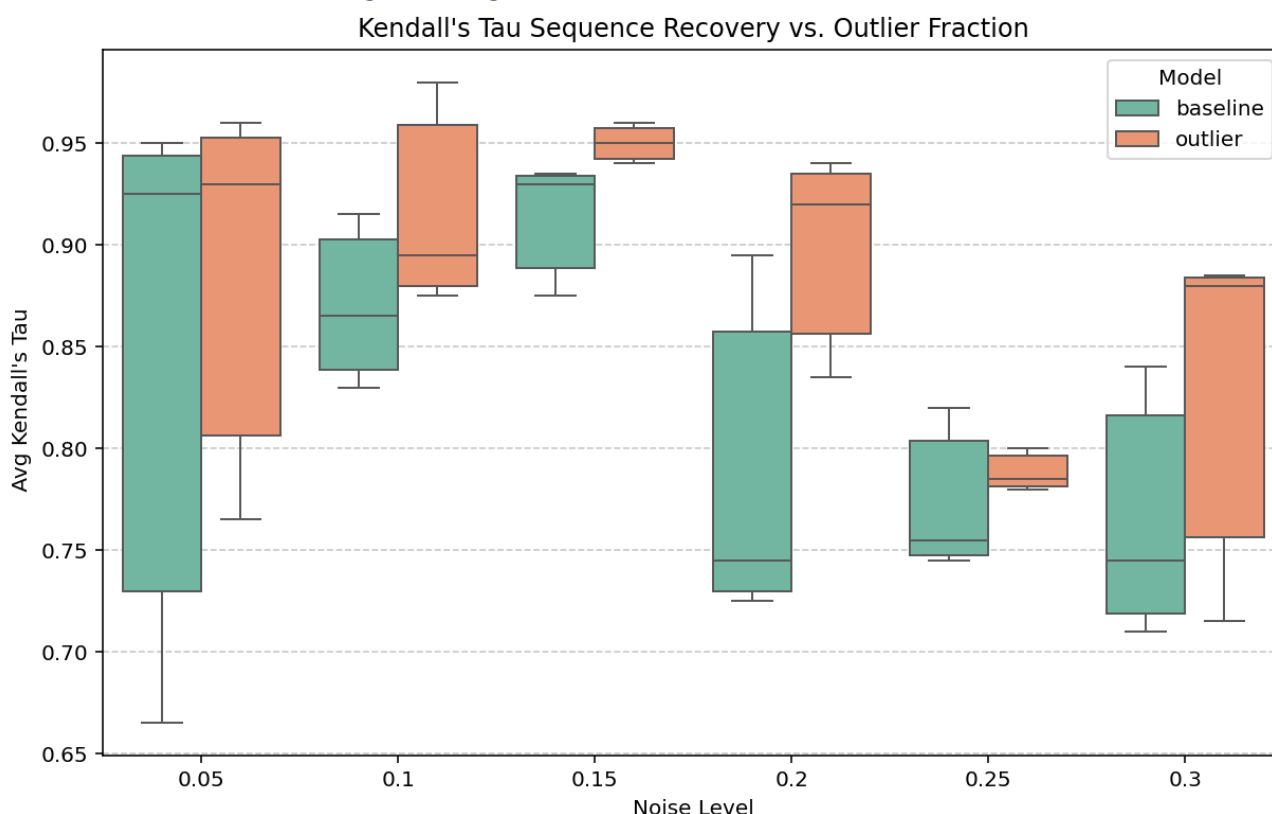
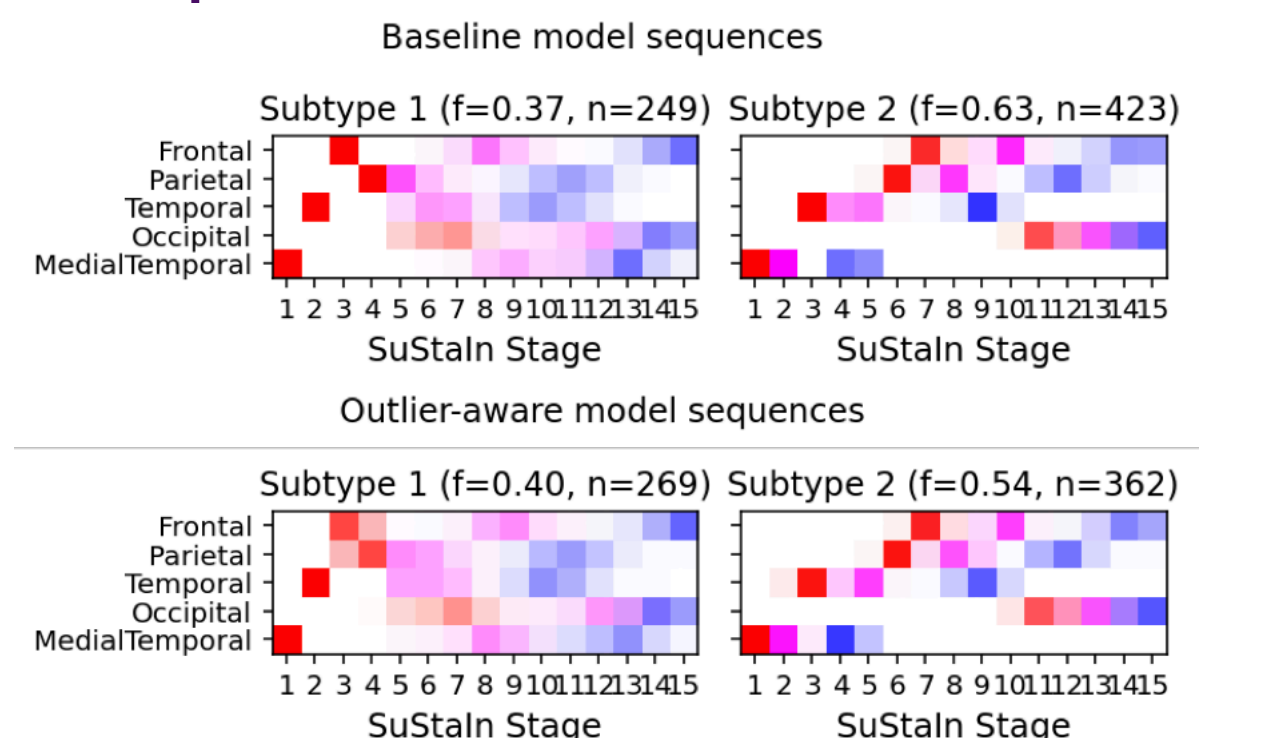


