MULTISCALE MODELING OF VASCULAR ADAPTATION

LA VIE EST UN LONG FLEUVE TRANQUILLE

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PLAN

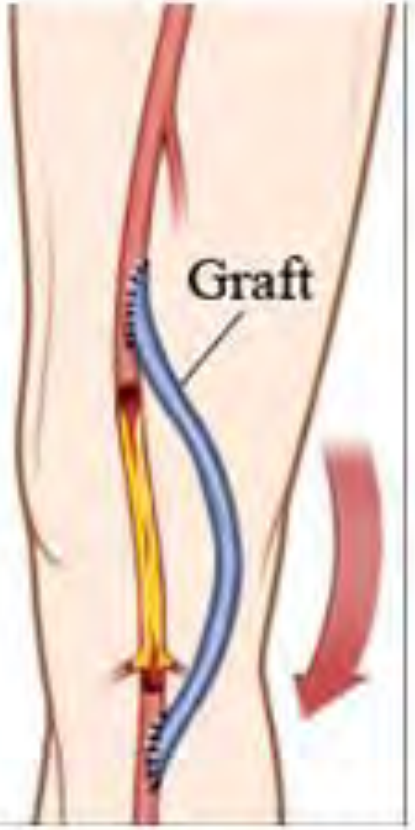
- Medical and Biology Background
- Dynamical System Approach
- Multiscale Computational Framework
- Toward control

Conflict of Interest: co-founder of ORintel specialized in smart operating room.

Angioplasty/Stent

1,133,000 coronary interventions

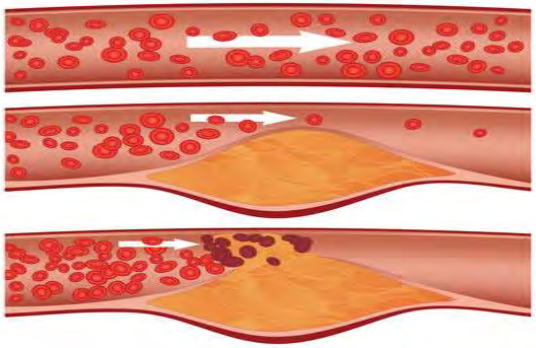
Vein Bypass Graft



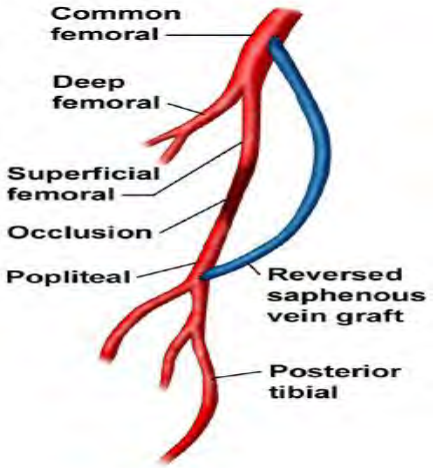
416,000 coronary and
150,000 peripheral
bypass grafts

OVERVIEW

Vascular disease (ex. arterial occlusion)



Surgical intervention
→ Vein graft bypass (femoral artery in the side picture just as example)



Intima HYPERPLASIA
migration of SMC in intima → proliferation → ECM deposition → Lumen narrowing

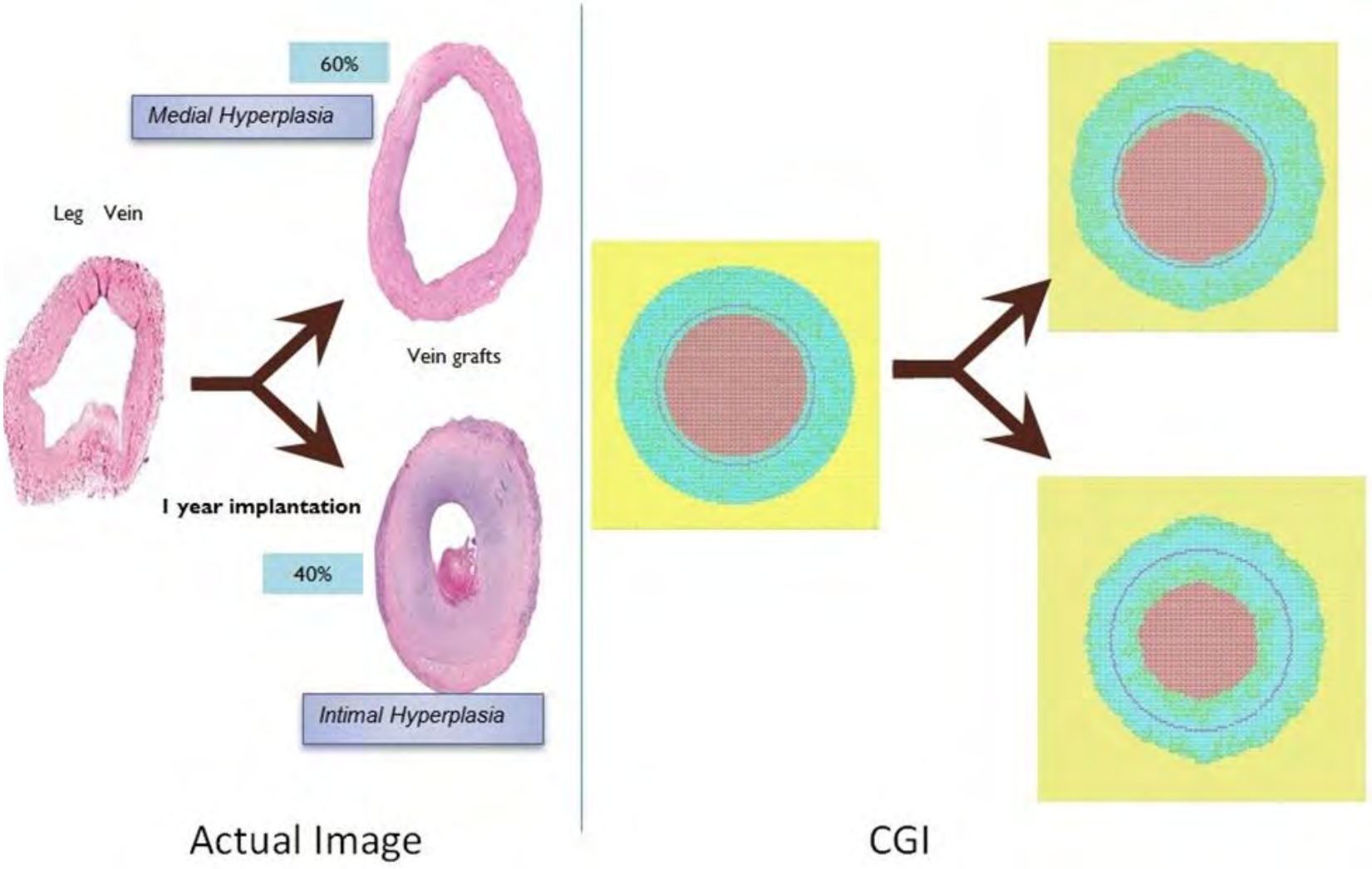
+

Wall REMODELING
cellular reorganization in media → preservation or loss of lumen

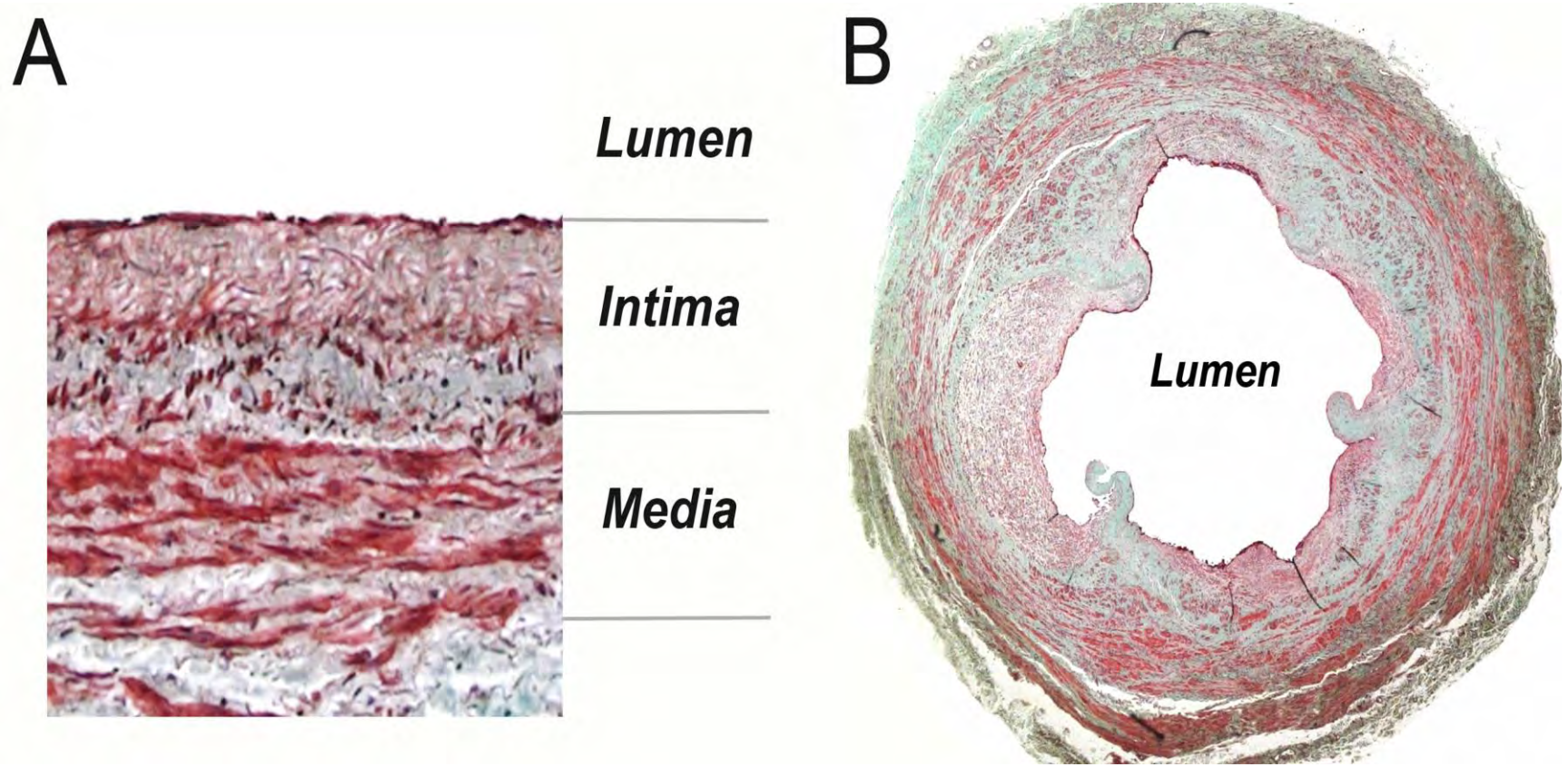
Vascular adaptation
→ due to change in flow regime (from continuous low pressure to pulsatile high pressure), vein graft faces 2 main adaptation process

Interplay between Hyperlasia and Remodeling may leads to total lumen narrowing after implant or transcient outward growth.

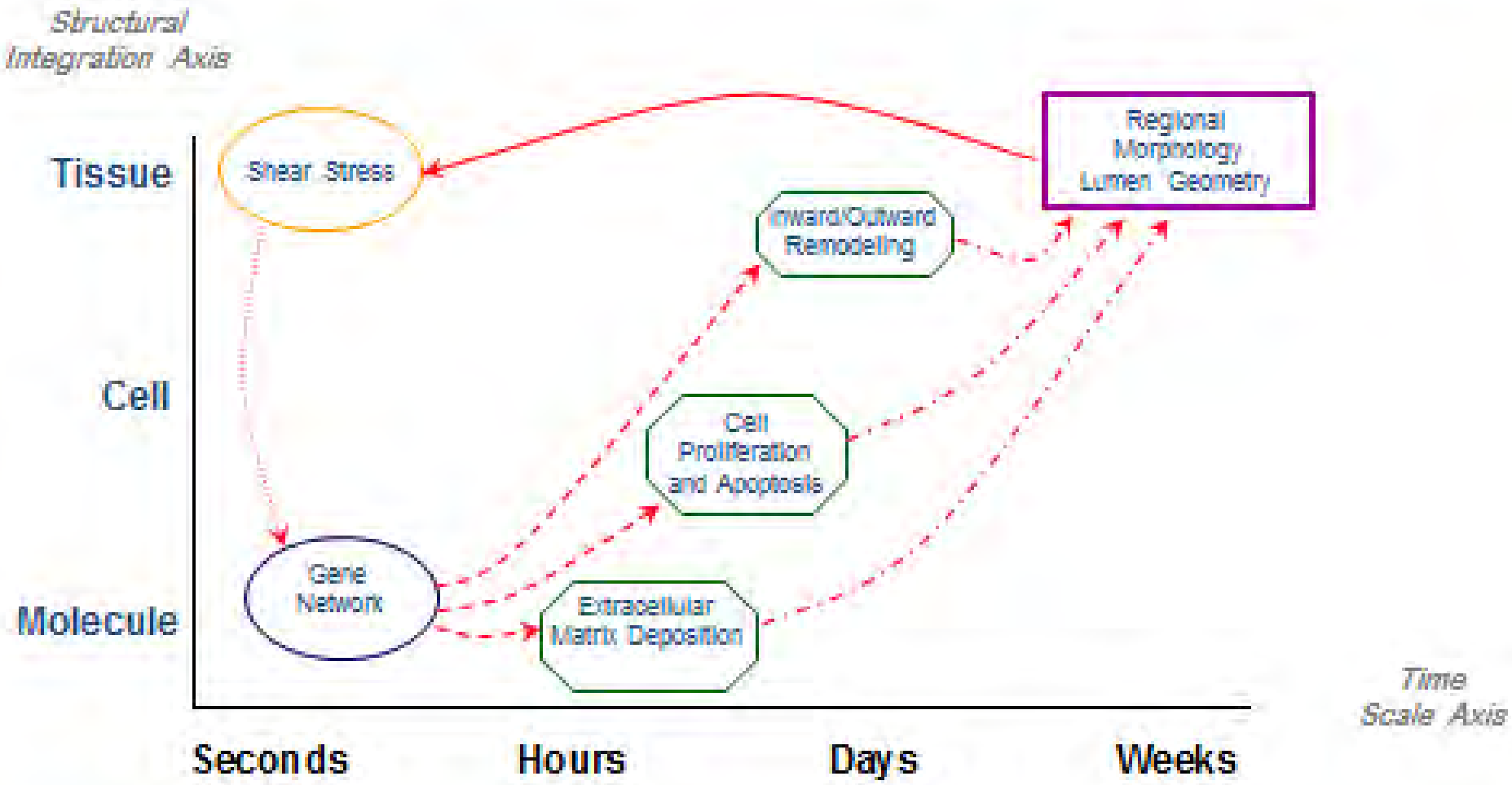
PATTERN FORMATION (ACTUAL IMAGE VS COMPUTER GENERATED IMAGE)



HISTOMORPHOLOGY OF A VEIN GRAFT AT IMPLANTATION (A) AND AT SIX MONTHS POST-IMPLANTATION (B)

