Spatial autocorrelation dimension as a potential determinant for the temporal persistence of human atrial and ventricular fibrillation.

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Word count: 4284 (including introduction, methods, results, discussion, and figure legends)

Supplementary information is provided for this manuscript.

Acknowledgements and funding: We appreciate the comments from Prof. Emeritus Henry Greenside of Duke University, North Carolina, that helped to improve our paper. This work is supported by the National Health and Medical Research Council of Australia Project Grant (1063754) and National Heart Foundation of Australia (101188).

Disclosures: Authors confirm they do not have any disclosures.

ABSTRACT

Background: Despite being central to atrial fibrillation (AF) and ventricular fibrillation (VF) mechanisms and therapy, the factors governing AF and VF termination are poorly understood. It has been noted that ratio of system size (L) and the two-point spatial correlation length (ξ_2) are associated with time until termination in transient spatiotemporally chaotic systems, but the relationship between these characteristics and termination has not been systematically studied in human AF and VF.

Objective: We aimed assess whether the time to cardiac fibrillation termination can be predicted using a novel estimator, the spatial autocorrelation dimension (D_i), defined as the ratio of L and ξ_2, in human AF and VF.

Methods: D_i was computed and compared in a multi-centre, multi-system study with data for sustained versus spontaneously terminating human AF/VF. VF data was collected during coronary-bypass surgery; and AF data during clinically indicated AF ablation. We analyzed: i) VF mapped using a 256-electrode epicardial sock (n=12pts); ii) AF mapped using a 64-electrode constellation basket-catheter (n=15pts); iii) AF mapped using a 16-electrode HD-grid catheter (n=42pts). To investigate temporal fibrillation persistence, the response of AF-episodes to flecainide (n=7pts) was also studied.

Results: Spontaneously terminating fibrillation demonstrated a lower D_i ($P<0.001$ all systems). Lower D_i was also seen in paroxysmal compared to persistent AF ($P=0.002$). Post-flecainide, D_i decreased over time ($P<0.001$). Lower D_i was also associated with longer-lasting episodes of AF/VF ($R^2>0.90$, $P<0.05$ in all cases). Using k-means clustering, two distinct clusters and their centroids were identified i) a cluster of spontaneously terminating episodes, and ii) a cluster of sustained epochs.

Conclusion: D_i predicts the temporal persistence of cardiac fibrillation. This finding provides potentially important insights into a possible common pathway to termination and therapeutic approaches.

Key words: *Atrial fibrillation, ventricular fibrillation, mechanisms, spiral waves, rotors, chaos*

INTRODUCTION

Cardiac fibrillation is a spatiotemporally disordered electromechanical state observed in either the atria or ventricles.[1] A fundamental property of the arrhythmia is the propensity for some episodes of fibrillation to spontaneously terminate and transition into sinus rhythm, while other episodes may persist. In the case of atrial fibrillation (AF), individual episodes may be as short as a few seconds, but may also last for hours, days or become permanent in individual patients.[2] Ventricular fibrillation (VF) episodes may also have the propensity VF to self-terminate. However, if VF persists for longer than 10 minutes without resuscitation, the arrhythmia can lead to irreversible neurologic harm or death.[3, 4]

The general properties of fibrillatory termination and persistence are of particular clinical interest as they have the potential to inform ongoing efforts to achieve personalized prediction of prognosis and therapy in both human fibrillatory disorders. Although extensive efforts have occurred over many decades to empirically identify predictors of termination or persistence in cardiac fibrillation,[5, 6] at present there is no universally accepted conceptual paradigm or metric to explain why individual episodes of fibrillation may have the propensity to persist or spontaneously terminate. Such a general paradigm, if it could be developed, would have significant practical relevance, as it could potentially inform unresolved contemporary clinical questions. Examples of such challenges could include the persistence of AF despite pulmonary vein isolation[7], the upper limit of effectiveness observed with PVI,[7] objective delineation of paroxysmal from persistent forms of AF,[8] or understanding why some episodes of VF are responsive or unresponsive to defibrillation shocks.[9]

Here, we sought to contribute to efforts to develop a conceptual paradigm, to account for the potential for episodes of fibrillation to either persist or self-terminate. The electromechanical complexity that characterizes AF and VF has frequently been compared to

the sustained disorder of nonequilibrium chaotic systems in nature that have been observed in physical,[10, 11] chemical[12] and biological systems.[13]. An important general property observed in these systems is synchronization of behavior between spatially connected neighboring regions, that gradually breaks down with distance, a property that can be measured with the two-point spatial correlation length (ξ_2).

In an early study of spatiotemporal chaotic systems by Egolf and Greenside, it was postulated that the ratio of system size (L) to correlation length (ξ_2), along with knowledge of spatial dimensionality (d) could be used to decompose the behavior of chaotic systems into 'independent regions.' [14] Here, we name this quantity, which was not formally defined in the original paper, as the spatial autocorrelation dimension (D_i). The spatial autocorrelation dimension is defined with the following equation:

$$D_i = (L/\xi_2)^d \quad (1)$$

where L the relative system size, ξ_2 the two-point correlation between pairwise electrodes spatially spaced Δx apart (i.e. inter-electrode spacing), and d the spatial dimensionality of the system. As an example of how the D_i estimator could potentially be computed, Egolf and Greenside suggested the following estimator for a heart with a radius R and d = 2 (2):

$$D_i \approx 4\pi R^2/\pi\xi_2 \quad (2)$$

To our knowledge, the association of the spatial autocorrelation dimension estimator with the persistence of termination with human cardiac fibrillation has never formally been assessed. In this study, we evaluate the hypothesis that differences in D_i may account for the relative time until termination in AF and VF.[14, 15] We explore this by calculating D_i in spontaneously-terminating versus sustained episodes of AF and VF, as well as in episodes of AF post pharmacological intervention, with supporting data from computer simulations.

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MATERIALS & METHODS

Epicardial sock recordings of human VF

The human VF study uses prospectively collected data as described by Nash et al.[16] The study recruited n=12 patients (n=8 sustained VF, n=4 self-terminating VF) undergoing routine coronary bypass graft procedures for ischemic heart disease with cross-clamp fibrillation. These studies were approved by the Hospital Ethics Committee (REC 01/0130) with written informed consent. Individual patient details are given in **Supplementary Materials S1, Supplemental Table 1**. Recordings were obtained using a 256-electrode epicardial sock (Δx = 10mm inter-electrode spacing) and unipolar electrograms (1kHz sampling) were preprocessed as previously described.[17, 18] In a subset of patients, VF spontaneously terminated before the full 210 seconds without requiring defibrillation, defined as 'self-terminating episodes'. This was compared to sustained VF episodes lasting the full duration. Additional study details are provided in **Supplement S1**.

Basket and HD grid recordings of human AF

The human AF study extends our previously published study.[19] The study was a multi-center observational design analyzing prospectively collected electrophysiologic data acquired prior to ablation (HREC110634). The inclusion criterion was AF undergoing ablation. Patient participation was by informed consent, with recruitment from Flinders University and Hamburg University. The patient cohort included n=15 patients (age 62±8, 13/15 male(87%), BMI 28.7±3.8 kg/m^2, non-paroxysmal 12/15(80%); **S1, Supplemental Table 2**). Basket catheter and HD-grid recordings were performed as previously.[20] 64-electrode basket catheters (Constellation, Boston Scientific, 48mm (Δx = 4mm), 60mm (Δx = 5mm) and HD-grid a 3-3-3 mm catheter with 16 electrodes to record human AF (Δx = 3mm) were utilized to record unipolar electrograms (1-500 Hz, 2000Hz sampling) and surface electrocardiograms during spontaneous or induced AF lasting >1 minutes. Spontaneously terminating AF

episodes were defined as those that terminated before the full 1-minute without requiring defibrillation, whilst sustained recordings were defined as those lasting the full window of observation. Signal filtering, cleaning, and processing are detailed further in **Supplement S3**.

