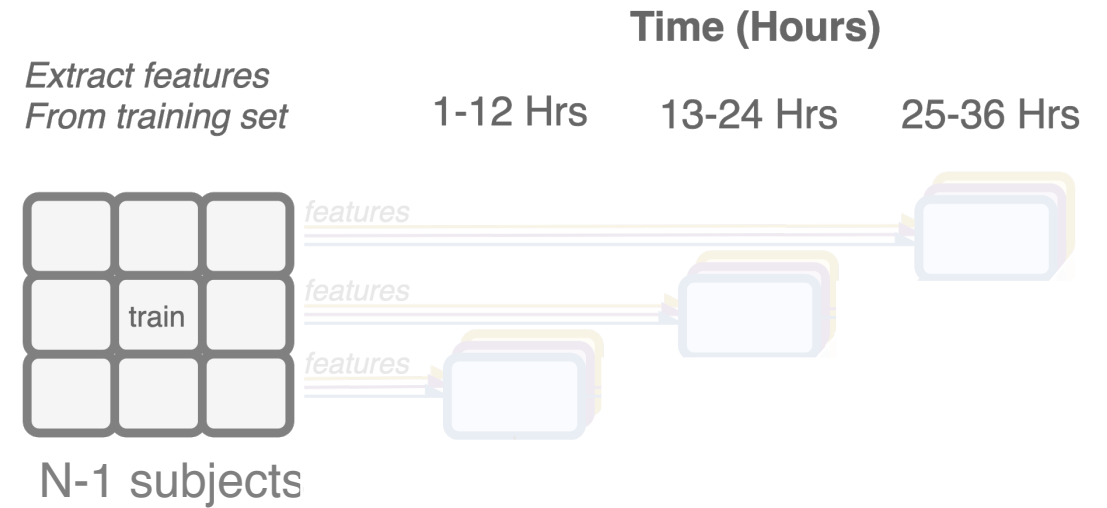
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- **Validation:**
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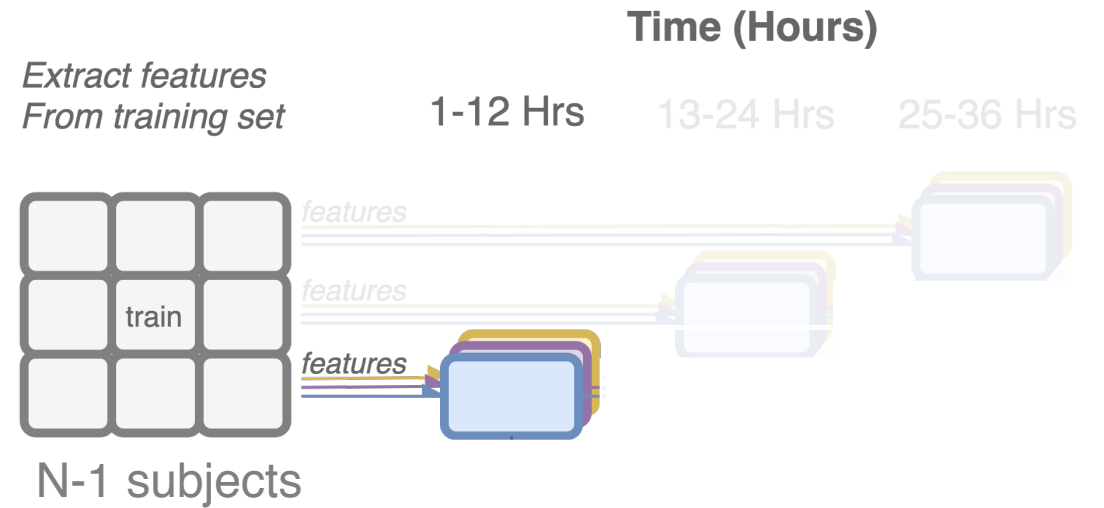
Logistic Regression with *DBN*

- We extracted features in 12 hour intervals:



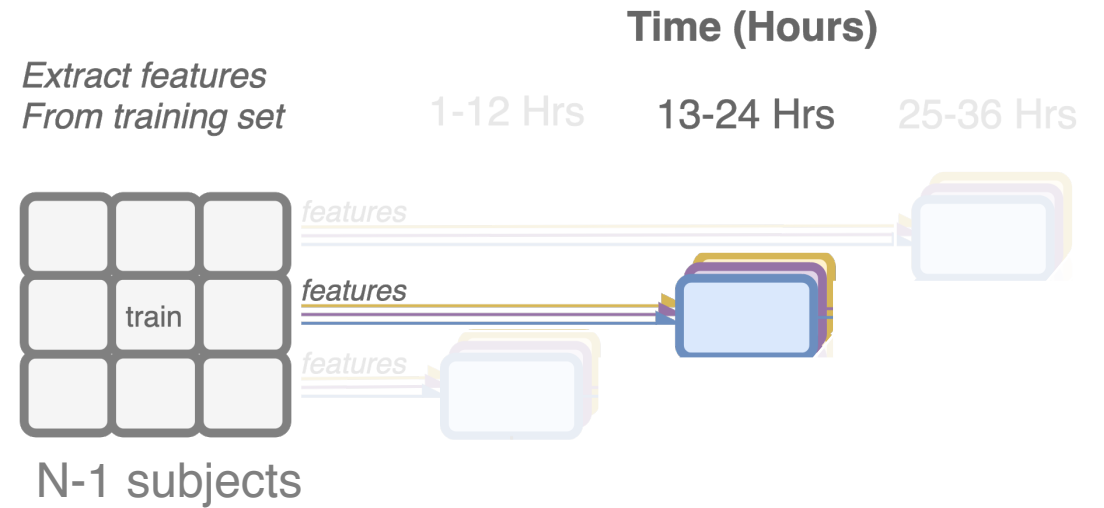
Logistic Regression with *DBN*

- We extracted features in 12 hour intervals:
- 1-12 hours



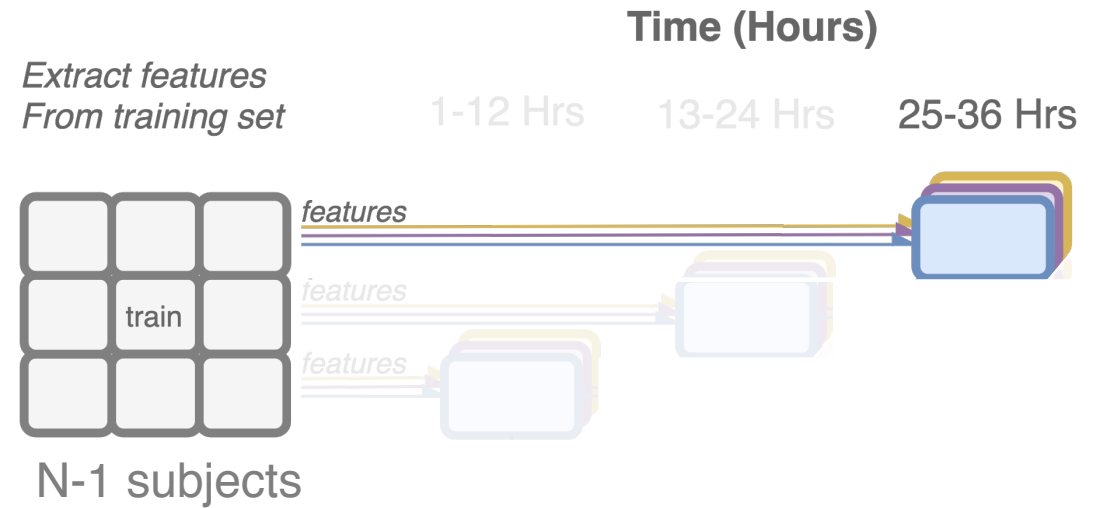
Logistic Regression with *DBN*

- We extracted features in 12 hour intervals:
- 13-24 hours



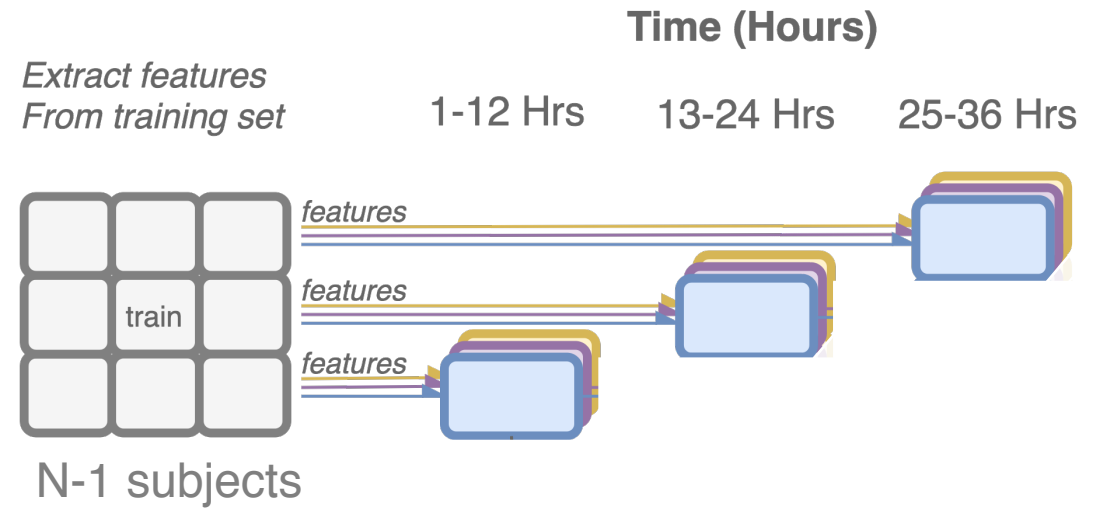
Logistic Regression with *DBN*

- We extracted features in 12 hour intervals:
- 25-36 hours



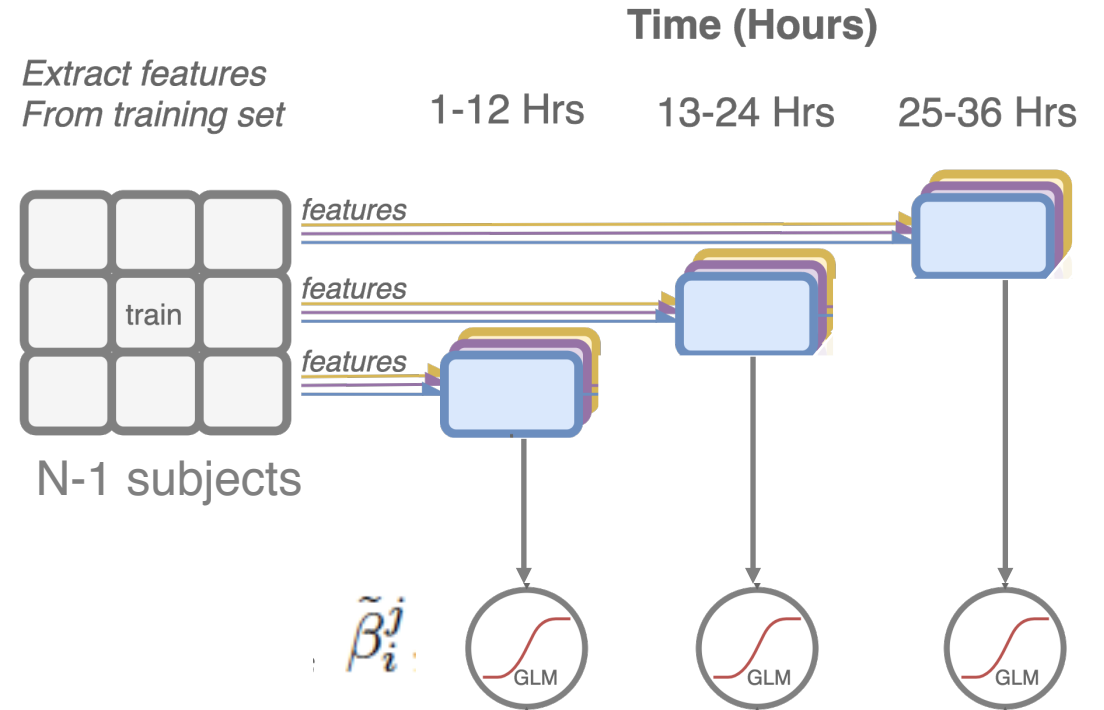
Logistic Regression with *DBN*

- We extracted features in 12 hour intervals:
- etc...



Logistic Regression with *DBN*

- We learn parameters of several logistic regressions: *coefficient measures* $\tilde{\beta}_i^j$
- With corresponding *coefficient measure errors* R_i^j , which are simply the standard errors



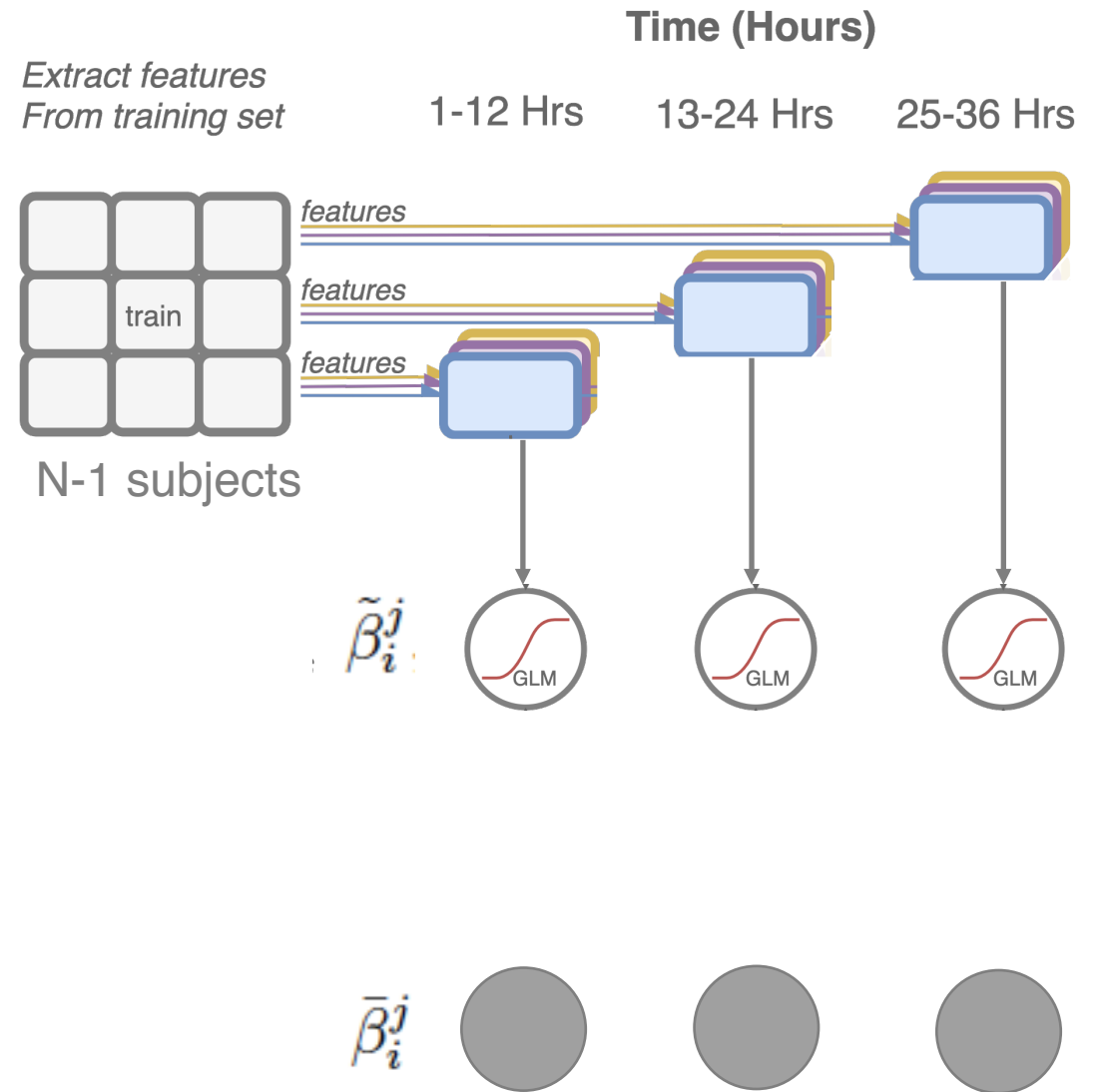
Logistic Regression with *DBN*

- To relate the coefficient measurements across time intervals, we specify a model of coefficient dynamics which provide *coefficient estimates* $\bar{\beta}_i^j$

