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Rotor Termination in a Patient-Specific Model of Atrial Fibrillation /

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Rotor Termination in a Patient-Specific Model of Atrial Fibrillation

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Bioengineering

by

Matthew James Gonzales

Committee in charge:

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2013
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University of California, San Diego
2013
DEDICATION

To Mom and Dad, who gave me the best childhood I could have asked for.
EPIGRAPH

Be true to your work, your word, and your friend.

Henry David Thoreau
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<th>Abbreviation</th>
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<tbody>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>APD</td>
<td>Action potential duration</td>
</tr>
<tr>
<td>AVO</td>
<td>Aortic valve orifice</td>
</tr>
<tr>
<td>BiA</td>
<td>Bi-atrial</td>
</tr>
<tr>
<td>BB</td>
<td>Bachmann’s bundle</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CRT</td>
<td>Cardiac resynchronization therapy</td>
</tr>
<tr>
<td>CS</td>
<td>Coronary sinus</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography; crista terminalis</td>
</tr>
<tr>
<td>CV</td>
<td>Conduction velocity</td>
</tr>
<tr>
<td>DT</td>
<td>Diffusion tensor</td>
</tr>
<tr>
<td>ERP</td>
<td>Effective refractory period</td>
</tr>
<tr>
<td>FIRM</td>
<td>Focal impulse and rotor mapping</td>
</tr>
<tr>
<td>FC</td>
<td>Four-chamber</td>
</tr>
<tr>
<td>FK</td>
<td>Fenton-Karma (ionic model)</td>
</tr>
<tr>
<td>GL</td>
<td>Gauss-Legendre (integration)</td>
</tr>
<tr>
<td>IPB</td>
<td>Inferoposterior bridge</td>
</tr>
<tr>
<td>IR</td>
<td>Intercaval region</td>
</tr>
<tr>
<td>IVC</td>
<td>Inferior vena cava</td>
</tr>
<tr>
<td>LA</td>
<td>Left atrium</td>
</tr>
<tr>
<td>LAA</td>
<td>Left atrial appendage</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>MVO</td>
<td>Mitral valve orifice</td>
</tr>
<tr>
<td>NURBS</td>
<td>Non-uniform rational B-splines</td>
</tr>
<tr>
<td>ODE</td>
<td>Ordinary differential equation</td>
</tr>
<tr>
<td>PDE</td>
<td>Partial differential equation</td>
</tr>
<tr>
<td>pLAw</td>
<td>Posterior left atrial wall</td>
</tr>
<tr>
<td>PM</td>
<td>Pectinate muscle</td>
</tr>
<tr>
<td>PV</td>
<td>Pulmonary vein</td>
</tr>
<tr>
<td>PVO</td>
<td>Pulmonary vein orifice</td>
</tr>
<tr>
<td>RA</td>
<td>Right atrium</td>
</tr>
<tr>
<td>RAA</td>
<td>Right atrial appendage</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>RFA</td>
<td>Radiofrequency ablation</td>
</tr>
<tr>
<td>RV</td>
<td>Right ventricle</td>
</tr>
<tr>
<td>SVC</td>
<td>Superior vena cava</td>
</tr>
<tr>
<td>S-LV</td>
<td>Septum, left ventricular aspect</td>
</tr>
<tr>
<td>S-RV</td>
<td>Septum, right ventricular aspect</td>
</tr>
<tr>
<td>VS</td>
<td>Ventricular septum</td>
</tr>
<tr>
<td>WL</td>
<td>Wavelength</td>
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The content of Chapter 2 is almost identical to a manuscript accepted for publication, with only formatting changes for this dissertation. The citation is Gonzales, M.J., Sturgeon, G., Krishnamurthy, A., Hake, J., Jonas, R., Stark, P., Rappel, W.J., Narayan, S.M., Zhang, Y., Segars, W.P., McCulloch, A.D., 2013. A three-dimensional finite element model of human atrial anatomy: New methods for cubic Hermite meshes with extraordinary vertices. Medical Image Analysis 17(5):525-537. The manuscript was accepted March 4, 2013. The authors of this manuscript would like to thank Chandrajit Bajaj and Joe Warren for providing advice about subdivision surfaces. This work was supported by by NIH grants NHLBI 1 R01 HL96544 (ADM), NHLBI 1 R01 HL083359 (SMN, WJR), NHLBI 1 K24 HL103800 (SMN), NHLBI 1 RO1 HL091036 (WPS), NHLBI 5 T32 HL007089, NHLBI 1 T32 HL105373, NIBIB 1 T32 EB009380 (ADM), NIGMS 8 P41 GM103426 (National Biomedical Computation Resource), and NIGMS P50 GM094503 (Virtual Physiological Center for the Study of Complex Diseases). This work was also supported by NSF Career Award OCI-1149591 (YZ), the San Diego Fellowship (MJG), and the Center of Excellence grant from the Research Council of Norway to the Center for Biomedical Computing at Simula Research Laboratory. Figure 2.6A-B is reprinted from a journal article with permission from British Medical Journal Publish Group Ltd. The full citation for this article is Wang, K., Ho, S.Y., Gibson, D.G., Anderson, R.H., 1995. Architecture of atrial musculature in humans. British Heart Journal 73:559-565.
The content of Chapter 3 is mostly an original document. Parts of Sections 3.3.1, 3.4.1, and 3.4.3 were adapted from an extended abstract that appeared in conference proceedings. The citation for this extended abstract is Gonzales M.J., Sturgeon G., Segars W.P., McCulloch A.D. (2012) A pipeline from non-invasive imaging to patient-specific models of cardiac electromechanics: An atlas-based approach. Workshop on Mesh Processing in Medical Image Analysis in Conjunction with 14th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI). Nice, France. Oct. 1-5, 2012 (Abstract). The author would like to thank Gregory Sturgeon for his technical assistance in providing Python implementations for many of the mesh regularization schemes used in this chapter, and for providing model FC-421 in Section 3.3.3. The author would like to thank René Jonas for helping to write the software plug-in HexBlender. Finally, the author would like to thank Adarsh Krishnamurthy for performing the biomechanics simulations in Section 3.3.4.

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Conference Proceedings

ABSTRACT OF THE DISSERTATION

Rotor Termination in a Patient-Specific Model of Atrial Fibrillation

by

Matthew James Gonzales

Doctor of Philosophy in Bioengineering

University of California, San Diego, 2013

Professor Andrew D. McCulloch, Chair
Professor Sanjiv M. Narayan, Co-Chair

Atrial fibrillation (AF) is the most common arrhythmia in the United States and is a risk factor for stroke and cardiac dysfunction. Pharmacological and surgical treatments of AF have limited efficacy, partly attributable to a limited understanding of its basic mechanisms. Patient-specific computational models have shown promise for planning personalized treatment strategies for AF, but progress is still nascent and computational studies do not
currently solve in clinical timescales. In this dissertation, the author describes new finite element methods for modeling human AF, and then uses these methods in a patient-specific model to suggest mechanisms for AF maintenance and termination.

A clinical description of AF and the basic mechanisms of AF are presented in Chapter 1. New methods for constructing cubic Hermite models of the atria from non-invasive imaging data are presented in Chapter 2, and these methods are extended to construct four-chamber models of the heart in Chapter 3. Heretofore, high-order finite element models have not been used on complicated shapes such as that of the atria and ventricular models with valve annuli, yet high-order models have attractive properties such as superior convergence compared to linear finite element models in electrophysiology and biomechanics problems, which can decrease the time required for simulations toward clinical timescales. Convergence properties of both cubic Hermite and cubic Hermite-style serendipity basis functions for the solution of the monodomain equation of cardiac electrophysiology are evaluated in Chapter 4. We find that cubic Hermite and cubic Hermite-style serendipity basis functions have superior convergence properties in the monodomain problem in comparison with linear finite elements for equal numbers of elements and integration points.

In Chapter 5, we examine an experimental case study of AF with the aid of a patient-specific model. We find that meandering rotors are important focal sources of AF, and are made possible by remodeling of the action potential shape and a decrease in electrical anisotropy. Virtual radiofrequency ablation may terminate AF by creating a spatial excitable gap near the rotor and decreasing the fractionation exacerbated by rotor meander. We then speculate how patient-specific models of AF might be used in the future.
Chapter 1

Human atrial fibrillation: clinical presentation, therapy, and basic mechanisms
Abstract

In this chapter, I briefly review several aspects of atrial fibrillation (AF). First, I review AF in clinical medicine and its current treatment modalities, including pharmacological therapy and radiofrequency ablation. Next, I describe normal atrial electrophysiology. I then review our current understanding of the basic mechanisms of AF, with a focus on uncertainties concerning the sustaining mechanisms and recently-acquired data from our group supporting the “focal source” hypothesis of AF maintenance. Finally, I review computational modeling of AF, and describe how the work in this dissertation may one day allow for clinical decision-making partially informed by computational models.

1.1 Atrial fibrillation in clinical medicine

Atrial fibrillation (AF) is the most common arrhythmia in the United States, affecting over 2 million people as of 2001 (Go et al., 2001) and is estimated to be affecting over 6 million people in 2013 (Miyasaka et al., 2006). The incidence of AF increases markedly with age (Feinberg et al., 1995), suggesting its prevalence in the United States will continually increase as the population ages. Those with AF are at an increased risk for stroke (Wolf et al., 1991), progressive cardiac dysfunction (Grogan et al., 1992; Redfield et al., 2000), and an overall increased risk of death (Benjamin et al., 1998).

Atrial fibrillation is characterized by spatiotemporal irregularity in the electrical activation of the heart confined to the atrial chambers. In health, the synchronous contraction of the atria occurs at the end of cardiac diastole and completes the filling of the ventricle. In AF, electrical dysfunction gives rise to mechanical dyssynchrony and a decrease in cardiac output, in turn contributing to ventricular dysfunction and heart failure. The mechanical dyssynchrony also allows for pooling of blood and thrombosis, particularly in the left atrial appendage (Al-Saady et al., 1999).
Risk factors for developing atrial fibrillation include age, hypertension, coronary artery disease, obesity, alcohol consumption, male sex, diabetes mellitus, hyperthyroidism, mitral valve disease, and family history of AF (Calkins et al., 2012; Psaty et al., 1997). The common pathways for these risk factors in the pathogenesis of AF are believed to be atrial dilatation, structural remodeling of the atria, electrical remodeling of the atria, and other cardiac dysfunction giving rise to higher atrial pressures (Calkins et al., 2012).

Atrial fibrillation patients can have clinical symptoms or be asymptomatic. Patients with AF may report syncope, fatigue, palpitations, shortness of breath, and angina. Clinical signs include an irregularly irregular pulse, a high heart rate, and the signs of any underlying disease giving rise to AF. Electrocardiogram studies show no p-waves before QRS complexes, but the QRS complexes may be morphologically normal.

The length of an AF episode can be as short as seconds, as long as months, or be permanent. Atrial fibrillation will thus be classified by the typical length of AF episodes for a patient. Patients with a history of two or more brief (less than 7 days) and self-terminating AF episodes are termed to have paroxysmal AF. Patients with at least two AF episodes longer than 7 days and requiring intervention for cardioversion to sinus rhythm are termed to have persistent AF. Patients with episodes of AF lasting over one year are sometimes termed to have permanent AF. Patients often have paroxysmal AF that over time progresses to persistent and permanent AF—after initial diagnosis of paroxysmal AF, about 10% of patients develop persistent AF after one year and about 25% develop persistent AF after five years (Kerr et al., 2005).
1.2 **Treatment of atrial fibrillation**

Patients with AF can be restored to sinus rhythm through electrical cardioversion, pharmacological therapy, surgical ablation, or radiofrequency ablation (RFA). In the inpatient setting, AF can be converted to sinus rhythm by pharmacological agents or more abruptly by electrical cardioversion when immediate restoration to sinus rhythm is required. Long-term, outpatient treatment of AF is accomplished by pharmacological agents or radiofrequency ablation. Pharmacological therapy and radiofrequency ablation treatment strategies are discussed immediately below.

1.2.1 **Anti-arrhythmic drugs**

Class I and class III anti-arrhythmic drugs can be used to maintain sinus rhythm in patients with a history of AF and also to cardiovert an episode of AF to sinus rhythm; class II and class IV anti-arrhythmics can be used for rate control, preventing the fast rates in the atria from causing fast rates in the ventricles. Rates of mortality and stroke are similar in AF patients treated by rate control and by rhythm control (Carlsson et al., 2003; Steinberg et al., 2004). The efficacy of both rate and rhythm control agents in promoting survival among AF patients remains unclear. Several clinical trials have found that neither rate control nor rhythm control agents promoted survival after statistically adjusting for medication side effects (Corley et al., 2004; Flaker et al., 1992).

1.2.2 **Pharmacological stroke prophylaxis**

Patients with paroxysmal, persistent, and permanent AF are all at risk for embolic stroke and are candidates for anti-coagulation therapy. Patients with low-to-moderate risk of stroke may be given anti-platelet agents such as aspirin, be given aspirin with clopidogrel, or be given no pharmacological prophylaxis; patients with moderate-to-high risk of stroke are given warfarin, an anti-coagulant. Patients receiving warfarin are about 50% less likely to
suffer ischemic stroke compared with patients with no anti-coagulation therapy (Go et al., 2003); the benefits of aspirin therapy are much smaller (van Walraven et al., 2002).

1.2.3 Radiofrequency ablation

Radiofrequency ablation (RFA) can be used to treat paroxysmal, persistent, or permanent AF. In this procedure, radiofrequency (RF) energy is delivered to atrial tissue and dissipated as heat, causing necrosis and eventual scarring of the underlying tissue. The RF energy is delivered via a catheter inserted percutaneously into the venous system and then into the heart. Radiofrequency ablation is used in the treatment of atrial fibrillation, atrial flutter, and other supraventricular tachycardias. Typical indication for RFA treatment of AF is the presence of AF symptoms and failure of at least one class I or class III anti-arrhythmic drug (Calkins et al., 2007).

The optimal locations and shapes of applied RF lesions in AF have been a subject of great debate. The most common patterns in RF ablation are pulmonary vein isolation (Haïssaguerre et al., 2000) and wide-area circumferential ablation (Pappone et al., 2000). It is believed that electrical isolation of the pulmonary veins prevents AF from being triggered, whereas lesions in the body of the atria prevent circuits of electrical activity needed to maintain fibrillation. Targeted RFA has been a subject of intense research; potential ablation targets include areas of dominant frequency (Sanders et al., 2005), complex fractionated electrograms (CFAEs) (Nademane et al., 2004), ganglionated plexi (Pokushalov et al., 2009), and focal sources (Narayan et al., 2012b).

Atrial fibrillation remission rates after RFA are only about 60-70% for paroxysmal AF (Oral et al., 2002; Wilber et al., 2010) and only about 30-50% for persistent AF (Cheema et al., 2007; Oral et al., 2007). With multiple RFA procedures, remission from persistent AF improves only to 50-55% (Cheema et al., 2007). Even so, treatment by RFA has lower
incidence of AF episodes, fewer hospitalizations, and improved patient-reported quality-of-life compared with treatment by anti-arrhythmic drugs (Wazni et al., 2005; Wilber et al., 2010).

One worldwide survey found that the major complication rate of RFA for AF was 6.0% (Cappato et al., 2005), with cardiac tamponade the most common major complication (1.0% of patients). A more recent study by the same group (Cappato et al., 2009) found that the overall rate of mortality during RFA was 0.1%. Aside from tamponade, other common major complications are embolism, pulmonary vein stenosis, phrenic or vagus nerve damage, atrioesophageal fistula, and acute coronary occlusion (Calkins et al., 2012). Minor bleeding at the site of catheter insertion common, but is a minor complication so long as infection is avoided.

1.3 Atrial electrophysiology

1.3.1 Biophysics of wave propagation

Cardiac tissue is composed mainly of muscular cells called cardiomyocytes, fibroblasts, and extracellular matrix proteins such as collagen. Potential differences within cardiac tissue give rise to current flow intracellularly and extracellularly with magnitude determined by tissue resistivity. Intracellular currents of sufficient magnitude do not dissipate and extinguish but rather cause a “renewable” wave to propagate: intracellular currents flow electrotonically to adjacent cardiomyocytes, giving rise to membrane depolarization, opening of voltage-sensitive ion channels, and flow of new charged species into the cell. The result is the unidirectional propagation of an electrical wave in three dimensions that normally will not extinguish until reaching an obstacle or boundary.

Cardiac tissue—like many other excitable media—has an activated state, a quiescent state, and a refractory state, owing to the recovery time of voltage-sensitive channels. A voltage-sensitive channel requires a finite amount of time to elapse between two electrical activations, even if the voltage has completely returned to the resting level in the time between
the two electrical stimuli. The cardiac action potential in both the ventricles and the atria lasts hundreds of milliseconds under normal conditions, tending to promote unidirectional propagation through cardiac tissue.

Current flows through adjacent cardiomyocytes by means of gap junctions. Gap junctions are low-resistance channels allowing for cell-to-cell transmission of ions and other small molecules. Although there is a transjunctional voltage drop between cells as current propagates from one cell to another, the resistance of gap junctions is quite low, and electrical propagation in physiological circumstances behaves as a continuum process at the tissue level. In the weakly excitable limit and under conditions of gap junctional uncoupling (e.g., myocardial infarction), the discrete nature of electrical propagation may be important in propagation failure and arrhythmia (Rudy and Quan, 1987; Spach, 1983).

The morphology of the cardiomyocyte plays a role in its electrical function. Cardiomyocyte morphology is often described as “brick shaped”—cardiomyocytes have a longer, dominant dimension along which the contractile myofibrils are oriented. Cardiomyocytes are coupled to about ten cells on average (Hoyt et al., 1989) by intercalated discs, with more connections to adjacent cells along their long axis (approximately 70%) than along their short axis (approximately 30%) (Saffitz et al., 1994). Moreover, large numbers of myocytes are organized into larger sheets of myocytes with consistent or smoothly-varying orientations (LeGrice et al., 1995). The predominantly long-axis coupling of myocytes and the tendency for myocytes to be organized into sheets with smoothly-varying fiber orientations gives rise to anisotropy of electrical propagation at the tissue scale. The ratio of conduction velocity in the longitudinal and transverse directions varies under different conditions (e.g., depolarization rate, ion concentrations) but is typically reported to be about 3 (Clerc, 1976; Roberts et al., 1979).
1.3.2 Ionic currents in the atrial myocyte

The genesis of a cardiomyocyte action potential normally is the electrotonic flow of current from adjacent cells that charges the membrane bilayer and causes activation of voltage-dependent ion channels in the membrane. The voltage-gated ion channels and currents responsible for the action potential morphology of the human ventricular myocyte and human atrial myocyte are mostly the same: both cells share the fast inward Na$^+$ current ($I_{Na}$), the L-type Ca$^{2+}$ current ($I_{CaL}$), the fast and slow delayed rectifier K$^+$ currents ($I_{Kr}$ and $I_{Ks}$), the transient outward potassium current ($I_{to}$), and the inwardly-rectifying potassium current ($I_{K1}$). The magnitudes of $I_{Kr}$ and $I_{Ks}$ in human atrial myocytes are low compared with the magnitudes in the human ventricular myocytes (FIREK and GILES, 1995). As a consequence, late ventricular myocyte repolarization is effected largely by $I_{Kr}$ and $I_{Ks}$, whereas late atrial myocyte repolarization is effected principally by the ultra-rapid delayed rectifier potassium current ($I_{Kur}$) and $I_{K1}$ (WANG et al., 1993). The action potential morphologies and durations may vary widely even within the same tissue preparation owing to heterogeneities in ion channel concentrations.

1.4 Basic mechanisms of atrial fibrillation

1.4.1 Trigger, substrate, and pulmonary vein ectopy

HAISSAGUERRE and colleagues made the seminal observation that AF could be initiated by rapid firing of focal sources originating in the pulmonary veins (HAISSAGUERRE et al., 1998). All the while, it had long been believed that intrinsic changes to atrial tissue must take place to sustain AF after it had been initiated. Thereafter, it was believed that AF required both a “trigger” and a “substrate”. The trigger is believed to be an ectopic driver originating in the pulmonary veins or great vessels; the trigger may also be iatrogenic pacing. The identity of the “substrate” is unknown.
The precise mechanism by which fast rates from ectopic foci give rise to AF initiation is unclear. Animal models have suggested that increased sympathetic tone may give rise to fast rates, increased automaticity, and early after-depolarizations, perhaps by means of abnormal activity of the Na⁺-Ca²⁺ exchanger (Patterson et al., 2006). Fast rates and ectopic beats may then be the appropriate conditions under which conduction block and electrical wavebreak occur, after which a single wavebreak will become fulminant AF in the presence of a pro-AF substrate. The events giving rise to conduction block at fast rates are not well understood; several mechanisms have been suggested. One, fast rates may precipitate ectopic activity, and a precisely-timed ectopic beat may fortuitously encounter another wave in a manner causing conduction block and wavebreak. Two, fast rates may give rise to action potential duration (APD) alternans, in turn causing decreased spacing between successive wavefronts and wavebacks, then wave collision and wavebreak (Fenton et al., 2002). Three, heterogeneities of tissue may give rise to dispersion of refractoriness (Liu and Nattel, 1997), promoting conduction block at fast rates. Last, waves may be interrupted directly by inexcitable scars and fibrosis and fractionate by formation of eddy waves (Cabo et al., 1996). It is possible that more than one of these mechanisms gives rise to AF initiation in humans.

1.4.2 Multiple wavelets and focal sources as sustaining mechanisms

As discussed above, it is believed that an AF episode requires both an initiating event (trigger) and a sustaining mechanism (substrate). Two principal hypotheses have emerged regarding the sustaining of AF: the multiple wavelet hypothesis and the focal source hypothesis. The multiple wavelet hypothesis was first proposed by Moe (1962) using a computer model of AF (Moe et al., 1964). Moe and colleagues proposed that multiple meandering wavelets randomly multiply and annihilate to sustain AF, and that if a critical
number of wavelets are present, AF will self-perpetuate, whereas if fewer wavelets are present, AF will terminate.

Allessie and colleagues proposed that the multiple wavelets existed as small functional reentrant circuits. According to their “leading circle” model, wavelets perpetuate by the availability of reentrant circuit of sufficient size: if the effective refractory period (ERP) is too short, a wavelet will collide with its refractory tail and extinguish. A wavelet having a sufficiently large ERP and thus a sufficiently large wavelength \((WL = CV \times ERP)\) can exist in a reentrant circuit (Allessie et al., 1977; Rensma et al., 1988). According to the leading circle model, the electrical circuit circulates around a perpetually refractory core by electrotonic current. The multiple wavelet hypothesis and leading circle model predict that atrial dilatation and factors shortening wavelength promote AF maintenance, suggesting that interventions lengthening the ERP decrease the number of wavelets present, ultimately giving rise to AF termination. Experimental validation of the multiple wavelet hypothesis in humans was first demonstrated by Konings et al. (1994).

An alternate hypothesis is that AF is not the result of multiple meandering wavelets but rather is driven by a small number of focal sources or a single focal source. The proposition that AF was not due to multiple reentrant circuits but rather to a single dominant circuit was proposed by Mines (1913) and Lewis (1920). Macroreentrant circuits were largely accepted to cause atrial and ventricular tachycardias, but the precise mechanism by which a single reentrant circuit could drive AF was unknown. In the 1980s and 1990s, theoretical (Winfree, 1987), computational (Courtemanche, 1996; Fenton and Karma, 1998; Zykov and Winfree, 1992), and experimental studies (Davidenko et al., 1992; Gray et al., 1998; Skanes et al., 1998; Witkowski et al., 1998) suggested that “rotors”, or electrical waves resembling a vortex, could drive fibrillation in the atria and ventricles. Unlike the unexcitable core in the leading circle model of Allessie, the electrical rotor has an excitable but quiescent core or tip.
The sustaining mechanism of a rotor is a “broken” free end of an electrical wave coalescing to a single pivot point (“spiral tip”) that may be meandering or stationary. The spiral tip is often referred to as a phase singularity to indicate that the wavefront and waveback coalesce to a single point. Emanating from the spiral tip is a curved electrical spiral wave.

A spiral wave will have one of three fates: One, it will collide with another wave or with a boundary and annihilate. Two, it will be stable owing to limited core meander and excite surrounding tissue in a “one-to-one” manner indefinitely (i.e., all tissue activates with a single frequency). Three, the arms of the spiral wave will “fractionate”, giving rise to new wavelets that are unattached to the “driving” rotor. The wavelets fractionating off of the driving rotor may multiply or annihilate with another wavelet randomly, giving rise to the spatiotemporal irregularity characteristic of AF (Jalife et al., 2002). This phenomenon of fractionation and multiplication of wavelets from a single wavefront giving rise to fibrillation is often referred to as “fibrillatory conduction”. One study in sheep found that waves from a singular, stationary reentrant source tend to fractionate at characteristic locations in remodeled tissue, providing experimental evidence for this model (Kalifa et al., 2006).

The extent to which animal models of AF maintenance extrapolate to human AF maintenance was unknown for a long time. Owing to technical challenges in electroanatomic mapping, it had been difficult to map human AF and determine whether human AF is sustained by rotors, multiple wavelets, or both. Recently, our group developed a computational mapping strategy to query the presence of reentrant rotors in human AF. It was determined that in almost all patients, focal drivers or reentrant rotors were present (Narayan et al., 2012a). Moreover, localized ablation of these drivers terminated AF abruptly and led to improved AF remission rates compared with conventional ablation (Narayan et al., 2012b). In spite of these promising results, the precise mechanisms by which localized ablation of focal sources terminates AF remains unclear, and the disease processes giving rise to stable
reentrant rotors is unclear. Future work uncovering the mechanisms of AF sustainment and termination may further optimize patient outcomes and predict which patients are likely to respond positively to RF ablation, pharmacological therapy, both, or neither.

1.5 Computational models of cardiac arrhythmias

Computational models have a distinguished history in our current understanding of arrhythmia in the atria and ventricles. Mathematical description of the action potential of Purkinje cells was first formulated by Noble (1962) by modifying the Hodgkin-Huxley formulation of neuronal action potentials. Cardiac myocyte models have become considerably more complex in the ensuing decades both in the numbers of ion currents and in the descriptive complexity of those currents. As experiments formulated a more complete picture of the currents constituting the cardiomyocyte action potential, and as computing power increased, it became tractable to use computational models to help explain phenomena involving wave propagation by coupling mathematical models of cardiac myocytes with cable theory of electrical propagation. In one computational study, Shaw and Rudy used a mathematical model of ventricular myocytes in a one-dimensional cable to investigate the relative contributions of elevated extracellular potassium and intracellular acidosis to conduction block in acute ischemia (Shaw and Rudy, 1997). In another study, Keener (1987) examined the effects of discrete coupling between myocytes and the conditions under which weak coupling gave rise to conduction block.

Simulation of electrical propagation on two- and three-dimensional domains rather than one-dimensional cables allowed for investigation not only of conduction block but also of more complicated spatial patterns of electrical propagation. In two- and three-dimensional domains, the effect of wave curvature on the propagation (Davydov and Zykov, 1991;
Franzone et al., 1990) and the propensity for rarefied waves to give rise to conduction block can be studied (Boyle and Vigmond, 2010; Cabo et al., 1994; Klos et al., 2008).

Moreover, two- and three-dimensional domains allow for the study of self-sustaining electrical reentry, a phenomenon long observed in excitable media (Keener and Tyson, 1986; Winfree, 1972). Cardiac tissue is a special case of an excitable medium, with its excitability parameters determined by the kinetics of the fast inward sodium current. It was thus posited that reentrant rotors are responsible for at least some cases of cardiac fibrillation, and in fact, experimental observations have corroborated this suggestion (Davidenko et al., 1992; Gray et al., 1998). Simulations of cardiac myocytes in two-dimensional sheets and three-dimensional slabs have provided insight into the roles of individual ion channels (Atienza et al., 2006; Comtois et al., 2008; Kneller et al., 2005; Samie et al., 2000) and fiber anisotropy (Fenton and Karma, 1998; Rogers and McCulloch, 1994) in the behavior of reentrant rotors—most notably, whether they remain stationary, or exhibit “meander” or drift. The motion of the rotor core has important consequences in its stability.

More recently, it has become possible to simulate normal and pathophysiological electrical propagation on realistic atrial geometries. Normal propagation in a realistic atrial model was first demonstrated by Harrild and Henriquez (2000). Subsequent investigators have constructed atrial models and demonstrated pathophysiological electrical phenomena such as wavebreak (Gong et al., 2007), reentry (Tobón et al., 2008; Vigmond et al., 2001), and unipolar electrogram fractionation (Jacquemet et al., 2003). Further work has made steps toward making computational models of the atria more accurate by adding functional information about known heterogeneities and even making atrial models patient specific. Seeman et al. (2006) added known heterogeneities of ion channel parameters to a computational model of the atria. Krueger et al. (2011) developed an approach to adapt a rule-based method for constructing fiber fields in patient-specific geometries. Dossel et al. (2011)
developed a method to further customize patient-specific atrial models using body surface potential maps. Most recently, McDowell et al. (2012) incorporated information about atrial fibrosis and scar into a patient-specific model from studies of late gadolinium-enhanced magnetic resonance imaging.

