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Hidden Markov Models (HMMs) for Medical Applications

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Abstract

Hidden Markov Models (HMMs) have emerged as a fundamental statistical tool in medical research, offering robust capabilities for modeling temporal processes characterized by unobservable hidden states. This review discusses the evolution and application of various HMM types in the medical field, including discrete, continuous, Hidden Semi-Markov, Hierarchical, and Coupled HMMs. These models have been used to address challenges across diverse medical contexts, from diagnosing disease states to tracking the progression of chronic conditions such as Alzheimer's and cardiovascular diseases. We outline the structured methodological framework necessary to build HMMs for medical applications, emphasizing the importance of data pre-processing, feature extraction, parameter estimation, and model validation. The utility of HMMs in modeling continuous physiological signals, such as EEG, ECG and MRI data is highlighted, demonstrating their relevance in personalized medicine and disease progression modeling. Evaluation metrics, including accuracy, sensitivity and specificity are discussed in relation to the model's clinical applicability and predictive power. The review concludes with a discussion of emerging trends in the use of HMMs, particularly their growing importance in genomics, pharmacometrics and infection transmission modeling. This comprehensive analysis underscores the versatility of HMMs in addressing complex temporal medical phenomena and their potential to enhance diagnostic, prognostic and therapeutic strategies in the future of healthcare.

Keywords: Hidden Markov Models; Medical; Time series; Artificial intelligence; Genetics

Introduction

HMMs have become an indispensable tool in medical research, particularly for analyzing time-series data where underlying processes are hidden from direct observation. Their ability to model dynamic systems through transitions between unobservable states makes them particularly suited for representing complex biological phenomena, such as disease progression, physiological processes, and patient health trajectories. The application of HMMs in medicine spans a broad range of contexts, from diagnostic tools to models for chronic disease progression, and has expanded as different categories of HMMs have been developed to address specific clinical challenges.

This review examines the diverse types of HMMs, including Discrete, Continuous, Hidden Semi-Markov, Hierarchical, and Coupled HMMs, each of which serves unique roles in addressing medical problems. We explore the methodological process involved in their application, including data collection, state-space definition and the calculation of transition probabilities. Furthermore, we provide a detailed discussion of how these models are validated and evaluated within the context of medical data, considering metrics such as accuracy, sensitivity, specificity and clinical relevance.

Through an analysis of key case studies and emerging trends, this article underscores the growing importance of HMMs in modern medicine, particularly as personalized medicine and genomic research continue to evolve. By modeling complex temporal data, HMMs offer a powerful framework for understanding hidden processes in disease and health, ultimately contributing to more informed clinical decisions and the development of targeted therapeutic interventions.

Types of Hidden Markov Models

Discrete Hidden Markov Models (DHMMs)

The Discrete Hidden Markov Model (DHMM) represents the most fundamental form of HMM, wherein both hidden states and observations are discrete variables. Despite its simplicity, the DHMM has found widespread use in medical diagnostics, particularly in classifying disease states based on categorical data such as clinical symptoms or diagnostic results. For example, Meloni et al., utilized a DHMM to categorize Alzheimer's disease stages, relying on cognitive and functional assessments to classify patients into discrete states [1].

The model's efficiency and straightforwardness make it well-suited for applications where medical data can be naturally categorized, such as the classification of ECG signals for arrhythmia detection [2]. However, the DHMM's limitation lies in its inability to capture the continuous nature of many medical phenomena, necessitating the development of more advanced models [3].

Continuous hidden markov models

To address the limitations of DHMMs, Continuous Hidden Markov Models (CHMMs) were developed, enabling the handling of continuous variables an essential advancement for modeling medical data such as vital signs, laboratory results, or imaging metrics. CHMMs are particularly effective in applications where the underlying processes are inherently continuous [4].

For instance, Michalopoulos et al., utilized CHMMs to analyze EEG signals for the early detection of Alzheimer's disease, where capturing

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the continuous nature of brain wave activity was essential for accurate modelling [5]. Similarly, CHMMs have been applied to MRI data, effectively modeling the subtle changes in brain structure associated with dementia progression [6].

CHMMs have also gained traction in genomic research, where continuous data such as gene expression levels are analyzed. Stjernqvist and Rydén applied CHMMs to microarray gene expression data, uncovering patterns that contribute to the understanding of genetic influences on disease progression [7].

