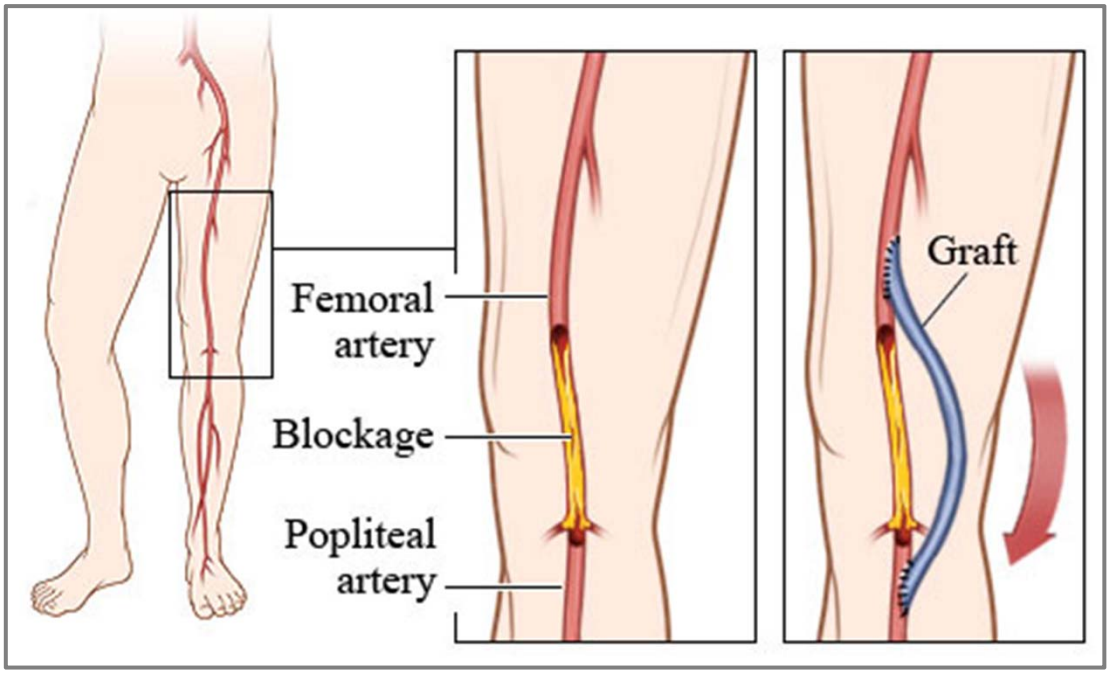
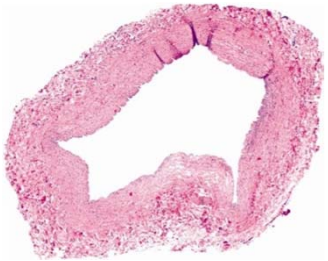


