PCR, Tropical Arithmetic, and Group Testing

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Slides
https://h-p.wang/isit

Preprint
https://arxiv.org/abs/2201.05440

Motivation of This Work

Overall goal is to screen many people for covid (or for the next pandemic).

Antigen testing and antibody testing = cheap and fast; but not too sensitive.

PCR (polymerase chain reaction) testing = sensitive but expensive and slow.
Keep track of the variants (alpha, delta, omicron, etc).

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Outline of This Talk

The working principle of PCR testing.

Variants of group testing (GT).

Our GT, called tropical GT.

Working Principle of PCR

A PCR machine is a sauna room for test tubes, with three settings: cold, warm, and hot.

Cold = annealing = a primer and a polymerase stick to a single-stranded DNA.
Warm = elongation = the polymerase synthesizes the complement strand of the DNA.
Hot = denaturation = a double-stranded DNA splits into two single-stranded DNAs.

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Repeat until we can detect presence of DNA.

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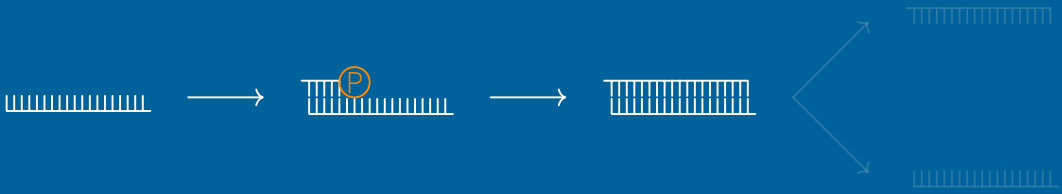

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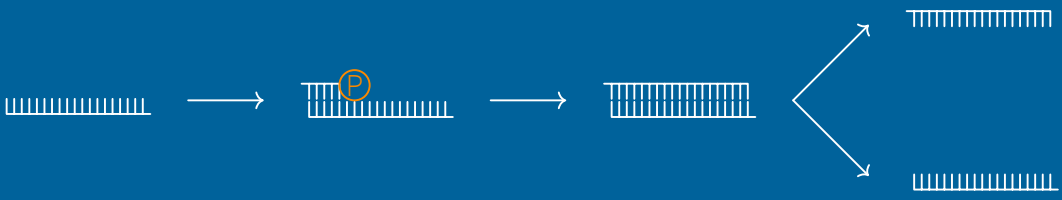

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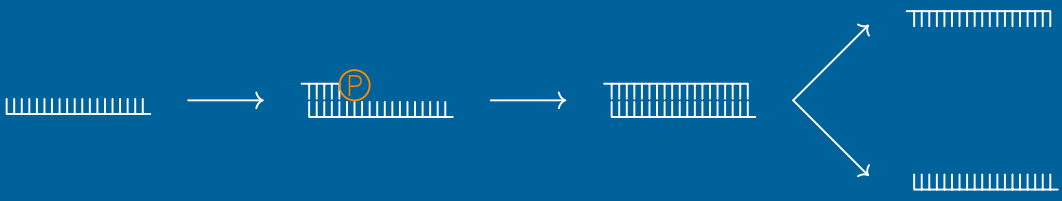

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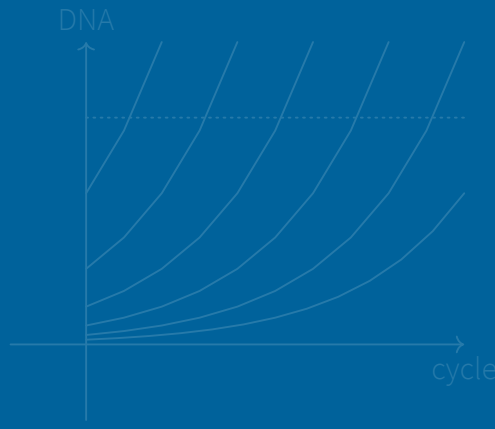
How to Detect DNA and What's Ct Value?

Insert fluorescent dyes that like to attach to DNA.
As the amount of DNA increases, the tube glows.

Ct value is #cycles before the tube glows.



