Biomaterials, Biomimetics and Biological Interfaces Research at the Oak Ridge National Laboratory

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Outline

- Biomaterials
  - Biocompatible Materials
  - Materials Science Approach to Characterizing Biological Materials
  - "Hybrid" Biomaterials
  - Biologically Produced Materials
- Biomimetics
  - Mimicking Biological Processes
  - Mimicking Biological Function
- Biological Interfaces Research
  - Interfaces with Materials (Signal Processing/Propagation)
  - Interfaces with Computing (Modeling Biological Function)

Outline

- **Biomaterials**
  - **Biocompatible Materials**
    - **Bio-ceramics (synthetic bone and implant materials)**
  - **Materials Science Approach to Characterizing Biological Materials**
    - **Residual stress analysis of bone**
  - **"Hybrid" Biomaterials**
    - **Bio-ligand-grafted polymers**
  - **Biologically Produced Materials**
    - **Bacterial magnetite crystals**

Outline

- **Biomimetics**
  - **Mimicking Biological Processes**
    - **Biomimetic process for inorganic thin-film growth**
  - **Mimicking Biological Function**
    - **Virtual human**

Outline

- **Biological Interfaces Research**
  - **Interfaces with Materials (Signal Processing/Propagation)**
    - **"Critters on a chip"**
  - **Interfaces with Computing (Modeling Biological Function)**
    - **Critters on a chip example**
    - **Virtual human**

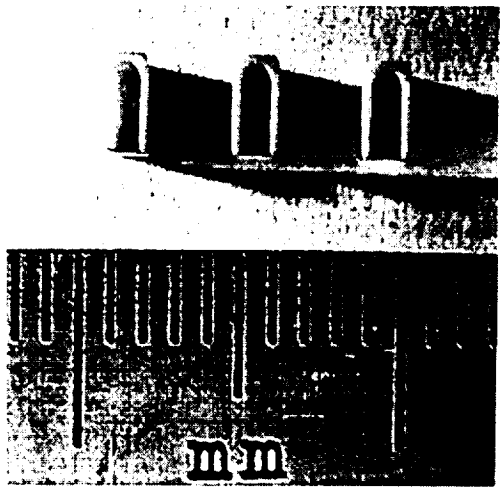
Biomaterials

- **Biocompatible Materials**
  - **Bio-ceramics (Synthetic Bone and Implant Materials)**
    - **Better biocompatible materials and composites**
    - **Formation of synthetic bone and dental materials using ceramic microsphere technology**
      - **Mimics natural porosity**
      - **Encourages vascularization and osteogenesis**
      - **Appropriate materials properties (strength, density, etc.)**

Biomaterials

- **Biocompatible Materials**
  - **Bio-ceramics (Synthetic Bone and Implant Materials)**
    - **Better biocompatible materials and composites**
    - **Net-shape forming of prosthetic devices, including rapid manufacturing**
    - **Gelcasting of ceramic mimics of bone for implants**
      - **Hydroxyapatite, alumina, zirconia, tricalcium phosphate, etc.**
      - **Can be cast to near net shape**
      - **Can control porosity**
      - **Very rugged process**
      - **Meets FDA requirements for implantation (phase content: >/= 95% HA;**
      - **</= 5% beta-tricalcium phosphate)**

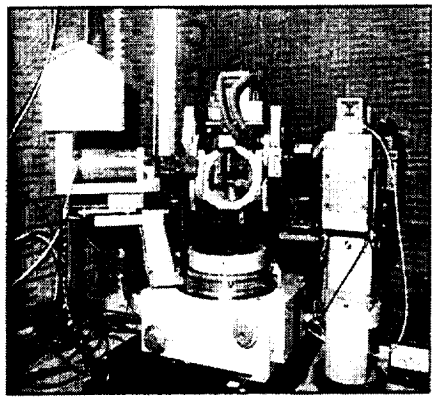
Ceramic Gelcasting of Bone Mimics



Biomaterials

- **Materials Characterization—Residual Stress Analysis**
  - **Abalone as a Model System**
    - **Watch change in lattice parameters in mineral phase**
    - **Neutrons allow one to surmise what is going on in the proteins**
  - **Natural Bone**

Biomaterials Characterization



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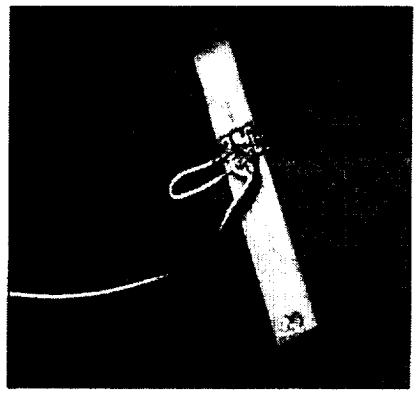
Biomaterials Characterization



