고에너지물질에 의한 약물 전달 시스템 연구

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Innovative Modeling of Explosive Shock Wave Assisted Drug Delivery

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ABSTRACT

Recent advances in energetic materials modeling and high-resolution hydrocode simulation enable enhanced computational analysis of bio-medical treatments that utilize high-pressure shock waves. Of particular interest is in designing devices that use such technology in medical treatments. For example, the generated micro shock waves with peak pressure on orders of 10 GPa can be used for treatments such as kidney stone removal, trans-dermal micro-particle delivery, and cancer cell removal.

In this work, we present a new computational methodology for applying the high explosive dynamics to bio-medical treatments by making use of high pressure shock physics and multi-material wave interactions. The preliminary calculations conducted by the in-house code, *GIBBS2D*, captures various features that are observed from the actual experiments under the similar test conditions. We expect to gain novel insights in applying explosive shock wave physics to the bio-medical science involving drug injection. Our forthcoming papers will illustrate the quantitative comparison of the modeled results against the experimental data.

Key Words : Explosive, Shock Wave, Microparticle Injection, Multimaterial Impact

1. INTRODUCTION

Conventional shock wave generation technique such as pulsed laser beam focusing for a small air breakdown with subsequent formation of laser plasma is known to cause tissue damage during a shock wave-assisted lithotripsy treatment of kidney, pancreatic, or salivary stone removal[1]. A conceptual micro-scale explosive device is devised that avoids subsequent tissue damaging by locally shocking the treatment area inside the human body.

As a preliminary work, we perform careful modeling of candidate high explosives such as silver azide or HMX that reacts to generate required high pressure shock waves. Based on the multi-material hydrocode methodology, mechanical, thermal, and chemical factors associated with both energetic and inert materials involved are carefully modeled.

Along the line of this work, we are working on developing a state-of-the-art interface tracing technique that can elegantly handle complex multi-material interaction between energetics and inerts, along with solid-liquid-gas phase transitions. The level-set resolved material boundaries will be treated with tree-based meshing system for the enhanced interface motion.

In the world of trans-dermal drug delivery, focus is placed on safely and elegantly

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bypassing the skin layers before applying the necessary micro-particle drug to the right depth (location) underneath the skin. Traditionally, microporation is used in such skin bypass operation where hundreds of tiny needles in the size of micron pierce only the upper most 10 microns of the epidermis, thus allowing the drug to bypass this important barrier[6]. The micro-needles are usually drug-coated projections of solid silicon or hollow, drug-filled metal needles. Because the nerves located deeper in the skin are not stimulated, the patient only feels the texture of sandpaper. A related means of delivering compounds is the use of medicated tattoos. Unlike the previously mentioned method, this patching medicine technique does not provide any means of controlling drug-release rates. Lastly, with iontophoresis, a small electric current forces molecules into the skin. An electrode patch containing the drug is placed on the skin and acts as the working electrode, which can be either positive or negative, depending on the characteristics of the drug. This technique utilizes energy to facilitate permeation of drugs across the skin, enhancing both the rate of release and the extent of penetration of the salt forms of drugs. Other form of trans-dermal drug delivery that is rather common is the needle injection method which uses liquid form of drug.

Unlike the traditional drug injection processes as outlined above, the shock wave assisted drug delivery method as it will be discussed next has several known advantages: using fine particles that are below the size of skin pores, the particle injector uses particles that are too small to trigger pain receptors, and the procedure is painless, making it suitable for patients who fear traditional needle injections. Furthermore, shock driven injection method can significantly reduce the risk of infection due to needle or hardware contamination and no blood exposure occurs during its use. Shock wave strength determines the penetration of particle into the layers of epidermis. This can be a break through technology in the trans-dermal drug treatment where the delivery of the vaccines to the immune system of viable epidermis becomes possible[7].

In the present work, we study how shock wave generated by the high explosive allows penetration of the main barrier for drug particle, namely the stratum corneum of human skin. Based on the experiments outlined in [3], trans-dermal particle delivery process is modeled by making use of the multi-material shock wave analysis tool called *GIBBS2D*[4].

2. DESCRIPTION OF *GIBBS2D*

The general conservation laws of multi-dimensional, multi-material physics can be written as

$$\frac{\partial U}{\partial t}+\frac{\partial F}{\partial x}+\frac{\partial G}{\partial y}=S(U) \tag{1}$$

where the variables represent a vector of conserved variables U, spatial fluxes in x and y-directions F and G, and a source, S.

