A Computational Model of Vascular Smooth Muscle Cell Mechanosensitivity, Mechanotransduction and Phenotype Modulation for the Multiscale Modelling of Arterial Failure in Ageing and Genetic Disease

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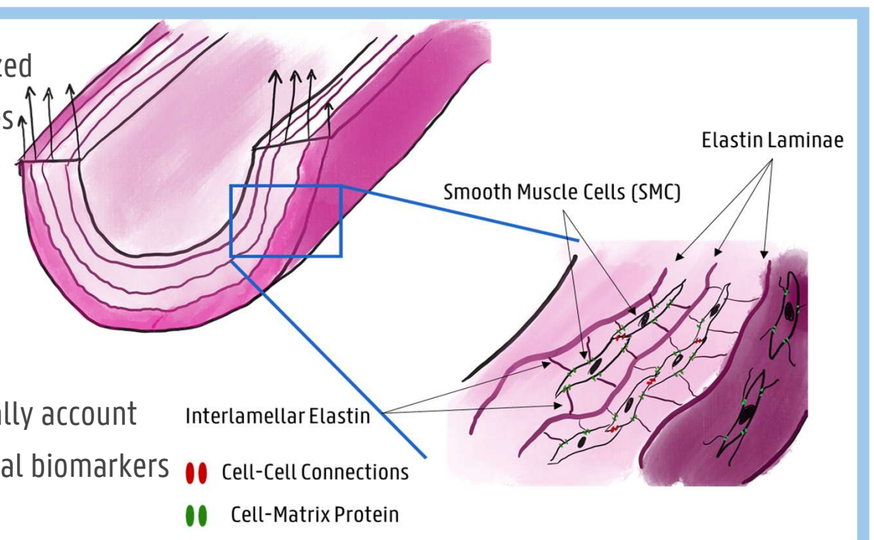
BACKGROUND

Arterial failure is a common consequence of **ageing** and **connective tissue disease**, and is hypothesized to be linked to **phenotype switching** of vascular smooth muscle cells (VSMCs) that occupy the spaces between elastic lamellae in the media of the large elastic arteries. Different factors, including **hypertension**, changes in the **extracellular matrix (ECM)**, and inflammation, can disrupt the mechanosensitivity of these cells, which modulate into aberrant phenotypes, triggering a cascade that can lead to full arterial disease.

