# COMPLEX MODEL OF THE LOWER URINARY TRACT

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**Abstract:** The complex model of the lower part of the urinary tract is introduced. It consists of the detrusor smooth muscle cell model and the detailed 1D model of the urethra flow. The nerve control is taken into account. In future this model will allow to simulate the influence of different drugs and mechanical obstructions in the bladder neck and urethra. A general muscle model involving the calcium dynamics in the smooth muscle cell and the growth and remodelling theory will be shortly introduced. For the modelling calcium dynamics the approach from Koenigsberger at al. (2008) was adopted. The model includes the ATP consumption calculation according to Hai and Murphy (1992). The main part is devoted to the development of a simple bladder model and the detrusor contraction during voiding together with the detailed model of the urethra flow.

Keywords: urinary tract, bladder, urethra fluid flow, steady state preserving

#### 1. Introduction

The voiding is a very complex process. As we can see from Fig. 1 it consists of the transfer of information about the state of the bladder filling in to the spinal cord. Next part is the sending of the action potentials to the smooth muscle cells of the bladder. Even this process is not simple and includes the spreading of the action potential along the nerve axon and the transmission of the mediator (Ach - acetylcholine) in the synapse. The action potential starts the process of the smooth muscle contraction.

The smooth muscles have a lot of different forms in contradiction with the striated muscles. They are present in vesicles, arteries and others hollow organs.

Although the own biological motor - sliding between actin and myosin fueled by hydrolysis of ATP-is the same here as well as in striated and heart muscles, there are important differences between these basic types of muscles and also between smooth muscles in different organs. The sliding between actin and myosin causing the change of the form (length) of the muscle cell and its stiffness can be observed as a kind of growth and remodeling. This approach described e.g. in Rosenberg and Hynčík (2008) and Rosenberg and Hynčík (2007) is used in this model. It should be mentioned that a lot of different smooth muscle cells (SMC) models exist. They are based either on Huxley model where the calcium dynamics is not taken into account in details or on the contrary the calcium dynamics and the phosphorilation is modeled very precisely but the mechanochemical coupling is based on the work on Hai and Murphy (1992) where the stress in the muscle cell depends linearly on the amount of the bonded crossbridges either phosphorilized or unphosphorilized (e.g. Parthimos at al. (2007), Koenigsberger at al. (2008), where the model is applied to the SMC in the vessels).

To be able to describe the very complex processes in the SMC in the efficient form it is necessary to use the irreversible thermodynamics. This approach was described in Rosenberg and Svobodová (2010).

Using all these approaches the algorithm published in Rosenberg (2011b) was developed. In this contribution we join on the results of this paper. The simple model of the whole bladder and the detailed 1D model of the urethra flow is added. Some examples of the numerical experiments are shown.

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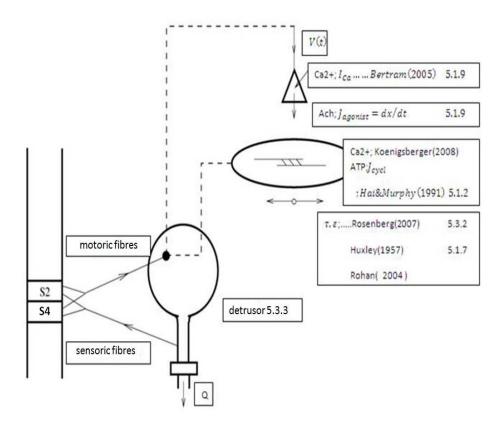


Fig. 1:

### 2. Bladder contraction

As it was already mentioned, the whole model of the bladder contraction is described in Rosenberg (2011a). It consists of the following parts:

- Model of the time evolution of the Ca2++ concentration five equations Koenigsberger at al. (2008). The Ca2++ intracellular concentration is the main control parameter for the next processes and finally for the smooth muscle contraction. Its increase depends on the flux J<sub>agonist</sub> of the mediator (in this case acetylcholine) via the nerve synapse.
- Model of the time evolution of the phosporilation of the light myosin chain three equations Hai and Murphy (1992). The muscle cell contraction is caused by the relative movement of the myosin and actin filaments. For this it is necessary that the phophorilation of the mentioned light myosin chain on the heads of the myosin occurs. Knowing this process also the time evolution of the ATP consumption ( $J_{cycl}$ ) can be determined. The ATP (adenosintriphosphate) is the main energy source for the muscle contraction.