Leg Vein



1 year implantation

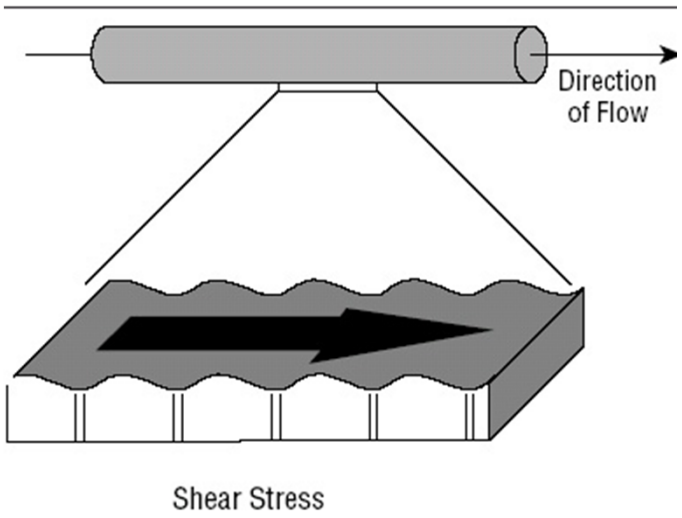
60%

Vein Grafts

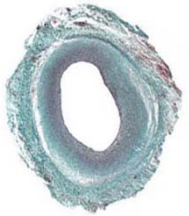
40%

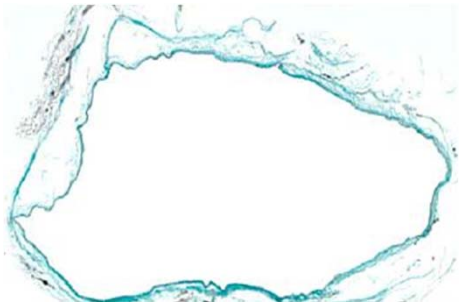
Systems Biology - Dynamic Homeostasis

Environment ⟷ Biologic System



