A Computer Simulation of Micturition

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Abstract

A modified version of the micturition model proposed by Hübener *et al* in 1994 [1] is presented. Relations between variables in the model are derived and explained then simulations are compared to published urodynamical data. Finally, the model is compared to other published models, and its implications and limitations are discussed.

Introduction

This paper is divided into several sections. Firstly the components of the lower urinary tract are introduced and then experimental methods of investigating urinary function and dysfunction are briefly discussed. A model of the process of micturition is then derived and used to investigate the effect of various anatomical, myogenic and neurogenic factors on voiding characteristics. The experienced reader may wish to go straight to the subsection entitled "The simulation in brief" (on page 7) that summarises the model and the simulation process.

The Lower Urinary Tract (LUT)

The Lower Urinary Tract consists of the urinary bladder, the external sphincter and the urethra. The LUT is one of the only parts of the body that is influenced by both the voluntary and involuntary nervous system. This makes the LUT very complex to model. It is a non-linear multivariable dynamic system variant in time and subjected to internal alterations (convulsions, dysfunctions and infections) and external alterations (coughing, sneezing, cold, fear etc…) [2]. The components of the LUT are now introduced in a little more detail.

Bladder

The bladder is a roughly spherical hollow muscle that collects and stores urine from the ureters until it is stimulated to contract and evacuate the urine through the urethra. The bladder wall mostly consists of one smooth muscle, the detrusor, and so normally the mechanical properties of the whole bladder are assumed to be those of the detrusor. When the detrusor is relaxed, the stress in the bladder wall depends on its viscoelastic properties. These properties can be modelled by a contractile element in series with an elastic element (or non-linear spring), both of which are in parallel with another elastic element. This is the method used by most authors in their mathematical models e.g.[3, 4, 5] and shall be returned to later.

Sphincter

The main mechanical functions of sphincter muscles are controlled constrictions and relaxations. The sphincter in the LUT is a contractile sheath of striated muscle around the urethra that is responsible for relaxing or constricting the urethra and therefore changing the urethral resistance. In most models of the LUT the sphincter is not modelled separately but integrated into the urethra. This is normally accomplished by multiplying the outflow by a simple block function (with possible values of 0 or 1) [6, 7] or by making use of a pressure threshold that, when exceeded, allows urine flow [1, 8, 9]. The latter will be the method employed in this paper.

Urethra

The urethra carries urine out of the body from the bladder during micturition. Early work on the urethra was based on flow through rigid tubes. This could not be more erroneous. Improvements were made in 1965, when Stibitz proposed a mathematical model where the urethra was considered as a generally tubular lining enclosed in a sheath of muscle (known as the pelvic floor) [10]. Sandwiched between these two layers is a layer of spongy tissue that Stibitz treated as if it were a fluid. The corresponding model consisted of a thin surface representing the muscular sheath which contained a fluid under pressure that represented the spongy tissue, the lining and the actual fluid.

Generally the urethra is considered as a distensible, elastic tube of varying cross section surrounded by a contractile sheath in the sphincteric zone.

Nervous Control

The neurogenic control system of the LUT is extensive and complicated. It contains sacral and pontine reflex loops as well as a suprapontine network [4]. There are various feedback loops such as voiding and guarding reflexes instigated by afferent and efferent nerve signals continuously going back and forth between the bladder, urethra, sphincters and different neural regions such as the parasympathetic unit, the somatic unit and control areas known as L (lateral) and M (medial) regions.

The subpontine/pontine part of this network has been studed extensively and the number of different reflexes that contribute to LUT function may be as many as 32 [11]. Many simplifications, involving only a few simple loops, have been proposed to get round this incredible complexity, but it has been suggested by Elbadawi that they are unrealistic [11] and that the LUT should be considered as being under the control of a single reflex with a complicated structure.

The LUT nervous control system has the property that it is always in one of two opposite states, namely storage/filling and voiding. Analogies have been drawn, to bistable electronic circuits, that suggest that the system should be simulated by means of two mutually inhibitive regions, one controlling the detrusor and one controlling the urethral sphincter [8]. Because of this mutual inhibition, either the sphincter region is active and the detrusor is inhibited (storage), or vice versa (voiding).

This suggests that the most simplistic (while still physiologically plausible) set of nerve signals, that could control the LUT and cause micturition, would be an excitatory signal controlling the detrusor working in conjunction with an inhibitory signal that controls the sphincter/urethra.

In the next section the model is derived and explained in full. Please refer to Appendix A for a brief discussion of the methods of studying urinary function and disorder, and the main motivations for creating a mathematical model of micturition.

The Model

The model can be compartmentalised into three main sections: the bladder, the urethra and their nervous control. Each of these components of the model shall be outlined in this section. Please refer to page 7 for a summarised version of this information without much of the derivation, explanation and discussion.

Nervous Control

Following the method of Hübener *et al* [1], the neurogenic control of micturition is modelled in a simplistic fashion. It is assumed that there are two nerve signals, one that controls the contraction of the bladder musculature and another that controls urethral relaxation, hereafter called s_1 and s_2 respectively.

Hübener *et al* chose linear forms for these two signals which increased to, or decreased from, a normalised value of 1, as can be seen in Figure 1. s_1 is described by the angle α which dictates the rate at which the bladder is stimulated. s_2 is described by the angle β which describes the rate of urethral relaxation and two other parameters δ and C. δ represents a variable time delay between the onset of bladder stimulation and urethral relaxation. Hübener *et al* found that increasing δ only had the effect of delaying the onset of micturition and so it was set to zero throughout this simulation. A new parameter C was added to the model. It represents the relative level that the urethral relaxation decreases to and can be seen in Figure 1.

These simplistic signals systematically introduce a discontinuity into the pressure-flow data because of their own inherent discontinuity when changing between their linearly increasing or decreasing sections and their constant sections. It is therefore desirable to propose another form for s_1 and s_2. The discontinuity could theoretically be "smoothed out" by employing a variety of approaches involving, for example, parabolas, exponentials or trigonometric functions. All these approaches were experimented with (see Figure 2), and the difference between their effects on the pressure-flow curves produced by the simulation were negligible. The motivation for a new form of neurogenic control was to "smooth out" the sharp discontinuity of the original signals. In light of this, exponential forms were chosen for s_1 and s_2, as they were the most dissimilar to the linear signals (the most "curvy"), as can be seen in Figure 2. The functions describing the nerve signals s_1 and s_2 in this model are given as:

$$s_1 = 1 - e^{-k_1 t} \quad \text{and} \quad s_2 = (1 - C)e^{-k_2 t} + C$$

where t is time, and k_1 and k_2 control the rate of increase or decrease and can be considered a parallel to the angles α and β in the linear model. Figure 3 shows the linear and exponential forms of s_1 and s_2 used in this paper.

Bladder

The pressure in the bladder and the rate of bladder evacuation are opposite ends of a reciprocal relationship that can be described by a modified version of the Hill equation [1], hereafter called the Bladder Output Relation (BOR).

$$\left(p+\frac{p_0}{4}\right)\left(Q+\frac{Q_0}{4}\right)=\frac{5}{16}p_0Q_0$$

p is detrusor pressure, and Q is flow rate. For a derivation of the BOR see Appendix B, [9]. This relation is represented by blue hyperbolae in Figure 4. p_0 and Q_0 are parameters that determine the shape of the curve as they represent the intercepts of the curve with the axes, i.e. $p = p_0$ when $Q = 0$ and $Q = Q_0$ when $p = 0$. Neither of these extreme conditions occurs clinically in general. Hübener *et al* [1] succinctly explain the cause for this as follows:

> The detrusor muscle can be thought of as a limited power source. This limited power can be used to generate force (expressed as a pressure in a hollow muscle like the bladder) or to shorten the muscle. Normally the urinary bladder operates somewhere between these two extremes, i.e. part of the muscle is used to generate force and another part for shortening.

In the model the nervous control of the BOR is assumed to simultaneously change both p_0 and Q_0, i.e. $p_0(t) = p_m\, s_1$ and $Q_0(t) = Q_m\, s_1$ for some p_m and Q_m. Combining this with the results from Appendix B we then have:

$$p_0(r,t) = p_0(r)\,p_0(t) = p_m\,\frac{F_0(r)}{\pi r^2}\,s_1 \quad \text{and} \quad Q_0(r,t) = Q_0(r)\,Q_0(t) = Q_m\,2r^2 v_{\max} s_1 .$$

where p_m and Q_m are intrinsic or maximum values. The effect on the BOR of s_1 increasing can be seen in Figure 4.

Urethra

The Urethral Resistance Relation (URR) is another equation that relates detrusor pressure to flow rate during voiding. It has been shown that a linear approximation to this relation is adequate to fit experimental data [12, 13] and has been used in previous models [1, 14]. Thus in this model the URR is described by:

$$p = p_{OP} + m\,Q$$

p_{OP} represents the urethral opening pressure (the pressure required to distend the elastic wall of the urethra and start flow) and m is the urethral resistance. This equation may be empirical but is consistent with the behaviour expected of a passively distensible tube [14].

Once again it is assumed that the nervous control acts simultaneously on both parameters, so we have:

$$p_{OP} = p_h \, s_2 \quad \text{and} \quad m = m_h \, s_2$$

where p_h and m_h are intrinsic or maximum values. The effect on the URR of s_2 decreasing can be seen in Figure 4, where the URR is represented by straight red lines.

The next section shall outline the step by step processes involved in performing the simulation.

Methods

The simulation in brief

Choices of parameter values are made, then if the discrete time increment is γ, at time t, when the bladder has volume V, the simulation process proceeds as follows:

- The values of the nerve signals s_1 and s_2 are calculated using t.
- $p_0(t)$, $Q_0(t)$, p_{OP} and m are calculated from s_1 and s_2.
- The bladder radius r is calculated from V.
- $Q_0(r)$ and F_0 are calculated using r.
- $p_0(r)$ is calculated from F_0 and r.
- Using these values, the BOR and the URR are simultaneously solved for p and Q (see Figure 5) to yield an instantaneous "snapshot" of the pressure-flow characteristics of the simulated voiding.
- Any other parameters representing contraction velocity etc. are then calculated.
- $\frac{dV}{dt} = -Q$ is integrated to give the voided volume, which is subtracted from V to give a new value for the bladder volume. Since the time steps are discrete, this may be written $V_{new} = V_{old} - \gamma Q$
- the values of Q, p, V, t and all other parameters are stored
- the simulation time is increased one increment $t_{new} = t_{old} + \gamma$

This whole process is carried out at each time step, for a given number of time steps, leaving the user with lists of data that can then be plotted and analysed. Repeating the simulation with different parameter values allows comparison of the resulting effects on pressure-flow relations and voiding characteristics in general.

