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Group Testing for Efficient SARS-CoV-2 Assessment

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Design of Experiments

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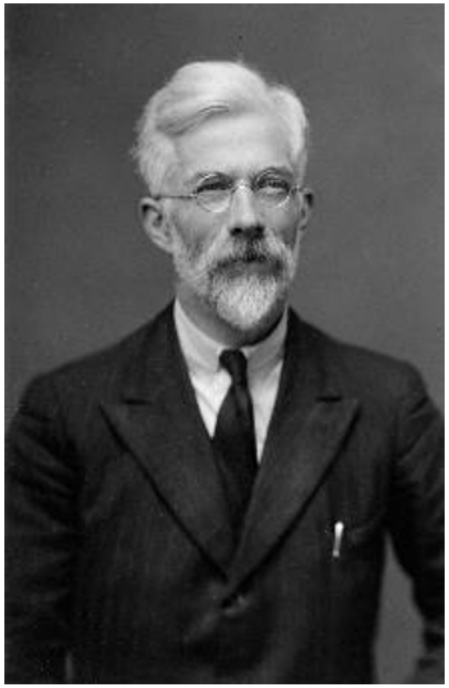
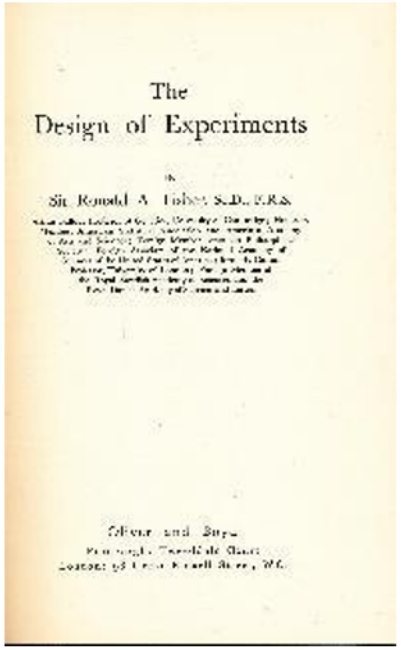


Sir Ronald Fisher
1890-1962


The
Design of Experiments
By
Sir Ronald A. Fisher Sc.D., F.R.S.

More Broadly

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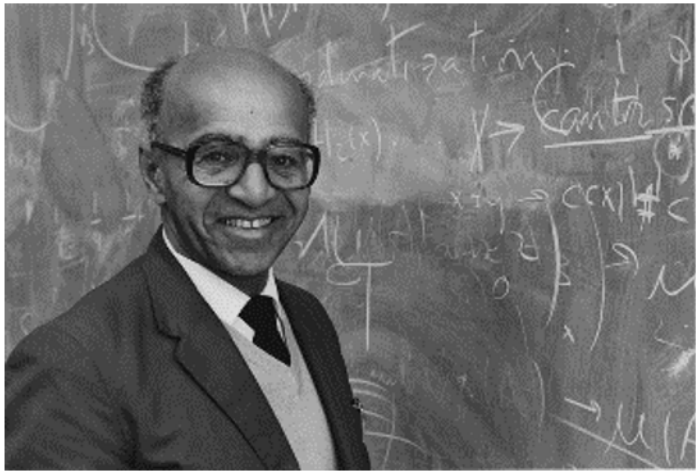
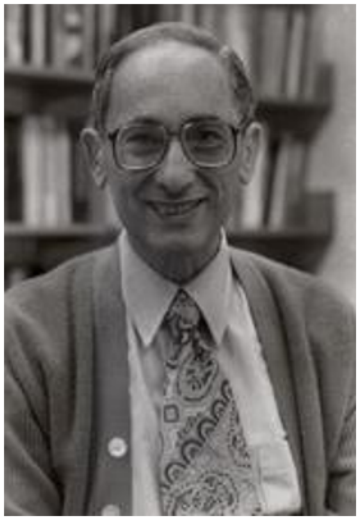


David Blackwell
1890-1962



Herman Chernoff
1923-

Abraham Wald
1902-1950

Classical SPRT

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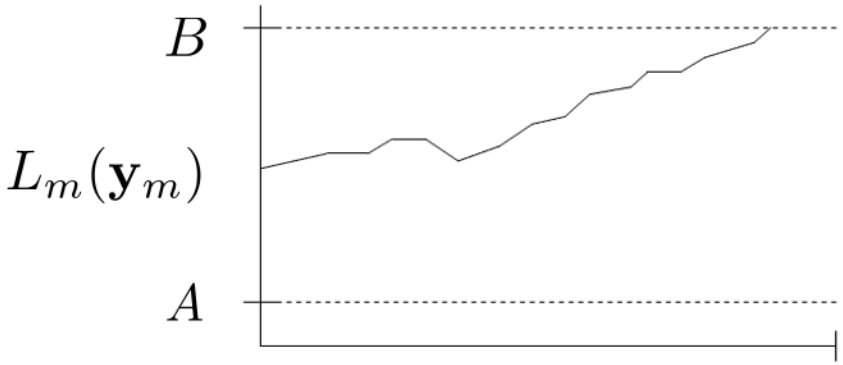
- Sequential probability ratio test
  - A Wald, *The Annals of Mathematical Statistics*, 1945
  - Samples: $\mathbf{y}_m = [y_1, y_2, \ldots, y_m]$
  - Likelihood ratio: $L_m(\mathbf{y}_m) = \dfrac{p_{\mathbf{y}_m|s_1}}{p_{\mathbf{y}_m|s_0}}$
  - Detection rule: $$\delta(L_m(\mathbf{y}_m)) = \begin{cases} s_0, & L_m(\mathbf{y}_m) \le A \\ s_1, & L_m(\mathbf{y}_m) \ge B \\ \text{sample}, & \text{else} \end{cases}$$



same experiment

Controlling Observations

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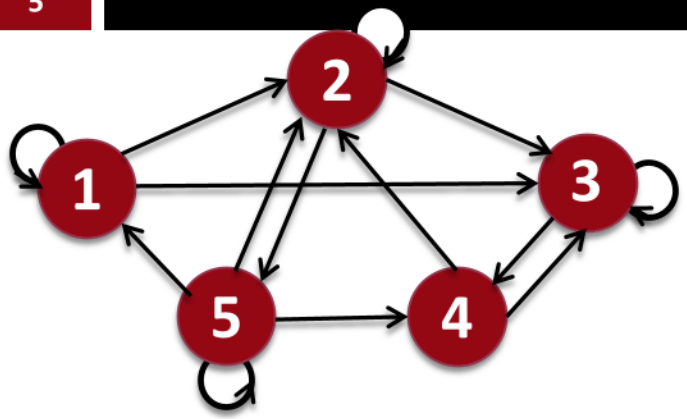

