Using Compressive Sensing For Large-Scale Covid-19 PCR Tests

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***Abstract*—Currently, the most reliable and widely-used testing scheme for Covid-19 uses a reverse transcription polymerase chain reaction (rtPCR). The process amplifies the number of a chosen type of RNA strand exponentially. A coloring agent makes the amplified RNA strands visible. For each sample from a tested person, a PCR test must be run. Thus the number of PCR tests grows linearly with the tested persons. So far, the fraction of people infected with Covid-19 has been small, i.e. most tests had a negative result. The signal is therefore sparse: only a small number of swabs contains any trace of the virus, with the others not containing any at all. We propose the use of Compressive Sensing (CS) to vastly increase testing capacity. In CS, a small number of measurements (i.e. rtPCR tests in this case) is used to reconstruct the unknown vector (i.e. the density of virus RNA of all swabs). The proposed approach is faster than classical pooled testing. The total number of PCR tests required depends on the fraction of positive swabs, but the tests are independent of each other and can therefore be run in parallel.**

I. Introduction

Detection of the 2019 novel corona virus is currently performed using rtPCR [1]. While it is the most reliable test for now, it can only be performed in special laboratories and requires considerable effort. This makes testing a large number of people difficult.

If the fraction of infected persons is small, a classical approach to efficient mass-testing is pooling. For this process, samples from a small number of people are mixed together and tested - if the result is negative, every person in the group can be assumed to not carry the virus with high probability. If the result is positive, each person that contributed to the initial mix is tested separately. Another approach is to split the participants into two groups and repeat the process until all infected persons have been identified. For either strategy, it is possible to determine the optimal size of groups, for the former see e.g. https://www.csh.ac.at/pooling-corona-samples-boosts-test-efficiency/.

The downside of the first strategy is that it is only effective when the fraction of infected people is small. Furthermore, it is a two-stage process where the first stage does not give any indication regarding which participants are infected. The second strategy is more efficient regarding the total number of tests, but there are probably practical reasons why it is not the preferred approach. The rtPCR process takes some time, and testing even a relatively small number N of people using pooling requires $\log_2(N)$ rtPCR runs which have to be performed sequentially.

It would be desirable to instantly receive results for every tested person, while retaining the advantages of pooling, i.e. "compressing" the number of required tests by mixing. We believe that compressed sensing provides the answer to that question.

In CS the compressed vector $\boldsymbol{y}$ is obtained by multiplication of the sensing ("mixing") matrix $\boldsymbol{A}$ with the unknown vector $\boldsymbol{x}$. The sensing matrix is "wide", i.e. $\boldsymbol{A} \in \mathbb{R}^{L\times N}$ with $L \ll N$ and often sampled from the standard normal distribution or a Rademacher distribution (i.e. entries are from $\{-1, 1\}$). Sometimes, additive measurement noise $\boldsymbol{w}$ is assumed:

$$\boldsymbol{y} = \boldsymbol{A}\boldsymbol{x} + \boldsymbol{w}\,. \tag{1}$$

The matrix $\boldsymbol{A}$, the vector $\boldsymbol{y}$ and the distribution $f_{\mathsf{x}}(\boldsymbol{x})$, from which the vector $\boldsymbol{x}$ is drawn, are assumed to be known. The goal is to reconstruct the vector $\boldsymbol{x}$ in the large-system limit, i.e. for N large.

For this setting, a wide variety of algorithms have been proposed, such as matching pursuit [2], [3], basis pursuit [4], the "LASSO" (least absolute shrinkage and selection operator) [5] and associated linear programming approaches, as well as iterative thresholding [6], [7] and approximate message passing [8].

The variables can easily be associated with quantities in rtPCR testing: the vector $\boldsymbol{x}$ of length N represents the virus density of swabs collected from N tested persons while the shorter vector $\boldsymbol{y}$ of length L contains the virus density in a test tube after mixing. The matrix $\boldsymbol{A}$ is the mixing matrix: the number in the a^{th} row and i^{th} column determines the "amount of fluid" transferred from a test swab i to a test tube a. Clearly, this classical setting is not suitable for rtPCR testing: firstly, the sensing ("mixing") matrix contains negative entries and in practice, samples collected from test swabs can only be mixed together additively and not subtracted. Secondly, the matrix is dense. While it is wide and thus has fewer rows than columns, each test swab would still have to be mixed into a large number of mix tubes, possibly diluting the sample too much. Furthermore, the time needed to create the mix grows quadratically with the number of participants, since the number of rows L is a fraction of N, $L = \rho N$.

