Research Report

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# Toward a Unified Multiscale Computational Model of the Human Body's Immediate Responses to Blast-Related Trauma

## A Review of the Scientific Literature

In the early 2000s, during the first several years of Operation Enduring Freedom and Operation Iraqi Freedom, improvised explosive devices (IEDs) accounted for a growing proportion of U.S. combat casualties and blast-related injuries. As incidence rates quickly rose, further research into the prevention, diagnosis, and treatment of blast-related injury was needed to identify those in need of care, how to determine their level of impairment, and the efficacy of various treatments and rehabilitation methods (Tanielian and Jaycox, 2008). Advancements in boundary conditions, material properties, the computational modeling of shock tubes that replicate blast waves, the use of animal models and cadavers for data, and validation have all contributed to enhance research about the human body's responses to blast exposure.

Developing comprehensive blast-related injury mechanisms remains an active area of research and exploration. Computational modeling has investigated some of the human body's responses to blast-induced injuries in various body parts, from the cellular level to the tissue system level. Such modeling grants researchers the ability to assess the vulnerability of organs exposed to blast and correlations with clinically measurable injury levels. However, despite significant progress, there are several important factors that remain difficult to measure directly in real time, including the fluid mechanics of the human body (especially the brain), electrochemical and electromechanical components, and the brain's mechanobiology, such as intracranial pressure (ICP), deformations, stretch, shear stress, shear strain, and maximum principal strain (MPS).

It is also important to note that, as critical as computational models highly focused on one body part or tissue system are to deepening our understanding, it is infrequent that service mem-

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bers incur injury to only one body part, making validated polytrauma predictive models essential to fully understanding the body's responses to blast. For example, if an individual is close to the detonation site, the initial pressure wave increases pressure in all of the gas-filled organs, such as the middle ear, eye, lungs, and bowels, and the individual typically incurs multiple injuries in more than one region (Ritenour et al., 2008).

Although computational research methodologies have advanced, additional research to validate the accuracy of models and address challenges in modeling the human body from the cellular level to the whole body is still needed. Specifically, a multidisciplinary, multiscale computational model that integrates body systems has not been developed, and researchers also have not combined a system of models across multiple scales to achieve the same goal. This report describes information about what computational modeling reveals about the human body's responses to blast trauma. Specifically, this literature review aims to

1. provide the state of the science of multiscale computational modeling of the human body's responses to blast-related trauma, including both descriptions of models used or developed and research findings
2. identify future opportunities to strengthen the current research on understanding the human body's responses to blast-related trauma, particularly across multiple scales.

Using our research questions, practical considerations, and input from our expert advisers, we developed a literature review approach that included (1) exploratory search strategies to retrieve articles, (2) initial search terms to search for articles, and (3) inclusion and exclusion criteria to identify potentially relevant articles.

We initially explored the literature on the computational modeling of the human body's responses to blast to identify key studies and develop a focus for a more comprehensive search. We then searched peer-reviewed literature using blast terms (e.g., explosion), body parts (e.g., cortex or brain), and computational modeling terms (e.g., finite element methods [FEMs]) to explore multiscale computational modeling that described the human body's responses to blast-related trauma. We searched the following databases: PubMed, Web of Science, the Cumulative Index to Nursing and Allied Health Literature, PsycINFO, the Institute of Electrical and Electronics Engineers, and the Defense Technical Information Center. Because the topic was specific to the human body's responses, we excluded nonhuman studies. It is important to note that this effort was not designed to be a systematic review but rather to assess the state of the science and highlight key themes across the body of literature. Therefore, it is possible that individual articles were missed in the search, despite all efforts made to include relevant literature.

**Abbreviations**

| | |
|---|---|
| 3D | three-dimensional |
| ALE | Arbitrary Lagrangian-Eulerian |
| AMR | adaptive mesh refinement |
| FEM | finite element methods |
| ICP | intracranial pressure |
| IED | improvised explosive device |
| ML | machine learning |
| MPS | maximum principal strain |
| mTBI | mild traumatic brain injury |
| TNT | trinitrotoluene |
| UBB | underbody blast |

An increased understanding of the mechanisms of blast trauma, as provided by such a literature review, might support a more detailed predictive methodology, leading to improved care and the development of enhanced personal protective equipment to reduce the severity of injury. We believe that computational modeling of the human body's responses to blast exposure is important to help better support service members.

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## Background on Blast Injury

Although the term *blast injury* has different meanings for different communities, for the purposes of this review, we used the definitions put forth in U.S. Department of Defense Directive 6025.21E, *Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries* (2006), which defines the entire spectrum of blast-injury mechanisms. We focused on injuries that are experienced immediately following an explosion and that are the result of one or more blast-injury mechanisms, ranging from primary to quinary. *Primary blast injuries* involve tissue damage (e.g., lung or ear membrane rupture) that occurs in response to the direct physical effects of a blast overpressure wave. *Secondary blast injuries* are those produced by fragments from the exploding device or secondary projectiles from the environment (e.g., debris, vehicle fragments). *Tertiary blast injuries* result from blast-related displacement of body parts that strike other objects, causing a variety of injury types (e.g., blunt, avulsion, crush). *Quaternary* and *quinary injuries* result from other explosive products or the clinical consequences of environmental contaminants (e.g., biologicals, radiation, released fuels), respectively. Therefore, in this review, we investigated the development of and findings from computational modeling of any of these blast-injury types. In moving toward a unified computational model of blast-related injuries, or in combining models, it is also important to recognize that blasts can cause *polytrauma*—multiple injuries to the body, including to the brain, auditory, ocular, circulatory, or respiratory systems.

Explosions—the cause of blast-related injuries—generate blast waves that consist of a shock wave, also known as *overpressure*, and a blast wind, also known as *underpressure* (Cullis, 2001). The rapid energy release during an explosion increases the temperature and pressure around the explosion source. The higher-pressure regions of air move faster than the low-pressure ones around the explosion source, creating a wave profile of very steep pressure and temperature gradient over a very short region in space, akin to a discontinuity in the temperature and pressure; this is called a *shock wave*. Immediately behind the shock wave, which moves at supersonic speeds, is the blast wind (Cullis, 2001). Shock waves and blast winds both can cause unique types of injuries; shock waves often affect air-filled organs, although blast winds typically cause injury because of their high speed and density. (For a more detailed explanation of blast waves, their interaction with a structure, and its subsequent response, see Cullis, 2001.) In a military context, many of the explosives modeled use C-4 (a plastic explosive substance) or trinitrotoluene (TNT).

