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## DISEASES DIAGNOSIS AND CLASSIFICATION AS PRIME NUMBER REPRESENTATIONS\*

#### PENGFEI ZHANG<sup>†</sup>

4 **Abstract.** Classification and diagnosis of diseases by criteria are prevalent in clinical medicine. 5 We demonstrate that prime number representation of these classifications can be used for automated 6 diagnosis generations as well as analyses of structural questions in disease classifications.

7 Key words. Disease Classifications, Applied Number Theory

8 MSC codes. 11Z05, 00A69

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**1.** Introduction. Criteria based classification of diseases is becoming the norm 9 in medicine. The classic example is the Diagnostic and Statistical Manual of Men-10 tal Disorders (DSM), a criteria based guideline used in psychiatry for diagnostic 11 purposes.[1] Similarly, the International Classification of Headache Disorders (ICHD), was conceived by neurologists in 1988, providing clinicians with an authoritative codified diagnostic paradigm for headache disorders. [5] In both basic research as well 14 as clinical practice, both Diagnostic and Statistical Manual of Mental Disorders, 5th 15 edition (DSM5) and the International Classification of Headache Disorders 3rd edition 16 (ICHD3) are widely used as the gold standard approach in diagnosis. Diagnosis by 17 18 criteria therefore fundamentally influence both fields. These are not the only examples, other criteria such as Innternational Classification of Vestibular Disorders and International classification of Orofacial Pain seek to 20

21 comprehensively classified diseases in a domain. Criteria also exists for fibromyalgia,

22 restlessless syndrome, and lupus, to name a few. [4] [6]

The benefits of codifying diagnosis is clear; diagnostic criteria allow clinicians to be precise in diagnosis and therefore treatments and research of diseases. However, as

25 in any classification, problems of internal structural consistencies rise to the fore-

<sup>26</sup> front when classifications are applied widely. This is evident in scholarly debates: In

headache, for example, whether post traumatic headaches should be classified by its phenotype or by the onset and duration after trauma is a hotly debated topic.[2] The

reason, is that phenotypically, chronic post traumatic headache, by the ICHD3 defi-

<sup>30</sup> nition, can be made to conform to a diagnosis of chronic migraine or chronic tension

31 type headache. [5] In other words, post traumatic headaches suffer from a classifica-

tion problem on "uniqueness": Does our current classification system for headaches

33 offers unique diseases with a unique classification?

On the other end of the spectrum, classifications often struggle with the "missing diagnosis" problem. Consider, for example, that the first version of International classification of headache disorders contains only 13 categories of diagnoses; its most recent embodiment, the ICHD3, contains 14 categories of disorders with an appendix.

Therefore we are diagnosing diseases today not diagnosible in ICHD's first version.

39 A similar phenomenon occurs in psychiatry; in the original DSM, a number of disor-

40 ders we now thought of as canonical were not included. These are what is considered

41 missing diagnosis questions: What disease entity are we missing in our current clas-

42 sifications? In other words, is our classification "complete"?

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Of course, "missing" diagnosis in a criteria is inevitable; it is a sign of scientific ad-43 44 vancements. Yet it is troublesome that there are missing diagnosis which seems to arise purely as downstream effects of "holes" in the Classification system. An ex-45 ample of a well known "gap" in headaches occurs in a category of headaches called 46the "trigeminal autonomic cephalaigas" (TAC): There is a diagnostic "gap" between 47 the longest of the TACs - hemicrania continua - and the second longest - "cluster 48 headaches"; the former being constant, the latter lasting maximum of only three 49 hours. TAC which are longer than 3 hours but not constant certainly exists but are 50often times unclassifiable under the current schema. [7] Therefore aside from the limitations of scientific advancement, what are these headache disorders with recognized

53 phenotypes and yet is undiagnosable in the current diagnostic criteria?

