

PCR, Tropical Arithmetic, and Group Testing

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Slides

<https://h-p.wang/isit>



Preprint

arXiv: 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:
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keep track of variants (alpha, delta, omicron, etc).



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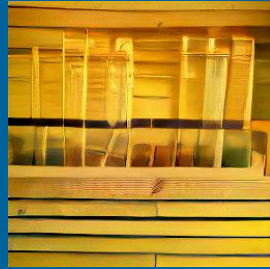
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Working Principle of PCR

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



<https://www.craiyon.com/>
prompt: test tubes in sauna

Cold = a primer and a polymerase stick to a single-stranded DNA.

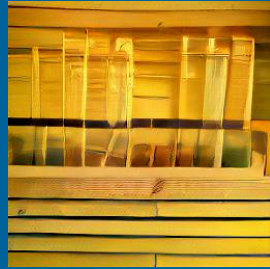
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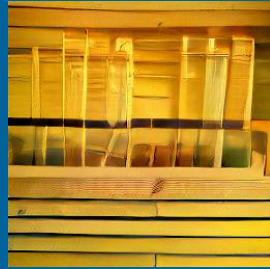
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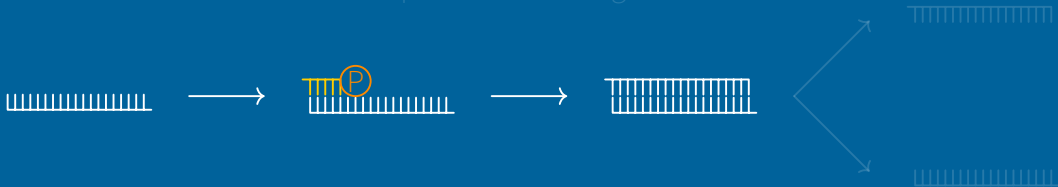


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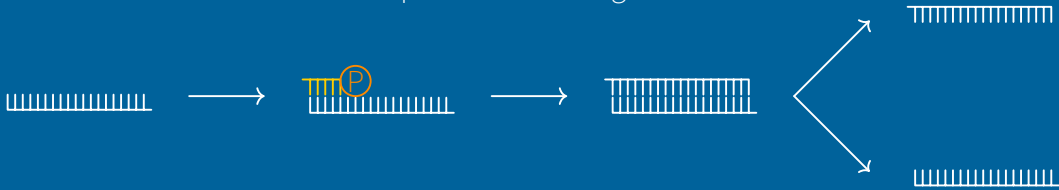


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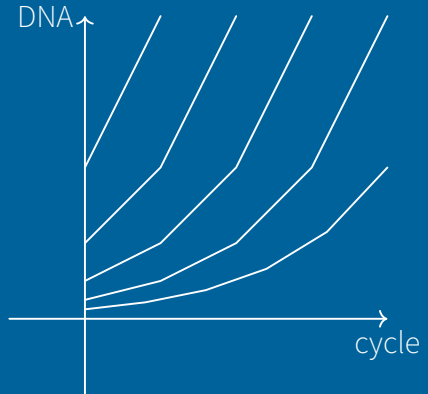


How to Detect DNA and What's Ct Value?

The amount of DNA **doubles** every cold-warm-hot cycle.

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

Ct value is #cycles before we see the tube glowing.

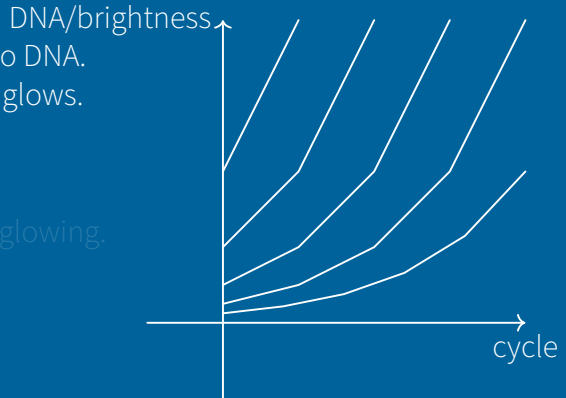


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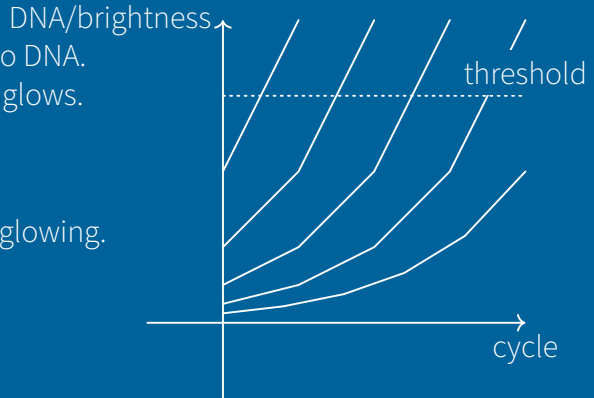


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So...

