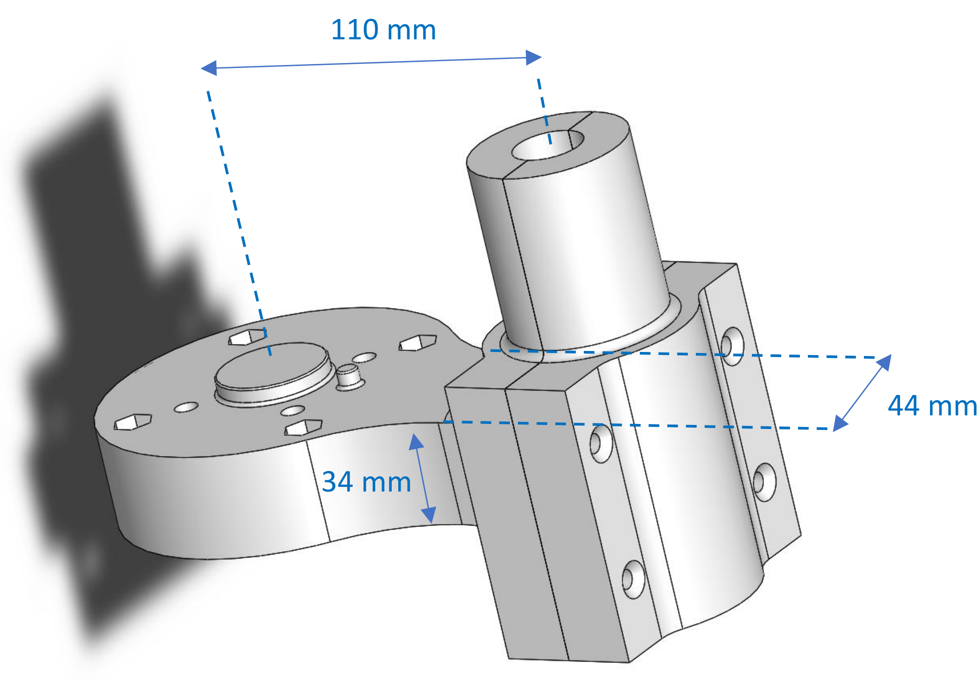
Supplementary Materials

The following sections report some supplementary materials of the paper: A. Noccaro, A. Mioli, M. D'Alonzo, M. Pinardi, G. Di Pino, and D. Formica, "Development and validation of a novel calibration methodology and control approach for robot-aided transcranial magnetic stimulation (TMS)," 2020, in IEEE Transaction on Biomedical Engineering.

Flange Design and Characteristics



3D model of the flange used to connect the alpha coil 40 mm to the panda robot end-effector.

Settings used for the 3D printer Ultimaker 2+:

Material: PLA

Filling Density: 70%

Filling Pattern: Grid

Weight: 600 g

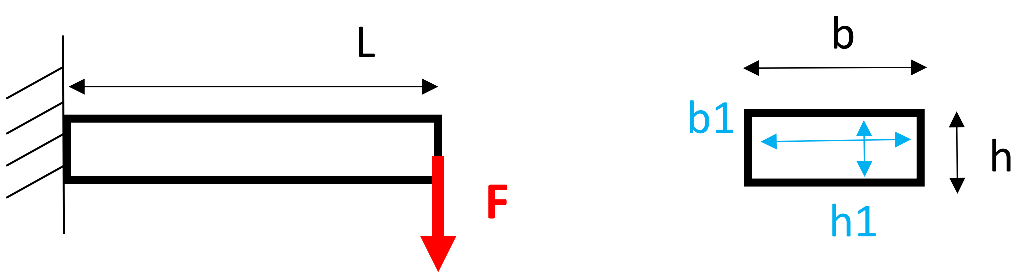
Estimation of flange maximum deformation

The assumption of negligible deformation of the flange is essential to evaluate the coil positioning errors.

As regards the deformation of the flange due to the weight of the coil, we estimated (using the Euler–Bernoulli beam approximation) the maximum bending of the flange at the tip to be lower than 0.01 mm, thus negligible for our application.

The deformation is estimated as follows:

The flange attached to the robot end-effector can be seen as a cantilever beam with a force applied (F) at the tip (due to the coil's weight).