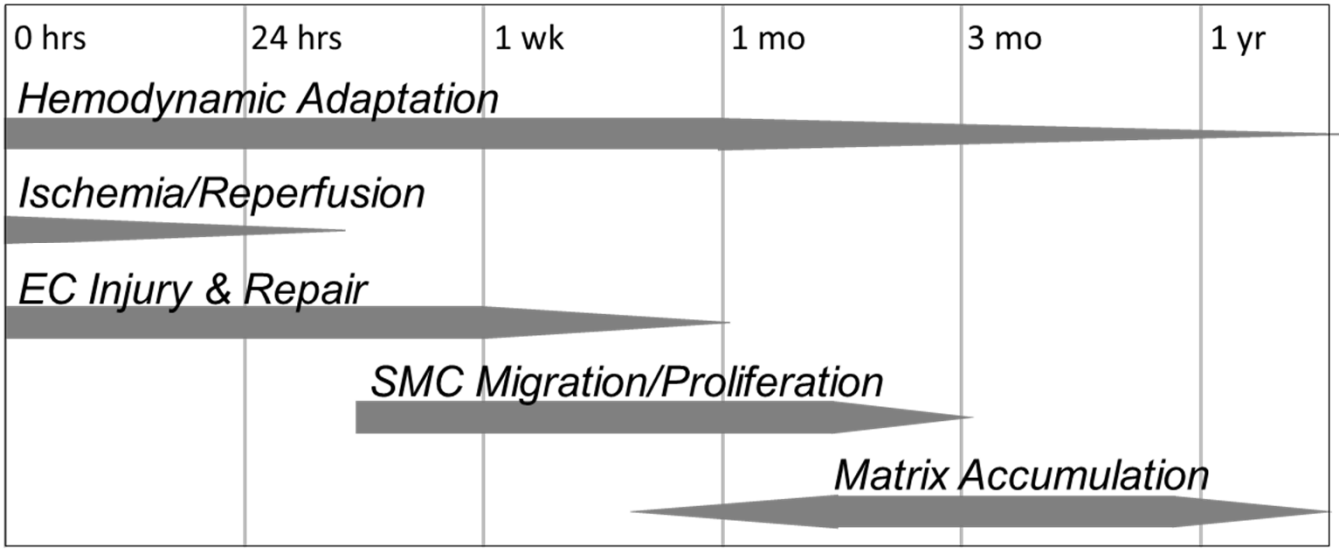
Low Shear Stress **High Shear Stress**



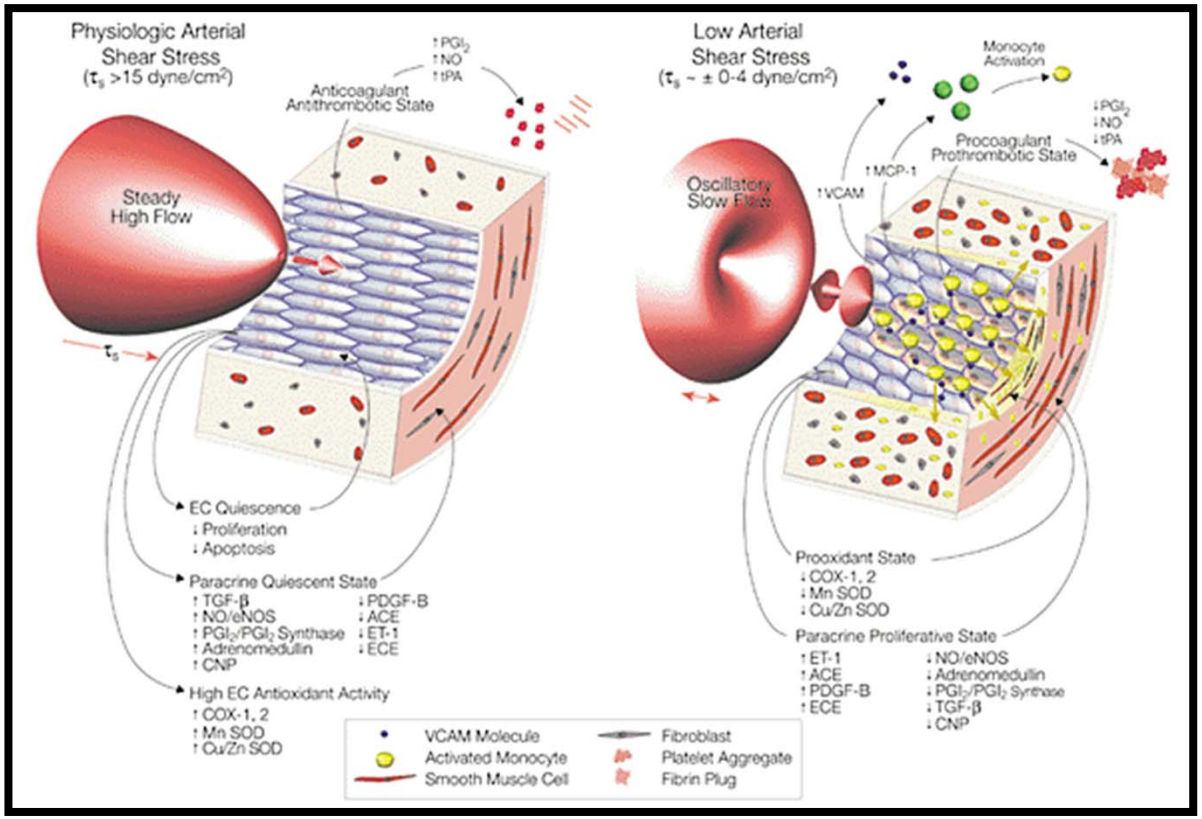


Frangos, Arch Surg. 1999

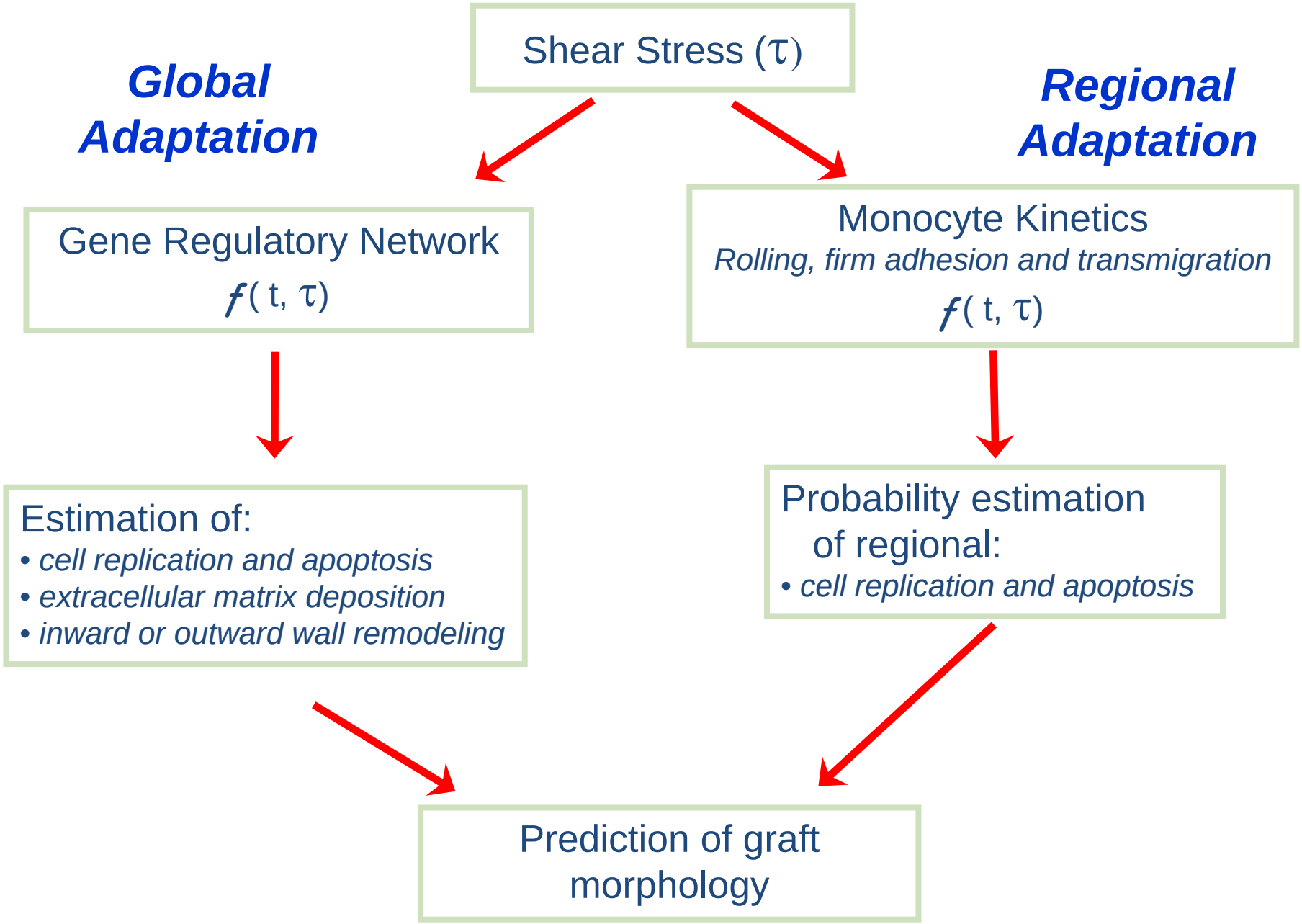
Vein Graft Implantation

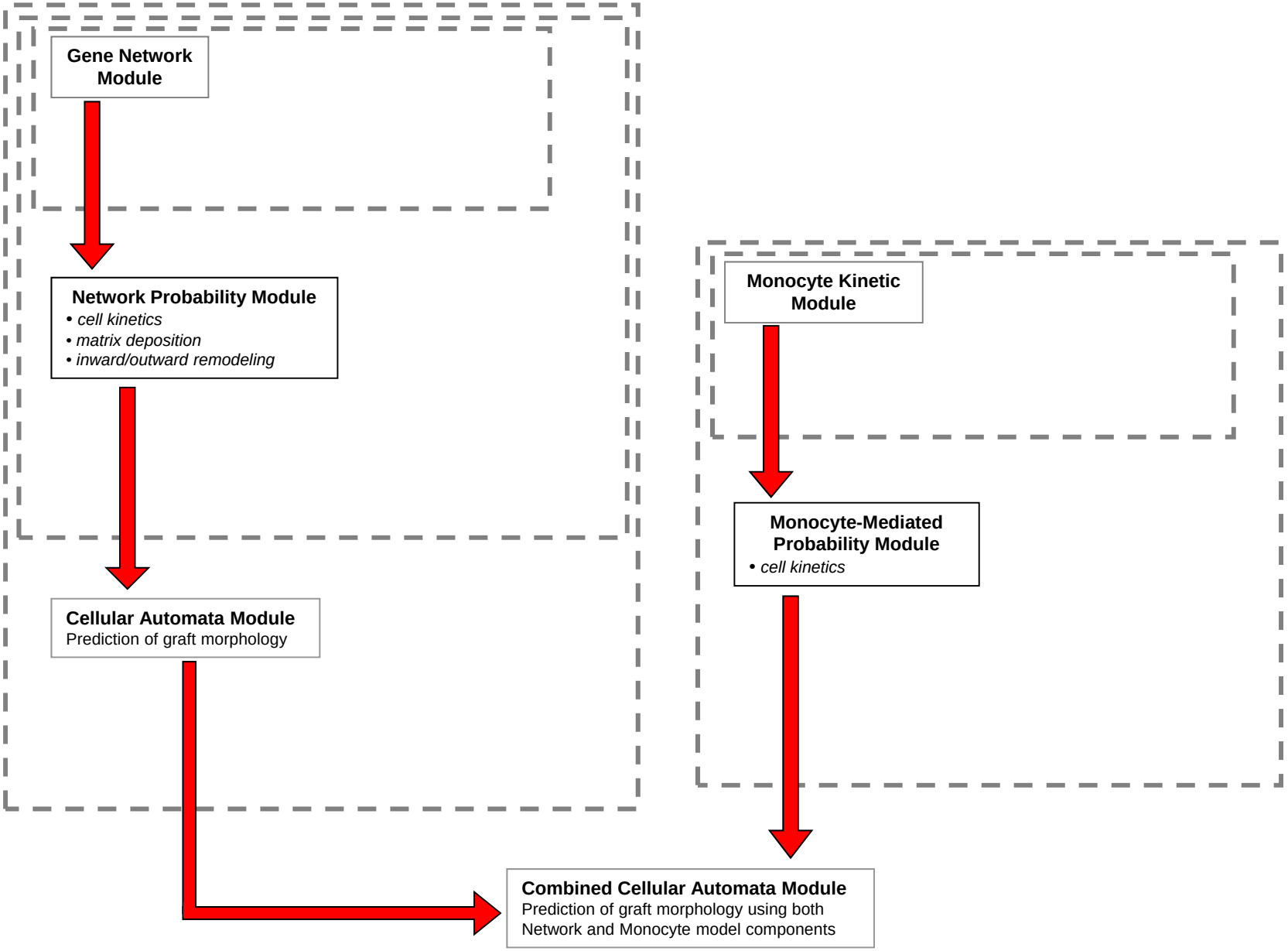


