**The m–b state framework: revealing metabolic states underlying the lactate/pyruvate ratio to guide personalized therapy in traumatic brain injury**

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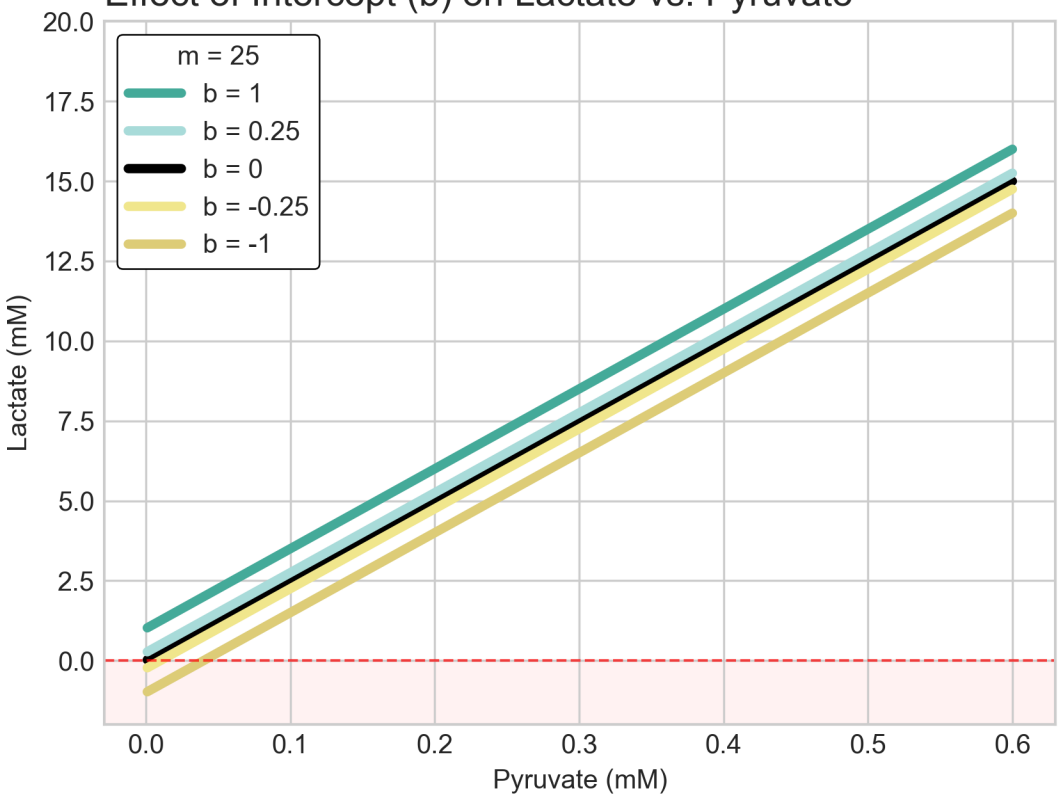
Background: Interpretation of cerebral microdialysis (CMD) data in traumatic brain injury (TBI) has centered on the lactate/pyruvate ratio (LPR), overlooking the lactate–pyruvate dynamics from which the LPR arises and missing opportunities for personalized metabolic insight.

Methods: We developed 21 pipelines to characterize lactate–pyruvate data by linear slope (m) and intercept (b), applying them to 51,036 multimodal monitoring observations from 521 TBI patients. The pipeline with the best cross-validated LPR prediction was used for all analyses.

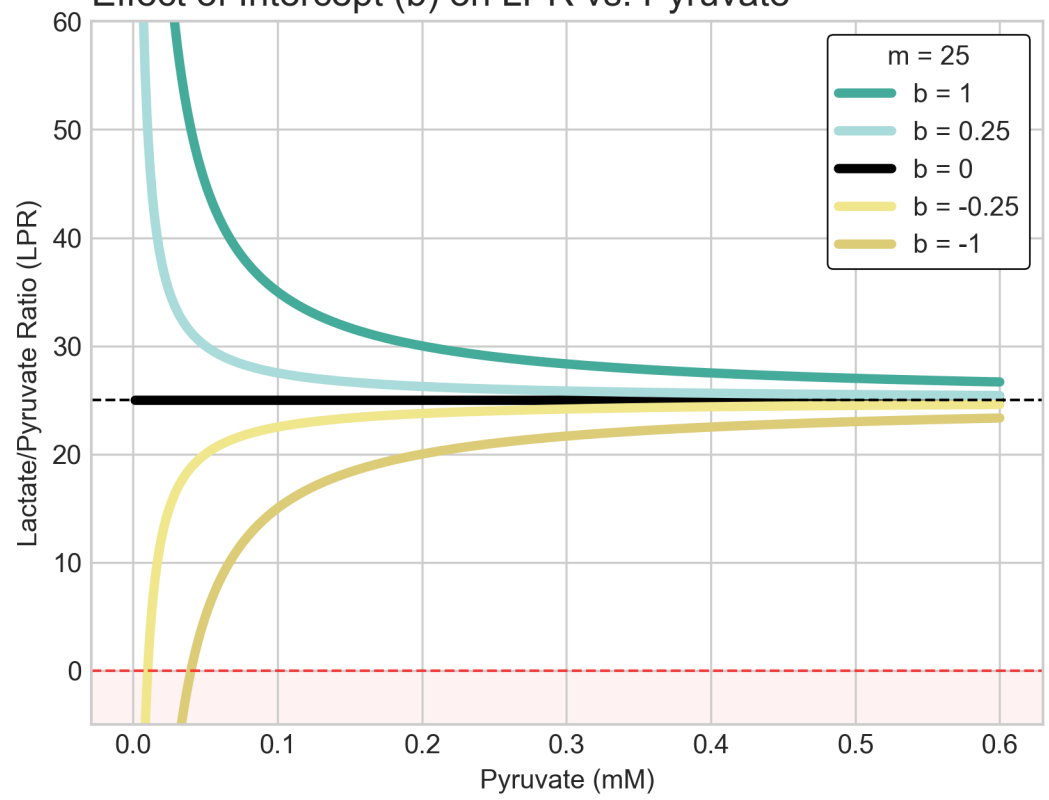
Results: The optimal pipeline split each patient's data into a median of 3 distinct linear segments. Within patients, m and b varied substantially and were strongly negatively coupled ($\rho=-0.894$). Higher volatility of b was significantly associated with unfavorable 6-month outcomes. We empirically validated that lactate–pyruvate linearity corresponds to LPR–pyruvate hyperbolicity (>92% deviance explained). This revealed two metabolic phenotypes based on b's sign: Type P (positive b), where LPR decreases with increasing pyruvate, and Type N (negative b), where LPR increases with pyruvate. This opposition explains the previously observed polarization of patient LPR values. Finally, mapping physiological associations with LPR onto the m–b state-space revealed a heterogeneous landscape of state-dependent trends.

