Methodology Considerations in Phase Mapping of Human Cardiac Arrhythmias

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Background—Phase analysis of cardiac arrhythmias, particularly atrial fibrillation, has gained interest because of the ability to detect organized stable drivers (rotors) and target them for therapy. However, the lack of methodology details in publications on the topic has resulted in ongoing debate over the phase mapping technique. By comparing phase maps and activation maps, we examined advantages and limitations of phase mapping.

Methods and Results—Seven subjects were enrolled. We generated phase maps and activation maps from electrocardiographic imaging–reconstructed epicardial unipolar electrograms. For ventricular signals, phase was computed with (1) pseudoempirical mode decomposition detrending and (2) a novel Moving Average (MVG) detrending approach. For atrial fibrillation signals, MVG was modified to incorporate dynamic cycle length (DCL) changes (MVG-DCL). Phase maps were visually analyzed to study phase singularity points and rotors. Results show that phase is sensitive to cycle length choice, a limitation that was addressed by the MVG-DCL algorithm. MVG-DCL was optimal for atrial fibrillation analysis. Phase maps helped to highlight high-curvature wavefronts and rotors. However, for some activation patterns, phase generated nonrotational singularity points and false rotors.

Conclusions—Phase mapping computes singularity points and visually highlights rotors. As such, it can help to provide a clearer picture of the spatiotemporal activation characteristics during atrial fibrillation. However, it is advisable to incorporate electrogram characteristics and the time-domain activation sequence in the analysis, to prevent misinterpretation and false rotor detection. Therefore, for mapping complex arrhythmias, a combined time-domain activation and phase mapping with variable cycle length seems to be the most reliable method. (Circ Arrhythm Electrophysiol. 2016;9:e004409. DOI: 10.1161/CIRCEP.116.004409.)

Key Words: atrial fibrillation ■ cardiac arrhythmias ■ electrocardiography ■ phase mapping

Characterization of spatiotemporal dynamics during cardiac fibrillation, particularly atrial fibrillation (AF), has been the subject of studies in many laboratories that have attempted to elucidate mechanisms and identify targets for therapy. This goal requires techniques, in addition to electrogram-based activation mapping, for determining the sequence of excitation and characterizing wavefront properties. Activation mapping, commonly used for determining the origin and pattern of excitation, assigns a specific time point on the unipolar electrogram (time of steepest negative deflection), as the marker of local activation. However, during fibrillation, information in electrograms is often ambiguous; the electrograms can contain multiple sharp deflections and, because of their low amplitude, they are prone to artifacts. Consequently, the electrogram is often transformed into the frequency domain. However, frequency domain mapping produces time-averaged frequency information over space, thereby losing the ability to track temporal variations of the signal. A third parameter that has been used to characterize a temporal signal is its instantaneous phase.1 Phase is a measure of where in its cycle of oscillation a signal is at a given point in time. Phase mapping computes oscillations in the signal over its entire duration, independent of its amplitude. Therefore, analysis of phase changes over space provides information on the patterns of organization (repetitive activity) and helps to assess their stability in time and space. This approach can be particularly useful during fibrillation. Phase mapping can help identify circulating wavefronts (rotors)1 that rotate about phase singularity points (core) composed of unexcited but excitable tissue.2

Phase analysis of cardiac fibrillation and the concept of cardiac rotors and spiral waves were introduced by Winfree.3 The experimental evidence for rotors in cardiac tissue was reported by Davidenko et al.4 Gray et al5 applied this concept...
WHAT IS KNOWN

- Phase mapping has suggested that stable rotors sustain human atrial fibrillation (AF).
- However, details of some electrogram-based phase mapping methods have not been completely described, and rotor-based ablation has achieved mixed outcomes in terminating AF.

WHAT THE STUDY ADDS

- This study develops a robust phase mapping method for analyzing cardiac electrograms in the presence of spatiotemporal cycle length variations as occur during AF, generating maps that are mostly consistent with activation time maps.
- Phase mapping highlights rotational wave fronts (rotors) and determines their center of rotation (singularity point) using a precise mathematical definition and properties that can facilitate analysis of wavefront dynamics during complex arrhythmias.
- However, phase mapping has the propensity to introduce false rotors during complex activation patterns, such as wavefront propagation about a line of block, suggesting that a combined approach using both time-domain activation maps and phase maps would improve the accuracy.

Contact electrograms with good results, but their approach assumed local stability of CL over a period of time.

Our goals for this project were (1) to introduce and assess a novel signal detrending approach that is less dependent on electrogram morphology and fluctuations, and can account for spatial and temporal CL variability during fibrillation, (2) to perform phase analysis on ventricular and atrial unipolar electrograms reconstructed by electrocardiographic imaging (ECGI), and (3) to shed light on the advantages and limitations of phase mapping and its relation to activation mapping, thereby addressing issues that can affect phase computation and interpretation. This project is not intended to study the mechanisms of fibrillation but to use selective examples to evaluate the properties of phase mapping.

Methods

Before analyzing fibrillatory rhythms, we generated phase maps in nonfibrillatory rhythms, to better understand the effects of CL and detrending on phase analysis. The following 7 subjects were studied, providing examples of various rhythms: 2 patients with ventricular tachycardia (focal and reentrant), a patient with typical right atrial flutter, a paroxysmal AF patient during normal sinus rhythm, and 3 persistent AF patients. All participants underwent ECGI at Washington University in St. Louis/Barnes Jewish Hospital. All subjects signed a written informed consent, and all protocols were reviewed and approved by the Human Research Protection Office at Washington University in St. Louis.