Can GT Make Good Use of Ct Values?

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, at least one is infected.



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 than U people are infected, the mixture is positive.
Inconclusive if between L and U .

Binary GT: $(L, U) = (0, 1)$.

[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: Compressed Sensing

Very similar to semi-quantitative GT.
Want to solve $\mathbf{y} = \mathbf{A}\mathbf{x} + \text{errors}$.

Some meta choices:

\mathbf{A} is zero-one matrix or with real numbers?

Usual matrix multiplication $(\mathbf{A} \cdot \mathbf{B})_{ik} := \sum_j (\mathbf{A}_{ij} \cdot \mathbf{B}_{jk})$

or logical version $(\mathbf{A} \wedge \mathbf{B})_{ik} := \bigvee_j (\mathbf{A}_{ij} \wedge \mathbf{B}_{jk})$?

Minimize $\|\mathbf{A}\mathbf{x} - \mathbf{y}\|_2^2 + \lambda \|\mathbf{x}\|_1$ or other metric?

Recent works: [Ghosh et al. 2021] [Shental et al. 2020] [Mutesa et al. 2021]

Survey: [Aldridge–Ellis 2022]



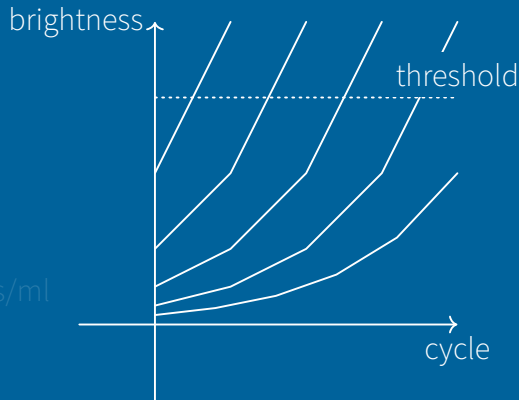
But...

Ct Values Do Not Fit.

PCR Precision Issue

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

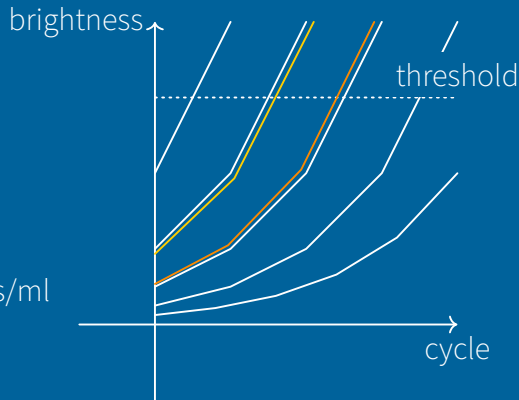
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The “Problem” with Logarithmic Scale



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

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



Magnitude 9 and magnitude 8 earthquakes together = 9.009.

Star with apparent magnitude 1 close to 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: $x \oplus y := \min(x, y)$.

Tropical multiplication $x \odot y := x + y$.

Hint: It's all about logarithm.

$2^{-x} + 2^{-y} \approx 2^{-\min(x,y)}$ (given that $|x - y|$ is not so small)

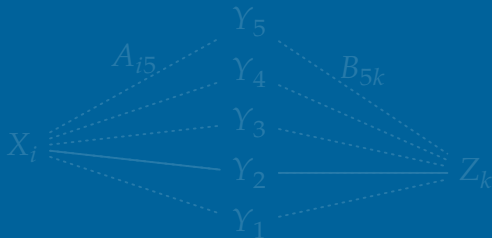
$2^{-x} \cdot 2^{-y} = 2^{-(x+y)}$



Tropical Arithmetics and Matrix Multiplication

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

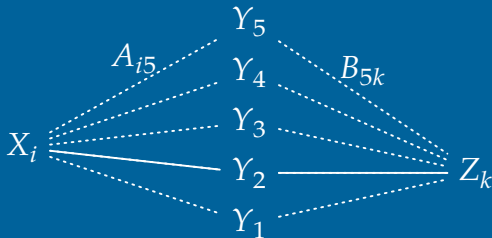
Combinatorial meaning: Suppose $X_1, \dots, X_\ell, Y_1, \dots, Y_m, Z_1, \dots, Z_n$ are points on a map. Let the distance from X_i to Y_j be A_{ij} . Let the distance from Y_j to Z_k be B_{jk} . $(A \odot B)_{ik}$ is the distance from X_i to Z_k via the best choice of Y_j .