$$f(\beta_i^{j-1}) = \beta_i^{j-1} + \Delta(\beta_i^{j-1}) = \bar{\beta}_i^j$$

- With *estimate error* denoted by $\bar{P}_i^j$

$$\bar{P}_i^j = P_i^{j-1} + Q$$



Logistic Regression with *DBN*

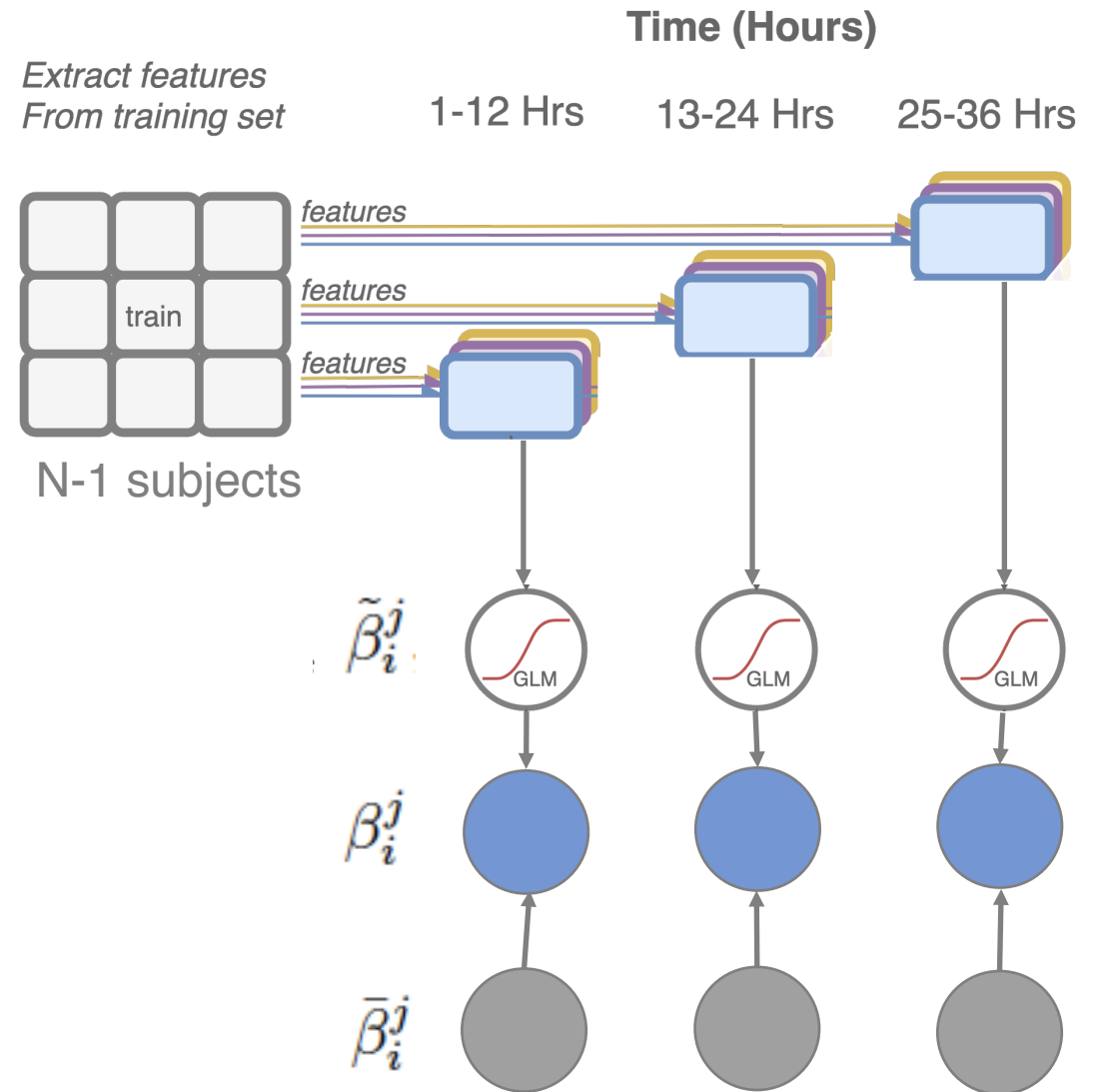
- A simple DBN (the kalman filter) recursively determine the **optimal coefficient estimates**

$$\beta_i^j = \bar{\beta}_i^j + K_i^j[\tilde{\beta}_i^j - \bar{\beta}_i^j],$$

$$K_{(i,j)} = \frac{\bar{P}_i^j}{\bar{P}_i^j + R_i^j}$$

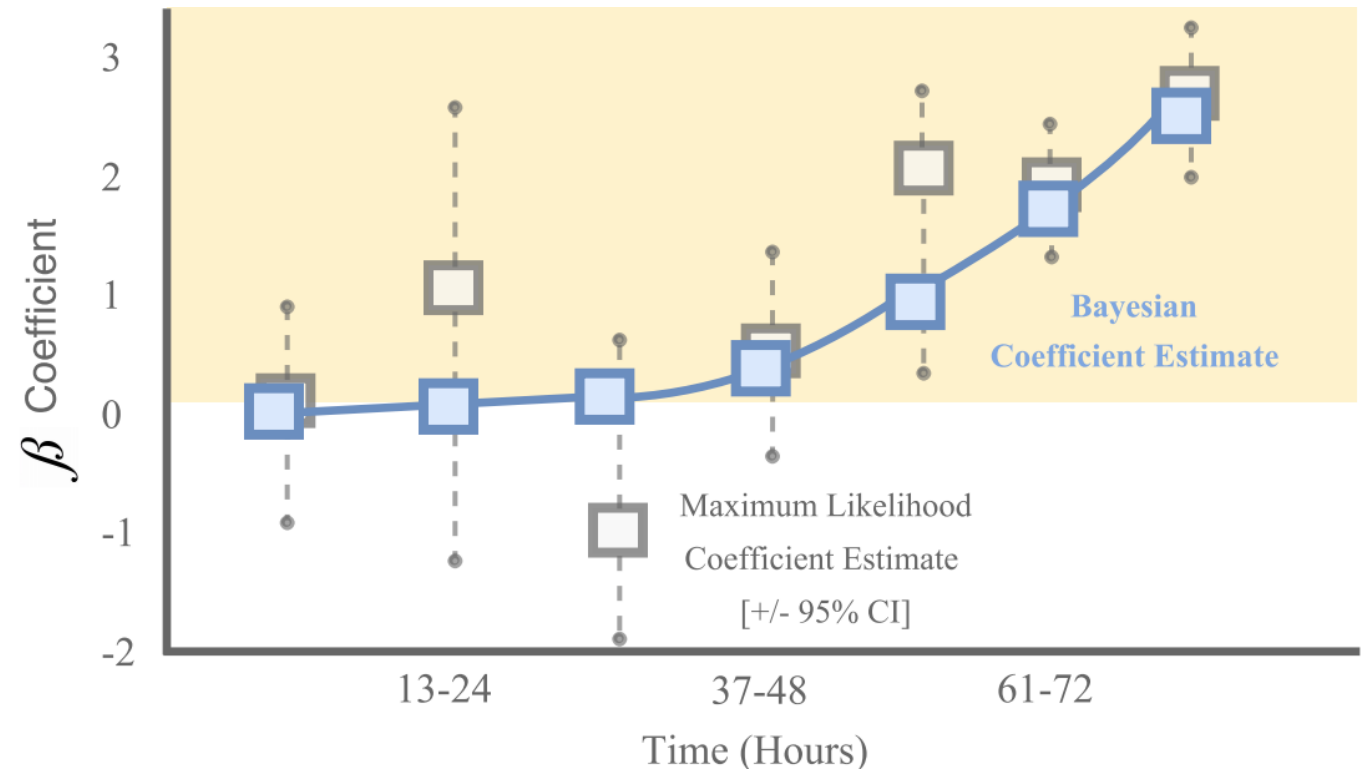
- With coefficient uncertainty

$$P_i^j = (1 - K_i^j)\bar{P}_i^{j-1}$$



Logistic Regression with *DBN*

- **DBN estimates** rely more strongly on prior estimates when present estimates have high standard error



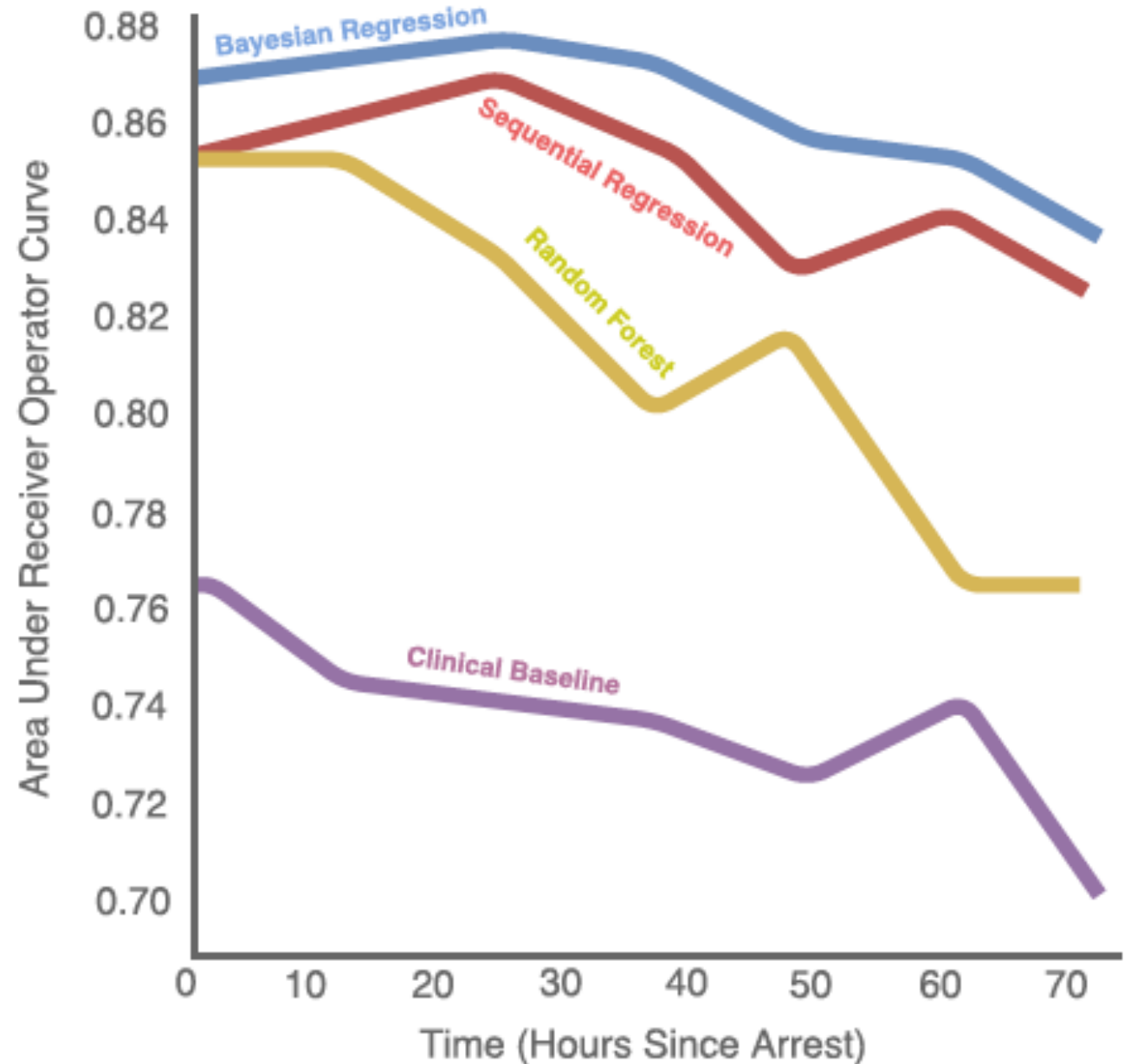
Results

The Sequential Logistic Regression with [DBN](#) had the best overall prognostic performance when compared to several baseline approaches.

Model	Features	Temporal Assumptions	AUC	TPR FPR=0.05	TPR FPR=0.01
Logistic Regression	5 Clinical, 10 EEG	Kalman Filter	0.86	0.49	0.29
Logistic Regression	5 Clinical, 10 EEG	Independent	0.84	0.46	0.26
Logistic Regression	10 EEG	Kalman Filter	0.83	0.47	0.25
Random Forest	5 EEG [2]	Independent	0.82	0.44	0.21
Logistic Regression	10 EEG	Independent	0.81	0.44	0.19
Logistic Regression	5 Clinical	None	0.73	0.26	0.11

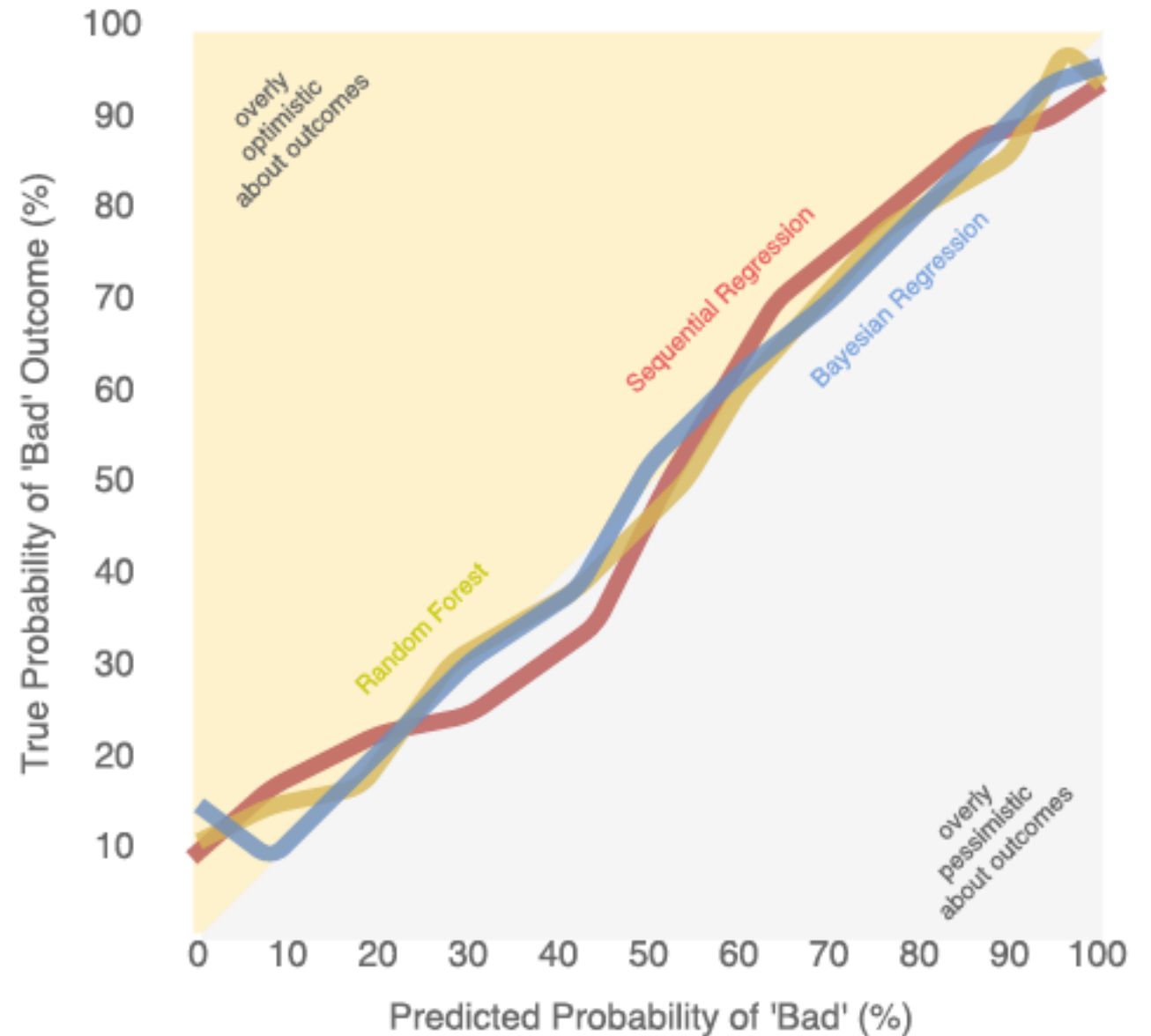
Results over time

- The **DBN approach** had the best performance over time (peak AUC: 0.87)
- performance decreases over time (min AUC: 0.84)



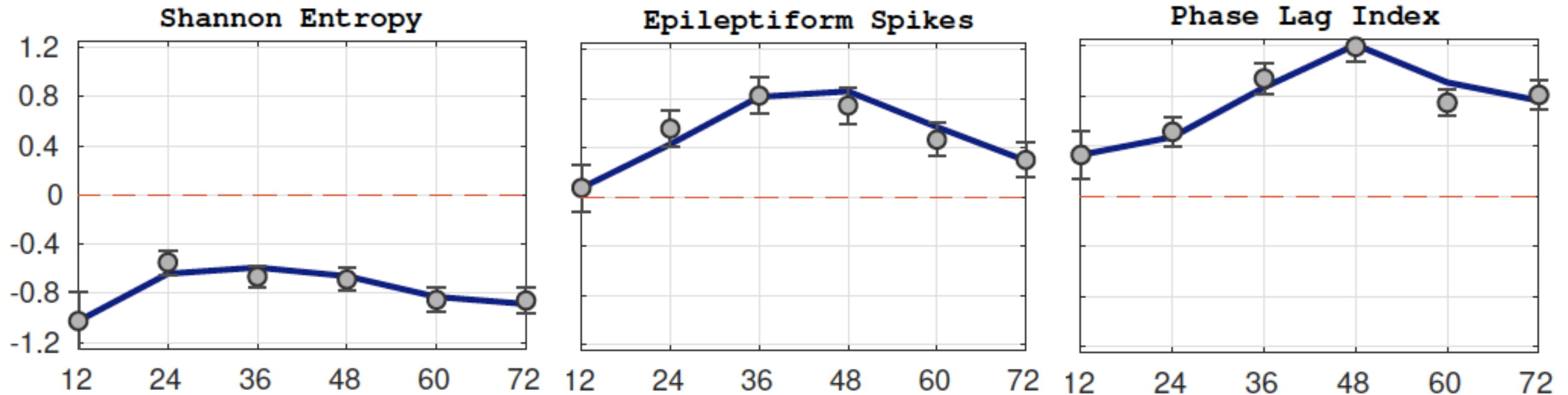
Calibration

- The **DBN approach** was the best calibrated of the tested approaches
- The direction of mis-calibration was '*optimistic*', tending to over-estimate '*good*' outcomes.



