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

P8
201

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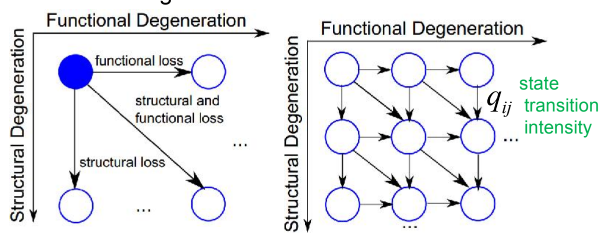
Purpose: Future observation prediction based on 2-D continuous-time hidden Markov model (2D CT-HMM)

- **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_{ij} (Q matrix):***

$$p(O,S^* \mid \lambda) = \max_{S^*=s_1,\dots,s_n} \{ p(o_1 \mid s_1) p(s_1) \prod_{k=2}^{n} \underbrace{p(o_k \mid s_k)}_{\text{state data emission prob.}} \underbrace{P_{s_{k-1},s_k}(t_k - t_{k-1})}_{\text{state transition prob. with time interval } (t_k - t_{k-1})} \}$$

where $P(d) = e^{Qd}$ is the state transition probability matrix with duration d, computed from the matrix exponential of intensity matrix Qd. The $P_{ij}(d)$ 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).

O: noisy observation sequence
S*: best hidden state sequence
(o_k, t_k): one visit's data (observations, time)
q_{ij}: state transition intensity between s_i, s_j
Q: state transition intensity matrix composed by q_{ij}
P(d): state transition prob. matrix with duration d
λ : model parameters

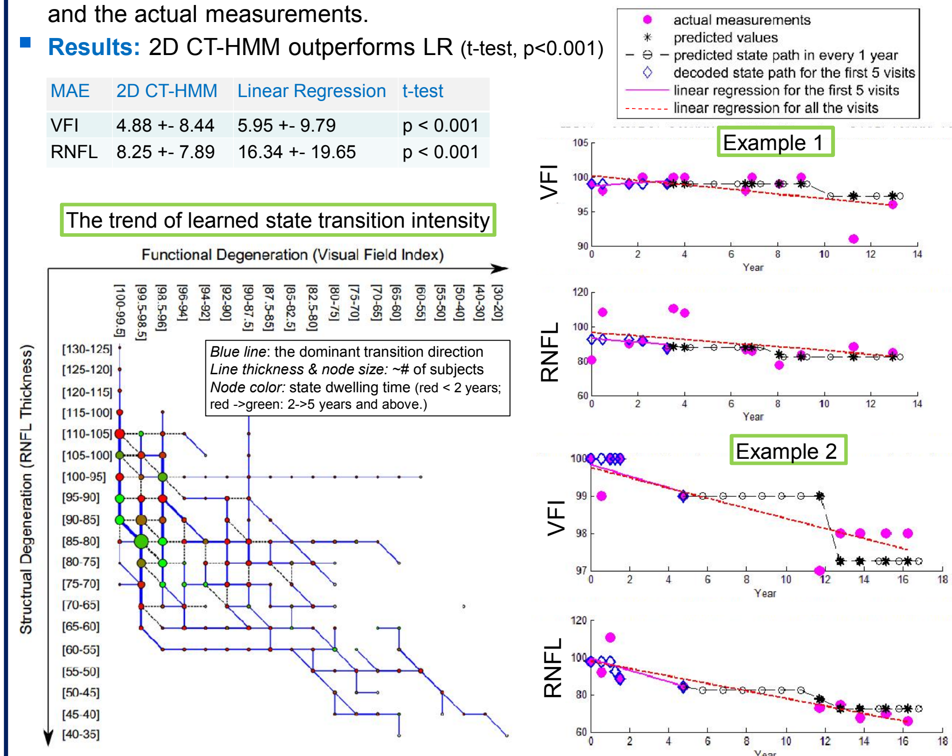
- **Maximize the overall likelihood from all individuals to estimate the parameters:**
  * Expectation-Maximization (EM)-based method to find the instantaneous state transition rates q_{ij} for each link, which defines the transition intensity matrix Q.
- **Future state prediction:** decode the hidden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

MAE	2D CT-HMM	Linear Regression	t-test
VFI	4.88 +- 8.44	5.95 +- 9.79	p < 0.001
RNFL	8.25 +- 7.89	16.34 +- 19.65	p < 0.001

The trend of learned state transition intensity



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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