Computational Modeling Framework for Multilevel Systems with Feedback, Uncertainty, and Heterogeneity—Case in Point: Concussion Recovery

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Abstract

We propose a computational model framework to address multilevel phenomena with complex feedback structures, high uncertainty/variability and considerable heterogeneity at the individual level as well as lower in the system hierarchy, e.g. at molecular and cellular levels. Although researchers often use hybrid models to address these different aspects, we propose a framework based on differential equations and Monte Carlo methods. The paper begins by describing the case that motivated framework development—recovery from concussion. Status of the project is a complex causal loop diagram. We review the process of developing this diagram as well as the literature on multiscale modeling and other potentially relevant methods. We describe the proposed framework and provide a mockup of what the results of using the framework might look like. This is a progress report, not a finished product.

1. Introduction

We are motivated to identify and develop a framework for modeling multi-level systems in order to understand better the pathophysiologies and healing processes associated with recovery from concussion. Concussion is an incredibly complex injury/disease syndrome, as is often the case with transdisciplinary problems. The brain is by far the most complex organ in the human body, and reliable biomarkers are still lacking(Kulbe and Geddes 2016) . There are few effective and reliable treatments, and it is difficult to know which treatment(s) to use for a given patient(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. Although the classification scale used for traumatic brain injury (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). It is not even clear whether concussion is useful as a diagnosis. Better models are needed to support research, diagnosis, and treatment.

Although computational models of such multi-level systems are necessarily vastly simpler than the system under study, they must nevertheless be able to 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 paper describes one particular modeling domain—that of concussion recovery—in some detail (Section 2), briefly surveys available modeling methods (Section 3), and then proposes a hybrid computational modeling framework (Section 4). Section 5 concludes the paper with a mockup of the anticipated results of applying the proposed framework to the problem domain of interest.

2. Background regarding the specific application domain: concussion recovery

Our endeavor to create a dynamic model of concussion recovery began in early 2014 at a meeting of 25 TBI/concussion researchers and practitioners, where we reviewed, corrected, and extended a very preliminary causal loop diagram (Figure 1). We provide several complex diagrams not for the reader to inspect thoroughly but rather to give a sense for the target domain and our evolving appreciation for the complexity of the problem.

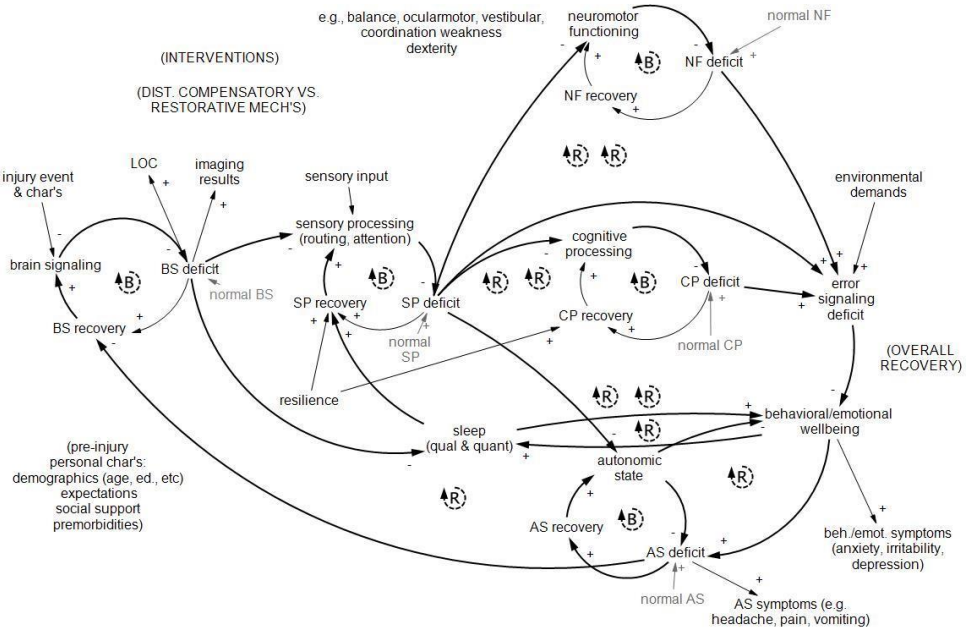

Figure 1: An early prototype causal loop diagram intended to illustrate key concept relevant to concussion recovery and stimulate discussion

At the investigator team meeting, the modeling group created a demonstration computational model to show the potential of system dynamics for calculating concussion recovery trajectories (Figures 2 and 3).