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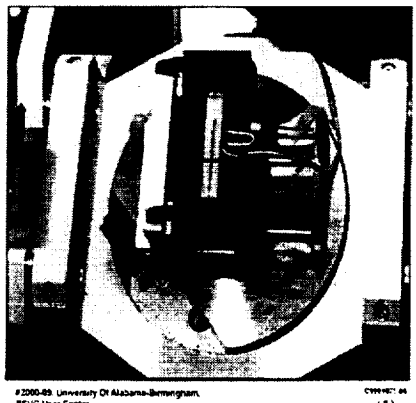
Biomaterials Characterization



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Biomaterials

- "Hybrid" Biomaterials
  - Biochemical Ligands Covalently Grafted to Polymer Structure of Polyurethane
  - Gel or Foam Structure of Final Materials
    - Ability to create high-specificity materials for chemical separations involving metal cations, radionuclides
    - Mimics natural biomolecular recognition properties of ligands from biochemical sources

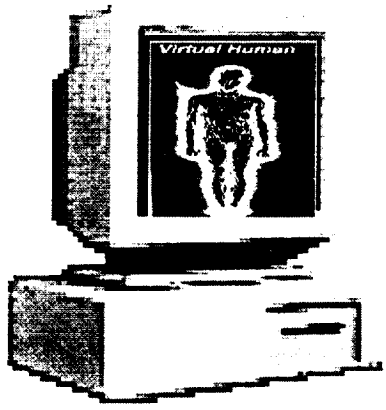
Biomimetics

- Mimicking Biological Processes
  - Biomimetic process for inorganic thin-film growth

Biomimetics

- **Mimicking Biological Function**
  - **The virtual human (the ultimate biomimetic!)**

Vision



- **Model the Human**
- **Link Biology with Physics and Chemistry**
- **Structure and Function**

Vision (Cont'd.)

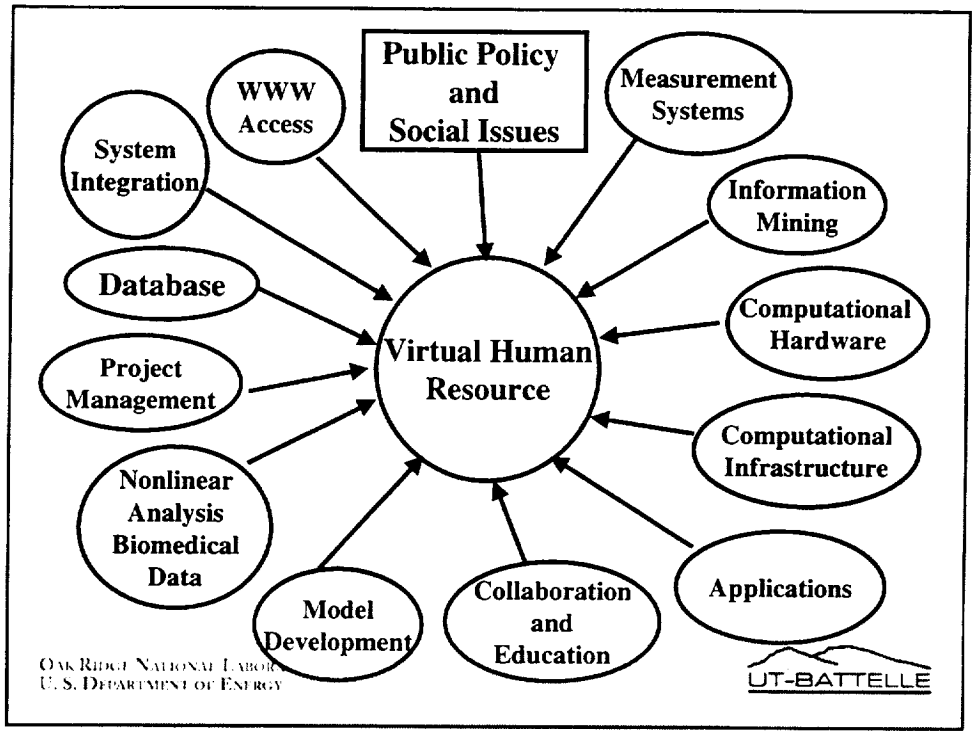
- Complete System Consistent with Current Science (Physiological and Cognitive)
- Collaborators Retain Ownership of Work
- Contribution From Oak Ridge National Laboratory
  - Catalyze idea
  - Integration
  - Specific modeling
  - Instrumentation/data

Functional Goals of Virtual Human Year 0+ 5 to 10

- Scalable by Age and Gender
- All Organs, Full Anatomy and Physiology
- Limited Pharmacokinetic Capability
- Radiation and Chemical Risk
- Biophysical Constants (Tissue Properties)
- Blood Flow, Breathing, Endocrine, GI, Renal, Sensory, Thermo-regulation, Shock, Limited Brain Function

