Brain haemodynamics and neurodegenerative diseases. A modelling approach

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Work done with former PhD student Lucas Mueller

Paper to read: Lucas O. Mueller and Eleuterio F. Toro. Enhanced global mathematical model for studying cerebral venous blood flow. Journal of Biomechanics, Volume 47, Issue 13, Pages 3361-3372, October 17, 2014.

December 5, 2014

The mechanics of the flowing blood interacts with the wall

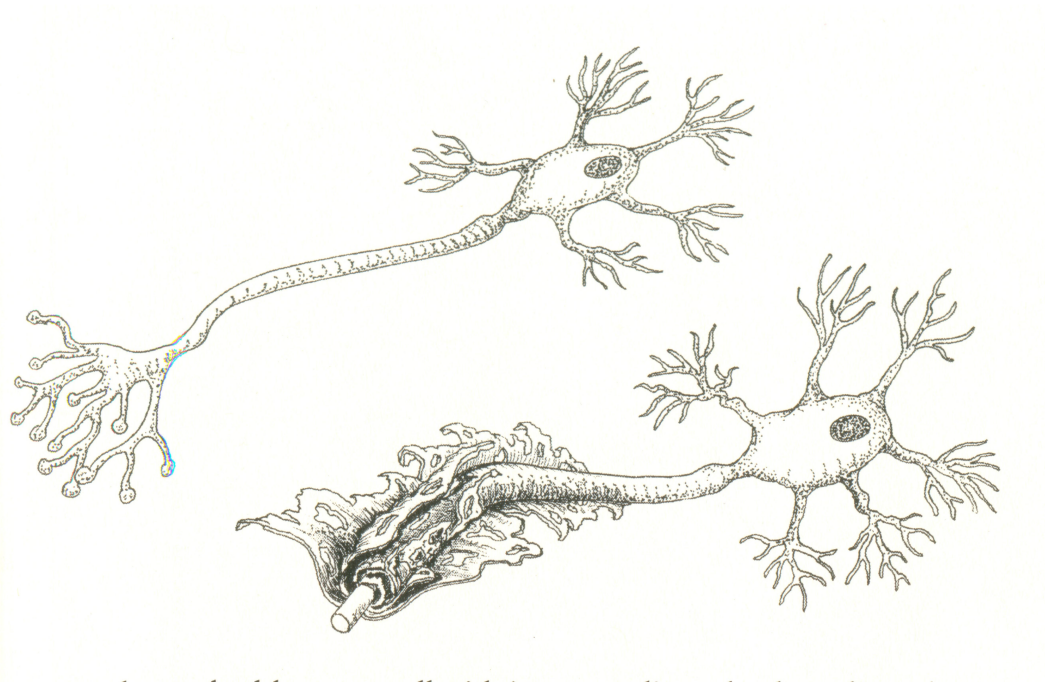
Contents

Neurodegenerative diseases

- Multiple Sclerosis (MS)
- Transient Global Amnesia (TGA)
- Transient Monocular Blindnes (TMB)
- Meniere's Disease (MD)
- Idiopathic Parkinson's Disease (IPD)

Multiple Sclerosis. what is it?

Multiple Sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system. The exact cause remains unknown, but most evidence favours an autoimmune mechanism (Laupacis et al. 2011)



Taken from M A Rhodes. CCSVI as the cause of multiple sclerosis. Mc Farland Health Topics (2011)

- Damage to the protective layer of axons, called myelin
- Axons cannot longer transmit signals efficiently

What happens to patients with MS?

- cognitive impairment
- muscle spasticity
- mobility, coordination, balance problems
- speech and visual problems
- chronic fatigue
- acute or chronic pain
- bladder and bowel problems

Patients with MS have a shorter-than-normal life span
as a consequence of the medical condition
suicide is fairly common, as a result of depression

Other facts about Multiple Sclerosis

- MS is the most common cause of neurological disabilities in young adults (20-50)
- Europe has about 400 thousand MS patients (60 thousand in Italy)
- USA has about 400 thousand MS patients
- The world has about 2.5 million MS patients
- Causes of the disease are unknown
- There is no cure at present
- Treatments on offer are simply aimed at modifying the course of the disease: *Disease Modifying Treatment*

Two main theories for MS:

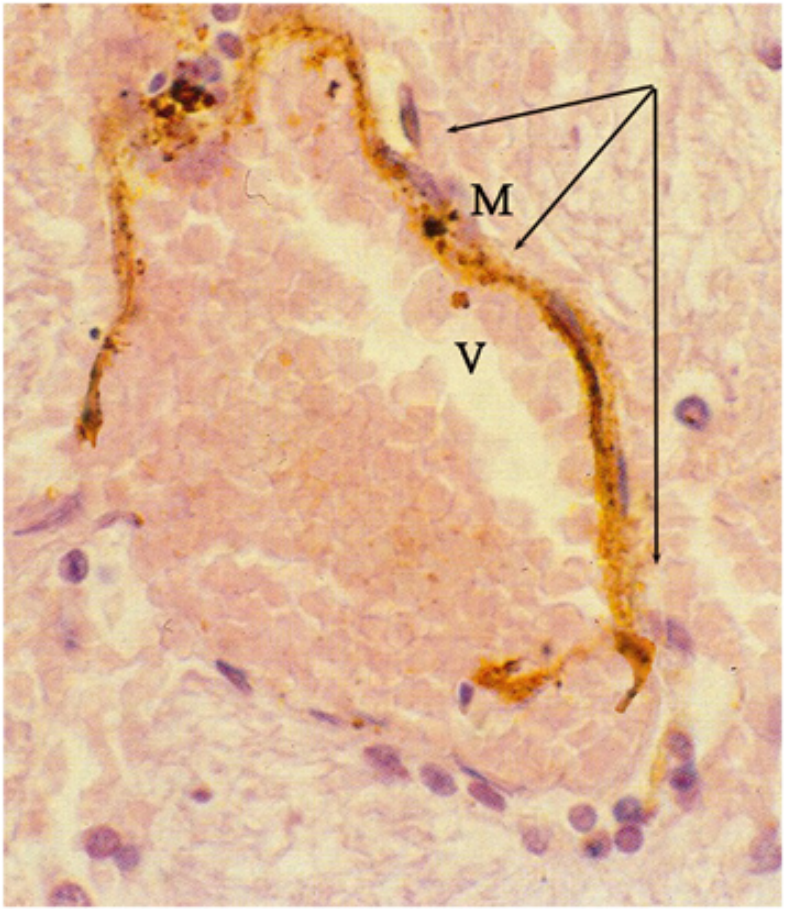
- **The autoimmune theory:** the immune system, for a yet unknown reason, attacks self cells. This is currently the dominant theory.

  Recall definition of MS from Laupacis et al. (2011):

  Multiple Sclerosis is a chronic demyelinating and degenerative disease of the central nervous system. The exact cause remains unknown, but most evidence favours an autoimmune mechanism

- **The vascular theory:** anomalous venous flow in the brain has important role to play
  - Charcot (1860), in post-mortem studies observed that lesions in CNS are invariably linked to veins
  - See also Tracey Putnam (1935); Fog (1965); Schelling (1986)
  - Adams (1988) established without any doubts that MS plaques are linked to veins
  - **Zamboni (2009) has resurfaced the vascular theory of MS**
- **Common ground:** the autoimmune theory accepts that T cells escape from blood stream through the Blood-Brain-Barrier (BBB)

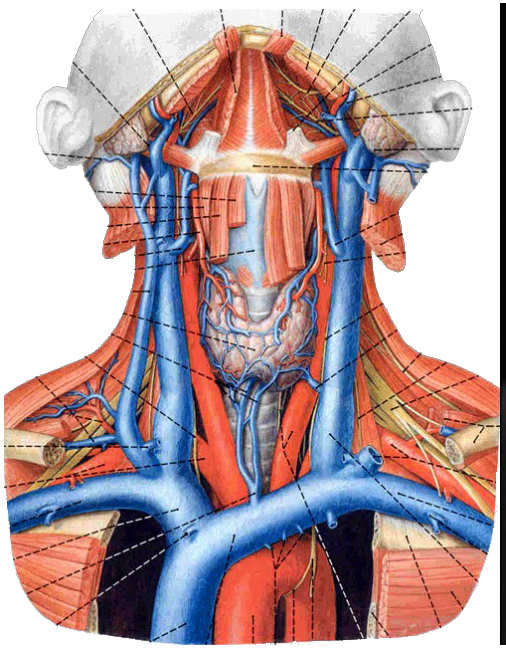
Adams's evidence for vascular link to MS



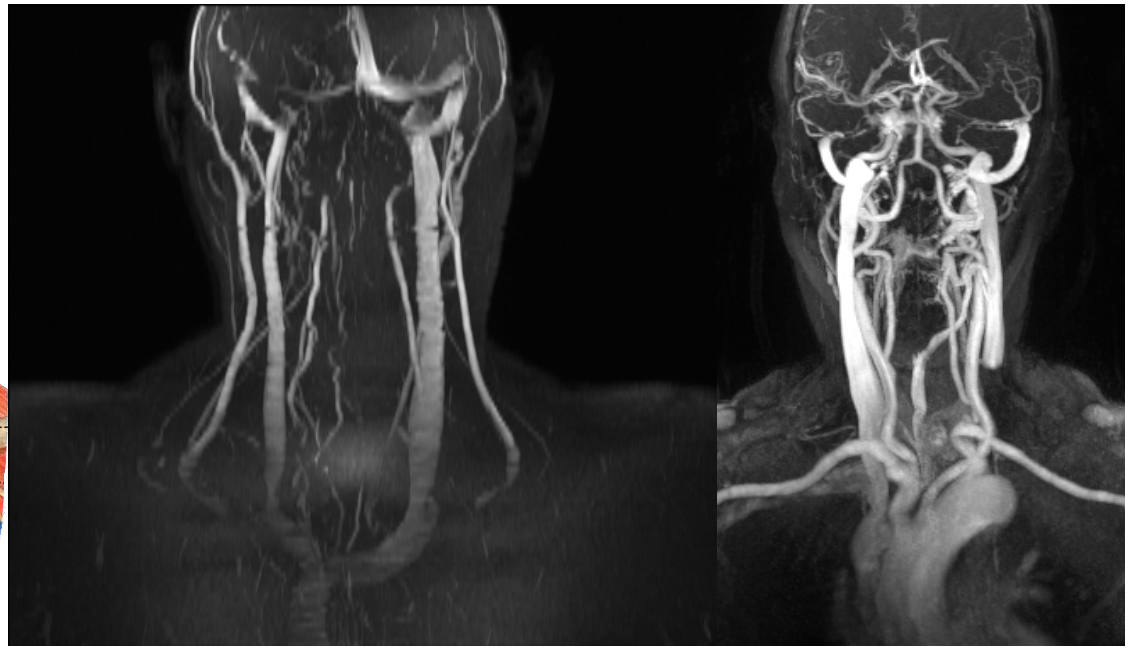
Streaks of blood (arrows) encircling wall of vein (V) at the centre of MS plaque in brain (Adams, 1988).

Zamboni's discovery: CCSVI

Zamboni et al. (2009) discovered that MS patients had vessel malformations in the extra cranial venous system causing anomalous venous return from brain (Chronic Cerebro Spinal Venous Insufficiency, or CCSVI)



Left: Main neck veins.



Right: MRI images from Haacke et al. (2012).

