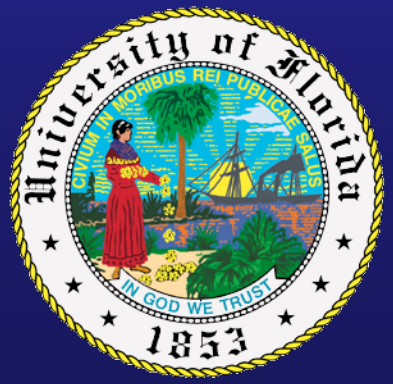
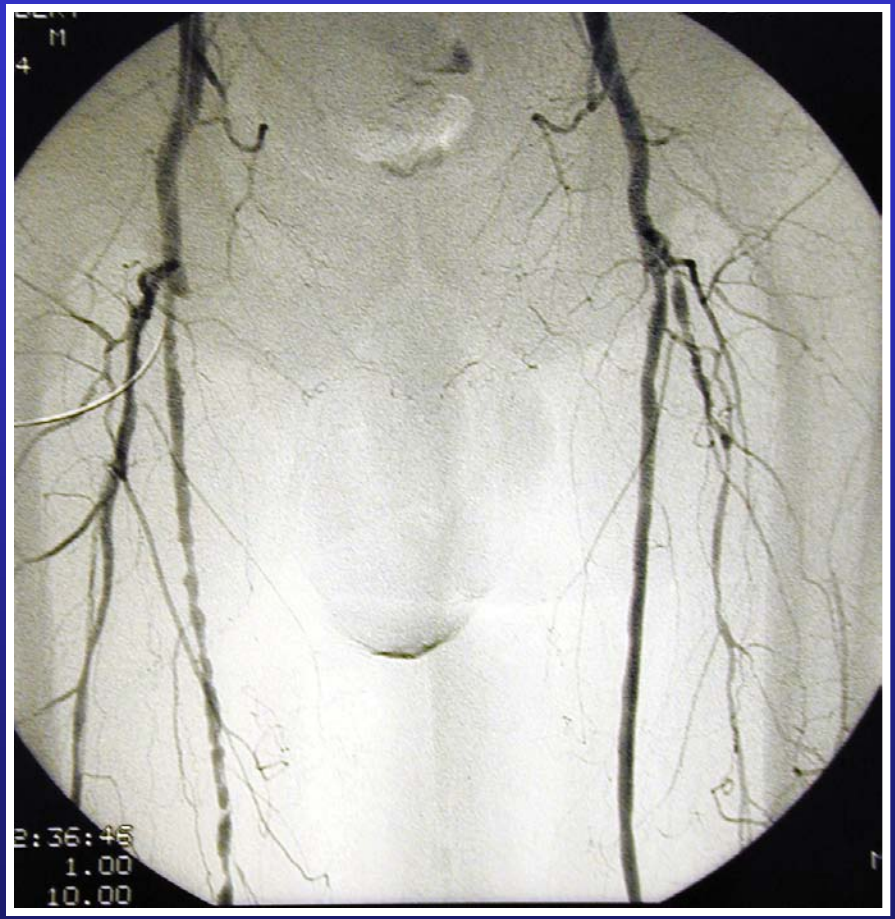
Multiscale Network Modeling of Hemodynamically-Driven Vascular Adaptation

