National Aeronautics and Space Administration

FORECASTING THE CHANGE OF RENAL STONE OCCURRENCE RATES IN ASTRONAUTS

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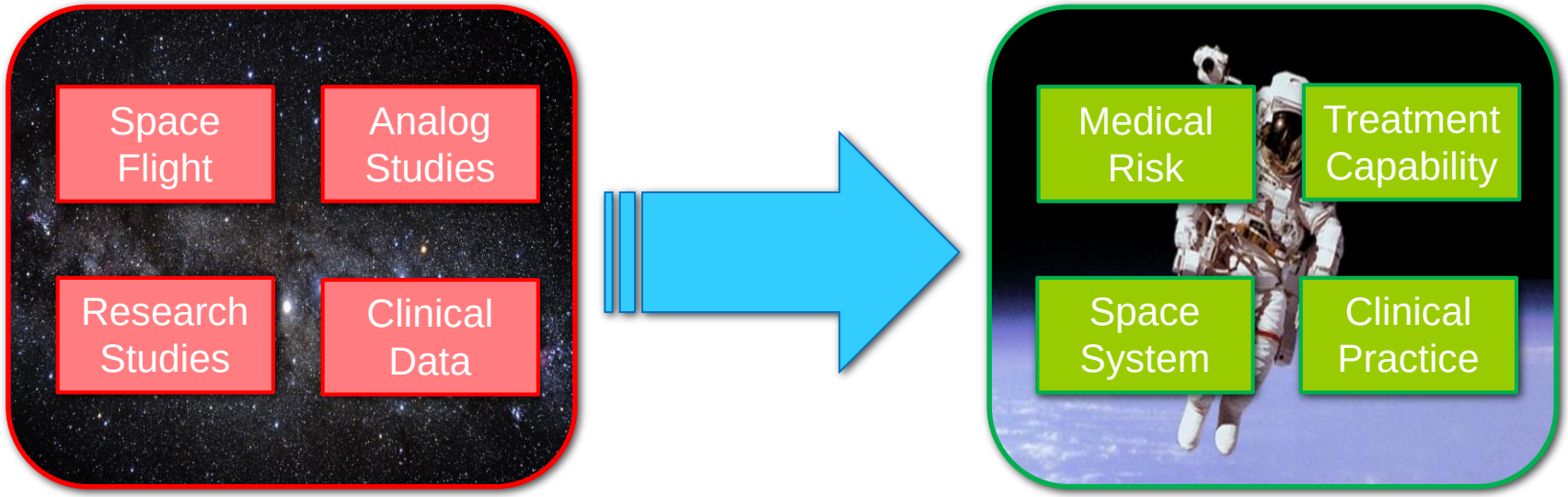
ASGSR 2016

A Challenge of Translational Medicine to Space Flight



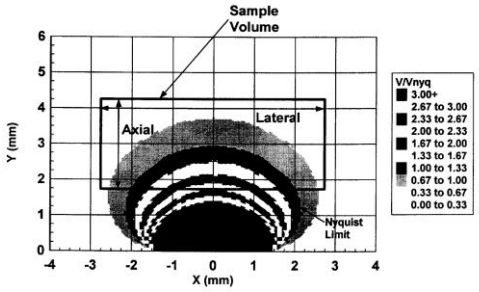
Informative Data

Actionable Knowledge

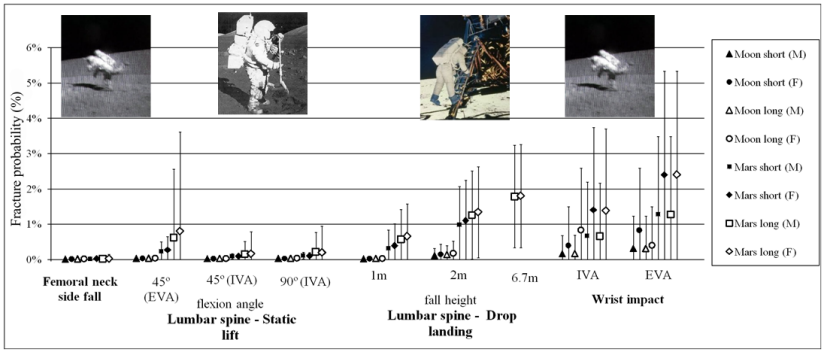
Computational Modeling and Medical Applications

Consider using a Mathematical or Computational Models-

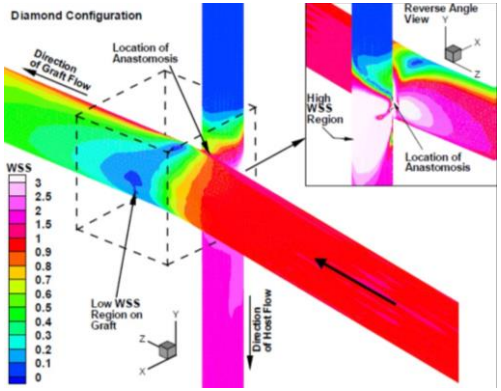
When the system is complex or complicated enough that your intuition, i.e. your forecasting knowledge, is insufficient to describe how the system will respond



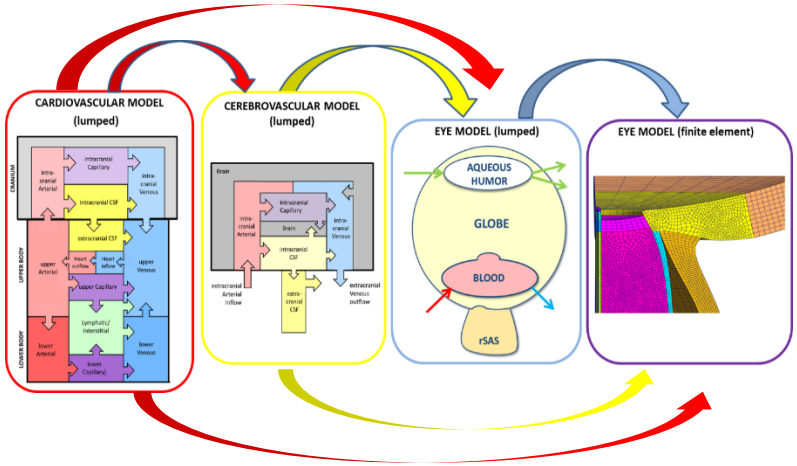
Ultrasound Diagnostics
Insufficient Heart Valves (Perry et al. 1996)



Bone Fracture Risk (Nelson et al. 2009)

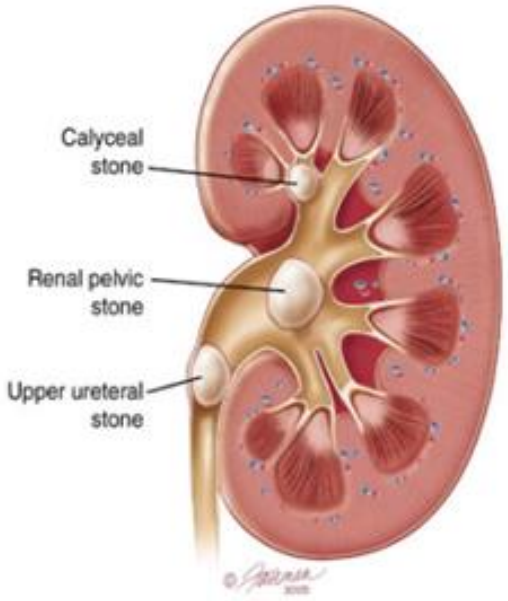


Surgical Intervention
CABG (Bonert et al. 2000)

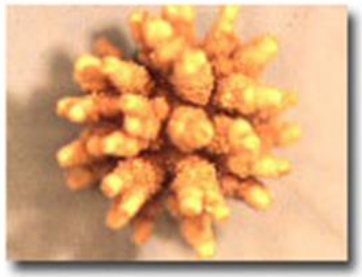


Space Flight Induced Visual Impairment (Feola et al. 2016)

Renal Stone Incidence Likelihood during Space Flight



Misery



Agony

- **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 estimate of CaOx stone incidence rate

Bayesian analysis including

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

Posterior Estimate

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

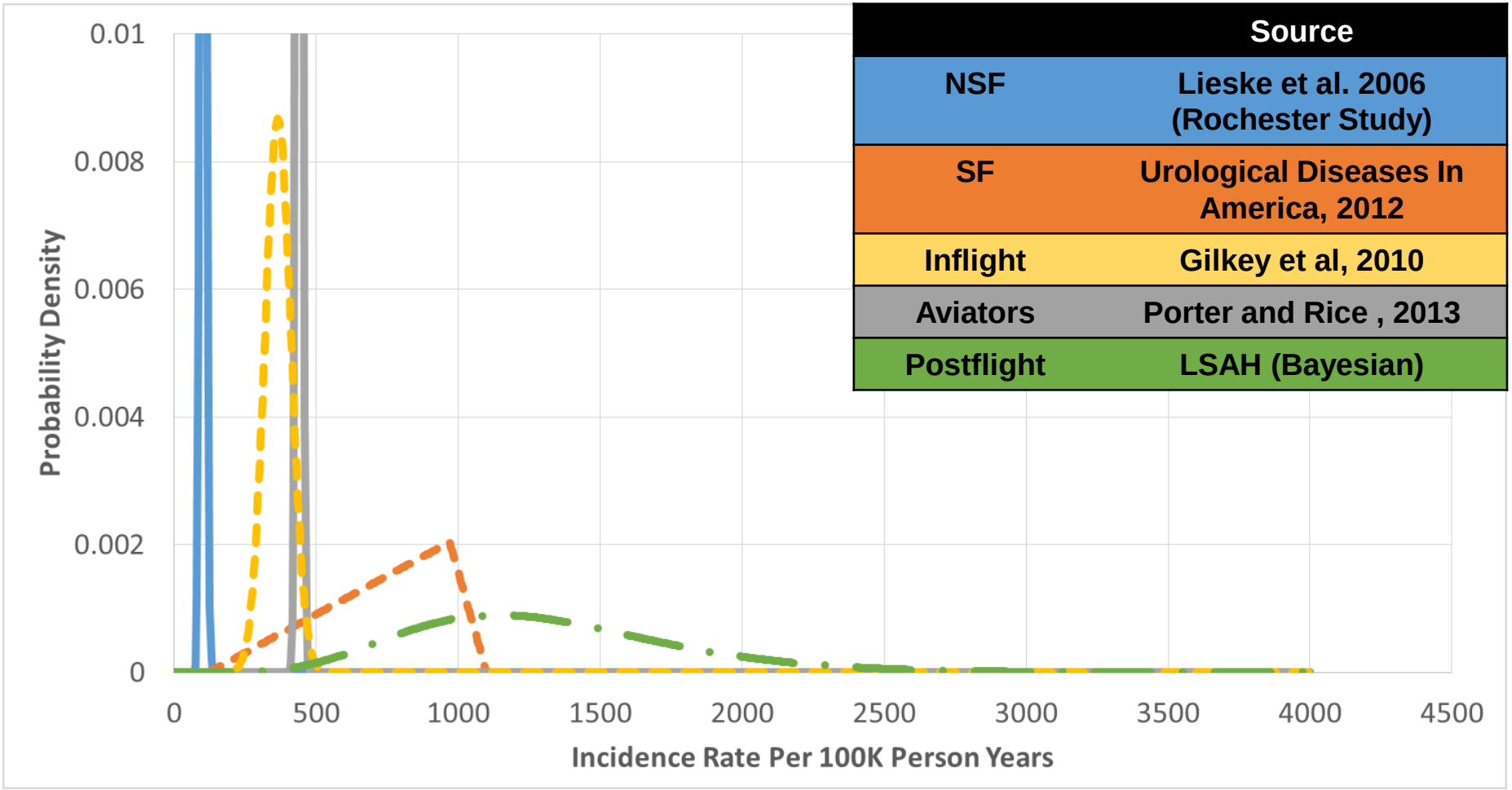
Does not address gravity, mission trades, or countermeasures

- what happens if I reduce water intake by 1 liter?

