An Open Source Mesh Generation Platform for Biophysical Modeling Using Realistic Cellular Geometries

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ABSTRACT Advances in imaging methods such as electron microscopy, tomography and other modalities are enabling high-resolution reconstructions of cellular and organelle geometries. Such advances pave the way for using these geometries for biophysical and mathematical modeling once these data can be represented as a geometric mesh, which, when carefully conditioned, enables the discretization and solution of partial differential equations. In this study, we outline the steps for a naïve user to approach `GAMer 2`, a mesh generation code written in C++ designed to convert structural datasets to realistic geometric meshes, while preserving the underlying shapes. We present two example cases, 1) mesh generation at the subcellular scale as informed by electron tomography, and 2) meshing a protein with structure from x-ray crystallography. We further demonstrate that the meshes generated by `GAMer` are suitable for use with numerical methods. Together, this collection of libraries and tools simplifies the process of constructing realistic geometric meshes from structural biology data.

SIGNIFICANCE As biophysical structure determination methods improve, the rate of new structural data is increasing. New methods that allow the interpretation, analysis, and reuse of such structural information will thus take on commensurate importance. In particular, geometric meshes, such as those commonly used in graphics and mathematics, can enable a myriad of mathematical analysis. In this work, we describe `GAMer 2`, a mesh generation library designed for biological datasets. Using `GAMer 2` and associated tools `PyGAMer` and `BlendGAMer`, biologists can robustly generate computer and algorithm friendly geometric mesh representations informed by structural biology data. We expect that `GAMer 2` will be a valuable tool to bring realistic geometries to biophysical models.

INTRODUCTION

The use of Partial Differential Equations (PDEs) in mathematical modeling of cellular phenomena is becoming increasing common, particularly, for problems ranging from electrostatics, reaction-diffusion, fluid dynamics, and continuum mechanics. Solutions to these equations using idealized geometries have provided insight into how cell shape can affect signaling (1, 2), and how blood flows in vessels (3).

On the other hand, in order to gain better insight into how cellular geometry can affect the dynamics of these mechanochemical processes, using realistic geometries is necessary. Already, freely available tools such as `Virtual Cell` (4) and `CellOrganizer` (5) have paved the way for using realistic cellular geometries in simulations. With increasing availability of high-resolution images of cellular ultrastructure, including the size and shape of organelles, and the curvature of the various cellular membranes, there is a need for computational tools and algorithms that can enable us to use these data as the geometry or domain of interest and conduct simulations using numerical methods (6).

For most relevant geometries, it is impossible to obtain analytical solutions for PDEs; this necessitates the use of numerical methods to provide an approximate solution. These numerical methods are based on *discretization* (approximating the PDE with a discrete algebraic system) combined with *solvers* (typically iterative methods that converge to the solution to the algebraic system). The first step usually requires the generation of a geometric mesh over which the problem can be discretized using techniques such as finite difference, finite volume, finite element, or other methods to build the algebraic system that approximates the PDE. The numerical approximation to the PDE is then produced by solving the resulting linear or nonlinear algebraic equations using an appropriate fast solver. One of the computational challenges associated with generating meshes of biological datasets is the presence of highly irregular surfaces with curvatures at the nanometer or Ångstrom length scales. Although many tools from the graphics community exist to generate meshes for visualization, these poor quality meshes, when used to solve a PDE, can both destroy the quality of the discretization as an

