Standardised, automatic description of uroflowmetry curve shapes

A thesis submitted in partial fulfillment of the requirements
for the degree of Master of Science in Technical Medicine

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February 2020

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Abstract

Rationale The shape of uroflowmetry curves might associate with voiding abnormalities. The lack of standardisation in flow shape description impairs this diagnostic value and further research into shape descriptors. Therefore algorithmic analysis that generates a complete shape description based on quantitative definitions for shape characteristics is proposed. A graphical user interface visually presenting the shape characteristics subject to the algorithmic evaluation makes this insightful for the end-user.

Methods Previously published quantitative definitions for flow shape are complemented with new proposals for standardised analysis when necessary. Objectivity in these proposals is improved by basing them on single center expert consensus. Urologists interpreted shape characteristics of sets of uroflowmetry curves together, resulting in a single assessment. Algorithmic performance and experience with the user interface are improved by obtaining expert evaluation with goal oriented questionnaires.

Results This resulted in an algorithm based on quantitative threshold evaluation for a well-arranged set of shape characteristics. The generated description is comprised of the descriptors bell shape, fluctuating, intermittent and plateau flow and comments on symmetry and maximal flow. Deviation from threshold is made visible in the uroflowmetry flow rate time graph for all shape characteristics. The user interface that makes the algorithm and the visualisation easily accessible is very well received amongst the targeted users.

Conclusion Algorithmic description of uroflowmetry curve shape makes application of standardised evaluation fast and simple. The connected user interface provides visual and textual substantiation for the generated description, encouraging the urologist to be actively involved in shape evaluation. This evaluation method improves the diagnostic value of uroflowmetry and is ready for clinical implementation and introduction elsewhere.

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Preface

This thesis is a product of the research I performed within the internship concluding the technical medicine masters programme. In this research, I undertook the challenge to automate a step in diagnosis that has no golden standard. My interest aroused during a short time internship on this subject a few months earlier. I returned to Utrecht motivated to make a meaningful contribution where technology and clinical practice seemed to mismatch. Looking back on the past year, I am happy to recognise that I have brought these two worlds closer together.

My enthusiasm was often fed by the two enthusiastic supervisors prof. de Kort and prof. Geurts. They have trusted me with much liberty in independently shaping and executing this research. Their appreciation of my work and support for further possibilities motivated me to take it up a notch.

I would like to acknowledge all students that went before me and researched what in hindsight proved to be more or less succesful approaches. This all has been a valuable reconnaissance paving parts of the road for me. For you are with many, I thank Eliene, Mattiènne, Erik, Denise, Stef and Jeroen.

Contents

CHAPTER 1

Introduction

1.1 Automating uroflowmetry curve shape assessment

Uroflowmetry, the measurement of urine flow rate during urination, is widely used in diagnosis for patients with lower urinary tract symptoms (LUTS). Apart from static parameters as voided volume and maximal flow, the shape of uroflowmetry curves might also associate with voiding abnormalities [1]. Assessment of the flow shape should therefore be part of evaluating the patient's urination in diagnosis and/or evaluation of treatment efficacy [2]. It lacks standardisation when it comes to assessment of the flow shape, making it susceptible to inter- and intra-observer variability. Algorithmic evaluation of curve shape characteristics is proposed to ensure structured analysis based on standardised evaluations.

There are no concise guidelines for uroflowmetry curve shape assessment. A normal flow shape has been defined as "arc-shaped with high maximum flowrate" by the International Continence Society (ICS) but no quantitative range for this normal shape was provided. Furthermore, there is no standardisation in describing abnormal flow shapes. This leaves assessment and description of flow shape to the individual urologist. Consequently, flow shapes are described inconsistently in literature. There is variability in quantitative definitions of the shapes, when presented, and in descriptors used for comparable flow shapes [2]. Recently, Netto et al. (2020)[3] have researched inter- and intra-observer variability in defining curve shape in a large, international scale study. They show how especially inter rater reliability is low and stretch how this makes shape definition unreliable for data analysis problems. A clear and consistent description is required to maximise diagnostic utility of uroflowmetry curve shape [4].

Li et al. (2018)[2] researched articles and ICS standardisation documents for flow shape descriptors used in literature. They recommended to use only "normal", "fluctuating", "intermittent", and "plateau" descriptions with comment on symmetry and maximal flow. Fluctuating is describing an irregular curve with multiple peaks. Intermittent is defined as flow stopping and starting during a single void. Plateau is a smooth, flat curve with lower flow rate and relatively longer flow time. Normal flow is an arc- or bell shaped curve without characteristics of these other flow shapes.

These flow shapes are carefully associated with underlying pathology. Flow curves described as fluctuating indicate detrusor-sphincter-dyssynergia. Intermittent flow relates to a poorly contractile detrusor muscle or voiding with abdominal straining. Plateau flow shapes indicate outflow obstruction or impaired detrusor contractility. Uroflowmetry results are nowadays not specific for underlying causes so it should always be interpreted together with examination and other adjunct investigations. However, when shape definitions are clearly defined and consistently applied, their association with underlying pathology can be thoroughly researched. [1, 5]

Standardised, quantitative definitions for the descriptors enable automated flow shape assessment. Advantageous is that this evaluation could be incorporated precisely in a computer algorithm. Automated flow curve description is fast, easy and less prone to human errors. Consequently, its role in diagnosis will be improved.

1.2 Objectives

The primary objective of the work reported in this thesis is algorithmic description of uroflowmetry curve shapes. This description should comprise the defining features of the curve shape. It is generated automatically based on quantitative definitions, therefore a complete set of parameters must feature what is defining for the curve. The generated description is adequate and does not include an interpretation of underlying pathology.

Secondly, it is targeted to make the algorithmic generated description insightful for targeted users. For the algorithmic description to be endorsed and be adopted in clinical practice, the urologist should understand how evaluation resulted in the given description. This is done by visual representation of the quantitative definitions. Markers, lines etc. highlight (parameters representing) curve characteristics in the uroflowmetry graph. An easily accessible user interface makes switching between different visualisations possible.

This thesis is structured as follows. Chapter 2 will walk through relevant background information, among which a short overview of important conclusions from previous attempts in taking on this challenge. After information about patient selection and the measurement device, in chapter 3 is worked on the first objective. It sets the desired output description and discusses considerations in all algorithmic evaluations. Chapter 4 is about the second objective, the users interaction with the algorithm. This comprises the visualisation of shape characteristics, the final graphical user interface and results from its evaluation. The last chapter is devoted to concluding remarks and future recommendations.

CHAPTER 2

Background

2.1 Anatomy

Continuously production of urine in the kidneys fills the bladder via the ureters. The urinary bladder must be able to adapt in size to a socially adequate volume to store urine. The bladder wall is made up for the majority by muscle active in urination, the detrusor muscle. In total, the bladder is composed of smooth muscle cells, collagen and elastin. The more collagen, the less compliant the bladder is. The bladder body must contract simultaneously to achieve effective voiding. Micturition relies on detrusor contraction. Muscle energy is transferred into force (increase detrusor pressure) or muscle shortening (decrease bladder volume) depending on outflow resistance. The latter leads to flow of urine. [6, 7]

Because of characteristic properties of muscle tissue, urine flow is dependent on bladder volume. The length for the muscle fibres at which potential bladder power is largest is usually reached at volumes of 150-250 ml. For volumes higher than 400-500 ml the muscles can become overstretched, decreasing contraction power. [1]

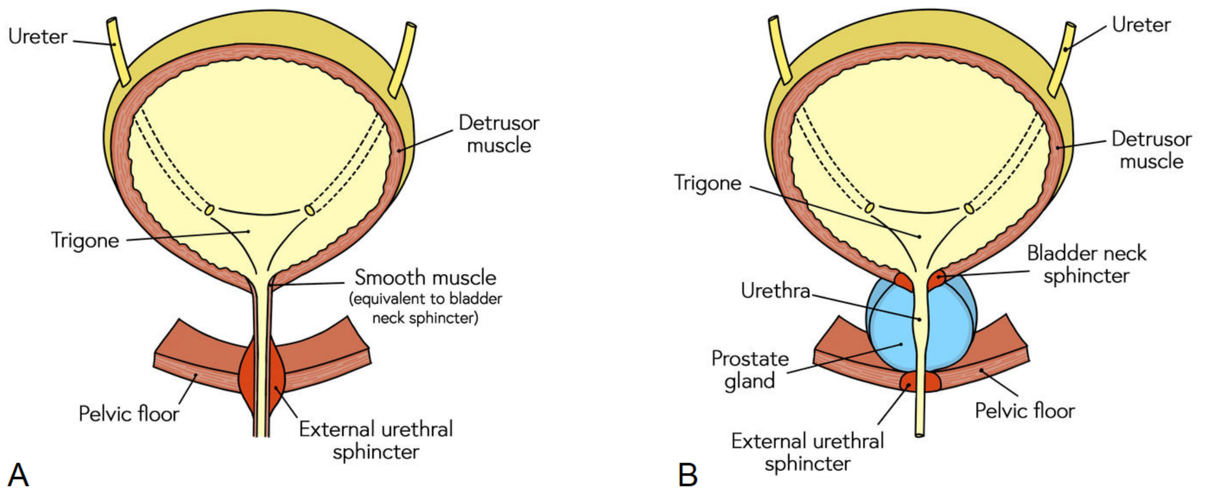

Figure 2.1: Anatomy of the bladder and urethral sphincters in A) women and B) men. Reprinted from [8].

At the bottom a funnel shaped extension of the bladder, the bladder neck, connects with the urethra (see Figure 2.1). The urethra is composed of striated and smooth muscles and is important in maintaining continence. Maintaining continence is a combination of active muscle tone and passive anatomic coaptation. The muscle structures aid in occlusion of the urethral muscles but as well in opening of the bladder neck during micturition.

There is more than one structure that acts as sphincter. Their distinction remains somewhat unclear and differs between genders. In women (Figure 2.1 A), muscle cells that extend from the proximal urethra distally form the internal sphincter. This internal smooth muscle sphincter is horseshoe-shaped. The external sphincter or rhabdosphincter consists of striated muscle in the urethra wall that gradually increases until the level of the periurethral muscles of the pelvic floor. During bladder filling the sphincters increase pressure along their circumference to maintain continence. Additional muscle structures are called compressor urethrae and urethrovaginal sphincter. In men (Figure 2.1 B), the internal sphincter locates between the bladder and the prostate. The rhabdosphincter configures near the prostatic apex. Men generally have a higher outflow resistance because of their longer urethra and the (with age increasing) obstructive effects of the prostate. [6, 7]

Innervation

The lower urinary tract receives parasympathetic, sympathetic and somatic innervation. Parasympathetic nerves that arise at sacral level excite the bladder and relax the urethra. Sympathetic nerves from spinal cord levels T10-L2 inhibit the bladder body but excite bladder neck and urethra (internal sphincter). The external urethral sphincter is excited by the somatic nervous system (spinal cord levels S2-4) and therefore under voluntary control. Thus, the storage phase of the bladder can be switched to the voiding phase either reflexively or voluntarily. Involuntary voiding occurs for example in children and patients with neuropathic bladder. [6, 7]

2.2 Uroflowmetry

Because it is both non-invasive and inexpensive, uroflowmetry is an accessible first-line screening test to provide objective and quantitative information about both storage and voiding function [1]. This information has diagnostic value and can indicate additional diagnostic tests. It also serves as a method for evaluation of therapy in follow-up. The first uroflowmeter was invented by Willard M. Drake Jr. in 1946 under the name “pissometer”, see Figure 2.2. The main structure was a balance with a container on one arm and a spring and pen on the other arm. Because of the increasing weight caused by urinating in the container the balance shifts and the other arm moves proportionally to the increase in voided volume. This is registered since the pen mounted to that arm writes on a kymograph. [9]

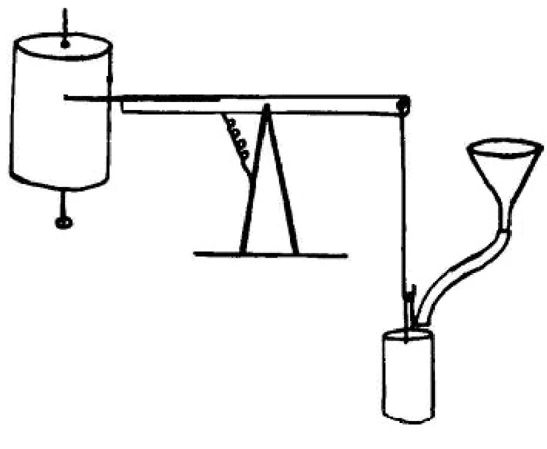

Figure 2.2: Design for first uroflowmeter by Willard M. Drake Jr. in 1946. From left to right the separate parts are a kymograph, a spring loaded balance with a writing arm, a fluid container and a collection funnel. Adapted from Chancellor (1998) [9].