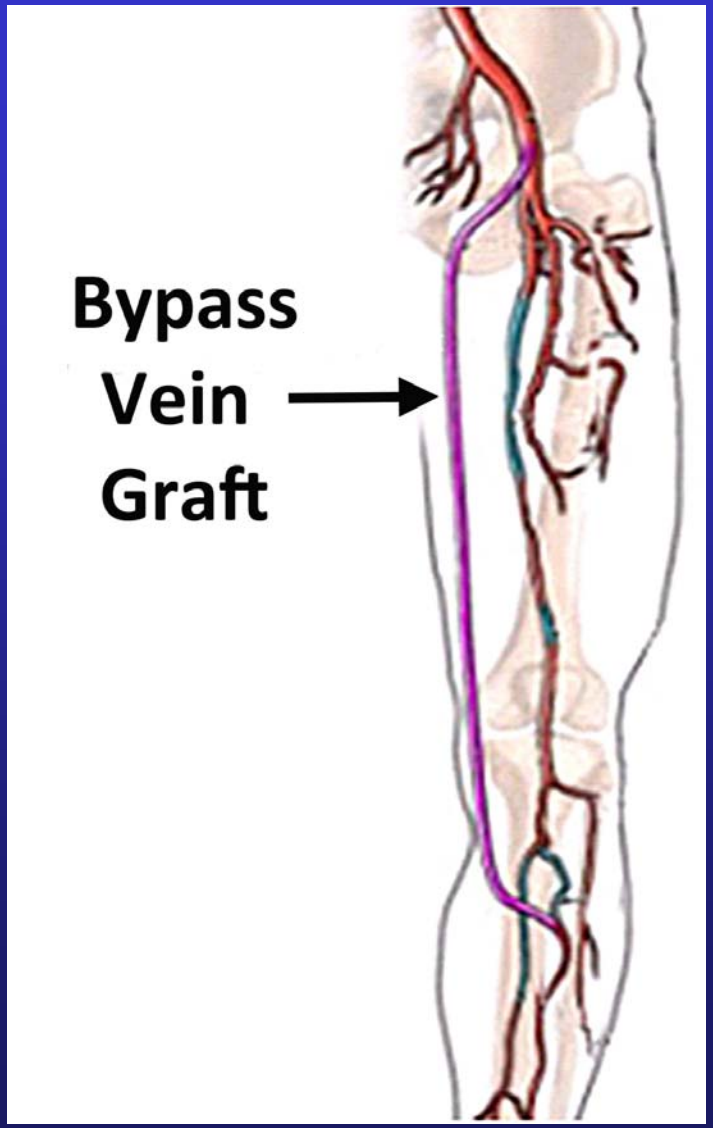
Scott Berceli, MD PhD

September 30, 2009

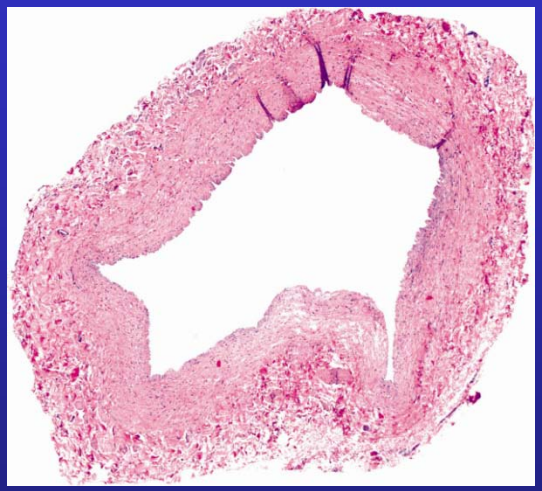


Lower Extremity Atherosclerosis





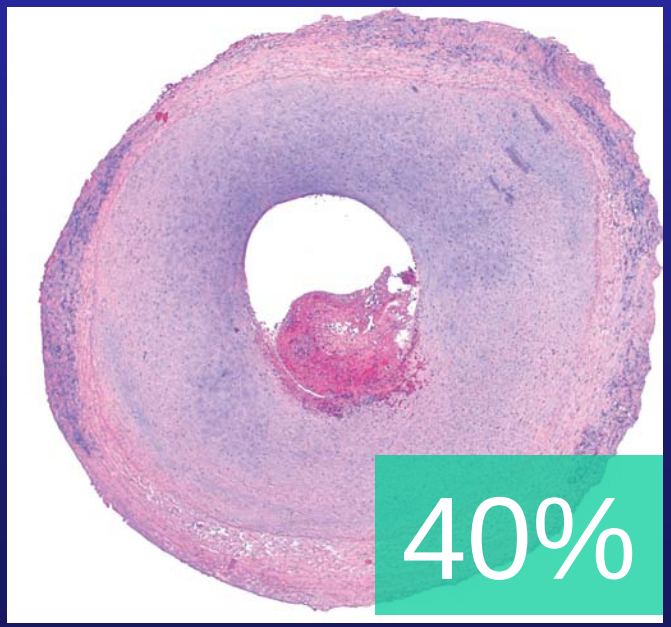
Leg Vein



1 year implantation

60%

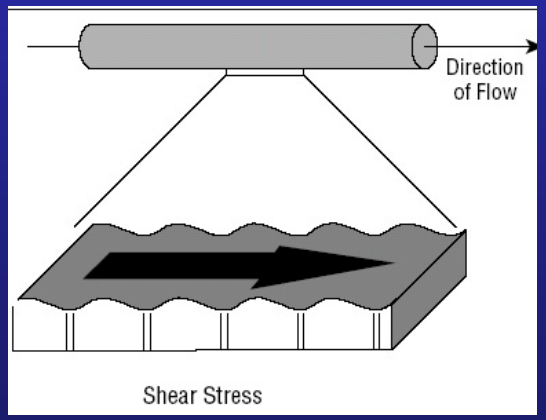
Vein Grafts

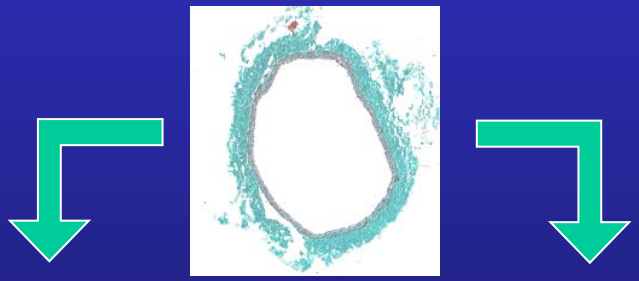


40%

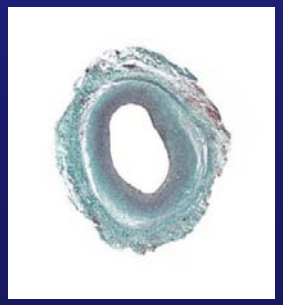
Dynamic Homeostasis

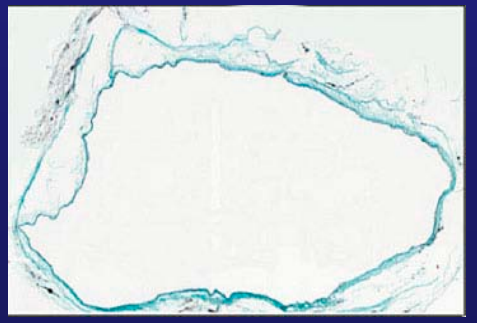
Environment ⟷ Biologic System





