Constrained Mixture Estimation for Analysis and Robust Classification of Clinical Time Series

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(joint work with Ivan Costa, Christoph Hafemeister and Alexander Schliep)

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Multiple Sclerosis (MS)

- Autoimmune disease
  - leads to neuronal disability
  - multiple genetic causes
  - Prevalence: 266,000 (U.S.)

- Treatment with IFNβ
  - stops disease progression
  - works only for half of the patients
Personalized Medicine

- Treatment selection according to patient genetics
- Machine learning methods to classify response to treatments
- Challenges:
  - dimensionality: more features (genes) than observations (patients)
  - gene expression: noise and missing data
  - patient classification: subjective and error prone
Treatment Response Classification

- **Clinical Time Series** (Baranzini et al., 2005)
  - 52 MS Patients after IFNβ treatment
  - Good and bad responders
  - Expression of 70 genes over 7 time points

- **Classification method (IBIS)**
  - uses only first time point
  - 75% accuracy

Caveats

- Temporal information relevant
  - patients have individual response time (Lin et. al 2008)
- MS has multiple genetic causes
  - response groups may display heterogeneous expression patterns
- Expert classification can be wrong

Our Approach

- Mixture Model based classification
  - Mixture Estimation with constraints (semi-supervised)
    - explore **sub-groups** within classes
    - robustness to **wrong labels**
- Models: linear HMMs
  - align time courses with respect to patient **response time**
  - support **missing value handling** and robust w.r.t. **noise**
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Patient Response Classification

Gene 1

Gene 2

- good responder
- bad responder
- unknown
Patient Response Classification

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Mixture Estimation with Constraints
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negative constraints
Mixture Estimation with Constraints

- Negative constraints
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negative constraints
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Robustness to Wrong Labels

- good responder
- bad responder
- unknown
Robustness to Wrong Labels

Potentially mislabelled
Robustness to Wrong Labels

Potentially mislabelled

“misclassified“
Experiments

• Comparison with
  – IBIS (Baranzini et al., 2005)
  – SVM Kalman (Borgwardt, et al., 2006)
  – HMM Discriminant Learning (Lin et al. 2008)

• Experiments
  – 5 times 4-fold cross validation
  – linear HMM with 4 states
  – feature selection and number of sub-classes
    • based on training error

## Results

<table>
<thead>
<tr>
<th>Method</th>
<th>Genes</th>
<th>Test Acc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBIS</td>
<td>3</td>
<td>75.00%</td>
</tr>
<tr>
<td>HMM Disc</td>
<td>7</td>
<td>85.00%</td>
</tr>
<tr>
<td>SVM Kal.</td>
<td>70</td>
<td>87.80%</td>
</tr>
<tr>
<td>HMM Const 2.</td>
<td>17</td>
<td>89.62%*</td>
</tr>
<tr>
<td>HMM Const 3.</td>
<td>17</td>
<td>90.39%*</td>
</tr>
</tbody>
</table>

*Significantly higher than other methods (paired t-test)*
Results - Consensus Analysis

All 5 x 4-fold classifications – HMM Const. 3

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Results – Selected Genes

- Caspase 10
- Tyk2
- Caspase 3
- MAP3K1
- BAX
- STAT4
- IRF4
- Jak2
- IFN-γRb
- IRF8
- IL-4Ra
- Caspase 2
- IRF5
- IRF2
- Caspase 5
- IL-2Rg
- IFNαR2

Legend:
- Red: bad responders
- Blue: good responders 1
- Cyan: good responders 2
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Conclusion

- Increase in classification accuracy
  - robustness to mislabeled patients
  - detection of sub-classes

- MS Treatment Classification
  - mislabeled sample was confirmed
  - sub-classes of good responders can have clinical implications
  - selected relevant MS genes as features
Acknowledgements

- **Benjamin Georgi**
  Max Planck Institute for Molecular Genetics

- **Katrin Höfl, Peter van den Elzen**
  Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver

- **Sergio Baranzini**
  Department of Neurology, UCSF

**Software:**
- GHMM – www.ghmm.org
- PyMix - algorithmics.molgen.mpg.de
- GQL – www.ghmm.org/gql (soon)

**Funding:**
- PIMS Fellowship
- CAPES (Prodoc Fellowship)
- FACEPE