This report also presents findings from measurable changes that might not lead to detectable injuries. It is important to clarify that, although measurable changes and detectable injuries are not mutually exclusive categories and might overlap, one does not always imply the other. Whenever there is a detectable change in the body—be it through biomarker measurement, histopathology, or physical variations, such as changes in pressure—these measurable changes might not manifest into clinically meaningful injury, meaning an individual might have a detectable increase in levels of a biomarker after a blast exposure but not experience any effects that would lead to a clinical injury diagnosis. For example, in Tschiffely et al. (2020), the authors assessed levels of glial fibrillary acidic protein (GFAP) to determine relationships with blast injury in a group of military personnel. In the study, the authors were able to correlate high levels of GFAP to blast exposure, meaning micro-level changes had occurred in the body; however, no clinical manifestations of injury (e.g., loss of consciousness, amnesia, or mild traumatic brain injury [mTBI]) were reported in any of the service members enrolled in the study. The study also provided context on another phenomenon of interest—that of cumulative damage and thresholds (Tschiffely et al., 2020).

The notion of cumulative damage is of great clinical importance when thinking about the threshold for macroscopic and functional impairment. Just as a slight elevation in ICP might not initially manifest itself clinically and might remain subclinical, or latent, there might be a tipping point where this elevated pressure triggers the classical clinical manifestations. For blast injuries, this tipping point, or threshold, is important to note to prevent injury and is still under investigation. When can we expect that the micro-level changes in the body in terms of cellular composition, biomarkers, and physical properties will translate into clinical manifestations? In the medical rehabilitation literature, the terms minimal detectable change (MCD) and minimal clinically important difference (MCID) are often used to express this notion of thresholds. MCD results from a statistical calculation that estimates the smallest amount of change detected by any measure (e.g., biomarkers, histopathology) that can change ability in any way. MCID, on the other hand, relies on the clinical and observable manifestations that a physician might consider relevant (Copay et al., 2007).

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## Computational Modeling of Blast Waves and the Human Body

Computational modeling has allowed researchers to determine which organs are most susceptible to blast injury, assess thresholds of injury and injury severity, and manipulate blast strength and proximity to determine what specific aspects of blast lead to injury. Additionally, the use of modeling and simulations could be used to investigate both the short- and long-term effects of blasts on the human physiology. However, developing these simulations is challenging and computationally expensive, requiring several spatial and temporal scales and numerous physical disciplines (Gupta and Przekwas, 2015).

The human body is composed of a wide variety of systems, each serving a critical function in keeping the human alive. Each of these systems is made up of organs, and each organ is made up of tissues and cells that are specific to the function performed. Therefore, a multitude of interconnected spatial and temporal scales govern the reaction of the human body to blast waves.

Modeling the interactions of the blast wave with the human body can be challenging, not only because of the physics of the blast wave itself but also because of the boundary conditions that exist between the numerous materials that make up the human body. The body is composed of different tissues, including skin, bones, blood and other fluids, and the different tissues that make up the organs. The interface between skin and tissue, or bone and tissue, or any other two different materials is referred to as a *boundary condition* in simulations. Boundary conditions are a challenge to model because information must be communicated on an interface of two different sets of materials having completely different properties, phases, or both (e.g., fluid and solid, blood and tissue, tissue and bone) (Yu and Ghajari, 2019).

The solid mechanics of deforming materials govern how different body tissues respond to blasts. Elastic materials, which can deform and return to their original form, can be used to simulate some organs, skin, or fat. On the other hand, plastic materials will not return to their original shape after deformation and instead experience permanent change, mimicking the behavior of bones. The physical property that measures a material's resistance to being deformed elastically is called the *modulus of elasticity*, or *Young's modulus* (E). Soft tissue and air-filled organs, such as the lung, tend to be very elastic (E~104 pascals) and can feel the full effect of a blast, while skin and fat (E~106 pascals) and bone (E~109 pascals) are more resistant to deformation (Chafi, Karami, and Ziejewski, 2010; Nishimoto and Murakami, 1998; Nyein, 2013).

## Multiscale Consideration

Modern computational power has facilitated the modeling and integration of data across multiple functional, temporal, and spatial scales in biological systems. Computational models that explicitly account for more than one level of spatial and temporal resolution are referred to as being *multiscale*. This is the case in biological systems, which span from the most basic amino acids, which form each protein, to critical organs connected in a biological system. The connectivity and interdependence of the disparate scales of biological functions lend quite naturally to modern computational modeling techniques (Walpole, Papin, and Peirce, 2013).

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Depending on the solutions space, computational techniques can be broadly classified as either continuous or discrete. Additionally, models can be either deterministic or stochastic. In *deterministic models*, the solutions obtained depend specifically on input conditions, while *stochastic models* involve a random probability distribution, presenting a certain level of randomness that cannot be precisely predicted. Typically, continuous solutions are deterministic and consist of modeling systems of ordinary differential equations or partial differential equations. This approach can be used to model, for example, chemical reactions on the nucleus of a cell and seeing its effects on a grander scale. In Scheff et al. (2011), authors used a multiscale model to study the effects of steady-state molecular, cellular, and neural concentrations of endotoxemia on heart rate variability, which could lead to inflammatory diseases, subsequently linking cardiac dynamics with detailed inflammatory response. The computational results matched clinical observations when simulating the injection of lipopolysaccharides around inflammation, thus predicting the acute response and recovery to baseline.

On the other side are discrete stochastic models, which are well suited for biological systems for which functions can be described as independent states. When researchers wanted to model how cancer cells attracted and maintained blood supply, they used a stochastic model in an effort to understand which biochemical molecule can trigger a cellular response (Bauer et al., 2010). They developed a discrete Boolean network that characterized each molecular

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species as binary (present or not) depending on the presence of other molecular species. Presence of certain molecules at high enough concentrations can trigger angiogenesis, or the development of new blood vessels. This is another example of multiscale modeling application in which there is a level of randomness in the concentration of certain molecules (small scale) and some randomness in the cell response (large scale).

