



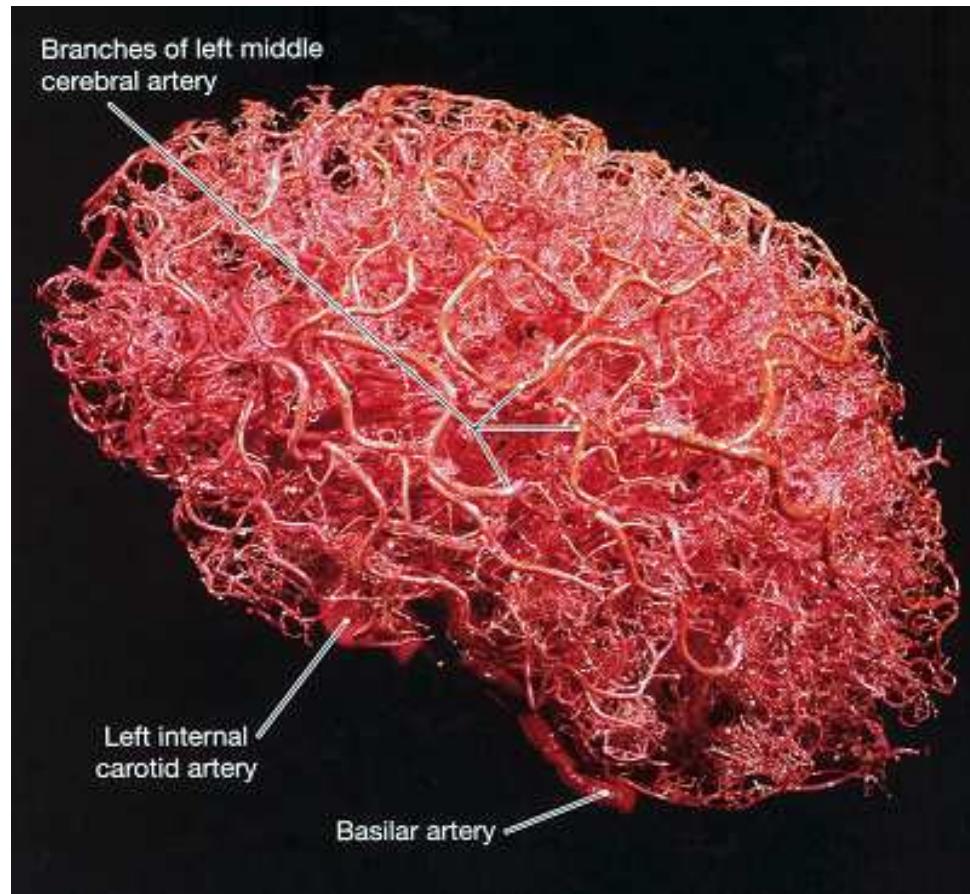
The Challenge of Multiple Scales in the Biological Sciences: Applications in Cerebro-vascular Perfusion



Biological Engineering problems have a multitude of physical scales:

- Major arteries (25mm - 1mm)
 - Vascular tree (1mm - 20 μ m)
 - cellular biochemistry (100 nm)

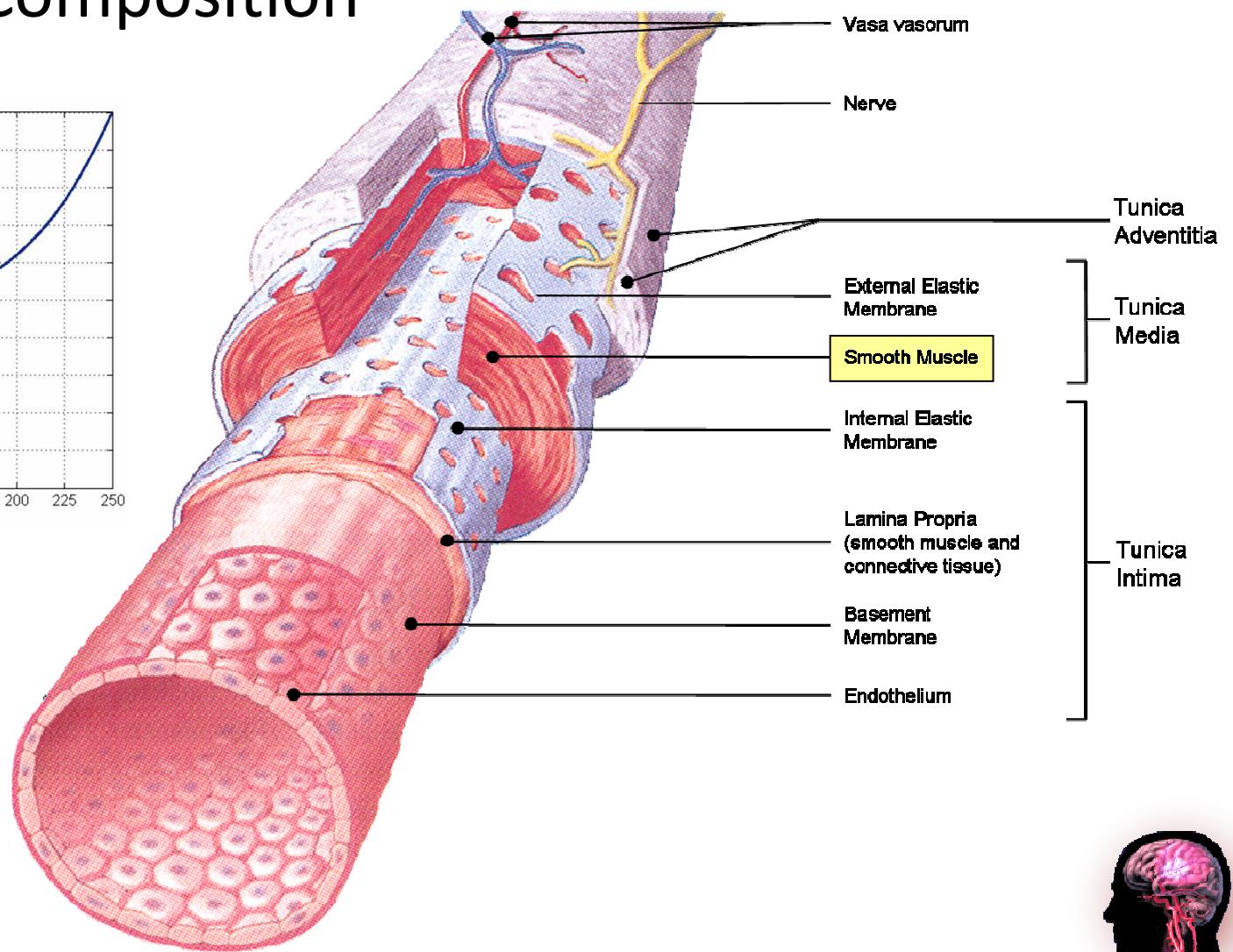
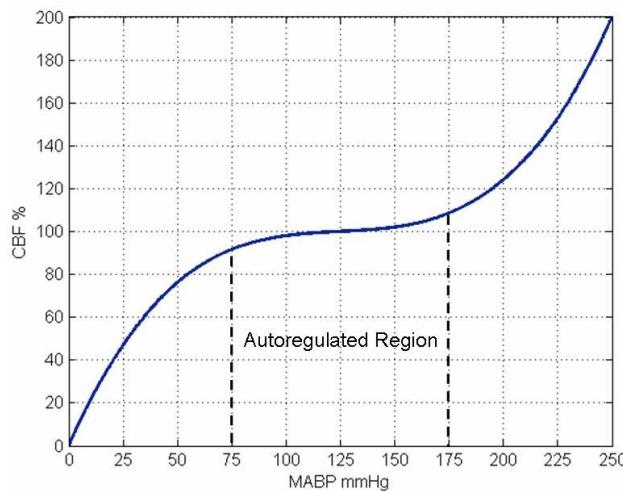




F.H. Martini. *Fundamentals of anatomy & physiology*. Benjamin Cummings, 7th edition, 2005.