Recent research (Haacke et al. 2012)

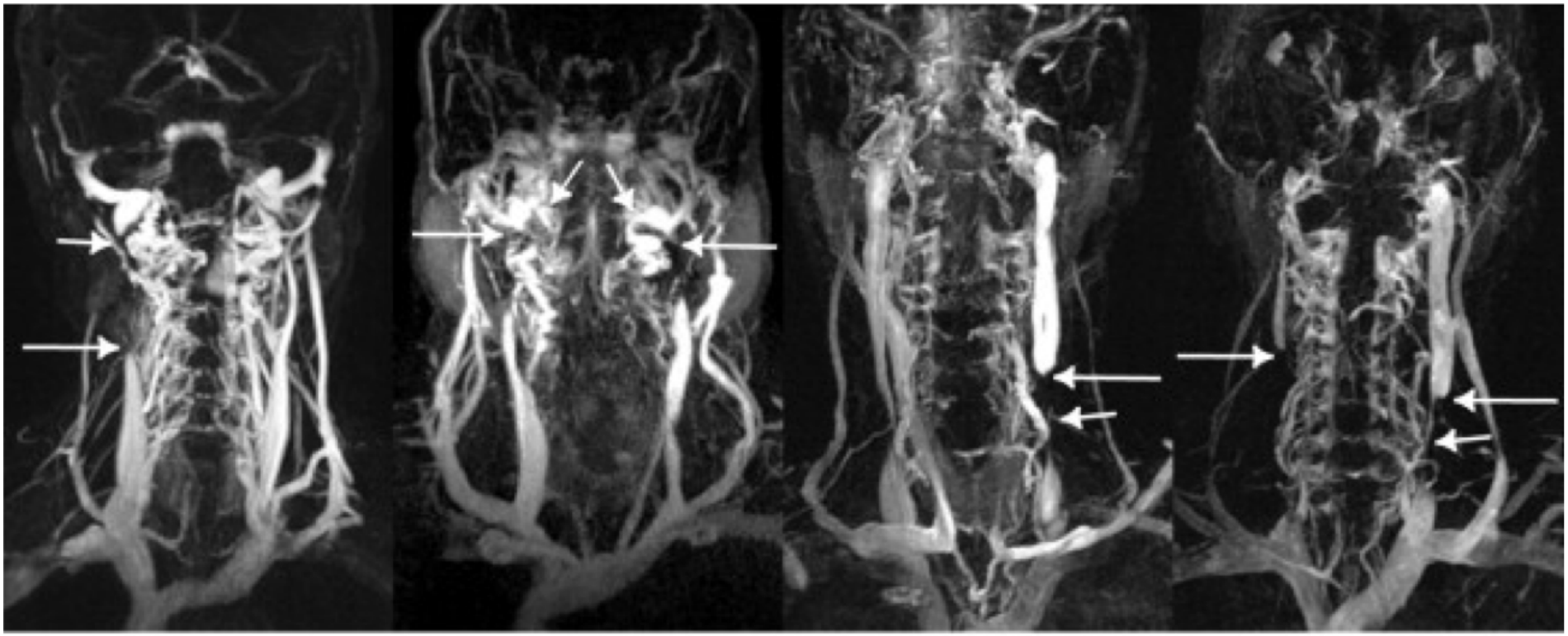


Fig. 1 of Haacke et al. (2012).
(a) RIJV is malformed (long arrow); right sigmoid sinus drains into vertebral plexuses (short arrow).

(b) both IJVs are truncated (long arrows); sigmoid sinuses drains into vertebral plexuses (short arrows).

(c) LIJV is truncated (long arrow); thin connection between midneck level and inferior jugular bulb near confluence with subclavian vein (short arrow).

(d) both IJVs show continuous enhancement from sigmoid sinus through upper neck level but are truncated near midneck level (long arrows).

Hypothesised sequence of events leading to MS:

1. Extracranial venous malformations (eg stenoses)
2. Chronic venous hypertension
3. Separation of tight junctions and disruption of blood-brain-barrier (BBB)
4. Filtration of colloids through the exposed porous basement membranes
5. Disruption of axon internal transport systems, leading to their disintegration
6. *Normal* inflammatory processes would follow, probably indistinguishable from those associated with autoimmune disease

Other venous-related pathologies

Transient Global Amnesia (TGA)

Transient Global Amnesia (TGA) is a sudden, temporary episode of memory loss. A TGA episode is rare and usually short-lived

Chung et al. (2006) hypothesize that retrograde venous hypertension plays a role in the pathogenesis of TGA. They found:

- Retrograde intracranial venous flow caused by left brachiocephalic vein occlusion was found only in patients with TGA and not in controls
- Compression of the vein is caused the sternum and the aorta during regular breathing
- TGA patients may have an underlying impairment of cerebral venous outflow that increases their vulnerability to TGA attack

C. Chung, H. Hsu, and A. Chao. Detection of intracranial venous reflux in patients of transient global amnesia. Neurology, 66:18731877, 2006

Transient Monocular Blindness (TMB)

TMB attacks may occur during straining activities that impede cerebral venous return. Disturbance of cerebral and orbital venous circulation may be involved in TMB

Chung et al. (2010) found:

- The frequency of **jugular venous reflux (JVR)** is higher in patients with transient monocular blindness (TMB)
- They hypothesize that JVR influences ocular venous outflow, and resulting disturbances in cerebral and ocular venous circulation might be a cause of TMB
- In the case-control study, TMB patients had a wider retinal venule diameter, especially TMB patients with JVR
- Conclusion: JVR associated with TMB impedes ocular venous outflow, and the subsequent disturbances in ocular venous circulation may be a cause of TMB

C. Chung, H. Hsu, A. Chao, C. Cheng, S. Lin, and H. Hu. Jugular venous reflux affects ocular venous system in transient monocular blindness. Cerebrovascular Diseases, 29:122129, 2010

Meniere's disease (MD)

MD is a disorder of the inner ear that causes vertigo, fluctuating hearing loss and tinnitus. The cause is unknown and there is no cure

Filipo et al (2013) found:

- A high prevalence of IJVs stenosis with haemodynamic changes (increased velocity or absence of flow) was observed (66.7 vs 33.3%)
- The results obtained showed a vascular pattern of cerebrospinal venous system present in patients affected by definite Meniere
- This vascular impairment affects the vascular areas more directly involved in the venous drainage of the inner ear. Thus venous stasis may be considered a further pathogenetic mechanism for development of Meniere's disease.

Filipo R, Ciciarello F, Attanasio G, Mancini P, Covelli E, Agati L, Fedele F, Viccaro M. Chronic cerebrospinal venous insufficiency in patients with Mnire's disease. Eur Arch Otorhinolaryngol. 2013 Dec 7

Idiopathic Parkinson's Disease (IPD)

Idiopathic Parkinson's disease (IPD) remains one of those neurodegenerative diseases for which the cause remains unknown

Liu et al. (2014) found:

- Many clinically diagnosed cases of IPD are associated with cerebrovascular disease and white matter hyperintensities (WMHs)
- The authors investigated the **presence of transverse sinus and extracranial venous abnormalities** in IPD patients and their relationship with brain WMHs
- Venous abnormalities (categories 1, 2, and 3) were seen in 57% of IPD subjects and in only 30% of controls
- *A major fraction of IPD patients appear to have abnormal venous anatomy and flow on the left side of the brain and neck and that the flow abnormalities appear to correlate with WMH volume*

M. Liu, H. Xu, Y. Wang, Y. Zhong, S. Xia, D. Utriainen, T. Wang, and E. M. Haacke. Patterns of chronic venous insufficiency in the dural sinuses and extracranial draining veins and their relationship with white matter hyperintensities for patients with Parkinsons disease. Journal of Vascular Surgery, pages na, 2014.

Modelling: aims and challenges

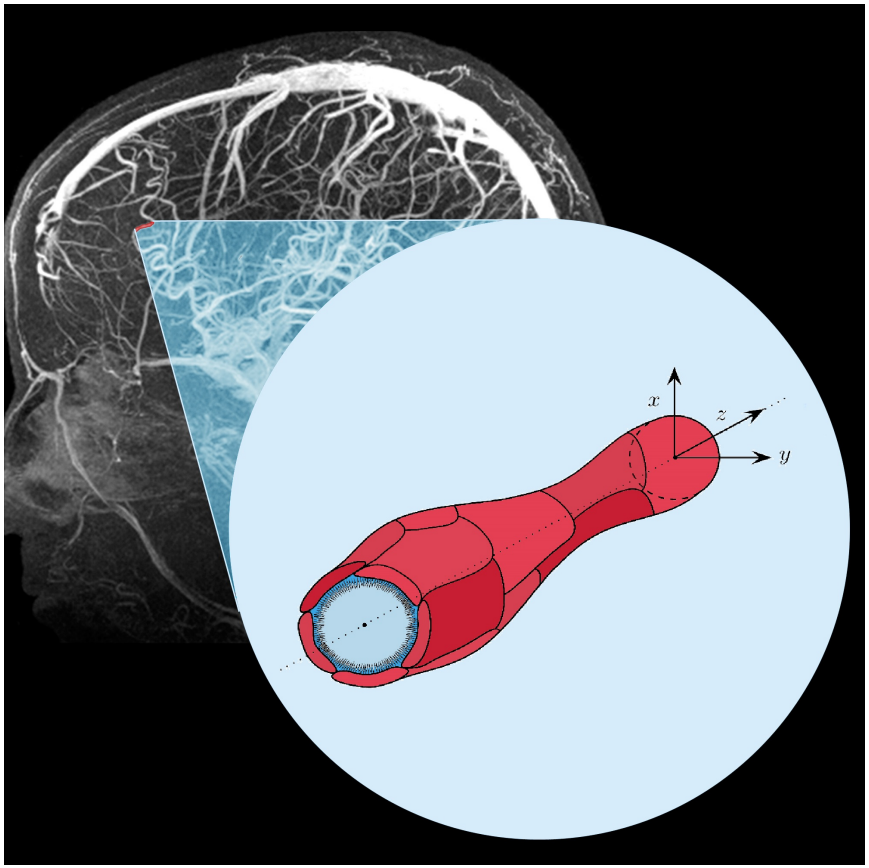
1. To develop a global, close-loop mathematical model for the entire human circulation
   - Use the model to understand the link between venous anomalies and Multiple Sclerosis, Idiopathic Parkinson's Disease and Meniere's Disease.
   - Understanding the dominant bio-physical mechanisms may contribute to explain the pathologies and may help in the design of potential cures
2. Develop a model for transport across the vessel wall (capillaries)
3. Couple haemodynamics to transport across vessel walls

The sought model for the human circulation

- Global, closed loop (BCs avoided)
- Model components to include:
  - the heart,
  - the arterial system,
  - the microvasculature,
  - the venous system,
  - the cerebral spinal fluid and
  - the pulmonary circulation
- Multiscale approach: 0D+1D+3D

Equations

Typical blood vessel configuration



- The full problem for the human body is computationally intractable
- Interaction of fluid mechanics and solid mechanics (FSI)
- Simplifications are needed. Multi-scale approach: 0D+1D+3D

One-dimensional models

Physical principles of mass and momentum balance give:

$$\begin{cases} \partial_t A + \partial_x q = 0, \\ \partial_t q + \partial_x \left(\hat{\alpha} \dfrac{q^2}{A} \right) + \dfrac{A}{\rho} \partial_x p = -Ru. \end{cases} \tag{1}$$

The unknowns are:

- $A(x,t)$: cross-sectional area of vessel;
- $q(x,t)$: flow;
- $p(x,t)$: internal pressure;

Parameters:

- R: viscous resistance of the flow per unit length of the tube;
- ρ: density of blood;
- $\hat{\alpha}$: parameter associated to assumed velocity profile.