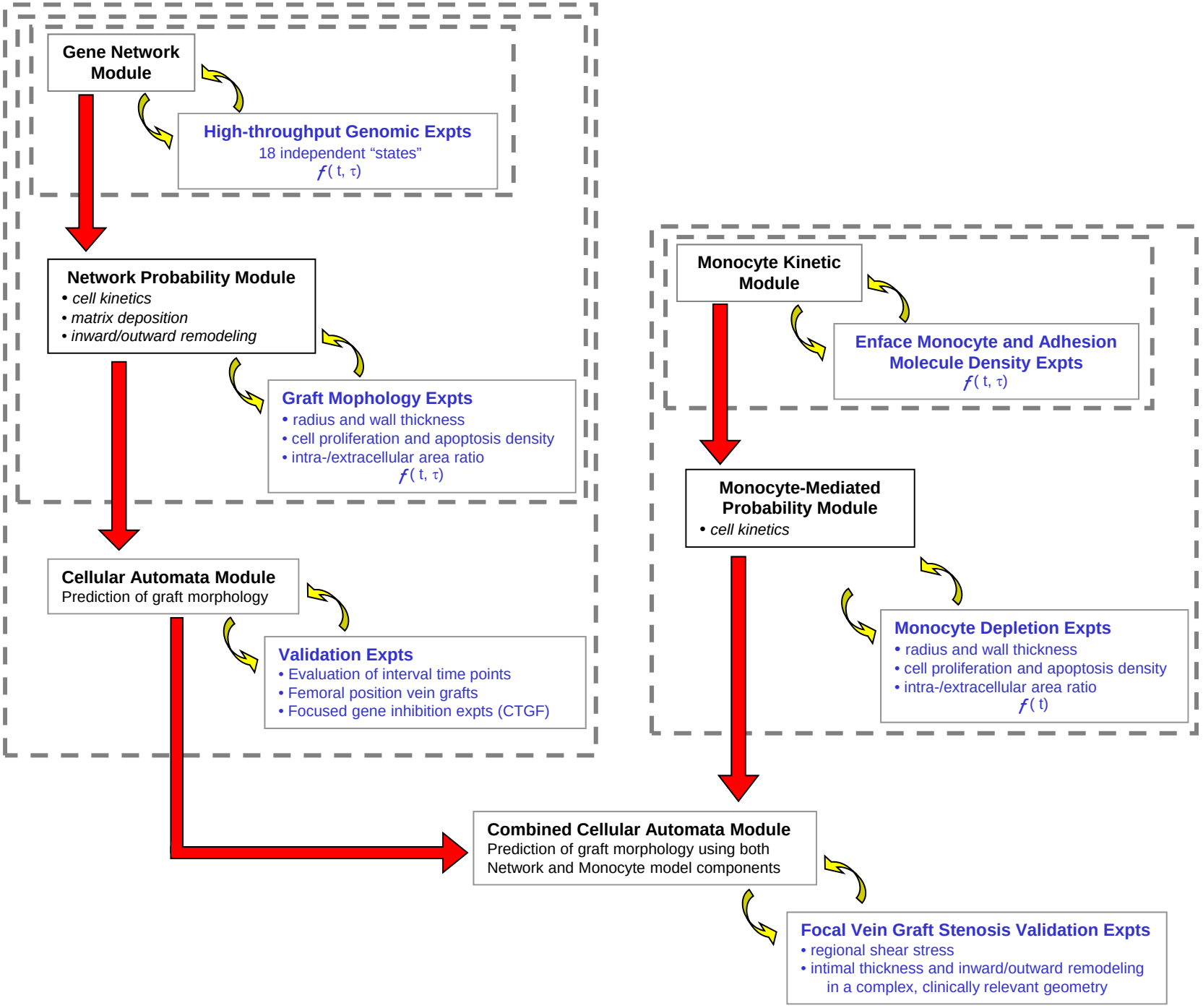
Conte, J Vasc Surg 2002

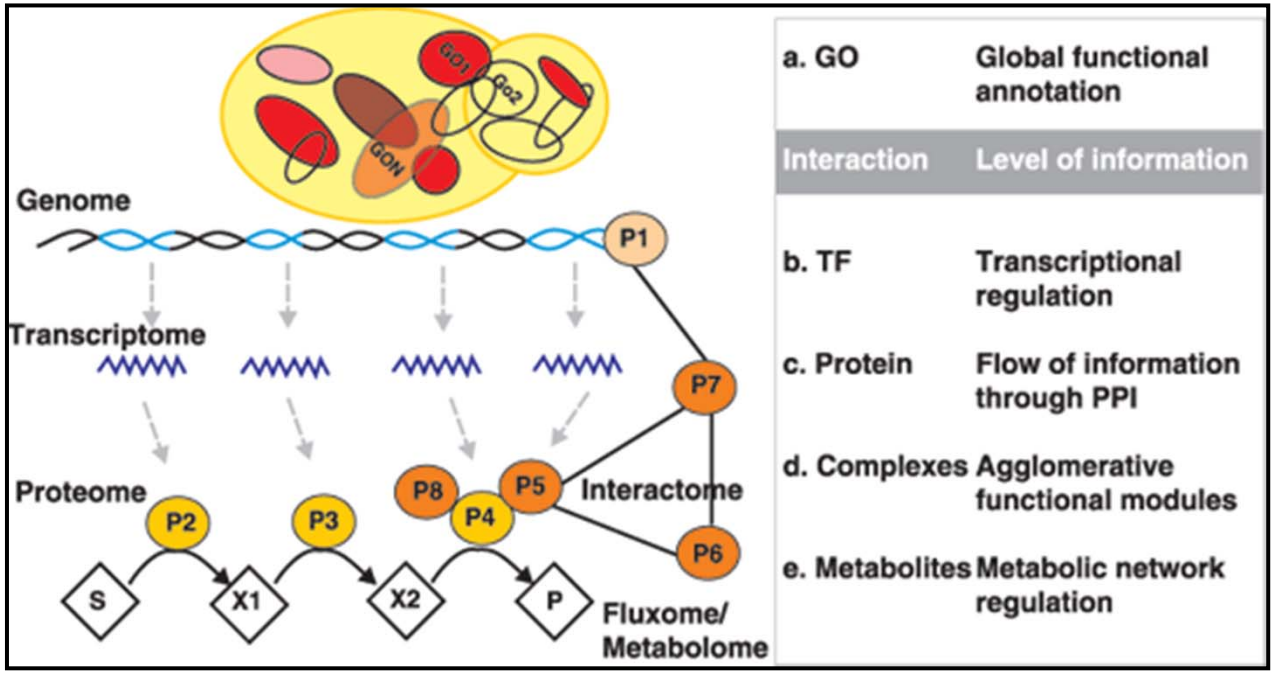


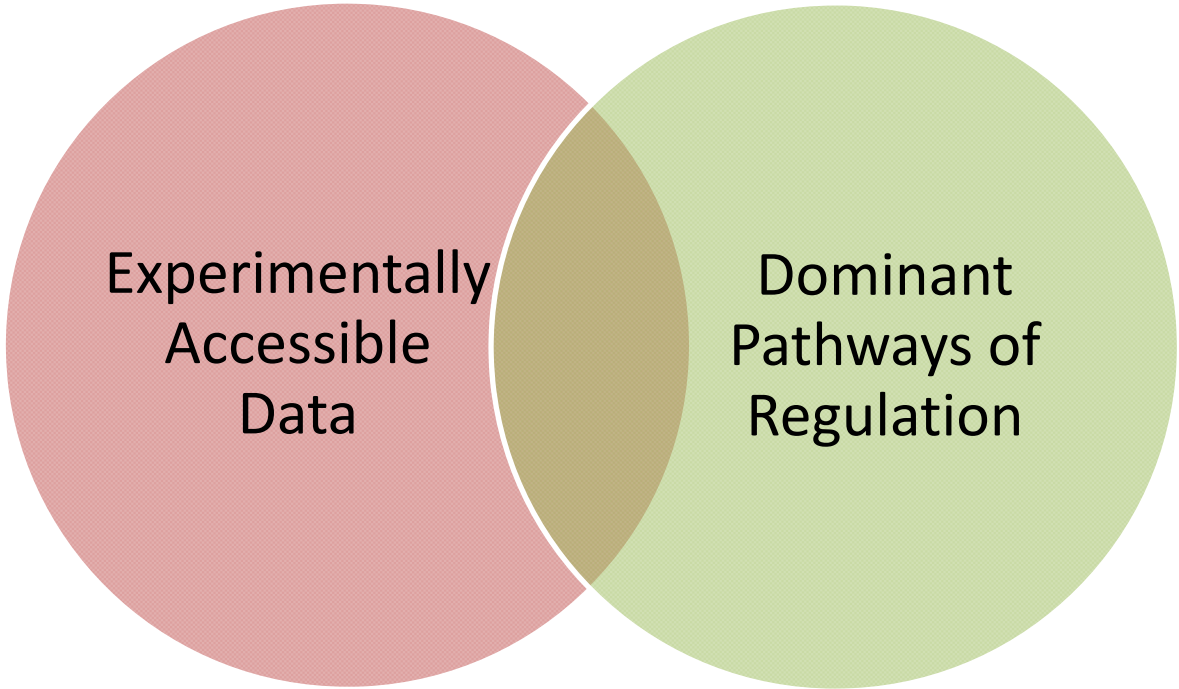
Malek, JAMA, 1999


Shear Stress (τ)
Global Adaptation
Regional Adaptation
Gene Regulatory Network
f(t, τ)
Monocyte Kinetics
Rolling, firm adhesion and transmigration
f(t, τ)
Estimation of:
• cell replication and apoptosis
• extracellular matrix deposition
• inward or outward wall remodeling
Probability estimation of regional:
• cell replication and apoptosis
Prediction of graft morphology