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Axiomatize PCR and Pooling

Suppose there are n samples with Ct values x_1, x_2, \dots, x_N .
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This quantity is close to, and we pretend that it is exactly,

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Problem Statement

A (T, N, D) -tropical code is a matrix $S \in (\mathbb{Z} \cup \{\infty\})^{T \times N}$ such that, for any two vectors $\mathbf{x}, \mathbf{y} \in (\mathbb{Z} \cup \{\infty\})^N$, each with at most D finite entries,

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A tropical code is said to be within maximum delay ℓ if $S \in \{0, 1, \dots, \ell, \infty\}^{T \times N}$.

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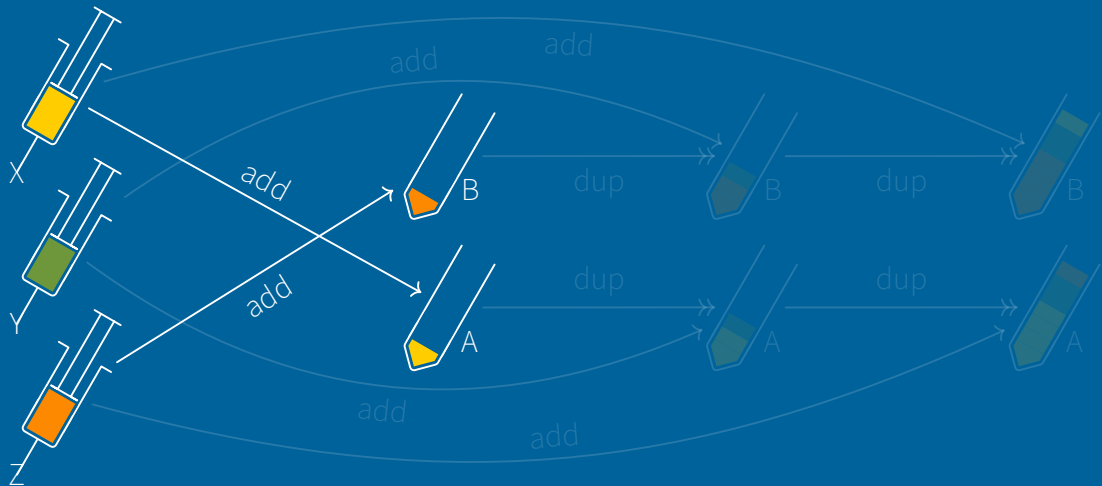
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Why Delay?

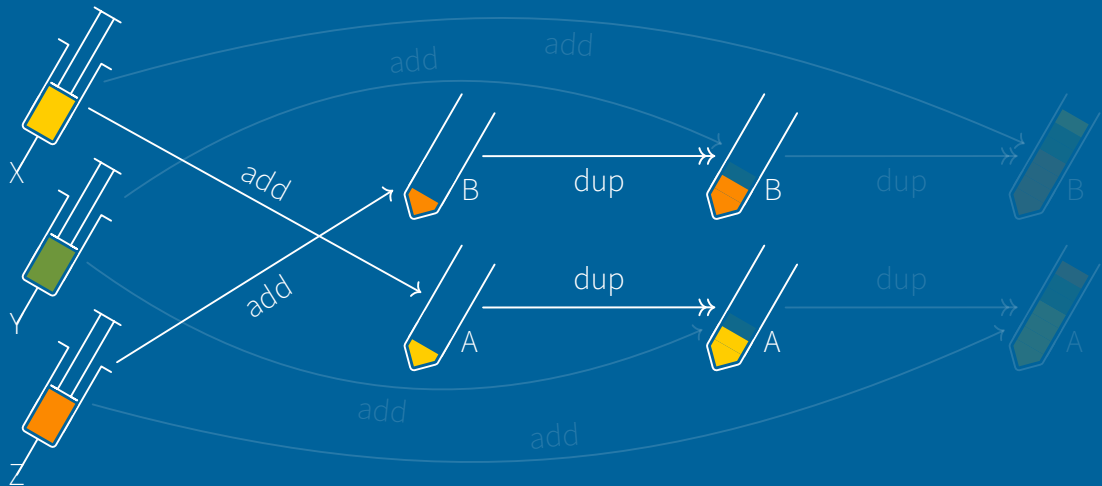
How Does Delaying Help GT?