We know that the deformation δ can be computed as:

$$\delta = \frac{F\,L^3}{3\,E\,J}$$

Where F is the applied force due to the coil's weight, which is 1.2 kg; L=110 mm is the beam's length; E= 3500 MPa is the Young's module (see http://2015.igem.org/wiki/images/2/24/CamJIC-Specs-Strength.pdf) for the PLA material (the flange material) and J= 162746 mm^4 is the moment of inertia of the beam's section in case of flexion, considering a rectangular empty section with outer dimensions b=44 mm, h=34 mm and inner dimensions b1=34 mm and h1= 24 mm. An easy-to-use tool to calculate the section moment of inertia for sections with different shapes can be found here https://skyciv.com/it/free-moment-of-inertia-calculator/.

This approximation underestimates the actual flange moment of inertia (thus overestimate the final deflection), that is indeed filled with a grid structure (see details on suggested 3D printer settings available on https://github.com/ANoccaro/Robot-aidedTMS and https://support.ultimaker.com/hc/en-us) and more robust that the approximated empty rectangle.

The applied force F=11.77 N computed considering the coil's weight is also an overestimation of the actual applied force, that is indeed distributed along the flange and not punctually applied at the flange tip.

All these conservative approximations considered the estimated deformation is δ=0.009 mm.

If we tried to further reduce the beam's section lowering the inner dimensions to b1=40 mm and h1= 30 mm, the moment of inertia for the flexion becomes J= 81354 mm^4 . In that case the maximum bending is δ=0.0156 mm, still negligible.

The same analysis can be applied considering the force due to the head's pressure on the coil. The maximum force that can be applied on the head to guarantee the subject's safety is 2.5 N. Even if we overestimate the possible applied force, e.g. considering a value of 10 N, applied to the coil, and tried to further reduce the section thickness to 1 mm (J= 22710 mm^4), we can still estimate the maximum bending to be lower than 0.05 mm, thus negligible for our application.

Impedance Settings

Impedance are numerically defined in section III A (along the contact direction the stiffness is set to 3000 N/m and the damping is set to 80 Ns/m) and they were defined a priori in the main application control. The impedance regulation is strictly related to the normal forces at the end-effector, that should be regulated to guarantee safety and avoid hitting the subjects. Thus, it is important that the impedance value does not exceed a maximum threshold, set by the experimenter.

The impedance value was set after preliminary tests in order to find the best compromise between high accuracy and low contact force. The stiffness and damping values are defined with respect to the coil stimulation plane, thus the estimated contact force is also referred to the coil and not to the robot end-effector.

The control of the robot does not directly regulate interaction forces at the end-effector, but rather set a robot impedance at the contact point, which generates an interaction force when robot desired position and the actual one is different due to the contact with subject's head.

Nevertheless, for safety reasons the interaction forces are continuously monitored during the whole protocol and an emergency stop intervenes when the force rises above a security threshold, set to 2.5N. During the recorded procedures, the force emergency stop was never triggered, and the maximum recorded value of interaction force was 2.2N.

Coil Pressure

The pressure helps to stabilize both the head and the coil. However, we wanted to highlight that the pressure is not required to have effective stimulations. Indeed, if the coil touches the head in the correct position and orientation, increasing the pressure does not affect the spatial relation between the coil and the above neural circuitry which the pulse targets. During manual sessions, or using robots with force control, the pressure helps to keep both the head and the coil still. Nevertheless, the impedance control we proposed aims to overcome this aspect, achieving the correct coil positioning without applying excessive forces on the scalp.

All that considered, our control does not cancel the pressure, but makes the robot enough compliant to have low pressures -increasing the subject comfort- while maintaining the coil in the hot-spot, gently touching the head.

Operators' contribute and related results

Both the operators who took part in the study, and who appear as co-authors of the study (Alessandro Mioli and Mattia Pinardi), have extensive experience in the use of TMS, as testified by several publications (Mioli et al., 2018; Zangrandi et al., 2019; Bassolino et al., 2018). In addition to the experience reported in the cited publications, unpublished works required the operators to use not only single pulse TMS protocols, but rTMS, SICI and LICI protocols as well, targeting several brain areas such as, and not limited to, M1, TPJ and OFC. Since the present work employs a rather simple TMS protocol (spTMS for MEP elicitation following stimulation of FDI-area on M1), we feel confident in claiming that the experience level of the operator was more than adequate.