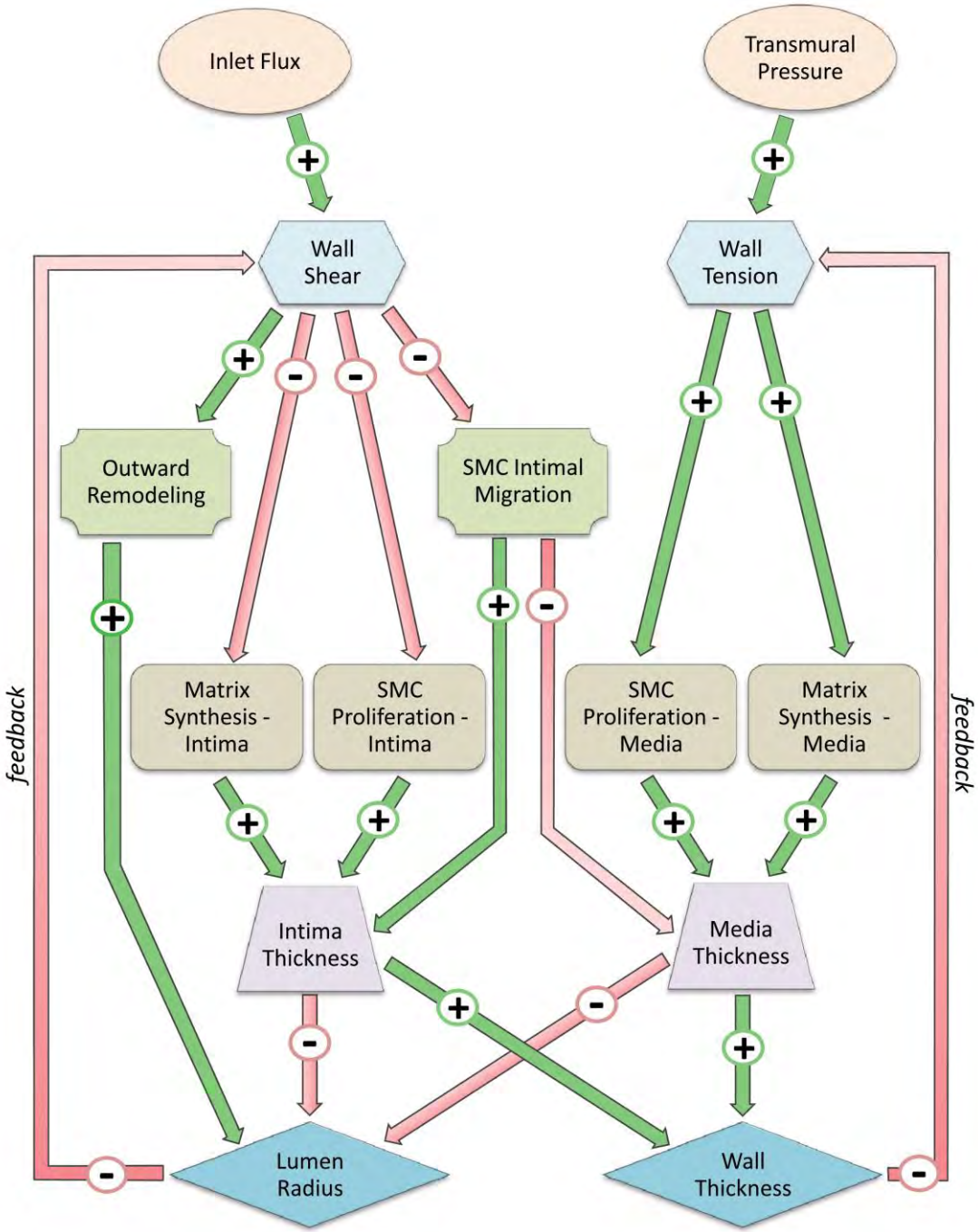


Events in Vascular Remodeling



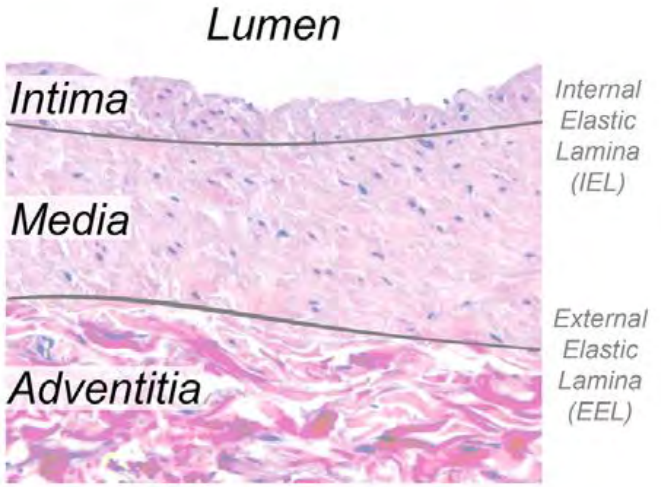
BIOLOGIC PROCESSES IN VEIN GRAFT ADAPTATION

	Day 1		Day 2 to 7		Week 2 to 4		Month 2 to 3		Long-term	
	Reduced Shear	Elevated Shear	Reduced Shear	Elevated Shear	Reduced Shear	Elevated Shear	Reduced Shear	Elevated Shear	Reduced Shear	Elevated Shear
Intimal Thickness	0	0	0	0	2	1	4	2	5	3
Medial Thickness	0	0	0	0	2	2	4	4	5	5
Outside Radius	0	0	0	0	1	2	3	4	4	5
Smooth Muscle Cell Proliferation	-4	-4	5	3	3	2	1	1	1	1
Matrix Content - Collagen	0	0	0	0	3	2	5	3	2	1
Matrix Content - Proteoglycan	0	0	`	3	2	1	1	0	0	0
Macrophage Content	0	0	5	3	3	2	1	0	0	0


Inlet Flux
Transmural Pressure
Wall Shear
Wall Tension
Outward Remodeling
SMC Intimal Migration
Matrix Synthesis - Intima
SMC Proliferation - Intima
SMC Proliferation - Media
Matrix Synthesis - Media
Intima Thickness
Media Thickness
Lumen Radius
Wall Thickness
feedback
feedback

DYNAMICAL SYSTEM

Assuming a linear dependence for each parameter on the driving mechanical quantities σ and τ, we can study the *intimal area variation*:



$$\dot{A}^{I}_{SMC} = -a_1 Dt \cdot A^{I}_{SMC} - a_5 Dt \cdot 2pR_{IEL} \frac{A^{M}_{SMC}}{A^{M}_{SMC} + A^{M}_{ECM}} \quad (1)$$

Intimal area variation due to migration/proliferation of SMC

Proliferation of SMC in intima = average between mitosis and apoptosis activity

Migration of SMC(smooth cells) from media to intima through the internal elastic lamina

$$\dot{A}^{I}_{ECM} = -a_2 Dt\, A^{I}_{SMC} \quad \text{if } A_{ECM} > 0 \text{ , 0 otherwise} \quad (2)$$

Intimal area variation due to ECM deposition by SMC in intima

Unknowns and Parameters

- $A_{SMC}^{I} + A_{ECM}^{I}$ = area of the intima
- $A_{SMC}^{M} + A_{ECM}^{M}$ = area of the media
- R_{IEL} = Internal Elastic Lamina radius
- α_i = coefficients of intimal dynamic

DYNAMICAL SYSTEM

Transmigration of monocytes and conversion to macrophages = critical force in vein graft adaptation. This time dependent component is modeled using an activity factor A(t), such as…

$$A(t) = \exp\left(-\left(\frac{t - T_i}{dT_i}\right)^2\right) \quad (3)$$

with $T_i = \alpha_8 > 0$, when macrophages' density reach maximum value
and $\delta T_i = \alpha_9 > 0$, time scale of decay of macrophage's density

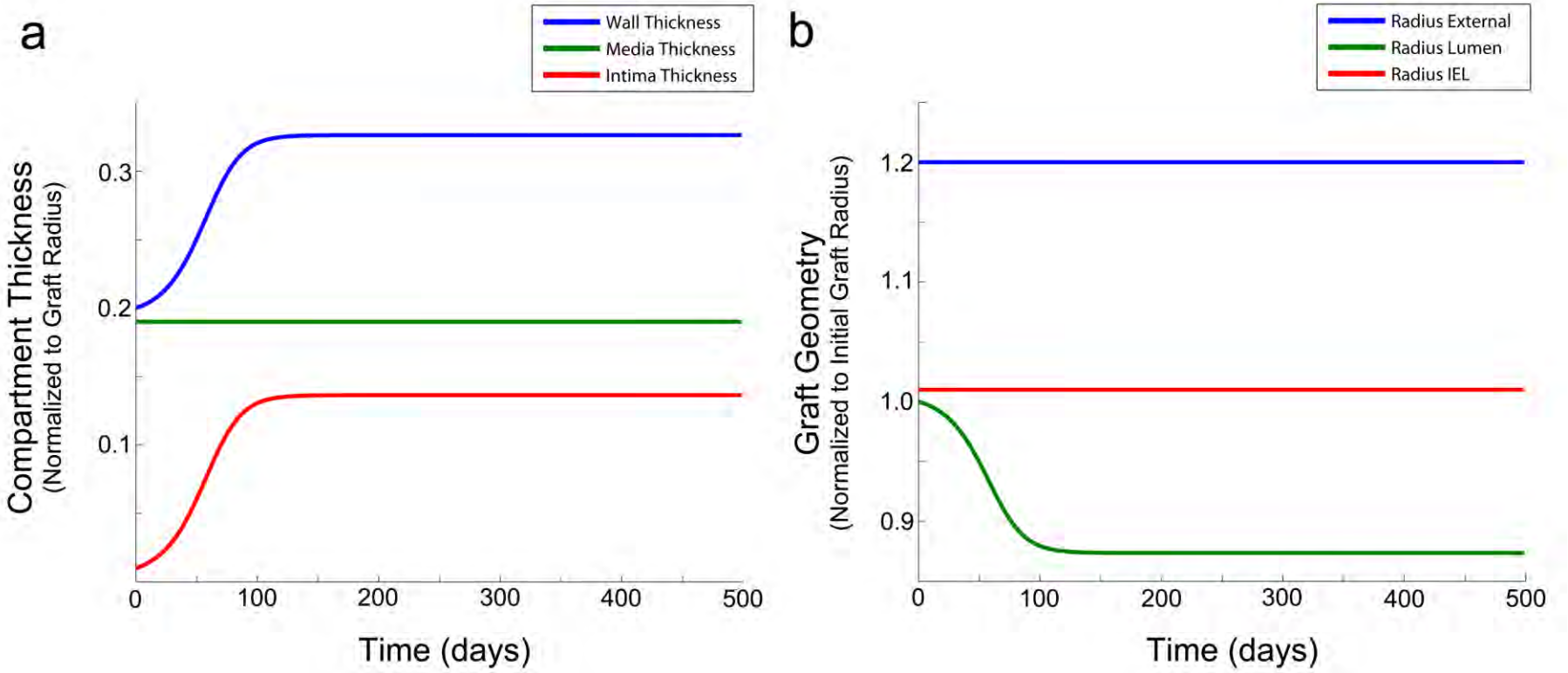
Just for insertion of (3) in dynamical system referred to the intima. equations (1) and (2), the following are reached:

$$\dot{A}^I_{SMC} = A(t)\left[-a_1 \Delta t \cdot A^I_{SMC} - a_5 \Delta t \cdot 2\pi R_{IEL} \frac{A^M_{SMC}}{A^M_{SMC} + A^M_{ECM}}\right] \quad (4)$$

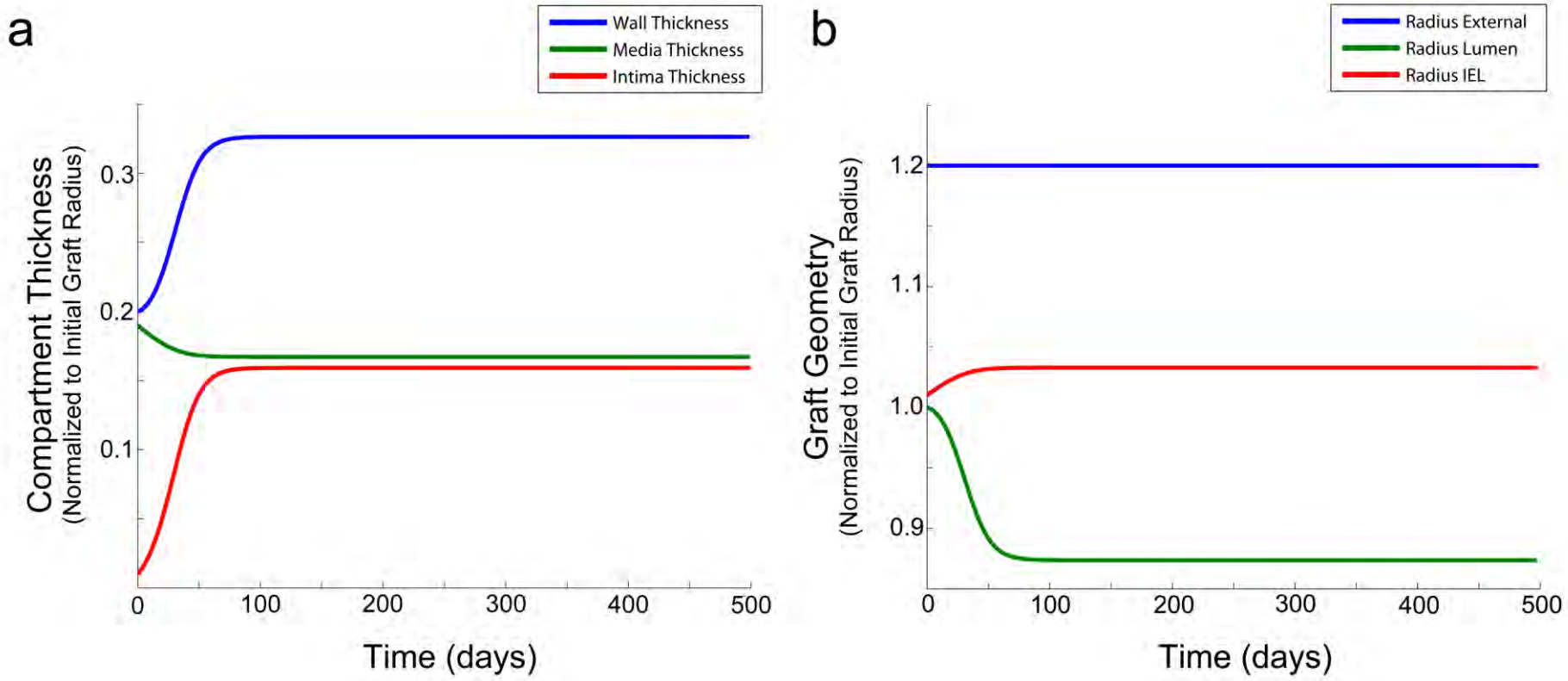
$$\dot{A}^I_{ECM} = A(t)\left[-a_2 \Delta t \cdot A^I_{SMC}\right] \text{ if } A_{ECM} > 0 \text{ , 0 otherwise} \quad (5)$$

Dynamical system has now to be coupled with expression density of probability of specific genes related to cellular activities of strongly interesting for the vein graft remodeling.

