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Modelling the contraction properties of smooth muscle cells in bladder tissue

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The major function of the urinary bladder is the storage and release of urine. Undergoing large deformations while keeping the chemically aggressive urine and maintaining a relatively constant pressure during filling, the bladder shows remarkable mechanical properties. Those properties are based on the highly complex structure of the bladder wall. However, irregularities within the bladder wall may have negative implications on the correct functioning. In order to improve the understanding of different physiological processes taking place within the bladder wall during bladder filling and contraction, a computation tool is presented based on a continuum mechanics approach. In that sense the model is applied to complex boundary value problems.

1 Introduction

The bladder is a hollow organ which controls the storage and release of urine. The complex multilayered structure of the bladder wall is capable to undergo high deformations during filling while maintaining a relatively low pressure. Although consisting of three main layers, namely the *mucosal* (inner), *muscular* (middle) and *serosal* (outer) layer, it is widely accepted that only the inner and middle layer contribute to the mechanical properties of the bladder wall. Both layers are reinforced with fibrous material embedded in a matrix. The inner layer consists of strongly coiled collagen fibres that act as loadbearing components especially at higher deformations when collagen fibres become untangled. The middle layer comprises two layers of smooth muscle cells (SMCs) predominantly oriented in longitudinal and circumferential direction. Acting as a trigger the internal calcium concentration ($[\mathrm{Ca}^{2+}]$) is mainly responsible for controlling SMC contraction and relaxation by regulating the cross-bridge attachment. $[\mathrm{Ca}^{2+}]$ increase can occur over different excitation pathways, including electro-chemical and mechano-electrochemical pathway. Electrical excitation causes depolarisation of the resting membrane. Guided by voltage gated ion channels external calcium ions are then able to enter the SMCs. Alternatively, stretch dependent channels in the cell membrane allow various cations to enter the cell where they depolarise the membrane potential to enable the inflow of calcium ions over voltage gated ion channels. The proposed model in this work is based on a monolitic approach to analyse the spatial and temporal evolution of the mechano-electrochemical state.

2 Model

The analysis of bladder contraction involves initially three main field measures, namely, the motion $\boldsymbol{\varphi}$, the electrical membrane potential Φ and $[\mathrm{Ca}^{2+}]$. The spatial and temporal evolution of the field measures is governed by the balance of linear momentum and two diffusion-reaction type equations. To control membrane depolarisation, repolarisation and the mechanical electrical coupling at cell level a two variable FitzHugh-Nagumo type membrane model [1–3] is used as the constitutive relation for the source term in the governing equation of Φ. Assuming that spatial propagation of SMC activation is exclusively controlled by Φ and excluding any diffusion driven fluxes of calcium ions enables the treatment of the evolution of $[\mathrm{Ca}^{2+}]$ as a local problem where $[\mathrm{Ca}^{2+}]$ is defined as an internal variable. Being a function of Φ the influx of calcium ions follows a bell shaped curve. Reaching its peak at complete depolarisation the influx does not start instantaneously with depolarisation. It rather has to reach a threshold value before $[\mathrm{Ca}^{2+}]$ increases significantly. One major goal of the present work was the layer specific characterisation of the mechanical properties of the bladder wall including the active contraction of the middle layer. Material data was obtained from mechanical testing performed on tissue strips of the entire wall and middle layer harvested from the bladder wall. In order to account for the isotropic matrix and anisotropic fibrous material the overall strain energy is additively decomposed for the inner and middle layer as

$$\psi(\boldsymbol{\varphi}) = \psi_{\mathrm{e}}(\boldsymbol{\varphi}) + \psi_{\mathrm{c}}(\boldsymbol{\varphi}) \;\text{ and }\; \psi(\Phi, \left[\mathrm{Ca}^{2+}\right], \boldsymbol{\varphi}) = \psi_{\mathrm{ECM}}(\boldsymbol{\varphi}) + \psi_{\mathrm{s}}(\Phi, \left[\mathrm{Ca}^{2+}\right], \boldsymbol{\varphi}) \tag{1}$$

, respectively. Herein, index e and ECM refer to the isotropic material contribution of elastin and extra cellular matrix, respectively, and index c and index s denote the anisotropic contribution of collagen and smooth muscle cell in the corresponding tissue layer. The active component of ψ_{s} is triggered by the four-state, cross-bridge model of Hai and Murphy [4] where each state represents the chemical condition of the cross-bridge during the contraction process with two non-force-generating