Investigation

Typical values were chosen for the parameter values (see Appendices C and D). Once this was done the simulation could begin in earnest. The effect on various voiding characteristics (such as maximum flow rate Q_{MAX} and maximum detrusor pressure p_{MAX}) of varying each of the parameters $k_1, k_2, C, r_0, p_0, v_{MAX}, p_h$ and m_h, as well as the initial bladder volume V from their "typical" values, was studied. Then graphs showing relationships between different simulation variables (e.g. pressure-flow, flow-time, flow-volume, pressure-time etc..) were plotted and analysed. The findings and implications are discussed in the next section.

Results

The resulting relations between parameters that the various simulations produced can be seen in Figures 6 to 10. For each parameter varied, four types of graph are shown. From top to bottom they are graphs of flow-rate against time, flow rate against instantaneous bladder volume, bladder volume against time and pressure against flow-rate.

Figure 6 shows the effect of varying initial bladder volume on these four relations. For this figure only, graphs calculated using the linear nerve signals are shown as a direct comparison to the new exponential forms of the proposed nerve signals. Figure 7 shows the effect of varying the rate of excitation or inhibition the two nerve signals provide to the LUT. Figure 8 shows the effect of varying the parameters in the URR, and Figure 9 shows the effect of varying the parameters in the BOR. Figure 10 shows the effect of varying the parameters r_0 and C. Many things can be deduced from these graphs.

The effect of initial bladder volume on voiding

Figure 6 shows that maximum flow rate increases with initial bladder volume up to a certain threshold limit as expected. Initial bladder volumes greater than this limit, share a similar maximum flow rate. Since the maximum flow rate is the same, the bladder takes longer to empty.
Notice that in the flow rate versus volume graph all the curves share the same ”descent” trajectory, at low volumes, close to the cessation of micturition. This is consistent with the findings of Griffiths *et al* [15]. The pressure-flow graph indicates that the pressure at which maximum flow occurs is fairly independent of the initial bladder volume. This is consistent with the findings of many studies, e.g. [16] and is because voiding pressure is mainly determined by outflow conditions and so is not volume dependent [3].

The effect on voiding of nervous control.

In figure 7 it can be seen that decreasing the rate of detrusor stimulation has many effects. It delays the onset of voiding, increases the voiding time, lowers the maximum flow rate and increases the pressure at which this maximum occurs. This is because slower detrusor stimulation results in the urethra being more relaxed for any given level of bladder excitation. A more relaxed urethra results in higher maximum flow rates (due to the lowered urethral resistance) and lower flow pressures (due to the lowered urethral opening pressure and the shallow gradient of the URR due to the lowered urethral resistance).

It can be seen in figure 7 that increasing the rate of urethral relaxation also decreases the maximum flow rate and raises the pressures at which they occur. This can be attributed to the same cause as for slower detrusor stimulation. Notice how the pressures and times at which voiding commences remain unchanged. This is because the bladder has reached peak excitation before the urethra has relaxed enough for flow to commence. In each case, once this same threshold pressure is breached, the flow commences.

The effect of the URR on voiding

Figure 8 shows the effects of varying the parameters in the URR. Increasing the pressure required to open the urethra increases the pressure at which micturition commences and ceases, as one would expect, but doesn't change the difference between them. The onset of voiding is once again delayed as the detrusor needs to wait for a higher level of stimulation before it can produce the forces required to overcome the higher urethral opening pressure. Since the forces and pressures produced by the detrusor remain unchanged, the pressure difference that causes the flow decreases as the urethral opening pressure increases. This lower pressure difference results in the lower maximum flow rates and the increased voiding time.

Increasing urethral resistance (also shown in Figure 8) has similar effects to increasing the pressure required to open the urethra. The only real difference is related to the pressures and times at which the flow begins, remaining unchanged in this scenario. This is as a direct result of the urethral opening pressure remaining constant throughout.

The effect of the BOR on voiding

Figure 9 shows that decreasing maximum contraction velocity and decreasing maximum detrusor pressure both increase voiding time and lower maximum flow rate. The rate of flow Q is directly proportional to maximum contraction velocity $v_{\max}$. So a decrease in contraction velocity results in a slower flow, and accounts for the lower maximum flow rate and longer voiding times.

Comparing Figure 8 and 9 it can be seen that lowering maximum contraction velocity has very similar effects to increasing urethral resistance. The only difference is in the pressure-flow plots. This can be readily explained. Decreasing $v_{\max}$ (e.g. from metabolic detrusor dysfunction), decreases Q and therefore decreases the factor $m\,Q$ in the relation $p = p_{OP} + m\,Q$ meaning the curves in the pressure flow plots get steeper. Increasing m obviously has the opposite effect on the factor $m\,Q$ and thus causes the gradient of the curves to shallow out.

In a similar vein, decreasing the maximum detrusor pressure can be seen in Figure 9 to have very similar effects to increasing the urethral opening pressure as seen in Figure 8. Once again the decreased maximum flow rate, and increased voiding time etc can be attributed to the lower pressure difference between the detrusor and the urethra.

Other parameters

Increasing *C,* has the effect of increasing p_{OP} and *m* simultaneously and the similarity of the effect can be seen in the graphs in Figure 10. More interesting is the result of varying r_0. This corresponds to changing the force-length characteristics of the muscle by some mechanism, e.g. an overstretching of the elastic element of the detrusor muscle. The "ideal" value of r_0 results in a force that vanished when then bladder is empty. A larger r_0 results in lower forces and the detrusor reaching zero force production before the bladder has been fully evacuated. In this case, residual urine is clearly apparent in both the flow-volume and volume-time curves.

A smaller r_0 results in larger forces at small volumes and the bladder tries to continue to produce force when the bladder is empty. This explains the abrupt end to the flow-time curves. The decreased maximum flow rate and increased voiding time can once again be understood in terms of reduced detrusor force (and pressure) production.

Residual Urine and Maximum Flow Rate

Figures 11 and 12 summarise the effects, if any, that varying the aforementioned parameters has on the residual urine volume and the maximum flow rate. Clearly, increasing the urethral opening pressure, decreasing the maximum detrusor pressure and decreasing r_0 all result in a decrease of maximum flow rate combined with an increase in residual urine. In fact if any of these parameters is shifted far enough micturition will not commence.

Van Mastrigt *et al* [17] describe the series-elastic characteristic of the bladder by assuming the bladder wall material has a mono-exponential elastic modulus. In terms of this model an overstretching in the bladder, could then be interpreted as an overstretching of this spring. This would have the effect of reducing peak contraction velocity without necessarily reducing peak contraction force, i.e. the bladder is slower but not weaker [18].

This is precisely the behaviour that the simulation exhibits when v_{MAX} is decreased (or *m* is increased – essentially the same thing in the URR). As can be seen in Figure 12, there is no increase in residual urine when these two parameters are varied yet there is still a change in the maximum flow rate.

Classically, when residual urine and a low maximum flow rate are present, the diagnosis is normally that of urethral obstruction (perhaps by prostatic hypertrophy). But, as pointed out in [19], "..an obstruction alone does not lead to a residual, since, if the bladder generates high pressures there is no reason why emptying should not be complete. Residual urine points to a failure of the bladder to maintain its contraction, probably as a result of changes in the bladder wall due to the obstruction".

Poor voiding function with normal unobstructed outflow conditions is common, and then typical "obstructive" symptoms such as poor flow rate, hesitancy and residual urine volume are because of poor detrusor contraction function [3]. This can be either neurogenic or myogenic in origin. Hence lower maximum flow rate and increased residual urine do not necessarily imply urethral obstruction, but urethral obstruction *does* imply a lower maximum flow rate [1].

Pressure-Flow plots

Idealised forms of pressure-flow plots, obtained by varying simulation parameters are shown in figure 13. When the urethra starts to relax after the bladder is already fully stimulated the pressure-flow curve follows the straight line of the URR.

Comment should be made on the form of the pressure-flow plots shown in Figures 6 to 10. They almost all exhibit a rise in pressure at the end of micturition. Petros *et al* report of a similar phenomenon. A frequent find during their study [20] was that of a sudden rise in detrusor pressure on the completion of micturition. Petros explains "It is consistent with a detrusor contracting against a urethral tube suddenly closed by elastic recoil of the vaginal hammock from the stretched position back to the closed position."

It is known that voiding in men and women differs considerably because of the differing anatomy of their genitourinary systems [21]. The reproductive organs in women are closely related to the urinary system and may exert direct or indirect effects on the function of the lower urinary tract. However, it would be overly optimistic, inaccurate and ultimately misleading, to conclude that the pressure flow plots are evidence of a good fit of the model to the female hydrodynamical data used in [16].

The combination of this anomaly and the lack of accurate output values for parameters such as the pressure at maximum flow rate, and residual urine volume for different initial bladder volumes (when compared to [16]), one is left to conclude one of several things: The most obvious answer would be that it is somehow related to the use of the exponential nerve signals, but by tweaking simulation parameters this behaviour can be eliminated (see Figure 13). It is highly unlikely that the results from [16] used in the fit are inaccurate and flawed so another explanation could be that the model makes too many simplifying assumptions and cannot be used quantitatively in this manner, or perhaps that the number of free parameters nedds to be increased.

This possibility and general limitations of the model are broached in the next section.

Discussion

The limitations of the model are discussed and the underlying assumptions questioned below. For a brief discussion of other models of the LUT please go to Appendix E.

It is well known that rarely does any model completely mimic every aspect of behaviour of the system that is being modelled. This is normally due to simplifications or assumptions being made. One such incorrect assumption could be that:

The bladder is assumed to remain spherical until it is empty. However, it is more likely that the bladder changes shape due to folding when its volume is small. Since the relation between mechanical stress in the bladder wall and the pressure depends on the shape of the bladder, this undoubtedly affects voiding characteristics in reality.

The model, although simplistic, describes variations in urodynamical parameters due to various myogenic and neurogenic causes and allows insight into possible mechanisms for urinary dysfunction. It also highlights the strong influence of urethral properties on voiding, particularly the end phase.

Limitations of the model

As Hübener *et al* point out in their original paper [1] the neurogenic control of the bladder and urethra in this simulation is very simple and not based on any physiological data. As mentioned previously, there could be as many as 32 different reflexes involved in the control of the LUT. Many other combinations of nerve signals are both imaginable and plausible, and a more complete model of the neurogenic control is desirable. Despite this, the signals combine to adequately describe realistic responses that allow investigation of the other non-neural components of the system.

