Role of Transport and Kinetics in Growth of Renal Stones

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Risk of Kidney Stones in Space

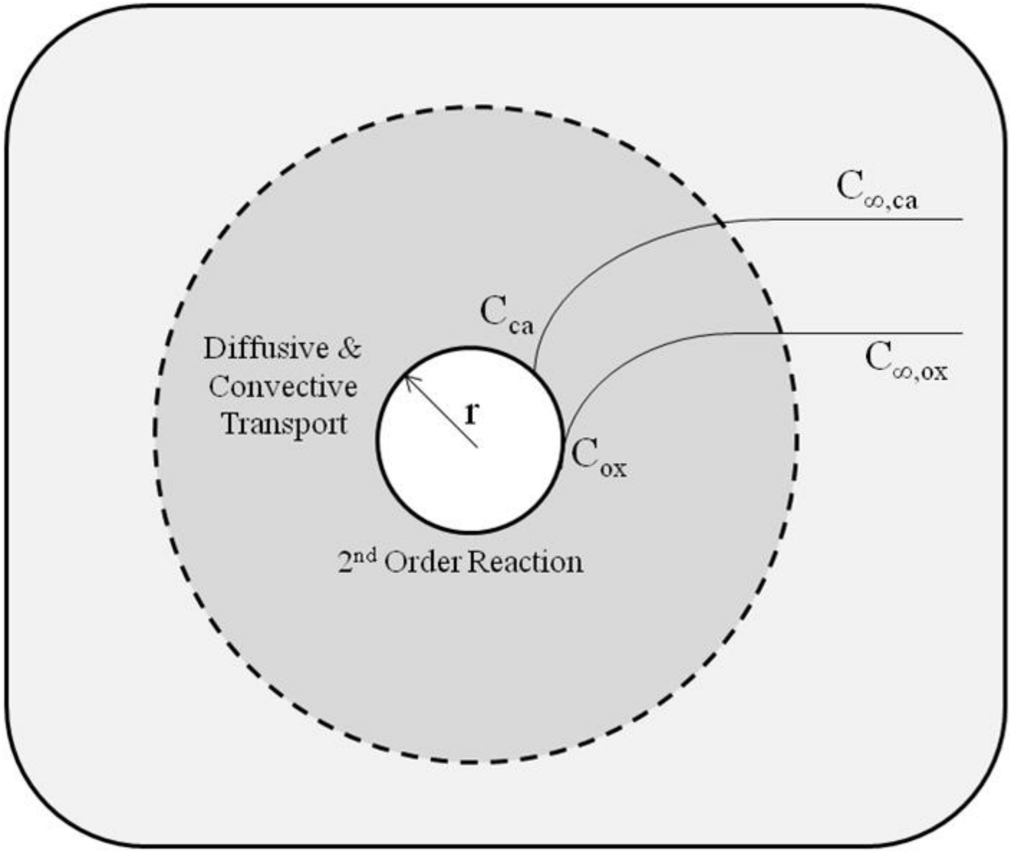
- The risk of astronauts developing kidney stones has become a serious issue.
- A recent survey of renal stone formation in US astronauts has revealed a total of 14 episodes (Pietrrzyk et al, 2007).
- Some of these episodes occurred in the preflight period (n=5) while others (n=9) were in the post flight phase.
- Multiple stone events also reported among the Soviet cosmonauts with one reported episode of in-flight renal stone occurrence that nearly resulted in mission abortion (Sibonga et al, 2008).

Renal Biochemistry Alteration in Microgravity

- The physiological, environmental and dietary conditions of space travel increase the risk for development of renal stones.
  - Bone atrophy ➔ increased concentration of calcium
  - Dehydration & the lower urine output ➔ reduced urine volumes
  - high sodium and animal protein diet ➔ increased salt - low pH
  - low urinary citrate and magnesium ➔ lack of sufficient stone-forming inhibitors
- These factors all provide favorable conditions for promoting increased crystallization and agglomeration (Whitson, 2010).

Renal Stone Growth Model

Kassemi et al (JCG, 2011)



- Balance between ***transport*** and ***surface reaction*** determines concentration of Ca and Ox at the surface of stone
- Surface concentrations determine the growth rate

Combined Reaction-Transport Model for Renal Stone Growth

2nd Order Surface Reaction:

$$\dot{r} = \frac{dr}{dt} = K_G\ V_m\ K_s^{1/2} \left\{ \left[\frac{C_{ca}^{*}\ C_{ox}^{*}\ f_2^2}{K_s} \right]^{1/2} - 1 \right\}^2$$

Damkohler Number

$$Da = \frac{K_G}{K_m(d)} \quad \boxed{\frac{\text{Reaction}}{\text{Transport}}}$$

Relative Supersaturation

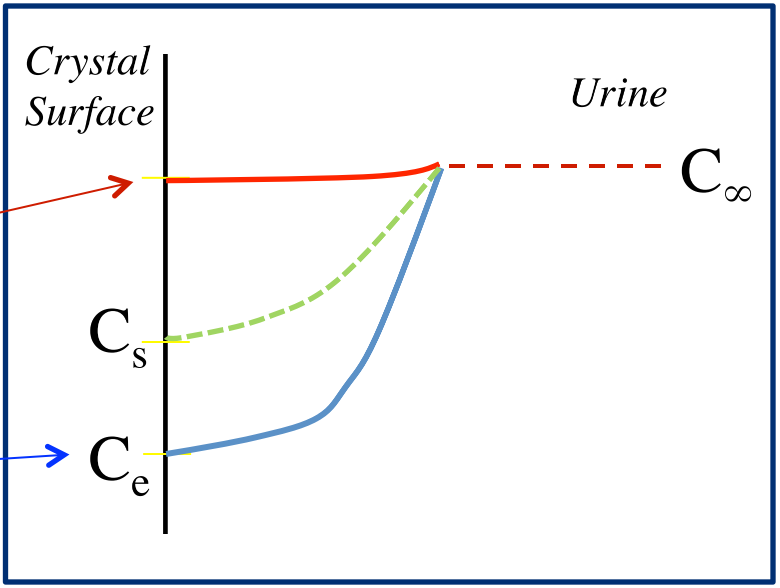
$$RS = \left[\frac{C_{ca}^{*}\ C_{ox}^{*}\ f_2^2}{K_s} \right]^{1/2}$$

