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Measures of organization during atrial fibrillation

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Summary. - Atrial fibrillation, a rhythm classically described as totally disorganized, is now recognized to have some structure in its activation. Even though that structure may be very complex, it clearly exists, and researchers continue to try to quantify that structure. One problem with this quantification is that "organization" is an ambiguous term that can have many interpretations. Rather than attempt to impose a particular definition of "organization," this review categorizes the methodologies for quantifying atrial fibrillation organization based on the number of recording channels used in the methods. This method of categorization is not only convenient, but is also descriptive of the different "philosophical" definitions of organization that various researchers have.

Key words: atrial fibrillation, organization, signal processing, non-linear dynamics, mapping.

Riassunto *(Misure di organizzazione durante fibrillazione atriale)*. - La fibrillazione atriale, ritmo classicamente descritto come totalmente non organizzato, è oggi riconosciuta essere caratterizzata da una certa struttura di attivazione. Anche se questa struttura può essere estremamente complessa, chiaramente esiste e i ricercatori continuano i tentativi per una sua descrizione quantitativa. Un problema associato alla ricerca di descrittori quantitativi consiste nell'ambiguità del termine organizzazione, che può avere molte interpretazioni. Piuttosto che un tentativo di identificare una particolare definizione di organizzazione, questa rassegna descrive le metodologie per quantificare l'organizzazione della fibrillazione atriale, raggruppandole in base al numero di segnali endocavitari utilizzati. Questo tipo di classificazione non solo risulta conveniente, ma è anche rappresentativa delle differenti filosofie adottate nella definizione di organizzazione dai vari autori.

Parole chiave: fibrillazione atriale, organizzazione, analisi del segnale, dinamiche non-lineari, mappaggio.

Introduction

Even as recently as a decade ago, a discussion of organization during atrial fibrillation would have seemed obscure, possibly inconsequential, or even patently inappropriate. In fact, for some, "chaotic" and "disorganized" are still considered quintessential characteristics of atrial fibrillation. However, a growing body of work based on both simple observation and more complicated signal processing methods strongly implies that atrial fibrillation is neither entirely "disorganized" nor random at all. In fact, numerous factors such as anatomy, refractoriness or other electrophysiologic parameters, autonomic innervation, etc., should all play some role in "organizing" atrial activation. There have been many methods proposed to quantify organization during atrial fibrillation. While there are many ways to categorize these methods, they are separated here into whether organization is quantified using single-site recordings, two simultaneous recordings, or multiple recordings (i.e. mapping). The number of recordings often implies various practical limitations in using these measures of organization, but it also discerns the almost philosophical differences in how "organization" is interpreted by various investigators.

Single-site measures

Single-site recordings are, by definition, myopic. During a rhythm as complicated and variable as atrial fibrillation, it is extremely difficult to say much, if anything, about distant atrial activity from information obtained locally. However, on a practical level, single-site recordings are the most accessible. Further, when compared to methods used for multiple-site recordings, methods for measuring organization using single-site recordings are often computationally less burdensome. For applications limited by the number of recording leads or by computational power as in basic catheter recordings or in implantable devices, it is likely that single-site recordings and the corresponding measures of organization will be the most accepted. Finally, organization measured using a single electrogram recording is philosophically different from that measured using multiple recordings. That is, since a single-site recording is spatially limited, these measures of organization are measuring temporal relationships and temporal organization. Measures using more than one site can incorporate spatial relationships.

While not directly aimed at quantifying organization, Wells *et al.* [1] published one of the earliest studies examining relative differences in atrial fibrillation

electrograms. From right atrial bipolar electrograms after open-heart surgery, Wells classified atrial fibrillation recordings into 4 categories based on the discreteness of the electrograms and the stability of the baseline. Briefly, type I was characterized by discrete complexes and a stable isoelectric interval; type II allowed for perturbations in the baseline; type III was characterized by neither discrete complexes nor a stable baseline; and type IV was an electrogram recording displaying more than one of the previous 3 types. While not specifically geared at quantifying organization, the authors did associate traits such as "orderly" to type I atrial fibrillation and "chaotic" to type III. The greatest weakness of this method is its subjectivity. That is, as described, the Wells classifications require manual interpretation and over-reading of the epicardial bipolar recordings. Thus, one person may categorize a recording as type I atrial fibrillation, while another may call it type II. This is not to say, however, that more quantitative measures of atrial fibrillation derived from the Wells definitions could not be used to measure organization. For example, measures of cycle length, frequency content, electrogram amplitude distributions, etc. described by others [2-5] could be interpreted as quantifying aspects of the Wells criteria and thus be used as measures of organization. Recently, Barbaro *et al.* have successfully implemented such a strategy [6].

