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ICD-10 - ORPHA: An Interactive Complex Network Model for Brazilian Rare Diseases

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Abstract

A disease is considered rare if it has a low prevalence. It is estimated that around 400 million people worldwide have a rare disease, including 15 million in Brazil. Consequently, it became a public health priority for the World Health Organization and the Brazilian Health Ministry. In 2014, the Brazilian government launched a national policy regarding the care for rare patients', the Ordinance nº199. The national politic defines guidelines, procedures, and descriptions of rare disease codes to provide access and diagnosis in the public health system to reduce mortality and improve patient's quality of life. Diseases are identified according to the International Classification of Diseases 10th Revision, a widely used terminology in this context. However, there are also different terminologies to codify a rare disease, such as the ORPHAcode provided by Orphanet. This paper proposes a complex network model using the terminologies' relationship to show that the International Classification of Diseases 10th Revision may be generic for diagnosing rare Brazilian patients. Moreover, there is no perfect nomenclature to define rare diseases, but each context has a better application. So, mapping the relationship between each terminology is fundamental for creating consistent

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semantic relationships in biomedical ontologies, providing a functional environment for carrying out tasks involving more than one terminology.

Keywords: Rare Disease, Complex Network, Biomedical Ontology, Graph Modeling.

1. Introduction

A Rare Disease (RD) is a medical condition that is characterized by a low prevalence compared to diseases that are commonly observed in the general population. The definition of RD varies across different countries. For the European Union, a disease must affect no more than 1 in 2000 people to be considered a RD [1], while in Brazil, RDs are defined according to the World Health Organization (WHO) criteria: 1.3 cases per 2000 individuals [2].

Mostly genetic, RDs can lead to serious health problems such as organ damage, neurological problems, and developmental delays [3,4]. A report from the 2005 European Conference on Rare diseases found that, given the longevity of 323 RD, 25.7% of these are potentially lethal before five years of age, 36.8% drive to a reduced life expectancy, while only 37.5% are associated with a typical lifespan [5, 6]. Also, on a macro level, although individually rare, collectively, they affect up to 10% of the total population. Thus, RD significantly impacts public health worldwide [7].

Besides the controversy in the definition of RD, another problem arises in this medical domain: the set of RDs is local. Brazil, an emerging country with a population of 215 million people [8], has up to 8000 RD, including Phenylketonuria, Osteogenesis Imperfecta, and Congenital hypothyroidism [9, 10]. However, Dengue Fever (ICD-10 - A90), which is considered a RD in Europe, is not uncommon in South America.

RDs are a global health priority for WHO [11]. In Brazil, a developing country, up to 15 million people are affected by a rare condition, and authorities know the importance of supporting and treating patients [13]. In this context, Ordinance nº199, from January 30, 2014, created the National Policy for Comprehensive Care for People with Rare Diseases. The goal is to present guidelines to guarantee universality, integrality, and equity for RD patients [11]. Moreover, the Brazilian Ministry of Health reports all diseases using the International Classification of Diseases 10th Revision (ICD-10). However, RD specialists commonly use Orphanet terminology to refer to a rare condition [10].

During the development of this study, the Brazilian Ministry of Health utilized the ICD-10 to classify RDs, which is a recognized international standard in the medical community [14]. However, only half of the RDs listed in the ICD-10 have unique codes [15]. To overcome this challenge, healthcare professionals frequently use the ORPHA code taxonomy, which was created specifically for classifying RD [23]. ORPHAcodes provide a cross-referenced with ICD codes, then researchers can gain valuable insights into the RD nomenclature's coding.

In this scenario, Complex Networks (CNs) are a valuable tool for analyzing correspondence and extracting features from the cross-reference model of the Brazilian Ministry of Health's RD list. Graph theory has been widely used to represent various systems and their connections, from social analysis to ontology construction [30]. Therefore, this study utilizes a graph theory model to compare two important terminologies for RDs, the ICD-10 and ORPHAcode, in order to understand the local set of RDs defined by the Brazilian Ministry of Health. Additionally, an interactive dashboard was developed to provide clinical staff and other interested users with the ability to visualize the network and examine important graph characteristics.

The organization of this paper is as follows: In Section 2, the importance of the subject and the nature of the ICD-10 and ORPHAcode relationship are discussed. Section 3 provides an in-depth examination of the methodology used to model the CN, including the data source and technical tools utilized in the study. Finally, Sections 4 and 5 present the results and conclusions of the study, respectively.

2. Background

The following sections describe the two terminologies used to build the complex network model: the ICD-10 and the ORPHAcode.