In time, uroflowmetry devices were improved. Nowadays, there are various systems with differences in appearance and underlying technology. This study remains limited to free flow uroflowmetry, voiding without restriction or alteration by a bladder catheter or such. The weight transducer is most popular.

Its mechanism is most similar to Drake's device since flow is derived from mass of voided volume. Because of the force the increasing weight of urine exerts on the measurement device, a strain gauge load cell deforms appropriately. The electrical resistance changes proportionally to weight causing deformation so electrical currents measured can be calibrated for voided volumes. Two other popular mechanisms are dipstick and rotating disc. A dipstick in uroflowmetry is a capacitor vertically placed in the urine collection reservoir. The height to which it is submerged in fluid, affected by the solutes in urine, changes the electrical capacitance of the dipstick. This allows for similar calibration as for the weight cell. A rotating disc measures the power necessary to maintain a constant rotation speed. Urine landing on the disc slows the disc down so measurable additional power from the rotation motor reflects the urine flow rate. [10, 11]

When working with uroflowmetry, certain restrictions of the measuring technique must be taken into account. For example the voiding may be influenced by a set of external factors. Therefore the patient should void when they feel what they personally recognise as a normal desire to do so. Afterwards, the patient should be asked if the current voiding was representative for their usual voiding. There are technical restrictions as well. The largest follow from the set-up. Due to physics, urine breaks into drops outside the urethra. This creates irrelevant high frequencies in the recording. Secondly, the funnel shaped recording device also causes modifications to the recording because it introduces a delay that is subject to where in the funnel the urine stream lands. [1]

Test result

Regardless of the type of uroflowmeter, result of the test is a registration of the amount urine over the time in which it is voided. Flow rate is the rate of volume change over time. The time derivative is a calculation and is therefore an indirect test result. Visual presentation is a graph of voided volume and/or flow rate against time. The latter (see Figure 2.3) is subject of this research. Conventional units are millilitres per second for flow rate and seconds for voiding time. Precision and smoothness of the curve are predominantly determined by sample rate and signal processing. The ICS recommends a sample rate of 10 Hz to deal with unwanted high frequencies and a moving average with two seconds window to minimize the funnel effects [1]. Major measurement parameters are maximal and average flow rate, voided volume, flow time and time to maximum flow as standardised by the ICS [10]. These are visualised in Figure 2.3.

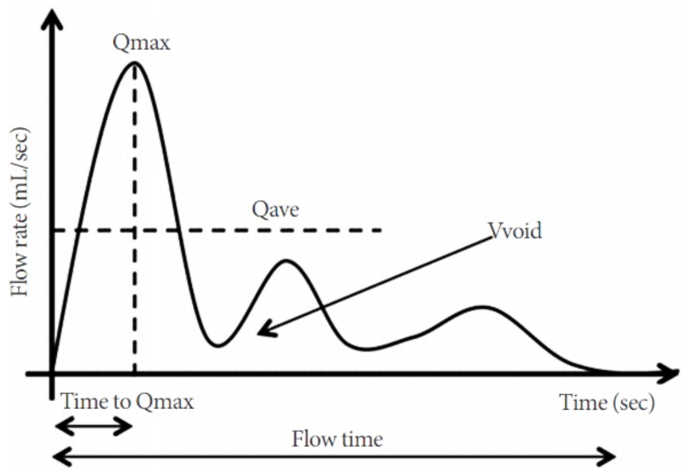

Figure 2.3: Example of an uroflow curve with parameters Qmax (maximal flow rate); Vvoid (voided volume); Qave (average flow rate); flow time, time to void in seconds; time to Qmax; time to reach Qmax in seconds. Reprinted from Chun et al. (2017) [10].

Urine flow rate measurements are influenced by detrusor contractility (neurogenic and myogenic), outflow resistance and bladder volume. Normal urine flow results in a bell-shaped curve. Reduced flow or an altered pattern could indicate underactive bladder or bladder outlet obstruction. An interrupted or straining pattern can be seen with impaired detrusor contractility, obstruction or voiding with abdominal straining. Notice all the careful formulations within these sentences since precise interpretation is yet only possible when flow rate is compared to simultaneously recorded pressure recordings in invasive urodynamics. [6, 1]

2.3 Previous research

Within a collaboration between University Medical Centre Utrecht (UMCU) and University of Twente (UT), the first step in algorithmic evaluation of uroflowmetry curves was made in 2014. Since then a series of seven student internships contributed directly to this project. This section will provide important considerations following from these internships, that are taken into account in order to reach the objective.

Classification

The first studies described the curve shapes by assigning them to one of four classes. The classes are normal, staccato, interrupted and long flow. In Figure 2.4 example curves for all classes are displayed. Classification was done by medical doctors of the urology department of UMCU. Over the course of all internships a variety of three scoring formats was used. First, experts classified the curve as one of four flow types and scored their certainty within range 1 to 10. Later, experts scored the curves for all four flow types independently, according to Vijverberg et al. (2011)[12]. This means a scoring range of 1-5, for class interrupted of 1-3. The last format asked the experts for a dependent distribution in percentages to what extent a curve belongs to either of the four classes. Table 2.1 contains the reported measures for inter- and intra observer variability. It can be concluded that agreement is far from perfect. Discussion of these results with the urologists revealed doubtful classifications of curves since they could be placed in more than one class. Therefore classification is deemed insufficient and a less restrictive description method should be pursued.

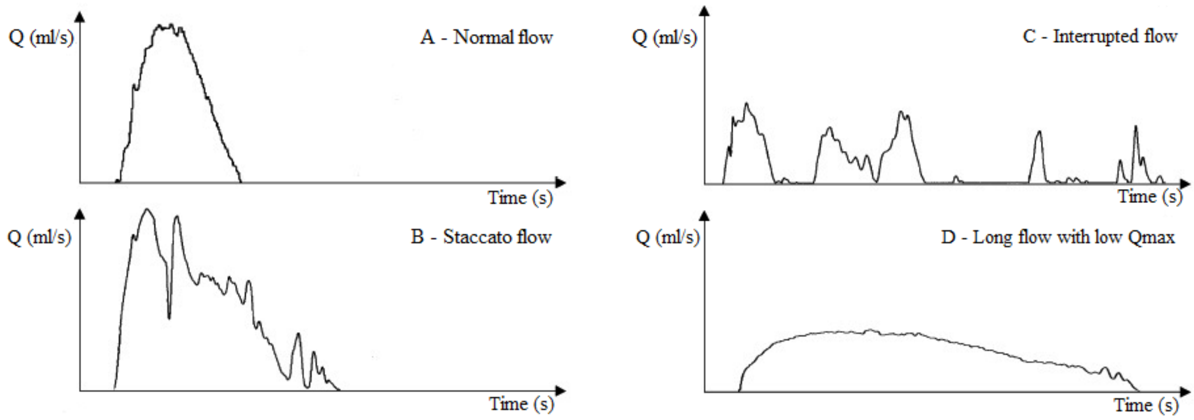

Figure 2.4: Reference curves for the four classes: A- normal flow, B- staccato flow, C- interrupted flow and D-long flow. Adapted from Brand [13].

Machine learning

Baas, an applied mathematics student, developed machine learning to generate algorithms for automatic classification [18]. After extracting possibly interesting features from the measurement, multiple machine learning classifier algorithms (classifiers) were trained. Training is the mapping of the feature values in relation to the different outcomes. The expert classifications discussed above were used as reference. Subsequently, a not yet seen uroflowmetry measurement could be classified by the algorithm. The regression

Table 2.1: Reported inter- and intra observer variability measures for different data sets and scoring methods. Kappa level of agreement is classified according to Landis et al. [14]. AUC MAE is area under the curve of the mean absolute error plot. * 1: one of four classes, 2: independent scores Vijverberg[12] 3: percentage distribution. ** Different number of experts scored three datasets, results are averages weighted for database size.

Researcher (no. of curves) {scoring method*}	No. of experts	Kappa	Kappa level of agreement	AUC MAE	Level of agreement
Inter observer variability					
Kamp, van der [15] (665) {1}	3	0.58	Moderate	0.82	-
Brand [13] (90) {1}	3	0.34	Fair	-	-
Boele [16] (84) {2}	3-5**	0.36	Fair	0.69	59 %
Haan, de [17] (100) {3}	4	-	-	0.84	37 %
Intra observer variability					
Kamp, van der [15] (100) {1}	3	0.86	Almost perfect	-	-
Brand [13] (10) {1}	3	-	-	-	87 %
Boele [16] (18) {2}	3-5**	0.73	Substantial	-	79 %
Haan, de [17] (17) {3}	4	-	-	0.90	70 %

forest classifier yielded the best results with an estimated accuracy of 97% on new measurements [18]. This showed a classifier could be trained well on a dataset of fixed expert reference classifications.

In the process of clinical validation was found that the reported accuracy of the machine learning classifier was overestimated. The algorithm lost accuracy when compared to expert classifications of new measurements. This is attributed to the subjective nature of these classifications. All disadvantages from the lack in consistency in the expert reference scoring apply here as well. The classifiers are inherently dependent on the expert reference scoring since they must learn from example classifications. [17]

Component based analysis

Validation of the machine learning classifier pointed out that automatic classification of the curve will not be fully endorsed when it works as a black box and provides its own conclusion that is not always accurate. Algorithmic evaluation of curves will probably be best accepted when it provides insight in how the conclusion was formed. It should improve objectivity and consensus between experts when it intelligently evaluates essential characteristics of the curve and in that way draws attention to the important information and presents this in a coherent way.

In one of the later internships, Haaren explored component-based analysis of uroflowmetry curves that provides insight in the analysis [19]. It allowed multiple descriptors to be applied to a single curve based on simple threshold evaluations. Furthermore it used visual indicators for the different parameters and their corresponding thresholds. This attempt proved to be very valuable since it removed dependability on training data subject to variance and connected well with clinicians wish to better understand the process of automatic curve description. Thresholds were, however, not very well substantiated and the presentation of information was quite overwhelming. Due to the promising results and clear starting points for improvement this direction was continued in the current research.

CHAPTER 3

Algorithm generation

3.1 Data acquisition

Uroflowmetry measurements used in this study are recent measurements of patients with LUT dysfunction symptoms from the urology outpatient clinic of UMCU. Patients are of both genders, aged 18 and up. All uroflowmetry measurements in the period from early July to mid-September 2019 are obtained, there is no selection on symptoms or diagnosis in hindsight. Data is fully anonymous except for gender. All patients are over 18 years old, measurements with a voided volume below 100 ml were excluded. This resulted in 219 uroflowmetry measurements available for evaluation. Of these measurements 145 (66%) were of male patients.

Uroflowmetry was done when patients felt normal desire to void. They were instructed to void like they normally would on a regular toilet, in a position of their preference. No additional action was required of the patients and measurements cannot be traced back to individual persons. The medical research ethical committee METC Utrecht ruled therefore that this research is not subject to the Medical Research Involving Human Subjects Act (WMO).

Measurements are performed on the FlowClean uroflowtoilet (Urotex, The Netherlands), a weight transducer uroflowmeter. The device has a sample rate of 10 Hz, device software filters the signals with a moving average filter with window length of one second. This window length is shorter than the two seconds as recommended by the ICS.