Hidden semi-markov models

Hidden Semi-Markov Models (HSMMs) extend the traditional HMM framework by allowing state durations to follow non-geometric distributions. This adjustment provides a more realistic representation of medical phenomena, where the time spent in each state (e.g., disease stages) varies between patients. HSMMs have proven particularly valuable in chronic disease modeling, such as Alzheimer's and Parkinson's disease, where accurately modeling the time spent in different disease stages is critical. For example, Yu et al., used HSMMs to model Alzheimer's progression, allowing for more precise predictions of state transitions based on variable disease stage durations [8].

Hierarchical Hidden Markov Models (HHMMs)

Hierarchical Hidden Markov Models (HHMMs) introduce a multi-level structure, wherein states at one level can themselves be modeled as HMMs. This hierarchical approach is advantageous in complex medical applications that involve multiple interacting systems, such as multi-organ disease modeling or the integration of diverse data types (e.g., genetic, clinical, and imaging data). HHMMs have been effectively applied to multi-level disease progression, particularly in neurodegenerative disorders, where the interaction of genetic, physiological, and environmental factors contributes to disease development. For instance, Lee et al., used HHMMs to model the complex interplay between brain states using fMRI data, offering a nuanced understanding of disease mechanisms [9,10].

Coupled Hidden Markov Models (CHMMs)

Coupled Hidden Markov Models (CHMMs) are designed to capture the interactions between multiple processes, making them ideal for scenarios where physiological processes influence one another. These models have found applications in cardiovascular research, where the interaction between heart rate and blood pressure dynamics can shed light on underlying disease mechanisms [11].

In a study by Ghahjaverestan et al., CHMMs were used to analyze coupled ECG and blood pressure signals, providing deeper insights into cardiovascular disease mechanisms [12,13]. The ability of CHMMs to model the interplay between multiple physiological signals makes them a valuable tool in systems biology and personalized medicine.

Building Hidden Markov Models for Medical Applications

The construction of a Hidden Markov Model (HMM) for medical applications follows a structured approach to model sequential or time-series data, often representing biological processes or disease progressions. The process involves identifying key variables, defining hidden states, estimating parameters, and validating the model to ensure its reliability in clinical contexts.

Data collection and identification of variables

The process of gathering information from relevant sources to address specific research questions or objectives are:

Time-series data (Observations): The primary input for HMMs in medical applications is time-series data, such as ECG, EEG, or longitudinal clinical records (e.g., biomarker levels over time). These sequential observations are used to infer underlying hidden states. For example, in heart rate detection models, the recorded ECG signals represent the observable data at regular intervals [14].

Hidden states (Unobserved variables): HMMs are particularly suited for modeling systems where the underlying states such as disease stages or brain states are not directly observable. These hidden states influence the observable data but must be inferred by the model. For example, in a disease progression model, hidden states might correspond to different stages of a disease (e.g., mild, moderate, severe) [15].

Influencing factors (Covariates or predictors): In some cases, additional covariates, such as patient-specific factors (e.g., age, gender, or treatment type), are incorporated to refine the model's ability to predict state transitions. These covariates can influence both the hidden states and transition probabilities, contributing to a more personalized model of disease progression [4,16,17].

Model components and parameters

The selection of model components and their associated parameters is crucial for accurately capturing system behavior:

State space: This defines the set of hidden states between which the system can transition. The number of states is often determined by domain knowledge and clinical expertise. For instance, in modeling Alzheimer's disease progression, the state space could consist of normal cognition, mild cognitive impairment and Alzheimer's disease [18].

Transition probabilities: These parameters represent the likelihood of moving from one hidden state to another over time. In medical applications, transition probabilities are estimated from data, and they must sum to one for each state. For example, in a heart rhythm abnormality model, the probability of transitioning from a normal heartbeat to an arrhythmia can be quantified [14].

Emission probabilities: These define the likelihood of observing specific data points given a hidden state. Emission probabilities link the hidden states to the observed data. For example, in EEG studies of brain activity, the emission probabilities represent the likelihood of specific EEG patterns in different brain states (e.g., alertness *vs.* drowsiness) [19].

