Results of Multimodal Integrated Imaging for Foetal Intervention - MIIFI project

Mario Ceresa[1*], Rodrigo Cilla-Ugarte[2], Karen Lopez-Linares[2], Elisenda Eixarch[3], Eduard Gratacos[3], Miguel Angel Gonzalez Ballester[1,4]

[1]Universitat Pompeu Fabra, Barcelona Spain; [2]Vicomtech, San Sebastian, Spain; [3]BCN Natal, Barcelona, Spain; [4] ICREA, Barcelona, Spain
*Corresponding author: mario.ceresa@upf.edu

ABSTRACT
In this paper we present the main ideas and results of the Multimodal Integrated Imaging for Foetal Intervention project (MIIFI). We obtained breakthrough results in multimodal image segmentation and fusion for surgical planning and navigation of TTTS interventions. We also present some initial prototypes of the traditional and VR-based clinical interfaces. Finally, we discuss the ideas for a potential continuation of this project in the upcoming Phase 2 of ATTRACT. We include concrete examples where the developed technology could make a positive impact such as Spina Bifida surgery, cardiovascular interventions, brain surgery and endoscopic interventions.
Keywords: Twin-to-twin transfusion syndrome; Foetal surgery; Surgical planning and simulation; Computer vision; Deep learning; Virtual reality

1. INTRODUCTION (409/400 WORDS)

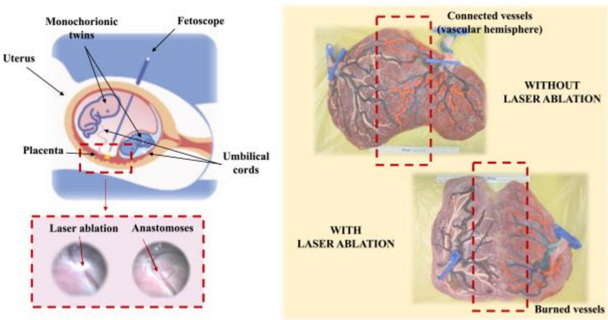


Fig. 1. - Fetoscopic laser photocoagulation procedure for TTTS: (*left*) illustration of the intrauterine environment, and (*right*) monochorionic placentas with (non-) coagulated vascular connections located on the surface (hemisphere) before and after the laser ablation. (Adapted from one of our papers [1])

Twin-to-twin transfusion syndrome (TTTS) is a disease affecting 20% of monochorionic twin pregnancies where small anastomoses connect the vasculature of the two fetuses at the placenta level. Due to the differences in the circulatory system of the twins this results in a dangerous unbalance of blood flow that is deadly if not promptly treated: one of the twins -the donor- will be depleted of blood and suffer from fetal growth restriction, while the other –the acceptor- will be overloaded of blood and suffer from cardiac insufficiency.
The elective therapy for TTTS is fetoscopic laser photocoagulation of placental anastomoses that is curative if performed early enough during pregnancy. The procedure is, however, complex and time sensitive. The surgeon has less than twenty minutes to (1) introduce the fetoscope into the amniotic sac, (2) Explore the uterus to locate the placenta and the vascular equator and (3) Follow the vessels to detect the anastomoses and photocoagulate them with the laser. There are several additional factors that increase the difficulty of the procedure: the field of view of the fetoscope is extremely limited, image quality and illumination are usually of low quality, correct orienting the instrument is difficult once inside the amniotic sac, the manoeuvrability of the fetoscope is extremely limited.
We believe that the impact of the abovementioned problems could be reduced thanks to algorithms that help the surgeon to simulate the intervention beforehand and quickly detect the placenta and the surgical targets (the anastomoses of the vessels) once inside, reducing the cognitive load and the danger of disorienting or missing some of the anastomoses in the photocoagulation step. Furthermore, in the intraoperative scenario, we aim to build an augmented reality system to assist the surgery by the automatic identification of the anastomoses in real-time. We expect to increase the success of the treatment, measured as the postnatal survival rate of the fetuses, and to reduce surgery times.
In the following sections we will present more in detail our results on segmentation of placenta and vessels in MRI magnetic resonance images, US ultrasound images and fetoscopic videos, fusion of those multimodal data in a single 3D model and creation of a VR interface for the explorations of the surgery.