Balance Between Transport & Reaction:

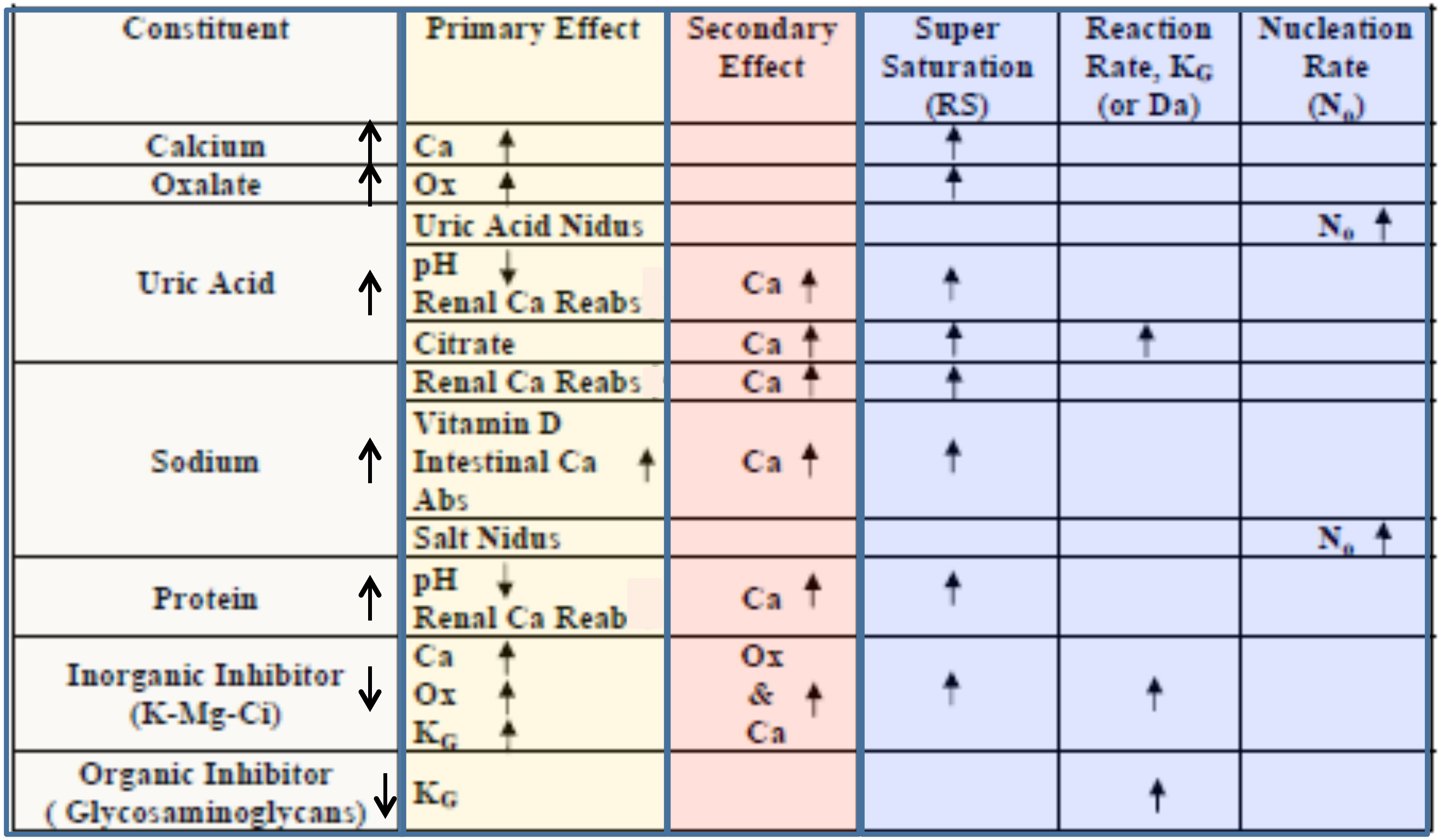
$$\begin{cases} K_m(\,C_{ca}^{*} - C_{\infty ca}^{*}) = -K_G K_s^{1/2} \left\{ \left[\frac{C_{ca}^{*}\ C_{ox}^{*}\ f_2^2}{K_s} \right]^{1/2} - 1 \right\}^2 \\ K_m(\,C_{ox}^{*} - C_{\infty ox}^{*}) = -K_G K_s^{1/2} \left\{ \left[\frac{C_{ca}^{*}\ C_{ox}^{*}\ f_2^2}{K_s} \right]^{1/2} - 1 \right\}^2 \end{cases}$$