3.2 Set desired description

Li et. al. (2018)[2] did a proposal for flow shape description in conclusion of their review article. Quote: "*We suggest that only 'normal', 'fluctuating', 'intermittent', and 'plateau' descriptions, with additional comment on symmetry and* QMAX*, be used to describe urine flow rate curve shape, and the definitions for these descriptors should follow the terms in the* ICS *standardisation documents* [2]." These descriptors refer to actual shape and are more easily defined than descriptions of the presumed cause of the shape. In the current research was chosen to stay close to this proposition. However, 'bell shaped' will be used instead of 'normal'. Normal urine flow results in a bell shaped curve, the latter being a shape descriptor instead of a diagnostic interpretation. Therefore it fits better with the goal of shape description and among the other descriptors. Comment on symmetry and QMAX (maximal flow rate) was not further defined in the proposal. In the current research is chosen for simple, not quantitative commentary on these characteristics. When maximal flow is considerably higher or lower than reference value this will be mentioned. Symmetry will be categorically distinguished between asymmetrical and fairly symmetrical.

The description described above is additional to essential information that uroflowmetry currently already presents. The graph depicting urine flow rate over time and standard parameters should remain within the test output. Most important parameters are QMAX, voided volume and total flow time. As standardised in the ICS technical report, uroflowmetry documentation should contain information in a certain format [1]. This format is VOID = Maximum Flow Rate/Volume Voided/Post Void Residual Volume. Therefore this was made part of the description except for residual bladder volume since it does not follow from the time/flow rate relationship.

3.3 Establish algorithm

In the algorithm all steps towards the desired description above are automated. Input is just the time and flow rate vector of the uroflowmetry measurement and the gender of the patient. To algorithmically evaluate applicability of the descriptors, quantitative components must be found for discriminating characteristics corresponding to those descriptors. The review by Li provides some parameters with quantitative thresholds. When sufficient and unambiguous these are adapted in the algorithm. However often directives for the curve shape descriptors were incomplete or contradict each other. Steps undertaken to come to a applicable evaluation are described below. Multiple times will be referred to a consensus meeting. This means that the challenge in question is discussed in a meeting with three to five medical doctors of the urology department of UMCU under supervision of the researcher. These doctors are tasked with interpretation of uroflowmetry measurements in their day to day work. Multiple uroflowmetry curves are discussed then with output (classification, selection of timestamps) depending on the question. In this way observer variability is of far less influence. Curve parameter thresholds referred to in text are accumulated in Table 3.1.

Start and stop of voiding

The initial step is assuring that the measurement data is fit for automatic analysis. While evaluating performance of algorithmic evaluation presented in previous research was found that often the time vector of the measurement is considerably longer than what urologists describe as relevant voiding. As will be seen, the majority of evaluated parameters is time dependent. Therefore correct definition of start and end of relevant voiding are important for the correct description. These points were not clearly defined before [2]. Together with technical medicine intern S. Pham work was done on adequate detection of relevant flow. His report reflects on four different algorithms [20]. These algorithms were compared with expert defined endpoints in the consensus meeting. Based on this information a combination of a flow- and volume threshold for evaluation of start and stop of voiding were applied in the description algorithm of the current study. As will be explained this evaluation has multiple applications.

Very low flow is not regarded as relevant flow. Therefore flow below the threshold of 0.5 ml/s is seen as no voiding in analysis. When flow rate crosses the threshold value this marks the start or stop of flow. Parts of flow are consequently defined from the first to last joined value above threshold. In interrupted flows, the flow rate rises again after it dropped below the threshold. These parts might be relevant since intermittent voiding is one of the characteristic flow shapes. To distinguish between intermittent voiding and eventual dribbling exceeding the flow threshold, the volume threshold was applied. A part of flow is deemed relevant when the volume voided in that part is at least 5 ml. Voided volume is equal to the area under the curve, approached by integration with MATLAB (version 2018b, Mathworks, USA) built in function *trapz*. When a flow curve consist of two of more relevant flow parts and thus at least an interruption the descriptor intermittent is applicable [2].

Previous research proposed 0.2 ml/s and 5 ml for flow- and volume threshold respectively [15]. Pham proposed the thresholds 1 ml/s and 2 ml based on a droplet simulation experiment, but due to a combination of limitations of this approach was not chosen to substitute the thresholds for these values. The flow threshold was increased to 0.5 ml/s in consultation with the urologists in Utrecht and according to the more recent proposal from a study by Gammie et al. (2016)[21]. For threshold 0.2 ml/s sometimes a for the eye evidently intermittent curve was described as fluctuating because the interruption was not recognised.

Another product of this evaluation is the main flow part. In flows that are intermittent, the main flow part is the part with the largest voided volume. In this study that always corresponds to the part in which QMAX is found. Evaluation of the rest of the flow part characteristics will concentrate on the main part. With the notion that these curves are intermittent, analysis of the main flow part provides most additional information about the time volume relationship while voiding. Figure 3.1 shows the differences between original flow, relevant flow and main flow part for an example flow curve.

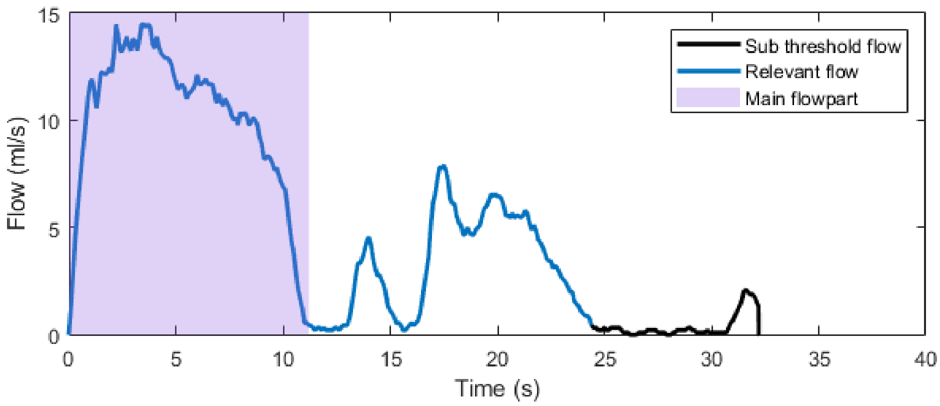

Figure 3.1: This line represents the complete flow time graph resulting from uroflowmetry in a single patient. The part that is black is deemed irrelevant because flow does not exceed 0.5 ml/s and when it does the volume excreted is less than 5 ml. As a result only the blue part of the curve is shown and used for analysis. The remainder is separated by flow (almost) reaching baseline. Of these three parts the first corresponds to the largest volume excreted and is considered the main flow part.

Fluctuations

The review by Li et al. presents three quantitative thresholds. Equal to the square root of Qmax in ml/s, to 20% of Qmax in ml/s and 5 ml/s [2]. A sub-study comparison of these thresholds was executed (Appendix IV). Mutual differences were investigated and the outcome per threshold was compared with expert classification yielded in a consensus meeting. This resulted in selection of threshold 20% of Qmax (ml/s).

Fluctuations were identified by detection of their peaks. Peak detection was executed with the MATLAB built in function *findpeaks*. This function finds local maxima by comparing sample values with adjacent values. To limit detected peaks to only the ones exceeding the threshold, the setting *MinPeakProminence* was used. The drop in signal value on either side before the signal attains a higher value is calculated. The smallest of the two is the prominence of that peak. Peak detection is limited to peaks where the prominence is at least 20% of Qmax.

Due to the calculation of prominence, two very close local maxima with the exact same flow rate are both detected as peak. They are however part of the same peak. The function has two output arguments: peak values and their corresponding instances. When two succeeding peaks have the same value and are within one second from each other, the second peak is deleted.

The ICS defines fluctuating flow as 'multiple peaks during a period of continuous urine flow' [22]. Therefore, peak detection is applied only to the main flow part in interrupted flow measurements. The amount of fluctuations is the number of peaks exceeding threshold value additional to the peak corresponding to Qmax. The peak corresponding with the maximal flow is also detected but this is not labelled as fluctuation. Therefore the vector with peak instances is compared to the instance of Qmax resulting in the deletion of this point. If there is one or more fluctuations, the curve is described as fluctuating.

Plateau

For the plateau descriptor multiple definitions are defined. Taken together, plateau curves have relatively longer flow time and are flattened with a constant Qmax very close to the average flow. More specific, quantitative definitions are aimed at different aspects of this description. The flattened shape with high average flow results in a high ratio of average flow to maximal flow (Qr (1)). As threshold for plateau, this ratio should be at least 0.8 [23]. The relative length of flow time is represented in parameter TQ (s^2/ml), the ratio of voiding time to Qmax. A plateau defined by a flattened shape with constant Qmax is restricted to variations less than 1 ml/s for at least 4 seconds [24, 25]. In case of a high Qr, the plateau characteristic is most complete since in these curves the maximal flow is most evidently restricted. However, with the currently aimed at shape description, different shape characteristics may be applicable for the same curve. When the plateau characteristic is present but not reflected in the entire duration of the measurement the Qr threshold is hard to be met. The other definitions are combined to also selectively recognise flow curves with a shorter plateau. When a plateau is present (variations >1 ml/s for at least 4 seconds) and the voiding time is relatively long (TQ > 2 s^2/ml [26]) the curve is also described as plateau flow. Essential requirement is that the point of Qmax lies within this interval otherwise the plateau does not represent a flattened curve.

Bell shape

Normal flow has been described accordingly in most articles. Definitions are bell shaped, approximately symmetrical, uninterrupted and without rapid amplitude changes [2]. Because all other characteristics are treated separately, now will be focussed on the bell shape. For this shape different thresholds are used for the parameters Qr and TQ. Characteristic for bell shaped curves is Qr higher than 0.63 and TQ lower than 1.28 s^2/ml [27]. A third relevant parameter is the ratio of time after Qmax to time before Qmax (DTAT (1)). Reported threshold values for bell shape; $0.85 <$ DTAT < 2.12 [27] and 2.33 [28], are now combined in $0.85 <$ DTAT < 2.33. Nishimoto et al. (1994)[27] are the only ones reporting a combination of three parameters. Other articles in the Li review used shape characteristics analogous to one or two of these three requirements. Therefore in this research a flow curve is described as bell shaped when two of these three parameters are within threshold limits. The conditions for plateau and bell shape flow are not automatically mutually exclusive. However, in perception, the presence of a plateau cannot coexist with a bell shaped pattern. Therefore, in the algorithm evaluation for the plateau descriptor happens first and when it is applicable this prevents the curve from being described as bell shaped.

Maximal flow

Maximum and average flow rates are related to volume. Research towards this relationship has resulted in multiple nomograms for either voided volume or bladder volume. These provide insight in normal limits for maximal flow rate, aiding in clinical interpretation of uroflowmetry. There is no standardised preference for a single nomogram. For adaptation in the current algorithm was chosen for the Liverpool nomograms by Haylen et al. (1989)[29]. That study produced nomograms for a wide range of voided volume for men/women separately. Voided volume is a direct result of uroflowmetry and using this does not require separate measurement of residual bladder volume. The wide range of flows for both genders makes the nomogram most suitable to the wide variety of the algorithm's target population. The nomograms for women and men can be seen in Figure 3.2. The equations of these graphs (50th percentiles) were supplied in the original article [29] and are implemented in the algorithm.

When the maximum flow rate of a flow curve is close to the reference maximum corresponding with the voided volume, the description is not altered. When it is substantially higher or lower it is referred to in the description. Boundaries for substantial are the 25th an 75th percentile graphs of the nomogram (see Figure 3.2 A and B). For these graphs representing the percentile lines no equations were supplied. Boundaries are therefore based on the deviation of the graphs in respect to the 50th percentile graph. This deviation of the 25th an 75th percentile was approached by 4 ml/s at 100 ml voided volume linearly increasing to 6 ml/s for men and to 10 ml/s for women at 600 ml. The nomogram can not be extrapolated for volumes higher than 600 ml because it can not be assumed that the corresponding maximum flow keeps increasing as well. At a certain point flow rate will be restricted by anatomical structures instead of bladder volume. Therefore values in measurements with voided volume over 600 ml will be compared with reference values corresponding to 600 ml voided volume. Volumes below 100 ml voided volume do not occur due to inclusion criteria.