2. STATE OF THE ART

The work proposed by Luks et al. [2] studied the feasibility of planning the preoperative TTTS phase with MRI and computerized volume rendering. Authors rendered the anatomy of each amniotic cavity and fetus, the umbilical cord insertions and the location of the placental equator membrane in relation to the port placement. This allowed surgeons to plan the entry point, as well as the length and angle required to reach the target region. However, authors did not implement a user-specific application to provide real functionality and visualization. Also, they did not segment the placenta vasculature, which is the main target in TTTS fetal surgery. This study was not validated quantitatively, as the 3D reconstructions were performed almost manually. Liao et al. [3] fused endoscopic image mosaics with 3D US for assisting directly the intrauterine laser photocoagulation therapy. The endoscope and US probe positions were tracked using a *Polaris Vicra* optical system, and subsequently registered to the surface of a placenta phantom. The image mapping accuracy was 2.8 mm on average.

Recently, Javaux et al. [4] presented a mixed-reality surgical trainer equipped with comprehensive mechanical sensing to develop the required motor skills for TTTS surgery. The simulator was focused on scope handling and target lasering on the placenta. The setup consisted of a fetoscope, a thin-walled flexible plastic cannula, a phantom of the maternal body wall, a force sensor, and a foot pedal to trigger the virtual laser. However, the training was only performed with artificial fetoscope images. Eight surgeons with different levels of experience considered the trainer to be close to reality (median score of 3.5 on the 5-point *Likert* scale).

A comprehensive overview of segmentation and classification approaches for the whole fetus and, more specifically, the fetal brain, lungs, liver, heart and placenta in MRI and (3D) US was presented by Torrents-Barrena et al. [5]. Despite all the above-mentioned advances most TTTS intervention are currently performed without the assistance of 3D planning and intra-operative guidance, missing some of the benefits that current technology could deliver to both the surgeon and the patient.

3. BREAKTHROUGH CHARACTER OF THE PROJECT

We aim to disrupt the current paradigm of foetal interventions by integrating multimodal medical imaging techniques in a surgical planning and placental GPS that reduces the cognitive load of the surgeon and speeds up the intervention. The surgeon will interact with this information with a mixed reality headset that superimposes this information in the OR operating room.

In order to realize this ambitious goal, we are advancing the state of the art in several aspects. On the *computer vision side*, segmentation of placenta, uterus and vascular structures in MRI, US and fetoscopy video is a difficult problem which is currently not solved. In MIIFI, we developed several novel machine-learning based algorithms to create detailed segmentations of those important tissues.

However, having a correct and detailed segmentation is not enough: different image modalities have different resolutions and must be combined or *fused* together to generate a single map that shows all relevant information to the surgeon.

With all this information it is easy to get lost into the details. For this reason, another breakthrough of MIIFI is the creation of a mixed reality interface that can be used to explore the anatomy of the patient before the intervention and determine the best entry point for the operation.

Finally, the end goal of MIIFI is to be useful in real interventions. For this reason, intraoperative navigation of the planned surgery is a very important task that will help the surgeon keep track of the current position inside the womb and the relative distance and number of surgical targets.

Tab. 1. Summary of the main breakthroughs achieved by MIIFI project

Before MIIFI	After MIIFI
No automatic segmentation of intra-uterine structures from medical images	We trained several neural networks to detect, localize and segment uterus, placenta and vasculature in MRI, US and fetoscopy video
Not possible to integrate information from multimodal images for TTTS	Surgeons can now consult a single image that includes all the relevant information from MRI and US
Surgical planning is done looking at a single image on a flat screen	Surgeons can now explore the multimodal planning in 3D using virtual reality or mixed reality headsets
No intraoperative guidance is performed	During surgery, surgeons can now know the real-time position of the tools inserted in the womb w.r.t. the planned image and the number, location and distance of the surgical targets (vascular anastomoses to photocoagulate)

4. PROJECT RESULTS

The first result of MIIFI project is the creation of a fetal imaging dataset with more than 88 cases of foetal interventions. In 25 cases, the procedure is TTTS and each patient has matching MRI, US, fetoscopic data and surgeon’s annotations. This in itself is a great breakthrough as, to date, no dataset of the same size is available for research purpose.