The challenge of multiscale modeling is determining how to couple the small-scale phenomena with the large-scale effect in a scientific way. The development of an accurate physiological-based model is not something that can be siloed and might require reliance on experimental observation or a deeper theoretical understanding of the dynamics of what is being modeled.

As we can see, the variety of modeling techniques used in multiscale modeling of a complex biological system is broad and depends on the function and spatial or temporal resolution of the system of interest. Walpole, Papin, and Peirce (2013) describes how the applicability of each model varies depending on its corresponding scale:

> Ascending from sub- to supercellular resolutions, continuous models that were once exceptionally accurate begin to lose resolving power. Conversely, discrete models are often computationally expensive and become most useful at lower resolution for cell networks and tissues where cells are easily viewed as individual modules. Yet, larger systems may require a return to network approaches to account for spatial distances and boundaries between organ systems that are too large to be explicitly modeled at the cellular level. (Walpole, Papin and Peirce, 2013, p. 6)

Recently, it has been proposed that machine learning (ML) could complement multiscale modeling of biological systems. ML aims to identify correlation and infers the overall dynamics of a system when a large amount of data is available. Alber et al. (2019) pointed to the benefits of the interaction on ML and multiscale modeling: "where machine learning reveals correlation, multiscale modeling can probe whether the correlation is causal; where multiscale modeling identifies mechanisms, machine learning, coupled with Bayesian methods, can quantify uncertainty" (Alber et al., 2019, p. 115). The synergy between the two has several challenges. This approach requires (1) the availability of a sufficient dataset; (2) the exploration of the large design space to identify correlations, which can be computationally expensive; (3) the development of a robust prediction of the overall system dynamics and identification of relevant features; and (4) the developer of the model to know the limitations of the model (e.g., ML algorithms can be prone to bias and overfitting).

## Computational Techniques

In the modeling and simulation of blast waves, there is a distinct need to account for the interactions taking place among the blast wave, fluids, and the body. Fluid structure interactions present a challenge because the model must be able to handle nonlinear, compressible fluid and properly model the interface between fluids and solid structures, which might not be trivial.

### Finite Element Methods

*FEMs* are numerical ways of making a computational domain discrete to solve differential equations numerically. Therefore, the domain is divided into several elements. In the simulation of a human body, it could be the case that each cubic centimeter (or millimeter) would be a finite element, for which such variables as temperature and density can be tracked. Each variable in an element is represented using a polynomial basis function, in which the order of the polynomial determines the order of accuracy of the method (Singh, Cronin, and Haladuick, 2014).

Because different polynomials (e.g., Lagrangian, Legendre) can be used as a basis, there are different types of FEMs. In addition, depending on whether continuity is enforced at the element edges, there can be continuous and discontinuous FEMs. Continuous FEMs are ideal for problems with smooth solutions, such as the human body, while discontinuous ones are better suited for problems with jump discontinuities (e.g., shock waves or blasts) (Koutromanos, 2018).

FEMs have been applied to multiple simulations of human body dynamics. In Trayanova and Rice (2011), authors developed an electrophysiological model of a whole human heart, using FEM spatial discretization. The model consisted of both electrical and mechanical elements. Each model required different spatial resolution (i.e., element sizes) and element types; therefore, two meshes were used. The electrical mesh required the spatial resolution to be on the order of 250–300 microns. The mechanical mesh was composed of hexahedral elements and used Hermite polynomials as a basis to enforce continuity and maintain incompressibility constraints. This problem of scale illustrated one of the significant advantages of using FEMs—specifically, its inherent flexibility and ability to use different element types to represent different areas or characteristics of the problem at hand. This approach can prove extremely useful in multiscale problems. FEMs have also played a prominent role in the simulation of other processes and systems in the human body. For example, the majority of blast injury to the head simulations use FEMs. The methods provide accurate simulations of both the blast wave propagation and its interaction with the human head (Lockhart, 2010). FEMs were applied to both in vivo and in vitro blast-induced neurotrauma models (Panzer, Matthews, et al., 2012) in extracorporeal shock wave treatment of musculoskeletal disorders (Wang, Matula, et al., 2013), as well as many more applications.

In summary, whenever the problem calls for spatial discretization of any form, it is unlikely that an approach allows for greater benefits, flexibility, and accuracy than FEMs do.

## Eulerian and Lagrangian Models

The two most often used formulations for modeling fluid dynamics and solid mechanics are the Eulerian and Lagrangian formulations.

In a Lagrangian formulation, the particles or fluid element properties are tracked as they move through the computational domain. Therefore, each fluid element or particle is characterized at each instant by its position and its properties (e.g., pressure). In the case of fluid elements, the shape of the element can change, but its mass remains constant (Koutromanos, 2018). In the Eulerian formulation, instead of tracking a fluid element or particle, the evolution of fluid properties is tracked at each location in the computational space as a function of time. In this case, the positions are fixed throughout the simulation, and only the evolution of the fluid properties is recorded over time.

In fluid simulations where there is fluid mixing or spinning of the flow, the use of the Lagrangian formulation in computational fluid dynamics has at least one disadvantage: It has a tendency for the grid to get entangled, which can break the physical conservation laws and lead to computational errors and singularities. Therefore, in most multidimension

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fluid codes, Eulerian formulations are used (Mojgani and Balajewicz, 2017).

### Arbitrary Lagrangian-Eulerian Methods

In problems where there are fluid or structure interactions, Arbitrary Lagrangian-Eulerian (ALE) methods are an efficient and practical solution for computational modeling without distortion of the problem mesh described earlier. The approaches to ALE methods combine Lagrangian and Eulerian methods and solve the computational problem in two steps: a Lagrangian step that deforms the mesh to follow the material and an Eulerian advection that restores the mesh's original shape while allowing the material to move through elements (Lockhart, 2010). ALE methods are suitable when modeling the propagation of incident blast waves. The blast waves can be modeled using an Eulerian method, and the interaction of the blast waves as they propagate through the human body can be modeled with the Lagrangian formulation (Yu and Ghajari, 2019).

