Jittered sampling - a potential solution for detecting high frequencies in GCaMP recordings

Andrei Ciuparu
Transylvanian Institute of Neuroscience
Ploiești 33, 400157 Cluj-Napoca, Romania
Technical University of Cluj-Napoca
Bariţiu 26-28, 400027, Cluj-Napoca, Romania
Email: ciuparu@tins.ro

Raul C. Mureșan
Transylvanian Institute of Neuroscience
Ploiești 33, 400157 Cluj-Napoca, Romania
Email: muresan@tins.ro

***Abstract*—Multi-photon microscopy is a widely used method to measure cortical activity through the use of calcium indicators called GCaMP. These methods have inherent limitations stemming from the fluorophore as well as from the microscope setup that effectively limit the rate at which the activity can be measured. According to the Nyquist-Shannon sampling theorem, this limits the bandwidth of activity that can be estimated using these methods. Here we introduce and test an extension to current recording setups based on irregular (jittered) sampling that may be able to partialle overcome these limitations. We generated synthetic datasets consisting of mixtures of oscillations at different frequencies, sampled far below the Nyquist rate. We show that by sampling the oscillations at multiple phases using a random delay between acquired samples it is possible to characterize the amplitude of an oscillation present in the signal. Furthermore, the predicted amplitude associated to aliases of the measured frequency is reduced. Finally, we show that it is possible to detect and characterize an oscillation packet embedded in a noisy, undersampled signal.**

***Index Terms*—Gamma frequency, Undersampling, irregular sampling, optimization, GCaMP**

I. Introduction

Using fluorescent proteins coupled with two-photon microscopy is a common experimental technique in brain research, as well as in other fields of biology and medicine. While this method can be used to analyze the structure (as well as structural changes) in various cells, it has also been used to measure the activity of neurons, by coupling two of these proteins into a structure that is sensitive to calcium (GCaMP) [1]. This approach, enables the measurement of the activation of hundreds of neurons simultaneously and had led to multiple discoveries. Although this method is powerful, it has several limitations that stem from how these proteins behave, as well as limitations stemming from the recording hardware itself [2]. These limitations constrain the frequencies that can be observed and thus limit the usefulness of the method. Here, we outline a possible, easy to implement solution which may allow the measurement of high-frequency activity in the brain (e.g. gamma oscillations) using GCaMP. The solution is based on irregular (jittered) sampling. We generate synthetic datasets sampled with both a regular and irregular sampling scheme and apply a fitting algorithm to detect and predict the amplitude of an oscillation at a given frequency, which is well above the Nyquist frequency.

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A. Problems arising from undersampling

One of the most well-known tenets of sampled signals is the Nyquist-Shannon sampling theorem, which states that in order to capture all of the available information in a signal such that it is possible to reconstruct it, one needs to sample at a rate that is at least double that of the highest frequency present in the signal [3]. The consequence of attempting to reconstruct signals sampled below the Nyquist rate is aliasing, whereby the undersampled oscillation appears as multiple false oscillations at lower frequencies distributed around multiples of the sampling frequency, a phenomenon known as spectral folding [4].

B. The limitations of GCaMP recordings

In order to study the functional mechanisms of the brain, it is often necessary to use animal subjects, as they offer the possibility of invasive recordings, as well as genetic tagging with fluorophores (such as GFP or GCaMP), which allow to record activity using various optical measurement techniques [2], or with opsins, which allow to directly influence the activity of the brain using light (referred to as optogenetics) [5]. Here, we will focus on multi-photon microscopy of neurons tagged with a calcium dependent fluorophore, GCaMP, which fluoresces when hit with a specific wavelength of light, only in the presence of calcium. This allows to measure the activity of the neurons because when these are active and fire action potentials, an influx of calcium rushes into the cell body [6]. This calcium influx is a correlate of the cell's activity. Recording signals from the brain using GCaMP has several advantages compared with electrophysiological recordings, as well as several limitations.