The second result is in the field of uterine organs segmentation and fusion. We developed several deep learning based methods [6, 7, 8] to automatically segment structures of interest in MRI, US and fetoscope videos. In Fig 2 we can see one of our proposed architectures for placenta segmentation in MRI with a downsampling and an upsampling path.

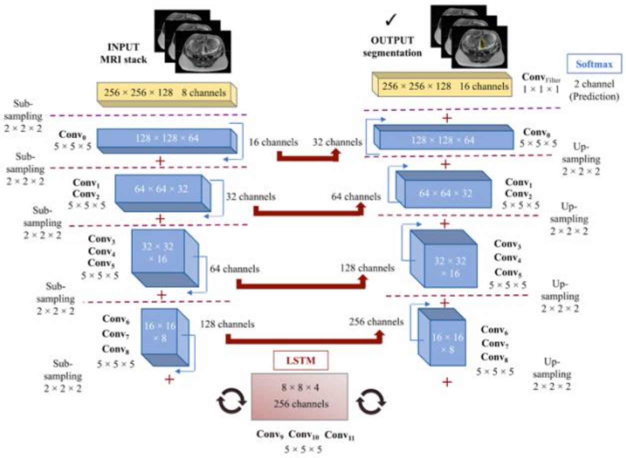


Fig. 2 - Recurrent 3D CNN architecture for the segmentation of placenta in MRI images

We employ a conditional generative adversarial network (cGAN) [9] (see Fig. 3) to automatically segment the placenta in US images by applying the image-to-image translation approach. cGANs learn a mapping from observed image and random noise vector, to the segmentation:

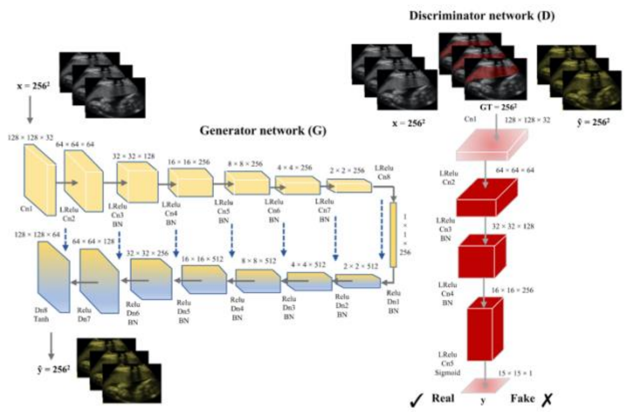


Fig. 3 - cGAN architecture for automatic segmentation of placenta in US images.

For the fetoscopic video segmentation, we propose an unsupervised approach based on image reconstruction, video-frame registration for Mosaic creation and segmentation with Hessian based Frangi Vesselness approach [10].

Finally, we researched several methods for automatic fusion of segmented organs in multimodal images and generate a single 3D model with all relevant information [11].

Once the information gathered from MRI and US is fused and a single 3D model is created, we generate a planning scene where the surgeons can explore the patient's anatomy well ahead of surgery and test several insertion point of the fetoscope (Fig. 4) to check that all surgical targets are within reach [12].