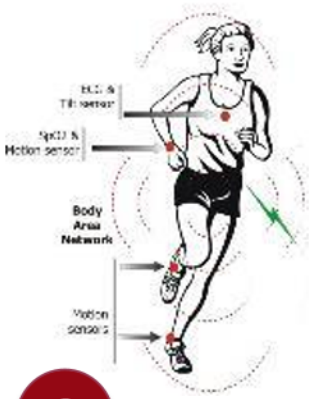

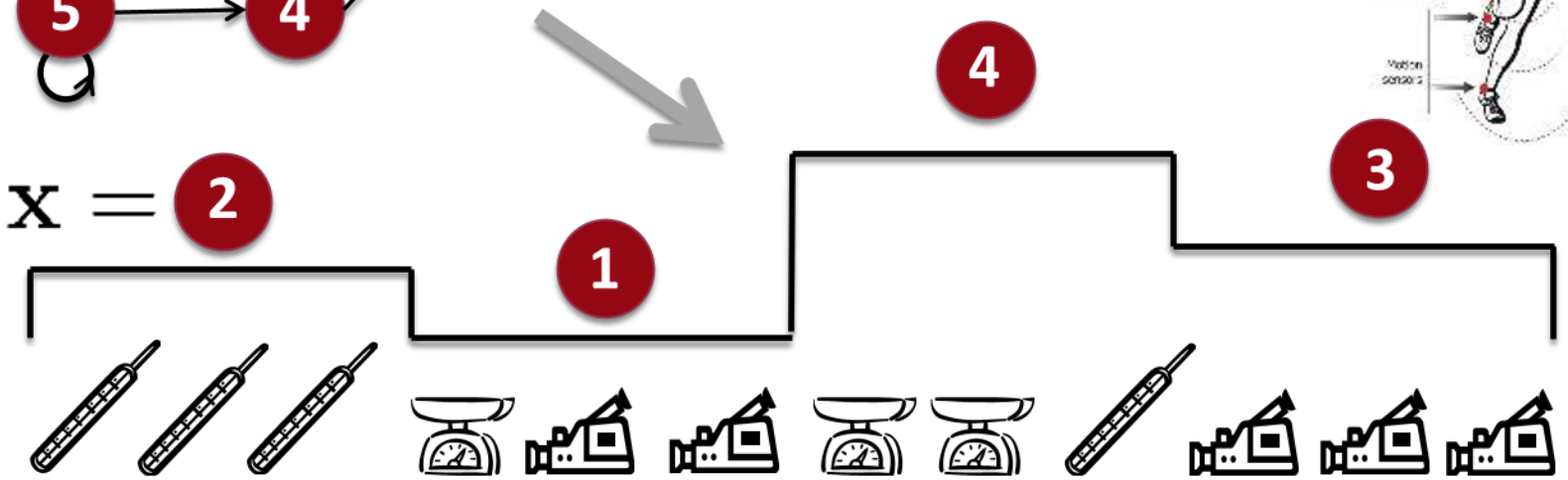

$$\mathbf{y} = f(\mathbf{x}, \mathbf{u}) \rightarrow \hat{\mathbf{x}}$$

observation state, control

active hypothesis testing

Jovanov *et al. Journal of NeuroEngineering and Rehabilitation* 2005

Heterogeneity

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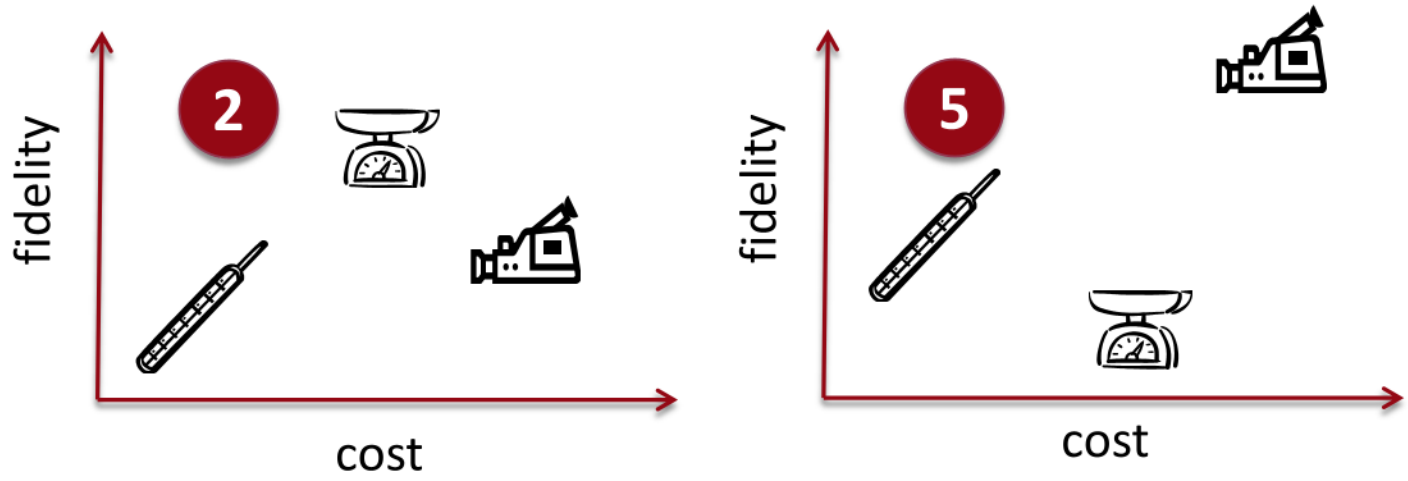

- Different sensors are good at discriminating different states
- True state influences best experiment/observations

The quality of observations

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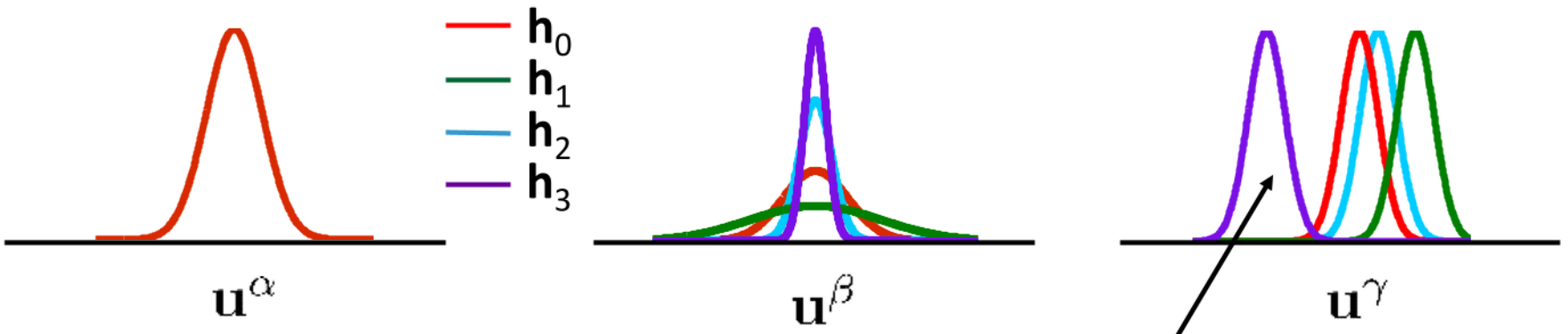
- How to quantify informativeness?



$\mathbf{u}^{\alpha}$ control = choice of experiment

likelihood of a particular hypothesis

- Choice of control makes hypotheses easier to distinguish

Metrics for distributions

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- Relative entropy (Kullback-Leibler distance)

$$
\begin{aligned}
D(p||q) &= \sum_{x \in \mathcal{X}} p(x) \log \frac{p(x)}{q(x)} \\
&\geq 0 \\
D(p||q) &\neq D(q||p)
\end{aligned}
$$

- Not a true distance – does not satisfy triangle inequality, asymmetry…

S. Kullback & RA Leibler, "On information and sufficiency," *Annals of Mathematical Statistics,* 22(1): 79-86, 1951

Active Hypothesis Testing

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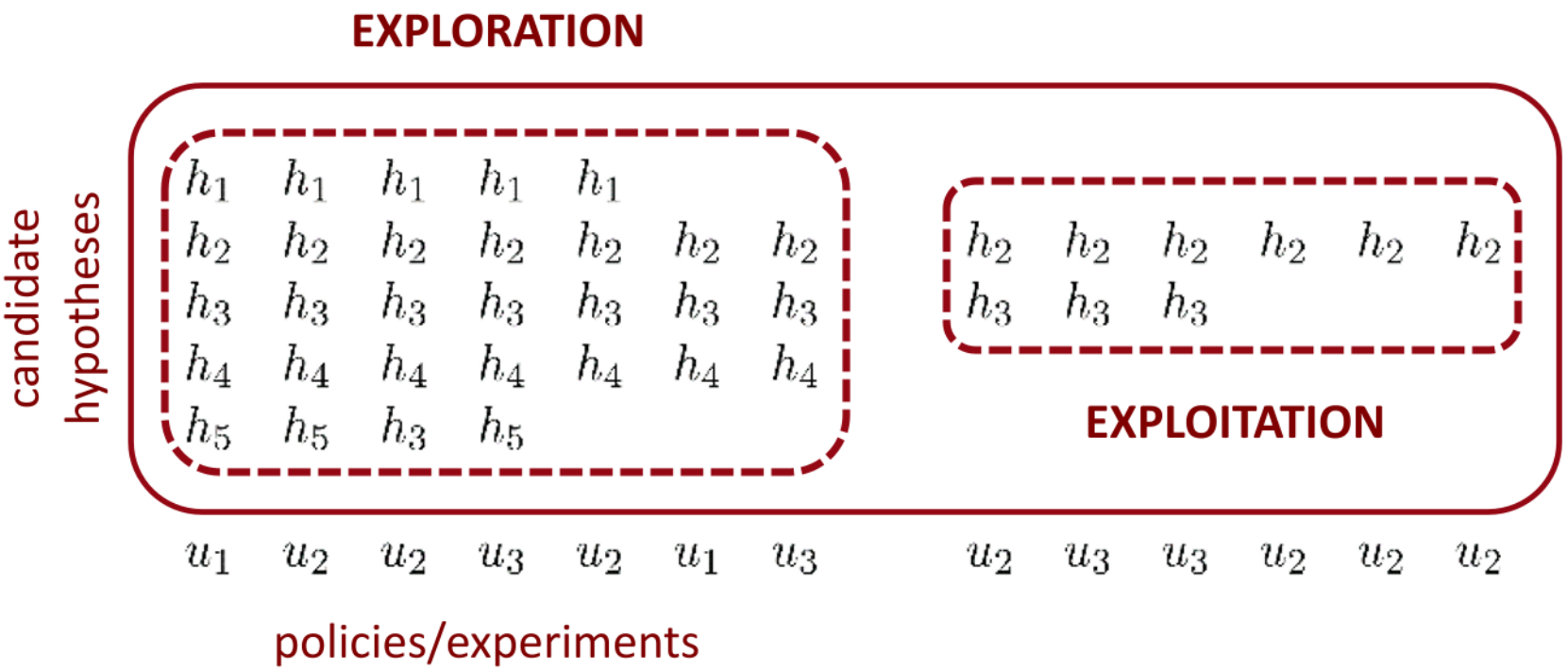