The main advantage of using GCaMP imaging is that it allows to simultaneously measure the activity of a large number of neurons, as well as measure the activity of structures that are much smaller, such as synaptic boutons [7]. The light from a

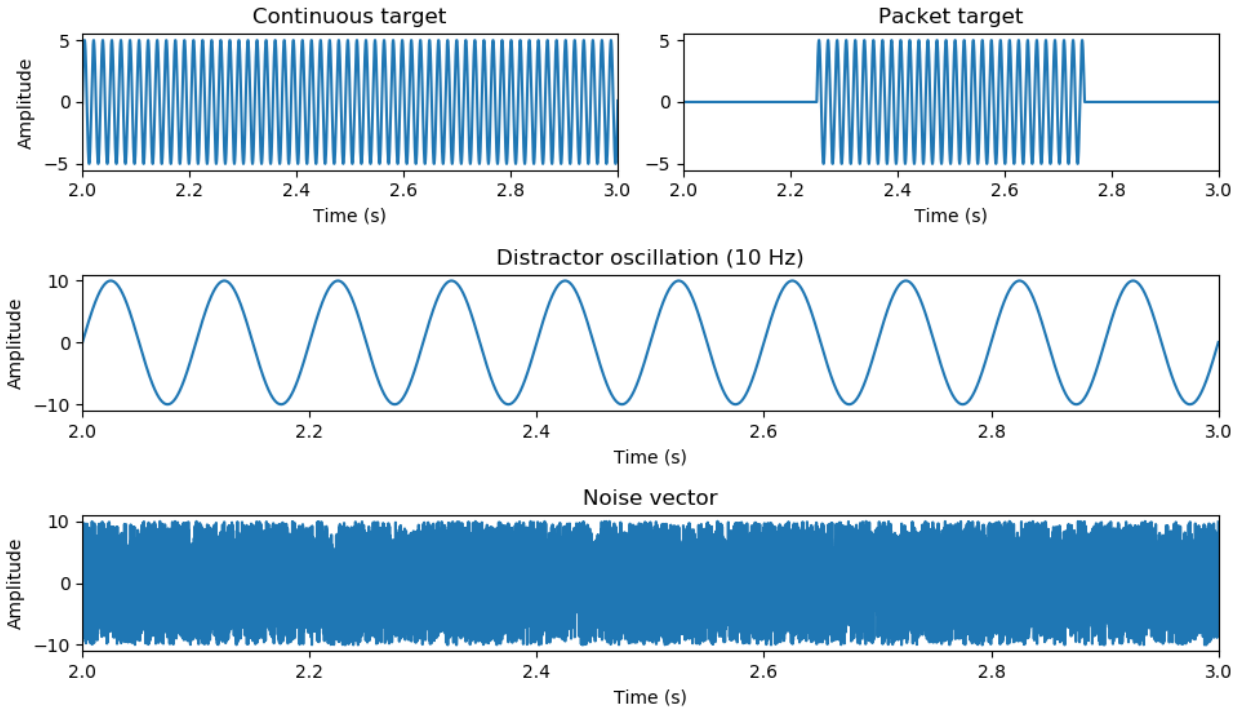

Fig. 1. **Components of generated signals** The title of each subplot describes the role of the component in the final test signal.

tuned laser is focused onto the sample repeatedly in a raster-style pattern, and the photons produced by fluorescence are measures, producing a "video" of the fluorescence variations in time [2]. The advantages of being able to measure a large number of neurons or smaller neuronal structures and of being able to track the neuron identity easily (compared to electrophysiological methods), come with several shortcomings of the fluorescent protein and of the hardware used to measure, both having a detrimental impact on the sampling rate that one can obtain. The first major drawback is that calcium signals have slower dynamics than the electrical fluctuations at the level of the neural membrane, effectively low-pass filtering the target signal [8]. This limits the bandwidth of activity that we are able to measure. With current calcium indicators this limit is around 30-40 Hz [8], however it is constantly being extended through the development of more advanced fluorophores with faster dynamics. Newer versions, such as GCaMP7 may be able to raise this limit to 60 Hz [9]–[11]. Another limitation that stems from fluorophore dynamics is that in order for the fluorophore to reach its excited state light must be provided for a period of time (in other words the amount of time that the light from the laser must be focused onto one "pixel" has a lower bound). Both of these limitations set an upper bound on the frequencies which can be routinely measured using this methodology.

