ABSTRACT. An important component of every country’s COVID-19 response is fast and efficient testing — to identify and isolate cases, as well as for early detection of local hotspots. For many countries, producing a sufficient number of tests has been a serious limiting factor in their efforts to control COVID-19 infections. Group testing is a well-established mathematical tool, which can provide a serious and rapid improvement to this situation. In this note, we compare several well-established group testing schemes in the context of qPCR testing for COVID-19. We include example calculations, where we indicate which testing architectures yield the greatest efficiency gains in various settings. We find that for identification of individuals with COVID-19, array testing is usually the best choice, while for estimation of COVID-19 prevalence rates in the total population, Gibbs–Gower testing usually provides the most accurate estimates given a fixed and relatively small number of tests. This note is intended as a helpful handbook for labs implementing group testing methods.

1. INTRODUCTION

Group testing is a standard technique for testing a population for a disease with a low incidence rate, while using fewer tests than if every individual were tested. This schema goes back to at least 1943, when Dorfman [Dorfman] proposed screening prospective soldiers for syphilis by using two-stage hierarchical group testing. Over the ensuing decades, the theory of group testing has been extensively developed, as surveyed in [Hughes-Oliver].

A basic example might proceed like this: instead of using 15 tests for 15 people, use 10 tests for 10 pooled groups of 5 individual samples each. If, on average, only one of those 10 groups is positive, the remaining 5 tests could be used to test the individual samples in that positive group. Therefore, in this example, 15 tests could reach 50 people on average instead of only 15. In general, when the incidence rate of the disease is low and the test is accurate, this method can provide accurate results while using many fewer tests.

If the number \( T \) of tests at our disposal is fixed, the number of individuals that we can test depends on the incidence rate. Several groups have worked out the optimal pooling architecture in various settings. One notable example is the \( \mathbb{R} \) package binGroup [binGroup], which can systematically deduce the optimal testing architecture.

In this note, we provide some sample calculations, using current estimates for coronavirus infection rates, to illustrate how pooled testing can help, both at the individual level and the population level — that is, both to tell whether a particular person has coronavirus, and to monitor the overall prevalence rate in the population.

This note is intended as a helpful guide for labs implementing group testing methods. The authors are happy to help any lab interested in leveraging these techniques to design optimal architectures given local constraints.

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2. Individual testing

2.1. Architectures.

2.1.1. Dorfman testing (i.e. simple 1-layer group testing). Perhaps the simplest version of group testing is simple 1-layer group testing. This was first suggested by Dorfman in 1943 as a method for screening military recruits for syphilis [Dorfman], so we refer to this method as Dorfman testing.

We begin with an overview of Dorfman testing. Suppose that we have a population of \( n \) individuals, and we would like to determine, using the minimal number of tests, whether each individual is positive or negative for a given disease. We proceed as follows:

1. Group the individuals into \( n/b \) batches of \( b \).
2. For each batch, mix the samples into a single pooled sample.
3. Using \( n/b \) tests, test these pooled samples.
4. For each pooled sample which tests negative, we deduce that all of the individuals in the corresponding batch are negative. For each pooled sample which tests positive, we use \( b \) tests to test each individual in the corresponding batch.

When the incidence rate is low, Dorfman testing will use fewer tests than \( n \), which is the number of tests that we would use if we followed a non-grouped approach and tested every individual.

The optimal batch size \( b \) has been studied in [Dorfman] and [Williams], among others. Making no claims of originality, we now derive the optimal choice of \( b \), supposing that the incidence rate is \( \rho \). The likelihood of a given batch containing at least one positive individual is

\[
P := 1 - (1 - \rho)^b,
\]

hence the expected number of positive batches will be

\[
\sum_{i=0}^{n/b} i \left( \binom{n/b}{i} P^i (1 - P)^{n/b - i} \right) = \frac{n}{b} P = \frac{n}{b} \left( 1 - (1 - \rho)^b \right).
\]

The expected number of tests is therefore

\[
T(b) := n \left( \frac{1}{b} + (1 - (1 - \rho)^b) \right).
\]

