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A Review of Physiological Simulation Models of Intracranial Pressure Dynamics

Wayne W. Wakeland
Portland State University, wakeland@pdx.edu

Brahm Goldstein
Robert Wood Johnson Medical School

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Corresponding Author: Dr. wayne wakeland, Ph.D.

Corresponding Author's Institution: Portland State University

First Author: wayne wakeland, Ph.D.

Order of Authors: wayne wakeland, Ph.D.; Brahm Goldstein, MD, MCR

Abstract: This paper reviews the literature regarding the development, testing, and application of physiology-based computer simulation models of intracranial pressure dynamics. Detailed comparative information is provided in tabular format about the model variables and logic, any data collected, model testing and validation methods, and model results. Several syntheses are given that summarize the research carried out by influential research teams and researchers, review important findings, and discuss the methods employed, limitations, and opportunities for further research.

Author Biography for Wakeland

In 1973, Wayne Wakeland was granted a B.S. in Engineering and Master of Engineering in from Harvey Mudd College. In 1977 he was granted a Ph.D. in Systems Science from Portland State University. In 1978, Wayne became an adjunct member of the core faculty of the Systems Science Ph.D. program, and began teaching a sequence of modeling and simulation courses. In 2000, he became an Associate Professor of Systems Science. Wayne has also held managerial positions in information systems and manufacturing at several high technology firms in Portland.

Brahm Goldstein attended medical school at the SUNY Health Sciences Center at Syracuse, NY, and did his residency at UCLA in Pediatrics, with additional training at Boston Children's Hospital and Massachusetts General Hospital. From 1986 to 1989 he was an Instructor at the Harvard Medical School. From 1989 to 1994 he was an Assistant Professor at the University of Rochester School of Medicine & Dentistry; and from 1994 to 2006, he was an Associate Professor at Oregon Health Sciences University, where he also served as Director of Medical Services for the Doernbecher Children's Hospital. He is currently Director, Clinical Research, Biopharmaceuticals at Novo Nordisk, Inc. in Princeton, NJ, and affiliated with the Robert Wood Johnson Medical School.

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None declared

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Key words: ICP, computer model, intracranial hypertension

Article Outline

INTRODUCTION

Elevated intracranial pressure (ICP) is a complex and clinically important pathophysiologic state that is most commonly due to severe traumatic brain injury (TBI), brain tumors, or obstruction of cerebral spinal fluid (CSF) drainage. Current treatment depends on the underlying disease and includes surgical removal of mass lesions, CSF drainage, administration of hypertonic medications, and mild hyperventilation. While patients are often responsive to these therapies, in non-surgical causes of elevated ICP it is unclear which may be most effective. Additionally, it is clear that in some cases repeated uses of the same therapy engenders a tolerance like state where an initial good response becomes less and less effective over time. Thus, there remains a significant need to further discover and evaluate treatments for elevated ICP.

While animal models were the primary historical tool to find ways to improve treatment, researchers have also developed a wide variety of mathematical models in order to attempt to increase understanding of the complex mechanisms that drive ICP dynamics. As computer technology advanced, these models became the basis for computer simulations. The earliest such models appeared in the literature some 35 years ago. Since then many teams of researchers have

developed a wide variety of mathematical and computer simulation models of ICP dynamics that attempt to reflect to varying degrees the underlying physiology and pathophysiology of elevated ICP. Some of these models are complex and comprehensive while others are simple and focused on one particular aspect, such as cerebrospinal fluid or auto regulatory mechanisms. Some models treat fluid flows and volumes as primary variable, while others focus directly on the pressure gradients. Some models are designed with clinical applications in mind, while others are conceptual or theoretical in nature.

Despite this rich history of computer simulation models related to ICP, this literature has never been comprehensively reviewed. For new researchers entering the field, an authoritative review would be invaluable, and experienced researchers who are focusing on a particular sub-problem may benefit from an overview exposure to the work of other researchers.

This review paper is organized as follows. The methods section describes the process for selecting the articles to be included in the review. The results section includes a summary regarding where and when the selected articles were published, followed by a detailed "guide to the literature" in the form of five detailed tables. **Table II** summarizes the major insights and contributions of each article, organized by first author, and showing co-authors. **Table II** also lists some of the other authors cited in each paper, along with the total number of citations given, since this information is not provided in the bibliography and may help readers to select articles for further investigation. **Table III** provides general information regarding whether the model is conceptual or clinically focused, the phenomena investigated, and what experimental data is provided. **Table IV** gives details of the various models, such as the types of diagrams provided, the number of state variables, time and bandwidth considerations, and key assumptions and logic. **Table V** describes model outputs, model testing, and results. For selected articles, **Table VI** provides additional notes and comments. The discussion section provides a synthesis that includes

an abbreviated history regarding the work done by key research teams, a summary of key findings, and an overview of the methods used to support them. The discussion then shifts to the limitations of the research to-date, current challenges faced by researchers, and promising future directions. The article closes with a summary.

METHODS

The selection of articles combined the results from computerized searches with a previously manually developed d bibliography. The computerized searches utilized both Medline and Compendex (Engineering Village) to assure that articles published in both the medical literature and the engineering literature were located. The primary keywords utilized were "intracranial pressure" & "simulation," and "intracranial pressure" & "mathematical model." Many other keywords were experimented with such as "theoretical model," but these did not yield additional relevant articles. Articles prior to 1972 were excluded since they pre-date the widespread application of digital computer simulation. Conference papers were generally not included, except as noted. 106 articles were initially reviewed in detail.

The pearling process involved the exclusion of articles for the following reasons (some articles were excluded for multiple reasons): 11 were focused on head impact (finite element models of brain tissue mechanics); 5 were focused on aneurism or edema; 17 were statistical or used a black box mode rather than physiological; 15 were not actually computer simulation or no model details were provided; 13 did not address ICP specifically; 4 were focused on CSF shunt design; 4 were actually focused on hydrocephalus; and 11 were focused on non-invasive measurement/monitoring. 64 articles remained after these exclusions. Review of the abstracts reduced the number of articles to 50, of which 40 were deemed to be highly relevant.

The authors had previously and manually accumulated a bibliography on ICP that included 310 articles, of which 210 had been acquired. This bibliography was much broader than just

simulation-oriented papers, and had been gleaned in large part from the citations in key articles collected early on. Scanning these 210 articles yielded 31 highly relevant articles on simulation.

Synthesizing the computer search results and the manual ICP simulation bibliography yielded 56 highly relevant works that were reviewed in detail. Most of these are journal articles, but two important dissertations are included, and two articles introducing key concepts were published at International Symposia focused directly on ICP. Three articles were later deleted when they were reviewed more closely, and six articles were subsequently added that were published during 2005-2007 (after the initial literature search had been completed), resulting a total of 59 items from 30 sources.

Each article was reviewed, and information was compiled into several tables to allow for easy comparison of the data, models, assumptions, methods, and findings reported in the articles reviewed.

RESULTS

Sources and timeline

Table I shows where the items were published, and **Figure 1** indicates when they were published. A strong upward trend is shown, until the year 2000. The volume of articles on this topic appears to have declined somewhat since then.

<Insert Table I and Figure 1 about here>

Detailed findings in tabular format

Table II is organized chronologically by major research team, and provides the year published, lead author, co-authors, the number of references given, selected authors cited, and a summary of the main thrust of each article. **Table III** provides information on the focus of model

(conceptual, clinical, etc.), the phenomenon studied (e.g., TBI, pressure/volume [P/V] relationship), and experimental data provided (e.g. ICP, PaCO2, blood flow, pressure volume index [PVI]). **Table IV** provides model details, such as the types of diagrams provided (e.g., hydraulic, electrical analog, block diagram), information about state variables, time and bandwidth, key assumptions/logic/constraints, use PVI, and the number and types of autoregulation. **Table V** describes the model outputs (e.g., graphs, tables, steady state or transient results, etc.), how the model was validated (e.g., versus experimental/clinical data, or versus data/models in the literature, test simulations, sensitivity analysis, runs with and without cerebral autoregulation [AR], etc.), and what sorts of experimental simulations were run (e. g., treatment options or experimental protocols). **Table VI** provides additional notes and comments for selected articles.

< Insert Tables II – VI about here>

DISCUSSION

The following discussion synthesizes the information provided in Tables II-VI, including seminal works and key investigators, important findings, limitations of current models, and promising future directions.

Seminal works and key investigators

Marmarou's 1973 dissertation [1] and 1978 journal article [2] developed a mathematical model of CSF pressure dynamics, expressed as an electrical analog, which was validated using experiments conducted on cats. He concluded that using a single compartment for CSF is appropriate because there was not a significant pressure gradient between the ventricles and subarachnoid space. CSF formation rate was treated as constant, and CSF absorption was a

function of the difference between the CSF pressure and the dural sinus pressure. The resistance associated with this absorption was shown to be constant (not to vary with pressure, as might have been thought). Thus, the response of the system to a rapid injection or withdrawal of CSF fluid is a rapid increase or decrease in pressure followed by a slow return to the baseline pressure. The response curve is fundamentally exponential in nature.

