Combining Augmented Reality and 3D Printing to Display Patient Models on Your Smartphone
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1   **TITLE:**
2   Combining Augmented Reality and 3D Printing to Display Patient Models on a Smartphone
3
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25   **KEYWORDS:**
26   augmented reality, 3D printing, anatomical models, clinical applications, surgical navigation,
27   image guidance, patient-to-model registration, education, pre-operative planning
28
29   **SUMMARY:**
30   Presented here is a method to design an augmented reality smartphone application for the
31   visualization of anatomical three-dimensional models of patients using a 3D-printed reference
32   marker.
33
34   **ABSTRACT:**
35   Augmented reality (AR) has great potential in education, training, and surgical guidance in the
36   medical field. Its combination with three-dimensional (3D) printing (3DP) opens new
37   possibilities in clinical applications. Although these technologies have grown exponentially in
38   recent years, their adoption by physicians is still limited, since they require extensive
39   knowledge of engineering and software development. Therefore, the purpose of this protocol is
40   to describe a step-by-step methodology enabling inexperienced users to create a smartphone
41   app, which combines AR and 3DP for the visualization of anatomical 3D models of patients with
42   a 3D-printed reference marker. The protocol describes how to create 3D virtual models of a
43   patient's anatomy derived from 3D medical images. It then explains how to perform positioning
44   of the 3D models with respect to marker references. Also provided are instructions for how to

45 3D print the required tools and models. Finally, steps to deploy the app are provided. The
46 protocol is based on free and multi-platform software and can be applied to any medical
47 imaging modality or patient. An alternative approach is described to provide automatic
48 registration between a 3D-printed model created from a patient's anatomy and the projected
49 holograms. As an example, a clinical case of a patient suffering from distal leg sarcoma is
50 provided to illustrate the methodology. It is expected that this protocol will accelerate the
51 adoption of AR and 3DP technologies by medical professionals.
52
53 **INTRODUCTION:**
54
55 AR and 3DP are technologies that provide increasing numbers of applications in the medical
56 field. In the case of AR, its interaction with virtual 3D models and the real environment benefits
57 physicians in regards to education and training[1–3], communication and interactions with other
58 physicians[4], and guidance during clinical interventions[5–10]. Likewise, 3DP has become a
59 powerful solution for physicians when developing patient-specific customizable tools[11–13] or
60 creating 3D models of a patient's anatomy, which can help improve preoperative planning and
61 clinical interventions[14,15].
62
63 Both AR and 3DP technologies help to improve orientation, guidance, and spatial skills in
64 medical procedures; thus, their combination is the next logical step. Previous work has
65 demonstrated that their joint use can increase value in patient education[16], facilitating
66 explanations of medical conditions and proposed treatment, optimizing surgical workflow[17,18]
67 and improving patient-to-model registration[19]. Although these technologies have grown
68 exponentially in recent years, their adoption by physicians is still limited, since they require
69 extensive knowledge of engineering and software development. Therefore, the purpose of this
70 work is to describe a step-by-step methodology that enables the use of AR and 3DP by
71 inexperienced users without the need for broad technical knowledge.
72
73 This protocol describes how to develop an AR smartphone app that allows the superimposing of
74 any patient-based 3D model onto a real-world environment using a 3D-printed marker tracked
75 by the smartphone camera. In addition, an alternative approach is described to provide
76 automatic registration between a 3D-printed biomodel (i.e., a 3D model created from a
77 patient's anatomy) and the projected holograms. The protocol described is entirely based on
78 free and multi-platform software.
79
80 In previous work, AR patient-to-image registration has been calculated manually[5] with surface
81 recognition algorithms[10] or has been unavailable[2]. These methods have been considered
82 somewhat limited when an accurate registration is required[19]. To overcome these limitations,
83 this work provides tools to perform accurate and simple patient-to-image registration in AR
84 procedures by combining AR technology and 3DP.
85
86 The protocol is generic and can be applied to any medical imaging modality or patient. As an
87 example, a real clinical case of a patient suffering from distal leg sarcoma is provided to
88 illsutrate the methodology. The first step describes how to easily segment the affected

89   anatomy from computed tomography (CT) medical images to generate 3D virtual models.
90   Afterwards, positioning of the 3D models is performed, then the required tools and models are
91   3D-printed. Finally, the desired AR app is deployed. This app allows for the visualization of
92   patient 3D models overlaid on a smartphone camera in real-time.

93

94   **PROTOCOL:**

95

96   This study was performed in accordance with the principles of the 1964 Declaration of Helsinki
97   as revised in 2013. The anonymized patient data and pictures included in this paper are used
98   after written informed consent was obtained from the participant and/or their legal
99   representative, in which he/she approved the use of this data for dissemination activities
100 including scientific publications.

101

102 **1. Workstation set-up for segmentation, 3D models extraction, positioning, and AR app**
103 **deployment**

104

105 NOTE: This protocol has been tested with the specific software version indicated for each tool.
106 It is likely to work with newer versions, although it is not guaranteed.

107

108 1.1. Use a computer with Microsoft Windows 10 or Mac OS as operating systems.

109

110 1.2. Install the following tools from the corresponding websites per the official instructions:

111

112 3D Slicer (v. 4.10.2): <https://download.slicer.org/>.
113 Meshmixer (v. 3.5): <http://www.meshmixer.com/download.html>.
114 Unity (v. 2019): <https://unity3d.com/get-unity/download>.
115 (For iOS deployment only) Xcode (last version): <https://developer.apple.com/xcode/>.

116

117 NOTE: All software tools required for completing the protocol can be freely downloaded for
118 personal purposes. Software to be used in each step will be specifically indicated.

119

120 1.3. Download data from the following GitHub repository, found at <https://github.com/BIIG-
121 UC3M/OpenARHealth>.

122

123 NOTE: The repository contains the following folders:

124

125 "/3DSlicerModule/": 3D slicer module for positioning 3D models with respect to the 3D-printed
126 marker. Used in section 3. Add the module into the 3D slicer following the instructions available
127 at <https://github.com/BIIG-UC3M/OpenARHealth>.

128

129 "/Data/PatientData/Patient000_CT.nrrd": CT of a patient suffering from distal leg sarcoma. The
130 protocol is described using this image as an example.

131

132 "/Data/Biomodels/": 3D models of the patient (bone and tumor).

133

134 "/Data/Markers/": Markers that will be 3D-printed, which will be detected by the AR
135 application to position the virtual 3D models. There are two markers available.

136

137 **2. Biomodel creation**

138

139 NOTE: The goal of this section is to create 3D models of the patient's anatomy. They will be
140 obtained by applying segmentation methods to a medical image (here, using a CT image). The
141 process consists of three different steps: 1) loading the patient data into 3D slicer software, 2),
142 segmentation of target anatomy volumes, and 3) exportation of segmentation as 3D models in
143 OBJ format. The resulting 3D models will be visualized in the final AR application.

144

145 2.1. Load patient data ("/Data/PatientData/Patient000_CT.nrrd") by dragging the medical
146 image file into the 3D slicer software window. Click **OK**. The CT views (axial, sagittal, coronal)
147 will appear on the corresponding windows.

148

149 NOTE: The data used here is found in "nearly raw raster data" (NRRD) format, but 3D Slicer
150 allows for loading of medical image format (DICOM) files. Go to the following link for further
151 instructions, found at <https://www.slicer.org/wiki/Documentation/4.10/Training>.

152

153 2.2. To segment the anatomy of the patient, go to the **Segment Editor** module in 3D slicer.

154

155 2.2.1. A "segmentation" item is created automatically when entering the module. Select the
156 desired volume (a medical image of the patient) in the **Master Volume** section. Then, right-click
157 below on the **Add** button to create a segment. A new segment will be created with the name
158 "Segment_1".

159

160 2.2.2. There is a panel called **Effects** that contains a variety of tools to properly segment the
161 target area of the medical image. Select the most convenient tool for the target and segment
162 onto the image windows area.

163

164 2.2.2.1. To segment the bone (tibia and fibula in this case), use the **Threshold** tool to set up
165 minimum and maximum HU values from the CT image, which corresponds to bone tissue. By
166 using this tool, other elements with HU outside these threshold values are removed, such as
167 soft tissue.

168

169 2.2.2.2. Use the **Scissors** tool to remove undesired areas, such as the bed or other anatomical
170 structures, from the segmented mask. Segment the sarcoma manually using the **Draw** and
171 **Erase** tools, since the tumor is difficult to contour with automatic tools.

172

173 NOTE: To learn more details about the segmentation procedure, go to the link found at
174 <https://www.slicer.org/wiki/Documentation/4.10/Training#Segmentation>.

