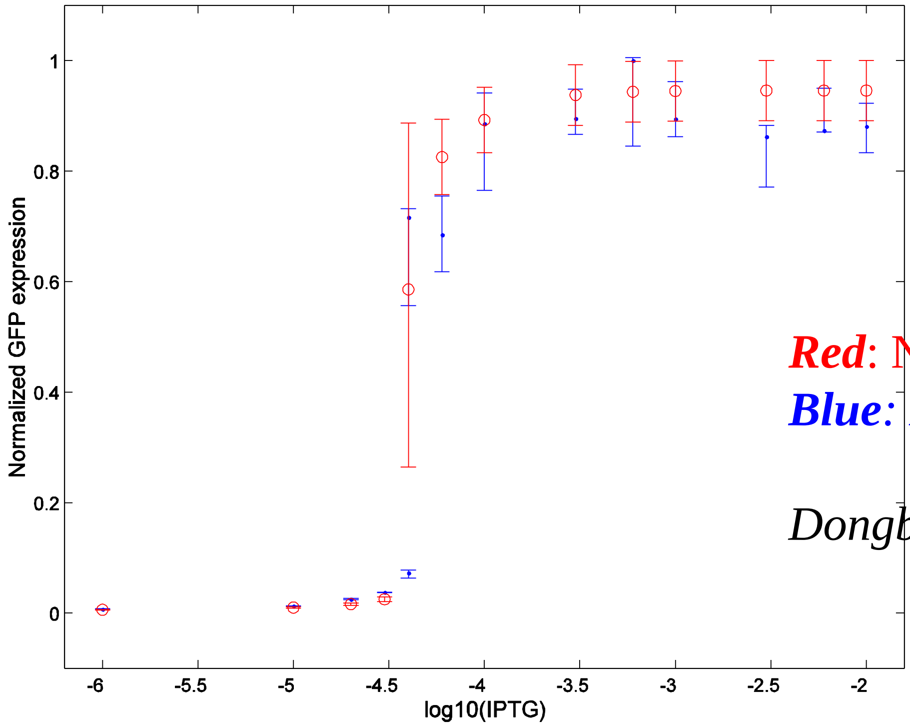
Uncertainty Quantification in Bio-Medicine

Genetic toggle Switch – Nature, vol. 403, 2000



Red: Numerical error bars

***Blue**: E*xperimental error bars (blue)

Dongbin Xiu, (Purdue University)

George Em Karniadakis

Applied Mathematatics, Brown University

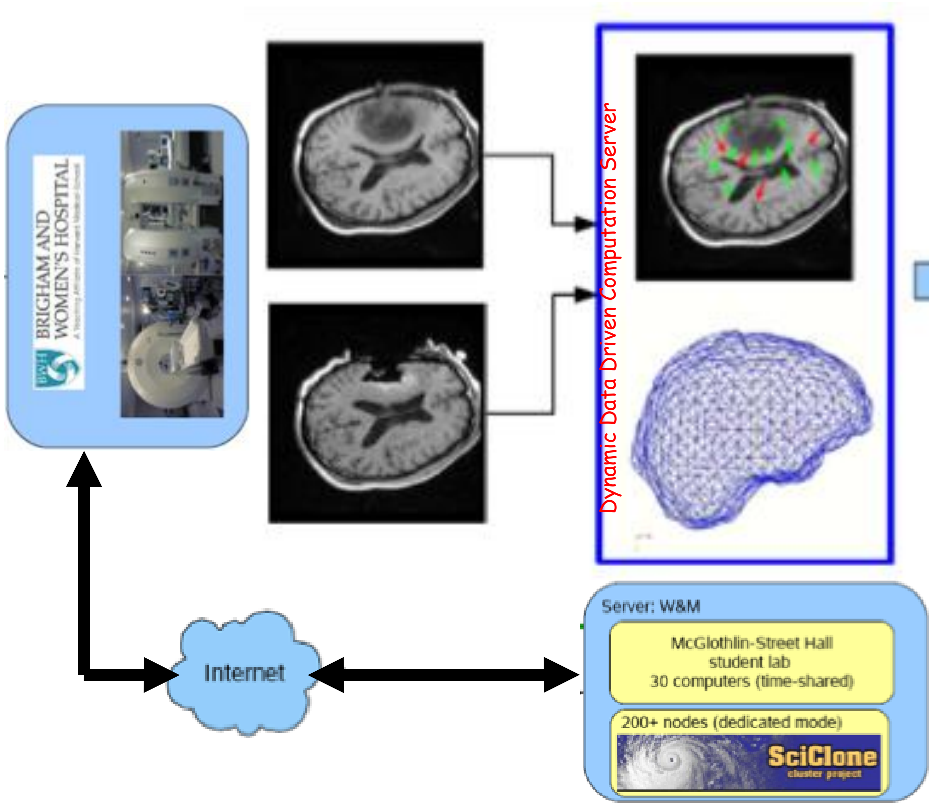
The CRUNCH group: www.cfm.brown.edu/crunch