Signal Processing

The ECGI methodology, developed in our laboratory, is described in previous publications and briefly in the Data Supplement. Epicardial potentials and unipolar electrograms are reconstructed from the measured body surface potential and patient-specific heart–torso geometry. These data can be used to generate activation and repolarization maps in the time domain. The data could also be analyzed to create phase maps in the phase domain. In this study, we compare the 2 forms of analysis. Figure 1 shows the workflow for phase mapping and its comparison to time-domain activation mapping. Time-domain activation mapping methods are summarized in the Data Supplement; Figure S1 in the Data Supplement illustrates how activation time (AT) is computed using the wavelet transform algorithm. Phase mapping methodology is described below.

High-curvature wavefronts were classified as follows:

1. Complete rotors: wavefronts completing at least one 360° rotation about a stationary or meandering singularity point (rotor core, composed of unexcited but excitable tissue).
2. Incomplete or partial rotors: high-curvature waves that do not complete a full rotation because of wave break or collision with other wavefronts.
3. Reentry: wavefronts rotating around an inexorable (anatomic) barrier.

Phase Mapping

The time dependence of phase 0 of an electrogram represents its repetition over time; it is computed as follows:

$$\theta(t) = \tan^{-1}\left[\frac{V_r(t)/V_r(t)}{V_r(t)}\right]$$

where $$V(t)$$ is the unipolar epicardial electrogram; $$V_r(t)$$ is a phase-shifted version of $$V(t)$$; and $$\tan^{-1}$$ indicates the inverse of the tangent function. In this study, HT was used to obtain $$V_r(t)$$, as it has been shown to be the most robust and therefore the most commonly used technique.
Input Signal Conditioning (Detrending)

We first evaluated the pEMD method6 of detrending. We applied this technique to reconstructed unipolar epicardial electrograms during monomorphic ventricular tachycardia (with the following desirable properties: high signal/noise ratio, propagation pattern known from invasive mapping during a previous study,17 and a fixed CL) and compared the resulting phase progression with the time-domain activation isochrones.

We also applied and evaluated the Moving Average (MVG) method,19 which involves detrending each signal $V_s(t)$ by subtracting the average of the entire signal over a sliding window of specific length:

$$V_s'(t) = V_s(t) - \text{average}[V_s(t)], \quad (2)$$

where $n$ is number of windows that cover the entire signal.

We compared the effects of these 2 detrending methods on phase computation of epicardial signals during ventricular tachycardia.

During a more complex arrhythmia such as AF, there is spatial variability in CL throughout the atria (Figure S5 in the Data Supplement), which limits the use of methods that rely on a single CL for all locations. For the purpose of phase analysis of atrial signals, we introduced a modification of the MVG detrending method to estimate the CL at each epicardial node independent of its neighbors, so that the phase computation is unaffected by spatial CL fluctuations. Complex arrhythmias such as AF may not only have spatial variability in CL across the atria but also multiple CLs instead of a single dominant CL at each location. This is reflected in the power spectrum of the signal, which contains multiple peaks. Some of these peaks can also result from noise. Therefore, it is difficult to compute reliably a single dominant CL (or equivalently single dominant frequency [DF]) during AF.

For an accurate phase computation during AF, the majority of CLs (or frequencies) present in the signal at each atrial region should be included in the analysis. We compute $f_{HRIF}$ (highest regularity index frequency) as the upper limit of frequencies that contribute 90% of the total signal power between 3 and 50 Hz. Using 90% of the power spectrum ensures that all significant frequency contributions are included. The MVG filter has a slow roll-off in the frequency domain19 and retains frequencies up to twice the input frequency $f_{HRIF}$ in our case). Therefore, we divide $f_{HRIF}$ by 2 to attenuate high frequencies above 90% of the spectrum, thereby eliminating noise contamination of the signal. Figure S2 in the Data Supplement illustrates how phase is computed using the HRIF algorithm.

We then use $f_{HRIF}$ computed over an R–R interval, to obtain the normalized sampling frequency (NSF) of the signal at each node as follows:

$$\text{NSF} = f_s / 0.5 \cdot f_{HRIF}, \quad (3)$$

where $f_s$ is the sampling frequency =2 kHz.

For each epicardial electrogram, the average of the signal was computed over a sliding window with a window length =1/NSF (calculated in Equation 3). This average was subtracted from the original signal $V(t)$ to obtain the detrended signal $V(t)$. We used this modified technique for AF signals.

In all approaches, the instantaneous phase 0 was computed using the following equation:

$$\theta(t) = \tan^{-1}\left[\text{HT}(V'(t))/\text{HT}(V(t))\right], \quad (4)$$

where $\text{HT}$ is the Hilbert Transform of the detrended signal $V(t)$. Equation 4 can be expressed as follows:

$$\theta(t) = \tan^{-1}\left[	ext{imag}(\text{HT}(V'(t)))/\text{real}(\text{HT}(V'(t)))\right] \quad (5)$$

Note that this is the standard formulation, commonly used and found in toolboxes.

