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Time-resolved Absolute Velocity Quantification with Projections

Michael C. Langham, Varsha Jain, Jeremy F. Magland, and Felix W. Wehrli

Laboratory for Structural NMR Imaging, Department of Radiology, University of Pennsylvania Medical Center, Philadelphia, PA, USA

Abstract

Quantitative information on time-resolved blood velocity along the femoral/popliteal artery can provide clinical information on peripheral arterial disease and complement MR angiography since not all stenoses are hemodynamically significant. The key disadvantages of the most widely used approach to time-resolve pulsatile blood flow by cardiac-gated velocity-encoded gradient-echo imaging are gating errors and long acquisition time. Here we demonstrate a rapid non-triggered method that quantifies absolute velocity on the basis of phase difference between successive velocity-encoded projections after selectively removing the background static tissue signal via a reference image. The tissue signal from the reference image's center k-space line is isolated by masking out the vessels in the image domain. The performance of the technique, in terms of reproducibility and agreement with results obtained with conventional phase contrast (PC)-MRI was evaluated at 3T field strength with a variable-flow rate phantom and *in vivo* of the triphasic velocity waveforms at several segments along the femoral and popliteal arteries. Additionally, time-resolved flow velocity was quantified in five healthy subjects and compared against gated PC-MRI results. To illustrate clinical feasibility the proposed method was shown to be able to identify hemodynamic abnormalities and impaired reactivity in a diseased femoral artery. For both phantom and *in vivo* studies, velocity measurements were within 1.5 cm/s and the coefficient of variation was less than 5% in an *in vivo* reproducibility study. In five healthy subjects, the average differences in mean peak velocities and their temporal locations were within 1 cm/s and 10 ms compared to gated PC-MRI. In conclusion, the proposed method provides temporally-resolved arterial velocity with a temporal resolution of 20 ms with minimal post-processing.

INTRODUCTION

Time-resolved peripheral blood flow can provide useful information on the presence and stratification of vascular disease (1–3). In peripheral arteries such as the femoral or popliteal artery, the normal tri-phasic flow waveform is characterized by high forward velocity associated with systole, retrograde flow during early diastole, and slow forward flow during end-diastole. In the case of severe stenosis, the downstream flow waveform approaches a monophasic waveform with a reduced peak forward velocity as well as absence of retrograde and late forward flow (1). Ultrasound (US) is currently the modality of choice for hemodynamic evaluation of the vascular system of the lower extremities (4) due to its real-time capability, portability and low cost. In spite of its unique features that make it potentially superior to US, including high spatial resolution and the ability to quantify volumetric flow rate in any direction, MRI has not made major inroads as a tool for functional assessment of peripheral vascular disease. This contrasts with the pivotal role that MR angiography (MRA) now has for structural evaluation of the vascular system (5). On the other hand, quantification of time-resolved velocity at multiple peripheral arterial sites

would provide a useful adjunct to MRA as a means to assess whether or not a stenosis is hemodynamically significant and reduce interobserver variability of grading stenosis (6).

Phase-contrast (PC)-MRI, the most commonly used MRI method for flow quantification, is based on gradient-echo imaging with velocity-sensitizing gradient pulses (see, for example, (7,8)). VENC (specified by the operator and typically chosen so that $VENC = 1.2v_{max}$) represents the velocity value that will lead to flow-induced phase accumulation of $\pm\pi$. In general, bi-polar gradients (null zeroth moment) are toggled to generate two interleaved images with opposite velocity encoding and the phase difference is taken to minimize the background phase error. Although generally accepted as the gold standard for quantifying flow velocity, cardiac gated PC-MRI has several limitations (9) that can degrade accuracy and reproducibility. For time-resolving velocity, cardiac-gated scanning is typically used but it is vulnerable to gating errors (10), and the combined effects of irregular heart rhythm and pulsatility lead to artifacts which may interfere with velocity estimation, e.g. ghosting along the phase-encoding direction in the case of cartesian scan. Lastly, cardiac gating is inefficient and unsuited for monitoring transient flow since it takes several minutes to derive a single velocity waveform and the total acquisition time can become excessive if velocity waveforms are desired at several arterial segments.

