BOOM: towards a digital twin of the bladder

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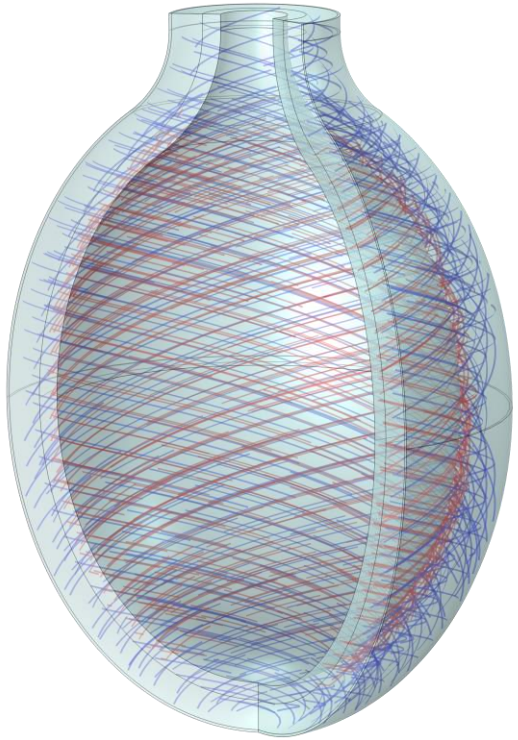
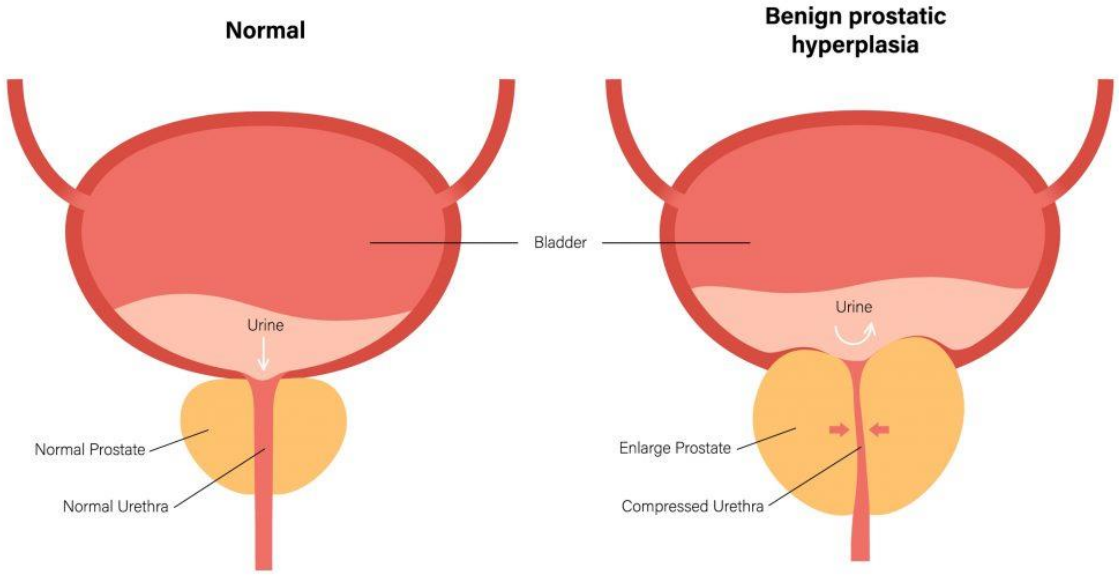


Bladder Outlet Obstruction (BOO)

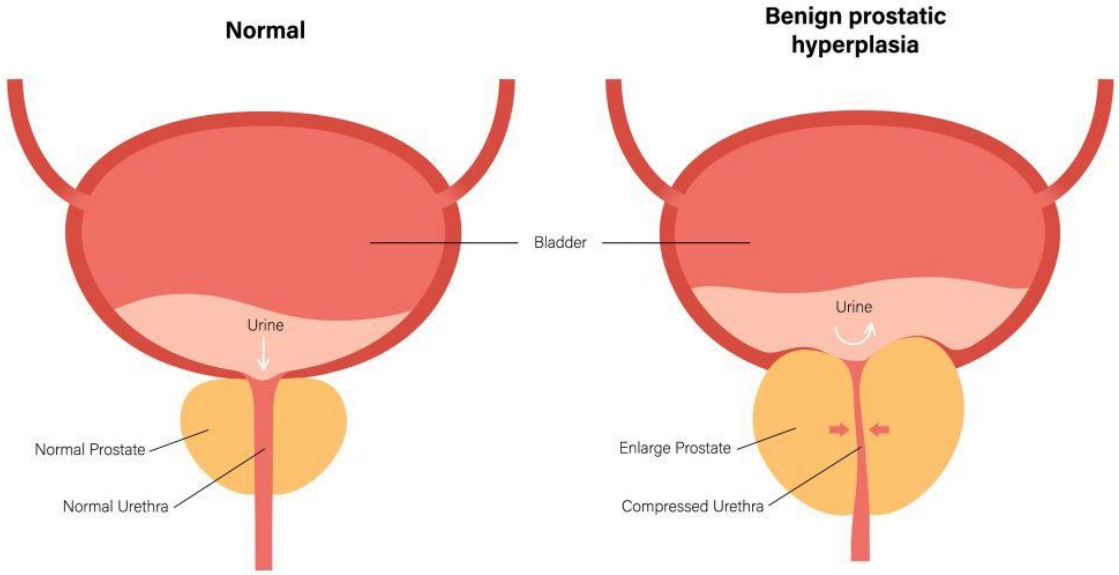
- The bladder is a compliant organ whose role is to store and empty urine
- Outlet obstruction is characterised by increased urethral resistance, typically due to benign prostate hypertrophy (BPH)
- Gives rise to myriad of lower urinary tract symptoms (LUTS), 50-75% of men over 50 experience LUTS because of BPH
- Affect bladder storage and function, resulting in lower quality of life
- Pharmacological interventions (anti fibrosis, reduce oxidative stress)
- Surgery to remove obstruction, $\frac{1}{3}$ of patients who undergo surgery remain symptomatic



https://aareurology.sg/conditions/bladder-outlet-obstruction/

Bladder outlet obstruction mechanobiology (BOOM)