Identification of Phase Singularity Points

The instantaneous phase was plotted over time for all the sites on the epicardium. This resulted in a dynamic phase movie showing the spatial phase distribution for each instance of time within 1 activation cycle. The phase values were color coded, and surrogates of the depolarization and repolarization wavefronts were computed from the isofrequency values equal to $-\pi$ (blue) and $\pi$ (red), respectively. From this movie, a phase singularity point was determined as a site, where all the phases converge and the surrounding elements exhibit a continuous progression of phase that is equal to $\pm 2\pi$.20

The dynamic phase movie was visually analyzed to determine the phase progression of high-curvature wavefronts on the epicardium.
Activation Time Map Derived From Phase

For any given time instance, the epicardial phase map shows the phase of each epicardial signal by assigning it a value between $-\pi$ and $\pi$ radians. The time instance when the phase transitions from $\pi$ to $-\pi$ (sharp discontinuities in the bottom row of Figure S2 in the Data Supplement) indicates the beginning of the next phase cycle. The wavefront AT corresponds to $0.5\pi$ radians in the phase plot, as explained in Section 1c in the Data Supplement. When phase is computed using (Equation 5), the time instances of phase discontinuities occurring at the minima of the signal (Figure S2 in the Data Supplement). For each epicardial site, a matrix containing time series of 1 and 0 was created, with value of 1 indicating time instances at which that site was at phase=0.5\pi radians (phase-derived AT). A dynamic activation movie was made for all sites on the epicardium for the duration of the analysis. This movie showed the propagation of the epicardial activation wavefront, computed from phase, during an arrhythmia. It was compared with the epicardial activation wavefront computed directly from ATs on the electrograms.

Results

The effects of input signal conditioning and CL on phase analysis are presented in the Data Supplement (Figures S3 and S4 in the Data Supplement).

Application of the Dynamic CL MVG Method for Atrial Arrhythmias

Figure S5 in the Data Supplement compares the atrial CL distribution computed using the HRIF algorithm (Equation 3) in 2 patients during 1 beat of atrial flutter (A) and AF (B), respectively. The CL distribution across the atria is fairly uniform in the case of atrial flutter, with a narrow range of values (200–290 ms) demonstrating greater organization than AF and a unique CL. However, during AF, the CL values exhibit spatial heterogeneity (shorter CL in LA compared with RA) with a wider range of values (80–200 ms). Because CL exhibits its spatial and beat-to-beat (not shown) variability during AF, use of a fixed CL value can lead to errors in phase computation. Movie 3 in the Data Supplement shows an example of a phase map constructed during 245 ms of human AF activity using fixed CL (left) and dynamic CL (right). The dynamic CL phase map highlights a singularity point meandering over the posterior LA and a high-curvature wavefront rotating in the counterclockwise direction. The rotor is not clearly seen in the fixed CL phase map. In addition, the phase progression (left) is less stable when computed using fixed CL.

Comparison of Phase-Derived Activation and Wavelet-Based Activation During Persistent AF

Figure 2 shows the time-domain biatrial epicardial activation sequence during AF, reconstructed by ECGI with wavelet analysis. The corresponding lead V2 of the body surface ECG indicates the interval chosen for analysis. The maps show the activation fronts (red) for a selected duration of 166 ms (red rectangle on the ECG) using 16 frames. White arrows show direction of propagation. Black arrows indicate transition between frames. Epicardial activation initiates from a breakthrough (RS morphology of the local electrogram) near the right inferior pulmonary vein (RIPV) on the posterior left atrium (LA; $t=145$ ms). The wavefront propagates toward the RIPV ($t=150$ ms) and breaks along the septum, resulting in 2 branches. The superior branch activates the LA as it rotates counterclockwise over the LA. Across the septum, the wavefront propagates along the lateral wall of the right atrium (RA) in a clockwise direction. The 2 wavefronts return to the septal region, where they collide ($t=216$ ms) and terminate. A new wavefront, continuing from the crista terminalis, propagates along the floor of the RA ($t=245$ ms) toward the septum. This wave breaks on the septum, resulting in 2 branches, propagating in a clockwise direction over the LA and RA. The 2 branches join near the septum ($t=312$ ms). The activation maps show complex patterns and multiple mechanisms (breakthrough, wave breaks and collisions, and rotating wavefronts) during 166 ms of persistent AF in a patient.

Figure 3 shows maps for 45 ms of atrial activity selected from Figure 2 (with a slightly different view to better show the rotor in phase map). The top map in each frame shows the time-domain activation sequence ($t=266–308$ ms of Figure 2). The sequence shows a wavefront propagating along the posterolateral LA with clockwise rotation, which then meets another wavefront from RA on the septum ($t=308$ ms). The corresponding phase maps (middle map in each frame) were obtained using MVG detrending with dynamic CL and HT for 502 sites on the LA and 502 sites on the RA. The maps show that the overall progression of phase (blue–red boundary) is consistent with the time-domain activation pattern. In addition, the phase maps indicate the presence of a phase singularity point on the inferior LA (black dot). Phase progression over the LA shows a clockwise rotation about the singularity point that does not complete 360° (a partial rotor). During the same time period, the phase progression on the RA shows a high-curvature wavefront along the lateral wall. This wavefront merges with the LA partial rotor along the septum. The bottom map in each frame shows the activation maps derived from the phase maps. The phase-derived activation maps are consistent with the time-domain activation maps for each time instance. Although the rotational wavefront can be inferred from the activation maps (top and bottom rows), the colors of the phase map emphasize the phase singularity point and the curvature of the rotor more clearly (middle rows).

Figure 4 shows 170 ms of atrial activity for another patient with persistent AF. Time-domain activation (top maps), corresponding phase progression (middle maps), and phase-derived activation (bottom maps) are shown for 6 time instances (frames). The time-domain activation maps show that the activation wavefront (red) propagates along the posterolateral wall of the RA and proceeds to activate the posterior LA across the septum ($t=4–40$ ms). It evolves into a broad wavefront that encompasses both atria and rotates in the clockwise direction ($t=75$ and 110 ms). At $t=170$ ms, activation returns to the initiation site to complete the circuit. The phase maps (middle rows of each column) show the corresponding phase progression (blue–red boundary) across the atria during the same time period. In addition, the phase maps show the presence of a phase singularity point (black dot) in the posterior RA and a rotor (white arrows) that rotates about it in the clockwise direction, completing 1 full rotation (360°). The singularity point meanders over the posterior RA. The ECGI panoramic mapping captures the overall dynamics of the wavefront as it spans both atria.
activation sequence (bottom rows of each column) is consistent with the wavelet-based activation sequence (top rows). The phase map visually highlights the location of the singularity point (where all colors touch), and the rotor is visualized more clearly than in the wavelet-based activation map and the phase-derived activation map.