Functional Goals (Cont.'d)

- Specific Disease Information
- Duplicates Physiology Tests
- Incorporates Certain Patient-Specific Data
- Emphasize Diagnostic Assistance
- Patient Education and Teaching Tool
- Fast Forward Capability



ORNL's Vision of Virtual Human Initiative

Simulate Human Biology to Advance Our Understanding of Complex Biological Systems

- **Infrastructure (National Resource)**

  Computational Infrastructure to Facilitate Use of Data and Models

- **Integration**

  Data and Models

Virtual Human Initiative Meeting National Academy, 28 Oct 1999

- **45 Attendees**
- **Presentations of Vision by Scientific Panel**
- **Responses by Agency Representatives**
- **Conclusion: To request that a report on the Virtual Human Initiative be prepared by the National Academy.**

What's Coming in the Near-Term?

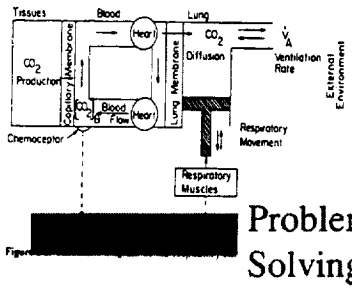
- Focused Workshops
- Kinetic Energy Effects
  - Current models
  - Active sources of data
  - Legacy models and data
  - Workshop designed to build database
  - Develop links between disparate data
- Series of Gordon-Like Conferences

Brief Glimpse of Work On-Going at ORNL

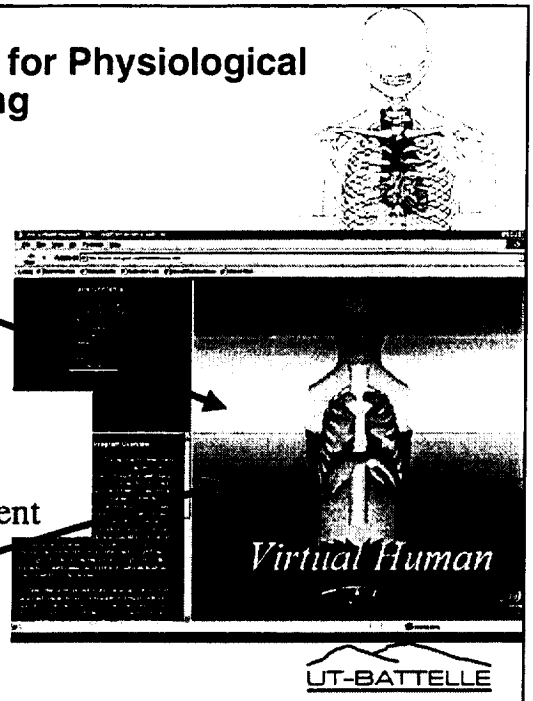
Three General Options Present Themselves:

1. Develop infrastructure that allows communication between models
2. Attempt to directly link existing models
3. Develop infrastructure that serves as unifying feature for future models