Conclusions: Our m–b state framework shifts focus to the dynamics governing the LPR, enabling a more personalized understanding of cerebral metabolism and establishing a basis for developing state-aware, individualized therapeutic strategies in TBI. Future work should validate our approach in other cohorts and conditions.

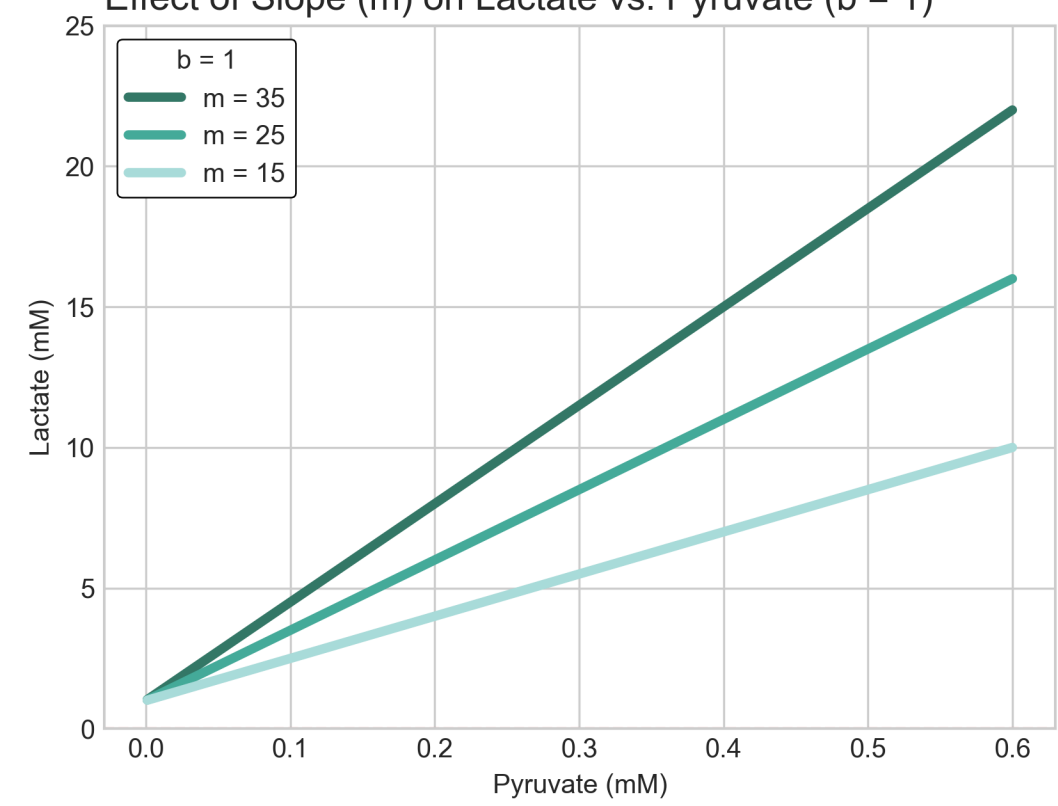
A.i




A.ii




B.i

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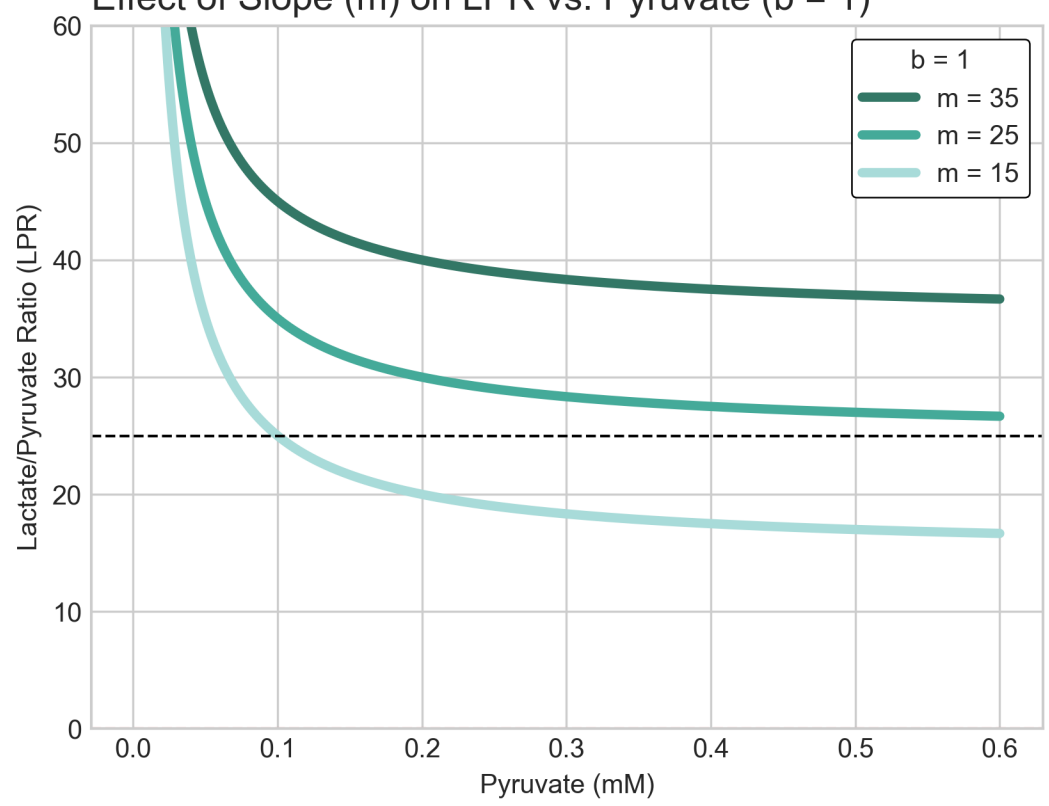
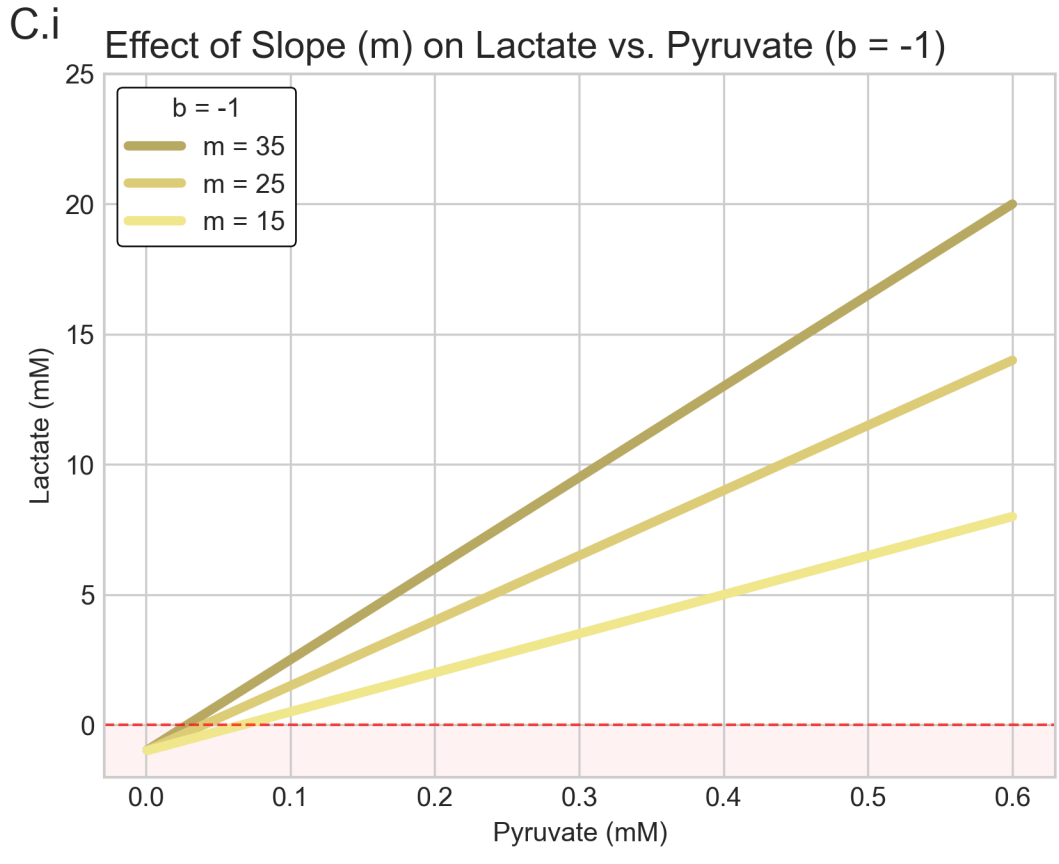



