Data Science Projects

Prevention and Treatment of Visual Loss

Study of Traumatic Brain Injury

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OPTICAL COHERENCE TOMOGRAPHY (OCT)

Provides cross-sectional pictures of the retina
Measures the thickness of the retinal layers and the optic nerve
Thickness in healthy eyes and diseased eyes helps with diagnosis and provides treatment options
Thickness measurements reflects the effects of concussions and brain trauma.

TRAUMATIC BRAIN INJURY

Ann McKee (Boston University)
CTE: Chronic Traumatic Encephalopathy
Degenerative brain disorder associated with repetitive head trauma
Build-up of Tau Protein: forms clumps that spread through the brain killing brain cells.
Affects athletes (football, boxing) and members of the military
Caused through repetitive (?) hits. Affects athletes (football, boxing) and members of the military

ASSESSING VISUAL FUNCTION AND STRUCTURE

Visual FUNCTION ("How well does one see")

best corrected visual acuity
visual field quantification
light evoked responses of eye and brain

Retinal and optic nerve STRUCTURE

digital fundus imaging
spectral domain optical coherence tomography (SD-OCT)

Detecting changes in either **functional (i.e. visual field)** or **structural (i.e. thickness of the retinal nerve fiber layer)** measurements

Average thickness of the retinal nerve fiber layer derived from the optic disc scan (RNFL)

Average thickness of the ganglion cell layer complex (GCL) derived from the macula scan

Measurements on

visual field (functional data)

thickness of the retinal fiber layer (structural data)

usually taken every 6-12 months to

check for onset of disease

monitor disease progression

Timing of onset and change in progression of loss is unknown and may vary greatly between patients

CUSUM procedures for the detection of the onset and the monitoring of the progression

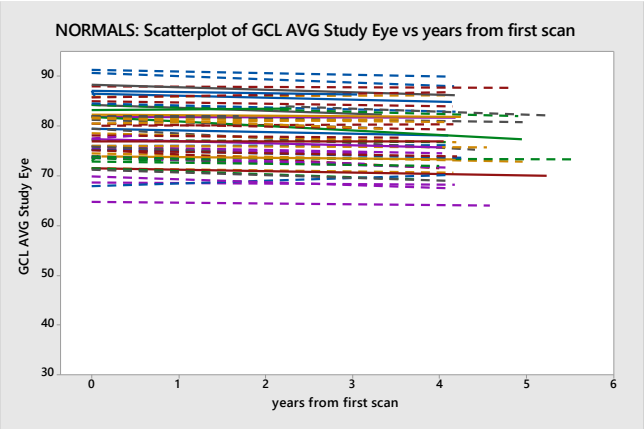
Ledolter, J. and Kardon, R.H.: "Detection of the Onset of Multiple Sclerosis from SD- OCT Thickness Measurements of the Retinal Nerve Fiber Layer." Quality Engineering, Vol. 25 (2013), 3-10.

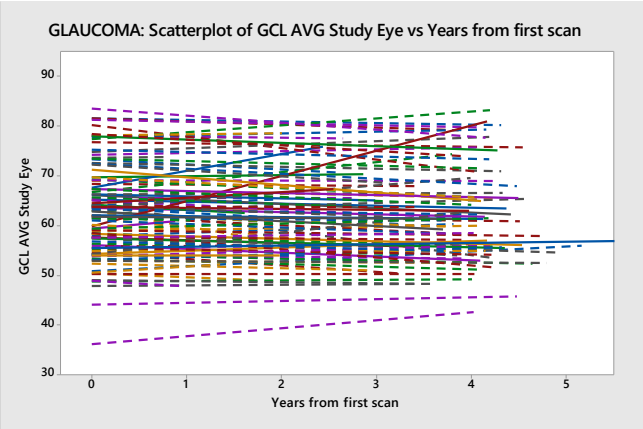
Ledolter, J. and Kardon, R.H.: "Borrowing the Best from Industrial Process Control for Detecting Progression of Eye Disease: CUSUM Charts for Assessing the Visual Field and Retinal Nerve Fiber Layer Thickness." Translational Vision Science & Technology, Vol. 2 (2013), No. 6, 1-9.