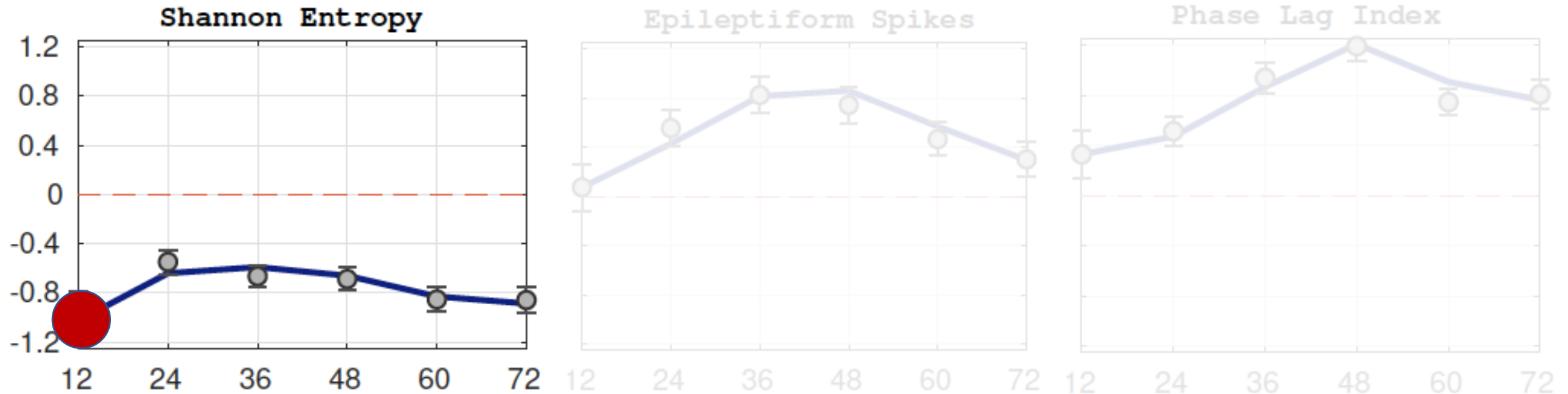
Feature coefficients over time

Model coefficients evolve over time in a sensible way, and are **interpretable**.



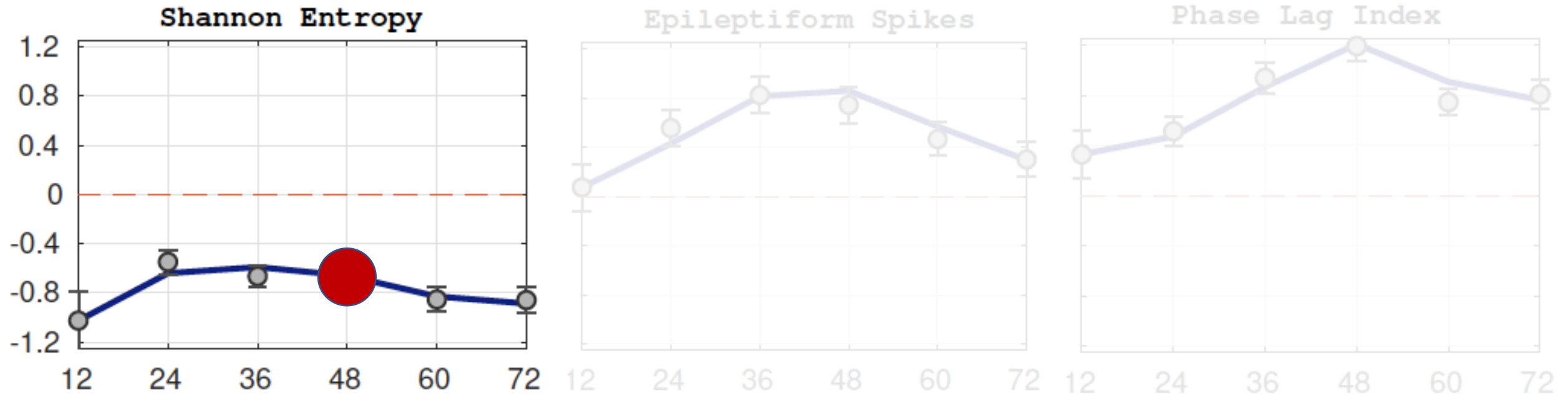
Feature coefficients over time

Entropy 1 std above the mean at 12 hours → 0.33 times as likely to have a bad outcome



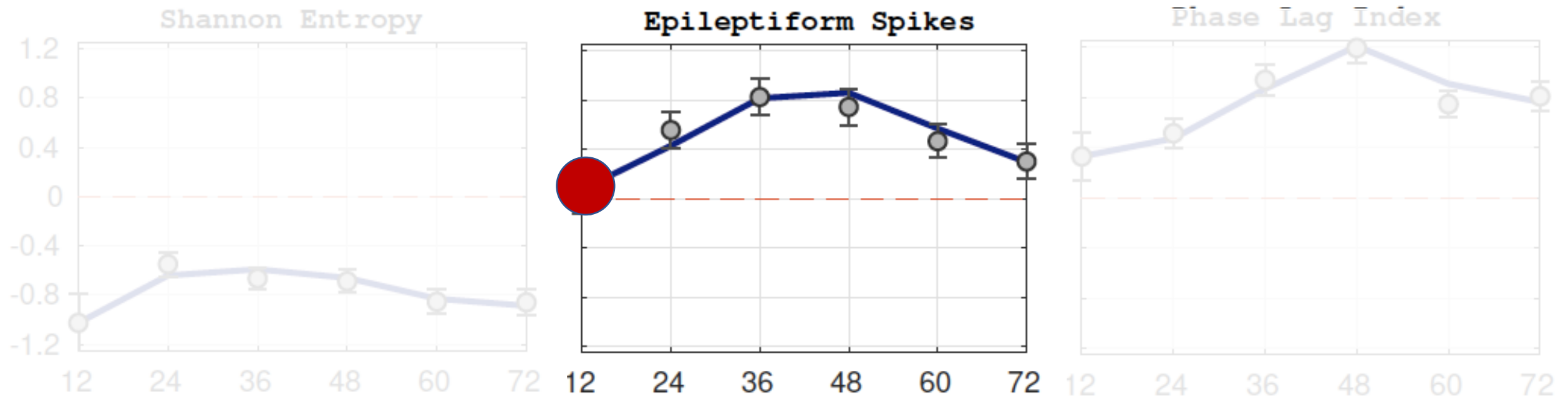
Feature coefficients over time

Entropy 1 std above the mean at 48 hours → 0.5 times as likely to have a bad outcome



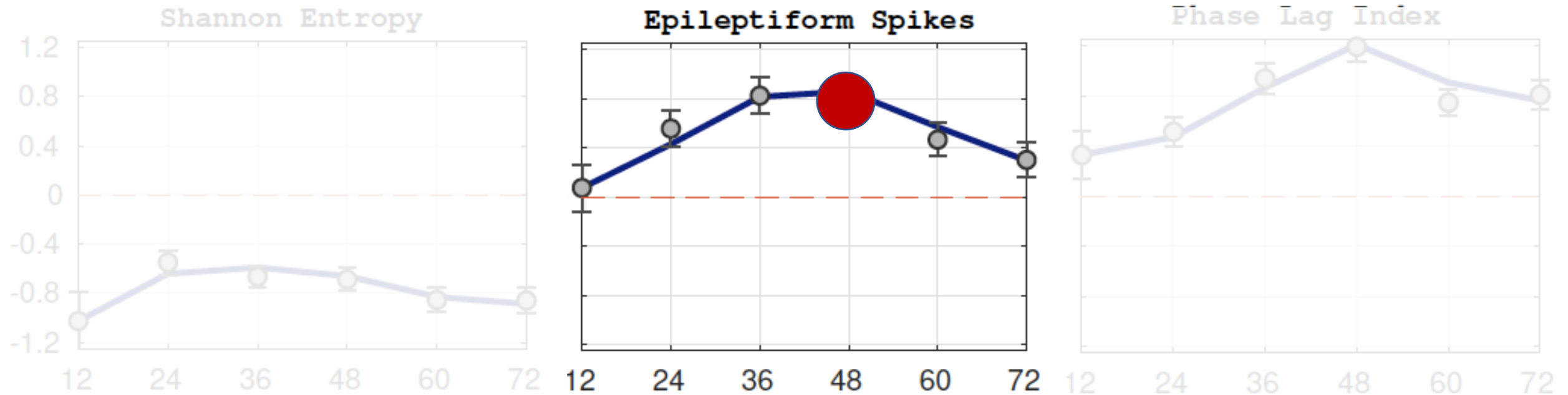
Feature coefficients over time

Epileptiforms 1 std below the mean at **12 hours** → **1.1** times as likely to have a bad outcome



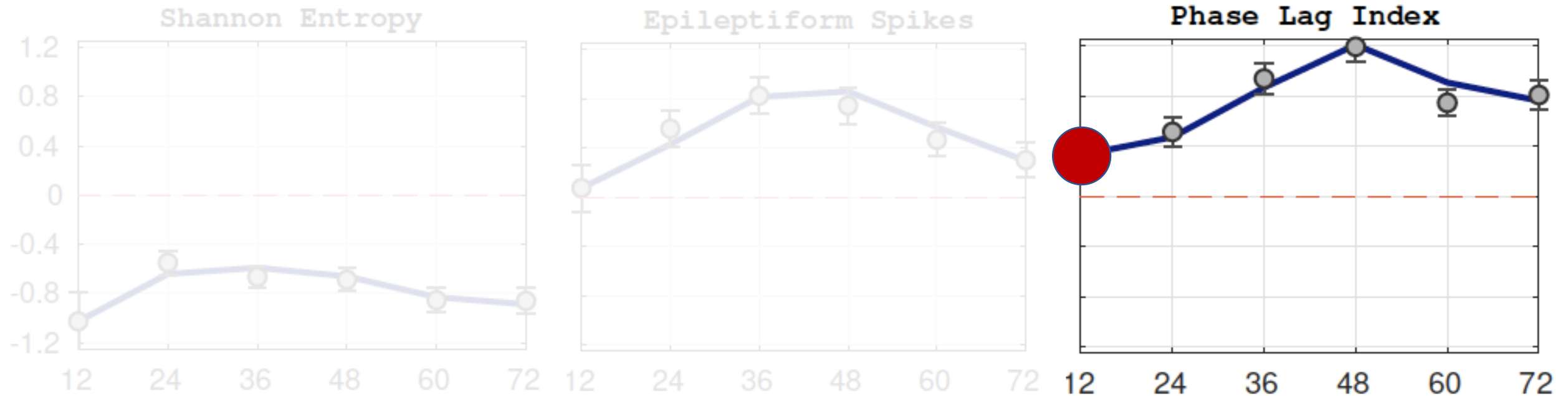
Feature coefficients over time

Epileptiforms 1 std below the mean at **48 hours** → **2.2** times as likely to have a bad outcome



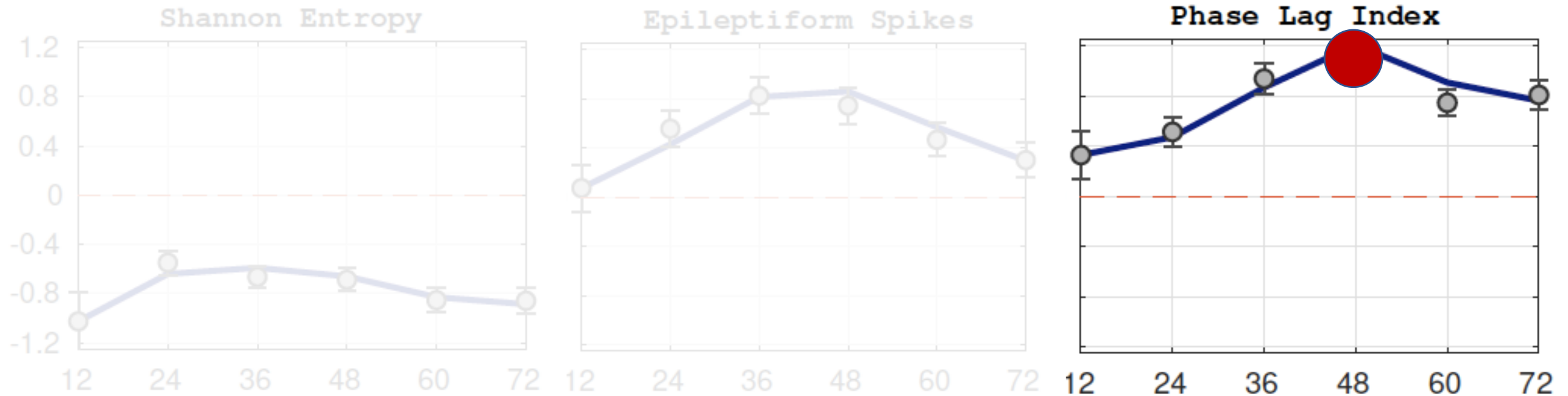
Feature coefficients over time

PLI 1 std below the mean at **12 hours** → **1.5** times as likely to have a bad outcome



Feature coefficients over time

PLI 1 std below the mean at **48 hours** → **3** times as likely to have a bad outcome



Pros/Cons of the Approach

- Advantages

- Features are lightweight: 10 in total
- Model is interpretable and may aid providers without formal deployment
- Excellent LOOCV prognostication performance relative to baselines

- Disadvantages

- Without 'memories', performance decreases over time
- Possibility that important features were overlooked
- Does not account for spatial information

Three Approaches

Feature Based:

- ~~1. Sequential Logistic Regression with 'Elastic' memories.~~
- ~~2. Sequential Logistic Regression with Dynamic Bayesian network constraints~~

Data Driven

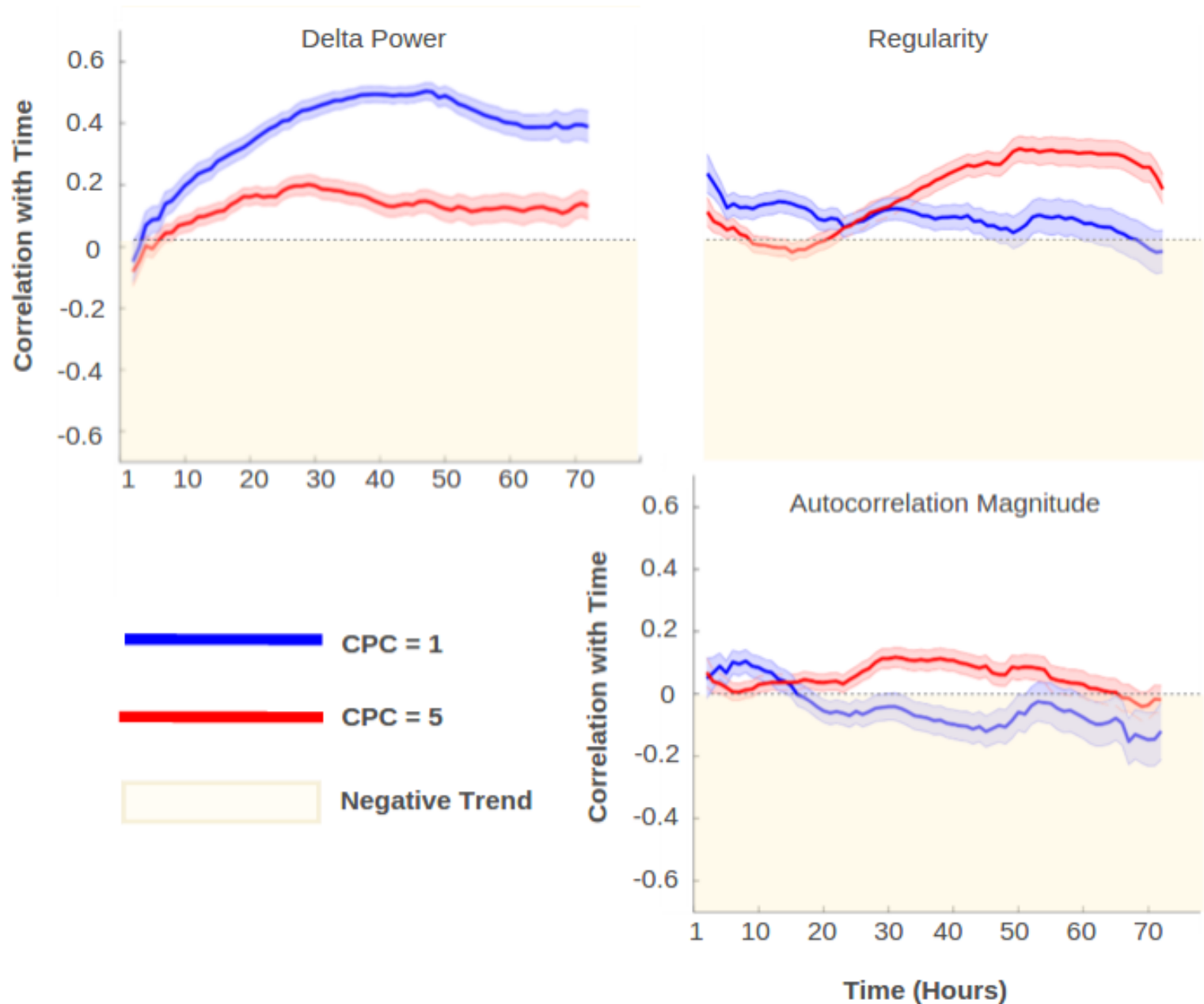
- 3. Deep neural networks

Limitations of the feature-based approaches

- Requires thoughtful pre-processing pipeline
- Requires computation of features
- By averaging over channels, features eliminate spatial information
- Possibility that certain features might have been missed