Initial state probabilities: These represent the likelihood distribution over hidden states at the initial time step. In a cancer progression model, for example, the initial state probabilities could reflect the probability that a patient begins in an early or advanced stage of the disease upon diagnosis [4,17].

Pre-processing and feature extraction

Before building the model, it is essential to pre-process the data:

Noise removal: In medical time-series data, such as EEG or ECG, noise and artifacts must be removed using techniques like bandpass filtering or wavelet denoising.

Feature extraction: In some cases, raw time-series data may be transformed into more informative features (e.g., power spectral density in EEG data, or heart rate variability in ECG data).

Model training: Estimating HMM Parameters; HMMs are typically trained using the Baum-Welch algorithm, which is an Expectation-

Maximization (EM) algorithm designed to optimize the model parameters.

Expectation step (E-step): In this step, the algorithm calculates the expected values of the hidden states based on the current parameter estimates.

Maximization step (M-step): The parameters (transition, emission, and initial state probabilities) are updated to maximize the likelihood of the observed data given the estimated hidden states.

This process iterates until the model converges to a set of parameters that best explain the observed data (Figure 1).

Model validation and testing

After training, the model must be validated to ensure it generalizes well to new, unseen data (Table 1):

Cross-validation: The dataset is split into training and testing subsets, allowing for the fine-tuning of model parameters and minimizing the risk of overfitting.

Evaluation metrics: In medical contexts, several evaluation metrics are typically used.

Accuracy: The proportion of correct predictions, such as accurate classification of disease stages.

Sensitivity and specificity: Sensitivity measures the model's ability to correctly identify true positive cases (e.g., disease presence), while specificity measures the correct identification of true negative cases (e.g., absence of disease).

Area Under the Curve (AUC): AUC of the ROC curve is commonly used to evaluate model performance, particularly in distinguishing between different states.

Precision and recall: These metrics are critical in unbalanced datasets, where some states, such as rare disease conditions, may be underrepresented.

Interpretation of Results and Clinical Relevance

The ultimate goal of HMMs in medical applications is to derive clinically actionable insights. Once a model is validated, the results must be interpreted within the context of the specific medical application. This involves linking the hidden states and transitions to real clinical phenomena and determining how these insights can influence patient care.

Interpretation of hidden states

The hidden states in an HMM represent underlying clinical or physiological conditions that are not directly observable but inferred from the data. For instance, in a model of Alzheimer's disease progression, the hidden states might correspond to cognitive stages such as normal, mild cognitive impairment, and Alzheimer's disease. These states, once identified, can serve as surrogate markers for disease severity.

Interpretation of these states requires domain-specific expertise. Clinicians or medical researchers must align the model's inferred states with known disease stages or physiological markers. This interpretation facilitates translating the HMM's outputs into meaningful clinical terms that can guide diagnosis or treatment decisions [16,20-24].