IOWA GLAUCOMA STUDY

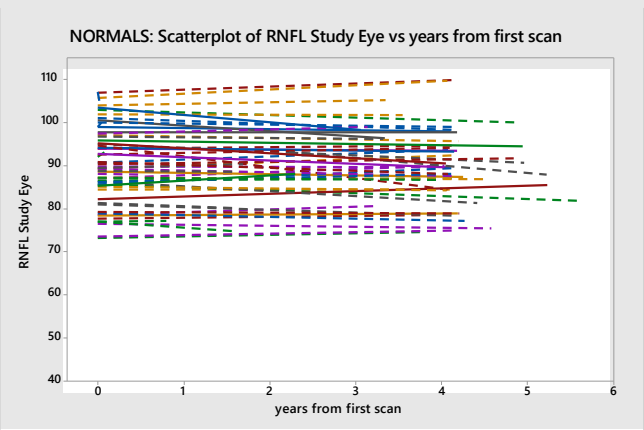
105 glaucoma patients and 55 normal subjects
Spectral OCT Testing

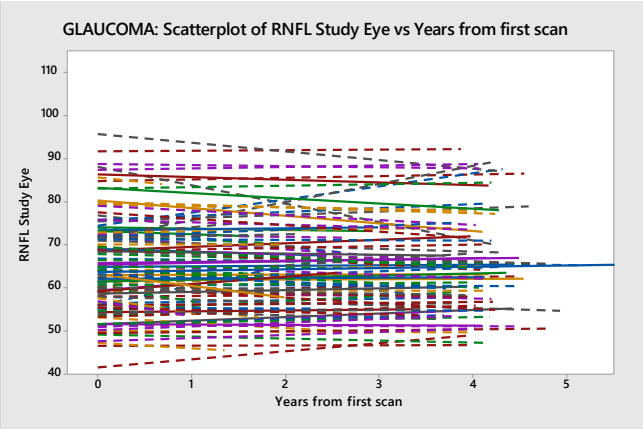
Graphs: GCL





Graphs: RNFL





Ganglion Cell Layer (GCL): Macula Scan
Retinal Nerve Fiber Layer (RNFL): Optic Disc Scan

Analysis 1: Random effects model
Modeling linear trends for several subjects from more than one group

$Y_{it}^{(j)}$ Observation on *i*th subject in group *j* (*j*=1 for normal; *j*=2 for glaucoma) at time *t*

$Time_{i1}^{(j)} = 0$ Time measured from first visit at clinic

$$Y_{it}^{(j)} = (\alpha^{(j)} + \tilde{\alpha}_i^{(j)}) + (\beta^{(j)} + \tilde{\beta}_i^{(j)})Time_{it}^{(j)} + \varepsilon_{it}^{(j)}$$

Subject variability in intercepts and slopes
Group-specific average intercepts and slopes (<u>fixed effects</u> $\alpha^{(j)}$ and $\beta^{(j)}$) and subject-specific <u>random effects</u> for the intercepts and slopes.

For two groups: groups of normal and glaucoma patients

$$Y_{it}^{(j)} = [\alpha + \alpha^* IND(Glaucoma)_i^{(j)} + \tilde{\alpha}_i^{(j)}]$$

$$+[\beta + \beta^* IND(Glaucoma)_i^{(j)} + \tilde{\beta}_i^{(j)}]Time_{it}^{(j)} + \varepsilon_{it}^{(j)}$$

$IND(Glaucoma)^{(j)} = 0$ when subject *i* is from for the normal group ($j = 1$) and

$IND(Glaucoma)^{(j)} = 1$ when subject *i* is from the glaucoma group ($j = 2$).

Table: Estimation results for the general random effects model in equation (3). Significant results are shown in bold. The correlation between the random intercept and slope were small, and $\rho^{(1)}_{\tilde{\alpha}\tilde{\beta}}$ and $\rho^{(2)}_{\tilde{\alpha}\tilde{\beta}}$ were set to zero.