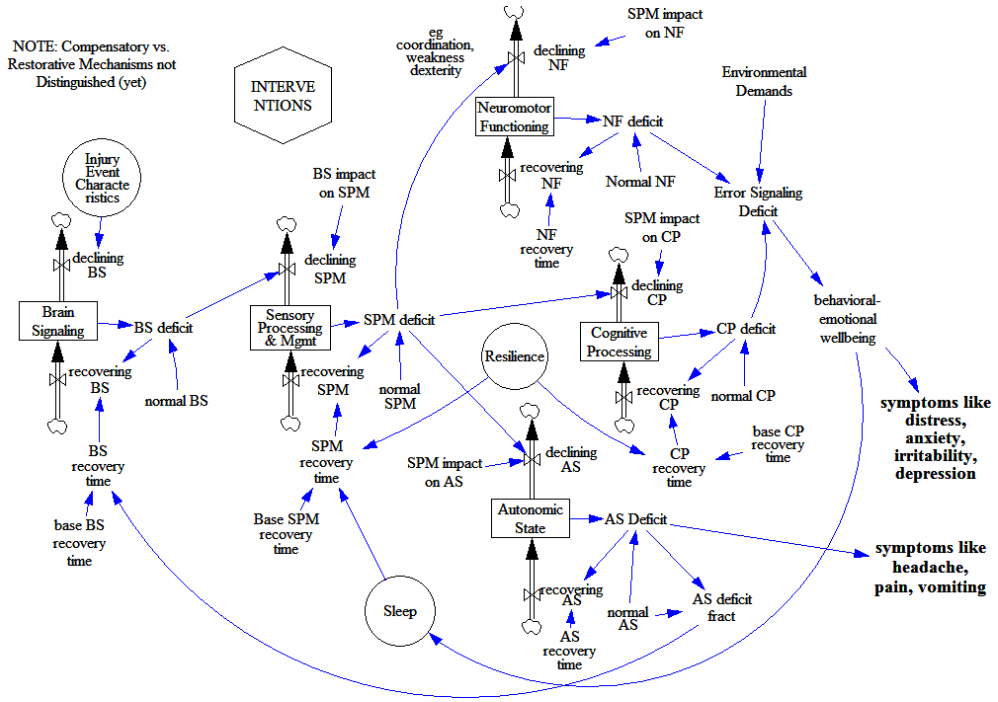

Figure 2: An illustrative computational version of the initial causal loop diagram.

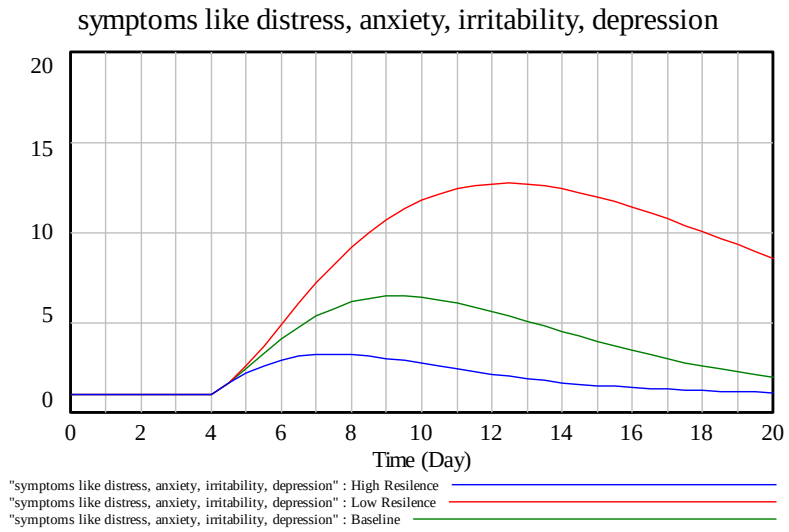

Figure 3: Simulated mock patient recovery trajectories

The investigator team of researchers and practitioners was very enthusiastic, so the modeling group began a detailed literature review; spoke with local neuroscientists, athletic trainers, and sports medicine physicians; and met with high school athletes recovering from concussion. Our revised conceptual model was especially influenced by concepts of predictive brain state (Ghajar and Ivry 2008; Ghajar and Ivry 2009) and neurometabolic cascade (Giza and Hovda 2001). We reviewed the revised CLD draft with these researchers and made further revisions. Figure 4 shows the result, which was presented at the second investigator team meeting in early 2015. We also located examples of reference behavior data (Figure 5).

