

Boolean Algebra with Modified Venn Diagrams for Definition of Lymphoma

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1. Abstract

Hematologic and lymphoid disorders include multiple subgroups, which are determined by the following methods: Cytology, histology, immune phenotyping, cytogenetics, molecular genetics. Especially the definition of lymphomas becomes more and more complicated, being continuously revised based on the most recent data. Because of the complex nature of these disorders verbal definitions may sometimes lead to ambiguity. A mathematical approach may help to avoid that. Boolean algebra also sometimes called “mathematical logic” has been demonstrated to be helpful for disease definition. In this study Boolean algebra has been applied for definition of lymphomas. All subgroups could be defined in a precise way by mathematical algorithms leaving no room for ambiguity. The binary number system was applied. A modified Venn diagram proved to be helpful for an easy and quick visualization of the Boolean algebraic operations in the binary system.

2. Introduction

Precise definition of disease is a necessary requirement of all disciplines in medicine. Only diagnosis of disease by defined criteria permits stratification by risk factors, determination of prognosis, and last not least patient-tailored treatment regimen. The international statistical classification of diseases and related health problems (ICD) from the World Health Organization (WHO) is a globally accepted and applied system, the latest version ID 11 [5]. For hematological neoplasms the WHO has established a globally accepted classification, definition, and diagnosis of disease [24,25]. A revised version was published in 2022 [1]. The diagnosis of

high-level entities such as lymphoma and acute leukemia will undoubtedly remain with morphology. However, genetic abnormalities have become the backbone of diagnosis of subgroups of risk stratification and treatment decisions [5]. The WHO classification enables the application of mathematical methods for definition and diagnosis of disease. Boolean algebra has been demonstrated to provide a tool of WHO classification, freed of linguistic ambiguity [29-31]. In this study we use a new system of Venn diagrams for the definition of Boolean operators. Since malignant lymphoma has become one of the most complex diseases, defined by various criteria and revised several times, we have used this disease system as a model for Boolean algebra based on a new version of Venn diagrams.

3. Methods

The methods have been described in detail elsewhere [29-31]. In brief, the binary system including 2 integers is used. It can be easily transferred from the decimal system:

0=0, 1=1, 2=10, 3=11, 4=100, etc.

The possible combinations of AB are listed in the table 1 below:

There are $2^4 = 16$ combinations of AB with binary integers [29-31]. From the 16 possible permutations the ones used in this study are listed below.

The algebra is defined as follows:

In the formulas, brackets “()” take precedence over each operator, NOT takes precedence over AND, AND takes precedence over OR, OR takes precedence over XNOR [26].

NOT 1 = 0

NOT 0 = 1

Boolean Algebras are not standardized [11]. To keep matters clear we do not use symbols but the acronyms of Boolean operators used in computer science. Instead of the acronym **XNOR** [18] we use the symbol $=$, since in this case in contrast to the other operators the symbol is better known (Table 2) (Figure 1).

All 16 permutations of Boolean operators are shown by Venn diagrams. The number 1 is represented by black or red areas, the

number 0 by white areas.

Since **NOTA**, **NOTB** are considered variables, there are only two Boolean operators, **AND**, **OR**. For example, **A NAND B** is equal to **NOTA OR NOTB**, **A NOR B** is equal to **NOTA AND NOTB**. **A = B** is equal to 2 alternatives, one includes **A AND B**, the other one includes **NOTA AND NOTB**. With the **AND** operator the variables can have the value **1** only in combination. With the **OR** operator the variables can have the value **1** independently from each other (Figure 1).

Table 1:

A	B
1	1
1	0
0	1
0	0

Permutation I

A	B	AB
1	1	1
1	0	0
0	1	0
0	0	0

A AND B

1 AND 1 = 1

1 AND 0 = 0

0 AND 1 = 0

0 AND 0 = 0

Permutation II

A	B	AB
1	1	1
1	0	1
0	1	1
0	0	0

A OR B

This operator was introduced by Jevons in 1864 (Brown 2003).