Analyses such as those used by Barbaro are based on "linear" approaches to signal processing. Nonlinear analyses can also be used to evaluate electrograms. Kaplan and Cohen first addressed the question "Is fibrillation chaos?" in 1990 by analyzing surface ECG recordings from dogs [7]. Since then, several others have used various nonlinear measures to quantify ventricular fibrillation [8-12], any of which could easily be applied to analysis of atrial fibrillation. Detailed explanations of these techniques and their calculation are too involved for this manuscript. Suffice it to say, however, that chaos theory and nonlinear dynamics have provided several tools for cardiac signal analysis. In 1995, Hoekstra *et al.* [13] published a nonlinear analysis technique specifically applied to atrial fibrillation electrograms. They analyzed epicardial mapping data obtained from atrial fibrillation patients undergoing surgical correction of an accessory pathway [14].They used measures of *correlation dimension* and *correlation entropy* on the epicardial signals. They found that their measures discriminated between the various types of electrograms as defined by Wells, thus suggesting that nonlinear dynamics plays a role in atrial fibrillation and can also be used to quantify atrial fibrillation organization. However, as pointed out in an accompanying editorial by Osaka *et al.* [15],"it is likely that other types of signal analysis might" discriminate between the three Wells types, implying that linear methods might perform equally well.

Recently, Berkowitsch *et al.* [16] have published an algorithm for analyzing atrial fibrillation recordings using a measure of complexity and symbolic dynamics. This method is very similar to that reported by Zhang *et al.* [11] for discriminating ventricular tachycardia from ventricular fibrillation. This technique uses an information theory measure that can be interpreted as quantifying "redundancies" in signal patterns of the atrial fibrillation electrograms. The more redundancies that are found, the lower the complexity will be. After including some clever signal pre-processing, Berkowitsch used this measure to demonstrate different levels of complexity in different patients, heterogeneous complexity among different regions of the atria, and changes in complexity after administration of propafenone. One potential advantage of this method is that, while it is a nonlinear measure of complexity, it is a very computationally efficient method.

An algorithm to quantify consistencies in activation direction during atrial fibrillation using multiple recordings from a single site has been described by Gerstenfeld *et al.* [17] and later expanded upon by Schoenwald *et al.* [18]. This technique involved measuring electrograms from three orthogonal bipoles that were mounted on a single catheter. Gerstenfeld derived the activation direction from vector loops, which were in turn generated from the simultaneous and orthogonal electrograms. Using a statistical argument, they reasoned that the similarities in activation direction for successive activations could not be random, and termed this phenomenon "linking" during atrial fibrillation. Schoenwald extended this analysis to longer segments of linking during atrial fibrillation and suggested that local properties of atrial tissue constrain activation. The concept of observing activation direction consistencies over time is similar to that described by Damle *et al.* [19] for ventricular fibrillation using two-dimensional cardiac mapping tools. While these papers do not directly use this measure to categorize different types of atrial fibrillation according to organization, it is obvious that such a study could be undertaken.

Measures between two sites

Since single-site measures are inherently limited, it would seem logical to attempt defining measures using more than one site. In a philosophical sense, measures of atrial fibrillation organization between two sites imply that activity at one site should be judged in relation to activity at another site. While absolute temporal behavior at a site is still important, these measures emphasize the relative temporal behavior between two sites (Fig. 1).

When distances between the recording sites are known, and especially when more than two sites are used to compute the organization, spatial organization concepts are also incorporated into these measures.

