FORECASTING THE CHANGE OF RENAL STONE OCCURRENCE RATES IN ASTRONAUTS

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A Challenge of Translational Medicine to Space Flight

Informative Data

Actionable Knowledge

Space Flight
Analog Studies
Research Studies
Clinical Data

Medical Risk
Treatment Capability
Space System
Clinical Practice
Consider using a Mathematical or Computational Models—
When the system is complex or complicated enough that your intuition, i.e. your forecasting knowledge, is insufficient to describe how the system will respond.

- Ultrasound Diagnostics
  Insufficient Heart Valves (Perry et al. 1996)

- Surgical Intervention
  CABG (Bonert et al. 2000)

- Bone Fracture Risk (Nelson et al. 2009)

- Space Flight Induced Visual Impairment (Feola et al. 2016)
Renal Stone Incidence Likelihood during Space Flight

- Clinically - Governed by precipitant supersaturation and presence of inhibitors in urine
- Evidence of altered urine volume and chemistry in space
  - Lower urine output and elevated calcium (bone demineralization)
  - Countermeasures that affect urine chemistry
    - Citrate treatments, Bisphosphonates, Fluid intake, intense exercise (ARED)
Bayesian analysis including

- Summary of Urological Diseases in America 2004
- JSC Control Population Data
- In-flight Data (up to ~2010)

Posterior Estimate

Astronaut – in-flight 365 (+/- 46) events per 100K person years

Does not address gravity, mission trades, or countermeasures
- what happens if I reduce water intake by 1 liter?

Gilkey et al. 2012 – NASA/TP -2012-217120
Rate of Stone Formation in Context

Distributions normalized to equal area under each curve

<table>
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<tr>
<th>Source</th>
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Incidence Rate Per 100K Person Years

Probability Density

0.01
0.008
0.006
0.004
0.002
0
0 500 1000 1500 2000 2500 3000 3500 4000 4500
Probabilistic Model for Renal Stone Incidence Likelihood

Problem: How does space flight and return affect the post flight one year rate of stone formation in astronauts?

Probabilistic Monte Carlo Simulation using Population Data

1. Urinalysis Data
   - LSAH
   - LSDA
   - CCF

2. Bio - Chemistry Model
   - Supersaturation Index (SI)
   - CaOx

3. Stone Growth Model
   - Free stone population balance

4. Correlated Stone Pop to Occurrence
   - Correlate incidence rates to stone formation

5. Risk of Renal Stone
   - Change in predicted incidence rate
Biochemistry Model

• **Joint Expert Speciation System : JESS**
  – Development: Peter May  Murdoch University, Western Australia
  – compiles 100+ applicable urine chemistry reactions and computes outputs based on system parameters and thermodynamics

• **Transforms total concentration, via system of equations into free ion concentrations ($c_i$) based on urine chemistry reactions**

• **Relative Supersaturation calcium oxalate (RSCaOx)**
  – JESS Provides the Saturation Index (SI = RSS²) : Metric that represents the ability of spontaneous crystallization of the solution

http://jess.murdoch.edu.au/jess_home.htm
Microgravity Astronaut: Average of 24-urine excretion rates obtained from 86 post-flight astronaut urine chemistries. (Whitson et al.)
Renal Stone Population Balance (PBE) System
Model: Nucleation, Growth & Agglomeration

Population Balance Equation:

\[
\frac{n(D)}{\tau} + G_D \frac{\partial n(D)}{\partial D} = \int_0^{D/2} \beta n(D-D')n(D')dD' - n(D) \int_0^\infty \beta n(D')dD' 
\]

Nucleation BC:

\[
n(D = 0) = n^o = B^o / G_D 
\]

Relative Supersaturation

Inhibition: Citrate, Pyrophosphate, Hydration

Kassemi M, Thompson DA. Am J Physiol Renal Physiol. 2016 - Microgravity
Kassemi M, Thompson DA. Am J Physiol Renal Physiol. 2016 - Dietary
PBE Model: Dietary Countermeasures for Microgravity Astronaut Subject: Effect of Citrate

nominal urine concentrations

(hypocitraturia)
Kassemi PBE model produces a population density of stones related to the input urine chemistry.