175

176 2.2.3. Click on the **Show 3D** button to view a 3D representation of the segmentation.

177

178   2.3. Export the segmentation in a 3D model file format by going to the **Segmentations** module
179   in 3D Slicer.

180

181   2.3.1. Go to **Export/import models and labelmaps**. Select **Export** in the operation section and
182   **Models** in the output type section. Click **Export** to finish and create the 3D model from the
183   segmented area.

184

185   2.3.2. Select **SAVE** (upper left) to save the model. Choose the elements to be saved. Then,
186   change the file format of the 3D Model to "OBJ" within the **File format** column. Select the path
187   where files will be stored and click on **Save**.

188

189   2.4. Repeat steps 2.2 and 2.3 to create additional 3D models of different anatomical regions.

190

191   NOTE: Pre-segmented models of the provided example can be found in the data previously
192   downloaded in step 1.3 ("/Data/Biomodels/").

193

194   3. **Biomodel positioning**

195

196   NOTE: In this section, the 3D models created in Section 2 will be positioned with respect to the
197   marker for augmented reality visualization. The **ARHealth: Model Position** module from 3D
198   Slicer will be used for this task. Follow the instructions provided in step 1.3 to add the module
199   to 3D Slicer. There are two different alternatives to position the 3D models: "Visualization"
200   mode and "Registration" mode.

201

202   3.1. **Visualization** mode

203

204   NOTE: **Visualization** mode allows positioning of the 3D patient models at any position with
205   respect to the AR marker. With this option, the user are able to use the AR app to visualize
206   biomodels using the 3D-printed AR marker as a reference. This mode may be used when
207   precision is not required, and visualization of the virtual model can be displayed anywhere
208   within the field-of-view of the smartphone camera and marker.

209

210   3.1.1. Go to the **ARHealth: Model Position** module, and (in the initialization section) select
211   **Visualization** mode. Click on **Load Marker Model** to load the marker for this option.

212

213   3.1.2. Load the 3D models created in section 2 by clicking on the **…** button to select the path of
214   the saved models from section 2. Then, click on the **Load Model** button to load it in 3D Slicer.
215   Models must be loaded one at a time. To delete any models previously loaded, click on that
216   model followed by the **Remove Model** button, or click **Remove All** to delete all models loaded
217   at once.

218

219   3.1.3. Click the **Finish and Center** button to center all models within the marker.

220

221   3.1.4. The position, orientation, and scaling of the 3D models can be modified with respect to
222   the marker with different slider bars (i.e., translation, rotation, scale).

223

224   NOTE: There is an additional "Reset Position" button to reset the original position of the models
225   before making any changes in the position.

226

227   3.1.5. Save the models at this position by choosing the path to store the files and clicking the
228   **Save Models** button. The 3D models will be saved with the extension name "_registered.obj".

229

230   3.2. **Registration** mode

231

232   NOTE: **Registration** mode allows combining of the AR marker with one 3D biomodel at any
233   desired position. Then, any section of the combined 3D models (that includes the AR marker)
234   can be extracted and 3D-printed. All biomodels will be displayed in the AR app using this
235   combined 3D-printed biomodel as a reference. This mode allows the user to easily register the
236   patient (here, a section of the patient's bone) and virtual models using a reference marker.

237

238   3.2.1. Go to the **ARHealth: Model Position** module, and (in the initialization section) select
239   **Registration** mode. Click on **Load Marker Model** to load the marker for this option.

240

241   3.2.2. Load the models as done in step 3.1.2.

242

243   3.2.3. Move the 3D models and ensure their intersection with the supporting structure of the
244   cube marker, since these models will be combined and 3D-printed later. The height of the
245   marker base can be modified. The position, orientation, and scaling of the 3D models can be
246   modified with respect to the marker with different slider bars (i.e., translation, rotation, scale).

247

248   3.2.4. Save the models at this position by choosing the path to store the files and clicking the
249   **Save Models** button. The 3D models will be saved with the extension name "_registered.obj".

250

251   3.2.5. The anatomy model may be too large. If so, cut the 3D model around the marker adaptor
252   and 3D-print only a section of the combination of both models using Meshmixer software.

253

254   3.2.6. Open Meshmixer and load the biomodel and supporting structure of the cube marker
255   model saved in step 3.2.5. Combine these models by selecting both models in the **Object
256   Browser** window. Click on the **Combine** option in the tool window that has just appeared in the
257   upper left corner.

258

259   3.2.7. In Meshmixer, use the **Plane Cut** tool under the **Edit** menu to remove unwanted sections
260   of the model that will not be 3D-printed.

261

262   3.2.8. To save the model to be 3D-printed, go to **File** > **Export** and select the desired format.

263

264   **4. 3D printing**

265

NOTE: The aim of this step is to 3D-print the physical models required for the final AR application. The marker to be detected by the application and the different objects needed depend on the mode selected in section 3. Any material can be used for 3D printing for the purpose of this work, when following the color material requirements requested at each step. Polylactic acid (PLA) or acrylonitrile butadiene styrene (ABS) are both sufficient choices.

4.1. Use a 3D printer to print the cubic marker. If a dual extruder 3D printer is not available, skip to step 4.2. Use a dual extruder 3D printer specifically to print the two-color marker provided in "Data/Markers/Marker1_TwoColorCubeMarker/". In the 3D printing software, select a white color material for the file "TwoColorCubeMarker_WHITE.obj" and black color material for "TwoColorCubeMarker_BLACK.obj".

NOTE: For better marker detection, print on high-quality mode with a small layer height.

4.2. If a dual extruder 3D printer is not available and step 4.1 was not performed, follow this step to print a 3D-printed marker with stickers as an alternative by doing the following:

4.2.1. Use a 3D printer to print the file "Data/Markers/ Marker2_StickerCubeMarker/ StickerCubeMarker_WHITE.obj" with white color material.

4.2.2. Use a conventional printer to print the file "Data/Markers/ Marker2_StickerCubeMarker/Stickers.pdf" on sticker paper. Then, use any cutting tool to precisely cut the images though the black frame by removing the black lines.

NOTE: It is recommended to use sticker paper to obtain a higher quality marker. However, the images can be printed on regular paper, and a common glue stick can be used to paste the images on the cube.

4.2.3. Place stickers in the 3D-printed cube obtained in step 4.2.1 in the corresponding order following instructions from the document "Data/Markers/ Marker2_StickerCubeMarker/Stickers.pdf".

NOTE: Stickers are smaller than the face of the cube. Leave a 1.5 mm frame between the sticker and edge of the face. "Data/Markers/Marker2_StickerCubeMarker/StickerPlacer.stl" can be 3D-printed to guide the sticker positioning and exactly match the center of the cube face.

4.3. 3D-print the adaptors, depending on the mode selected in section 3.

4.3.1. If **Visualization** mode (section 3.1), was selected, 3D-print "Data/3DPrinting/Option1/ MarkerBaseTable.obj", which is a base adaptor used to place the marker in vertical position on a horizontal surface.

4.3.2. If **Registration** mode (section 3.2) was selected, 3D-print the model created in step 3.2.8

309 with the marker adaptor attached.

310

311 NOTE: 3D printed objects from step 4.2 can be printed in any color material.

312

313 **5. AR app deployment**

314

315 NOTE: The goal of this section is to design a smartphone app in Unity engine that includes the
316 3D models created in the previous sections and deploy this app on a smartphone. A Vuforia
317 Development License Key (free for personal use) is required for this step. The app can be
318 deployed on Android or iOS devices.

319

320 5.1. Create a Vuforia Developer account to obtain a license key to use their libraries in Unity. Go
321 to the link found at <https://developer.vuforia.com/vui/auth/register> and create an account.

322

323 5.1.1. Go to the link found at <https://developer.vuforia.com/vui/develop/Licenses> and select
324 **Get Development Key**. Then, follow the instructions to add a free development license key into
325 the user´s account.

326

327 5.1.2. In the **License Manager** menu, select the key created in the previous step and copy the
328 provided key, which will be used in step 5.3.3.

329

330 5.2. Set up the smartphone.

331

332 5.2.1. To get started with Unity and Android devices, go to the link found at
333 <https://docs.unity3d.com/Manual/android-GettingStarted.html>.

334

335 5.2.2. To get started with Unity and iOS devices, go to the link found at
336 <https://docs.unity3d.com/Manual/iphone-GettingStarted.html>.

337

338 5.3. Set up a Unity Project for the AR app by first opening Unity v.2019 and creating a new 3D
339 project. Then, under **Build Settings** in the **File** menu, switch the platform to either an Android
340 or iOS device.

341

342 5.3.1. Enable Vuforia into the project by selecting **Edit** > **Project Setting** > **Player Settings** > **XR**
343 **Settings** and checking the box labeled **Vuforia Augmented Reality Support**.