In this dissertation, I developed new methods for constructing patient-specific models of the human atria and then used the methods developed to interpret recently-obtained clinical data demonstrating that AF is maintained in humans by a small number of rotors or focal sources (Narayan et al., 2012a; Narayan et al., 2012b). Chapter 2 presents new methods for constructing cubic Hermite patient-specific models of the atria. The hexahedral cubic Hermite models decrease the time required to construct patient-specific atrial models toward clinical timescales by allowing fiber orientations to be incorporated into the model easily and by the adaptation of already-existing atrial models to new patient imaging data by deformable registration. Chapter 3 extends the methods developed in Chapter 2 to four-chamber models of the heart that could be used to study heart failure and cardiac resynchronization therapy. Chapter 4 presents high-order finite element methods for study of the monodomain equation, including cubic Hermite-style serendipity basis functions for optimal computational efficiency. High-order finite elements are superior to linear finite elements in modeling the electrical wavefront curvature accurately, an important consideration in modeling AF. Chapter 5 investigates the mechanism of termination by RF ablation in a patient-specific model, making use of information from electroanatomic mapping of the same patient. It investigates why some reentrant rotors meander whereas others are stationary, and finds that a stationary rotor may be explained as being a reentrant rotor with a wavelength slightly less than the path length around an inexcitable region, whereas a meandering rotor may be explained by a reentrant rotor with wavelength slightly larger than the path length around an inexcitable region. I discuss how meandering rotors may be critical to AF maintenance by
increasing wave fractionation, decreasing the likelihood that all AF sources fortuitously extinguish. Finally, I use the patient-specific model to propose a mechanism by which RF ablation terminates focal sources without creating a new substrate for anatomic reentry: the RF ablation scar increases the size of the inexcitable regions allowing for both meandering rotors and stationary rotors, creating a spatial excitable gap that allows an external wave to invade the rotor core and exterminate it.

There are many reasons to believe that computational models—and specifically, patient-specific models, rather than simulations on plane and cuboid geometries—may further improve our understanding of AF. First, the multi-wavelet hypothesis as well as the focal source hypothesis for AF maintenance depend critically on the concept of wavelength—it is believed that smaller wavelengths promote self-sustaining fibrillation. For the role of wavelength to be evaluated properly, the spatial size of the model must be correct. Second, a proper understanding of AF dynamics must incorporate at least a qualitatively accurate fiber architecture. Cardiac tissue demonstrates marked electrical anisotropy, and computational models cannot even recapitulate normal sinus activation sequences without incorporation of fiber anisotropy. Moreover, gross fiber discontinuities are posited to be important in AF initiation and maintenance and thus should be included in a computational model. Last, technology is now becoming available to obtain patient-specific information that can be incorporated into the computational model. Examples are late gadolinium-enhanced magnetic resonance imaging, monophasic action potential recording of electrical activity, and body surface potential maps. With recent progress in the field, patient-specific models can help physicians and basic scientists interpret the basic mechanisms of AF by modeling the clinical data available. In the future, I believe that patient-specific models will be used to tailor pharmacotherapy and ablation procedures to individual cases of AF and improve outcomes.
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Chapter 2

Modeling of the human atria with cubic Hermite finite elements
Modeling of the human atria with cubic Hermite finite elements

Abstract

High-order cubic Hermite finite elements have been valuable in modeling cardiac geometry, fiber orientations, biomechanics, and electrophysiology, but their use in solving three-dimensional problems has been limited to ventricular models with simple topologies. Here, we utilized a subdivision surface scheme and derived a generalization of the “local-to-global” derivative mapping scheme of cubic Hermite finite elements to construct bicubic and tricubic Hermite models of the human atria with extraordinary vertices from computed tomography images of a patient with atrial fibrillation. To an accuracy of 0.6 millimeters, we were able to capture the left atrial geometry with only 142 bicubic Hermite finite elements, and the right atrial geometry with only 90. The left and right atrial bicubic Hermite meshes were G1 continuous everywhere except in the one-neighborhood of extraordinary vertices, where the mean dot products of normals at adjacent elements were 0.928 and 0.925. We also constructed two biatrial tricubic Hermite models and defined fiber orientation fields in agreement with diagrammatic data from the literature using only 42 angle parameters. The meshes all have good quality metrics, uniform element sizes, and elements with aspect ratios near unity, and are shared with the public. These new methods will allow for more compact and efficient patient-specific models of human atrial and whole heart physiology.

2.1. Introduction

Computational models of cardiac biomechanics and electrophysiology have been used to study normal cardiac physiology (Kerckhofts et al., 2007; Niederer et al., 2011) and pathological conditions such as heart failure (Kerckhofts et al., 2010) and atrial fibrillation (Ashihara et al., 2012; Comtois and Nattel, 2011; Gong et al., 2007; Haissaguerre et al., 2007; Jacquemet et al., 2003; Tobón et al., 2008). Recent advances in non-invasive imaging
technology have made it feasible to generate patient-specific computational models of the atria and the ventricles, and these models show promise for improving the interpretation of clinical data from patients.

High-order cubic Hermite finite element interpolation schemes have been popular in ventricular finite element modeling: they capture smooth geometries with few finite elements, they can be subdivided to have more degrees of freedom while preserving exact shape, and they represent anisotropy compactly and smoothly by means of fiber angle fields referred to local coordinate axes. Furthermore, cubic Hermite and other high-order solution spaces have convergence advantages in finite element simulations of ventricular biomechanics (Costa et al., 1996) and electrophysiology (Arthurs et al., 2012; Rogers et al., 1996) compared with linear solution spaces, and give rise to continuous currents between elements in electrophysiology problems and continuous stresses between elements in biomechanics problems. The continuity of field solutions in these finite element problems necessitated the use of a “local-to-global mapping” proposed by Nielsen (1987) to define a global set of finite element basis functions and to allow for arc-length continuity between finite elements of different sizes.

A limitation of cubic Hermite finite element problems of the ventricles is that the geometries must be described by a single set of parametric coordinates on a regular grid to guarantee smoothness. Each atrium has a smooth shape and thus could be described compactly by cubic Hermite elements, but the irregular atrial shapes require that such a mesh be discretized into a number of sub-regions, each with its own set of parametric coordinates. At the interface between these regions, there will be vertices with an irregular number of neighboring elements, known as extraordinary vertices. In quadrilateral meshes, extraordinary vertices are best placed at critical points of the principal curvature field to prevent element skew (Alliez et al., 2003) and to capture regions of high curvature. Even so, regions of high
curvature are often captured poorly by linear elements compared with high-order finite elements. Moreover, placement of extraordinary vertices is adversely affected by the noise in medical imaging, which worsens calculation of the principal curvature field.

Here we describe new methods for constructing high-quality bicubic and tricubic Hermite finite element meshes of the atria with extraordinary vertices derived from segmentation of non-invasive imaging data. In our patient, we accurately capture the endocardial surface of the left atrium with only 142 bicubic Hermite finite elements, and the endocardial surface of the right atrium with only 90. These meshes are then used to construct a tricubic Hermite biatrial model. Our methods can be applied to atria with variations in pulmonary vein anatomy, wall thicknesses, and fiber architecture, as these variations are important components of patient-specific atrial models (Dössel et al., 2012; Hanna et al., 2011; Jacquemet et al., 2008). As geometric models from in vivo imaging studies are often output as fine triangulations, our methods could be utilized to construct coarse, high-quality models of other irregularly shaped structures as well.

The organization of this chapter is as follows: First, we show that a coarse, high-quality atrial mesh can be constructed using a minimum set of extraordinary vertices computed by the Euler characteristic number of the atrium, and that finer geometric details can be captured if additional extraordinary vertices are utilized. Second, we show how Hermite derivatives can be calculated from a linear mesh using a subdivision surface scheme. Third, we show how the local-to-global mapping customarily used in cubic Hermite interpolation can be generalized to meshes with extraordinary vertices to preserve smoothness between elements and to define global basis functions for finite element problems. We then use the global basis functions to solve a penalized least-squares finite element problem and capture the atrial geometries to the accuracy of the segmented data. Fourth, we show our models provide a convenient way to approximate atrial fiber architecture compactly and give rise to
smooth fiber orientations between elements. Last, we show that our methods extend readily to
patients with anomalous pulmonary vein anatomies, and discuss how precise C1 and G1
continuity can be achieved near extraordinary vertices.

All of the atrial models described here are available to the public in a database as part
of the Continuity software project (http://www.continuity.ucsd.edu).

2.2. Methods

2.2.1. Definitions

Two contours (surfaces) have tangent continuity, or G1 continuity, at their joining
point (edge) if their tangent (normal) vectors point in the same direction. If their magnitudes
are also equal in their current parameterizations, they have parametric (C1) continuity. Two
contours \( f \) and \( g \) are arc-length continuous if \( df / ds = dg / ds \) for the differential of the arc-
length function \( ds \); as defined, continuity of arc-length requires G1, but not C1 continuity.
Barsky and DeRose (1989) elaborate the differences in more detail. We sometimes call a
surface “smooth” to indicate it is nearly, but not precisely G1 continuous; we elaborate this
choice of terminology in Results, Section 2.3.1.

We define an ordinary vertex to be a vertex on a surface having four connected
surface edges; otherwise, it is extraordinary, unless on a boundary. The valence of a vertex is
the number of connected surface edges; an ordinary vertex not lying on a boundary has
valence four. The elements containing an extraordinary vertex constitute its one-
neighborhood. Continuity around an extraordinary vertex means continuity along the common
edges in its entire one-neighborhood, and continuity at an extraordinary vertex means
continuity in the infinitesimal neighborhood around the point.

Derivative parameters of cubic Hermite interpolation with respect to the parametric
coordinates \( \xi \) are called local derivatives, and their dual basis functions \( \Psi \) are called local
basis functions. Derivative parameters transformed into the arc-length coordinates $s$ are called global derivatives or ensemble derivatives, and their dual basis functions $\Psi^*$ called global basis functions or ensemble basis functions.

We refer to the interpolating subdivision scheme utilized in this paper as the Li-Kobbelt subdivision scheme (Li et al., 2005). We use Li-Kobbelt subdivision to calculate Hermite derivatives, and also can use it to refine linear meshes. In contrast, we refine cubic Hermite meshes by interpolating the coordinate functions of each element to interior points. We refer to this subdivision as refinement by Hermite interpolation. Both Li-Kobbelt subdivision and refinement by Hermite interpolation add only ordinary vertices to the refined meshes—the number of extraordinary vertices remains unchanged.

### 2.2.2. Overview

A 68 year-old male was referred to the Veterans Administration Hospital, San Diego for surgical ablation of his persistent atrial fibrillation. He gave informed consent to participate in an Institutional Review Board-approved study and underwent a clinically-indicated computed tomography (CT) study (General Electric 64-slice Lightspeed CT Scanner, 0.5x0.5x0.625 mm) with retrospective electrocardiogram gating. Images were segmented manually with the assistance of an expert cardiac radiologist (P.S.) and structures (left atrium, right atrium, tricuspid valve, and mitral valve) were triangulated using a marching cubes algorithm implemented in ITK-SNAP (www.itksnap.org; Yushkevich et al., 2006). The triangular models were smoothed and coarsened with feature-preservation using GAMer (www.fetk.org/gamer; Yu et al., 2008). The crista terminalis was identified readily in the imaging study as a muscular protrusion in the intercaval region of the right atrium. Owing to insufficient contrast in the imaging study, we were unable to identify Bachmann’s bundle or determine atrial wall thicknesses.
Quadrilaterals were overlaid manually onto the endocardial surface triangulations of
the left and right atria. Using visual estimation, extraordinary vertices were placed in
accordance with principal directions of curvature, and were most often placed at apparent
saddle points of the triangular surfaces. The left atrial mesh had 142 elements, and the right
atrial mesh had 90. To improve element quality, a regularization step was employed on the left
and right endocardial surface meshes using a scheme by Ohtake et al. (2000). The linear
quadrilateral meshes were used to calculate bicubic Hermite derivative parameters using the
Li-Kobbelt subdivision scheme (Section 2.2.3). The generalized “local-to-global map”
commonly used in cubic Hermite interpolation was used to enforce smoothness at ordinary
vertices (Section 2.2.4) as well as extraordinary vertices (Section 2.2.5). A geometric
optimization scheme (Section 2.2.6) was used to deform the left and right atrial surface
meshes to the vertices of the smoothed triangular meshes obtained above until root-mean
squared (RMS) error was 0.62 mm (the largest voxel dimension). We then tested G1
continuity near extraordinary vertices in the geometrically optimized left and right atrial
meshes and also in subdivided versions of these meshes (Results, Section 2.3.1). We
calculated the quality metrics of our left atrial mesh and compared them to the quality metrics
of a geometrically optimized left atrial mesh constructed from the same patient, but using a
different pattern of extraordinary vertices and only 103 elements (Results, Section 2.3.2).

The left and right atrial surface meshes were refined by Hermite interpolation of
coordinates until mean edge length was approximately 2.0 mm. Left and right atrial
hexahedral meshes were constructed by extruding the endocardial surface meshes outward in
the vertex normal direction 2.0 mm in most regions (Table 2.1). Literature values were used
to assign thicknesses to the left atrial roof (Hall et al., 2006), the pulmonary veins (Ho et al.,
2001), and the posterior wall of the left atrium (Platonov et al., 2008). Hexahedra representing
Bachmann’s bundle, the limbus of the fossa ovalis, the coronary sinus, and two inferoposterior
**Table 2.1:** Topology regions in the biatrial tricubic Hermite mesh. Regions 39-42 are present in the model BiA-75888 but not in the model BiA-9486. Region 23 in BiA-9486 was divided into regions 23, 40, 41, and 42 in BiA-75888; accordingly, their thicknesses were approximately halved in BiA-75888.

<table>
<thead>
<tr>
<th>Region number</th>
<th>Location</th>
<th>Transmural thickness, mm</th>
<th>Fiber orientation (numbers in parantheses in degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tricuspid valve annulus #1</td>
<td>2.0</td>
<td>Circumferential (TVO)</td>
</tr>
<tr>
<td>2</td>
<td>Tricuspid valve annulus #2</td>
<td>2.0</td>
<td>Circumferential (TVO)</td>
</tr>
<tr>
<td>3</td>
<td>Superior Vena Cava</td>
<td>1.0</td>
<td>Circumferential (SVC)</td>
</tr>
<tr>
<td>4</td>
<td>Inferior Vena Cava</td>
<td>1.0</td>
<td>Circumferential (IVC)</td>
</tr>
<tr>
<td>5</td>
<td>Inferior intercaval region</td>
<td>2.0</td>
<td>Circumferential (SVC)</td>
</tr>
<tr>
<td>6</td>
<td>Inferior intercaval region (1.5 septum)</td>
<td>2.0</td>
<td>Oblique (70)</td>
</tr>
<tr>
<td>7</td>
<td>Free wall of RAA</td>
<td>2.0</td>
<td>Right-left</td>
</tr>
<tr>
<td>8</td>
<td>Anterior aspect of RAA</td>
<td>2.0</td>
<td>Circumferential (RAA tip)</td>
</tr>
<tr>
<td>9</td>
<td>Superoseptal RA</td>
<td>2.0</td>
<td>Oblique (45)</td>
</tr>
<tr>
<td>10</td>
<td>Right atrial floor</td>
<td>2.0</td>
<td>Right-Left</td>
</tr>
<tr>
<td>11</td>
<td>Coronary sinus ostium</td>
<td>2.0</td>
<td>Circumferential (CSO)</td>
</tr>
<tr>
<td>12</td>
<td>Coronary sinus musculature</td>
<td>3.0</td>
<td>Right-left</td>
</tr>
<tr>
<td>13</td>
<td>Limbus of the fossa ovalis</td>
<td>6.0</td>
<td>Right-left</td>
</tr>
<tr>
<td>14</td>
<td>Bachmann’s bundle</td>
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</tr>
<tr>
<td>15</td>
<td>Inferoposterior bundle #1</td>
<td>1.3</td>
<td>Right-left</td>
</tr>
<tr>
<td>16</td>
<td>Inferoposterior bundle #2</td>
<td>1.3</td>
<td>Right-left</td>
</tr>
<tr>
<td>17</td>
<td>Mitral valve annulus</td>
<td>2.0</td>
<td>Circumferential (MVO)</td>
</tr>
<tr>
<td>18</td>
<td>Left atrial roof</td>
<td>1.5</td>
<td>Oblique (45)</td>
</tr>
<tr>
<td>19</td>
<td>Left atrial septum</td>
<td>1.5</td>
<td>Anterior-posterior</td>
</tr>
<tr>
<td>20</td>
<td>Left atrial floor, septal</td>
<td>2.0</td>
<td>Oblique (45)</td>
</tr>
<tr>
<td>21</td>
<td>Left atrial floor, middle</td>
<td>2.5</td>
<td>Right-Left</td>
</tr>
<tr>
<td>22</td>
<td>Left atrial lateral wall</td>
<td>2.0</td>
<td>Superior-inferior</td>
</tr>
<tr>
<td>23</td>
<td>Left atrial posterior wall</td>
<td>2.1 – 2.5</td>
<td>Superior-inferior</td>
</tr>
<tr>
<td>24</td>
<td>LSPV</td>
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<td>Circumferential (LSPV)</td>
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<td>LIPV</td>
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</tr>
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<td>RSPV</td>
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<td>RIPV</td>
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<td>Between LSPV and LIPV</td>
<td>1.5</td>
<td>Right-left</td>
</tr>
<tr>
<td>29</td>
<td>Between RSPV and RIPV</td>
<td>1.5</td>
<td>Right-left</td>
</tr>
<tr>
<td>30</td>
<td>Ligament of Marshall</td>
<td>1.5</td>
<td>Superior-inferior</td>
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<tr>
<td>31</td>
<td>Near RIPV</td>
<td>1.5</td>
<td>Oblique (45)</td>
</tr>
<tr>
<td>32</td>
<td>Base of LAA</td>
<td>2.0</td>
<td>Circumferential (LAA ostium)</td>
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<tr>
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<td>LAA #1</td>
<td>2.0</td>
<td>Circumferential (LAA ostium)</td>
</tr>
<tr>
<td>34</td>
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<td>Circumferential (LAA tip)</td>
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<td>38</td>
<td>LAA #6</td>
<td>2.0</td>
<td>Circumferential (LAA tip)</td>
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<td>Crista Terminalis</td>
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<td>Superior-inferior</td>
</tr>
<tr>
<td>40</td>
<td>Septoatrial bundle, lateral</td>
<td>-</td>
<td>Oblique (-30)</td>
</tr>
<tr>
<td>41</td>
<td>Septoatrial bundle, middle</td>
<td>-</td>
<td>Superior-inferior</td>
</tr>
<tr>
<td>42</td>
<td>Septoatrial bundle, septal</td>
<td>-</td>
<td>Oblique (30)</td>
</tr>
</tbody>
</table>
bridges were used to connect the two atria. A tricubic Hermite hexahedral mesh having 9,486 elements was constructed using Li-Kobbelt subdivision generalized to volumes, and then the local-to-global map was applied again to enforce smoothness. Using refinement by Hermite interpolation, a second mesh having 75,888 elements was constructed.

Atrial fiber orientations were defined as angles relative to local finite element coordinate axes. One angle at each point defines orientation if atrial fibers are assumed not to lie oblique to endocardial and epicardial surfaces—otherwise, two are required. We captured the principal directions of fiber tracts in our geometric model using consensus fiber orientations described in multiple studies (Cabrera et al., 2008; Ho and Sanchez-Quintana, 2009; Nathan and Eliakim, 1966; Papez, 1920; Wang et al., 1995). We visually compared our results to the description of fiber architecture of Wang and colleagues (Section 3.3). Local angles were represented by a linearly interpolated field with Lagrange basis functions. In most regions (35 of 42 in BiA-75888), the fiber orientation was defined to coincide with the first coordinate axis (i.e., angle zero). In the remaining regions, angles (Table 2.1) were assumed constant with respect to local coordinate axes. Loci of gross discontinuity between fiber tracts (e.g., each lateral border of the septopulmonary bundle) lay at the interface of adjacent mesh regions by construction. Since BiA-9486 was one layer of hexahedra thick, it was unable to capture the abrupt differences in fiber orientation between the subepicardium and the subendocardium known to exist in the posterior left atrial wall and the region of the crista terminalis (Papez, 1920). These transmural differences of fiber orientation were included in BiA-75888, which has two layers of hexahedra. Fibers in the crista terminalis were defined to course in a superior-inferior direction.

A schematic diagram of the process is displayed in Figure 2.1.
Figure 2.1: A schematic diagram for construction of a biatrial tricubic Hermite hexahedral mesh and intermediate bicubic Hermite surface meshes from a segmented computed tomography study.

2.2.3. Construction of bicubic and tricubic Hermite meshes using subdivision surfaces

A unitary tricubic Hermite hexahedron is constructed as a mapping from the parametric space \((\xi_1, \xi_2, \xi_3)\) to the coordinate system \((Y_1, Y_2, Y_3)\). Each coordinate function \(Y\) is expressed as a linear combination of geometric coefficients \(y_i\) in a set of basis functions \(\Psi_i\) (Eq. 2.1)

\[
Y = \sum_{i=1}^{64} y_i \Phi^{(i)}(\xi_1) \Phi^{(i)}(\xi_2) \Phi^{(i)}(\xi_3) = \sum_{i=1}^{64} y_i \Psi_i(\xi_1, \xi_2, \xi_3) \tag{2.1}
\]

The geometric coefficients are coordinate values and coordinate derivatives in the parametric space (e.g., \(\partial Y / \partial \xi_i\)), whereas basis functions \(\Psi\) are tensor products of cubic Hermite
polynomial basis functions $\Phi$. A bicubic Hermite hexahedron is constructed similarly, but with only two parametric coordinates ($\xi_1$, $\xi_2$) and only sixteen geometric coefficients and basis functions. More complete descriptions of cubic Hermite splines are given elsewhere (Nielsen et al., 1991; Petera and Pittman, 1991).

Bicubic and tricubic Hermite meshes were constructed from linear quadrilateral and linear hexahedral meshes based on a subdivision surface scheme. A subdivision surface scheme can be used recursively to subdivide a linear surface mesh into more refined instances of itself. Customarily, a sequence of subdivision surfaces will have C1 or C2 continuity properties in a piecewise-linear sense in the infinite limit. Here, we truncate the subdivision surface sequence after two iterations, giving rise to cubic Hermite elements that are nearly but not precisely C1 continuous (see Section 2.4.2). In contrast to most subdivision schemes, such as that of Catmull and Clark (1978), interpolating subdivision schemes feature vertices in the “parent” surface that remain stationary in each subdivided “daughter” surface. Owing to this constraint, interpolating subdivision captures geometric features that otherwise would be lost, whereas non-interpolating subdivision schemes smooth a surface after comparatively fewer iterations of subdivision.

For an interpolating subdivision surface scheme, the natural correspondence between a parent quadrilateral and the sixteen quadrilaterals resulting from two subdivisions provides a means to select derivative parameters for cubic Hermite interpolation. The global and parametric coordinates of 16 of the 25 vertices (21 are newly-added) can be selected to construct a linear system (Eq. 2.2) in the 16 unknown derivative parameters of cubic Hermite interpolation in one quadrilateral from the parent surface. Adjacent vertices lie $\xi = 0.25$ apart in the parametric coordinates of the parent quadrilateral (Figure 2.2). In the present work, we used Li-Kobbelt subdivision to select cubic Hermite derivative parameters because it gives
rise to $C_1$ continuity and finite Gaussian curvature at ordinary and extraordinary vertices in the infinite limit.

\[ Y = \sum_{i=1}^{16} y_i \Phi_i(\xi^{(i)}) \Phi_j(\xi^{(j)}) \]  

Eq. 2.2

A similar scheme was used to define cubic Hermite derivative parameters for hexahedral meshes: a twice-subdivided hexahedron became 64 hexahedra having 125 vertices, 64 of which were selected to calculate the 64 geometric degrees of freedom of each coordinate function. The interpolating subdivision surface scheme used above was extended to solids by applying the scheme separately to each surface in the model, and using linear interpolation to place new vertices between corresponding surfaces. The use of linear interpolation to place internal vertices (i.e., between surfaces) adversely affected element quality and led to inverted elements in some cases; these problems could be avoided by applying one scheme to minimize

Figure 2.2: One linear quadrilateral is subdivided twice by the Li-Kobbelt scheme into 16 linear quadrilaterals containing 25 vertices. The coordinates of 16 of the new vertices (red) are used to solve Eq. 2.2 and calculate the 16 Hermite parameters for the original unsubdivided quadrilateral.
element skew (Zhang et al., 2007a) and another to regularize hexahedral element volumes (Vartziotis and Wipper, 2011).

2.2.4. Interpolation near ordinary vertices: A review

A spatial domain discretized into quadrilaterals or into hexahedra constructed as tensor products of cubic polynomials is guaranteed to be C1 continuous everywhere except at the boundary interfacing neighbor elements. Tangent (G1), parametric (C1), or arc-length continuity may be enforced at element interfaces. Parametric derivatives of equal magnitude may have different arc-length derivatives (speeds), as noted by Nielsen (1987). Arc-length continuity may be preferred to parametric continuity in finite element analysis because the arc-length connects derivatives to physical space—$\frac{\partial u}{\partial s_i}$ is the directional derivative for an arbitrary scalar-valued function $u$ in the direction tangent to the $\xi_1$ contour—in contrast, the derivative $\frac{\partial u}{\partial \xi_1}$ has only mathematical significance. Consequently, Nielsen proposed arc-length derivatives be used as an “ensemble” coordinate frame at each mesh vertex to define a canonical length of tangent vectors—the collection of ensemble, or global, field parameters and their dual basis functions would then be used as the functional space for a finite element problem, and arc-length derivatives computed would be consistent in neighboring elements. Fernandez et al. (2004) suggested nodal tangent vectors have unit arc-length magnitude (i.e., $\| d\mathbf{r} / ds \|=1$ for $f: I \rightarrow \mathbb{R}^3$), and local parametric derivatives (i.e., $d\mathbf{r} / d\xi_1$) be calculated using non-linear iteration of the arc-length equation, with the approximation that arc-length (speed) of each contour is constant. Using this scheme, an arc-length parameterization of the cubic Hermite splines is unnecessary—only the integrated arc-length function need be considered. Surface derivative terms in the two frames are related by

$$\frac{\partial Y}{\partial \xi_i} = \sum_{i=1}^{2} \frac{\partial Y}{\partial s_i} \cdot \frac{\partial s_i}{\partial \xi_i}$$

Eq. 2.3
\[
\frac{\partial^2 Y}{\partial \xi_1 \xi_2} = \frac{\partial^2 Y}{\partial s_1 \partial s_2} \cdot \frac{\partial s_1}{\partial \xi_1} \cdot \frac{\partial s_2}{\partial \xi_2} 
\]

Eq. 2.4

Where \( s \) is the ensemble frame, \( \xi \) is the local frame, and the terms \( \partial s / \partial \xi \) are the scalar correctors determined by integration of the arc-length equation.

Henceforth, continuity would be imposed among neighboring cubic Hermite elements using a matrix of these scalar correctors, or “scale factors”. The matrix of scale factors is a derivative map (Jacobian) for a change-of-coordinates transformation between “local” parametric coordinate systems of the element, and “global” ensemble coordinate systems of Nielsen. In the present work, we use the scale factors described in Eq. 2.3 and Eq. 2.4 to enforce arc-length continuity at ordinary vertices, and to enforce G1 continuity along the contours joining ordinary vertices (see Discussion, Section 2.4.2).

2.2.5. Interpolation near extraordinary vertices

In a mesh with only ordinary vertices, the derivative maps between element and global coordinate systems will only scale vector magnitudes. More generally, the derivative maps may also transform vectors between coordinate systems whose axes are skew to one another. In a mesh with extraordinary vertices, it is necessary to utilize derivative maps this way: if local coordinate vectors and ensemble coordinate vectors are skew to one another, a linear transformation maps the components of a vector in one frame to components in a new frame.

Thence, the normed coordinate axes of one reference element at each extraordinary vertex may be selected as the local ensemble frame (Figure 2.3), and a linear transformation \( \Gamma \) computed for each element containing that vertex. The matrix values in the linear transformation \( \Gamma \) are obtained by finding the contravariant components of local coordinate vectors of an element in the ensemble frame. First, ensemble tangent vectors of form
**Figure 2.3:** An extraordinary vertex lies at the interface of the right superior pulmonary vein (light grey), posterior left atrial wall (darker grey), and a third region between the right pulmonary veins (darkest grey), at a saddle point. Ensemble coordinates \( s_1 \) and \( s_2 \) (solid arrows) coincide with parametric coordinates \( \xi_1 \) and \( \xi_2 \) (broken arrows) of one element but have unit magnitude. A neighboring element has parametric coordinates \( \xi'_1 \) and \( \xi'_2 \) relatable to ensemble coordinates by linear transformation. Geometric continuity of adjoining patches in the one-neighborhood of an extraordinary vertex was evaluated along the shared contours at three points per contour (asterisks).

\[
g_i := \partial / \partial s_i = a_1^{(i)} e_1 + a_2^{(i)} e_2 + a_3^{(i)} e_3 \text{ are arranged in matrix columns } \forall i, \text{ and the dual basis vectors computed by the matrix inverse (or the matrix pseudoinverse for surfaces). Second, for the local coordinate vector expanded in the reference frame } \partial / \partial \xi_j = \sum_i b_i^{(j)} g_i, \text{ the } i^{th} \text{ component } b_i^{(j)} \text{ of the } j^{th} \text{ local coordinate vector } \partial / \partial \xi_j \text{ can be computed in ensemble coordinates with the dot product}\]

\[
b_i^{(j)} = \frac{\partial}{\partial \xi_j} \left( \frac{\partial}{\partial s_i} \right)^* \tag{Eq. 2.5}
\]

Where the star indicates the dual basis vector. Thus calculated, the relationship between vectors in local coordinates and ensemble coordinates is
\[ \frac{\partial Y}{\partial \xi_j} = \sum_i \frac{\partial Y}{\partial s_i} \cdot \frac{\partial s_i}{\partial \xi_j} \]  

Eq. 2.6

instead of Eq. 2.3, where the term \( \partial s_i / \partial \xi_j = b_j^{(i)} \). The indices \( i, j = \{1, 2\} \) for surfaces and \( i, j = \{1, 2, 3\} \) for volumetric solids.

