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A Computational Model for Recovery from Traumatic Brain Injury

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A COMPUTATIONAL MODEL FOR RECOVERY FROM TRAUMATIC BRAIN INJURY

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Abstract

A computational simulation model calculates estimated recovery trajectories following traumatic brain injury (TBI). Prior publications include a multi-scale conceptual framework for studying concussion, a systems-level causal loop diagram (CLD) and an analysis of key feedback processes. A set of first order ordinary differential equations and their associated parameters determines recovery trajectories. The model contains 15 state variables, 73 auxiliary variables, and 50 parameters describing TBI pathology in an aggregate fashion at the cellular, network, cognitive and social levels. There are 1200 feedback loops, which give rise to a variety of behavior modes, many of which are highly nonlinear. Exogenous parameters include patient and injury characteristics, treatments, and time constants for recovery processes. Model testing has focused on reviewing the causal diagram with subject matter experts and determining sensitivity of model results to injury severity and patient characteristics, especially the time constants associated with healing/recovery processes. The model produces outcome trajectories that represent quick or slow recovery with no deficits, partial recovery, and the patient remaining indefinitely in a pathological state. While highly speculative, the model serves to demonstrate the potential utility of computational models in this context and to further discussion about the complex dynamics involved in recovery from TBI. The model also generates counterintuitive results, as is characteristic of complex systems. Much more research will be needed to create a properly supported research model that could be used or for precision medicine or to aid clinical trial design.

Introduction

There is a critical need to better understand the pathophysiology and healing processes associated with recovery from traumatic brain injury (TBI), which is an incredibly complex condition. The brain is by far the most complex organ in the human body, and reliable biomarkers for recovery are still lacking (Kulbe and Geddes 2016). Few effective and reliable treatments exist, and personalization of treatment is difficult (Stein 2015). While many studies and clinical trials have collected some data on traumatic brain injury (TBI), data relevant to concussion (mild TBI) remains scant, especially at the patient level and for multiple time points. Further, although the Glasgow Coma Scale has greatly benefited treatment and outcomes for those with severe injuries, the GCS has not shown to be as useful for mild cases of concussion (Chung and Khan 2013). Better models are needed to support research, diagnosis, and treatment.

Prior research by our team has resulted in publication of a multi-scale framework for studying concussion (Kenzie et al. 2017) and a systems-level causal loop diagram (CLD) focused on concussion (Kenzie et al. 2018). Both articles included substantial literature reviews. The second article discusses feedback processes in considerable detail and provides an interactive

model using Kumu to allow readers to study and comment on the diagram and the empirical support for its content and structure.

The present research project created a demonstration computational model which calculates recovery trajectories following traumatic brain injury using the system dynamics method. Such computational models of complex multi-level systems can incorporate a variety of considerations, including circular causality (feedback), uncertainty, variability, non-stationarity, and heterogeneity. Although modeling and simulation software packages with enhanced flexibility and capability are becoming increasingly available, most computational modeling environments feature one or in some cases perhaps two or three of the preceding considerations.

This research builds upon previous work to address all levels of TBI. The computational model is preliminary and serves as a demonstration of the potential capability of a computational model in this context. A key advantage of operationalizing this model is that it allows for the generation of synthetic recovery trajectories (graphs of behavior over time for key system variables) based on hypothesized model structure. These trajectories e suggest how the dynamic relationships between physiological, psychological, and social variables may be influencing heterogeneous recovery patterns.

An empirically supported computational model would allow researchers to examine alternative explanations for differential outcomes, and, perhaps, to evaluate possible treatment scenarios.

Methods

The computational model was constructed in Vensim. The primary diagram, referred to as a stock-and flow-diagram (SFD), shows the relationships between variables, and can include labels to identify feedback loops. Associated with the elements of the diagram are equations quantifying the relationships between variables. The equations constitute a set of ordinary differential equations, and support (or auxiliary) equations that are simple constants or algebraic relationships. The solution to this equation set for a given set of initial conditions and parameters determines the values of the variables over time, which can be graphed to show a calculated patient recovery trajectory.

Equations were hypothesized for the flows and auxiliary variables. Most are straightforward, including a dozen healing processes specified as first order (proportional) rates that strive to restore stocks to equilibrium. In some cases, the equation was more complex and required the modeler to create a more complex hypothesis regarding its structure. Knowledge of the physiology was used inform the equation in some cases, but in many cases no theory was available, so a speculative equation form was used.

Model parameters were determined so that all of the variables remain constant in the absence of any impact. This is referred to as “initializing the model in steady state,” meaning that balancing processes are perfectly offsetting any reinforcing processes. The human body has thousands of balancing processes that maintain the body in a state of dynamic equilibrium.

Calibrating the model to be in steady state serves as an important initial check of the model logic and equations. Furthermore, the fact that the parameter values needed to achieve steady state are intuitively reasonable indicates that it may be possible for the model behavior to resemble reality.

The model has been informed by qualitative input from dozens of experts. However, empirical support is scant. This is not due to lack of effort, but rather to the paucity of publicly available high-quality time-course TBI data sets covering the acute post-injury period and longer-term recovery. Therefore, considerably more research would be needed to transition the model from a mere demonstration to a properly supported research model that could be applied in a precision-medicine context and/or be used to help design better clinical trials for treatment of TBI.

Results

Model Description

The model contains 15 state variables, 73 auxiliary variables, and 50 parameters that represent various aspects of TBI pathology, from the cellular and network level to cognition and social functioning, as shown in Figure 1.

Of the 50 parameters, eight represent patient characteristics, seven represent injury characteristics, and nine indicate treatments. The remaining parameters mostly represent time constants or reaction rates for various recovery processes. See the online supplement for a complete list of model equations and parameters. Patient