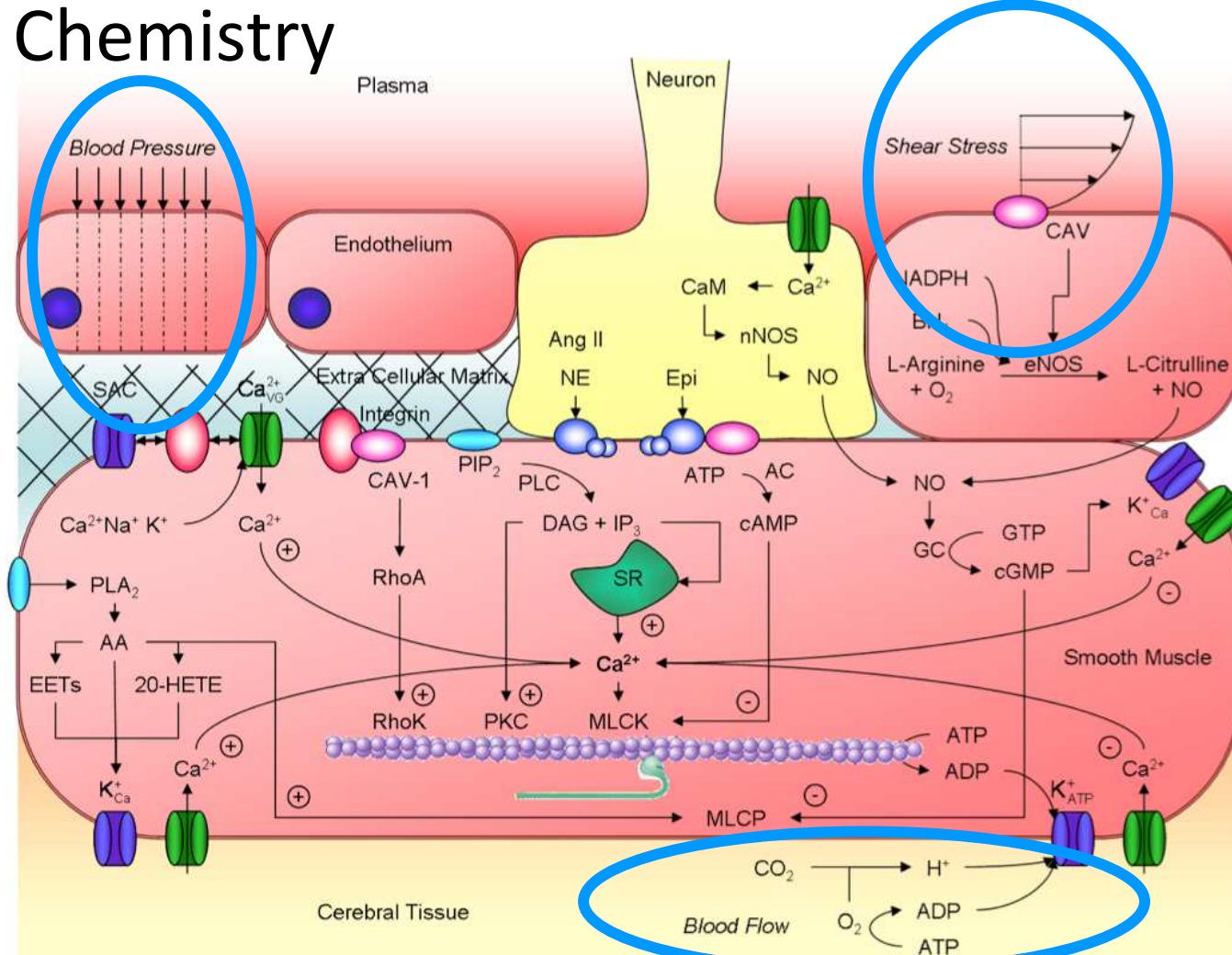


Blood Vessel Composition



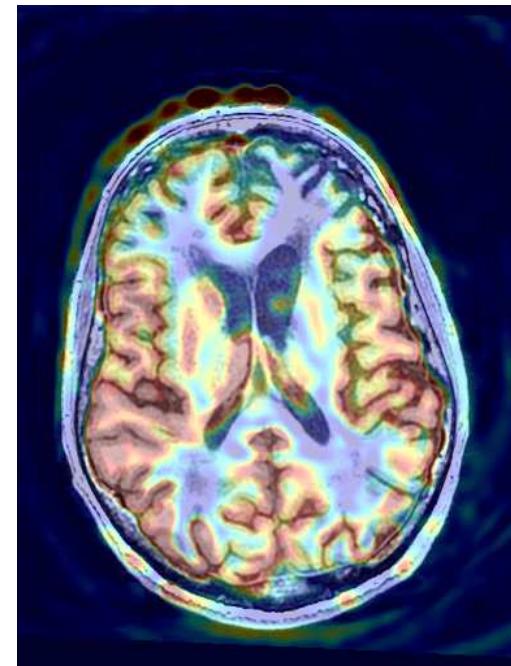
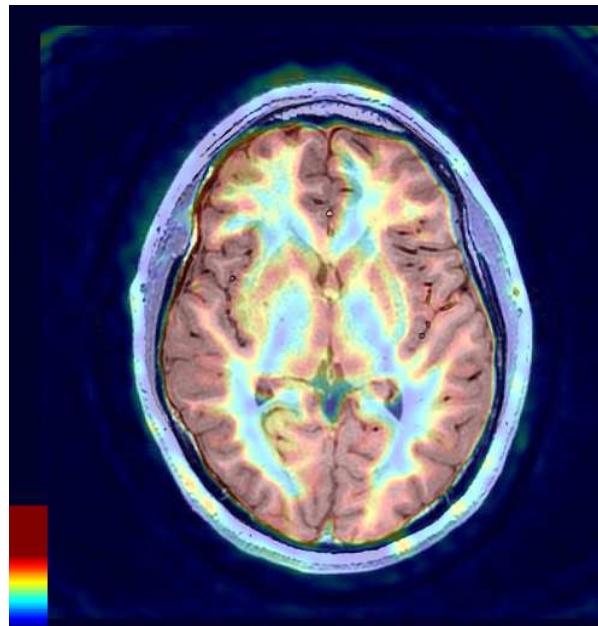


Cellular Chemistry

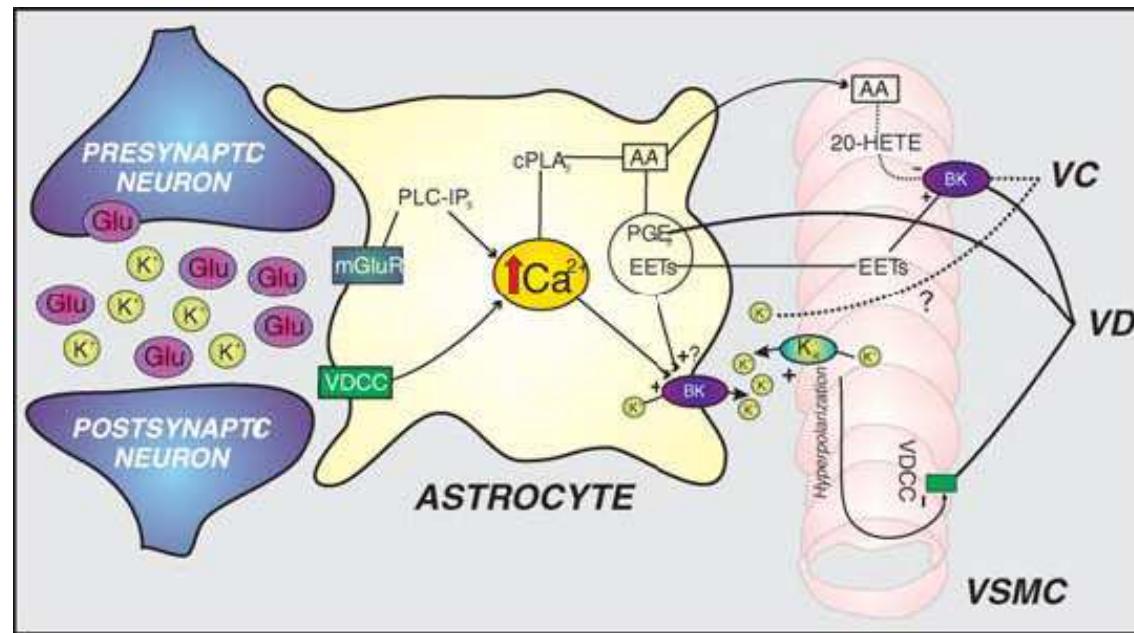




- Experimental evidence for variable perfusion
- Arterial Spin labelling, quantitative perfusion measurements
- Left: healthy volunteer.
- Right : 65 year-old male with Alzheimer's disease.



- Functional hyperaemia: local control of blood to tissue
- Neuro-vascular coupling: link between neuronal activity and blood supply
- Filosa, J. and V.M. Blanco, (2007)



Start with modelling the vasculature .

A single vascular tree in the brain providing blood to a volume of cerebral tissue:

- ~ 1 - 4,000,000 segments
 - 500,000 – 2,000,000 “leaves”
 - Can connect a Capillary bed per “leaf”



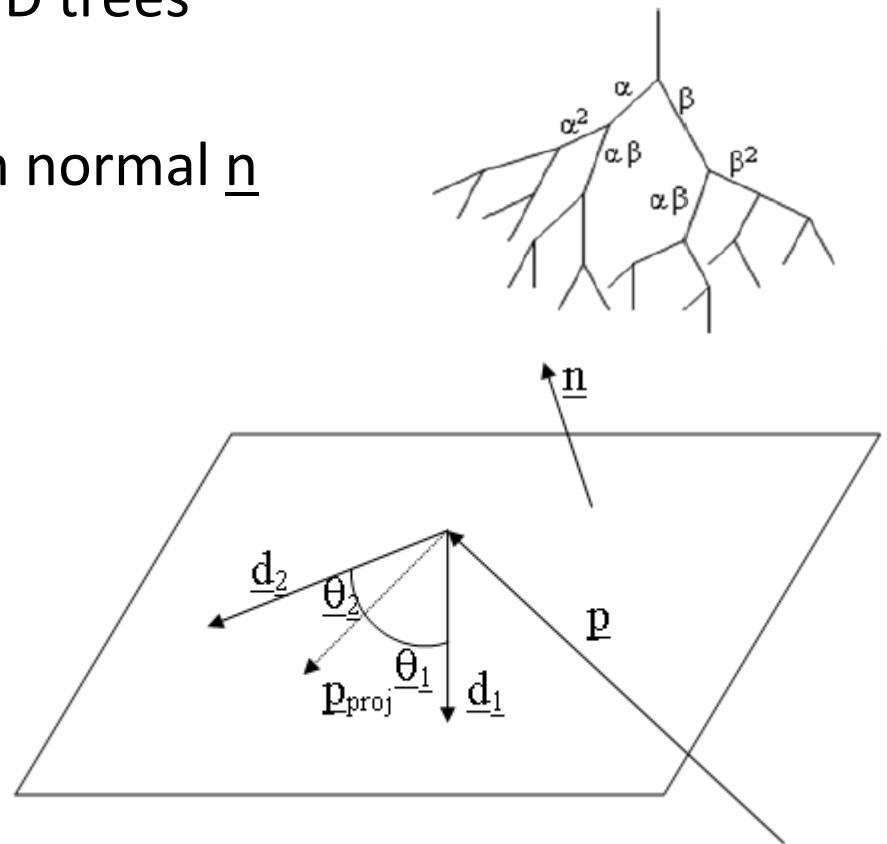


- How we make asymmetric 3D trees
 - Olufsen et al
 - Daughters lie in a plane with normal n

$$r_{d1} = \alpha r_p; r_{d2} = \beta r_p$$

$$\alpha = \left(1 + \gamma^{\frac{\kappa}{2}}\right)^{-\frac{1}{\kappa}}; \beta = \sqrt{\gamma}\alpha$$

$$\cos \theta_1 = \frac{r_p^4 + r_{d1}^4 - r_{d2}^4}{2r_p^2 r_{d1}^2}; \cos \theta_2 = \frac{r_p^4 + r_{d2}^4 - r_{d1}^4}{2r_p^2 r_{d2}^2};$$





- Staged growth (Karch et al)
- The normal \underline{n} is drawn from a prescribed distribution
- Family of PDFs , parametrised by λ .

$$g(\mathbf{n}, \lambda) \geq 0; \quad \int_{\square} g(\mathbf{n}, \lambda) d\mathbf{n} = 1; \quad p(\lambda) \geq 0; \int_0^1 p(\lambda) d\lambda$$

$$\Rightarrow \int \int_0^1 p(\lambda) g(\mathbf{n}, \lambda) d\lambda d\mathbf{n} = 1$$

- Define the staged growth as a function of arterial radius such that

$$\lambda: [0,1] \rightarrow [0,1], t \rightarrow \lambda(t(r))$$

$$t(r) = \frac{r_{root} - r}{r_{root} - r_{term}}$$

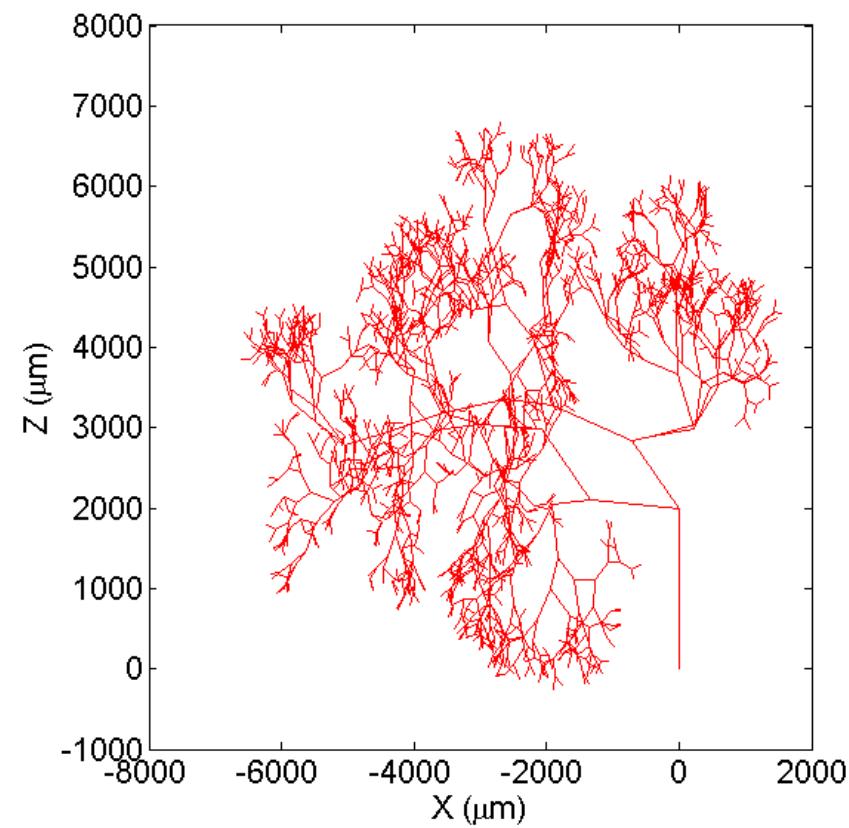
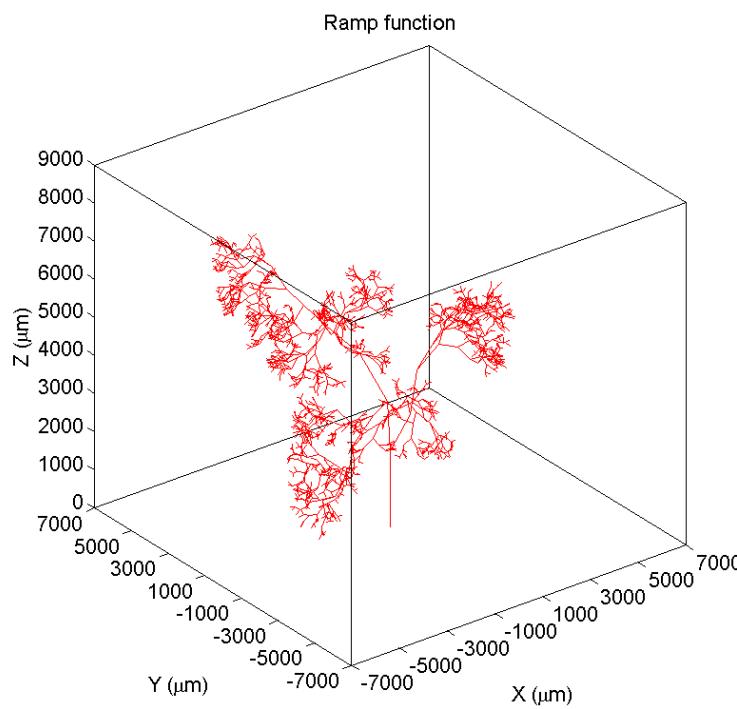
- λ can be a ramp or heaviside function for instance and with ξ drawn from a uniform distribution.