Marmarou's major contribution in this work is the definition of the pressure volume index (PVI) as the amount of fluid which, when rapidly added, causes the pressure to increase by a factor of 10. In cats with normal physiology this was reported to vary from 0.5 to 1.4 mL. The value is, of course, much larger for humans.

Several non-clinical experiments were conducted using an animal model and compared with the theoretical model. These consisted of a series of small, rapid injections of varying amounts of saline small, somewhat less rapid removals of CSF in various amounts; and a stair-step sequence of saline infusions that simulated changes in the CSF formation rate. These tests all supported the basic formulation of the theoretical model, including the PVI index.

Marmarou also studied the reliability of using a single injection to measure compliance and found that a single injection could be used to estimate the compliance factor (K) to within $\pm$10%, whereas the resistance to absorption could not be accurately estimated from a single injection (K = PVI/P).

In 1987, Hoffman [8] provided the first comprehensive intracranial simulation model that included cerebral blood volumes and flow rates, CSF volume and flow rates, baroreceptor-based flow regulation, and regional blood flow. Some relationships were portrayed graphically, rather than functionally. Hoffman was also the first researcher working in this field to demonstrate the use of optimization to estimate unknown parameter values.

Ursino (1988-2003) has been the most prolific contributor to the ICP modeling literature, with 19 articles from his research team included in this review.

Ursino [14] described an intracranial simulation model that focused on the shape and pulse amplitude of the ICP waveform. Application and validation was described in subsequent studies [15][16]. Ursino and Di Giammarco [17] describe a major extension to the earlier model, with considerable model detail and a stability analysis. Other investigations that year [18][19] focused on cerebral auto-regulation and reproducing clinically observed oscillations in the ICP waveform such as Lundberg's A and B waves.

Ursino et al [20] described a complex ICP model that had several blood compartments. They also determined and provided basal values for all important model parameters, many of which were derived experimentally. The model included many variable conductances and compliances; and auto-regulation was modeled in detail, including pressure differentials due to muscle tension, vessel wall tension, and viscous forces. The model was fitted to prospectively collected subject-specific data including the ICP response to PVI testing (injection and removal of CSF). The reported fit was very good.

Ursino and Lodi [22] offered a simplified model based on the team's experience with more complex models. The report also discussed the feedback loops in the model and the stability characteristics of the equations. A companion study applied the simpler model to the same prospective data used to fit the more complex model. The simple model worked nearly as well as the more complex model. Additional validation was reported by Lodi et al [24] based on prospective data from a CO_2 challenge protocol. Also that year, the model was extended to permit comparison with transcranial Doppler ultrasound (TCD) data [25]. Lodi and Ursino [27] reported on using the model to study cerebral arterial vasospasm, and Russo et al [28] reported on using the model to help explain clinical experiments to measure cerebrovascular reserve.

Ursino et al [29] analyzed the changes in cerebral hemodynamics and ICP evoked by challenges in arterial blood pressure (ABP) and $PaCO_2$. These tests used their simpler model aimed at routine clinical investigations. The model was validated by comparing model results (flow in the middle cerebral artery was assumed in the model to be 1/3 of the total cerebral blood flow) with blood velocity measured in the middle cerebral artery via TCD during the challenges. Six model parameters were estimated statistically via least squares fit, including CSF resistance, intracranial elastance, AR gain, and CO_2 reactivity (gain, time constant, and normal set point). A key difference between this model and some of the earlier models was that CSF production was not held constant; rather, it was modulated by variations in CBF.

One of the physiologic challenge protocols that provided the dynamic data needed to estimate model parameters was gradual hyperventilation followed by a period of hypoventilation, and then a return to baseline. A second physiologic challenge utilized a norepinephrine perfusion to change ABP. Once a new ABP was achieved, the $PaCO_2$ challenge was repeated. 44 tracings from 13 patients were obtained and analyzed. Results were quite good in most cases, with the standard deviation of the residuals for ΔICP and Δ middle cerebral artery blood flow velocity (ΔVMCA) being on the order of the measurement error. Any exceptions to these generally favorable results are discussed in detail.

Ursino et al [30] described yet another variation of the model that looked at the microcirculation and was validated using prospective clinical data regarding response of patients with internal carotid artery (ICA) occlusion to CO_2 challenges. The so-called cerebral blood flow "steal" phenomenon was demonstrated by the model.

Ursino and Magosso [31] extended the AR aspects of their model to include a third local AR mechanism--tissue hypoxia. The model was used to study how these three AR responses interact. Initially, only the PaO_2 response was allowed to act. The resulting vasodilation was

insufficient to maintain flow. An additional mechanism was then enabled, still without the $PaCO_2$ response. Thus, four gains were estimated, two for each of the arterial compartments. The two mechanisms together were able to cause sufficient vasodilation, such that the model results matched experimental data where $PaCO_2$ has been held constant. Finally, the CO_2 response was activated and various model experiments were run. The first set computed CO2 reactivity as a function of PaO_2, as it varied from hypoxia to hyperoxia. The model reproduced previously published data from rabbit studies showing highly non-linear behavior. This was with ICP held constant (open skull). More runs were made with closed skull conditions. The Lundberg A wave was reproduced, as were long period oscillations. Hemodilution was then studied, with favorable results.

Ursino and Guilioni [32] reported on the use of their mathematical model to develop a CAR index based on the pulse morphology of the TCD velocity waveform that was both sensitive and selective.

Another highly influential team, lead by M. Czosnyka (1992-2001), with J. Pickard and S. Piechnik, published seven of the articles included in this review. Seminal papers in 1993 [34] and 1997 [36] presented an ICP model that treated the blood volume as two compartments (arterial blood storage [a] and capillary plus venous blood storage [v]), with CSF storage [c] as a third compartment. These three volumes were constrained to add up to a fixed volume per the Monro Kellie doctrine. CSF was modeled per Marmarou. The model was shown as an electrical circuit analog, and differential equations were provided for each of the three pressures Pa, Pv, and Pi (ICP). In 2001, Piechnik, the principal modeler on the team, published his dissertation [39], which provided a detailed review of the literature on intracranial physiology and models in additional to several chapters organized as independent reports. Our current review is intended to complement that excellent review.

The Czosnyka team cites reports describing Ursino's highly complex ICP model. Although the most influential model from the Czosnyka team is attractive for its simplicity and resulting insights, Piechnik's work also included several more complex models to address phenomena such as cerebral blood flow "steal" where asymmetric malformations are not properly compensated for via the Circle of Willis [37]. He also created a physical model to study the appropriateness of the "Starling resistor" model for the bridging veins [38]. This research showed specifically how the Starling resistor model is inappropriate when ICP is less than the saggital sinus pressure, and provided an alternative model. Much of this team's primary work focused on ICP monitoring and hydrocephalus, and therefore was not included in this review.

The final highly productive ICP modeling team, led by W. Lakin, entered the field in 1995 with a strong mathematical focus. Nine of this group's articles are included in this review. Their approach emphasized mathematical approaches to model simplification and steady state initialization. They reference the work by Marmarou, Karni, and Czosnyka, but, curiously, did not reference Ursino until very recently (2005). One very ambitious contribution from this team was a 16-compartment "whole body" model (Lakin et al [45]) that modeled the changes in total intracranial volume rather than invoking the Monroe-Kellie hypothesis. This model was validated by simulating infusion tests and catastrophic events such as the loss of a large fraction of the body's blood.

In 2005, Stevens et al [46] reported on using a simplified version of their 2003 model to study ICP in microgravity conditions (it remained "normal"). The primary method was steady state analysis. Two Stevens et al [47] reported on a further simplified model applied to idiopathic intracranial hypertension (IIH). Stability analysis was performed regarding events that could trigger the transition from a steady state with normal ICP to one with elevated ICP. Stevens et al [48]

added a Starling-like resistor to better model the transverse sinus. The model was calibrated such that it perfectly fit the data for three subjects.

Two other very recent papers deserve mention. Gaohua [58] provided an ambitious whole body model focused on the use of hypothermia to treat elevated ICP. Much model detail was provided regarding the equations and parameters, along with some validation tests and a demonstration of using a controller to quickly bring a simulated patient to a target ICP value using hypothermia. Hu et al [59] documented their ambitious work that combined simulation (drawing heavily on Ursino), parameter identification, and intracranial state estimation using extended Kalman filters. The use of these dynamic filters reduced model fit error significantly.

Key findings

Key findings are grouped as follows: CSF production and absorption, Relationship between pressure and volume, Cerebral autoregulation, and Other findings.

CSF production and absorption

Marmarou [1][2] supported with animal models the use of a constant CSF formation rate and a constant CSF uptake resistance in simulation models. The resulting graphs for how the system returns to steady state when perturbed are exponential in shape.

Eijndhoven [5] argued that the CSF formation rate is not constant, but based on the pressure differential. Ahearn et al [7] studied this question, but did not provide a conclusive answer supported with empirical data. Hoffman [8] suggested that the CSF formation rate is a function of blood flow volume, not pressure differential.

