Computer simulation of Cerebral Arteriovenous Malformation - validation analysis of hemodynamics parameters (#8828)

First revision

Please read the **Important notes** below, and the **Review guidance** on the next page.
When ready **submit online**. The manuscript starts on page 3.

Important notes

Editor and deadline

Jafri Abdullah / 4 Mar 2016

Files	1 Tracked changes manuscript(s) 1 Rebuttal letter(s) 1 Raw data file(s) Please visit the overview page to **download and review** the files not included in this review pdf.
Declarations	No notable declarations are present

Review guidelines

Please in full read before you begin

How to review

When ready **submit your review online**. The review form is divided into 5 sections. Please consider these when composing your review:

1. **BASIC REPORTING**
2. **EXPERIMENTAL DESIGN**
3. **VALIDITY OF THE FINDINGS**
4. General comments
5. Confidential notes to the editor

You can also annotate this **pdf** and upload it as part of your review

To finish, enter your editorial recommendation (accept, revise or reject) and submit.

BASIC REPORTING

- Clear, unambiguous, professional English language used throughout.
- Intro & background to show context. Literature well referenced & relevant.
- Structure conforms to **PeerJ standard**, discipline norm, or improved for clarity.
- Figures are relevant, high quality, well labelled & described.
- Raw data supplied (See **PeerJ policy**).

EXPERIMENTAL DESIGN

- Original primary research within **Scope of the journal**.
- Research question well defined, relevant & meaningful. It is stated how research fills an identified knowledge gap.
- Rigorous investigation performed to a high technical & ethical standard.
- Methods described with sufficient detail & information to replicate.

VALIDITY OF THE FINDINGS

- Impact and novelty not assessed. Negative/inconclusive results accepted. *Meaningful* replication encouraged where rationale & benefit to literature is clearly stated.
- Data is robust, statistically sound, & controlled.
- Conclusion well stated, linked to original research question & limited to supporting results.
- Speculation is welcome, but should be identified as such.

The above is the editorial criteria summary. To view in full visit **https://peerj.com/about/editorial-criteria/**

Computer simulation of Cerebral Arteriovenous Malformation - validation analysis of hemodynamics parameters

Kiran Kumar, Shashi Mehta, Manjunath Ramachandra

The purpose of this work is to provide some validation methods for evaluating the hemodynamic assessment of Cerebral Arteriovenous Malformation (CAVM). This paper emphasizes the importance of validating noninvasive measurement using lumped models in complex vessels. The validation of hemodynamics assessment is based on invasive clinical measurements and with cross-validation techniques. Firstly, modeling results were compared with clinical measurements from vessel locations of cerebral regions. Secondly, model is cross validated with Philips propriety validated software's Qflow and 2D-Perfursion. The modeling results are validated for 30 CAVM patients for 150 vessel locations. Our results shows difference between the measured results and clinical results is within acceptable range of ±10% as per clinicians after validating with visual inspection. The cross validation results are within acceptable range of ±8%.

Suggestion: The writing requires major revision by a native English speaker.

Computer Simulation of Cerebral Arteriovenous Malformation- Validation Analysis of Hemodynamics Parameters

Note: The 3rd author should be marked as 2.

Y.Kiran Kumar[1], Dr. Shashi Bhushan Mehta[2], Dr. Manjunath Ramachandra[3]

[1]Philips Research Bangalore, Research Scholar, Manipal University Manipal.

[2, 3] Manipal University Manipal

No need for "3" here.

Abstract:

The purpose of this work is to provide some validation methods for evaluating the hemodynamic assessment of Cerebral Arteriovenous Malformation (CAVM). This paper emphasizes the importance of validating noninvasive measurement using lumped models in complex vessels. The validation of hemodynamics assessment is based on invasive clinical measurements and with cross-validation techniques. Firstly, modeling results were compared with clinical measurements from vessel locations of cerebral regions. Secondly, model is cross validated with Philips propriety validated software's Qflow and 2D-Perfursion. The modeling results are validated for 30 CAVM patients for 150 vessel locations. Our results shows difference between the measured results and clinical results is are within acceptable range of ±10% as per clinicians after validating with visual inspection. The cross validation results are within acceptable range of ±8%.

Keywords: Arteriovenous Malformation, Validation, Simulation, Hemodynamics, Cross-Validation.