- Bladder must generate greater pressures to void to overcome increased resistance
- Mechanobiological response to this increased resistance
- Changes in bladder structure, impacting functionality
- 3 key stages of BOO progression



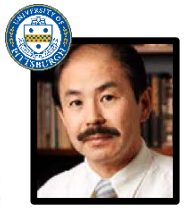
BOO Progression

- **Hypertrophy**: SMC growth to overcome increased urethral resistance
- **Compensation**: growth stabilises and increased ECM deposition
- **Decompensation:** increased collagen deposition, SMC apoptosis and loss of functionality

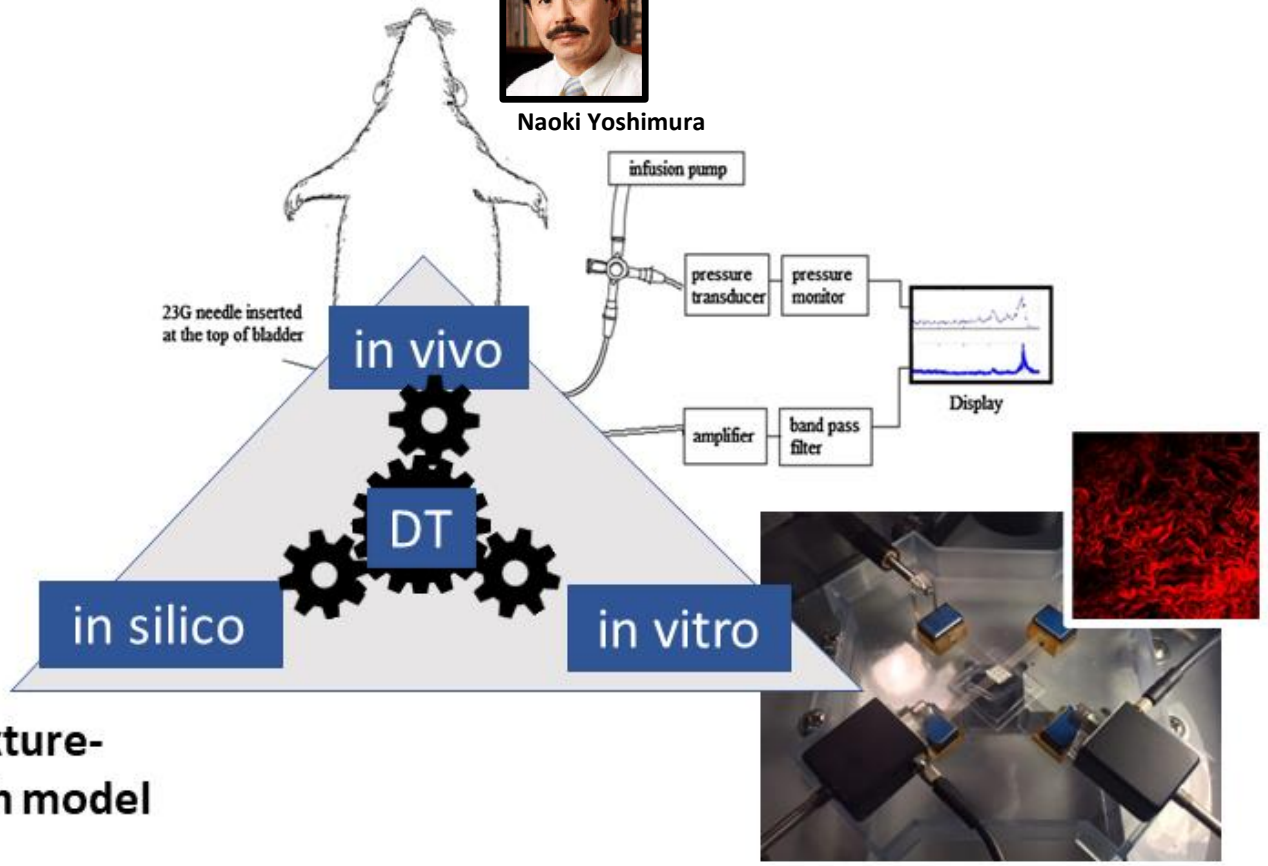
Objectives

- Develop a digital twin of the bladder to understand mechanistic relationship between bladder remodelling and function
- Understand, predict and design surgical treatments and pharmacotherapies
- Predict response to surgery
- *Rate based constrained mixture models* to simulate changes in wall structure
- ***First steps:*** develop a framework for tissue growth and remodelling in COMSOL

