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The Computational Man: A Predictive Dynamic Model of Human Physiology

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14. ABSTRACT

We are developing the Computational Man, which is a dynamic and very fast-running numerical model that computes the time-varying transport of gases, liquids and solids in a human body. C-Man will consist of a coupled network of high-fidelity, reduced-order submodels, each representing a major physiological system, such as the circulatory, respiratory or excretory system. Each physiological system or submodel will be represented as an arbitrarily complex network of multiphase flows in flexible, interconnecting channels and chambers. This report presents the overall vision of the project, the approach, a discussion of the mathematical and numerical issues, and a collection of slides that have formed the basis of presentations in recent years.

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The Vision and Overview

We are developing the *Computational Man*, or *C-Man*, a calibrated, dynamic, and very fast-running numerical model that computes the time-varying transport of gases, liquids, and solids in a human body. C-Man can compute the physiological state and response of a human body to a range of conditions and environmental changes which may be natural, imposed, internal, or external. There are many applications of C-Man related to maintaining health and treating injury or illness. There are also many applications related to military circumstances, traumatic accidents, and space flight. C-Man's uses are only limited by our insight and imagination.

C-Man could be calibrated for an average human body, or for an average man, woman, adult or child. At this level, the model could be used as a tool for drug development and testing, to assess the physiological effects of changes in air quality and content, or to study how a human body responds to imposed or naturally occurring changes. C-Man could be used as an educational tool for students and professionals. If it included statistical distributions of parameters, it could be used to explore the bounds of possible body response.

Now suppose we calibrate C-Man to an individual person. At this level, it could be used to evaluate or prescribe specific treatments for injury or illness. Because it runs much faster than real time on a desktop computer, it could be used in an emergency to select and tailor medical procedures and drug doses. After quickly testing a number of scenarios, C-Man could suggest or even select an optimized treatment. Perhaps, in the future, C-Man could be put on a chip and worn by a person. Then it could be online permanently for real-time diagnostics and monitoring for injury, illness, contamination, poisoning, or preexisting medical conditions. In this case, it might detect small changes that indicate eventual catastrophic events and then send appropriate warning.

A possible objection to developing C-Man is that the current level of computational technologies is simply not adequate for the task. To respond to this, we take a step back and consider one of the basic ideas underpinning the process of modeling of any complicated system (see, for example, *Numerical Simulation of Reactive Flow*, Cambridge Press, 2001). It is not always productive or necessary to compute the behavior of a physical system in three dimensions and from first physical, chemical, and biological principles. What we need is the simplest model we can construct which has just *enough* accuracy.

There are two extremes of modeling complicated systems: a *global approach* and a *detailed approach*. In a global approach, we describe the large-scale system behavior using efficient, relatively simple models. A detailed approach is an opposite modeling extreme in which we focus on small-scale processes. At that level, we do not need, or perhaps cannot afford to look at the larger picture. The detailed approach is what is now applied to many biological systems. We see models

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of one system, or part of a system or organ. The hope in these cases is that, if we can compute a large enough system with enough detail, we will learn something new and useful about the organ or system under scrutiny.

A global approach is necessary, however, when we do not know or cannot afford to compute details. It is the approach to take first when global conservation laws and constraints are known, and hypotheses can be tested against observations and physical consistency.

The Approach

The Computational Man is a global model that combines many individual components. Each component itself is a calibrated reduced-order model of a specific physiological system. Our hypothesis is that if we construct models of individual physiological systems, calibrate them with just enough detail and the right level of physical and chemical complexity, and couple the interactions of these different physiological systems, we will be able to predict the behavior and response of the entire system much more quickly than detailed models while retaining a level of accuracy appropriate to the applications.

We are suggesting this approach for C-Man based on results we have obtained for other extremely complex reactive-flow systems, ones for which we know that there are myriad chemical reactions and many different physical processes. We have learned from experience that when a suite of calibrated, reduced-order models of these individual processes are coupled, the total model reproduces observations both qualitatively and quantitatively. This multilevel approach has two main advantages over straightforward detailed modeling. First, the resulting numerical model is many orders of magnitude faster. Second, a systematically constructed global model can actually be more accurate than a detailed model because it is calibrated to reality at many points. Because of this, predictions of these coupled reduced-order models have gone far beyond simple interpolation, but are valid for a considerable range of extrapolation.