### 3. Model of the own contraction based on the GRT and the irreversible thermodynamics

The growth and remodelling theory Dicarlo and Quiligotti (2002) together with the laws of irreversible thermodynamics with internal variables was applied in Rosenberg and Svobodová (2010) to describe the mechano-chemical coupling of the smooth muscle cell contraction. The product of the chemical reaction affinity (the ATP hydrolysis) with its rate plays an important role in the discussed model. Further it can be assumed that the rate of the ATP hydrolysis depends on the ATP consumption. The corresponding equations in the non-dimensional form are following:

$$\dot{x} = \frac{g}{h} \left[ \tau' - zy(x-1) \right] = k_1 \left[ \tau' - zy(x-1) \right],\tag{1}$$

$$\dot{y} = \frac{y}{k_2} \left[ x\tau' - \frac{1}{2}zy(x-1)^2 + C' \right],\tag{2}$$

where

$$\dot{z} = \operatorname{sgn}(m) \cdot \left[ r - \frac{1}{2} z (x - 1)^2 \right],$$

$$x = \frac{l'}{l'_r}, y = l'_r, z = k,$$

$$\frac{l}{l_0} = x \cdot y$$

$$k' = k \sqrt{\frac{|m|}{g}},$$

$$l'_r = \frac{l_r}{l_0},$$

$$t' = \frac{t}{\sqrt{g|m|}}.$$

$$(3)$$

 $l_0$  is the initial length of the muscle fibre,  $l_r$  its length after stimulation when the fibre is unloaded (s. c. resting length), l the actual length (when the contraction is isometric this is the input value), t' the stress and k is the fibre stiffness. The non-dimensional values are labeled with the single quote mark. The others symbols are the parameters. The most important parameter is C'. Using the irreversible thermodynamics we can obtain the following relations

$$C' = p \cdot (C - a_{chem}Y) \sqrt{\frac{|m|}{g}},$$

$$C\sqrt{\frac{|m|}{g}} = C_0 + C_t e^{q\left(\frac{l}{l_0} - \frac{l}{l_0}|_{opt}\right)^2},$$

$$p = p_0 e^{s\left(\frac{l}{l_0} - \frac{l}{l_0}|_{opt}\right)^2},$$
(4)

where for the afinity of the chemical reactions especially for the hydrolysis of the ATP gilt

$$a_{chem} = -Q \cdot Y. \tag{5}$$

Q is the constant and Y is the concentration of ATP. For its time evolution gilts Pokrovski (2005)

$$\dot{Y} = -QQ \cdot Y + L \cdot J_{cycle}. \tag{6}$$

Here QQ is the damping parameter. Than the whole model is finished because the ATP consumption  $J_{cycl}$  as a function of the Ca2+ concentration in the cytoplasm was already determined.

# 4. Bladder and voiding model

To model the contraction of the bladder during the voiding process we will use the very simple model according Laforet and Guiraud (2007) and Arts at al. (1991). The bladder is modelled as a hollow sphere with the output corresponding to the input into urethra.

For the pressure in the bladder the following formula is introduced in Laforet and Guiraud (2007)

$$p = \frac{V_{sh}}{3V} \cdot \tau, \qquad \tau = \frac{F}{S},\tag{7}$$

where  $V_{sh}$  is the volume of the wall, V the inner volume,  $\tau$  stress in the muscle fibre, S the inner surface and F the force in the muscle cell.

For the flux q gilts

$$q = \frac{dV}{dt},\tag{8}$$

where  $\rho$  is the density of the fluid.