The quality of observations

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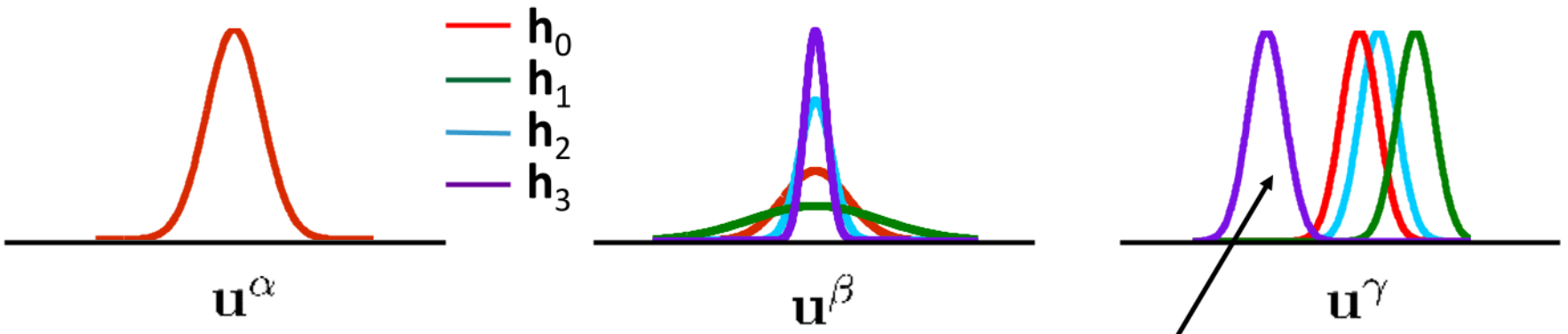

$\mathbf{u}^{\alpha}$ control = choice of experiment

likelihood of a particular hypothesis

- The most informative experiment depends on the true hypothesis

System Model

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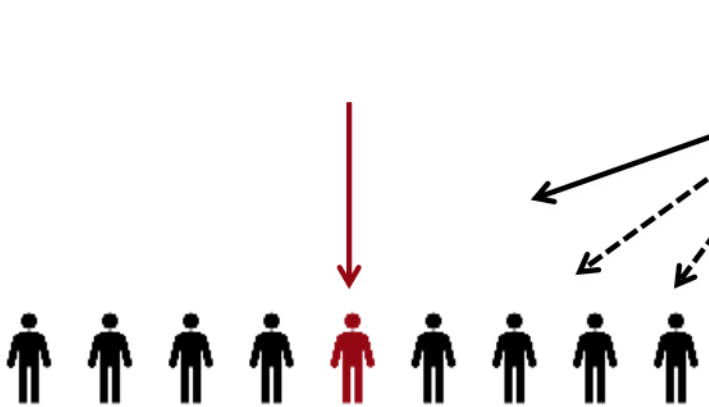


controller decides who to test at each time

one test for each person

M people

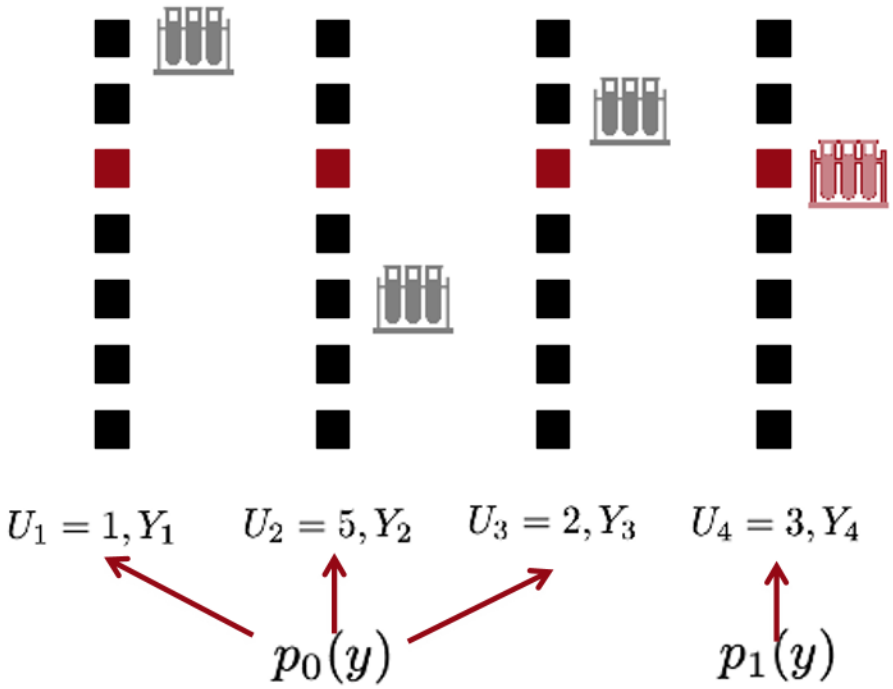
X = true system state

$$X = \begin{cases} 0 & \text{if no anomaly} \\ j & \text{if component } j \text{ anomalous} \end{cases}$$

$$X \in \{0, 1, \ldots, M\}$$

$$M = 7, X = 3$$

System Evolution



Person u

Observation y

conditional density

We assume these are known

We will need to learn these

Goals

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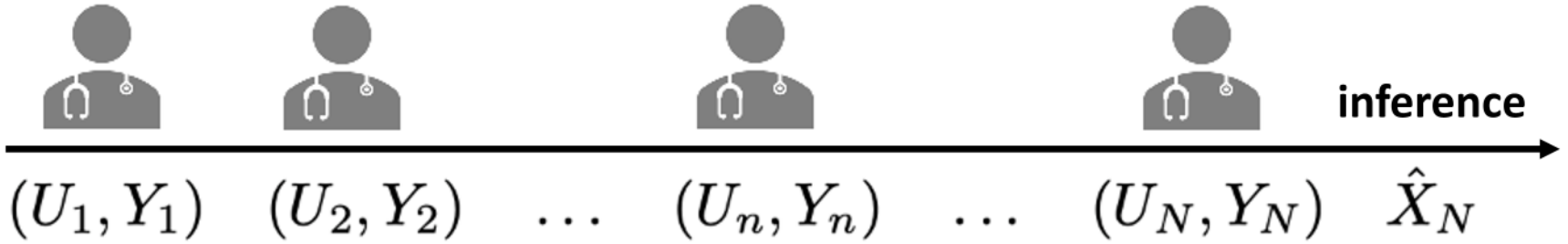
- Experiment Selection Strategy:



$$U_n \sim g_n(I_n)$$

experiment choice – which person to test?