Gilkey et al. 2012 – NASA/TP -2012-217120

Rate of Stone Formation in Context

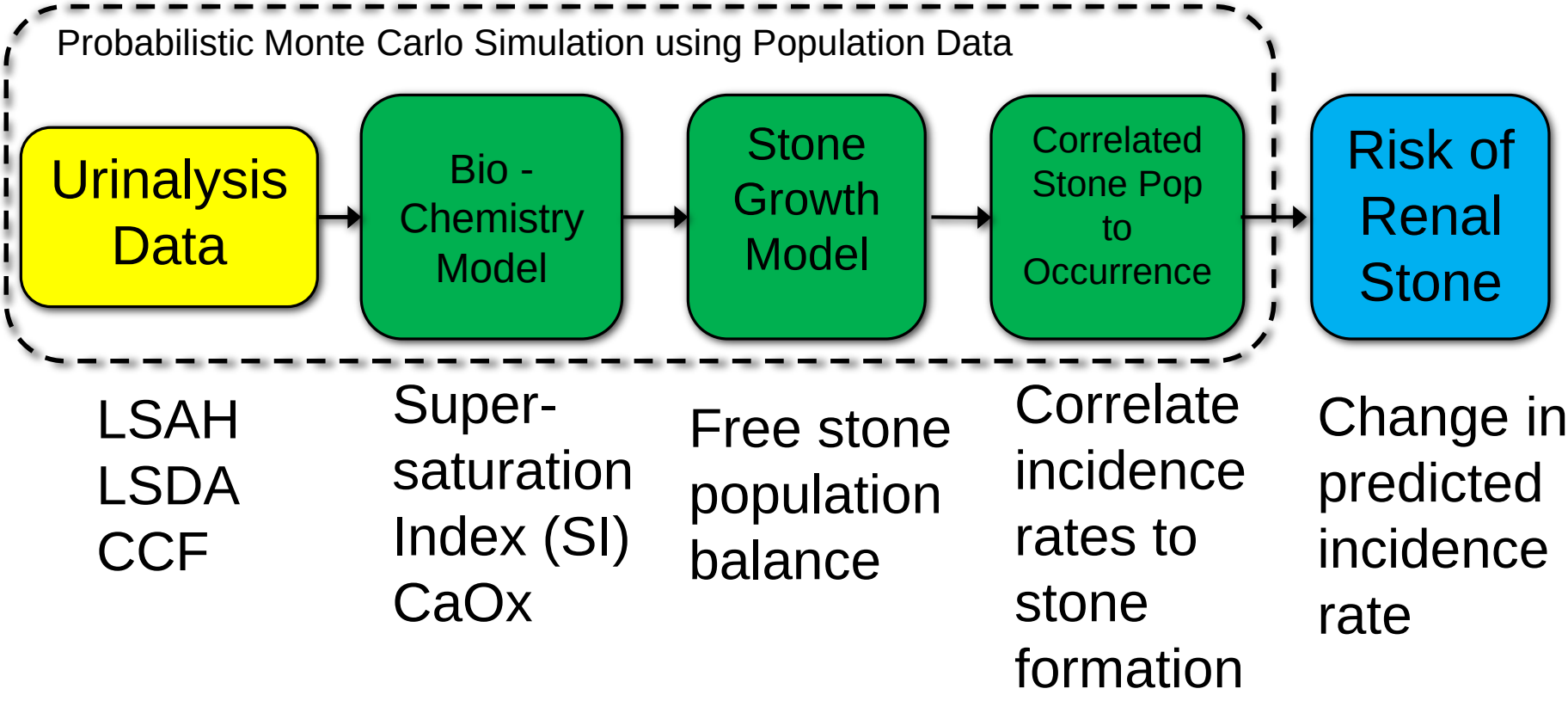
Distributions normalized to equal area under each curve



	Source
NSF	Lieske et al. 2006 (Rochester Study)
SF	Urological Diseases In America, 2012
Inflight	Gilkey et al, 2010
Aviators	Porter and Rice , 2013
Postflight	LSAH (Bayesian)

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?



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

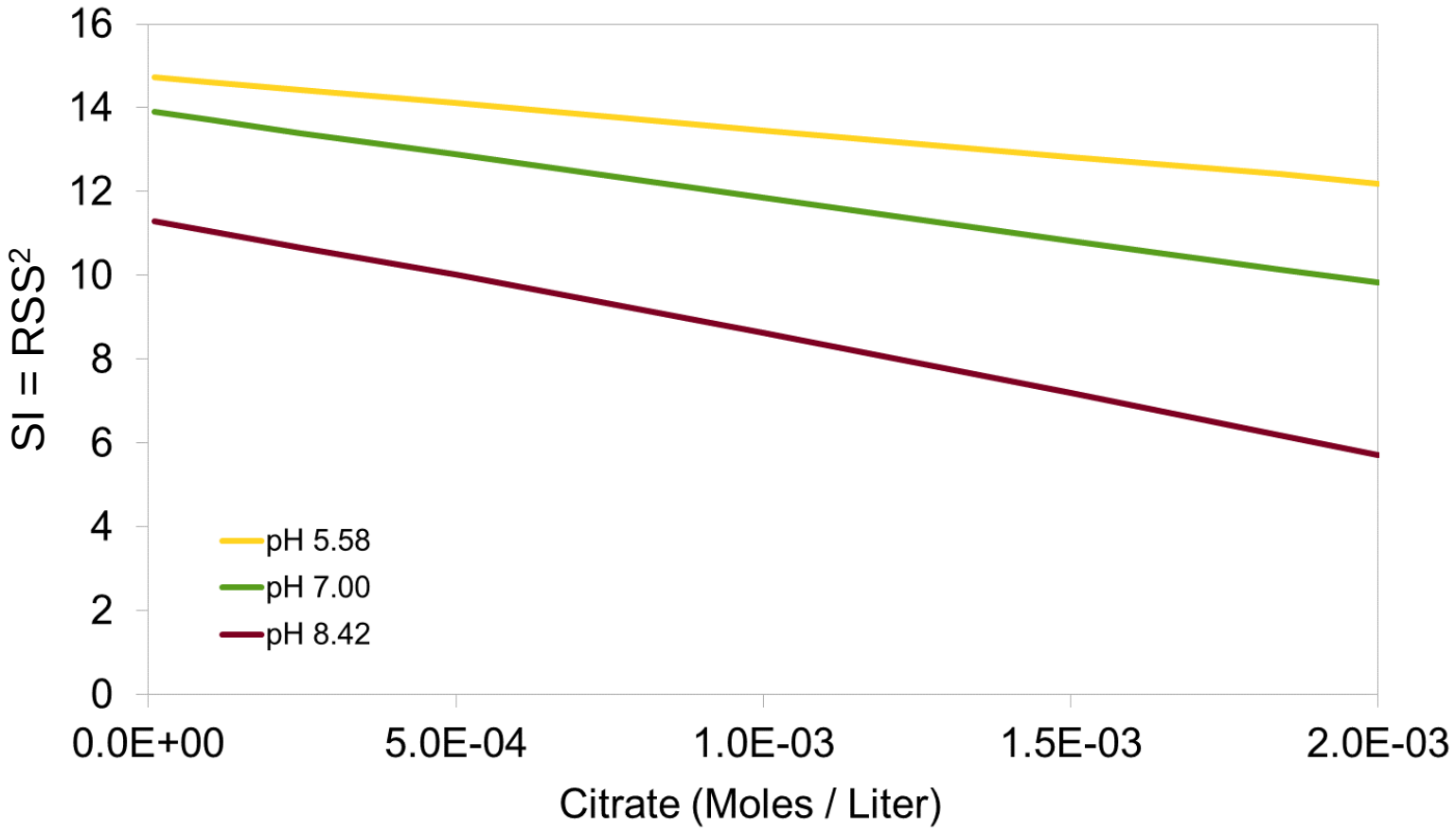
- **Transforms total concentration, via system of equations into free ion concentrations (c_i) based on urine chemistry reactions**

- **Relative Supersaturation calcium oxalate (RSCaOx)**
  - JESS Provides the Saturation Index (SI = RSS^2) : Metric that represents the ability of spontaneous crystallization of the solution

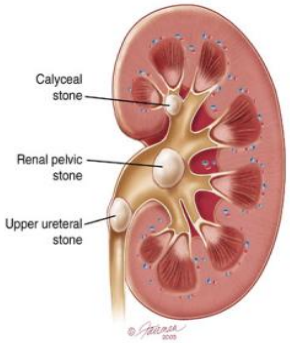
http://jess.murdoch.edu.au/jess_home.htm

Jess: Effect of Direct Inhibition by Speciation on the Urinary CaOx Supersaturation

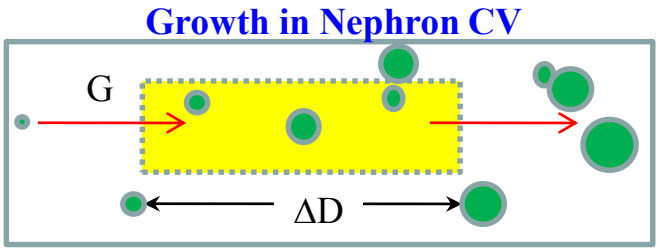
- **Microgravity Astronaut:** Average of 24-urine excretion rates obtained from 86 post-flight astronaut urine chemistries. (Whitson et al.[36])

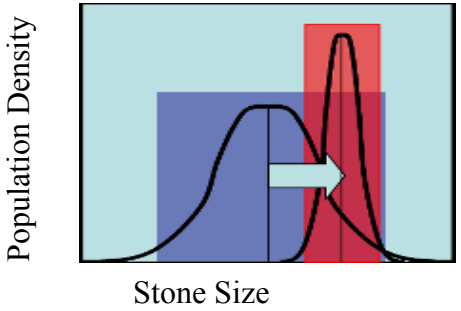


Renal Stone Population Balance (PBE) System Model: Nucleation, Growth & Agglomeration



Kidney:
Mixed Suspension Mixed Product Removal Crystallizer





Population Balance Equation:

$$\frac{n(D)}{\tau} + \underbrace{G_D \frac{\partial n(D)}{\partial D}}_{\text{Growth}} = \underbrace{\int_0^{D/2} \boldsymbol{\beta} n(D-D')n(D')dD'}_{\text{Agglomeration-Birth}} - \underbrace{n(D)\int_0^{\infty} \boldsymbol{\beta} n(D')dD'}_{\text{Agglomeration-Death}}$$

Nucleation BC:

