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COMPUTER GRAPHICS IN SIMULATION OF CARDIOVASCULAR TRANSPORT PHENOMENA*

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Abstract

Simulation is a necessary tool if we are to understand better the complexities involved in cardiovascular transport. While some of the phenomena modeled can be described analytically, perusal of the equations alone often doesn't result in full appreciation of the model system. It therefore becomes pertinent to utilize computer graphics in order to enhance simulation of physiologic transport processes. Graphic representation not only facilitates interaction between the investigator and the simulation, it provides a juxtaposition of the model to the real system, as well as a simplification of relationships between various features of the model.

Increased mathematical sophistication required in the investigation of cardiovascular transport phenomena often makes traditional graphic representation cumbersome. Therefore several different types of graphics have been utilized, including 2-, 3-, and 4-dimensional displays. The methods and algorithms for these displays have been generalized to make them easy to use over a broad spectrum of applications. In some cases we have generated motion pictures of sequential model solutions which have increased and accelerated model comprehension, as well as been valuable for teaching purposes.

Computer graphics can be used to enhance simulation of physiologic transport processes. Graphic representation not only facilitates interaction between the investigator and the simulation, it also serves as an invaluable aid to communicating the insights about transport systems.

Folkways have long expressed the value of pictorial representation of ideas by the statement: a picture is worth a thousand words! That truism has proven to be valid in modeling transport phenomena in the cardiovascular system including simulation of transmembrane transport of calcium in cardiac muscle, and capillary transport of both permeant and impermeant solutes. Graphical representation has aided in juxtapositioning the model to the real system, and often simplifies appreciation of the relationship between various parameters of the model. Indeed graphic representation has occasionally demonstrated unexpected features of the model and greatly accelerated understanding of the system being modeled.

While some of the phenomena modeled can be described analytically, perusal of the equations alone often doesn't result in full appreciation of the phenomena, and pictures convey concepts and relationships to non-mathematical audiences much faster than cumbersome explanations of equations. The graphic displays and equations can be used in complementary fashion for teaching purposes. Further, the displays can be used to test for agreement between experimental data and models proposed to describe the transport processes underlying the experimental data.

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The complexity of transport processes often renders two-dimensional representation inadequate, but due to the ease of generating three-dimensional displays with the aid of the computer they have come to play an integral role in understanding those processes. The increased mathematical sophistication of investigation of cardiovascular transport phenomena makes traditional graphic representation cumbersome; three-dimensional displays have facilitated presentation of ideas and data.

METHODS

SIMCON[3], a simulation controlling system for online man-machine interaction was used to generate solutions to FORTRAN models from a peripheral computer terminal which consists of a standard storage oscilloscope (CRT) and an alphanumeric BCD keyboard. Model solutions were displayed on the CRT in real time and were scaled and/or adjusted either prior to or during a solution via keyboard entered parameters.

Further graphical labeling and experimental data were superimposed over the model solution with the aid of another computer program, GRAPHCON[1]. GRAPHCON, which can function independently of SIMCON, provides a keyboard controlled cursor which allows entry and editing of such things as variable sized upper and lower case alphanumeric characters and special symbols, super and subscripts, lines, and various types of axes. Coordinates for two-dimensional data can be keyed in, scaled in log or arithmetic fashions and displayed as points or special symbols (Fig. 1). Successive data values can, by a keyboard option, be connected with dashed or straight lines. Figure 4 was generated on the CRT and illustrates some of the capabilities of GRAPHCON. Graphic information can be stored on the disc and later recalled as needed for the reproduction of a picture or for editing and the creation of a new similar picture.

Photographing the image on the CRT with either a polaroid or 35 mm camera served as a convenient mechanism for obtaining hard copy. Optimal f stop, and oscilloscope beam intensity are determined by trial and error. Triggering frame advancement of a motion picture camera with a voltage pulse on a digital/analog line produces motion pictures when a series of sequential model solutions are displayed on the CRT. Maintaining visual continuity requires that the image does not change greatly from one frame to the next. When sequential solutions are sufficiently similar the motion picture can be lengthened by photographic duplication of each frame, visual continuity having been maintained in one case with a 25:1 expansion of the film. As a less time consuming alternative, multiple frames can be made of each solution by photographing a television screen using a Princeton Electronic Products intensity modulated scan converter to renew the video image. That technique proved less satisfactory as the scan converter had a tendency to 'bleach' during exposure of a series of frames resulting in an annoying flicker in the film.