- Inference Strategy: decide **infected** or **not infected**

binary valued inference $\hat{X}_N \sim f(I_{N+1})$

not infected $X = 0$

infected $X \neq 0$

Max-min KL-Divergence

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- Define

α, β distributions

$$D^* \doteq \max_{\alpha \in \Delta\mathcal{U}} \min_{j \in \mathcal{U}} \sum_{u \in \mathcal{U}} \alpha(u) D_j^u$$

argmax: α^*

$$= \min_{\beta \in \Delta\mathcal{U}} \max_{u \in \mathcal{U}} \sum_{j \in \mathcal{U}} \beta(j) D_j^u$$

argmin: β^*

- Lemma: we can compute D*

$$D^* = \left(\sum_{u \in \mathcal{U}} \frac{1}{D_u^u} \right)^{-1}$$

Non-asymptotic Bounds - Symmetric

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- **Theorem:**

Strong converse: from decomposition and
strong converse in Polyanskiy, Poor and Verdu Trans IT 2010

$$-\log \phi_N^* \leq \text{INV}_N\left(\epsilon_N + \frac{\epsilon_N}{\eta}\right) + \log \frac{\eta}{\epsilon_N}$$

$$-\log \phi_N^* \geq \text{INV}_N\left(\epsilon_N - \frac{\epsilon_N}{\eta}\right) - O\left(\log \frac{\eta}{\epsilon_N}\right)$$

function of D*

- **Bounds enable the design of strategies**

INV_N: quantile function of $\bar{Z}_N + D(\beta^* || \tilde{\rho}_1)$

Comparisons

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- Open-loop randomized (**OPE**): asymptotically optimal

  randomly select component from distribution α^*

  uniform in symmetric case

- Deterministic adaptive (**DAS**): also asymptotically optimal

  at each time n, select the component j
  that minimizes $Z_{n-1}(j) - \log \tilde{\rho}_1(j)$

  function of previous observations and experiment choices

- Example setting: two-people and binary observations

Numerical Results

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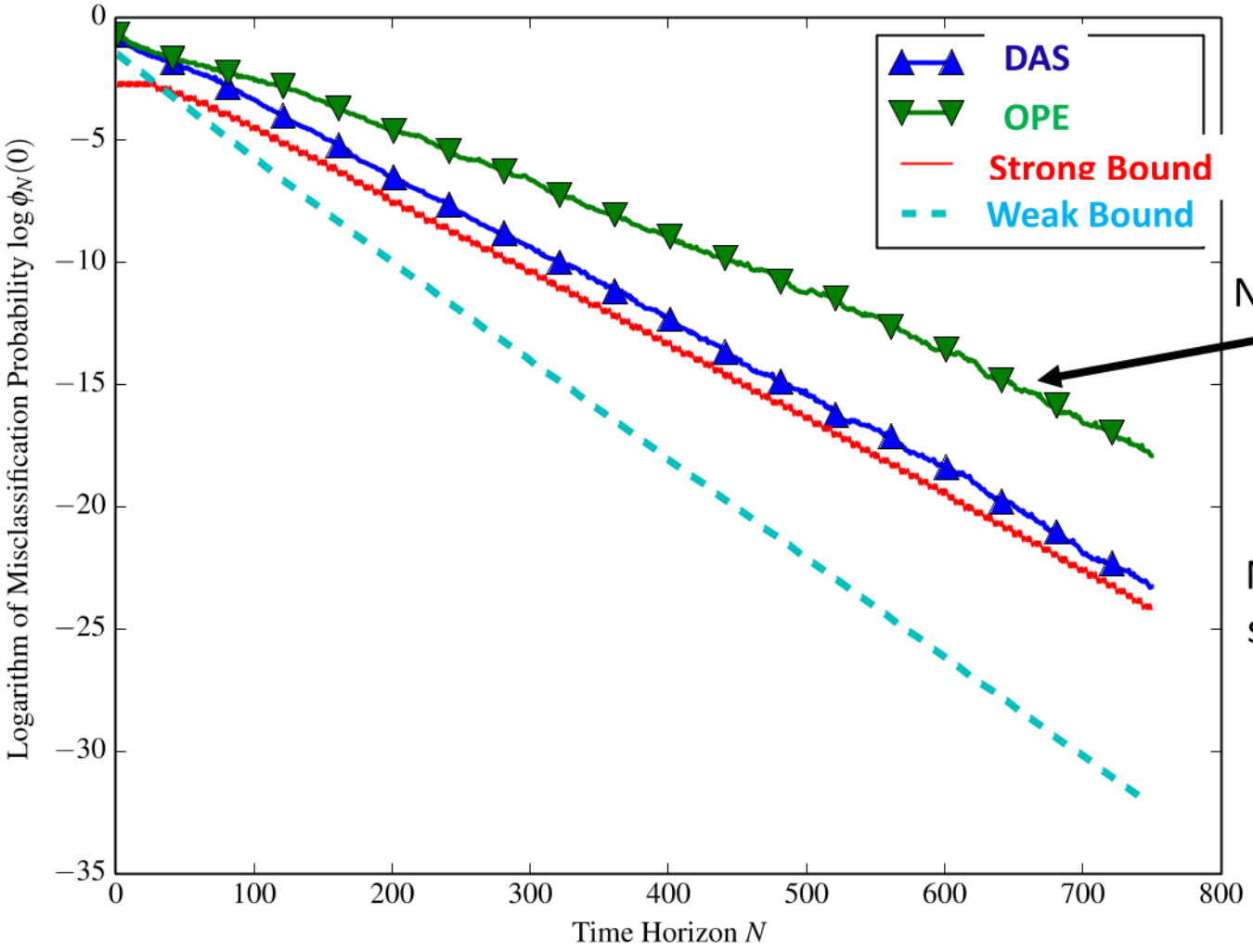

Open-loop:
Not second-order optimal

Need to be adaptive for second-order optimality

Practical SARS-CoV-2 Testing

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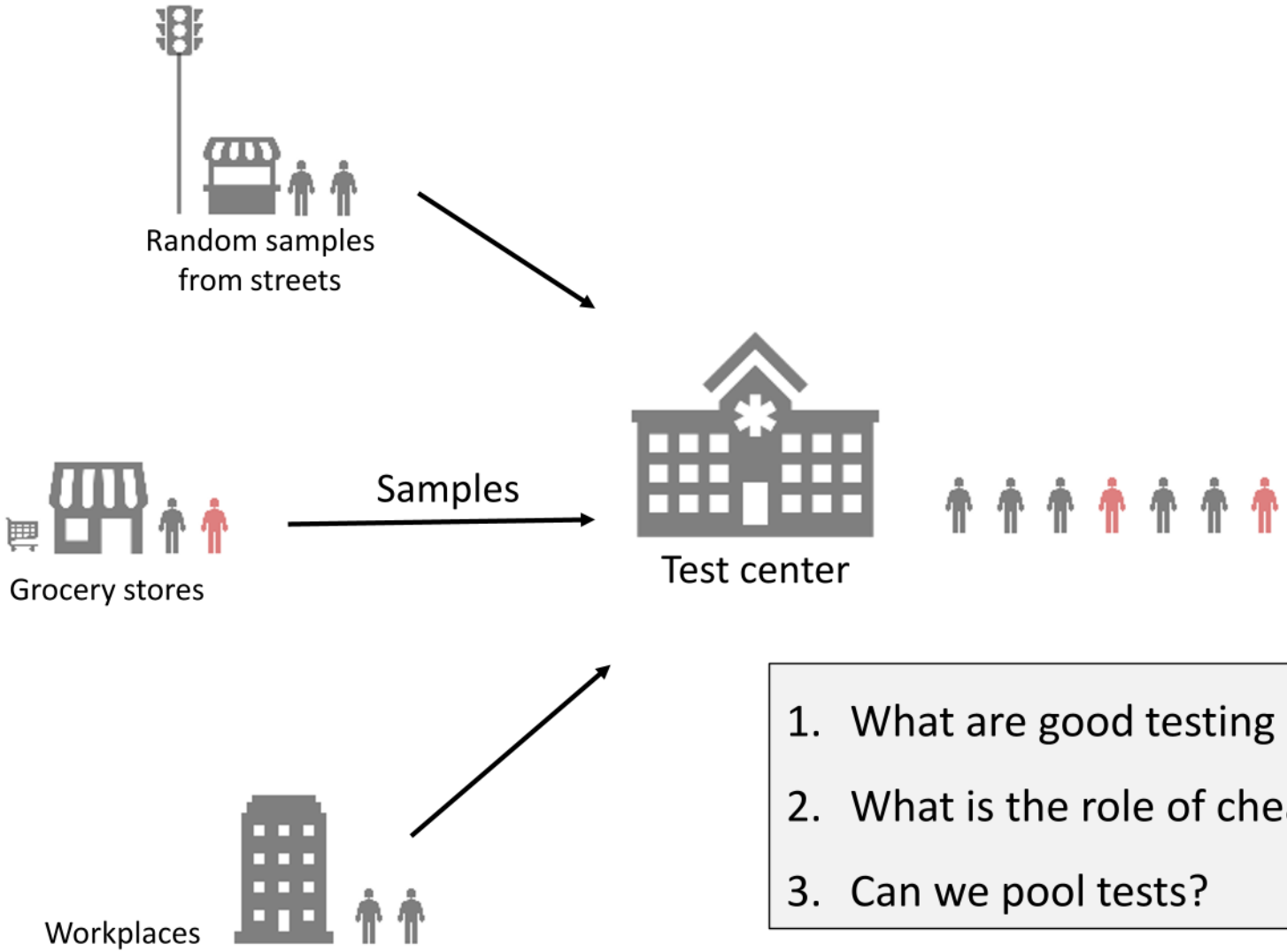