For C-Man, we are constructing reduced-order models, which are functional representations of individual physiological systems, and then coupling these models together. Each of the main physiological systems is being described as a *physiological network*, which is a reduced-order, low-dimensional representation that incorporates key geometric and connectivity features of the actual system. Increasing complexity is added as more networks are coupled. As C-Man grows, initial functional models may be replaced as needed by more complex, calibrated numerical models and phenomenologies (see Chapter 3, *Numerical Simulation of Reactive Flow*). For example, it will not be necessary to describe, or even understand, all the electrochemical aspects of muscle contraction to make the muscle contract and relax correctly. Such features can be input at the level at which they are known and needed.

Mathematically, each network is represented by a set of coupled partial differential or integral equations with appropriate boundary conditions, sources, sinks, and constraints. For example, the circulatory system is described by a set of quasi-one-dimensional partial differential equations for an incompressible, viscous liquid, which is blood. Blood flows through a network representing veins and arteries ("channels") with elastic walls where there are multiple branchings to smaller and larger channels. All of this is driven by a fluid-dynamic pump that simulates a heart with valves. The respiratory system is a gaseous fluid system in which air is drawn through passages into the lungs, where oxygen is extracted and transmitted to the blood, and carbon dioxide is taken from the blood.

Circulatory, respiratory, digestive, excretory, and lymphatic systems involve material transport, and thus they can be described by mathematical formalisms and solution techniques called Asymptotic Flow Networks (AFN). These networks use conservative continuity equations to describe how the body moves and processes liquids, gases, and solids. For an AFN describing a circulatory system to compute thousands of heartbeats a minute of computer time, we require a time step to advance the model equations of 0.01 seconds or greater. To achieve this, changes in pressure gradients along a vein or artery must be modeled by asymptotic methods, and acoustic waves, which transmit change in pressure throughout a system, should be treated implicitly.

The muscular, nervous, endocrine, and other systems may require more complex treatments than thoseused for the initial flow-based networks, Initially, however, these are treated more simply as driving terms controlled by local models. An example is muscle contractions that drive the heart, which, in turn, drives blood circulation. To cause a chamber or channel to contract, it is not necessary to model how muscles actually work or how nerve pulses propagate. There must also be appropriate external driving terms and interactions specified among the networks. One such major coupling interaction is the transpiration of oxygen and carbon dioxide between the circulatory and the respiratory networks.

Each physiological system has to be developed first at a rudimentary level of description that allow for upgrades without changing the fundamental mathematical representation or numerical implementation. From the individual networks, we assemble the Computational Man – an interaction of physiological, reduced-order network models. Coupling of the separate physiological networks has to be done carefully, along with extensive testing of the complete, evolving global model.

From the mathematical and programmatic points of view, constructing the Computational Man involves setting up an efficient model for each system and coupling these with well-established numerical techniques. Previous work has given us implicit methods and asymptotic algorithms for quickly solving either complex networks of flows or electrical signals with many branchings, sources, and sinks. These can be solved quickly on current small-scale computers, and we can count on even faster speeds in the future. The target speed for C-Man to be operationally practical is that it runs 20 to 50 times faster on a computer than they actually take in real time – that is, thousands of heartbeats per minute.

Mathematical Issues and Numerical Issues

Based on our previous and current research, we believe there are enough data available in the literature to create this model. Much of the initial work in this project involved collecting and determining an adequate description of enough physiological systems, and many colleagues have contributed to this. We have been formulating the overall problem in the last few years and conducting numerical tests of possible representations and numerical methodologies. In doing this, we have been able to identify a number of mathematical and numerical issues that are being addressed in a more systematic way.

Mathematical issues include how to represent flow moving from a single large channel (such as an artery) to many small channels and then to smaller channels (such as small capillaries), and then back again to a large channel. This is the problem of a fluid undergoing a transition from a convective flow to a diffusive flow, and back again. Another important issue involves imposing different types of boundary conditions and constraints to represent real-world drivers on the differential equations.

Numerical and computational issues include efficiently solving many nonlinear, interacting set of equations and networks of equations, how to start with a simple system but build it in a way that allows it to evolve into a more accurate one, and how to represent phenomena on ranges of time and space scales. Another issue involves display and analysis of the resulting data in a form that can be tested against observation without severely degrading the performance of the model.

Chances of Success

When a hypothesis or theory is proposed, we cannot say *a priori* whether it is correct. It needs to be tried and tested against observation. Here we are dealing with two hypotheses.

