WAVE-SHAPE OSCILLATORY MODEL FOR BIOMEDICAL TIME SERIES WITH APPLICATIONS

YU-TING LIN, JOHN MALIK, AND HAU-TIENG WU

ABSTRACT. The oscillations observed in physiological time series exhibit morphological variations over time. These morphological variations are caused by intrinsic or extrinsic changes to the state of the generating system, henceforth referred to as dynamics. To model such a time series, we provide a novel hierarchical model: the wave-shape oscillatory model. In this model, time-dependent variations in cycle morphology occur along a manifold called the wave-shape manifold. To estimate the wave-shape manifold associated with an oscillatory time series, study the dynamics, and visualize the time-dependent changes along it, we apply the well-established diffusion maps (DM) algorithm to the set of all observed oscillations. We provide a theoretical guarantee on the dynamical information recovered by the DM algorithm under the proposed model. Applying the proposed model to arterial blood pressure signals recorded during general anesthesia leads to the extraction of nociception information. Applying the wave-shape oscillatory model to cardiac cycles in the electrocardiogram (ECG) leads to a new ECG-derived respiratory signal.

1. INTRODUCTION

Oscillatory time series are ubiquitous in various scientific fields, such as physiology, medicine, epidemiology, and economics. In the time series literature, such an oscillation is usually called seasonality if the period is fixed and cyclicity if the period is not fixed. An physiological oscillatory time series can be viewed as a sequence of oscillations generated by a system whose state changes over time due to interactions between its components or interactions with its environment. See Figure 1 for an example of a typical physiological time series that is encountered frequently in the modern hospital environment. A visual inspection indicates several fundamentally interesting quantities that changes from time to time – the period, the amplitude, the oscillatory morphology, and the trend. In general, time series analysts want to capture the dynamics of the underlying system by detecting and quantifying these changes. The past few decades have seen abundant developments of several approaches to quantifying the available dynamical information from time series with seasonality, e.g., the seasonal auto-regressive integrated moving average (SARIMA) [12] and the trigonometric Box-Cox transform, auto-regressive moving average errors, the trend and seasonal components algorithm (TBATS) [19], among others [31, 32, 18, 30, 17, 23, 50, 56, 53, 11]. However, due to the limitations inherited in SARIMA, TBATS, and other traditional methods as discussed in [14], this problem is still challenging despite those efforts, particularly when the time series exhibits time-varying quantities like frequency and amplitude, and the modern time-frequency analysis, like the synchrosqueezing transform (SST) [14], has been considered. However, as we will discuss carefully in the later section, the phenomenological model considered in [14] and its generalization [40] are still limited
Figure 1. An illustration of a detrended arterial blood pressure (ABP) signal recorded from a patient undergoing general anesthesia before and after the endotracheal intubation at the 10-th second (indicated by the red arrow). This is a typical oscillatory physiological time series with non-sinusoidal oscillations that has time-varying amplitude and frequency and oscillatory morphology.

to capture various physiological time series, specifically when the oscillatory morphology may also change from one cycle to another, in addition to the time-varying frequency and amplitude. For this challenge, to the best of our knowledge, existing tools are limited. We thus need a different model and analysis tools to proceed with the modern physiological time series, particularly to extract the dynamics encoded in the time-varying oscillatory morphology. Below, we present some existing methods and challenges in the context of the subfield of pulse waveform analysis.

Pulse and its rate are the most basic and widely known measures of the cardiovascular system. Pulse rate can be estimated by measuring blood flow at nearly any place in the human body because of the transportation efficiency of our circulation system, so it is a convenient surrogate for heart rate. Pulse waveform analysis provides further information regarding the cardiovascular system. For example, factors such as vascular wall tension, blood volume, and heart contraction affect the morphology of the pulse waveform and can therefore be inferred \[49, 73, 71, 45\]. Due to the abundant information hidden in the pulse waveform, pulse waveform analysis has been widely applied in clinics. On the one hand, indices are derived from a patient’s “mean” waveform and compared with the indices of other patients for the purpose of diagnosis, and this approach has been proposed as a guide for the medical treatment of high blood pressure \[2\]. On the other hand, indices are derived from a sequence of waveforms and examined over time to summarize a patient’s progress during surgery or treatment. For example, commercial monitoring instruments use pulse waveform analysis to bring physicians a relatively non-invasive assessment of cardiac output \[69\]. The FloTrac\textsuperscript{TM} system marketed by Edwards Lifesciences Inc. (Irvine, CA, USA) uses the arterial blood pressure (ABP) waveform to derive various circulation-related indices to facilitate clinical management \[60\,66\].

The waveform analysis techniques that currently exist can be classified as either landmark methods (time-domain) or spectral methods (frequency-domain). Unifying these approaches is the implicit assumption that there exists a template guiding the oscillation. For example, an ABP waveform is often quantified in terms of its forward-propogating and reflected components \[2\]. In general, each waveform is classified with reference to the assumed template, and one obtains indices useful for clinical purposes such as diagnosis. Time-domain parameters quantifying the
relative positions of landmarks in the blood pressure waveform include augmentation pressure [2, 71] and the augmentation index [48, 13, 35]; both have been proposed as indicators of cardiovascular status. Spectral methods interpret pulse waveforms in the frequency domain, providing information about the inflection of the waveform. The spectral content of the ABP waveform has been found to be related to the physical properties of the artery [41]. For example, Taylor et al. use spectral analysis to reveal the relationship between low-frequency variations and the baroreflex [65], and the spectral content of the ABP waveform is used to study the effects of certain diseases [39]. Moreover, it has been shown that by arbitrarily assembling a million features from the wave-shape of the ABP signal, including time- and frequency-domain features, researchers can predict hypotension [89]. In [68], the whole waveform is analyzed by principle component analysis to predict hypovolemia in the low body negative pressure experiment. Note that both spectral and landmark methods are not limited to analyzing pulse waveforms and their associated time series. They can be used to analyze other oscillatory physiological time series.

While these “template-based” approaches have been widely applied, they are challenged when we encounter long-term physiological time series or when the subject is pathological. Particularly when one template may not be enough to model the oscillatory signal. See Figure 2 for an illustration of a subject possessing premature ventricular contractions (PVC), where one template is insufficient to model the oscillation. Paying mind to long-term physiological time series, the oscillatory pattern may exhibit changes over larger time scales, in which case one template is again insufficient for summarizing all of the observed activity.

![Figure 2](image_url)

**Figure 2.** A twenty-second two-lead electrocardiographic (ECG) signal shows dynamic beat-to-beat waveform changes. This patient has a polymorphic premature ventricular contraction (PVC) arrhythmia. The red and blue arrows indicate two morphologically different types of PVCs. We do not apply any filter to the signals.

In order to succeed in the above-mentioned situations, we need to develop a more sophisticated approach to modeling and analyzing oscillatory time series. There are at least two challenges toward such an approach. First, we need to replace the “single oscillatory template” model by a suitable model with “multiple oscillatory
templates.” This multiple oscillatory templates model should encode the underlying dynamics, and the analysis should weigh equally the relationship between templates and the information encoded by each individual template. The model could rely on field-specific background knowledge, if available. Second, we need an algorithm to estimate the desired dynamics from the recorded time series, based on the proposed multiple oscillatory templates model. A desirable algorithm should at least possess the following properties. It should be able to efficiently capture as much information as possible from one oscillation. Moreover, it should be able to quantify the dynamics encoded by a series of oscillations.

1.1. Our contribution. Our main contribution is providing a solution to the above-mentioned challenges. First, we provide a multiple oscillatory templates model, referred to as the wave-shape manifold model. With this model, we then provide a novel hierarchical model to describe oscillatory physiological time series, referred to as the wave-shape oscillatory model. Second, we suggest analyzing a physiological time series adhering to the wave-shape oscillatory model by applying the diffusion map (DM) to its set of oscillatory cycles, and we provide a theoretical guarantee on recovering the dynamics in which we have interest. We study two clinical databases to demonstrate that the proposed model and algorithm allow us to generate a compact representation of the dynamical information hidden in oscillatory physiological time series.

1.2. Paper organization. In Section 2, we review existing models for oscillatory physiological time series, and we propose the wave-shape oscillatory model for oscillatory physiological time series; this model is itself based on a model for morphologically varying oscillatory cycles which we call the wave-shape manifold model. In Section 3, we apply the DM algorithm to a time series adhering to the wave-shape oscillatory model to uncover its associated wave-shape manifold and parametrize the changes in cycle morphology (dynamics) which occur along it. In Section 4 and Section SI.2 in the Online Supplementary, we demonstrate how to apply the proposed model and algorithm to various real clinical data types. The paper is closed with a discussion in Section 5.

2. The wave-shape oscillatory model

In this section, we review existing models for oscillatory physiological time series and provide a novel model based on the notion of a “wave-shape manifold.”

2.1. Existing phenomenological model. Take the ABP time series as an example. Cycle morphology changes with time. In particular, cycle lengths and amplitudes change. These changes occur over various time scales. Unfortunately, the mechanical information underlying the ABP waveform is complex. While there has been progress [45], a complete understanding of blood flow is still lacking. A phenomenological model is proposed in [75, 77, 36] which nevertheless may be used to quantify the time-varying frequency and time-varying amplitude properties of such a signal. In this model, the ABP time series is modeled as a realization of the following random process:

\[ Y(t) = a(t)s(\phi(t)) + T(t) + \Phi(t), \]

where \( t \in \mathbb{R} \). We need to quantify the terms \( a, s, \phi, T, \) and \( \Phi \).
\( a \in C^1(\mathbb{R}) \) is a positive smooth function indicating the time-varying amplitude of the ABP signal. We call \( a \) the “amplitude modulation” (AM);

- \( s \in C^{1,\alpha}(T) \), where \( \alpha \in (0, 1] \) and \( T = [-1/2, 1/2) \) is the 1-dim circle, is a smooth 1-periodic function. It quantifies how the ABP signal oscillates once, and is coined the wave-shape function in [75]. Physiological landmarks such as the dicrotic notch or the reflection wave manifest as bumps in \( s \);

- \( \phi \in C^2(\mathbb{R}) \) is a smooth and monotonically increasing function quantifying how fast the ABP signal oscillates. We call \( \phi \) the phase function and \( \phi' \) the instantaneous frequency (IF);

- \( T \in C^1(\mathbb{R}) \) models the trend, which intuitively is a “locally constant” term. The definition of a trend depends on the application; see [14, (6)] for an example. In the ABP signal, it models the mean blood pressure;

- \( \Phi \) models the inevitable random noise, which we assume to be stationary to simplify the discussion.