Integrative modelling approach



Naoki Yoshimura



CMMG:
Constrained mixture-micturition-growth model

Paul Watton

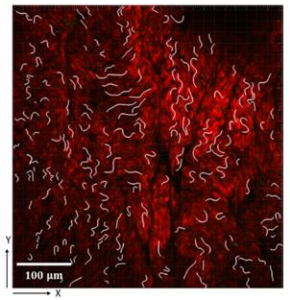
Anne Robertson

Constrained mixture models

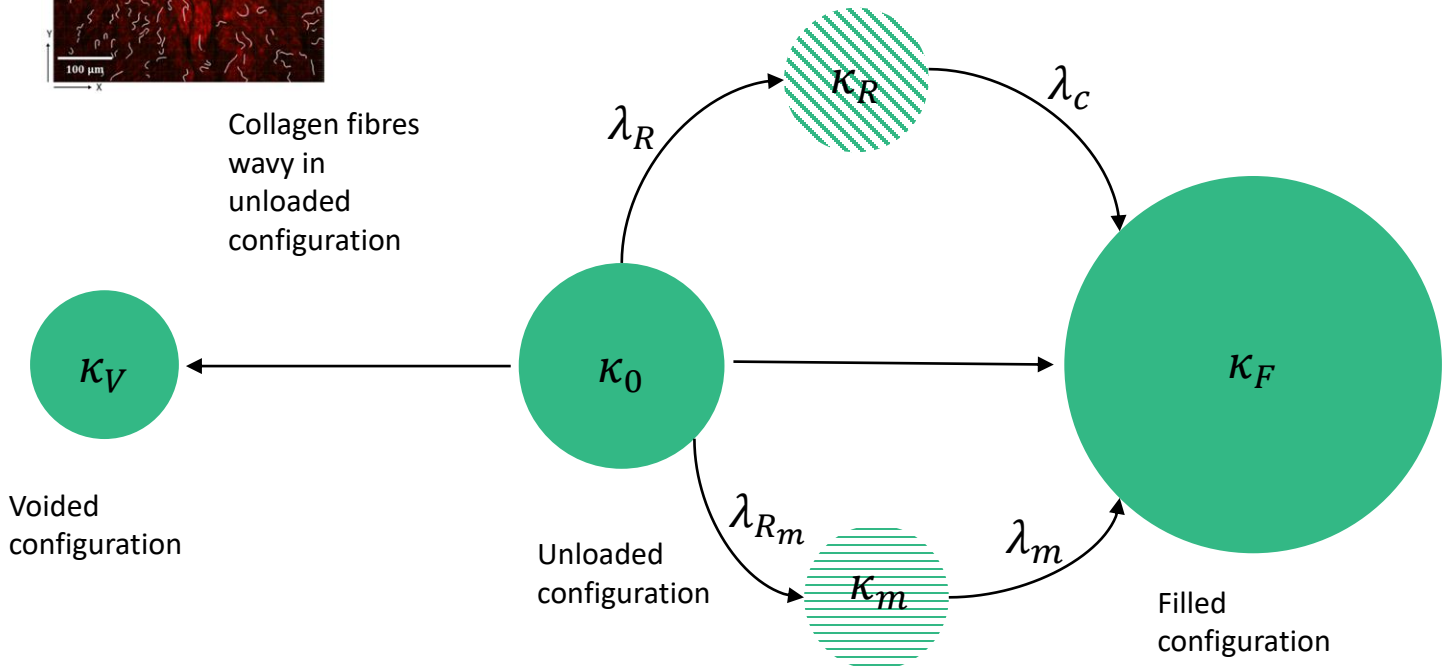
- Biological tissues are made of several distinct constituents/cells
- Each constituent/cell:
  - Have distinct unloaded configurations
  - These configurations can *evolve*
- Tissues evolve to maintain *homeostasis,* i.e. a stable internal environment

How do tissues remodel in response to changes due to e.g. development, ageing, disease?

Multiple natural configurations



Collagen fibres wavy in unloaded configuration



Voided configuration

Unloaded configuration

Filled configuration

Homeostasis

$$\lambda_c = \lambda_c^h$$
$$\lambda_m = \lambda_m^h$$

Constrained mixture model of the bladder

- Bladder wall is modelled as a multi-layered, heterogenous tissue with passive (collagen, ground matrix) and active (smooth muscle cells) components
- Total stress in the bladder wall is given by

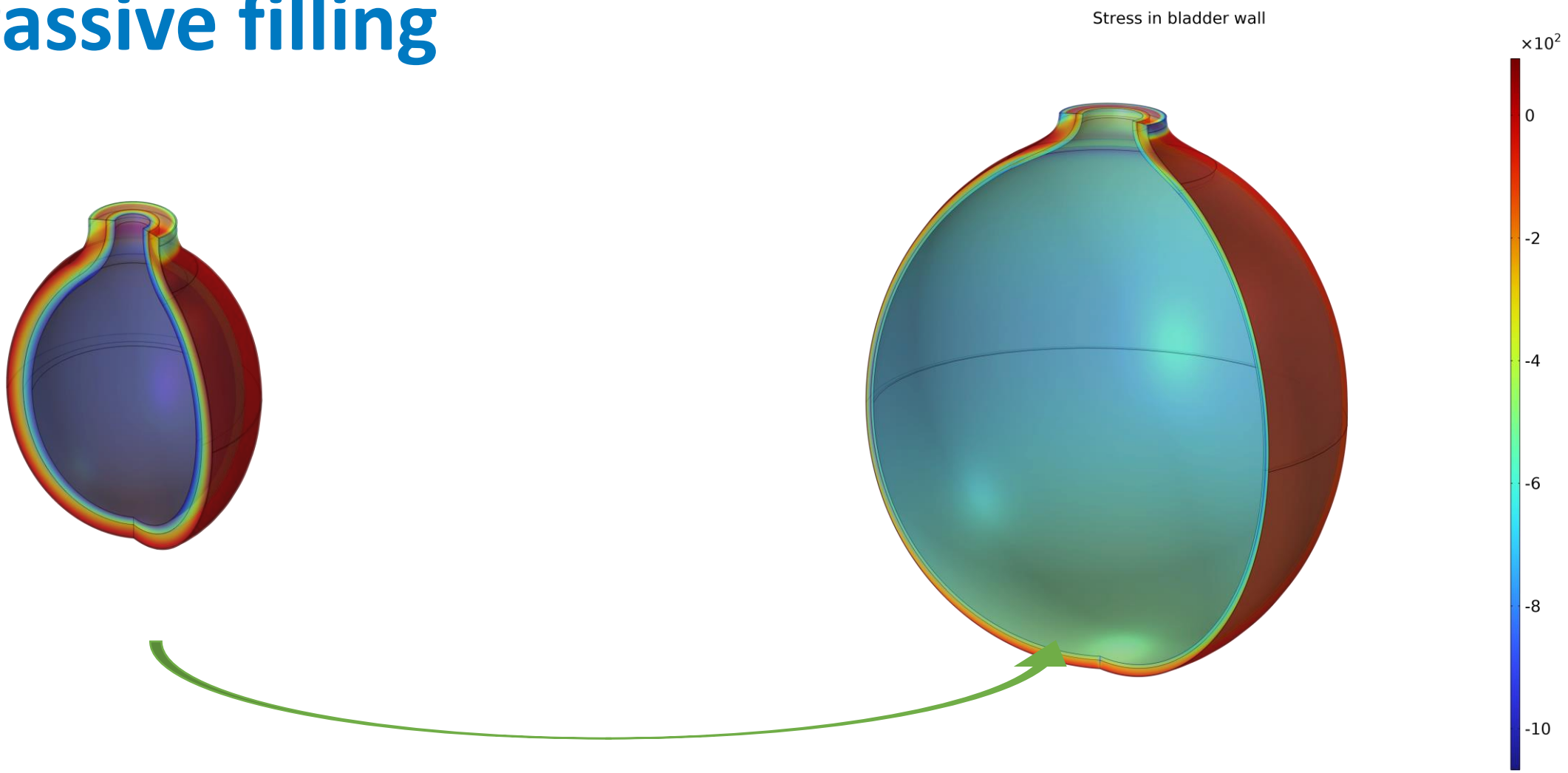
$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_E(\lambda_E) + \boldsymbol{\sigma}^c_{LP}(\lambda_c) + \boldsymbol{\sigma}^c_{DSM}(\lambda_c) + \boldsymbol{\sigma}^A_{SMC}(\lambda_m)$$