Ursino et al [29] modeled the CSF production rate as being proportional to the differential between intracranial arterial and capillary pressure. They also reported that the estimated CSF outflow resistance in their study was significantly elevated from basal values in all but one patient,

supporting the general belief that impaired CSF uptake is an important contributor to elevated ICP in a large fraction patients with severe TBI.

Relationship between pressure and volume

Marmarou [1][2] showed that an exponential equation for the intracranial pressure/volume relationship that features a pressure volume index (PVI, the amount of added fluid that increases pressure by a factor of ten from baseline) is a practical way to model the relationship between volume and pressure. Marmarou also determined that a single mock CSF injection can be used to determine the value of PVI.

Chopp [4] introduced the use of a "Starling" resistor formulation and used the resulting model to clarify the efficacy and meaning of Marmarou's PVI test. Another alternative to PVI is a logistic function (Kadas et al [41], Lakin et al [42][45]). Stevens and Lakin [43] employed an empirical and highly nonlinear P/V curve.

Piechnk et al [38] used a physical apparatus and mathematical model to study cerebral venous outflow. He found that the Starling resistor model did not perform well, and provided an alternative. Cirovic et al [56] provided a new volume-pressure test that better reproduced classic results from Chopp[4], and showed that the state of CAR does *not* have a dominant effect as might be expected.

Cerebral autoregulation (CAR)

Zagzoule and Marc-Vergnes [6] modeled cerebral blood circulation in 34 segments to study how much vasodilation (via CAR) is needed to maintain flow when ABP is lowered. Ursino [16] reported model results with and without intact CAR. Ursino [18] modeled five distinct CAR mechanisms in the rat (two chemical, one mygenic, and two neurogenic). Czosnyka et al [33]

defined a measure termed “state of autoregulation” (SA). Kadas et al [41] modeled CAR as an instantaneous change in vascular resistance.

Ursino et al [30] considered the CAR response to changes in $PaCO_2$ in addition to the AR response to changes in cerebral blood flow. The two control signals could reinforce the response, or the two signals could modulate each other in some fashion. CAR gain varied from 0.2 (severely impaired) to 1.5 (normal). The authors reported that in some patients CAR was normal, whereas it was below normal in others. This is discussed in terms of the static AR index, sARI (defined as % change in CVR divided by % change in cerebral perfusion pressure [CPP]). AR gain and sARI were found to be highly correlated. The CO_2 reactivity index (% change in VMCA/change in $PaCO_2$) is particularly interesting. The authors show that this index is not representative of the “true” CO2 reactivity because it depends strongly on CPP. By contrast, the gain associated with CO_2 reactivity, GCO_2, is quite independent of CPP. The reduced compensatory response to CO_2 during hypotension is reflected in their model due to their inclusion of the CO_2 component of the CAR response.

A revised model reported by Ursino and Magosso [31] featured three CAR control mechanisms, where the smooth muscle state was adjusted separately for the arteries and the arterioles. As with their previous models, each section of control logic was characterized by a gain parameter and a time constant. An attenuation factor that depended on CBF mediated the CO_2 reaction since it normally works to contract rather than dilate the vessels—an effect that is attenuated when CBF is substantially compromised. The three control signals were then added and passed through an S-shaped function that implements the asymmetric physiological limits to the smooth muscle response. Venous O_2 concentration was computed by subtracting from the arterial O_2 concentration the brain O_2 consumption rate divided by the flow rate. Brain O_2 consumption rate was constant for the reported model experiments. PaO_2 concentration was computed using

parameters and formulae from the literature. The time constant for the PaO_2 response was estimated to be 20 s. by assuming that the mechanism works via vasodilatory factors such as adenosine that metabolize in approximately one minute. Ursino and Guilioni [32] demonstrated a sensitive and specific CAR index based on pulse morphology.

Other findings

Rekate [12] failed to find support for a hypothesis regarding brain "turgor" as a compliance element.

Several researchers (Yu et al [40], Ursino and Lodi [22], Ursino et al [23], Czosnyka et al [33], Stevens et al [47]) found that simple models were often nearly as effective as complex models and were probably more useful because they are easier to understand and ran much faster. Yu specifically suggested treating slowly changing variable as constants.

Lodi et al [24] found support for clinical guidelines to maintain CPP > 70 mmHg. Ursino et al [25], and Ursino and Guilioni [32] used models to help develop non-invasive estimates of ICP and the status of CAR based on shape of the transcranial Doppler (TCD) waveform and other data. Lodi and Ursino [27] showed that TCD measurements alone were not a reliable indicator of arterial vasospasm.

Ursino and Belardinelli [19] and Czosnyka et al [35] reproduced and explained the mechanisms behind Lundberg's A and B waves seen in the clinical environment. Ursino et al [30] and Piechnik et al [37] created models that demonstrate the "steal" phenomena (regarding compensatory response between the left and right hemispheres). Stevens et al [46] showed that ICP was not significantly impacted by microgravity.

Primary computer modeling methods reported

Table V described model outputs, model testing, and results. In most cases, the primary methods used to establish the findings discussed above included the development and solution of systems of ordinary differential equations (ODEs). In some cases, a set of simultaneous equations were solved instead of or in addition to ODEs.

Another important method involved some form of parameter estimation (sometimes called model identification), where parameters are adjusted (optimized) in order to minimize the error between the model-calculated ICP vs. the actual data. This was first demonstrated by Hoffman [8]. Ursino et al [20][23][24] estimated four parameters in order to create patient-specific models for 18 subjects with very good results, including classification of the patient's CAR status. Ursino et al [29] estimated six parameters to identify patient specific models, with excellent results.

Steady state analysis was first employed in the ICP simulation domain by Karni et al [41]. Related to this, stability analysis and state transition analysis were used by Ursino and Di Giammarco [17], Ursino and Lodi [22], and Stevens et al [48] to better understand normal versus pathophysiological states, and what triggers the shifts between these states.

Hu et al [59] reported that the addition of a nonlinear filtering method to improve the estimation of hidden state variables in the model dramatically reduces model fit error.

Limitations of Current Computer Models

In our opinion, the most significant limitation is that virtually no tangible clinical impact has been reported, due in part to the fact that the models are not intuitive, are very complex, and the results are not sufficiently relevant and useful to garner the attention of clinicians.

A related challenge is the limited availability of high quality, annotated, prospective clinical data that is needed to fuel progress in the ICP dynamic modeling field. Some data has been reported, but these data are generally not shared widely within the research community. This might

be due in part to the lack of standardized data formats for clinically annotated data, and the lack of incentives and simple mechanisms for sharing data.

Future Directions

Some teams have experimented with adding more "compartments" (creating whole body models) such as reported in Lakin et al [45] and Gaohua and Kimura [58]. The first of these incorporated ABP regulation and modeled the larger closed loops that extend outside the cranial cavity, whereas the second team focused on temperature regulation and the effects of hypothermia on ICP.

Bekker [49][50] reported on the integration of PK models and ICP dynamic models, which would seem to hold much promise. More work is needed to continue improve models of primary mechanisms and processes such as CAR in order to improve our understanding of these critical physiological mechanisms.

More carefully annotated prospective data collection is needed to improve model calibration and testing. Many groups report the use of prospective data (e.g., Ursino and others), but practical ways to share the data and generally accepted data format standards are very much needed. We suggest that a central repository such as Physiobank (www.physiobank.org) would be an ideal solution. Datasets need to include physiologic waveform and parametric data, clinical information (e.g. age, sex, type and severity of injury, outcome), and, most importantly, clinical annotations with time stamped information about treatment start and stop times, concurrent medication administration, changes in mechanical ventilation, and detailed laboratory and radiographic test results [60][61].

In order to improve the acceptance of model-based findings by clinicians, model logic must be very carefully explained using simplified diagrams and pictures. The work of Czosnyka et

al [34][35], Ursino and Lodi [22], and Wakeland and Goldstein [57] represents a start, but much more progress is needed.

Algorithms are need to quickly "fit" non-specific models to data collected for specific patients, and then identifying promising treatment options for these patients. The hidden state variable estimation methods demonstrated by Hu et al [57] may lead the way here.

There exists a need to improve models in order to better understand phenomena of secondary mechanisms and secondary insults as discussed by Czosnyka et al [36]. This phenomenon may involve cellular breakdown from prolonged ischemia, or changes in osmotic pressure gradients due to increased quantities of large molecules in the interstitial fluid. This topic was discussed in detail by A. Marmarou at his plenary talk at the ICP2004 Symposium in Hong Kong, but work in this area has been limited.

SUMMARY

Over the past several decades, considerable research has been done to create, validate, and apply computer simulation models of ICP dynamics that strive to reflect the underlying physiology and pathophysiology. The sophistication of the models and the quality of the results has improved significantly as computer hardware and computer simulation software has improved. However, the clinical impact of these models remains negligible, due in part to the lack of substantial databanks of clinically annotated data, and also, of course, to the fact that intracranial physiology and the associated autoregulatory mechanisms are complex and only partially understood.

This paper reviewed 57 central articles and two Ph.D. dissertations covering three decades of research. The paper provided not only detailed tabular information to allow for quick comparison of model details, analysis methods, and results; but also various summaries and syntheses that allow the reader to quickly develop an appreciation for this particular body of literature. The details included the main thrust of each article, and information regarding the phenomenon studied, the experimental data provided, the types of diagrams provided, model state variables, key assumptions/logic/constraints, the types of model outputs provided, how the model was validated, and what sorts of experimental simulations were run, such as different treatment options or experimental protocols.