Note that \( a \) and \( \phi' \) may not be constant; that is, the notion of amplitude and frequency is generalized, and we allow them to change with time. Other oscillatory physiological time series could be modeled in the same way. Under this phenomenological model, changes in \( Y \) are quantified and summarized by changes in \( a, s, \phi, \) and \( \Phi \). The usual mission in time series analysis is estimating \( a, s, \phi, \) and the statistical properties of \( \Phi \) from one realization of \( Y \). To this end, we need the following slowly varying assumption. Given \( \epsilon > 0 \), the following conditions hold:

- \(|a'(t)| \leq \epsilon \phi'(t)\) and \(|\phi''(t)| \leq \epsilon \phi'(t)\) for all \( t \in \mathbb{R} \);
- \( \|\phi''\|_{\infty} = M \), where \( M \geq 0 \).

When \( \epsilon \) is “small”, this assumption essentially says that while the AM and IF may vary, they vary slowly. We mention that since we focus on the oscillatory pattern in this work, we always assume that the trend [14, (6)] has been removed. We now provide examples other than the ABP signal showing how \( a, \phi, \) and \( s \) encode physiological information. We start with \( a \) and \( \phi \).

**Example 1.** The AM of a single-lead ECG signal is directly related to respiration via the variation of thoracic impedance. When the lung is full of air, thoracic impedance increases, and ECG amplitude decreases, and vice versa [16, Chapter 8]. This fact has lead to the design of algorithms which estimate the respiratory signal from the ECG signal. The estimated respiratory signal is called the ECG-derived respiration (EDR) signal.

**Example 2.** Physiologically, it is known that while the pulse rate of the sinoatrial (SA) node is constant, heart rate is generally not constant. The discrepancy comes from neural and neuro-chemical influences on the pathway from the SA node to the ventricle. This non-constant heart rate could be modeled as the IF of the ECG signal, which is the quantity that we intend to study in the field of heart rate variability (HRV) analysis.

The wave-shape function deserves some more discussion that involves mathematical consideration and physiological facts. Due to the smoothness of \( s(t) \), it can be expanded pointwise into

\[
s(t) = a_0 + \sum_{k=1}^{\infty} a_k \cos(2\pi kt + \beta_k)
\]
based on its Fourier series, where \( \alpha_0 \in \mathbb{R}, \alpha_k \geq 0, k \in \mathbb{N} \) are associated with the Fourier coefficients of \( s \), and \( \beta_k \in [0, 2\pi), k \in \mathbb{N} \). So we have the following expansion for \( a(t)s(\phi(t)) \) in (1):

\[
a(t)s(\phi(t)) = a(t)\left[\alpha_0 + \sum_{k=1}^{\infty} \alpha_k \cos(2\pi k \phi(t) + \beta_k)\right].
\]

Note that the same signal \( a(t)s(\phi(t)) \) can be interpreted in two different ways. First, we could view it as an oscillatory signal with one oscillatory component; in this case, the oscillation is non-sinusoidal. Second, we could view it as an oscillatory signal with multiple oscillatory components, each having a cosine oscillatory pattern (10); in this case, we call the first oscillatory component \( a(t)\alpha_1 \cos(2\pi \phi(t) + \beta_1) \) the fundamental component and \( a(t)\alpha_k \cos(2\pi k \phi(t) + \beta_k), k \geq 2, \) the \( k \)-th multiple of the fundamental component. Clearly, \( \alpha_0 \) is the zero-frequency term of the waveform function, and the IF of the \( k \)-th multiple is \( k \)-times that of the fundamental component. While the second viewpoint is easier to analyze theoretically, the first viewpoint is more physiological.

**Example 3.** *Since the oscillatory morphology of the cardiac cycle as recorded by the ECG signal reflects the electrical pathway inside the heart, physicians diagnose various cardiac diseases by reading this oscillatory morphology. However, physicians read the waveform in the time domain and not in terms of the waveform’s Fourier decomposition. To diagnose the polymorphic PVC arrhythmia shown in Figure 2, physicians would perform a template-based visual inspection via quantifying landmarks.*

This example shows that the terms \( a, \phi, \) and \( s \) in the decomposition (1) have relevance for physiological analysis, thus confirming the utility of the wave-shape function approach to modeling and studying an oscillatory physiological time series.

### 2.2. A first generalization of the phenomenological model.

While the above phenomenological model (1) is able to capture the non-sinusoidal nature of cycles in an oscillatory time series, it does not capture time-dependent changes in oscillatory morphology (aside from those deviations due to AM and FM). Physiologically, this time-varying oscillatory morphology is important. See Figure 2 for an example. Clearly, it is not feasible to use one wave-shape function to model both the normal sinus beats and the PVCs.

Motivated by this concern, in [40], the above phenomenological model is generalized to fully capture the time-varying morphology of cycles. A similar model is considered in the followup research articles [76, 78]. The main idea is intuitive. We generalize \( a_l, l \in \mathbb{N} \cup \{0\}, \) in (2) to be time varying; that is, for each \( l \in \mathbb{N} \cup \{0\}, \) by generalizing \( a(t)\alpha_l \) to a new function \( A_l(t), \) and \( k\phi(t) + \beta_k/(2\pi) \) to a new function \( \phi_k(t), \) we have

\[
a(t)s(\phi(t)) = A_0(t) + \sum_{k=1}^{\infty} A_k(t) \cos(2\pi \phi_k(t)),
\]

where \( A_k \) and \( \phi_k \) satisfy some conditions. In addition to the slowly varying condition imposed in the phenomenological model, we have \( |\phi_k'(t) - k\phi_l'(t)| \leq c\phi_l'(t) \) and \( A_l(t) \leq c(l)A_1(t) \) for all \( k, l \in \mathbb{N}, \) where \( \phi_l'(t) > 0, A_1(t) > 0, \) and \( c(l) \) is an \( \ell^1 \) sequence; \( |\phi_k'(t)| \leq k\phi_l'(t) \) and \( |A_l'(t)| \leq c(l)\phi_l'(t) \) for all \( k, l \in \mathbb{N}, \) and other regularity conditions listed in [40 Definition 2.1] also hold. Here, the conditions
\[ |\phi_k'(t) - k\phi_1'(t)| \leq c_0 \phi_1'(t) \text{ and } A_1(t) \leq c(l) A_1(t) \]

\[ |\phi_2''(t)| \leq c_1 \phi_1'(t) \text{ and } |A_1'(t)| \leq c(l) \phi_1'(t) \]

The conditions capture the fact that the wave-shape is not fixed. The conditions and \[ A(t) \leq c(l) A_1(t) \]

capture the fact that the wave-shape may not change dramatically from one cycle to the next. While this model has been used to design algorithms which handle various physiological problems such as fetal ECG analysis [62], fetal magnetocardiography [25], simultaneously heart rate and respiratory rate estimation from the PPG [15], and cardiogenic artifact recycling [42], its dependence on the “slowly varying wave-shape” assumption limits its application to physiological time series. Specifically, when the subject is not of “normal” physiology, as is shown in Figure 2, the model is limited. Moreover, since the generalized phenomenological model in [40] captures the time-varying wave-shape in the frequency domain, the wave-shape interacts with the IF in a non-trivial way, which further limits its ability to quantify dynamics encoded in the IF and wave-shape. We refer readers with interest in this “time-varying wave-shape” topic to [40, 76, 78] for theoretical details and to [62, 25, 15, 42] for applications of this model.

As useful as this model is, however, it still cannot accurately model signals like the one shown in Figure 2. Clearly, due to the sudden appearance of PVCs, the wave-shape is not slowly varying as required by the model considered in [40, 76, 78]. Our main target is capturing the (non-slowly) time-varying morphology of cycles in an oscillatory physiological time series. Specifically, we have interest in those dynamics encoded by the time-varying cycle morphology which are not due to slow variations in amplitude and frequency.

2.3. Wave-shape manifold. Based on the above physiological facts and existing research results like [33], we know that how the oscillatory pattern varies encodes abundant information about physiological dynamics. We thus hypothesize that modeling oscillatory pattern variation in general will allow us to quantify the underlying physiological dynamics. Since the traditional one-template model cannot help us, and the generalized phenomenological model considered in [40] might not be suitable, we take a direct non-parametric approach to modeling the existence of time-varying morphology.

For an oscillatory physiological time series \( f(t) \), we assume that there exists a set of functions \( M_f \subseteq L^2(\mathbb{R}) \) so that each \( s \in M_f \) represents the morphology of one cycle in \( f(t) \). We assume that each \( s \) is compactly supported on \([-1/2, 1/2]\). An analysis is not yet feasible if we do not impose any conditions on \( M_f \). We take the following physiological fact into consideration. While the physiological status of an organism varies from time to time, it is not unreasonable to assume that internal physical and chemical conditions are steadily maintained. Even under pathophysiological status, unless extreme, we can assume that the organism’s physiological status is well-constrained. This well-constrained condition leads us to assume that \( M_f \) is a low-dimensional structure embedded in \( L^2(\mathbb{R}) \). To simplify the qualitative description and analysis, we further assume that this “low-dimensional structure” is a low-dimensional, smooth, and compact manifold.

**Definition 2.1.** Let \( \mathcal{H} \) be the subspace of \( C^1_{1.\alpha}(\mathbb{R}) \) consisting of functions whose support is a subset of \([-1/2, 1/2]\). A wave-shape manifold is a low-dimensional, smooth, and compact manifold embedded in \( \mathcal{H} \).

Note that in general \( \mathcal{H} \) is a pre-Hilbert subspace in \( L^2(\mathbb{R}) \). We do not impose conditions on the appearance of \( M_f \); in general, \( M_f \) may be disconnected. For
example, to model the arrhythmic ECG signal shown in [2], we the manifold would be disconnected. In other words, we acknowledge the complicated nonlinear structure underlying the time-dependent variations in oscillatory pattern, and we model these variations by a nonlinear manifold.

The structure of the wave-shape manifold for a given physiological time series under consideration is obviously guided by its classical landmark structure. However, it is also guided by other morphological features that we may not be able to quantify easily via landmarks. In the traditional one-template approach, the template could be viewed as the most representative waveform or the “mean” in the wave-shape manifold; the traditional focus is capturing how the wave-shape deviates from this “mean.” With the proposed wave-shape manifold model, we expect to further quantify this deviation.