Integrated Environment for Physiological and Anatomical Modeling



Problem Solving Environment



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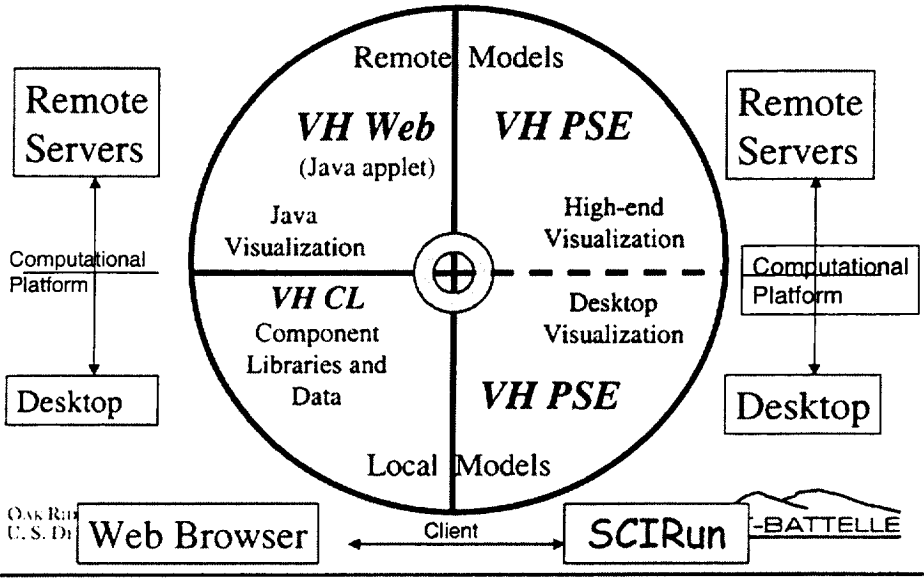
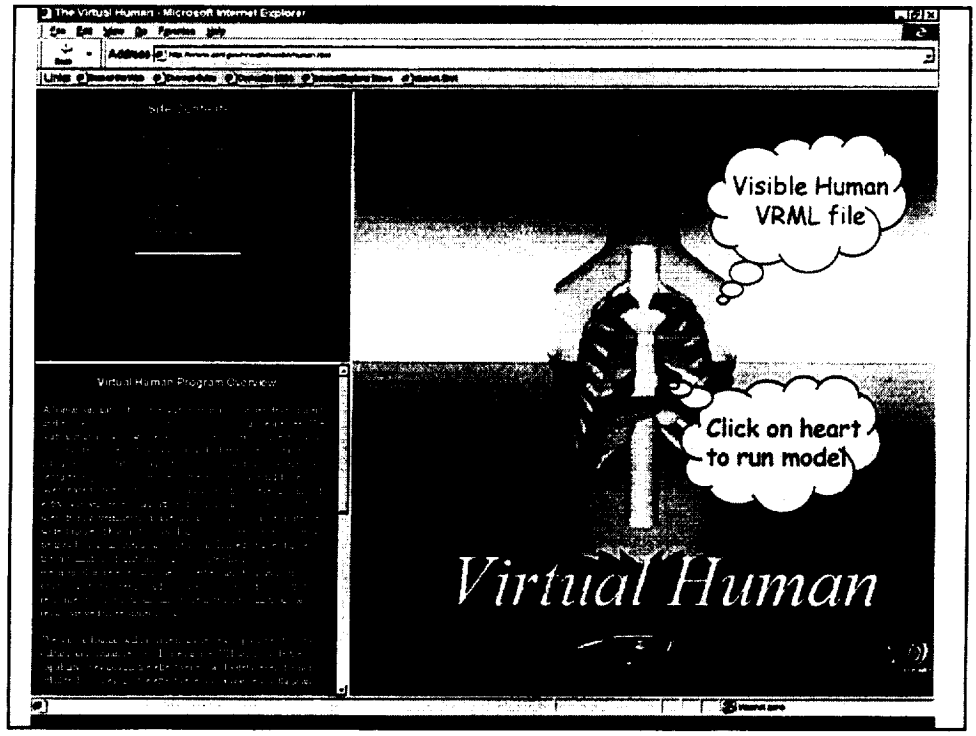
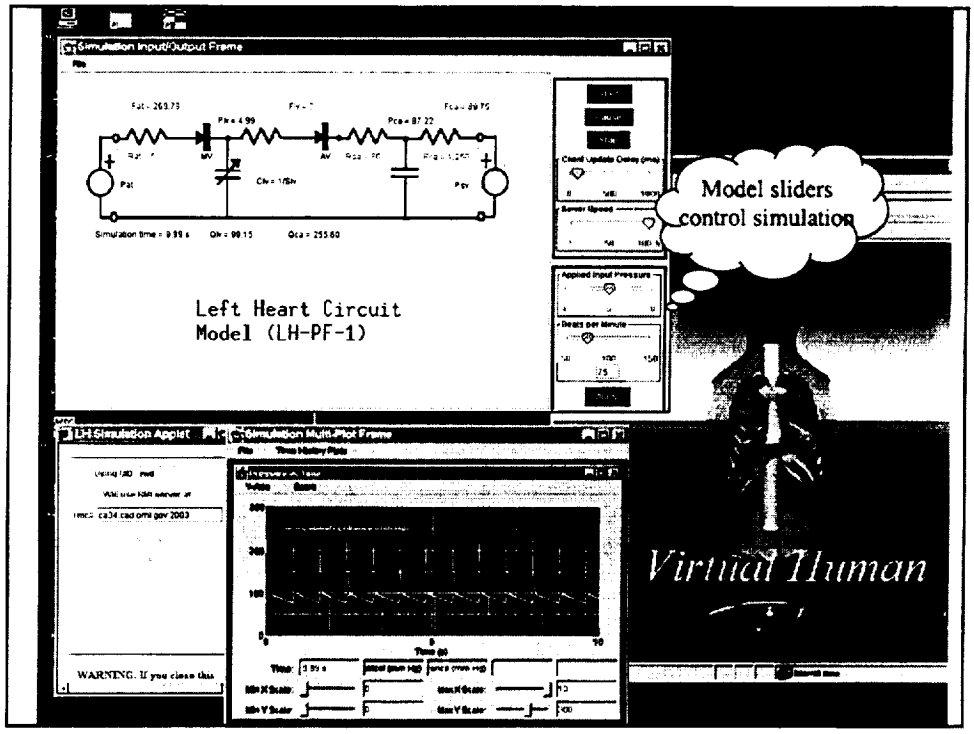
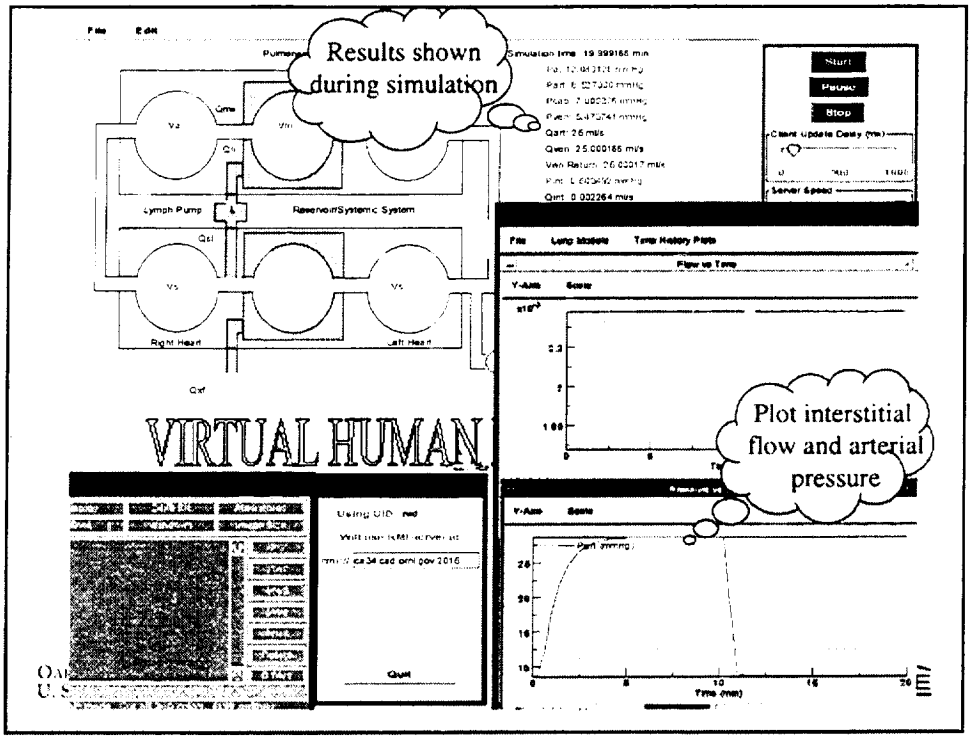
Virtual Human Portal

