Body Fluid Biomarker Mathematical Modeling of Traumatic Brain Injuries

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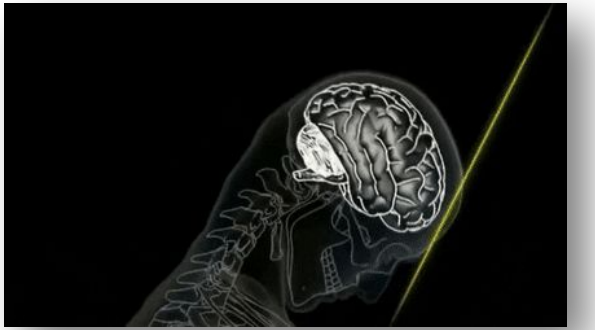
Overview of TBI Mathematical Modeling

- Objective: Data-driven TBI Medical Decisions
- Define TBI and Body Fluid “Biomarkers”
- TBI Biomarker Pathology
- Mathematical Simulation & Prediction Concept
- What are Partial Differential Equations (PDEs)?
- Diffusion Equations & Transport Equations
- What does a successful project look like?
- Next Steps

Goals of Presentation:

1. Consistent team understanding of problem and ideas
2. Simple recruiting pitch
3. Prepared ideas for future proposal writing



Objective: Data-driven TBI Medical Decisions

Traumatic brain injury (TBI) accounts for over 2.8 million USA emergency room visits annually[1].

Persistent disabling symptoms can prevent return to work for civilians, return to play for athletes, and return to duty (RTD) for warfighters.

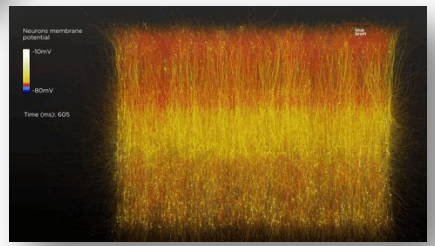
Improved medical determinations have an estimated economic value of $76.5 billion[4].

Problem Statements

What is a TBI?

CDC defines a traumatic brain injury (TBI) as a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury.[1]

Credit: Slow Mo Guys YouTube



Credit: Stanford Neuroscience

Key Problems:

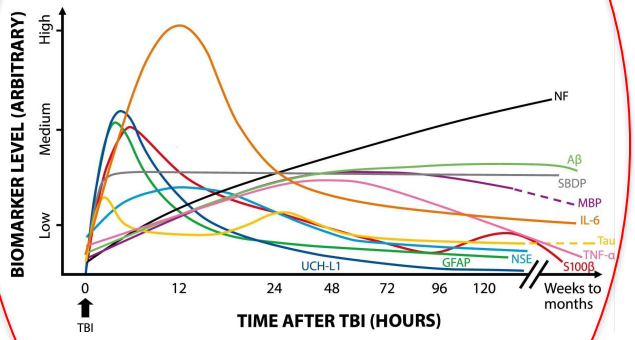
- Currently no “gold standard” for the diagnosis of concussion.
- Assessments of TBI are largely qualitative.
  - Patient self-reported symptoms often misleads medical decisions.

Solution:

We are engineering powerful quantitative mathematical tools for clinicians to use to augment their medical training.

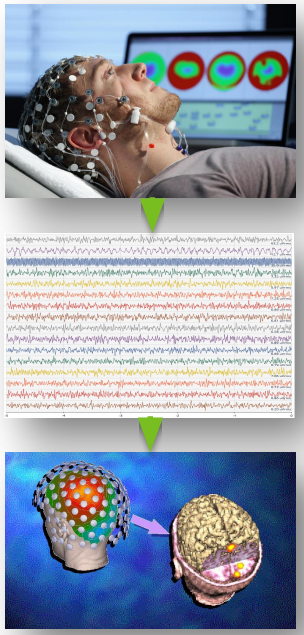
Current Paradigms of Interest

1. Body Fluid TBI Biomarkers from Blood and Urine Samples



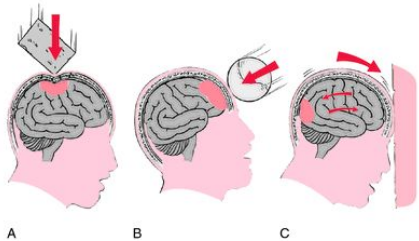
Credit: Biomarkers of Traumatic Brain Injury: Temporal Changes in Body Fluids, Adrian et al.