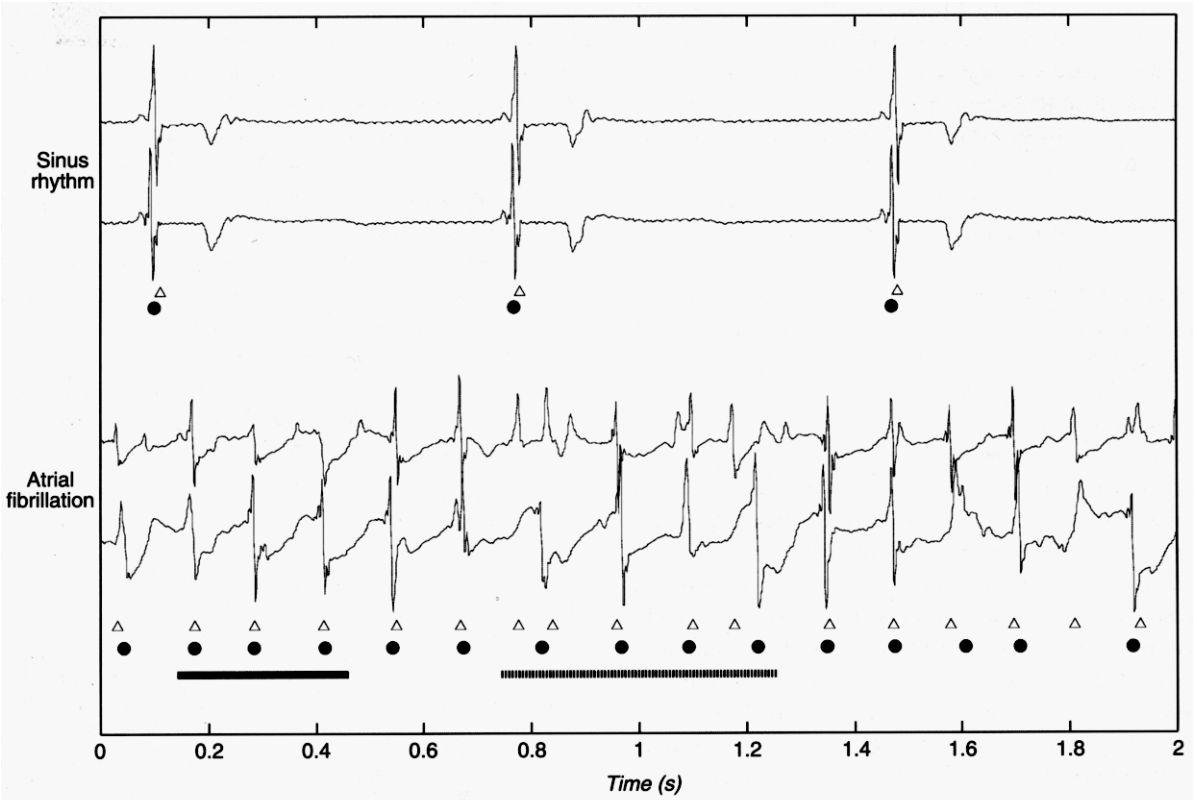

Fig. 1. - Relative relationships between simultaneous atrial recordings. The solid bar indicates relative synchrony of activation during atrial fibrillation, while the dashed bar shows asynchrony. Reproduced with kind permission from [31] (© 1999 IEEE).

In 1989, Ropella *et al.* [20] published a spectral technique that was initially used to discriminate between fibrillatory and non-fibrillatory rhythms. Later, they quantified relative levels of organization with this technique [21]. This spectral measure, called the coherence spectrum, has also been used by others in cardiac mapping applications [22-24] and evaluating drug effects during ventricular fibrillation [25, 26]. The coherence spectrum is a normalized cross-spectral measure between two signals and is defined as

