A New Microscope for the Kidney: Mathematics

Running head: Computational Modeling

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The discovery of the microscope in the late 17th century revealed otherwise invisible processes, and revolutionized biology. Years later, mathematics has the potential to do the same. We will highlight recent studies that utilize computational modeling techniques to investigate kidney function.

Like a microscope, mathematical models offer a variety of “magnification levels” that focus on different aspects of the kidney. For example, “macroscopic” models may focus on whole-animal or whole-kidney function and metabolism (e.g., [3, 4, 6]), whereas “microscopic” models may simulate membrane transport kinetics (e.g., [14]). Below we discuss mathematical models that represent epithelial transport processes along the nephron. These models are particularly interesting, because not only can they predict nephron transport and metabolism, they can also be used to provide insights into the effects of therapeutic treatments.

It is fair to say that Weinstein founded the field of computational modeling of epithelial transport in the kidney. He was the first to develop detailed models of solute and water transport of renal epithelial cells in the rat kidney [15, 17]. These epithelial models were then extended into tubular segments [16, 18], and eventually into populations of nephrons [19, 20]. Similar rat nephron models have since been developed by other groups [1, 10, 12, 11, 9]. Given a set of model parameters, these nephron-level models can predict tubular fluid and solute flows, water and solute fluxes through individual transporters or channels, as well as urine flow and solute excretion rates. Researchers can use these models as microscopes to reveal underlying mechanisms that explain experimental observations. Mathematical models are particularly useful in simulating “clean” knockout experiments. Because a computational knockout model does not share an animal’s desire to live, it will not attempt to compensate
by adjusting other transport mechanisms.

Using nephron models as building blocks, one may construct whole-kidney models. The author’s group has developed a series of mathematical models of the rat kidney [13] or renal medulla [7, 8]. These models, which include the renal vasculature and its effects on tubular transport, were applied to better understand one of the longest-standing mysteries in traditional physiology—the urine concentrating mechanism of the mammalian kidney. These models were further extended to include renal metabolism [2, 5, 3, 4], in which several cytokines influence each others’ production and degradation, ultimately impacting both location oxygen delivery, local Na\(^+\) transport activity, and oxygen consumption. Model simulations were conducted to study tubulo-vasular cross-talk and renal oxygenation. It can be argued that a computational model is needed for a meaningful examination of these processes, given their intricate and often unintuitive nature.

To construct a whole-kidney model or a detailed epithelial model, one must amass a rather large set of parameters, including anatomic data, transport activity levels, channel open probabilities, and so forth. Many of these parameters are not well characterized, or cannot be measured using current techniques. Thus, in practice some parameter values are chosen so that model predictions match experimental findings, such as micropuncture data. Because these measurements are relatively plentiful in the rat, the majority of the epithelial transport models were developed for the rat. In contrast, many of the knockout experiments were conducted in the mouse. The development of a mouse epithelial transport model has been hampered by the relatively limited micropuncture and microperfusion data.

Mathematics and the associated computer simulations can be a great asset in data interpretation. Mathematical models provide a systemic approach for investigating system
perturbations, such as those induced by drug administration or genetic alterations. The effects of these perturbations can be studied rather straightforwardly by modifying relevant model parameters. Also, model simulations are not as limited by experimental constraints as wet experiments. Thus, simulations can be used to investigate novel scenarios and to develop and test hypotheses which can then guide the design of new experiments. Additionally, mathematical models can provide insights into the relevance of a specific molecule or pathway for the macroscopic behavior of the system. Given these considerations, examples of which can be found among the works previously cited, mathematics and simulations are increasingly gaining recognition among biologists. Indeed, the recent fast-growing synergy between biology and mathematics promises to enrich both fields tremendously in the coming decades.

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**References**