Well-known mechanisms that are omitted from this model are the series and parallel elasticity elements of the detrusor muscle [3, 4, 5] that are commonly proposed to explain pressure development in an isometric contraction . In the original model [1], this is justified by quoting an earlier work of van Mastrigt [22] that found that a muscle shortening of only a few percent was enough to make the contribution from the elastic element negligible. The parallel elastic element can provide up to 35 % of the active pressure in optimum conditions. It has been shown that voiding normally occurs at bladder volumes well below this optimum condition, and that is why it was not included in the original model [1]. As with neural control, a more complete description is desirable, and any “complete” model will have to include these components.

Underlying assumptions

It is well known that there is a relationship between maximum flow rate and initial bladder volume. The flow rate increases with bladder volume until a certain threshold limit where there is no further increase and the flow rate reaches a plateau [15, 16]
This peak flow rate has been described as "quite closely proportional to the square root of the bladder volume" [8] in one study.

Schäfer *et al* found that the maximum contraction velocity appears to be almost independent of the volume voided [3]. This leads to the interesting conclusion that peak flow should occur at the same detrusor contraction velocity in one patient. This, in turn, results in the relation $Q \propto V^{\frac{2}{3}}$ that fits well with previous clinical data [23], and forms the basis for the assumption made in both [1] and this paper that Q is proportional to the square of the bladder radius. However, another study [24] found that average flow rate (that is strongly correlated with maximum flow rate) had no particular volume dependence at all. Another shadow cast on this assumption, is made by van Duyl *et al* who claim from their study [25] that maximum contraction velocity is unpredictably variable and so is therefore not a very useful contractility index.

Another problem with this model relates to the Hill equation. As mentioned previously, the contractility of (urinary bladder) smooth muscle can be described in terms of a relation between its contraction force and its shortening velocity. This relation can be approximated by the hyperbolic Hill equation. Van Mastrigt *et al* found that only 12% of 2073 pressure flow studies he examined could be fitted in this way with a Hill curve [26].

A whole other issue to be considered is that of experimental error and assumptions. e.g. Valentini, quite rightly asks: is the pressure measured in the rectum really equal to the abdominal pressure (defined as the counter pressure acting on the bladder) [27]?

Conclusion

The model worked well to show how various myogenic and neurogenic factors affect urodynamical features. The fit to the model ended up being unsuccessful. It is unclear whether that is because of an inherent error in the model, the data, or the assumptions made to combine the two. This is something I would like to have explored further if given more time. The outlook for the future in this field is good. The models whilst getting ever more complex, are also getting ever more accurate. As more advanced imaging and measuring techniques arrive, combined with, faster cheaper computing power for manipulating, recording and analysing the raw data, the models can only improve. One can only hope that a model is created that is sufficiently accurate so as to circumvent the need for the invasive techniques that are commonplace in research in this field.

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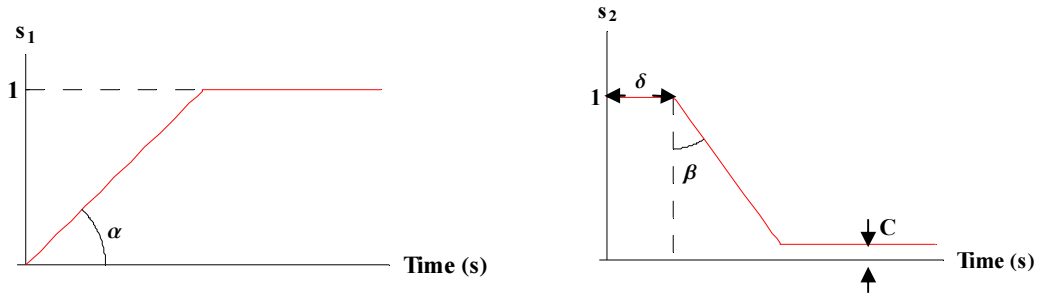


Figure 1: These graphs show the (linear) nerve signals that control bladder excitation (left) and urethral relaxation (right) in the model of Hübener *et al* [1] .

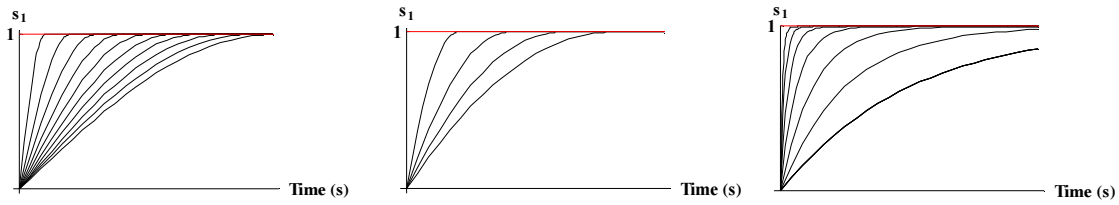


Figure 2: These graphs show a variety of approaches used to try and avoid the discontinuities that are inherent in the (linear) nerve signals shown in Figure 1.
From left to right they make use of: sinusoidal curves, parabolas and exponentials.

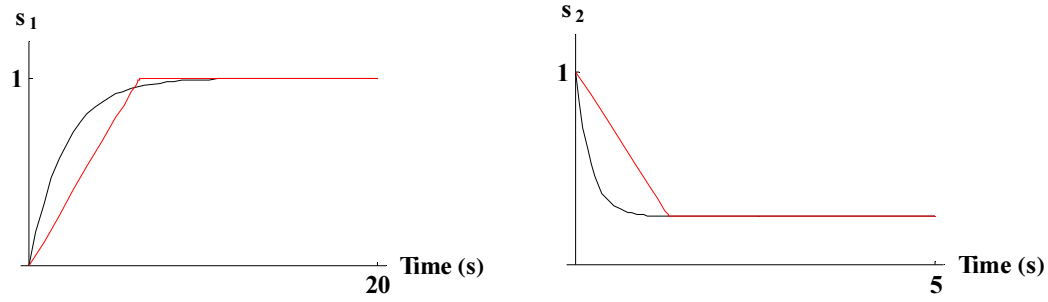


Figure 3: When comparing the linear and exponential forms of s_1 and s_2 the parameters defining the curves were chosen in a way that made the rates of excitation or inhibition similar.

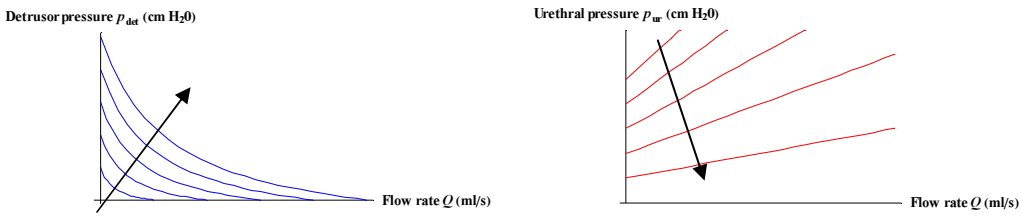


Figure 4: The graphs above show how the BOR (left) and the URR (right) change in response to nerve signals s_1 and s_2 respectively. The arrow shows the direction of increasing stimulation on the left and increasing relaxation on the right.

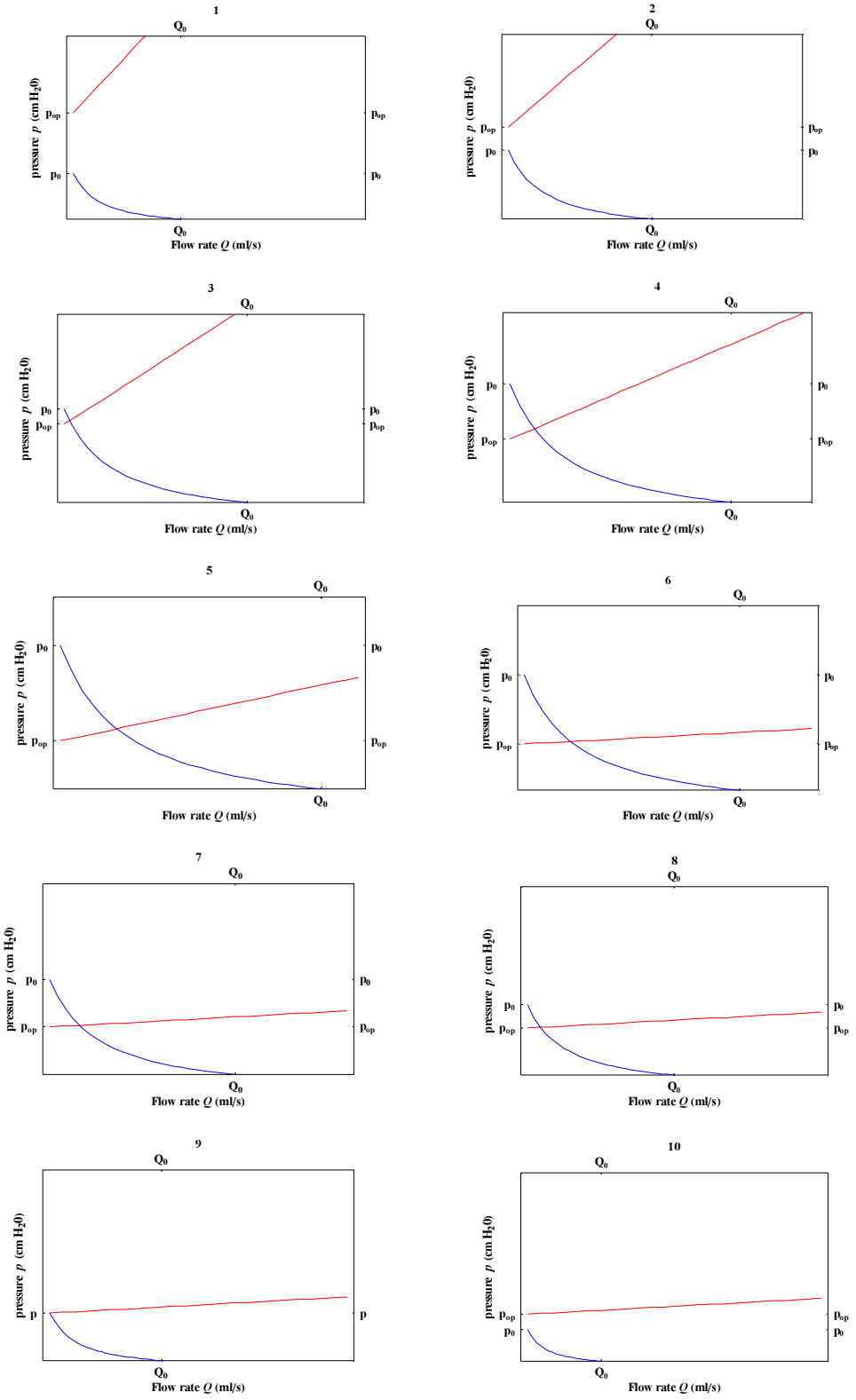


Figure 5: These graphs show how the URR and BOR are simultaneously solved during a typical voiding. When the two graphs intersect, the point of intersection is (Q, p) where Q is the flow rate and p is the pressure. When the two graphs do not intersect, $Q = 0$.