Spatial autocorrelation dimension estimation

To calculate the spatial autocorrelation dimension, D_i, atrial and ventricular volumes were first calculated using the convex hull of electrode co-ordinates from one of the following i) mapping catheter (for atrial fibrillation), ii) epicardial sock (ventricular fibrillation) or iii) grid nodes (computer simulations). This volume was then used to estimate the radius, R, which was related to the two-point correlation, ξ_2, to give the spatial cross-correlation as given by equation (2) (a graphical overview of D_i calculation and further details are provided in **Extended Data Figure 1**, **Supplement S3**).[21] Specifically, ξ_2 gives the association between the maximum cross correlation and distance between two pairwise signals recorded at different electrodes, which are spatially distanced Δx apart. This can often be modelled by an exponential relationship[22] (details in **Supplement S3**):

$$C(r) = e^{-r/\xi} \quad (3)$$

The cross-correlation function between two sequences of normalized activations were calculated over windows shifted throughout the duration of the recording, with a range of lag values encompassing slightly more than one cycle length (~170ms for VF and ~150ms for AF). The maximum cross-correlation was given by the correlation coefficient for the sequence of activations between the two corresponding locations. This process was repeated in a pairwise fashion to calculate the correlation between all possible combinations of locations, with locations corresponding to electrodes for AF and VF data, or mesh vertices for computer simulations.

168 **Assessing the effect of pharmacological intervention**

169 To understand the effect by which anti-arrhythmic medicines facilitate termination of
170 fibrillation, we studied the action of prototype sodium-channel blockade as archetypal
171 pharmacologic rhythm modulation strategy on spatial autocorrelation dimension. This was
172 assessed in: i) n=9 computer simulated epochs of AF with varying levels of I_{Na} inhibition
173 (20%-60%) leading to AF termination; and ii) n=21 epochs from 7 AF patients administered
174 flecainide during an electrophysiology study, mapped using the HD-grid catheter.

175 To simulate the effect of sodium-channel block in computer simulated AF, the two-
176 dimensional Courtemanche-Ramirez-Nattel cell model was implemented as previously
177 described (run on 7x6cm square grids).[23] Differential equations were solved with a 25ms
178 time-step, with simulations run for 5 seconds. AF epochs were initiated by a standard S1-S2
179 cross-shock protocol. To achieve spontaneous AF termination, ACh gradients were altered to
180 a range of values to achieve self-termination before the full 5 seconds (**Supplement S2**).

181 **Comparison with other metrics characterising arrythmia dynamics**

182 ***Electrogram-based metrics***

183 To evaluate whether D_i provides new information, we evaluated whether established
184 electrogram-based metrics used to characterise arrythmia dynamics would associate with
185 spontaneously terminating AF and VF. This was assessed by calculating four metrics using
186 the HD-grid human AF data: i) Dominant Frequency (DF)[24], Shannon Entropy (ShEn)[25],
187 mean bipolar voltage[26], and peak-peak bipolar voltage. Details on the calculation of these
188 metrics are provided in **Supplement S4**.

189 ***Renewal rate constants***

190 A common motif of extensive spatiotemporally disordered systems is the continuous creation
191 and annihilation of topological defects known as phase singularities (PS) PS.[20, 27] The average
192 rates of PS formation (given by λ_f) and PS destruction (λ_d) can be measured using renewal

theory based approaches.[18, 20] We have previously shown that spontaneous termination of AF and VF may be reflected by lower mixing rates compared to sustained AF and VF, governed by the interaction λ_f and λ_d as reflected by the second largest eigenvalue modulus (SLEM) of the Markov transition matrix (Supplement S4).

Here, we build on this observation and hypothesized that changes in λ_f, λ_d, the mixing rate should associate with changes in D_i. The average rate of phase singularity (PS) formation (given by λ_f) and destruction (λ_d) can be measured by calculating the exponential decay constant from the inter-event time distribution as previously described[19] (further detailed in **Supplement S6**). The interaction of λ_f and λ_d is given by the '*mixing rate*', which represents the time taken to reach the stationary state distribution (**Supplement S6**). In this study, λ_f and λ_d were calculated as previously described from pre-processed and Hilbert transformed unipolar electrograms, with the PS detection algorithm further detailed **Supplement S7**. [18, 20]

Statistical Analysis

The association of D_i with temporal persistence of fibrillatory episodes was determined using non-linear least squares regression with D_i as the independent variable and time until observed termination as the dependent variable. Differences in spatial autocorrelation dimension, correlation length, λ_f, λ_d and mixing rates between cases of sustained and spontaneously terminating AF, VF, and computer simulated fibrillation were assessed using generalized linear mixed models (significance at $P<0.05$) (**Supplement S8**). A similar approach was used to study spatial autocorrelation dimension and correlation length across different stages of VF and post flecainide administration. To study the relationship between λ_f and λ_d with spatial autocorrelation dimension and correlation length, a k-means clustering

approach was implemented using 10 replicates and a city-block algorithm as the distance metric. Additional details are provided in **Supplement S8**.

RESULTS

Spatial autocorrelation dimension reflects the likelihood AF/VF self-termination and observed epoch length

Sustained episodes of basket-catheter mapped human AF were associated with lower spatial autocorrelation dimension (D_i) (mean terminating = 7.10,95%CI:4.77,9.44; mean sustained = 34.38,95%CI:16.87,51.88; P<0.001). This was also seen in HD-grid mapped human AF (mean sustained = 78.78,95%CI:63.35,94.21; mean terminating = 9.41,95%CI:4.49,14,33; P=0.001) and human VF (mean terminating = 10.30,95%CI:-1.90,22.50; mean sustained = 52.80,95%CI:27.13,78.48; P<0.001) (**Figure 1A-C**). Higher D_i also associated with increasing epoch lengths that was best fit to a power-law relationship in basket-mapped human AF (R^2 = 0.940; P<0.001), HD-grid mapped human AF (R^2 = 0.910; P<0.001), and human VF (R^2 = 0.817; P=0.035) when compared to a first-degree polynomial (Basket: R^2 = 0.921; HD: 0.844; VF: R = 0.817; P<0.001 all systems) and exponential relationship (Basket: R^2 = 0.913; HD: R^2 = 0.906; VF: R = 0.753; P<0.001 all systems). (**Fig.1D-F)**.

Relationship to the evolution of human atrial and ventricular fibrillation

D_i were also further assessed in 380 epochs arising from n=24 paroxysmal AF patients, and 282 epochs arising from n=18 persistent human AF patients. Epochs from paroxysmal AF patients were associated with consistently lower D_i in paroxysmal AF (31.09,95%CI:25.47,36.70) when compared to persistent AF (57.73,95%CI:43.93,71.52) (P=0.002; **Figure 2A**).

