THE VIBE OF THE BURNING AGENTS: SIMULATION AND MODELING OF BURNS AND THEIR TREATMENT USING AGENT-BASED PROGRAMMING, VIRTUAL REALITY, AND HUMAN PATIENT SIMULATION

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“SAPERE AUDE”
Horace, Ars Poetica

Animal models in biomedicine

Accordingly to the Concise Oxford Dictionary of English (1982), a model is a “representation in three dimensions of existing or proposed structure, etc. esp. on a smaller scale (working model); simplified description of system etc. to assist calculations and predictions”. Webster’s New Riverside University Dictionary of English (1988) expands the concept and adds “**2.** A preliminary pattern serving as the plan from which an item not yet constructed will be produced. **3.** A tentative description of a theory or system that accounts for all of its known properties.

Seen in their most restrictive context, none of the definitions fit what is collectively described as “models” of injury. None of the current models work on a smaller scale since pathologies of rat and human appear to be very similar. A cell in the cell culture exposed to anoxic conditions or mechanical damage can hardly be viewed as a “plan” for future construction of the processes involved in, e.g., traumatic brain injury. And, despite the massive accumulation of new data, we are still very far from a “tentative description that accounts for all known properties” of most, if not all, forms of injurious processes that affect living organisms.

The linguistic definitions of a “model” apply only when used in the context of human pathologies that a trauma team confronts following a major car accident. It is also in this context that a debate on the utility of the currently used models of injury is conducted. The best example of this situation are studies of stroke where “validity of rodent brain-ischemia models is self-evident” (14). Yet, while experimental therapies are quite effective, there is practically no demonstrable effect of these studies on clinical outcomes (9, 20). Moreover, the art of modeling pathological processes in the brain did not progress much during the past 10 years. The currently used tools in injury research are still the same and are based on cell and cell culture methods, isolated tissue (e.g., brain or heart slices), and surgical/pharmacological manipulation of animals to produce conditions similar to those observed clinically. It is the range of the analytical tools and techniques that now assist in the discovery, analysis, and understanding of the processes evoked by our modeling efforts that has changed and it is these new analytical methods that helped to discover phenomena whose existence, until quite recently, was entirely unsuspected. Yet, in similarity to with all experimental approaches to human disease, majority of these methods have demonstrable limitations (5, 8,17). Interpretation of the results is also quite difficult, and often involves translation of phenomena characterized by the high spatial and temporal complexity of the constituent events into linear patterns of cause and effect that are inadequate to represent biological interactions. Implementation of computer-based models may assist in circumventing this critical problem.

Computer-based models of normal and pathological cell/tissue interactions

Despite highly promising results of the initial work, computational models and simulation have not yet gained the popularity they deserve (21, 29. Several reasons may explain the reluctance in accepting the blend of very advanced computing, simulation, visualization, and information technologies in the studies of stroke and brain injury. First of all, the level of the required knowledge is seemingly daunting – maximum utilization of the techniques that are becoming rapidly available and approach "off the shelf" level exceeds current technical abilities of many among biomedical investigators. "Communication gap" that still separates the computer and medical scientists prevents meaningful exchange of ideas (3). The underlying mistrust within the biomedical spheres that meaningful simulation-based models of systems as complex as the brain can be ever attained (2) also ads to the reluctance with which computer-based simulation finds acceptance. Finally, the costs of simulation using the most widely accepted object-based approach may be very high, and the equipment needs exceed the capacity of the majority of biomedical research centers (11, 16). Even at the laboratories equipped with the necessary hardware, the practical execution of a simulation session may require very creative approaches in order to provide the necessary materiel support (16)!