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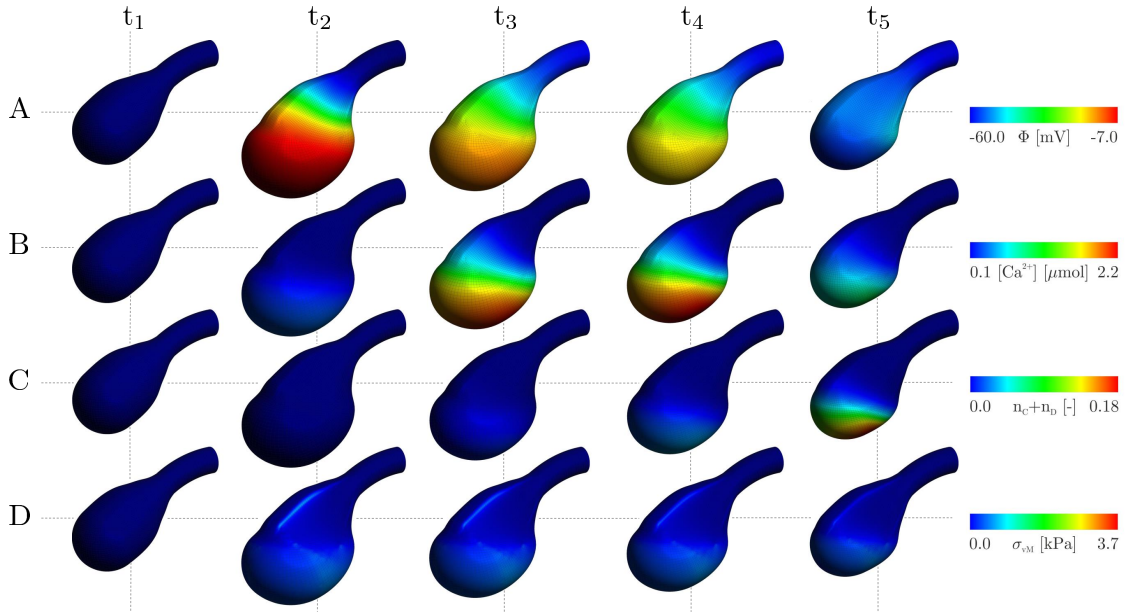

Fig. 1: Numerical results showing the evolution of Φ, Ca^{2+}, $\mathrm{n_c} + \mathrm{n_d}$ and σ_{vM} during bladder inflation and contraction [5].

and two force-generating states. Finally, $[\mathrm{Ca}^{2+}]$ is incorporated into the cross-bridge model to be the driving force for SMC contraction [6].

3 Results

In order to show the capability of the proposed model, bladder filling and contraction are simulated using a simplified three-dimensional geometry of the bladder. Thereby, the incoming urine is simply modelled as a linearly increasing pressure acting on the lower half of the bladder wall. At the beginning, the bladder is empty and all measures characterising the mechano-electrochemical state remain in their initial state as shown in Figure 1 for $\mathrm{A_{t_1}}$-$\mathrm{D_{t_1}}$. Herein, the amount of active SMCs is represented by the expression $\mathrm{n_c} + \mathrm{n_d}$ referring to the portion of force-generating states of the four state, cross-bridge model of Hai and Murphy. During bladder inflation the mechano-electrical coupling enables the depolarisation of Φ and therefore the increase of Ca^{2+}, see $\mathrm{A_{t_2}}$ and $\mathrm{B_{t_2}}$. Due to the delay between Ca^{2+} and $\mathrm{n_c} + \mathrm{n_d}$ the contribution of active stresses remain nearly zero, see $\mathrm{C_{t_2}}$ and $\mathrm{D_{t_2}}$. Since pressure remains constant and SMC contraction starts propagating, repolarisation of Φ is initiated while Ca^{2+}, $\mathrm{n_c} + \mathrm{n_d}$ and consequently the amount of active stresses are still increasing, see $\mathrm{A_{t_3}}$-$\mathrm{D_{t_3}}$. After Φ has dropped significantly due to contraction, Ca^{2+} reaches, unlike $\mathrm{n_c} + \mathrm{n_d}$ and the portion of active stresses, finally its peak value, see $\mathrm{A_{t_4}}$-$\mathrm{D_{t_4}}$. In the final state of the analysis the initial resting condition of Φ and Ca^{2+} is partly restored as shown for $\mathrm{A_{t_5}}$ and $\mathrm{B_{t_5}}$. Due to the level of contraction almost the entire load is carried by the active material contribution with almost zero passive stresses, see $\mathrm{C_{t_5}}$ and $\mathrm{D_{t_5}}$.

4 Conclusion

This work presents a three dimensional continuum mechanics based computation tool to simulate the evolution of the mechano-electro-chemical state of the bladder wall during the process of filling and contraction. In order to improve computational efficiency a monolithic approach, where the mechanical and electrical state variable are computed simultaneously, is embedded in the framework of finite elements. A simplified geometry of the real bladder was created, where the two loadbearing components of the bladder wall are modelled as separate layers using layer specific material data. SMC contraction can be initiated by either the (direct) electro-chemical or the (indirect) mechano-electrochemical excitation pathway.

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