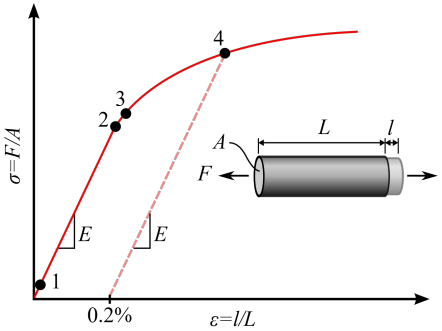
2. Electrical Signal Modeling with EEG



Credit: michelsonmedical.org

3. Elastostatic Modeling of TBI Impact Forces (Future Work)



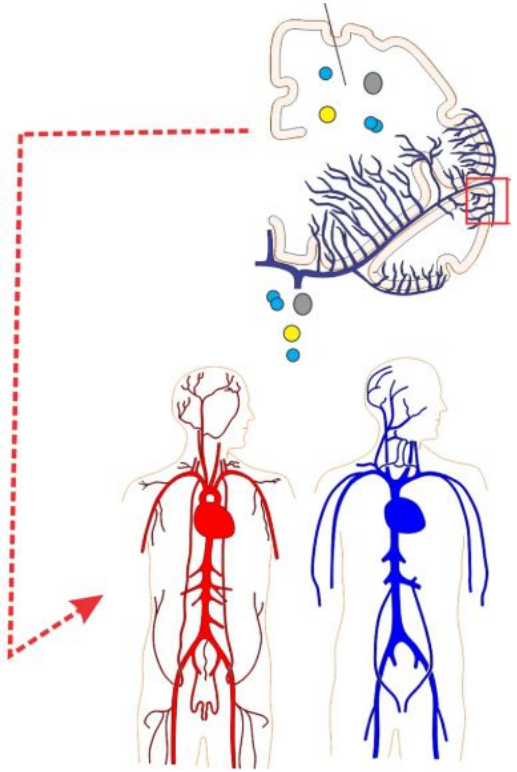


What are TBI Body Fluid “Biomarkers”?

“Biomarkers can be broadly defined as qualitative or quantitative measurements that convey information on the physiopathological state of a subject at a certain time point or disease state.” [6]

These are proteins produced in brain tissue that secrete through “mirco-tear” of fine neural substrate called the blood-brain barrier (BBB) into many bodily fluids.[6,7]

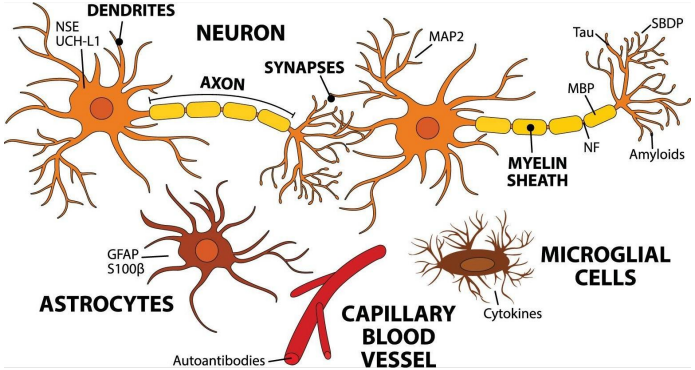
Biomarkers found present in the Spinal Fluid, Blood, Urine, and Saliva.[6]



Protein Biomarkers being released from the brain into the circulatory system. Venous (red) concentration = Arterial (blue) concentration [9]

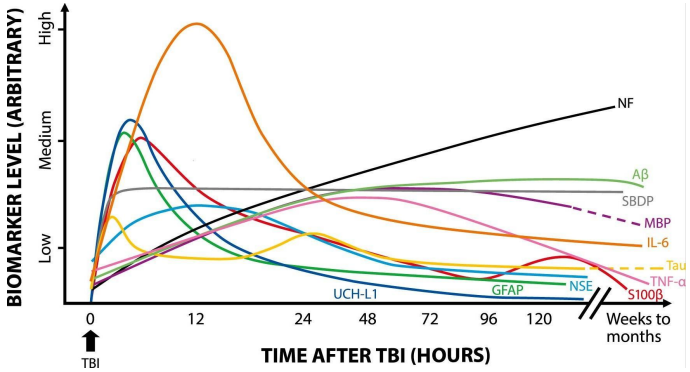
Mathematical Modeling of Brain Impairment Goals

Blood, Urine, and Saliva samples can each be utilized to identify key predictable proteins released from brain tissue following a head impact.