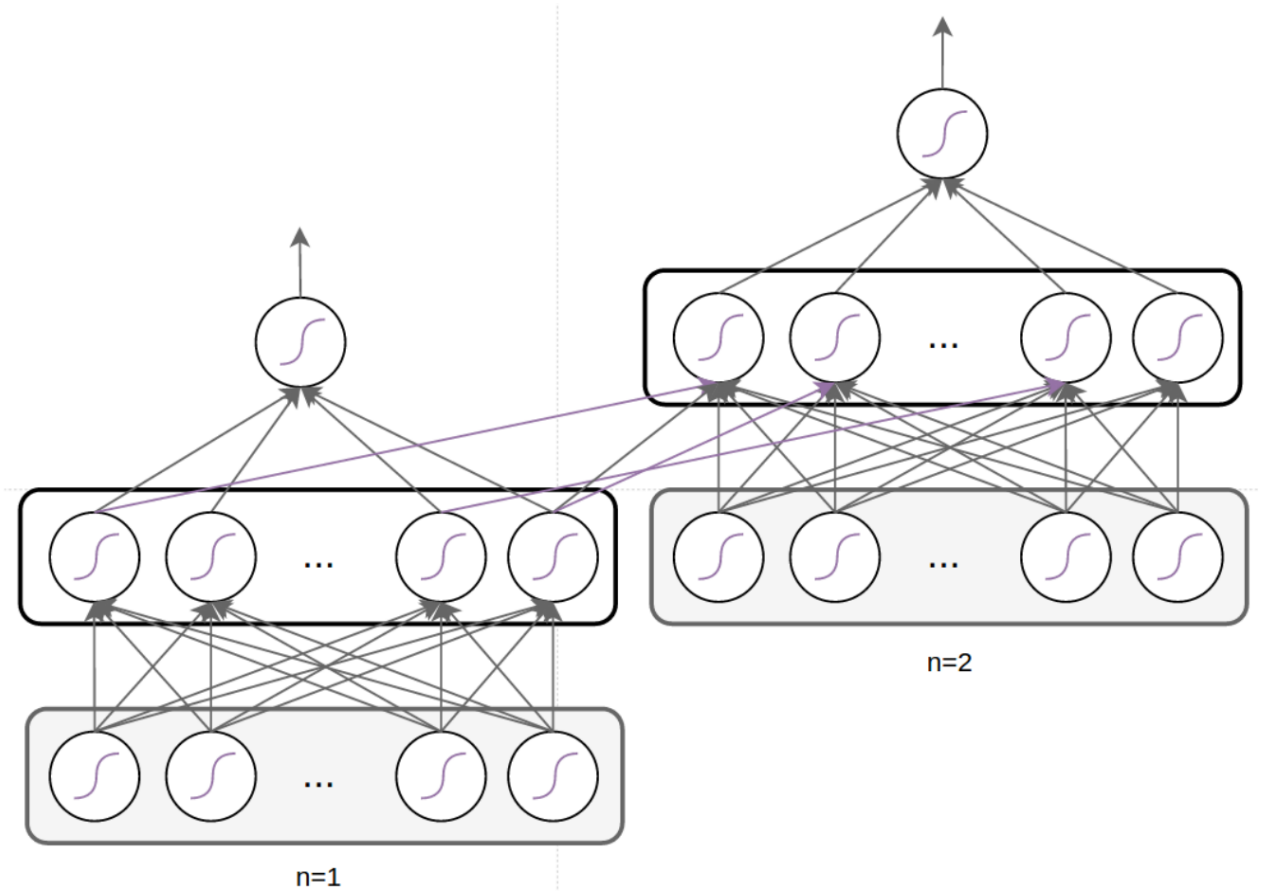
Motivation

- Even if all 57 features were used, **derivatives** of features may be useful features



Motivation

- Deep Neural Networks provide a potential solution to this problem because they **derive features from the data automatically**

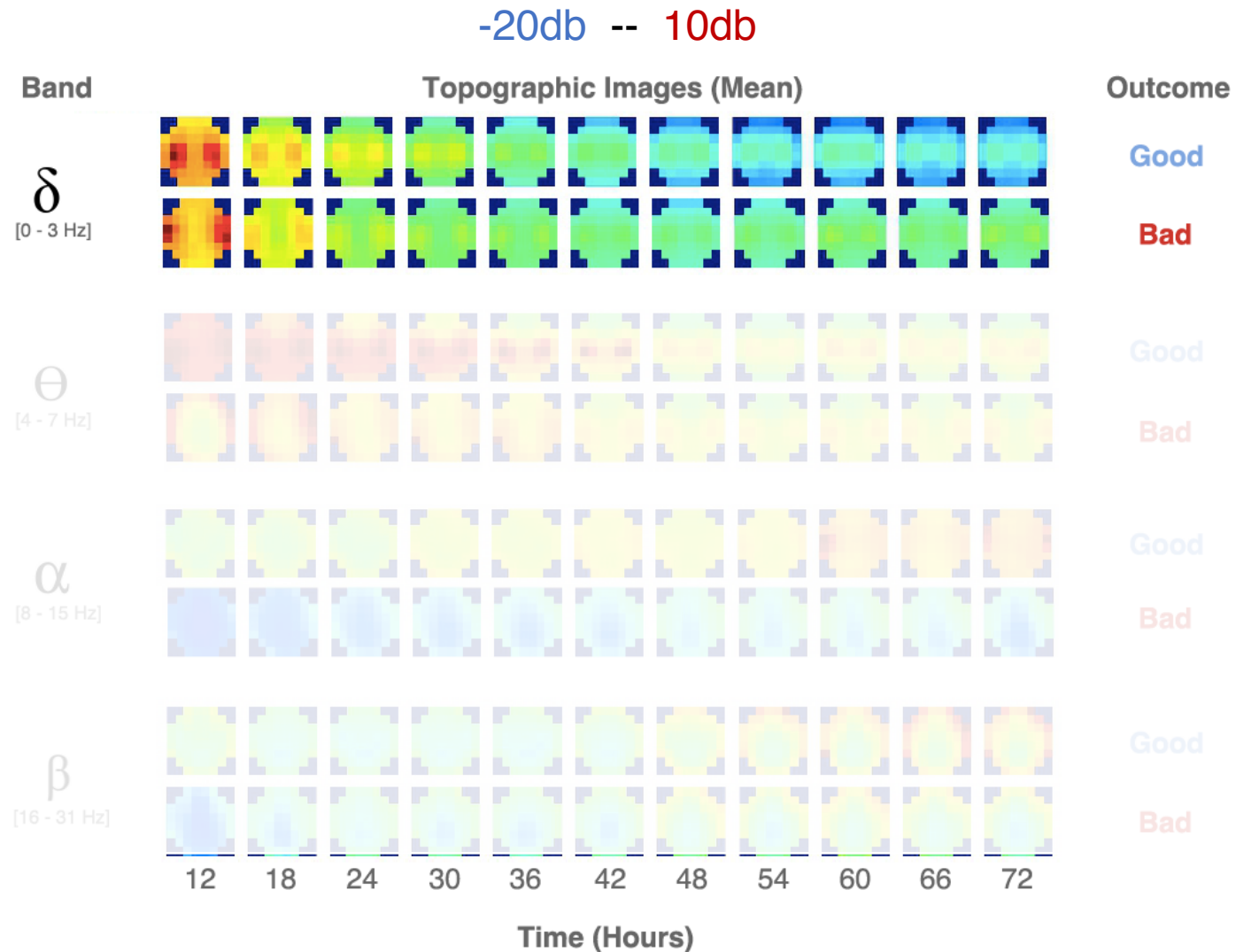


Deep Networks

- $n = 724$ patients
- 4 topographic energy plots:
[0-3, 4-7, 8-15, 16-31] Hz
- Pseudo-subject generation
- Validation:
Leave-one-institution-out

