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INVITED REVIEW

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Is the time right for a new initiative in mathematical modeling of the lower urinary tract? ICI-RS 2023

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Abstract

Introduction: A session at the 2023 International Consultation on Incontinence – Research Society (ICI-RS) held in Bristol, UK, focused on the question: Is the time right for a new initiative in mathematical modeling of the lower urinary tract (LUT)? The LUT is a complex system, comprising various synergetic components (i.e., bladder, urethra, neural control), each with its own dynamic functioning and high interindividual variability. This has led to a variety of different types of models for different purposes, each with advantages and disadvantages.

Methods: When addressing the LUT, the modeling approach should be selected and sized according to the specific purpose, the targeted level of detail, and the available computational resources. Four areas were selected as examples to discuss: utility of nomograms in clinical use, value of fluid mechanical modeling, applications of models to simplify urodynamics, and utility of statistical models.

Results: A brief literature review is provided along with discussion of the merits of different types of models for different applications. Remaining research questions are provided.

Conclusions: Inadequacies in current (outdated) models of the LUT as well as recent advances in computing power (e.g., quantum computing) and methods (e.g., artificial intelligence/machine learning), would dictate that the answer is an emphatic "Yes, the time is right for a new initiative in mathematical modeling of the LUT."

KEYWORDS

bladder, mathematical modeling, mechanical modeling, nomogram, statistical modeling, urethra, urodynamics

1 | INTRODUCTION AND MOTIVATION

A mathematical model describes a system with a set of variables and a set of equations that establish quantitative relationships between the variables. Mathematical models can provide insights into physiology, pathophysiology, and clinical decision-making for different organ systems. The lower urinary tract (LUT) is a complex system, comprising various synergetic components (i.e., bladder, urethra, neural control), each with its own dynamic functioning and high interindividual variability. Notably, the bladder and urethra undergo considerable shape changes during micturition, therefore, nonlinear theory is required for mechanical modeling.[1] Several modeling approaches have been developed for the different LUT components, including nomograms which are designed to assist with clinical decision making,[2] machine learning models to automate identification of pathology in clinical tests,[3] as well as biomechanical models,[4] and neural control models.[5] These models can increase our understanding of the complex interactions between different tissues and organ systems that are required for proper function of the LUT and can help identify targets for therapy in pathological situations.[6] However, to date, comprehensive studies modeling the LUT in its entirety are limited. A recent review of mathematical modeling of the LUT determined that current models are missing important physiologically-based mathematical descriptions (e.g., neural connections).[6] As a result of this and other deficiencies, the authors concluded that no current mathematical model is functionally predictive of the LUT.[6]

When addressing the LUT, the modeling approach should be selected and sized according to the specific purpose, the targeted level of detail and the available computational resources. Simple models such as nomograms can be utilized to determine clinical value and thresholds for a specific dysfunction related to clinical and laboratory tests. Several nomograms have been developed for LUT assessment, most often, but not exclusively for facilitating interpretation of clinical tests for diagnosis based on LUT symptoms.[7–10] However, nomograms cannot describe the complexities involved in LUT function and dysfunction.

Over the past few decades computing power has been increasing at a dramatic rate, enabling more and more complex models to be developed and then to be utilized not only by academics and other experts, but also by clinicians, patients, and other interested parties. Everyday use of artificial intelligence (AI) is also exponentially increasing. Programs such as ChatGPT and blockchain technology are two examples of the broad daily utility and widespread use associated with increasing computational capacity. Novel computational paradigms and use of large data sets, including quantum computing can enable innovative complex mathematical models that could improve our understanding of LUT physiology and pathophysiology.[11]

Mathematical models should be targeted to address specific hypotheses, which then determine what assumptions can be utilized and which aspects of the model need to be developed in detail. The specific modeling approach should be selected and tailored to address the scientific or clinical question and/or hypotheses being tested. Assumptions must also be detailed. In this article, we provide four examples of mathematical models which could be used to improve our understanding of the LUT, simplify clinical diagnostic tests, or provide input into clinical decision-making.

