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# Advances in Chinese Medicine Diagnosis: From Traditional Methods to Computational Models

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## 1. Introduction

Ancient Chinese medicine practitioners deduced about 5,000 years ago that the exterior appearance of the body was closely related to the functions of the internal organs and viscera. They sought for explanations for this interior-exterior connection by establishing relationships between human beings and Nature. Other natural philosophers also applied such reasoning, *e.g.* Aristotle [384-322 BC], Leonardo Da Vinci [1452-1519], and René Descartes [1596-1650]. Although it is not possible to say that Chinese medicine practitioners were unique in this task, they organized those relationships in a pioneer manner long before their Western counterparts. Chinese and Western physicians were not distinct in their conceptual framework, but their respective medical practices evolved on different cultures and historical contexts. Therefore, it is expected that the advances on medical knowledge represent this cultural divergence.

Many efforts have been made to integrate the ancient, traditional knowledge of Chinese medicine into contemporary, Eastern medical practice. Diagnosis is a key element in this integration of medical systems since it links the patient's needs to the available therapeutic resources. The art of Chinese medicine diagnosis was enriched throughout history but its main traditional aspect remains unchanged: the exclusive use of information available to the naked senses. Clinical information provided by vision, hearing, smelling, and touching is interpreted in a framework of Chinese medicine theories of physiology. No equipment or instrument was developed with specific diagnostic purposes or based on Chinese medicine theories. However, advances in computation and biomedical instruments allowed more powerful analysis of clinical data and quantification of parameters otherwise assessed only in a qualitative fashion. As a consequence, computer models for diagnosis in Chinese medicine were developed and tested in the last few decades and are promising tools in the clinical environment.

This chapter introduces the traditional methods of diagnosis in Chinese medicine and introduces their evolution into computational models. Current methods for validation of computational model by the assessment of their diagnostic accuracy and possible sources of errors are also presented. Finally, perspectives on the issue of computational diagnosis are discussed.

## 2. Science and art in Chinese medicine diagnosis

Science may be understood as the common sense refinement through a prospective effort to transform sensorial impressions into sequential, logic facts with intra- and inter-experimental

relationships subjected to verification and reproducibility at a certain level of confidence. Such relationships should minimize the quantity of basic principles while maximize the explained medical events. Such an organized knowledge has been guiding clinical practice in China since early times and may have interacted with other cultures on a reciprocal manner, either by knowledge transmission or acquisition. Ancient textbooks present extensive details regarding the empirical search for a cause-effect relationship, as well as the necessary training to become a physician. As a matter of fact, Chinese medicine practitioners held distinct positions in old China (Tao, 1953b). Systematization of Chinese medical knowledge allowed the accumulation of “positive” trial-and-error results, the discussion of “negative” results for therapy improvement, and the transmission of medical knowledge. Accordingly, new methods for diagnosis and intervention were developed in consonance with this systematization. In this sense, Chinese medicine is thus composed of scientific knowledge since its wide theoretical framework differentiates it from the popular knowledge.

Such scientific approach of medical theories is also reflected in the diagnostic field. From the historical point-of-view, diagnostic methods probably started with the simple need to answer dichotomous questions, such as “Is the subject dead or alive?”. From this starting point, diagnostic methods evolved into more complex methods capable of identification of several constitutional aspects, different aetiologies and their relationships, as well as the differentiation of multiple morbid or comorbid states. Descriptions of prognosis based on the patient’s examination reflect this high evolution of diagnostic methods since accurate prognosis depends on accurate diagnosis and extensive theory-based practice.

The main approach to scientific research on Chinese medicine has been to explain the observed phenomena by means of its experimental verification. By doing this, the validity of the Chinese medical knowledge is indirectly assessed by observing physiologic or therapeutic responses to acupuncture or herbs prescriptions. An interesting, alternative approach is to seek for the scientific evidence that corroborate or not data reported by Chinese medicine practitioners – ancient and contemporary ones included. Such an integrative approach is a very attractive strategy for development of robust methods in the diagnostic field.

### 3. Recognition of morbid states and the concept of pattern

Apparently, the first group of morbid conditions to be recognized were infections. As early as the Chin [221-207 BC] and Han [206 BC-219 AD] dynasties, outbreaks of epidemics led to the differentiation of infections and classification of their symptoms. In sequence, disorders of the digestive system were recognized and also named according to key-symptoms. Neurologic, metabolic, cardiovascular, and ophthalmic disorders are among the other early-recognized conditions (Tao, 1953a). Progressively, other morbid conditions were identified in the field of nutrition, paediatrics, otorhinolaryngology, stomatology, dermatology, urologic obstetrics and gynaecology (Tao, 1958a; Tao, 1958b). The recognition of new diseases, as well as the improvement of information regarding manifestations, diagnosis and prognosis were continuously developed until nowadays.

The definition of morbid conditions in Chinese medicine differs from its counterpart in Western medicine. A pattern (or syndrome, *zheng*) is the morbid entity of Chinese medicine and can be derived from any physiologic theory: *Ba-gan*, *Zang-fu*, *Liu-jing*, *Wei-qi Ying-xue*, *San-jiao*, *Bing-yin*, *Qi-xue*, *Jin-ye*, *Wu-xing*, *Jing-luo* (Zaslavski, 2003). A pattern is a set of manifestations that are absent or present depending on individual, social and environmental

conditions. This set of manifestations is similar to a “cluster of symptoms” in Western medicine (Dodd et al., 2001). Each pattern presents a wide description of manifestations including its onset, duration, location, progression and severity, collectively known as pattern dynamism (Zaslawki, 2003). Manifestations are not limited to signs and symptoms, but also body characteristics and shape, psychological statuses, personality, emotional conditions, interaction with environmental climate, and behaviours. The term “manifestation profile” describes a subset of all possible manifestations related to the pattern presented by a patient. Hence, different patients may present different manifestation profiles and yet get the same pattern as a diagnosis. As a corollary, the same manifestation profile exhibited by different patients may be related to different patterns.

