Enhancing the number of lab tests with a "poisoned wine" approach

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Abstract. Rapid testing of appropriate specimens from patients suspected for Coronavirus is of a great importance for the disease management and control. We propose complementary approaches to enhance processing large amounts of collected samples. The approaches are based on mixing samples in testing cups as opposed to testing single samples in each cup. As a result, the number of tests can be boosted by factors of magnitude, and the effective testing time can be reduced drastically.

The World Health Organization has declared the growing epidemic of novel coronavirus infectious disease (2019-nCoV) a global pandemic. The virus emerged in Wuhan, China, at the end of 2019, and as of April 08, 2020 almost one and a half million cases were identified in 209 countries and territories, with nearly 100,000 deaths being reported [1] . In some countries, such as the United Kingdom and the United States, it is believed that the number of cases is much larger than reported. The relatively low reported number is attributed to a number of factors, including but not limited to mismanagement of the epidemic at the political level, high ER visit costs (over $700), and a lack of resources that limit the number of tests drastically. For example in the UK 25,000 tests were carried out in the period since January 2020 and up until March 11, 2020, which is equivalent to the number of tests carried out in South Korea in two and half days according to the World Health Organization. Thus, while in some countries there is a (front-end) problem of sample collection, in other countries the main concern is in processing the collected samples (back-end problem). Here we are concerned with the second type of problem, namely processing a large amount of collected samples.

Rapid testing of appropriate specimens from suspected patients for 2019- nCov is of great importance for clinical management and outbreak control. Specimens can be collected from the upper respiratory tract as nasopharyngeal and oropharyngeal swab or wash in an ambulatory regime [2] . The laboratory confirmation of the COVID-19 is based on the Nucleic Acid Amplification Tests (NAAT); the assay detects the genomic sequences of virus RNA by real-time reverse transcription polymerase chain reaction rRT-PCR. On the other hand, the serologic method based on using the enzyme-linked immunoassay (ELISA) can measure the viral-specific host antibodies immunoglobulin M (IgM) and IgG. in contrast to the rRT-PCR assay this method avoids false negative results regarding specimen quality or absence of the virus in the upper respiratory tract [3].

Approach I

In order to enhance the number of tests, to groups with less severe symptoms, and to individuals that may potentially have the virus we suggest adapting two parallel types of testing. The first type is the current testing which considers a single patient per test, whereas the second type adapts the poisoned wine approach, where patients are tested in batches mixed in same cups following binary numbers allocated to each patient. Let n be the number of patients (sample size), m the size of the test cup set, and l the size of a subset of the cup test set. Select m and l such that $C(m,l) \geq n$. Note that $C(m,l)$ is the combinations function, and this simply means we want enough combinations. As an example, take a sample saliva (or blood etc.) of a number of patients n are mixed in m testing cups. Let us assume there are $n = 8{,}000$ patients. The patients samples are ordered and each is given a binary number, for example patient 13 is given the binary number 0000000001101. The number of digits denotes the total number of test cups, in this case there is a total of 13. The test cups are ordered, say from left to right, such that each test is associated with a digit of the binary number. Whenever the digit is 1 the patient's samples are added to the associated cup, e.g. in the case of patient 13 their samples are added to tests number 10,11 and 13. If there was a single patient with positive Covid-19, then the tests that return positive, will denote the binary number of that patient. This methods allows enhancing the number of tests enormously, $O(2^m)$. However, since we do not know the number of patients that have Covid-19 a priori, the suggested approach can give negative results and clear most of the patients given that a small percentage of tested patients is expected to carry the disease.

Approach II

Definite test results can be obtained by requesting that equal number of samples from each patient are distributed to a fixed number of test cups. Moreover, one could allocate a unique ratio, r_i , $(i = 1,2,3, \dots n)$, for each patient denoting the ratio of inserted in each cup when combining the sample, i.e. from the i^{th} patient sample, a ratio r_i is added to all relevant test cups. Moreover, we choose ratios that are not a possible combination of other ratios within the group, that's easily done using prime numbers. The results of the tests can now be expressed as a set of m equations,

$$R_j = \sum_{i=1}^{n} r_i \delta_{ij}, \qquad (j = 1,2,3, \dots m)$$

where δ_{ij} is a step function (takes the values of either 0 or 1) that denotes whether the sample of the i^{th} patient is added (δ_{ij}=1) to the j^{th} cup or not (δ_{ij}=0), in the corresponding ratio r_i. In order to illustrate the suggested method, let us consider a small group example of $n = 20$ patients. In this case, if we require that samples from each patient to be added to a fixed number of cups, l, it is easy to show that we require a total of $m = 6$:

$$n = \frac{m!}{l!\,(m-l)!}$$

Assume that the test returns positive result for cups: 4, 5 and 6, and negative for the rest, with $R_4 = R_5 = R_6 = a$, where a is constant. In this case it is obvious that only Patient #1 tests positive (highlighted in light orange in Table 1), and the ratio might be used for confirmation purposes. However, in case that more than one patient is testing positive we make use of the ratios. For example, assume that cups 2, 3, 4 and 5 are positive and 1, 6 are negative; and the conditions (i) $R_2 = b$; (ii) $R_3 = R_4 = c$; and (iii) $R_5 = d$, where $b \neq c \neq d$ are constants (denoting ratio/amount of positive particles in cup). Applying the three conditions, we find that patients 4 and 10 test positive (highlighted in blue in Table 1).

Patient #	**Patient Binary #**						**Ratio in cup**
	Cup #						
	1	2	3	4	5	6	
1	0	0	0	1	1	1	r_1
2	0	0	1	0	1	1	r_2
3	0	0	1	1	0	1	r_3
4	**0**	**0**	**1**	**1**	**1**	**0**	r_4
5	0	1	0	0	1	1	r_5
6	0	1	0	1	0	1	r_6
7	0	1	0	1	1	0	r_7
8	0	1	1	0	0	1	r_8
9	0	1	1	0	1	0	r_9
10	**0**	**1**	**1**	**1**	**0**	**0**	r_{10}
11	1	0	0	0	1	1	r_{11}
12	1	0	0	1	0	1	r_{12}
13	1	0	0	1	1	0	r_{13}
14	1	0	1	0	0	1	r_{14}
15	1	0	1	0	1	0	r_{15}
16	1	0	1	1	0	0	r_{16}
17	1	1	0	0	0	1	r_{17}
18	1	1	0	0	1	0	r_{18}
19	1	1	0	1	0	0	r_{19}
20	1	1	1	0	0	0	r_{20}

Table 1. Samples of 20 patients distributed over 6 test cups, at unique ratios, r_i, (i =1,2,…).

In the example above we allow samples of a maximum of 10 patients to be shared in one cup. Yet, we are able to test 19 patients with as few as 6 cups. With the same number of cups and without the restriction of number of maximum samples mixed above, we can have tests for over 1,000 patients. If we double the number of test cups, $m = 12$, while keeping $l = 3$, we will be able to test as many as 220 patients; and if we triple it, $m = 18$, the number of patients that can be tested will be 816, and so on. In order to further demonstrate the effectiveness of the proposed approach, assume that we have 800 patients, and a single device that is capable in providing 6 parallel tests within 5 minutes. It will require 134 tests and consume 11 hours and 27 minutes for the tests to be completed by a single device. However, using the suggested approach, and assume that it requires 2 minutes extra to mix and distribute the samples using current technology (probably much less time), then it will require 3 tests to finish the job, i.e. after 18 minutes only we shall have the results for all 800 patients.

The lack of the number of testing in countries such as the US and the UK (and many other developing countries) is directly related to the lack of number of available tests as highlighted by experts, both at the collection and processing phases. The World Health Organization had made it clear and repeatedly that testing is an essential part of fighting against the virus. We believe that the proposed approaches, if realized properly, would largely help in the processing phase - given that samples have been collected - and thus allow access to a larger population. Even with devices such as the one recently launched by Abbott - molecular point-of-care test - that is capable in detecting the novel Coronavirus in as Little as 5 minutes, there is still a problem when handling very large numbers of tests where samples need to be held on queue – thus effectively the testing time becomes much longer than just 5 minutes. Integrating our approach, as an intermediate phase, by using standard mixing machines (an existing technology) one could achieve a further boost in the numbers of patients tested, and thus reducing the testing time while maximizing the number of tests carried out.

The feasibility of this approach is subject to biological, logistical and technical aspects that are left for experts in the field. We hope that the proposed approach will be considered and realized by governments sooner than later. It is worth noting that given the generality of the approach, it can be implemented in various laboratory tests.

Acknowledgement
The author is grateful to A. Kadri, A. Mansour, and M. Abu-Khalaf for fruitful discussions.

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