C.i

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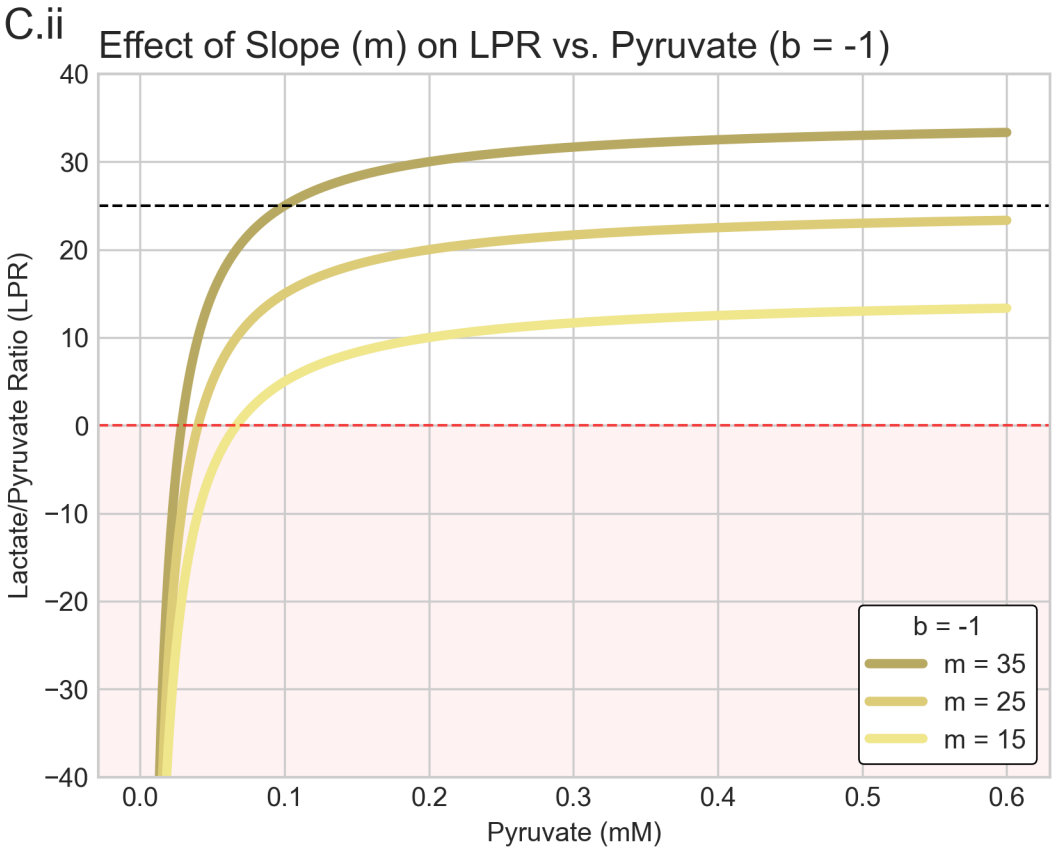