The discussion section reviewed the seminal articles in more detail, especially the contributions by key investigators and research teams; and also summarized the specific findings regarding CSF production and absorption, the relationship between volume and pressure, different cerebral auto regulation mechanisms, and other topics such as model simplicity and the appropriateness of clinical guidelines regarding the maintenance of cerebral profusion pressure. The computer modeling methods employed were then discussed, as well as the limitations of current computer models, and promising future directions.

Significant opportunities for advancement in the field exist, including the possibility for making important clinical contributions, but these depend on several factors: 1) that the requisite data needed to calibrate and validate computer simulation models be collected and disseminated, 2) that additional physiologic mechanisms be incorporated into the models, and 3) that newer, systems-oriented analysis methods be applied in clinically relevant ways.

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Table I: Journal or source for the articles reviewed

Journal or Source	**Count**
Annals of Biomedical Engr	6
Acta Neurochirurgica	5
IEEE Trans Biomed Engr	4
AJP	4
Neurological Research	3
Neurosurgery	3
Medical & Biological Engineering & Computing	2
J. of Cerebral Blood Flow & Metabolism	2
Mathematical and Computer Modeling of Dynamical Systems	2
J. Neurosurgery	2
J. of Biomechanics	2
Computers & Biomedical Research	2
J. of Applied Physiology	2
J.of Clinical Monitoring [and Computing]	2
Dissertations	2
ICP Symposia papers	2
J. of Neurosurgical Anesthesiology	1
J. of Neurology, Neurosurgery& Psychiatry	1
Surgical Neurology	1
J. of Mathematical Biology	1
Pediatric Neuroscience	1
Childs Nervous System	1
Neurological Sciences	1
J. of Vascular Research	1
Medical Engineering & Physics	1
Comments Theoretical Biology	1
Studies in Applied Mathematics	1
Mathematical Medicine and Biology	1
J. of Theoretical Biology	1
Aviation, Space, and Environmental Medicine	1

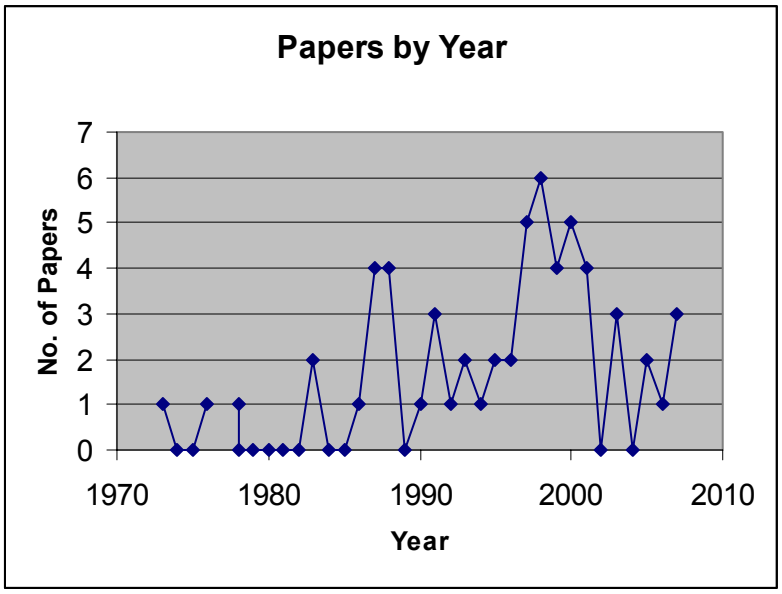

Figure 1: Number of articles by year of publication

Table II. Major insights and contributions of each article, grouped by research team, and sorted by when each team entered the field.

#	Year	Lead Author	Co-authors	# Cits	Other authors cited (sel.)	Major insights, contributions
1	1973	Marmarou, A.		31	Davson 65,67,72	First simulation model of CSF dynamics (hydrocephalus focus.). Studies PV relationship and introduces concept of PVI (~ 1 ml in cats) as a measure of lumped cranial compliance, and also defines infusion test to measure PVI and CSF uptake resistance. Validated vs. animal model, clinical case, and physical model. Determines if single mock CSF injection could be sufficient to estimate PVI.
2	1978	Marmarou, A.	Shulman K, Rosende RM	21	Guinane 72, Lofgren 73, Benabid 75, Hofferberth 75	Seminal work on mathematical modeling of CSF dynamics; clearly defines key variables and parms; explains PVI and methods for est. Ro and PVI. Carefully validated against animal models, showing model vs. actual data for cat. Clinical relevance discussed. Several useful tables and data.
3	1976	Hakim, S.	Venegas JG, Burton JD	20	Marmarou 73	Mathematical model of intracranial cavity, including brain parenchyma, ventricles, dura, etc., focused on hydrocephalus. Also includes physical models and clinically collected experimental data.
4	1983	Chopp, M.	Portnoy H, Branch C	6	Avezaat 79, Lofgren 73, Marmarou 73 75 78	Clarify form of P-V curve via hydraulic "Starling" resistor model. Curve is similar to Lofgren data except at extremes. Suggests that PVI test is NOT an indicator of intracranial elastance, but rather venous outflow resistance
5	1983	Eijndhoven, J.	Avezaat C.	5	Marmarou 73	Alternative CSF model (vs. Marmarou); CSF formation is a function of pressure differential (not constant)
6	1986	Zagzoule, M.	Marc-Vergnes J	48	Kontos 78, Hillen 82, Lassen 59	Models cerebral circulation using 34 segments. Given pulsatile input, flows and pressures in all segments are computed and shown to match physiological measurements. AR is investigated by lowering ABP and finding how much vasodilation is needed in different segments.
7	1987	Ahearn, E.P.	Randall KT, Charlton JD, Johnson RN	29	Argarwal 69, Guinane 72, Hofferberth 75, Marmarou 75,78, Shapiro 80,85	Provides electrical circuit and control system model for CSF ventricles and subarachnoid CSF storage. Considers impact of constant vs. pressure-driven CSF formation rate and constant vs. pressure-sensitive compliance (as possible control mech.) Also, considers effects of pulsatility. Var. formation response is probably S/T only. Impact of var. compliance may be complicated by variable outflow resistance. No one factor explains "creep" in PVI. There may be a critical Pv-Ps value beyond which perm. deformation of CSF ventricles occurs. Pulsations may exacerbate this effect.
8	1987	Hoffman, O.		48	Eijndhoven 80,86, Hakim 76, Avezaat 87,76, Lofgren 73, Benabid 85, Marmarou 78	Most comprehensive pre-Ursino simulation model of cerebral blood and CSF dynamics, including heart and baroreceptor regulation. Some key equations are essentially graphical, expressed mathematically (CVRA and CA). Also considers regional blood flow. CSF formation rate = fn. of flow (Hoffman 82: flow thru choriod plexus = fn of total flow based on poly. fit to data). Studies influence of ABP on ICP-PP relationship and volume pressure test. Parameter est. via opt. also demonstrated.
9	1987	Karni, Z.	Bear J, Sorek S, Pinczewski Z	17	Chopp 80, Hakim 76, Lundberg 74, Marmarou 75	Seven compartment mathematical model that particularly separates choroid plexus from rest of capillary bed and uses 3 venous compartments. Clear explanation of steady state parameter values. Finds resonant frequency consistent with Lundberg's "B" waves (.144 Hz).
10	1988	Sorek, S.	Bear J, Karni Z	20	Chopp 80, Davson 60, Hakim 76, Marmarou 75	Additional mathematical analysis based on prior compartmental model (Karni 87) to address non-steady flow case. Mentions model findings that are documented elsewhere.
11	1987	Takemae, T.	Kosugi Y, Ikebe J, Kumagai Y, Matsuyama K, Saito H	13	Agarwal 69, Marmarou 75	Simulation study based on electrical circuit of cerebral blood and CSF flow inspired by Agarwal circuit and focused on impact of mean ICP on ICP pulse wave shape. Goal is non-invasive ICP estimate.