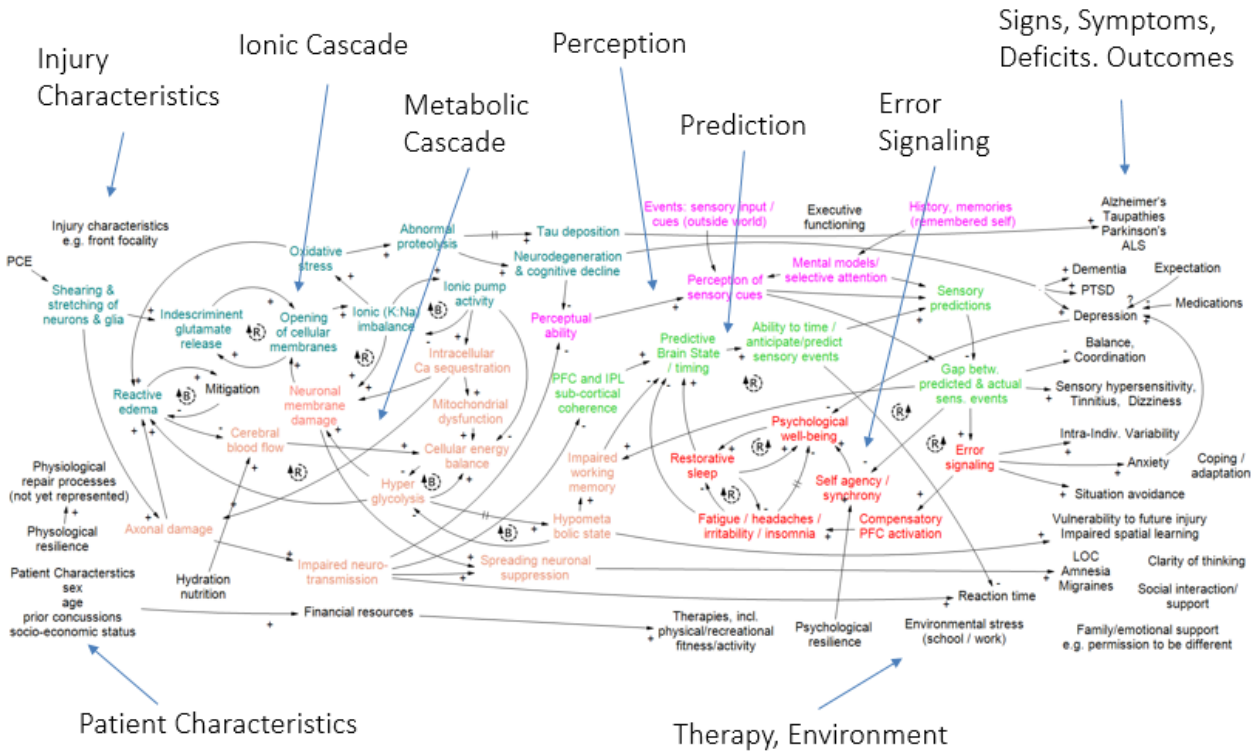

Figure 4. Significantly enhanced (Phase II) causal loop diagram describing concussion

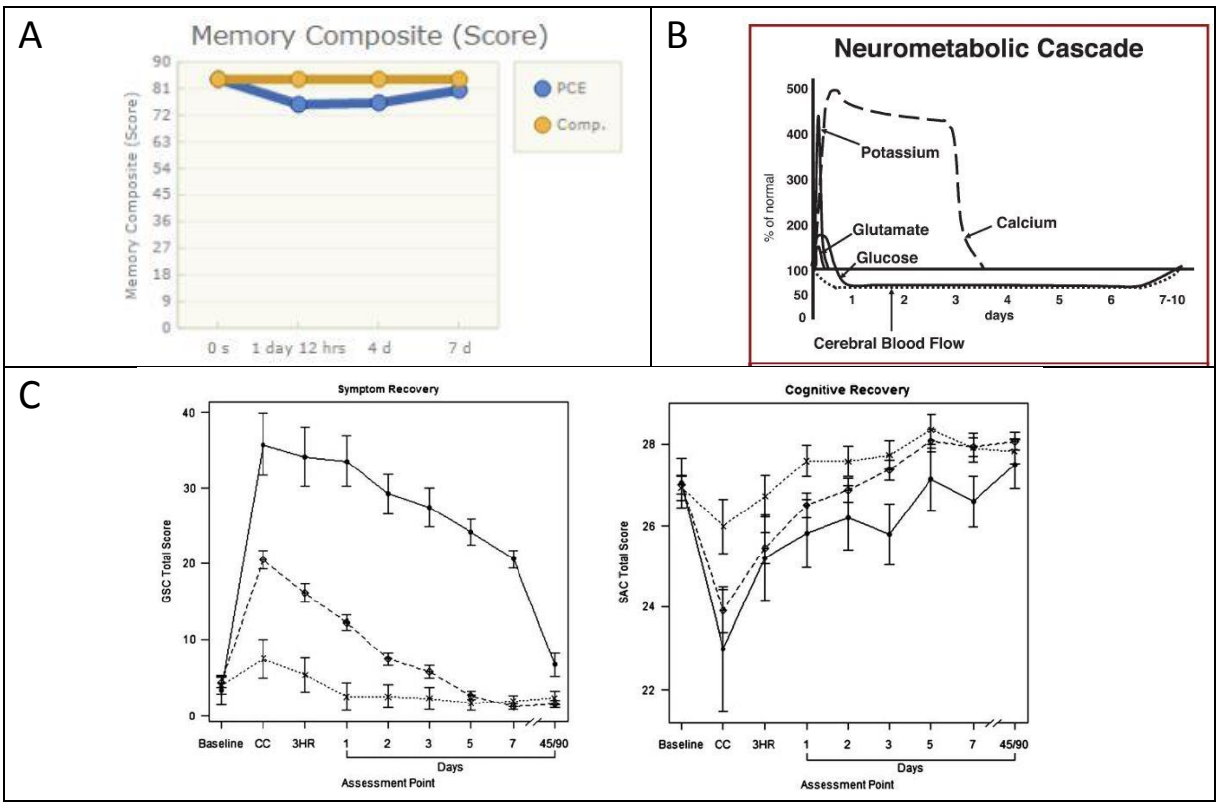

Figure 5: Reference behavior data. A. Memory recovery time (Lovell et al. 2003), B. Cellular level (Giza and Hovda 2014), C. Symptom and cognitive recovery time (McCrea, Broshek, and Barth 2015)

Based on the well-received updated result, the modeling group further improved its understanding and the diagram via meetings with national concussion and TBI experts during 2015. By early 2016, the diagram had evolved considerably, as shown in Figure 6.