Human ventricular fibrillation episodes from n=12 patients undergoing cardiac surgery were also studied. Three distinct stages of VF were studied: i) the perfusion stage (initial 30 seconds); ii) ischemia (following 150 seconds); and iii) reflow (last 30 seconds). **Extended Data Fig.2, Supplement S9** depicts the propagation of electrical activity as VF evolves throughout the three stages, which can be seen to depict more turbulent behaviour as VF

243 progresses. This evolution was associated with larger D_i (mean perfusion =
244 14.78,95%CI:5.33,24.67); mean ischemia = 45.48,95%CI:33.36,57.12); mean reflow =
245 82.06,95%CI:41.78,122.22). Specifically, D_i between the perfusion and ischemia (P=0.012),
246 and perfusion and reflow (P<0.001), and ischemia and reflow stages were significantly
247 different (P=0.011) (**Figure 2B**).

248 **Relationship to other fibrillatory metrics**

249 ***Rates of PS formation and destruction***

250 In all model systems, the rate of PS formation, λ_f, was lower in spontaneously terminating
251 basket-mapped human AF (terminating = 0.017,95%CI:0.015,0.019); sustained =
252 0.027,95%CI:0.025,0.030), HD-grid human AF (terminating = 0.0022,95%CI:0.0017,0.0028;
253 sustained = 0.007,95%CI:0.0066,0.0075), and human VF (terminating =
254 0.011,95%CI:0.010,0.012; sustained = 0.023,95%CI:0.024,0.025). Similar trends were seen
255 for the rate of PS destruction, λ_d in basket-mapped human AF (terminating =
256 0.016,95%CI:0.014,0.017; sustained = 0.022,95%CI:0.021,0.23), HD-grid human AF
257 (terminating = 0.026,95%CI:0.021,0.031); sustained = 0.060,95%CI:0.055,0.065), and human
258 VF (terminating = 0.0103,95%CI:0.009,0.0106; sustained = 0.46,95%CI:0.42,0.50).

259 When related to the spatial autocorrelation dimension and assessed using k-means clustering,
260 two distinct clusters and their centroids were identified: i) a cluster of self-terminating epochs
261 situated towards the upper right-hand side of graph (orange), and ii) a cluster of sustained
262 epochs on the lower left-hand side of the graph (blue) (**Fig.3A-C i and ii**). In all model
263 systems, the two clusters gave large positive silhouette values (**Fig.3A-C iii and iv**),
264 indicating that the clusters are well separated. The changes seen in λ_f and λ_d also led to larger
265 SLEMs and slower mixing rates characterizing episodes of spontaneously terminating
266 fibrillation in all model systems (**Fig.4A-D**).

267 ***Electrogram-based measures***

268 When applied to human AF data, it was found that DF showed a trend towards lower values
269 in in spontaneously terminating epochs, however, no statistically significant differences were
270 found when compared to sustained AF epochs (mean sustained = 7.11Hz,95%CI:6.46,7.76;
271 mean terminating = 6.522Hz,95%CI:5.74,7.31; P = 0.26) (**Fig.3D**). Similar observations were
272 made for other electrogram-based metrics, with a downward trend in values associated with
273 terminating episodes, but no statistically significant differences observed for ShEn (mean
274 sustained = 4.59 bits,95%CI:4.02,5.16; mean terminating = 4.31 bits,95%CI:3.85,4.77;
275 P=0.49), mean bipolar voltage (mean sustained = $4.5\text{x}10^{-4}$ mV,95%CI:$0.26\text{x}10^{-3}$,$0.63\text{x}10^{-3}$;
276 mean terminating = $4.20\text{x}10^{-4}$ mV,95%CI:$0.14\text{x}10^{-3}$,$0.70\text{x}10^{-3}$; P=0.85), and peak-peak
277 bipolar voltage (mean sustained = 0.57 mV,95%CI:0.41,0.73; mean terminating = 0.28
278 mV,95%CI:0.22,0.35; P=0.08) (**Fig.3D**).

279 **Changes in response to anti-arrhythmic drug modulation**

280 In cases of computer simulated AF, generalized linear mixed models identified a decreasing
281 trend in spatial autocorrelation dimension (D_i) (**Figure 5A ii**), rate of PS formation (λ_f),
282 Figure **5A iii**) and PS number (Figure **5C iv**) with increasing Na+ block, but no significant
283 change was seen for the rate of PS destruction (λ_d). Statistically significant differences were
284 also observed in control versus Na^+-channel block simulations for D_i (P<0.001) and PS
285 number (P<0.001), but not the PS formation rate λ_f (P=0.19).

286 In cases of human AF, the generalized linear mixed model identified a decreasing trend in D_i
287 (**Figure 5B ii**), rate of PS formation (λ_f, **Figure 5B iii**) and PS number (**Figure 5B iv**) in
288 post-flecainide recordings over time, but no significant change in the rate of PS destruction
289 (λ_d). Statistically significant differences were also observed pre- versus post-flecainide for D_i
290 (P<0.001), λ_f (P<0.001) and PS number (P=0.003).

DISCUSSION

Key insights from this study

In this study we aimed to evaluate the hypothesis that spatial autocorrelation dimension (D_i) could represent a potentially useful approach to evaluating the potential for persistence or termination in atrial and ventricular fibrillation. In multiple human systems studied, we observed that D_i was consistently higher in episodes that were more sustained (lasting the full period of observation) relative to episodes that self-terminated. This trend was also observed in patients classified using the clinical persistent (lasting >7 days) definition of AF, and further supported in episodes of AF where no anti-arrhythmic drugs were administered. These findings demonstrate that differences in D_i may be a useful tool to characterise the potential for persistence or termination of individual AF and VF episodes. Evidence supporting this hypothesis may offer potentially important clinical and mechanistic implications including: i) provide a quantitative framework to understand the termination of cardiac fibrillation; ii) link termination in both atrial and ventricular to a common mechanism; iii) link the termination of cardiac fibrillation to other nonlinear systems; and iv) inform future investigations of unresolved clinical challenges in human fibrillatory disorders.

Electrophysiologic characterisation of human AF & VF is an important clinical need

Despite extensive research, the optimal approach to electrophysiologically characterise human fibrillatory dynamics remains incompletely defined. At present, in AF in particular, fundamental challenges remain such as why AF progresses from paroxysmal to persistent in some but not all patients,[8] why a proportion of patients respond to anti-AF medicines but others do not,[28] why AF persists despite durable pulmonary vein isolation in some patients,[7, 29] and why substrate and linear ablation has not led to dramatically improved clinical

outcomes.[30] These problems have led many in the clinical field to suggest that understanding of the biophysical processes sustaining fibrillation is not complete,[31] providing an important rationale to support the exploration of new strategies for electrophysiologic characterization of human fibrillatory dynamics.

Spatial autocorrelation dimension may add to available tools to characterise AF and VF dynamics

D_i is an estimator of local electrophysical spatial synchronization in AF and VF, in comparison to overall system size, with the key finding that this metric appears to be a potentially important predictor of the potential for the temporal persistence of fibrillatory episodes. Here, we use the term estimator in the statistical sense, of acting as a rule or criterion for calculating an estimate of a parameter from observable data.[32]

D_i offer a number of potential advantages for the purpose of characterisation of human fibrillatory dynamics, that may make this metric provide useful information in addition to established quantitative tools to explore fibrillatory dynamics. Firstly, the information captured by D_i leverages the inherent spatial properties of the AF and VF. While traditional metrics of fibrillatory dynamics, such as dominant frequency[24], entropy[25], voltage[26] and fractionation[33] are primarily reliant on local timing and electrogram properties, D_i is an integrated measure over spatially distributed data points, taking into account the overall system size. This may potentially provide important nuanced insights into the system's underlying dynamics. The spatially informed perspective provided by D_i potentially allow for more accurate consideration of the multi-scale and nonlinear behavior, providing insight into the structural and functional organisation of AF and VF as biophysical processes.

