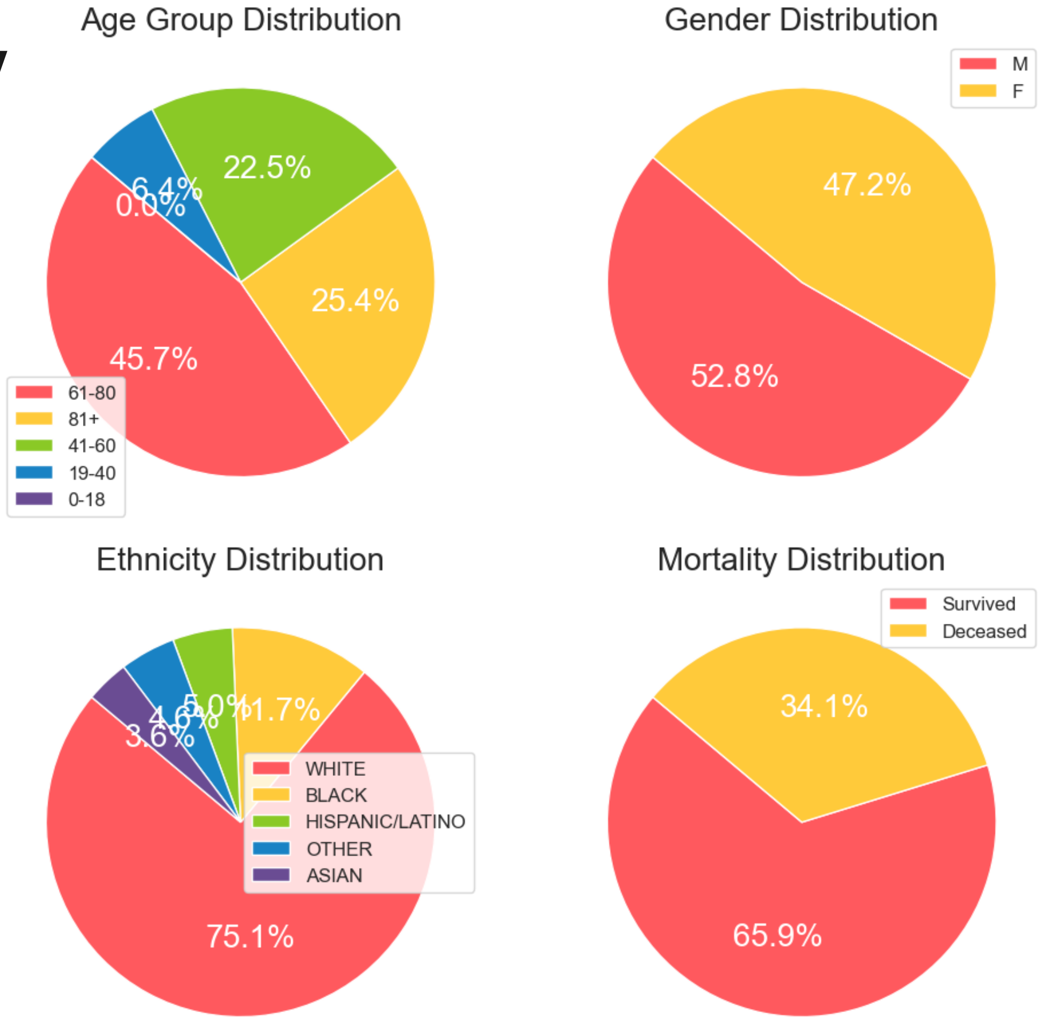
# Sepsis Subphenotype Clustering: Critical Timing and Early-Warning Prediction

Presenter: Panyu Chen, Jiayu Gao

# Sepsis -- Reality

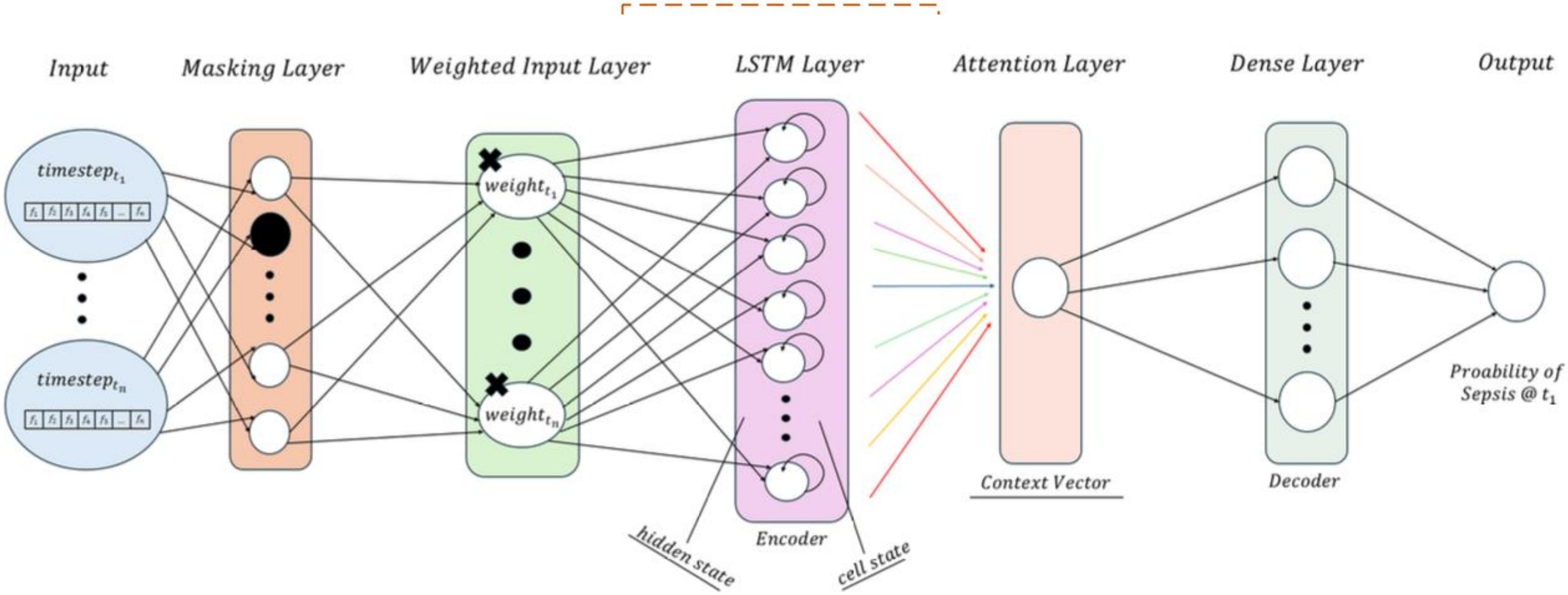
- “Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection” [1]

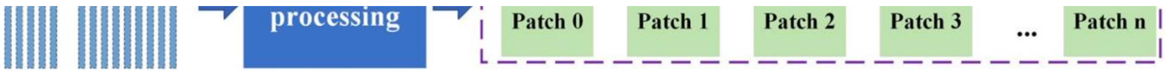


| System | Score 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Respiration | | | | | |
| $PaO_2/FIO_2$, mm Hg (kPa) | ≥400 (53.3) | <400 (53.3) | <300 (40) | <200 (26.7) with respiratory support | <100 (13.3) with respiratory support |
| Coagulation | | | | | |
| Platelets, $\times 10^3/\mu L$ | ≥150 | <150 | <100 | <50 | <20 |
| Liver | | | | | |
| Bilirubin, mg/dL ($\mu$mol/L) | <1.2 (20) | 1.2–1.9 (20–32) | 2.0–5.9 (33–101) | 6.0–11.9 (102–204) | >12.0 (204) |
| Cardiovascular | MAP ≥70 mm Hg | MAP <70 mm Hg | Dopamine <5 or dobutamine (any dose)[b] | Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b] | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b] |
| Central nervous system | | | | | |
| Glasgow Coma Scale score[c] | 15 | 13–14 | 10–12 | 6–9 | <6 |
| Renal | | | | | |
| Creatinine, mg/dL ($\mu$mol/L) | <1.2 (110) | 1.2–1.9 (110–170) | 2.0–3.4 (171–299) | 3.5–4.9 (300–440) | >5.0 (440) |
| Urine output, mL/d | | | | <500 | <200 |

# Sepsis – Related Works

- Sepsis Prediction [2][3]



# Related Works

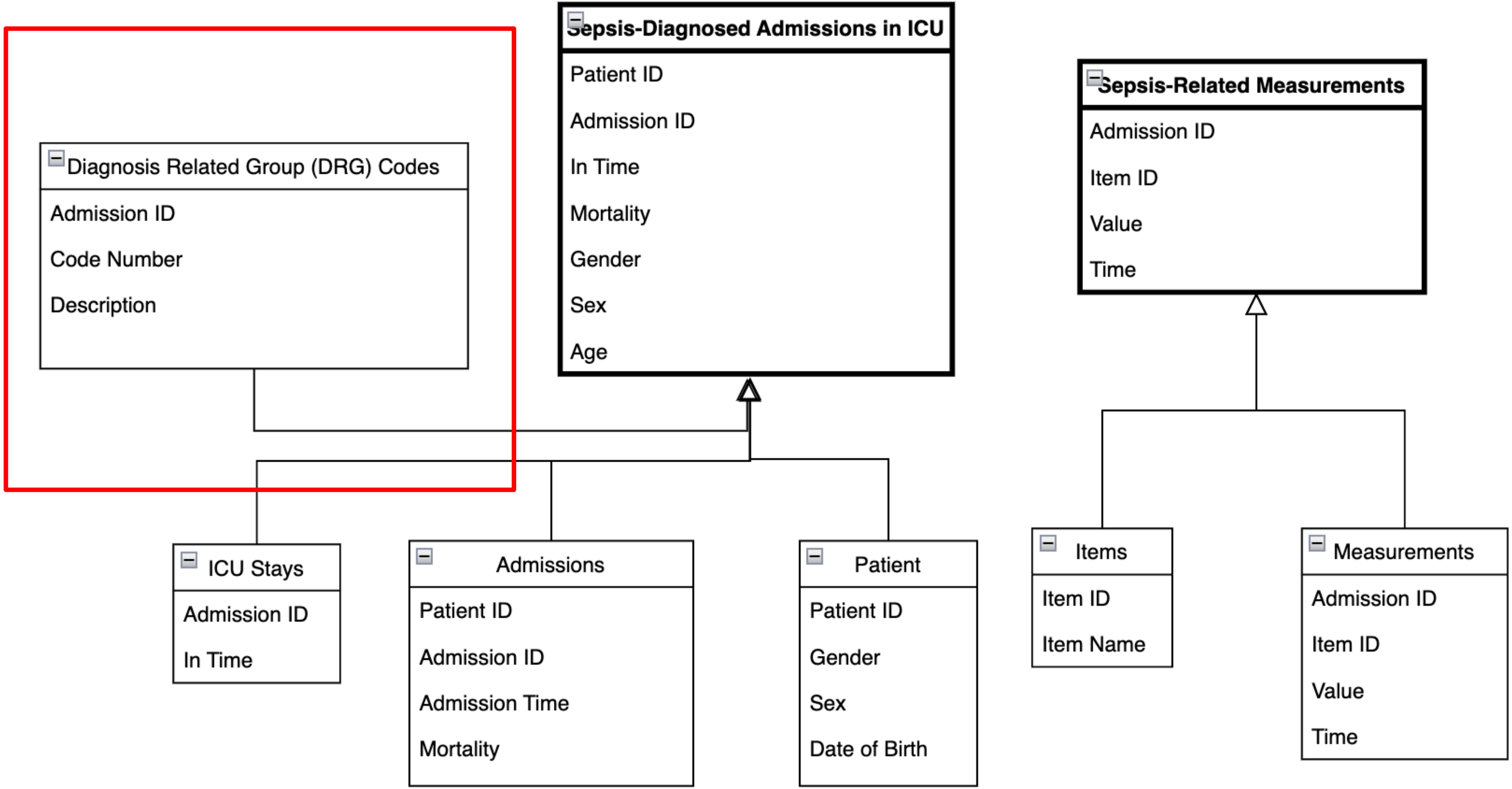
- Disease Subphenotype Clustering
  - Latent Dirichlet Allocation[4]
  - Sepsis -- Hierarchical Clustering [5]
  - COVID 19 -- Consensus K-Means Clustering[6]

- No Time-Series Data is used!

