Computational modelling of bladder outlet obstruction mechanobiology

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Abstract:
Bladder outlet obstruction (BOO) is a prevalent condition characterised by increased urethral resistance. BOO gives rise to a myriad of lower urinary tract symptoms (LUTS) including voiding hesitancy, increased voiding frequency and incontinence. Prolonged BOO can lead to irreversible complications, such as kidney failure, that ultimately impact bladder functionality and significantly lowers quality of life.

In an obstructed bladder, smooth muscle cells (SMCs) must generate greater pressures to void. This initiates a biological response that drives the bladder through three stages of remodelling: hypertrophy, compensation, and decompensation. This remodelling process results in structural changes in the bladder wall, but the relationship between increased bladder pressure, remodelling-driven wall changes and bladder functionality is poorly understood.

To better understand these changes, we develop a novel rate-based constrained mixture model of BOO, informed by experimental rat models using an integrative in vivo - in vitro - in silico approach. The bladder wall is modelled as a multi-layered, fibre-reinforced, hyperelastic, constrained mixture in COMSOL Multiphysics. Over a long time scale, constituent growth and remodelling algorithms act to restore bladder function. The active mechanics of voiding are considered over a shorter time scale, with voiding metrics contributing to bladder growth and remodelling.

The model is calibrated to a healthy rat bladder and predictions of evolving structure and function are compared with in vivo/in vitro observations of an obstructed bladder. We investigate the effect of anisotropic, volumetric growth on bladder function. Furthermore, we explore the later stages of bladder remodelling (compensation, decompensation) by coupling a system of ODEs to model biochemical signalling in fibrotic and anti-fibrotic pathways. The model can then be used for in-silico investigations to predict the response of the bladder to obstruction removal and guide the design of pharmacological treatment to maintain bladder functionality.