Prevalence Estimation for Infectious-Disease Surveillance

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SWIM 2025, Heidelberg

Figure courtesy: Alina Grubnyak

Outline

(1) How This Project Came About

(2) Aggregating Results From Multiple Tests

(3) Summary and Outlook


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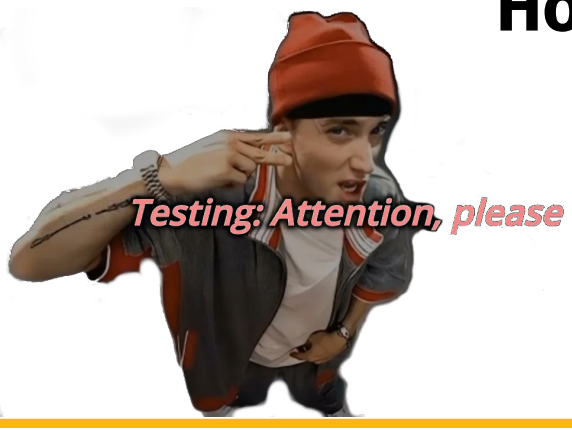
Tom Chou


Nana Owusu-Boaitey


Stefan Felder

Böttcher, L., D'Orsogna, M. R., & Chou, T. (2025). Aggregating multiple test results to improve medical decision-making. PLOS Computational Biology, 21(1), e1012749.

How This Project Came About



Physical Biology

PAPER

Why case fatality ratios can be misleading: individual- and population-based mortality estimates and factors influencing them

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Research

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A statistical model of COVID-19 testing in populations: effects of sampling bias and testing errors

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COVID-19

Using excess deaths and testing statistics to determine COVID-19 mortalities

Lucas Böttcher[1,2] · Maria R. D'Orsogna[1,3] · Tom Chou[1,4]

PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Aggregating multiple test results to improve medical decision-making

Lucas Böttcher[1]*, Maria R. D'Orsogna[2,3], Tom Chou[3,4]

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Statistics in Medicine

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Statistics in Medicine

RESEARCH ARTICLE OPEN ACCESS

Determining the Optimal Sequence of Multiple Tests

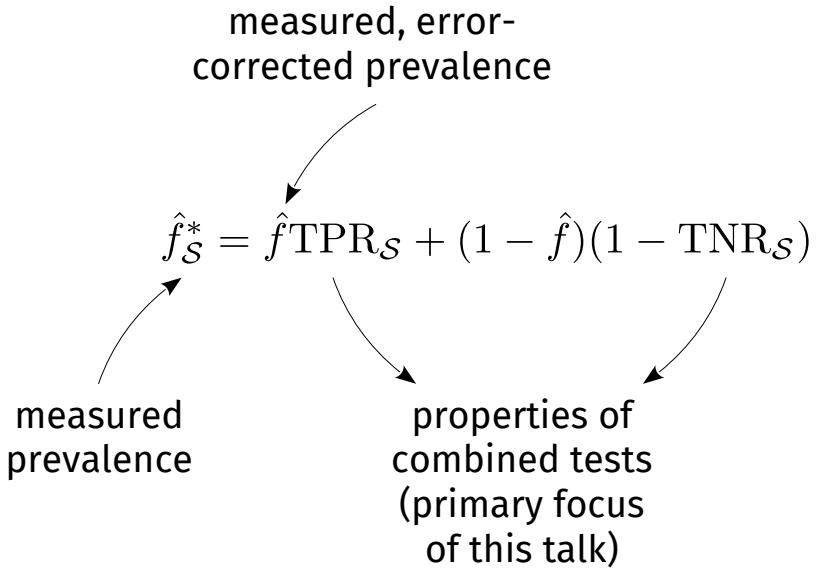
Lucas Böttcher[1,2] | Stefan Felder[3,4]