Next, we show that this wave-shape manifold model is not arising from thin air. Indeed, there is an intimate relationship between the phenomenological model mentioned in Section 2.1 and the proposed wave-shape manifold. In the next section, we provide a connection between these two models.

2.4. Connecting the phenomenological model and the wave-shape manifold. We now provide an argument showing that the wave-shape manifold is intimately related to the phenomenological model [1]. To this end, we show that for a given physiological signal satisfying the phenomenological model, the collection of all oscillatory patterns can be well-approximated by a one-chart manifold. The slowly varying assumption is used to show that each oscillatory pattern in the physiological signal is “close” to one whose amplitude and frequency are constant. The following theorem says that the collection of all such constant-amplitude, constant-frequency oscillatory patterns is an one-chart manifold. The proof is postponed to the Online Supplementary.

**Theorem 2.2.** Suppose \( s \) is the 1-periodic wave-shape function defined in (1) so that the support of \( s \) is a subset of \([−1/2, 1/2]\). Let \( U = I_1 \times I_2 \), where \( I_1 \subset (0, \infty) \) and \( I_2 \subset (1, \infty) \) are two open intervals of finite lengths. Define a map \( \Phi: U \rightarrow \mathcal{H} \subset L^2(\mathbb{R}) \) by

\[
(5) \quad \Phi(a, f) = \begin{cases} \text{as}(ft) & \text{when } t \in \left[\frac{-1}{2f}, \frac{1}{2f}\right] \\ 0 & \text{otherwise,} \end{cases}
\]

where \( t \in \mathbb{R} \). Then \( \Phi \) is a \( C^1 \) diffeomorphism onto an open subset \( \mathcal{M} := \Phi(U) \subset L^2(\mathbb{R}) \); that is, \( \mathcal{M} \) is a manifold with one chart.

See Figure 3 for an example of the wave-shape manifold in Theorem 2.2. We can clearly see the nonlinear structure of the one-chart wave-shape manifold determined by the 1-periodic wave-shape function. Next, we show that for a signal satisfying the phenomenological model [1], it can be well-approximated by the manifold indicated in Theorem 2.2. The proof is again postponed to the Online Supplementary.

**Theorem 2.3.** Take \( \epsilon > 0 \) to be sufficiently small. Consider \( f: \mathbb{R} \rightarrow \mathbb{R} \) satisfying the phenomenological model [1]:

\[
(6) \quad f(t) = A(t) s(\phi(t)).
\]
Assume without loss of generality that \( \inf_{t \in \mathbb{R}} A(t) > 0 \) and \( \inf_{t \in \mathbb{R}} \phi'(t) = 1 \). Define \( t_n := \phi^{-1}(n) \), where \( n \in \mathbb{Z} \), and define functions on \( \mathbb{R} \) as

\[
(7) \quad g_n(t) := \begin{cases} A(t_n)s(\phi'(t_n)t) & \text{when } \frac{-1}{2\phi'(t_n)} \leq t \leq \frac{1}{2\phi'(t_n)} \\ 0 & \text{otherwise}, \end{cases}
\]

and

\[
(8) \quad f_n(t) := \begin{cases} A(t_n + t)s(\phi(t_n + t)) & \text{when } \frac{-1}{2\phi'(t_n)} \leq t \leq \frac{1}{2\phi'(t_n)} \\ 0 & \text{otherwise}. \end{cases}
\]

We then have uniformly over \( n \) that

\[
(9) \quad \|g_n - f_n\|_{\infty} \leq C\epsilon,
\]

where \( C = C(\|A\|_{\infty}, \|\phi'\|_{\infty}, \|s\|_{C^1}, M) \).

A direct consequence of this theorem is that \( \{g_n\}_{n \in \mathbb{Z}} \) is a subset of the one-chart manifold \( M := \Phi(U) \) described in Theorem 2.2 where \( U = I_a \times I_f \), \( I_a = (\inf_n A(t_n), \sup_n A(t_n)) \), and \( I_f = (1, \sup_n \phi'(t_n)) \). As a result, the collection of oscillatory cycles, \( \{f_n\}_{n \in \mathbb{Z}} \), can be parametrized by \( M \) up to a controllable error depending on \( c\mathcal{C}(\|A\|_{\infty}, \|\phi'\|_{\infty}, \|s\|_{C^1}, M) \). We mention that a similar argument can be applied to the signal satisfying the generalized phenomenological model summarized in Section 2.2 with more tedious notation and calculation. Since it does not shed more light upon the topic, we omit the details. An illustration of such an approximation can be found in Figure 8 in Section SI.2.3.

2.5. A new model for oscillatory physiological time series. With the above discussion concerning the wave-shape manifold and its relationship with the phenomenological model considered in (1), we now consider the following hierarchical model that generalizes (1) in a way which differs from that considered in [40, Definition 2.1].

For an oscillatory physiological signal, consider a wave-shape manifold \( M \subset H \). Model an oscillatory physiological signal by the random process

\[
(10) \quad Y(t) = \sum_{j \in \mathbb{Z}} \delta_{t_j} \ast s_j + \Phi(t),
\]

where \( t_j \) is when the \( j \)-th oscillation occurs, \( s_j \in M \), \( \ast \) means convolution, and \( \Phi \) is the observational noise. We assume that \( \inf_{j \in \mathbb{Z}} (t_j - t_{j-1}) > 0 \) and the changes in cycle morphology occur along \( M \). Note that \( \delta_{t_j} \ast s_j \) is well-defined as a function...
in the distribution sense. We call the model \( (10) \) the wave-shape oscillatory model. See Figure 4 for an illustration of the model.

The temporal and morphological dynamics of an oscillatory physiological signal can now be modeled in how \( \{s_j\} \subset \mathcal{M} \) and \( \{t_j\} \subset \mathbb{R} \) are generated. In general, we may model the generating process as

\[
(s_j, t_j) = T((s_{j-1}, t_{j-1}), (s_{j-2}, t_{j-2}), \ldots),
\]

where \( T \) is a discrete dynamical process encoding the fact that succeeding cycles and their locations may depend on the location and morphology of any number of preceding cycles. Models describing the generation of \( \{s_j\} \) and \( \{t_j\} \) are different for different physiological signals, and it is not possible to exhaustively discuss all cases here. To illustrate the idea, we take the ECG as an example.

There have been several approaches to modeling \( \{t_j\} \) for the sake of HRV analysis, such as the long-range correlation model \[51\], the Poisson process \[3\], and others \[16, Chapter 4\]. However, to the best of our knowledge, there is no model discussing the generation of \( \{s_j\} \). Moreover, \( \{t_j\} \) and \( \{s_j\} \) are in general not independent; for example, for the ECG signal, there is a nonlinear relationship between the QT interval (i.e., the support of \( s_j \)) and the RR interval (i.e., \( t_j - t_{j-1} \)) \[44\]. When a wave-shape manifold \( \mathcal{M} \) consisting of two connected components, the sequence of observed oscillations might jump from one component of \( \mathcal{M} \) to the other from time to time, which could be modeled by driven by some “exterior force.” For example, abnormal triggering points located in the ventricle are the exterior force responsible for the PVCs shown in Figure 2. Below, we provide an example to model the respiratory information encoded in the ECG signal.
Example 4. Denote the ECG signal as $E : \mathbb{R} \rightarrow \mathbb{R}$. Assume that there is an intrinsic phase space that hosts the respiratory drive. To simplify the discussion, we assume that this intrinsic phase space is a smooth and compact manifold, denoted as $\mathcal{N}$. Suppose there is a smooth vector field $X$ on $\mathcal{N}$ that describes the respiratory drive. Let

\begin{equation}
\theta_t : \mathcal{N} \rightarrow \mathcal{N}
\end{equation}

be the flow of $X$. Or, more generally, we could assume $\theta_t$ satisfies the following stochastic differential equation defined on $\mathcal{N}$:

\begin{equation}
\mathrm{d}\theta_t = X(\theta_t)\mathrm{d}t + \mathrm{d}\omega_t,
\end{equation}

where $X$ is a vector field and $\omega$ is the canonical Brownian motion defined on $\mathcal{N}$. In either case, $\theta_t$ describes the status of the respiratory drive at time $t$.

In general, the phase space $\mathcal{N}$ is not accessible, and we do not know where the manifold is. However, we are able to “design” a sensor to “detect” this manifold, and hence “sense” the respiratory drive. As discussed in Example 1, the ECG signal is such a sensor. To model it, we assume that there is a diffeomorphism $\Psi$ that maps $\mathcal{N}$ to the wave-shape manifold $\mathcal{M}$ associated with the ECG signal. Therefore, the dynamical flow $\theta_t$ is mapped to a dynamical flow $\psi_t := \Psi \circ \theta_t$ defined on $\mathcal{M}$. Clearly, under the model (12), $\psi$ is the flow associated with the vector field $\Psi^*X$ defined on $\mathcal{M}$. Under the model (13), by Ito’s formula, $\psi$ satisfies the stochastic differential equation defined on $\mathcal{M}$:

\begin{equation}
\mathrm{d}\psi_t = \left(\frac{1}{2} \Delta \Psi|_{\psi_t} + \nabla \Psi|_{\psi_t} X(\psi_t)\right) \mathrm{d}t + \nabla \Psi|_{\psi_t} \mathrm{d}\omega_t.
\end{equation}

As a result, if $t_j$ is the temporal location of the $j$-th R peak, $\psi_{t_j}$ is the oscillatory pattern of the $j$-th cardiac cycle of the ECG signal; that is, according to the discussion in Section 2.4, we have $E(t_j + t) \approx \psi_j(f_j t)$ when $t \in [-1/2, 1/2]$, where $f_j > 0$ is the IF of the ECG signal at time $t_j$. The model considered in Example 3 can be generalized to other physiological oscillatory signals, while the interpretation of $\theta_t$, $\mathcal{N}$, and $\psi_t$ will be different. In general, we call $\mathcal{N}$ the phase space for the dynamics we care about, $\theta_t$ the intrinsic dynamics, and $\psi_t$ the observable dynamics. In Section SI.2 in the Online Supplementary, we will extend this discussion to a new ECG-derived respiration algorithm.

Clearly, the wave-shape oscillatory model (10) differs from the phenomenological model (1) in how the oscillation is modeled. The main benefit of (10) is twofold. First, the dynamics encoded in the oscillatory morphology can be fully modeled and captured. Second, even if the oscillatory pattern dramatically changes from one cycle to the next, it can be captured by (10).