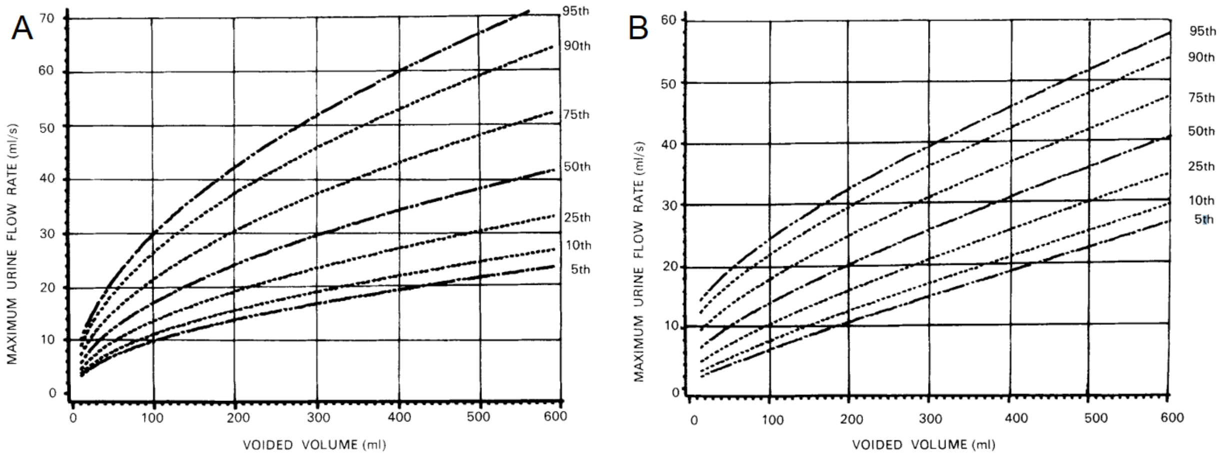

Figure 3.2: Liverpool nomograms for maximum urine flow rate. A) In women, B) In men under 50 years (median age 35). Dotted lines represent the 5th, 10th etc. percentile. Reprinted from Haylen et al. (1989) [29].

Symmetry

In Li's review article, comment on symmetry was suggested as additional part of uroflowmetry shape evaluation [2]. No strong substantiation for describing this characteristic was provided in that or other articles. The review points out how it provides nuance among the four descriptors, preventing the need for extra descriptors. For example the descriptor "compressive" should not be used since it implies a cause. This shape can now be described as asymmetric flow with low maximum flow. Just like the other descriptors, additional diagnostic value of reporting symmetry can be retrospectively evaluated when compared to additional diagnostic tests. There is no precedent in systematically determining symmetry of uroflowmetry curves. The aim is evaluating symmetry with respect to a vertical symmetry axis. A flow shape would be perfectly symmetric when this axes is at the point of QMAX with equal curve slope on either side. Symmetry is mentioned as characteristic of bell shaped curves. Of parameters related to this descriptor, DTAT is best in comparing the slope before and after maximum flow. Experimenting with this parameter for symmetry pointed out that it is too dependent on the time stamp of QMAX. When qmax is for example caused by a fluctuation or is in reality not very restricted to that single point in case of a plateau, DTAT did not successfully represent symmetry.

A more successful way of comparing how flow rate increases and decreases was implemented from the internship of E. Biel [30]. This student researched new parameters of uroflowmetry curves among which the maximal and minimal slope of the curve. These were calculated as tangents to a smoothed version of the curve achieved by curve fitting. According to that study a fourth order polynomial fit and a 0.10 Hz low-pass Butterworth filter performed best. In consultation with Biel was expressed that the latter was likely to perform best when applied to a wider variety of uroflowmetry shapes because of inherent properties of the polynomial fit. As measure for symmetry is chosen for the point where the maximal and minimal slope tangents intersect. An example of a fitted curve with its tangents can be seen in Figure 4.3 D. The parameter SIP is the intersection time normalised by dividing it by the total voiding time. A range for this parameter that corresponds to symmetric curves was set with aid of another consensus meeting. A team of three physicians classified 40 curves as 'asymmetrical' or 'fairly symmetrical' unanimously. Of this set 17 curves were classified fairly symmetrical, SIP 0.21 ± 0.07 (median $\pm$ standard deviation). The remaining 23 asymmetrical curves had SIP value 0.09 ± 0.06. Threshold optimization was done to best match algorithmic classification to this consensus classification. This way a lower bound of SIP $= 0.15$ was found. No curve was classified as asymmetrical with a high SIP value. What follows from the range for DTAT in bell shape definition (0.85-2.33), is that skewness to the left is anticipated more than skewness to the right. Therefore the upper bound for SIP was now carefully set at 0.6.

Table 3.1: Overview for parameter thresholds. Thresholds marked with '*' are part of simultaneous evaluation of multiple parameters, see text for details.

Parameter	**Description**	**Thresholds**
interruptions	Number interruptions between parts of flow	Intermittent; interruptions > 0, Flow rate threshold part of flow = 0.5 ml/s, Volume threshold part of flow = 5 ml
fluctuations	Number of fluctuations in flow rate above threshold	Fluctuating; fluctuations > 0, Fluctuation threshold = 0.2 × Qmax (ml/s)
Qr	Ratio of average flow rate to maximal flow rate	Plateau; Qr > 0.8 Bell shape; Qr > 0.63*
TQ	Ratio of voiding time to maximal flow rate	Plateau; TQ > 2 s^2/ml* Bell shape; TQ < 1.28 s^2/ml*
plateau	Duration of constant flow with no fluctuations above threshold	Plateau; plateau > 4 s*, Fluctuation threshold = 1 ml/s
DTAT	Ratio of time after maximal flow to time before maximal flow	Bell shape; $0.85 <$ DTAT < 2.33*
Qmax	Maximal flow rate	Low/ high Qmax outside first and third quartile of Liverpool nomograms
SIP	Symmetry intersection point of tangents to fitted curve	Fairly symmetric $0.15 <$ SIP < 0.6

CHAPTER 4

User interaction

4.1 Visualisation

This section focusses on considerations in presenting data for end users. First there is attention for presentation of the standard parameters and the time flow rate graph. Then will be addressed how additional parameters and the algorithmic description are made insightful. This generally consists of a visual and a textual component. Relevant characteristics of the time flow rate graph are highlighted and supporting text or additional parameters are presented.

Original uroflowmetry

The ICS technical report recommended the following standards for the time flow rate graph: a range of 0-50 ml/s for flow rate and that 1 ml/s on the y-axis corresponds to 1 ml on the x-axis. Additionally it contains recommendations on the presentation and documentation of some parameters. Considering the technical accuracy of uroflowmetry, flow rate (ml/s) should be rounded to integers. Voided volume should be rounded to nearest plural of 10 ml. [1]

Reference curve and maximal flow

To present context for the shape of the uroflowmetry curve, a reference curve is plotted together with the time flow rate graph. This reference curve is based on the bell shape corresponding to normal voiding adapted to the current measurement. Starting point to make it measurement specific is the relationship between maximal flow rate and voided volume of the Liverpool nomograms. For the specific void and patient gender the resulting maximal flow is set as tip of the reference curve. The curve itself is based on the generic formula for statistic normal distribution since this is a bell shape as well. A slight adjustment was made to delete the lowest part of this distribution since it is to flat for a uroflowmetry measurement. The value that normally represents the standard deviation an influences the width of the graph was empirically adjusted so that the area under the reference curve (equal to volume) is about equal to the voided volume of the measurement. This value scales with voided volume. The specific creation of this reference curve with the adjusted formula can be found in Appendix III. The result can be seen in Figure 4.1. This figure additionally shows how high or low maximal flow in the description is made insightful. Horizontal lines above and below the reference curve Qmax show boundaries for this evaluation.

Fluctuations and interruptions

Providing insight in the descriptors fluctuating and intermittent is straightforward. The applicability of these descriptors follows directly from the presence of respectively fluctuations and interruptions. Substantiation consists of pointing out this presence. In Figure 4.2 can be seen how detected fluctuations and interruptions are emphasized. Fluctuation indicators are placed on detected peaks above fluctuation threshold. The peak corresponding with Qmax is a different color since it is a peak above threshold but it is not considered a fluctuation. Interruptions are usually very short hence they are marked as a single point. This point is located at the middle of the interruption. Textual output is the number of fluctuations/interruptions or mention that there are none.

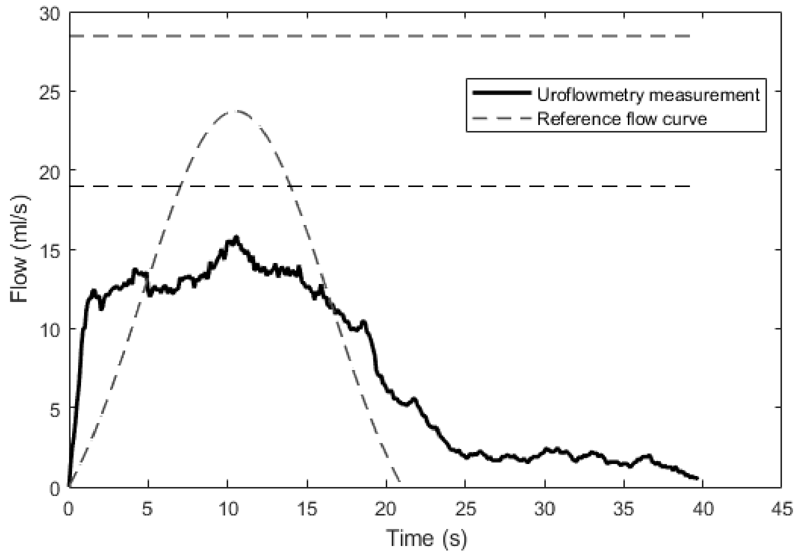

Figure 4.1: The dotted curve is the reference curve for the voided volume in the uroflowmetry measurement. Qmax of this reference curve follows from voided volume and gender using the Liverpool nomograms. Horizontal dotted lines equal the 25th and 75th percentile of the nomogram. Consequently, this curve will be described as having a low maximum flow.

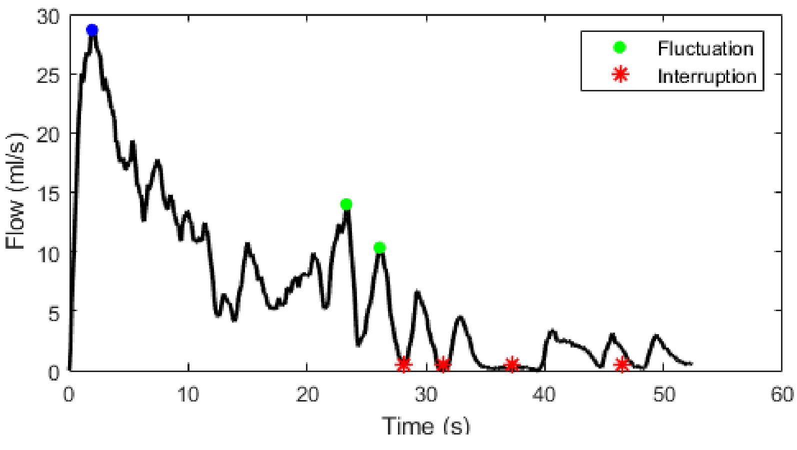

Figure 4.2: Fluctuations and interruptions highlighted in an uroflowmetry curve. Green dots are for fluctuation peaks, the peak corresponding with Qmax has a blue dot. A red asterisk indicates the middle of an interruption. The last asterisk is simultaneous with some flow. This means that this part of flow does not meet the flow and/or volume threshold for relevant flow.

Additional parameters

The additional parameters Qr, TQ and DTAT are of relevance for the descriptor bell shape and, except for the latter, for the descriptor plateau. Values for these parameters are presented when these descriptors are considered. Here, visualisation aims at showing how the parameters are calculated and how they relate to threshold values. To keep the imagery clear, these visualisations are only shown when parameter values are deviating. The results can be seen in Figure 4.3 A-C. Visualisation of symmetry is based in full on the components of its calculation. These can be seen in Figure 4.3 D.