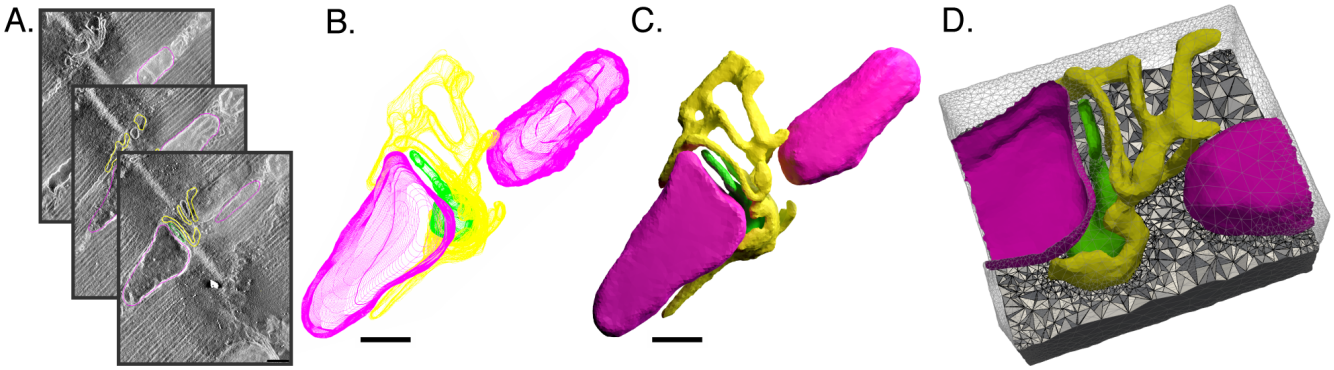

Figure 1: Example workflow using `GAMer` to construct a tetrahedral domain suitable for use with Finite Element simulations. A) Segmented Electron Tomogram of a murine cardiac Calcium Release Unit (CRU) from the Cell Image Library entry 3603. B) Stacks of contours from traced model. C) Conditioned surface mesh of the model. D) Tetrahedralized domain which can be used for simulating cytosolic diffusion. Note that we have inverted the tetrahedralized domain to represent the free space surrounding the CRU geometry. Scale bars are 200 nm.

approximation to the PDE, and also produce algebraic systems that are badly conditioned and difficult to solve efficiently or accurately with iterative solvers.

While it is possible to design discretizations of PDE problems on surfaces using finite volume methods or other techniques, we prefer the Finite Element Method (FEM) here for a number of reasons. To begin with, the FEM first arose in the 1960s in the engineering community as a response to the poor performance of existing discretization techniques for PDEs involving shells and other complex physical shapes. In addition, methods such as the FEM that are built on basis function expansion provide a natural framework both for treating highly nonlinear problems, and for discretizing multiple PDE that couple together to form a larger multi-physics system. Lastly, the FEM framework is quite general, and can in fact be shown to reproduce finite volume, spectral, and other discretizations through appropriate choices of basis and test functions.

One challenge preventing the routine use of experimental structural data with PDE-based mathematical modeling is the difficulty to generate a discretization, or commonly a mesh, which accurately represents the structures of interest. Building upon existing meshing codes, such as `TetGen` (7), `NetGen` (8), `TetWild` (9), `MeshLab` (10), `Gmsh` (11), `CGAL` (12), along with commercial codes such as `ANSYS Meshing` among others, we describe the development of a meshing framework, the Geometry-preserving Adaptive MeshER software version 2 (`GAMer 2`), which is designed specifically for biological mesh generation. This code has been completely rewritten from version 1, which was previously described by Yu *et al.* (13, 14), Gao *et al.* (15, 16), and (17). `GAMer 2` features the original `GAMer` algorithms but with significantly improved ease of use, distributability, and maintainability. We have also developed a new Python Application Programming Interface (API): `PyGAMer`, and streamlined the `GAMer Blender` add-on: `BlendGAMer`. The complete explanation of the mathematics and underlying algorithms are available in (13–18). In what follows, we provide an overview of the `GAMer` mesh generation capabilities for the general biophysicist.

METHODS

At its core, `GAMer` is a mesh generation and conditioning library which uses concepts from the graphics and engineering literature. It can be used to produce high quality surface and volume meshes from several types of input: 1) PDB/PQR file (Ångstrom–nanometer), 2) Volumetric dataset (Ångstrom–meters), or 3) Initial surface mesh (Ångstrom–meters). To enable FEM-based applications, `GAMer` also has utilities to support boundary marking. Tetrahedral meshes of a domain can be constructed in `GAMer` through the use of functionality provided via `TetGen` (19). Surface or volume meshes can be output to several common formats for use with other tools such as `FEniCS` (20, 21), `ParaView` (22), `MCell` (23), and `FFEA` (24) among others. We note that although `GAMer` is designed primarily with FEM-based applications in mind, conditioned meshes of realistic geometries can also be used for geometric analysis such as the estimation of curvatures, volumes, and surface areas (25). Conditioned meshes can also be used in other tools such as `MCell` (23) and 3D printing. Example tutorials of using `GAMer 2` to generate surface and volume meshes of a protein structure (PDB ID: 2JHO) and a subcellular scene of a calcium release unit from a murine cardiac myocyte imaged using Electron Tomography (ET) (Cell Image Library: 3603 (26)), Fig. 1, are provided in the documentation and described in this report. Here we will summarize the key implementation steps and refer the interested reader to (25) for the technical details.