1. *Hypothesis* – The human body can be described as a complex, dynamic, reactive-flow problem on a system of coupled networks.
2. *Hypothesis* – When these networks are created and allowed to function at a reasonable level of complexity, accurate overall behavior will emerge from the complex nonlinear dynamic system.

Whether or not these hypotheses are shown to be entirely correct, there is an enormous amount to be learned along the route about the individual physiological systems and about the nature of their coupling. This information can have many different specific biological and medical applications and the payoff can be huge if there is some level of truth in either of the two hypotheses.

There are a number of reasons why we are optimistic about success using this approach and its underlying philosophy. One is that we already have a prototype asymptotic-implicit model of the circulatory system. The description includes simple interactions with musculature through prescriptions for heart contractions and the operation of valves. This model can compute thousands of heartbeats per minute on a single laptop (2.8 GHz) processor. This model computes the velocity of blood flow by combining an asymptotic solution, based on local pressure gradients, with an implicit treatment of sound waves, which transmit dynamic pressure changes throughout the system. The model is constructed from segments with variable areas, branchings, and different types of valves.

Perhaps the most compelling reason for our optimism and confidence is that we have had success with two other complex-geometry problems in the past: the analysis of the Mars Observer failure for NASA and analysis of proposed systems for enhanced oil-field gas recovery for Shell Oil. Each of these problems involved developing a model of many different channels, vessels, and their interconnections, interactions, and boundaries. For both problems, the flow in the geometrical segments were very different with respect to speed, content, and reactivity. These problems made it necessary to create the Pipeline Data Architecture (PDA), a data structure for complex fluid networks based on principles of graph theory in which topologically complicated inter-connecting geometrical spaces are mapped to one-dimensional arrays. An automated approach, through a graphical user interface, would then be used to specify geometry and increasingly complex spatial connections. C-Man will be much more complex than either of these applications, but computers have also improved by over a factor of one hundred in the interim.

Acknowledgments

The authors wish to acknowledge a number of contributors to the project. Ms. Sharon Li did the preliminary research needed to collect, analyze, and synthesize physiological data required for this project. Dr. Anne Staples, who was a DTRA/JSTO-NAS/NRC Research Associate, developed important aspects of the pulsed flow equations and demonstrated their capabilities. Dr. Stanley Foster provided much of the medical direction used in early stages of this program. Dr. Gregory Lakas continues to provide information that helps form our generic approach to this problem. The scientific staff of the Laboratory for Computational Physics and Fluid Dynamics provided an environment in which any numerical problem can be solved and any computer problem overcome. We thank NRL, ONR, DARPA, and DTRA/JSTO for supporting the development of the algorithms and capabilities being assembled and exercised in this effort.

Appendix: Extended Presentation of This Material

To describe this effort further, we have appended a presentation developed to explain the effort in more detail to NRL management (2002), NASA (2004), NIH (2007), and at the Keck Futures Program of the NAS (2008).

The following collection of slides formed the basis of presentations at NRL (2002), NIH (2007), Keck Futures Program (NAS, 2008), and other venues.

*The Computational Man**

A Predictive Model of Human Physiology

LONG-TERM PROJECT OBJECTIVE

To create a dynamic, fluid-based, computational model of coupled physiological systems in a functioning human body.

The model will be low-dimensional, very high-speed, and include representations of reaction kinetics, transport, electro-chemical, multiphase, and diffusion processes.

This is an extensive effort that will require many years to develop, test, and bring into use. It is an important effort that should have been started years ago, and, to our knowledge, has not been.

OBJECTIVE OF CURRENT WORK

To create and demonstrate an initial version of the C-Man, consisting of (at least) two physiological systems (circulatory and respiratory) and their interactions.

Potential Applications

Diagnosis - Establish a prediction base for a particular patient, then look for irregularities, changes
- Diagnose shock and trauma effects (Hazard assessment)

Treatment - Determine interactions of drugs with the body
- Aid in complex medical procedures
- Help to speed recovery and rehabilitation
- Dose determination and monitoring

Monitoring - Part of a system to monitor and protect military and civilian personnel during hazardous situations (e.g., Warfighter Physiological Status Monitoring System)

Drugs - Design, development, and testing

Educational Tool - medical, undergraduate, and perhaps K-12

(2)

Possible Early Uses of the Model ...

Study the *dynamic interaction of coupled systems* to:

- Analyze the effects of changing gravity and other forces on the body, which is mostly fluid

- Look for signals of problems, changes in the body ... exploring connections and inter-relations

- Design - Are there better or simpler physical or flow configurations we can use to repair the body?