There are several strategies to resolve pulsatile flow without the need for cardiac gating. One approach is to cover k-space rapidly via echo-planar (11,12) or spiral (13,14) trajectories in conjunction with spatially-selective RF pulses, yielding a temporal resolution of 50–120 ms. The projective approach of Thompson et al. (15) is another method that can resolve pulsatile flow virtually in real-time with temporal resolution of 60 ms. The method removes background static tissue signal by computing the complex difference (CD) of a pair of velocity-encoded projections. However, unlike the phase difference, CD does not isolate the flow-induced phase (16). Therefore, subsequent calibration is required to remove the scaling factor that accounts for spin density, transverse magnetization, RF receiver-coil sensitivity, imaging parameters, spin relaxation and background phase.

In this work, we present new projection-based velocity quantification method where the phase difference is computed between velocity-encoded projections after isolating blood signal. Partial volume errors is avoided by subtracting the velocity-encoded projections with a projection consisting only of tissue signal, which is the Fourier transform of the center k-space line of a reference image whose vessels have been masked out. The method's performance was evaluated with a variable-flow phantom and by quantifying the triphasic pulsatile flow of the femoral and popliteal arteries in healthy subjects. Lastly, the technique's potential utility for quantifying post-occlusive blood velocity for assessing vascular reactivity (17,18) is illustrated in a healthy young subject and a patient with PAD.

MATERIALS AND METHODS

Principle of Projection Flow Imaging

The principle of the method is illustrated in Figure 1. The idea is to first acquire a reference image in which the vessels of interest are masked out manually (Figures 1a and b) following which the data are converted back to k-space. The projection of the resulting $k_y=0$ line, which contains tissue signal only (Figure 1c) is then subtracted from the velocity-encoded projections prior to computing the phase difference. Figures 1d and e show time series of velocity-encoded projections, before and after removing tissue signal, respectively. In Figure 1f three cardiac cycles illustrating the temporal variations involving systolic antegrade, retrograde and late antegrade flow. Alternatively, in lieu of performing the subtraction in k-space it could be done in image space since FT is a linear operation. Since the projection

direction is not resolved vessel overlap could occur, which is avoided by appropriately selecting the readout direction on the basis of scout images.

Pulse Sequence

The pulse sequence consists of a standard gradient-recalled echo (GRE) with flow compensation (Figure 2a) for the acquisition of the reference image, followed by velocity-encoded projections (Figure 2b). In the present implementation the flow-compensating gradient lobes are used to encode velocity instead of toggling bipolar gradients in order to minimize the difference in gradient structure between the two encoding steps and thus subtraction errors from residual eddy currents (15). The pulse sequence was programmed in SequenceTree™ (19), a custom-designed pulse-sequence design and editing tool.

Phantom Experiments

Experiments were conducted with a flow phantom consisting of a vinyl tube (1.27 cm² cross-section area), placed in a cylindrical plastic container (20 cm long, 10 cm in diameter) containing 1.5% agarose gel doped with 0.1 mM Gd-DTPA to mimic spin relaxation properties of muscle tissue. The inner tube, containing 1.5 mM Gd-doped water, was part of a closed circuit connected to an electrical pump (No.31-TX, Nu-Calgon, MO). The average velocity was varied from 20 to 50 cm/s by connecting the pump to a variac (Model TDGC-2kM, PHC Enterprise, CA) and was quantified successively with the previously described projection method and PC-MRI. The overall agreement was assessed with the root-mean-square (RMS) of the % difference at each velocity setting.

In vivo Studies

For the purpose of assessing agreement between the projection method and conventional gated PC-MRI, blood velocity was time-resolved with the both methods at five different arterial segments covering common femoral and popliteal artery of a healthy, 38 year-old, male subject and specific velocity components of the triphasic flow waveform were compared (Figure 3): mean peak forward velocity $\bar{v}_{1,max}$, mean peak retrograde velocity $\bar{v}_{2,max}$, mean peak late forward velocity $\bar{v}_{3,max}$, and the temporal locations of the pulse peaks $\bar{v}_{i,max}$, i.e. t_{v1} , t_{v2} , and t_{v3} . At each arterial segment the % difference was computed for each velocity component, and the values averaged over the various segments. As a figure of merit for overall agreement the root mean square % difference was calculated. For further evaluation against gated PC-MRI, the temporally resolved velocity in the popliteal artery was evaluated in five healthy subjects (average age, 31 ± 6 yrs). Performance was assessed by computing the average difference of the various velocity components between the projection and gated PC technique.