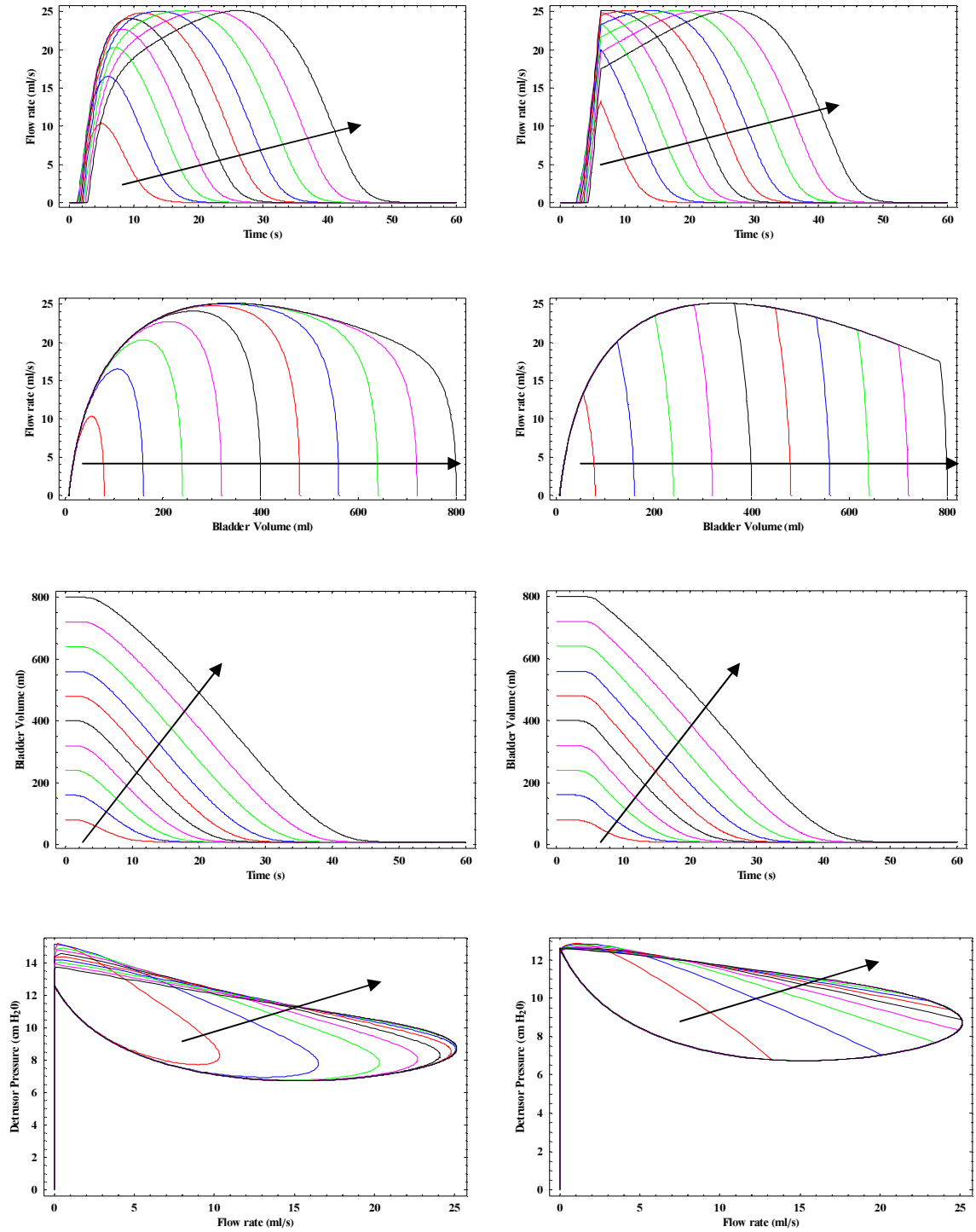


Figure 6: The effect of initial bladder volume V on voiding function. The arrows are in direction of increasing V. The value of V was varied from $80\ ml$ to $800\ ml$ in steps of $80\ ml$. The exponential and linear cases are on the left and right respectively.

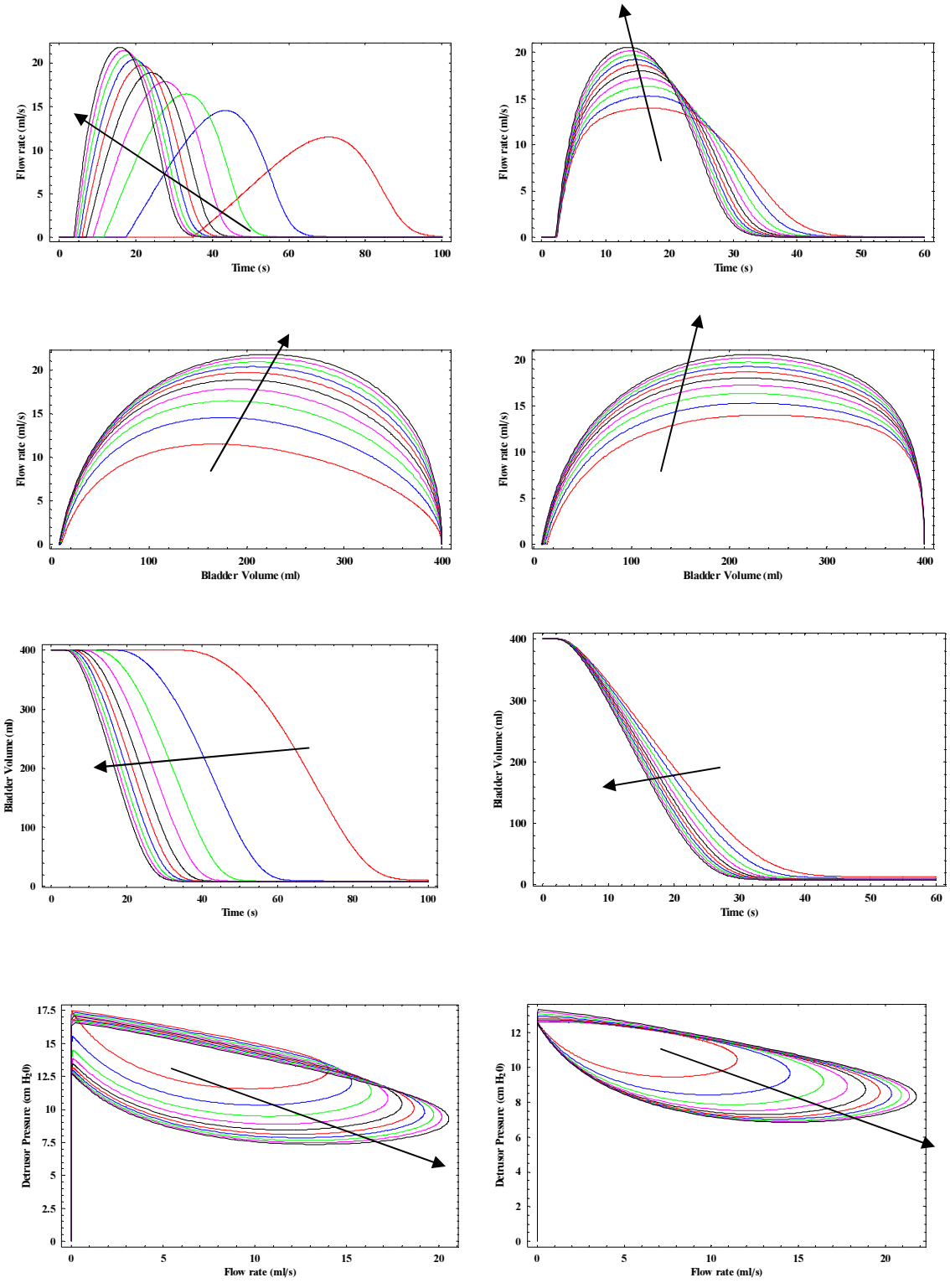


Figure 7: The effect of the nerve signal constants k_1 and k_2 on voiding function, shown on the left and the right respectively. The arrows are in direction of increasing rate of stimulation (k_1) and relaxation (k_2). The values of k_1 and k_2 were varied between 0.02 and 0.2