[1]Department of Computational Science and Philosophy, Frankfurt School of Finance and Management, Frankfurt am Main, Germany | [2]Laboratory for Systems Medicine, Department of Medicine, University of Florida, Gainesville, Florida, USA | [3]Faculty of Business and Economics, University of Basel, Basel, Switzerland | [4]Faculty of Business and Economics, University of Duisburg-Essen, Essen, Germany

Rogan—Gladen Estimator

Basic idea: Use of seroprevalence data (ideally an age-stratified random sample) to estimate "true prevalence":

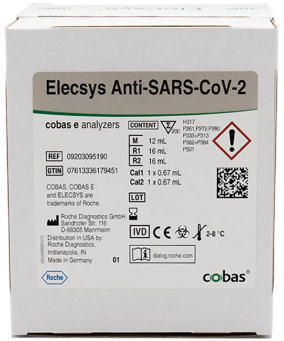
$$\hat{f} = \frac{\hat{f}^*_{\mathcal{S}} + \mathrm{TNR}_{\mathcal{S}} - 1}{\mathrm{TPR}_{\mathcal{S}} + \mathrm{TNR}_{\mathcal{S}} + 1}$$



Rogan, W. J., & Gladen, B. (1978). Estimating prevalence from the results of a screening test. American Journal of Epidemiology, 107(1), 71-76.

The Variety of SARS-CoV-2 Tests

- Wide variety of assays: commercial platforms + in-house ELISAs targeting N, S, or total antibodies.
- Studies used 1–4 combined tests with OR, AND, or other Boolean functions.
- Effective sensitivity varied (≈50–100%) while specificity was usually high (≈98–100%).
- Seroprevalence estimates depend strongly on assay choice, combination strategy, and adjustment methods.



Aggregating Results From Two Tests

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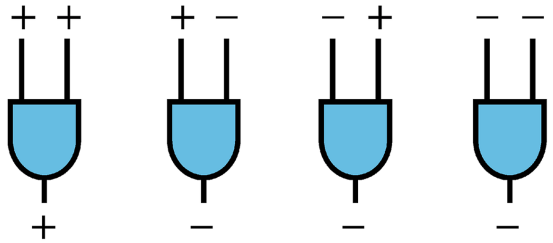
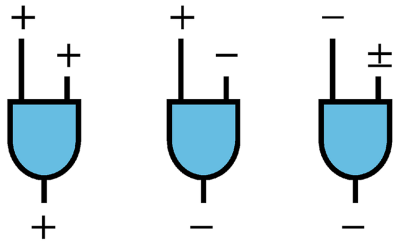
parallel testing

series testing

AND





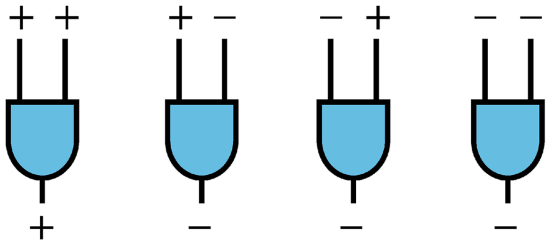
Both input signals are measured at the same time.

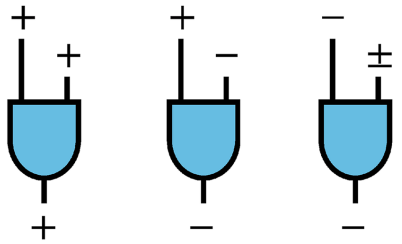
The signal on the left input is measured before the signal on the right input.

parallel testing

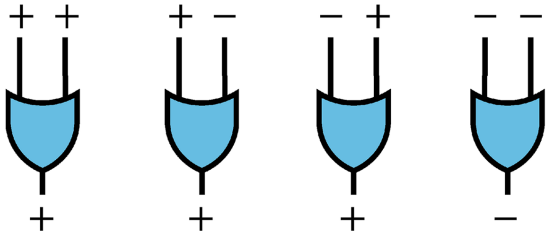
series testing

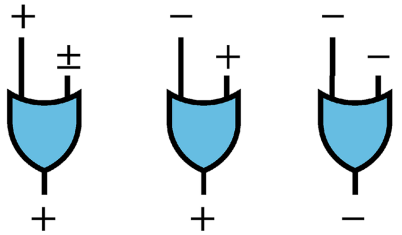
AND





OR





Both input signals are measured at the same time.

