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Boolean Algebra (Mathematical Logic) for Grading of Toxicities Associated with Cellular Immune Therapy

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ABSTRACT

In clinical practice toxicity grading is guided by scales such as the Common Terminology Criteria for Adverse Events. These scales assign grades (usually from 1 to 5) to various toxicities based on severity. Cellular Immunotherapies, whose mechanism of action incudes directing T cells to target cells can be associated with special side effects such as cytokine release syndrome or neurologic toxicity. The American Society for Transplantation and Cellular Therapy has developed an easily applicable, logical and concise system to categorize and grade cytokine release syndrome and neurologic toxicity. Cytokine release syndrome is a systemic inflammatory response that can occur after immune cell therapy. Neurologic toxicity can also occur after immune cell therapy. It can include encephalopathy, delirium, headache, anxiety, sleep disorder, dizziness, aphasia, motor dysfunction, tremor, ataxia, seizure, dyscalculia, myoclonus. Boolean algebra can be used to automate and standardize this grading process by translating it into a mathematical framework that combines different clinical signs and symptoms. In this study we apply Boolean algebra as mathematical tool to define and grade Cytokine release syndrome and neurologic toxicity by the criteria of the American Society for Transplantation and Cellular Therapy.

Introduction

Boolean algebra is a branch of mathematics that uses the binary system with the manipulation of variables that have 2 possible values 1 or 0. It enables calculations with operators such as AND, OR, and NOT. The operator AND is identical to multiplication, the operator OR is identical to addition with the exception that 1 OR 1 = 1 and not 10 as in the regular binary system. The Boolean binary system differs from the regular binary system in that all calculations can only have the result 1 or 0. Boolean algebra is widely used in medicine, particularly in areas that involve decision-making, diagnostic systems, medical imaging, and bioinformatics. It serves as basis of clinical systems, which assist healthcare providers in diagnosing and treating diseases by processing complex medical data [1]. In medical diagnostics, Boolean algebra combines multiple test results and clinical findings to find a diagnosis [2,3,4,5]. Boolean operations are used to evaluate the presence or absence of symptoms or test results [6]. Boolean algebra is used in medical imaging for pattern recognition [7,8] and has been shown to be useful for the definition of hematologic malignancies [2,3,4,9].
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These properties make Boolean algebra an ideal tool for calculating the Grades of toxicities. The American Society for Transplantation and Cellular Therapy (ASTCT) criteria for grading cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) provide a standardized framework for assessing the severity of these conditions, which can occur following treatments like CAR T-cell therapy [10].

Cytokine Release Syndrome Grading

Cytokine Release Syndrome (CRS) is a systemic inflammatory response that can occur after immune cell therapy. The ASTCT criteria grade CRS as follows [10]:

- **Grade 1:**
  - **Fever** (≥ 38°C)
  - No hypotension or hypoxia.
- **Grade 2:**
  - **Fever** (≥ 38°C)
  - Hypotension responsive to fluids or low-dose vasopressors (e.g., norepinephrine ≤ 0.1 µg/kg/min).
  - Hypoxia requiring low-flow oxygen (nasal cannula ≤ 6 L/min or face mask ≤ 10 L/min).
- **Grade 3:**
  - **Fever** (≥ 38°C)
  - Hypotension requiring high-dose vasopressors (e.g., norepinephrine > 0.1 µg/kg/min or multiple vasopressors).
  - Hypoxia requiring high-flow oxygen (non-rebreather mask, high-flow nasal cannula, or ventilator support).
- **Grade 4:**
  - **Fever** (≥ 38°C)
  - Life-threatening hypotension requiring multiple vasopressors and/or hypoxia requiring positive pressure ventilation (e.g., CPAP, BiPAP, or intubation).

Immune Effector Cell-Associated Neuro-toxicity Syndrome Grading

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is a neurological toxicity that can occur following immune effector cell therapy [10].

ICANS is evaluated using the Immune Effector Cell-Associated Encephalopathy (ICE) score and the level of consciousness, seizure activity, motor symptoms, and cerebral edema [10].