The second set of limitations arises from the hardware itself. Practically, the speed at which the sample is scanned (the time it takes to measure a frame of activity) is limited by how fast one can move the light from the laser. The location of the focal point is usually controlled by a two-mirror setup, one oscillating quickly which determines the x position, and one oscillating more slowly determining the y position [2]. As such, the bottleneck in this system comes from how quickly the x position mirror is capable of scanning a line. There are many more factors which can influence this scanning speed (such as the size of the sample, its depth compared to the cortical surface, and so on), but essentially the net effect is that in order to obtain good data, there is a hard upper bound on the sampling rate that one can reach. Current microscopes are capable of reaching a sampling rate of tens of Hz. Taken together, the limitations associated to GCaMP imaging result in an effective reduction, by several orders of magnitude, of the sampling rate when compared to electrophysiological methods, effectively limiting the types of activity that one can observe. Nevertheless, the capacity to measure so many cells at the same time is a major advantage for many experimental applications. Therefore, being able to infer faster processes from GCaMP imaging is highly desirable. Here, we investigate a way to increase the scope of this measurement paradigm by overcoming its bandwidth limitations through the use of non-uniform (jittered) sampling.

C. Jittered sampling in other domains

Jittered sampling is the practice of measuring samples at random (rather than fixed) time points [12]–[14]. Many factors can contribute to a limitation of the sampling rate, effectively setting a lower bound for the amount of time that can exist between consecutive samples. Jittering these samples does not violate this lower bound, but rather decreases the sampling rate further by introducing random delays on top of the minimum

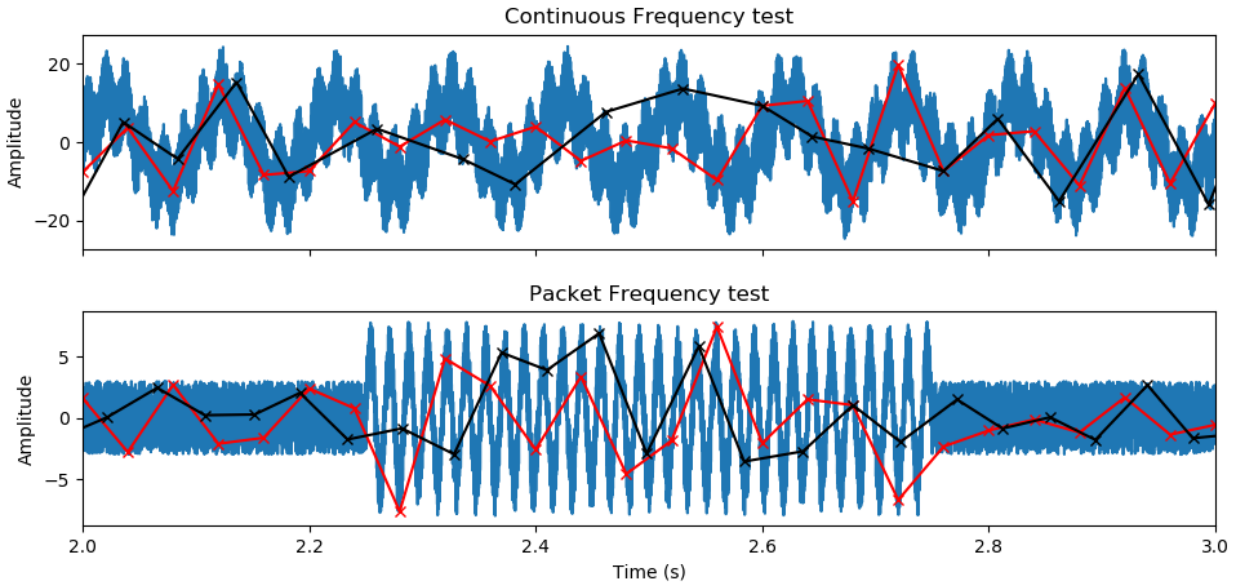

Fig. 2. **Undersampling schemes applied to test signals.** The red markers and line represent regular sampling, while the black markers and line represent irregular sampling applied to the constant case (top), and packet case (bottom) respectively

time between samples. This has the effect of producing a finer sampling grid and measuring the oscillations at more phases than regular sampling does [15]. We can consider that this is analogous to measuring at a much higher sampling rate, dependent on the delay step that is introduced, and downsampling randomly to the actual sampling rate.

