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Original paper

Time series prediction of lung cancer patients' breathing pattern based on nonlinear dynamics

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ABSTRACT

This study focuses on predicting breathing pattern, which is crucial to deal with system latency in the treatments of moving lung tumors. Predicting respiratory motion in real-time is challenging, due to the inherent chaotic nature of breathing patterns, i.e. sensitive dependence on initial conditions. In this work, nonlinear prediction methods are used to predict the short-term evolution of the respiratory system for 62 patients, whose breathing time series was acquired using respiratory position management (RPM) system. Single step and N-point multi step prediction are performed for sampling rates of 5 Hz and 10 Hz. We compare the employed non-linear prediction methods with respect to prediction accuracy to Adaptive Infinite Impulse Response (IIR) prediction filters. A Local Average Model (LAM) and local linear models (LLMs) combined with a set of linear regularization techniques to solve ill-posed regression problems are implemented. For all sampling frequencies both single step and N-point multi step prediction results obtained using LAM and LLM with regularization methods perform better than IIR prediction filters for the selected sample patients. Moreover, since the simple LAM model performs as well as the more complicated LLM models in our patient sample, its use for non-linear prediction is recommended.

Introduction

Tumor motion due to breathing poses challenges for precise radiation dose delivery to a tumor while sparing surrounding healthy organs. Mostly, all respiratory-compensating methods developed or being investigated require predictive filters to tackle inherent system latencies in radiation delivery systems. The synergistic approach of real-time imaging with a powerful and accurate prediction engine is a key to successful tumor motion management. The review article by Verma et al. presents mathematical models for all major prediction algorithms that have been developed in the last decade. In summary, the review concludes that predictions with long latency are error prone and are not accurate enough to be implemented clinically [1]. Specifically, the prediction algorithm by Vedam et al. [2] uses least mean square (LMS) to update the filter coefficients after each prediction. Other adaptive models of the respiration motion include neural network models with integrated linear or nonlinear filters [3,4], and the finite state model of Wu et al. [5]. Ruan et al. [6] used subspace projection methods to derive models of periodic respiratory signals. The Ruan projection models use Fourier spectra and least-squared-error analysis to find the best-fit periodicity of the respiration signal. Recently, Ernst et al. [7] have compared normalized least mean square (nLMS), recursive least squares (rLS), and a wavelet-based autoregression (wLMS) as well as a support vector regression algorithm and a Kalman filtering approach for prediction horizons ranging from 77 ms to 307 ms. They conclude that for a prediction horizon of 300 ms, their support vector machine (SVM) regression implementation yields the best results.

In this work, we present state-space based non-linear methods for the prediction of respiratory signals for prediction horizons ranging from 400 ms to 3000 ms. The presented non-linear prediction methodologies can be directly implemented on tumor coordinates once they become available with the advent of newer tumor tracking technologies such as the Calypso™ tracking system (Calypso, Seattle, Washington) or the MRIdian™, a real-time MR Radiotherapy system developed by Viewray (Viewray Inc., Cleveland, OH) with which it will be possible to acquire real-time MR images at

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a frame rate of 4 images/sec. While linear predictive (LP) models, such as infinite impulse response (IIR) prediction filters, have been employed with great success for short prediction horizons ranging from 50 to 200 ms for a deterministic non-linear systems that exhibit sensitive dependence on initial conditions, their capacity to yield accurate prediction deteriorates for N-point multi-step prediction for different sampling/imaging rates especially in the presence of measurement noise. In our previous work, we have established that the breathing of lung cancer patients can be described as a 5 to 6 dimensional nonlinear, stationary and deterministic system that exhibits sensitive dependence on initial conditions, and hence any of the existing linear prediction models can only be used successfully for short prediction horizons($\leq$300 ms) [8]. The intended purpose of this paper is to investigate non-linear prediction algorithms that yield long prediction horizons (>300 ms). In particular, a one-dimensional time series obtained by measuring the behavior of a multidimensional dynamical system as a function of time can be used to reconstruct the underlying attractor using the time-delay embedding theorem [9]. We have applied a number of nonlinear prediction methods to successfully predict the time evolution of the breathing pattern for 62 lung cancer patients for a time ahead prediction horizons ranging from 400 to 3000 ms. Both single-step and N-point multi-step prediction are performed for sampling rates of 5 Hz and 10 Hz. For N-point multi-step ahead prediction, an iterative scheme is used and the single-step ahead predictions from previous steps are used to make prediction at the current step. We have also compared the non-linear prediction methods to the prediction accuracy from an Adaptive Linear Predictive (ALP) model based on an IIR prediction filter.

Methods and materials

1. *State space representation*

Scalar time series data of respiratory signals were obtained using the respiratory position management (RPM) system with a rate of 30 frames/sec. Suppose x_i are scalar samples acquired at times t_i separated by a fixed time interval t_s, yielding the scalar time series $S = \{x_i\}_{i \in T}; T = \{1,\ldots,M\}$. Using time delay embedding, the data can be represented in an m-dimensional state space as shown in Eq. (1), where τ is the embedding time delay and m is the embedding dimension.

$$\tilde{\boldsymbol{x}}_i = \left(x_{i-(m-1)\tau}, x_{i-(m-2)\tau}, \ldots, x_{i-\tau}, x_i\right), i = 1 + (m-1)\tau, \ldots, t \quad (1)$$

The reader is referred to [8] for a detailed description of the chaotic characteristics of breathing. Signals were normalized such that the maximum peak-to-peak amplitude is equal to unity.