The difficulties notwithstanding, substantial results have been already obtained in simulation/modeling of cytotoxic and vascular events in ischemia (19), pathogenic mechanisms in stroke (15), calcium-related physiology (6), blood flow dynamics (28), and spreading depression in focal cerebral ischemia (30). Very importantly, computational models of cognitive deficits following brain damage that are currently developed (7, 22) and will provide a natural extension of the model-based studies of cerebral pathology. The creation of the GENESIS simulator-based database (part of the Human Brain Project; see 2) and several other neural simulation programs (10) indicates that the field of simulation rapidly gains strength as an important research tool.

Contemporary approaches to computer based modeling of cell/tissue interactions

Formal models of complex physiological and metabolic processes are conventionally created using coupled differential equations (1, 4, 12, 13, 18, 23). While this approach is appropriate for monolithic systems, it has serious shortcomings for systems with many interacting components such as brain. In the latter systems, the monolithic models quickly become cumbersome to construct, debug, and maintain. Furthermore, small differences in parameter values in different components of a system (represented by a single "lumped" parameter in a monolithic model) may lead to divergent trajectories of system components due to the nonlinearity of the underlying dynamics.

Current approaches to tissue/organ modeling are based either on the concepts of linear relations and dependencies that result in very inaccurate "toy" models used in high-school education (31). More sophisticated approaches are based on object-based programming suitable for modeling complex systems providing these are adequately described by differential equations. The best example of the latter is the model of Purkinje cell (11). However, in the ultracomplex systems (e.g., brain) in particular, variations within the "assumed constants" (lumped constants) will be particularly pronounced, especially when pathological environments are modeled. As the direct result of the cumulative effect of such progressively increasing deviation from reality the model will perform either inaccurately or even erroneously.

The New Wave: agent-based modeling of injury

Agent-based modeling (ABM) represents a new and powerful alternative to the dilemma of simulation and modeling of complex biomedical events, where each entity in the system is represented by a separate computational process. While experience in implementing both classes of models (object-based vs. agent-based) has led to a deep understanding of the relative strengths and weaknesses of these alternative modeling methods (25, 26), agent-based approaches have never been tested in biomedical applications. Yet, the advent of agent-based modeling may represent the most exciting avenue for simulation and modeling of complex biological systems both under normal and pathological conditions encountered in humans

In agent-based modeling, each agent is represented by its own independent computational element that, apart of its characteristics (code and persistent state), is also endowed with a “will”, i.e., the ability to sample the environment and respond to it in an appropriate manner. Moreover, there is no scale to the agent: a receptor subunit may be an agent as much a treating physician. Thus, a very large number of agents can represent a multidimensional system in which spatial and temporal determinants play as important role as the functional characteristics of the involved elements as, for example, in the penumbra zone of a focally injured brain or periphery of a severe burn. Agent based modeling offers the additional advantages of integration with the visual rendition of the physiological processes either in a fully immersive (CAVE) or semi-immersive virtual reality (e.g., ImmersaDesk) systems (31), and of creating interactive environments that are essential for experimentation, testing hypotheses, etc. Thus, agent-based models that operate visual interfaces capable of responding to interactive manipulation represent a substantial leap in the ability of an investigator to observe a very large number of processes taking place within a cell while standing within its virtual cytoplasm, manipulate individual subsystems of that cell (e.g., turn off metabolic pathways, activate receptors or enzymes, control expression of intracellular messengers, etc.), and observe the cumulative effect of these interactions.

VIBE (Virtual Interactive Burn Environment) – the first step

VIBE (Virtual Interactive Burn Environment) represents the first attempt at a practical implementation of agent-based modeling directed at biomedical problems. The goal of VIBE project initiated recently through collaboration of University of Michigan and ERIM is to provide a sophisticated training and research tool assisting in dealing with the complex issues of the treatment of burns (32)

Physiological response to thermal injury (and the potential danger) depends on the extent rather than the intensity of the burn, and the physiological processes involved in burns interact in complex ways. There are four kinds of dynamics involved in burn pathologies (Table 1) and the agent-based model “driving” the Virtual Burn Mode will support all four classes of dynamics.