The minimum is achieved at

\[
b_0 = \frac{2W_0 \left( -\frac{1}{2} \sqrt{-\log(1 - \rho)} \right)}{\log(1 - \rho)} \\
\approx \frac{1}{\sqrt{\rho}} - \frac{1}{2} + \frac{1}{\sqrt{8\rho}} + \frac{1}{3\rho} + \cdots,
\]

where \( W_0 \) denotes the principal branch of the Lambert W-function (i.e. the product logarithm), and this minimum value is

\[
T(b_0) = \left( 1 - \exp \left( 2W_0 \left( -\frac{1}{2} \sqrt{-\log(1 - \rho)} \right) \right) \right) \frac{\log(1 - \rho)}{2W_0 \left( -\frac{1}{2} \sqrt{-\log(1 - \rho)} \right)} n \\
\approx \left( 2\sqrt{\rho} - \frac{1}{2} \rho + \frac{5}{12} \rho \sqrt{\rho} - \frac{7}{24} \rho^2 + \cdots \right) n \\
\approx 2\sqrt{\rho} \cdot n.
\]

Note in particular that \( b_0 \) depends only on \( \rho \), not on \( n \) (!).

We note that when there are significant rates of false positives or false negatives, the optimal batch size and expected number of tests may differ substantially from the formulas we have derived here. This situation has been considered in [HanelThurner].
2.1.2. Early stopping. There is a well known modification of Dorfman testing that was suggested by Sterrett [Sterrett]. It is based on the assumption that when a batch turns out positive, most likely only few individuals in the batch are positive. The method follows Steps 1–3 of Dorfman’s approach identically (see Section 2.1.1), however proceeds differently with each pooled sample:

(1) For each pooled sample which tests negative, we deduce that all of the individuals in the corresponding batch are negative.

(2) For each pooled sample which tests positive, we consecutively test the \( b \) individuals in the corresponding batch.

(3) If the test of the sample of the \( i \)-th individual is negative, move to the next individual. If the test is positive, pool the remaining \( b - i \) samples, and repeat the process with this new pooled sample.

While it is harder to find formulas for the optimal batch size \( b \) and the expected number of tests per hundred people, Sterrett computed them for many useful values of the incidence rate \( \rho \). Berrett’s approach offers moderate savings over Dorfman’s in the number of tests. On the other hand, it is a more complicated process, and takes longer to complete the tests, because the individuals in positive batches need to be tested sequentially. This becomes more and more important the larger the batch size \( b \).

2.1.3. Array testing. Finally, we mention an alternative to the simple or hierarchical procedures described above: array testing. In the simplest variant — described, for instance, as the \( d = 2 \) case in [Hughes-Oliver, §2] — the population is arranged in a 2-dimensional array with \( \sqrt{n} \) rows and \( \sqrt{n} \) columns. Each row is tested, and each columns is tested, using a total of \( 2\sqrt{n} \) tests. If either the \( i \)-th row or the \( j \)-th column both test negative, then we can conclude that the \((i, j)\)-th individual is negative. There are two variants regarding how to treat the individuals whose row and column both test positive:

(1) Test each such individual, thus establishing precisely which individuals are positive.

(2) Presume that each such individual is positive, reducing the total number of tests used at the expense of a modest (so long as \( \rho \) is small) rate of false positives.

We now calculate, in variant (1), the total number of tests used. To test all rows and columns, we use \( 2\sqrt{n} \) tests. To determine the number of tests used in the next stage, we must compute the expected number of pairs \((i, j)\) such that the \(i\)-th row and the \(j\)-column both test positive. We can approximate this by assuming that the number of positive rows and the number of positive columns are independent:

\[
\left( \left( 1 - (1 - \rho)\sqrt{n} \right) \sqrt{n} \right)^2 = \left( 1 - (1 - \rho)\sqrt{n} \right)^2 n.
\]

It follows that an approximation for the expected total number of tests is

\[
2\sqrt{n} + \left( 1 - (1 - \rho)\sqrt{n} \right)^2 n.
\]

A somewhat more sophisticated version of array testing, which we might call batched array testing, proceeds as follows:

(1) Divide the population of \( n \) individuals into \( n/b \) batches of \( b \) individuals.