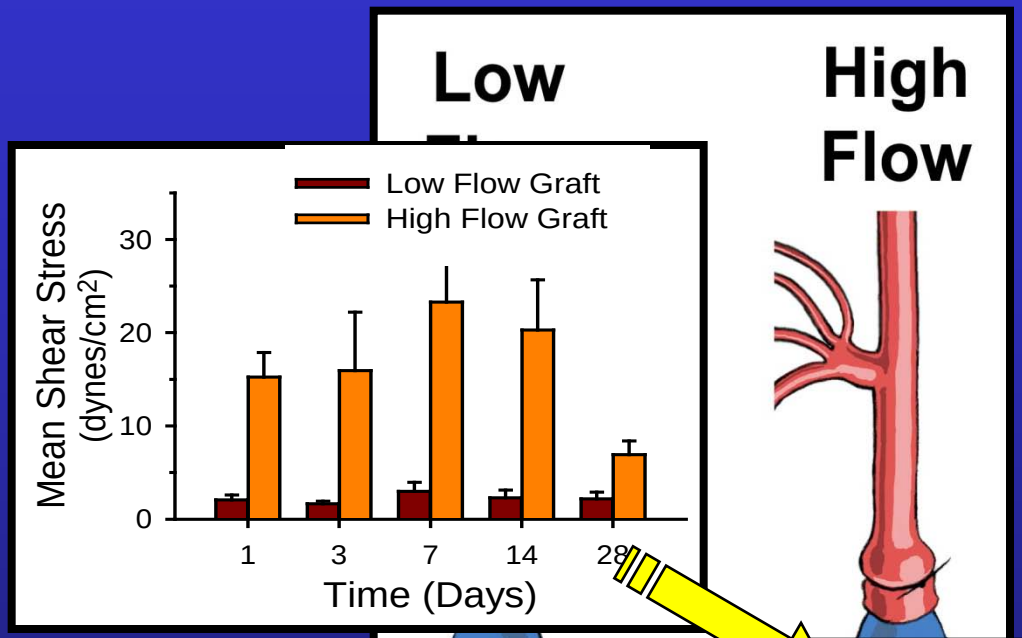
Low Shear Stress **High Shear Stress**

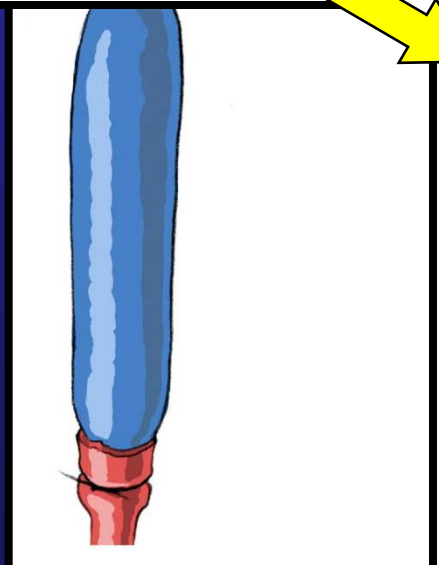


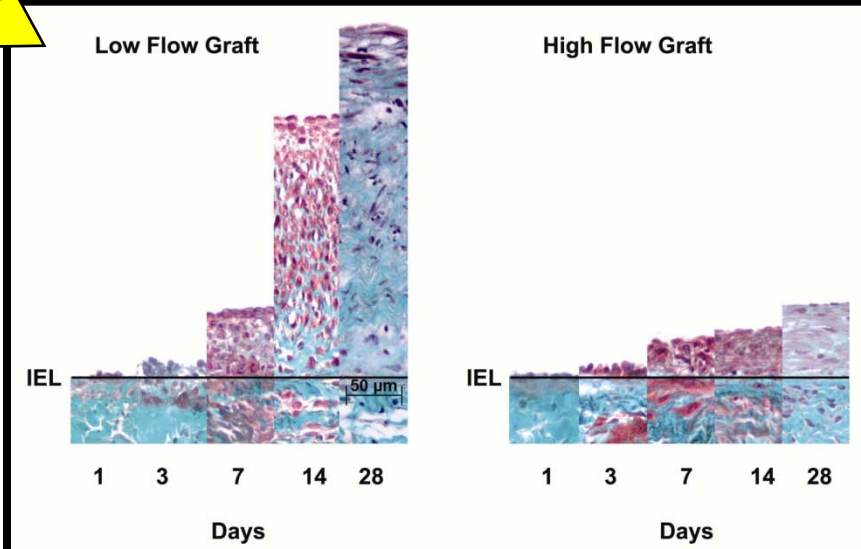


Shear-Mediated Vein Graft Adaptation

Rabbit Vein Graft







Global Adaptation

Shear Stress (τ)

Gene Regulatory Network

$f(t, \tau)$

Mono

Rolling, firm adh

Estimation of:

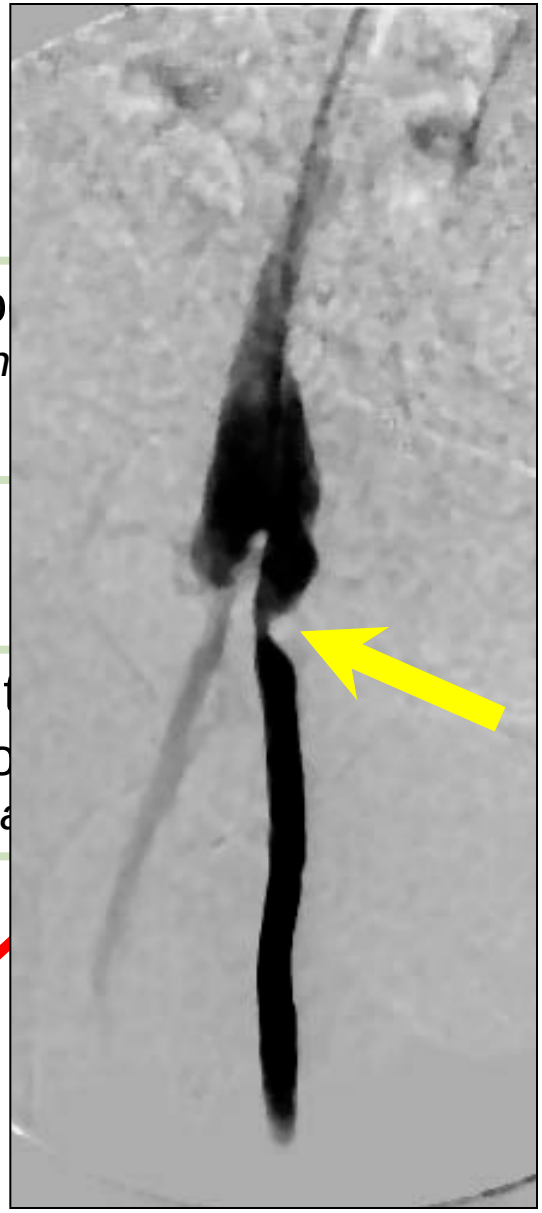
- *cell replication and apoptosis*
- *extracellular matrix deposition*
- *inward or outward wall remodeling*