344

345 5.3.2. Create an "ARCamera" under **Menubar** > **GameObject** > **Vuforia** > **ARCamera** and import
346 Vuforia components when prompted.

347

348 5.3.3. Add the Vuforia License Key into Vuforia Configuration settings by selecting the
349 **Resources** folder and clicking on **Vuforia Configuration**. Then, in the **App License Key** section,
350 paste the key copied in section 5.1.2.

351

352 5.3.4. Import the Vuforia Target file provided in "/Data/Vuforia/ AR_Cube_3x3x3.unitypackage"

353 into Unity, which contains the files that Vuforia requires to detect the markers described in
354 section 4.
355
356 5.3.5. Create a Vuforia MultiTarget under **Menubar** > **GameObject** > **Vuforia** > **MultiTarget**.
357
358 5.3.6. Select the marker type that will be used for detection by clicking on the MultiTarget
359 created in the previous step. In the **Database** option under **Multi Target Behaviour**, select
360 **ARHealth_3DPrintedCube_30x30x30**. In the **Multi Target** option under **Multi Target**
361 **Behaviour**, select either **TwoColorCubeMarker** or **StickerCubeMarker**, depending on the
362 marker created in section 4.
363
364 5.3.7. Load the 3D models created in section 3 into Unity Scene under **MultiTarget** by creating a
365 new folder with the name "Models" under the "Resources" folder. Drag the 3D models into this
366 folder. Once loaded in Unity, drag them under the "MultiTarget" item created in step 5.3.5. This
367 will make them dependent on the marker.
368
369 NOTE: Models should be visible in the Unity 3D view scene.
370
371 5.3.8. Change the colors of the 3D models by creating a new material and assigning the new
372 materials to the models.
373
374 5.3.8.1. Create a new folder named "Materials" under the "Resources" folder by going to
375 **Menubar** > **Assets** > **Create** > **Material**. Select the material and change the color in the
376 configuration section. Then, drag the file under the 3D model hierarchy.
377
378 5.3.9. Optional: if there is a webcam available, click on the play button located in the upper-
379 middle portion to test its application on the computer. If the marker is visible to the webcam, it
380 should be detected, and the 3D models should appear in the scene.
381
382 5.3.10. If an Android smartphone is used for app deployment, go to **File** > **Build Settings** in
383 Unity, and select the plugged phone from the list. Select **Deploy and Run**. Save the file with
384 extension .apk on the computer and allow the process to finish. Once deployment is done, the
385 app should be on the phone and ready to run.
386
387 NOTE: This protocol has been tested on Android v.8.0 Oreo or above. Correct functionality is
388 not guaranteed for older versions.
389
390 5.3.11. If the app will be deployed in an iOS device, go to **File** > **Build Settings** in Unity and
391 select **Run**. Select the path to save the app files. Allow the process to finish. Go to the saved
392 folder and open the file with the extension ".projectxcode".
393
394 5.3.11.1. In Xcode, follow the instructions from step 5.2.2 to complete deployment.
395

396　NOTE: For more information about Vuforia in Unity, go to the link found at
397　<https://Library.vuforia.com/articles/Training/getting-started-with-vuforia-in-unity.html>.
398

399　**6. App visualization**

400

401　6.1. Open the installed app, which will use the smartphone's camera. When running the app,
402　look at the marker with the camera from a short distance away (40 cm minimum). Once the app
403　detects the marker, the 3D models created in previous steps should appear exactly at the
404　location defined during the procedure on the smartphone screen.

405

406　NOTE: Illumination can alter the precision of marker detection. It is recommended to use the
407　app in environments with good lighting conditions.

408

409　**REPRESENTATIVE RESULTS:**

410

411　The protocol was applied to data from a patient suffering from distal leg sarcoma in order to
412　visualize the affected anatomical region from a 3D perspective. Using the method described in
413　section 2, the portion of the affected bone (here, the tibia and fibula) and tumor were
414　segmented from the patient's CT scan. Then, using the segmentation tools from 3D Slicer, two
415　biomodels were created: the bone (section of the tibia and fibula) (**Figure 1A**) and tumor
416　(**Figure 1B**).

417

418　Next, the two 3D models were positioned virtually with respect to the marker for optimal
419　visualization. Both modes described in section 3 were followed for this example. For
420　visualization mode, the models were centered in the upper face of the marker (**Figure 2**). For
421　registration mode, the marker adaptor was positioned in the bone (specifically, the tibia [**Figure
422　3**]). Then, a small section of the tibia was selected to be 3D-printed with a 3D marker adaptor
423　(**Figure 4**). An Ultimaker 3 extended 3D printer with PLA material was used to create the 3D-
424　printed markers (**Figure 5A,B**), marker holder base (**Figure 5C**) for the "visualization" mode, and
425　section of the tibia for "registration" mode (**Figure 5D**). **Figure 5E** shows how the marker was
426　attached to the "visualization" mode 3D-printed base. **Figure 5F** shows the attachment with the
427　"registration" mode 3D-printed biomodel. Finally, Unity was used to create the app and deploy
428　it in the smartphone.

429

430　**Figure 6** shows how the app worked for "visualization" mode. The hologram was accurately
431　located in the upper part of the cube as previously defined. **Figure 7** shows the application for
432　"registration" mode, in which the app positioned the complete bone model on top of the 3D-
433　printed section. The final visualization of the holograms was clear and realistic, maintained the
434　real sizes of the biomodels, and positioned accurately. When using the smartphone application,
435　the AR marker needs to be visible by the camera for the app to correctly display the holograms.
436　In addition, the light conditions in the scene must be of good quality and constant for proper
437　marker detection. Bad light conditions or reflections on the marker surface hinder the tracking
438　of the AR marker and cause malfunctioning of the app.

439

440   The time required to create the app depends on several factors. The duration of section 1 is
441   limited by the download speed. Regarding anatomy segmentation (section 2), factors affecting
442   segmentation time include complexity of the region and medical imaging modality (i.e., CT is
443   easily segmented, while MRI is more difficult). For the representative example of the tibia,
444   approximately 10 min was required to generate both 3D models from the CT scan. Biomodel
445   positioning (section 3) is simple and straightforward. Here, it took approximately 5 min to
446   define the biomodel position with respect to the AR marker. For the 3D printing step, the
447   duration is highly dependent on the selected mode. The "dual color marker" was manufactured
448   at high quality in a period of 5 h and 20 min. The "sticker marker" was manufactured in a period
449   of 1 h and 30 min, plus the time required to paste the stickers. The final step for app
450   development can be time-consuming for those with no previous experience in Unity, but it can
451   be easily completed following the protocol steps. Once the AR markers have been 3D-printed,
452   the development of an entirely new AR app can be performed in less than 1 h. This duration can
453   be further reduced with additional experience.
454
455   **FIGURE AND TABLE LEGENDS:**
456
457   **Figure 1: Representation of 3D models created from CT image of a patient suffering from**
458   **distal leg sarcoma. (A)** Bone tissue represented in white (tibia and fibula). (**B**) Tumor
459   represented in red.
460
461   **Figure 2: Results showing how "visualization" mode in 3D Slicer positions the virtual 3D**
462   **models of the bone and tumor with respect to 3D-printed marker reference.** The patient 3D
463   models (**A**) are positioned above the upper face of the marker cube (**B**).
464
465   **Figure 3: Results showing how "registration" mode in 3D Slicer positions the virtual 3D**
466   **models of the bone and tumor (A) with respect to 3D-printed marker reference (B).** The
467   marker adaptor is attached to the bone tissue model.
468
469   **Figure 4: Small section of the bone tissue and 3D marker adaptor.** The two components are
470   combined then 3D-printed.
471
472   **Figure 5: 3D printed tools required for the final application. (A)** "Two color cube marker" 3D-
473   printed with two colors of materials. (**B**) "Sticker cube marker" 3D-printed, with stickers pasted.
474   (**C**) Marker base cube adaptor. (**D**) Section of the patient's bone tissue 3D model and marker
475   cube adaptor. (**E**) "Sticker cube marker" placed in the marker base cube adaptor. (**F**) "Two color
476   cube marker" placed in the marker adaptor attached to the patient's anatomy.
477
478   **Figure 6: App display when using "visualization" mode.** The patient's affected anatomy 3D
479   models are positioned above the upper face of the 3D-printed cube.
480
481   **Figure 7: AR visualization when using "registration" mode.** The 3D-printed marker enables
482   registration of the 3D-printed biomodel with the virtual 3D models.
483

DISCUSSION:

AR holds great potential in education, training, and surgical guidance in the medical field. Its combination with 3D printing opens may new possibilities in clinical applications. This protocol describes methodology that enables inexperienced users to create a smartphone app combining AR and 3DP for the visualization of anatomical 3D models of patients with 3D-printed reference markers.