(2) Apply array testing to each batch.

The advantage of array testing is that the quantity (6) is not of the form \( f(\rho)n \), so by choosing \( b \) carefully, we can optimize the number of individuals tested per test.
2.2. Examples. The most important features in determining which group testing architectures are best suited to a given testing scenario are:

- the positive rate $\rho$ of the test population;
- the false positive rate $f_p$ of the test;
- the false negative rate $f_n$ of the test; and
- the time and cost to run each leg of the test.

We begin with an overview of the current values of these parameters for the COVID-19 qPCR assay, which is a common way to test for active COVID-19 infections. In the all of the pooling schemes we will discuss below, we assume just one swab is taken from each patient, and all sub-samples we refer to are subsamples of the liquid that is held in the lab. We thank Joshua Batson for help collecting this information [Batson].

- For COVID-19, a wide range of test population positive rates $\rho$ are being observed around the world. In April 2020, $\rho$ values vary greatly from one community to another, and values from 0.1%–10% are commonly observed.
- The false positive rate of the COVID-19 qPCR assay is very low, and in this note we do not discuss variations on group testing that are designed to address false positives.
- The false negative rate of the COVID qPCR assay can be high — as high as 30%. However, false negatives are overwhelmingly due to lack of virus on the swab collected, and the false negative rate due to lab error is low. Therefore, in this note we also do not discuss variations on group testing that are designed to address false negatives.
- In the COVID-19 qPCR assay, a nasal swab is taken from the patient and then the sample is sent to a lab. There it is immersed in liquid, and a sample of the liquid is plated. Then the RNA is extracted (this might take 1–2 hours) and PCR is run (another 1–2 hours).

Next, we do some example calculations comparing optimal tests for different variations on the Dorfman method for three hypothetical COVID-19 testing labs, with expected $\rho$ values of 3 in 10, 3 in 100, and 3 in 1000. We do not consider variations designed to address false positives and false negatives, because for COVID-19 testing, false positive and false negative rates are low.

| architecture          | optimal batch size | individuals tested per test |
|-----------------------|--------------------|-----------------------------|
| $\rho = 0.3$          |                    |                             |
| simple Dorfman        | 3                  | 1.01                        |
| Sterrett testing      | 2                  | 1.11                        |
| batched array testing | N/A                | < 1                         |
| $\rho = 0.03$         |                    |                             |
| simple Dorfman        | 6                  | 3.03                        |
| Sterrett testing      | 9                  | 3.70                        |
| batched array testing | 153                | 3.84                        |
| $\rho = 0.003$        |                    |                             |
| simple Dorfman        | 19                 | 9.09                        |
| Sterrett testing      | 30                 | 12.50                       |
| batched array testing | 2694               | 16.84                       |

3. Prevalence estimation

In the previous section, we focused on the goal of using group testing to classify whether each individual in a population has a certain disease. On the other hand, there are situations where we merely want to estimate the proportion of infected individuals.
In this section, we focus on the latter problem. Just as for classification, we will see that batching tests can be a valuable tool for the estimation problem. In fact, group testing can be even more effective in this setting, because we can estimate the number of positive individuals in a positive group without further testing each individual in the group.

### 3.1. Description of a simple group-testing algorithm for the estimation problem.

We now describe the simplest way to apply group testing to the estimation problem. This method was first proposed by Gibbs–Gower \[\text{GibbsGower}\] in 1960 (by the name “multiple-transfer method”) \[\text{GibbsGower}\], and further studied by Thompson in 1962 \[\text{Thompson}\]. We refer to \[\text{Hughes-Oliver, § 3.1.2}\] for further review of the literature.