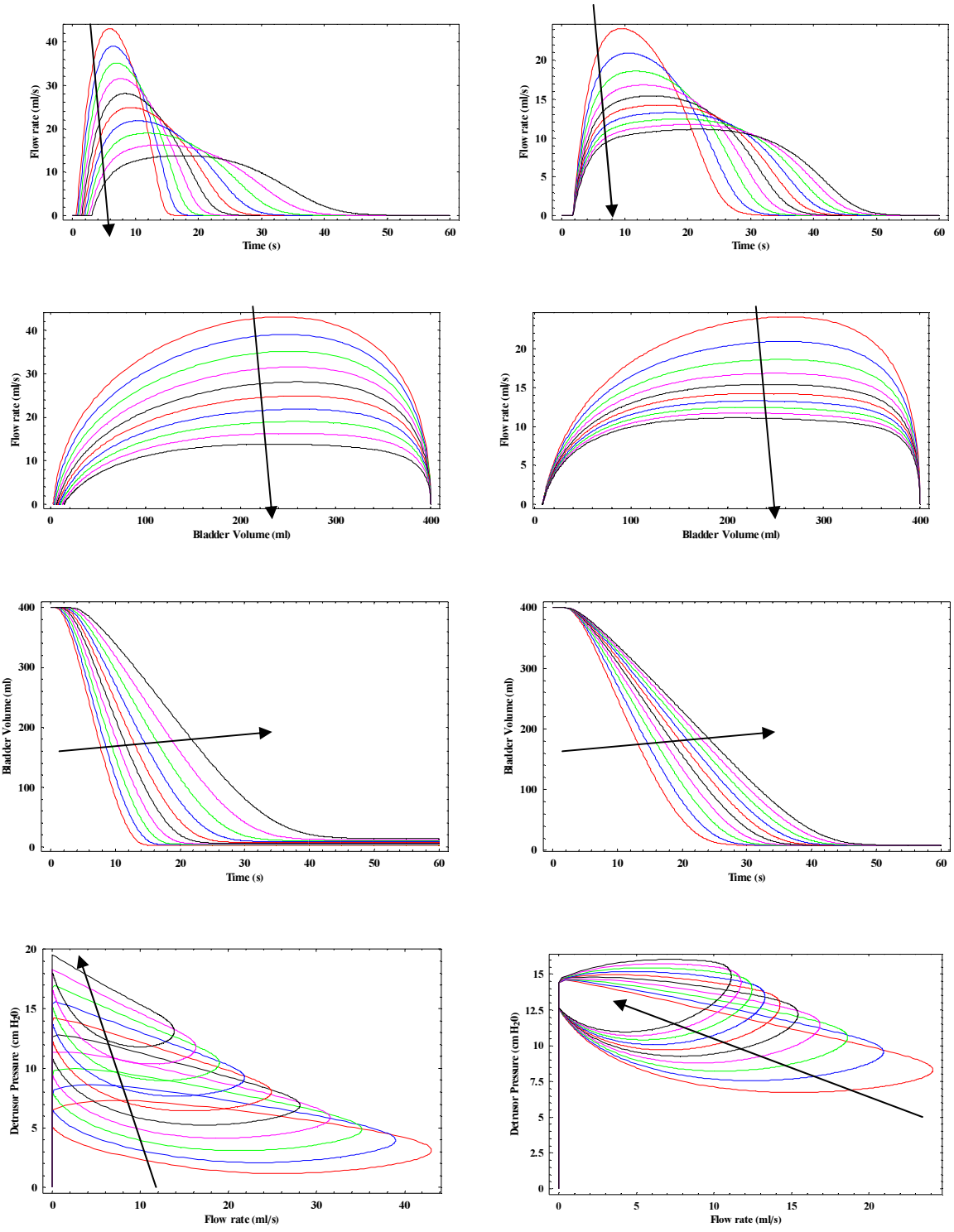


Figure 8: The effect of p_h and m_h on voiding function, shown on the left and right respectively. The arrows are in direction of increasing p_h and m_h. The value of p_h was varied from $7\,cm\,H_2O$ to $25\,cm\,H_2O$ in steps of $2\,cm\,H_2O$ and the value of m_h was varied from $0.05\,cm\,H_2O/ml\,s^{-1}$ to $1.85\,cm\,H_2O/ml\,s^{-1}$ in steps of $0.2\,cm\,H_2O/ml\,s^{-1}$.

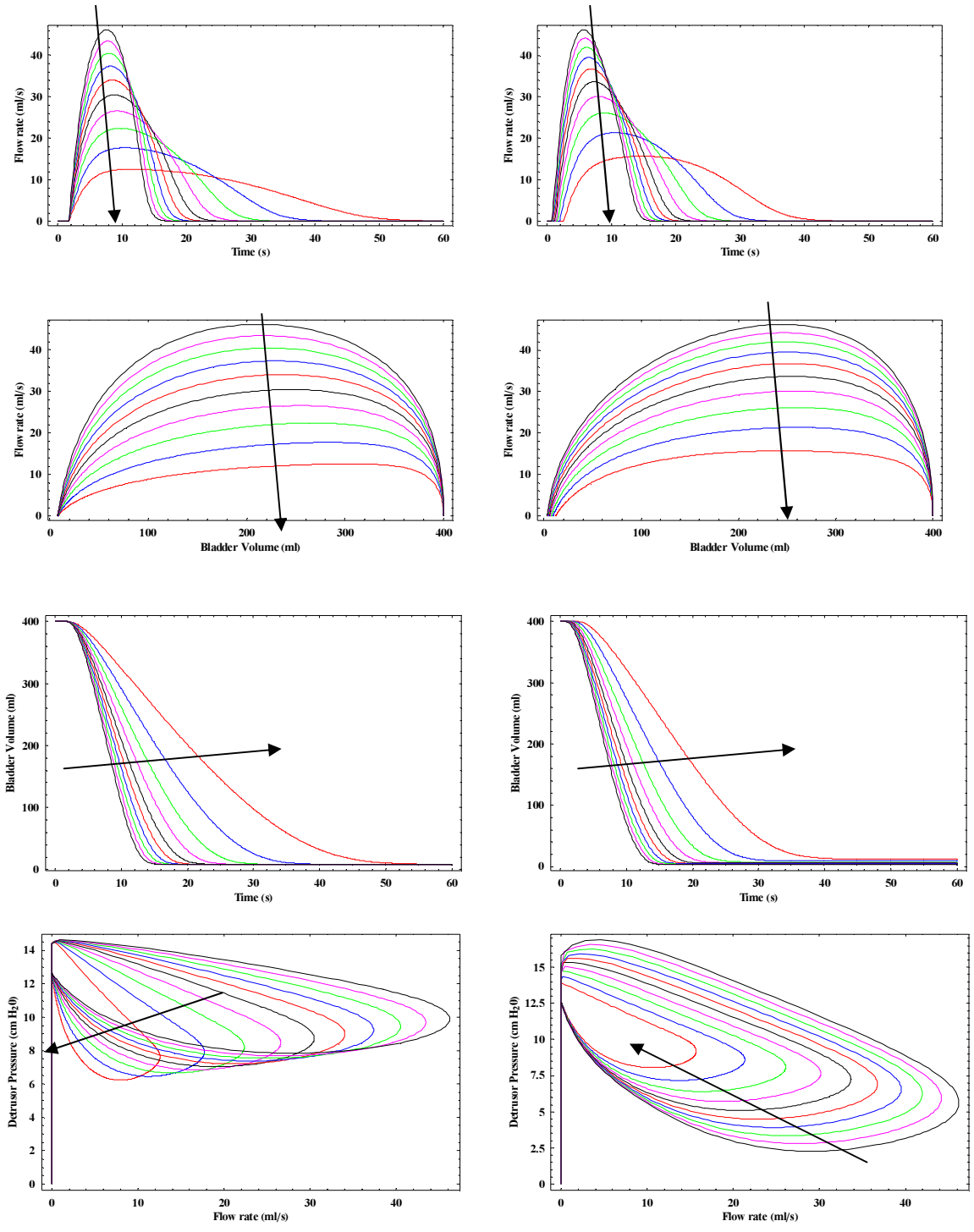


Figure 9: The effect of $v_{\max}$ and $p_{\max}$ on voiding function, shown on the left and right respectively. The arrows are in direction of decreasing $v_{\max}$ and $p_{\max}$. The value of $v_{\max}$ was varied from $10\,mm/s$ to $55\,mm/s$ in steps of $5\,mm/s$ and the value of $p_{\max}$ was varied from $25\,cm\,H_2O$ to $70\,cm\,H_2O$ in steps of $5\,cm\,H_2O$.

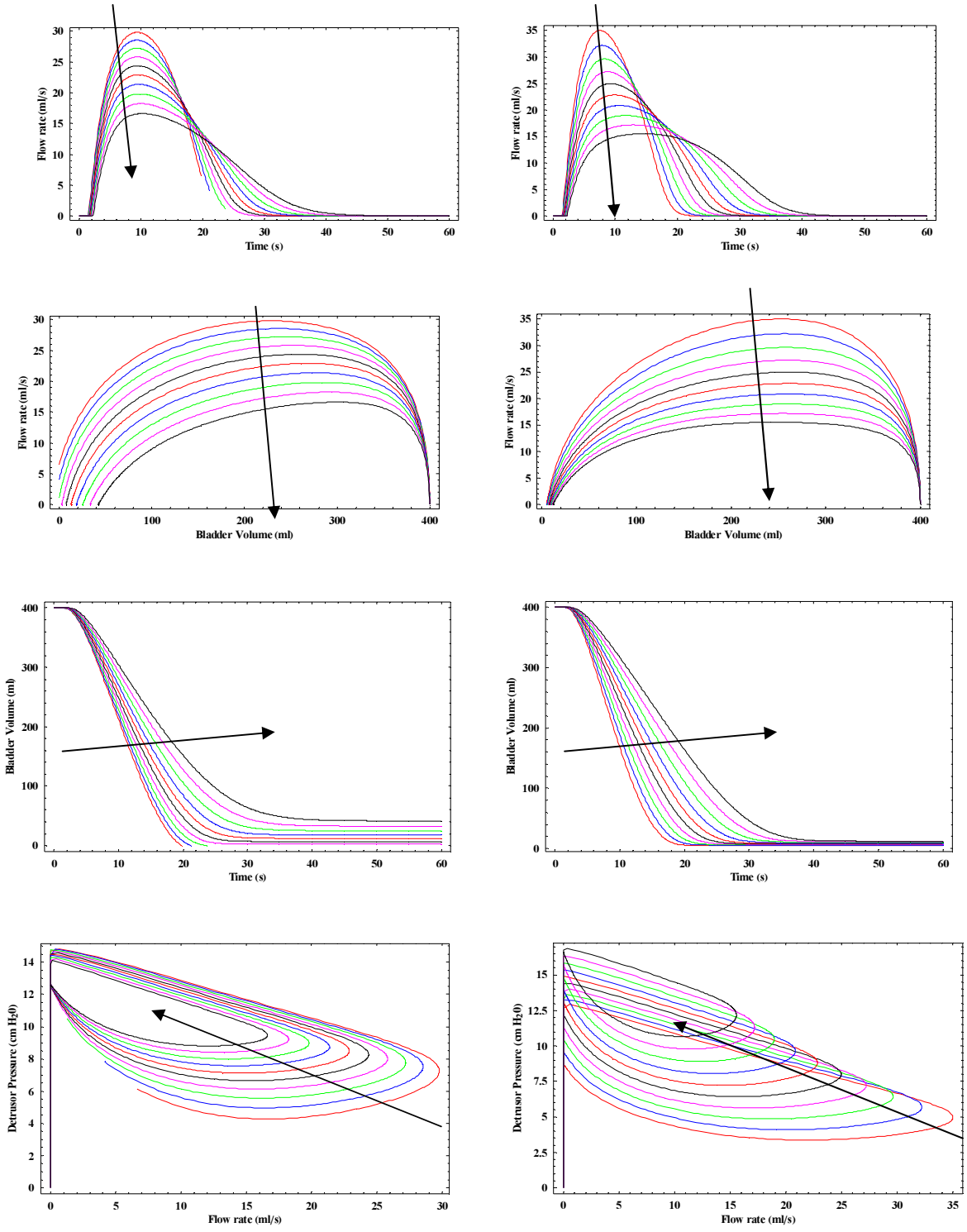


Figure 10: The effects of r_0 and C on voiding function, shown on the left and right respectively. The arrows are in direction of increasing r_0 and C. The value of r_0 was varied from $50mm$ to $72.5mm$ in steps of $2.5mm$ and the value of C was varied from 0.5 to 0.95 in steps of 0.05 .