With the wave-shape oscillatory model, we expect to determine the dynamics encoded by the time-varying morphology of oscillatory cycles. The main challenges are the nonlinearity of the wave-shape manifold and the possible noise that deviates the observed oscillatory pattern from the wave-shape manifold. In the next section, we handle these challenges and achieve our goal using the diffusion geometry based algorithm, the DM.
3. Proposed algorithm to estimate the dynamics

With the wave-shape manifold hosting the dynamics of interest, we apply the well-established manifold learning algorithm, the DM [17], to recover these dynamics. In a nutshell, the DM integrates local similarities and finds a global description of the data set, and it generalizes the original eigenmap [7]. We choose the DM as our main tool not only because of the nonlinear structure of the manifold, but also because of its sound theoretical support. The spectral embedding in terms of spectral geometry is discussed in [10]. Based on the manifold model, we review the GL and the DM. We also provide theoretical results about the spectral convergence rate are reported in [67, 70]. In [29] the central limit theory of the GL is provided. The problem of embedding via a finite convergence of the GL to the Laplace-Beltrami operator of the associated manifold is studied in [8, 34, 58]. The spectral convergence of the GL is studied in [59], and results about the spectral convergence rate are reported in [67, 70]. In [29] the central limit theory of the GL is provided. The problem of embedding via a finite number of eigenfunctions of the Laplace-Beltrami operator is studied in [37] [5] [54].

Before we propose our new algorithm for dynamics estimation based on the wave-shape manifold model, we review the GL and the DM. We also provide theoretical support for the proposed algorithm.

3.1. Review of spectral graph theory and the DM. Take a point cloud $X := \{x_i\} \subset \mathbb{R}^p$. Construct an $n \times n$ affinity matrix $W$ so that

$$W_{ij} = e^{-\|x_i - x_j\|^2/h}, \text{ for } i, j = 1, \ldots, n,$$

where the bandwidth $h > 0$ is chosen by the user. We mention that in practice, when the signal-to-noise ratio is low, it is beneficial to set $W_{ii} = 0$ [23]. Here, to simplify the discussion, we use the radial basis function to design the affinity, but in practice we are free to choose a more general kernel. Moreover, the DM can be defined on a point cloud in a general metric space, but we focus on compact subsets of Euclidean space. Define a random walk on the point cloud $X$ whose transition matrix $A(W)$ is

$$A(W) := D^{-1}W,$$

where $D$ is a diagonal $n \times n$ matrix given by

$$D_{ii} = \sum_{j=1}^{n} W_{ij}, \text{ for } i = 1, \ldots, n. \tag{17}$$

We call $D$ the degree matrix associated with $W$. Define the GL by $L(W) := \frac{I - A(W)}{\Lambda}$, where $I$ is the $n \times n$ identity matrix. Clearly, $A(W)$ is diagonalizable since $A(W)$ is similar to the symmetric matrix $D^{-1/2}WD^{-1/2}$, which has an eigen-decomposition $O\Lambda O^T$. Therefore, we have $A(W) = U\Lambda V^T$, where $U = D^{-1/2}O$ and $V = D^{1/2}O$. Here, $U \in GL(n)$ contains the right eigenvectors $\phi_1, \phi_2, \ldots, \phi_n \in \mathbb{R}^n$ in its columns, and the corresponding eigenvalues are $1 = \lambda_1 > \lambda_2 \geq \ldots \geq \lambda_n \geq 0$. By a direct calculation, we know that $\phi_1 = [1, 1, \ldots, 1]^T \in \mathbb{R}^n$, and $L(W) = U\Lambda V^T$, where $\Lambda = \text{diag}(|\lambda_1, \ldots, \lambda_n|$ and $\lambda_k = 1 - h\lambda_k$. Here, $\lambda_1 > \lambda_2$ since the graph associated with $W$ is complete, and hence connected. Moreover, $\lambda_n \geq 0$ comes from the chosen positive definite kernel and the Bochner theorem [27]. With the decomposition $A(W) = U\Lambda V^T$, the DM is defined as

$$\Phi_{d}^t : x_j \mapsto (\tilde{\lambda}_2^t \phi_2(j), \tilde{\lambda}_3^t \phi_3(j), \ldots, \tilde{\lambda}_{d+1}^t \phi_{d+1}(j)) \in \mathbb{R}^d, \tag{18}$$

where $\tilde{\lambda}_k^t = \frac{\lambda_k^t}{\sum_{k=1}^n \lambda_k^t}$.
where \( j = 1, \ldots, n, t > 0 \) is the diffusion time chosen by the user, and \( \hat{d} \in \mathbb{N} \) is the embedding dimension chosen by the user. Note that \( \hat{\lambda}_1 \) and \( \hat{\phi}_1 \) are ignored in the embedding since they are not informative. In practice, \( \hat{d} \) can be determined in a more adaptive way according to the decay of the eigenvalues; for example, \( \hat{d} \) can be chosen to be the largest \( j \) satisfying \( \hat{\lambda}_j > \delta > 0 \), where \( \delta \) is chosen by the user. There is no universal rule guiding the choice of \( \hat{d} \). It depends on the problem at hand and can be obtained by optimizing some quantities of interest. Clearly, if \( \hat{d} \) is less than \( p \), we have nonlinearly reduced the dimension; if \( \hat{d} = 3 \), we can visualize the high-dimensional data set.

3.2. Proposed algorithm. We now propose a novel algorithm to explore dynamics under the wave-shape oscillatory model. The algorithm is composed of 4 main steps, and the details of each step depend on the physiological oscillatory time series that is under consideration. Suppose the time series is sampled uniformly at \( f_s \) Hz for \( T > 0 \) seconds; that is, there are in total \( n := \lfloor T \times f_s \rfloor \) sampling points. Denote the time series as \( f = (f(1), \ldots, f(n))^\top \in \mathbb{R}^n \).

(Step 1) Apply any suitable beat tracking algorithm to determine all oscillatory cycles. Suppose there are \( N \) resulting cycles. Denote the temporal location of the \( i \)-th oscillation as \( t_i \), where \( i = 1, \ldots, N \); that is, \( t_1 < t_2 < \ldots < t_N \).

(Step 2) Extract wave-shapes from \( f \) in the following way. Denote the \( i \)-th wave-shape from \( f \) as \( x_i \in \mathbb{R}^p \), which represents the \( i \)-th oscillatory cycle, where \( p > 0 \) depends on the frequency scale of the oscillation. Note that in general these segments might overlap. Define

\[
X_f := \{x_i\}_{i=1}^N \subset \mathbb{R}^p.
\]

Based on our model, \( X_f \) is a noisy set sampled from the wave-shape manifold \( M_f \) associated with the oscillatory physiological time series.

(Step 3) Construct the transition matrix (16) on \( X_f \), and find its eigenvalues and eigenvectors. Denote the \( k \)-th eigenvector of the \( A(W) \) as \( \phi_k \in \mathbb{R}^N \), and let \( \hat{\lambda}_k \) be the associated eigenvalue, where \( k = 1, \ldots, N \).

(Step 4) Run the DM (18) with \( \phi_k \) and \( \hat{\lambda}_k \) to recover or visualize the underlying wave-shape manifold.

We mention that the \( j \)-th entries of the “first few” eigenvectors recover the dynamical state of the system at the \( t_j \)-th second. We will carefully explain what this means in the next section by providing some theoretical support. In any case, the functions \( t_j \mapsto \phi_k(j) \) contain the dynamics of interest, and we can apply any suitable time series analysis tools or time-frequency analysis tools [26] to study them.

3.3. Theoretical support for the proposed algorithm – recovery of the dynamics. In general, the point cloud \( X_f = \{x_i\}_{i=1}^n \subset \mathbb{R}^p \) is generated from a dynamical system supported on the wave-shape manifold and contaminated by noise. The dynamical system might be non-trivial and in general it is not easy to provide an accurate model. However, for the purpose of recovering the wave-shape manifold (prior to visualizing the dynamics of interest), the temporal relationship among points in \( X_f \) can be forgotten.

Assumption 3.1. Assume the wave-shape manifold \( M_f \) is a \( d \)-dimensional, closed (compact without boundary) and smooth Riemannian manifold embedded in \( \mathbb{R}^p \) with
the Riemannian metric \( g \) induced from the canonical metric of \( \mathbb{R}^p \), where \( d \leq p \). We assume that \( S_f = \{s_i\}_{i=1}^n \) is independently and identically sampled from a random vector \( S : (\Omega, \mathcal{F}, \mathbb{P}) \to \mathbb{R}^p \), where the range of \( S \) is supported on the wave-shape manifold \( M_f \), and the noise \( \xi_i \) is independent of \( S \).

**Assumption 3.2.** We assume that the induced measure on the Borel sigma algebra on \( M_f \), denoted as \( \mathcal{S}_S, \mathbb{P} \), is absolutely continuous with respect to the Riemannian measure \( dV_g \). Furthermore, we assume that the function \( p := \frac{S_f}{dV_g} : M_f \to \mathbb{R}^+ \) given by Radon-Nikodym theorem is bounded away from zero and is sufficiently smooth. We call \( p \) the probability density function (p.d.f.) on \( M_f \) associated with \( X \). When \( p \) is a constant function, we say \( X \) is uniform; otherwise \( X \) is nonuniform.

Denote by \( g_k \) and \( \mu_k \) the \( k \)-th eigenfunction and eigenvalue of the Laplace-Beltrami operator \( \Delta_g \) of the wave-shape manifold \( M_f \), where \( k \in \mathbb{N} \); that is \( \Delta_g g_k = -\mu_k g_k \). According to basic elliptic theory [9], the spectrum of \( \Delta_g \) is discrete and accumulates at \( \infty \); that is, \( \mu_1 = \mu_2 = \ldots = \mu_{n_c} = 0 < \mu_{n_c+1} \leq \mu_{n_c+2}, \ldots \), where \( n_c \in \mathbb{N} \) is the number of connected components of \( M_f \), and the dimension of each eigenspace, denoted as \( E_k \), is finite, except at the accumulation eigenvalue. As above, we denote by \( \phi_k \) and \( \lambda_k \) the \( k \)-th eigenvector and eigenvalue of the GL, \( L(W), \) constructed from the point cloud \( S_f = \{s_i\}_{i=1}^n \subset \mathbb{R}^p \) [16].

Now, assume Assumptions 3.1 and 3.2 hold, and assume that \( p \) is uniform (see Remark [1]). Suppose \( \varphi : \mathbb{R} \to M_f \) represents the dynamics in which we have interest so that \( \varphi(t_j) = s_j \); that is, \( s_j \) is located at time \( t_j \). We now claim that we can recover the dynamics \( \varphi \) by the DM.

