Interactive 3D Visualization of Actual Anatomy and Simulated Chemical Time-course Data for Fish

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Abstract

Outputs from a physiologically-based toxicokinetic (PB-TK) model for fish were visualized by mapping time-series data for specific tissues onto a three-dimensional representation of a rainbow trout. The trout representation was generated in stepwise fashion: 1) cross-sectional images were obtained from an anesthetized fish using a magnetic resonance imaging (MRI) system, 2) images were processed to classify tissue types 3) images were stacked and processed to create a three-dimensional representation of the fish, encapsulating five volumes corresponding to the liver, kidney, muscle, gastrointestinal tract, and fat. Kinetic data for the disposition of pentachloroethane in trout were generated using a PB-TK model. Model outputs were mapped onto corresponding tissue volumes, representing chemical concentration as color intensity. The visualization was then animated, to show the accumulation of pentachloroethane in each tissue during a continuous branchial (gill) exposure.

1. Introduction

Combining data from disparate sources can pose a challenge for visualization. Unless all data sets share a common spatial reference system, establishing the necessary correspondence between different data sources requires a substantial effort. In the visualization described here, anatomical data sampled on a rectilinear grid were combined with discrete model output based on tissue type identifier rather than spatial position. Specifically, organs of a three-dimensional trout representation were colored according to model computations. The anatomical context promotes understanding of the model data by a wider audience than might otherwise be the case.

There are three basic stages in the visualization described here. First, acquisition and classification of the fish volume. Slices were acquired by an MRI system and manually classified by tissue type. Second, generation of the kinetic data for the disposition of pentachloroethane by the model. This data was calculated by a PB-TK model and exported as an ASCII file. Third, the integration of the two types of data and the creation of a representation.

2. The Model

Physiologically-based toxicokinetic (PB-TK) models are based on the anatomy, physiology, and biochemistry of the exposed organism and are used to generate, chemical concentration time-course predictions for specific tissues and organs. This information can in turn be related to research on a compound's mechanism of action to improve understanding of relationships between applied dose and observed effect [McKim and Nichols 1994; Andersen 1987].

Despite their many advantages, however, there has been resistance to the use of PB-TK models on the part of both scientists and non-scientists. This resistance derives largely from the perception that these models are too complicated and therefore do not yield useful information. Consequently, individuals who could benefit from their use do not do so. The purpose of this study was to develop the capability to visualize PB-TK model outputs in a more accessible way than traditional graphs.

The disposition of pentachloroethane, an industrial solvent, in rainbow trout was simulated using a PB-TK model running under Advanced Continuous Simulation Language (ACSL, from Mitchell and Gauthier Associates Inc., Concord MA). The model is described in greater detail elsewhere [Nichols, et al. 1994; Erickson and McKim 1990].

Chemical time-course predictions for each of the model compartments were exported from ACSL as ASCII files. The system could be used interactively by making parameter changes in the ACSL runtime environment. An

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output file was generated each time the model was run which then served as input for subsequent visualization efforts. New model results were automatically loaded into the visualization system as soon as they became available.

3. Volume Acquisition and Classification

The anatomical information was obtained from cross-sectional slices acquired by a magnetic resonance imaging system (MRI; General Electric Signa 1.5 Tesla). Anesthetized fish were placed in water in a V-shaped plexiglass support. Images were acquired using a send-receive extremity coil and fast spin double echo technique. Two settings were used to distinguish between tissues in the first echo primarily on the basis of lipid content, while in the second echo differences between tissues reflect differences in water content. Slice thickness was set to 3 mm, with 1.5 mm spacing between slices to minimize cross-talk. A scan of the entire fish yielded 30 slices and 60 total images (30 each of the first and second echoes). The MRI was then electronically offset by 3 mm, and a second image series was acquired.

Classification is the process of assigning an identifier (or hierarchy of identifiers) to each pixel of an image. In this case, we needed to isolate individual organs so that model outputs could be mapped onto them. Automatic and semi-automatic classification algorithms make assignments based on pixel intensity, intensity gradients, geometry, combinations of multiple echo values, or statistical properties of the image [for instance, Cline, et al. 1990; Gerig, et al. 1991]. The quality of resulting classifications is influenced by both the quality of the classification algorithm and the characteristics of the image. Images with pixels which are large relative to features, with small intensity differences between tissue types, with large intensity response from background areas, or with significant amounts of noise are particularly difficult to classify automatically. Unfortunately, MR images of fish in water have all these characteristics (Figure 1).

The plexiglass support also introduces problems for automatic classification techniques. Partial voluming along the edges of the support (the boundary between the very low response support and the very high response water) contributed background voxels with intensities spanning that of the fish. This made intensity and feature space approaches problematic, due to the large number of false positives generated by a purely statistical (Bayesian) classifier. Additionally, the very presence of the support made it impossible to use simple intensity thresholding to even make the differentiation between fish and background.

Consequently, classification was done by a completely manual process. All image processing was performed on the second of the two echoes obtained at each location, although in many cases the first echo was examined to confirm tissue types and boundaries. Tissues and organs were classified, pixel by pixel, using a paintbrush option which ascribed to each a unique numerical identifier. Figure 2 shows a completely classified slice. While this process would have been too time-consuming were multiple volumes of interest, for this application only one classified volume was required.