The signal on the left input is measured before the signal on the right input.

Aggregating Results From Two Tests

What are the sensitivity and specificity of a test that combines two constituent tests using the AND function?

$$\mathrm{TPR}_{1\wedge 2}^{(\mathrm{p})} = \Pr(Z = 1 \mid X = 1) = \Pr(Y_1 = 1, Y_2 = 1 \mid X = 1) = \mathrm{TPR}_1 \mathrm{TPR}_2$$

sensitivity assuming **conditional independence** of test results given the disease status

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correlation effects → Boole–Fréchet inequalities

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Aggregating Results From Two Tests

What are the sensitivity and specificity of a test that combines two constituent tests using the AND function?

$$
\begin{aligned}
\mathrm{TNR}_{1\wedge 2}^{(\mathrm{p})} &= \Pr(Z = 0 \mid X = 0) \\
&= 1 - \Pr(Y_1 = 1, Y_2 = 1 \mid X = 0) \\
&= \Pr(Y_1 = 0, Y_2 = 0 \mid X = 0) + \Pr(Y_1 = 0, Y_2 = 1 \mid X = 0) \\
&\quad + \Pr(Y_1 = 1, Y_2 = 0 \mid X = 0) \\
&= \mathrm{TNR}_1 + (1 - \mathrm{TNR}_1)\mathrm{TNR}_2
\end{aligned}
$$

specificity assuming **conditional independence** of test results given the disease status

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Aggregating Results From Two Tests

correlation effects → Boole–Fréchet inequalities

$$\max\left(0, \sum_{i=1}^{n} \mathrm{TPR}_i - (n-1)\right) \leq \mathrm{TPR}_{1\wedge\ldots\wedge n} \leq \min_i\left(\mathrm{TPR}_i\right)$$

$$\max_i\left(\mathrm{TNR}_i\right) \leq \mathrm{TNR}_{1\wedge\ldots\wedge n} \leq \min\left(1, \sum_{i=1}^{n} \mathrm{TNR}_i\right)$$

(These are tight bounds.)

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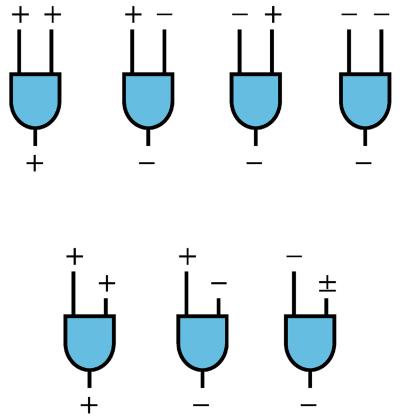
Parallel Versus Sequential Tests

- **Sensitivity** and **specificity** remain **the same** for both **parallel** and **sequential** test aggregation.



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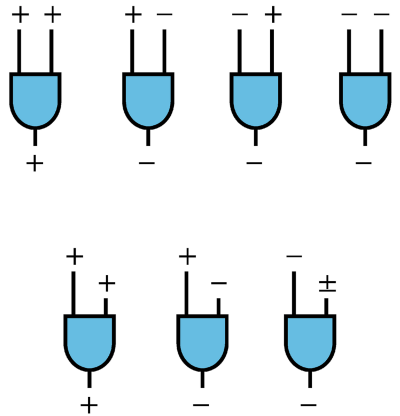
- **Sequential testing** requires **fewer tests**, reducing costs.