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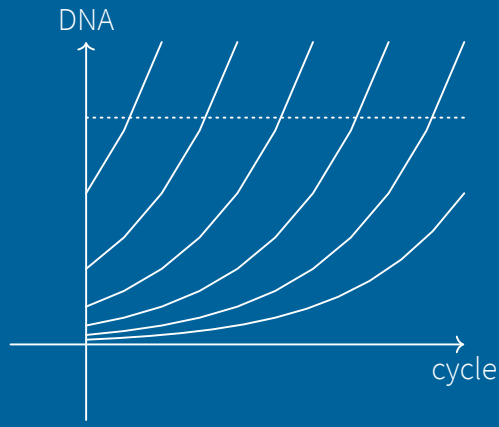

So...

How to Combine Ct and GT?

Review: Binary GT

In binary GT, a test result is either negative or positive.

Mix samples of five people.
If the mixture is negative, all five people are healthy.
If the mixture is positive, someone is infected.
You won't know who so you call them back to retest individually.

Origin = [Dorfman 1943]. Book = [Du–Hwang 1993]. Lecture note: [Ngo–Rudra 2011].
Survey paper: [Aldridge–Johnson–Scarlett 2019].

Review: Threshold GT

If less than L people are infected, the mixture is negative.
If more then U people are infected, the mixture is positive.
Inconclusive if between L and U.

[Damaschke 2006] [Dyachkov 2013] [Cheraghchi 2013]

Review: Quantitative GT

You have ten bags of coins, each containing many coins.
Each coin weighs 5 grams.
One bag contains fake coins; each fake coin weighs 4.5 grams.
Task: Use a spring scale to find the fake bag.

Another name = coin-weighing problem.
[Hwang 1987] [Guy–Nowakowski 1995] [Bshouty 2009]

Review: Semi-Quantitative GT

The spring scale is rusty, accurate up to 1 gram.

This version is basically a combination of quantitative GT and threshold GT.

[Emad–Milenkovic 2014] [Cheraghchi–Gabrys–Milenkovic 2021]

Review: Compressed Sensing

Very similar to semi-quantitative GT.
Want to solve $y = Ax +$ errors.

Variants: A is zero-one matrix or with real numbers?
Usual matrix multi'n $(A \cdot B)_{ik} := \sum_j (A_{ij} \cdot B_{jk})$ or logical $(A \wedge B)_{ik} := \bigvee_j (A_{ij} \wedge B_{jk})$?
Minimize $|A\mathbf{x} - \mathbf{y}|_2^2 + \lambda |\mathbf{x}|_1$ or other metric?

Recent works: [Ghosh et al. 2021] [Shental et al. 2020] [Mutesa et al. 2021]
Survey: [Aldridge–Ellis 2022]

Our argument: PCR needs a new GT approach.

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PCR Precision Issue

DNA can double many many times. So PCR is as sensitive as 100 copies/mililitter.

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The “Problem” with Logarithmic Scale

White noises of 50dB and 30dB combined = 50.043dB.

Mixing pH 1 and pH 3 acids of same volume = diluting pH 0.9957 by two-fold.

Magnitude 9 and magnitude 8 earthquakes happen same time same place = 9.009.

A star with apparent magnitude 1 approaches a star with 6 = looks like 0.9892.

Actual Question is..

How to “Add” under Logarithmic Scale?

Use Tropical Arithmetics!

Rules are as follows:
The domain is real numbers and infinity $\mathbb{R} \cup \{\infty\}$.
Tropical addition: $x \oplus y := \min(x, y)$. $(x \oplus \infty = x)$
Tropical multiplication $x \odot y := x + y$. $(x \odot \infty = \infty)$

Hint: It's all about logarithm.
$2^{-x} + 2^{-y} \approx 2^{-\min(x,y)}$
$2^{-x} \cdot 2^{-y} = 2^{-(x+y)}$

Tropical Arithmetics and Matrix Multiplication

Let $A \odot B$ be a matrix whose (i,k)th entry is let to be $\bigoplus_j (A_{ij} \odot B_{jk}) = \min_j (A_{ij} + B_{jk})$.

Combinatorial meaning: Suppose $X_1, ..., X_\ell, Y_1, ..., Y_m, Z_1, ..., Z_n$ are some places. Let the distance from X_i to Y_j be A_{ij}. Let the distance from Y_j to Z_k be B_{jk}. $(A \odot B)_{ik}$ is the distance from X_i to Z_k via the best choice of Y_j.

Example: Shortest path problem: $A \oplus (A \odot A) \oplus (A \odot A \odot A) \oplus \cdots$.