RNFL							
	Intercept			**Slope**			**Measurement Error**
	α	α^*	$(\sigma_\alpha^{(j)})^2$	β	β^*	$(\sigma_\beta^{(j)})^2$	$(\sigma_\varepsilon^{(j)})^2$
M1	90.14 (N)	**-25.87 (G)** **se = 1.53** **pv < 0.001**	71.46 (N) 106.56 (G)	-0.145 (N) se = 0.089 pv = 0.107	+0.089 (G) se = 0.141 pv = 0.527	0.207 (N) 0.894 (G)	4.390 (N) 4.078 (G)
M2	90.10 (N)	**-25.81 (G)** **se = 1.53** **pv < 0.001**	71.44 (N) 106.56 (G)	-0.109 se = 0.069 pv = 0.116		0.205 (N) 0.892 (G)	4.391 (N) 4.077 (G)

GCL							
	Intercept			**Slope**			**Measurement Error**
	α	α^*	$(\sigma_\alpha^{(j)})^2$	β	β^*	$(\sigma_\beta^{(j)})^2$	$(\sigma_\varepsilon^{(j)})^2$
M1	78.16 (N)	**-15.85 (G)** **se = 1.23** **pv < 0.001**	36.15 (N) 88.19 (G)	**-0.291 (N)** **se = 0.041** **pv < 0.001**	-0.027 (G) se = 0.083 pv = 0.749	0.054 (N) 0.451 (G)	0.659 (N) 0.953 (G)
M2	78.68 (N)	**-15.86 (G)** **se = 1.23** **pv < 0.001**	36.15 (N) 88.19 (G)	**-0.297** **se = 0.035** **pv < 0.001**		0.054 (N) 0.447 (G)	0.659 (N) 0.953 (G)

Results RNFL

- Measurement variability the same in each group
- Subject-variability among intercepts and slopes larger in the glaucoma than in the normal group
- Average level (intercept) of RNFL thickness in glaucoma group significantly thinner (by 25.9 micron units) than average level in normal group
- Overall average reduction of 0.11 units per year (standard error of 0.069; p-value = 0.11), but no statistically significant difference between average slopes in normal and glaucoma groups

Results GCL

- Measurement variability the same in each group
- Subject-variability among intercepts and slopes larger in glaucoma group than in normal group
- Average level (intercept) of the GCL thickness in glaucoma group significantly thinner (by 15.8 micron units) than average level in normal group.
- Statistically significant evidence for negative average slope in normal group (0.29 micron unit reduction per year, with standard error of 0.041), but no statistically significant difference between average slopes in normal and glaucoma groups

Analysis 2:
Classifying subjects into normal/glaucoma groups

Classification on **summary statistics (intercept and slope)** for subjects with at least 4 measurements

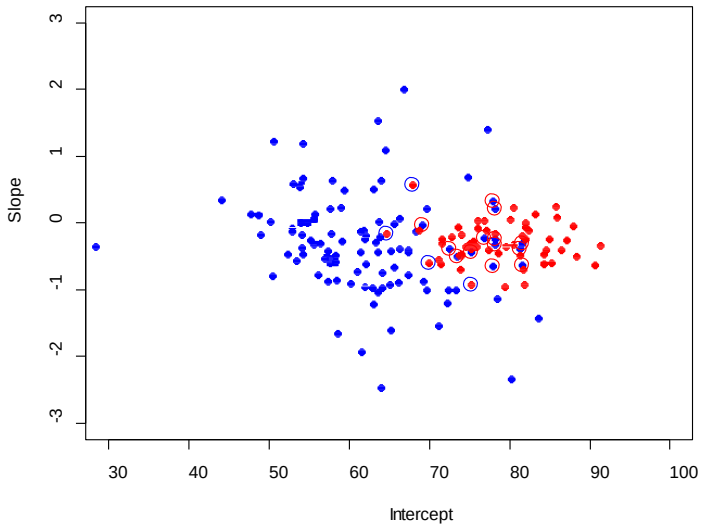
Fisher's linear (quadratic) discriminant functions

