Paper 08 / 2022 doi: 10.7795/320.202208

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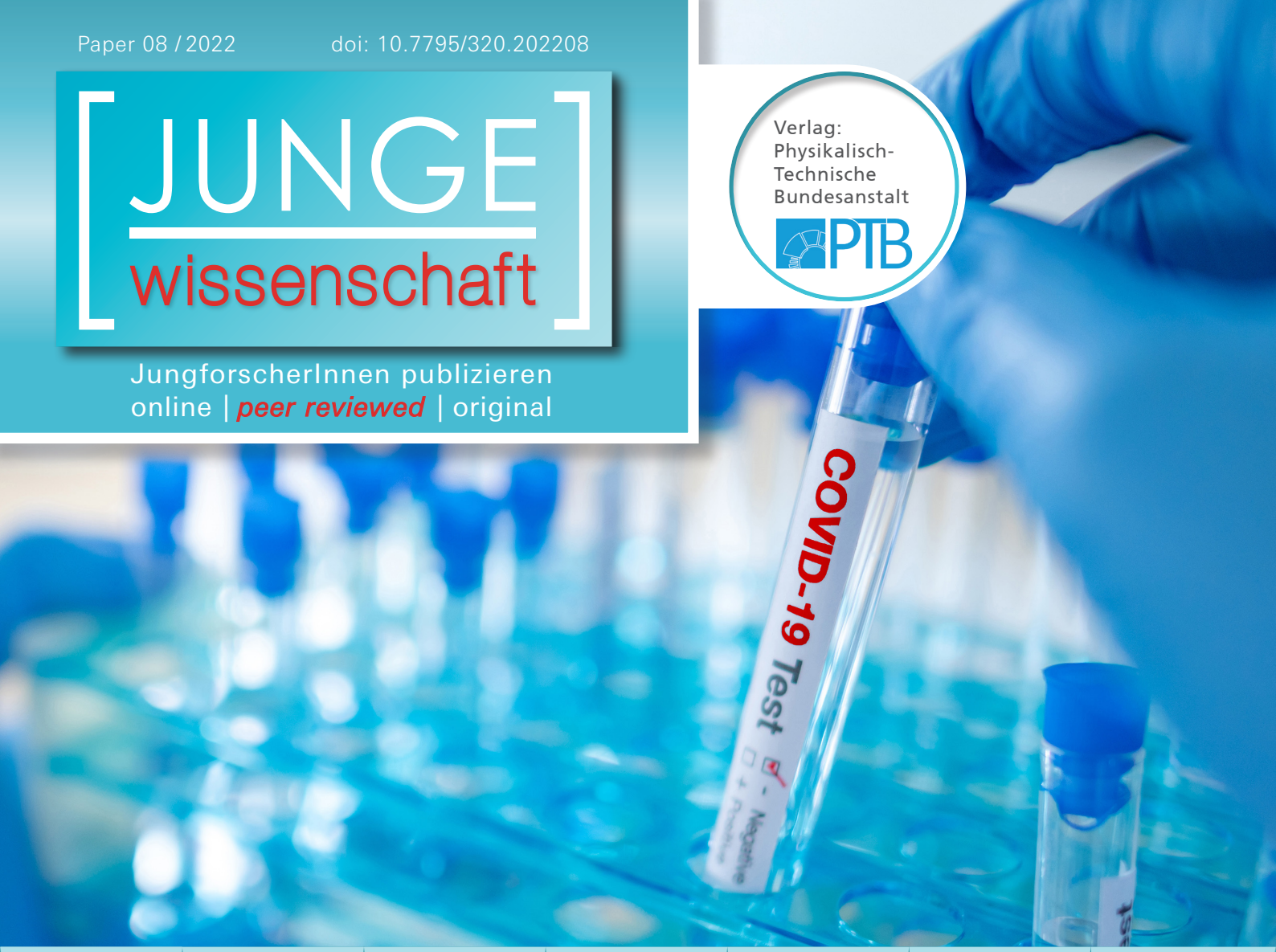
online | *peer reviewed* | original

Verlag:
Physikalisch-
Technische
Bundesanstalt
PTB



Mathematik & Informatik

Pooling to optimize mass testing

Group Testing Protocols in Higher Dimensions to Combat the COVID-19 Pandemic

Most nations and their healthcare systems have been overwhelmed by the current COVID-19 pandemic. Strategies and measures to curb the spread of the SARS-Cov-2 virus require data on symptomatic infections, as well as asymptomatic carriers. Many countries, especially in the global south, lack the resources and infrastructure to conduct mass testing campaigns. In this paper a testing protocol is presented that significantly reduces the number of required tests while still exactly identifying infections.