**Misinterpretation of Phase Maps**
Phase maps highlight curvature of the activation wavefront. As demonstrated in the examples above, this property helps to identify rotors. However, it can also introduce bias toward rotor detection, examples are provided below.

**Normal Sinus Rhythm**
Figure 5 shows the time-domain activation map (Figure 5A) and corresponding phase map (Figure 5B) for 6 time instances during 1 beat of sinus rhythm atrial activation. Lead V2 for 4 consecutive beats shows the underlying normal rhythm. The activation maps show a normal activation pattern with the wavefront originating from the sinus node, curving along posterior RA (t=20 ms), activating the RA (t=55–86 ms) followed by LA activation (t=100 ms). The LA appendage is the latest region to activate (t=140 ms). This curvature of the activation front along the RA wall is also shown in the phase map. However, snapshots of the phase map at time instances 55, 70, and 86 ms identify a phase singularity point (black dot) and a rotational phase pattern (white arrow) about it. The existence of the phase singularity point implicates a rotor in the RA, although the activation wavefront does not become a rotor. Therefore, interpretation of these phase maps in isolation, without referring to the activation map, could lead to false identification of a rotor.

**Lines of Block and Sequential Activation**
Figure 6 shows the activation isochrones map during 1 cycle of typical atrial flutter (Figure 6A; 2 views). The map shows
a typical counterclockwise macroreentrant circuit about the cavotricuspid region (anterior view). This circuit was the driver of the flutter as verified by electrophysiology laboratory results and successful ablation of the cavotricuspid isthmus. This is consistent with the ECGI-reconstructed activation pattern reported previously (Ramanathan et al, their Figure 5b, anterior view). Posterior activation occurs sequentially on 2 sides of a line of block (thick black line) by 2 activation fronts, 1 propagating superiorly (green) and the other inferiorly (blue). However, the phase map (Figure 6B) shows a complete rotor (white arrow) rotating about a singularity point (black dot) with a clockwise chirality on the posterior RA. This example demonstrates that sequential activation about a line of block can be interpreted erroneously as a rotor based on the phase map.

Figure 7 also demonstrates that sequential activation of regions separated by a line of block can be interpreted as a rotor based on the corresponding phase map. Maps in Figure 7A show epicardial activation isochrones during 1 beat of ventricular tachycardia. The asterisk indicates the earliest site of epicardial activation, from which 2 branching wavefronts emanate. The inferior branch proceeds to activate the right ventricle (green) and encounters a line of block (thick black line in anterior view). The superior branch proceeds anteriorly toward the left ventricle base to activate the left ventricle from base to apex (blue). Thus, the 2 regions flanking the line of block are activated sequentially by 2 different wavefronts. Figure 7B shows the corresponding phase maps, which show a rotor on the anterior right ventricle, rotating around a singularity point near the right ventricular apex with clockwise chirality (black arrow). The location of the singularity point is in the region of conduction block, which was associated with low voltage during invasive electrophysiology mapping, indicating the presence of a scar and an anatomic barrier. This example reiterates that phase maps can be misinterpreted to indicate the presence of rotors, when in fact activation is from multiple wavefronts that activate neighboring regions sequentially.
In this study, we devised a novel application of MVG in phase mapping of cardiac arrhythmias. This approach is particularly useful for mapping complex activation patterns during fibrillation because it is not affected by transient fluctuations in electrogram morphology or amplitude, including noise. To evaluate phase analysis, we needed an independent method to compute AT. During fibrillation, the commonly used method of determining AT using \(-dV/dt_{\text{max}}\) is prone to error because of the multiple deflections in the signal and the low signal:noise ratio. The wavelet transform algorithm used in this study (and in past studies\(^\text{16}\)) overcomes the limitations of the common AT computation approach by reducing the effect of noise and resolving multiple AT in the signal. In this study, all time-domain AT computations during fibrillation were conducted using the wavelet algorithm.

Although the time-domain AT map is essential for understanding the overall wavefront propagation patterns, it is difficult to determine from this map the precise point about which a wavefront rotates. This can be easily achieved with phase computation, which determines singularity points based on a precise mathematical definition. Phase mapping also highlights wavefront curvature and organized activity during fibrillation. Because of these properties, phase mapping can be a valuable additional analysis method. However, as shown in the article, phase mapping results require careful interpretation because it can sometimes introduce false rotors. Therefore, it should be used in combination with a robust time-domain AT mapping method for characterizing arrhythmia mechanisms during fibrillation.

We demonstrate that phase computation depends strongly on correct determination of CL. The correct choice of CL is more critical for pEMD detrending (Figure S3B in the Data Supplement) than for MVG detrending. This is to be expected because the pEMD method (originally developed for optically recorded action potentials) involves detrending the input signal by interpolating between local maxima and minima for a given window, and the estimation of the window length depends on accurate knowledge of CL. Sensitivity analysis was conducted to test the CL dependency of the pEMD and MVG algorithms, and the results are shown in the Figures S6 and S7 in the Data Supplement, respectively. Figure S6 in the Data Supplement demonstrates that pEMD is more affected by changes in CL and requires a priori knowledge of the correct CL to yield correct results. Figures S9 and S10 in the Data Supplement show that at
incorrect CL, the algorithm has the propensity to miscalculate maxima or minima, which results in incorrect morphology of the detrended signal and hence erroneous phase computation. In contrast, the MVG method uses the entire signal information (not only its extrema) by averaging the signal over a window; it does not require maxima/minima determination. Consequently, phase progression computed using the MVG method corresponded better with the activation pattern over a wide range of CL (Figures S7 and S12 through S14 in the Data Supplement).