To assess reproducibility, the velocity waveform in the popliteal artery of a healthy, 25 year-old, male subject was quantified from five successive scans. For each of the five measurements the subject's leg was repositioned. Medical tapes were applied above and below the knee cap to provide landmarks for positioning the leg in the extremity coil. Also, for each trial, multi-slice scout images were acquired for quantifying the vessel tilt angle to correct for the repositioning error. For each velocity component the coefficient of variation was calculated and overall reproducibility was assessed as the RMS of the coefficients of variation.

The feasibility of quantifying reactive hyperemia in response to 5 mins of cuff-induced ischemia in the femoral artery was demonstrated in a healthy subject. Ischemia was induced by applying a blood pressure cuff (Aspen Labs A.T.S 1500 Tourniquet System). The cuff was positioned on the upper-most part of the thigh to minimize perturbation of the imaging region (lower thigh) during cuff inflation or deflation. The cuff was inflated to 200 mmHg

for a period of 5 minutes and blood velocity was quantified during the ten seconds prior to and 70 seconds after cuff deflation. TR of 40 ms was used to reduce the data size and VENC of 150 cm/s was selected.

Finally, to demonstrate the method's clinical potential, baseline velocity and velocity time-course during reactive hyperemia were quantified in right femoral artery of a 74 yr-old patient with PAD whose ankle-brachial index (ABI) is 0.72, which correspond to mild-to-moderate blockage (20); ABI is the ratio between systolic pressure at ankle and brachial artery. Written informed consent was obtained prior to the human study following an Institutional Review board-approved protocol.

MRI Protocol

All imaging was performed on a 3T Siemens Trio. Phased-array eight-channel knee coil (Invivo Inc., Pewaukee, WI) was used for the flow phantom experiment and *in vivo* reproducibility study. For the *in vivo* "accuracy" study, the images of the lower extremity were acquired with a Siemens' body matrix coil. The following imaging parameters were used for the flow phantom: TE/TR = 5.23/20 ms, flip angle = 15°, dwell time = 10 μ sec, voxel size = $1 \times 1 \times 5$ mm³, matrix size = 128 $\times$ 128 and VENCs of 30, 40, 60 and 80 cm/s. The same imaging parameters were used for acquisition of the reference image and velocity-encoded projections (TR, TE, flip angle, dwell time and number of readout samples). In the femoral and popliteal artery, TR of 10 ms was chosen to resolve blood flow with temporal resolution of 20 ms and VENC of 60 cm/s. The above *in vivo* scan parameters were chosen to minimize saturation effects caused by spins experiencing multiple rf pulses during periods of relatively slow flow. Naturally, the saturation effect depends on TR, flow velocity, flip angle and slice thickness. For our imaging parameters the saturation factor α (21) (the ratio between the partially saturated magnetization and equilibrium magnetization) was greater than 0.81 for velocities exceeding 5 cm/s (note that $\alpha = 1$ for $v \geq \Delta z/TR$, where Δz is the slice thickness). The same imaging parameters were used for gated PC-MRI except for TR (the scanner optimization required TR of 18 ms). An acquisition window was set at 120% of RR-interval to ensure that full cardiac cycle was captured.

Data Analysis

The raw k-space data from the projection method were saved and processed off-line. Projection velocity images were then generated from the phase difference using the relation between phase ϕ and velocity v , as $v = \phi \cdot VENC/\pi$. Subsequently, spatially averaged velocities of the vessels of interest were computed by averaging the velocity along the readout direction within the vessel boundaries. The PC-MRI data were analyzed by computing the average velocity within a circular ROI encompassing the lumen of the vinyl tube or the vessel. The vessel boundaries and average cross-sectional area were determined by averaging the CD magnitude images, which provide high contrast between vascular lumen and tissue. The vessel boundary was then transferred to the phase contrast images to derive the average velocity at each cardiac phase. The same diameter of the vessel along the readout direction was used for selecting ROI in the phase difference image constructed from the velocity-encoded projections. The uncertainty of the average velocity (σ_v) derived from projections was estimated as $\sigma_v = \sigma_\phi \cdot VENC/\pi$, where $\sigma_\phi = |SNR|^{-1}$ and SNR was computed from the magnitude image of projections after subtracting the static tissue signal.