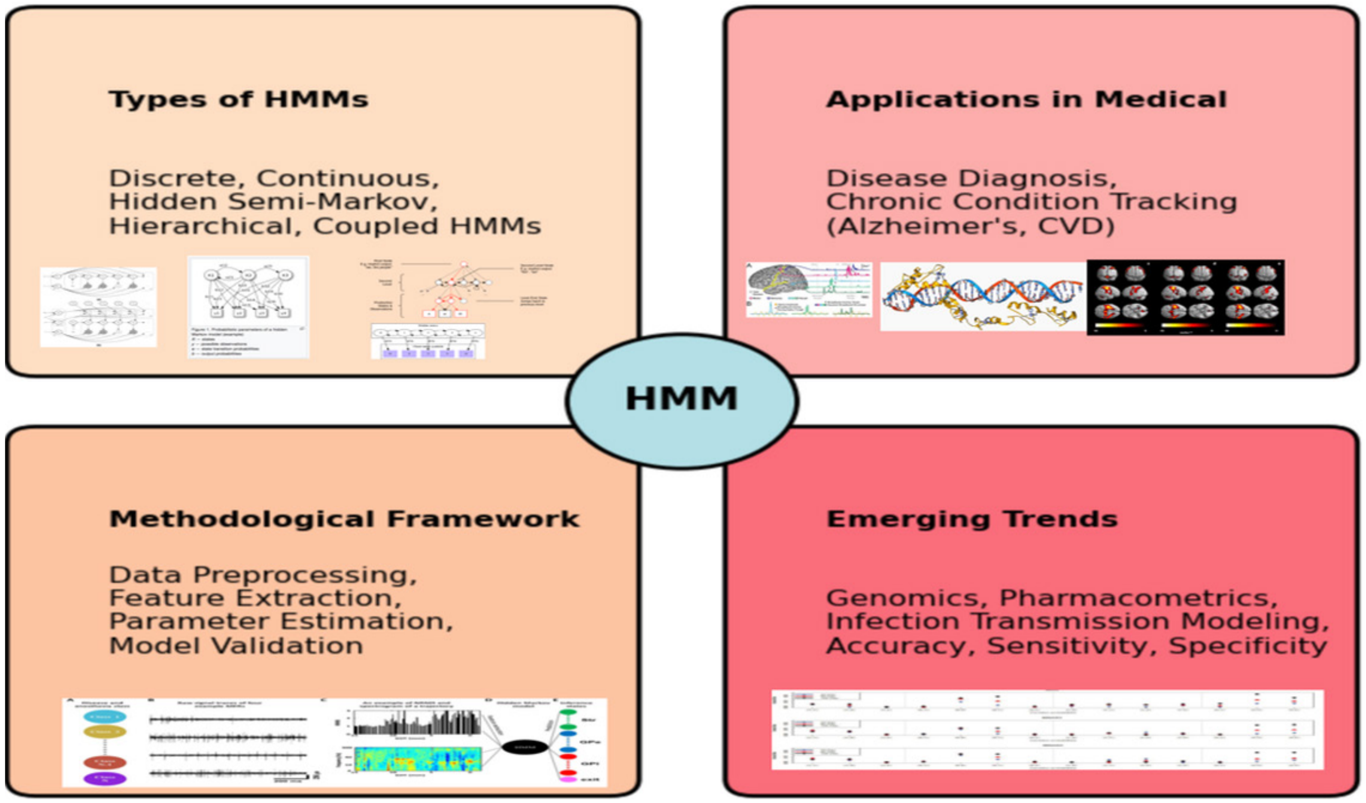

Figure 1: Overview of the radiomics pipeline, this pipeline consisted of data collection, identification of variables, model components, parameters, pre-processing, feature extraction, model training and parameter estimation.

For example, a three-state model for a neurodegenerative disease might reveal hidden states corresponding to pre-symptomatic, early symptomatic and advanced stages. Understanding these states can help clinicians identify the current phase of disease progression and anticipate upcoming transitions, informing patient management strategies such as adjusting medication regimens or recommending lifestyle interventions [25].

One prominent study explores the use of HMMs in analyzing the temporal dynamics of functional brain connectivity through Electroencephalogram (EEG) data, specifically for Alzheimer's Disease (AD) detection [3,19,22].

Transition probabilities and disease dynamics

The transition probabilities between hidden states provide crucial insights into disease dynamics. These probabilities reflect the likelihood of moving from one disease state to another over time, offering a quantitative understanding of disease progression. In clinical practice, understanding these transition dynamics helps predict future disease states and their timings. For instance, in a cardiovascular model, a high probability of transitioning from a normal heart rhythm to arrhythmia may prompt earlier interventions or more frequent monitoring. Similarly, in chronic diseases such as Parkinson's or cancer, transition probabilities can inform decisions about treatment escalation or de-escalation based on the predicted trajectory of the disease [26,27].

Clinicians can use these transition probabilities to simulate different scenarios, such as the effects of delaying or accelerating transitions between states through various therapeutic interventions. This predictive capability enhances personalized medicine, where treatment plans are tailored to an individual's predicted disease progression [28].

Clinical decision support

HMMs can serve as valuable tools for clinical decision support by providing real-time insights into patient status. For example, in Intensive Care Units (ICUs), HMMs can monitor patient's physiological data and predict critical events such as sepsis onset or respiratory failure. The model's ability to infer hidden states from real-time data and predict transitions can provide early warnings, allowing clinicians to intervene before a critical event occurs [29].

Moreover, in chronic disease management, HMMs can inform decisions about when to initiate new therapies or modify existing treatments. For instance, an HMM might predict when a patient with diabetes is likely to transition to a more severe stage of the disease, prompting earlier intensification of therapy. The model's outputs could be integrated into Electronic Health Records (EHRs) to automatically alert clinicians when a patient's risk of disease progression reaches a critical threshold [30].