where stresses are functions of each constituent/cell stretch

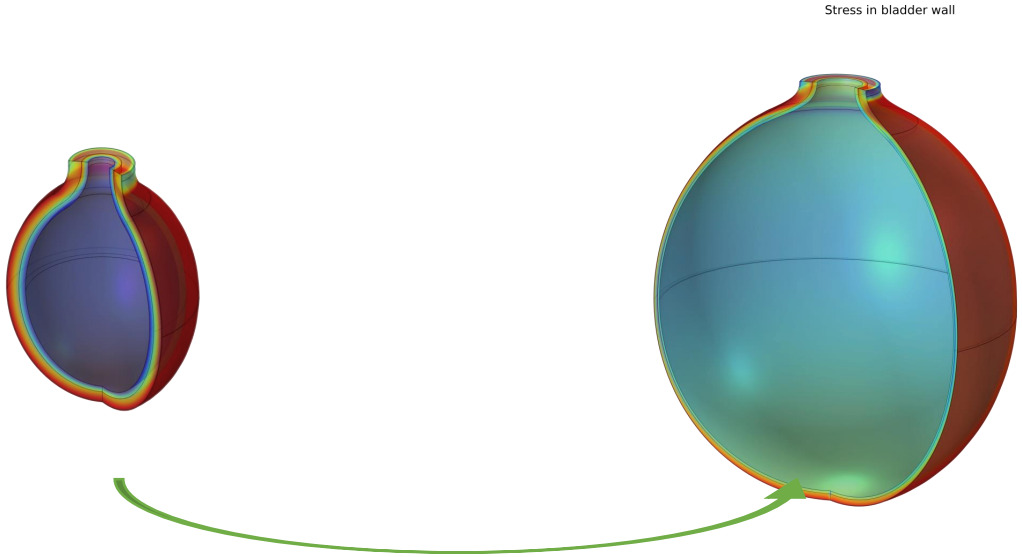
Growth and remodelling in COMSOL

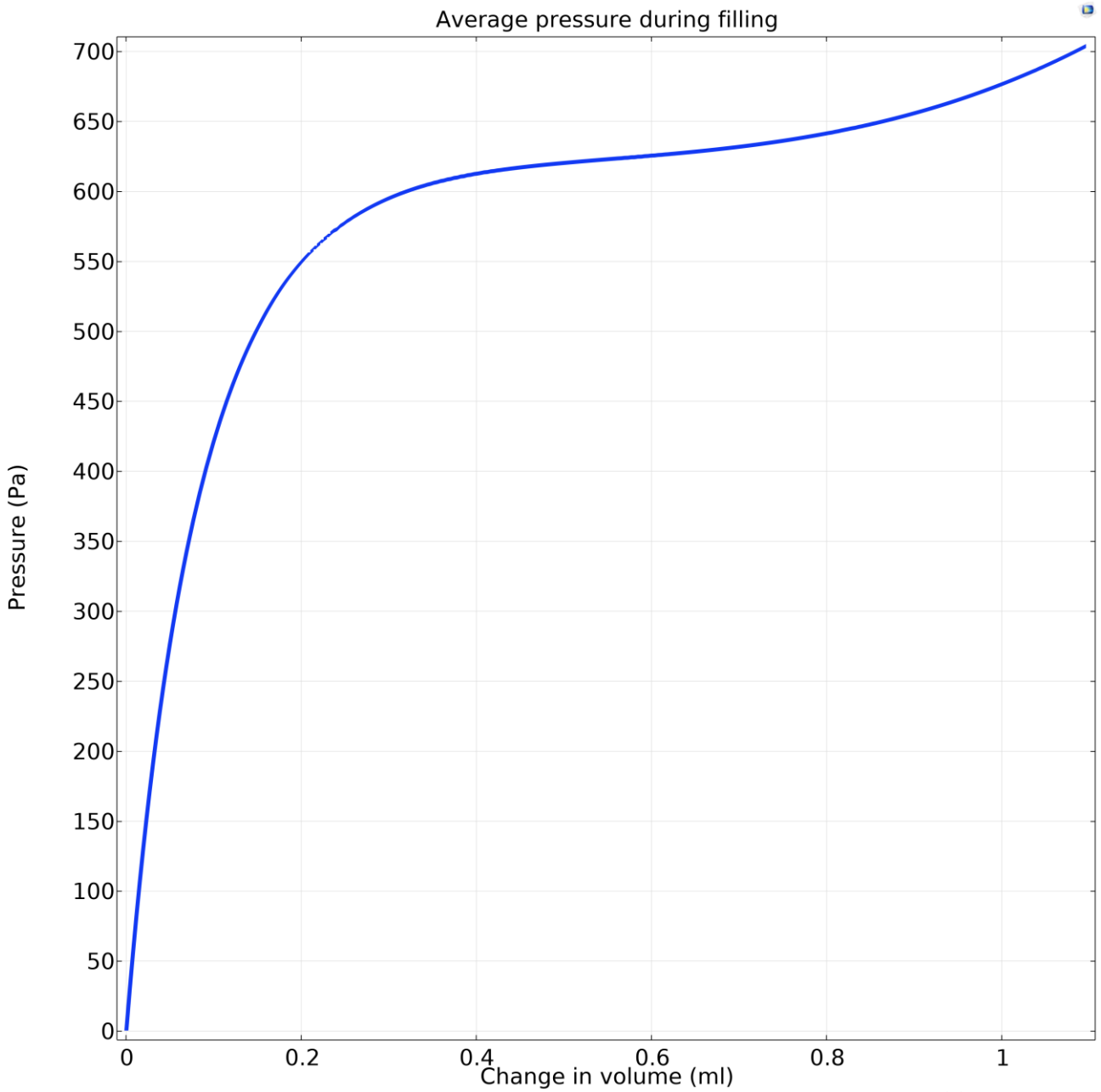
Passive ground matrix	*Nonlinear Structural Materials module* Passive components modelled as incompressible, isotropic neo-Hookean Filling of the bladder implemented using the *Enclosed Cavity* feature
SMC contraction and hypertrophy	Active stress decomposition: $\sigma = \sigma^P + \sigma^A$ with the active stress a function of muscle stretch (implement using *External Stress* node) SMC growth: $\mathbf{F} = \mathbf{F}_e\mathbf{G}$, where $\mathbf{G}$ describes changes in shape and volume due to growth (implement using *External Strain* node)
Collagen remodelling	Collagen fibres modelled using the *Fiber* node Remodelling to maintain homeostasis ⇨ update recruitment stretch $\frac{\partial \lambda_R}{\partial t} = \alpha_c \left(\frac{\lambda_c - \lambda_c^h}{\lambda_c^h} \right)$, Update recruitment stretch at end of each time step, implemented using *State Variables* node

