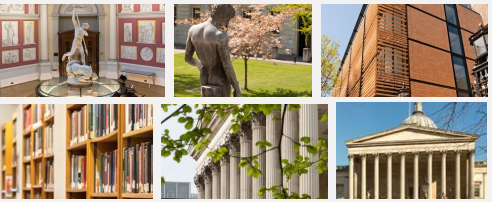


Multi-scale, patient-specific modelling approaches to predict neointimal hyperplasia growth in femoro-popliteal bypass grafts

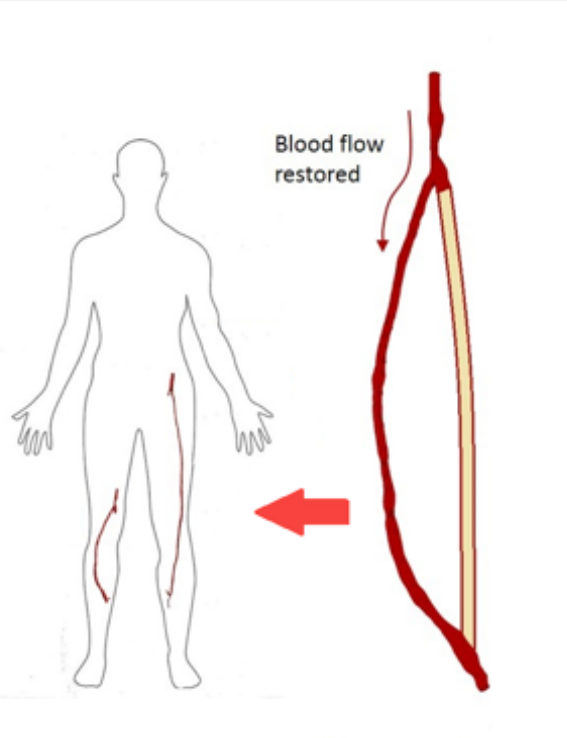
Dr Mirko Bonfanti[1], Dr Francesca Donadoni[1], Dr Cesar Pichardo-Almarza[1], Prof Alan Dardik[2], Prof Shervanthi Homer-Vanniasinkam[1], Prof Vanessa Díaz-Zuccarini[1]

1. University College London, UK; 2. Yale University School of Medicine, New Haven, USA;

Background: how do grafts fail?

The problem

- Peripheral bypass (femoro-popliteal, femoro-distal)
- **High failure rate** of bypass grafts
- Major clinical problem still **not fully resolved**



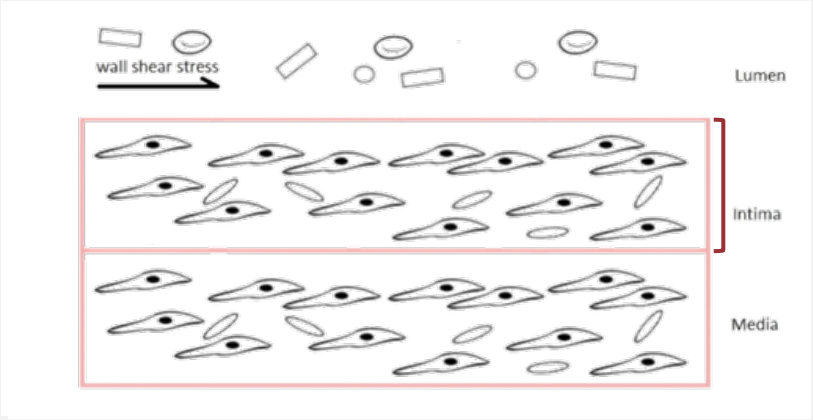
Background: how do grafts fail?

The problem

- Peripheral bypass (femoro-popliteal, femoro-distal)
- **High failure rate** of bypass grafts
- Major clinical problem still **not fully resolved**

Neointimal hyperplasia (NIH)

- Main process leading to **restenosis**
- After vein-graft creation, the vein undergoes a dramatic **remodelling**
- Smooth muscle cells (SMCs) proliferate in the media layer and migrate into the intima, leading to intimal **thickening**