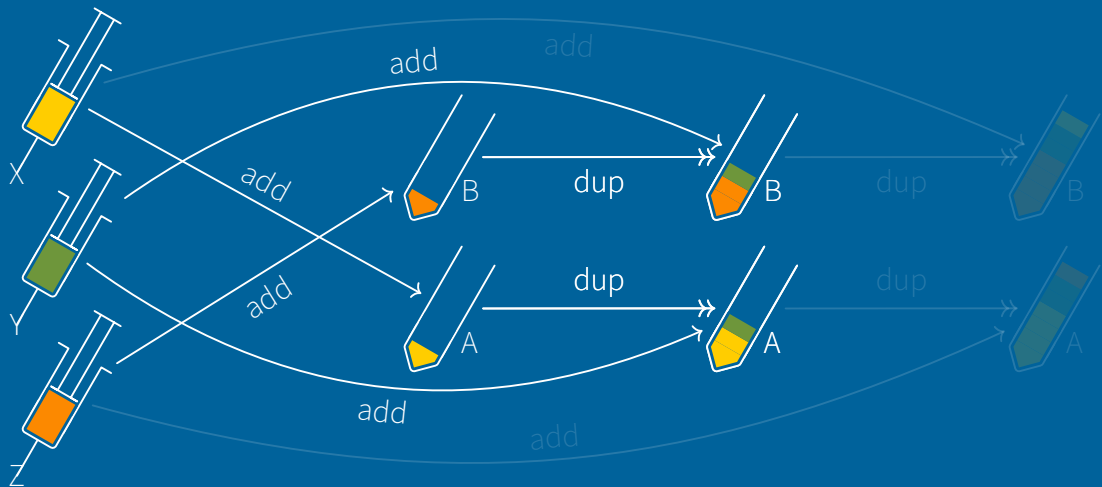
$$\begin{bmatrix} a \\ b \end{bmatrix} := \begin{bmatrix} 0 & 1 & 2 \\ 2 & 1 & 0 \end{bmatrix} \odot \begin{bmatrix} x \\ y \\ z \end{bmatrix} = \begin{bmatrix} \min(0 + x, 1 + y, 2 + z) \\ \min(2 + x, 1 + y, 0 + z) \end{bmatrix}$$