K_G ↓ Da ↓

K_m ↓ Da ↑

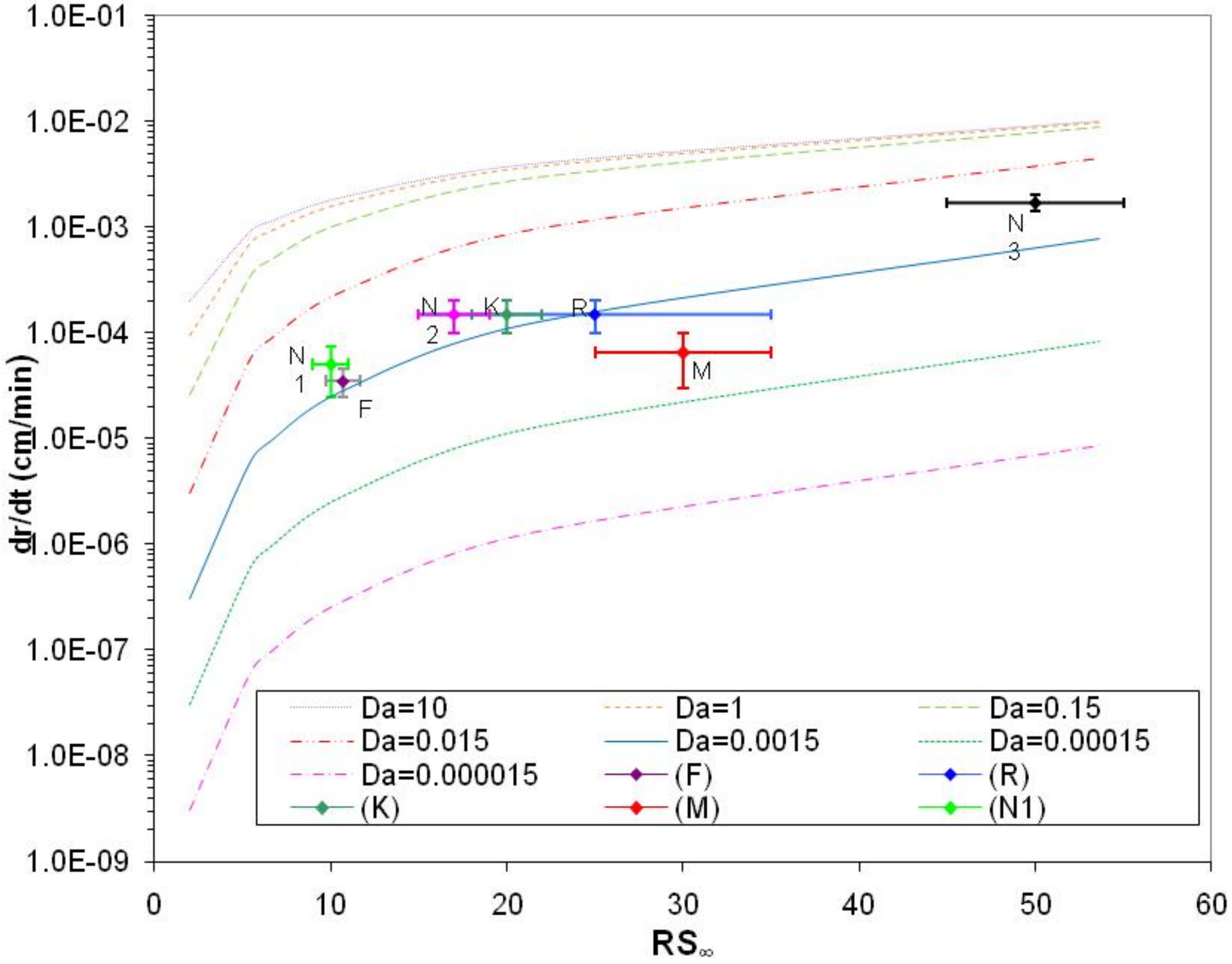


Impact of Microgravity On Renal Biochemistry



Constituent	Primary Effect	Secondary Effect	Super Saturation (RS)	Reaction Rate, K_G (or Da)	Nucleation Rate (N_o)
Calcium ↑	Ca ↑		↑		
Oxalate ↑	Ox ↑		↑		
Uric Acid ↑	Uric Acid Nidus				N_o ↑
	pH ↓ Renal Ca Reabs	Ca ↑	↑		
	Citrate	Ca ↑	↑	↑	
Sodium ↑	Renal Ca Reabs	Ca ↑	↑		
	Vitamin D Intestinal Ca Abs ↑	Ca ↑	↑		
	Salt Nidus				N_o ↑
Protein ↑	pH ↓ Renal Ca Reab	Ca ↑	↑		
Inorganic Inhibitor (K-Mg-Ci) ↓	Ca ↑ Ox ↑ K_G ↑	Ox & Ca ↑	↑	↑	
Organic Inhibitor (Glycosaminoglycans) ↓	K_G			↑	

Effect of Solution Supersaturation on CaOx Growth Rate



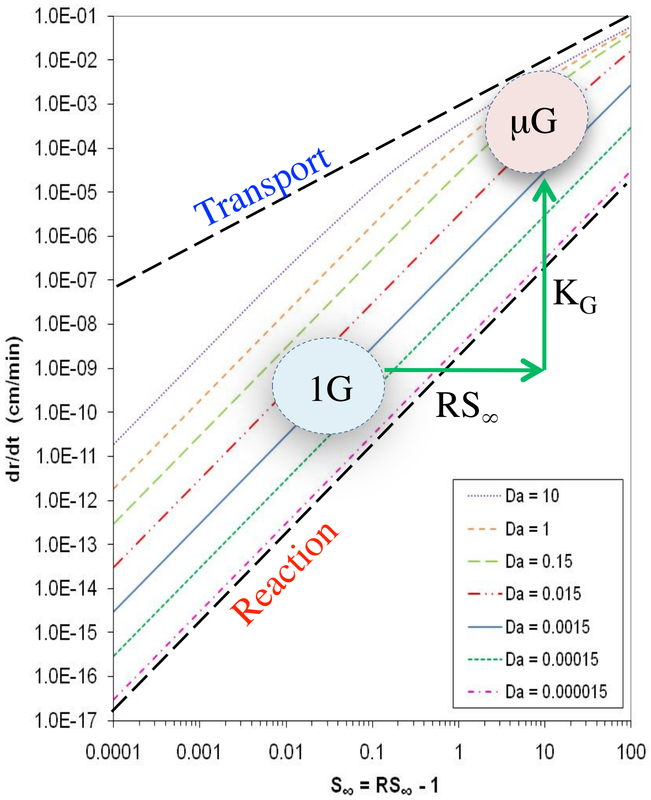
Meyer & Smith (1975):
$K_r = 22$
(cm⁄(sec) (liter⁄(mole)