The discretized system of PDEs in Eqn. 1 can be solved by independent steps of space and time integration. For this two-dimensional system, the x and y fluxes are treated with the fourth-order convex ENO scheme. Once the two advection terms are approximated by spatial differences, Eqn. 1 is approximated by a system of ODEs that are solved in time with a third-order TVD Runge-Kutta scheme.

2.1 Equation of motion for propagating interface

A level-set function provides a simple way to track material interfaces and contact surfaces that divide two different media (or materials). We will consider two main types of multi-material interfaces, namely, material-material contact, and material-void (or vacuum) interface. We show how to treat jumps in state variables that are discontinuous, like the density.

The level-set equation,

$$\frac{\partial \phi}{\partial t}+v_1\frac{\partial \phi}{\partial x}+v_2\frac{\partial \phi}{\partial y}=0 \tag{2}$$

is used to track the location of the material interface represented by the zero-level contour $\phi(x,y)=0$. Initially, we take ϕ to be the signed normal distance function to the

interface. The material interface evolves with the local material velocity $v=(v_1,v_2)$. The material velocity on either side of the interface provides the velocity extension that is used for advection of ϕ in the level-set domain. The level-set function ϕ is taken positive outside of material and negative inside.

2.2 Material modeling

We consider ductile metals and rubber elastic material for illustration of material modeling involved in the shock wave assisted bio-medical procedure. Based on classical *incremental small-strain theory*[5], the governing equations can be stated as,

$$\begin{aligned} &\dot{\rho}+\rho\nabla\cdot v=0 \\ &\rho\dot{v}=-\nabla p+\nabla\cdot s \\ &\rho\dot{E}+\nabla\cdot(pv)=\nabla\cdot(sv) \end{aligned} \tag{4}$$

where the evolution variables are density, velocity vector, and total energy per unit mass ($E=e+1/2v\cdot v$). The equation of state (EOS) relates pressure with internal energy and density, such that $p=p(e,\rho)$. The deviatoric stress s is introduced. The Cauchy stress, defined in the spatial configuration is $\sigma_{ij}=s_{ij}-p\delta_{ij}$ so that the stress may consist of a volumetric term (namely the hydrostatic pressure p) and a deviatoric (or traceless) part.

2.2.1 Elasto-plasticity equations for metal

The deviatoric part of stress is treated as a source term in the present formulation. Based on the hyperbolic equations of motion for high speed impact and explosive dynamics, the evolution variables, spatial fluxes, and the source vector are defined elsewhere[4].

2.2.2 Rubber-elasticity equations for human skin

For brief description of artificial skin model, we introduce two kinds of elastic potentials from the well known rubber elasticity theory. First is a Blatz-Ko solid[6] which is given by

$$\psi=\frac{\mu}{2\rho_0}(I_B-3)+\frac{\mu(1-2\nu)}{2\rho_0\nu}(III_B^{\nu/(1-2\nu)}-1) \tag{8}$$

The potential ψ is a function only of the first invariant, I_B and the third invariant, III_B suggesting that simple isotropic elasticity is assumed (i.e. no dependence on the second invariant, II_B). Noting that I_B=trace $\boldsymbol{B}$ where $\boldsymbol{B}$ is the left Cauchy-Green tensor, the contribution to the stress associated with Blatz-Ko solid potential in purely isotropic deformation is related to, $\sigma_{ij}=2\rho\frac{\partial\psi}{\partial B_{ij}}B_{il}$

The second rubber elastic material model is the Mooney-Rivlin model whose potential is given by

$$\psi=a(I_B-3)+b(II_B-3)+c(III_B^{-2}-1)+d(III_B-1)^2 \tag{10}$$

where the coefficients a,b,c,d are related through simple algebraic relations with two coefficients specified for materials under consideration. In the case of human skin, suggested values are reported elsewhere[7].