In general, one of the most interesting clinical applications of AR and 3DP is to improve patient-to-physician communication by giving the patient a different perspective of the case, improving explanations of specific medical conditions or treatments. Another possible application includes surgical guidance for target localization, in which 3D-printed patient-specific tools (with a reference AR marker attached) can be placed on rigid structures (i.e., bone) and used as a reference for navigation. This application is especially useful for orthopedic and maxillofacial surgical procedures, in which bone tissue surface is easily accessed during surgery.

The protocol starts with section 1, describing the workstation set-up and software tools necessary. Section 2 describes how to use 3D Slicer software to easily segment target anatomies of the patient from any medical imaging modality to obtain 3D models. This step is crucial, as the virtual 3D models created are those displayed in the final AR application.

In section 3, 3D Slicer is used to register the 3D models created in the previous section with an AR marker. During this registration procedure, patient 3D models are efficiently and simply positioned with respect to the AR marker. The position defined in this section will determine the hologram relative position in the final app. It is believed that this solution reduces complexity and multiplies the possible applications. Section 3 describes two different options to define the spatial relationships between the models and AR markers: "visualization" and "registration" mode. The first option, "visualization" mode, allows the 3D models to be positioned anywhere with respect to the marker and displayed as the whole biomodel. This mode provides a realistic, 3D perspective of the patient's anatomy and allows moving and rotating of the biomodels by moving the tracked AR marker. The second option, "registration" mode, allows attachment and combining of a marker adaptor to any part of the biomodel, offering an automatic registration process. With this option, a small section of the 3D model, including the marker adaptor, can be 3D-printed, and the app can display the rest of the model as a hologram.

Section 4 provides guidelines for the 3D printing process. First, the user can choose between two different markers: the "dual color marker" and "sticker marker". The whole "dual color marker" can be 3D-printed but requires a dual extruder 3D printer. In case this printer is not available, the "sticker marker" is proposed. This is a simpler marker that can be obtained by 3D-printing the cubic structure, then pasting the images of the cube with sticker paper or sticker glue. Furthermore, both markers were designed with extensible sections to perfectly fit in a specific adaptor. Thus, the marker can be reused in several cases.

528 Section 5 describes the process to create a Unity project for AR using the Vuforia software
529 development kit. This step may be the hardest portion for users with no programming
530 experience, but with these guidelines, it should be easier to obtain the final application that is
531 presented in section 6. The app displays the patient's virtual models over the smartphone
532 screen when the camera recognizes the 3D-printed marker. In order for the app to detect the
533 3D marker, a minimum distance of approximately 40 cm or less from the phone to marker as
534 well as good lighting conditions are required.
535
536 The final application of this protocol allows the user to choose the specific biomodels to
537 visualize and in which positions. Addtionally, the app can perform automatic patient-hologram
538 registration using a 3D-printed marker and adaptor attached to the biomodel. This solves the
539 challenge of registering virtual models with the environment in a direct and convenient
540 manner. Moreover, this methodology does not require broad knowledge of medical imaging or
541 software development, does not depend on complex hardware and expensive software, and
542 can be implemented over a short time period. It is expected that this method will help
543 accelerate the adoption of AR and 3DP technologies by medical professionals.
544