1.0 Introduction:

CAVM is one of the neurovascular malformations. In healthy normal's, arteries and veins are connected by capillaries. In CAVM - capillaries are absent resulting in tangled cluster of vessels. The vessel geometry in CAVM is complex in nature. The CAVM patient is affected by hemodynamics changes. Current clinical procedure is for diagnosis and treatment procedure is invasive technique. The invasive technique is riskier to patients as CAVM get rupture. The figure 1 shows complex structure of CAVM. The gold standard imaging for CAVM is Digital Subtraction Angiogram (DSA), figure 2 shows the CAVM – DSA image [Liu 1993; Omar Saleh 2008; Yasargil MG 1987].

In this paper, we have validated our modeling results with clinical measurements and with cross –validation techniques. We replicate actual patient condition, by simulating similar condition of patient using Matlab simulation. Lumped models are created and simulated using different signal combinations. This helps to validate our results with clinical measurements.

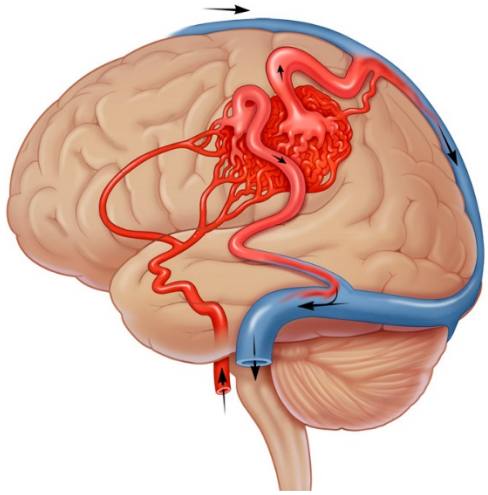


Figure 1- Cerebral Arteriovenous Malformation (CAVM).

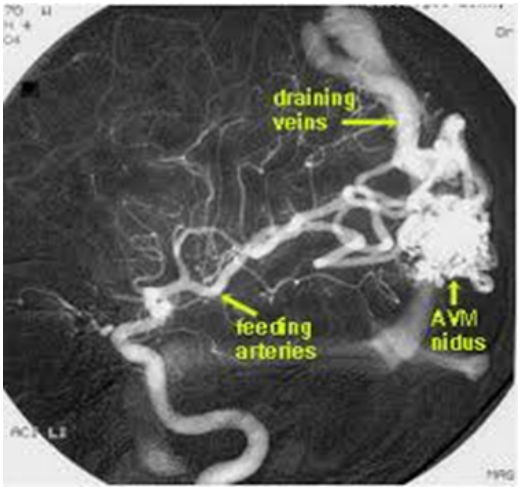


Figure 2- Digital Subtraction Angiogram of CAVM Image.

2.0 Methodology:

The non-invasive technique to measure hemodynamics in the complex vessel in CAVM is based on lumped model. In this paper, we focus on the different validation techniques to validate our modeling results. The non-invasive measurements are validated in two ways: Invasive technique and Cross validation. The complex vessel structures are formed by combinations such as bifurcation, vessel feedback, vessel deformation, vessel collapsing, vessel bending, tortuosity, etc. The analysis for complex vessel structure is performed using lumped modeling [Y.Kiran Kumar, Shashi Mehta, and Manjunath Ramachandra 2014; Y.Kiran Kumar, Shashi Mehta, and Manjunath Ramachandra 2013; Y.Kiran Kumar, Shashi Mehta, and Manjunath Ramachandra 2013]. The output pressure measurement of model is validated with invasive and cross-validation techniques for 30 CAVM patients, with 150 vessel locations

Note: In the in-text references, it seems that only the last names, not the full names, of authors need to be listed.

2.1 **Invasive Techniques:**

The clinician performed procedure for acquire data from patient is to insert catheter from femoral artery by performing single and multi-puncture of the femoral artery, based on the patient physiological condition. The catheter is of 0.08 inch /0.2 mm with 200mm length [Omar Saleh 2008]. The catheter wire is propagated slowly with various stuck-up at various bends and various structures changes of the vessels as shown in figure 3. The catheter is navigated slowly in between the path, till it reaches the CAVM vessels [Yasargil MG, 1987; Ondra SL, Troupp H, George ED, Schwab K 1990]. ~~The ethical clearance is received for this study.~~ The KMC Manipal has approved the clearance for this study, the ethical clearance details are submitted as supplementary document for reference.

Note: For four or more authors, abbreviate with 'first author' et al. (e.g. Ondra et al., 1990).