Probabilit

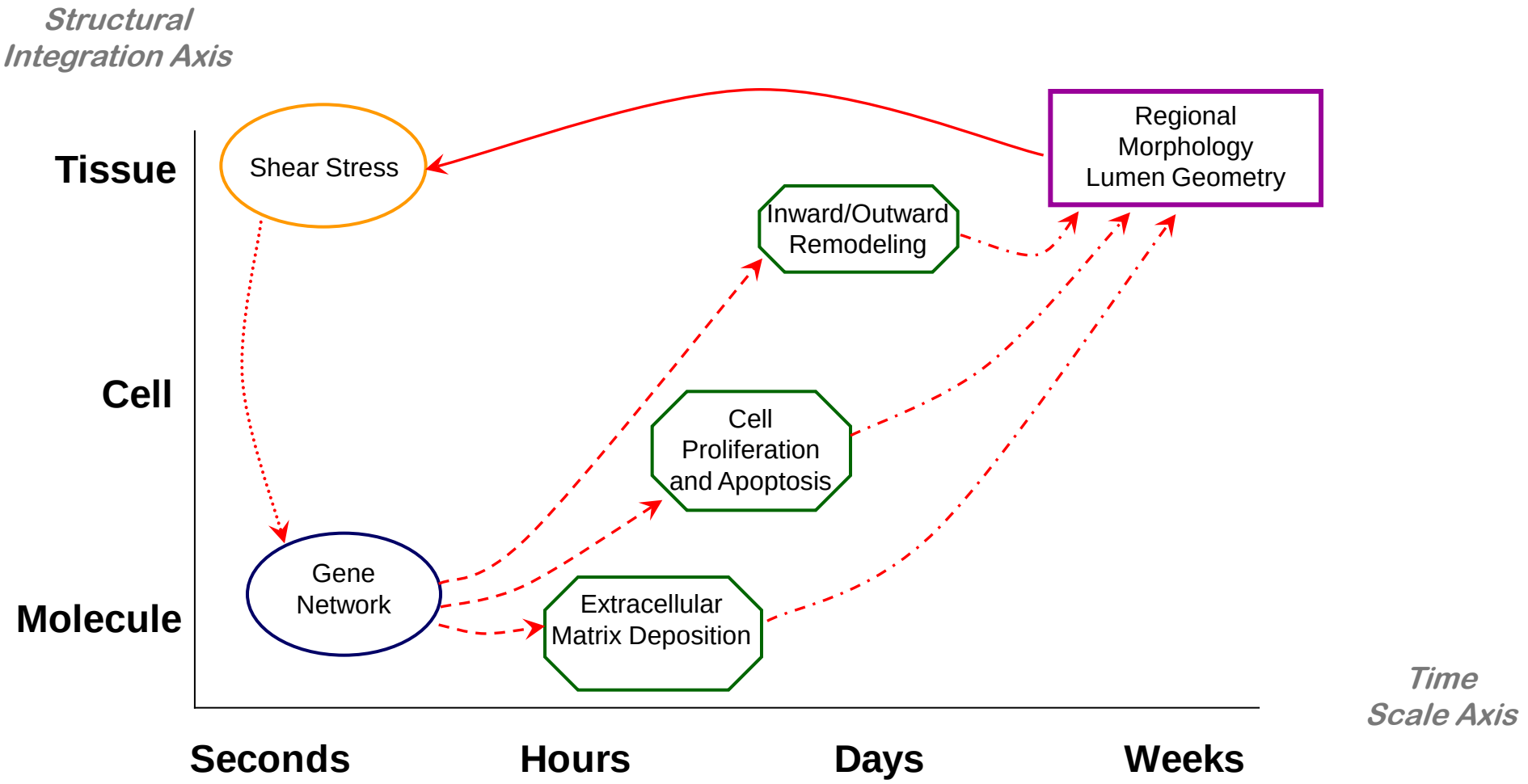
of regio

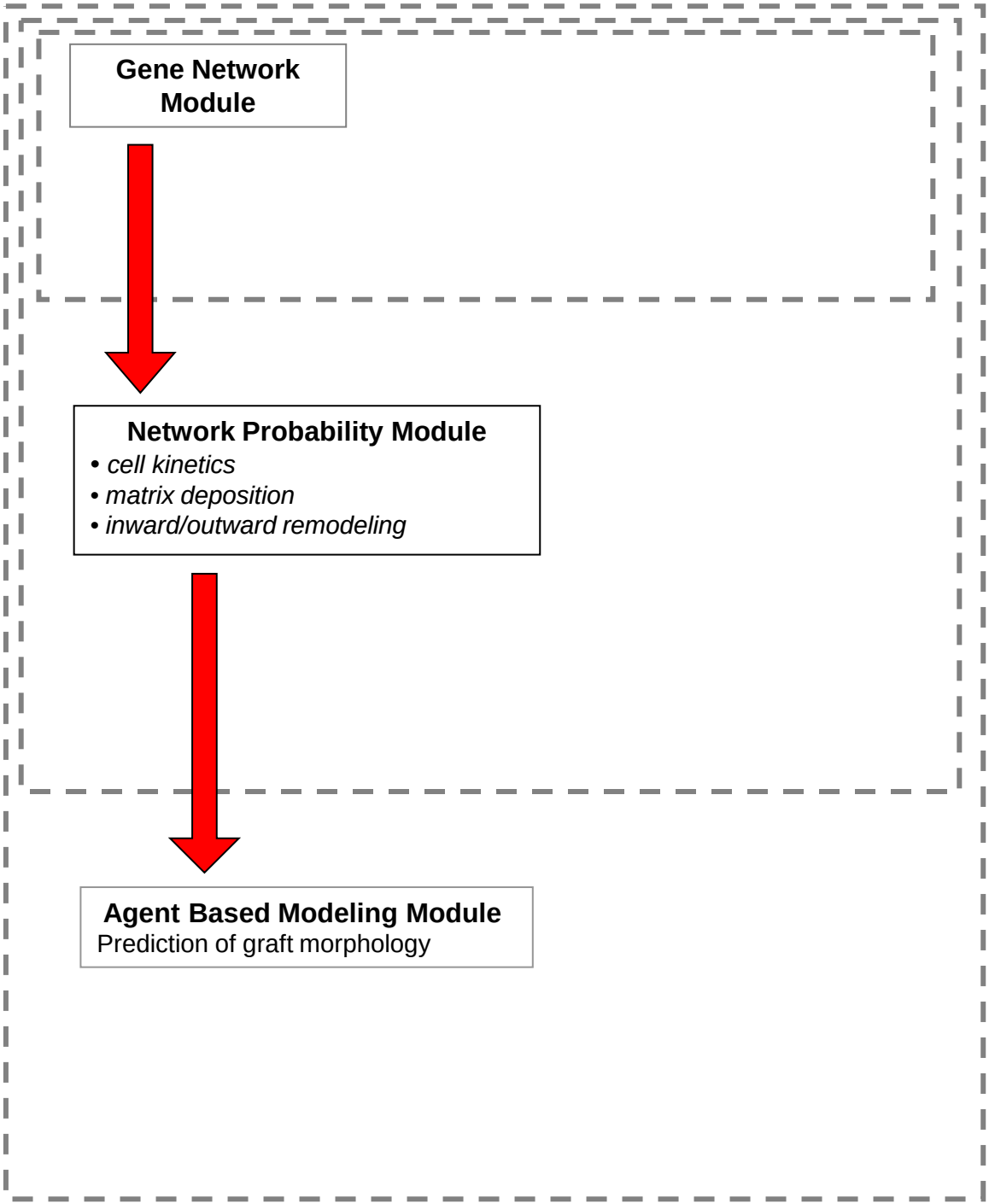
- *cell replica*

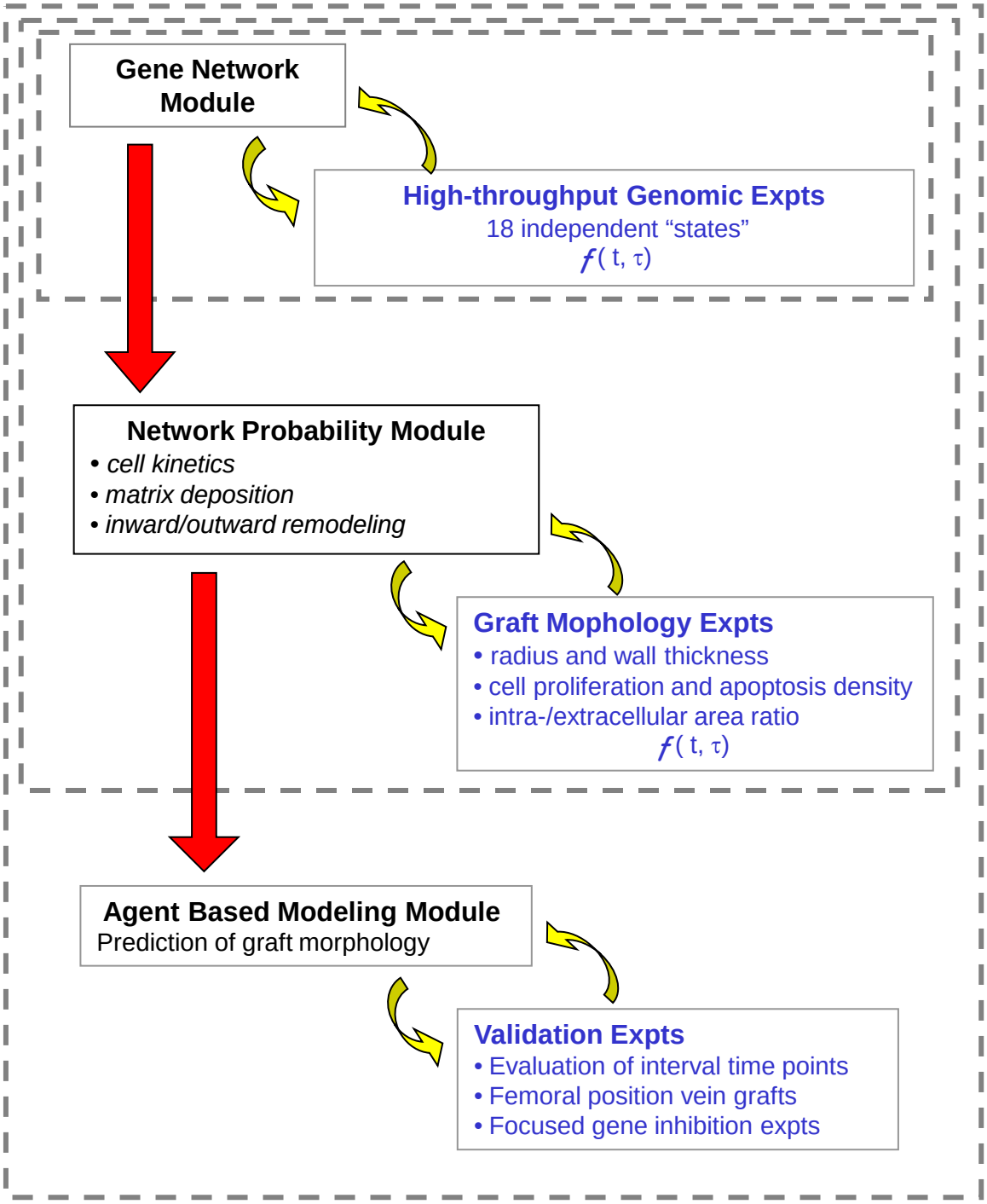
Prediction of graft morphology



Events in Vascular Remodeling




Gene Network Module
Network Probability Module
• cell kinetics
• matrix deposition
• inward/outward remodeling
Agent Based Modeling Module
Prediction of graft morphology