Quadratic discriminant functions perform best

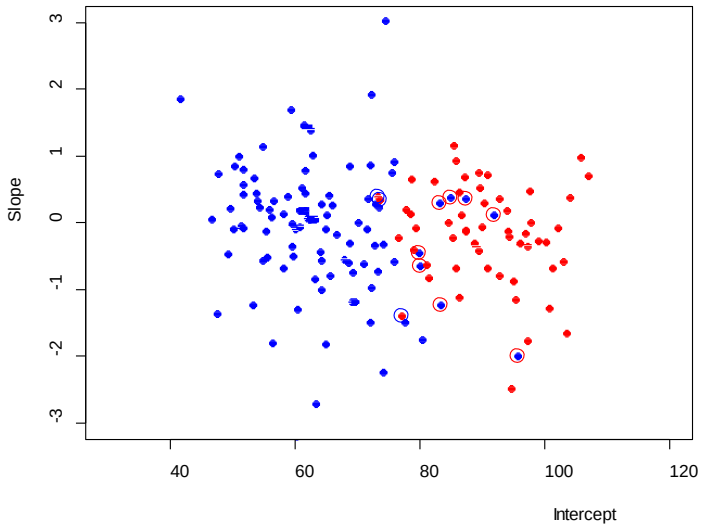
Misclassification rates:
10.7 for GCL and 6.9 percent for RNFL

Basically classification on intercepts.
Estimated slopes cannot distinguish the two groups
Misclassification rates when using just intercepts: 9.4 percent (for both GCL and RNFL)
Misclassification rates when using just slopes:
48.8 percent (for both GCL and RFNL)