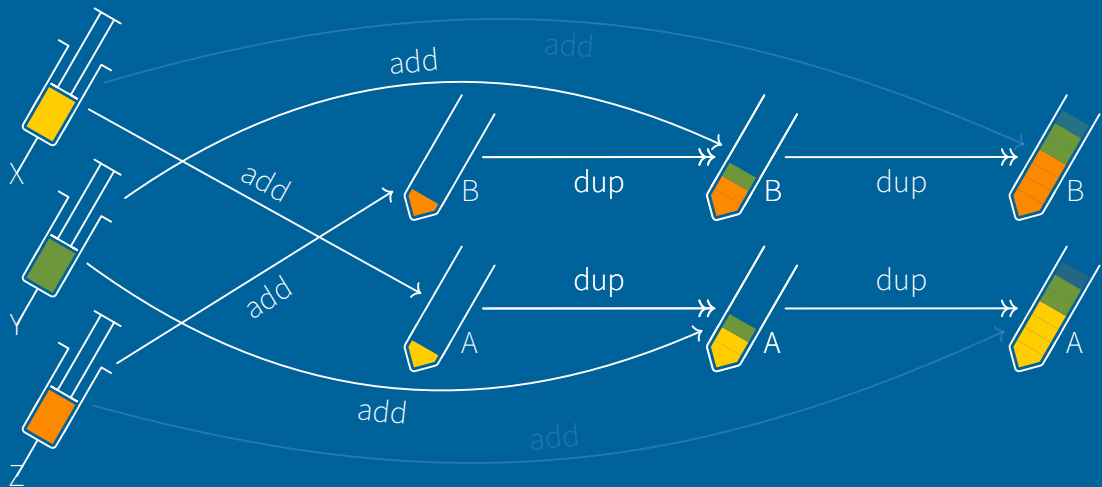
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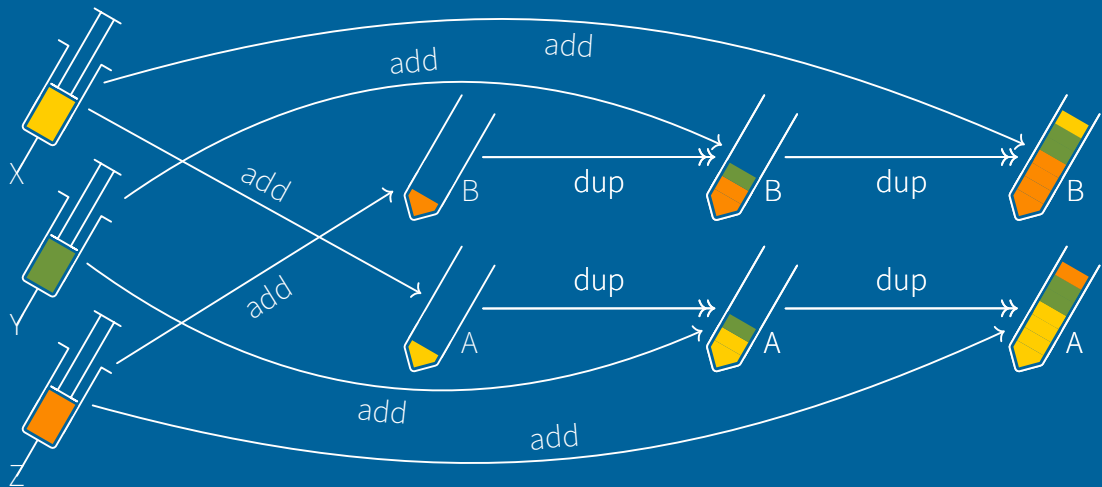
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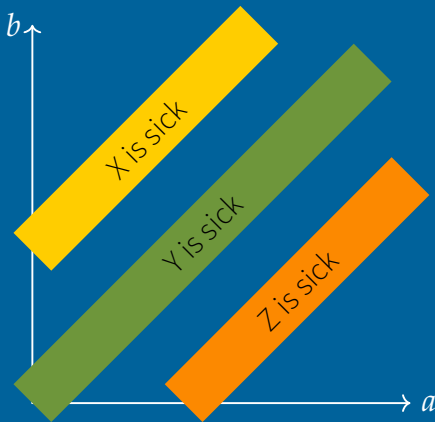
Decoding the Previous Slide

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 $a - b = 2$.



Main Results on Nonadaptive Tropical GT

When there is $D = 1$ infected person in a population of size N , and the delay is limited to ℓ cycles, we have a construction with $N \approx T\ell^{T-1}$.

When there are $D = 2$ infected persons in a population of size N :

- ▶ The first construction uses $T \approx 2\sqrt{N}$ tests.
In this construction, every person is present in only two tests.
- ▶ The second construction limits the delay to $\ell \approx \log_2(N) / \log_2(\log_2 N)$ cycles and uses $T \approx 1.01 \log_2 N$ tests. This outperforms the IT bound of binary GT.

For general D , we give one necessary condition and two sufficient conditions.

Main Results on Adaptive Tropical GT

When adaptive testing is allowed, $T = 4$ tests are sufficient to find $D = 2$ infected persons among arbitrarily many persons.

In general, $T = 3D + 1$ adaptive tests are sufficient to locate D infected persons among arbitrarily many persons. For this construction, one does not need to know D beforehand.

When delays are limited to ℓ cycles, we show that $T \approx 4D \log_{\ell} N$ tests suffice.

Summary of Novelty

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

2. We use $\delta \odot x := \delta + x$, i.e., delaying, to enhance GT. This inspires new combinatorics problems.

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Future Works

Open to Questions

- To what extent does compressed sensing apply to tropical case?
- Random coding approach? Asymptotics?
- Noisy/erroneous measurements?



Slides

<https://h-p.wang/isit>



Preprint

arXiv: 2201.05440

Appendix

PCR Error Models

Error Models of PCR

Error model 1: Ct value is rounded to the nearest integer.

Error model 2: Use fractional cycle counts (whatever that means).

