~~Are Computer Simulations Misleading Us About the Nature of Blood Flow in the Brain?~~

~~Image based Computational Fluid Dynamics - ready for clinical use or Colors For Doctors?~~

Perspective on the Status of Computational Biomedical Engineering

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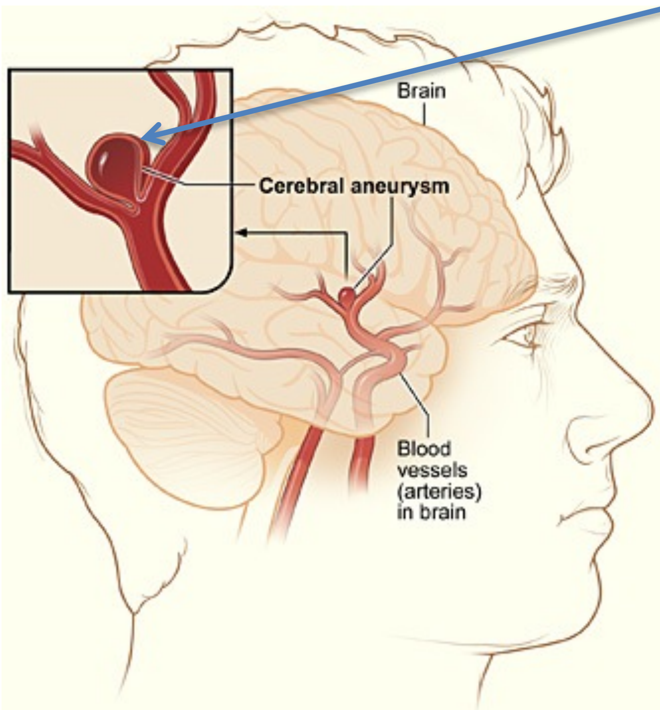
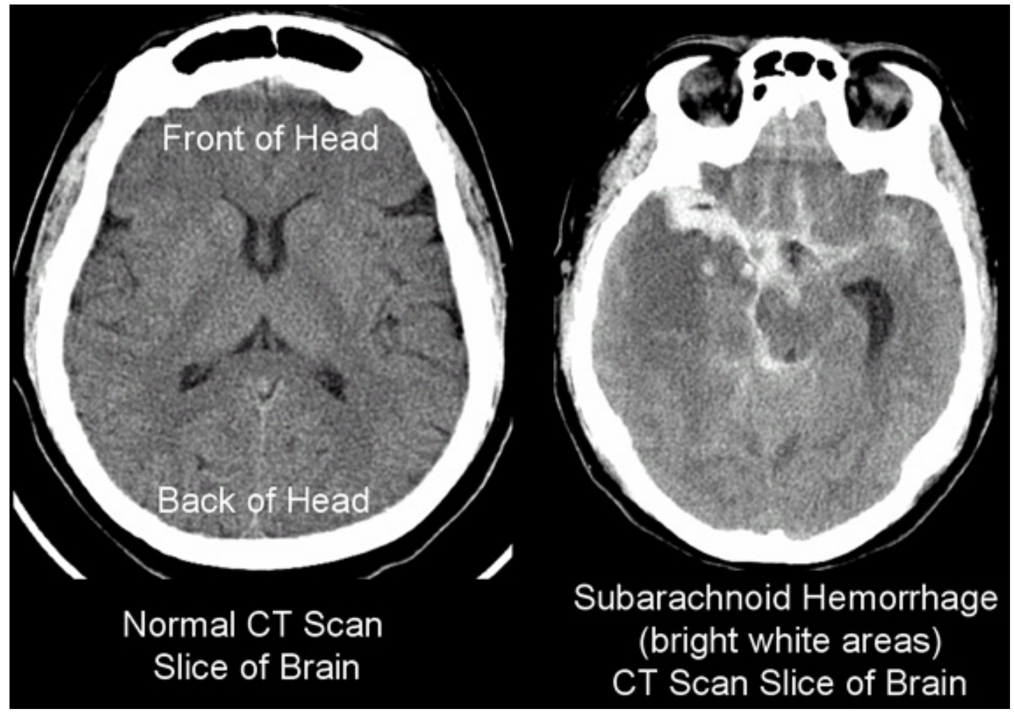
Ask questions!

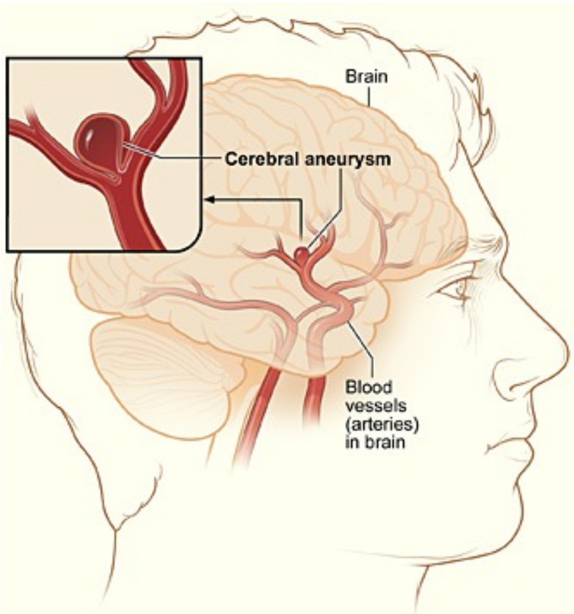
- We are here to learn
- If there is something that doesn’t make sense….
  - It simply means that I haven’t explained it well enough
  - Not that you are stupid (the person next to you understands even less)

~5% of the population harbor aneurysms – rupture leads to stroke

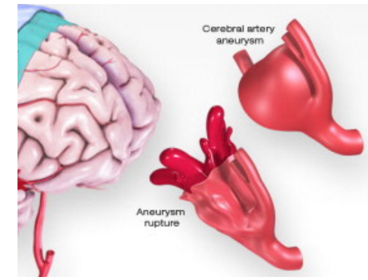




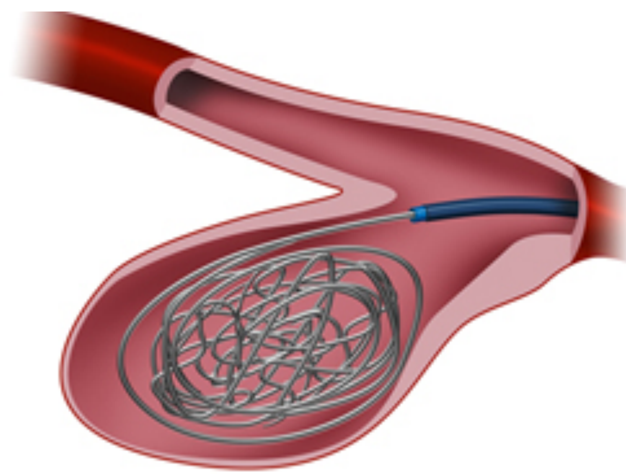
Unruptured aneurysms frequently detected during unrelated MRI scans. 1% annual risk of rupture – what to do?

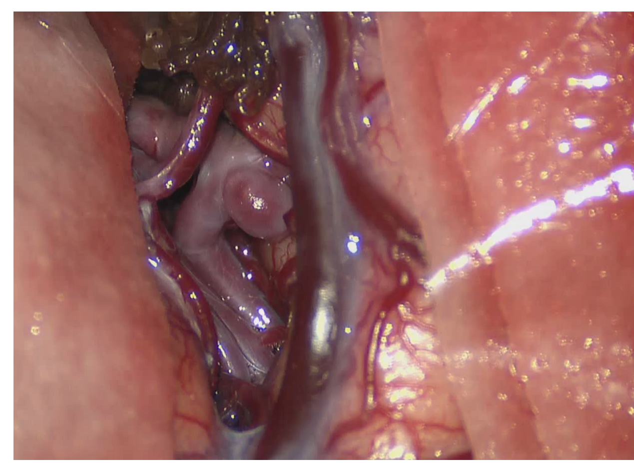


- Watch and wait?
  - Risk of stroke…



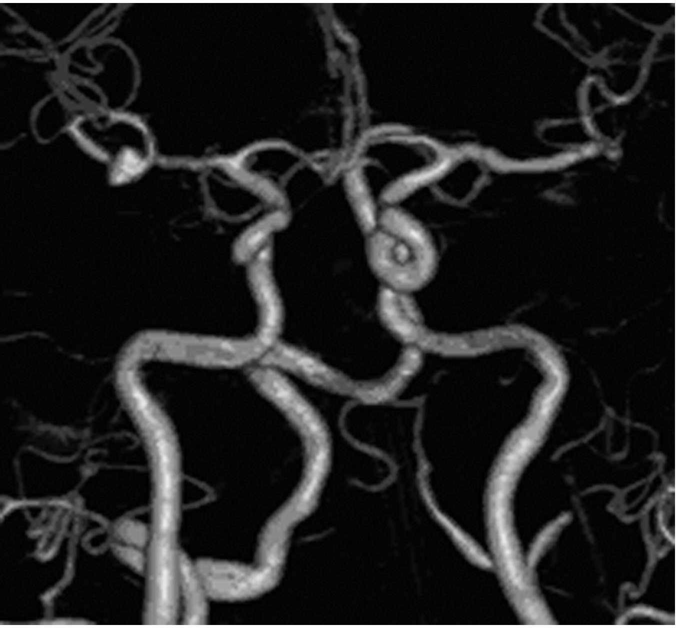
- Proactively intervene?
  - Coils sometimes fail, and open head surgery is risky…



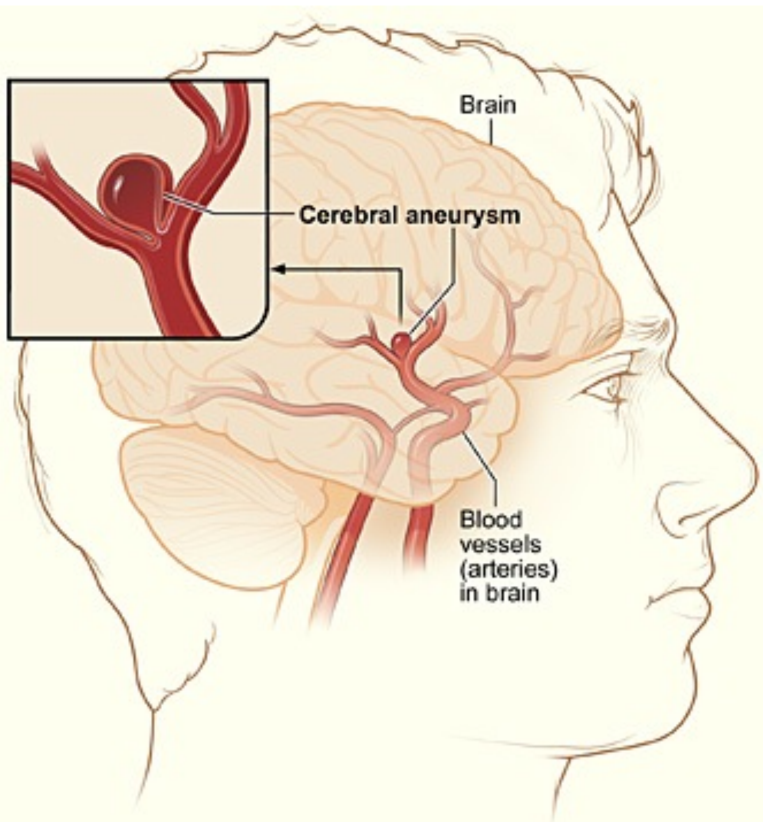


Rupture when **stress > strength…**

Can’t measure/image wall thickness/properties



Use the geometry and simulate the blood flow: Abnormal forces a surrogate of wall weakness (And there is a good reason for that: Detour)



Detour: Mechanotransduction

(mechano- + transduction) is any of various mechanisms by which cells convert mechanical stimulus into electrochemical activity.