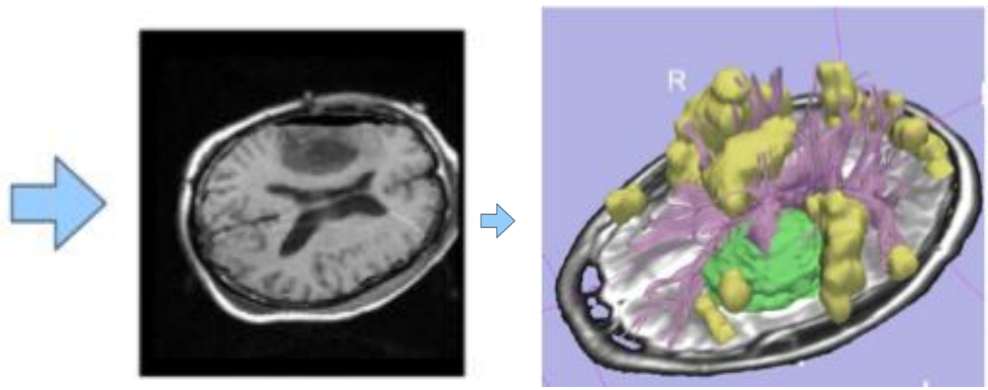
CRUNCH GROUP

Near Real-Time 3D Non-Rigid Registration for Image Guided Neurosurgery

Center for Real Time Computing (Dr. Nikos Chrisochoides)

Harvard Medical School, BWH (Dr. Ron Kikinis and Dr. P. Black)