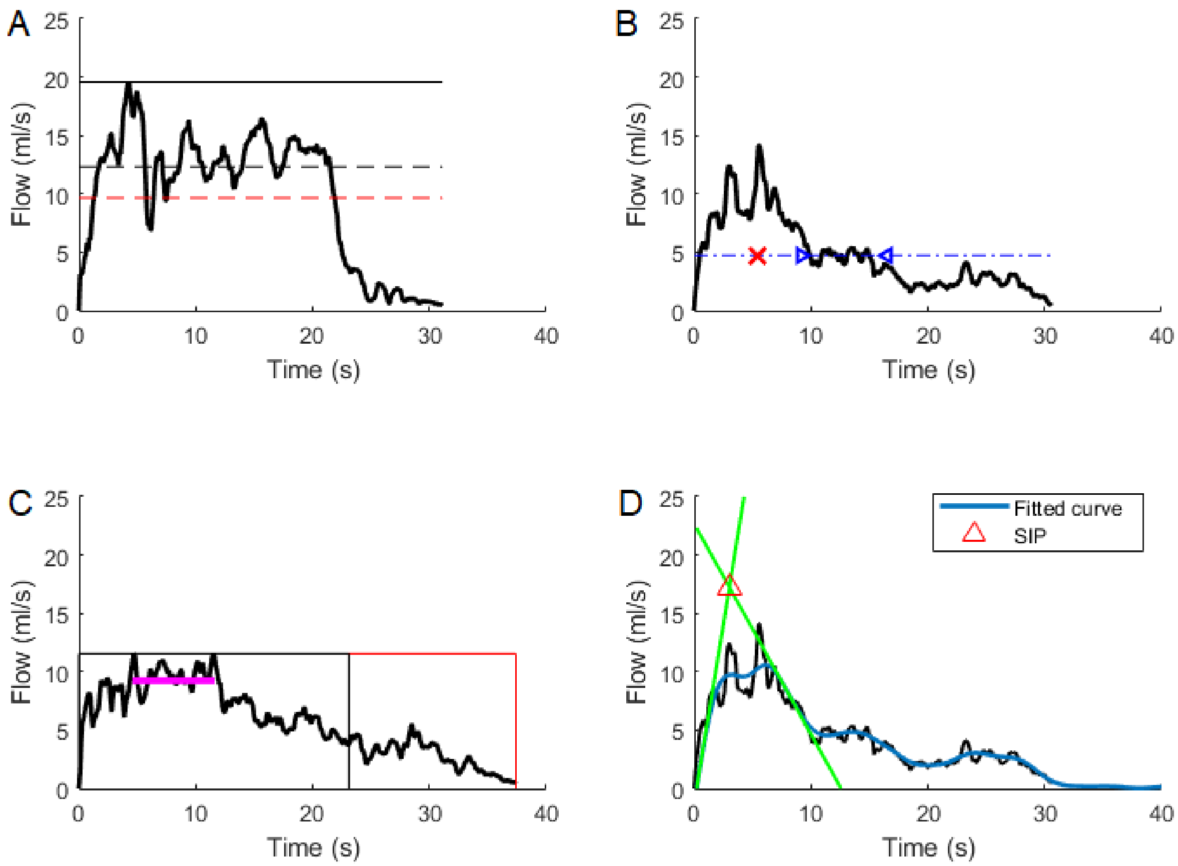

Figure 4.3: Additional parameter visualisations. A) Qmean (red) is lower than visualised Qr threshold 0.63×Qmax. B) For this curve DTAT is too high as shown with the position of Qmax outside the indicated interval. C) A plateau of 7 seconds is highlighted and the curve shows to be longer than the TQ threshold indicates. D) Fitted 0.1 Hz low pass Butterworth filtered curve with minimal and maximal slope tangents. The red indicator is for the symmetry intersection point.

To visualize Qr, two black horizontal lines are shown, one at the level of Qmax and one at the threshold value. This is either 0.63 × Qmax or 0.8 × Qmax. A third horizontal line in red shows the actual value for Qmean. Considering bell shape it shows that Qr is below 0.63 and therefore not bells shape. In contrary, for plateau curves where Qr >0.8, the red line for Qmean is above the threshold line.

For parameter TQ the ratio of voiding time to Qmax is visualised by a square through Qmax and end of voiding. A black square is defined by Qmax and the time defined by the threshold, 1.28 or 2 s^2/ml multiplied with Qmax depending on the evaluated descriptor. This square is elongated in red until end of voiding to represent the actual value for TQ.

Parameter DTAT reflects the ratio of the time after to the time before Qmax. It is therefore dependent on the timing of Qmax relative to the voiding time. A horizontal line from start to end of voiding is drawn and the segment where occurrence of Qmax would lead to DTAT value between boundaries is marked with arrows. The actual timing of Qmax is marked with a red cross.

A plateau is as previously described as constant flow with fluctuations <1 ml/s for at least 4 seconds. When a plateau is found, it is highlighted with a thick horizontal line and its duration is mentioned. Due to the steps in the algorithm this phenomenon is always shown along the visualisation of high TQ, just like in Figure 4.3 C.

4.2 Graphical user interface

To make the algorithm and its supporting visualisations available for clinicians, they are combined in a graphical user interface or GUI. This was created with MATLAB GUIDE (version 2.5, Mathworks, USA). This GUI is constantly updated alongside the algorithm itself together with two urologists. The end result can be seen in Figure 4.4. Most dominantly displayed is the time flow rate graph with the bell shaped reference curve. The graph has a grid to aid in connecting axis values to data points. On the right, the standard parameters are presented. On the same side in the middle the algorithmically generated description is displayed. This is only the result, insight it its substantiation is provided by the six buttons below it. In the box 'Explanatory', there is a button for all four descriptors, symmetry and maximal flow.

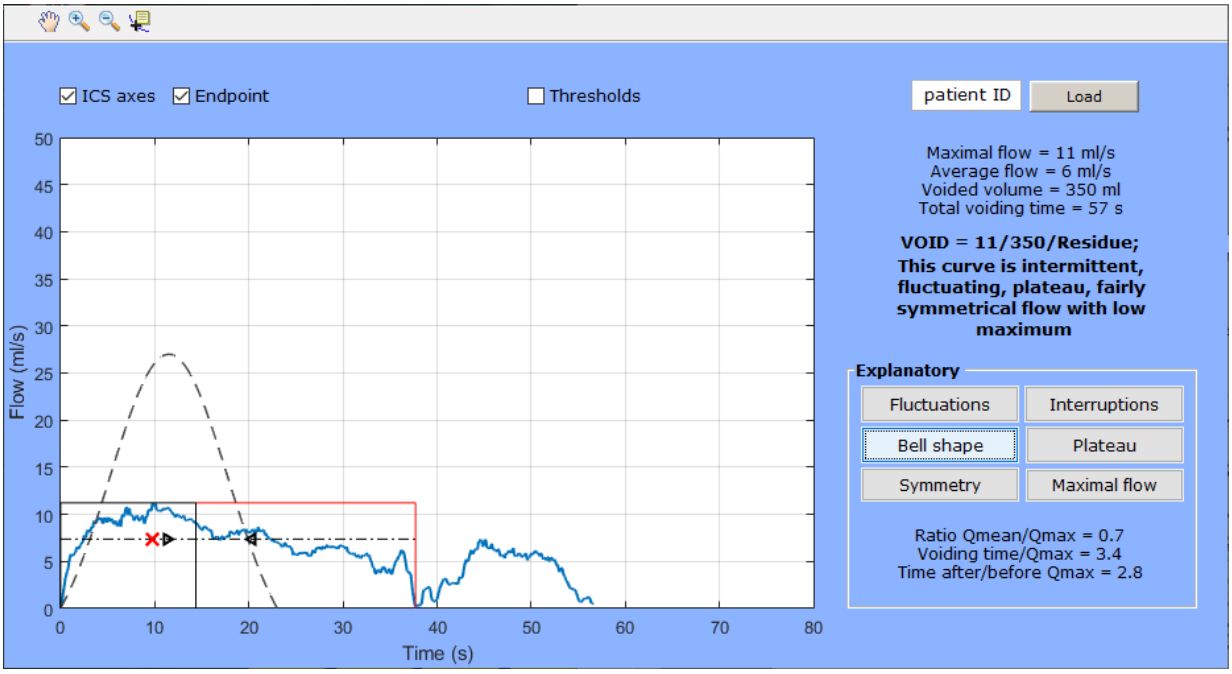

Figure 4.4: Graphical user interface for descriptive algorithm and visualisations. In this example the button 'Bell shape' is clicked on so the for this descriptor relevant parameters are displayed on the right. Visualisations of TQ and DTAT show how these parameters do not meet threshold values, explaining why this descriptor is not present in the generated description.

The time flow rate graph presents the relevant flow with ICS recommendations. The x-axis is 80 s long to prevent the graph from becoming to small and almost all curves fit within this range. Also not every curves fits vertically with the ICS recommended 50 ml/s. This, and the selection of relevant flow for the graph are aimed at presenting the important information in the clearest, most constant way but in doing so some information might be lost. Therefore these two steps can be neglected by deselecting the tick boxes 'ICS axes' and 'Endpoint'. The tools in the grey lint provide extra options in display of the graph, such as zooming and reading data points. The third tick box reads 'Thresholds' and enables the possibility to adjust the flow rate and volume thresholds for determination of the relevant flow. This is aimed at future improvement of the algorithm.

4.3 Evaluation of usability

The algorithm came to be in three versions. After every version followed an evaluation with clinicians to match with demands of end-users. This consisted of five open questions considering algorithm performance and a validated questionnaire for user experience.

- Does the algorithm make a structural error? If yes, which?
- What is abundant in the current display/functionality?
- What is missing in the current display/functionality?
- What must change in order for you to put the algorithm into practice?
- Other remarks/advice.

Especially the evaluation for bell shape and plateau benefited from these evaluation steps. Evaluation for these descriptors involves the most parameters and share parameters. By evaluating description for a large amount of curves, combination of these evaluations was improved greatly by adapting combinations of the thresholds. Several attempts for defining symmetry were tried and these evaluation sessions aided in selection of the currently presented method. With respect to the interface, evaluation mainly led to deletion of buttons. In the first version, aspects that are now directly visible were hidden behind buttons as can be seen in Appendix I.

In evaluation of the last version no weaknesses were found any more by the three consulted urologists in Utrecht. They expressed that they found the generated description complete and thorough and would adopt this as their professional evaluation. The only step that separates the algorithm from being used in clinical practice is implementation. This is already done for UMC Utrecht. When the physician searches for a patient identification number, dedicated code distils the time flow rate from the measurement device output. This has a standard build up that allows storage of additional information. Therefore information relevant for analysis and or description can automatically serve as input for the algorithm. Patient gender and age improve the reference flow and post void residual volume could be filled in in the description. Due to information technology aspects, this step will vary between institutions and uroflowmetry devices.

A positive experience with the algorithm and its interface is essential for clinical interpretation. To evaluate this, the end-user experience questionnaire by Laugwitz et al. (2008)[31] is used. This questionnaire "*...should allow the users in a very simple and immediate way to express feelings, impressions, and attitudes that arise when experiencing the product under investigation* [31]". This is done by a list of 26 items with two opposing adjectives with a seven stage scale between them. The English version of this questionnaire can be found in Appendix II. All these items could be divided in seven domains: attractiveness, perspicuity, efficiency, dependability, stimulation and novelty. Attractiveness represents the overall impression of the product and whether it is likeable or not. Perspicuity reflects how easy it is to get familiar with using the product. An easy and fast workaround is reflected in efficiency. Dependability is about feeling in control and secure and predictable outcomes. Stimulation is high when it is exciting and motivating to use the product and novelty reflects innovation and creativity. Laugwitz et al. also provided a data analysis tool in a Microsoft Excel sheet for correct evaluation of the obtained data. [31]

The questionnaire was filled out by three urologists for version 3 of the GUI. Evaluation with the data analysis tool resulted in a value within a range from -3 to 3 for all seven domains, see Table 4.1. According to Laugwitz et al. a score higher than 0.8 translates to positive evaluation. All scores are much higher, resulting in an average overall score of 2.2 reflecting excellent user experience. A contributing factor could be that two out of three end-users were the urologists involved with improvement of the user interface. However, for the third urologist this was the first encounter and the predominantly low variance shows that score was quite like the rest. In Figure 4.5, the mean score for all items of the questionnaire is visible. This figure explains the higher variance for perspicuity and efficiency. Within efficiency, slow/fast has a noticeable lower score than other items within that domain. However still positively evaluated, this reflects room for improvement in performance speed. High variance and the relatively lower score for perspicuity are traced back to the neutral -0.3 score on complicated/easy. The analysis tool recognised a inconsistency within the domain, indicating that the end-user might misunderstood an item. One user rated complicated/easy with -3. Verbal elucidation on this score pointed out that this user wanted to express experiencing the algorithm as sophisticated.

