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The use of compressive sensing and peak detection in the reconstruction of microtubules length time series in the process of dynamic instability

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ABSTRACT

Microtubules (MTs) are intra-cellular cylindrical protein filaments. They exhibit a unique phenomenon of stochastic growth and shrinkage, called dynamic instability. In this paper, we introduce a theoretical framework for applying Compressive Sensing (CS) to the sampled data of the microtubule length in the process of dynamic instability. To reduce data density and reconstruct the original signal with relatively low sampling rates, we have applied CS to experimental MT lament length time series modeled as a Dichotomous Markov Noise (DMN). The results show that using CS along with the wavelet transform significantly reduces the recovery errors comparing in the absence of wavelet transform, especially in the low and the medium sampling rates. In a sampling rate ranging from 0.2 to 0.5, the Root-Mean-Squared Error (RMSE) decreases by approximately 3 times and between 0.5 and 1, RMSE is small. We also apply a peak detection technique to the wavelet coefficients to detect and closely approximate the growth and shrinkage of MTs for computing the essential dynamic instability parameters, i.e., transition frequencies and specially growth and shrinkage rates. The results show that using compressed sensing along with the peak detection technique and wavelet transform in sampling rates reduces the recovery errors for the parameters.

1. Introduction

Microtubules (MTs) are linear intra-cellular polymers made of tubulin protein dimers [1–4]. Microtubules are found in all eukaryotic cells and play key roles in intra-cellular trafficking, mitosis [4], cell motility [2], and chromosome segregation [5]. Aberrations in MTs functions have been correlated with various diseases including Alzheimer's disease [6], Parkinson's disease [7], different forms of cancer [8], and transmission of bacterial infection [9]. Above a threshold concentration, tubulin dimers assemble into a hollow cylinder, typically consisting of 13 protofilaments, which can extend by polymerization to many thousands of subunits [2,4,10–12]. Mitchison and Kirschner found that MTs reach a steady state under fixed external conditions with alternating periods of polymerization (growth) and more rapid depolymerization (shrinking) [2,4]. The individual microtubules in the steady state exhibit stochastic transitions from growth to shortening (catastrophe) or shortening to growth (rescue) over time. They termed this unique behavior dynamic instability [1,4,13–15]. Switching frequencies are modulated during certain cellular transitions to change the length probability distribution and density of the filaments [13].

This stochastic switching behavior is described by a molecular timer exposed at one end of the growing MT. The exposed β-tubulin monomer undergoes a conformational change after association of the dimer into the polymer, thus increasing the probability of hydrolyzing the associated guanosine 5-triphosphate (GTP) to guanosine diphosphate (GDP). The GDP-bound subunits have a relatively low affinity for other tubulin dimers; therefore, GTP hydrolysis is believed to act as a switch for

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changing the binding affinity of the subunit. The competition between the rate of GTP hydrolysis in the MT and binding of new GTP-bound dimers is believed to be the reason for the transition from a state of high affinity dimer binding to very low affinity. Different mathematical models have been developed to evaluate quantities such as the MT length distribution and dynamic parameters , but the stochastic nature of the switching process between polymerization states complicates the procedure of sampling and construction of the distribution of microtubule lengths [16]. The mechanisms governing dynamic instability are still an active subject of both experimental and theoretical investigation [14,16–29].

Optical microscopes have been used to collect time-lapse data of cellular processes for more than 100 years. In the modern era of single molecule sensitivity and microsecond frame rates, the major limitation on data collection is typically the damage to the specimen or probe over the time course of the experiment. The specimen or probe can only be illuminated for a finite accumulated period of time, and therefore, the collected time-lapse data are often sparse with respect to the time scale of the intra-cellular events. Note that high temporal resolution observation of dynamic behavior of MT parameters is very imperative for understanding the MTs behavior and many other cellular activities. Since in practice we have substantial limitations on the sampling of the MT parameters such as experimental equipment precision, and spatiotemporal resolution, therefore, we investigate the use of Compressed Sensing (CS) to improve the resolution and the value of the time-lapse observations in life-sciences research.