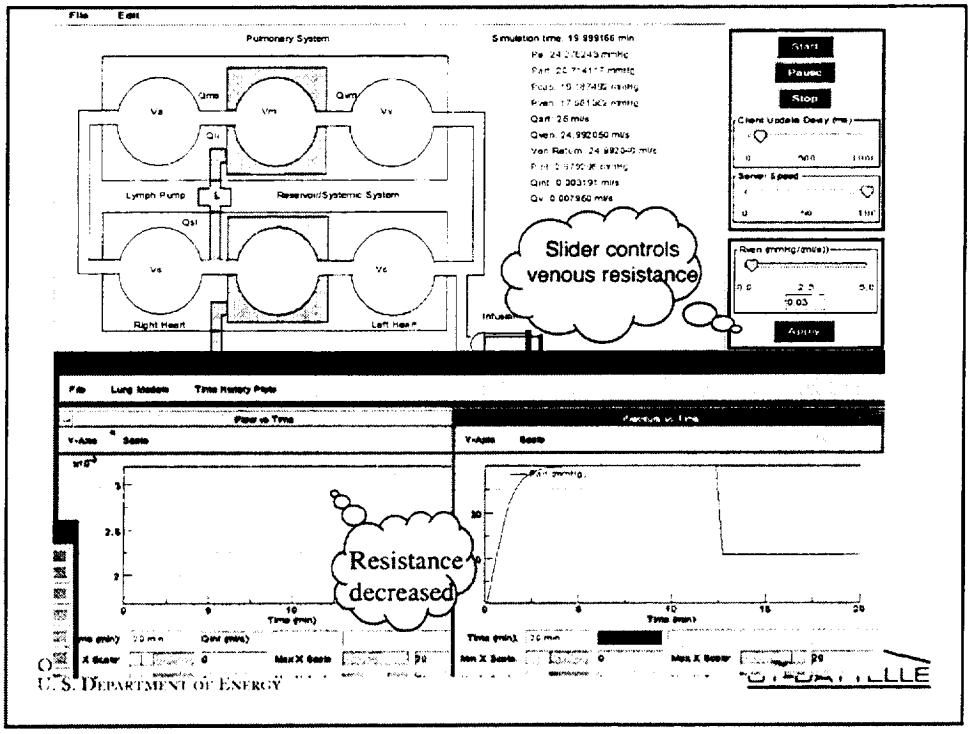
ornl




Visible Human
VRML file
Click on heart
to run model
Virtual Human


Left Heart Circuit
Model (LH-PF-1)
Model sliders
control simulation
Virtual Human


Results shown during simulation
VIRTUAL HUMAN
Plot interstitial flow and arterial pressure


Slider controls venous resistance
Resistance decreased
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Why Now?