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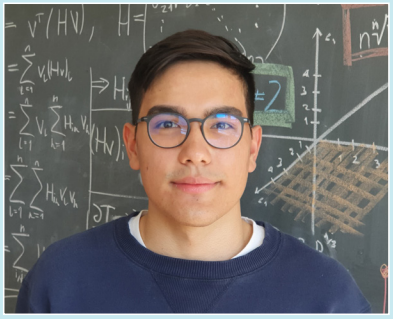

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Eingang der Arbeit:
8.11.2021
Arbeit angenommen:
13.7.2022

Pooling to optimize mass testing

Group Testing Protocols in Higher Dimensions to Combat the COVID-19 Pandemic

1. Introduction

In late 2019, several cases of a novel coronavirus were first detected in China. Only a few months later, COVID-19 had already spread around the world. Many countries and their healthcare infrastructure have been subsequently overwhelmed. More than a year later and despite a wide offering of vaccines, COVID-19 continues to impact the world.

Before the development of effective treatments and vaccinations against SARS-COV-2, the only way to curb the spread of the virus was through public health measures such as contact tracing, quarantines, and lockdowns. For these measures to be effective, extensive and current data on community transmission are required. Timely mass testing is thus central to a country's national corona strategy. Widespread testing programs have allowed countries such as South Korea [1–3] to fare far better than others during the early days of the pandemic. Testing also plays a key role when reopening economies. As lockdowns are lifted, authorities are better able to track resurgent clusters and impose localized restrictions. Even as vaccination campaigns progress rapidly, testing remains relevant, especially with emergent SARS-Cov-2 variants that are more contagious and drive third or fourth waves of infections in various parts of the world. As long as vaccines are not globally accessible, local hotspots may breed new variants that are more infectious or resistant to vaccines and pose a threat to the global community. Thus, recurrent mass testing remains an essential tool in the global fight against the coronavirus.

However, testing can be prohibitively expensive and laborious. Many countries, especially in the global south, lack the resources and infrastructure to conduct mass testing campaigns. Thus, it is of general interest to formulate more efficient ways to test large groups. I, therefore, developed a testing protocol that significantly reduces the number of required tests for large populations while still accurately identifying infections [4–6].

Because of the rapidly evolving situation around the COVID-19 pandemic, it is important to note that this project was written during the timeframe of April-June 2020 [4]. The findings are based on early data from this period. Moreover, pooled group testing, a technique that is central to our protocol, was not widely discussed at the time. Since then much research has been published on this technique (for example [5]) and group testing protocols have entered the mainstream, with health bodies such as the U.S. Food and Drug Administration (FDA) recommending pooled tests [6].

2. Group Testing and Square Array Protocol

The results of this paper are motivated by the descriptions in [7] and [8] of group testing methods to identify diseases. (I refer the reader to [5] and the therein mentioned references or to a review of group testing focussing on COVID-19.)

The 1943 paper by R. Dorfman [7] describes a pooled testing technique to identify syphilis infection among military recruits. Instead of testing every recruit individually, one may group several, e.g., five of them together. One collects a test sample from each of the group members and then pools them into a grouped sample which is subsequently evaluated using a single

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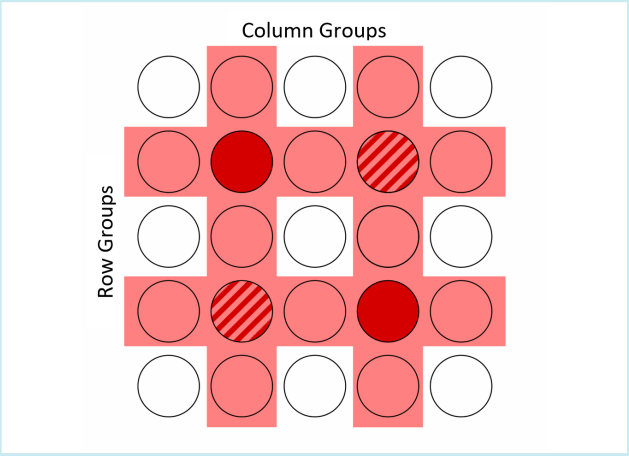

Fig. 1: Each circle represents a test sample. The 25 samples are distributed on the nodes of a five by five square grid (lattice). All samples on a row or column are then tested as a pooled group. If the result is positive, the row or column is marked red. Samples on intersections of the red lines are potentially positive. In the figure, two and only two individual probes are assumed to be truly positive and are correspondingly colored with dark red. Two in reality negative probes also lie on light red intersections. These false positives are represented by striped circles.

