Architecture of zero-latency ultrafast amplitude detector for high-speed atomic force microscopy

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Submolecular-scale biofunctional dynamic processes play central roles in life science, and hence, unraveling the mechanisms underlying these dynamic processes is essential for the advancement of such fields. High-speed atomic force microscopy (HS-AFM) is an emerging paradigm-shifting technique that can perform real-time observation of living biomolecular dynamics at submolecular spatial and sub-second temporal resolutions. However, there are numerous biofunctional processes that cannot be imaged by the current HS-AFM system due to its inadequate temporal resolution, e.g., imaging the motion of ion transporters and lipid rafts embedded in a suspended lipid bilayer or cell membrane requires at least 1–10 ms temporal resolution. Therefore, further broadening of the bandwidth of HS-AFM to fill the gap between the current and required temporal resolutions is an important challenge.

The critical scan rate-limiting devices in the current HS-AFM system are the Z piezo scanner, cantilever, and amplitude detector. The latencies of the Z piezo scanner and cantilever are dictated by their resonance frequencies ($f_z$ and $f_{cl}$, respectively), which can be improved by miniaturizing their dimensions. A complementary approach is to double the scan rate by simply skipping the backward scan. Most importantly, the HS-AFM setup adopts an amplitude-modulation scheme, where the cantilever oscillation amplitude is exploited for the feedback signal, and thus, the amplitude detector constitutes the heart of the technology and is one of the most important rate-limiting devices. By improving its bandwidth, we aim to improve the scan rate and temporal resolution of HS-AFM, broadening its applicability to short timescale biofunctional processes.

In this study, we conceived a differential-based (DB) detection algorithm by modifying a recently proposed phase-shift-based (PSB) algorithm. Our method is simple and eliminates intrinsic latency; hence, it is much faster than conventional methods. We believe that this invention will be an indispensable component in the faster HS-AFM.

The standard dynamic-mode AFM setups adopt a common RMS-DC converter, but its bandwidth is inadequate for HS-AFM applications because sufficient ripple suppression requires the time integral over at least several cantilever oscillation periods. Therefore, three types of amplitude detector have hitherto been proposed,
delay becomes 360° respectively (supplementary material, Note 1 and Figs. S2 and S5). In this study, we have conceived a DB method with no intrinsic latency, which results in the fastest performance. Below we compare and contrast the DB and PSB methods since they are analogous, demonstrating the utility of the DB method.

Figure 2 shows the schematics of the PSB and DB methods, which are based on the basic trigonometric theorem as follows:

\[ A = \sqrt{(A \sin \omega t)^2 + (A \cos \omega t)^2}, \]

where \( A \) and \( \omega t \) are oscillation amplitude and radial carrier (driving) frequency, respectively. Since \( f_c (= \omega / 2\pi) \) is not necessarily \( f_d \), the cantilever drifts do not disturb the measurements. The input sine wave first undergoes a high-pass filter (HPF) to remove the low-frequency cantilever deflection arising from the tip–sample interaction force. The HPF cutoff frequency \( (f_{c,0}) \) should be higher than \( f_c \), above which the force is not modulated (Supplementary Note 1). Then, it is divided into two lines, one of which is converted to a cosine wave via a 90° phase shifter (PS) according to the following relationship:

\[ -A \cos \omega t = A \sin (\omega t - 90°). \]

Then, both the signals are squared and summed up again to produce the squared amplitude \( (A^2) \), followed by a square root conversion to generate the \( A \) signal. Theoretical simulations revealed that the phase delay of the PSB analog circuit is predicted to be 30°.

The DB method can be achieved by simply replacing the PS with a differentiator circuit to produce the cosine wave as follows:

\[ A \cos \omega t = \frac{1}{\omega_c} \frac{d}{dt} (A \sin \omega t), \]

where there is no theoretical phase delay and only the circuit processing limits the conversion rate. As discussed later, we revealed that the square root computation is the bottleneck in the analog circuit; to overcome this, the \( A^2 \) output can also be exploited for the feedback signal with a remarkably faster throughput than the \( A \) signal. Moreover, a simulation revealed that the \( A^2 \) output shows superior frequency characteristics over the \( A \) output even excluding the analog latency (Fig. S2). Hereafter, we abbreviate the \( A^2 \) and \( A \) output of DB (PSB) as DB-A2 (PSB-A2) and DB-A (PSB-A), respectively. Importantly, for the PSB operation, the center frequency must be tuned to \( f_d \) for each experiment. Similarly, for the DB operation, since the differential value is proportional to the cantilever frequency, the differentiator gain must be optimized for each experiment.

We built two types of DB and PSB test circuits; an analog circuit employing commercial operational amplifiers (Fig. S1) and a digital circuit employing a field-programmable gate array (FPGA) (National
Instruments: PXIe-7966R). To demonstrate the superiority of the DB method, we first measured the frequency characteristics using amplitude-modulated signals with $f_c$ of 300–1500 kHz [Fig. 3(a)]. The sweeping of the modulation signal (modulation depth was 0.5) and the response detection were carried out using a frequency response analyzer (NF: FRA5097). In this experiment, we did not use an HPF to characterize the intrinsic detector performance, but an HPF with $f_{\text{HPF}}$ of 159 kHz was used in all other subsequent experiments.