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12	1988	Rekate, H.L.	Brodkey JA, Chizeck HJ, Sakka WE, Ko WH	29	Agarwal 69, Marmarou 73,75,78, Ahearn 87, Guinane 72, Hakim 85	Seven compartment multiple ventricle CSF model applied to hydrocephalus, especially NPH and pseudotumor celebri. Plausible parameters reproduce the indicated effects, although the model is not fully validated. Hypothesized Kb = brain turgor.
13	1994	Rekate, H.L.		15		Application of 1988 model, validated with animal data. Insight: Pressures in all CSF compartments were equal; could not support Kb. Applied to pediatrics cases with diffuse head injury that did not respond to standard therapy. Similarity to pseudotumor celebri exploited with success.
14	1988	Ursino, M.		47	Marmarou 78, Chopp 82, Hyashi 80, Portnoy 82, Hoffman 83	Describes intracranial model in detail. Focused on application of ICP pulse amplitude and wave form shape as a function of ICP. PA is nonlinear with mean ICP due to highly nonlinear compliances as a function of ICP.
15	1988	Ursino, M.		27	Belardinelli 85, Miller 72, Eijndhoven 83,86, Guilioni 86, Avezaat 79, Eksted 77,78	Application and validation of author's 1988 ICP dynamic model to study the shape of blood flow velocity wave form, response to CSF infusion and bolus injection, and venous obstruction. Good agreement with data from literature in all cases.
16	1990	Ursino, M.		32	Aaslid 82,86, Guilioni 88, Marmarou 75,78, Avezaat 79, Ekstedt 77-78	Applies prior model, adding simulated pulsatility index and Pourecelot index, and showing the diastolic and systolic pulse height with and without AR as a function of ICP.
17	1991	Ursino, M.	Giammarco P Di	47	Kontos 78, Auer 84 87, MacKenzie 79, Avezaat 83, Hayashi 80 86, Hoffman 87, Rosner 84, Lundberg 60 68, Sorek 89	Major extension of 1988 model to differentiate AR at arteries vs. arterioles, allowing plateau waves to be generated. Much discussion of model logic, equations, and parameter values. Also includes stability analysis of system equations showing parameter values that lead to instability.
18	1991	Ursino, M.		49	Heistad 78,83, Kontos 78,85	Detailed mathematical/simulation model of CAR in the rat including five mechanisms--two chemical, one myogenic, and two neurogenic--each acting on three of five compartments. Does not include interactions between the various volumes. Compares favorably with literature data.
19	1991	Ursino, M.	Belardinelli E	36	Kontos 78, Osol 85, Marmarou 73, Winn 79, Hoffman 87, Betz 78, Sercombe 79, Kuchinisky 75	Reports results of two earlier studies/models, with emphasis on reproducing lab. and clinical results including oscillations such as Lundberg's A and B waves.
20	1995	Ursino, M.	Iezzi M, Stochetti N	38	Hoffman 87, Sorek 89, Takame 87 Mamarou 75 78 87 89 91, Avezaat 79 84 86, Kosteljanetz 84 87	Applied prev. model to prospectively-collected clinical data on 18 subjects during CSF inj./removal. Model fit to each subj. by modifying only 4 parameters. Fit is very good, despite paradoxical responses in many subjects. Results contrasted with Marmarou.
21	1996	Guilioni, M.	Ursino M	17	Kontos 78, Rossner 84 87	Ursino model run to show impact of hypotension in normal vs. pathophysiological cases (increased CSF uptake resistance and impaired AR)
22	1997	Ursino, M.	Lodi CA	42	Hoffman 87, Sorek 89, Mamarou 75 78 87 89 91, Avezaat 79 84 86, Kosteljanetz 84 87, Rossner 84 87 90, Gray 87, Chopp 83, Czosnyka 93	Much simplified model is nevertheless able to show instability and oscillation, ICP response to acute SAP reduction, and paradoxical response to PVI tests. Clarifies possible FB loops and show limit cycle and bifurcation plots. Much sensitivity analysis.
23	1997	Ursino, M.	Lodi CA, Rossi, S, Stochetti N	25	Gray 87, Kosteljanetz 84, Marmarou 75 78 87, Rossner 84, Aaslid 89 91, Avezaat 79	Applies '97 (simpler) model to prospective clinical data that was previously analyzed with more complex model. New model works very well and is much faster. Parameters estimated for specific patients, and patients classified as to AR status
24	1998	Lodi, C.A.	Minassian AT, Beydon L, and Ursino M	35	Guilioni 96, Rosner 87	Validation of previously reported model using an experimental protocol (CO2 challenges) to collect prospective clinical data. Model parameters are estimated to minimize error in predicteed ICP and blood flow. Very encouraging results. Supports recommendation of maintaining CPP greater than 70-80 mmHg. Improves knowledge of how AR mechanisms interact.

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25	1998	Ursino, M.	Guilioni M, Lodi CA	44	Auer 87, Czosnyka 94 96, Gray 87, Hyashi 80, Klingelhofer 88 91, Kontos 78 89, Marmarou 75, Rossner 84 95	Extends 88 (complex) model model to calculate MCA velocity in order to interpret TCD data. Mono exponential rel. between vessel radii and transmural pressure. Computes TCD indices and flow as fn. of ICP, MSAP, CPP. Concludes that mean, peak-peak, and PI (pulsatility index) must be considered
26	1998	Ursino, M.	Lodi CA	53	Marmarou 75, Lundberg 60, Rossner 87, Kontos 78, Wei 80, Harper 65 66 84	Extends '88 model to calc. MCA velocity and separates arteries into two compartments, each with different regulatory mechanisms. Applies model to show effects of SAP changes and CO2 pressure changes, thereby clarifying how they interact. Model results compare favorably with data from literature.
27	1999	Lodi, C.A.	Ursino M	49	Sorek 89, Aaslid 82,84,89,91, Avedzaat 79, Czosnyka 92,93, Kadas 97, Marmarou 78	Extends prior model to study vasospasm by subdividing blood compartments. Addresses the question "is TCD reliable for estimating vasospasm?" Thorough discussion of model logic, parameters, and validation, including sensitivity analysis. Suggests TCD measurements alone may not be a reliable indicator of flow when vasospasm is possible or likely. Well supported with citations from literature.
28	2000	Russo, G.	Lodi CA, Ursino M	37	Aaslid 82, Smielewski 97	Applies existing simulation model to explain clinical experiments to measure cerebrofascular reserve using a relative CO2 reactivity measure. Serves to help validate the model.
29	2000	Ursino, M.	Minassian AT, Lodi CA, Beydon L	56	Bouma 92, Hayashi 79, Hoffman 87, Marmarou 75 87, Rossner 84 95, Shapiro 80 83	Simplification of '98 model and validation against data from prospective clinical challenges involving SABP and PaCO2. Six parameters are estimated to identify patient-specific models (actually episode-specific). Vmca is predicted as well as ICP.
30	2000	Ursino, M.	Lodi CA, Russo G	48	Kontos 78, Avezaat 79, Aaslid 82, Hillen 86	Model extends Lodi 99 & Ursino 97 model, adding CO2 reactivity, circle of Willis, CO2 interaction with AR, and microcirculation. Model validated by comparing its predictions with data for 20 healthy volunteers vs. 14 patients w/ICA occlusion, both subjected to hyper-ventilation challenge (CO2 down 30%) and hypo-vent. (rebreathing to raise CO2 by 30%). Model behavior matches real world data. Perf. sens. analysis. TCD used to measure flow velocity. Studied effect of contralateral stenosis to determine critical value (50%). Reduced caliber of AcoA and CcoA by 75%; results are asymmetric. Model demonstrates "Steal" and shows poss. mechanisms.
31	2001	Ursino, M.	Magosso E	38	Kontos 78, Kiening 96, Muizelaar 83 92	Adds role of O2 in CAR to previous model. Parameter estimated via best fit algorithm applied progressively, first to each mechanism in isolation (hypercapnia, hypoxia, CPP changes), then acting together. Also used to study hemodilution, first with ICP held constant, then not.
32	2003	Ursino, M.	Guilioni M	34	Aaslid 82, Czosnyka 94 97, Panerai 98, Kontos 78, Giller 91	Uses a theoretical model to develop a CAR index based on pulse morphology of TCD velocity waveform. Index is shown to be linear and highly sensitive to AR state and insensitive to changes in other important parameters such as CSF uptake resistance and intracranial elasticity.
33	1992	Czosnyka, M.	Pickard J, Whitehouse H, Piechnik S	15	Giller 91	Hyperaemic response to reduction in CPP (measured by TCD). SA defined as State of Autoregulation (0-1). Non-invasive assessment of SA.
34	1993	Czosnyka, M.	Harris N, Pickard J, Piechnik S	25	Ursino 88, Guilioni 88, Hoffman 83	Considers pulsatility effects (vs. CPP and PaCO2) --> pulse amplitude is useful; theoretical discussion only
35	1993	Csoznyka, M.	Piechnik S, Koszewski W, Laniewski P + 5 more		Ekstadt 78, Gray and Rossner 87, Hoffman 83	Uses sim. model to attempt to explain rel. between ICP, ICP-PP, CPP, and CBF in different states of AR. Claims to elucidate the origin of plateau wave--Pi exceeds Ps (inversion) triggers cascade. Calls into question Gray and Rossner findings on rel. of PVI to CPP.