Secondly, D_i is attractive because it is conceptually plausible as potential metric to explain the persistence of fibrillation. In its provenance, D_i has clear theoretical foundations in nonlinear

systems theory, although fascinatingly, in the Egolf and Greenside study that motivated this paper D_i was not formally named or defined[14], despite the hypothesis that this estimator could potentially be used to characterise spatial synchronization in fibrillation being presented as a potential use case.[14] Mechanistically, D_i is dependent on three factors: (i) the system size; (ii) correlation length; (iii) and spatial dimensionality, analogous to the aspect ratio in extensive chaotic systems.[34] Furthermore, the foundations for D_i are supported by long-standing empirically derived principles in cardiac fibrillation. The critical mass hypothesis has long been a principle[35 36, 37] underlying the persistence of fibrillation, and the clinical association of increasing chamber size with the probability of AF maintenance is a generally accepted clinical principle.[36, 37] Separately, the association of spatial correlation as tool to differentiate paroxysmal from persistent forms of AF has historically been independently clinically validated.[38, 39] D_i, as an integrated estimator of spatial synchronisation relative to system size, has the potential to usefully add to available tools for the electrophysiologic characterization of fibrillation.

Thirdly, a key strength of strength of D_i is that it is potentially able to be measured using clinically available data and has the potentially to leverage recent advances in catheter mapping technologies. Quantification of other similar metrics such as wavelength, has been a challenge for in vivo clinical implementation due to the need for the precise calculation of conduction velocity (CV), effective refractory period (ERP) or action potential duration (APD), difficult to obtain in human patients .[40] In contrast, D_i can be rapidly calculated from commonly recorded electrical signals such as the intracardiac unipolar & bipolar electrograms, which are routinely collected in electrophysiology studies.

Recent advances in electroanatomic mapping have expanded the potential applications of spatial synchronisation metrics. Novel array catheters[41-43] allow simultaneous measurement of

electrical synchronisation spatial dispersed electrogram information in a variety of potential configurations, which was historically limited in the era of linear mapping catheters.[38] Additionally, advances in 3D electroanatomic mapping allow rapid and accurate volumetric estimation of cardiac chamber dimensions, allowing system size to be determined.[44] With new systems integrating real-time export of electrogram information, measurement of D_i has the potential to be clinically available on existing commercial mapping platforms.

It is important to note that because D_i is dependent on system size, its numerical value will vary due to differences in measurement. However, it is interesting to note that D_i estimates were within the same order of magnitude across all model systems. These estimates were also comparable to the number of independent regions originally predicted by Egolf paper et. al. for the fibrillating rabbit heart (~70).[14] Another important point to note is that the relationship between D_i and the observed time until AF and VF termination (epoch length) best fit to a power-law, potentially indicating that D_i more accurately predicts shorter lasting episodes of fibrillation with a higher likelihood of impending termination, as opposed to more temporally persistent episodes where termination will occur much later. Therefore, D_i may be clinically useful in applications such as stratifying episodes of AF/VF likely to resolve on their own in the short-term, versus those likely to persist for some time.

Clinically, the spatial autocorrelation dimension could provide a valuable additional quantitative metric to those currently available to measure fibrillatory dynamics.[39, 40] Firstly, a potential benefit of this approach is that it could contribute to an overarching explanation of why cardiac fibrillation self-terminates. Existing contemporary clinical theories of fibrillation, such as the multiple wavelet re-entry, rotor, or focal source theories of AF and VF[45-47]do not specifically quantitatively address why any individual episode of should have a propensity for self-termination. Similarly, existing quantitative metrics of fibrillatory dynamics such as

387 dominant frequency, entropy, fractionation, or voltage-based substrate characterisation, also
388 leave a potential gap as to why individual epochs of AF and VF self-terminate.[48]

389 **Links to spatiotemporal turbulence in other systems**

390 An important point to mention is that D_i as presented here to quantify the propensity of AF
391 and VF terminate is linked to concepts that have been extensively explored in theoretical
392 models that have been used to study transient spatiotemporal chaos.[49, 50] The termination of
393 such transient spatiotemporal chaos has been proposed to occur due to underlying differences
394 in the system phase space, which describes how a system tends to evolve under a variety of
395 initial conditions.[51] For example, transient spatiotemporal turbulence occurs when a *'chaotic*
396 *saddle'* or '*non-attracting chaotic set'* is present, which allows turbulent behaviour to
397 eventually terminate when the system escapes into the asymptotic attractor.[15, 52] D_i represents
398 an index of complexity that approximates the degree of turbulence and number of
399 independent regions in the system[53], which potentially relates to the likelihood of the system
400 escaping into such an asymptotic attractor.

401 **Translational perspective**

402 The results presented here may be conceptually useful for understanding and predicting the
403 propensity for the persistence of fibrillation in a variety of clinical contexts. Clinical studies
404 are underway to validate the role of cardiac fibrillation in objectively determining the
405 association of clinically measured D_i with atrial fibrillation persistence, and clinical response
406 to ablation.[54] D_i has the potential to contribute to the development of new metrics to predict
407 anti-arrhythmic drug response. Clinical studies have recently been commenced to determine
408 the association of D_i and the long-term efficacy of anti-AF treatment. D_i may also have a
409 potentially important role in determining response to AF ablation. An important incompletely
410 resolved clinical question is the role of what if further substrate or linear

compartmentalization should occur in patients beyond pulmonary vein isolation.[18] It is possible that cardiac D_i could play a role in determining which patients could require further ablation beyond PVI, and used as an objective metric to guide clinical responses. Future investigations are underway to answer these questions.

CONCLUSION

Lower spatial autocorrelation dimension, D_i, characterizes the termination of fibrillation. This observation could provide insights into the factors governing termination and persistence of fibrillation and could allow for the development of improved therapeutic approaches based on spatial autocorrelation dimension modulation

Figure 1 Spatial correlation dimension reflects the likelihood of human AF/VF termination and epoch length

