# Mechanistic Modelling of the Linkage Between Proximal Tubule Cell Sublethal Injury and Tubular Sodium Reabsorption Impairment

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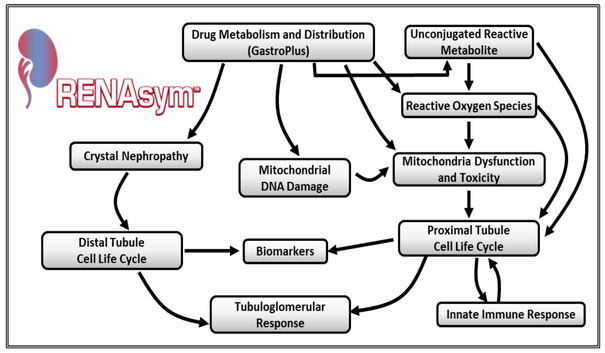
## INTRODUCTION

- Sublethal renal epithelial cell injury, a key manifestation of drug-induced acute kidney injury (AKI), is characterized by loss of brush border and cellular polarity of proximal tubular cells (PTCs).
- The key cellular alterations caused by sublethal injury involve impaired energetics and associated disruptions in cytoskeletal structure and sodium transporters activity.
- Our objective is to develop a mechanistic model relating cellular injury of AKI with renal tubular dysfunction needed to represent the complexity of renal pathophysiology.

## METHODS

- We developed a model of sublethal PTCs injury and sodium reabsorption impairment within the framework of **RENAsym™**.
- **RENAsym™** is a quantitative systems toxicology model of drug induced acute kidney injury currently under development.




- The mathematical model represents major components of sublethal injury of PTCs in a system of equations that account for ATP decline, microfilament redistribution, and $Na^+/K^+$ ATPase activity reduction.

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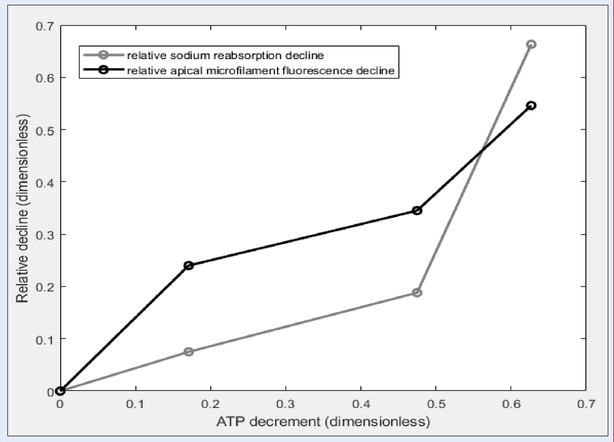
## RESULTS

**Sublethal injury**
- ATP decline
- Impaired bioenergetics
- Cytoskeletal structure disruption
- Loss of cell polarity and brush border
- Decline of Na+ transporter activity

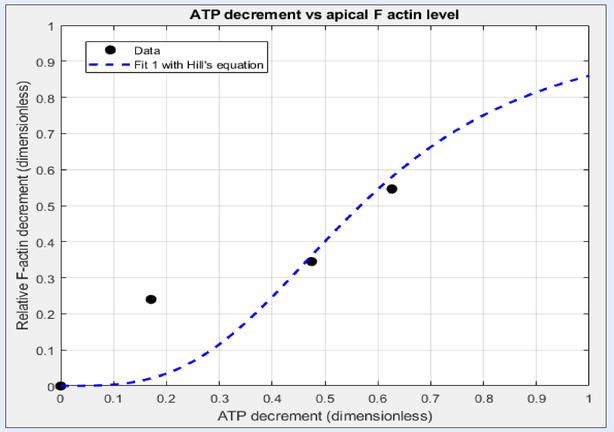
- The model equations were parametrized based on an experimental study that induced sublethal injury in rats by selectively inhibiting cortical ATP production using maleic acid and then measured the effect of dose-dependent ATP decrement on apical F-actin networks and tubular sodium reabsorption [1].
- Here, we assumed that $Na^+$ reabsorption decline comes from reductions in the active transport of sodium ions.




- Microfilament disruption was quantified using ATP decrement and then related to translocation-based loss of $Na^+/K^+$ ATPase, while a decline in the molecular activity of a sodium pump was directly related to ATP decrement.

### ATP decline to microfilament disorganization

$$F_D = f(ATP_D)$$

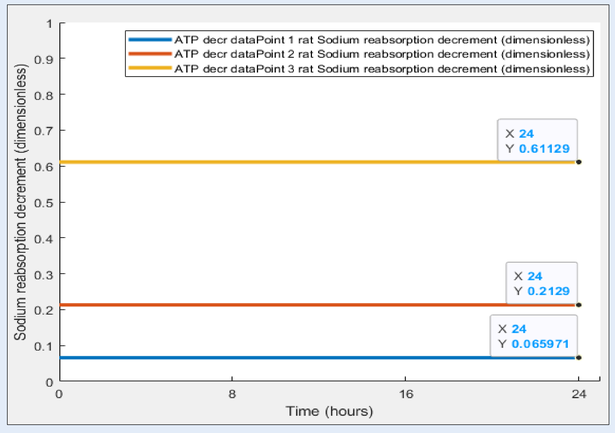



### Microfilament organization to translocation of $Na^+/K^+$ ATPase

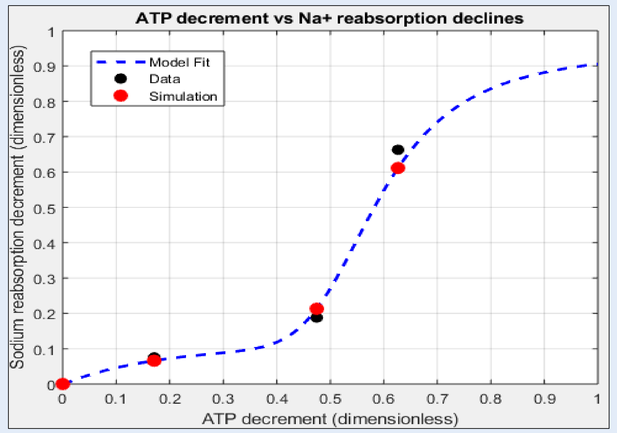
$$n_c = f(F_D)$$

### Molecular activity of a $Na^+/K^+$ ATPase directly related to ATP decrement

$$Q = (1 - f(ATP_D)) \times Q_0$$




- Simulations of varying ATP decrement reveals a sharp decline in sodium reabsorption as the relative ATP decrement exceeds 40%, in accord with observations [1].




## CONCLUSIONS

- A mechanistic model of subcellular injury is developed to link cellular ATP decrement and tubular sodium reabsorption impairment.
- The model serves as a bridge between cellular toxicity and renal tubular functional impairment, allowing mechanistic prediction of AKI induced renal hemodynamics.

## REFERENCES

1) P. S. Kellerman, J. Clin. Invest. 1993. 92:1940-1949.

## ACKNOWLEDGEMENTS

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