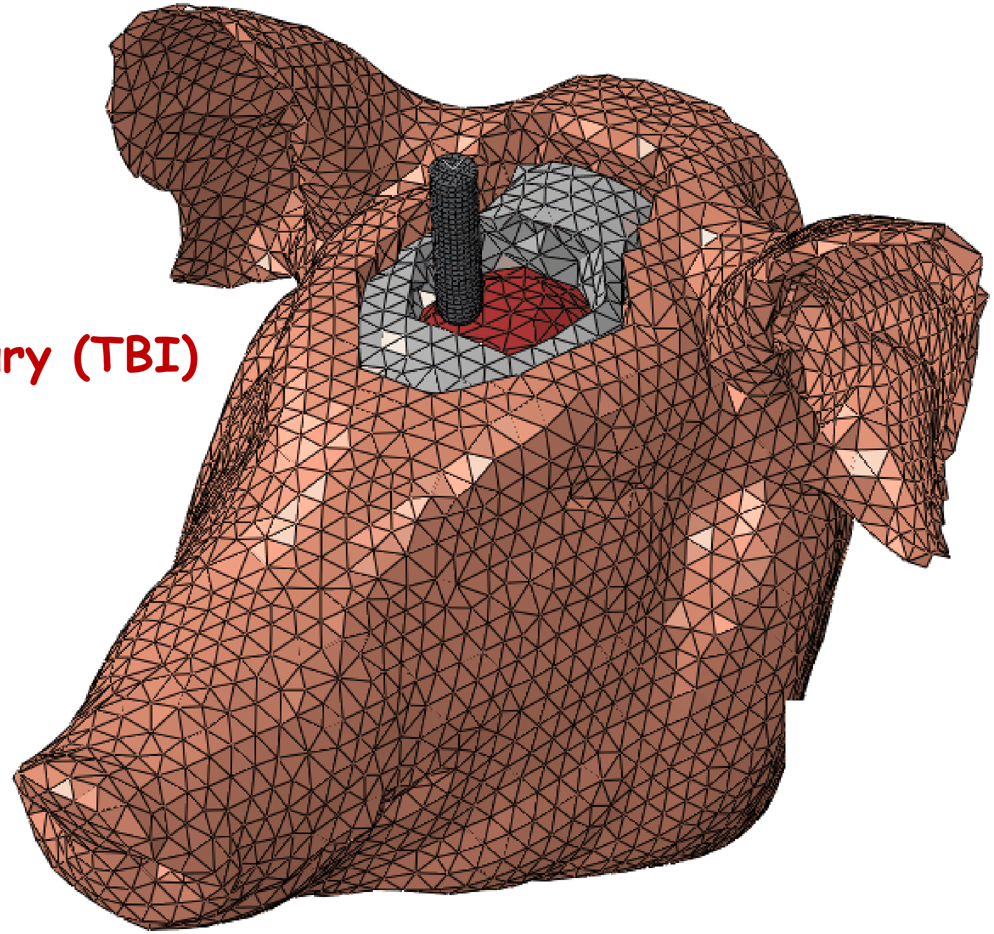


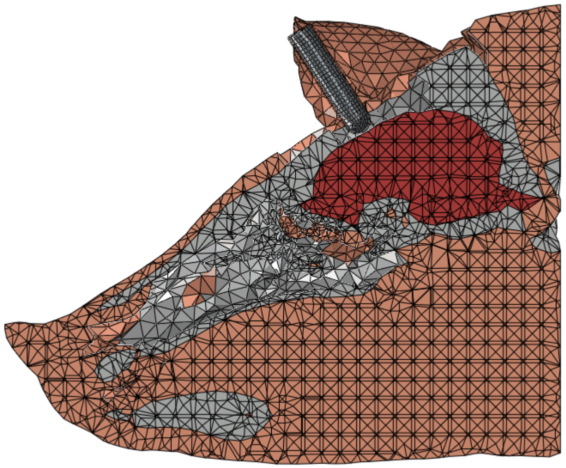
- Requirements:
- accurate (less than 0.75mm)
- fast (< 1 min end-to-end)
- fault-tolerant, easy-of-use, etc…

Supported in part by NSF grants (Dr. F. Darema): CSI-0719292, ITR-0426558, ACI-0312980 and John Simon Guggenheim Foundation.

Constitutive Equation Under Uncertainty

Traumatic Brain Injury (TBI)

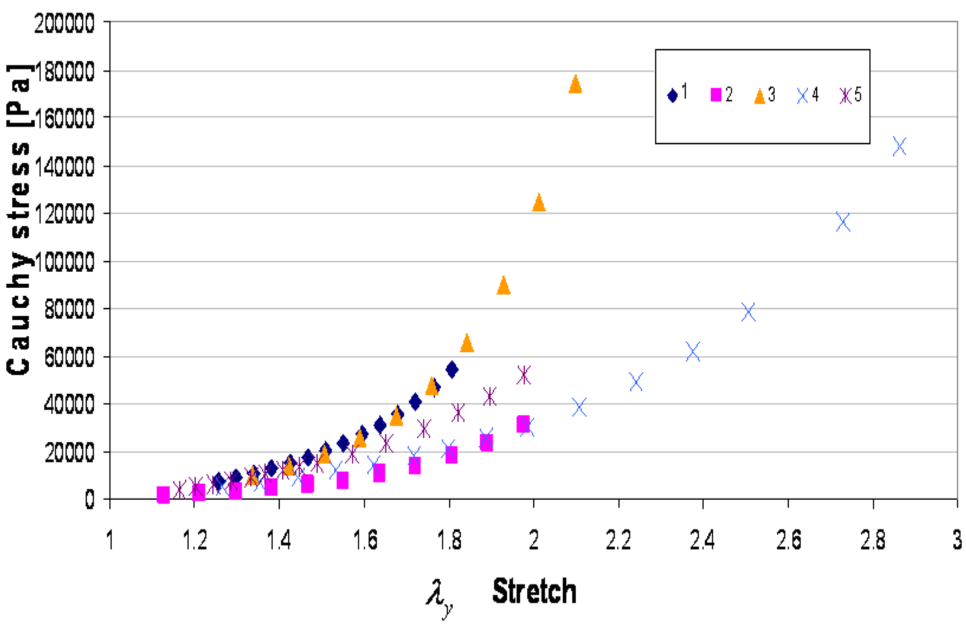




Work at MIT & MGH by:
Thibault Prevost, Subra Suresh and Simona Socrate
Supported by US Army