The second and third-order mixed derivatives \( \partial^2 Y / \partial \xi_i \partial \xi_j (i \neq j) \) and \( \partial^3 Y / \partial \xi_i \partial \xi_j \partial \xi_k \partial \xi_3 \) are selected from the element whose basis vectors are chosen to coincide with the local ensemble frame, and determined in other elements with the chain rule (Appendix I, Section 0).

Cubic splines such as Hermite’s have degrees of freedom sufficient to enforce \( C_1 \) continuity at regular vertices, but insufficient to enforce \( C_1 \) continuity near extraordinary vertices. Continuity for cubic splines is achieved only for special configurations of the vertex “one-neighborhood” (Wang and Zhang, 2010). Using Eq. 2.2 to select Hermite derivative parameters does not guarantee \( C_1 \) continuity because we truncate the subdivision surface sequence at its second member. If some deviation from \( C_1 \) continuity can be tolerated, special configurations in the one-neighborhood of the extraordinary vertex need not be utilized, and regions of high curvature can be captured at coarser mesh resolutions (Discussion, Section 2.4.2). In the present work, we tolerate this deviation from \( C_1 \) and \( G_1 \) continuity (Results, Section 2.3.1).

2.2.6. Global basis functions are dual to the ensemble frame

In functional analysis and differential geometry, vector coefficients and basis set are mathematically dual to one another. The choice of an ensemble frame at each vertex defines the dual ensemble (i.e., global) set of basis functions \( \{\Psi_1^*, \Psi_2^*, \ldots, \Psi_N^*\} \) required for a finite element problem. As finite element equations are written in “local” element basis functions,
they must be transformed to the global frame—this transformation was termed the “element-to-ensemble mapping” by Nielsen (1987). For non-derivative values (and thus for linear finite elements), the transformation is Boolean, but in general is real-valued and linear in the local element degrees of freedom.

Let the matrix $\Gamma$ encapsulate the chain rule transformation from ensemble (global) coefficients to element (local) coefficients in the functional space spanned by the tensor product Hermite basis functions (Eq. 2.1). As discussed in Section 2.2.4 and Section 2.2.5, $\Gamma$ effects the transformations given by Eq. 2.3, Eq. 2.4, Eq. 2.6, and Eq. 2.12-Eq. 2.15. The column vector of global coefficients $u^*$ are transformed to local coefficients $u$ by

$$u = \Gamma u^*$$

Eq. 2.7

Where we use $u$ for the coefficient vector to emphasize it may be for any field interpolant, not exclusively a coordinate function, previously represented by $y$. Defined this way, the matrix transpose $\Gamma^T$ transforms the column vector of local basis functions $\psi$ to the column vector of global basis functions $\psi^*$—again an encapsulation of the chain rule, but for the basis functions, dual to the coefficients

$$\psi^* = \Gamma^T \psi$$

Eq. 2.8

It is worthwhile to emphasize $\Gamma$, as defined, maps coefficients from global to local, whereas $\Gamma^T$ maps basis functions from local to global, if both operate on column vectors. An analog in differential geometry might be more familiar: for some change-of-coordinates $A: \mathbb{R}^n \to \mathbb{R}^m$, the associated Jacobian matrix $J$ transforms tangent vectors from $\mathbb{R}^n \to \mathbb{R}^m$, whereas $J^T$ transforms dual vectors from $\mathbb{R}^m \to \mathbb{R}^n$. The matrices $J^{-1}$ and $J^{-T}$ enact the other transformations.
The product of local basis functions often appears in finite element problems in an integral

$$\int_{\Omega} \Psi_i \Psi_j \, d\Omega$$  \hspace{1cm} \text{Eq. 2.9}$$

Where the domain $\Omega$ is one element, and $i$ and $j$ are indices for element basis functions. In matrix form, the product of local basis functions is the Cartesian product $\psi \otimes \psi$, which transforms to the global frame as would a second-order tensor

$$\psi^* \otimes \psi^* = \Gamma^T [\psi \otimes \psi] \Gamma^T$$  \hspace{1cm} \text{Eq. 2.10}$$

With these basis function transformations applied to the finite element problem, the unknown coefficients are determined in the ensemble (global) frame.

We tested the behavior of our methods in a finite element problem with regularized least-squares optimization (see Results, Section 2.3.2). The objective function $F$ can be written (Fernandez et al., 2004)

$$F(\mathbf{u}) = \sum_d \| \mathbf{u}(\xi_d) - \mathbf{u}_d \|^2 + \int_{\Omega} \left( \alpha_1 \left\| \frac{\partial \mathbf{u}}{\partial \xi_1} \right\|^2 + \alpha_2 \left\| \frac{\partial \mathbf{u}}{\partial \xi_2} \right\|^2 + \alpha_3 \left\| \frac{\partial^2 \mathbf{u}}{\partial \xi_1^2} \right\|^2 + \alpha_4 \left\| \frac{\partial^2 \mathbf{u}}{\partial \xi_2^2} \right\|^2 + \alpha_5 \left\| \frac{\partial^2 \mathbf{u}}{\partial \xi_1 \partial \xi_2} \right\|^2 \right) \, d\Omega \hspace{1cm} \text{Eq. 2.11}$$

Where $\mathbf{u}$ is a vector of field variables, $d$ is an index over data points, $\mathbf{u}_d$ is the value of the field for data point $d$, $\xi_d$ are the parametric coordinates of the $d^{th}$ data point projected onto a surface, $\mathbf{u}(\xi_d)$ are the interpolated field coefficients for data point $d$, $\Omega$ is the finite element domain, and $\alpha_k$ is the Sobolev smoothing weight for the $k^{th}$ derivative term. The choice of smoothing weights is arbitrary, but we used $\alpha_k = 1$ for the smoothing weights multiplied with the first derivative terms $\partial \mathbf{u} / \partial \xi_1$ and $\partial \mathbf{u} / \partial \xi_2$, and $\alpha_k = 5$ for the other
three smoothing weights multiplied with second derivative terms, whenever Eq. 2.11 is used in this paper. Detailed guidelines for the choice of smoothing weight values are described elsewhere (Mazhari et al., 1998). The data points fitted were the vertices from the marching cubes surface triangulations of segmented endocardial surfaces after geometric fairing with feature preservation by GAMEr (Yu et al., 2008). The data point parametric coordinates $\xi_d$ were determined as follows: First, all bicubic Hermite patches were tessellated into fine triangles. Second, the triangles to which each data point projects normally were identified. Last, the triangle with minimum distance to each data point was identified, and its parametric coordinates $\xi_d$ with respect to its original quadrilateral recorded.

We use the scaled Jacobian and condition number to assess mesh quality at nine interpolated Gauss-Legendre quadrature points for each surface mesh (three points along each parametric coordinate). The scaled Jacobian and condition number are calculated as described by Zhang et al. (2007a). The scaled Jacobian equals one for right-handed orthogonal coordinate axes, equals zero if coordinate axes are coplanar (and thus, do not span $\mathbb{R}^3$), is negative if coordinate axes are left-handed, and decreases from one towards zero as coordinate axes become skewed. The condition number equals one for orthogonal coordinate axes with equal magnitudes, increases from one as coordinate axes become skewed, increases from one also as tangent vectors to coordinate axes have increasingly different magnitudes, and is unbounded if coordinate axes are coplanar. Further descriptions are given by Knupp (2000).

2.3. Results

2.3.1. Geometry is smooth and almost G1 continuous near extraordinary vertices

We constructed one coarse right atrial mesh (90 quads) and one coarse left atrial mesh (142 quads), and used Eq. 2.2 to construct cubic Hermite derivatives (Figure 2.4)—henceforth, we refer to these meshes as RA-90, and LA-142; other meshes were named by the
Figure 2.4: Anterolateral views of bicubic Hermite mesh RA-90 (A) and bilinear mesh RA-360 (B), and septal views of bicubic Hermite mesh LA-142 (C) and bilinear mesh LA-568 (D) after geometric optimization with Eq. 2.11. Valence 5 vertices (teal), valence 3 vertices (red), and one valence 6 vertex (black) were used. The tricuspid and mitral valve rings are shaded dark grey for visual contrast. See Results, Section 3.2 for details. SVC = Superior Vena Cava; IVC = Inferior Vena Cava; RAA = Right atrial appendage; TVO = Tricuspid valve orifice; CS = Coronary sinus ostium; RSPV = Right superior pulmonary vein; RIPV = Right inferior pulmonary vein; LAA = Left atrial appendage; MVO = Mitral valve orifice.

same scheme. Extraordinary vertices were needed to capture the morphology of the pulmonary veins, atrial appendages, coronary sinus ostium, and venae cavae without producing severe element distortions. The number of extraordinary vertices was consistent with the Euler characteristic number $\chi$ of each atrial surface model: for the left atrial model, $\chi = -3$, and for the right atrial model, $\chi = -2$ (see Discussion, Section 2.4.3). Vertices of valence 5 were
placed near orifices to capture their circumferential shape compactly (e.g., coronary sinus ostium, Figure 2.4A), and at regions of high curvature (e.g., right superior and right inferior pulmonary veins, Figure 2.4C) to avoid element skewing that otherwise resulted. Vertices of valence 3 typically were placed near vertices of valence 5; this resulted in quadrilaterals with regular angles (i.e., angles were close to 90 degrees) and aspect ratios close to unity throughout the meshes. After geometric optimization (Section 2.6), the bicubic Hermite surfaces LA-142 and RA-90 (Figure 2.4A and Figure 2.4C) captured pulmonary veins, venae cavae, and regions of high curvature more compactly than did refined bilinear surfaces (Figure 2.4B and Figure 2.4D) with a comparable number of geometric degrees of freedom (LA-568 and RA-360). Whereas the bicubic meshes LA-142 and RA-90 had RMS errors of 0.6 mm, the linear meshes LA-568 and RA-360 had RMS errors of 0.8 mm and 0.7 mm.

Table 2.2: Analysis of normal vectors in the one-neighborhood of extraordinary vertices as a measure of smoothness. Three quadrature points on the contour bounding two quads were selected within the one-neighborhood, and for each point, unit normals were computed in the two adjoining elements. Last, the dot product was computed for each pair of normals.

<table>
<thead>
<tr>
<th></th>
<th>RA-90</th>
<th>RA-360</th>
<th>RA-1440</th>
<th>LA-142</th>
<th>LA-568</th>
<th>LA-2272</th>
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<tbody>
<tr>
<td>Mean dot product</td>
<td>0.925</td>
<td>0.974</td>
<td>0.990</td>
<td>0.928</td>
<td>0.981</td>
<td>0.992</td>
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<tr>
<td>Fraction of points with dot product &gt; 0.99</td>
<td>0.42</td>
<td>0.66</td>
<td>0.83</td>
<td>0.39</td>
<td>0.63</td>
<td>0.84</td>
</tr>
<tr>
<td>Fraction of points with dot product &gt; 0.95</td>
<td>0.74</td>
<td>0.86</td>
<td>0.96</td>
<td>0.66</td>
<td>0.89</td>
<td>0.96</td>
</tr>
<tr>
<td>Fraction of points with dot product &gt; 0.5</td>
<td>0.96</td>
<td>1.0</td>
<td>1.0</td>
<td>0.98</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Since we truncate the subdivision surface scheme after two iterations, we tested G1 continuity in the one-neighborhood of extraordinary vertices using the dot product of normal vectors at points where two adjacent quads coincide (asterisks in Figure 2.3); in other regions, G1 or C1 continuity could be guaranteed (see Discussion, Section 2.4.2). For RA-90 and LA-142, mean dot products of normal vectors rooted at coincident points were 0.931 and 0.928.
The analysis was repeated on two successive Li-Kobbelt subdivisions; the twice-subdivided meshes had mean dot products of 0.990 and 0.992, and additional data are provided in Table 2.2.

2.3.2. **Extraordinary vertices capture geometric detail while minimizing element distortion**

We were able to capture the left atrial geometry accurately with 142 bicubic Hermite elements (LA-142), but we had considered using a coarser model with 103 bicubic Hermite elements (LA-103). The meshes LA-103 and LA-142 were identical except at the left atrial appendage (LAA), where 10 extraordinary vertices and 29 ordinary vertices were added to LA-103 to capture anatomic detail. The additional extraordinary vertices in LA-142 allowed finer details of the geometry to be captured (i.e., RMS error was lower) and improved mesh quality, at the cost of mesh simplicity (more topological regions were required), as shown in Figure 2.5. The LAA of LA-103 had three topological regions, whereas the LAA of LA-142 had six, attributable to the additional extraordinary vertices in LA-142 (Figure 2.5C-D). The mesh LA-103 (LA-142) was refined one iteration by Li-Kobbelt subdivision to produce LA-412 (LA-568). These subdivisions add only ordinary vertices.

Geometric optimization using Eq. 2.11 was completed recursively on each mesh until RMS error was less than 0.62 mm. Regional RMS error of the LAA in LA-103 was 1.0 mm, whereas regional RMS error of the LAA in LA-142 was 0.6 mm. The decrease in regional RMS error of the LAA could not be attributed solely to an increase in the number of degrees of freedom; error of the LAA for LA-412 (a refined version of LA-103) was 0.9 mm, yet it had slightly more degrees of freedom per coordinate in the LAA (228) than did LA-142 (224).

A similar pattern was followed for two quality metrics, the scaled Jacobian and condition number: mean and worst values for LA-142 were superior to mean and worst values
Figure 2.5: Lateral views of bicubic Hermite meshes LA-142 (A) and LA-412 (B). Compared to LA-142, LA-412 cannot capture the geometric detail of the left atrial appendage (LAA), in spite of more geometric degrees of freedom. The additional extraordinary vertices in LA-142 are needed to capture the geometric shape of the LAA and preserve element quality. Cartographic projections of LA-142 and LA-412 are displayed in (C) and (D). The distorted quadrilaterals in the cartographic projection (C) become regular in LA-142 (A), whereas the regular quadrilaterals in cartographic projection (D) become distorted in LA-412 (B) as they are deformed to capture the irregular shape of the LAA. Colors in (C) and (D) are used to indicate distinct topology regions. Valence 5 vertices are teal in (A) and (B), and are indicated by asterisks (*) in (C) and (D). Valence 3 vertices are red in (A) and (B), and are indicated by the symbol $\otimes$ in (C) and (D). Four valence 3 vertices at the tip of the LAA are indicated by the symbol $\otimes$ in (C). In (A) and (B), the mitral valve is shaded dark grey for visual contrast. LAA = Left atrial appendage; MVO = Mitral valve orifice; LSPV = Left superior pulmonary vein; LIPV = Left inferior pulmonary vein.
of LA-103 and LA-412, owing to its additional extraordinary vertices in the LAA. Successive optimizations by Eq. 2.11 could reduce the regional error of the LAA for LA-412 to be lower than 0.9 mm at the expense of the mean and worst values of the quality metrics, which were already worse than the mean and worst values of the quality metrics for the LAA of LA-142 for regional error of 0.6 mm. Mean quality metrics in the refined meshes LA-412 and LA-568 were superior to the values in their non-refined counterparts LA-103 and LA-412, whereas the worst value of quality metrics typically was inferior for the refined meshes, owing to torsion introduced by capture of sharp curvature near the pulmonary veins. Additional mesh statistics, including statistics for RA-90 after geometric optimization, are provided in Table 2.3.

Table 2.3: Statistics for bicubic Hermite left atrial (LA) and right atrial (RA) surface meshes after geometric optimization. Mesh quality metrics were evaluated at 9 quadrature points per element. Meshes were named in accordance with the number of elements (e.g., mesh with 103 elements is named LA-103). d.o.f. = degrees of freedom.

<table>
<thead>
<tr>
<th></th>
<th>LA-103</th>
<th>LA-142</th>
<th>LA-412</th>
<th>LA-568</th>
<th>RA-90</th>
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<tbody>
<tr>
<td>Vertices, total</td>
<td>116</td>
<td>155</td>
<td>441</td>
<td>597</td>
<td>103</td>
</tr>
<tr>
<td>Geometric d.o.f. per coordinate</td>
<td>464</td>
<td>620</td>
<td>1764</td>
<td>2388</td>
<td>412</td>
</tr>
<tr>
<td>Geometric d.o.f. per coordinate, LAA</td>
<td>68</td>
<td>224</td>
<td>228</td>
<td>852</td>
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<td>13</td>
<td>8</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Vertices, valence 5</td>
<td>20</td>
<td>25</td>
<td>20</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>Vertices, valence 6</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Topology regions</td>
<td>17</td>
<td>20</td>
<td>17</td>
<td>20</td>
<td>11</td>
</tr>
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<td>Mean edge length, mm</td>
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<td>10.8</td>
<td>6.4</td>
<td>5.3</td>
<td>14.3</td>
</tr>
<tr>
<td>RMS error, mm</td>
<td>0.6</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>RMS error, LAA, mm</td>
<td>1.0</td>
<td>0.6</td>
<td>0.9</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>Scaled Jacobian – mean, worst</td>
<td>0.96, 0.49</td>
<td>0.96, 0.49</td>
<td>0.96, 0.49</td>
<td>0.97, 0.48</td>
<td>0.96, 0.43</td>
</tr>
<tr>
<td>Condition number – mean, worst</td>
<td>1.10, 2.62</td>
<td>1.08, 2.56</td>
<td>1.10, 2.95</td>
<td>1.09, 2.79</td>
<td>1.11, 2.45</td>
</tr>
<tr>
<td>Scaled Jacobian, LAA – mean, worst</td>
<td>0.94, 0.57</td>
<td>0.97, 0.70</td>
<td>0.95, 0.61</td>
<td>0.97, 0.70</td>
<td>-</td>
</tr>
<tr>
<td>Condition number, LAA – mean, worst</td>
<td>1.15, 1.76</td>
<td>1.07, 1.48</td>
<td>1.13, 1.69</td>
<td>1.07, 1.56</td>
<td>-</td>
</tr>
</tbody>
</table>
2.3.3. Atrial fiber architecture is described compactly in a tricubic Hermite model

Qualitative fiber patterns from explanted human atria are depicted in Figure 2.6A-B. Enlarged views of the biatrial model BiA-9486 corresponding to the regions boxed in Figure 2.6A-B are depicted in Figure 2.6C-D with the constructed fiber patterns overlaid. In Figure 2.6C, fiber tracts course from the superior border of the region of the crista terminalis (white region) anteriorally and septally, towards Bachmann’s bundle. Fiber tracts on the left atrial roof course posterolaterally, whereas fiber tracts closer to the mitral valve course laterally, towards the left atrial appendage. A fiber tract courses circumferentially around the tricuspid valve. In Figure 2.6D, fiber tracts of the posterior left atrial wall (upper-left blue region) course inferiorly before blending with fiber tracts of the left atrial floor, which course left-to-right. Fiber tracts of the left atrial septum course from anterior to posterior (green), and encircle the right inferior pulmonary vein. Fiber tracts of the intercaval band originate between the venae cavae (lower-right white region) and course obliquely. The atria are connected inferiorly by the coronary sinus musculature. Views of the hexahedral mesh with prominent coordinate lines are displayed in Figure 2.6E-F.

The posterior left atrial wall and the crista terminalis each feature separate subepicardial and subendocardial fiber tracts with distinct orientations (in Figure 2.6B, only the subepicardial fibers superficial to the crista terminalis are visible). We captured the abrupt intramural fiber orientation transitions in these two regions using refinement by Hermite interpolation on BiA-9486 to give BiA-75888, which was two hexahedra thick. A visualization of the resulting fiber pattern near the crista terminalis is displayed in Figure 2.7. Additional details of the tricubic Hermite hexahedral mesh BiA-9486 and the refined model BiA-75888 are provided in Appendix II, Section 0.
Figure 2.6: Fiber orientations in a tricubic Hermite model. Images (A) and (B) are depictions of typical fiber orientations from explanted human atria, reprinted from Wang, Br. Heart J., 1995 with permission. The regions indicated by boxes are enlarged in (C) and (D), in which a qualitatively-matching fiber pattern is displayed. Each block of color indicates a region with consistent coordinate axes (a single topological region). See Results, Section 3.3 for details. Images (E) and (F) are equivalent views of the tricubic Hermite hexahedral model. The epicardial surface is colored brown and the endocardial surface is colored white. Valence 3 vertices are colored red, and valence 5 vertices are colored teal. SVC = Superior Vena Cava; BB = Bachmann’s bundle; TVO = Tricuspid valve orifice; pLAw = Posterior left atrial wall; MVO = Mitral valve orifice; RIPV = Right inferior pulmonary vein; CS = Coronary sinus; IR = Intercaval region; PM = Pectinate muscles, IPB = Inferoposterior bridge.
Figure 2.7: Model BiA-75888 is two layers of hexahedra thick and thus can capture abrupt transitions of fiber orientation within the atrial walls readily. A right lateral view of the model BiA-75888 is displayed in (A). The box indicates a region of the mesh enlarged as a wireframe in (B). Fibers of the crista terminalis (red) course in a superior-inferior direction subendocardially. Fibers in the subepicardium of the same region (black) course obliquely towards the venae cavae, as displayed in Figure 2.6B. Fibers representing the insertion of pectinate muscles onto the crista terminalis (light green) course left-to-right in the right atrial appendage. SVC = Superior vena cava; IVC = Inferior vena cava; RAA = Right atrial appendage; CT = Crista terminalis; IR = Intercaval region; PM = Pectinate muscles.

2.4. Discussion

2.4.1. Related Work

Computational meshes of the human atria have been constructed previously (Harrild and Henriquez, 2000; Seemann et al., 2006; Vigmond et al., 2001; Virag et al., 2002)—to our knowledge, ours is the first atrial mesh that is tricubic Hermite. Most previous computational meshes of the atria have been composed of simplices or linear hexahedra. Detailed descriptions of existing human atrial models are described in reviews by Dössel and colleagues (2012) and Jacquemet and colleagues (2008).

Cubic Hermite meshes with some topological complexity have been constructed using “duplicate” vertices with derivative constraints, most typically at the joining points of the right ventricle and the ventricular septum, as in the work of Usyk and colleagues (2002). To our knowledge, no general framework has been proposed to construct more complicated shapes
while preserving smoothness between elements. A previous work constructed a tricubic Hermite model of porcine ventricles with topological complexity just sufficient to capture the valve annuli (Stevens et al., 2003). Fernandez and colleagues (2004) constructed cubic Hermite models of more complicated shapes with extraordinary vertices and “hanging” vertices, but did not attempt to preserve smoothness near these points. We previously demonstrated deformable registration of a cubic Hermite four-chamber heart model (Zhang et al., 2012), but as we had not yet defined the local-to-global map in meshes with extraordinary vertices, we could only apply the deformations to the linear hexahedral mesh. In the future, our deformable registration scheme will be used on the higher-quality models created by the methods here, and may also utilize the local-to-global map to deform the cubic Hermite meshes directly.

Zhang and colleagues (2007b) constructed a hexahedral non-uniform rational B-splines (NURBS) model with extraordinary vertices, and simulated elastic deformation of the aorta coupled with incompressible Navier-Stokes equations (Bazilevs et al., 2006). The NURBS meshes can be “k-refined” (Hughes et al., 2005) to increase the order of their basis functions while preserving continuity, but enforcing continuity near extraordinary vertices is difficult, as with cubic Hermite splines. Cubic Hermite splines (and other interpolating splines) connect functional space to underlying geometry directly because coefficients of the solution space include parametric derivatives of the solution field. Approximating splines such as NURBS have other advantages, discussed by Hughes and colleagues (2005).

We use subdivision surfaces to define parameters of spline surfaces; previously, Catmull-Clark subdivision has been used to parameterize bicubic Beziér splines (Loop and Schaefer, 2008), biquadratic B-splines (Zheng et al., 2005), and non-uniform rational B-splines (Peters, 2000). Our approach differs principally in that Eq. 2.2 computes parametric derivatives of cubic Hermite splines rather than control points of approximating splines, and
we parameterize the derivatives of tricubic hexahedra as well as bicubic quadrilaterals. Subdivision surfaces have been useful in cardiac modeling for purposes aside from computing cubic Hermite derivatives. Chandrashekara and colleagues (2007) use subdivision surfaces to track cardiac deformation in tagged MRI, using the coarseness of the subdivision surface template to decrease computational burden. Sheehan and colleagues (2008) use subdivision surfaces to analyze right ventricular shape and volume in patients with tetralogy of Fallot, and in so doing are able to include the two right ventricular valve annuli in their geometric models.

2.4.2. Precise G1 and C1 Continuity

Bicubic splines have degrees of freedom insufficient to enforce C1 continuity near extraordinary vertices; consequently, C1 continuity in these regions is achieved only for special geometric configurations. Wang and Zhang (2010) demonstrated these requirements mathematically in non-uniform rational B-splines (NURBS), but only for vertices with valence five. We selected Hermite derivative parameters using the Li-Kobbelt scheme with limit-surface C1 continuity rather than enforcing the requirements for splines.

In spite of Hermite derivative parameterization with the Li-Kobbelt scheme, our meshes do not achieve precise G1 or C1 continuity in the one-neighborhood of extraordinary vertices. The subdivision scheme utilized demonstrates continuity properties of the limit surface by eigenanalysis, which cannot be applied directly to our meshes because we truncate the subdivision surface sequence at its second member. In general, this will induce normals with different directions at the boundary of adjoining elements, as tabulated in Table 2.2.

In principle, the truncation problem could be eliminated if the one-neighborhood vertices are arranged symmetrically around an extraordinary vertex, and are placed in a common plane—this was called the “natural configuration” by Ball and Storry (1988). The natural configuration is flat, but configurations with non-zero curvature may also give rise to
C1 continuity. Ball, Storry, and Sabin noted the natural configuration could be transformed to all C1 continuous configurations around extraordinary vertices by affine transformation, but did not specify for which affine transformations. Ball and Storry also noted the natural configuration eliminates the Fourier coefficients of high-frequency components in the subdivision matrix for arbitrary valence, while Doo and Sabin (1978) earlier had noted convergence occurs because contributions of high-frequency components diminish. We did not place one-neighborhood vertices of extraordinary vertices symmetrically—this worsened quality metrics of the surrounding elements severely. However, if desired, G1 continuity can be achieved precisely at the extraordinary vertex by projection of the parametric tangent vectors (derivatives) of different elements at the extraordinary vertex into a common plane defined by the span of the ensemble derivatives.

As with extraordinary vertices, calculation of cubic Hermite derivatives by Li-Kobbelt subdivision only approximates C1 continuity at ordinary vertices. Nonetheless, tangent (G1) or parametric (C1) continuity can be enforced by the local-to-global map at ordinary vertices (see Section 2.4.2). The sufficient conditions were described by Bradley et al. (1997). Bradley and colleagues showed adjacent bicubic Hermite patches are C1 continuous when scale factors of adjoining splines are chosen to be the same, but with this choice, arc-length continuity is satisfied only in special cases. Alternatively, scale factors of bicubic Hermite patches can be constructed as described by Nielsen (1987), in which case the scale factors of adjoining splines may have different values. With the approach of Nielsen, arc-length continuity is enforced at the ordinary vertex, tangent (G1) continuity is satisfied along contours joining ordinary vertices, and in general, C1 continuity is satisfied neither at vertices nor along contours joining vertices. Ensemble derivatives may be transformed to parametric derivatives of adjacent elements with Eq. 2.5, Eq. 2.6 and Eq. 2.12-Eq. 2.15 using the scale factor definition of Bradley or of Nielsen. In the present work, we used the scale factor convention of
Nielsen: arc-length continuity was enforced at ordinary vertices, and tangent (G1) continuity was satisfied along contours joining ordinary vertices.

2.4.3. **Topology of a human atrial geometric model**

A completely unstructured quadrilateral mesh, as may be generated by triangle pairing, has more extraordinary vertices than is necessary for capturing the morphologic features of the atrial geometries. Such meshes can have high-quality elements at the expense of topological structure. As structure is simplified (by use of fewer extraordinary vertices), mesh quality is compromised, especially for coarse meshes. Nonetheless, a topologically simple mesh may be preferred for domain decomposition, fiber field construction, or to match the topologies of other biatrial hexahedral models for comparative studies.

In the future, the pipeline from non-invasive imaging data to high-quality hexahedral finite element model may be automated. Our previous study (Zhang et al., 2012) utilizes a “sweeping” method to construct an atlas of linear hexahedral four-chamber models directly from imaging data—subsequent geometries may be constructed *de novo* or by deformable registration to atlas models. Owing to limitations of the sweeping method, we used freehand to construct topological patterns in this study, which may be incorporated into the atlas. Automatic triangular mesh generation, followed by conversion to quadrilaterals (Velho and Zorin, 2001), followed by transmural extrusion to a hexahedral mesh was considered, but for the present study, it was advantageous to define the topological patterns manually—this approach enabled fiber fields to be defined easily. In general, a topological pattern can be chosen objectively for a given surface by identification of its critical points of curvature (Campen et al., 2012; Pennec et al., 2000).

Topology choice by freehand does not lead to an endless number of possible topology patterns—extraordinary vertices are placed naturally in some locations (e.g., at saddle points),
and extraordinary vertices together must be consistent with the Euler characteristic number $\chi$ of the surface. The Euler characteristic number of a surface must satisfy the relation $\chi = V - E + F$, where $V$ is the number of mesh vertices, $E$ is the number of mesh edges, and $F$ is the number of mesh faces. Furthermore, our surface meshes are orientable, and homeomorphic to the sphere if their boundaries (holes) are filled by disks to make them closed surfaces. For such a surface having $b$ boundaries, $\chi = 2 - b$ (Kinsey, 1993). If valence 3 vertices are assigned a characteristic index of +1/4, valence 5 vertices assigned an index of -1/4, and valence 6 vertices assigned an index of -1/2, then the sum of characteristic indices for all extraordinary vertices of the surface equals its Euler characteristic number. For example, the left atrium has 5 boundaries (the four pulmonary vein orifices and the mitral valve orifice), so $\chi = -3$. The mesh LA-103 has eight valence 3 vertices, each having index +1/4, and twenty valence 5 vertices, each having index -1/4. The sum of all extraordinary vertex indices is -3. We added extraordinary vertices to LA-142 to capture geometric detail that LA-103 could not capture, but we were required to add the same number of valence 3 and valence 5 vertices (in this case, five) for the left atrial appendage to remain a blind pouch (i.e., have no holes). Further description is given by Koenderink (1990), who describes the Euler characteristic number and its relationship to indices of surface umbilical points.