GCL: Quadratic Discriminant Class



RNFL: Quadratic Discriminant Class



Figure

Scatter plots of intercepts and slopes for GCL and RNFL

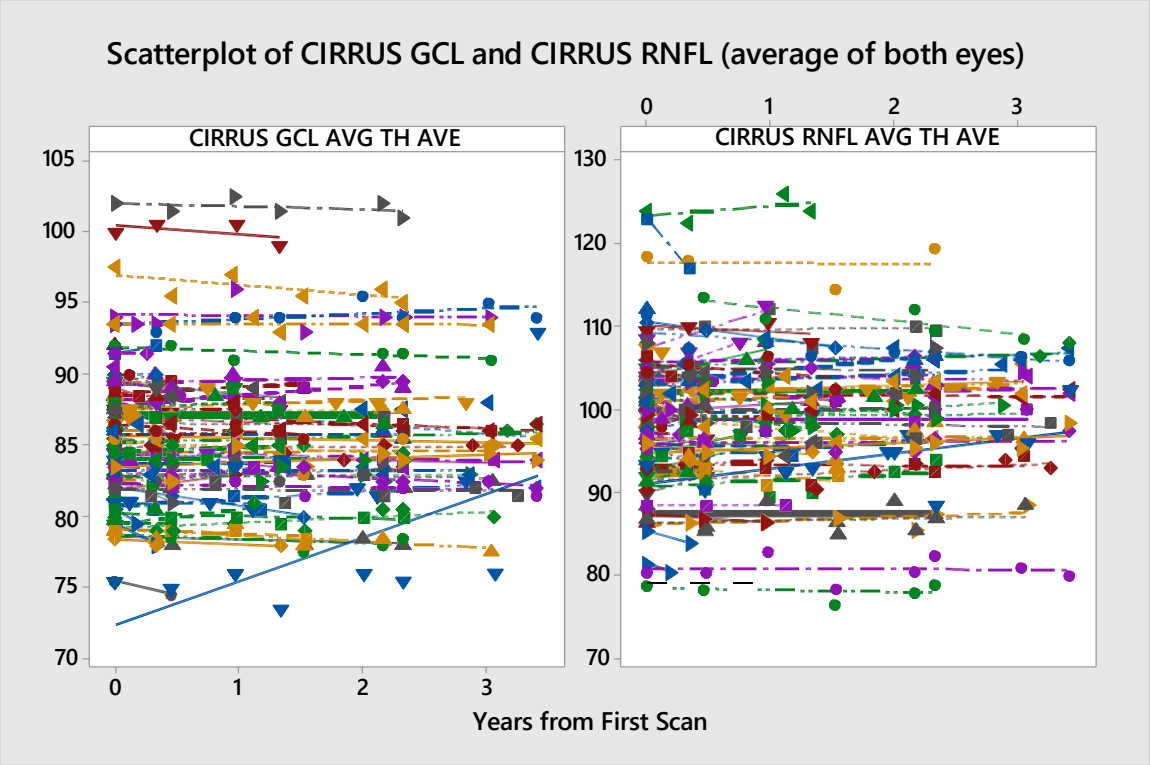
IOWA FOOTBALL

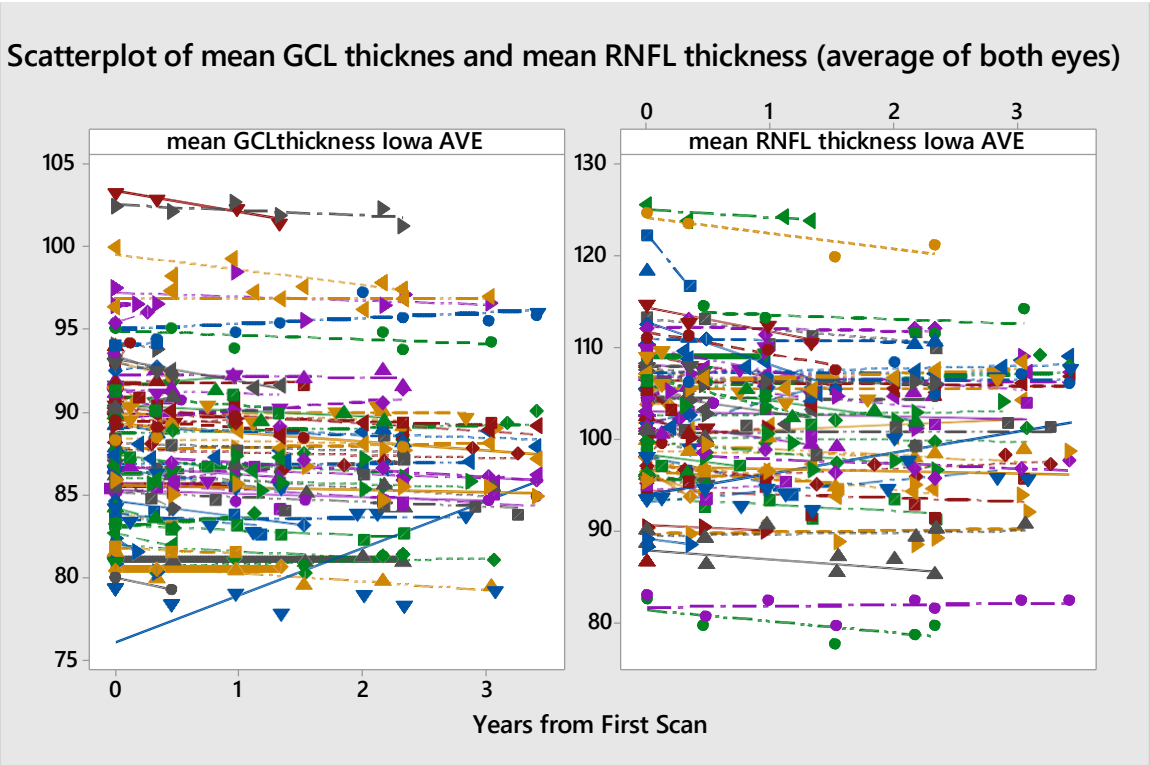
Data

University of Iowa data on football players.
4 seasons (2013 through 2016)

Comprehensive measurements (visual system) at the beginning and at the end of the season.
For some players data for all 4 seasons; for 2016 freshman only two observations

Measurements: GCL thickness and RNFL thickness, measured two different ways – standard proprietary measures provided by the manufacturer (CIRRUS; Heidelberg) as well as measures provided by the University of Iowa research group. Other thickness measurements over different areas of the optic nerve


Scatterplot of CIRRUS GCL and CIRRUS RNFL (average of both eyes)
CIRRUS GCL AVG TH AVE
CIRRUS RNFL AVG TH AVE
105
100
95
90
85
80
75
70
130
120
110
100
90
80
70
0
1
2
3
Years from First Scan