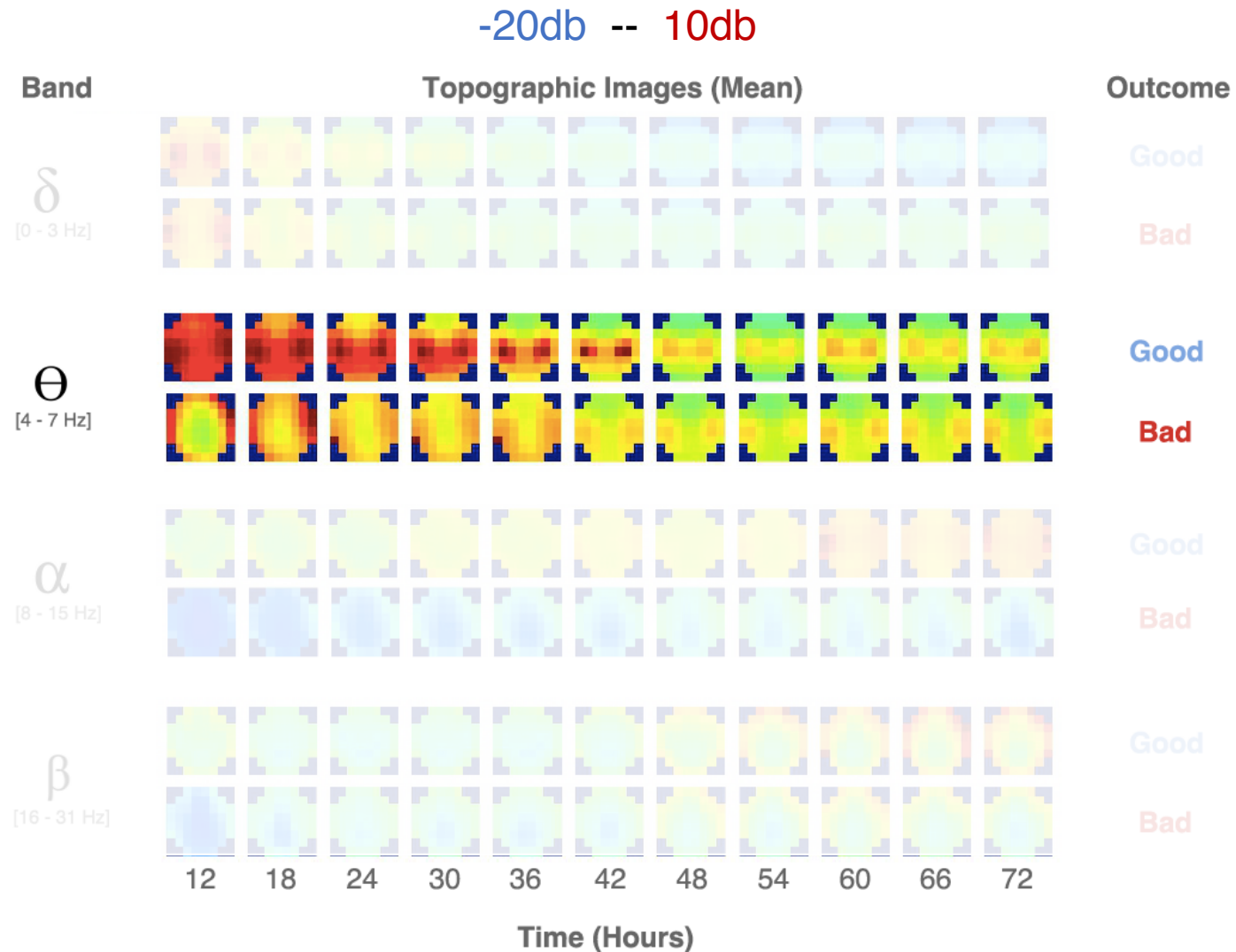
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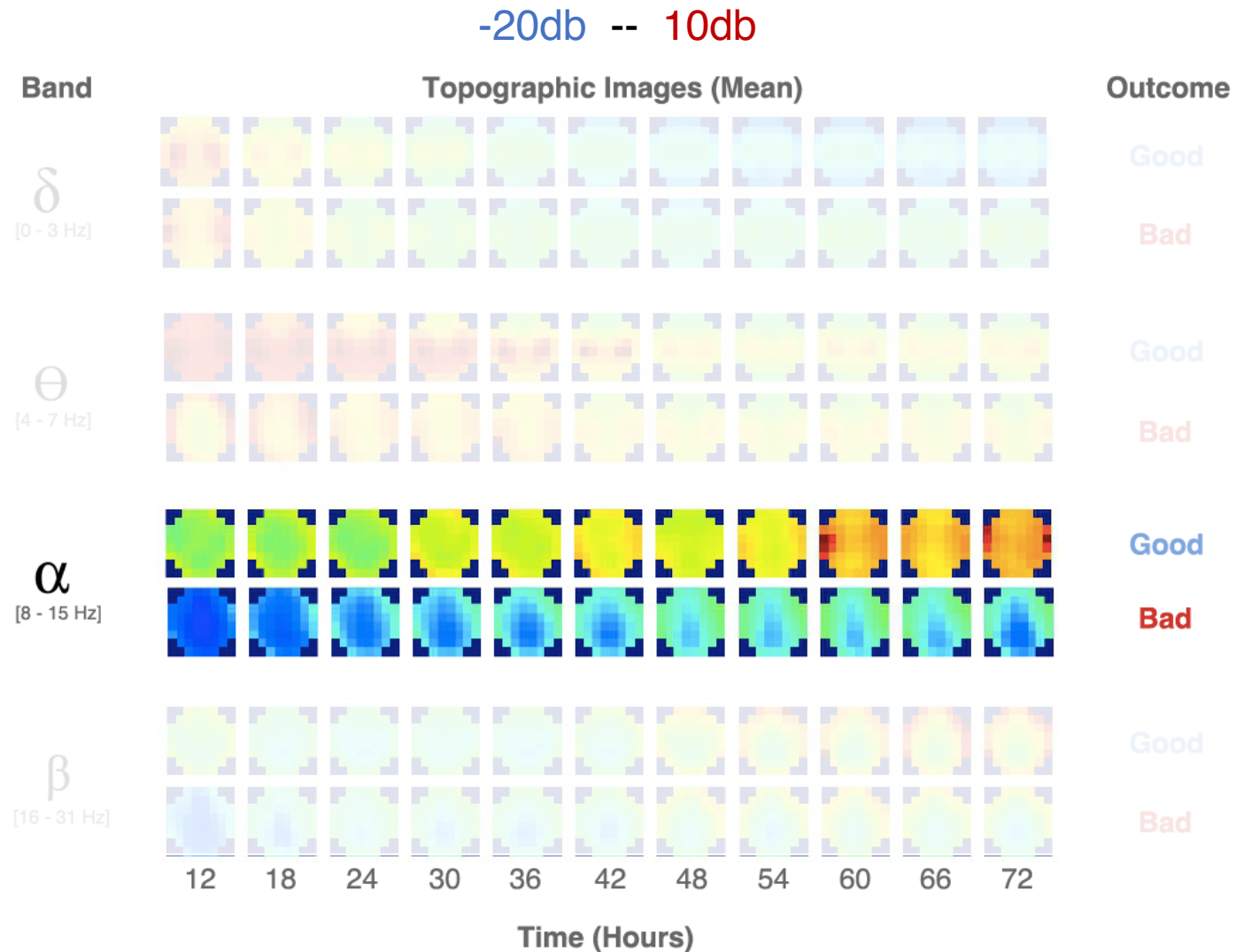
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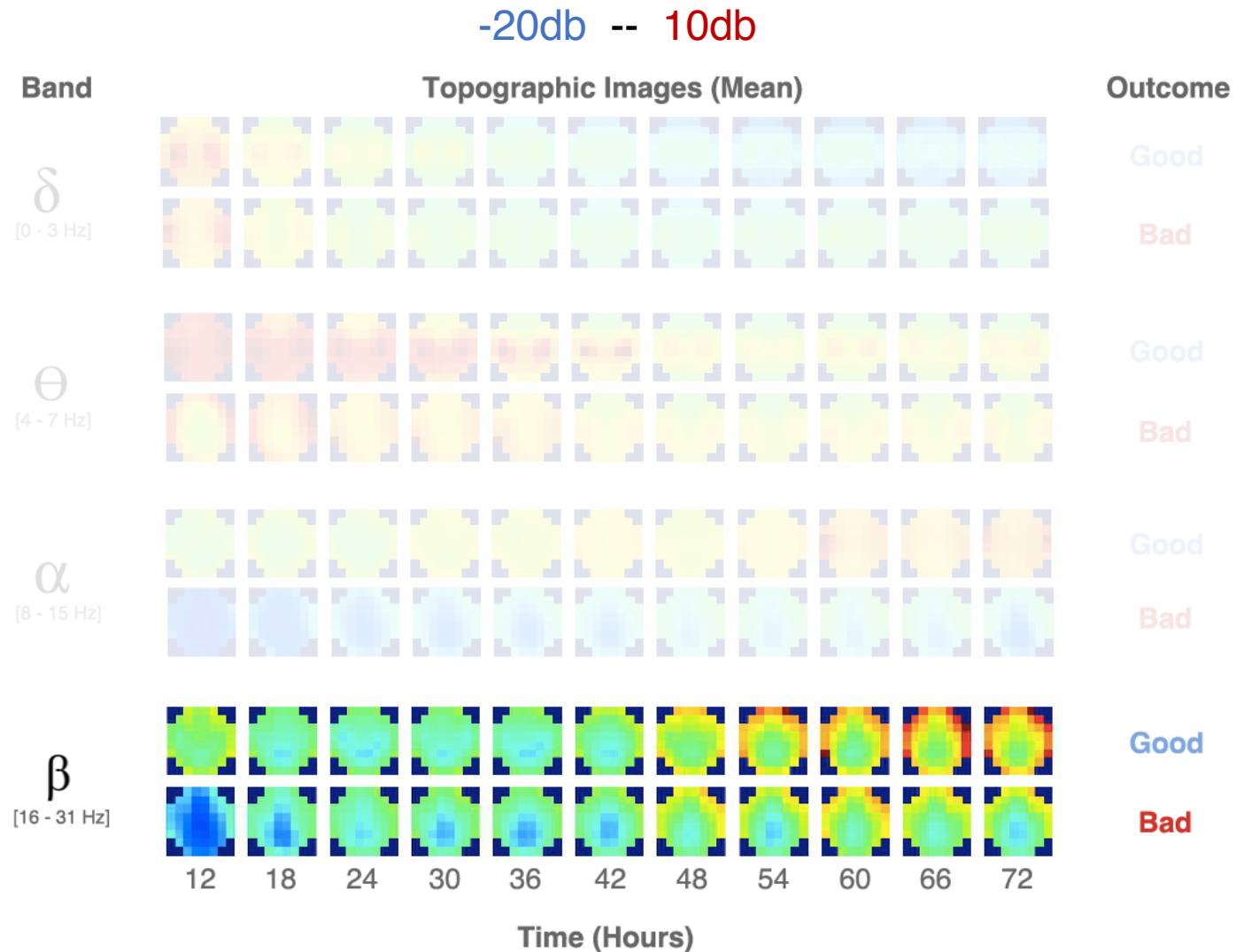
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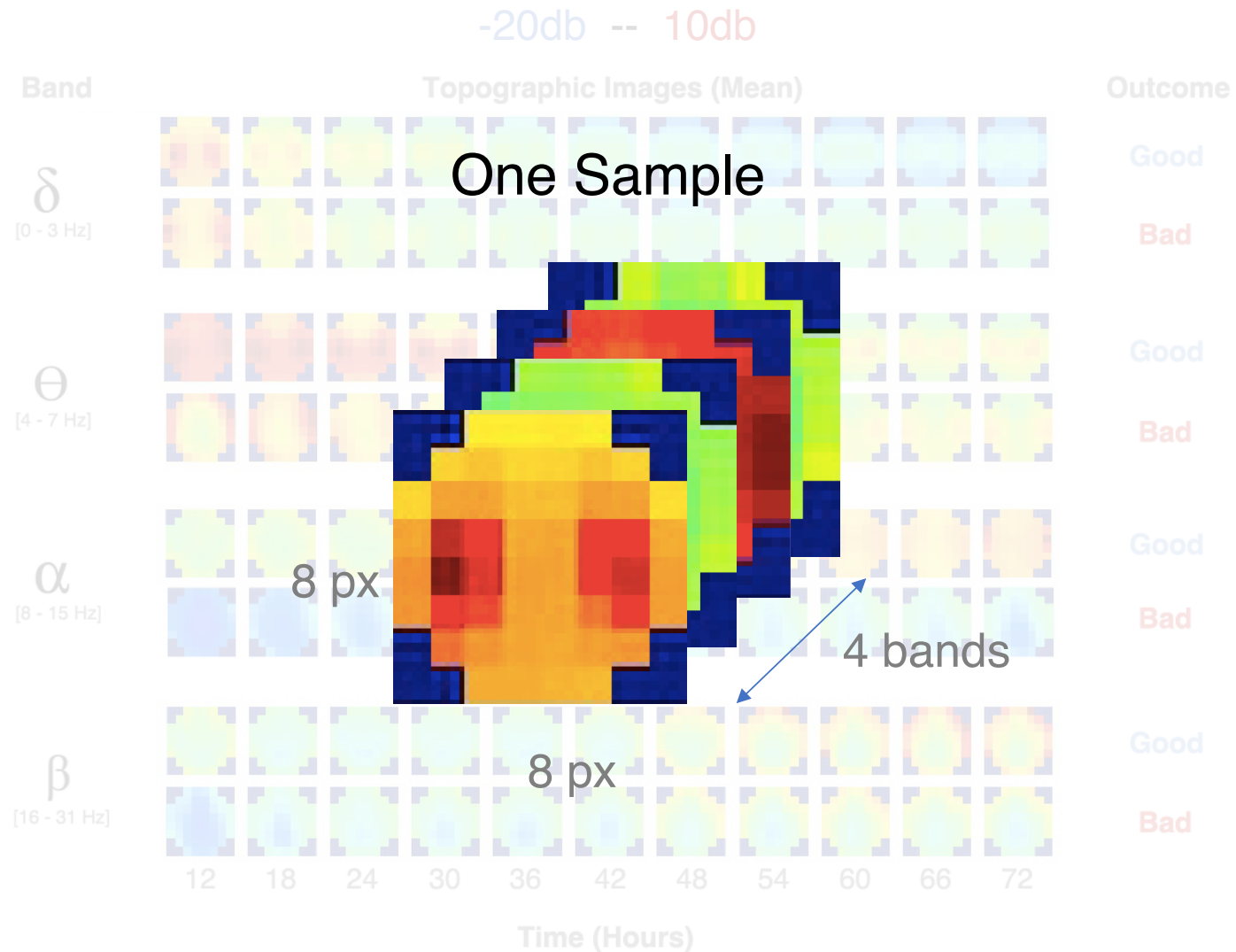
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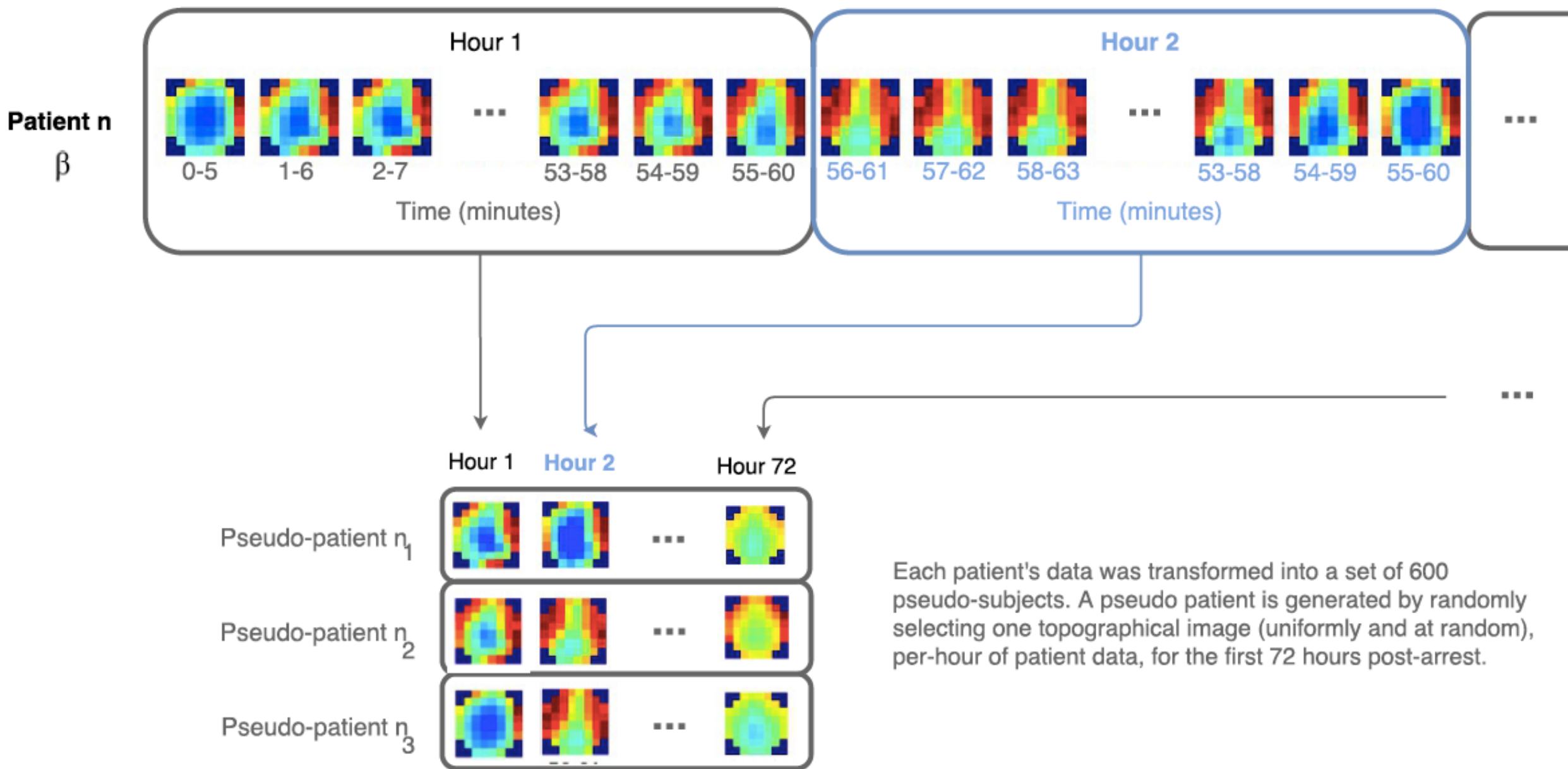


Figure 8.3: Pseudo-patient Generation.



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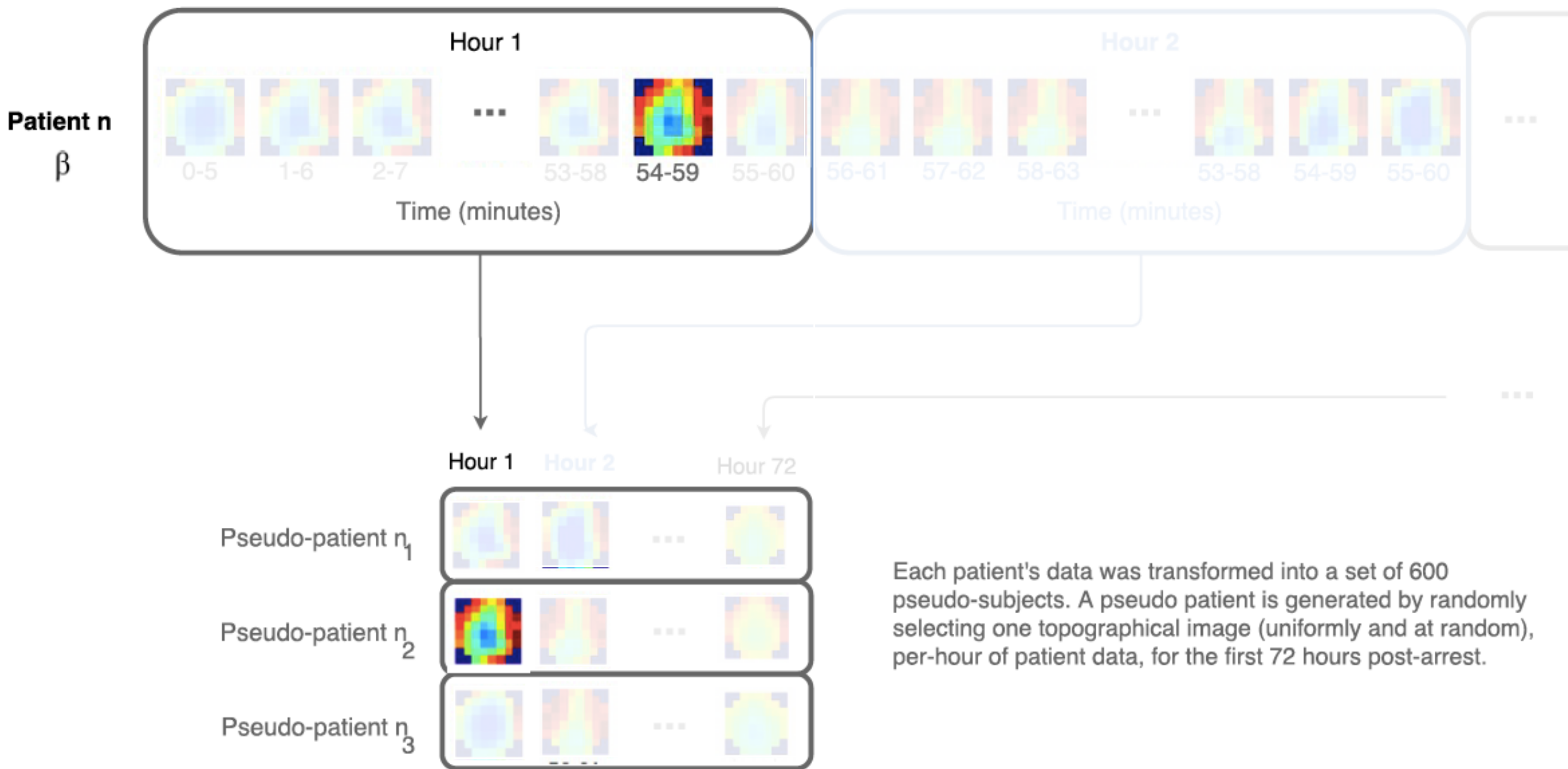


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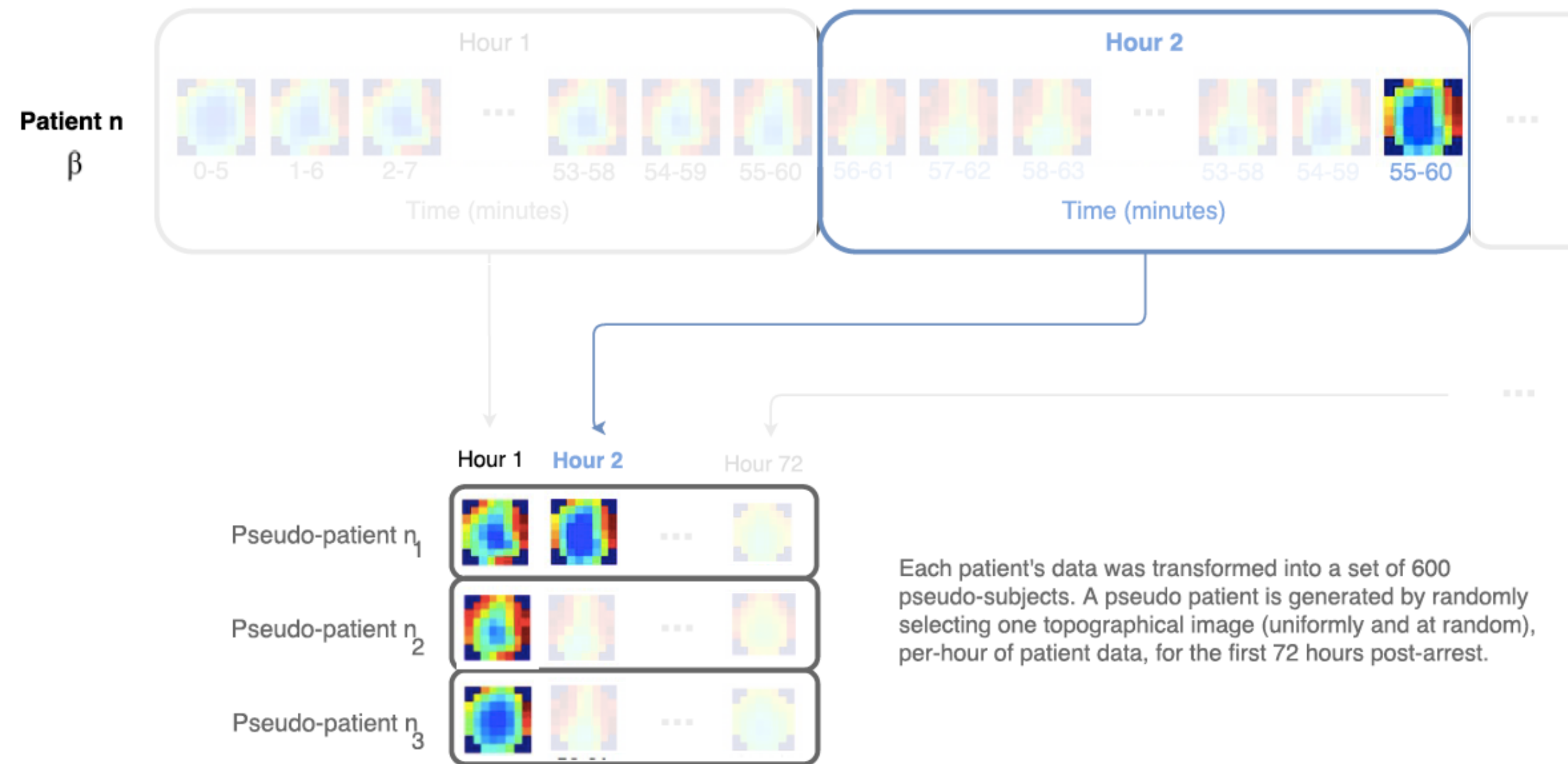