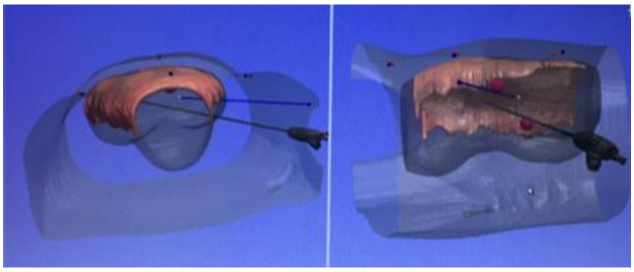


Fig. 4 - Visualization of fused 3D model, surgical targets and fetoscope insertion planning

In addition to the clinical interface shown in Fig. 4, we also created a proof of concept of a planning interface with the HTC Vive Virtual Reality headset [13] (See Fig. 5). The prototype was well received but many of the doctors that tested it initially said that they would like to work in Mixed Reality instead, because it allows to maintain awareness of the surroundings. We are now testing it with the Magic Leap augmented reality headset.

Fig. 5 - Example scene from the initial prototype of a clinical interface with HTC Vive Virtual Reality headset.

Finally, we are developing an online platform that clinical partners can use to upload the images, run the developed algorithms and obtain the results. This is an important first step in the scalability and commercialization of the proposed technology as we will discuss more extensively in next section.

5. FUTURE PROJECT VISION

In the following section we highlight the core importance of promoting MIIFI project to ATTRACT Phase 2. In our analysis we consider a typical Future and Emerging Technologies project in H2020: 3 years duration, 1 million Euros funding and a Consortium around 5-9 partners.

5.1. Technology Scaling

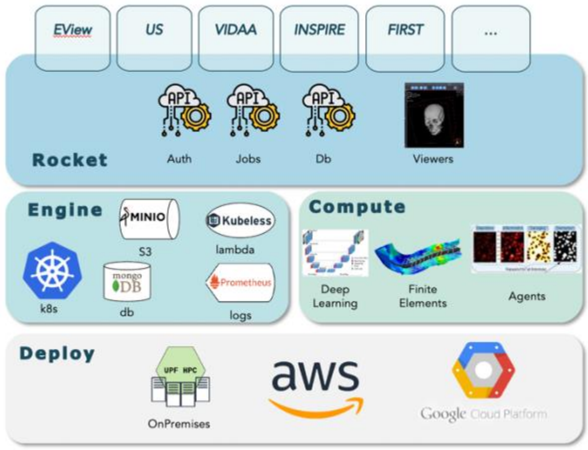


Fig. 6 - Multi-layered architecture for scaling the technology in Phase 2.

We are developing MIIFI as a platform (Fig. 6 ReImagine platform) for researchers and clinicians to collaboratively manage clinical data and to automate analysis using Machine Learning, Finite element simulations, Agent based modelling and Mixed Reality. We plan to use a zero-asset strategy, where the platform is initially hosted in a cloud server to avoid incurring in fixed costs and high initial investments. Thanks to its cloud-based nature, scaling is easy and cheap.

5.2. Project Synergies and Outreach

We are actively seeking partnership with different entities both inside and outside ATTRACT's ecosystem. We have already contacted the PI of *"Mixed reality for brain functional and structural navigation during neurosurgery"* project, Antonio Ferretti, to explore synergies between our approaches.

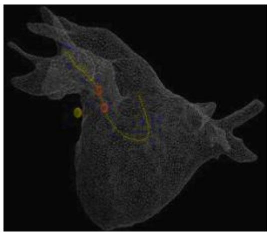
We will participate in accelerators and incubators as MWC COLLIDER, Barcelona Activa, B-venture, EIT KIC Health, Yuzz Banco Sabadell, IE Venture Lab and Everis entrepreneurship awards. Additionally, we will prepare and pitch to Business Angel Forums as the ones organized by ESADE and IESE Business schools. The UPF Business shuttle and UPF Venture unit will help contacting and pitching possible investor funds like Genesis Venture, Healthequity, InverReady and Keiretsu Forum.

Based on our experience in ATTRACT Phase 1, we plan to facilitate public dissemination of the results and activities during ATTRACT Phase 2 with interviews with local media, press releases and dissemination of multimedia content in social networks and news aggregators.

