Assessment of Age Effect in Structural and Functional Glaucoma Progression Analysis

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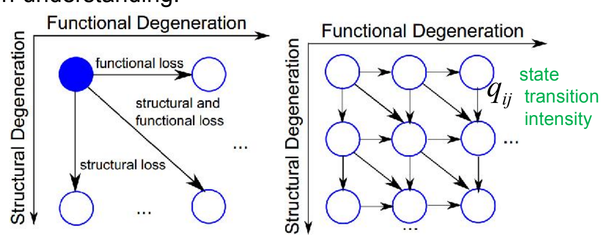
Purpose: To assess the age effect in glaucoma progression using a novel 2-D state-based continuous-time hidden Markov model (2D CT-HMM)

- **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: Cox proportional hazard model is used to assess the age effect in state transition intensity

- **2-D disease state definition: :** visual field index (VFI) and global mean circumpapillary retinal nerve fiber layer (RNFL) thickness from OCT.
- **Age effect:** age-varying state transition intensity (q_{ij,t_k}) using Cox proportional hazard model:

$$q_{ij,t_k} = q_{ij0} e^{w_m \cdot age_{t_k}}$$

where 1 year of aging is associated with a factor e^{w_m} of baseline transition intensity q_{ij0}

> O: noisy observation sequence
> S*: best hidden state sequence
> (ok, tk): one visit's data (observation, time)
> qij: state transition intensity between si, sj
> wm: weight of the age effect for direction m
> Q: transition intensity matrix composed by qij
> P(d): transition prob. matrix with duration d
> λ : model parameters

- **The likelihood function for one individual:**

$$p(O,S^*|\lambda) = \max_{S^*=s_1,\ldots,s_n} \{p(o_1|s_1)p(s_1)\prod_{k=2}^{n} p(o_k|s_k)[P_{t_{k-1}}(t_k - t_{k-1})]_{s_{k-1},s_k}\}$$

where $P_{t_{k-1}}(d) = e^{Q_{t_{k-1}} d}$ — *state data emission prob.* ($p(o_k|s_k)$); *state transition prob. with time interval* $(t_k - t_{k-1})$

is the state transition prob. matrix with duration *d*, computed from the matrix exponential of transition intensity matrix $Q_{t_{k-1}} d$. The $\{P(d)\}_{i,j}$ entry represents the prob. that given the current state is s_i, then the state will be s_j after duration *d* (many state jumps in between is possible).

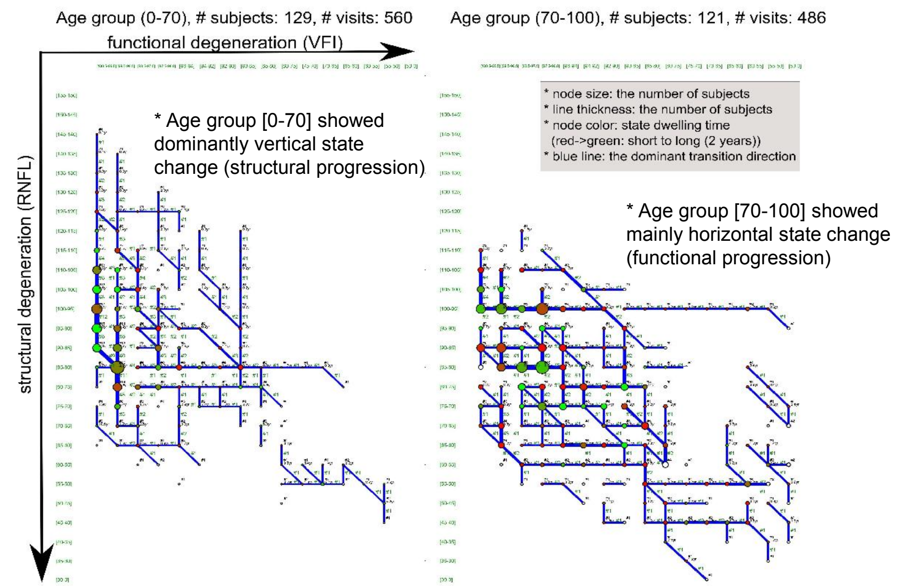
- **Maximize the overall likelihood from all individuals to estimate the parameters:**
  *** Two sets of parameters:** the baseline state transition intensity (q_{ij0}) for each link and the age effect (w_m) for each of the three state transition directions (→ ↓ ↘).
  *** Expectation-Maximization (EM)-based method**: alternatively optimize the two sets of parameters until converges.

Results: Significant age effect in functional degeneration

- **Dataset:** 197 glaucomatous eyes followed for 10.6+/-5.0 years.
- **Results of age effect assessment:**

Loss Type / Risk	1-Year Aging Effect
Functional (F) loss →	2.24% (95% CI: 0.87%~3.61%) *
Structural (S) loss ↓	0.84% (95% CI: -0.18%~1.82%)
Concurrent F and S loss ↘	0.30% (95% CI: -1.59%~2.19%)

* 1 year of aging is significantly associated with 2.24% of greater risk of functional loss.



Conclusion and Future Work

- **Age-varying modeling:** may aid in more informed progression analysis and prediction.
- **Intuitive state-based visualization:** our model can quantify and intuitively visualize the intricate relationship between structural and functional progression.
- **Future work:** model more covariates (age, treatment options, etc.) together, design and test different hazard models, test on prediction tasks.

Reference

- Y-Y. Liu, et al, "Longitudinal Modeling of Glaucoma Progression Using 2-Dimensional Continuous-Time Hidden Markov Model", MICCAI 2013.

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