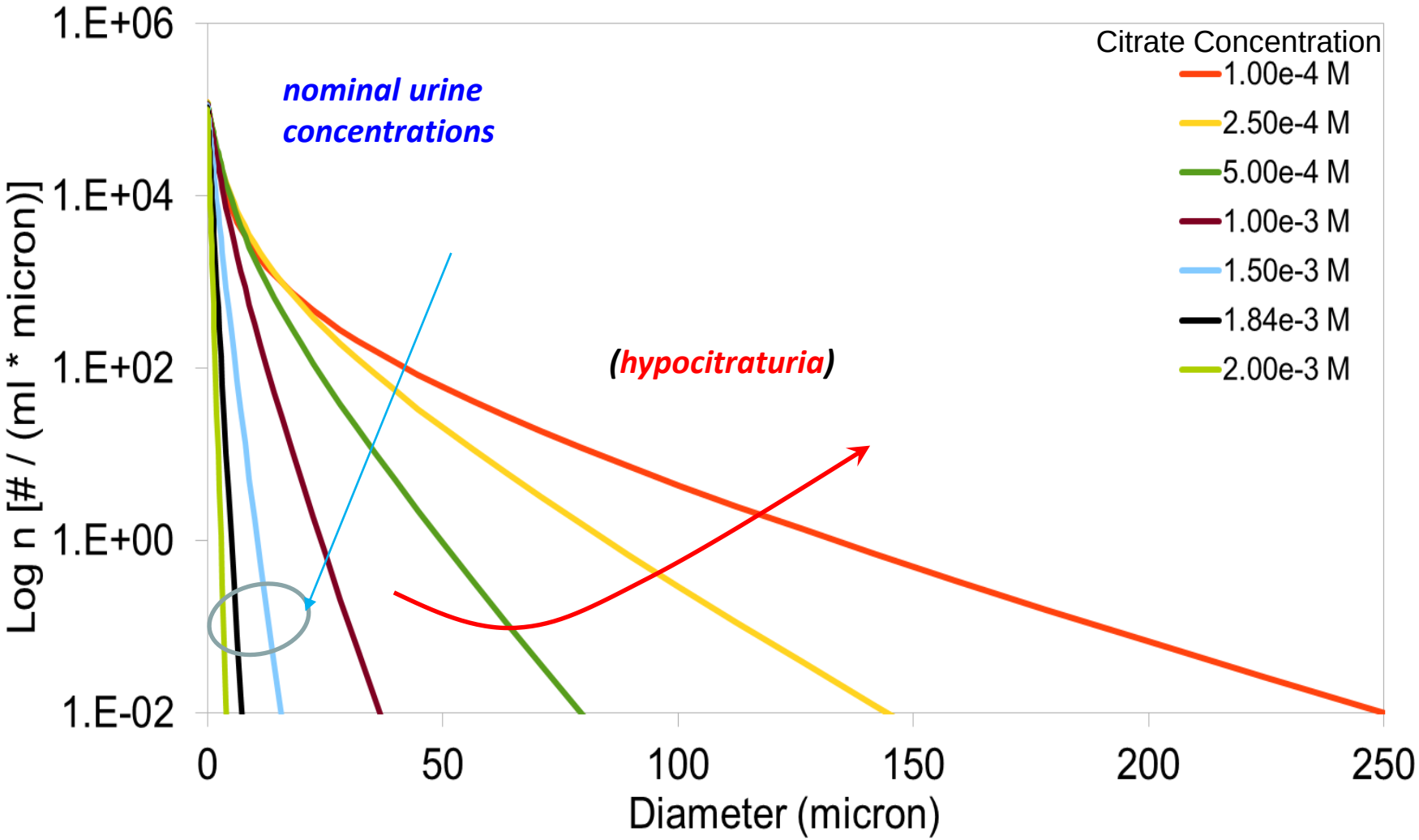
$$n\,(D=0) = n^o = {}^{B^o}/_{G_D}$$

Relative Supersaturation

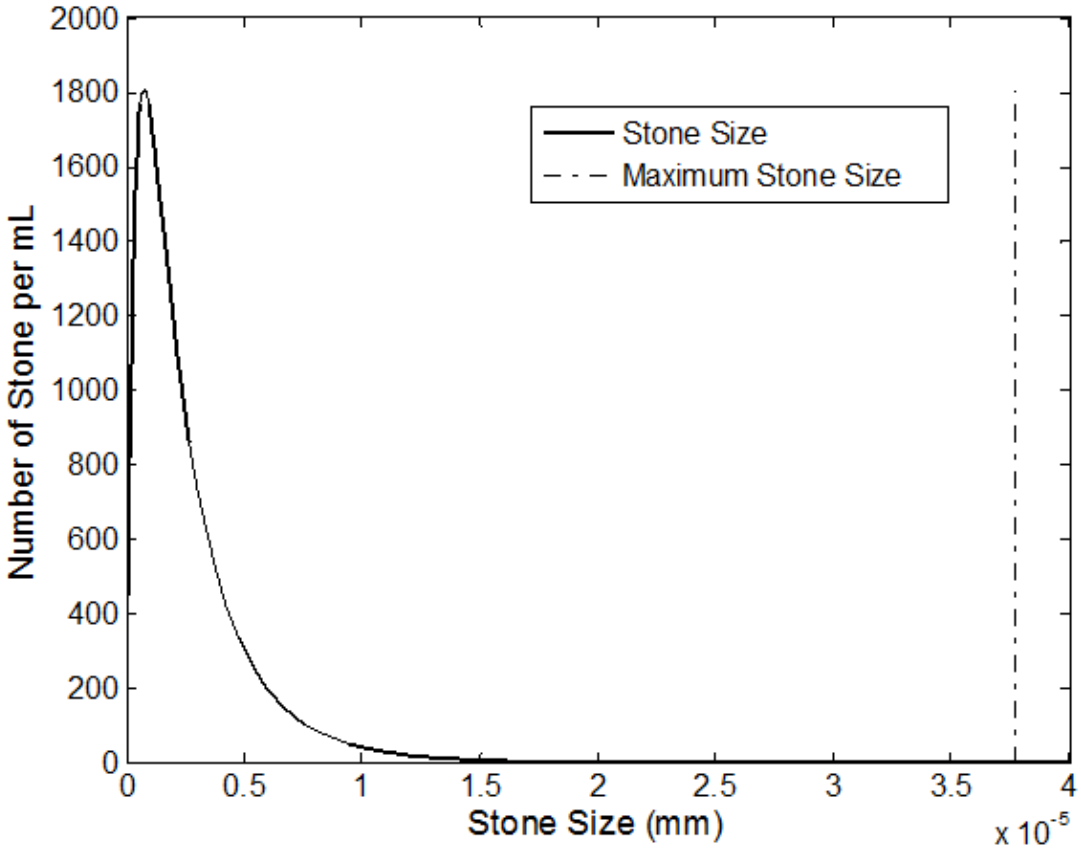
Inhibition: Citrate, Pyrophosphare, Hydration

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



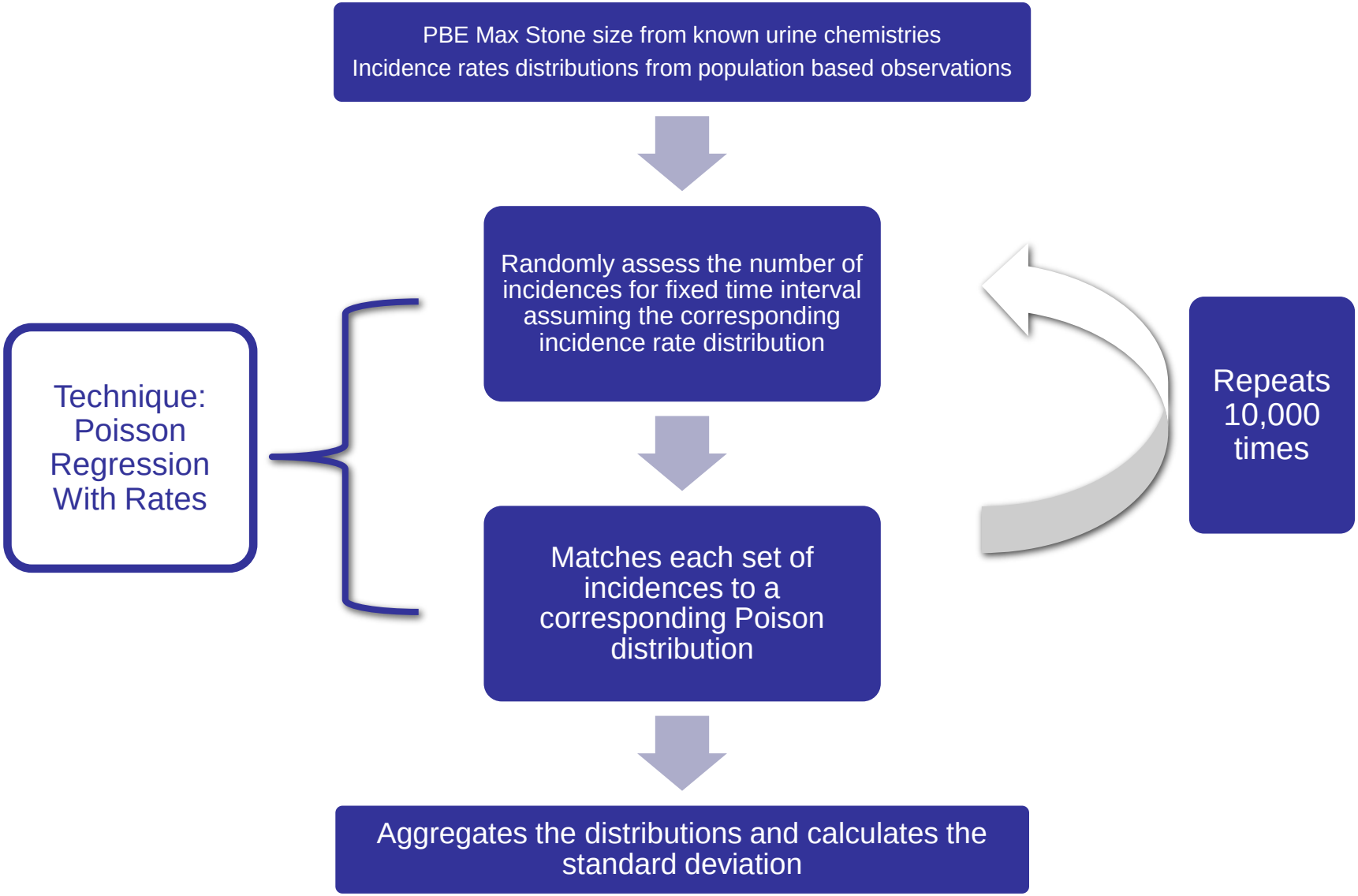
Representative Output - PBE Model Max Stone Size



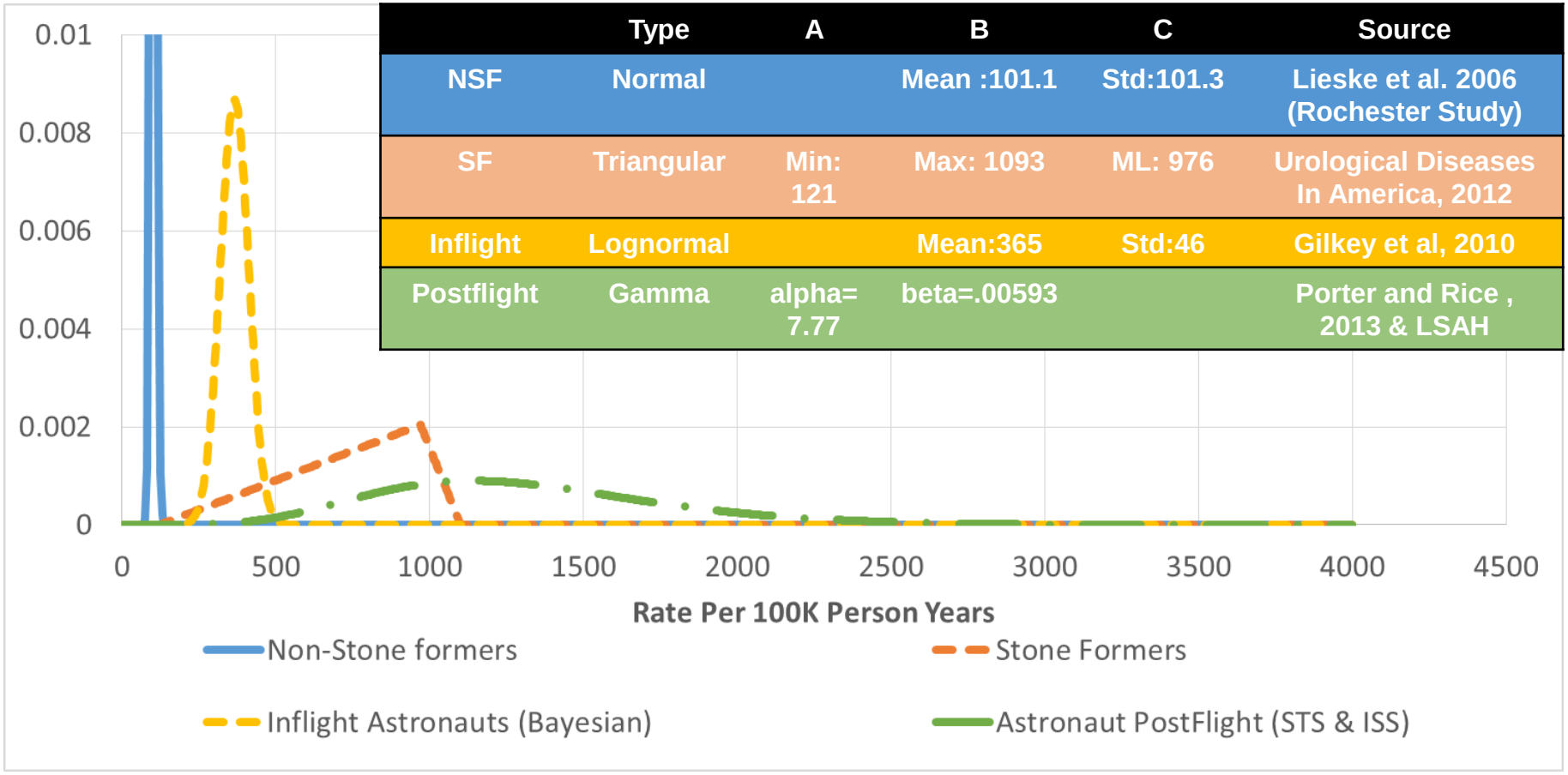
Kassemi PBE model produces a population density of stones related to the input urine chemistry

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



Rate of Stone Formation in Context



	Type	A	B	C	Source
NSF	Normal		Mean :101.1	Std:101.3	Lieske et al. 2006 (Rochester Study)
SF	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= 7.77	beta=.00593		Porter and Rice , 2013 & LSAH

Dataset Sources: Training and Testing

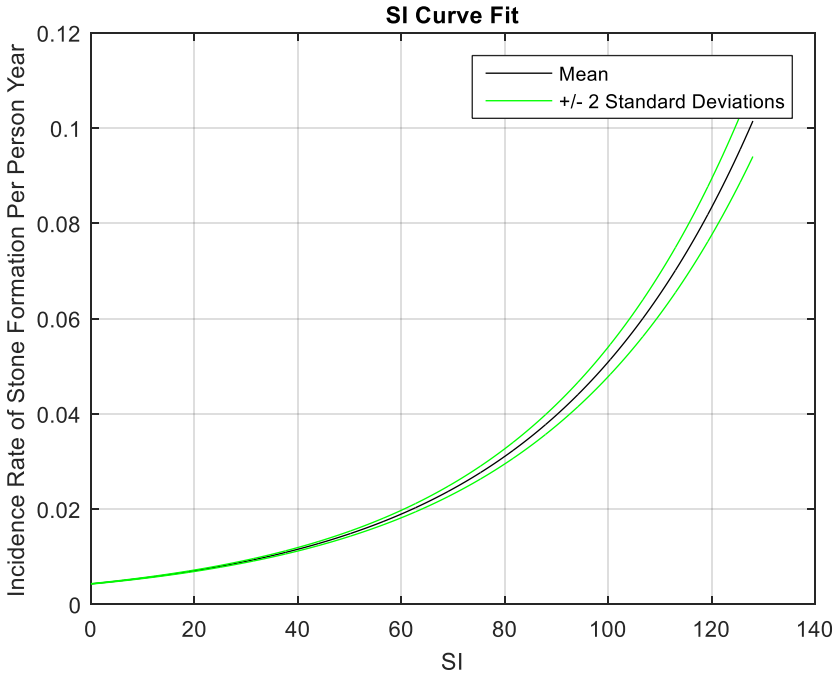
- **LSAH Population Data**

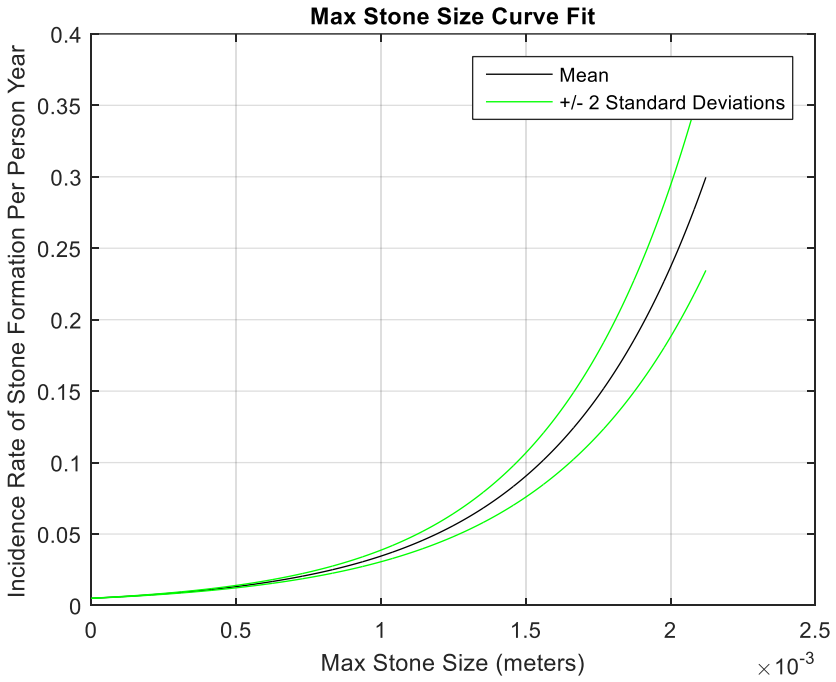
1517 Urine Samples from 581 individual astronauts (pre-, in-, and post-) flight

