The NLM Visible Human Project and the DARPA Virtual Soldier Programs

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Registered Visible Human Female Data Displayed in Applets
Simulation: The Third Pillar of Science

• **Traditional scientific and engineering method:**
  1. Do **theory** or paper design
  2. Perform **experiments** or build system

• **Limitations:**
  – Too difficult—build large wind tunnels
  – Too expensive—build a throw-away passenger jet
  – Too slow—wait for climate or galactic evolution
  – Too dangerous—weapons, drug design, climate experimentation

• **Computational science and engineering paradigm:**
  3. Use high performance computer systems to simulate and analyze the phenomenon
  - Based on known physical laws and efficient numerical methods
  - Analyze simulation results with computational tools and methods beyond what is used traditionally for experimental data analysis
High-end simulation in the physical sciences = 7 numerical methods:

1. Structured Grids (including locally structured grids, e.g. Adaptive Mesh Refinement)
2. Unstructured Grids
3. Fast Fourier Transform
4. Dense Linear Algebra
5. Sparse Linear Algebra
6. Particles
7. Monte Carlo

• Benchmarks enable assessment of hardware performance improvements
• The problem with benchmarks is that they enshrine an implementation
• At this point in time, we need flexibility to innovate both implementation and the hardware they run on!
• Dwarves provide that necessary abstraction

Map Reduce

Slide from “Defining Software Requirements for Scientific Computing”, Phillip Colella, 2004
History of VHP

• Roots were the 1986 long-range planning effort of the National Library of Medicine.

• August 1991- Contract was awarded to the University of Colorado@Denver with Victor M. Spitzer, Ph.D, and David G. Whitlock, M.D., Ph.D.

• Launched July 1995

• Next Generation Internet Contract to UMich in 1997 to put VHP onto the Internet
AIM OF VHP

• Initial Aim: Create a digital image data set of a complete male and female cadaver in MRI, CT, and anatomical modes.

• Long-term Aim: Link the print library of functional-physiological knowledge with the image library of structural-anatomical knowledge into one resource of health information. Extended by DARPA Virtual Soldier Project, 2003-2005.
VHP

- Public access with Internet Male and female cadavers
- Visible Human Explorer (VHE)-direct manipulation user interface
- 2 orthogonal 2D cross-section views: coronal section and front-view longitudinal (head to toe)
- Miniature version of VHP( 20 MB)
Male Cadaver

- MRI, CT, and anatomical images
- 1 mm intervals
- 15 gigabytes
Female Cadaver

- MRI, CT, and anatomical images
- Intervals at 0.33 mm
- 40 MB
Integrative Informatics Challenge: Synthesis of Knowledge at Multiple Levels (Spatial and Temporal)

- Populations
- Patients
- Organs, Tissues
- Cells
- Molecules, Genes

- Public Health Informatics
- Medical Informatics
- Medical Imaging/Modeling
- Systems Biology
- Bioinformatics

- Multiscale Science
  - Epidemiology
  - Phenotypic Stratification
  - Genomic Understanding

- Mesoscale Science
  - e.g. NanoBiology NanoMedicine
How best to move from the Macroscopic to the Microscopic  
*Top-down vs. Bottom-up*

- NLM UMLS Semantic Network + the “Semantic Web”  
  W3C and Science Commons

- NLM UMLS/Snomed-CT(Linked to ~50 Others)

- Foundational Model of Anatomy (FMA)

- Cells
  - Proteome
  - Gene Regulation

- Gene Expression

- Neurons
  - Gene
  - Expression

- “Systems Biology”
- “Biological Systems”
- “10^9”
- “Physiology/Function”
- “High Throughput Structural Biology”

- Organs & Tissues

- Genes

- Populations
  - Phenotypes
  - Geneotypes

- Bioinformatics Databases and Data Standards (Genome Ontology, MIAME)
Background: The Visible Human Project in the 1990’s
Medical Teaching Theatre to Internet Collaboratory
Visible Human Project: Linking Rendering and Labeling enabled Web-based “Navigation” in the late 1990s
The Digital Human needs to be extended to integrating subsystems. Early work from the mid-1990s.
Multi-scale Human Anatomy is Described by the Foundational Model of Anatomy (FMA)

University of Washington, Michigan and Stanford University
DARPA Virtual Soldier Project Objectives

Build a Virtual Soldier on an Electronic “Dog Tag” to Diagnose and Predict Combat Injury