Passive filling

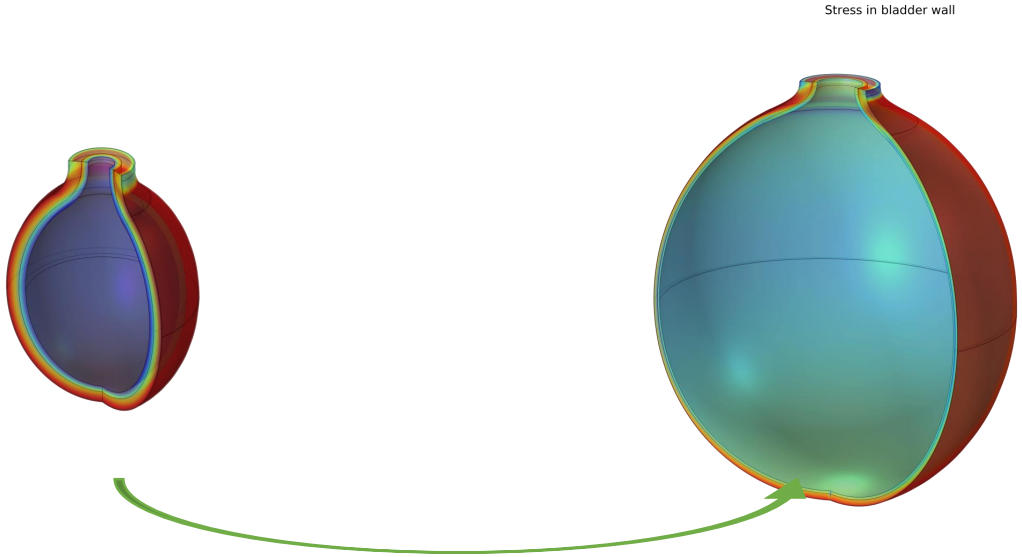


Passive filling



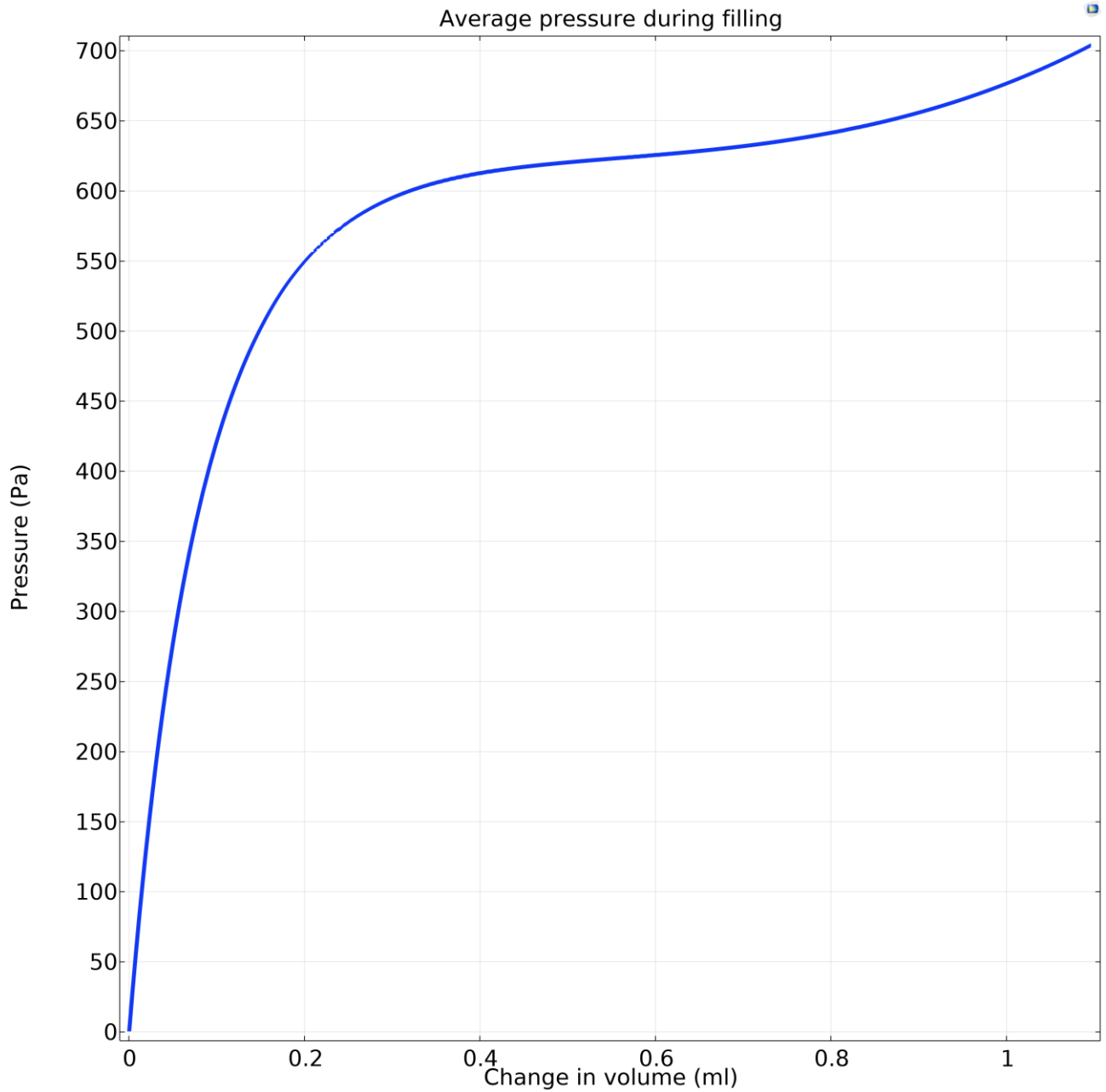


Passive filling



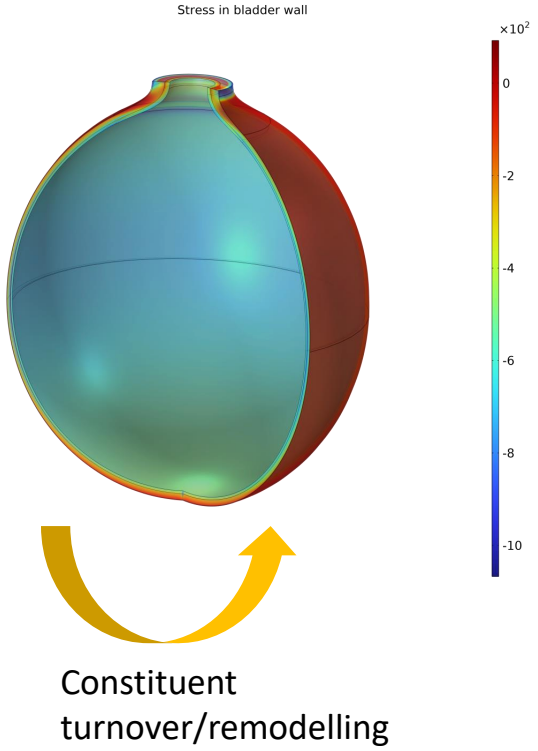
Filling

