FORECASTING THE CHANGE OF RENAL STONE OCCURRENCE RATES IN ASTRONAUTS

D. Goodenow¹, S. Gokoglu¹, M. Kassemi², J. Myers¹

¹National Aeronautics and Space Administration Glenn Research Center
²National Center for Space Exploration Research (NCSER).

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Presentation Overview

- Population Incidence Rates
- Simulation Architecture and Methodology
- Simulation Results
- Summary
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# Rate of Calcium Oxalate Stone Formation in Context

<table>
<thead>
<tr>
<th>Distr. Type</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonstoneformer (general population)</td>
<td>Normal</td>
<td>Mean: 101.1</td>
<td>SE 6.6</td>
<td>Lieske et al. 2006 (Rochester Study)</td>
</tr>
<tr>
<td>Stoneformer (general population)</td>
<td>Triangular</td>
<td>Min: 121</td>
<td>Max: 1093</td>
<td>Urological Diseases In America, 2012</td>
</tr>
<tr>
<td>Inflight</td>
<td>Lognormal</td>
<td>Mean: 365</td>
<td>Std: 46</td>
<td>Gilkey et al, 2010</td>
</tr>
<tr>
<td>Postflight</td>
<td>Gamma</td>
<td>alpha=7.7</td>
<td>beta=.00593</td>
<td>Porter and Rice, 2013 &amp; LSAH (Bayesian)</td>
</tr>
</tbody>
</table>

![Graph showing probability density and incidence rate per 100K person-years](image-url)
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Problem: How does spaceflight and return affect the postflight one year rate of stone formation in astronauts?

Propose the use of Probabilistic Computational Models - *When the system is complex or complicated enough that your intuition, or your forecasting knowledge, is insufficient to describe how the system will respond.*

Probabilistic Monte Carlo Simulation using Population Data

1. Urinalysis Data
2. Bio-chemistry Model
3. Stone Growth Model
5. Risk of Renal Stone
Dataset Sources: Training and Testing

LSAH Population Data:
1517 Urine Samples from 581 individual astronauts (pre-, in-, and post-) flight.

- **Samples include**
  - Mol/L measurements of Calcium, Oxalate, Citrate, Magnesium, Uric Acid, Sulphuric Acid, Phosphoric Acid, Sodium, Potassium
  - Volume in Liters
  - Urine ph

- **Data to train the model transfer function**
  - 957/1517 urine samples
  - Preflight : 515 astronaut urine samples, including 7 stoneformer samples
  - Postflight : 442 astronaut urine samples, including 4 stoneformer samples

- **To test the model forecasting ability**
  - 560/1517 urine samples used to construct representative population distributions
  - Incomplete Preflight and Postflight data
  - 120 Inflight datasets both complete and incomplete was used to form the Inflight renal chemistry distributions
**Biochemistry Model and PBE Models**

- **Joint Expert Speciation System: JESS**
  - Transforms total concentration, via system of equations into free ion concentrations \( c_i \) based on urine equilibrium chemistry
  - JESS Provides the Saturation Index (SI = RSS\(^2\)): Metric that represents the propensity for spontaneous crystallization/precipitation in the solution
  
  [Link to JESS](http://jess.murdoch.edu.au/jess_home.htm)

- Kassemi Population Balance Equation (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 Incidence Rate: Poisson Regression-based Transfer Function

- Known Chemistries - PBE Max stone size
- Status - Population Incidence-rate distributions

- Fixed time interval & incidence rate distribution estimates the number of incidences
- Incidences fit to corresponding Poisson distribution

Technique: Poisson Regression With Rates

Simulation Model
- Repeats 10,000 times

Aggregates findings and calculate relevant statistics
Simulation analysis - Correlation of Rates

Saturation Index Curve Fit

Max Stone Size Curve Fit

Incidence Rate of Stone Formation Per Person-Year

- Mean
- +/- 2 Standard Deviations

Incidence Rate of Stone Formation Per Person-Year

- Mean
- +/- 2 Standard Deviations

SI

Max Stone Size (meters)
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Sampled Incidence Rate Per Person-Year

Incidence Rate Histograms: Preflight
Inflight Incidence Rate Histograms

Sampled Incidence Rate Per Person-Year

- Inflight Max Stone
- Inflight Saturation Index (SI)
Incidences Rate Histograms: Postflight

Sampled Incidence Rate Per Person-Year

Postflight Max Stone

Postflight Saturation Index (SI)
PBE Model: Microgravity Astronaut Subject: Effect of Citrate Countermeasure

nominal urine concentrations

(hypocitraturia)
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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 spaceflight and return than supersaturation alone
    - Minimal attributable difference in predictive potential at lower SI levels typical of non-stone former, pre-flight rates

- We cannot yet assess if this particular application illustrates overall improvement in forecasting than current clinical practice
  - Does indicate a promising means to quantify the relative change in risk to astronauts
  - Provides the opportunity to glean some insight into the efficacy of interventions and address the:
    - Effect of hydration
    - Effect of inhibitors
    - Effect of reducing urinary calcium through other countermeasures (exercise)
Thank you!

Questions?
Simulation of Astronaut Population Incidence Rates: Preflight, Inflight, and Postflight

Monte Carlo Simulation – 150K trials
Convergence $\Delta$STD < 0.001 per person-year / per 1000 trials
Urine samples 9 astronauts, at each flight phase that received potassium citrate as part of a renal stone countermeasure study.

Note: Data included only 2 placebo subjects, totaling 14 urine samples
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
    • Generally urine samples have high degree of variability from time point to time point
    • Astronaut urine chemistries do not address relative timing of the sample acquisition and any stone occurrence
    – Data not separated for factors such as sex or age

• PBE model has wide range of values for kinetic 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