

Active Monitoring of Adverse Drug Reactions with Neural Network Technology

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INTRODUCTION

An adverse drug reaction (ADR) is unintended injuries caused by the drug at normal doses during normal use.^[1] ADR monitoring is a long-term work of medical institutions. Medical institutions at all levels have their corresponding requirements of reporting ADRs.^[1] On December 12, 2010, the National Health and Family Planning Commission of the People's Republic of China issued the "Administration of adverse drug reaction report and monitoring". The aims were to enhance drug postmarketing surveillance, standardize ADR monitoring and reporting, and control drug risks in a timely and effective manner to ensure the safety of patients. It was suggested that local pharmaceutical supervisory and administrative departments should establish an ADR monitoring institution responsible for timely ADR reporting and monitoring within their respective administrative areas.^[2] Currently, there are three main methods used to monitor ADRs namely regular review, patient follow-up, and spontaneous reporting which is widely used in local hospitals. However, due to the lack of incentives for local medical staff in reporting ADRs and shortage of personnel in pharmacy departments monitoring ADRs, the most critical step in the reporting and monitoring system does not work effectively. Thus, problems have emerged that ADR monitoring is not timely, accurate and comprehensive, which posts a direct threat to people's health.^[2]

Nowadays, big data technology is highly developed. With the help of intelligent information mining of a large number of electronic medical records (EMRs), it becomes possible to automatically detect adverse drug events which are hidden in the EMRs and are not timely reported. It has become a hot issue to be solved by current medical management

organizations as how to establish an automatic and intelligent system to monitor ADRs in local hospitals. The system should be capable of detecting ADRs in a timely and accurate manner. Therefore, this paper discussed how to use artificial intelligence technology, such as neural network and deep learning, to analyze abnormal phenomenon in a large number of EMRs of medical institutions, and thus to accomplish intelligent screening of adverse drug events.

AUTOMATIC MONITORING METHODS ON ADVERSE DRUG REACTION AND DEFICIENCIES

With the development of hospital information system (HIS) data integration, HIS-based ADR automatic monitoring system gradually progressed. Some related concepts of this new research area have been defined by the professors of Harvard University and Duke University. Meanwhile, they expanded and identified a number of methodologies. Automatic screening method mainly has two types natural language process and trigger technical principles.^[3] The latter is widely used in domestic automatic monitoring systems, but it can only screen out the adverse reactions which set the trigger phrases. Unfortunately, these trigger phrases are always limited to drug concentration, test indicators, and other quantitative index. In China, the programming of medical language coding processing is

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yet to be developed, the technology of text information automatic recognition is not mature, thus the medical records of doctors and nurses could not be well identified.^[4] The latest ADR monitoring system is to use information technology, trigger technical principles, and identification technology to extract, collect, and analyze information from the electronic medical database, finally identify the clinically significant ADR. In this field, commonly used analysis methods include proportional ADR reporting ratio, reporting odds ratio, Bayesian Confidence Propagation Neural Network (BCPNN), empirical Bayesian Gamma Poisson Shrinker, *etc.*^[4] The WHO's Uppsala International Drug Monitoring Collaboration Center used BCPNN to analyze, by which they identified a number of ADRs, such as identification of acidosis and esophagitis as the most common adverse reaction of alendronate sodium and confirmation the association between pericarditis and practolol.^[4]

Currently, there are mainly two methods used to monitor ADRs world widely, including spontaneous reporting and active surveillance. Due to the lack of interest and incentives, local medical staffs are often not willing or are too busy to report actively ADRs. With regard to the local hospital management, due to concerns about the impact of medical disputes, they often lack the drive to report accurately ADRs. These failings lead inevitably to a realistic lack of spontaneous reporting.^[3] In terms of active surveillance, the limitations of medical management institutional capacity results in time lag and limited coverage of ADRs monitoring. A delay in bringing ADRs information to the health-care team threatens the healthy operation of the hospital and patient safety.^[3] With the maturity of the network technology and the popularization of HIS, Computerized Physician Order Entry and EMRs could store medical diagnoses, clinical examinations, tests, and medical documents during patient hospitalization. Under the help of intelligent data-mining, it is possible to detect existing ADRs in medical records with a massive database of patient data.^[5] This methodology is still in its initial stages in China because of the limited availability of data-mining technology.

DEVELOPMENT OF RELATED INFORMATION TECHNOLOGY

Big data technology

In 2009, Google published a paper about *flu* prediction in *Nature*, which is the paradigm of data technology applied in medical and public health, and attracted much attention from health-care professions. The most frequent 50 million retrieved entries on Google were compared with data about the seasonal influenza transmission period from the Center for Disease Control between 2003 and 2008. The retrieved records were used to determine whether *flu* occurred or not. Analysis of the results showed that the data statistical curve from Google could not only predict the *flu* situation, but also specify the district or state where the *flu* outbreak occurred.