Gene Network Module
High-throughput Genomic Expts
18 independent "states"
ƒ(t, τ)
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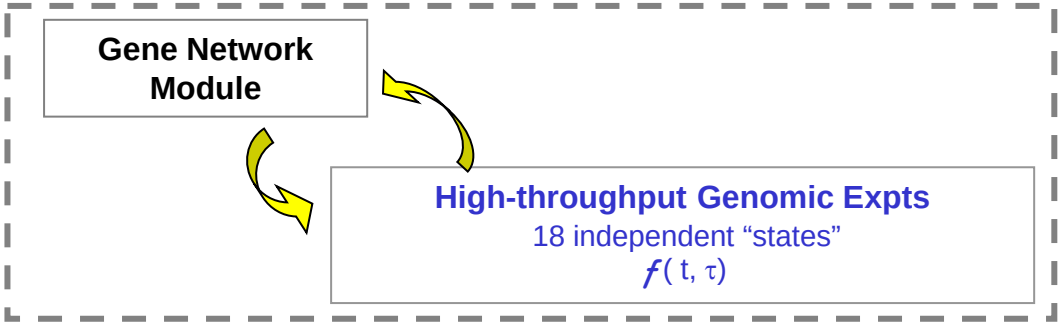
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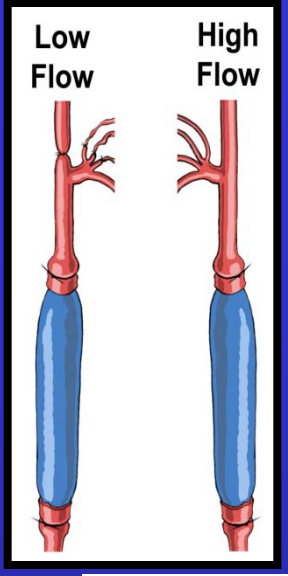
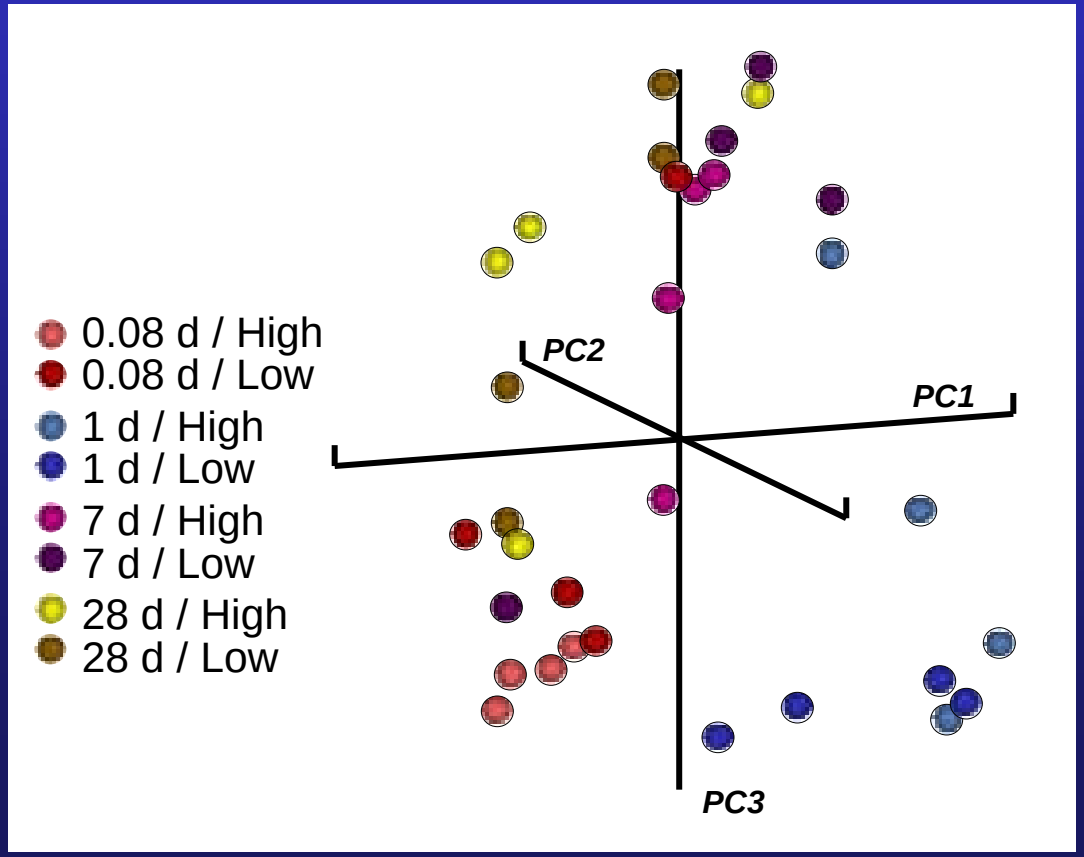
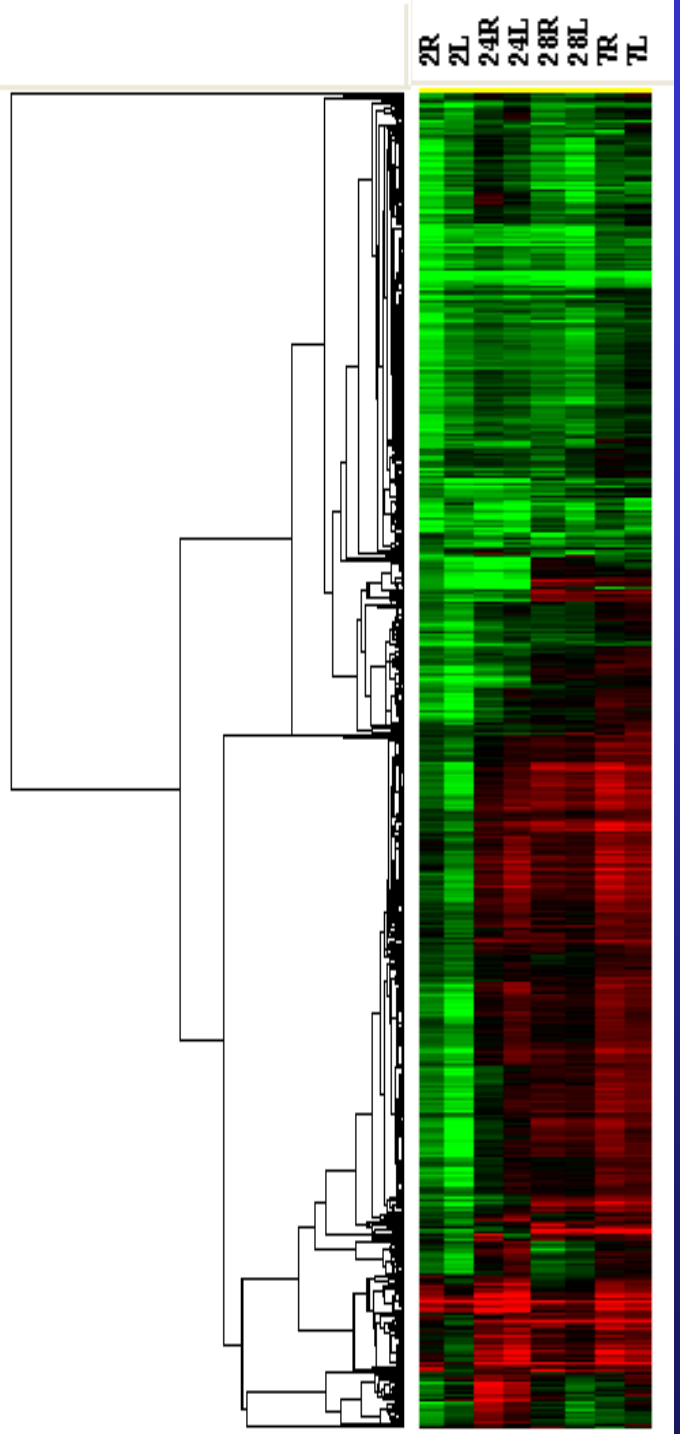
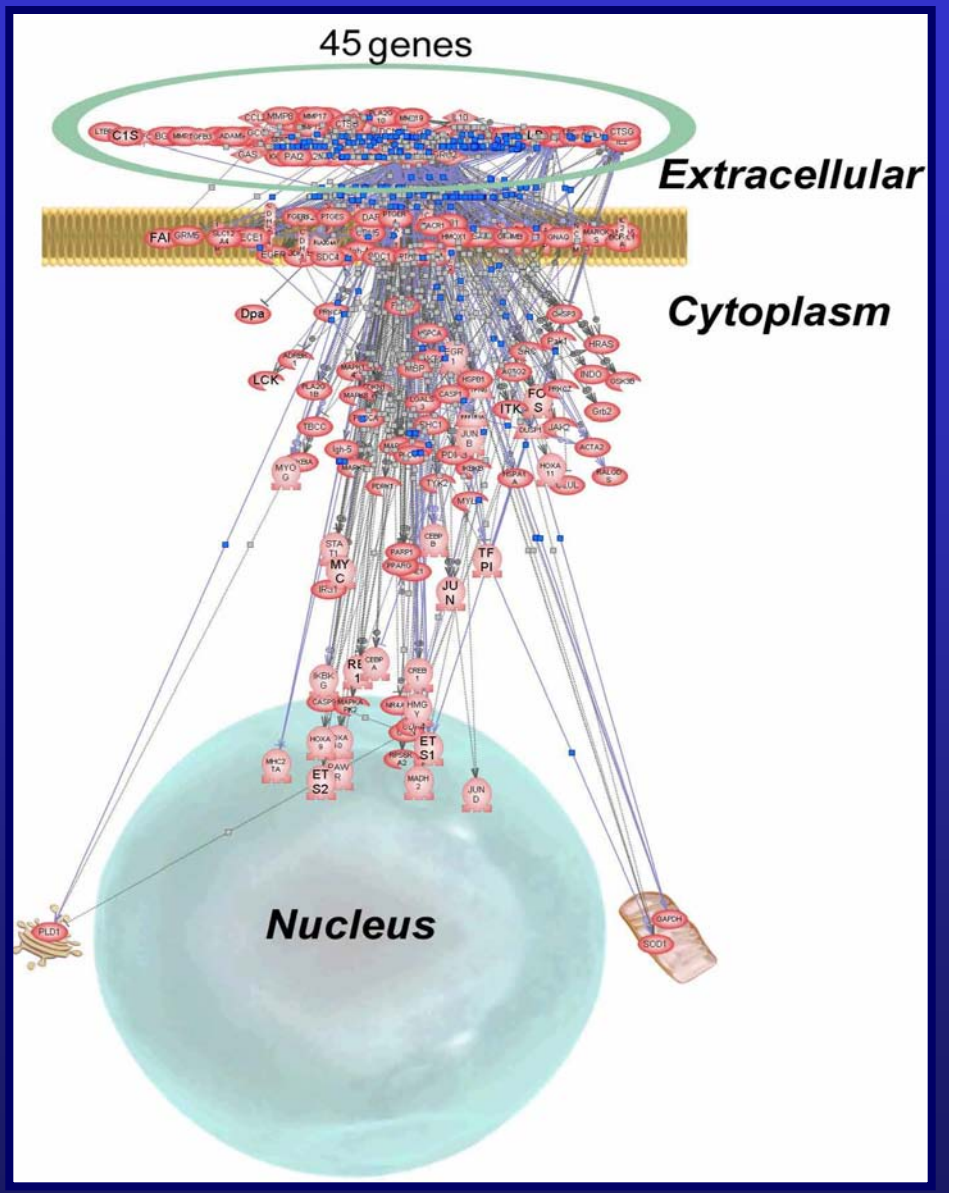