Several types of patterns are distinguished, namely single, complex and multiple patterns. Single patterns are those related to a unique affected internal system (*zangfu*) or channel (*jingmai*). For instance, *Shen-yin* deficiency and *Gan-xue* deficiency are both single patterns. Complex patterns consist of two or more affected internal systems or channels and often share aetiologies or risk factors, being an example the *Gan-Dan* damp-heat. Multi-patterns are those in which several single patterns are observed due to either to pattern transmission or exposure to multiple aetiologies. For an example of multi-patterns, consider the following transmission, *Shen-yin* deficiency leading to *Gan-yang* rising.

Notice that the concept of pattern is not strictly related to diseases or syndromes in the Western medicine (Lu & Chen, 2009). In contemporary Chinese medicine literature, diseases were assigned to patterns based on matched ‘signs and symptoms’ to integrate both medical practices (O'Connor & Bensky, 1987; Auteroche & Navailh, 1992; Maciocia, 1996; Ross, 2003). Indeed, the scientific approach has been to assess the pair disease/pattern model. In this context, the same disease may be related to several patterns as well as the same pattern may be observed in several diseases. It is very important to observe this disease/pattern interaction because of the implications to statistical analysis and consequently data interpretation. Very often, a study sample is firstly selected from individuals with disease already diagnosed and secondly is subjected to the traditional Chinese medicine diagnostic procedure. Hence, statistical inference and data interpretation cannot be extrapolated to the overall population – implying limited external validity – but is limited to the disease under investigation.

#### 4. Diagnosis as a pattern differentiation process

Ancient Chinese medicine literature does not to explicitly discuss diagnostic reasoning (Yang & Li, 1993; Luo, 1995; Yang, 2003; Flaws, 2004; Yang & Chase, 2004). Contemporary literature reports that Chinese medicine practitioners apply only the differentiation reasoning for decision-making (Maciocia, 1996; Zaslawki, 2003). The diagnosis in Chinese medicine is obtained through a process named “pattern differentiation” or “syndrome differentiation” (*bian zheng*). In such a process, the practitioner examines the patient to seek for meaningful manifestations that indicate a single, a complex or an even a multi-pattern condition. Recently, Chinese medicine diagnosis started to incorporate other strategies from Western medicine (Zhou & Zhang, 2006; Zhu et al., 2006; N.L. Zhang et al., 2008), such as the deductive-inductive reasoning, tests that confirm a target hypothesis, eliminate an alternative hypothesis, or discriminate among competing ones (McSherry, 1999).

Pattern differentiation is performed in a three-stage process, namely: information gathering, data interpretation, and decision-making:

- Information gathering: refers to the assessment of manifestations present or absent in patients using traditional examination, possibly in coadjutant with contemporary methods. It is highly dependent on the physician's ability to recognize manifestations and to consider those reported by the patient.
- Data interpretation: involves the understanding of the acquired clinical information and its consideration. Also, it encompasses the selection of the best physiologic theory to explain the patient's manifestation profile. If a particular theory does not explain the interaction among manifestations (and possibly patterns), another theory - more general or specific - can be selected in the next stage.
- Decision-making: is the process of identification of a pattern among other possible ones. If it was possible, practitioners should rely on pathognomonic manifestations to perform pattern differentiation. However, not all patterns exhibit such a feature, and many patterns share common manifestations. Moreover, patterns have several manifestations that can be present or not depending on individual constitution and environmental factors.

It is worth notice that pattern differentiation is "always possible" due to the wide concept of manifestation and the diversity of physiologic theories to better differentiate the true pattern (or patterns) from possible ones.

## 5. Traditional examination methods in Chinese medicine

In the medical diagnostic context, "traditional" refers to methods, knowledge, skills, and beliefs indigenous to different cultures applied to health obtainment, maintenance and restoration. Often, when adopted by different cultures it is termed "alternative" or "complimentary" medicine (WHO, 2008). For information gathering, the traditional methods are still applied nowadays and are essentially similar to those practiced by Western physicians (Peterson et al., 1992).

The traditional Chinese ontology of examination is named "Four Examinations" (*sizhen*). It consists of the sequential application of inspection (*wang*), auscultation and olfaction (*wen*), inquiry (*wen*), and palpation (*qie*) (Tao, 1958a). Several classic authors discussed detailed information regarding this sequence of examination and its impact on diagnostic errors and potential cure rates. For instance, a "superior" Chinese medicine practitioners collect data from patients according to the Four Examinations and interpret those manifestations using medical theories, obtaining a cure rate of 90%; "mediocre" and "inferior" doctors have cure rates of 70-80% and 60% patients, respectively (Yang & Li, 1993; Luo, 1995; Yang, 2003; Flaws, 2004; Yang & Chase, 2004). Recently, it was shown that individual examination methods provide diagnostic accuracies compatible with "inferior doctors" (Ferreira, 2008) and are significantly improved after cumulative application of all Four Examinations (Ferreira, 2009).

According to such ontology, the naked senses are considered sufficient to the trained, skilled practitioner to recognize and label patterns. While elaborated instrumentation was invented and developed for acupuncture and moxibustion treatment - including different types and shapes of needles, moxa presentations - not an instrument was developed for diagnostic purposes. This subjective, personal practice inputs an extremely high dependency in the examiner's knowledge and the applied procedures.

Several contemporary textbooks are devoted to the patient's examination following that ontology and will not be explored here. Some categories worth mention regarding each examination method (Zhou et al., 2004; Ferreira, 2008). Inspection is performed to collect

information regarding the patient's: general aspect; face aspect; tongue body, fur, and movement; body constitution; gait; urine and stools aspect. Children under 2-3 years old must have their throat, orifices, finger veins, and *luo* channels inspected (S.C. Wang et al., 2002). Auscultation and olfaction are executed to collect information on the patient's: breath; speech; cough; secretion; and excretions. Inquiry is conducted to observe the patient's preferences; cold and fever; transpiration; head and body; chest and abdomen; pain; excretions; diet and appetite; sense organs; sleep; medical history; habits; and quality of life ("present dignity, past obscurity"). Palpation is performed to identify: painful areas; skin temperature; points; cubital skin; and pulse images.