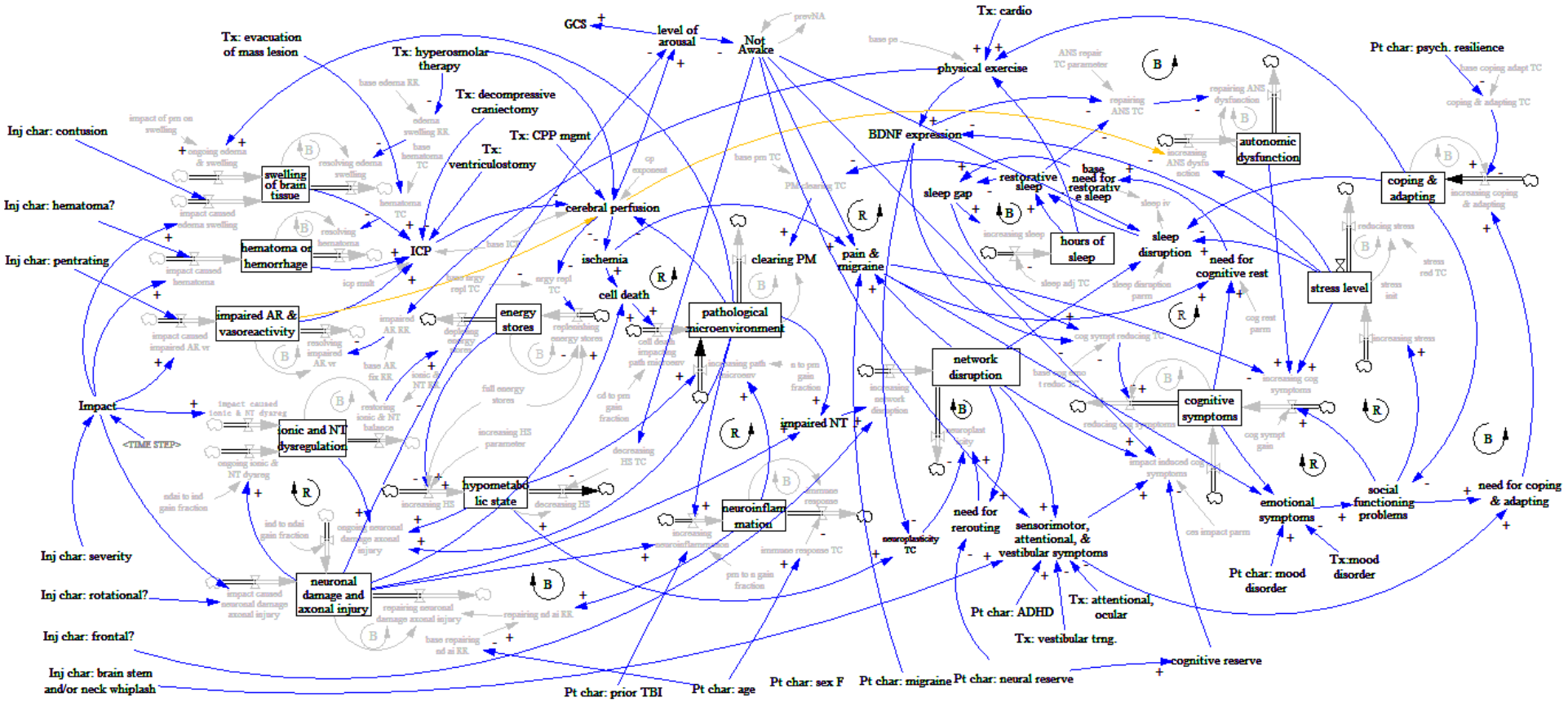


Figure 1. Computational model hybrid (stock, flow, and causal loop) diagram. The model contains 15 state variables, 73 auxiliary variables, and 50 parameters that represent various aspects of TBI pathology, from the cellular and network level to cognition and social functioning. These include brain swelling, hematoma, impaired cerebrovascular autoregulation, ionic dysregulation, neuronal injury, compromised cellular energy supply, neuroinflammation, pathological microenvironment, network disruption, autonomic dysfunction, cognitive symptoms, stress, sleep, and coping & adapting. Other key calculated variables include intracranial pressure, cerebral perfusion, level of arousal, GCS, pain & migraine, need for cognitive rest, sensorimotor, attentional & vestibular symptoms, emotional symptoms, sleep disruption, and social functioning problems. Additional endogenous variables include the flow logic and a myriad of auxiliary variables. Connections among the endogenous variables create over 1200 feedback loops.

characteristics include prior TBI, age, sex, neural reserve, prior migraine, prior ADHD, prior mood disorder, and resilience. This short list is only a small portion of the numerous personal and injury characteristics that shape heterogeneous trajectories, and has been included to demonstrate the different roles these characteristics can play. Several injury characteristics, such as degree of rotation and presence of hematoma, are similarly included.

Potential treatment options include evacuation of mass lesion, hyperosmolar therapy, CPP management, decompressive craniectomy, ventriculostomy, cardio therapy, mood disorder therapy, attentional/ocular therapy, and vestibular training. This list is also representative, and not in any way exhaustive of all possible treatments.

Visible/measurable outcomes of interest include ICP, level of arousal, cognitive symptoms, coping & adapting, and sleep. Hidden state variables of interest include brain swelling, hematoma, impaired AR & vasoreactivity, ionic and NT dysregulation, neuronal damage and axonal injury, hypometabolic state, pathological microenvironment, and neuroinflammation.

Finally, the model includes over a dozen exogenous time constants or "gain fractions" associated with the recovery processes for the pathologies across the different scales. Some of the time constants have an exogenous baseline value, but the runtime value is entangled in the feedback structure, and is therefore partially endogenously determined.

Small-scale cellular and molecular variables are shown on the left-hand side of Figure 1, and larger-scale cognitive, emotional, or social variables are shown on the right-hand side. The basic logic is that following impact, hematoma/hemorrhage or swelling can cause an increase in ICP, which reduces perfusion. The level of arousal is impacted by neuronal damage and perfusion. If someone is in a coma ("not awake" in the model), several key subsystems are taken offline due to lack of consciousness. Several additional injury characteristics, patient characteristics, and treatment variables are shown at the periphery of the diagram.

The model contains over 1200 feedback loops, of which 24 are labeled in Figure 1 via "R" and "B" symbols. Twelve of these are simple balancing loops with a single stock and its outflow, with logic whereby the outflow strives to return the stock to baseline (often zero). The other 12 labeled loops are slightly more complex, with seven of them being reinforcing and five of them being balancing. These 12 loops help to clarify the core logic of the model and we describe them in somewhat more detail below.

The current version of the model has 138 components, which includes 15 state variables (computed by integrating their rates of change), 73 auxiliary variables (computed as algebraic functions of other model components which could be variables or constants), and 50 constants (mostly rate constants and other patient characteristics, plus injury characteristics, and treatments).

Three of the reinforcing loops (or cascades) are physiological:

1) As "ionic and NT dysregulation" increases it influences "ongoing neuronal damage axonal injury" causing "neuronal damage and axonal injury to increase, which influences "ongoing ionic & NT dysreg" causing more "ionic and NT dysregulation"
2) As "pathological microenvironment" increases, "cerebral perfusion" decreases, causing increased "ischemia" which causes "cell death" to increase, which influences "cell death impacting path microenv" which increases "pathological microenvironment"

3) Increasing “pathological microenvironment” influences “increasing neuroinflammation” which causes “neuroinflammation” to increase, which influences “Increasing path microenv” which further increases “pathological microenvironment.”

Three reinforcing loops are experiential and involve the variable “cognitive symptoms” (CS), as follows:

4) Increasing CS influences “emotional symptoms” which influences “social functioning problems” which influences “increasing cog symptoms” causing CS to increase further
5) Increasing CS influences “emotional symptoms” which influences “social functioning problems” which influences “increasing stress,” so “stress level” increases, which influences “increasing cog & emot symptoms” causing CS to increase further
6) Increasing CS increases “need for cognitive rest,” which increases “base need for restorative sleep,” which increases “sleep gap,” which increases the time constant governing processes that that help to reduce CS.

The final reinforcing loop is both physiological and experiential, as follow:

7) Increasing “restorative sleep” decreases “PM clearing TC” which increases “clearing PM” which reduces “pathological microenvironment” which reduces “impairing NT” which reduces “increasing network disruption” which reduces “sleep disruption” which increases “restorative sleep.”

Of the five labeled, somewhat longer balancing loops, two involve physiological variables, as follows:

8) As “neuroinflammation” increases “repairing nd ai RR” increases which causes “neuronal damage and axonal injury” to decrease, which causes “increasing neuroinflammation” to decrease, which reduces “neuroinflammation.”
9) As “network disruption” increases, “need for rerouting” increases, which increases “neuroplasticity” [processes] which reduce “network disruption.”

The other three labeled, somewhat longer balancing loops include one or more experiential variables, as follows:

10) Increasing “coping & adapting” reduces “social functioning problems” which reduces “need for coping & adapting,” which reduces “increasing coping & adapting” which reduces “coping & adapting.”
11) Increasing “coping and adapting increases “physical exercise,” which increases “BDNF expression” which speeds up processes that help reduce “cognitive symptoms” which reduces “emotional problems” which reduces “social functioning problems” which reduces the “need for coping & adapting” which reduces “increasing coping & adapting” which reduces “coping & adapting.”
12) Increasing “hours” of sleep” increases “restorative sleep” increases (all other things being equal) which reduces the “sleep gap,” which reduces “increasing sleep” which reduces “sleep.”

Model Behavior

One type of result that a computational model can provide is to show possible behaviors for a wide variety of different parameter settings, patient characteristics, and injury

characteristics. Figure 2 shows the time trajectories for three of the key physiological state variable for the baseline model run.