$$n_z = s\lambda + \sqrt{2}\sigma \operatorname{erf}^{-1}(2\xi - 1); n_z \in (1 - \varepsilon, 1 + \varepsilon)$$





- Some examples

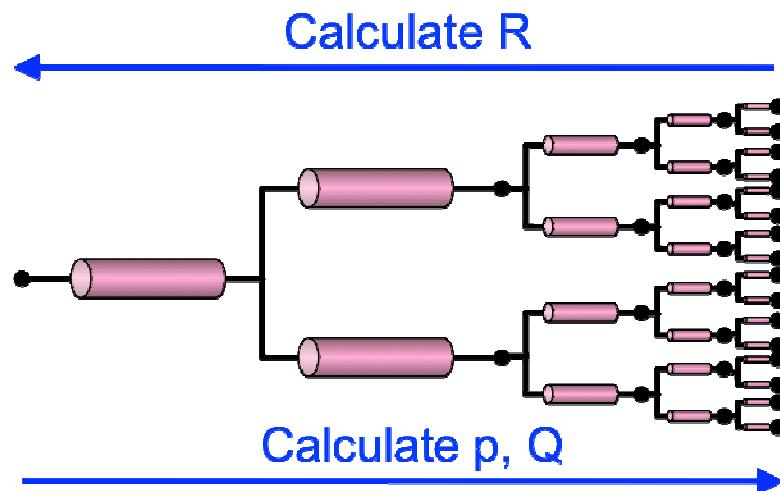
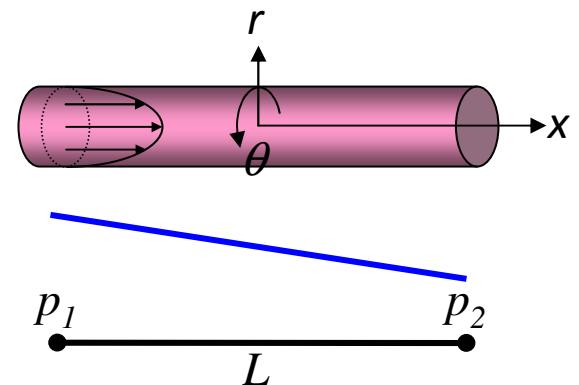




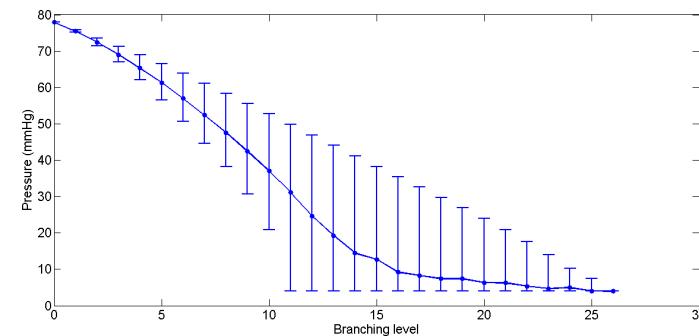
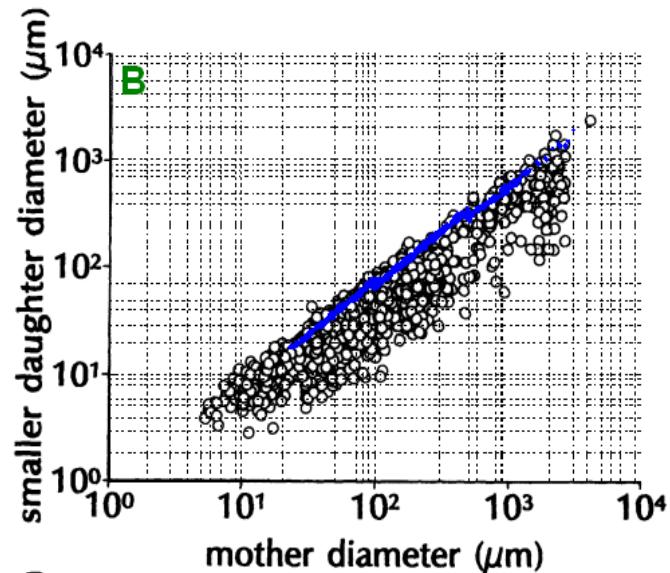
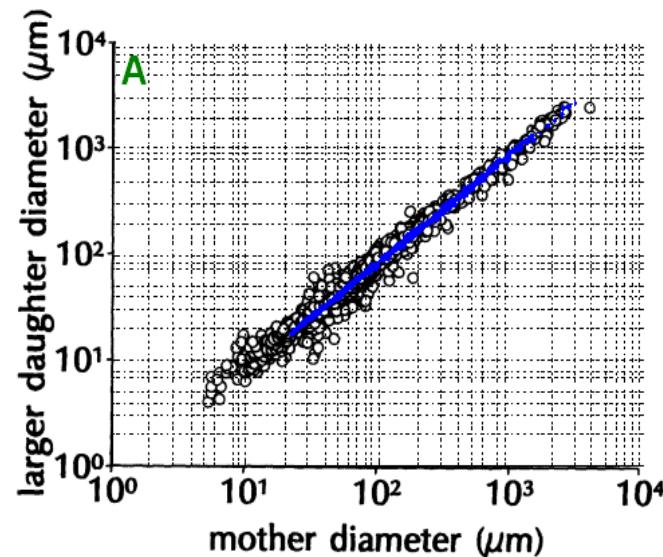
Flow in the tree: 0D Formulation

$$\frac{\partial \rho \mathbf{u}}{\partial t} + \nabla \cdot (\rho \mathbf{u} \mathbf{u}) = \mu \nabla^2 \mathbf{u} - \nabla p$$

$$\Delta p = QR \quad R = \frac{8\mu L}{\pi r^4}$$



- Comparison with anatomy
 - Log plots large/small daughters compared with vanBavel & Spaan (1992) for coronary tree.





- Simple model of functional hyperaemia
- Autoregulation of the tree, based on conservation of CO₂

$$\frac{dC_{O_2}}{dt} = G_{CO_2} \left(CMRO_2 + CBF \left(C_{CO_2, \text{artery}} - C_{O_2} \right) \right)$$

$$\frac{dr}{dt} = -G_r \left(\left(C_{CO_2, \text{sp}} - C_{O_2} \right) \right)$$

Non-dimensionalisation Analysis for a Symmetric tree: eigenvalues of linearised system

$$\frac{dc_i}{d\tau} = \alpha \hat{m}_i + \beta \frac{Q_i}{Q_{i,eq}} (1 - c_i)$$

$$\lambda_i = \frac{1}{2} \left(-(\gamma_i + \beta) \pm i\omega_i \right)$$

$$\frac{dr_i}{d\tau} = c_i - 1 - \frac{\alpha}{\beta} + \gamma_i \left(r_{i,eq} - r_i \right) \exp \left\{ \frac{\left(c_i - 1 - \frac{\alpha}{\beta} \right)^2}{\varepsilon} \right\}$$

$$\omega_i = 4\delta_i - (\gamma_i + \beta)^2$$

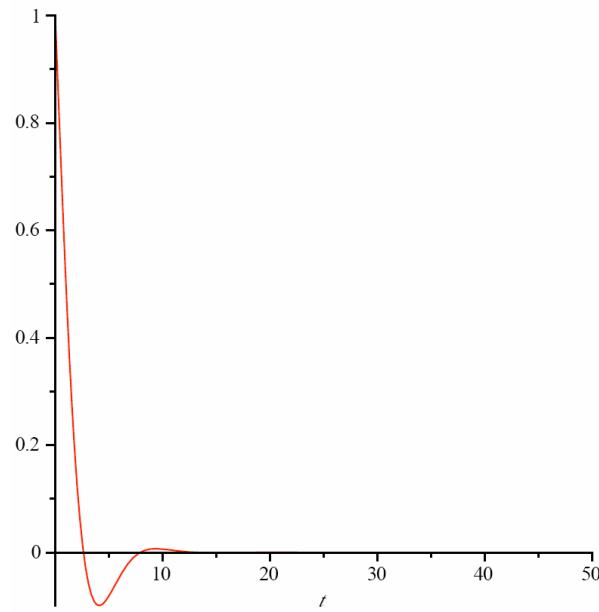
$\delta_i = \delta(\phi)$, ϕ = parent/daughter ratio