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Axiomize PCR and Pooling

Suppose there are n samples with Ct values $x_1, x_2, \ldots, x_n$.
The Ct value of the mixture should be $-\log_2\left(\sum_j 2^{-x_j}\right)$.

This quantity is close to, and we pretend that it is exactly, $\mathbf{0} \odot \mathbf{x} = \bigoplus_j x_j = \min_j x_j$.
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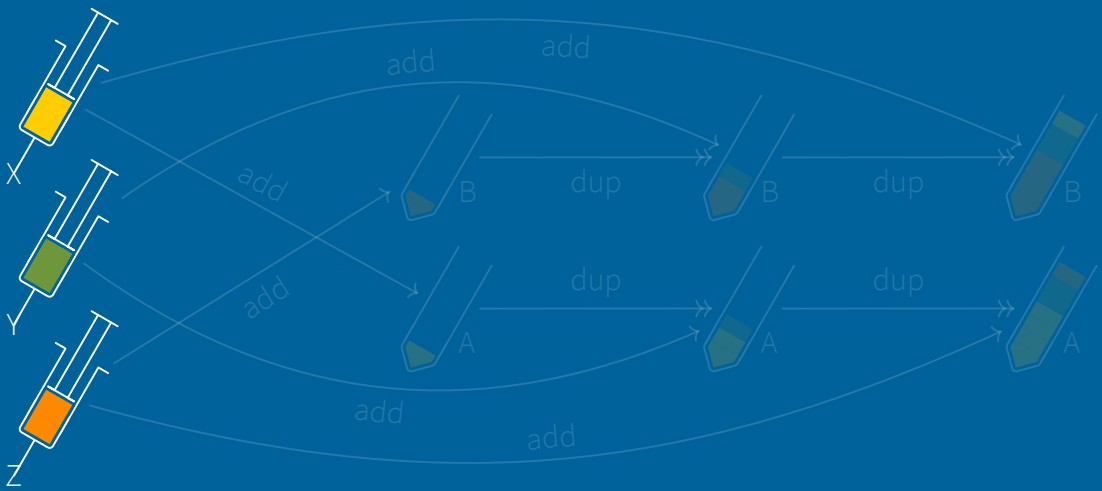
Why Delay?

How Does Delaying Help GT?



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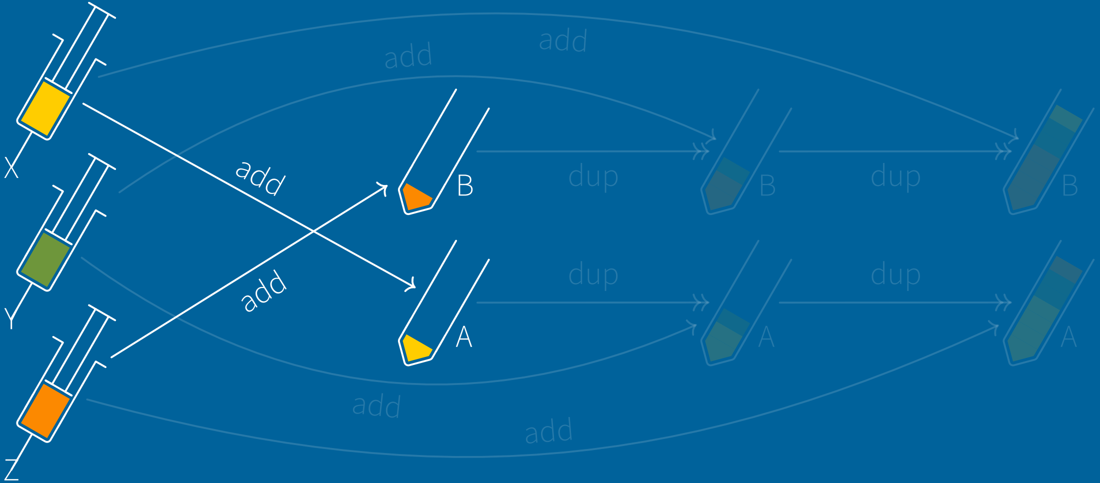