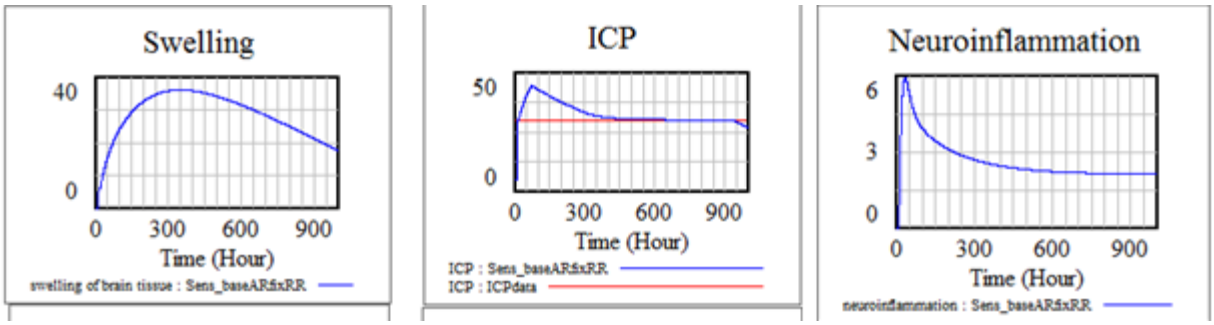


Figure 2. Baseline model run, showing time trajectories for key physiological variables. Model parameters were set to represent a 70-year old patient with a severe injury.

Preliminary Model Testing

To better understand how the model structure and especially how parameter values influence recovery processes, we first conducted a sensitivity analysis, as follows. Several of the model parameters were varied over a uniform range from specified minimum and maximum values, with a specified increment. For many parameters, the test array was set to generate 10 runs; less in a few cases. To easily see test results, additional "model views" were created within the model, two focused on physiology (the left-hand side of the model diagram) and two focused on cognition and psychological/ social aspects (the right-hand side of the model diagram). These views provided easy access to parameter values and featured sensitivity graphs that show how the time trajectories change for seven key state variables as parameters are varied.

A wide variety of these sensitivity tests were performed, varying different recovery rate time constants and related parameters, injury characteristics, and patient characteristics. Time behavior was simulated for 1000 hours, just under six weeks. These tests included relatively "extreme values" as well as the more typical type of sensitivity test in which parameters are varied by a relatively small percentage (+/- 10 to 30%) to determine the relative influence of model parameters.

The first set of sensitivity tests focused on the effects of key physiological parameters in the model for an elderly patient with a severe injury, for which baseline outcomes for three key physiologic al state variables: brain swelling, intracranial pressure (ICP), and neuroimflammation as shown in Figure 2. We varied each of the 16 selected parameters shown in Table 1 over a range from approximately 1/3 to 3 times their baseline values shown in the table. Figure 3 shows the trajectories for the three key state variables when five of the 14 physiological parameters were varied as described in Table 1. Although not shown here, similar results were generated and for the other nine physiological parameters in Table 1. Figure 4 shows the trajectories of the three key state variables when patient age and injury severity are varied.

Table 1. Selected model parameters: physiological, patient characteristics, Injury characteristics

Parameter Type	**Parameter Name**	**Parameter Description**	**Base Value**	**Units**
Physiological	base AR fix RR	Base autoregulation recovery rate	0.03	
	base hematoma TC	Base hematoma recovery time constant	70	hours
	Impact of pm on swelling	Impact of pathological microenvironment on swelling	0.2	
	icp mult	Icp multiplier	2.5	
	cd to pm gain fraction	Cellular death to pathological microenvironment gain fraction	0.33	
	base pm TC	Base pathological microenvironment clearing time constant	0.7	hours
	n to pm gain fraction	Neuroinflammation to pathological microenvironment gain fraction	0.2	
	pm to n gain fraction	Pathological microenvironment to neuroinflammation to gain fraction	0.1	
	base nrgy repl TC	Base energy replacement time constant	1	hours
	increasing HS parameter	Increasing hypometabolic state parameter	0.05	
	ndai to ind gain fraction	Neuronal damage & axonal injury to Ionic & neurotransmitter dysregulation gain fraction	0.05	
	ind to ndai gain fraction	Ionic & neurotransmitter dysregulation to neuronal damage & axonal injury gain fraction	.08	
	ionic and NT RR	Ionic and neurotransmitter dysregulation recovery rate	1	
	base edema RR	Base edema recovery rate	.2	
Patient char.	Pt char: age	Patient characteristic: age	70	
Injury char.	Inj char: severity	Injury characteristic: injury severity	5	

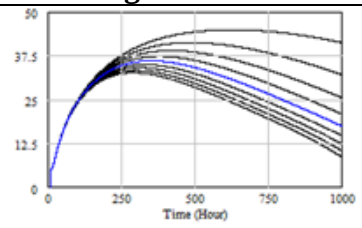
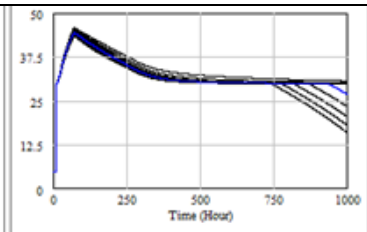
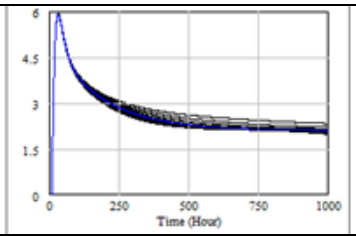
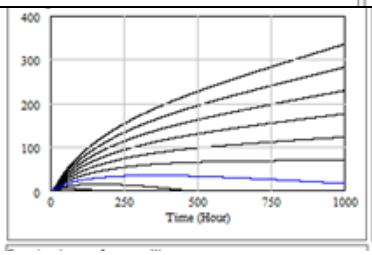
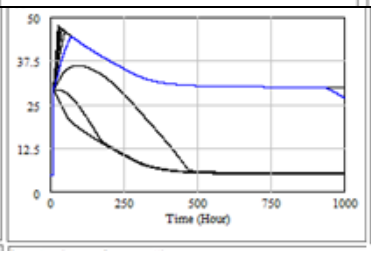
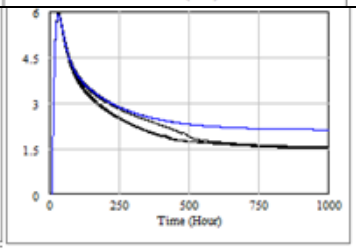
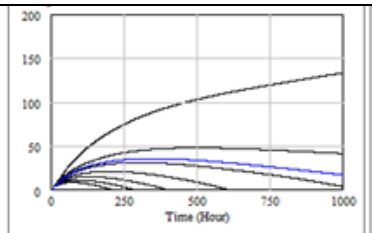
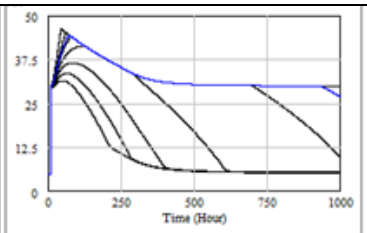
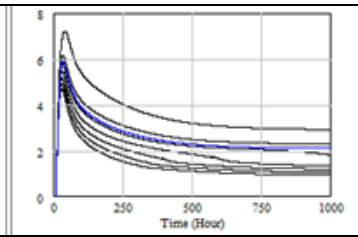
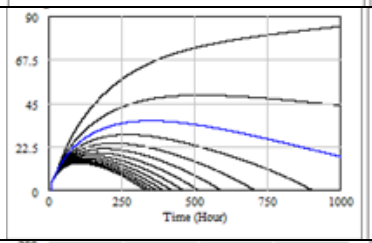
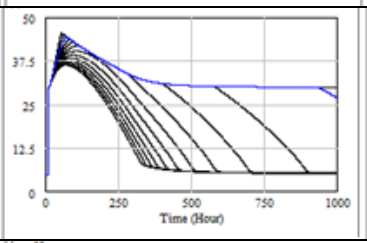
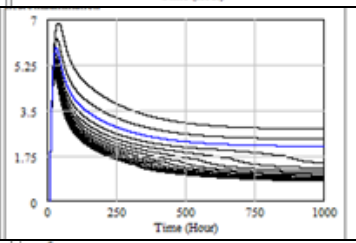
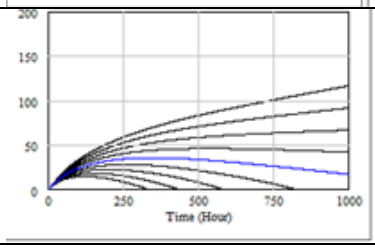
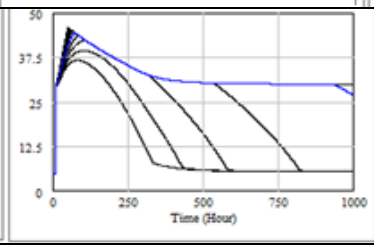
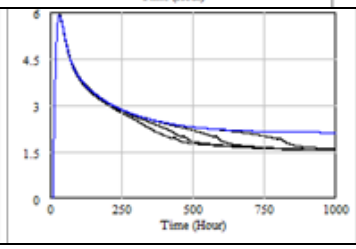
Varied	Swelling of Brain Tissue	Intracranial Pressure	Neuroinflammation
A. Base AR fix rate 0.01 - 0.05			
B. Impact of pm on swelling 0.05 - 0.5			
C. cd to pm gain fraction 0.2 - 0.4			
D. ionic and NT RR 0.8 - 2			
E. base edema RR 0.1 - 0.3			