WHY?
Quickly & Accurately diagnose internal combat injury (Heart)

HOW?
Build Predictive models from total body scan on “Dog Tag” (3-D Anatomy & Physiology)
Compare to data acquired on the battlefield after wounding (CT, Physiology, and other key data)

Predict likelihood of battlefield mortality

“Holographic” Medical Electronic Representation
Holomer

Accurate Diagnosis & Treatment Saves Lives

FOR THE INDIVIDUAL SOLDIER THIS MEANS:
Empowering the individual medic at the point of wounding to make a diagnosis of an injury with the same expertise as having an expert surgeon on site.
Functional Overview of the DARPA Virtual Soldier Project

**Preparation**
- Detailed Individual Medical Records
- Store records on "dog tags"
- Build computer model of "generic" patient

**Post wounding**
- Post wounding information
- Pre-wounding information
- Use pre and post wounding individual data to create predictive model of specific patient
- Computer model provides total informational awareness for forward medical team
DARPA Program Manager Goals for Virtual Soldier Project (as interpreted by PI)

- Develop a 21st Century medical record for the soldier that is not print-based, but instead instantiates a full hierarchal model representation of the patient: “The Holomer”
- Provide support for the Medic at the time of wounding (improve ability to assess warfighter status—triage)
- Provide support for “downstream” surgery team: “practice” on a virtual representation of the injured soldier
- Jump-start the Digital Human Project for transfer back to NIH by establishing a “dream team” of researchers from academia, industry, and government labs
DARPA Virtual Soldier Team

General Electric Corporation
ATK Mission Research Corporation
Crowley Davis Research
Xtria, LLC
SanDisk, Corp.

University of Michigan
Stanford University
University of Washington
University of Utah
UCSD
San Diego State University
University of South Carolina
Harvard University
Highly Integrated Physiology (HIP) Models Provide Global Context (University of Washington)

James Bassingthwaighte
Highly Integrated Physiology (HIP) Modeling Objectives

- Create ordinary differential equation (ODE)-based whole body models for simulating clinically relevant human and porcine physiology.
- Use UW's JSim simulation system to code models, provide system and models to other institutions (ORNL, UCSD, U. Michigan, Stanford)
- Parameterize model to reflect normal resting human physiology
- Enable simulation of cardiovascular penetrating injuries to the heart
- Parameterize model to match specific baseline and post-injury data gathered from porcine experiments at ISR
- Use model simulations in conjunction with statistical methods at the University of Michigan to aid in prediction/simulation of battlefield wounds
- Support UW knowledge representation team by providing HIP model as a collection of entities that will help inform the structure of the Virtual Soldier Knowledge Base (VSKB)
Highly Integrated Physiology (HIP) Model Outputs were Expanded to:

Pressures, volumes, forward flow and radial flow in the:
• Left atrium, Left ventricle, Proximal aorta, Distal aorta, Systemic arteries, Systemic arterioles, Systemic capillaries, Systemic veins, Vena cava, Right atrium, Right ventricle, Proximal pulmonary artery, Distal pulmonary artery, Small pulmonary arteries, Pulmonary capillaries, Pulmonary veins, Proximal epicardial arteries, Distal epicardial arteries, Large coronary arteries, Small coronary arteries, Coronary capillaries, Small coronary veins, Large coronary veins, Epicardial veins, and Pericardium (injury flow)

Pressures, volumes, forward flow, radial flow, [O2], [CO2], and [N2] in:
• Upper airways, collapsible airways and alveoli
• pO2, pCO2, pH, [HCO3] and [Carbaminohemoglobin] in the aorta and pulmonary artery
• Diffusion capacity of O2, CO2 and N2 across the alveolar membrane
• Heart and respiratory rates
• Heart chamber elastances

Injury specifications:
• Conductances of penetrating “wounds”
• Blood in pericardial space
• Blood lost from circulation

363 variables and 75 Ordinary Differential Equations were included in the HIP models
Subject P87 data curves (thick) and corresponding HIP model fits (thin)
Physiological Status Monitor Displays
Baseline Data and Response

- Store/replay (forward and backward) physiological response
- Developed to understand comparison of modeled with real data
- Developed by Visualization team: U Utah, U Michigan, and ORNL
3D Finite Element & Multiscale Models provided by UCSD, the University of Auckland, and the University of Utah
Scientific: Developed and validated anatomically and biophysically detailed 3D models of ventricular electromechanics in interaction with functionally integrated comprehensive models of circulatory physiology to model trauma.