For the problem of modeling blast waves through the human body, ALE methods can be grouped into three types (Yu and Ghajari, 2019):

- In the **multi-material ALE** method, each element is allowed to contain more than one material, and the explosive wave front is modeled with Eulerian meshes by converting it into a high temperature and pressure gas upon detonation. The method is able to predict the peak pressure.
- The **coupled load-blast–enhanced and ALE (LBE-ALE)** method relies on a database of equations developed by conducting full-scale experimental blasts using different explosive charge weights and stand-off distances. This method works by applying blast loadings on segments of the structure's surface. The LBE-ALE method shows promising results when predicting the pressure wave history. This method requires that careful consideration be applied to the boundary conditions and transitions between the ambient layer and the computational mesh.
- The **prescribed inflow ALE (PIF-ALE)** method is similar to the LBE-ALE method in the way that the internal variables' time history is prescribed as an inflow formula applied to a thin layer of the air mesh. No modeling of an explosive is needed, which allows not only spherical blast waves but also planar ones.

Often in problems involving blast or explosions, another computational method is used called adaptive mesh refinement (AMR). AMR in general leads to better temporal and spatial resolution. AMR works by (1) subdividing cells into a more refined mesh in areas of high gradients and (2) combining grid cells into a larger grid cell in a smooth region. AMR is ideal for multiscale problems where there are large, localized gradients separated by regions and where the solution is smooth, which is the case with the human body's responses to blast (Yang et al., 2011). As the blast wave propagates through different body organs and tissues, there are high gradients, although the regions immediately before and after are smooth. This AMR method allows for higher special resolution on the high gradient regions by refining the mesh there while using a much coarser mesh in smooth regions, therefore decreasing the computational cost of the simulation (Nyein, 2013).

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In summary, in modeling the effects of blast-related trauma, it is essential to account for small-scale effects of the trauma on the different cells and organs of the body and their consequences on the overall body system, which is inherently multiscale in nature. FEMs are an ideal tool to conduct these multi scale models because they provide great flexibility and a high level of accuracy.

Brain-related injuries, including traumatic brain injury, are prominent injuries sustained during military service, but modeling the brain is challenging.

## Findings from the Computational Modeling of the Human Body's Responses to Blast Exposure

This section presents results from computational modeling of various body parts; such modeling can be used to understand in what ways humans are susceptible to blast damage. (For another review of computational modeling of select body responses to blast, see Chanda and Callaway, 2018.)

### Brain and Skeletal Trauma

#### Skull and Brain Tissue Trauma

Brain-related injuries, including traumatic brain injury, are prominent injuries sustained during military service (Tanielian and Jaycox, 2008; Kim, Tsao, and Stanfill, 2018; Okie, 2005; Xydakis et al., 2005), but modeling the brain is challenging. For one, the brain tissue, brain stem, spinal cord, cerebrospinal fluid—the main parts of the nervous system—have different densities and biomechanical properties (Wang, Pahk, et al., 2014). Additionally, primary concussive blast injuries might be caused by the primary blast wave injury (the direct transmission of the blast wave across the skull and the brain), by secondary blast wave injury (the impact from blast ballistics on the head), or by tertiary injury (the impact of the individual striking an object, such as a fall against the ground or the inside of a vehicle) (Tan, Saunders, and Bagchi, 2017).

An additional consideration when modeling is that the initial blast wave is generally a pure pressure wave; however, the blast wave can change into a combination of pressure and shear waves when interacting with the complex geometry and biological material of the human head and brain (Tan, Saunders, and Bagchi, 2017). The motion of blast waves between the brain and skull can cause axonal injuries, subdural hemorrhaging, and contusions (Kocsis and Tessler, 2009; Pan et al., 2013; Sarvghad-Moghaddam et al., 2017; Wang, Pahk, et al., 2014). Other injuries might occur from direct propagation of the blast wave through the skull to the brain tissue (Chafi, Karami, and Ziejewski, 2010; Courtney and Courtney, 2011); axonal strains because of rotational accelerations experienced by the human head (Finkel, 2006; Garimella, Kraft, and Przekwas, 2018); propagation of the blast wave through the great vessels and then to the brain tissue (Moore et al., 2008); and cavitation secondary to the blast underpressure (a negative pressure wave), together with any accompanying blast electromagnetic pulses that cause cellular damage (Taylor and Ford, 2009). Although it is understood that a potential cause of brain injury from blast is intracranial fluid cavitation, it is not understood how this occurs (Haniff and Taylor, 2017). Additionally, the timescale during which primary blast injury occurs is fewer than five milliseconds, while shear waves travel at lower speeds in the brain (~10 miles per second), leading to a slow evolution of the strains along the axons (Garimella, Kraft, and Przekwas, 2018; Przekwas, Somayaji, and Gupta, 2016).

In a Wayne State Head Injury Model, a FEM was used to understand the mechanism of mTBI. Researchers attempted to correlate the internal mechanical parameters with pathophysiological and clinical manifestations of mTBI from blunt impact (as opposed to blast wave exposure). The model showed that the brain tissue faced the highest compressive and tensile stresses, while the central region faced the most strain. The results were modeled on spherical air bursts rather than ground bursts, making them less applicable for IED risk (Zhang, Makwana, and Sharma, 2013). Furthermore, although the distribution of blast-induced ICP is still not fully understood, computational modeling has been used to elucidate the effects of the ICP pattern and stress on the brain, which can then be used to estimate the likelihood and severity of injury in different brain regions. The results from other computational modeling studies described the coup-contrecoup pattern of injury from blast exposure (i.e., injury at the point of contact and the opposite side of contact). These results supported that the left and right side of the head were more susceptible to injury than other regions were, which could be because of low skull curvature or the fact that the skull is broader in the middle and narrower in the front and back (Tan et al., 2021).