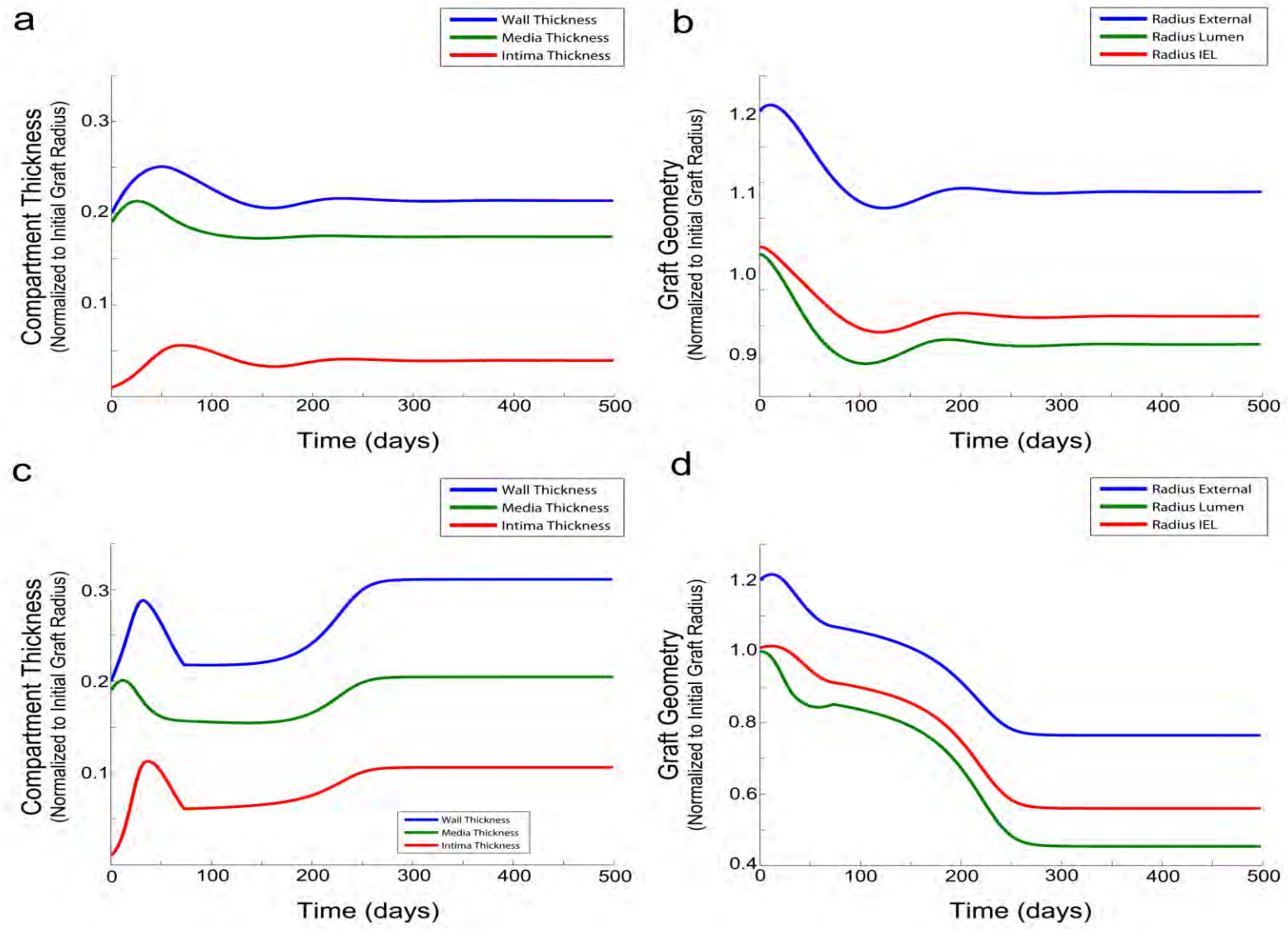
INFLUENCE OF SHEAR ON THE GRAFT GEOMETRY, WITH INCLUSION OF AN ACTIVE LUMEN AREA - SHEAR FEEDBACK LOOP AND EXCLUDING THE EFFECT OF WALL TENSION. COMPARTMENT/ LAYER THICKNESS (A) AND GRAFT RADIUS (B).



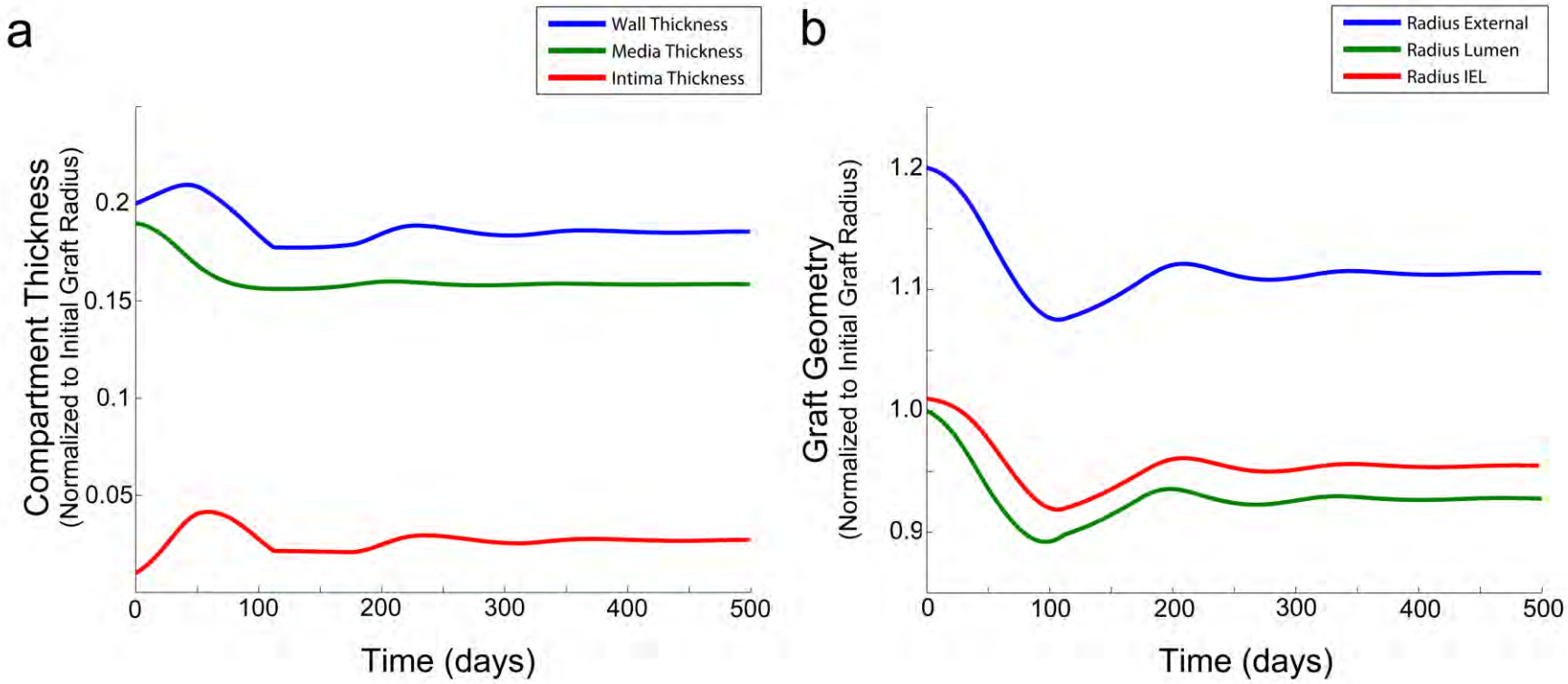
INFLUENCE OF SHEAR ON GRAFT GEOMETRY, WITH AN ACTIVE LUMEN AREA - SHEAR FEEDBACK LOOP AND THE INCLUSION OF SMOOTH MUSCLE CELL MIGRATION FROM THE MEDIA TO INTIMA. COMPARTMENT/ LAYER THICKNESS (A) AND GRAFT RADIUS (B).



INFLUENCE OF NONLINEAR COUPLING BETWEEN OUTWARD REMODELING AND WALL THICKENING ON GRAFT GEOMETRY.

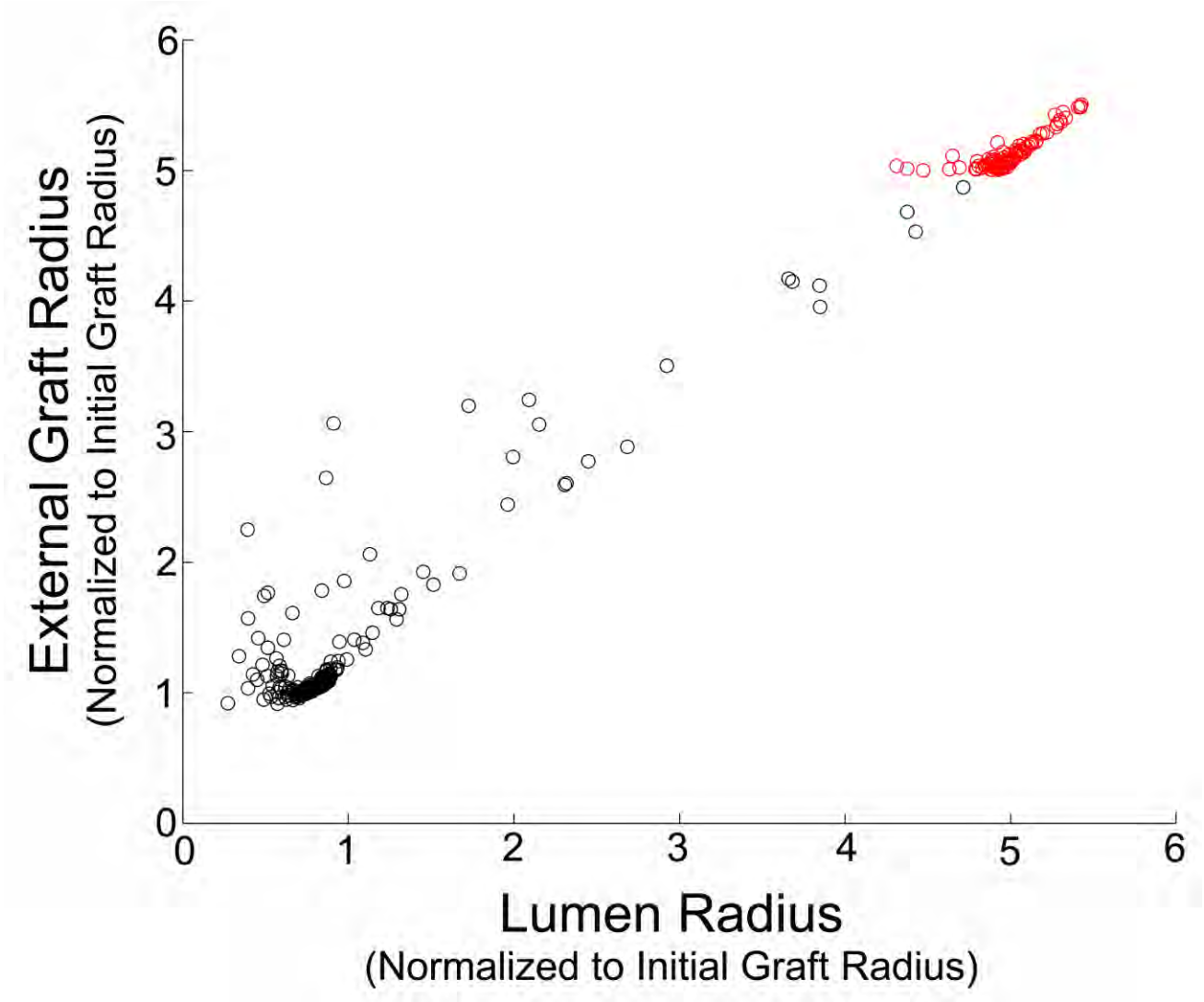


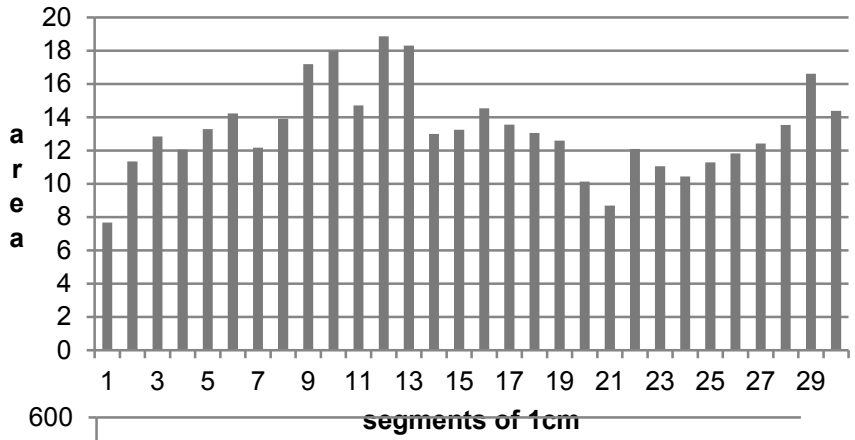
SIMULATION RESULT OBTAINED WITH A 20 PER CENT REDUCTION IN FLUX, WHILE THE OBJECTIVE FOR SHEAR STRESS AND TENSION ARE SET TO THE INITIAL STAGE. COMPARTMENT/ LAYER THICKNESS (A) AND GRAFT RADIUS (B).

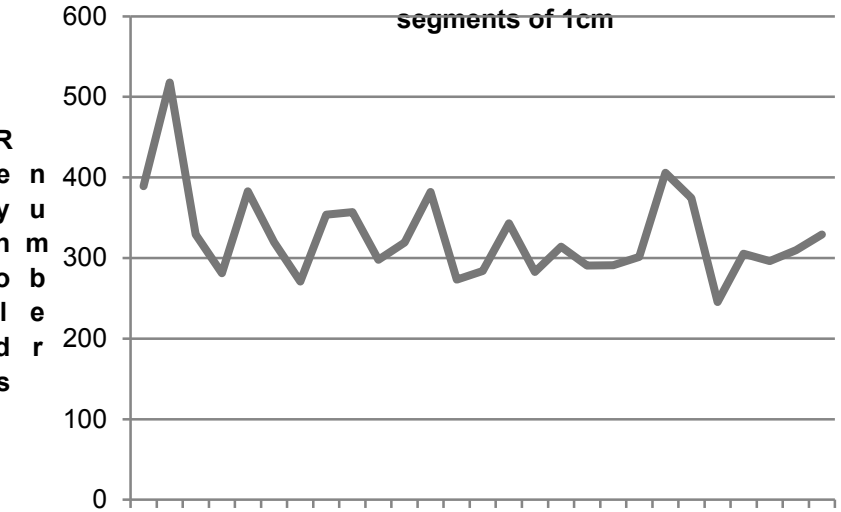


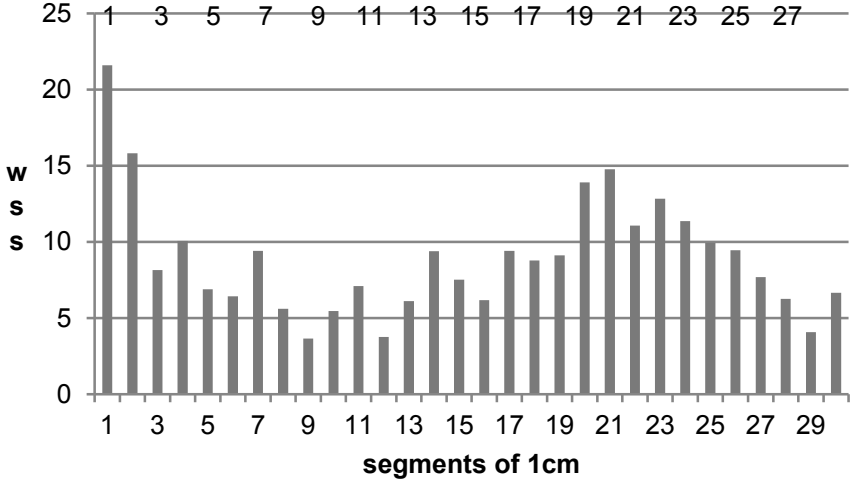
PARAMETER SPACE EXPLORATION OF THE DYNAMICAL SYSTEM USING A MONTECARLO SIMULATION

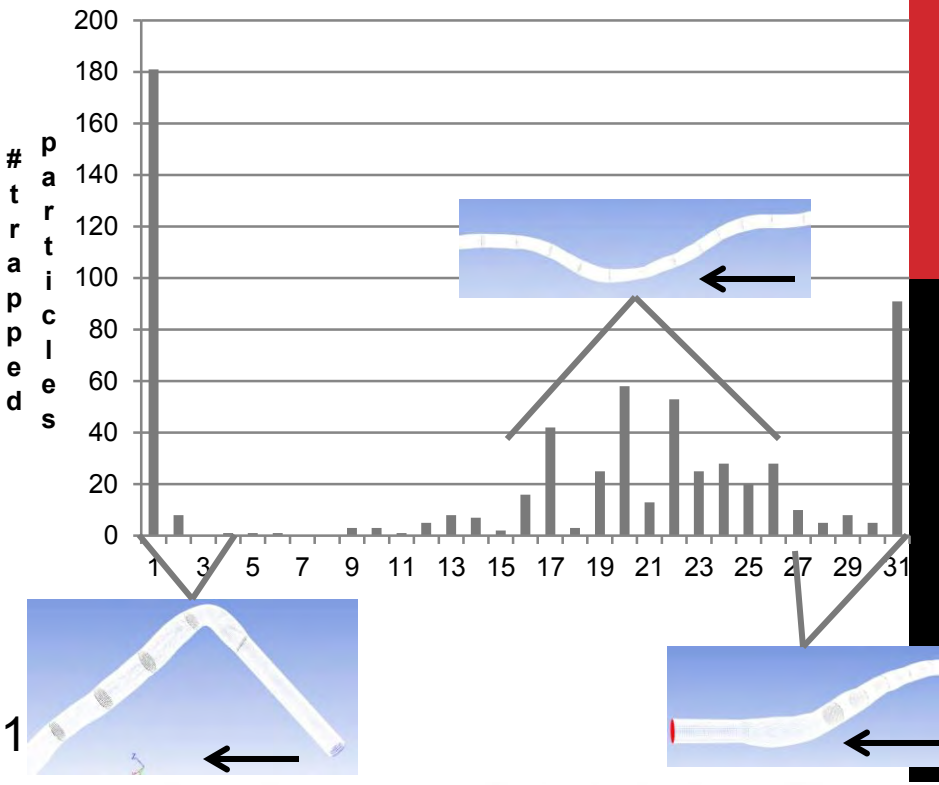
EXTERNAL RADIUS VERSUS LUMEN RADIUS . RED SYMBOLS DEMONSTRATE THOSE SIMULATIONS WHERE A GREATER THAN 5-FOLD INCREASE IN THE EXTERNAL RADIUS WAS PREDICTED.

