FORECASTING THE CHANGE OF RENAL STONE OCCURRENCE RATES IN ASTRONAUTS

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Presentation Overview

- Population Incidence Rates
- Simulation Architecture and Methodology
- Simulation Results
- Summary

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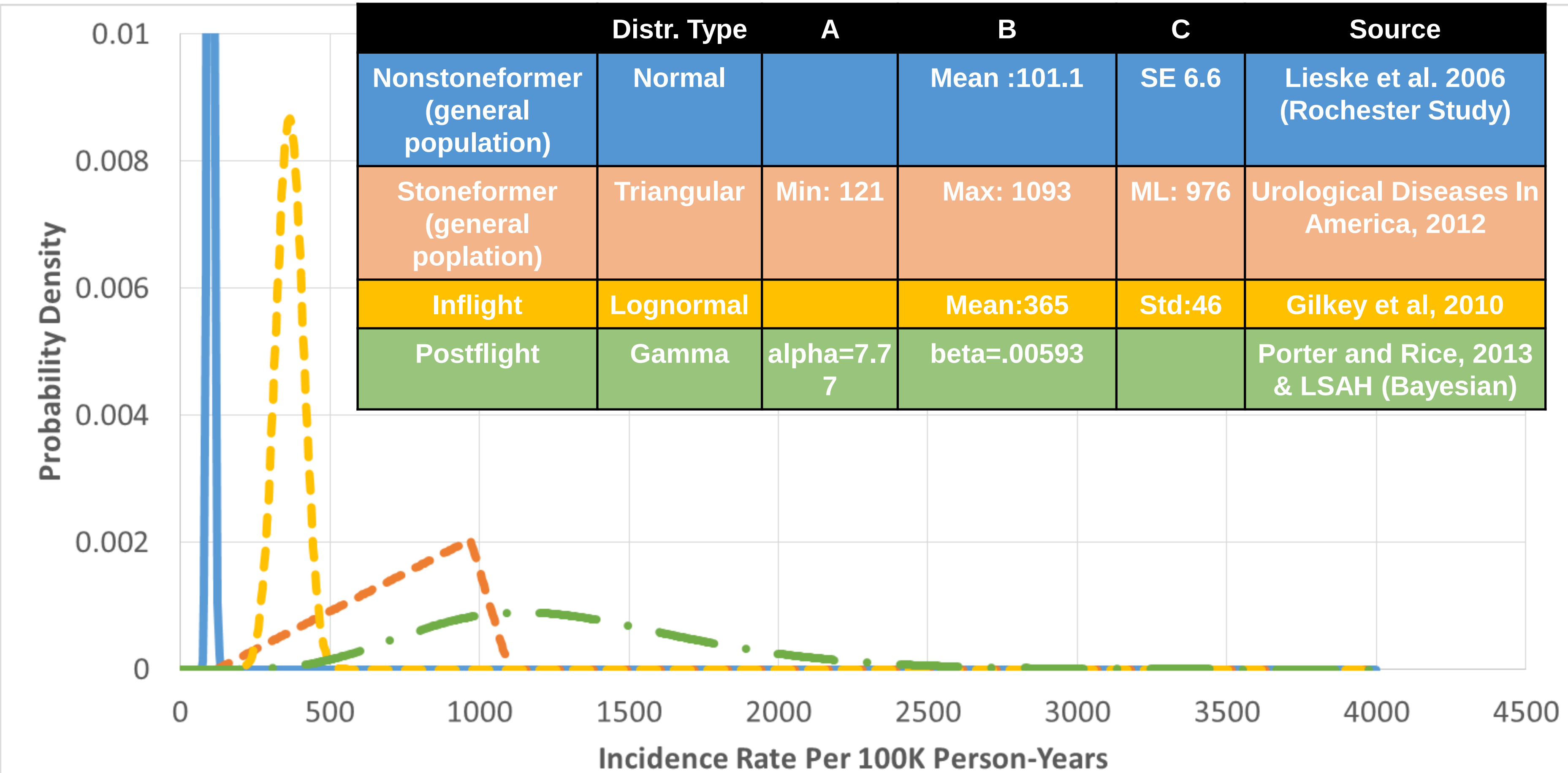
Rate of Calcium Oxalate Stone Formation in Context



	Distr. Type	A	B	C	Source
Nonstoneformer (general population)	Normal		Mean :101.1	SE 6.6	Lieske et al. 2006 (Rochester Study)
Stoneformer (general poplation)	Triangular	Min: 121	Max: 1093	ML: 976	Urological Diseases In America, 2012
Inflight	Lognormal		Mean:365	Std:46	Gilkey et al, 2010
Postflight	Gamma	alpha=7.7 7	beta=.00593		Porter and Rice, 2013 & LSAH (Bayesian)