Table 4.1: Mean and variance within a range from -3 (horribly bad) to 3 (extremely good) for seven domains of user experience.

Domain	Mean	Variance
Attractiveness	2.4	0.1
Perspicuity	1.8	0.8
Efficiency	2.2	1.1
Dependability	2.1	0.3
Stimulation	2.4	0.3
Novelty	2.4	0.2

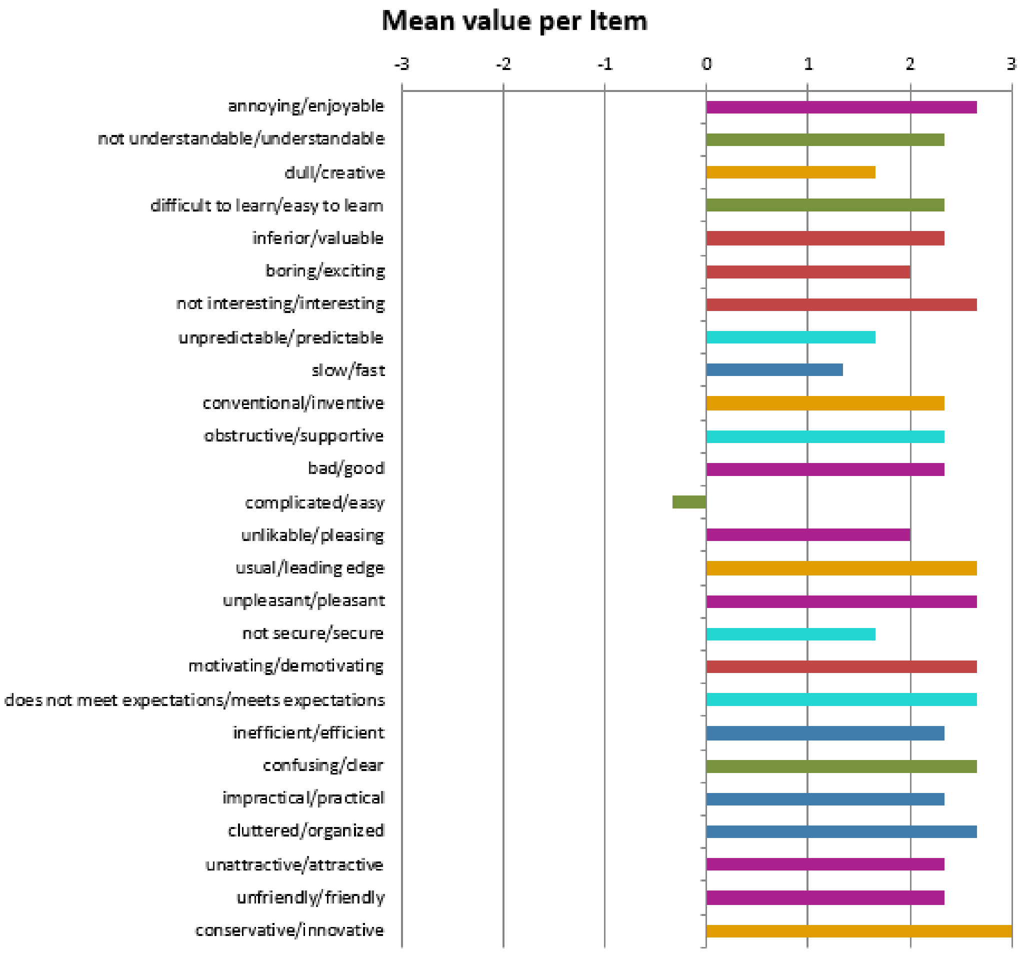

Figure 4.5: Mean score for all adjectives within a range from -3 (horribly bad) to 3 (extremely good) for the separate adjectives assessing user experience. The seven domains are marked with color, purple for attractiveness, green for perspicuity, dark blue for efficiency, light blue for dependability, red for stimulation and yellow for novelty.

CHAPTER 5

Outlook and conclusions

5.1 Future recommendations

The algorithm achieved high approval ratings in this single centre. All of the algorithmic evaluation, its resulting shape description, the visual substantiation and use of the combining user interface were very well received in UMC Utrecht. That is very promising since previously was determined that expert opinion was not unambiguous here (Table 2.1). The foundation for the algorithmic evaluations came from consulting articles and ICS standardisation documents. Available information did not cover all aspects or was not unanimous. Choices are made as objectively as possible by basing them on judgements made within the consensus meetings. This method might have made the algorithm specific for the urology department in Utrecht. Regardless of their different backgrounds the urologists might have different consensus judgement than elsewhere. This ought to be tested by introducing the algorithmic evaluation in more centres and repeating evaluation. If it proves to mismatch with urologist interpretation elsewhere, the benefit of threshold based evaluation is that these can be easily adapted to match with a wider consensus.

Four descriptors and two additional comments allow for a limited variability. So far it seems sufficient for specific curve shape description. However, especially since the thresholds are not set in stone, parameters around threshold value might be of interest. In the current explanatory display is not visible when a parameter approaches threshold value and therefore is for example 'almost bell shape'. More subtleties in descriptors might provide extra information for intermittent and fluctuating as well. Currently these descriptors apply from one interruption/fluctuation and up and no distinction is made between curves with 2 or 9 fluctuations. Possible benefit of these nuances should be carefully weighed because it could make the algorithmic result more tenuous.

The evaluation excludes inter- and intra observer variability and the generated description has a standardised registration format. This allows reliable comparison of uroflowmetry results and creates possibilities for both comparative research uncovering underlying pathology and clinical follow-up. In clinical setting, comparison of two or more consecutive uroflowmetry tests can inform about treatment efficacy or representativeness of voiding. Parameters would easily be reported as e.g. VOID1 = 17/180/20, VOID2 = 21/310/0. How important changes in shape descriptions are and whether these are sensitive to interesting developments are yet unknown. The quantitatively defined descriptors consistently divide uroflowmetry test results into groups, for example fluctuating and not fluctuating. Now diagnoses based on adjunct investigation can be compared for these groups, increasing the diagnostic value of uroflowmetry.

5.2 Conclusion

This study presented an algorithm for automatic uroflowmetry curve shape description. The description is comprised of the descriptors bell shape, fluctuating, intermittent and plateau flow and comments on symmetry and maximal flow. The corresponding threshold evaluations are as objectively as possible by combining previously published proposals for shape evaluation. Quantitative definitions for shape characteristics that were still missing, are added based on expert consensus. As a result this is the first uroflowmetry evaluation tool that evaluates all relevant shape characteristics in an entirely reproducible way, increasing the diagnostic value of uroflowmetry.

A connected user interface makes the algorithmic evaluation insightful for end-users. As a whole it is very well received in terms of both efficacy and user experience and is ready for clinical implementation. Automatic evaluation makes spreading standardisation easy and the interface invites the user to maintain a conscious look when assessing the uroflowmetry test result.

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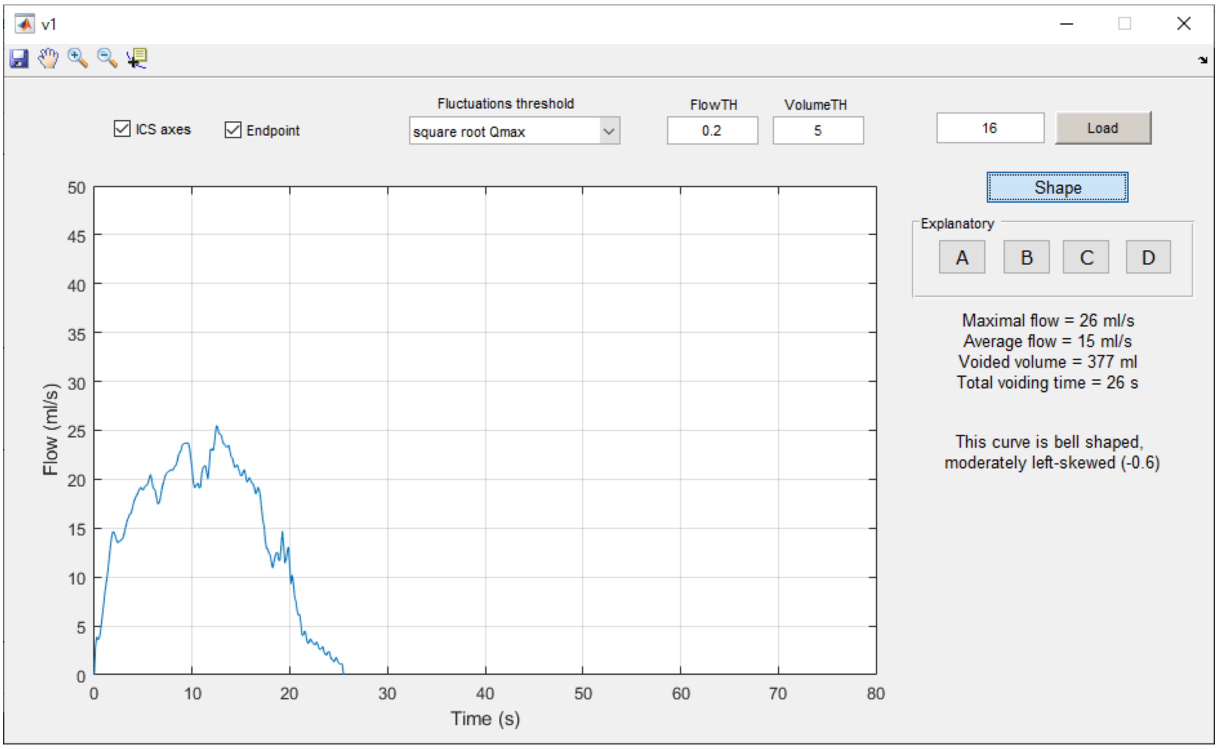
Appendix I - User experience questionnaire

Please assess the product now by ticking one circle per line.