550 **DISCLOSURES:**
551 The authors have nothing to disclose.
552

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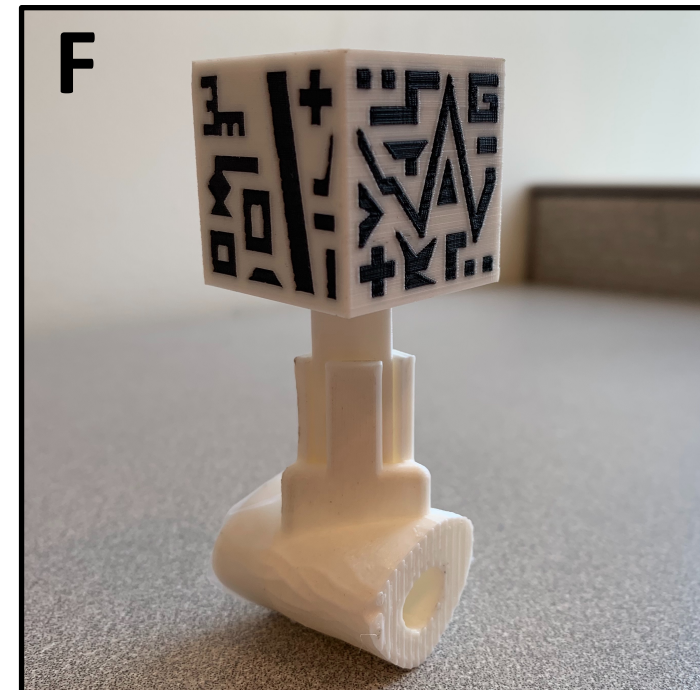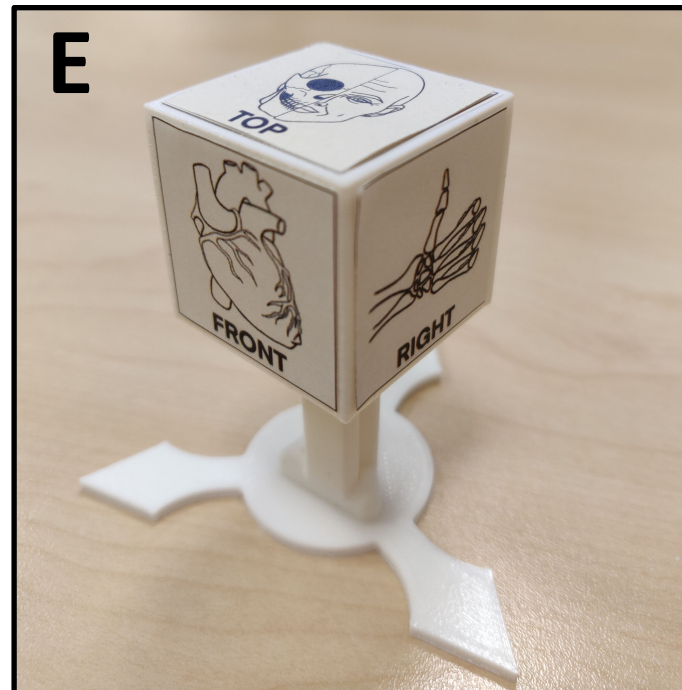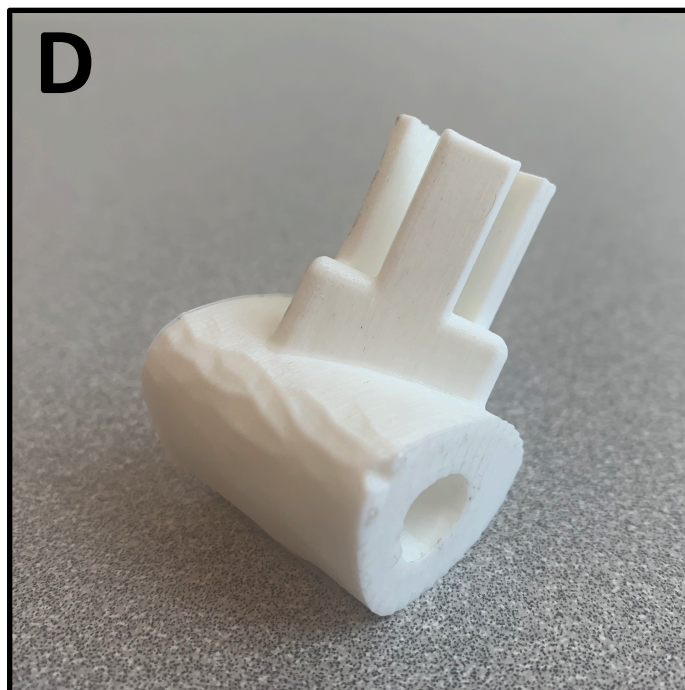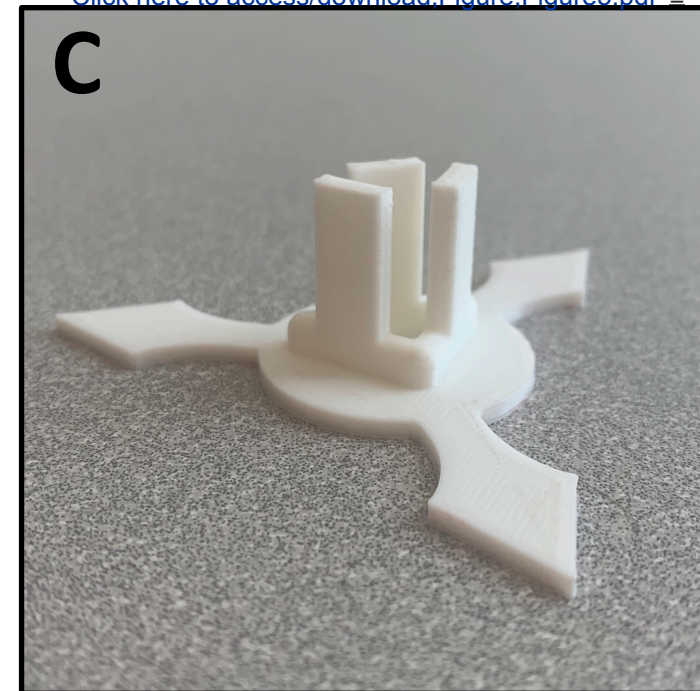609