As specified in the manuscript, the position of the target hotpost (for FDI muscle) was manually set by the expert operator gradually moving the coil over the motor cortex to find the location that evokes the largest EMG responses, while applying a series of pulses at a relatively high intensity. During this procedure the neuronavigation system was only used to record the position on the scalp of the hotspot selected by the operator, in order to use it as reference stimulation point during the experiments.

Under this procedure, and assuming a correct functioning of the neuronavigation hardware, which is a commercial ad-hoc system validated for this specific purpose, the main condition in which the system could fail is when the markers are moved during the experiment; however the experimental setup was built in order to avoid such movements. This possibility is very easily countered by double-checking the stability of the markers positioning, assuring that they never moved during the experiments. This simple precaution could help ensure the fidelity of the information regarding the position tracking of the head-coil system.

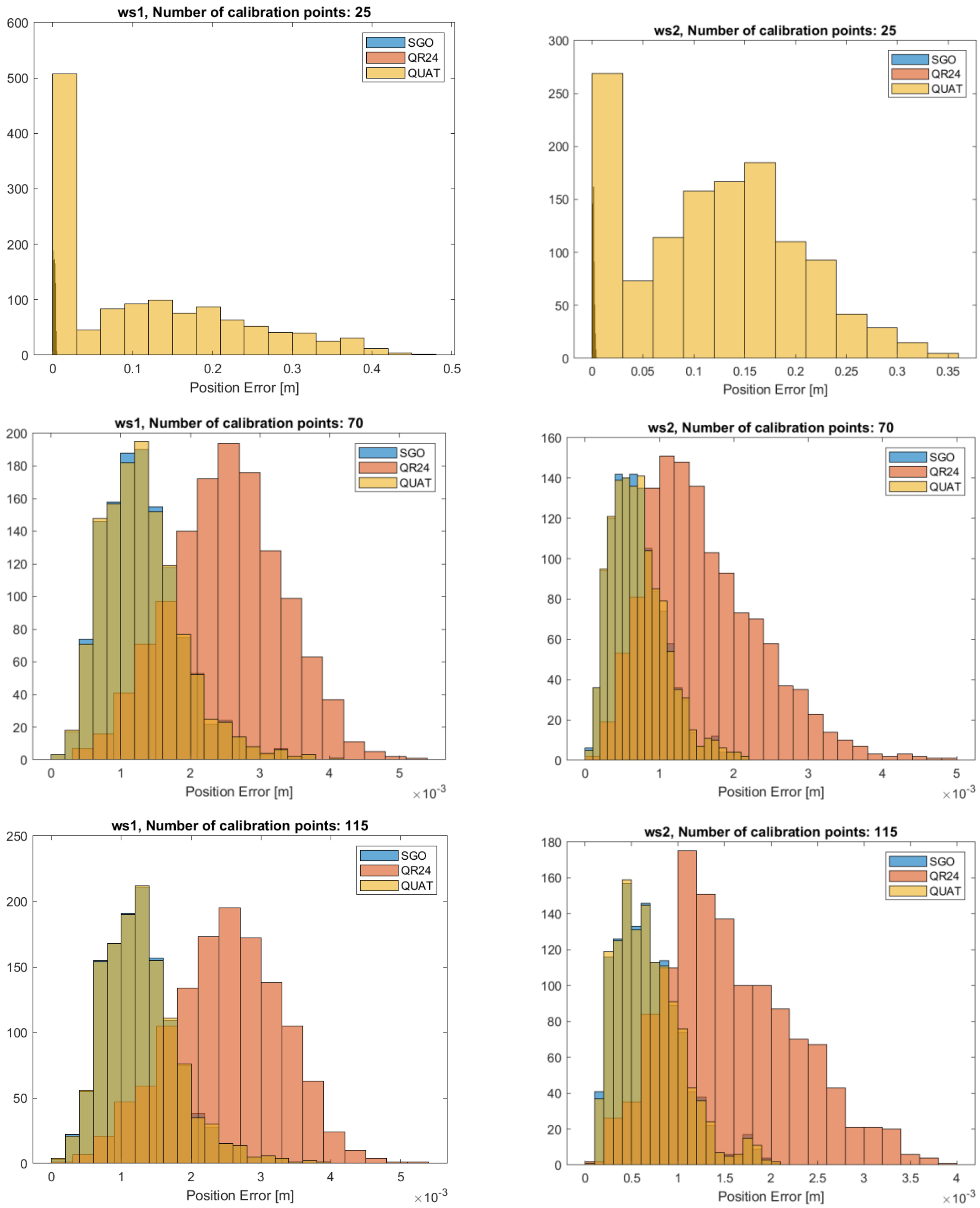
In the present experiment, operators were instructed to follow the neuronavigator's visual feedback, both in position and orientation, but we cannot exclude that the expert operators involved in this study preferred to rely more on their experience that on the neuronavigator feedback; indeed, one of the operator explicitly stated that in few cases he was more driven by his own experience than by the neurovigator feedback. In fact, we reported this information in the manuscript for the sake of clarity, but it is important to recall that: i) the maximum acceptable error for providing a TMS pulse was set to be under 5 mm in both conditions (robotic and manual procedures), so to have the results comparable; for this reasons if some deviations from the hotspot occurred during manual stimulation, these displacements were limited ii) the operator reported to slightly changed the coil positioning only in few stimulations in a single session on one subject, thus probably not enough to affect the overall result; iii) because of its subjective nature, and the lack of statistical difference between the operator and robot's performance, there is no way to judge if the operators' experience was actually helpful or not.