Using the formulas for the isotonic contraction, we can at first obtain the relation for the volume. It gilts

$$l' = \frac{l}{l_0} = x \cdot y \tag{9}$$

and then

$$V = \kappa \cdot (x \cdot y)^3,\tag{10}$$

where  $\kappa$  is the constant which in the theoretical case if only one cell will occupy the circumference of the spherical bladder will be  $1/6\pi^2$ . Putting this formula into the equation for q and using the equations for the derivatives of x and y mentioned before we obtain the equation, from which we can calculate  $\tau$ :

$$\tau = \frac{\frac{q}{3\kappa(x\cdot y)^2} + \left[k_1 z y^2 (x-1) + \frac{z y^2 x}{2k_2} (x-1)^2 - \frac{x y}{k_2} C'\right]}{k_1 y + \frac{x^2 y}{k_2}}.$$
(11)

For the pressure gilts then

$$p = \frac{V_{sh}}{3\kappa \cdot (x \cdot y)^3} \cdot \frac{\frac{q}{3\kappa(x \cdot y)^2} + \left[k_1 z y^2 (x - 1) + \frac{z y^2 x}{2k_2} (x - 1)^2 - \frac{x y}{k_2} C'\right]}{k_1 y + \frac{x^2 y}{k_2}}.$$
 (12)

This will be putted into the equations for the isotonic contraction.

### 5. Urethral flow

We now briefly introduce a problem describing fluid flow through the elastic tube represented by hyperbolic partial differential equations with the source term. In the case of the male urethra, the system based on model in Stergiopulos at al. (1993) has the following form

$$a_t + q_x = 0,$$

$$q_t + \left(\frac{q^2}{a} + \frac{a^2}{2\rho\beta}\right)_x = \frac{a}{\rho} \left(\frac{a_0}{\beta}\right)_x + \frac{a^2}{2\rho\beta^2} \beta_x - \frac{q^2}{4a^2} \sqrt{\frac{\pi}{a}} \lambda(Re),$$
(13)

where a=a(x,t) is the unknown cross-section area, q=q(x,t) is the unknown flow rate (we also denote v=v(x,t) as the fluid velocity,  $v=\frac{q}{a}$ ),  $\rho$  is the fluid density,  $a_0=a_0(x)$  is the cross-section of the tube under no pressure,  $\beta=\beta(x,t)$  is the coefficient describing tube compliance and  $\lambda(Re)$  is the Mooney-Darcy friction factor ( $\lambda(Re)=64/Re$  for laminar flow). Re is the Reynolds number defined by

$$Re = \frac{\rho q}{\mu a} \sqrt{\frac{4a}{\pi}},\tag{14}$$

where  $\mu$  is fluid viscosity. This model contains constitutive relation between the pressure and the cross section of the tube

$$p = \frac{a - a_0}{\beta} + p_e,\tag{15}$$

where  $p_e$  is surrounding pressure.

Presented system (13) can be written in the compact matrix form

$$\mathbf{u}_t + [\mathbf{f}(\mathbf{u}, x)]_x = \psi(\mathbf{u}, x), \tag{16}$$

with  $\mathbf{q}(x,t)$  being the vector of conserved quantities,  $\mathbf{f}(\mathbf{q},x)$  the flux function and  $\psi(\mathbf{q},x)$  the source term. This relation represents the balance laws. For the following consideration, we reformulate this problem to the nonconservative form.

# **5.1.** Nonconservative problems

We consider the nonlinear hyperbolic problem in nonconservative form

$$\mathbf{u}_t + \mathbf{A}(\mathbf{u})\mathbf{u}_x = \mathbf{0}, \ x \in \mathbf{R}, \ t \in (0, T),$$
  
$$\mathbf{u}(x, 0) = \mathbf{u}_0(x), \ x \in \mathbf{R},$$
 (17)