A multi-scale, mechanistic perspective

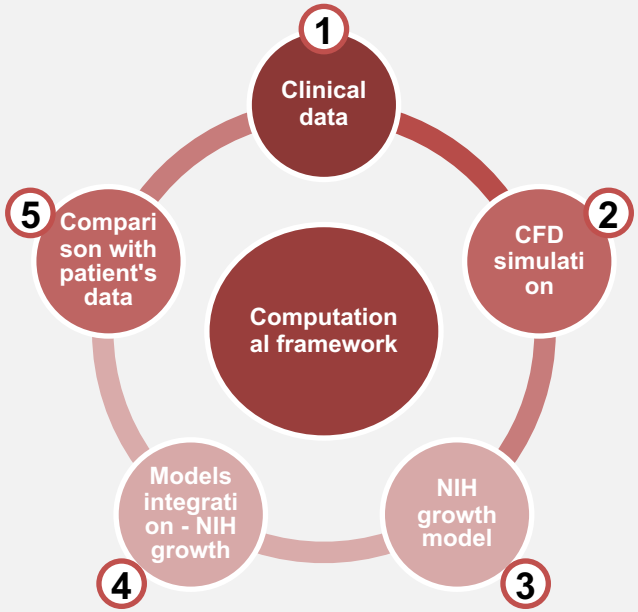
Objective

- To calculate NIH growth and predict occlusion in (*patient-specific*) vein-grafts in humans using a **multi-scale**, **mechanistic computational** framework

Why?

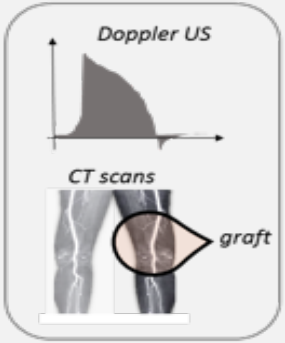
- Grafts in animal models exhibit better patency than in humans, **animal models have failed**
- Mechanistic models help understanding **mechanisms** quantitatively
- Add further **levels of analysis** to NIH
- Potential to **test hypotheses** in a short time, for instance testing different surgical approaches

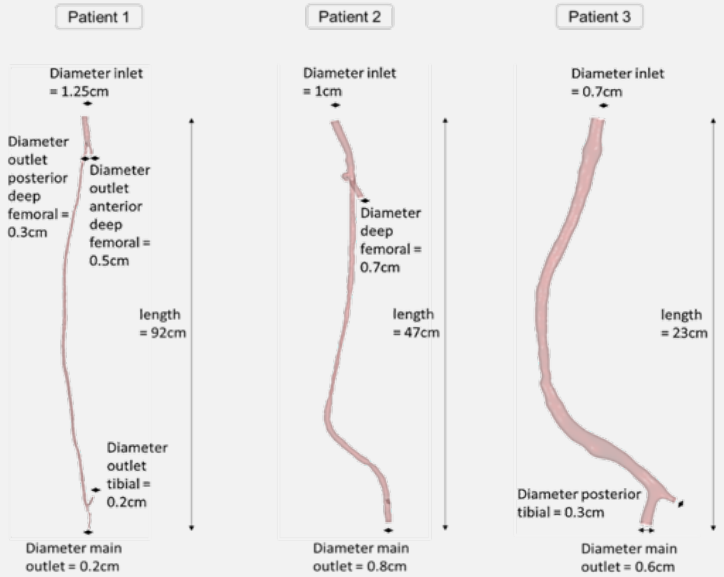
Methods: how we model NIH progression



1 Clinical data

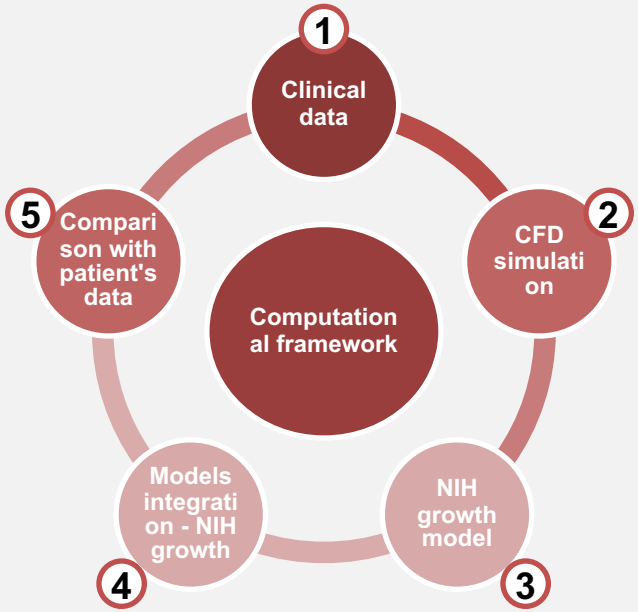
Ethical approval from the institutional review board (No. AD0009, Veteran Affairs Connecticut Healthcare System, West Haven, CT, USA)