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#	Year	Lead Author	Co-authors	# Cits	Other authors cited (sel.)	Major insights, contributions
36	1997	Czosnyka, M.	Piechnik S, Richards H, Kirkpatrick P, Smielewski P, Pickard J	47	Portnoy 82, Ursino 88, Sorek 86, Rossner 84	Application of model to secondary insults. AR reserve to enhance interpretation of bedside tests.
37	2001	Piechnik, S.K.	Czosnyka M, Harris NG, Minhas PS, Pickard JD	18	Aaslid 89, Gao 97, Eksted 77, Hillen 86, Hoffman 85,87, Hudetz 82 93, Ursino 90	Modification of earlier model to study the so-called "steal" phenomenon when arterial stenosis is not present (as with most TBI cases). Models extreme case to accentuate effects. Findings suggest "steal" effect is not likely to occur without stenosed carotid arteries. Suggests no special therapy is indicated. Proposes a non-invasive method for assessing collateral flow and quantify asymmetry.
38	2001	Piechnik, S.K.	Czosnyka M, Richards HK, Whitfield PC, Pickard JD	43	Gao 98, Hoffman 85, Luca 82, Marmarou 96, Ursino 90,97,98, Zagzoule 86	Models cerebral venous outflow both physically and mathematically. Finds that flow does not cease, even when ICP exceed ABP; rather it is reduced considerably (80%). Suggests "Starling resistor" model may not be appropriate for bridging veins; provides alternative.
39	2001	Piechnik, S.K.		238		Detailed review of intracranial physiology and thorough lit review of IC models. Presents several models focused on different aspects of ICP and CSF dynamics. Three models are published as separate papers and are reviewed elsewhere, and two additional papers are not focused on modeling. Much model detail is provided.
40	1995	Yu, J.	Lakin WD, Penar P	7	none	ICP dynamics model can be simplified by treating variables that change slowly as constants over short time. This can dramatically reduce stiffness of the system and reduce numerical integration issues.
41	1997	Kadas, Z.M.	Lakin WD, Yu J, Penar PL	37	Portnoy 82, Guilioni 88, Gray 87, Agarwal 69 71, Chopp 80, Marmarou 78 Hakim 76, Hoffman 87, Rekate 88	Introduces AR as nonlinearity to otherwise linear 4-compartment mathematical model of intracranial pressures, volumes, and flows. AR modeled as instantaneously variable resistance. model. Non-constant compliance between CSF and brain. Used MAPLE to solve. Logistic rather than Exponential.
42	1999	Lakin, W.D.	Yu J, Penar PL	14	Kadas 97, Karni 87, Marmarou 75, Sorek 88	Seven compartment model without AR but with nonlinear (logistic) CSF/brain compliance; calibrated with prospective animal data--uses logistic curve, not PVI. Predicts ICP over time in response to bolus injection of CSF in rabbit model. Good fit obtained.
43	2000	Stevens, S.A.	Lakin WD	22	Chopp 80, Czosnyka 93,97, Friden 83, Hakim 76, Karni 87, Marmarou 75, Sorek 88, Sullivan 85	Provides four compartment mathematical model of intracranial blood and CSF, with supporting equations to reproduce highly nonlinear aggregate P-V curve. Simulated infusion tests provide textbook curve nearly exactly.
44	2000	Stevens, S.A.		11	Karni 87, Friden 83, Portnoy 83, Lakin 96, Albeck 91, Sorek 88	Clinical CSF infusion experiments by Albeck 91 augment mathematical analysis using seven-compartment model by Karni (87) to deduce mean pressures not easily measured, using a minimum of assumptions. Normal physiology assumed, but could be adapted for pathophysiology.
45	2003	Lakin, W.D.	Stevens SA, Tranmer BI, Penar PL	42	Hakim 76, Chopp 80, Hoffman 87, Czosnyka 93,97, Kadas 97, Karni 86,87, Rekate 88, Sorek 88	Ambitious 16-compartment "whole body" mathematical model, half of which are extracranial. Nonlinear equations, reduced assumptions (e.g. Monroe-Kellie not assumed). Includes filtration and lymphatics in addition to direct flows. Has partial lit. review. Extensive calibration at steady state provided. Many variable compliances and resistances. Validated by simulated infusion tests and two catastrophic events. Also provides significant historical development of predecessor models.
46	2005	Stevens, S.A.	Lakin W, Penar P	41	Friden 83, Karni 87, Marmarou 78, Sorek 88, Ursino 88	Uses simplified variant of 2003 model to study ICP in supine, head-down tilt and microgravity conditions (outer space). Steady state closed form solutions are utilized. Important considerations include the effects of changes in blood-brain filtration over time. Model shows ICP remains normal in microgravity.

Table II. Major insights and contributions of each article, grouped by research team, and sorted by when each team entered the field.

#	Year	Lead Author	Co-authors	# Cits	Other authors cited (sel.)	Major insights, contributions
47	2007	Stevens, S.A.	Previte M, Lakin W, Thakore N, Penar P, Hamschin B	49	Csoznyka 97, Friden 83, Karni 87, Piechnik 01, Sorek 88	Further simplified version of 2005 math. Model, applied to idiopathic intracranial hypertension. Model shows multiple steady states. The nalysis may help to resolve controversy re stenosis role. Thorough discussion of eqns., parameter estimation, and stability/state transition analysis in terms of phase space and basins of attraction.
48	2007	Stevens, S.A.	Thakore N, Lakin W, Penar P, Tranmer, B	45	Sorek 88, Ursino 88, Csoznyka 97, Piechnik 01, Marmarou 78,	Uses 2005 model with Starling-like resistor added to show effect of non-rigid transverse sinus on CSF flow/uptake. Studies IIH via analysis of steady state & transient response. Shows how two stable states can result from triggering even: 1 normal, 1 w/elevated ICP. Calibrated to 3 specific subjects w/perfect fit.
49	1996	Bekker, A.	Wolk S, Turndorf H, Kristol D, Ritter A	59	Sorek 89, Ursino 88 90 91, Paulsen 90, Harper 85 Marmarou 78	PK interaction plus P and V to achieve a systematic examination. Uses graphical functions for conductance vs. MAP (artery to arteriole). Goal is reduction of elevated ICP induced by surgical procedures.
50	1999	Bekker, A.	Mustry A, Ritter AA, Wolk SC, Turndorf H	33	Ursino 90 91, Aaslid 89	Combines P-K model with model of cerebrovascular dynamics, to study ICP during anesthesia and laryngoscopy under conditions of AR and no-AR. Model results match clinical data from several studies to varying degrees.
51	1997	Gao, E.	Young W, Ornstein E, Pile-Spellman E, Ma Q	47	Foggarty-Mack 96	Models vasculature more fully than other models, with a focus on AVM shunts and associated surgical procedures.
52	1998	Gao, E.	Young W, Pile-Spellman E, Ornstein E, Ma Q	44	Kontos 78	Reports improved AR formula vs. those frequently used, based on 4 compartment (288 vessel) model of arteries and arterioles. Effective resistance as a fn. of pressure, instantaneous formula
53	1998	Bergsneider, M.	Alwan A, Falkson L, Rubinstein E	7	Avezaat 79, Marmarou 78, Ursino 88	Elevated ICP is a response to reduced CBF not the cause of reduced CBF, often due to interference in pulsatile CSF movement that increases venous pulsatility…which reduces flow.
54	1998	Thoman, W.J.	Lampotang S, Gravenstein D, Aa J	11	Leenders 90	Intracranial dynamic model linked to patient simulator. Used for teaching clinicians, especially anesthesiologists, about complex intracranial interactions. Achieves purpose even though modeling approach is at variance with the bulk of intracranial modeling literature.
55	1999	Thoman, W.J.	Gravenstein D, Aa J, Lampotang S	21	Michenfelder 88, Leenders 90, Ursino 88 91	Extended 1998 work adding cerebro intracranial dynamic model to patient simulator to now include AR, and further validated model against published "curves."
56	2003	Cirovic, S.	Walsh C, Fraser W	50	Chopp 83, Portnoy 94, Sorek, Ursino	Volume-Pressure test: full range of Pcsf change. No capillarial compartment; splits venous into 2 compartments. Clear derivation. Reproduces Chopp results more completely. Auto regulation does not have a dominant effect.
57	2005	Wakeland, W.	Goldstein B	8	Csoznyka 97,Lakin 03, Marmarou 78, Ursino 97, 01	An ICP dynamic model that treats the various intracranial volumes as the state variables instead of the pressures. Uses a non-standard approach to model the AR limits. Diagram & flow logic are more approachable for clinicians.
58	2006	Gaohua, L.	Kimura H	52	Lakin 03, Marmarou 75 78, Ursino 97 00	Ambitious whole body 13-compartment model focused on the reduction of elevated ICP via hypothermia. Full hydrodynamic model + biothermal model. Details of equations and parameters provided. Some model validation tests performed. Features use of a [PID] control circuit to maintain a target ICP of simulated patient.
59	2007	Hu, X.	Nenov V, Bergsneider M, Glenn T, Vespa P, Martin N	43	Takame 87, Sorek 89, Csnoznyka 97, Ursino 88 91 95 97 98 03, Lodi 98, Aaslid 89, Kontos 78, Friden 94	Ambitious synthesis of simulation, parameter identification, and nonlinear Kalman filters (KF) to accomplish model-based intracranial state estimation. Uses Ursino 88 ICP dynamic model w/simplications from 97 model. Reviews physiology and provides many model details, incl. analysis of feedback loops. Offline nonlinear optimization to id. initial parameter values. KF state estimation then reduces fit error (profoundly).