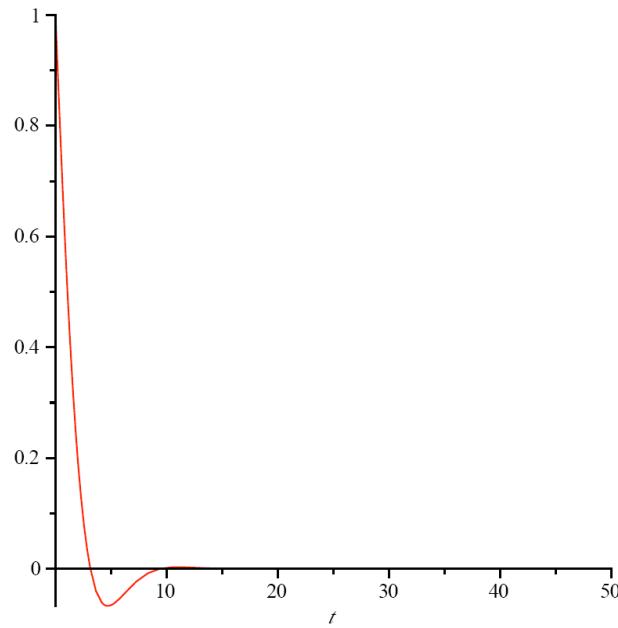


- Perturbation solution

$$y(t) = \exp(-\beta) \cos(\sqrt{\omega_i}t)$$



- Terminal node $\gamma=0$

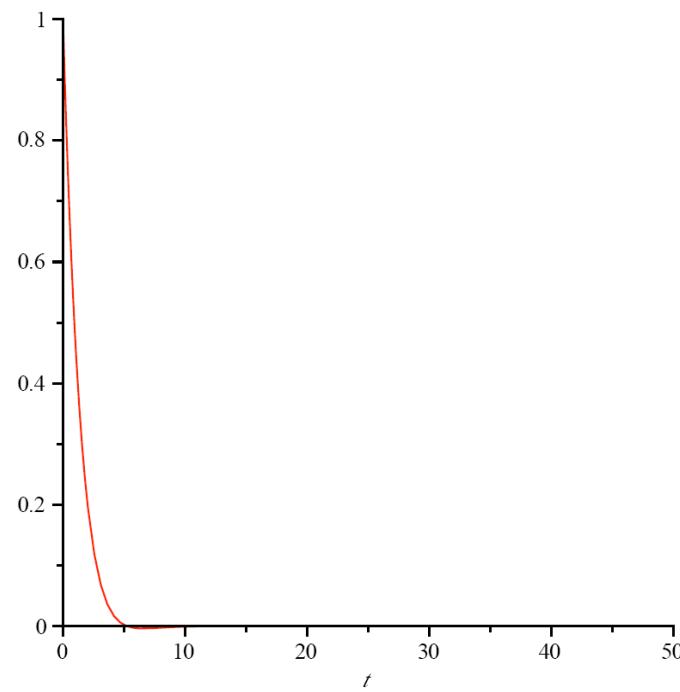


- Root node $\gamma=0$

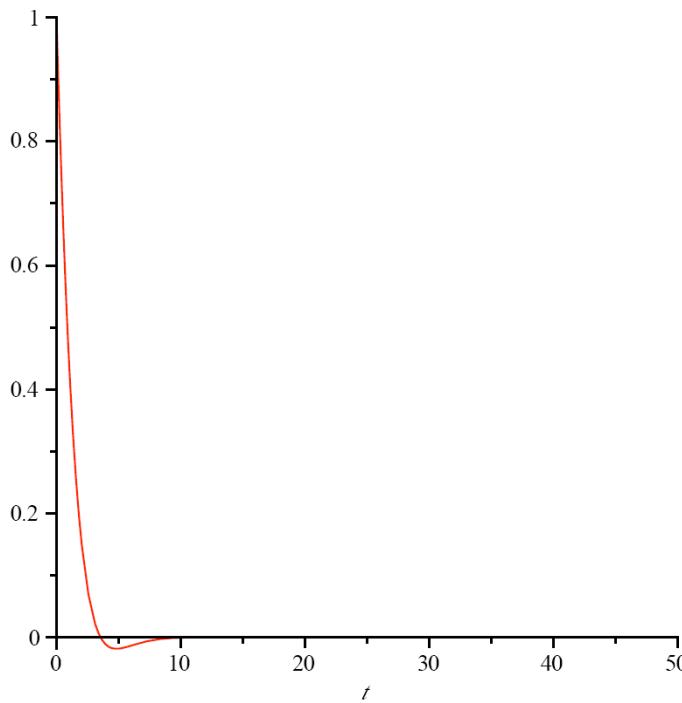


- Perturbation solution

$$y(t) = \exp(-(\gamma_i + \beta)) \cos(\sqrt{\omega_i}t)$$



- Root node $\gamma=0.2$

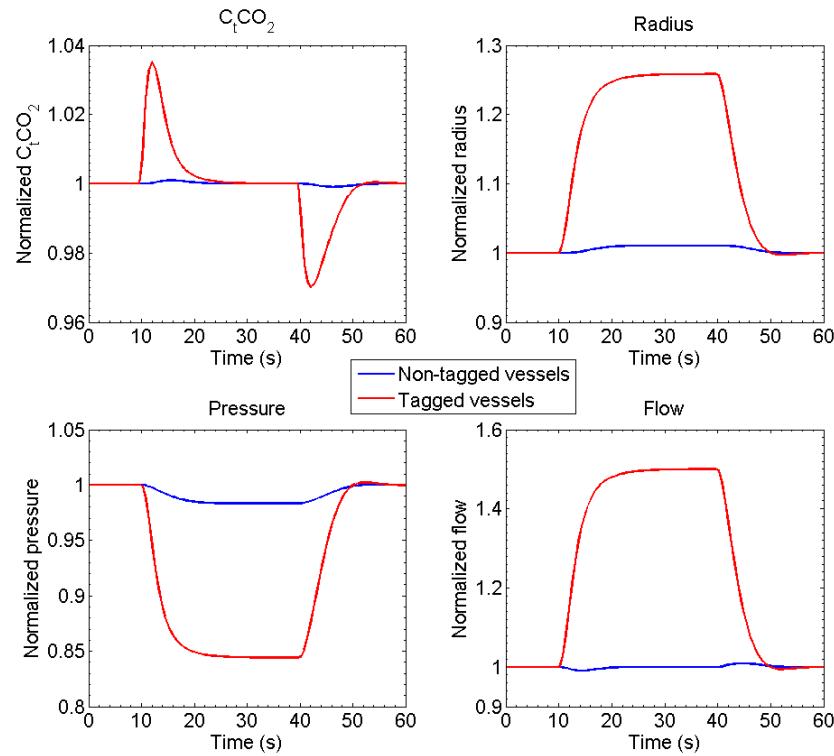
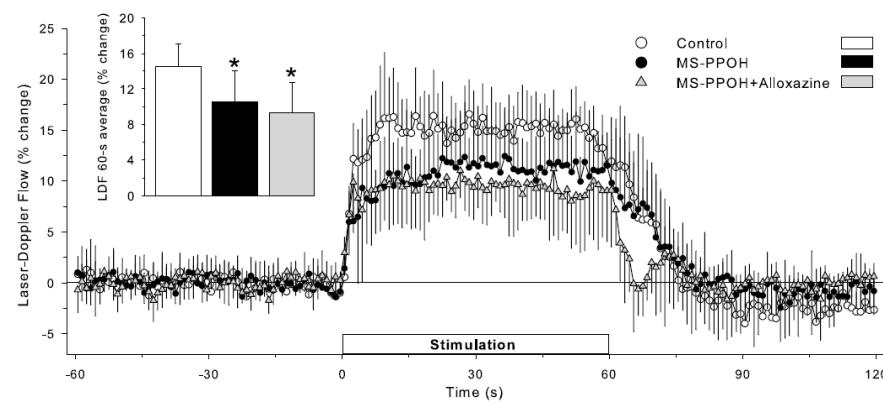


- Terminal node $\gamma=0.2$



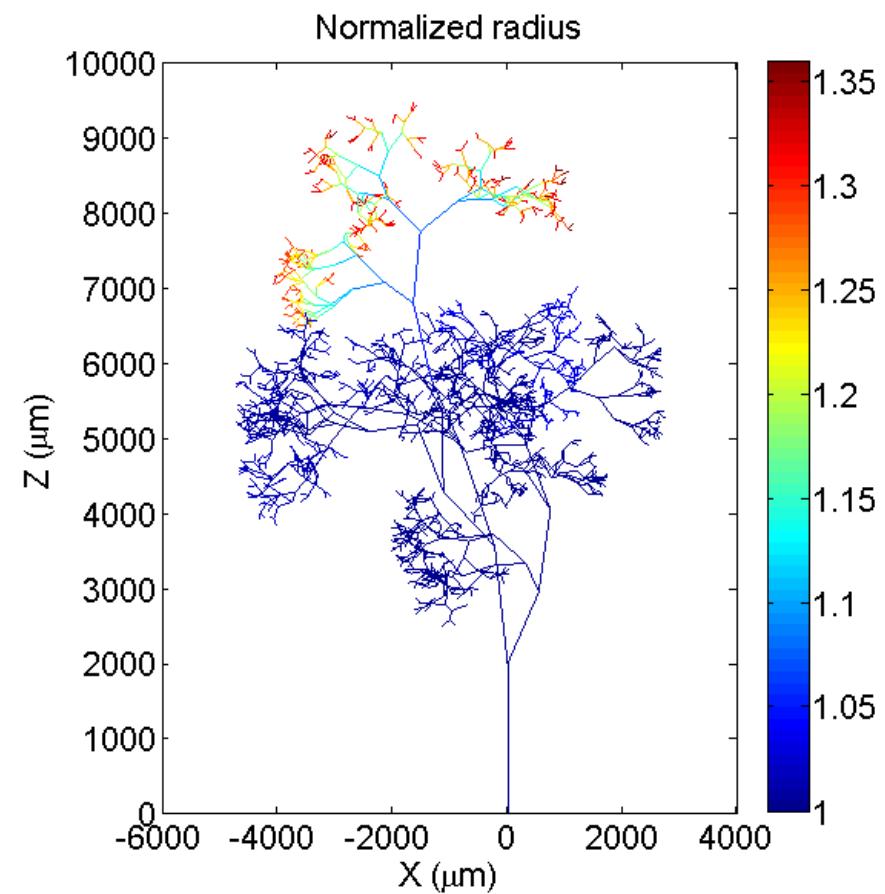


- Full non-linear solutions for the “Tagged” Asymmetric tree
- Averaged radius plots (vs t) , metabolic rate increased at t=10, returned to original at t=40
- Red lines tagged vessels (average), blue lines untagged vessels





- Radius distribution in tree

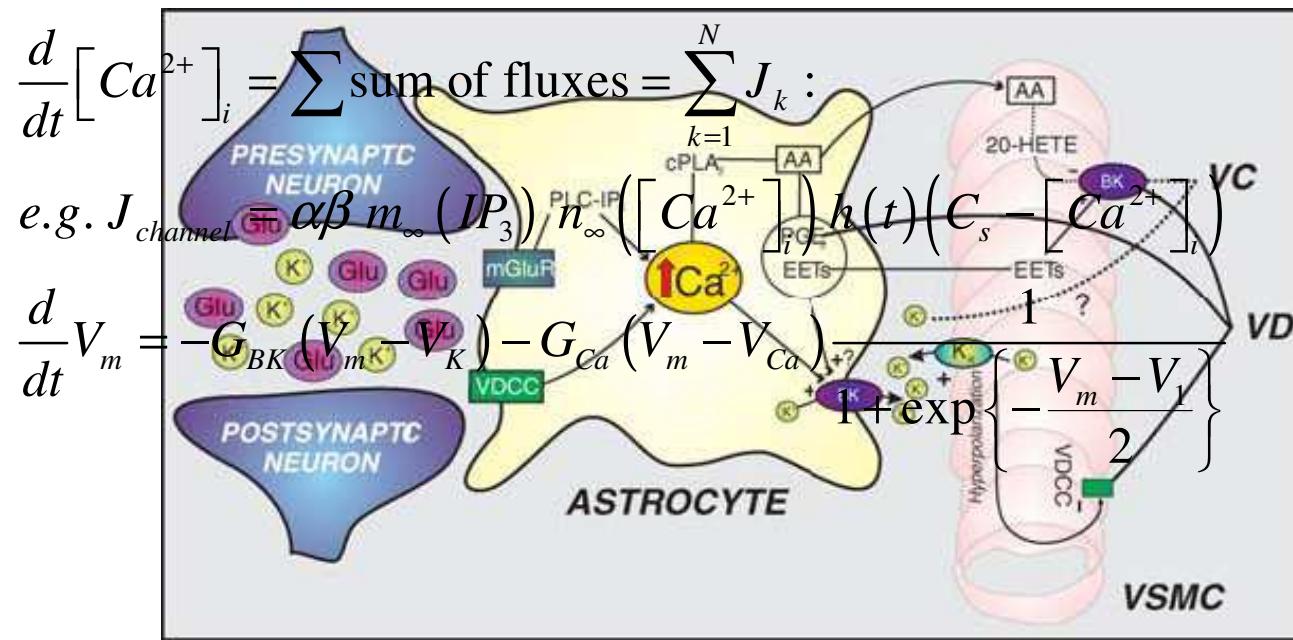




- But the 2 equation CO₂ model is a negative feedback system .
- Neuronal activity -> alkaline extracellular space (should be acidic with CO₂).
- The neurovascular coupling is a feed forward system. So
- Need cellular complexity.