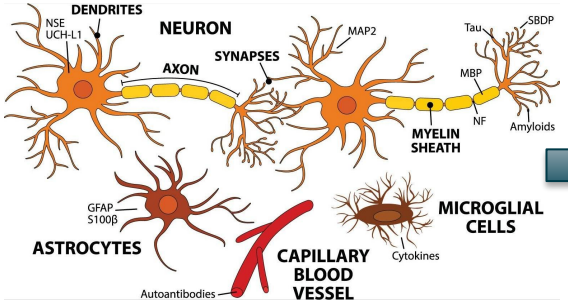
Brain tissue cells and proteins (biomarkers) commonly associated with TBIs [5]

Brain Cells to Predictable TBI Biomarker Curves



Body fluid biomarkers commonly associated with TBIs [5]

Brain Injury Biomarker Pathology



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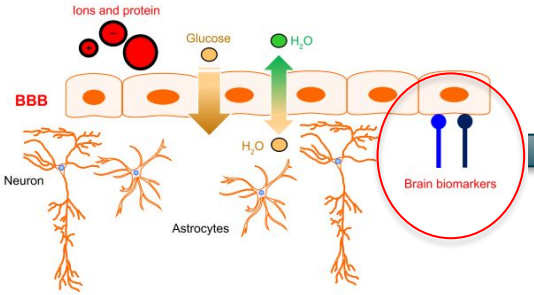
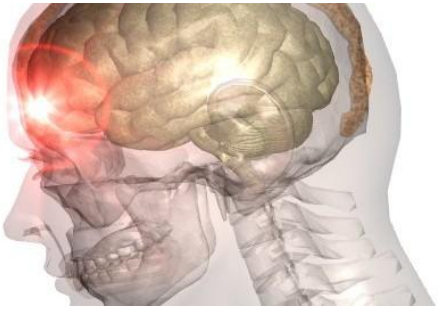
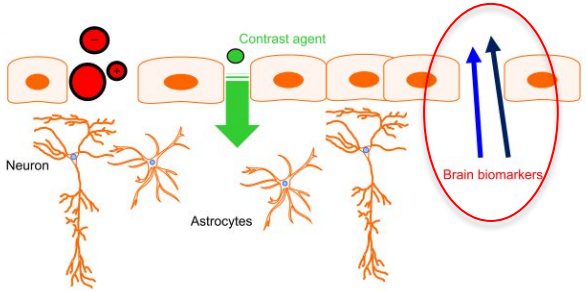


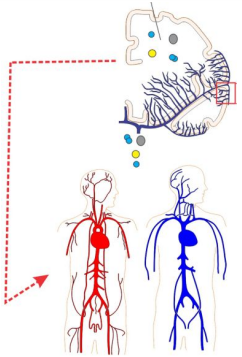
Behavior of brain biomarkers with **intact** BBB [6]
(No TBI)



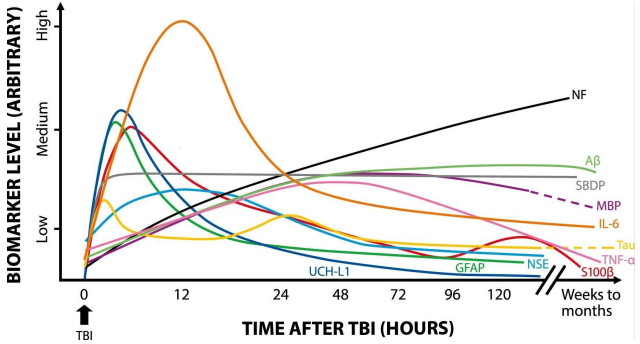
TBI: (Credit: https://www.braininjury-explanation.com/)



Behavior of brain biomarkers with **disrupted** BBB [6]