54 In this paper we construct a mathematical tool to answer these classification ques-

tions. Specifically, we first propose that prime number factorization can be used to encode disease classifications as long as the latter can be represented by propositional logic. This method allows for automated diagnosis of diseases. From this ability we can then seek to provide a foundation for answering these structural questions of com-

<sup>59</sup> pleteness and uniqueness that arises from disease classification.

60 This paper is organized in the following fashion: Since the technique is novel, we will

61 demonstrate this technique by applying it to International Classification of Headache

62 Disorders (ICHD3). We will then supply the reader with the formal justification 63 mathematically. Finally, in the last two sections we will sketch out how to apply our

mathematically. Finally, in the last two sections we will sketch a
 methods to uniqueness and completeness problems.

65

2. Demonstration of Method by Application to ICHD3. ICHD3 is a
widely used and canonical way of diagnosing headache disorders and follows a criteria
system; headache disorders are classified by groupings of phenotypes. For example,
the criteria for migraine without aura are presented below, and the disorder is defined
by the existence of a specific set of headache phenotypes.

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72 DEFINITION 2.1. (from [5]) Migraine without aura diagnostic criteria:

- 74 A. At least five attacks1 fulfilling criteria B-D
- 75 B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)
- 76 C. Headache has at least two of the following four characteristics:
- 77 1. unilateral location
- 78 2. pulsating quality
- *3. moderate or severe pain intensity*
- 4. aggravation by or causing avoidance of routine physical activity (e.g. walking
- 81 or climbing stairs)
- 82 D. During headache at least one of the following:
- 83 1. nausea and/or vomiting
- 84 2. photophobia and phonophobia
- 85 E. Not better accounted for by another ICHD-3d diagnosis
- 86
- 87 One can translate this criteria directly into propositional logic statements as follows:
- (We use the alphanumeric designation of the criteria as short-hand for each phenotype.)
- 90 DEFINITION 2.2 (propositional translation of ICHD3). Migraine without aura is

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91 defined as the following:  $A \land B \land [(C1 \land C2) \lor (C1 \land C3) \lor (C1 \land C4) \lor (C2 \land C3) \lor$ 92  $(C2 \land C4) \lor (C3 \land C4)] \land (D1 \lor D2) \land E$ 

This definition can be expanded, of course, into its disjunctive normal form:

### $(A \land B \land C1 \land C2 \land D1 \land E) \lor (A \land B \land C1 \land C2 \land D2 \land E) \lor (A \land B \land C1 \land C3 \land D1 \land E) \dots$

93 In clinical practice, given a set of headache phenotype, such as a patient profile, 94 headache disorders can be diagnosed based on satisfactions of the above criteria. This 94 headache disorders can be diagnosed based on satisfactions of the above criteria.

<sup>95</sup> is therefore equivalent to diagnosis based on propositional logic statements.

96 Of course, migraine without aura is not the only possible headache diagnoses in 97 ICHD3. Indeed more than 200 headache disorders exist. Each of these headache 98 disorders are also defined by a diagnostic criteria similar to the one presented above. 99 We will refer the reader to the actual ICHD3 for more detail. [5]

**3. Translations of propositional logic criteria into encoding.** Since every
 ICHD3 criterion can be translated to propositional logic statements in its disjunctive
 normal form, one can translate the classification into prime number encoding using
 the following algorithm:

105 Step 1: All headache phenotypes in a diagnosis paradigm are assigned a unique 106 prime number. (Appendix 1) Notice that negations crucial to diagnostic criteria are 107 also assigned a prime number.

108 Step 2: If AND is used between two phenotypes in the criteria, then the 109 corresponding prime number for those two phenotypes are multiplied together. If 110 OR is used between two phenotypes, then the prime numbers for the corresponding 111 headache phenotypes are put in a list.

Step 3: Compositions of Step 2 operations are then used throughout the whole encoding procedure.