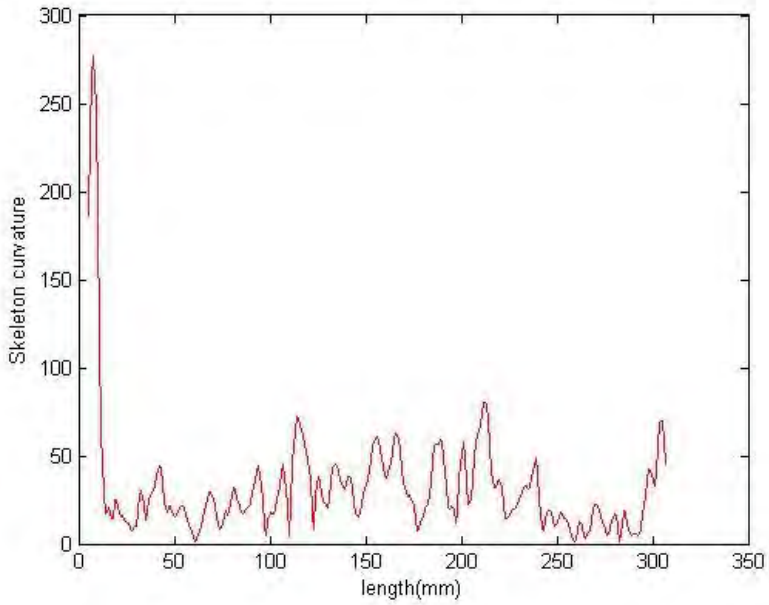



area
segments of 1cm

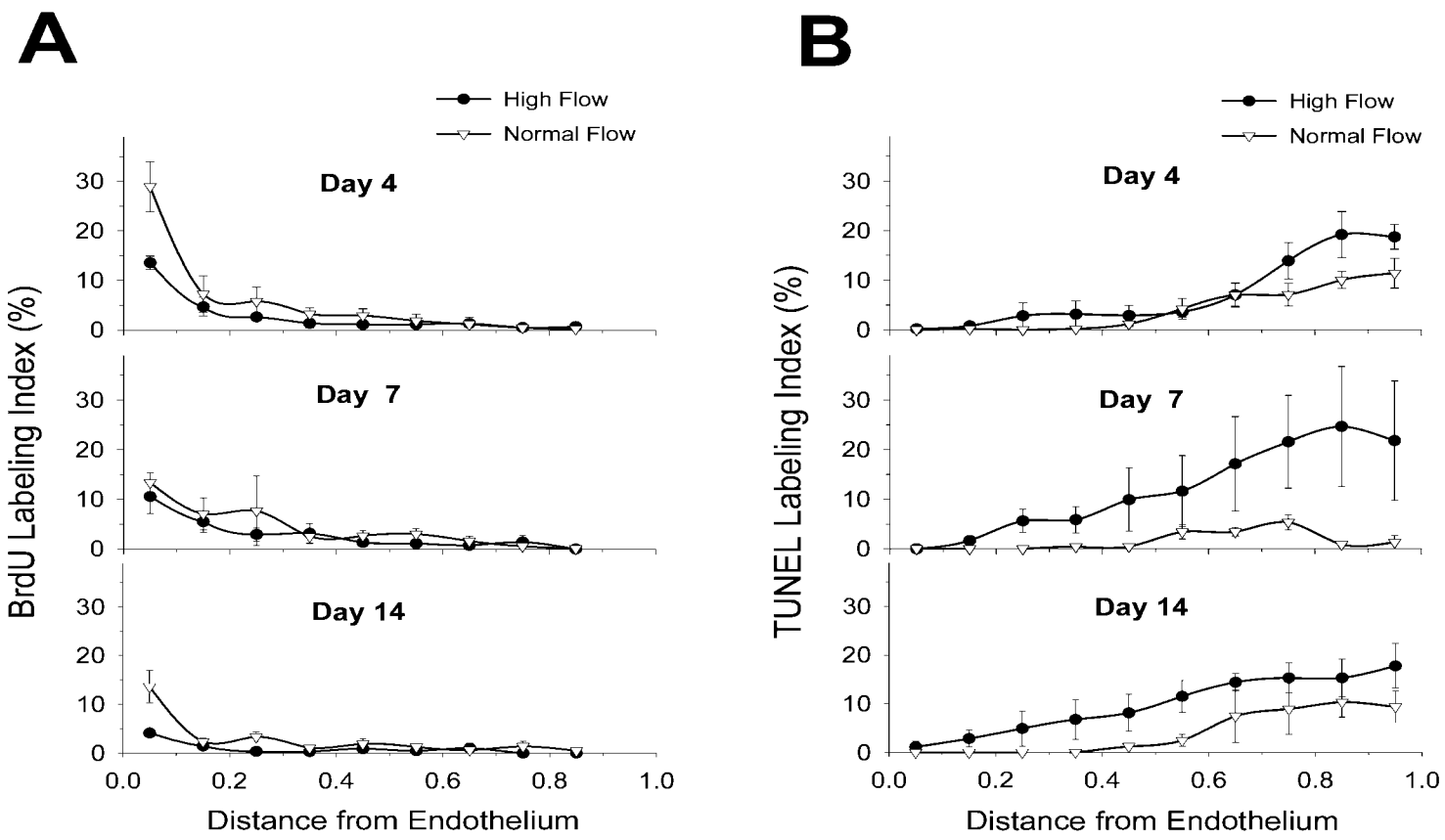

Reynolds number


wss
segments of 1cm

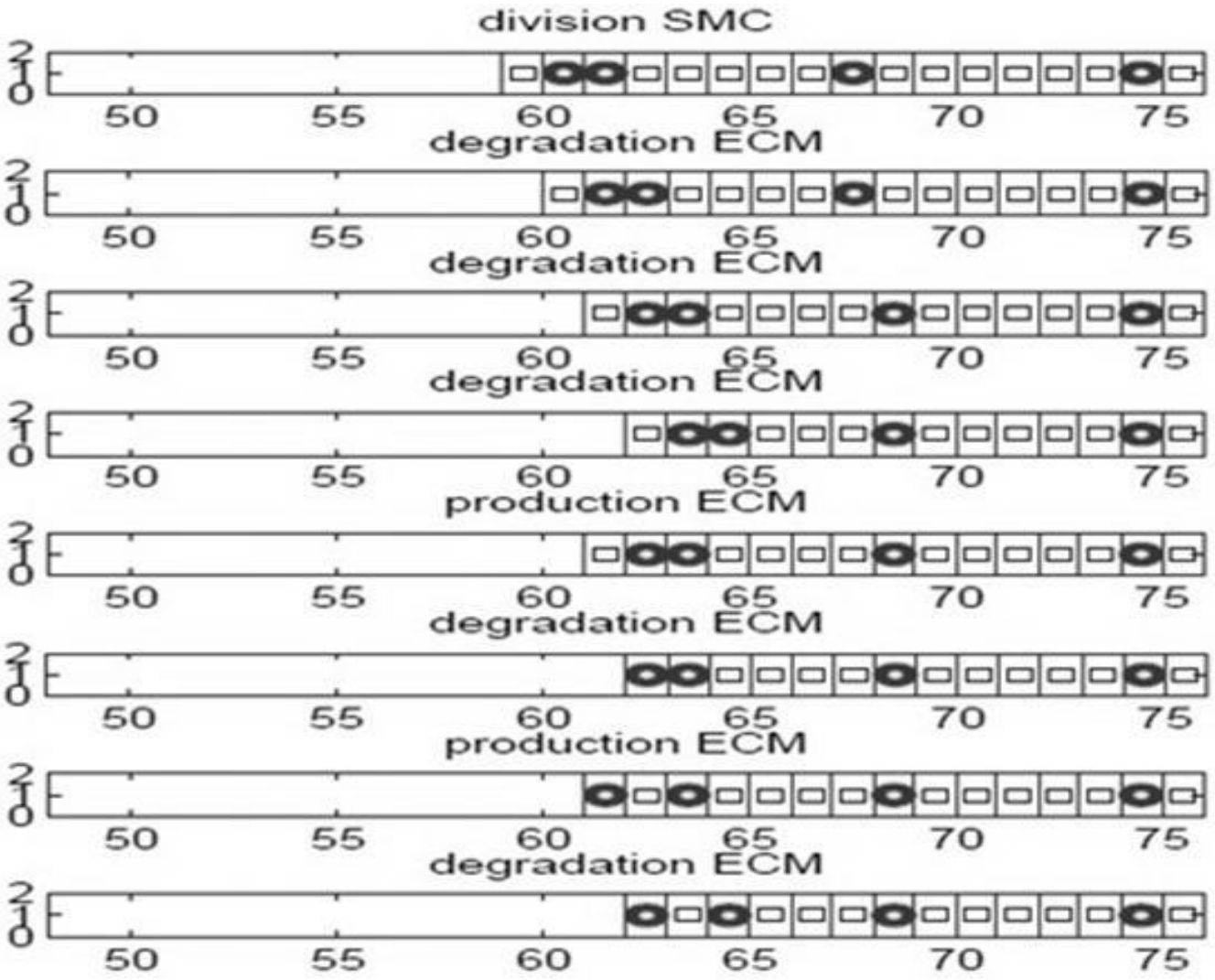

trapped particles
Pn31

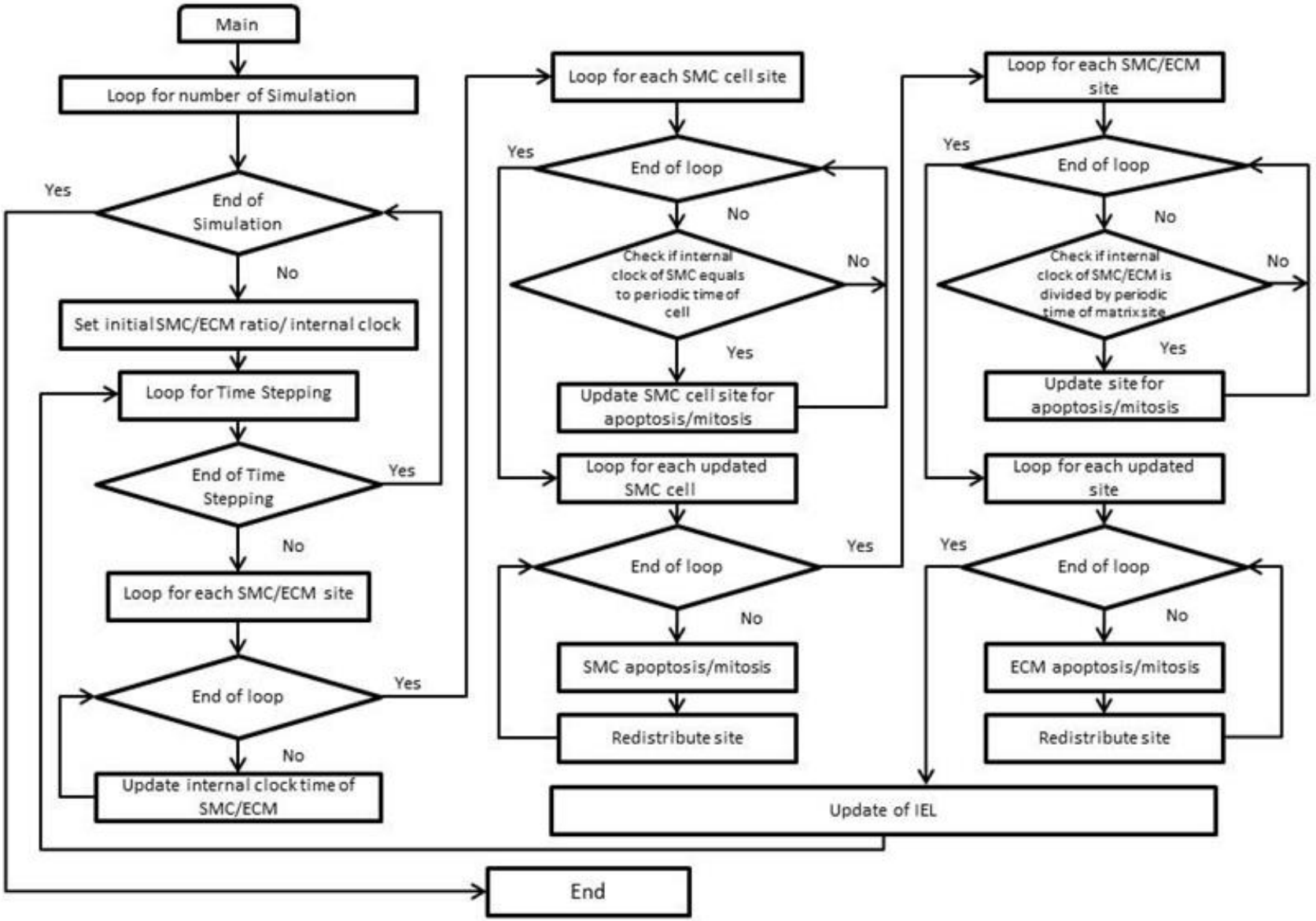

Skeleton curvature
length(mm)

SPATIAL DISTRIBUTION OF CELL PROLIFERATION AND APOPTOSIS IN RABBIT VEIN GRAFTS HARVEST AT 4, 7, AND 14 FOLLOWING EXPSOURE REDUCED OR ELEVATED SURFACE SHEARING FORCES