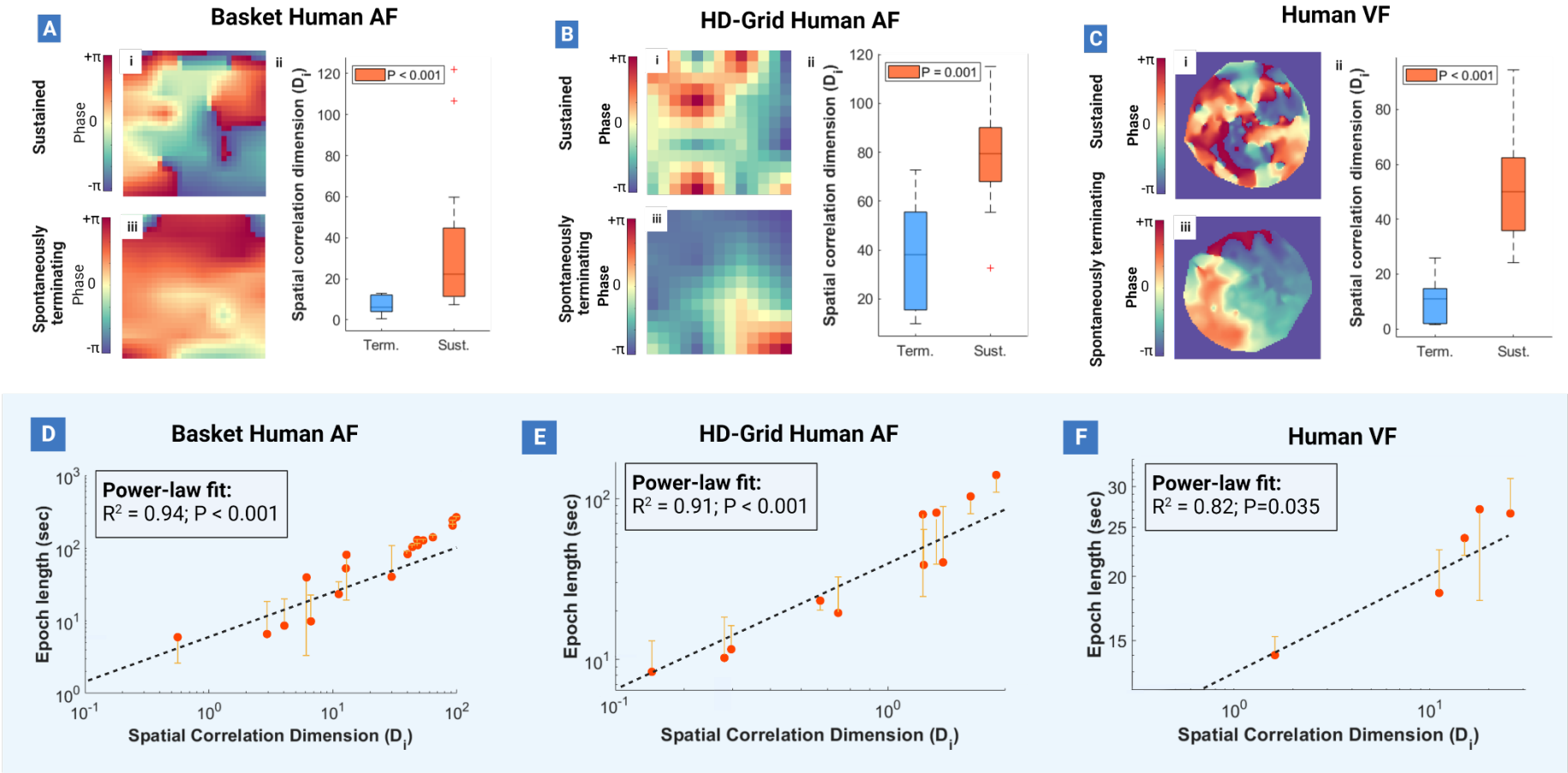

Figure 1: Spatial autocorrelation dimension reflects the likelihood of AF/VF termination and epoch length

(**1A-C**): Terminating epochs of AF and VF are associated with lower spatial autocorrelation dimensions (1A-Cii). Observed epoc lengths (which gives time until termination) increased with larger spatial autocorrelation dimensions, with a relationship that best fit to a power-law (**1D-F**).

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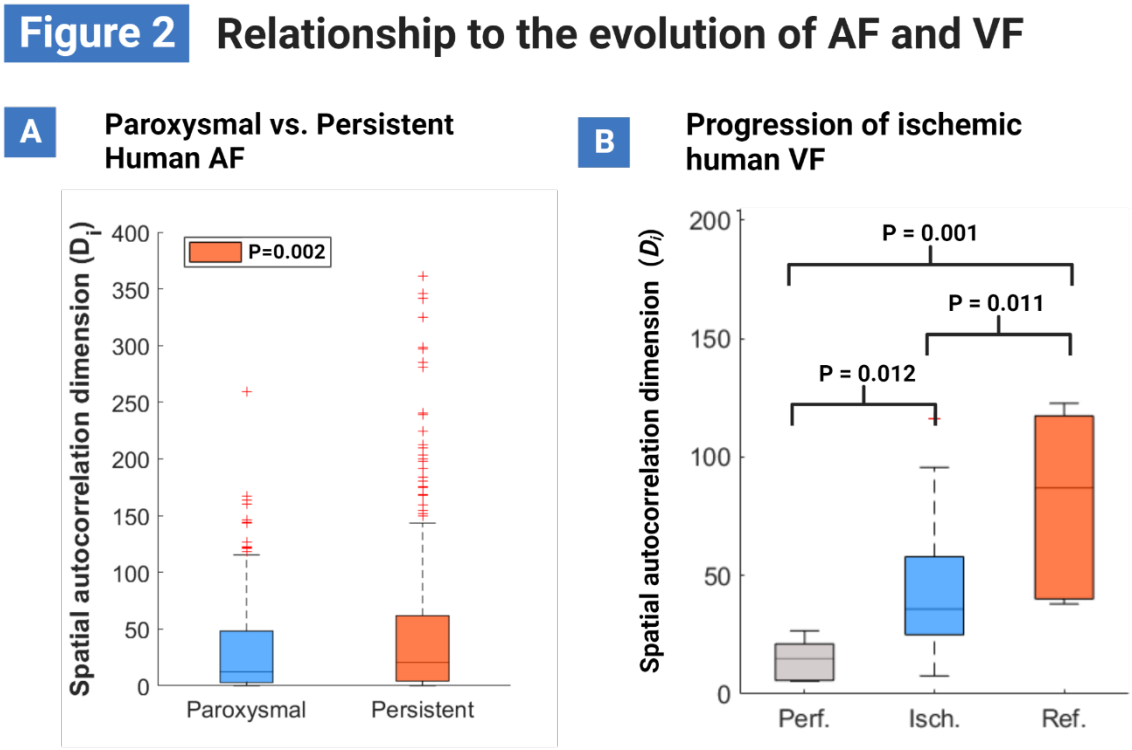

430 ***Figure 2: Relationship to the evolution of AF and VF***

431 (**2A**): Paroxysmal AF was associated with lower spatial autocorrelation dimensions
432 compared to persistent AF. (**2B**): As ischemic VF evolves and becomes more
433 turbulent and disordered, spatial autocorrelation dimension increased.

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Figure 3 Spatial correlation dimension vs. renewal rates and comparison to other fibrillatory metrics