- Analyze alternate inter-relationships e.g., relation of Western and Chinese medicine

Work on nonlinear dynamics systems shows that we often observe complex, realistic behavior without the need to represent all of the details.

(3)

Levels and Types of Physiological Models

- **Comprehensive Models and Visualizations**
  - Visible Human Project (NLM/NIH)
  - Virtual Human Project (ORNL)
  - Virtual Soldier Project (DARPA)
- **Physical Simulators - Mannequins or replica models**
  - Human Patient Simulator (HPS; specifically, STAN)
- **Detailed 3D Fluid/Elastic Models of Single Organs**
  - Full Heart Models (e.g., Courant);
  - Lungs (e.g., JAYCOR); Arteries, Veins (e.g., Stanford)
- **One-Dimensional Systems Models**
  - Functional Analog Models (ODEs, based on circuit theory)
  - Fluid Models (Circulatory system, PDES; e.g., Stanford, Ottawa)
  - Physiologically based Pharmacokinetic (PBPK) Models (ODEs describing rate processes; hybrid with fluid dynamics)
- **Quasi-Multi-Dimensional Multiple-Systems Model**
  - Computational Man

(4)

Approach to Constructing C-Man

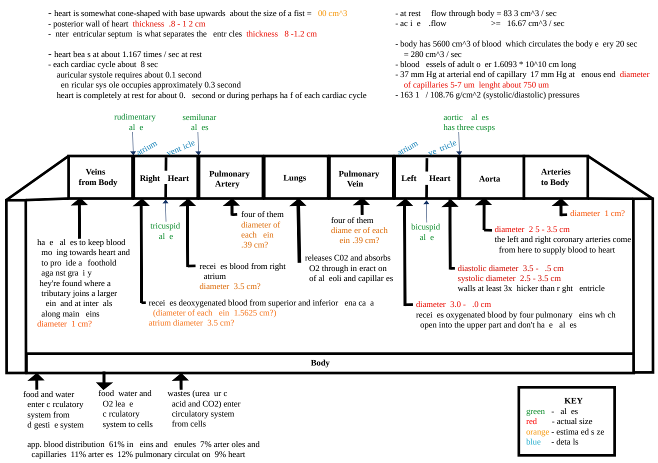
- **Assemble and classify body-system information at the appropriate level to model several physiological systems and their interconnections.**
- **Develop and extend the *Pipeline Data Architecture* (PDA), a computational data structure for optimizing handling elements of topologically complex interconnecting geometrical spaces.**
- **Select and develop appropriate fluid dynamics models for fast solution on complex flow networks.**
- **Develop mathematical formalism for treating flow transition from Convection $\leftrightarrows$ Diffusion.**
  Specifically, need methods for representing fluids that move from large channels to many very small ones, and then comes together again in large channels.
- **Develop models for coupled circulatory & respiratory systems. Calibrate these using real data and real people.**

(5)

Approach to the Problem

- **Assemble and classify body-system information at the appropriate level to model several physiological systems and their interconnections.**

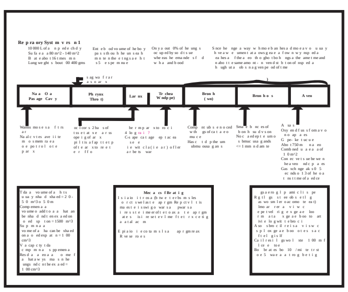
Circulatory System - Outline / Cheat Sheet



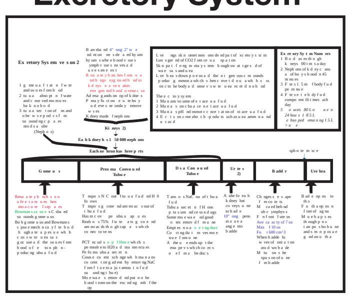
(6)