Max Stone Size as the maximum stone Diameter predicted to have >1 stone/mL of urine.
Correlate Stone Size to Rate of Occurrence: Poisson Regression based Transfer Function

- PBE Max Stone size from known urine chemistries
- Incidence rates distributions from population based observations
  - Randomly assess the number of incidences for fixed time interval assuming the corresponding incidence rate distribution
  - Matches each set of incidences to a corresponding Poisson distribution
  - Aggregates the distributions and calculates the standard deviation

Technique: Poisson Regression With Rates

Repeats 10,000 times
# Rate of Stone Formation in Context

<table>
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<tr>
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<tbody>
<tr>
<td><strong>NSF</strong></td>
<td><strong>Normal</strong></td>
</tr>
<tr>
<td>A</td>
<td>Mean: 101.1</td>
</tr>
<tr>
<td>B</td>
<td>Std: 101.3</td>
</tr>
<tr>
<td>C</td>
<td><strong>Lieske et al. 2006 (Rochester Study)</strong></td>
</tr>
<tr>
<td><strong>SF</strong></td>
<td><strong>Triangular</strong></td>
</tr>
<tr>
<td>Min:</td>
<td>121</td>
</tr>
<tr>
<td>Max:</td>
<td>1093</td>
</tr>
<tr>
<td>ML:</td>
<td>976</td>
</tr>
<tr>
<td><strong>Inflight</strong></td>
<td><strong>Lognormal</strong></td>
</tr>
<tr>
<td>Mean:</td>
<td>365</td>
</tr>
<tr>
<td>Std:</td>
<td>46</td>
</tr>
<tr>
<td><strong>Postflight</strong></td>
<td><strong>Gamma</strong></td>
</tr>
<tr>
<td>alpha:</td>
<td>7.77</td>
</tr>
<tr>
<td>beta:</td>
<td>.00593</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td><strong>Gilkey et al, 2010</strong></td>
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<td><strong>Porter and Rice , 2013 &amp; LSAH</strong></td>
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Dataset Sources: Training and Testing

- **LSAH Population Data**
  1517 Urine Samples from 581 individual astronauts (pre-, in-, and post-) flight
  - Data to TRAIN the model
    - 957 urine samples, from the Preflight, and Post flight datasets
      - Inflight was omitted to be used to test the model
    - Preflight
      - 515 astronaut urine samples, including 13 stoneformer samples
    - Postflight
      - 442 astronaut urine samples, including 13 stoneformer samples
  - To TEST the model
    - 560 Urine samples
    - Incomplete Preflight and Postflight data
      - eg. pH was not measured in all cases so a distribution created from the data that did include preflight was used to determine the pH for the dataset
    - Inflight data both complete and incomplete was used to form the Inflight renal chemistry distributions

- **Whitson et al. J Urology 2009**
  - Urine samples 9 astronauts, at each flight phase that received potassium citrate as part of a study on renal risk formation in spaceflight.
Simulation analysis - Correlation of Rates

SI Curve Fit

Max Stone Size Curve Fit

Incidence Rate of Stone Formation Per Person Year

0 0.02 0.04 0.06 0.08 0.1 0.12

SI

0 20 40 60 80 100 120 140

Incidence Rate of Stone Formation Per Person Year

0 0.05 0.1 0.15 0.2 0.25 0.3 0.35 0.4

Max Stone Size (meters) x 10^-3

0 0.5 1 1.5 2 2.5

Mean

+/- 2 Standard Deviations
Simulation of Astronaut Population Risk - Convergence of Simulation

Convergence Values: Incidence per Person Years

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<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard Deviation of the Mean</th>
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<tbody>
<tr>
<td>PreFlight</td>
<td>5.4697E-03</td>
<td>4.9452E-03</td>
</tr>
<tr>
<td>PostFlight</td>
<td>6.4767E-03</td>
<td>1.4341E-02</td>
</tr>
<tr>
<td>Inflight</td>
<td>6.8544E-03</td>
<td>1.3473E-02</td>
</tr>
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</table>
Sampled Incidence Rate Per Person-Year

Incidence Rate Histograms: Preflight
Sampled Incidence Rate Per Person Year
Sampled Incidence Rate Per Person Year

Incidence Rate Histograms: Postflight
Inhibition Factors: Dietary Citrate and Placebo
Whitson et al. J Urology 2009

Note: Data included only 2 placebo subjects, totaling 14 urine samples
Summary of Findings

• We have shown that combining physics based modeling and numerical analytics provides deeper insight into the renal stone risks for astronauts
  – PBE forecasts an increase in the extent of possible incidence rates due to space flight and return then supersaturation alone
    • Adding PBE/kinetics appears to be provide a higher predictive resolution at SI > 5
      – Revelation of a possible second mode
    • Minimal attributable difference in predictive potential at lower SI levels typical of non-stone former, pre-flight rates
  – Consistent with published findings of underlying PBE model in assess the effects of inhibition
    • Citrate has minor impact above normal levels