*Figure 3. Sensitivity of brain swelling, ICP, and Neuroinflammation to five key parameters, Rows A to E. In row **A**, the parameter primarily impacts impaired AR & vasoreativity, which strongly impacts brain swelling. In row **B**, the parameter effects the gain of a reinforcing loop, and thus profoundly impacts brain swelling and ICP. The effect on ICP seems less because the baseline ICP is already severe (elderly patient w/severe injury). In row **C**, even modest changes in this gain parameter significantly impacted several state variables, including brain swelling and ICP. Uncontrolled cascades occurred for values above .4, indicating an opportunity for model improvement to address the lack of mechanisms that act to counteract such cascades. Also, when cell deaths exceed some threshold, recovery is not likely possible. In row **D**, values below .8 were not viable. Strong impact on many state variables. In row **E**, variation was limited to avoid triggering a cascade. High impact on brain swelling as would be expected, and, accordingly, on ICP. Only modest impact on the other state variables.*

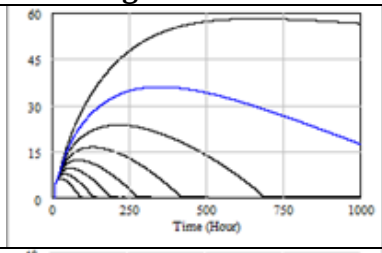
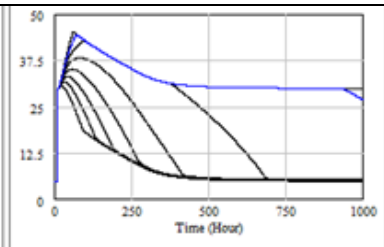
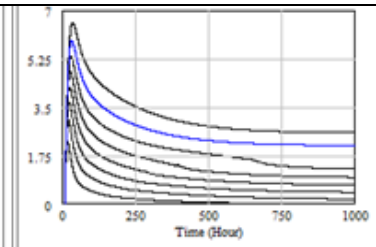
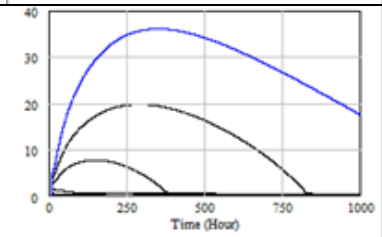
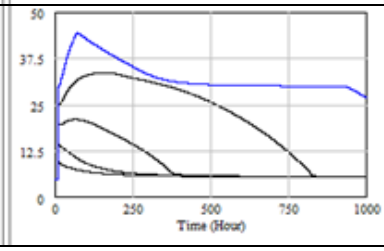
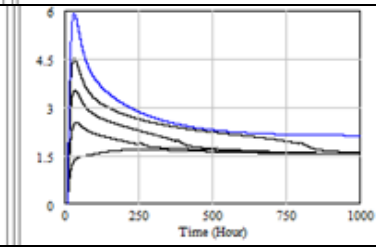
Varied	Swelling of Brain Tissue	Intracranial Pressure	Neuroinflammation
A. Pt char: age 10 - 80			
B. Inj char: severity 1 - 5			

*Figure 4: sensitivity of brain swelling, ICP, and neuroiflammation to patient age and injury sensitivity. For row **A,** Since the base run was for age 70, the blue line is near the top.The impact of age on restorative/healing rates is very simplistic and consequently its impact in the model may be exaggerated and therefore not plausible. In row **B,** high severity causes an unfavorable cascade in a simulated 70 year old patient. Younger patients could potentially survive a more severe injury. Less severe injuries exhibit ICP levels that return eventually to baseline. While this could happen, the simulated trajectories may not represent the most likely time to recovery.*

Next, we made sensitivity runs for the cognitive and psychological/ social parameters that influence the recovery process for a less severe TBI, both acute and intermediate to longer term. These parameters are also relevant to medium and long-term recovery processes for severe TBI. For these tests, the base case is a mild TBI involving a concussion for which the injury severity is "1" and there is no hematoma. Patient age is 20. Figure 5 shows the baseline recovery trajectory for three of the key cognitive state variables. This case represents a relatively slow but steady recovery from the injury.

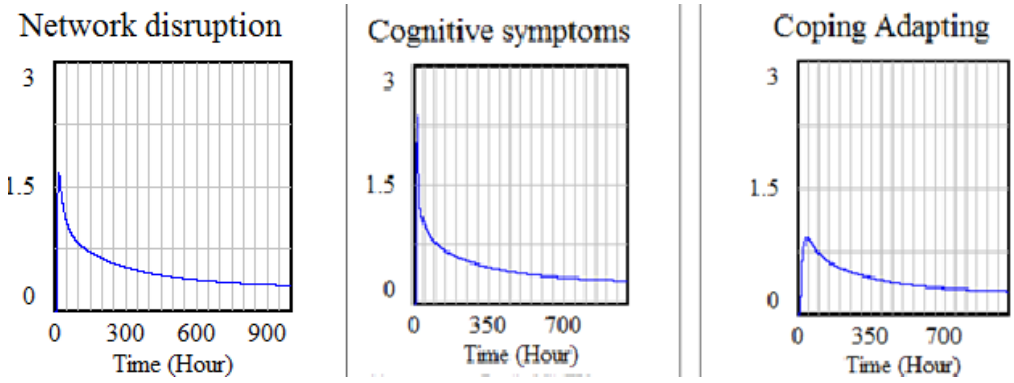


Figure 5: Baseline cognitive outcome trajectories

Table 2 shows the model parameters that were tested and their baseline values, grouped by cognitive, patient characteristics, injury characteristics and treatment-related. Figure 6 provides examples of how the trajectories for the selected outcomes changed when parameters were varied over a broad range of values.