... And for several other physiological systems

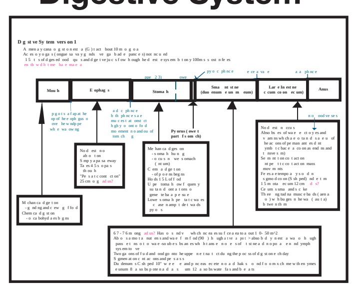
Respiratory System



Excretory System



Digestive System



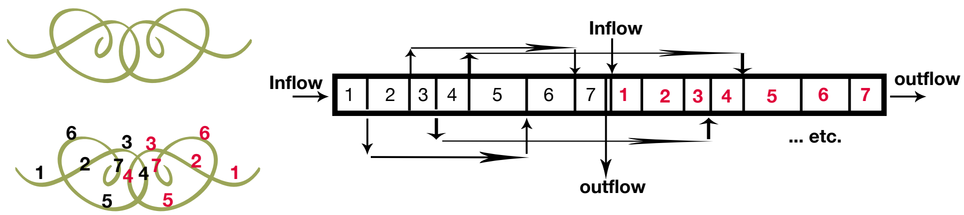
(7)

Pipeline Data Architecture (PDA)

- **Develop and extend the *Pipeline Data Architecture* (PDA), a computational data structure for optimizing handling elements of topologically complex interconnecting geometrical spaces.**

Topologically complicated inter-connecting geometrical spaces mapped to one-dimensional arrays.

Automated (GUI) approach can be developed to specify geometry and increasingly complex spatial connections.



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Applications of PDA

A complex network of pipes, valves, filters, tanks, connected by assorted types of junctions and various kinds of feedback.

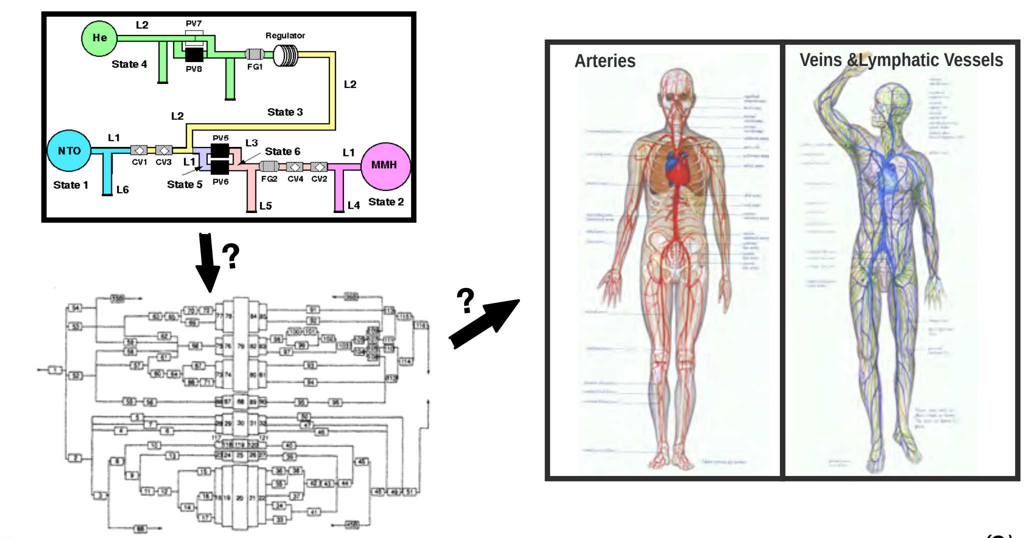


Fig.1 Blood vessel segment connections for human systemic circulation (Table 1)
Medical & Biological Engineering & Computing January 1995

(9)

Basic Fluid Dynamic Algorithms Developed in LCP&FD (1)

- Select and develop appropriate fluid dynamics model for fast solution on complex flow networks.

Algorithm & Characteristics	Documented Applications
FCT (Flux-Corrected Transport) Well documented Flexible physical complexity* Flexible complex geometry; 1,2,3	**Compressible** Reactive flows; Combustion Inertial confinement fusion Astrophysics, Pipeflow Contaminant transport
BICFCT (Implicit Correction to FCT) Well documented Flexible physical complexity* Flexible complex geometry; 1,2,3D	**Low-Mach number, compressible** Combustion Astrophysics Flexible complex geometry; 1,2,3D

(10)

Basic Fluid Dynamic Algorithms Developed in LCP&FD (2)

- Select and develop appropriate fluid dynamics model for fast solution on complex flow networks.