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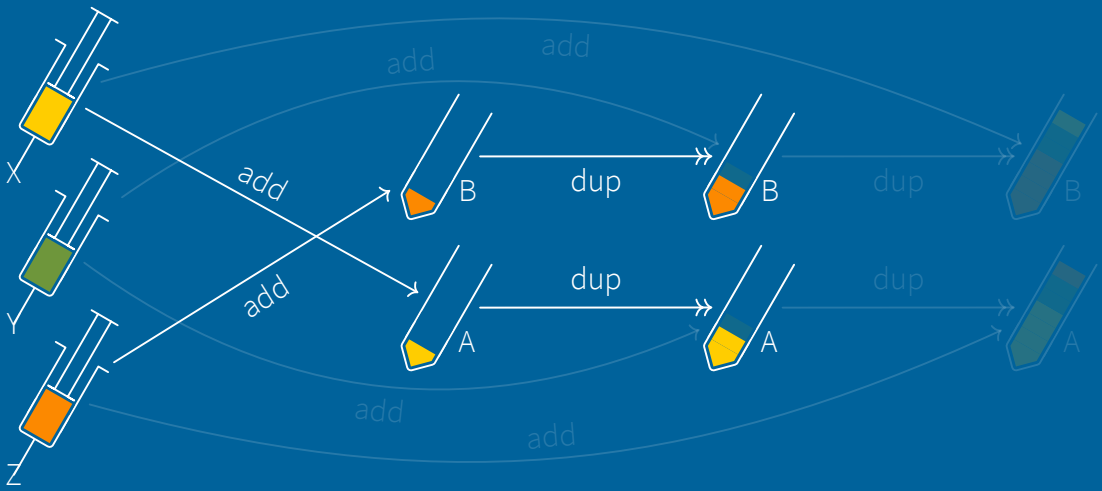

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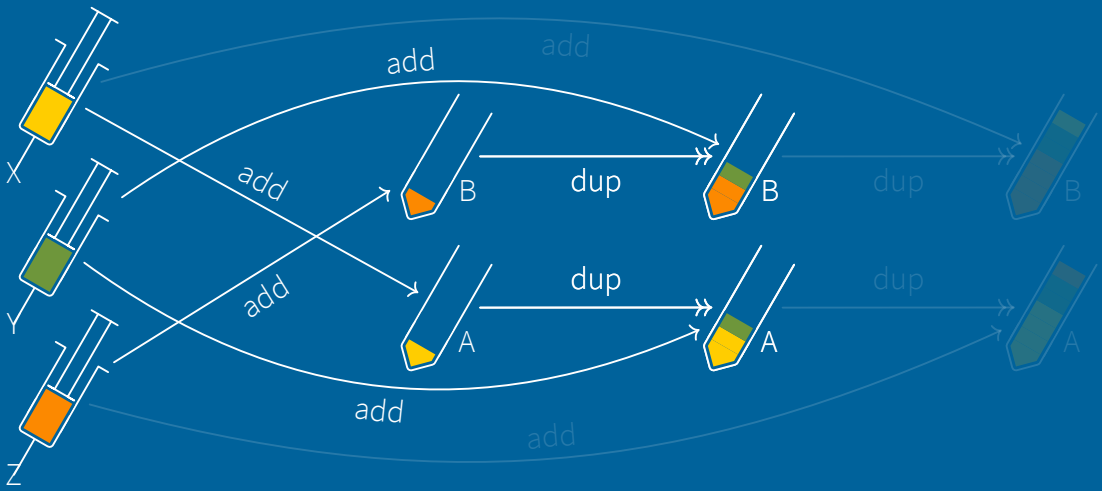

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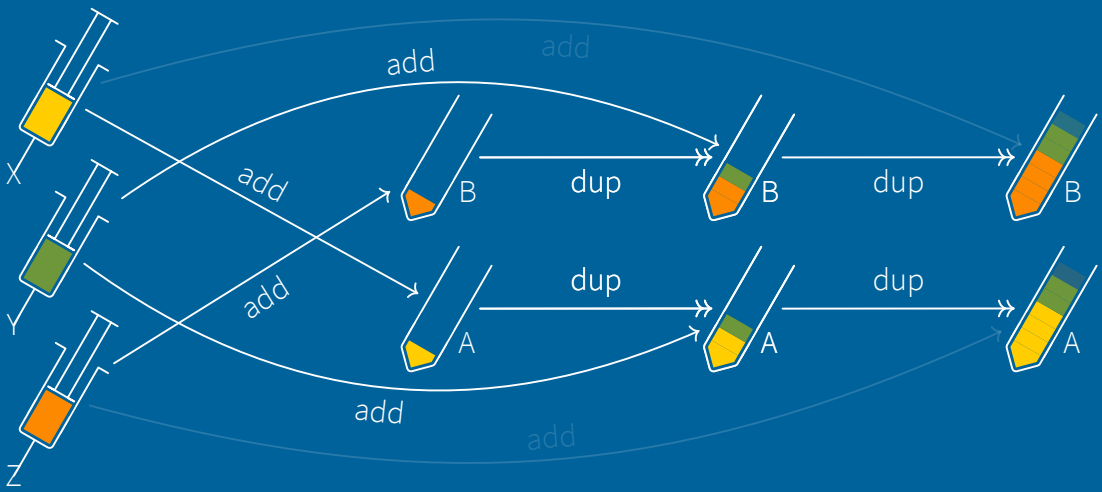