2.1. International Classification of Diseases 10th Revision (ICD-10)

The ICD-10 is the most widely used disease classification system worldwide, with the goal of standardizing disease codification and related health problems. The ICD is part of the WHO's efforts to universalize and organize data related to conditions, procedures, mortality, and morbidity [17]. The ICD codes are language-independent, enabling statistical comparisons across different countries worldwide.

This standard has undergone several changes over the years to reflect advances in medicine and technology and the reality of the current health area. ICD-10 has more than 70,000 codes, representing a significant increase compared to ICD-9 [18]. However, a new version, ICD-11, has been available since January 2022, with classification changes that reflect modern society's diseases and scenarios [19]. Nevertheless, it will take a long time to implement the novel nomenclature in a developing country, such as Brazil, where the previous terminology has been used since 1996 [20]. According to WHO, countries using an earlier version of ICD are expected to take up to five years to implement the new terminology [21]. By the time this study was developed, the Brazilian government had been using ICD-10 to identify and report any patient's condition.

Assigning a code to a given condition is complex, with some conditions having multiple matching ICD-10 codes. The complexity poses difficulties for the medical team and complicates the search for treatments and diagnosis [22]. As researchers continuously search for new knowledge regarding RD, it is understandable that such codes appear since some conditions are only partially defined. Using ICD codes can make establishing epidemiology and prognosis challenging for RD due to its generality. For instance, a single ICD-10 code, Q87.0, is related to over 130 RDs with different conditions in the ORPHAcode [10]. Considering the difficulty of centralizing RD in a single ICD code, an alternative classification system, the ORPHAcode terminology, has shown interest. ORPHAcodes were specifically developed for classifying RDs and are cross-referenced with ICD codes. Below, we present the ORPHAcode terminology and explain why it is a better alternative for classifying RDs.

2.2. ORPHAcode

A group of academic researchers and professionals from 40 countries led by the National Institute of Health and Medical Research (Inserm) developed the Orphanet, a multilingual online observatory to accomplish RDs [10]. This website contains information on over 6100 RD codes, the ORPHAcodes, and is used globally to identify RDs. Orphanet is a comprehensive resource for RD characteristics, prevalence, orphan drugs, health centers, and other rare disease ecosystem details.

The observatory also provides, for each disease, the inheritance, age of onset, diagnosis procedures, and clinical description. Still under development, As of 2018, the system accounted for 81.2% of annotated RD, and data collection is carried out through a systematic review of rare diseases using population-based studies, meta-analysis, and population surveys [15]. The platform is supported by a relational database designed around the disease concept and maps the codes with other six terminologies, including ICD-10 [23,24]. Thus, we can navigate from different nomenclatures and establish a parallel among codes.

Regarding the focus of the system and the availability of cross-reference between ICD codes and the ORPHAcodes list, it became clear that the WHO terminology is not the best fit for RD definition. Vasant & al. shows that only around 500 RDs are listed in ICD-10, and half of them have generic codes, making it challenging for specialists to initiate trial treatments without additional information on symptoms and diagnosis [24]. However, it is known that Brazil has 40 times more RDs [9]. Despite this problem, the need to report ICD-10 to the Brazilian Ministry of Health remains a requirement, but the use of ORPHAcode provides a common language for a more uniform understanding of RD. Considering the context, the ORPHAcode nomenclature is a better option when dealing with RD, mainly due to its specificity [10]. Thus, the following section shows a visual and statistical model to demonstrate and quantify the nonlinear relationship between the ORPHAcode and ICD-10.

3. Methods

In this section, the methodology of the proposal is explained, including the construction of the ICD10-ORPHA Brazilian Model according to the Ordinance nº199 and the development of the web-app system implemented in this study.

3.1. ICD-10 - ORPHA Brazilian Model

The usage of ontology systems to link disease terminologies is not a novel concept. Usually, a Disease Ontology (DO) describes a set of diseases based on hierarchical characteristics of the condition, and it is associated with metadata, such as definition, symptoms, synonyms, and cross-references. It has been used in many studies to structure data [27, 28, 29]. Furthermore, the ontology of a single disease can be associated with another one according to specific criteria defined by an expert in the domain [36].

Moreover, researchers have noticed that several natural phenomena, such as social and biological arrangements, are composed of structures where elements are related to each other, given a specific link [42]. The methodology can cover a wide range of applications such as social dynamics and epidemic processes [43, 44].