Table 1: Four classes of dynamics in burn pathologies. The systems listed are examples, not an exhaustive list.

	Localized	**Distributed**
Slow	Kidney Heart	Skin Circulatory system
Fast	Brain	Nervous system

The distinction between “slow” and “fast” (Table 1) is relative to the time scale of interventions in the ER. Fast dynamics are virtually instantaneous in comparison with ER activities, and agents that participate in them can communicate instantaneously by messages even if they are remote from one another. Slow dynamics evolve concurrently with medical interventions, and agents that participate in them must propagate their influences step-wise over space.

It is straightforward to assign an individual agent to each localized system in Fig. 1. Dynamics in the distributed systems are represented by a one-dimensional (for circulatory and nervous pathways) or two-dimensional (for tissue) structure of agents. Although the current work with distributed dynamics performed at ERIM uses a regular hexagonal grid (27), in the burn model, it may prove advantageous to use an irregular tiling of the patient based on the polygonization underlying the visual display. Thus, while the burned patient is presented visually in three dimensions, the major dynamics occur within the dermis, a two-dimensional covering over the body. Thus the initial phase of the functional model will consist of a two-dimensional structure representing the dermis, and supporting pathological processes involving first and second degree burns. A subsequent phase will implement a parallel two-dimensional structure representing processes in the subdermal tissues, coupled to the dermal layer, thus accounting for dynamics into the third dimension.

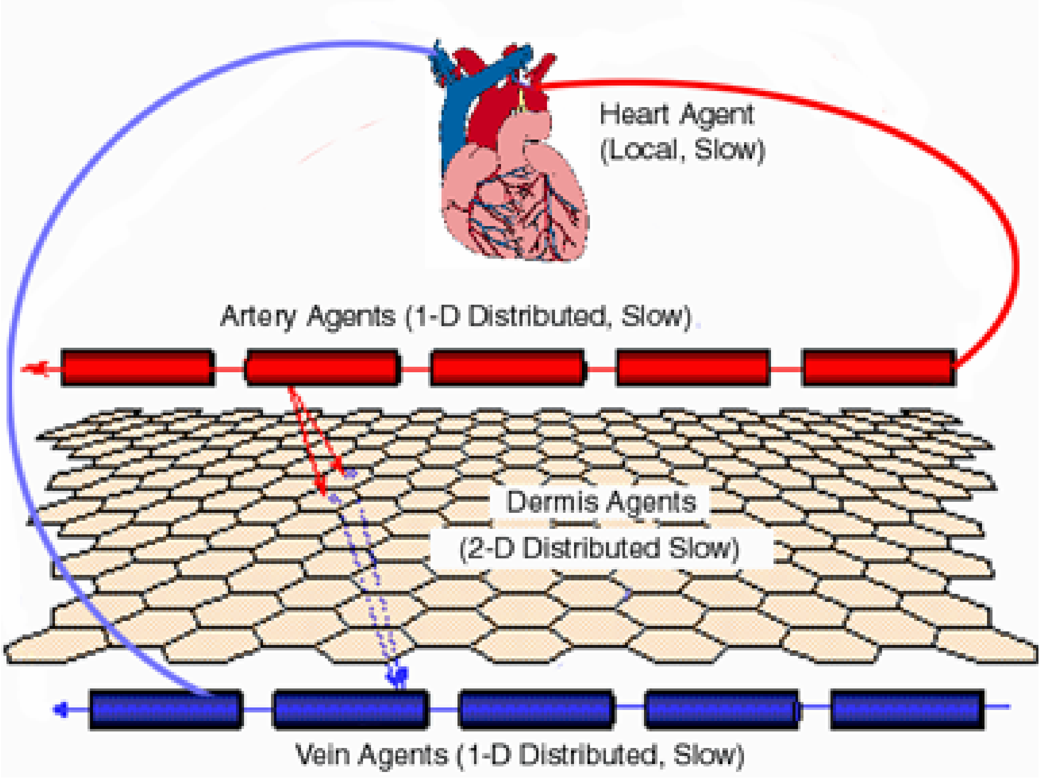

Figure 1. Interactions of various agent dynamics. VIBE combines localized and distributed agents, with both slow and fast dynamics.