- Neurovascular coupling via the astrocyte
 - Glutamate receptors mediate IP₃ and induce Ca²⁺ from stores
 - Ca²⁺ mediates the BK channel producing extracellular K⁺
 - ODEs modelling pathways





- Equation of wall motion (contraction/dilation of the SMCs) => cylindrical/circumferential stress
- Kelvin- Voigt-Maxwell (visco-elastic)

$$\sigma_{\theta\theta} = \frac{E(\textcolor{red}{F})}{1-\xi^2} \left[\frac{R-R_0}{R_0} + c_1 \left(\frac{R-R_0}{R_0} \right)^2 \right] + \varphi \frac{dR}{dt} c_2 \textcolor{red}{F}$$

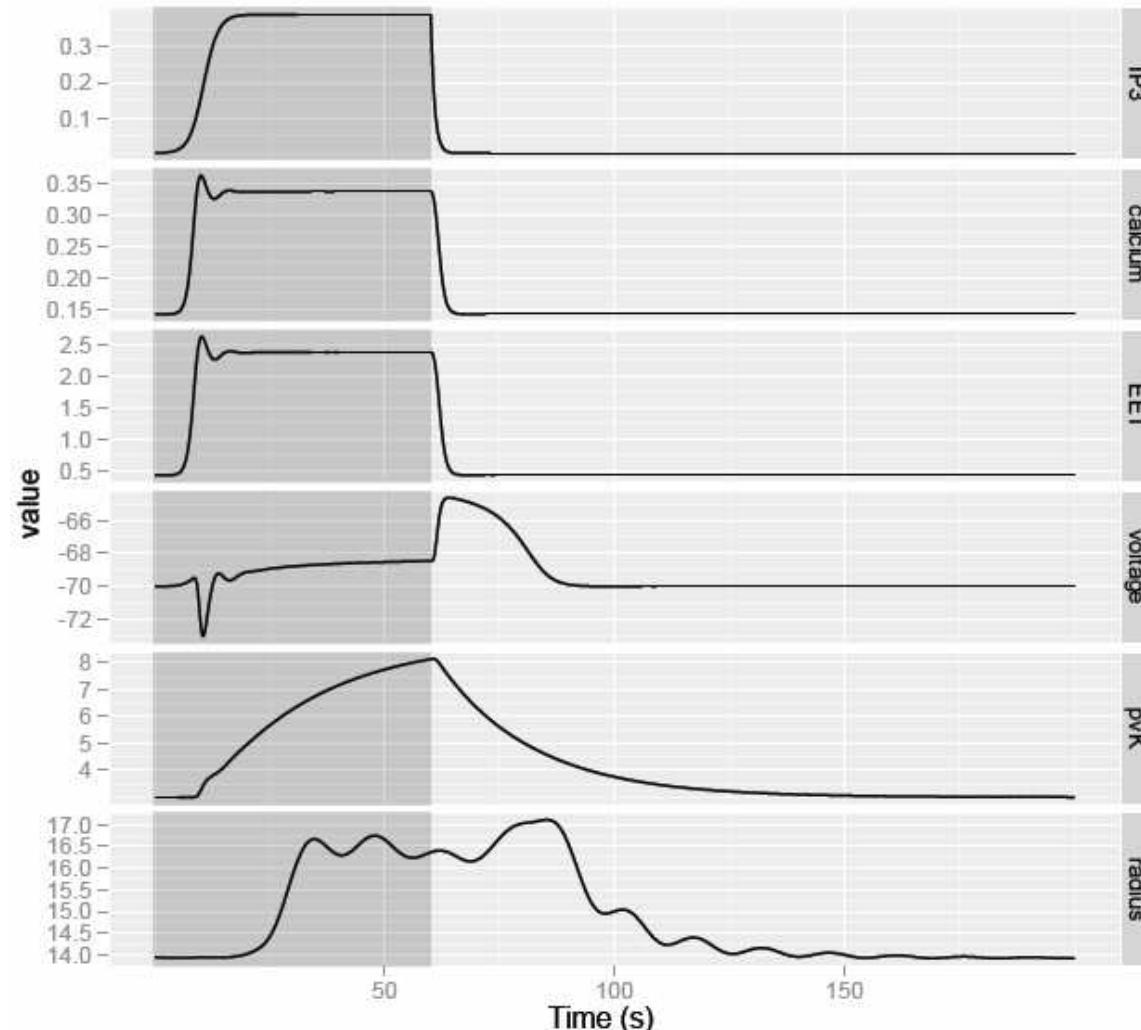
$$R = R_0 (1 + \eta)$$

$$\rho_w h_0 R_0 \frac{d^2\eta}{dt^2} + \varphi h_0 \frac{d\eta}{dt} + \frac{h_0 E(\textcolor{red}{F})}{R_0 (1 - \xi^2)} [\eta + c_1 \eta^2] = \Delta p - \frac{h_0}{R_0} c_2 \textcolor{red}{F}$$