Regardless of the structure of the data, when the information is not modeled as a complex network, the first step is to transform the raw data into a graph G, (G = {E,V}) , where V is the vertices (nodes), and E is the edges (links) connecting the elements in V. As mentioned, the Orphanet observatory has a cross-reference between ORPHA and ICD codes. Thus, the Brazilian model is created as follows:

$$CN_{ij} = \begin{cases} 1, & \text{if code i is related to code j} \\ 0, & \text{otherwise.} \end{cases}$$

It is essential to notice that an ORPHAcode will never directly link to another ORPHAcode due to the nature of the system. In addition, the network is undirected, which means that if node *i* is connected to node *j*, the contrary is also correct. Also, differing from ontology systems, in graph theory, one of the goals is also to compute statistical metrics to permit us to comprehend the graph quantitatively. The metrics computed in this study are defined as follows: degree, average degree, number of connected components, clustering coefficient and betweenness coefficient [33]. There are a considerable number of metrics in graph theory but not all suit our study.

Next, we show how the proposed complex network model and the web-app system for its visualization were built. The algorithms were developed with *Networkx*, a package in Python for creating and manipulating complex networks. It also gives us access to different functions to compute each node's clustering coefficients, betweenness, and degree [34]. Additionally, as seen in the next section, each connected component, i.e., subgraph where all pairs of nodes have finite path length, is decomposed as a single graph.

3.2. Interactive Web-app System

To enhance user interaction and facilitate the visualization of node distribution, a web-based application system was developed. First, the system features a select box that enables users to choose a RD based on an ICD-10 code list from Ordinance nº199 of the Brazilian Ministry of Health [11]. Then, the graph component shows the selected disease, the number of related codes (node degree), the clustering coefficient, and the betweenness. To distinguish between ICD codes and ORPHAcodes identifiers, vertices from the international classification are colored in red, while the second terminology is painted in blue. The aim is to demonstrate the structure's complexity and build a visualization of the connections between the RDs in Brazil and Orphanet context, a commonly used terminology by geneticists and other clinical specialists. Section 4 presents the study's results in figures and metrics.

The visualization is rendered by a graph library *pyvis*, an interactive network framework [35]. Users can zoom in, check the labels of each element in the network, and drag components around the canvas. The most basic metric in the image is the number of components.

4. Results and Discussion

Fig. 1 provides an overview of the web-based system, which shows the correspondence between Rare Brazilian Diseases' ICD-10 codes from the Ministry of Health and Orphanet codes. As mentioned before, the Orphanet codes, or ORPHAcodes, are presented in blue, while the ICD-10 codes are in red. The web page also displays the cumulative degree distribution of the model, its the average degree (1.87), and the number of connected components (89). The plateau in degree distribution suggests that most diseases in the network have a low number of connections. However, since the average degree is not one, it is evident that many diseases do not have a one-to-one correspondence between ICD-10 and ORPHAcode terminologies. The link to the application is found online at *https://tinyurl.com/bnv4zdma*.

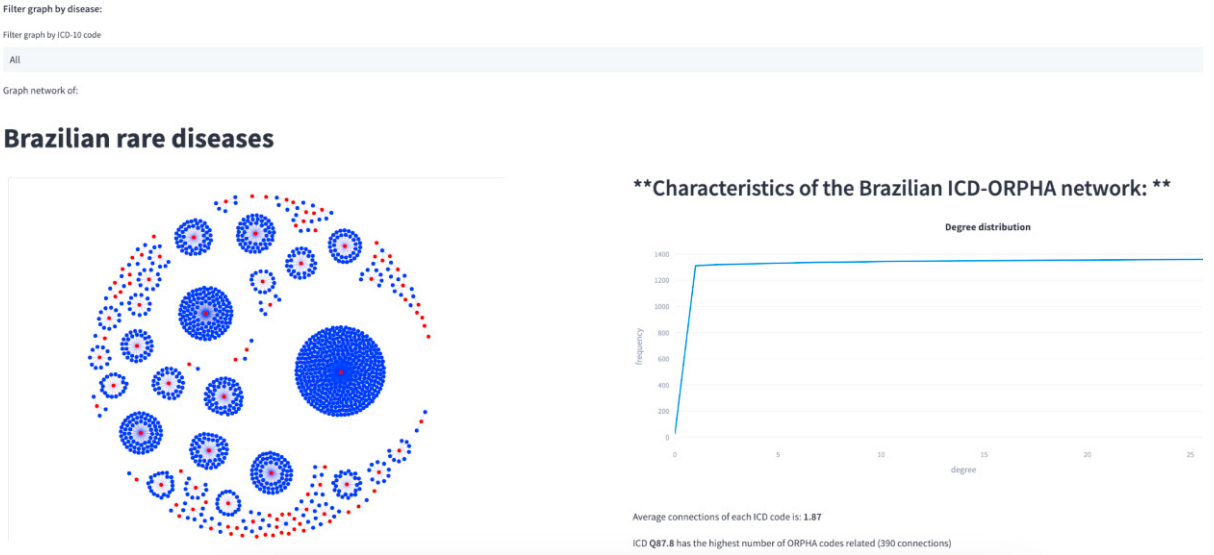

Fig. 1. The initial page of the interactive web-based system. On the left, Brazilian ICD-ORPHA Brazilian full network. On the right the cumulative distribution of the degree is shown.