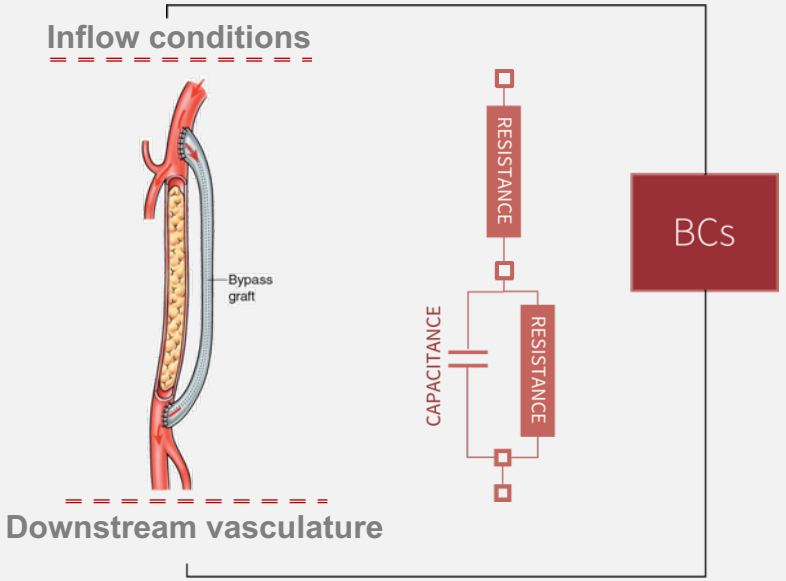


- Doppler ultrasound scans immediately after surgery
- Geometry extracted from CT-scans (Simpleware, Synopsys, US), NIH *virtually* removed to obtain post-intervention conditions

Methods: how we model NIH progression

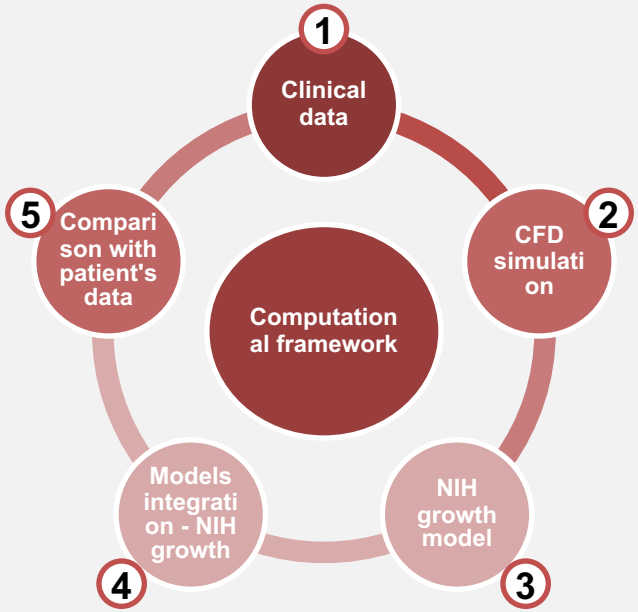


2 Computational fluid dynamic (CFD) simulation



- Haemodynamic simulation (CFX, ANSYS, US) to calculate mechanical stimuli (wall-shear stress)
- Patient-specific boundary conditions (BCs): **inlet** flow wave from Doppler ultrasound, Windkessel BCs at **outlets**

Methods: how we model NIH progression



3 Biochemical model of NIH growth

Donadoni et al, (2017)
Frontiers in Physiology

SMC

$$\frac{dS_i}{dt} = \gamma \times Q_i + (p_i - a_i) \times S_i - m \times S_m) + \phi \times (G_P + G_F) \text{ in } \Omega_i$$

$$\frac{dS_m}{dt} = \gamma \times Q_m + (p_m - a_m - m)\, S_m \text{ in } \Omega_m,$$