# Related Works

- Sepsis Detection with Time-Series Data
    - Jensen-Shannon's Divergence [7]
- Disease Subphenotype Clustering with Time-Series Data
    - Acute Kidney Injury Subphenotype [8]
    - Liver Diseases Subphenotype [9]
    - **Sepsis Sub-Phenotyping with Lung, Kidney, Heart-Related Diagnosis Calibration [10]**

# ICU Admissions in MIMIC-III



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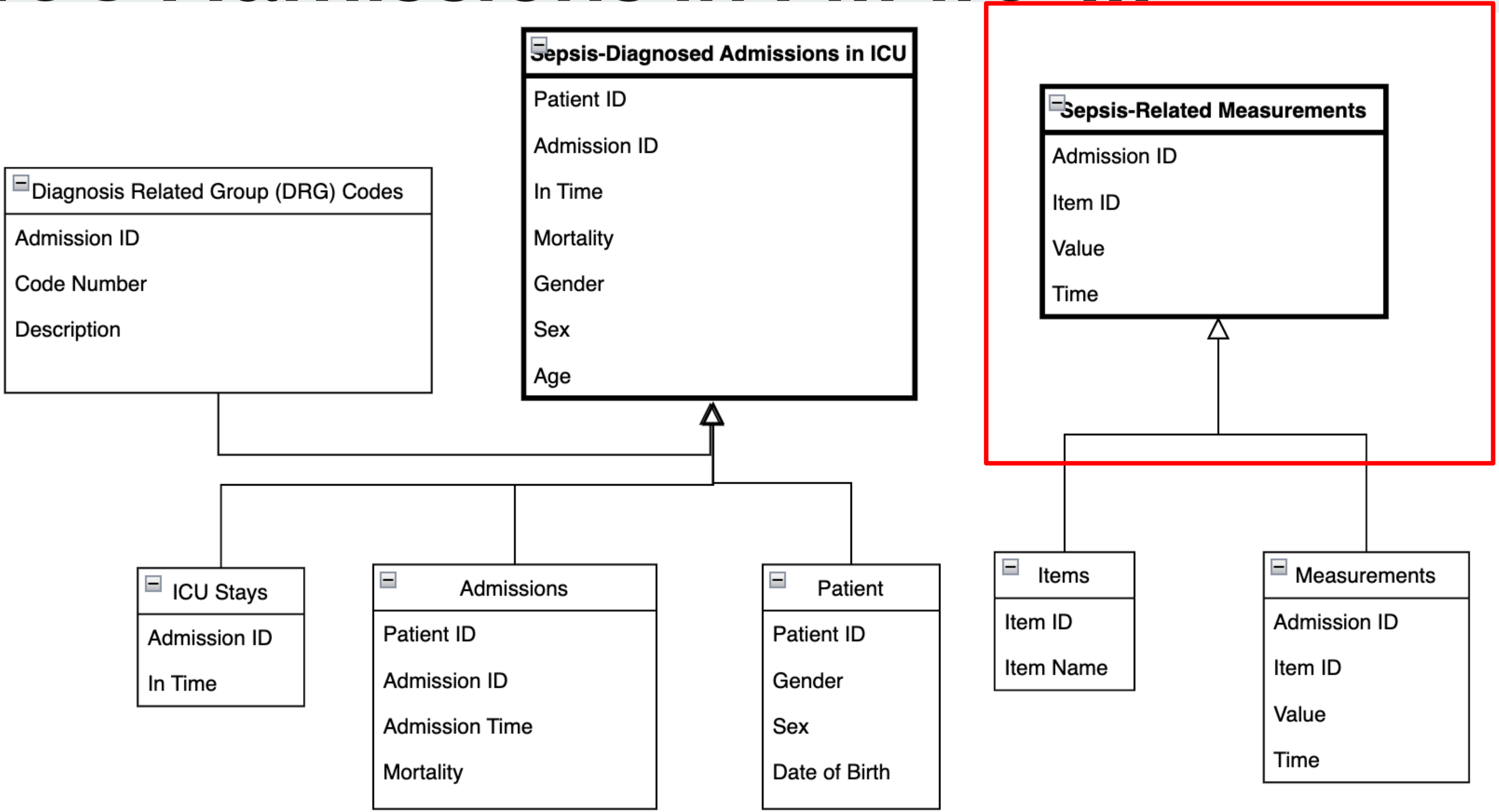
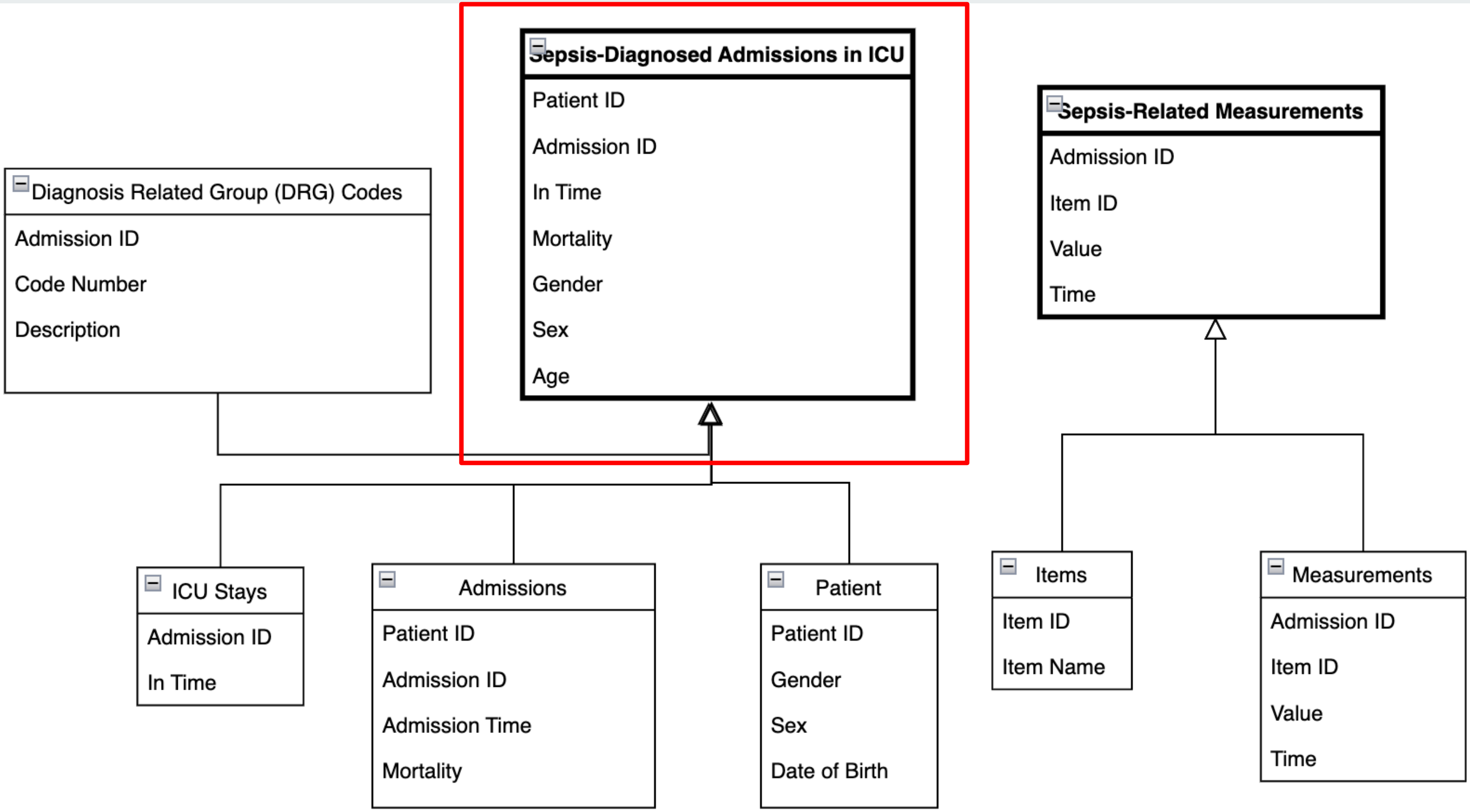


# ICU Admissions in MIMIC-III



# MIMIC-III: Sepsis-Related Items Measured

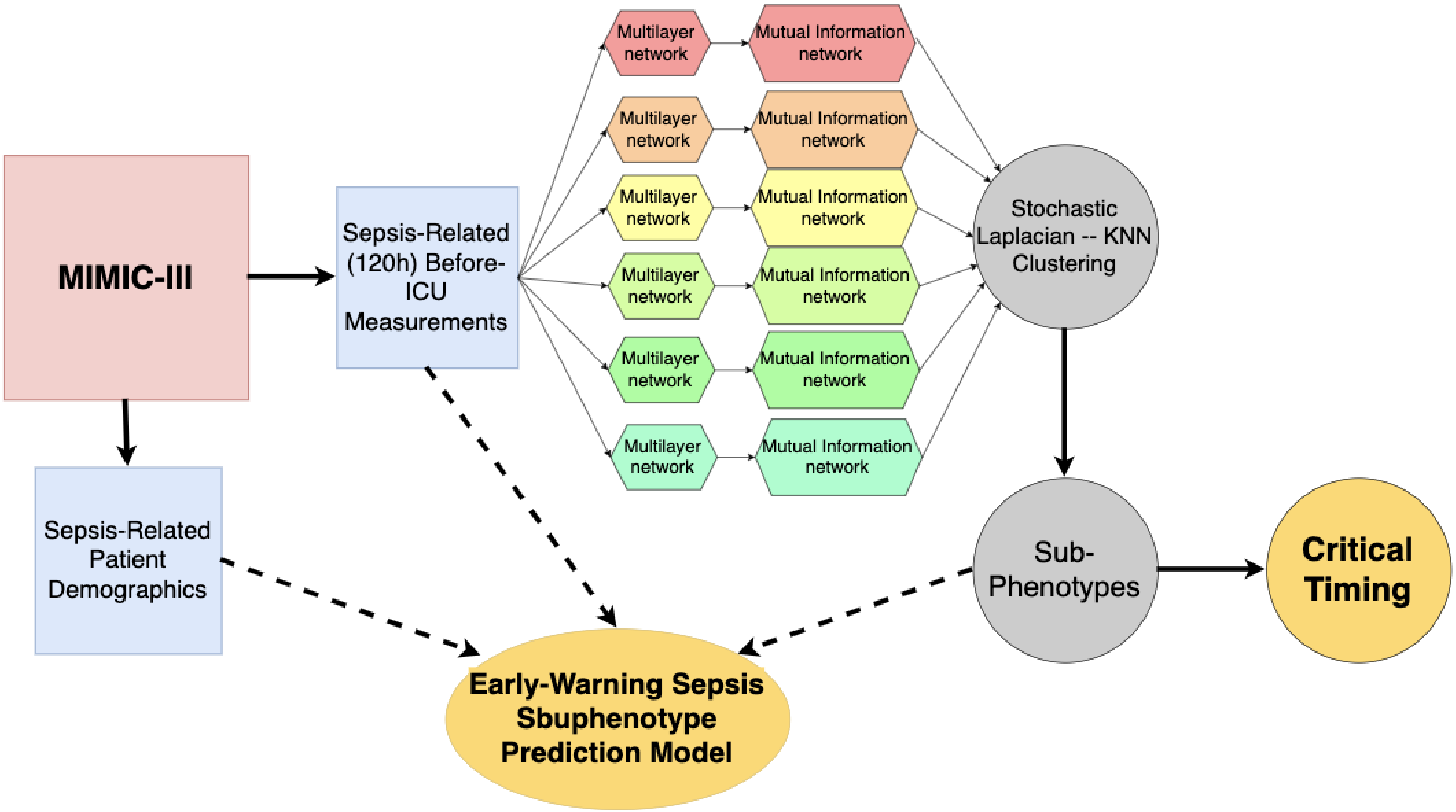
- #220210, #224688, #224689, #224690 -- Respiratory Rate (Respiratory)
- #227457 -- Platelet Count (Coagulation)
- #225651, #225690, #226998 – Bilirubin (Renal)
- #220045 -- Heart Rate (Cardiovascular)
- #220615, #226751, #226752, #227005 – Creatinine (Renal)
- #224828 -- Base Excess (Liver)

# Workflow

- Sepsis Diagnoses from MIMIC-III
- Mutual Information Graph Construction
- Finding: Sepsis Sub-Phenotypes and Critical Time Points
- Sub-Phenotype Early-Warning Prediction with Machine Learning

# ICU Admissions in MIMIC-III – Sepsis-Related Measurements (120h) before ICU Admission

| | SUBJECT_ID | HADM_ID | before_ICU_time | ITEMID | VALUE | VALUENUM |
|---|---|---|---|---|---|---|
| 336 | 85 | 112077 | 22.156389 | 220045 | 100.0 | 100.0 |
| 337 | 85 | 112077 | 22.156389 | 220210 | 30.0 | 30.0 |
| 338 | 85 | 112077 | 23.156389 | 220045 | 106.0 | 106.0 |
| 339 | 85 | 112077 | 23.156389 | 220210 | 34.0 | 34.0 |
| 340 | 85 | 112077 | 24.156389 | 220045 | 114.0 | 114.0 |
| ... | ... | ... | ... | ... | ... | ... |
| 2054661 | 48935 | 177563 | 23.900000 | 220210 | 20.0 | 20.0 |
| 2054662 | 48935 | 177563 | 23.916667 | 220045 | 97.0 | 97.0 |
| 2054663 | 48935 | 177563 | 23.916667 | 220210 | 14.0 | 14.0 |
| 2054664 | 48935 | 177563 | 23.933333 | 220045 | 95.0 | 95.0 |
| 2054665 | 48935 | 177563 | 23.933333 | 220210 | 33.0 | 33.0 |

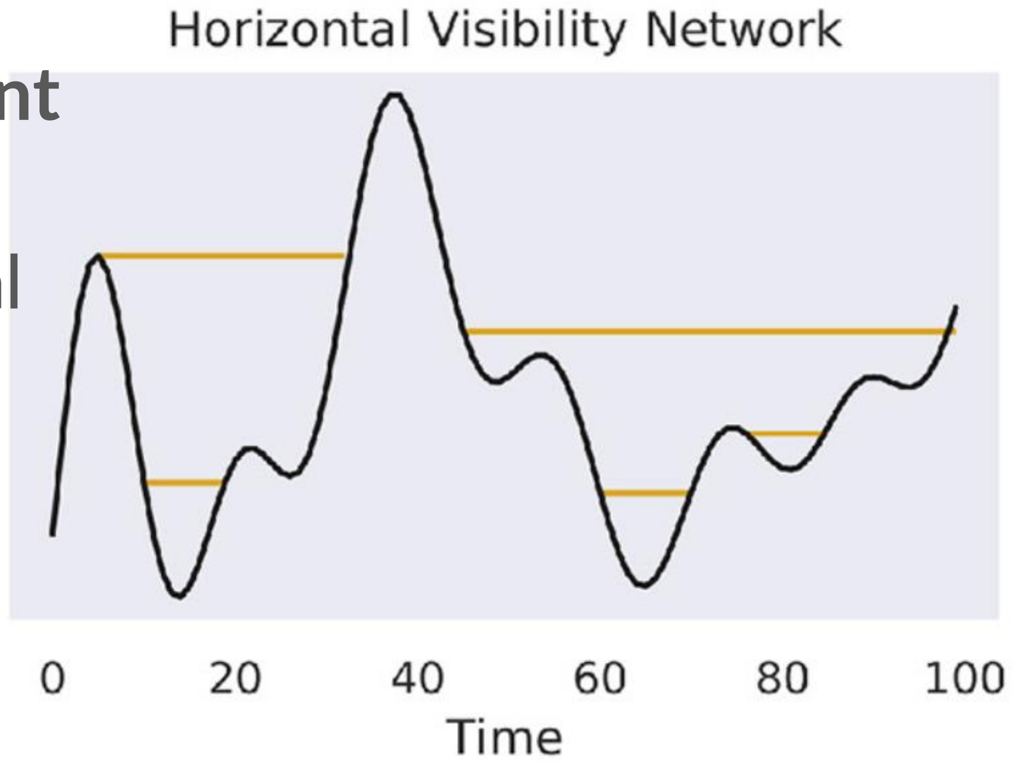

MIMIC-III
Sepsis-Related (120h) Before-ICU Measurements
Sepsis-Related Patient Demographics
Multilayer network
Mutual Information network
Stochastic Laplacian -- KNN Clustering
Sub-Phenotypes
Critical Timing
Early-Warning Sepsis Sbuphenotype Prediction Model