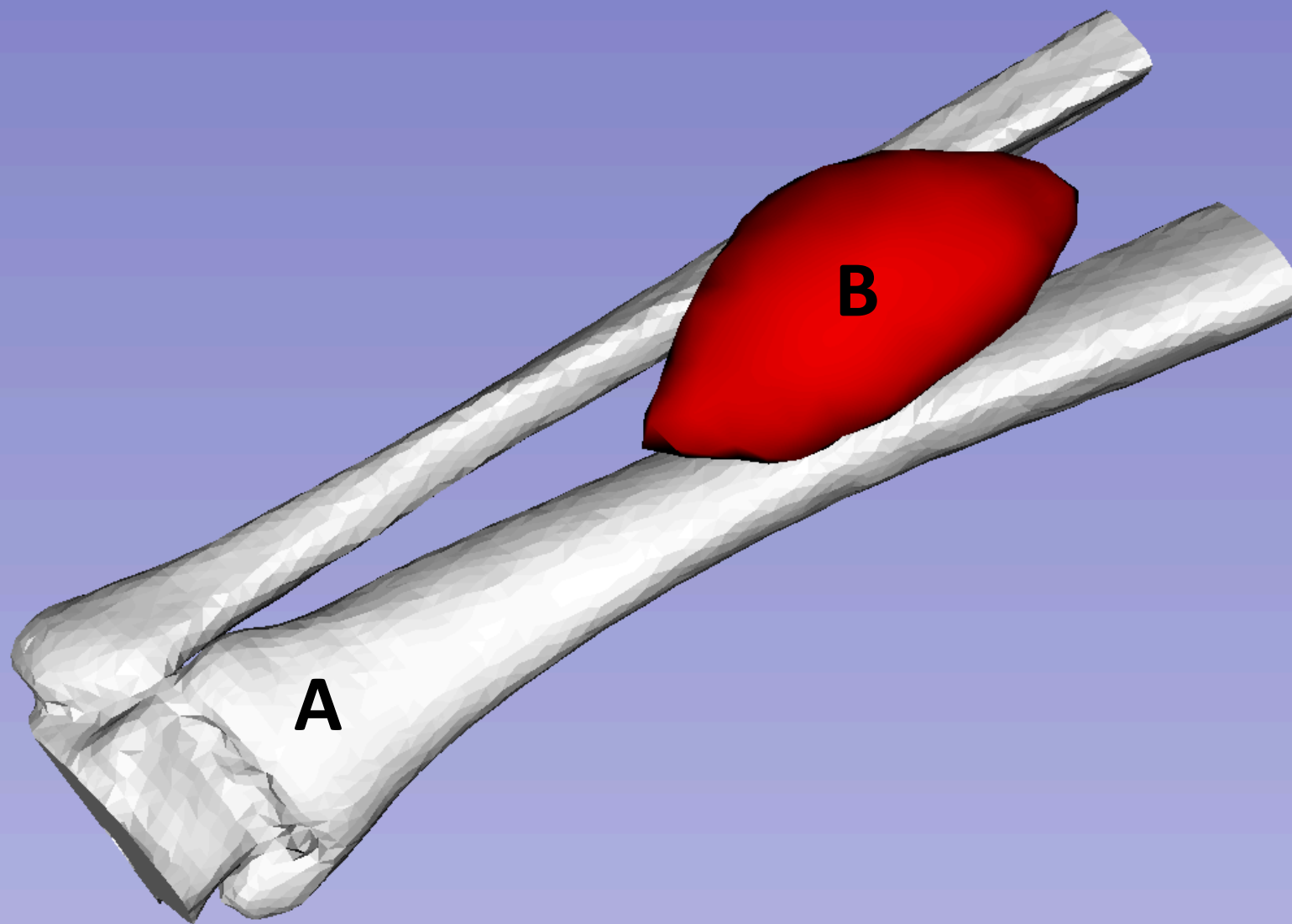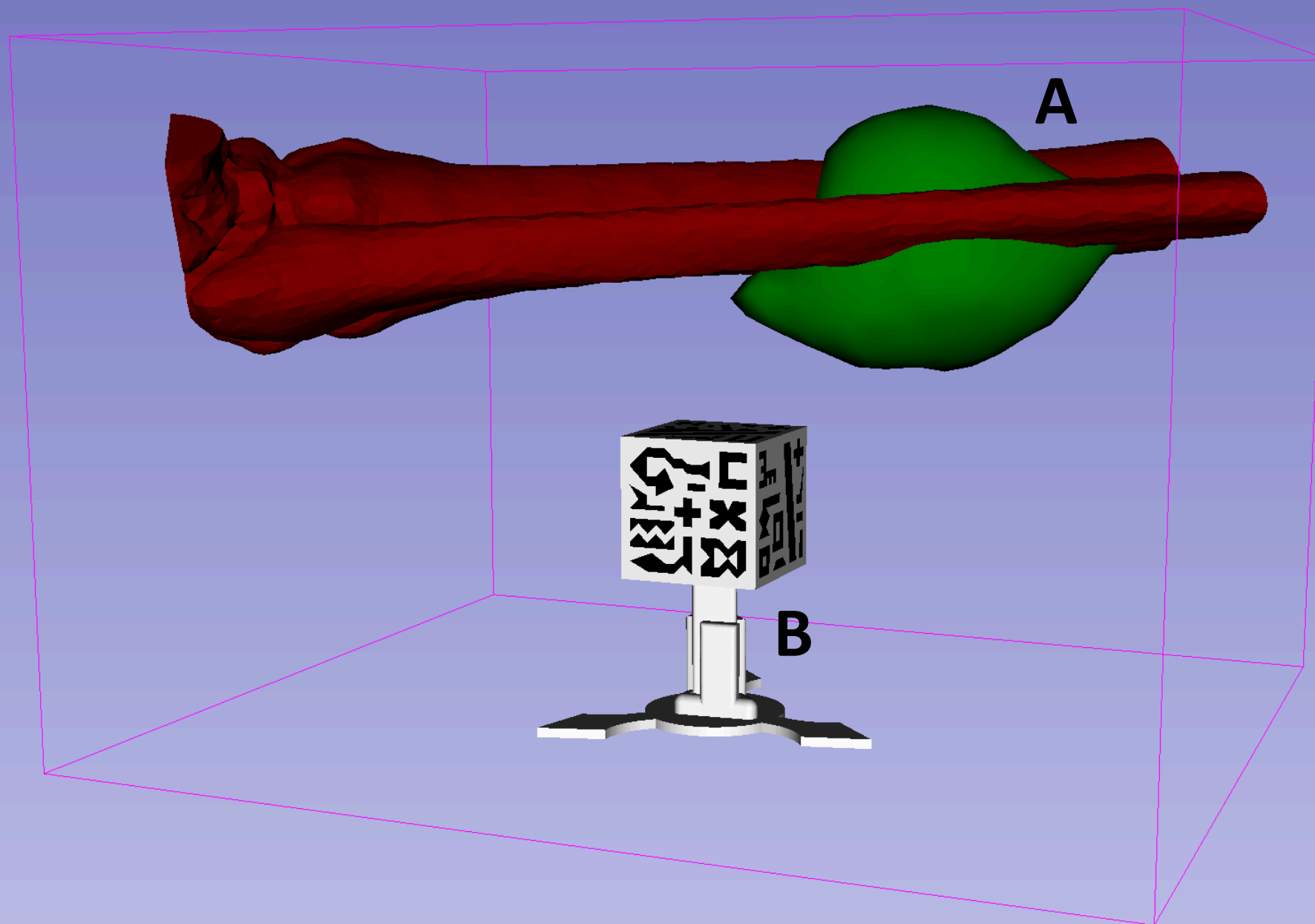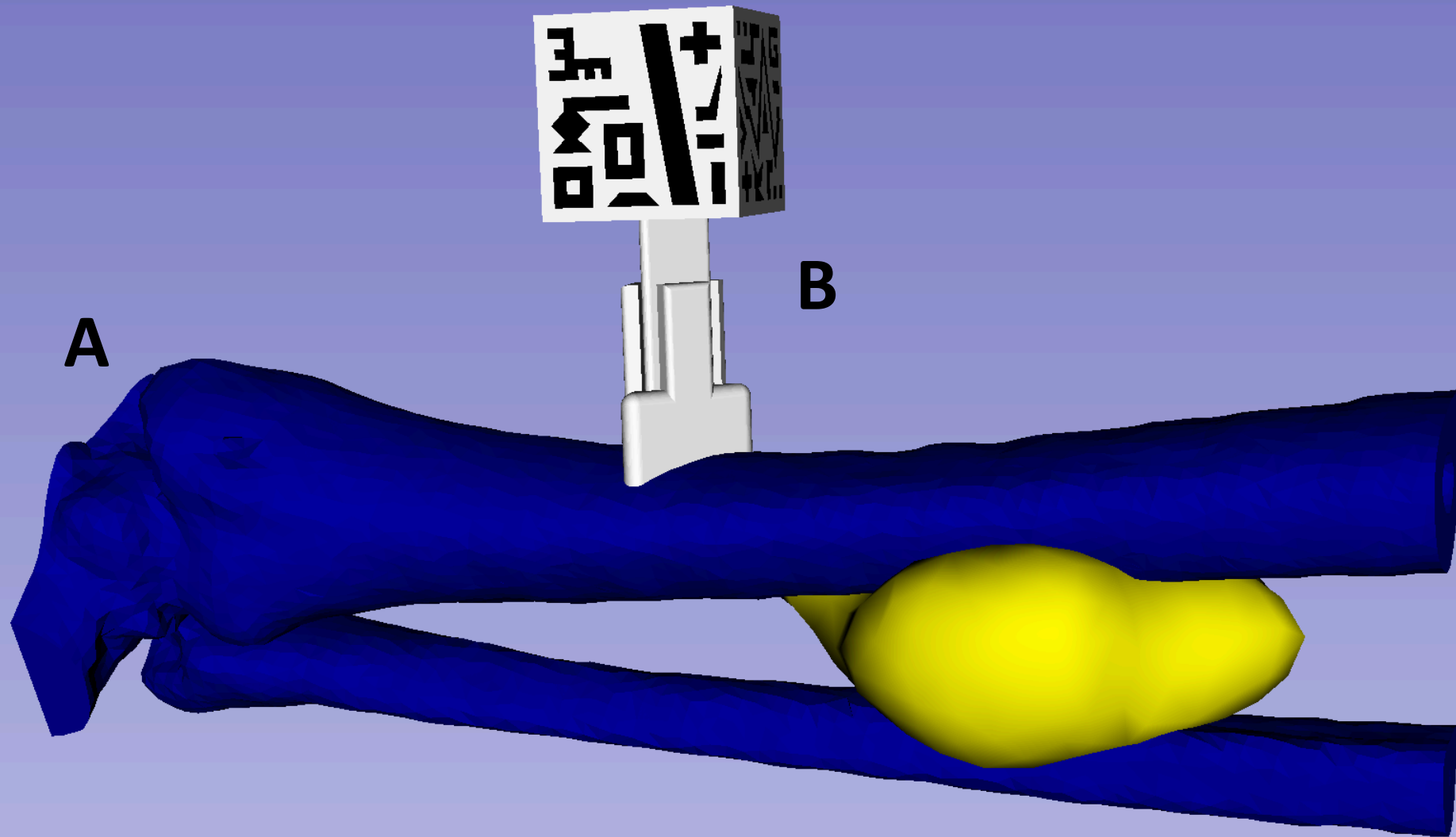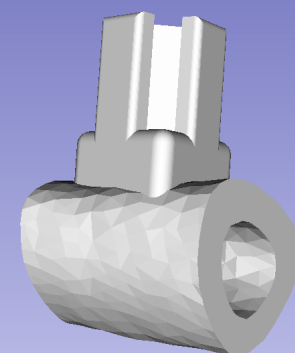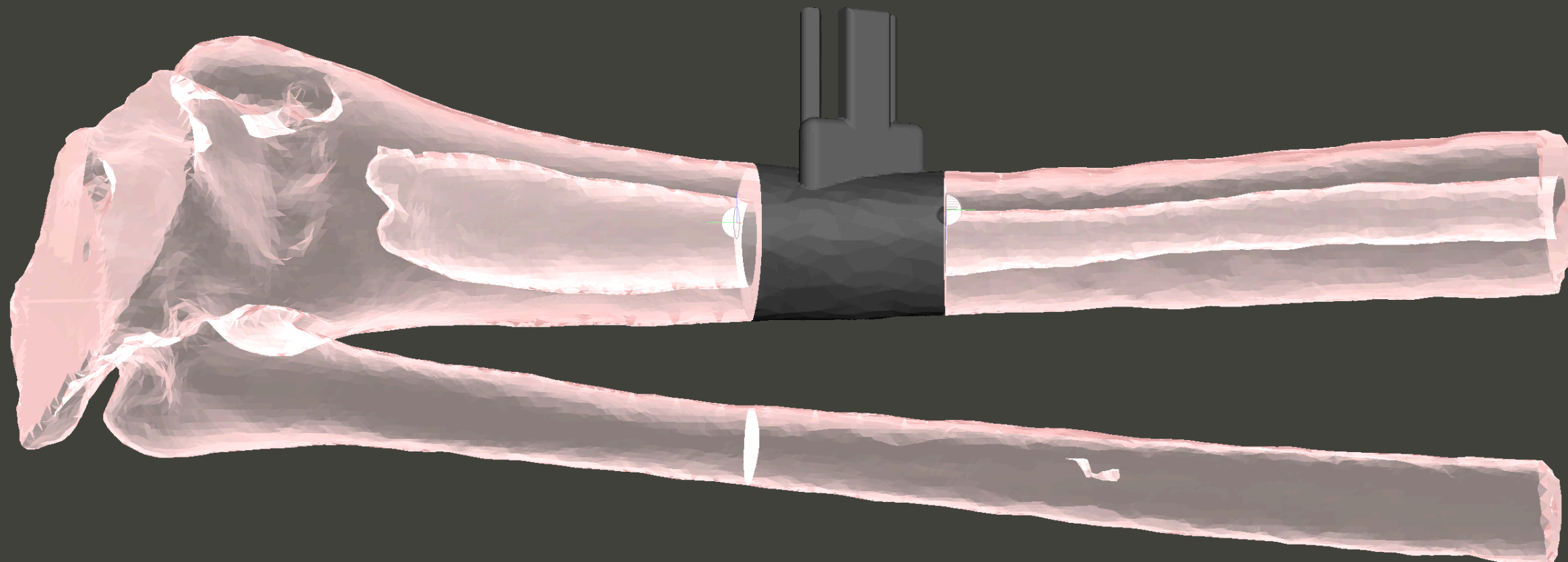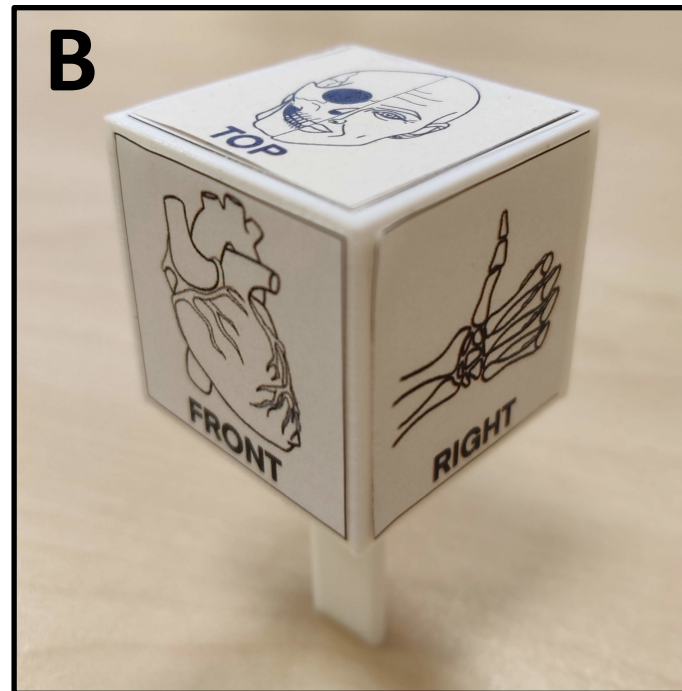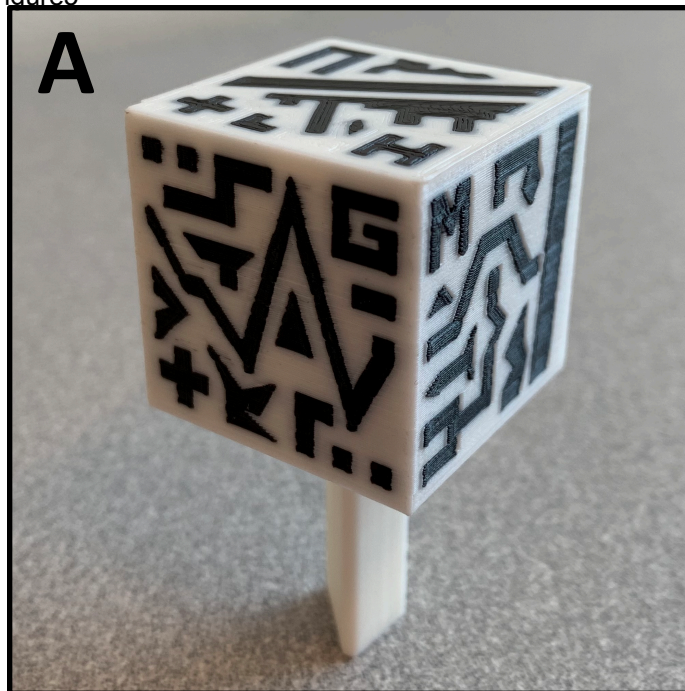
Figure1

