Using Concurrent Cardiovascular Information to Augment Survival Time Data from Orthostatic Tilt Tests

Alan H. Feiveson¹, James Fiedler², Stuart M. C. Lee³, Christian M. Westby², Michael B. Stenger¹, and Steven H. Platts¹

Joint Statistical Meetings 2014, Boston, MA

¹NASA Johnson Space Center, Houston, TX
²Universities Space Research Association, Division of Space Life Sciences, Houston, TX
³Wyle, Integrated Science and Engineering Group, Houston, TX
Contents

Orthostatic Intolerance (OI)
Assessment of OI: orthostatic tilt testing
Test Outcomes
Exploratory Study Plan
Cox regression results
concurrent measurements (examples)
measures of variability HA, RD, PL
inference methodology
comparison of variability measures
conclusions / remarks
Orthostatic Intolerance (OI)

Propensity to develop symptoms of fainting during upright standing.

OI is associated with changes in heart rate, blood pressure and other measures of cardiac function.
Orthostatic Intolerance (OI)

Propensity to develop symptoms of fainting during upright standing.

OI is associated with changes in heart rate, blood pressure and other measures of cardiac function.

Problem: NASA astronauts have shown increased susceptibility to OI on return from space missions.

Current methods for counteracting OI in astronauts include fluid loading and the use of compression garments.
Assessment of OI: Orthostatic Tilt Tests (OTTs)

- Subject initially is supine.
- 80° upright tilt for preset time ($T_{\text{max}} = 5 - 30 \text{ min}$.)
- “Survival” time = $T$
- Endpoint: $T_c = \min(T, T_{\text{max}})$

Concurrent measurements $\mathbf{x}(t) = [x_1(t), \ldots, x_8(t)]$ ($t \leq T_c$):
- $x_1(t) = \text{heart rate (hr)}$
- $x_2(t), \ldots, x_5(t) = \text{measures of blood pressure (dbp, map, sbp, pp)}$
- $x_6(t) = \text{stroke volume (sv)}$
- $x_7(t) = \text{cardiac output (co = sv \times hr)}$
- $x_8(t) = \text{total peripheral resistance } tpr = (\text{map} - \text{mvp})/\text{co}$
Time trajectories of $x_1, \ldots, x_8$ (completed OTT)

- $x_1$: heart rate ($hr$)
- $x_2$: diastolic bp ($dbp$)
- $x_3$: mean arterial bp ($map$)
- $x_4$: systolic bp ($sbp$)
- $x_5$: pulse pressure ($pp$) = $sbp - pp$
- $x_6$: stroke volume ($sv$)
- $x_7$: cardiac output ($co$)
- $x_8$: total peripheral resistance ($tpr$)
Uncompleted OTT

Time trajectories of \{x_i(t); \ t = 1,\ldots, T_c\}
Causative Flow (no censoring)

We assume all the information about the degree of OI would be contained in the survival time $T$, if there were no censoring.

\[ \text{OI} \quad \rightarrow \quad \text{Concurrent measurements} \quad \{x(t); \ (t \leq T)\} \quad \rightarrow \quad T \]
Causative Flow (censoring)

With censoring present, both \( \{ x(t); (t \leq T_c) \} \) and \( T_c \) provide information about the survival time \( T \).

\[
\{ x(t); (t \leq T_c) \}
\]

\( T_c = \min (T, T_{\text{max}}) \)
Bedrest simulation of spaceflight

- 27 subjects (10F, 17M)
- 60-day bedrest
- OTTs pre and post-bedrest
- $T_{\text{max}} = 30\ \text{min.}$

Endpoint: $T_c = \min(T, T_{\text{max}})$ (in min.)