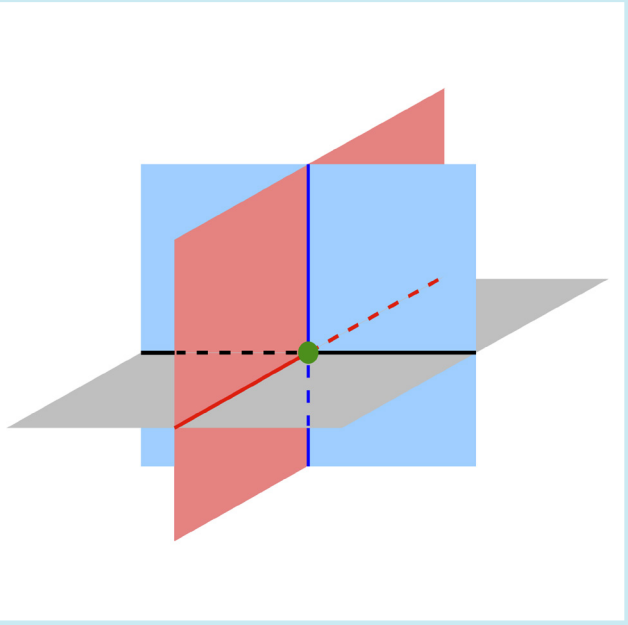

Fig. 2: A point in 3-dimensional space can be specified by the intersection of three non-parallel planes in space. The intersection of two planes forms a line. Two lines or a line and a plane intersect in a point.

test. If the group test is negative, then all the five recruits are negative. If the result is positive, then at least one or more of the members have syphilis and the whole group must be tested again individually. If the prevalence of syphilis is low, as it is in most cases, one can test a whole company with just a few tests.

The second paper published in early 2020 by researchers at Cornell [8] uses Dorfman's pooled testing technique in combination with a square grid testing layout. For example, 25 persons are tested for COVID-19. A sample is taken from each of the 25 participants and assigned to one and only one intersection of a five by five square grid (lattice) as shown in Fig. 1. One proceeds as follows: For every row of the grid, the five samples within the row are pooled into a grouped test. If the result is positive, the row is marked with a red line, otherwise it is left blank. One proceeds in the same way for the columns. On the intersections of red lines, one then finds the potentially positive samples (see Fig. 1).

Assuming that only two of the 25 samples are positive, as shown in Fig. 1, at most 14 tests are required to identify the infected individuals. Indeed, five tests are required for the rows, another five for the columns, and additional four tests are required when individually testing the potentially positive probes in order to resolve which individual contributed a positive sample.

Dorfman's method would have required 15 tests: testing five lines, two of which are red, and testing all five individuals in each of the two red lines. Testing individually, as is done nowadays, would have required 25 tests. One can show that for most cases the square array method will be as or more efficient than Dorfman's technique. In general, the number of tests T for the square array method is estimated to be (see Appendix and [4]):

$$T \approx 2\,P^{1/2} \qquad (1)$$

where P is the number of samples to be tested. Note that this formula does not consider a second round of testing for the potentially positive probes.

3. Generalization

3.1 3-dimensional and *n*-dimensional Arrays

The square array protocol [8] uses a 2-dimensional array, which can be represented as a square lattice. The main goal of this paper is to generalize this method for arbitrary n-dimensional arrays to explore potential gains in efficiency.

As a warm up, we consider a protocol making use of a 3-dimensional array. In analogy to the square grid method, we can imagine the 3-dimensional array as a cubic lattice. Each lattice point represents an individual sample. Instead of testing rows and columns, slices, or more accurately planes of the cube are tested (see Fig. 2).