Table III: Focus of model, phenomena studied, and data provided

	Focus of Model															Phenomena investigated/ Application											Clin./Exp. Data Provided?							
#	Conceptual/theoretical	parametric relationships	parameter estimation	elasticity/compliance	PVI (Press. Vol. Index)	Autoregulation	Drug effects	Physical Model	Clinical Emphasis	Prediction	Eval. trtmt. opts./procedures	Clinical/laboratory validation	Assessment (e.g. state of AR)	Animal Data	Interpretation of tests	TBI (adult or pediatric)	Compensatory Reserve	Vasospasm	Hydrocephalus	malformation)	Steal	Anesthesia	CSF flow/dynamics	P/V relationship	Venous outflow resistance	ICP pulse waveform	Cerebral blood flow	ICP	ABP (SAP)	PaCO2	Blood flow/velocity	AR limits/slopes	CSF uptake resistance	PVI	CPP
1	X	X	X	X	X							X		X				X					X	X	X			X					X	X	
2	X	X	X	X	X									X	X								X	X	X			X					X	X	
3		X	X	X				X			X	X	X						X				X	X										
4	X	X		X	X																			X	X										
5	X													X									X					X							
6	X					X																								X					
7		X		X	X	X													X				X	X	X										
8	X	X	X	X	X	X								X		X							X	X						X					
9		X	X	X										X									X	X					X						
10		X	X																X				X												
11				X									X											X		X									
12	X										X								X				X												
13										X	X			X					X				X												
14		X	X	X		X																	X	X		X									
15		X	X	X		X									X								X	X		X									
16													X													X									
17		X	X	X		X																		X											
18						X																					X				X				
19	X					X											X						X	X			X				X				
20	X		X	X	X	X			X			X	X		X	X	X						X	X	X			X	X		X				X
21	X	X	X	X	X	X			X		X		X		X	X	X					X		X	X							X			
22	X			X	X	X							X		X	X	X						X	X	X										
23	X		X			X			X			X	X		X	X	X						X	X	X			X	X					X	X
24	X	X	X	X		X					X	X			X	X	X											X	X	X	X				
24	X	X		X		X							X		X	X	X							X											
25	X	X		X		X			X		X		X		X	X	X							X				X	X	X	X				
27	X	X	X			X							X		X	X	X	X													X				
28															X						X									X	X				
29	X		X			X			X			X	X		X	X	X							X				X	X	X	X				
30						X			X			X			X		X			X	X									X	X				
31	X	X	X			X				X			X	X			X											X		X	X	X			X
32	X	X		X		X							X			X	X																		
33			X	~	~	X							X				X							X							X				
34	X					X							X				X							X											
35		X		X	X	X								X			X						X	X	X			X			X				
36						X			X				X		X	X	X							X				X	X		X				
37	X					X							X			X	X				X														
38	X	X						X																	X										
39		X	X	X		X				X		X	X	X	X	X	X	X		X	X		X	X	X			X	X		X	X			
40	X																																		
41	X	X				X																		X											
42	X	X	X	X	X									X										X				X							
43				X	X																		X	X											
44			X																				X	X	X										
45	X	X	X	X	X	X																	X	X											
46	X	X	X							X													X		X			X							
47	X	X	X	X			X				X												X	X											
48	X		X	X								X											X												
49	X	X				X	X				X											X													
50		X					X				X											X													
51				X		X	X					X	X									X					X								
52	X										X									X								X		X				
53	X	X	X			X																									X				
54	X			X																			X												
55		X				X	X				X											X													
56	X	X																						X	X										
57	X					X																X				X	X								
58	X	X	X								X																								
59	X	X	X				X									X										X	X	X		X					

Table IV: Model Details

			Model Diagram						State variables							Time		Bandwidth			Model Assumptions/Logic/Constraints																					
#	Equations given?	Parameter values given?	Concept Diagram	Electrical analog	Hydraulic analog	Block diagram	Compartment diagram	Schematic or flowchart	Total #	# Pressures	# Velocities	# Volumes	# of compartments	# cranial blood/CSF state vars.	# of other state vars.	Basic time unit	Run duration	Mean	Pulsatile	Pulsatile with harmonics	Enforce Monro Kellie?	Solve simult. Eqns (~non DE)	Use PVI to calc.ICP=mono-exp.	Solve Diff. Eqns.	# of flow reg. mechanisms	Logistic PVI	Arctangent AR limits?	Sigmoidal AR limits	Graphical AR curve	Neurogenic AR	Metabolic AR (vasogenic)	Perfusion press. AR (myogenic)	CO2 (and possibly O2) AR	Control of CBF or CBV	Graphical ICP curve	Adjust SAP (SNS)	Baroreceptor reflex modeled	Logistic compliance	Exp. P-V (compliance)
1	X	X	X	X					1	1				1		min	8	X					X	X																
2	X	X		X					1	1				1		min	8	X					X	X																
3	X	X	X		X																																		
4	X			X	X				1	1				1				X			--	N	N																
5	X	X							1			1				min	5	X						X															
6	X	X				X			68		34	34	34	34		sec	2	X	X			X																	
7	X	~		X		X			2	2			2	2	2	sec	80-800	X	X				X	X	2														
8	X	X	X		X	X			8	4		4	4	6	2	min	1-5 min	X	X		X		~	X	2				X			X				X	X		
9	X	X					X		6	6			7	6		sec	16	X			X	X	N		n/															
10	X						X		K																														
11	X	X	X	X					4	4				4		sec	2	X	X		N																		
12	X	X	X				X		6			6	7	6		days	2	X			X		X	X															
13	(see above)																																						
14	X	X	X	X					4	3				3	1	sec	2	X	X		Y		N	X	1		X					X			X				
15																sec	2	X	X		Y		N	X	1		X					X			X				
16	X	X				X			4	3				3	1	sec	4	X	X		X		N	X	--		X					X			X				
17	X	X		X					5	5				5		sec	300-3000	X			?	N	N	X	2		X			X		X								X
18	X	X				X			5	5				5		sec	150-400	X			N	N	N	X	5		X			X	X	X								
19						X			5	5				5		sec/	60-600	X			N	N	N	X	5		X			X	X	X								X
20	X	X		X					7	3		2		5	2	sec	150-750	X	~		Y		N	X	2		X				X	X								
21	X	X														sec	15 min.	X	X		X		X	X	2						X	X								
22			X	X	X				2	1				1	1	sec	150-300	X			Y		Y	X	1			X			X								
23									2	1				1	1	sec	150-400	X			Y		Y	X	1			X			X								
24		X	X													min	20-90	X							3						X	X	X						
24			X			X												X	X	X				X															
25	X	X		X					10	4		2		6	4	sec	50-60	X			Y		N	Y	2			X			X	X							
27	X	X	X		X				6	2		2		4	2			X					X	X	1			X			X								
28			X		X				Lo																														
29	X	X			X	X			6	2		2		4	2	sec	30-50	X			Y		N	Y	2			X			X	X							
30		~			X				12							sec	150	X			Y		N	Y	2							X	X						
31	~	~				X										sec	2000+	X			Y		N	Y	4			X			X	X	X						
32	X	X		X					7	3		2		5	2	sec	250 sec	X	X		Y		N	Y	2			X			X	X							
33	~			X	X	X			4			3		3	1	sec.	60	X	X		X	X	N		1		N		X										
34					X				4			3		3	1	sec.	30 min.	X	X		X	X	N		1		N		X										
35	~	~		X					2	2				2	2	sec	300	X	X			X	N		2				X		X	X							
36	~		X	X	X				4			3		3	1	sec.	60	X	X		X	X	N		1		N		X										
37	X	X	X	X				X	10			10	10	9	1	--	--	X			N	X		X	2					X	X							
38	X	X	X	X														X																					
39	X	X	X	X					*							min	60	X	X		N		N	X	1-3			X		X	X								
40	X	X							5	5						sec	1000 sec	X			Y			Y															
41	X	X					X	X	4	4			4	4	--	min	0.06	X	X		X	X	N		1							X							
42	X	X							7	7			7	5	2	min	2-3	X			X		N	X		X												X	
43	X	X					X		3			3	4	2	1			X			N		N	X															
44	X	X					X		5	5			7	5				X			Y		N																
45	X	X					X		13	13			16	7	6	min	10-30	X	X		N		N	X	4	X					X	X				X		X	
46	X	X					X		6	6			6	5	1	n/a	n/a	X			N		N	X														X	
47	X	X					X		5	5			5	4	1	n/a	n/a	X			N		N	X														X	
48	X	X					X		6	6			6	5	1	min	1-Oct	X			N	X	N	X														X	
49	X	X		~	X	X			10			7			3			X			X		X		1				X										
50	X	X						X								min	8	X																					
51							X		7			3	7	3	4	sec	300	X			X	X	N		2				X		X	X				X			
52	X	X						X	4				4	4		*	?	X	X			X		X	1								X						
53	X	X	X			X			4				4	4				X				X		X	1								X						
54	X			X					4	4				4					X		X	X	N		1														
55	X	X						X								--		X							1				X			X		X					
56	X	X			X	X	X		4			4		4				X			Y	X																	
57	X				X				5			5		4	1	min	4	X			N		X	X	1									X					X
58	X	X	X						26	13			13	2	13	hr	8-48	X			N			X	0														
59	X	X		X				X	5	1				2	2	min	3,20,40	X			N	X		X	2			X			X		X						

