Modeling a Human Microfluidic Glomerulus and Proximal Tubule-On-A-Chip

Stephanie Zhang, Dr. Ian Claydon, and Dr. Gretchen Mahler
Biomedical Engineering, Binghamton University, Binghamton, NY, USA

INTRODUCTION

- Preclinical drug studies in animal and static human cell cultures fail to characterize *in vivo* renal interactions, hindering the drug discovery process [1].
- Nephron-on-a-chip technology incorporates structural, mechanical, transport and absorptive properties of a human kidney in a 3D dynamic microenvironment [2].
- Within the human nephron (**Fig 1**), a kidney functional unit, the glomerulus and proximal convoluted tubule (PCT) filter, osmoregulate and reuptake compounds from blood [3].
- Goal: Create a physiologically realistic glomerular filtration and proximal convoluted tubule (PCT) microfluidic model that houses human endothelial, proximal tubule, and podocytes for 7 days, and can filter human serum albumin.

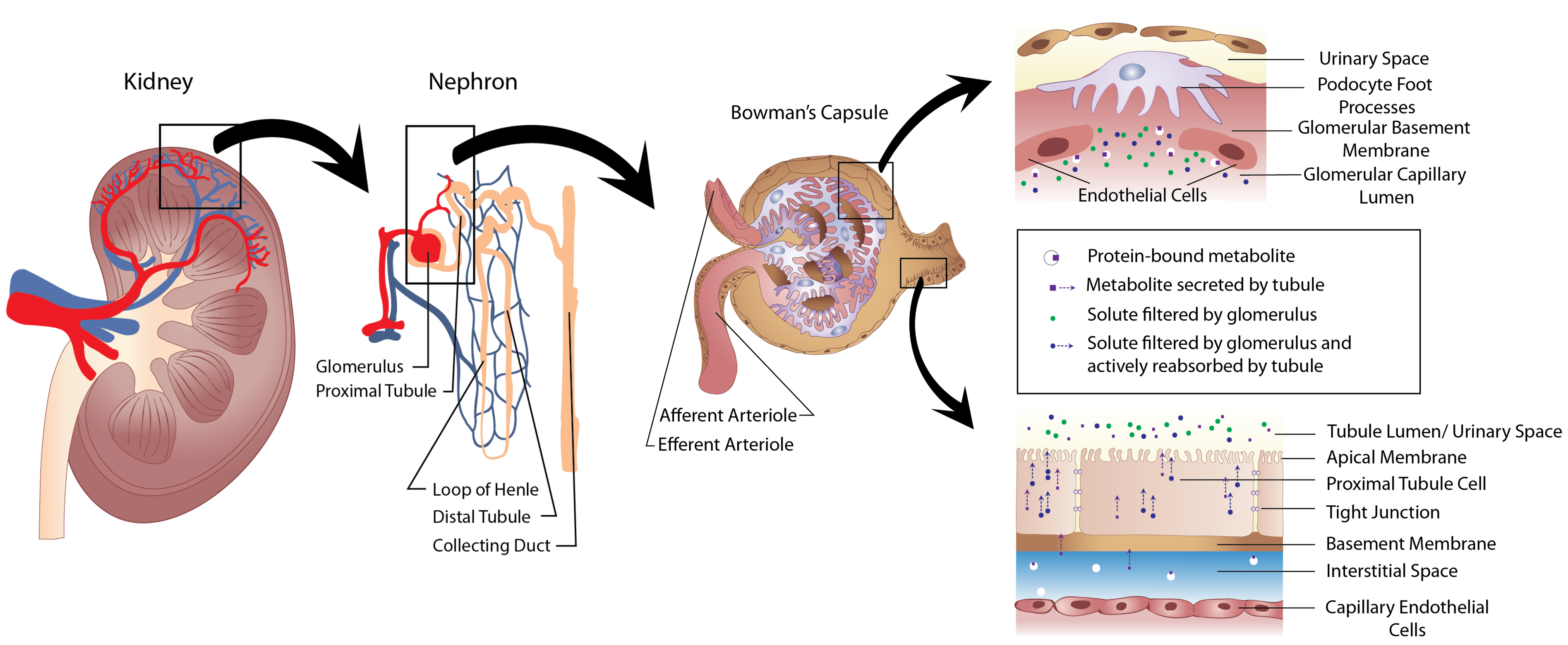

Figure 1. Human Kidney Glomerulus and Proximal Tubule

COMPUTATIONAL METHODS

- 2D/3D model design of the nephron-on-chip was optimized based on tubing internal diameter (ID) and length, and flow rate from the pump using COMSOL®.
- Design parameters are shown in **Table 1**
- Free and Porous Media Flow physics package was used to define the fluid and matrix properties of porous membranes in the system.
- Simulations were validated experimentally (**Fig 2**) in the nephron-on-chip system using a peristaltic pump and 18 MΩ water for 24 hours.