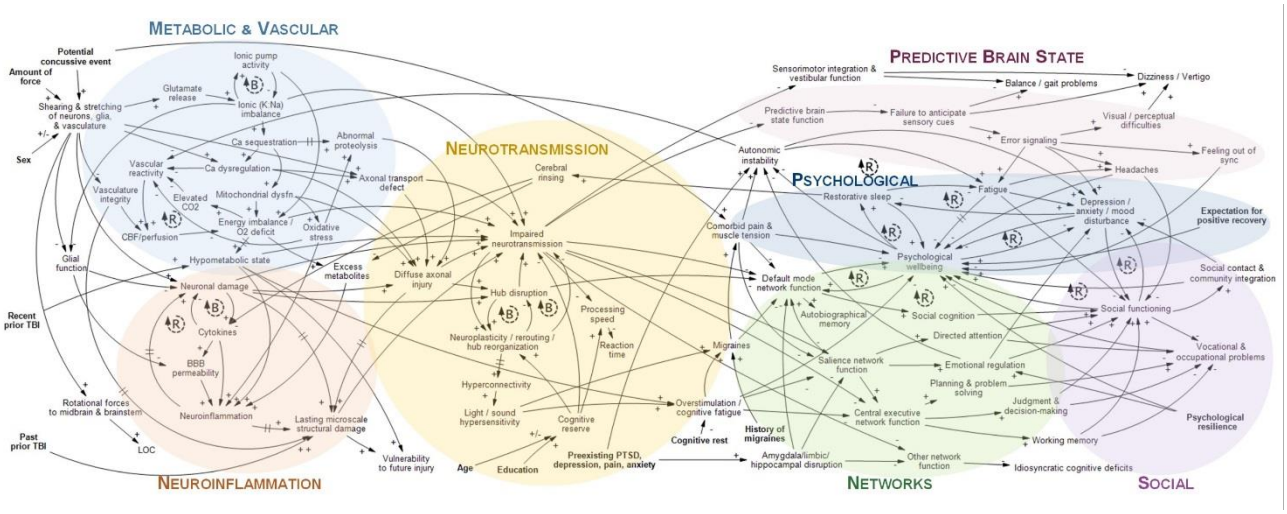

Figure 6: Phase III causal loop diagram of concussion and recovery

The modeling group was encouraged to publish these findings, but soon realized that before they could publish the causal loop diagram, it would be necessary to describe the multiple scales over which the phenomena of interest operates. An additional and necessary diagram (Figure 7) was developed, and the CLD was further revised (Figure 8).