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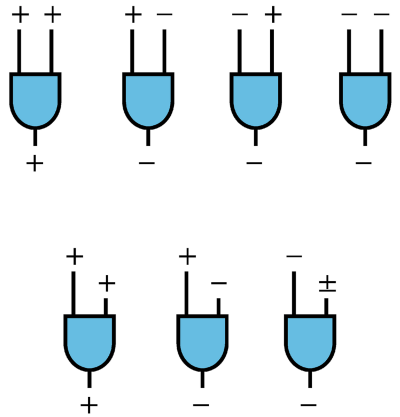
Parallel Versus Sequential Tests

- **Sensitivity** and **specificity** remain **the same** for both **parallel** and **sequential** test aggregation.
- **Sequential testing** requires **fewer tests**, reducing costs.
- **Parallel testing** may be **preferable** for **slow-processing tests** (*e.g.*, ELISA, RT-PCR) to minimize delays.



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Properties of AND and OR Combined Tests

- At **low prevalence**, **false positives** are the primary **source of error**. Therefore, the **AND protocol** is useful as it **maximizes specificity** (false positive rate = 1 – specificity).

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Properties of AND and OR Combined Tests

- At **low prevalence**, **false positives** are the primary **source of error**. Therefore, the **AND protocol** is useful as it **maximizes specificity** (false positive rate = 1 – specificity).

- At **high prevalence**, **false negatives** become the dominant **source of error**. In this case, the **OR protocol** is preferable as it **maximizes sensitivity** (false negative rate = 1 – sensitivity).

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Aggregating Results From *n* Tests

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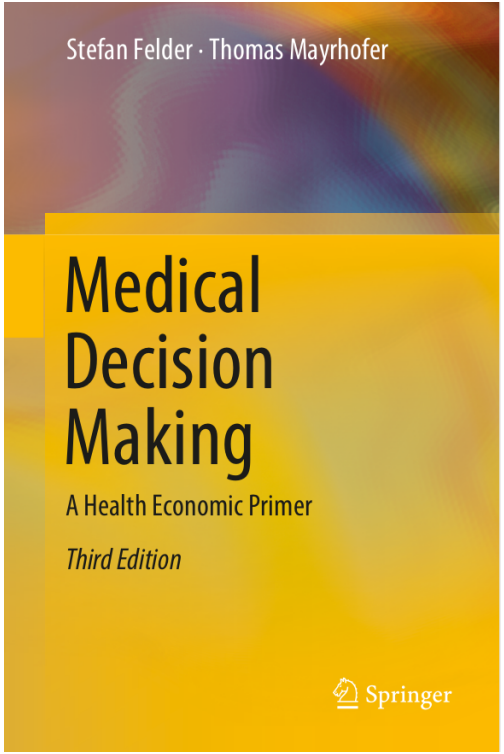
Efficiently Combining *n* Tests

Chapter 7
Optimal Strategy for Multiple Diagnostic Tests

7.2 Combining Two Tests

If two tests are combined, a positivity criterion for the composite test must be defined. The criterion can be either conjunctive or disjunctive. A conjunctive positivity criterion implies that the outcome of the composite test is positive if both tests are positive and negative in all other cases. A disjunctive positivity criterion implies that the outcome of a composite test is negative if both individual tests are negative and positive in all other cases. According to the conjunctive positivity criterion, the decision maker treats the patient only if both tests are positive. According to the disjunctive positivity criterion, the patients are always treated except in the case of two negative results (see Table 7.1).