Statistical Analysis

At the beginning we performed two separated analysis for the two main factors, i.e. “method” and “workspace”, using a Kruskal-Wallis test due to the non-normal distribution of the data, tested with Kolmogorov-Smirnov test. The first analysis we ran was on the median value of each dataset because of the huge amount of data (250 points for each dataset, that correspond to 1250 for each method and workspace). However, we ran a further analysis (two Kruskal-Wallis tests with “method” and “workspace” as main factors) on the entire dataset. In particular we ran two tests: one test considering the entire dataset (all the datasets corresponding to all the cases of different number of calibration points) and another test considering only the cases with more than 70 calibration points, as well as the analysis presented in the previous version of the manuscript. The analysis considering only the cases with more than 70 calibration points showed the same results presented in the manuscript. Moreover, the analysis conducted on the entire dataset revealed also that the SGO method is significantly better ($p<0.001$) than the QUAT method in term of the position error and the QUAT approach is significantly worse ($p<0.001$) than the other two methods in term of orientation error. These results confirm the stability problem of the QUAT approach when few calibration points are taken into account.

Residuals of MiX – Yni

We reported here the histogram plot of the residuals of MiX-YNi for the three methods and the two workspaces ws1 (sphere) and ws2 (spherical shell) for some of the calibration points groups (we reported one representative dataset for 25, 70, 115, 160, 205, 250 calibration points). Given the page limit of the paper, we included in the manuscript only one representative dataset with 250 calibration points.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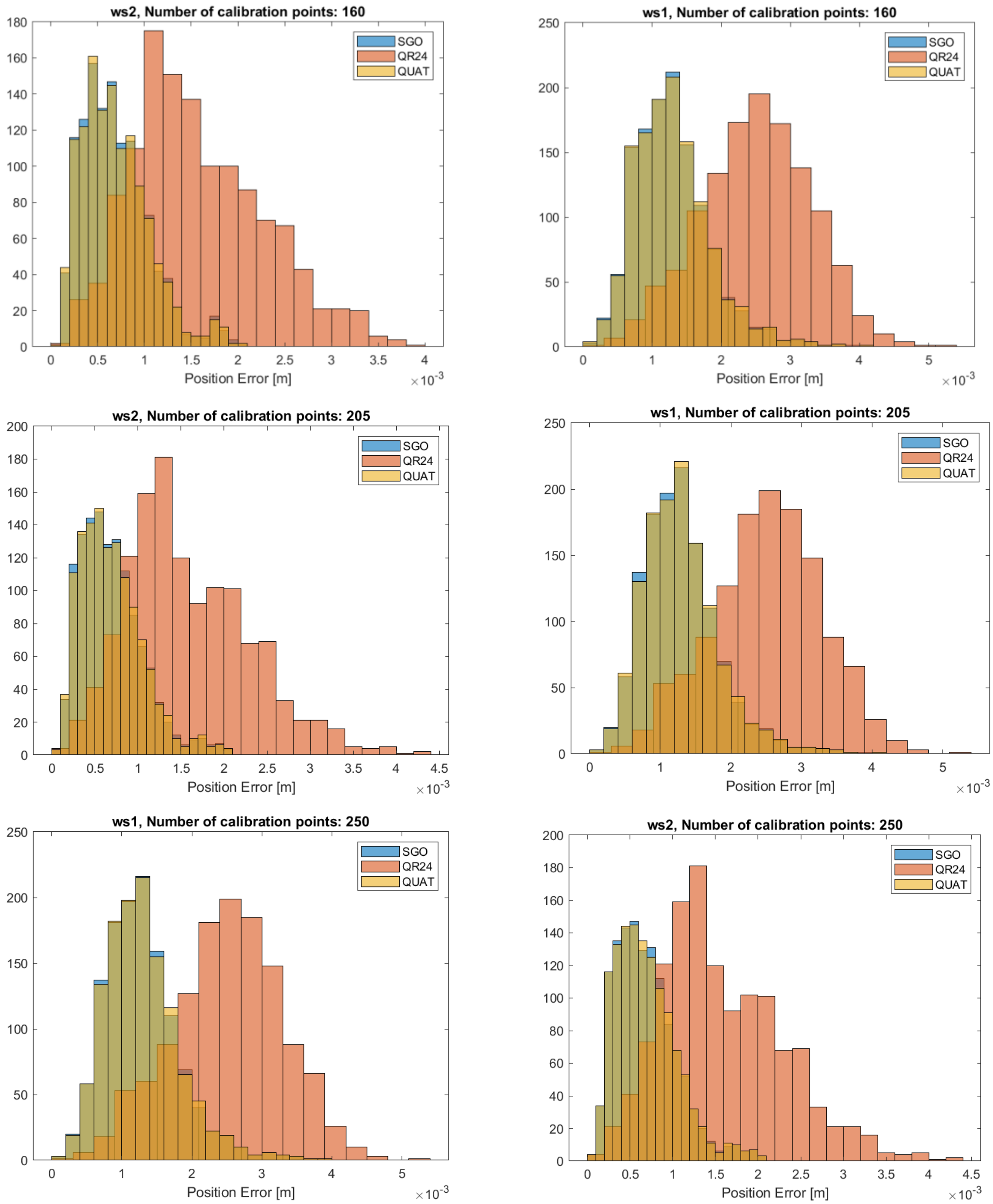
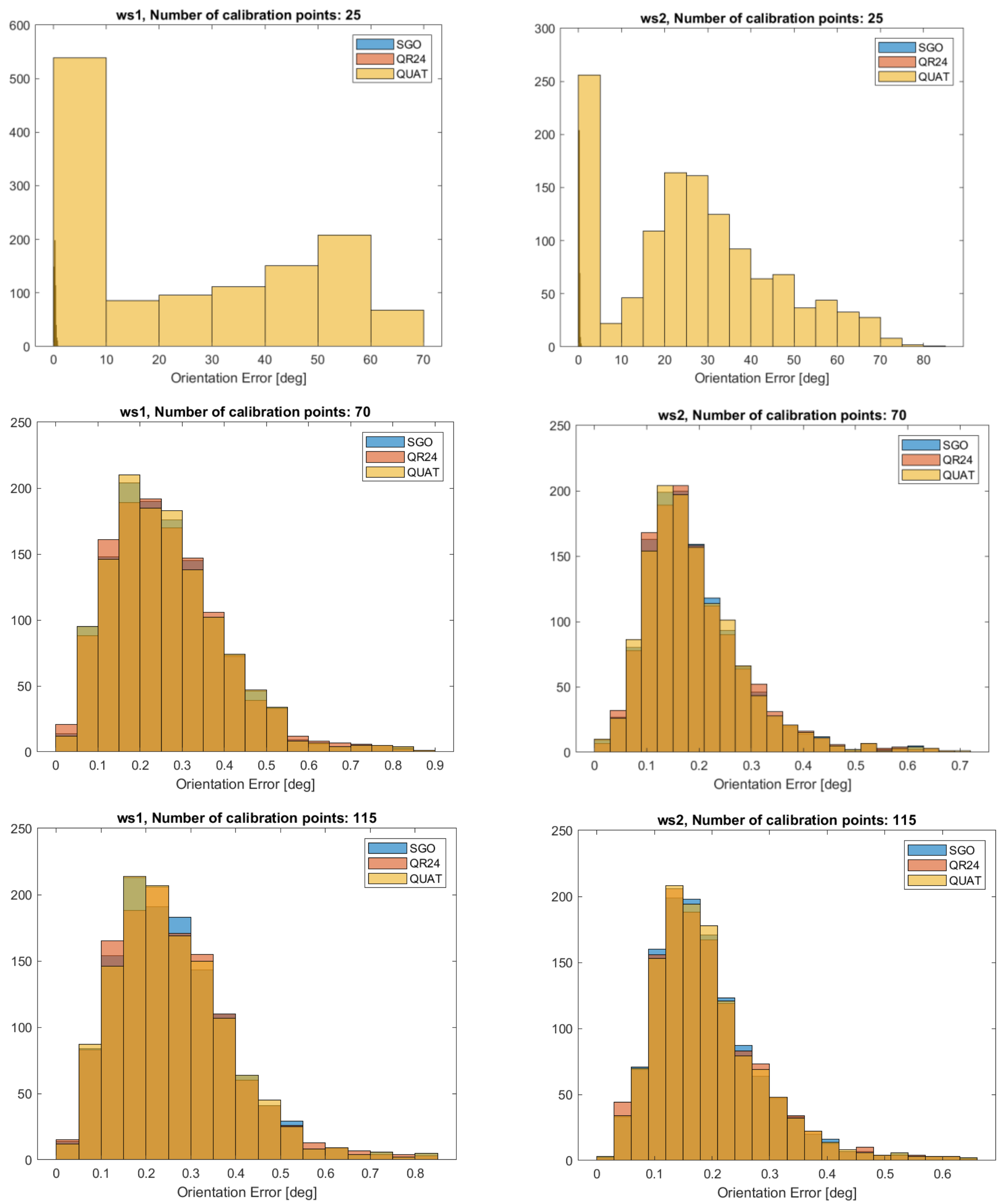
ws2, Number of calibration points: 25
ws1, Number of calibration points: 70
ws2, Number of calibration points: 70
ws1, Number of calibration points: 115
ws2, Number of calibration points: 115
SGO
QR24
QUAT
Position Error [m]
×10^-3