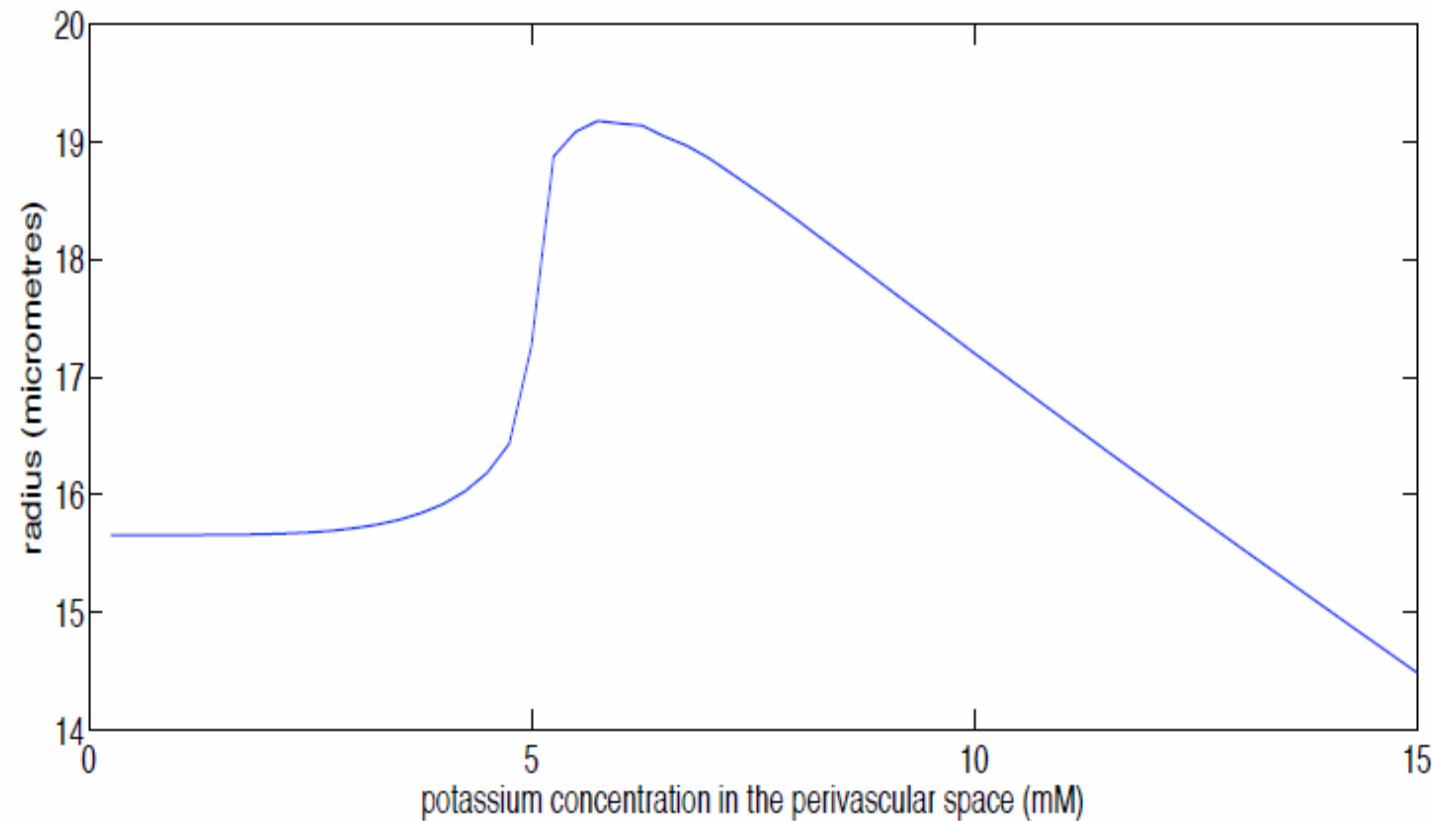




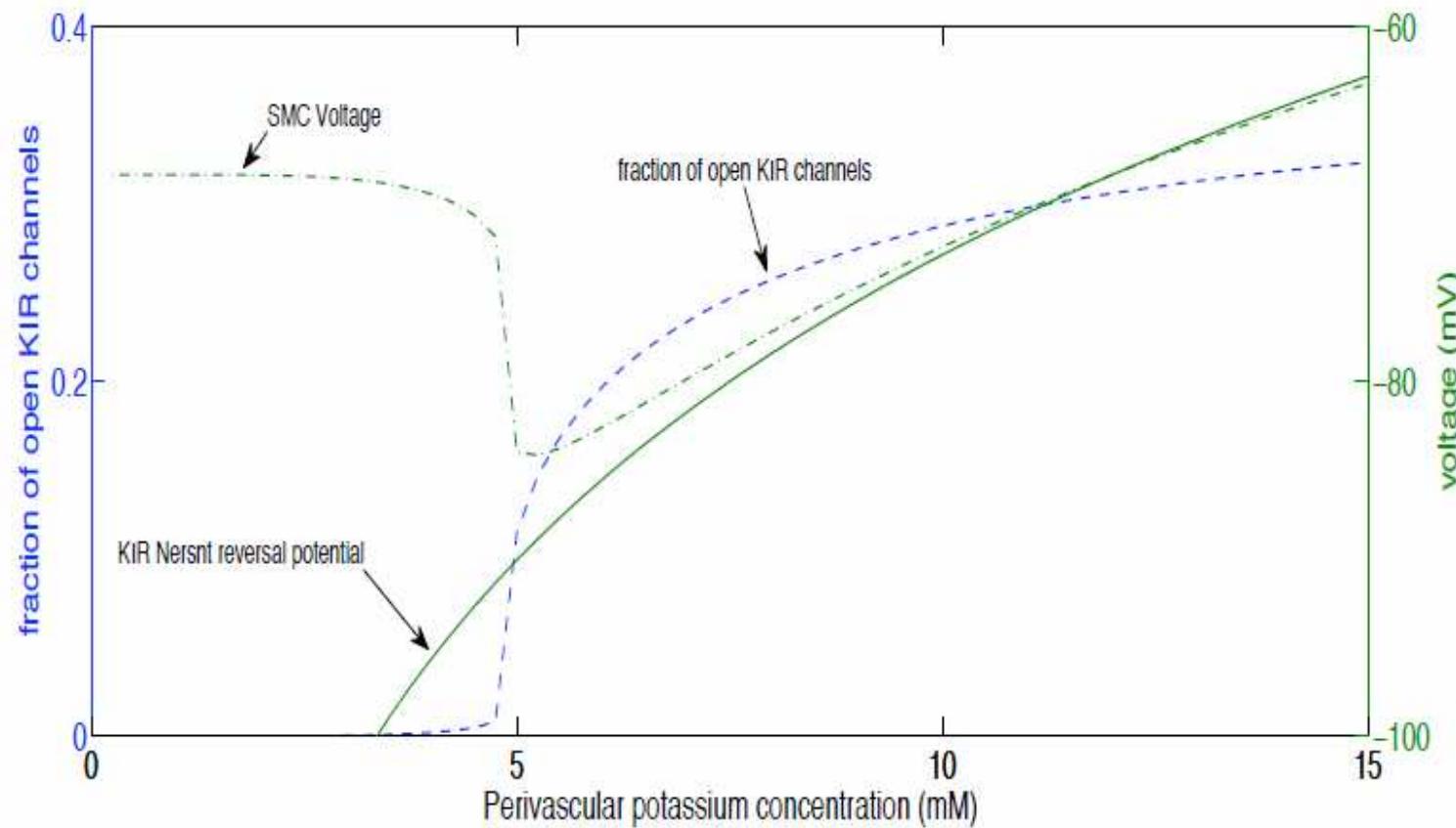
- Neurovascular coupling dynamics



- Radius vs K⁺ in perivascular space



- Extra cellular K+, link to arteriole via inward rectifying ion channels on SMC

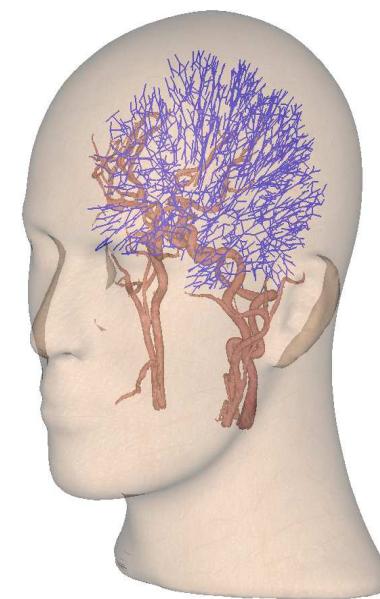
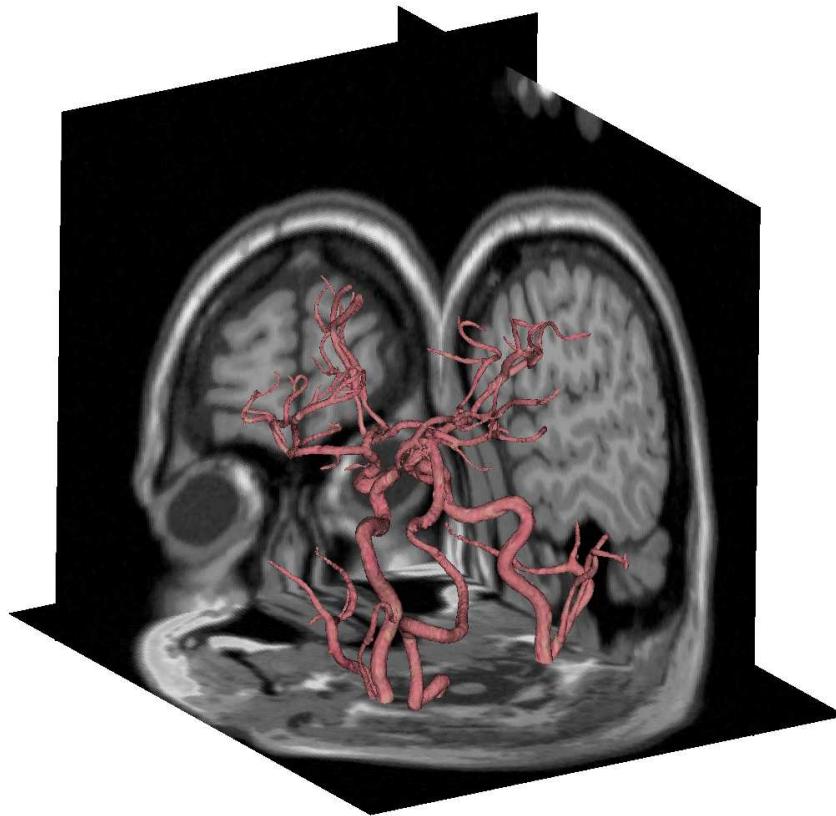




- How to link large vessels with small?
 - System Level Acceleration
 - linking two different architectures on a single problem
 - MPP Blue Gene for the binary tree
 - SMP p-575 for the 3D fluid dynamics



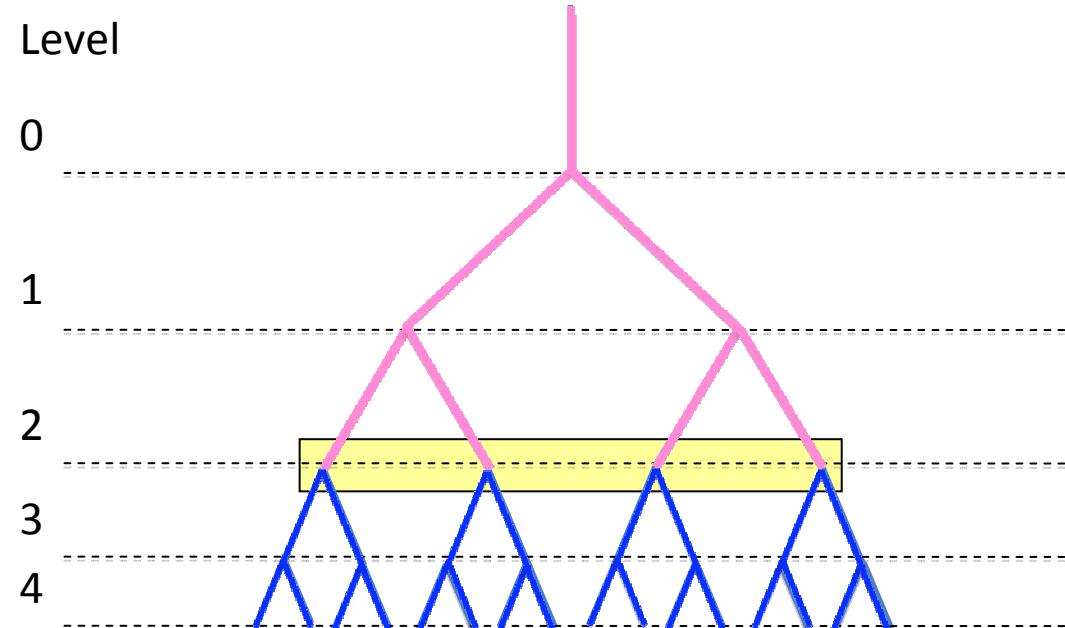
- 3D vascular trees form the outlet boundary conditions





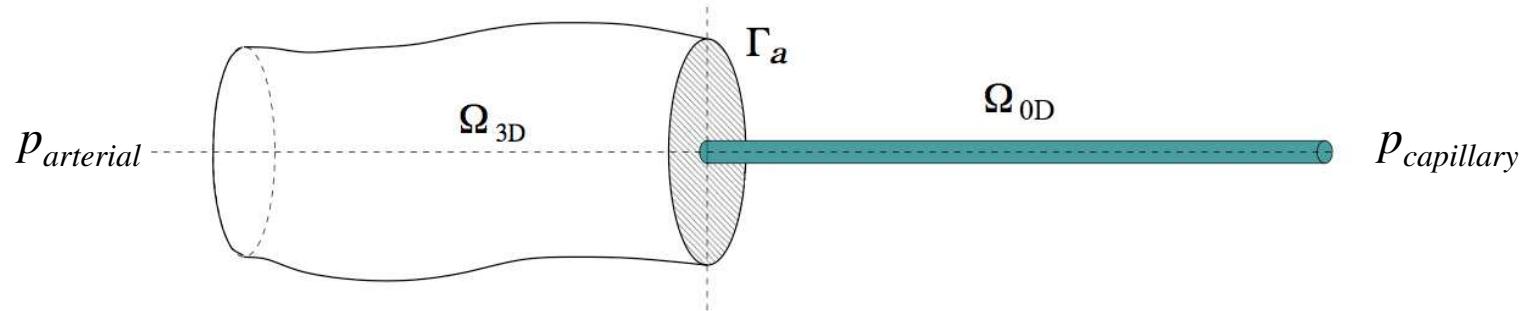
Partitioning a Tree for parallelism

$$\text{Num segments Per Tree} = \sum_{i=1}^N 2^i + 1$$





0D – 3D Coupling



$$A_{3D} = A_{0D}$$

$$Q \dashrightarrow$$

$$Q_{3D} = \int_{\Gamma_a} \mathbf{u} \cdot \mathbf{n} dA = Q_{0D}$$

$$\dashrightarrow p$$

$$\bar{p}_{3D} = \frac{1}{\Gamma_a} \int_{\Gamma_a} p dA = p_{0D}$$



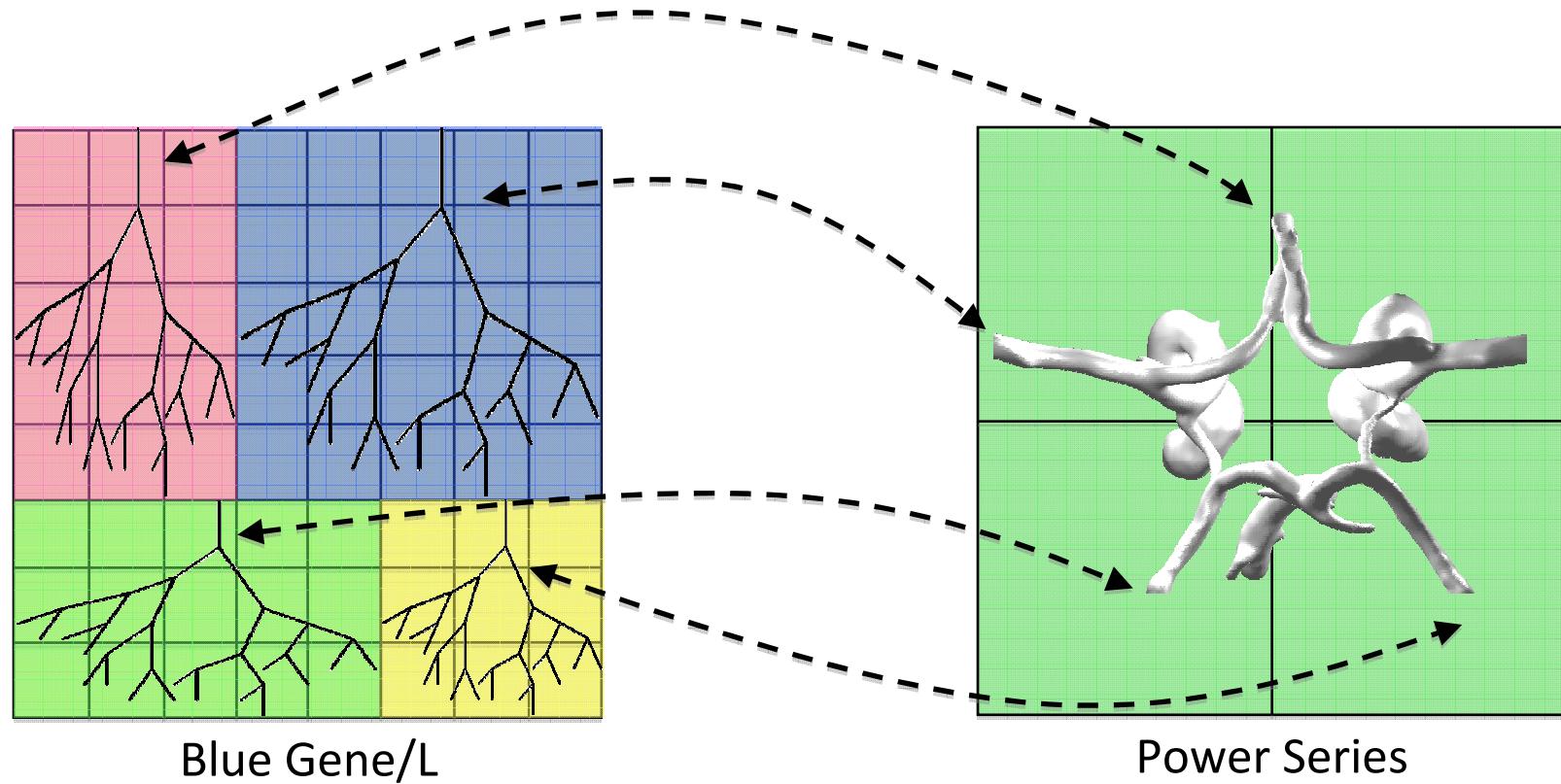


- BG: Read input file (artery labels and port numbers)
- BG: creating communicators
- BG: creating the trees (each processor creates a portion of a tree)
- BG: root processors connect to p575
- BG: loop waiting for p575 to send pressure request





Heterogeneous computing : System Level Acceleration (SLAMM)



- Outer loop until convergence of pressure variation
 - BG: calculate resistance
 - BG: Flow rate received by root processor
 - BG: calculates root pressure
 - Loop down tree to calc pressures and flow rates
 - Autoregulation loop change radii using pressures and flow rates
 - Loop up the tree to re-calculate resistance
 - Loop down to calculate pressures and flow rates
 - BG: root pressure sent to p575