Figure 3 - Neurovascular Catheter Procedure

(Adapted from http://weillcornellbrainandspine.org/condition/stroke/surgery-ischemic-stroke)

The pressure bag has the pressure sensors that are connected externally to the guided catheter. The pressure bag readings are seen in patient monitor system. After reaching vertebra, the clinician measured the pressure value, which is measured from the patient monitor. The patient monitor also shows ECG, heart rate, respiratory rate along with pressure value. The figure 4 shows the snapshot of patient monitor along with pressure values obtained from Cathlab KMC Manipal. The pressure is measured for various arteries – left external carotid artery, internal carotid artery, posterior cerebral ~~carotid~~ artery, middle cerebral ~~carotid~~ artery, near Nidus. This procedure is commonly used procedure to measure pressure at various vessels locations in Cathlab. The pressure values obtained by clinical procedure is taken as reference for validation of modeling results.

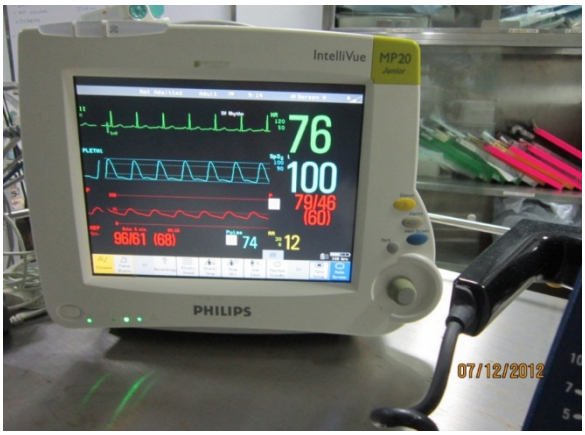


Figure 4- Clinical Pressure Measurements
(Courtesy: Kasturba Medical College & Hospital, Manipal)

2.2 Cross Validation:

The cross validation techniques is type of validation, where the modeling results are cross validated with equivalent software, which produces same results. In our paper, we validated our results with Philips propriety software's such as Q-Flow and 2D-Perfusion analysis software.

2.2.1 Q-Flow Software:

The validations of complex geometries, feeding arteries are performed using Philips propriety product called Qflow. Qflow is developed and validated by Philips Healthcare. Qflow is common practice in hospitals for clinical diagnosis and treatment. This is as validated software, accepted by clinicians [Lotz J 2002; Kondo 1991]. The Qflow application requires MR Angiogram (MRA) data – Fast Field Echo (FFE) & Phase, for processing. MRA data of CAVM patient with different phase information is obtained from KMC hospital. The MR Angiogram is an imaging technique to obtain phase, flow analysis of the patient. The MRA for cerebral patients gives cerebral flow parameters. Using Qflow software, we obtain the velocity of the blood flow. The velocity is converted to pressure, which is used for our validation analysis.

2.2.2 2D-Perfusion Software:

The modeling results are validated with Philips Propriety Cathlab software - 2D-Perfusion. The input data is DSA image. Philips validated 2D Perfusion software is a software product that provides functional information about tissues perfusion based on a digital subtraction angiography (DSA). It can visualize multiple parameters related to perfusion.

3.0 Results and Discussion:

3.1 Invasive Validation:

The invasive hemodynamics measurement inside NIDUS is risker, due to complex geometric structure of NIDUS. However, with help of clinicians in Cathlab, KMC Manipal, able to measure pressure values near locations of Nidus. The various locations are External ~~Cerebral~~ Carotid artery, Internal ~~Cerebral~~ Carotid artery, and Posterior Cerebral arteries [Standring 2008.]. The simulation is performed for the complete path node1 to node5, refer figure 5. The pressure measurements for loop structure is shown in table 1.The model is simulated with different signal magnitude variations.