Suppose that we have a population of \(n\) individuals, which we divide into \(n/b\) groups of \(b\) individuals. Denote the true incidence rate by \(p\). The likelihood that a given group has at least one positive individual is then:

\[
P := 1 - \left(1 - p\right)^b.
\]

Next, we test \(t \leq n/b\) of the groups. Denoting the number of groups testing positive by \(t_+\), we obtain an estimate

\[
\hat{P} := \frac{t_+}{t}
\]

for \(P\), and an estimate

\[
\hat{p} := 1 - \left(1 - P\right)^{1/b}
= 1 - \left(1 - \frac{t_+}{t}\right)^{1/b}
\]

for \(p\).

The estimate \(\hat{p}\) is biased, and more precisely an overestimate (when \(b > 1\)) with expected value

\[
E(\hat{p}) = 1 - \sum_{i=0}^{t} \binom{i}{t} \binom{t}{i} \left((1 - p)^b\right)^i (1 - (1 - p)^b)^{t-i}.
\]

The mean squared error (MSE) of the estimate is given by

\[
E((\hat{p} - p)^2) = \sum_{i=0}^{t} \binom{i}{t}^2 \binom{t}{i} \left((1 - p)^b\right)^i (1 - (1 - p)^b)^{t-i} + (p - 1)(p + 1 - 2E(\hat{p})).
\]

An approximation of this is the asymptotic variance

\[
\frac{1 - (1 - p)^b}{tb^2(1 - p)^{b-2}}.
\]

When \(b = 1\), the expected value is \(E(\hat{p}) = p\), and the MSE specializes to

\[
E((\hat{p} - p)^2) = \frac{p(1 - p)}{t}.
\]

### 3.2. Examples.

In this section, we consider several choices of prevalence rates, and compare the accuracy of the estimate produced the standard method of testing a random sample of the population to two variations. In the first, a larger random sample of the population is tested using the same number of tests, by using Dorfman testing. In the second, an even larger random sample of the population is tested by the same number of tests, using the Gibbs-Gower testing methodology just described. Specifically, we make two comparisons:

- In Table 1, we compare the root mean squared error of the same three testing architectures.
- In Table 2, we compare the number of tests needed to produce a root mean squared error of less than 15% of the prevalence.
In both settings, we find that Gibbs–Gower testing outperforms Dorfman testing, which outperforms non-group testing.

Table 1. Root MSE of the prevalence estimate produced by two architectures, under several different true prevalences, if we have 100 total tests at our disposal. Again, for the two group testing architectures, we used the optimal group size.

| prevalence | non-group testing | Dorfman testing | Gibbs–Gower testing |
|------------|-------------------|-----------------|---------------------|
| 5%         | $2.18 \times 10^{-2}$ | $1.42 \times 10^{-2}$ | $6.28 \times 10^{-3}$ ($b = 28$) |
| 1%         | $9.95 \times 10^{-3}$ | $4.40 \times 10^{-3}$ | $1.28 \times 10^{-3}$ ($b = 143$) |
| 0.1%       | $3.16 \times 10^{-3}$ | $7.92 \times 10^{-4}$ | $1.29 \times 10^{-4}$ ($b = 1428$) |
| 0.01%      | $1.00 \times 10^{-3}$ | $1.41 \times 10^{-4}$ | $1.29 \times 10^{-5}$ ($b = 13726$) |

Table 2. How many tests are needed to obtain a root MSE of 15% of the prevalence.

| prevalence | non-group testing | Gibbs–Gower testing with group size 5 | Gibbs–Gower testing with optimal group size |
|------------|-------------------|--------------------------------------|-------------------------------------------|
| 5%         | 845               | 189                                  | 73 ($b = 27$)                             |
| 1%         | 4400              | 899                                  | 76 ($b = 138$)                            |
| 0.1%       | 44400             | 8899                                 | 77 ($b \approx 1320$)                     |
| 0.01%      | 444400            | 88899                                | 79 ($b \approx 12150$)                    |

The regimes we have considered here span a range of realistic prevalence rates for COVID-19, and we see that in all of them, Gibbs–Gower testing provides the most accurate estimation of prevalence rates given a fixed number of tests. At low prevalence rates, the optimal group size for Gibbs–Gower testing can be quite large — for example, when $\rho = 0.01\%$, the optimal group size is approximately 12K. Of course, in practical settings, not only are the chemical tests limited and expensive to run, but sample collection can also be a limiting factor.