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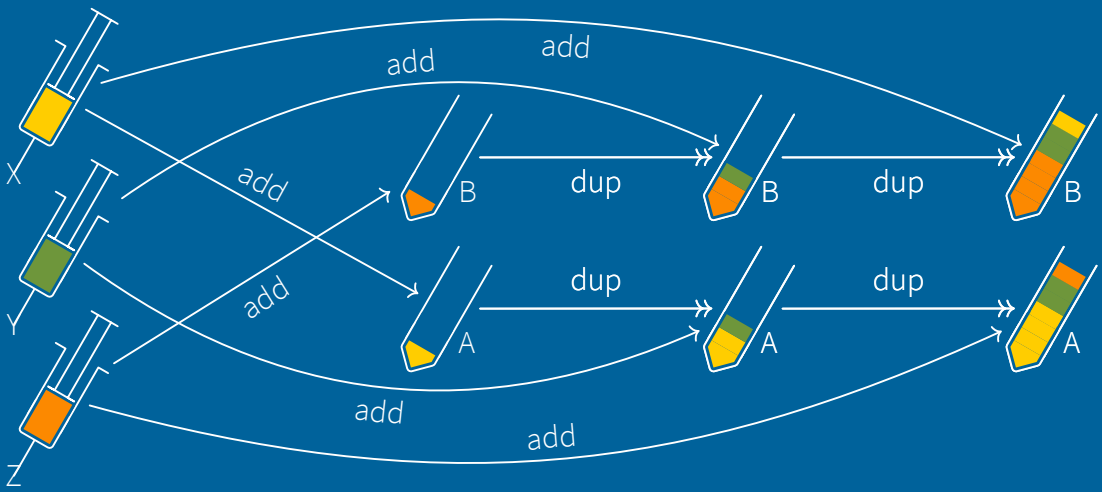

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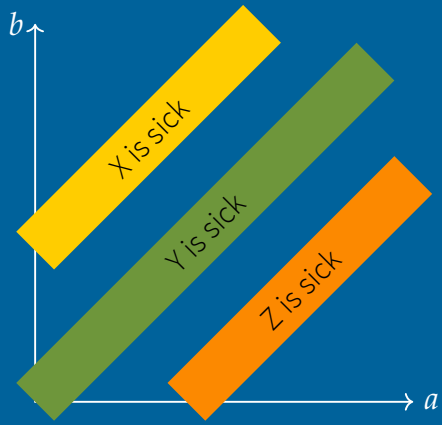
Decoding the Previous Slide

Suppose at most one person is infected.

X is infected iff $a - b = -2$.
Y is infected iff $a - b = 0$.
Z is infected iff $a - b = 2$.



Summary

1. We use $x \oplus y := \min(x, y)$ to characterize the result of mixing Ct values x and y.
This simplifies the decoder.

2. We introduce $\delta \odot x := \delta + x$, id est, delaying, to enhance GT.
This introduces new combinatorial problems into the field.

3. Tropical matrix multiplication becomes a succinct language
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Future Works
Open to Questions

- Can we reformat decoding as a convex optimization problem (LASSO-fy)?
- Little is known when number of patients ≥ 3.
- Asymptotic behaviors as #tests, #people, and #patients go to infinity.
- Noisy/erroneous measurements.