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Efficiently Combining *n* Tests

Calculator for Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for individual tests and combined

		Prevalence	5.0%					
Test 1		**Test 1**						
Sen1	Sp1	%Pos1 (Test1=pos)	**PPV1 for (Test1=pos)**	%Neg1 (Test1=neg)	NPV1 for (Test1=neg)			
97.0%	93.2%	11.3%	**42.9%**	88.7%	99.8%			
Test 2		**Test 2**						
Sen2	Sp2	%Pos2 (Test2=pos)	**PPV2 for (Test2=pos)**	%Neg2 (Test2=neg)	NPV2 for (Test2=neg)			
88.0%	96.0%	8.2%	**53.7%**	91.8%	99.3%			
		Combined						
		%Pos (Test1=pos, Test2=pos)	**PPV for (Test1=pos, Test2=pos)**	%Discordant (Test1=pos, Test2=neg)	NPV for (Test1=pos, Test2=neg)		%Neg (Test1=neg)	NPV for (Test1=neg)
		4.5%	**94.3%**	6.8%	91.4%		88.7%	99.8%

official “state-of-the-art” FDA calculator for two tests

Food and Drug Administration calculator for positive predictive value (PPV) and negative predictive value (NPV) for individual tests and combined; Accessed: March 14, 2024. Available from: https://www.fda.gov/media/137612/download.

Efficiently Combining *n* Tests

We developed an **algorithm** that calculates **sensitivities** and **specificities** of combined tests that are based on ***n* constituent tests**.

The **“efficient frontier”** can be determined with a **convex-hull algorithm**.

	sensitivity	specificity
Abbott—Panbio COVID-19 Ag	74.8% (67.6—80.8%)	99.7% (99.6—99.8%)
Innova Medical Group—Innova SARS-CoV-2 Ag	68.1% (47.2—83.6%)	99.0% (98.5—99.3%)
Siemens—CLINITEST Rapid COVID-19 Ag	68.7% (48.0—83.8%)	100% (98.0—100%)

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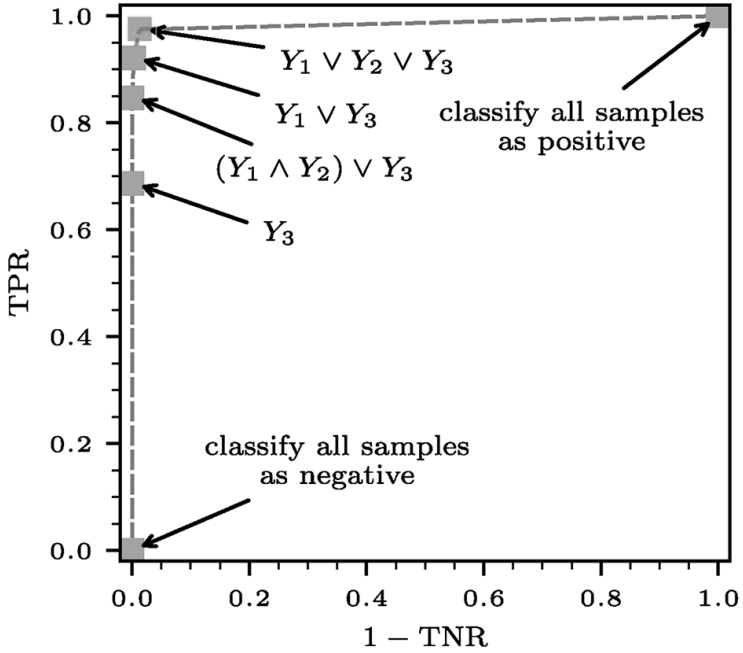
Efficiently Combining *n* Tests