Our methods are readily extendable to patients with accessory pulmonary veins or pulmonary vein bifurcations. A left atrial model with an accessory (fifth) pulmonary vein will have $\chi = -4$. Accordingly, four additional extraordinary vertices of valence 5 will be placed to decrement the Euler characteristic number by one. The vertices should be placed near the accessory pulmonary vein to minimize element distortions (Figure 2.8A). A left atrial model with early bifurcation of one pulmonary vein will also have $\chi = -4$. In this case, mesh
Figure 2.8: Placement of extraordinary vertices for two meshes in different patients with an Euler characteristic number of -4. In a patient with an accessory pulmonary vein (A), four extraordinary vertices of valence 5 (asterisks) are placed around the circumference of an accessory pulmonary vein to capture the abrupt change in curvature at the vein ostium. To capture a pulmonary vein bifurcation (B), two extraordinary vertices of valence 6 are placed (colored black). Either four valence 5 vertices or two valence 6 vertices can decrement the Euler characteristic number by one. The view in (A) is left lateral, and the view in (B) is left inferolateral. The mitral valve orifice is shaded dark gray, and the inner surface of the pulmonary veins pink, for visual contrast. Valence 3 vertices are colored red, and valence 5 vertices teal. LAA = Left atrial appendage; LSPV = Left superior pulmonary vein; RSPV = Right superior pulmonary vein; LIPV = Left inferior pulmonary vein; RIPV = Right inferior pulmonary vein; APV = Accessory pulmonary vein; MVO = Mitral valve orifice.

quality will be highest when two valence 6 vertices—which also decrement the Euler characteristic number by one—are placed near the point of vein bifurcation (Figure 2.8B).

2.4.4. Atrial fiber architecture

Finite element simulations of cardiac mechanics and electrophysiology require material anisotropy (defined in part by a vector field representing fiber orientation) to capture essential features of deformation and electrical activation sequence. In this regard, fewer data exist for fiber architecture of the atria compared to ventricles because histology and diffusion tensor magnetic resonance imaging (DT-MRI) of atria are difficult, owing to their thin walls. As a consequence, previous studies (Krueger et al., 2011) and the current work use rule-based methods to define atrial fiber architecture qualitatively based on published diagrams of atrial fiber tracts. Since no detailed human atrial fiber data are available currently, it is unknown if
qualitatively-described fiber data compromise computational models of healthy or diseased atria.

Human atrial musculature comprises fiber tracts spanning large areas, and the fiber tract orientations partially follow geometric features. Extraordinary vertices may be placed to align coordinate axes of mesh regions with dominant directions of fiber tracts, and demarcate loci of gross fiber discontinuity or abrupt directional change. Abrupt transmural changes in fiber orientation can also be represented if a model is two or more layers of hexahedra thick, as was demonstrated in BiA-75888 (Figure 2.7). Moreover, a C1 continuous cubic Hermite mesh features local coordinate frames that vary smoothly between elements. Interpolation of angles referred to these frames gives rise to smooth fiber orientations between elements in each subregion. An alternative approach for fiber modeling uses twenty-two “seed points” to drive fiber orientations throughout the biatrial model without using element coordinate axes (Krueger et al., 2011; Krueger et al., 2013). In both approaches, a limited number of parameters was sufficient to give qualitative agreement with diagrams of fiber architecture.

More detailed fiber field information has been obtained in imaging studies by Zhao and colleagues in sheep (2012) and by Aslanidi and colleagues in canine (2013) using imaging of tissue microstructure. In humans, DT-MRI has been used to construct fiber orientations near the sinoatrial node (Aslanidi et al., 2011), but extracting fiber direction by DT-MRI remains difficult in the atria. As with the approach of Krueger and colleagues, our approach for representing fiber orientations has no loss of generality, and can incorporate more detailed human fiber data when they become available by imaging of tissue microstructure or DT-MRI.
2.4.5. Potential applications

Cubic Hermite meshes (and other high-order splines) have several well-known advantages in numerical analysis of cardiac function: One, they capture smooth geometries with few finite elements and can be deformed easily from template meshes (Lamata et al., 2011). Two, they have convergence advantages in biomechanics (Costa et al., 1996) and electrophysiology (Arthurs et al., 2012; Rogers et al., 1996). Third, they are useful for modeling electrical mapping studies when data are missing or poor-quality (Bayly et al., 1998). Last, a C1 continuity of geometry allows for continuous stresses across element boundaries for biomechanics problems, continuous currents across element boundaries for electrophysiology problems, and continuous fiber orientation fields across boundaries when fibers are represented as angular fields referred to local coordinate axes. However, the problem of retaining smoothness between cubic Hermite elements with extraordinary vertices has prevented these meshes from being used for atrial modeling. In the present work, we propose a solution to this problem so that these advantages can be utilized in complex geometries such as that of the atria.

Even so, our work has other potential applications. Automatic meshing from *in vivo* imaging typically creates fine surface triangulations with triangle sizes near the sizes of the image voxels, yet applications such as biomechanics and deformable registration do not require such refined meshes for accurate solutions. Here, we suggest a strategy to coarsen these fine triangulations not only with bicubic Hermite quadrilaterals but also with linear quadrilaterals, both of which capture the smooth shapes of the heart more compactly than do linear simplices. As noted above, automatic methods for placement of extraordinary vertices have been reported previously (Alliez et al., 2003; Kälberer et al., 2007). Nonetheless, manual placement of extraordinary vertices may be preferred when *in vivo* imaging data have appreciable noise, and also when it is advantageous to define coordinate lines manually—here,
for example, we place some of the extraordinary vertices to define discontinuities in the fiber orientation field easily.

2.4.6. Limitations and future directions

The interpolating subdivision scheme utilized has deficiencies: First, its limit surface is not defined in spline form, unlike Catmull-Clark subdivision. Second, as a hexahedral subdivision, it requires topological consistency between inner and outer surfaces to define tricubic Hermite derivative parameters. Restriction to topological correspondence between inner and outer surfaces may be lifted by using volumetric hexahedral meshing schemes with more general topology (Nieser et al., 2011) and interpolating subdivision schemes for hexahedral meshes (Bajaj et al., 2002; McDonnell et al., 2004), but this approach is not needed for the present work, and descriptions of C1 continuity requirements for hexahedral subdivision schemes are sparse compared to surface schemes. Our models do not include pectinate muscles, patient-specific wall thicknesses, or patient-specific interatrial connections, owing to limitations of imaging technology in vivo. In the future, advances in imaging technology may allow finer details to be captured.

2.5. Conclusion

We generalized the local-to-global mapping used in cubic Hermite modeling to construct smooth meshes with extraordinary vertices, and solve finite element problems with smooth solutions. We utilized a subdivision surface scheme, adapted for hexahedral meshes, to select cubic Hermite parameters to achieve arc-length continuity at ordinary vertices and near-G1 continuity around extraordinary vertices. Next, we used the topological structure of the mesh to represent fiber fields compactly. Finally, we described how our methods could be applied to patients with different pulmonary vein anatomies.
Acknowledgements

The content of this chapter is almost identical to a manuscript accepted for publication, with only formatting changes for this dissertation. The citation is Gonzales, M.J., Sturgeon, G., Krishnamurthy, A., Hake, J., Jonas, R., Stark, P., Rappel, W.J., Narayan, S.M., Zhang, Y., Segars, W.P., McCulloch, A.D., 2013. A three-dimensional finite element model of human atrial anatomy: New methods for cubic Hermite meshes with extraordinary vertices. Medical Image Analysis. The manuscript was accepted March 4, 2013. The authors of this manuscript would like to thank Chandrajit Bajaj and Joe Warren for providing advice about subdivision surfaces. This work was supported by by NIH grants NHLBI 1 R01 HL96544 (ADM), NHLBI 1 R01 HL083359 (SMN, WJR), NHLBI 1 K24 HL103800 (SMN), NHLBI 1 RO1 HL091036 (WPS), NHLBI 5 T32 HL007089, NHLBI 1 T32 HL105373, NIBIB 1 T32 EB009380 (ADM), NIGMS 8 P41 GM103426 (National Biomedical Computation Resource), and NIGMS P50 GM094503 (Virtual Physiological Center for the Study of Complex Diseases). This work was also supported by NSF Career Award OCI-1149591 (YZ), the San Diego Fellowship (MJG), and the Center of Excellence grant from the Research Council of Norway to the Center for Biomedical Computing at Simula Research Laboratory. Figure 2.6A-B is reprinted from a journal article with permission from British Medical Journal Publish Group Ltd. The full citation for this article is Wang, K., Ho, S.Y., Gibson, D.G., Anderson, R.H., 1995. Architecture of atrial musculature in humans. British Heart Journal 73:559-565.
Appendix I

The chain rule can be used to determine the relationship between second and third-order mixed derivatives in the local and global frames:

\[
\frac{\partial^2 Y}{\partial \xi_1 \partial \xi_2} = \frac{\partial^2 Y}{\partial s_1 \partial s_2} \left[ \frac{\partial s_1}{\partial \xi_1} \cdot \frac{\partial s_1}{\partial \xi_2} + \frac{\partial s_2}{\partial \xi_1} \cdot \frac{\partial s_2}{\partial \xi_2} \right] + \frac{\partial^2 Y}{\partial s_1 \partial s_3} \frac{\partial s_1}{\partial \xi_1} \left[ \frac{\partial s_3}{\partial \xi_2} \frac{\partial s_2}{\partial \xi_3} + \frac{\partial s_2}{\partial \xi_1} \frac{\partial s_3}{\partial \xi_3} \right] + \frac{\partial^2 Y}{\partial s_2 \partial s_3} \frac{\partial s_2}{\partial \xi_1} \left[ \frac{\partial s_3}{\partial \xi_2} \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_1}{\partial \xi_1} \frac{\partial s_3}{\partial \xi_3} \right]
\]

Eq. 2.12

\[
\frac{\partial^2 Y}{\partial \xi_2 \partial \xi_3} = \frac{\partial^2 Y}{\partial s_1 \partial s_2} \left[ \frac{\partial s_1}{\partial \xi_2} \cdot \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_2}{\partial \xi_2} \cdot \frac{\partial s_2}{\partial \xi_3} \right] + \frac{\partial^2 Y}{\partial s_1 \partial s_3} \frac{\partial s_1}{\partial \xi_2} \left[ \frac{\partial s_3}{\partial \xi_2} \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_1}{\partial \xi_1} \frac{\partial s_3}{\partial \xi_3} \right] + \frac{\partial^2 Y}{\partial s_2 \partial s_3} \frac{\partial s_2}{\partial \xi_2} \left[ \frac{\partial s_3}{\partial \xi_2} \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_1}{\partial \xi_1} \frac{\partial s_3}{\partial \xi_3} \right]
\]

Eq. 2.13

\[
\frac{\partial^2 Y}{\partial \xi_3 \partial \xi_3} = \frac{\partial^2 Y}{\partial s_1 \partial s_2} \left[ \frac{\partial s_1}{\partial \xi_3} \cdot \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_2}{\partial \xi_3} \cdot \frac{\partial s_2}{\partial \xi_3} \right] + \frac{\partial^2 Y}{\partial s_1 \partial s_3} \frac{\partial s_1}{\partial \xi_3} \left[ \frac{\partial s_3}{\partial \xi_2} \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_2}{\partial \xi_1} \frac{\partial s_3}{\partial \xi_3} \right] + \frac{\partial^2 Y}{\partial s_2 \partial s_3} \frac{\partial s_2}{\partial \xi_3} \left[ \frac{\partial s_3}{\partial \xi_2} \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_1}{\partial \xi_1} \frac{\partial s_3}{\partial \xi_3} \right]
\]

Eq. 2.14

\[
\frac{\partial^3 Y}{\partial \xi_1 \partial \xi_2 \partial \xi_3} = \frac{\partial^3 Y}{\partial s_1 \partial s_2 \partial s_3} \left[ \frac{\partial s_1}{\partial \xi_1} \cdot \frac{\partial s_1}{\partial \xi_2} \cdot \frac{\partial s_1}{\partial \xi_3} + \frac{\partial s_2}{\partial \xi_1} \cdot \frac{\partial s_2}{\partial \xi_2} \cdot \frac{\partial s_2}{\partial \xi_3} + \frac{\partial s_3}{\partial \xi_1} \cdot \frac{\partial s_3}{\partial \xi_2} \cdot \frac{\partial s_3}{\partial \xi_3} \right]
\]

Eq. 2.15
We note Eq. 2.12 simplifies to Eq. 2.4, the previous definition for high-order scale factors, for singular topology (i.e., extraordinary vertices are absent) because the terms \( \frac{\partial s_i}{\partial \xi_j} \) are zero for \( i \neq j \). Arc-length parameterization of each spline is avoided if second derivatives mapped between the coordinates \( s \) and \( \xi \) are estimated to be zero (i.e., the speed of the contour is constant).

Appendix II

The biatrial tricubic Hermite model had 19,359 vertices (of which 146 were extraordinary) and 9,486 hexahedra. Of the 146 extraordinary vertices, 53 lay on each of the endocardial and epicardial surfaces, and 40 new extraordinary vertices were introduced by interatrial connections. Mean edge length was 2.0 mm. There were 38 regions of contiguous topology. The right atrium has topology regions numbered 1-11, interatrial connections have regions numbered 12-16, and the left atrium has regions numbered 17-38. The left atrium had 22 regions, rather than the 20 listed for LA-568 in Table 2.3, because the left atrial floor was divided into three regions: numbers 18, 19, and 20—this allowed more accurate description of the fiber pattern. A refined model constructed by Hermite interpolation had 114,970 vertices and 75,888 hexahedra. Mean edge length was 1.0 mm. Four new topology regions (39-42) were introduced to capture transmural variations in fiber orientation.

Transmural thickness data and fiber orientation information used to construct the biatrial hexahedral meshes are provided in Table 2.1. Contrast of the computed tomography study was insufficient to resolve transmural thickness in most regions, in which case a thickness of 2 mm was assumed. Population-representative values were used for the venae cavae, the pulmonary veins and their immediate surroundings (Ho et al., 2001), the posterior left atrial wall (Platonov et al., 2008), and the left atrial roof (Hall et al., 2006). The posterior left atrial wall was given a thickness gradient from superior (2.1 mm) to inferior (2.5 mm).
Dimensions and location of the coronary sinus, limbus of the fossa ovalis, and Bachmann’s bundle were based on population-representative values from human studies. The coronary sinus dimensions were based on a study by Chauvin et al. (2000), the dimensions of the limbus of the fossa ovalis based on a study by Reig et al. (1997), and Bachmann’s bundle dimensions based on a study by Saremi et al. (2008). When adjoining regions had different transmural thicknesses, intermediate values of thickness were assigned near the borders. Smoothing with the scheme of Zhang et al. (2007a) modified thicknesses as well.

In 19 regions, fiber orientations were arranged circumferentially around an orifice. In these cases, the orifice names are in parentheses in Table 2.1. In BiA-9486 (BiA-75888), fiber orientations were defined by an angle referred to local coordinate axes in five (seven) regions. In these cases, the angles of interpolation with respect to local coordinate axes are in parentheses.

All of the atrial models in this paper are available by the following identification numbers in the Continuity database (http://www.continuity.ucsd.edu): LA-103: 1149; LA-142: 1247; LA-412: 1151; LA-568: 1152; RA-90: 1153; RA-360: 1251; LA-142 (hexahedral): 1249; RA-90 (hexahedral): 1248; BiA-9486: 1304; BiA-75888: 1302. These models can be exported as linear meshes or cubic Hermite meshes in portable formats by following the directions at the following link: http://www.continuity.ucsd.edu/Continuity/Documentation/DeveloperDocs/ExportGuide.
References


Chapter 3

Interactive modeling of the atria and the whole heart
Abstract

Chapter 2 presented a framework for building patient-specific cubic Hermite models of the human atria from non-invasive imaging, and concentrated primarily on the challenges overcome for including extraordinary vertices in these models. Further care is necessary to optimize these models for computational efficiency. In this chapter, I elaborate the details of interactive modeling of the atria that are required to create a computationally efficient model. I then extend these principles, and the principles discussed in Chapter 2, to construct cubic Hermite meshes of the ventricles and of the whole heart.

3.1 Introduction

3.1.1 Biventricular and four-chamber finite element models in the study of human cardiac disease

An estimated one in five people in the United States will suffer from congestive heart failure (CHF) at some point (Lloyd-Jones et al., 2002), and once diagnosed, patients with CHF have a median survival time of less than five years (Owan et al., 2006). Treatment by pharmacological agents and cardiac resynchronization therapy (CRT) can reduce morbidity and mortality of CHF patients, but both treatments have limited efficacy, and many patients undergoing CRT (up to 30%) do not show an improvement. Patient-specific computational models of the cardiac ventricles have shown promise in interpreting clinical data (Aguado-Sierra et al., 2011; Kerckhoffs et al., 2010; Niederer et al., 2011) and one day might be used to predict non-responders to CRT a priori and optimize lead placement for alleviating electrical and mechanical dyssynchrony.

In order for patient-specific computational models to be useful clinically, the computational model must be built and solved in a clinical timescale. Both building and solving computational models in clinical timescales are challenging problems. Though triangle- and tetrahedron-based meshes can be created readily from segmented medical
images, these meshes often are not suitable for finite element analysis due to poor finite element quality. Moreover, even linear triangles and tetrahedra with improved quality are particularly prone to “shear locking” in mechanical simulations (Bower, 2011), and also cannot capture the smooth shape of the ventricles efficiency, leading to increased computational costs.

Creating hexahedral computational models of the ventricles or of all four chambers of the heart as an alternative to simplicial models allows for coarser models with lower computational costs. As discussed in Chapter 2, it is difficult to construct quadrilateral and hexahedral meshes of irregular shapes from medical images, with much of the difficulties attributable to optimal placement of extraordinary vertices. (In fact, this difficulty is so great, it induces many groups to construct and use biventricular models without valve annuli or great vessels.) Constructing cubic Hermite hexahedral meshes is more difficult still, but cubic Hermite finite element models of biomechanics allow for continuous stresses across finite elements, are less prone to shear locking than linear finite elements, and have convergence advantages compared to linear finite element problems with an equal number of degrees of freedom. In the current chapter, I present a pipeline for building computationally efficient patient-specific tricubic Hermite models. Rather than require all steps in the pipeline be automated, I propose to build a limited number of template models as part of an atlas, and then non-rigidly deform one of the atlas models directly to imaging data of new patients (Zhang et al., 2012).

3.1.2 The Euler characteristic number

The Euler characteristic number, often denoted by \( \chi \), is a fundamental invariant in the field of algebraic topology used to classify like-surfaces. The two fundamental surfaces are the sphere (\( \chi = 2 \)) and the torus (\( \chi = 0 \)). These surfaces are orientable, meaning they have “two
sides”, and *closed*, meaning they do not have a boundary. A boundary can be introduced into a closed surface by removing a disk (\( \chi = 1 \)). All other orientable surfaces are relatable to the sphere, the torus, or the disk by homeomorphism, by removing disks (i.e., creating holes), or by both homeomorphism and removal of disks. For example, the left and right atrial surfaces constructed in Chapter 2 are homeomorphic to the sphere, but with a disk removed for each great vessel and valve annulus.

The Euler characteristic of a surface can be computed using the formula

\[
\chi = 2 - 2g - b
\]

where \( g \) is the genus of a surface and \( b \) is the number of boundaries of the surface. The genus is often misunderstood to be the number of holes in a surface. In fact, it is the number of penetrating holes through a volume-enclosing surface. The disk does not enclose a volume and thus has genus zero. A sphere does enclose a volume but has no penetrating holes, so it also has genus zero. A torus encloses a volume and has a penetrating hole, and thus has genus one. Adding a boundary to a surface decrements its Euler characteristic number by one. For instance, the hemisphere and the disk have genus zero, have a boundary (i.e., a contour), and thus have \( \chi = 1 \); a sphere has genus zero, has no boundaries, and thus has \( \chi = 2 \).

It is useful for the geometric modeler to classify structures by their Euler characteristic number because this number dictates which finite element connectivities are permissible for each topological surface. First, the Euler characteristic number constrains the number of possible vertices, edges, and faces coexisting in a surface discretization according to the formula

\[
\chi = V - E + F
\]

Eq. 3.2
where $V$ is the number of vertices, $E$ is the number of edges, and $F$ is the number of faces of the surface. Thus, vertices, edges, and elements cannot be added indiscriminately if the geometry is to retain its topological structure; they must be added in groups known as Euler operators (Alavala, 2008). Second, the Euler characteristic number constrains the number and type of extraordinary vertices that must be present. It also can be used to compute the minimum number of extraordinary vertices that must be present, enabling the coarsest possible model to be built. Once the minimum number of extraordinary vertices is added, additional extraordinary vertices can be added to capture geometric detail if desired, as shown in Section 2.3.2 and as discussed in Section 2.4.3. Vertices of each valence have characteristic indices: vertices of valence 3 have index $+1/4$, vertices of valence 5 have index $-1/4$, and vertices of valence 6 have index $-1/2$. The sum of the indices of all extraordinary vertices must be equal to the Euler characteristic number. For example, the hemisphere and the disk have $\chi = 1$, and thus must have at least four extraordinary vertices of valence 3. It is worth noting that Eq. 3.1 and Eq. 3.2 assume no extraordinary vertices lie on boundaries of a surface. For instance, the plane discretized as quadrilaterals has no extraordinary vertices, but its boundary cannot be smooth owing to vertices at the corners of the plane. At these points, the normals are not well defined. Such configurations are permissible in geometric modeling and finite element analysis, but usually are avoided whenever possible.

3.1.3 Mesh quality, the condition number, and simulation error

Meshes with high quality are preferred in computer graphics applications and also in finite element analysis. Three properties of high quality meshes are as follows: One, element sizes within the mesh are similar. Two, the anisotropy ratio of elements—the ratio of the longest and shortest side of an element—are near unity. Three, the internal element angles are regular (e.g., all angles of a quadrilateral are close to 90 degrees). For the general object with
complex shape, it is not possible to have a mesh with equally sized elements, elements with unit aspect ratios, and elements with equal angles—in fact, the improvement of one of these mesh quality metrics by moving vertices usually comes at the cost of another. The most important of these three quality metrics can vary by application.

Element anisotropy ratios, element angles, and element size uniformity all affect a quantity known as the condition number in numerical analysis (Armaly et al., 1972; Knupp, 2000; Knupp, 2001). For a linear system $A\mathbf{x} = \mathbf{b}$, the condition number is a property of the matrix $A$ and is defined as the ratio of its largest eigenvalue to its smallest eigenvalue. Depending on the numerical scheme used to solve the linear system (i.e., an iterative matrix inversion scheme or a factorization), a poorly-conditioned matrix may give rise to higher solution errors, slower numerical convergence, or both (Shewchuk, 2002).

While maintaining good mesh quality optimizes the condition number of a linear system, other factors adversely affecting the condition number are properties of the physical system and thus cannot be avoided. For example, a non-unit anisotropy ratio for the elastic modulus adversely affects the condition number of a mechanics problem, and a non-unit anisotropy ratio for the electrical conductivity adversely affects the condition number of an electrophysiology problem.

3.2 Methods

3.2.1 The Blender environment for geometric modeling

As discussed in Section 3.1.1, it is required that the pipeline for geometric modeling of the atria and all four heart chambers be adaptable to anatomical variations between patients, but it is not required that every step be automatic. As discussed below, many geometric modeling tools have limitations. These limitations can be addressed by interactive manipulation of the model before and after the modeling scripts are applied. Many software
programs are available for geometric modeling and animation with a target audience of the entertainment industry—some examples are Blender, Cinema 4D, Maya, Rhinoceros, and 3D Studio Max. Here, I use Blender (http://www.blender.org/) as a mesh manipulation environment because it is freely available and scriptable using Python (http://www.python.org/). Python is attractive because it has plug-ins Numpy (http://www.numpy.org/) and Scipy (http://www.scipy.org/) highly optimized for expensive numerical computations, as is required with the mesh improvement schemes.

Although Blender was not written for finite element applications, it nonetheless has several built-in functionalities useful for modeling of the atria and of the whole heart. First, it allows for a mesh to be constructed by manual placement of vertices and faces such that they “snap” to an existing mesh. This is useful because the output of medical segmentation is often a fine triangular mesh poorly-suited for finite elements. The user can define a new, coarser mesh manually while maintaining geometric accuracy. Second, Blender allows for intuitive manipulation of mesh primitives (vertices, edges, and faces) in three-dimensions, which is a difficult challenge in the field of computer graphics. Third, Blender allows for manipulation of “edge-loops”, a string of edges sharing contiguous coordinates, allowing for fast manipulation of large regions of the mesh and indirectly helping improve mesh quality (see Section 3.3.1).

A principal limitation of Blender and other geometric modeling software is that volumetric objects, such as hexahedra and tetrahedra, are not understood natively—only surfaces are. To leverage the full capabilities of Blender, it was necessary to write a software plug-in that enabled Blender to understand hexahedra as a volumetric object; it also provided a natural way to interface Blender with mesh quality improvement scripts written in Python. I called this software plug-in to Blender HexBlender. The schemes implemented in HexBlender are discussed in Section 3.2.2 below.
3.2.2 Mesh quality optimization schemes

In this section, I briefly review the mesh quality improvement schemes used in improving the quality of patient-specific atrial and whole heart models, and point out their strengths and weaknesses.

Many surface smoothing and regularization schemes are based on Laplacian smoothing. A Laplacian smoothing scheme calculates a motion vector for each vertex as a weighted average of the distance between that vertex and each of its neighbors. The flexibility of Laplacian smoothing is that the weights in such a scheme can be calculated in different ways, giving rise to smoothing processes with distinct properties. Subdivision surface schemes customarily define the insertion points of new vertices in a similar way—the new vertices are placed at locations calculated by the weighted averages of surrounding vertices. Different schemes for calculating the weights give rise to subdivision surface schemes with different properties of surface continuity and surface curvature.

Once a tentative surface connectivity is constructed in accordance with the Euler characteristic number (Section 3.1.3), the angles and element sizes can be optimized with a scheme by Ohtake et al. (2000). Like most smoothing schemes, the Ohtake scheme is a modification of a Laplacian smoothing scheme. It calculates weights as to use mean curvature flow for smoothing and Laplacian flow for regularization. The Ohtake scheme has three strengths: it regularizes angles and element sizes well, its computational operations are data parallel, and it can be used in conjunction with “edge-loops” to optimize element sizes and angles interactively (Section 3.3.1). It has weaknesses as well: it contains a computationally expensive eigen-decomposition, the minimum reached depends on the initial conditions, and its behavior is not ideal for applications in which highly anisotropic elements are used. These drawbacks aside, the applications I encountered never required the implementation of another surface mesh quality optimization scheme aside from the Ohtake scheme.
Uniform “one-to-four” subdivision can be used to refine a mesh when it is required. I almost exclusively use the Li-Kobbelt scheme (Li et al., 2005) to refine linear quadrilateral meshes for reasons discussed in Section 2.2.3, but also use the Catmull-Clark (1978) scheme sometimes on fine meshes because unlike the Li-Kobbelt scheme, its limit surface approaches C2 continuity at ordinary vertices. Discontinuities in curvature are not expected to be present at most points in the heart, and their presence in geometric models gives rise to rendering artifacts. For sufficiently fine meshes, the permitted motion of vertices by Catmull-Clark in the parent mesh is less than the uncertainty of the imaging from which the parent mesh came.

A combination of Ohtake regularization, edge-looping, and refinement by subdivision surfaces can be used to construct high-quality finite element surface models. If a hexahedral mesh is desired rather than a surface mesh, one strategy is to start with an optimized surface mesh and to complete a process native to Blender called extrusion. Extrusion simply creates a new surface by creating new vertices in the outward normal direction of every existing vertex on the mesh. Meshing the arbitrarily-shaped three-dimensional object is difficult, but since most tissue in the heart has an inner surface and an outer surface, extrusion is useful as a starting point. Tissues without inner and outer surface correspondence, such as the ventricular and atrial septa, can be constructed manually.

One method for regularizing hexahedral meshes is the scheme of Zhang et al. (2005). This method uses the Laplace-Beltrami operator and the concept of mean curvature flow to move vertex locations in the normal direction while (approximately) preserving volume. The motion of vertices in each coordinate is given by

\[
\frac{\partial \mathbf{x}}{\partial t} = v(\mathbf{x})\mathbf{T}(\mathbf{x}) \pm \Delta H(\mathbf{x})\mathbf{n}(\mathbf{x})
\]

Eq. 3.3
where \( \mathbf{x} \) is the coordinate of a vertex, \( v(\mathbf{x}) \) is a velocity calculated in the tangent direction \( \mathbf{T}(\mathbf{x}), \Delta \) is the Laplace-Beltrami operator, and \( H(\mathbf{x}) \) is the mean curvature. If the sign in Eq. 3.3 is positive, the mean curvature will evolve so that local curvature is locally spherical. If the sign is negative, the mean curvature will evolve so that local curvature is locally flat. It is advantageous to evolve the curvature with the positive sign in regions where the geometric object being modeled is known to have positive curvature, and to evolve the curvature with the negative sign when the object being modeled is known to be locally flat and any curvature present is likely the result of noise from imaging and segmentation. In the Zhang scheme, the discretization of the first term in Eq. 3.3 uses a center-of-mass approach to move surface vertices in the tangent direction to homogenize element sizes as well as internal (i.e., non-surface) vertices in the hexahedral mesh to homogenize element volumes. A drawback of the center-of-mass approach is that it does not directly optimize element angles or even penalize for skew angles, and thus can give poor results if the initial condition of the regularization is not already close to optimized.