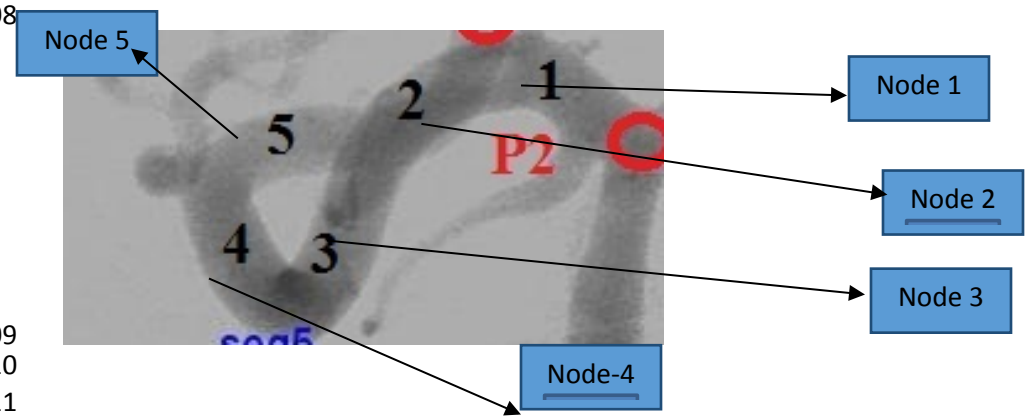


Figure 5- Complex Vessel Structure

Table 1- Loop Structure Pressure Measurements and Analysis

Nodes	Input voltage Pressure = 0.8 volt / 80mmHg		
	Measured value	Clinical results	Deviation %
Node1	0.72v/72mmHg	0.74v/74mmHg	2.7
Node2	0.7v/70mmHg	0.72v/72mmHg	2.7
Node3	0.57v/57mmHg	0.60v/60mmHg	5
Node 4	0.52v/52mmHg	0.55v/55mmHg	5.4
Node5	0.47v/47mmHg	0.50v/50mmHg	6

The table 1 shows modeling results are validated with clinical measurements. The input voltage/pressure used for simulation is 80mmHg/0.8 volts. Each node represents corresponding cerebral vessel location. Each node is modelled using lumped elements and the corresponding outputs are compared with clinical measurements. The amount of percentage deviation shows the difference between the measured results and clinical results. The deviation is within acceptable range as per clinicians after validating with visual inspection.

3.2 Cross Validation Techniques:

3.2.1 Q-Flow Validation:

The study is validated by comparing results of Qflow results with modeling results. The Qflow processing results are velocity components for specific node/region. The velocity is converted to pressure values and compared with our modeling results. The figure 6 shows the MRA image of CAVM patient with velocity results for the drawn region of interest in cerebral vascular region. The table 2 shows comparison of modeling results and Qflow results along with amount of

difference between them. The Qflow validation analysis is performed for each phase acquisition of MRA of CAVM patient. The table shows various locations such as location 1, location 2, depicts the pressure measurements at corresponding location for various phases.

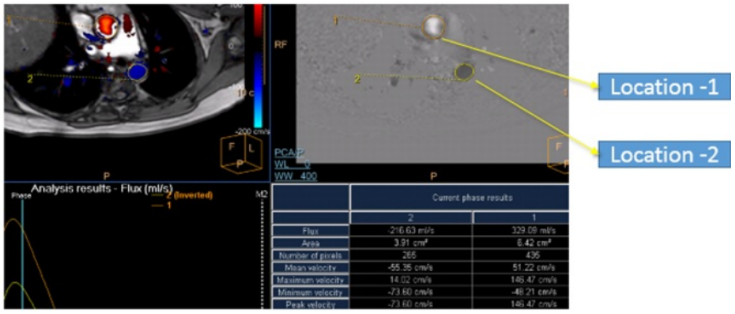


Figure 6- Qflow analysis with node locations

Pre-requisite: Conversion of maximum velocity to volts

Table 2: Qflow validation with modeling results

Vessel location as per figure 6	Flow outputs Peak velocity as per Qflow outputs in volts	Electrical Network – Modeling output	Deviation %
Input	0.02Volts – input voltage (Qflow initial velocity –max 200cm/s)	0.0187Volts	6.5
Location 1	0.012 volts	0.01 volts	0.001
Location 2	0.003 volts	0.0225	0.0195

The table 3 shows the comparison of pressure values obtained from each phase with the modeling results. The percentage deviation shows amount of variation between modeling results with Qflow pressure results. The deviation is within acceptable range of ±8%.