Some criticism may arise from the sequence of the traditional ontology for examination. As a corollary of the holistic approach of Chinese medicine, the order in which Examination methods are applied does not change the pattern differentiation outcome. Assuming that practitioners always use the Four Examinations and are successful in this task, they conclude their screening procedure with the same manifestation profile no matter the applied order. This must not be confused with the timeline of onset of manifestations because when at screening, the patient presents simultaneously all manifestations. Although each Examination contributes differently for reducing pattern differentiation errors, it seems that the order in which the Four Examinations are used is just a matter of keeping a rigid routine to ensure that every aspect of screening was performed (Ferreira, 2011).

## 6. Introduction to computational models for pattern differentiation

With the advance in computing techniques and equipment, the pattern differentiation process is properly evolving into a computer-based procedure. The rapid evolution of mathematical methods based on computational algorithms allowed the implementation of diagnostic techniques derived from simple to complex routines. Additionally, study designs, statistical methods for data analysis, and guideline reports are also available for assessment of diagnostic accuracy and epidemiologic performance of automated methods. However, the computerization of Chinese medicine cannot overlook its theoretical foundation since it provides the basis for intervention.

### 6.1 Attributes of computational models for pattern differentiation

It is not difficult to build computational models for diagnostic purposes – the difficulty lies in making them good and reliable. An idealized pattern differentiation model should perform as a "superior" practitioner or even better. Thus, a computational model of pattern differentiation must present the following attributes:

- Respectful concerning the theoretical framework of Chinese medicine;
- Robust performance across a variety of suitable physiologic theories with minimal computational cost;
- Ability to perform despite having different amounts of manifestations in the manifestation profile;
- Ability to identify exams composed of single, complex and multi-patterns;
- Ability to merge manifestations that correspond to the same pattern;
- Ability to split manifestations that correspond to more than one pattern;
- Ability to decompose multiple patterns despite "noisy" manifestations and biological variability;

- Minimal use of arbitrary thresholds and minimal sensitivity to any required thresholds;
- Multi-pass algorithm to allow classification context to grow iteratively;
- Valid stopping criteria for iterative process;
- Ability to decouple low-assignment rate versus low-error rate trade-off as much as possible;
- Accuracy and completeness of pattern differentiation;
- Ability to supply some measurement of confidence regarding the pattern differentiation results.

## 6.2 Dataset of computational models for pattern differentiation

Despite the use of different approaches to perform pattern differentiation, some elements are common to those methods, such as the usage of knowledge datasets, training and testing databases, and questionnaires. As far as the manual insertion is the most frequent method applied, some discussion is needed on this topic.

Although many efforts have been made to standardize medical terms, currently there is no standard dataset for patterns and manifestations. In general, datasets have been generated by manual insertion of terms collected from literature (Ferreira, 2008; Ferreira, 2009, Ferreira, 2011) or by data mining algorithms (refer to Lukman et al., 2007 for a revision on mining methods applied to Chinese medicine; Zhou et al., 2010). Patterns on database must be mutually exclusive and collectively exhaustive (Harding, 1996), *i.e.*, for each manifestation there is at least one possible pattern, and there is no pattern without manifestations. Manual insertion leads datasets subjected to common errors of:

- Typography: typos, case-sensitive letters, and medical synonymous;
- Manifestation redundancy: for the same pattern, typing a manifestation twice or more in the same examination method or among different methods regarding the same pattern;
- Pattern label redundancy: typing the same pattern's label twice in the dataset, making such label not unique and possibly with different descriptions;
- Pattern description redundancy: typing the same pattern's description twice in the dataset yet with distinct labels, making their content not mutually exclusive (in this case, both patterns are indeed the same pattern).

The errors described above can be minimized or even eliminated with the use of simple routines for intra-pattern and inter-pattern exploratory analyses using common string search algorithms. It is strongly recommended running such routines for quality control of manually inserted datasets before model validation, especially when dealing with large datasets or even multiple datasets simultaneously. For instance, intra-pattern consistency can be obtained by excluding any repetitions of manifestations in the same examination method, as well as among the Four Examinations describing the respective pattern (Ferreira, 2008). Inter-pattern consistency can be obtained by ensuring that two patterns were not described with the same complete manifestation profile (Ferreira, 2008; Ferreira, 2009). Analysis of dual pattern similarity by means of the Jaccard coefficient (Jaccard, 1901) and associated confidence interval (Real, 1999) is an alternative to check for pattern redundancy (Ferreira, 2011). The use of a controlled vocabulary from dataset avoids the typos, eliminates language ambiguity and ensures that every one is using the same terms to mean the same attribute which limits the use of synonymous.

## 7. Computational models for pattern differentiation

The application of objective rules for pattern differentiation may help diminish diagnosis variability (G.G. Zhang et al., 2005; G.G. Zhang et al., 2008) dependent on the practitioner's expertise. A large amount of computational methods have been published, too many to list them all. Some of them were developed and tested against simulated and real cases, in different disease models, and are discussed here. In chronological sequence, this work includes the Traditional Chinese Medicine *Sizheng* Integrated Recorder and Aided Syndrome Differentiator (TCM-SIRD), modified Greedy Bayesian Pattern Search algorithm (GBPS\*), Information Management System of Traditional Chinese Medicine Syndrome Project based on Prior Knowledge Support Vector Machine (P-SVM), Chinese Medical Diagnostic System (CMDS), Pattern Differentiation Algorithm (PDA), and Multi-Label k-Nearest Neighbour (ML-kNN).

### 7.1 Traditional Chinese Medicine *Sizheng* Integrated Recorder and Aided Syndrome Differentiator (TCM-SIRD)

Zheng and Wu (2004) developed the Traditional Chinese Medicine *Sizheng* Integrated Recorder and Aided Syndrome Differentiator (TCM-SIRD). This system performs information gathering based on sensors (image, pulse and odor signal acquisition) and text information. A computational routine, namely "Integrated *Sizheng* Information Application", merges the data transferred from sensors and provides assistant diagnosis service by means of data interpretation. The provided output (such as type of tongue coating, face image, and pulse) is used to form a primary differentiation of syndromes by the "*Sizheng* Expert Decision", the decision-making modulus based on rules extracted from Chinese medicine experts' experience. The objective rules extracted from expert practitioners were not described, neither their computational implementation.