Two-dimensional displays were generated in the standard manner on a 1024 by 1024 Cartesian Coordinate System. Three-dimensional displays were presented as either a grid (Fig. 7) and/or surface (Fig. 2) on the CRT. The calculated surface can be rotated to optimum viewing projection, by keyboard control, by changing the azimuth and/or elevation angle. The grid is projected onto the CRT as contour lines connecting calculated points having specified Y values and contour lines connecting points having specified X values. Data points, such as those shown in Fig. 7, can be entered via the keyboard and displayed as the heads of arrows projecting above or below the model surface, with oscilloscope beam dwell time reduced for points below the surface, so that when photographed they appear dim, as if partially hidden.

The number of points that must be calculated so that the model is faithfully represented by the display depends on the model and is usually determined by trial and error. Using a zeroth order interpolation to fill in the discontinuities in the grid converts it to a three-dimensional surface. When the surface is rotated so that the Z axis has a projection on the CRT the hidden line algorithm of Coulam *et al.*[2] is used to suppress hidden surfaces. When the Z axis has no projection on the CRT, beam dwell time is modulated in proportion to the anti-logarithm of the Z value for each point. (Beam Dwell Time = $8 + K^N \mu$ sec, N being the index of the gray level, and K a constant found by trial and error. Photographing the CRT in the non-store mode yields a picture with brightness proportional to Z value, producing a Z modulated display from an oscilloscope without analogue Z modulation. (Photographic emulsion responds logarithmically to increased exposure time, hence proportionality to logarithm of Z value.) Minimal oscilloscope beam dwell time for each point displayed was determined by the duration of the analogue pulses used to activate the beam. Longer beam dwell times were related to each other exponentially with an arbitrary restriction to 32 different dwell times (gray levels), as that number proved to give smooth gradation of one brightness level into the next.

RESULTS

Simulation of the relationship between calcium flux and internal and external calcium concentration for hypothetical two-site calcium carrier, thought to be important in myocardial calcium sequestration, required three-dimensional representation to give a clear picture of the relationship as illustrated in Fig. 2. Although not all of the parameters involved in the model can be displayed simultaneously, those that are variable in a biological preparation are presented. The influence of the permeability of the various carrier forms was examined by filming a series of solutions in which permeability was varied between solutions, using the movie to show this fourth dimension.

Presentation of carrier transport relationships as a three-dimensional surface not only is convenient, but it is also a thought provoking presentation as well because of its uniqueness. Presentations that schematically resemble the system being simulated have the advantage of simplifying a correlation between the system and the simulation, as illustrated in the simulation of capillary tissue exchanges in Fig. 3. Here both capillary and tissue are displayed in a geometric relationship similar to that occurring in tissue. Simulation is used to predict the time course of the spatial distribution of permeant and/or impermeant solutes in capillary and tissue during passage of a bolus of solute through the capillary. The brightness of shading indicates the fraction of the solute present at any point in the tissue and capillary (blank square represents the center of solute mass for the tissue, and the plus that for tissue plus capillary). Conventionally the distribution occurring in an experimental preparation is inferred from the curve of the concentration of solute in the effluent from the organ versus time. Beneath the representation of the capillary in Fig. 3 is the simulated dye curve that would result for this particular simulated spatial distribution of solute, allowing comparison with experimental results. The arrow beneath the dye curve indicates the time after the solute injection at which the spatial distribution was observed. Capillary flow rate, capillary permeability, and intratissue and intracapillary diffusion are important parameters in determining the characteristics of capillary-tissue exchanges.

Sequential solutions of the type in Fig. 3 were made into a motion picture so that one could better comprehend the dynamic relationship between the spatial distribution of solute and the venous solute dilution curve. Use of a special projector which allowed variable speed coupled with stop action projection was of great aid to us, and was especially valuable when explaining the concept to others.