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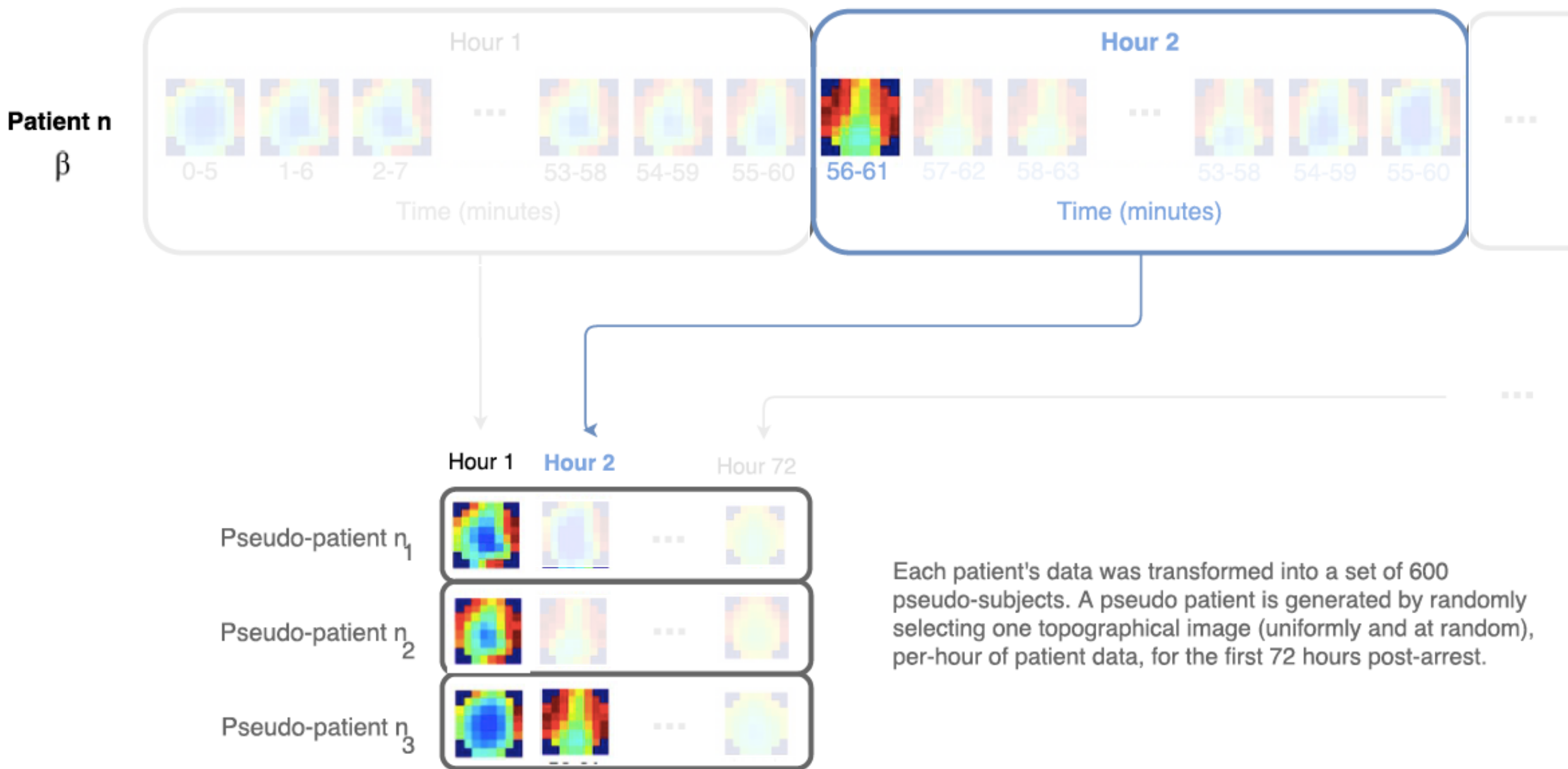


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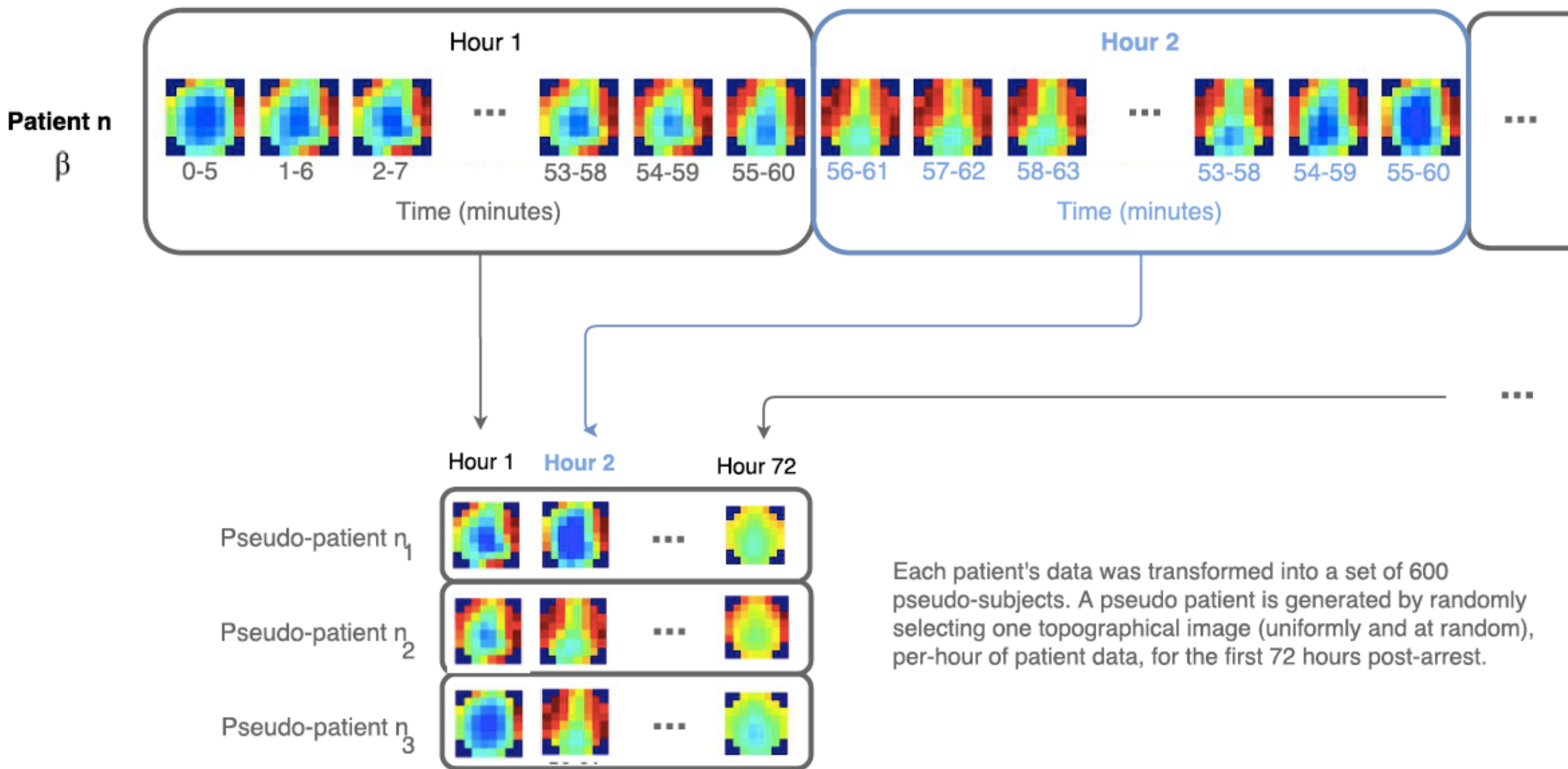
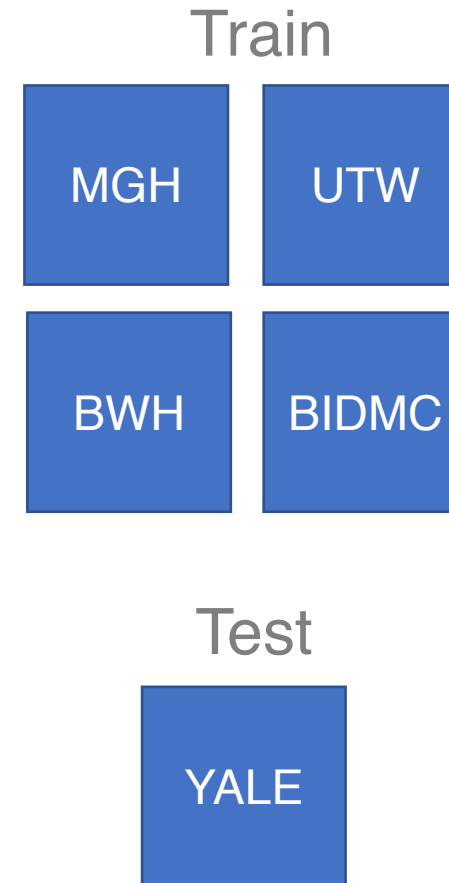


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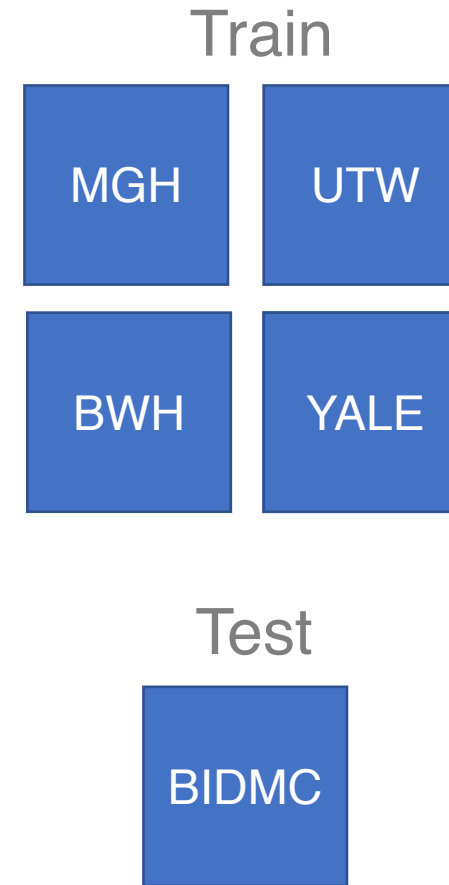
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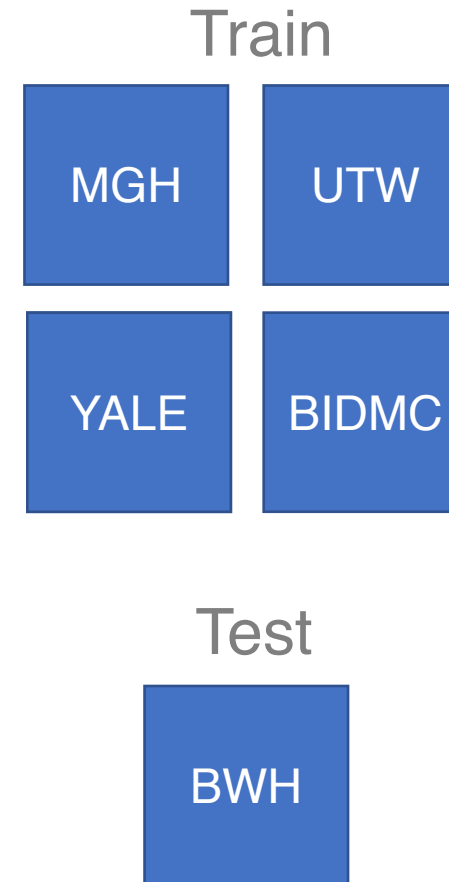
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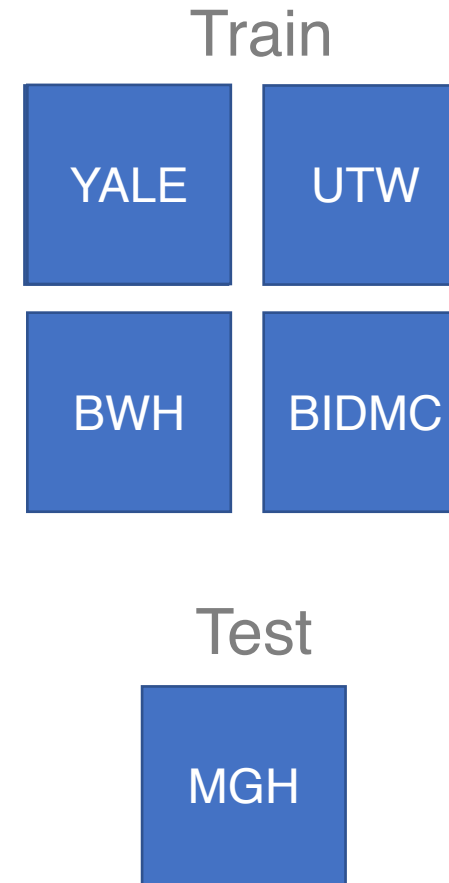
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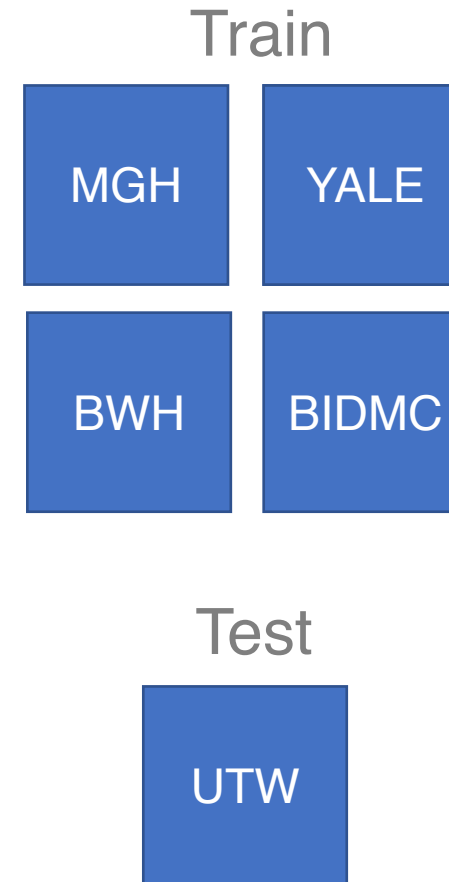
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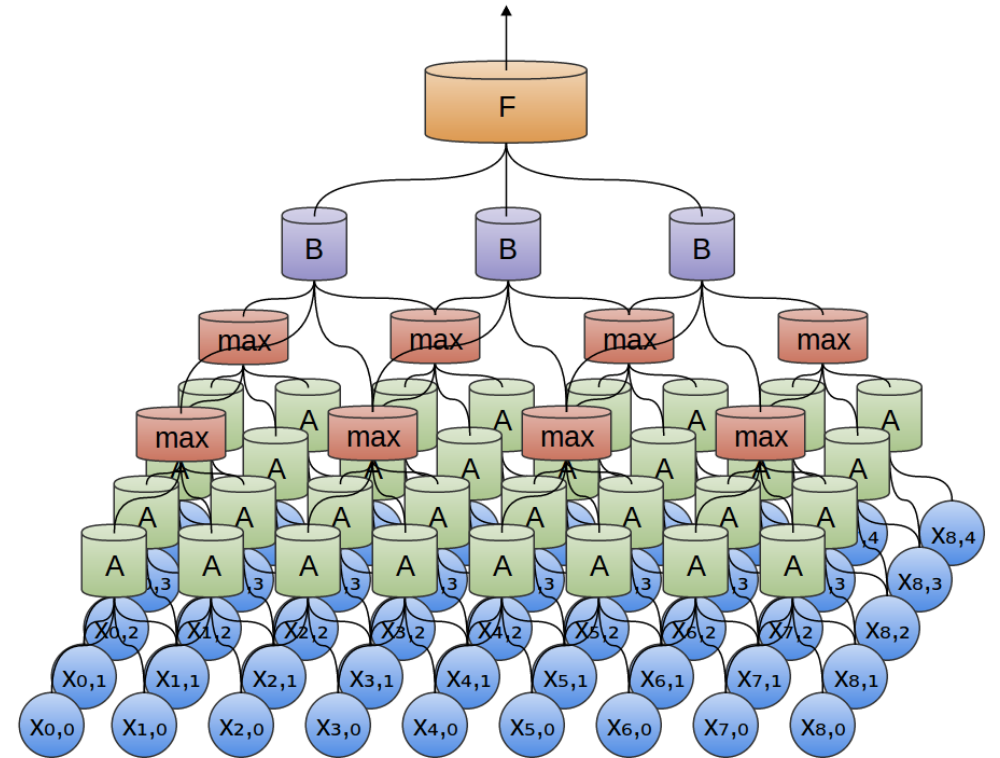