1. What are good testing strategies?
2. What is the role of cheap tests?
3. Can we pool tests?

Practical SARS-CoV-2 Testing

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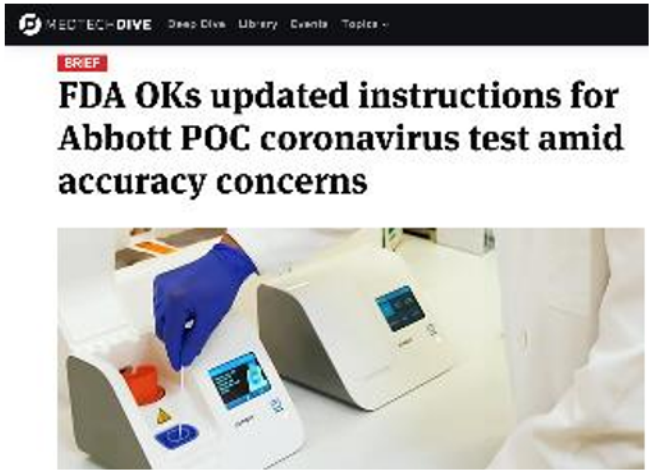
Random samples from streets



Grocery stores

Samples

Test center

Workplaces

1. What are good testing strategies?
2. What is the role of cheap tests?
3. Can we pool tests?

Group Testing – pooling samples

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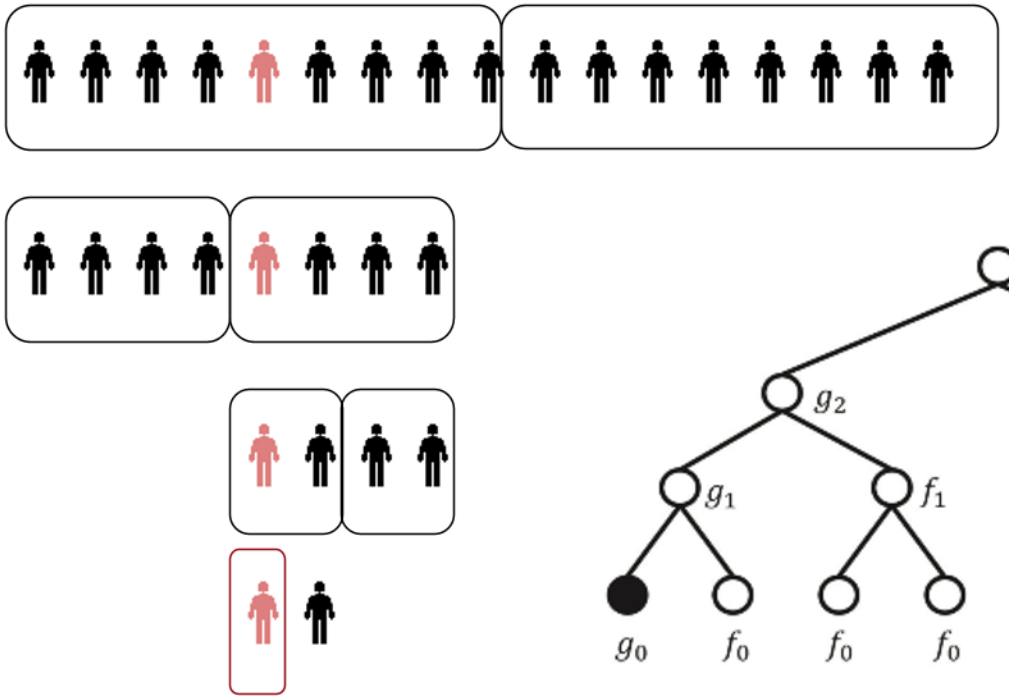
- Used in WW2 to test soldiers for syphilis
  - R. Dorfman, "The Detection of Defective Members of Large Populations," The Annals of Mathematical Statistics, 1943.



- N tests → log (N) tests

Prior Belief: At Most One Anomaly

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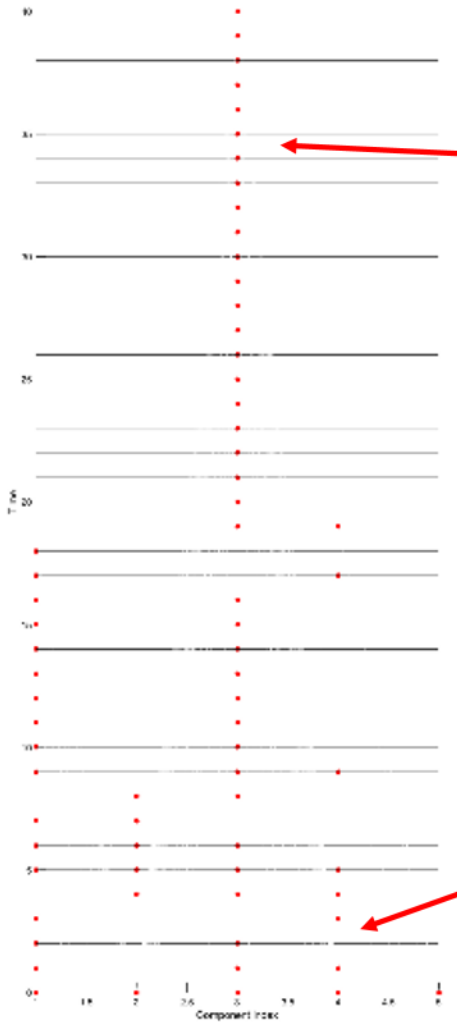
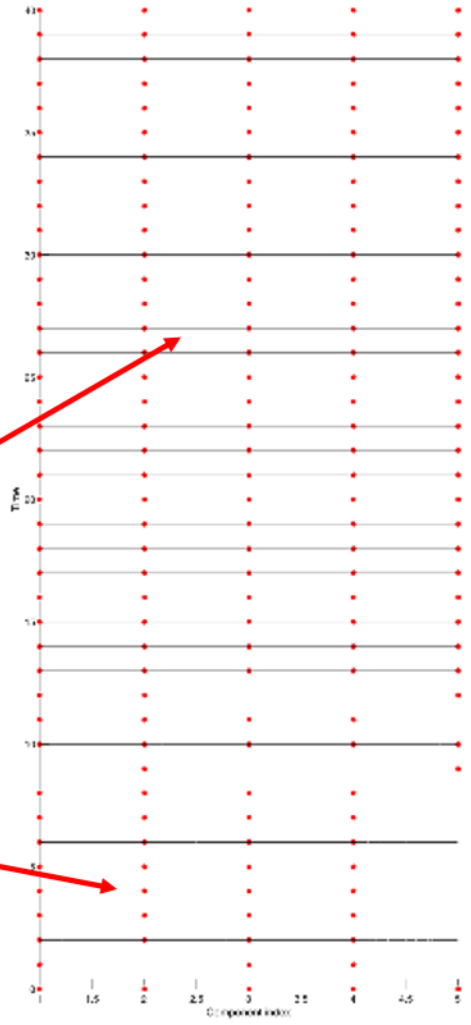