2. *Adaptive linear prediction model (ALP model)*

A linear predictor is a system that predicts the future output signal as a linear function of a set of inputs [2,10]. We consider linear predictors that are based on an AR (autoregressive) model, i.e. that have the form

$$\begin{aligned}\widehat{x}_{t+\Delta} &= \sum_{j=1}^{m} a_j x_{t-j\cdot t_s} \\ \varepsilon_{t+\Delta} &= \widehat{x}_{t+\Delta} - x_{t+\Delta}\end{aligned} \quad (2)$$

where x_t is the amplitude of the scalar signal at time t, m is the order the AR model. The estimated signal at $\widehat{x}_{t+\Delta}$ is therefore predicted as a linear combination of the known previous positions x_t through $x_{t-j\cdot ts}$. Note that the noise component has been suppressed, which for prediction purposes has to be averaged over the AR part only. In case of an ALP model, the optimum set of coefficients are continually found by minimizing the mean squared error ($\varepsilon_{t+\Delta}$) of predictions on a set of training samples based on the respiratory motion data collected prior over a signal history length (SHL). Using the so determined optimum set of coefficients, $\{a_j\} j \in \{1,\ldots\ldots,SHL\}$ the breathing signal was predicted 400–3000 ms into the future.

3. *Model free local prediction method in state space (LAM model)*

The simplest form of non-linear local prediction in state space is to consider the most similar segment of a given scalar time series $S = \{x_i\}_{i \in T}; T = \{1,\ldots,M\}$ in the past, that is one uses the nearest neighbor vectors of $\tilde{\boldsymbol{x}}_t$ on the time-delay reconstructed attractor formed from the scalar time series S, $\tilde{\boldsymbol{x}}_{t(i)}$, with time indices $t(i) < t-\tau$ in the past, to predict the time series point x_t N-time steps ahead, $\widehat{x}_{t+N}$, by taking the average of nearest neighbors in the past, $\mathcal{N} = \{\tilde{\boldsymbol{x}}_{t(1)}, \ldots, \tilde{\boldsymbol{x}}_{t(k)}\}$ that are mapped N-time steps ahead on the time-delay reconstructed attractor formed from S. The set of vectors $\mathcal{N} = \{\tilde{\boldsymbol{x}}_{t(1)}, \ldots, \tilde{\boldsymbol{x}}_{t(k)}\}$ and $\tilde{\boldsymbol{x}}_t$ are vectors of length m, where m is the embedding dimension. This can be expressed mathematically as follows

$$\widehat{x}_{t+N} = \frac{1}{|\mathrm{N}|} \sum_{\tilde{\boldsymbol{x}}_{t(i)} \in \mathrm{N}} x_{t(i)+N} \quad (3)$$

where $|\mathcal{N}|$ denotes the number of elements contained in $\mathcal{N}$, the set of nearest neighbor vectors. The idea of analogues, i.e. finding similar segments in scalar time series data using a time-delay reconstruction of the underlying attractor, is directly related to the property of recurrence of orbits of dynamical systems, which furnishes the theoretical underpinning for the use of non-linear local predictions [11,12]. Hence, the problem of predicting the future value of x_t N-time steps ahead is reduced to finding the nearest neighbor vectors of $\tilde{\boldsymbol{x}}_t$ in the past record on the time-delay reconstruction of the underlying attractor and to use them to obtain the prediction $\widehat{x}_{t+N}$. We have employed as our distance measure the Euclidean norm (l_2-norm) between the query vector $\tilde{\boldsymbol{x}}_t$ and the input vectors $\tilde{\boldsymbol{x}}_{t(i)}$ defined as $\left\|\tilde{\boldsymbol{x}}_t - \tilde{\boldsymbol{x}}_{t(i)}\right\| = \sqrt{(\tilde{\boldsymbol{x}}_t - \tilde{\boldsymbol{x}}_{t(i)})^T(\tilde{\boldsymbol{x}}_t - \tilde{\boldsymbol{x}}_{t(i)})}$. Compared to the other two frequently used norms, namely the l_1-norm and the Supremum norm (l_∞-norm), the Euclidian norm allows one to find an intermediate number of nearest neighbor vectors, while the l_1-norm will yield the least and the l_∞-norm the most nearest neighbor vectors. Since all the breathing waveforms are normalized, this distance measure has no units.

Even if the original dynamics is chaotic, close orbits diverge only gradually from each other and hence some degree of short-term prediction can be achieved using this method [11]. However, if the reconstructed state space dimension is too low, then orbits starting from $\tilde{\boldsymbol{x}}_t$ and its nearest neighbor vectors in the past may not deviate as smoothly on the time-delay reconstructed attractor formed from S as they do on the true underlying attractor. Therefore, careful state space reconstruction is of immense importance for local prediction, and this does not only rely on the selection of embedding dimension, m, and delay time τ but rather on the selection of embedding window length, τ_w. The embedding window length $\tau_w = (m-1)\tau$ is the length of data segments on the trajectory of the underlying attractor. If one maintains a constant embedding length τ_w, state space reconstructions for varying m are qualitatively the same [13] (adjusting τ accordingly, so that $\tau_w = (m-1)\tau$ is constant).