Statistical Challenges in Biomedical Research
NASA Johnson Space Center
SLSSI Lecture Series
June 23, 2010

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HACD Laboratories and Human Research Program Elements

- cardiovascular
- bone
- muscle
- space
- radiation
- exploration
- behavior health & performance
- exercise physiology
- immunology
- nutrition
- neuroscience
- pharmacology

- identify mechanisms for debilitating effects of spaceflight environment on the human physiology.

- develop countermeasures
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- develop countermeasures

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biostatistics lab
Potentially Debilitating Effects of Spaceflight Environment

- Bone Demineralization – Osteoporosis
- Impaired Fracture Healing – Non-Union
- Renal Stone Formation & Soft Tissue Calcification
- Orthostatic Intolerance (on return to gravity)
- Cardiac Arrhythmias
- Dehydration (on return to gravity)

- Decreased Aerobic Capacity
- Impaired Coordination
- Muscle Atrophy (Loss of Strength)
- Radiation Sickness
- Increased Cancer Risk
- Impaired Immune Function
- Behavioral Changes & Performance Decrements
- Altitude Decompression Sickness during EVA
Research Venues

Flight Experiments

• long-duration space missions
• short-duration space missions
• parabolic trajectory aircraft

Ground-based analog experiments

• bed-rest (unloading of bones, muscles)
• Antarctica (isolation)
• NEEMO (isolation + confinement)
• Houghton-Mars (exploration, space medicine)
Ways in which the Biostatistics Laboratory participates in the research process:

Design of experiments

• numbers of subjects
• how often measurements are made

Extracting information from experiment data

• develop or suggest data analysis procedures
• perform data analysis

Reporting results

• presentations
• assist with manuscript preparation for publication
Constraints

• extremely limited human subject pool
• support of NASA operations must be maintained
Dependent Measures (examples)

- Clinical
  ECG, bone density, muscle strength, urinalysis, blood, standard neuro, eye exams, VO₂ max, HR

- Specialized
  locomotion performance, nutritional markers, tilt test time, balance control, viral reactivation, cytokine production, buckling ratio, subjective sleepiness or discomfort scores
Longitudinal Setting

pre-flight  |  spaceflight with countermeasure  |  post-flight

1          |                              |          
2          |                              |          
N          |                              |          

Astronaut

time
Statistical challenges

• effective display of data
• longitudinal data (pre, in, post-flight)
• high variability between subjects
• highly unbalanced design (dictated by operations)
• multivariate measurements
• rich variety of distributions
  - skewed
  - limited range
  - time-to-event (“survival”)
  - discrete
  - zero-inflated
• multiple imputation
• models for simulation
• sample size / power estimation
• model selection - multiple testing
femoral neck bmd

old pre
old post
new pre
new post
femoral neck bmd

Graphs by cm
Graphs by cm
Is the new CM any better than the old?
Typical approach:
Judge effectiveness by difference in means.

Alternative approach:
Judge effectiveness by difference in percent of population protected against a big loss.
effect of CM on mean change in bmd
Typical approach:

Judge effectiveness by difference in means.

Alternative approach:

Judge effectiveness by difference in percent of population protected against a big loss.

How?

• Estimation with uncertainty interval

Ex. 0.020 ±0.008
Typical approach:
Judge effectiveness by difference in means.

Alternative approach:
Judge effectiveness by difference in percent of population protected against a big loss.

How?
• Estimation with uncertainty interval
  Ex. 0.020 ± 0.008
• Statistical inference
  “P-value”
effect of CM on proportion of population protected
effect of CM on proportion of population protected
Typical approach:

Alternative approach:

How?

• Estimation with uncertainty interval
  Ex. 63% (33%, 78%)

• Statistical inference
Statistical Inference

Calculate something from the data (a “statistic” – call it “T”) that gets larger as the observed effect of the new CM relative to the old CM increases.

data → T
Statistical Inference

Calculate something from the data (a “statistic” – call it “T”) that gets larger as the observed effect of the new CM relative to the old CM increases.