Concurrent measurements: $(t = 0, 1, 2, ..., T_c)$
- $x_1(t) = \text{heart rate (hr)}$
- $x_2(t) ... x_5(t) = \text{measures of blood pressure (dbp, map, sbp, pp)}$
- $x_6(t) = \text{stroke volume (sv)}$
- $x_7(t) = \text{cardiac output (co = sv \times hr)}$
- $x_8(t) = \text{total peripheral resistance } tpr = (map - mvp)/co$
<table>
<thead>
<tr>
<th>id</th>
<th>pre BR</th>
<th>post BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>15</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>17</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>22</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>id</th>
<th>pre BR</th>
<th>post BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>28</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>16</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>19</td>
<td>19</td>
<td>29</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>23</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>25</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>26</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>27</td>
<td>30</td>
<td>26</td>
</tr>
</tbody>
</table>
Pre vs. post bedrest comparison (univariate)

\[ x_1 = \text{heart rate (hr)} \]
\[ x_2 = \text{diastolic blood pressure (dbp)} \]
\[ x_3 = \text{mean arterial pressure (map)} \]
2-d Trajectories

raw values with supine time point

Graphs by brday
2-d Trajectories

raw values with supine time point

Graphs by brday

Sub 2

Pre BR

Post BR

HR

DBP
2-d Trajectories

raw values with supine time point

Graphs by brday

Sub 3

HR

DBP
Summarizing Behavior of Concurrent Measurements

In practice we seek a summary statistic $A$ that captures the essential information in $\{x(t)\}$.

\[ A = A(x(t)) \quad (t \leq Tc) \]

Desirable properties of $A$
- Summarizes relevant behavior of $(x_1(t), \ldots, x_8(t))$.
- Can be calculated for OTT of any (reasonable) length.
- $A$ and $T_c$ explain OI better than $T_c$ alone for short tests.
Candidates for $A = A(x(t))$

$p$-dimensional functional data $x(t)$ is observed at discrete common time points $\{t_1, t_2, \ldots, t_k\}$.

1. determinant: $A_k = |S_k|^{1/p} ; S_k = \frac{1}{k-1} \sum_{i=1}^{k} (x(t_i) - \bar{x}_k)(x(t_i) - \bar{x}_k)'$

2. path length: $A_k = \sum_{i=1}^{k} |x^*(t_i) - x^*(t_{i-1})|$

3. convex hull area/volume: $A_k = (CHA)^{1/p}$
Properties of $A = A(x(t))$

Generally increases with time.

For longer surviving subjects, average slope is lower.
Properties of $A = A(x(t))$

Generally increases with time.

For longer surviving subjects, average slope is lower.

Outcome for inference: $y = A(x(T_c))/T_c$
Inference on effect of bed-rest on OI.

\[ y_{ij} = \mu + u_i + \alpha_j + e_{ij} \quad (i\text{-th subject}; j\text{-th treatment}) \]

\[
\begin{align*}
T_{ij} \leq T_{max} & \quad y_{ij} = \frac{A(x(T_{ij}))/T_{ij}}{T_{ij}} \\
T_{ij} > T_{max} & \quad y_{ij} \in (0, \frac{A(x(T_{max}))/T_{max}}{T_{max}})
\end{align*}
\]

\(T_{ij} = \) survival time (may be censored)

Assume \(y_{ij} \sim \text{Normal} \)

max likelihood (integrate out random effects)
Contents

Orthostatic Intolerance (OI)
Assessment of OI: orthostatic tilt testing
Test Outcomes

Exploratory Study Plan
Cox regression results
concurrent measurements (examples)
measures of variability HA, RD, PL
inference methodology
comparison of variability measures
conclusions / remarks
Exploratory Study Plan

Observe survival and functional data $x(t)$ from OTTs given to subjects pre- and post-bedrest.

Formulate some candidates for $A = A(x(t)) \quad (t \leq T_c)$.