Single anomaly at index 3

Eventually anomaly is localized and sampled for confirmation

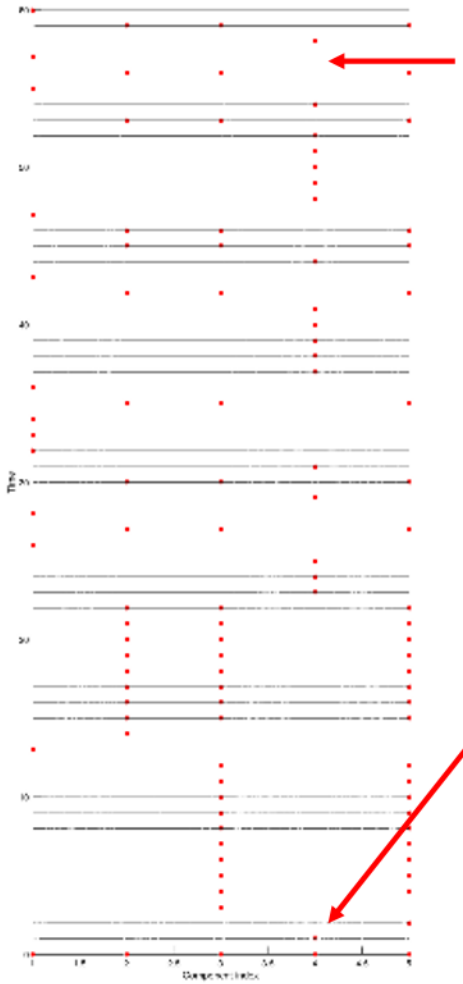
All components grouped together to confirm there is no anomaly

Initial groups aimed at searching



No anomaly

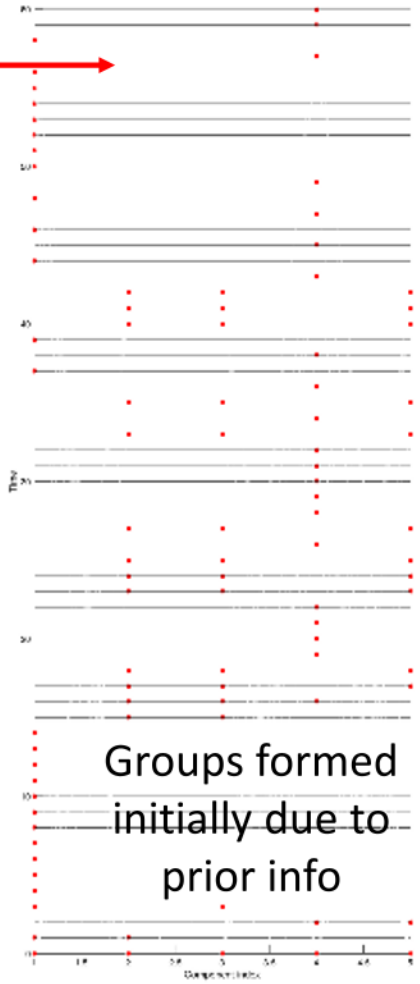
Two Anomalies



Confirmation: normal components are pooled and anomalies are tested individually

Initial tests are individual - known to be optimal with uniform prior - but groups are formed as belief improves

Anomalies at 1 and 4



Prior: Any number anomalous

Prior: At most two anomalous

A single type of test

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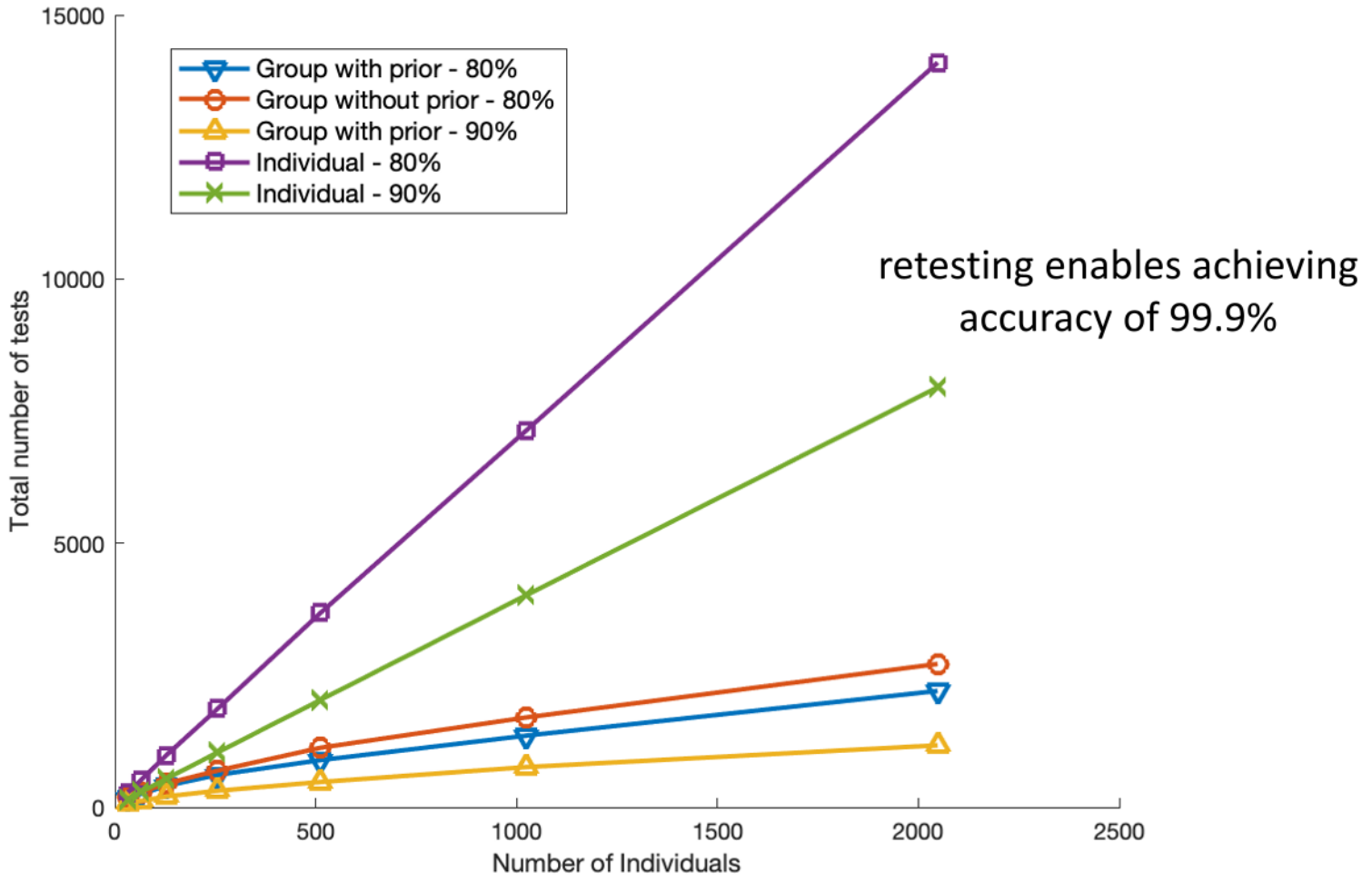