The authors described methods to be implemented for an objective assessment of diagnostic with description of a single test case. Although the model for pattern differentiation was not detailed described, the authors advocated the use of the Four Examinations. No description was given on how the information was processed for diagnosis. No result regarding its diagnostic accuracy was reported.

### 7.2 Modified Greedy Bayesian Pattern Search algorithm (GBPS\*)

X. Wang et al. (2004) designed a self-learning expert system with a novel hybrid learning algorithm based on Bayesian networks, called the modified greedy Bayesian pattern search algorithm (GBPS\*). The proposed pattern differentiation model was based on the GBPS algorithm (Spirtes & Meek, 1995) with a modified version in the search procedure algorithm. The maximum accuracy of 88% obtained for pattern differentiation was estimated by pseudo-random generation of a sample. The authors discussed the high dimensionality of patient instances represented by multiple manifestations and diagnostic hypotheses. Their results suggested the use of most frequent attributes to reduce such dimensionality and consequently increase diagnostic accuracy.

The authors developed based on the "united system of syndrome differentiation" characterized by two characteristics. The first characteristic, the "key elements for syndrome differentiation", was abstracted from keywords in medical theories and grouped in two categories (the place where diseases occur; and the pathological state of the body or possible causes that make disease break out). As each key element usually exhibits a variable



strength of association to manifestations, the pattern identification could be performed according to whether the key element is present or not. The second characteristic, the "standard syndrome-name database," was used to solve the problem that a pattern could be assigned with different labels by different practitioners. In the database, a standard pattern label includes at least one of the key elements described above. A dataset of 800 cases from real patients was used to train the Bayesian classifier.

The complete system for pattern differentiation is designed in modulus and its architecture consists of three parts: (1) input of the system, thereof one is sample database with attributes of symptoms and key elements, the other two are key-elements database and database of clinical observations to be diagnosed; (2) Analysis and diagnosis part, that is, the kernel part of the system, including: module for variable selection, module for discovering dependency relationship, module for learning classifiers, module for syndrome differentiation, module for mining frequent sets among key elements, and module for modification by experts; and (3) user interface, through which users and the system can interact with each other.

The computational model for pattern differentiation proceeds in two phases and its pseudo-code was provided (X. Wang et al., 2004). During the first phase, the key elements present by a patient are identified. The second phase searches the standard syndrome-name database, inquiring whether the corresponding patterns consist of these identified key elements. The algorithm considers all the attributes (including manifestations, key elements and patterns) as Boolean variables that take only two values: absent and present. The module for syndrome differentiation used the learned classifier to compute the posterior probability of every key element with Bayes theorem, and output those elements whose probability exceeds the threshold set by experts. Then the module queries and outputs the names of those patterns containing these key elements from standard pattern-name database. Furthermore, the module computes occurrence probability of each pattern by multiplying the probabilities of its corresponding key elements, under the assumption that these key elements are independent. Finally, the module selects the patterns with the probability excess diagnosis threshold.

### **7.3 Information Management System of Traditional Chinese Medicine Syndrome Project based on Prior Knowledge Support Vector Machine (P-SVM)**

Yang et al. (2005) developed the Information Management System of Traditional Chinese Medicine Syndrome Project based on Prior Knowledge Support Vector Machine (P-SVM). SVM aims to process training and generalization with limited information provided by the sample data set without consideration of knowledge from application background. In the framework of limited sample data set learning, SVM makes maximum use of the information provided by sample data set theoretically regardless the application related knowledge. The authors reported an accuracy rate of 95% with the trained P-SVM to classify a sample set of 2,000 simulated records.

The general principle of the method is described here, and its pseudo-code was provided (Yang et al., 2005). A pattern dataset is used to train and test the P-SVM model. The test procedure consists of: a) generation of an expert knowledge dataset; b) description of the expert knowledge as rules to train the dataset to create the scale of confidence values; c) input data with confidence values to the Platt's Sequential Minimal Optimization (P-SMO) algorithm; d) comparison of the accuracy rates under different amount of training samples. The pattern dataset included the literature from 1978 to 2004 with approximately 400,000

entries and its ontology was organized with the entries: author, origin, title, subject heading, subheading, key word, and abstract. In the classification system of SVM with prior knowledge, the classifier will learn the traits of the certain thematic information from the corresponding prior knowledge. Therefore, based on the prior knowledge, the classifier is able to find out the appropriate literary information from the massive data.

No description of how the cases were simulated is available; thus, it is not possible to repeat the simulation procedure and to compare accuracy results. Moreover, the P-SVM theory was not discussed in light of the mode-of-thinking of Chinese medicine experts.

#### **7.4 Chinese Medical Diagnostic System (CMDS)**

Huang and Chen (2007) developed the Chinese Medical Diagnostic System (CMDS) for pattern differentiation of diseases related to the digestive system. It uses a Web interface and expert system technology in diagnosing 50 types of digestive system diseases. The authors compared the diagnosis of 20 simulated cases made by CMDS and diagnosticians and found the results satisfactory; however, they did not report either simulation procedures or statistical validity. The authors also stated that the Four Examinations were necessary for achieving a correct diagnosis. The authors reported 'high reliable and accurate diagnostic capabilities' in 95% of 50 simulated cases without any description of either how cases were simulated or possible sources and types of error.

The CMDS departed from an ontology-based model, in which the proposed ontology was derived from the traditional one but focused on digestive diseases and patterns. The whole system is composed by three main components: a) Java Expert System Shell (JESS); b) Database set; and c) knowledge extractor. The routine for pattern differentiation is depicted in the inference engine modulus of the JESS and automatically matches facts (user's entries) against patterns and concludes which rules are fired in CMDS. Two databases (general and knowledge databases) are used to store all information and rules necessary for pattern differentiation, respectively.

