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COMPUTER MODELING IN PHYSIOLOGY: FROM CELL TO TISSUE.

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Over the last two decades there have been tremendous advances with quantitative experimental techniques in physiology and signal transduction. On the cellular level these techniques include the scanning confocal microscopy, single channel recordings from intracellular channels, fluorescent dyes that allow visualization of the spatial and temporal dynamics of second messengers, and bioengineered indicators that can be specifically targeted to particular intracellular organelles.

These techniques have already provided a substantial amount of quantitative data and will provide even more in the immediate future. These data reveal a high degree of spatial and temporal organization of intracellular signal transduction processes. Examples of such organization include local events in intracellular calcium signaling, anchoring of protein kinases to various subcellular locations by specialized proteins, association of effectors with the compartments where second messengers are produced or released, and others.

On the tissue level optical and multiple electrode recording techniques are now available that allow the spatial spread of excitations to be monitored. The data obtained by these methods also show complex patterns of spatio-temporal activity.

An adequate understanding of the organization of subcellular processes and the way in which they are related to functioning of an organ or a tissue opens new possibilities in medicine, pharmacology, and biomedical engineering. In particular, effective treatments for cardiac arrhythmias and new strategies for targeting drugs to the signal transduction apparatus are now realistic goals. Interaction with the emerging field of functional genomics is also beginning to occur as computer physiologists begin to simulate the effects of altering or deleting certain genes on both cell and tissue properties.

Given the complexity of these processes, detailed mechanisms can be understood only with the aid of computer modeling. Fortunately, advances in computer power now permit realistic modeling in cell physiology and signal transduction. Current "whole cell models" integrate the network of relevant intracellular biochemical reactions with cellular and organelle geometry, the subcellular distribution of the elements of signaling pathways, diffusion of second messengers, and the elements of cellular motility. The value of such modeling is dual. On one hand, it helps to verify hypotheses about unknown signal transduction mechanisms and design strategies for further experiments. On the other hand, it can be used to predict outcomes of various alterations made to cells, and thus identify optimal intracellular targets for drugs and cellular engineering.

On the tissue level it has become possible to perform simulations of 3-dimensional patterns of activity with models that are accurate anatomically and physiologically realistic. In particular, such simulations are extensively used in cardiac electrophysiology to address the problem of heart defibrillation and have been used to help understand the regulation of glucose-stimulated insulin secretion from pancreatic islets.

This session contains papers which address issues of building physiologically realistic model of a cell and use of computer simulations to understand a mechanism of heart defibrillation. The paper by Schaff and Loew describes the "Virtual Cell"- a computational framework for cell biological modeling. This framework uses mapping of experimental biochemical data onto experimental images for model construction. The paper by Trayanova et al presents a simulation study of the mechanisms by which a strong electric shock halts life threatening arrhythmias. Additional examples of how computer modeling is helping to elucidate mechanisms in the heart, in insulin secreting pancreatic islets, and in fertilization are provided in the posters and tutorials for this session.