ICE score

	YES	NO
Orientation	4	0
Naming	3	0
Following commands	1	0
Writing	1	0
Attention	1	0

Thus, the ASTCT criteria grade ICANS as follows [10]

- **Grade 1:**
  - **ICE Score:** 7–9
  - **Level of Consciousness:** Awake and oriented.
  - **Seizures:** None.
  - **Motor Symptoms:** None.
  - **Cerebral Edema:** None.
- **Grade 2:**
  - **ICE Score:** 3–6
  - **Level of Consciousness:** Awake but disoriented or somnolent.
  - **Seizures:** None.
  - **Motor Symptoms:** Mild.
  - **Cerebral Edema:** None.
- **Grade 3:**
  - **ICE Score:** 0–2
  - **Level of Consciousness:** Somnolence or stupor but arousable with verbal stimuli.
  - **Seizures:** Seizures responsive to treatment.
  - **Motor Symptoms:** Significant motor weakness.
  - **Cerebral Edema:** None.
- **Grade 4:**
  - **ICE Score:** 0
  - **Level of Consciousness:** Unarousable, comatose.
  - **Seizures:** Life-threatening seizures or status epilepticus.

- **Motor Symptoms:** Life-threatening motor weakness.
- **Cerebral Edema:** Severe cerebral edema, potentially fatal.

- **Grade 5:**
  - **Death due to ICANS.**

In this study we have combined Boolean equations and The ASTCT criteria for CRS and ICANS.

Methods

Basic Notations in Boolean Algebra

1. Boolean Variables:
   - Typically represented by capital letters (e.g., A, B, C). These letters can represent any parameter, such as symptoms, clinical signs, laboratory values, cytologic data, cytometric data, genetic data.
   - Each Boolean variable can take one of two values: 1 (true) or 0 (false).
2. Boolean Operations:
   - AND Operation:
     - Symbol: · (multiplication symbol) or ∧
     - Expression: A · B or A ∧ B
     - Meaning: The result is 1 if both A and B are 1; otherwise, it is 0.
     - Example: 1·1=1, 1·0=0
   - OR Operation:
     - Symbol: + (addition symbol) or V
     - Expression: A + B or A V B
     - Meaning: The result is 1, if A or B or both are 1); if both are 0), the result is 0.
     - Example: 1 + 0 = 1 0 + 0 = 0
   - NOT Operation, [11]
     - Symbol: ¬ A (negation)
     - Expression: ¬ A
     - Meaning: The result is the inverse of A; if A is 1, ¬A is 0, and vice versa.
     - Example: ¬ 1 = 0, ¬ 0 = 1
   - XOR Operation (Exclusive OR):
     - Symbol: A ⊕ B
     - Expression: The result is 1, if exactly one of A or B is 1 , but not both. It is also 0, if both A and B are 0.
     - Example: 1 ⊕ 0 = 1, 1 ⊕ 1 = 0
   - XNOR Operation (Equality = negation of Exclusive OR):
     - Symbol: A = B or ¬ (A ⊕ B)
     - Expression: The result is 1if A and B are both 1 or both0 .
     - Example: 1 = 1, 0 = 0

The common notation of the expression "if A, then B" is: A → B

This can be read as "if A is 1, then B must also be 1." In Boolean terms, this implication is 0 only if A is 1 and B is 0 ; in all other cases, the implication is has the result 1. The implication A → B is usually expressed using the OR and NOT operations: A → B = ¬ A V B. This equivalence is derived from the definition of the term in Boolean algebra. The expression ¬ A V B has the result 1 in all cases except for A is 1 and B is 0.

In principle there are only two 2-digit combinations together with ¬ necessary, ∧ or v and with ⊕ or =. The combination with ∧ can be expressed as negations of the combination with v and vice versa, example: ¬ A v B = ¬ (A ∧ ¬ B).
The same accounts for combinations with ⊕ and =, example: ¬ (A = B) = A ⊕ B.
All combinations can be replaced by combinations with the operator NOR (¬ (A v B)), or the operator NAND (¬ (A ∧ B)). However, replacement of other operators by one of these 2 operators results in multi – digit combinations, example: (A NAND B) NAND (A NAND B) = A ∧ B.

In the formulas the following operators take precedence:

- () over each operator
- ¬ over ∧
- ∧ over v,
- v, ⊕ over = (Takeuti 1987)

Results

Grading of CRS

Grade 1 = fever ≥ 38C

Grade 2 = fever ≥ 38C ∧ (hypotension v (hypoxia ∧ low flow canicula) = fever ≥ 38C ∧ hypotension v fever ≥ 38C ∧ hypoxia ∧ low flow nasal canicula

Grade 3 = fever ≥ 38C ∧ (hypotension ∧ 1 vasopressor v hypoxia ∧ (low flow nasal canicula) = fever ≥ 38C ∧ hypotension ∧ 1 vasopressor v fever ≥ 38C ∧ hypoxia ∧ low flow canicula