Deep Networks

- 300 topologies were tested
- 100, 2 Dimensional Convolutional Neural Networks
- 100, 3 Dimensional Convolutional Neural Networks
- 100, Long-term Recurrent Convolutional Networks

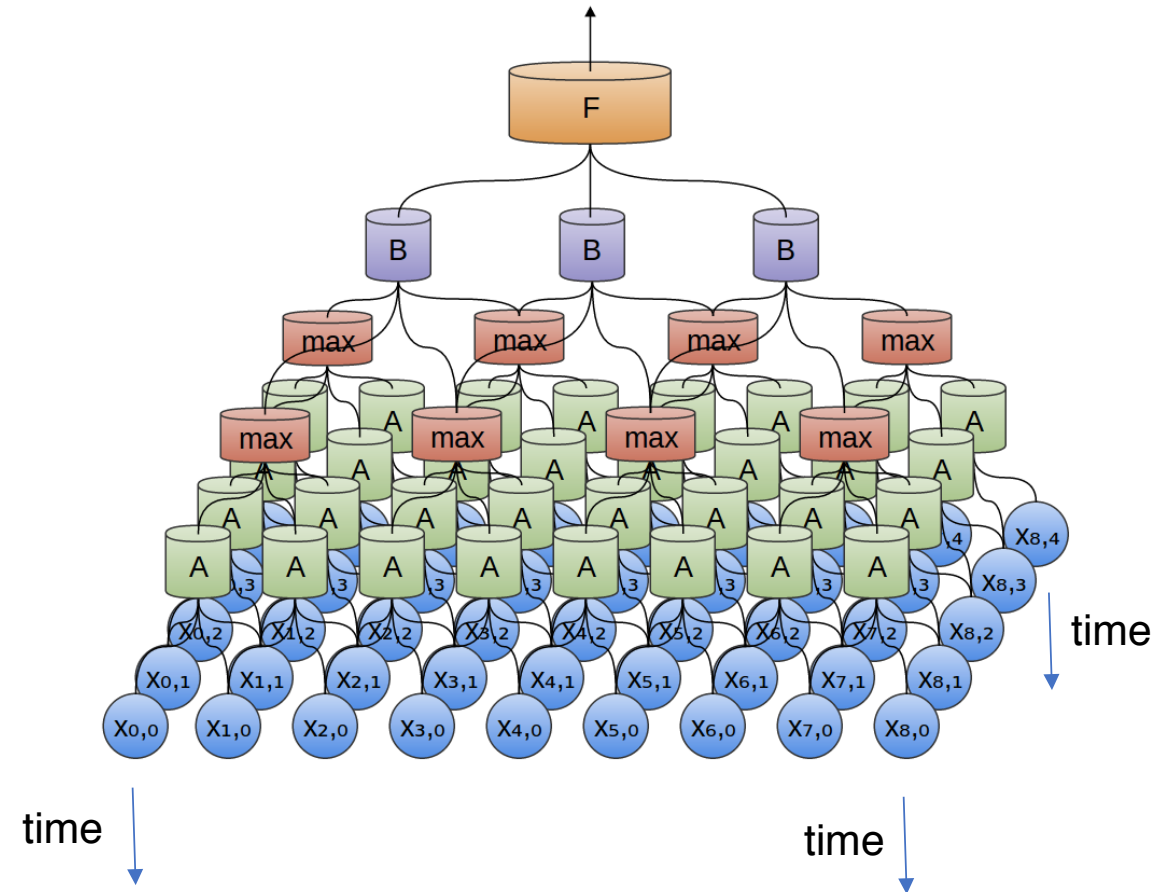
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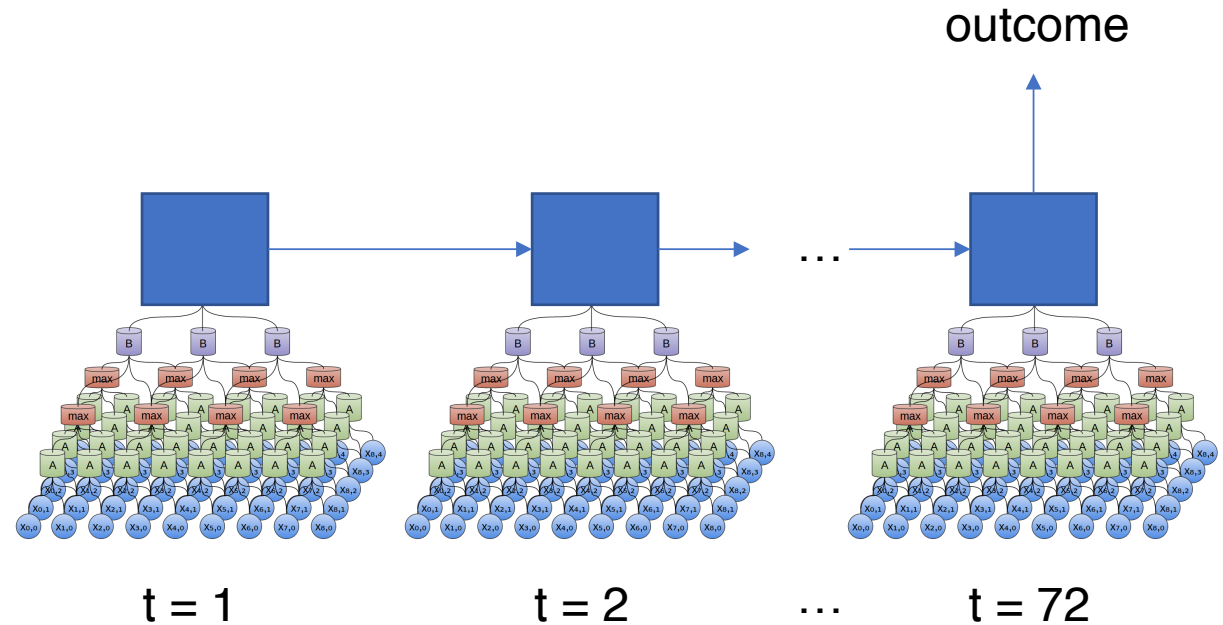
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Deep Networks

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Results

- 3D CNNs provide performance on par with the best-performing feature-based approaches.

	AUROC	TPR FPR=0	TPR FPR=1%	TPR FPR=5%
Neural Networks				
2D CNN	0.71 (0.09)	0 (0.0)	0.09 (0.06)	0.23 (0.10)
**3D CNN	0.81 (0.04)	0.24 (0.05)	0.30 (0.05)	0.45 (0.09)
LRCN	0.79 (0.08)	0.19 (0.11)	0.34 (0.15)	0.48 (0.15)
SVM				
*Linear	0.76 (0.13)	0.17 (0.18)	0.21 (0.16)	0.32 (0.19)
Quadratic	0.72 (0.14)	0.14 (0.09)	0.16 (0.09)	0.26 (0.12)
Fine Gaussian	0.75 (0.14)	0.18 (0.14)	0.2 (0.12)	0.31 (0.19)
Medium Gaussian	0.56 (0.03)	0.01 (0.02)	0.01 (0.02)	0.06 (0.04)
Coarse Gaussian	0.71 (0.13)	0.07 (0.12)	0.08 (0.12)	0.15 (0.1)
Discriminant Analysis				
Linear	0.77 (0.15)	0.21 (0.13)	0.23 (0.14)	0.34 (0.25)
*Quadratic	0.78 (0.14)	0.22 (0.13)	0.25 (0.14)	0.4 (0.22)
Cubic	0.72 (0.13)	0 (0)	0 (0)	0.15 (0.24)
Decision Trees				
Simple	0.68 (0.11)	0 (0)	0 (0)	0 (0)
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Complex	0.69 (0.07)	0 (0)	0 (0)	0 (0)
*RUS Boosted	0.8 (0.1)	0.25 (0.2)	0.25 (0.2)	0.39 (0.17)
Ensemble Boosted	0.74 (0.12)	0.12 (0.17)	0.12 (0.17)	0.14 (0.19)
Ensemble Bagged	0.77 (0.1)	0.09 (0.14)	0.11 (0.13)	0.22 (0.15)

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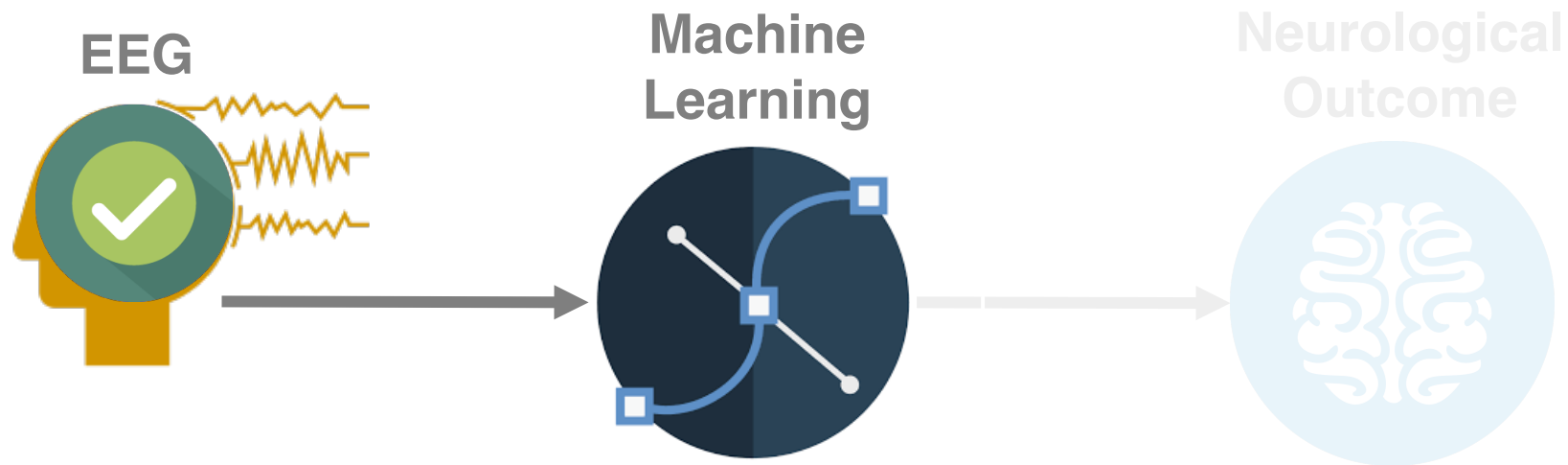
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Pros/Cons of the Approach

- Advantages
 - No feature engineering
 - No pre-processing required
 - Performance is on par with, or exceeds, feature-based approaches
- Disadvantages
 - Requires 72 hours of data
 - Requires tuning of 300K+ parameters
 - Models are difficult to interpret