Table 2. Selected model parameters: cognitive, patient characteristics, Injury characteristics, and treatments

Parameter Type	**Parameter Name**	**Parameter Description**	**Base Value**	**Units**
Cognitive	ces impact parm	cog emot symptoms multiplier	.5	
	cog rest parm	cog rest parameter	.2	
	cog sympt gain	cog symptom gain	.2	
	base cog emot reduc TC	cog emotional symptom reduction time constant	1	hrs.
	sleep adj TC	sleep adjustment time constant	5	hrs.
	sleep disruption parm	sleep disruption parameter	1	
	stress red TC	stress reductions time constant	1	hrs
	base coping adapt TC	coping/adapting time constant	20	hrs.
	ANS repair TC parameter	Autonomic nervous system repair time constant	20	hrs.
	base pe	physical exercise	1	hr./wk.
Patient char.	Pt char: age	age	20	yrs.
	Pt char: prior TBI	prior TBI	0	
	Pt char: migraine	history of migraine	0	
	Pt char: mood disorder	history of mood disorder	0	
	Pt char: ADHD	ADHD diagnosis	0	
	Pt char: neural reserve	neural reserve	1	
	Pt char: psych. resilience	psychological resilience	1	
Injury char.	Inj char: severity	injury severity	1	
	Inj char: rotational?	rotational: yes/no	0	
	Inj char: brain stem and/or neck whiplash	brainstem and/or neck whiplash: yes/no	0	
Treatment	Tx: attentional, ocular	attentional, ocular therapy	0	
	Tx: vestibular trng	vestibular training	0	
	Tx: mood disorder	mood disorder drugs	0	
	Tx: cardio	cardio therapy	0	

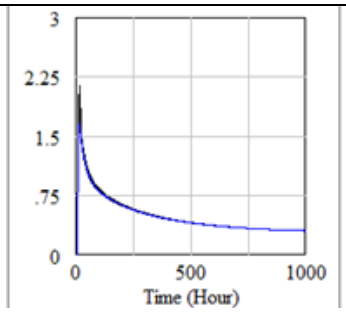
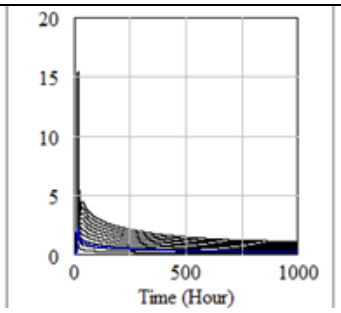
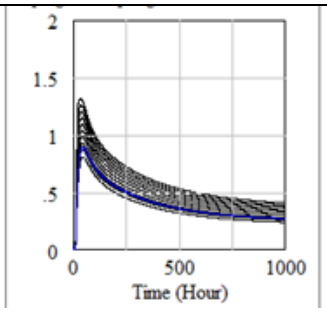
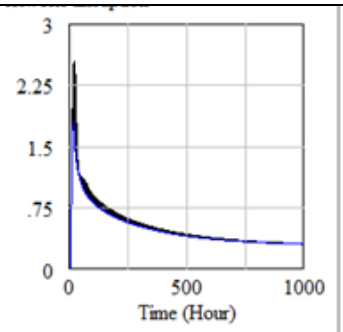
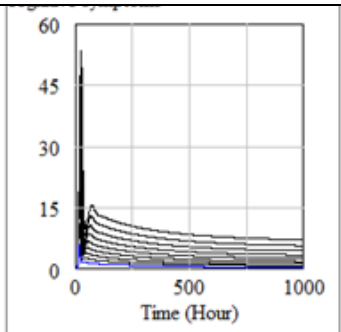
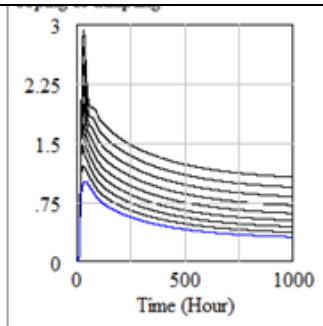
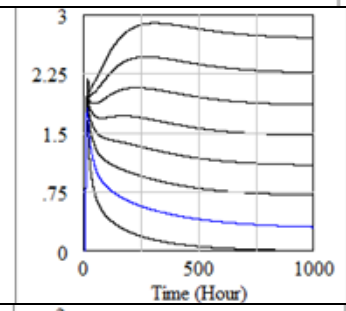
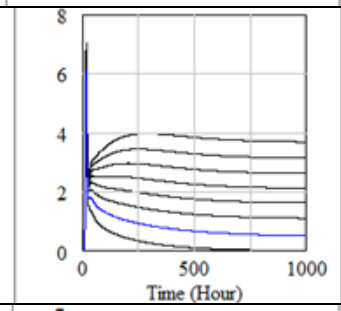
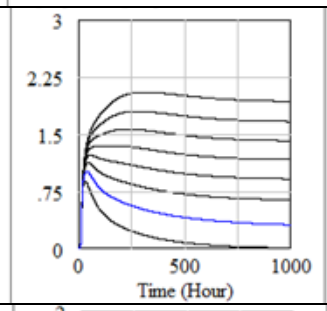
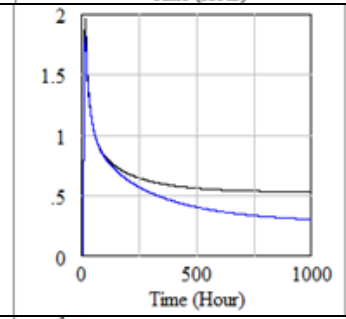
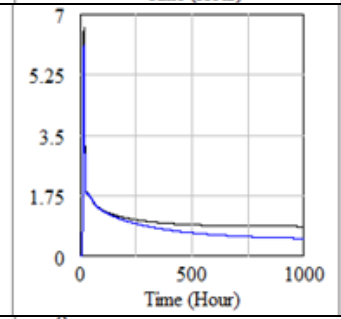
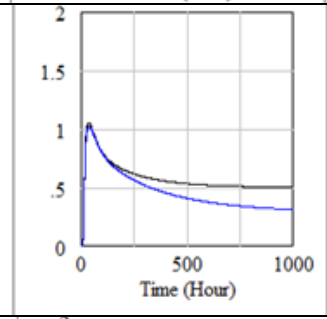
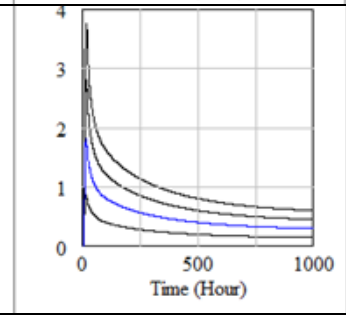
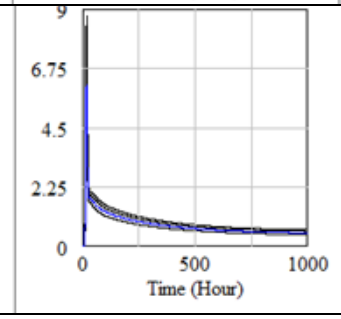
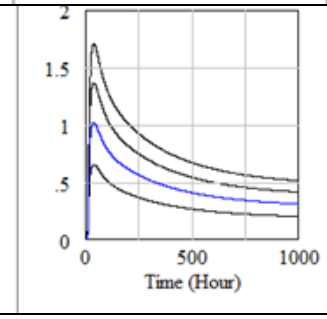
Varied	Network disruption	Cognitive symptoms	Coping & adapting
A. ces impact parm 0.2 - 2			
B. Base cog emot reduc TC 0.5 - 5			
C. Pt char: age 10 - 80			
D. Pt char: prior TBI 0 or 1			
E. Pt char: neural reserve 0.5 - 2			

Figure 6: Sensitivity of Network disruption, Cognitive symptoms, and Coping & adapting to five key parameters, Rows A to E, including two cognitive parameters and three patient

*characteristics. In row **A**, higher values significantly change the magnitude of the initial symptoms, which then subside relatively quickly. In row **B**, larger values increase initial spike and tend to slow recovery to a degree. For row **C**, age significantly affects network disruption recovery, which in turn impacts cognitive symptoms, and coping. In row **D**, prior TBI retards network disruption recovery, which influences cognitive and other variables; these remain in a mildly pathological state as a result. In row **E**, network disruption and coping & adapting are significantly impacted.*

Figure 7 shows the sensitivity of outcomes to two of the injury characteristics.