The numerical schemes for solving problems (17) can be written in fluctuation form

$$\frac{\partial \mathbf{U_j}}{\partial t} = -\frac{1}{\Delta x} [\mathbf{A}^-(\mathbf{U}_{j+1/2}^-, \mathbf{U}_{j+1/2}^+) + \mathbf{A}(\mathbf{U}_{j+1/2}^-, \mathbf{U}_{j-1/2}^+) + \mathbf{A}^+(\mathbf{U}_{j-1/2}^-, \mathbf{U}_{j-1/2}^+)], \tag{18}$$

where  $\mathbf{A}^{\pm}(\mathbf{U}_{j+1/2}^-, \mathbf{U}_{j+1/2}^+)$  are so called fluctuations. They can be defined by the sum of waves moving to the right or to the left. The directions are dependent on the signs of the speeds of these waves, which are related to the eigenvalues of matrix  $\mathbf{A}(\mathbf{u})$ . In what follows, we use the notation  $\mathbf{U}_{j+1/2}^+$  and  $\mathbf{U}_{j+1/2}^-$  for the reconstructed values of unknown function. Reconstructed values represent the approximations of limit values at the points  $x_{j+1/2}$ . The most common reconstructions are based on the minmod function (see for example Kurganov and Tadmor (2000)) or ENO and WENO techniques Črnjarič-Zič at al. (2004).

The reconstruction can be applied to each component of  $\mathbf{u}$ . But this approach does not work well in general. It is better to apply the reconstruction to the characteristic field of  $\mathbf{u}$ . It means that each jump is decomposed to the eigenvectors  $\mathbf{r}$  of Jacobian matrix  $\mathbf{A}(\mathbf{u})$ .

$$\mathbf{U}_{j+1} - \mathbf{U}_{j} = \sum_{p=1}^{m} \alpha_{j+1/2}^{p} \mathbf{r}_{j+1/2}^{p}.$$
 (19)

Then the reconstruction based on minmod function can be defined by following

$$\mathbf{U}_{j+1/2}^{+} = \mathbf{U}_{j+1} + \sum_{p} \phi_{I+1/2}^{p,+} \alpha_{j+1/2}^{p} \mathbf{r}_{j+1/2}^{p},$$

$$\mathbf{U}_{j+1/2}^{-} = \mathbf{U}_{j} + \sum_{p} \phi_{I+1/2}^{p,-} \alpha_{j+1/2}^{p} \mathbf{r}_{j+1/2}^{p},$$
(20)

where

$$\phi_{I+1/2}^{p,\pm} = \mp \frac{1}{2} \left( 1 + \mathrm{sgn}(\theta_{I+1/2}^p) \right) \min(1, |\theta_{I+1/2}^p|) \tag{21}$$

and

$$I = \begin{cases} j - 1/2, & \text{if } s_{j+1/2}^p \ge 0, \\ j + 3/2, & \text{if } s_{j+1/2}^p < 0. \end{cases}$$
 (22)

The function  $\theta_{i+1/2}^p$  can be determined by the following way

$$\theta_{j+1/2}^{p} = \frac{\alpha_{j+1/2}^{p} \mathbf{r}_{j+1/2}^{p} \cdot \mathbf{r}_{I+1/2}^{p}}{\alpha_{I+1/2}^{p} \mathbf{r}_{I+1/2}^{p} \cdot \mathbf{r}_{I+1/2}^{p}}.$$
(23)

When the problem (17) is derived from the conservation form (16), i.e.  $\mathbf{f}'(\mathbf{u}) = \mathbf{A}(\mathbf{u})$  is the Jacobi matrix of the system, fluctuations can be defined as follows

$$\mathbf{A}(\mathbf{U}_{j+1/2}^{-}, \mathbf{U}_{j-1/2}^{+}) = \mathbf{f}(\mathbf{U}_{j+1/2}^{-}) - \mathbf{f}(\mathbf{U}_{j-1/2}^{+}), 
\mathbf{A}^{-}(\mathbf{U}_{j+1/2}^{-}, \mathbf{U}_{j+1/2}^{+}) = \mathbf{F}_{j+1/2}^{-} - \mathbf{f}(\mathbf{U}_{j+1/2}^{-}), 
\mathbf{A}^{+}(\mathbf{U}_{j-1/2}^{-}, \mathbf{U}_{j-1/2}^{+}) = \mathbf{f}(\mathbf{U}_{j-1/2}^{+}) - \mathbf{F}_{j-1/2}^{+}.$$
(24)