Additionally, coup-contrecoup force can cause contusions before spreading extensively throughout the brain (Hua, Lin, and Gu, 2015). FEM research simulating blast impacts to the head and brain demonstrated that negative pressures from contrecoup force were able to produce cavitation—generally when vapor bubbles form from a liquid—with the application of increased pressure rather than the addition of heat (Goeller et al., 2012; Panzer, Myers, et al., 2012). Haniff and Taylor (2017) used computational microscale modeling to simulate the effects of cavitation bubble collapse, and the associated microjetting phenomena that occur in white matter structures suggested that, in all cases, the myelin suffered significant damage.

Another consequence of blast exposure is diffuse axonal injury, which occurs when the brain rapidly accelerates and decelerates inside the skull, simultaneously shearing axons. Using a FEM modeling approach to understand axonal injury, results from Pan et al. (2013) suggested that the local stress and strain fields were "heterogeneous near the axon, even though a uniform global strain field was applied" (Pan et al., 2013, p. 7). Findings from a computational modeling study by Garimella, Kraft, and Przekwas (2018) that considered the dimorphism of male and female skull thickness suggested that axonal strains and strain rates depend on the skull thickness. Females have a higher average skull thickness than males. Specifically, they used two FEM head models (one female and one male) to examine the axonal response that results from brain injuries caused by skull flexures. In every simulation, the results showed that skull flexural displacements depend on skull thickness, and skull flexures themselves increased axonal strains and strain rates (Garimella, Kraft, and Przekwas, 2018).

FEMs have also been used to examine the role of vascular networks in blast-induced brain injury. However, results have been contradictory as to whether there is an increase or decrease of the MPS, shear strain, and ICP. A two-dimensional human head FEM was developed, and results showed that the inclusion of arteries in the brain led to a decrease in the peak MPS, shear strain, and ICP (Zhang et al., 2002). Another group developed a three-dimensional (3D) human head FEM, with results showing a 2-percent reduction in peak MPS, implying that the vascular network plays a minimal role in brain dynamics (Ho and Kleiven, 2007). By contrast, results from Hua, Lin, and Gu (2015) about the role of blood vessel networks in brain dynamics revealed that peak MPS increased in the corpus callosum and brainstem by about 180 percent.

Chafi, Karami, and Ziejewski (2010) used an integrated computational approach to investigate brain responses in the first few milliseconds after shock waves induced by TNT and other high-yield explosive blasts. The authors found that blasts generated substantial pressure on the brain during the impact before any overall motion of the head occurred. The authors also noted that shock waves originating from blasts can cause contusions of the frontal and temporal lobes.

## Mandible Trauma

Injuries to the jaw and facial area have also increased in recent military conflicts, due largely to a combination of increased use of IEDs and minimal protection for these exposed areas (Lei, Xie, et al., 2012). According to Lei, Xie, et al. (2012), research efforts existed on treatment and reconstruction; however, the fundamental research needed to advance understanding of the precise mechanisms behind the injury was overlooked. To begin addressing this gap, Lei, Xie, et al. constructed a FEM using a pig mandible to start to understand human maxillofacial blast-related injuries. This model allowed for dynamic simulations and analyses of the mechanisms of injury and severity of trauma from a blast directed at the middle mandibular angle. The model also explored mandibular damage and the dynamic distribution of biomechanical indices (e.g., stress and strain), which would be needed for a combined model of the human body's responses to blast trauma.

### Pelvis and Spine Trauma

Injuries from underbody blasts (UBBs) can result in severe injuries to multiple areas of the body—most notably, the pelvis, lumbar spine, and lower extremities. Approximately 67 percent of injuries from the Afghanistan and Iraq wars involved the pelvis, spine, and lower extremities (Lei, Zhu, et al., 2018). Pelvic fractures are of particular concern because they are associated with high rates of death and disability (Tse et al., 2020; Weaver et al., 2021).

Computational modeling of pelvic injury is beginning to elucidate the effect of UBBs on the injury response to the pelvis and lumbar spine while simultaneously accounting for various blast levels and field conditions, including vertical loading in different seated positions (Tse et al., 2020) and adjusting peak acceleration and time duration of the UBB pulses (Lei, Zhu, et al., 2018; Weaver et al., 2021). Findings demonstrated that decreased posterior pelvis tilt slightly reduced sacral fracture severity, while an increased sacral angle increased the area of anterior sacral fracture but reduced the extent of the dorsal sacrum fracture. The findings suggested that an upright initial seated posture prior to UBB might reduce the risk of pelvic injuries (Tse et al., 2020). Other findings demonstrated a relationship between injury patterns and impact parameters, suggesting that injury severity because of UBBs is closely related to loading conditions, and, in the pelvis, sacrum, and ilium, fractures are mainly caused by shear and compression (Lei, Zhu, Jiang, et al., 2018). Additionally, the findings from Weaver et al. (2021) suggested that FEM modeling is accurately modeling pelvic area injury using data from postmortem human cadavers.

Nevertheless, the literature available on computational modeling of pelvic and lumbar blast-related spine injuries is limited, perhaps because of the structural complexity of these regions and the complicated boundary and loading conditions (Lei, Zhu, et al., 2018; Weaver et al., 2021). Furthermore, modeling of the skeletal structures as a whole is limited. Additional research to fully elucidate the mechanism of injury that accounts for a variety of field conditions could be valuable to future design of vehicles and protective equipment.

### Auditory Trauma

Blast exposure can result in hearing loss because of high-intensity sound or blast overpressure waves, both of which military personnel encounter on a regular basis, regardless of their specific duties. Given how vulnerable the auditory system is to damage from blast overpressure, it is critical to improve our understanding of how blast waves affect the ear, particularly if there is hope of developing adequate

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hearing protection devices (Leckness, Nakmali, and Gan, 2018).

To our knowledge, Leckness, Nakmali, and Gan (2018) is the only published study that used computational modeling to explore blast wave propagation through the ear to increase understanding of the mechanisms behind auditory injuries and to improve auditory hazard assessment models. The authors built a 3D FEM model of the human ear and then applied blast pressure waveforms at the entrance of the ear canal. The results showed that the model-derived waveforms near the tympanic membrane were consistent with results recorded in human cadaver ears during blast simulations, demonstrating the utility of the FEM model of the human ear for predicting blast overpressure propagation through the ear canal into the middle ear. The model can be used to investigate the biomechanical response of the human ear to blast overpressure and, subsequently, evaluate hearing protection devices (Leckness, Nakmali, and Gan, 2018).