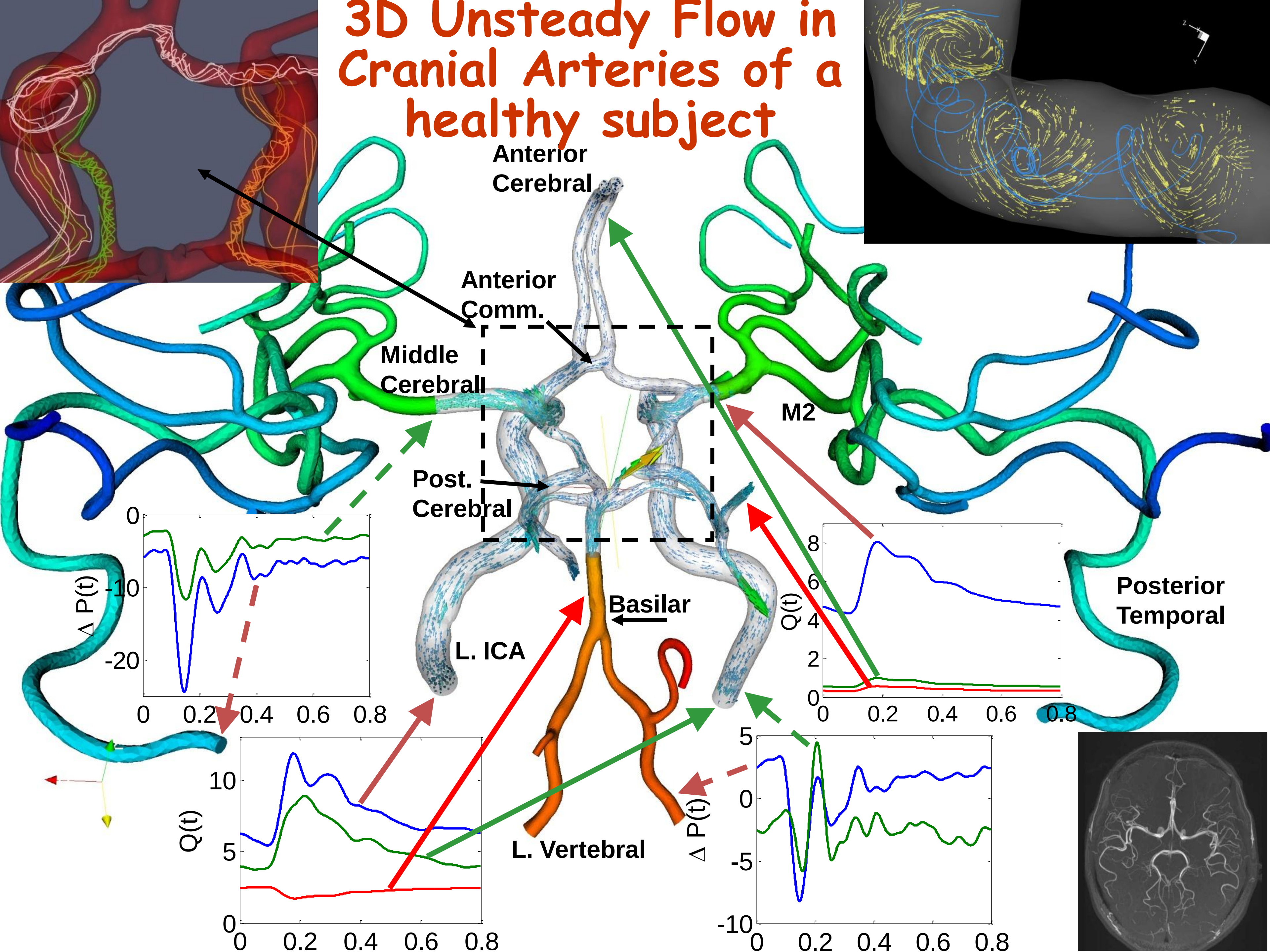
Arterial Wall Mechanics (Zohar Yosibash, Ben Gurion)