Although the MVG-based phase computation is more robust over a wider range of CL, if an erroneous CL is chosen, the phase maps show drastically different and incorrect patterns with multiple colliding rotors, as shown in Figure S4B in the Data Supplement. It is not always possible to determine a single CL value, especially during complex arrhythmias such as AF in which CL changes spatially and temporally (the spatial variability of CL is shown in Figure S5 in the Data Supplement).

To overcome this difficulty, we formulated a dynamic CL approach, which automates CL computation for each epicardial site independent of its neighbors, using an \( f_{HRIF} \) parameter. The phase for each electrogram is computed using its own \( f_{HRIF} \). In contrast, DF uses a single value for all electrogram locations, disregarding the spatial dependence of frequency and CL. Also, computation of DF is unreliable for regions with multiple peaks in the frequency spectrum, a common occurrence during fibrillation. Not surprisingly, DF has been shown to poorly correlate with AF CL. Phase maps computed with MVG detrending with a dynamic CL correlated well with the time-domain activation maps, as shown in Figures 3 and 4.

**Singularity Points and Rotors**

Phase analysis was performed using 502 epicardial electrograms per chamber, with an average distance of 5 to 10 mm between neighboring nodes. The high-resolution mapping inherent in ECGI methodology allowed for detection of high-curvature wavefronts and rotors without the need for interpolation. This approach is different from Narayan et al, who used linear interpolation of the phase state between 64 basket electrodes because of insufficient coverage. In our study, the panoramic biatrial mapping allowed for determination of wavefront dynamics across the atria. The results show that the location of a singularity point (or core) was not fixed in AF during the mapping period, causing the rotor to meander over the mapped surface. This behavior is consistent with the findings from simulations and human mapping studies.

**Incomplete, “Wannabe”, and False Rotors**

The presence of a phase singularity point was not always accompanied by a complete rotor. For instance, in Figure 3, the phase maps during AF (middle rows) show a LA phase singularity point and a rotational pattern around it. However, the rotating wavefront merged with another wavefront from the RA near the inferior septum and did not complete a 360° rotation. The rotational wavefront could be termed an incomplete or partial rotor.

The phase map of sinus rhythm (Figure 5) displayed a phase singularity point and rotational pattern around it at certain time instances (Figure 5B). If viewed in isolation, this pattern of the phase map could be interpreted incorrectly to represent a rotor.

Activation isochrone maps for a typical right atrial flutter (Figure 6A) reveal a line of block and sequential activation in the posterior RA. The phase map (Figure 6B) highlights a high-curvature wavefront pivoting about a singularity point on this line of block. This wavefront may be misinterpreted as a rotor, and ablation at this phase singularity point is unlikely to terminate typical right atrial flutter. It fits the definition of a “wannabe” rotor coined by Lee et al, who used high-density epicardial mapping during AF. They reported wavefronts emanating from focal sources, which pivoted around the end of a line of block, but failed to complete a rotation because of wavebreak or collision. The location of the phase singularity point occurred at one of the edges of the line of block. This is because at the edge, there is a continuous progression of phase from \(-\pi\) to \(\pi\) in the neighboring nodes, which fulfills the requirement for formation of a phase singularity point. Figure 7 also demonstrates that sequential activation about a line of block can generate a false rotor in the phase map. These 2 examples, 1 atrial and 1 ventricular, affirm the prediction by Berenfeld et al...
that the phase algorithm has a propensity to introduce rotors by combining wavefronts that activate a region sequentially. The examples further demonstrate that if interpretations were made solely based on phase maps, without examining the underlying electrograms or the time-domain activation sequence, false rotors could be detected and inappropriately targeted for ablation. Therefore, in such cases, it is important to use additional nonphase information to validate the results of phase mapping before labeling a region as an ablation target. In the application of phase analysis to the current data sets, we have not encountered an example where phase analysis obscured an existing rotor that was captured by activation mapping. In fact, phase analysis highlights the curvature of the activation front and therefore can visually emphasize existing rotors.

**Limitations**

Atrial signals during fibrillation typically have a low amplitude and a low signal:noise ratio. The presence of noise can generate artifacts in the phase computation because the detrending algorithm amplifies all oscillations of the recorded signal. In this study, we used a low-pass filter with cut-off frequency of 12 Hz to mitigate this problem. This value was chosen based on our time-domain analysis.

We applied a signal detrending algorithm (MVG detrending) and modified it to improve the accuracy of phase computation in situations, where CL varies in time and space. We tested this method against a widely used algorithm—the pEMD detrending. Although a broader comparison, involving other detrending techniques, could be suggested, we feel that it is outside the scope of the current project. Our goal was to apply phase analysis to unipolar electrograms, compare it with activation mapping, and thereby understand the relationship between the two. To achieve this goal, we applied MVG detrending with dynamic CL. This method provided optimal results, as demonstrated by correlation between phase maps and activation maps.

We worked with a limited, yet well-defined set of data, obtained from intact human hearts using detailed panoramic mapping. Although phase mapping is currently being used in AF ablation, the methodology and properties of electrogram-based phase mapping have not been established nor adequately described. This study aims to fill this gap. The selected examples were chosen to demonstrate the properties of phase, present associated problems, and suggest possible solutions. A statistical evaluation of phase mapping, as a detector of rotors, is a different (albeit related) objective that requires a separate study with a different study design. A
meaningful statistical analysis requires a much larger study, in a large cohort of patients and is outside the scope and objective of this article.