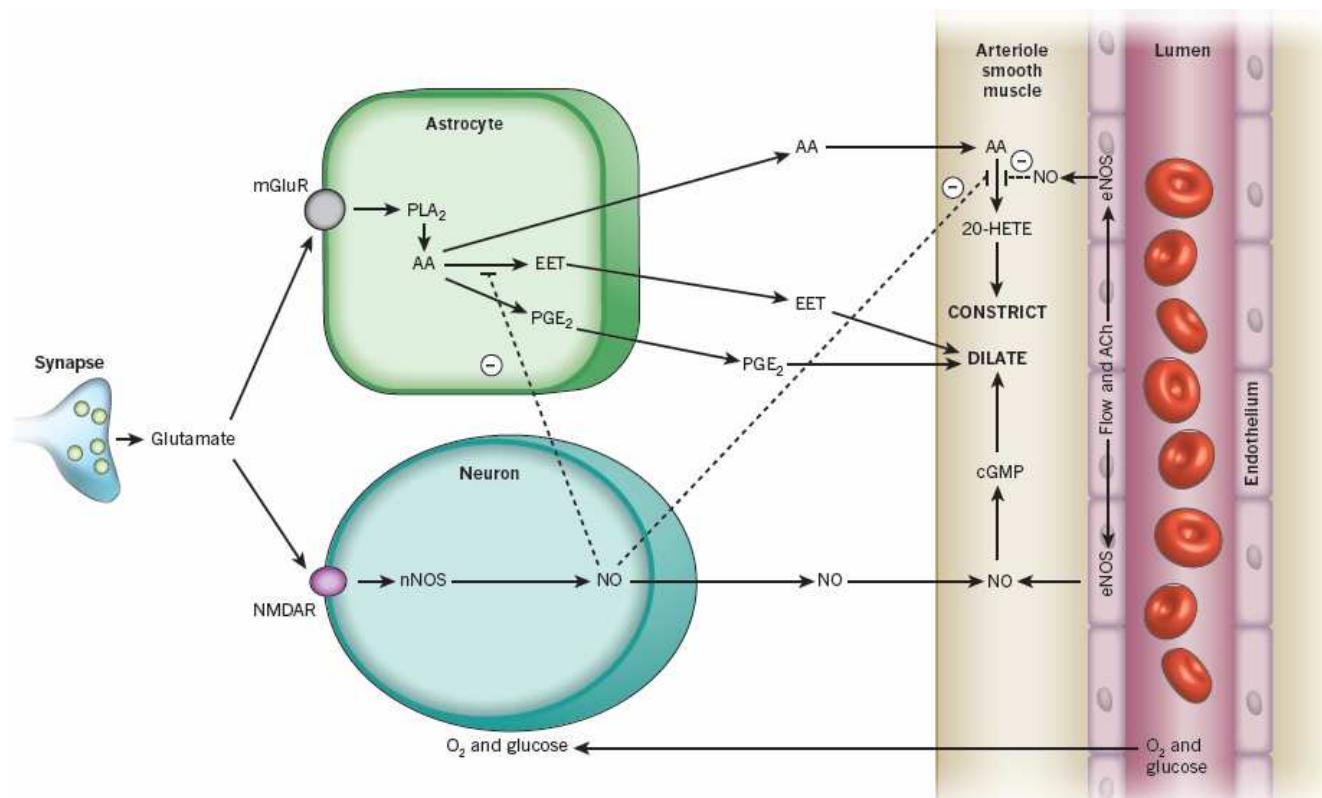


The Challenges

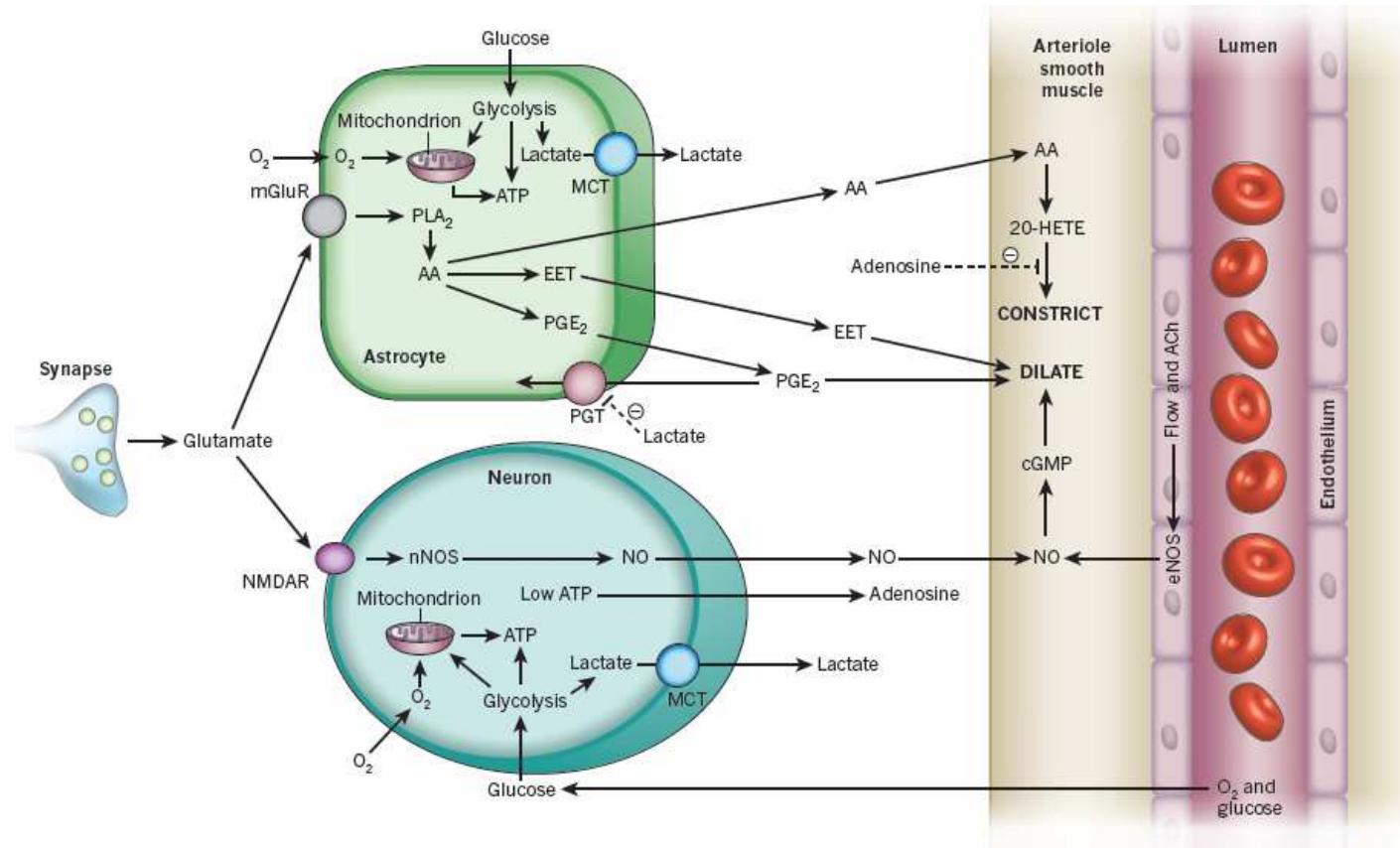
- Validation by in vivo experiments (blood flow makes a difference)
- Collateral arterial networks
- How far into molecular mechanisms do we need to go ?
- Load balancing in heterogeneous computing (comp sci issue)
- The whole human vasculature ?



- Future Work (inhibition by NO)
 - Atwell et al (Nature 2010)



- Future Work (mitochondrial energy)





• Future Work

- Improve tree growing algorithms to be constrained by regions of the brain
- Implement a compliant 1D model between the 3D and 0D models
- Capillary network perfusion models at the terminal end of vascular tree
- Emboli motion in the vascular network (a precursor to stroke prediction)
- Cortical spreading depression models





- Thanks to :
- Hannah Farr, Phil Wilson, HuaXiong Huang, Navid Safaeien, Nick Jaensson, Steve Moore, Thomas van Kampen, Samara Alzaidi, Robin Chatelin.
- At IBM (New York):
Jim Sexton and Kirk Jordan.

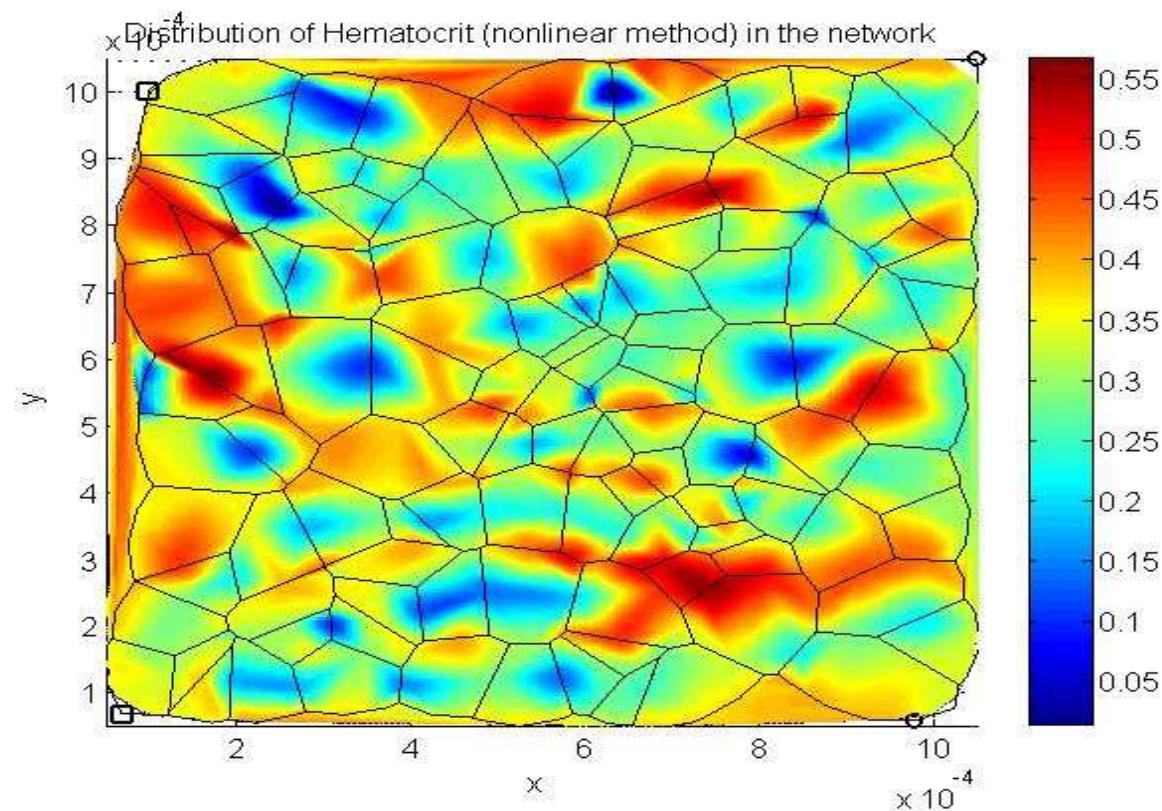






Capillary Models

- Network (voronoi from uniform distrn of points in the plane)
- Feeding arteriole to the left , venule to the right.