Grade 4 = fever ≥ 38C ∧ (hypotension ∧ > 1 vasopressors v hypoxia ∧ intubation) = fever > 38C ∧ hypotension ∧ > 1 vasopressors v fever > 38C ∧ hypoxia ∧ intubation

From the linear equation above the linear equations below follow:

Grade ≥ 1 CRS → fever ≥ 38C

Grade ≥ 2 CRS → fever ≥ 38C ∧ (hypotension v hypoxia) = Grade ≥ 2 CRS → fever ≥ 38C ∧ hypotension v fever ≥ 38C ∧ hypoxia

ICE score

	YES	NO
Orientation	4	0
Naming	3	0
Following commands	1	0
Writing	1	0
Attention	1	0

ICE > 7 = orientation ∧ naming ∧ (following commands v writing v attention)

ICE 7 = orientation ∧ (naming ⊕ following commands ∧ writing ∧ attention)

ICE 7 → orientation = ¬ orientation → ¬ ICE 7. This means, if the ICE is 7, then it must include at least "orientation". Otherwise, the score would not add up to 7. If it does not include orientation, then the ICE score must be < 7.

Grading of ICANS for adults

Grade 1 = ICE score (7 – 9) v depressed consciousness ∧ awakens spontaneously

Grade 2 = (ICE score (3 – 6) v depressed consciousness ∧ awakens only to voice

Grade 3 = (ICE score (0 – 3) v depressed consciousness ∧ awakens only to tactile stimulus v generalized seizure rapidly resolving v nonconvulsive size v focal edema v ICE score 0 ∧ awake with global aphasia

Grade 4 = ICE score 0 v coma v seizure ≥ 5 minutes v paresis v diffuse edema v cranial nerve VI palsy v papilledema v Cushing's triad

ICANS = encephalopathy v delirium v headache v anxiety v sleep disorder v dizziness v aphasia v motor dysfunction v tremor v ataxia v seizure v dyscalculia v myoclonus

Discussion

In this study, we have applied Boolean equations to define and grade CRS and ICANS. Linear equations in Boolean algebra have been investigated over decades [12]. Boolean equations help to find the correct Grade of CRS and ICANS. For example, the system shows that an ICANS of least Grade 2 has to be associated with a depressed level of consciousness. A Grade 1 ICANS has to be associated with a normal level of consciousness.

Boolean algebra can be used to define an adverse event by specifying the conditions, under which it occurs. For example, an adverse event might be defined as the occurrence of condition A and condition B, but not condition C. This can be written as A ∧ B ∧ ¬ C. In medical studies, adverse events often depend on a combination of symptoms, test results, and patient history. Boolean expressions can capture these complex conditions. By Boolean algebra combinations of risk factors can be defined. Boolean expressions can be applied for generating decision trees to handle adverse events [13,14,15].

Boolean algebra has been applied on a wide scale in medicine. This includes all areas of medical research [2,3,4,5,9,16,17,18,19,20,21,22]. Boolean algebra is only one example of the application of mathematics in medicine. Mathematics has become not only a tool but a component of all medical sciences. Medicine came rather late after physics, computer science and chemistry. Nowadays clinical research cannot be conducted without mathematics [23]. Two issues pose major challenges for the application of mathematics including Boolean algebra in medicine, the lack of standard in notation and the mix up of mathematic and logic.

Unfortunately, mathematics in many cases lacks a standard in notation. Boolean algebra is not exempt from this issue. Various symbols are used interchangeably. The lack of standard notation can lead to confusion and ambiguity, especially when mathematical concepts are being communicated across different disciplines, educational levels, and geographical regions. While some notations have been standardized, many mathematical symbols and conventions vary depending on the context, leading to potential misunderstandings. Below key reasons and challenges related to the lack of standard notation in mathematics are listed [24,25,26,27,28]:

1. HISTORICAL DEVELOPMENT OF NOTATION

Mathematical notation has evolved over centuries, and there is no central authority governing it. Different mathematicians, regions, and schools of thought have developed their own notations independently. For instance:

Leibniz and Newton both developed their own notations for calculus.

Vector notation: Some people use boldface letters to denote vectors, while others use arrows over letters.

Set notation: In different countries, the notations for set theory can differ.

Challenge: Different historical roots and local conventions have caused variations in notation that persist even today, making it difficult to establish a universal system.

2. CONTEXTUAL VARIATION

Mathematics is applied in many different contexts, such as physics, engineering, economics, and computer science. Each field has developed its own notation that is optimized for its specific needs.

Probabilities: The notation for probabilities in statistics can vary.