Conclusions
Phase maps can provide important information on the spatio-temporal characteristics of complex arrhythmias by computing phase singularity points and highlighting existing rotors. However, given the inherent nature of the phase algorithm to emphasize rotational wavefronts, a thorough analysis and careful interpretation must incorporate electrogram characteristics and the time-domain activation sequence to avoid detection and targeting of false rotors and singularity points. Therefore, for mapping complex arrhythmias, a wavelet-based time-domain activation combined with phase mapping with variable CL seems to be a more reliable method for identifying true rotational activity.

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Methodology Considerations in Phase Mapping of Human Cardiac Arrhythmias
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1a. ECGI

256 body-surface ECGs were recorded at sampling frequency (f_s) of 2 kHz. Following this, the patients underwent a thoracic CT scan while wearing the electrodes, which yielded patient-specific heart-torso geometry. The ECG data and geometry were combined using our laboratory custom-developed mathematical algorithms to noninvasively reconstruct epicardial potentials and unipolar electrograms. ECGI was performed with the clinically-indicated CT scan when possible, avoiding any additional radiation exposure.

1b. Time-domain Activation Mapping

**Ventricular Signal Processing**

Body surface potentials (BSP) recorded during the body surface QRS were analyzed. The BSP were detrended and filtered using a low pass Bessel filter with cutoff frequency at 20 Hz. Using ECGI, epicardial electrograms were reconstructed at 502 sites of the entire ventricular surfaces. For each electrogram \( V(t) \), activation time was computed as the time of the steepest negative deflection during QRS \( (-dV/dt_{max}) \), providing panoramic maps of activation.

**Atrial Signal Processing**

ECGI allows for beat-by-beat analysis. T-Q segments of beats with long R-R intervals (500 - 1000 ms) during atrial fibrillation (AF) were selected for analysis. This eliminated the need for QRS subtraction, which can introduce artifacts. BSP were filtered using a high pass Butterworth filter with cutoff frequency at 0.5 Hz to remove baseline drift, followed by a low pass Butterworth filter with cutoff frequency at 12 Hz. This value is consistent with other human atrial epicardial mapping studies, in which the dominant frequency of a signal was restricted to 3-15 Hz. The Butterworth filter better attenuates the harmonics of the fundamental frequencies of the signal. This preprocessing step must be applied before phase computation using the HRIF algorithm in
order to prevent amplification of unwanted frequencies and erroneous phase transitions.

Epicardial potentials and unipolar electrograms were reconstructed at 502 sites on each atrium or at 1002 sites on both atria.

*Activation Time Mapping using Wavelet transform*

During Atrial fibrillation, the signal $V(t)$ has multiple deflections, which implies that activation times cannot be reliably determined using $-dV/dt_{\text{max}}$. Continuous wavelet transform (CWT) can be used to identify local periodic repetitions that are physiologically based and are not created by noise. CWT with Gaussian wavelet was applied to each epicardial electrogram to decompose it into multiple scales (maximum 100). The time instances of the wavelet transform modulus maxima (WMM) at the large scales represent the activation times of the signal. To generate an activation movie, a matrix containing time series of 1 and 0 was created for each epicardial electrogram, with values of 1 indicating the time instances at which that site was activated. A dynamic activation movie was generated using all sites on the epicardium for the duration of the analysis. This movie showed the propagation of epicardial activation wavefronts during arrhythmia. The movies were visually analyzed for the presence of high-curvature wavefronts classified as given in the main paper under Methods section.

Figure S1 shows atrial epicardial electrogram (top row). Each sample represents 0.5 ms. CWT with Gaussian wavelet was applied to the electrogram to decompose it into 40 scales. The plot of wavelet transform coefficients (also called wavelet scalogram) is shown in the bottom row. The colors indicate the magnitude of wavelet transform coefficients as shown by the color bar. Low scale values represent high frequency content of the signal; high scale values represent low frequencies. Time instances of wavelet transform modulus maxima across the scales are tracked using a line (black vertical line on the wavelet scalogram plot). Only the lines extending to the x axis correspond to true activation times on the signal (in this example, samples: 58, 599
and 1180). The activation times calculated using the WT method are indicated on the electrogram plot (top row) using red dots.

Figure S1. Activation Time computation using wavelet transform.
1c. Phase Mapping: Highest Regularity Index Frequency ($f_{\text{HRIF}}$) Computation

Figure S2 shows an epicardial electrogram during AF (blue line, top row). Each sample represents 0.5 ms. The signal was filtered using the Butterworth filter as described in the previous section. Activation times computed using time-domain wavelet-transform method are shown in red dots (top row). The power spectral density plot is shown in the middle row. Note that the dominant frequency (DF) and highest regularization index frequency ($f_{\text{HRIF}}$) are different; DF is 6.7 Hz and $f_{\text{HRIF}}$ is higher (as expected) at 9.6 Hz, a difference of 30%.

![Graph of epicardial electrogram during AF](image1)

![Power spectral density plot](image2)

![Phase computed with MVG detrending and Hilbert Transform](image3)

**Figure S2. Phase computation using HRIF algorithm**
The area under the power spectrum is calculated. The highest regularization index frequency $f_{HRIF}$ is computed as the frequency corresponding to 90% of total power. The normalized sampling frequency (NSF) is computed as $f_s/0.5f_{HRIF}$, where $f_s$ is the sampling frequency (2 kHz). The window length for MVG detrending is $1/NSF$. Phase was then computed for the detrended signal using equation (5) in the Methods section of the manuscript. In the bottom row of the plot, the resulting phase values (black line) are superimposed on the electrogram (blue line). The phase discontinuities (phase transition from $\pi$ to $-\pi$ radians) indicate the beginning of next phase cycle. Note that in this plot, the phase discontinuities occur near the minima of the signal. However, the wavefront activation coincides with the steepest negative slope of the signal (top row).