Under the above setup, recall the recent spectral convergence result reported in [67, Theorem 1, Theorem 2, and Theorem 5]. Consider \( h = h(n) \) so that \( h = \sqrt{\frac{\log(n)^{p_d}}{n^{1/d}}} \), where \( p_2 = 3/4 \) and \( p_d = 1/d \) when \( d \geq 3 \). For \( M_f \), denote by \( V \) its volume, \( \iota_0 \) its injectivity radius, \( K \) its global upper bound on the sectional curvature, and \( R \) its reach. Take \( \beta > 1 \). For all \( k \leq C_{K,V,d,\iota_0,\beta} \sqrt{\frac{n}{\log(n)^{p_d}}} \) when \( d \geq 2 \), with probability at least \( 1 - C_{K,V,d,\iota_0} n^{-\beta} \), we have

\[
|\lambda_k - \mu_k| \leq C_d \left( \frac{\log(n)^{p_d}}{hn^{1/d}} + (1 + \sqrt{\mu_k})h + (K + R^{-2})h^2 \right)
\]

and

\[
\|\mathcal{E}\phi_k - g_k\|_{L^2(M_f, p dV_g)} \leq C_d \frac{C_d}{\min_{j \neq k} |\mu_k - \mu_j|}
\times \left( \frac{\log(n)^{p_d}}{hn^{1/d}} + \left[ 1 + (1 + \min_{j \neq k} |\mu_k - \mu_j|)\sqrt{\mu_k} \right]h + (K + R^{-2})h^2 \right),
\]

where \( \mathcal{E} \) is an extrapolation operator extending a function defined on \( S_f \) to \( M_f \) [67, (1.24)]. As a result, for each fixed \( k \geq 2 \) we have

\[
|\lambda_k - \mu_k| \to 0 \quad \text{and} \quad \|\mathcal{E}\phi_k - g_k\|_{L^2(M_f, p dV_g)} \to 0
\]

when \( n \to \infty \) almost surely at the rate \( \sqrt{\frac{\log(n)^{p_d}}{n^{1/d}}} \).

This spectral convergence result of the GL emphasizes what \( \phi_k \) estimates. Particularly, by composing the eigenvectors and the temporal information, the above shows that \( \phi_k = [\phi_k(1), \ldots, \phi_k(n)]^T \) is actually an estimate of \( [g_k \circ \varphi(t_1), \ldots, g_k \circ \varphi(t_n)] \).
The spectral embedding of the proposed algorithm is a surrogate for the dynamics of interest. It contains useful information concerning the intrinsic dynamics; in this sense the product of the proposed algorithm is a surrogate for the dynamics of interest.

The above result can be immediately combined with the spectral embedding theory \[10\] to justify how the DM recovers the manifold, and hence the dynamics on it. The spectral embedding of \(M_f\) is defined as follows \[10\]. Take an \(L^2(M_f)\) basis \(\{g_k\}_{k=1}^\infty \in \Pi_{k=1}^\infty O(\text{dim}(E_k)).\) Define

\[
\Psi^a_t : x \mapsto (2t)^{d+2} \sqrt{2(4\pi)^\frac{d}{2}} (e^{-t\lambda_k g_i(x)})_{i=1}^\infty \in \ell^2,
\]

where \(t > 0\) is the diffusion time. It is shown in \[10\] Theorem 5 that \(\Psi^a_t\) is not only an embedding for any \(t > 0\), but also an almost-isometric embedding when \(t > 0\) is sufficiently small; that is, the pulled-back metric \((\Psi^a_t)^*\) can, where \(\text{can}\) is the canonical metric on \(\ell^2\), satisfies

\[
(\Psi^a_t)^* \text{can} = g + \frac{2t}{3} \left(\frac{1}{2} \text{Scal}_g g - \text{Ric}_g\right) + O(t^2)
\]

when \(t \to 0\), where \(\text{Scal}_g\) is the scalar curvature and \(\text{Ric}_g\) is the Ricci curvature. Recently, the spectral embedding theory of the Laplace-Beltrami operator was generalized to the finite-dimensional setting \[5\] \[54\]. Denote by \(\kappa\) the lower bound on the Ricci curvature of \(M_f\). Then, for a given tolerable error \(\epsilon > 0\), there exists a \(t_0 = t_0(d,\epsilon,\kappa,\iota_0)\) such that for all \(0 < t < t_0\), there exists an \(n_E = n_E(d,\epsilon,t,\kappa,\iota_0,V)\) such that if \(q \geq n_E\), the finite-dimensional map

\[
\Psi^{a,q}_t : x \mapsto \sqrt{2(4\pi)^\frac{d}{2}} (2t)^{d+2} (e^{-t\lambda_l g_i(x)})_{i=1}^q \in \mathbb{R}^q
\]

is an embedding and satisfies

\[
1 - \epsilon \leq \|\left(d\Psi^{a,q}_t\right)_x\| \leq 1 + \epsilon.
\]

Note that the DM defined in \[18\] can be viewed as a discretization of \(\Psi^{a,q}_t\) without the universal constant \((2t)^{d+2} \sqrt{2(4\pi)^\frac{d}{2}}\), while the eigenvalues and eigenvectors are estimated from the data.

Now put everything together. Fix \(\beta > 3/2\). For a given sufficiently small \(\epsilon\), take \(0 < t < t_0(d,\epsilon,\kappa,\iota_0)\). When \(\hat{d} \geq n_E(d,\epsilon,t,\kappa,\iota_0,V)\) and \(n\) is large enough so that

\[
\frac{n}{\log(n)^{3/2}} \geq C\frac{p^2}{\ell^2},
\]

with probability at least \(1 - C_K, \ell, p, \beta \frac{1}{n^{1/2 - \beta}}\), the spectral convergence \[20\] and \[21\] hold for all \(k\)-th eigenvalues and eigenvectors when \(k \leq \hat{d}\). Here we use the simple uniform bound \(dn^{-\beta} \leq C_{K, \ell, p, \beta} \frac{1}{n^{1/2 - \beta}}\). Now, extend the DM defined in \[18\] to

\[
\Phi^{\hat{d}}_t : x \mapsto \left((1 - h\lambda_2)^t \phi_2(x), (1 - h\lambda_3)^t \phi_3(x), \ldots, (1 - h\lambda_{d+1})^t \phi_{d+1}(x)\right).
\]

As a result, when \(n\) is finite, via \(\Phi^{\hat{d}}_t\), with high probability, the DM recovers the manifold \(M\) due to the finite spectral embedding \[25\].

Example 5 (Continuation of Example 4). Recall the observable dynamics \(\psi_t\) on the wave-shape oscillatory model shown in Example 4. Suppose the respiratory dynamics are periodic; that is, \(\theta_t \approx \theta_{t+T}\), where \(T > 0\) is the period, and suppose variations in the ECG waveform can be parametrized fully in terms of respiratory dynamics. In this case, \(\psi_t \approx \psi_{t+T}\), and since \(g_k\) is smooth, we have \(g_k \circ \psi_t \approx g_k \circ \psi_{t+T}\) for all \(k\). While there is no guarantee that the period of \(g_k \circ \psi_t\) is again...
due to the nonlinearity of $g_k$, the periodicity information is captured in the $k$-th eigenvector $\phi_k$.

**Remark 1.** We focus on the uniform density assumption to simplify the above discussion. If the sampling scheme is nonuniform, by estimating the density function, we could correct the diffusion process by the $\alpha$-normalization scheme proposed in [17]. Since the theorem statement and proof are more complicated and do not provide more insight to the whole problem, we simplify the discussion by assuming the uniform sampling scheme. Similarly, we may discuss the manifold with boundary case [59], but we choose to discuss the closed manifold case to simplify the discussion. Moreover, we focus on the observable dynamics on $M$. If we have interest in the intrinsic dynamics $\theta$ on $N$ shown in Example 4 and Figure 4, we can further apply the empirical intrinsic geometry [64] approach, which we again skip to simplify the discussion.

### 3.4. Theoretical support for the proposed algorithm – robustness to noise.

A real physiological time series is inevitably noisy. The wave-shape $x_i \in X_f$ is a noisy version of $s_i \in S_f \subset M_f$. When the data is noisy, it has been shown in [22, 23] that under some mild assumptions, the DM is robust to noise, which we summarize here. Denote by $W$ and $W_0$ the affinity matrices associated with $X_f$ and $S_f$ respectively. By [22, 23] when the connection group is the trivial $SO(1) := \{1\}$ group, if $\sup_{i,j} |W_{i,j} - (W_0)_{i,j}| \leq \varepsilon$ for $\varepsilon > 0$, and $\inf_i \sum_{j \neq i} W_{i,j} / n > \gamma$ and $\gamma > \varepsilon$, we have

\[
\|A(W) - A(W_0)\| \leq \frac{\varepsilon}{\gamma} \left(1 + \frac{1}{\gamma - \varepsilon}\right),
\]

where $\| \cdot \|$ is the operator norm. By Weyl’s inequality and the Davis-Kahan $\sin(\theta)$ theorem, the first $q'$ eigenvectors and eigenvalues are well-reconstructed up to a controllable error, where the number $q'$ depends on the noise level. When $q'$ is large enough so that $q' \geq n_E(d, \epsilon, t, \kappa, \iota, V)$, with the finite-dimensional embedding result, we are guaranteed a reconstruction of the manifold. We thus conclude that the DM affords us a reconstruction of the clean data up to a tolerable error. Below, we demonstrate the usefulness of the proposed algorithm by applying it to analyze a clinical time series.

### 4. Testbed – pulse waveform analysis during general anesthesia

We use a clinical data set, the “noxious stimulation” data set, to study physiological responses of the cardiovascular system to surgical events. To this end, we analyze the pulse waveform obtained from the ABP signal. We study a particular surgical event, namely endotracheal intubation. It is well known that this procedure elicits nociception and a response by the autonomic nervous system (ANS). This response includes a change in heart rate and an elevation in blood pressure. The change in heart rate corresponds to frequency modulation in the ABP signal, and the change in blood pressure corresponds to the trend. However, we are concerned with morphological changes to the waveform which are not due to AM, FM, or the trend.

#### 4.1. Material.

All ABP signals were collected in the operating room. With the goal of analyzing the dynamic response of the human body to distinct surgical steps, the database’s collection was approved by the local institutional ethics review boards (Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; IRB No.:
and written informed consent was obtained from each patient. By using standard patient monitoring (Philips Intellivue) instruments, the data was collected via the third-party software, ixTrendExpress ver. 2.1 (ixellence GmbH, Wildau, Germany). The sampling rates of the ABP channels was 125 Hz. The moment of each surgical step was registered using purpose-made software so that precision was less than one second.