  - 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

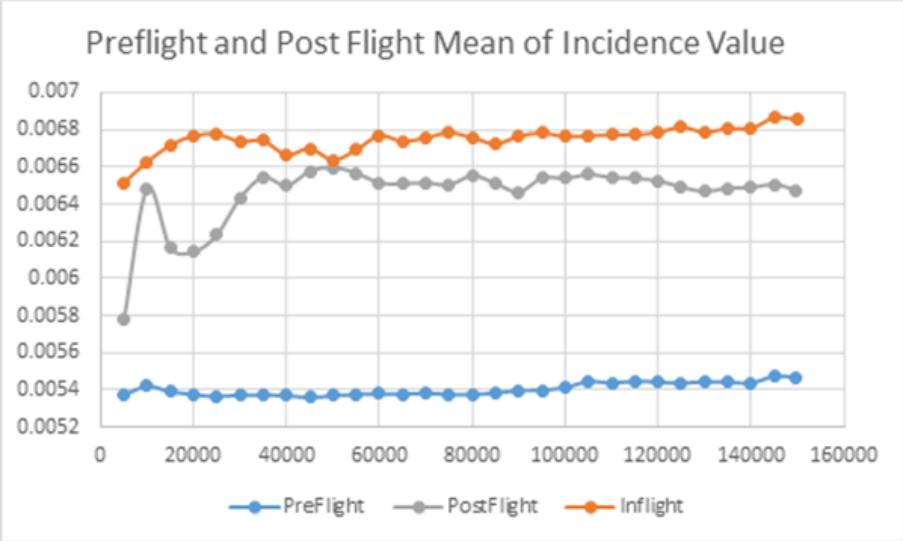
- **Whitson et al. J Urology 2009**
  - Urine samples 9 astronauts, at each flight phase that received potassium citrate as part of a study on renal risk formation in spaceflight.

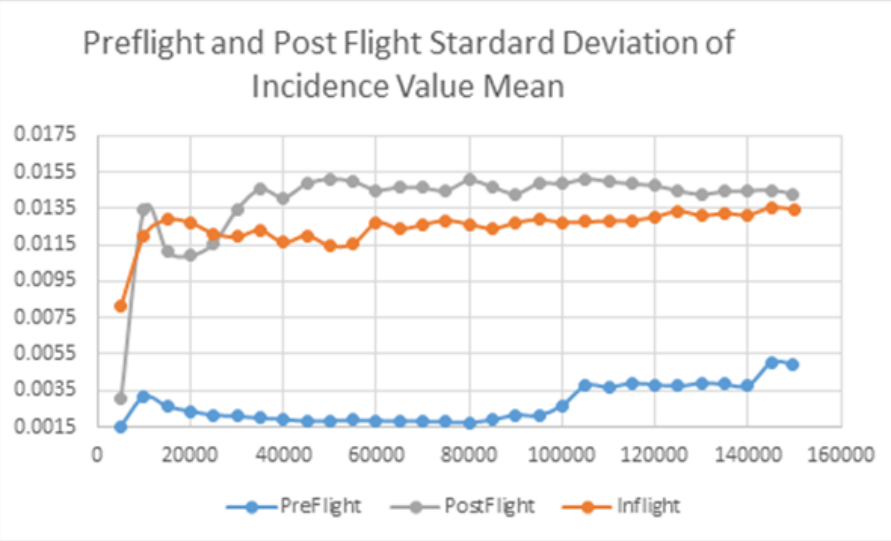
Simulation analysis - Correlation of Rates





Simulation of Astronaut Population Risk - Convergence of Simulation

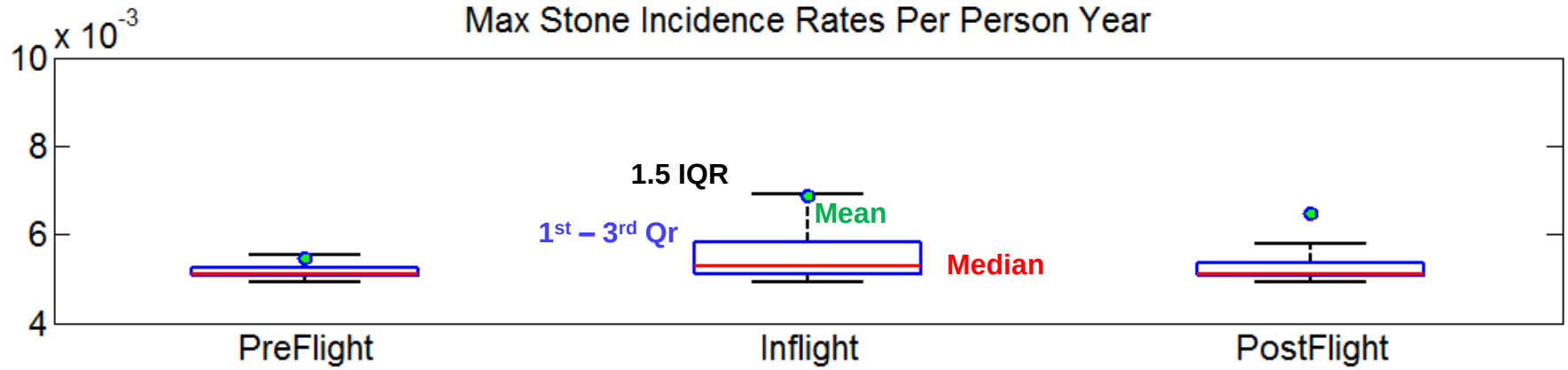


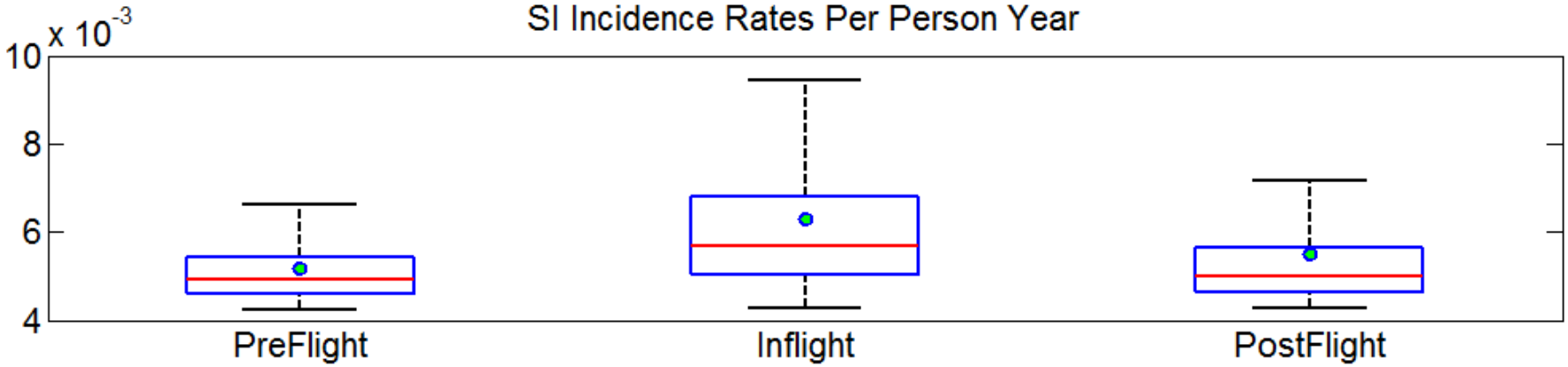


Convergence Values : Incidence per Person Years

	Mean	Standard Deviation of the Mean
PreFlight	5.4697E-03	4.9452E-03
PostFlight	6.4767E-03	1.4341E-02
Inflight	6.8544E-03	1.3473E-02

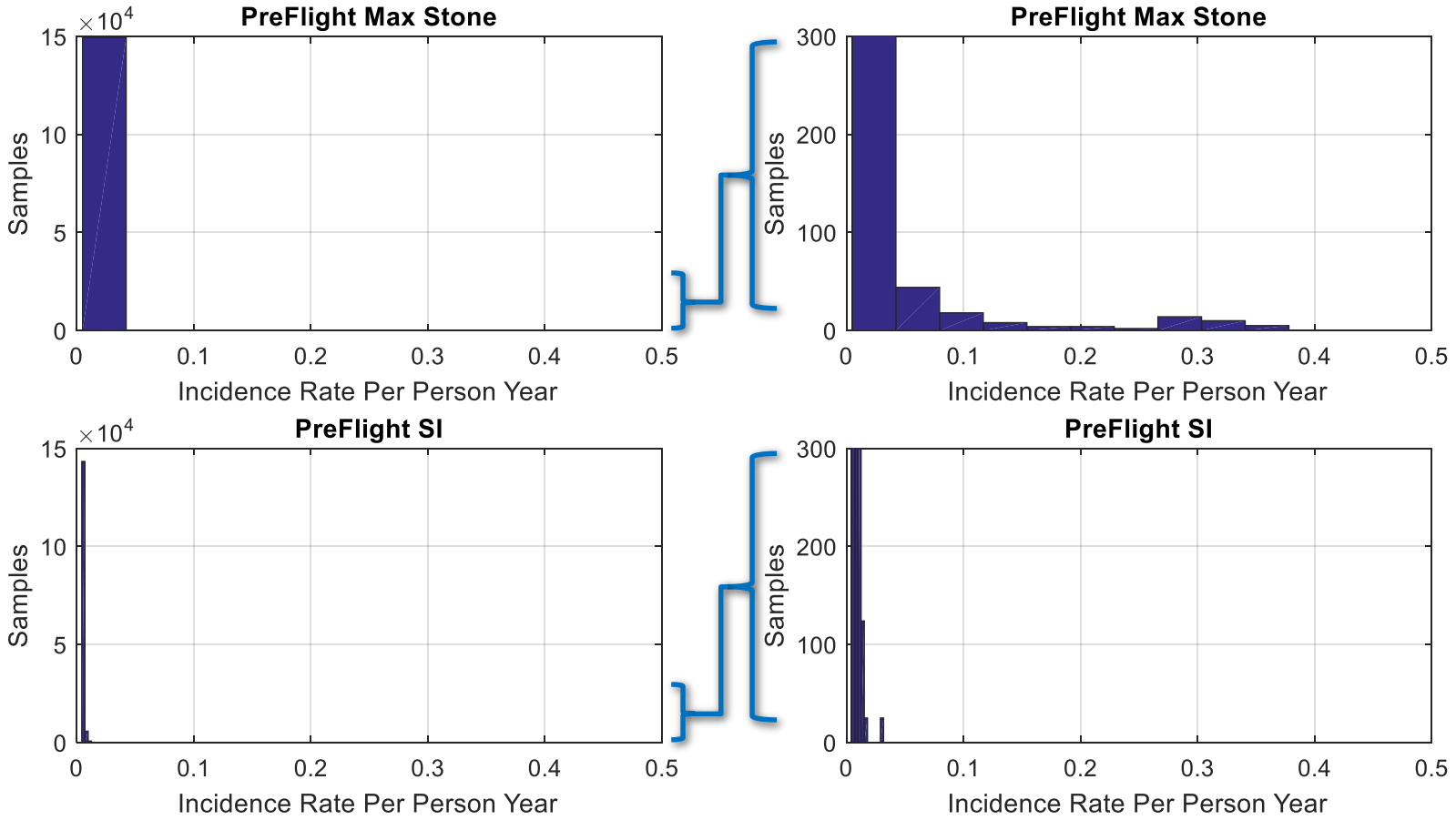
Astronaut Population Incidence Rates: Preflight, Inflight, and Postflight