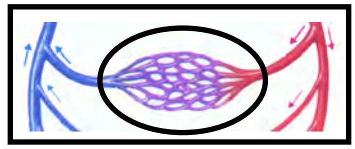
ADINC (Adiabatic Incompressible) Well documented Flexible physical complexity* Variable 1D geometry	**Low-Mach number** Compressible & incompressible : Variable 1D geometry
FCTINC (FCT Incompressible) Well documented Flexible physical complexity* Flexible complex geometry; 1,2,3D	**Low Mach number, incompressible** *C-Man*, Microfluidics Biosensor design
AFE (Asymptotic Flow Equations) 1D, Quasi 2D	**Under development specifically as a building block for C-Man**

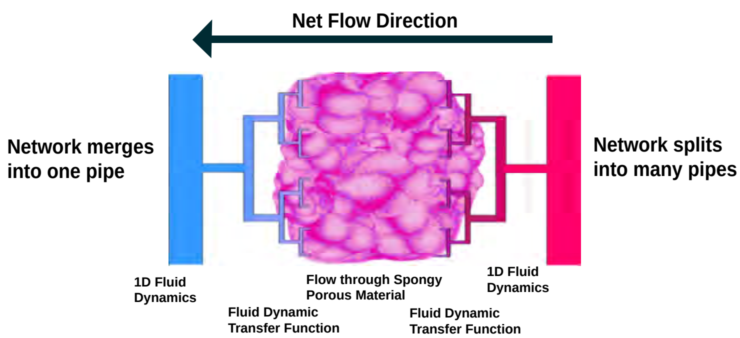
* Flexible addition of other physical processes, such as viscosity, diffusion conduction, chemistry, radiation,etc.

(11)

- Develop mathematical formalism for treating flow transition from Convection ⇆ Diffusion.
  Specifically, need methods for representing fluids that move from large channels to many very small ones, and then comes together again in large channels.

Artery, Blood Capillaries, etc





(12)

Approaches to Solving Convection-Diffusion Transition

Two approaches are being considered now --

(1) Transition effected by spatial and temporal variation of coefficients in the Navier-Stokes equations:

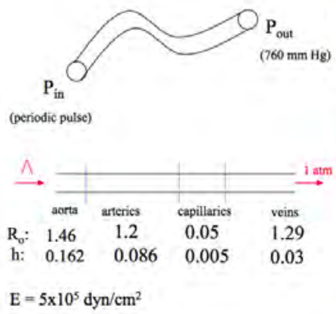
$$\frac{\partial u}{\partial t} = -\nabla P + \nu \nabla^2 u + f, \qquad \nu = \nu(x,t)$$

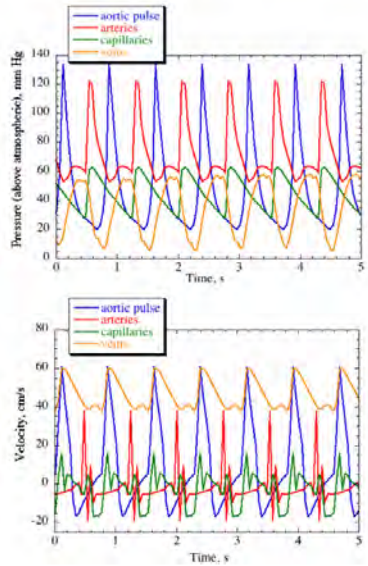
(2) Transition to smaller pipes done through adjusting ν and R in the flow equations, where n is the number of channels and r is the radius, and u becomes the mean velocity $\overline{u}$ through the channels.

(13)

❁ Develop models for coupled circulatory & respiratory systems. Calibrate these using real data and real people.

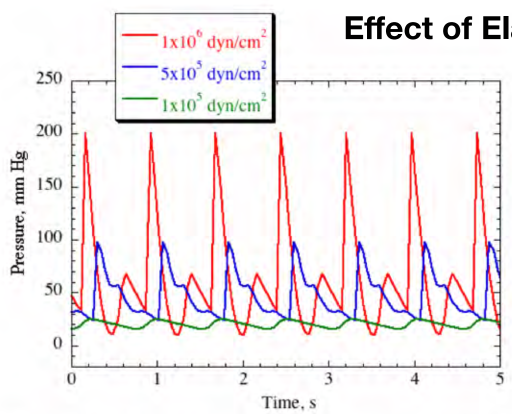
Blood Flow in Arteries, Veins, and Capillaries





(14)

Effect of Elasticity on Arterial Pressure



Wave speed:

$$C^2 = \frac{AdP}{\rho dA} \propto E_L$$

State equation:

$$P = P_o + E_L\left(\frac{A}{A_o} - 1\right)$$

Increased elastance (more rigid) is primary cause of increased systolic and pulse pressure with advancing age.