While irregular sampling schemes have been discussed and proposed in mathematical theory since 1990, they have seen limited use in practical applications [12]–[14]. Hennenfent I& Herrmann (2008) proposed a method based on random undersampling for wavefield reconstruction in the field of seismology, arguing that random undersampling renders coherent aliases as incoherent random noise [16]. Hollingsworth (2015) also developed a method based on irregular undersampling which would speed up structural MRI recordings by requiring fewer samples, but be able to capture enough detail to be useful [17]. To the best of our knowledge, nobody has proposed this type of method for the measurement of cortical activity, which has the particularities of not being stable (compared to the MRI structure) and evolving on fast timescales (compared to seismological data).

Our goal in this study was to evaluate if we could characterize an oscillation from an undersampled signal, given the known frequency of that oscillation. Multiple paradigms elicit oscillatory activity in the brain at known frequencies, such as the alpha oscillation (10 Hz) produced in the occipital lobe when eyes are closed [18], or entrainment of gamma oscillations (30-150 Hz) by a flickering light at the flicker frequency [19]. Gamma oscillations are of a particular interest because recent studies have shown that entraining these oscillations may be a viable treatment for Alzheimer's disease [20]. To better understand how this process occurs, a tool which would allow the measurement of gamma oscillations in many neurons simultaneously is needed. Thus, here we attempt to find a way to extend current procedures for GCaMP recordings such that such a measurement is possible.

II. Materials and Methods

To test whether we could extract higher frequency information from a signal sampled below the Nyquist rate, we generated multiple synthetic examples consisting of a target oscillation, a distractor oscillation, and noise at a high sampling rate, and then downsampled using either a fixed sampling rate or a jittered one.

A. Test signal generation

For a first dataset, we generated long signals with mixtures of pure oscillations. We began by generating a time vector of 5 seconds with a sampling rate of 10 kHz. We then applied a sine function (eq. 1) on this time vector (t) with A equal to 5, ω equal to 59 * 2 * π and ϕ equal to 0. This yielded a sine wave with a frequency of 59 (we chose the frequency 59 as this does not have divisors or multiples in the range 0-100) and an amplitude of 5 (arbitrary units), sampled at 10 kHz, which we considered our target oscillation (figure 1, left). Similarly, we generated a signal representing the distractor oscillation with an amplitude of 10 (figure 1, middle). The phase offset and frequency of this distractor oscillation varied as a function of the specific experiment, but in all cases, we only considered integer frequencies between 1 and 100 Hz.

$$f(t) = A * sin(\omega * t + \phi) \quad (1)$$

We then also generated uniform white noise with values between -10 and 10 to simulate very noisy measurement conditions (figure 1, bottom). The final signal was then the sum of the target oscillation, the distractor oscillation, and a