With the help of data-mining in medical research, resolving specific historical problems in medicine (such as identifying ADRs) has become possible.

Neural network and deep learning

In 1943, the psychologist W. McCulloch and mathematical logician W. Pitts established neural networks and mathematical models, known as the mathematical programming (MP) models.^[6] Using an MP model, they proposed a formal mathematical description and a network structure method of neurons, which proved that the single neuron could perform the logic function, thus creating the era of artificial neural network research. At present, neural networks and deep learning provide the best solution for many problems in image and speech recognition, and in natural language processing.

In 2006, Prof. Hinton, the founder of the academic field of deep learning and a professor at the University of Toronto, Canada, based on the hierarchical nature of human brain cognitive processes, proposed to increase the number of layers and neurons in the artificial neural network to construct deep neural networks to obtain excellent feature learning ability, which was confirmed in a series of subsequent experiments. This event aroused great interest in academia and industry and stimulated a wave of deep learning studies with large data applications.^[7]

Conventionally, the process of data analysis involves experience and knowledge of random samples, building up models, and the analysis and mining of the data and information based on specific models.^[8] It used to be a useful approach because the objectives are always structured and simple involving a small dataset. However, in the big data environment, the traditional data analysis has inherent shortcomings – too much dependency on professional knowledge, difficulty of data migration, inaccuracy, *etc.* In the big data environment, it is necessary to analyze the rules and characteristics from huge, unstructured databases, to extract the useful information from massive, complicated, and multi-sourced data. The practice has proved that it is feasible for intelligent calculation of big data analysis – using a combination of depth study and neural analysis to sort through multi-sourced data.

CONSTRUCTION OF INTELLIGENT ACTIVE MONITORING SYSTEM FOR HOSPITAL ADVERSE DRUG REACTIONS

With the application of big data analysis and in-depth learning in a large number of EMRs, the abnormal events of medical procedures can be more comprehensive found, which provide an efficient and accurate evaluation model for actively monitoring of drug safety. Among them, it is one of the hot topics that active detection and detection of possible ADRs with the multi-mode mining in clinical medical information resources, and a number of more feasible detection theories and model are formed.^[9]

Main technologies of intelligent monitoring system

Trigger technology

With the technology of big data analysis, establish basic standards for regular diagnosis related groups and design a trigger to detect an ADR by monitoring patients' medical records in real time. When patients receive a nonprimary disease-related treatment, the trigger alarm will be activated if abnormal treatment is given. Subsequently, a medical administrator will review the treatment of such a patient and discover the problem.

Key words automation mining technology

Trigger technology can only deal with the standard structural data, leading to a limitation in information collection. With the help of speech recognition and word segmentation technology, text records of medical treatments can be automatically recognized, thereafter making it possible to determine whether an ADR occurs in one or a large cohort of patients.^[5] This technology can help a medical administrator to monitor and analyze ADRs events more efficiently and with great accuracy.

On the basis of the above two technologies, analyze the relationship of indexes changing in medical records, establish multiple association regulations, and establish a calculation detection model. This model could be used to screen EMRs of patients to discover any existing abnormal cases. The potential ADRs detected by computer will be finally identified by physicians and pharmacists to discover the true extent of ADRs in a potentially huge cohort of patients.

Design of main system modules

There are four main sections that constitute the Medical Behavior Intelligent Monitoring System:

1. Insightful data-mining: By data-mining on massive medical histories, the system will extract data from different systems that related to ADRs monitoring, and build up a big-data platform afterward. By doing this, there will be relevant records including doctors' orders, course of disease, check-sickbed records, operation records, and body-check index collected and stored in HIS
2. Intelligent data processing: Using the techniques of Chinese Word Segmentation and part-of-word tagging, keyword auto-mining, deep learning/nerve net and image recognition, an ADRs monitoring and filtering model can be built up. The model will analyze patients' medical information and checking results, and simultaneously find suspected ADRs
3. Artificial confirmation: Based on the big-data platform and keyword auto-mining sections, the system contains an experts-involving data filtering system which can monitor ADRs spontaneously. Experts need to check, track, and confirm the ADRs filtered by machine. After the artificial processing, a conclusion of ADRs can be drawn
4. Data reporting and docking: A data standard will be determined for the docking between current and new

systems. Therefore, the intelligent analysis result of ADRs can be automatically tracked and reported.