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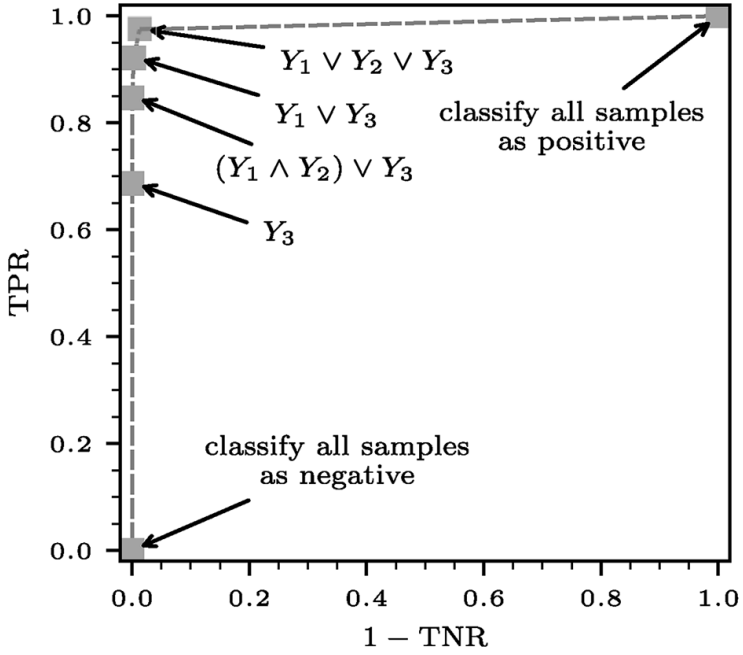

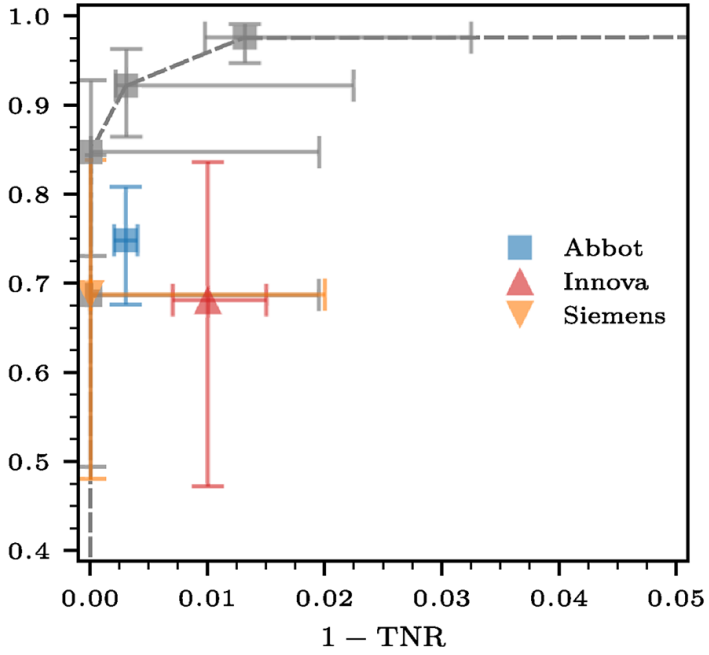

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Summary and Outlook

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Summary and Outlook

- We developed statistical tools to **efficiently combine tests**, adjusting the false positive-false negative tradeoff for specific applications.

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Summary and Outlook

- We developed statistical tools to **efficiently combine tests**, adjusting the false positive-false negative tradeoff for specific applications.

- We showed how our method can help **improve disease prevalence estimates** in infectious-disease surveillance.

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Summary and Outlook

- We developed statistical tools to **efficiently combine tests**, adjusting the false positive-false negative tradeoff for specific applications.

- We showed how our method can help **improve disease prevalence estimates** in infectious-disease surveillance.

- **Collaborating with manufacturers** is important for future work to account for empirical **correlation effects**, which are often not reported on manufacturer sheets.

