Time Lapse of Frog Embryo Development from MRI Data

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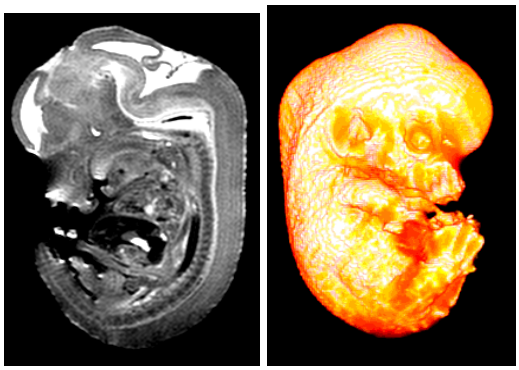
Abstract

Many imaging techniques (MRI, CT) map values from three-dimensional space. Such data is often easier to analyze using volume graphics, which allows for the visualization of a three-dimensional grid of data values. Such models can give a more intuitive sense of structures and their locations. Using methods such as this to show changes over time, one can gain a clear visual model of complex biological processes.

A μMRI time-lapse data set of frog embryos undergoing gastrulation was chosen to create a short movie. The natural alignment of the cell from one scan to the next, the short time step and the relative simplicity of it internal structure made the frog data set a top choice. A combination of common smoothing techniques and subdivision surfaces was used to build surfaces that are clean and smooth. Also subdivision surfaces can be used to allow for smooth morphing between time steps to give a clean continuous look to the video.

Background

Various volumetric imaging techniques, such as MRI and CT, take data by using sets that store the location of a sample in three dimensions and the value of the variable being observed. Volume graphics is used to represent such data in a more intuitive form and is especially useful in the case of data from medical scanners. Volume graphics can be used to highlight complex structures and to computationally section the data at arbitrary angles. A wide variety of data can be stored in such a manner and allow all quantitative information on an animal to be presented and stored in a concise framework. The idea for the work presented came from three-dimensional animal atlases, for example, Caltech's Biological Imaging Center's new Mouse Atlas[1]. Being able to show a single organism's development over time in three-dimensions is a powerful learning tool. Thus the goal became to make a time lapse movie of a frog embryo using μMRI data from the Caltech Biological Imaging Center. Such a movie helps in the visualization of the embryo's development and is a valuable teaching tool. Making such a movie is challenging for many reasons. The alignment of the volumes would be non-trivial as the embryo moves. Furthermore any real data would have associated noise that would need to be resolved before the project could move forward. In many cases, defining boundaries that illustrate the structures of the embryo is a difficult task. These difficulties all have to be handled even before tackling the difficulties in pulling everything together into a movie.



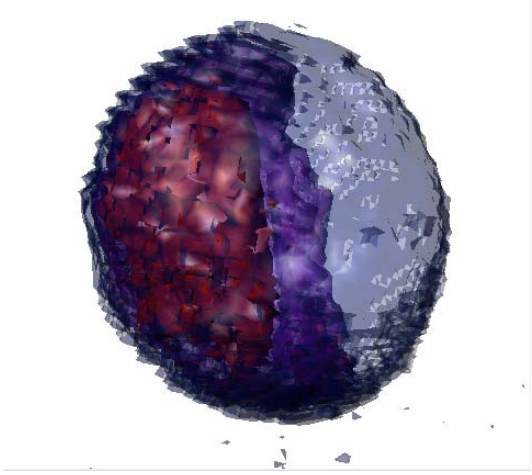
Left: A "slice" of data from a mouse embryo with each shade of gray representing a different value

Right: A picture of a volumetric representation of the same mouse embryo

Process

The process of making the movie began with finding data that would be appropriate. At the time, the goal was to create a time lapse movie showing development, but the question of what data would work was an issue. The data used needed to meet several qualifications. First, the data needed to have a fine enough resolution to see the details of development. Second, a relatively short time lapse was needed between the images. In the imaging process, the developing embryo is scanned at regular intervals. In order to have any hope of accuracy in the transition between one time period and the next, the time lapse needed to be short so that the changes in structure remained small. This is important in getting an accurate picture of the development. Also the process used to morph between the different surfaces requires the two surfaces to be quite similar to work properly. Third, the embryo needed simplicity, that is, a limited number of important structures that could be readily identified. Finally, the movie required some interesting process too occur. This tied into the goal of making the movie for educational purposes. After conferring with Caltech's Biological Imaging Center the decision was made to show the process of gastrulation in *Xenopus*, a frog commonly examined in developmental biology[2]. It was an ideal candidate with a resolution of 30-40 μm^3, a time lapse of an hour between scans (instead of a day mice), three simple, well-defined structures and a well known and easy to see process of development[3].