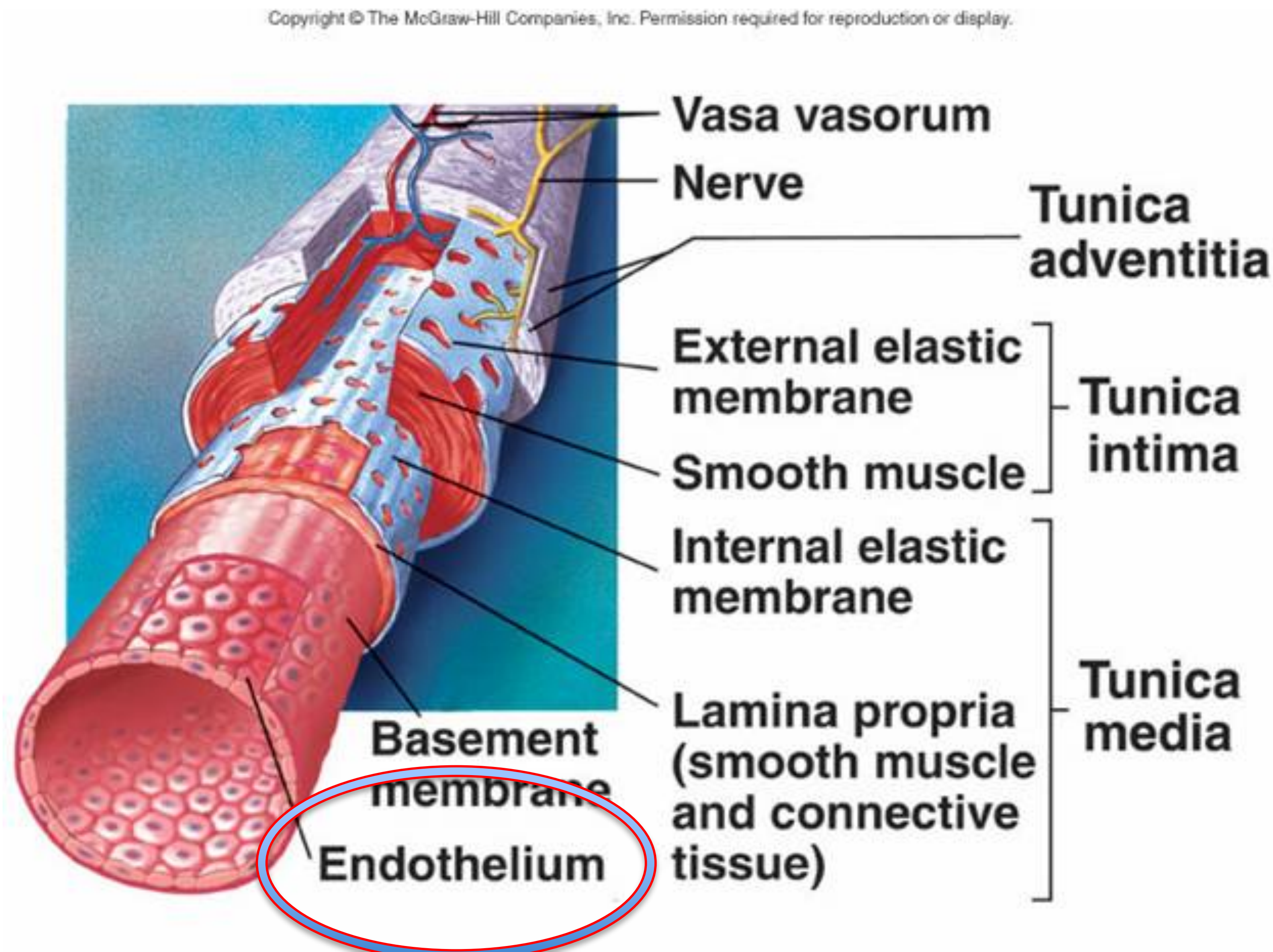


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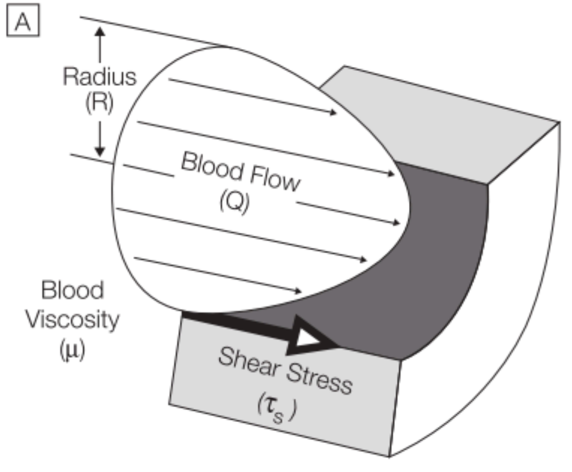
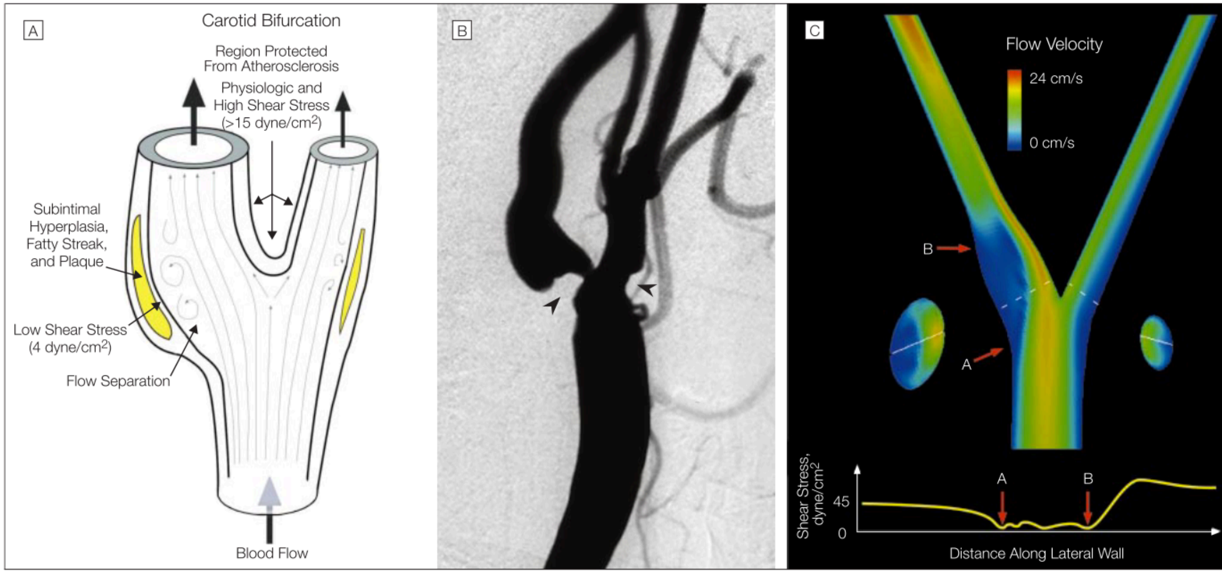
Figure 1. Hemodynamic Shear Stress



Poiseuille's Law $\tau_s = \dfrac{4\mu Q}{\pi R^3}$

Figure 2. Localization of Atherosclerosis Lesions



A, Cross-sectional schematic diagram of a blood vessel illustrating hemodynamic shear stress, τ_s, the frictional force per unit area acting on the inner vessel wall and on the luminal surface of the endothelium as a result of the flow of viscous blood. B,Tabular diagram illustrating the range of shear stress magnitudes encountered in veins, arteries, and in low-shear and high-shear pathologic states.

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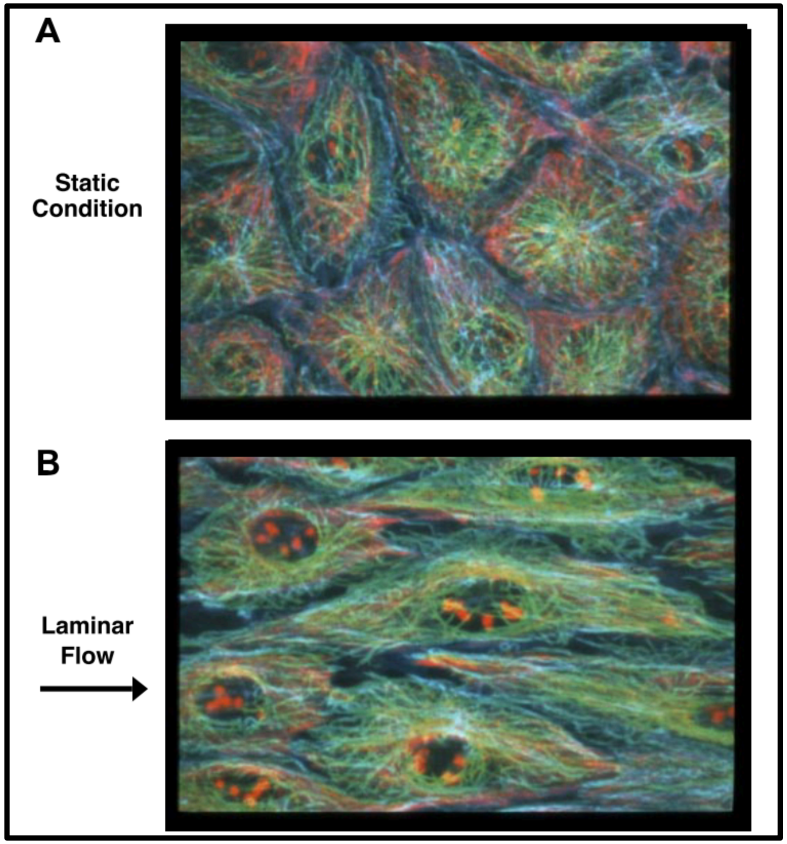

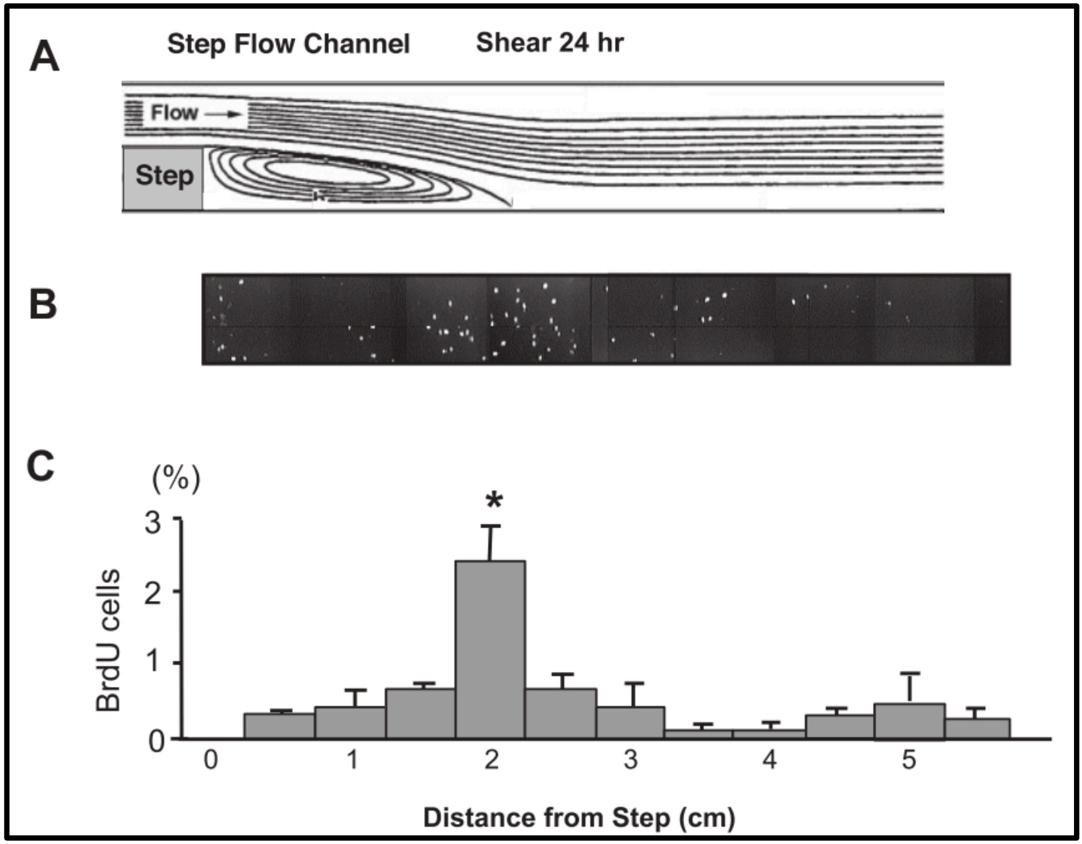

Chien, Shu. "Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell." *AJPhysHeartCircPhys*, 2007.
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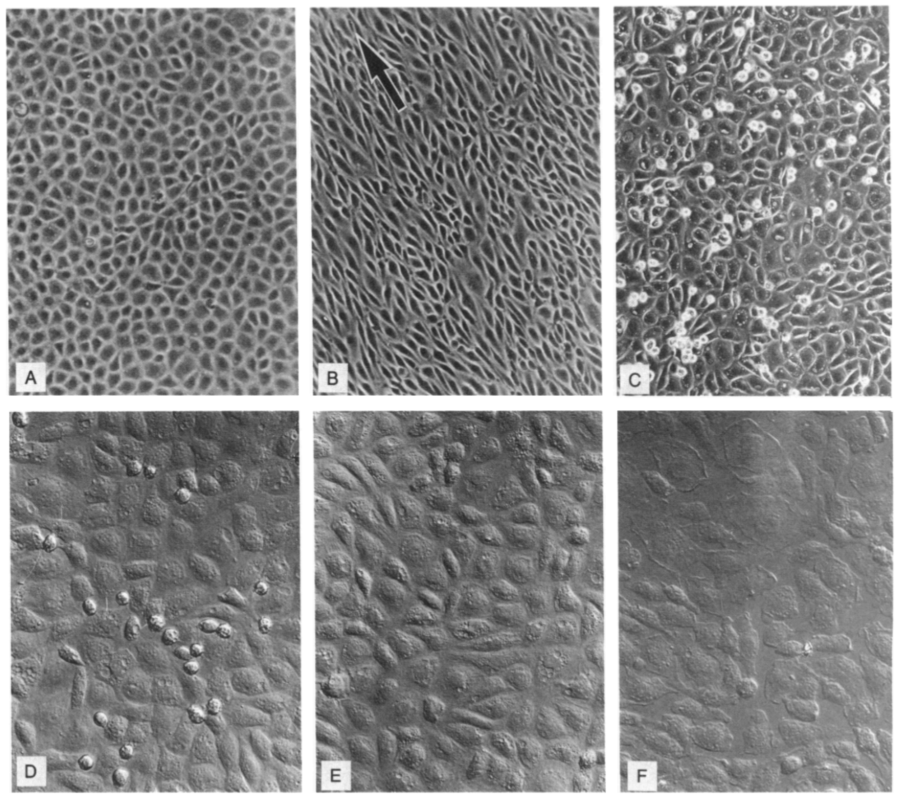

FIG. 1. Morphological changes induced in confluent bovine aortic endothelial cells by exposure to shear stress in laminar and turbulent flow. (*A*) Monolayer in static culture. Under no flow conditions, cells exhibit a polygonal configuration with no preferred orientation. (Phase-contrast microscopy; ×280.) (*B*) Alignment of cells in a confluent endothelial monolayer after 24 hr of exposure to shear stress at 8 dynes/cm² in laminar flow. Note ellipsoidal shape change. Arrow indicates direction of flow. (Phase-contrast; ×280.) (*C*) Confluent endothelial monolayer after 16 hr of exposure to shear stress at 1.5 dynes/cm² in turbulent flow. Cell shape in the monolayer is more variable than in *A*, no alignment is apparent, and significant numbers of rounded cells can be seen attached to the upper surface of the monolayer. Similar effects were noted after 16 hr of exposure to 3, 5, and 14 dynes/cm² in turbulent flow. (Phase-contrast; ×300.) (*D*) Higher-power Nomarski image of rounded cells attached to the monolayer under the effects of low shear stress in turbulent flow (1.5 dynes/cm²; 16 hr). Most appeared to remain attached to adjacent cells. (×600.) (*E*) Nomarski image after 5 hr of exposure to shear stress at 14 dynes/cm² in turbulent flow showing a confluent monolayer without evidence of cell–cell retraction. Forty percent of these cells, however, go on to synthesize DNA. (×580.) (*F*) Appearance of gaps in the cell monolayer reflecting cell retraction and cell loss after 24 hr of exposure to shear stress at 14 dynes/cm² in turbulent flow. (Nomarski; ×600.)

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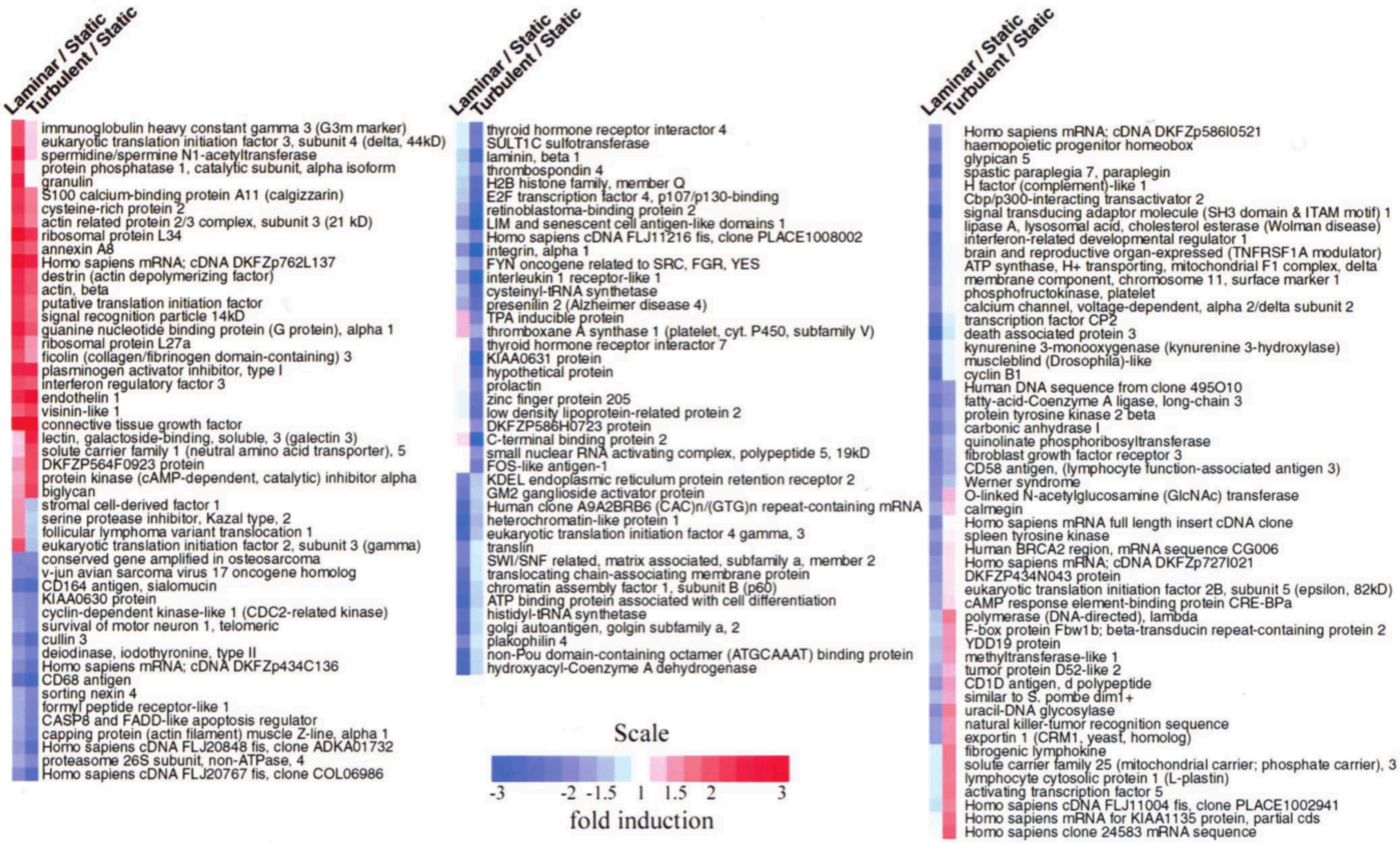