Main process of system operation

Data extraction of patients' medical records

During data extraction, the main factor that must be considered is the efficiency of data transmission; a large amount of data must be extracted from the operation system to the data pool for processing in a certain period.^[10] Microsoft Server Integration Services provides concurrent and multiple pipelining extraction capabilities. Although concurrent operation can speed up the transmission speed, the influence on the operation system database must be taken into account. The amount of pipelining and the throughput must be controlled. Medical order information, electronic pathology, surgical information, medication information, and examination information of each patient will produce hundreds of thousands or even millions of detailed data which need to be extracted to the data pool according to project requirements. Each data extraction operation will consume much time, therefore, an optimized data extraction program based on the original method must be developed.

After analysis of operation data, the data are classified into two categories according to the update status and data volume: (1) One type of data is characterized by a low frequency of updates; the amount of data has always been maintained at an order of magnitude, such as dictionary tables and code tables; (2) Another type of data is characterized by a large amount of data and frequent updates, which always accompanied by corresponding update time information such as doctor's orders and surgical tables. Based on the characteristics of these two types of data, we designed a program that can take into account both of them, using a complete data extraction model and an incremental data extraction model, respectively. Complete data extraction model: all the data in the current target database should be deleted when the data are extracted each time, and then all the data are extracted from the data source. The advantage of this approach is to solve completely the inconsistency of data between the data source and target database. However, one drawback is that a large amount of data needs to be extracted and this will take a long time to analyze. Each extraction may take several hours or even more than 10 h for the massive data table to be evaluated.^[11] Incremental data extraction mode: only the data in the data source different from those in the target database are extracted every time. In general, a time-stamp is used to extract the data updated after the last extraction.^[11] This approach greatly reduces the amount of data extracted each time, but the drawback is that it is very likely to cause missing data if the incremental extraction rules are not perfect during each data extraction, and the data in the target database can not be updated in real time when the data in the data source are changed.

Intelligent screening and monitoring

In the intelligent screening of adverse medical events, an important factor of poor performance of Chinese natural

language processing in the terminological database is the large number of unrecorded words (so-called words that cannot be found in the dictionary, such as “cerebral infarction” or “anorexia”), especially, the recognition of medical field acronyms and professional words. We used a professional lexicon from a large number of medical dictionaries, which greatly improved the accuracy of word segmentation.^[12] For the new word recognition algorithm, we used the dynamic n-gram model, dynamic sliding window algorithm, high-performance word frequency statistical technique, long-term accumulation, and professional dictionary management, thus ensuring the dictionary’s universality and authority.

For example, to predict whether the associated diagnosis could trigger an allergic reaction and to obtain a more accurate probability through the models based on much data. This idea is based on the concept of neural network technology; it also can identify the cause of this forecast and the factors for the probability of allergic reactions.

Using the graph theory algorithm, related graph-based learning techniques and the associated graph database, a relational network capable of describing the complex semantics of the real world can be established among the language elements. The program can start from a language element node (e.g., “cerebral infarction”) to obtain approximate, extended and other important elements through different depth, breadth, weight, and direction.^[12] This concept revealed a huge supporting role in considering a medical corpus based on time, spatial cues, and global analysis, which were not available using traditional machine learning techniques.

Participation of experts

The artificial analysis provided by a team of relevant experts is necessary for every result of intelligent processing. It can ensure the accuracy of the data monitoring and avoid errors of automatic processing.

Connecting with reporting system

A data standard and interface needs to be built up after the big data platform producing the ADRs monitoring results and hence that the results can be reported automatically through systems. With the help of hierarchical information push technique, the ADRs monitoring results can be batch uploaded directly, which will save the time of doctors’ work, reduce the work pressures of clinical departments, decrease the time from determining ADRs to reporting it, and enhance monitoring quality.

CONCLUSIONS AND EXPECTATIONS

This paper discussed a variety of active ADRs monitoring methods and considered related technologies including neural network (deep learning) and big data analysis technology. We also intent to provide a feasible method for intelligent monitoring of adverse drug events to accomplish massive medical record data-mining and smart processing, realize intelligent analysis of ADRs for local

medical organizations, and provide technical support to automatically detect ADRs in a fully operational system. However, due to the feature of dynamic revolution on monitoring ADRs, working personnel must have a strict, rigorous attitude, and be trained to work with the developing technology. Learning from advanced experience from other country, we completed an automatic monitoring system for ADRs, realized the conversion from “reporting after event” to “monitoring in real time”, which will provide the technical support for health-care personnel, and will greatly improve patient safety when drugs are administered.

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Conflicts of interest

There are no conflicts of interest.

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