Fully-adaptive Tests

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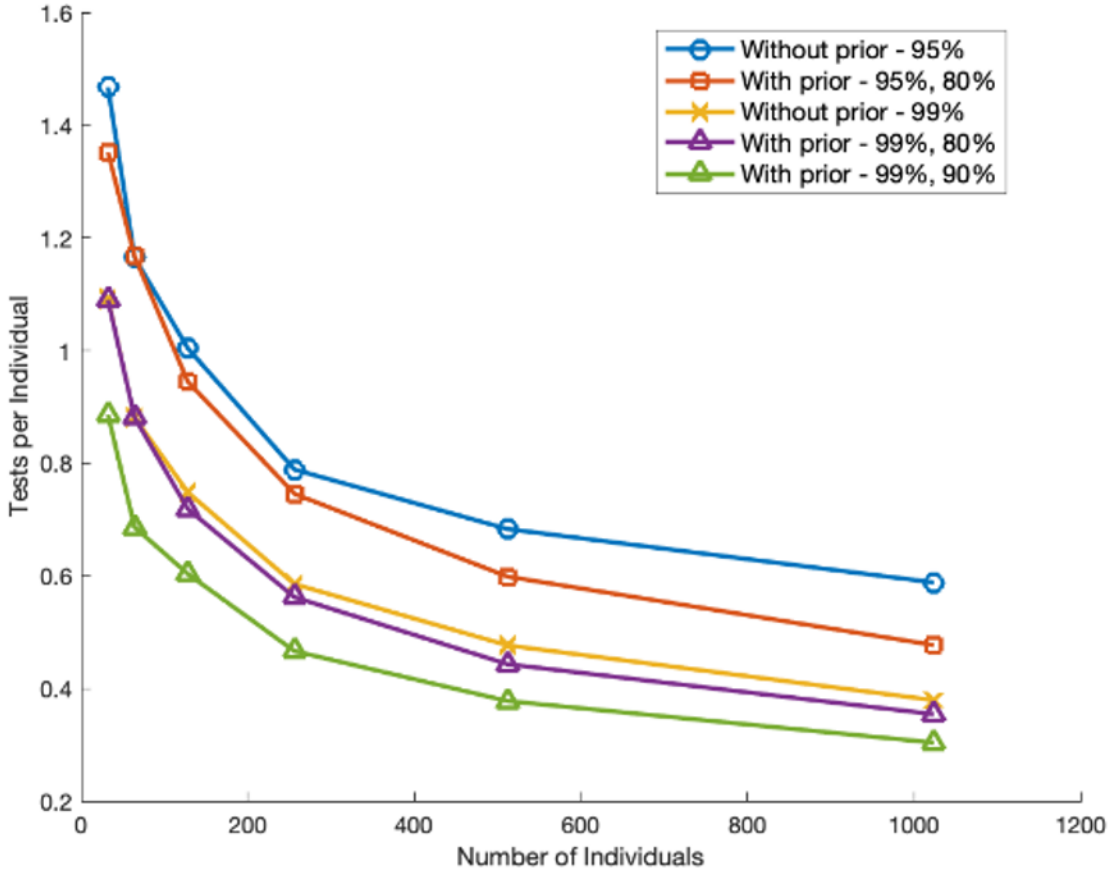


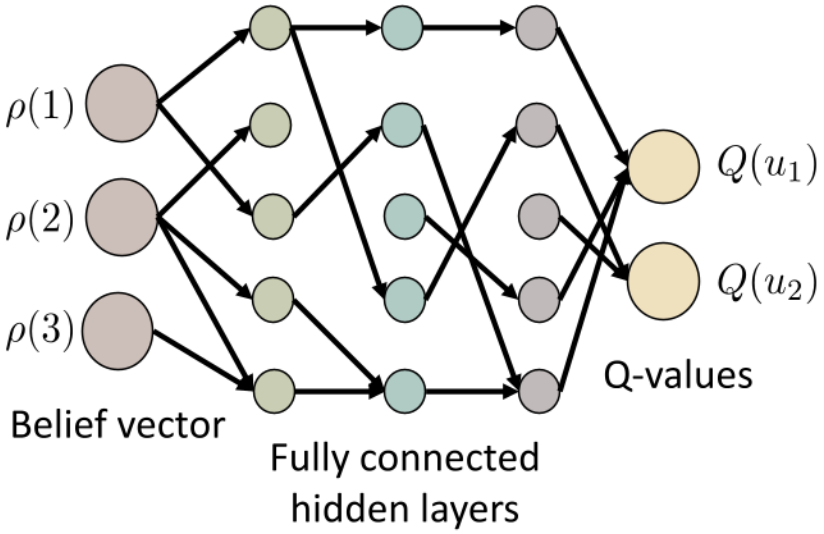
- Perform a cheap test first on each individual – we consider tests with 80% and 90% accuracy
- Use the prior for group testing subsequently
- Can reduce number of group tests by 20%

- Performing cheap tests first better when the cost of cheap test is about 10-15 times smaller

Fully adaptive tests can take a lot of time – need to parallelize

Challenges

- Optimal test design is computationally expensive
- We can exploit machine learning/neural network tools to compute optimal solution



- Have to do this carefully
  - recursive neural networks did not not work
  - Need the output of experiment sequences
- Exploit structural properties of optimal solution to design NN

Deep Q Network

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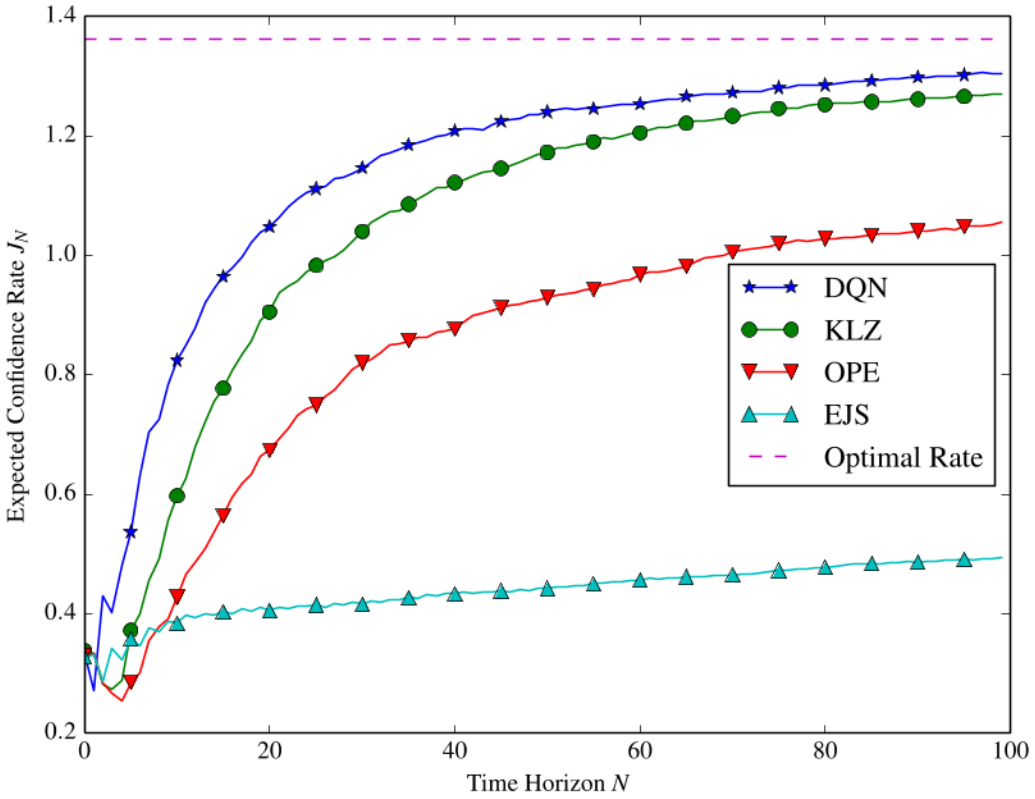
- Evolution of expected confidence under hypothesis h_0 over time

DQN learns the best policy

- **DAS** close to optimal rate
- **OPE** asymptotically optimal but very slow convergence
- **EJS** not optimal