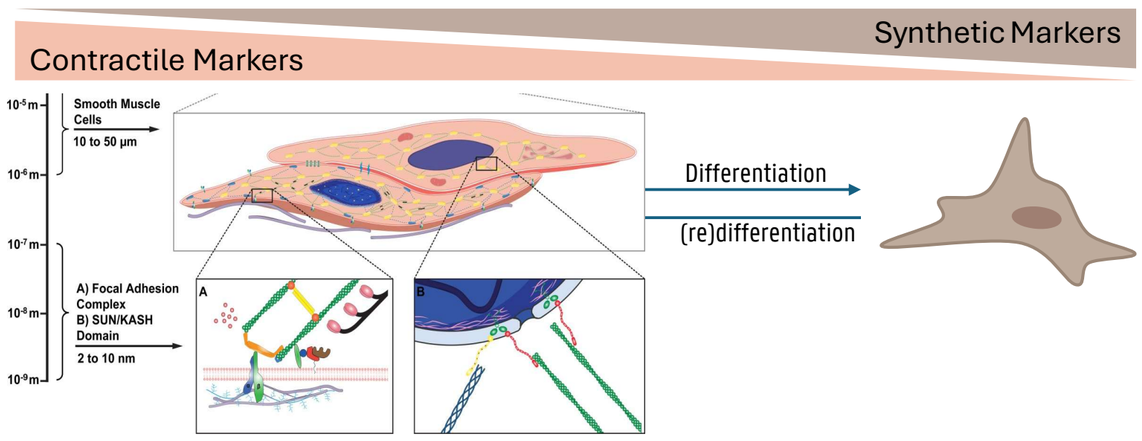


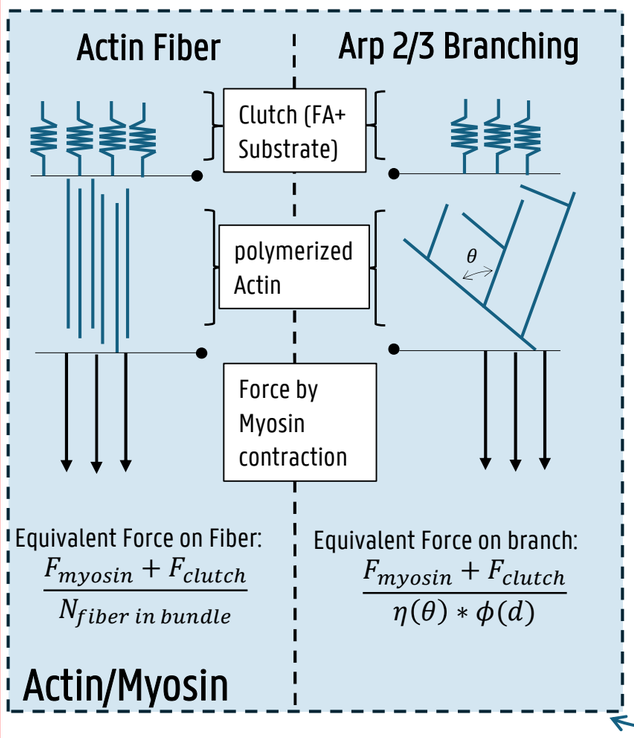
We have previously shown that numerical biomechanical models of arteries that phenomenologically account for phenotype plasticity due to disrupted mechanosensitivity and remodelled ECM can recoup clinical biomarkers of disease including medial degradation, fibrosis, increased stiffness and aneurysm.

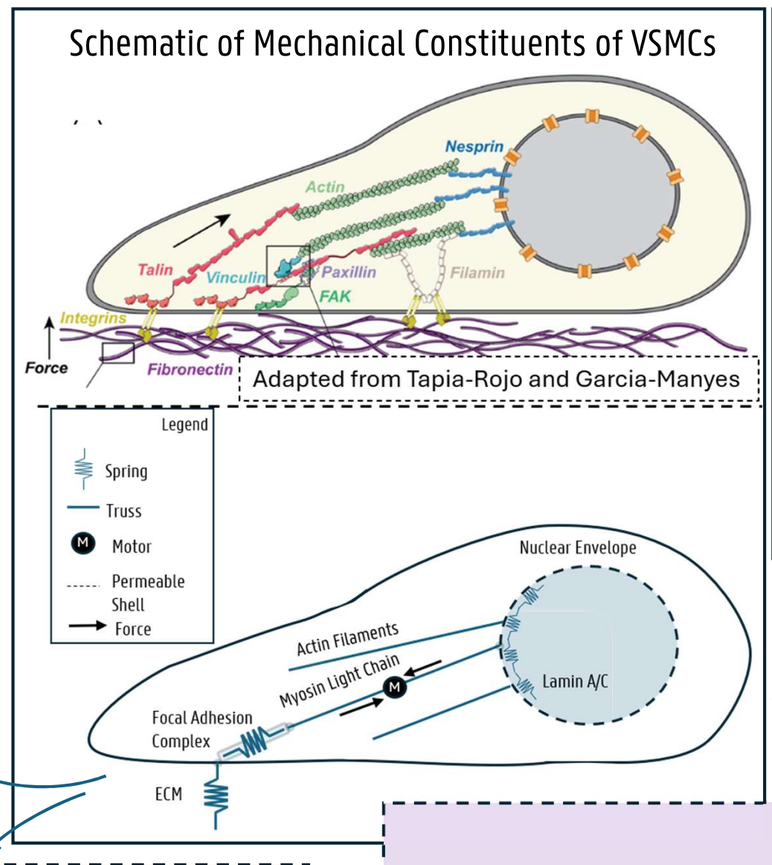
We demonstrate a numerical model that mechanistically incorporates ECM stiffness (κ_{sub}) on the mechanosensitive and mechanotransduction tools of contractile VSMCs. Phenotypic markers and active genetic circuits exist on a spectrum between contractile and synthetic expression.

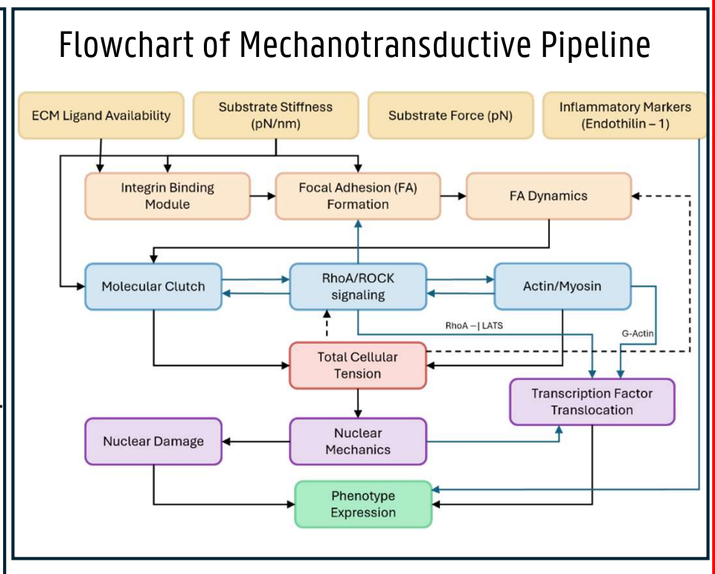
This work, models the molecular clutch, actin dynamics, nuclear mechanics and the most prominent genetic circuits of developed VSMCs, including signalling of the YAP/Taz, MRTF-A/B, myocardin and KLF4 genes, downstream of the FAK-Src and Rhoa-GTP/Rac1-GTP pathways.