Compare their ability to test for an effect of bedrest at various censoring times with a simple non-parametric analysis.
Contents

endurance testing with concurrent measurements
orthostatic intolerance
orthostatic tilt testing
study plan
bedrest study
Cox regression results
concurrent measurements (examples)
measures of variability HA, RD, PL
inference methodology
comparison of variability measures
conclusions / remarks
Cox regression (OTT survival times)
censoring time: 30 minutes

```
. stcox brday,cluster(isub) nolog

        failure _d:  fail
        analysis time _t:  tmax

Cox regression -- Breslow method for ties

No. of subjects       =           46                Number of obs       =        46
No. of failures       =           34
Time at risk          =          840

Wald chi2(1)          =     17.03
Log pseudolikelihood  =   -108.11632                Prob > chi2         =    0.0000

(Std. Err. adjusted for 27 clusters in isub)

                          |     Robust
_t    |   Haz. Ratio   |     Std. Err.   |      z     |      P>|z|   |    [95% Conf. Interval]
----------+----------------+-----------------+------------+-----------+-----------------------------------------
   brday   |    3.189786    |     0.8966697   |     4.13   |    0.000  |          1.838583                   5.534009
```
Cox regression (OTT survival times)
censoring time: 15 minutes

```
. stcox brday,cluster(isub) nolog
    failure _d:  fail15
    analysis time _t:  tmax15

Cox regression -- Breslow method for ties

No. of subjects = 46
No. of failures = 19
Time at risk = 551

Wald chi2(1) = 17.29
Prob > chi2 = 0.0000

Log pseudolikelihood = -63.369599

(Std. Err. adjusted for 27 clusters in isub)

|       | Haz. Ratio | Std. Err. | z    | P>|z| | [95% Conf. Interval] |
|-------|------------|-----------|------|-----|---------------------|
| _t    | _t         |           |      |     |                     |
| brday | 4.66871    | 1.730109  | 4.16 | 0.000 | 2.258201            | 9.652309 |
```
Cox regression (OTT survival times)
censoring time: 10 minutes

. stcox brday,cluster(isub) nolog

    failure _d:  fail10
    analysis time _t:  tmax10

Cox regression -- Breslow method for ties

<table>
<thead>
<tr>
<th></th>
<th>Robust</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haz. Ratio</td>
<td>Std. Err.</td>
<td>z</td>
</tr>
<tr>
<td>_t</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>brday</td>
<td>6.313793</td>
<td>3.227091</td>
<td>3.61</td>
</tr>
</tbody>
</table>

(Std. Err. adjusted for 27 clusters in isub)
Cox regression (OTT survival times)
censoring time: 7 minutes

. stcox brday,cluster(isub) nolog
  
  failure _d:  fail7
  analysis time _t:  tmax7

Cox regression -- Breslow method for ties

No. of subjects = 46                Number of obs = 46
No. of failures = 8
Time at risk = 300

Wald chi2(1) = 4.98
Prob > chi2 = 0.0257

Log pseudolikelihood = -25.673825

(Std. Err. adjusted for 27 clusters in isub)

<table>
<thead>
<tr>
<th>_t</th>
<th>Robust</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haz. Ratio</td>
</tr>
<tr>
<td>---</td>
<td>------------</td>
</tr>
<tr>
<td>brday</td>
<td>11.96172</td>
</tr>
</tbody>
</table>
Cox regression (OTT survival times)
censoring time: 5 minutes

. stcox brday,cluster(isub) nolog

    failure _d: fail5
    analysis time _t: tmax5

Cox regression -- Breslow method for ties

No. of subjects = 46                Number of obs  =  46
No. of failures =  4
Time at risk   =  221

[no analysis]
## Best Results
(by Outcome Type and Censoring Time)