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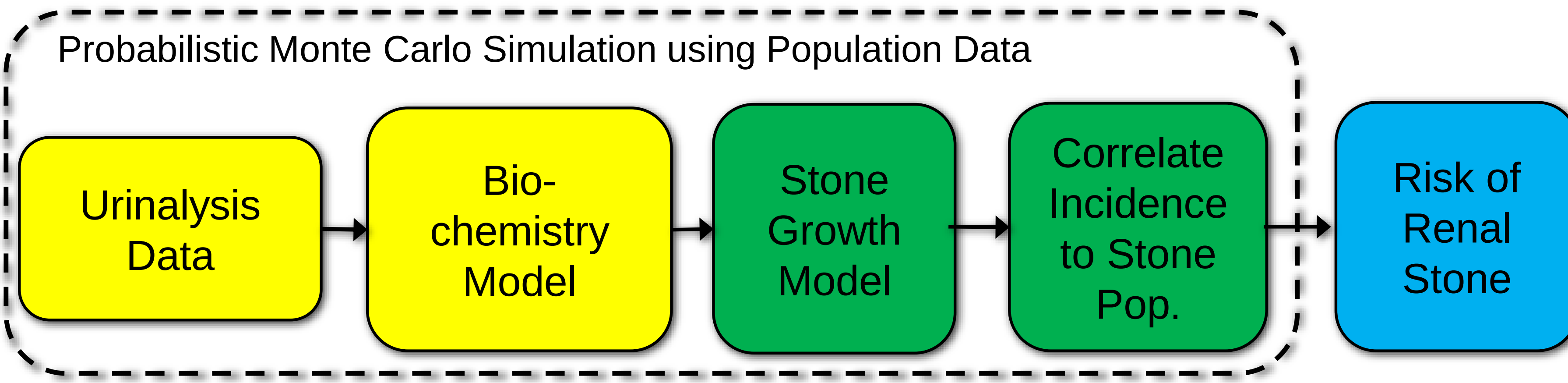
Probabilistic Model for Renal Stone Incidence Likelihood

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



Dataset Sources: Training and Testing

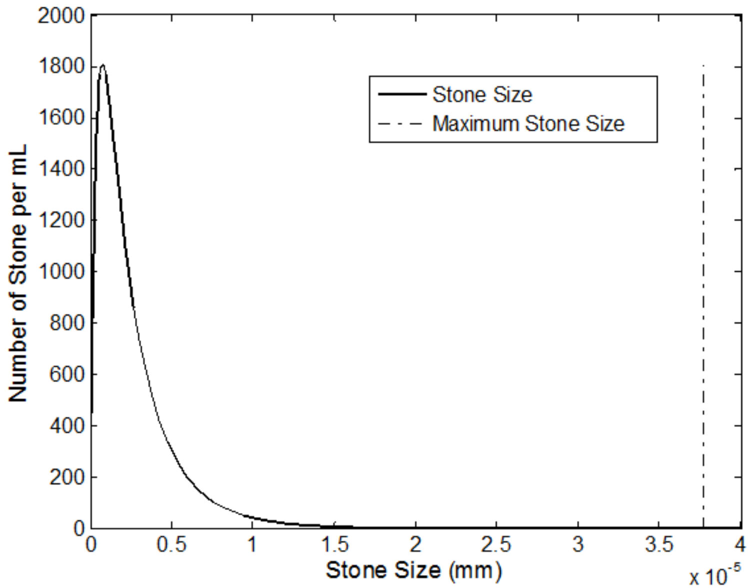
LSAH Population Data :
1517 Urine Samples from 581 individual astronauts (pre-, in-, and post-) flight.

- **Samples include**
  - Mol/L measurements of Calcium, Oxalate, Citrate, Magnesium, Uric Acid, Sulphuric Acid, Phosphoric Acid, Sodium, Potasium
  - 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

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

Technique: Poisson Regression With Rates

Fixed time interval & incidence rate distribution estimates the number of incidences

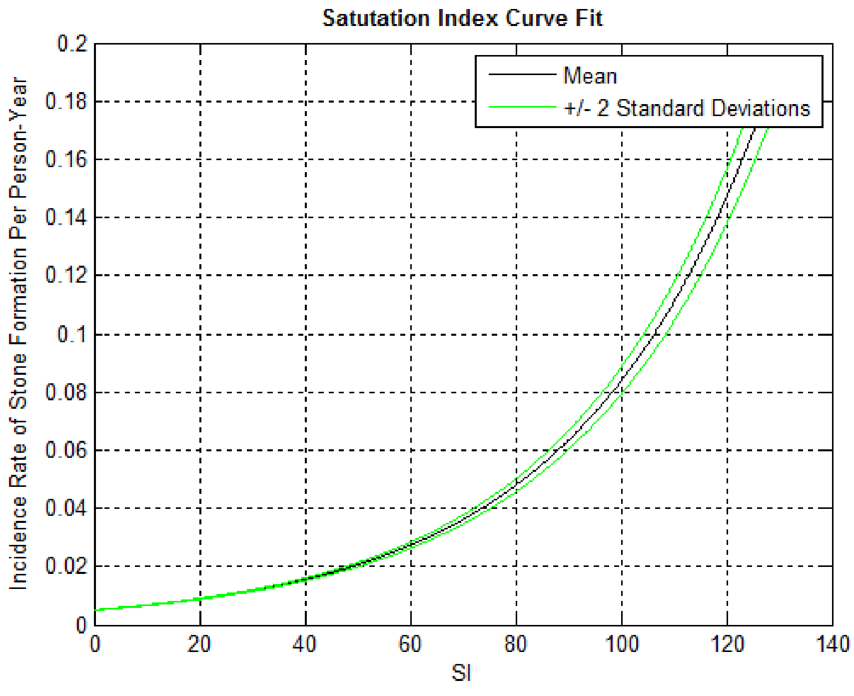
Incidences fit to corresponding Poisson distribution