Figure2 Click here to access/download;Figure;Figure2.pdf ⬇

Figure3

Figure4

Figure5

Figure6

Figure7
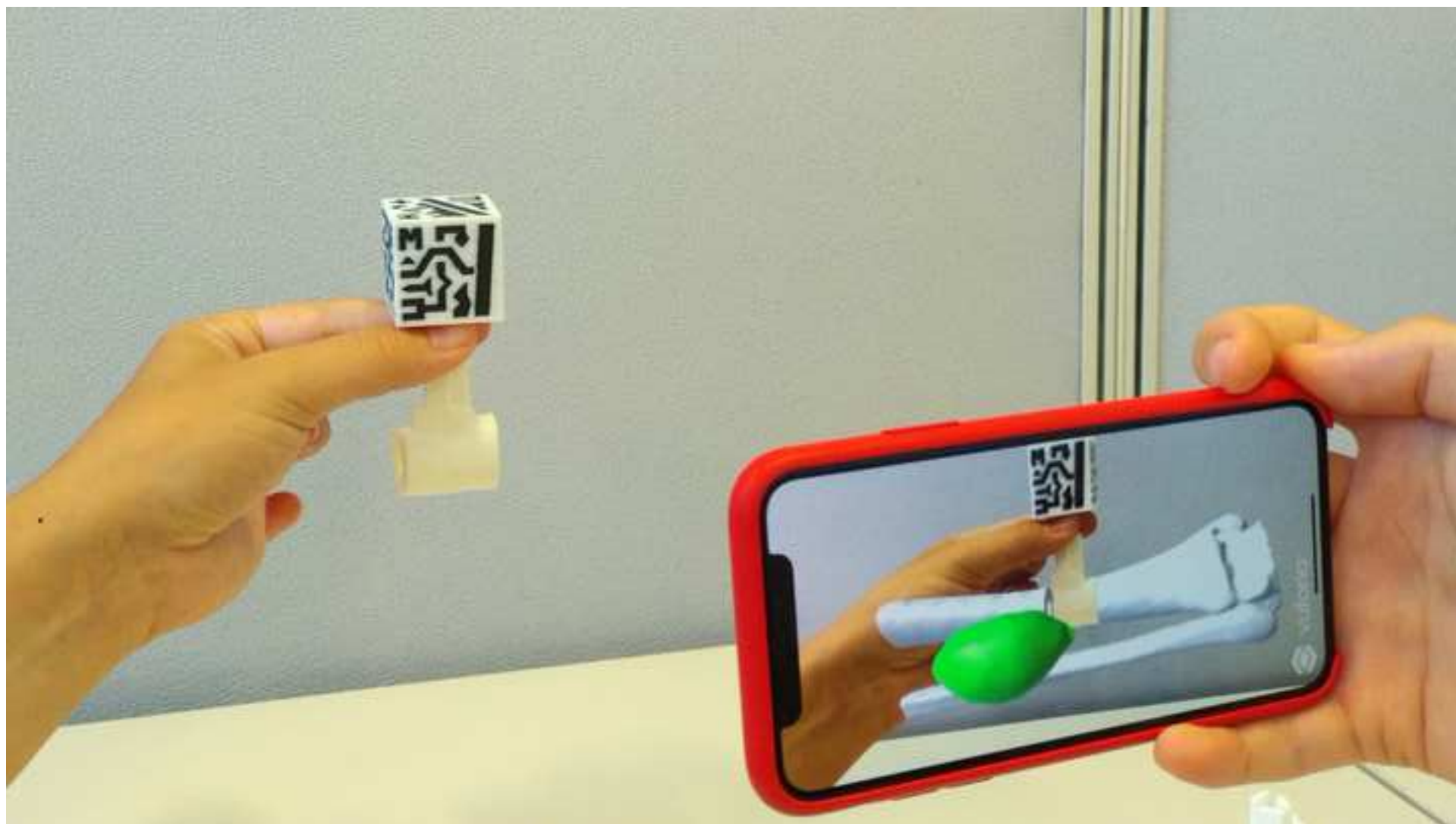
Name of Material/Equipment	Company	Catalog Number
3D Printing material: Acrylonitrile Butadiene Styrene (ABS)		
3D Printing material: Polylactic Acid (PLA)		
3D Slicer		
Android	Alphabet, Inc.	
Autodesk Meshmixer	Autodesk, Inc.	
iPhone OS	Apple, Inc.	
Ultimaker 3 Extended	Ultimaker BV	
Unity	Unity Technologies	
Xcode	Apple, Inc.	

Comments/Description

Thermoplastic polymer material usually used in domestic 3D printers.

Bioplastic material usually used in domestic 3D printers.

Open-source software platform for medical image informatics, image processing, and three-dimensional visualization

Android is a mobile operating system developed by Google. It is based on a modified version of the Linux kernel and other open source software, and is designed primarily for touchscreen mobile devices such

Meshmixer is state-of-the-art software for working with triangle meshes. Free software.

iPhone OS is a mobile operating system created and developed by Apple Inc. exclusively for its hardware.

Fused deposition modeling 3D printer.

Unity is a real-time development platform to create 3D, 2D VR & AR visualizations for Games, Auto, Transportation, Film, Animation, Architecture, Engineering & more. Free software.

Xcode is a complete developer toolset for creating apps for Mac, iPhone, iPad, Apple Watch, and Apple TV. Free software.

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Rebuttal Document

Manuscript JoVE60618

Title: Combining Augmented Reality and 3D Printing to Display Patient Models on Your Smartphone

We would like to thank the reviewers and the editorial for their insightful comments and their interest in our work.

First, we would like to summarize the major changes made for the paper revision:

- In the protocol section, the levels of subtitles have been modified to have a more appropriate format following the editorial instructions. Now sublevels 4 are sparingly used.

- Segmentation procedure in 2.2.2 is now more deeply explained.

- A new paragraph has been added in the introduction section to give a clearer vision of the proposed method in the context of the state-of-the-art.

- The introductory paragraph of step 3 of the protocol section has been modified to improve the explanation of "Visualization" and "Registration" modes.

- Possible applications of our method are discussed in a new paragraph in the discussion section.

- Software improvements in the repository provided for the 3D Slicer Module "AR Health: Model Position". A new button has been added for restarting the process without having to restart 3D Slicer.

- Figures 2 and 3 have been updated, highlighting different elements in the image.

In the following pages of the document, you will find a separate answer to each reviewer's comments.

Editorial comments:

We would like to thank the Editorial for their insightful review of the manuscript and for their comments.

General:
1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.
2. Please limit the use of personal pronouns (you, your
3. Please include email addresses for all authors in the manuscript.

Answer:
1. We apologize for any spelling or grammar issues. The paper has been reviewed again and corrected.
2. The use of personal pronouns has been reduced or avoided. Examples can be found in steps 2.2.1, 3.1.4, 3.2.3, 3.2.5, 4.2, 5.1.2, 5.2, 5.2.9.2, 5.3.10, 5.3.12.1.1., 6. All these steps are referenced to the first version of the manuscript.
3. Email addresses for all authors have been included in "Authors and Affiliations" section.