Another simulation that has been used to clarify a complex system is that of a sodium–calcium exchange carrier. The carrier is a hypothetical system for controlling myocardial calcium content. Figure 4 has been used to help present the hypothesized carrier system, indicating that carrier is confined to membrane, and combines with sodium and calcium at the membrane surfaces. Figure 5 shows the model solutions for solute concentrations and solute fluxes that prevail for the given set of carrier and carrier-solute complex permeabilities.

This figure uses a similar format to present the effect changing relative concentrations has on the distribution of carrier in the system, and the resultant net flux of calcium. The display is generated rapidly (about $\frac{1}{2}$ S) which simplified making a movie illustrating the relationship of sodium concentration of net calcium flux which has also proved useful in presenting the sodium–calcium exchange carrier concept.

Many valuable simulations simply are displays that can be readily compared with data plotted on a standard two-dimensional plot as illustrated in Fig. 6. The ability to rapidly generate model curves for comparison to data has provided a means for obtaining an eyeball fit to data. Figure 6 illustrates the comparison of experimental data on calcium fluxes to a curve predicted by the sodium–calcium carrier model. Data is displayed on the oscilloscope face using a subroutine of GRAPHCON that allows the entry of data points and axis scaling from the peripheral terminal.

Straightforward two-dimensional displays are perhaps the most useful way of comparing data and a model when the data can be expressed in two dimensions. However, the complexity of biological problems often makes consideration of more than two dimensions necessary. The Na–Ca exchange model is one such situation, with data on efflux being functions of both sodium and calcium concentrations. To avoid having multiple curves on a two-dimensional display we have represented the model surface as a grid with a projection in each of three dimensions, indicating the relative location of data points by the heads of arrows, brighter arrows for points above the surface, fainter for those below (brightness again captured photographically with modulation of beam dwell time). Figure 7 illustrates the fit of some experimental data to the model situation for the Na–Ca exchanges. Data are entered from the keyboard, and the scaling of the plot is selected via the keyboard. Solution generation requires 3–5 s, depending on the density of the grid. Keyboard parameter entry allows rotation of the axis of projection for optimization of display, and to allow careful visual examination of the correspondence between data and model.

Stereoscopic images can be produced by taking two pictures rotated 5–10° from one another about the verticle axis.

DISCUSSION

Careful simulation allows mathematical definition of the importance of many assumptions made in interpreting experimental data. Consideration of the relative permeabilities of the forms of carrier involved in transmembrane transport can be viewed as theoretically very important based on simulations of carrier kinetic phenomena [4]. The theoretical roles of other assumptions can be tested against experimental data by comparing results predicted by simulation to data, as in the case of the role of capillary permeability in shaping dye curves. Model curves can often be used as a reference in the display of data collected from experiments and for making a visual assessment of the fit of data to model. While evaluating the fit of one curve to another visually may not yield the statistically optimum values for parameters, or allow calculation of correlation coefficients it can provide a means of making order of magnitude estimates of parameter values for a complex model. In many cases, data

collected from biological preparations is fraught with noise, which, if non-random and not easily defined, abrogates the use of standard statistical measures of goodness of fit. When applicable, fits obtained by least squares techniques can also be displayed graphically.

Being able to display a matrix of data points can be helpful in presentation of the parameter domain covered experimentally, and areas yet to be tested.

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Fig. 1. GRAPHCON generated flow digram illustrating the relationships between graphic options and model solution display.

Fig. 2. Flux of calcium from outside to inside of cell membrane due to a two site carrier as a function of the calcium concentration on two sides of the membrane (S_0 , S_1). The 3-D surface is displayed using a hidden line algorithm and contour lines are at levels of equal flux.

Fig. 3.
Distribution of diffusible indicator as calculated by a model of capillary–tissue exchange.

Fig. 4.
GRAPHCON generated illustration of a model for transmembrane exchange of sodium and calcium.

Fig. 5.
 Display format used in motion picture generation to illustrate relative sodium and calcium concentrations.

Fig. 6.
Comparison of experimental data (X's) to the model solution curve.

Fig. 7. Three-dimensional model solution surface compared to experimental data (arrowheads) which lie above or below the grid.