Cauchy stress vs stretch - 5 ITA segments

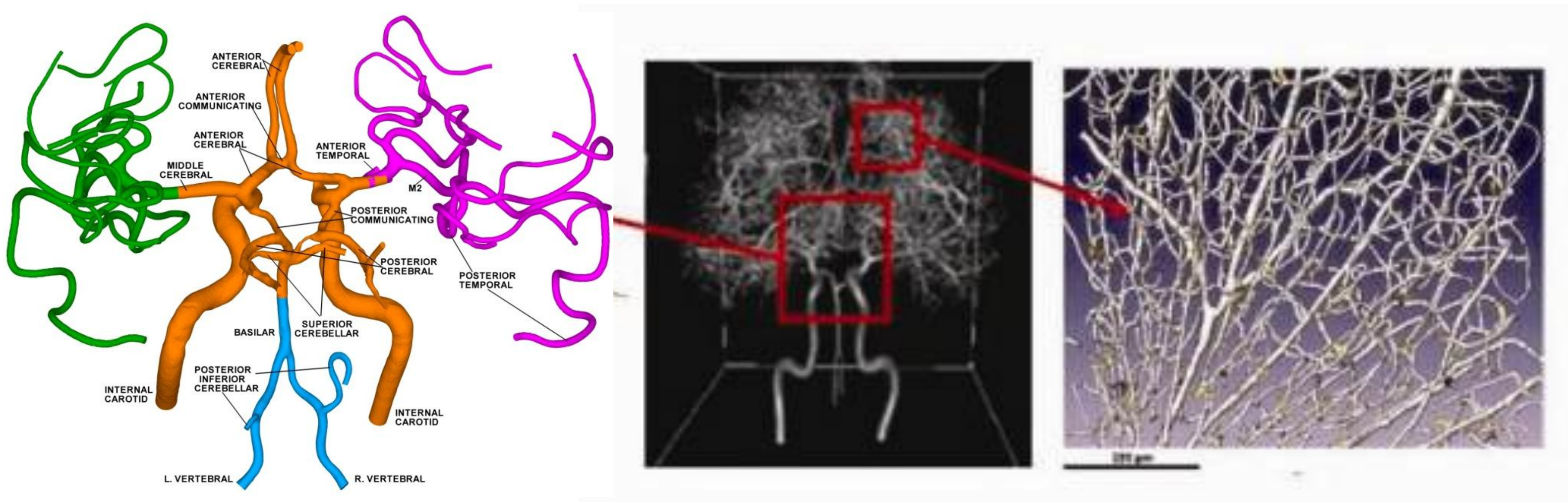


Stress vs stretch – 5 ITA's segments produce different response.

3D Unsteady Flow in Cranial Arteries of a healthy subject



Multiscale Modeling: Three levels (MaN-MeN-MiN)



1. Macrovascular Network (MaN): Image-Based, down to 0.5 mm (3D NS)
2. Mesovascular Network (MeN) : Stochastic 1D PDE, down to 10 microns
3. Microvascular Network (MiN): Stochastic replicas of capillary beds (Darcy & DPD)

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By Stephanie Pappas, TechNewsDaily Contributor
29 April 2010 5:57 PM ET

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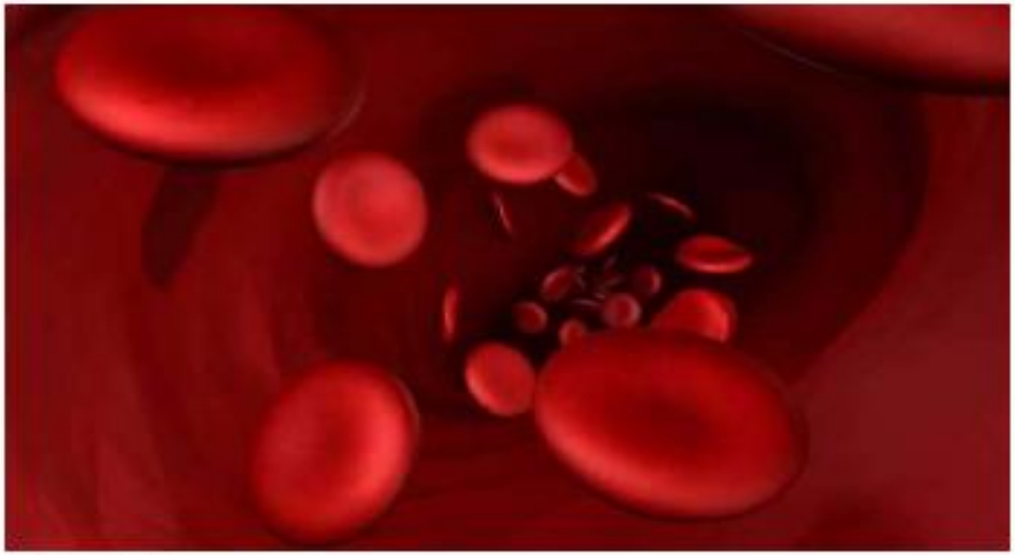

Credit: Dreamstime

Mapping the blood stream

Think you have a pretty good idea of how your blood flows? Think again. The total length of all of the veins, arteries and capillaries in the human body is between 60,000 and 100,000 miles. To map blood flow through this complex system in real time, Brown University professor of applied mathematics George Karniadakis works with multiple laboratories and multiple computer clusters.

In a 2009 paper in the journal Philosophical Transactions of the Royal Society, Karniadakas and his team describe the flow of blood through the brain of a typical person compared with blood flow in the brain of a person with hydrocephalus, a condition in which cranial fluid builds up inside the skull. The results could help researchers better understand strokes, traumatic brain injury and other vascular brain diseases, the authors write.

Pre-diction versus Post-diction

High Performance Computing:

- Are we computing the wrong answers faster?

Multi-University Research Initiative (AFOSR/MURI)

- Brown, MIT, Caltech, Cornell (Brown leads)

Multi-Scale Fusion of Information for Uncertainty Quantification and Management in Large Scale Simulations

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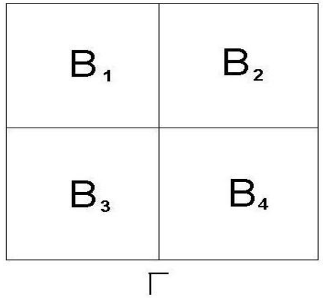
Representation of a Random Process

$$T(\mathbf{x},t;\xi(\omega)) = \sum_{i=0}^{\infty} T_i(\mathbf{x},t)\Psi_i(\xi(\omega))$$