2 | MODELS TO NOMOGRAMS

Two models with clinical application to human urodynamics are the Perugia urodynamic method of analysis (PUMA),[12] an empirical model, and the Valentini Besson Nelson VBN model,[2,13] a knowledge model. However, because of their complexity, these and other mathematical models can be difficult to use by a team other than the inventing team because of constraints such as size and skills of required teams and the time required to achieve reliable analysis. Other groups and clinical practices may not have the computational power to be able to efficiently run a model developed elsewhere. Open source availability of models and other algorithms has helped reduce this difficulty of translation of models to other research groups, but has not eliminated it entirely. In addition, the results of any model is only as accurate as the data used to create it, placing a high standard on data collection for use in mathematical models. Thus, mathematical models of the LUT are rarely used in daily practice.

The purpose of nomograms is very different from that of models. A nomogram is a simplified description of a process, making it a useful tool for reducing complexity of complex phenomena. A nomogram applies to a single type of dysfunction and is used to characterize that dysfunction. If only two parameters are required (e.g., voiding pressure and flow rate for characterization of benign prostatic obstruction, BPO) a nomogram can be graphed in two dimensions for practical useability in daily practice, or even easier still, can be calculated from an index derived from the nomogram, in this case, the bladder outlet obstruction index. When more than two parameters are required, a nomogram usable by a clinical practitioner can be proposed (e.g., detrusor contractility of women).[14] Although nomograms cannot be used to predict outcomes to unknown situations, they are easier to use for clinicians than a mathematical model that fully describes the LUT. However, nomograms need to be externally validated for broad clinical use. Two examples are the nomogram developed by Griffiths et al.[7] and the ICS nomogram[8] for clinical evaluation of BPO in men, both of which have been externally validated.

3 | FLUID MECHANICAL MODELING OF THE LUT

The development of fluid mechanical models of the LUT has been historically motivated to address scientific and clinical questions. "Fluid" refers to a substance capable of flowing and adapting to the shape of its container, encompassing both liquids and gases. In this context, "fluid" specifically addresses the liquid form, that is, urine. Urine flow in the LUT is unsteady during voiding, typically with large Reynolds number, up to 4000.[15] Notably, while the bladder shape (and its changes during contraction) drives the flow toward the urethra, known as shape driven flow, the flow in the urethra depends on its mutual interaction with the urethral lumen, since the urethra is a collapsible vessel.[16] All these intrinsic LUT properties are difficult to model.

Fluid mechanical models of the LUT aim at (i) improving insight into physiological and pathological processes and the resulting urodynamic pressure and flow curves, (ii) assisting surgical planning, and (iii) optimizing medical device design (e.g., stents and catheters). Moreover, these models, once validated experimentally, can be used to predict more complex physiological and/or pathological scenarios. A classification of fluid mechanical modeling methods is provided below.[17] For each approach, examples of relevant LUT studies are briefly introduced.

3.1 | Reduced order methods

Reduced order methods are designed to retain the key physics of the systems with minimized computational cost. They are normally used to complement full order models in anatomically realistic geometries[17] or to replace full order models in settings with limited computational resources (or where it is not feasible to perform full order numerical simulations). The first LUT mathematical models were based on reduced order methods and were designed to replicate the behavior of the bladder and urethra. In this regard, pioneering modeling work was conducted by Griffiths who combined clinical and experimental fluid mechanical measurements of the bladder and urethra to develop a mathematical micturition model mimicking urine flow curves observed in healthy humans.[18,19] Later studies expanded this initial modeling to cover more complex pathological scenarios.[13,20]

3.2 | Computational methods

Computational fluid mechanical methods can be classified into three categories[17]:

3.2.1 | Computational fluid dynamics (CFD)