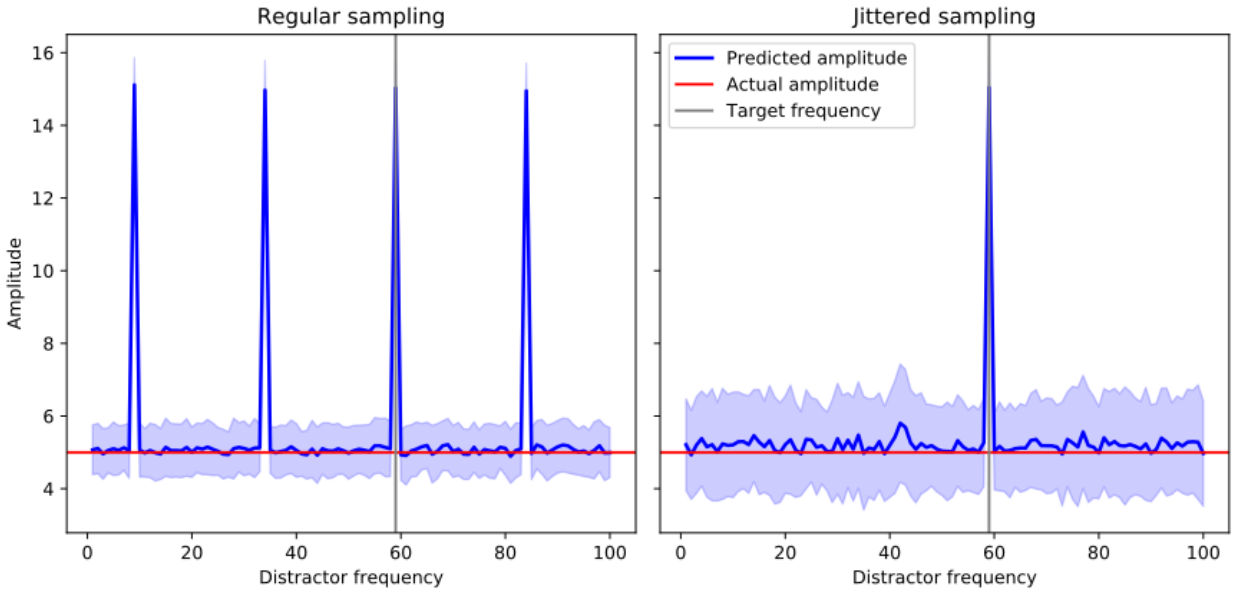

Fig. 3. **Predicted amplitude on constant oscillation sets** undersampled with regular (left) or irregular (right) schemes. The shaded areas represent the standard deviation over 100 runs. Predicted amplitude of the target (blue) is shown as a function of the frequency of the distractor component (x axis). The actual amplitude of the target is shown in red

noise vector. This final signal, as well as the original time vector were then downsampled such that the sampling rate was 25 Hz, yielding the 125-length input and time vectors.

For a second set of tests, we generated a localized burst of oscillation at the target frequency instead of a pure, constant frequency (figure 1, right). This was accomplished by taking a 500 ms segment of the pure frequency we used before, and adding it to the noise vectors we used above in the middle of the generated signal. Here, we did not add a distractor oscillation, because the goal was to see if we could localize the oscillation packet in time as well as frequency. Furthermore, the noise amplitude was reduced to 3, reflecting more realistic conditions.

While standard undersampling to 25 Hz was accomplished by taking the samples at a fixed distance of 40 ms in time (figure 2, red), jittered undersampling was accomplished by taking samples at a random uniform distance between 40 and 80 ms with an allowed step of 2 ms (samples could be taken at 40, 42, 44…80 ms; figure 2, black). For the second set of tests, we reduced the maximum jitter time (between 40 and 50 ms) so that we had more total samples from which to extract information. For the characterization of the target oscillation the minimum necessary sampling rate (as postulated by the Nyquist-Shannon sampling theorem) is 118 Hz, thus all sampling schemes applied here were significantly below this minimum, i.e. signals were undersampled.

B. Gamma estimation procedure

To estimate the target oscillation amplitude, we attempted to use a simple function fitting procedure. The model that we attempted to fit was (eq.1), where the variables were A and ϕ, and ω was a fixed parameter. The loss function that we attempted to minimize was the mean squared error between the observed amplitude at the given timepoints and the predicted amplitude at those points. Finally, we used the BFGS optimization algorithm [21] to minimize the loss function of the given model by adjusting the variables.