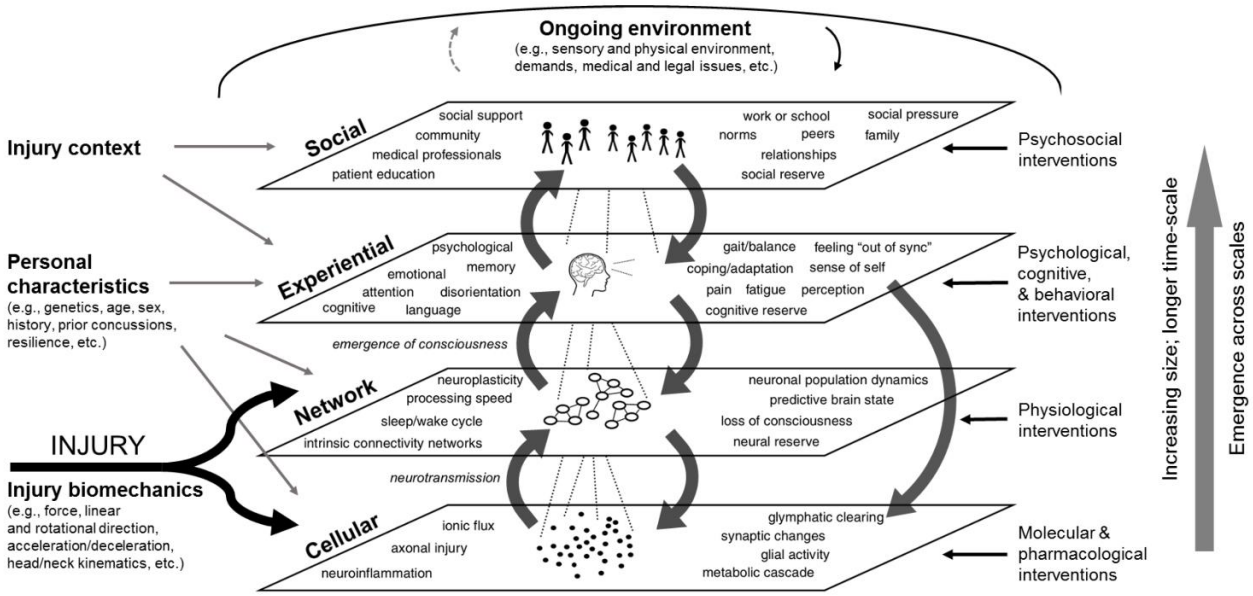

Figure 7. The multiple scales involved in concussion and recovery

In parallel with enhancing their understanding of the phenomena reflected in these diagrams, the modeling group was also determining how best to create a useful computational model of at least part of the diagram. Creating a stock and flow version of the diagram in Vensim and guesstimating the equations and parameter values would likely be neither feasible nor sufficient. The next section considers some of the options for computational modeling.

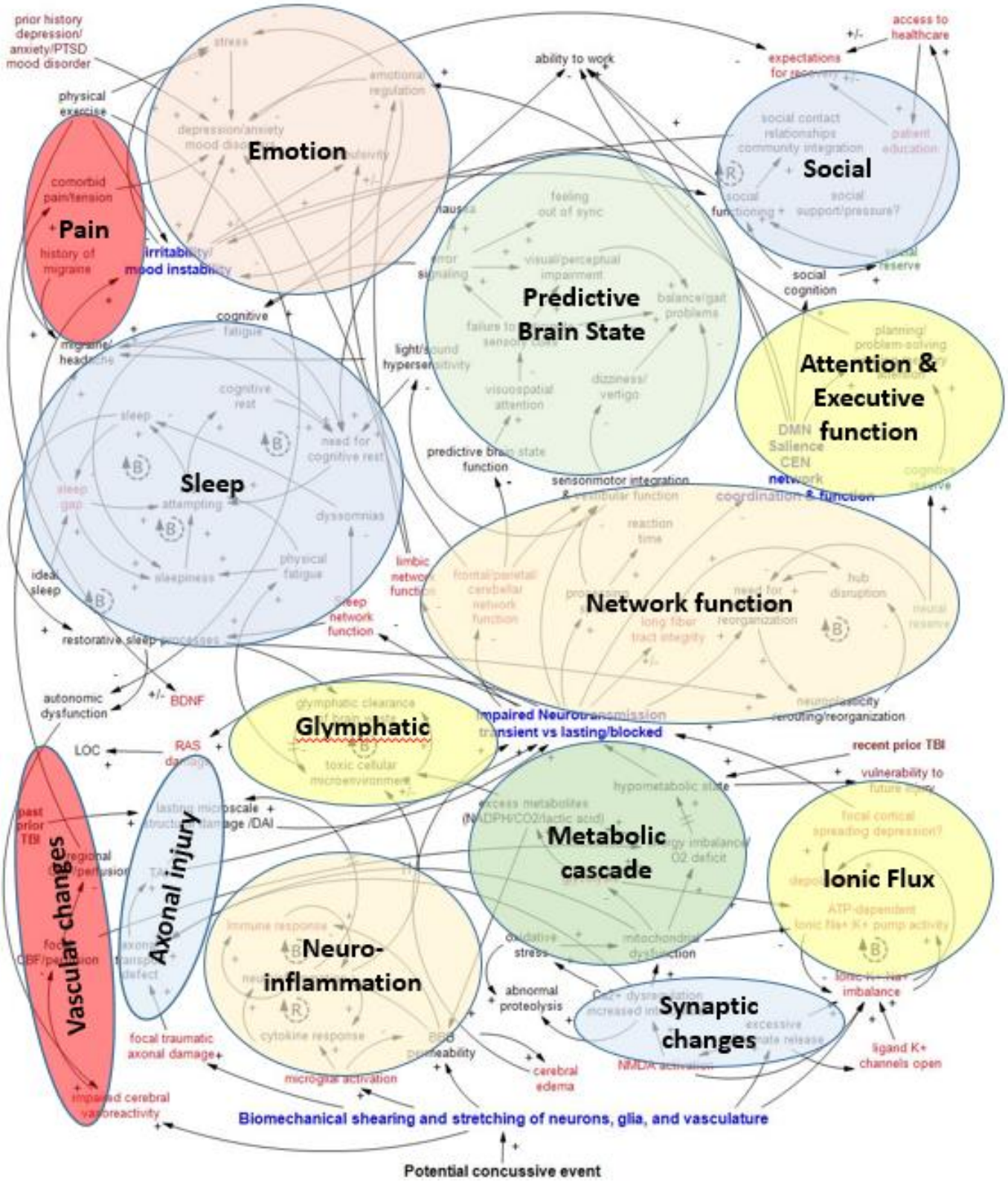

Figure 8: Phase IV version of the causal loop diagram for concussion and recovery

3. Background: Potentially Useful Methods and Related Fields

Hybrid modeling methods could be useful because they allow a modeler to blend together, for example, aggregate variables modeled via ODEs and algebraic equations, along with system characteristics that are treated as unique heterogeneous entities that interact in complex ways, perhaps using disaggregated network logic of some sort. Such hybridization might operate at a single scale or integrate across scales, with entities at lower scales and equations at higher scales, for example.