RESULTS

Phantom Experiments

The results of the phantom experiment are summarized in Table 1. The differences in the measured velocities between the projection technique and PC-MRI ranged from 1.7 to 4%,

being largest for the lowest velocities, and the mean difference between the two methods was less than 3%. The small uncertainty of the projection measurements (third column) reflect high SNR (~ 45), calculated as the ratio of the projection signal inside the tube and background region outside of the plastic container.

In vivo Studies

A representative *in vivo* data set is displayed in Figure 4. The subject has superficial femoral vein duplication, a normal variation in venous anatomy (22). The reference and the magnified view of the velocity images are shown in Figures 4a and b, respectively; the time-course of the average velocity derived from the data in Figure 4b is shown in Figure 4c. The averaged data from the five cardiac cycles in Figure 4c is plotted in Figure 5 along with the velocity wave-form derived from the gated PC-MRI scan. The average velocity in the femoral vein was not computed since the typical velocity is less than 5 cm/s, which is far less VENC (60 cm/s) by an order of magnitude. Table 2 lists the quantitative comparisons made in one subject between gated PC and projection technique at five different levels of the femoral and popliteal artery. On average, the temporal locations of the velocity peaks differed by less than or equal to 10 ms between the two approaches. Similarly, the systolic mean peak velocities were in good agreement with each other, differing by 2%, on average. Differences were greater for $\bar{v}_{2,\max}$ (4.7%) and $\bar{v}_{3,\max}$ (7.3%). In five healthy subjects (first row of Table 3), the average differences in the mean peak velocities and their temporal locations were less than 1 cm/s and 10 ms, respectively. For the repeated *in vivo* measurements, the average values of the velocity components and the corresponding standard deviations of popliteal artery are reported in Table 3 (2nd row). The vessel tilt angle of the arterial segment varied by less than one degree between the trials. The overall reproducibility of the velocity parameters quantified (computed as RMS of the coefficient of variation) was less than 5%.

Velocity quantification during reactive hyperemia—Time-resolved velocity data during reactive hyperemia in response to the cuff-induced ischemia are displayed in Figure 6. The magnified reference and projection velocity images are shown in Figure 6a and b, the time-course of femoral artery and vein blood velocity in Figure 6c. The cuff release time was at $t=0$, i.e. time-course of the average blood velocity included ten seconds prior to cuff release and seventy seconds thereafter. The velocity-time course indicates that the mean peak velocity is reached within 20 s after cuff deflation and the major portion of the transient flow occurred within 30 s. These observations are qualitatively consistent with the findings by Nishiyama et al (17), a study performed with Doppler ultrasound.

PAD patient—The PAD patient velocity data (Figure 7a) display substantially reduced retrograde and late antegrade flow components, which are not well defined compared to those of a young healthy subject (cf. Figure 4c). A monophasic velocity wave is expected with further progression of PAD. During reactive hyperemia (Figure 7b), the average velocity is significantly lower than that found in a typical healthy subject (Figure 6c), but this deficit is compensated by a longer period of the forward flow. This phenomenon can be understood by the fact that during cuff occlusion the tissue continues to extract oxygen from the blood trapped in tissue, which leads to an “oxygen debt” (23). Due to the impaired reactivity forward flow is maintained longer in response to the slower repayment rate. In contrast, forward flow lasts for about 20s in the healthy subject since normal vascular function typically returns the venous saturation to the baseline value in about 40s (24).

DISCUSSION AND CONCLUSION

The key feature and strength of the present method is the short acquisition time, which mitigates sensitivity to involuntary patient motion compared to gated PC-MRI. Its high temporal resolution allows full resolution of pulsatile flow without gating. As suggested from the results in Tables 1–3, the method is reliable and the data are in good agreement with those from gated PC-MRI. The largest discrepancies between the projection method and gated PC-MRI were the mean peak speed associated with retrograde $\bar{v}_{2,\max}$ and late diastolic flow $\bar{v}_{3,\max}$. During mid to late diastole blood velocities are significantly less than the prescribed VENC, hence lower accuracy and reproducibility are thus expected for both methods. Further, we note that a small disagreement (e.g. 1 cm/s) will lead to large relative difference (>10%) because the velocity amplitude is on the order of 5 – 10 cm/s only during retrograde and late antegrade flow.