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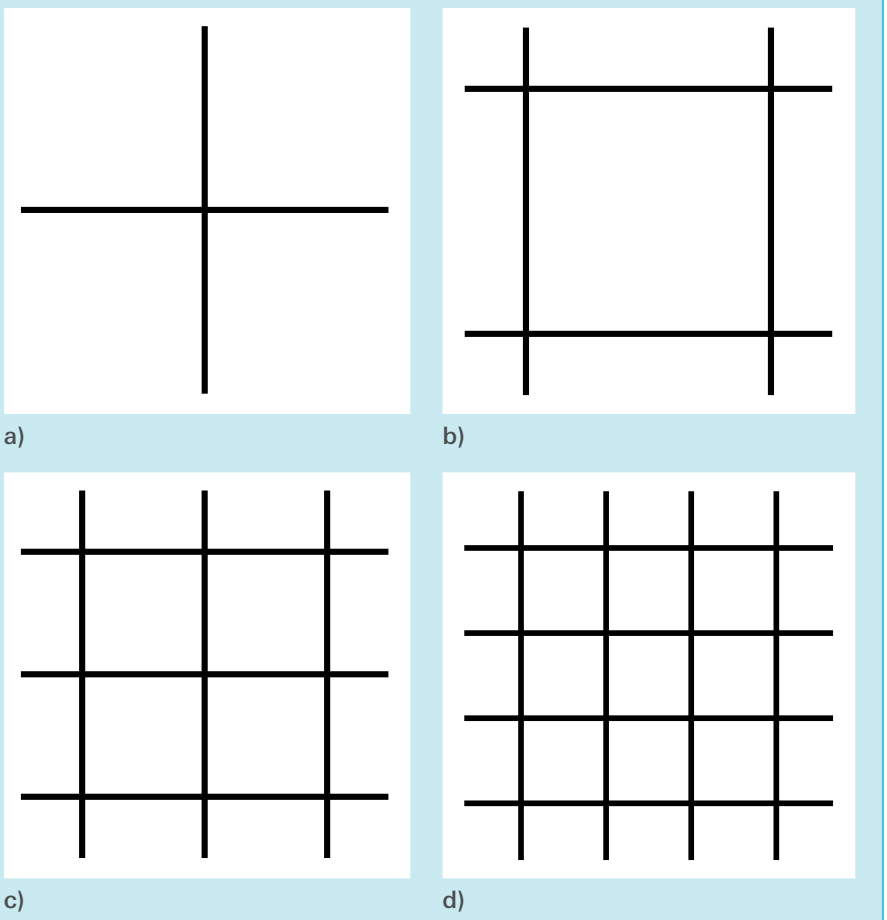

Fig: 3: (a) A pair of orthogonal lines intersect in one point.
(b) Two pairs of orthogonal lines intersect in $2^2 = 4$ points.
(c) Three pairs of orthogonal lines intersect in $3^2 = 9$ points.
(d) Four pairs of orthogonal lines intersect in $4^2 = 16$ points.

As before, all samples within a shared plane will be tested as a pooled group and the plane will be marked if the result is positive. From vector geometry it is known that the intersection of two orthogonal planes produces a line in space, the intersection of three planes a point. Thus, the intersection of three orthogonal positive planes identifies a potentially positive probe. The number of required tests is then estimated to be (see Appendix and [4])

$$T(P) \approx 3\,P^{1/3} \qquad (2)$$

given the number P of probes to be tested.

The generalization of Eq. (2) by which the protocol makes use of an n-dimensional array is (see Appendix and [4])

$$T(P,n) \approx n\,P^{1/n} \qquad (3)$$

Subsequently, we can estimate the optimal dimension for given P for which the number of tests is minimized with the help of differential calculus and show that the minimum number of tests is given by (see Appendix and [4])

$$T_{\mathrm{opt}}(P) \approx e\,\ln P \qquad (4)$$

where e is Euler's constant.

An n-dimensional array has no easy visual analogy. One should think of all the samples being distributed on the nodes of an n-dimensional hypercubic lattice. We would then group test the different $(n-1)$-dimensional hyperplanes. Concretely, we distribute every sample in $\mathbb{N}^n$–dimensional Cartesian discrete space. Every sample is identified with a unique coordinate vector with n components. A hyperplane would then be the set of samples that share a given value for a given component of their coordinate vector.

3.2 Inaccuracy

Any method that tests for a viral infection is prone to errors. Testing a sample from one person gives two outcomes, positive or negative. If the person is truly infected, a positive testing outcome is called a true positive. Otherwise, the positive testing outcome is called a false positive. The same distinction between true and false negative applies. A false positive can be inherent to the methodology. This can be the case with the group testing protocol as we shall see shortly. A false positive can also arise because of contamination of a sample when it is manipulated in the laboratory. A false negative can, for example, arise because the testing method can only detect a virus load above some threshold value. In such a case, the false negative is due to a lack of testing sensitivity. Because group testing mixes individual samples, most of which are negative, it effectively dilutes the viral load of a positive sample. Thus, one should make sure that the testing sensitivity is high enough to reliably test a group of mixed samples.

As previously indicated, the n-dimensional lattice protocol only identifies potential positives so far. Indeed, all samples that are potential positives in the group testing method must be tested again individually. The number M of potential positive samples in the group testing method grows as a function of the number W of positive individual samples. The number W of individual samples that are positive can be estimated if the prevalence r of the disease is known. We outline this issue in two dimensions. Each individual

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$$T(P,n) \approx n\,P^{1/n} \qquad T_{\mathrm{opt}}(P) \approx e\,\ln P,$$

Equation (6)

sample that is positive will produce two positive lines in the square array. If there is only one individual sample that is positive, this is not an issue. If there are two however, they will produce 4 lines in total which might in the worst case intersect four times. This inaccuracy continues to grow as the number of individually positive samples increases as illustrated in Fig. 3.