In some cases, representative tissue masses were chosen to describe model compartments. Adipose tissue, which is distributed throughout the animal, was represented by the dorsal fat pad located just beneath the dorsal surface of the animal. The richly perfused compartment was represented by the stomach and intestinal tract. A portion of the poorly perfused compartment was given its own classification to create a representative muscle mass.

4. Visualization Process

The 3D visualization was constructed using the Application Visualization System (AVS, Advanced Visual Systems, Inc., Waltham MA) [Upson, et al. 1989]. Custom modules were developed to check for new model results, read the model data, register the fish volume to actual coordinates, extract a single tissue type from the fish volume, and color tissue types by model values.

TIFF files for each of the 60 classified slices were imported into AVS. The slices were then stacked to generate a three-dimensional volume containing the fish. Since sample spacing in the three dimensions was not uniform, the resulting volume was rectilinear. Accordingly, each voxel was a rectangular prism (0.78 x 0.59 x 3 mm).

In order to create a geometric representation of an organ or tissue compartment, that compartment was first extracted from the segmented fish volume. The resulting single-tissue volume had voxels of the target type enabled and all other voxels disabled. An isosurface was then computed from this volume. Finally, the five isosurfaces corresponding to each tissue type, along with the isosurface showing the boundary between fish and background were combined and rendered together (Figure 3).

The voxels containing fish were confined to a 60 X 115 X 60 subvolume of the scanned volume. Noticeable voxel artifacts appear in isosurfaces made from the original segmented volume. Figure 4 shows top and side views of the fish exterior computed from the original segmented volume. This silhouette has a very blocky appearance, especially in the fin region. In order to reduce this blockiness, the segmented volume was convolved with a kernel having a Gaussian distribution with a frequency domain standard deviation of 1 voxel (the corresponding spatial domain frequency domain standard deviation was $1/2\pi$). Figure 5 shows the resulting exterior. Visible artifacts from the voxel structure have been greatly reduced with the side-effect of some erosion of the fins. A similar smoothing was performed on each individual segment volume. Since the purpose of this

visualization is illustration, rather than diagnosis, the resulting slight loss of accuracy is acceptable.

Chemical time-course predictions for each of the model compartments were imported into AVS as ASCII files. Model compartment isosurfaces were colored according to the concentration of chemical modeled for that compartment. Concentration was represented by color saturation, with white indicating a low concentration and strong red representing high concentration (Figures 6 through 8).

In computer simulations corresponding to 1 hour of exposure, all tissues are colored to a similar degree (Figure 6). This is because differences in chemical partitioning to tissue are offset at early time points by differences in relative blood perfusion, resulting in similar chemical concentrations. With continued exposure (3 hr), differences in chemical partitioning begin to dictate the distribution pattern (Fig 7). By 4 hours (Figure 8), accumulation in most tissues has leveled off. Only fat continues to accumulate significant amounts of toxin. At steady-state (> 240 hr; image not shown), 75% of the total pentachloroethane burden is contained in the fat compartment, despite the fact that it comprises only 9% of the mass of the animal.

While the isosurfaces themselves were constant for all time steps, as well as for other model runs on the same fish species, the coloring was recomputed for each time step. Individual time steps could be selected or the entire series could be shown in sequence.

5. Conclusions

This project demonstrates the display of sparse model output values on the actual 3D anatomical structures of the species of interest. Fish tissues are classified and then isolated, establishing a volumetric correspondent to each tissue type. Each organ surface is tiled and then painted with the model values, showing the physical meaning of model outputs. Animation of the representation shows toxin accumulation patterns over the course of simulated exposure.

The visualization methods presented here are well-suited to the display of PB-TK model outputs, since they are consistent with the compartmental structure of these models. They allow modelers to see their model results in an anatomical context. These techniques can then be used by modelers to communicate the results of their work to individuals who are not skilled in the interpretation of more conventional outputs. Finally, visualization of model results can be used to alert policy-makers and the general public of the dangers of water-borne pollutants.

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Figure 1. Raw MRI slice of rainbow trout. This image shows the second echo, which highlights differences in water content. This is slice 43, located roughly two-thirds of the way from tail to head. The diagonal structures outside fish are the plexiglass support.

Figure 2. Segmented image (slice 43). Tissues and organs are colored to roughly correspond to their actual appearances: fat = off-white, kidney = dark brown, liver = light brown, intestine = yellow, and muscle = pink..

Figure 3. 3D trout colored by tissue type.

Figure 4. Fish exterior from segmented volume. Voxel artifact is visible in the block structure of the surface.

Figure 5. Fish exterior from blurred volume. Voxel artifact is greatly reduced, but fins have eroded somewhat.

Figure 6. Tissues colored by concentration, after one hour of simulated exposure. Uptake happens most quickly in the GI tract.

Figure 7. Tissues colored by concentration, after three hours of simulated exposure. Levels in tissue other than fat have begun to plateau, while concentrations in fat continue to climb.

Figure 8. Tissues colored by concentration, after four hours of simulated exposure. Concentrations in fat begin to dominate the toxin distribution.