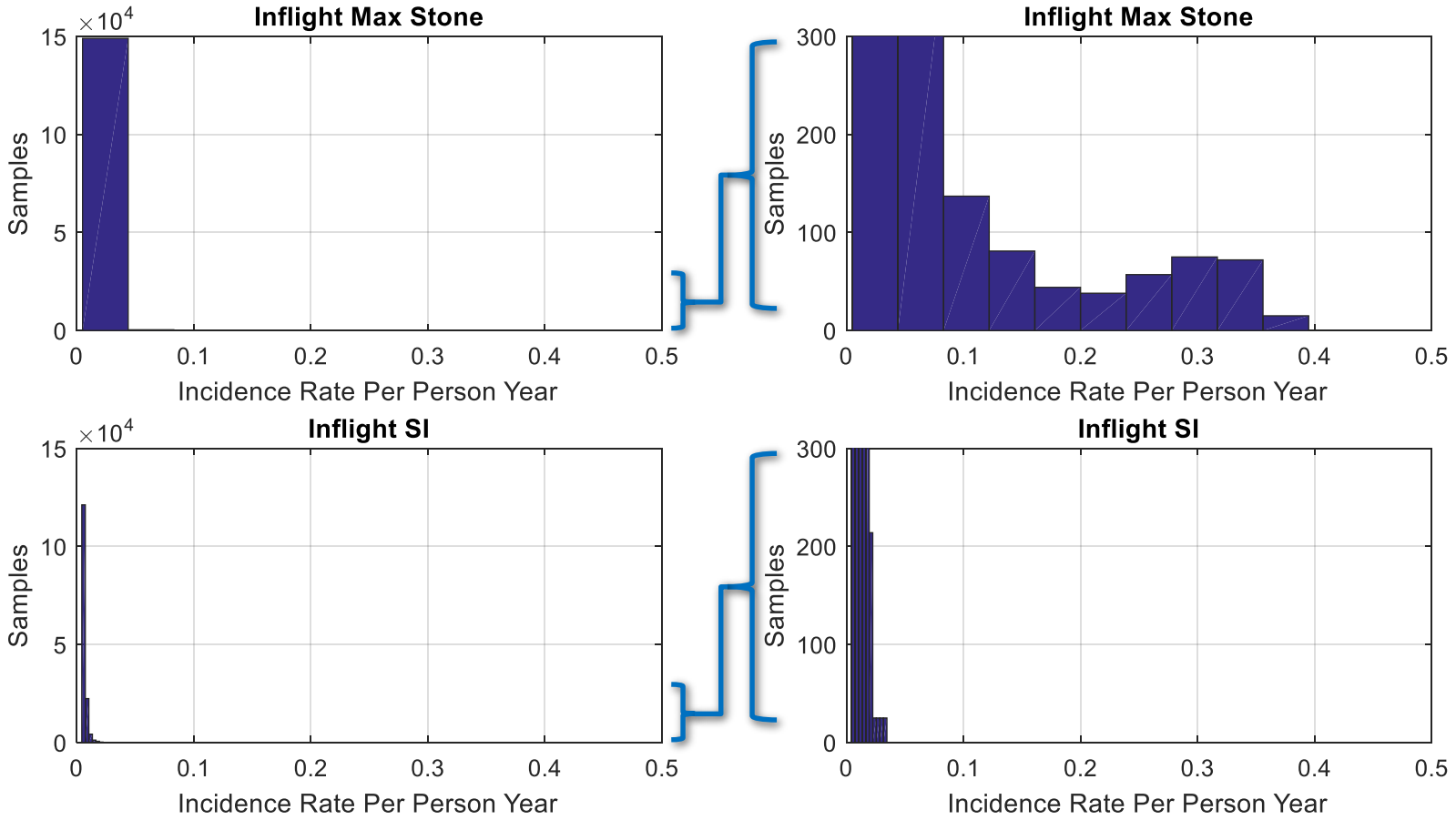
Incidence Rate Histograms: Preflight

Sampled Incidence Rate Per Person-Year



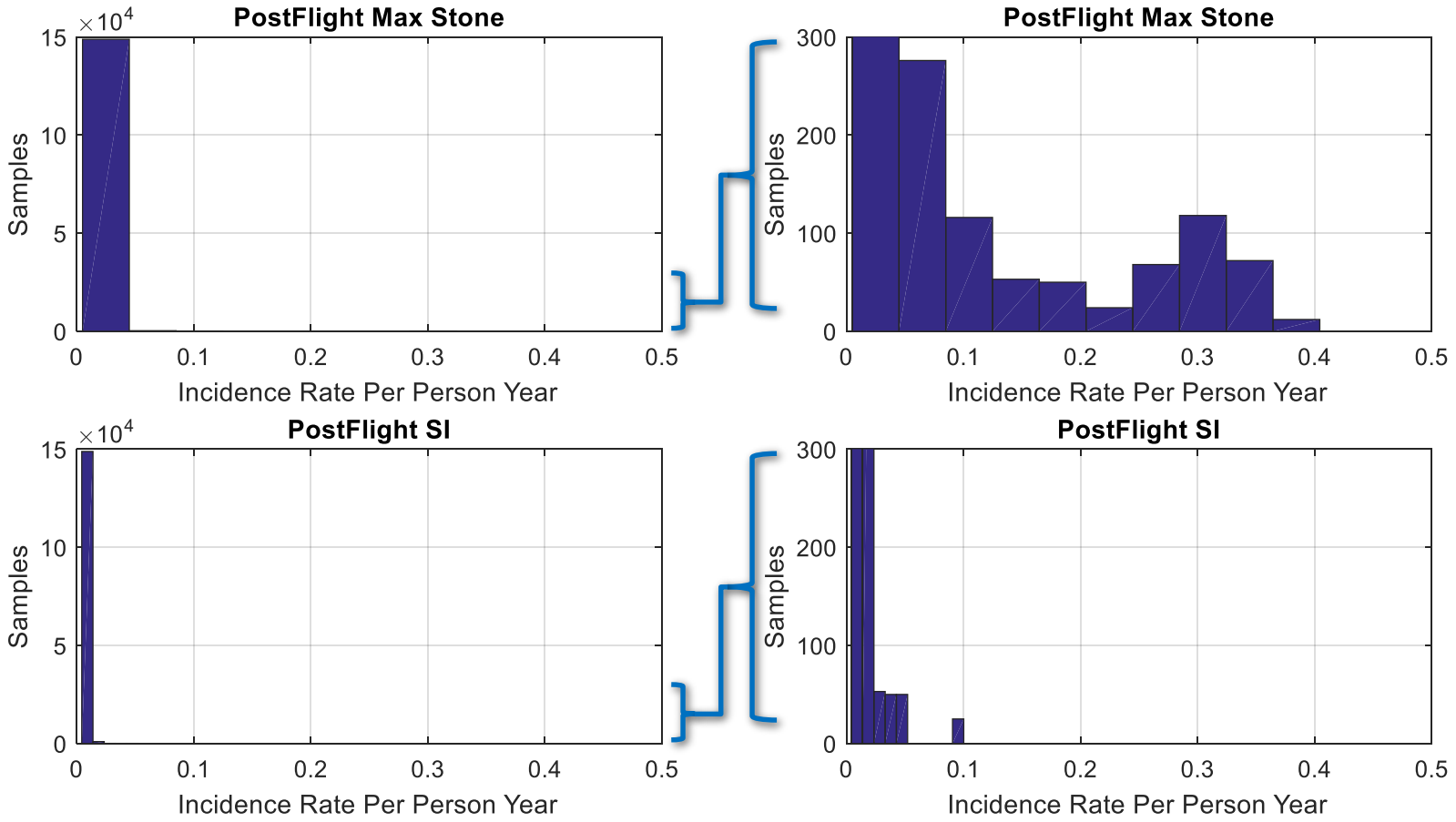
Incidence Rate Histograms: Inflight

Sampled Incidence Rate Per Person Year

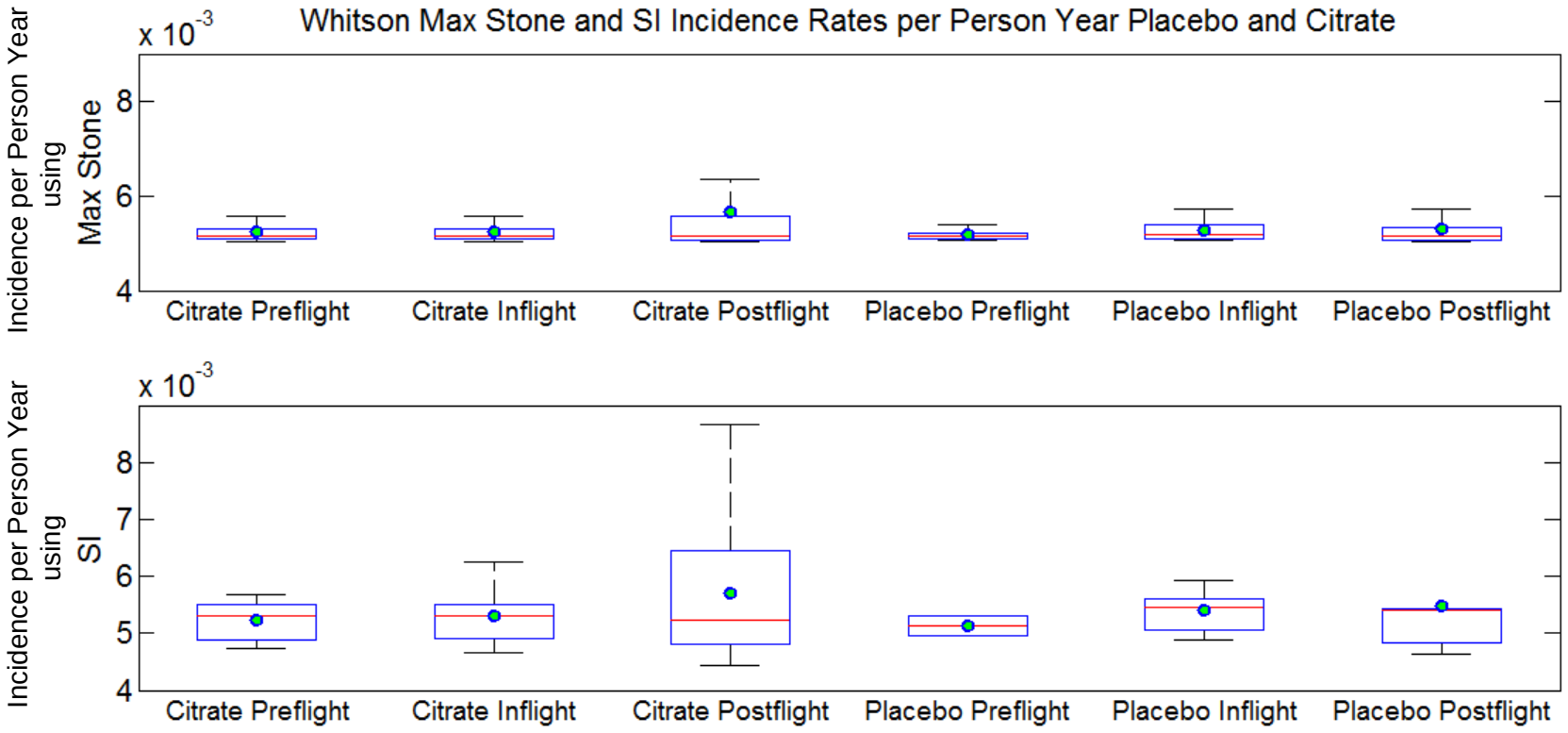


Incidence Rate Histograms: Postflight

Sampled Incidence Rate Per Person Year

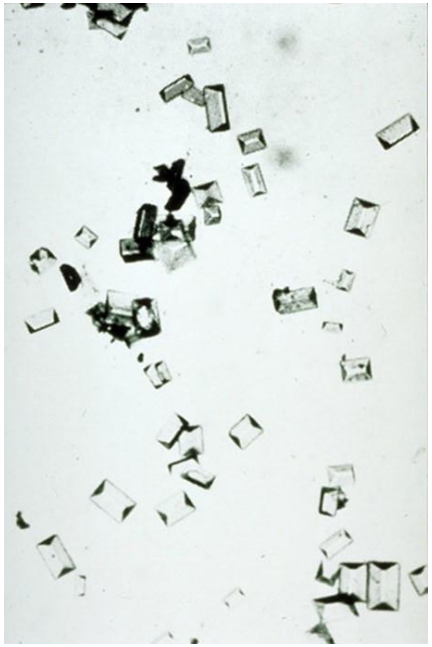


Inhibition Factors: Dietary Citrate and Placebo
Whitson et al. J Urology 2009



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

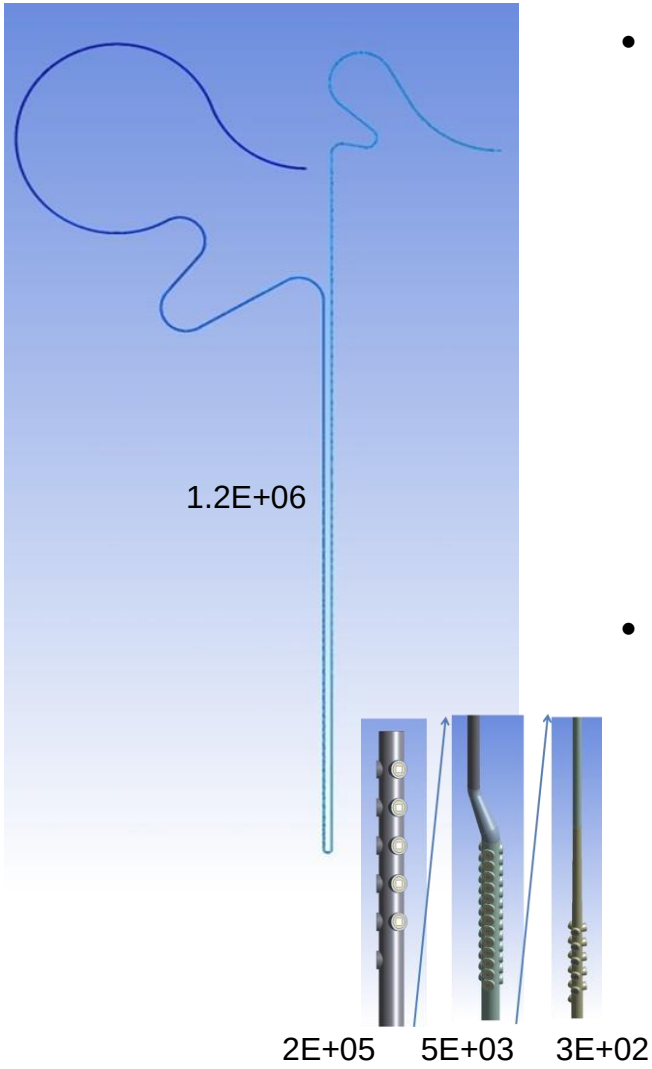
Summary of Findings



imgarcade.com

- **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, 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