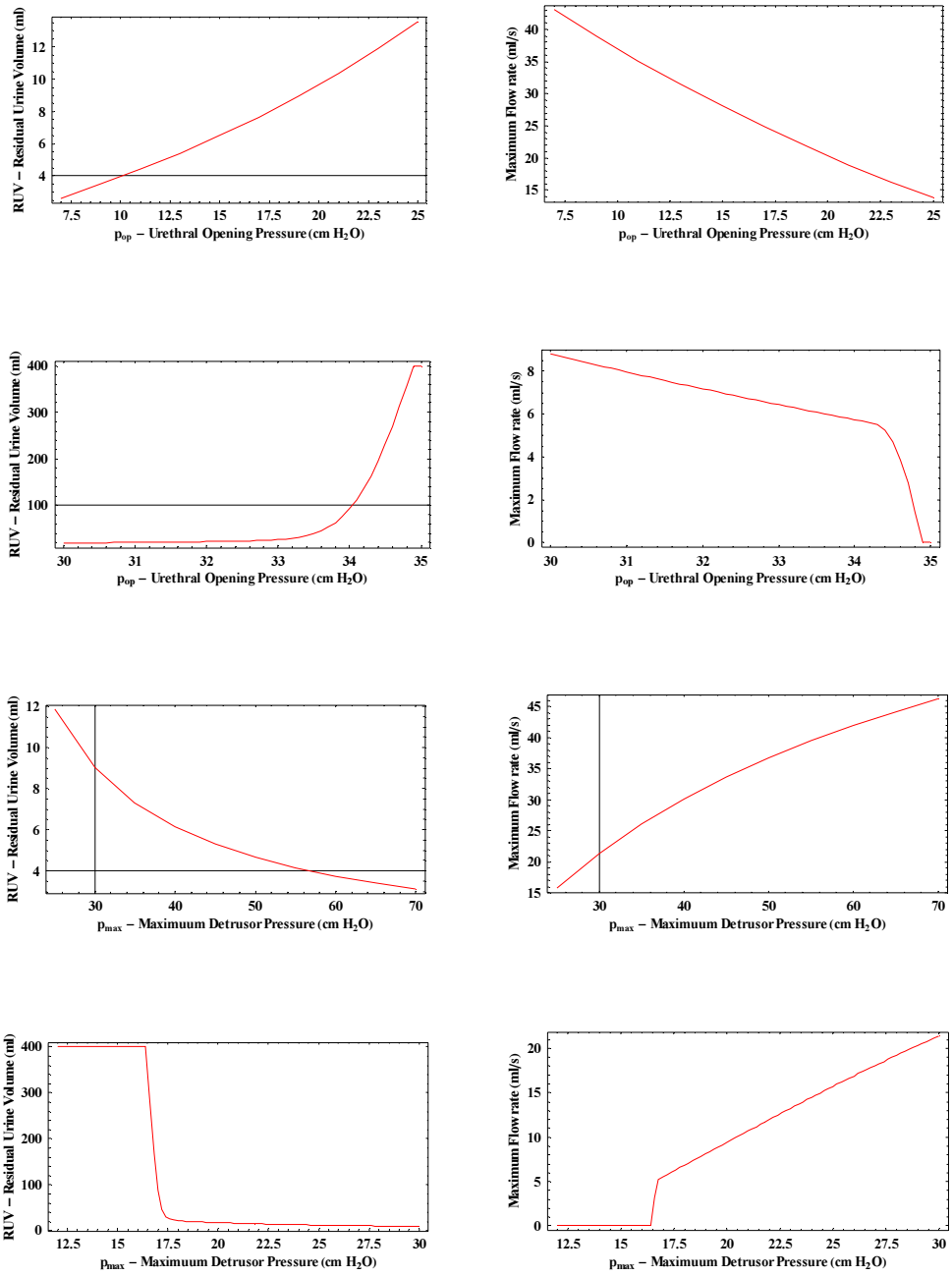


Figure 11: The effects of p_{OP} and p_{MAX}, on residual urine volume (RUV – graphs on the left) and the maximum flow rate ($Q_{\max}$ – graphs on right).

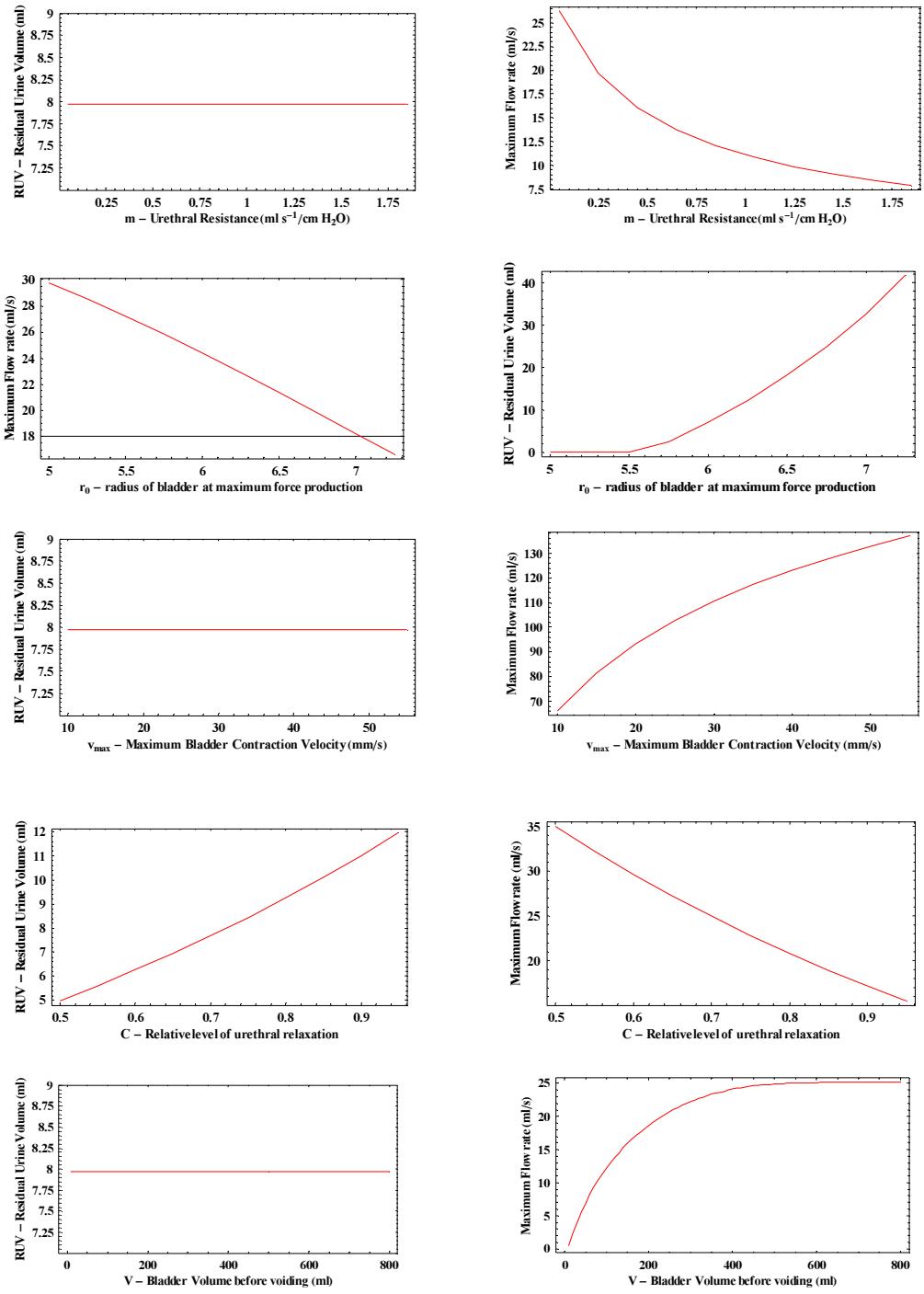


Figure 12: The effects of m, r_0, v_{MAX}, C and initial bladder volume V, on residual urine volume (graphs on the left) and maximum flow rate (graphs on right).

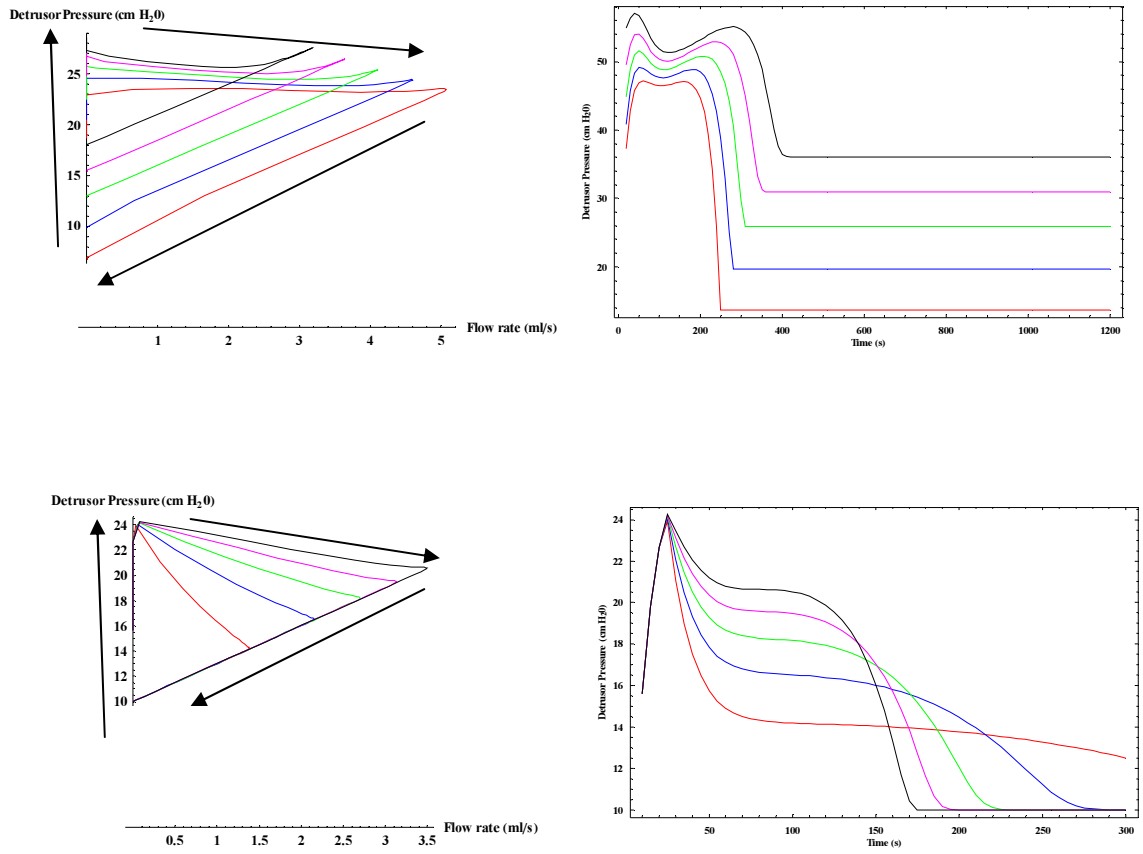


Figure 13: Typical pressure-time plots (on the right) and pressure-flow plots (on the left) that can be obtained from the model by fine tuning the simulation parameters. From top to bottom the graphs represent varying p_h and $v_{\max}$, and on the left the arrows indicate the direction of time during the flow.