To rectify the problem of skew angles in hexahedral meshes induced by the Zhang scheme, the Vartziotis and Wipper scheme (2011) of hexahedral regularization was implemented. This scheme defines a “dual” octahedron for every hexahedron, and calculates a displacement vector as to regularize the outward normals of the octahedron faces such that the sum of all face unit normals is zero. This scheme is able to complement the Zhang scheme in that it generally moves internal vertices without skewing elements and also can be used to improve the quality of elements with anisotropy ratios far from unity.

A hexahedral interpolating scheme can be used to refine a hexahedral mesh. To insert new external vertices (i.e., vertices lying on a surface), the Li-Kobbelt subdivision scheme can be used. To insert new internal vertices, the coordinates of the corresponding external vertices or of the nearest-neighbor internal vertices can be averaged. This last strategy is somewhat
naïve: First, internal vertices need not have corresponding inside and outside points (though they do for atrial meshes). Second, this approach can give rise to elements with poor quality and even inverted elements, especially when local curvature is large compared to the sizes of the elements, and the elements have large anisotropy ratios. The problems with mesh quality and element inversion could usually be solved by applying the Vartziotis and Wipper scheme to the mesh after subdivision. For some cases, the Vartziotis and Wipper scheme was unable to resolve the inverted elements because the input mesh was of too low quality. In this case, the thin plate splines warping scheme of Bookstein (1989) was employed to correct inverted elements. This scheme moves internal vertices to minimize bending energy of the intermediate surfaces.

The strategy of extrusion, smoothing, and regularization of hexahedral meshes must be adapted for locations where the geometry of the atria and ventricles are not smooth. This is the case at the atrial and ventricular septa. Here, geometric regions are separated by boundary contours called ridges. The hexahedral interpolation, smoothing, and regularization schemes do not have inherent knowledge of where sharp edges in the mesh are features of the underlying geometry and where they are not. Behavior at these edges can be controlled using the materials attribute in Blender. The user, having a priori knowledge of the geometric features, can assign elements to each region. Then, the subdivision and regularization schemes can be executed piecewise on each component of the mesh to preserve model smoothness in the manner desired.

3.3 Results

3.3.1 Element uniformity is improved in a Blender environment

To improve element size uniformity, isotropy, and element angles of surface meshes, the Ohtake scheme was used in concert with Li-Kobbelt interpolating subdivision and with
Figure 3.1: Optimization of element shape and size using a combination of manual edge-loop insertion and automatic regularization. Uniform subdivision (not shown) cannot improve element size uniformity, yet the left atrial appendage (asterisks) requires smaller elements to capture geometric detail at the coarsest mesh resolutions. In (A), edge loops (highlighted) are inserted in the posterior left atrial wall to decrease the size of the largest mesh quadrilaterals. In (B), the result of optimization by the Ohtake scheme is displayed. The quadrilaterals are isotropic, have regular angles, have uniform sizes, and are closer in size to the quadrilaterals of the left atrial appendage.

manual insertion of edge loops (Figure 3.1A). Application of edge loops followed by element regularization by the Ohtake scheme improved element size uniformity (Figure 3.1B).

Coarse quadrilateral surface meshes of the left atrium (LA) and right atrium (RA) were constructed that captured their major geometric features; the models were named LA-170 and RA-80, where the numeral indicates the number of quadrilaterals. Using edge-loop insertion, a one-to-four interpolating subdivision, and the surface regularization scheme of Ohtake, the anisotropy ratio of the quadrilaterals were decreased, as well as the coefficients

Table 3.1: Areas, anisotropy ratios, and angles of coarse meshes (LA-170, RA-80) and refined meshes (LA-4524, RA-4829). Values are presented as means, and coefficients of variation (parentheses). LA = Left atrium; RA = Right atrium.

<table>
<thead>
<tr>
<th></th>
<th>LA-170</th>
<th>LA-4524</th>
<th>RA-80</th>
<th>RA-4829</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (mm²)</td>
<td>95.7 (51)</td>
<td>3.8 (43)</td>
<td>219 (51)</td>
<td>3.9 (44)</td>
</tr>
<tr>
<td>Anisotropy Ratio</td>
<td>1.30 (23)</td>
<td>1.26 (16)</td>
<td>1.32 (24)</td>
<td>1.31 (20)</td>
</tr>
<tr>
<td>Angle (degrees)</td>
<td>88.5 (17)</td>
<td>89.9 (14)</td>
<td>90.6 (21)</td>
<td>89.9 (17)</td>
</tr>
</tbody>
</table>
of variation of the areas, anisotropy ratios, and angles of the quadrilaterals (Table 3.1).

3.3.2 Minimal biventricular meshes with valve annuli are constrained to have one connectivity

A minimal (i.e., coarse) biventricular mesh constituted by hexahedra was constructed as follows: First, the inner surface of the base plane of the heart and the inner surface of the body of the two ventricles were constructed as two hemispherical shells; thereafter, the two hemispherical shells were joined to give the endocardial shell. Second, extrusion was used to construct an epicardial shell and to turn the model from an inner surface model to a hexahedral model with thickness. Third, the ventricular septum was added to separate the left ventricular and right ventricular chambers.

Both the ventricular body hemisphere and the base plane hemisphere were constructed with the guidance of the Euler characteristic number $\chi$. The ventricular bodies were modeled as a hemispherical shell with Euler characteristic number $\chi = 1$, owing to their one contour.

Figure 3.2: Two candidate topological patterns for the ventricular bodies. Four extraordinary vertices of valence 3 can be placed to have two regions of contiguous local coordinates—a “circle-square topology” (A)—or to have three regions of contiguous local coordinates (B). The topology in (B) was used to construct the biventricular model in this study because it gave rise to elements with more uniform sizes and more regular angles. Valence 3 extraordinary vertices are indicated with a red circle, and regions of contiguous local coordinates are indicated with colors.
Figure 3.3: Cartographic projections of two candidate topological patterns for the valve annuli. In (A), only six extraordinary vertices are required, all of valence 6. In (B), three valence 6 extraordinaire vertices were used and six valence 5 extraordinary vertices were used. The additional extraordinary vertices allowed the septum to be attached to this base region as to avoid irregular corners and ridges. Valence 6 extraordinary vertices are indicated with a red circle, valence 5 extraordinary vertices with a black circle. Regions of contiguous local coordinates are indicated with colors.
boundary; the base plane was modeled as a hemispherical shell with Euler characteristic number $\chi = -3$, owing to its five contour boundaries: the circumferential boundary of the hemisphere, and the four disks removed to represent the four valve annuli. To decrement the Euler characteristic number of the ventricular bodies to 1, four extraordinary vertices of valence 3 were used. A “circle-square” pattern could have been used to place the four needed extraordinary vertices (Figure 3.2A), but instead, a more complicated connectivity was used (Figure 3.2B). This connectivity enabled elements with more uniform sizes and regular angles to be used. To decrement the Euler characteristic number to $-3$ in the base plane, six extraordinary vertices of valence 6 could have been used (Figure 3.3A), but instead a combination of valence 5 vertices and valence 6 vertices was used (Figure 3.3B). The topology was chosen so that each of the four valve annuli (mitral, tricuspid, aortic, and pulmonary) had a “polar” topology (i.e., all of its elements had unambiguous radial and circumferential parametric coordinate axes), such that it could be subdivided in the circumferential direction without affecting the mesh structure elsewhere.

Only certain connectivities of the biventricular body, the ventricular base, and the septum allowed for the three to be sewn together without inducing irregular connectivities (see Section 3.4.2). Two requirements had to be satisfied: First, the number of circumferential vertices in the biventricular body had to be the same as the number of circumferential vertices in the ventricular base (Figure 3.3B and Figure 3.4A). Second, the number of vertices in a long-axis section at the ventricular septum had to allow for a disk (having four extraordinary vertices of valence 3) to be sewn to both the biventricular septum and the ventricular base (Figure 3.4B). In order to obtain a coarse geometry with good quality elements, fourteen vertices were used to circumscribe the base plane and twenty vertices were used to circumscribe a long-axis cross-section.
Figure 3.4: Construction of a ventricular body and ventricular septum for attachment with the ventricular base. A cartographic projection of the ventricular body displayed in Figure 3.2B is displayed in (A). The elements constituting the ventricular septum are attached to the region colored in light blue. In (B), the elements constituting the ventricular septum are colored yellow. The coarsest configuration allowing for attachment of the ventricular base, the biventricular bodies, and the ventricular septum without irregular corners and ridges had 14 vertices circumscribing the plane of the base and 20 vertices circumscribing a short axis section. In (A), a dashed line indicates the location of the septum in the cartographic projection. In (B), extraordinary vertices of valence 3 belonging to the septum are indicated with a red circle. LV = Left ventricle; RV = Right ventricle; AVO = Aortic valve orifice; S-LV = Septum, left ventricular side; S-RV = Septum, right ventricular side.

The resultant linear hexahedral model had 162 elements. Tricubic Hermite derivatives were calculated as described in Section 2.2.3 with some modifications. One, the hexahedral interpolating subdivisions and the Vartziotis and Wipper regularization steps were completed separately on two different parts of the mesh: the ventricular septum, and the union of the biventricular body and the ventricular base. This allowed for a smooth transition between the biventricular body and the ventricular base and regular ridges (i.e., lacking corner singularities, see Section 3.4.2) at all joining points of these two components with the ventricular septum. Two, the thin plate splines mapping discussed in Section 3.2.2 was applied after the first hexahedral subdivision and before the second hexahedral subdivision. This corrected most poor-quality elements. Third, vertices of the twice-subdivided mesh were
moved manually in a limited number of cases where thin plate splines warping and Vartziotis and Wipper regularization were unable to correct elements with extreme skew. This way, no tricubic Hermite elements had negative scaled Jacobians. Anterior and base plane views of the linear hexahedral models and the tricubic Hermite models are displayed in Figure 3.5.

**Figure 3.5:** Views of the linear hexahedral mesh (A-B) and of the tricubic Hermite mesh (C-D). Views (A) and (C) are anterior; views (B) and (D) are basal. In panels (C) and (D), the inner surfaces of the chambers are colored red for contrast.
3.3.3 A minimal four-chamber model has 474 elements

A four-chamber model was constructed using the same basic scheme presented in Section 3.3.2: the biventricular bodies, the ventricular base, and the ventricular septum were constructed separately and joined together, after which the atria were attached. The only additional constraint was that the number of vertices circumscribing the annulus of the mitral (tricuspid) valve was the same in the left (right) ventricle and the left (right) atrium.

The left and right atrial models constructed in Chapter 2 could not be immediately connected to the biventricular model constructed in Section 3.3.2 because the mitral and tricuspid valve annuli had different numbers of vertices in the ventricular models and the atrial models. For example, the left atrium had 16 vertices circumscribing the mitral valve annulus whereas the left ventricle had 12. Extraordinary vertices in the left atrium must lie near pulmonary vein ostia to preserve element quality (Section 2.3.1), and as a consequence, the number of vertices circumscribing the mitral valve annulus in the left atrium cannot change much without affecting element size uniformity markedly. To preserve element size uniformity, an alternate biventricular model having 236 hexahedral elements was constructed and then connected to the left and right atria. This model had 20 vertices circumscribing the ventricular base and 24 vertices circumscribing the short-axis section along the ventricular septum, compared to the 16 vertices and 20 vertices in the model from Section 3.3.2. Images of the four-chamber control mesh and the four-chamber tricubic Hermite mesh are provided in Figure 3.6. Hereafter, this model is called FC-474.

The properties of FC-474 were compared to two other four-chamber hexahedral models: FC-2560, published in Zhang et al. (2012); and FC-421, a model constructed with the mesh regularization utilities in HexBlender, but constructed to be coarser than FC-474 (Table 3.2). The use of the fully-automatic methods in Zhang et al. gave rise to a mesh with more skewed elements and more variance in element sizes than FC-474, and accordingly, inferior
Figure 3.6: A 474-element four-chamber model of the human heart. The linear control mesh is pictured in (A) and the tricubic Hermite mesh is pictured in (B). RV = Right ventricle; LV = Left ventricle; RA = Right atrium; LA = Left atrium.

Table 3.2: Mesh statistics in three four-chamber (FC) models named by number of constituent elements. The coefficient of variation of the edge lengths, face areas, and angles in FC-474 was the smallest among the three meshes. In turn, its mean and worst values of two mesh quality metrics, the scaled Jacobian and condition number, were also the best.

<table>
<thead>
<tr>
<th></th>
<th>FC-474</th>
<th>FC-2560</th>
<th>FC-421</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edge lengths, CV</td>
<td>0.48</td>
<td>0.84</td>
<td>0.57</td>
</tr>
<tr>
<td>Face areas, CV</td>
<td>0.84</td>
<td>1.61</td>
<td>0.91</td>
</tr>
<tr>
<td>Angles, CV</td>
<td>0.19</td>
<td>0.24</td>
<td>0.26</td>
</tr>
<tr>
<td>Anisotropy ratio, mean</td>
<td>4.3</td>
<td>8.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Scaled Jacobian (mean, worst)</td>
<td>0.91, 0.22</td>
<td>0.83, -0.40</td>
<td>0.83, 0.08</td>
</tr>
<tr>
<td>Condition number (mean, worst)</td>
<td>2.4, 17.3</td>
<td>4.2, 4405</td>
<td>2.9, 43.1</td>
</tr>
</tbody>
</table>
mesh quality metric values. The model FC-421 had a similar connectivity to FC-474, but some changes in connectivity were made to allow for the use of fewer elements to capture the geometry. The mesh FC-421 had elements much more homogeneous in size and with less skew than the elements in FC-2560, but had elements less homogeneous in size and with more skew than the elements in FC-474.

3.3.4 Biomechanics simulations of biventricular models with extraordinary vertices do not have artifactual strains

The biventricular mesh connectivity presented in Section 3.3.2 used extraordinary vertices to capture the valve annuli, and with few elements. The use of extraordinary vertices also avoided poor-quality elements near the ventricular apex that were present in meshes with only ordinary vertices.

![Image](image.png)

**Figure 3.7:** End-systole images of strains along the fiber axis from simulations of human biventricular models without (A) and with (B) extraordinary vertices. In (A), there are artifactual strains near the apex, owing to the skewness of the elements there. There are also artifactual strains near the base plane, owing to less realistic boundary conditions compared to the model in (B).

To demonstrate the benefits of meshes with extraordinary vertices in mechanics simulations, simulations on two biventricular models were performed: one model with only ordinary vertices having no valve annuli, and one model with extraordinary vertices and
including valve annuli. Compared to the model with only ordinary vertices, the biventricular model with extraordinary vertices avoided artifactual strain solutions near the cardiac apex and at the base plane (Figure 3.7). This was attributable to the more realistic boundary conditions in the model with valve annuli compared to the models without valve annuli—the constraint of material points in the latter does not represent the true mechanics of the heart as accurately.

3.4 Discussion

3.4.1 Optimization of mesh quality in an interactive environment

The condition number of a finite element problem is increased by non-uniform element sizes and elements with poor angle quality. Higher condition numbers increase solution error if a direct solver is used, and adversely affect simulation time if an iterative solver, such as the biconjugate gradient method, is used (Shewchuk, 2002). Motivated by this point, we showed that systematic addition of extraordinary vertices or ordinary vertices can add geometric detail while preserving or improving element quality: Extraordinary vertices can be added to capture geometric detail that would cause severe element skew with only ordinary vertices (Section 2.3.2). Once the level of geometric detail to be captured has been determined by the extraordinary vertices, ordinary vertices can be added using a combination of Ohtake regularization, edge-loop insertion, and Li-Kobbelt refinement to further improve mesh quality and element regularity (Section 3.3.1 and Table 3.1).

In the current work, I strove to keep element anisotropy near unity because doing so tends to decrease the condition number in a finite element problem. However, allowing for element anisotropies further from unity may decrease simulation time in biomechanics problems, owing to directional differences in strain gradients—i.e., elements can be longer in dimensions where it is known a priori that strain gradients are smaller without paying a
penalty in solution error. In contrast, isotropic elements decrease solution time and solution error in electrophysiology problems because gradients of potential with similar magnitudes may arise in any direction, depending on the orientation of the traveling wave. Thus, the optimal mesh to build in general depends on the type of problem (biomechanics versus electrophysiology), the desired accuracy, and time constraints for solving. The interactive Blender environment allows for easy execution of optimized mesh regularization scripts while also allowing for mesh-specific and problem-specific manual correction.

**3.4.2 Inclusion or exclusion of corner singularities**

A principal goal of this chapter was to construct four-chamber models and biventricular models with a minimal number of elements, and hence a low computational burden. Demanding that the number of vertices (and concomitantly, elements) used be minimal limits the geometric detail that can be captured (Section 2.3.2). Further demanding that “hanging corners” and “hanging ridges” not be present dictates the method by which I choose to join the left ventricle, right ventricle, ventricular base, and ventricular septum together.

Hanging corners, or corner singularities, do not have well-defined normals but nevertheless are perfectly valid in finite element problems. Indeed, corners are present in many real-life objects, and the L-shaped domain is a common benchmark problem in finite element analysis. Nevertheless, I proscribe that the meshes not have hanging corners, or the closely-related hanging ridges. The presence of hanging corners (ridges) in the meshes would necessitate that intraventricular pressures be applied to three (two) different faces of a single element (Figure 3.8) as part of the boundary conditions. In so doing there is the tendency for those elements to become badly skewed and even inverted as they deform, in turn giving rise to numerical stability and simulation failure.
Figure 3.8: Geometric meshes with (A) and without (B) corner singularities. The biventricular mesh connectivity in Section 3.3.2 and (A) was constructed to avoid corner singularities, so that chamber pressures are applied to one face per element at most. Arrows indicate the directions of pressure applied the ventricular septum (yellow), left ventricular free wall (light blue), and mitral valve annulus (red). The three regions are separated by a ridge (dashed white). The left ventricular free wall in (A) has been removed. An example of an irregular ridge (broken white line) and corner singularity (asterisk) is displayed in (B). When pressures are applied to multiple faces on the same element (arrows), deformation can give rise to numerical instability owing to element skew and inversion. AVO = Aortic valve orifice; PVO = Pulmonic valve orifice.

The biventricular model FC-474 presented in this chapter joined the ventricular bodies and the ventricular septum together differently than most previous hexahedral models of the ventricles. In Section 3.3.2, the biventricular model was constructed with a “bowl-and-wall” topology, the left and right ventricle together constituting the bowl and the ventricular septum constituting the wall (Figure 3.9A). The “bowl-and-wall” topology features ridges along the joining contours of the ventricular septum with both the left and right ventricles. (By definition, it is not possible to maintain smoothness crossing across the ridges.). In contrast, most hexahedral models with both ventricles have modeled the left ventricle and septum as a “bowl-and-handle”: the left ventricle and ventricular septum together constitute one contiguous “bowl”, whereas the right ventricle is added topologically as a “handle” attached to the bowl (Figure 3.9B). The “bowl-and-handle” topology is similar to the “bowl-and-wall” topology in that there is a ridge at the inner joining contour of the right ventricle and the
Figure 3.9: Comparison of the “bowl-and-wall” topology (A) to the “bowl-and-handle” topology (B) for a biventricular model without the ventricular base or valve annuli. The red broken line in (A) indicates a ridge in the bowl-and-wall topology. The corresponding tricubic Hermite model is $C^1$ discontinuous at the ridge. In contrast, the yellow broken line in (B) indicates the analogous line in the bowl-and-handle topology which is not a ridge. The corresponding tricubic Hermite model is $C^1$ continuous here. The orange asterisks (*) indicate the endpoints of a ridge contour joining the ventricular septum and the right ventricle present in the models pictured in (A) and (B). RV = Right ventricle; LV = Left ventricle; VS = Ventricular septum.

ventricular septum, but different in that there is no ridge at the joining contour of the left ventricle and the ventricular septum, and thus the corresponding tricubic Hermite model is smooth there.

The similar thickness between the left ventricle and the septum as well as the usual smoothness between the left ventricle and ventricular septum make the “bowl-and-handle” topology a more natural choice for biventricular models, but the need for a coarse, high-quality biventricular model with valve annuli necessitated that a “bowl-and-wall” topology be used nonetheless. The “bowl-and-handle” topology has disadvantages with regard to maintaining mesh coarseness: the left ventricle must be two hexahedra thick, increasing the total number of elements without capturing extra geometric detail. Moreover, the number of elements that must be added to avoid the presence of hanging corners and hanging ridges in the “bowl-and-handle” models is even greater than in the “bowl-and-wall” models. Last, I have found from experience that using the “bowl-and-handle” topology with valve annuli
gives rise to models with elements having higher anisotropy ratios and increased element skew compared to the “bowl-and-wall” topology.

3.4.3 Obtaining patient-specific geometries from non-rigid deformable registration of atlas models

Automatic methods place extraordinary vertices in a surface at critical points of Gaussian curvature, and construct sub-domains in accordance with the principal directions of curvature (Alliez et al., 2003; Marinov and Kobbelt, 2004). Nonetheless, these approaches rely on trial and error with user-defined parameters, and may be sensitive to image noise in unpredictable ways. In contrast, I placed extraordinary vertices manually and optimized geometric accuracy, element angles, element isotropy, and element size uniformity according to the final application of the meshes.

A cardiac mesh for a new patient can be constructed easily if the size and topology of the heart are sufficiently similar to an existing template in the atlas, as we have shown previously (Zhang et al., 2012). If the heart of the new patient is dissimilar to all templates in the atlas, its topology can be constructed manually and added to the atlas.

3.5 Conclusion

By using the Blender modeling environment and by considering the constraints imposed by the Euler characteristic number, a biventricular hexahedral model with only 162 elements and a four-chamber hexahedral model with only 474 were captured. The quality of the linear hexahedral meshes and tricubic Hermite meshes (i.e., the element size uniformity, the anisotropy ratios of the elements, and the element angles) were improved using automated mesh improvement schemes with some manual corrections. It was then shown that coarsening the four-chamber model further can usually not be achieved without sacrificing mesh quality, using hanging corners or ridges, or both. Finally, we showed that ventricular meshes with
extraordinary vertices improve mesh quality and reduce artifactual strains in biomechanical simulations compared to meshes without extraordinary vertices.

Acknowledgments

The content of this chapter is mostly an original document. Parts of Sections 3.3.1, 3.4.1, and 3.4.3 were adapted from an extended abstract that appeared in conference proceedings. The citation for this extended abstract is Gonzales M.J., Sturgeon G., Segars W.P., McCulloch A.D. (2012) A pipeline from non-invasive imaging to patient-specific models of cardiac electromechanics: An atlas-based approach. Workshop on Mesh Processing in Medical Image Analysis in Conjunction with 14th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI). Nice, France. Oct. 1-5, 2012 (Abstract). I would like to thank Gregory Sturgeon for his technical assistance in providing Python implementations for many of the mesh regularization schemes used in this chapter, and for providing model FC-421 in Section 3.3.3. The author would like to thank René Jonas for helping to write the software plug-in HexBlender. Finally, the author would like to thank Adarsh Krishnamurthy for performing the biomechanics simulations in Section 3.3.4.
References


Chapter 4

Electrical wave propagation with high-order solution spaces
Abstract

Chapters 2 and 3 presented numerical methods for constructing high-quality and topologically complex cubic Hermite meshes of the human atria and whole heart from non-invasive imaging data. In the present chapter, I derive the Galerkin formulation of the monodomain equation of cardiac electrophysiology using cubic Hermite basis functions. I then show that the implementation with cubic Hermite basis functions converges to the consensus solution of a benchmark problem from the computational cardiac electrophysiology community, and with far fewer elements than are required with linear Lagrange basis functions. Then, I show that serendipity basis functions can be used in the monodomain problem to obtain a convergence rate nearly equal to that of cubic Hermite basis functions but with a reduced computational cost. Finally, I show that the convergence rate can be further optimized with slight modifications to the Gauss-Legendre quadrature scheme. These methods may assist in reducing the time for electrophysiological simulations toward clinical timescales.

4.1 Introduction

4.1.1 Mathematical descriptions of cardiac wave propagation

Local electrical activation serves as the stimulus for the cardiomyocyte contractile apparatus to develop stress, in turn giving rise to heightened intrachamber pressures and the ejection of blood to the peripheral tissues. An electrical excitation originating from one location gives rise to the flow of charged particles down local voltage gradients. In healthy cardiac tissue, excitation at one point in space is sufficient to create a self-renewing wave that propagates throughout all adjacent tissues. This electrical wave can be modeled mathematically as a reaction-diffusion system: flux of charge carriers gives rise to local transmembrane currents which can be modeled by reactions, whereas the currents arising from local voltage gradients depend on local anisotropic diffusivities.
The wave equations typically used to solve for electrical propagation in the heart are the bidomain and monodomain equations. Both of these equations are partial differential equations with the mathematical form of a reaction-diffusion problem. The bidomain equation models the geometric domain of propagation as having separate intracellular and extracellular compartments coupled by transmembrane currents; the monodomain equation models wave propagation as occurring in only one compartment. The bidomain equation can account for differences in intracellular and extracellular diffusivity, but at a higher computational cost than the monodomain equation. Most phenomena of electrical wave propagation in the heart can be modeled mathematically by the monodomain equation; an important exception is the development of virtual electrodes, which are important in electrical defibrillation.

### 4.1.2 The Péclet number and mass lumping

A physics problem may show entirely different behavior depending on the physical parameters at which the problem takes place, and also can affect how the problem is solved numerically. A systematic way to evaluate physical behavior in different parameter regimes is by first combining physical parameters algebraically into dimensionless numbers as indicated by the Buckingham pi theorem. For example, the Reynolds number $Re$ of fluid dynamics is the ratio of inertial forces to viscous forces. At low Reynolds numbers, flow is laminar; at high Reynolds numbers, the flow is turbulent. Two physical systems having vastly different spatial scale but the same Reynolds number can be expected to behave the same qualitatively.

The Péclet number $Pe$ similarly is used to quantify the relative magnitudes of convection and conduction of heat, advection and diffusion of mass, and reaction and diffusion of mass. The generic equation for a reaction-diffusion problem can be written

$$\frac{\partial u}{\partial t} = \nabla \cdot D \nabla u + k \cdot u$$

Eq. 4.1
where \( u \) is the concentration of the reacting and diffusing species, \( k \) is the rate constant of reaction, and \( D \) is the diffusivity. The Péclet number for such a reaction-diffusion problem is defined as (Quarteroni, 2009)

\[
P e = \frac{kL^2}{6D}
\]

Eq. 4.2

where \( k \) is the reaction rate, \( D \) is the diffusivity, and \( L \) is the characteristic length of the problem. In the heart, there are many reactions determining electrical propagation and thus many reaction rate constants, but the characteristic reaction rate is the inverse of the \( \mathrm{Na}^+ \) channel activation gate time constant, \( \sim 7 \text{ ms}^{-1} \) (Nagatomo et al., 1998; Ten Tusscher et al., 2004). The characteristic length is the space constant of cardiac electrophysiology \( \lambda \) (\( \sim 1 \text{ mm} \) and the diffusion constant is \( 0.1 \text{ mm}^2/\text{ms} \) (Glass et al., 1991), giving

\[
P e = \frac{(7 \text{ ms}^{-1})(1\text{ mm})^2}{6(0.1\text{ mm}^2/\text{ms})} = 11.6
\]

Eq. 4.3

The Péclet number is larger than one, indicating that under normal conditions in the heart, the characteristic reaction is responsible for more current flow than diffusion.

The value of the Péclet number also has numerical consequences. An addition to the physical Péclet number, there is also a local Péclet number \( P e_L \) associated with the numerical scheme used to solve the governing differential equation. When time is discretized and operator splitting is employed, the local Péclet number is

\[
P e_L = \frac{h^2}{6D\Delta t}
\]

Eq. 4.4
Figure 4.1: Spatial (A) and temporal (B) oscillations in the voltage solution of a monodomain problem with the Fenton-Karma ionic model for $Pe_L = 17$. In (A), the black arrow indicates spatial oscillations at the interface between activated areas (red) and quiescent areas (blue) as a sinusoidal variation of blue color. In (B), the voltage waveform at a single vertex is displayed. The asterisks indicate the temporal oscillations at the beginning and end of the action potential upstroke.

where $h$ is the element diameter (side length), $D$ is the diffusivity, and $\Delta t$ is the timestep of the partial differential equation. (The presence of the timestep $\Delta t$ instead of the characteristic rate constant $k$ is a consequence of considering the non-steady reaction-diffusion PDE and employing operator splitting; see Section 4.2.1.) By examining the steady-state version of Eq. 4.1, Quarteroni (2009) found that for a Galerkin formulation of a reaction-diffusion problem, a problem with $Pe_L > 1$ displays artifactual oscillations in the solution due to the Gibbs phenomenon (Figure 4.1) whereas problems with $Pe_L < 1$ do not. These spurious oscillations give rise to activation time errors, errors in the shape of action potentials, and numerical instability of the problem. The Gibbs oscillations can be avoided by refinement of the numerical domain so that the element diameter $h$ is decreased until $Pe_L < 1$, though at an increase in computational cost. Another way to avoid the Gibbs oscillations is to use a strategy known as mass lumping of the finite element equations. After the mass matrix is calculated (see Section 4.2.1), mass lumping can be achieved by summing the values of each row in the mass matrix and placing the result on the diagonal entry of that row. Quarteroni found that
when mass lumping of the finite element equations is employed, the oscillations do not appear at any $Pe_L$.