4.2. Data Preparation. To obtain all pulses from the ABP signal, we detect a landmark on each cycle associated with the pulse wave arrival time. This landmark is determined by finding the maximum of the first derivative during the ascending phase of the ABP waveform; that is, the point at which the pulse ascends fastest.

Suppose the ABP time series is discretized as \( \mathbf{A} \in \mathbb{R}^n \), where \( n = \lfloor f_s \times T \rfloor \), \( f_s \) is the sampling rate, and \( T \) is the duration of the recording in seconds. Suppose there are \( N \) detected pulse arrival points, and their locations in samples are \( \{ a_i \}_{i=1}^N \). The interval between two consecutive oscillations is \( L_i := a_{i+1} - a_i \), where \( 1 \leq i \leq N-1 \).

Set \( L := \min_{i=1}^{N-1} L_i \). Delineate the cycles in the ABP signal as

\[
X_i(j) := \mathbf{A}(a_i + j),
\]

where \( i = 1, \ldots, N \) and \( -\lfloor f_s \times 0.08 \rfloor \leq j \leq L \). Clearly, \( \mathbf{X}_i \in \mathbb{R}^p \), where \( p := \lfloor f_s \times 0.08 \rfloor + L + 1 \). Next, we remove the blood pressure information by normalizing each \( \mathbf{X}_i \). Set

\[
\bar{X}_i(j) := \sigma_i^{-1}(X_i(j) - \mu_i)
\]

for \( j = 1, \ldots, p \), where \( \mu_i \) is the mean of \( \mathbf{X}_i \) and \( \sigma_i \) is the standard deviation.

Finally, assemble the collection of ABP pulses as \( \mathcal{X}_A := \{ \bar{X}_i \}_{i=1}^n \). The point cloud \( \mathcal{X}_A \) encodes the morphological information of the ABP waveform and the temporal information is preserved in the sequence \( \{ a_i \} \).

4.3. Result. The three-dimensional embedding of \( \mathcal{X}_A \) via the DM provides an intuitive visualization. We show the embedding of the signal shown in Figure 1 in Figure 5. In this ABP recording, the stimulus event, endotracheal intubation, happened around the 10-second mark. To read the physiological evolution elicited as nociception, we read the trajectory shown in Figure 5, where the trajectory is colored by time, \( a_i \).

It is apparent that each subject’s trajectory forms a loop-like structure. Before the noxious stimulus, the pulse waveform is stable. The blue points in the embedding represent the patient’s normal ABP waveform. In response to the stimulus event, the embedded cycles “fly away” because of large changes in cycle morphology (see the green points). However, the heart rate response happens later. After a while, the morphology returns back to normal, as indicated by the red points converging near the blue circles. Compared with the morphology, the heart rate does not return to normal at the end of this recording. This finding indicates a nonlinear relationship between the wave-shape and the heart rate. It is worth mentioning that since the blood pressure information has been removed (detrended), the embedding only reflects the dynamics encoded in the time-varying oscillatory morphology.

The above finding coincides with our physiological knowledge: the stimulus invokes a series of physiological responses including vasoconstriction, increased heart contractility, and their subsequent interactions. The impact of the stimulus decays after a while, and the physiological status gradually returns to normal. In sum,
this embedding helps visualize the transient dynamics in response to the stimulus event from the integrated vascular wall tension, blood volume and heart contraction effect on the pulse waveform.

**Figure 5.** We show a three-dimensional embedding of the pulse waveforms extracted from a 200-second arterial blood pressure (ABP) signal. The signal was recorded from a patient undergoing general anesthesia before and after an endotracheal intubation event. The ABP signal is shown in Figure 1. The event happens at the 10th second, indicated by the black arrow. Left: the embedded points are coloured by time; right: the points are coloured by heart rate.

### 4.4. Global coordinates for noxious stimulus quantification.

Note that while the proposed algorithm helps visualize changes in pulse waveform morphology, it does not automatically provide a quantification of noxious stimuli. While we can apply the same approach to analyze the ABP signals recorded from different subjects, a quantification of how the body responds to noxious stimuli regardless of inter-individual variability is challenging. In fact, embeddings of different ABP signals may vary from subject to subject (figures not shown). This is due to a critical limitation of the DM: the embedding is in general unique only up to rotation. We propose to resolve this challenge via an intuitive idea, which we coin the *global coordinate system*. It is done by passing all pulse cycles from all available subjects through the DM. By pooling together all pulse cycles from all available subjects, the DM constructs a coordinate system that is shared by all subjects.

In Figure 6, we show the embedding of all pulse cycles from 8 subjects recorded under the same stimulus. The trajectory of the subject shown in Figure 5 is shown in the left subplot of Figure 6 colored with time, and another subject is shown in the right subplot of Figure 6. Notice that the trajectory of each individual in the global coordinate system features the subject’s underlying physiological dynamics, and this global coordinate system allows us to compare subjects and hence quantify the response to the stimulus. We mention that once the global coordinate system is constructed, a newly-arriving subject’s data can be incorporated into this coordinate system via any extrapolation scheme, like Nyström’s [74]. Since the
quantification of dynamics is itself an important topic and depends on the application, we will report details and application results in future clinical work.

![Figure 6](image)

**Figure 6.** An illustration of the three-dimensional global coordinate system constructed from all pulse waveforms from eight subjects (including the subject shown in Figure 5). Each subplot shows the information from one subject, and the colour indicates time.

5. Discussion and Conclusion

In this paper, we propose a novel “wave-shape manifold” to model the time-varying morphology of cycles commonly observed in oscillatory physiological time series. We mention that the proposed wave-shape manifold model has been implicitly applied in fetal ECG analysis [62], f-wave analysis [33], and intracranial electroencephalogram analysis [1]. This is the first time we provide a systematic discussion of the model. This wave-shape manifold model is then used to model oscillatory physiological time series; we coin this model the “wave-shape oscillatory model.” The wave-shape oscillatory model generalizes the traditional phenomenological model by capturing nonlinear changes in cycle morphology which occur due to all factors and not simply amplitude and frequency modulation. Moreover, it bypasses the troublesome “slowly varying” assumption and allows for multiple templates. Given a time series adhering to the wave-shape oscillatory model, we apply the well-established DM algorithm to its set of oscillations to recover the dynamics encoded by their time-varying morphologies. The performance and usefulness of the proposed model and algorithm are evaluated on two real physiological time series: the ABP signal shown in Section 4 and the ECG shown in Section SI.2. We show that the proposed approach has the potential to obtain clinically relevant information from a non-traditional perspective. Last but not least, it is worth mentioning that, compared with our approach, using landmarks to quantify the oscillatory pattern is a dimension reduction step from the machine learning viewpoint, which might result in the loss of important information.
5.1. **Clinical application.** In this study, we use two data sets to demonstrate the proposed model and algorithm. The first database consists of single-lead ECG signals, and we introduce a new EDR algorithm. The result shows that the proposed algorithm based on the wave-shape oscillatory model provides respiratory dynamics from a non-traditional perspective. The second database consists of ABP signals recorded during the endotracheal intubation surgical procedure. Through this database, we observe the cardiovascular effects of endotracheal intubation exhibited in the ABP waveform. Even though patients in an unconscious state would not feel pain, the surgical step still elicits nociception in the human body and produces dynamic effects on the circulation system; these changes are encoded in the subtle variation in blood pressure waveform morphology. The proposed algorithm has the potential to help quantify noxious stimuli during surgery, and we will report this application in future work.

A direct application of the proposed algorithm is a visualization of long-term physiological time series. As technology advances, ultra-long-term monitoring systems are getting popular [4]. However, there is a lack of complimentary analysis tools for such an ultra-long signal, even for visualization. Specifically, it is difficult to directly visualize a 3-hour physiological time series, such as an ABP signal, using the current patient monitor system. Most of the time, the transition from one state to another is not that transient, and it is difficult to be perceived by direct vision of the time series. Our approach, however, has the potential to reveal this kind of “long-term” dynamical information by excising the times series’ cycles and embedding them into a low-dimensional space via the DM. The result is a set of information-dense time series recorded at a much lower sampling rate than the original signal. Ultimately, we expect to generate a holographic visualization of a given long-term physiological time series. While this topic is out of the scope of the current paper, we will explore it in future work.

5.2. **Comparison with existing literature.** It is important to mention that there have been several attempts to study time series by taking a manifold model into account. A well-known approach is Takens’ lag map [63]. Suppose the discrete dynamics of interest, \( X(n), n \in \mathbb{N} \), are supported on a \( d \)-dimensional manifold \( \mathcal{M} \), and that we observe the dynamics via an observational function \( f: \mathcal{M} \rightarrow \mathbb{R} \); that is, we have a time series \( Y(n) := f(X(n)), \) where \( n \in \mathbb{N} \). Takens’ lag map is obtained by constructing \( y_{i}^{(\tau)} := (Y(i), \ldots, Y(i + \tau(p - 1)))^T \in \mathbb{R}^p \), where \( \tau \in \mathbb{N} \) and \( p \in \mathbb{N} \) are chosen by the user. According to \([63, 57, 61]\), when \( p > 2d \), under a mild condition on \( \tau \), \( f \), and the underlying dynamics, we can reconstruct the underlying manifold up to a diffeomorphism via \( Y_{p,\tau} := \{y_i^{(\tau)}\} \subset \mathbb{R}^p \). Usually, the next step is evaluating the invariant features which depend only on the differential structure of the dynamics, like fractal dimensions of attractors, from \( Y_{p,\tau} \). In [52], \( y_i \) is understood as a “1-dimensional patch” when \( \tau = 1 \); that is, consider \( Y_{p,1} \). This patch idea is generalized to higher dimensional signals, like images [21] [52]. In these approaches, the collection of patches of a given signal (any dimension) is assumed to be a manifold called the *patch manifold*. When the signal is an image, the manifold structure is applied to handle various image processing missions. In our model, however, the manifold comes from the oscillatory cycles, not Takens’ lag map. Note that to recover the wave-shape manifold, we collect oscillatory cycles by taking the temporal location of “landmarks” into account. Due to the non-constant \( p \), those landmarks do not appear regularly. If the cycle is of length \( p \), the collected
oscillatory cycles form a strict subset of \( \mathcal{Y}_{p,1} \), which is clearly different from Takens’ lag map. When the IF is constant, the oscillation appears every \( L \) samples, and the set of oscillatory cycles is exactly \( \mathcal{Y}_{p,L} \).