For the purpose of demonstration, one example of the encoding migraine without aura

- 115 is shown below.[8]
- 116 [4075291, 9333731, 9596653, 26304151, 27045113, 61942033, 28934661, 297496243,
   117 450154441, 681362363, 1030998881, 1060041103, 1920203023, 2905542301,

1182987388563, 6842083483, 21122233253, 31960965311, 32861274193, 75262918313,119212104587979, 2333150467703]

A patient profile, thought of as a collection of headache phenotypes, can be expressed using only logic conjunction. Therefore, a patient profile can be expressed as one composite integer. For example, a patient who has the phenotype of five headaches, each lasting 4 to 72 hours, unilateral, pulsating, with nausea, photophobia and no other diagnosis can be represented by 19\*17\*71\*73\*37\*67 = 4150116211. (We do not encode criteria E as it is in every single ICHD3 diagnoses. However, this modification can be make and the algorithm would still remain intact.)

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We will show below that a patient profile, represented as a composite number, divides at least one number in its corresponding diagnosis' encoding. In other words, a patient who has migraine without aura must have an encoding which divide by at least one number in the migraine without aura encoding. This observation forms the basis for automated diagnosis.

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For example, 61942033 divides 4150116211 in example above, therefore migraine without aura is diagnostic. Since the above process need not limit itself to headache classification, this result can be applied to any disease classification following a similar

criteria paradigm. 137

138Finally, we must note two peculiarities to our formulation: 1) the encodings are square

free since one cannot count a criteria twice; 2) although theoretically possible, in prac-139

tice logical conflicts cannot exist in a patient nor a criteria encoding. (For example, 140

it makes no sense to be both photophobic and not photophobic at the same time in 141 either the criteria or user encoding.) Both of these peculiarities will be exploited in 142

our analysis of "uniqueness" and "completeness" below. 143

4. Mathematical Justification of the Technique. We will now construct a 144 formal definition of "encoding" for a given collection of diagnostic criteria. We will 145146first construct the following abstraction:

DEFINITION 4.1. Let S be the following sequence:

$$S = \{S_1, S_2, S_3 \dots S_i \dots S_{m-1}, S_m\}$$

where  $S_i$  represents individual statements (i.e. phenotype) in a classification. 147

We now define a function that "encodes" the propositional values for each indi-148 vidual statements based on whether the users answers True or False. 149

**DEFINITION 4.2.** Define the following:

$$\varphi(S_i) = \begin{cases} P_i^1 & \text{if } S_i = True \\ P_i^0 & \text{if } S_i = False \end{cases}$$

where  $P_i$  is the *i*<sup>th</sup> prime. Here "True" or "False" assigned by the user for each  $S_i$ 150151statement.

DEFINITION 4.3. The "encodina" for a set of user assigned phenotype is the following:

$$Q(S) = \prod_{i}^{m} \varphi(S_i))$$

Notice that the "space" in which these encodings exist is simply the square free inte-152gers up to the  $m^{th}$  prime. We will call this  $I_m$ , representing all possible values of a 153user's questionnaire: 154

155

Definition 4.4.

$$I_m = \{i | i \in P_1^{n_1} P_2^{n_2} P_3^{n_3} \dots P_m^{n_m}, n_m \le 1, m \in \mathbb{Z}, p \in \mathbb{P}\}$$

We will first prove that prime factorization and propositional values in the user's 156answers are connected for logic conjunction: 157

THEOREM 4.5. Given  $a \in I_m$ , if  $P_i$  divides a, then  $S_i = True$ . 158

*Proof.* By fundamental theorem of arithmetic:

$$a = P_1^{n_1} P_2^{n_2} P_3^{n_3} \dots P_m^{n_m}$$

- Since  $P_i$  divides a, then  $n_i \ge 1$ . Now  $I_m$  is square free and  $a \in I_m$ , therefore  $n_i = 1$ . 159
- Suppose to the contrary that  $S_i = False$ , then  $\varphi(S_i) = P_i^0$ . This implies that  $n_i = 0$ , 160Π

reaching a contradiction. 161

162 Now we will prove the following relationship between two encoding:

163 THEOREM 4.6. Let  $\iota, \pi \in I_m$ , where  $\pi = P'_{a1}P'_{a2}...P'_{aj}$  and the user assigns 164  $S_1, S_2...S_j$  such that  $\iota$  is the encoding by definition 4.3. If  $\pi$  divides  $\iota$ , then  $S_{a1} =$ 165  $True, S_{a2} = True...S_{aj} = True$ 

166 (We use the subscript a1, a2, ...aj to differentiate arbitrary collections of prime from 167 the  $j^{th}$  prime.)