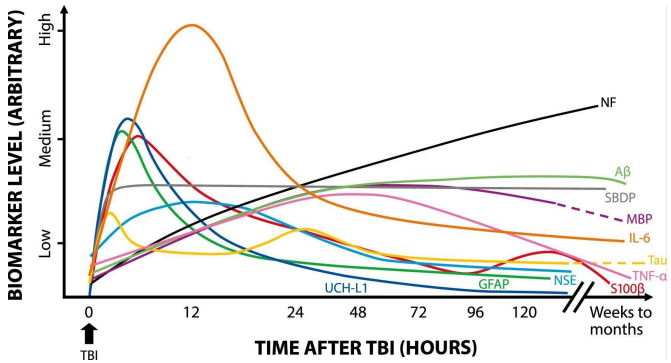


Protein Biomarkers being **released from the brain into the circulatory system** [9]



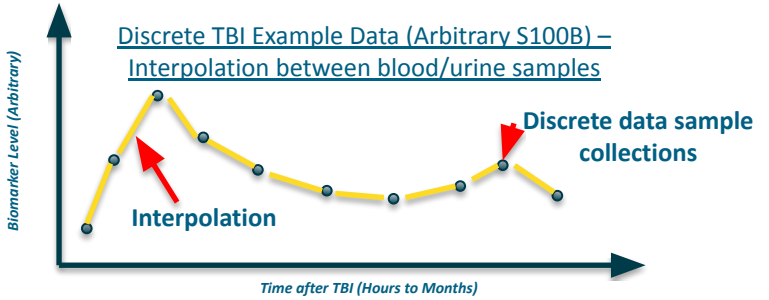
Body fluid **biomarker time-series** commonly associated with TBIs [5]

Mathematical Simulation & Prediction Concept



Body fluid biomarkers commonly associated with TBIs [5]

1.



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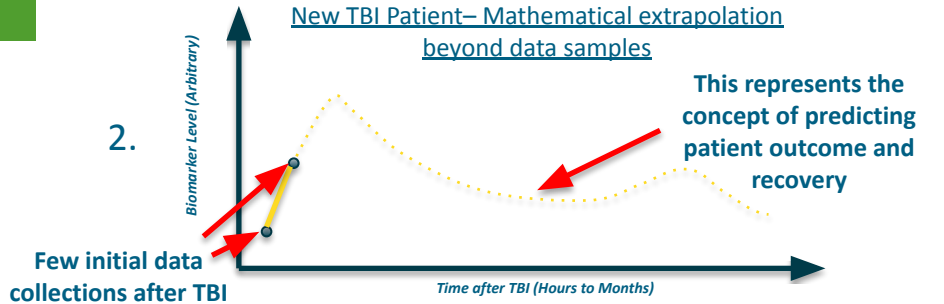

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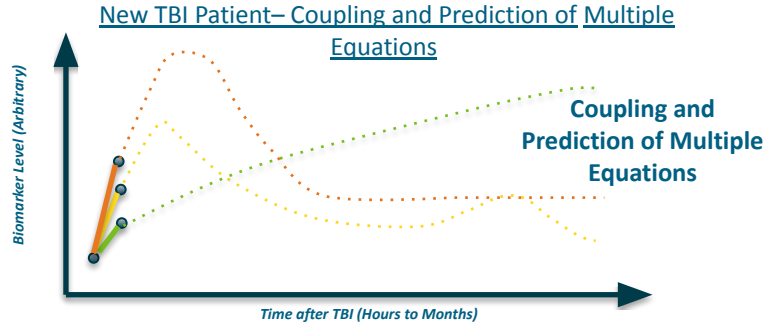
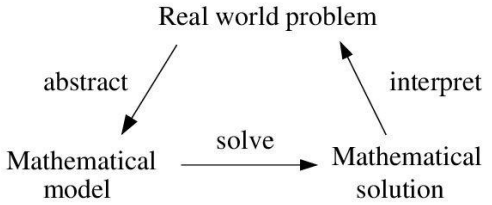


Partial Differential Equations (PDE) Discussion

What is a PDE?

"A differential equation that contains two or more independent variables, an unknown function and partial derivatives of this function with respect to those variables.

PDEs are used to mathematically formulate and solve physical problems which involve functions of several independent variables . [?]"