Conversion:
$K_G = K_r K_s^{1/2} V_m$

K_G = 5.0 x10^{11} (m ⁄sec)

Milan et al (1998):
K_G = 2.5 x10^{11}
(m⁄(sec)

Microgravity Parametric Shift



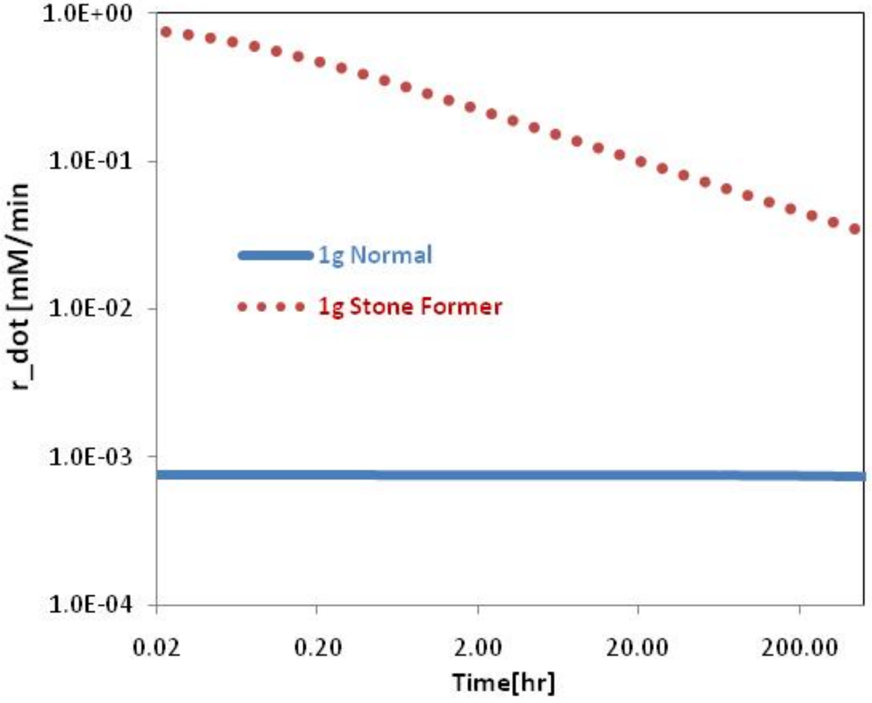
Case Studies: Renal Stone Growth on Earth & in Space

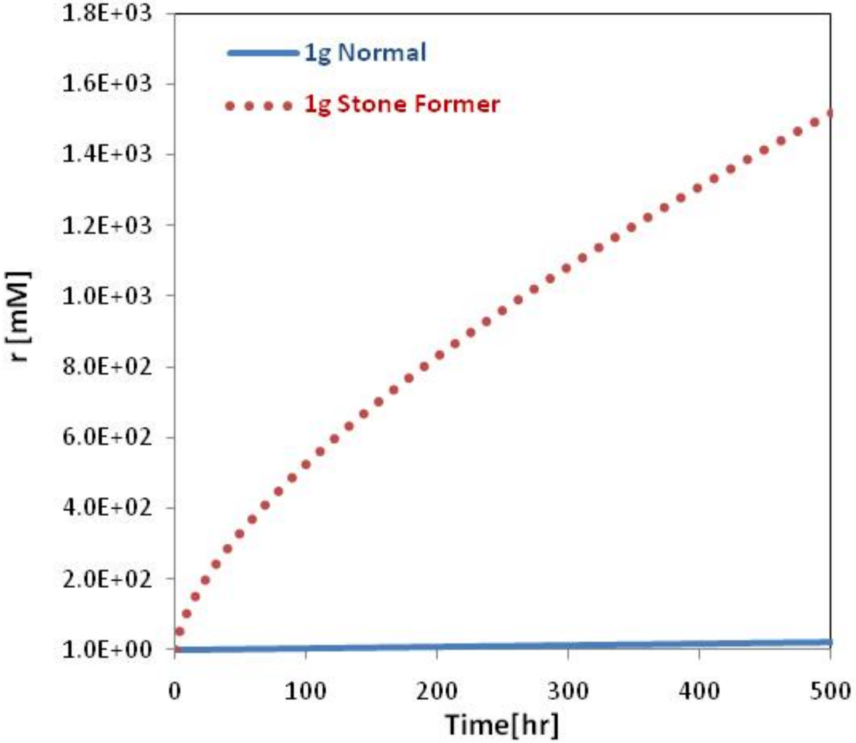
Microgravity is marked by increased Ca concentration, lower inhibitor concentration and unaltered urine flow rate.

Case	**Condition**
Earth - Normal	• Low super-saturation • 75% reduction of reaction constant by inhibition
Earth - Stone Former	• High super-saturation • No reduction of reaction constant by inhibition
Microgravity - Normal	• Moderately high super-saturation • 50% reduction of reaction constant by inhibition
Microgravity - Stone Former	• Very high super-saturation • No reduction of reaction constant by inhibition