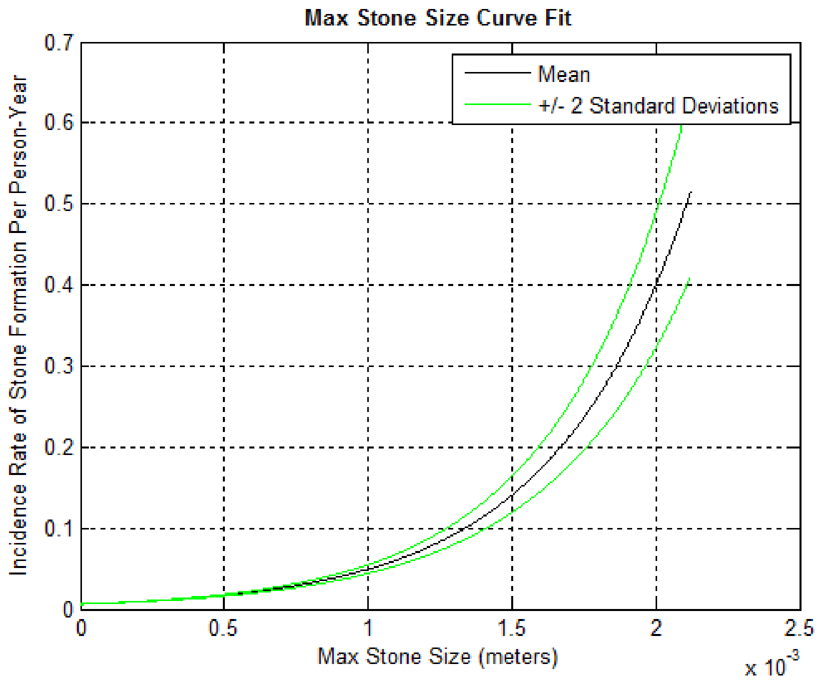
Simulation Model

Repeats 10,000 times

Aggregates findings and calculate relevant statistics

Simulation analysis - Correlation of Rates





