MODEL BASED DYNAMICS ANALYSIS IN MICROTUBULE VIDEOS

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ABSTRACT

Microtubule dynamics research investigates cellular regulatory mechanisms to understand properties of microtubule dynamic behavior. The current manual nature of image analysis is a severe impediment in extracting potentially valuable information from microtubule videos. In this work, we present computer vision and machine learning based methods for extracting novel dynamics information from microtubule video databases.

1. INTRODUCTION

Microtubules (MT) are filamentous subcellular structures involved in cell division, movement, morphology, and distribution of critical cellular components. Abnormalities of MT-associated proteins –the regulators of dynamic instability– are associated with cancer and certain neurodegenerative diseases such as Alzheimer's and FTDP-17. A clear understanding of the regulation of MT dynamic behavior may elucidate causal factors in these diseases and may reveal new therapeutic targets and strategies.

MT dynamics are regulated by endogenous agents, such as MT associated proteins (MAPs), or exogenous agents, such as MT-targeted drugs (MTDs). MT dynamics research seeks to understand the complex mechanisms that underlie cytoskeletal responses to changes in environmental conditions. Conventionally, time-series images of MT populations are collected following treatment with MTDs or MAPs. Dynamics parameters are then manually calculated from image sequences. Resulting statistics of each condition are compared with the control behavior to quantify the effects of the examined agent on dynamics parameters such as growth and shortening. Due to the manual nature of dynamics quantification task, a limited sample for each experimental condition must

represent all MTs collected in that condition. Analysis of dynamic behavior is further limited by pairwise comparisons of behavioral features between control and treated conditions. In this fashion, regulatory effects of each individual agent are studied through a laborious set of tasks. Quantifying sufficient image data to achieve statistical significance and limited comparative capabilities in the presence of innumerous possible agents pose an enormous challenge to researchers.

Potential computational contributions to MT dynamics research include automating the data collection task by tracking individual MTs in videos, and introducing machine learning tools that provide novel analysis capabilities. Recently, we developed automated methods that can track substantially more MTs per video than the manual method with increased accuracy and decreased subjectivity. Furthermore, Hidden Markov Models (HMM) were used in describing dynamics characteristics instigated by the regulatory mechanisms in each experimental condition. By representing the dynamics characteristics of each agent with HMMs, it is possible to quantify dissimilarities between regulatory agents. Furthermore, this measure can be used for querying MT video databases in terms of their dynamics content. A noteworthy difference from manual analysis is the fact that MT life histories are kept intact as opposed to being parsed into independent growth and shortening events: now preserving both spatial and temporal context for each event.

In this work, we describe how biologically motivated queries can be executed to extract previously inaccessible information from a MT video database. The proposed technique utilizes information captured by the HMMs to facilitate database operations for dynamics based retrieval of information from MT videos. Assuming that the tracking and modeling tasks were undertaken, the MT video database would then contain a collection of individual MT tracks and parameters of HMMs representing each experimental condition in addition to original

videos. This framework permits novel content searching capabilities for researchers as illustrated below.

Given a model λ_C of an experimental condition, a probability score can be efficiently computed for each track to be generated by the model as $P(mt|\lambda_C)$. We adopt this quantity as the measure of association between the track mt and the model λ_C. Consequently, a behavioral distance measure between conditions can be defined as the relative distance of models representing conditions. For example, for the set of tracks observed from an experimental condition, $\mathbf{mt}_{C_1}$, one such possible distance measure between the condition C_1 and all others is given by

$$D(\lambda_{C_2}, \lambda_{C_1}) = \frac{1}{T} \left[\log P(\mathbf{mt}_{C_1}|\lambda_{C_2}) - \log P(\mathbf{mt}_{C_1}|\lambda_{C_1}) \right].$$

Due to the probabilistic nature of association measures, model confidence is defined as the likelihood of a model to explain observed data. Between conditions, the classification accuracy can also be used as an assessment of model fit. Efficient computation of such probabilities enables retrieval operations for dynamics features –a spatiotemporal content– from a MT database. Queries can be executed to retrieve individual MT tracks or videos, MT or video collections, and spatial or temporal regions from videos.

For example, dynamics characteristics typical of an individual MAP or MTD can be examined in isolation for an assessment of the agent's direct effects on MT dynamics by establishing individual dose-response relationships. A similarity search in a MT database can extract conditions within behavioral similarities to known conditions. Furthermore, tracks can be grouped and visualized based on their behavior characteristics on a MT video, Fig.1. This is accomplished by evaluating all tracks with a given model.

Model based content retrieval provides unique advantages in query design. Model parameters can be manually designed to extract particular behavior characteristics, or they can be estimated from track samples for an arbitrary set of tracks. By overlaying returned track information on the original MT video the researcher is presented with visual cues about regional dynamics within a cell. This may be especially important in studies of polarized cell types, such as neurons, where specific regional regulation of dynamics is critical to processes such as outgrowth and transport. Alternatively, regions of individual videos can be studied by evaluating included tracks in the region with estimated models to assess dynamic similarity.

Finally, temporal queries can be executed to extract an arbitrary sequence of events from videos at a given confidence level. To the biological researcher, this presents the ability to correlate dynamic events in time, between neighboring or distant MT populations within a given cell. Temporal comparisons between events such as catastrophe (rapid disassembly) and rescue (ensuing reassembly) in adjacent populations may provide insight to the inner workings of flux between the soluble and polymeric tubulin fractions within the cytoplasm. The ratio between these two functionally distinct, but co-dependent phases and a kinetic coefficient describing the transition between the two may indicate cell-autonomous or drug-influenced regulation.

With the introduction of accurate tracking and data mining facilities, researchers can study MT dynamics at a superior spatial and temporal quantification. From the engineering perspective, model based mining enables extracting spatial and temporal information from video databases by way of efficient probabilistic queries.
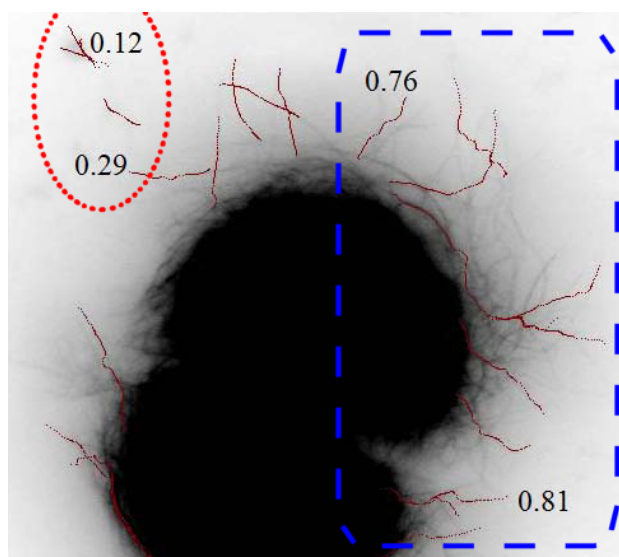
Fig. 1. Example microtubule video frame with overlaid tracks. Tracks on the upper left are less likely to exhibit dynamics characteristics of the modeled experimental condition, marked as dotted circle. Tracks on the right side of the frame are significantly more likely to exhibit characteristics of modeled dynamics. Example scores are computed by evaluating $P(mt_i|\lambda)$, where i is the track index, and λ is the dynamics model (HMM) of the experimental condition from which the particular video frame was obtained.