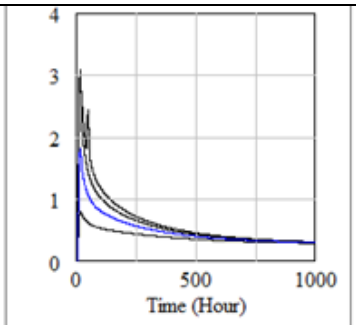
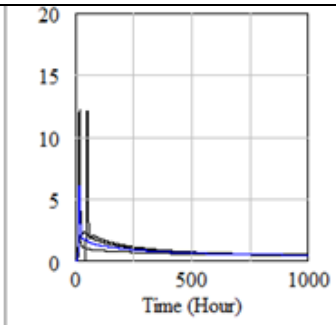
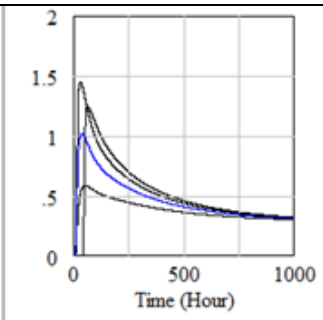
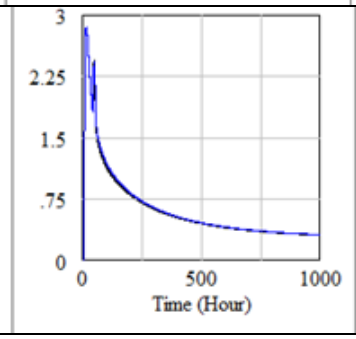
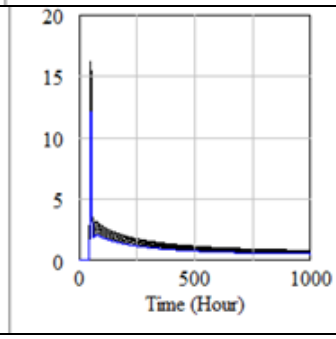
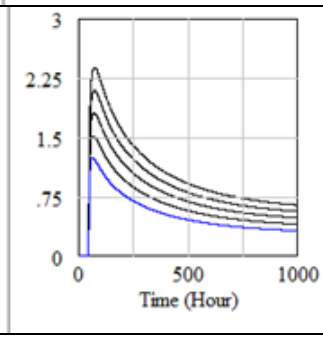
Varied	Network disruption	Cognitive symptoms	Coping & adapting
A. Inj char: severity 0.5 - 2			
B. Inj char: brainstem and/or neck whiplash 0.5 - 2			

*Figure 7: Sensitivity of Network disruption, Cognitive symptoms, and Coping & adapting to two injury characteristics: severity and brainstem, and/or neck whiplash. In row **A,** Injury severity remains in the realm of relatively mild TBI. Network disruption varies significantly, and at the injury severity of 2, the modeled patient was not fully conscious for four days post injury (GCS 11), so the effect on cognition, etc. are delayed. And since physiological repair process begin during this period, the peak of the trajectory of "coping & adapting," for example, does not exceed that for a slight less severe injury that did not result in a full coma. In row **B**, the type of injury increases the cognitive and psychological impact, most noticeable in the need for more coping &adapting.*

These sensitivity tests have shown that the model behaves plausibly over a range of conditions, and shows potentially interesting behaviors. In fact, however, much more model testing and refinement is needed for a model of this complexity. Additional tests would include comparison of model behavior to high-quality reference behavior data, additional sensitivity analysis, hypothesis testing, analyses of model feedback structure, and fully characterizing the range of applicability of the model in terms of the extreme values of parameters and exogenous variables. Furthermore, the dimensions for every parameter and variable would be specified and

dimensional consistency analyzed in detail. This full battery of testing would be carried out after a realistic and empirically supported model is achieved…one that incorporates to a much greater extent the body of TBI knowledge. Detailed model experimentation would commence after the full battery of tests has been completed.

However, since the model was developed to *demonstrate* how a computational model could potentially be applied to recovery from brain injury, the next section provides the results of model experiments that go beyond what would normally be warranted given the current conceptual nature of the model. These experiments focus on finding sets of parameters and conditions associated with various recovery trajectory patterns. Conditions could include parameters and characteristics, as well as possible treatments.

To demonstrate this, computational models are paired with optimization methods using an objective function that minimizes the difference between model calculated recovery trajectory and idealized recovery trajectories. We also searched for combinations of simulated treatments that result in the quickest and most complete patient recovery. Consider a recovery trajectory in which ICP remains at 30 mmHg. While this ICP would not be survivable indefinitely, it is a simple pathology to describe, and knowing the associated parameter values could be informative.

The analysis, implemented in Vensim, required a data file called ICPdata, to be created, containing a constant value of 30. The "payoff" function in the optimization tool was set to minimize the difference between the "ICP" data in this data file and the ICP calculated in the model. Seven parameters were selected to be varied, and min/max values were specified for each of them: base AR fix RR, base hematoma TC, impact of pm on swelling, icp mult, cd to pm gain fraction, base pm TC, and n to pm gain fraction. 1000 simulation runs were done, to find an ICP trajectory that matched the "data" file. Three parameters were significantly changed: base AR fix RR, from .03 to .01, icp mult, from 2.5 to 7.7, and cd to pm gain fraction, from .33 to .66.

Figure 8 shows the resulting state variable trajectories. Allowing the "icp mult" parameter to be increased beyond 3 was not intended; this may not have a valid physiological interpretation, but it may have inadvertently led to an interesting insight regarding the persistence of high ICP as often seen clinically.

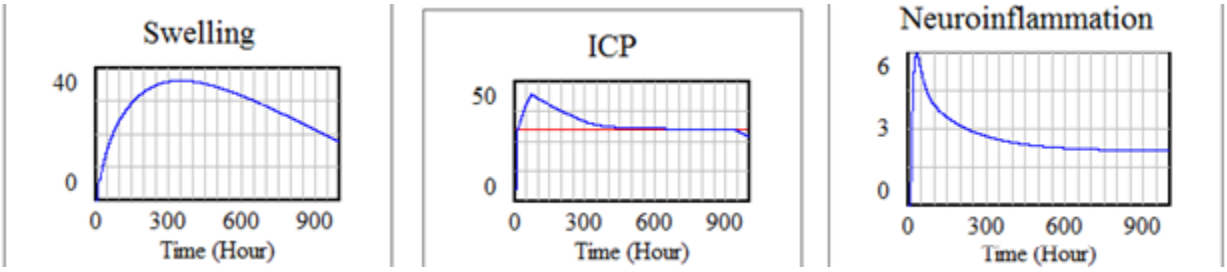


Figure 8. Trajectories based on parameter values that result in ICP staying high

Early in the run, ICP exceeds 30 which would likely not be survivable. Still the analysis does show a way that ICP could remain at 30. The changes in parameter values may or may not be interpretable. The 3X reduction in the "AR fix RR" represents significant impairment in the speed at which the body can repair impaired cerebral auto-regulation and/or vasoreactivity. Such a reduction may or may not be plausible. The tripling of the icp Mult dramatically increases

sensitivity of ICP to impaired AR/VR and/or brain swelling, and the doubling of the cd to pm gain fraction (governing how cell death influences the pathological microenvironment) may similarly suggest possible pathologies for consideration.