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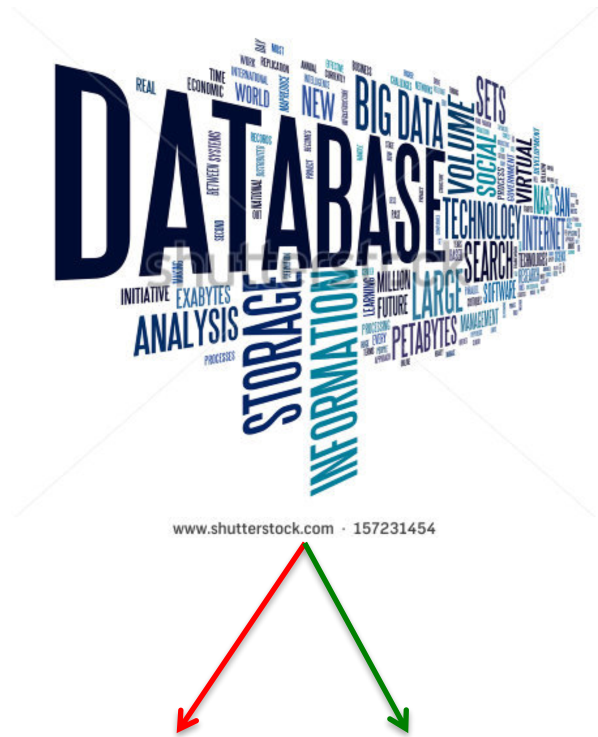
Back on track: Risk-of-rupture prediction

- Ideal study impossible ☹

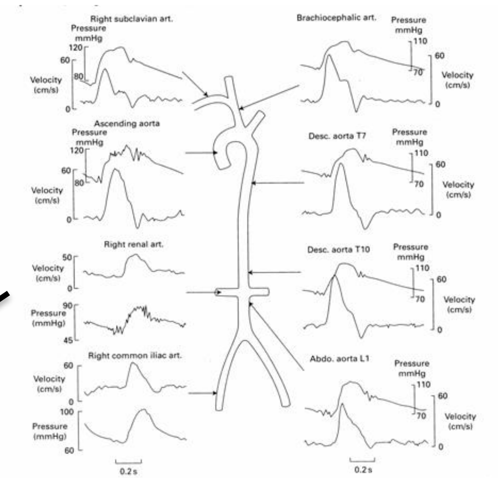
- Large image databases with known clinical outcome used for “training” (think Machine Learning)

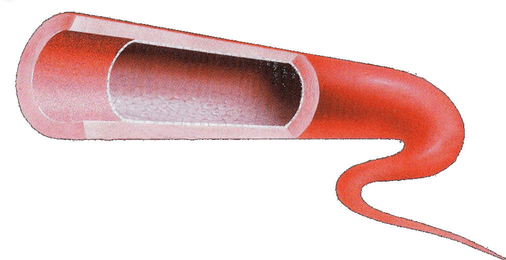
- Ultimate goal is that CFD can be a prospective clinical tool



Ruptured Un-Ruptured

Input to ‘patient-specific’ blood flow modeling





CFD
Solver

“42”

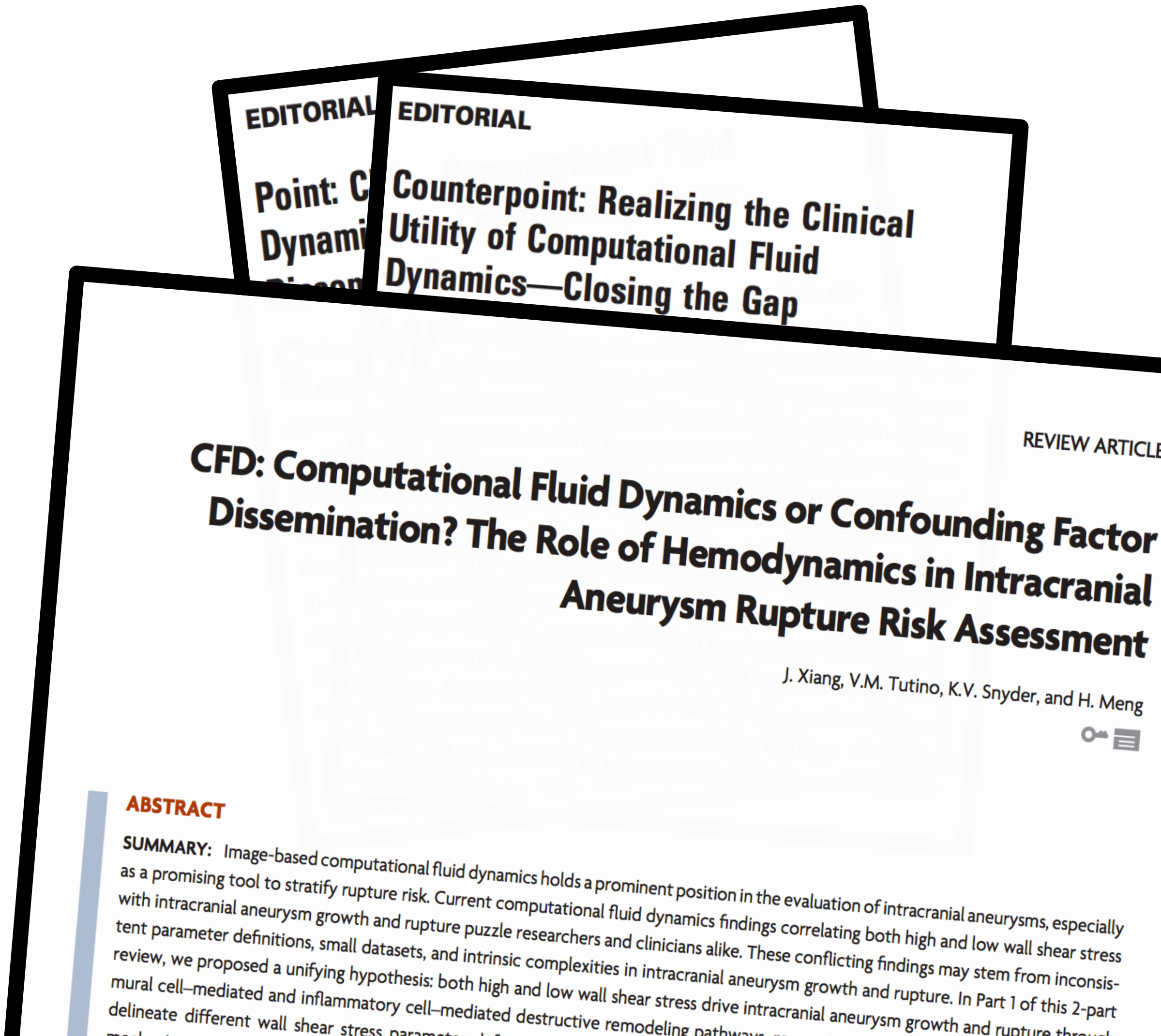
Huge variability of basic metrics – not getting anywhere

Author, year	Mean WSS (SD) Rup	Unrup	*P*
Jou, 2008[6]	1.90 (1.10)	2.60 (1.90)	.5
Xiang, 2011[4]			
Miura, 2012[17]	7.19 (5.98)	9.55 (5.89)	<**.01**
Lauric, 2013[18]	0.06 (0.04)	0.13 (0.07)	**.03**
Goubergrits, 2011[19]	2.01 (1.51)	2.94 (1.85)	>.05
Chien, 2009[52]	10.66 (5.99)	6.31 (6.47)	<**.01**
Castro, 2009[36]			
Lu, 2011[21]	6.49 (3.48)	10.17 (7.48)	.13
Xu, 2013[22]			
Takao, 2012 (1)[23]	5.10 (0.96)	5.19 (1.96)	.7
Takao, 2012 (2)[23]	6.14 (2.06)	5.35 (1.96)	.38
Pereira, 2014[24]	1.20 (0.50)	2.20 (1.00)	.37

Results from CFD in the aneurysm literature have been equivocal

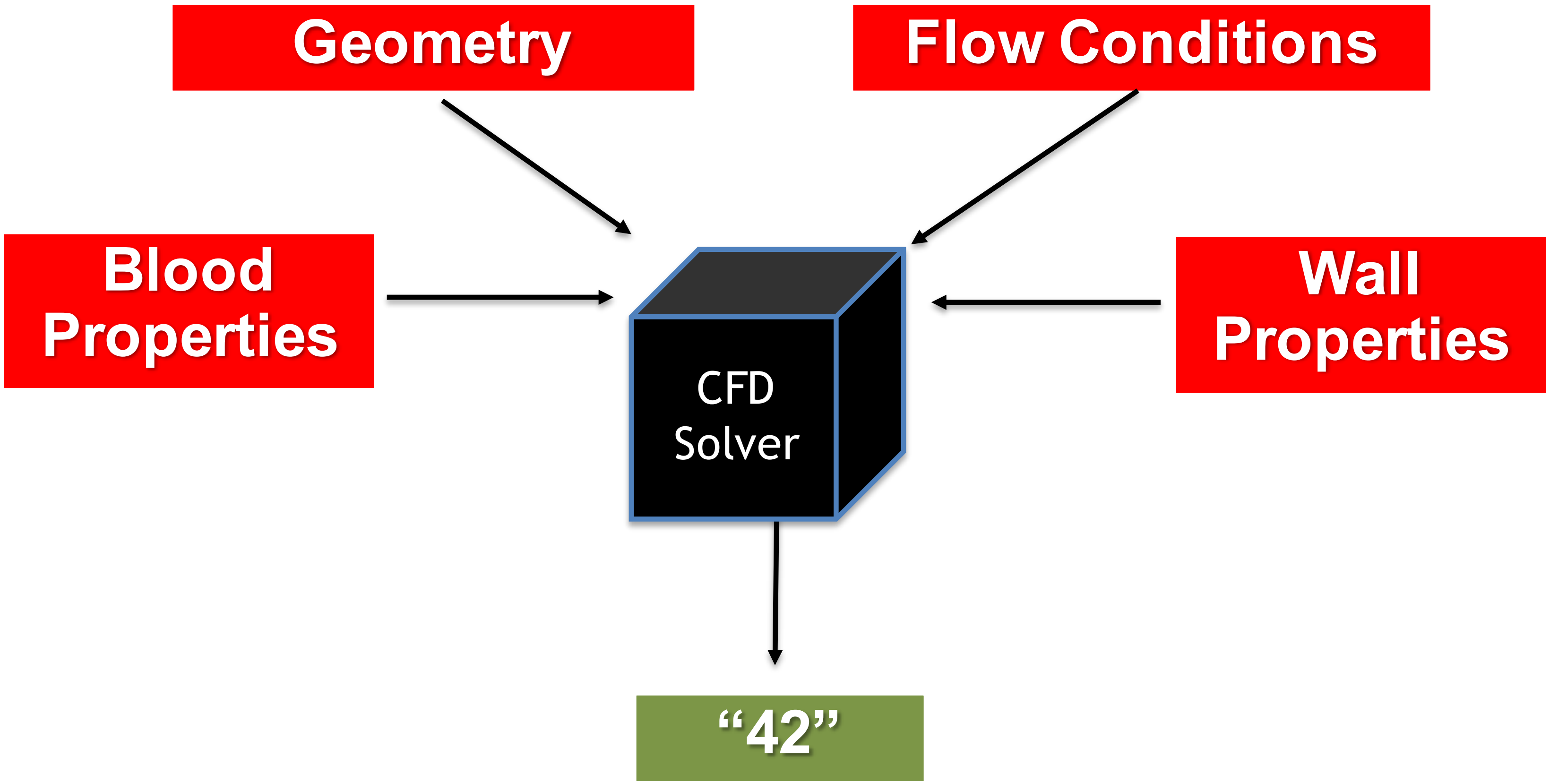
- Conflicting results on whether **too high*** or **too low**** wall shear stress (WSS) is associated with aneurysm rupture status in large retrospective studies

- Editorials in "high impact" factor journals from clinicians describing CFD as *color for doctors* and *confounding factor dissemination*



* Cebral JR et al. AJNR. 2005
** Xiang J et al. Stroke. 2011

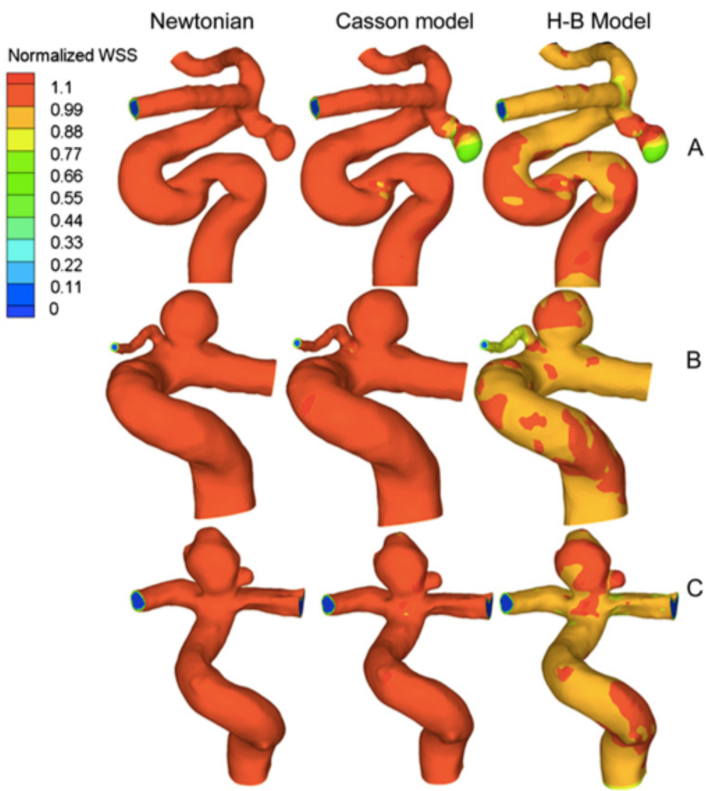
Leave no stone unturned; ‘patient-specific’ CFD has been sought to be made <u>patient-specific</u>