Other methods to consider include meta modeling, spatial modeling, Markov chains/networks, Bayesian networks, artificial neural networks, fuzzy logic, finite element methods, multi-compartment models and various data-driven (black box or machine-learning) methods and models, structure-oriented statistical methods such as HLM, SEM, and path models, signal processing models and methods. Computational biology methods, which tend to be computer science inspired, and include SBML (Systems Biology Markup Language, focused on defining species, compartments, reactions, etc.) and methods used to model tissues and organ systems from the cellular level to overall functioning. Computational neuroscience aims to create realistic and/or simplified brain models, and models of neural networks and information processing.

Materials science employs hierarchical, multilevel/multiscale models and methods that may be relevant in the concussion context due to the broad range of relevant physical and temporal scales. These methods employ different methods at different scales, and strive to facilitate the communication of information across scales. Meta-models and response surface approximations are frequently utilized (see Table 1).

Table 1. Metamodeling overview (from (Wang and Shan 2007))

Table 1 Commonly used metamodeling techniques.

Experimental Design/Sampling Methods	Metamodel Choice	Model Fitting
- Classic methods ▪ (Fractional) factorial ▪ Central composite ▪ Box-Behnken ▪ Alphabetical optimal ▪ Plackett-Burman - Space-filling methods ▪ Simple Grids ▪ Latin Hypercube ▪ Orthogonal Arrays ▪ Hammersley sequence ▪ Uniform designs ▪ Minimax and Maximin - Hybrid methods - Random or human selection - Importance sampling - Directional simulation - Discriminative sampling - Sequential or adaptive methods	- Polynomial (linear, quadratic, or higher) - Splines (linear, cubic, NURBS) - Multivariate Adaptive Regression Splines (MARS) - Gaussian Process - Kriging - Radial Basis Functions (RBF) - Least interpolating polynomials - Artificial Neural Network (ANN) - Knowledge Base or Decision Tree - Support Vector Machine (SVM) - Hybrid models	- (Weighted) Least squares regression - Best Linear Unbiased Predictor (BLUP) - Best Linear Predictor - Log-likelihood - Multipoint approximation (MPA) - Sequential or adaptive metamodeling - Back propagation (for ANN) - Entropy (inf.-theoretic, for inductive learning on decision tree)

Looking specifically at multiscale / multilevel methods, (Weinan, Engquist, and Huang 2003) describe a heterogeneous multiscale methodology for efficient numerical multi-scale computation. Their method relies on efficient coupling between macro- and micro-scale models. Applications include homogenization, dislocation dynamics, and crack propagation.

(Kevrekidis, Gear, and Hummer 2004; Kevrekidis and Samaey 2009) suggest that the best descriptions of complex systems are often expressed at a microscopic (atomistic or agent) level, whereas the important tasks to be done are meaningful only at more aggregate levels, including parameter estimation, behavioral prediction, and optimization. They offer an approach referred to as "equation-free" that allows a modeler to implement macroscopic tasks directly on microscopic models via computational experiments. The method relies on matrix free numerical analysis and systems theory tools to enable one to explore complex systems dynamics.

Deep uncertainty (Kwakkel and Pruyt 2013; Pruyt and Islam 2015) is a method for addressing the uncertainty inherent in dynamic models intended for prediction. The method has been used with various simulation approaches including systems dynamics, agent based methods, and hybrid techniques. Results include classification of the dynamic complexity of simulation runs and iterative techniques for sampling simulation outputs to identify interesting cases.

A review of modeling formalisms used in systems biology is provided by (Machado et al. 2009) including the criteria that must be addressed by an integrating framework. They identify Petri nets as a suitable model, recognizing that no one formalism supports all relevant purposes. Specifically useful for modeling metabolism networks. (Ayton, Noid, and Voth 2007) review progress regarding multiscale modeling of complex biological processes, including the structure and dynamics of lipid membranes, proteins, peptides and DNA over scales from atomic to macroscopic. Advances rely on theories and methods for constructing accurate multiscale bridges for transferring information between scales. Eissing and colleagues (Eissing et al. 2011) describe a computational systems biology software platform for multiscale modeling of whole body physiology. Modeling of pancreatic tumor progression and response to pharmacotherapy in virtual patients demonstrates the use of platform. Core components include: 1) PK-Sim for pharmacokinetics, 2) MoBi, a graphical biological modeling tool for developing differential equation systems as well as export to Matlab, and 3) MoBi integrations with Matlab and R to facilitate analysis and visualization.