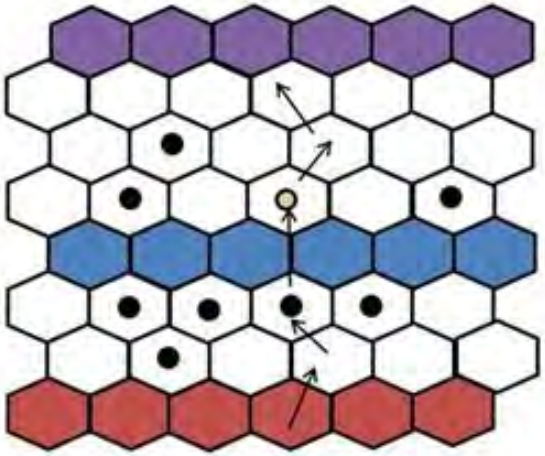


ONE DIMENSIONAL AGENT BASE MODEL

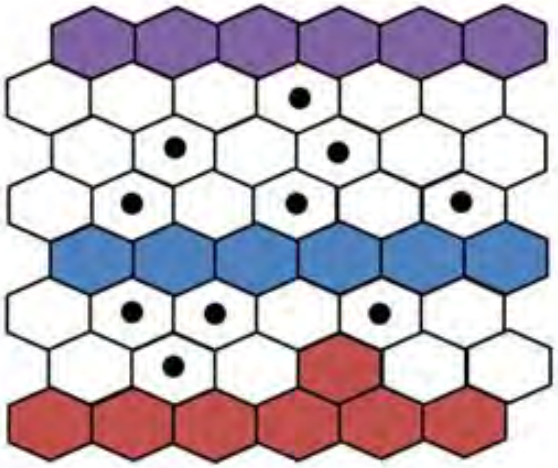



Main
Loop for number of Simulation
End of Simulation
Yes
No
Set initial SMC/ECM ratio/ internal clock
Loop for Time Stepping
End of Time Stepping
Yes
No
Loop for each SMC/ECM site
End of loop
Yes
No
Update internal clock time of SMC/ECM
Loop for each SMC cell site
End of loop
Yes
No
Check if internal clock of SMC equals to periodic time of cell
No
Yes
Update SMC cell site for apoptosis/mitosis
Loop for each updated SMC cell
End of loop
Yes
No
SMC apoptosis/mitosis
Redistribute site
Loop for each SMC/ECM site
End of loop
Yes
No
Check if internal clock of SMC/ECM is divided by periodic time of matrix site
No
Yes
Update site for apoptosis/mitosis
Loop for each updated site
End of loop
Yes
No
ECM apoptosis/mitosis
Redistribute site
Update of IEL
End

1

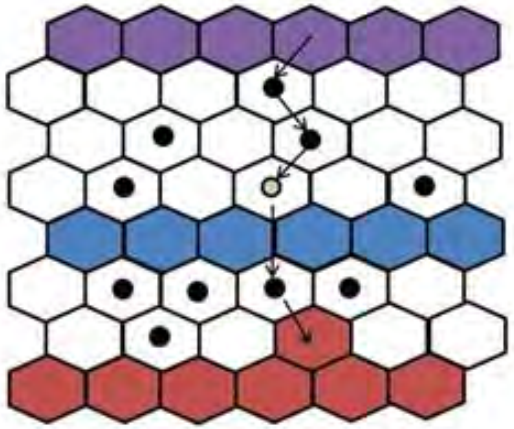


2

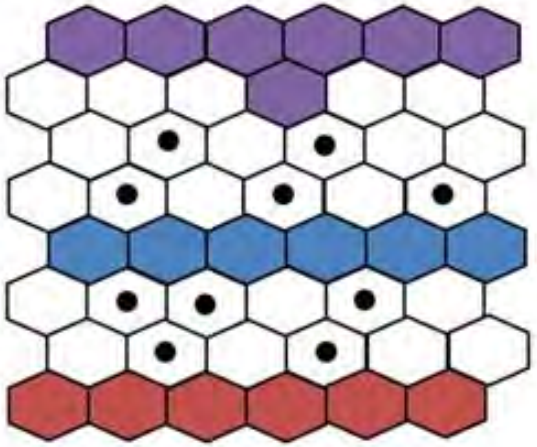


1. Hexagonal sites shifting path before cell/matrix mitosis.
2. Hexagonal sites after cell/matrix mitosis.

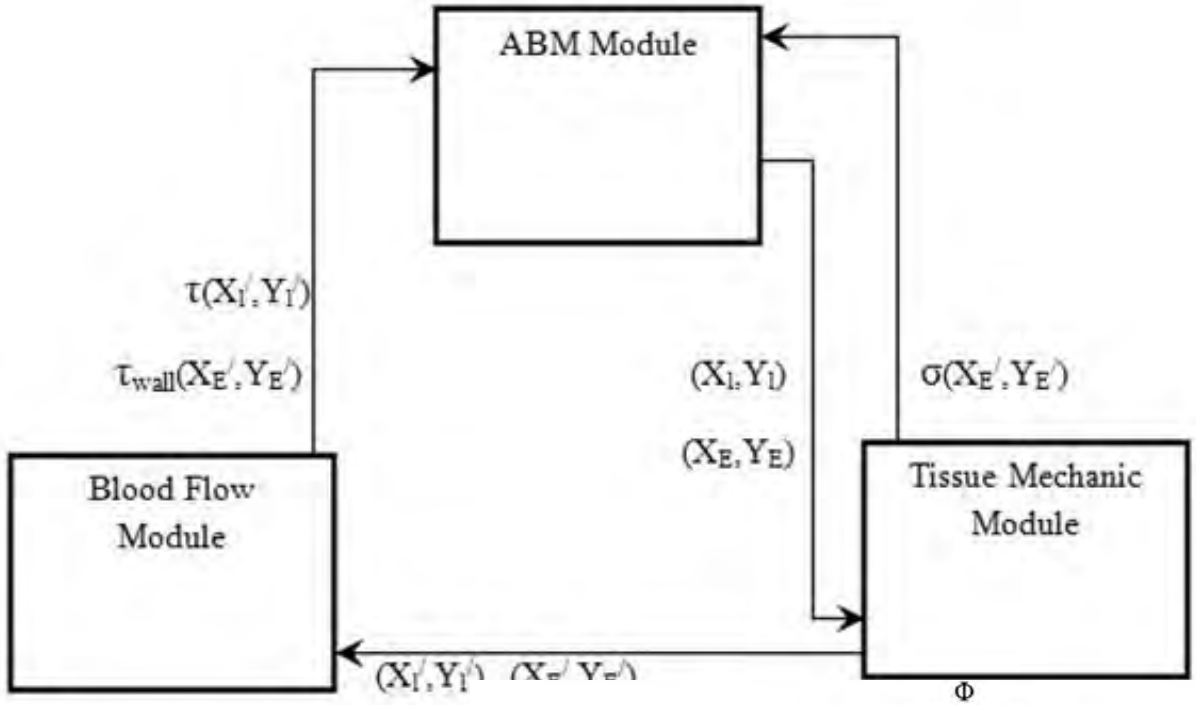
3

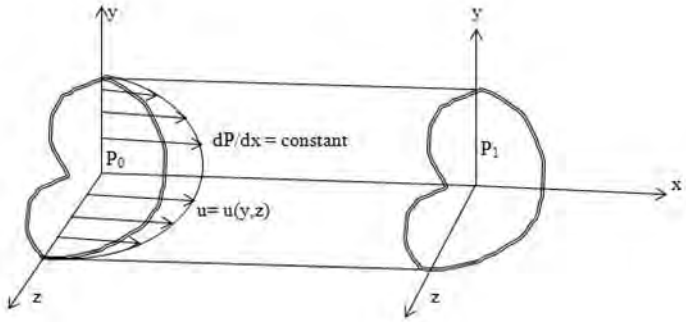


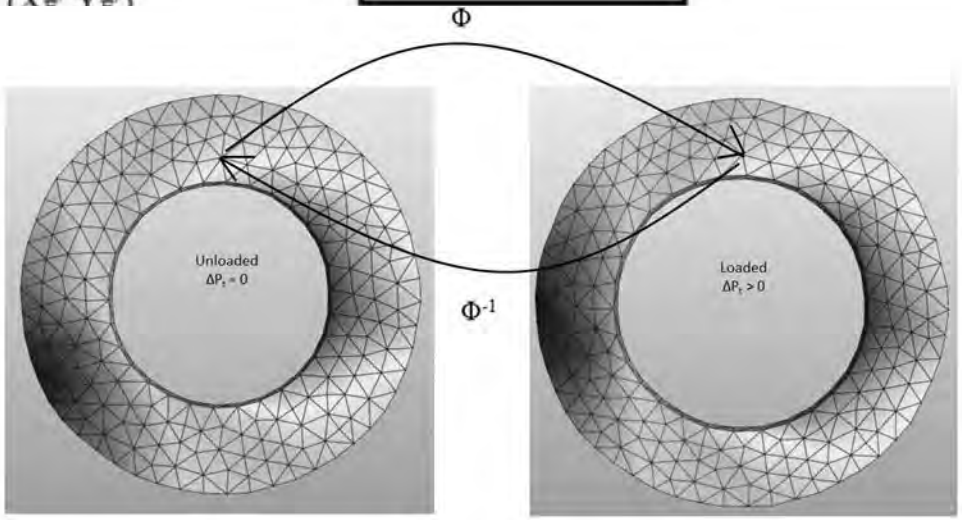
4



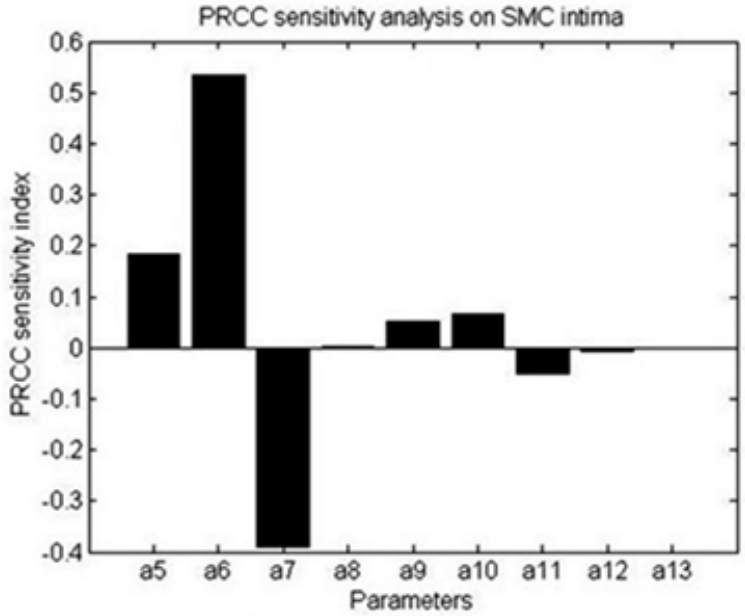
3. Hexagonal sites shifting path before cell/matrix apoptosis.
4. Hexagonal sites after cell/matrix apoptosis.

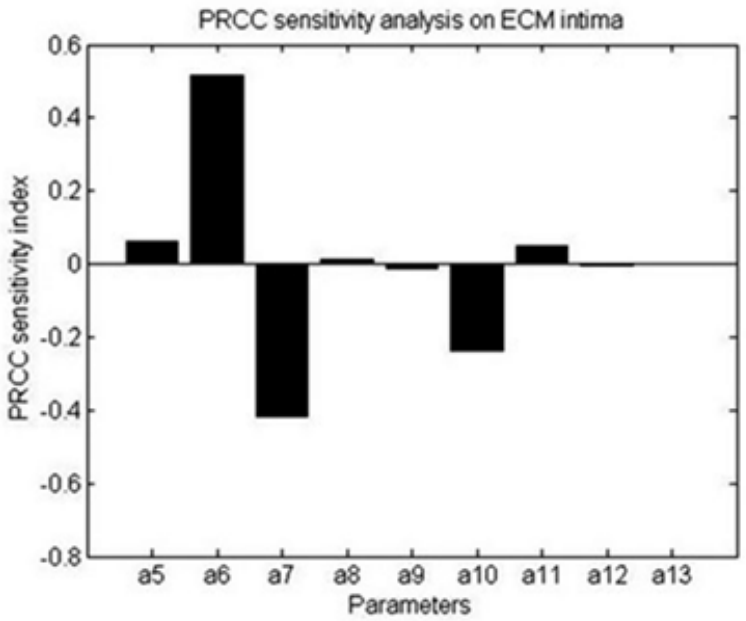

ABM Module
$\tau(X_I', Y_I')$
$\tau_{wall}(X_E', Y_E')$
(X_I, Y_I)
(X_E, Y_E)
$\sigma(X_E', Y_E')$
Blood Flow Module
Tissue Mechanic Module
(X_I', Y_I') (X_E', Y_E')

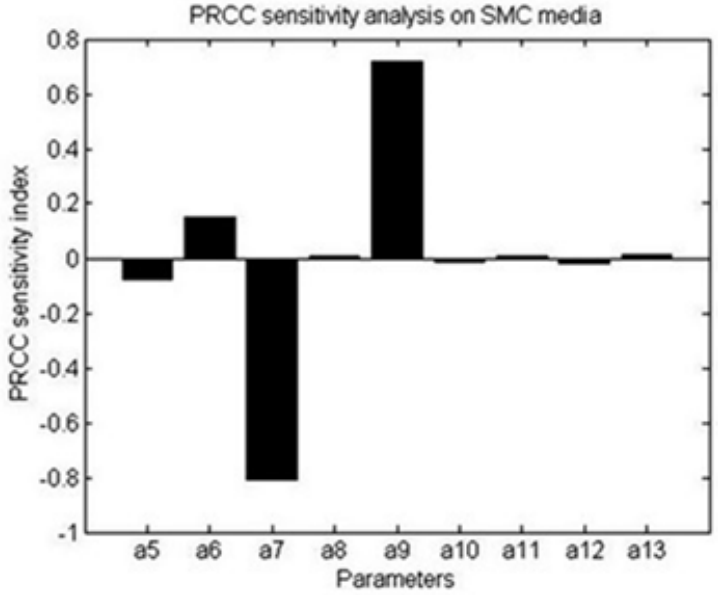

y
y
dP/dx = constant
P_0
P_1
u= u(y,z)
x
z
z

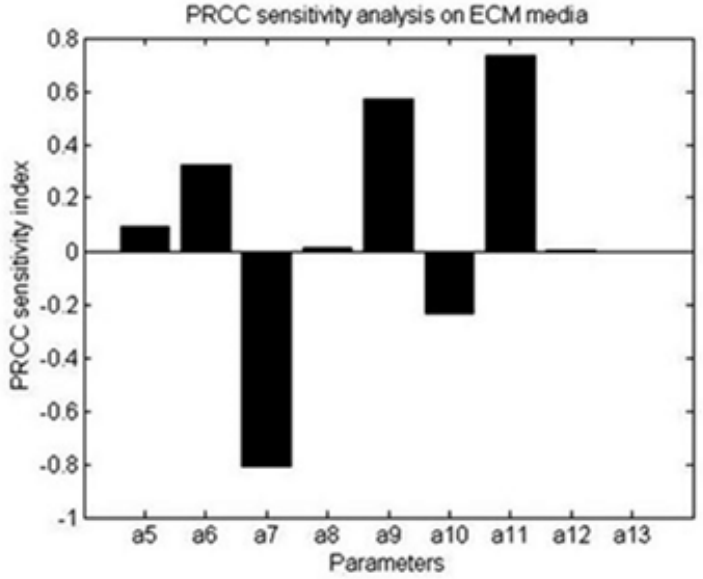

Φ
Unloaded
$\Delta P_1 = 0$
Φ^{-1}
Loaded
$\Delta P_1 > 0$

Axiomatic rules	Comments
1. $p_{division}=p_{apoptosis}, \beta p^{*}_{degradation}=p_{production}$.	SMC/ECM apoptosis/mitosis.
2. $p_{division}=\alpha_1>0, p_{production}=\alpha_2>0$.	Basic solution.
3. $A(t)=\exp-(\frac{t-T_i}{\delta T_i})^2$.	Macrophage activity.
4. $T_i=\alpha_3>0, \delta T_i=\alpha_4>0$.	Macrophage growth and decay time.
5. $p_{through}=\alpha_5 A(t)(1+\alpha_{13}\Delta\tau(y)/\bar{\tau})(1+\alpha_{14}\Delta\sigma_r(y)/\bar{\sigma}), \alpha_5>0$.	The probability that an SMC crosses the IEL.
6. $P_{division} = \alpha_1 A(t)(1+ \alpha_6 \Delta\tau(y)/\bar{\tau})$	The probability that an SMC divides inside intima.
7. $\Delta\tau(y)=\Delta\tau_{wall}\exp(-\frac{y-R_{lumen}}{\alpha_8 d_{SMC}})$	Shear stress calculation (6).
8. $p_{apoptosis}=\alpha_1 A(t)$,	The probability that an SMC dies inside intima.
9. $Pdivision=\alpha_1 A(t)(1+ \alpha_9 \Delta\sigma_r/\bar{\sigma})$	The probability of mitosis of SMC inside media.
10. $p_{apoptosis}=\alpha_1 A(t)$,	The probability of apoptosis of SMC inside media.
11. $p^{*}_{production}=\alpha_2 A(t)$,	ECM degeneration inside intima.