GAMer 2 Development

One of the limitations of prior versions of GAMer is the inability to robustly represent meshes of arbitrary manifoldness and topology. This limitation prevented the safe application of GAMer to non-manifold meshes, which often produced segmentation faults or other undefined behaviors. To ameliorate this, in GAMer 2 we replaced the underlying mesh representation to use the Colored Abstract Simplicial Complex (CASC) data structure (27). CASC keeps careful track of the mesh topology and therefore makes it trivial to track the manifoldness of a given mesh object. By eliminating the need for code to handle encounters with non-manifold elements, the code base is significantly reduced and segmentation faults no longer occur. Another benefit of using CASC is that it can represent both surface meshes (2D simplices embedded in 3D) and volume meshes (3D simplices embedded in 3D), allowing users to interact with both surface and volume meshes using an identical API. This simplification contributes to the long-term maintainability of the GAMer 2 code.

In the development of GAMer 2, we have also migrated to use the cross-platform CMake build toolchain, and away from the previous GNU build system Autotools. Using CMake, GAMer 2 can now be compiled and run on major operating systems including Linux, and Mac OS–along with Windows which was previously unsupported. We note that the Windows binary can be built directly using Microsoft Visual Studio and does not require the installation of Unix-like environments such as Cygwin. By supporting compilation of GAMer 2 using native and preferred tools, this improves binary compatibility with other libraries and simplifies distribution.

Collaborative Workflow

To further improve code availability and to encourage community collaboration, the GAMer code is now hosted on Github[1]. In this environment, users can file issues to report bugs or ask questions. Users are also encouraged to contribute to the code by submitting pull requests. All pull requests are put through rigorous continuous-integration testing to ensure code compatibility across a wide range of operating systems, compilers, and versions prior to integration with the main deployment branches. Along with source control, GAMer 2 also implements git tagging based semantic versioning to track the software version. Compiled code can report the source version which aids in reporting and debugging.

Implementation of a New PyGAMer API

In addition to the complete redesign of the core library, the corresponding Python interface, now called PyGAMer, is now generated using PyBind 11 (28) instead of SWIG (29). PyBind 11 was designed to expose C++ types to Python and vice-versa while minimizing boilerplate code by capitalizing upon the capabilities of the C++ compiler. One of the benefits of this approach is the ability to bind complex template types, which are extensively used in CASC. This enables users to develop Python script to interact with elements of mesh and call C++ methods. Another benefit of using PyBind 11 is its support for embedding Python docstrings which enable straightforward documentation of PyGAMer using popular Python tools such as Sphinx. To this end, documentation for GAMer 2 and PyGAMer is now automatically generated and hosted online[2].

Using scikit-build, which connects setuptools and CMake, installation of PyGAMer in any Python environment can be achieved easily using pip install pygamer. pip will automatically download and resolve dependencies and build the PyGAMer Python extension module.

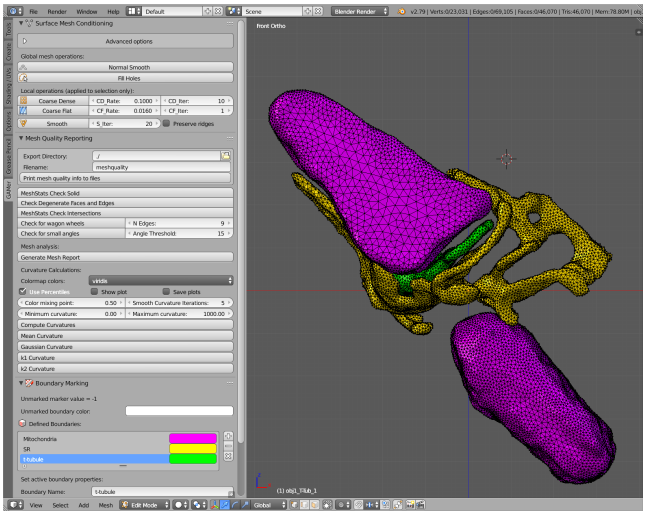

Figure 2: Screenshot of the BlendGAMer toolshelf menu in 3D modeling software Blender. The user can call GAMer mesh conditioning, analysis, boundary marking, and tetrahedralization functions by clicking buttons and adjusting settings in the toolshelf. Shown on the right is a conditioned surface mesh of the calcium release unit model.