Microarray Genomic Analysis

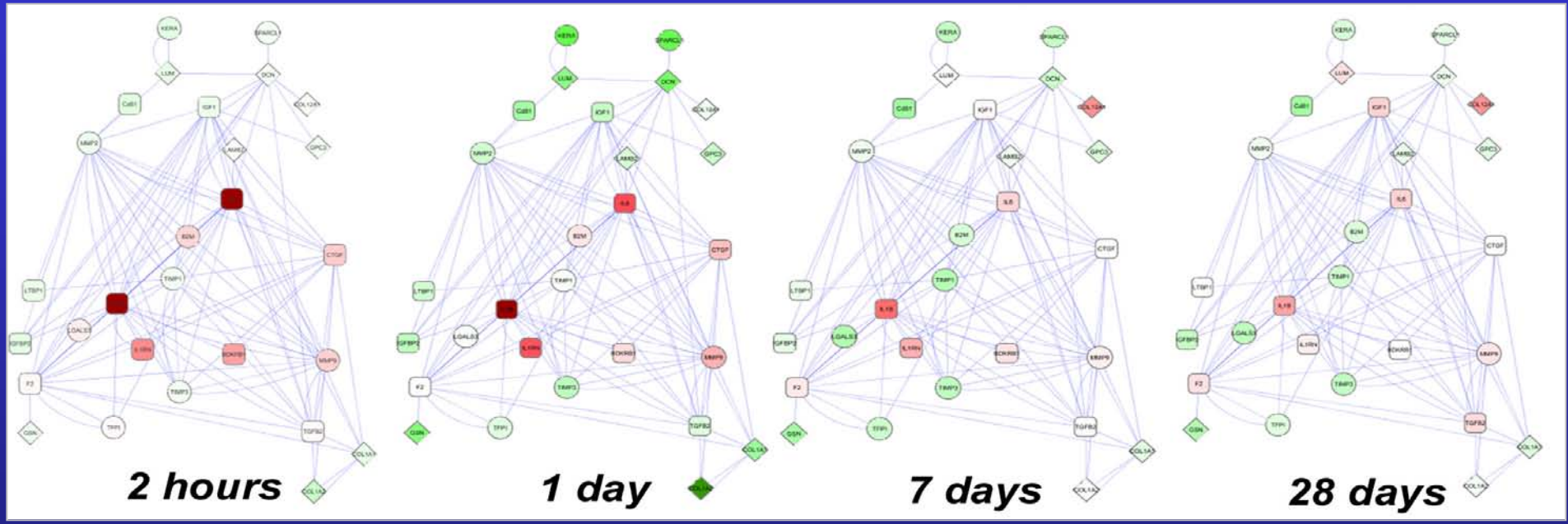






Mediators	Effectors	Structural Elements
Platelet-derived growth factor receptor-like protein	*Fibroblast activation protein α*	*Keratan sulfate proteoglycan*
interleukin 6	*Cystatin C*	*Lumican*
Insulin-like growth factor 1	*SPARC-like 1*	*Bone proteoglycan II*
Insulin-like growth factor binding protein 2	*Procollagen C-endopeptidase enhancer 2*	*Collagen Type I, α 2*
Transforming growth factor β-binding protein 3	*Keratocan*	*Dermatan sulfate proteoglycan 3*
Interleukin-1 receptor antagonist	*Metalloproteinase inhibitor 3*	*Collagen type XII, α1*
Interleukin-1β	*Tissue factor pathway inhibitor*	*Decorin*
Transforming growth factor-β 2	*Galactose-specific lectin 3*	*Collagen Type XI, α1*
Bucentaur	*β-2-microglobulin*	*Collagen Type I, α2*
Protein-tyrosine-phosphatase receptor type O	*Neutrophil granules matrix glycoprotein*	*Collagen III, α1*
B1 bradykinin receptor	*Protein S*	*Glypican 3*
MHC class II antigen	*Matrix metalloproteinase-9*	*Laminin, β2*
Thrombin	*Metalloproteinase inhibitor 1*	*Laminin, α4*
Serum amyloid A-3 protein	*Matrix metalloproteinase-2*	*Gelsolin isoform b*
Connective tissue growth factor	*Transforming growth factor-β 2*	*Collagen Type VIII, α1*

Database within PathwayStudio (Ariadne Genomics) used to develop the functional network comprising these extracellular elements

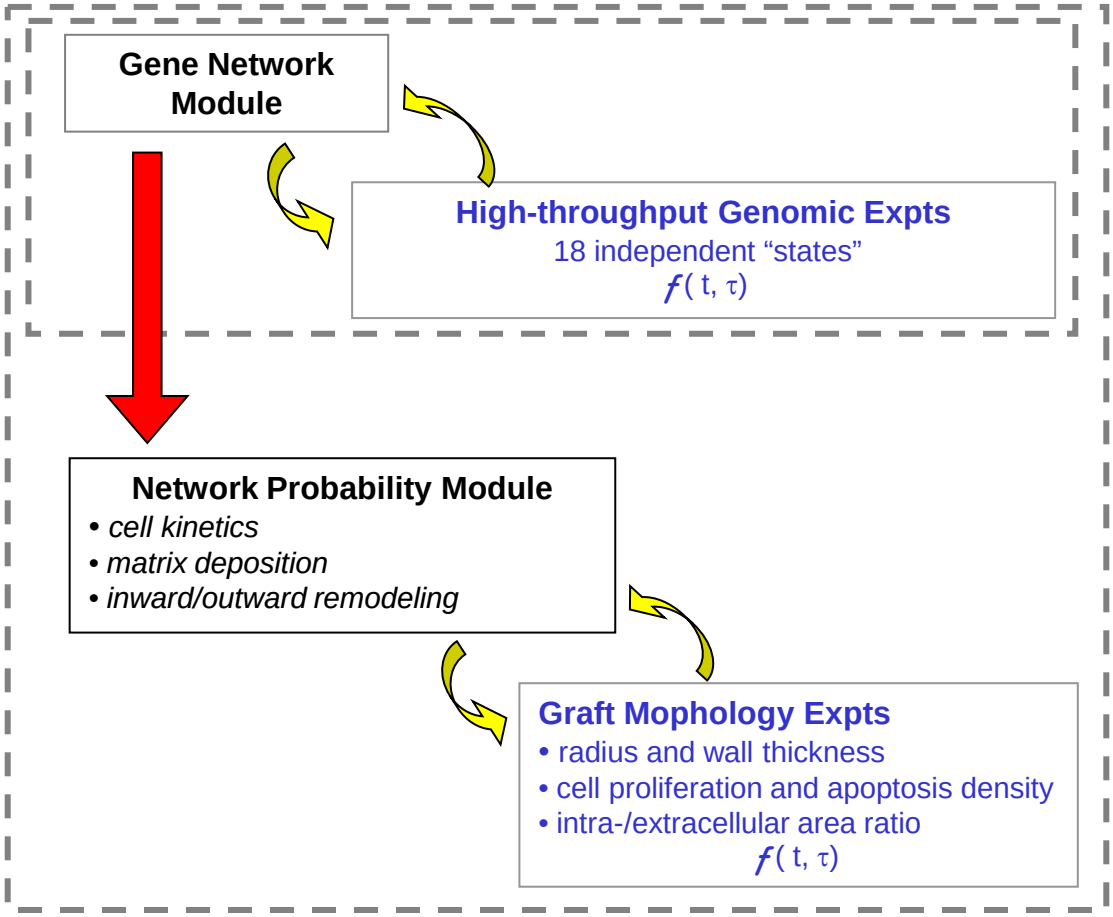


Problem: Network is known at only 12 discrete “states” (4 times, 3 shear conditions)

Solution: Bayesian Network

- probability model used to determine the mathematical relationship between gene elements

- functionally defines the network “state” at any given time or shear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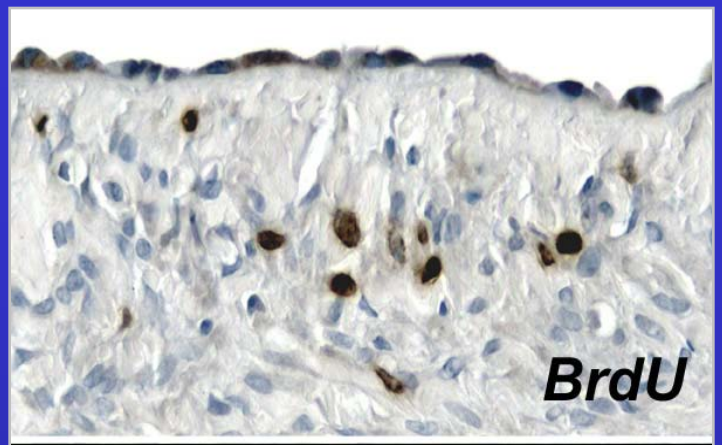
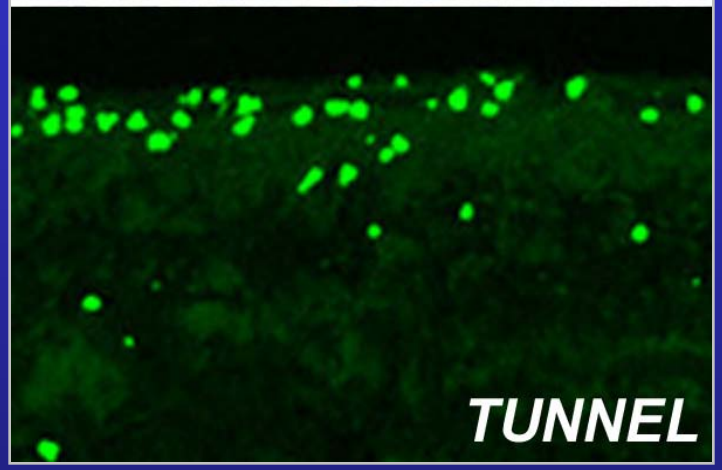
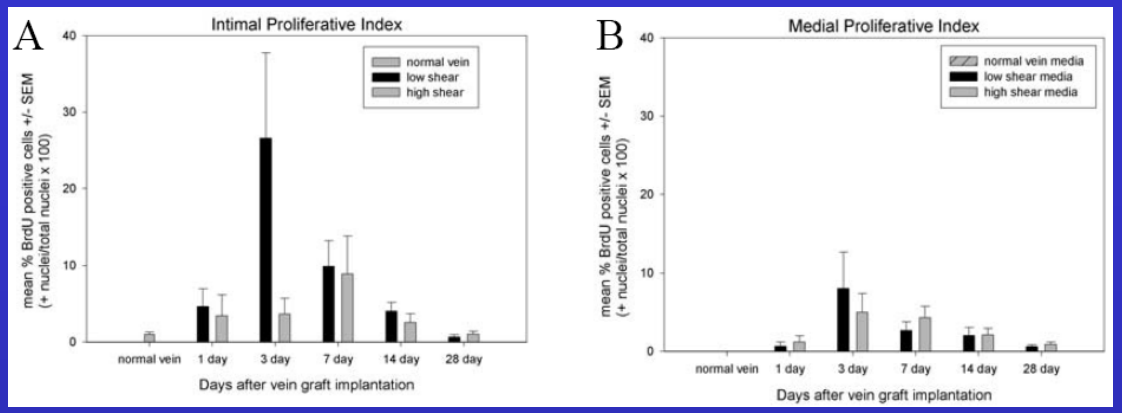
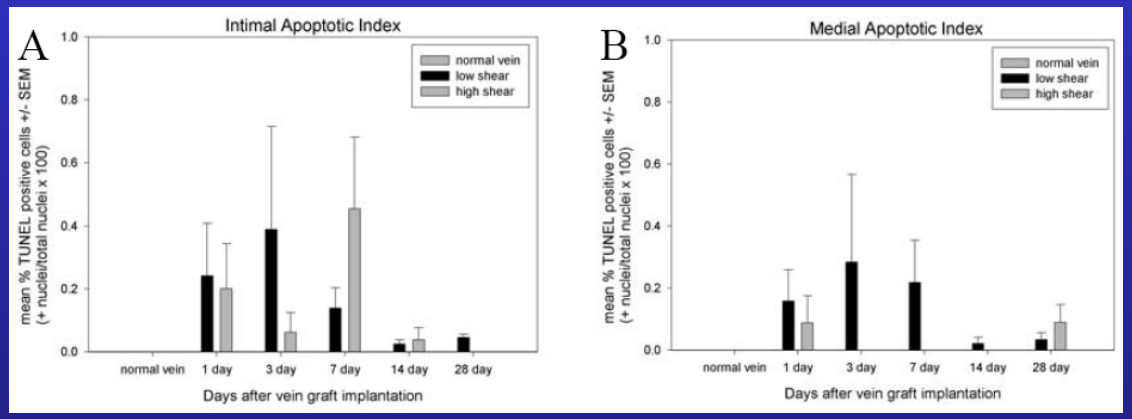