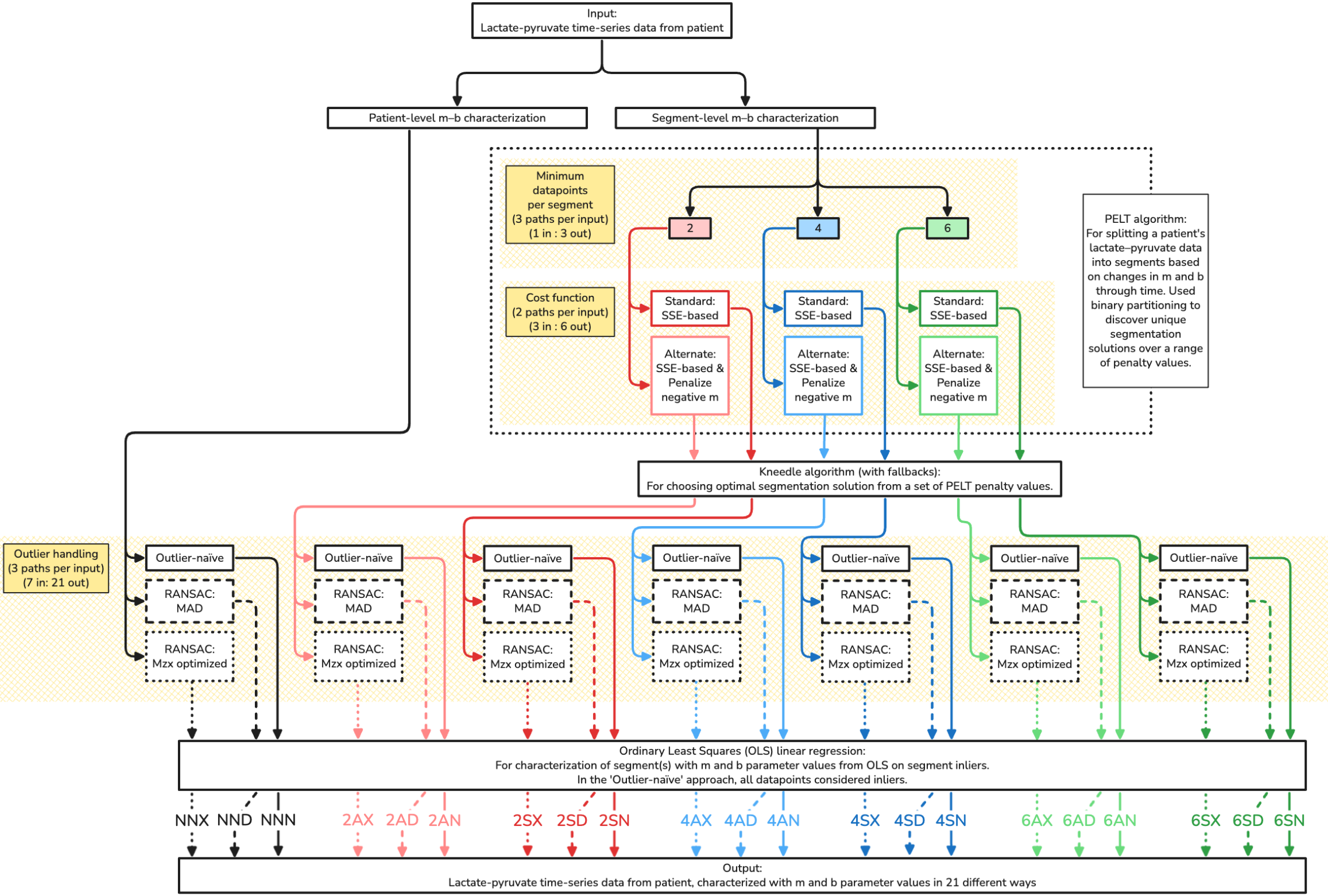
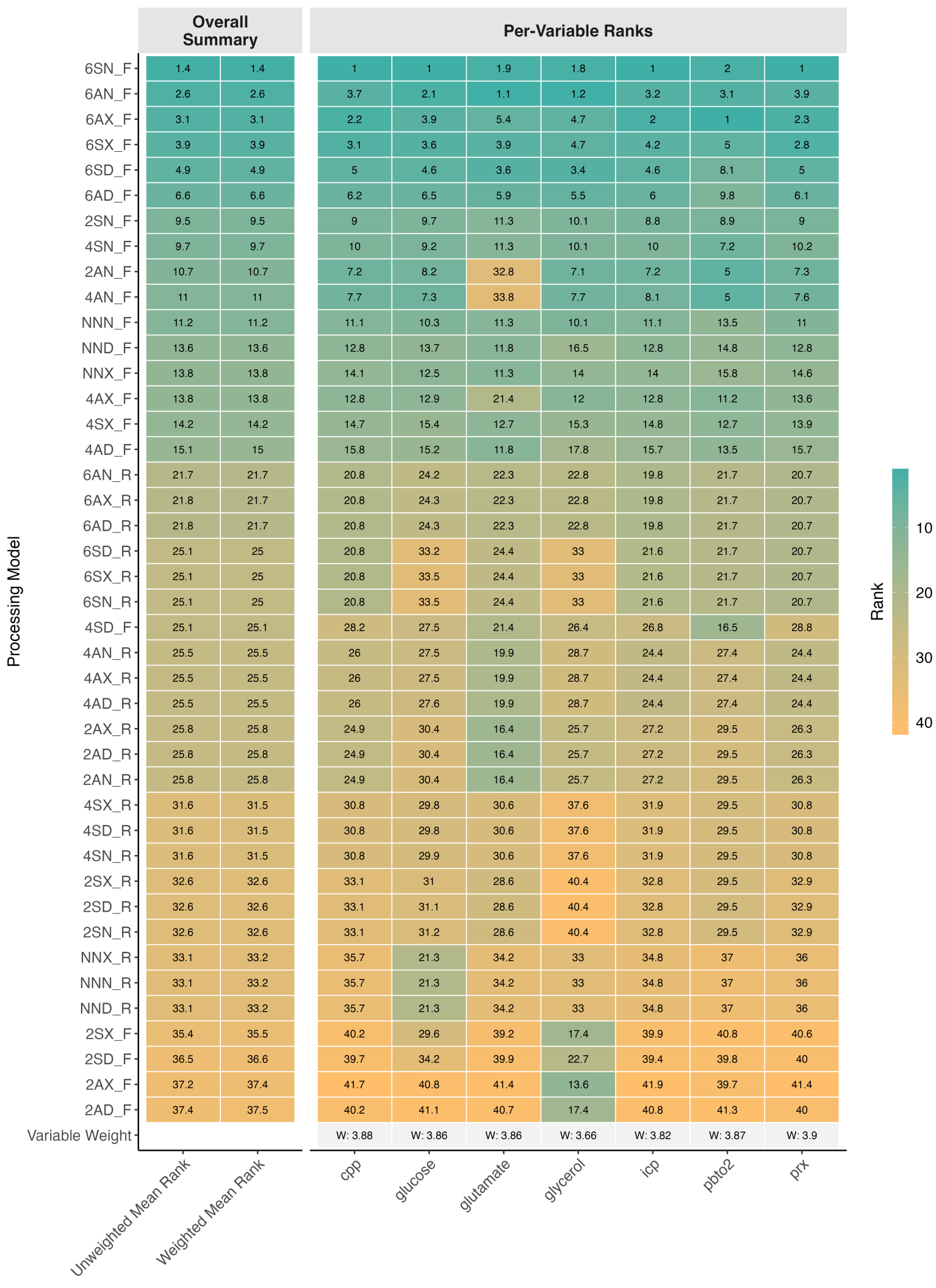