In Fig. 2, we can observe a section of the interactive system where users can select a specific disease from the dropdown menu at the top. Once a condition is selected, the corresponding subgraph is displayed, along with its degree, clustering coefficient, and betweenness centrality. The largest component, with central node in ICD-10 Q87.8 - Other specified congenital malformation syndromes, not elsewhere classified is shown in Fig. 2. As we can see, Q87.8 has an extensive number of connections, with a total of 390 related ORPHAcodes. Two examples are ORPHAcode - 2669 - Nephrosis-deafness-urinary tract-digital malformations syndrome and ORPHAcode - 1270 - Bowen-Conradi syndrome [28]. Both diseases have different natures. While ORPHAcode 2669 ranges urinary tract anomalies, nephrosis, conductive deafness, and digital malformations, ORPHAcode 1270 is characterized by microcephaly, a distinctive facial appearance [10]. Showing that ICD-10 codes weakly represent RD.

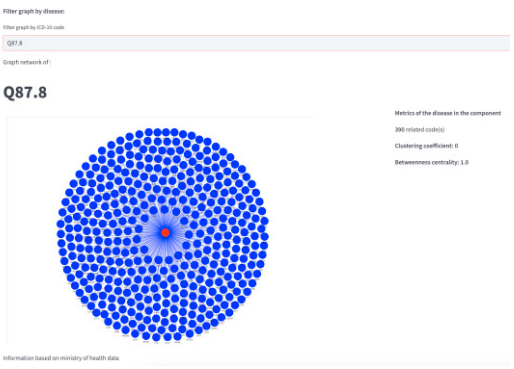

Fig. 2. The largest component of the ICD-ORPHA network' page

Furthermore, the graph metrics show that with a high betweenness, Q78.8 is in the path of any other two nodes in the subgraph. In contrast, a clustering coefficient of zero indicates a lack of connectivity between Q78.8 connections.

We have presented the largest component as an example, but many components possess the same star structure, where a central ICD node has numerous ORPHAcode connections in the Brazilian CN. For instance, Q87.0 (k = 120), Q87.1 (k = 67), G71.0 (k = 68), E77.8 (k = 50), G12.2 (k = 24) also have the same one-to-many relationship in the ICD-ORPHA model.

Secondly, another fascinating subgraph is represented by Fig. 3 (left). In this subgraph, ORPHAcode 881, Turner syndrome, is associated with seven different ICD-10 codes (Q96.0, Q96.1, Q96.2, Q96.3, Q96.4, Q96.9, and Q96.8). This complex structure illustrates the possibility of a many-to-many relationship between ICD-10 and ORPHAcode identifiers, a disadvantage when using ICD-10 to represent RD. Furthermore, besides ORPHAcode 881, Q96.8 is associated with another ORPHAcode, the code 444048, which represents 46,XX ovarian dysgenesis-short stature syndrome. This aspect is the inverse of what we usually check in the entire graph, where the ICD-10 code is the component's main element (highest degree node) and this complexity shows the possibility of a many-to-many relationship between ICD-10 and ORPHAcode identifiers. The hybrid structure reflects the specialists' difficulty finding proper information, data and treatments to support patients. If there are several branches, the literature for a single ICD code can be imprecise for a specific condition.