Once again, we extrapolate from the lower dimensional cases an upper bound for the inaccuracy in n dimensions, which is then proven inductively. The inaccuracy is given by the power law

$$M(W,n) = W^n \tag{5}$$

if one uses an n-dimensional testing protocol.

One possibility to overcome the power-law growth of the error (Eq. 5) is to divide larger populations into subsets that are treated independently using the n-dimensional array protocol. In that way, we can limit the number of individual, positive samples and thus the inaccuracy within an array. We find that the subset size is optimally chosen when there is on average only one individual sample that is positive per subset. The population is thus divided into subgroups whose size is fixed by the prevalence of COVID-19.

3.3 Physical Limitations

The aim was to develop a testing protocol specifically for COVID-19. To make the method realistically applicable we must consider real life diagnostic limitations of testing. The most important parameter is the pooled group testing capacity of a testing agent. When using the pooled testing technique, it is central that group tests are evaluated accurately. Testing sensitivity however is finite, and one cannot pool so many samples without risking false negatives caused by dilution. To account for this real-world physical limitation, we introduce a maximal pooled group size S. We used S=64 as an upper bound estimation for PCR-COVID-19 group testing capacity [9] and [10] in Eq. (8).

4. Results

Our first original finding is the generalization of the pooled testing method using 1- and 2-dimensional arrays described by Dorfman and the Cornell researchers for arbitrary n-dimensional arrays. The number of required tests for arbitrary and optimal dimension n are estimated to be Eq. (6) respectively.

Moreover, we have shown that the inaccuracy inherent to the n-dimensional array method increases with growing number of infections W. We find an upper bound for the imprecision given by the total number of potential positives

$$M(W,n) = W^n \tag{7}$$

This result also applies to Dorfman's and Cornell's testing methods. Eq. (7) serves as a criterion for determining when high infection rates require 1-dimensional array or even individual testing, i.e., when $M(W) \gg W$.

Finally, we have formulated a testing protocol utilizing n-dimensional array pooled testing. By subdividing the sample set, the method inaccuracy can be limited and infections precisely identified. Furthermore, we take into account physical limitations of testing agents by introducing a maximum test pooling size S. Using this testing protocol, the approximate number of tests is given by (see Appendix and [4])

$$T(P,n) = \left[n\,S^{-1} + (r\,S)^n\right]\,P \tag{8}$$

A rough estimate for the optimal dimension n_{opt} as a function of prevalence r and test pool size S is given by (see Appendix and [4]).

$$n_{\mathrm{opt}} \approx \frac{\ln\left(S\,|\ln(r\,S)|\right)}{|\ln(r\,S)|} \tag{9}$$

This estimate serves as a rough guide for testing layouts and shows that for most cases relating to COVID-19, 2-dimensional arrays are near optimal. For low prevalence, the optimal dimension n_{opt} generally becomes larger. For such situations, the protocol excels by utilizing higher dimensional arrays. However, one must take into account that n_{opt} is singular at $r = 1/S$ and thus special care must be taken when studying prevelance values near this singularity.

We outline the significant test reductions of our protocol using Switzerland as an example. Let the sample size be P=8,570,000, the maximal test pool size

Table 1: Required number of tests $T(P,n)$ given by Eq. (8), whereby $n \approx n_{opt}$ determined from Eq. (9), P=8,570,000, and S =64.

Prevalence r in %	1	0.1	0.05	0.01
Tests T	1,312,474	302,915	276,588	188,754
Dimension n_{opt}	8	2	2	1

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be S =64, and the prevalence be r. The number of required tests in dependence of the prevalence r to accurately identify every infection are found in Table 1.

5. Concrete Example

A village is to be tested for COVID-19. The goal is to identify all infections using as few tests as possible. Assume that the village has P=10,000 inhabitants, an estimated prevalence of SARS-Cov-2 of r=0.5 %, and a maximal test pool size of S=64. We will outline our testing protocol stepwise.

With Eq. (9), we find the optimal dimension $n \approx 4$. Using Eq. (8) we estimate the required number of tests to be $T \approx 730$.

One can show that the villagers are to be subdivided in subsets of size $G = S^{\frac{n}{n-1}} = 256$ (see Appendix and [4]). For each subset we proceed in the same fashion. Every villager from the subset is assigned a coordinate $(\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ from a 4-dimensional array, whereby $1 \leq \lambda_i \leq 4 = G^{\frac{1}{n}}$ holds for each component, i.e., (3, 1, 4, 4). Proceed by collecting from each villager n=4 test samples.