The definition of phase angle can vary from study to study, but this will not affect the overall phase pattern. Therefore, an alternative formulation can be used as:

$$\theta(t) = \tan^{-1}[\text{real}(HT(V'(t)))/-\text{imag}(HT(V'(t)))] \quad (1)$$

generating the following phase plot for the same signal:
**Figure S2b. Alternative computation of phase**

Note that for this formulation, the phase discontinuities align with the time instances of steepest negative slope of the signal. Mathematically, this new formulation is equivalent to shifting the original phase by $0.5\pi$ radians.

In the present study, phase was defined using equation (5) and then shifted by $0.5\pi$. Shifting the phase plot by $0.5\pi$ is equivalent to choosing $0.5\pi$ on the original plot as the point corresponding to the steepest negative slope of the electrogram and hence as the AT (dotted red lines in the bottom row of Figure S2).

For obtaining phase-derived AT maps, a matrix containing time series of 1 and 0 was created for all the epicardial regions, with value of 1 indicating time instances at which that site was at phase $= 0.5\pi$ radians (phase derived activation time). A dynamic activation movie was made for all sites on the epicardium for the duration of the analysis.
References


Section 2: Effects of Signal Conditioning and CL
Effect of Input Signal Conditioning on Phase

Online Supplement Figure S3 demonstrates the effect of input signal conditioning, also known as detrending, on phase computation. Panel A shows the epicardial activation isochrone map for a patient who had focal VT, mapped with ECGI during a single beat. Lead V2 of the body surface ECG (right) shows the CL of the VT (340 ms). The epicardial activation originates on the lateral wall of the left ventricle (LV, black asterisk) and proceeds to activate the LV superiorly and inferiorly (yellow arrows). The latest region to activate is the right ventricular (RV) basal region (blue). pEMD detrending was performed on the same beat with two different window lengths (WL): one corresponding to the true CL of the VT, and one that is half the CL (WL: 340 ms and 170 ms respectively). The phase maps after HT are shown for four time instances in Panel B. MVG detrending was performed on the same beat using the same window lengths, and the phase maps after HT are shown in Panel C. The overall phase progression (border between blue and red wavefront; panels B and C) is consistent with the time-domain activation sequence (panel A). Both detrending methods preserved accuracy compared to activation maps. However, an incorrect choice of CL (and hence WL) leads to errors in the pEMD method and causes artifacts in phase computation (shown by black arrows in Row 2 of panel B) even for this favorable case of a signal with high signal-to-noise ratio and fixed CL. Panel C shows how the artifacts are eliminated with the MVG detrending. Movie 1 shows phase progression maps during one beat of focal VT generated using pEMD detrending (left) and Moving Average (MVG) detrending (right), respectively. The map on the right shows radial progression of phase from a region in the lateral wall of the left ventricle (LV) towards the right ventricular (RV) basal region. This pattern is consistent with the activation isochrone map (Figure S3). The map on the left, obtained with the pEMD method, shows artifacts in the phase movie.
Movie 2 demonstrates that the pEMD detrending is unsuitable for AF signal analysis. The movie shows the phase progression during AF obtained with pEMD (left) and MVG detrending with dynamic CL (right). As can be seen, the phase calculation is more prone to artifacts with pEMD detrending, whereas the MVG method yields a stable phase progression.

**Figure S3. Effect of Input Signal Conditioning.** A, Epicardial activation isochrones in a patient with monomorphic focal VT. Asterisk indicates site of earliest activation. Arrows show
direction of wavefront propagation. Lead V2 of body surface ECG (right) shows the CL of VT. B, pEMD detrending was performed on the same beat using two window lengths, WL (Row 1 – 340 ms, Row 2 – 170 ms) and the phase maps after HT are shown for four time instances. Arrows point to artifacts introduced by the pEMD detrending technique. C, Moving Average (MVG) detrending was performed on the same beat using the same two WL and the phase maps after HT are shown. AO, aorta; CL, cycle length; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; VT, ventricular tachycardia; WL, window length. Animation is provided in Movie 1 of Online Supplement.

Effect of CL on Phase

Online Supplement Figure S4 demonstrates the effect of CL, as determined from unipolar electrograms, on phase computation. Panel A shows phase maps for one beat during reentrant VT, using HT and MVG detrending. Phase computation was performed with WL equal to the CL of VT (620 ms). Lead V2 of the body surface ECG is shown on the right. The phase map highlights a singularity point (black dot) near the RV apex and a rotational phase pattern about it. This pattern progresses in the clockwise direction (black arrow), indicating a rotor with clockwise chirality. The location of the singularity point exhibits small changes during the beat. Panel B shows phase maps for the same beat, also obtained by HT and MVG detrending, but with a much shorter CL (50 ms). With this incorrect CL, the phase map shows two singularity points (black dots) anchoring two rotors (yellow and white arrows) with opposite chiralities. This example demonstrates that phase computation is CL-dependent and the use of an incorrect CL can change drastically the pattern of phase maps, including the number of identified singularity points and rotors.
**Figure S4. Effects of CL choice on phase maps.**

**A,** Phase maps during one beat of VT, obtained with HT and MVG detrending, using WL equal to the CL of VT (620 ms). Maps are shown for seven time instances. Lead V2 of the body surface ECG is shown on the right. The phase map shows a single singularity point and clockwise rotor.  