#### **7.5 Pattern Differentiation Algorithm (PDA)**

Ferreira (2008) proposed the pattern differentiation algorithm (PDA) based on an objective criterion developed to account for pattern holism (Guang, 2001). A second criterion was proposed and provided a significant increase in diagnostic accuracy of the model, being up to 94.7% (sensitivity = 89.8%; specificity = 99.5%) with the Four Examinations for *Zangfu* patterns (Ferreira, 2009). This method allowed testing the impact of different combinations of the Four Examinations and the amount of available information presented by patients on PDA's statistical performance. Also, its associated method of model validation uncovered types of diagnostic errors otherwise not assessed by other computational models (Ferreira, 2011). Clinically, PDA was applied to patients with arterial hypertension and help understand that *Zangfu* patterns associated to this disease are indeed evidence of the progression of target-organ damage (Luiz et al., 2011).

PDA works in a three-stage schema and its pseudo-code was provided elsewhere (Ferreira, 2009). The first stage – data collection and dataset search – uses the data entry from patient's exam to search for free terms and quoted phrases, e.g., *headache* and "*headache*". The former term recalls patterns with *headache* within its manifestations profile (*ocular headache, occipital headache, etc.*); the latter term recalls patterns with the exact term. Combinatorial procedure (Zuzek et al., 2000) was used after data collection because the diagnosis does not depend on

the sequence of the results obtained during the exam (Wolff, 2006). Manifestations were described as specifically as possible including onset (“palpitation in the morning”, “palpitation in the evening”), duration (“acute headache”, “chronic headache”), location (“occipital headache”, “ocular headache”) and severity (“dry tongue”, “slight moist tongue”, “moist tongue”), as well as any other characteristic that may be necessary to allow the pattern differentiation. Manifestations that co-occur in two or more patterns were assigned with the same term to increase the accuracy of string search algorithm.

At the second stage - selection of candidate patterns - a pattern is considered as a ‘candidate’ if it presents at least one manifestation collected at the exam. Patterns with no manifestations recognized were not used for further analysis. The “strength” of such indication of the candidate pattern is calculated as an objective criterion  $F_{\%,K}$ . This is an important stage since it recalls any possibility ( $F_{\%,K} > 0$ ) within the dataset and increases the sensitivity of the algorithm. Since patterns maybe described by different quantities of manifestations, the available information must be normalized to allow comparison among them and hence was used as a second objective criterion,  $N_{\%,K}$ . It is expected that the occurrence of a successful pattern differentiation increases with decreasing  $F_{\%,K}$ . It is also expected that the occurrence of a successful pattern differentiation increases with increasing  $N_{\%,K}$ . However, as the accuracy of a diagnostic test is expected to decrease with either lower or higher cutoff values, it is appropriate to subtract a cutoff values from  $N_{\%,K}$  to dislocate the accuracy curve to its optimum operating point. As such, the maximum accuracy is associated with the minimum  $N_{\%-cutoff,K}$ . Hence, the candidate patterns simultaneously ranked in descending order of  $F_{\%,K}$  and ascending order of  $N_{\%-cutoff,K}$  represent a list of diagnostic hypotheses.

The last stage - pattern differentiation - identifies the diagnosis. The diagnostic algorithm receives the manifestation profile and outputs for each tested profile: a) the identified diagnosis; b) the list of diagnostic hypotheses. Pattern differentiation is considered successful in either of two situations: 1) if PDA finds a unique diagnostic hypothesis that explains simultaneously all collected manifestations, *i.e.*  $F_{\%,K} = 100\%$ ; or 2) if there is one pattern among all diagnostic hypotheses with a highest, unique  $F_{\%,K}$  value and lowest, unique  $N_{\%-cutoff,K}$  value. Otherwise, if multiple diagnostic hypothesis were found with equal values of  $F_{\%,K}$  and not unique values of  $N_{\%,K}$  the procedure is considered unsuccessful since differentiation among competing patterns was not possible. In this case, physicians have access to the diagnostic hypotheses list and may want to revise the collected manifestations, continue examination of the patient to search for other manifestations, replace the collected symptoms/signs with more specific ones, or even subjectively chose a pattern.

PDA’s average time for pattern differentiation of each case with the Four Examinations is estimated in less than 0.1s, which is suitable for clinical applications. There is no need to train PDA, which is a mathematical process already subject to bias. PDA’s method is simple, and both criteria can be calculated even manually by a Chinese medicine practitioner (for a low number of candidate patterns). It’s reasoning is entirely based on the actual process executed by Chinese medicine experts and thus reduces the error in data collection and analysis. PDA is more stable than other learning algorithms because the final diagnosis does not depend on the initial guess or sequence of manifestations used during the learning phase (Ferreira, 2009).

However, PDA is dependent on the pattern dataset. PDA’s dataset was built in a form of open base, in which new information can be added (or modified) to the knowledge database

to increase statistical performance of the criterion. As a corollary, the proposed methodology relies on human experts, not only to select the knowledge, but also to provide the database organization. To reduce the implications of the manual insertion of information, computational routines for inter-pattern and intra-pattern consistency were implemented. The major limitation of PDA is that it was tested only for *Zangfu* single patterns (Ferreira, 2008; Ferreira, 2009; Ferreira, 2011). Such case is the simplest one found in clinical practice for *Zangfu* patterns since the pathological process just begun to promote changes in homeostasis. The same subject may present several patterns simultaneously that are not mutually exclusive. Additionally, common etiologies and pattern transmissions among *Zangfu* are contributing factors to limit the model's performance. Finally, other theories are often used to perform diagnosis and were not yet evaluated (Maciocia, 1996).

### 7.6 Multi-Label k-Nearest Neighbour (ML-kNN)

Liu et al. (2010) obtained up to 78% accuracy using only the Inquiry method (n=185 manifestations) for identification of multi-patterns (based on 6 ZFSPs) related to coronary heart disease obtained from real cases. The pseudo-code of the ML-kNN was provided by the authors.

The kNN is an algorithm that searches for the nearest point in a training data set. This theory regards an instance as a point in synthesis space; thus, the label of a test instance is probably similar to those of several nearest points. The data set for pattern differentiation of coronary heart disease belongs to multi-label; whereas kNN only processes single label data sets, so the collected data set should be split into many groups of single label to be calculated. In the multi-label data, there is much relationship among each label, so simple splitting inevitably result in data loss. For this reason, multi-label learning algorithms are developed so as to better reveal the correlation of the labels, of which multi-label kNN (ML-kNN) is a popular technique. ML-kNN is a lazy multi-label learning algorithm developed on the basis of kNN. Based on the theory of kNN, ML-kNN aims to find k nearest instances for each test instance. In ML-kNN, the labels of test instances are judged directly by nearest instances, which is different from kNN.