Collagen

$$\frac{dC_i}{dt} = S_i \times \lambda - C_i \times \chi \text{ in } \Omega_i$$

$$\frac{dC_m}{dt} = S_m \times \lambda - C_m \times \chi \text{ in } \Omega_m$$

Growth Factors

$$\frac{d(G_P)}{dt} = \zeta_g - \zeta_d \times G_P \text{ in } \Omega_i$$

$$\frac{d(G_F)}{dt} = \theta_g - \theta_d \times G_F \text{ in } \Omega_m,$$

Volume

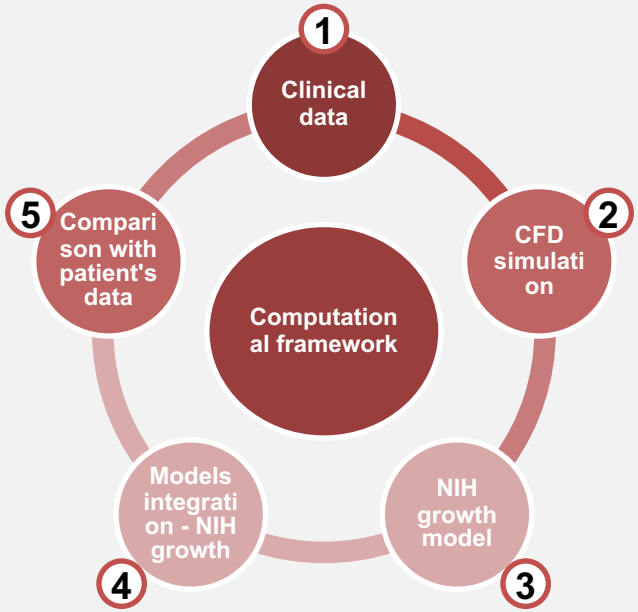
$$V_i = (S_i + Q_i) \times \rho_s^{-1} + C_i \times \rho_c^{-1}$$

$$V_m = (S_m + Q_m) \times \rho_s^{-1} + C_m \times \rho_c^{-1}$$

$$R_{NO} = 1.74 + 7.52 \times WSS$$

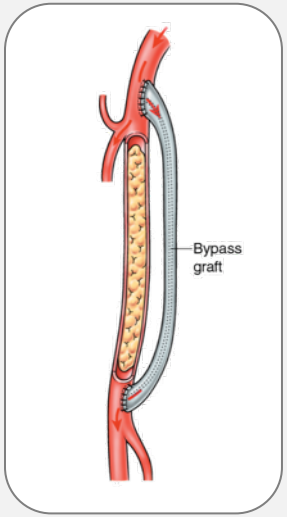
- NIH growth modelled using ODEs (MATLAB, MathWorks, US)
- **Growth factors** degradation and **SMCs** migration, apoptosis and proliferation affected by **Nitric Oxide (NO)**
- **NO production rate** as a function of the Wall-Shear Stress (**WSS**)

Methods: how we model NIH progression



4 Model coupling – NIH Growth

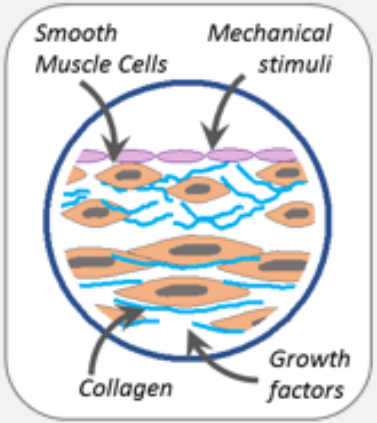
CFD MODEL



NIH GROWTH MODEL

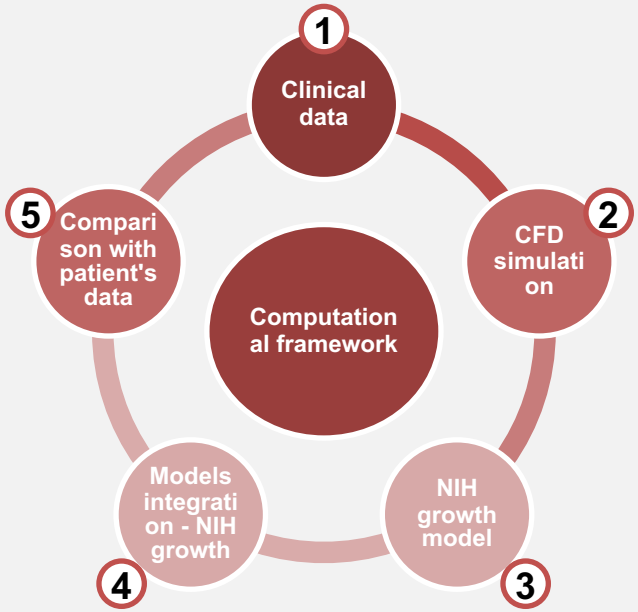
$$R_{NO} = 1.74 + 7.52 \times WSS$$

TAWSS *or*
HOLMES *= TAWSS ⍰ (0.5 – OSI)*



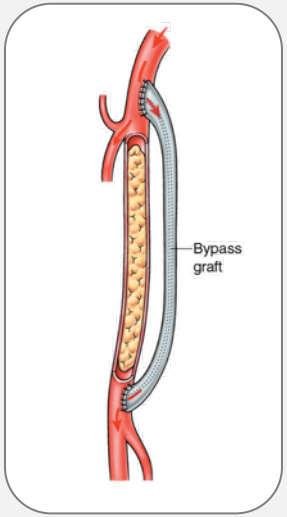
- **WSS-index distribution** from CFD simulation as **input** to the cell model:
  → *Time-averaged wall shear stress* (**TAWSS**)
  → or *highly oscillatory, low-magnitude shear* (**HOLMES**)