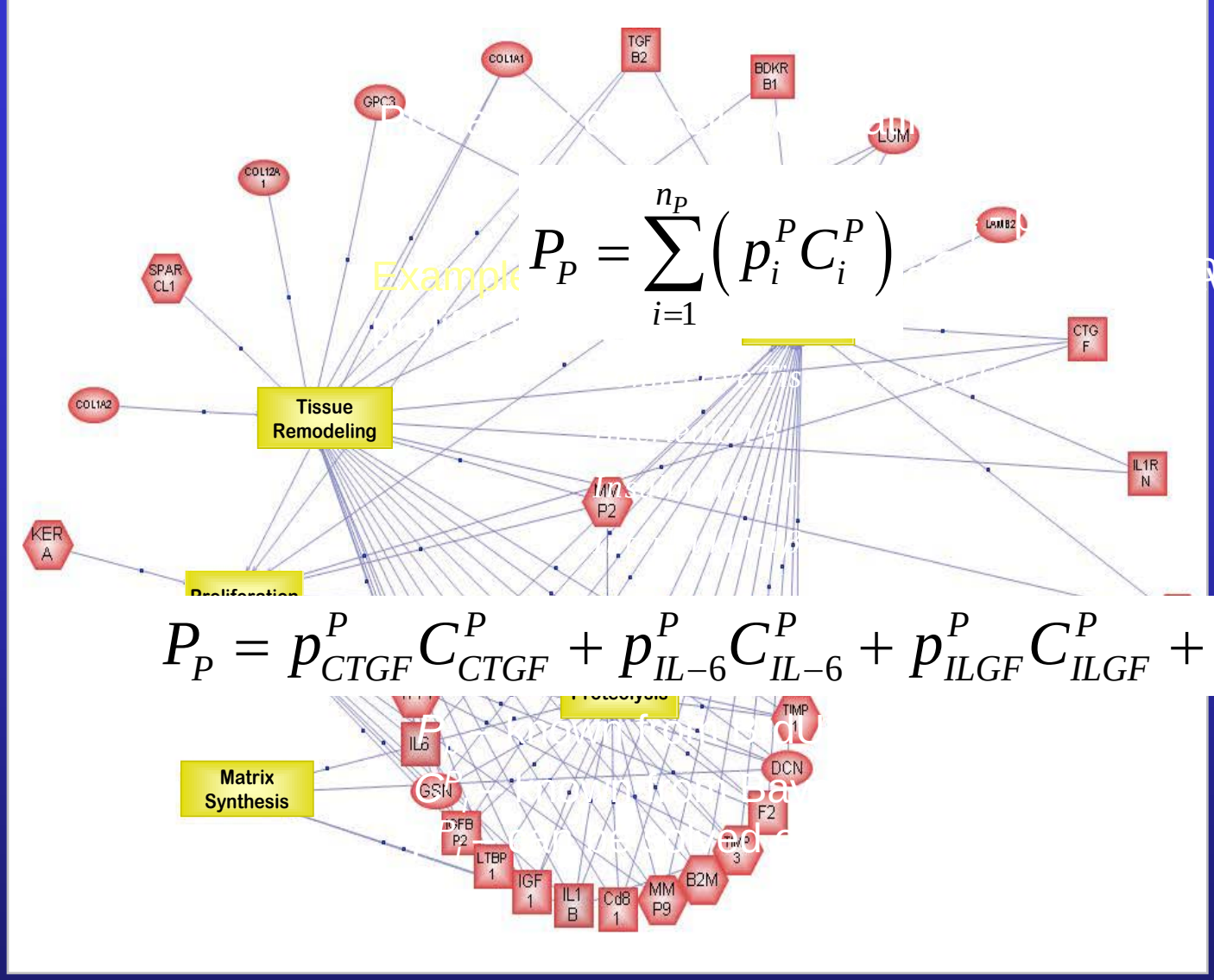






Task: Correlate cell kinetic, matrix synthesis/degradation and remodeling to the gene Bayesian network

Solution: Develop a series of linear probabilities that relate the relative concentration of a specific set of genes to a biologic process



Approach: Use a gene ontology analysis to define that set of genes that influence

- Cell replication
- Apoptosis
- Matrix degradation
- Matrix synthesis
- Local tissue remodeling