## 8. Validation of computational models for diagnosis in Chinese medicine

For the model to be useful, expert practitioners must have confidence in the results and predictions that are inferred from it. Verifying or validating the model can provide such confidence. In principle, model validation is done by comparing the model's behaviour with the patient's and evaluating the difference. In the diagnostic field, the computational model is compared to either a gold-standard or a reference-standard method.

### 8.1 Model validation with "gold-standard" and "reference-standard"

The main issue related to diagnostic accuracy tests is the need for a "gold-standard" method or at least a "reference-standard" method to compare the results obtained with the model being tested. The gold-standard method for diagnosis is the one that provides the *true* health status of a person while the reference-standard method for diagnosis is the one that provides the health status *closest to the true one*. Obviously, gold-standard methods are preferred for model validation and assessment of a model's diagnostic accuracy. However, it is almost impossible to test clinical diagnostic models with gold-standard methods since the true

health status is unknown a priori. In this case, a diagnostic model with known statistical properties is applied to obtain a result that is used as the reference-standard.

Patterns identified by a panel of expert Chinese medicine practitioners has been used as the standard for diagnostic accuracy tests of computational models using data from population samples (Zhou & Zhang, 2006; Zhu et al., 2006; N.L. Zhang et al., 2008). This method presents a major drawback since the real diagnosis is not known and samples may be biased (hospital patients, community subjects, etc.). Moreover, the agreement in diagnosis among practitioners may be low (31.7%; 27.5–35%) (G.G. Zhang et al., 2005), despite some improvement after training (73%; 64.3–85.7%) (G.G. Zhang et al., 2008). The Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) (MacPherson et al., 2010) recommend that the experience of Chinese medicine practitioners should be reported in clinical studies because such experience may influence diagnosis. As such, new diagnostic tests should not be compared to diagnoses made by Chinese medicine practitioners but with methods that guarantee correct diagnosis.

For the determination of the accuracy of Chinese medicine diagnostic tests, a large number of patients with possible combinations of the manifestations for each pattern must be generated. Thus, it is virtually impossible to estimate the diagnostic accuracy without computer methods. Stochastic simulation models have been used for research in health sciences. A well-known simulation method is the Monte Carlo (Metropolis & Ulam, 1949), in which the basic idea is to stochastically generate examples of a numerical variable and then evaluate the outcome of the model under evaluation. With stochastic methods, simulated patients can have their health status characterized by a computational model. The simulation of cases fixes both issues by randomly selecting manifestations only from the selected single pattern (Ferreira, 2009). Stochastic method allows a focus on the properties of manifestation profiles instead of individual manifestations. This procedure generates a large number of examples of any given pattern (stochastic process) and then examines the relative proportion of successes of the diagnostic test (deterministic process). Some modifications of the original Monte Carlo method are needed to enable stochastic methods to process nominal variables. Because cases are simulated from all possible manifestations of each pattern in the dataset, the output of the computational model can be compared to the actual name of the simulated pattern in the dataset. Thus, simulation of cases can be considered as a gold-standard method. Moreover, patient simulation models can be composed of independent algorithmic codes (i.e., there is no code sharing), so the results of the identification are blinded to the simulation parameters.

Currently, the computational model for simulating patients and testing diagnostic accuracy is the Manifestation Profile Simulation Algorithm (MPSA) (Ferreira, 2008; Ferreira, 2009, Ferreira, 2011). MPSA generates the study population according to different strategies to create case (true positive) and control (true negative) groups, as well as a proposal for identifying and handling missing cases. The inclusion criterion is the simulation of cases representing a single pattern in the knowledge dataset. For simulation purposes, MPSA assumes that the probability of each manifestation in the general population is given from previous studies or, if unknown, it is suggested to follow a uniform distribution (Ferreira, 2009). The comparison between the simulated pattern and the identified diagnosis yields the binary classification of the proposed method for pattern differentiation.

In MPSA, true positive (TP) cases of a pattern  $K$  are simulated by selecting from the dataset a random quantity of manifestations  $N_{R,K}$ . Each sorted manifestation is excluded from the

set of possible manifestations to prevent multiple occurrences of the same manifestation at the respective simulated case. This iterative process continued until the  $N_{R,K}$  manifestations were sorted to generate the manifestation profile. To obtain a true negative (TN) control for the same pattern  $K$ , two alternatives were proposed. In the first alternative, this respective pattern  $K$  is removed from the dataset and the same quantity  $N_{R,K}$  is selected from the entire dataset and respective examination methods (Ferreira, 2008; Ferreira, 2009). The second alternative is to sort  $N_{R,K}$  manifestations from another pattern pseudo-randomly chosen in the dataset after exclusion of pattern  $K$  (Ferreira, 2011). In both alternatives, the procedure allows a quantitative pair-wise comparison between TP and TN profiles with respect to the available information for pattern  $K$ ,  $N_{%,K}$ . Although the TP pattern was removed from the dataset, its manifestations that co-occur in other patterns are still present and could be selected to compose a TN manifestation profile. Since patterns may not present manifestations for some of the examination methods, empty manifestation profiles related to these examination methods represent missing cases and were excluded from analysis.

Despite the main advantage of knowing a priori the true pattern and methodological blinding, some limitations need to be mentioned. Manifestations may be sampled multiple times within the same run, resulting in less variation of manifestations profile than it would be expected to see in real patients. Also, manifestations may not be chosen at all, resulting in not tested data. However, large simulated samples from the dataset diminished these limitations (Ferreira, 2008). To assess the quality of the simulated cases and controls, a routine can be implemented to check if all manifestations were used for simulation of manifestations profiles. The algorithm performs a 'reverse engineering' by recreating the dataset from all simulated true positive cases. The algorithm searched among all manifestation profiles simulated for each pattern and grouped the manifestations present at least once among the simulated cases into a temporary dataset. After comparison with the original dataset, the algorithm reports whether the patterns that were completely simulated (*i.e.* all manifestations were used for analysis), partially simulated and not used for simulation (Ferreira, 2011).