# Method: Multi-Layer Horizontal Visibility Graph (MHVG)

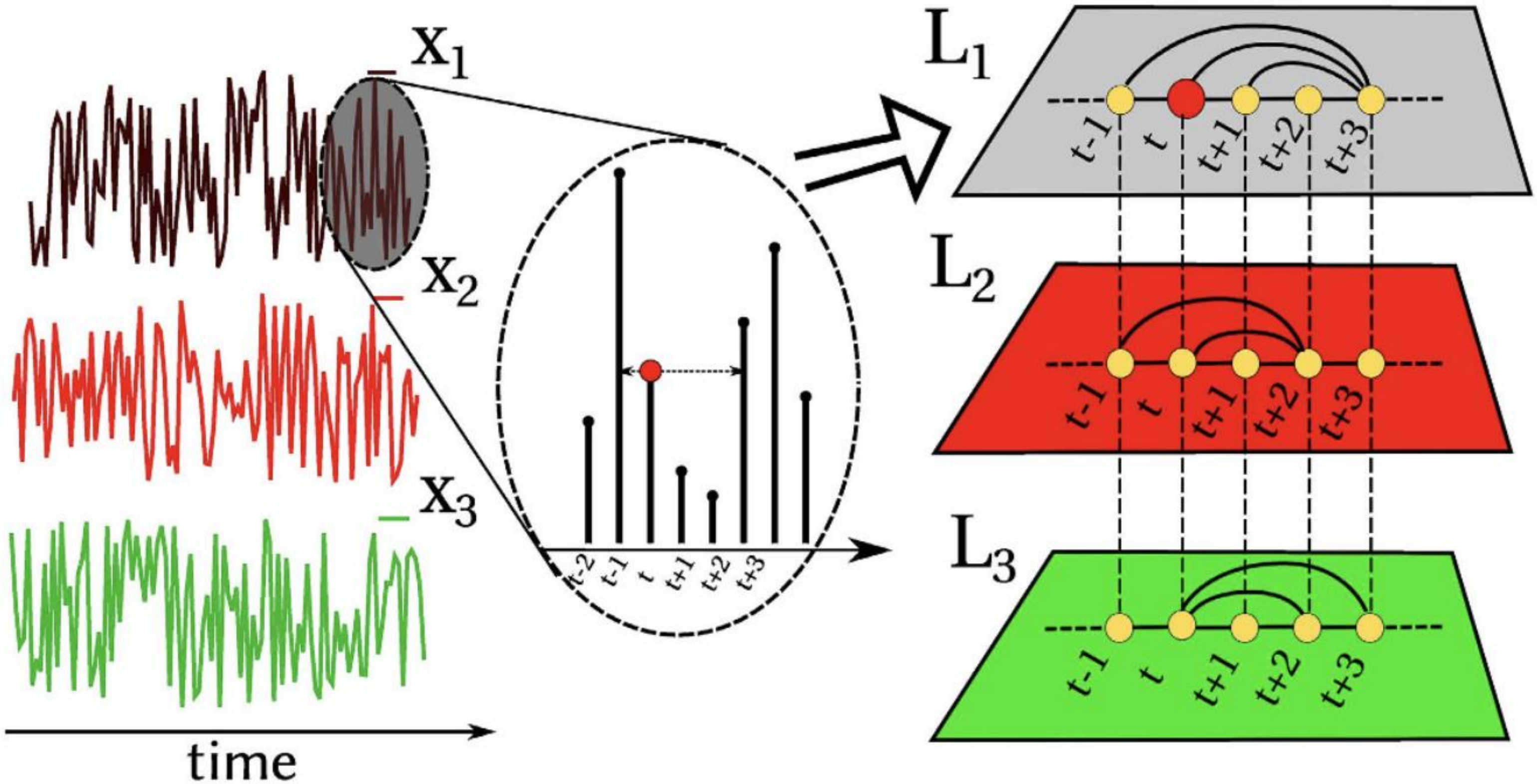
- Fix timepoints 1, 2, ..., $T$ hours for **a Measurement**

  $T = 120$, **before ICU**
- **Patient-Wise** Horizontal Visibility

  $$x_k < \min\{x_i, x_j\},$$
  $$\forall i < k < j$$
- Impute Missing Time Points with $-\infty$



# Method: Multi-Layer Horizontal Visibility Graph (MHVG) [11]



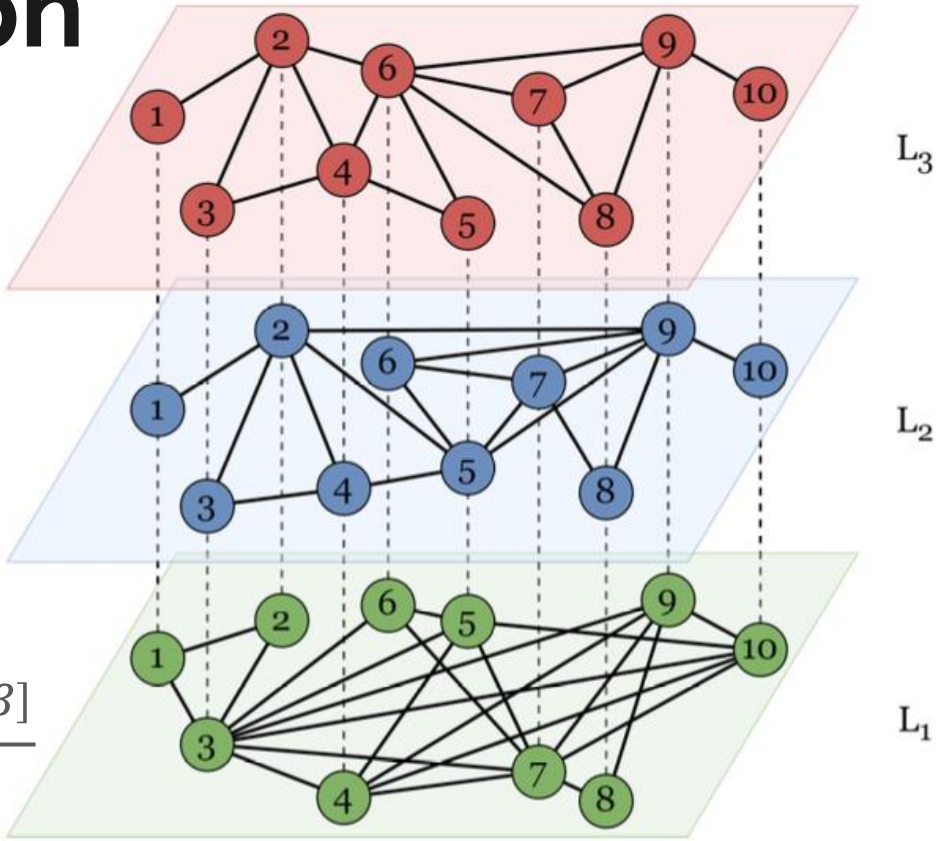
# Method: From MHVG to Mutual Information Graph

- Single-Layer Degree Distribution

$$P\left(k^{[\alpha]}\right) = \frac{N_{k^{[\alpha]}}}{N}$$

- Joint-Layer Degree Distribution

$$P\left(k^{[\alpha]}, k^{[\beta]}\right) = \frac{N_{k^{[\alpha]},k^{[\beta]}}}{N}$$



# Method: From MHVG to Mutual Information Graph

- **Inter-Patient** Mutual Information

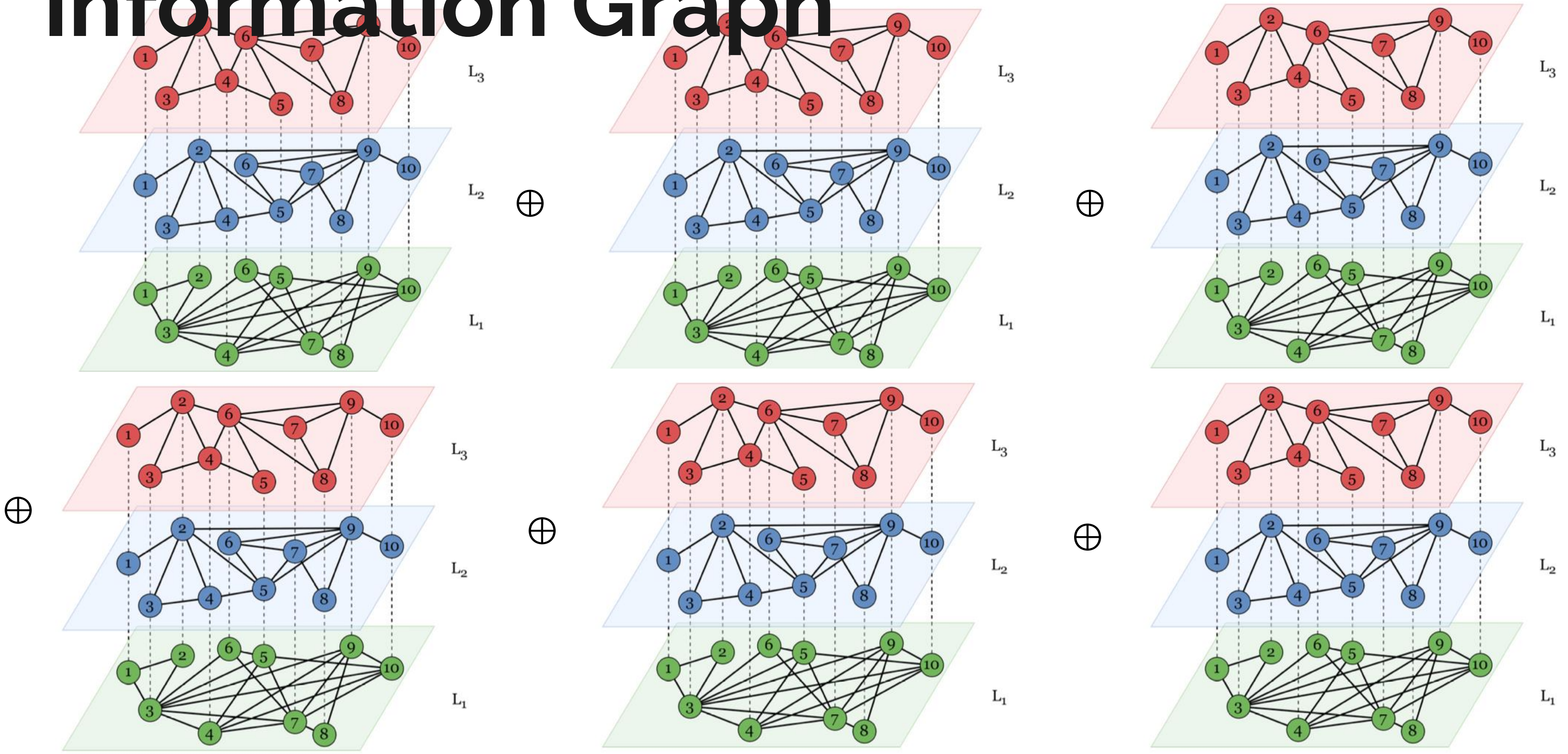
$$I_{\alpha,\beta} = \sum_{k^{[\alpha]},k^{[\beta]}} P\left(k^{[\alpha]}, k^{[\beta]}\right) \log \frac{P\left(k^{[\alpha]},k^{[\beta]}\right)}{P\left(k^{[\alpha]}\right)P\left(k^{[\beta]}\right)}$$

$$I_{\alpha,\beta} = D_{\mathrm{KL}}[P\left(\boldsymbol{k}^{[\alpha]}, \boldsymbol{k}^{[\beta]}\right)||P\left(\boldsymbol{k}^{[\alpha]}\right) \otimes P(\boldsymbol{k}^{[\boldsymbol{\beta}]})]$$