Scatterplot of mean GCL thicknes and mean RNFL thickness (average of both eyes)
mean GCLthickness Iowa AVE
mean RNFL thickness Iowa AVE
105
100
95
90
85
80
75
130
120
110
100
90
80
0
1
2
3
Years from First Scan

Analysis
Random effects model

Player position. Categorical variable with 3 outcomes

1 (low): Place Kicker, Long Snapper, Punter
2 (medium): Defensive Back, Wide Receiver, Quarterback
3 (high): Defensive End, Defensive Line, Line Backer Full Back, Offensive Line, Running Back, Tight End

Combine groups 1 and 2 into a new "moderate" group for hit-potential

Contrast this group with group 3 (the "high" hit-potential group)

2-level categorical variable, HPOT, used in models discussed below

Random effects models for subject-specific intercepts and slopes. Models allow for the mean of the intercepts and the slopes to depend on the subject's hit-potential.

Model M1

$$Y_{it} = [\alpha + \alpha^* IND(HPOT_i) + \alpha_i] + [\beta + IND(HPOT_i)\beta^* + \beta_i]Time_{it} + \varepsilon_{it}$$

Model M2

$$Y_{it} = [\alpha + \alpha^* IND(HPOT_i) + \alpha_i] + [\beta + \beta_i]Time_{it} + \varepsilon_{it}$$

Model M3

$$Y_{it} = [\alpha + \alpha_i] + [\beta + \beta_i]Time_{it} + \varepsilon_{it}$$

Findings

- Average **slopes** for the two groups are the same; common average slope is small and not always statistically significant
- For almost all measures the average **intercepts** for the two groups are different. The high exposure group has reduced levels

Table: Estimation Results. Estimates for probability values between 0 and 0.10 shown in red

	Intercepts		Slopes	
	α	α*(p-value)	β(p-value)	β*(p-value)
CIRRUSGCLOD				
M1	86.548	-1.344(0.072)	0.005(0.977)	0.050(0.805)
M2	86.521	-1.303(0.075)	0.039(0.681)	
M3	85.703		0.027(0.770)	
CIRRUSGCLOS				
M1	86.861	-1.492(0.060)	0.021(0.909)	-0.013(0.952)
M2	86.864	-1.500(0.054)	0.012(0.908)	
M3	85.926		-0.002(0.982)	
CIRRUSGCLAVE				
M1	86.681	-1.382(0.065)	0.012(0.941)	0.019(0.923)
M2	86.668	-1.363(0.063)	0.026(0.785)	
M3	85.813		0.013(0.887)	
CIRRUSRNFLOD				
M1	100.480	-1.671(0.166)	-0.128(0.582)	0.261(0.354)
M2	100.330	-1.444(0.222)	0.049(0.709)	
M3	99.424		0.036(0.779)	
CIRRUSRNFLOS				
M1	100.420	-2.877(0.011)	0.101(0.610)	0.367(0.127)
M2	100.230	-2.571(0.021)	0.346(0.003)	
M3	98.613		0.321(0.005)	
CIRRUSRNFLAVE				
M1	100.250	-1.968(0.063)	-0.009(0.962)	0.306(0.166)
M2	100.080	-1.704(0.101)	0.198(0.060)	
M3	99.015		0.182 0.078)	
meanGCLThicknessOD				
M1	89.498	-1.437(0.054)	-0.113(0.503)	-0.000(0.998)
M2	88.493	-1.429(0.050)	-0.113(0.246)	
M3	88.596		-0.125(0.189)	
meanGCLThicknessOS				
M1	89.503	-1.189(0.106)	-0.123(0.436)	0.017(0.929)
M2	88.491	-1.171(0.104)	-0.111(0.222)	
M3	88.757		-0.122(0.177)	
meanGCLThicknessAVE				
M1	89.487	-1.292(0.075)	-0.117(0.457)	0.012(0.952)
M2	88.477	-1.277(0.072)	-0.109(0.231)	
M3	88.676		-0.120(0.180)	
meanRNFLThicknessOD				
M1	102.980	-1.488(0.220)	-0.388(0.118)	0.363(0.226)
M2	102.760	-1.147(0.332)	-0.131(0.341)	
M3	102.040		-0.132(0.324)	
meanRNFLThicknessOS				
M1	102.810	-1.402(0.241)	-0.365(0.116)	0.064(0.821)
M2	102.760	-1.330(0.255)	-0.317(0.017)	
M3	101.930		-0.325(0.013)	
meanRNFLThicknessAVE				
M1	102.900	-1.362(0.233)	-0.461(0.048)	0.269(0.337)
M2	102.730	-1.099(0.322)	-0.266(0.040)	
M3	102.040		-0.269(0.033)	