Methods: how we model NIH progression

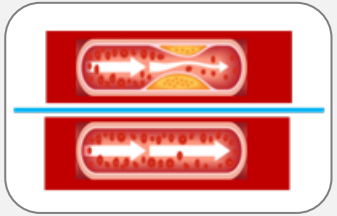


4 Model coupling – NIH Growth

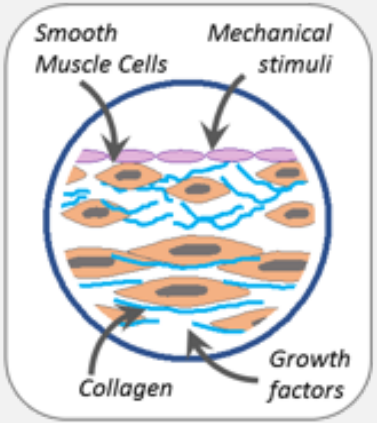
CFD MODEL



NIH GROWTH IN 3D DOMAIN

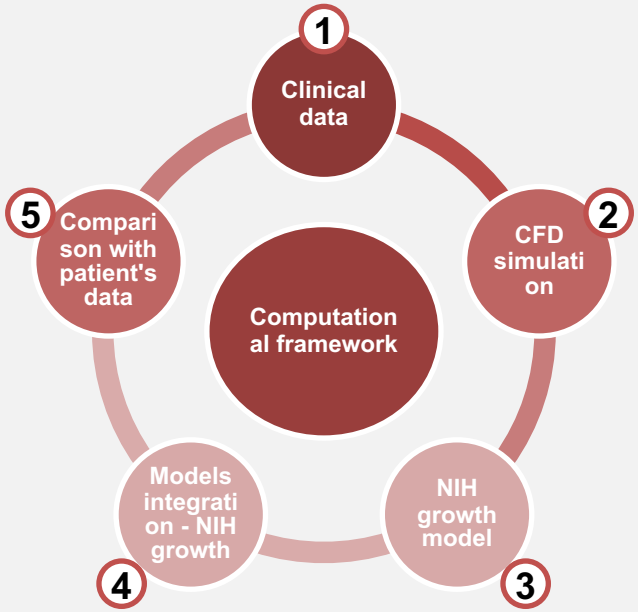


NIH GROWTH MODEL

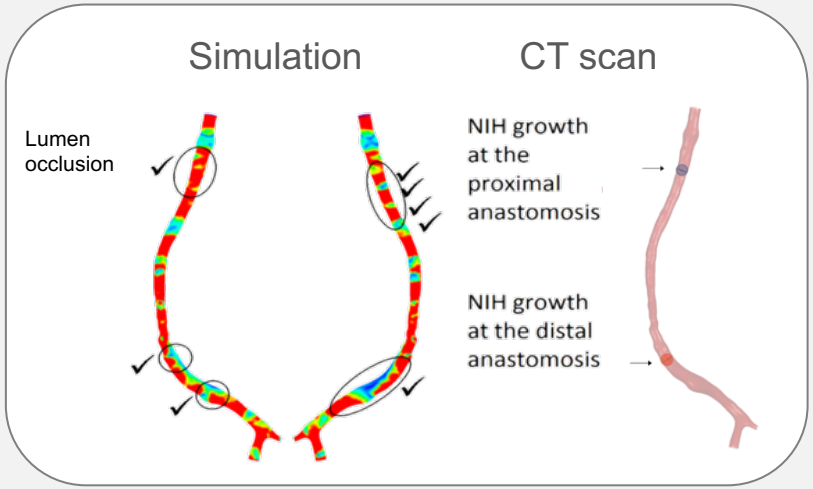


- **WSS-index distribution** from CFD simulation as **input** to the cell model:
  → *Time-averaged wall shear stress* (**TAWSS**)
  → or *highly oscillatory, low-magnitude shear* (**HOLMES**)
- **Months of NIH growth** simulated in the 3D domain