$$\frac{|S_{XY}(f)|^2}{S_{XX}(f) \cdot S_{YY}(f)}$$

where X and Y are any two signals, and S is the auto- or cross-power spectra of the signals. In general terms, this is often considered a measure of synchronicity between the two signals but can also be shown to be a measure of how well the two signals are related by a linear transfer function. To reduce this measure of organization to a single number, the coherence spectrum is often averaged over frequency to obtain a mean coherence. This mean coherence is bounded between 0 and 1, where 1 indicates that the two signals are perfectly related by a linear transfer function, and 0 indicates that the signals are "perfectly" unrelated by any linear transfer function. One weakness of the coherence method is the temporal resolution implied in calculating the spectral components, S_{XY}, S_{XX}, and S_{YY}. In Ropella's original paper, the temporal resolution was approximately 4 seconds. While this resolution could be described as a unique way of summarizing 4 seconds of atrial fibrillation, the coarseness of this technique limits its applicability, especially when considering timed therapies like a timed defibrillation shock. Subsequent work by Lovett and Ropella [27] resolved the temporal resolution issue by computing a coherence time-frequency distribution that theoretically has a sample-by-sample resolution. This high-resolution coherence spectra, however, is not easily computable in real-time, thus again limiting its overall applicability.

Botteron and Smith have described a method for analyzing spatial organization during atrial fibrillation by comparing multiple bipolar signals from catheter recordings [28-30]. In their method, each of the bipolar signals is band-pass filtered, rectified, and low-pass filtered. After segmenting the signals to contain 10-12 activations per segment, each segment is then normalized to obtain a unit-energy signal. This signal is then proportional to the amplitude of the high-frequency components in the original signal. The cross-correlation is then calculated between pairs of the pre-processed signals, and the maximum of the cross-correlation is taken as a measure of organization for that pair. The astute reader will recognize that the cross-correlation of the Botteron and Smith method should be closely related to the cross-spectral component of the coherence

