Study of Glaucoma Change Probability for Open-angle Glaucoma

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Outline

- Background and Significance
- Objectives
- Methodology
- Results and Discussion
- Conclusion
- Future work
- Acknowledgements
Background and Significance
What is Glaucoma?

• Glaucoma is a sight-threatening disorder marked by an increase in intraocular pressure (IOP) that is too high for the optic nerve to tolerate.

• It is the most common optic nerve disorder, affecting 1-2% of the US population and one of the leading causes of blindness.$^{1,2}$

• There are two types of glaucoma: open angle and closed angle.

• The number of persons estimated to be blind as a result of primary glaucoma is 4.5 million, accounting for slightly more than twelve percent of all global blindness.$^{3}$
Background and Significance

What is Glaucoma?(Cont’d)

- Open angle glaucoma
  - Excessive buildup of aqueous humor, increasing IOP.
  - When IOP remains elevated or continues to rise, fibers in the optic nerve are compressed and destroyed, leading to a gradual loss of vision over a period of years.

- Closed angle glaucoma
  - Is relatively uncommon.
  - Primarily characterized by rapid and extreme elevations of IOP, often causing acute symptoms such as severe eye pain and rapid blurring of vision¹.
Perimetry Test (Quantification of VF)
Perimetry Test (Quantification of VF)
Single Field Analysis

Name: Z CARDONA, GLORIELL
ID: DOB: 09-13-1987

Central 24-2 Threshold Test

Stimulus: III, White
Background: 31.5 ASB
Strategy: SITA-Fast
Pupil Diameter: 7.5 mm
Visual Acuity: RX: DS DC X

Date: 07-20-2010
Time: 9:23 AM
Age: 22

Test Duration: 02:58

Fovea: 34 dB

GHT
Within normal limits
VFI 100%
MD -1.55 dB P < 10%
PSD 1.21 dB

Visual Field Laboratory
University of Iowa
College of Medicine
Iowa City, IA
(319) 356-1611

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HFA II 750-10127-4.2/4.2
Single Field Analysis

PRE-LAUNCH EVALUATION SOFTWARE.

Eye: Right

DOB: 10-19-1990

Central 24-2 Threshold Test

Fixation Monitor: Gaze/Blind Spot

Fixation Target: Central

Fixation Losses: 0/12

False POS Errors: 0%

False NEG Errors: 0%

Test Duration: 02:50

Fovea: 39 dB

Stimulus: III, White

Background: 31.5 ASB

Strategy: SITA-Fast

Pupil Diameter: 6.6 mm

Visual Acuity:

RX: DS DC X

Date: 07-20-2010

Time: 9:42 AM

Age: 19

GHT

Within normal limits

VFI: 100%

MD: +0.16 dB

PSD: 1.13 dB

Total Deviation

Pattern Deviation

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Background and Significance

Methods for detecting change/disease progression at a visual field location

- Point wise regression on the 52 locations over time to identify decrease in regression slope

- Glaucoma Change Probability (GCP)
  - Examines the difference in threshold deviation at individual locations between a given field and baseline test results
  - The baseline test result is obtained through a test retest mechanism
    - 32 patients were tested once every week for 5 weeks
      - Repeated testing of both normal and patients with varying degrees of visual loss.
      - Construction of confidence limits for retest variability.
Methods for detecting light sensitivity threshold

**Staircase procedure**

- Begins from high intensity stimulus and it is reduced until the observer makes a mistake in which case the procedure is reversed and then increased until observer responds correctly.

Analogy

This is similar to two other optimization methods:

- Escalation/ De-escalation in Clinical Trials to reach MTD
- Stochastic Approximation in Statistics
Objectives

• To program and compare the performance of three variants of GCP on longitudinal clinical data gathered at the University of Iowa department of neurology.
  • 120 glaucoma subjects and 60 normal subjects
• Each of these variants is characterized by the following:
  • Threshold crossing from a test-retest baseline data gathering (probabilistic)
  • Confirmation of threshold crossing on overlapping (not necessarily spatially contiguous) visual fields in time (clinician input)
  • Number of locations affected in a visual field (clinician input).
Methodology

GCP Methods Considered

Criteria for progression / change assessment

- GCP(2x4): 4 or more locations fall below a threshold and are confirmed at the next two tests

- GCP(8,2x4): 8 or more locations fall below a threshold and are confirmed at one of two tests

- GCP(3x4): 4 or more locations fall below a threshold and are confirmed at the next three tests
Normal Eye

Test #1

Test #2

Test #3
Normal Eye

GCP(8,2x4)

Test #1

Test #2

Test #3
GCP(3x4)

Test #1

Test #2

Test #3

Test #4
Methodology

Basis for comparing GCPs and ROC

- Since the data is highly variable, it is necessary to determine which GCP method has the highest sensitivity and specificity.