Methods: how we model NIH progression



5 Model validation – comparison against *in vivo* data

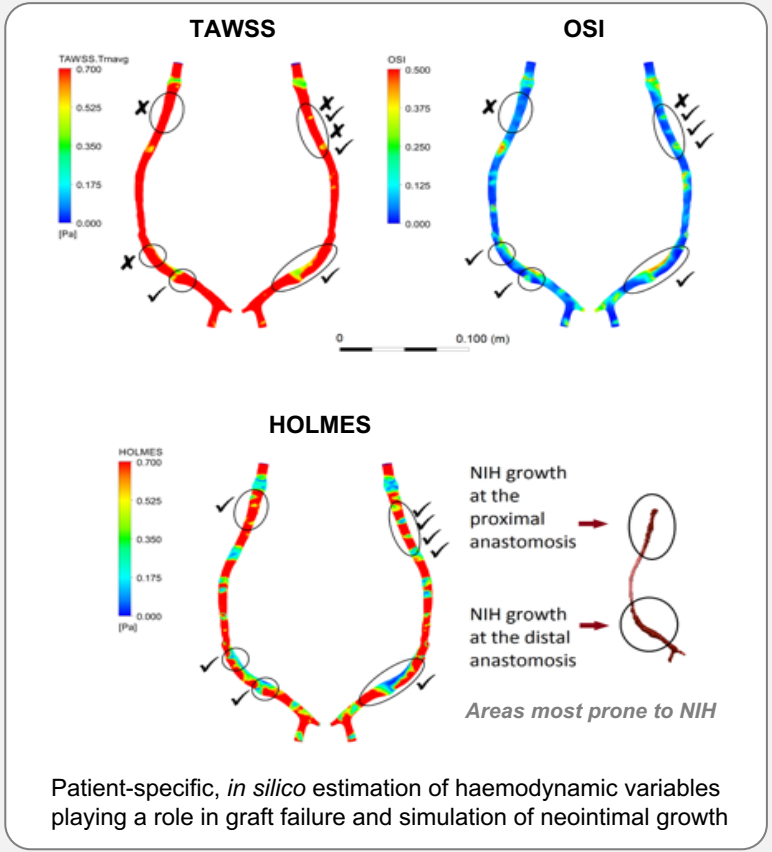


- Comparison of the **NIH growth model predictions** against **CT scans**
- Identification of the locations most prone to NIH and measurement of the **lumen occlusion percentage**, both in the *in silico* model and *in vivo* images

Results: TAWSS or HOLMES?

Findings

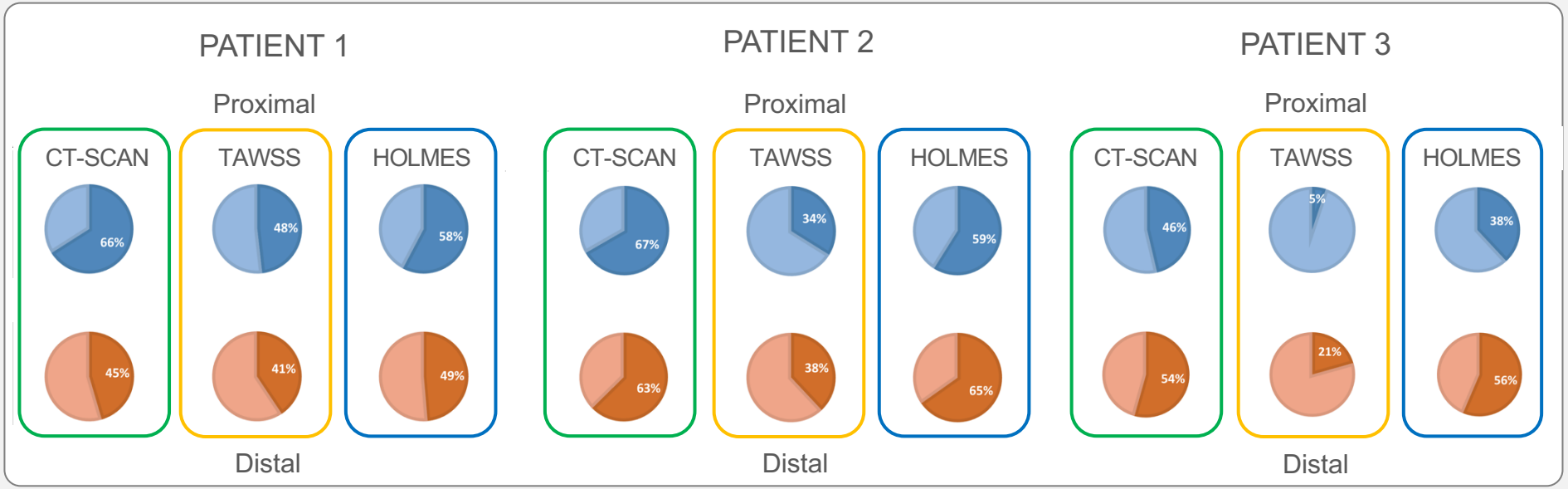
- Wall Shear Stress **alone** is an unreliable predictor of graft failure/NIH growth
- A combined index, taking into account **wall shear stress** and **oscillations** captures locations much better
- Surrogate haemodynamic indices or **morphometric** indices alone provide **poor** metrics to predict graft failure



Patient-specific, *in silico* estimation of haemodynamic variables playing a role in graft failure and simulation of neointimal growth

Donadoni et al . 2019. bioRxiv 624312;
doi: https://doi.org/10.1101/624312

Results: Comparison against CT scans



- Results of the simulations in % occlusion (NIH) at the most severely affected locations after the time of NIH development for each patient.
- The simulation model predicts NIH growth:
  - → TAWSS **underpredicts** occlusion
  - → HOLMES **predicts well** the occlusion

A balance

The Advantages

- **Interpretation is strong** and firmly rooted in vascular biology
- **It captures complex behaviour** and the models are able to offer a mechanistic explanation and are validated against *in vivo* data.
- The mechanistic model allows us to **test research hypotheses**

The **compliance mismatch** at the anastomoses is believed to lead to NIH due to **alterations of the local haemodynamics**

Can we test this hypothesis?