The main focus of CFD models is on fluid dynamics as they often rely on rigid wall simplification to significantly reduce the computational cost. For this reason, the bladder and urethra are often modeled as rigid boundaries and the flow regime is solved at the defined computational domain. CFD models are often used to investigate the effects of bladder and urethral geometries on urine flow as well as to optimize design of medical devices (e.g., stents and catheters). Several CFD studies, have focused, for example, on modeling the effects of urethral strictures (e.g., BPO)[15,21,22] and/or surgical procedures on urine flow.[23]

3.2.2 | Computational solid mechanics (CSM)

In biomedical applications, CSM focuses on modeling the structural behavior of soft biological tissue using their constitutive equations. Applied to LUT, CSM provides tools for the investigation of stress and strain fields within the bladder and urethral wall, during bladder filling and emptying cycles.[24,25] Recent CSM work has focused on investigating the effects of artificial urinary sphincters (AUS) used to treat urinary incontinence, for example by assessing the shape evolution of the urethral lumen following AUS cuff compression by inflation, and urethral reopening by cuff emptying.[26,27]

3.2.3 | Fluid-structure interaction (FSI)

FSI models are implemented to investigate solid mechanics of soft biological tissues, fluid dynamics, and their mutual interactions. Because of their complexity, they demand high computational capabilities. In LUT modeling, FSI models have focused on bladder and urethral tissue mechanics and their interaction with urine flow. Recently, they were used to investigate stress urinary incontinence.[28] and to account for the external occluding action of AUS on urethral lumen and urine flow.[27]

The urinary bladder and the heart are very similar from a modeling point of view: they are both hollow muscular organs which periodically relax and contract to generate a fluid motion. In both cases, the organ contraction is triggered by an electrical signal. These similarities promote the interchange of engineering approaches and technologies between these two fields. Historically, cardiovascular fluid mechanical modeling[29,30] has received more attention than urological modeling. However, this trend has been evolving in recent years due to increased interest in ageing related diseases affecting the LUT. Considering all these reasons, scientific discussions on advances and future trends in fluid mechanical modeling for Urology often look to cardiovascular modeling as a reference. In the last decade, the focus of cardiovascular computational modeling has shifted toward patient-specific analyses, the so-called "inverse modeling" approach that combines computational fluid mechanical modeling with medical imaging technology.[31]

Rapid technological advances in echocardiography, magnetic resonance imaging (MRI), and machine learning have led to high resolution measurements of tissue motion and blood flow (e.g., 4D MRI).[31] The pairing of this kinematic information with tissue mechanics, fluid dynamics, and fluid structure methods is shedding light on realistic material properties and dynamic data (e.g., shear stresses and forces), which are not directly measurable in living individuals.[31] These approaches are unveiling several strong correlations between retrieved data and corresponding clinical risk factors. We envision that similar methods will soon become more widespread in Urology. MRI imaging, in particular, is suitable for LUT anatomical investigations as it consists of a noninvasive technique which offers extraordinary soft tissue contrast and full field-of-view options.[32] Pewowaruk et al. have recently proven the feasibility of performing MRI studies in LUT.[33] They measured bladder wall displacement during voiding and, by combining MRI results with CFD modeling, they found more pronounced fluid recirculation in the bladders of BPO patients.[33] Preliminary MRI results on urethral dynamic changes, during maximum voiding flow, were recently coupled with CFD simulations to determine wall shear stress, pressures, and fluid velocities along the entire urethral length.[34]

The coupling of medical imaging with fluid mechanical modeling is driven by the need for optimized and personalized treatments. For Urology, it requires interdisciplinary teams (physicians, engineers, and biologists) to delve into urinary flow studies and develop custom solutions for urological issues. Collaboration among experts, combined with enhanced computational capabilities for personalized approaches, is crucial in achieving scientifically and clinically meaningful outcomes using these models.