From acquired spectra (Figs. S6–S9), we revealed that FAB and SHB produce dips at the harmonic frequencies of $f_c$ while PSB creates a single broad dip at the second harmonics of $f_c$, and thus, these techniques do not produce flat gain and phase curves. These characteristics were reproduced by the simulation, confirming the intrinsic latency that exists in these techniques. In contrast, the gain curve of DB-A$^2$ showed a nearly flat characteristic, especially at the frequency below $f_c$ [Fig. 3(b)]. Although the phase curve decreased with increasing modulation frequency, this is not intrinsic latency but rather the analog circuit latency arising from the differentiator because this curve was well fitted by the dead time theorem, wherein the phase delay ($\Delta \varphi_{\text{dead}}$) is expressed by

$$\Delta \varphi_{\text{dead}}(\omega) = -\omega \Delta \tau,$$

where $\Delta \tau$ is the dead time.

We defined the detector bandwidth ($f_D$) as the frequency that results in a 45° phase delay [orange broken arrow in Fig. 3(b)] beyond which the feedback loop cannot be appropriately controlled. In the summarized $f_D$ graph [Fig. 3(c)], the FAB and SHB results showed an almost linear increase in $f_D$ as $f_c$ increases. Notably, the SHB curve overlapped well with the theoretical 180° line while FAB was slightly lower than the theoretical 360° line due to the digitalization latency. In contrast, DB-A and PSB-A (the latter being equivalent to the previously published setup$^{14}$) exhibited almost a saturated flat appearance, indicating that the throughput of the whole device was bottlenecked by the square root circuit whose latency is much larger than the intrinsic ones.

DB-A$^2$ and PSB-A$^2$ were 5 times faster than DB-A, and PSB-A, respectively, while DB-A$^2$ was almost twice as fast as PSB-A$^2$, 10–20

![FIG. 3. Schematics of the experimental setups (a), (d) and typical frequency response characteristics of the DB-A$^2$ method (b), (e), for detector (a), (b) and feedback (d), (e) circuits. In (b), green broken curve indicates a theoretical fitted line by the dead time theorem. (c) Dependency of detector bandwidth on carrier frequency. (f) Dependency of feedback bandwidth on the setpoint/free amplitude ratio. Theoretical values calculated by approximate equation (4) and simulation ( ) are also displayed. For the calculations, the phase delay of SHB and FAB (190° and 540°) was taken from the data shown in Fig. 3(c), while those of DB-A$^2$ and PSB-A$^2$ (30° and 90°) were taken from the experimental data obtained with HPF (data are not shown).](image-url)
times faster than FAB and 3–8 times faster than SHB. The PSB-A2 curve showed a linear dependence on \( f_0 \) due to the intrinsic latency, but gradually saturated in the high frequency range because of the latency in the square processing. In contrast, DB-A2 showed almost a saturated appearance over the entire \( f_c \) range. Although zero latency could not be observed experimentally due to the analog circuit latency, surprisingly, below \( f_c \) of 1 MHz, \( f_0 \) went beyond \( f_c \) (corresponding to the 45° line) and even the theoretical PSB bandwidth of the 30° line. These observations clearly evidence the zero latency of the DB method.

This saturated appearance is more clearly visible in the DB-A2 digital circuit (see square marked broken line), whereby \( f_0 \) was 330 kHz over the entire \( f_c \) range, because the cutoff frequency of the differentiator circuit slightly correlates with \( f_c \) while the dead time of digital processing is constant. In our FPGA system, the main latency is from the transceiver (300 ns), an interface that converts the signals from analog to digital. Although \( f_0 \) was not as high as that achieved by the analog circuit [Fig. 3(c), Figs. S10–S12, and supplementary material, Note 2], it exceeded those of the conventional methods. In the digitalization, DB has an additional advantage over PSB because DB retains the zero-latency performance while the phase delay of PSB slightly deteriorates from 30° to 45° (supplementary material, Note 1).

Note that we did not employ the fastest models of operational amplifiers and transceiver because the present work is intended as a demonstration, and hence, the performance could be further improved using faster models. (We expect \( f_0 \) of faster than 2 and 1 MHz for the analog and digital circuits, respectively.)

Importantly, in practical experiments, the signal-to-noise ratio (i.e., noise performance) of DB and that of the other methods are comparable. This is because the cantilever transfer function suppresses the noise in the high frequency range, averting significant deterioration in the noise performance of DB even through the derivative- and square-computations. A detailed analysis of the noise performance of all methods will be published elsewhere.