Parameters	Value	Units
Shear Stress (across PCT device)	0.4-1.5	dynes/cm^2
Inlet Mass Flow Rate	6.67 x10^{-7}	kg/s
Permeability of Polycarbonate Membrane	5.4 x 10^{-14}	m^2
Permeability of PES Membrane	3.2 x 10^{-14}	m^2

Table 1. Design Parameters

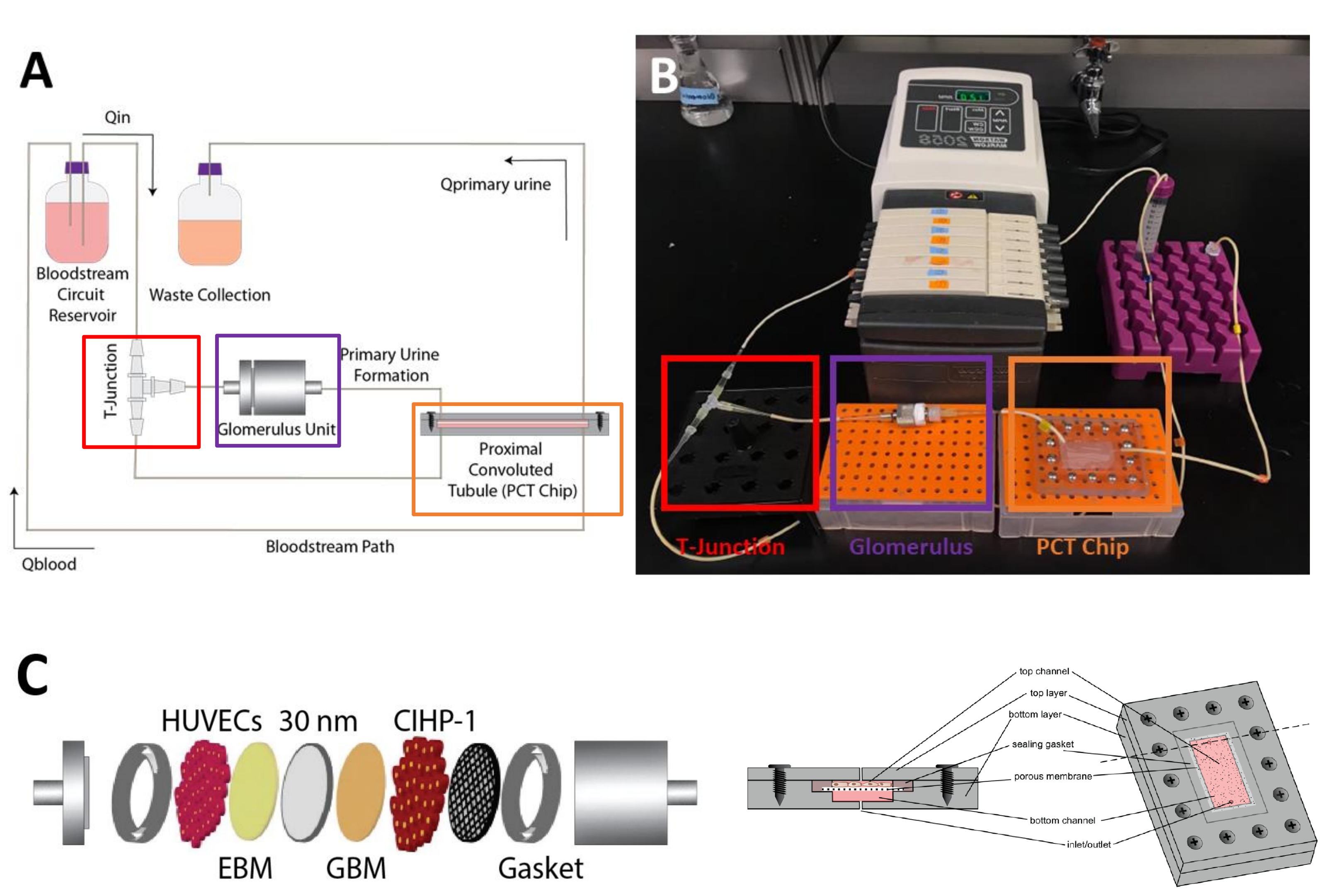

Figure 2. Nephron-on-Chip System (A) Schematic of System (B) Validation Testing of System (C) Schematic of Glomerulus Unit and PCT Device

RESULTS

- Velocity simulations (**Fig 3**) optimized the experimental design and operation of the microfluidic device for 2 hours
- Filtration of Fluorescein Isothiocyanate- Human Serum Albumin (FITC-HSA) in the system over 12 hours was simulated to be over 90% (**Fig 4**).
- Experimental validation tests determined that with a total pump flowrate of 40.5 µL/min, there was 16.23 µL/min (± 5.59 µL/min) exiting the waste stream and a shear stress over the proximal tubule cells was within the physiological range.