Table V: Model outputs, testing, results

	Outputs				How validated?							Test Runs				Experimental Simulation Runs										
#	Graphical	Tabular	Steady state values	Transient response	Vs. retrospective clin. data	Vs. prospective clin./lab. data	Derivation provided	Vs. animal data	Vs. physical model	Vs. data from literature	Vs. models from literature	Extreme conditions	Model sensitivity	With and w/o AR (chg. AR gain)	Parameter variation	Treatment &/or drug effect	Experimental protocol/treatment	Dosages	Simulated clinical event/cond.	Not subject-specific	Subject-Specific	Venous thrombosis	Mock CSF injection volumes	Mock CSF injection rates	CSF flow resistance changes	SABP and CO2 challenges	Notes
1	X	X	X	X		X		X	X	X							X				X		X	X			see TableV
2	X			X				X		X							X				X		X	X			see TableV
3	X		X			X	X		X				X														see TableV
4	X		X							X													X	X			see TableV
5	X	X		X				X		X							X						X	X			Infusion rate vs. bolus injection
6	X		X	X						X									X								see TableV
7	X		X	X	X		X			X									X	X					X		see TableV
8	X		X	X			X												X	X			X				see TableV
9	X			X	X		X	X		X																	see TableV
10							X																				Difficult to see clinical relevance.
11	X	X	X	X						X	X				X				X	X							
12	X			X						X									X	X							Possible hydrocephalus etiologies tested.
13	X			X		X		X								X					X						see TableV
14	X			X			X			X										X				X			see TableV
15	X			X						X					X					X		X	X	X			Assertion in discussion is an overstatement.
16	X		X	X										X									X	X			see TableV
17	X		X	X			X			X					X				X	X							see TableV
18	X			X			X	X		X				X					X	X							see TableV
19	X			X				X		X				X					X	X							see TableV
20	X	X		X		X													X		X		X				One key assumption is pressure dependent CSF formation.
21	X			X				X		X				X	X				X	X							see TableV
22	X		X	X						X	X								X	X			X	X			Press. dependent CSF formation
23	X	X	X	X		X				X									X		X		X				see TableV
24	X	X		X		X							X	X	X		X		X		X						see TableV
24	X		X							X		X	X	X	X					X							Limited validation (subsequent paper)
25	X		X	X						X		X			X					X							see TableV
27	X	X	X				X			X			X	X	X				X	X							see TableV
28	X		X	X		X									X		X		X	X							
29	X	X	X	X		X				X									X		X					X	Contrasts CO2 reactivity and AR gain/time constant
30	X		X	X		X				X			X						X		X					X	Some model details not provided
31	X		X	X			X	X		X				X					X	X							see TableV
32	X		X	X									X	X	X					X							see TableV
33	X		X	X		X				X				X	X		X										see TableV
34	X		X			~				~																	Limited validation; demonstration runs only
35	X			X	X			X											X	X							see TableV

Table V: Model outputs, testing, results

	Outputs				How validated?							Test Runs				Experimental Simulation Runs										
#	Graphical	Tabular	Steady state values	Transient response	Vs. retrospective clin. data	Vs. prospective clin./lab. data	Derivation provided	Vs. animal data	Vs. physical model	Vs. data from literature	Vs. models from literature	Extreme conditions	Model sensitivity	With and w/o AR (chg. AR gain)	Parameter variation	Treatment &/or drug effect	Experimental protocol/treatment	Dosages	Simulated clinical event/cond.	Not subject-specific	Subject-Specific	Venous thrombosis	Mock CSF injection volumes	Mock CSF injection rates	CSF flow resistance changes	SABP and CO2 challenges	Notes
36	X			X										X			X										Models help with clinical interpretation.
37	X		X				X							X	X				X	X							Very Nice "cartoon" of system/model.
38	X		X						X																		see TableV
39	X			X		X	X	X	X	X	X						X		X	X			X				see TableV
40	X			X			X																				see TableV
41	X		X	X			X				X			X													see TableV
42	X	X		X			X	X									X				X		X				see TableV
43	X		X				X			X										X				X			see TableV
44							X			X	X									X				X			
45	X			X			X			X	X	X	X	X	X				X	X			X				see TableV
46	X	X	X				X			X			X		X				X	X				X	X		
47	X		X				X			X			X		X	X			X	X				X	X		
48	X	X	X	X						X			X		X				X		X			X	X		3 subjects
49	X		X	X	X									X		X		X		X							see TableV
50	X			X						X									X								see TableV
51	X	X		X	X					X				X		X			X	X							see TableV
52	X	X	X							X				X	X					X							see TableV
53	X	X	X		X			X		X				X	X				X	X							Black box approach
54																											Not simulation, but very relevant
55	X		X							X									X								see TableV
56	X		X				X			X	X											X					see TableV
57	X			X	X												X				X						
58	X	X	X	X						X	X						X			X				X			see Table V
59	X	X		X	X	X				X	X	X				X	X		X		X						

Table VI: Additional notes and comments for selected articles

#	
1	Excellent demonstration of scientific method blending physical, animal, and mathematical models plus clinical data. Pioneering work, solid methods and results.
2	A few typos in terms of units and equations may hinder the reader slightly, but a classic nonetheless. Non-linear compliance fn.
3	Not a simulation model per se, but very informative nonetheless.
4	Primary article. PVI neglects systemic and saggital sinues pressures
6	Establishes lower limit of AR computationally; explores AR contribution of different vessels
7	Did not determine likelihood of either feedback mechanism
8	Many approximations, some perhaps not totally persuasive, but useful and practical. Regional blood flow data is puzzling. AR graph is expressed as an equation + DE w/TC = 10 sec
9	Arterial B-waves "validated" with data from single recording from a dog in 1965, may not be representative of typical human intracranial arterial pressure signals.
13	Successful brain turgor inspired-treatments for hydrocephaus reported.
14	Discussion of venous compliance is confusing, although final result may be satisfactory. Comment that CSF absorption can act in seconds to lower ICP after CSF infusion seems incorrect.
16	Clinical relevance is limited, due to emphasis on unrealistically high ICP levels
17	Much emphasis on vessel radii and other properties allows for AR logic that more closely resembles known physiology.
18	Model does not reflect full in-vivo response, either in magnitude or speed, suggesting the presence of additional mechanisms
19	Attribution of oscillation. to positive FB seems unusual (s.b. comb. of +/- and delays).
21	Shows feedback loops; CSF formation proportional to delta P at capillaries; excellent discussion of model logic; see Ursino for model details
23	AR status classified as strong, weak, in-between; calculated "indifference" regions to parameter sens. to help with AR classification; would have liked to see longer tracings
24	Supports CPP >70-80 mmHg guideline, excellent methods and modeling
25	Mostly supports Rossner's theories, e.g., plateau wave due to vasodilitory cascade; urges care in interpreting clinical test data
27	Speculative, but well-supported. Efficacy of therapies mentioned but not addressed.
31	Good fit, including hemodilution. Relevant to study of elevated ICP. Only new eqns. Given
32	Discussed possible clinical relevance; relied on prior validation of model; theoretical only, future work will individual settings vs. their indices
33	Blood flow from Giller. Other state var. is low pass filter
35	Figures not clear, abbreviations unclear (e.g. AMP is not arterial mean pressure, driving waveform not provided.)
38	Important, relatively unresearched topic; more res. and model validation needed.
39	Must read for ICP/CSF modeling. Reports less successful experiments, as well, eg animal model for venous outflow.
40	Potentially useful mathematic technique; recent advances in solvers may reduce the value of this approach.
41	Excellent diagram. Pointless graphs of sine waves. Limited insight; of course flow would be maintained if R can vary instantly; Uses gaussian elim to remove simultaneity (to avoid need to use simulation)
42	Numbers not fully explained (some of the graphs seem inconsistent in terms of mean ICP compared to the tables provided). Interesting validation with animal model.
43	"Clinically observed" P-V is qualitative from a textbook (not supported by clinical data). Are non-differential compliance curves physiologically realistic? (Why is the slope of compliance at maxima so large and discontinuous?)
45	Incredible model. extreme cond = cardiac arrest. var = lie/stand = haemorrhagic shock (45%). Model validation rather limited given scope and complexity of model. Not applied to clinically elevated ICP problems.
49	Validity not discussed, but indicated that "model prediction agrees with available data" and provided very thorough discussion of limitations.
50	Included esp. for clinical relevance (missing on much of the tech. lit.)
51	Notes limitations of lumped models and other limitations, e.g. artificial simulated clinical scenario. Why is it constant volume (overall? yes). Is CSF production a fn. of delta P or not. Two extremes, non-regulation/regulation only. VISSIM used
53	Included in review as counterpoint to highly aggregated models
55	Non-standard approach seems to "beg" to be better-linked with modeling lit. but incl. for clinical relevance.
56	Why bother with Pcsf > Part ? (acknowledged). Used Newton Raphson method to solve. Tube law profoundly non-linear for veins (exponent > 10)
59	Fig. 5 shows a drift in response beyond target time; this drift is not explained and seems important