3. TRANS-DERMAL DRUG INJECTION VIA SHOCKED PLATE

Figure 5(a) is a sketch of a micro particle delivery system based on shock focusing technique from [3]. Laser beam (labeled 2) is focused through the lens (labeled 1) on to a plate (a foil labeled 4). The high temperature condition generates plasma on the foil layer, causing the vapors to form a strong shock that rapidly transmits stress waves (compression to the right side of the diagram). The foil, as a consequence, experiences very high speed plastic deformation which launches the sprinkled particles (drug substance, say) on to a receiving end (labeled 5). This conceptual particle launch system or a micro drug delivery system which uses laser shock focusing technique is being studied[3]. The numerical simulation shown in Fig. 5(b) is a generic explosively driven plate impact simulation that shows how a plate deforms as a result of detonic wave passing through it. The pre-impact condition or the upstream shock strength and velocity in both cases are on the orders of 10 GPa and in thousands m/s, respectively. This similarity in the pre-impact condition is what motivates the use of the multi-material shock physics code, *GIBBS2D*, in analysis of modern bio-medical

science.

We are developing constitutive models for human skins and organs that may represent receiving ends on the shock impact system. To a certain limit, human skin may be considered rubber elastic and thus can be modeled as a compressible Mooney-Rivlin rubber material or a Blatz-Ko material. The Blatz-Ko elastic model is used for large strains experienced by the impacting detonation wave. The Blatz-Ko formulation yields a slightly compressible material. Only one input parameter is required, and therefore this model may be useful when detailed test data is not available for the material of interest, as in the case of human skin. A single or multiple Lagrangian particles are introduced on the surface of foil plate. Each particles limited to a few tens in numbers advect with the local flow velocity. Given the explosive launching speed at the foil surface, particles immersed in the vacuum region between 4 and 5 would be propelled out on to the receptor labeled 5.

Like all other multi-material dynamic simulation, careful modeling of each material is important. The laser-focused shock wave generation is modeled by a detonator. The aluminum foil is modeled as a ductile material whose elasto-plastic properties are well known. Particles are so called passive scalars that are simply 'sprinkled' on the outer layer of metal for tracking and thus visualizing of the motion of local flow velocity. The gap between 4 and 5 is modeled as a vacuum, whose numerical model was described earlier. The receiving end of the system labeled 5 is varied depending on the type of applications. Rat's liver as experimented in [3], or a composite structure of typical human skin is a possibility. Our current research focuses on building such models for comprehensive dynamic numerical simulation of micro particle (e.g. drug) injection onto human skin.

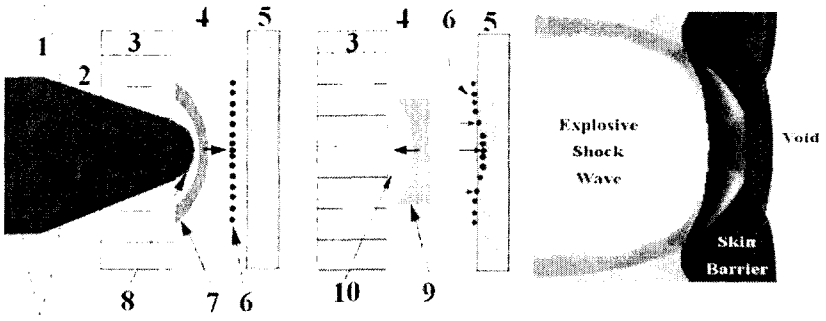

Fig. 1 Illustration of shock-metal-skin (rubber) impact process. (a) Laser ablation and foil/particle acceleration[3]. (b) Detonic wave impact simulation involving modeled skin (Blatz-Ko elastic rubber) using *GIBBS2D*[4].

4. CONCLUSIONS

We have outlined a methodology for simulating the micro particle acceleration for drug delivery using the *GIBBS2D*, our research code for shock physics simulation involving energetic materials. Models for materials (biological and artificial) were briefly discussed with a plan for full simulation.

Accurate modeling and simulation of micro-particle injection via shock wave is only a beginning of general applications of *GIBBS2D* in the bio-medical engineering field. Nearly every application in the field involves contacts, between two similar or distinct materials that are often times immersed in another fluid. Correct modeling of such composite materials (organs or skins) and the intermediate fluid such as body fluid or blood is required for successful computational analysis of the bio-medical engineering experiments that offer great promise for future scientific innovation.

Work is on the way to add Lagrangian particles[8,9] to the material interface region where improved accuracy is desired. A comparison of tungsten metal injection test data against the *GIBBS2D* calculation result will be reported in the forthcoming paper.

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