Nevertheless, in Table 2 we see that even with a fixed group size of 5, Gibbs–Gower testing can achieve 15% accuracy with approximately 1/5 the number of tests required by the standard method. Furthermore, we can optimize the Gibbs–Gower method to minimize any function of the number of samples and the number of chemical tests. For example, suppose in some locality the cost to run a chemical test is about ten times the cost to collect each sample. One can optimize the Gibbs–Gower method to minimize $f(s, t) := s + 10t$, where $s = bt$ is the number of samples collected, and $t$ is the number of tests run. We give an example calculation in Table 3.

Table 3. We minimize the quantity $bt + 10t$, subject to the constraint that Gibbs–Gower testing gives a root MSE of 15% of the prevalence. All numbers are approximate.

| prevalence | optimal group size | total tests | total samples |
|------------|--------------------|-------------|---------------|
| 5%         | 13                 | 93          | 1209          |
| 1%         | 37                 | 145         | 5365          |
| 0.1%       | 131                | 363         | 47553         |

Given the importance of daily monitoring of the prevalence rate of COVID-19 in every locality to allow early detection of local hotspots, Gibbs–Gower testing provides an important tool for regular prevalence monitoring of COVID-19.
4. Conclusion

In this note, we have seen that group testing has significant potential to increase COVID-19 testing capacity, given a limited number of tests. We have restricted ourselves to qPCR testing, which is the standard method for detecting active cases of COVID-19. We expect group testing could also be helpful in antibody testing for COVID-19, but we defer to a future paper a discussion of the concerns specific to that application.

We believe that group testing should immediately be deployed in the US. The current capacity in the U.S. is for testing approximately 250K people per day [COVID] (as of May 5, 2020). Meanwhile, [JhaTsaiJacobson] have recently suggested that the necessary testing threshold that must be met before it is possible to safely reopen the economy is the ability to test 500K people per day, representing a factor of approximately 2. At a positive rate of 10%, the methods we describe here can allow approximately 2 times as many people be tested with a fixed number of test kits, which would achieve this target factor of 2.

References

[Batson] J. Batson. Personal communication, April 23, 2020
[binGroup] C.R. Bilder, B. Zhang, F. Schaarschmidt, and J.M. Tebbs. The R journal 2 (2010), no. 2, p. 56.
[COVID] The COVID tracking project. Publicly available at https://covidtracking.com/.
[Dorfman] R. Dorfman. The detection of defective members of large populations. The Annals of Mathematical Statistics 15 (1943), no. 4, pp. 436–440.
[GibbsGower] A. Gibbs, J. Gower. The use of a multiple-transfer method in plant virus transmission studies — some statistical points arising in the analysis of results. Annals of Applied Biology 48 (1960), no. 1, pp. 75–83.
[HanelThurner] Boosting test-efficiency by pooled testing strategies for SARS-CoV-2. Preprint; publicly available at https://arxiv.org/abs/2003.09944.
[Hughes-Oliver] J.M. Hughes-Oliver Pooling experiments for blood screening and drug discovery. Screening. Springer, New York, NY, 2006. pp. 48–68.
[JhaTsaiJacobson] K. Jha, T. Tsai, and B. Jacobson. “Why we need at least 500,000 tests per day to open the economy — and stay open.” Publicly available at https://globalepidemics.org/2020/04/18/why-we-need-500000-tests-per-day-to-open-the-economy-and-stay-open/.
[McCrady] M.H. McCrady. The numerical interpretation of fermentation-tube results. The Journal of Infectious Diseases 1957, pp. 183–212.
[Sterrett] A. Sterrett. On the Detection of Defective Members of Large Populations. Annals of Mathematical Statistics 28 (1957), no. 4, pp. 1033–1036.
[Thompson] K.H. Thompson. Estimation of the Proportion of Vectors in a Natural Population of Insects. Biometrics 18 (1962), no. 4, pp. 568–578.
[Williams] Optimal pooling strategies for laboratory testing. Preprint; publicly available at https://arxiv.org/abs/1007.4903.