A **closure condition** is required: the **tube law**.

$$p(x,t) = p_e(x,t) + K(x)\phi(A(x,t),x)\ , \tag{2}$$

with

$$\phi(A,x) = \alpha^m - \alpha^n\,; \quad \alpha = \frac{A}{A_0}\ . \tag{3}$$

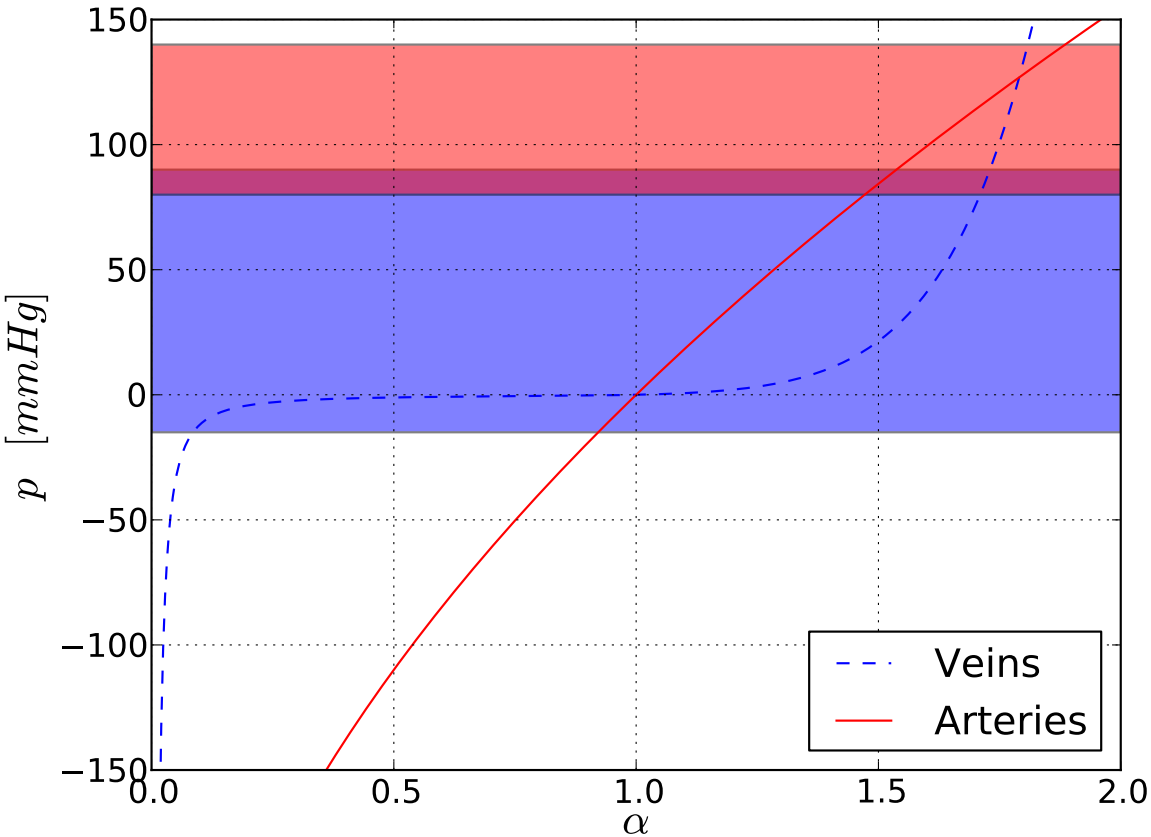
$A_0(x)$ is the vessel cross-sectional area at a reference configuration.

$$K(x) = \frac{E(x)}{12(1-\nu^2)}\left(\frac{h_0(x)}{R_0(x)}\right)^3\ . \tag{4}$$

$h_0(x)$: vessel thickness; $R_0(x)$: radius at equilibrium; $E(x)$: Young's modulus; ν: Poisson ratio.
There are mathematical (and physical) restrictions on m and n.

- For arteries one takes $m = 1/2$, $n = 0$.
- For collapsible vessels, such as veins, one takes $m \approx 10$, $n = -3/2$.

Tube law: pressure behaviour



Qualitative behaviour of pressure as function of non-dimensional cross-sectional area, for arteries and veins.

$$\partial_x p = \psi_A \partial_x A + \psi_K \partial_x K + \psi_{A_0} \partial_x A_0 + \partial_x p_e(x,t) \ . \tag{5}$$

The complete system reads

$$\left.\begin{aligned} \partial_t A + \partial_x(uA) &= 0 \ , \\ \partial_t(uA) + \partial_x(Au^2) + \tfrac{A}{\rho}\psi_A \partial_x A &= \\ -\tfrac{A}{\rho}\psi_K \partial_x K - \tfrac{A}{\rho}\psi_{A_0} \partial_x A_0 - \partial_x p_e(x,t) - Ru & \end{aligned}\right\} \tag{6}$$

with

$$\left.\begin{aligned} \psi_A = \tfrac{\partial \psi}{\partial A} &= \tfrac{K}{A}\left[m\alpha^m - n\alpha^n\right] \ , \\ \psi_K = \tfrac{\partial \psi}{\partial K} &= \alpha^m - \alpha^n \ , \\ \psi_{A_0} = \tfrac{\partial \psi}{\partial A_0} &= -\tfrac{K}{A_0}\left[m\alpha^m - n\alpha^n\right] \ . \end{aligned}\right\} \tag{7}$$

Variable material properties

Treat parameters of the problem as new unknowns (LeFloch, 1989). Add trivial PDEs:

$$\left.\begin{aligned} \partial_t K(x) &= 0 \,, \\ \partial_t A_0(x) &= 0 \,, \\ \partial_t p_e(x) &= F(x,t) \,. \end{aligned}\right\} \tag{8}$$

Add advection equations for transport of species concentration $\phi_k(x,t)$

$$\partial_t \phi_k + u \partial_x \phi_k = 0 \,. \tag{9}$$

The resulting, enlarged system in quasi-linear form reads

$$\partial_t \mathbf{Q} + \mathbf{A}(\mathbf{Q}) \partial_x \mathbf{Q} = \mathbf{S}(\mathbf{Q}) \,, \tag{10}$$

where

$$\mathbf{Q} = \begin{bmatrix} q_1 \\ q_2 \\ q_3 \\ q_4 \\ q_5 \\ q_6 \end{bmatrix} \equiv \begin{bmatrix} A \\ Au \\ K \\ A_0 \\ p_e \\ \phi_k \end{bmatrix}, \ \mathbf{S}(\mathbf{Q}) = \begin{bmatrix} s_1 \\ s_2 \\ s_3 \\ s_4 \\ s_5 \\ s_6 \end{bmatrix} \equiv \begin{bmatrix} 0 \\ -Ru \\ 0 \\ 0 \\ F(x,t) \\ 0 \end{bmatrix}, \tag{11}$$

$$\mathbf{A}(\mathbf{Q}) = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 \\ \frac{A}{\rho}\psi_A - u^2 & 2u & \frac{A}{\rho}\psi_K & \frac{A}{\rho}\psi_{A_0} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ -u\phi & \phi & 0 & 0 & 0 & u \end{bmatrix}. \tag{12}$$

Eigenstructure

- Eigenvalues

$$\lambda_1 = u - c\,, \quad \lambda_2 \equiv \lambda_3 \equiv \lambda_4 = 0\,, \quad \lambda_5 = u\,, \quad \lambda_6 = u + c\,, \tag{13}$$

where

$$c = \sqrt{\frac{A}{\rho}\psi_A} = \sqrt{\frac{K}{\rho}\left[m\alpha^m - n\alpha^n\right]} \tag{14}$$

is the *wave speed*. All eigenvalues are real provided:

$$m\alpha^m \geq n\alpha^n\,. \tag{15}$$

- Eigenvectors. Complete
- Charactaeristic fields. The λ_1 and λ_6 characteristic fields are genuinely non-linear provided

$$m(m+2)\alpha^m \neq n(n+2)\alpha^n \tag{16}$$

and the λ_i-characteristic fields, for $i = 2, \ldots, 5$, are linearly degenerate.

Toro E F and Siviglia A. *Flow in collapsible tubes with discontinuous mechanical properties: mathematical model and exact solutions.* Communications in Computational Physics. Vol. 13, Number 2, pp 361-385, Feb. 2013.

Difficulties

For a simple version of the model, the Riemann problem

$$\left.\begin{array}{l} \partial_t \mathbf{Q} + \mathbf{A}(\mathbf{Q})\partial_x \mathbf{Q} = \mathbf{0}\ , \quad x \in \mathcal{R}\ , \quad t > 0\ , \\ \\ \mathbf{Q}(x,0) = \left\{ \begin{array}{ll} \mathbf{Q}_L & \text{if} \quad x < 0\ , \\ \mathbf{Q}_R & \text{if} \quad x > 0\ . \end{array} \right. \end{array}\right\} \tag{17}$$

has been studied in detail by Han et al. (2014). They found:

- The enlarged system is resonant
- The Riemann problem (17) has multiple solutions
- All solutions have been determined, for both the sub and supercritical cases.

Han E, Warneche G, Toro E F and Siviglia A. *On Riemann solutions to weakly hyperbolic systems: Part 1. Modelling subcritical flows in arteries.* **SIAM Journal of Mathematical Analysis** (Submitted, 2014)

Han E, Warneche G, Toro E F and Siviglia A. *On Riemann solutions to weakly hyperbolic systems: Part 2. Modelling supercritical flows in arteries.* **SIAM Journal of Mathematical Analysis.** (Submitted, 2014)

Numerical methods: ADER

The ADER approach: first published results

E F Toro, R C Millington and L A M Nejad. *Towards Very High Order Godunov Schemes.* In Godunov Methods: Theory and Applications. Edited Review. E. F. Toro (Editor), pages 905-937. Kluwer Academic/Plenum Publishers, 2001.

E F Toro and V A Titarev. *Solution of the generalised Riemann problem for advection-reaction equations.* Proceedings of the Royal Society of London. Series A. Vol. 458, pages 271-281, 2002.

T Schwartzkop, C D Munz and E F Toro. *ADER: High-order approach for linear hyperbolic systems in 2D. Journal of Scientific Computing. Vol. 17, pages 231-240, 2002.*

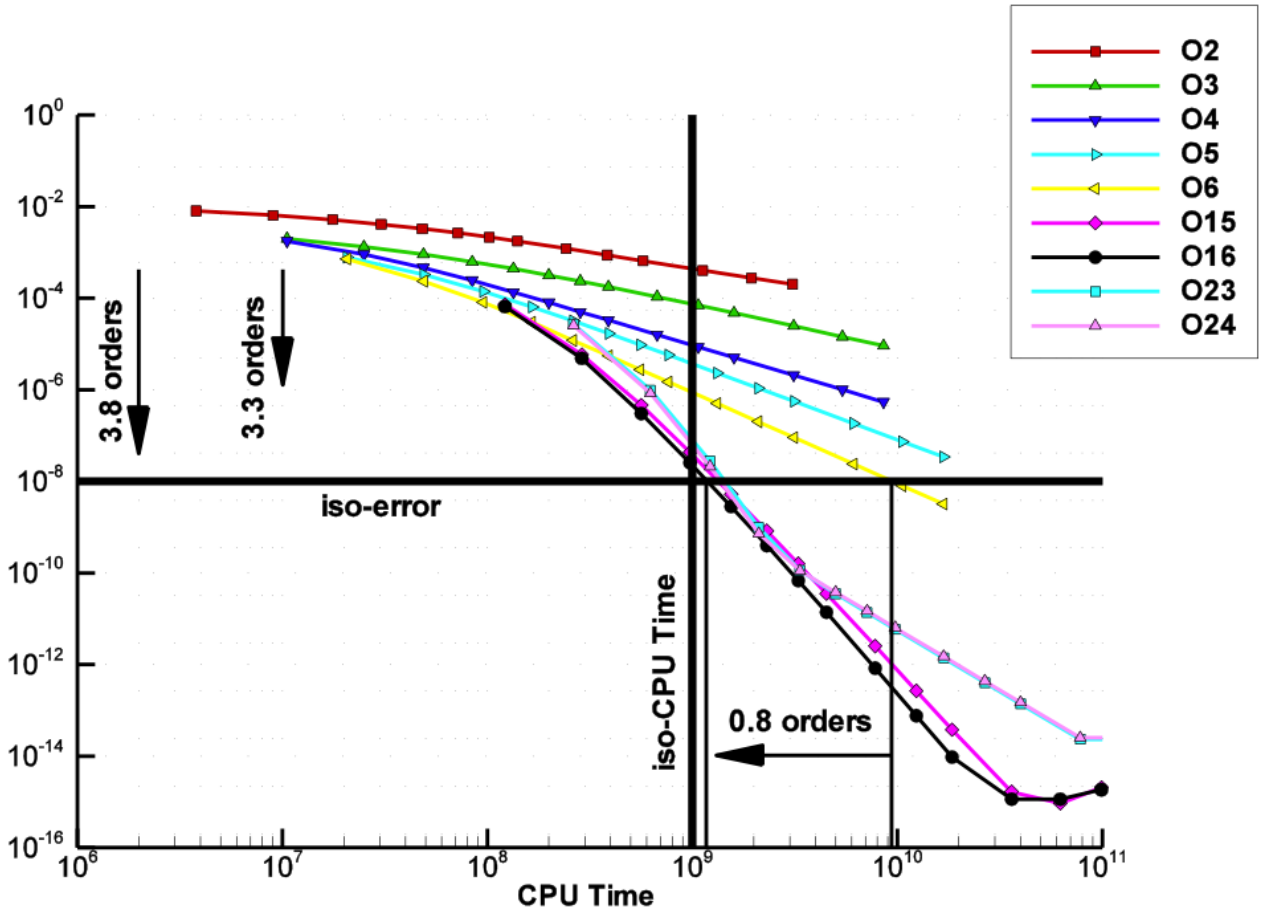
ADER:

Arbitrary Accuracy **DE**rivative **R**iemann problem

Collaborators in ADER research:

Mauricio Caceres, Richard Millington, Thomas Schwarzkopff, Claus-Dieter Munz, Vladimir Titarev, Yoko Takakura, Michael Dumbser, Martin Kaeser, Armin Iske, Cedric Enaux, Cristobal Castro, Giovanni Russo, Carlos Pares, Manuel Castro, Arturo Hidalgo, Gianluca Vignoli, Giovanna Grosso, Matteo Antuono, Alberto Canestrelli, Annunziato Siviglia, Gino Montecinos, Lucas Mueller, Junbo Cheng, Jiang Song, Claus Goetz

Why high accuracy ?