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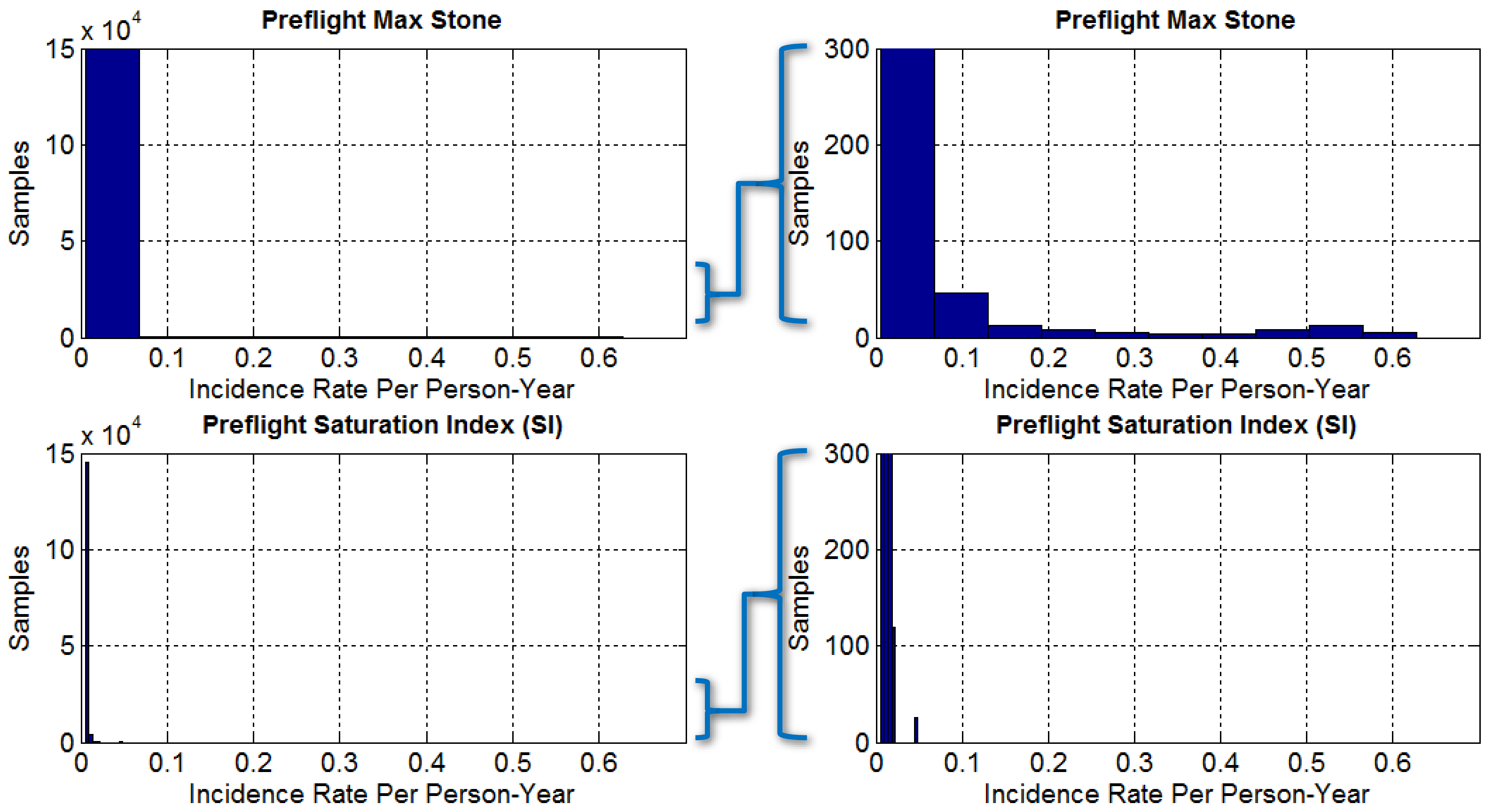
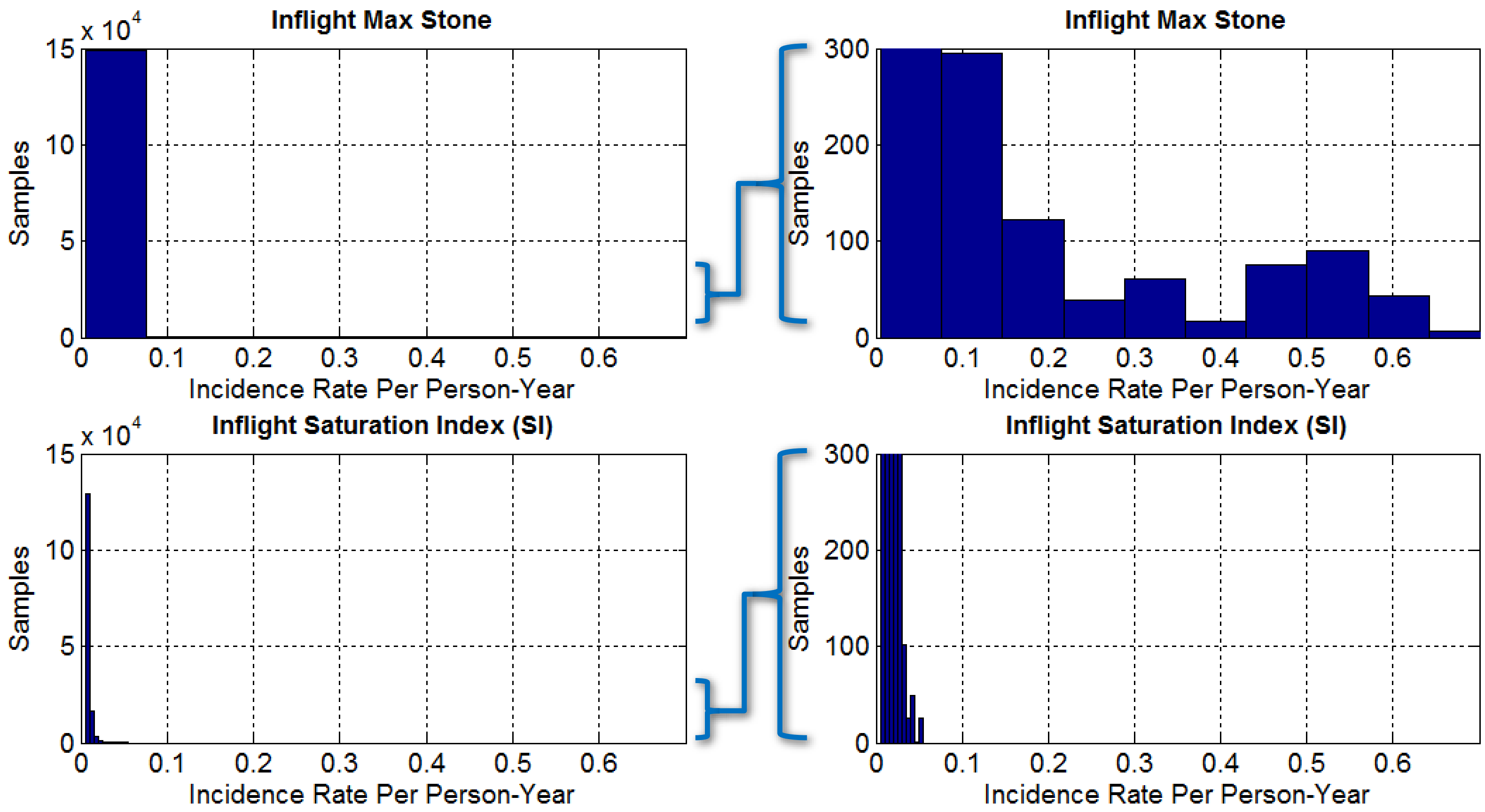
Incidence Rate Histograms: Preflight