ws2, Number of calibration points: 160
SGO
QR24
QUAT
Position Error [m]
$\times 10^{-3}$
ws1, Number of calibration points: 160
SGO
QR24
QUAT
Position Error [m]
$\times 10^{-3}$
ws2, Number of calibration points: 205
SGO
QR24
QUAT
Position Error [m]
$\times 10^{-3}$
ws1, Number of calibration points: 205
SGO
QR24
QUAT
Position Error [m]
$\times 10^{-3}$
ws1, Number of calibration points: 250
SGO
QR24
QUAT
Position Error [m]
$\times 10^{-3}$
ws2, Number of calibration points: 250
SGO
QR24
QUAT
Position Error [m]
$\times 10^{-3}$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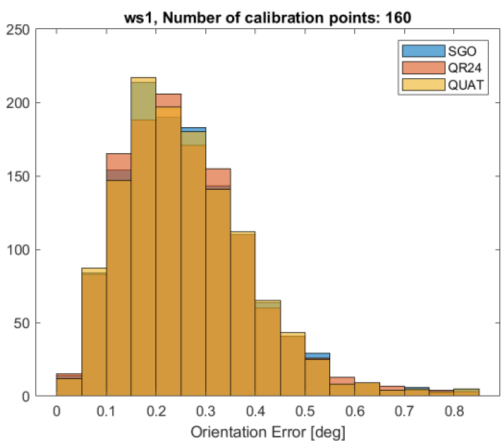
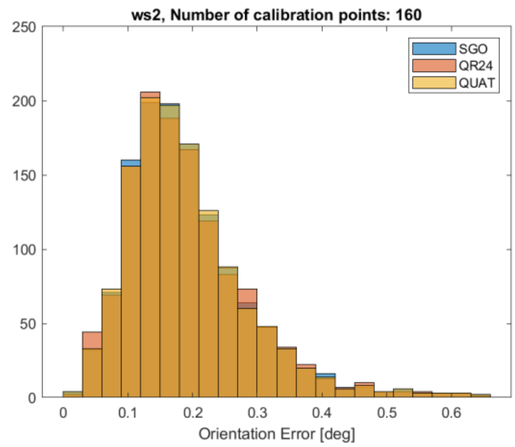
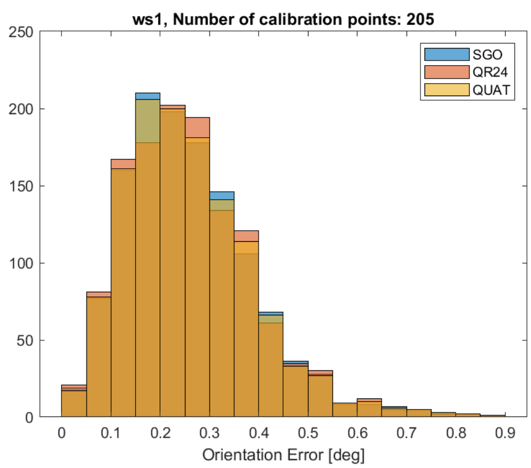
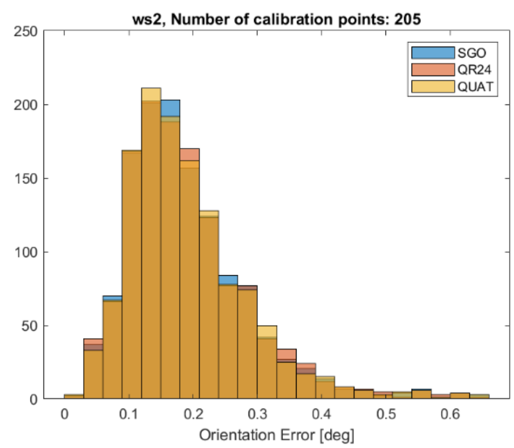
ws2, Number of calibration points: 25
ws1, Number of calibration points: 70
ws2, Number of calibration points: 70
ws1, Number of calibration points: 115
ws2, Number of calibration points: 115
SGO
QR24
QUAT
Orientation Error [deg]