- A receiver operating characteristic (ROC) curve illustrates the relationship between sensitivity and specificity.
Methodology

Datasets

- 120 subjects with glaucoma (4 year period, every 6 months)
- 60 subjects with no disease (control)
- 32 test-retest subjects for constructing the threshold confidence interval
- 3 functions were written for obtaining the sensitivity and specificity of each GCP method and comparing their efficiency.
Methodology: R Code

# Create function with patient number and population to get any patient's data
GCP <- function(i, population, q_trt){
  M <- subset(population, PNUM==i)
  NewM = M[,-1]
  avg_population <- colMeans(NewM[1:2,])
  population_avg <- rbind(avg_population, NewM[3:10,])
  result <- (population_avg < q_trt)
  N <- t(result[, -c(26,35)])
  prog.2by4 <- 0
  prog.3by4 <- 0
  prog.8_2by4 <- 0
  for(i in 1:7) {
    P <- data.frame(unname(N[, i:(i + 2)]))
    v <- rowSums(subset(P, X1 == 1))
    if(length(v[v>=2]) >= 4) { prog.2by4 <- 1 }
    if(length(v[v==3]) >= 4) { prog.3by4 <- 1 }
    if(sum(colSums(P, na.rm = TRUE), na.rm = TRUE)>=8 & length(v[v>=2]) >= 4) { prog.8_2by4 <- 1 }
  }
  return(c(prog.2by4, prog.3by4, prog.8_2by4))
}
# Create a function to calculate the specificity and the sensitivity

R Code (Cont.)

```
DT<-function(quant) {
  q_trt=matrix(quantile(c(as.matrix(test_retest)),quant),9,54)
  R_glaucoma<-matrix(NA,120,3)
  for (i in 1:120) {R_glaucoma[i,]<-GCP(i+3000,glaucoma,q_trt)}
  R_normal<-matrix(NA,60,3)
  for (i in 1:60) {R_normal[i,]<-GCP(i+3000,normal,q_trt)}
  sens.2x4<-sum(R_glaucoma[,1])/120
  spec.2x4<-1-sum(R_normal[,1])/60
  sens.3x4<-sum(R_glaucoma[,2])/120
  spec.3x4<-1-sum(R_normal[,2])/60
  sens.8_2x4<-sum(R_glaucoma[,3])/120
  spec.8_2x4<-1-sum(R_normal[,3])/60
  return(c(sens.2x4, spec.2x4, sens.3x4, spec.3x4,sens.8_2x4, spec.8_2x4 ))
}
```
# Compute sensitivity and 1-specificity for each method over the percentile range of .70 and .90

\[
v \leftarrow \text{seq}(0.70, 0.90, 0.01) \\
GV \leftarrow \text{matrix}(\text{NA}, \text{length}(v), 6) \\
\text{for}(i \text{ in } 1:\text{length}(v)) \\
\hspace{1em} GV[i, ] \leftarrow \text{DT}(v[i]) \\
\}
\]

VG <- \text{data.frame}(\text{cbind}(v, GV))
colnames(VG) <- c("quant", "sens.2x4", "spec.2x4", "sens.3x4", "spec.3x4", "sens.8_2x4", "spec.8_2x4")

plot(1-GV[,2], GV[,1], main="", xlab="1-specificity", ylab = "sensitivity" , col=1, lty=1, type="l", lwd=2)
lines(1-GV[,4], GV[,3], col=2, lty=2, type="l", lwd=2)
lines(1-GV[,6], GV[,5], col=3, lty=3, type="l", lwd=2)
legend(0.2, 0.9, bty = "n", lty = 1:3, col = 1:3, c("GCP(2x4)", "GCP(3x4)", "GCP(8,2x4)"))

# Create a function to compute the area under the ROC curve
A <- \text{function}(dat) \\
\hspace{1em} \text{dat} \leftarrow \text{rbind}(\text{c}(0,1),\text{dat},\text{c}(1,0))
\hspace{1em} \text{colnames}(\text{dat}) \leftarrow \text{c}("sensitivity", "specificity")
\hspace{1em} \text{return}(\text{aucRoc}(\text{dat}))
\}

A(GV[,1:2])
A(GV[,3:4])
A(GV[,5:6])
Results
Results and Discussion

- According to the ROC curves, GCP(2x4) and GCP(8,2x4) show the highest sensitivity and specificity.
- Data analysis suggests that optimal lower bound is between .82 and .85
Which one detects change first?

- We examine all three methods in a Kaplan-Meier (KM) analysis
- We record the time each method signals a change
- Event is change/progression
- Subjects are censored if they don’t show change by the end of study (9\textsuperscript{th} time point)
- The stratified KM plots provide a pictorial representation
Which one detects change first?
Conclusion/Recommendation

- Note that our glaucoma population has been severely damaged at baseline
- All three methods have signaled a change/progression at the third visit after baseline in more than half of this cohort
- For this group the 3 GCP rank as follow:

<table>
<thead>
<tr>
<th>Rank</th>
<th>GCP Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GCP(2x4)</td>
</tr>
<tr>
<td>2</td>
<td>GCP(8,2x4)</td>
</tr>
<tr>
<td>3</td>
<td>GCP(3x4)</td>
</tr>
</tbody>
</table>

- Our recommendation is 2x4 and 8, 2x4
Future Work
Future Work

Progression seems to occur according to the nerve fiber bundle zones

Temporal, supero-temporal, infero-temporal, nasal, supero-nasal, infero-nasal
Future work

- Model Temporal-Spatial structure to define a bundle zone specific threshold

- Cluster analysis may reduce variability
  - Re-defining the time-indexed glaucoma change probability in a cluster specific way
Acknowledgements

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References


Thank you!

Any questions?