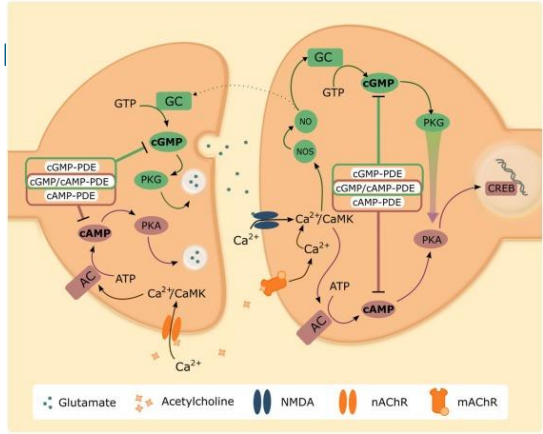


Why are PDEs the right tool for the job?

Though this is a simplification, we are designing nuanced, sophisticated models by coupling multiple equations.

Why are PDEs the right tool for the job?

- If not all, most of important parameters (independent variables) ca be studied at once.
- Mathematics are not a “black box” and are clinically explainable
- Offers opportunities for projecting hypothetical medical treatment methods based on parameters in an equation and can produce results quickly.
- Potential to inform TBI pharmacological research to advancement drug treatment methods to reduce the need for human and animal experimentation. (Mathematical simulation)



Proposed Partial Differential Equations (PDEs)

- **Elasticity Equation:**
  This can be used to model the moment of the injury and correlate the severity of TBI with other parameters of interest such as biomarkers.

- **Transport Equation:**
  This can be used to model the motion of a particle in a flow. This is a very simple PDE and can be used to derive other PDEs.

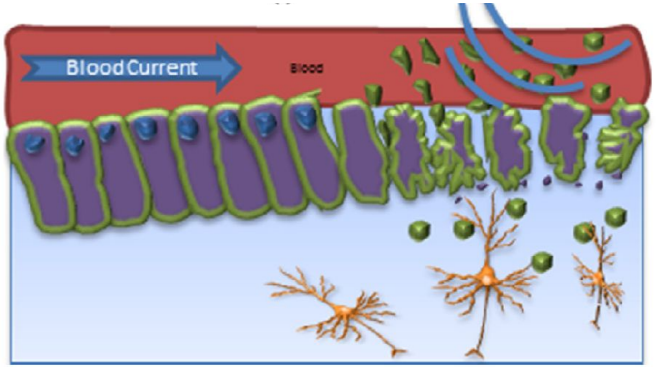
- **Diffusion Equation:**
  This equation not only describes the motion of a particle in a flow, it also considers the rate of change (production/consumption) of such particle.

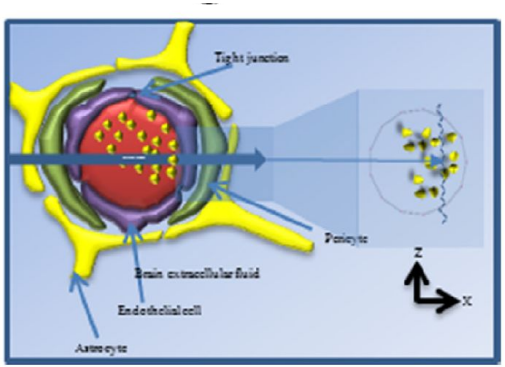
- **Electromagnetic Equation:**
  More details are given under EEG section.

Intro to Diffusion Equation PDEs

Simply it can tell us how fast a given particle (usually solid) can vanish/dissolve in its surrounding (usually gas or liquid).

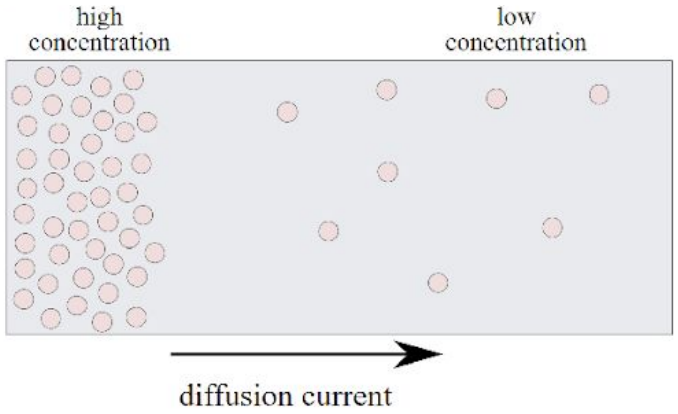
The diffusion rate is the main driver of this equation. While the surrounding can be immobile, the concentration of the particle changes due density difference, chemical reaction, or the flux of the particle. Diffusion is happening every moment at any cell in the entire of your body!