Economics: In economics, functions representing utility, cost, or profit are often represented differently than in other fields, sometimes omitting explicit dependencies for clarity.

Challenge: These variations arise from the need to optimize notation for specific applications, but they can cause confusion when crossing disciplines or reading work from other fields.

3. AMBIGUITY AND OVERLOADING OF SYMBOLS

Many mathematical symbols are overloaded, meaning that the same symbol can have different meanings depending on the context:

Challenge: The same symbol being used in different contexts leads to ambiguity, especially when working with multidisciplinary problems or switching between subjects.

4. LACK OF UNIVERSAL STANDARDS

The absence of a universal standard leads to inconsistencies in notation, making it difficult for students and researchers from different regions or fields to interpret each other's work.

5. EDUCATIONAL AND CULTURAL VARIATIONS
The lack of consistent educational standards can lead to confusion when students or researchers encounter different notations during international collaboration or study.

6. EFFORTS TOWARD STANDARDIZATION
In some cases, attempts have been made to standardize notation:
SI Units: In science and engineering, the International System of Units (SI) has created a standard for units of measurement, although variations still exist in notation for certain derived quantities.
LaTeX: The widespread adoption of LaTeX for typesetting mathematical documents has encouraged more consistency in how mathematical expressions are presented, though it hasn't fully solved the problem.
Challenge: Despite efforts toward standardization in some areas, full standardization has not been achieved across mathematics as a whole, and even widely accepted systems like SI units can conflict with older or regional standards.

7. CHALLENGES IN COMMUNICATION AND LEARNING
The lack of standard notation can be a significant barrier for students learning mathematics and for researchers communicating complex ideas.
Learning Curve: Students often need to re-learn different notations when moving from one mathematical domain to another (e.g., from linear algebra to functional analysis, or from statistics to pure mathematics).
Collaboration: When mathematicians from different subfields collaborate, they often need to clarify or redefine notation, which can slow down the communication of ideas.
Challenge: The differences in notation not only complicate learning but can also hinder collaboration and interdisciplinary research.

8. COMPUTATIONAL AND PROGRAMMING CONTEXTS
Adapting mathematical notation for computational purposes requires converting abstract symbols into a more concrete syntax, which can introduce errors or inefficiencies
The lack of standard notation in mathematics, while reflective of its rich historical and interdisciplinary nature, poses challenges for communication, learning, and collaboration. Although some fields have made strides toward standardization, complete consistency remains elusive due to the diversity of mathematical applications, cultural and regional variations, and the evolving nature of mathematical discoveries. As mathematics continues to grow, balancing the need for standardized notation with the flexibility required for different contexts will remain a challenge.

The terms “mathematical” logic and “Boolean algebra” are often used interchangeably. This leads to the impression that logic is a mathematical discipline and mathematics is the basis of logic. Boolean algebra or mathematical logic is indeed different from logic, and it should not be confused with the broader discipline of logic. It uses operations such as AND, OR, and NOT for arithmetic calculations. It is a specialized mathematical system designed for specific applications [29]. The term Boolean algebra used primarily in specific technical fields. The term mathematical logic, which is synonymous to the term Boolean algebra, is more commonly used in pure mathematics. The operators AND, OR and NOT are defined by mathematical axioms and can be replaced by different symbols or other words.

In contrast, logic is not confined to mathematics; rather, it is a universal system of reasoning that applies to all areas of knowledge, guiding the development of scientific theories, philosophical arguments, and computational systems alike. Thus, logic although independent of the language used can only be explained by natural language. Symbols and graphics may be used but only for better illustration and explanation and not as a system of operators defined by axioms. Logic and grammar are the only disciplines that have natural language as their meta language and object language.

This distinction underscores the importance of recognizing the unique roles each plays: Boolean algebra as a powerful tool in binary mathematics and logic as the foundation of rational thought across all domains [30,31,32].

The concept of logic as being a mathematical discipline has been followed by some authors [33]. The consequence is the outcome of multiple circular statements. “Logical formulae” need to be defined by logic expressed in verbal terms. Artificial words such as “iff” for necessary and sufficient conditions [33] need to be generated. The term “truth values”, not mathematically defined, should be reserved for logic and not used in mathematics. We apply numbers instead of truth values as we use arithmetic calculations and not logic operations [34]. The approach in this study is purely mathematical.

Conclusion

Boolean algebra has been demonstrated to facilitate many processes in medicine. Mathematics including artificial intelligence may enable to take unnecessary work off the busy clinician so she or he has more time for the patients. The lack of standard in notation and the mix up with logic pose a major change to a universal application.

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