Test problem for linear acoustics.

Collaborators: M. Dumbser, T. Schwartzkopff, and C.-D. Munz. Arbitrary high order finite volume schemes for linear wave propagation. Book Series Notes on Numerical Fluid mechanics and Multidisciplinary Design. Springer Berlin / Heidelberg ISSN 1612-2909, Volume 91/2006

ADER numerical flux and numerical source

Consider the 1D case with source terms:

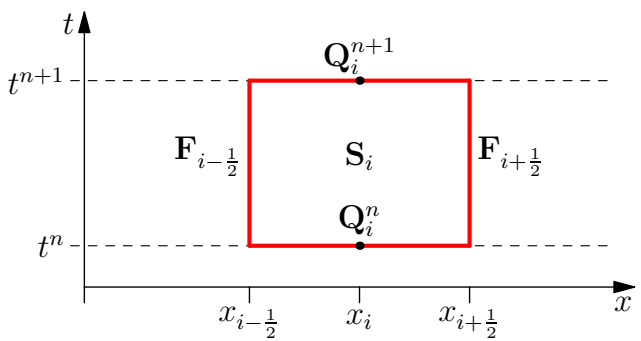
$$\partial_t \mathbf{Q}(x,t) + \mathbf{F}(\mathbf{Q}(x,t)) = \mathbf{S}(\mathbf{Q}(x,t)) \tag{18}$$

Finite volume explicit, one-step, fully discrete scheme reads:

$$\mathbf{Q}_i^{n+1} = \mathbf{Q}_i^n - \frac{\Delta t}{\Delta x}(\mathbf{F}_{i+\frac{1}{2}} - \mathbf{F}_{i-\frac{1}{2}}) + \Delta t \mathbf{S}_i \tag{19}$$

where

$$\left.\begin{aligned} &\text{Numerical flux: } \mathbf{F}_{i+\frac{1}{2}} \approx \frac{1}{\Delta t}\int_0^{\Delta t} \mathbf{F}(\mathbf{Q}_{i+\frac{1}{2}}(\tau))d\tau \\ &\text{Numerical source: } \mathbf{S}_i \approx \frac{1}{\Delta t \Delta x}\int_0^{\Delta t}\int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}} \mathbf{S}(\mathbf{Q}_i(x,\tau))dx d\tau \end{aligned}\right\} \tag{20}$$



Main ingredients of the ADER approach:

- High-order non-linear spatial reconstruction: $P_i(x)$, $i = 1, 2, \ldots, M$
- *Numerical flux:* solve high-order Riemann problem (or GRP): $\mathbf{Q}_{i+\frac{1}{2}}(\tau)$
  - Initial conditions are piece-wise smooth (e.g. polynomials of any degree), and
  - Source terms are included
- *Numerical source:* solve high-order Cauchy problem in cell i: $\mathbf{Q}_i(x, \tau)$

The Generalized Riemann Problem (GRP)

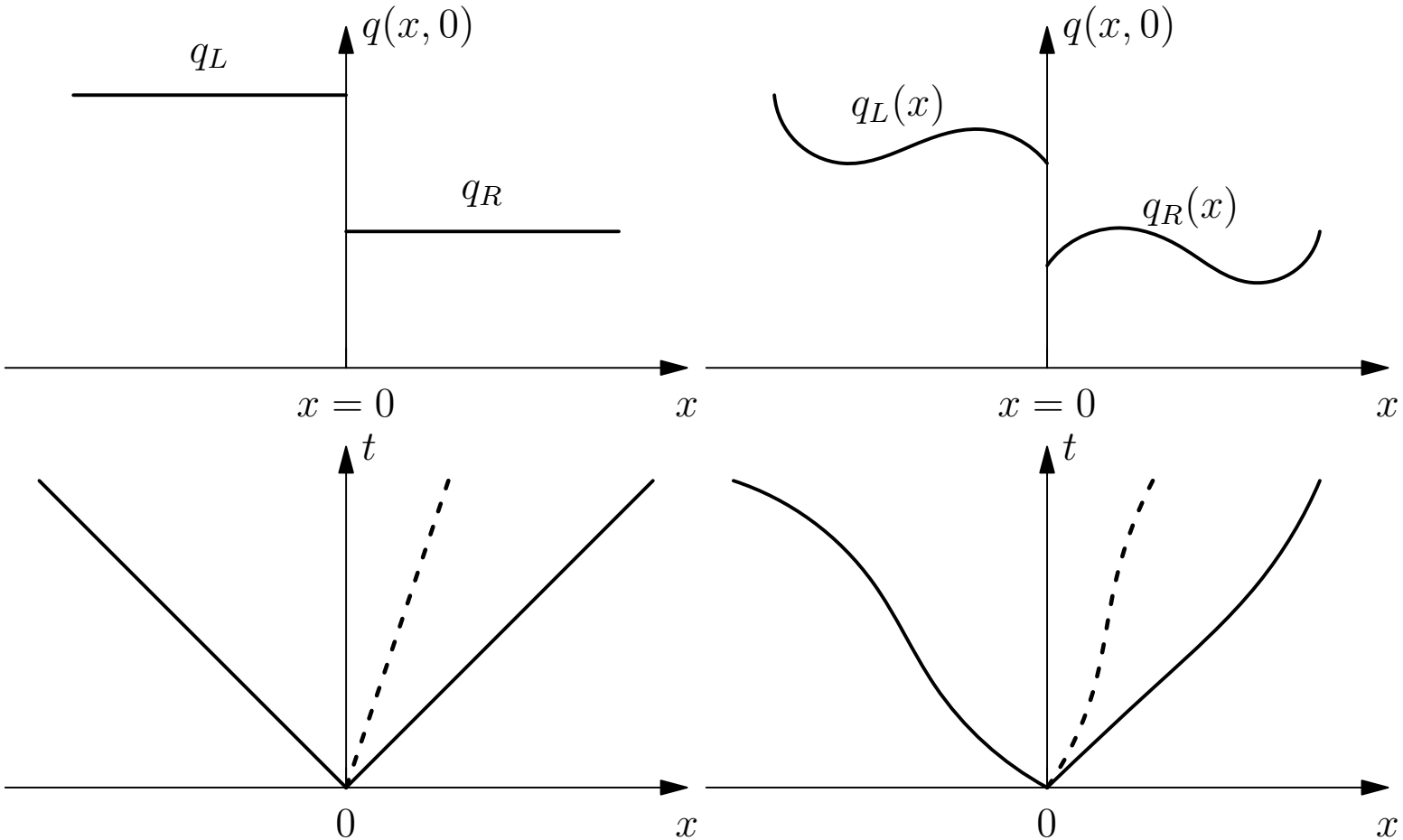
Generalized Riemann problem for hyperbolic systems of balance laws:

$$\left.\begin{array}{ll} \text{PDEs:} & \partial_t \mathbf{Q} + \partial_x \mathbf{F}(\mathbf{Q}) = \mathbf{S}(\mathbf{Q}) \ , \quad x \in (-\infty, \infty) \ , \quad t > 0 \\ \\ \text{ICs:} & \mathbf{Q}(x,0) = \begin{cases} \mathbf{Q}_L(x) & \text{if} \quad x < 0 \\ \\ \mathbf{Q}_R(x) & \text{if} \quad x > 0 \end{cases} \end{array}\right\} \tag{21}$$

Related works:

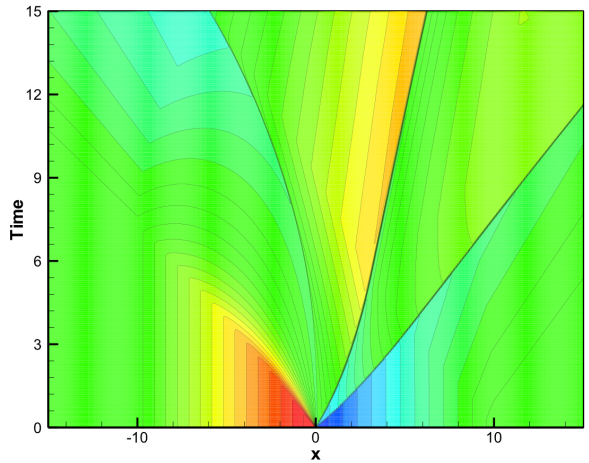
- Glimm et al. (1984)
- Ben-Artzi and Falcovitz (1984)
- Harten et al. (1987)
- LeFloch and Raviart (1989)
- Men'Shov (1990)
- LeFloch and Tatsien (1991)

Classical and Generalized Riemann Problems

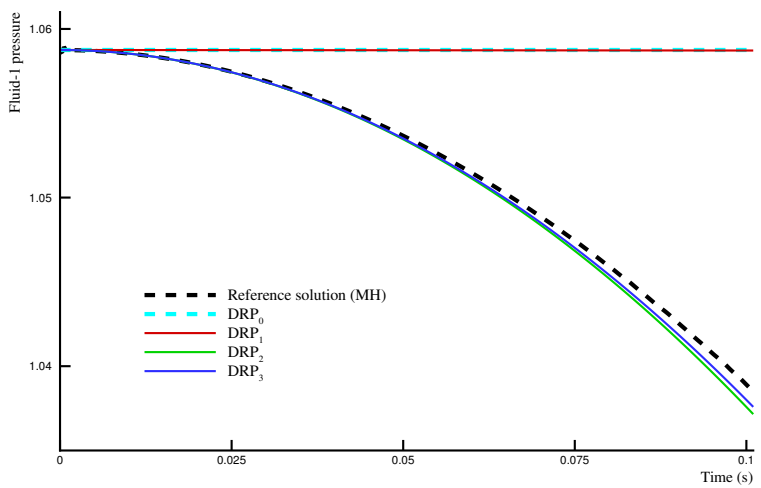


Local initial conditions and structure of solution of Riemann problem:
Left side: classical case; Right side: generalized case.

Examples of the Generalized Riemann Problem



Example: Structure of the solution of the Generalized Riemann Problem (courtesy of Dr V A Titarev)



Baer-Nunziato equations. GRP solution for solid phase pressure (Castro and Toro, 2006)

Solvers for the Generalized Riemann Problem used in ADER

1. Toro and Titarev (Proc. Roy. Soc. Lond. 2002). Semi-analytical solution using Raviart/Le Floch expansion. Extension of Ben-Artzi-Falcoviz method
2. Castro and Toro (JCP, 2008). Semi-analytical solution, analogous to (1)
3. Dumbser, Enaux and Toro (JCP, 2008). Numerical evolution of data coupled to interaction of evolved data at integration points via classical Riemann problem. (Extension of Harten's method). Can deal with stiff source terms
4. Goetz and Iske (2014)
5. Montecinos and Toro (JCP, 2014), analogous to (1) but implicit. Can deal with stiff source terms

ADER: a generalisation of Godunov's method

One-step conservative formula

$$\mathbf{Q}_i^{n+1} = \mathbf{Q}_i^n - \frac{\Delta t}{\Delta x}(\mathbf{F}_{i+\frac{1}{2}} - \mathbf{F}_{i-\frac{1}{2}}) + \Delta t \mathbf{S}_i \tag{22}$$

Numerical flux

$$\mathbf{F}_{i+\frac{1}{2}} = \frac{1}{\Delta t}\int_0^{\Delta t} \mathbf{F}(\mathbf{Q}_{i+\frac{1}{2}}(\tau))d\tau \quad \rightarrow \mathbf{F}_{i+\frac{1}{2}}^{God} = \mathbf{F}(\mathbf{Q}_{i+\frac{1}{2}}(0) \tag{23}$$