Example Diffusion Equation Mathematics

Table of Variables



Diffusion equation can be derived as following:

$$M = \int_{x_0}^{x_1} u(x,t)\,dx$$

$$\frac{dM}{dt} = \int_{x_0}^{x_1} u_t(x,t)\,dx = flow\ in - flow\ out$$

$$\int_{x_0}^{x_1} u_t(x,t)\,dx = Du_x(x_1,t) - Du_x(x_0,t)$$

$$u_t = Du_{xx}$$

or we can simply say:

$$u_t = D\Delta u$$

and if there is an external source/sink it gets:

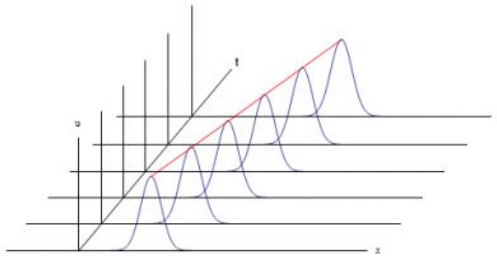
$$u_t = \nabla.(D\nabla u) + f(x,t)$$

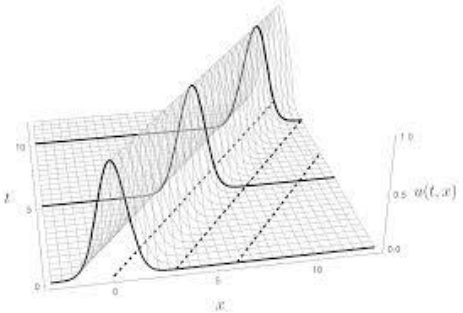
Intro to Transport Equation PDEs

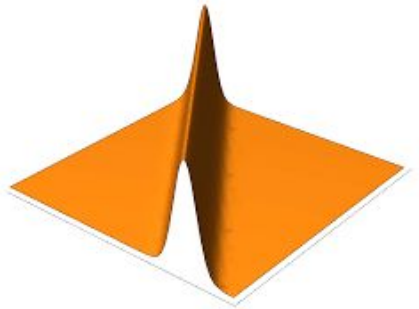
Pin two sides of a long rope and make a wave at one end. How does the wave move through the rope? The same concept holds when a contaminant moves within a fluid, say blood.

$$u_t + Au_x = 0$$

1-D, time dependent, simple transport equation







Example Transport Equation PDEs

Steady state (time-independent) 1-D transport equation:

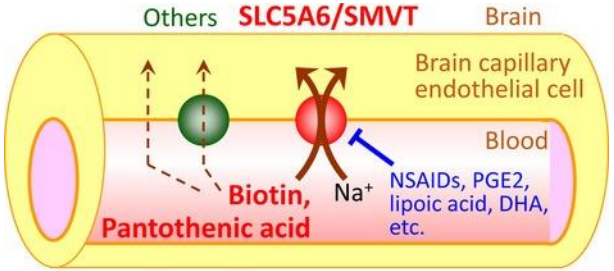
$$u(x)\frac{dC(x)}{dx} + \frac{dj(x)}{dx} + K_r C(x) = m$$

$$j(x) = -D(x)\frac{dC(x)}{dx}$$

Fick's law

$$u(x)\frac{dC(x)}{dx} - \frac{d}{dx}\left[D(x)\frac{dC(x)}{dx}\right] + K_r C(x) = m$$

General PDE for mass transport.