• An accurate finite element geometry of porcine left and right ventricle with a realistic myofiber orientation from Auckland University was used to solve cardiac electromechanics. General Electric provided porcine-specific geometries.
• Modeling of excitation-contraction and mechano-electrical feedback by coupling cellular ionic models to models of myofilament activation and crossbridge formation in combination with a mono- or bi-domain formulation of propagation.
• Simulated transmembrane potentials were used by University of Utah to calculate potentials on the porcine torso. Torso potentials are measurable and served as a means of tuning and validation.
• Complete integration of ventricular electromechanics and circulatory model from University of Washington, such that the FE model is the driving force of the circulation.
• Geometry of porcine left and right ventricles scaled to match specific subjects acquired from porcine CT scans (ISR)
• Realistic myofiber architecture: spans scales of cells, tissue and organ
• Local cellular properties based on detailed ionic-currents and realistic excitation-contraction coupling mechanisms
• ECG simulated by solving the bioelectric forward solution in a 3-component model of the torso, heart, and lungs
• Nonlinear, anisotropic 3D passive and active material properties
• Ventricular hemodynamics determined by highly integrated circulatory model initialized from and tuned to empirical data (ISR)
• Penetration wound modeled based on MPM results and coronary perfusion model (Auckland) by decoupling cells electrically, altering ionic currents and inhibiting active contraction around site of wound
• Reduction of contractility based on regional perfusion measurements (ISR)
• Real-time visualization done using a unique multi-mesh interpolation scheme triggered by the highly integrated circulatory model
Algorithm for 3-D Electromechanical integration

Level 2b - Circulation model
  LV/RV pressures
  LV/RV flows
  Pressure estimation algorithm
  LV, RV pressures and volumes

LEVEL 1 - Crank-Nicholson
  Galerkin solution of Mechanics PDEs

LEVEL 2a - Crank-Nicholson
  Collocation Solution of Propagation PDE

LEVEL 3 - Implicit RK
  Integration of cell dynamics

First ½ time step - Cell Systems ODEs
  Ionic Currents
  Calcium Fluxes
  Thin Filament Activation
  Crossbridge Cycling

Second ½ time step of Level 2 - Voltage PDE Solution
  Change in Membrane Voltage

Stress Calculation

Colors denote time and space scale differences. Level 1 is the largest. Dashed lines indicate data flow across problem levels.
Comparison between Simulated (−) and Experimental Data (▲)

Rotational Angle versus Time

Rotation Angle (Degrees)

Time (microseconds)

-200

-180

-160

-150

-125

-100

-75

-50

-25

0

0

50

100

150

200

Wedge Orientation at Impact

360 microseconds

1.230 milliseconds

Posttest Wound Tract
Stress Contours on LV Surface at 95 milliseconds after impact. Peak stress is 20 bars.
Total Penetration Depth vs Striking Velocity

- Low Velocity Asymptote can be reconstructed from quasistatic material properties which is available for human tissue.
- High Velocity Asymptote can be reconstructed from material densities which is available for human tissue.
- Intermediate Velocities can be deduced from matching slopes of the high and low velocity asymptotes.
Heart

- Anatomically accurate porcine heart
- Discretized into ~1.5 mil material particles
- Modeled as a transversely isotropic hyperelastic material: an isotropic matrix reinforced by an elastic fiber family (fiber directions vary through the wall thickness)
- A two-surface strain failure criteria is embedded in the model

Projected fragment (or shell casing)

- Modeled to experiment specific geometry
- Elasto-plastic (metallic) material model
- 76 ft/s initial speed
- Frictional contact enforced between tissue and probe
Holomer Wounding Location based on SCIRun Visualization Environment

VSP Interface

List of tissues adjacent to probe (arrow) in lower right lobe of lung

SCIRun display of thorax model
Kalman Filter-based Statistical Prediction Engine
The 31 model development experiments ISR conducted before November 30th, 2004 constitute the "model development" set used to develop and refine procedures and gain familiarity with the data.