- Confluence of Complementary Technologies
- Faster Networks and Communications
- Network Software Technologies such as CORBA, Java, XML, etc.
- "Big Science" is inherently distributed and collaborative, and needs to migrate to the Internet to progress.

Is the Type of Mathematical Approach Important to the Application?

- Application determines degree of complexity.
- Blunt trauma, testing military gear, forensic,... applications not requiring time series data... may not benefit significantly.
- Biomedical data... many types of data require chaos analysis to move beyond interpretation available 30 years ago.
- Applicability will change as understanding of human system matures.

Biomaterials

- Biologically Produced Materials
  - Magnetic nano-particle formation by bacteria from the deep subsurface
    - Extracellular metal reduction/precipitation/ crystallization
    - Iron reduction results in highly ordered nanocrystalline magnetite, maghemite, and siderite
    - Culture conditions affect phase mixture
    - Doping magnetite crystals with other metals (e.g., Ni, Co, Zn) is possible by adding them as soluble minerals in growth medium.

Biological Interfaces Research

- Interfaces with Materials (Signal Processing/ Propagation)
  - Whole-cell sensing and bio-computing in a microelectronic format ("critters on a chip")

Bioluminescent Bioreporter Integrated Circuits (BBICs)

CMOS IC-based whole-cell biosensors that detect chemical and biological agents.

- *Environmental monitoring*
- *Chem/bio hazard detection*
- *Therapeutic drug discovery*
- *Medical diagnostics*
- *Disease control/management*

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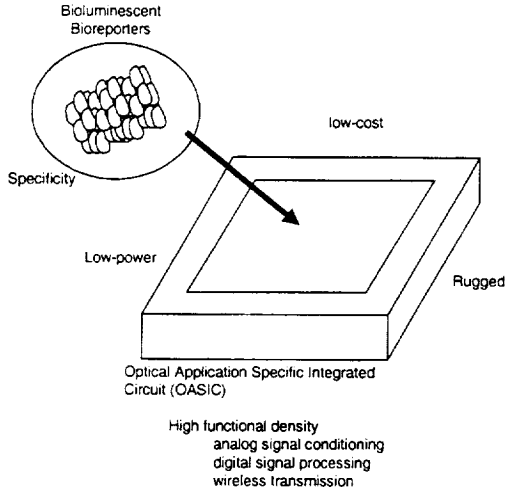
BBIC Concept



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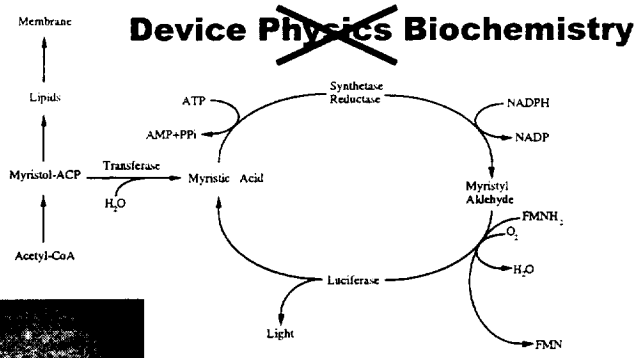
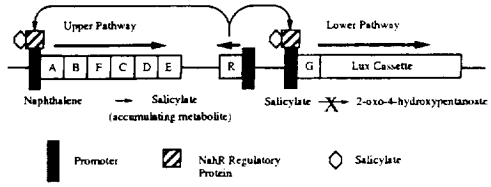
Device ~~Physics~~ Biochemistry

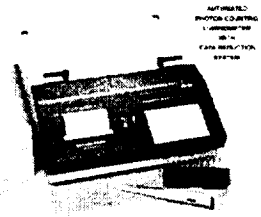
Note: no exogenous addition of substrate