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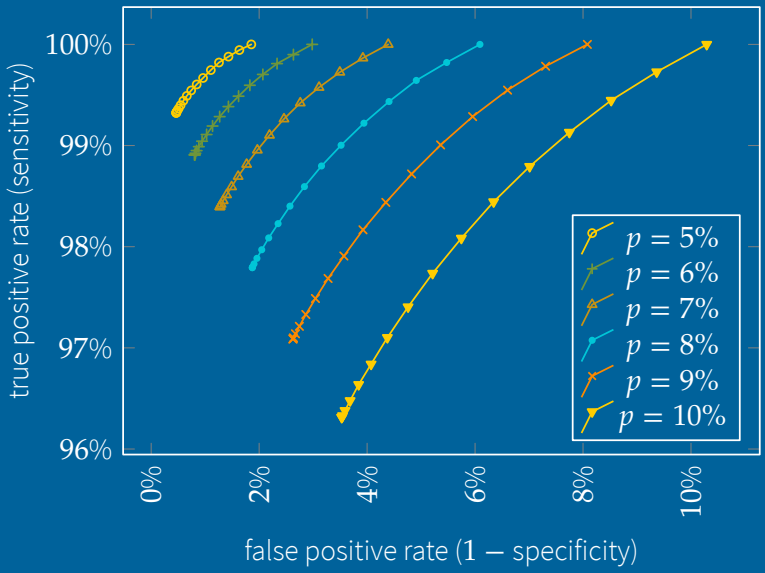
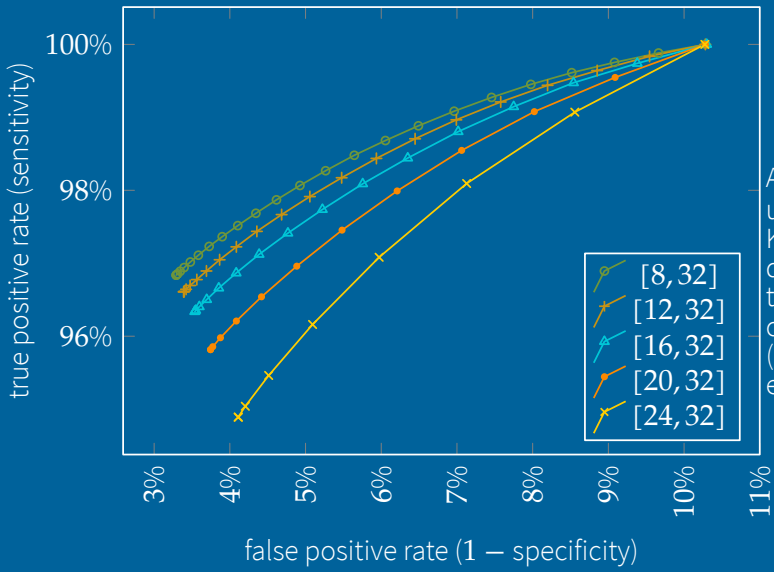
Appendix