1 OR 1 = 1

1 OR 0 = 1

0 OR 1 = 1

0 OR 0 = 0

Permutation III

A	B	AB
1	1	1
1	0	0
0	1	0
0	0	1

A XNOR B

1 XNOR 1 = 1

1 XNOR 0 = 0

0 XNOR 1 = 0

0 XNOR 0 = 1

Table 2: Summary of Boolean Operators

A	B	\wedge (AND)	\vee (OR)	XNOR	NAND	NOR	XOR
1	1	1	1	1	0	0	0
1	0	0	1	0	1	0	1
0	1	0	1	0	1	0	1
0	0	0	0	1	1	1	0

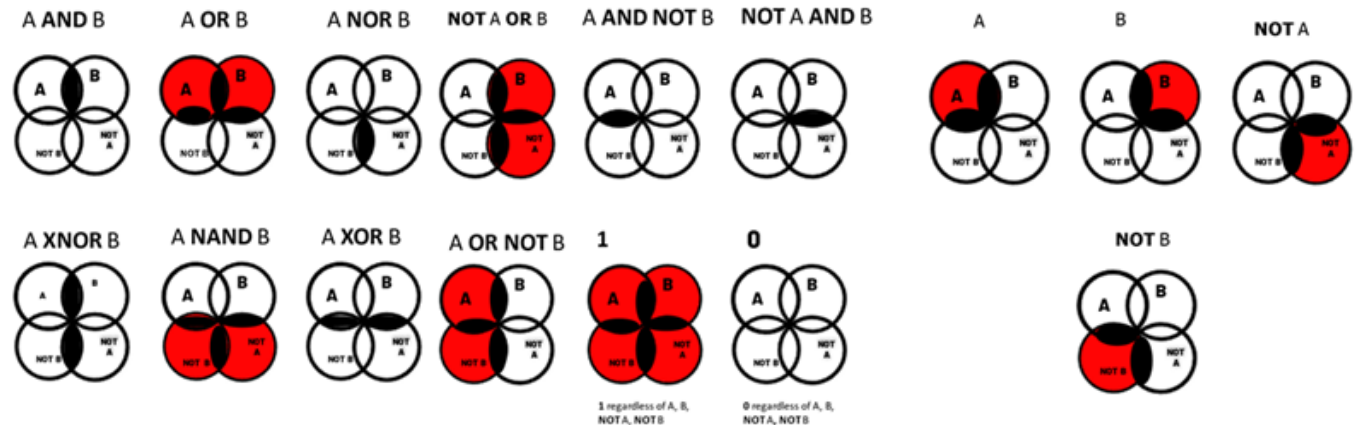


Figure 1:

4. Results

B-cell lymphoid proliferation AND lymphomas = tumor-like lesions **AND** B-cell predominance **OR** precursor B-cell neoplasms **OR** Mature B-cell neoplasms **OR** plasma cell neoplasms **AND** other diseases with paraproteins

Tumor-like lesions AND B-cell predominance = reactive B-cell rich lymphoid proliferation that can mimic lymphoma **OR** Ig64-related disease **OR** unicentric Castleman disease **OR** idiopathic multicentric Castleman disease **OR** KSHV/HHV8-associated multicentric Castleman disease

Precursor B-cell neoplasms = B-cell lymphoblastic leukemia/lymphoma

Mature B-cell neoplasms = preneoplastic **AND** neoplastic small lymphocytic proliferations **OR** splenic B-cell lymphomas **AND** leukemias **OR** lymphoplasmocytic lymphoma **OR** marginal zone lymphoma **OR** follicular lymphoma **OR** cutaneous follicular Center lymphoma **OR** mantle cell lymphoma **OR** transformation of indolent B-cell lymphoma **OR** large B-cell lymphomas **OR** Burkitt lymphoma **OR** KSHV/HHV8-associated B-cell proliferations and lymphomas **OR** lymphoid proliferations **AND** lymphomas associated with immunodeficiency **AND** dysregulations **OR** Hodgkin lymphoma