- Growth and remodelling algorithms run about this full state



G&R Illustration

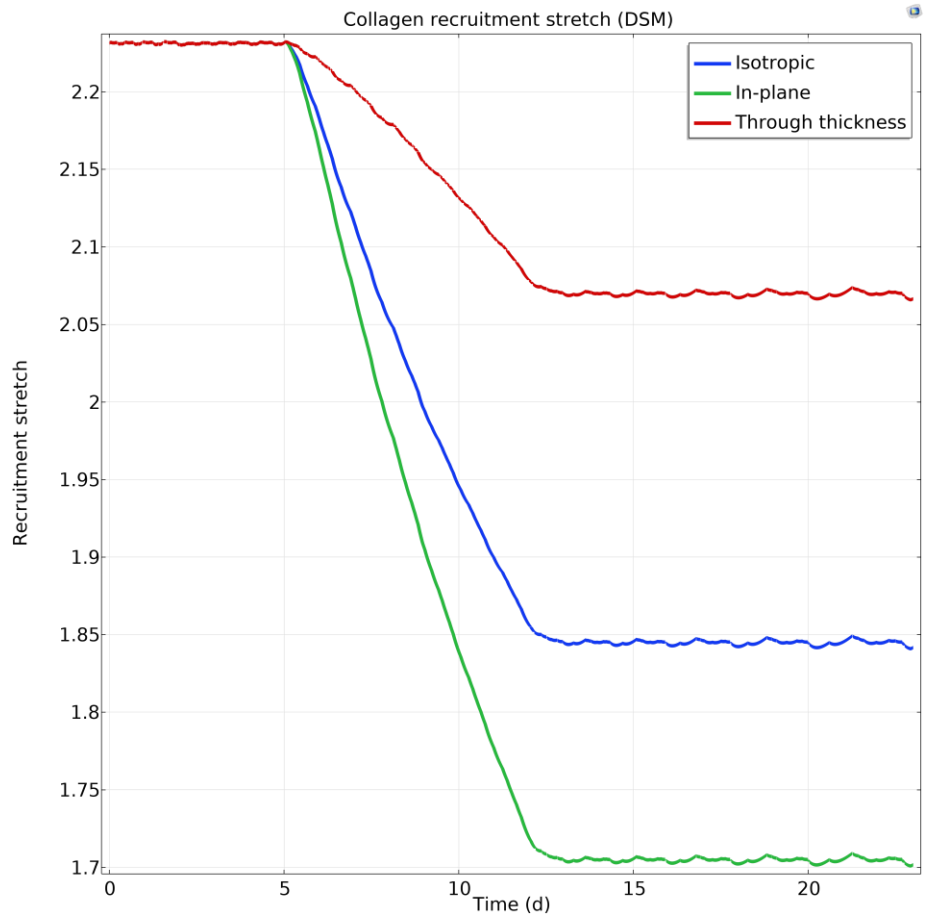
- Growth and remodelling algorithms run about this full state