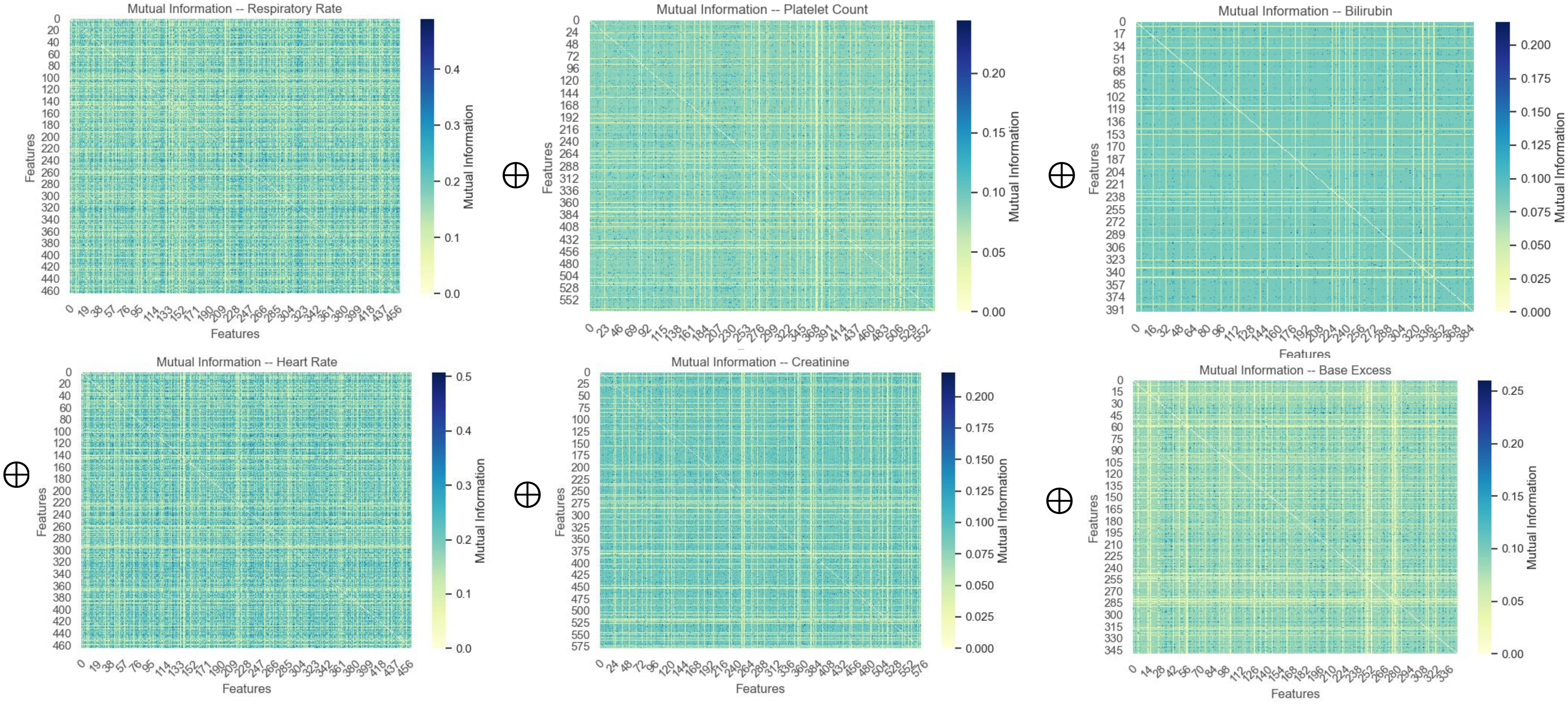
- Stochastic Laplacian

$$L = I - D^{-1}A$$

# Method: From MHVG to Mutual Information Graph



# Method: Mutual Information Graph



# Method: From MHVG to Mutual Information Graph

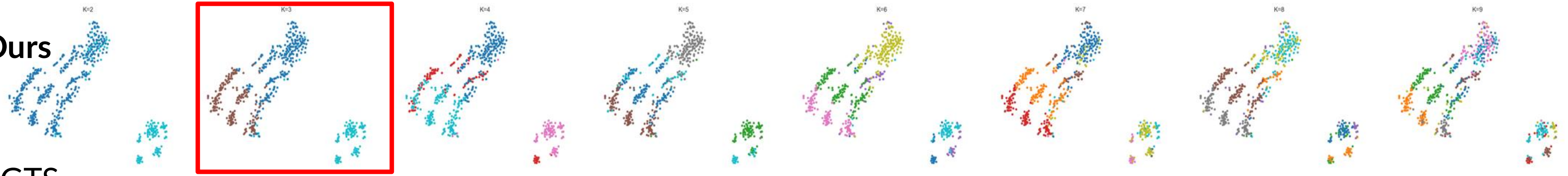
- Normalization of each Row

- Stochastic Laplacian

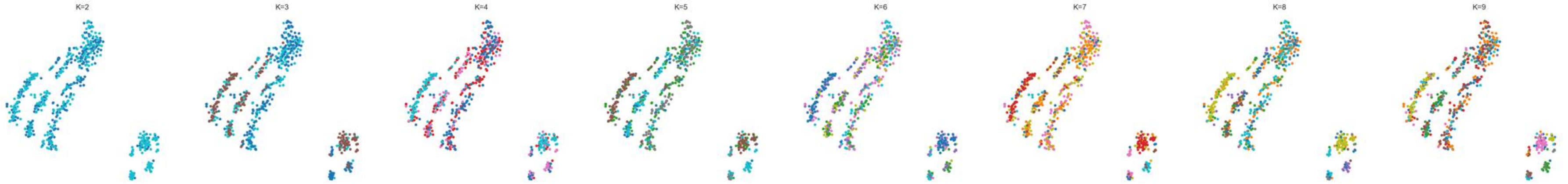
$$L = I - D^{-1}A$$

# Method: Clustering with Mutual Information Graph

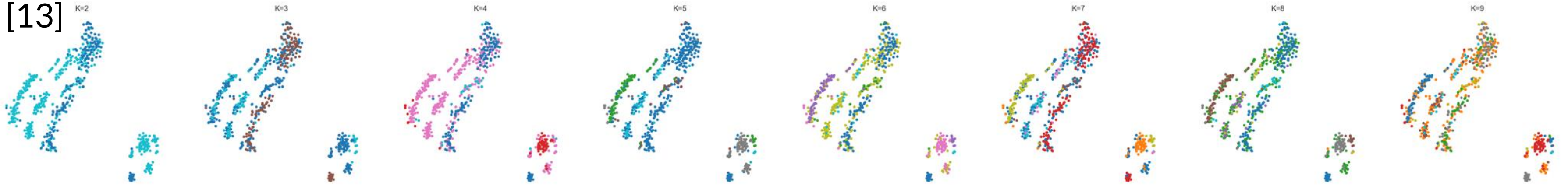
**Ours**



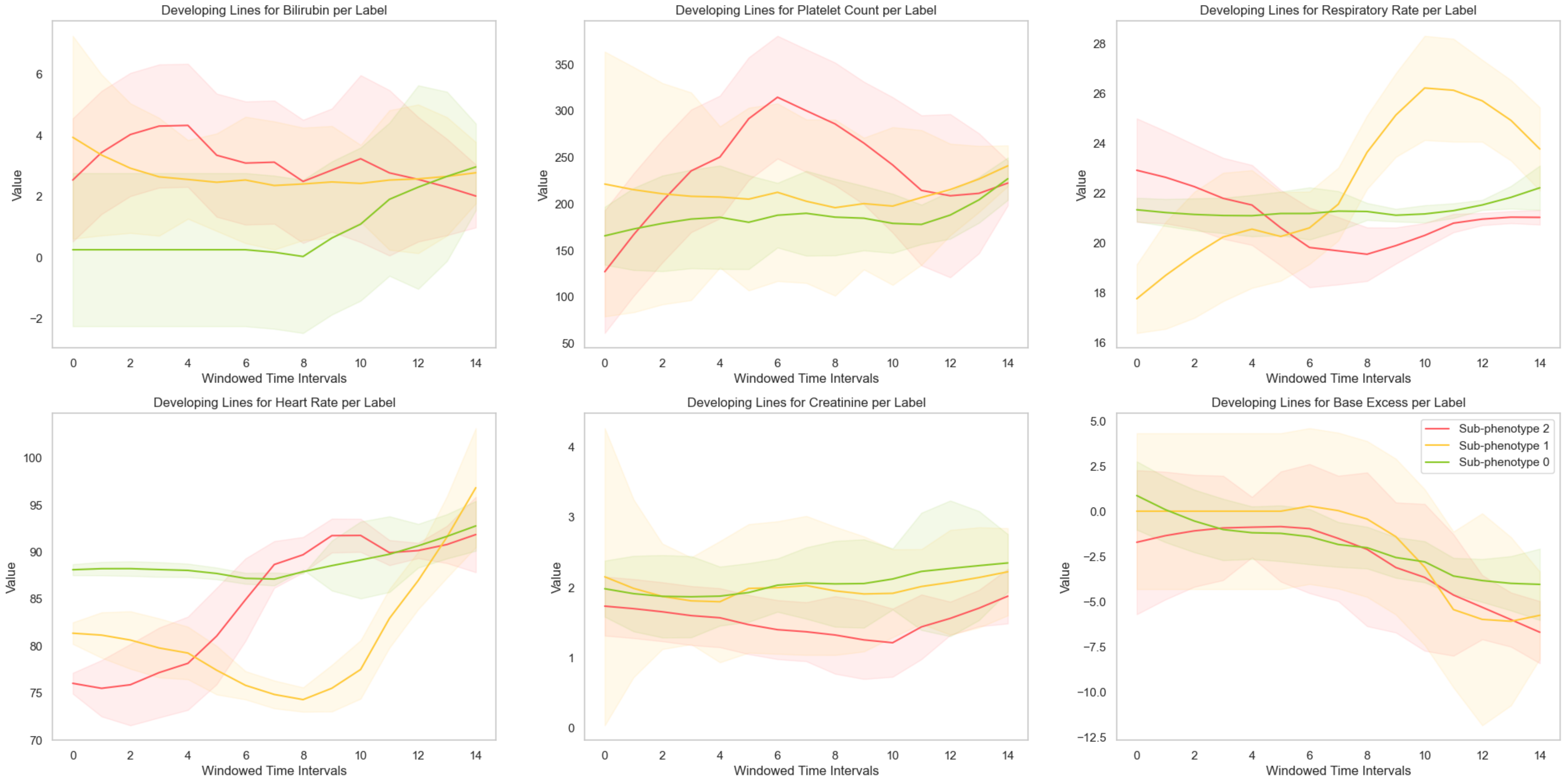

SGTS NE-$\pi$ [12]




Hinton-Roweis Kernel [13]