# Robust Disease Progression Modelling With Explicit Outlier Handling

P2-07  
#0653

Mihaela Croitor, Gonzalo Castro Leal, Lawrence P. Binding, Neil P. Oxtoby, Daniel C. Alexander, Alexandra L. Young

Incorporating an explicit outlier class into the SuStaln model improves the stability of disease subtyping and enhances the prognostic value of disease staging in heterogeneous datasets.

| INTRODUCTION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | METHODS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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| <p><b>Context:</b> Data-driven models like SuStaln [1] characterise the temporal evolution of Alzheimer’s disease progression using cross-sectional data.</p> <p><b>The Problem:</b> Clinical datasets are inherently "noisy" because they include misdiagnosed subjects [2], cases of mixed pathology [3] and atypical presentations of disease.</p> <p><b>The Goal:</b> We developed an enhanced SuStaln algorithm with explicit outlier handling to enable robust subtyping and staging despite noise.</p> | <p><b>Model Innovation:</b> Extended the SuStaln mixture model with a uniform distribution outlier class to capture subjects who do not fit existing clusters.</p> <p><b>Validation:</b></p> <ul style="list-style-type: none"><li>• <b>Synthetic Data:</b> Used Kendall’s tau to quantify sequence recovery performance against ground truth as noise increased.</li><li>• <b>Clinical Data:</b> Applied to lobular cortical thickness in 672 Aβ+ subjects (ADNI cohort [4]).</li></ul> <p>Compared against standard SuStaln using subtype stability (Cohen’s kappa), cognitive score correlations, and MCI-to-dementia conversion (Cox proportional hazards).</p> | <ul style="list-style-type: none"><li>• Outlier-aware SuStaln improves sequence recovery in noisy synthetic data</li></ul>  <ul style="list-style-type: none"><li>• In ADNI data, it identified 23 subjects (3.4%) as outliers exhibiting atypical atrophy without disrupting disease sequences</li></ul>  | <ul style="list-style-type: none"><li>• The method improves <b>longitudinal stability</b> (K=0.81 vs 0.74), maintains/strengthens <b>cognitive correlations</b> and improves <b>MCI-AD prognostic fit</b> (C-index 0.625 vs 0.623).</li></ul> <table><tr><th>Analysis Domain</th><th>Metric / Variable</th><th>Standard SuStaln</th><th>Outlier-Aware</th></tr><tr><td rowspan="2">Stability</td><td>Subtype Consistency (12 mo, Cohen's kappa)</td><td>0.77</td><td>0.78</td></tr><tr><td>Subtype Consistency (24 mo, Cohen's kappa)</td><td>0.74</td><td>0.81</td></tr><tr><td rowspan="3">Clinical Correlations (Pearson's r)</td><td>Global Cognition (ADAS-Cog13)</td><td>r = 0.623</td><td>r = 0.626</td></tr><tr><td>Episodic Memory (RAVLT-Imm)</td><td>r = -0.523</td><td>r = -0.525</td></tr><tr><td>MiniMentalState (MMSE)</td><td>r = -0.572</td><td>r = -0.576</td></tr><tr><td rowspan="2">MCI-to-AD Survival (Cox Model)</td><td>Model Performance</td><td></td><td></td></tr><tr><td>Model Fit (AIC)</td><td>518.7</td><td>516.6</td></tr><tr><td></td><td>Prognostic Accuracy (C-index)</td><td>0.623</td><td>0.625</td></tr><tr><td colspan="4">Predictors of Interest</td></tr><tr><td></td><td>Disease Stage (Hazard Ratio)</td><td>HR = 1.13 (p=0.008)</td><td>HR = 1.16 (p=0.003)</td></tr><tr><td></td><td>Subtype Risk (Hazard Ratio)</td><td>HR = 1.39 (p=0.33)</td><td>HR = 1.55 (p=0.13)</td></tr><tr><td colspan="4">Covariates (Control Variables)</td></tr><tr><td></td><td>APOE4 Status (Positive)</td><td>HR = 1.53 (p=0.03)</td><td>HR = 1.49 (p=0.05)</td></tr><tr><td></td><td>Age</td><td>p=0.88</td><td>p=0.61</td></tr><tr><td></td><td>Sex (Male)</td><td>p=0.82</td><td>p=0.84</td></tr><tr><td></td><td>Education (Years)</td><td>p=0.94</td><td>p=0.91</td></tr></table> <p><b>Conclusions:</b> Explicit outlier modeling produces cleaner, more stable subtypes in heterogeneous datasets.</p> | Analysis Domain                                                                                                                                                                                                                                                                                                                                          | Metric / Variable | Standard SuStaln | Outlier-Aware | Stability | Subtype Consistency (12 mo, Cohen's kappa) | 0.77 | 0.78 | Subtype Consistency (24 mo, Cohen's kappa) | 0.74 | 0.81 | Clinical Correlations (Pearson's r) | Global Cognition (ADAS-Cog13) | r = 0.623 | r = 0.626 | Episodic Memory (RAVLT-Imm) | r = -0.523 | r = -0.525 | MiniMentalState (MMSE) | r = -0.572 | r = -0.576 | MCI-to-AD Survival (Cox Model) | Model Performance |  |  | Model Fit (AIC) | 518.7 | 516.6 |  | Prognostic Accuracy (C-index) | 0.623 | 0.625 | Predictors of Interest |  |  |  |  | Disease Stage (Hazard Ratio) | HR = 1.13 (p=0.008) | HR = 1.16 (p=0.003) |  | Subtype Risk (Hazard Ratio) | HR = 1.39 (p=0.33) | HR = 1.55 (p=0.13) | Covariates (Control Variables) |  |  |  |  | APOE4 Status (Positive) | HR = 1.53 (p=0.03) | HR = 1.49 (p=0.05) |  | Age | p=0.88 | p=0.61 |  | Sex (Male) | p=0.82 | p=0.84 |  | Education (Years) | p=0.94 | p=0.91 | <p>[1] Alexandra L Young et al. “Uncovering the heterogeneity and temporal complexity of neurodegenerative diseases with Subtype and Stage Inference”. In: Nature communications 9.1 (2018), p. 4273.</p> <p>[2] Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging 2010; 31: 1275–83.</p> <p>[3] Kurt A Jellinger. “Clinicopathological analysis of dementia disorders in the elderly–an update”. In: Journal of Alzheimer’s disease 9.s3 (2006), pp. 61–70.</p> <p>[4] ADNIMERGE: Alzheimer’s Disease Neuroimaging Initiative. Available online: <a href="http://adni.loni.usc.edu">http://adni.loni.usc.edu</a></p> |