4.1.3 The Benchmark study: a community exercise in convergence analysis

The large voltage gradients present in the cardiac electrophysiology problem dictate that a highly refined mesh be used, with a large accompanying computational cost. Owing both to the multitude of numerical schemes available to solve the electrophysiology problem and to the variable use of schemes to decrease computational cost, the criteria needed for convergence of the monodomain and bidomain problems have been estimated (Pathmanathan et al., 2010) but are not well known between many codes. Niederer formulated an electrophysiology problem to the community using canonical parameters to allow for comparison of solutions among various software implementations (Niederer et al., 2011). The problem featured a cuboid geometry with transversely isotropic conductivities with a stimulus current contained in a cubical region at one corner. Electrical propagation was governed by the monodomain equation and ionic currents were modeled using the ten Tusscher system of ordinary differential equations (Ten Tusscher et al., 2004). The numerical schemes used to solve for propagation were left to the discretion of each group. The accuracies of solution were compared superficially by the total time required for activation of the geometry and more completely by the $L^2$ norm of difference in activation times in the entire domain.

The results of the study featured surprisingly large discrepancies in the total activation time of the geometry, even at the most spatially and temporally refined scales. At the highest spatial and temporal resolution ($\Delta x = 0.1 \text{ mm}$ and $\Delta t = 0.005 \text{ ms}$), results among the codes varied by up to 28.8%; at the lowest spatial resolution ($\Delta x = 0.5 \text{ mm}$), results varied by as much as 200%, and for multiple codes resulted in simulation failure.
The largest differences in simulation behavior were attributable to the use of mass lumping in all but two codes and differences in interpolation schemes of the ionic currents. Codes using mass lumping exhibited large differences in error at the coarsest mesh resolution ($\Delta x = 0.5 \text{mm}$) but also exhibited errors at fine resolutions larger than codes not using mass lumping. Differences in the scheme used to interpolate currents gave rise to errors as large as 8% at the finest spatial resolution ($\Delta x = 0.1 \text{mm}$). The effects of mass lumping (Pathmanathan et al., 2012) and current interpolation scheme (Pathmanathan et al., 2011) were explored further in separate works. A principal conclusion of the Benchmark study was that finer levels of spatial discretization are required for convergence of activation time than was previously believed.

A limitation of the Benchmark study was that high-order interpolation schemes were not explored, yet high-order interpolation schemes of the monodomain problem have been shown to have convergence advantages compared to linear interpolation schemes of the monodomain problem with the same number of degrees of freedom (Arthurs et al., 2012; Rogers et al., 1996). High-order interpolation schemes are not widely used in cardiac electrophysiology in part because constructing high-order finite element meshes with irregular connectivity is difficult, and a requisite of improved convergence by high-order finite element schemes is that the computational domain is sufficiently smooth. This is precisely the limitation we overcame in Chapter 2. In the present chapter, I validate that high-order interpolation schemes to solve the monodomain problem converge to the consensus benchmark answer and find the computational effort required to do so.
4.2 Methods

4.2.1 The Galerkin formulation of the monodomain equation

The monodomain equation is a parabolic partial differential equation stating the conservation of charge. The only assumption it makes is that the electric field $E$ has a scalar potential function $u$. It is given by

$$\frac{\partial u}{\partial t} = \nabla \cdot D \nabla u + \frac{I_{\text{net}}(u, \mathbf{n})}{C}$$

Eq. 4.5

where $u$ is the voltage, $D$ is the diffusivity, $I_{\text{net}}$ is the net flow of charge through the cell membrane, and $C$ is the specific capacitance of the cell membrane. $I_{\text{net}}$ is a complicated function of the voltage $u$ and other state variables $\mathbf{n}$. The term on the left-hand side is an accumulation term; the first term of the right-hand side represents the flux of current coming into and out of the control volume; and the second term of the right-hand side is a source term, encapsulating the net charge flow into and out of ion channels in the cell membrane. This is the strong form of the monodomain equation.

The monodomain equation has an analytic solution only for a limited number of geometries, a limited number of boundary conditions, and a limited number of forms of the term $I_{\text{net}}(u, \mathbf{n})$. A weak form of the partial differential equation can be solved on irregular geometries with more complicated boundary conditions and more complicated forms of the term $I_{\text{net}}(u, \mathbf{n})$. Customarily, such a problem can be solved using a variational formulation, which, instead of demanding an exact solution at each point of the domain, aims to minimize the difference between an approximate solution and the true solution under some norm, usually the $L_2$ norm. I will derive the Galerkin formulation for the monodomain problem with
high-order basis functions using the approach of Belik et al. (2004). Their variational solution was obtained is using the formulation

$$\int_{\Omega} L \omega \, d\Omega + \int_{\Gamma} B \omega \, d\Gamma = 0$$

Eq. 4.6

Where $L$ is the partial differential equation, $B$ is the boundary condition of the problem, $\Omega$ is the computational domain, $\Gamma$ is the boundary of the computational domain, and the term $\omega$ is called a weighting function. This form of solution is called a weighted residual method. The left-hand side of Eq. 4.6 is called the residual, and the goal of the method is to minimize the residual to be as close to zero as possible. The term $L$ is given by

$$L = \nabla \cdot D \nabla u - \frac{\partial u}{\partial t} + \frac{I_{\text{net}}}{C}$$

Eq. 4.7

Where all terms of Eq. 4.5 were moved to one side of the equation so that the right-hand side is zero. The term $B$ represents the boundary conditions. The most common boundary conditions used in problems of cardiac electrical propagation are the no-flux (Neumann) boundary conditions. With no-flux boundary conditions, the following term is equal to zero

$$B = -D \nabla u \cdot \mathbf{n}$$

Eq. 4.8

Substituting Eq. 4.7 and Eq. 4.8 into Eq. 4.6 gives

$$\int_{\Omega} \left( \nabla \cdot D \nabla u - \frac{\partial u}{\partial t} + \frac{I_{\text{net}}}{C} \right) \omega \, d\Omega + \int_{\Gamma} \left( -D \nabla u \cdot \mathbf{n} \right) \omega \, d\Gamma = 0$$

Eq. 4.9

$$-\int_{\Omega} \frac{\partial u}{\partial t} \omega \, d\Omega + \int_{\Omega} \left( \nabla \cdot D \nabla u \right) \omega \, d\Omega + \int_{\Omega} \frac{I_{\text{net}}}{C} \omega \, d\Omega - \int_{\Gamma} \left( D \nabla u \cdot \mathbf{n} \right) \omega \, d\Gamma = 0$$

Eq. 4.10
After applying the Green-Gauss theorem to the second term in Eq. 4.10 and reordering, we get

\[-\int_{\partial\Omega} \frac{\partial u}{\partial t} \omega \ d\Omega + \int_{\Omega} I_{\text{net}} \omega \ d\Omega - \int_{\Omega} (\nabla u \cdot \nabla \omega) \ d\Omega \]

\[+ \int_{\Gamma} (\nabla u \cdot \mathbf{n}) \omega \ d\Gamma - \int_{\Gamma} (\nabla u \cdot \mathbf{n}) \omega \ d\Gamma = 0 \tag{Eq. 4.11}\]

The last two terms in Eq. 4.11 cancel, giving

\[\int_{\Omega} \frac{\partial u}{\partial t} \omega \ d\Omega + \int_{\Omega} (\nabla u \cdot \nabla \omega) \ d\Omega = \int_{\Omega} I_{\text{net}} \omega \ d\Omega \tag{Eq. 4.12}\]

after reordering. We note that the cancelation of these terms occurs only for the special case of no-flux boundary conditions. If a different set of boundary conditions is used, surface integral terms will remain.

Next, the unknown voltage \( u \) is expanded with respect to a basis set. This basis expansion of \( u \) is called the trial solution. The expansion of \( u \) with respect to some basis set \( \Psi \) is

\[u = \sum_{j=1}^{N} u_j \Psi_j \tag{Eq. 4.13}\]

where the index \( j \) is over the number of members in the basis set. The terms \( u_j \) are the coefficients of \( u \) expanded in the basis set \( \Psi \). For a Galerkin formulation, the weight functions \( \omega \), also called the test functions, are selected to be the same as the trial functions. One equation for each basis in the basis set is written, so for a basis set with \( N \) members, there will be \( N \) equations. If the test functions are indexed by \( k \), the \( k^{th} \) equation will be
\[
\int_{\Omega} \frac{\partial}{\partial t} (u_j \Psi_j) \Psi_k \, d\Omega + u_j \int_{\Omega} (D \nabla \Psi_j \cdot \nabla \Psi_k) \, d\Omega = \int_{\Omega} \frac{I_{\text{net}}}{C} \Psi_k \, d\Omega
\]
for \( k = \{1, \ldots, N\} \)  

Eq. 4.14

where the summation convention is adopted over the index \( j \).

Next, Eq. 4.14 must be discretized in time. We use \( n \) superscripted to indicate the \( n^{\text{th}} \) timestep is being considered. Discretizing the partial derivative on the left-hand side of Eq. 4.14 in time gives

\[
\int_{\Omega} \left( \frac{u_{j}^{n+1} - u_{j}^{n}}{\Delta t} \right) \Psi_j \Psi_k \, d\Omega = -u_j \int_{\Omega} (D \nabla \Psi_j \cdot \nabla \Psi_k) \, d\Omega + \int_{\Omega} \frac{I_{\text{net}}}{C} \Psi_k \, d\Omega
\]

for \( k = \{1, \ldots, N\} \)  

Eq. 4.15

The right-hand side, represented by \( G \), can be evaluated in this scheme by a \textit{theta method}

\[
\frac{\Delta u}{\Delta t} = \frac{u_{j}^{n+1} - u_{j}^{n}}{\Delta t} = \theta G^{n+1} + (1 - \theta)G^n
\]

for some \( 0 < \theta < 1 \). If \( \theta = 0 \), the scheme is said to be \textit{fully explicit}. If \( \theta = 1 \), the scheme is said to be \textit{fully implicit}. If \( \theta = \frac{1}{2} \), the scheme is called the Crank-Nicolson scheme.

Applying Eq. 4.16 to Eq. 4.15 gives

\[
\frac{u_{j}^{n+1} - u_{j}^{n}}{\Delta t} \int_{\Omega} \Psi_j \Psi_k \, d\Omega = \theta \left[ -u_j^{n+1} \int_{\Omega} (D \nabla \Psi_j \cdot \nabla \Psi_k) \, d\Omega + \int_{\Omega} \frac{I_{\text{net}}^{n+1}}{C} \Psi_k \, d\Omega \right]
\]

\[
+ \left[ -u_j^n \int_{\Omega} (D \nabla \Psi_j \cdot \nabla \Psi_k) \, d\Omega + \int_{\Omega} \frac{I_{\text{net}}^n}{C} \Psi_k \, d\Omega \right]
\]

\[
- \theta \left[ -u_j^n \int_{\Omega} (D \nabla \Psi_j \cdot \nabla \Psi_k) \, d\Omega + \int_{\Omega} \frac{I_{\text{net}}^n}{C} \Psi_k \, d\Omega \right]
\]

for \( k = \{1, \ldots, N\} \)  

Eq. 4.17
The discretization of the current term $I_{\text{net}}$ is often achieved using a two-step procedure known as *operator splitting*. More details on the numerics of operator splitting are described elsewhere (Sundnes et al., 2005). We now use the symbol $I_{\text{net}}'$ to replace the terms $I^n_{\text{net}}$ and $I^{n+1}_{\text{net}}$ evaluated during operator splitting:

$$\frac{(u_{j}^{n+1} - u_{j}^{n})}{\Delta t} \int_{\Omega} \Psi_{j} \Psi_{k} \, d\Omega = -u_{j}^{n} \int_{\Omega} (D \nabla \Psi_{j} \cdot \nabla \Psi_{k}) \, d\Omega + \int_{\Omega} \frac{I'_{\text{net}}}{C} \Psi_{k} \, d\Omega$$

$$-\theta (u_{j}^{n+1} - u_{j}^{n}) \int_{\Omega} (D \nabla \Psi_{j} \cdot \nabla \Psi_{k}) \, d\Omega$$

Eq. 4.18

for $k = \{1, ..., N\}$

In the context of the monodomain problem, the mass matrix $M$ is defined as $\Psi \otimes \Psi$ and the stiffness matrix $K$ is $D \nabla \Psi \otimes \nabla \Psi$. The components of the mass matrix and the stiffness matrix are given by

$$M_{jk} = \int_{\Omega} \Psi_{j} \Psi_{k} \, d\Omega$$

Eq. 4.19

$$K_{jk} = \int_{\Omega} D \nabla \Psi_{j} \cdot \nabla \Psi_{k} \, d\Omega$$

Eq. 4.20

Adopting the convention that the $j^{th}$ row of $M$ and $K$ can be written $M_{j}$ and $K_{j}$, and using the summation convention over $j$, Eq. 4.18 for one finite element can be written

$$u_{j}^{n+1} M_{j} - u_{j}^{n} M_{j} = \int_{\Omega} \Delta t \frac{I'_{\text{net}}}{C} \Psi_{j} \, d\Omega - \Delta t u_{j}^{n} K_{j}$$

$$-\theta \Delta t u_{j}^{n+1} K_{j} + \theta \Delta t u_{j}^{n} K_{j}$$

Eq. 4.21

The $k^{th}$ equation can be written
\[ u^{n+1}_j \left[ M_j + \Delta t \, \theta \, K_j \right]_k = u^n_j \left[ M_j - \Delta t \, (1 - \theta) \, K_j \right] + \int_{\Omega} \Delta t \, \frac{I_{net}}{C} \Psi \, d\Omega \quad \text{for } k = 1, \ldots, N \quad \text{Eq. 4.22} \]

The first term on the right-hand side of Eq. 4.22 is called the \textit{stiffness vector}. In direct notation, Eq. 4.22 can be written

\[ u^{n+1}_j [M + \Delta t \, \theta \, K] = u^n_j [M - \Delta t \, (1 - \theta) \, K] + \int_{\Omega} \Delta t \, \frac{I_{net}}{C} \Psi \, d\Omega \quad \text{Eq. 4.23} \]

The diffusion tensor \( D \) is most often defined in terms of locally orthogonal fiber coordinate system, whereas it is most convenient to evaluate Eq. 4.20 for the stiffness matrix in Cartesian coordinates. Components of \( D \) in the fiber coordinate system are relatable to components of \( D \) in global Cartesian coordinates by

\[ D_{(\text{Cartesian})}^{ab} = D_{(\text{fiber})}^{\bar{ij}} \frac{\partial Y^a}{\partial \nu^\bar{i}} \frac{\partial Y^b}{\partial \nu^\bar{j}} \quad \text{Eq. 4.24} \]

Where \( \nu \) is the fiber coordinate system. Eq. 4.24 can also be written in direct notation as

\[ D_{\text{cart}} = Q D_{\text{fiber}} Q^t \], where \( Q \) is orthogonal and \( Q_{ij} = \frac{\partial Y^j}{\partial \nu^i} \). It is advantageous to write the tensors in Eq. 4.20 in Cartesian coordinates \( x \) with basis set \( \mathbf{\hat{e}} \). This way, the gradient operator simplifies to partial derivatives in Cartesian coordinates. The term \( K_{jk} \) is then given by
\[
\int_D \nabla \Psi_j \cdot \nabla \Psi_k \, d\Omega = \int_D \frac{\partial \Psi_j}{\partial \xi_e} \left( \frac{\partial \xi_e}{\partial x_a} \right) - \frac{\partial \Psi_k}{\partial \xi_f} \left( \frac{\partial \xi_f}{\partial x_a} \right) d\Omega
\]

\[
= \int_D \frac{\partial \Psi_j}{\partial \xi_e} \frac{\partial \xi_e}{\partial x_a} \delta_{ae} - \frac{\partial \Psi_k}{\partial \xi_f} \left( \frac{\partial \xi_f}{\partial x_a} \right) d\Omega \tag{Eq. 4.25}
\]

For trilinear Lagrange basis functions, \( j, k = \{1, \ldots, 8\} \); for tricubic Hermite basis functions, \( j, k = \{1, \ldots, 64\} \).

### 4.2.2 Cubic Hermite-style serendipity basis functions

Serendipity functional spaces allow for a reduction in the number of degrees of freedom in a finite element problem while retaining the maximum order of convergence. For the square, the number of degrees of freedom is reduced from 16 for bicubic Hermite interpolation to 12 for the bicubic Hermite-style serendipity interpolation; for the cube, the number is reduced from 64 to 32.

A well-known theoretical result in finite elements for solution of partial differential equations is the Bramble-Hilbert lemma. In the context of the monodomain problem, the Bramble-Hilbert lemma states that there exists a polynomial, denoted \( p_h \), of total degree at most \( p \) such that

\[
\|u - u_h\|_{H^1} \leq C \cdot h^p \|u\|_{H^p} \tag{Eq. 4.26}
\]
where \( u \) is the solution to the continuous problem, \( u_h \) is the finite element approximation of the solution, \( C \) is a constant depending only on the domain, \( h \) is the maximum width of a mesh element, and \( \| \cdot \|_{H^m} \) and \( \cdot |_{H^m} \) are standard \( H^m \) Sobolev norm and semi-norm.

The finite element method produces a piecewise, degree \( p \) polynomial approximation \( u_h \) to the continuous solution \( u \). Under additional assumptions on the nature of the partial differential equation and the computational method, one can derive an \( a \) priori estimate of the error as described by the Bramble–Hilbert lemma in Eq. 4.26; this analysis can be found in many finite element textbooks (Brenner and Scott, 2008). However, the Bramble–Hilbert lemma does not specify the sufficient conditions to obtain convergence of order \( p \).

In two and three dimensional space, it is common to construct polynomials as tensor products of one-dimensional splines. For example, a bicubic spline surface \( S \) with coordinates \( x \) and \( y \) is order three in \( x \) and \( y \) and has total order six. In the monomial basis, the bicubic spline will have the form

\[
\begin{align*}
  a_1 x^3 y^3 + a_2 x^3 y^2 + a_3 x^2 y^3 + a_4 x^3 y + a_5 x^2 y^2 + a_6 x^2 y + a_7 x y^3 + \\
  a_8 x^2 y + a_9 x y^2 + a_{10} x^2 + a_{11} y^2 + a_{12} x y + a_{13} y + a_{14} + a_{15} y + a_{16} = 0
\end{align*}
\]

Eq. 4.27

Since the monomial tensor splines are of order three, the Bramble–Hilbert lemma specifies that convergence will have order three. However, the Bramble–Hilbert lemma says nothing about whether all of these terms are needed to achieve cubic-order convergence.

Recently, a theoretical explanation was developed (Arnold and Awanou, 2011, 2012) for why some polynomial solution spaces omitting some monomials, as in Eq. 4.27, found faster convergence than might be expected. The key insight made was that the inclusion of \textit{superlinear monomials} up to and including the degree \( p \) in some space \( \mathbb{R}^n \) are sufficient
conditions for $p$-order convergence. The superlinear degree $\text{sldeg}(\cdot)$ of a monomial is the total degree of a monomial discounting variables which are linear. For example, the monomial $x^3y^2z$ has superlinear degree five rather than six, since the variable $z$ is linear. The work of Arnold and Awanou indicate that a finite element problem can retain cubic-order convergence without the first, second, third, and sixth terms in Eq. 4.27 because $\text{sldeg}(\cdot)$ of those terms is greater than three. Thus, the only required terms necessary for cubic-order convergence are

$$b_1x^3y + b_2xy^3 + b_3x^3 + b_4y^3 + b_5x^2y + b_6xy^2$$
$$+ b_7x^2 + b_8y^2 + b_9xy + b_{10}x + b_{11}y + b_{12} = 0$$

Eq. 4.28

A convenient way to visualize the superlinear monomials in many dimensions is using Pascal’s triangle (Figure 4.2).

![Figure 4.2](image)

**Figure 4.2:** A binomial expansion demonstrates a pattern for the monomial terms present in the two-dimensional serendipity space. A bicubic Hermite tensor product in $x$ and $y$ gives sixteen monomial terms, indicated by the yellow diamond. The twelve superlinear degree terms required for cubic-order convergence are enclosed within the red boundary.

More recently, cubic Hermite-style serendipity basis functions were derived (Gillette, 2012), which are employed in the current work. The two-dimensional and three-dimensional cubic Hermite-style serendipity basis functions are provided in Appendix I (Section 0).
4.2.3 Global system assembly and solution scheme

In Section 4.2.1, an expression was derived for the monodomain equation on a unitary finite element. To solve a finite element problem on a domain $\Omega$ composed of many finite elements, the basis functions in each element $\Psi$ must be transformed into a global set of basis functions $\{\Psi_1^*, \Psi_2^*, \ldots, \Psi_N^*\}$ such that when the coefficients are determined by solving the finite element equations, the solution is in terms of the ensemble coefficients $\{u_1^*, u_2^*, \ldots, u_N^*\}$.

As discussed in Section 2.2.6, the local basis functions $\Psi$ are transformed to global basis functions $\Psi^*$ by applying the linear transformation $\Gamma$ to the local basis functions $\Psi$. As detailed in Section 2.2.6, the element basis functions $\Psi$ arranged as a column are transformed into global basis functions $\Psi^*$ by the two relations $\Psi^* = \Gamma^T \Psi$ and $\Psi^* \otimes \Psi^* = \Gamma [\Psi \otimes \Psi] \Gamma^T$.

Since the mass matrix $M$ and the stiffness matrix $K$ are constructed from dyads of the basis functions $\Psi$, and since the distributive property holds for matrices with respect to matrix addition, the left-hand side of a finite element equation in Eq. 4.23 is transformed the following way

$$[M^* + \Delta t K^*] = \Gamma [M + \Delta t K] \Gamma^T \quad \text{Eq. 4.29}$$

The last term in Eq. 4.23 is transformed into global basis functions $\Psi^*$ by

$$\int_{\Omega} \Delta t \frac{I_{net}}{C} \Psi^* \, d\Omega = \int_{\Omega} \Delta t \frac{I_{net}}{C} \Gamma^T \Psi \, d\Omega \quad \text{Eq. 4.30}$$

Thereafter, the $J \times K$ element degrees of freedom can be mapped to the $M \times N$ global system degrees of freedom by matrix addition. ($J = K$ and $M = N$.) Each local degree of freedom $j$ has a corresponding global degree of freedom $m$; local basis function $k$ has a corresponding global basis function $n$. Assembly into a global linear system of the form
\( \mathbf{Ax} = \mathbf{b} \) gives rise to a sparse matrix \( \mathbf{A} \) with a banded pattern of nonzero entries. \( \mathbf{A} \) is symmetric and positive-definite. In general, the number of nonzero entries in each row (corresponding to one global finite element equation) will be different. This number, called the 

**bandwidth**, corresponds to the number of nonzero basis functions for that one finite element equation. The number of nonzero basis functions for a finite element equation can be determined \textit{a priori} if the connectivity of the mesh is known. The number of nonzero entries in a row corresponding to one finite element equation in the global system will be equal to the number of nonzero basis functions at that field degree of freedom. For a quadrilateral surface mesh, ordinary vertices (with valence 4) will have a bandwidth \( b \), extraordinary vertices of valence 3 will have bandwidth less than \( b \), and extraordinary vertices of valence 5 will have bandwidth greater than \( b \).

None of the integral terms in Eq. 4.23 can be evaluated exactly because at least one term—the change-of-variables term introduced for the local coordinate system \( \xi \)—is not a polynomial or constant. Thus, a numerical quadrature scheme approximates the integrals. I used Gauss-Legendre quadrature points to evaluate all three integrals in Eq. 4.23. However, the number of quadrature points used to evaluate each integral need not be the same. Evaluation of the first term (the left-hand side) of Eq. 4.23 with fewer than four Gauss-Legendre quadrature points per parametric coordinate sometimes gives rise to a rank-deficient left-hand side matrix \( \mathbf{A} \). In contrast, it is not necessary to use four Gauss-Legendre quadrature per parametric coordinate for the last term (the source term) in Eq. 4.23. In most cases, using three Gauss-Legendre quadrature points per parametric coordinate instead of four reduces accuracy only slightly and comes at a much lower computational cost. An examination of the effects of different numbers of integration points is given in Section 4.3.3.
The global linear system was solved with a biconjugate gradient method implemented in Trilinos (http://trilinos.sandia.gov/) using an incomplete LU factorization for the preconditioner.

4.3 Results

4.3.1 Oscillations vanish for Péclet numbers less than 1

To test for the presence or absence of oscillations for simulations with discrete Péclet numbers greater than one and less than one, I prepared modified versions of the benchmark study with stimuli bound by the slab $0 \leq x \leq 1$ so that propagation was strictly along the x axis. Versions of the problem were prepared with every combination of $\Delta h / \text{mm} = \{0.1, 0.2, 0.25, 0.5\}$, and $D / \text{mm}^2/\text{ms} = \{0.0953, 0.0126\}$. All problems had $\Delta t_{PDE} = \Delta t_{ODE}$. For each simulation, the magnitude of oscillation was determined at the center node of the mesh as the largest negative value of voltage below the steady-state initial condition of $-85.23 \text{ mV}$. Oscillation magnitudes were normalized to a representative ten Tusscher action potential amplitude (108.8 mV).

A plot of oscillation magnitude against discrete Péclet number on a semi-log scale is displayed in Figure 4.3. The oscillation magnitude increases monotonically with the Péclet number. At the smallest three discrete Péclet numbers tested (0.785, 1.75, and 5.94), the oscillation magnitude was a constant 0.0362 mV (corresponding to a value of 3.3E-4 in Figure 4.3). For the simpler Fenton-Karma model, it was verified that simulations with discrete Péclet numbers less than 1 did not display oscillations (data not shown, see Discussion, Section 4.4.2).
Figure 4.3: Oscillation amplitude as a fraction of action potential (AP) amplitude plotted against Péclet number with a semi-log scale using the ten Tusscher ionic model. Oscillation magnitude increase monotonically with increased Péclet number. The dotted black line indicates a Péclet number of 1.

4.3.2 For equal numbers of elements, convergence of cubic Hermite and serendipity solution spaces is superior to convergence of linear solution spaces

I next performed the benchmark study using cubic Hermite basis functions and linear Lagrange basis functions using $\Delta h / \text{mm} = \{0.1, 0.2, 0.5\}$ and $\Delta t / \text{ms} = 0.01$. Using the same number of elements with linear Lagrange and cubic Hermite interpolation changed the number of degrees of freedom in the problem, but allowed for comparison for simulations with the same number of ODE integration points that also were at identical locations.

The most refined cubic Hermite solution ($\Delta x = 0.1 \text{mm}$) lay in the midpoint of the consensus solution range for total mesh activation time of the benchmark problem (between 42.5 ms and 43.0 ms), whereas the linear Lagrange solution trended toward the consensus solution range with increased refinement and had a fractional error of 0.036 in the most refined case ($\Delta x = 0.1 \text{mm}$). Both cubic Hermite and linear Lagrange solutions displayed slow conduction times (or inversely, fast conduction velocities) at coarser mesh resolutions, which monotonically slowed with mesh refinement with only one exception. Increasing the number
of integration points for each element (i.e., 27 Gauss-Legendre quadrature points per element instead of 8) reduced error for the cubic Hermite basis functions. Results for total activation time for many problem set-ups are provided in Table 4.1 and are displayed in Figure 4.4.

The three curves with linear Lagrange basis functions exhibited smaller activation times (i.e., larger apparent conduction velocities) than the three curves with cubic Hermite basis functions. In the case of cubic Hermite basis functions, using 8 integration points per element gave rise to error that tended to slow conduction. This behavior is exhibited by the top curve in Figure 4.4, which is the only curve converging toward the consensus solution from activation times which were slow. When the number of integration points was increased to 27 and 64, the conduction was more rapid than the consensus solution, and slowed toward the consensus solution with more integration points. The behavior for linear Lagrange basis was similar: increasing the number of integration points from 27 to 64 slowed conduction toward the consensus solution, but decreasing the number of integration points to 8 paradoxically resulted in more accurate solutions.
Figure 4.4: Total activation time of the benchmark problem at different combinations of spatial discretization, number of integration points per element, and linear Lagrange versus cubic Hermite basis functions. The range of the consensus solution is indicated by two broken black lines. The three lowest lines (broken) all are curves from simulations with linear basis functions, whereas the three highest lines (dotted and dashed) are curves from simulations with cubic Hermite basis functions.
Table 4.1: Total activation time of the benchmark problem for various combinations of $\Delta x$, number of integration points per element, and linear Lagrange versus cubic Hermite basis functions. All simulations were conducted with $\Delta t_{ODE} = \Delta t_{PDE} = 0.01$ ms.