## 8.2 Detection and classification problems

In general, the diagnostic process is designed to detect if the subject is healthy or ill. In this case, two groups of subjects with known true conditions are used: a group of individuals in which the condition to be tested is truly present; and a group of individuals in which the condition to be tested is truly absent. Adapted to Chinese medicine framework, a "healthy pattern" diagnosis must be described in the same manner as the "ill" patterns. For instance, the "liver-blood deficiency" pattern should have the mutually exclusive counterpart "liver-blood healthy" pattern. The description of such health-related patterns is possible because pattern differentiation process is not limited to assessing presence/absence of manifestations (e.g. asymptomatic individuals may also have their patterns identified). A completely healthy person will present all healthy patterns simultaneously. However, in clinical practice it is difficult to find a patient that is completely healthy and thus the pattern differentiation process must be applied to patients. In this case, the diagnostic model must recognize the underlying pattern (or patterns) and not the healthy or ill statuses.

## 8.3 Sample sizes, participant recruitment and sampling

A important issue in diagnostic accuracy studies is the sample sizes determination, which can be estimated based on equations derived for detecting differences in accuracy tests

using receiver operating characteristic (ROC) curves (Hanley & McNeil, 1982). For calculations, it is necessary the expected difference in accuracy between the reference and the index test, the level of significance (usually  $\alpha=5\%$ ,  $Z\alpha=1.645$ , one-sided), and the power of the test (usually  $\beta=90\%$ ,  $Z\beta=1.28$ ). The equation designed to real cases can be used in simulated ones provided that the absolute consistency between original and recreated datasets is proved as described before. This is an important issue related to the quality control in this study and should not be omitted in other simulations studies were pattern differentiation outcomes are assessed (Ferreira, 2011).

#### 8.4 Estimating the diagnostic accuracy of a diagnostic model

Diagnostic models present domains of validity, *i.e.* they should not be used outside the validation scope since there is no estimation concerning its performance. The implications range from underestimation to overestimation of the model's diagnostic accuracy. The Standards for Reporting of Diagnostic Accuracy (STARD) (Bossuyt et al., 2003) summarized the necessary steps for conducting scientific works to determine diagnostic accuracy of models. Although not specified in the STARD, such methodology can be also be adopted by studies in which computational models perform diagnosis, even in case of simulated patients. The validity of a new diagnostic model is obtained by comparison of the new model's results with the actual result. However, very often the actual value is not known most commonly due to absence of gold-standard diagnostic methods.

Accuracy, sensitivity, specificity, positive and negative predictive values are the most common measures of a model's performance. Accuracy is defined as the proportion of true results in the population. Sensitivity is the probability that the test is positive given that the patient is sick (Altman & Bland, 1994a), while specificity is the probability that the test is negative given that the patient is not sick (Altman & Bland, 1994a). Positive and negative predictive values are proportions of true positives and true negatives out of all positive results, respectively (Altman & Bland, 1994b). All those estimators are obtained from  $2 \times 2$  confusion matrices (Table 1) made from classification of simulated and identified diagnosis (Jekel, 1999; Altman & Bland, 1994a; Altman & Blend, 1994b). Departing from Table 1 and adapting the epidemiological concepts to Chinese medicine framework, computational models can be evaluated with estimations of:

		Gold-standard test result	
		Simulated pattern (Case)	Other pattern (Control)
New test result	Identified pattern	True positive (TP)	False positive (FP)
	Other pattern	False negative (FN)	True negative (TN)

Table 1. Confusion  $2 \times 2$  matrix for assessment of diagnostic accuracy between the reference test and pattern differentiation algorithm.

- Accuracy: proportion of successful pattern differentiation (true results) in the population (equation 1). Diagnostic accuracy indicates the total sum of corrected assigned cases.

$$Accuracy = \frac{TP + TN}{TP + FN + TN + FP} \times 100\%; \quad (1)$$

- b. Sensitivity: proportion of successful pattern differentiations correctly predicted by PDA in cases (equation 2).

$$\text{Sensitivity} = \frac{TP}{TP + FN} \times 100\%; \quad (2)$$

- c. Specificity: proportion of successful pattern differentiations correctly predicted by PDA in controls (equation 3);

$$\text{Specificity} = \frac{TN}{TN + FP} \times 100\%; \quad (3)$$

- d. Negative predictive values: proportion of unsuccessful pattern differentiation correctly predicted by PDA (equation 4).

$$\text{Negative predictive value} = \frac{TN}{TN + FN} \times 100\%; \quad (4)$$

- e. Positive predictive values: proportion of successful pattern differentiation correctly predicted by PDA (equation 5).

$$\text{Positive predictive value} = \frac{TP}{TP + FP} \times 100\%. \quad (5)$$

ROC plots are used to visualize and estimate accuracy of the model's classification. Those estimators are readily available from 2x2 crosstabs obtained from simultaneous classification of the results regarding the "gold-standard" and the new model under evaluation. In ROC plots, the smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other tested cutoff values were the averages of two consecutive ordered observed test values (Hanley & McNeil, 1982; Hanley & McNeil, 1983; Altman & Bland, 1994c).

### 8.5 Comparing diagnostic accuracy of two computational models

Consider now the situation where two computational models can be used. It is of interest to select the best model in terms of diagnostic accuracy. Such a comparison can be performed based on a pair of 2x2 confusion matrices (Table 2) made from classification of simulated and identified diagnosis simultaneously by the two computational models.

		True negative				True positive			
		Model 1	-	+			Model 1	+	-
Model 2	-		A	B	Model 2	+	a	b	
	+		C	D		-	c	d	

Table 2. Confusion 2x2 matrices for comparison of binomial proportions between the two diagnostic tests. (+) and (-) indicate positive and negative test results respectively. B is the number of TN cases classified correctly by test 2 and falsely by test 1 and conversely for C cases and analogously for the TP group.