Plasma cell neoplasms AND other diseases with paraproteins = monoclonal gammopathies **OR** monoclonal immunoglobulin deposition **OR** heavy chain disease **OR** plasma cell neoplasm

Large B-cell lymphomas = Diffuse large B-cell lymphoma NOS **OR** T-cell / histocyte-rich large B-cell lymphoma **OR** high-grade B-cell Lymphoma **AND** MYC **AND** BCL2 rearrangements **OR** ALK-positive large B-cell lymphoma **OR** large B-cell lymphoma **AND** IRF4 Rearrangements **OR** high-grade B-cell lymphoma **AND** 11q aberrations **OR** lymphomatoid granulomatosis **OR** EBV-positive diffuse Large B-cell lymphoma **OR** large B-cell lymphoma **AND** chronic inflammation **OR** fibrin-associated large B-cell lymphoma **OR** fluid overload **AND** large B-cell lymphoma **OR** plasmablastic lymphoma **OR** primary large B-cell Lymphoma of Immune privileged Sites **OR** primary cutaneous diffuse large B-cell lymphoma, leg-type **OR** Intravascular large B-cell lymphoma **OR** Primary mediastinal large B-cell lymphoma **OR** mediastinal grey zone lymphoma **OR** high-grade B-cell lymphoma NOS

5. Discussion

In this study, we applied algebra for the definition of non-Hodgkin lymphoma (NHL).

Mathematics has become an essential part in medicine like in physics and chemistry clinical research could not be conducted without biostatistics and mathematical modeling [19].

Boolean algebra has been applied in bioinformatics including investigation of gene regulatory networks or signaling networks [2,16,22] and analysis of genomics [17].

Boolean algebra has been used to determine the association of gene expression with the outcome of malignant tumors [27].

A **NOT**- gated signal integrator called the T mod system was applied to select cancer treatment regimens [6].

Boolean models have been used in pathology [21], for prediction of clinical outcome in acute myeloid leukemia [20], acute leukemias [29,30] and myeloid neoplasms [31].

Boolean algebra has the advantage of operators being numerically defined by the binary system.

The modified Venn diagrams used in this study provide a quicker and easier way of defining Boolean operators than the conventional tables.

Venn diagrams have been used in various forms [3,7]. Our mathematical approach differs from the logical approaches by the additional use of **NOT** within the diagrams. This method makes the Venn diagram usable for the graphic presentation of the permutation of binary integers, This mathematical form of a Venn diagram has never been used before.

We have avoided the term “mathematical logic”. Logic is an essential basis of any discipline. e.g. law, but it is not part of mathematics [7]. Some studies mix logic and mathematics in a circular manner [15]. For these reasons we have avoided confusing terms such as “truth values” and have only used numbers to define Boolean operators [23].

Thus, the approach used in this study includes mathematics being free of any logical linguistic elements. Mathematics has no relation to propositional logic. The variables do not stand for propositions but for laboratory values or other medical findings. We do not view algebra as part of logic or vice versa. Our approach is solely based on natural integers as outlined by Carl Friedrich Gauss [9].

Selection of mathematical notation is a challenge and standardization is often not accepted by mathematicians [28]. This also includes Boolean algebra, whose notation varies between different regions and consensus is lacking [12] In addition, the same notation is sometimes used for different purposes. For these reasons we use the acronyms from computer science in this study.

The binary system has the same structure as the decimal system. Both number systems use natural integers. Other systems use p-adic numbers, based on geometrical concepts [13]. We consider this method a step backwards from the achievements of Gauss.

In conclusion Boolean algebra has been demonstrated to be a useful tool of disease definition. It may allow highly accurate classification of hematologic neoplasms. Together with artificial intelligence these tools may enable the busy clinician to not only come to a rapid and precise diagnosis but also have more time to interact with the patient. However, at the end of the day, physicians will always be the decision makers.

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