II. Mixing Matrix Design

Using limited knowledge regarding the processes involved in rtPCR testing and what is generally possible in a biological

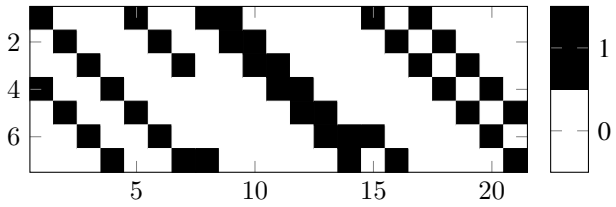

Fig. 1. Toy example of a mixing matrix obtained from an LDPC code check matrix. Larger matrices are much sparser, see e.g. [11, p.49].

laboratory, the following guesses regarding process requirements can be made. Firstly, it is desirable for any necessary mixing step to take as little time as possible. The time is at least partly dependent on the number of samples that need to be mixed. It is therefore desirable for the mixing matrix $\boldsymbol{A}$ to be itself sparse, i.e. contain only a small number of non-zero entries, since every one of these corresponds to a step in the procedure. Secondly, any mixing process has limited accuracy. Any inaccuracies add noise to the system. In order to minimize noise and maximize repeatability, any non-zero entries in the mixing matrix should be identical, or from a small set (e.g. either "one droplet" or "two droplets").

Fortunately, matrices with these properties can easily be obtained from a completely different field of research, namely that of low-density parity check (LDPC) codes, where the requirements for the so-called "check matrix" are similar (even though the matrix is defined over a finite field instead of $\mathbb{R}$). An example of such a matrix can be seen in Fig. 1. It is composed of three circulant sub-matrices of size 7×7. Each column is different from any other column, which is a basic requirement: it ensures that the entries of the unknown vector $\boldsymbol{x}$ can be distinguished. Furthermore, each column contains exactly two non-zero entries, while each row has six non-zeros, i.e. using this mixing matrix each test swab appears in two rtPCR test tubes, and each test tube contains samples from six participants.

There are many approaches to the generation of such matrices with varying degrees of sparsity and flexibility regarding the dimensions L and N. The matrix in Fig. 1 is obtained using Euclidean geometries [9], but even simple approaches such as the one suggested by Gallager [10] are worth considering here.

III. Algorithms

Unfortunately, the proposed mixing matrices severely limit the applicability of popular CS recovery algorithms. Two approaches remain possible: solutions based on convex optimization, which have very loose requirements regarding the mixing matrix, and message-passing based algorithms. Both are computationally intensive for large dimensions. Since "large" means $N > 10^4$, this is not a problem in the rtPCR setting. Due to the fact that message-passing based algorithms make it easy to use prior information regarding the signal (i.e. knowledge about the probability of virus densities in swabs), the proposed solution uses message passing.

The first algorithm is dubbed Gaussian message passing (GMP) and can be found in [12]. It is an intermediate result first found by Maleki et.al. [8], [13], who further simplified and optimized it using assumptions about the sensing matrix which are overly restrictive here. Since the sparse matrix is not zero-mean (a requirement of GMP), the mean has to be removed via a pre-processing step from both the measurements and the matrix. This process incurs a small error, which can be iteratively canceled out using techniques presented in [14] and suitably adjusted for Gaussian message passing.

Other approaches include CS recovery for sparse matrices, such as the one presented in [15, ZA-BAMP]. This approach is promising since its complexity scales with the number of non-zeros in the matrix and is therefore much smaller than that of Gaussian message passing, where the matrix is dense after subtraction of the mean. All non-zero entries are identical when using LDPC check matrices directly, however. Since ZA-BAMP requires a certain variation in the matrix entries, the mixing procedure would be more complicated. The algorithm's performance has so far not been analyzed in the case of mean-removal.

IV. Simulation Results

Preliminary results have been obtained using GMP and a rough guess of model parameters. For the simulation, a fixed matrix of size $N = 315$ and $K = 63$ has been used. This matrix realizes a modest compression factor of 5. Measurement noise of 30dB SNR has been assumed. The number of positive participants varies from one to 39. The virus density was assumed to be Bernoulli-exponential distributed, i.e. an exponential distribution is assumed to describe the virus density of positive participants' swabs, while every other swab has a virus density of zero. For each number of positive participants, 10^3 simulations have been performed.

The individual results for a fraction of these, along with an average signal-to-distortion ratio (SDR) can be seen in Fig. 2. The SDR in Decibel is defined as

$$\mathrm{SDR}_{\mathrm{dB}} = 10 \log_{10} \left(\frac{\|\boldsymbol{x}\|_2^2}{\|\boldsymbol{x} - \hat{\boldsymbol{x}}\|_2^2} \right) . \tag{2}$$

The data indicates that the algorithm is usable for up to 20 positive participants, corresponding to about 6%. For larger fractions of positives, the probability of the algorithm producing poor results becomes large, given the used compression ratio. The transition between usable and unusable results depends on the compression ratio $\rho = L/N$. Smaller ρ improves efficiency, since fewer rtPCR tests are needed per participant, but allows signal recovery only when the fraction of infected participants is small as well. Results for a single run are shown in Fig. 3, with Fig. 4 showing simulated noisy measurements obtained from rtPCR.