# Results: *Critical Timing* in Prognosis



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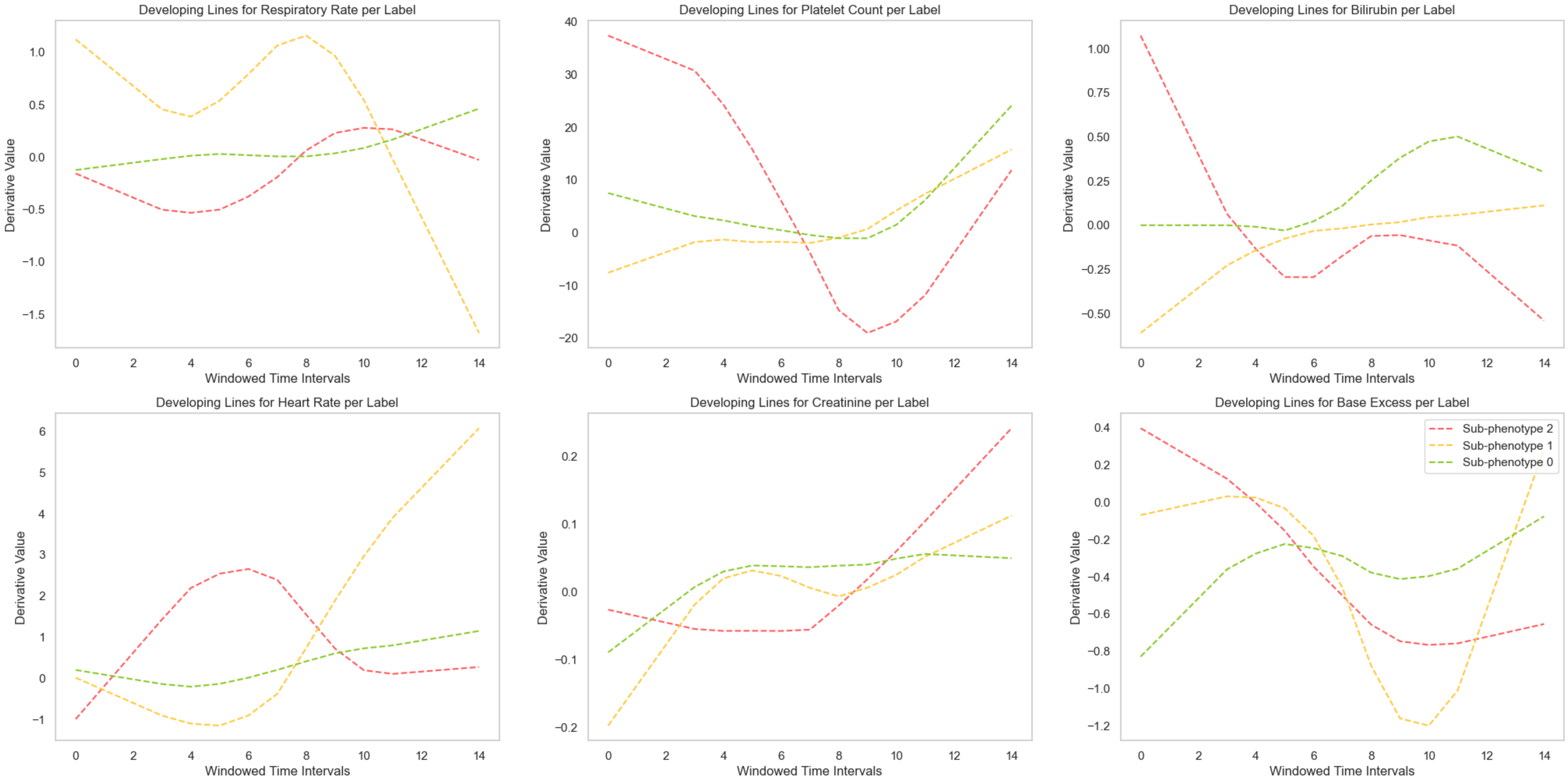
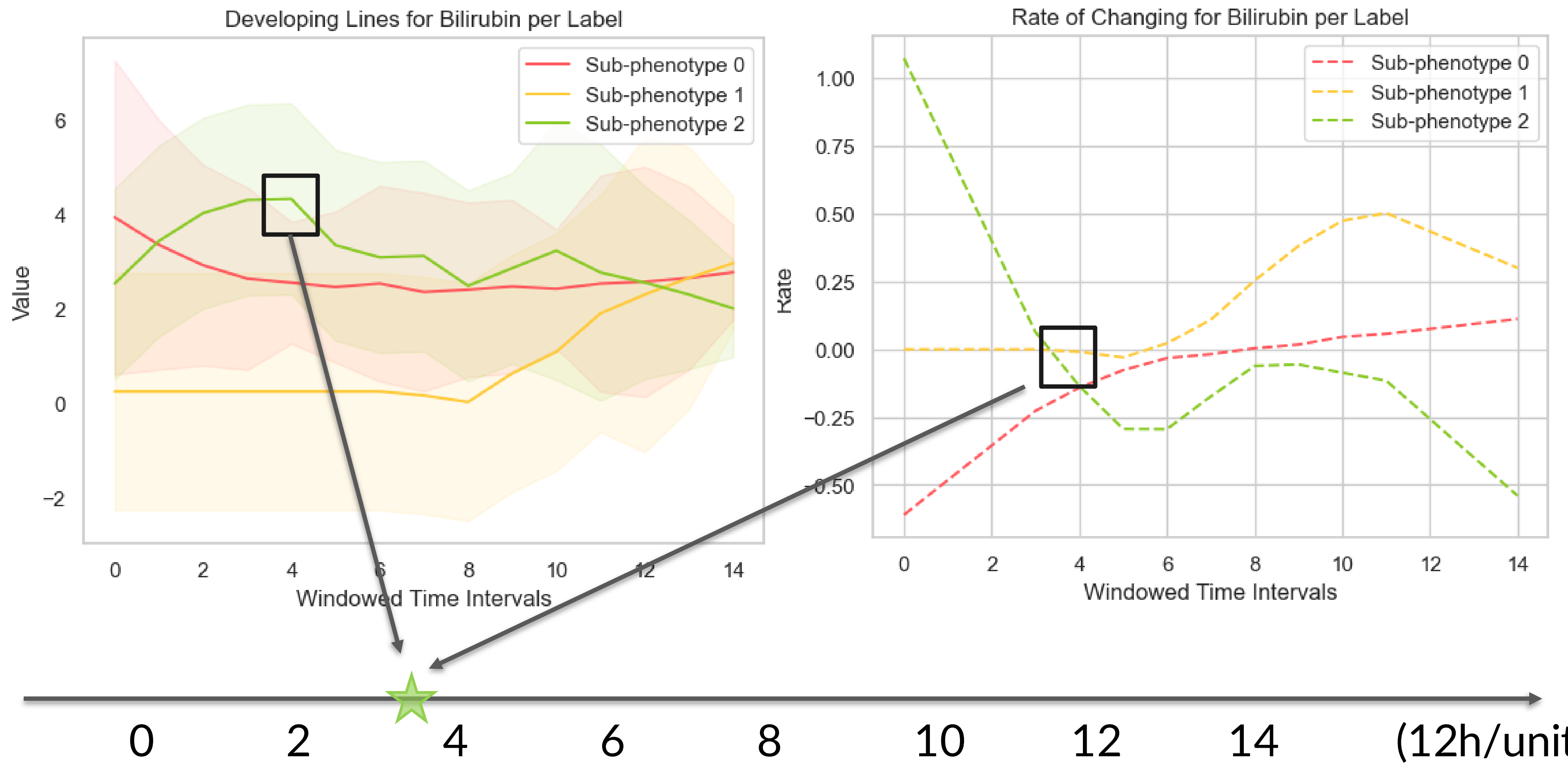


# Results: *Critical Timing*



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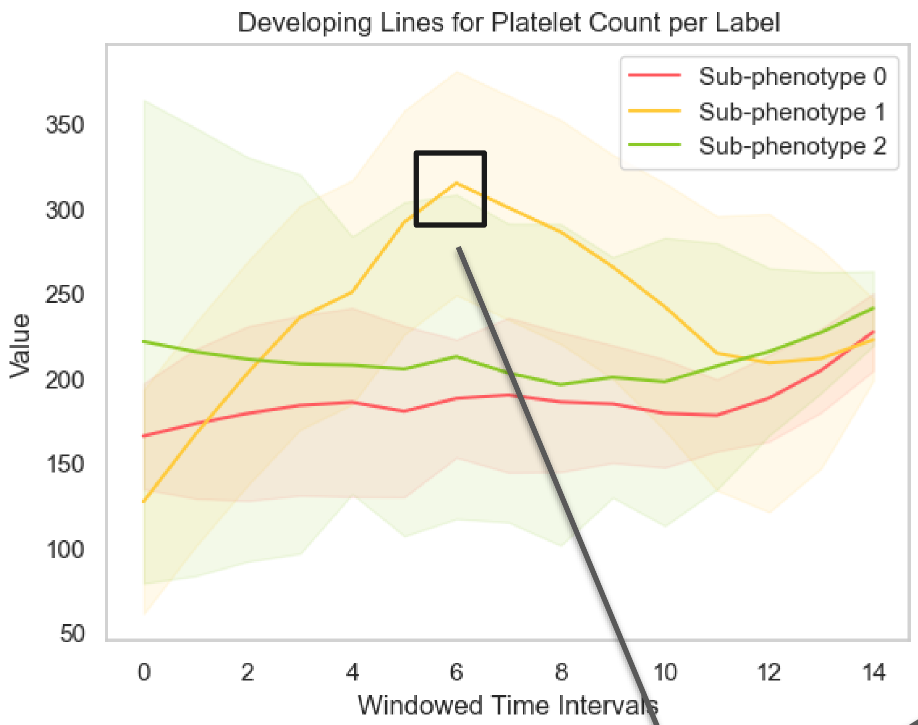


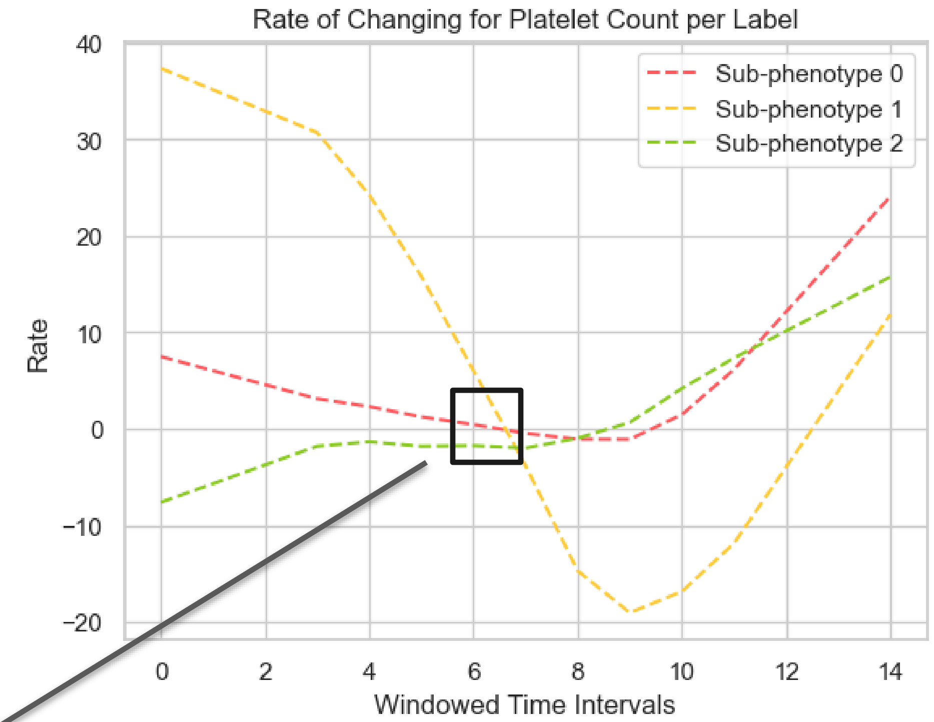


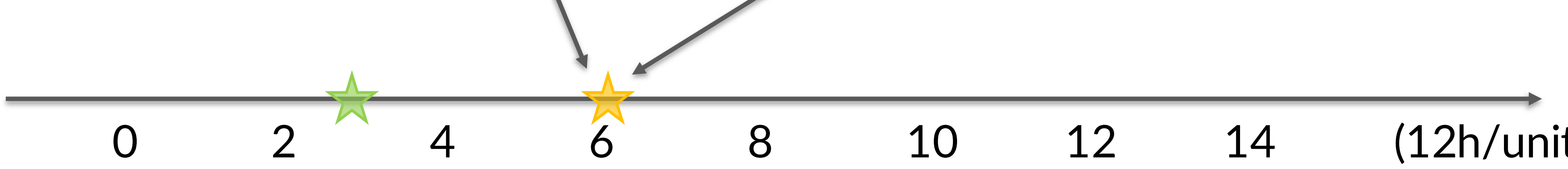

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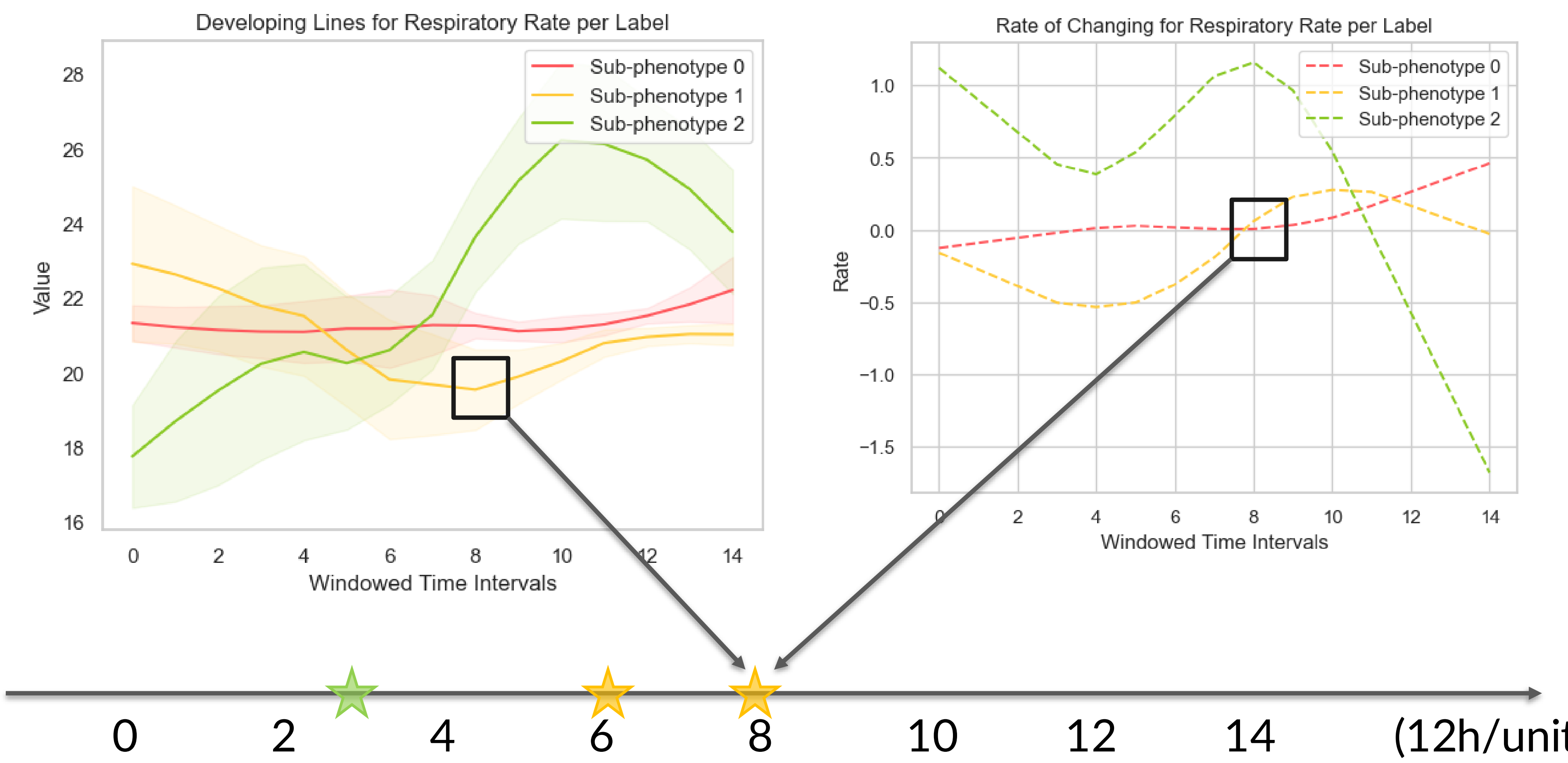