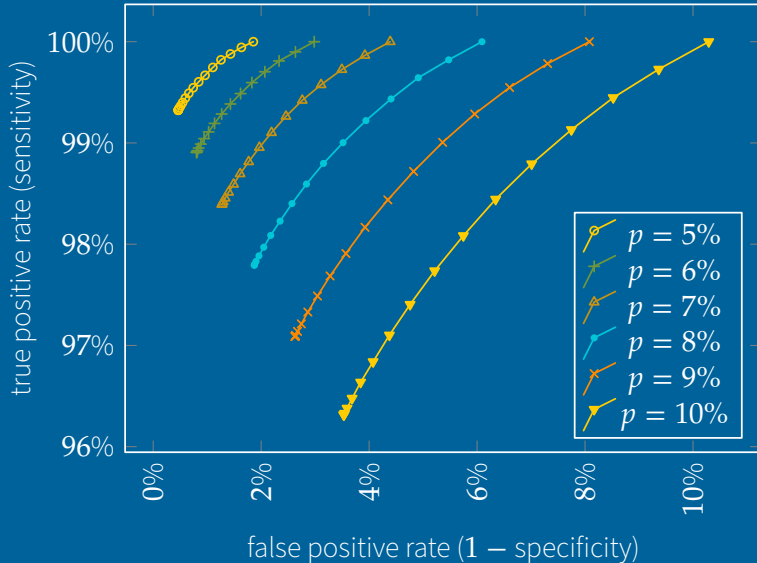
(When optimizing PCR for time, earlier cycles take more time and later cycles take less time.)

Not all single-stranded DNA will be completed; DNA increases **1.9**-fold or **2**-fold.

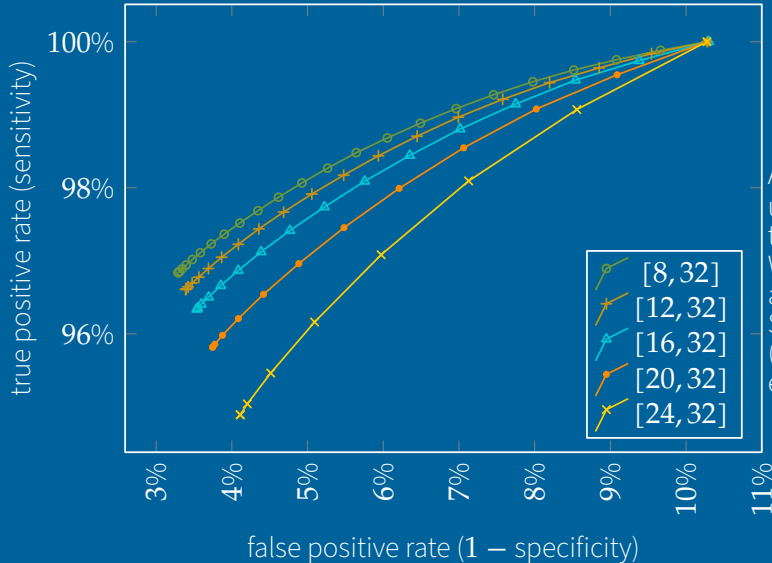
Error introduced independently: Assume tropical addition.