# 5.2. Decompositions based on augmented system

This procedure is based on the extension of the system (13) by other equations (for simplicity we omit viscous term). This was derived in George (2008) for the shallow water flow. The advantage of this step is in the conversion of the nonhomogeneous system to the homogeneous one. In the case of urethra flow we obtain the system of four equations, where the augmented vector of unknown functions is  $\mathbf{w} = [a, q, \frac{a_0}{\beta}, \beta]^T$ . Furthermore we formally augment this system by adding components of the flux function  $\mathbf{f}(\mathbf{u})$  to the vector of the unknown functions. We multiply balance law (16) by Jacobian matrix  $\mathbf{f}'(\mathbf{u})$  and obtain following relation

$$\mathbf{f}'(\mathbf{u})\mathbf{u}_t + \mathbf{f}'(\mathbf{u})[\mathbf{f}(\mathbf{u})]_x = \mathbf{f}'(\mathbf{u})\psi(\mathbf{u}, x). \tag{25}$$

Because of  $\mathbf{f}'(\mathbf{u})\mathbf{u}_t = [\mathbf{f}(\mathbf{u})]_t$  we obtain hyperbolic system for the flux function

$$[\mathbf{f}(\mathbf{u})]_t + \mathbf{f}'(\mathbf{u})[\mathbf{f}(\mathbf{u})]_x = \mathbf{f}'(\mathbf{u})\psi(\mathbf{u}, x). \tag{26}$$

In the case of the urethra fluid flow modelling we add only one equation for the second component of the flux function i.e.  $\phi=av^2+\frac{a^2}{2\rho\beta}$  (the first component q is unknown function of the original balance law), which has the form

$$\phi_t + (-v^2 + \frac{a}{2\rho\beta})(av)_x + 2v\phi_x - \frac{2av}{\rho} \left(\frac{a_0}{\beta}\right)_x - \frac{a^2v}{\rho\beta^2}\beta_x = 0.$$
 (27)

Finally augmented system can be written in the nonconservative form

briefly  $\mathbf{w}_t + \mathbf{B}(\mathbf{w})\mathbf{w}_x = \mathbf{0}$ , where matrix  $\mathbf{B}(\mathbf{w})$  has following eigenvalues

$$\lambda^1 = v - \sqrt{\frac{a}{\rho\beta}}, \lambda^2 = v + \sqrt{\frac{a}{\rho\beta}}, \lambda^3 = 2v, \lambda^4 = \lambda^5 = 0$$
 (29)

and corresponding eigenvectors

$$\mathbf{r}^{1} = \begin{bmatrix} 1\\ \lambda^{1}\\ (\lambda^{1})^{2}\\ 0\\ 0 \end{bmatrix}, \mathbf{r}^{2} = \begin{bmatrix} 1\\ \lambda^{2}\\ (\lambda^{2})^{2}\\ 0\\ 0 \end{bmatrix}, \mathbf{r}^{3} = \begin{bmatrix} 0\\ 0\\ 1\\ 0\\ 0 \end{bmatrix}, \mathbf{r}^{4} = \begin{bmatrix} \frac{-a}{\rho\lambda^{1}\lambda^{2}}\\ 0\\ \frac{a}{\rho}\\ 1\\ 0 \end{bmatrix}, \mathbf{r}^{5} = \begin{bmatrix} \frac{-a^{2}}{\rho\beta^{2}\lambda^{1}\lambda^{2}}\\ 0\\ \frac{a^{2}}{2\rho\beta^{2}}\\ 0\\ 1 \end{bmatrix}. \tag{30}$$

We have five linearly independent eigenvectors. The approximation is chosen to be able to prove the consistency and provide the stability of the algorithm. In some special cases this scheme is conservative and we can guarantee the positive semidefiniteness, but only under the additional assumptions (see Brandner at al. (2009)).