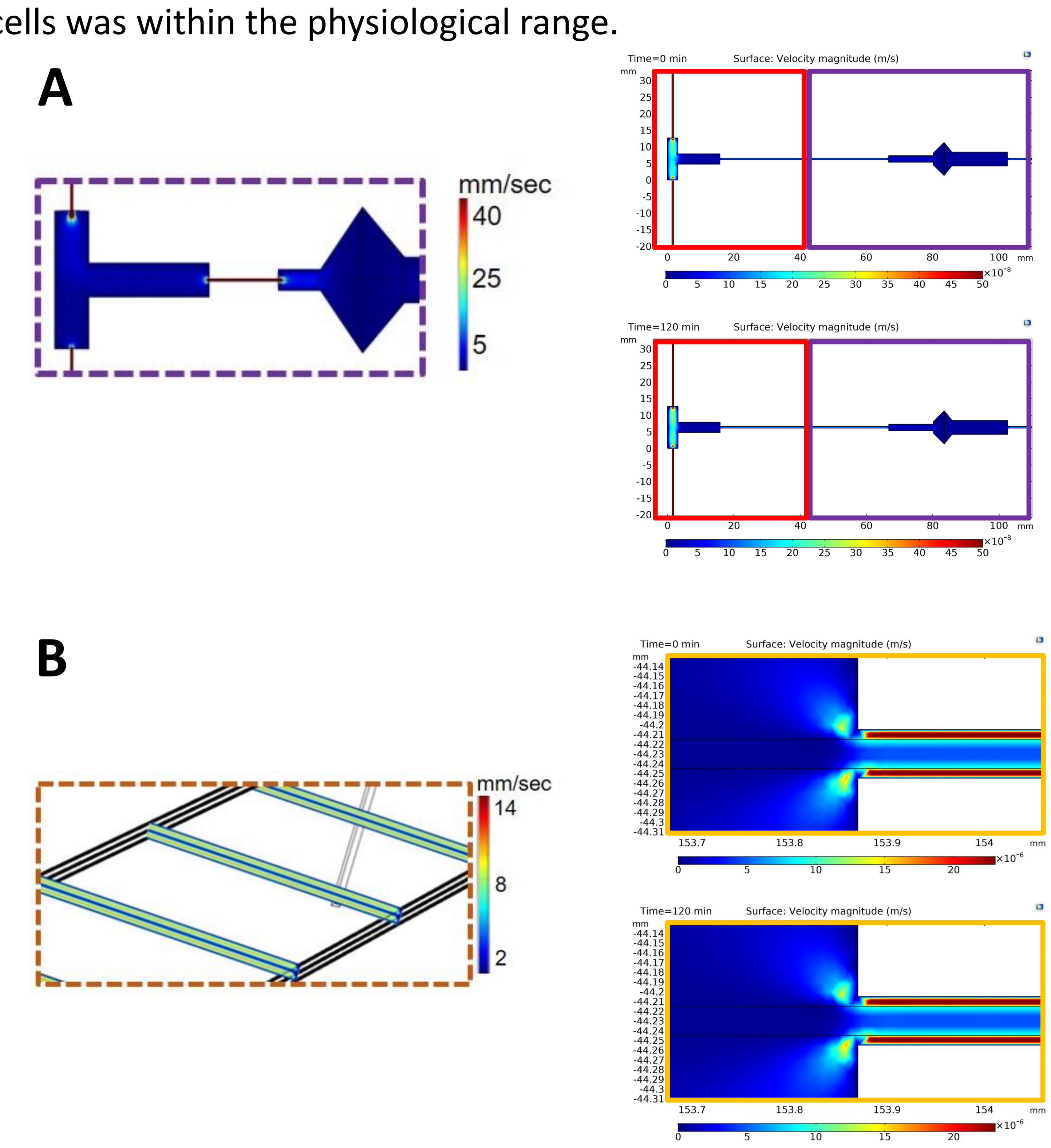

Figure 3. Velocity Profiles of 2D/3D Nephron-on-Chip Model in Stationary and Time Dependent Study. (A) T-Junction. (B) PCT Microfluidic Device.