Stroke Models

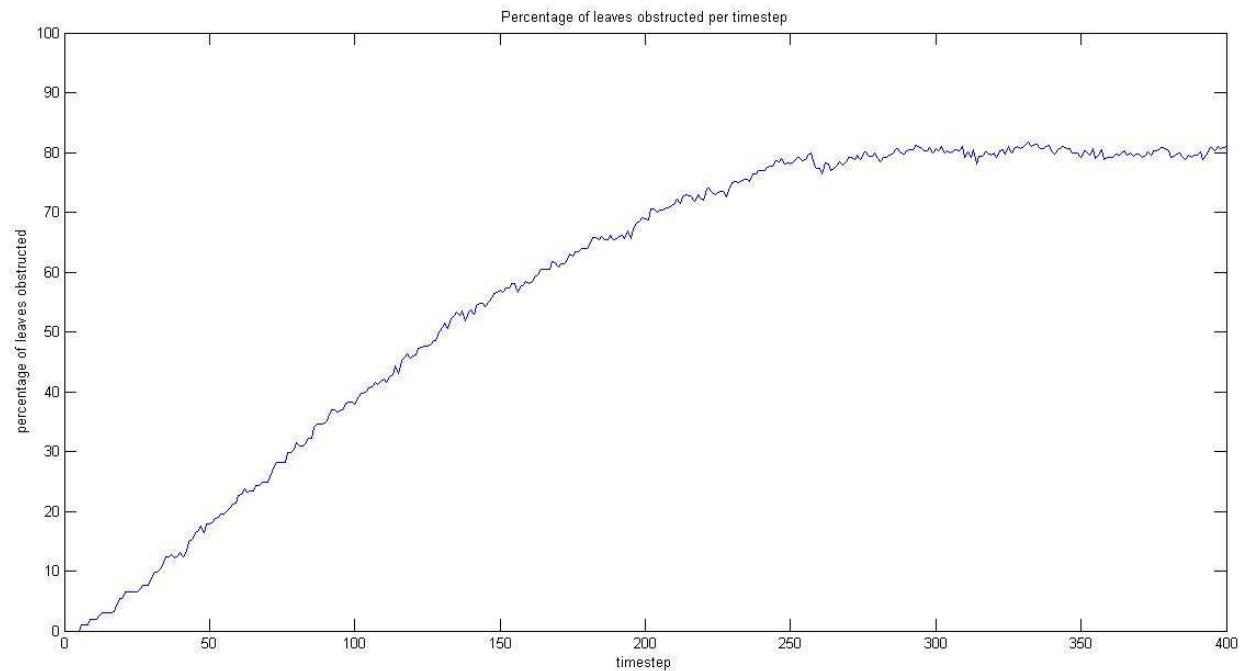
- Emboli can be “released” into the binary tree
 - At each time step
 - An embolus is released
 - Emboli in the tree are moved from a parent to a daughter artery (a function of flow).
 - Test for emboli blocking an artery
 - Emboli are “dissolved” => $dr/dt = \text{constant}$





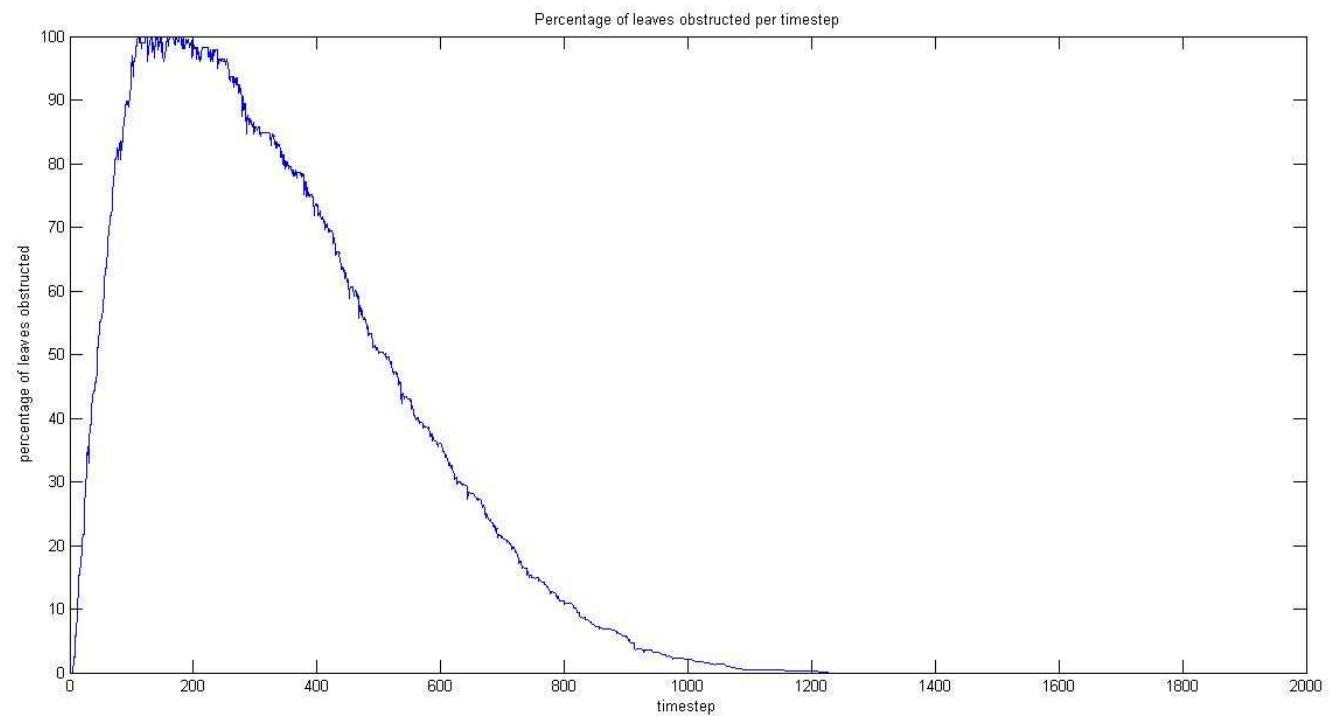
- % terminal arteries blocked vs time

$$\bar{r} = 20\mu m; \sigma_r = 5\mu m;$$





- % terminal arteries blocked after finite time release of emboli
- Released stopped at t= 150 secs. (dissolution rate of 100 μm / hour).



- Myogenic models (Ermentrout)

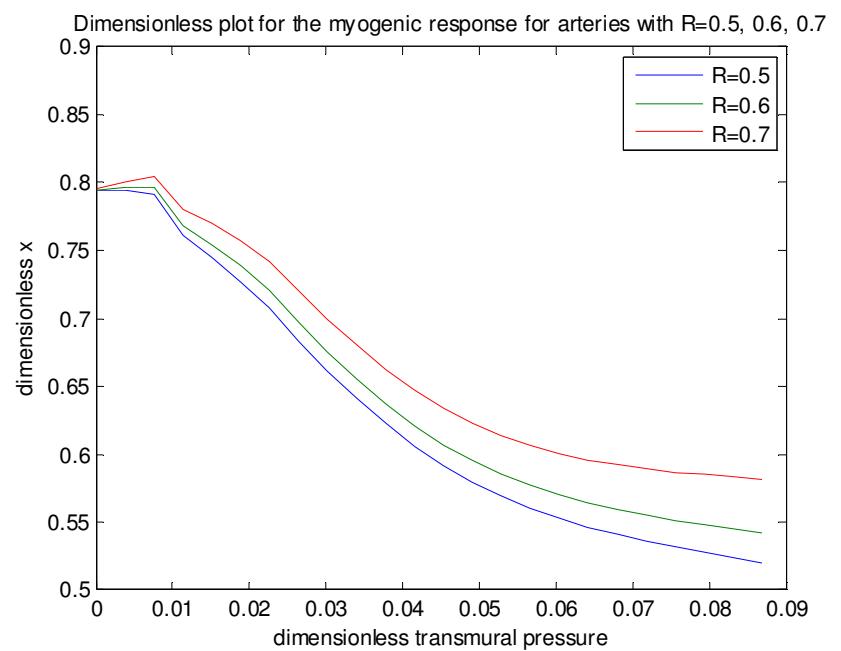
$$m_{\infty} = \frac{1}{2} \left(1 + \tanh \left(\frac{v - v_1}{v_2} \right) \right); v_1 = v_1(p)$$

$$\frac{dv'}{dT} = -(g_L'(v' - v_L') + g_K' \cdot n'(v' - v_K') + m_{\infty}'(v' - 1))$$

$$\frac{dC_{a_i}'}{dT} = -\rho [m'_{\infty}(v' - 1) + k'_{Ca} C_{a_i}']$$

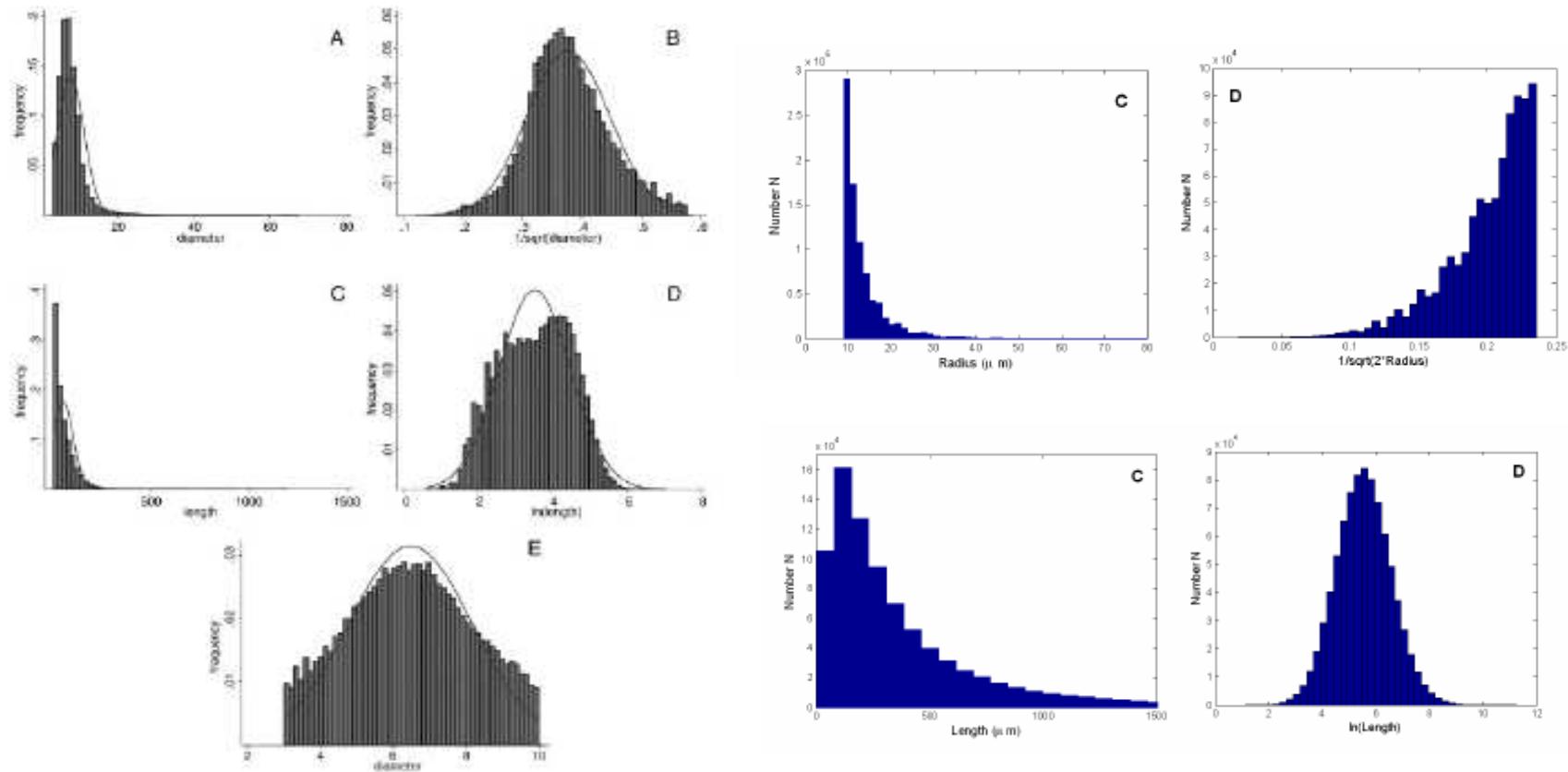
$$\frac{d\omega'}{dT} = k_{\psi} \left(\frac{\psi'}{\psi_m + \psi} - \omega' \right)$$

$$\frac{dx'}{dT} = \frac{\sigma_0^{\#} \cdot S}{x_0 \cdot g_{Ca}} \frac{C}{g_{Ca}} \cdot (f_{\Delta p}' - f_x' - f_u')$$





- Cerebro-vasculature :Lauwers et al data on cerebrovascular morphometry





Blue Gene loop times

levels of tree		7	9	11	13	15	17	19	21		X6 efferent arteries
# proc	17	0.005	0.001	0.003	0.0108	0.0427	0.2354	0.7512	2.8218		16.9308
	33	0.007	0.001	0.002	0.0058	0.0217	0.1348	0.3919	1.4276		8.5656
	65	0	0.0015	0.0019	0.0039	0.0119	0.0764	0.2042	0.7195		4.317
	129	0	0.0026	0.0028	0.0038	0.0078	0.0482	0.1121	0.3688		2.2128
	257	0	0	0.005	0.0055	0.075	0.0317	0.0635	0.1911		1.1466

P-575 iteration times

# elements (millions)	# proc	1	4	8	16
0.5		76.37	18.07	8.98	6.83
1		140.4	38.1	19.56	13.95
2.5		398.7	92.89	47.01	31.8
5		758.1	183.98	87.96	61.28
10		1516.2	367.96	175.92	122.56