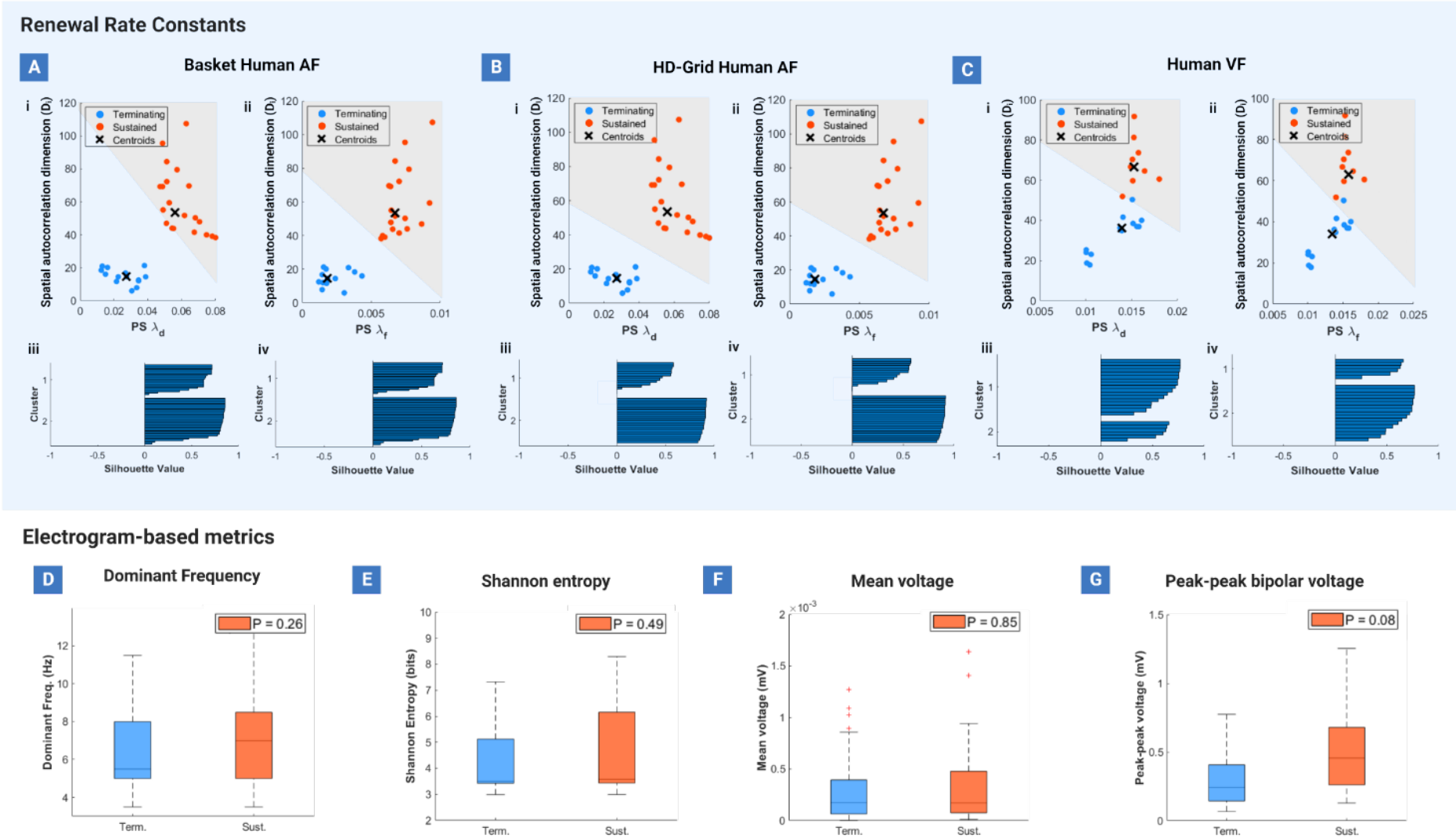
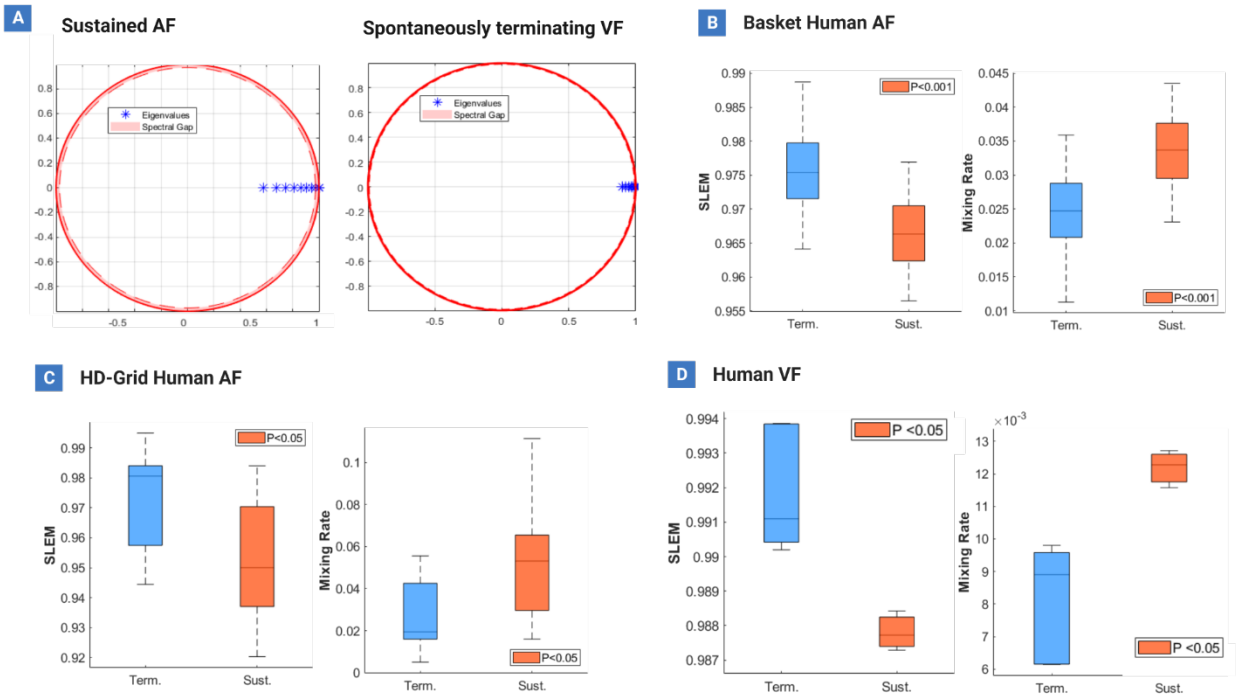


Figure 3: Spatial autocorrelation dimension vs. renewal rates and comparison to other metrics

(**3A-C**): Rates of PS formation (λ_f) and destruction (λ_d) reduced with lower spatial correlation (D_i) in terminating epochs of AF and VF. When compared to sustained AF and VF epochs, two clusters were identified by k-means clustering. This separated and spontaneously terminating (blue) and sustained (orange) simulations ((i) and (ii)). The large positive silhouette values indicate good separate of these clusters ((iii) and (iv)). (**3D-G**): Electrogram-based metrics such as dominant frequency (DF), Shannon entropy, mean bipolar voltage, and peak-peak bipolar voltage showed a trend towards lower values in terminating AF/VF, but no statistically significant differences when compared in sustained versus spontaneously terminating AF and VF epochs.

Figure 4 Changes in SLEM and mixing rate



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446 ***Figure 4: Changes in SLEM and mixing rate***

447 (**4A**): Decreases in λ_f and λ_d are reflected by increases in the second largest eigenvalue
448 modulus (SLEM) of the Markov transition matrix. In all model systems, cases of sustained
449 fibrillation demonstrated lower SLEM compared to self-terminating episodes, indicated
450 by the greater spread of eigenvalues on the eigenvalue spectrum plot. (**4B-D**): The higher
451 SLEM seen in self-terminating episodes also lead to a lower mixing rate when compared to
452 sustained episodes in all model systems.