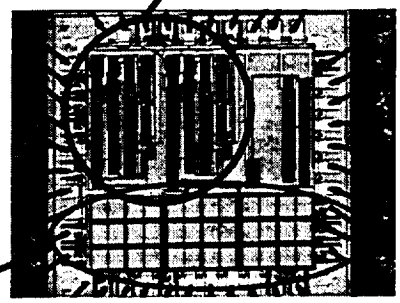
First Microluminometer Prototype

"Macroluminometer"
BG-250 LUMINOMETER



1.2-μm bulk CMOS process

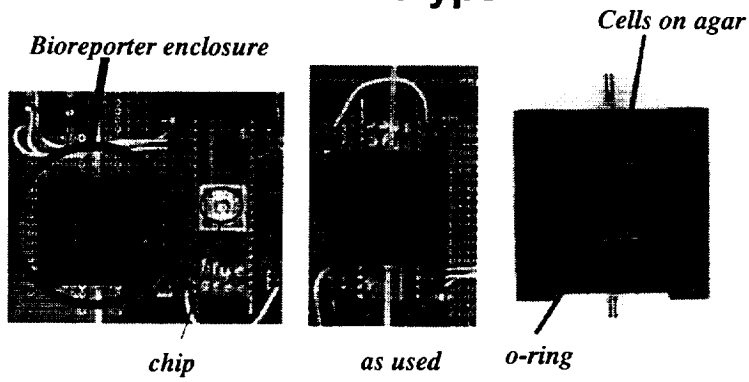
Signal processing



p-diff/n-well photo-detector

2.2 mm

BBIC Prototype

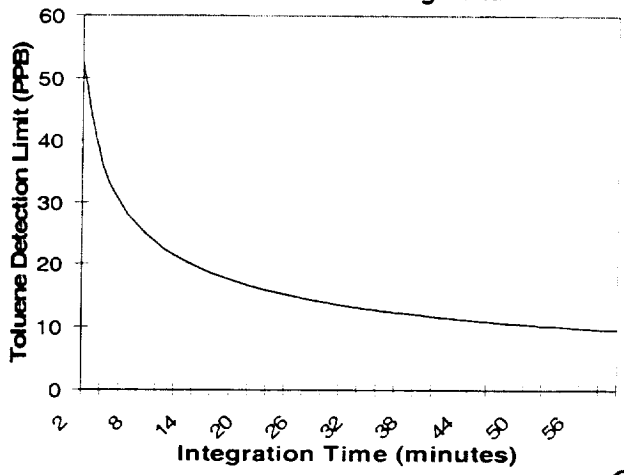


Reference

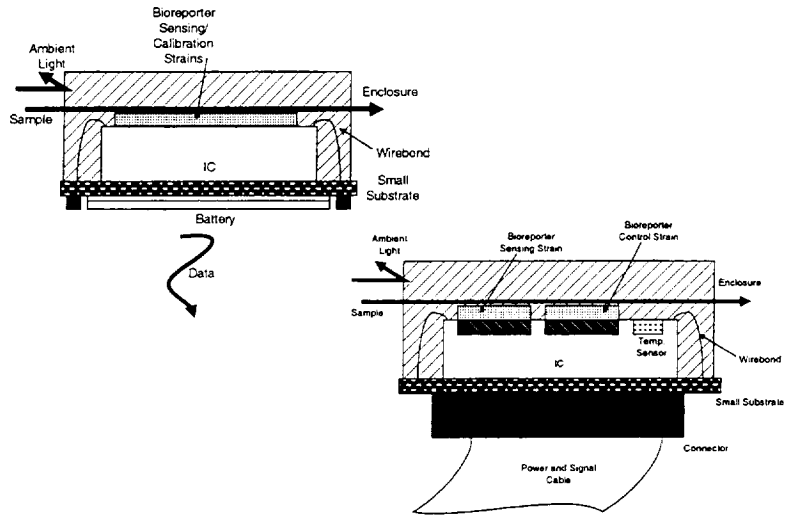
Simpson, Michael L., Sayler, Gary S., Ripp, Steven, Nivens, David E., Applegate, Bruce M., Paulus, Michael J. and Jellison, Jr., Gerald E., "Bioluminescent-Bioreporter Integrated Circuits Form Novel Whole-Cell Biosensors," (invited) *Trends in Biotechnology*, Vol. 16, August 1998, pp. 332-338.

Toluene Sensing: Pseudomonas Putida TVA8

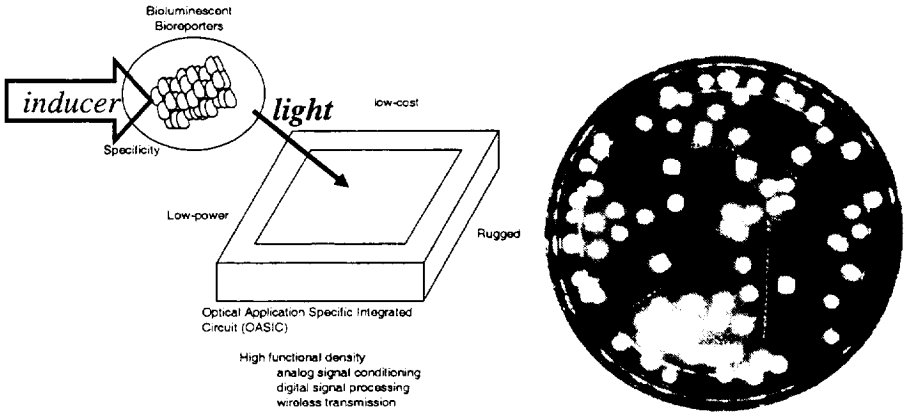
~1ppm toluene signal = 12 counts/minute
MDS = 2σ above background