Appendix A - Experimental methods and motivations for creating a model

Investigation of the process by which urine is expelled from the body, named "micturition", is normally both obtrusive and inconvenient to the patient. This is due to the need for simultaneous knowledge of the detrusor pressure and flow rate. As an example consider the process a patient had to endure to take part in a typical study that was carried out by Schmidt *et al* [28] in 2002.

Detrusor pressure is normally taken to be the difference between the pressure inside the bladder and the abdominal pressure. As part of the experiment [28], in order to measure these two pressures, each patient had a suprapubic double catheter passed into the bladder (under ultrasound guidance) and a balloon catheter inserted into the rectum. Every time the patient voided they were asked to hook themselves up to pressure transducers and a flowmeter, then collect their expelled urine.

Other studies often involve vaginal or transurethral catheterization, the need for participants to keep detailed diaries of their daily defecation and micturation habits, or require that participants follow a strict diet or fluid intake regimen. These studies are more than just an inconvenience to participants, they can be physically damaging and psychologically distressing. On top of this there is often the chance of infection and data obtained about the whole process is, at best, incomplete or imprecise. There is another approach that can be taken.

Instead of pressure-flow studies, voiding nomograms of uroflowmetry are a simple non-invasive screening test for voiding dysfunction. Every recorded flow curve contains a great deal of information. Only a small amount of this information is taken into account by normal methods of analysis. As Valentini *et al* point out [27], much more significant data can be extracted from the recorded curves by comparing them to curves calculated from a theoretical model.

It is therefore understandable that there is great motivation in the urological community to create an accurate, reliable mathematical model of micturition. Ideally such a model could be used as a diagnostic tool to replace invasive experimental measurements, or at least reduce the frequency of their necessity.

Appendix B - Derivation of the BOR

In order to model the bladder one must consider the force that it can produce. Almost all papers concerning this topic reference the work of Hill [29] in 1938. By investigating the contractile behaviour of detrusor muscle strips, Hill derived the following well known force-velocity relation for striated muscle:

$$(F+a)(v+b)=(F_0+a)b$$

where F is force, v is the velocity of the muscle shortening, a and b are constants and F_0 is the isometric force, i.e. $F=F_0$ when $v=0$. Hill found that $\frac{a}{F_0}\approx 0.25$. This was confirmed, via in vitro measurements of complete pig bladders, by van Mastrigt *et al* [17], who found a similar value of $\frac{a}{F_0}\approx 0.27$.

Similar experiments by Hellstrand [30] and Murphy [31] confirm this. Infact, for urinary bladder muscle, and muscle in general, $\frac{a}{p_0}$ (and $\frac{a}{F_0}$ for strips of muscle) is found to be approximately equal to 0.25 [26].

Griffiths et al [32] performed experiments on urinary bladder strips and showed that although F and F_0 both depend on the extension of the strip, $\frac{F}{F_0}$ depends only on v to first order. So we can write the Hill equation in a normalised form:

$$\left(\frac{F}{F_0}+\frac{a}{F_0}\right)\left(v+b\right)=\left(1+\frac{a}{F_0}\right)b$$

This equation, sometimes called the Bladder Working Function [3], only describes the behaviour of muscle strips. It is therefore necessary to transform this equation from one describing a force-velocity relation into one describing a pressure-flow relation. A widely used approach to relate force and pressure [17] is to consider the force F as the total force acting around the circumference of the bladder which is itself treated as a thinly walled sphere of radius r.

$$F=\pi r^2 p \quad \text{and} \quad F_0=\pi r^2 p_0 \quad \Rightarrow \frac{F}{F_0}=\frac{p}{p_0}$$

Thus the Hill equation can be written in the following form: $\left(\frac{p}{p_0}+\frac{1}{4}\right)(v+b)=\frac{5}{4}b$

Comparing with $\left(\frac{p}{p_0}+\frac{a}{p_0}\right)\left(v+\frac{a}{p_0}v_{\max}\right)=\left(1+\frac{a}{p_0}\right)\frac{a}{p_0}v_{\max}$ [26] we can simply write:

$$\left(p+\frac{p_0}{4}\right)\left(v+\frac{v_{\max}}{4}\right)=\frac{5}{16}p_0v_{\max}$$

This equation can be transformed further. If the bladder's volume is V, the flow rate of urine to the urethra is Q and v is the contraction velocity of the bladder wall, (i.e the velocity of the shortening of the bladder circumference) then we can derive a velocity-flow relation as follows [17].

$$Q=-\frac{dV}{dt}=-\frac{d}{dt}\left(\frac{4\pi}{3}r^3\right)=-4\pi r^2\frac{dr}{dt} \quad \text{and} \quad v=-\frac{d}{dt}(2\pi r)=-2\pi\frac{dr}{dt}$$

$$\Rightarrow\ Q=2r^2v$$

This yields the equation used by Hübener *et al* in their 1994 paper [1] which shall be employed at the core of this simulation.

$$\left(p+\frac{p_0}{4}\right)\left(Q+\frac{Q_0}{4}\right)=\frac{5}{16}p_0Q_0$$

where $p=p_0$ when $Q=0$, $Q=Q_0$ when $p=0$ and $Q_0=2r^2v_{\max}$. This equation relates p (detrusor pressure) to Q (rate of flow from the bladder) at any particular point in time. The relation is represented by blue hyperbolae in Figure 4 and the equation shall henceforth be referred to as the BOR (Bladder Output Relation).

Note that $p_0(r)=\frac{F_0}{\pi r^2}$ and $Q_0(r)=2r^2v_{\max}$.

An example of the length dependence of force generation in urinary bladder is shown in [22]. The curve representing this relation was fitted using a parabola which, assuming the bladder has a spherical geometry, may be written:

$$F_0=-2.04\left(\frac{r}{r_0}\right)^2+4.08\left(\frac{r}{r_0}\right)-1.04$$

This is the equation employed to describe the bladder force in this paper.

Appendix C - Choice of parameter values

In order to attempt making the model more than a purely theoretical tool, the number of free parameters must be reduced somehow. This is done by identifying physiological values for parameters wherever possible.

In this model so far we have 7 parameters, namely $k_1, k_2, C, r_0, v_{MAX}, p_h$ and m_h. As Griffiths *et al* point out; almost any arbitrary curve could be fitted by adjusting so many parameters. Griffiths was referring to his own model [14] (also with 7 parameters) when he said this. He approached the problem by directly estimating 5 of these parameters from independent clinical measurements and assuming that any difference between calculated and measured flow curves was down to the final 2 parameters. A similar process was attempted in this paper.

Intrinsic Parameters

There is a scarcity of physiological data on which to base the relative rates and strengths of the excitation and inhibition provided by the theoretical signals s_1 and s_2. In light of the "mutual inhibition" mechanism that has been proposed [8], equal but arbitrary values of $k_1 = k_2 = 0.5$ were chosen in this paper.

F_0 depends on r_0 as well as r. The value r_0 represents the bladder radius at which F_0, the isometric force produced, reaches its maximum value of 1, i.e. $F_0(r_0) = 1$. Now at $r \approx 0.3\, r_0$ and $r \approx 1.7\, r_0$ the bladder generates no force ($F_0(0.3r_0) = F_0(1.7r_0) = 0.0004 \approx 0$). Based on this, the assumption was made that for $r = 0.3\, r_0$ the bladder is totally empty with a tissue volume of V_0. V_0 represents a dead volume of effectively non-contracting tissue enclosed by the contracting part of the detrusor and may be taken as a variety of values. For example, Hübener *et al* [1] use $V_0 = 20ml$, Griffiths *et al* [8] use $V_0 = 10ml$ and Colding-Jørgensen *et al* [8] use $V_0 = 50ml$. An intermediate value of $V_0 = 25ml$ was used in this paper.

$$V = \frac{4\pi}{3} r^3 \text{ , implies } 0.3\, r_0 = \frac{3}{4\pi}\left(V_0\right)^{\frac{1}{3}} \text{, i.e. } r_0 = \frac{3}{0.3 \times 4\pi}\left(25\right)^{\frac{1}{3}} = 6.05\, cm \text{ to 2 DP.}$$

A typical figure for v_{MAX}, the maximum contraction velocity of the bladder, is given by Griffiths *et al* [8] as $v_{MAX} = 20\ mm/s$. A similar figure of $v_{MAX} = 22\ mm/s$ was empirically calculated by Rollema *et al* [15] and it is this figure that shall be used in this paper.

$$p_0 = p_m \frac{F_0}{\pi r^2} s_1 \quad \text{where} \quad F_0 = -2.04\left(\frac{r}{r_0}\right)^2 + 4.08\left(\frac{r}{r_0}\right) - 1.04$$

Now, $p_m \frac{F_0}{\pi r^2}$ has a single maximum (when $s_1 = 1$) that can easily be calculated to be at $r = 0.509804\, r_0$. Using the value for r_0 above and rewriting $p_m = D\, p_{MAX}$ where D is a constant chosen so that the maximum of $D\frac{F_0}{\pi r^2}$ is equal to 1 gives $p_0 = 58.6\, p_{MAX} \frac{F_0}{\pi r^2} s_1$. In this way a maximum value of p_0 called p_{MAX} can be explicitly given to the simulation.