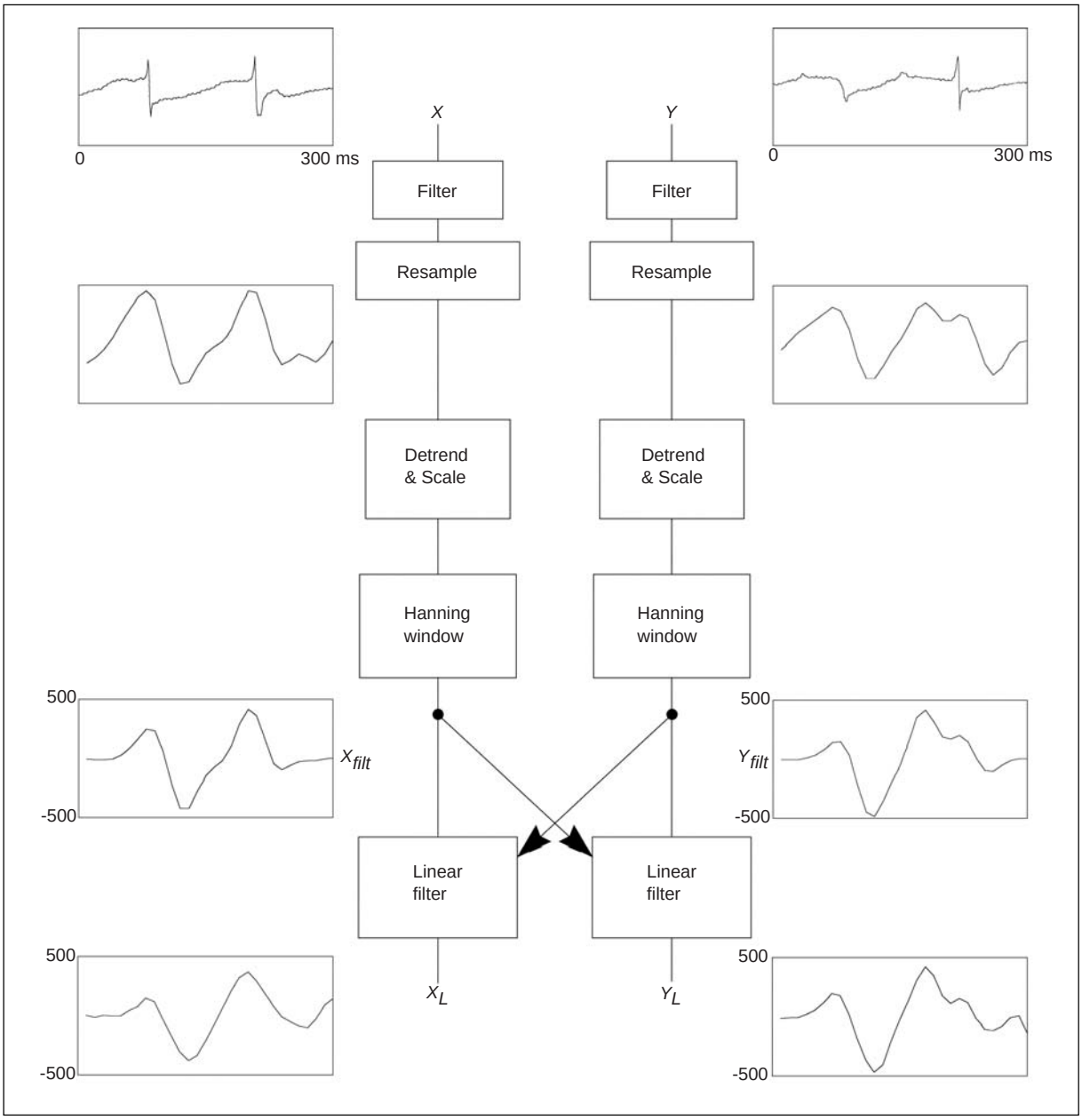

Fig. 2. - An example algorithm for measuring organization between two sites. Reproduced with kind permission from [31] (© 1999 IEEE).

function. While different degrees of signal conditioning and pre-processing distinguish the two methods, both methods do quantify the linearity between the two signals and may, in fact, yield very similar results when measuring organization. One key advantage of this method over others is its relative computational simplicity. A disadvantage, however, is the parsing required. That is, according to their methods, the data is segmented such that each segment contains 10-12 activations. One might attempt to estimate the average rate, then preset the segment length to encompass the required 10-12 activations. However, changes in rate or extreme variability in rate will violate this segmentation scheme.

Recently, Sih *et al.* [31] have published an algorithm that measures synchronicity between two sites and then compared the performance of this algorithm to coherence and the algorithm proposed by Botteron and Smith. This algorithm also quantifies linear relationships between two sites, but does so using adaptive filters. Briefly, after filtering and scaling short segments (300 ms) of atrial fibrillation electrograms, the electrograms were passed through two parallel, linear adaptive filters (Fig. 2). One way of interpreting an adaptive filter is that it attempts to predict one electrogram through linear filtering of a second electrogram. If the two electrograms are linearly related, then the prediction process would theoretically

be perfect. However, if there are non-linearities between the electrograms, the adaptive filter would yield a prediction error. The algorithm used by Sih *et al.* defines organization according to the prediction errors from the parallel adaptive filters. The algorithm was shown to compare favorably to coherence calculations and to the Botteron and Smith algorithm, but with a theoretically finer temporal resolution. The algorithm could also be implemented in a real-time computing environment and was theoretically extensible to account for non-linear relationships between electrograms by simply altering the nature of the adaptive filters. This group recently used the algorithm to quantify organization differences between acute and chronic models of atrial fibrillation [32]. Because this algorithm is slightly more difficult to implement than other published methods, its broader acceptance may be limited.

Very recently, Censi *et al.* [33] have quantified organization between two electrograms using a technique known as *recurrence plotting*. As described in their manuscript, a recurrence plot is generated by calculating the normalized distance between points $[x(t_1), y(t_1)]$ and $[x(t_2), y(t_2)]$, and if that distance is sufficiently small, a dot is plotted on a two-dimensional domain (t_1, t_2). In their application, x and y are the sequences of activation intervals (cycle lengths) for two atrial sites during atrial fibrillation, and t_1 and t_2 are time variables. A recurrent point thus indicates that the interaction between x and y at t_1 is the same as the interaction at t_2. This technique still yields a complex two-dimensional plot that needs further parameterization. They defined a measure of the *percent determinism* that quantified the duration of "stable" recurrence patterns, as well as a measure of *entropy* in the recurrence plots. The authors then used these measures on the atrial fibrillation cycle length data and compared it to "manufactured" data that had identical linear statistical properties. Their data suggested that there may exist non-linear relationships between electrograms from the right versus the left atrium that would otherwise be missed by algorithms relying on linear analyses. This analysis technique, while free of some of the constraints that other measures using two electrograms have, is still very computationally intensive and clearly can only be performed offline.