A second scenario of interest are conditions that result in full recovery from a mild injury within a few weeks, as is the case for most mild injuries. For this case the state variable of interest is "cognitive symptoms," for which the goal is to return to zero within two weeks (340 hrs.). The search process varied within plausible limits nine physiological parameters, four cognitive parameters, and one patient characteristics.

The search algorithm ran 2512 simulations and five parameters were changed by factors of 2 to 2.5, three physiological, one cognitive, one patient characteristic. The results are highlighted in Table 3.

Table 3. Parameters found by search that help to assure quick recovery. The algorithm changed highlighted values by a factor of two or more

Type	**Variable**	**Base value**	**Revised Value**
Physiological	base AR fix RR	0.03	0.034
	impact of pm on swelling	0.2	0.50
	cd to pm gain fraction	0.33	0.13
	base pm TC	0.7	0.80
	pm to n gain fraction	0.1	0.1
	base nrgy repl TC	1	1.5
	ind to ndai gain fraction	0.1	0.65
	ionic & NT RR	1	
	base edema RR	0.2	0.1
Cognitive	ces impact parm	0.5	0.62
	base cog emot reduc TC	1	1.13
	stress red TC	1	1.36
	base coping adapt TC	20	10.3
Pt Characteristic	Pt char: age	20	10

Figure 9 shows the resulting trajectories for the three primary physiological state variables and three primary cognitive state variables.

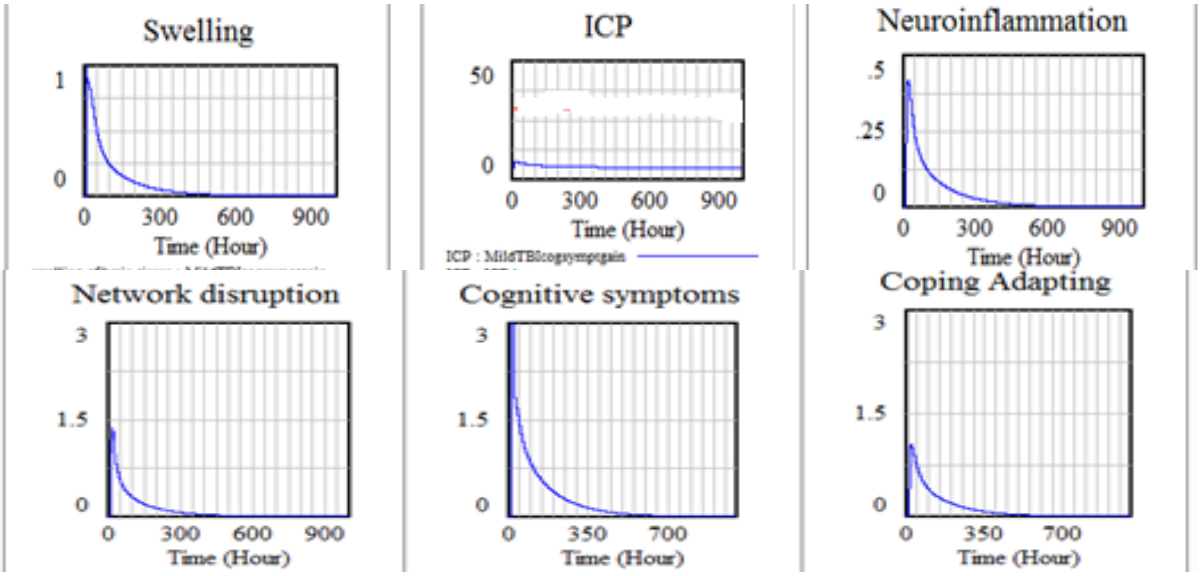


Figure 9. Graphs of full recovery optimization results

Many additional experiments could be done to further demonstrate the potential utility of systems level computation model for traumatic brain injury, but the two examples shown provide an initial demonstration of the potential.

Discussion

The computational model underscored the complex behavioral impacts, both beneficial and pathological, related to the role of inflammation in TBI. The tight coupling of processes makes it difficult to determine cause vs. effect. There is clearly a need to better understand repair processes, including how age influences repair processes. One general implication is that physiological processes tend to more sensitive to parameter changes, due in part to the number of reinforcing processes or cascades, underscoring the need for longitudinal data regarding patient state during recovery, both as indicated by signs, symptoms, and deficits, but also biomarkers tied to key physiological processes.

The system dynamics method demonstrated in this report is widely considered to be capable of providing value and add value even when data is scant (Sterman 2002). Furthermore, there are several systems analysis tools that create models based on structural (as opposed to parametric) information to create models that can be used productively to analyze behavior of complex systems. Early applications include ecological systems (Puccia and Levins 1991). So it is not necessarily surprising that a conceptual model could be useful even without empirical support. Of course, model utility will increase significantly with appropriate data.

An important and difficult challenge is determining the “right” model boundary. This involves deciding which processes to include at least at the outset, and which to exclude despite their potential relevance. The modeler must also determine which aspects to treat as exogenous, either as constants or as exogenous time series. Such aspects can influence the recovery process and the patient experience, but not the other way around. Conversely, the modeler must

determine what to include as endogenous components/aspects/variables that influence patient experience and recovery, and are in turn influenced and changed during the recovery process.

To further the potential for systems level computational modeling, in additional to improving empirical support, it could also be advantageous to migrate the model from the system dynamics framework to a more robust computational environment, perhaps a combination of R and its many packages, and Python and its various and extensions. This would allow researchers to assemble a database with actual and/or speculative sets of injury and patient characteristics, as well as estimates of uncertainty/variability, and then to run the model in "Monte Carlo" mode in order to obtain a cloud of trajectories based on these uncertainties and variabilities instead of a single trajectory.

Future Opportunities

More research is needed to transition the computational model from a demonstration model to a properly supported research model that could potentially be used for precision-medicine application or to use as an aid to clinical trial design.

The significant future step in this endeavor would be to create an appropriate computational model framework to address these multilevel phenomena with complex feedback structures, so as to address the high uncertainty/variability and the considerable heterogeneity at the individual level as well as lower in the system hierarchy, e.g. at molecular and cellular levels.

Estimating the recovery trajectory for a particular TBI patient will require effective representation of the individual's particular characteristics and details regarding their injury via sets of unique parameter values. That every patient is different is referred to as patient heterogeneity, and the research community believes that capturing these differences is one of the keys to increasing understanding of complex biological systems such as TBI pathology and the associated recovery processes. It is not known yet whether it will be necessary to model individual patients or if it may be sufficient to model groups or clusters of patients whose responses to TBI and their associated recovery processes are similar.

The characteristics of a patient or patient group/cluster could be a vector of parameter values that may or may not include both mean values and degree of variability. It is not yet clear whether the latter could be determined from the overall patient population or will need to be different for each patient/cluster.

It seems likely that in order to provide confidence bands around estimated trajectories, it will be necessary to use a Monte Carlo approach to make a set of model runs for each patient or cluster. Each model run would sample from probability distributions for highly uncertain parameter values, thereby creating a family of trajectories for outcome metrics. Confidence intervals could be estimated at key time points for these metrics to create plausible upper and lower bounds for the estimated trajectories. However, doing so might be highly computationally intensive, and therefore necessitate the development of an efficient sampling strategy.

Once data regarding the recovery trajectories in terms of key metrics for individuals/clusters is available, it may be possible to estimate unknown or latent parameter values. Such data could also help to estimate the variability of key input parameters and outcomes, both at the population level and within identified clusters of patient trajectories.

It seems likely that it may also be the case that rather than treating the brain as a single aggregate organ it may be necessary to estimate different parameters for various "regions" of the brain, either for an individual or for a group of similar individuals. Open questions include how best to represent/model brain/network properties/logic/functioning/behavior and at what resolution, and whether parameters differentiated by brain region are orthogonal to or highly correlated with parameters differentiated by patient group/cluster.