<table>
<thead>
<tr>
<th>cens time</th>
<th>path length</th>
<th>Z</th>
<th>convex hull</th>
<th>Z</th>
<th>determinant</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>HR*, DBP*</td>
<td>4.97</td>
<td>HR</td>
<td>4.71</td>
<td>HR, MAP, SV</td>
<td>3.05</td>
</tr>
<tr>
<td>7</td>
<td>HR*, PP*</td>
<td>6.59</td>
<td>HR, DBP, SBP</td>
<td>4.48</td>
<td>HR, DBP, SBP</td>
<td>4.5</td>
</tr>
<tr>
<td>10</td>
<td>HR*, TPR*,PP*</td>
<td>7.13</td>
<td>HR, DBP, SBP</td>
<td>6.08</td>
<td>HR, DBP, SBP</td>
<td>5.84</td>
</tr>
<tr>
<td>15</td>
<td>HR*, TPR*,PP*</td>
<td>7.58</td>
<td>HR, DBP, SBP</td>
<td>6.67</td>
<td>HR, DBP, SBP</td>
<td>6.05</td>
</tr>
<tr>
<td>30</td>
<td>HR*, TPR*,PP*</td>
<td>6.65</td>
<td>HR, DBP, SBP</td>
<td>6.49</td>
<td>HR, DBP, SBP</td>
<td>6.28</td>
</tr>
</tbody>
</table>
Contents

endurance testing with concurrent measurements
orthostatic intolerance
orthostatic tilt testing
study plan
bedrest study
Cox regression results
concurrent measurements (examples)
measures of variability HA, RD, PL
inference methodology
comparison of variability measures
→ conclusions / remarks
Summary of approach used to developing the statistic $A = A(x(t)); \ t < T_c$

1. Used training data with control condition and provocative condition known to cause OI.
Summary of approach used to developing the statistic $A = A(x(t)); t < T_c$

1. Used training data with control condition and provocative condition known to cause OI.
2. Observed increased variability of functional data $x(t)$ for the provocative condition.
Summary of approach used to developing the statistic $A = A(x(t)); t < T_c$

1. Used training data with control condition and provocative condition known to cause OI.
2. Observed increased variability of functional data $x(t)$ for the provocative condition.
3. Formulated several measures of this variability as candidates for $A$. 
Summary of approach used to developing the statistic $A = A(x(t)); \ t < T_c$

1. Used training data with control condition and provocative condition known to cause OI.
2. Observed increased variability of functional data $x(t)$ for the provocative condition.
3. Formulated several measures of this variability as candidates for $A$.
4. Used simple non-parametric test that combines survival data with cumulative evaluations of each $A$-candidate to make inference on the effect of condition.
Summary of approach used to developing the statistic $A = A(x(t)); t < T_c$

1. Used training data with control condition and provocative condition known to cause OI.
2. Observed increased variability of functional data $x(t)$ for the provocative condition.
3. Formulated several measures of this variability as candidates for $A$.
4. Used simple non-parametric test that combines survival data with cumulative evaluations of each $A$-candidate to make inference on the effect of condition.
5. Compared results.
conclusions / remarks

Multivariate trajectory spread is greater as OI increases.
Pairwise comparisons at the same time within subjects allows incorporation of pass/fail outcomes.
Path length, convex hull area, and covariance matrix determinant do well as statistics to summarize this spread.

Missing data problems
Time series analysis
need many more time points per OTT session

Treatment of trend?

How incorporate survival information?
id = 224, brday = 0
minute = 3

id = 224, brday = 1
minute = 3
id = 224, brday = 0
minute = 5

id = 224, brday = 1
minute = 5
id = 224, brday = 0
minute = 7

id = 224, brday = 1
minute = 7
id = 224, brday = 0
minute = 9

id = 224, brday = 1
minute = 9
id = 224, brday = 0
minute = 11

id = 224, brday = 1
minute = 11
id = 224, brday = 0
minute = 19

id = 224, brday = 1
minute = 19
id = 224, brday = 0
minute = 29

id = 224, brday = 1
minute = 29
id = 224

Graphs by brday

Pre BR

Post BR

minute

area_0011

0  10  20  30

0  10  20  30
id = 9139

Graphs by brday

Pre BR

Post BR

area_0011

minute