Constituent turnover/remodelling

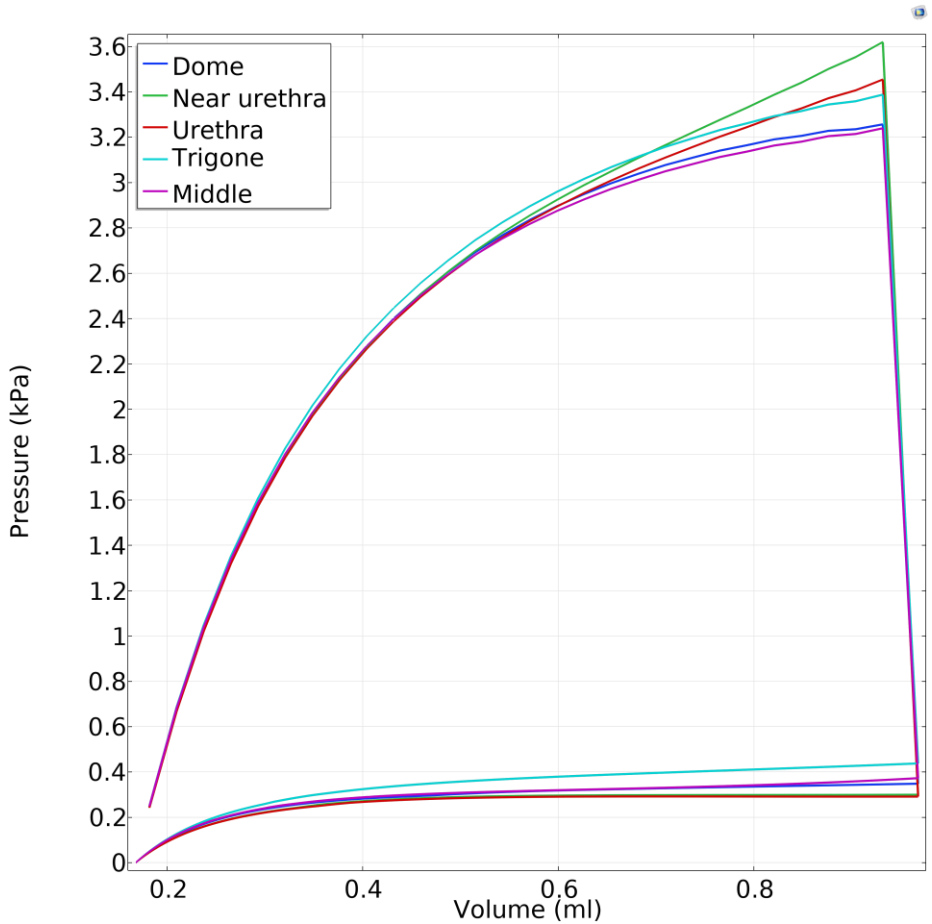
- SMC growth triggered after 5 days
- This perturbs tissue from homeostasis
- Remodelling acts to return tissue to its homeostatic state, i.e. until $\lambda_i = \lambda_i^h$

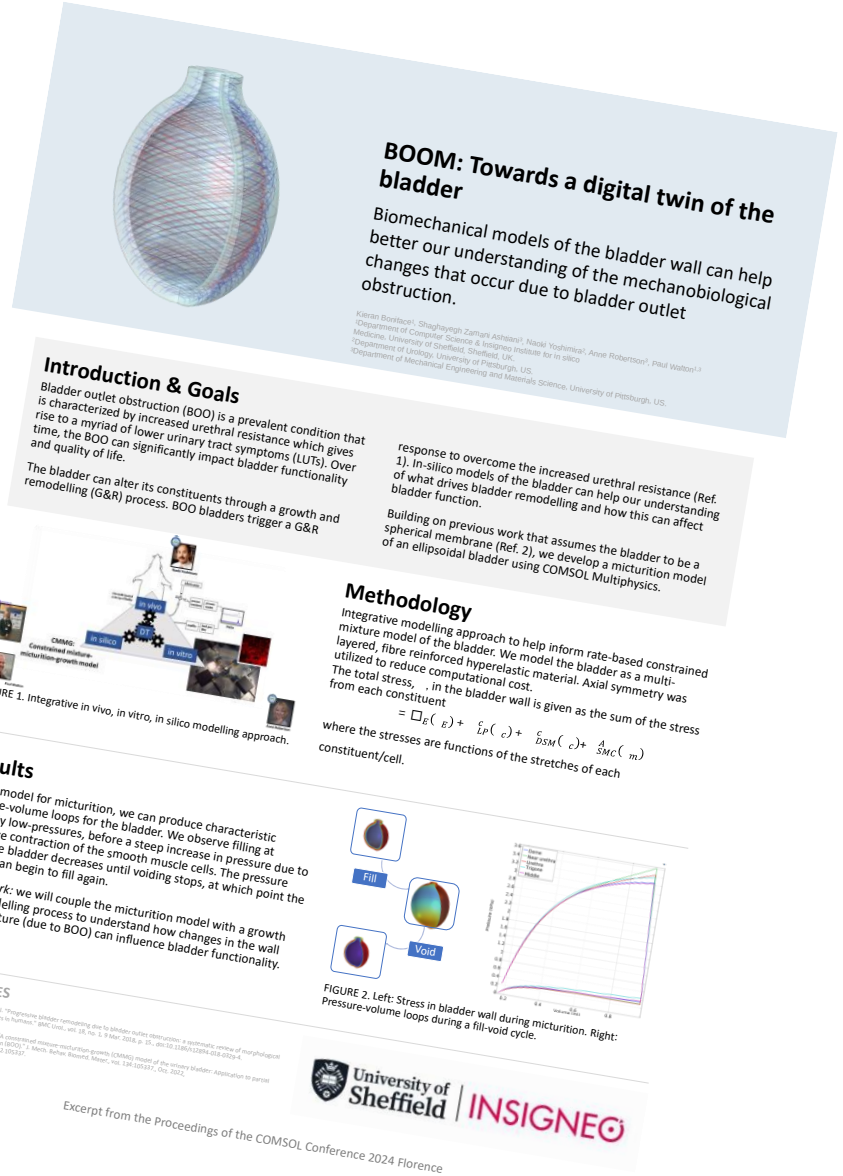
$$\lambda_c = \frac{\lambda}{\lambda_R}$$



Micturition model

- See my poster!





BOOM: Towards a digital twin of the bladder

Biomechanical models of the bladder wall can help better our understanding of the mechanobiological changes that occur due to bladder outlet obstruction.

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Introduction & Goals

Bladder outlet obstruction (BOO) is a prevalent condition that is characterized by increased urethral resistance which gives rise to a myriad of lower urinary tract symptoms (LUTs). Over time, the BOO can significantly impact bladder functionality and quality of life.

The bladder can alter its constituents through a growth and remodelling (G&R) process. BOO bladders trigger a G&R response to overcome the increased urethral resistance (Ref. 1). In-silico models of the bladder can help our understanding of what drives bladder remodelling and how this can affect bladder function.

Building on previous work that assumes the bladder to be a spherical membrane (Ref. 2), we develop a micturition model of an ellipsoidal bladder using COMSOL Multiphysics.

FIGURE 1. Integrative in vivo, in vitro, in silico modelling approach.