Other Strategies

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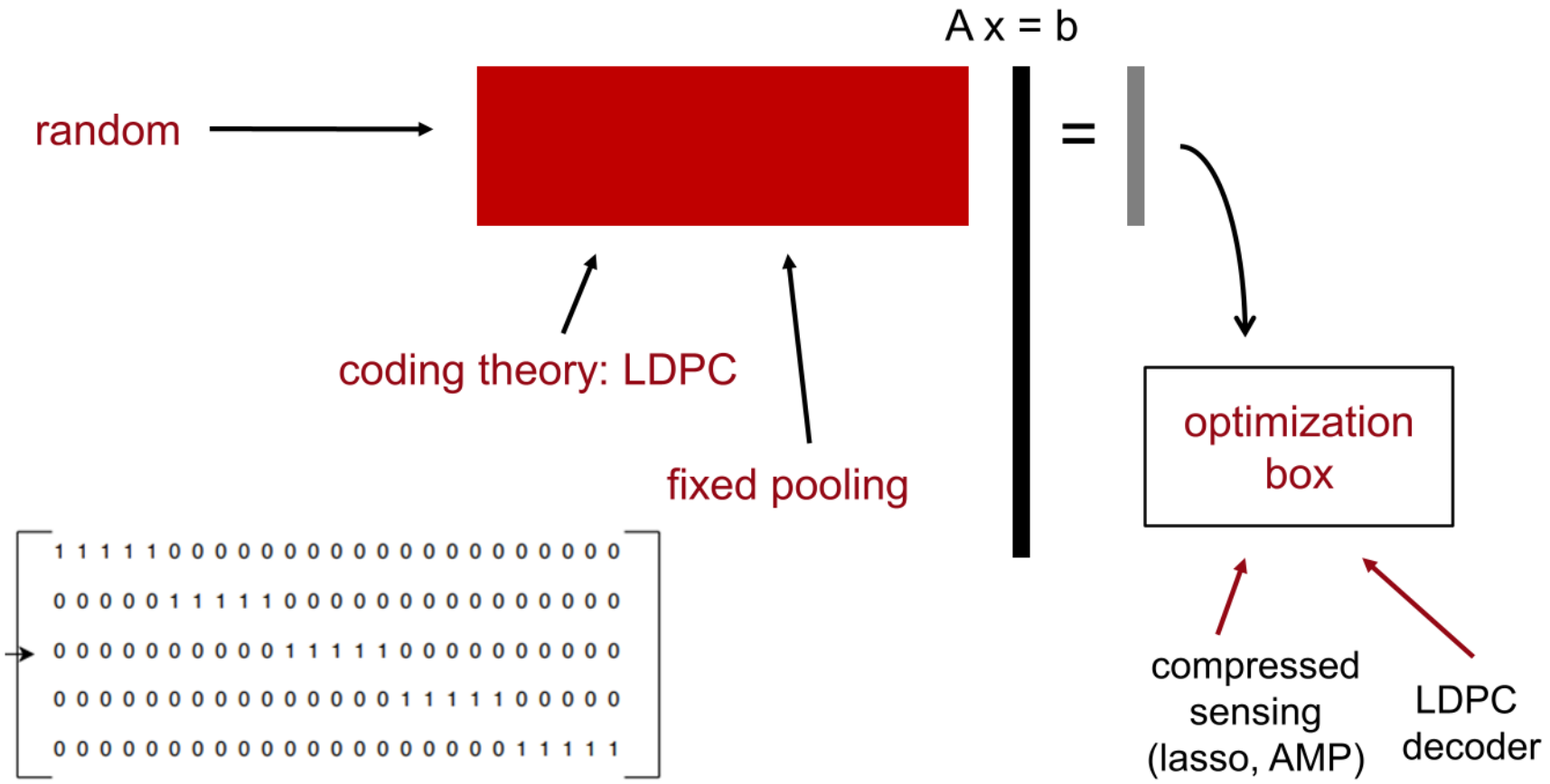

NON-ADAPTIVE, but can be parallelized

Contrasts

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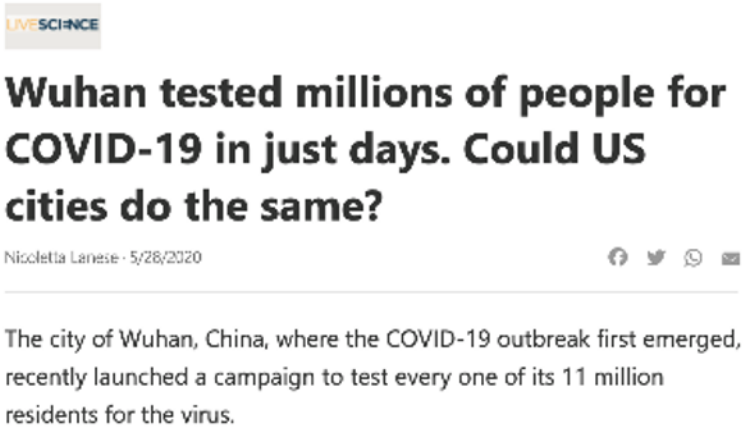
- Our method is data adaptive
  - More challenging to parallelize
- The test matters
  - Serological tests are blood based – easy to pool?
- Gold standard: PCR (polymerase chain reaction)
  - For SARS-CoV-2 test on RNA
  - Can parallelize

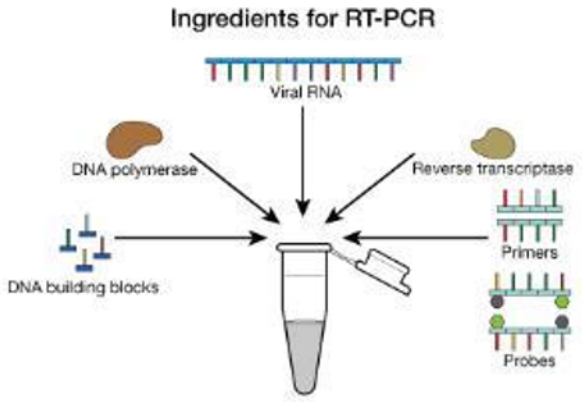


LIVESCIENCE

Wuhan tested millions of people for COVID-19 in just days. Could US cities do the same?

Nicoletta Lanese · 5/28/2020

The city of Wuhan, China, where the COVID-19 outbreak first emerged, recently launched a campaign to test every one of its 11 million residents for the virus.



Mayo Clinic explainer

Contrasts

USC Viterbi

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- Gold standard: PCR (polymerase chain reaction)
  - For SARS-CoV-2 test on RNA
  - Can parallelize


UCSF

Testing the Tests: COVID-19 Antibody Assays Scrutinized for Accuracy by UCSF, UC Berkeley Researchers


NEWS | CORONAVIRUS (COVID-19) | JUNE 10, 2020

COVID-19 Genetic PCR Tests Give False Negative Results if Used Too Early

A new study confirms what many suspected, that PCR testing even 8 days after infection shows 20 percent false positives

June 10, 2020 — In a new study, Johns Hopkins researcher
testing people for SARS-CoV-2 (COVID-19) too early in the course of infection is likely to result in a false negative test, even though they may eventually test positive for the virus.[1] This is important to understand since many hospitals are using these COVID tests to screen patients before imaging exams, diagnostic testing or procedures.

Conclusions

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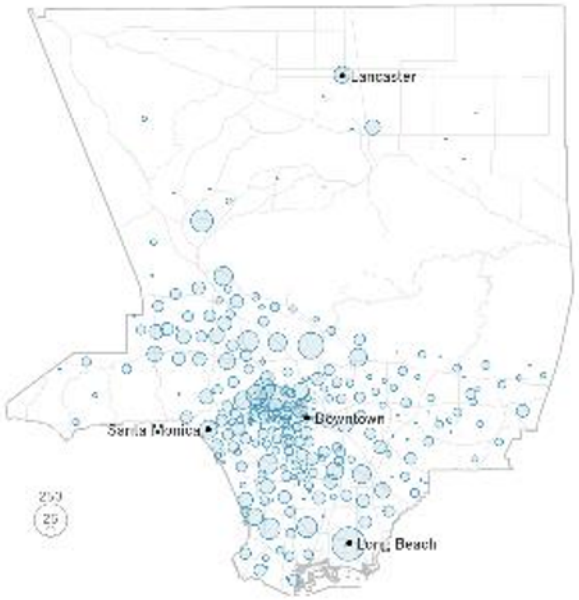
- Optimized solutions for a finite number of observations/tests
  - Not asymptotics as in traditional methods
- We can design for both the exploration and the exploitation phases
- We can accommodate different kinds of information
  - Prior medical history, outcomes of other measurements (temperature, symptoms)
  - We can accommodate different kinds of SARS-CoV-2 tests, each with different efficacies
- Optimal testing for hot spots?
- Challenges
  - Complexity
  - Unknown onset
  - Parallelization



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