After an appropriate data set was found, rough visualizations of the data needed to be made. The data received from the MRI is a set of values corresponding to points in space. These values give information about what different parts of the embryo are made up of. Areas of rapidly changing values indicate a boundary between different structures within the embryo. These values must be converted into an image of where the boundaries are within the embryo. The algorithm used to do this conversion was based on the original Marching Cubes algorithm[4] for forming three dimensional surfaces from a set of values corresponding to points in space. The algorithm looks at a cube made up of eight of these points and determines a surface based on which points are "filled" (greater than some threshold value). In order to determine what threshold value would best work slices of the data sets were analyzed. There existed three rapid changes in values in these images giving a general range for each of three surfaces. After getting an initial range for each of the three surfaces, a variety of values within each range was run as a threshold value for the Marching Cubes algorithm to find a surface that minimized noise over the entire time series. The resulting files were put together into a three-dimensional "flipbook" to get a rough feel for a final product. The setup used allowed for the objects to be moved and rotated while going through the time series, giving ideas



Initial Results
Notice the noise evident in the spiking on the top left of the picture and the extra separated blobs on the bottom of the picture

about what angles would be most useful in the final product.

After this rough data was examined it was time to clean up the noise in the surfaces. This noise had many forms, the most obvious of which was a spiked pattern. Other noise was an accurate representation of the embryo, but obscured the major changes in the embryo. One idea was to implement a "shrink wrapping" mesh that would conform to the surface without resolving the spikes[5, 6]. Such a method would employ subdivision surfaces to progressively approach the surface[7, 8]. After close examination this idea was rejected in favor of a simpler method involving a signed distance function.

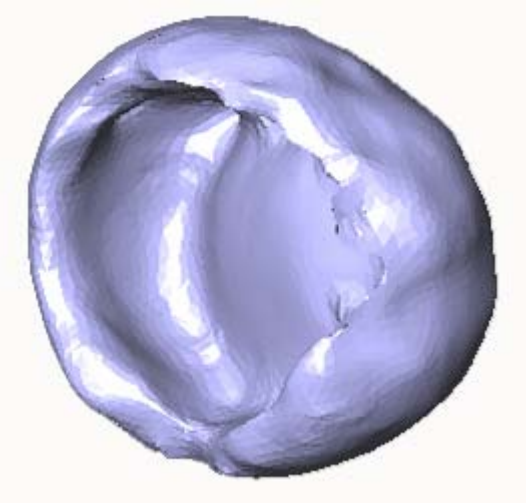
For each value in the grid, the distance function calculated the distance to the nearest surface of a given value using linear interpolation.

The end result is a grid of distances to the specified surface. Manipulating the distance function resulted in surprisingly clean and accurate surfaces. This data was reviewed in flipbook format to optimize certain parameters. Software was used to smooth the chunky surfaces, but the results have yet to be written into a form that can be displayed in a flipbook format. Currently it is being debated as to whether the original or the smoothed data would be better for creating a smooth transition for the movie.

Results

Currently the volumes have been cleaned into a readily usable state and are ready to go into the final stage of development. The smooth surfaces illustrate how powerful even simple techniques, like distance functions, can be. Also, there are several ways the work can be continued. One of the simplest and fastest would be to take the smoothed surfaces and convert them into the proper form to be used in a flipbook. Such a flipbook could be made relatively quickly and would have the benefit of allowing one to move and rotate the embryo model as time passes. The downside of such a method is that it lacks elegant transitions between each time and the additional software needed to view it. Still this form of displaying the developing embryo is compelling even when it is "noisy". A smoothed, focused version of the same data would be even more powerful. Another path would be to make a video in which the embryo morphed to make a smooth transition between images. Though this path would certainly be longer and more difficult, it leaves open the possibility of a very professional looking product in a standard file format. Though goal of creating a time-lapse movie of embryo development has not yet been reached, the current results suggest the feasibility of such movies in at least some other cases.