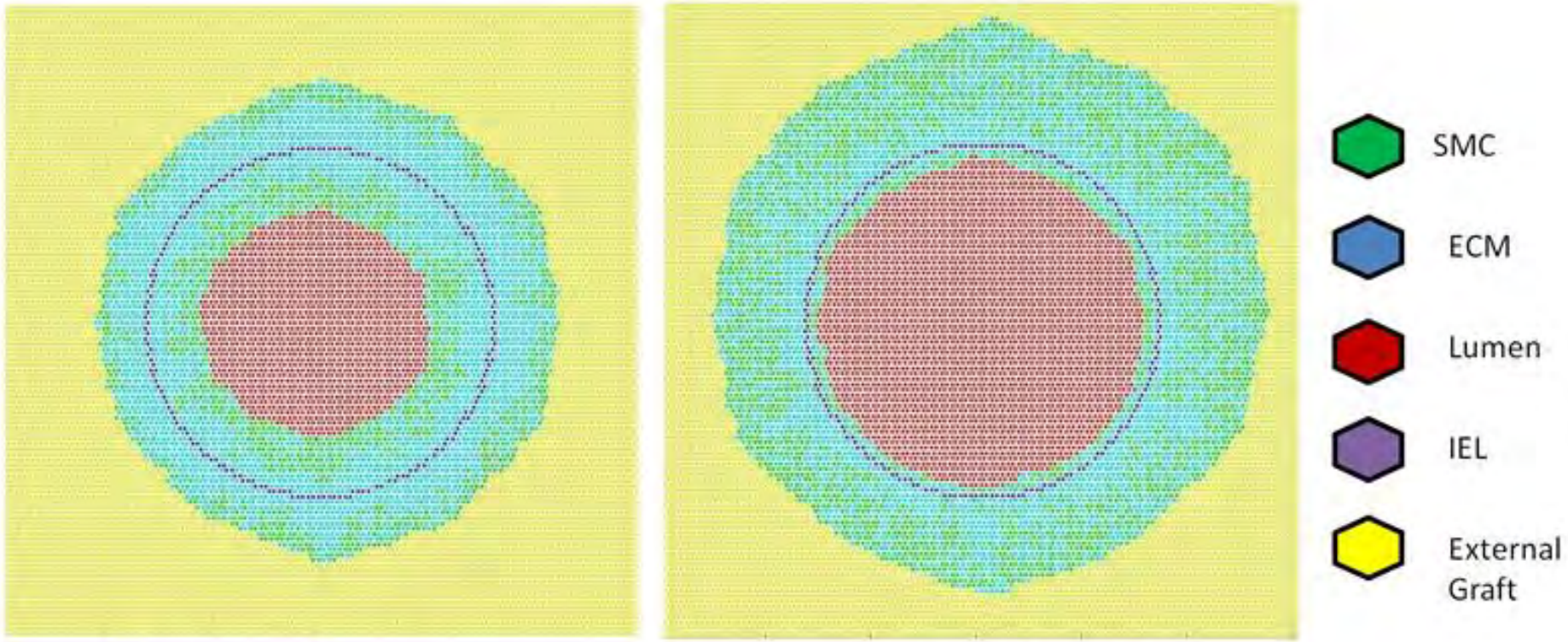

PRCC sensitivity analysis on SMC intima
PRCC sensitivity index
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
a5 a6 a7 a8 a9 a10 a11 a12 a13
Parameters


PRCC sensitivity analysis on ECM intima
PRCC sensitivity index
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
a5 a6 a7 a8 a9 a10 a11 a12 a13
Parameters


PRCC sensitivity analysis on SMC media
PRCC sensitivity index
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
a5 a6 a7 a8 a9 a10 a11 a12 a13
Parameters


PRCC sensitivity analysis on ECM media
PRCC sensitivity index
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
a5 a6 a7 a8 a9 a10 a11 a12 a13
Parameters

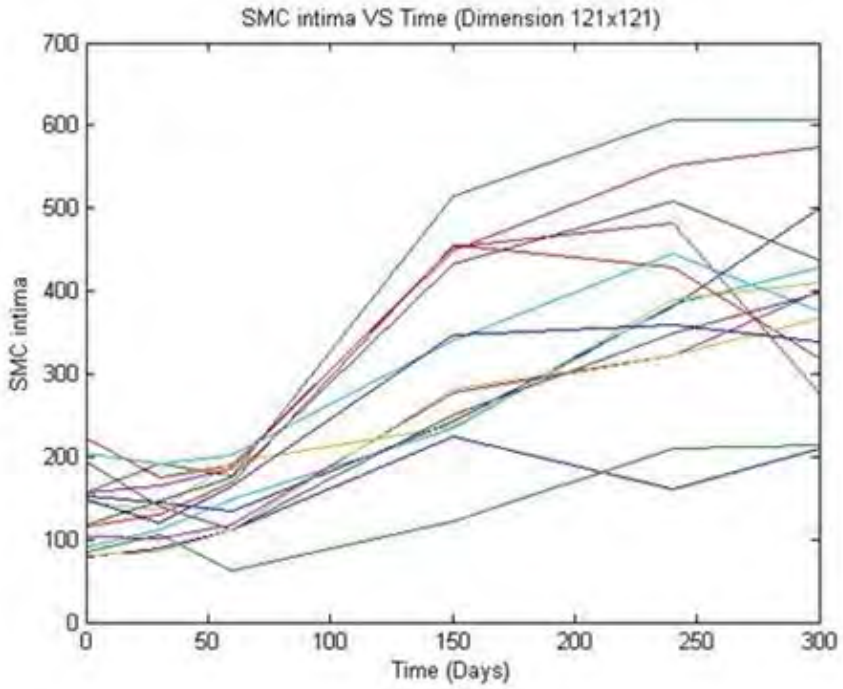
INTERESTING PATTERN INFORMATION DURING INTIMAL AND MEDIAL GROWTH.

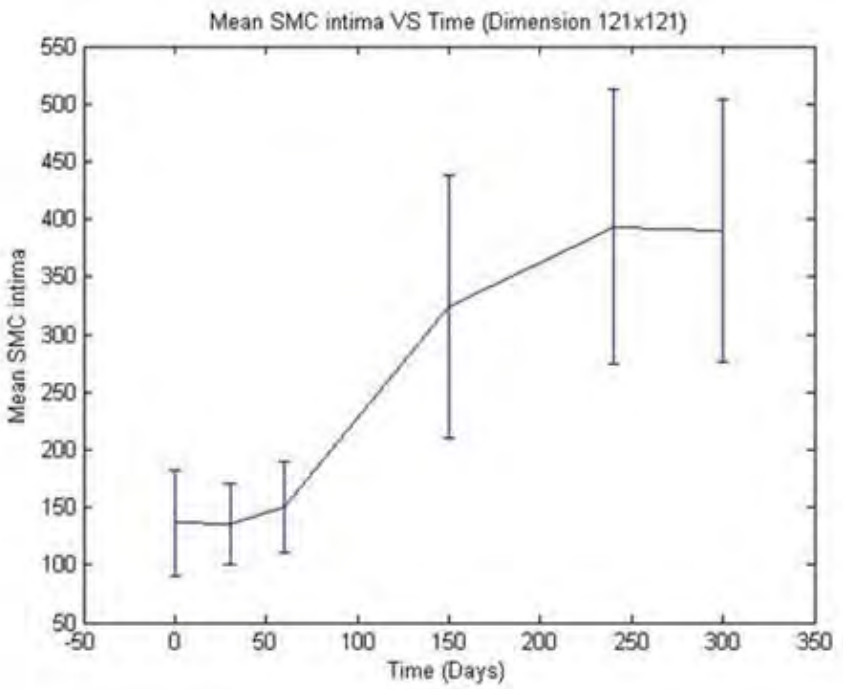


Intimal Hyperplasia

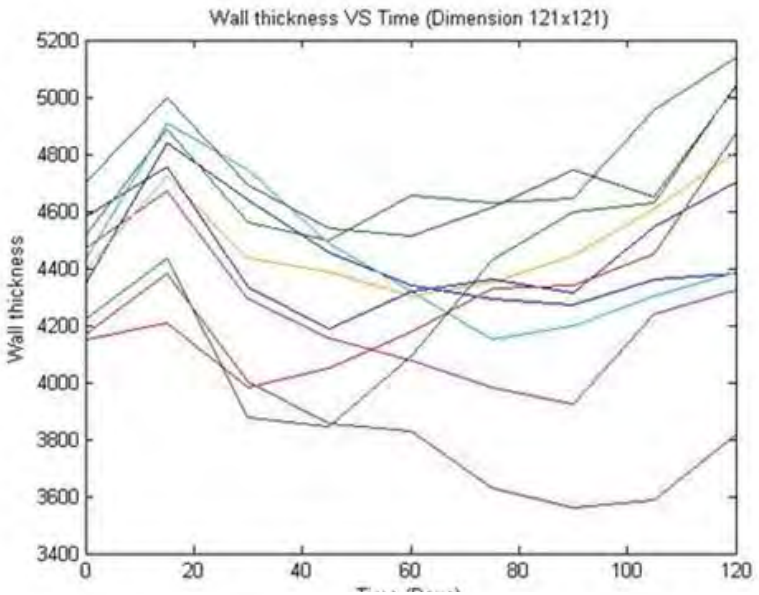
Outward Remodeling

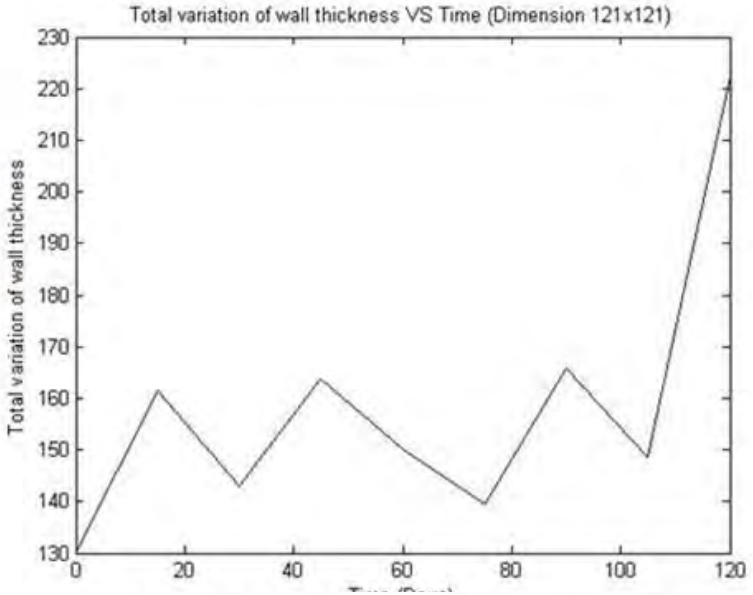
SMC INSIDE INTIMA VS TIME AT 75% PERTURBATION RATE