4 | USING MODELS TO SIMPLIFY URODYNAMICS

Multichannel urodynamics is central to the diagnosis of LUT dysfunction as it provides an objective measure of the type and subtype of LUT dysfunction.[35] A recent systematic review and meta-analysis demonstrated that urodynamic studies "are not replaceable in diagnostics, since there is no other equivalent method to find out exactly what the LUT problem is."[36] However, multichannel urodynamic studies are complicated by insertion of both a transurethral catheter in the bladder and a rectal or vaginal catheter. These catheters are uncomfortable for the patient and can lead to artifactual results.[37] Urodynamic events such as coughs and Valsalva maneuvers, that are generated by contraction of abdominal muscles, occur with faster onset than detrusor contractions, and therefore contain significant representation of higher frequencies than detrusor contractions.[38] Thus, it should be possible to use sophisticated signal processing methods and/or machine learning to identify and separate the detrusor pressure component from measured vesical pressure, negating the need for an abdominal pressure catheter. This would have the potential of reducing both patient distress and complexity of the procedure, but may be applicable only for a subset of patients. For example, Cheriyan et al. suggested that the incremental benefit of measuring abdominal pressure may be of questionable value in certain groups of pediatric patients, which could require further investigations by a pediatric urodynamicist.[39]

In a retrospective study of 14 patients with neurogenic bladder, Karam et al. developed a wavelet-based algorithm to identify bladder events from vesical pressure data alone using a context-aware thresholding algorithm consisting of a novel, tunable, wavelet-based adaptive algorithmic framework.[40] They expanded this method using retrospective urodynamic data from a cat ambulation experiment to predict detrusor pressure using thresholding with a discrete wavelet transformation and filtering using an exponential moving average filter (to remove artifacts and abdominal generated pressure events from vesical pressure) while maintaining representation of detrusor pressure.[41] They achieved an 80%

correlation between estimated detrusor pressure and detrusor pressure obtained by subtracting abdominal pressure from vesical pressure.[41]

Majerus et al. recently expanded the algorithm for estimating detrusor pressure by developing a real-time, wavelet-based signal reconstruction algorithm for extracting the low-frequency detrusor pressure signal from vesical pressure data using a nonlinear event-driven reconstruction weighting approach based on statistical features.[42] Overall, detrusor pressure was estimated with root mean square error of 10 cm H_2O and an *R* value of 88%,[42] which is not ideal but is a start that can be improved upon. The same group also proposed use of a machine learning classifier using discrete wavelet transform coefficients and independent time-domain statistical features. Of the three classifier architectures used to identify feature selection, the best performing was a k-nearest classifer.[42] However, an artificial neural network (ANN) classifier presented the best balance between accuracy and computational efficiency for real-time use.[42]

This approach to single catheter urodynamics, while promising, has only been tested retrospectively on a limited patient population. Computation in real-time will require significant computing power. Recent advances in computing power and reductions in cost make real-time single channel urodynamics a future possibility. Future directions of using mathematical models to estimate detrusor pressure for single catheter urodynamics include a machine learning classifier to identify events and testing in a larger and more diverse sample, as well as implementation and testing in a real-time situation.

5 | STATISTICAL MODELS

Statistical prediction models for detrusor overactivity[43] and detrusor underactivity[44] have been developed to reduce the need for invasive urodynamic studies. Examples of objectives of other statistical prediction models are prediction of outcomes of interventions such as supervised pelvic floor muscle training[45] and midurethral sling surgery[46] for women with stress urinary incontinence. However, the current literature lacks evidence for the potential use of advanced statistical modeling or supervised machine learning in development of management plans for patients with LUT dysfunction.