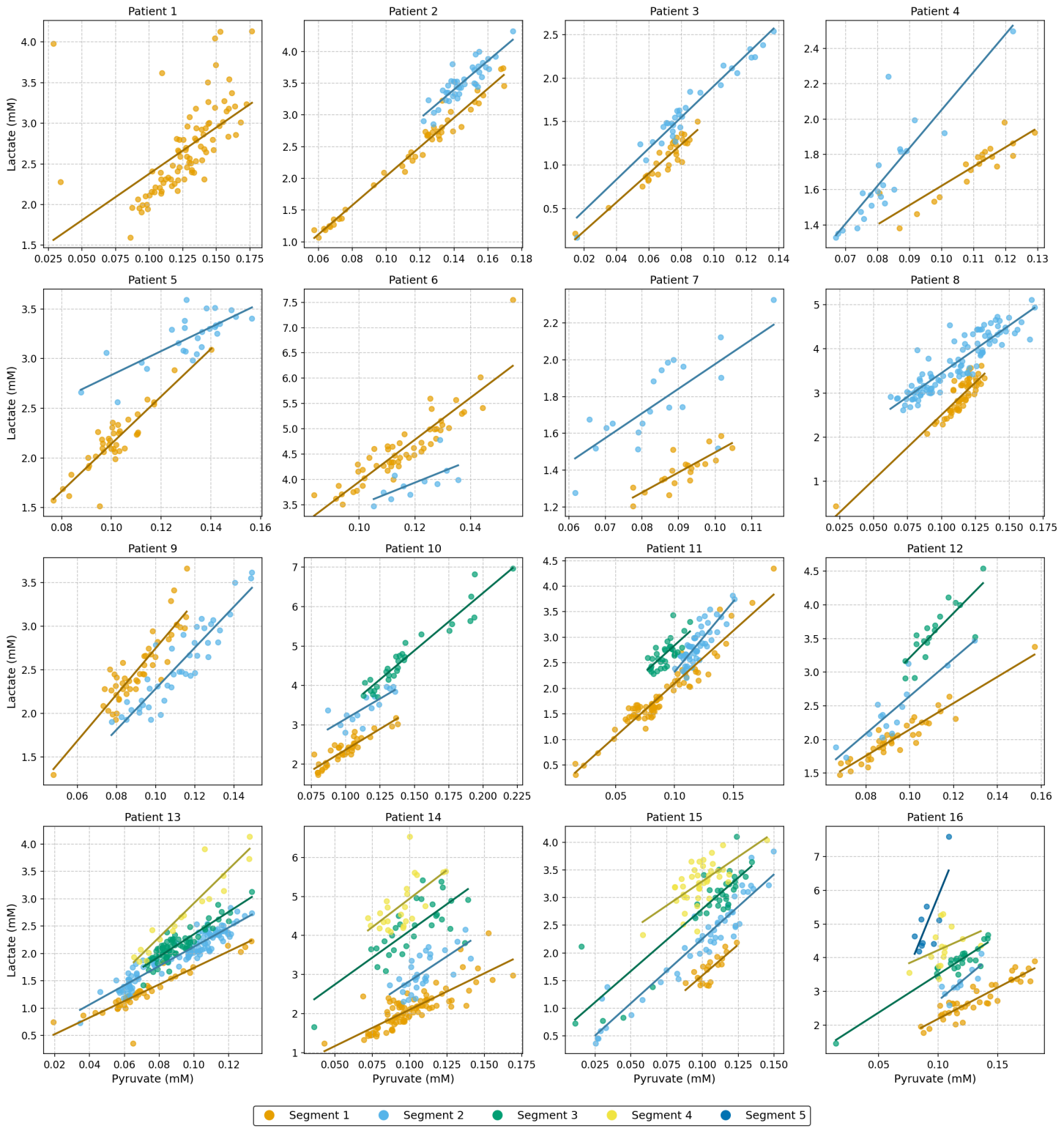
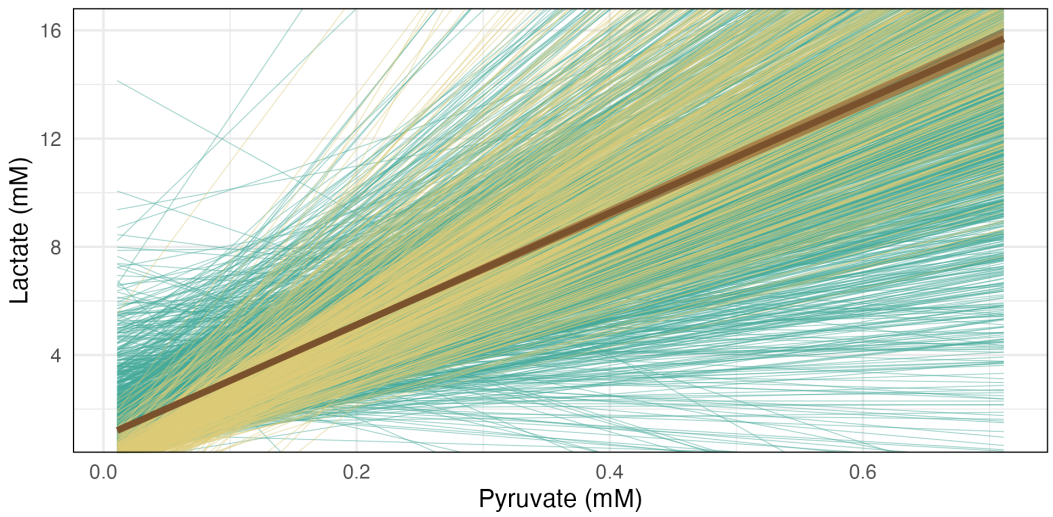