The samples will be tested as follows. From each subject whose first coordinate component is $\lambda_1 = 1$ one of four samples is taken and pooled with the others. These are subsequently tested for SARS-Cov-2 as a pooled group using a single test. If the result is positive, each group member is marked once. Repeat for all $1 < \lambda_1 \leq 4$. Proceed the same way for the remaining three components.

The results are evaluated as follows. Each time a villager was part of a positive group test pool, they were given a mark. Every villager that has received n=4 positive marks is considered potentially positive. Anyone in this group must now be tested individually. The individual positives are then found. All infections will have been identified if one assumes a negligible test inaccuracy.

The population of 10,000 has consequently been tested for COVID-19 using approximately 730 tests.

6. Conclusion

Most nations and their healthcare systems have been overwhelmed by the COVID-19 pandemic. Strategies and measures to curb the spread of the virus require timely data on symptomatic infections, as well as asymptomatic carriers. Recurrent mass testing is central when tracing and breaking chains of community transmission. However, SARS-Cov-2 testing can be prohibitively expensive. Many countries, especially within the global south, lack the resources and infrastructure to conduct mass testing campaigns.

We developed and presented testing protocols based on the group testing technique. Several samples can be pooled and evaluated as a group using a single test. We showed that such testing procedures are far more efficient than individual testing. Moreover, by cleverly choosing overlapping group tests one can dramatically reduce the number of required tests. By subdividing the population according to disease prevalence, individual infections can still be exactly identified. To make the protocols realistically applicable, we considered the most relevant real-world limitations of SARS-Cov-2 testing.

The obtained testing protocols describe such an optimized approach as a function of population, prevalence, and limitations of the group testing method. Application of these protocols can lead to considerable improvements to testing efficiency and costs. We provided criteria and stepwise instructions such that the protocols may be used without a mathematical background and demonstrate them on the concrete example of Switzerland.

Acknowledgements

I am grateful for useful discussions with and guidance from Dr. Markus Müller, Dr. Rolf Herb, and the support from the Schweizer Jugend Forscht foundation.

Appendix

1. Optimization

1.1 Generalized *n*-dimensional lattice protocol

If the total number of individual samples P is arranged on the sites of an n-dimensional hypercubic lattice made of L^n sites, where L can be thought of as the length of an edge of the hypercube, and if one pools all individual samples into $n \cdot L$ test tubes, then the number of required group tests $T(n)$ scales like

$$T(n) = n\,L = n\,P^{1/n}. \tag{A1}$$

We have recovered Eqs. (1), (2) and (3).

This function of n must be optimized. To this end, we introduce the auxiliary function

$$f :]0,\infty[\to \mathbb{R},$$
$$x \mapsto f(x) = x\,P^{1/x} = x\,e^{\frac{\ln(P)}{x}}. \tag{A2}$$

The condition for an extremum is

$$\begin{aligned} 0 &= f'(x) \\ &= \left(x\,P^{1/x}\right)' \\ &= P^{1/x} + x\,\left(P^{1/x}\right)' \\ &= P^{1/x} - P^{1/x}\,x\,\frac{\ln(P)}{x^2} \\ &= x^{-1}\,P^{1/x}\,[x - \ln(P)] \end{aligned} \tag{A3}$$

with the solution

$$x_{\min} = \ln(P). \tag{A4}$$

As f is divergent as $x \to 0, \infty$ and it possesses only one extremum, x_{min} must be an absolute minimum. The value of f at this minimum is

$$\begin{aligned} f(x_{\min}) &= \ln(P)\,P^{1/\ln P} \\ &= \ln(P)\,\left(e^{\ln P}\right)^{1/\ln P} \\ &= e^1\,\ln(P) \equiv e\,\ln(P), \end{aligned} \tag{A5}$$

where e denotes Euler's number. We have derived Eq. (4).

1.2 Subgroup lattice protocol with supplementary individual testing

The n-dimensional lattice protocol with the number of group tests given by Eq. (A1) is free of error if and only if the number W of truly positive individual samples is W=1. Otherwise, the number of false positives is estimated to grow like the power law as given in Eq. (5). The value taken by W depends on the prevalence r, which is the ratio between the number of active infections in the population and the population number P. The number of true positives in the population is thus

$$W = r\,P. \tag{A6}$$

Because of the inaccuracy as given in Eq. (5) the n-dimensional lattice protocol is useless once $P > \frac{1}{r}$. To overcome this problem, we break P into P/G subgroups made of G individual samples with G of order $1/r$. The n-dimensional lattice protocol is applied to the subgroups made of G individual samples and this exercise is repeated independently P/G times. The number of tests needed to identify the number of true positive individual samples is then