COMMENTS ON TYPICAL ANIMAL STUDIES

Animal experiments with carefully controlled blast exposure

Data collected through designed statistical experiments:
Randomization of subjects to treatments (helps avoid biases)
Blocking arrangements (help increase the precision of experiments)

Set-up of mouse experiments

Blast chamber: Rupture of mylar membrane.
Calibration of resulting shock waves with those from military explosions (IEDs – Improvised explosive devices)

Experiment 1

Factor 1: Blasted (1=Yes; 0=No)
Factor 2: Time (1 = one week, 2 = two weeks; 3 = 4 weeks)

Repeated measurements on each mouse (one week, two weeks, four weeks)

The three observations on each mouse are correlated, but observations from different mice are independent. We assume that correlation is the same for all mice.

Different mice in the 2 blast groups (that is, mouse is nested within blast). Blast and Time are fixed effects; Mouse is random

Model:

$$Y_{ijk} = \alpha + \beta_j + \pi_{i(j)} + \gamma_k + \beta\gamma_{jk} + \varepsilon_{i(j)k}$$

i (subject); j (blast); k (time)

Sample size determination:

Determine needed number of mice in each group so that we detect certain blast effect with specified power

Here: 12 mice in blast group, and 13 mice in control

ANOVA Analysis (with resulting data)

Source	DF	SS	MS	F	P
blast	1	390.74	390.74	3.89	0.061
mouse(blast)	23	2313.24	100.58	4.89	0.000
		used as denominator for between subject comparisons			
time	2	690.42	346.69	16.86	0.000
blast*time	2	42.99	21.50	1.05	0.360
Error	46	945.66	20.56		
		used as denominator for within subject comparisons			
Total	74	4383.05			

Two different error sum of squares:
Testing effect of blast
Testing main effect of time and blast x time interaction

Wrong to look at F statistics that relate the sums of squares to the single error sum of squares (as this single sum of squares assumes independence and ignores (1) the repeated and (2) the nested nature of the experiment). We must separate the analysis/error into a between subject and a within subject analysis.

Experiment 2

Additional factor **Alcohol**

Experiment has blasted and non-blasted mice of either sober/alcoholic status

Each mouse observed at three different times

Design looks as follows:

		Time (Week)			
Blast=YES	Alc=Sober	G1	G1	G1	6 mice
Blast=YES	Alc=Alcoholic	G2	G2	G2	5 mice
Blast=NO	Alc=Sober	G3	G3	G3	7 mice
Blast=NO	Alc=Alcoholic	G4	G4	G4	4 mice

Model

$$Y_{ijkl} = \alpha + \beta_j + \gamma_k + \beta\gamma_{jk} + \varepsilon_{i(jk)} + \delta_l + \beta\delta_{jl} + \gamma\delta_{kl} + \beta\gamma\delta_{jkl} + \varepsilon_{i(jk)l}$$

i (subject); j (blast); k (alcohol); l (time)

Sample size determination:

Determine the needed number of mice in each group so that we can detect blast and alcohol effects with certain specified power

Analysis (with resulting data):

```
Source
Between subjects
blast
alcohol
blast*alcohol
mouse within groups=blast*alcohol
Within subjects
time
blast*time
alcohol*time
blast*alcohol*time
time*subject within groups=blast*alcohol
```

Effects are tested with F test that relates the sum of squares of the effect of interest (main effects and interactions) to the error sum of squares that is given in the row beneath it.