Cancer is simulated at multiple biological spatial and temporal scales (Deisboeck et al. 2011) and is a useful tool for sharpening hypotheses, experiments, and prediction. These successes rely on methods for linking model components at different scales fostered by interdisciplinary collaboration facilitated by web-based infrastructure. The result is models with increased clinical applicability. These models represent the interactions among cancer cells and with their microenvironment. Researchers believe that biological experiments are not enough; cancer is a systems disease and must be studied across scales ranging from atomic and molecular to tissues to macroscopic (tumor behavior and morphology). Techniques include discrete, continuum, and hybrids to effect the necessary balance between realism and computational resources. Cancer is a highly context dependent and emergent phenomena, much like concussion. Models include hybrid agent-based and artificial neural networks at the cellular level(Gerlee and Anderson 2007), continuum models with heterogeneous time-dependent parameters at the macroscopic level(Smallbone, Gatenby, and Maini 2008), and adaptive hybrid models that combine the two(Stolarska, Kim, and Othmer 2009).

Another systems biological multiscale modeling endeavor is the virtual physiological rat project (Beard et al. 2012). Referred to as VPR, the project involves integration of multiple models and data sources; the resulting composite models exhibit emergent behavior not predicted by the individual models, including pathophysiological functioning. Tools include workflows to facilitate connections between component models and use of the software package SemGen, Web Ontology Language, and the Mathematical Modeling Language in JSim. VPR focuses specifically on cardiovascular dynamics, solute transport, energy metabolism, and mapping genetic variability to model parameters. Model representation relies on the

systems biology markup language (SBML) and CellML standards, and participants share models and associated metadata via online repositories. Supported mathematics include algebraic equations, ordinary differential equations, and a limited class of partial differential equations. Use of biomedical reference ontologies is key to integration efforts, including gene ontology, cell type ontology, functional model of anatomy ontology, systems biology ontology, and kinetic simulation algorithm ontology. Example demonstrates modeling vascular blood flow regulation in a single vessel.

An example of brain-specific multiscale modeling that integrates across scales from receptors and ion channels to cellular function to multiple neuron populations to neural system function and behavior is (Bouteiller et al. 2011). Relevant timescales range from milliseconds to minutes, hours, and longer. While much research has focused on the levels from cellular to systems, Bouteiller et al. focus on integration of molecular events into synaptic and neuronal function, with a key application being to study the effects of drugs on the nervous system. And, DAngelo et al. (2013) describe methods to model neurons and synapses, microcircuits, and large-scale brain networks to help understand signal coding, communication, and plasticity as well as the details of neuronal connectivity and dynamics and their impact on brain functioning. Effectively balancing reductionist and holistic approaches is necessary.

While the present research would benefit at some point from the formalisms and tools of systems biology, at the current early prototyping stage it will likely be most practical to develop the system of equations in Vensim and transfer them to R or MATLAB for data integration and development of algorithms to address heterogeneity and uncertainty. The next section describes the proposed computational framework.

4. Methods: A hybrid computational modeling framework

The starting point for developing a computational model in our case is a detailed causal diagram depicting a large number of elements and their interconnections. One must then determine how to represent and clarify the meaning of connections between elements. For example, a connection could mean that the impacting element should be present on the right-hand side of the equation for the impacted element, or it could represent some type of a contingency or discontinuous dependency/threshold. There is also is a desire to determine (calculate?) behavior through time, which is often done by solving a set of differential equations, typically a set ordinary first-order differential equations in time (rates of change).

In the present case, estimating the recovery trajectory for a particular individual 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 concussion pathology and the associated recovery processes. We hope, however, that rather than needing to treat each patient as unique, groups or clusters of patients whose responses to a concussion and the associated recovery process are similar enough that they can be considered/studied/modeled as a group or cluster.

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.

If data regarding the recovery trajectories in terms of key metrics for individuals/clusters is available, then it might 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. 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 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.

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 9 synthesizes the requirements for the framework into block diagram. From the causal loop diagram, a Vensim model is specified and calibrated, reflecting baseline or typical parameter values. Data arrays are developed containing typical and patient specific parameter values. Some of the parameter values will be constants and others with specify the parameters of probability functions (pdfs) reflecting sources of uncertainty/variability. Then scripts will 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 will be summarized visually to facilitate interpretation.