Possible Embodiments

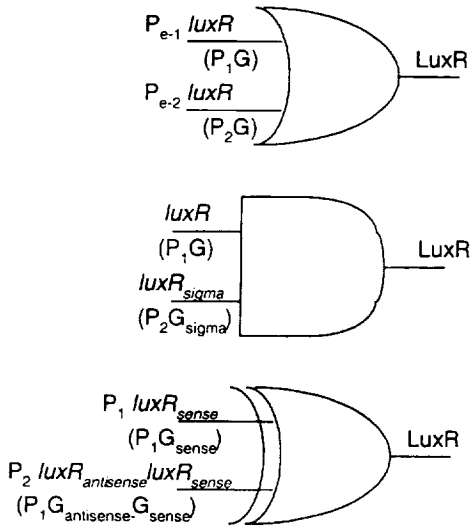


Bioluminescent Bioreporter Integrated Circuit (BBIC) Operates by Observing Single Gene Regulation



Can we do more?

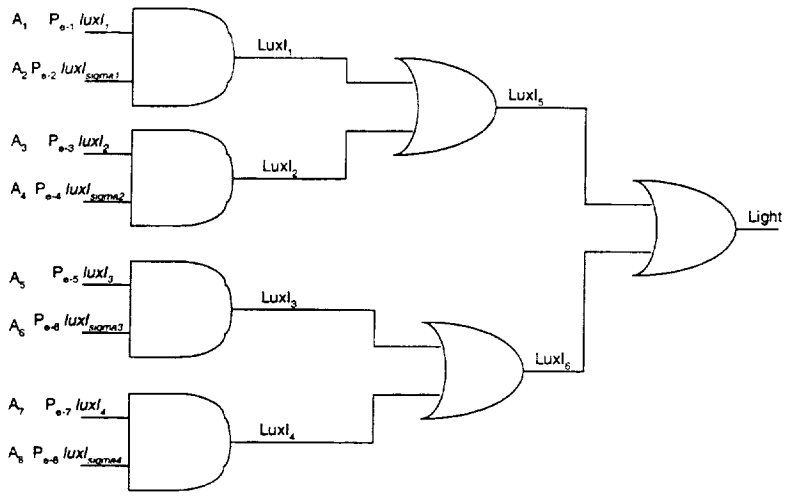
Engineered Information Processing in Whole Cells:
in vivo Combinatorial Logic



We can realize any combinatorial logic function with these three gates.

Latched devices can be made by adding feedback to these gates.

A Reporter Gene Multiplexer Made
with *in vivo Logic Devices*

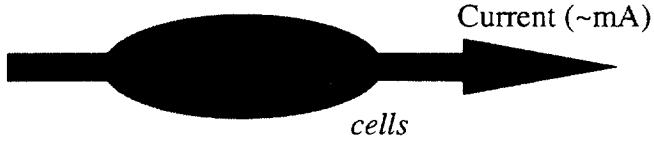


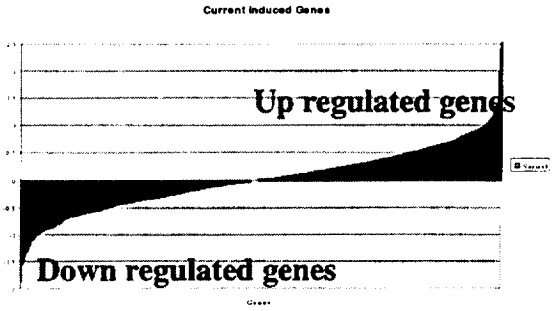
Communication to Cells

- *Chemical induction*
- *Thermal control of gene expression or enzyme activity*
- *Physical inducers (e.g., UV light)*

Question: **Could we control gene expression from a microelectronic chip?**

Electrically-Inducible Promoters?





Summary—Critters on a Chip

- *BBICs are novel whole-cell biosensors that combine the specificity of engineered bioluminescent bioreporters with the functionality, flexibility, and low cost of CMOS integrated sensor/circuit.*
- *We have developed a large number of bacterial and yeast bioluminescent bioreporters for BBIC sensing applications.*
- *We are now working to combine in vivo computing capabilities with the sensing functionality -- flexible, configurable, sensing devices.*

Biological Interfaces Research

- **Interfaces with Materials (Signal Processing/ Propagation)**
  - **Photon Bridging Between Biotic and Abiotic Components**
    - **Critters on a chip**
  - **Electron Bridging Between Biotic and Abiotic Components**
    - **Platinized Photosystem I particles**
      - **Hydrogen evolution**
      - **Sensing/biomolecular electronics applications**
- **Interfaces with Computing**
  - **Critters on a Chip Example: Biologically Based Logic Components**
  - **Virtual Human Example: Modeling Biological Function**