Imagine the experiment being repeated many times,
Statistical Inference

Calculate something from the data (a “statistic” – call it “T”) that gets larger as the observed effect of the new CM relative to the old CM increases.

Imagine the experiment being repeated many times,

For each of these hypothetical experiments, imagine that T is recalculated.

\[ T_1, T_2, T_3, \ldots, T_{1000}, \ldots \text{etc.} \]
Statistical Inference

Calculate something from the data (a “statistic” – call it “T”) that gets larger as the observed effect of the new CM relative to the old CM increases.

Imagine the experiment being repeated many times,

For each of these hypothetical experiments, imagine that T is recalculated.

How likely is it that a “T” for one of these hypothetical null experiments would be greater than the value of T we calculated from the real data?

P-value:
Examples of Projects, Data

- environmental physiology
- behavioral health and performance
- neurological
- bone
- radiation
- cardiovascular
Monitoring Metabolic Rate during EVA

- Spacesuit is a closed life-support system.
- Consumables are used up in proportion to how hard an astronaut is working (met rate).
- To predict how much longer an astronaut can safely continue an EVA, need to monitor his/her met rate (BTU/h).
Monitoring Metabolic Rate during EVA

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• To predict how much longer an astronaut can safely continue an EVA, need to monitor his/her met rate (BTU/h).

Data:
• 4 disparate sensors – O₂, CO₂, HR, LCG
• each provides an estimate of met rate
• all estimates have errors
Monitoring Metabolic Rate during EVA

- 4 disparate sensors – O₂, CO₂, HR, LCG
- each provides an estimate of met rate
- all estimates have errors

Problem:
How should one combine the individual met-rate estimates to obtain the most reliable single estimate?
What the data looks like?
Our “Best Estimate”

Estimated MetRate

W4 Coefficients
O2: 0.52
CO2: 0.11
LCG: 0.11
HR: 0.26
Our “Best Estimate”

W4 Coefficients
- O2: 0.52
- CO2: 0.11
- LCG: 0.11
- HR: 0.26

Estimated MetRate
Techniques used

• thermal/gas-exchange models
Techniques used

• thermal/gas-exchange models

• factor analysis
factor analysis model
Techniques used

• thermal/gas-exchange models

• factor analysis

• accuracy assessment using autoregressive error model
autoregressive error model
Examples of Projects, Data

- environmental physiology
- behavioral health and performance
- neurological
- bone
- radiation
- exercise
Compare two cognitive tests that are designed to show degraded performance with increasing sleepiness.

Subjects take promethazine (PMZ).

At each of 12 timepoints:
- measure PMZ concentration in blood
- obtain subjective report of sleepiness (1-9 scale)
- record cognitive test performance - Test1, Test 2
Compare two cognitive tests that are designed to show degraded performance with increasing sleepiness.

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Which test is more sensitive to (true) sleepiness?
Latent Variable Model

PMZ → Sleepiness

Time → Sleepiness

Time x PMZ → Sleepiness

Other → Sleepiness

Sleepiness → KSS

Sleepiness → Scores 1, 2
Examples of Projects, Data

• environmental physiology
• behavioral health and performance
• neurological
• bone
• radiation
• exercise
Sensory Organization Test (neurological)
\[ 100 \left( 1 - \frac{\theta}{12.5} \right) = 100 - 8\theta \]
Equilibrium Score

days after landing

rookies veterans

SOT 6
Equilibrium Score

days after landing

rookies veterans
SOT Data

• longitudinal design
• limited range (0 – 100)
• left-skewed distribution
SOT 6 EQ scores
post mission
SOT Data

• longitudinal design
• limited range (0 – 100)
• left-skewed distribution
• falls
SOT Data

longitudinal design

limited range (0 – 100)

left-skewed distribution

falls

Score of zero for falls is arbitrary.

Averaging in a zero for falls is not valid:

e.g. (60, fall ) is not the same as (30, 30).
SOT Data

longitudinal design
limited range (0 – 100)
left-skewed distribution
falls

Score of zero for falls is arbitrary.