**B,** Phase maps for the same beat using the same method, but with a much shorter CL (50 ms). With this erroneous choice of very short CL, the phase map shows two singularity points (black dots) anchoring two rotors (yellow and white arrows) with opposite chiralities, in disagreement with the phase map in B. In this phase map, black dot indicates singularity point.
Figure S5. Cycle Length during Atrial Flutter and Atrial Fibrillation. Panel A shows the CL distribution during one beat of atrial flutter. Panel B shows the CL distribution during one beat of atrial fibrillation (530 ms). The corresponding ECG during fibrillation is shown in the red box. Note different scales in panels A and B and the much greater spatial variability of CL during AF.
Section 3: Comparison of pEMD and MVG detrending
The following figures S6 and S7 illustrate the sensitivity of the pEMD and MVG detrending algorithm, respectively, to error in input cycle length.

The input signals consisted of 8 sine waves with frequencies of 4, 6, 8, 10, 12, 16, 20 and 30 Hz respectively (see Figure S6 legend). The sine waves were sampled at a frequency of 2048 Hz for duration of 2 seconds. For each input signal, pEMD was performed by varying the window length (WL) as follows: 0.25*f, 0.5*f, 0.75*f, f, 1.5*f and 2*f. The resulting phase transitions were used to compute the activation time (AT) for the input signal. The phase-derived AT values were compared with the time-domain AT and the errors are plotted in figure S6.

The procedure was repeated for MVG detrending and the corresponding errors in phase-derived AT are plotted in figure S7.

As shown in figure S6, pEMD-based phase computation is accurate only when the window length equals the exact cycle length of the input signal (f Hz), resulting in zero error in AT. Any deviation from this value produces errors in the AT. Note that the error increases with increased deviation from f and reduced input frequency of the signal. Also false AT (not shown) were introduced when WL = 2f for input signals between 16 Hz and 30 Hz. Thus, even for a highly periodic sinusoidal signal with one frequency, the pEMD method requires a priori knowledge of CL to produce reliable results.
Figure S6. Sensitivity of pEMD detrending to CL

Figure S7. Sensitivity of MVG detrending to CL

Figure S7 shows that the errors in phase-derived AT computation are minimized with MVG detrending.
The following figures (S8-S10) illustrate the dependency of the pEMD method on cycle length choice. Each sample represents 0.5 ms.

The input signal is a mixture of two sinusoids of frequencies 3 Hz and 5 Hz and 1 sec duration. The sampling frequency is 2 KHz.

**pEMD Detrending with Window length (WL) equal to Cycle length of signal**

WL = 326

**Figure S8: pEMD detrending with Window length equal to cycle length of signal.**
As shown in figure S8, when the window length is equal to correct cycle length of the input signal, the pEMD method works correctly in determining the maxima and minima within the window and results in correct computation of phase.

**pEMD Detrending with Window Length greater than Cycle Length**

\[ WL = 400 \]

![Image of pEMD detrending with Window length greater than the cycle length of signal.](image)

**Figure S9:** pEMD detrending with Window length greater than the cycle length of signal.
Figure S9 shows that due to the incorrect window length, the maximum at sample 500 and minimum at sample 1550 (both highlighted by orange oval) were missed. This results in incorrect morphology of detrended signal (shown in brown) and error in phase computation (black).

**pEMD Detrending with Window Length less than Cycle Length**

WL = 150

**Figure S10: pEMD detrending with Window length less than the cycle length of signal.**
Figure S10 shows that when the window length is less than the actual cycle length of the signal, the pEMD method computes erroneous extrema (highlighted by orange oval); this results in incorrect morphology of the detrended signal.
The following figures S11-S14 illustrate how Moving Average (MVG) method overcomes the limitations of pEMD detrending and produces robust phase computation over a wide range of cycle lengths for the same input signal. Each sample represents 0.5 ms. **Moving Average Detrending with Window Length equal to Cycle Length of Signal**

WL = 326

**Figure S11: Moving Average Detrending with Window Length equal to Cycle Length of Signal**
Moving Average Detrending with Window Length greater than Cycle Length

WL = 400

Figure S12: Moving Average Detrending with Window Length greater than Cycle Length of Signal

Figure S12: Moving Average Detrending with Window Length greater than Cycle Length of Signal
Moving Average Detrending with Window Length less than Cycle Length

WL = 150

Figure S13: Moving Average Detrending with Window Length less than Cycle Length of Signal
Figure S14: Moving Average Detrending with Window Length much less than Cycle Length of Signal
Section 4: Movie Captions
Movie 1 (Corresponding to Figure S3 in Online Supplement)

Animated phase progression maps during one beat of VT obtained with HT and pEMD detrending (left) and Moving Average (MVG) detrending (right), respectively. The map on the right shows radial progression of phase from a region in the lateral wall of the left ventricle (LV) towards the right ventricular (RV) basal region. This pattern is consistent with the activation isochrone map (Figure S3). The map on the left, obtained with the pEMD method, shows artifacts in the phase movie.

Movie 2

Animated phase progression maps obtained for a patient with persistent Atrial Fibrillation using pEMD (left) and MVG detrending with dynamic cycle length (right), respectively. Maps show phase changes during 270 ms of atrial activity in posterior view. The phase map obtained with MVG detrending shows a stable progression of phase during the mapped interval, with one singularity point in the posterior floor of the LA and another along the RA free wall. Both singularity points meander. The phase map on the left shows highly unstable phase transitions and erroneous patterns.

Movie 3

Animated phase progression maps obtained with HT and MVG detrending with fixed CL (left) and dynamic CL (right) during 245 ms of AF activity, shown in posterior view. The dynamic CL phase map shows a more stable phase progression pattern. It highlights a singularity point, meandering over the posterior LA, and a high curvature wavefront rotating in the counterclockwise direction. The phase map on the left shows unstable phase transition patterns and does not show the rotor clearly.