Conversion factor:
Input location: mean – 0.4cm/s = 0.03Volts – input voltage
Location 1- 0.2cm/s-0.015 volts
Location 2- 0.1cm/s-0.01 volts

Table 3: CAVM -MRA flow study for various phases & CSF region

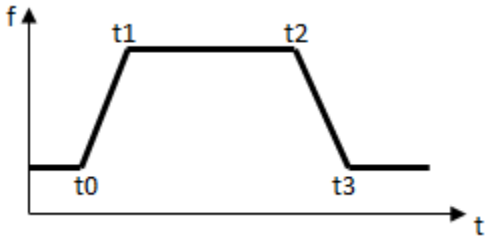
Phase 3:			
Vessel locations as per figure 6	Flow outputs Mean velocity (in volts)	Electrical Network Modeling output	Deviation %
Input	0.03	0.0278	0.0022
Location 1	0.015	0.01	0.005
Location 2	0.01	2x10-4	0.0098

Phase - 8			
Vessel locations as per figure 6	Flow outputs Mean velocity (in volts)*	Electrical Network Modeling output	Deviation %
Input	0.35	0.337	0.013
Location 1	0.28	0.268	0.012
Location 2	0.19	0.178	0.012

3.2.2 2D-Perfusion validation:

. 2D Perfusion can be used for identification of perfusion alterations in blood vessel perfusion behavior e.g. in CAVM. The following are the list of parameters that are used for validation with modeling outputs:

- Model fit to the Time density Curve:



- Time of Arrival = t0

- Time to Peak = (t1+t2) / 2
- Wash-in rate:

$$r = \frac{f(t0) - \frac{\int_{t1}^{t2} f(t)dt}{t2 - t1}}{tp - t0} = \frac{(t2 - t1)f(t0) - \int_{t1}^{t2} f(t)dt}{(t2 - t1)(tp - t0)}$$

- Width = (t2+t3)/2 - (t0+t1)/2
- Area under Curve:

$$A = \int_{t0}^{t3} (f(t) - f0)dt$$

- Mean Transit Time:

$$MTT = \frac{\sum_{i=0}^{3} t_i f(t_i)}{\sum_{i=0}^{3} f(t_i)}$$

These clinical parameters are the output of perfusion software. These parameters are converted in to the electrical equivalent for validation analysis, the details are as follows:

- Cerebral Blood flow (CBF) ~ Wash in Rate- Flow rate ~ current
- Cerebral Blood Volume (CBV) ~ Area under Curve / Width – velocity ~ pressure
- Mean Transit Time (MTT) ~ CBV / CBF = (Area under Curve / Width) / Wash in Rate-Friction coefficient ~ Resistance

The model is validated with 15 DSA data of CAVM patients. The results are nearly matching with accuracy of 85%. The effect of conversion approximation of software have effect of accuracy between modeling results, yet the results are acceptable by clinicians after visual inspection. The snapshot of 2D-Perfusion along with clinical parameters is shown in figure 7, are as follows:

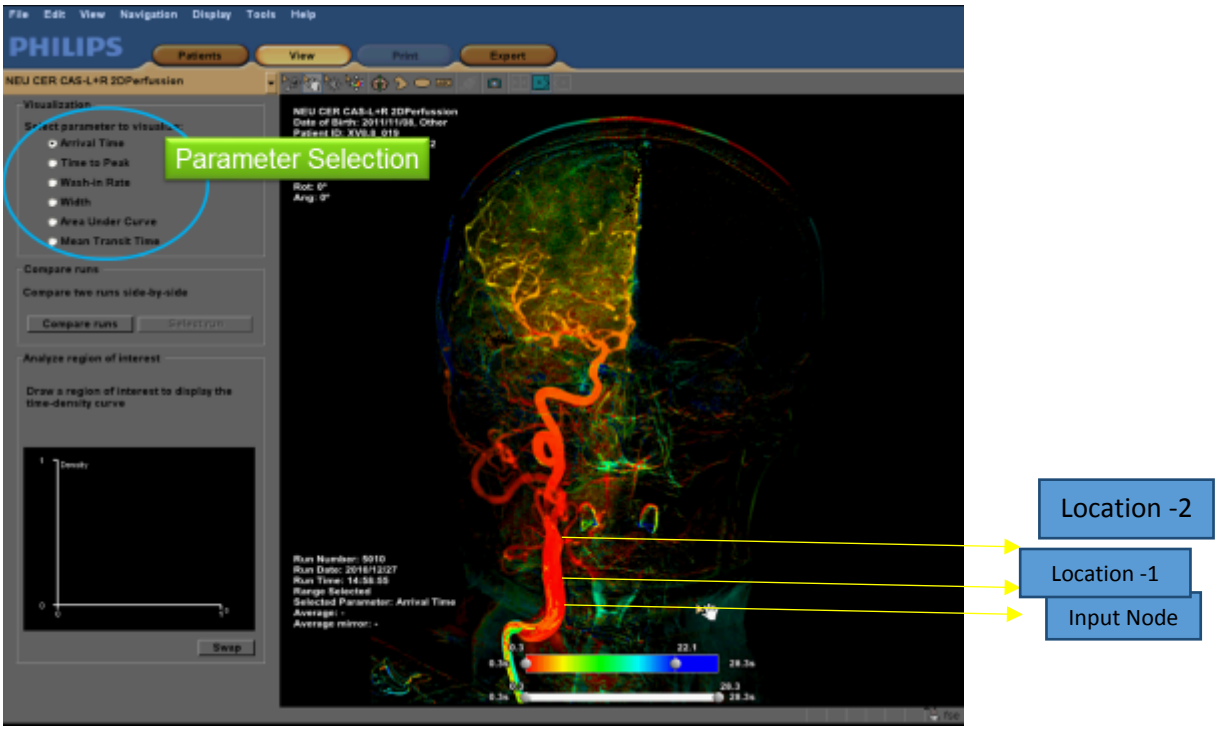


Figure 7- 2D-Perfusion analysis

The table 4 shows validation analysis for various locations of vessels along with percentage deviation. The location-1, location-2 represents different vessel location in 2D perfusion image as shown in figure 7.

Table 4- 2D Perfusion – Cross validation.

Vessel location as per figure 7	Cerebral Blood Volume (Pressure in volts)	Electrical Network Modeling output	Deviation %
Input	0.12Volts	0.115Volts	4.1
Location 1	0.22 volts	0.209 volts	5
Location 2	0.43 volts	0.415 volts	3.4

Statistical Analysis:

Mean flow, diameter, and pressure were compared between modeling results and with clinical/cross validation measurements, using independent 2-tailed Student t test. Exponential regression analysis was used to assess the relationship between blood flow, vessel diameter, and pressure between them. Univariate analysis is used to assess the relationship between vessel diameter, vessel cross-sectional area, AVM volume, AVM pressure, and AVM flow results was

performed with linear or exponential regression. All the collected data were submitted to usual descriptive statistical analyses. Two-way tables were checked by using Fisher's exact test, and regular logistic regression was used to evaluate the association between pressure and diameter variation in the vessel. All analyses were performed with SPSS (Version 22; IBM Inc.)[Anna M. Fica, Derek B.Inghamb, Maciej K. Ginalskic, Andrzej J. Nowakd,Luiz C. Wrobelea 2014].

Node voltage outputs were expressed as mean value ±Standard deviation. A P-value<0.05 was considered significant. A total of 30 AVM patients were studied with evaluation of 150 vessels locations as node point were evaluated for complex structure, with accuracy of 89%. The statistical analysis for various node output of loop structure is shown in table 5. Refer figure 3, for node details.

Table 5: Statistical analysis for various node output of loop structure

`

Quantification Parameters	Node1 Output voltage	Node2 output voltage	Node3 output voltage	Node4 output voltage	Node5 output voltage
Count	12	12	12	12	12
Minimum	3.4159	3.4159	3.4159	3.4159	3.4159
Maximum	4.3	4.3	4.3	4.3	4.3
Sum	19.42477	19.42477	19.42477	19.42477	19.42477
Mean	4.4159	3.4159	3.4159	3.4159	3.4159
Median	3.14159	3.14159	3.1414	3.15	3.15
Mode	N/A	N/A	3.1414	N/A	N/A
Range	0	0	0.00018	0	0
Interquartile range	0	0	0.00018	0	0
Standard deviation (range)	5.43896E-16	5.43896E-16	5.43896E-16	0	0
Standard deviation (Population)	5.44089E-16	5.44089E-16	5.44089E-16	0	0
Variance (Sample)	3.95823E-31	3.95823E-31	3.95823E-31	0	0
Variance (Population)	1.97215E-31	1.97215E-31	1.97215E-31	0	0
Sum of Squares	39.60876318	39.60876318	39.60876318	39.60876318	31.7675

Note: The table seems distorted in the final two rows.