| Analysis Domain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Metric / Variable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Standard SuStaln                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Outlier-Aware                                                                                                                                                                                                                                                                                                                                                                                      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| Stability                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Subtype Consistency (12 mo, Cohen's kappa)                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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| Clinical Correlations (Pearson's r)                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Global Cognition (ADAS-Cog13)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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| MCI-to-AD Survival (Cox Model)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Model Performance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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| Predictors of Interest                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Disease Stage (Hazard Ratio)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Subtype Risk (Hazard Ratio)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | HR = 1.39 (p=0.33)                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | HR = 1.55 (p=0.13)                                                                                                                                                                                                                                                                                                                                                                                 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| Covariates (Control Variables)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | APOE4 Status (Positive)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | HR = 1.53 (p=0.03)                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | HR = 1.49 (p=0.05)                                                                                                                                                                                                                                                                                                                                                                                 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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Sex (Male)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | p=0.82                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | p=0.84                                                                                                                                                                                                                                                                                                                                                                                             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|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Education (Years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | p=0.94                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | p=0.91                                                                                                                                                                                                                                                                                                                                                                                             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| CONTACT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <div><div>Mihaela Croitor<br/>PhD Candidate<br/>I4health CDT<br/>Hawkes Institute<br/>UCL<br/><a href="mailto:zcemmcr@ucl.ac.uk">zcemmcr@ucl.ac.uk</a></div></div> <div></div> |                   |                  |               |           |                                            |      |      |                                            |      |      |                                     |                               |           |           |                             |            |            |                        |            |            |                                |                   |  |  |                 |       |       |  |                               |       |       |                        |  |  |  |  |                              |                     |                     |  |                             |                    |                    |                                |  |  |  |  |                         |                    |                    |  |     |        |        |  |            |        |        |  |                   |        |        |                                                                                                                                                                                                                                                                                                                                                                                                                              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