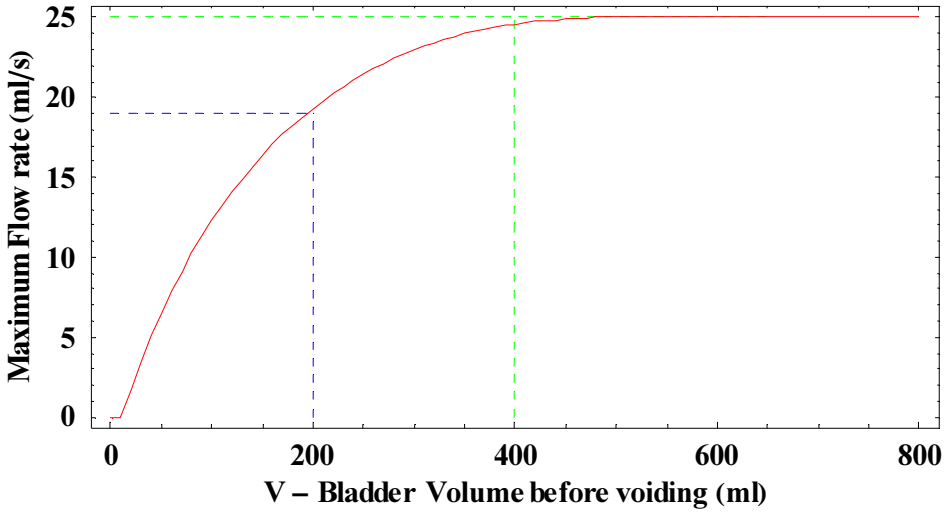
Appendix D - "Fine Tuning" Parameters

The model is perfectly capable of producing physiologically feasible data from very unphysiological values for its parameters. An attempt was made to pick the remaining parameters according to clinical data.

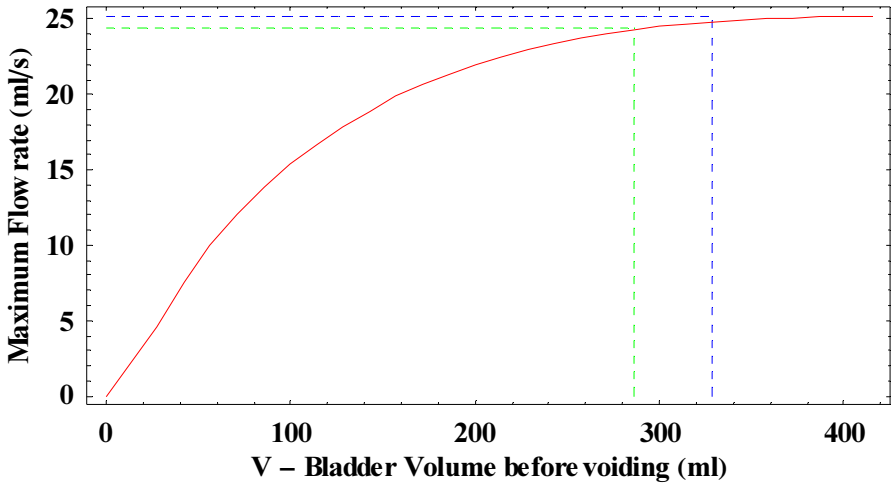
A study of the hydrodynamics of micturition in healthy females [16] found that the maximum flow rate of urine from the bladder increased with volume up to a certain threshold limit, whereafter the maximum flow rate was independent of initial bladder volume. This phenomenon has been noticed before [15] and is presented as a result of the original version of this model by Hübener *et al* [1]. Therefore this is a feature that is desirable for the model to recreate when using "physiological parameters".

The authors of [16] identify just such a threshold limit (of 400ml) and outline empirical values for many of the remaining parameters derived from the study. The urethral resistance, the detrusor and intravesical pressures, and the maximum flow rates for micturition from different initial bladder volumes are all given, along with statistical analysis of the significance of the results. The values of p_{MAX}, p_h, and m_h were taken directly from this data. The statistically soundest results in the study are from a bladder volume of 400ml and so it is these results (and an initial bladder volume of 400ml) that were used in this simulation.

The remaining parameters Q_m and C were then varied by an iterative method until the curve of initial bladder volume versus maximum flow rate approximated the data given in [16]. The values chosen were $Q_m = 2$ and $C = 0.72$, and the approximation can be seen in the graph on the following page.



A similar process was also attempted with the data from a separate study [28] concerning healthy males. The values for the URR used in this case were those found empirically by Bates *et al* [33] and used by Griffiths in his model [14]. The fit produced for this scenario is shown below.



Due to a lack of explicit values for other parameters needed to "fit" or check the model this line of enquiry was not pursued for the male urodynamical data.

Ultimately the "fitting process" did not produce output values of parameters that correlated with the raw data in [16]. This could be down to invalid assumptions made in this Appendix but given more time I would have liked to investigate what seems like an inconsistency in the units of the urethral resistance measure (or an implication of a quadratic URR) used in [16] that may have been the cause.

Appendix E - Alternatives to BOR and URR and other models

There are many other models published in the literature that try to describe the process of micturition. Some are based on mechanical properties [3, 34], some on neural properties [8] (largely because most dysfunctions are either neurogenic or myogenic in origin), some try and combine the two [35], but most don't consider every aspect of the problem.
In many cases parameters are adjusted manually to provide a fit to clinical data, as was attempted in this paper. This Appendix will briefly mention some of the other published models and their differences to the model proposed in this paper.

As Hosein *et al* point out [8], any model necessarily contains arbitrary features and simplifications and can therefore never be completely realistic. However it can suggest if a particular control system is possible in principle. There are many differing approximations to real urodynamical flow that have been employed over the years.

Griffiths *et al* [14] used a linear URR of the same form as the one used in this paper. But instead of the hyperbolic form of the BOR used in this paper, they approximated bladder pressure-flow characteristics with a linear function:

$$\frac{p_{\det}}{p_{iso}} = 1 - \frac{v}{v^*} = 1 - \frac{Q}{Q^*}$$

where $p_{\det}$ is the detrusor pressure, p_{iso} is the isometric pressure, v is the contraction velocity of the bladder musculature, Q is the rate of flow and v^* and Q^* are estimates of the maximum contraction velocity and the maximum flow rate the bladder would produce if it were to discharge through a urethra of zero resistance.

Considerations of energy conservation gave rise to an alternative form for the URR, first proposed by Schafer *et al* [36] in 1985:

$$p = p_{OP} + \frac{Q^2}{2A}$$

where Q is the rate of flow and p_{OP} is the same urethral opening pressure as described in this paper. A is the mean cross sectional area of the urethra, which varies considerably in males [9]. A similar form of the URR with a quadratic dependence on Q but no dependence on urethral area:

$$p = p_{OP} + R\,Q^2$$

is used in some models [8] and given more time this equation would have been tested in the model. In particular, the fit to the clinical data in [16] would have been attempted with this function, as the term R here is also often referred to as the "urethral resistance" (the phrase used by the authors of [16]).

Work done by Kranse *et al* suggest that the linear form of the URR is a better approximation to the lowest part of pressure flow plots [12] than a quadratic form and that was the motivation for Hübener *et al* to choose the linear form to begin with. At any rate, all these relations are just approximations.

To get the best results one needs to simplify as little as possible. Take the urethra for example: Existing mathematical models are based on frictional resistance to flow through the urethral tube [37] or urodynamic parameters through an elastic tube [38, 39, 40]. The urethra is generally assumed to be a straight, smooth walled circular tube. Measured detrusor pressure and flow rate are used to determine an "effective" urethral diameter and therefore, urethral restriction.

Recent dynamic video x-ray studies have demonstrated that the urethra is not a straight tube, either at rest or during micturition [41, 42]. The model proposed by Petros *et al* is centred on the far more complex equation:

$$\Delta P = P_{ves} - P_0 = \frac{8 \rho Q^2 L f}{\pi^2 d^5} + \frac{1}{2} \rho V^2 - \rho g \Delta h$$

where the pressure difference ΔP is the difference between the intravesical pressure P_{ves}, and the pressure acting at the tube exit P_0. Q is the volume flow rate, ρ is the fluid density, g is the acceleration due to gravity, f is the frictional factor, and Δh is the change in height of the urethra from one end to the other. Petros *et al* have shown that this equation gives an extremely good first approximation to the pressure-flow characteristics of an actual urethral tube [42]. As well as considering the effects of gravity and friction this model takes into account the effect of the pelvic floor muscles. The most successful models seem to follow this pattern of simplifying as little as possible.

Probably the most successful published model at the moment is the VBN model, named after its three creators Valentini, Besson and Nelson [5, 9]. In this model the changing cross-sectional area and elastical properties of the urethra are considered and a simple sphincteric control region is included. The muscular force that the bladder wall produces in the model is complex, the elasticity is described as "elaborate" and the force interacts with the relatively simple nerve signals in an intricate way. Perhaps most importantly, the flow through the urethra is not approximated in any way. The flow is calculated directly from the basic equations of hydrodynamics, the urethral resistance is calculated from the flow and varies during micturition. Friction is considered, (so Bernouilli's equation cannot be used) and adds only a slight component to the urethral resistance [9].

In idealized voiding, urine is expelled by detrusor contraction and the contributions from gravity and abdominal straining are ignored. As the effective abdominal pressure is only a weak contribution to the flow rate, for the identification of detrusor contractile strength, the contribution of abdominal straining has to be eliminated. [3]

The unaltered calculated flow curves produced by the VBN model [9] are very convincing and when other effects, such as abdominal straining, are taken into account, the agreement between calculated and recorded flow curves is quite remarkable.

There are a variety of other types of published model. Some are based on iterative methods, like [43] which is mathematically very complex, others are based on finite element methods [44]. Another approach is to employ a model based on neural networks [2] since they are "a tool which adapts well to this type of system" in having a high tolerance to faults, a low sensitivity to noise and ease with modelling non-linear functions.

[35] is a biomechanical model of the lower urinary tract which is able to respond to input signals from a neural network control model previously developed by the authors. This model makes use of Bernouilli's equation. Unlike most models of urinary function [35] is not lacking a description of urethral sphincter dynamics. Sphincters can be the topic of models themselves. [45] is one such model, that also employs neural networks. It is a multi compartment model that provides neural signals at the level of action potentials.

The variety of methods employed in modelling the processes involved in the LUT means that there will be many more attempts to refine, and possibly combine, these models in years to come. There is a very real need and demand, amongst the urological community, for a good, accurate and working model that could perhaps one day replace all the invasive and distressing experimental methods outlined in Appendix A.