The 46 experiments ISR conducted between November 30, 2004 and April 28, 2005 were divided into the following three groups:

- 25 analyzable open chest experiments (regular ECG and full instrumentation);
- 3 analyzable closed chest experiments (60+ lead ECG and limited instrumentation); and
- 18 experiments un-analyzable according to criteria established in advance (incomplete or missing data, time to death of 10 minutes or less).
Phase Space Representation of Experimental Data

Key:
- **(A)** Subject, **(B)** time of death
- **(C)** time of alarm
- **A** = Subject, **B** = time to death, **C** = time of alarm(s)
- **W** = wounding
- **●** = alarm

All times are minutes post-injury, baseline generally starts in upper-right-hand corner.
Statistical Display Details

- A green circle indicates that the subject is expected to survive.

- A red octagon indicates that the subject is expected to die within a relatively short period of time and there is no time for interventions to change the outcomes.

- A yellow triangle indicates that the subject is expected to die, but there is time to intervene to change the outcome.

- To the right of the icons, text gives the percentage probability of survival or death and if death is the forecast an estimate of time to death in minutes.
Within the set of 14 non-quarantined analyzable open chest fragment experiments the Statistical Analysis showed:

- Detected an alarm in all 8 non-survivors and no alarm in all 6 survivors (100%)
- Correctly forecast death or survival for 13 of 14 (93%) at 4 minutes post-injury
- Forecast a TTD correlating 0.75 with actual TTD for the 7 non-survivors still alive at 20 mins. post-injury
- Forecast a TTD of 21 mins. ±9 mins. at 20 mins. before actual death for 6 non-survivors that lived >25 mins.
- Forecast a median TTD of 30 mins. from first alarm for all 8 non-survivors vs. the actual median TTD of 24 mins.
- Within a test subset of 6 non-quarantined analyzable open chest fragment experiments:
  - Correctly identified injury location (LV vs. RV) for 5 cases with one ambiguous result (83%)
VSP Causal Reasoning Model
Machine readable ontologies enable reasoning which can provide the ability to ask "what if?"

Virtual Soldier Knowledge Base (VSKB)
- extended Foundational Model of Anatomy (eFMA)
- Pathology Reference Ontology (PathRO)
- Physiology Reference Ontology (PRO)
Symbolic Reasoning in Final Demonstration

- Inference of damaged anatomic structures (both primary injuries and injury propagation) based on a wound description or spatially-oriented patterns of tissue strains. Raw data tell the field medic little about the war fighter’s internal injuries. Stanford reasoning services provide the field medic with needed insights.

- Developed a software platform to integrate anatomic knowledge with geometry data from image label maps. We created reasoning services using OWL, an emerging standard in knowledge representation that permits automatic classification, to deduce primary and propagated injuries.

- Created a system to demonstrate our reasoning capability. A user specifies the trajectory of the projectile, and the application infers the anatomic structures that are directly injured as well as secondary injuries.

- These reasoning services can be used to provide the field medic decision support, and they can be combined with patient physiological and anatomical data to enhance triage and increase survivability of battlefield casualties.
Anatomy from Anatomy Forecast and Comparison to Autopsy Findings

- Analyze postmortem image data, including:
  - porcine CT images from ISR,
  - postmortem isolated heart CT images from ISR,
  - manual segmentation by UW,
  - smoothed, segmented, and labeled anatomy from GE,
  - the Virtual Soldier Knowledge Base (VSKB) from UW, and
  - autopsy reports from UW
- Determine which anatomical structures are injured
- Display information for use by the medic/physician
- Compare forecast and autopsy results
- Results of comparison show ability to predict injury from segmented image
Anatomy from Anatomy Data Flow Diagram
General Electric Corporation
Automatic Segmentation
Data Compression and Transfer Rates onto DoD B-MIST Platform

Transfer time is reduced significantly with compression.

3 min 9 sec to complete compressed file transfer
6 min 29 sec to complete un-compressed file transfer
Models of Electrophysiological Responses to Regional Injury

UCSD and University of Auckland

Regional coronary blood flow

3D visualization of the Electrical Finite Element results

8.4 240 msec

3D visualization of the Mechanical Finite Element results
Phase I Final Demonstration
Ann Arbor, Michigan
June 14, 2005

90 Second Video

DARPA
U.S. Army MRMC/TATRC
University of Michigan
ATK-Mission Research
Brigham and Women’s Hospital
Case Western Reserve University
Crowley Davis Research
Federation of American Scientists
General Electric Research
Oak Ridge National Laboratory

Stanford University
University of Auckland
University of California San Diego
University of South Carolina
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