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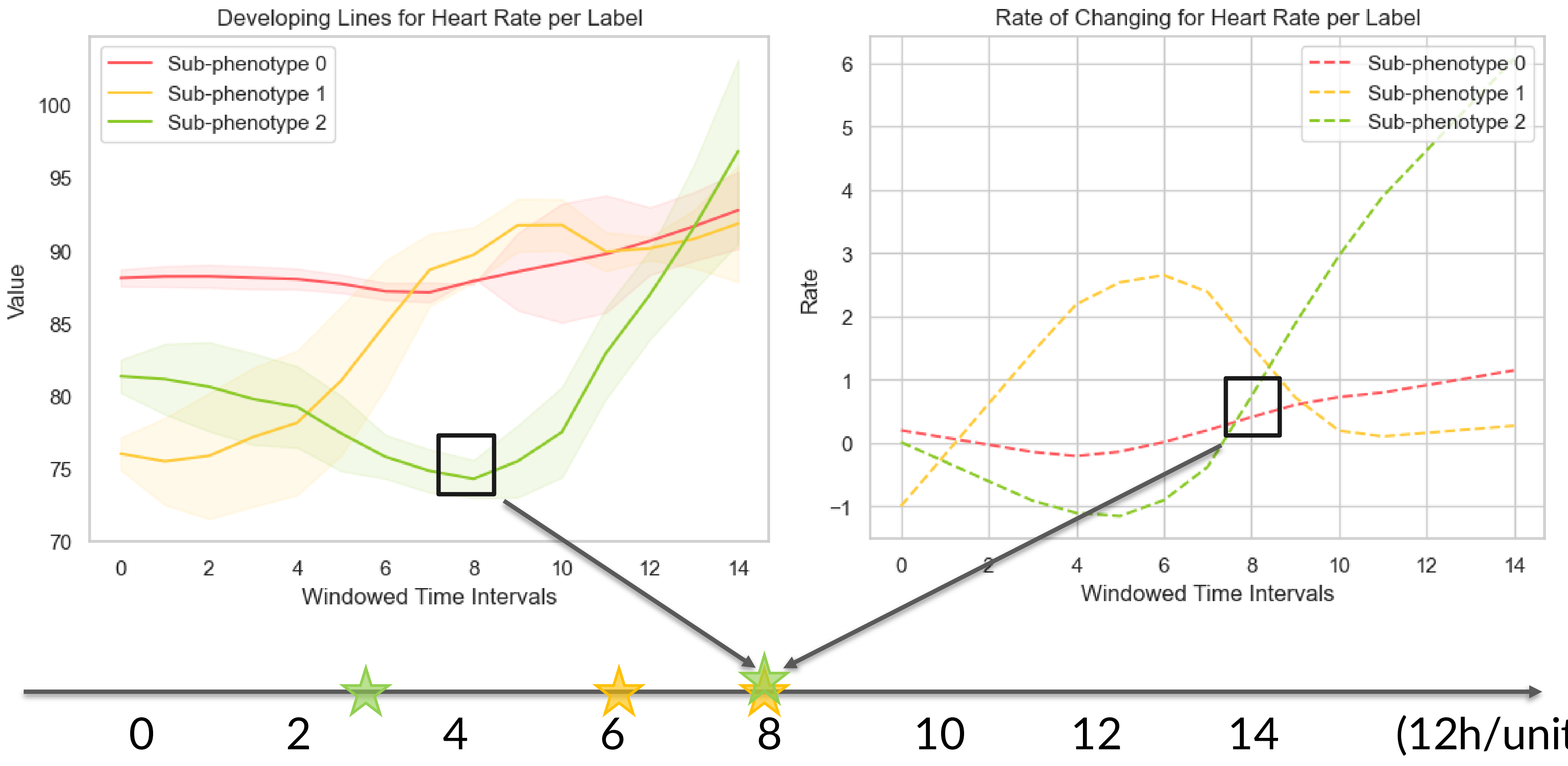

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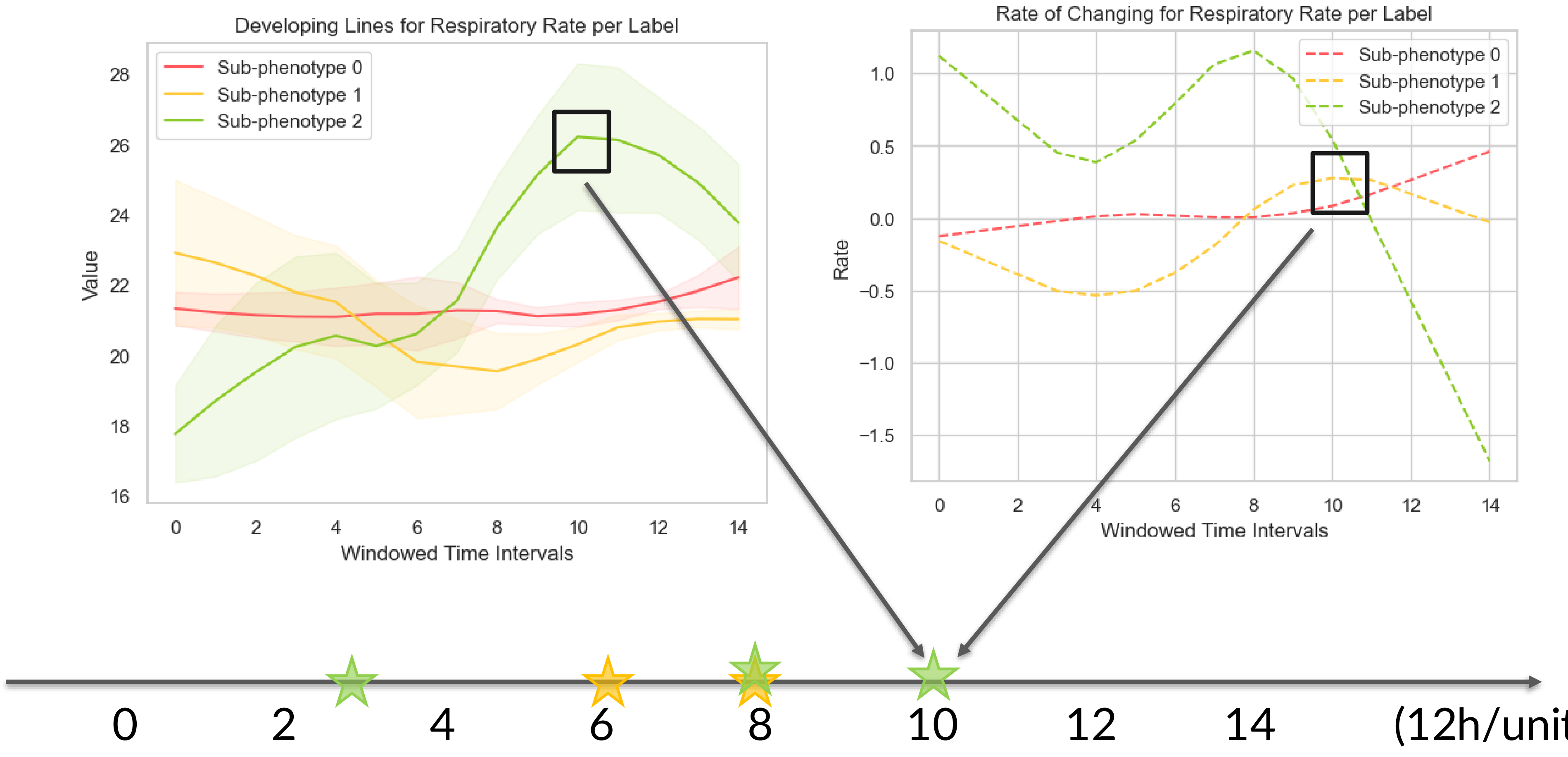

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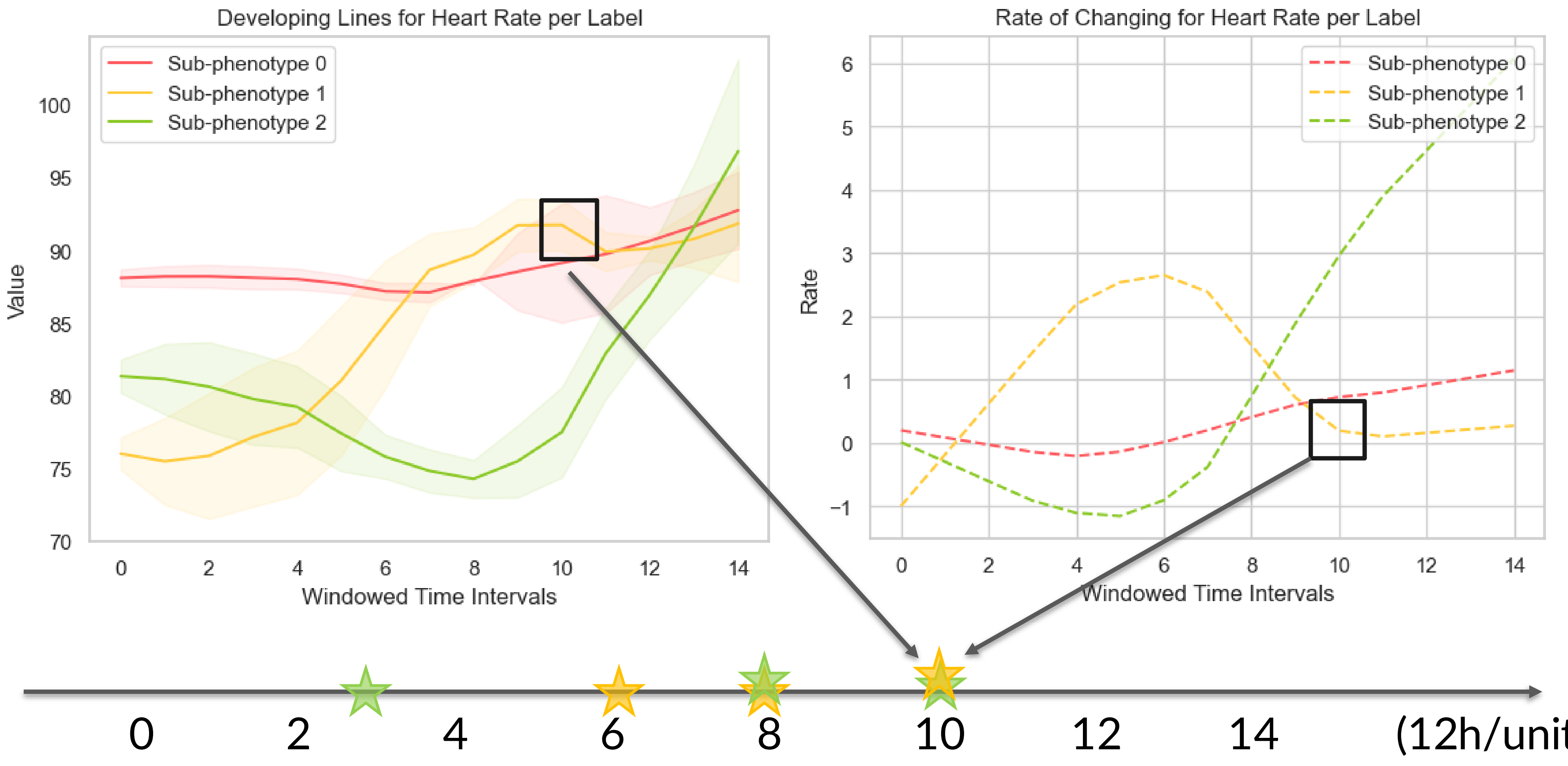