The fluctuations are then defined by

$$\mathbf{A}^{-}(\mathbf{U}_{j+1/2}^{-}, \mathbf{U}_{j+1/2}^{+}) = \begin{bmatrix} 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 1 \end{bmatrix} \cdot \sum_{p=1, s_{j+1/2}^{p, n}}^{m} \gamma_{j+1/2}^{p} \mathbf{r}_{j+1/2}^{p},$$

$$\mathbf{A}^{+}(\mathbf{U}_{j+1/2}^{-}, \mathbf{U}_{j+1/2}^{+}) = \begin{bmatrix} 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 & 1 \end{bmatrix} \cdot \sum_{p=1, s_{j+1/2}^{p, n}}^{m} \gamma_{j+1/2}^{p} \mathbf{r}_{j+1/2}^{p},$$

$$\mathbf{A}(\mathbf{U}_{j-1/2}^{+}, \mathbf{U}_{j+1/2}^{-}) = \mathbf{f}(\mathbf{U}_{j+1/2}^{-}) - \mathbf{f}(\mathbf{U}_{j-1/2}^{+}) - \mathbf{\Psi}(\mathbf{U}_{j+1/2}^{-}, \mathbf{U}_{j-1/2}^{+}),$$
(31)

where  $\Psi(\mathbf{U}_{j+1/2}^-, \mathbf{U}_{j-1/2}^+)$  is a suitable approximation of the source term and  $\mathbf{r}_{j+1/2}^p$  are suitable approximations of the eigenvectors (30).

### 5.3. Steady states

The steady state for the augmented system means  $\mathbf{B}(\mathbf{w})\mathbf{w}_x = \mathbf{0}$ , therefore  $\mathbf{w}_x$  is a linear combination of the eigenvectors corresponding to the zero eigenvalues. The discrete form of the vector  $\Delta \mathbf{w}$  corresponds to the certain approximation of these eigenvectors. It can be shown Brandner at al. (2009) that

$$\Delta \begin{bmatrix} A \\ Q \\ \Phi \\ \frac{a_0}{\beta} \\ \beta \end{bmatrix} = \begin{bmatrix} \frac{\bar{A}}{\rho} \frac{1}{\lambda^1 \lambda^2} \\ 0 \\ \frac{\bar{A}}{\rho} \frac{\widehat{\lambda}^1 \lambda^2}{\lambda^1 \lambda^2} \\ 1 \\ 0 \end{bmatrix} \Delta \begin{pmatrix} a_0 \\ \beta \end{pmatrix} + \begin{bmatrix} \frac{\bar{A}^2}{\rho \beta_{j+1} \beta_j} \frac{1}{\lambda^1 \lambda^2} \\ 0 \\ \frac{\bar{A}^2}{\rho \beta_{j+1} \beta_j} \frac{\widehat{\lambda}^1 \lambda^2}{\lambda^1 \lambda^2} - \frac{\tilde{A}^2}{2\rho \beta_{j+1} \beta_j} \\ 0 \\ 1 \end{bmatrix} \Delta \beta,$$
(32)

where 
$$\bar{A} = \frac{A_j + A_{j+1}}{2}$$
,  $\bar{\beta} = \frac{\beta_j + \beta_{j+1}}{2}$ ,  $\tilde{A}^2 = \frac{A_j^2 + A_{j+1}^2}{2}$ ,  $\tilde{V}^2 = |V_j V_{j+1}|$ ,  $\bar{V}^2 = \left(\frac{V_j + V_{j+1}}{2}\right)^2$  and 
$$\widetilde{\lambda^1 \lambda^2} = -\tilde{V}^2 + \frac{\bar{A}\bar{\beta}}{\rho\beta_{j+1}\beta_j}, \qquad \overline{\lambda^1 \lambda^2} = -\bar{V}^2 + \frac{\bar{A}\bar{\beta}}{\rho\beta_{j+1}\beta_j}.$$
 (33)

Therefore we use vectors on the RHS of (32) as approximations of the fourth and fifth eigenvectors of the matrix  $\mathbf{B}(\mathbf{w})$  to preserve general steady state.