Blood Properties

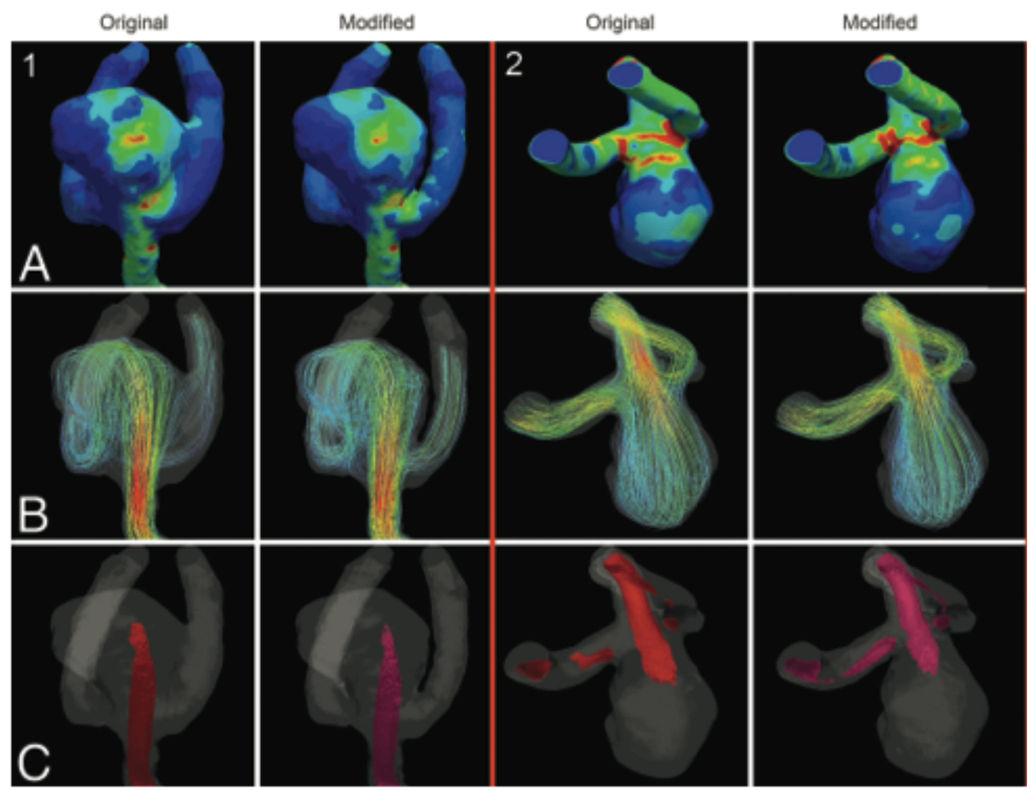
Geometry

"Newtonian viscosity model could overestimate wall shear stress in intracranial aneurysm domes"



Xiang+, NeuroIntervent Surg 2011

Imaging modality (3DRA/2D DSA): "Neck size overestimation on 3DRA can have non-negligible consequences"

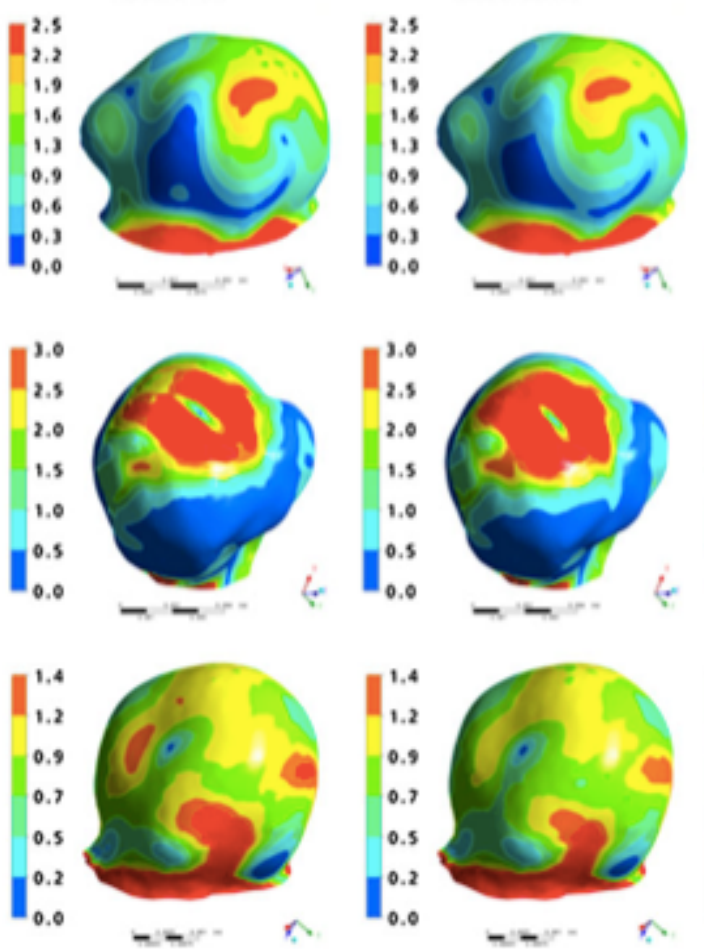


Schneiders+, AJNR 2013

Flow Conditions

“discrepancies were **significantly reduced** … normalized indices”

Measured ***Assumed***

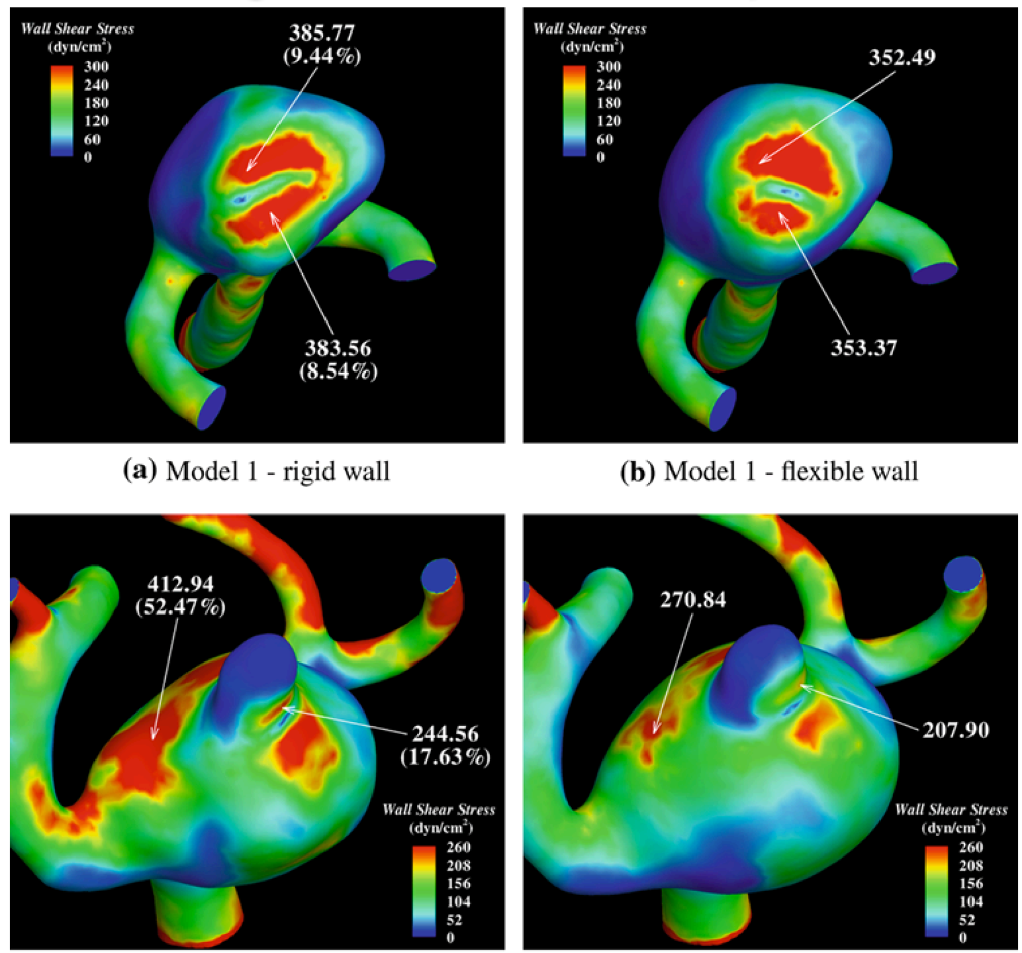


Marzo+, Ann Biomed Eng 2010

Wall Properties

“flexible wall modeling plays an important role”

Rigid ***Compliant***

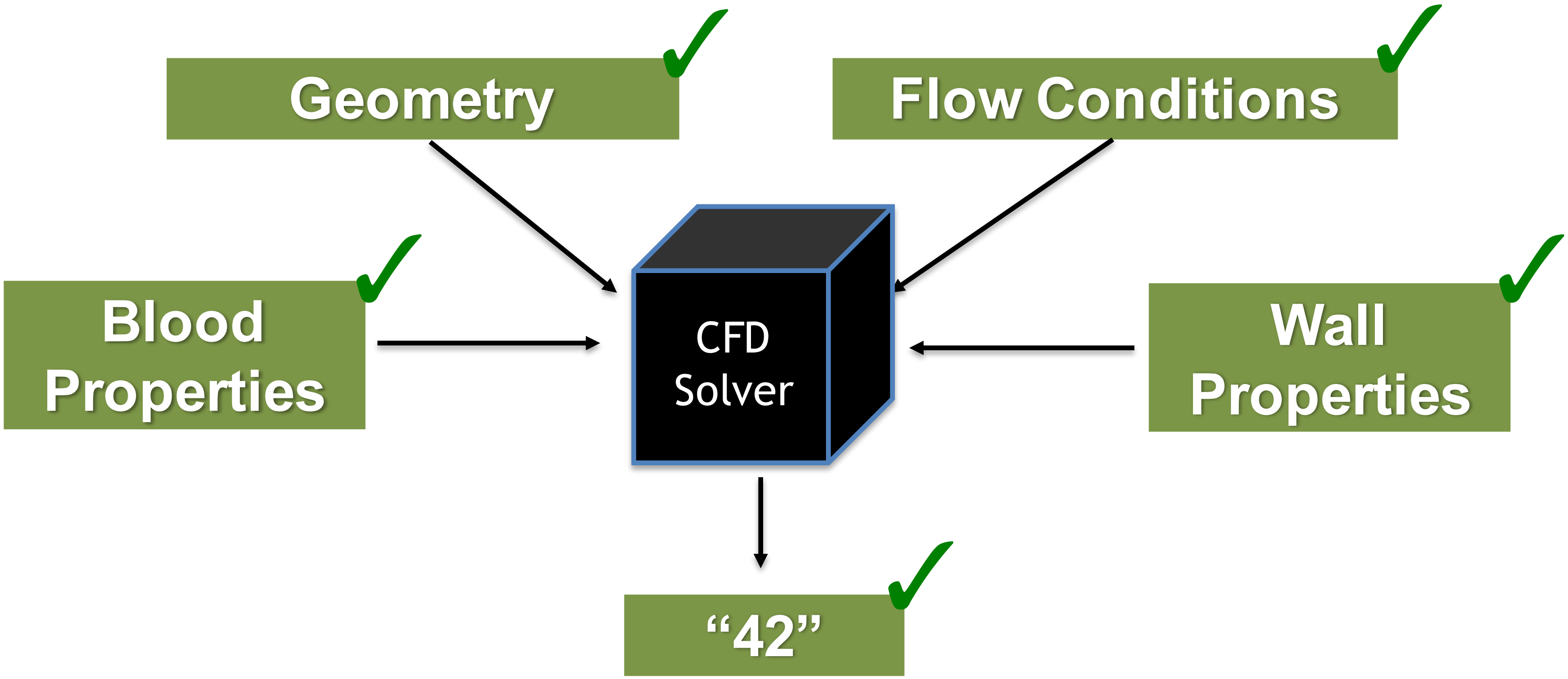


(a) Model 1 - rigid wall

(b) Model 1 - flexible wall

Bazilevs+, BMM 2010

Clinical CFD - so it is patient-specific!



The CFD is OK, right?

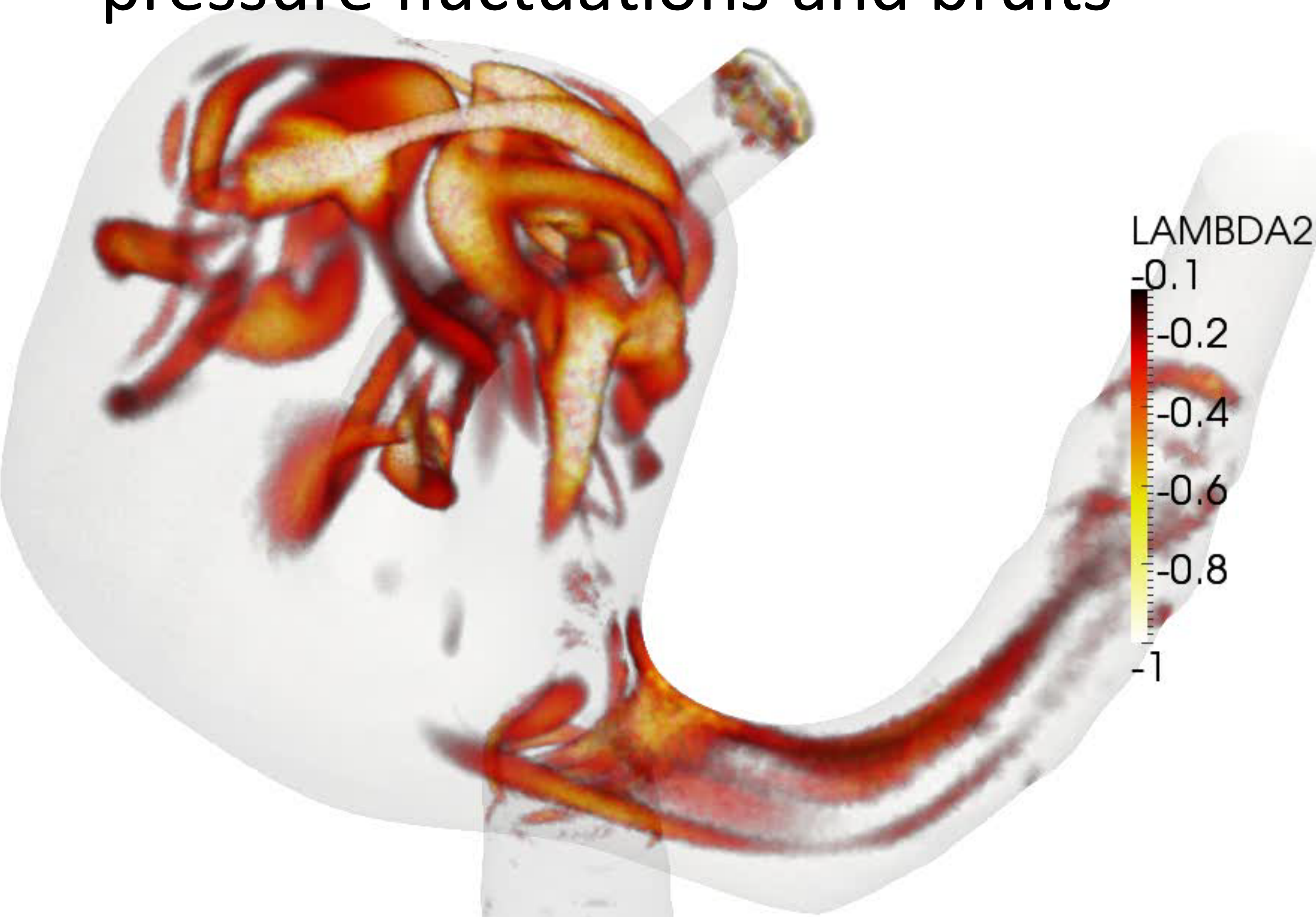
Direct Numerical Simulations detected energetic high frequency flow fluctuations