Methodology

Integrative modelling approach to help inform rate-based constrained mixture model of the bladder. We model the bladder as a multi-layered, fibre reinforced hyperelastic material. Axial symmetry was utilized to reduce computational cost.

The total stress, , in the bladder wall is given as the sum of the stress from each constituent

$$= \square_E(\ _E) + \ _{LP}^{c}(\ _c) + \ _{DSM}^{c}(\ _c) + \ _{SMC}^{A}(\ _m)$$

where the stresses are functions of the stretches of each constituent/cell.

Results

With a model for micturition, we can produce characteristic pressure-volume loops for the bladder. We observe filling at relatively low-pressures, before a steep increase in pressure due to the active contraction of the smooth muscle cells. The pressure inside the bladder decreases until voiding stops, at which point the bladder can begin to fill again.

Future work: we will couple the micturition model with a growth and remodelling process to understand how changes in the wall microstructure (due to BOO) can influence bladder functionality.

FIGURE 2. Left: Stress in bladder wall during micturition. Right: Pressure-volume loops during a fill-void cycle.

REFERENCES

Excerpt from the Proceedings of the COMSOL Conference 2024 Florence

Summary and outlook

- We have developed an initial framework for tissue growth and remodelling in COMSOL
- Rate-based constrained mixture model for healthy bladder growth and remodelling
- Can use this framework to test G&R hypotheses
- Next steps:
  - Combine G&R model with micturition model
  - Introduce obstruction and simulate response to BOO
  - Pathway signalling model and collagen growth (fibrosis)

US NIH-R01 (Aug 2023-July 2028)

A Digital Twin for Designing Bladder Treatment informed by Bladder Outlet Obstruction Mechanobiology

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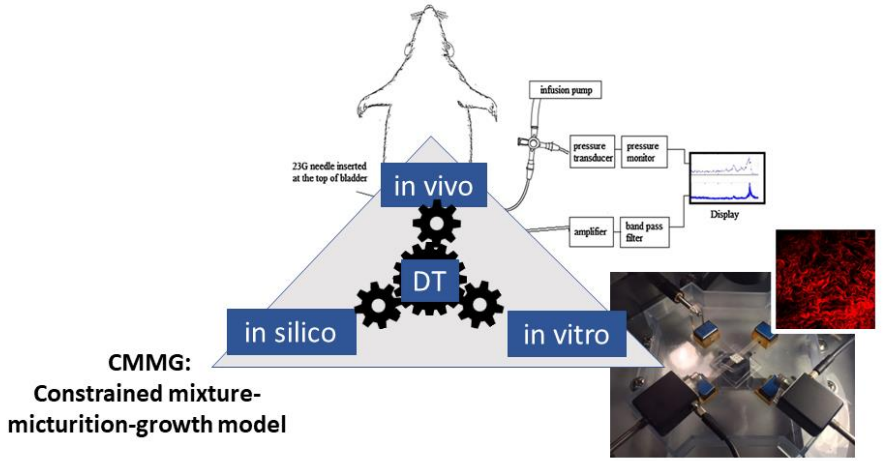
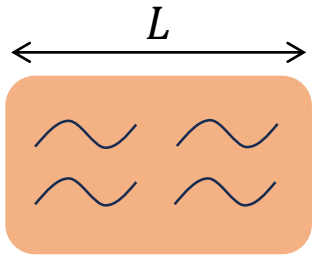


CMMG: Constrained mixture-micturition-growth model

Recruitment and homeostatic stretches

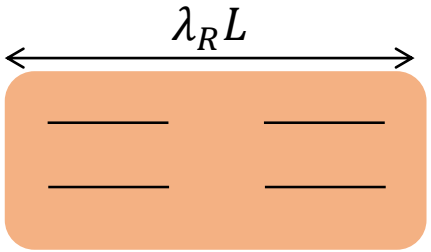
- **Collagen fibres bear load when in tension only**
  - Hence collagen fibres do not contribute to stress unless taut
- **Recruitment stretch, λ_R:** the stretch at which collagen fibres start to be load bearing

Homeostatic stretch, λ_i^h: stretch of constituent i when tissue is in homeostasis

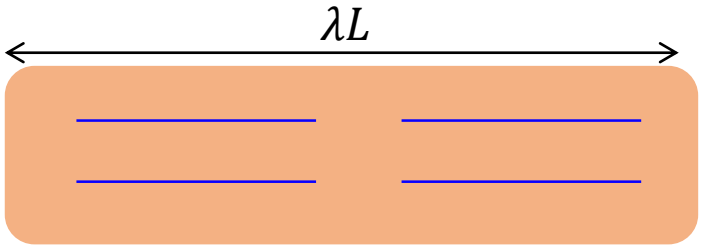


Collagen stretch, λ_c

$\lambda_c < 1, \boldsymbol{\sigma}_c = 0$



$\lambda_c = 1, \boldsymbol{\sigma}_c = 0$



$\lambda_c > 1, \boldsymbol{\sigma}_c > 0$

$$\lambda_c = \frac{\lambda}{\lambda_R}$$

Constrained mixture model of the bladder

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_E(\lambda_E) + \boldsymbol{\sigma}^c_{LP}(\lambda_c) + \boldsymbol{\sigma}^c_{DSM}(\lambda_c) + \boldsymbol{\sigma}^A_{SMC}(\lambda_m)$$

Passive neo-Hookean response

$$W_E = \frac{1}{2} k_E (I_1 - 1)$$

$$\sigma_E = \lambda_E \frac{\partial W_E}{\partial \lambda_E} - p$$

Exponential response of collagen fibres

$$W_c = \frac{1}{2}\frac{k_1}{k_2}\left(e^{k_2(I_4-1)^2} - 1\right)$$

$$\sigma^c_L = \lambda_c \frac{\partial W_c}{\partial \lambda_c}$$

Active response

$$\sigma^A_{SMC} = \begin{cases} k_m(\lambda_m^4 + \lambda_m^2)\left(\lambda_m - \lambda_m^{min}\right)\left(\lambda_m^{max} - \lambda_m\right), & \lambda_m \in \left[\lambda_m^{min}, \lambda_m^{max}\right] \\ 0, \quad \text{otherwise} \end{cases}$$