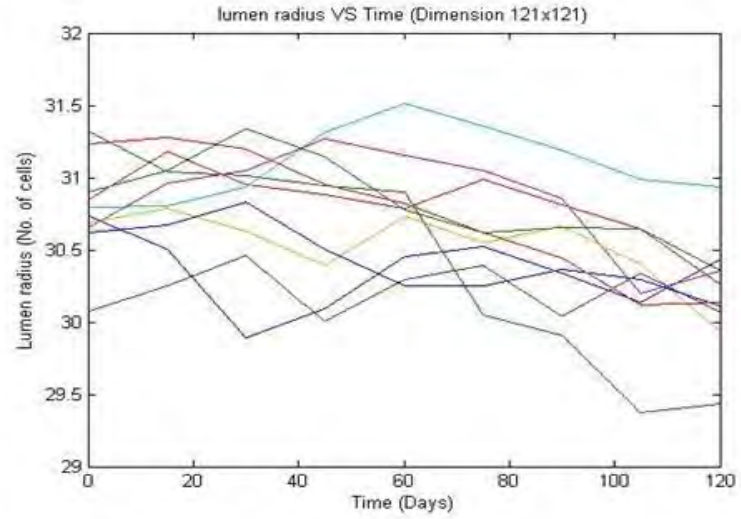


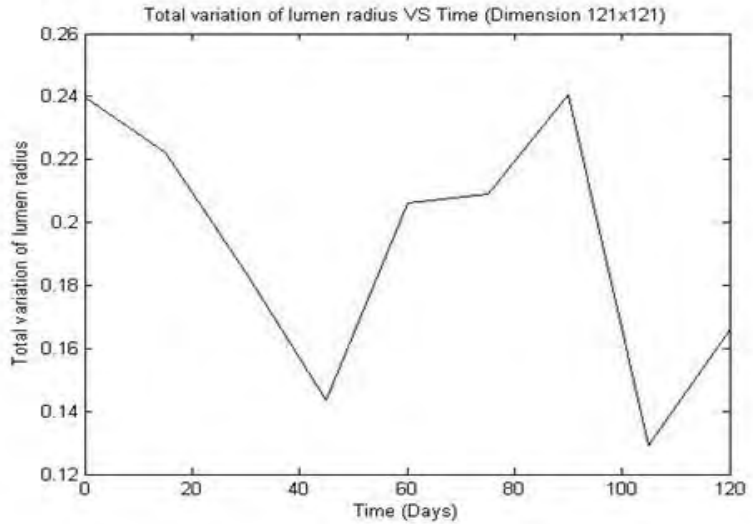


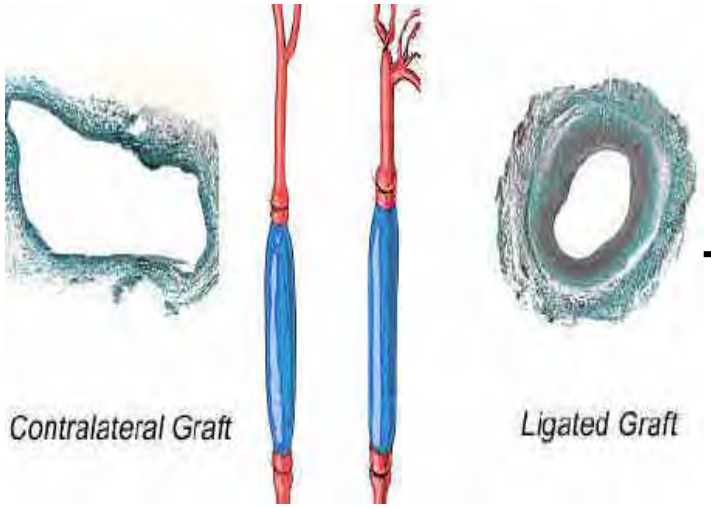
SOME INTERESTING TEMPORAL OSCILLATIONS



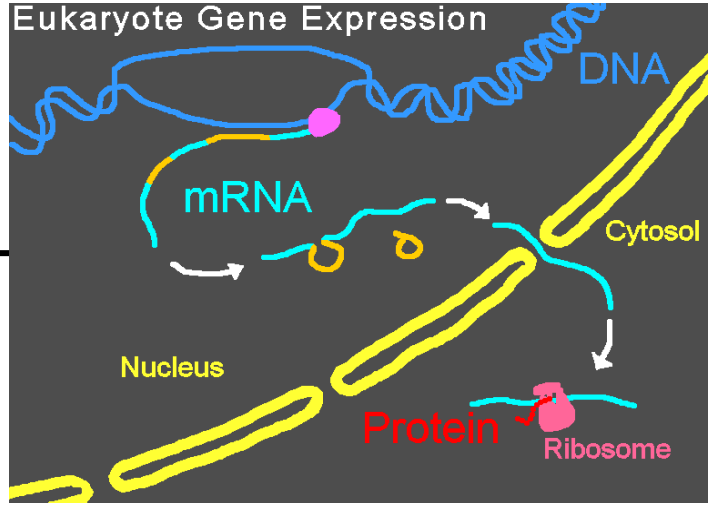




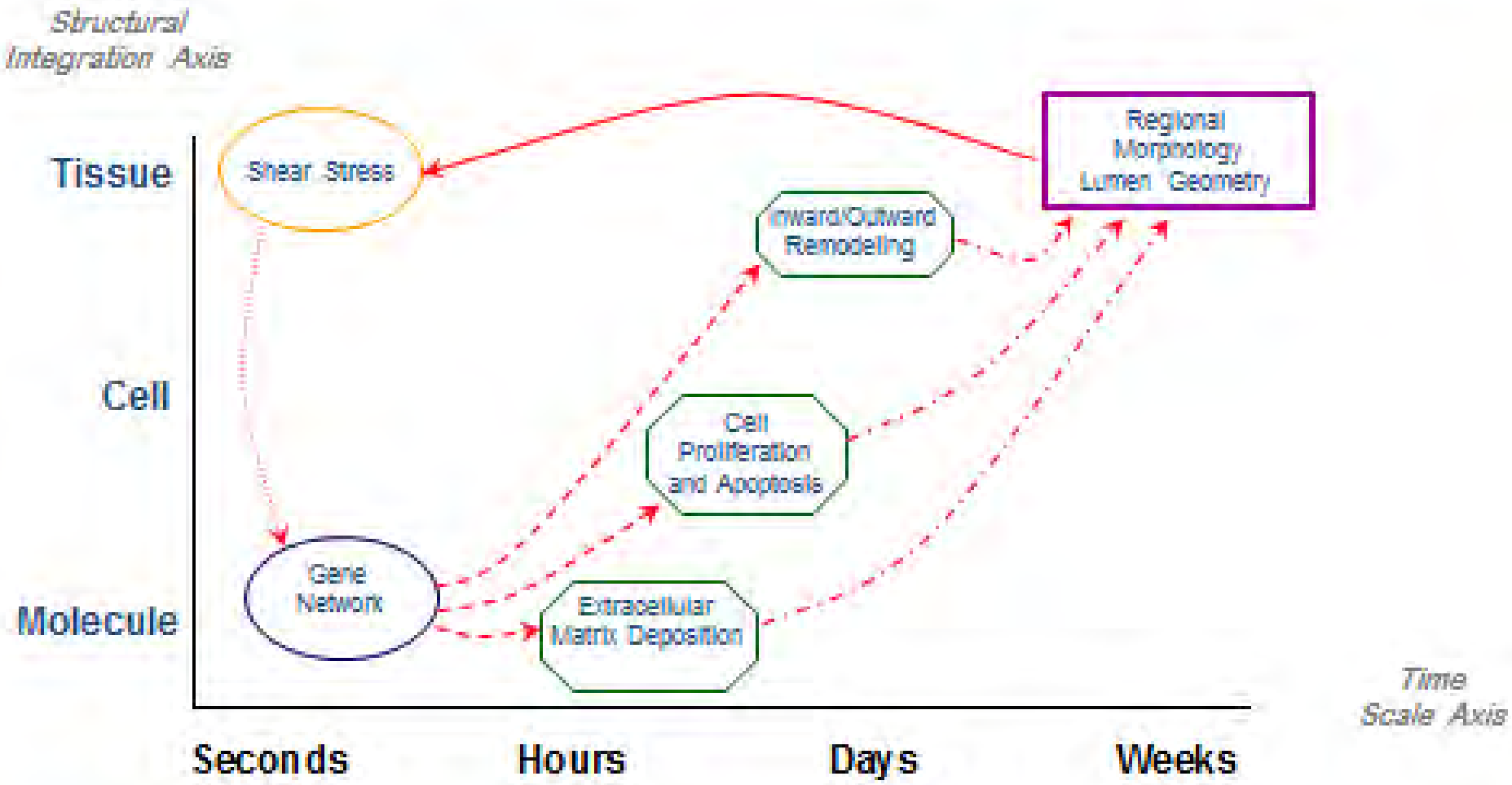




COUPLING A DYNAMIC SYSTEM DESCRIBING THE VEIN GRAFT POST SURGICAL REMODELING WITH DENSITY PROBABILITY OF SPECIFIC GENES' EXPRESSION



Events in Vascular Remodeling



GENE CLUSTERING

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How to cluster gene expression dynamics in response to environmental signals

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Submitted: 25th February 2011; Received (in revised form): 16th May 2011

- Can we identify a gene (or a small set of genes) that control intimal growth?
- Can we define a density of probability related to their rate of expression?
- Can we coupled the dynamical system described previously with the genetic aspect?

ELABORATION OF THE ORIGINAL DATA

N=9271; M=29; T=7 (0.08,1,3,7,14,28 days)

Gene name	Gene expression values (τ_{low})	Gene expression values (τ_{high})	Cluster	Cellular activity
g_1	$G^{1l}_{t1}, G^{1l}_{t2}, \dots, G^{1l}_{tT}$	$G^{1h}_{t1}, G^{1h}_{t2}, \dots, G^{1h}_{tT}$	1	P M E A
g_2	$G^{2l}_{t1}, G^{2l}_{t2}, \dots, G^{2l}_{tT}$	$G^{2h}_{t1}, G^{2h}_{t2}, \dots, G^{2h}_{tT}$	1	P M E A
…	…	…	…	…
g_n	$G^{nl}_{t1}, G^{nl}_{t2}, \dots, G^{nl}_{tT}$	$G^{nh}_{t1}, G^{nh}_{t2}, \dots, G^{nh}_{tT}$	m	P M E A
…	…	…	…	…
g_N	$G^{Nl}_{t1}, G^{Nl}_{t2}, .., G^{Nl}_{tT}$	$G^{Nh}_{t1}, G^{Nh}_{t2}, \dots, G^{Nh}_{tT}$	M	P M E A

- N= total number of genes
- g_n= generic n-th gene

- T= total number of time steps
- G^{nl}_{tt}= gene expression value for the n-th gene at time t in low flow conditions

- T= total number of time steps
- G^{nh}_{tt}= gene expression value for the n-th gene at time t in high flow conditions

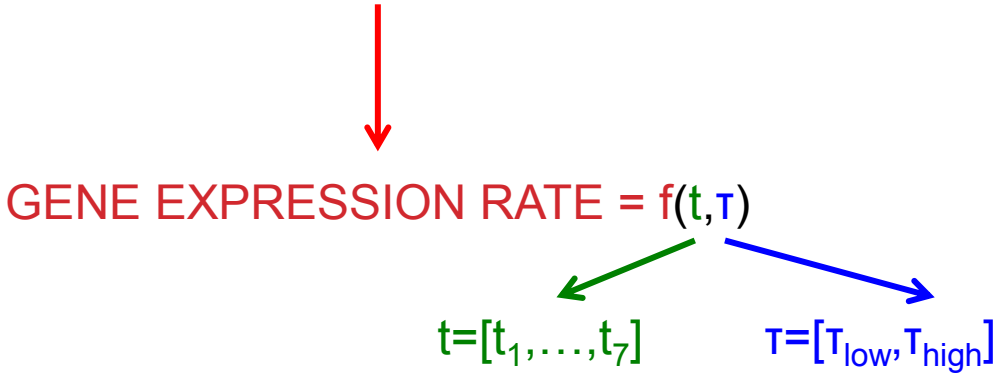
- M= total number of clusters (each gene belongs to one of the M clusters)

- In red the cellular activities influenced by specific gene

GENE CLUSTERING

Remarks:

- Variations in environment → Variation in gene expression (experimental set up in 2 different environments: low shear stress τ_{low} and high shear stress τ_{high})
- Time evolution → Variation in gene expression



- Which genes? 5 clusters → A, D, F, G, H are the main drivers for our analysis

  Hypothesis: 1 cluster = 1 "gene"

Gene of interest influence the vein graft remodeling trough acting on the following cellular events

- Mitosis
- Apoptosis
- Mobility
- Metabolism (ECM production)

CURVE FITTING OF GENE EXPRESSION: FIRST MODEL USED

BASE MODEL: We choose as base model an exponential trend for each single cluster:

- A_1 drives the amplitude
- A_2 drives the asymptote

$$\frac{d}{dt}x_i = A_1(x_i - A_2)$$

CLUSTER INTERACTION and SYSTEM SOLVER: each cluster is influenced by all the others. The model turns in a ODE system like the following (see next slide for the complete system). System solved by ode45 function with initial conditions $x_i(0)=x_i^0$

$$\begin{cases} \frac{d}{dt}X_{12} = A_1(X_{12} - A_2) + \ldots + A_9(X_{21} - A_{10}) \\ \frac{d}{dt}X_{14} = \ldots \\ \ldots \\ \frac{d}{dt}X_{21} = A_{26}(X_{12} - A_2) + \ldots + A_{30}(X_{21} - A_{10}) \end{cases}$$

Fitting parameters
$A=[A_1,A_2,\ldots,A_{30}]$

RMS DEVIATION: For each cellular event in specific environment conditions, we have a reference trend and a parameterized one. We evaluated the RMS deviation between them. The result is basically the following

$$RMS_{xref/xfit} = f(A_1,A_2,\ldots,A_{30})$$

GENETIC ALGORITHM: In order to get the fitting parameters ($A_1,\ldots,A_{30}$) for each system, we need to minimize the RMS deviation through a genetic algorithm implemented in Matlab

CURVE FITTING: KEEPING THE "ESSENTIAL"

System can be simplified (number of unknown parameters reduced) taking in account that interaction between a generic cluster i and an other j may be neglected.

$$\frac{d}{dt}X_{12} = A_1(X_{12} - A_2) + A_3(X_{14} - A_4) + A_5(X_{15} - A_6) + A_7(X_{16} - A_8) + A_9(X_{21} - A_{10})$$

$$\frac{d}{dt}X_{14} = A_{11}(X_{12} - A_2) + A_{12}(X_{14} - A_4) + A_{13}(X_{15} - A_6) + A_{14}(X_{16} - A_8) + A_{15}(X_{21} - A_{10})$$

$$\frac{d}{dt}X_{15} = A_{16}(X_{12} - A_2) + A_{17}(X_{14} - A_4) + A_{18}(X_{15} - A_6) + A_{19}(X_{16} - A_8) + A_{20}(X_{21} - A_{10})$$

$$\frac{d}{dt}X_{16} = A_{21}(X_{12} - A_2) + A_{22}(X_{14} - A_4) + A_{23}(X_{15} - A_6) + A_{24}(X_{16} - A_8) + A_{25}(X_{21} - A_{10})$$

$$\frac{d}{dt}X_{21} = A_{26}(X_{12} - A_2) + A_{27}(X_{14} - A_4) + A_{28}(X_{15} - A_6) + A_{29}(X_{16} - A_8) + A_{30}(X_{21} - A_{10})$$

fitting parameters estimation

$A=[A_1,A_2,\ldots,A_{30}]$

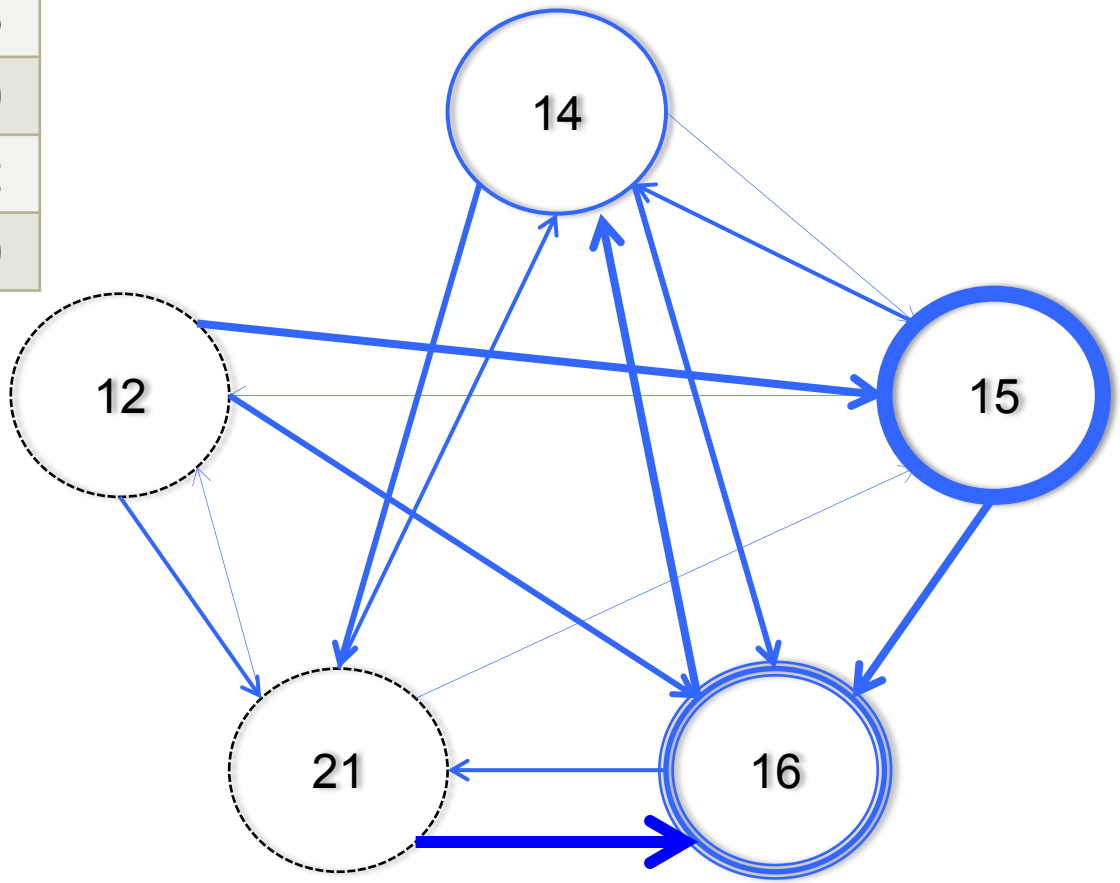
New set of fitting parameters doesn't consider weak interaction between cluster
$A=[A_1,A_2,\ldots,A_N]$

Parameters reduction = system simplification

- Normalization of vector A by its maximum value
- Cutoff below the threshold of 0.1 on resulting vector

NETWORK REPRESENTATION : MITOSIS LOW FLOW

$w_{i/j}$	12	14	15	16	21
12	0	0	4	3	2
14	0	2	1	3	3
15	1	2	6	4	0
16	0	4	0	7	2
21	1	2	1	5	0