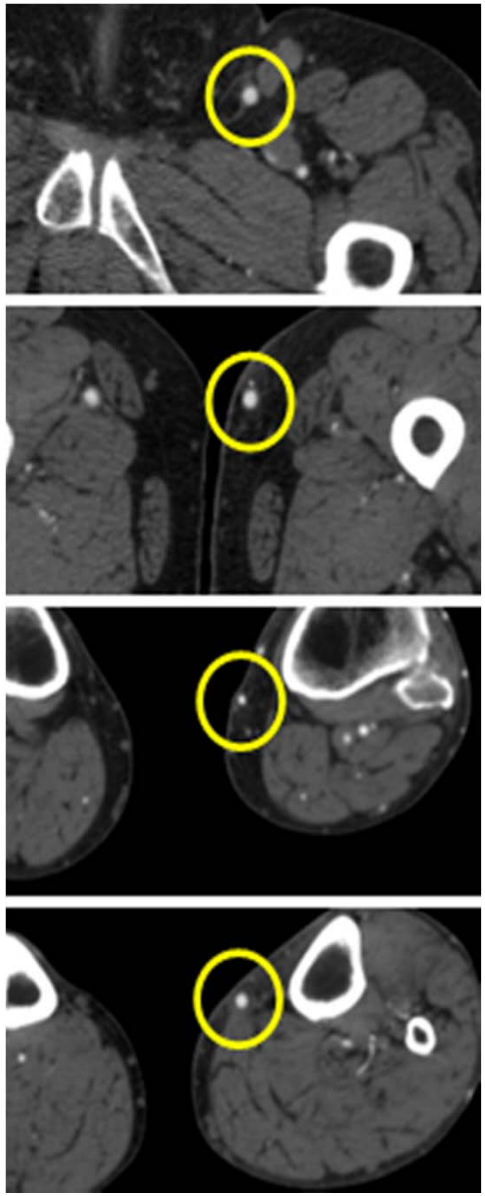

Gene Network Module
Network Probability Module
• cell kinetics
• matrix deposition
• inward/outward remodeling
Cellular Automata Module
Prediction of graft morphology
Monocyte Kinetic Module
Monocyte-Mediated Probability Module
• cell kinetics
Combined Cellular Automata Module
Prediction of graft morphology using both Network and Monocyte model components

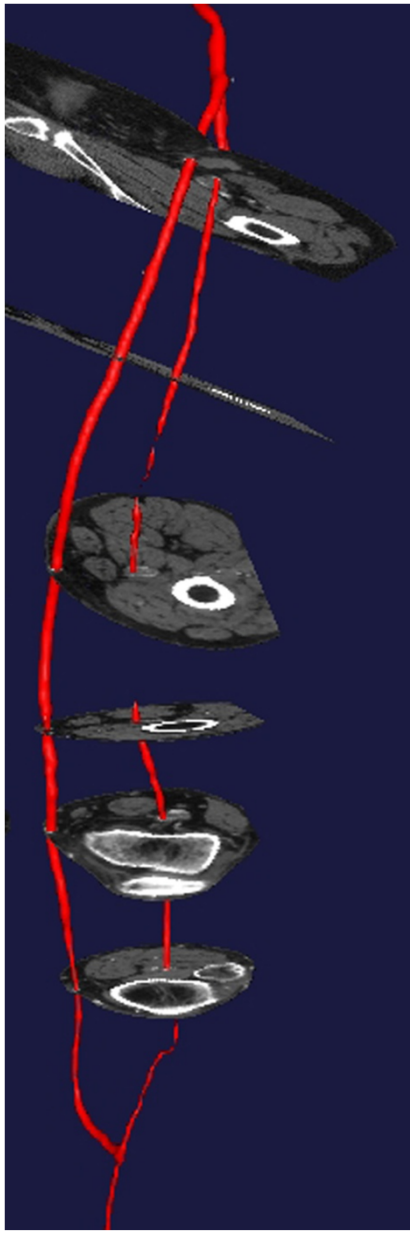

Gene Network Module
High-throughput Genomic Expts
18 independent "states"
f(t, τ)
Network Probability Module
• cell kinetics
• matrix deposition
• inward/outward remodeling
Graft Mophology Expts
• radius and wall thickness
• cell proliferation and apoptosis density
• intra-/extracellular area ratio
f(t, τ)
Cellular Automata Module
Prediction of graft morphology
Validation Expts
• Evaluation of interval time points
• Femoral position vein grafts
• Focused gene inhibition expts (CTGF)
Monocyte Kinetic Module
Enface Monocyte and Adhesion Molecule Density Expts
f(t, τ)
Monocyte-Mediated Probability Module
• cell kinetics
Monocyte Depletion Expts
• radius and wall thickness
• cell proliferation and apoptosis density
• intra-/extracellular area ratio
f(t)
Combined Cellular Automata Module
Prediction of graft morphology using both Network and Monocyte model components
Focal Vein Graft Stenosis Validation Expts
• regional shear stress
• intimal thickness and inward/outward remodeling in a complex, clinically relevant geometry


GO1
Go2
GON
Genome
P1
Transcriptome
P7
Proteome
P2
P3
P8
P4
P5
Interactome
P6
S
X1
X2
P
Fluxome/
Metabolome
a. GO
Global functional annotation
Interaction
Level of information
b. TF
Transcriptional regulation
c. Protein
Flow of information through PPI
d. Complexes
Agglomerative functional modules
e. Metabolites
Metabolic network regulation