When using cardiac gating, the velocity-to-noise ratio (VNR) can be improved with variable VENC (25). Similarly, variable VENC can be incorporated into the projection method, but this also requires careful timing of the trigger delay and will be susceptible to errors due to normal heart rate variations, primarily affecting diastolic timing. Alternatively, VNR can be optimized during diastole with the projection method by repeating the scan with lower VENC, at minimal cost in added scan time.

The proposed method shares same limitations and similarities with the projection-based method by Thompson et al (15). Because projections spatially resolve only one direction, velocity quantification at anatomic regions with multiple vessels of interest is more challenging or not possible at all. Thus, the user has to identify the vessels' spatial location on the scout images to avoid overlap in the projection images. We note, however, that even for gated PC-MRI the readout direction has to be appropriately chosen to avoid pulsation ghosts obscuring vessels of interest. Another limitation associated with projection method is the inherent averaging of the velocity along the projected lumen. Hence, the method does not quantify actual peak velocity but rather an average in projection direction.

Thompson et al's method eliminates partial volume errors because velocity is quantified by taking complex difference between velocity-encoded projections. However, in order to linearly approximate the sine function, large VENC is necessary, which leads to significantly lower VNR during late antegrade flow. Resolving late antegrade flow of a triphasic waveform may provide useful clinical information because reduced late antegrade velocity amplitude may reflect early signs of arterial stenosis since the waveform becomes monophasic with increasing severity of the constriction. For example, the late antegrade flow is absent but there is some trace of the retrograde flow in the velocity waveform of the patient (Figure 7a). Secondly, for the calibration step, it is assumed that the transverse magnetization is time-independent throughout the cardiac cycle. This assumption holds if the saturation factor (21) is one for every TR, which is not possible for multi-phasic flow unless TR exceeds several hundred milliseconds. The complex difference technique may be better suited for evaluation of monophasic flow as it occurs in the cerebral circulation. In contrast, our method does not require compliance with the small-angle approximation and "calibration" merely requires masking out the vessels to isolate intravascular signals in the velocity-encoded projections prior to computing the phase difference. One limitation of the method is some potential sensitivity to subject motion which, however, is mitigated by short scan time (<10s).

The efficiency of the projection method lends itself for quantifying post-occlusive blood velocity (transient increase of blood flow in response to cuff ischemia), one of the key physiological parameters for evaluating peripheral arterial disease (PAD) (2,12,26,27). In

addition to quantifying reactive hyperemia, the high-speed projection method can complement structural information from MRA since time-resolved velocity can help to identify hemodynamically significant stenoses (3) and the velocity information can reduce interobserver variability of grading stenosis (6). Further, the method's efficiency may allow examination of multiple arterial segments.

Currently, initial screening of arterial stenoses is performed non-invasively in vascular laboratories with segmental pressure recording (SPR) and pulse volume recording (PVR) (28). In SPR, four blood pressure cuffs are applied to the thigh (upper and lower), calf and ankle, to locate sites of arterial obstructions by estimating the pressure gradients between the cuffs. However, SPR is relatively insensitive and has poor localization (29). The method is unreliable in patients with arterial calcification as it often results from diabetes mellitus (30), renal failure and heavy smoking (31). PVR uses an air bladder cuff to detect the changes in the volume of the limb during each cardiac cycle, a non-quantitative technique that estimates blood volume in a limb and does not evaluate intra-arterial hemodynamics directly. In contrast, the new projection technique has the potential to yield hemodynamic information at virtually any peripheral arterial segment, including infrarenal aorta, iliac and popliteal arteries where cuff compression is not possible. The accuracy is unaffected by obesity or leg edema, and the protocol does not require highly skilled technicians as does duplex ultrasound (time consuming at aortoiliac and femoral-popliteal segments (32)) since the scan procedure is identical to that of conventional PC-MRI.

In conclusion, the proposed method has the potential to yield hemodynamic information at peripheral arterial segments without significantly prolonging total scan time as an adjunct, for example, to MRA.