<table>
<thead>
<tr>
<th>$\Delta x$ (mm)</th>
<th>Integration points per element</th>
<th>Linear or Cubic</th>
<th>Total activation time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>8</td>
<td>Linear</td>
<td>34.0</td>
</tr>
<tr>
<td>0.5</td>
<td>27</td>
<td>Linear</td>
<td>29.1</td>
</tr>
<tr>
<td>0.5</td>
<td>64</td>
<td>Linear</td>
<td>29.4</td>
</tr>
<tr>
<td>0.2</td>
<td>8</td>
<td>Linear</td>
<td>39.1</td>
</tr>
<tr>
<td>0.2</td>
<td>27</td>
<td>Linear</td>
<td>37.9</td>
</tr>
<tr>
<td>0.2</td>
<td>64</td>
<td>Linear</td>
<td>38.0</td>
</tr>
<tr>
<td>0.1</td>
<td>8</td>
<td>Linear</td>
<td>41.5</td>
</tr>
<tr>
<td>0.1</td>
<td>27</td>
<td>Linear</td>
<td>41.2</td>
</tr>
<tr>
<td>0.1</td>
<td>64</td>
<td>Linear</td>
<td>43.2</td>
</tr>
<tr>
<td>0.5</td>
<td>8</td>
<td>Cubic</td>
<td>59.0</td>
</tr>
<tr>
<td>0.5</td>
<td>27</td>
<td>Cubic</td>
<td>37.1</td>
</tr>
<tr>
<td>0.5</td>
<td>64</td>
<td>Cubic</td>
<td>37.9</td>
</tr>
<tr>
<td>0.2</td>
<td>8</td>
<td>Cubic</td>
<td>45.3</td>
</tr>
<tr>
<td>0.2</td>
<td>27</td>
<td>Cubic</td>
<td>41.9</td>
</tr>
<tr>
<td>0.2</td>
<td>64</td>
<td>Cubic</td>
<td>42.2</td>
</tr>
<tr>
<td>0.1</td>
<td>8</td>
<td>Cubic</td>
<td>43.2</td>
</tr>
<tr>
<td>0.1</td>
<td>27</td>
<td>Cubic</td>
<td>42.8</td>
</tr>
</tbody>
</table>

Figure 4.5: Total activation time of the benchmark problem for three spatial discretizations using linear Lagrange, serendipity, and cubic Hermite basis functions. All simulations used 27 integration points per element. The range of the consensus solution is indicated by two broken black lines.
For serendipity basis functions, the difference between the consensus total activation time and the simulated activation time was larger than for cubic Hermite basis functions but smaller than for linear Lagrange basis functions at all three spatial discretizations with 27 integration points per element (Figure 4.5).

4.3.3 Integration points can be moved to increase accuracy

As evidenced by Figure 4.4, using only 8 integration points per element gave rise to unexpected conduction slowing for both linear and cubic basis functions—in the case of linear Lagrange basis functions, this paradoxically gave rise to more accurate solutions. Closer examination revealed that the electrical wave speed oscillates while traveling through elements when only 8 integration points per element are used. Along the real line $[0,1]$, Gauss-Legendre quadrature with two integration points evaluates an integral at $\approx 0.211$ and $0.789$, so that integration points within elements and between elements are not equally spaced. Reasoning that this might have led to the conduction slowing observed for simulations with 8 integration points per element, I investigated the benchmark problem for cubic Hermite basis functions with 8 integration points per element, but with locations $\{0.25,0.75\}$ instead of $\{0.211,0.789\}$.

The results are displayed in Figure 4.6. As demonstrated in Figure 4.4, using 27 Gauss-Legendre integration points per element gives rise to fast conduction at coarser mesh resolutions, whereas using 8 Gauss-Legendre integration points per element gave rise to slow conduction at coarser mesh resolutions. At each mesh resolution, the use of 8 integration points per element and at locations $\{0.25,0.75\}$ gave rise to smaller activation time errors than the use of 8 integration points per element at locations $\{0.211,0.789\}$, but gave rise to larger activation time errors than the use of 27 Gauss-Legendre integration points per element. The total activation times for 27 Gauss-Legendre integration points and 8 equally-spaced
integration points (42.8 ms and 43.0 ms) lay within the consensus solution range for the most refined mesh, whereas the activation time for 8 Gauss-Legendre integration points (43.2 ms) did not.

![Graph showing convergence of cubic Hermite basis functions](image)

**Figure 4.6:** Convergence of cubic Hermite basis functions in the benchmark problem using 27 Gauss-Legendre (GL) integration points per element, 8 GL integration points per element, and 8 equally spaced (Eq) integration points per element.

### 4.4 Discussion

#### 4.4.1 The choice of basis functions for cardiac electrophysiology problems

In the present study, I show that among simulations with the same number of elements and the same number of integration points, cubic Hermite basis functions have more converged activation times than serendipity basis functions, and serendipity basis functions have more converged activation times than linear Lagrange basis functions. This behavior is not particularly surprising: with equal numbers of elements, a finite element problem with high-order basis functions has a larger functional space (compared to linear basis functions) with which to approximate the finite element solution, and this comes at an increased
computational cost. I do not show that cubic Hermite and serendipity basis functions show superior convergence behavior to linear finite elements in problems with equal numbers of degrees of freedom. It is difficult to make a fair comparison because problems with equal numbers of degrees of freedom in turn have different numbers of integration points, which also influences the convergence. Moreover, a degree-of-freedom comparison may be problem dependent, with high-order basis functions more likely to be beneficial in electrophysiology problems having large voltage gradients and large wave curvatures (see Section 4.4.3). Nevertheless, previous studies (Arthurs et al., 2012; Rogers et al., 1996) have shown that convergence for the monodomain problem with high-order basis functions is superior to convergence with linear basis functions in select problems with the same number of degrees of freedom.

4.4.2 The Péclet number, mass lumping, and the Gibbs phenomenon

Quarteroni (2009) showed that a Galerkin formulation of the reaction-diffusion problem with local Péclet number greater than one gives rise to oscillations, an occurrence of the Gibbs phenomenon, whereas a problem with local Péclet number less than one does not. Simulations with the ten Tusscher model showed that when the Péclet number is less than six, oscillations effectively vanish (Figure 4.3). At these low local Péclet numbers, the voltage decreases in value very slightly and does not complete even one oscillation cycle. It was not clear whether this negative excursion of voltage was in fact the Gibbs oscillations or some other consequence of complex system of ODEs describing the ten Tusscher model, or even the operator splitting scheme.

Unlike linear finite elements, high-order finite elements do not presently have theories for mass lumping. Thus, as opposed to linear finite elements, it is impossible to guarantee that solutions with high-order basis functions are completely devoid of oscillations. However, the
results (Figure 4.3) indicate that for local Péclet numbers sufficiently small, oscillations should be extremely small or may vanish completely, and even if any oscillations in voltage are present, they do not appear to prohibit the high-order scheme from converging to the correct total activation time. Moreover, the benchmark problem of Niederer and the subsequent study by Pathmanathan (2012) indicated that for at least some problems and in some parameter domains, mass lumping gives rise to appreciable simulation errors by other mechanisms, indicating the lack of mass lumping theory for high-order finite elements should not be prohibitive.

4.4.3 Activation time as a measure of convergence

The benchmark problem of Niederer used only activation times at mesh nodes to evaluate convergence because activation times are portable and easy to compute. This approach has disadvantages: One, it is possible that errors are smaller or larger at the mesh nodes compared to the remainder of the element. Two, the canonical measure of finite element convergence is the solution error—in this case, the error in voltage and its spatial derivatives—not a derived quantity like activation time. Three, it is possible that certain numerical schemes capture activation times well but fail to capture the complicated wave behavior present in wavebreak and fibrillation. This third point is particularly pertinent to high-order finite elements, which capture waves with high curvature more compactly than do linear basis functions. Thus, the advantage of high-order finite elements may be most prominent in the instance of wavebreak and reentry, which are the applications of computational cardiac electrophysiology most applicable to human disease.

4.4.4 Optimal quadrature schemes

Here, I analyzed convergence by integrating the ODEs governing ionic currents at Gauss-Legendre quadrature points. Customarily, the ODEs governing ionic currents are
solved at mesh vertices and interpolated to quadrature points, although Pathmanathan and colleagues reported that this approach gives rise to systematic errors (Pathmanathan et al., 2011). By instead integrating the ODEs at all quadrature points, I avoid the possibility that the errors attributable to current interpolation from vertices to quadrature points serves as a confounder and obtain a fairer comparison between cubic Hermite and linear Lagrange interpolation of the solution function.

The Gauss-Legendre quadrature scheme utilized here may not be optimal for high-order interpolation, and further investigation of quadrature schemes may allow for convergence advantages, speed advantages, or both. This is evidenced by Section 4.3.3, where I found that the error introduced by slowdown in conduction velocity observed when using two Gauss points per parametric coordinate could be alleviated by moving the quadrature points to $\xi_i = 0.25, 0.75 \ \forall i$. Moreover, a previous study finding convergence advantages for cubic interpolation compared with linear interpolation used Gauss-Lobatto quadrature rather than Gauss-Legendre quadrature (Arthurs et al., 2012). The use of Gauss-Lobatto quadrature should be explored.

### 4.4.5 Convergence on more complicated geometries

The benchmark study was selected to be a simple cuboid geometry to ensure portability among finite difference, finite volume, and finite element implementations and among hexahedral and tetrahedral representations. As the authors of the benchmark study acknowledge, a more meaningful community problem would be a comparison of activation times on a realistic cardiac geometry that does not have perfectly cubical elements. Finite elements in a realistic cardiac geometry introduce additional variations in solution accuracy: One, variations in element size and shape give rise to differences in convergence in different areas of the mesh, especially when the elements are highly skewed. Two, a high-order
representation and linear representation of a computational domain fundamentally differ in that the boundary of a high-order domain can have continuous normals everywhere on its domain whereas in general, a linear representation cannot; there is an error associated with a linear representation of the geometric boundary termed error due to a polygonal domain. The errors associated with a polygonal rather than smooth domain have been described for finite element analysis of partial differential equations previously (Chatzipantelidis et al., 2004; Thomée, 1997), but to my knowledge have not been described for the monodomain equation. Although here I do not explore convergence on more complicated geometries, it is reasonable to posit that in that case the convergence advantage with high-order basis functions is more pronounced.

4.4.6 Other high-order solution spaces

Here, I use cubic Hermite and cubic Hermite-style serendipity basis functions to assess the behavior of high-order interpolation schemes, but other high-order basis functions could also be used. Two such examples are spectral finite elements, which use Fourier basis functions, and non-uniform rational B-splines (NURBS), which are quotients of polynomials rather than simple polynomials. Since neither of these basis functions are simple polynomials, it is not obvious whether serendipity basis functions could be constructed for spectral finite elements or NURBS. The use of these basis functions in the cardiac electrophysiology problem is grounds for future investigation.

4.5 Conclusion

High-order cubic Hermite and serendipity basis functions converge to the consensus activation time solution for the community benchmark problem of the monodomain equation, and with fewer elements than are required for a problem with linear Lagrange basis functions. Since previous studies have also shown convergence advantages for high-order solution
spaces per degree of freedom, I expect that this approach will further decrease the times of computational cardiac electrophysiology simulations toward clinical timescales.

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Appendix

The three-dimensional cubic Hermite-style serendipity basis functions are provided below for parametric coordinates $\xi_1$, $\xi_2$, and $\xi_3$ each on the interval $[0,1]$.
$$\Psi_{\text{ser,3D}} = \begin{bmatrix}
\psi^{(1)}_1 \\
\psi^{(2)}_1 \\
\psi^{(3)}_1 \\
\psi^{(4)}_1 \\
\psi^{(2)}_2 \\
\psi^{(3)}_2 \\
\psi^{(4)}_2 \\
\psi^{(3)}_3 \\
\psi^{(4)}_3 \\
\psi^{(4)}_4 \\
\psi^{(5)}_1 \\
\psi^{(5)}_2 \\
\psi^{(5)}_3 \\
\psi^{(5)}_4 \\
\psi^{(6)}_1 \\
\psi^{(6)}_2 \\
\psi^{(6)}_3 \\
\psi^{(6)}_4 \\
\psi^{(7)}_1 \\
\psi^{(7)}_2 \\
\psi^{(7)}_3 \\
\psi^{(7)}_4 \\
\psi^{(8)}_1 \\
\psi^{(8)}_2 \\
\psi^{(8)}_3 \\
\psi^{(8)}_4
\end{bmatrix} = \begin{bmatrix}
(\xi_1 - 1)(\xi_2 - 1)(\xi_3 - 1) \\
(\xi_1 - 1)^2(\xi_2 - 1)(\xi_3 - 1) \\
\xi_2(\xi_1 - 1)(\xi_2 - 1)^2(\xi_3 - 1) \\
\xi_3(\xi_1 - 1)(\xi_2 - 1)(\xi_3 - 1)^2 \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1)(-3\xi_1 + 2\xi_1^2 - 2\xi_2^2 - \xi_3 + 2\xi_3^2) \\
\xi_1^2(\xi_1 - 1)(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1^2(\xi_2 - 1)^2(\xi_3 - 1) \\
-\xi_1^2(\xi_2 - 1)(\xi_3 - 1)(-2\xi_1^2 - 2\xi_2^2 - \xi_3 + 2\xi_3^2) \\
-\xi_1^2(\xi_2 - 1)(\xi_3 - 1)(-3\xi_1 + 2\xi_1^2 - 3\xi_2^2 + 2\xi_3^2) \\
-\xi_1(\xi_2 - 1)^2(\xi_3 - 1) \\
-\xi_1^2(\xi_2 - 1)^2(\xi_3 - 1) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1)(-\xi_1 + 2\xi_1^2 - 2\xi_2^2 - \xi_3 + 2\xi_3^2) \\
-\xi_1^2(\xi_2 - 1)(\xi_3 - 1)(-\xi_1 + 2\xi_1^2 - \xi_2 + 2\xi_3^2) \\
-\xi_1^2(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1^2(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1^2(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1)(2 + 3\xi_1 - 2\xi_1^2 + 3\xi_2^2 - 2\xi_3^2 + 3\xi_3^2 - 2\xi_3^2) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1) \\
-\xi_1(\xi_2 - 1)(\xi_3 - 1)
\end{bmatrix}
where the superscripted number of $\Psi$ indicates the node number and the subscripted number of $\Psi$ indicates the basis function corresponding to the value (1), directional derivative of $\xi_1$ (2), the directional derivative of $\xi_2$ (3), or the directional derivative of $\xi_3$ (4). It is notable that the basis functions corresponding to the values $\Psi_i^{(1)}$ can no longer be split into a product of separate functions of $\xi_1$, $\xi_2$, and $\xi_3$, i.e., their tensor product nature is lost. A consequence of this is that $C_1$ continuity cannot be guaranteed between neighboring finite elements in the general case.

Using the same notation, the two-dimensional cubic Hermite-style serendipity basis functions on the intervals $[0,1]$ are

\[
\Psi_{\text{ser,2D}} = \begin{bmatrix}
\Psi_1^{(1)} \\
\Psi_2^{(1)} \\
\Psi_3^{(1)} \\
\Psi_1^{(2)} \\
\Psi_2^{(2)} \\
\Psi_3^{(2)} \\
\Psi_1^{(3)} \\
\Psi_2^{(3)} \\
\Psi_3^{(3)} \\
\Psi_1^{(4)} \\
\Psi_2^{(4)} \\
\Psi_3^{(4)}
\end{bmatrix} = \begin{bmatrix}
-(\xi_1 - 1) (\xi_2 - 1) (-1 - 2\xi_1^2 - 2\xi_2^2 + 2\xi_2^2) \\
-\xi_1 (\xi_1 - 1)^2 (\xi_2 - 1) \\
-\xi_2^2 (\xi_1 - 1) (\xi_2 - 1)^2 \\
\xi_1 (\xi_2 - 1) (-3\xi_1^2 + 2\xi_2^2 - 2\xi_2^2 + 2\xi_2^2) \\
-\xi_1^2 (\xi_1 - 1) (\xi_2 - 1) \\
\xi_1\xi_2 (\xi_2 - 1)^2 \\
\xi_2 (\xi_1 - 1) (-3\xi_1^2 + 2\xi_2^2 - 3\xi_2^2 + 2\xi_2^2) \\
\xi_1^2\xi_2 (\xi_2 - 1)^2 \\
-\xi_2^2 (\xi_1 - 1) (\xi_2 - 1) \\
-\xi_1\xi_2 (\xi_2 - 1) (-3\xi_1^2 - 3\xi_2^2 + 2\xi_2^2) \\
\xi_1^2\xi_2^2 (\xi_1 - 1) \\
\xi_1^2\xi_2 (\xi_2 - 1)
\end{bmatrix}
\]
References


Chapter 5

Maintenance and termination of atrial fibrillation in a patient-specific model
Abstract

In this chapter, I explore mechanisms of atrial fibrillation (AF) using monodomain simulations with the patient-specific biatrial model constructed in Chapter 2. First, I show that with normal physiological anisotropy ratios and effective refractory periods (ERP) of atrial myocytes, free wavelets do not attach to small (~1 cm), inexcitable regions and become rotors. Second, I show that at the depressed excitability, depressed anisotropy, and shorter ERPs present in AF, stationary rotors form around large (>1 cm) inexcitable regions and have a small spatial excitable gap; in contrast, meandering rotors are stabilized by small (<1 cm) inexcitable regions but anchor only transiently to them, colliding with their waveback and drifting until a region of space recovers and allows them to pivot. Based on these results, simulated RF ablation scars could terminate AF by two mechanisms: One, RF lesions increase the inexcitable region size for both meandering and stationary rotors, creating or widening a spatial excitable gap and allowing impingement and extermination of the rotor by an external wave. Two, the RF lesions increase the AF cycle length by increasing the path length of a rotor, in turn both regularizing the atrial activation sequence and decreasing global fractionation, promoting spontaneous termination. I then discuss how future studies might elucidate the precise mechanisms sustaining AF, and discuss how computational modeling could be used to improve treatment of AF in the future.
5.1 Introduction

In this chapter, I investigate mechanisms of AF using the computational methods developed in Chapter 2 and Chapter 4. The methods discussed in Chapter 2 and Chapter 4—the development of new methods to construct high-order finite element geometries and to perform high-order finite element simulations—offer several advantages in modeling of AF. First, the development of hexahedral models with local coordinate axes spanning large regions of the model allows fiber orientations to be incorporated into the model easily. Second, high-order finite element methods capture wave curvatures more accurately than do linear finite element methods, and wave curvature is critically important in modeling wave fractionation, an important maintenance mechanism in AF. Finally, the computational efficiency of the high-order finite element models may allow computational times to approach clinical timescales in the future, allowing patient-specific models to potentially be used to guide clinical decision making.

Presently, I use the computational model to examine the mechanism of AF termination by RF ablation. I hypothesized that RF ablation terminates AF successfully by increasing the size of the spatial excitable gap of a reentrant rotor, allowing an external wave to invade the rotor core and extinguish it. Multiple electroanatomic mapping studies have shown that rotors may meander or be stationary, and RF ablation may convert a meandering rotor into a stationary rotor. Whereas a stationary rotor might be explained by anatomic reentry around an inexcitable scar, the mechanism for the stability of a meandering focal source is unknown. I hypothesized that a meandering focal source could be explained by transient attachment to an inexcitable region, and used the computational model to examine the precise conditions under which stable meander around an inexcitable region might occur. Experimental evidence will be needed to examine the last hypothesis against the alternate hypothesis, which is that stable meander is explained by functional heterogeneity (e.g., action
potential duration heterogeneity) alone, in the absence of an inexcitable region. This study is an example of how a computational model can be used to generate new hypotheses about AF maintenance that can be tested experimentally and in a patient-specific manner. These computational experiments will need to be repeated in more patients in order to strengthen the conclusions of this study.

Hereafter, I will use the term “rotor termination” to indicate that an electrical rotor ceases to be constrained to one area of space—the electrical wave constituting the rotor thereafter may extinguish or may migrate unconstrained throughout the atrial anatomy. Rotor termination presumably is a necessary but not sufficient condition for “AF termination” and resumption of sinus rhythm. I will also classify rotors as “stationary” or “meandering”. I loosely define a stationary rotor to have a rotor core with no apparent motion in a FIRM epoch. A meandering rotor is one with visibly detectable motion of the rotor core in a FIRM epoch. I use the term “meandering rotor” to mean that the motion of the rotor core is akin to a “random walk”, but with spatial constraint. The term “meandering rotor” should not be confused with the term “meandering wavelet”—the latter is often used to describe non-focal source wavelets in the multiple wavelet hypothesis of AF.
5.2 Methods

A 68 year-old male with a history of persistent atrial fibrillation was referred to Veterans Administration Hospital, San Diego for radiofrequency ablation (RFA) of his AF. He gave informed consent to participate in an Institutional Review Board-approved clinical research study. Thereafter, he underwent a computed tomography (CT) study to evaluate atrial structure and the presence or absence of a thrombus in advance of his RFA surgery. The images from the CT study were segmented, and a tricubic Hermite patient-specific computational model constructed as described in Chapter 2 (Gonzales et al., 2013).

The patient underwent focal impulse and rotor mapping (FIRM) to determine the presence of repetitive focal beats, rotors, or both, as described previously (Narayan et al., 2012a). In this electrophysiological study, two rotors were identified. One was located in the lateral right atrial wall near the tricuspid valve annulus, about half-way between the venae cavae; the other was located in the left atrial floor on the lateral (left) side, likely in the vicinity of the ligament of Marshall. From an anterior view, both the rotor in the right atrium and the rotor in the left atrium had a clockwise chirality. The right atrial rotor meandered in the superior-inferior direction for a distance between 1 and 2 cm. The left atrial rotor but not appear to meander appreciably. Both rotors had rotational frequencies of about 5 Hz. Though fractionation customarily occurs close to a meandering rotor, the right atrial rotor did not exhibit fractionation close to its core—this might be attributable to its close proximity to the pectinate muscle network, which tends to prevent fractionation. Lesions were placed by RFA at the apparent rotor cores in the right atrium and the left atrium so that the total lesion size in each location was about 2 cm².

After RF lesions were placed at both rotor cores, iatrogenic pacing was used to attempt to uncover additional localized sources driving AF, and was only able to induce atrial tachycardia. After pulmonary vein isolation by RFA, neither AF nor atrial tachycardia could
be induced. Retrospective examination of electrical mapping data revealed that an additional rotor with counter-clockwise chirality and rotational frequency of about 5 Hz may have been located in the superior left atrium, near the right superior pulmonary vein. It is possible that this source was responsible for the atrial tachycardia observed after the two targeted source ablations, and itself was ablated incidentally during pulmonary vein isolation. Evidence for the incidental ablation of localized sources was discussed in a separate work (Narayan et al., 2013).

The patient-specific model BiA-9486 with fiber orientations from Chapter 2 was used for finite element simulations of the monodomain equation using high-order cubic Hermite basis functions (Chapter 4). The mean edge length in the model BiA-9486 was 1.9 mm, and the time step $\Delta t$ was 0.1 ms. Diffusivities spanning two orders of magnitudes have been used to simulate electrical propagation in the atria; in the present work, I used transversely isotropic diffusivity: $D_{fiber} = 0.4 \text{ mm}^2/\text{ms}$, and $D_{cross-fiber} = 0.1 \text{ mm}^2/\text{ms}$, unless indicated otherwise. Point stimulus in the region of the sinoatrial node with these diffusivities gave rise to a total biatrial activation time of about 100 ms with the Fenton-Karma ionic model in BiA-9486 and the Maleckar-Giles-Trayanova ionic model in the more refined BiA-75888. (Typical p-wave durations are 80 ms, and customarily are slightly longer in patients with atrial enlargement, as is the case here.) Use of the Fenton-Karma model in BiA-75888 gave rise to apparent conduction velocities that differed by less than 10% from the apparent conduction velocities in BiA-9486. The base parameter set used for Fenton-Karma model was parameter set 1 in Fenton et al. (2002). The excitability value of the model could be adjusted by the parameter $\tau_d$—increasing (decreasing) excitability also caused the action potential duration to increase (decrease) by increasing (decreasing) magnitude of the slow inward current, which is analogous to the L-type calcium current. The value used for $\tau_d$ was 2.95 except for in Section
5.3.1 because this gave rise to reentrant rotors with frequency approximately equal to that observed of the reentrant rotors in the patient (5 Hz).

Figure 5.1: Visualization of electrical activity by FIRM. This image is taken from the FIRM-guided radiofrequency ablation of the case study patient. Blue lines are wavefronts and green lines are wavebacks, as calculated by phase mapping and the Hilbert transform. The red contour is the calculated meander of the right atrial rotor.

5.3 Results

5.3.1 Normal atrial anisotropy and normal atrial myocyte effective refractory period prevents stabilization of a broken wave to an inexcitable region

The normal atria may be protected from AF by all of the following: the absence of a trigger, the unlikelihood of wavebreak, and the absence of a substrate for broken wave attachment. A computational model with a scar at the site of the RA rotor was used to investigate how normal physiology in the atria (versus pathophysiologic remodeling) might prevent a broken wave from attaching to an inexcitable region, preventing a stable source of AF.

Anisotropy of electrical propagation has been reported to be depressed in AF. I thus investigated the attachment of a broken wave to an inexcitable scar with a physiologic anisotropy ratio (nine) rather than the depressed value used (four). Images of the resulting
simulation are presented in Figure 5.2. Whereas the simulation with the lower anisotropy ratio was able to support anatomic reentry around the inexcitable scar (not shown), the simulation with the greater anisotropy could not support anatomic reentry. This is because the spiral tip is always the location within a spiral wave with the highest electronic load, and in the simulation, the additional electrotonic load imposed on the wave by rapid propagation in the fiber direction caused the wave tip to detach from the inexcitable region.

**Figure 5.2:** A wave cannot attach to an inexcitable region when the anisotropy ratio is nine. The spiral attaches to the inexcitable region in (A) and continues to rotate around it in (B); an increase in wavelength in (A) compared to (B) due to electrotonic effects is apparent. Upon rotating once around the unexcitable region, the electrotonic load is too great and the tissue excitability too low to support the high curvature at the wave tip, and it detaches (C and D).
Figure 5.3: A normal atrial myocyte action potential is unable to support anatomic reentry around an unexcitable obstacle. The broken wave initially is attached (A) but upon circulating about halfway around the obstacle, the wavetail has not moved appreciably (B), leading to failure of propagation and wave extinguishment (C). The normal atrial action potential has an extended repolarization phase (phase 3) which prohibits formation of anatomic reentry, especially at resting activation rates.

The normal effective refractory period (ERP) and normal (comparatively long) APD in atrial myocytes also prevent anatomic reentry from occurring, whereas in AF, ERP and APD may be shortened by increases in the inward rectifier potassium current (I_{K1}) (Zhang et al., 2005) and decreases in the L-type calcium current (I_{CaL}) (Christ et al., 2004). To investigate the effect of the normal late repolarization of atrial myocyte action potentials, simulations were performed with the Fenton-Karma ionic model, but with model parameters chosen to recapitulate the action potential of the Courtemanche-Ramirez-Nattel model (Oliver and Krassowska, 2005). A simulation with these parameters is presented in Figure 5.3. Owing
to the extended wave “tail” of the physiological action potential (Figure 5.3D), the wavefront collided with the wavetail after one circulation around the obstacle, causing the wave to extinguish.

5.3.2 Non-meandering rotors anchor to larger inexcitable regions and are unlikely to fractionate close to their core

Experimental studies with FIRM have shown that most rotors have a small amount of meander (approximately 1-2 cm), but some rotors are completely stationary. Stationary rotors could be attributable to anatomic reentry around an inexcitable region. Experimentally, stationary rotors were observed less frequently than meandering rotors because the anatomic circuit for a stationary rotor must match the wavelength closely—if the anatomic circuit is too small, the wavefront would collide with its wavetail; if the circuit is too large, there would be a spatial excitable gap, and the reentrant wave would be prone to termination by an external wave. It was found that anatomic reentry with activation frequency near that of the AF of the patient (5 Hz) could be sustained by inexcitable scars of sizes greater than 1 cm (Figure 5.4) where the inexcitable region is disc-shaped with a diameter of 1.4 cm.

The rotor in Figure 5.4 had a spatial excitable gap but appeared to be stable indefinitely. This could possibly be attributable to two factors: One, there was no fractionation and thus no external wave that could potentially invade the rotor core and terminate it. Two, the relatively large wavelength could in theory serve to “screen” external waves from invading the rotor core and terminating it. A rotor circumscribing a large inexcitable region is more likely to have a longer wavelength because the electrotonic load on the spiral is smaller at every point along the spiral wave and particularly at the core, allowing for a longer APD and thus a longer wavelength.
Figure 5.4: Stable anatomic reentry around a large inexcitable scar. The broken wave in (A) attaches to the scar and circulates stably and indefinitely with no broken wavelets in other areas of the atria (B and C).

5.3.3 Meandering rotors transiently anchor to smaller inexcitable regions and may meander by stable interactions with their tail

As discussed in Section 5.3.2, anatomic reentry could be supported when the wavelength of a reentrant wave is smaller than the path length around an inexcitable region. However, if a wavelet attaches to an inexcitable scar with a circumferential path length which is too short, conduction block is not necessarily the result. Under conditions in which the local action potentials display abrupt repolarization (Shaw and Rudy, 1995), the reentrant wave instead can meander for a short distance until sufficient tissue has recovered, at which time it will “pivot” (Figure 5.5). Thereafter, the reentrant wave may undergo cycles of intermittent attachment and free meander. Thus, the model suggests that a reentrant wave may attach to a small inexcitable region intermittently, and the stabilization conferred by the inexcitable region could explain long periods of focal source stability.

Discontinuities in the fiber architecture may also provide a means for stable meander of spiral waves intermittently anchored by small inexcitable regions. In Figure 5.6, a spiral wave drifts away from the inexcitable region leftward toward the intercaval region. However,
the left-to-right fibers present in the area of the pectinate muscles cause the meandering spiral to drift back toward the right border of the tricuspid valve orifice. Moreover, the circumferential fibers do not allow the spiral to continue rightward and annihilate at the valve orifice but instead “pull” the spiral toward the scar, where it attaches (Figure 5.6C). It was noted in this case and at least two other FIRM cases that spirals localize to areas of well-known fiber discontinuities with high frequency.