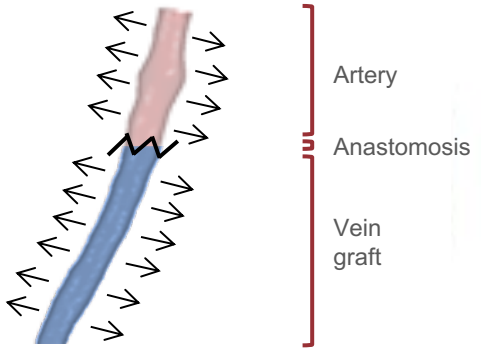
The limitations

- **Better quantification methods** are necessary. Despite numbers, it remains fairly qualitative
- **There are limitations with the biomechanical and cellular models (and imaging data)** about the so-called 'patient-specific' parameters/data. Uncertainty is important.
- **Time consuming**…
- **Needs significant validation** in a patient cohort

Methods: compliance mismatch in the CFD model

Clinical Data	CFD model	Growth model
• Doppler Ultrasound • CT Scans	• Blood flow simulations • Haemodynamic indices	• Patient-specific simulations of NIH progression

Patient 1	• Femoro-distal bypass • Length: 82 cm • ϕ_{INLET}: 12.5 mm	Rigid wall (R) • Artery: rigid • Stitches: rigid • Graft: rigid
Patient 2	• Fem-pop bypass • Length: 47 cm • ϕ_{INLET}: 10.0 mm	Post-op (PO-NA) • Artery: compliant • Stitches: rigid • Graft: rigid
Patient 3	• Fem-pop bypass • Length: 23 cm • ϕ_{INLET}: 7.0 mm	Post-op arterialised (PO-A) • Artery: compliant • Stitches: rigid • Graft: compliant



Artery distensibility parameter from literature

- Vessel wall motion modelled via **Moving Boundary Method**[1]
  → **two-way coupling** between boundary motion and fluid dynamics
- Three scenarios were simulated:
  → Rigid **(R)**, Post-operative & Non-arterialised **(PO-NA)**, Post-operative & Arterialised **(PO-A)**

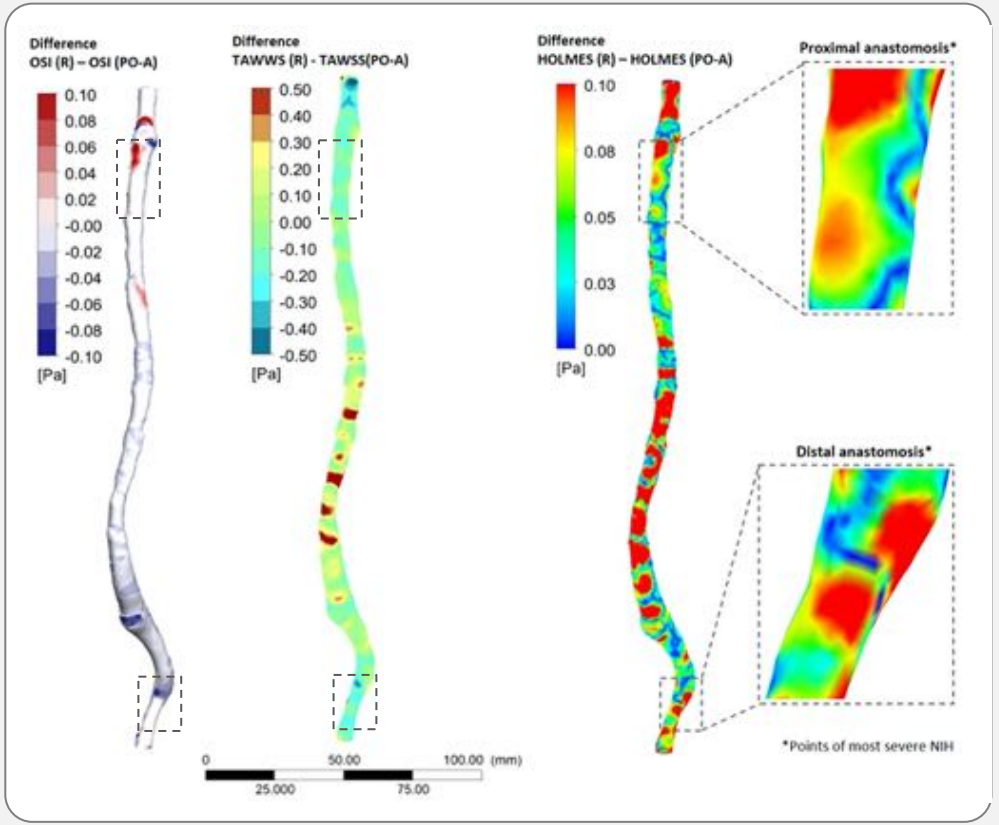
[1] Bonfanti et al. Med. Eng. Phys. 2018; 58:72-79