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**

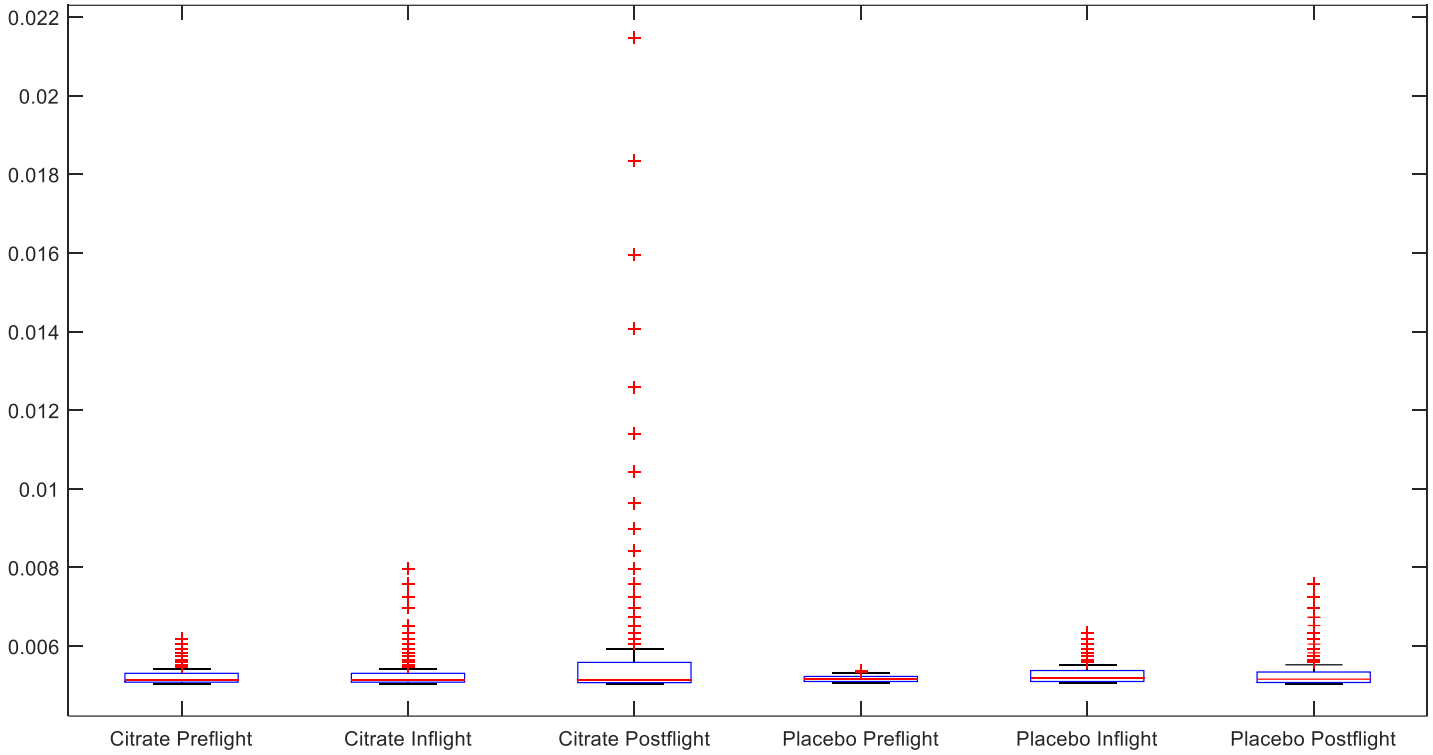
Rule	Description
Define context clearly	Develop and document the subject, purpose, and intended use(s) of the model or simulation.
Use appropriate data	Employ relevant and traceable information in the development or operation of a model or simulation.
Evaluate within context	Verification, validation, 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.
List limitations explicitly	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.

Web: https://simtk.org/home/cpms
e-mail: cpmsinhealthcare@gmail.com

Thank you!

Questions?

Whitson


0.022
0.02
0.018
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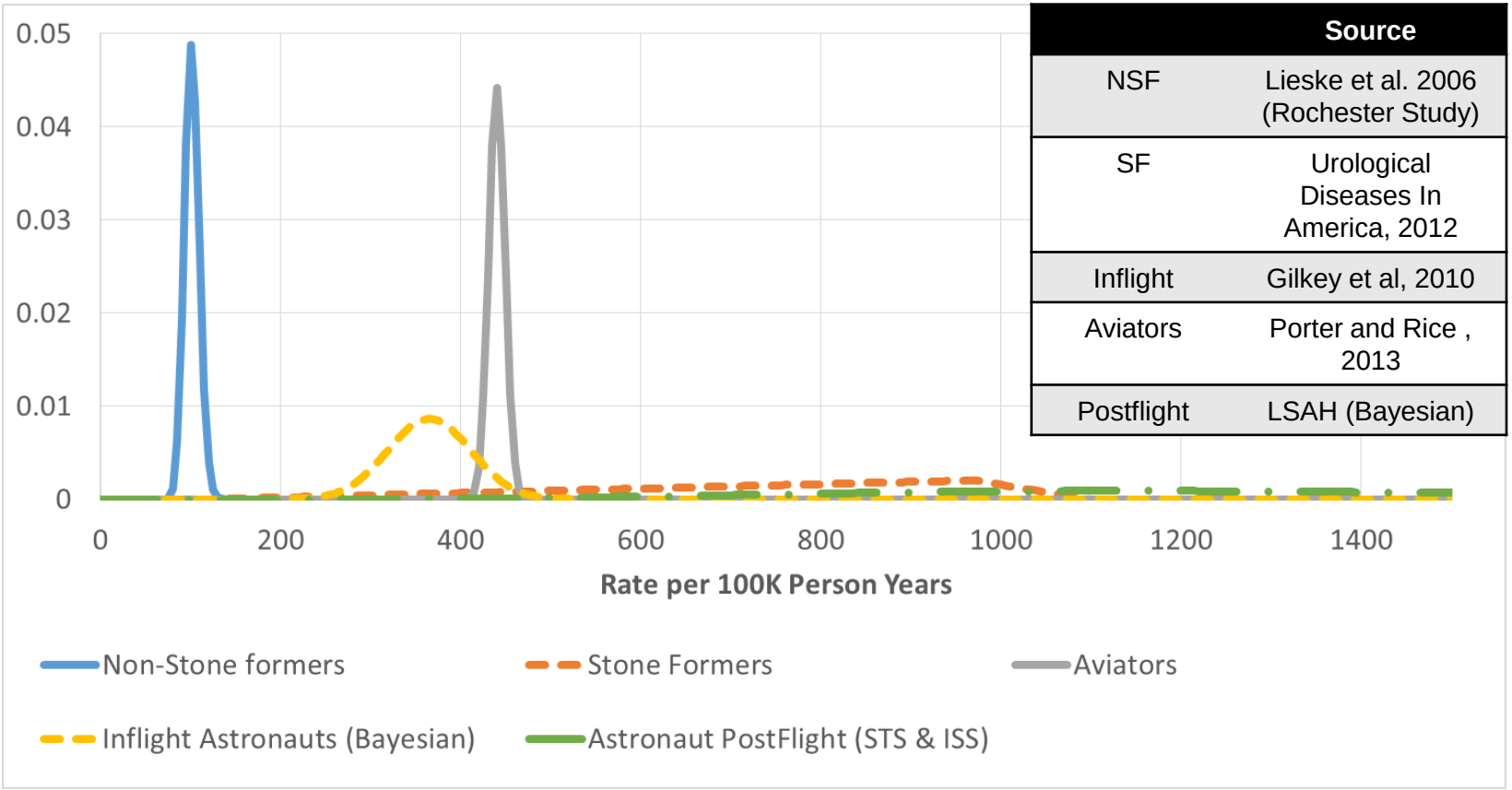
0.014
0.012
0.01
0.008
0.006
Citrate Preflight
Citrate Inflight
Citrate Postflight
Placebo Preflight
Placebo Inflight
Placebo Postflight

Rate of Stone Formation in Context

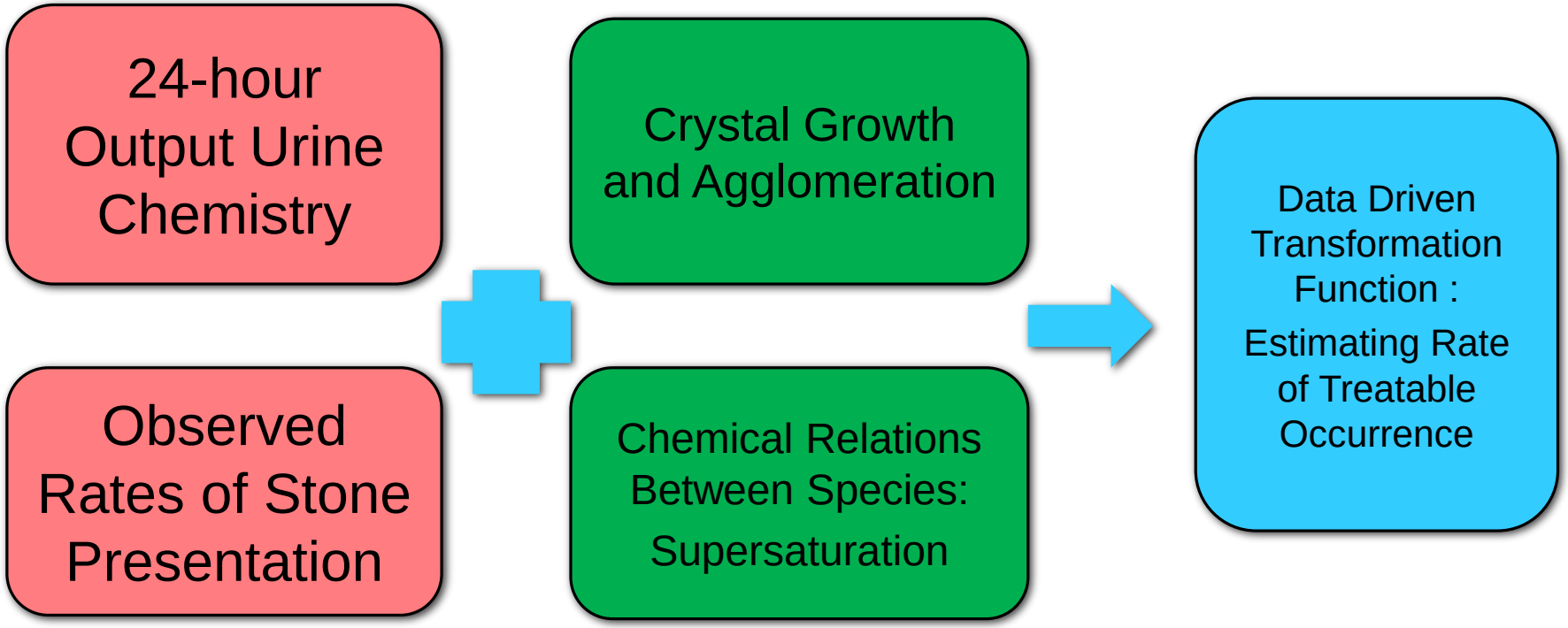
Distributions normalized to equal area under each curve