## Ocular Trauma

Although the human eye constitutes only a small portion (less than 0.1 percent) of the human body's frontal surface area, eye injuries are disproportionately common in survivors of explosions (Karimi et al., 2016; Liu et al., 2015). Ocular trauma has become more frequent in recent military conflicts; the ratio of ocular traumatic injuries to all injuries during Operation Desert Storm (1991) was nearly six times larger than in World War II (Notghi et al., 2017). One plausible reason for the increase in incidence is an increased use of IEDs. A study from Weaver, Stitzel, and Stitzel (2017) reported that IEDs were the cause of up to 51 percent of ocular injuries in U.S. military conflicts, while other studies reported that more than 80 percent of ocular injuries in the Iraq war were caused by blasts from munitions and IEDs (Bhardwaj et al., 2014; Karimi et al., 2016).

Blast-related trauma often results in ocular morbidity and visual impairment, with studies showing that more than 10 percent of blast injury survivors suffer from severe ocular injuries (Karimi et al., 2016; Liu et al., 2015). Primary blast injuries can cause ruptured globes or hyphemas. Secondary blast injuries typically lead to eye or orbital damage because of injury to the eye's structural components, open globe fractures, and adnexal lacerations of the lacrimal system (Chanda and Callaway, 2018). In the military setting, evidence suggests that secondary blast injuries from fragments or other particles are typically responsible for eye injuries (Abbotts, Harrison, and Cooper, 2007).

Computational studies of ocular injury have taken into consideration several factors, such as blast load, distance from blast exposure, and blast injury caused by primary and secondary blast effects. Multiple simulations considered various blast exposure distances and different blast load conditions. Lui et al. (2015) used distances of 0.75, 1, and 1.25 meters to assess the dynamic responses of the globe to different loads, showing that the peak stress of "25.5 MPa [megapascals] in the limbus exceeded the threshold of globe rupture at the victim distance of 0.75 m[eters]" (Liu et al., 2015, p. 5). This finding suggested that globe rupture will occur under the overpressure of 2080 kilopascals (Liu et al., 2015), which is also far greater than lethal pressure (estimated to be between 240–450 kilopascals) (Kluger, 2003). Karimi et al. (2016) evaluated the effects of realistic detonation conditions on the loading of the eye from a distance of 25 centimeters. Results from that study showed the highest stresses on the sclera and ciliary body and the lowest on the vitreous and aqueous humor; however, both stresses and strains on the optic nerve and macula were enough to cause loss of vision (Karimi et al., 2016).

Additionally, there is some variation in the computational techniques used to evaluate ocular damage. Using a FEM and a Lagrangian mesh, one study investigated globe rupture caused by primary blast effects (Liu et al., 2015). Another model used by Karimi et al. included a cornea, sclera, lens, ciliary body, zonules, and the aqueous and vitreous bodies. The authors then coupled this model with an Eulerian mesh of a blast to simulate how blast wave generation and propagation interact with the eye. To determine the stresses and deformations of ocular components attributable to a TNT explosion, a Lagrangian-Eulerian computational coupling model was developed. This model included each component of the eye modeled as Lagrangian mesh and the TNT, air domain, and aqueous components using ALE mesh (Karimi et al., 2016).

A 3D computational model was used by Notghi et al. (2017) to calculate intraocular pressure, the stress state of the eye wall, and the internal ocular structure. This research showed that blast loading can induce significant stresses to the different components of the eye. The 3D model included detailed descriptions of the skull and internal ocular structures. Another 3D fluid-structure interaction computational model was developed by Bhardwaj et al. (2014) to simulate stress on, and deformation of, the globe caused by realistic blast conditions. The model factored in the interaction of the wave with the extraocular tissues of the orbit. The results showed that blasts caused asymmetric loading on the eye, leading to globe distortion and large deviatoric stresses in the sclera. These large stresses might indicate the risk of interfacial failure between the tissues of the sclera and the orbit.

Weaver, Stitzel, and Stitzel (2017) and Rossi et al. (2012) investigated injury severity using blast intensity, by simulating the impacts of TNT blasts using different amounts and victim distances from the blast. Specifically, Weaver, Stitzel, and Stitzel (2017) used a predictive Lagrangian-Eulerian FEM model of the eye to analyze 2.27 and 0.45 kg TNT-equivalent blasts detonated from 24 different locations. The model simulated both open air and ground-level blasts. Results suggested that corneoscleral stress, intraocular pressure, and injury risks increased as the blast size increased and the blast was located closer to the eye. Rossi et al. (2012) developed a FEM model mesh of the eye, orbit, and skull, calculating pressure, stress, and strain rates for the cornea, vitreous base, equator, macula, and orbit apex at pressures known to cause other injuries. Findings suggested that small quantities of TNT could cause extensive damage to the retina, choroid, and optic nerve.

Findings from various computational models that analyzed different blast intensities and blast distances could be helpful in designing eye protection equipment to mitigate blast-related eye injuries.

## Thoracic Trauma

### Lung Injuries

Another potential consequence of blast exposure is lung damage. Van der Voort et al. (2016) investigated the blast-injury mechanism of lung rupture and described a method for predicting lethality caused by Friedlander blast waves. A *Friedlander wave* occurs when an explosive detonates in a free field with no surfaces nearby with which it can interact (Stuhmiller, Phillips, and Richmond, 1991). The authors found that the explosive loading on an individual standing in front of a reflecting surface was equivalent to the explosive loading on an individual standing in an open field for a short-duration blast wave. The authors also found that lung injuries occurred at close proximity to the blast exposure and in directions where there were fewer fragments or less debris (Van der Voort et al., 2016).