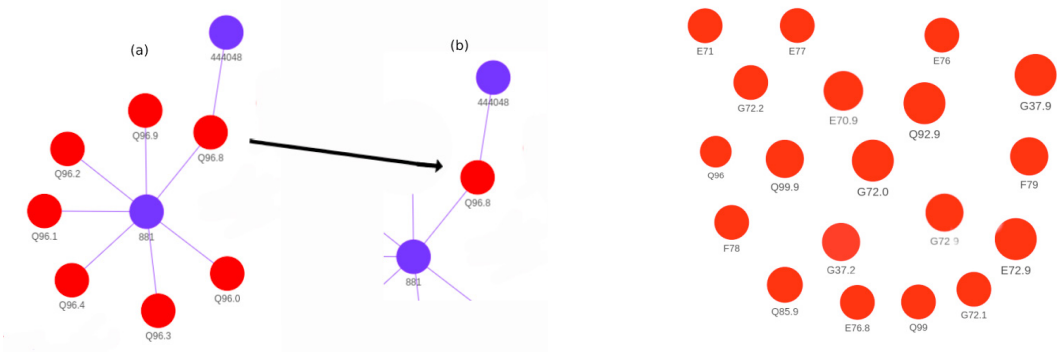

Fig. 3 (right) depicts the complexity of a single subgraph, highlighting a situation where one ICD-10 code is associated with two ORPHAcodes. On the other hand, Fig. 3 (left) showcases instances where several ICD-10 codes from the Ministry of Health list have no corresponding ORPHAcode.

Although most of the ICD-10 connects for one or more ORPHAcodes, 19 RDs in this terminology does not match any classification in the Orphanet observatory. The third analysis case is shown in Fig. 3 (right). In the Brazilian RD list, we found the following ICD-10 codes that match this characteristic: E72.9; G72.9; Q92.9; Q85.9; E70.9; G37.9; Q99.9; G72.0; G72.1; G72.2; F79; E76; E77; Q99; F78; Q96; E71; E76.8; and G37.2. According to specialists, G72.0 - Drug-induced myopathy, G72.1 - Alcoholic myopathy, and G72.2 - Myopathy due to other toxic agents are not considered rare. Also, ICD codes with the final .9 are non-specific diseases, meaning no definitive or well-defined diagnosis to the patient. At the same time, Orphanet provides greater specificity by having multiple branches for a

single ICD-10 code [10]. To illustrate this, some examples of codes are E70.9 - Disorder of aromatic amino-acid metabolism, unspecified; G72.9 - Myopathy, unspecified; Q92.9 - Trisomy and partial trisomy of autosomes, unspecified; Q85.9 - Phakomatosis, unspecified; G37.9 - Demyelinating disease of central nervous system, unspecified; Q99.9 - Chromosomal abnormality, unspecified.

Furthermore, the categories: F79 (Unspecified intellectual disabilities); E76 (Disorders of glycosaminoglycan metabolism); E77 (Disorders of glycoprotein metabolism); Q99 (Other chromosome abnormalities, not elsewhere classified); F78 (Other intellectual disabilities); Q96 (Turner's syndrome); and E71 (Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism) are groups of diseases which also do not define a conclusive diagnosis to the patient but appear in the RD list from the Ministry of Health. Finally, E76.8 (Other disorders of glucosaminoglycan metabolism) is another undetermined disease, while G37.2 (Central pontine myelinolysis) is not found in the Orphanet repository but remains in the Brazilian Rare Disease list from the Ministry of Health.

5. Conclusion

The Orphanet, featuring a repository of over 6,100 RD codes, serves as a valuable resource for identifying and comprehending RDs. As Orphacode is tailored to the European context, it is essential to examine the approach employed by Brazil's Ministry of Health, which relies on ICD-10 for reporting. Our proposed web application offers visualization and the results of the complex network model created from ICD-10 and ORPHAcode terminologies in relation to Brazilian RDs.

As illustrated in Figures 1, 2, and 3, devising a flawless terminology for RD classification remains challenging, particularly for developing countries. More specifically, the entire network consists of 89 components of various shapes. Generally, a single ICD-10 code corresponds to multiple ORPHAcodes, forming a star-shaped component. However, we demonstrate the opposite, where one ORPHAcode is linked to multiple ICD-10 codes. Additionally, this relationship is not star-shaped due to another connection present in element Q96.8.

These graph evaluations and complexities assist specialists in visualizing and quantifying the challenges in determining a definitive diagnosis for RDs, given the numerous generic codes found in the Brazilian ICD-10 rare disease classification. Furthermore, this highlights the need for ongoing research efforts to examine patient cases, clarify, and encode unidentified conditions.

Although the ICD-11 has been released, the Brazilian Ministry of Health is expected to update its RD list in the coming years. This updated list will undoubtedly simplify cross-referencing and streamline the search for treatments and diagnosis, thanks to the improved terminology. Nevertheless, the majority of literature and medical facilities still utilize and report conditions based on ICD-10. This complexity must be documented and made accessible to Brazilian specialists to enable them to search for relationships within their national domain. Therefore, this technical contribution can be used to minimize data complexity in RDs international classifications.

In future work, we plan to assess the new ICD-11 codes for the Brazilian RD list and enrich the node with essential metadata, ultimately constructing a more robust ontology system that could serve as a foundation for disease diagnosis.

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