Multi-electrode measures

Cardiac mapping tools have brought a wealth of information to cardiac electrophysiology. These tools have also implied a need for sophisticated analysis of this data, especially for atrial fibrillation. With such a large amount of information to draw upon, measures of organization can take on very diverse forms. Through all the diversity, however, the concept of a combined spatial and temporal organization is most easily realized. The greatest weakness of multi-electrode measures is the high overhead needed to acquire and process the data. Many of these techniques were originally investigated using in vitro or epicardial mapping systems. While the analysis techniques could be used with newer catheter based mapping systems, these systems are still not widely available. Also, it is unclear if the analysis and computation requirements make these methods impractical beyond the research setting.

Similar to the Wells criteria using single bipolar recordings, Konings *et al.* [14] categorized atrial fibrillation using epicardial mapping techniques in Wolff-Parkinson-White syndrome patients. In this study, patients undergoing open-chest surgery were epicardially mapped using a 244-channel mapping system and a circularly shaped mapping plaque (diameter, 3.6 cm). After determination of activation times and mapping isochrones, they categorized activation patterns during atrial fibrillation according to wave front characteristics and the prevalence of block. Like Wells, Konings defined 3 basic types of activation patterns. Type I has single broad wave fronts that propagated without significant

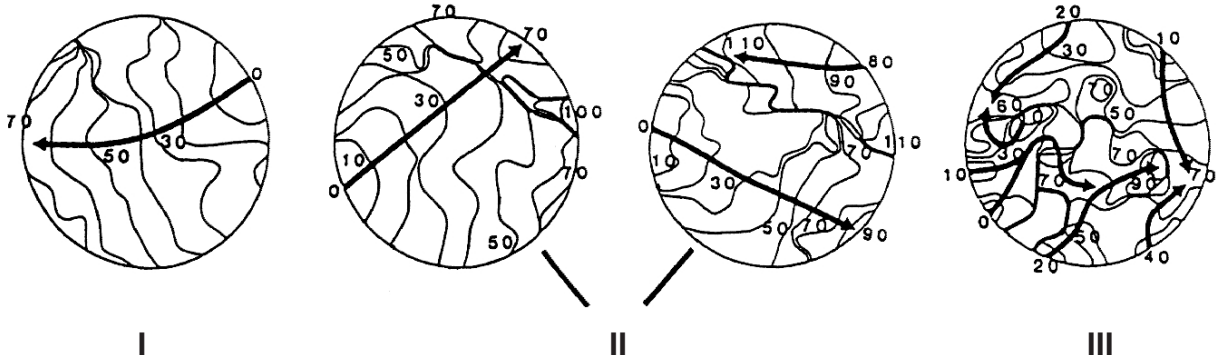

Fig. 3. - Example activation maps demonstrating different categories of Konings type activations. Reproduced with kind permission from [14].

conduction delay. Type II has either one wavelet with "considerable" conduction block or slow conduction, or it has two wavelets. Type III has three or more wavelets with slow conduction and multiple arcs of block. Examples of these types of activation patterns are shown in Fig. 3. While not immediately apparent, this method has several levels of manual interpretation. Activation times must be discerned from the recorded electrograms. While computer based algorithms and rules can be applied to delineate activation times, these rules are not perfect, especially during atrial fibrillation, and manual over-reading of activation times is necessary. Once the activation times are delineated, two-dimensional activation maps must be determined. Without a sufficiently dense array of electrodes, delineating unambiguous activation maps and then determining wavelet characteristics by hand can be problematic. For example, at what point do two merging wavelets become one? How do you track a wavelet once it has passed beyond the mapped region? Regardless of its limitations however, this work clearly demonstrates that not all atrial fibrillation is alike and that subjective notions of activation organization are mechanistically relevant.

For ventricular fibrillation, Rodgers *et al.* [34, 35] have more rigorously quantified wave front characteristics from epicardial mapping data. In these papers, they define an algorithm for quantifying the dimensions of wavelets as well as to observe recurrent patterns of activation. One clear advantage of their methods was that it made direct and fairly objective measurements of wavelets and activation. Unfortunately, this method may require a substantial number of electrodes for mapping (~ 500) with a very tight inter-electrode spacing (1 mm). While impractical for most laboratories to implement in its current rendition, Rodgers *et al.* were able to use their measures to derive a simple and relatively direct measure of the reproducibility of wave front activation during ventricular fibrillation. If their techniques could be adapted to less invasive mapping tools that are now becoming available and if their methods could be implemented for real-time analysis, then this could be a powerful tool for analyzing atrial fibrillation.