5.3. Future work. The proposed model opens several research directions. First, while the wave-shape oscillatory model and the proposed algorithm have been shown to work well for several physiological time series, fully quantifying the wave-shape dynamics depends on the assumption that oscillatory cycles do not overlap, or that we do not need the information encoded in the overlapping. We may need a better algorithm when recovering the information encoded in the overlapping is critical. On the other hand, except showing the recovery of the dynamics in Sections SI.2 and 3 in this paper we do not systematically model and explore the dynamics of \( \{t_j\} \) and \( \{s_j\} \) in (10) for the purposes of system quantification and prediction. An exploration depends on the signal type and the clinical problem of interest. We will report its application in the future work.

Second, in our algorithm we implicitly assume that we are able to determine at least one landmark for the oscillatory pattern, so that we can delineate cycles and construct the point cloud associated with the wave-shape manifold. However, it might not always be possible to achieve. When the IF is slowly varying, we may count on the de-shape short-time Fourier transform proposed in [40] to determine the cycles. In general it is challenging [20] and might depend on the problem.

Third, from the theoretical perspective, the spectral embedding and spectral convergence results we count on to validate the DM algorithm are not complete. For example, while the spectral embedding result helps explain how the DM works, it does not fully explain if, and when, the DM can achieve dimension reduction. Specifically, to the best of our knowledge, there is no result discussing how to estimate \( n_E \) in (25) from the given geometric and topological profile of the manifold. Without this piece of information, we cannot even estimate the number \( d \) (18) of eigenvectors needed to reconstruct the manifold. To further understand the embedding, the spectral convergence of each eigenvector shown in (21) needs to be boosted to recover the regularity of the eigenfunction. Moreover, the robustness property of the DM mentioned in Section 3.4 needs to be improved by taking random matrix theory into account. According to our best knowledge, this direction is relatively empty and needs more exploration.

Fourth, concerning clinical applications, the “global coordinate system” considered in Section 4 is critical for handling the non-unique embedding issue of the DM. However, by pooling subjects together to construct these global coordinates, we run into the issue of increasing computational loads. Moreover, for application at the bedside, a real-time implementation of the proposed algorithm is necessary. We will systematically handle the above-mentioned statistical challenges, theoretical problems, and numerical issues concerning clinical applications in future work.

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APPENDIX SI.1. PROOF OF THEOREMS 2.2 AND 2.3

Proof of Theorem 2.2. Note that since $s \in C^{1,\alpha}$, $\Phi(U) \subset C^{1,\alpha}_c(\mathbb{R})$. Suppose $(a_1, f_1) \neq (a_2, f_2)$ while

\begin{equation}
\| \Phi(a_1, f_1) - \Phi(a_2, f_2) \|_2 = 0.
\end{equation}

We abuse the notation and denote $\Phi(a_1, f_1) = a_1 s(f_1 t)$, where $t \in \mathbb{R}$ to simplify the discussion when there is no danger of confusion. Since $s$ continuous, we have

\begin{equation}
 a_1 s(f_1 t) = a_2 s(f_2 t)
\end{equation}

for all $t \in \mathbb{R}$. Suppose $a_1 s(f_1 t)$ has support $[a, b] \subset [-1/2 f_1, 1/2 f_1]$. Without loss of generality, assume $f_2 > f_1$, $a < 0$, and $b > 0$. The support of $a_2 s(f_2 t)$ is thus $[a f_2 / f_1, b f_2 / f_1] \subset [a, b]$. Hence, we can find $x \in [a, a f_1 / f_2] \cup [b f_1 / f_2, b]$ so that $a_1 s(f_1 x) \neq 0$ but $a_2 s(f_2 x) = 0$, which contradicts (SI.2). As a result, we have shown that $\Phi$ is one-one and onto $M := \Phi(U)$.

Since $\Phi$ is a Hilbert-space valued function, by checking the definition, we claim that its total differential is

\begin{equation}
 D\Phi|_{(a_0, f_0)}(h_1, h_2) = h_1 s(f_0 t) + h_2 a_0 t s'(f_0 t),
\end{equation}

where $(a_0, f_0) \in U$ and $(h_1, h_2) \in \mathbb{R}^2$. Indeed, when $(h_1, h_2) = (a - a_0, f - f_0)$, we have

\begin{equation}
 \Phi(a, f) - \Phi(a_0, f_0) - D\Phi|_{(a_0, f_0)}(a - a_0, f - f_0)
\end{equation}

\begin{equation}
 = as(f) - a_0 s(f_0 t) - [(a - a_0) s(f_0 t) + (f - f_0) a_0 t s'(f_0 t)]
\end{equation}

\begin{equation}
 = a_0 s(f_0 t) - s(f_0 t) - (f - f_0) t s'(s_0 t) + (a - a_0) (s(f_0 t) - s(f_0 t)).
\end{equation}

By the integral form of Taylor’s expansion, we have

\[
 s(f_0 t) - s(f_0 t) - (f - f_0) t s'(s_0 t) = \int_{f_0 t}^{f_0 t} s'(z) dz \quad \text{and} \quad s(f_0 t) - s(f_0 t) = \int_{f_0 t}^{f_0 t} (f - z) t^2 s''(z) dz.
\]

Here, we view $s(f_0 t)$ as a function of $f$. Next, we bound the $L^2$ norm of $\Phi(a, f) - \Phi(a_0, f_0) - D\Phi|_{(a_0, f_0)}(a - f_0)$.
for some \( a \). Indeed, we have

\[
\begin{align*}
\text{(SI.5)} & \quad \left\| \int_{f_0}^f (f-z)t^2 s''(zt)dz \right\|_{L^2} \\
& = \int_{f_0}^f \int_{f_0}^f (f-z)t^2 s''(zt)(f-z')t^2 s''(z't)dzdz' dt \\
& = \int_{f_0}^f \int_{f_0}^f (f-z)(f-z') \left[ \int t^2 s''(zt)t^2 s''(z't)dzdz' \right] dt.
\end{align*}
\]

Note that since \( s \in C^2_c \), we have

\[
\left| \int t^2 s''(zt)t^2 s''(z't)dt \right| \leq \left( \int t^4 |s''(zt)|^2 dt \right)^{1/2} \left( \int t^4 |s''(z't)|^2 dt \right)^{1/2} = \frac{C}{zz'}
\]

for some \( C > 0 \) depending on the fourth absolute moment of \( s'' \) only. As a result, we have

\[
\text{(SI.6)} \quad \left\| \int_{f_0}^f (f-z)t^2 s''(zt)dz \right\|_{L^2} \leq C \int_{f_0}^f \int_{f_0}^f \frac{|(f-z)(f-z')|}{zz'}dzdz' \\
\quad \leq \frac{C}{f_0} \left( \int_{f_0}^f |f-z|dz \right)^2 = \frac{C|f-f_0|^4}{4f_0^2}.
\]

Similarly, we can bound \( \int_{f_0}^f ts'(zt)dz \). Therefore,

\[
\text{(SI.7)} \quad \| \Phi(a,f) - \Phi(a_0,f_0) - D\Phi(a_0,f_0)(a-a_0,f-f_0) \|_{L^2} \leq C|f-f_0|^4,
\]

which leads to

\[
\text{(SI.8)} \quad \frac{\| \Phi(a,f) - \Phi(a_0,f_0) - D\Phi(a_0,f_0)(a-a_0,f-f_0) \|_{L^2}}{\| (a-a_0,f-f_0) \|} \to 0
\]

when \( \| (a-a_0,f-f_0) \| \to 0 \).

To finish the proof, we show that the total differential of \( \Phi \) at \( (a,f) \in U \), \( D\Phi|_{(a,f)} \), is of full rank for any \( (a,f) \in U \). It suffices to show that \( s(ft) \) and \( ats'(ft) \) are linearly independent in \( L^2(\mathbb{R}) \). Suppose there are constants \( c_1, c_2 \in \mathbb{R} \) such that for all \( t \in \mathbb{R} \),

\[
\text{(SI.9)} \quad c_1s(ft) = c_2ats'(ft).
\]

Suppose \( c_1 \neq 0 \). In this case, \( c_2 \neq 0 \); otherwise, we have a contradiction. Since \( s \in C^2_c \), there exists \( t \neq 0 \) such that \( s(ft) \neq 0 \) is the extremal value of \( s \); that is, \( fs'(ft) = 0 \). Since \( f > 0 \), \( s'(ft) = 0 \). Therefore, we have \( c_1s(ft) \neq 0 \) but \( c_2ats'(ft) = 0 \), which is a contradiction. As a result, we conclude that \( c_1 = 0 \). In this case, \( c_2 \) must be 0; otherwise, we have a contradiction. This concludes the claim that \( D\Phi|_{(a,f)} \) is of full rank. We conclude that \( \Phi: U \to L^2(\mathbb{T}) \) is a diffeomorphism.

\[
\square
\]

\textbf{Proof of Theorem 2.3}. Note that for each \( n \in \mathbb{Z} \), \( g_n \) and \( f_n \) are all supported in \([-1/2,1/2]\]. By a directly calculation, we have

\[
\text{(SI.10)} \quad |g_n(t) - f_n(t)| \leq |A(t_n) - A(t_n + t)||s(\phi'(t_n)t)| \\
\quad + A(t_n + t)|s(\phi'(t_n)t) - s(\phi(t_n + t))|.
\]
for all \( t \in [-1/2, 1/2] \), and \( |g_n(t) - f_n(t)| = 0 \) for all \( t \notin [-1/2, 1/2] \). By a direct bound, we have

\[
|A(t_n) - A(t_n + t)| \leq \int_{t_n}^{t_n + t} |A'(x)|dx \leq \epsilon \int_{t_n}^{t_n + t} |\phi'(t_n)| + \int_{t_n}^{t_n + t} \phi''(z)dz dx
\]  

(SI.11)

\[
|\phi'(x)| + \epsilon^2 M|t|^2 \leq \frac{1}{2} \epsilon \left[ \phi'(t_n) + \frac{1}{4} M \right],
\]

where the last bound holds since we only need to control \( t \in [-1/2, 1/2] \). For the other term, note that \( s(\phi(t_n + t)) = s(\phi(t_n)) + \phi'(t_n) + \left[ \int_{t_n}^{t_n + t} \phi''(z)dz \right] \) since \( \phi(t_n) \in \mathbb{Z} \) and \( s \) is 1-periodic. Therefore, by denoting \( J := \int_{t_n}^{t_n + t} \phi''(z)dz \), we have

\[
|s(\phi(t_n))/d - s(\phi(t_n + t))/d| \leq \int_{t_n}^{t_n + t} |s'/(x)|dx = J||s'||_{\infty}.
\]

\( J \) is controlled by the same way:

\[
|J| \leq \epsilon \int_{t_n}^{t_n + t} \phi''(z)dz \leq \epsilon \int_{t_n}^{t_n + t} z \phi'(t_n) + \int_{t_n}^{t_n + t} \phi''(w)dw dz
\]

\[
\leq \epsilon \left( \phi'(t_n) + \frac{1}{2} M|t|^2 \right) \leq \frac{1}{4} \epsilon \left( \phi'(t_n) + \frac{1}{4} M \right).
\]

As a result, we obtain the claim with \( C = C(||A||_{\infty}, ||\phi'||_{\infty}, ||s'||_{C^1}, M) \). \( \square \)

**Appendix SI.2. Another Testbed – the Electrocardiogram**

Landmark-based and spectral approaches to ECG waveform analysis are fundamental to electrocardiography. Approaches to interpreting the ECG waveform for various clinical purposes are well-documented. We show that the mature results in ECG waveform analysis may be reproduced via the wave-shape oscillatory model. This testbed has been chosen to provide a comfortable and systematic demonstration of the algorithm’s application.