168 Proof. Given that  $\pi$  divides  $\iota$ , then  $P'_{a1}$  divides  $\iota$ ,  $P'_{a2}$  divides  $\iota$ ,  $P'_{a3}$  divides  $\iota$ .... $P'_{aj}$ 169 divides  $\iota$ 

170 By Theorem 4.5,  $S_{a1} = True, S_{a2} = True...S_{aj} = True$ 

171 We now need to define the notion of diagnostic criteria and what it means to 172 diagnose a disorder.

173 DEFINITION 4.7. A diagnostic statement,  $\sigma$ , for a specific disorder is the assign-174 ments of True to a subsequence of S and the assignments of False otherwise.

175 DEFINITION 4.8. A diagnostic criteria for a specific disorder is a collection of 176 diagnostic statements for that disorder.

For example, a migraine diagnostic statement is assigning each of  $S_1, S_2, S_3, S_4, S_5$ 177 to True if  $S_1$  is "at least five headaches",  $S_2$  is "each lasting 4 to 72 hours",  $S_3$ 178is "unilateral",  $S_4$  is "pulsating", and  $S_5$  is "nausea". This diagnostic statement 179describes one of a number of conditions that satisfies migraine without aura according 180 to ICHD3. A diagnostic criteria is the collection of all such statements which satisfies 181 migraine without aura. We are able to define a diagnostic criteria as a collection 182of diagnostic statements due to the fact that all propositional statements can be 183translated into a disjunctive normal form. 184

185 DEFINITION 4.9. We say that i', an assignment of True and False to elements 186 of S, is considered a "diagnosis" of a diagnostic criteria,  $M' = [\sigma_1, \sigma_2, ... \sigma_j ..., \sigma_k]$ , if 187  $\sigma_j^T$  is a subsequence of  $i'^T$  for some j, where  $\sigma_j^T$  the subsequent of  $\sigma_j$  that is assigned 188 as True and  $i'^T$  is the subsequent of i' that is assigned as True.

This should be intuitive as any assignment that conforms to a diagnostic criteria 189 is the diagnosis. The i' here is really just the representation for a set of phenotype, 190such as a patient profile. (This set needs to be ordered in order to be assigned a 191192 prime number by  $\varphi$ , therefore sequence is used and not set in our definitions.) The definition simply suggests that if there is a diagnostic statement,  $\sigma_i$ , which matches 193a subsequence of True as i', then it is diagnostic. Notice that False is not taken in 194to consideration here, specifically due to the fact that negations are assigned a prime 195number and encoded directly. 196

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We can pin down these definitions mathematically by directly considering encodings:

DEFINITION 4.10. A diagnosis set, M, for a diagnostic criteria

$$M' = [\sigma_1, \sigma_2, \dots \sigma_k]$$

is defined as the following:

$$M = [Q_1(S), Q_2(S), Q_3(S)...Q_n(S)]$$

200 where  $\sigma_1$  assigns True or False to elements of S in  $Q_1(S)$  in accordance to Definition

201 4.3. The same applies to  $\sigma_2$  to  $Q_2(S)$  ... etc.

This is the mathematical encoding for a diagnostic criteria where every element in the set M is a composite number encoding a diagnostic statement. A concrete example of this is shown in section 3.

205 206

Now we find prove the crux of our argument:

THEOREM 4.11. Let M be a diagnostic set for diagnostic criteria M', i an encoding for i', and let  $\pi \in M$  where  $\pi$  encodes  $\sigma \in M'$ . Then if  $\pi$  divides i, then i' is diagnostic of M'.