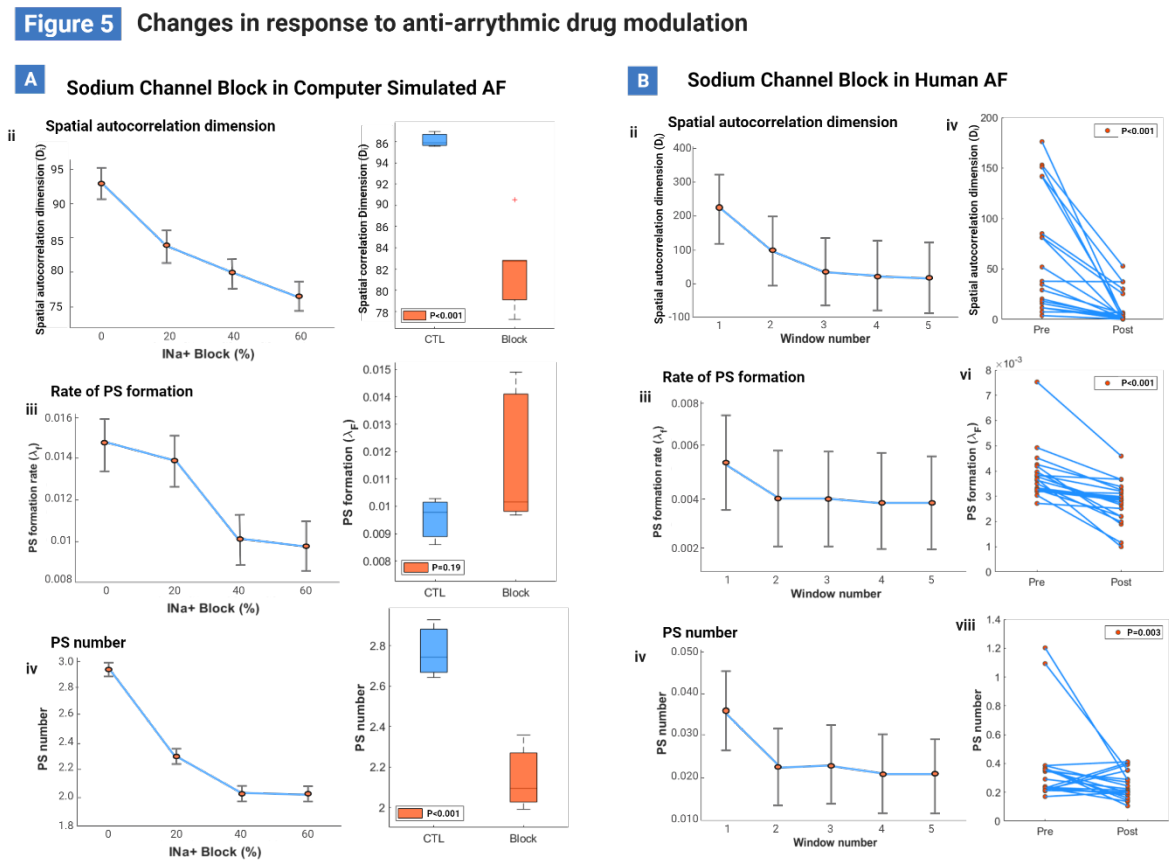

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Figure 5: Changes in response to anti-arrhythmic drug modulation

(**5A**): A decrease in spatial autocorrelation dimension D_i, λ_f and PS number was observed over time in Na^+ block simulations, but not λ_d. (**5B**): In episodes of flecainide-infused human AF, a decrease in spatial autocorrelation dimension D_i, λ_f and PS number was also seen, but not λ_d.

REFERENCES

1. Gray RA, Pertsov AM and Jalife J. Spatial and temporal organization during cardiac fibrillation. *Nature*. 1998;392:75-8.

2. Michaud GF and Stevenson WG. Atrial Fibrillation. In: J. L. Jameson, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo and J. Loscalzo, eds. *Harrison's Principles of Internal Medicine, 20e* New York, NY: McGraw-Hill Education; 2018.

3. Weisfeldt ML and Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA*. 2002;288:3035-8.

4. Clayton RH, Murray A, Higham PD and Campbell RWF. Self-terminating ventricular tachyarrhythmias—a diagnostic dilemma? *The Lancet*. 1993;341:93-95.

5. Rostock T, Salukhe TV, Steven D, Drewitz I, Hoffmann BA, Bock K, Servatius H, Müllerleile K, Sultan A and Gosau N. Long-term single-and multiple-procedure outcome and predictors of success after catheter ablation for persistent atrial fibrillation. *Heart rhythm*. 2011;8:1391-1397.

6. Takahashi Y, O'Neill MD, Hocini M, Dubois R, Matsuo S, Knecht S, Mahapatra S, Lim K-T, Jaïs P and Jonsson A. Characterization of electrograms associated with termination of chronic atrial fibrillation by catheter ablation. *Journal of the American College of Cardiology*. 2008;51:1003-1010.

7. Benali K, Barré V, Hermida A, Galand V, Milhem A, Philibert S, Boveda S, Bars C, Anselme F, Maille B, André C, Behaghel A, Moubarak G, Clémenty N, Da Costa A, Arnaud M, Venier S, Sebag F, Jésel-Morel L, Sagnard A, Champ-Rigot L, Dang D, Guy-Moyat B, Abbey S, Garcia R, Césari O, Badenco N, Lepillier A, Ninni S, Boulé S, Maury P, Algalarrondo V, Bakouboula B, Mansourati J, Lesaffre F, Lagrange P, Bouzeman A, Muresan L, Bacquelin R, Bortone A, Bun S-S, Pavin D, Macle L and Martins RP. Recurrences of Atrial Fibrillation Despite Durable Pulmonary Vein Isolation: The PARTY-PVI Study. *Circulation: Arrhythmia and Electrophysiology*. 0:e011354.

8. Lubitz SA, Benjamin EJ, Ruskin JN, Fuster V and Ellinor PT. Challenges in the classification of atrial fibrillation. *Nat Rev Cardiol*. 2010;7:451-60.

9. Cheskes S, Verbeek PR, Drennan IR, McLeod SL, Turner L, Pinto R, Feldman M, Davis M, Vaillancourt C and Morrison LJ. Defibrillation strategies for refractory ventricular fibrillation. *New England Journal of Medicine*. 2022;387:1947-1956.

10. Egolf DA, Melnlkov IV, Pesch W and Ecke RE. Mechanisms of extensive spatiotemporal chaos in Rayleigh-Benard convection. *Nature*. 2000;404:733-736.

11. Ecke RE and Hu Y. Spiral defect chaos in Rayleigh-Be´nard convection: defect population statistics. *Physica A: Statistical Mechanics and its Applications*. 1997;239:174-188.

12. Winfree AT. Spiral waves of chemical activity. *Science*. 1972;175:634-6.

13. Tan TH, Liu J, Miller PW, Tekant M, Dunkel J and Fakhri N. Topological turbulence in the membrane of a living cell. *Nature Physics*. 2020;16:657-662.

14. Egolf DA and Greenside HS. Relation between fractal dimension and spatial correlation length for extensive chaos. *Nature*. 1994;369:129-131.

15. Lai Y-C. Persistence of supertransients of spatiotemporal chaotic dynamical systems in noisy environment. 1995;200:418-422.

16. Nash MP, Mourad A, Clayton RH, Sutton PM, Bradley CP, Hayward M, Paterson DJ and Taggart P. Evidence for multiple mechanisms in human ventricular fibrillation. *Circulation*. 2006;114:536-42.

17. Nash MP, Mourad A, Clayton RH, Sutton PM, Bradley CP, Hayward M, Paterson DJ and Taggart P. Evidence for multiple mechanisms in human ventricular fibrillation. *Circulation*. 2006;114:536-542.