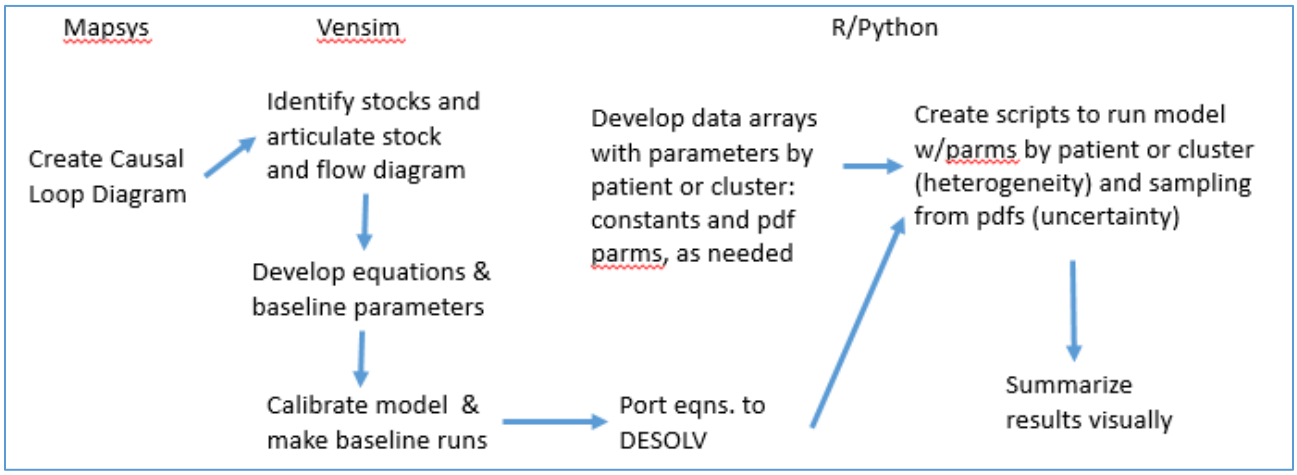

Figure 9. Computational framework block diagram

This preliminary 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 yet fully accommodate the multilevel nature of the problem portrayed in Figure 7. It is likely that the conceptual and temporal model boundary will be drawn so that the core logic of the model can appropriately be a set of differential equations; suggesting further that cellular and network-related processing would need to be treated in an aggregate, perhaps regional, fashion that could be amenable to modeling with equations rather than agents.

5. Anticipated Results

We anticipate that the computational model will 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 9 provided a mock up a dashboard showing the results of applying the model and framework to clustered patient level data. Model trajectories are not expected to match the data to the degree shown in the mockup.

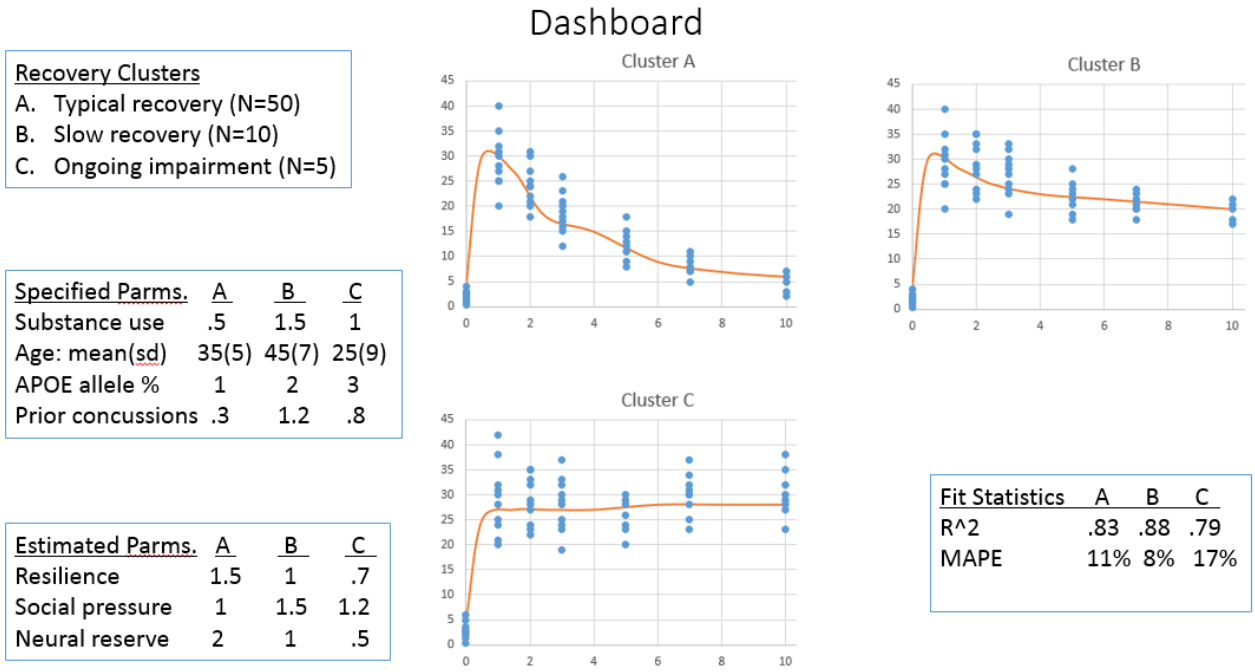

Figure 10. Mockup of Model Results Dashboard. Purely fictitious for illustration only. Would show key user-specified parameter values, estimated parameter values, plots of case data, and model calculations by cluster along with fit statistics. Final results will likely look significantly different.

6. Conclusion

This progress report has demonstrated that a causal loop diagram describing the relevant factors and variables germane to understanding the pathophysiology of concussion is very complex. It is not known how best to create a useful computational model. It remains to be seen whether the somewhat augmented but fundamentally system dynamics approach outlined in this paper be up to the task, or if it will be necessary to move fully into the world systems biology and take advantage of its emerging and truly multiscale ontologies and methods.

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