Real-world applications and future directions

HMMs have already demonstrated their value in various medical domains, from predicting the progression of neurodegenerative diseases to modeling the spread of hospital-acquired infections. As computational power and data availability continue to grow, the potential for HMMs in personalized medicine is vast.

Future directions may involve the integration of HMMs with other machine learning models, such as deep learning networks, to improve predictive accuracy. Hybrid models that combine the temporal modeling strength of HMMs with the feature extraction capabilities of neural networks may provide even more nuanced insights into disease processes.

Additionally, with the rise of wearable technology and continuous monitoring, HMMs can be applied to real-time health data, offering unprecedented opportunities for early detection and intervention in chronic diseases [31].

Title	Authors	Method type	Disease	Hidden States	Covariates	Endpoint	Evaluation metrics
Prediction of class I T-cell epitopes: Evidence of presence of immunological Hot spots inside antigens [32]	Srinivasan KN	Artificial Neural Networks (ANN) and Hidden Markov Models (HMM)	Diseases involving immune response, particularly focused on predicting T-cell epitopes relevant to infectious diseases	N/A	9-mer peptides	Identification of immunological hot spots within antigens that are likely to be recognized by T-cells, aiding in vaccine design	N/A
Patient-specific early classification of multivariate observations [33]	Ghalwash MF	Hybrid model combining Hidden Markov Models (HMM) and Support Vector Machines (SVM)	Multiple Sclerosis and sepsis, with applications to other biomedical datasets	Different phases or disease states	Multivariate time series data	Patient states	Accuracy, Earliness, Coverage
Metascan: Metabolic analysis, screening and annotation of metagenomes [34]	Cremers G	HMM annotation techniques	N/A	N/A	Metagenomic datasets, metabolic pathways, gene annotations	N/A	BEACON,F1
The relationship between machine-learning-derived sleep parameters and behavior problems in 3- and 5-year-old children: results from the CHILD Cohort study [35]	Hammam N	Hidden Markov Models (HMM)	Behavioral problems	Sleep behavior	Sleep duration, sleep efficiency, Wake After Sleep Onset (WASO), demographic data like age, sex, and duration of breast Feeding, Household smoke, maternal stress.	Specific sleep parameters are associated with the risk of developing behavioral problems	Coefficient