Appendix

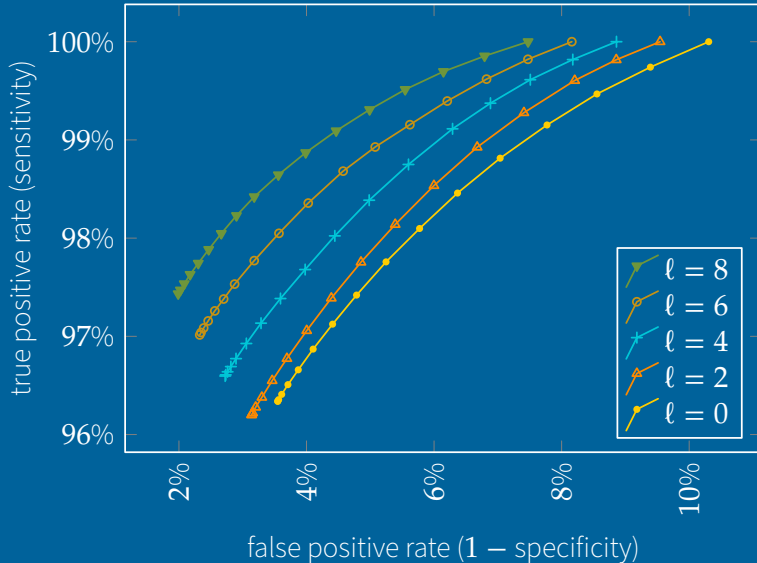
Simulation Plots



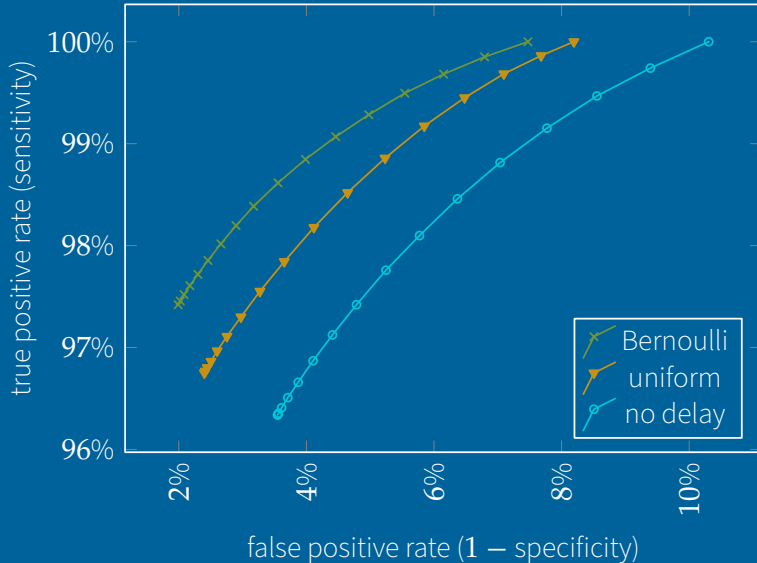
Assume uniform Ct values on the interval $[16, 32]$, 15×35 Kirkman triple system, and no delay ($\ell = 0$). We vary the prevalence rate p and plot the ROC curves.



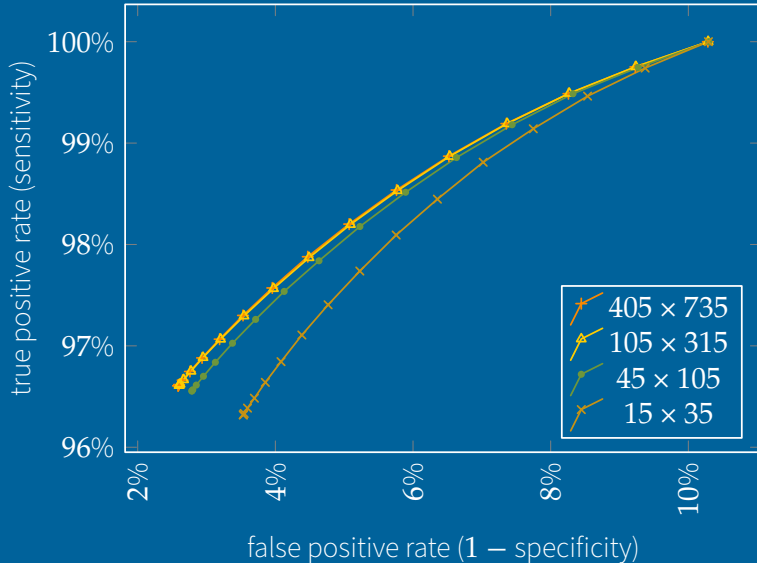
Assume prevalence rate $p = 10\%$, uniform Ct values, 15×35 Kirkman triple system, and no delay ($\ell = 0$). We vary the range of the Ct values and plot the ROC curves. Surprisingly, larger interval (consequently larger variance) is easier to decode.



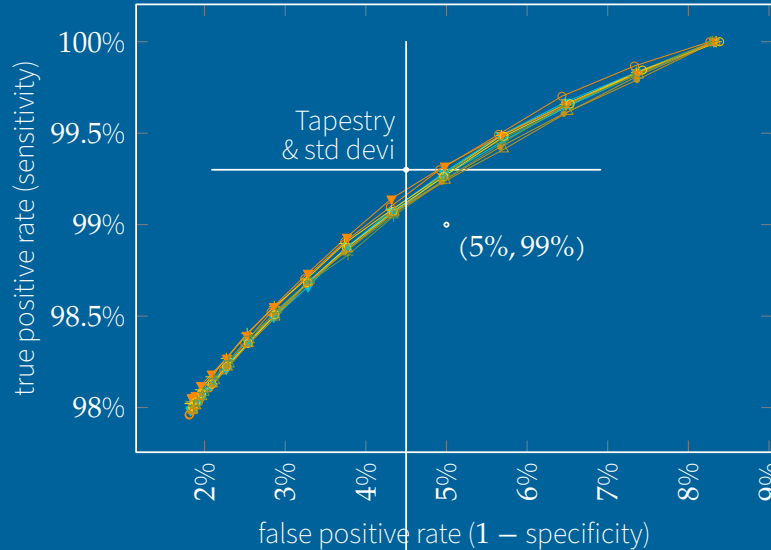
Assume prevalence rate $p = 10\%$, uniform Ct values on the interval $[16, 32]$, 15×35 Kirkman triple system, and $\ell \cdot \text{Bernoulli}(1/2)$ delay. We vary the limit of delay ℓ and plot the ROC curves.