Protocol:
1. Please include an ethics statement before the numbered protocol steps, indicating that the protocol follows the guidelines of your institution's human research ethics committee.
2. If possible, please limit substeps to no more than 4 levels (e.g., 1.1.1.1), with a 4th level used sparingly.
3. For each protocol step, please ensure you answer the "how" question, i.e., how is the step performed? Alternatively, add references to published material specifying how to perform the protocol action. If revisions cause a step to have more than 2-3 actions and 4 sentences per step, please split into separate steps or substeps.

Answer:
1. The following ethics statement has been included before the numbered protocol steps: "This study was performed in accordance with the principles of the 1964 Declaration of Helsinki as revised in 2013. The anonymized patient data and pictures included in this paper are used after written informed consent was obtained from the participant and/or their legal representative, where he/she approved the use of this data for dissemination activities including scientific publications."
2. Most of the level 4 steps have been removed to higher-level steps.
3. The manuscript steps and substeps have been modified to a more appropriated format following the instructions given by the Editorial.
    - Step 3.1.2 has been split, adding step 3.1.3, to avoid explaining too many actions in the same substep.
    - Step 3.2.5 and its substeps have been modified to level 3 substeps in order to avoid level 4 steps. "How" question has been answered specifically in some substeps.

- Steps and substeps from 4.1. have been extended to steps 4.1 and 4.2.
- Substeps in steps 5.3 have been adapted to avoid level 4 steps.

Table of Materials:
1. Please ensure the Table of Materials has information on all materials and equipment used, especially those mentioned in the Protocol.

Answer:
1. The Table of Materials has been modified by adding new materials that were not previously included.

Reviewers' comments

Reviewer #1
Manuscript Summary:
The authors describe a method for presenting segmented medical images in an augmented reality smartphone app with virtual content registered to a 3D printed model. Registration is performed by manually adjusting a virtual model to a Vuforia marker 3D model.
Major Concerns:
None.
Minor Concerns:
Item 2.2.2 summarizes the segmentation details with a link to the Slicer documentation on segmentation. Although this is an acceptable description, I would prefer to see 2-4 sentences on the specific effects the authors used to segment the distal leg sarcoma images. Or even one summary summarizing the effects used: "To segment the desired patient geometry, we used the threshold, etc... effects."

Answer:
We would like to thank Reviewer #1 for his time on reading and commenting on our paper.
Now we will proceed to answer the reviewer's minor concerns:

Regarding the segmentation step in item 2.2.2, we agree with the reviewer that summarizing the segmentation procedure with a link to Slicer documentation tutorial may not be enough to show a user how to segment properly the proposed patient case. Therefore, a new substep 2.2.2.1 has been added explaining briefly which tools were used from the Slicer Segmentation module to finally obtain the given 3D models of the patient. The added step is the following: "2.2.2.1 To segment the bone (tibia and fibula in this case), the "Threshold" tool was used to set up a minimum and a maximum HU value from the CT image which correspond to bone tissue. By using this tool, other elements with HU outside these threshold values are removed, such as soft tissue. Then, "Scissors" tool was used to remove some undesired areas such as the bed or other anatomical structures from the segmented mask. The sarcoma region was segmented manually using "Draw" and "Erase" tools since the tumor is difficult to contour with automatic tools".

Reviewer #2

Manuscript Summary:

This article proposes a method to display AR scene based on markers on a smartphone. A step-by-step methodology was described to realize this work. 3D slicer was used to segment and reconstruct the anatomical 3D models of patients from CT or MR images. An AR Health module was also developed to design the location relationship between marker and visual 3D models through two modes of Visualization and Registration. Meshmixer was used to modify the combination of both models. Then, the physical models required were 3D printed for the final AR application. An AR smartphone app in Unity engine was designed and deployed on Android or iOS devices. Finally, a real clinical case of a patient suffering from a distal leg sarcoma was to describe the propose methodology.

This manuscript is well organized.

My major concerns are as follows:

1. The proposed method is not clear. Compared with other work about AR using smartphone, the differences and similarities among the proposed method and other AR methods should be described more clearly. Using markers to display AR scene has been proposed in previous articles.

2. The accuracy of AR in the proposed method is not described. The author could show an in-situ superposition of 3D images on patients. Actually, it is very different to install the marker on bones and on deformed tissues. Tissue deformation affects registration accuracy. So, please give examples of some suitable clinical applications.

3. In AR Health module, both Visualization and Registration modes obtain the location of the marker and the 3D models by translating and rotating them. It is hoped that the differences between the two operations can be further explained.

4. The proposed method seems to be a combination of several software and the existing methods. For some diseases, medical image segmentation is difficult, especially for inexperienced doctors. Also, the process described in this manuscript is complicated. Authors may describe each process simply and express them in pictures.

5. I have tried the AR Health module, which can only be executed once and needs further optimization. For examples, it cannot return to remove or add models after "Finish and Center", and the registration process cannot be performed after the visualization process.

Answer:

We would like to thank Reviewer #2 for his time on reading and commenting insightfully our paper. In the following paragraphs we answer all reviewer's major concerns:

1. The purpose of this paper is not to present a new method for showing AR scenes with data coming from medical images but to offer inexperienced users a complete protocol on how to use AR technology for that purpose. We include several references showing how this technology has been used previously in the biomedical field, providing context to the reader about the interest of these solutions. We have considered that a JOVE video and a full step-

by-step protocol will help novel users to try AR since our method is based on inexpensive tools. Markers-based AR has been proposed before and has shown its potential, particularly in one of our previous papers. With this protocol, we want to encourage more users to try this technology thanks to its simplicity. The novelty of our work is that we facilitate image-to-world registration, which has been previously considered a limiting factor. We have added a paragraph in the introduction section of the paper to better answer the reviewer's concerns.

2. We have previously evaluated the accuracy of the proposed protocol on a phantom in reference[19], where we used HoloLens as the AR device. The protocol described in the paper is not intended to introduce any accuracy measure, but the reader can check our reference to better understand the limitations of the protocol. The limitations regarding the use of a marker attached to the bone were also identified in our previous paper. The referee is correct when pointing out that a marker attached to soft tissue would limit the utility of the protocol. We have added a paragraph in the discussion section with more clinical examples of the use of the proposed methodology: "In general, one of the most interesting clinical applications of AR and 3DP is to improve patient to physician communication by giving the patient a different perspective of her case, improving the explanation of a specific medical condition or treatment. Other possible application includes surgical guidance for target localization, where 3D printed patient-specific tools (with a reference AR marker attached) can be placed on rigid structures, such as bone, and used as a reference for the navigation. This application can be especially useful for orthopedic and maxillofacial surgical procedures in which bone tissue surface is easily accessed in the surgical field."

3. In order to describe the differences between Visualization and Registration methods, we have improved the description of the 3D Slicer module. In addition, the differences between both methods have been further explained in protocol sections.

4. Segmentation might be a difficult task for some diseases, even more, if the region of interest includes other tissue than bone. To answer the reviewer's concerns, we have added an explanation in section 2.2.2.1 of how to perform the segmentation step. We think that the whole protocol is now easier to follow and, although it may seem complex at some points, the document will be a good step-by-step guide for the reader when combined with the final video.

5. We apologize for the problems experienced when testing the version of the code available during the review. The 3D Slicer module has been updated and new functionalities have been added. One of the main improvements is the addition of a new button which allows the user to restart the process without the need of restarting 3D slicer when the button is pressed.

Minor Concerns:

1. Previous research proposed an AR method using a mobile device. You can refer to this article.
Z. Fan, et al.: 3D Interactive Surgical Visualization System using Mobile Spatial Information Acquisition and Autostereoscopic Display, Journal of Biomedical Informatics, Vol.71, pp.154-164, 2017.
2. You can mark some important components in figures for better understanding. For example, you can mark "3D CT model" and "3D printed marker reference".
3. A flowchart of the proposed method can be added for better understanding.

Answer:

The following paragraphs include our responses to the reviewer's minor concerns:

1. We would like to thank the reviewer for identifying that reference, that has been included in the introduction section of our paper (reference number 10).

2. Considering the reviewer comment, Figures 2 and 3 have been modified by remarking the different elements in the image.

3. A flowchart could help in understanding the method. However, we believe that the final video will serve as a flowchart and adding and extra figure illustrating the steps of the protocol will extend the paper length, so we did not include a flowchart.

References

19. Moreta-Martínez, R., García-Mato, D., García-Sevilla, M., Pérez-Mañanes, R., Calvo-Haro, J., Pascau, J. Augmented reality in computer-assisted interventions based on patient-specific 3D printed reference. *Healthcare Technology Letters*. (2018).