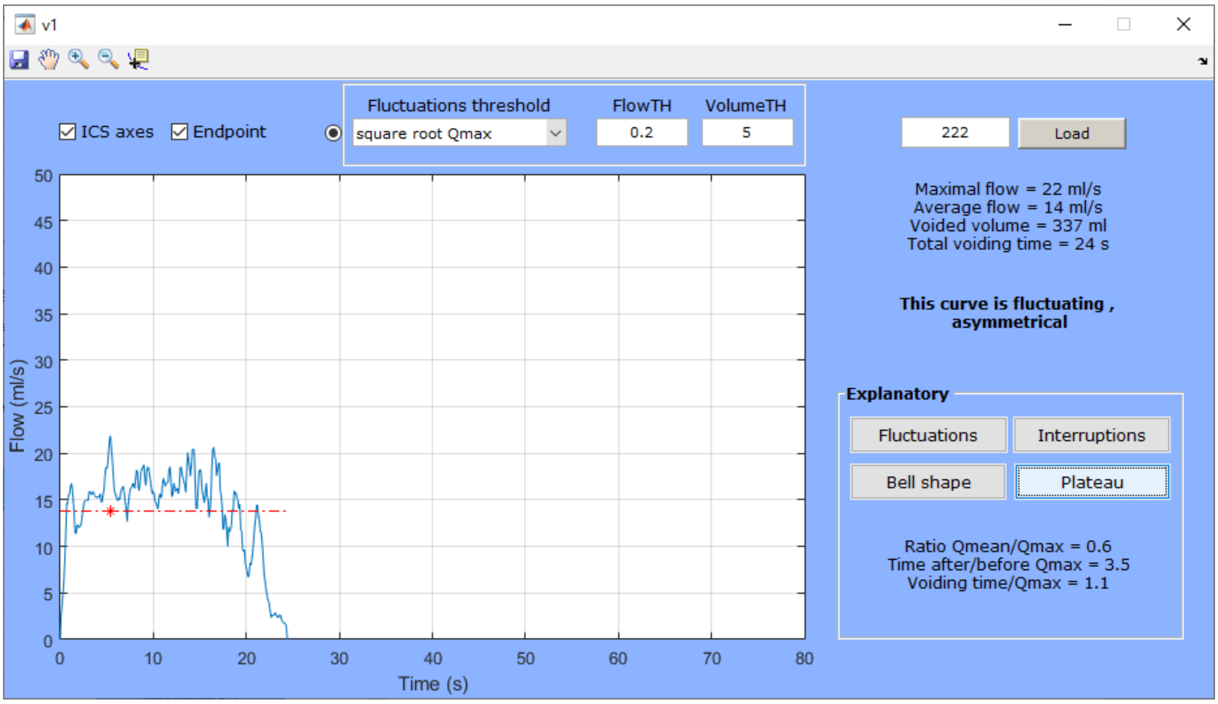
	1	2	3	4	5	6	7		
annoying	○	○	○	○	○	○	○	enjoyable	1
not understandable	○	○	○	○	○	○	○	understandable	2
creative	○	○	○	○	○	○	○	dull	3
easy to learn	○	○	○	○	○	○	○	difficult to learn	4
valuable	○	○	○	○	○	○	○	inferior	5
boring	○	○	○	○	○	○	○	exciting	6
not interesting	○	○	○	○	○	○	○	interesting	7
unpredictable	○	○	○	○	○	○	○	predictable	8
fast	○	○	○	○	○	○	○	slow	9
inventive	○	○	○	○	○	○	○	conventional	10
obstructive	○	○	○	○	○	○	○	supportive	11
good	○	○	○	○	○	○	○	bad	12
complicated	○	○	○	○	○	○	○	easy	13
unlikable	○	○	○	○	○	○	○	pleasing	14
usual	○	○	○	○	○	○	○	leading edge	15
unpleasant	○	○	○	○	○	○	○	pleasant	16
secure	○	○	○	○	○	○	○	not secure	17
motivating	○	○	○	○	○	○	○	demotivating	18
meets expectations	○	○	○	○	○	○	○	does not meet expectations	19
inefficient	○	○	○	○	○	○	○	efficient	20
clear	○	○	○	○	○	○	○	confusing	21
impractical	○	○	○	○	○	○	○	practical	22
organized	○	○	○	○	○	○	○	cluttered	23
attractive	○	○	○	○	○	○	○	unattractive	24
friendly	○	○	○	○	○	○	○	unfriendly	25
conservative	○	○	○	○	○	○	○	innovative	26

Appendix II: GUI evaluated versions

Version 1



Version 2



Appendix III - Generation of reference flow curve

Formula for Qmax according to Liverpool nomograms. Value 6 is added to adjust for translation later on.
Women: $Qmax, ref = 6 + \exp(0.511 + 0.505 \cdot \log(volume))$
Men: $Qmax, ref = 6 + (2.37 + 0.18 * \sqrt{volume} - 0.014 \cdot age)^2$

Formula for normal distribution (bell shape):
$Qref = Qmax, ref \cdot exp((-(t-\mu)^2)/(2*sd^2))$; with $\mu = 0.5 \cdot$ voiding time and sd empirically determined to make volume of reference curve agree with true voided volumes:
Women: $sd = 0.01 \cdot volume + 4$
Men: $sd = 0.008 \cdot volume + 6$

To represent uroflowmetry, the graph represented as Qref = f(t) is translated: Qref + 6 = f(t-μ)

The accepted deviaton from Qref, according to the quarter percentiles in the nomogram for volumes 100-600 ml:
Women: deviation(volume) $= 4 + (6/500 \cdot (volume - 100))$
Men: deviation(volume) $= 4 + (2/500 \cdot (volume - 100))$

Appendix IV – Manuscript sub study fluctuation thresholds

Evaluation of quantitative thresholds for defining fluctuations in uroflowmetry curves

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Abstract

Objectives: A variety of shape descriptors apply to fluctuations in urine flow rate. There is no unanimity for a cut-off that quantitatively defines this flow shape. This study aims at evaluating the current thresholds and proposing a universal quantitative threshold for fluctuations in uroflowmetry curves to increase objectivity of uroflowmetry interpretation and open up possibilities in comparative research.

Methods: In a single centre study, 219 uroflowmetry measurements of patients in the outpatient clinic with lower urinary tract symptoms were evaluated. Fluctuation detection was applied using three thresholds for the change in flow rate: the square root of maximum flow, 20% of maximum flow and 5 ml/s. The number of fluctuations as well as descriptive outcome are compared between the thresholds and with expert consensus.

Results: Classification of the curve shape as fluctuating or not resulted in agreement between outcomes of the three thresholds for 82% of all included flow curve. Comparison of the remaining cases against consensus classification resulted in agreement between 32% and 63% with the threshold outcomes.

Conclusion: The three quantitative threshold options are not interchangeable. Due to threshold dependency on maximal flowrate, sensitivity varies. Based on expert opinion and sensitivity for the most common range maximal flowrate range of curves it is proposed to consider a fluctuation larger than 20% of the maximal flow rate as the shape defining characteristic of choice.

Introduction

Uroflowmetry is a test to provide quantitative information about voiding function in patients with lower urinary tract symptoms. Apart from parameters as maximum flow rate, voided volume and voiding time to separate normal from abnormal, the shape of the uroflowmetry flow rate curves can also indicate voiding abnormalities [1]. However, currently there is no standard for describing abnormal flow shapes. Diagnosis of flow shape abnormalities is therefore operator dependent. Consequently, flow shapes are described inconsistently in literature. Li et al. (2018)[2] researched articles and International Continence Society (ICS) standardisation documents for observed flow shapes and the corresponding descriptors used. There is likewise considerable variability in quantitative definitions for the shapes, when presented, as in descriptors used for comparable flow shapes. This is troubling comparative research, for example aimed at discovering pathophysiology associated with the curve patterns. When application of descriptors is clearly defined it becomes valuable to associate them with diagnoses nowadays made based on more invasive investigations. [2]

The shape descriptor that is subject of this article is 'fluctuating'. According to the ICS it applies to a continuous urine flow having multiple peaks [1]. When flow rate decreases and increases rapidly this causes a local peak in the time flow rate graph. Other terminology describing similar shape characteristics is: 'staccato', 'multiple peak', 'intermittent', 'sawtooth', 'undulating' and multiphasic [2,3]. Four articles discussed in the review by Li et al. provided quantitative thresholds. These thresholds are the square root of maximum flow, 20% of maximum flow and 5 ml/s [4-7]. When a variation in flow rate exceeds the threshold, it is considered a fluctuation.

These differences in thresholds may result in differences in recognising patterns of fluctuations and therefore in a different shape description for the uroflowmetry curve. The present study investigates the differences that are consequent to the three described thresholds and proposes a substantiated choice for a universally applicable threshold.

Methods

Uroflowmetry data used in this study are recent measurements of patients with lower urinary tract symptoms visiting the urology outpatient clinic of the University Medical Centre Utrecht. All uroflowmetry measurements in the period from begin July to mid-September 2019 with a voided volume above 100 ml are included, there is no selection on symptoms or diagnosis. Data is fully anonymous except for gender. All patients are over 18 years old.

Uroflowmetry was done when patients felt normal desire to void. They were instructed to void like they normally would on a regular toilet, in a position of their preference. Measurements are performed on the FlowClean uroflowtoilet (Urotex, The Netherlands). This weight sensor device has a sample rate of 10 Hz, embedded software applies a moving average filter with one second window length.

All three quantitative thresholds used to define fluctuations reported in the review by Li et al. are used for comparison. Two evaluated thresholds are in terms of the maximal flow rate (Qmax), found as the highest value in the measurements flow vector. The first threshold (ThSq) is equal to the square root of Qmax in ml/s [4,5]. The second threshold (Th20p) is equal to 20% of Qmax in ml/s [6] and the third (Th5) is equal to 5 ml/s [7].

Fluctuations were identified by detection of their peaks. Peak detection was executed with the MATLAB (version 2018b, Mathworks, USA) built in function *findpeaks*. This function finds local maxima by comparing sample values with adjacent values. To limit detected fluctuations to only the ones exceeding the researched thresholds, the setting *MinPeakProminence* was used. The decrease in flow rate is calculated. On either side, within the time segment from the potential peak to the point where the signal attains a higher value or the end of the signal the lowest value is found. The difference between the highest of the two and peak value is the prominence of that peak. Peak detection is limited to peaks where the prominence is at least as large as the threshold value. The function has two output arguments: peak values and their corresponding timestamps. [8]

Based on the previously mentioned ICS definition, peak detection is applied only to periods of continuous urine flow. This means that in case of interrupted flow measurements, just the uninterrupted flow part with the largest volume was evaluated.

The number of fluctuations equals the number of detected peaks minus the peak corresponding with the maximal flow. Therefore the term additional peaks is used for all detected peaks exceeding the threshold value next to the peak corresponding to Qmax. According to definition, presence of one additional peak is enough to classify as fluctuating. This causes a dichotomous distinction of curves between one or more additional peaks and no additional peaks. To further research threshold differences, the number of additional peaks detected per threshold is determined and compared.

<u>Consensus meeting</u>
Since there is no unique, generally agreed, recommendation for the threshold value to be used, no standard method in clinical application can be assumed. Therefore, classifications of uroflowmetry curves as fluctuating or not that are conflicting between the thresholds is compared to clinical team judgement. These reference judgements followed from a consensus meeting with four medical doctors of the urology department of University Medical Centre Utrecht under supervision of the first author, referred to as 'researcher'. These doctors are tasked with interpretation of uroflowmetry measurements in their day-to-day work. Subject for the meeting are curves where the three thresholds did not agree about the presence of additional peaks (zero versus one or more).

The uroflowmetry measurement curve was shown on a large screen. Question for each curve was whether the team would classify that curve as fluctuating, given the explanation that this means the curve has one or more relevant fluctuations. This applies to fluctuations that might be clinically relevant so the urologist would not want to miss it in analysis. The attendants discussed about the pattern of fluctuations in the curve. When the discussion tended to either a yes or no answer, this was proposed by the researcher as final answer. When none of the attendants objected this was noted as an unambiguous yes or no. When one or more team members did object, discussion continued and this step was repeated once more. When there was no consensus by then was concluded that consensus could not be reached and the curve was excluded from analysis.

<u>Statistics</u>
Statistical analysis of the peak detection outcomes was performed with SPSS Statistics (version 25, IBM, USA). To test whether the differences in the number of additional peaks detected for each of the three thresholds is significant, the distributions are compared between themselves. Each distribution is the collection of the number of additional peaks for all the curves per threshold. Each value per threshold is related to a value in the two other distributions, the values representing the number of additional peaks according to the other thresholds. Additionally, the distributions contain nominal data and are not normally distributed. Therefore was chosen to adopt Friedman's two-way non-parametric ANOVA. Post hoc analysis for when this test showed a significant difference was done with the Bonferroni-corrected Dunn's test.

The three distributions reflecting the presence or absence of additional peaks according to the three thresholds are as well related and not normally distributed. Unlike the previous comparison these distributions are binominal instead of nominal. Differences in these distributions are therefore analysed by means of Cochran's Q test. In case of a significant difference, post hoc pairwise comparison was performed with McNemar's test for related samples. For all statistical analyses a significance level of $p < 0.05$ will be regarded.

Results

<u>Descriptive</u>

Inclusion criteria were met by 222 curves. Three curves had to be excluded due to measurement errors. These were recognised as such because the flow measurements reflected physically impossible voiding. As a result, 219 uroflowmetry measurements were available for analysis. Of these measurements 145 (66%) were of male patients. Maximal flow rate for the total group of measurements was 19.3 ± 10.9 ml/s (mean ± s. d.). The maximal flow rate determines the value of two of the three thresholds.

The graph in Figure 1 visualizes the dependency of the threshold value on the maximal flow. Fluctuations above the lines are detected. The histogram below shows the number of curves with Qmax in a certain range.