- Cell replication

$$P_P = \sum_{i=1}^{n_P} \left(p_i^P C_i^P \right)$$

- Apoptosis

$$P_A = \sum_{i=1}^{n_A} \left(p_i^A C_i^A \right)$$

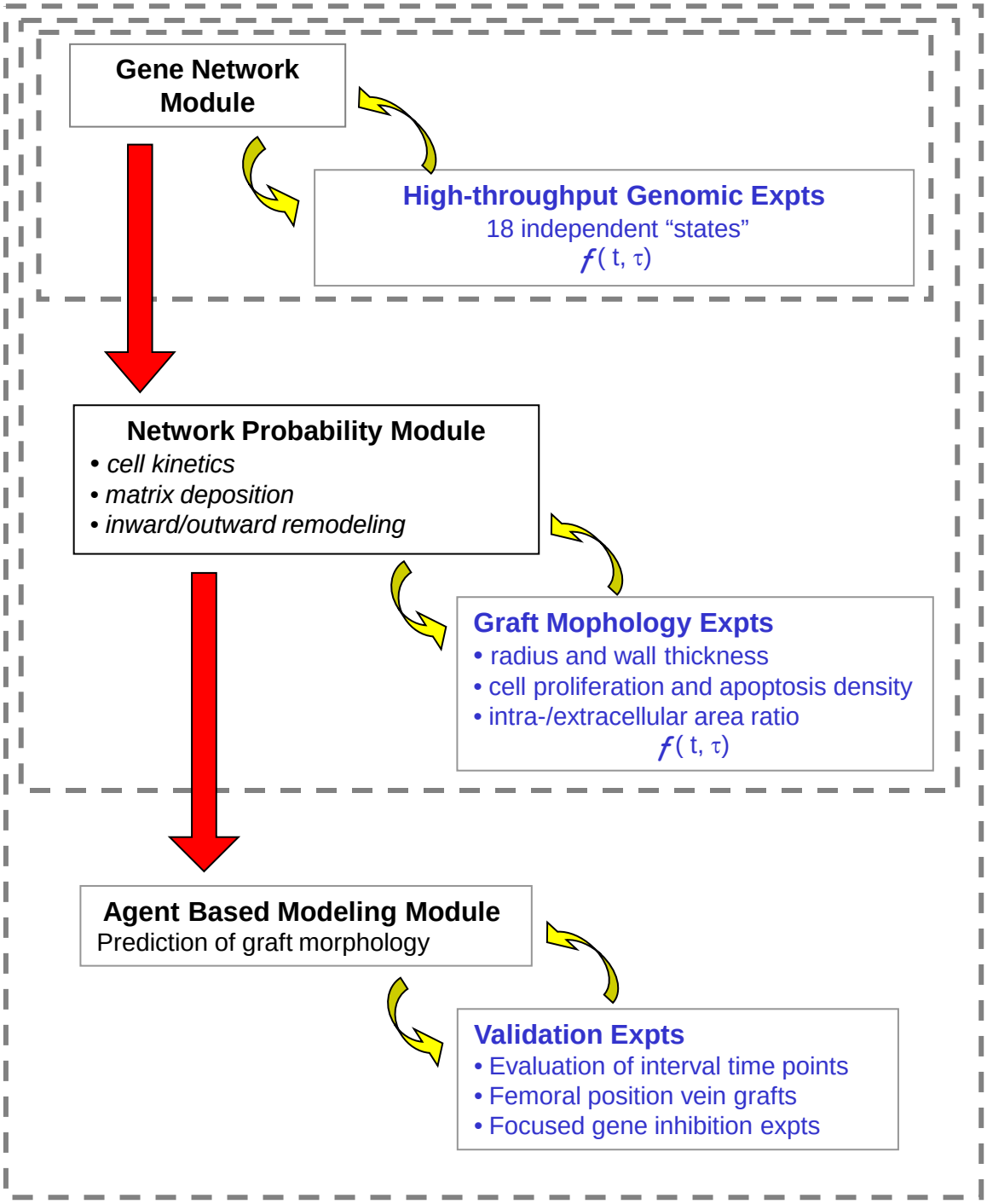
- Matrix degradation
- Matrix synthesis

$$P_M = \sum_{i=1}^{n_{MS}} \left(p_i^{MS} C_i^{MS} \right) - \sum_{i=1}^{n_{MD}} \left(p_i^{MD} C_i^{MD} \right)$$

- Local tissue remodeling

$$P_R = \sum_{i=1}^{n_R} \left(p_i^R C_i^R \right)$$

Task: Correlate cell kinetic, matrix synthesis/degradation and remodeling to the gene Bayesian network, providing a method to determine these parameters at any time or shear condition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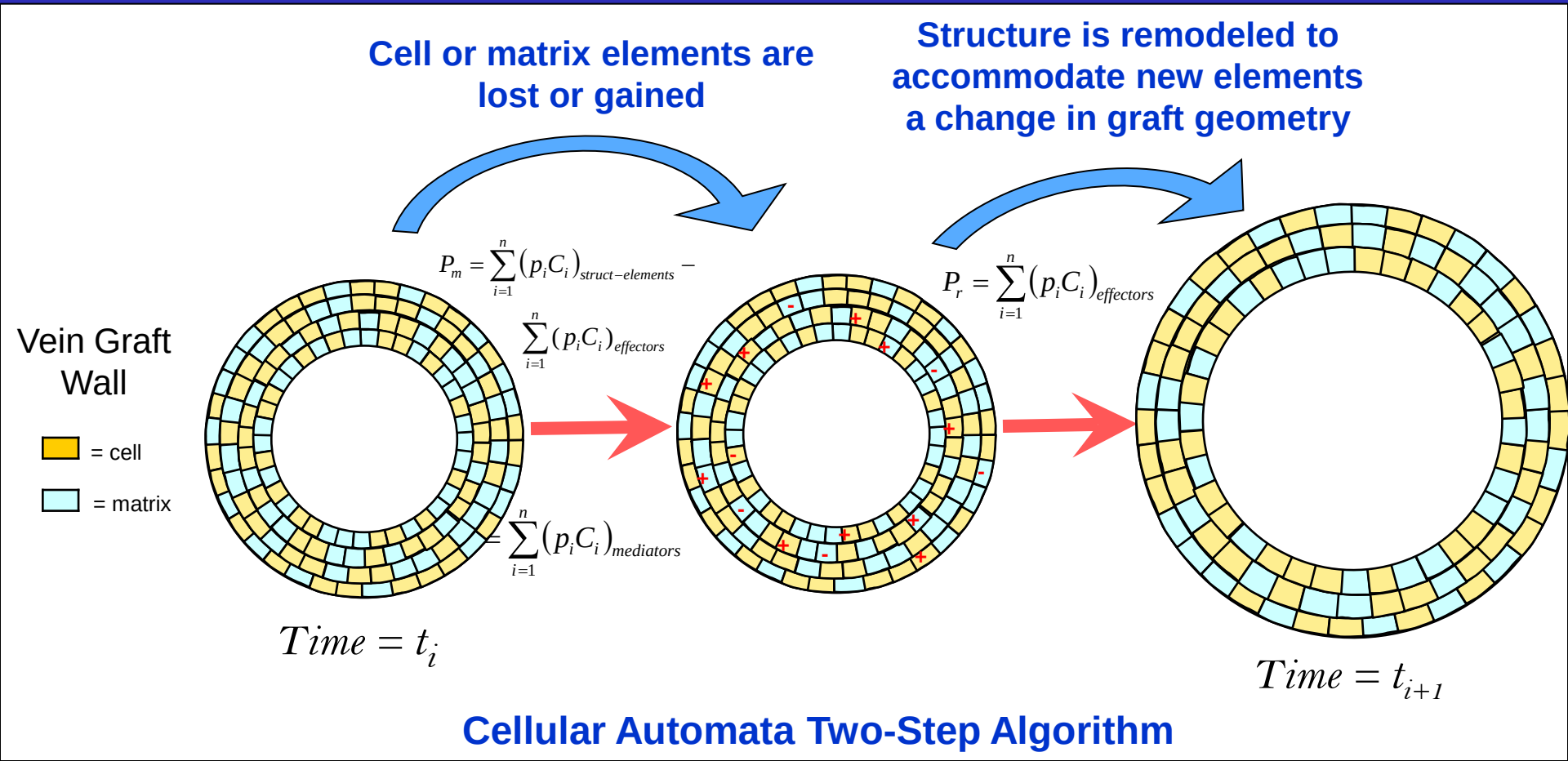
Problem: How do we integrate the cell kinetic, matrix accumulation, and remodeling information to predict vein graft morphology

Solution: Agent Based Modeling

- a computational model for simulating the actions and interactions of autonomous individuals in a network, with a view to assessing their effects on the system as a whole



Cellular Automata Two-Step Algorithm

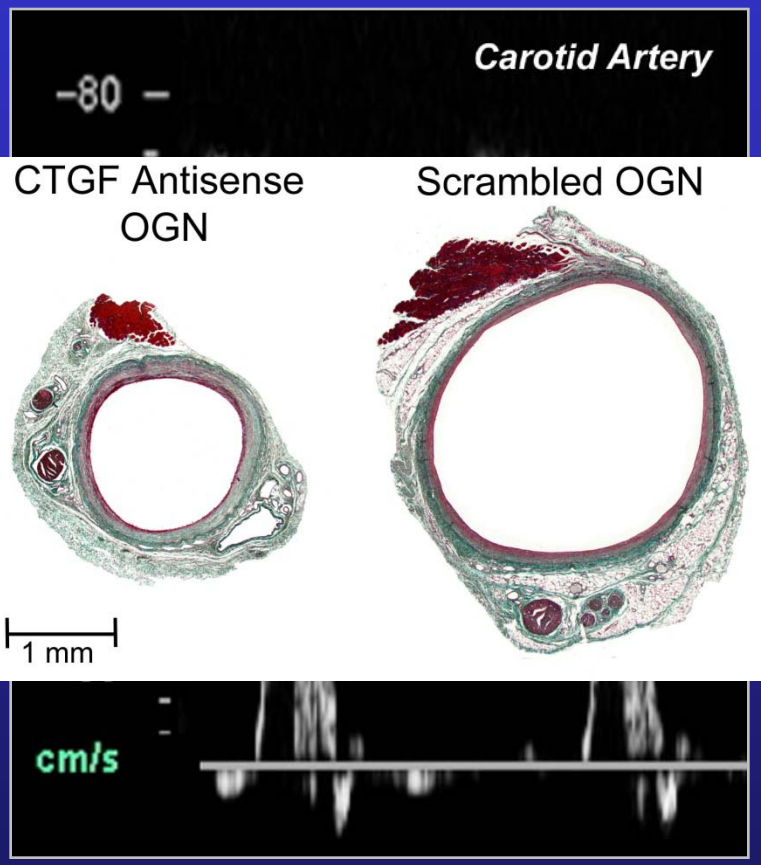
Model Validation and Refinement:

Testing performance against an independent dataset

- Phase I –
  Interval time points

- Phase II
  Evaluation of flow dynamics using femoral vein graft

- Phase III
  Bayesian network perturbation expts – CTGF inhibition



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