BlendGAMer Development

In order to support interactive modeling with graphical feedback, we have a GAMer addon for Blender (30) (BlendGAMer). BlendGAMer has also been rewritten to use PyGAMer. In addition to this update, the user interface has been redesigned to be easier to use, shown in Fig. 2. The boundary marking capability now uses Blender attribute layers instead of lists of values. Many features now have corresponding toggles in the interface, for example, the number of neighborhood rings to consider when computing the Local Structure Tensor (LST). Several mesh conditioning operations have also been updated to operate only upon selected vertices. There is also a new Mesh Analysis panel which contains several helpful

[1] https://github.com/ctlee/gamer

[2] https://gamer.readthedocs.io

features for analyzing the quality of a mesh and includes curvature estimation. Based upon the newly implemented semantic versioning, `BlendGAMer` can now track the version of metadata which is stored in a given file. Using this information `BlendGAMer` and perform automatic metadata migration from version to version as improved schemes for metadata storage are created.

Modeling Diffusion in the CRU Geometry

To demonstrate the use of the generated mesh with the FEM, we model the diffusion of a molecule with concentration u in the CRU geometry, Fig. 3. The dynamics of u are modeled as

$$\frac{\partial u}{\partial t} = D\nabla^2 u - \frac{u}{\tau} \text{ in } \Omega, \quad (1)$$

$$u(\mathbf{x}, t = 0) = 0, \quad (2)$$

where D is the diffusion constant, τ is a decay constant, Ω is the cytosolic domain, and t is time. We define boundary conditions:

$$D(n \cdot \nabla u) = J_{\text{in}} \text{ on } \partial\Omega_{\text{t-tubule}}, \quad (3)$$

$$D(n \cdot \nabla u) = 0 \text{ on } \partial\Omega_{\text{other}}, \quad (4)$$

$$\partial\Omega = \partial\Omega_{\text{t-tubule}} \cup \partial\Omega_{\text{other}}, \quad (5)$$

where J_{in} is the inward flux on the t-tubule membrane ($\partial\Omega_{\text{t-tubule}}$). No flux boundary conditions are applied to all other boundaries. The following system is solved using `FEniCS` (20, 21) and visualized using `ParaView` (22). We note that the boundaries $\partial\Omega_{\text{t-tubule}}$ and $\partial\Omega_{\text{other}}$ are differentiated by markers applied using `BlendGAMer`.

RESULTS AND DISCUSSION

We demonstrate that `GAMer` is capable of generating high quality surface and volume simplex meshes of geometries as informed by structural biology datasets. The incorporated Python library, `PyGAMer`, and `Blender` add-on, `BlendGAMer`, enable users to prototype or interact with meshes as they are conditioned. Collectively these tools enable the facile mathematical modeling of biological systems using realistic geometries. The `GAMer` workflow has been previously applied in several works (25, 31–36).

Several examples are described in the online `GAMer 2` documentation. Shown in Fig. 1, are the steps to go from ET data to simulation quality mesh. In this example, a segmented ET dataset (Fig. 1 A) featuring a murine Calcium Release Unit (CRU) is retrieved from the Cell Image Library, shown in Fig. 1 B. This is the same starting geometry previously used by Hake et al. (34). From the model contours, we generated a preliminary mesh which was then conditioned using `BlendGAMer` to produce Fig. 1 C. Using `Blender` Boolean mesh operations, the geometry was inverted to represent the cytosolic space surrounding the CRU and tetrahedralized (Fig. 1 D). In this case, the mesh is sufficiently high quality and suitable for use with FEM-based simulations as shown in Fig. 3.