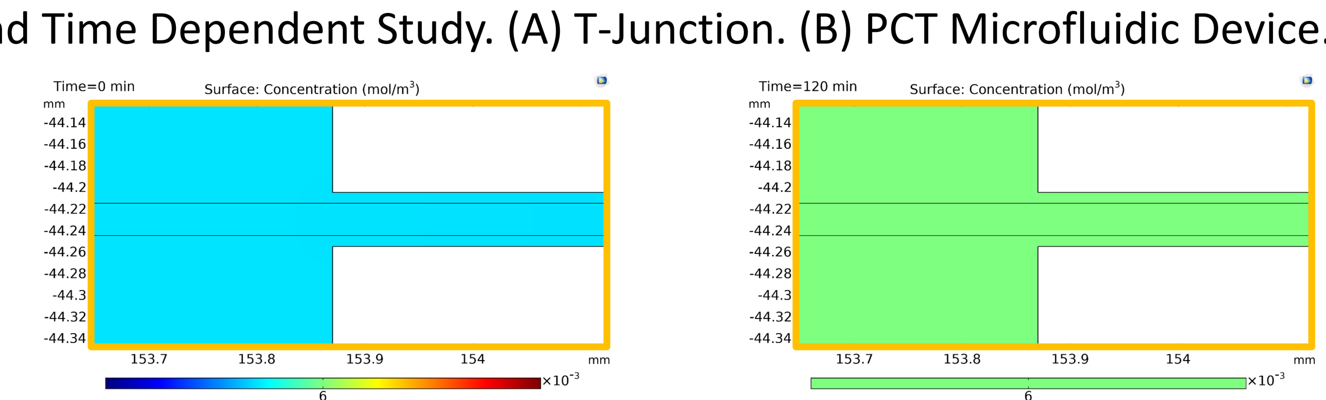

Figure 4. Concentration Profiles of FITC-HSA in 2D Nephron-on-Chip Model for a Time Dependent Study

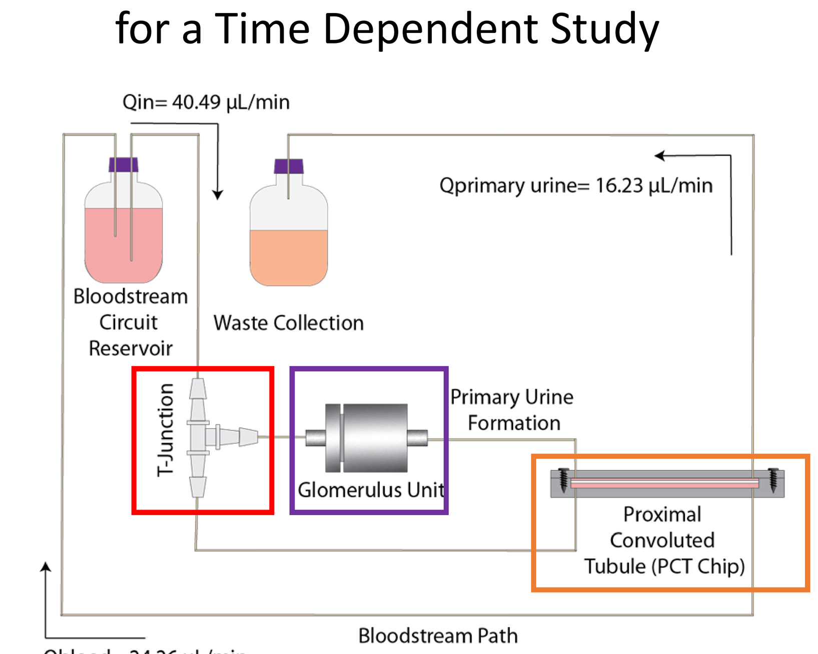

Figure 5. Experimental Validation of Nephron-on-Chip System.

CONCLUSION

- The computational model demonstrates an optimized nephron-on-chip system that has been experimentally validated.
- COMSOL® provided an efficient and accurate assessment of the microfluidic model.
- Future directions include redesigning the system to incorporate measurements of real-time transepithelial resistance to determine tight junction integrity.

ACKNOWLEDGEMENTS: Funded by the Alternatives Research and Development Foundation

REFERENCES

1. Redfern, Will S., et al. "Impact and prevalence of safety pharmacology-related toxicities throughout the pharmaceutical life cycle." Journal of Pharmacological and Toxicological Methods 2.62 (2010): e29.
2. Jang, Kyung-Jin, et al. "Human kidney proximal tubule-on-a-chip for drug transport and nephrotoxicity assessment." Integrative Biology 5.9 (2013): 1119-1129.
3. Kriz, Wilhelm, and Michel Lehir. "Pathways to nephron loss starting from glomerular diseases—insights from animal models." Kidney international 67.2 (2005): 404-419.
4. Raghavan, Venkatesan, et al. "Shear stress-dependent regulation of apical endocytosis in renal proximal tubule cells mediated by primary cilia." Proceedings of the National Academy of Sciences 111.23 (2014): 8506-8511.