$$T(P,G,n) \approx \left[n\,G^{1/n} + (r\,G)^n\right]\frac{P}{G}. \tag{A7}$$

Here, $n \cdot G^{1/n}$ is the number of tests in Eq. (3) with the substitution $P \to G$, while $(rG)^n$ is the number of supplementary tests in Eq. (7) with the substitution $W \to r\,G$. If L is the linear size of the hypercube in the n-dimensional lattice protocol, then $G = L^n$. Substitution of G in Eq. (A7) by $G = L^n$ gives

$$\begin{aligned} T(P,L,n) &\approx \left[n\,(L^n)^{1/n} + (r\,L^n)^n\right]\frac{P}{L^n} \\ &= \left(n\,L^{1-n} + r^n\,L^{n^2-n}\right)P. \end{aligned} \tag{A8}$$

This function must be optimized with respect to the dimension n of the lattice protocol. To this end, we introduce the auxiliary function

$$f :]0,\infty[\times]0,\infty[\to \mathbb{R},$$
$$(x,y) \mapsto f(x,y) = \left(x\,y^{1-x} + r^x\,y^{x^2-x}\right). \tag{A9}$$

Differentiation with respect to y gives

$$\begin{aligned} 0 &= \left(\frac{\partial f}{\partial y}\right)(x,y) \\ &= x\,(1-x)\,y^{-x} + r^x\,(x^2-x)\,y^{x^2-x-1} \\ &= x\,(1-x)\,y^{-x}\left(1 - r^x\,y^{x^2-1}\right). \end{aligned} \tag{A10a}$$

Eq. (A10a) has the solution

$$y_{\min}(x) = r^{\frac{x}{(1-x)(1+x)}}. \tag{A10b}$$

Insertion of $y_{min}(x)$ into Eq. (A9) gives the function

doi: 10.7795/320.202208

$$\begin{aligned} g(x) &= x\,[y_{\min}(x)]^{1-x} + r^x\,[y_{\min}(x)]^{x(x-1)} \\ &= x\,r^{\frac{x(1-x)}{(1-x)(1+x)}} + r^{x+\frac{x^2(x-1)}{(1-x)(1+x)}} \\ &= x\,r^{\frac{x}{1+x}} + r^{x-\frac{x^2}{1+x}} \\ &= (1+x)\,r^{\frac{x}{1+x}}. \end{aligned} \tag{A11}$$

The derivative g' of g with respect to x is

$$\begin{aligned} g'(x) &= \left[(1+x)\,e^{\ln(r)\,\frac{x}{x+1}}\right]' \\ &= r^{\frac{x}{x+1}} + \ln(r)\,(1+x)\left(\frac{x}{x+1}\right)' r^{\frac{x}{x+1}} \\ &= r^{\frac{x}{x+1}} + \ln(r)\,(1+x)\,\frac{x+1-x}{(x+1)^2}\,r^{\frac{x}{x+1}} \\ &= \left[1+\ln(r)\,\frac{1}{(x+1)}\right] r^{\frac{x}{x+1}}. \end{aligned} \tag{A12}$$

The condition for an extremum is

$$\begin{aligned} 0 = g'(x) &\iff 0 = x_{\min} + 1 + \ln(r) \\ &\iff x_{\min} = \ln(r^{-1}) - 1. \end{aligned} \tag{A13}$$

When

$$\ln(r^{-1}) > 1, \tag{A14a}$$

one finds the solution

$$\begin{aligned} y_{\min}(x_{\min}) &= r^{\frac{x_{\min}}{(1-x_{\min})(1+x_{\min})}} \\ &= r^{\frac{\ln(r^{-1})-1}{\ln(r^{-1})[2-\ln(r^{-1})]}} \end{aligned} \tag{A14b}$$

together with

$$\begin{aligned} g(x_{\min}) &= (1+x_{\min})\,r^{\frac{x_{\min}}{1+x_{\min}}} \\ &= \ln(r^{-1})\,e^{\ln(r)\,\frac{\ln(r^{-1})-1}{\ln(r^{-1})}} \\ &= \ln(r^{-1})\,e^{1-\ln(r^{-1})} \\ &= e\,\frac{\ln(r^{-1})}{r^{-1}}. \end{aligned} \tag{A14c}$$