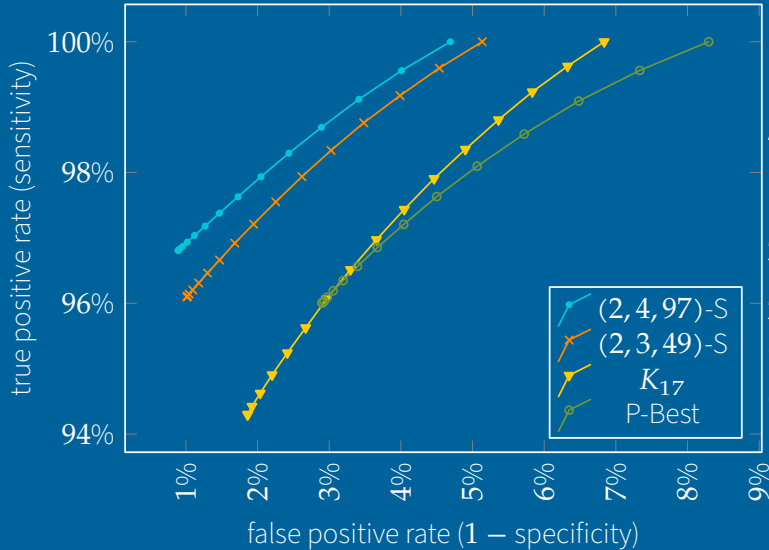
Assume prevalence rate $p = 10\%$, uniform Ct values on the interval $[16, 32]$, 15×35 Kirkman triple system, and $\ell = 8$. We vary the distribution of the random delay δ and plot the ROC curves.



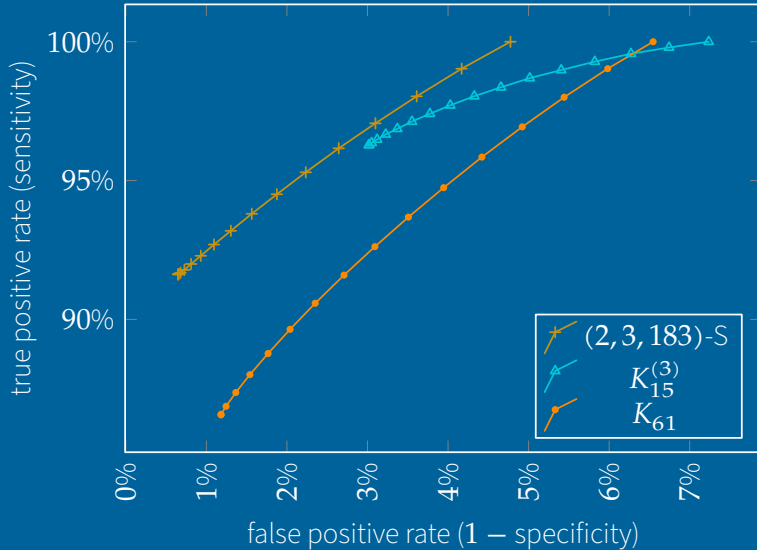
Assume prevalence rate $p = 10\%$, uniform Ct values on $[16, 32]$, and no delay ($\ell = 0$). We consider Kirkman triple systems of different size (after truncation so that the code rate $N/T = 7/3$ is fixed) and plot the ROC curves.



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.

Appendix

Comparison of GT Models

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 | $2^{-\infty}, 2^{-40}, \dots, 2^{-12}$ | $\min(30, 15) = 15$ |
| Semiquantitative | $[0, 3), [3, 6), [6, 9), \dots$ | $[0, 3) + [3, 6) = [3, 9)$ |
| Quantitative | $0, 1, 2, 3, 4, 5, \dots$ | $8 + 9 = 17$ |