Experimentally Accessible Data
Dominant Pathways of Regulation

Translational to Clinical Research

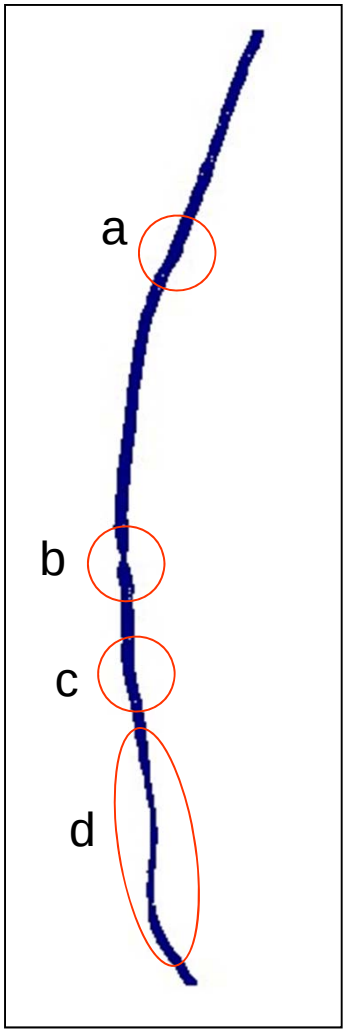


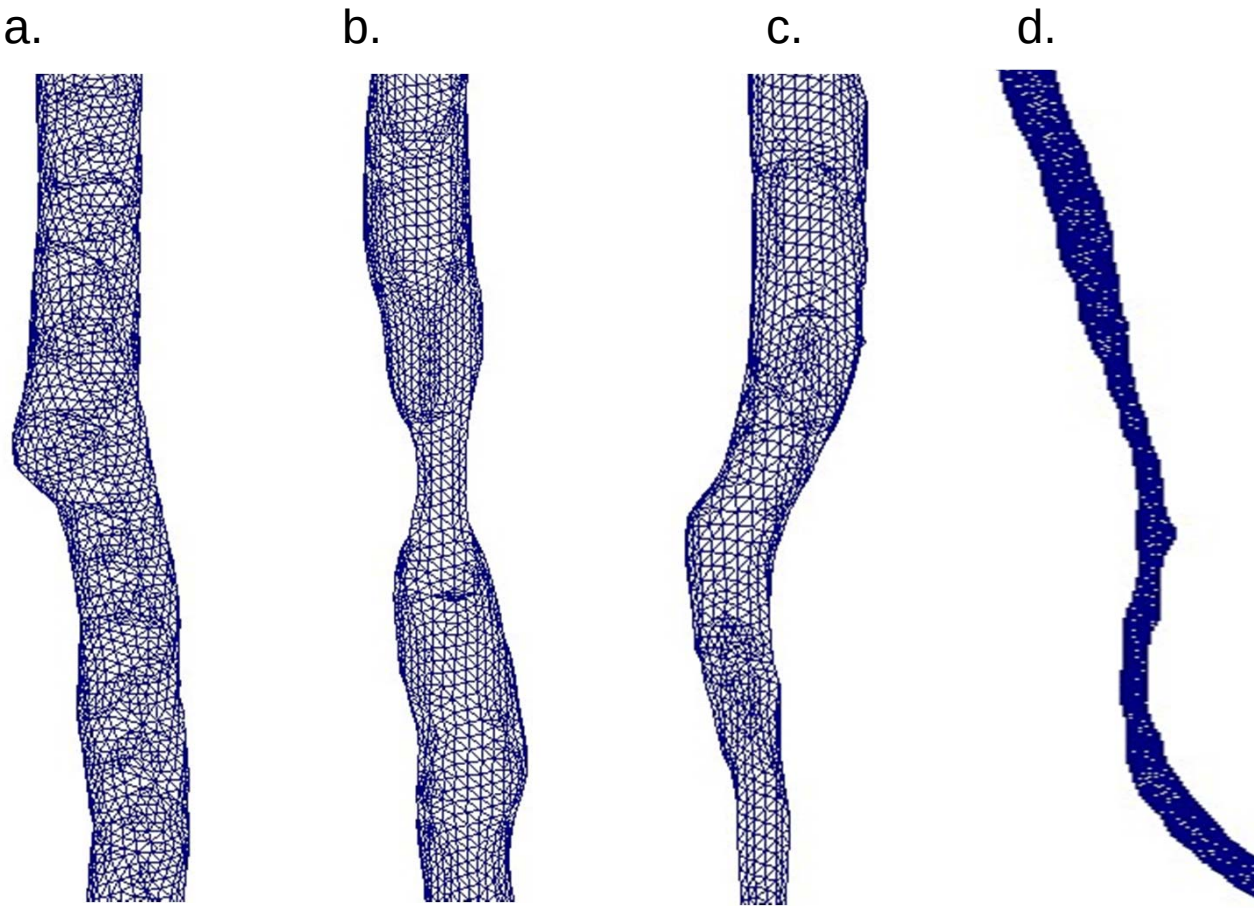


Vein Graft Geometry

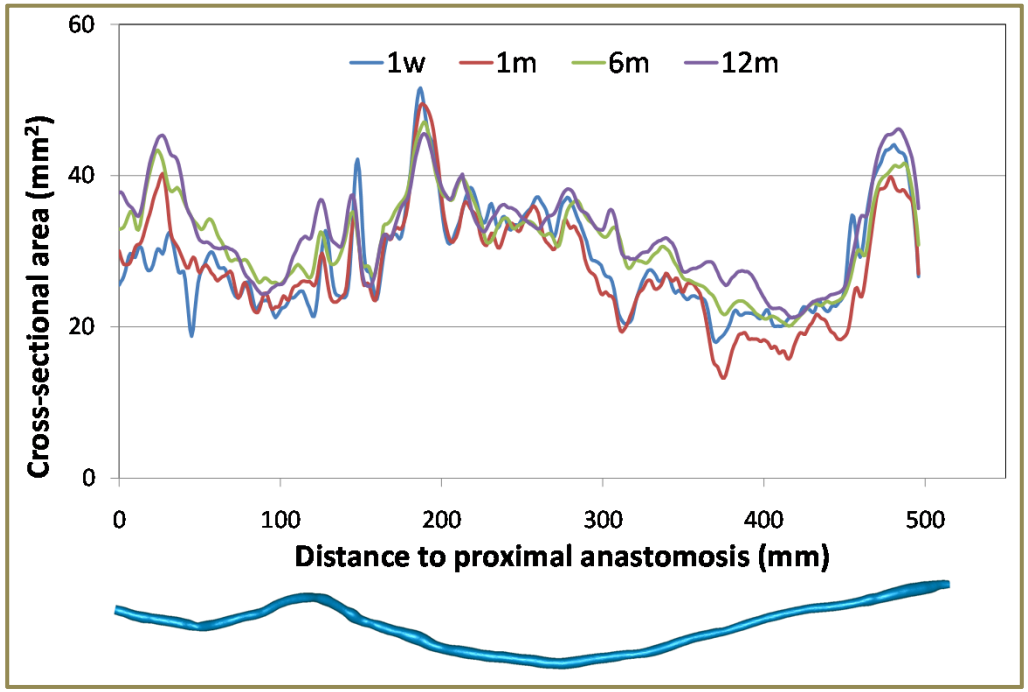