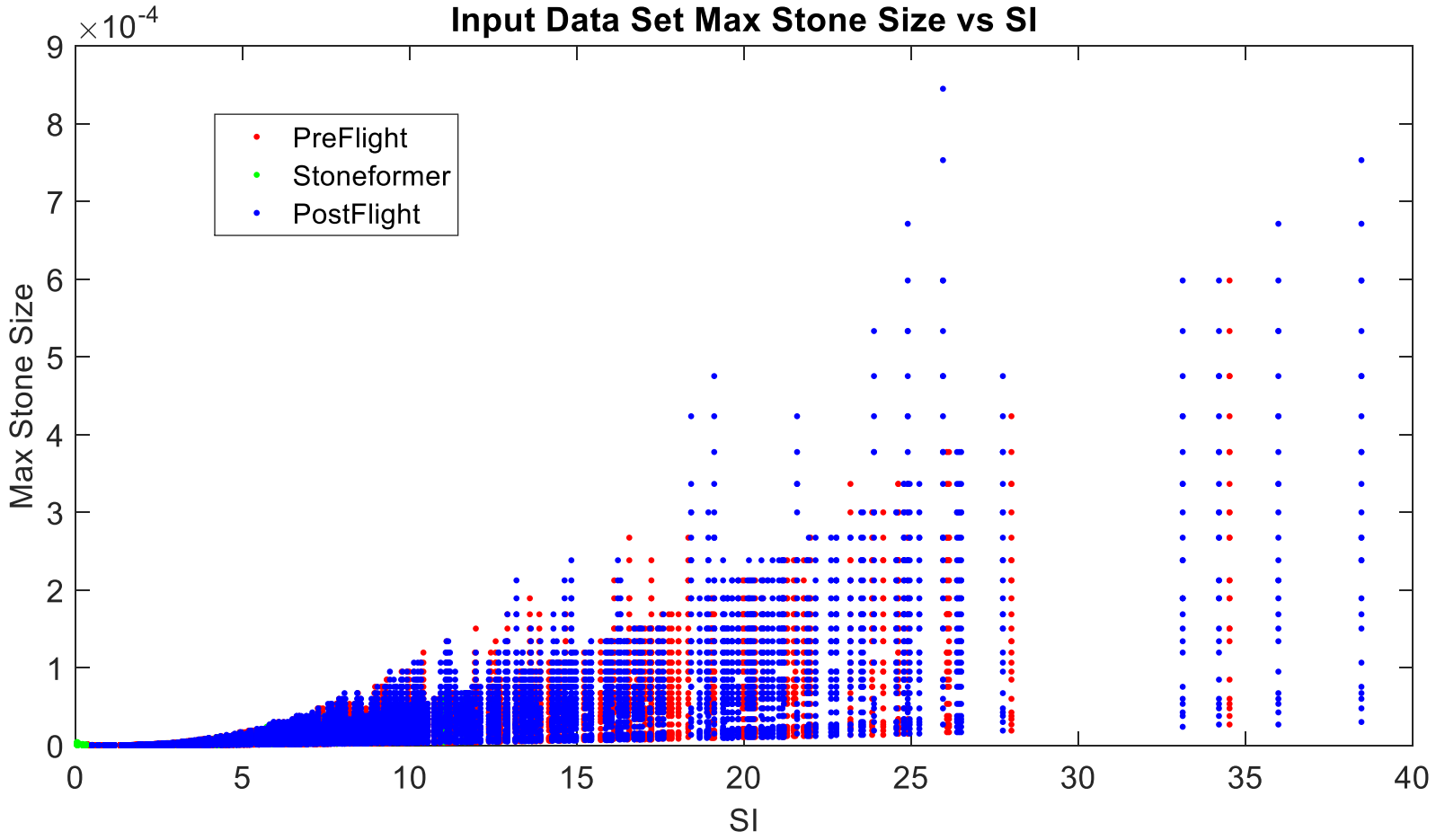
	Source
NSF	Lieske et al. 2006 (Rochester Study)
SF	Urological Diseases In America, 2012
Inflight	Gilkey et al, 2010
Aviators	Porter and Rice , 2013
Postflight	LSAH (Bayesian)

Break the problem down into constitutive information

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

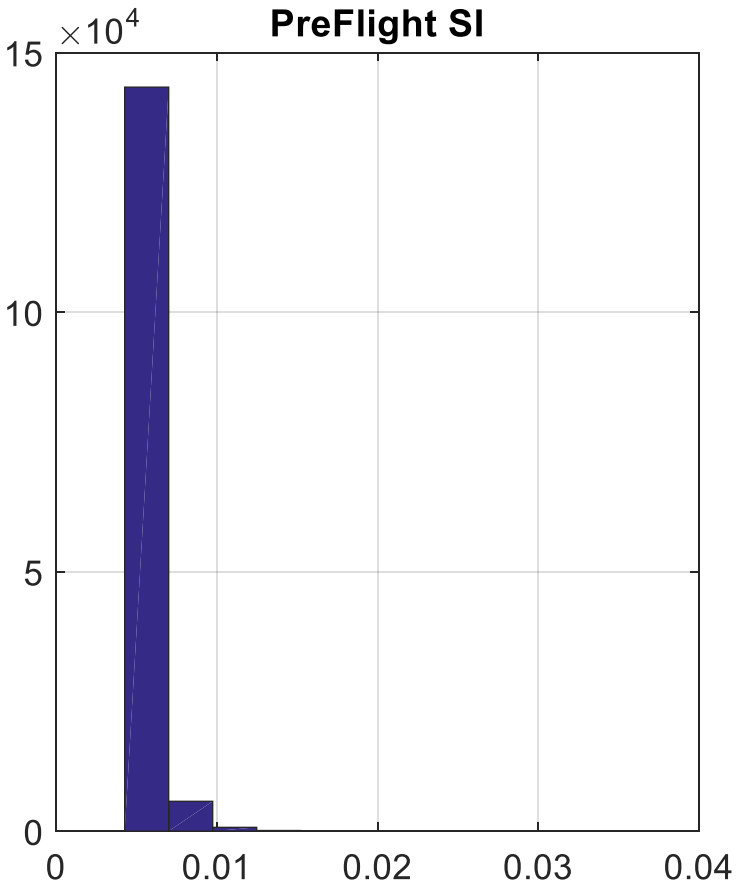


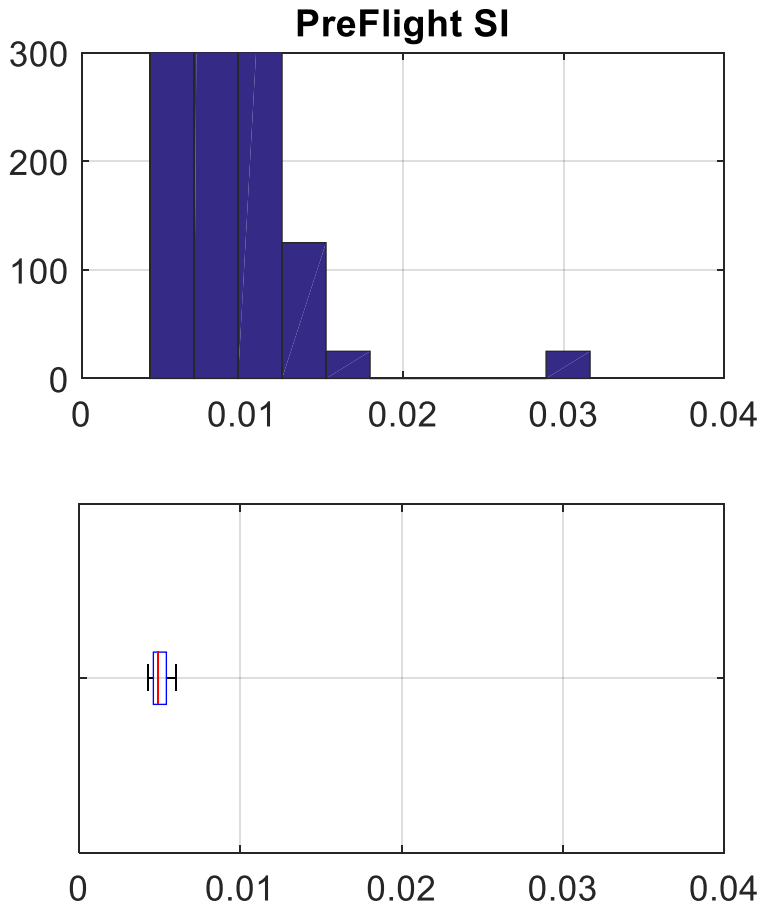
Max Stone Size vs SI – Input Data



Result 1

Sampled Incidence Rate Per Person Year





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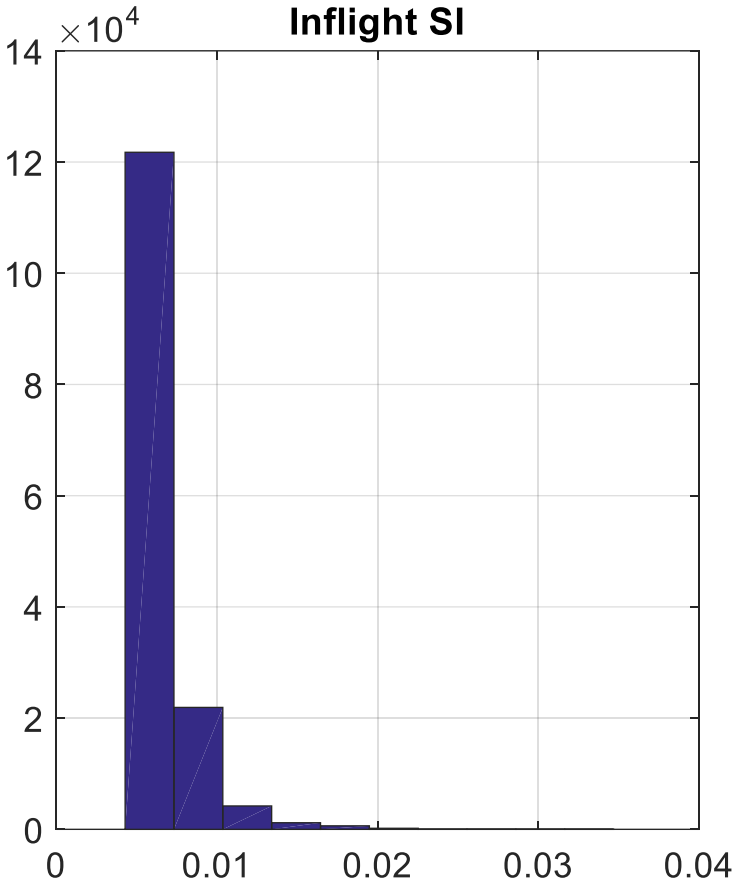