### Chest Wall Injuries

Chest injuries often occur after a blast event where the individual is in a closed vehicle. Studies that measure the external force, head acceleration, chest deflection, chest acceleration, and rib velocity would be aided by having well-established thresholds of clinically detectable injury outcomes. Nonetheless, FEMs have been developed to realistically reflect the typical mechanical response of the chest wall to blast wave loadings, demonstrating that they can be used for further studies on blast-injury mechanisms (i.e., injury prediction) (El-Jawahri et al., 2009; Kang et al., 2015; Poplin et al., 2017). Findings from the 3D FEM developed by Kang et al. (2015) are consistent with previous results that report that a maximum rib velocity of 1.6 meters per second does not cause injury to ribs. Additionally, results suggest that a 3D FEM can be developed to study the propagation of a blast wave through the lung tissue and ribs in a multiscale manner. Findings from a study by Poplin et al. (2017) suggest that chest deflection is associated with severe injury. These studies have limited validity because of a lack of real-world data with which to compare computational outcomes.

### Cardiac Injuries

In modeling the cardiac response, the field has benefited from rich cellular-level data and modeling of the whole organ (Noble, 2002). The initial wave of a blast can create blunt force trauma to the chest, exerting overpressure on the heart and causing injuries, including cardiac contusion, cardiac tamponade, myocardial infarction from air embolism, shock, hematoma, vasovagal bradycardia, and vasovagal hypotension (El-Menyar et al., 2012; Ozer et al., 2009; Singh et al., 2018). However, to our knowledge, there has been no computational modeling of the heart or related injuries specifically in a military setting.

### Abdominal Trauma

To our knowledge, there has been no computational modeling of the human spleen or gastrointestinal systems' responses after a blast trauma.

### Facial Dermal Burn Trauma

Dermal burns occur because of direct or indirect exposure of an individual to a heat source that can cause damage to facial skin, the eyelids, and the lips and burning of facial hair (Shuker, 2010). Different aspects of the environment might influence the severity of blast burns. For example, in a review of facial burns, Shuker noted that burns related to blasts were more severe in closed settings, where the blast wave was less likely to dissipate (Shuker, 2010). A mathematical model coupled with a live, controlled experiment of a bus explosion revealed that burns related to blasts were more severe in closed settings, where the blast wave was less likely to dissipate (Antanovskii, Remennikov, and Winter, 2010). To our knowledge, there are no other reports of computational modeling of dermal burns on humans except for on the face.

In summary, although computational research has advanced with a focus on individual body parts, additional research to validate the accuracy of models and address challenges in modeling the human body from the cellular level to whole-body dynamics is still needed.

The literature review sought to provide answers to this basic question: What does computational modeling tell us about the human body's responses to blast injury?

## Summary of the Findings of the Human Body's Responses

The literature review sought to provide answers to this basic question: What does computational modeling tell us about the human body's responses to blast injury? The following summary of results begins to answer that question.

### What Does Computational Modeling Elucidate About Brain Trauma?

Computational modeling has been used to explain the effects of blast waves on the brain. As noted in the literature, an understanding of the pattern of injury and changes in the stress of the brain can be used to estimate severity of injury or the likelihood of injury in different brain regions (Chafi, Karami, and Ziejewski, 2010; Pan et al., 2013). Computational modeling findings have also increased our knowledge of the increases and decreases associated with blast exposure on ICP, shear stresses, shear strains, and relative displacements in brain tissues (Tan et al., 2021; Zhang, Makwana, and Sharma, 2013). Furthermore, computational modeling results provide an understanding of the role of skull thickness, skull shape and size, vascular networks, and myelination (Garimella, Kraft, and Przekwas, 2018; Ho and Kleiven, 2007; Zhang et al., 2002).

## What Does Computational Modeling Elucidate About Skeletal Trauma?

Injuries from UBBs often cause injury to multiple areas of the body and can sometimes be fatal (Lei, Zhu, et al., 2018; Weaver et al., 2021). Computational modeling results described effects of posture in a vehicle on injury (Tse et al., 2020). Notably, modeling of the skeletal structures as a whole is limited. This may be the case because much of the research conducted is focused on the blast wave's effect on soft fluid or air-filled organs. Additional research to fully understand the mechanism of injury that accounts for a variety of field conditions could be valuable to future design of vehicles and protective equipment.

## What Does Computational Modeling Elucidate About Ocular Trauma?

Computational studies provide various results related to ocular injury after blast exposure. Primary blast injuries can induce ruptured globes, hyphemas, serous retinitis, conjunctival hemorrhage, and orbital fracture. More common are secondary blast injuries that typically lead to eye or orbital damage. Findings from studies show how blast waves can cause stresses and strains that can be severe enough to cause loss of vision (Bhardwaj et al., 2014; Karimi et al., 2016; Liu et al., 2015; Notghi et al., 2017; Rossi et al., 2012; Weaver, Stitzel, and Stitzel, 2017).

## What Does Computational Modeling Elucidate About Auditory Trauma?

Research conducted with human data is limited. We found one article investigating auditory injury after a blast or explosion using a human cadaver (Leckness, Nakmali, and Gan, 2018). Nonetheless, this finding demonstrates the feasibility of using computational modeling to (1) explore the biomechanical response of the human ear to blast overpressure and (2) subsequently evaluate hearing protection devices. Combining this model of the human ear with other systems could successfully lead to a unified model of the human body's responses to blast trauma.

## What Does Computational Modeling Elucidate About Thoracic Injuries?

Although the literature describes findings regarding lung injury (Van der Voort et al., 2016) and rib injury (El-Jawahri et al., 2009; Kang et al., 2015; Poplin et al., 2017) after blast exposure, to our knowledge, there is a lack of a unified computational model of the complete thoracic area, including the heart and related injuries, specifically in a military setting.

## What Does Computational Modeling Elucidate About Abdominal Trauma?

We found no computational or experimental research in humans of the abdominal response to blast-related trauma.

## What Does Computational Modeling Elucidate About Skin Trauma Because of Burns?

Although burns are particularly common in cases in which the victim is close to the blast site (Shuker, 2010), computational modeling of burn in humans is almost nonexistent. Using multiscale computational models to understand the mechanisms and progression of injury and the subsequent use of protective equipment and treatment could be quite valuable.

# Future Directions

Although meaningful progress has been made in the computational modeling of the human body's responses to blast exposure, several important issues need to be addressed.