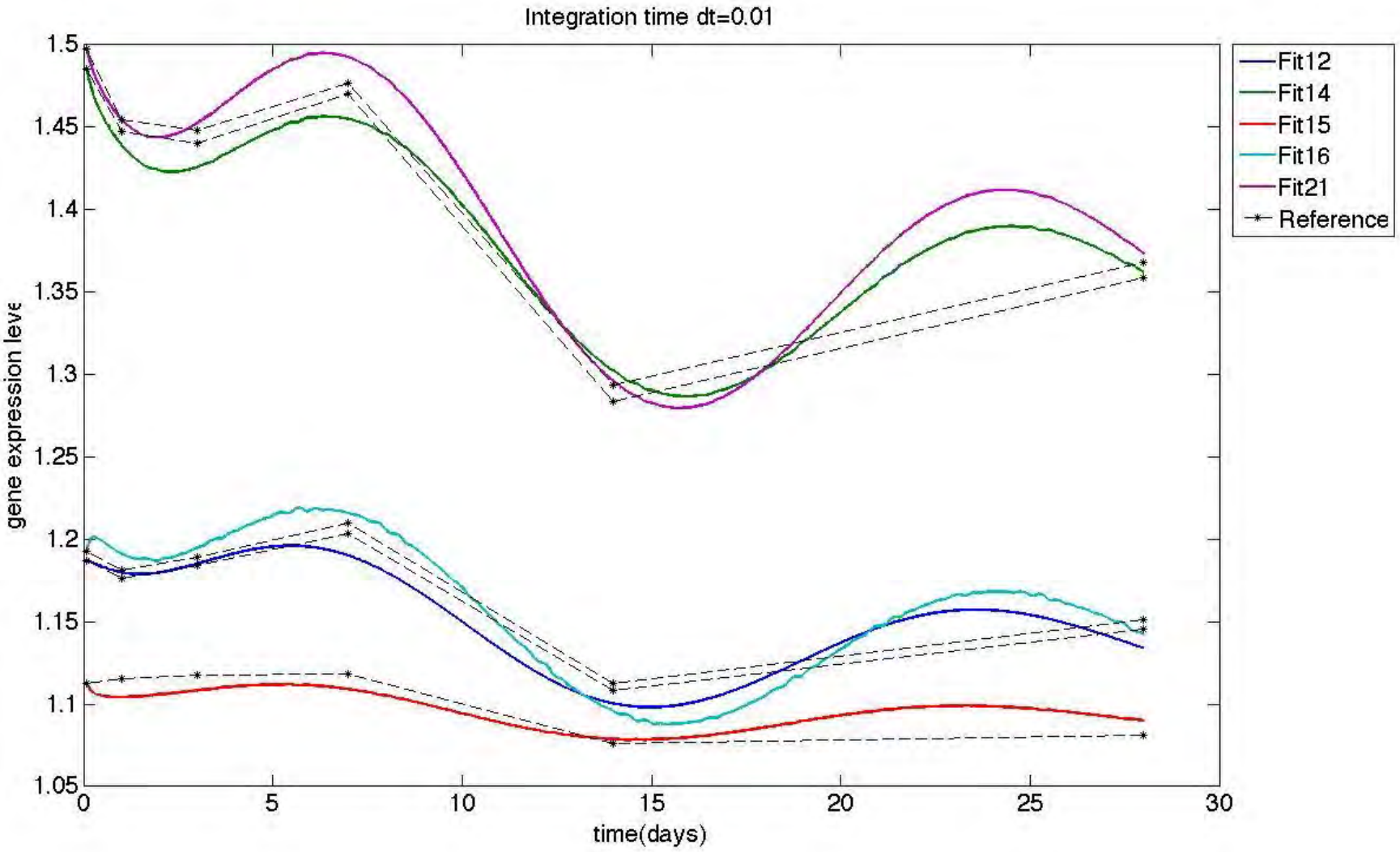
Interaction legend

: 1
: 2
: 3
: 4
: 5
: 6
: 7

NB: solid cluster border indicates an auto influence of the cluster itself!

5 – OSCILLATIONS ANALYSIS : APOPTOSIS LOW FLOW

Hypothesis: time step discretization = 0.01days



DENSITY OF PROBABILITY (1)

How to write the general form for the density of probability referred to the cellular events of interest?

↓

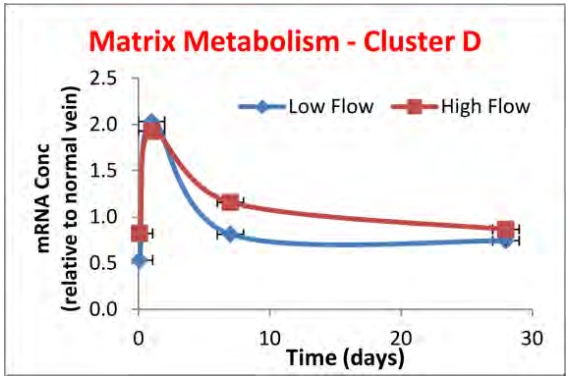
The density of probability is again function of time and shear stress. We use linear interpolation in order to solve the shear stress dependence knowing the analytical trend for the generic $P_i^j(t)$ in low and high shear stress case (as done for the gene expression level).

$$P_i^j(t,\tau) \longrightarrow P_i^j(t)$$

linear interpolation

Starting with the simplest case of ***matrix metabolism*** (due to gene D activity):

$$P_E(t) = \alpha(t)\left[ed\,P^D_{Et\,low}(t) + (1-ed)\,P^D_{Et\,high}(t)\right]$$



Dataset need!

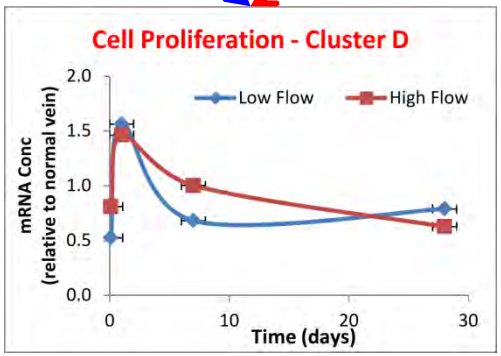
$$ed = \frac{P_E(t) - P^D_{Et\,high}(t)}{P^D_{Et\,low}(t) - P^D_{Et\,high}(t)}$$

$$(1-ed) = \frac{-P_E(t) + P^D_{Et\,low}(t)}{P^D_{Et\,low}(t) - P^D_{Et\,high}(t)}$$

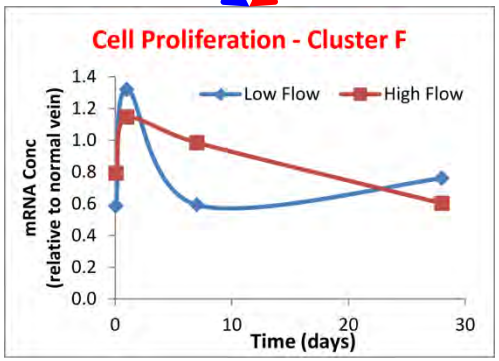
DENSITY OF PROBABILITY (2)

Density of probability of ***cellular proliferation*** (due to genes D and F activity):

$$P_P(t) = d(t)\left[pd\,P^D_{Pt\,low}(t) + (1-pd)\,P^D_{Pt\,high}(t)\right] + f(t)\left[pf\,P^F_{Pt\,low}(t) + (1-pf)\,P^F_{Pt\,high}(t)\right]$$



Dataset need!



$$\begin{cases} pd = \dfrac{P_P(t) - P^D_{Pt\,high}(t)}{P^D_{Pt\,low}(t) - P^D_{Pt\,high}(t)} \\ (1-pd) = \dfrac{-P_P(t) + P^D_{Pt\,low}(t)}{P^D_{Pt\,low}(t) - P^D_{Pt\,high}(t)} \end{cases}$$

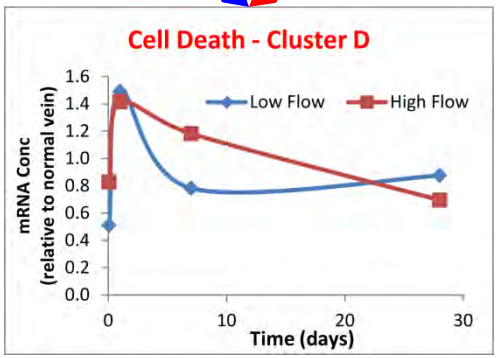
$$\begin{cases} pf = \dfrac{P_P(t) - P^F_{Pt\,high}(t)}{P^F_{Pt\,low}(t) - P^F_{Pt\,high}(t)} \\ (1-pf) = \dfrac{-P_P(t) + P^F_{Pt\,low}(t)}{P^F_{Pt\,low}(t) - P^F_{Pt\,high}(t)} \end{cases}$$

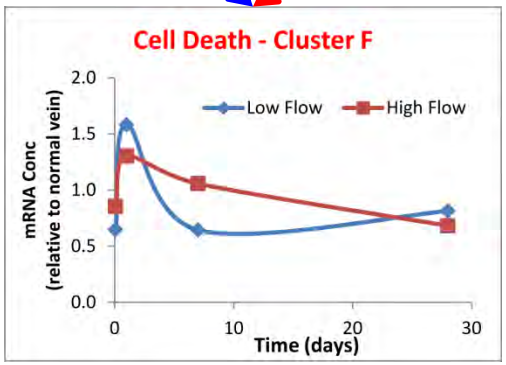
DENSITY OF PROBABILITY (3)

Density of probability of ***apoptosis*** (due to genes D and F activity):

$$P_A(t) = d(t)\left[ad\,P^D_{At\,low}(t) + (1-ad)\,P^D_{At\,high}(t)\right] + f(t)\left[af\,P^F_{At\,low}(t) + (1-af)\,P^F_{At\,high}(t)\right]$$

Dataset need!





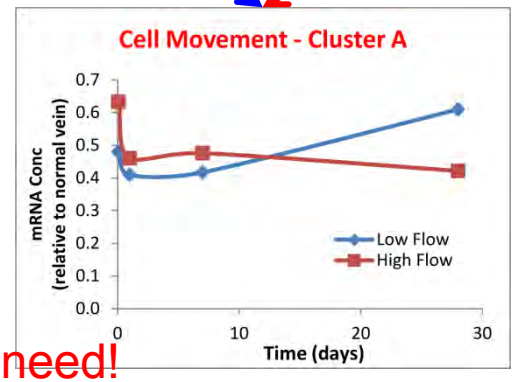
$$\begin{cases} ad = \dfrac{P_A(t) - P^D_{At\,high}(t)}{P^D_{At\,low}(t) - P^D_{At\,high}(t)} \\ (1-ad) = \dfrac{-P_A(t) + P^D_{At\,low}(t)}{P^D_{At\,low}(t) - P^D_{At\,high}(t)} \end{cases}$$

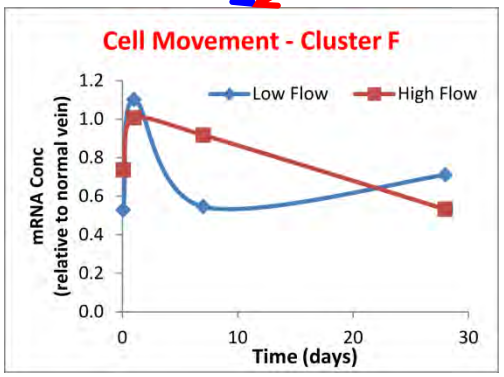
$$\begin{cases} af = \dfrac{P_A(t) - P^F_{At\,high}(t)}{P^F_{At\,low}(t) - P^F_{At\,high}(t)} \\ (1-af) = \dfrac{-P_A(t) + P^F_{At\,low}(t)}{P^F_{At\,low}(t) - P^F_{At\,high}(t)} \end{cases}$$

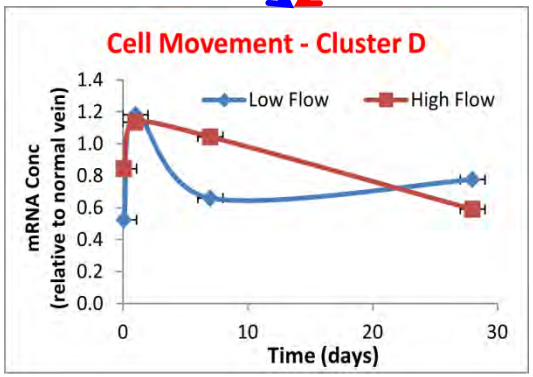
DENSITY OF PROBABILITY (4)

Density of probability of ***mobility*** (due to genes A, F and D activity):

$$P_A(t) = a(t)\left[ma\,P^A_{Mtlow}(t) + (1-ma)\,P^A_{Mthigh}(t)\right] + f(t)\left[mf\,P^F_{Mtlow}(t) + (1-mf)\,P^F_{Mthigh}(t)\right] + d(t)\left[md\,P^D_{Mtlow}(t) + (1-md)\,P^D_{Mthigh}(t)\right]$$







Dataset need!

$$\begin{cases} md = \dfrac{P_M(t) - P^D_{Mthigh}(t)}{P^D_{Mtlow}(t) - P^D_{Mthigh}(t)} \\ (1-ma) = \dfrac{-P_M(t) + P^A_{Mtlow}(t)}{P^A_{Mtlow}(t) - P^A_{Mthigh}(t)} \end{cases} \quad \begin{cases} mf = \dfrac{P_M(t) - P^F_{Mthigh}(t)}{P^F_{Mtlow}(t) - P^F_{Mthigh}(t)} \\ (1-mf) = \dfrac{-P_M(t) + P^F_{Mtlow}(t)}{P^F_{Mtlow}(t) - P^F_{Mthigh}(t)} \end{cases} \quad \begin{cases} ma = \dfrac{P_M(t) - P^A_{Mthigh}(t)}{P^A_{Mtlow}(t) - P^A_{Mthigh}(t)} \\ (1-md) = \dfrac{-P_M(t) + P^D_{Mtlow}(t)}{P^D_{Mtlow}(t) - P^D_{Mthigh}(t)} \end{cases}$$

SYSTEMS COUPLING

We can now close the loop, feeding the dynamical system referring to the intimal section variation, equation (4), (5), with the densities of probability defined.

$$\dot{A}^{I}_{SMC} = A(t)\left[- a_1 \Delta t \, A^{I}_{SMC} - a_5 \Delta t \, 2\pi R_{IEL} \frac{A^{M}_{SMC}}{A^{M}_{SMC} + A^{M}_{ECM}} \right]$$

$P_{mitosis}-P_{apoptosis}=P_P(t)-P_A(t)$

$P_{mobility}=P_M(t)$

$$\dot{A}^{I}_{ECM} = A(t)\left[- a_2 \Delta t \, A^{I}_{SMC} \right]$$ if $A_{ECM} > 0$, 0 otherwise

$P_{ECM}=P_E(t)$

We reach a time dependent system that links the environment modified activity of specific genes with the dynamic of adaptation and remodeling of a vein graft post implant

SYNTHESIS

HYPOTHESIS: A SPECIFIC, FINITE SET OF SHEAR-REGULATED GENES ARE CRITICAL TO CONTROLLING PATHOLOGIC VEIN GRAFT ADAPTATION. USING THE INTEGRATION OF MULTISCALE MODELING AND EXPERIMENTAL TECHNIQUES, THESE GENES CAN BE IDENTIFIED AND MANIPULATED *IN VIVO* TO IMPROVE VEIN GRAFT DURABILITY.

***SPECIFIC AIM 1*: IDENTIFY THOSE MODEL PARAMETERS, AND CORRESPONDINGLY THOSE *CORE* BIOLOGIC PROCESSES, THAT ARE MOST CRITICAL FOR ACCELERATED LOSS OF THE VEIN GRAFT LUMEN.**

***SPECIFIC AIM 2*: CREATE AND EXPLORE A DYNAMIC GENE REGULATORY NETWORK, WHICH WHEN INTEGRATED WITH AN AGENT-BASED MODEL OF VASCULAR ADAPTATION, IDENTIFIES THE SUBSET OF GENES THAT HAVE THE MOST SIGNIFICANT IMPACT ON REDUCING INTIMAL HYPERPLASIA AND PRESERVING VEIN GRAFT LUMEN.**

***SPECIFIC AIM 3*: VALIDATE THE MODEL PREDICTION AND EXPLORE COMBINATIONS OF *KEY* HUB GENES THAT PROVIDE THE MOST CRITICAL IMPACT ON THE BIOLOGIC PROCESSES THAT ARE CENTRAL TO PATHOLOGIC VEIN GRAFT ADAPTATION.**

***SPECIFIC AIM 4*: IDENTIFY THE OPTIMUM COMBINATION OF GENES THAT WILL MOVE FORWARD INTO A LARGE ANIMAL VALIDATION MODEL AND TRANSLATED INTO A THERAPEUTIC TOOL TO IMPROVE VEIN GRAFT SURVIVAL.**

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