- CDP (2nd order accurate code from *Stanford Center for Turbulence Research*)
- 50,000 time-steps/cycle
- 64 million linear elements
- Rapid and random fluctuations in space (3D) *and* time
- u'_{rms} energy up to 1250 Hz

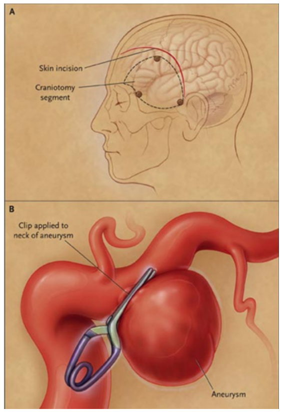
- All textbooks and journal publications say that the flow should be laminar and stable, typically because the parent artery Reynolds number is low

Valen-Sendstad et. al., Journal of Biomechanics, 2011

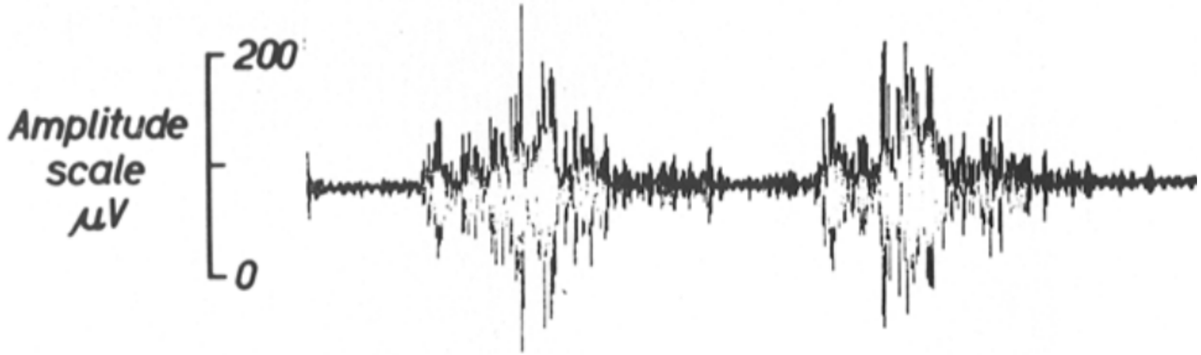
Flow eddies are associated with pressure fluctuations and bruits

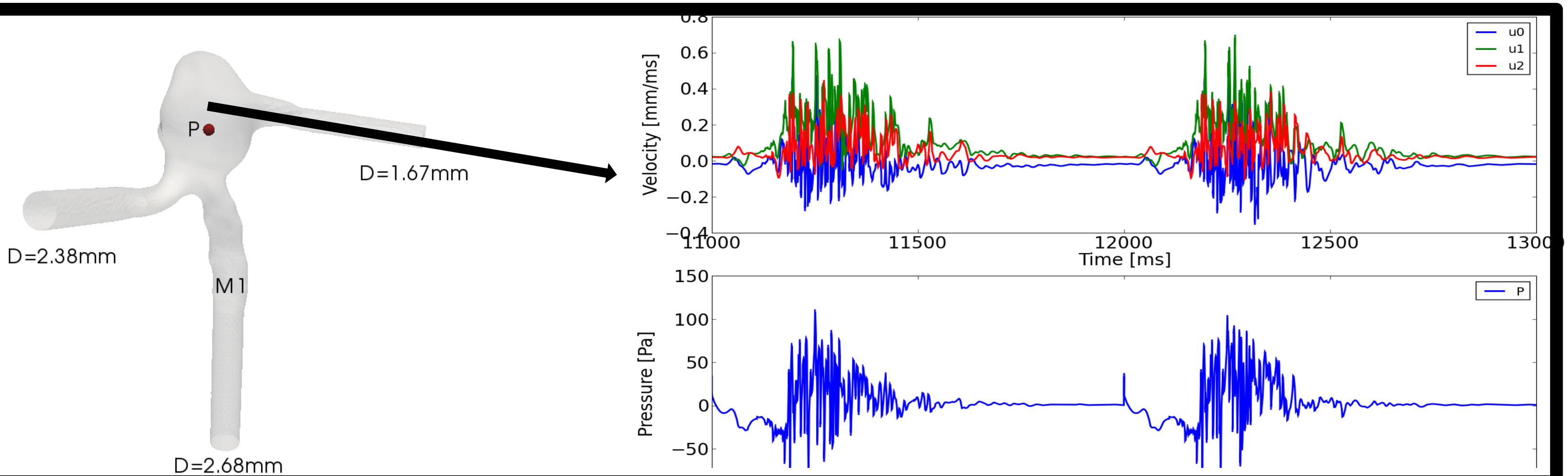


Consistent with clinical observations



Predominant frequency of 460Hz*





"Turbulence in human intracranial saccular aneurysms",
Ferguson, Gary G., Journal of Neurosurgery, 1970

Hundreds of CFD studies. No reports of high frequency flow fluctuations. What is correct?

My results

- Energetic high frequency flow fluctuations
- Cycle to cycle differences
- Consistent with clinical observations and experimental evidence

Previously Reported

- Laminar flow
- Cycle to cycle convergence
- Additional theories to explain aneurysm bruits

Do not have the aneurysms from other studies, but can compare methods

We designed a numerical experiment intended to be as simple as possible

Same finite element mesh

"Normal resolution" (NR)

- 1st order accurate (space&time)
- 1.1-2M tet. cells* (~0.12mm)*
- 1,000 time steps/cycle*
- SUPG stabilization**
- PISO solver**

"High resolution" (HR)

- 2nd order accurate (space&time)
- >8.8-16M tet. cells (~0.06mm)
- 20,000 time steps/cycle
- No stabilization
- IPCS solver

*Better of temporal and spatial resolutions from the largest studies to date[1,2].

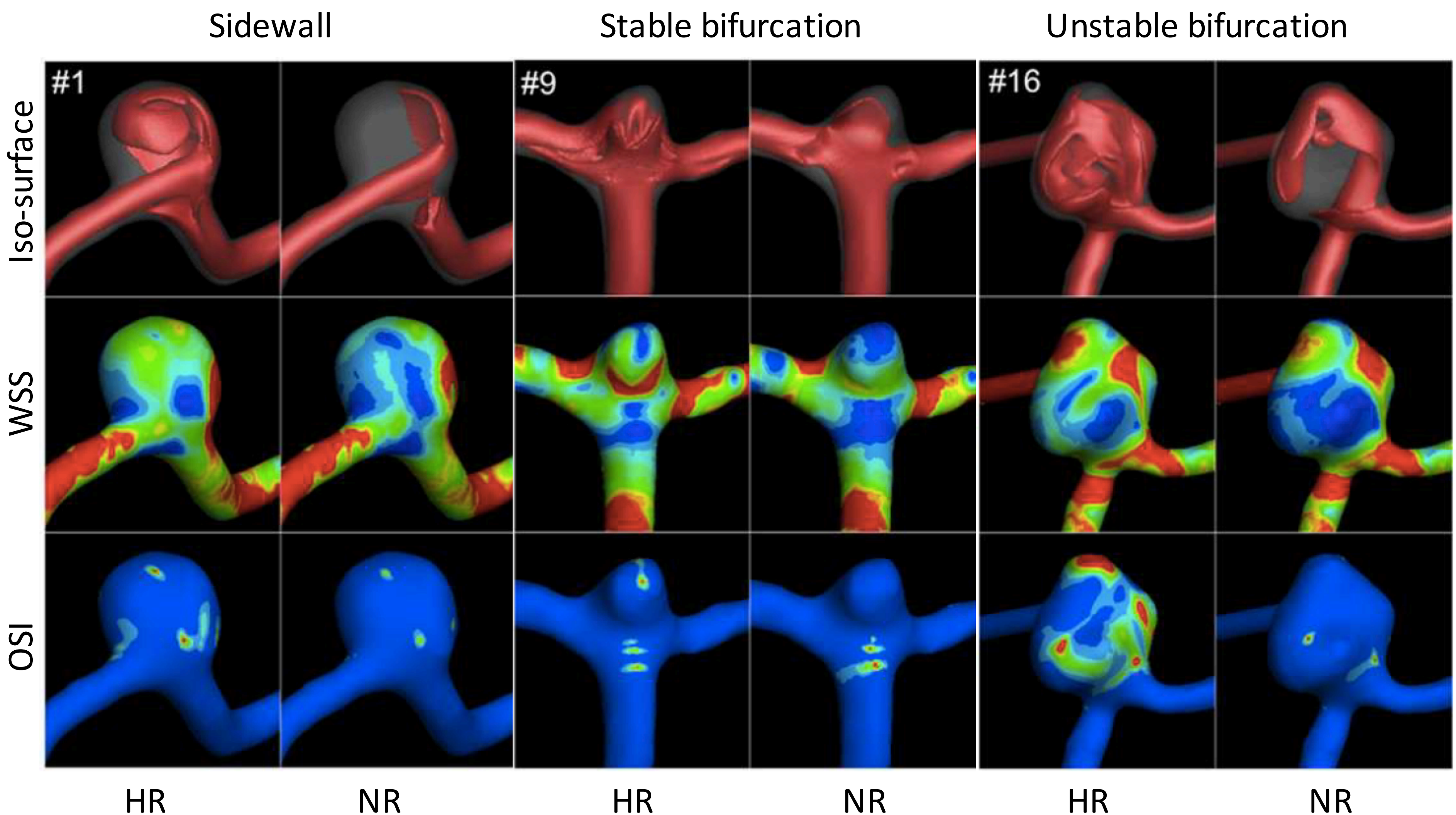
** PISO/SUPG is the default and recommended method in both Fluent and Star-CD and is the most common strategy in the literature and in a CFD Challenge[3].

1 Cebral et al., ***Quantitative characterization of the hemodynamic environment in ruptured and unruptured brain aneurysms***, AJNR 2011

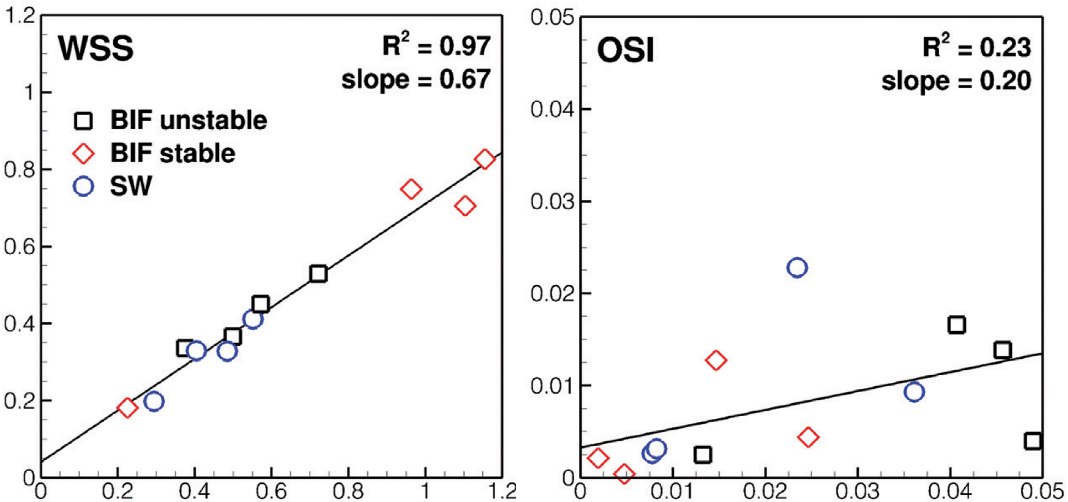
2 Xiang et al., ***Hemodynamic–Morphologic Discriminants for Intracranial Aneurysm Rupture***, Stroke 2011

3 Steinman et al. ***Variability of Computational Fluid Dynamics Solutions for Pressure and Flow in a Giant Aneurysm: The ASME 2012 Summer Bioengineering Conference CFD Challenge,*** J Biomech Eng. 2013

Qualitative differences are evident for all flow phenotypes



A numerical experiment intended to be as simple as possible



HR **NR**

- NR CFD is “good enough” for *some time averaged* hemodynamic indices
- NR CFD under-predicts *consistently;* rank ordering OK
- Need HR CFD for *mechanobiological stimuli*

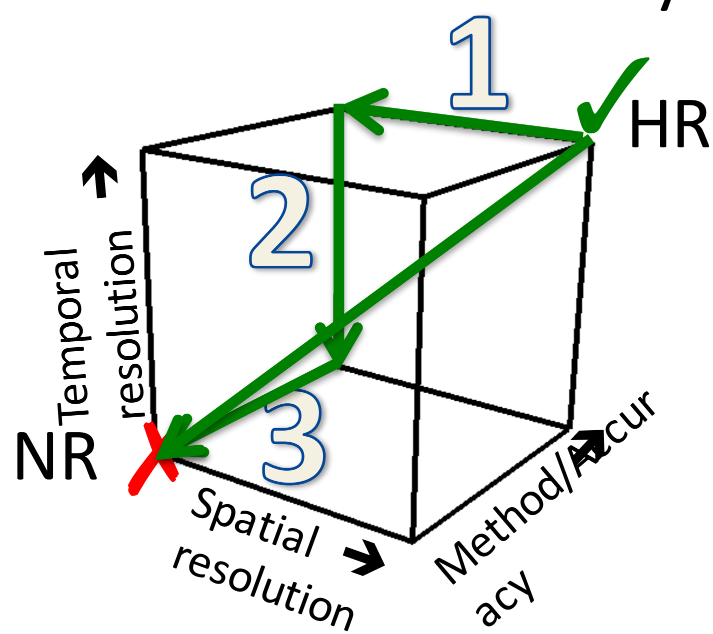
*Valen-Sendstad, K., and D. A. Steinman. *Mind the Gap*, AJNR 2014, 35, 536-543. Commentary, 544-545.