The 95% confidence interval (95%CI) for the binomial proportions  $p$  (accuracy, sensitivity, specificity, negative predictive value, positive predictive value; equations 1-5) can be calculated with Wilson's method (Agresti & Coull, 1998). If both models are to be evaluated on the same samples of TP and TN cases, an adaptation of McNemar's test for correlated proportions is applied (Linnet & Brandt, 1986). The TP and the TN profiles are divided into four parts according to their test responses (Table 2). Estimations related to ROC curves (AUC and respective 95%CI) can be obtained with the nonparametric Wilcoxon statistic (Hanley & McNeil, 1982; Hanley & McNeil, 1983).

Since the Four Examinations provide the basic ontology for pattern differentiation, it is of interest to study the partial contribution of each Examination as well as their cumulative, sequential application. Hence, the diagnostic accuracy may be studied in terms of the following sets of the Four Examinations:

1. Inspection;
2. Auscultation & Olfaction;
3. Inquiry;
4. Palpation;
5. Inspection, Auscultation & Olfaction;
6. Inspection, Auscultation & Olfaction, Inquiry;
7. Inspection, Auscultation & Olfaction, Inquiry, Palpation.

Indeed, as manifestations are closely related to the interdependent internal organs, combined Examination methods are preferable since they cover several forms of presentation of the same pattern.

### 8.6 Recognition of diagnostic errors in pattern differentiation

All models have a certain domain of validity. This may determine how exactly they are able to describe the system's behavior. It is hazardous to use a model outside the area it has been validated for. Reports of errors for Chinese medicine practitioners are available from ancient literature (Yang & Li, 1993; Luo, 1995; Yang, 2003; Flaws, 2004; Yang & Chase, 2004) including non-skilled practice, misdiagnosis and mistreatment; however, little contemporary literature is available on this subject. Evidence shows that subjectivity of manifestations or limited detection of clinical features is the major causes of unreliable pattern differentiation made by Chinese medicine practitioners (Kim et al., 2008; O'Brien et al., 2009). While diagnostic errors can never be eliminated, they can be minimised through understanding factors related to the pattern differentiation process.

Recognition of factors related to the performance of diagnostic methods is relevant to the development of reliable methods that can be implemented for clinical and research purposes. The first limitation to pattern differentiation algorithms is that the user must possess a certain level of knowledge to discriminate or interpret the patient's complains (Harding, 1996). Therefore, an implicit assumption to all current computational models is that the patients are capable of reporting their symptoms and that the Chinese medicine practitioners are able to correctly identify manifestations.

Pattern similarity is intrinsic to Chinese medical knowledge. Pattern similarity introduces errors in the pattern differentiation process, as the patient's true pattern may not be properly assigned. Dual pattern similarity has moderate, statistically significant effect on pattern differentiation outcome but cumulative application of the Four Examinations progressively reduces the strength of significant association between pattern similarity and diagnostic errors (Ferreira, 2011).

Currently three pattern differentiation outcomes can be distinguished, namely (a) identification of the true pattern (correct diagnosis), (b) identification of a pattern that is not the true pattern (misdiagnosis) and (c) no identification of pattern at all (undiagnosis). For discrimination of those types of diagnostic errors, 2x3 crosstabs (Table 3) are used to differentiate among correct diagnosis, misdiagnosis and undiagnosis.

		Gold-standard test result	
		Simulated pattern (Case)	Other pattern (Control)
New test result	Identified pattern	Correct (TP)	Erroneous (FP)
	Other pattern	Erroneous (FN)	Correct (TN)
	No pattern identified	Absent	Absent

Table 3. Crosstabs (2x3) for investigation of diagnostic errors of computational models.

The distinction of error types in this study is possible if the manifestation profiles of true negative controls are any other true pattern that was not its true positive counterpart, and not just random manifestations from all patterns in dataset as in other studies. This modification expands the interpretation of false negative cases from one wide option ('it can be any other pattern, no pattern at all, or it was not possible to uniquely identify any pattern  $K$ ') into two separate options ('it is pattern  $K$ ' or 'it was not possible to uniquely identify any pattern in dataset'). With this true condition made known a priori it is possible to distinguish misidentification from no identification among unsuccessful outcomes (Ferreira, 2011).

### 9. Future directions

Although validated diagnostic models are available, several issues limit their application in patient care. For instance, almost all computational models deal with single patterns - a condition rarely seen in clinical practice - or a single disease. Complex and multiple patterns present additional difficulties in the diagnostic task since there are several combinations of two or more patterns that could result in the same diagnosis. Multiple patterns decomposition is then an open field of research with direct clinical applications and should be investigated.

Standardization of treatment prescription is possible since well-defined, consistent diagnosis can be achieved with computational models. Current trends focus in computer-aid to perform diagnosis and treatment. It is believed that the combination of traditional methods and modern resources may improve the efficacy of Chinese medicine intervention.

Suggested topics for future research on computational models for pattern differentiation:

- Construction of an internationally available Chinese medicine ontology and web-based knowledge dataset with patterns and manifestations.
- Use of qualitative, "fuzzy-like" scales developed in Eastern medicine. Ex.: tongue fur.
- Discovery of which subsets of manifestations lead to a more accurate diagnosis  
Determination of the distribution of manifestations in each pattern (and patterns in the dataset) to improve the simulation of manifestation profiles.
- Incorporation of common etiologies and pattern transmissions into computational models to extend its application in general clinical practice.

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During the recent years, traditional Chinese medicine (TCM) has attracted the attention of researchers all over the world. It is looked upon not only as a bright pearl, but also a treasure house of ancient Chinese culture. Nowadays, TCM has become a subject area with high potential and the possibility for original innovation. This book titled Recent Advances in Theories and Practice of Chinese Medicine provides an authoritative and cutting-edge insight into TCM research, including its basic theories, diagnostic approach, current clinical applications, latest advances, and more. It discusses many often neglected important issues, such as the theory of TCM property, and how to carry out TCM research in the direction of TCM property theory using modern scientific technology. The authors of this book comprise an international group of recognized researchers who possess abundant clinical knowledge and research background due to their years of practicing TCM. Hopefully, this book will help our readers gain a deeper understanding of the unique characteristics of Chinese medicine.

### **How to reference**

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