Sampled Incidence Rate Per Person-Year



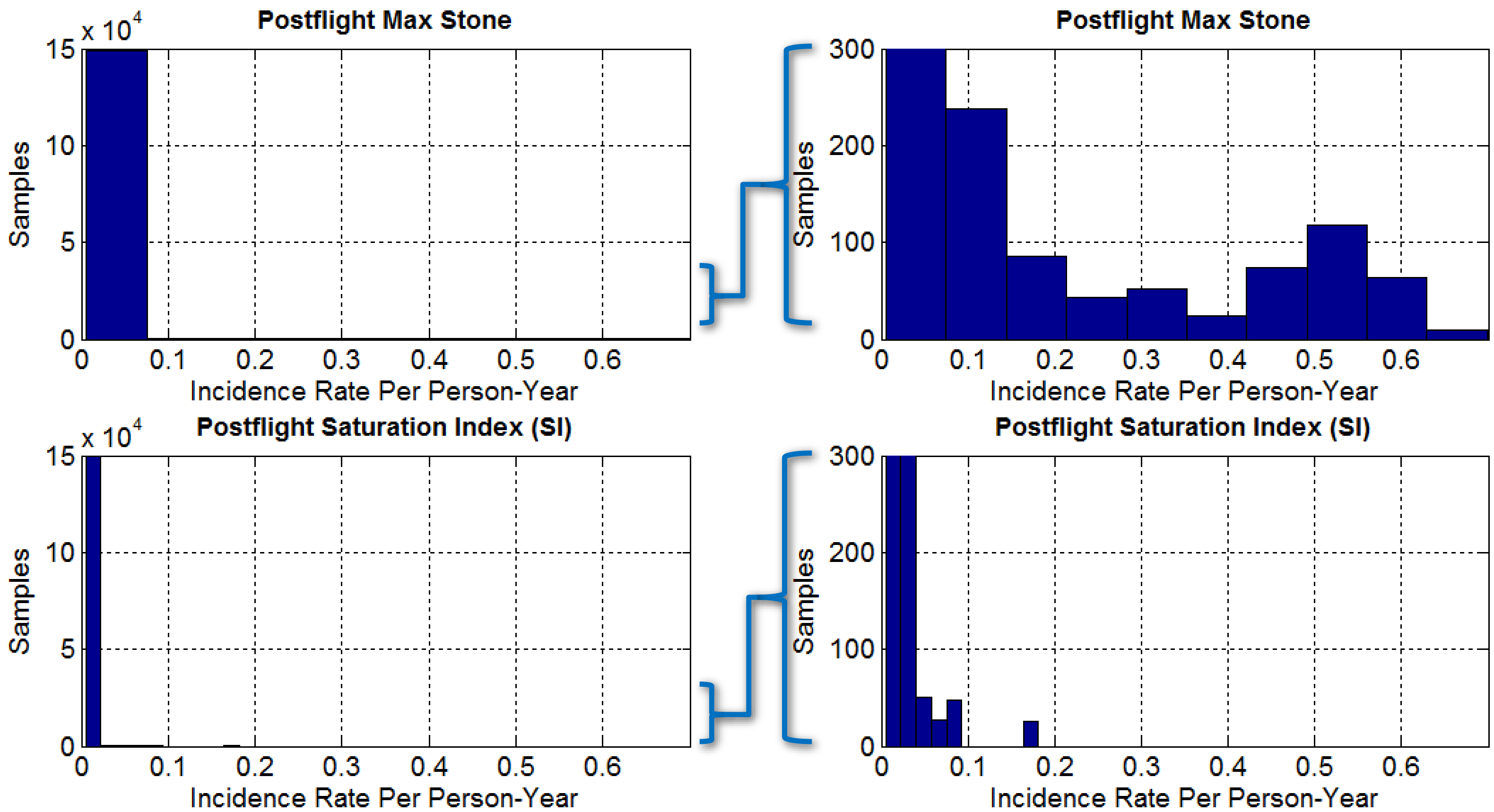
Incidence Rate Histograms: Inflight

Sampled Incidence Rate Per Person-Year

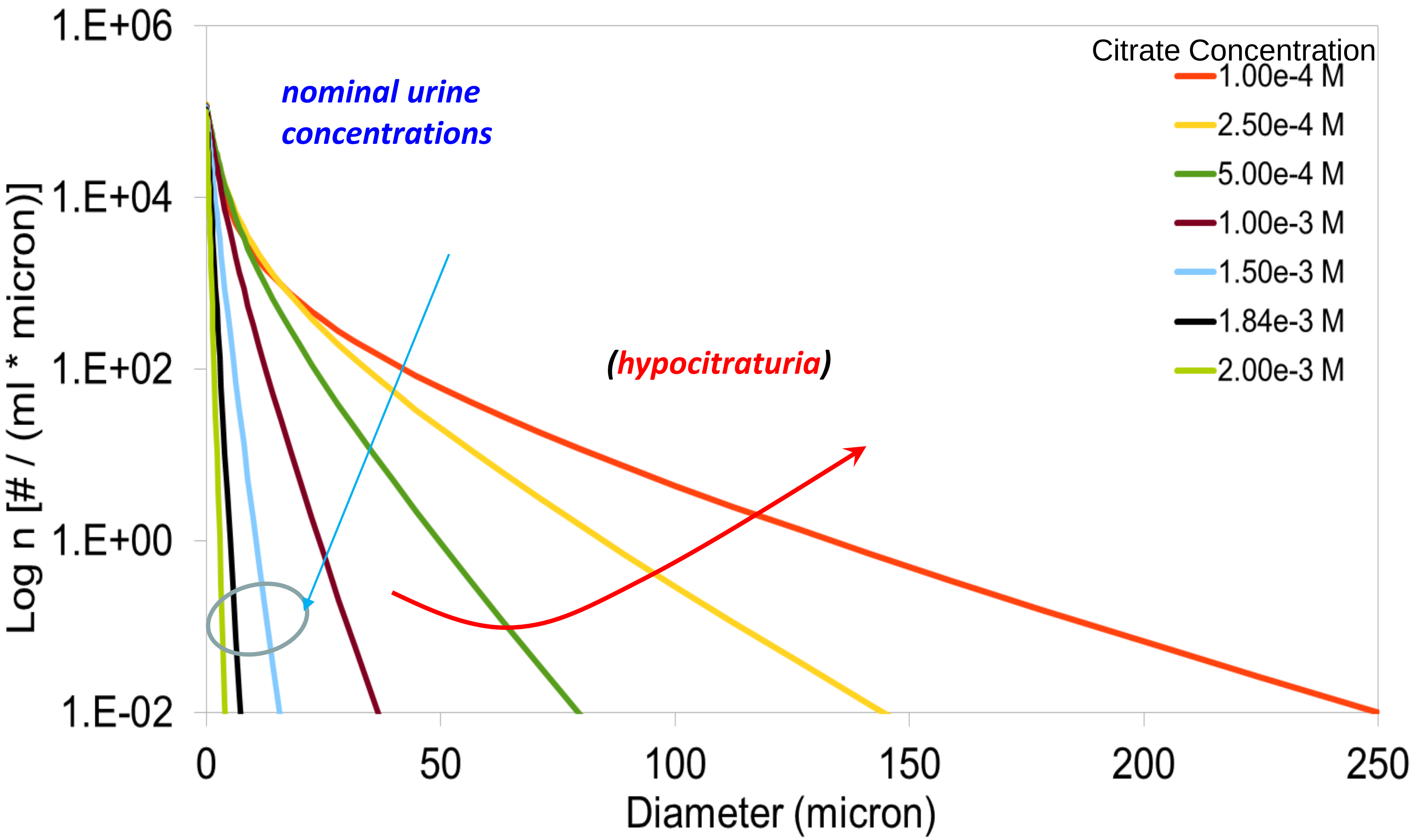


Incidence Rate Histograms: Postflight

Sampled Incidence Rate Per Person-Year



PBE Model : Microgravity Astronaut Subject: Effect of Citrate Countermeasure



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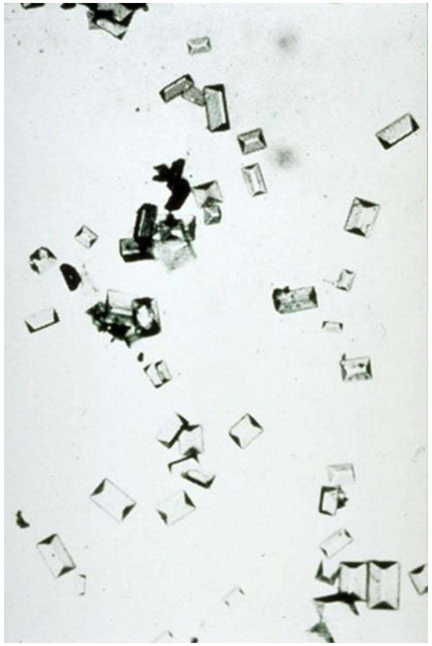
Summary of Findings