Another question regards how to incorporate, integrate, or couple the computational model to the results of statistical/correlational/black-box data analysis/datamining/machine learning models. These latter models are applied to datasets that may contain aggregate data and/or individual data regarding injury nature and severity, patient signs, symptoms, and deficits (SSDs) collected immediately post injury, as well as treatments, therapies and other interventions applied at different time points. Ideally, these datasets would also provide longitudinal data regarding the patient's recovery "trajectory" in terms of SSDs, and their ultimate outcome.

Figure 10 expresses the requirements for a possible data/model integration framework as a flow chart. From a causal loop diagram, a Vensim model is specified and calibrated, reflecting baseline or typical parameter values. Data arrays would be developed containing typical and pathological patient-specific parameter values. Some of the parameter values would be constants and others would specify the parameters of probability functions (pdfs) reflecting sources of uncertainty/variability. Scripts would be developed to make sets of simulation runs representing different patients or clusters of patients (heterogeneity) and also reflecting uncertainty via sampling from probability distributions in Monte Carlo fashion. Results would be summarized visually to facilitate interpretation.

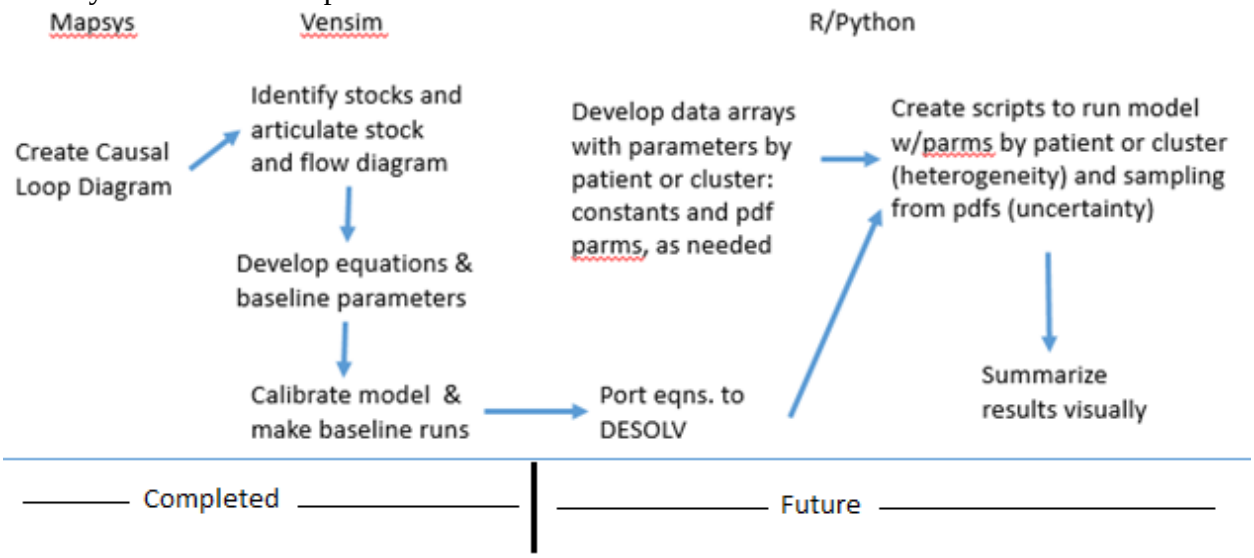


Figure 1. Computational framework block diagram

The suggested framework does not include the logic for estimating model parameters for a particular patient or cluster in order to achieve the best fit between model-calculated trajectories and the empirical data. More importantly, the framework does not fully accommodate the multilevel nature of the problem. It is likely that conceptual and temporal model boundaries will need to be drawn so that the core "logic" of the system can be

appropriately modeled as a set of differential equations. This would imply that cellular and network-related processing would need to be treated in some sort of aggregate fashion, perhaps by brain region, rather than striving to create logic at the level of individual neurons and their milieu.

A model developed using the suggested computational framework would be capable of being calibrated to generate differential recovery trajectories at the patient or patient cluster level. Some of the parameters would be specified based on empirical data, and other parameters would be estimated using optimization methods to minimize model fitness error. Figure 11 shows a mockup dashboard showing how the results of applying the model and framework to clustered patient level data might be displayed. Model trajectories would almost certainly not match the data to the degree shown in the mockup.

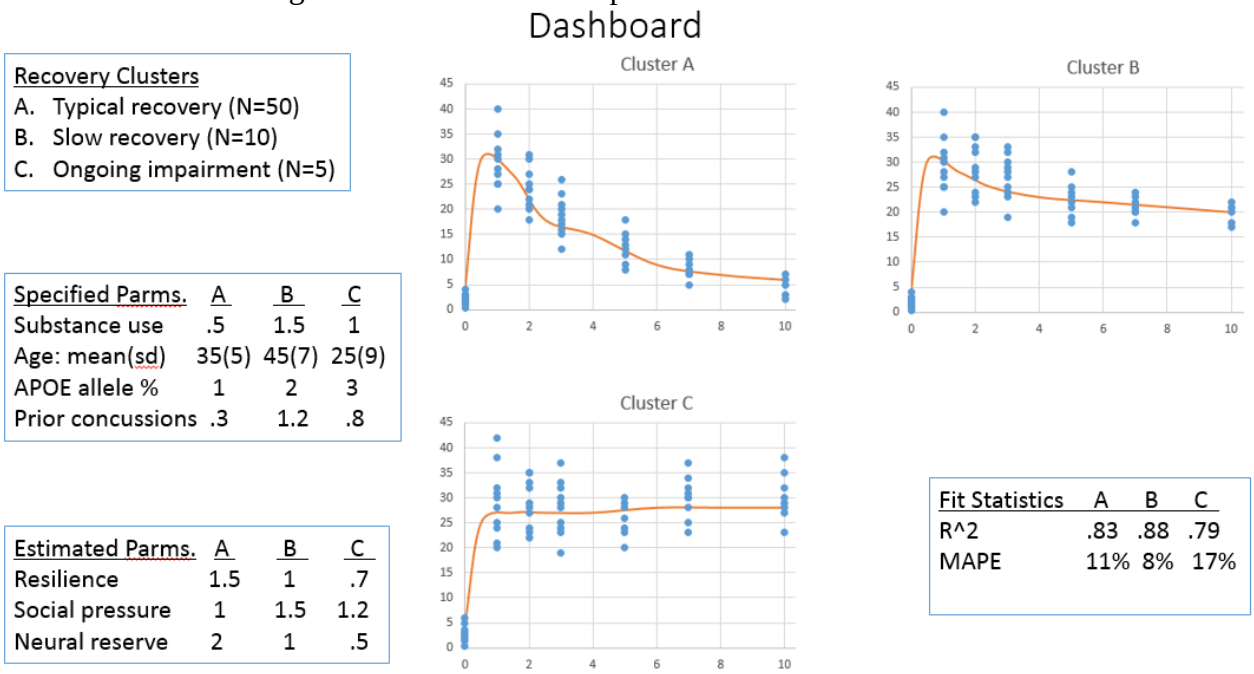


Figure 2. Mockup of Model Results Dashboard. Fictitious #'s for illustration only. Wd. show parms. plots of case data, and model calcs by cluster along w/fit stats.

Another use for combined optimization and simulation could be to search for effective combinations of therapies for different combinations of injury and patient characteristics. The present demonstration computational model represents treatments in a very simple fashion such that the use of optimization would not likely reveal useful or novel insights. An empirically supported model would be necessary.

Conclusion

Despite the dizzying complexity of traumatic brain injury, a systems-level dynamic model could potentially contribute to increased understanding and help to sharpen future research. With even a modest degree of patient-level longitudinal data, this type of model could

likely contribute to the development of more nuanced TBI classification, personalization of therapies and their timing, and more effective clinical trial design.

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