In practical measurements, a bandpass-like cantilever resonance characteristic suppresses even the AM signals, significantly deteriorating the feedback bandwidth (\( f_{FB} \)). To quantify the superiority of DB in such conditions, we subsequently evaluated \( f_{FB} \) by employing an AFM mock circuit [Fig. 3(d)].14 We set the resonance frequencies (\( f_{cl} \) and \( f_0 \)) to 1200 and 150 kHz and the quality factors of the cantilever and Z scanner (\( Q_{cl} \) and \( Q_z \)) to 1.5 and 0.7, respectively. Upon optimizing the PID feedback parameters under certain criteria (Fig. S13), the frequency response characteristics of the whole feedback circuit were measured by sweeping the frequency of a sinusoidal topography wave [Figs. 3(e) and S14–S17].

We defined \( f_{FB} \) as the 45°-crossover frequency and plotted them in Fig. 3(f) as a function of the setpoint/free amplitude ratio. The cantilever oscillation amplitude was set to five times larger than the topographic wave amplitude (also see Fig. S18 for other oscillation amplitudes). The bandwidth gradually increased as the setpoint ratio was reduced for all devices. DB-A2 showed 20%–30% better performance than PSB-A2 and SHB, and it was almost three times faster than FAB. DB-A2 showed several times greater \( f_{FB} \) than that of SHB, but this difference became slight in \( f_{FB} \) due to the existence of \( Q_{cl} \) and \( Q_z \).

To explain this difference, we also make a theoretical consideration below. The \( f_{FB} \) can be estimated by an explicit analytical equation, formulated based on a dead time theorem approximation in the open-loop system,15

\[
 f_{FB} = \frac{1}{\left( \frac{4\pi f_{AMP}}{f_{AMP} + \frac{8\pi Q_{cl}}{f_{cl}} + \frac{8\pi}{f_{2z}} + \frac{8\pi}{\delta}} \right)}, \tag{5}
\]

where \( \Delta f_{AMP} = \pi/8 \times f_{cl}/f_0 \) is the phase delay in the amplitude detector and \( \delta \) is the latency in the other components. Although the calculated values are on the same order as the experimental data, it could not reproduce the significantly large difference in \( f_{FB} \) with respect to \( \Delta f_{AMP} \). This discrepancy may arise since the real transfer functions of the cantilever and Z piezo scanner are not expressed by the dead time theorem. To verify this hypothesis, we also simulated \( f_{FB} \) based on the closed-loop feedback system (supplementary material, Note 3 and Fig. S19) and obtained a much more quantitative agreement between the overall experimental and theoretical results with respect to the individual amplitude detectors [Fig. 3(f)]. Note that spurious peaks caused by the acoustic excitation increase the apparent \( Q_{cl} \) in liquid-AFM,1 but it ought not to correlate with \( f_{FB} \) because the tip–sample interaction force is directly exerted on the tip.

Finally, to experimentally validate the performance of the DB-A2 method, we performed HS-AFM imaging of biopolymeric actin filaments with FAB and DB-A2 because they are easily depolymerized by the tip perturbation and well-suited for the evaluation of the noninvasiveness of the feedback control. We used a lab-built AFM setup with a BL-AC7DS-KU4 (Olympus) cantilever and a standard Z scanner whose resonance frequencies were 1440 and 190 kHz, respectively. The scan range and frame rate were 200 × 200 nm² (100 × 100 pixels²) and 50 ms/frame, respectively. This corresponds to a scanning velocity of 800 μm/s, four times faster than a typical velocity of 200 μm/s in the standard setup. Although the sampling frequency (400 kHz) is over-sampling, the resulting Nyquist frequency is 200 kHz, which is sufficiently above \( f_{FB} \) (~80 kHz for DB-A2, see Fig. 3(f)) to avoid aliasing noise and maximize the effect of subsequent image processing.

In Fig. 4, both the first images exhibited a clear 36-nm-pitch helical structure (highlighted by the cyan arrows). However, in the FAB result, after 1 s elapsed, the filament began to collapse due to the insufficient feedback bandwidth. In contrast, using DB-A2, the molecule was stably observed and remained intact over a period of 30 s owing to the significantly faster feedback operation than FAB. Importantly, the noise performance of DB-A2 did not produce any practical problems in AFM imaging. Furthermore, by performing force curve measurements, we found that the square conversion makes the amplitude distance dependence steeper; this could further reduce the invasiveness of bioimaging as a side effect (supplementary material, Note 4 and Fig. S20).

The amplitude detector is a key device even in many AFM techniques, e.g., the viscoelastic measurements in frequency-modulation AFM,15,18 bimodal AFM,19,20 Kelvin-prove force microscopy,27 and three-dimensional hydration measurements.14,23 Moreover, this method can also be utilized for improved phase shift detection with further diverse applications (supplementary material, Note 5).

In summary, we developed a differential-based amplitude detection method with no intrinsic latency, which achieves significantly faster performance than the conventional methods. This technique also contributes to reducing invasiveness of AFM imaging, making it possible to observe fragile biomolecules. By overcoming the obstacle of the amplitude detector bandwidth, we have opened the road to

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increasing the temporal resolution of HS-AFM. When improving the speed performance of Z-scanner and cantilever, it will bring out the full potential.

See the supplementary material for the details of the experimental works and theoretical considerations.

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AUTHOR DECLARATIONS
Conflict of Interest
The authors declare no competing financial interest.

DATA AVAILABILITY
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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