[2] Donadoni et al. Med. Eng. Phys. doi.org/10.1016/j.medengphy.2019.09.011

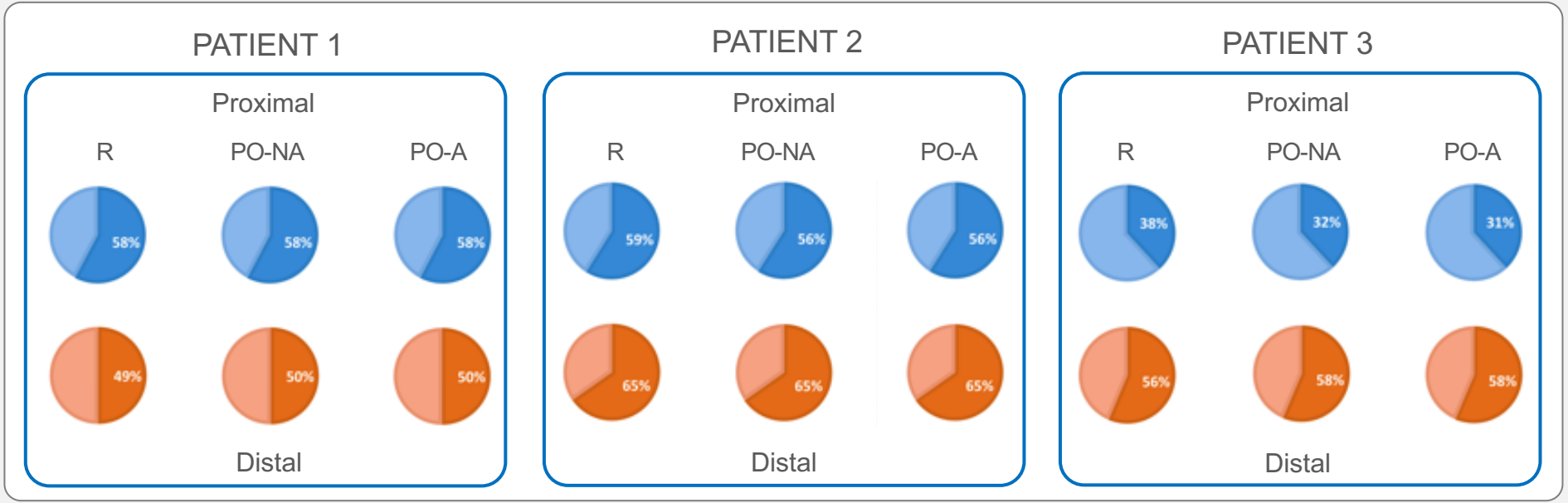
Results: compliance mismatch in the CFD model

- **Negligible effect** on TAWSS and OSI distributions at the location of the proximal and distal anastomosis
- **Slight difference** in HOLMES values at the anastomosis

PATIENT 1 – Comparison between Rigid and PO-A cases

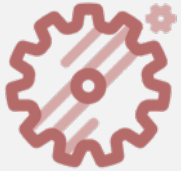


Results: NIH growth comparison



- Our initial findings showed only a **small effect** of compliance mismatch on the simulated occlusion
  → **Haemodynamic changes** due to the **compliance mismatch** may have a **small impact on NIH development**

A summary



- **A promising multiscale, multifactorial approach** has been proposed
- **The computational framework** takes into account cell behaviour and integrates information from the state-of-the-art
- **The approach offers mechanistic explanations** with strong interpretability and physical meaning
- **Our preliminary data** shows an improvement when compared to standard methods
- We must carefully consider what kind of **surrogate metrics** we are using to understand complex biological phenomena

Thank you

European Commission

EPSRC
Engineering and Physical Sciences Research Council

Dr Francesca Donadoni

Prof Alan Dardik

Prof Vanessa Diaz