Develop *time-sensitive* modeling approaches

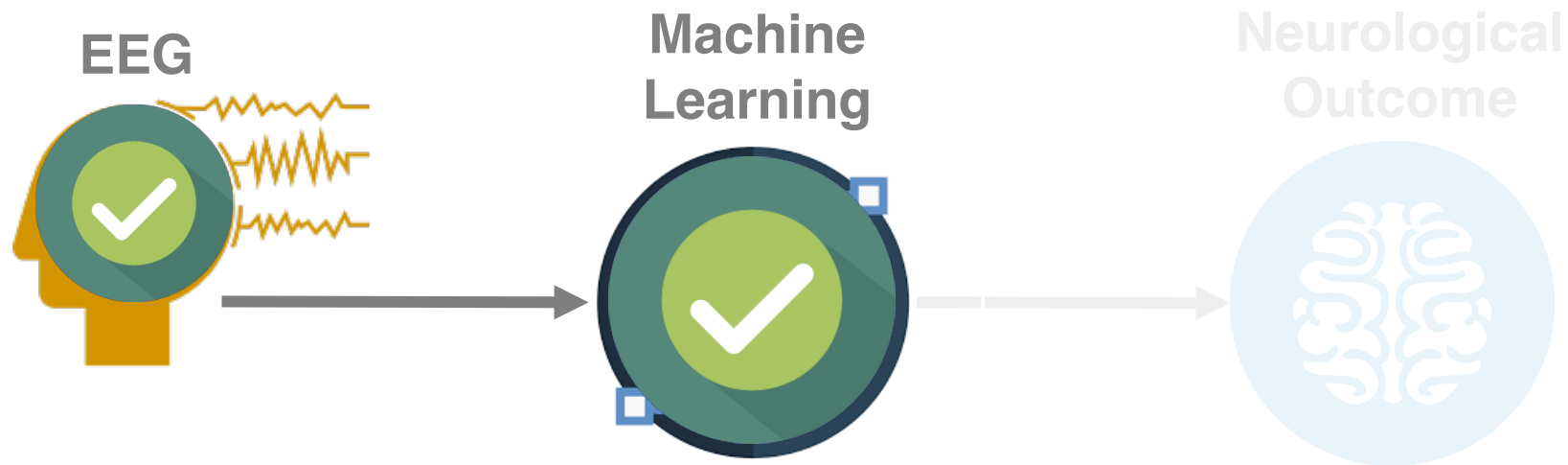


1. Collected an EEG archive 2x larger than largest set previously described in the literature

2. Time-sensitive

3. Deployable

Develop *time-sensitive* modeling approaches

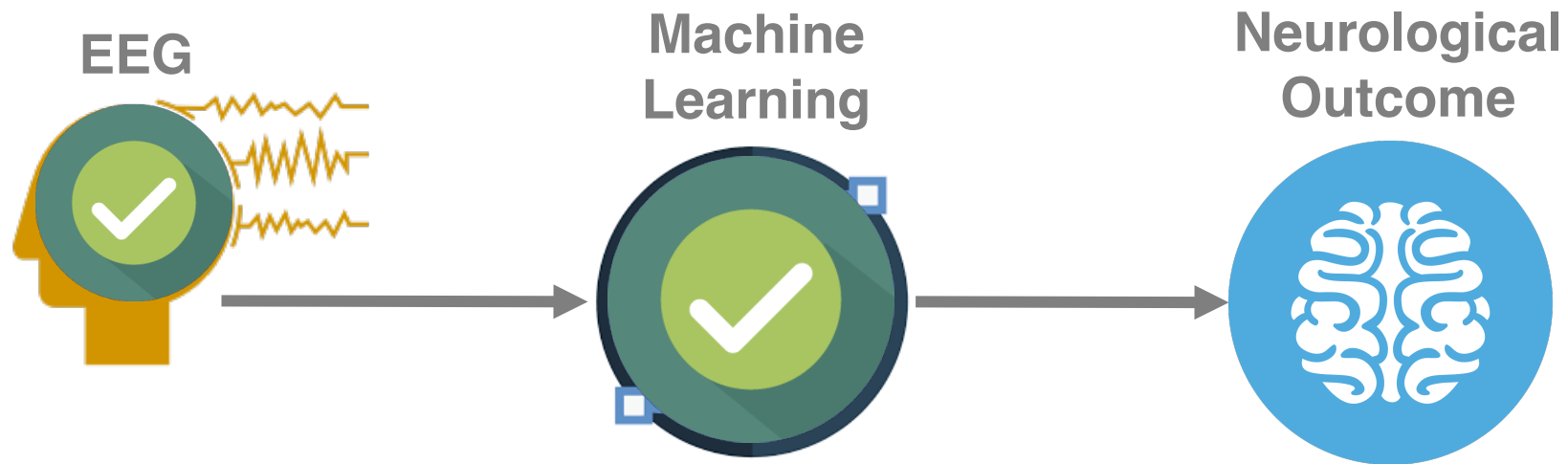


1. Collected an EEG archive 2x larger than largest set previously described in the literature

2. Demonstrated 3 time-sensitive approaches that out-perform state-of-the-art

3. Deployable

Choosing a model for deployment



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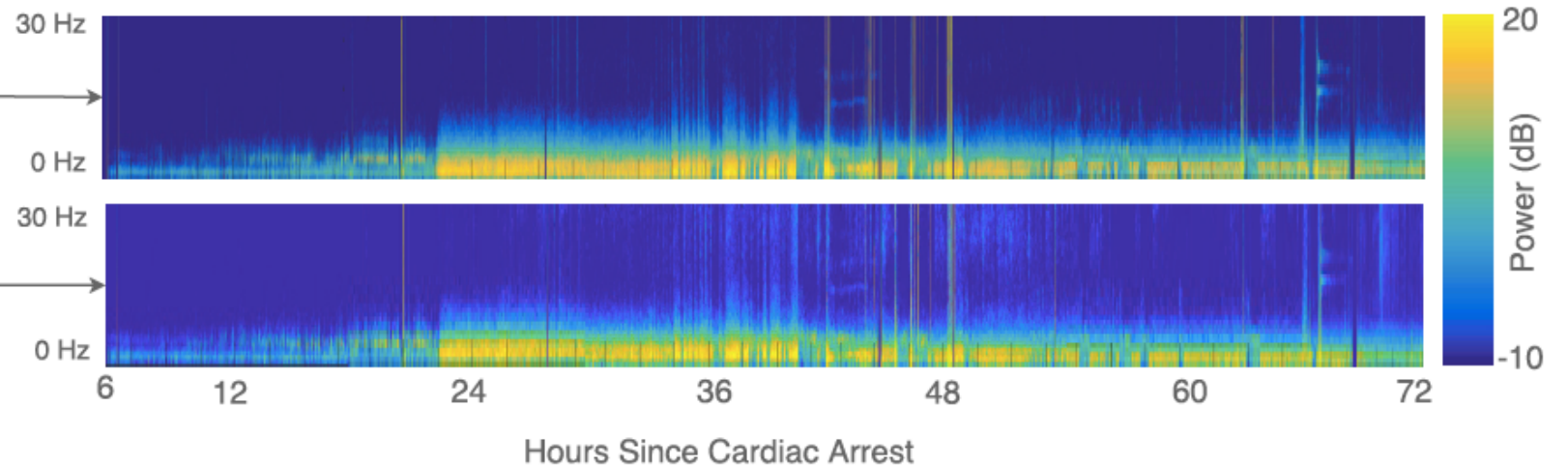
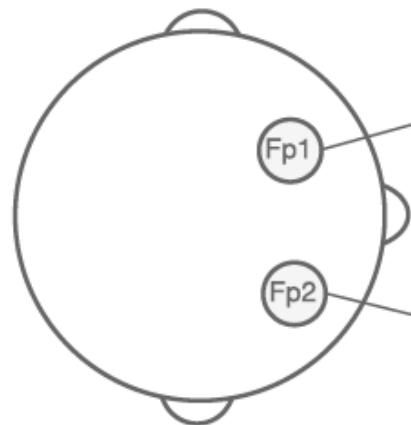
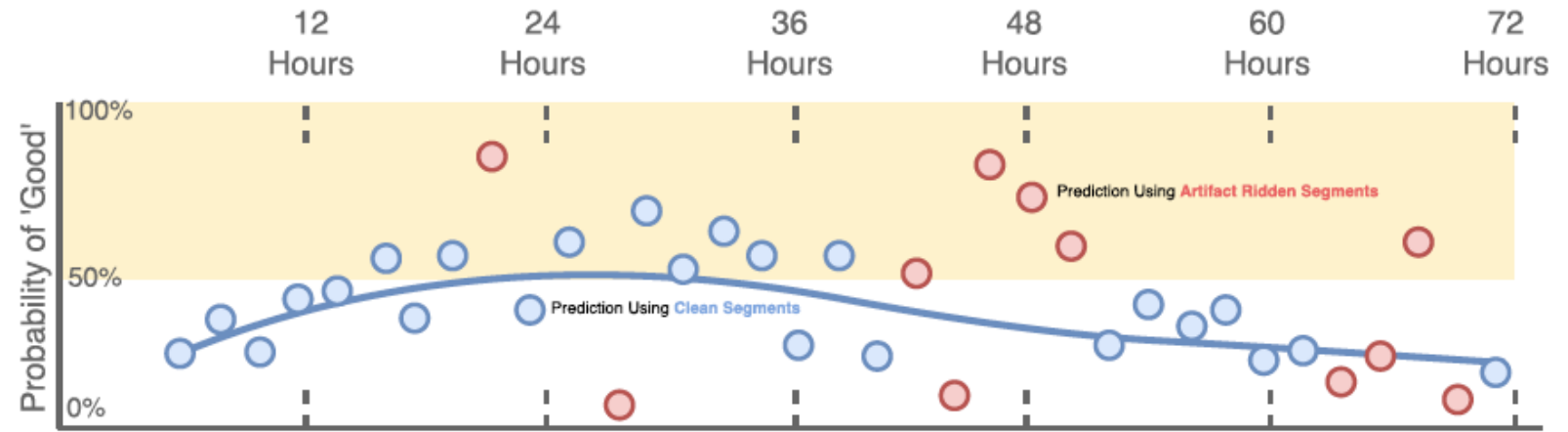
3. Deployable

Criteria for deployment

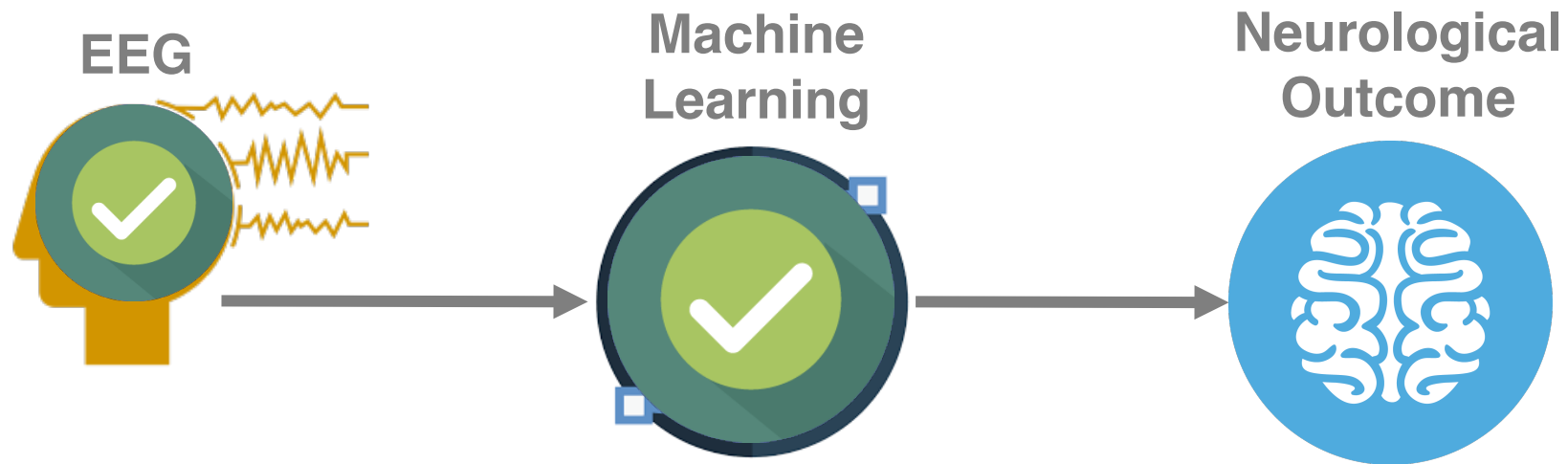
- Interpretable
 - Clear why model has provided the prognostication at hand
- Robust
 - Robust to issues of missing data (e.g. lost channels)
- Well-calibrated
 - Accurate mapping between predicted and actual probabilities of outcome

Proposed model for deployment: *sequential logistic regression with DBN constraints*

Age	81
Gender	Male
Arrest Rhythm	Shockable
Arrest Location	Out of Hospital
Time to ROSC	6 Minutes
Outcome	Bad



Choosing a model for deployment

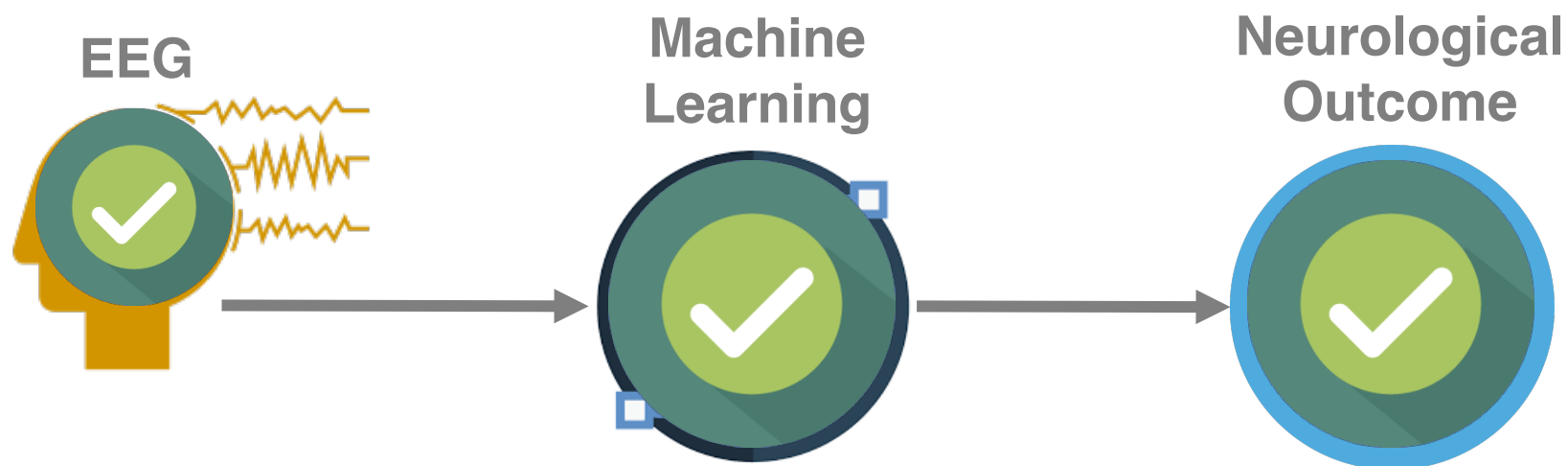


1. Collected an EEG archive 2x larger than largest set previously described in the literature

2. Demonstrated 3 time-sensitive approaches that out-perform state-of-the-art

3. Deployable

Assessing performance: classification and calibration



1. Collected an EEG archive 2x larger than largest set previously described in the literature

2. Demonstrated 3 time-sensitive approaches that out-perform state-of-the-art

3. Our proposed approach provides excellent classification, is well-calibrated, and Interpretable

Summary

Collected 785 PAC patients from five university affiliated hospitals

- 35,000 hours of 21-channel continuous EEG recordings,
- A selection of clinical covariates and an ordinal measure of

Extracted 57 quantitative EEG features that capture three signal properties

- Complexity: the degree of randomness in the EEG signal,
- Category: qualitative descriptors of signal characteristics or behaviours and
- Connectivity: interactions between EEG electrodes.

Tested novel methods for time-sensitive classification of outcomes

- Penalized, sequential, logistic regression using 57 multi-scale features,
- Logistic regression using 10 qEEG features constrained by a DBN and
- A variety of deep neural network architectures

Acknowledgements and thanks

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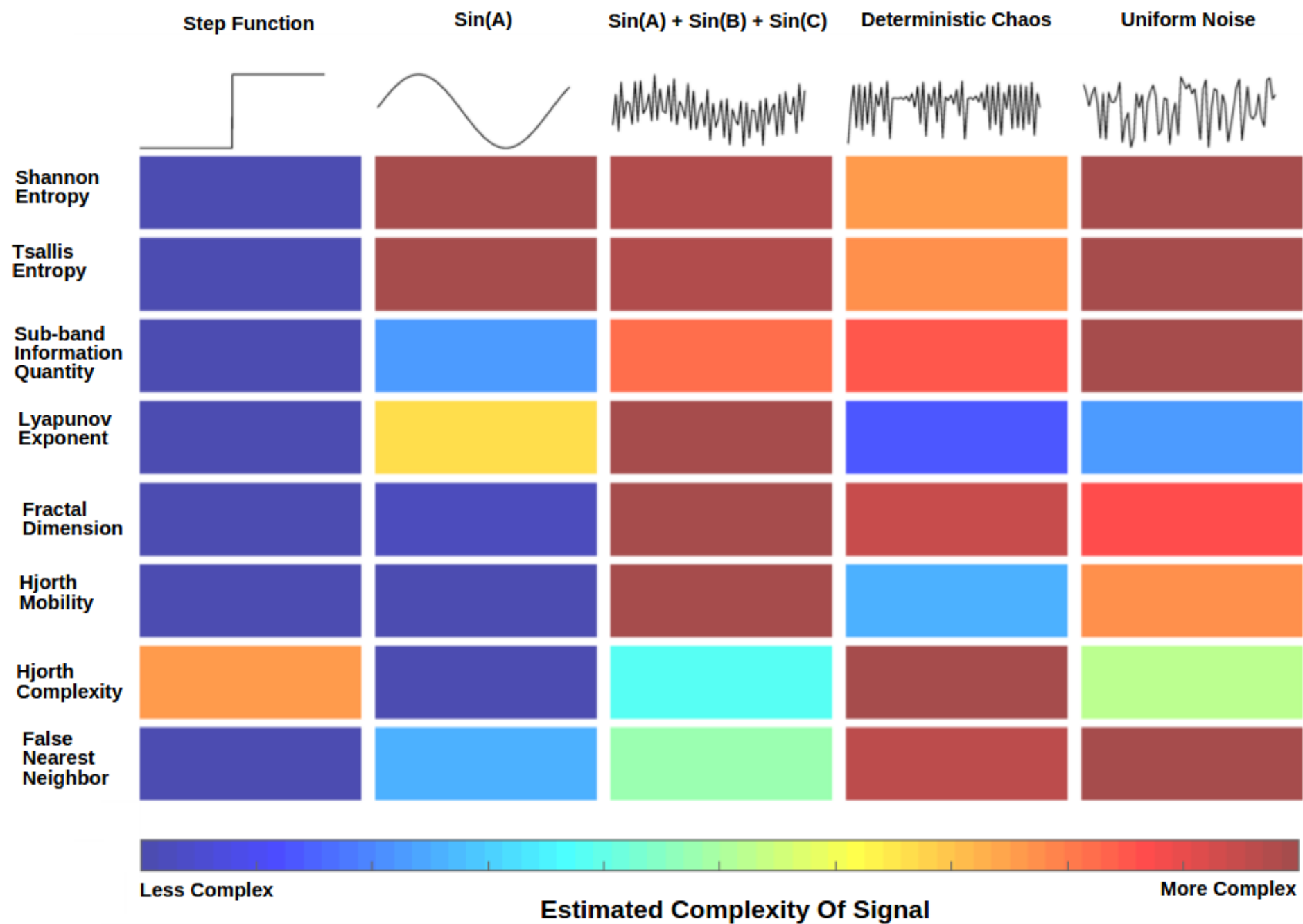
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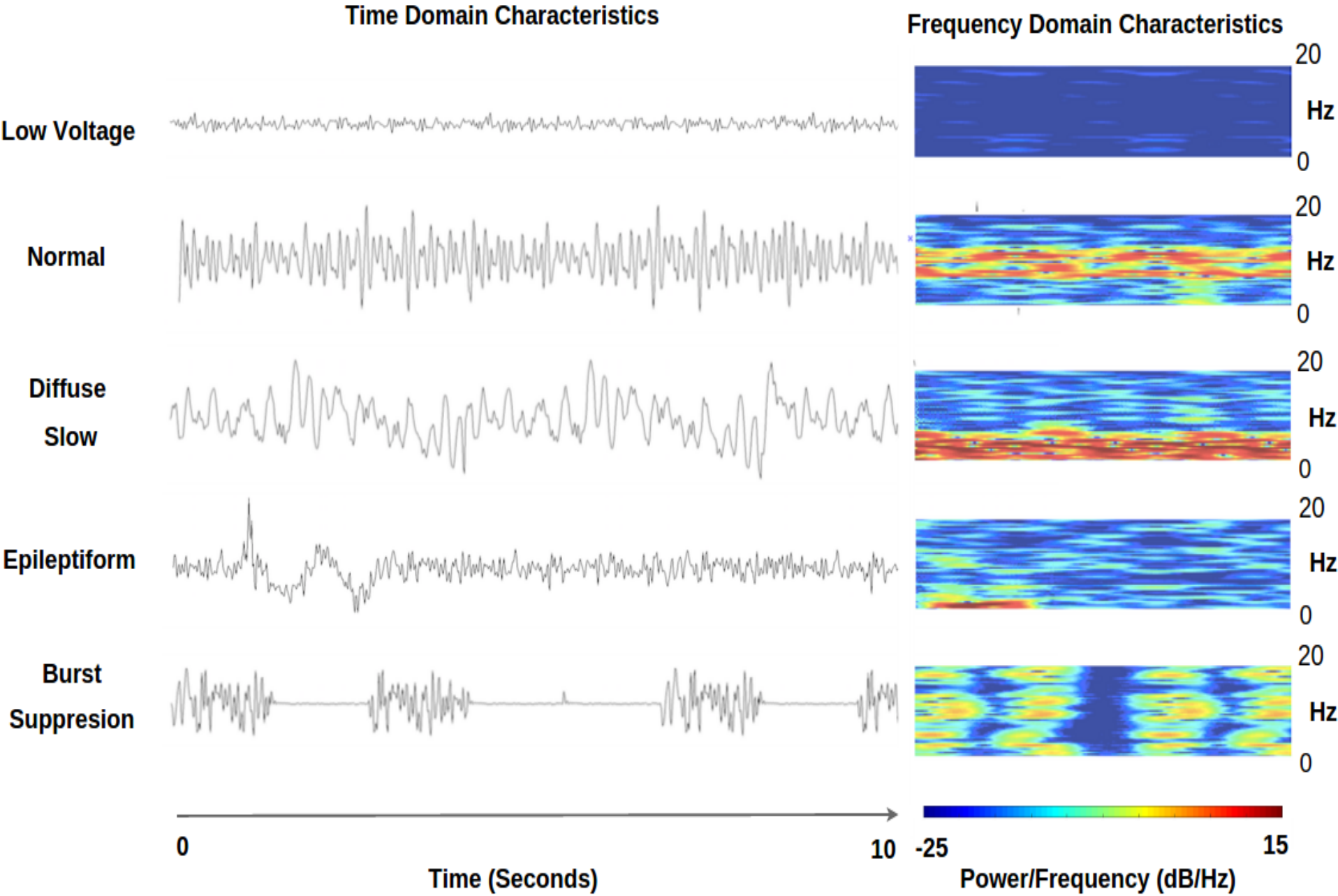
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Complexity



Category



Connectivity