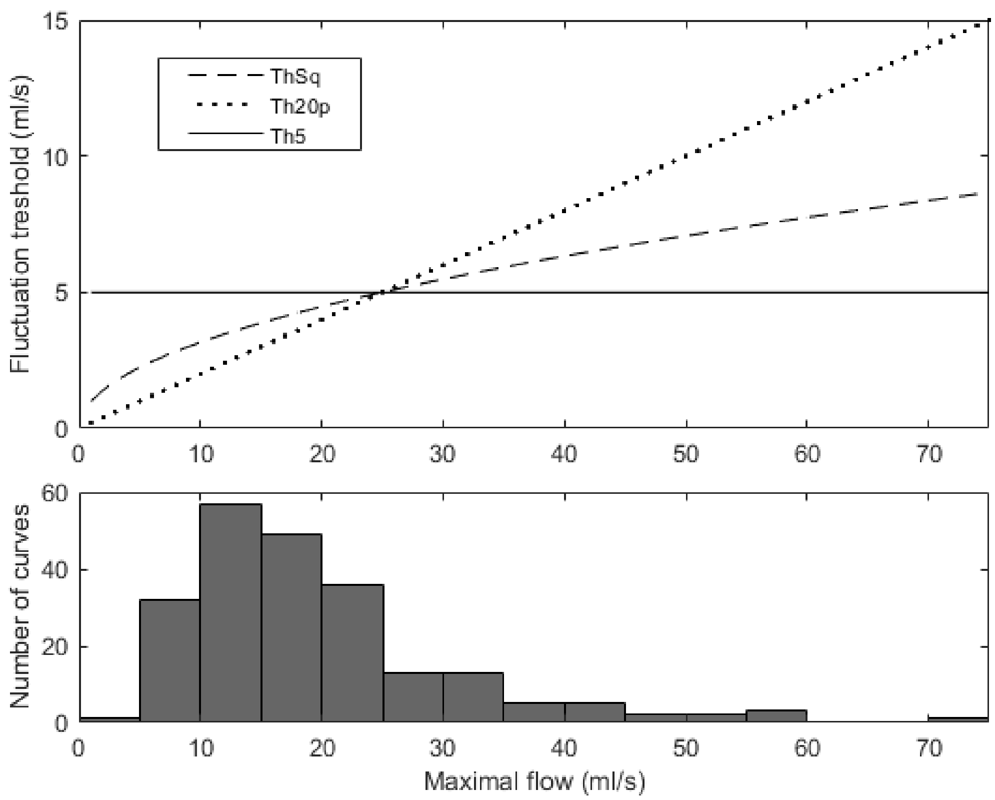

Figure 1: Top: All three threshold values in ml/s as function of maximum flow. The threshold is the lowest value that is considered a fluctuation. Bottom: Histogram representing the number of curves with maximal flow in a certain range.

Number of peaks

In 120 cases (55%) all three threshold definitions resulted in the same number of additional peaks per curve. Of these cases, for 73 curves this number is zero. For all 219 curves the frequencies of curves per number of detected fluctuations can be seen in Figure 2. Friedman's repeated measures ANOVA was used to compare these outcomes between the thresholds. Bonferroni corrected significance values are presented in Table 1. It shows that the number of detected additional peaks differed significantly for the three different thresholds ($p < 0.001$). Dunn-Bonferroni post hoc tests were carried out and there were significant differences between Th20p and the other two thresholds. The difference between ThSq and Th5 is not significant with Bonferroni corrected p-value 0.23. This means that the threshold equal to 20% of Qmax is most distinct compared to the other two.

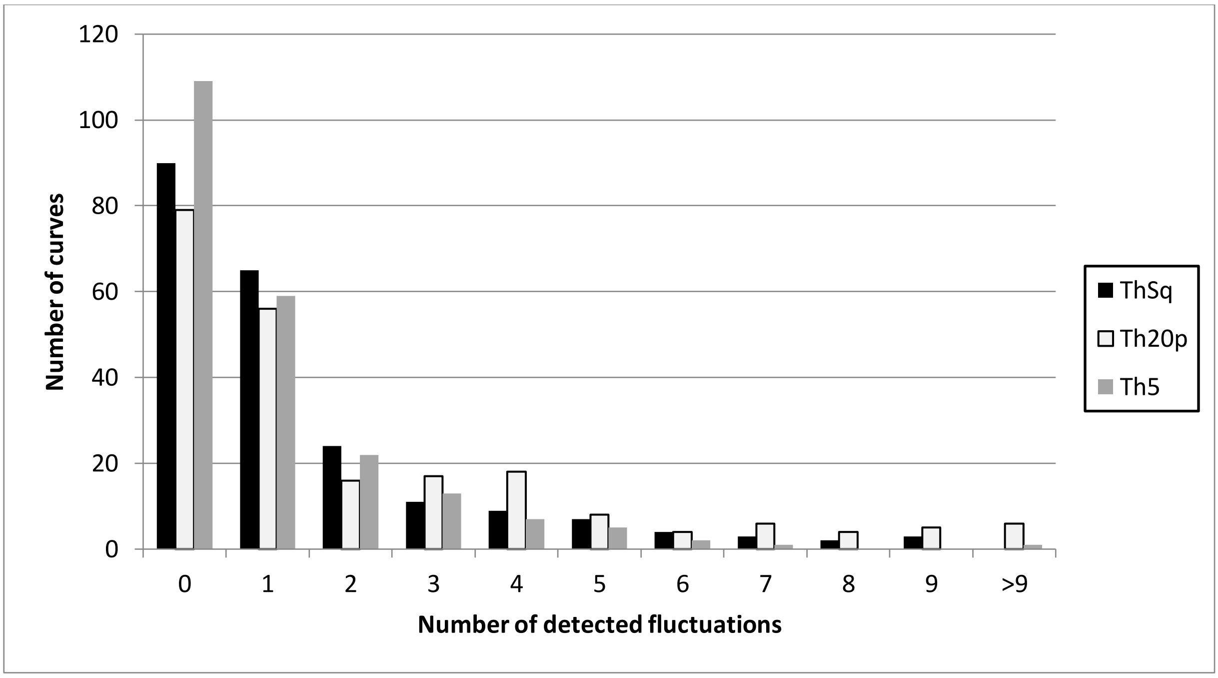

Figure 2: Histogram for the frequencies of curves per number of detected fluctuations resulting from the three thresholds.

Table 1: Dunn's test pairwise comparison of detected peaks per threshold. Displayed is Bonferroni corrected significance. This underpins that ThSq and Th5 are comparable with each other and Th20p is distinguishably different.

	Significance
ThSq – Th20p	0.001
ThSq – Th5	0.231
Th20p – Th5	0.000

Presence of peaks

In 146 of the curves at least one of the three threshold definitions resulted in detection of peaks next to the maximal flow peak. Comparison of the dichotomous notation for the three thresholds for the presence of additional peaks resulted in agreement in 179 curves (82%). In Table 2 the frequencies of flow rate curves with and without additional peaks are shown for all three thresholds.

Table 2: Frequency table distinguishing curves for presence of additional peaks according to the different thresholds.

	Not fluctuating (Single peak)	Fluctuating (Additional peaks)
ThSq	91	128
Th20p	78	141
Th5	110	109

Cochran's Q test was applied to the binominal distributions. The null hypothesis that these related distributions are the same for the three thresholds was rejected with significance p < 0.001 (Cochran's Q = 38.85). Post hoc pairwise comparison with McNemar's test returned that all threshold results differ significantly (p = 0.000 till 0.001). This means that none of the thresholds are interchangeable when they are used to determine whether a uroflowmetry curve is fluctuating. Combined with information from Figure 2 and Table 1 can be concluded that the agreement about the number of curves between ThSq and Th5 (Table 1) is more in the domain of more fluctuations than the only for classification defining number, zero fluctuations.

Consensus meeting

Of all curves, for 40 curves the three thresholds did not agree regarding the presence of additional peaks. For two of these curves no consensus could be reached. Of the remaining 38 curves, 27 were classified to have a fluctuating pattern, i.e., to have additional peaks. The number of curves for which the threshold-based conclusion agreed with the classification was counted. For thresholds ThSq, Th20p and Th5 these numbers are respectively 22 (58%), 24 (63%) and 12 (32%). Although not high, the similar agreement with ThSq and Th20p is considerably higher than the agreement with Th5.

Discussion

The initial conclusion is that the different thresholds result in significant differences in uroflwometry flow shape description. Therefore, the choice for peak identification threshold is relevant and should be uniform since interpretations using different thresholds are not comparable in all cases. Standardisation will unify interpretation of clinical uroflowmetry. When large amounts of uroflowmetry measurements are structually classified based on this shape characteristic, any relation between this characteristic and symptoms and/or final diagnosis can be researched.

Threshold differences

Differences in the number of detected additional peaks per threshold were pointed out. For the verbal classification 'fluctuating', the exact number of fluctuations is irrelevant. The presence of one or more additional peaks is decisive, following the ICS definition [1]. Evaluation of the results in this respect (Table 2) showed significant differences between the researched thresholds.

In Table 2 it can be seen that Th20p classifies curves most likely as fluctuating and threshold 3 the least likely. This can be explained by the visualisation in Figure 1. For Qmax = 25ml/s the choice in threshold is irrelevant, since then all threshold values are equal. The more Qmax deviates from this value the larger the effect of the particular choice becomes. According to the histogram, the difference in threshold value in the range 5 < Qmax < 25 ml/s is most influential due to the fact that the majority of uroflowmetry measurements lies within this range. Since this range is below 25 ml/s, the absolute fluctuation threshold value 5 ml/s is most likely to ignore fluctuations and the 20% Qmax criterion the least.

It is beneficial to incorporate the dominant range of Qmax in the choice between threshold options since Qmax does not vary over a very wide range. For the total group of measurements we observed Qmax = 19.3 ± 10.9 ml/s. In a study of Kumar et al. who reported peak urinary flow rate for a larger male and female group, Qmax values were 22.8 ± 9.33 ml/sec and 20.53 ± 7.75 ml/sec, respectively [9]. These values might be somewhat higher since symptom free participants were included.

Expert interpretation

All of the quoted articles fail to provide physiolocial substantiation for the chosen thresholds [4-7]. Therefore, it makes sense to consult physicians with yearlong experience of interperting uroflowmetry measurements. Furthermore, implementation of scientific results in patient diagnostics benefits from involvement of physicians in the research [10]. Limitation of this approach is that the reference rating could be subjective for this small group that works in the same hospital. Future work, including more experts from a wider range of teams will substantiate the reference interpertation.

Th5 was evidently less supported by the clinicians than the other two. The level of agreement was only 32% compared to 58% and 63% for ThSq and Th20p respectively. The absolute threshold 5 ml/s is not sensitive enough to detect fluctuations in low-flow voiding patterns.

Clinical relevance

The choice between ThSq and Th20p is less obvious. However since the assessments baed on these thresholds resemble eachother quite closely (see Table 2) the distinction is also less critical. Comparison with the concensus reference showed a small preference for threshold 2. Most important is that a choice is made and that the use of this threshold is standardised.

An argument in favor of Th20p is that it is more sensitive to fluctuations in the primary range of maximal flowrate values. When automatic detection of peaks results in labelling the curve as fluctuating, this indicates a possible pathological situation. The findings can be placed into clinical context to interpretet the shape characteristic. Anyway, detection prompts the urologist to look more closely at the uroflowmetry and therefore false positives are better than false negatives.

For optimal implementation, automatic comparison of fluctuations prominence with the threshold like in this research is essential. Uroflowmetry devices do report Qmax and 20% is easily calculated. However, the precise size of a fluctuation is not easily determined from a time flow rate graph. Additionally, automatic evaluation is faster and makes less errors.

Conclusion

Whether or not a uroflowmetry curve is interpreted as fluctuating is dependent on the quantitative threshold definition used. Both clinical diagnosis and associative research would therfore benefit from a standardised threshold. Based on expert opinion and sensitivity for the most prevalent curves it is proposed to consider a fluctuation larger than 20% of the maximal flow rate as the most appropriate shape defining characteristic. This value is now dictated by choice. Future knowledge of underlying physiology or experiences while using this threshold type could serve in optimisation of this value.

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