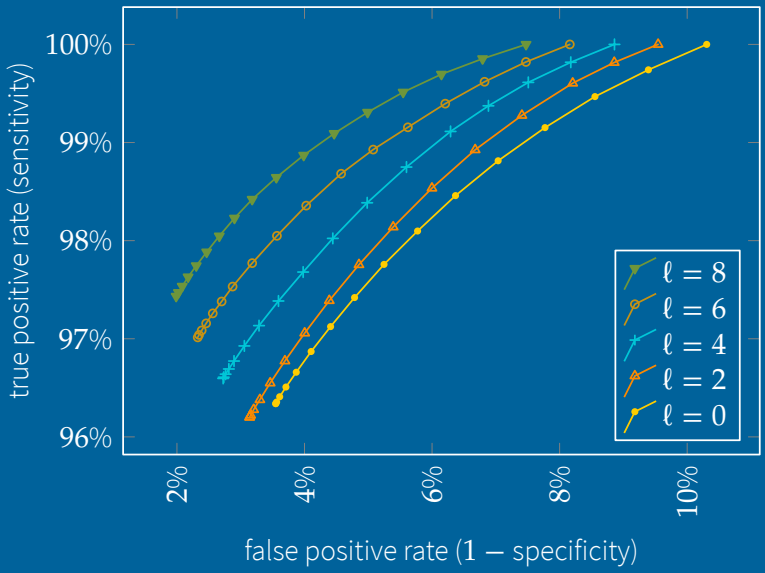
Simulation Plots



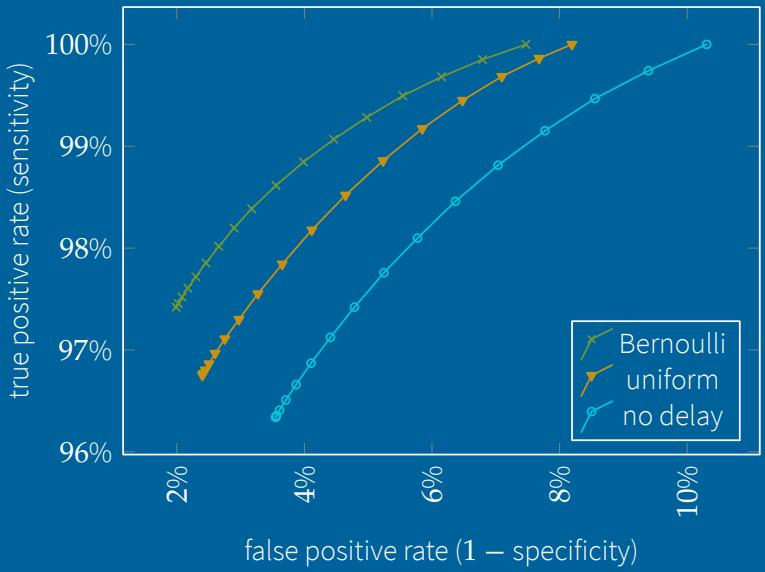
Assume uniform Ct values on the interval $[16, 32]$, 15×35 Kirkman triple system, and no delay ($\ell = 0$). We vary the prevalence rate p and plot the ROC curves.



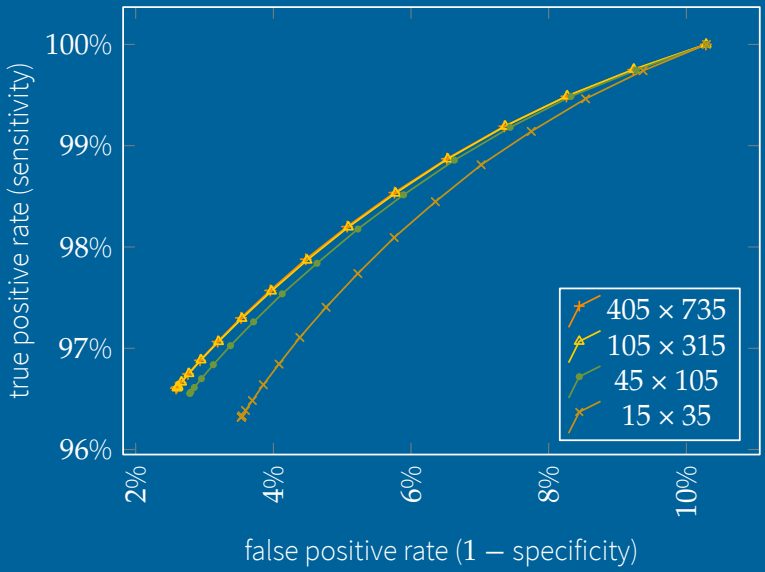
Assume prevalence rate $p = 10\%$, uniform Ct values, 15×35 Kirkman triple system, and no delay ($\ell = 0$). We vary the range of the Ct values and plot the ROC curves. Surprisingly, larger interval (consequently larger variance) is easier to decode.



Assume prevalence rate $p = 10\%$, uniform Ct values on the interval $[16, 32]$, 15×35 Kirkman triple system, and $\ell \cdot \text{Bernoulli}(1/2)$ delay. We vary the limit of delay ℓ and plot the ROC curves.

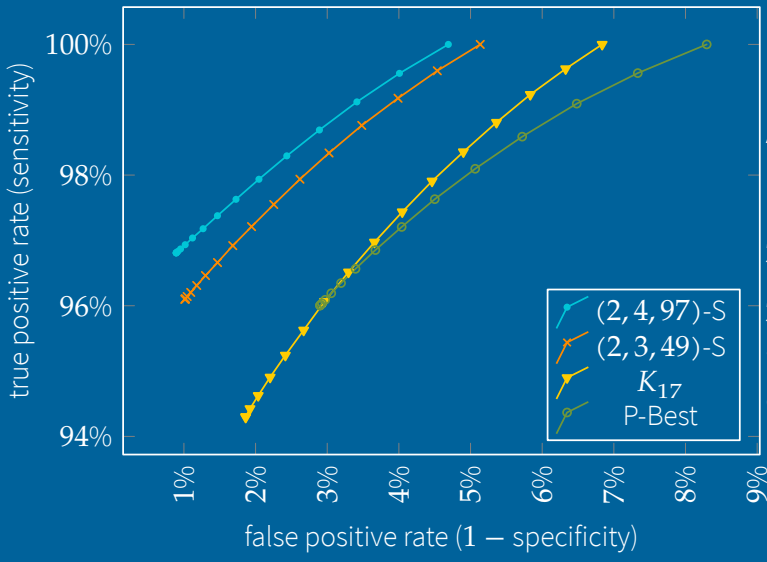


Assume prevalence rate $p = 10\%$, uniform Ct values on the interval $[16, 32]$, 15×35 Kirkman triple system, and $\ell = 8$. We vary the distribution of the random delay δ and plot the ROC curves.