- $T(\mathbf{x},t;\omega)$ - **Random process**
  - $(\mathbf{x},t)$ - **Space/Time dimensions**
  - ω - **Random dimension**
- $T_i(\mathbf{x},t)$ - **Deterministic coefficients**
- $\Psi_i(\xi)$ - ***Generalized*** **Polynomial Chaos (gPC)**

[*Xiu & Karniadakis SIAM J. Sci. Comput. 24(2) (2002)*]()

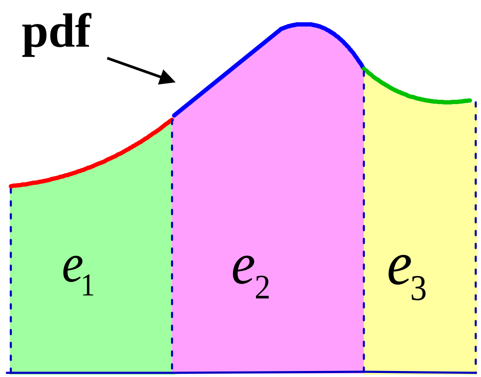
Multi-Element Probabilistic Collocation Method (ME-PCM)



- Decompose Γ into non-overlapping elements B^i
- Define $A_k = \mathbf{Y}^{-1}(B^k)$
- Define new random variable $\eta_k : A_k \to B_k$ on the restricted space $(A_k, \mathcal{F} \cap A_k, P(\cdot|A_k))$ with conditional PDF $\hat{\rho}(x|A_k) = \dfrac{\rho(x)}{P(A_k)}$
- Numerically reconstruct local polynomial chaos basis on each element, orthogonal with respect to $\hat{\rho}$
- Perform PCM on each element. No C^0 requirement on boundaries (measure 0).

$$\tilde{u}(\boldsymbol{x}, \boldsymbol{y}) = \sum_{i=1}^{N_e} \mathcal{I}_{B^i} u_k(\boldsymbol{x}, \boldsymbol{y}) \mathbb{I}_{\{\boldsymbol{y} \in B^i\}} \quad \forall \boldsymbol{x} \in \overline{D}, \ \forall \boldsymbol{y} \in \Gamma$$