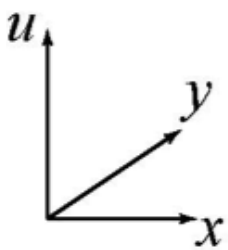
Numerical source

$$\mathbf{S}_i = \frac{1}{\Delta t \Delta x}\int_0^{\Delta t}\int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}} \mathbf{S}(\mathbf{Q}_i(x,\tau))dx d\tau \tag{24}$$

The three dimensional case

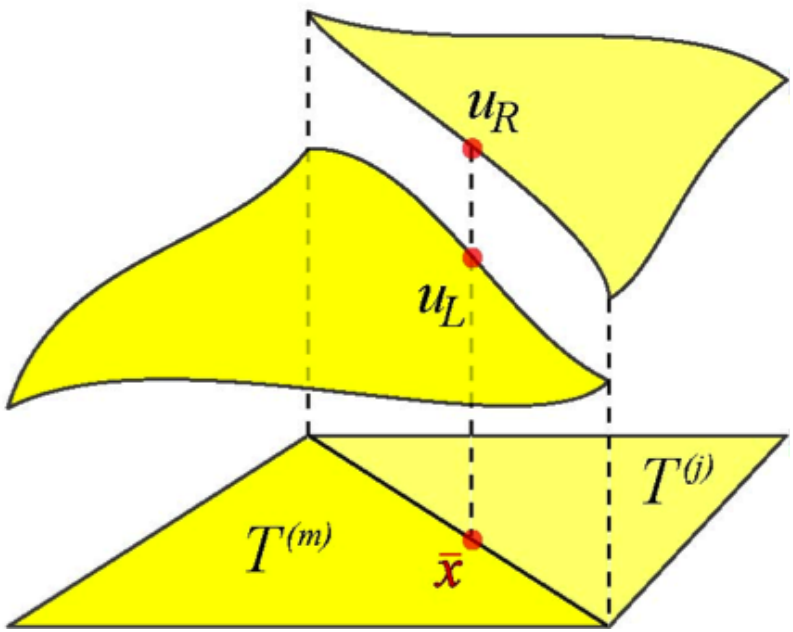
$$\partial_t \mathbf{Q} + \partial_x \mathbf{F}(\mathbf{Q}) + \partial_y \mathbf{G}(\mathbf{Q}) + \partial_z \mathbf{H}(\mathbf{Q}) = \mathbf{S}(\mathbf{Q}) \tag{25}$$

$$\mathcal{D}_{i+\frac{1}{2}} = \frac{1}{\Delta t} \int_0^{\Delta t} \left(\int \int_{A_k} \mathbf{D} \cdot \mathbf{n}_k d\mathbf{A} \right) d\tau \tag{26}$$



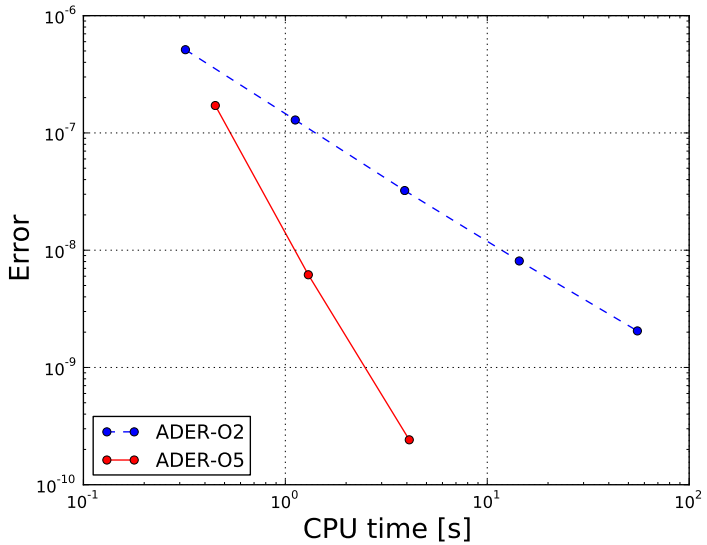
$u_L = u^{(m)}(\bar{x})$

$u_R = u^{(j)}(\bar{x})$



ADER scheme for 1D blood flow

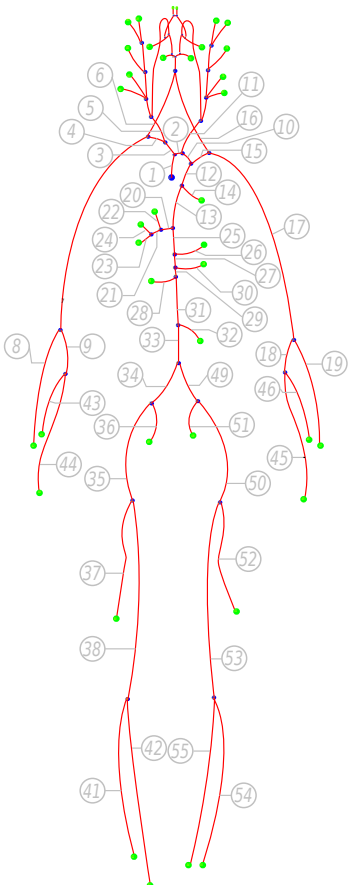
- GRP solver (Dumbser, Enaux, Toro, 2008)
- Underlying solver for classical RP (Dumbser, Toro, 2011)
- Well-balanced version (Mueller-Pares-Toro, 2013)+(Mueller-Toro, 2013)

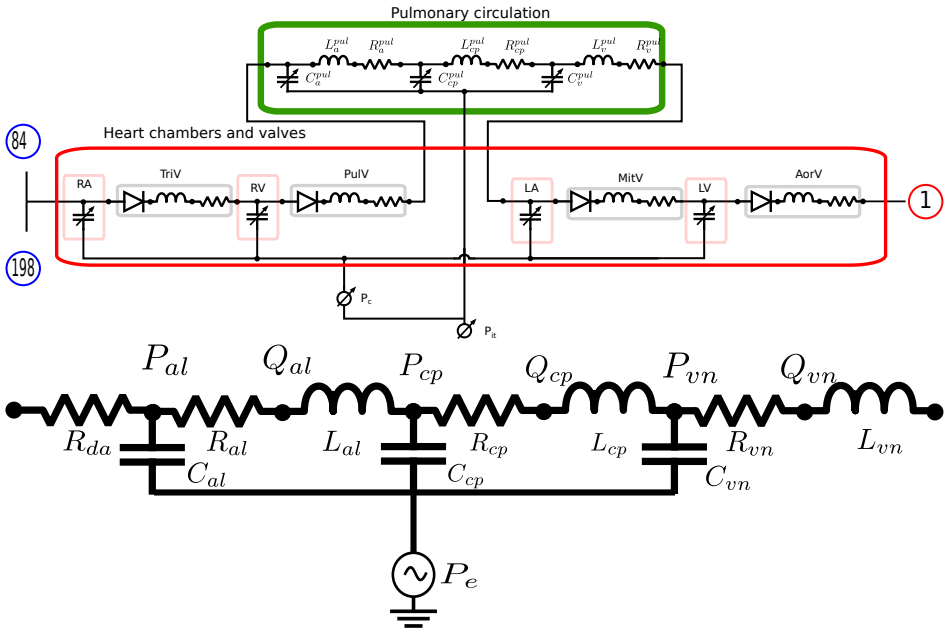


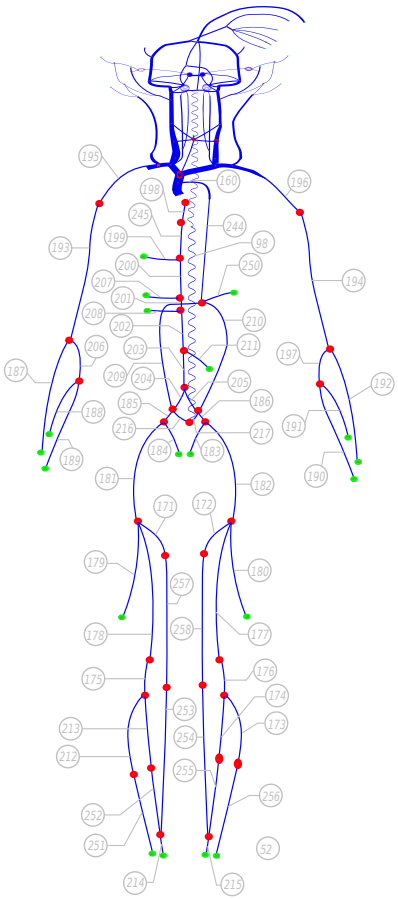
For small errors efficiency gains of high order methods can be of two orders of magnitude.