210 Proof. Since  $\pi \in M$ ,  $\pi \in I_m$ . Similarly, since *i* is an encoding,  $i \in I_m$  also. 211 Let  $\pi = P'_{a1}P'_{a2}...P'_{aj}$ . By theorem 4.6, since  $\pi$  divides *i*, then  $S_{a1} = True, S_{a2} =$ 212 True... $S_{aj} = True$  for *i'*. Furthermore,  $S_{a1} = True, S_{a2} = True...S_{aj} = True$  for 213  $\sigma$  by theorem 4.6, since  $\pi$  divides itself. Since  $\sigma \in M$ , and the above suggests that 214 whichever element of *S* is *True* for  $\sigma$  is *True* also for *i'*, therefore the former is a 215 subsequence of the latter. By definition 4.9 *i'* is diagnostic of *M'*.

THEOREM 4.12. Let i' be diagnostic of M'. Then there exists  $\pi \in M$  where  $\pi$ encodes  $\sigma \in M'$  such that  $\pi$  divides i.

218 Proof. Let *i* be an encoding of *i'* and *i'* be a diagnostic of *M'*. Then there exists 219  $\sigma_j$  such that  $\sigma_j^T$  is a subsequence of  $i'^T$  by definition 4.9. Applying definition 4.3 to 220 this  $\sigma_j$  yield a  $\pi$  such that  $\pi = Q_j(S)$ . Therefore  $\pi \in M$  by definition 4.10. Now we 221 need to show that this  $\pi$  divides *i*: Since  $\sigma_j^T$  is a subsequence of  $i'^T$ , so  $Q(\sigma_j)$  divides 222 Q(i').

223 The above two theorems therefore justify the following claim:

THEOREM 4.13. Let M be the diagnostic set of M', i be an encoding of i', and  $\pi \in M$  where  $\pi$  encodes  $\sigma$ . Then  $\pi$  divides i if and only if i' is diagnostic of M'.

5. Sketch of Applications to The Question of "Uniqueness". The problem of dual diagnosis, or codiagnoses, is essentially a problem of uniqueness. In other words, the question is whether one disease with a specific phenotype can receive two different diagnosis under the same classification schema. In order to tackle the problem it is useful to generate all possible combinations of duo diagnosis directly by utilizing the encodings above in the following fashion:

Let *i* be diagnostic of M' and N' where  $M' = [\sigma_1, \sigma_2, \sigma_3...\sigma_k]$  and  $N' = [\tau_1, \tau_2, \tau_3...\tau_l]$ . Then by theorem 4.13, there exists both  $\sigma \in M'$  such that  $\sigma$  divides *i* and  $\tau \in N'$ such that  $\tau$  divides *i*. Therefore,  $\sigma$  multiplies  $\tau$  divides *i*. In other words, the set  $C = [\sigma\tau]\sigma \in M', \tau \in N', \forall \sigma, \tau]$  yield the condition for all possible codiagnoses.

In practice, however, this is an overcounting of duo diagnoses, since we allow both a phenotype as well as its negation to occupy unique prime numbers. For example, in Appendix 1, "no photophobia" (prime encoding 43) and "photophobia" (prime 67). Therefore we simply need to remove from C all elements that is divisible by the encodings of conflicting phenotypes. (That is, 43\*67, in our example above.)

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6. Sketch of Applications to The Question of "Completeness". The problem of missing diagnosis is essentially a problem of completeness. In other words we want to characterize which sets of disease phenotypes cannot have a diagnosis under a classification schema. One way to answer this question is to screen through all possible combinations of disease phenotype and see which one cannot be diagnosed. However, even in our examples above, screening through all possible combinations would involve screening through 2<sup>27</sup> combinations. In a large set of criteria, such as