III. Results

A. Jittering reduces the predicted amplitude at aliased frequencies

In the first analysis we tried to detect the amplitude of a constant oscillation of 59 Hz from the signal containing noise and a distractor frequency with the goal of determining which frequencies would interfere. We first attempted to measure only the effect of frequency of the oscillation, so in this case, the phase offset between target and distractor oscillations was set to 0. We ran 100 different simulations for distractor oscillations of each frequency, generating different noise vectors, and computed the standard deviation and average absolute predicted amplitude. We considered the absolute amplitude because the algorithm tended to set a negative amplitude and the phase to the antiphase of the actual target. This tendency is not in itself a problem because it is easily corrected by checking if the amplitude is negative and correcting it by inverting the amplitude and subtracting π from the phase.

In this test, with standard sampling (figure 3, left) we were able to observe several large peaks in the predicted amplitude at specific frequencies of the distractor (9, 34, 59, 84 Hz), while in all other cases, the predicted amplitude was very close to the actual amplitude of the target frequency. These results are to be expected due to aliasing. Jittered undersampling, however, proved to make a dramatic difference when compared to regular sampling, effectively enabling the detection of the correct amplitude of the target frequency in

all cases (figure 3, right). The target oscillation was correctly predicted in all cases, including the peak present at 59 Hz, where the true amplitude of the oscillation was 15 (sum of target and distractor). The variance of the predicted amplitude was slightly higher in the case of jittered undersampling, and the average predicted amplitude had peaks around the target oscillation frequency at a distance of 17 Hz.

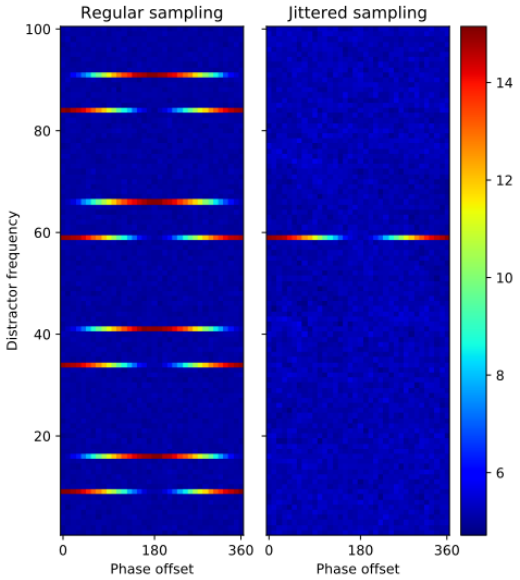

Fig. 4. **Predicted amplitude on constant oscillation sets** with a phase delay between target and distractor oscillations undersampled with regular (left) or irregular (right) schemes. The color represents the predicted amplitude as a function of distractor frequency (y axis) and phase offset between the distractor and target (x axis)

To further understand the effect of interfering frequencies and what happens when we sample the mixtures irregularly, we ran a similar analysis where we varied the phase offset as well as the frequency of the distractor oscillation (figure 4). Practically, the first column in this figure represents the average predicted amplitudes that were plotted in the previous figure, and each subsequent column represents the average predicted amplitude of the oscillations with a phase offset.

B. Jittering allows us to localize and characterize a gamma packet

While this first series of tests allowed us to verify and understand both how jittered sampling impacts our ability to extract high-frequency information from undersampled signals, as well as the limits of our ability to predict, they are very far from a real test case. Activity in the brain is rarely constant over such long time periods; in other words, we would expect the oscillation amplitude and frequencies to change over a period of 5 seconds, hence the reason for generating the packet sets [22]. For this set of tests, we attempted to fit all integer frequencies from 1 to 100 on each analysis window of 500 ms with an analysis step of 10 ms, yielding a time by frequency plot with the predicted amplitude for the regular as well as irregular sampling schemes. This procedure was repeated 100 times with different noise vectors in order to obtain an average.