### 5.4. Positive semidefiniteness

Positive semidefiniteness of this scheme is shown in George (2008) for the case of shallow water equation. It is based on a special choice of approximations of the eigenvectors (30). This, in the case of urethra flow, is more complicated because of the structure of the eigenvectors. Some necessary conditions for approximation of these eigenvectors are presented in Brandner at al. (2009).

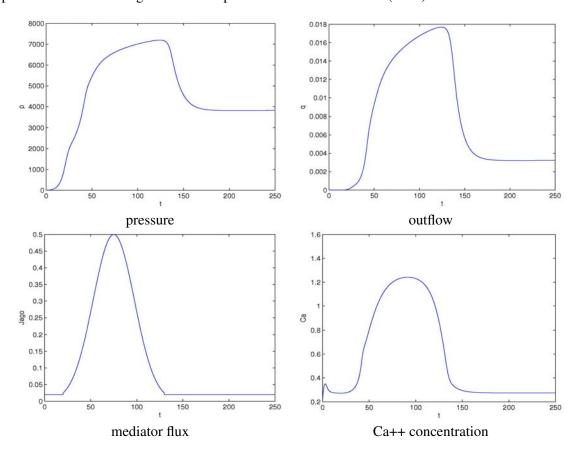


Fig. 2: Time evolution of the quantities at the bladder neck.

### 6. Numerical experiment

Now we present numerical experiment based on the system of differential equations described detrusor smooth muscle cell model (12 equations) and urethral flow (30 equations). The equations describing urethral flow are based on spatial high-resolution discretization of the urethra (15 finite volumes) described in section 5.2. The parameters used in this experiment are the same as in Rosenberg (2011a). The figures 2 illustrate time evolution of the quantities at the bladder neck. For the further application it is necessary to fit the parameters because of non-dimensionality of the equations describing the muscle contraction.

- 1. For the simplicity the precious modelling of the synapse is neglected and the mediator flux  $J_{agonist}$  is chosen see Fig. 2. The IC units are used although in the medical paper are used for intravesical pressure cm $H_2$ O ( 1 cm $H_2$ O = 0.1 kPa) and for the outflow ml/s. The concentration is measured in  $\mu$ M where M=mol/l.
- 2. At the Fig. 3 there are shown the cross-section area, velocity and flow rate along the whole urethra in two different times after beginning of voiding.

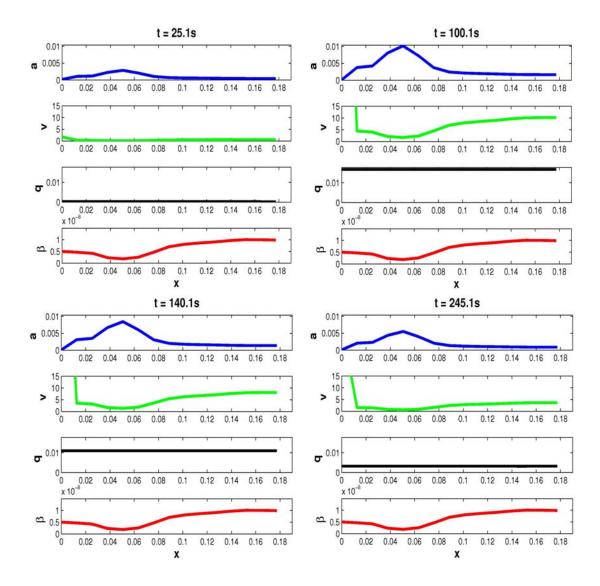


Fig. 3: Time evolution of the quantities through the urethra (cross section area, velocity, flow rate, tube compliance).

### 7. Conclusion

We presented the complex model of the lower part of the urinary tract. A simple bladder model and the detrusor contraction model were developed during voiding together with the detailed model of urethra flow. The urethra flow was described by the high-resolution positive semidefiniteness method, which preserves general steady states. For the practical application the identification of the parameters is necessary.

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