This must be a minimum, for

$$\lim_{x\to\infty} g(x) > \lim_{x\to 0} g(x) = 1$$

and the root of Eq. (A13) is unique. Insertion into Eq. (8) gives

$$(L_{\min})^{n_{\min}} = r^{-\kappa(r)} \tag{A15a}$$

$$\kappa(r) = \frac{\left[1-\frac{1}{\ln(r^{-1})}\right]^2}{1-\frac{2}{\ln(r^{-1})}} \tag{A15b}$$

$$\frac{T_{\min}(r)}{T} = e\,\frac{\ln(r^{-1})}{r^{-1}} \tag{A15c}$$

$$0 < r < 1, \tag{A15d}$$

$$\lim_{r\to 0} \kappa(r) = 1. \tag{A15e}$$

1.3 Subgroup lattice protocol with a bound on the pooling size and with supplementary individual testing

Suppose that S is the maximum number of individual samples that can be pooled without compromising the accuracy of the testing sensitivity. If we do the substitution

$$S = G^{\frac{n-1}{n}} \iff G = S^{\frac{n}{n-1}} \tag{A16}$$

in Eq. (A7), we obtain

$$T(P,n) \approx \left(\frac{n}{S} + r^n\,S^n\right) P. \tag{A17}$$

We have derived Eq. (8).

We need to optimize this function as a function of the dimensionality n of the lattice protocol. To this end, we use the auxiliary function

$$\begin{aligned} &f :]0,\infty[\to \mathbb{R}, \\ &\qquad x \mapsto f(x) = \left(\frac{r}{\lambda}\,x + \lambda^x\right), \qquad \lambda = r\,S. \end{aligned} \tag{A18}$$

The derivative f' of f with respect to x is

$$f'(x) = \frac{r}{\lambda} + \ln(\lambda)\,\lambda^x. \tag{A19}$$

A solution to

$$0 = f'(x) = \frac{r}{\lambda} + \ln(\lambda)\,\lambda^x \tag{A20}$$

with $x>0$ is only possible if

$$\ln(\lambda) = -|\ln(\lambda)| \iff 0 < \lambda < 1. \tag{A21}$$

Under this assumption

$$\begin{aligned} &e^{-|\ln(\lambda)|\,x} = r\,\lambda^{-1}\,|\ln(\lambda)|^{-1} \\ &\quad\iff -|\ln(\lambda)|\,x = \ln(r) - \ln(\lambda) - \ln\left(|\ln(\lambda)|\right). \end{aligned} \tag{A22}$$

A solution is only possible if

$$\frac{r}{\lambda\,|\ln(\lambda)|} < 1 \iff \ln(r) - \ln(\lambda) - \ln\left(|\ln(\lambda)|\right) < 0. \tag{A23}$$

With the assumption

$$0 < \lambda < 1, \qquad 0 < \frac{r}{\lambda\,|\ln(\lambda)|} < 1, \tag{A24a}$$

one finds one and only one solution

$$x_{\min} = \frac{\ln\left(r^{-1}\,\lambda\,|\ln(\lambda)|\right)}{|\ln(\lambda)|} \tag{A24b}$$

together with

$$f(x_{\min}) = \frac{r}{\lambda}\,x_{\min} + \lambda^{x_{\min}}. \tag{A24c}$$

This solution must be a minimum, for

$$\lim_{x\to\infty} f(x) > \lim_{x\to 0} f(x) = 1$$

and x_{min} is unique. If we trade λ for S in $\lambda = r \cdot S$, one then finds

$$\begin{aligned} 0 < r\,S < 1 &\iff 0 < S < r^{-1} < \infty \\ &\iff 0 < r < S^{-1} < \infty, \end{aligned} \tag{A25a}$$

$$\begin{aligned} 1 < S\,|\ln(r\,S)| = S\,\ln\left(r^{-1}\,S^{-1}\right), \qquad 0 < r\,S < 1 \\ \iff e^{\frac{1}{S}}\,S < r^{-1} < \infty,\ 0 < r\,S < 1, \end{aligned} \tag{A25b}$$

$$n_{\min} \approx \frac{\ln\left(S\,|\ln(r\,S)|\right)}{|\ln(r\,S)|}. \tag{A25c}$$

One observes that condition Eq. (A25a) is met when condition Eq. (25b) holds. We have derived Eq. (9).

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doi: 10.7795/320.202208

Impressum

Junge Wissenschaft
c/o Physikalisch-Technische
Bundesanstalt (PTB)
www.junge-wissenschaft.ptb.de

Redaktion
Dr. Sabine Walter, Chefredaktion
Junge Wissenschaft
Paul-Ducros-Str. 7
30952 Ronnenberg
E-Mail: sabine.walter@verlag-jungewissenschaft.de
Tel.: 05109 / 561 508

Verlag
Dr. Dr. Jens Simon,
Pressesprecher der PTB
Bundesallee 100
38116 Braunschweig
E-Mail: jens.simon@ptb.de
Tel.: 0531 / 592 3006
(Sekretariat der PTB-Pressestelle)

Design & Satz
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