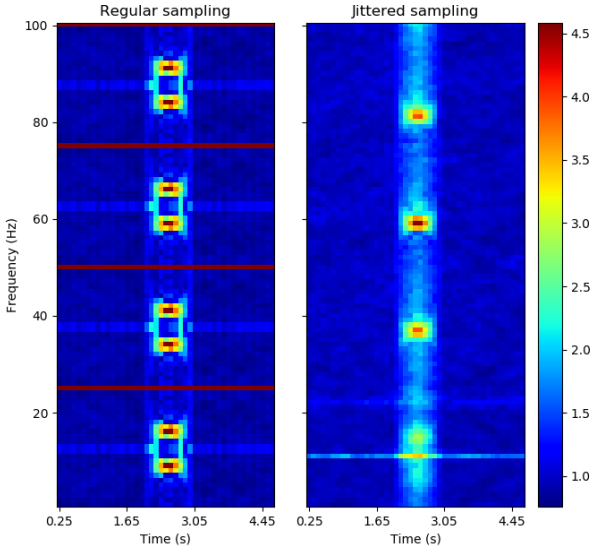

Fig. 5. **Predicted amplitude on packet oscillation sets** in time undersampled with regular (left) or irregular (right) schemes. The predicted amplitude of each frequency (y axis) is shown in time (x axis).

The results can be seen in figures 5 and 6, where we show the predicted amplitude for all frequencies over time and averaged over the time during which the pulse was present, respectively. Similar to the continuous case, the fitting algorithm predicted a higher amplitude for the target oscillation than any other frequency only in the case of irregular sampling. In the regular sampling condition, on the other hand, oscillations with a frequency which is a multiple of the sampling frequency had the highest amplitude, as well as a series of smaller aliased peaks. These analyses show that it is possible to describe an oscillation well in both frequency and time, even given undersampled signals, provided that the sampling times are jittered with respect to one another.

IV. Discussion

Here we have shown that introducing a random jitter between the frames in a GCaMP recording could enable the inference of information about high-frequency activity, which is not normally accessible in regular sampled calcium signals. First, we have shown that given a long enough time interval on which to measure an unchanging signal, one can accurately predict the amplitude of an oscillatory component at a given frequency. While with a regular sampling scheme, this achievement is not possible due to the appearance of aliases, using irregular sampling one can recover the true oscillation amplitude for the known frequency. This is most likely enabled by the multiple phase sampling that occurs due to the jitter between the samples. This result was reinforced when generalizing the analysis to conditions where distractor oscillations with a phase offset were mixed with the target oscillation. Furthermore, these results show beyond reasonable