- ICHD3, the number of combinations becomes astronomical and this method become impractical.
- However, for large enough numbers we can estimate the number of "gaps" in the
- classification by applications of theorem on square free numbers:
- Since  $I_m$  is the set of square free integers, the question of "impossible" diagnoses is equivalent in asking which of square free integers are not divisible by specific sets of prime. For example, the number of ways in which a headache phenotype which is "photophobic" has no ICHD3 diagnosis is equivalent to the following heuristic: (the number of integers in  $I_m$  that is divisible by 67) - (the number of all square free integer divisible by prime factorization of each ICHD3 dx 1, etc) - (all square free integer
- <sup>259</sup> divisible by prime factorization by any of the illogical combinations).
- All variables in the above heuristics can be estimated either considering the natural density of square free numbers through a method developed by Brown in 2021. The main result is reproduced below:[3]
- 263

THEOREM 6.1. Given two sets of disjoint primes P and T, where T is finite, Then the porportion of all numbers which are square-free and divisible by all of the primes in T and by non of teh primes in P is:

$$\frac{6}{\pi^2} \prod_{p \in T} \frac{1}{1+p} \prod_{p \in P} \frac{p}{1+p}$$

Our approach therefore offers a theoretical solution for the open question of "impossible" diagnosis.

7. Discussion:. This paper proposes a methods of prime number encoding for 266disease diagnosis and classification. We first present a demonstration using the 267ICHD3. Following this demonstration, we then introduce the language of prime num-268269 ber encoding mathematically. Then we applied it to disease diagnosis and proved that diagnosis can be interpreted as a prime number divisibility problem. Finally, we 270show how the encoding can be applied to the uniqueness problem directly. We also 271 show how the properties of square free integers can be used to tackle the completeness 272273problem.

An important limitation of our construction is the inherent logical inconsistency of 274275various disease diagnosis paradigms. For example, in ICHD3, The last criteria of every single diagnostic criteria requires an exclusion of other diagnosis. This is, of 276course, not logically consistent. In fact, the ICHD3 itself notes this inconsistency 277in the section on diagnosis of New Daily Persistent Headaches; In this section, the 278279criteria allows for duo diagnosis of multiple different disorders to satisfy this logical inconsistency due to exclusion. [5] We can, of course, indirectly incorporate the last 280criteria of exclusion into our diagnostic prime number paradigm. However, if we do 281so, then the burden of deciding whether this exclusion criteria applies will lie with the 282user. In other words, no mathematical construction or model can correct for internal 283284logical inconsistencies of a diagnostic guide.

Future directions of this research involves direct application of our theory in real life settings. Fortunately, unlike other kinds of data, diagnostic criteria are readily available and free to most clinicians. Therefore prime number encodings of diagnostic criteria should be an easy undertaking. A corollary to our project, is that prime number encoding can be used for automated diagnosis of diseases. In a world where psychiatrical and headache access is limited financially in various parts of the world,

291 this may provide hey importantly diagnostic tool for clinicians.

Finally, we must note that the assumptions and indeed the goal of this project is a Kantian one. Indeed, what we are investigating is not so much true disease pathophysiology but the condition of possibility of our thinking, as a scientific community, on headaches and psychiatric disorders. In other words, we are investigating what Foucault would called the "Order of Things" in medicine whenever criteria based

297 categorization of disease is applied.

298 8. Conclusions. Prime number encoding of disease classification in criteria al-

299 lows for automated diagnosis . This automated diagnosis allows us to investigate

the uniqueness and completeness of disease classifications. This paper provides the theoretical language necesary for such an investigation.

## DISEASES DIAGNOSIS AND CLASSIFICATION AS PRIME NUMBER REPRESENTATIONS 9

# 302 Appendix 1:303

Statement Number	Description of Criteria
2	1 to 14 episodes per month
3	10 episodes but less than 1 per month
5	15 days per month
7	30 min to 7 days in duration
11	aggravated by physical activity
13	bilateral location
17	duration between 4 to 72 hours
19	greater than 5 episodes
23	hours to days or unremitting
29	mild to moderate pain
31	moderate to severe
37	nausea/vomiting
41	no nausea/vomiting
43	no phonophobia
47	no photophobia
53	not pulsating
59	not aggravated by activity
61	Phonophobic
67	Photophobic
71	pulsating
73	unilateral

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