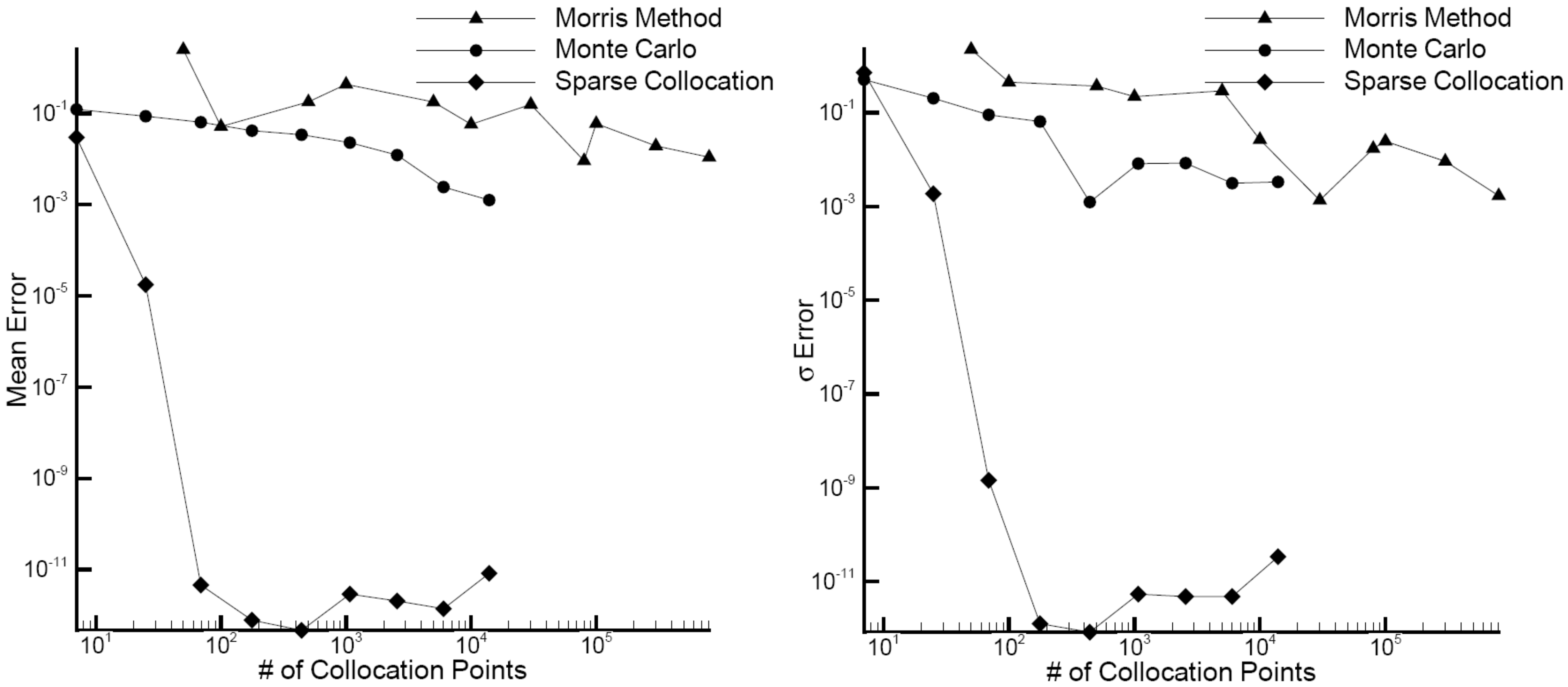
choose spatial discretization method



Convergence Study of Stochastic Sensitivity Methods

$$y = 63e^{4x_1} - 70e^{3x_2} + 15e^{2x_3}$$

$$Mean\ error = \frac{|E_{num}[d_i^j] - E_{ext}[d_i^j]|}{|E_{ext}[d_i^j]|}, \quad \sigma\ error = \frac{|\sigma_{num}(d_i^j) - \sigma_{ext}(d_i^j)|}{|\sigma_{ext}(d_i^j)|}$$



ME-PCM for Sensitivity Analysis

Suppose we have system S whose output X depends on a set of parameters, $R_1,\ldots,R_N$.

$$R_1,\ldots,R_N \rightarrow \boxed{S} \rightarrow X$$

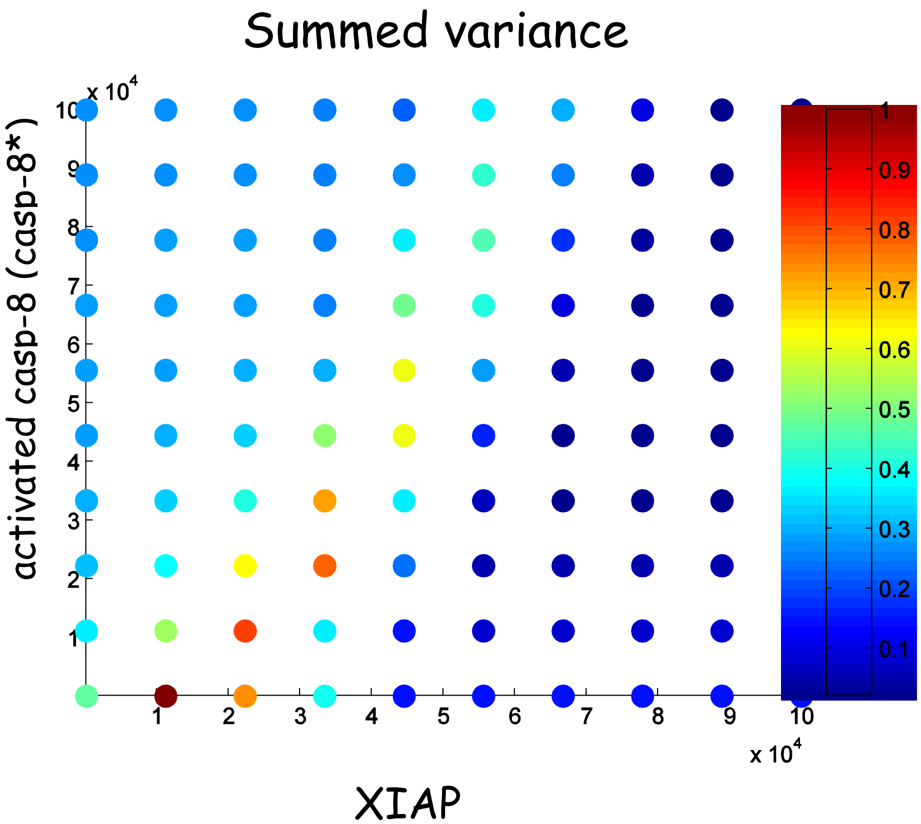
Example **- Apoptosis model**
- $R_1,\ldots,R_N$ -- initial conditions
- S -- set of ODEs modeling the system
- X -- chosen output of interest. For example, X can be the amount of each caspase at a fixed final time, or the integrated value of a particular species over a time period.

