Predicting Future Observations of Functional and Structural Measurements in Glaucoma Using a Two-Dimensional State-based Progression Model

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Purpose: Future observation prediction based on 2D continuous-time hidden Markov model (2D CT-HMM)

- **Glaucoma progression**: structural (retinal nerve fiber loss) and functional (visual field loss) degeneration processes often occur asynchronously over the disease course.
- **The proposed 2-D state-based CT-HMM model**:
  * Define disease states based on joint structural and functional measures, and model their transition intensities to capture their intricate dynamic relationship.
  * The learned state transition intensities, and state dwelling time distribution, can be intuitively visualized for progression understanding.
  * Covariate (such as age, treatments, etc.) effects can also be learned and incorporated into the model for individual-specific disease state decoding and future state path prediction.

Methods: Learn the state transition intensities from the longitudinal data for state-based future path prediction

- **2-D disease state definition**: visual field index (VFI) and global mean circumpapillary retinal nerve fiber layer (RNFL) thickness from OCT.
- **The likelihood function for one individual with unknown parameters $q_i$ (Q matrix)**:

$$p(O, S^* | \lambda) = \max_{S_{t=1}^{t_{k-1}}} \prod_{t=1}^{t_{k-1}} p(o_t | S_t) p(S_t | S_{t-1}) (t_k - t_{k-1})$$

where $P(d) = e^{Qd}$ is the state transition probability matrix with duration $d$, computed from the matrix exponential of intensity matrix $Q$. The $P(d)$ entry represents the probability that if the current state is $s_i$, then after duration $d$, the state will be $s_j$ (there can be many state jumps in the time interval).

- **Maximize the overall likelihood from all individuals to estimate the parameters**:
  * Expectation-Maximization (EM)-based method to find the instantaneous state transition rates $q_i$ for each link, which defines the transition intensity matrix $Q$.
- **Future state prediction**: decode the hidden disease state path from the noisy history data using Viterbi algorithm, then predict the future state given any future time $t$ by $j = \max_j P_j(t)$, where $j$ denotes the current state.

Results: 2D CT-HMM method outperforms linear regression (LR) prediction

- **Dataset**: 81 glaucomatous eyes from 46 patients followed for 12.4±4.3 years; each eye has at least 6 visits (average 8.5±2.9 visits).
- **Testing**: 10-fold cross validation; for a testing eye, the first 5 visits were used as history data to decode the hidden states, then used for future observation prediction.
- **Performance assessment**: mean absolute error (MAE) between the predicted values and the actual measurements.

### Results: 2D CT-HMM outperforms LR (t-test, p<0.001)

<table>
<thead>
<tr>
<th>MAE</th>
<th>Linear Regression</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VFI</td>
<td>4.88 ± 8.44</td>
<td>5.95 ± 9.79</td>
<td>p &lt; 0.001</td>
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<tr>
<td>RNFL</td>
<td>8.25 ± 7.89</td>
<td>16.34 ± 19.65</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
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### Conclusion and Future Work

- **Conclusion**: the proposed state-based model resulted in more accurate estimates of future observations (VFI and RNFL thickness) compared to linear regression method.
- **Future work**: incorporate covariates (age, treatment, etc.) for individual-level prediction.

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