Methodology



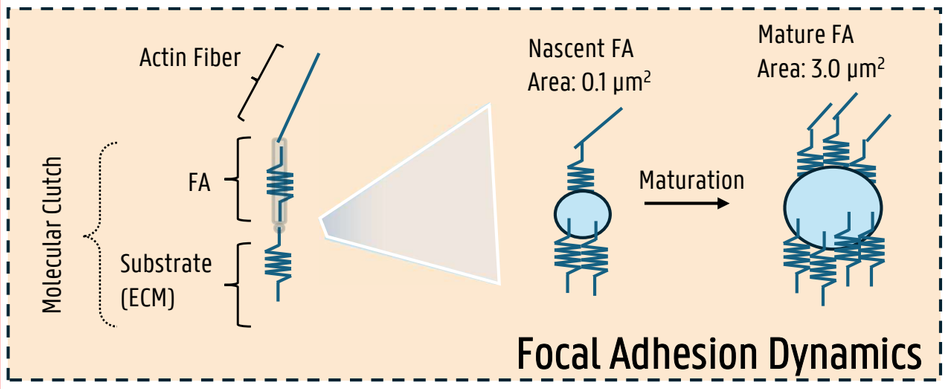


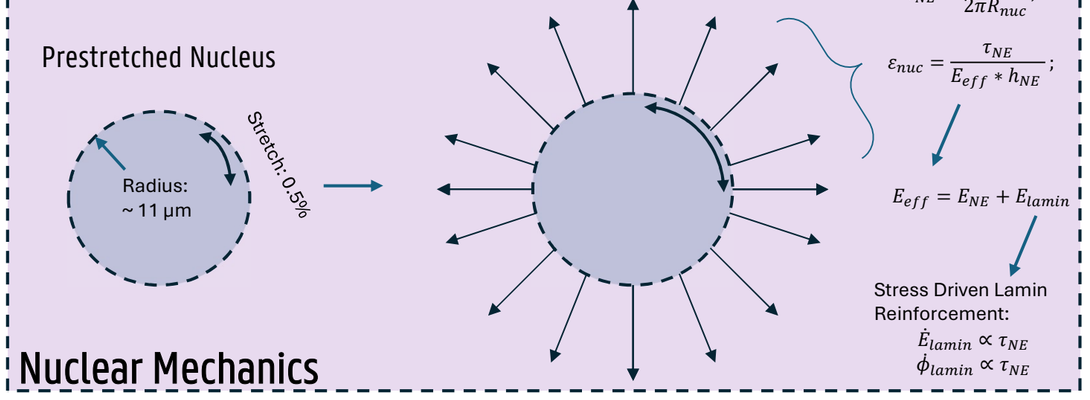




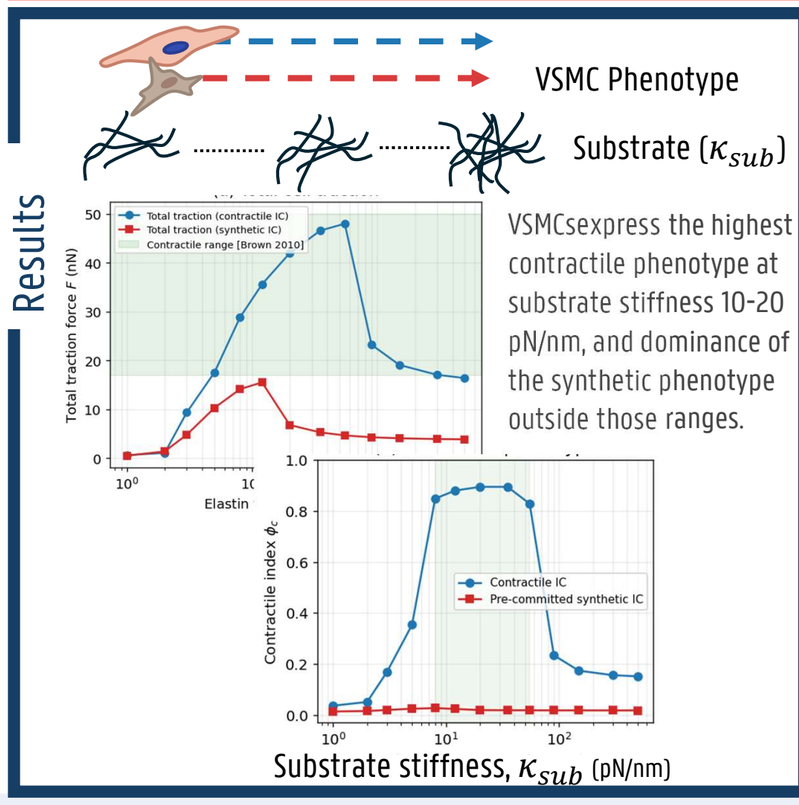
Where

τ_{NE}	Nuclear Envelope Tension
R_{nuc}	Nuclear Radius
h_{NE}	NE Thickness
E_{eff}	NE effective stiffness
ε_{nuc}	NE deformation

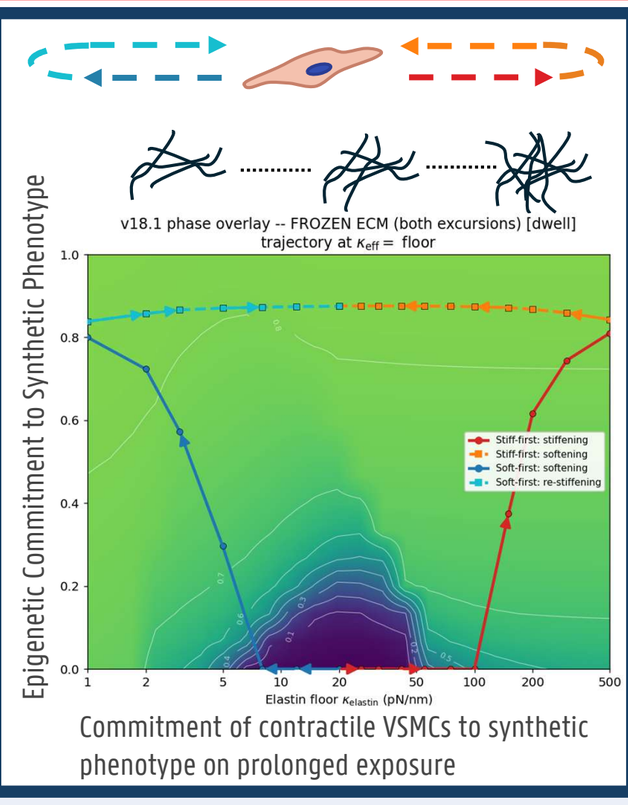




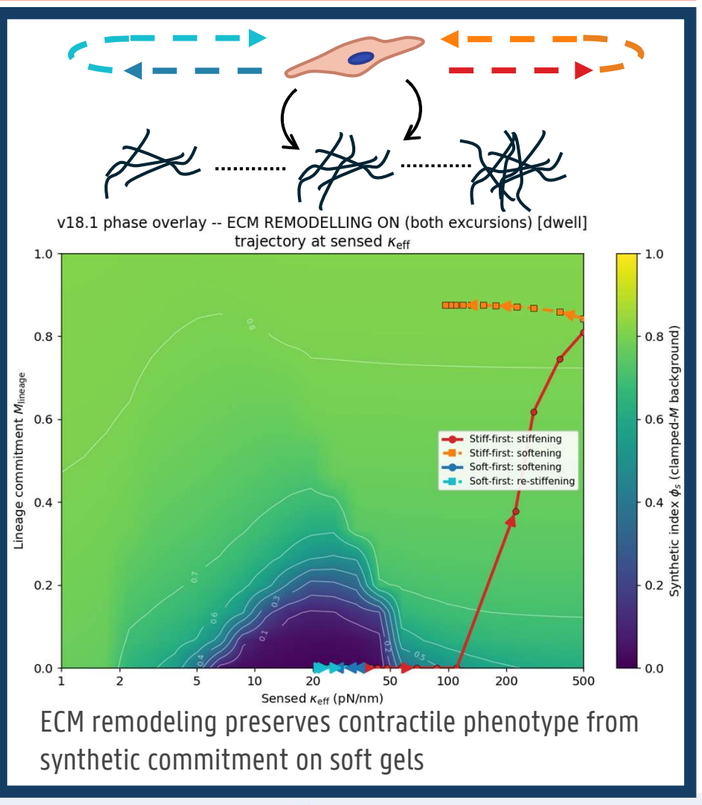
Results



VSMCsexpress the highest contractile phenotype at substrate stiffness 10-20 pN/nm, and dominance of the synthetic phenotype outside those ranges.



Commitment of contractile VSMCs to synthetic phenotype on prolonged exposure



ECM remodeling preserves contractile phenotype from synthetic commitment on soft gels

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