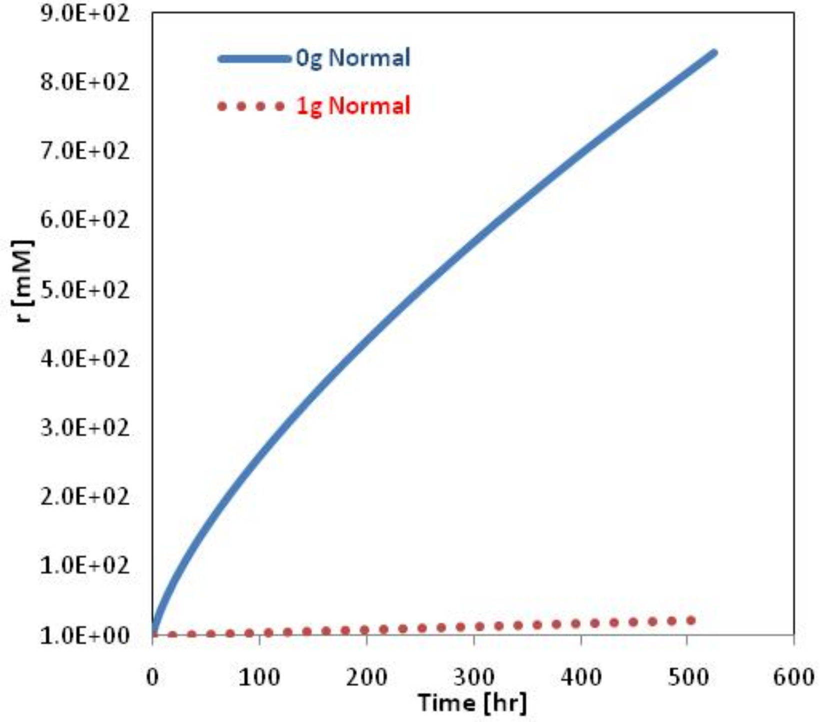
- Uninhibited reaction constant from Meyer Smith (1975): $Kr = 22\ (cm/(sec)(liter/(mole)$
- $C_{\infty ca} / C_{\infty ox} = 10$

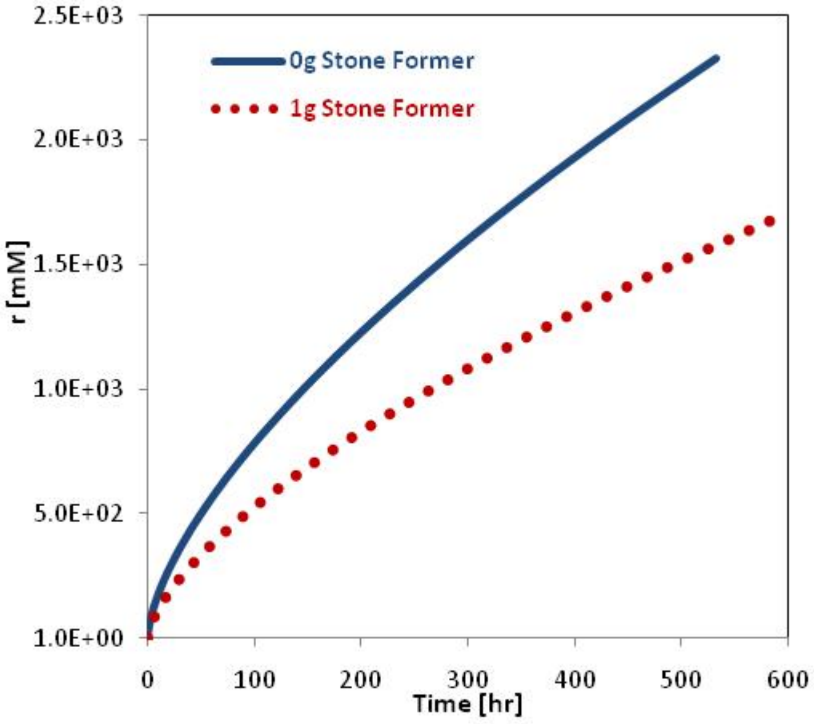
1G Comparison: Normal versus Stone-Former