Another mapping analysis tool for analyzing organization during ventricular fibrillation was described by Bayly *et al.* [36, 37]. Using a 22 x 23 array of electrodes that had a 1.12 mm inter-electrode spacing, Bayly took one-second blocks of data during ventricular fibrillation and performed a spatial correlation function. The two-dimensional spatial correlation function is entirely analogous to the one-dimensional auto-correlation function. That is, for a general function of time and space, $g(t,\vec{\alpha})$, the spatial correlation function is:

$$R(d\vec{\alpha}) = E\left\{g(t,\vec{\alpha})g(t,\vec{\alpha}+d\vec{\alpha})\right\}$$

where $\vec{\alpha}$ is a two-dimensional vector representing the spatial components and *E* denotes the ensemble average. In Bayly's application, the function *g* represents a 1-second epoch of data from the electrodes in the array. So, if adjacent electrodes record similar activity, spatial correlation should be high, while if adjacent electrodes are unrelated, the spatial correlation will be low. Using this method, Bayly demonstrated that the spatial correlation initially decreased after ventricular fibrillation induction, but then partially normalized within the first minute. One limitation of this method is that it is calculated for a broad region of tissue, in this case a region ~ 2.5 cm x 2.5 cm. For atrial fibrillation, it is unknown if spatial organization has a finer resolution than 2.5 cm x 2.5 cm. The performance of this algorithm, both for real-time analysis and for higher resolutions, has not yet been evaluated.

Bayly *et al.* [38] published another method for predicting patterns in epicardial mapping data during ventricular fibrillation, which could be extended as a technique to quantify organization. This technique uses auto-regressive (AR) modeling to predict the linear components of unipolar epicardial electrograms during fibrillation. They compared AR modeling on individual electrograms to AR modeling that used contextual, spatial information inherent in mapping. That is, to use the spatial information, they first decomposed the mapping data using Karhunen-Loeve kernels and applied the AR modeling to a "reduced" set of kernels. The method of AR modeling on the individual electrograms, which in the context of this review could be considered as a single-site measurement, did not on average differ substantially from the more refined method with the Karhunen-Loeve decomposition. However, they note that AR prediction on an individual electrogram "fails badly when [the] electrogram is very complex." If one quantifies organization as predictability, it is obvious how one might apply this algorithm to measure organization during atrial fibrillation. While more complicated, this technique could be extended to incorporate non-linear modeling schemes to enhance its sensitivity. The output of an AR model is fairly easy to calculate and could easily be generated in real-time provided that the model parameters were calculated *a priori*. However, with fibrillation, it is unlikely that *a priori* model parameters would remain valid for long durations due to the inherent non-stationarity of the fibrillatory process.

A less mathematical definition of organization has been used by Roithinger *et al.* [39, 40] with multi-electrode catheter recordings. Knowing the inter-electrode spacing of bipoles on their catheters, they defined organized activation during atrial fibrillation as the presence of "discrete atrial complexes, separated by an isoelectric baseline, with a constant activation sequence, …during three or more cycles over at least 3 cm". While certainly a reasonable definition, the criterion of at least three cycles over at least 3 cm is somewhat arbitrary. Further, gradations in organization are not accounted for with this definition. That is, the activation

sequence is categorized as either "organized" or "disorganized" without accounting for intermediate levels of organization (though such gradations can easily be defined through logical extensions of the original definitions). Nonetheless, with this retrospective, off-line analysis technique, Roithinger was able to make intriguing observations on the transition between atrial fibrillation and atrial flutter [39], as well as local patterns of organization during atrial fibrillation that resembled flutter-like patterns in the right atrium [40].