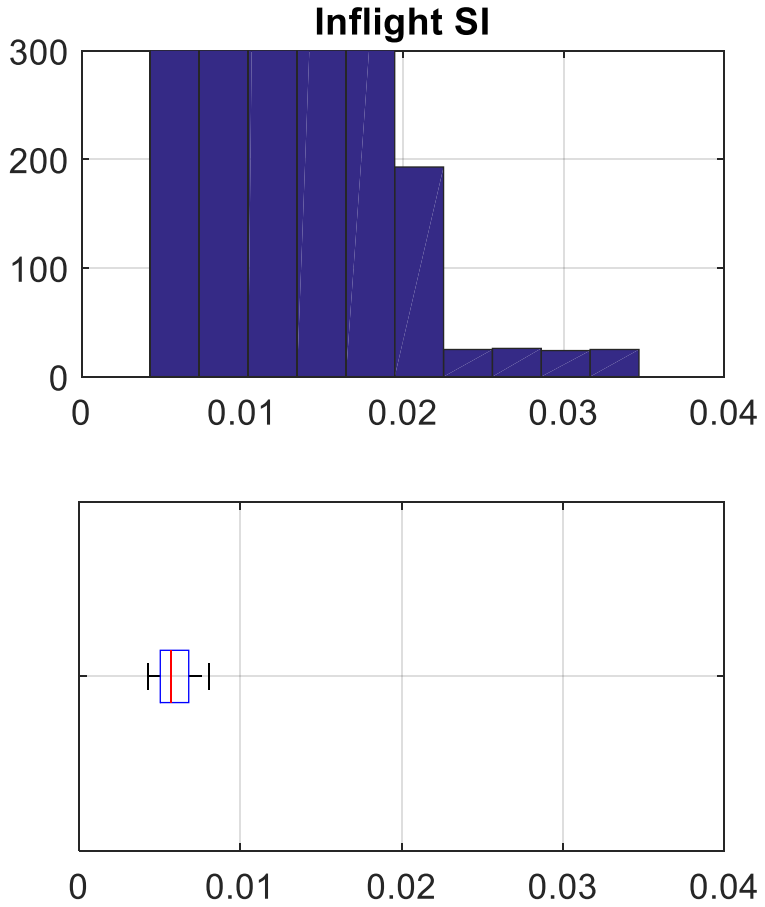

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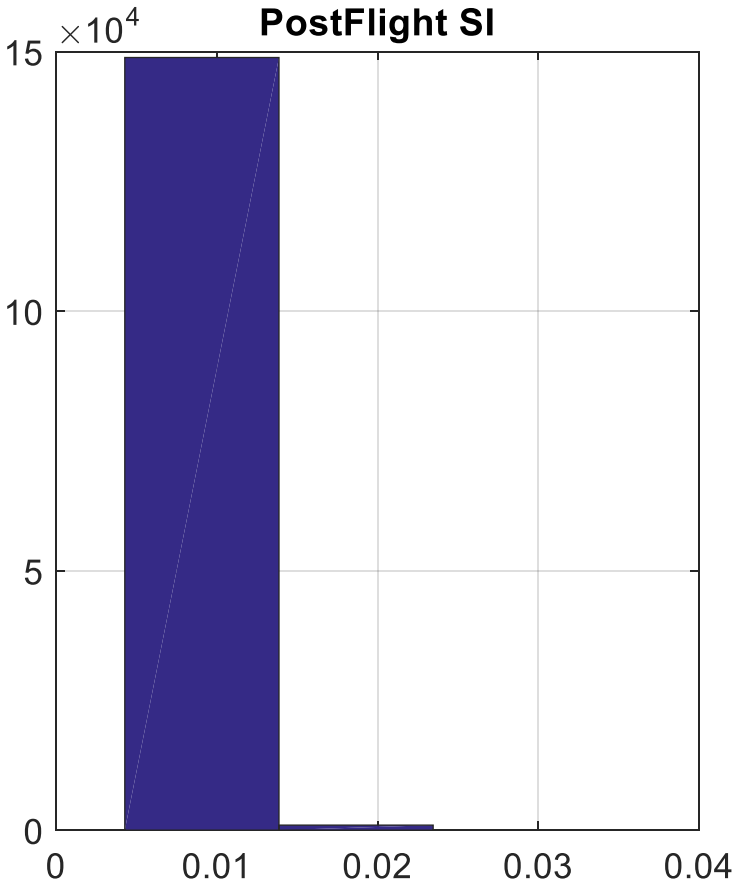
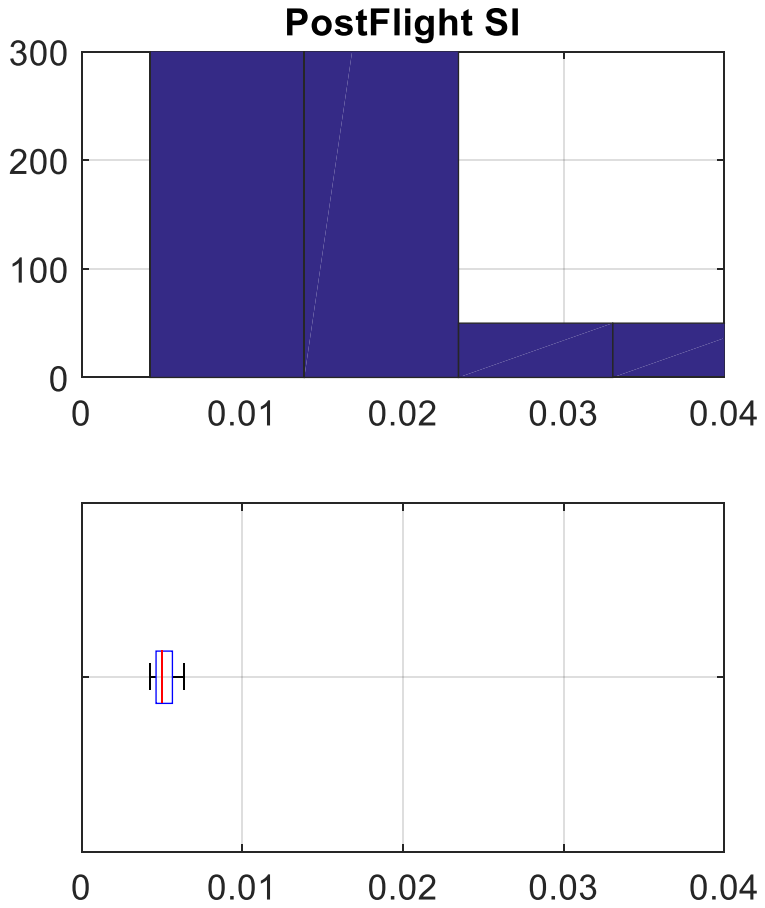
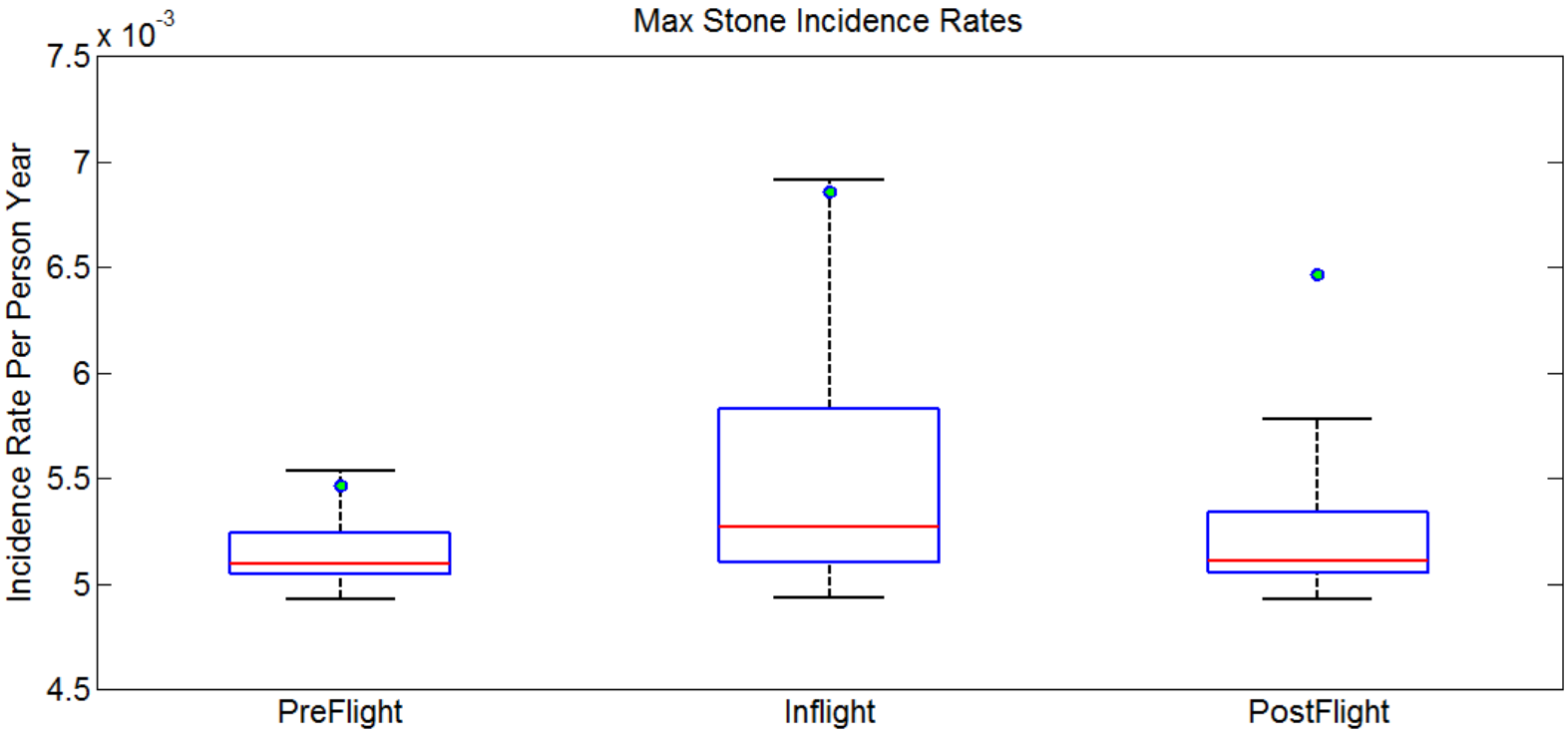


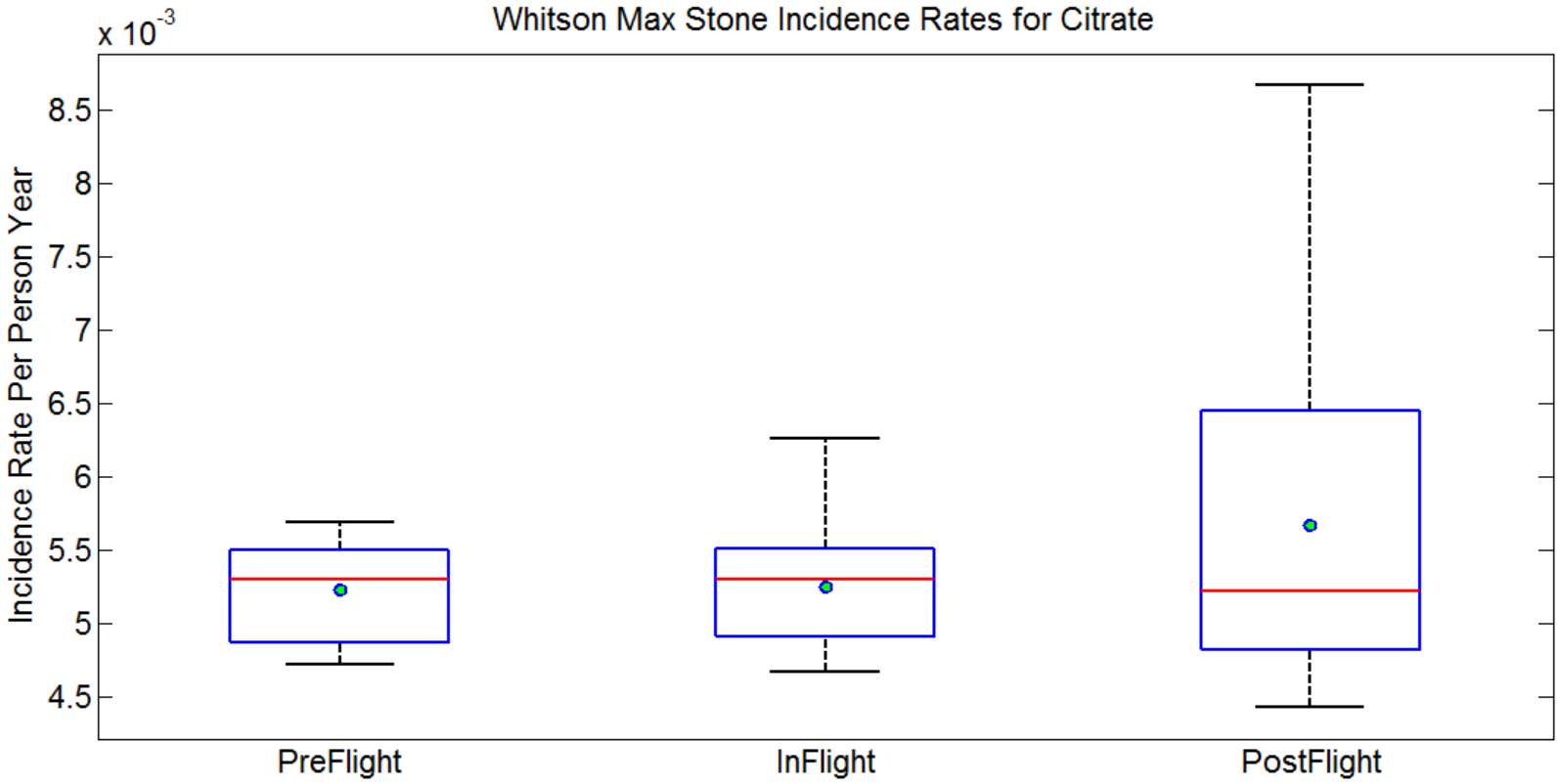


Whitson Combined

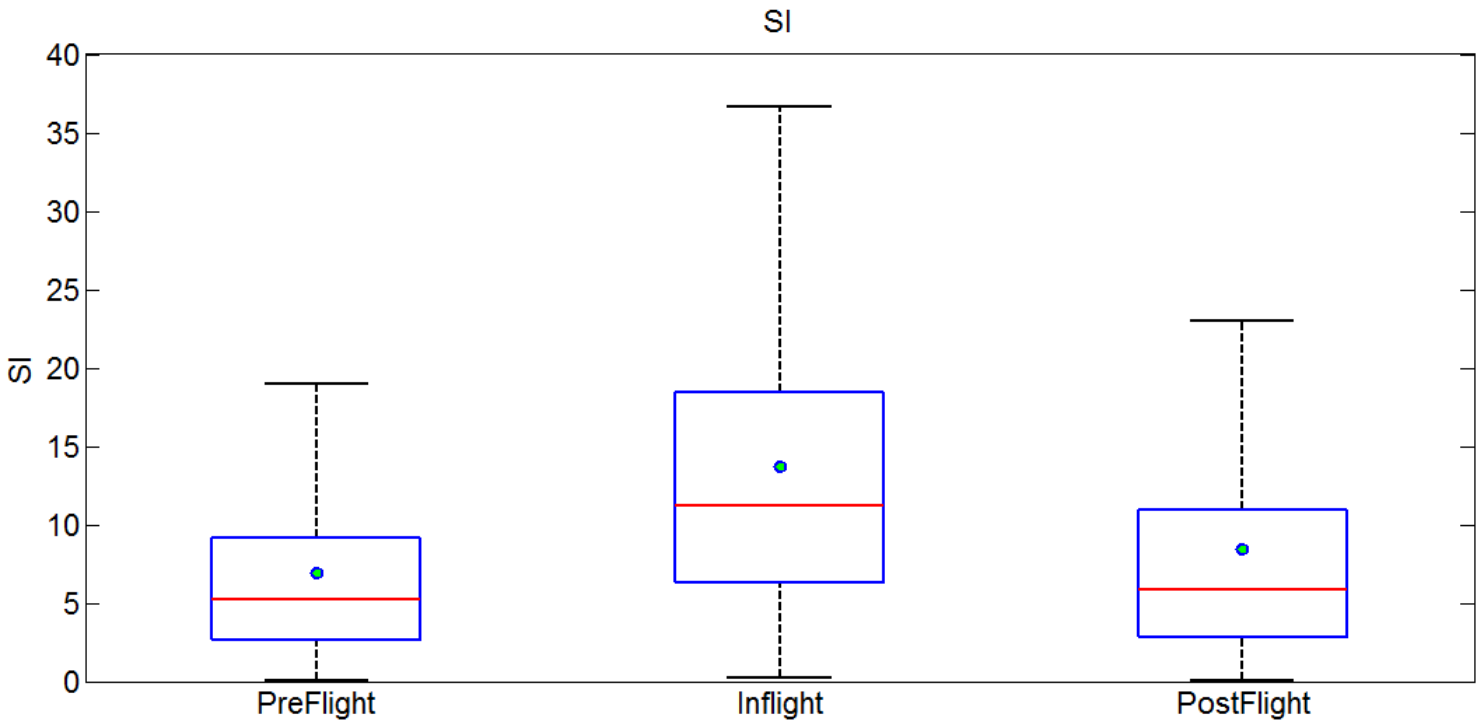
Max Stone Size Per Flight Phase



Add Preflight, Postflight, and Inflight Boxplots



SI Per Flight Phase



SI Incidence Per Flight Phase