Input:
Lactate-pyruvate time-series data from patient
Patient-level m–b characterization
Segment-level m–b characterization
Minimum datapoints per segment (3 paths per input) (1 in : 3 out)
2
4
6
Cost function (2 paths per input) (3 in : 6 out)
Standard: SSE-based
Alternate: SSE-based & Penalize negative m
PELT algorithm: For splitting a patient's lactate–pyruvate data into segments based on changes in m and b through time. Used binary partitioning to discover unique segmentation solutions over a range of penalty values.
Kneedle algorithm (with fallbacks): For choosing optimal segmentation solution from a set of PELT penalty values.
Outlier handling (3 paths per input) (7 in: 21 out)
Outlier-naïve
RANSAC: MAD
RANSAC: Mzx optimized
Ordinary Least Squares (OLS) linear regression:
For characterization of segment(s) with m and b parameter values from OLS on segment inliers.
In the 'Outlier-naïve' approach, all datapoints considered inliers.
NNX NND NNN
2AX 2AD 2AN
2SX 2SD 2SN
4AX 4AD 4AN
4SX 4SD 4SN
6AX 6AD 6AN
6SX 6SD 6SN
Output:
Lactate-pyruvate time-series data from patient, characterized with m and b parameter values in 21 different ways

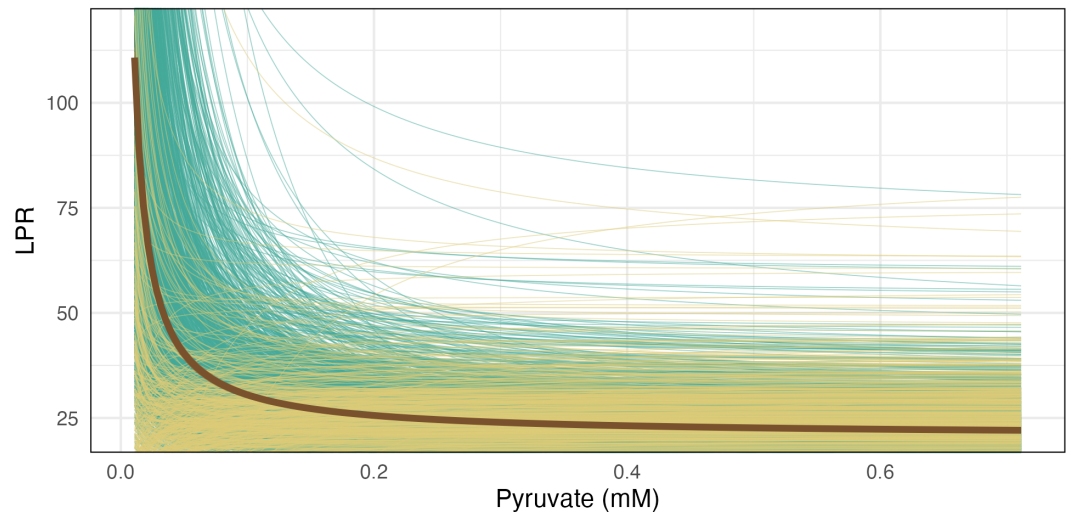

Overall Summary
Per-Variable Ranks
Processing Model
Rank
10
20
30
40
6SN_F 1.4 1.4 1 1 1.9 1.8 1 2 1
6AN_F 2.6 2.6 3.7 2.1 1.1 1.2 3.2 3.1 3.9
6AX_F 3.1 3.1 2.2 3.9 5.4 4.7 2 1 2.3
6SX_F 3.9 3.9 3.1 3.6 3.9 4.7 4.2 5 2.8
6SD_F 4.9 4.9 5 4.6 3.6 3.4 4.6 8.1 5
6AD_F 6.6 6.6 6.2 6.5 5.9 5.5 6 9.8 6.1
2SN_F 9.5 9.5 9 9.7 11.3 10.1 8.8 8.9 9
4SN_F 9.7 9.7 10 9.2 11.3 10.1 10 7.2 10.2
2AN_F 10.7 10.7 7.2 8.2 32.8 7.1 7.2 5 7.3
4AN_F 11 11 7.7 7.3 33.8 7.7 8.1 5 7.6
NNN_F 11.2 11.2 11.1 10.3 11.3 10.1 11.1 13.5 11
NND_F 13.6 13.6 12.8 13.7 11.8 16.5 12.8 14.8 12.8
NNX_F 13.8 13.8 14.1 12.5 11.3 14 14 15.8 14.6
4AX_F 13.8 13.8 12.8 12.9 21.4 12 12.8 11.2 13.6
4SX_F 14.2 14.2 14.7 15.4 12.7 15.3 14.8 12.7 13.9
4AD_F 15.1 15 15.8 15.2 11.8 17.8 15.7 13.5 15.7
6AN_R 21.7 21.7 20.8 24.2 22.3 22.8 19.8 21.7 20.7
6AX_R 21.8 21.7 20.8 24.3 22.3 22.8 19.8 21.7 20.7
6AD_R 21.8 21.7 20.8 24.3 22.3 22.8 19.8 21.7 20.7
6SD_R 25.1 25 20.8 33.2 24.4 33 21.6 21.7 20.7
6SX_R 25.1 25 20.8 33.5 24.4 33 21.6 21.7 20.7
6SN_R 25.1 25 20.8 33.5 24.4 33 21.6 21.7 20.7
4SD_F 25.1 25.1 28.2 27.5 21.4 26.4 26.8 16.5 28.8
4AN_R 25.5 25.5 26 27.5 19.9 28.7 24.4 27.4 24.4
4AX_R 25.5 25.5 26 27.5 19.9 28.7 24.4 27.4 24.4
4AD_R 25.5 25.5 26 27.6 19.9 28.7 24.4 27.4 24.4
2AX_R 25.8 25.8 24.9 30.4 16.4 25.7 27.2 29.5 26.3
2AD_R 25.8 25.8 24.9 30.4 16.4 25.7 27.2 29.5 26.3
2AN_R 25.8 25.8 24.9 30.4 16.4 25.7 27.2 29.5 26.3
4SX_R 31.6 31.5 30.8 29.8 30.6 37.6 31.9 29.5 30.8
4SD_R 31.6 31.5 30.8 29.8 30.6 37.6 31.9 29.5 30.8
4SN_R 31.6 31.5 30.8 29.9 30.6 37.6 31.9 29.5 30.8
2SX_R 32.6 32.6 33.1 31 28.6 40.4 32.8 29.5 32.9
2SD_R 32.6 32.6 33.1 31.1 28.6 40.4 32.8 29.5 32.9
2SN_R 32.6 32.6 33.1 31.2 28.6 40.4 32.8 29.5 32.9
NNX_R 33.1 33.2 35.7 21.3 34.2 33 34.8 37 36
NNN_R 33.1 33.2 35.7 21.3 34.2 33 34.8 37 36
NND_R 33.1 33.2 35.7 21.3 34.2 33 34.8 37 36
2SX_F 35.4 35.5 40.2 29.6 39.2 17.4 39.9 40.8 40.6
2SD_F 36.5 36.6 39.7 34.2 39.9 22.7 39.4 39.8 40
2AX_F 37.2 37.4 41.7 40.8 41.4 13.6 41.9 39.7 41.4
2AD_F 37.4 37.5 40.2 41.1 40.7 17.4 40.8 41.3 40
Variable Weight
W: 3.88 W: 3.86 W: 3.86 W: 3.66 W: 3.82 W: 3.87 W: 3.9
Unweighted Mean Rank
Weighted Mean Rank
cpp
glucose
glutamate
glycerol
icp
pbto2
prx


Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Lactate (mM)
Pyruvate (mM)
Segment 1
Segment 2
Segment 3
Segment 4
Segment 5