ws1, Number of calibration points: 160
SGO
QR24
QUAT
Orientation Error [deg]


ws2, Number of calibration points: 160
SGO
QR24
QUAT
Orientation Error [deg]


ws1, Number of calibration points: 205
SGO
QR24
QUAT
Orientation Error [deg]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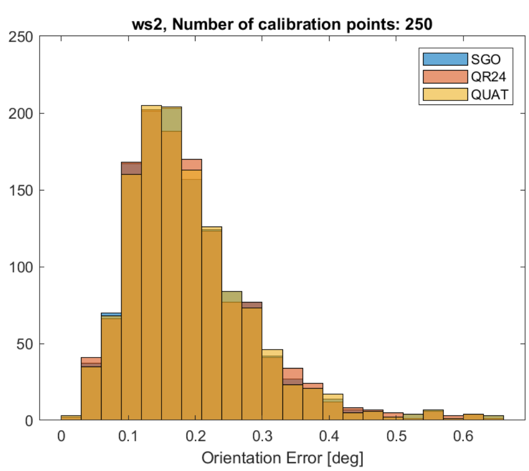
SGO
QR24
QUAT
Orientation Error [deg]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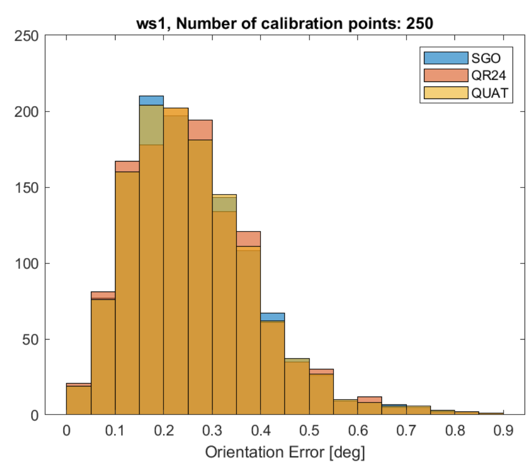
SGO
QR24
QUAT
Orientation Error [deg]


ws1, Number of calibration points: 250
SGO
QR24
QUAT
Orientation Error [deg]