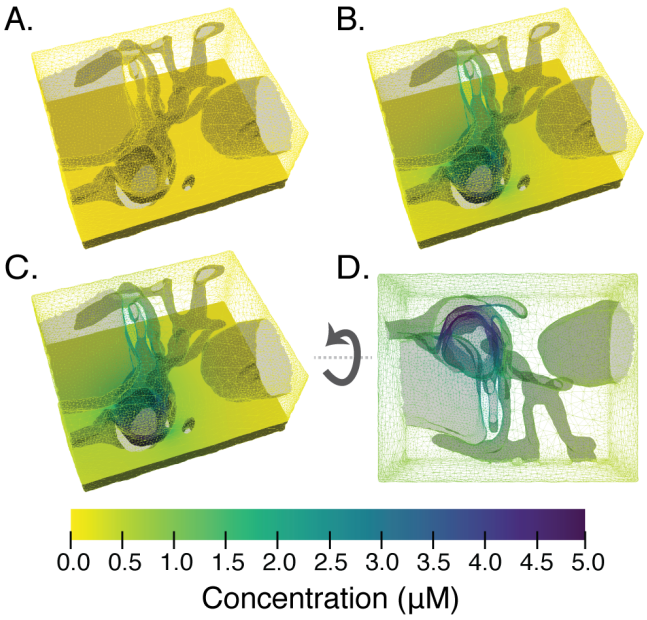

Figure 3: Snapshots of molecular diffusion in the calcium release unit geometry. A) initial condition; B) 200 μs; C) 400 μs; D) 5000 μs. The molecules can be trapped in locally confined regions leading to enriched concentrations.

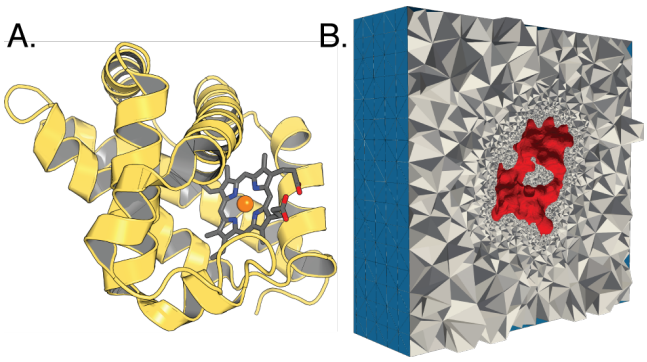

Figure 4: Example demonstrating the meshing of protein myoglobin (PDB ID: 2JHO). A) Rendered cartoon representation with heme and iron shown as sticks. B) Tetrahedralization of the space excluding the protein volume. Red denotes faces marked as protein and blue denotes faces on the boundary of the enclosing cube.

In Fig. 4, we demonstrate the mesh generation capabilities of `GAMer` from atomistic protein structural data such as those available from the Protein Data Bank. A volume dataset representing the approximate occupied space of all atoms is generated by applying a Gaussian kernel over the atomic positions. An isosurface of the dataset can then be meshed using the marching cubes algorithm (37). While `GAMer` includes a

basic table of atom types to assign radii, more sophisticated atomic radius assignment tools (e.g., `PDB2PQR` (38)) can be used and radius information passed via the PQR file format.

CONCLUSION

The realism of biophysical models can be enhanced by incorporation realistic geometries from structural biology. `GAMer 2` brings the community closer to this goal by simplifying the mesh generation process. Our design strategies in implementing `GAMer 2` encourage community collaboration. We believe that, moving forward, `GAMer 2` can serve as an integrative platform for meshing biological mesh generation.

SOFTWARE AVAILABILITY

`GAMer` is licensed under GNU Lesser General Public License (LGPL), version 2.1 or later. Full documentation and examples are available at the project home page, gamer.readthedocs.io, and development is hosted on GitHub at http://github.com/ctlee/gamer. The latest release v2.0.3 is archived on Zenodo (doi:10.5281/zenodo.2340294).

AUTHOR CONTRIBUTIONS

C.T.L., J.G.L., J.B.M., and M.J.H. developed the software; C.T.L. drafted the article; C.T.L., J.G.L., J.B.M., J.A.M., R.E.A., M.J.H., and P.R. edited the article; and all authors read and approved the final article.

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