Averaging in a zero for falls is not valid:
e.g. (60, fall ) is not the same as (30, 30).

Use latent variable model to represent unobserved balance control ability when there is a fall.
Examples of Projects, Data

- environmental physiology
- behavioral health and performance
- neurological
- bone
- radiation
- exercise
longitudinal study of bone loss
femoral neck bone density

![Graph showing femoral neck bone density over age]
longitudinal study of bone loss
femoral neck bone density
longitudinal study of bone loss

femoral neck bone density
longitudinal study of bone loss

femoral neck bone density

\(\text{g/cc}\)
longitudinal study of bone loss
femoral neck bone density

![Graph showing femoral neck bone density over age]

- **y-axis**: g/cc
- **x-axis**: age
- The graph illustrates the longitudinal study of bone loss, focusing on femoral neck bone density.
Examples of Projects, Data

- environmental physiology
- behavioral health and performance
- neurological
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- radiation
- exercise
mouse weight vs time since exposure

Graphs by Group I and sub within group
mouse weight vs time since exposure

Graphs by Group I and sub within group
Distinguishing characteristic:

AR1 regression coefficient (L1)

• Control group:
  • L1 small => random (high frequency variation)

• Radiation group:
  • L1 large => carryover (low frequency variation)
mouse weight vs time since exposure

Graphs by sub within group
Examples of Projects, Data

- environmental physiology
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Exercise data - (27 ISS astronauts)

Predictors:

- $x_1$: TVIS sessions per week
- $x_2$: TVIS avg session time
- $x_{1x2}$: TVIS min/week
- $x_5$: $\ln[-(TVIS \text{ Load(lbs)}) + 134.4]$  
- $x_6$: TVIS mph
- $x_7$: CEVIS avg session time
- $x_8$: CEVIS sessions per week
- $x_{7x8}$: CEVIS min/week
- $x_{13}$: RED avg squat load
- $x_{14}$: $\ln[(RED \text{ avg DL load}) -110.9]$
Exercise data (cont.)

Outcomes:

y1 Post-Pre Alk Phos
y2 Post-Pre NTELO
y3 Post-Pre Osteo
y4 Post-Pre BSAP

y5 Post-Pre Lspine BMD
y6 Post-Pre fneck BMD
y7 ln[ -(Post-Pre troc BMD)+.0183]
y8 ln[ -(Post-Pre whoebody BMD) + .0098]
y9 Post-Pre calc BMD
y10 Post-Pre pelvis BMD
Exercise data (cont.)

Outcomes (cont.)
y11 Post-Pre Back Ext
y12 Post-Pre Trunk Flex
y13 Post-Pre Ankle Consentric Plantar
y14 Post-Pre Ankle Consentric Dorsi
y15 Post-Pre Ankle Eccentric Plantar
y16 Post-Pre Ankle Eccentric Dorsi
y17 Post-Pre Hamstring Total Work
y18 Post-Pre Hamstring Strength
y19 Post-Pre Quads Total Work
y20 Post-Pre Quads Strength

y21 Post-Pre Estimated VO2 (raw)
y22 Post-Pre Weight-Adjusted Estimated VO2
Main Research Questions

Does exercise (in general) mitigate the adverse effects of space on these outcomes (bone markers, bone mineral density, muscle strength, fitness level (VO2))? 

If so, which aspects of exercise appear to have the most important effects?
• Treadmill
• Cycle
• Resistive

$(X_1, X_2, \ldots, X_{14})$

- Bone markers
  - $y_1$ – $y_4$
- BMD
  - $y_5$ – $y_{10}$
- Muscle strength
  - $y_{11}$ – $y_{20}$
- VO₂ max
  - $y_{21}$, $y_{22}$
Treadmill
Cycle
Resistive

\((X_1, X_2, \ldots, X_{14})\)

canonical correlation analysis

- Bone markers
  \(y_1 - y_4\)
- BMD
  \(y_5 - y_{10}\)
- Muscle strength
  \(y_{11} - y_{20}\)
- VO_{2\, max}
  \(y_{21}, y_{22}\)
Data Matrix
Missing data
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