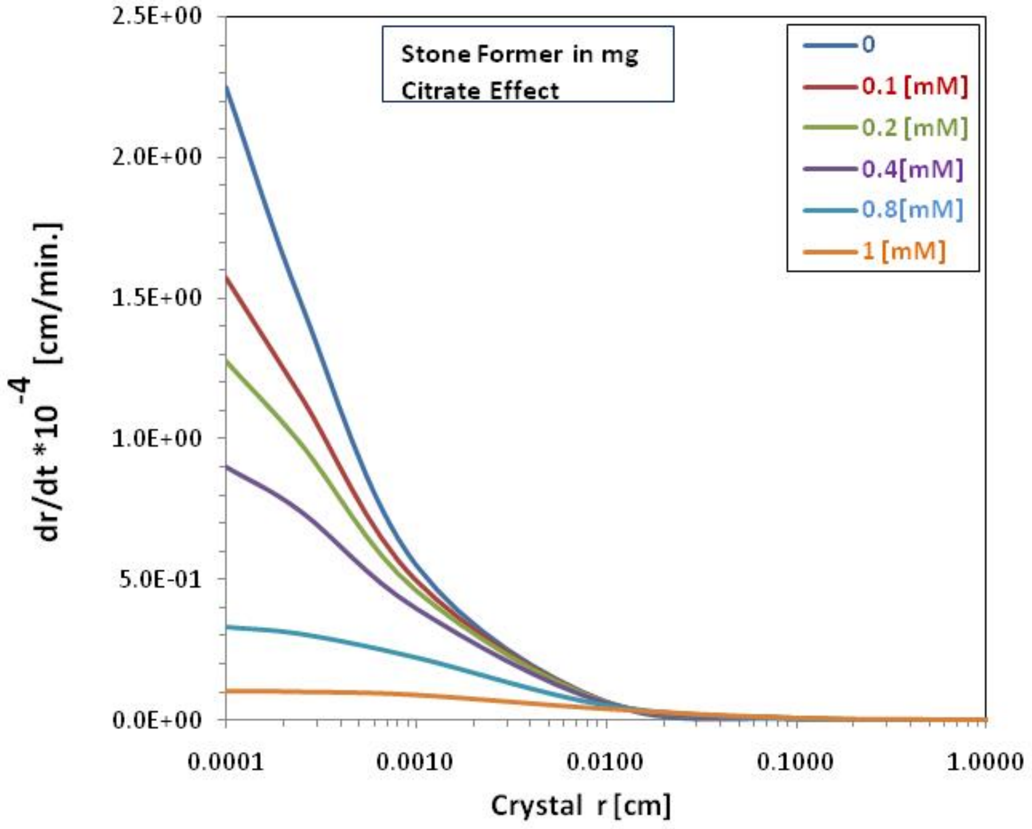


Microgravity Versus 1G Comparisons for Normal and Stone-Former





Effect of Citrate on Growth Rate for Stone Former in Microgravity



Effect of Urine Citrate Concentration on CaOx

Reaction rate co-related from published data

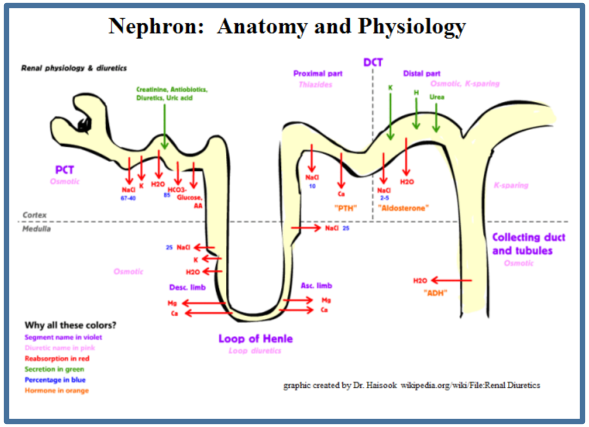
(L. Wang et al, JCG, 2006)

Agglomeration and Breakage

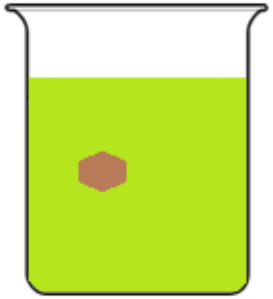
- The previous prediction were based on growth as the only mechanism for increasing the stone size.
- The renal calculi problem is not a single stone event but a multiple stone phenomena.
- Stones can also change size by agglomeration and breakage
- A new mathematical framework is needed for enhancing the model to include the effects of calculi interaction

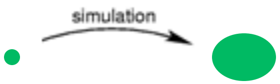
Future Directions: Nucleation, Agglomeration, Breakage

Kavanagh (2004): ***Kidney is not a beaker but a Continuous Crystallizing Chemical Reactor***



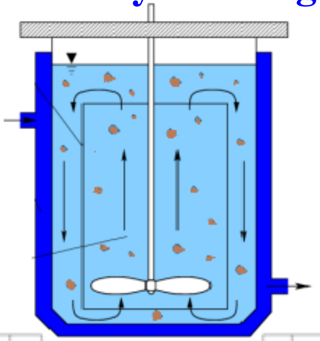
Crystal Growth Beaker

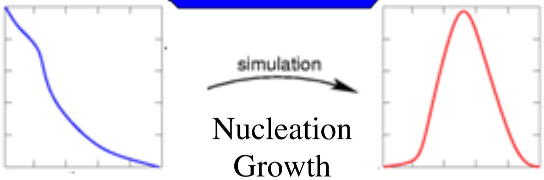




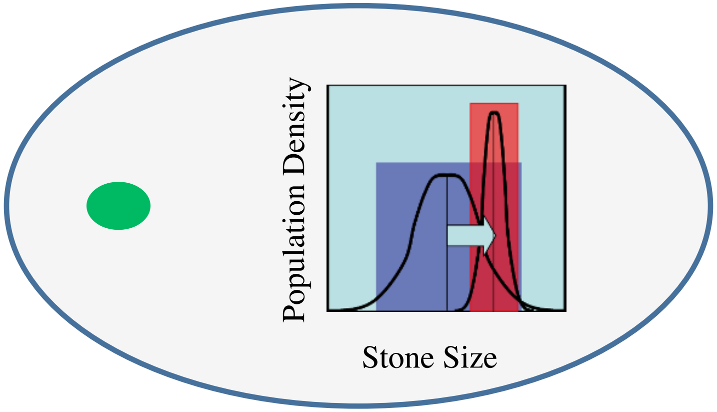
Nucleation
Growth

Continuous Crystallizing Reactor





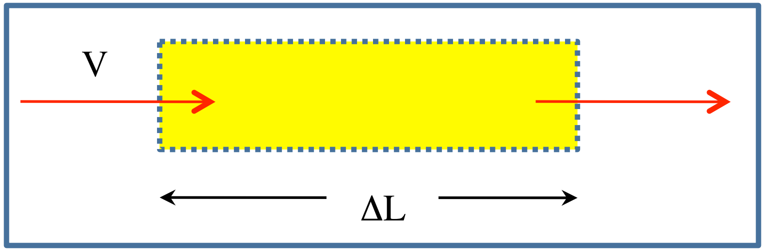
Nucleation
Growth
Agglomeration
Breakage



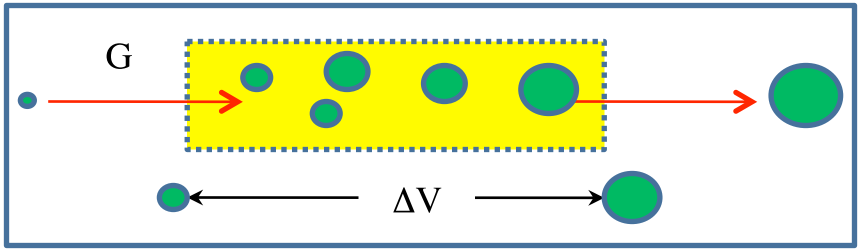
Future Directions: Population Balance Framework