The coupling between local and global dynamics occurs is by means of anatomical pathways (e.g., nerve bundles, veins and arteries) that join global agents with selected local agents, corresponding to the anatomical distribution of these features. For example, Figure 1 shows a partial schematic of agent interactions to account for the diffusion of fluid that eventually leads to tissue edema. Each agent (polygon) in the model of dermis aggregates the interactions of capillaries, cells, and inter-cellular spaces within its region, and takes on the average pressure at its center. Several approaches are available to model the interactions within an agent, including rule-based programming, Petri nets, neural nets, and systems dynamics models.

Modeling fluid diffusion between polygons using methods is inspired by finite-element analysis. Thus, each polygon exchanges with its neighbors proportional to their shared boundaries, the pressure differential between them, and the distance between their centers of gravity. Veins and arteries interact directly with the polygons through which they run, and generate pressure differentials that drive the diffusion between intermediate tissues.

Nerve pathways are similarly adjacent to selected polygons. However, they differ in two ways from the circulatory pathways. First, they constitute a one-way path to the brain; the return path is mediated via the circulatory system. Second, because nerves are "fast," propagation along a nerve is not modeled although the distributed nature of the nerves is. Thus, injury mediated signal interruption, e.g., if the nerve is cut, can be represented. However, as long the pathway is intact, propagation of the signal from an offended site to the brain is considered to be instantaneous.

The resulting model includes three classes of techniques indicated in Figure 1 that schematically depicts an agent-based model. Interactions among distributed slow agents, whether one-dimensional (circulatory system) or two-dimensional (dermis) will draw on techniques from finite element modeling. The internal dynamics of individual agents will draw on a tool kit that includes system dynamics models.

The fact that agent-based models are computer-based permits their eventual placement in the "e-world", as public-owned Web based tools available to any investigator anywhere on the globe. Thus, providing appropriate standards are developed (as, for example an extension of the already existing KQML or FIPA), the existing models can be continuously enriched with the latest discoveries, and the accuracy of their performance can be continuously monitored and tested. and their practical use as rapid hypothesis-testing tools will increase the speed of research. Moreover, the inherent plasticity of agent based modeling allows fusion of models with training simulation either in virtual reality alone or using Human Patient Simulators integrated with virtual environments. Basic concepts of distributed training using Human Patient Simulators remotely operated from the distance of 3000 miles have been recently explored (Fig. 2, see ref.32).

Dimidium facti cui coepit habet: sapere aude

The complexities of the suggested simulation and modeling effort cannot be underestimated. Neither can be its scientific and, ultimately, economic importance. Major injury, such as burns, brain or open trauma, etc. are still the leading causes of morbidity and mortality and is associated with an enormous economic burden. The "economy of injury" is encumbered even further by the rapidly raising costs of new drug development that combines with the increasing restrictions on the experimental use of animals already felt in Europe and soon to arrive in the USA as well. The cumulative impact of the last two factors may have catastrophic repercussions on the effective development of new drugs, and advanced simulation and modeling will become the only viable alternatives. The urgency of rapid introduction of simulation and modeling tools into routine medical practice is also stressed by the need to maintain adequate readiness of medical personnel. It is a particularly daunting task in the context of rural and remote regions and where advanced computer-based simulation tools appear to provide a realistic solution to the dilemma of dwindling skills, limited access to training, and their most dangerous consequence: the less-than-adequate treatment of major injury (Fig.2, see also ref.32).