Mean Squared Error	9.869587728	9.869587728	9.868770939	9.9225	9.93
Root Mean Squared Error	3.14159	3.14159	3.141460001	3.15	3.151
Mean Absolute Deviation	4.44089E-16	4.44089E-16	8E-05	0	0
Skewness	2.449489743	2.449489743	1.732050808	65535	65535
Standard error of Skewness	1.224744871	1.224744871	1.224744871	1.224744871	1.224744871
Excess Kurtosis	65535	65535	65535	65535	65535
Standard Error of Kurtosis	65535	65535	65535	65535	65535
Jacque-Bera Test Stat	65535	65535	65535	65535	65535
Durban-Watson Test Stat	0	0	1.6416E-09	0	0

Discussion:

The clinical procedure to measure hemodynamics in CAVM is invasive procedure. The current procedure is risky, as catheter may rupture, can cause patient death [Erzhen Gao a, William L. Young 1998; WayneWakeland 2008.]. The proposed non-invasive methodology address the issue by simulating the actual patient condition using lumped model. The modeling results are validated with clinical measurements. Our results shows that simulated results are matching with the actual clinical measurements. The results are visually inspected by clinicians as well. The cross validation is a novel approach for CAVM validation. Qflow and 2D-perfusion software's are based on mechanical simulation. The lumped modeling results matching with Philips propriety software's, confirms the matching of results between electrical and mechanical simulation. This work can be extended for different geometry using three dimensional volume data.

Conclusion:

In this paper, we have validated our modeling results with clinical measurements. The new approach for cross-validation is proposed, by validating our results with validated product in

clinical environment. The results are validated for 30 CAVM patients with 150 vessel locations validation showed significantly results compared to the invasive measurements. Secondly, model is cross validated with Philips propriety validated software.

References

Liu 1993. Recursive tracking of vascular networks in angiograms based on the detection-deletion scheme. IEEE Trans Med Imaging. 12(2):334-41.

Omar Saleh 2008. Arteriovenous Malformation, complications, and perioperative anesthetic management. M.E.J. Anesth19 (4): 737-56. Yasargil MG 1987. Association of aneurysms and AVM. In: Yasargil MG, ed Micro neurosurgery. Vol IIIA Stuttgart: George Thieme Verlag.182-189.

Y.Kiran Kumar, Shashi Mehta, and Manjunath Ramachandra 2014. Cerebral Arteriovenous Malformation Modeling. Advanced Science, Engineering and Medicine. 6:105-107.

Y.Kiran Kumar, Shashi Mehta, and Manjunath Ramachandra 2013. Review Paper: Cerebral Arteriovenous Malformations Modelling. International Journal of Scientific and Engineering Research 4:129-139.

Y.Kiran Kumar, Shashi Mehta, Manjunath Ramachandra 2013.Lumped Modelling of Bifurcation – Cerebral Arteriovenous Malformation. International Journal of Applied Information Systems 6:19-21.

Omar Saleh 2008. Arteriovenous Malformation, complications, and perioperative anesthetic management. M.E.J. Anesth19 (4): 737-56.

Yasargil MG, 1987. Association of aneurysms and AVM. In: Yasargil MG, ed. Micro neurosurgery. Vol IIIA Stuttgart: George Thieme Verlag182-189.Ondra SL, Troupp H, George ED, Schwab K 1990. The natural history of symptomatic arteriovenous malformations of the brain: A 24 year follow-up assessment. J Neurosurg73:387-391.

Lotz J 2002. Cardiovascular Flow Measurement with Phase-Contrast MR Imaging: Basic Facts and Implementation. RadioGraphics 22:651–671.

Kondo 1991. . Right and left ventricular stroke volume measurements with velocity-encoded cine MR imaging: invitro and in vivo validation. AJR Am J Roentgen. 157(1):9-16.

Standring 2008. Gray's Anatomy: The Anatomical Basis of Clinical Practice, 40th Edition, Churchill Livingstone..

Anna M. Fica, Derek B.Inghamb, Maciej K. Ginalskic, Andrzej J. Nowakd,Luiz C. Wrobelea 2014. Modelling and optimization of the operation of a radiant Engineering Bristol, United Kingdom Centre for CFD. Medical Engineering & Physics 36(1):81-87.

Erzhen Gao a, William L. Young 1998. Theoretical modelling of arteriovenous malformation rupture risk: a feasibility and validation study', a Department of Electrical Engineering, Columbia University, New York, NY 10027, USA, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY 10032, USA, IPEM.

306 WayneWakeland 2008. Areviewof physiological simulation models of intracranial pressure
307 dynamics. Computers in Biology and Medicine 1024–1041.

308