V. Challenges

In practice, we expect there to be a number of challenges. Firstly, it should be noted that the proposed message-passing based algorithms recover a number in $\mathbb{R}$, while rtPCR testing

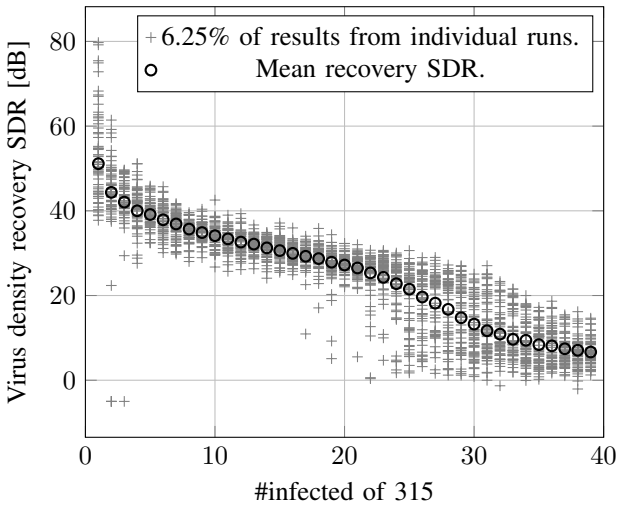

Fig. 2. Results in terms of SDR from CS recovery simulation using GMP with mean removal and iterative error cancellation.

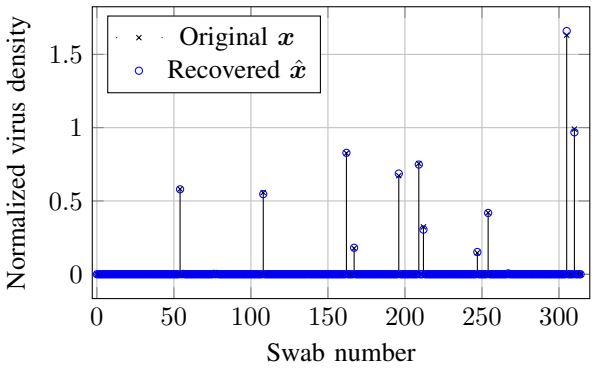

Fig. 3. Results of a single simulation. The recovered SDR is 34.7dB. There are 11 infected participants.

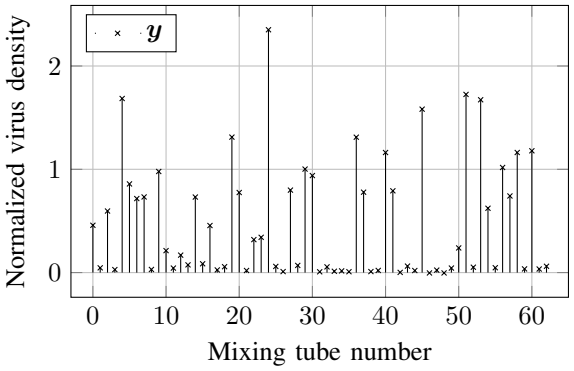

Fig. 4. Noisy measurements of RNA density in mixed test tubes.

usually results in a single diagnosis ("positive" or "negative"). Depending on the measurement noise, it is possible that swabs containing small traces of the virus cannot be distinguished from measurement noise. While this of course also affects testing when each individual is tested separately, the effect of measurement noise will be larger when mixing.

Secondly, while the proposed algorithms show state-of-the-art performance, their sub-sampling limit is about $\rho = 0.1$ even for extremely sparse signals, i.e. the number of measurements L must be at least[1] 10% of the number of participants N. In the special case of rtPCR it is possible to make use of effects visible for small infection rates. Consider the case where all participants are healthy: none of the test tubes will contain traces of the sought-after RNA. The participants contributing to the mixture of any test tube where the rtPCR confirms the absence of RNA have obviously tested negative and can be removed from the unknown vector $\boldsymbol{x}$. For the toy example above, a zero in a single row removes 6 participants from the set, while only removing a single measurement. This procedure can be repeatedly applied to remove all participants who have certainly tested negative, thereby increasing ρ.

The vector $\boldsymbol{y}$ of measurements is obtained as the result of rtPCR, necessitating equipment that has the option to produce detailed data regarding the RNA density of the mixture for a given test tube. Due to saturation effects we expect the readings' accuracy to depend on its magnitude. The measurement noise can therefore be expected to be non-uniform. While both proposed algorithms allow for anisotropic measurement noise (cf. [15], [16]), their performance has not yet been numerically analyzed for the rtPCR case, where more data is necessary to create an accurate simulation model.

Finally, there are cases where the recovery algorithm fails, i.e. it diverges and does not produce meaningful results. These cases are indicated by points at -5dB SDR in Fig. 2. Out of 39000 simulations, the algorithm failed 46 times, i.e. about 0.12%. The failures occur almost exclusively in instances where the number of infected participants is small (< 7). The algorithm is iterative and in many cases, the true signal is visible in intermediate iterations before the algorithm diverges. Furthermore, removing healthy participants using the process outlined above should stabilize a large fraction of instances where the algorithm initially fails.

VI. Conclusions

An approach to large-scale Covid-19 testing is outlined. Possible challenges are identified and mitigation strategies discussed. Preliminary simulation shows that the proposed algorithm yields usable results. Several challenges remain, some of which can only be approached with the help of experts in the field of molecular biology and people with laboratory experience. Further testing is required to assess the viability of the approach in a practical setting.

[1]The theoretical sub-sampling limit according to information theory is $L = K$ (for linear measurements), where K is the number of infected participants.

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