In the past few years, there have been several publications that analyze aspects of fibrillation using *in vitro* models and optical mapping techniques. Optical mapping yields repolarization data and high spatial resolution recordings during atrial fibrillation. In various animal models of ventricular fibrillation, Gray *et al.* [41] used spatial phase mapping to identify rotor behavior during fibrillatory activation. Phase was calculated by taking each optical fluorescence signal and plotting it versus a time-shifted version of itself. This type of plot is referred to as a *phase portrait*. These phase portraits could take on the shape of loops, and the angle relative to the center of these loops could then be tracked over time and plotted over the mapped region. Gray showed that rotors and their formation and annihilation could be tracked with these phase maps. Thus, phase maps allow one to quantify activation in terms of the rotors and their behavior, which in turn can be used as measures of complexity and organization during fibrillation.

Others have also analyzed optical maps during atrial fibrillation to reveal aspects of organized activation. Skanes *et al.* [42] and Berenfeld *et al.* [43] have used the dominant frequency of activation to investigate atrial fibrillation mechanisms. To define the dominant frequency, the optical signals are processed using straightforward Fourier analysis, and the frequency that contains the greatest power is defined as the dominant frequency. Skanes then correlated dominant frequency measures to activation rates and patterns from their optical maps. Consistent with earlier observations using orthogonal bipolar recordings [17, 18] Skanes observed consistencies in activation direction over multiple cycles during atrial fibrillation. Further, the frequency observed in the activation maps correlated to the dominant frequencies calculated using Fourier analysis. They conclude that the source or sources of the periodic activations were likely the dominant source of activity maintaining atrial fibrillation. Berenfeld extended these observations by calculating the dominant frequency from each optical signal and then plotting it over the mapped region. They observed that different dominant frequencies can be found over the atria and that identical dominant frequencies are often spatially contiguous. These domains with distinct dominant frequencies furthered their arguments for spatio-temporal organization during atrial fibrillation. One potential weakness of their arguments, however, is that multiple parameters could influence the dominant frequency and its characteristics. It is unclear if, e.g. anatomy, innervation, refractoriness, or some other physiologic parameter is modulating or regulating the dominant frequencies. Further, such modulators may influence the activation and dominant frequencies regardless of the nature of the source or sources of the fibrillation.

Conclusions

Clearly, there are many ways to measure organization during atrial fibrillation. A valid question is whether any one method is better than the others. Unfortunately, this question is impossible to answer by the very nature of the question. That is, "organization" is a nebulous concept that is riddled with subjectivity. Is organization the temporal regularity of atrial activation? Is it similar electrogram morphologies in a set epoch of time? Is it synchronicity/chronicity between different locations? Is it the degree to which the electrogram can be predicted from past knowledge? Since "organization" is such a labile term, the answer to all these questions is "yes." In many ways, the questions that have been answered by these algorithms have not been "How organized is it?" but rather "How is it organized?". With such ambiguity, one cannot choose the optimal algorithm.

Rather than try to select an algorithm based on how it categorizes atrial fibrillation, we can instead set different criteria. Measures of organization may instead be selected based on their utility. That is, can a measure of organization be practically applied to affect therapy for atrial fibrillation in some way? It has long been suggested that defibrillation shocks, entrainment stimuli, ablation lesions, or pharmacologic therapy might be more efficacious if accompanied by measures of organization. Measures of organization might then be optimized to within a certain therapy modality.

On a more theoretical level, a measure of organization that can be used to fundamentally enhance our understanding of the basic mechanisms of atrial fibrillation should also be pursued. This is perhaps the more daunting task, as it requires careful and thoughtful observation on the atrial activity. It also demands that we come up with creative and rigorous methods of "prospectively" testing these algorithms to confirm which aspects affecting atrial fibrillation are the most important to the algorithm.

As a final *caveat*, we must guard ourselves from manufacturing measures of organization simply for the sake of doing so. As interest in atrial fibrillation gathers momentum in the broader scientific community, more measures of organization will crop up. However, these additional measures may not add any value to our understanding of the rhythm if they only quantify the

raw signals in a different way. Clearly, if one "churns the data" hard enough, one can find relationships that could be construed as representing "organization". Measures of organization that cannot be related to the underlying mechanisms or cannot be applied in some practical sense risk being marginalized as "just more number crunching". Since several papers have demonstrated a tangible meaning for organization of atrial fibrillation, we must strive for more than just new algorithms.

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