A global model for the human circulation

Global mathematical model for the human circulation

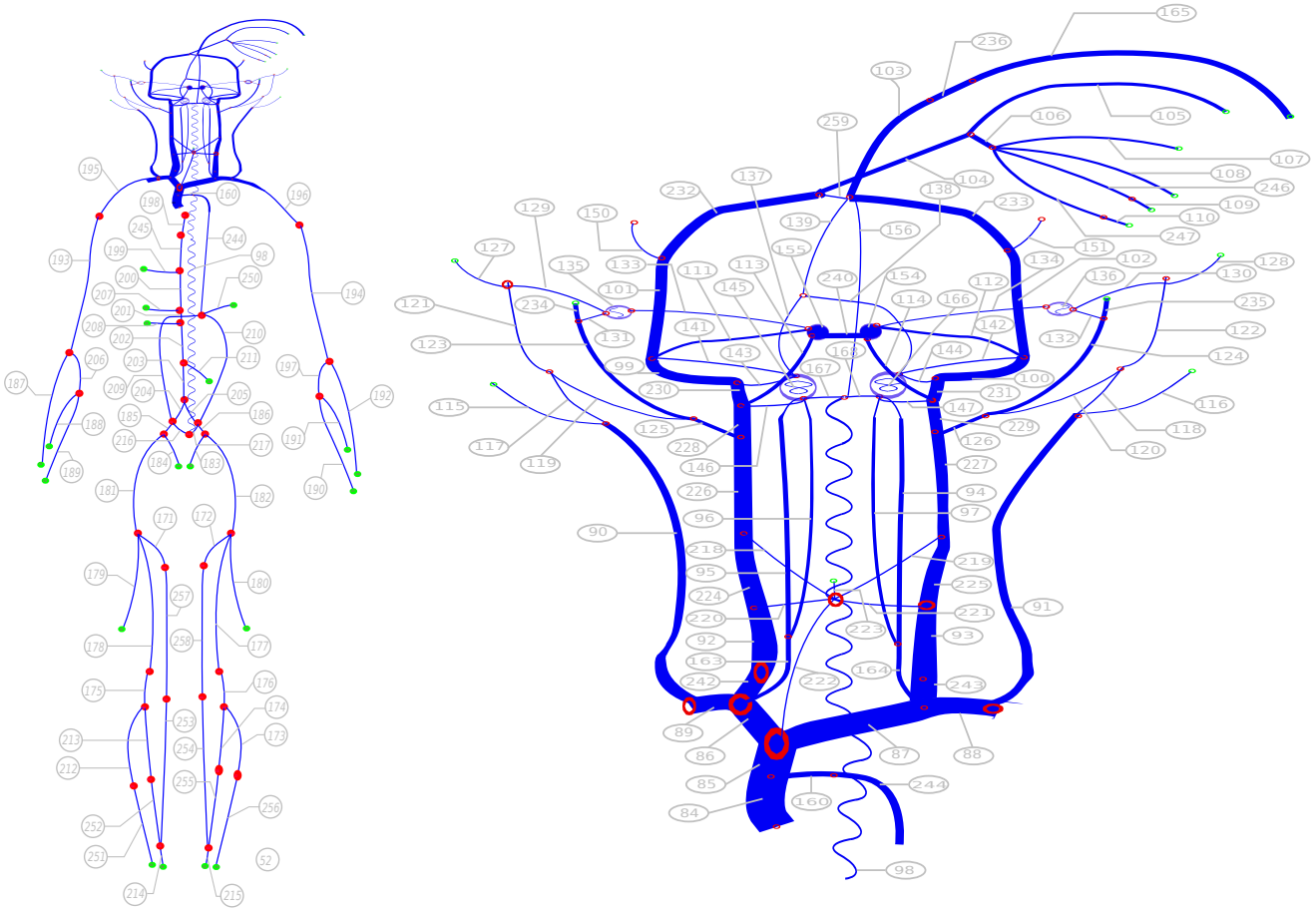






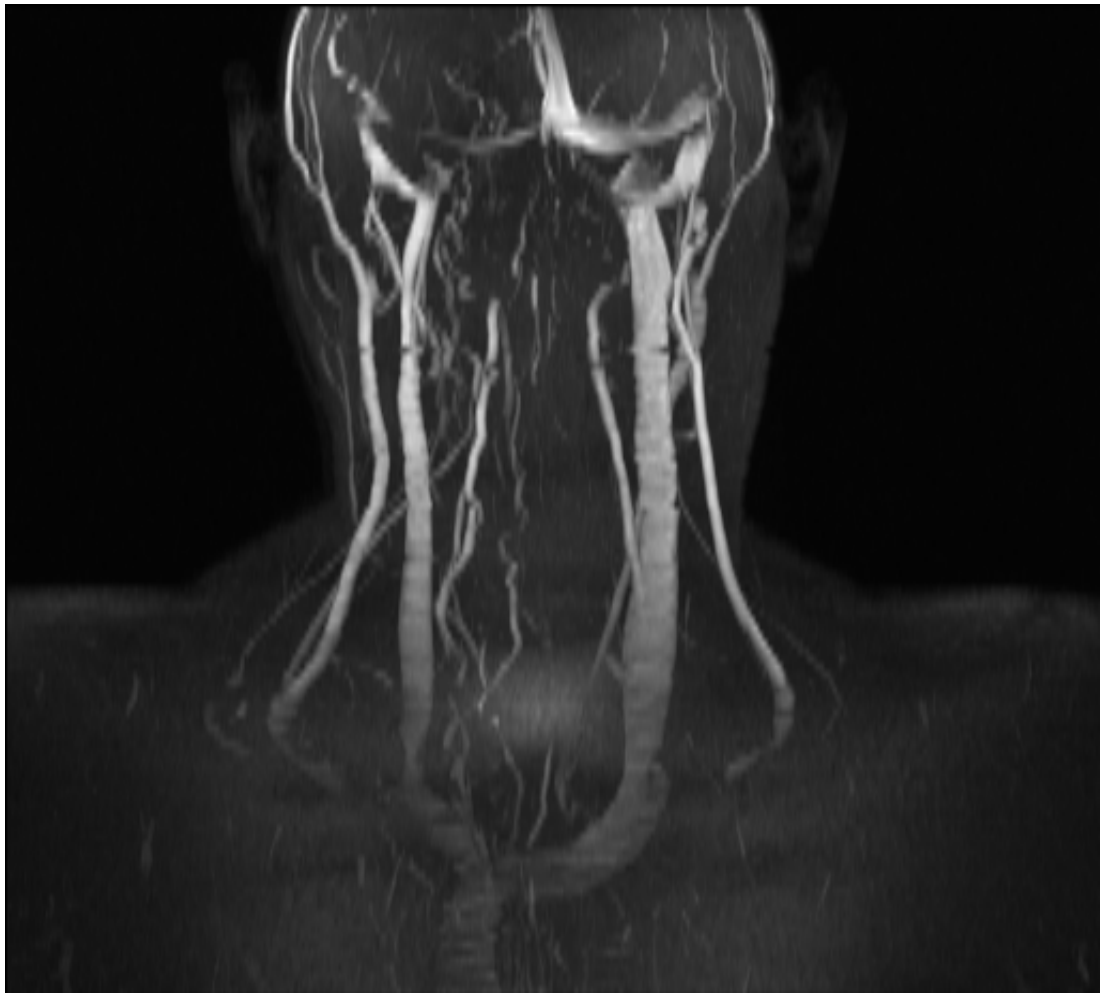
- Lucas O. Müller and Eleuterio F. Toro. *A global multi-scale model for the human circulation with emphasis on the venous system. International Journal for Numerical Methods in Biomedical Engineering.* Article first published online: 15th January 2014; DOI: 10.1002/cnm.2622
- Lucas O. Müller and Eleuterio F. Toro. Enhanced global mathematical model for studying cerebral venous blood flow. 20 March 2014. Pre-print. Isaac Newton Institute for Mathematical Sciences, University of Cambridge, UK. http://www.newton.ac.uk/preprints2014.html

Veins



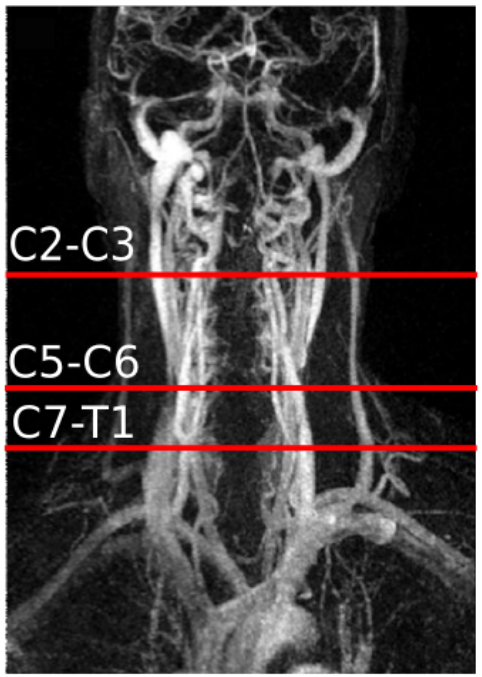
Schematic representation of venous network (left). Detail of head and neck veins (right).

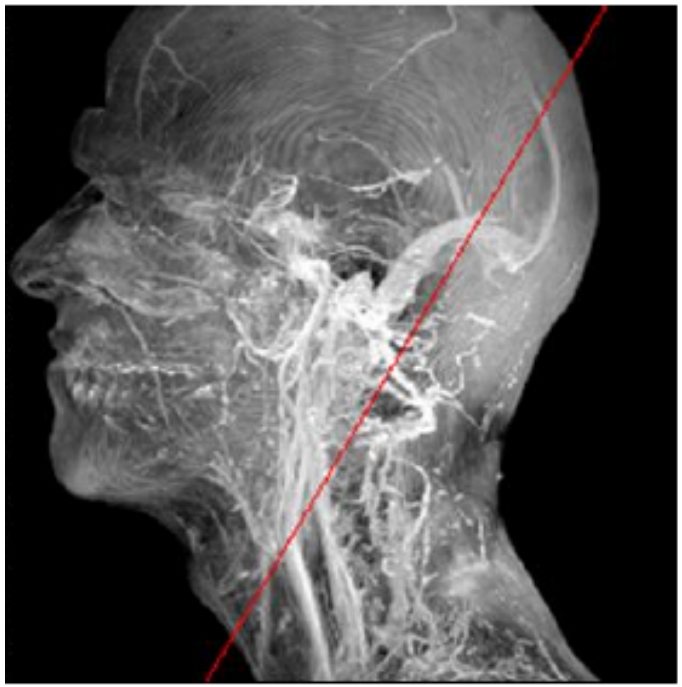
Veins (anatomical data from Prof. M Haacke, Detroit)



MIP-TOF for a healthy patient.

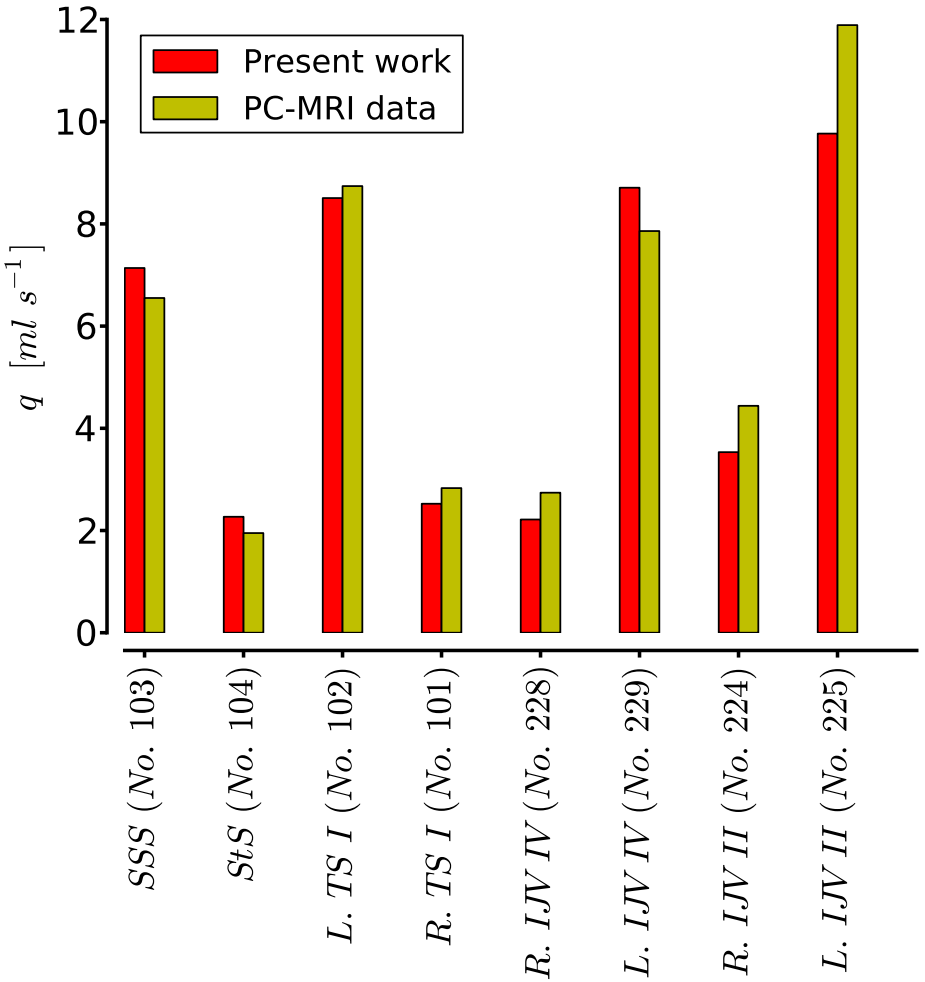
Veins (anatomical data from Prof. M Haacke, Detroit)





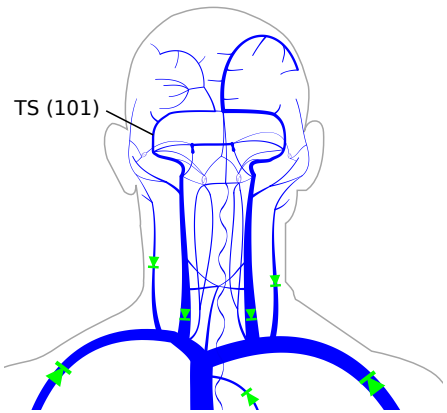
Planes at which PC-MRI flow measures were acquired for neck veins at C2-C3, C5-C6 and C7-T1 levels (left) and for dural sinuses (right). The three acquisition planes along the neck allow to evaluate how flow rate increases as tributary veins merge the internal jugular veins, whereas the acquisition plane for dural sinues allows the evaluation of flow for the Superior Sagittal Sinus, the Straight Sinus and both Transverse Sinuses.