As discussed in Example 1, electrocardiogram-derived respiration (EDR) is an old technique which uses a multiple- or single-channel ECG to estimate respiratory activity. Deriving the respiratory signal from a single-channel ECG has been attempted using a number of methods. Traditionally, the EDR signal is obtained by interpolating the time series of R peak amplitude,

\[
\text{EDR}(r_i) := \mathbf{E}(r_i) - \mathbf{E}(s_i),
\]

where \( \mathbf{E} \) is the ECG signal, \( r_i \) is the location of the \( i \)-th R peak, and \( s_i \) is the location of the following S peak, using piece-wise cubic spline interpolation [16, Chapter 8]. Another landmark-based method involves estimating the area of each QRS complex [16, Chapter 8]. In [35], principal component analysis (PCA) is used to obtain an EDR signal, and in [72], kernel principal component analysis (kPCA) is used. Since respiratory dynamics are known to manifest as amplitude modulation in the ECG waveform, recovering the respiratory signal via the wave-shape oscillatory model should be achievable.

Second, as is reflected in Figure 2, one template may not be enough to model the cardiac cycles present in a pathological ECG signal. We display how the non-parametric approach taken by the wave-shape oscillatory model circumvents this limitation by considering a subject with PVC arrhythmia. This approach amounts
to spectral clustering of the cardiac cycles observed in the recording for the purpose of beat classification. This idea is not new \[55\], but it is a demonstration of the advertised versatility of our model.

1. Detect R peaks  
2. Align cardiac cycles  
3. Diffusion map to $\mathbb{R}^\hat{d}$  
4. Interpolate eigenvectors at 10 Hz

**Figure 7.** A visualization of the application of the wave-shape oscillatory model to ECG waveform analysis. The R peaks are labeled as green crosses.

**SI.2.1. DM-EDR algorithm.** We provide a detailed implementation of the algorithm in Section \[3.2\] tailored for the ECG signal. The overall algorithm is summarized in Figure 7.

**SI.2.1.1. Pre-processing.** The ECG is upsampled to a sampling rate of 1000 Hz. Noise in the ECG signal is surpressed by applying a bi-directional lowpass filter with cutoff frequency 44 Hz. The baseline wandering (or trend) is removed using the method found in \[72\]. The baseline is estimated by applying a median filter with window size 200 ms, followed by a median filter with window size 600 ms. We detect the R peaks in the recording by applying a modified version of the algorithm in \[24\]. This step allows us to delineate cardiac cycles. Write the pre-processed ECG signal as a vector $E \in \mathbb{R}^n$, where $n = [f_s \times T]$, $f_s = 1000$ Hz is the sampling rate, and $T$ is the duration of the recording in seconds. Suppose there are $N$ detected R peaks in the ECG signal. Write the location in samples of the $i$th R peak as $r_i$ ($1 \leq i \leq N$). For the purpose of analyzing the traditional EDR signal, the S peak following each R peak is determined by

\[
s_i = \arg\min_{1 \leq t \leq 60} E(r_i + t),
\]

where 60 ms is chosen according to normal electrophysiology.

**SI.2.1.2. Estimating the underlying dynamics.** By defining a window surrounding each R peak that extends 250 ms to the left and 400 ms to the right, we are able to roughly extract each cardiac cycle.

\[
Q_i(j) := E(r_i + j),
\]

where $-250 \leq j \leq 400$. Clearly, $Q_i \in \mathbb{R}^p$, where $p = 651$. Note that $Q_i$ subliminally encodes the temporal information since it is the $i$-th cardiac cycle in the ECG signal. According to the wave-shape manifold model, the set of cardiac cycles lie on a low-dimensional manifold embedded in $\mathbb{R}^p$. The bandwidth $h$ for the
affinity matrix is determined by squaring the median of all pairwise distances in the data set. For $k = 1, \ldots, N$, denote by $R_k \in \mathbb{R}^N$ the $k$-th eigenvector of the transition matrix $D^{-1}W$. Write the eigenvalues as $1 = \lambda_1 \geq \lambda_2 \geq \ldots \geq \lambda_N \geq 0$.

As discussed in Section 3.2, $R_k$ can be viewed as a time series in which $R_k(i)$ represents the measurement made at time $r_i$ ms. As discussed in Section 3.2, $R_k$ is an “observation” of the dynamics on the wave-shape manifold.

To seek out this dynamical information, $R_k$, $k = 2, \ldots, N$, are interpolated at a sampling rate of 10 Hz over the duration of the recording using piece-wise cubic spline interpolation. By abusing notation, we use $R_k$ to indicate the interpolated vectors. Note that, in the case of EDR, due to the interactions between the eigenfunctions and the dynamics on the manifold, it is not guaranteed which eigenfunction will most accurately capture the respiratory dynamics. Automating a selection of the best eigenfunction requires further ingenuity. In the worst case, the respiratory information may be spread non-linearly across multiple eigenfunctions.

SI.2.2. Material. The ECG signals featured in our experiment are from a set of standard overnight polysomnogram (PSG) studies which were performed to confirm the presence of sleep apnea syndrome in clinical subjects suspected of sleep apnea at the sleep center in Chang Gung Memorial Hospital (CGMH), Linkou, Taoyuan, Taiwan. The Institutional Review Board of CGMH approved the study protocol (No. 101-4968A3). All recordings were acquired on the Alice 5 data acquisition system (Philips Respironics, Murrysville, PA). One subject with PVC arrhythmia is chosen manually from the database. We focus on the first lead of the ECG recording, which, before upsampling, is sampled at 200 Hz. An automated signal quality index called rSQI [6] is used to identify 15-minute segments of each ECG signal which can be trusted for analysis.

SI.2.3. Result. We visualize the dynamics in each 15-minute ECG signal in two ways. First, we visualize the wave-shape manifold by showing the image of the time-1 diffusion map, namely a scatter plot whose points are $(R_2(i), R_3(i)), 1 \leq i \leq N$. In Figure 8, we show that one subject has a wave-shape manifold roughly characterized in terms of R peak height and the interval between the R peak and the end of the T wave. (This second parameter is a surrogate for the width of the cardiac cycle.)

![Figure 8](image-url)

**Figure 8.** We map the set of cardiac cycles to $\mathbb{R}^2$ using the diffusion map. Each point corresponds to one cardiac cycle in the recording. Left: we colour each point by the amplitude of the cycle’s R peak; right: we colour each point by the length of the corresponding R-to-T interval, measured from the R peak to the end of the T wave.
To visualize the dynamics on the wave-shape manifold, we turn to the interpolated eigenfunctions. In Figure 9, we show that respiratory dynamics are encoded and well-captured by the second eigenfunction $R_2$. The accompanying airflow signal (Flow) from the PSG device is used to confirm this fact. From a clinical application perspective, the EDR signal obtained from either method is useful when the respiratory flow signal is of low quality or missing (see Figure 10). In Figure 11, we show that the eigenfunction is sensitive to PVC activity in a recording featuring such an arrhythmia. This comes from the mixing effect of the eigenvectors. While PVCs lie on a disconnected component of the wave-shape manifold, we do not have this information a priori and a complete graph is constructed. As a result, the non-trivial eigenvectors are distorted. To obtain the respiratory dynamics of a PVC patient, we should apply the DM to only those cardiac cycles which are classified as normal. The result is shown as $N_2$ in Figure 11.

**Figure 9.** The second eigenvector $R_2$ (the first coordinate of the diffusion map) is strongly correlated with the respiratory flow signal.

While no quantitative performance measurement is provided due to the page limit, this series of results demonstrates that, based on the wave-shape oscillatory model, we can extract respiratory and beat classification information from a non-traditional viewpoint. In the case of EDR, we do not claim that the proposed approach outperforms the traditional one, but this result suggests that we may combine the new approach with the traditional one to obtain a better estimate for the respiratory information. On the other hand, as is indicated in [72], using the whole cycle deteriorates the performance of estimating the respiratory signal, and it is better to solely use the QRS morphology. This might be explained by the nonlinear relationship between depolarization, repolarization, and the impedance level. Therefore, to improve the performance of DM-EDR, we may consider focusing...
The EDR signal (obtained from either method) is useful when the respiratory flow signal is ambiguous.

Morphological differences between normal and PVC beats are reflected in the second eigenvector \( R_2 \). Because of the mixing of eigenvectors, compensating for the presence of abnormal beats by ignoring them during interpolation does not yield respiratory information (\( R_{\text{normal}}^2 \)). Alternatively, using the DM to recover each connected component individually succeeds (\( N_2 \)).

on the QRS morphology, or we may design a new metric to compare oscillatory morphology. We will systematically explore this possibility in future work.

Department of Anesthesiology, Taipei Veteran General Hospital, Taipei, Taiwan
Department of Mathematics, Duke University, Durham, NC, USA
Department of Mathematics, Duke University, Durham, NC, USA; Department of Statistical Science, Duke University, Durham, NC, USA; Mathematics Division, National Center for Theoretical Sciences, Taipei, Taiwan

E-mail address: hauwu@math.duke.edu