This work relates to many things happening at Caltech. For example, the Mouse Atlas[1] and Xenopus[2] work being done by the Biological Imaging Center are ongoing projects that directly influenced this work. This project joins in the spirit of such work by using technology to make biological processes easier to examine. On the side of computer graphics, the Multires Lab has many projects involving



An Example of a Smoothed Surface

volume graphics[9]. Though there is the common thread of volume graphics, the use of medical scanning and biological data are an addition to the areas the lab as a whole is looking at.

Concerning future research, the first thing to be done is to reach the goal of a movie. Work will continue this fall and should complete the project though the exact path to be taken is yet to be determined. Though the entire movie was not completed this summer the results achieved were important for the completion of the project. Many of the challenges involved were centered on the co-ordination of the variety of tools used. Simply some way to tie more of these tools together would be useful. The streamlining of the process used in this project would be a big step in doing more movies of this type. After completing the movie the mouse atlas seems to be a good place to do research. The form of the mouse atlas under production has many ambitious plans. The project has goals beyond showing the important structures of the mouse embryo at various stages of development (a far more difficult task than the frog embryo for a variety of reasons). It hopes to map the developmental genes of the mouse and act as a research resource in the study of these genes. In the long term, a similar MRI movie of a mouse embryo would be a lofty yet worth while idea for research, though it would be far more difficult to do than the frog embryo.

Methods

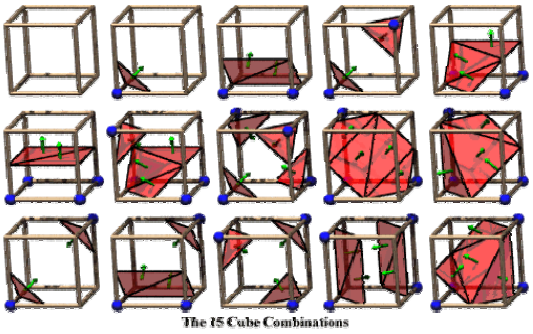
Marching Cubes[4]

The marching cubes algorithm locates the surface in a logical cube created from eight pixels, four each form adjacent slices of data. The algorithm determines how the surface intersects with this cube and then "marches" to the next.

To find this surface intersection, one defines a vertex as filled if the data is greater than or equal to the values whose surface is being constructed. They are considered to be within or on the surface. The other vertices are considered empty and outside of the surface. The surface of the value intersects those cube edges where one vertex is filled and the other is empty.

Since there are eight vertices in each cube, there exist only $2^8 = 256$ ways a surface can intersect a cube. By looking at complementary and rotational symmetries one can reduce these 256 cases to 15 patterns of edges. An index is created for each of the 256 cases which acts as a pointer to a precalculated edge table. The table gives all edge intersections for that case. Using the index to tell what edges are intersected, the location of intersection of the edge and the surface is calculated using interpolation.

The next step in the algorithm is the calculation of a unit normal for each triangle vertex. Finally the triangle vertices and vertex normals are displayed.



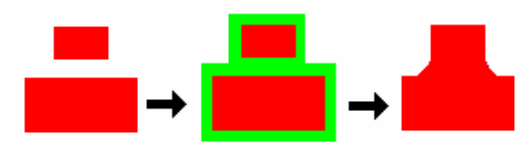
Possible Cube Combinations[4, 10]

Distance Function Manipulation

Distance functions can be used as a simple noise reduction technique. One begins by applying the distance function to a value of interest to get a field of floating point numbers that represent the distance of the given point from the nearest surface of that value.

Once this field is formed one can join pieces of an object together while maintaining a degree of accuracy by expanding and then contracting the surface. Similarly one can remove small unwanted noise from the field by contracting then expanding the object. By making sure the expansion and contraction are by the same factor one ends up with a simplified version of the original surface that is the correct size.

Expansion was done by rerunning the distance function algorithm on the original field, setting the value of interest to be some distance outside the current surface of interest. Contraction is done by setting the value of interest to be some distance within the current surface of interest.



Joining Objects by Expanding then Contracting the Distance Function

Removing Noisy Objects by Contracting then Expanding the Distance Function

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