(Randolph & Larson 1988)

Physical Flow CV (Nephron)



Imaginary Growth CV

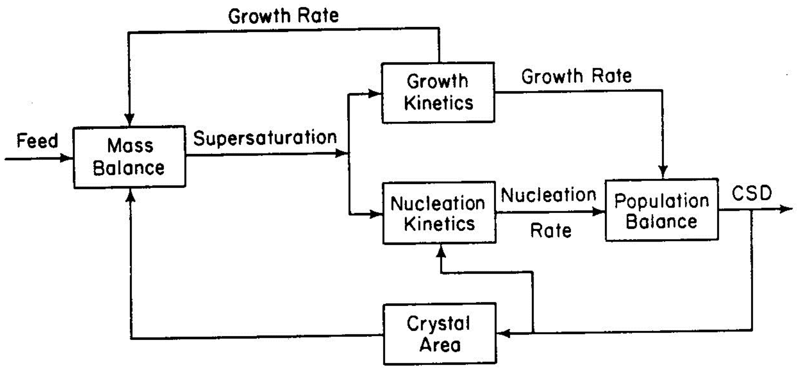


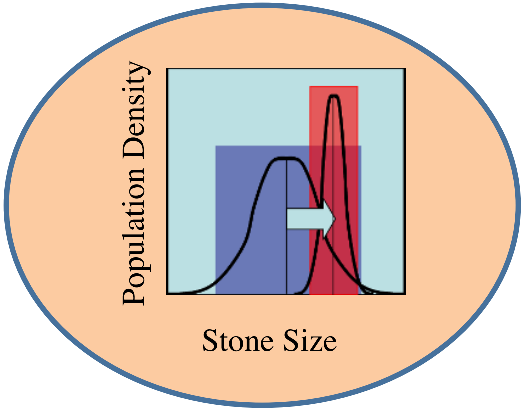
Population Balance Equation

$$\frac{\partial}{\partial t}[n(V,t)] + \nabla\cdot[\vec{u}n(V,t)] + \underbrace{\nabla_v\cdot[G_v n(V,t)]}_{\text{Growth term}} = \underbrace{\frac{1}{2}\int_0^V a(V-V',V')n(V-V',t)n(V',t)dV'}_{\text{Birth due to Aggregation}} - \underbrace{\int_0^\infty a(V,V')n(V,t)n(V',t)dV'}_{\text{Death due to Aggregation}}$$

$$+ \underbrace{\int_{\Omega_v} \nu g(V')\beta(V \mid V')n(V',t)dV'}_{\text{Birth due to Breakage}} - \underbrace{g(V)n(V,t)}_{\text{Death due to Breakage}}$$