Hemodynamic Modeling

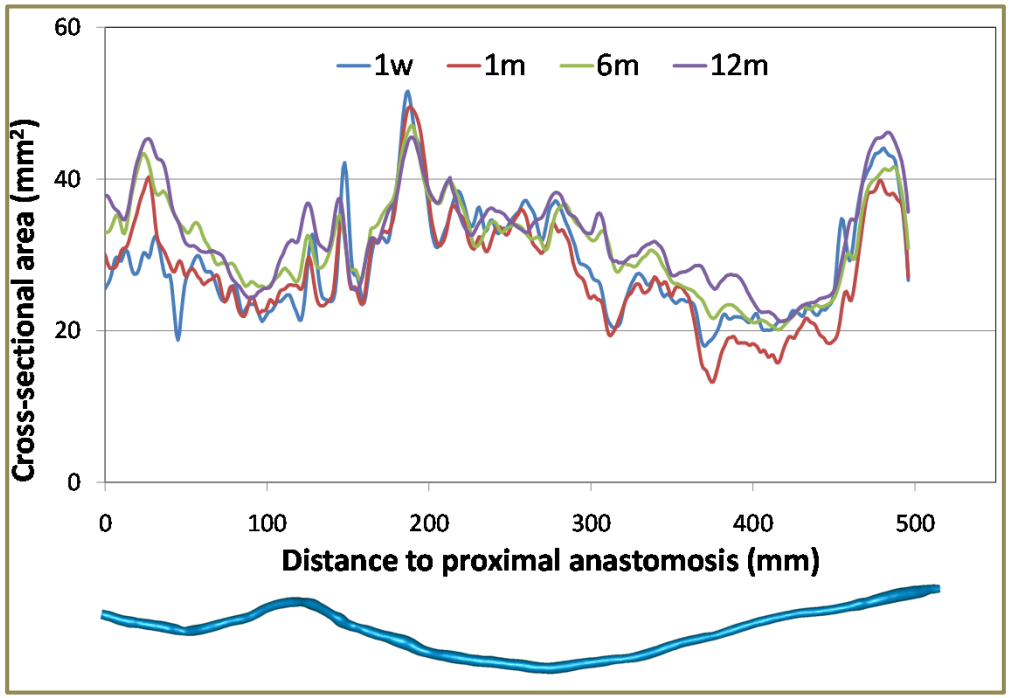
Human Veins Grafts - Limited to Non-invasive Assessments

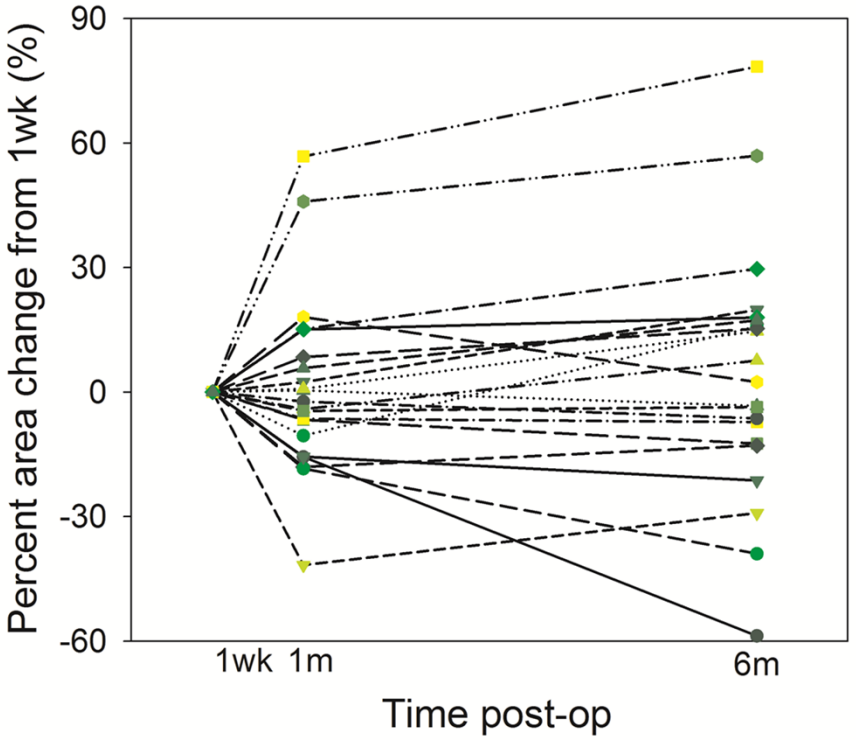




Human Veins Grafts -
Geometric Complexity







Human Veins Grafts – Heterogenity