As elastance increases, transmission velocity of forward and reflected travelling wave increases (reflected wave arrives earlier in aorta) and augments pressure in late systole.

Vasodilator drugs reduce wave reflection amplitude by decreasing elastance of muscular arteries and reducing pulse wave velocity.

(15)

Issues: Numerics and Alogorithms

Modeling non-Newtonian flows, multiphase, porous flows
Computations of fluids in flexible structures
Design of efficient data structures
Representing dynamics of flow in fractal-like networks
Determining appropriate model levels
Connecting convection (veins, arteries)
to pseudo-diffusion dominated flows (porous)
Connecting compressible and incompressible flows
Allowing hookups to more detailed, complex models
(e.g., heart, lungs)
Multiscale effects - temporal and spatial

(16)

Issues: Physical and Chemical

Non-Newtonian flows (e.g., effects of cells, impurities in flow)
Multiphase, multispecies flows
Surface effects (e.g., deposition, absorption, transmission)
Porous flow through organs, cartilage, connective tissue, etc.
Elastic and deforming walls
Electro-chemical interactions (nervous system)
Effects of gravity and changing gravity
Chemical reactions
Electrochemical reactions
Diffusive and osmotic forces - physics of membranes

(17)

Related work in LCP&FD

Algorithms for fluid dynamics and reactive flows
- Time-dependent, multidimensional reactive flows
- Complex dynamic structured and unstructured adaptive gridding
- Large data structures for multiphysics, multidisciplinary models
- Asymptotic methods for partial and ordinary differential equations

Network modeling for fluids and kinetcs
- Model to describe multiply connected segments, complex topologies
- Initially used to analyze reactive flow in the Mars Observer (NASA)
- Extended to problem of natural gas extraction (Shell Oil)

Algorithms for, and studies of multiphase flow
- Ranging from individual droplet interactionsthrough,full Navier-Stokes multicomponent flow problems

Multiscale systems modeling
- Range of problems from atonic to cosmological

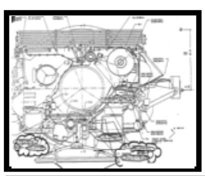
Experience in many fields of fluid dynamics and reactive flow
- Incompressible flows in microchannels
- Fully Compressible and low-Mach Number flows

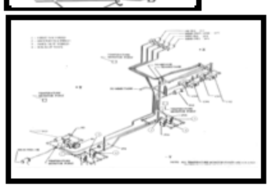
(18)

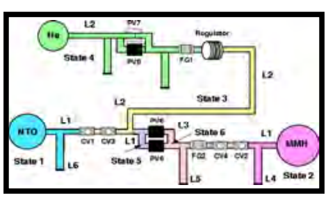
One-Dimensional Flow Model with Multidimensional Properties

Mars Observer Spacecraft -- Reducing Complexity

Genesis of *PIPELINE*, a fuel-line network systems model.







A complex network of pipes, valves, filters, tanks, connected by assorted types of junctions and various kinds of feedback.

Structural Representation and Geometry Models
- *Connected network of 1D, variable cross-section pipes*
- *Valves, filters, tanks in the feed system are active*
- *Represent T junctions connecting different pipes*
- *Pipes have hard walls with finite heat capacity*

Chemistry and Thermophysics
- *Single step, T-dependent gas-phase reaction*
- *Hypergolic action converts droplets to vapor*
- *Liquid droplets vaporize to local vapor pressure*
- *Variable gamma computed locally*

Fluid Dynamics and Flow Physics
- *FCT multiphase flow model*
- *Each liquid has two components - droplets & coating*
- *Liquid compressibility is self-consistently included*
- *Viscosity included as averages, turbulent drag*

(19)

Why Should This Project Succeed? (1)

* **If the two hypotheses underpinning this work --**

  1. The human body can be described as a complex, dynamic, reactive-flow problem on a system of coupled networks.

  2. When these networks are created and allowed to function at a reasonable level of complexity, the predicted behavior will be qualitatively and quantitatively correct.

  are even partially correct, there is an enormous amount to be learned!

* **Any success means a large payoff in human health and lives.**

(20)

Why Should This Project Succeed? (2)

* **There is a wealth of data to use to calibrate the model.**
* **Medical personnel are eager to collaborate**
* **We are experts at creating such models.**
* **Although C-Man is more complex than our previous applications, computers have improved 100 fold in the interim!**

And again ...

Any success means a large payoff in human health and lives.

(21)