$$G = dV/dT$$

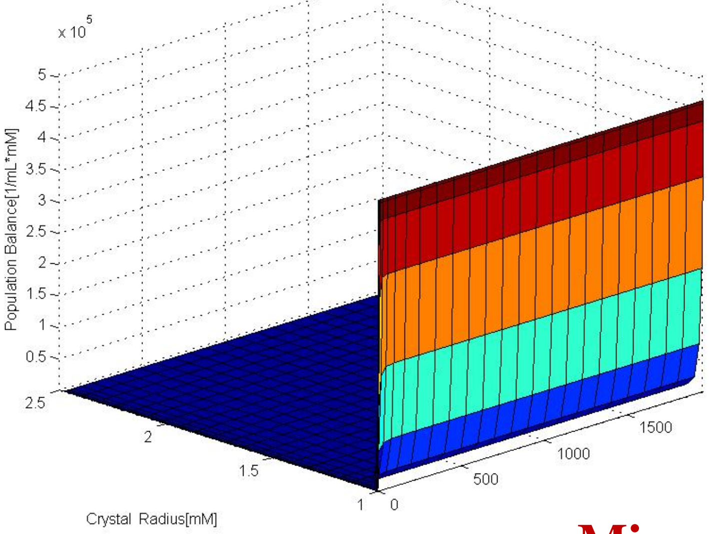




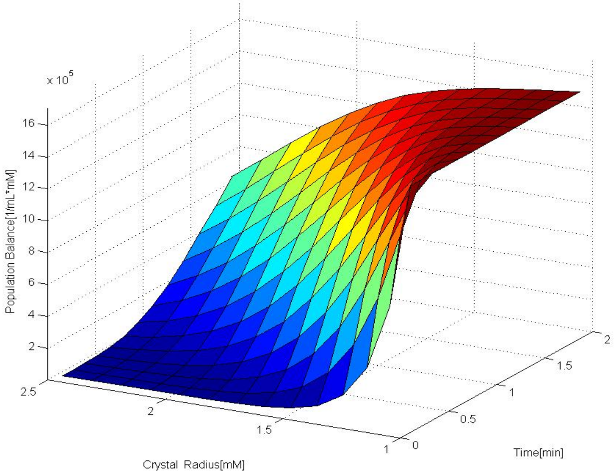
Microgravity Versus 1G Comparisons

Stone Size Distribution for Normal Subject

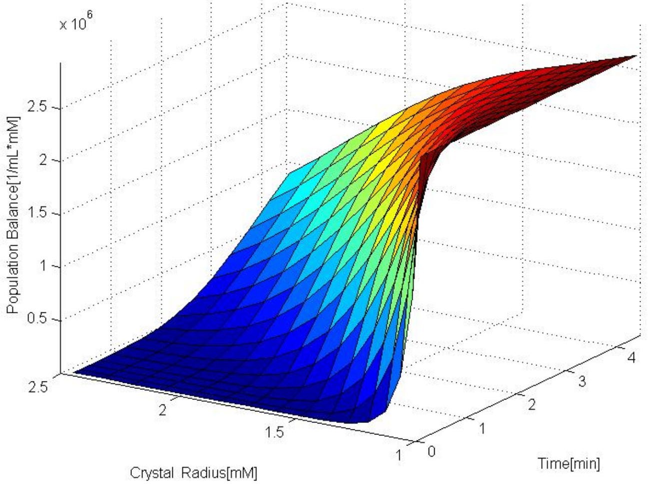
1G Normal



1G Stone-Former



Microgravity Normal



Conclusions

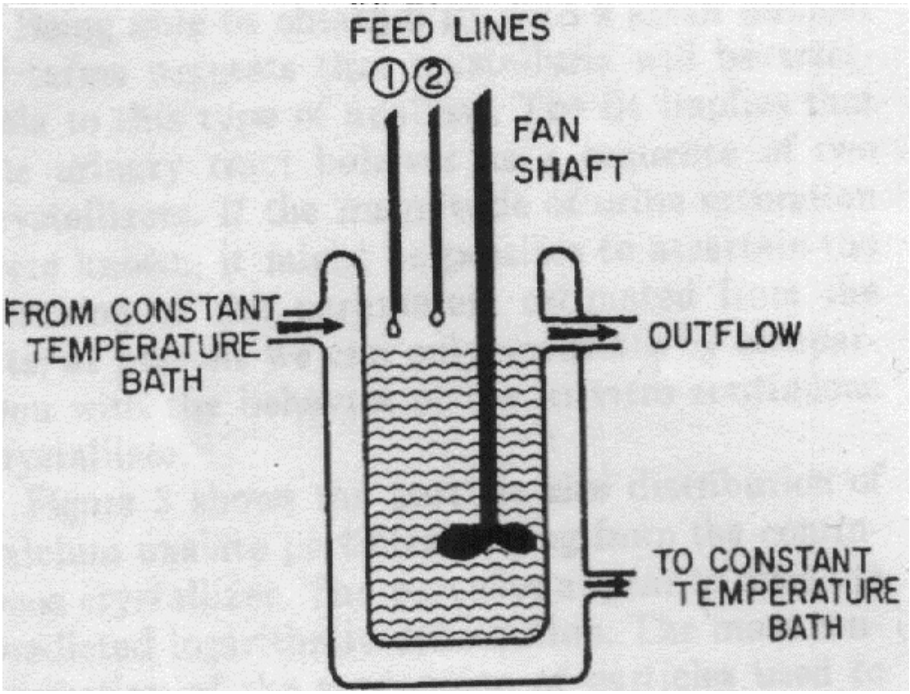
- A combined kinetics-transport model for growth of renal calculi was developed and validated against published data.
- Our numerical results point to three interesting and important trends:
  - **Adverse effect of microgravity** seems to be relatively **greater for a non stone-former** than for a stone-former – This may prove important to astronaut screening protocols.
  - Administration of inorganic inhibitors such as **citrates may provide an effective countermeasure for reducing the risk of renal stone** development in space - even for inherent stone-formers.
  - **Growth rates in microgravity will most likely be transport-limited** and not determined by the surface reaction rate - as assumed a priori in most other predictive models.
- The Growth model was cast into a PBE framework :
  - Account for the important effects of agglomeration and breakage.
  - Predict evolution in renal calculi size distributions (CSD)

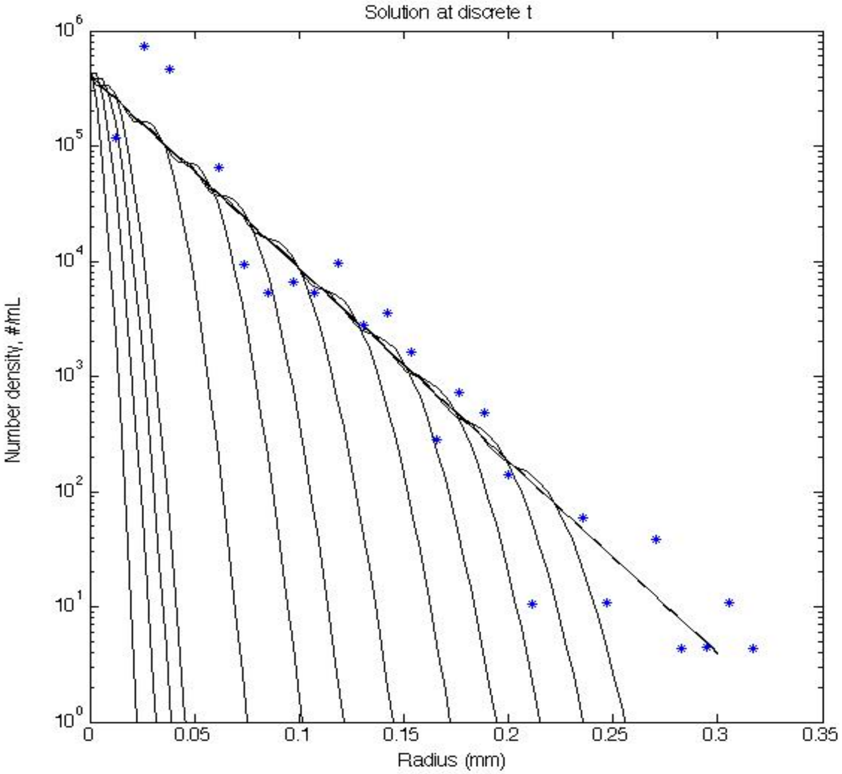
Extra Backup Slides

Preliminary Validation of the Renal PBE

(Finlayson, 1972)

Finlayson's Single Stage Continuous Crystallizer





Key Experimental Parameters

In-Flow: $CaCl_2$, $K_2C_2O_4$, NaCl

$\tau = V/Q = 55$ min

G = .0008 mm/min

$$\frac{\partial n(t,r)}{\partial t} + G \cdot \frac{\partial n(t,r)}{\partial r} = \frac{-n}{\tau}$$