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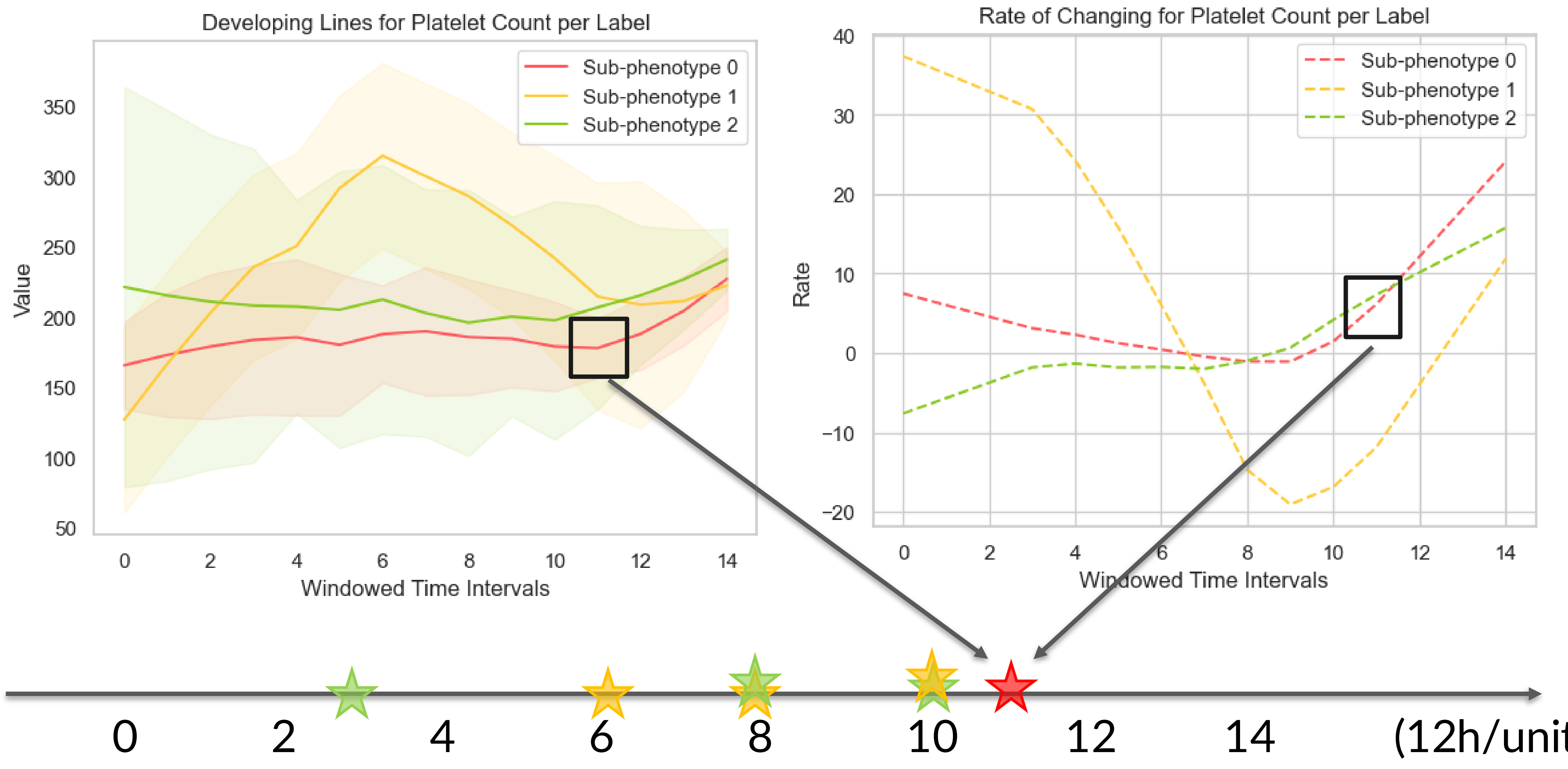
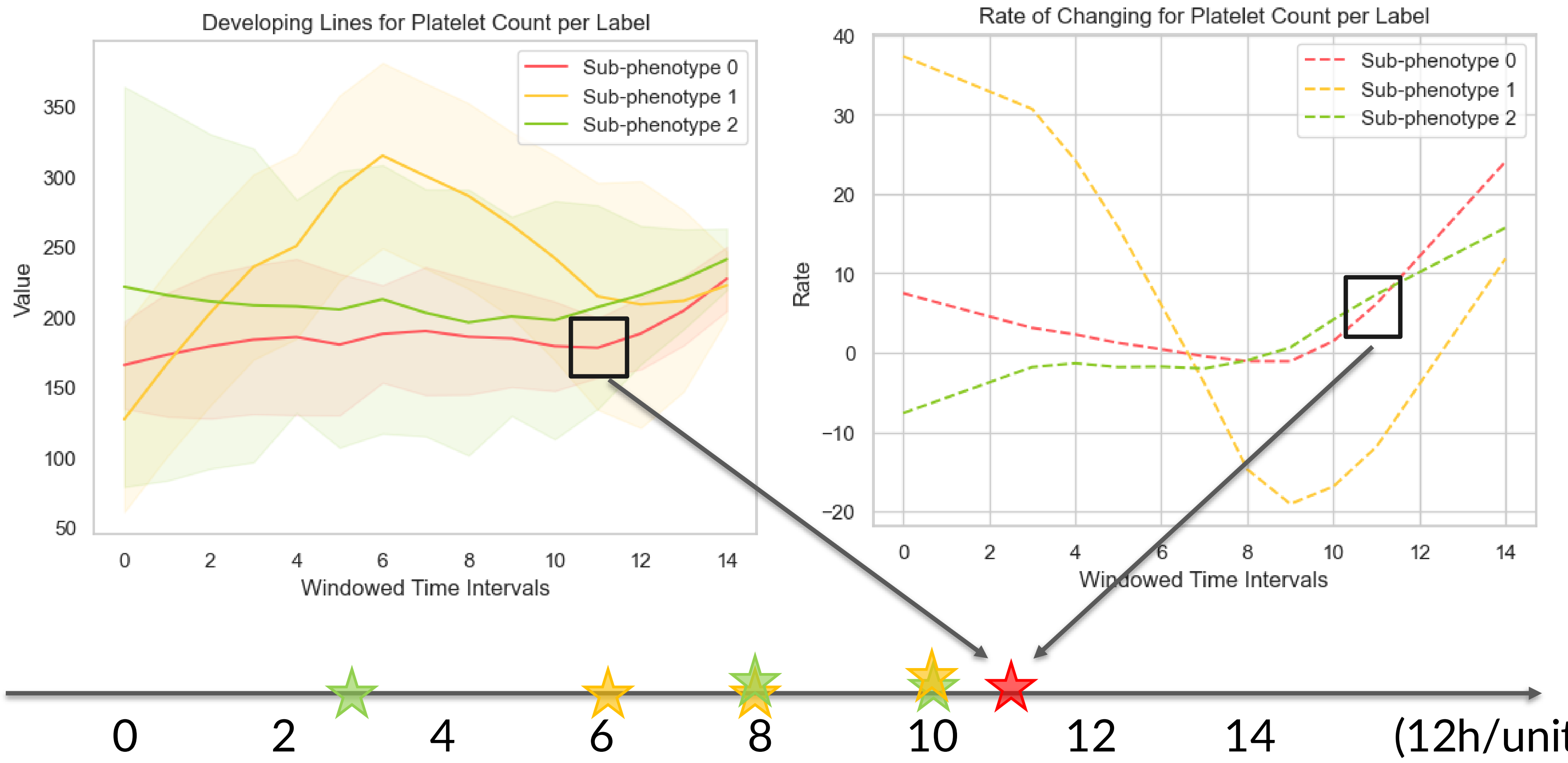
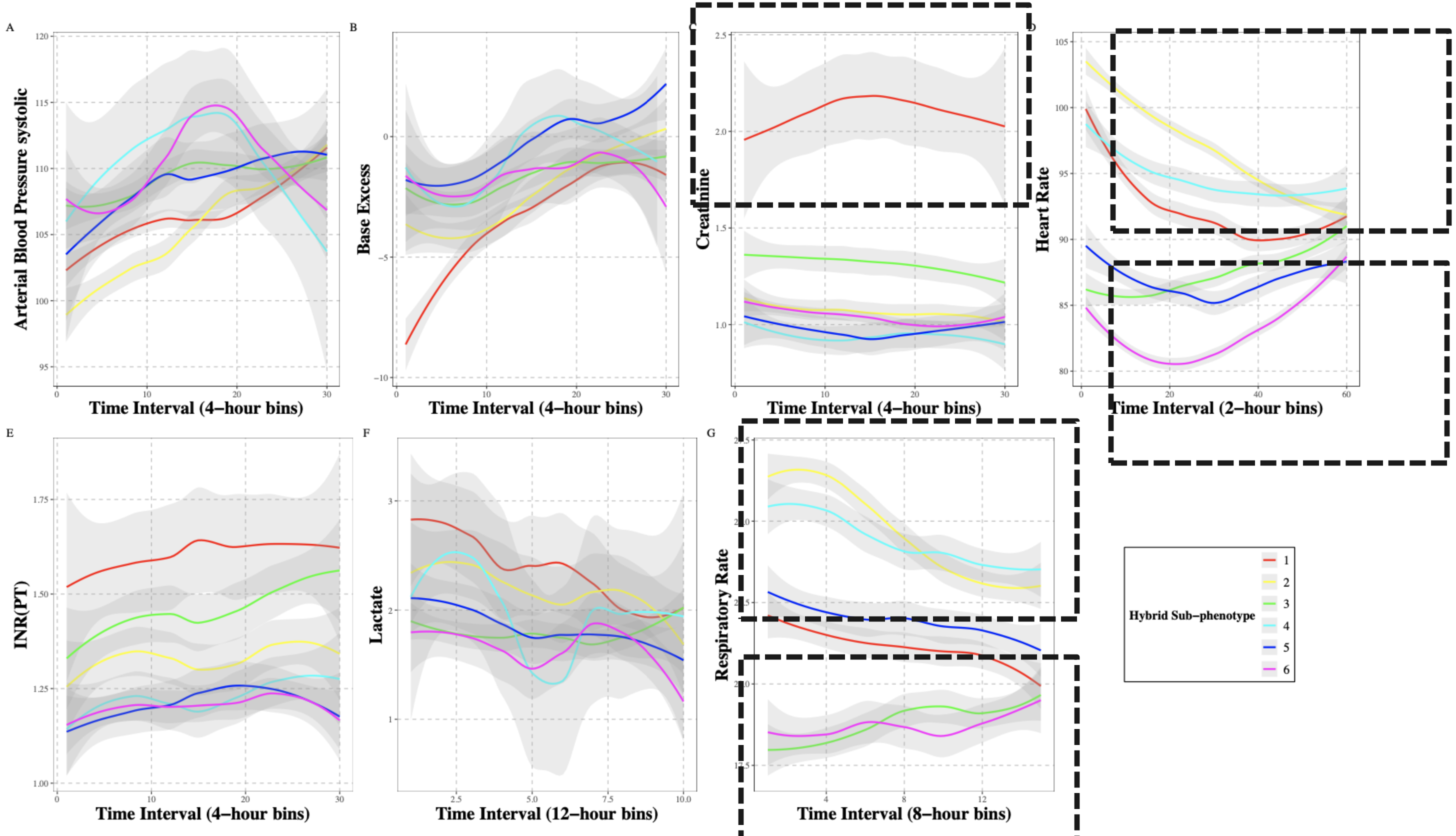


# Results: *Critical Timing*



# Results: Critical Timing Overlooked by Previous Works [10]

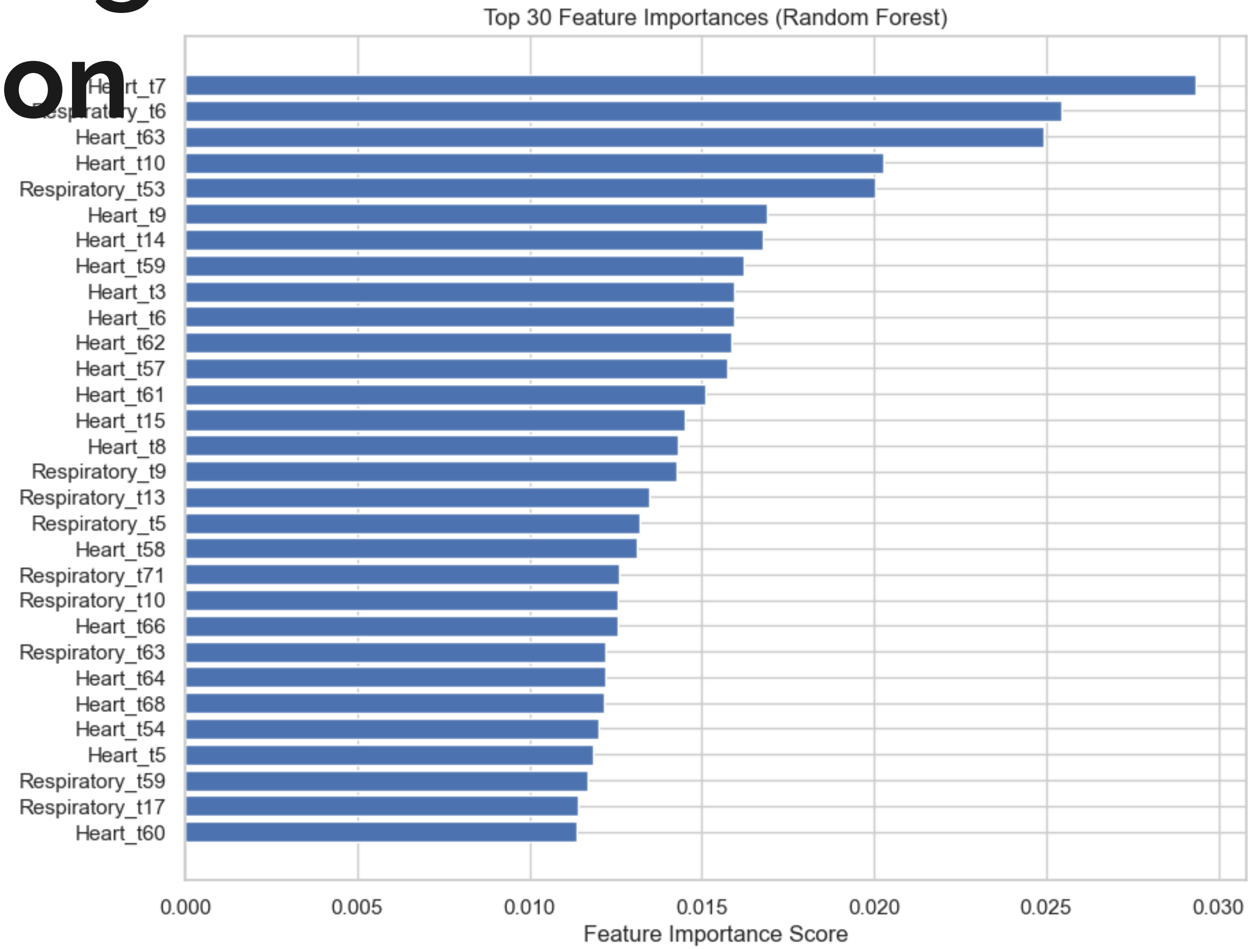
Clustering with lung, kidney, and heart-related calibration data



# Early-Warning Prediction: Time-Series Data


| Window | Model | Accuracy | Precision | Recall | F1-score | AUC-ROC |
|---|---|---|---|---|---|---|
| 12h | Logistic Regression | **0.5983** | **0.6110** | **0.5983** | **0.6020** | 0.6972 |
| | Random Forest | 0.5897 | 0.5998 | 0.5897 | 0.5936 | **0.7873** |
| | XGBoost | 0.5726 | 0.5818 | 0.5726 | 0.5767 | 0.7533 |
| 24h | Logistic Regression | 0.6068 | 0.6204 | 0.6068 | 0.6080 | 0.7488 |
| | Random Forest | **0.6923** | **0.6990** | **0.6923** | **0.6944** | **0.8262** |
| | XGBoost | 0.6752 | 0.6809 | 0.6752 | 0.6761 | 0.8103 |
| 48h | Logistic Regression | 0.8034 | 0.8146 | 0.8034 | 0.8048 | 0.8960 |
| | Random Forest | **0.8889** | **0.8910** | **0.8889** | **0.8881** | **0.9456** |
| | XGBoost | 0.8632 | 0.8661 | 0.8632 | 0.8637 | 0.9354 |
| 120h | Logistic Regression | 0.8632 | 0.8689 | 0.8632 | 0.8645 | 0.9192 |
| | Random Forest | **0.8974** | **0.9105** | **0.8974** | **0.8986** | **0.9830** |
| | XGBoost | 0.8889 | 0.8998 | 0.8889 | 0.8901 | 0.9192 |