• We cannot assess if this particular application illustrates overall better forecasting for the general population
  – Does indicate a better means to quantify the relative change in risk to astronauts
  – Provides the opportunity to glean some insight into the efficacy of interventions that modify
    • Effect of hydration
    • Effect of inhibitors
    • Effect of reducing urinary calcium through other countermeasures (exercise)
Assumptions and Limitations

- **Possibility the data does not correlate to the rates specified**
  - Renal Stone occurrence rate is multifactorial
    - Unique anatomy plays a role
    - Gravity vector and wall interactions affect residence time
  - Timing
    - Astronaut urine chemistries does not address relative timing of the sample acquisition and any stone occurrence
    - Data not separated for sex, gender or any age factors

- **PBE model has wide range of values for kinetics factors $K_g$, $K_b$, $\beta$**
  - Values are not known with precision and may potentially represent a source of large uncertainty in the analysis
    - May not accurately assess the range of effects of inhibition
Conclusions and future work

Future Work

• Complete the current analysis

• Peer Review of the work
  – Formal panel review and/or Peer publication(s)

• Validation And Credibility
  – Used a referent data for performance assessment and validation
    • Partnered with researchers at Cleveland Clinic to identify appropriate data
Credible Practices For Models and Simulations

• Models and simulations of all types governed by NASA-STD-7009a
  – Communications tool that seeks to specify the credibility (degree of
    trustworthiness) of the model or specific simulation to the context of it’s
    application
  Data Pedigree - Verification – Validation – Input Pedigree – Uncertainty
  Characterization – Robustness (Sensitivity) – Use History – Product Management

• The NIH Committee on Credible Practice of Modeling & Simulation in Healthcare

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<td>Employ relevant and traceable information in the development or operation of a model or simulation.</td>
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<tr>
<td>Evaluate within context</td>
<td>Verification, validation, uncertainty quantification, and sensitivity analysis of the model or simulation are accomplished with respect to the reality of interest and intended use(s) of the model or simulation.</td>
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<td>List limitations explicitly</td>
<td>Restrictions, constraints, or qualifications for or on the use of the model or simulation are available for consideration by the users or customers of a model or simulation.</td>
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Web: https://simtk.org/home/cpms
e-mail: cpmsinhealthcare@gmail.com
Thank you!

Questions?
Rate of Stone Formation in Context

Distributions normalized to equal area under each curve

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Problem: How does space flight and return affect the post flight one year rate of stone formation in astronauts?

- 24-hour Output Urine Chemistry
- Observed Rates of Stone Presentation
- Crystal Growth and Agglomeration
- Chemical Relations Between Species: Supersaturation

Data Driven Transformation Function: Estimating Rate of Treatable Occurrence
Max Stone Size vs SI – Input Data

Input Data Set Max Stone Size vs SI

- PreFlight
- Stoneformer
- PostFlight

Max Stone Size vs SI
Sampled Incidence Rate Per Person Year

$1 \times 10^4$

PreFlight SI

PreFlight SI

0 0.01 0.02 0.03 0.04

0 100 200 300

0 0.01 0.02 0.03 0.04

0
Result 1

Sampled Incidence Rate Per Person Year

- Inflight SI

![Graph showing sampled incidence rate per person year.](image)
Result 1

Sampled Incidence Rate Per Person Year

PostFlight SI

\[ \times 10^4 \]

0
0.01
0.02
0.03
0.04

0
10
20
30

0
0.01
0.02
0.03
0.04

0
5
10
15

0
10
20
30

0
5
10
15

0
10
20
30

0
0.01
0.02
0.03
0.04

0
5
10
15

0
10
20
30

0
0.01
0.02
0.03
0.04

0
5
10
15
Whitson Combined

Whitson Max Stone Incidence Rates

Incidence Rate Per Person Year

x 10^{-3}

PreFlight  InFlight  PostFlight
Max Stone Size Per Flight Phase

Max Stone Incidence Rates

Incidence Rate Per Person Year

PreFlight  Inflight  PostFlight
Add Preflight, Postflight, and Inflight Boxplots

Whitson Max Stone Incidence Rates for Citrate

PreFlight

InFlight

PostFlight
SI Per Flight Phase

The graph shows the distribution of SI (SI) per flight phase, with three distinct phases: PreFlight, Inflight, and PostFlight. The box plots indicate the variability and central tendency of the data across these phases.
SI Incidence Per Flight Phase

SI Incidence Rates

Incidence Rate Per Person Year

- PreFlight
- Inflight
- PostFlight