18. Dharmaprani D, Jenkins E, Aguilar M, Quah JX, Lahiri A, Tiver K, Mitchell L, Kuklik P, Meyer C, Willems S, Clayton R, Nash M, Nattel S, McGavigan AD and Ganesan AN. M/M/Infinity Birth-Death Processes – A Quantitative Representational Framework to Summarize and Explain Phase Singularity and Wavelet Dynamics in Atrial Fibrillation. *Frontiers in Physiology*. 2021;11.

19. Dharmaprani D, Schopp M, Kuklik P, Chapman D, Lahiri A, Dykes L, Xiong F, Aguilar M, Strauss B, Mitchell L. Circulation: Arryhthmia and Electrophysiology. Renewal theory as a universal quantitative framework to characterize phase singularity regeneration in mammalian cardiac fibrillation. *Circulaiton: Arrhythmia and Electrophysiology*. 2019;12:e007569.

20. Dharmaprani D, Jenkins EV, Quah JX, Lahiri A, Tiver K, Mitchell L, Bradley CP, Hayward M, Paterson DJ and Taggart P. A governing equation for rotor and wavelet number in human clinical ventricular fibrillation: Implications for sudden cardiac death. 2021.

21. Egolf DA and Greenside HSJN. Relation between fractal dimension and spatial correlation length for extensive chaos. 1994;369:129-131.

22. Botteron GW and Smith JM. Quantitative assessment of the spatial organization of atrial fibrillation in the intact human heart. 1996;93:513-518.

23. Courtemanche M, Ramirez RJ and Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. *American Journal of Physiology - Heart and Circulatory Physiology*. 1998;275:H301-H321.

24. Sanders P, Berenfeld O, Hocini M, Jaïs P, Vaidyanathan R, Hsu L-F, Garrigue S, Takahashi Y, Rotter M and Sacher F. Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. 2005;112:789-797.

25. Ganesan AN, Kuklik P, Lau DH, Brooks AG, Baumert M, Lim WW, Thanigaimani S, Nayyar S, Mahajan R, Kalman J. Circulation: Arryhthmia and Electrophysiology. Bipolar electrogram shannon entropy at sites of rotational activation: implications for ablation of atrial fibrillation. 2013;6:48-57.

26. Jadidi AS, Lehrmann H, Keyl C, Sorrel J, Markstein V, Minners J, Park C-I, Denis A, Jaïs P and Hocini M. Ablation of persistent atrial fibrillation targeting low-voltage areas with selective activation characteristics. *Circulation: Arrhythmia and Electrophysiology*. 2016;9:e002962.

27. Winfree AT. *When time breaks down: the three-dimensional dynamics of electrochemical waves and cardiac arrhythmias*: Princeton University Press; 1987.

28. Hohnloser SH, Kuck K-H and Lilienthal J. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *The Lancet*. 2000;356:1789-1794.

29. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts‐Thomson KC and Sanders P. Long‐term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta‐analysis. *Journal of the American Heart Association*. 2013;2:e004549.

30. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu L-F and Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. *Heart Rhythm*. 2010;7:835-846.

31. Sauer WH and Aguilar M. Mapping Atrial Fibrillation and Finding a Method to the Madness. 2019;5:830-832.

32. Kay SM. *Fundamentals of statistical signal processing: estimation theory*: Prentice-Hall, Inc.; 1993.

33. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C and Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J Am Coll Cardiol*. 2004;43:2044-53.

34. Cross M and Greenside H. *Pattern formation and dynamics in nonequilibrium systems*: Cambridge University Press; 2009.

35. Kim YH, Garfinkel A, Ikeda T, Wu TJ, Athill CA, Weiss JN, Karagueuzian HS and Chen PS. Spatiotemporal complexity of ventricular fibrillation revealed by tissue mass reduction in isolated swine right ventricle. Further evidence for the quasiperiodic route to chaos hypothesis. *J Clin Invest*. 1997;100:2486-500.

36. Zipes DP, Fischer J, King RM, Nicoll Ad and Jolly W. Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium. 1975;36:37-44.

37. Garrey WE. The nature of fibrillary contraction of the heart.—Its relation to tissue mass and form. 1914;33:397-414.

38. Botteron GW and Smith JM. Quantitative assessment of the spatial organization of atrial fibrillation in the intact human heart. *Circulation*. 1996;93:513-8.

39. Hoekstra B, Diks C, Allessie M and DeGoede J. Spatial correlation analysis of atrial activation patterns during sustained atrial fibrillation in conscious goats. *Archives of physiology and biochemistry*. 2000;108:313-331.

40. Jacquemet V, Virag N and Kappenberger L. Wavelength and vulnerability to atrial fibrillation: Insights from a computer model of human atria. 2005;7:S83-S92.

41. Hong KL, Redfearn D, Chacko S, Baley J, Baranchuk A and Glover BM. High-resolution mapping of the atria using the HD Grid catheter. *HeartRhythm Case Reports*. 2019;5:351-353.

42. Sroubek J, Rottmann M, Barkagan M, Leshem E, Shapira‐Daniels A, Brem E, Fuentes‐Ortega C, Malinaric J, Basu S, Bar‐Tal M and Anter E. A novel octaray multielectrode catheter for high‐resolution atrial mapping: Electrogram characterization and utility for mapping ablation gaps. *J Cardiovasc Electrophysiol*. 2019;30:749-757.

43. Yavin HD, Bubar ZP, Higuchi K, Sroubek J, Yarnitsky J and Anter E. Propagation Vectors Facilitate Differentiation Between Conduction Block, Slow Conduction, and Wavefront Collision. *Circulation: Arrhythmia and Electrophysiology*. 2021;14.

44. Borlich M and Sommer P. Cardiac Mapping Systems: Rhythmia, Topera, EnSite Precision, and CARTO. *Card Electrophysiol Clin*. 2019;11:449-458.

45. Nattel S and Dobrev D. Controversies about atrial fibrillation mechanisms: aiming for order in chaos and whether it matters. *Circulation Research*. 2017;120:1396-1398.

46. Schotten U, Verheule S, Kirchhof P and Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiological Reviews*. 2011;91:265-325.

47. Jalife J. Deja vu in the theories of atrial fibrillation dynamics. *Cardiovascular research*. 2011;89:766-775.

48. Baumert M, Sanders P and Ganesan A. Quantitative-electrogram-based methods for guiding catheter ablation in atrial fibrillation. *Proceedings of the IEEE*. 2016;104:416-431.

49. Braun R and Feudel F. Supertransient chaos in the two-dimensional complex Ginzburg-Landau equation. 1996;53:6562.

50. Kaneko K. Supertransients, spatiotemporal intermittency and stability of fully developed spatiotemporal chaos. 1990;149:105-112.

51. Lilienkamp T and Parlitz U. Terminating transient chaos in spatially extended systems. 2020;30:051108.

52. Crutchfield JP and Kaneko KJPrl. Are attractors relevant to turbulence? 1988;60:2715.

53. Egolf DA, Melnikov IV, Pesch W and Ecke R. Mechanisms of extensive spatiotemporal chaos in Rayleigh–Bénard convection. 2000;404:733-736.

54. Quah J, Dharmaprani D, Lahiri A, Schopp M, Mitchell L, Selvanayagam JB, Perry R, Chahadi F, Tung M and Ahmad W. Prospective cross‐sectional study using Poisson renewal theory to study phase singularity formation and destruction rates in atrial fibrillation (RENEWAL‐AF): Study design. *Journal of Arrhythmia*. 2020;36:660-667.