# Early-Warning Prediction: Interpretation

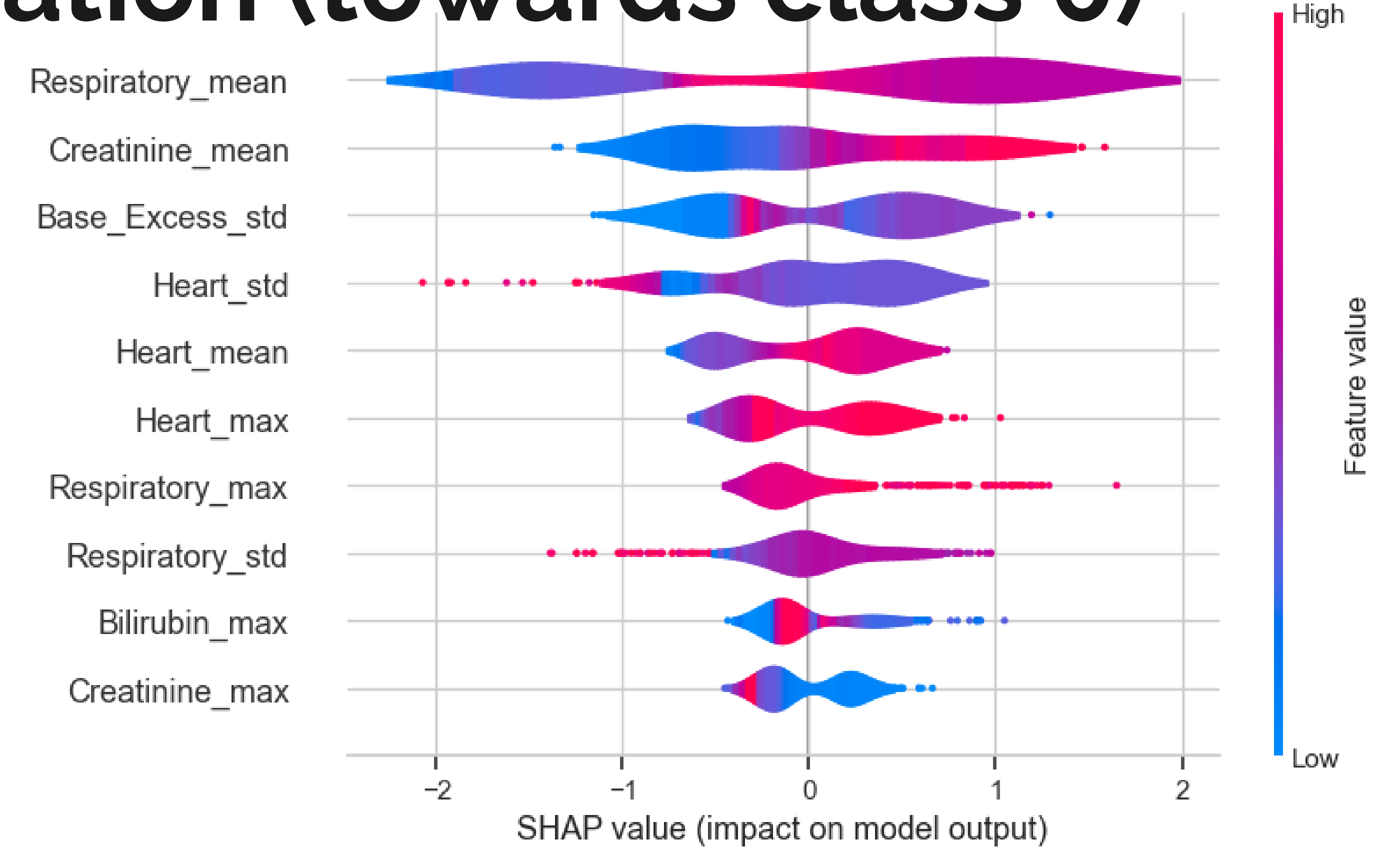


# Early-Warning Prediction: Time-Window Characteristics

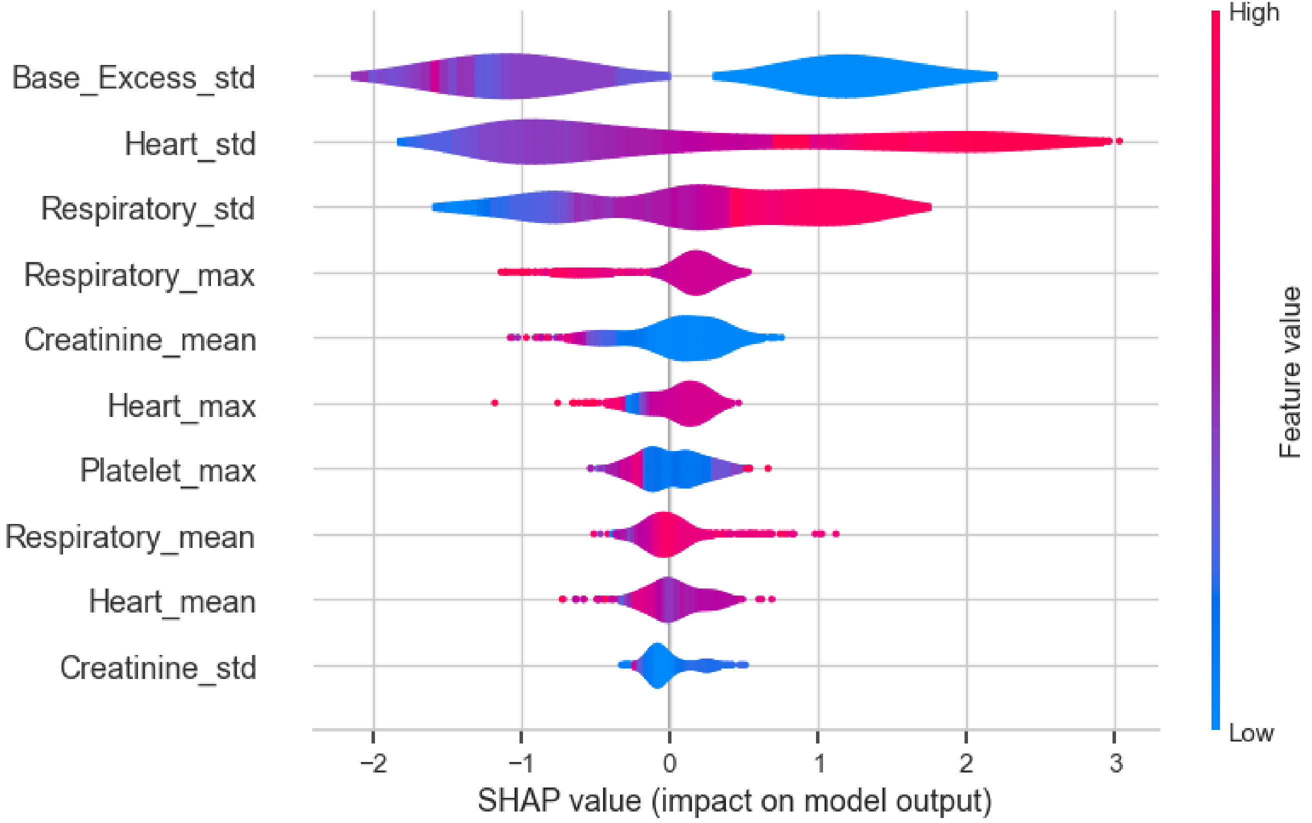
- Take window sizes: first 12h, 24h, 48h
- Take as Features in each Window: Maximum, Minimum, Mean, Standard Deviation

| Window | Model | Accuracy | Precision | Recall | F1-score | AUC-ROC |
|---|---|---|---|---|---|---|
| 12h | Logistic Regression | 0.6752 | 0.6884 | 0.6752 | 0.6793 | 0.7868 |
| | Random Forest | **0.7094** | **0.7184** | **0.7094** | **0.7126** | **0.8040** |
| | XGBoost | 0.6239 | 0.6331 | 0.6239 | 0.6263 | 0.7631 |
| 24h | Logistic Regression | 0.7350 | 0.7502 | 0.7350 | 0.7391 | 0.8439 |
| | Random Forest | **0.7607** | **0.7741** | **0.7607** | **0.7641** | **0.8948** |
| | XGBoost | 0.7350 | 0.7454 | 0.7350 | 0.7376 | 0.8698 |
| 48h | Logistic Regression | 0.8632 | 0.8667 | 0.8632 | 0.8643 | 0.9474 |
| | Random Forest | 0.8632 | 0.8749 | 0.8632 | 0.8646 | **0.9560** |
| | XGBoost | **0.8889** | **0.8941** | **0.8889** | **0.8900** | 0.9510 |

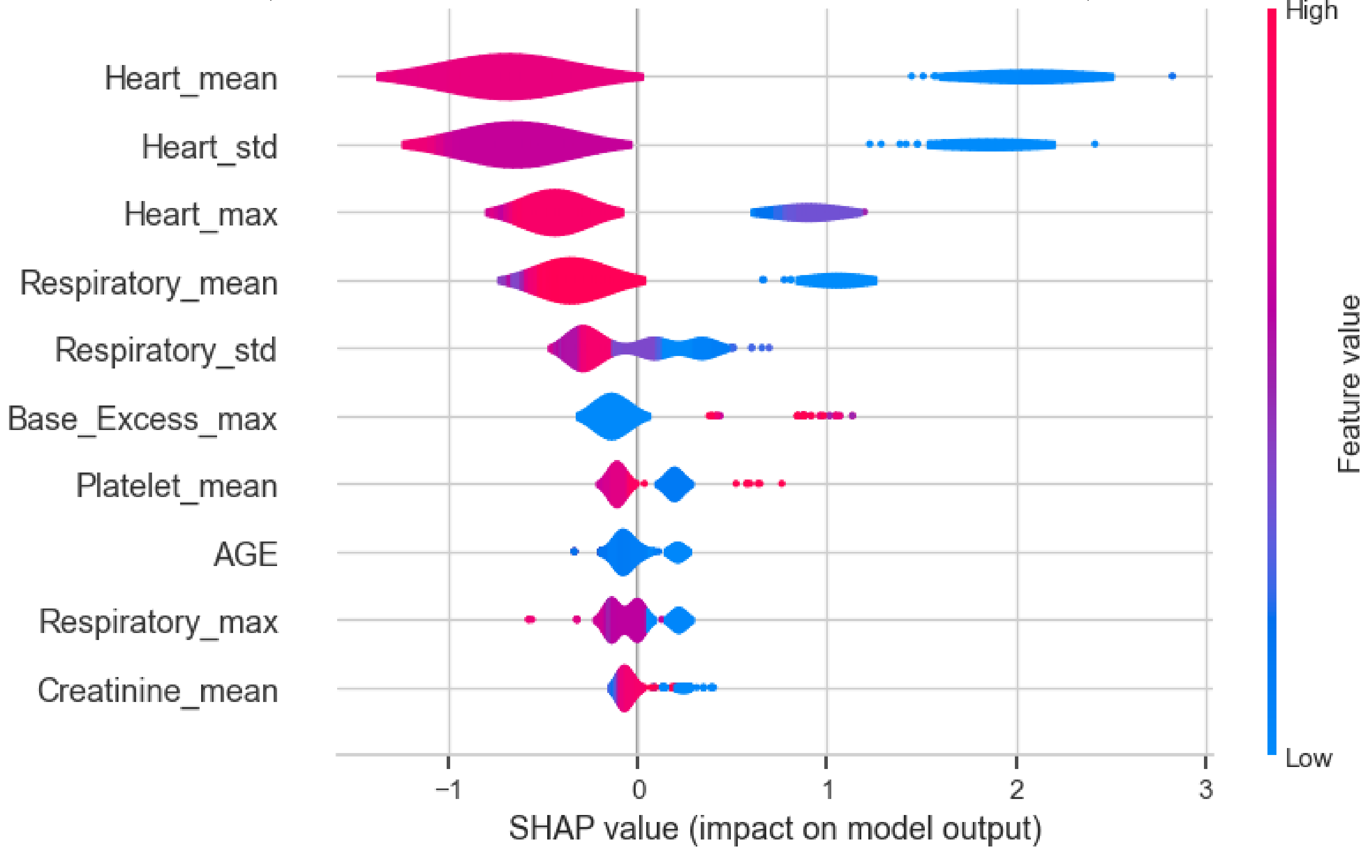
# Early-Warning Prediction: SHAP [14] Interpretation (towards class 0)



# Early-Warning Prediction: Interpretation (violin class 1)



# Early-Warning Prediction: Interpretation (towards class 2)



Feature Importance by Class (Horizontal Stacked SHAP Values)
Class
Class 0
Class 1
Class 2
ETHNICITY
GENDER
AGE
Base_Excess_std
Base_Excess_mean
Base_Excess_min
Base_Excess_max
Creatinine_std
Creatinine_mean
Creatinine_min
Creatinine_max
Heart_std
Heart_mean
Heart_min
Heart_max
Bilirubin_std
Bilirubin_mean
Bilirubin_min
Bilirubin_max
Platelet_std
Platelet_mean
Platelet_min
Platelet_max
Respiratory_std
Respiratory_mean
Respiratory_min
Respiratory_max
Features
0
200
400
600
800
1000
Total SHAP Value

# Conclusion

- We construct **multi-layer networks** for each sepsis-diagnosed admission
- We construct a **mutual information graph** that encodes all sepsis diagnoses
- We compute sepsis subphenotypes from mutual information, and derive **critical timepoints**
- We conduct **early-warning prediction** of subphenotypes by machine learning

# References

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# Agenda

- Sepsis Diagnoses from MIMIC-III
- Mutual Information Graph Construction
- Finding: Sepsis Sub-Phenotypes and Critical Time Points
- Sub-Phenotype Early-Warning Prediction with Machine Learning

**Grateful for your Attention!**