Figure 5.5: A rotor is partially stabilized by a small inexcitable region (7 mm). The anchored rotor (A) detaches from the inexcitable region (B), meanders superiorly (C), and then reattaches to a small inexcitable region (D). The pattern of detachment and reattachment repeats for the duration of the simulation (1.5 seconds).
Figure 5.6: Fiber discontinuities help to stabilize a meandering rotor. A rotor is initially attached to a small inexcitable region (A) and detaches. The rotor meanders for several rotations (B) but reattaches (C-D) because of drift induced by left-to-right fiber tracts in the region of the pectinate muscles and superior-inferior fiber orientations in the region of the tricuspid valve orifice.

5.3.4 A radiofrequency ablation lesion may terminate AF by creating a spatial excitable gap for both non-meandering rotors and meandering rotors

It has been shown in FIRM mapping that RF lesions placed at the approximate center of meandering spiral waves may extinguish the spiral wave abruptly or cause it to anchor as a non-meandering spiral wave. A surviving non-meandering spiral wave is less arrhythmogenic than a meandering wave (Section 5.4.3) and can be terminated by further RF ablation. A potential mechanism for AF termination by an RF ablation scar is presented in Figure 5.7. A scar with approximate diameter of an AF lesion (approximately 1.2 cm) was created under the
same conditions giving rise to the rotating spiral waves attached to smaller obstacles in Section 5.3.3.

Figure 5.7: A rotor is displaced after a virtual RF lesion is applied. The rotor is stably attached in (A). A separate wavelet approaches the rotor in (B) and collides into the rotor in (C). Multiple wavelets continue to circulate in the atria, but for the duration of the simulation (5 seconds), no waves are able to reattach to the inexcitable scar (D).

With a larger scar size, the rotor had a spatial excitable gap. As opposed to the simulation in Figure 5.4, here fractionation of the primary wave occurred, giving rise to wavelets circulating in the right atrium. This was attributable to the slightly smaller inexcitable region (1.2 cm vs. 1.4 cm) causing an increased electronic load on the spiral wave, with subsequent fractionation. The presence of these wavelets invaded the rotor core and displaced the spiral wave away from the focal source (Figure 5.7C), causing a transient period
during which AF was maintained by multiple wavelets and no focal sources. Presumably, this state would spontaneously terminate given sufficient time of simulation.

5.4 Discussion

5.4.1 Criteria for spatial constraint of reentrant rotors

Visualization by FIRM has indicated that AF is maintained by reentrant rotors that may be stationary or may meander in a small area. Presumably, a stationary rotor is “anchored” to inexcitable tissue (“anatomic reentry”) whereas a meandering rotor could be constrained to lie within a small area in the absence of a well-defined obstacle (Allessie et al., 1977) (“functional reentry”) or be partially stabilized by inexcitable tissue. Our observations have shown that whether stationary or meandering, application of a lesion to the approximate center of the rotor core could terminate AF abruptly. Two questions could be critical in preventing AF and eliminating it by RF ablation: One, how does structural and electrical remodeling in AF allow for spatially constrained rotors? Two, why do lesions created by RFA not create a substrate for wavelet attachment and maintenance of AF by anatomic reentry?

In Section 5.3.1, I found that healthy atria may prohibit attachment of wavelets to inexcitable regions by two mechanisms: One, physiological anisotropy may prevent attachment of waves by incurring large electrotonic loads. Two, the prolonged spatial wavetail of an action potential in a normal atrial myocyte may lead to conduction block and propagation failure. In this study, anisotropy prevented attachment of spiral waves by increasing the electrotonic load along the long axis of the fibers so that the spiral wave tip was unable to remain attached to an unexcited region. Under the same conditions but with anisotropy ratio decreased (by decreasing the long-axis conductivity), the wave tip was able to remain attached to the inexcitable obstacle. Whether anisotropy ratio increases or decreases in AF is somewhat controversial, but here I modeled the anisotropy ratio as decreased in AF. The
rationale for this is the report of lateralization of connexin 43 in AF and a concomitant decrease in the anisotropy of apparent conduction velocity in intact tissue preparations in AF (Polontchouk et al., 2001). Others have argued that anisotropy might increase, since it is known that there is increased fibrotic septation between juxtaposed sheets of cells (Yao et al., 2003). These findings could be reconciled by the dependence of conduction anisotropy not only on gap junction connections but also on the magnitude of the fast inward sodium current, which may be depressed in AF (Gaspo et al., 1997), disproportionately decreasing the conduction velocity along the fiber axis. The idea that normal uniform anisotropy of conductivity could be anti-arrhythmic was proposed by Spach and Starmer (1995), who also stipulated that the tissue anisotropy be spatially uniform.

Ionic current remodeling may promote AF as well. Ionic currents such as the $I_{K1}$ (Zhang et al., 2005) and $I_{CaL}$ (Christ et al., 2004) change in magnitude in AF, shortening the ERP and APD. Figure 5.3 shows one causal mechanism by which normal magnitudes of ionic currents in human atria prevent AF—the waveback is too long to allow an anchored wave to circulate around inexcitable objects and establish a focal source. Others have demonstrated the importance of changes in atrial myocyte ionic current magnitudes on rotor dynamics in AF. Atienza et al. (2006) demonstrated that upregulated $I_{K1}$ promotes AF stability by increasing rotor frequency in human studies and simulations. Sarmast et al. (2003) showed that rotor frequencies increase and AF stabilizes by increased $I_{K,Ach}$ in a cholinergic model of AF owing to the shorter ERP and APD. The role of $I_{K,Ach}$ remodeling and its spatial heterogeneities could explain why RF ablation of ganglionated plexi has some success in preventing AF (Pokushalov et al., 2009). Evidence for the importance of short ERP and APD in AF is also provided by the fact that AF can be induced transiently in healthy atria by iatrogenic pacing of progressively shorter basic cycle length. Progressively decreasing paced cycle length can “coax” normal human atrial myocytes into having short ERPs and APDs almost as short as
myocytes in AF (Franz et al., 1997) and without conduction block. These AF episodes in healthy atria probably terminate quickly without the structural and electrical remodeling present in typical AF patients.

We found experimentally that AF-sustaining rotors are focal—they meander little (<2 cm) or not at all. Whereas stationary rotors may be explained by anatomic reentry around an inexcitable region, the genesis of meandering waves is less clear. A previous simulation study using an atrial myocyte ionic model showed that functional heterogeneities alone are capable of constraining rotors to small regions of space, at least for the time course of seconds (Comtois and Nattel, 2011); whether or not functional heterogeneities are able to spatially constrain rotors for longer periods of time (hours to days) is unclear.

Another possible explanation for focal but meandering waves is that they are spatially constrained by inexcitable regions of tissue, but anchor only transiently to them. In Section 5.3.1 and Figure 5.3, I showed that for atrial myocyte action potential shapes in normal atria and at normal rates, the slow and spatially extended waveback causes the reentrant wavefront to block and extinguish precisely when the spatial excitable gap is extinguished. In contrast, an action potential with a different waveback shape may allow the wave to meander for a short distance—without an excitable gap and without blocking—until more excitable tissue recovers (Section 5.3.3 and Figure 5.5).

The differential ability of waves to meander depending on different waveshapes is closely related to the idea of the “vulnerable window” applied to multi-dimensional propagation. Shaw and Rudy (1995) conducted a simulation study of one-dimensional propagation and found that one condition allowing for a vulnerable window is the presence of a high spatial gradient of sodium channel recovery. This gradient in turn is manifested as high spatial gradients of voltage along the waveback and an increase in the size of the vulnerable window. Further, Shaw and Rudy found that depressed excitability and depressed gap junction
conductivity both may contribute to an increase in the vulnerable window—changes which are also present in AF. The confirmation of reentry as being a multi-dimensional manifestation of the excitable gap was conducted in simulation studies using a circular ring by Quan and Rudy (1990) and in two dimensions by Moreno et al. (2011). Thus, the high excitability, high diffusivity, and low-magnitude dV/dt of phase 3 of the AP in the normal atria and at normal sinus rates protect against a vulnerable window and against reentry.

The sizes at which a rotor attached to an inexcitable obstacle is likely to impinge on its tail rather than meander is unknown. Ikeda et al. (1997) showed in canine that rotors could attach to obstacles 6-mm and larger but not to smaller obstacles due to insurmountable electrotonic source-sink requirements at the spiral tip. Furthermore, they observed modest meander caused by wave tips spontaneously detaching from the inexcitable object and then reattaching. If the results from Ikeda and coworkers in canine apply to humans, it would suggest that smaller scars—smaller than 1 cm in diameter but larger than 6 mm—are substrates for meandering rotors, whereas scars larger than 1 cm are substrates for stationary rotors. The typical ablation lesions used in FIRM were disc-shaped and about 2 cm² (diameter 1.4 cm) in size. Thus, RF lesions may increase the size of the small, inexcitable regions to be larger, turning the more arrhythmogenic meandering rotor (see Section 5.4.3) into a less arrhythmogenic stationary rotor (Section 5.3.4). Further, if a spatial excitable gap is created, the rotor can be displaced from the inexcitable scar by an external wave, promoting AF termination, as suggested previously (Kawase et al., 2003).

There is also reason to believe that difference between pathophysiological and iatrogenic scar could be responsible for differences in arrhythmogenicity, even if the scars are of the same size: whereas pathophysiological scars often have “border-zones”, Haines showed (2008) that RF ablation gives rise to tissue injury just outside the RF lesion that is transient and followed by complete functional recovery. Though presumed, remodeled tissue is still
present near the RF ablation scar, the lack of a border zone just adjacent to the RF lesion may further narrow the vulnerable window for reentry by the mechanisms discussed above.

Maintenance of AF depends on long-term stability of focal sources. Why some episodes are self-limiting (paroxysmal AF) and others are not (persistent AF) is unknown. Although the difference potentially could be attributed to differential stability of single focal sources, it also could be attributable to the number of focal sources present—FIRM studies showed that most episodes of AF (both paroxysmal and persistent) had two or more focal sources. Maintenance of AF by multiple focal sources is the topic of the next section.

5.4.2 Are multiple focal sources required for maintenance of paroxysmal AF, persistent AF, or both?

The pathophysiological basis of paroxysmal versus persistent AF is unclear but could be of great consequence to AF therapeutics. It is generally accepted that paroxysmal as well as persistent AF require both a “trigger” and a “substrate”. Some potential factors accounting for the different stability between paroxysmal and persistent AF are (1) the number of sources present, (2) the stability of the sources (i.e., their tendency not to spontaneously terminate), (3) the dominant frequency of the sources, and (4) the structural and dynamic properties of the tissue in the remainder of the atria.

Paroxysmal and persistent AF episodes have focal sources maintaining AF, with paroxysmal AF having fewer sources than persistent AF (1.5 ± 0.8 versus 2.0 ± 0.8, p < 0.01) (Narayan et al., 2012a). It is reasonable to posit that AF is maintained so long as there is at least one source present, whereas AF spontaneously terminates when all rotors fortuitously extinguish. Under this premise, persistent AF is more stable than paroxysmal AF because the increased number of sources makes fortuitous termination of all sources statistically unlikely. Future studies should determine whether AF episodes driven by a single source have additional characteristics that confer protection from spontaneous termination. It is worth
noting that FIRM detection is naturally prone to false negatives, i.e., it is possible that some sources cannot be visualized and thus are not ablated. This could be responsible for some of the patients in whom FIRM-guided ablation does not lead to AF remission; however, it is also possible that AF can only rarely be sustained by one source, and thus failure for FIRM to detect one source does not preclude FIRM-guided ablation from preventing AF.

Another possible basis for paroxysmal AF versus persistent AF is that sources in persistent AF are more stable than in paroxysmal AF—though one putative measure of the stability, the amount of source meander, was not different (2.5 ± 1.4 cm² versus 2.2 ± 1.0 cm², p = NS) (Narayan et al., 2012a). Nonetheless, meander should be investigated further using more detailed quantification schemes. Using the total area of meander as in this study might overestimate the typical meander of a wave that meanders little on average but significantly in a small number of cycles. Moreover, it would be expected that limitations in spatial resolution amplify meander, with this systematic error likely to penalize rotors that meander little compared to rotors that meander appreciably, impairing statistical power to detect a difference. Meander is discussed further below in the context of fractionation (Section 5.4.3).

The frequency of sources could be the basis of the stability of paroxysmal versus persistent AF, as paroxysmal AF cycle length was larger compared to that of persistent AF (Left atrium, 182 ± 24 ms vs. 162 ± 18 ms; Right atrium, 179 ± 17 ms vs. 173 ± 25 ms; p = 0.01) (Narayan et al., 2012a). It is unclear whether high frequencies give rise to more stable episodes of AF or whether the higher frequencies in persistent AF are an epiphenomenon. It is possible that higher-frequency sources are more stable because increasing frequency of a localized source confers protection from invasion and termination of the rotor core from an external wave. Alternatively, higher-frequency sources might increase the stability of AF by inducing more wavebreak, which in turn sustains AF (see Section 5.4.3). Circumstantial evidence for this last mechanism was provided by Mandapati et al. (2000) in sheep, who
showed that AF disorganization, measured by dispersion of frequency in the power spectra, is increased at higher frequencies. Jalife (2003) proposed that the localized source with the highest frequency, the “mother-rotor”, drives the overall activity, with additional localized sources playing an ancillary role. However, Jalife also noted that one would expect that a localized source with higher frequency might entrain and extinguish a source with lower frequency. Interestingly, the three rotors observed in the patient in this case study had approximately the same frequency—about 5 Hz. Although only examined in one patient, this suggests that multiple sources co-existed in this patient precisely because they did not extinguish one another. If this finding was observed in other patients, it would suggest that multiple sources are needed to sustain most cases of AF, but those sources can only drive AF if their frequencies are similar.

Finally, the stability of paroxysmal versus persistent AF may be mostly attributable not to number and characteristics of sources but rather to the remainder of the structural and electrical milieu in the atria. Much of the remodeled behavior is encapsulated by the APD and CV restitution curves. Flat and steep APD restitution curves can both promote arrhythmia and prevent arrhythmia through different mechanisms (Franz, 2003), some related to AF initiation, others related to AF maintenance. In human AF, previous studies have shown that APD and CV restitution are “flatter” (i.e., less restitution) in persistent AF compared to paroxysmal AF (Narayan et al., 2008). It is reasonable to expect that flat APD restitution stabilizes AF by decreasing the wavelength (see Section 5.4.4) whereas flat CV restitution effectively increases the size of the atria, reducing the chance that a meandering wave reaches the boundary and annihilates.

In addition to the four mechanisms of AF maintenance discussed above, co-existing sources of different phenotype (e.g., focal beat vs. rotor, meandering rotor vs. stationary rotor) may influence how AF is sustained. For example, in AF driven by both repetitive focal beats
and rotor sources, rotors may not extinguish focal beats in the way that a higher frequency rotor can extinguish a lower frequency rotor, since the putative mechanism of a focal beat is enhanced automaticity rather than reentry. Moreover, focal beats coexisting with rotors may increase the meander of rotors (Yamazaki et al., 2009), giving rise to increased fractionation by Doppler shifting of frequency, as described by Fenton et al. (2002). The same behavior might be expected of AF sustained by meandering rotors and stationary rotors. In this patient (and at least two others), stationary rotors tend to be stable further away from the rotor core, whereas rotors that meander appreciably tend to fractionate close to the rotor core. Since stationary rotors are less likely than meandering rotors to fortuitously annihilate at a boundary, and meandering rotors are more likely than stationary rotors to give rise to fractionation and in turn perpetuate AF (see Section 5.4.3), it is reasonable to speculate that a combination of one stationary rotor and one meandering rotor gives rise to a more stable AF episode than an AF episode driven only by stationary rotors or meandering rotors.

5.4.3 Fractionation: Innocent bystander, or driver of AF?

It has long been observed that RF ablation may terminate AF into sinus rhythm or into non-sinus atrial tachycardia (Chugh et al., 2005; Jais et al., 1997). In the multiple wavelet hypothesis of AF, this could be explained by a spatial lengthening of AF wavelet circuits progressively until only a single, macro-reentrant, flutter-like circuit was permissible for reentry (Waldo, 2002). An explanation for AF conversion to non-sinus atrial tachycardia also exists for the focal source hypothesis, motivated by the work of Jalife and colleagues. In the focal source hypothesis, AF wavelets are the result of the focal source activating too quickly for 1:1 conduction to surrounding tissue, causing fractionation. Post-ablation tachycardia could then explained by (1) preservation of the focal source, but with 1:1 conduction to surrounding tissue, (2) post-ablation survival of the AF-driving focal source but with 1:1
conduction to surrounding tissue, or (3) modulation or anchoring of the focal source, in turn decreasing nearby fractionation. Any of these could in principle give rise to the more organized electrograms characteristic of non-sinus atrial tachycardia.

Of course, based on the evidence presented by FIRM, focal sources do exist in AF and play a critical role in sustaining it. But there is reason to believe that fractionation itself is not an “innocent bystander” but in fact a driver of AF by a mechanism similar to that proposed by the multiple wavelet hypothesis of AF. Jalife proposed that fractionated wavelets in AF could collide with a boundary and annihilate, extinguish by decremental conduction, or develop into spirals waves themselves, in turn sustaining AF (Jalife et al., 1998). Thus, it is reasonable to suspect that in the event of a fortuitous termination of one focal source, a fractionated wavelet might reattach and continue to drive AF. Simulation studies by Kneller et al. (2005) suggested that this could be one mechanism for AF termination by sodium channel blockade—decreased fractionation allowed for fewer wavelets that could “re-seed” a focal source.

5.4.4 Do multiple wavelets as well as focal sources play a role in AF maintenance?

Jalife (1998) proposed a compromise of sorts between the focal source hypothesis and the multiple wavelet hypothesis: that both focal sources and multiple wavelets are responsible for AF maintenance. The way by which the two could be reconciled depends on the concept of wavelet “re-seeding” of focal sources, discussed above in Section 5.4.3: In the event that a rotor fortuitously is annihilated, or meanders away from an area in which it is normally constrained, AF need not terminate but instead may be maintained transiently by multiple wavelets. In this model, AF will terminate if the wavelets spontaneously annihilate before they are able to reattach to a stable source location.

I observed that fibrillation could be maintained in the computational model without a focal source (Figure 5.7), but that this fibrillatory state had different characteristics depending
on the action potential shape and APD restitution curve, both of which are governed principally by the excitability parameter \( \tau_d \) (in the Fenton-Karma model). With high excitability, the APD restitution curve is steep at short diastolic interval and shallow at long diastolic interval. Consequently, some wavelets in the simulations had very long wavelengths whereas others had short wavelengths, depending mainly on the diastolic interval at each particular region of tissue and also on electronic effects. At sufficiently high excitability, a wave with long previous diastolic interval could become so long that very few wavelets (1 or 2) were able to be maintained in an atrial chamber. With few wavelets present, the likelihood of spontaneous termination increased. In contrast, simulations with low excitability—and thus flat APD restitution—prevented spontaneous termination. Since APD restitution was flat, variations in local diastolic interval due to wave directionality and curvature were unlikely to allow a wave with a very long wavelength to be formed and cause termination of AF by means of extinguishing the other wavelets present. Instead, wavelengths were consistently very short, regardless of variations in local diastolic interval and electrotonic effects. Often, these simulations came to a “meta-stable” steady state, in which a small number of waves (fewer than 3) activated the atrial chambers with a beat-to-beat consistency for the time course of the simulation (seconds). It appeared that fibrillation would persist indefinitely as multiple wavelets unless some large disturbance was introduced into the system.

Based on the results from the computational model, and past studies of AF in humans and animals, the lack of focal sources in certain epochs of FIRM studies may be explained by AF being transiently maintained by multiple wavelets, rather than limitations in the mapping procedure. The circumstantial evidence for multiple wavelets playing some role in AF maintenance is extensive. Previous studies have suggested that multiple wavelets maintain AF, including in humans (Allessie et al., 1985; Cox et al., 1991; Konings et al., 1994); these wavelets often meandered randomly. Moreover, some contribution of multiple wavelets in AF
maintenance is corroborated by the success—though variable—of surgical ablation by the Cox-Maze procedure (Cox et al., 1995; Damiano Jr et al., 2003). Multiple wavelets with short wavelengths also can explain the epidemiological correlation between increased atrial size and prevalence of AF that is preserved even after statistically adjusting for other comorbidities correlated with atrial size (Psaty et al., 1997; Vaziri et al., 1994).

Simulations of a multiple wavelet state maintaining AF demonstrate some characteristics of AF that usually are attributed to the focal source hypothesis. One, in the low excitability (flat APD restitution) simulations, it was observed that multiple wavelets could give rise to an activation pattern with surprising spatiotemporal periodicity, a property that Jalife attributed only to a focal source mechanism. Two, the present simulation studies with low excitability showed a frequency gradient between chambers, which has been shown experimentally (Mansour et al., 2001; Sarmast et al., 2003). In the present study, the frequency gradient was attributable to the ability of the interatrial connections to “filter” wavelets between chambers, in the same way that the atrioventricular node filters electrical impulses between the atria and the ventricles. As with filtering by the atrioventricular node, the interatrial connections act as a “pinch point” or node for transmission of electrical waves in the proximal chamber, decreasing the dominant frequency in the distal chamber. Two results are particularly notable: One, fractionated wavelets in one chamber may transmit to the other chamber unfractionated. Two, a meta-stable steady state of wave activation may be induced by the interatrial connections, in the same way that a standing wave permits only certain harmonics. This is naturally facilitated by APD restitution, which allows APD and thus wavelength to acclimate until a steady-state wavelength for the chamber size is reached.

Future experimental investigations could indicate or exclude multiple wavelets as a mechanism for this observation by querying the presence of alternative explanations, such as more focal sources in larger atria, or increased sites of wave fractionation in larger atria.
Moreover, there could be some patients in whom multiple wavelets are partially responsible for AF and others in whom it is not a contributing mechanism. I propose pre-operative and post-operative telemetry in FIRM patients and patients with conventional ablation be completed to query the possible roles of multiple wavelets and multiple focal sources as sustaining mechanisms for AF. The relation between clinical characteristics (i.e., frequency of AF episodes, length of AF episodes, and degree of AF disorganization) and characteristics of intraoperative mapping (i.e., number of sources, type of sources, and degree of fractionation) could suggest how intraoperative characteristics of AF translate into clinical features of AF. This evidence would be circumstantial; further in the future, high-quality, high-density electroanatomic mapping in humans will become possible, enabling the mechanisms of AF maintenance to be studied more mechanistically.

5.4.5 Limitations

One limitation of the present study is the accuracy of the computational model of patient anatomy. The accuracy of the geometry of the model was limited by the uncertainty of the computed tomography study, which had a resolution of 0.5 x 0.5 x 0.625 mm—thus, at best, the resolution of our model was accurate only to 0.625 mm. Error in constructing the model could be attributed to (1) uncertainty in the imaging study, (2) errors in the segmentation, and (3) least-squares fitting of the cubic Hermite mesh (Chapter 2). It should also be noted that the atrial model is static—i.e., its mechanics are not being considered.

Another limitation is that the current model uses a phenomenological ionic model (Fenton-Karma) rather than a biophysical ionic model such as Courtemanche-Ramirez-Nattel (Courtemanche et al., 1998) or Maleckar-Giles-Trayanova (Maleckar et al., 2009). This limitation means the present work can only suggest phenomenological mechanisms, not more meaningful biophysical mechanisms for my results. For example, the Fenton-Karma model
can be used to examine the effect of depressed excitability and of spatial variations in excitability, but cannot distinguish between changes in the biophysical constituents of excitability such as sodium channel remodeling, increased cardiomyocyte-fibroblast coupling, or resting membrane potential elevation. Moreover, the parameter governing excitability $\tau_d$ in the Fenton-Karma model is not based on an actual biophysical measurement; in contrast, excitability in biophysical models is based on measurements of the fast inward sodium current. The extent to which these differences lead to different conditions for wavebreak and wave fractionation is unknown.

On the other hand, several insights gained into rotor dynamics and specifically into AF by computational models are completely attributable to the shape of the action potential waveform and its effect on spiral tip meander, dominant frequency, and fractionation (Atienza et al., 2006; Kneller et al., 2005). Consequently, results depending principally on the wave shape, such as the number of wavelets that can be supported in a normal versus an enlarged atrium, should be unchanged if the Fenton-Karma model can recapitulate the action potential shape of a more detailed model. A principal reason I chose the Fenton-Karma model for the present study is because according to a recent computational study (Wilhelms et al., 2012), both “normal” and “AF” parameter values in five recent human atrial myocyte models fail to capture experimental APD and CV restitution behaviors observed by other groups or by our group (Narayan et al., 2008). Specifically, the restitution curves for “normal” and “AF” parameters were far more flat than has been observed experimentally, and the disagreement was worst at the fast rates (>4 Hz) of sources in our FIRM studies. In the future, the present study should be completed with more biophysically detailed models if parameter values can be found that agree with experimental APD and CV restitution curves.

Another limitation of the present study is that APD and CV restitution curves were not obtained in this patient. In the future, APD and CV restitution curves could be used to modify
the parameters of the ionic model (whether phenomenological or biophysical) to make it patient specific. Since the number of wavelets sustainable by AF depends on the CV and APD restitution properties, the inclusion of these data could help distinguish between different phenotypes of AF.

Finally, this study is limited because it considers only one patient. Future studies should test these results about reentrant rotor stability in many patients; these simulations might differ from the results presented here due to differences in the distance of a focal source from a boundary, the location of sources relative to high-curvature regions (e.g., the pulmonary vein ostia), or the location of sources relative to well-known locations of fiber discontinuity.

5.5 Conclusion

Experimental observation and results from the patient-specific computational model suggested mechanisms for the maintenance of AF. I speculate that stationary rotors driving AF may be maintained by large inexcitable regions, whereas meandering rotors might meander because they are circulating about inexcitable regions slightly too small for their wavelengths. Meandering rotors might be important driving sources of AF because they lead to increased wave fractionation compared to stationary rotors, and thus increase the chance that a fortuitously-extinguished focal source is re-seeded before all wavelets in the atria terminate. Finally, I suggest that RF ablation might terminate AF by converting meandering rotors to stationary rotors, and by creating a spatial excitable gap for both meandering rotors and stationary rotors, allowing for focal source extermination by an external wave.

5.6 Epilogue

The advances in AF ablation made in the past years on the basis of localized source mapping (FIRM) and targeting have dramatically improved remission from AF in clinical
trials (Narayan et al., 2012b; Shivkumar et al., 2012). Remission rates from AF by FIRM-guided RF ablation are impressive—one-year remission rates are about 80%—but those rates could be improved. Aside from improving success rates of RF ablation, patient quality of life could be improved—and medical costs lowered—by predicting *a priori* which patients would respond well to anti-arrhythmic drugs, to RF ablation, or to neither.

The new FIRM-guided ablation studies have shown that atrial fibrillation has phenotypic differences between patients that could form the basis for patient-specific therapies. One, different patients have AF episodes driven by different numbers and types of localized sources (rotors versus focal beats). Two, rotors may either be stationary or exhibit a meandering trajectory. Three, some rotors fractionate near to their core, whereas others fractionate only far away or not at all. Last, both rotors and focal beats have characteristic rotation frequencies that are variable. Among all of these phenotypic differences of AF, it is reasonable to expect that patients with different AF phenotypes will have different responses to treatment. For example, a patient exhibiting only focal beat sources may benefit from Class I anti-arrhythmics (sodium channel blockers) since repetitive focal beats may be driven by abnormal automaticity. Patients exhibiting only meandering rotors could also benefit from Class I anti-arrhythmics since Class I anti-arrhythmics may cause them to meander into a boundary (Kneller et al., 2005). On the other hand, patients with non-meandering rotors may not benefit from Class I anti-arrhythmics at therapeutic doses.

I believe that patient-specific computational models could be a decisive component of future AF therapeutics by determining the optimal termination strategy for AF episodes with different phenotypes. In practice, a patient-specific model might predict that in certain phenotypes of AF—perhaps phenotypes showing extensive fractionation—additional ablation lesions aside from targeted source lesions will lead to higher rates of remission. Though the patient-specific details of computational models currently are at most the atrial structure and
restitution curves, this information alone could be sufficient to account for differences in AF phenotype, particularly if AF is in fact maintained by multiple wavelets at times, as posited above. This would suggest that knowledge of the size of the atria and an approximate knowledge of their restitution properties could be sufficient to predict the number of wavelets that typically are present in the atria, and thus predict the stability of an episode and the likelihood that it will fortuitously terminate. Both atrial size and restitution properties (specifically, flat APD and CV restitution) have been indicated in sustaining AF: enlarged atrial size is an independent risk factor for developing AF (Psaty et al., 1997; Vaziri et al., 1994), whereas mapping studies from our group showed that patients with persistent AF have flatter APD and CV restitution curves compared to patients with paroxysmal AF (Narayan et al., 2008), which can lead to differences in fortuitous wave termination by a mechanism suggested by Frame and Simson (1988).

Recent developments in minimally-invasive imaging have made the opportunity for predictive power by computational models of AF even more pronounced. A technique in magnetic resonance imaging known as late gadolinium enhancement (McGann et al., 2008) has allowed for visualization of atrial scars. Computational models including atrial scar determined by this method have already been developed (Krueger et al., 2013; McDowell et al., 2012), but to date, no computational model of AF has knowledge both of the location of AF sources by FIRM and of the locations of atrial scars as determined by late gadolinium-enhanced MRI. Computational models informed with both could better explain phenomena such as spiral wave anchoring and quasi-stable spiral meander with patient-specific knowledge of inexcitable regions; this could clarify whether fibrotic scar anchors spiral waves and gives rise to fractionation of spiral waves, or whether the role of other pathological processes in AF such as ion channel remodeling are responsible for one or both of these phenomena. I am optimistic that computational modeling of AF nearly has the final components required to
propose and test patient-specific therapies of AF with a clear underlying biophysical rationale and, in concert with improved mapping strategies, improve AF therapeutic outcomes.

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References