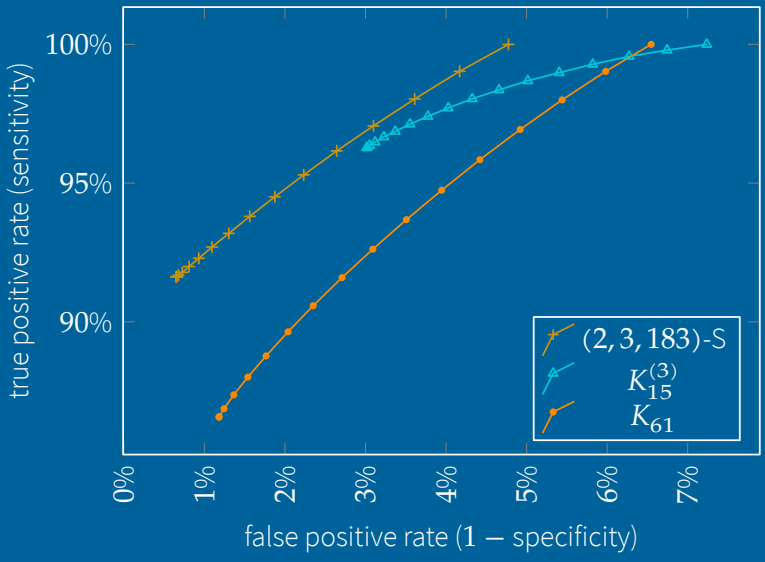


Assume prevalence rate $p = 10\%$, uniform Ct values on $[16, 32]$, and no delay ($\ell = 0$). We consider Kirkman triple systems of different size (after truncation so that the code rate $N/T = 7/3$ is fixed) and plot the ROC curves.

Assume $D = 10$ patients within $N = 105$ persons (infection rate 9.52%), uniform Ct values on $[16, 32]$, 45×105 Kirkman triple system (truncation of a 45×330 Kirkman triple system), and no delay ($\ell = 0$). We plot 10 ROC curves. Each curve is 10,000 encoding–decodings, i.e., 450,000 tubes, 100,000 patients, and 1,050,000 test takers. Compare this to Tapestry's data point and its standard deviations ($4.50\% \pm 2.41\%, 99.30\% \pm 2.55\%$) (Table S.XII of the preprint version [Ghosh et al. 2020]).



Assume prevalence rate $p = 2\%$, uniform Ct values on $[16, 32]$, and no delay ($\ell = 0$). We consider $(2, 4, 97)$-Steiner system (aka 2-$(97, 4, 1)$ design), $(2, 3, 49)$-Steiner system (aka 2-$(49, 3, 1)$ design), complete graph on 17 vertices, and P-BEST [Shental et al. 2020]. They all have code rate $N/T = 8$. We plot their ROC curves.



Assume prevalence rate $p = 0.5\%$, uniform Ct values on $[16, 32]$, and no delay ($\ell = 0$). We consider Kirkman triple system on 183 vertices, complete 3-uniform hypergraph on 15 vertices, and complete graph on 61 vertices. The first two have code rate $N/T = 30 + 1/3$; the last one has code rate $N/T = 30$. We plot their ROC curves.

Four ways to quantify and combine test outputs. Binary tests output "negative" or "positive"; combining samples means logical OR. Quantitative tests output numbers; combining samples means addition. The other two regimes lie in between.

Regime	Reading	Remixing
Binary	Negative, Positive	Neg $\vee$ Pos = Pos
Tropical	$2^{-\infty}, 2^{-40}, \ldots, 2^{-12}$	$\min(30, 15) = 15$
Semiquantitative	$[0,3), [3,6), [6,9), \ldots$	$[0,3) + [3,6) = [3,9)$
Quantitative	$0, 1, 2, 3, 4, 5, \ldots$	$8 + 9 = 17$