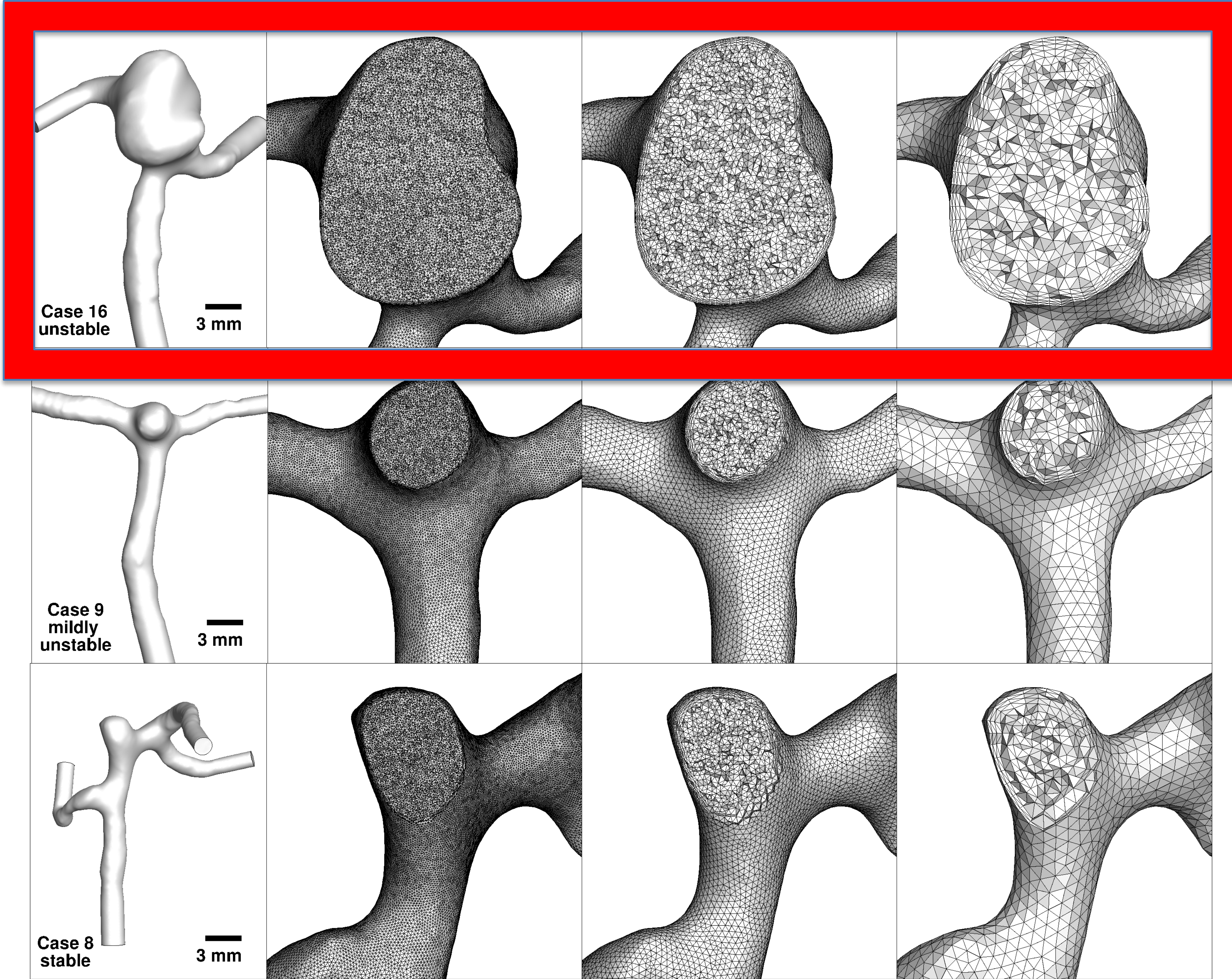
Can we close the gap between experts and users?

Errors is CFD are intertwined with:

- Spatial (mesh) resolution ✓
- Temporal resolution, i.e., number of time steps ✓
- Solver discretization scheme and accuracy ✓

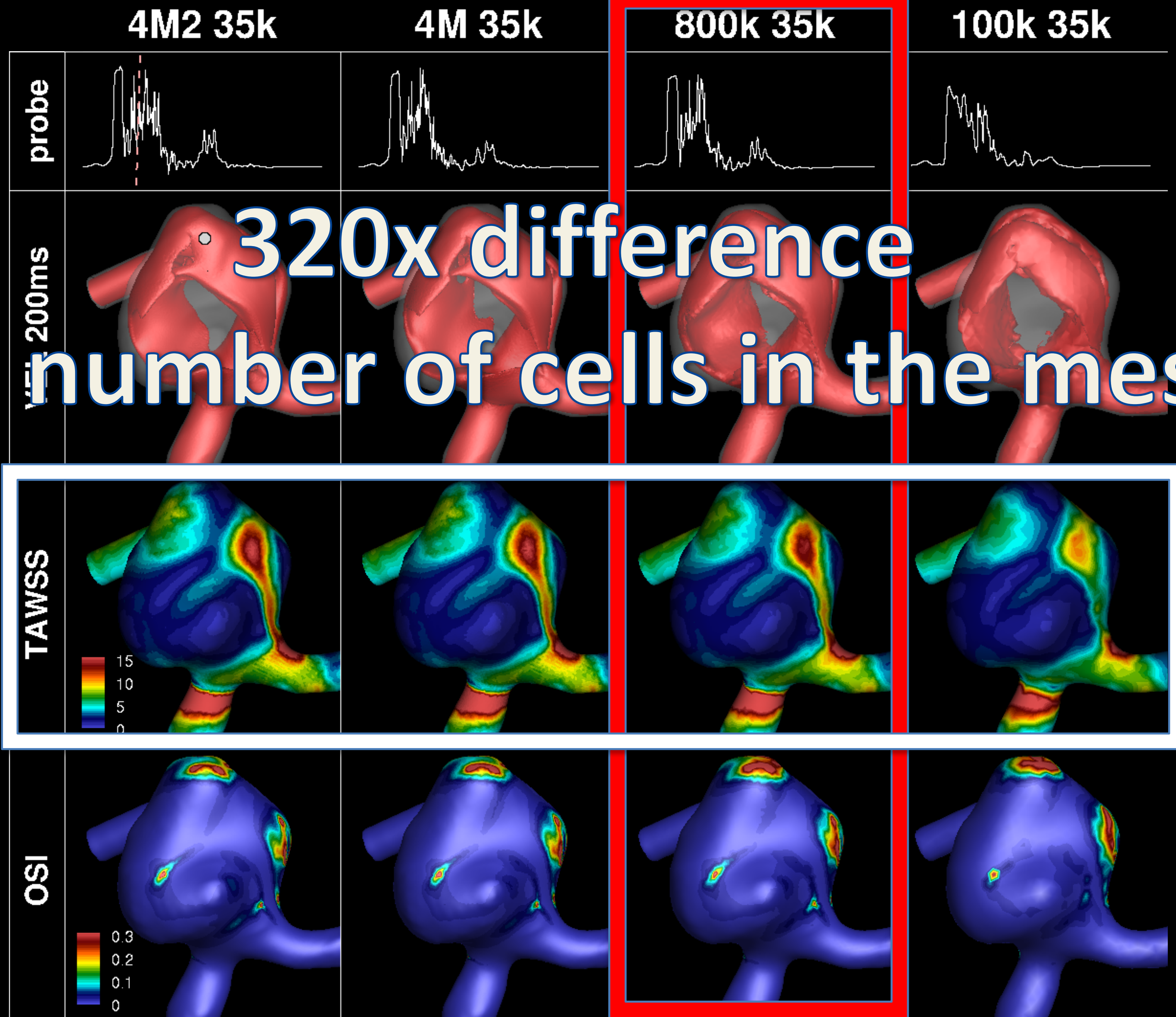
"Mind The Gap"





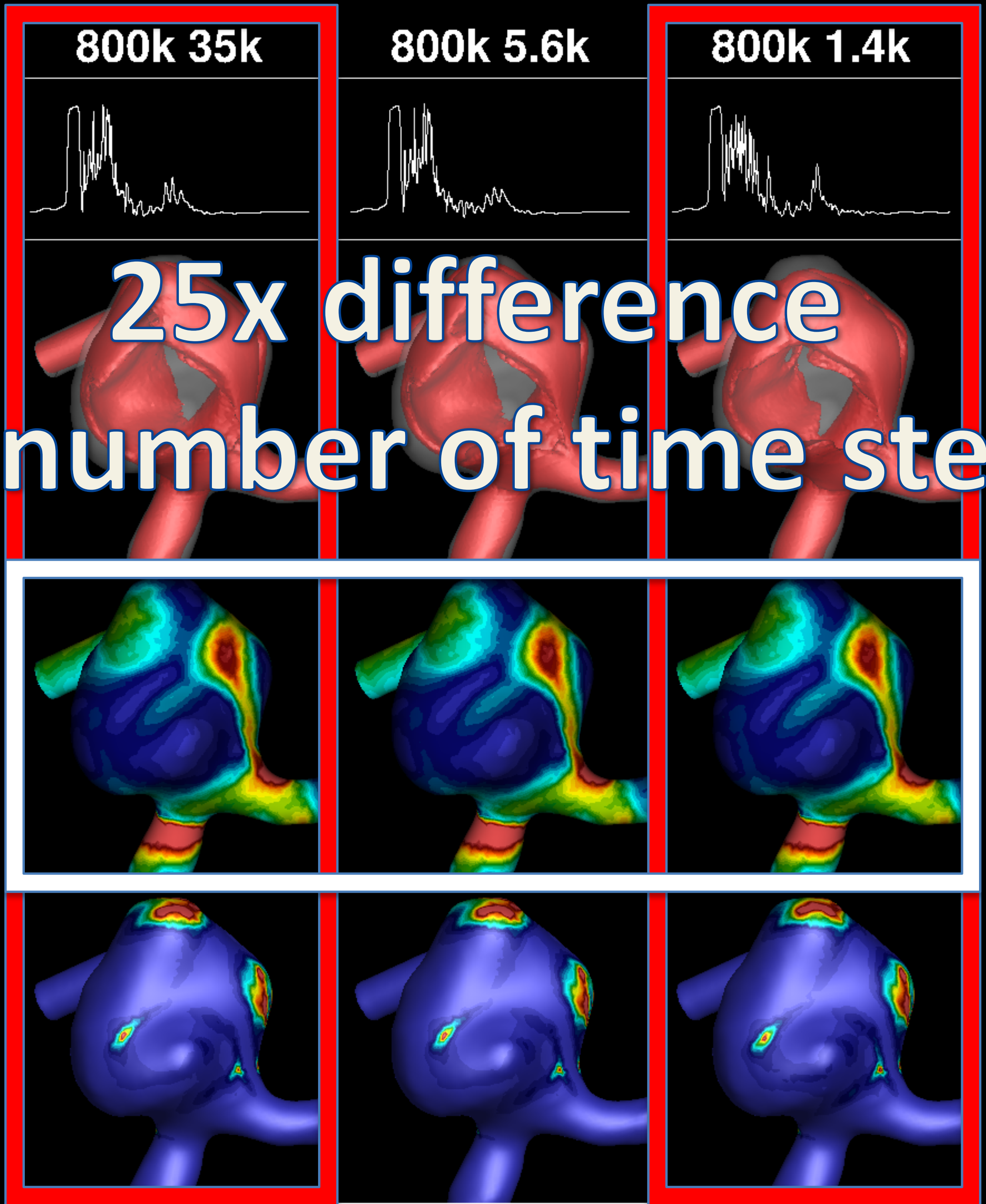
Case 16
unstable
3 mm
Case 9
mildly
unstable
3 mm
Case 8
stable
3 mm