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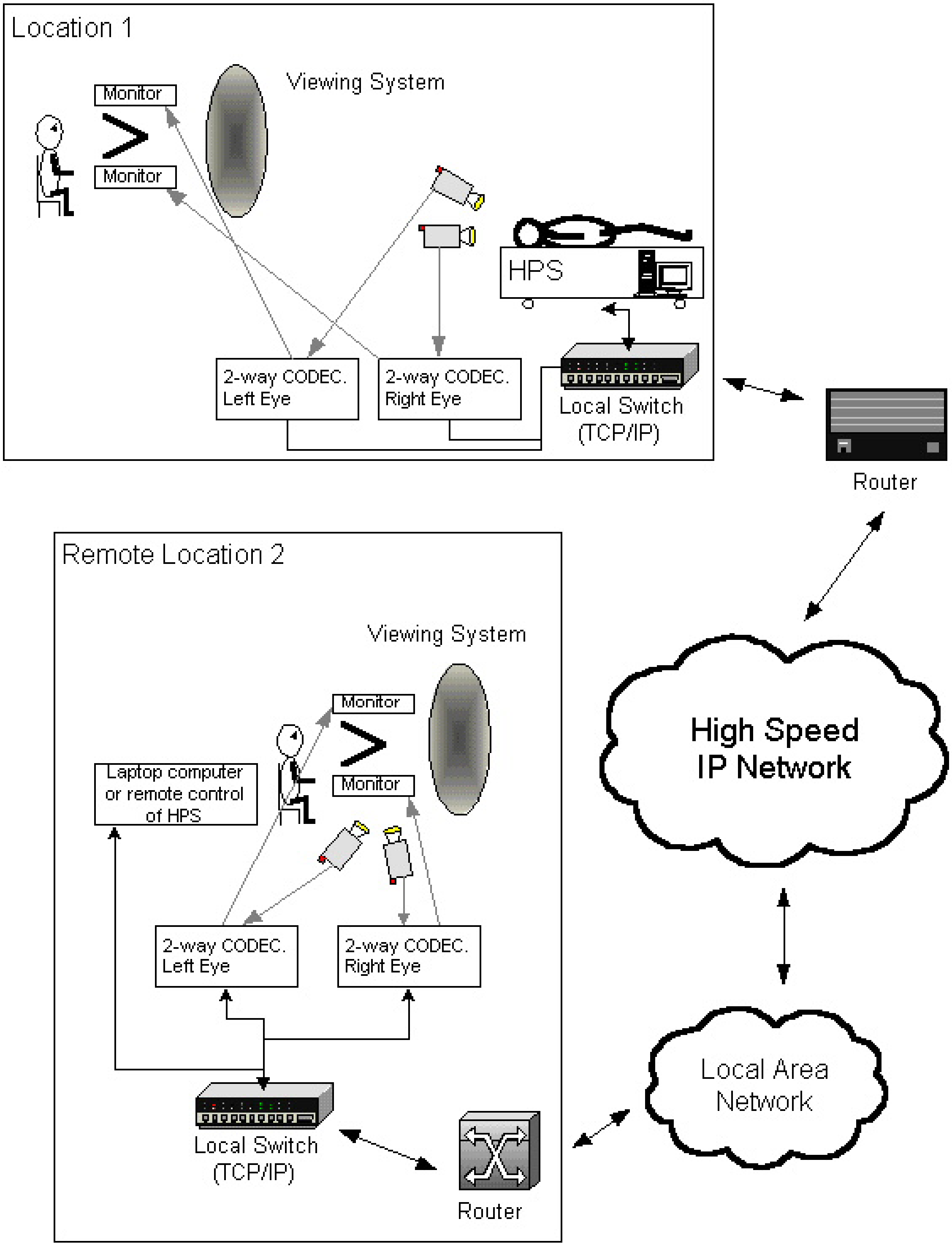

Figure 2. Schematic diagram of Advanced Distributing Learning system capable of providing training at ultra-long distances. CAVE, ImmersaDesk, Ethereal Technologies, Inc. "MIRROR", and other devices can be used the interactive components of the viewing/training environments.

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