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Figure 1.

a) Axial reference image through the middle of the thigh; **b)** corresponding image with vessels of interest masked out; **c)** stack of projections corresponding $ky=0$ of **b)**; **d)** time-series of velocity-encoded projections before and **e)** after subtracting tissue signal to isolate the signal from the vessels; **f)** phase difference between velocity-encoded projections; systolic (solid arrow), retrograde (dashed arrow) and late antegrade (black arrow) flow can be seen. Each horizontal line is a projection phase difference. Time progresses from top to bottom. The streaking artifacts in **Figures 1d** and **e** are caused by motion and occur immediately before and after the systole when the artery's diameter dilates and relaxes, respectively. The streaks are more visible on **Fig. 1e** because the tissue signals are removed from **Fig 1d**.

Figure 2.

a) Flow compensated GRE pulse sequence for removing background static tissue signal from **b)** velocity-encoded projections (no phase encoding), acquired by toggling between I and II in the dashed box.

Figure 3.
Various components of tri-phasic pulsatile used to evaluate the projection method.

Figure 4.

a) Representative reference image of the femoral artery at the level of the mid-thigh. **b)** Time series of 224 velocity projection images. Dashed lines encompass region of velocity averaging along the readout direction. **c)** Time-course of the average velocity in the femoral artery at 20 ms temporal resolution.

Figure 5.
Comparison between flow waveforms derived from conventional cardiac gated and high-speed projection technique.

Figure 6. Effect of cuff-induced ischemia on arterial and venous blood velocities: **a)** Magnified view of the reference image and **b)** velocity images with the background cropped. **c)** The time course of the average blood velocity in femoral artery after a 5 min-long cuff-induced ischemia. The cuff deflation starts at $t = 0$ s and the temporal resolution is 80 ms.

Figure 7. Reduced pulsatility and impaired reactivity in a diseased femoral artery. **a)** Velocity waveform at rest. Approximately ten cardiac phases are shown and note the respiratory modulation of the peak systolic velocities with a period of about five heartbeats. **b)** The time course of the average blood velocity in the femoral artery after a 5 min-long cuff-induced ischemia.

Table 1

Results from phantom study. At four velocity settings, the average velocity was quantified successively with the proposed projection method and PC-MRI. All measurements differ by less than 1 cm/s.

VENC (cm/s)	PC-MRI (cm/s)	Projection (uncert.) (cm/s)	% Difference
30	20.9	20.1 (0.4)	4.0
40	21.0	20.2 (0.6)	3.9
60	47.5	47.2 (0.3)	0.72
80	51.9	52.8 (0.2)	1.7
			RMS _[%Diff] = 2.9%

Comparison between the projection and conventional gated PC-MRI derived velocity components of triphasic pulsatile waveform in peripheral arterial segments.

Table 2

Arterial Segment	$V_{3,max}$ (% diff)	$V_{3,max}$ (% diff)	$V_{3,max}$ (% diff)	t_1 (% diff)	t_2 (% diff)	t_3 (% diff)
Common femoral	2.5	3.7	6.3	1.0	0.4	1.63
Femoral artery at mid-thigh	1.4	2.8	4.7	0.3	0.6	0.1
Proximal popliteal	2.2	10.9	7.8	0.3	0.2	0.1
Popliteal	3.7	2.6	11.5	2.4	0.88	0.39
Distal popliteal	0.2	3.6	6.3	1.5	0.4	0.5
Average (stdev)	2.0 (1.3)	4.7 (3.5)	7.3 (2.6)	1.1 (0.9)	0.49 (0.25)	0.54 (0.64)

Table 3

Comparison between the projection and conventional gated PC-MRI, and *in vivo* reproducibility of the projection method. Methods are compared by deriving velocity components of triphasic waveform in five healthy subjects and reproducibility is assessed with five repeated measurements in the same popliteal artery.

	$V_{1,max}$ Avg. diff (cm/s)	$V_{2,max}$ Avg. diff (cm/s)	$V_{3,max}$ Avg. diff (cm/s)	t_1 (ms)	t_2 (ms)	t_3 (ms)
Projection vs. PC-MRI	0.84 ± 0.47	1.03 ± 0.87	0.5 ± 0.46	6.5 ± 2.2	6.0 ± 4.2	10.5 ± 14.2
Reproducibility of projection method	28 ± 1.3	-7.5 ± 1.4	2.7 ± 0.5	0.12 ± 0.01	0.33 ± 0.01	0.53 ± 0.02