SPATIAL RESOLUTION

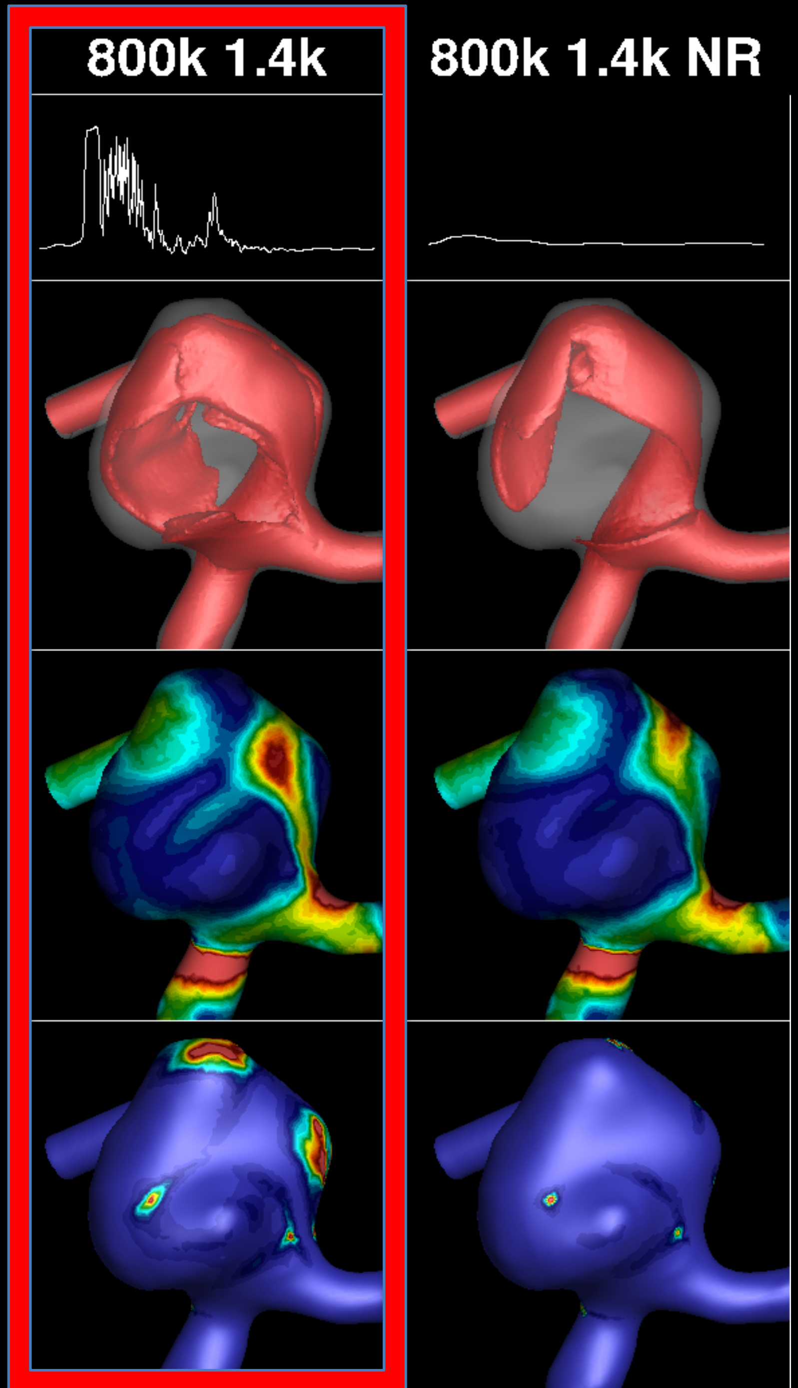


320x difference in number of cells in the mesh

TEMPORAL RESOLUTION



CFD METHOD AND SETTINGS



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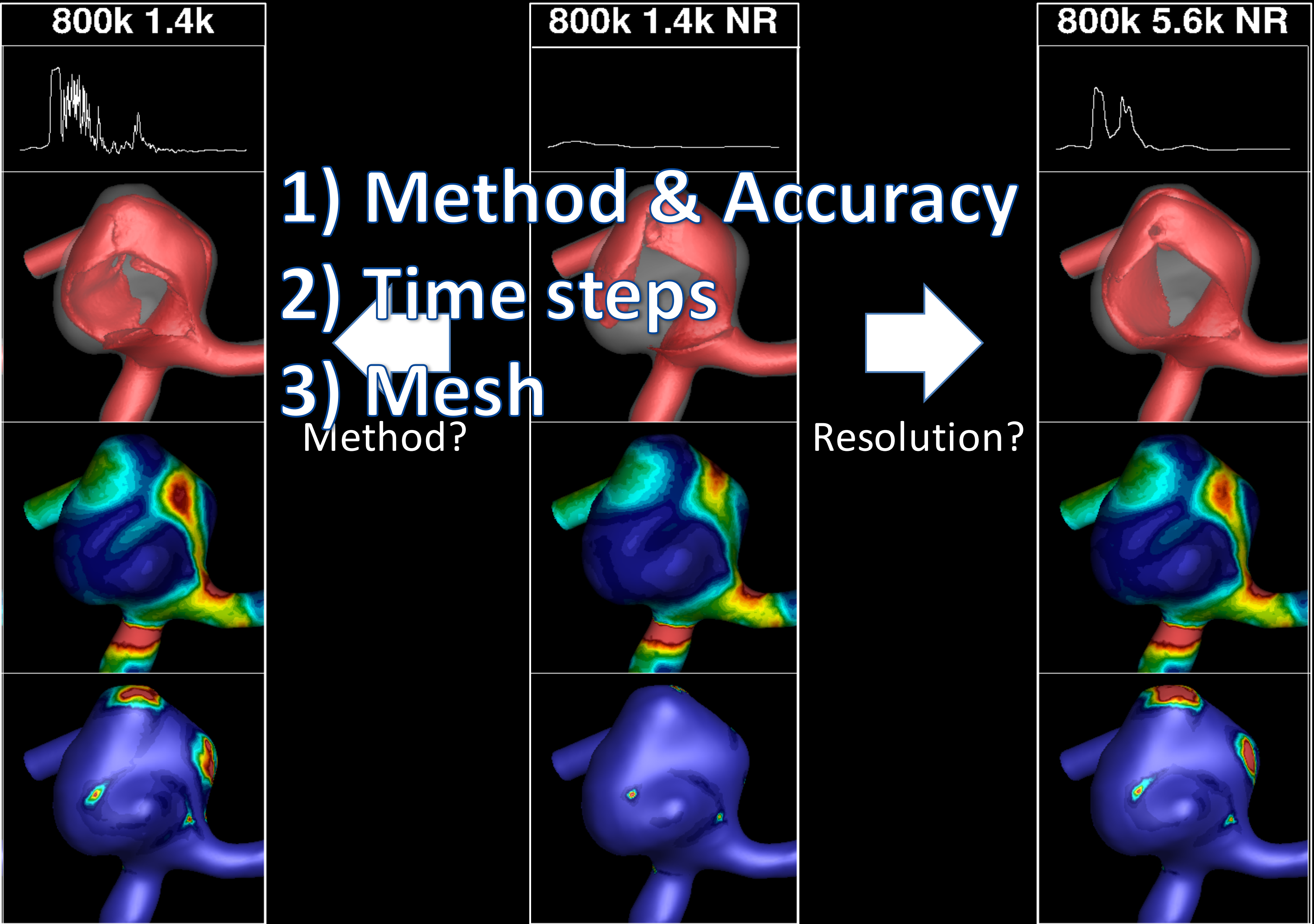
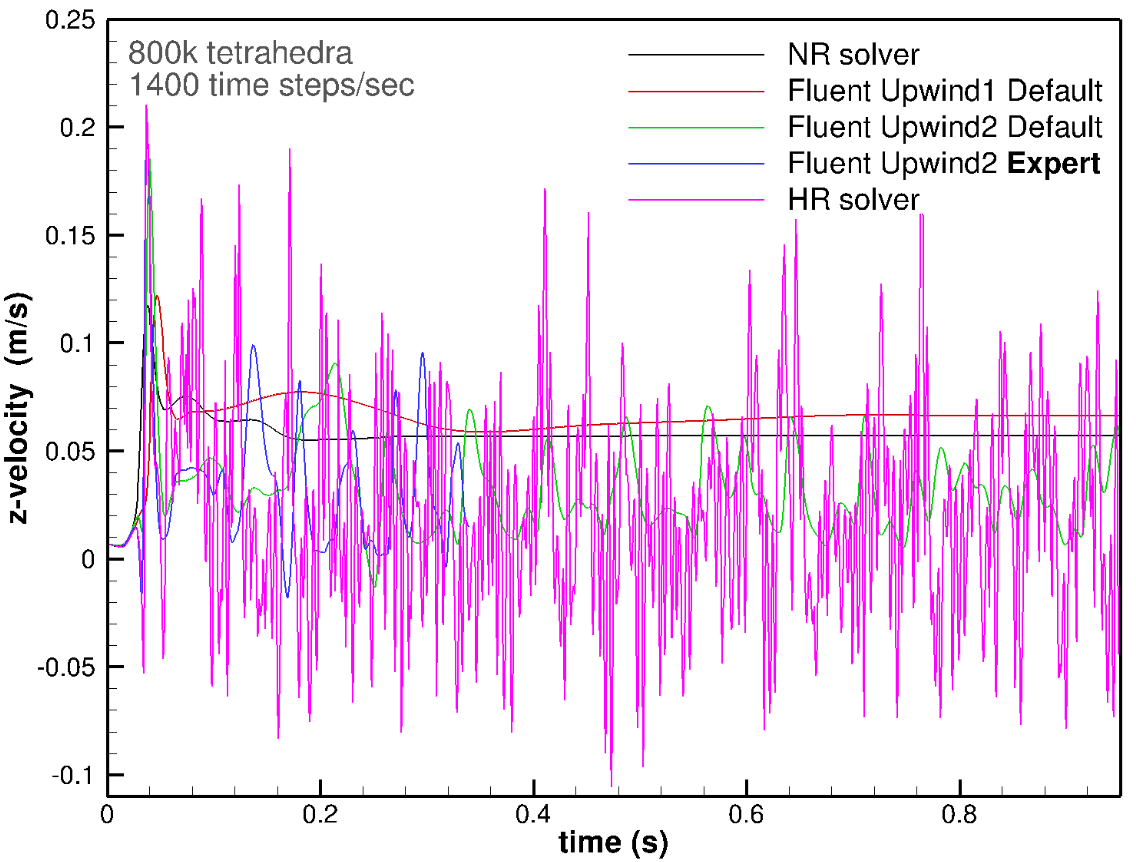
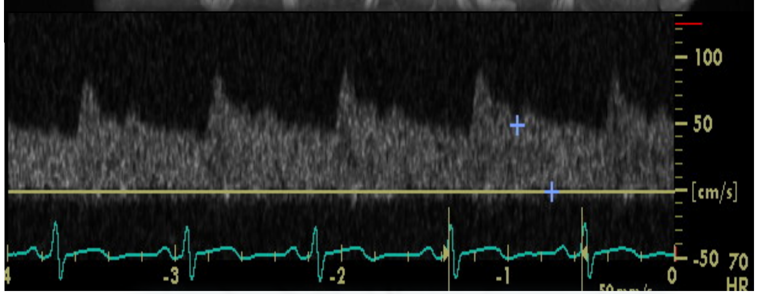


Do our findings hold for a commercial CFD solver?

- **Fluent v14:** transient N-S, steady inflow
  - our case 16, 800k elements, 1,400 steps/sec
- **Default**: 1^{st} TS, 1^{st} or 2^{nd} order upwind, and:
  - SIMPLE
  - 20 iterations
  - Conv. crit. 10^{-3}
- **Expert**: Everything 2^{nd} order, and:
  - PISO
  - 50 iterations
  - Conv. crit. 10^{-5}



For a ***straight pipe* and *stationary flow*,** transition to turbulence occurs at Re~2300. Re is *insufficient* to determine flow regime in aneurysms.



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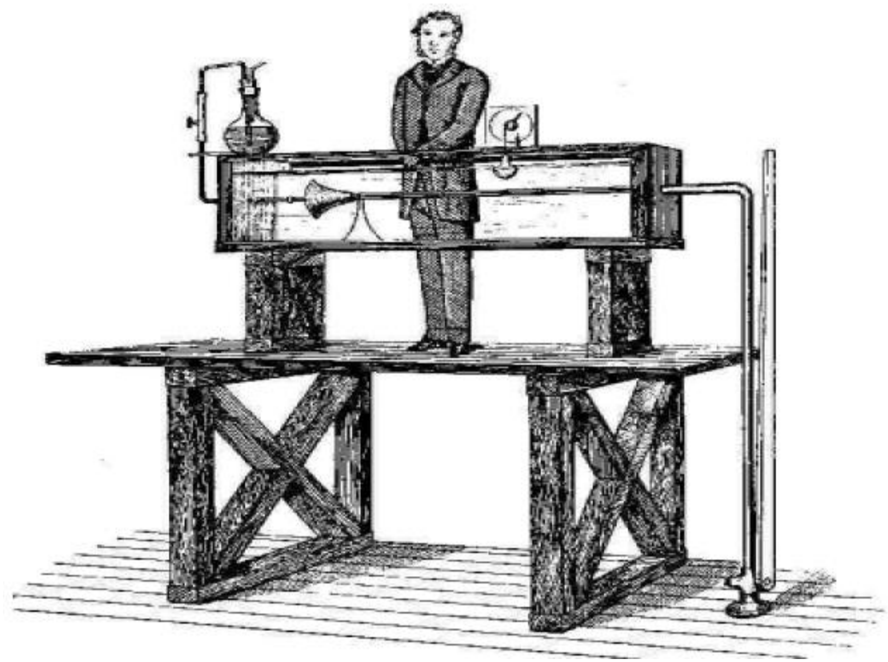
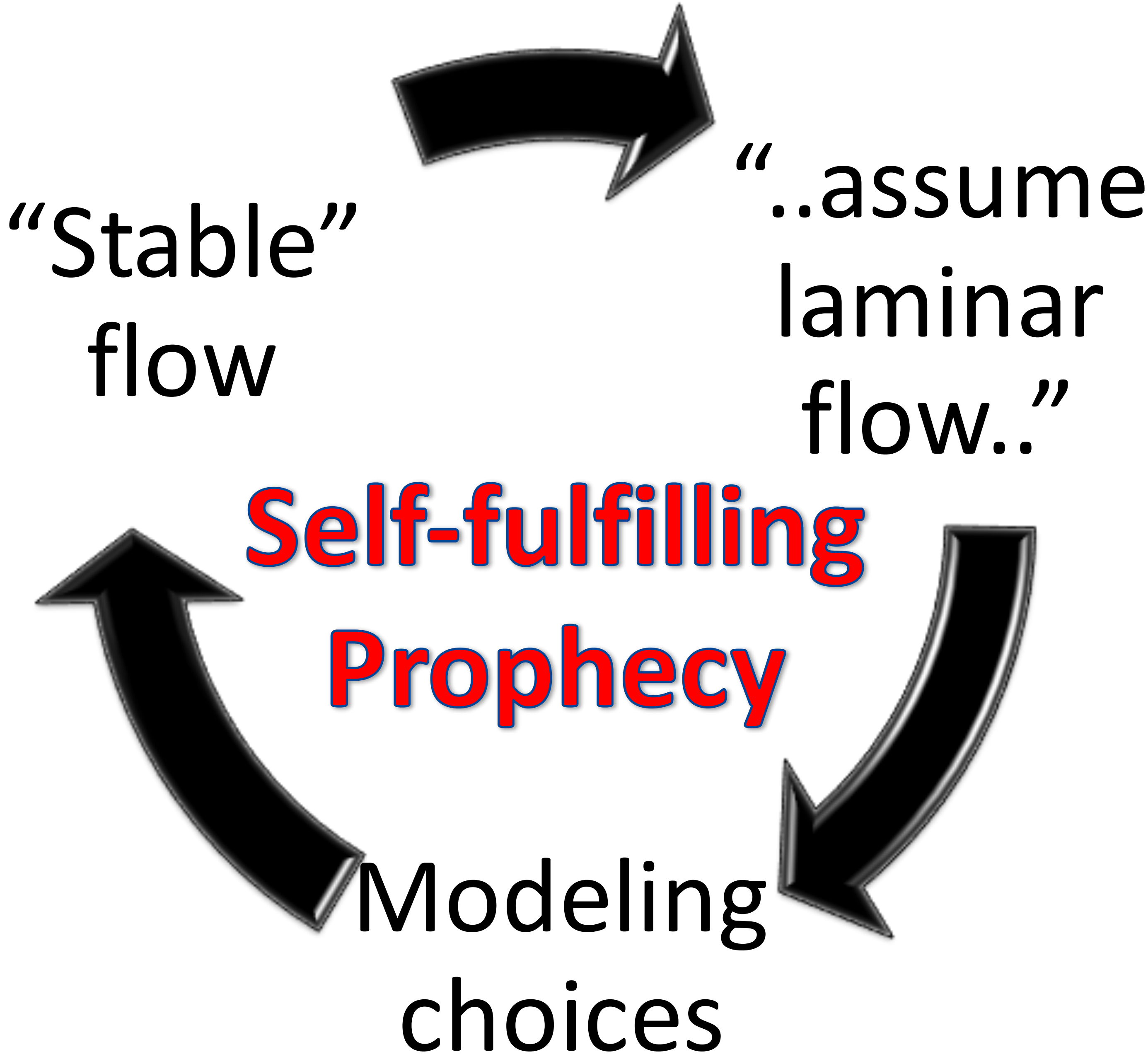


Reynolds O. 1883. 'An experimental investigation…'
Proc. R. Soc. Lond. Ser. A 35:84–99


"Stable" flow
"..assume laminar flow.."
Modeling choices
Self-fulfilling Prophecy

Conclusion

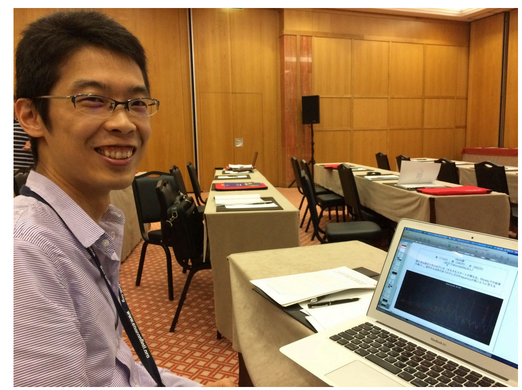
- ASME Journal of Fluids Engineering’s 1986 editorial policy:
  - “It has been demonstrated many times that for first-order methods, the effect of **numeric diffusion on the solution accuracy is devastating**,”
  - “A single calculation of a fixed grid is **not acceptable**.”
  - We asked for V&V in a community challenge: Majority replied “None”.

- There are no Standard Operating Procedures in computational biomechanics
  - Would such be helpful?

- For results to be consistent we need:
  - Agree on standardized and objective techniques
  - Methodological rigor
  - Large multi center studies
  - Meta analyses

Status of Computational Biomedical Engineering

- Well intended fishing expedition?
- Will we get "there"?
- How did we get "here"?
  - Computational tools presented as validated
  - Multidisciplinary research – multi-mess?