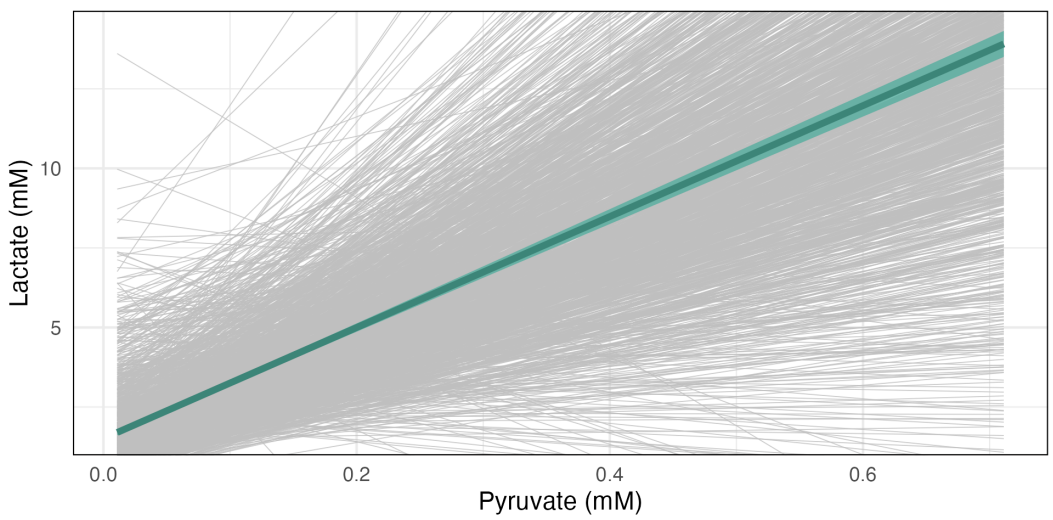
A.i



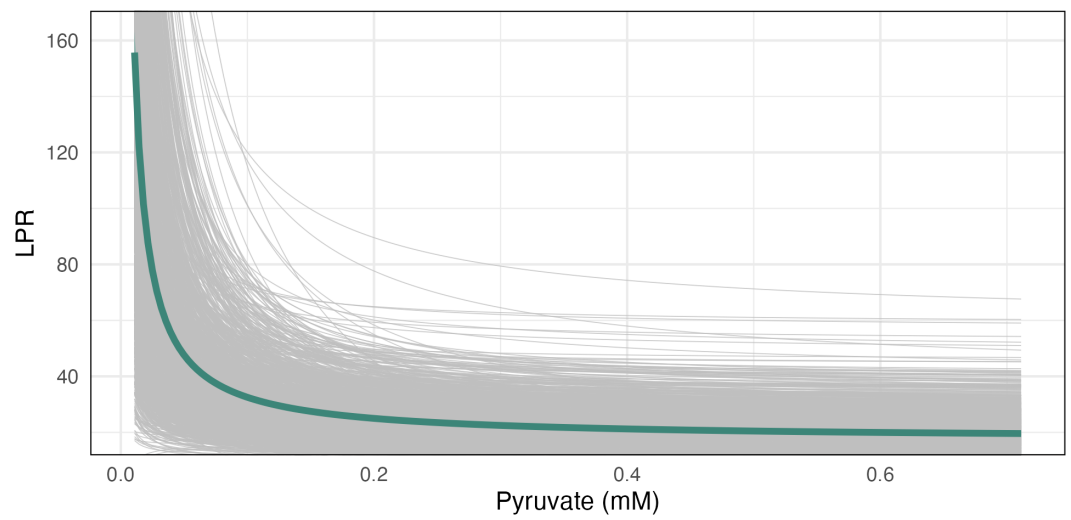

A.ii



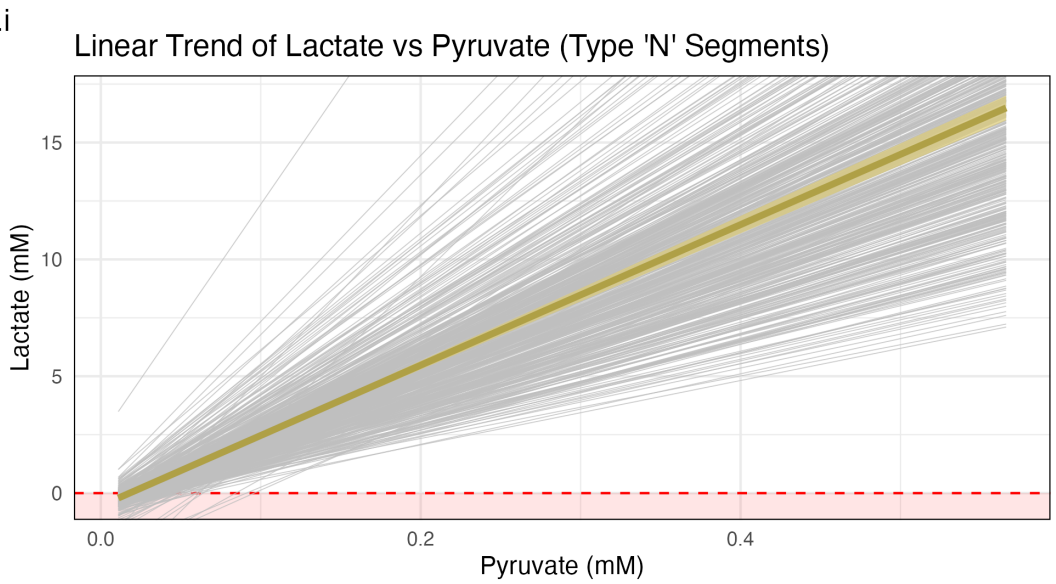

B.i



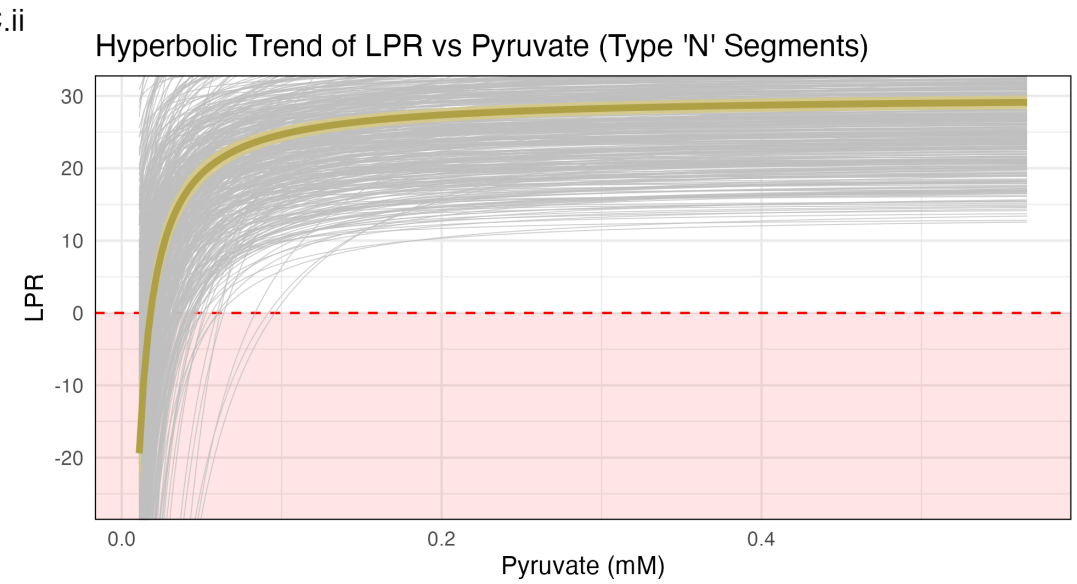

B.ii



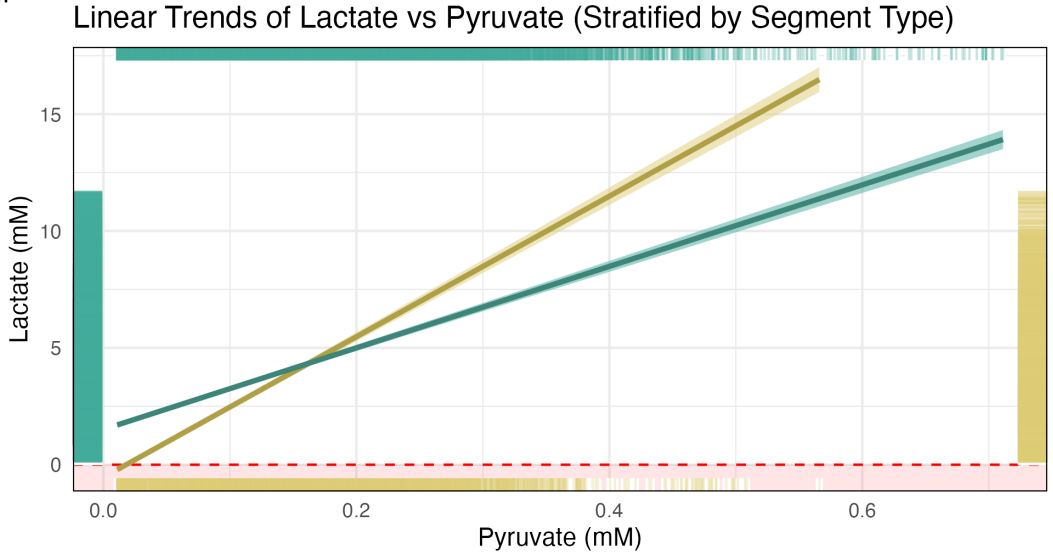

C.i



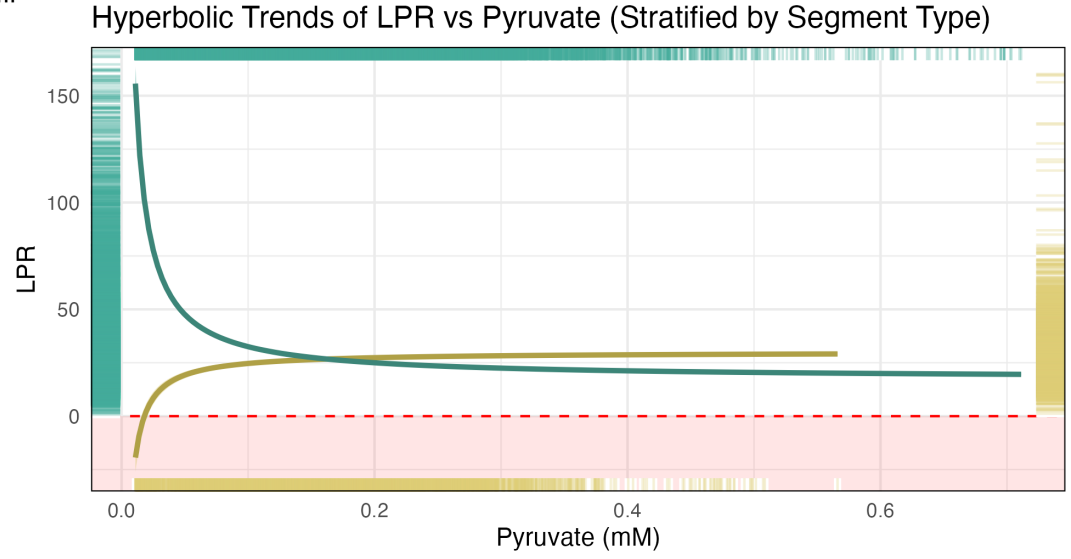

C.ii

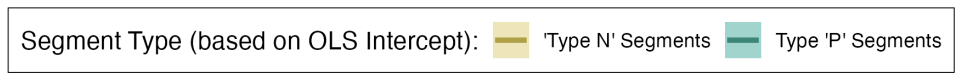


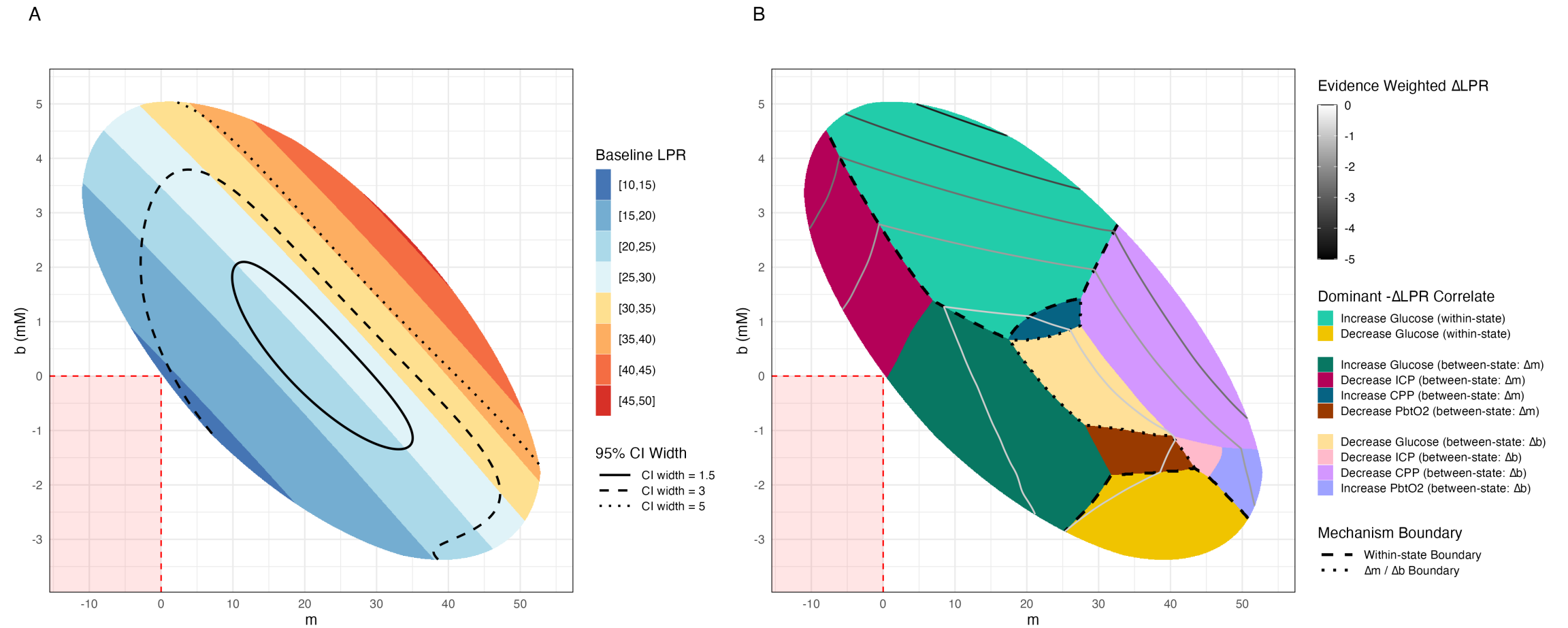

D.i




D.ii




A
B
b (mM)
m
Baseline LPR
[10,15)
[15,20)
[20,25)
[25,30)
[30,35)
[35,40)
[40,45)
[45,50]
95% CI Width
CI width = 1.5
CI width = 3
CI width = 5
Evidence Weighted ΔLPR
0
-1
-2
-3
-4
-5
Dominant -ΔLPR Correlate
Increase Glucose (within-state)
Decrease Glucose (within-state)
Increase Glucose (between-state: Δm)
Decrease ICP (between-state: Δm)
Increase CPP (between-state: Δm)
Decrease PbtO2 (between-state: Δm)
Decrease Glucose (between-state: Δb)
Decrease ICP (between-state: Δb)
Decrease CPP (between-state: Δb)
Increase PbtO2 (between-state: Δb)
Mechanism Boundary
Within-state Boundary
Δm / Δb Boundary