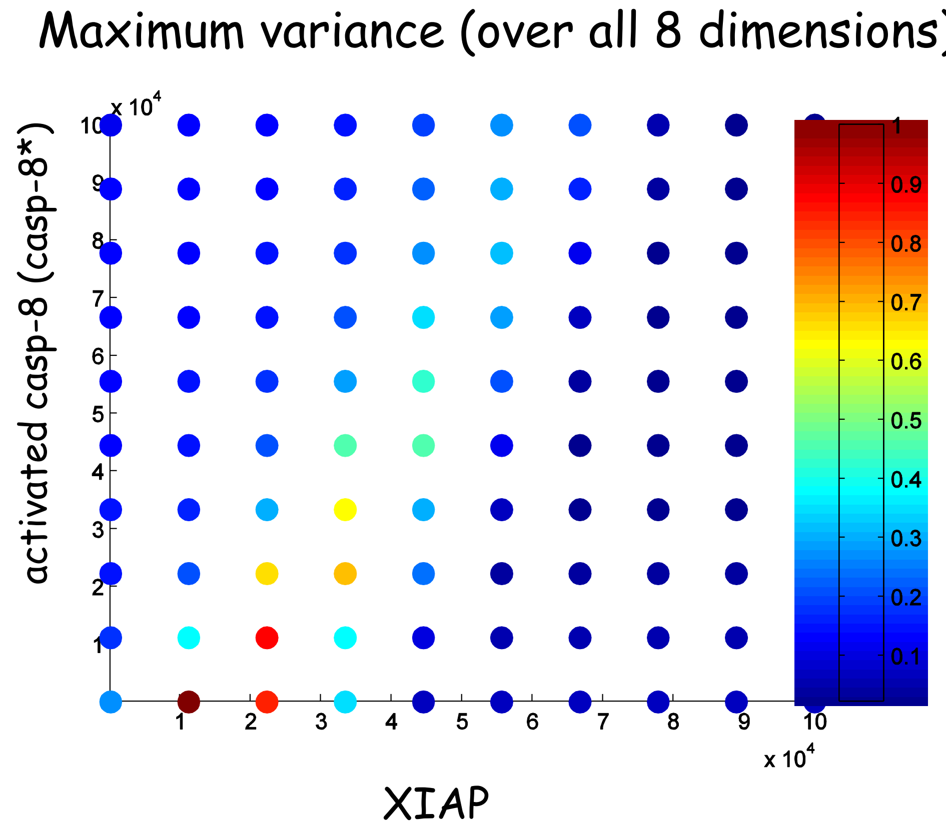
Goal - in what regions of parameter space are the outputs most sensitive?

Procedure (Cast as stochastic problem in which $R_1,\ldots,R_N$ are random variables)
- Define Γ as the N-dimensional parameter space defined by the allowable range of the inputs R_i.
- Define ρ to be the joint density function of $R_1,\ldots,R_N$. (if known, otherwise choose uniform)
- Discretize Γ into non-overlapping N-dimensional hypercubes
- Use ME-PCM to calculate the moment statistics of X on each hypercube.
  - Through the variance of X, we obtain a measure of sensitivity of X in each hypercube -> providing a map of sensitive regions throughout Γ .
  - Other statistical quantities, e.g. skew, kurtosis, provide additional information about sensitivity.

Foo, Sindi & Karniadakis, IET Systems Biology, vol. 3 (2009)

8D input: all initial conditions random





Initial conditions:

- XIAP, Casp-8*: $[10^2, 10^5]$
- Inactive casp-8: $[1.2*10^5, 1.6*10^5]$
- Inactive casp-3: $[2.3*10^5, 2.8*10^5]$
- Intermediates: $[10^2, 3.9*10^4]$
- Casp-3*: $[10^2, 1.1*10^4]$

Time = 6 hours

- 100 8-dimensional elements
- CC sparse grid, 17 points per element
- Quantities plotted are normalized between 0 and 1
- Convergence tests performed, using 145, 829 points per element - exhibit same qualitative behavior

Sources of Uncertainty

Kennedy & O'Hagan, 2001

- **Discretization Error/Code Uncertainty:**
  - spatio/temporal resolution, sampling; round-off; random-number generation; system errors.

- **Parameter Uncertainty:**
  - inputs as unknown parameters of the model; specific applications or global parameters with common values over a range of contexts or even in all contexts.

- **Parametric Variability:**
  - model parameters are left unspecified, e.g., in risk analysis; measurement errors; inherent stochasticity.

- **Model Inadequacy:**
  - non-parametric uncertainty; difference between the true *mean* values of the real-world process and the code output at the true values of the inputs.

UQ-Related Research Needs

1. Propagation of Uncertainty across scales

2. Gappy Data: To Krig or Not to Krig?

2. Modeling of Input PDFs – Robust PCA

3.Model inadequacy – Non-parametric Uncertainty

4. Rigorous low-dimensional stochastic modeling

5. Long-time integration of SPDEs/ROM

6. Parameter Estimation under Uncertainty

The discovery that randomness can be harnessed to create science and beauty, c.1945

Jackson Pollock, *Autumn Rhythm, #30*, 1950