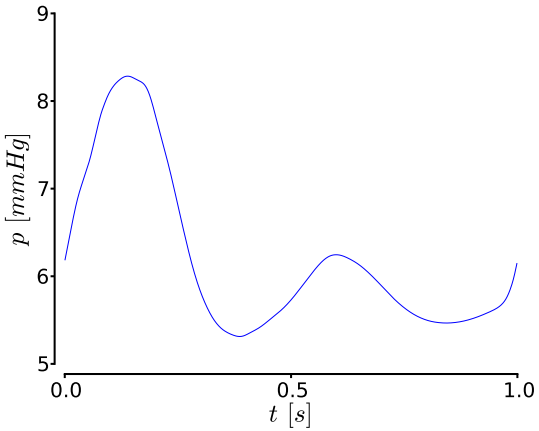
First validation exercise: flow in head and neck veins

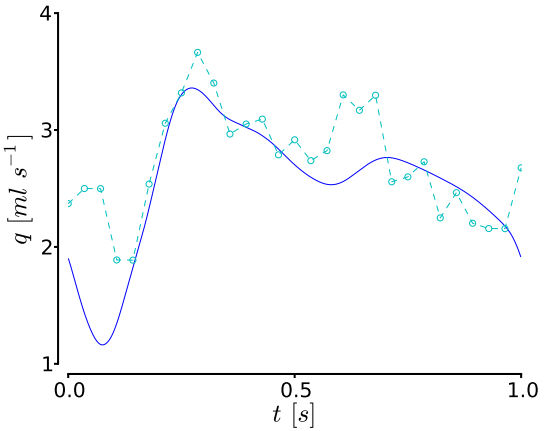


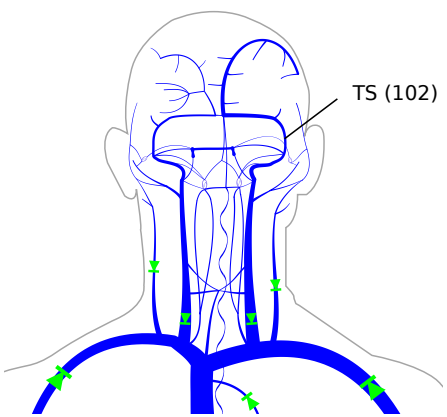
Comparison between model results and MRI measurements

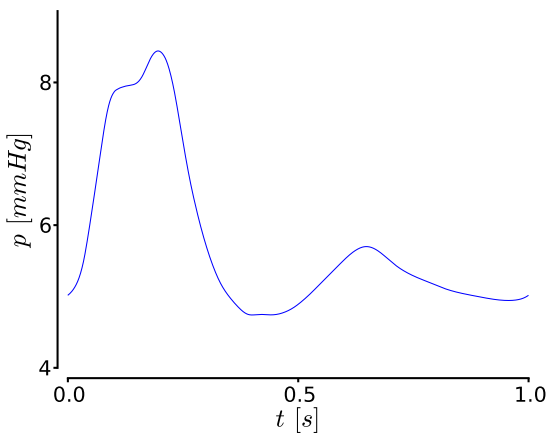
Second validation exercise: pressure and velocity in dural sinuses

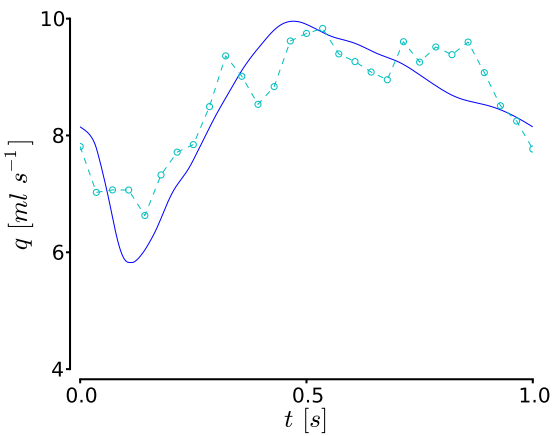








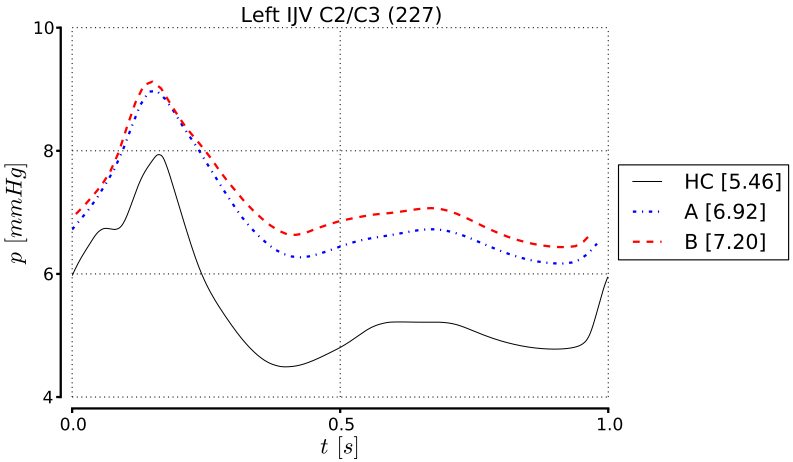


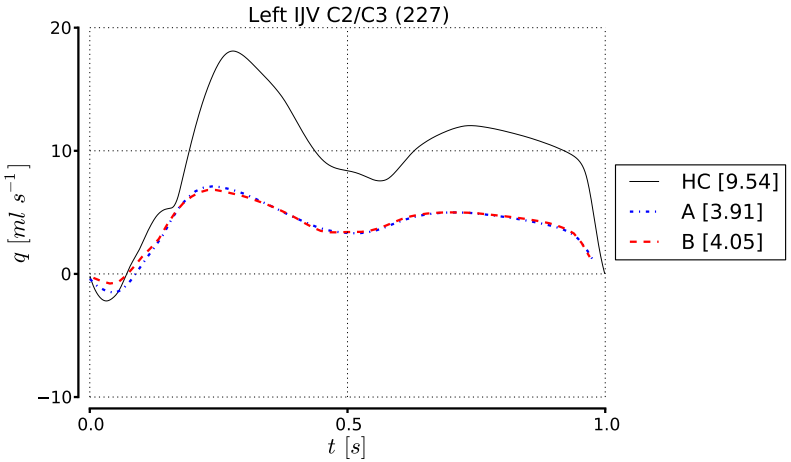


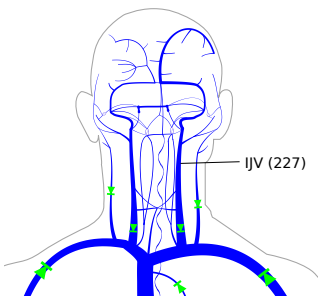
Computational results (lines) and MRI measurements (symbols). Measurements, curtesy of Prof. M E Haacke

Brain haemodynamics: a computational study

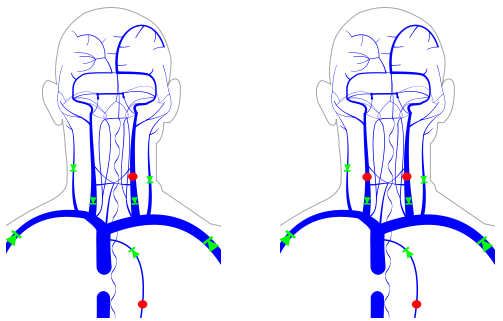
Left Internal Jugular Vein (LIJV)







Vessel position computation.

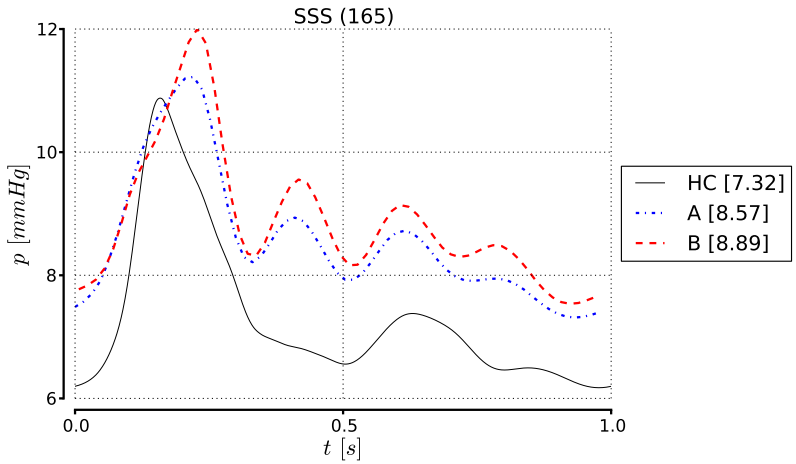


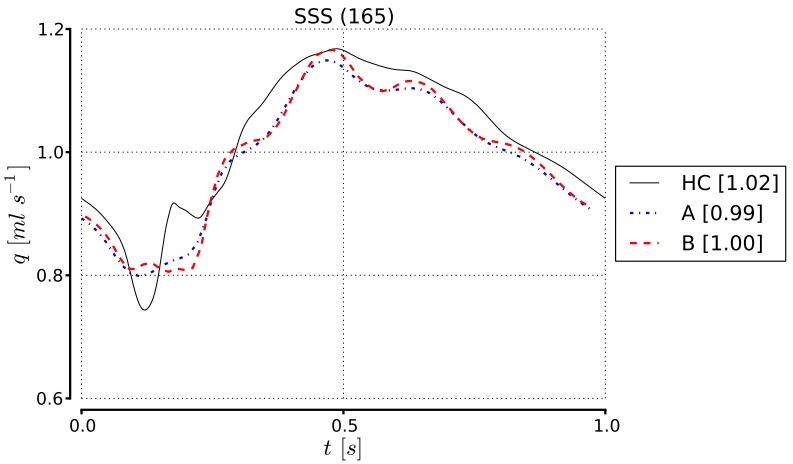
CCSVI cases A and B.

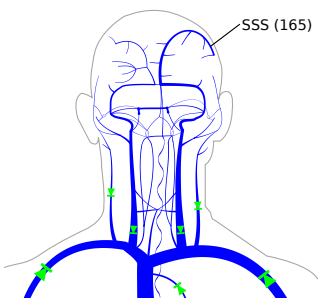
Predicted results.

Computed pressure and flow in left IJV at C2/C3 level (distal level).

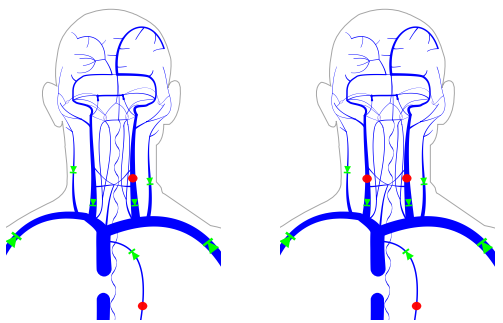
Superior Sagittal Sinus







Vessel location.

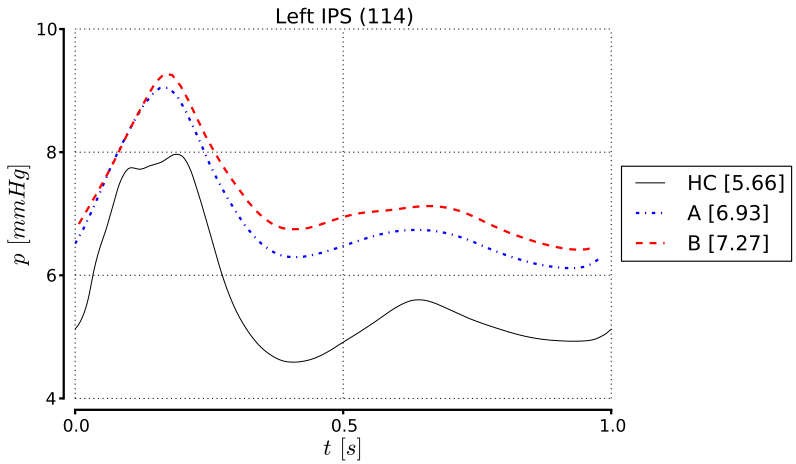


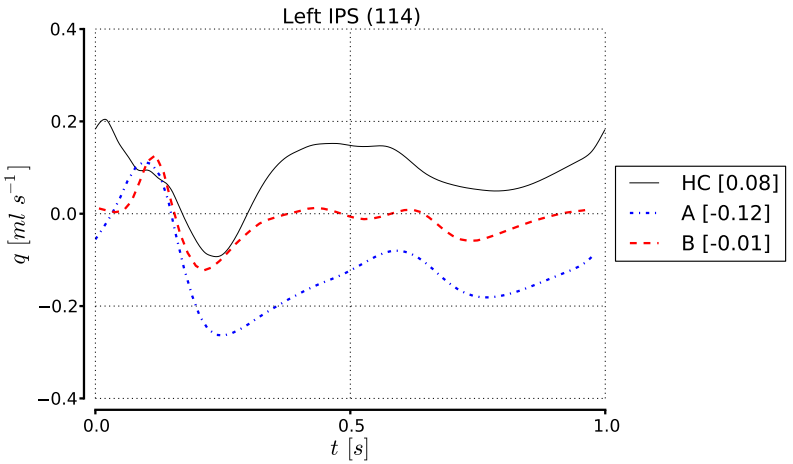
CCSVI cases A and B.

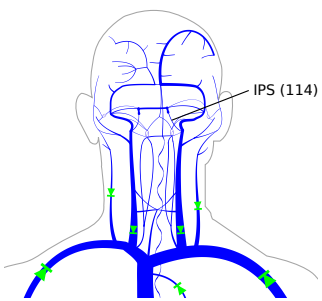
Predicted results.