Compressed sensing has recently found its applications in a variety of areas such as biomedical imaging, communications, and remote sensing [30–34]. Using the commonly applied Nyquist–Shannon sampling theorem, accurate capturing of a signal requires that samples to be taken at a rate at least two times faster than the signal bandwidth to avoid losing information or aliasing [35]. The general concept for CS is that signals can be represented by only a few non-zero coefficients, where the number of samples required recovering a signal without error is determined by its bandwidth. In CS, a nonlinear optimization can recover a signal by using considerably fewer measurements rather than suggested by the Nyquist–Shannon sampling theorem [30,36–38]. In this regard, CS will find its application in many areas of life-sciences research, where time-lapse is a significant problem. To the best knowledge of the authors, CS has not yet been applied to reconstruct MTs and improve the MT dynamic instability parameterization.

This study is focused on using a CS based framework for the reconstruction of the MTs filament length and estimation of the characteristic parameters based on minimum sampling measurements. MT length is a stochastic signal which is also generally characterized by four parameters, growth and shrinkage rate, catastrophe and rescue frequencies [28,29]. These four parameters are also evaluated from sampled data of the MTs length through microscopy. As such, an accurate estimation of them depends upon the time-lapse observations (sampling) of the MT length and the frequency of this observation. We use experimental data as the original signal, and by applying CS with different sample rates, we try to recover the original signal and validate the method. The reason we are using the experimental data as the original data is to evaluate the CS recovery method. We also apply the peak detection technique to the wavelet coefficients to detect and closely approximate the growth and shrinkage of MTs for computing the essential dynamic instability parameters, i.e., transition frequencies and growth and shrinkage rates. We hope that this study combined with state-of-the-art experimental assays paves the way to the use of CS-based methods for biologists interested in the observation and characterization of microtubules and other biological filaments such as actin or intermediate filaments. We hope that this study combined with state-of-the-art experimental assays paves the way to the use of CS-based methods for biologists interested in the observation and characterization of microtubules and other biological filaments such as actin or intermediate filaments.

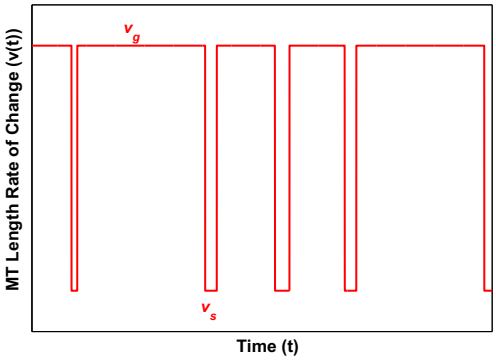

Fig. 1. Microtubules as a dichotomous Markov noise.

2. Methods

2.1. Dichotomous Markov noise model for microtubules length time series

Microtubules are growing and shrinking with constant rates but the time spending in the growth and shrinkage is random. This growth and shrinkage can be interpreted as random switching (transitions) between growth and shrinkage state. Let $X(t)$ be a continuous positive random variable, representing the length of the MTs under study. The rate of change of $X(t)$, the velocity $v(t)$, is randomly switching between positive and negative constant levels (v_g and v_s) measured from the zero scale for the growth and shrinkage rate [39,40] (See Fig. 1). Dichotomous Markov noise (DMN) is defined as a two-valued stochastic process with the state space values v_g and v_s with constant transition frequencies of f_g and f_s for the growth (g) and shrinking (s) rate. The switches of $v(t)$ are modeled as a Poisson process. The equilibrium point of the system is characterized by [28,29]:

$$V = \frac{v_g f_s - v_s f_g}{f_s + f_g} \tag{2.1}$$

Microtubule length distribution is exponential with the average length of [39]:

$$L = \frac{v_g v_s}{v_s f_g - v_g f_s} \tag{2.2}$$

2.2. Wavelet transform

Distinct from the Fourier transform, in which the basis functions are sinusoids, wavelet transforms are based on small waves with varying frequency and limited duration, i.e., wavelets. These time-limited basis functions help to determine the corresponding frequency and its usage in the expansion. Eq. (2.3) describes a 1D-discrete-time function, which is expanded, by wavelet basis functions in the time and frequency domain as [41]:

$$f(n) = \sum_k \sum_j a_{j,k} \psi_{j,k}(n) \tag{2.3}$$

where $f(n) \in L_2(R)$, $k, j \in Z$. k stands for time and j represents the frequency (or translating variables and scale, respectively) [10].