Characterising the transmission dynamics of Acinetobacter baumannii in Intensive Care Units Using Hidden Markov Models [29]	Doan TN	Continuous-time structured Hidden Markov Model (HMM)	Acinetobacter baumannii in Intensive Care Units (ICUs)	Total number of patients colonized with A. baumannii	Incidence data of the number of detected colonized patients.	Sources of A. baumannii acquisition in ICUs	Cross-Transmission Coefficient (β), Sporadic Acquisition Coefficient (ν), Proportion of Acquisition Due to Cross-Transmission (p), Basic Reproduction Ratio (R_0)
Altered brain dynamics in major depressive disorder: state and trait features [24]	Javaheripour N	Hidden Markov Model (HMM) analysis on resting-state functional MRI (rs-fMRI).	Major Depressive Disorder (MDD)	Six distinct brain states	Demographic variables (age, gender), Hamilton Depression Rating Scale (HAMD-17) scores, Beck Depression Inventory (BDI) scores	How brain functional dynamics are altered in MDD patients	Fractional Occupancy (FO), Averaged Lifetime (ALT), Switching Rate (SR)7.
Handling underlying discrete variables with bivariate mixed hidden Markov models in NONMEM [28]	Brekkan A	Bivariate Mixed Hidden Markov Model (MHMM) implemented in NONMEM	Chronic Obstructive Pulmonary Disease (COPD)	Emission and exacerbation states in COPD patients	Patient-Reported Outcomes (PROs) and Forced Expiratory Volume (FEV1)	The effects of treatment	SLP Drug Effect, ω_πRE^2
DPVis: Visual Analytics with Hidden Markov Models for disease progression pathways [16]	Kwon BC	Hidden Markov Models (HMM) integrated with visual analytics in a tool called DPVis	Type 1 Diabetes (T1D), Chronic Obstructive Pulmonary Disease (COPD)	Stages of disease progression	Observed health records, biomarkers, genetic profiles, and other clinical variables	Disease progression pathways in longitudinal health data	N/A
Methods for estimating kidney disease stage transition probabilities using electronic medical records [15]	Luo L	Hidden Markov Models (HMM) applied to Electronic Health Records (EHR)	Chronic Kidney Disease (CKD)	CKD stages	Glomerular Filtration Rate (eGFR), patient demographics (age, gender), and time intervals of clinical measurements	Probabilities between CKD stages	Transition Probabilities, State-Dependent Probabilities , Bias and Variability
Real-time machine learning classification of pallidal borders during deep brain stimulation surgery [36]	Valsky D	Machine Learning with Hidden Markov Models (HMM) for real-time classification.	Parkinson's Disease (PD) and Dystonia, with focus on Deep Brain Stimulation (DBS) surgery	Anatomical regions	Microelectrode Recording (MER) data, including Normalized Root Mean Square (NRMS) values and Power Spectral Density (PSD)	Identifying pallidal borders during DBS surgery	N/A
Brain state dynamics differ between eyes open and eyes closed rest [22]	Ingram BT	Hidden Markov Models (HMM) applied to concurrent EEG-fMRI data	Brain dynamics during resting states with Eyes Open (EO) and Eyes Closed (EC)	Brain states inferred from EEG and fMRI data	EEG alpha power, BOLD signal from fMRI	To compare brain state dynamics between EO and EC resting conditions	Cohen's d, Difference
HMM sampling and applications to gene finding and alternative splicing [26]	Cawley SL	HMM and Viterbi Algorithm	N/A	N/A	Gene	Gene Finding, Alternative Splicing	N/A
Coupled Hidden Markov Model based method for Apnea Bradycardia detection [37]	Ghahjaverestan NM	Virtual Comparative Genomic Hybridization (vCGH) using Hidden Markov Models (HMM)	Lymphomas, specifically Diffuse Large B-Cell Lymphoma (DLBCL) and Mantle Cell Lymphoma (MCL)	The hidden states represent DNA Copy Number Alterations (CNAs)	Gene Expression Profiling (GEP) data from microarray experiments	To predict CNAs from GEP data using HMMs	Sensitivity, Specificity, Accuracy

Hidden Markov model-based heartbeat detector using electrocardiogram and arterial pressure signals [14]	Altuve M	Hidden Markov Models (HMMs)	heartbeat detection	Presence and absence of a heartbeat	Electrocardiogram (ECG), Arterial Blood Pressure (ABP), and Pulmonary Arterial Pressure (PAP)	To create a robust heartbeat detection system	Sensitivity (Se), Positive Predictivity (+P), Detection Error Rate (DER)
A comparative study of functional connectivity measures for brain network analysis in the context of AD detection with EEG [3]	Abazid M	Hidden Markov Models (HMMs)	Alzheimer's Disease (AD)	N/A	EEG data	Distinguishing between stages of cognitive impairment	Accuracy, Specificity, Sensitivity
A hidden Markov model for lymphatic tumor progression in the head and neck [17]	Ludwig R	Hidden Markov Models (HMMs)	Lymphatic tumor progression in the head and neck	Lymph nodes microscopic involvement	(1) Imaging information on the location of macroscopic metastases, and (2) T-category.	Predicting the lymphatic progression of Head and Neck Squamous Cell Carcinoma (HNSCC)	N/A

Table 1: Summary of selected HMM related studies in medicine-HMM methods.

Conclusion

As HMMs evolve, they will increasingly contribute to the development of predictive analytics tools that are not only accurate but also interpretable and clinically useful. Their ability to model complex temporal processes, coupled with ongoing advancements in computational techniques, positions HMMs as a powerful tool for advancing medical research and improving patient outcomes. While HMMs present challenges such as the need for quality data and careful interpretation, their potential in enhancing early diagnosis and tailored treatments is undeniable. As computational methods continue to evolve, HMMs are expected to play an increasingly critical role in advancing medical research and improving patient outcomes.

Authors' Contributions

Writing and discussion of the article: Qiangqiang Gang; Drawing all the pictures and tables: Fangzhou; Agreed to the publication of the final version: Ke Zhang.

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Conflicts of Interest

There is no conflict of interest between the authors.

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