## Work Toward Developing a Unified Multiscale Model or Combining Models to More Fully Investigate the Human Body's Responses to Blast Exposure

Research on multiscale modeling of the human body's responses to blast exposure remains nascent. To date, computational models have largely explored individual human body parts, likely because of the

The development of a unified multiscale model of the human body's responses to blast trauma could improve the understanding of both the short- and long-term effects of a blast on the human physiology.

challenges associated with modeling complex biological systems. A significant obstacle to developing a unified multiscale computational model of the human body—from the cellular level, to the tissue level, to the whole-body level—is the need to integrate many different techniques, as described in the computational modeling section of this report. Another challenge to the development of a multiscale model, or combining models, is the need to understand different levels of spatial and temporal detail to fully grasp the effects of blast trauma on the human body.

Consider the example of understanding the effects of blast exposure on the chest. Modeling the effects of the blast wave requires a complete understanding of the mechanisms involved as the wave propagates through the body armor, skin, ribs, and then lungs. In this example, a unified model would require multiple computational methods to describe the functioning of the body, which is made up of different solid and fluid types, as well different scales. Difficulty occurs in determining what scales are involved in this incident, how each scale should be modeled (in terms of elements, properties, and biomechanics), and how different scales should be integrated.

Nonetheless, interest in the ability of computational modeling to provide mechanistic insights into the consequences of the human body being exposed to blast waves is increasing. The field should continue its efforts to assess the feasibility of integrating information about the blast wave's path through the human body to help determine the effects of blast exposure. The development of a unified multiscale model of the human body's responses to blast trauma, or combining multiple computational models in a systems manner, could improve the understanding of both the short- and long-term effects of a blast on the human physiology.

## Establish Clinical Injury Thresholds

To our knowledge, although there are studies that describe multiple aspects of the human body's responses to blast, there are few well-established clinical injury criteria with respect to mechanical responses of the human body to blast shock waves, with the exceptions of lung and chest injuries. This is likely because of several factors, including significant variability in exposures, limited quantification of expected strain and strain rate values, the large variation in published mechanical properties of tissue, and differences in the measurement of tissue, blood, shear stress, and ICP (Singh, Cronin, and Haladuick, 2014). Accordingly, models are unable to relate any kinematical or biomechanical parameters to any injury threshold. Correlating measured response to clinically detectable injury could help improve understanding of the effects of blast injury preclinically and clinically, particularly in the case of multiple subclinical blast exposures (Tan et al., 2021).

## Simulate a Wider Variety of Blast Exposures

Many of the discussed papers model events with only a single blast condition, such as distance from blast or charge size, which limits the ability to assess the underlying biomechanics of blast injury, particularly in military-related environments. As multiscale modeling research advances, integrating aspects of the blast environment—such as explosive types (e.g., C-4, TNT, dynamite), charge sizes, charge distances, and field conditions (e.g., open spaces or closed spaces)—should be investigated. To fully understand the potential for injury and the underlying mechanisms, computational models need to provide an understanding of the human body's responses under a wider variety of blast exposures.

### Collect More-Relevant Blast-Related Military Data for the Purpose of Validating Computational Models

There are limited blast-related data collected in military settings, making it difficult to validate computational blast models and thereby limiting these models' utility. The use of nonmilitary data might not fully correlate with military injury because of the unique features of military-related blast exposure, such as varying explosive types, protective equipment used, and field conditions (e.g., being subject to a blast inside a military vehicle versus in a warehouse or in an open field). Additionally, many of the findings are reported on blast exposures with charge sizes that might not be typically experienced in a military setting (Yokohama et al., 2015). Thus, to validate computational models, there is a need to collect blast-related military data to account for varying conditions specific to military settings.

### Evaluate Responses with Multiple Representative Bodies

To fully understand the human body's responses to blast trauma, models needs to account for anatomical variation. In the military, weight differences might be minimal. However, other size differences between individuals could affect the results of the models. For example, women have a higher average skull thickness compared with men (Garimella, Kraft, and Przekwas, 2018). Additionally, height differences might correlate to different effects of blast exposure. Developing multiple representative human body models could improve understanding of the effects of blast for the variety of service members exposed to them.

To validate computational models, there is a need to collect blast-related military data to account for varying conditions specific to military settings.

## Limitations

There are a few limitations to consider with regard to this literature review. One is that this is not a systematic review. Thus, there very well might be publications that are relevant to include that we missed. Secondly, when looking for publications and research to include in this report, we did not assess the quality of the science completed. We are reluctant to assess the quality without greater collaborative involvement of appropriate subject-matter experts. Therefore, this literature review is not a substitute for expert interpretation and review of research quality. Lastly, we chose to include only studies on humans, which excluded a large number of publications that were non–human-focused. Therefore, there might be foundational research of interest being conducted at this time that has not been scaled up to the human level and thus was not mentioned in this review.

## Concluding Observations

To our knowledge, this is one of very few reports on the state of the science of computational modeling of the human body's responses to blast—from the cellular level, to the brain, to whole-body dynamics. This literature review summarizes the development of computational models and documents computational challenges, particularly with respect to developing a unified multiscale model of the human body's responses to blast or in combining models for a systems perspective. The review discusses in detail the challenges associated with computational modeling, including modeling the material of the body, assigning loads and boundary conditions, and modeling multiple scales of resolution. We also report results from modeling the effect of blasts on several human body parts, including the skeletal system, brain, eyes, ears, thorax, and skin.

This review is meant to serve as a roadmap to inform additional computational and experimental research investigating the human body's responses to blast-related trauma. As the field advances, the next generation of models will require more-detailed material modeling between tissue layers, individual organs, and the articular cartilage and ligaments. The most valuable investigations will require an understanding of the interactions among cells, organs, and systems and how these interactions change in response to blast exposure over time. The hope is that, in time, continued computational modeling of the human body's responses to blast exposure will better support service members, leading to improved personal protective equipment to reduce injury severity and improved care for those injured.

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## About This Report

The report describes the state of the science of multiscale computational modeling of the human body's responses to blast-related trauma, including both descriptions of models used or developed and research findings, and identifies future opportunities to strengthen the current research on understanding the human body's responses to blast-related trauma, particularly across multiple scales. The research reported here was completed in August 2021 and underwent security review with the sponsor and the Defense Office of Prepublication and Security Review before public release.

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