Computed pressure and flow in the left Inferior Petrosal Sinus.

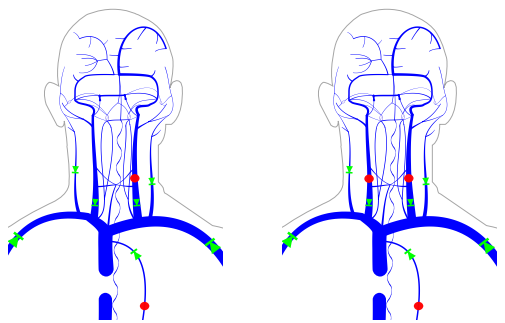
Left Inferior Petrosal Sinus







Vessel location.

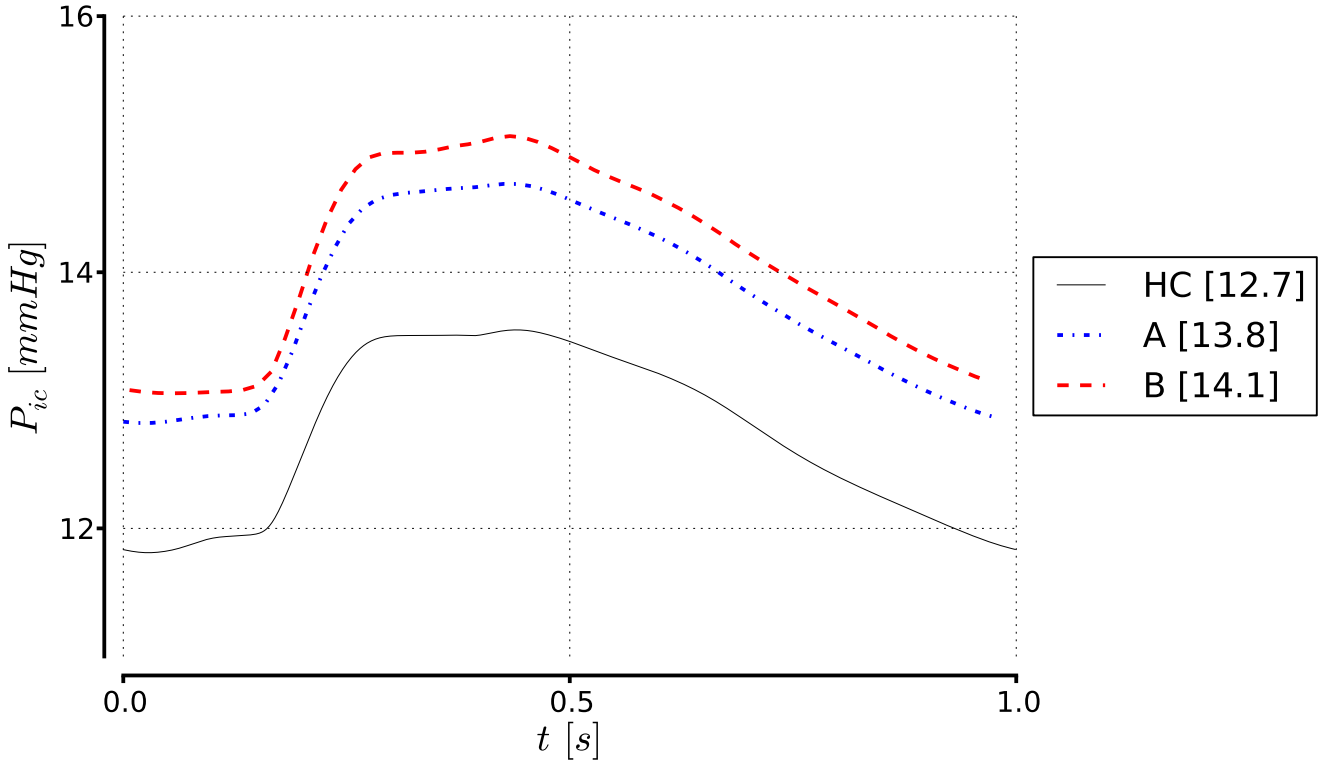


CCSVI cases A and B.

Predicted results.

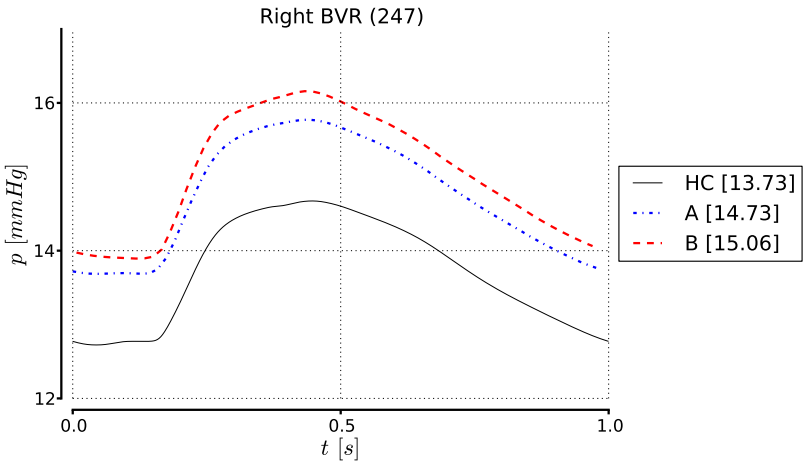
Computed pressure and flow in the left Inferior Petrosal Sinus.

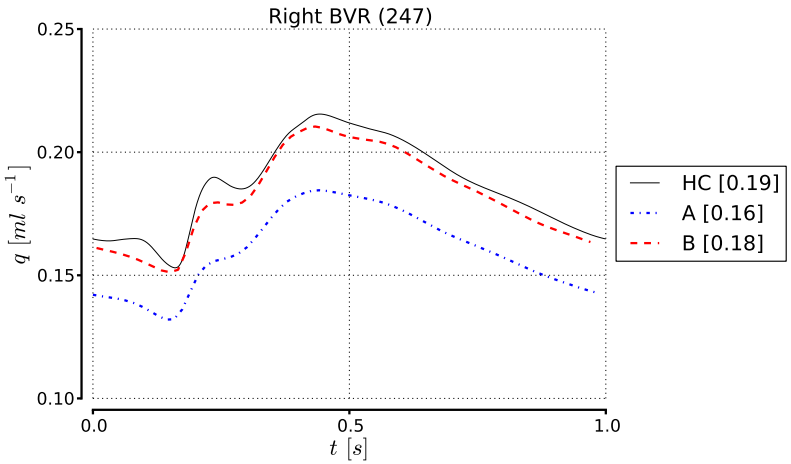
Intracranial Pressure

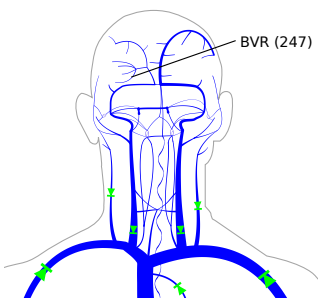


Predicted results.
Intracranial pressure for a healthy control and two CCSVI cases.

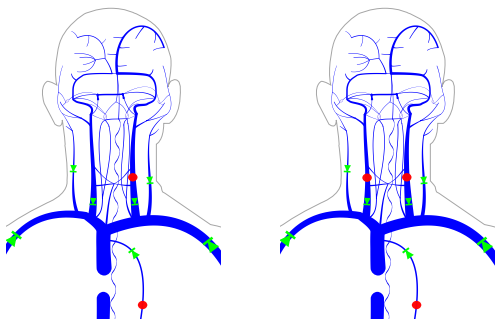
Right Basal Vein of Rosenthal







Vessel location.

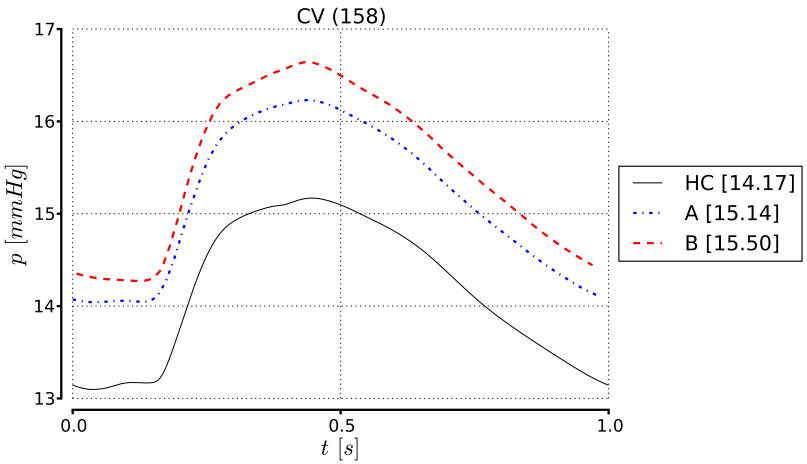


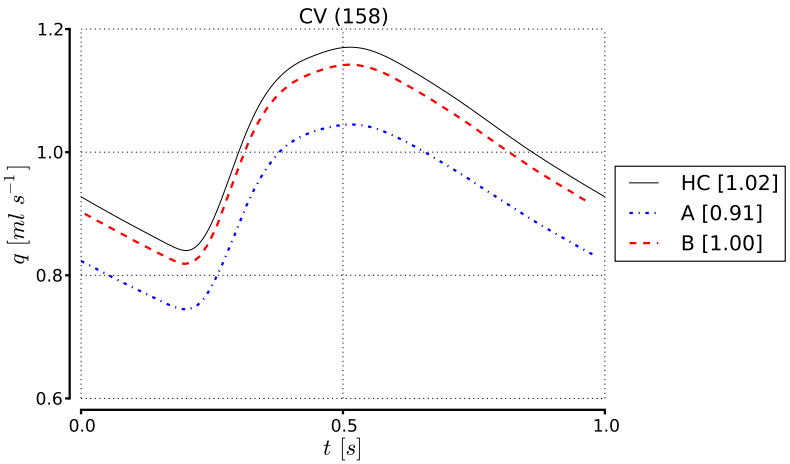
CCSVI cases A and B.

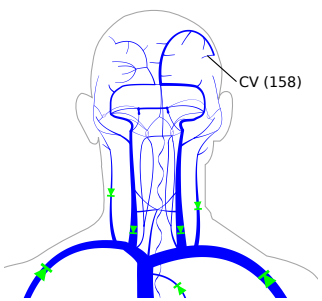
Predicted results.

Computed pressure and flow in the right Basal Vein of Rosenthal.

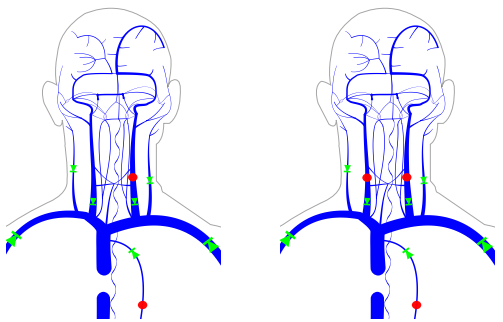
Cortical Vein







Vessel location.



CCSVI cases A and B.

Predicted results.

Computed pressure and flow in a cortical vein that drains into the SSS

Impact of CCSVI on brain haemodynamics

- We predict increased pressure and disturbed blood flow in brain venous vasculature
- Extra-cranial venous anomalies have
  - a direct impact on pressure in dural sinuses
  - an indirect impact on pressure in cerebral veins
- Intracranial pressure increase is modest (15 %) but chronic
- Our predictions are for subjects on **supine position**
- Real life posture is likely to accentuate the predicted impact

Concluding remarks

- Our global mathematical model can predict the haemodynamics of the entire human circulation system
- In particular, pressure in the brain can be predicted (non-invasively, obviously). Major practical implications
- Our predictions support Zamboni's hypothesis: extracranial venous strictures produce intra-cranial venous hypertension
- Work in progress on Idiopathic Parkinson's Disease. Preliminary results support MRI observations
- Work in progress on Hearing Loss Pathologies. Preliminary results
- Work in progress on improvements of the model

Acknowledgements

- Dr (MD) Paolo Zamboni, Dr MD E Menegatti and Dr MD M Tessari (University of Ferrara, Italia) for mutual visits, for multiple discussions and exchange of ideas.
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- Dr L O Mueller, Mariapaola Cristini, Federica Caforio, Qinghui Zhang (University of Trento, Italy)
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THE END