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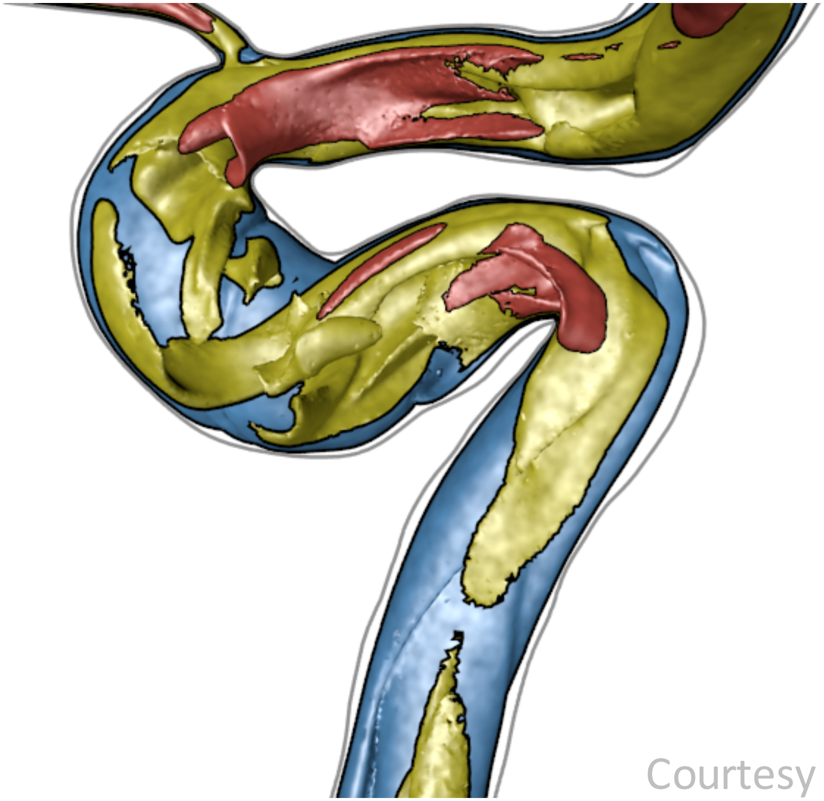
- **Prof. F. Loth (Department of Mechanical Engineering, University of Akron, US)**

- **K. Kono (Department of Neurosurgery, Wakayama Rosai Hospital, Japan)**



Courtesy of Max Julian

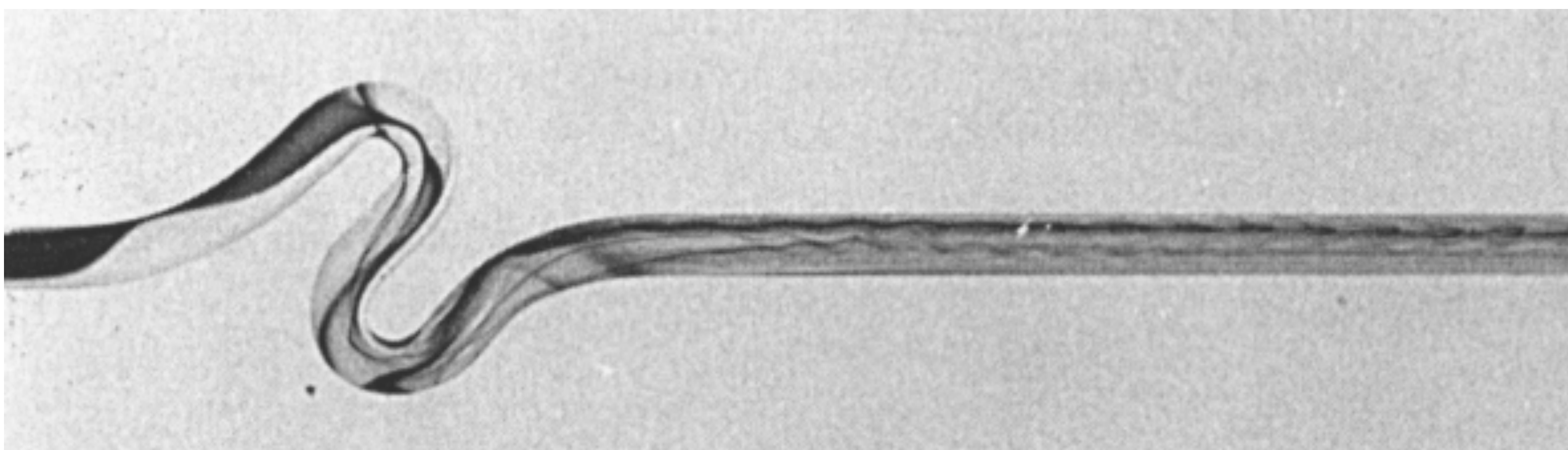
- To reproduce some of the results, please visit:
  - CFD solver: https://github.com/mikaem/Oasis
  - Models: http://ecm2.mathcs.emory.edu/aneuriskweb/index
  - VMTK parent vessel reconstruction tutorial:

    http://www.vmtk.org/tutorials/ParentVesselReconstruction.html

Strother

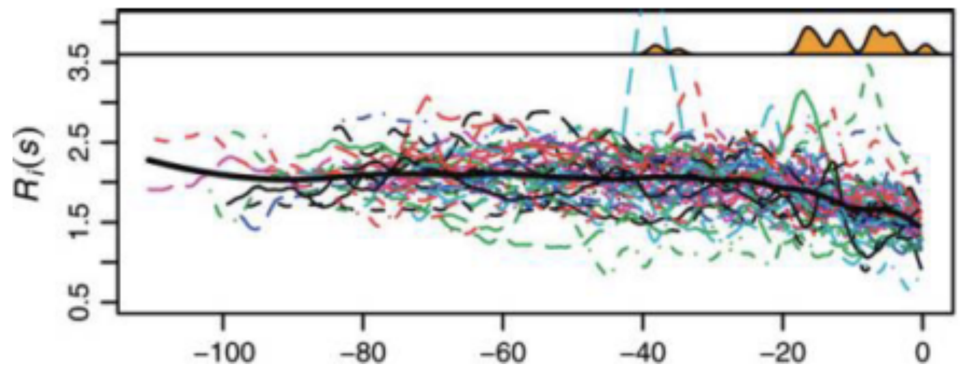
"Six months in the lab can save you a day in the library" - Albert Migliori.

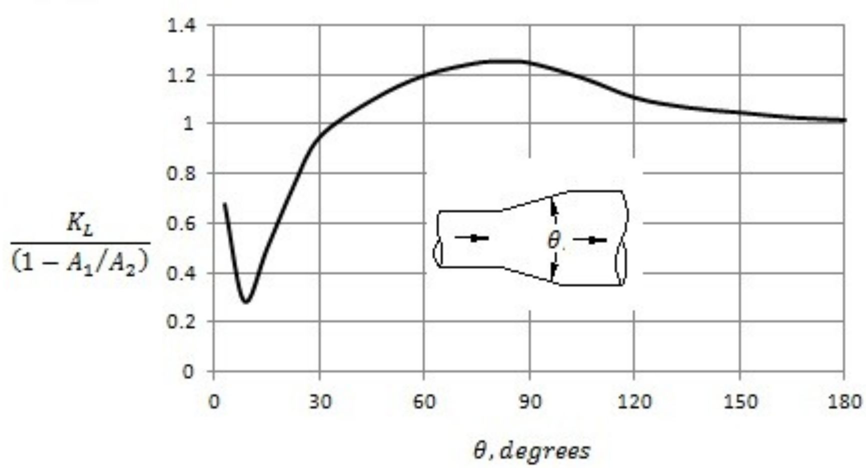
- Stehbens*, Re ~500, constant area, steady flow
- Characteristic scales:
  - U ~1m/s, D ~1mm
  - V = D/T => T = D/V = 1/1000s, or 1 msec
- To numerically resolve 1k Hz => 10-20k time steps



*Stehbens et al., **Flow through S-shaped glass models simulating arterial tortuosities.** Q J Exp Physiol. 1987 Apr;72(2):201-13.

"A computation is a temptation that should be resisted as long as possible" J.P. Boyd

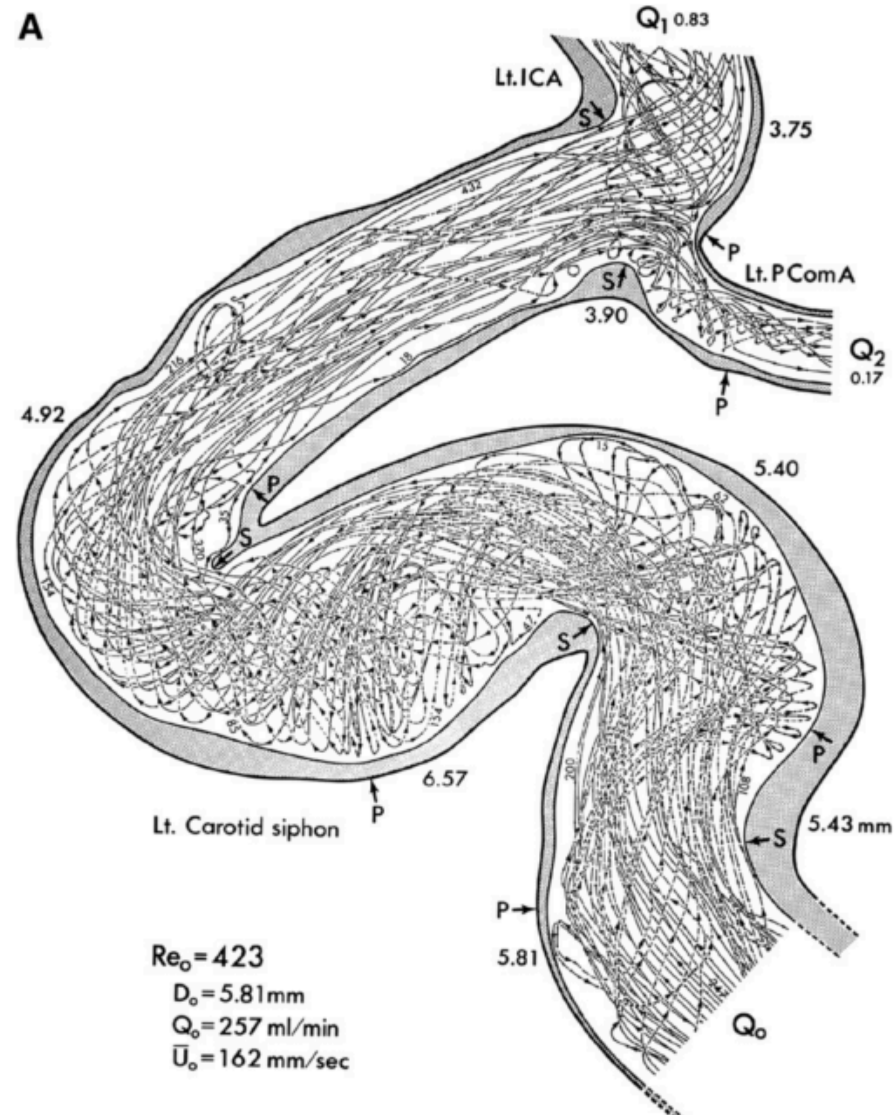




Sangalli et al. "A case study in exploratory functional data analysis: geometrical features of the internal carotid artery." *Journal of the American Statistical Association* 104(485), 2009.

"Six months in the lab can save you a day in the library" - Albert Migliori.

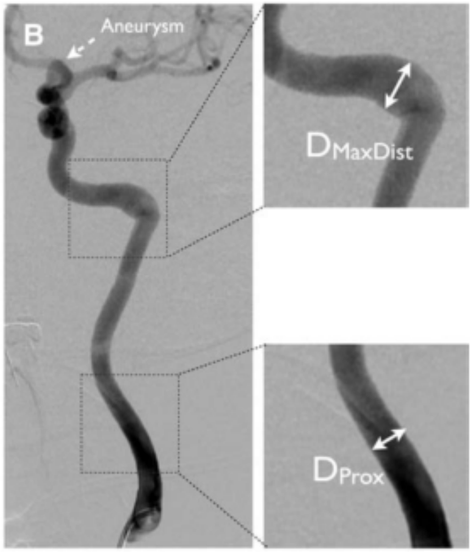
- Steady state flow in patient-specific casts*
- "suddenly changed its direction and rejoined the mainstream"
- "highly disturbed by the presence of a strong helical flow"

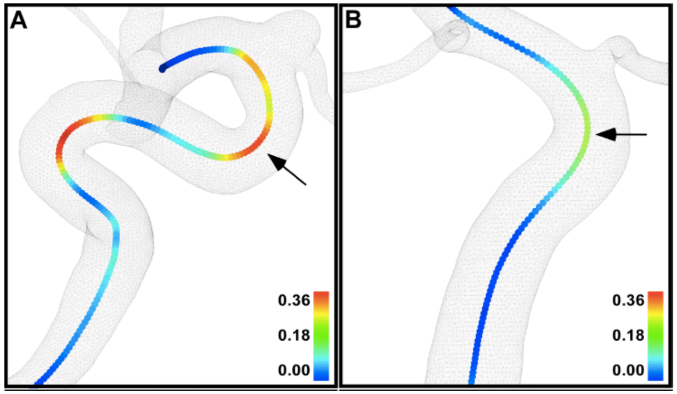


*Takeuchi, S., Karino, T., 2010. World Neurosurgery 73, 174–85; discussion e27

Clinical hints of flow instabilities

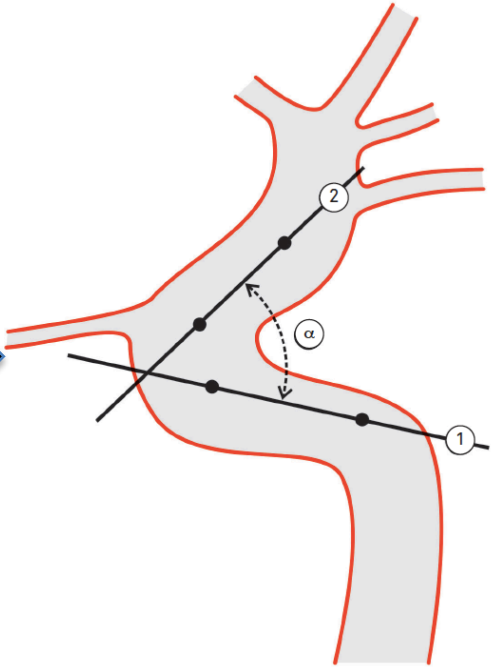
- Extracranial ICA area variations associated with intracranial aneurysms*





- Peak curvatures**

- Narrower angle***

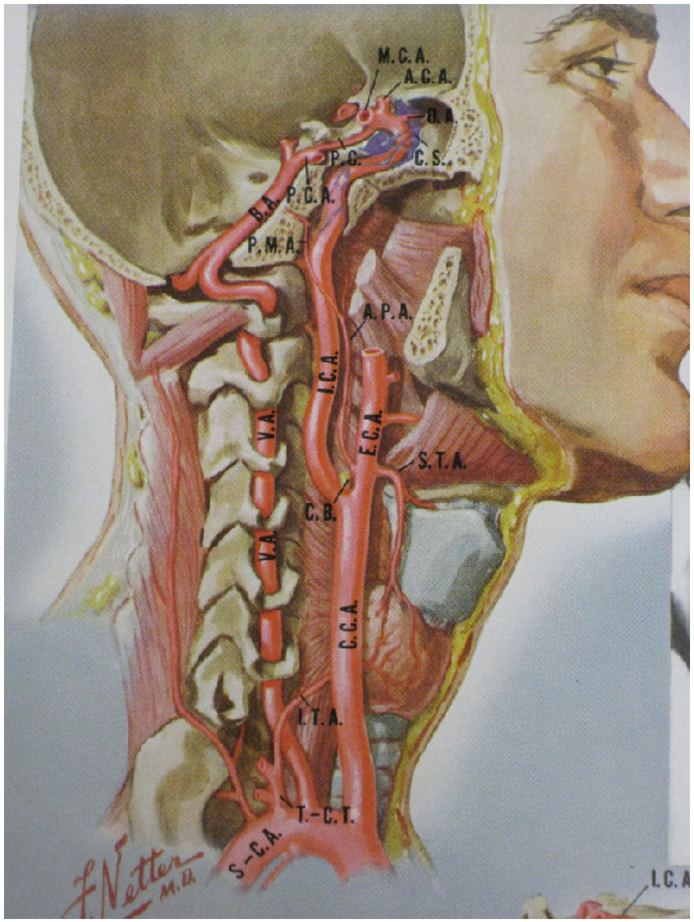


*Schimansky et al., Stroke. 2013 Dec;44(12):3561-4

**Lauric et al. J Neurointerv Surg. 2013 Dec 11

***Silva Neto et al. Arq Neuropsiquiatr. 2012 Dec;70(12):917-21.

Clinical hints of flow instabilities



- Extra cranial aneurysms in the ICA are rare – normally caused by an upstream stenosis*
- “Normal carotid arteries were found in 32% of patients with a bruit.”**

*Rosset et al. JVascSurg, 2000, 31:713-723.

**Davies et al. *PostgradMedJ, 1994,* 70: 433-435.