As multifactorial variables are involved in the development of LUT dysfunction, sophisticated statistical methods are necessary for multivariate analysis. The most commonly used technique is logistic regression. An alternative tool is ANN, a subset of machine learning models. ANN are similar to regression models in their nature and use. They are comprised of input (independent or predictor variable) and output (dependent or outcome variable) nodes, use connection weights (regression coefficients), bias weight (intercept parameters), and cross-entropy (maximum likelihood estimation) to learn or train (parameter estimation) a model.[47] For the development of statistical models, the available data are divided into two sets; a training set used to develop the model and a test set, used to evaluate the model's performance. ANNs have been shown to be more accurate than multivariate regression in identifying predictors of urodynamic diagnosis in women with pelvic organ prolapse.[48]

The selection of relevant clinical variables, with clinicians rather than statisticians or engineers leading the process, is of paramount importance in the development of statistical models. The presence or severity of LUT symptoms has been successfully incorporated in several prediction models.[43–46] The use of validated patient reported outcome measures, such as questionnaires and bladder diaries, allow more accurate quantification of each patient's symptoms. Age, body mass index, parity, and surgical history have been identified as predictors in models of LUT dysfunction. Addition of appropriate ultrasound findings (e.g., bladder neck position, prostate volume, bladder wall thickness) might improve the accuracy of the statistical models. Although there is lack of individual biomarkers validated as diagnostic tools for LUT dysfunction,[49] their value could be optimized with mathematic modeling that could identify complex interactions between the biomarkers and the investigated clinical conditions.

Despite the potential advantages of statistical models, there are several limitations that could prevent their use in clinical practice. Large datasets are essential for construction and validation of mathematical models. However, large datasets are not easily available to researchers. Missing data in large datasets are very common and advanced statistical techniques such as multiple imputation should be applied to improve accuracy. An investigator-led best model selection approach is superior to the most commonly used machine-led step-wise regression. Existing models have shown an acceptable but not an outstanding overall predictive ability. The concordance index or area under curve of the published models ranges between 0.645 and 0.8.[43–46] To avoid the risk of overfitting, all prediction models should be externally validated in a different data set before being introduced in clinical practice. Studies that evaluate statistical models without developing a scoring system or reporting a logistic regression equation have limited clinical value.

6 | CONCLUSIONS

With recent advances in computing power and diverse computing methods (e.g., quantum computing), modeling methods (e.g., artificial intelligence/machine learning), and medical imaging (e.g., MRI), unprecedented powerful tools have become accessible to the field of LUT mathematical modeling. Based on this, new avenues are opening and leading toward patient-specific modeling approaches which could improve insight into pathophysiology of the LUT and provide inputs into clinical decision-making. Moreover, due to the multiphysics/multiscale nature of the LUT, collaboration among multidisciplinary teams of experts is necessary. This inspires the translation of tools and methodologies from several other research fields into LUT modeling. So, is the time right for a new initiative in mathematical modeling of the LUT? Our answer is an emphatic "Yes, the time has come."

7 | REMAINING RESEARCH QUESTIONS

- *Where does the utility of nomograms end and mathematical models begin?*

  With increasing computational power, our ability to add complexity to nomograms increases, thereby improving accuracy of predictions. For example, we could add a 3rd and even a 4th dimension to the standard two-dimensional nomogram to account for additional variables and risk factors.
- *Could the computational requirements for fluid mechanical models be reduced sufficiently for broad clinical and research use?*

  To date, fluid mechanical models are too complex to be utilized at the bedside; however, they could be simplified for restricted use cases, such as a single pathology, and the outcome could be focused on clinically actionable parameters. With increasing computing power, clinical use of fluid mechanical models could become a reality in the near future.
- *What testing would be required to sufficiently validate a single catheter urodynamics system that uses an algorithm to estimate detrusor pressure and abdominal pressure?*

  Prospective studies in which diagnoses are made from both standard urodynamics and single channel urodynamics on the same patients would need to be conducted to determine if single catheter urodynamics results in the same diagnosis and treatment plan as two catheter urodynamics in different patient populations.
- *What would sufficiently validate statistical models for clinicians to use them in daily clinical practice?*

  A large prospective study would be needed for each predicted outcome to determine how well the statistical models predict the outcome based on patient-specific data.

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