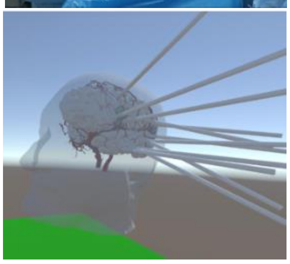
5.3. Technology application and demonstration cases

In ATTRACT Phase 2 we will implement technology demonstration cases for the four following interventions: **Spina bifida, Cardiovascular interventions, brain surgery and endoscopic/colonoscopy** interventions as detailed in Fig. 7. We think those are our best options to bring **concrete** benefit to the areas of Scientific Research, Industry and the *Health, demographic change and wellbeing* Societal Challenge.

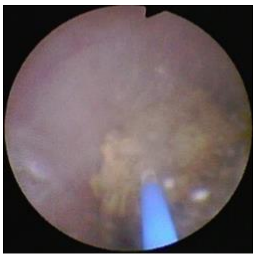
Spina bifida is a promising target to apply our technology as it is a very complex intervention, that requires high precision movements, where multimodal imaging and operational guidance can make a difference. In Figure, our clinical team during fetal intervention.



Cardiac interventions benefit from multimodal imaging and simulations of both electric activity and blood flow. Integrating and visualizing all this complex information can help the clinician. In Figure, an example from our VIDA platform.



Brain interventions such as intracranial recording for epilepsy can benefit from multimodal fusion and intuitive mixed reality and haptic visualizations. In Figure, one of our early results with HTC Vive and Leap Motion.



Many **endoscopic and colonoscopy procedures** share similarities with video fetoscope interventions and could benefits from the results of this project. In Figure, a frame of an endoscopic camera during nefrolithiasis intervention.

Fig. 7 – Suggested application and demonstration cases to be developed in Phase 2.

5.4. Technology commercialization

In this subsection we detail the main steps to commercialize MIIFI technology.

First, we will run extensive interviews with main clinical stakeholders in Europe to ensure that our technology includes all the main aspects they see value in. We have already started with Hospital Clinic and San Juan de Deu in Barcelona, Spain, and KU-Leuven, Belgium.

Second, we will build an online platform usable by clinicians to upload images and retrieve results. This is very important to make the business scalable to a huge number of clients. We have already started to build a prototype system as detailed in Section 5.1

Third, we are currently planning a clinical trial with several European hospitals to assess the efficacy of our technology. Additionally, we are currently discussing a **private partnership** with Epic to use their Unreal Engine to power the Mixed Reality clinical interface.

The business model will be a two-sided market where researchers and clinicians can interact. The former will provide algorithms and solutions and the latter data, annotations and feedback.

We have already received public funding in the past for technological transfer and product development such as: LLAVOR and PRODUCTE organized by the local Catalan government; CaixaImpulse, a program promoted by La Caixa Foundation; Mind the GAP from Botin Foundation. We found this program very helpful in early steps to market. Should we decide to launch a new company, we plan to apply to Neotec from CDTI and to the European funding the European Innovation Council Fast Track to Innovation and the EIC Accelerator Pilot.

5.5. Envisioned risks

There are several risks that we could face in Phase 2 of MIIFI project, summarized in Tab. 2 along with corresponding mitigation strategies.

Tab. 2. Risks and mitigations for MIIFI Phase 2 proposal

Risk description	Possible Impact	Mitigation strategy
Integration of the various components of the system is slower than expected	Low	Hire more developers
Mixed reality interface is not helpful to clinicians	Medium	Redesign
Monetization is harder than expected	High	Pivot
Consortium is not working as expected	Medium	More meetings and communications

5.6. Liaison with Student Teams and Socio-Economic Study

Collaboration with Master level students is highly valued for the continuation of our project. Unfortunately, the pandemic situation of the last months blocked all possibilities to meet face to face with interested students abroad. For the Phase 2, we will nominate an experienced person of our team to facilitate MSc. level interaction and use online collaboration tools to help interested students engage with the project.

We will be also willing to participate into the expert-driven socio-economic study of the ATTRACT initiative and ecosystem that will be held in Phase 2. Our contribution could be with personal interviews, technology impact references and economic indicators.

6. ACKNOWLEDGEMENT

This project has received funding from the ATTRACT project funded by the EC under Grant Agreement 777222

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