Human blood-brain barrier

Notes:

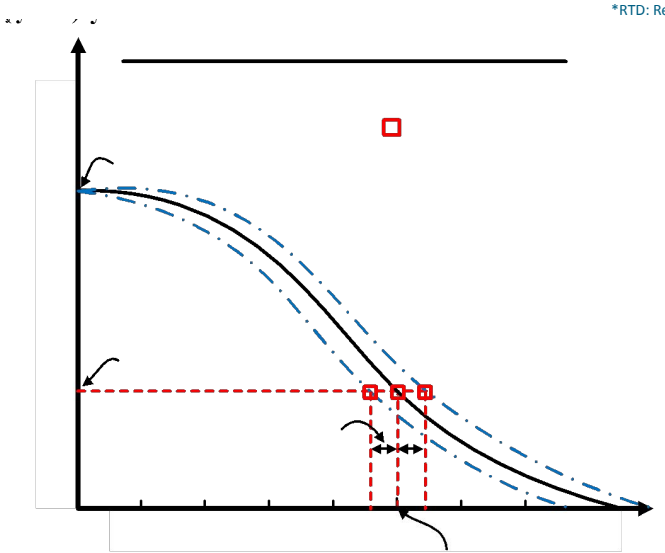
* u is velocity of the mixture, C is the concentration of dilute species, j is the flux of the species, K_r is the reaction (chemical) rate, m is the external source of mass, D is Diffusivity.

Clinical Explainability & Healthcare Tool Deployment

We must create tools that clinicians globally can trust to augment their professional expertise.

Clinical Explainability objectives [13] :

- Extensive model validation
- Statistical confidence assessments
- Transparency about model limitations
- Clearly describe the process



Prioritizing simple and scalable deployment into the healthcare system.

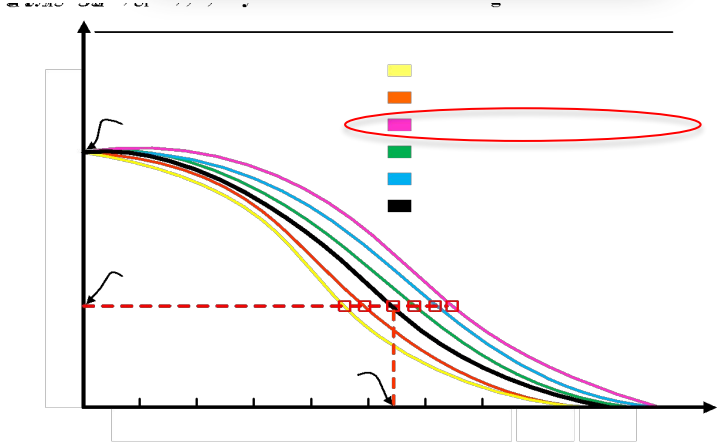
What does a successful project look like?

Software Mathematical Model Input:

- Accept data from Blood/Urine/Saliva samples
- Few data points of body fluids following injury

Software Mathematical Model Output:

- Injury Severity Score
- Patient Recovery Prediction
- Recovery Curves
- Risk Assessment
- Confidence Intervals
- Understandable “breakdown” of calculations (Not Black Box)



Key Design Constraints

1. Rely on preexisting medical tests such as Blood, Urine, and Saliva samples.
2. Utilize current medical infrastructure as well as leverage recent advancements in TBI data analytics.
3. Use recent preexisting research study data.
4. Quantitatively assess injury severity with a detailed injury severity score.
5. Accurately predict patient recovery and corresponding risk-assessment.
6. Provide clinical clarity about certainty and statistical confidence intervals.
7. Results must be clinically explainable.[13]

Next Proposed Research Steps

1. Identify Data to utilize in both short and long term
2. Validate Published Results (3-6 Months?) ***Publish?***
3. Accurately Model a Single Protein Biomarker (e.g S100B, GFAP) ***Publish***
4. Adapt our Mathematical Model to Different Proteins ***Publish***
5. Couple the Equations to create a Sophisticated Model ***Publish***

BANYAN BIOMARKERS®

TRACK-TBI LONG
Transforming Research and Clinical Knowledge in Traumatic Brain Injury Longitudinal

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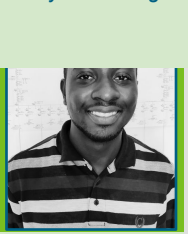

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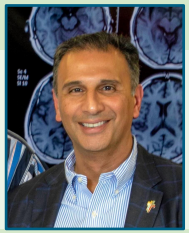

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Citations & Relevant Publications

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