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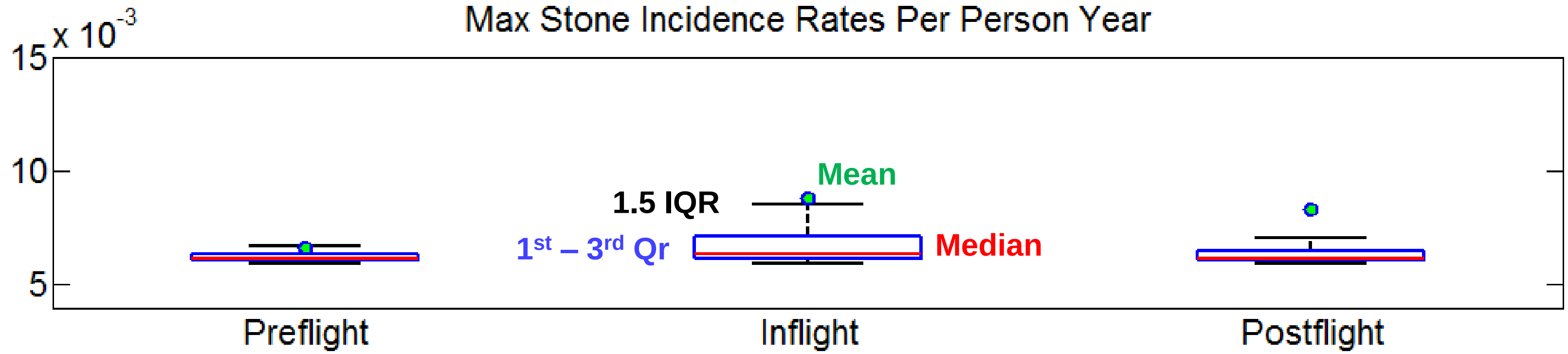
- **We have shown that combining physics-based modeling and numerical analytics provides deeper insight into the renal stone risks for astronauts**
  - PBE forecasts an increase in the extent of possible incidence rates due to spaceflight and return than supersaturation alone
    - Minimal attributable 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)

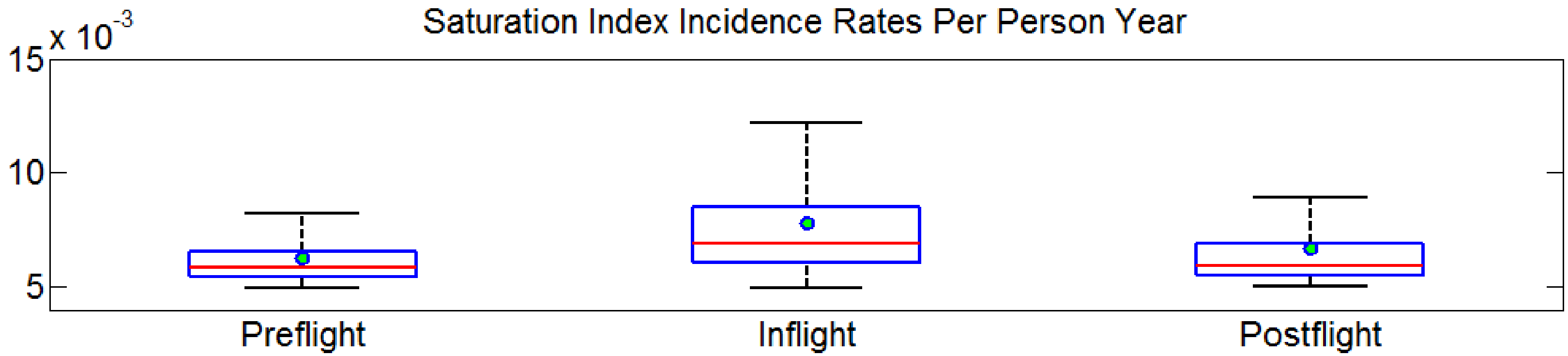
Thank you!

Questions?