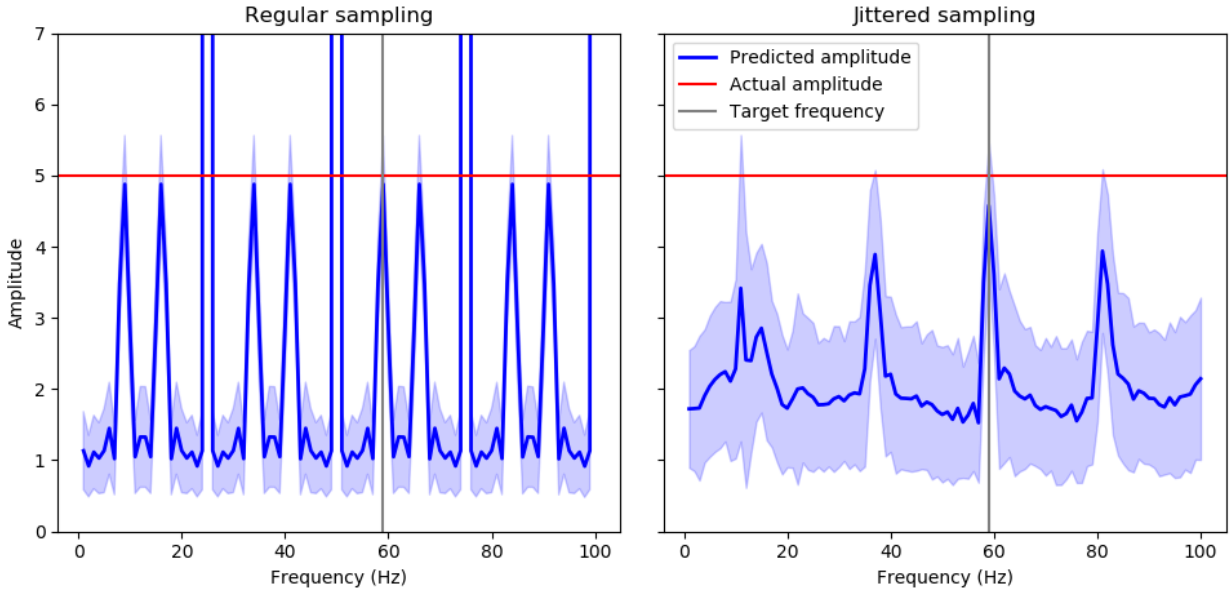

Fig. 6. **Predicted amplitude on packet oscillation sets** averaged over the time windows where the oscillation was present in signals undersampled with regular (left) or irregular (right) schemes. The shaded areas represent the standard deviation over 100 runs. The predicted amplitude of oscillations at each frequency (x axis) is shown, where the only real oscillation present is at the intersection of the grey and red lines.

doubt that these feats are possible, given the ability of the algorithm to function in such difficult signal to noise ratio conditions (noise and distractor amplitudes were twice that of the target signal). Finally, we tested the capabilities of the algorithm by trying to predict the frequency, amplitude, and timing of an oscillatory packet from a more realistic signal. While in this case, due to the analysis window being much smaller, the random jitter had to be reduced, and the algorithm's performance suffered under more noisy conditions, we were able to accurately distinguish the target oscillatory packet under more realistic conditions. Given these findings, we propose using irregular sampling schemes in conjunction with multi-photon microscopy on GCaMP fluorophores for the detection and characterization of oscillations in the brain.

A. Implementing jittered undersampling in recording hardware

Here, we generated toy datasets at a very high sampling rate (essentially mimicking an analog signal), and applied two different undersampling schemes in order to simulate recording an analog signal with either a fixed, or jittered sampling rate. In order to apply irregular sampling in real recording cases, the jittering of the samples must be achieved through the recording setup itself. In the case of two-photon microscopy, this may be achieved by measuring more than one frame while scanning, which would amount to changing the software that controls the vertical axis mirror, such that it measures one or more extra lines in each frame, before resuming the ordinary raster pattern. This would effectively introduce a random delay between frames with a minimum time offset equal to the duration it takes to measure one line, achieving a jittered sampling scheme.

B. Testing on real data

While our results show that it is possible to characterize high frequency activity given a long enough packet in high amplitude white noise conditions, these conditions do not fully match what we would expect to see in the brain. The first major difference between natural brain activity and our generated signal is that the amplitude of brain oscillations changes in time, which could lead do erroneous estimations of amplitude. Secondly, the oscillation packet length is often smaller than the one used in this experiment, which could potentially limit the use of this method to experiments where the oscillation is entrained powerfully. Finally, the statistics of the noise in the brain more closely match pink noise, which has a 1/f power distribution, rather than white, which has a flat power distribution. These differences may impact the accuracy of our estimation in various ways, but it is difficult to test all combinations of possible sources of error without access to real data recorded with irregular sampling.

To further consolidate these results, cementing this methodology for the measurement of high frequency activity in the brain, further experiments on real data could be performed. One example of such a study would be to apply a stimulation paradigm known to cause high-frequency activity in the brain and to alternatively measure the resulting oscillations using the method outlined above. One could then use high sampling rate electrophysiological methods to cross-validate the results. This way, we could prove that the methodology is viable for in vivo use cases, as well as see what other practical problems or limitations arise from its application.

V. Conclusions

Here we have introduced and tested a new measurement paradigm for high frequency brain activity on simulated datasets based on irregular sampling. We have shown that the finer sampling grid provided by such a sampling scheme offers the possibility of correctly estimating the amplitude, frequency, and timing of oscillations with frequencies above the Nyquist frequency. Current two photon microscopy of calcium signals is a very powerful tool for the measurement of cortical activity, with the major limitations stemming from the limited sampling rate. We argue that introducing a jitter between samples by measuring extra lines at the end of each frame would enable calcium imaging to reveal high-frequency oscillations, which can normally not be accessed through this technique.

VI. Acknowledgements

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