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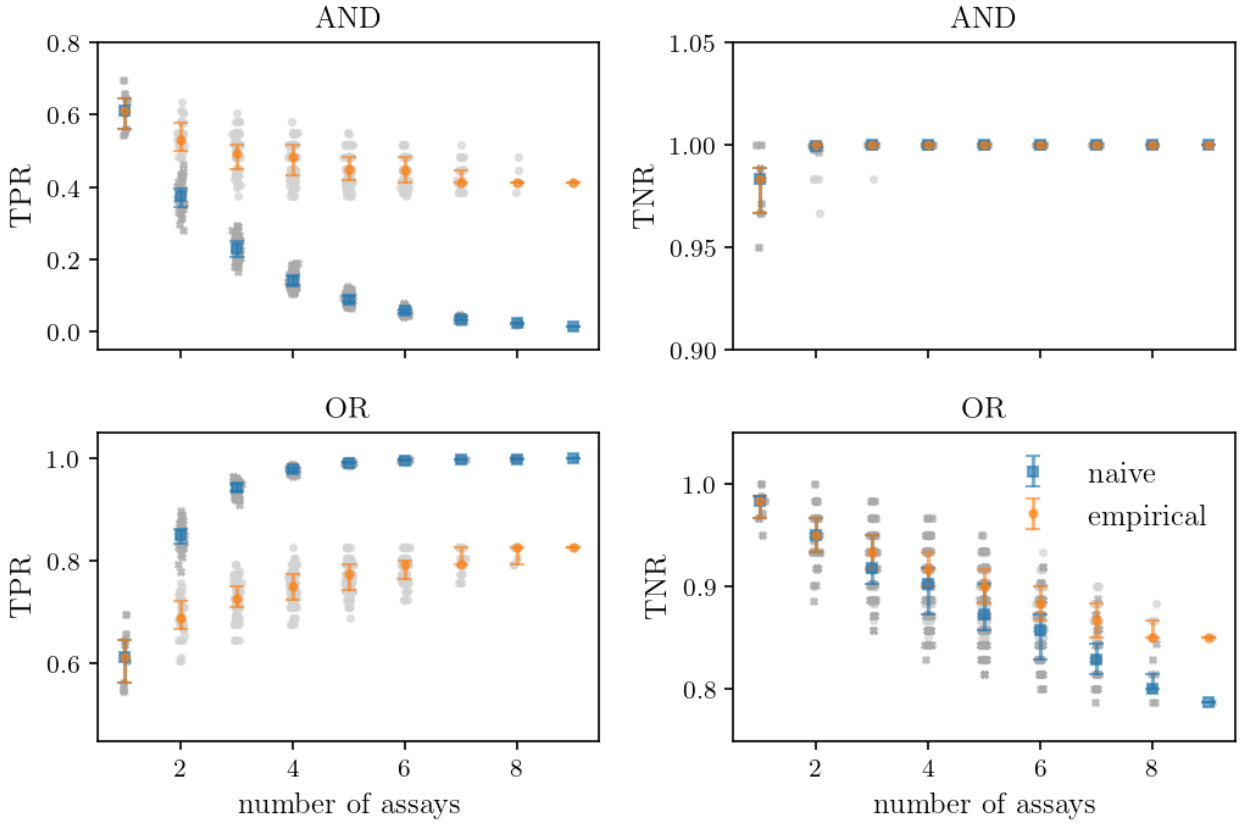
(1) How does adding one additional test affect TPR and TNR across different aggregation functions?



(2) Can one develop an algorithm for generalized Boole—Fréchet bounds?

BEST POSSIBLE INEQUALITIES FOR THE PROBABILITY OF A LOGICAL FUNCTION OF EVENTS

THEODORE HAILPERIN, Sandia Corporation and Lehigh University

1. Introduction. If E denotes the event "A_1 or A_2 or $\cdots$ or A_n", where $A_1, \cdots, A_n$ are n events with respective probabilities $a_1, \cdots, a_n$ and if $\mathsf{P}(E)$ denotes the probability of E, then the following inequality holds:

$$(1.1) \qquad \max [a_1, \cdots, a_n] \leqq \mathsf{P}(E) \leqq \min [1, a_1 + \cdots + a_n].$$

Similarly, if F denotes the event "A_1 and A_2 and $\cdots$ and A_n," then

$$(1.2) \qquad \max [0, a_1 + \cdots + a_n - (n-1)] \leqq \mathsf{P}(F) \leqq \min [a_1, \cdots, a_n].$$

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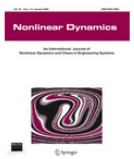

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