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

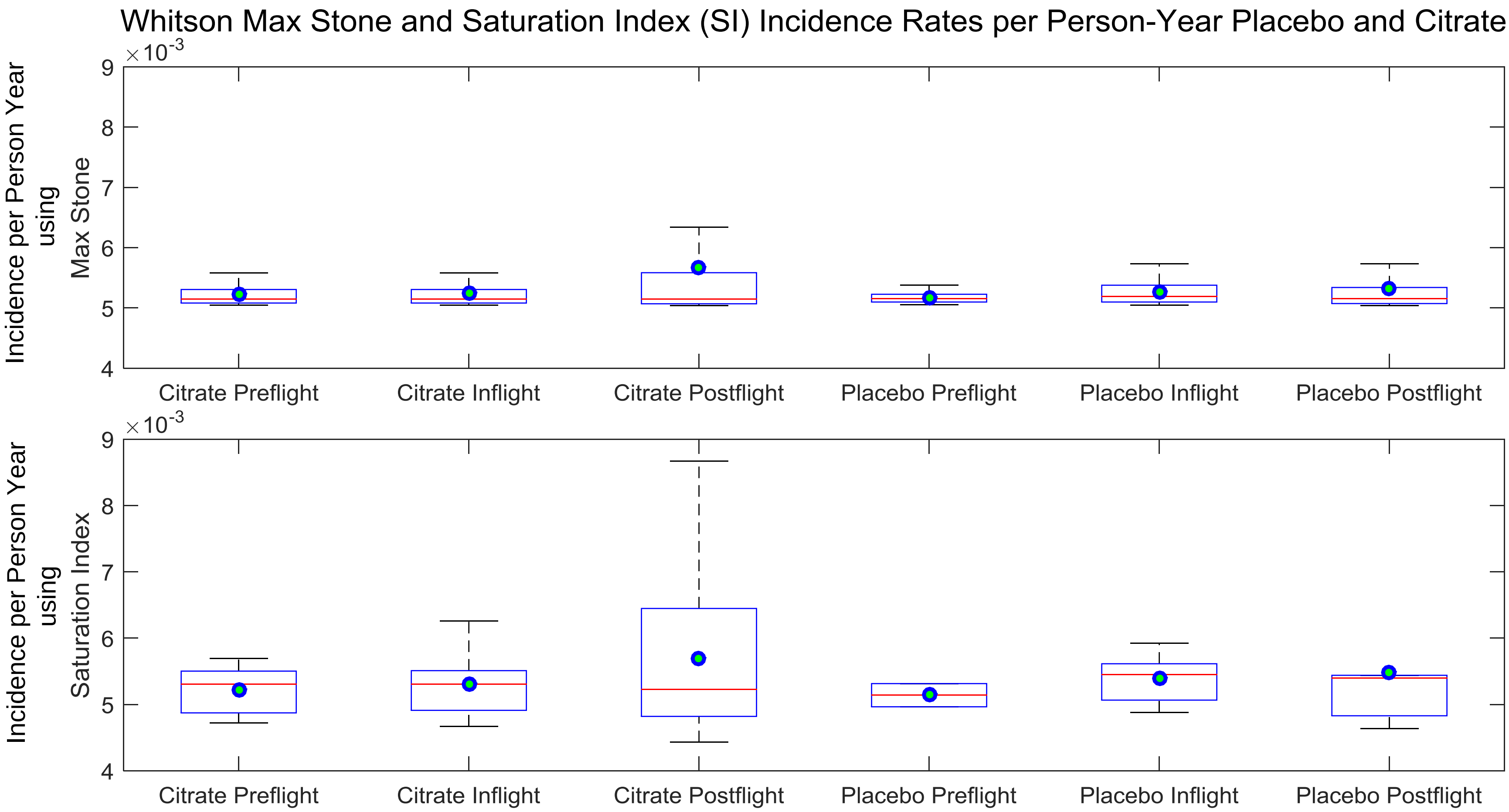
Monte Carlo Simulation – 150K trials
Convergence ΔSTD < 0.001 per person-year / per 1000 trials





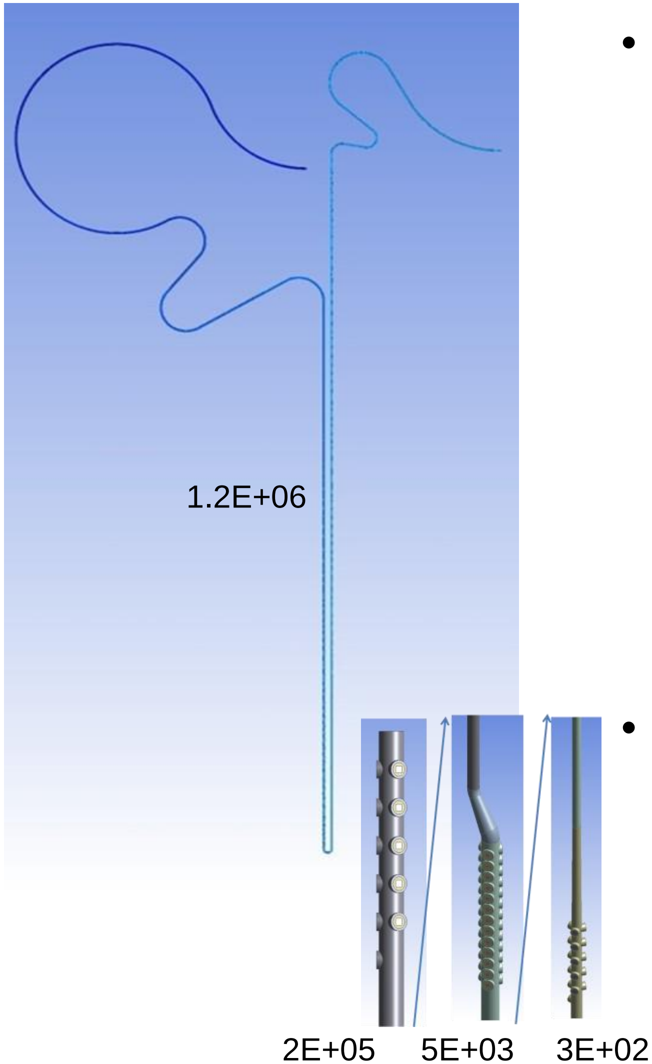
Inhibition Factors: Dietary Citrate and Placebo
Whitson et al. J Urology 2009

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, β**
  - 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